Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2022.172940.2678 Volume 30, Issue 1, January 2024

Manuscript ID ZUMJ-2211-2678 (R1)
DOI 10.21608/ZUMJ.2022.172940.2678

ORIGINAL ARTICLE

Management of Muscle Invasive Bladder Cancer with Weekly Gemcitabine Concurrent with Radiotherapy Post-Transurethral Tumor Resection in Old Fragile Patients: our Experience Institute

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Submit Date 2022-11-05
Revise Date 2022-11-21
Accept Date 2022-11-25

ABSTRACT

background: Muscle-invasive bladder cancer is common in Egypt. Trimodality chemoradiation post transurethral resection of bladder tumor proved high benefits**.** Our aim is to show our institute's experience in using gemcitabine concurrent with radiotherapy post-TURB in an old frail group of patients diagnosed with MIBC regarding efficacy and tolerability.**Aim of work:**to show the safety and efficacy of using low-dose weekly gemcitabine as a radiosensitizer concurrent with radiotherapy post-TURBT in an old frail group of patients diagnosed with MIBC and unfit for radical surgery.

Methods: This prospective study included 47 patients diagnosed with de novo MIBC in the period between October 2016 and October 2020. Patients who qualified underwent maximal TURBT followed by radiation therapy with 65 GY in two phases concomitant weekly gemcitabine (100 mg/m2). **Results:** The median age was 65.9 years. Males were more common (80.9%) than females. The Median follow-up was 24 months. A complete response was achieved in 34 patients (72.3%). Salvage cystectomy was done for 3 patients who did not achieve CR. chemotherapy was given to another 5 patients of those who did not achieve CR (gemcitabine plus cisplatin /carboplatin). While 5 patients refused any further treatment, only for follow-up regimens. **Survival**: Median PFS and OS were 40 months and 42 months, respectively. Three-year progression-free survival (PFS) and overall survival (OS) were 66.6% and 75.4%, respectively. **Conclusions:** Chemoradiation with low dose Gemcitabine is well tolerated and effective post-TURT. It provides an alternative organ-preserving strategy in invasive TCC for old fragile patients.

Keywords: bladder cancer, cystectomy, bladder preservation, Gemcitabine.

INTRODUCTION

Bladder cancer (BC) is among the more commonly occurring cancers. It ranks tenth in worldwide absolute incidence: sixth in men and seventeenth in women **[1]**. Bladder cancer is one of commonest malignancies in Egypt, it ranks as the 3rd most common cancer **[2]**.

Bladder cancer, the sixth most common cancer in the United States **[3]**, is diagnosed in individuals younger than 40 years of age very infrequently. Considering the median age at diagnosis is 73 years, medical comorbidities are frequently taken into account in patient management [4].

Twenty-five to thirty percent of newly diagnosed instances of bladder cancer are muscle-invasive bladder cancer MIBC, while the remainder is non-MIBC or superficial **[5,6]**.

The standard treatment for non-metastatic, (MIBC) is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) with pelvic lymph node dissection although this procedure is associated with increased morbidity **[7]**.

Trimodality therapy (TMT) including maximal Transurethral Resection of Bladder Tumor (TURBT) followed by concurrent chemoradiation has achieved the best alternate outcomes have consistently been seen as bladder sparing modality for muscle-invasive bladder cancer (MIBC) **[8]**.

Concurrent chemotherapy and radiotherapy raised 2-year loco-regional disease-free survival (DFS) rates from 54% to 67% in a study by James et al **[9]**

Overall survival rates (OS) improved from 35% to 48% after 5 years. Because the majority of patients recommended for definitive radiation therapy are older, with many having compromised renal function and poor performance status, cisplatin as a radiosensitizer is not the best chemotherapeutic drug **[10]**.

Trimodality therapy achieves success; the first-choice drug for CCRTH in bladder cancer is cisplatin which is associated with a toxicity profile not tolerated by some patients, especially the elderly, so confirming the presence of effective well tolerated another radiosensitizer is a need. Numerous studies have examined the synchronized use of radiation with Gemcitabine as a radiosensitizer with high tolerance and efficiency **[11]**.

Trimodality treatment choice of muscle-invasive bladder cancer formed of complete TURT followed by concurrent chemoradiotherapy emerging as a good modality that can provide a cure for those who refuse cystectomy or for old fragile patients. Patients with MIBC who are unfit for radical surgery or refusing it are a considerable number. Tolerability and efficacy are two important needs to be achieved with a suitable plan of management [12].

