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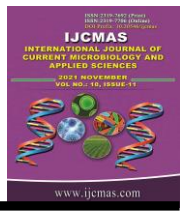

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Bladder Sparing Treatment versus Radical Cystectomy in Muscle Invasive Bladder Cancer: A Randomized Controlled Trial

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A B S T R A C T

Bladder sparing treatment is an alternative to radical cystectomy (RC) in non-metastatic muscle invasive bladder cancer (MIBC), especially in patients willing to preserve their bladder or unfit for cystectomy. No randomized controlled trials (RCT) compared between both treatment options. This study aim to perform a randomized, controlled trial comparing between bladder sparing treatment (BST) and RC in management of non-metastatic MIBC. The present study was a RCT including patients with MIBC (T2,3/N0,1/M0) presented to Clinical Oncology & Nuclear Medicine and Urology Center during the period from April 2018 to June 2020. Patients were randomized into 2 groups: group (A) included 25 patients who underwent maximal transurethral resection of bladder tumor followed by concurrent chemoradiotherapy, while group (B) included 24 patients who received 3 cycles of chemotherapy followed by RC. In group (A): 68% had complete response, 4% had progression of the disease, 8% had partial response and 20% had stable disease. While in group (B): 20.9% achieved pCR, 33.3% achieved pPR, 33.3% had pSD, and 12.5 % developed PD. Mean PFS and OS were (28.9and 29.2 month) and (30.4 and 29.2 months) in group A & B respectively. PFS and OS were higher in BST group but without statistically significant difference (P= 0.71& 0.96 respectively). Both treatment options were well tolerable without major toxicities. BST is an emerging procedure with tolerable toxicities and similar oncologic outcomes to RC for patients with MIBC.RCTs & long-term follow up are warranted to define best candidates, regimen for BST and RC.

Introduction

Bladder cancer (BC) is the 11th most common cancer worldwide (1). Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) is the standard treatment for localized MIBC (2). Based on data from multicentric randomized controlled trials

(RCTs); the role of neoadjuvant chemotherapy (NAC) before cystectomy is supported for T2, 3& 4a with negative lymph node (LN) involvement (3). BC survivors following RC have a significant impact on their quality of life with an Ileal conduit leading to an altered body image and genitourinary or sexual dysfunction (4). Bladder sparing treatment strategy (BST) has been commonly used with curative intent for patients medically unfit for surgery. Due to the better quality of life and the preservation of the patient's own bladder, BST strategy is becoming an attractive alternative to cystectomy for fit patients aimed at bladder preservation (5). NCCN guidelines recommended two main treatment options for T2-4a/N0,1 MIBC either BST or RC (6).There are no completed randomized controlled trials (RCT) comparing the outcome of BST with RC (7). A review and meta-analysis compared between RC and BST and reported no differences in OS, PFS, DSS and treatment-related toxicities between both arms and recommended further RCTs to identify the optimal treatment for specific patients (8).

So, in the present study aim to perform a randomized, controlled trial comparing between BST and RC in management of non-metastatic MIBC.

Patients and Methods

In the present study is a prospective randomized, controlled trial that included patients with non-metastatic MIBC who were treated in Department of Clinical Oncology & Nuclear Medicine and Urology& Nephrology Center at Mansoura University Hospitals, Egypt from April 2018 to June 2020 inclusive. Patients included in this study fulfilled inclusion and exclusion criteria and were randomized into two groups.

Inclusion criteria were: the age 18-75years, pathologically proven TCC of the bladder, clinical tumor stage (T2, 3/ N0, 1/ M0), performance status ≤ 1 as determined by Eastern Cooperative Oncology Group (ECOG) performance status, adequate bone marrow, renal &hepatic function. Patients were fit for both treatment modalities (BST&RC). Exclusion criteria were: patients with active concurrent or previous malignancies, T4 or metastatic disease, neuropathy ≥ grade 2, poor performance status and poor renal functions, diffuse carcinoma in situ, simultaneous upper tract, urethral or prostatic urethral TCC and untreated hydronephrosis.

Patients meeting the inclusion criteria were subjected to base line evaluation by complete history & physical examination then CBC, LFT and KFT were done. Abdomino-pelvic MRI or CT with contrast, CXR or CT chest if there is suspicious CXR and bone scan were done. Cystoscopic TUR biopsy and pathological examination were done from suspicious lesions including the muscle layer.