Gemcitabine is a potent radiation sensitizer and has shown activity in the setting of metastatic urothelial cancers. The use of 100 mg/m2 weekly gemcitabine during radiotherapy as a component of TMT was tested in a recently completed Phase II trial **[13]**.

Our study aimed to show the safety and efficacy of using low-dose weekly gemcitabine as a radiosensitizer concurrent with radiotherapy post-TURBT in an old frail group of patients diagnosed with MIBC and unfit for radical surgery.

METHODS

This prospective study was done at the medical oncology, clinical oncology, and urology departments at Zagazig University between October 2016 and October 2020. All participants provided written informed consent, and the study was approved by the Faculty of Medicine, Zagazig University's ethical research committee with IRB #1092/9-2022. The study was conducted by the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies. Our study included 47 patients diagnosed with de novo MIBC who are not fit for surgery because of being old and fragile or refusing.

Baseline clinical evaluation and workup were done for all patients. Computerized tomography (CT); chest, abdomen, and pelvis with contrast and Magnetic resonance imaging (MRI) were fixed if needed. Accepted baseline complete blood count (CBC) as well as renal and liver functions, were required. Patients with prior non-MIBC or MIBC with distant metastasis

were excluded, and patients with hydronephrosis were also excluded.

All patients underwent maximum TURBT, and within 3 months of it, the treatment plan was given over 6 weeks, weekly gemcitabine treatment was given within 30 minutes of the IV infusion with 100 mg/m2 one per week started on day 1 with the treatment planned to continue weekly, until the last week of RTH (2-4 hours before RTH). Physical assessment, CBC, kidney, and liver functions were reviewed weekly.

All patients planned for 3D conformal radiotherapy by using CT simulation, as the patient was in a supine position with an empty bladder. The dose delivers by 18 MV as the whole pelvis (pelvic lymph node and bladder) received 4500 cGY/1.8 over 25 fractions, then boosted the bladder up to 2000cGY/200 over 10 fractions.

All Patients received concurrent chemoradiotherapy with acceptable toxicity. Every week toxicity evaluation and side effects were recorded according to the common toxicity criteria v 5.0 **[14]**.

Statistical analysis:

Data were analyzed using SPSS win statistical package version 22. Numerical data were expressed as mean and standard deviation (SD) or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Survival analysis was done using the Kaplan-Meier method.

Statistical analyses of progression-free survival (PFS) were measured from the date of CRT initiation to the date of progression. The overall survival (OS) was measured from the date of CRT initiation to the date of death from any cause or loss to follow-up. $P \leq 0.05$ were accepted as statistically significant.

RESULTS

We treated 47 patients, their characteristics shown in table (1), 38 males (80.9%) and 9 females (19.1%). The median age was 65.9 (range, 52–77). Most of the study patients were with Performance status (PS) 1, thirty-two patients (68.1%). Stage II disease was presented in 12 patients (25.5%), stage III in 35 patients (74.5%), and all patients were transitional cell carcinoma (TCC) pathological type.

Maximum TURBT as per cystoscopy reports was performed on all study populations; complete TURBT was confirmed for 27 patients (57.4%), while 20 patients showed residual.

Cystoscopy and imaging three months post-CCRTH were done to assess response to treatment; CR was achieved in 34 patients, including all who underwent complete TURBT (72.3%). For three patients of those 13 who did not achieve CR, cystectomy was done for them, and chemotherapy was given to another 5 patients of those who did not achieve CR, in the form of 4 cycles of gemcitabine plus carboplatin. Five patients were kept without any interference because they refused any further treatment, only for follow-up regimens.

Median follow-up was 24 months range (6-48) as shown in Tables (1). All patients continued follow-up with cystoscopy and CT chest, abdomen, and pelvis every 3 months for the first 2 years, then every 6 months after that.

During the follow-up duration, the failure rate was 26/47 patients. Eight patients developed distant metastasis, and 7 patients had local recurrence MIBC, while 11 patients failed local and distant, 8 of them out of 34 patients achieved CR to CCRTH.

Median PFS and OS were 40 months and 42 months, respectively. Three-year progression-free survival and OS for all study patients were 66.6% and 75.4%, respectively, as in tables (2, 3) and figures (1, 2).