Randomization into 2 groups was performed using computer generated random tables using stratified blocked randomization in 1:1 ratio**.**

Treatment of group (A) was by BST; it commenced by maximal TURBT of the tumor mass. After that, the patients were treated with 3D conformal radiotherapy (3D CRT) with concurrent platinum based chemotherapy. Radiotherapy was applied in to 2 phases: Phase I was received by whole pelvic field 45Gy /5 weeks/25 fractions and phase II was localized bladder field. Total dose was 60-66Gy/6-6.5 weeks/30-33 fractions.

Planning was done by CT planning with contrast with slices each 3-5 mm using 3D Precise Treatment Planning System version 2.12. Three dimensional CRT was delivered by high energy linear accelerator (Elekta, Precise Treatment System), Version 5, with 6 or 15MEV photon energy. Two cycles of paclitaxel- cisplatin (paclitaxel 50 mg/m^2, day 1, 8, 15& cisplatin15mg/m^{2}day1-3,8-10,15-

17) or weekly cisplatin 40mg/m^2 were given concurrently during radiotherapy.

Treatment of group (B) was by NAC followed by RC after 3-4 weeks. The three cycles were gemcitabine-cisplatin or gemcitabine-carboplatin. Gemcitabine 1000mg/m^2 day 1, 8IV over 30-60 minutes with (cisplatin 70mg/m2 day1 or carboplatin (AUC=2) d1, 8 every 3 weeks). RC included the urinary bladder, proximal urethra, perivesical fat, covering peritoneum, pelvic LN, lower part of the ureters, and the true and false ligaments of the bladder. In males: pelvic part of the vas deference, prostate and seminal vesicles were included in the removed specimen.

In females: the uterus, upper third of the vagina, fallopian tubes and one or both ovaries were included in the removed specimen. The lymphadenectomy field is extended from the distal half of the common iliac artery, laterally to the genitofemoral nerve, distally to the inguinal ligament and posteriorly to the obturator fossa and pararectal LN. The lymph node and the cystectomy specimen will be removed in toto or on a LN template.

Group (A) patients were evaluated regarding toxicities and response on a weekly basis during concurrent CRT then 2-3 months after end of radiotherapy. While group (B) patients were evaluated during the course of NAC then one month after RC. Patients were followed up for 2 years after the end of treatment every 2-3 months. Cystoscopy was done in group (A) according to clinical and/or radiological findings.

The primary end points were treatment related toxicities and response rate (RR). Toxicities were reported according to the Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. RR was assessed as per new response evaluation criteria in solid tumors (RECIST 1.1) **(9)**.The secondary end points included PFS and OS.

Statistical analysis

The collected data were coded, processed, summarized, tabulated and analyzed. IBM SPSS software package version 20 (Statistical Package for Social Sciences, for Windows was applied for statistical analysis& the appropriate statistical tests were used. Qualitative data were presented as numbers and percent; comparison between both groups was done using Pearson Chi-square or Fisher's exact test when appropriate. Quantitative data was presented as mean and standard deviation (comparison between both groups was done using Student T test) after testing normality. In non-parametric data presentation was done with median and rang.

Survival data (Overall and progression free survivals) was analyzed using Kaplan Meier survival curves and comparison between both groups done by log rank test. Cox regression was used to perform univariate analysis. The level of significance was considered at 5% (i.e. $P \leq 0.05$).

Results and Discussion

Fifty-eight patients were randomized in to 2 groups. Group (A):28 patients were randomized to be enrolled in BST group; however, 3 patients had been excluded (2 patients had lost follow up after planning, one patient died from cerebral stroke before starting the treatment protocol), so 25 patients were included in this group. Group (B);30 patients were randomized to be enrolled in RC group; however, 6 patients had been excluded (3 patients refused surgery after randomization; the other 3 patients developed persistent thrombocytopenia after NAC so they received radical radiotherapy only), so24 patients were included in this group.

Characteristics of the patients and tumors are summarized in the table 1 (Table.1). Almost, the base line characteristics of the patients were well balanced between the two treatment groups.

The primary end points of the present study are RR and treatment related toxicities. *Regarding response rate;* in group (A):17patients (68%) had complete response (CR), one patient (4%) had progression of the disease (PD) and then started 2nd line chemotherapy. Two patients (8%) had partial response (PR) and five patients (20%) had stable disease (SD), of those seven patients; 3 patients refused salvage cystectomy, 1 patient lost follow up and 3 patients were unfit for cystectomy and so they received chemotherapy. While in group (B): Out of 24 patients assessed radiologically after completion of NAC course; 12 patients achieved CR (50%), 3 patients achieved PR (12.5%), 7 patients had SD (29.2%) and 2 patients developed PD (8.3%). However, pathological assessment done after surgery showed different results (20.9% CR, 33.3% PR, 33.3% SD, and 12.5 %PD).