In the multivariate analysis; the relation between PFS and demographics, only gender was statistically significant to PFS as shown in table (4) and figure (3). only maximal TURBT was statistically significant to OS rates, as in table (5) and figure

Toxicity

Of 47 patients treated in our study with CCRTH, 15 patients developed anemia normocytic normochromic type grade I seen with 6 patients, while 9 patients were grade II blood transfusion given to those who indicated. Thrombocytopenia grade I was seen in 5 patients, and no dose adjustment or delay was required. Cystitis was the most common irritating symptom that occurred in 10 patients, it was grade I, and 7 patients were grade II relieved by mild analgesics. Tenesmus happened to 5

patients, and it was grade I. Hemorrhagic cystitis as late toxicity grade I in 2 patients as late toxicity table (6).

Table 1: Demographic characteristics of Bladder Cancer Patients:

		N = 47	%
Age (Mean ±Sd) (Range)		65.91±5.90 (52.0-77.0)	
Sex	**Male**	38	80.9
	Female	9	19.1
stage			
	II	12	28.6
	III	35	71.4
Grade	**G II**	11	23.4
	G III	36	40.4
Pathology	**TCC**	47	100.0
PS 0	9		19.1
1	32		68.1
2	6		12.8
Complete TURBT	**Incomplete**	20	42.6
	Complete	27	57.4
Unfit		34	72.3
Refused		13	27.7
CR post-CCRTH	YES	34	72.3
	NO	13	27.7
FU / Month Median (Range)		24.00(6.0-48.0)	
Recurrence	No	21	44.7
	Yes	26	55.3
Local Recurrence	No	29	61.7
	Yes	18	38.3
Distant Metastasis	No	28	59.6
	Yes	19	40.4

PS performance status, TCC transitional cell carcinoma, TURBT Transurethral Resection of Bladder Tumor, CCRTH concurrent chemoradiotherapy

Table 2: Progression Free Survival (PFS) of the urinary bladder patients included in the study:

Median PFS (months)	SE	95.0% CI		12 Month	24 month	36 month
		Upper limit	Lower limit			
40.0	-	-	-	92.3%	80.8%	66.6%

Table 3: Overall Survival (OS) of the urinary bladder patients included in the study:

Median OS	SE	95.0% CI		12 Month	24 Month	36 Month	48 Month
		Upper limit	Lower limit				
42.0	-	-	-	93.4%	83.8%	75.4%	46.9%

Table 4: Relation between progression-free survival (PFS) and demographics and patients' characteristics:

variables		Total N	N of events	PFS (months)		95.0%CI		P value
				median	SE	lower	upper	
Age	≤65 >65	21 26	12 14	30.0 30.0	12.097 2.917	6.290 24.283	53.710 53.717	0.479
Sex	Male Female	38 9	23 3	30.0 -	2.255 -	25.580 -	34.420 -	**0.028***
Stage	II III	10 25	6 14	20.0 33.0	4.916 7.998	10.365 17.323	29.635 48.677	0.244
Grade	II III IV	11 19 17	6 12 8	30.0 30.0 33.0	14.027 5.339 4.983	2.507 19.537 23.233	57.493 40.463 42.767	0.542
Complete TURBT	Incomplete Complete	20 27	13 13	30.0 30.0	9.901 2.950	10.594 24.218	49.406 35.782	0.201
Unfit /Refuse	Unfit Refuse	34 13	20 6	30.0 33.0	2.447 12.324	25.205 8.846	34.795 57.154	0.530