Regarding Treatment related toxicities of BST and NAC, cystitis was the most frequent toxicity in group (A) with high statistically significant difference between both groups (p value= <0.001) followed by diarrhea (p value =0.002). The renal toxicity mandated discontinuation of the planned chemotherapy regimen in 3 patients in the BST group and shift to gemcitabine-carboplatin regimen instead of gemcitabine-cisplatin in 2 patients in the NAC group. Hepatic toxicity mandated discontinuation of chemotherapy in one patient after deterioration of liver functions. Regarding the hematological toxicities, there was no statistically significant difference between both groups (P value=0.608). The detailed toxicities were mentioned in (Table.2).

Regarding Treatment related toxicities of surgery; pouch-colonic fistula was reported in one patient, another patient had respiratory complications and was admitted in the ICU for this reason. Two patients suffered from paralytic ileus, another two developed leakages from anastomotic site and were managed by exploration and PCN insertion. Wound infection was reported in one patient and was managed by sutures under general anesthesia.

The follow up period ranged from 5-36 month with a median of 22 months. PFS was higher in the group (A) than group (B) but without statistically significant difference (p value=0.714). The mean PFS was 28.91 months (95% CI, 24.63-33.19) in the BST group compared to 29. 21 months (95% CI, 24.99-33.43) in the RC group. The one and two-year PFS were (88 %, 86% and 74%, 77%) for BST and RC group respectively (Figure.1).

OS was higher in the BST group than RC group but without statistically significant difference (p value=0.960).The mean OS of 25 patients in BST group was 30.43months (95%CI, 26.52-34.34), the one-year OS was 88%, while two- years OS was 80%. However in the RC group, the mean OS was 29.21months (95%CI, 25.06-33.37), the one-year OS was 91%, while two- years OS was 76 % (Figure.2).

On analyzing the prognostic factors affecting the PFS, it was found that symptoms of presentation, DM and chemotherapy type used were significant predictors for survival (P=0.037, 0.022, 0.081 respectively). While, the univariate analysis affecting the OS was found that chemotherapy type used was significant predictor for survival (P=0.019) as shown in (Table.3). In multivariate analysis for factors affecting PFS, DM and T stage at presentation were statistically significant

affecting PFS (P= 0.033, 0.017 respectively). In multivariate analysis for factors affecting OS, chemotherapy type was the only statistically significant factor affecting OS (P= 0.023) as shown in (Table.3).

Eight patients in the BST group and four patients in the RC group had progression (p value= 0.212). Four patients in each group developed local tumor progression (total 8 patients). One patient in the BST group showed regional LN failure. Six patients developed distant metastasis (4 patients in BST group, 2 patients in RC group). The most common site of distant metastases was bone metastases then brain and lung metastasis which was reported in 1 patient for each in the BST group. Regarding number of deaths, 7 patients died in the BST group compared to 4 in the RC group (p value= 0.342). In the BST group; 4 patients died due to progression of the disease, 2 patients died from complications of treatment and one patient died from unrelated cause while in the RC group the deaths were from the disease progression or post-surgical complication (total 4 patients) as shown in (Table.4).

Here, we present one case of this study from group (A) who received BST. Male patient aged 65 yrs old, bladder cancer (T2N0), underwent TURBT then received RT concurrent with paclitaxel-cisplatin. Radiotherapy was given in 2 phases: phase I (whole pelvis), phase II (localized bladder). MRI before starting treatment and the assessment with MRI after 3 month showed disappearance of the bladder mass were shown in (Figure.3: A&B).

According to cancer registry report in Mansoura University Hospital, Egypt in 2015; BC constituted 5 % of all cancers with more frequency occurred in patients age 60-70years. BC was the most common cancer among males (9.7%) especially in patients aged more than 65 years constituting 22% of patients in this age group [10]. Standard management of MIBC involves RC with pelvic lymph node dissection but the associated morbidity and mortality remain significant concerns [11]. In patients who are medically unfit or refuse cystectomy; BST has emerged as alternative treatment option that can provide comparable oncologic outcomes while maintaining patients' QOL [12]. In this study; we compared between NAC followed by RC and BST in patients with MIBC. The primary endpoints were to evaluate treatment related toxicities and RR. While the secondary end points included evaluation of PFS& OS.

Stenzl et al. at 2011 reported that failure after RC is relatively common, distant metastasis is more common than loco-regional recurrence (20%-50% versus 5%-15%). So, there is emerging trend towards NAC in MIBC to improve treatment outcomes [13]. Currently, gemcitabine-cisplatin (GC) is the most widely used NAC regimen. A prospective Brazilian study included 22 patients with MIBC reported 26% pCR rate in patients received neoadjuvant GC [14]. Dash et al., compared GC to MVAC regimen, there was similar tumors down-staged, DFS and minimal or no residual in both groups [15].

In the present study, radiological assessment of the response was done for 24 patients in RC group; achieved CR, PR, SD and PD in (50%, 12.5%, 29.2% and 8.3% respectively). In the Present study result was better than data reported by Khaled et al. at 2008. Their patients received neoadjuvant GC, 9.4% of patients achieved CR [16]. Their study included patients with non-urothelial pathology (15 had squamous cell carcinoma, 2 had adenocarcinoma, and 3 had undifferentiated cell carcinoma) and this may be the cause that the CR is higher in the present study. Khateeb and his colleagues at 2017 also evaluated NAC. The study included

85 patients who were treated with NAC GC or gemcitabine-carboplatin. Patients older than 60years old, with T4 disease and active smoking history had lower overall RR than others [17]. In the present study results are also comparable to results of Herchenhorn et al., study that treated 22 patients with neoadjuvant GC. NAC resulted in high percentage of complete/partial radiological response (70%) [14].

In the present study; pathological assessment of response was done after surgery for patients in the RC group, they achieved pCR, pPR, pSD, and pPD in (20.9%, 33.3%, 33.3% and 12.5% respectively). A prospective trial was consistent with us where 83 patients received 3 cycles GC then underwent RC with pCR was achieved in 22.5% and near pCR was seen in 33.7% of the patients [18]. Because of small sample size, the present study results are different from some of data that was reported from other studies. In Petrelli et al. study, 886 patients were received NAC then RC. The pCR rate was 28.6% [19].Yin et al., study compared GC to MVAC in 1,067 patients, and the pCR of GC was 25.7% [20]. The pCR rate was higher in these trials due to large sample size.

In the present study patients did not receive adjuvant RT after RC as the role of adjuvant RT after RC is poorly defined [21]. Concerns for significant toxicity after PORT have been a major reason why adoption of this adjuvant therapy has been rather limited [22].

In 2018; Zaghloul's conducted a study at the NCI in Cairo comparing sequential PORT and chemotherapy versus adjuvant chemotherapy alone. There was significant benefit in local control, the 2-year local control was (96%) for sequential CRT group versus (69%) for chemotherapy group ($P < 0.01$) [23]. Significant toxicity after PORT has been a major reason for limited application of adjuvant RT. However, Zaghloul et al. used more modern 3D conformal RT and reported low rates of late GI toxicity (7% of patients had late grade 3 gastrointestinal tract) [23].

In the present study; we have 25 patients in BST group. The patients had CR, PR, SD and PD in 68%, 8%, 20% and 4% respectively. Mohamed and his colleagues at 2021 analyzed retrospectively the data of 166 patients treated at south Egypt Cancer Institute (SECI) in 10 years, 81 patients treated with BST with chemosensitizer while 85 patients had RC ± adjuvant therapy. The majority of patients who had BST achieved CR, PR and PD in 81.5%, 13% and 5% respectively [24]. This result was better than ours may be due to large sample size and relatively younger patients. Fabiano et al. also retrospectively analyzed the data of 313 patients after induction CRT. The pathologic response rate was 83% which was also better than ours, may be due to large sample size and inclusion of patients with lower T stage [25]. The present study results are consistent with the majority of studies described response rate after BST as Mak et al at 2014 and Giacalone et al at 2017 they achieved cCR (70-80% and 88% respectively) [26, 27].