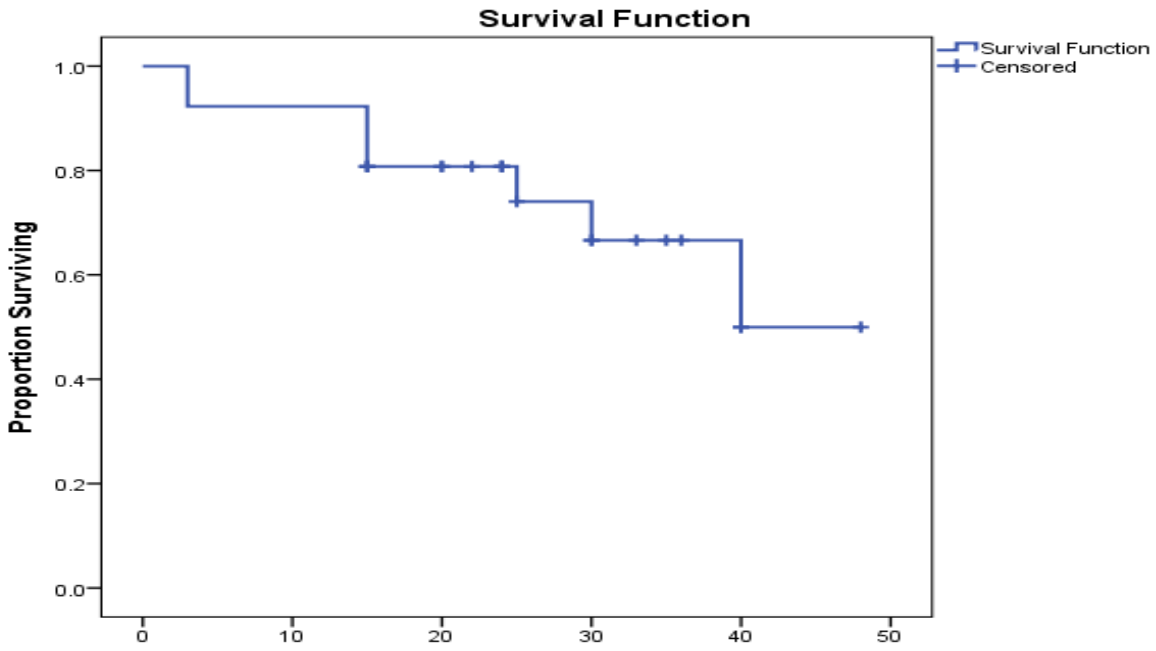

Figure (1): Progression Free Survival (PFS)

Figure (2): Overall Survival (OS)

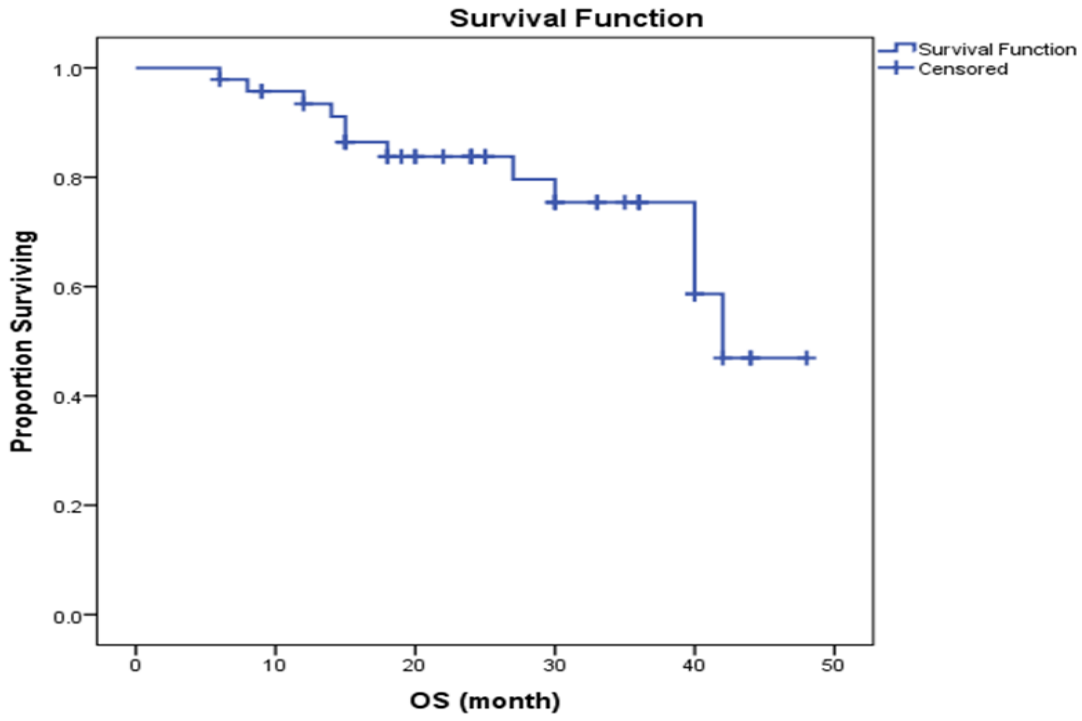

Figure (2): Overall Survival (OS)

Table 5 (Supp): Relation between Overall survival (OS)and demographics and patients' characteristics

variables		Total N	N of events	OS (months)		95.0%CI		P value
				median	SE	lower	upper	
Age	≤65	21	8	44.0	4.152	35.862	52.138	0.217
	>65	26	12	40.0	6.472	27.316	52.684	
Sex	Male	38	17	40.0	5.899	28.439	51.561	0.265
	Female	9	3	40.0	17.99	4.738	75.262	
Stage	II	10	3	44.0	0.00	27.179	56.821	0.348
	III	25	10	40.0	11.298	17.856	62.144	
Grade	II	11	4	40.0	11.784	16.904	63.096	0.823
	III	19	9	40.0	11.601	17.261	62.739	
	IV	17	7	40.0	12.811	14.890	65.110	
Complete TURBT	Incomplete	20	9	40.0	16.083	8.478	71.522	**0.017***
	Complete	27	11	40.0	5.799	28.634	51.366	
Unfit/ Refuse	Unfit	34	14	40.0	5.378	29.442	50.558	0.760
	Refuse	13	6	44.0	13.288	17.955	70.045	

TURBT Transurethral Resection of Bladder Tumor. * Significant.

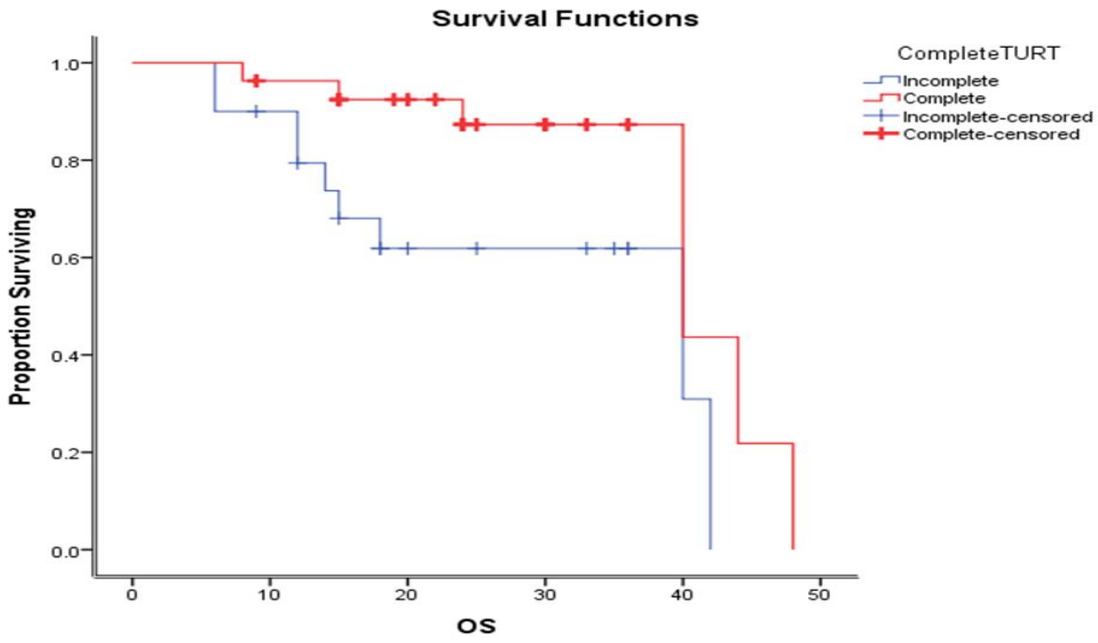

Figure (4) (Supp): OS

according to TURBT status

Table **6 (Supp): Treatment Toxicity**

	GRADE I	GRADE II	GRADE III
Anemia	6 (12.7%)	9 (19.1%)	0 (0%)
Thrombocytopenia	10.6%)	5 (0 (0%)	0 (0%)
Bladder	10 (21.2%)	7 (14.8%)	0 (0%)
Rectal	5 (10.6%)	0 (0%)	0 (0%)

DISCUSSION

Radical cystectomy has been widely accepted as the standard treatment in MIBC, while this procedure needs urinary diversions with impaired quality of life. It is also associated with a significant risk of postoperative complications and mortality. Bladder preservation therapy has been explored as a potential alternative to overcome such pitfalls of radical cystectomy. A growing body of evidence suggests that bladder preservation therapy could become the primary treatment strategy in muscle-invasive bladder cancer patients **[15].**

For localized MIBC, we are aiming for a cure. A retrospective study including 3320 patients undergoing RC, showed five-year overall survival at 40%, 34%, 28%, and 23%, with age stratified as < 70, 70 - 74, 75 - 79, and ≥ 80 years, respectively. It is expected that early mortality increases with increased age due to impaired functional reserves **[16]**.

Meta-analysis suggests that the efficacy of TMT proved to be non-inferior to that of RC at < 10-year OS . Also, Lin et al. (2018) found no significant difference in overall survival rates between patients who underwent radical cystectomy and those who were treated with chemoradiotherapy using the national cancer database in the United States **[12]**. A recent meta-analysis that included 11 cohort studies involving 1735 individuals showed that bladder preservation is a better therapeutic option than radical cystectomy, especially for older patients **[17].**

The median age in our study was 65.9 (range 52 - 77), which is consistent with the median ages reported by Demerci et al. (69; range, 55-86) **[18]**and Ghannam et al., who conducted a trial with participants aged 69.5 (range, 65-78) **[19]**. Atasoy et al. found a median age of 73, with a range of 49-89, in their study **[20].**

In the course of our research, 72.3% of participants managed to give a complete response (CR). In line with the findings of Pos et al., who found a CR rate of 74% **[21]**, and Turgeon et al., who found a CR rate of 72%, respectively **[22]**. The Christie group, which employed a similar regimen with 60 patients, reported a CR rate of 75%, which we found to be comparable to our own data **[23].** Although **[13]** Choudhury et al. reported a greater CR rate of 88%, this may be attributable to the exclusion of T4 tumors from their study; comparatively, **[20]** Atasoy et al. reported a CR rate of 62.5% among their study group while using a weekly Gemcitabine dose that was 25% less than ours. Patients' advanced age was a major factor in the 66.7% CR rate in the trial by Ghannam et al. **[19].**

Among the 34 patients with CR in our study, 8 (23.5%) had a local recurrence in the bladder. Twenty-one percent of patients who had a CR after a bladder preservation protocol were found to have MIBC, according to a study by Tunio et al[24].

According to formal research, the rate of recurrence in the bladder ranged from 19 to 58%, with almost half of the cases being muscle invasive. Because the remaining tumor has such a big negative influence on survival, total TURBT should be the goal whenever it is feasible to perform the procedure. Approximately one-quarter of patients require salvage cystectomies, which is consistent with the findings of other research **[25]**.

At three years after therapy, 57.4% of our patients still retain an intact bladder. Results from the RTOG 8903 trial, which indicated a two-year bladder-free survival rate of 64.2%, are consistent with these findings **[26]**. Choudhury et al. found that 89% of patients had intact bladders **[13]**. This may be because our study included patients with T4a which is more advanced than the prior trial, which only involved patients with T2-3 with less local recurrence.

No significant treatment interruptions occurred due to our treatment protocol's good tolerance. grade IV toxicity not documented. This is consistent with the toxicities noted in the RTOG study **[27]**. and a recent trial [25]**.**

Our study's median OS was 42 months, three years of progression-free survival, and overall survival was 66.6% and 75.4%, respectively. According to Choudhury et al., the three-year OS was 75%, and the DFS was 82 % **[13]**. The reported 5 years OS and DFS in the aforementioned trial by the Christie group were 61% and 69%, respectively **[23].**

According to the findings of a univariate study, an incomplete transurethral resection was a risk that portended a poor prognosis for overall survival.

Our trial uses 10% of the dose of gemcitabine utilized in neoadjuvant or metastatic treatment. Thus, gemcitabine's influence on response rate in our study may be attributable to its activity as a radiosensitizer, which may improve survival through local control rather than micrometastatic disease treatment.

Even though our results could be a good option for older people, they should be taken with caution because there were so few participants. Also, we only reported the 3-year DFS. The 5-year DFS, with more patients and a longer follow-up time, will be more informative.

Limitations of the study: The sample size was limited and all patients had the same treatment with no comparison groups. Also short period of follow-up. So extended research with a larger sample size is needed and a longer follow-up time is advised.

Conclusions:

A practical and successful treatment approach for muscle-invasive BC was found to be multimodal therapy. For patients with muscle-invasive BC who cannot have surgery due to medical reasons or being old or frail, gemcitabine-based chemoradiation is an active therapy option with a low hazard profile.

Conflict of interest : none

Financial disclosure : none

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To Cite :

Elfarargy, O., Salem, R., Obaya, A., Kamel, M., Ali, M., Atef, N., ELSAYED, D. Management of Muscle Invasive Bladder Cancer with Weekly Gemcitabine Concurrent with Radiotherapy Post-Transurethral Tumor Resection in Old Fragile Patients: our Institute Experience. ***Zagazig University Medical Journal,*** **2024; (120-130): -. doi: 10.21608/zumj.2022.172940.2678**