In the present study; the GC regimen was well tolerated by patients with grade III toxicity in only 3 patients (11.1%), no grade IV toxicity or chemotherapy related deaths. Persistent elevation of s.creatinine reported in 2 patients after 1 cycle of GC and so they were shifted to gemcitabine-carboplatin regimen. Contrarily; Khateeb et al. used the same chemotherapy regimens in his study but reported grade IV nephrotoxicity in one patient which was corrected with hemodialysis and supportive measures [17]. Also, Kaneko et al. reported grade III-IV neutropenia in 14.3% of patients, anemia in 2.4% and thrombocytopenia in 21.4% of patients, which is higher than we encountered in the present study [28].

Table.1 Patient and tumor characteristics in both groups

	BST (n=25)	RC (n=24)	p-value
	N (%)	*N (%)*	
Age /years *Mean (SD)*	65.48(9.59)	62.00(6.44)	0.144
Sex **Male** **Female**	19(76%) 6(24%)	22(91.7%) 2(8.3%)	0.138
Smoking history **No** **Yes**	12(48%) 13(52%)	9(37.5%) 15(62.5%)	0.458
Co-morbidities **DM** **HTN**	3(12%) 3(12%)	6(25%) 2(8.3%)	0.237 0.671
Tumor stage **T2** **T3**	7(28%) 18(72%)	7(29.2%) 17(70.8%)	0.928
LN **N0** **N1**	21(84%) 4(16%)	16(66.7%) 8(33.3%)	0.158
Pathological grade **G1** **G2** **G3**	1(4%) 1(4%) 23(92%)	0(0%) 0(0%) 24(100%)	0.185

Table.2 Treatment toxicities in both groups

Toxicities	BST group)			RC groupn=27)			P value
	G1 N(%)	G2 N(%)	G3 N(%)	G1 N(%)	G2 N(%)	G3 N(%)	
Cystitis	**5(20%)**	**10(40%)**	**9(36%)**	**3(11.1%)**	**0(0%)**	**0(0%)**	**<0.001****
Vomiting	**8(32%)**	**0(0%)**	**0(0%)**	**8(29.6%)**	**1(3.7%)**	**1(3.7%)**	**0.359**
Diarrhea/ abdominal pain	**3(12%)**	**3(12%)**	**3(12%)**	**0(0%)**	**0(0%)**	**0(0%)**	**0.002***
Proctatitis	**2(8%)**	**1(4%)**	**0(0%)**	**0(0%)**	**0(0%)**	**0(0%)**	**0.113**
Renal toxicity	**7(28%)**	**4(16%)**	**0(0%)**	**4(14.8%)**	**2(7.4%)**	**0(0%)**	**0.117**
Hepatic toxicity	**1(4%)**	**1(4%)**	**0(0%)**	**0(0%)**	**0(0%)**	**0(0%)**	**0.160**
Hematological toxicity(all)	**2(8%)**	**4(16%)**	**1(4%)**	**5(18.5%)**	**4(14.8%)**	**2(7.4%)**	**0.608**
Anemia	**0**	**1**	**0**	**2**	**0**	**0**	
Thrombocytopenia	**1**	**2**	**0**	**3**	**2**	**1**	
Neutropenia	**1**	**0**	**0**	**0**	**1**	**1**	
Pancytopenia	**0**	**1**	**1**	**0**	**1**	**0**	

* Significant difference ($p \leq 0.05$) **Highly Significant< 0.001

Table.3 Univariate and multivariate analysis for factors affecting progression free survival and overall survival time among studied cases

	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
Factor	95% CI for Exp(B)	P value	95% CI for Exp(B)	P value	95% CI for Exp(B)	P value	95% CI for Exp(B)	P value
Age	0.949- 1.087	0.656	0.890-1.075	0.643	0.942-1.091	0.714	0.891-1.094	0.807
Sex	0.369- 5.636	0.599	0.068-13.294	0.970	0.217-5.261	0.936	0.040-5.265	0.531
Smoking	0.261- 2.622	0.748	0.115-13.219	0.862	0.268-3.033	0.866	0.153-4.494	0.840
UTI	0.252-16.871	0.500	0.170-177.181	0.337	0.276-19.369	0.439	0.156-75.643	0.434
DM	1.226.12.995	**0.022***	1.324-888.713	**0.033***	0.219-5.091	0.945	0.050-4.955	0.552
HTN	0.766-10.648	0.118	0.015-8.527	0.523	0.421-9.107	0.392	0.000-14.942	0.968
Grades	0.213-5.167	0.954	0.028-2.997	0.298	0.001-67383.8	0.616	0.00-0	0.988
T stage	0.028-1.671	0.142	0.000-0.459	**0.017***	0.376-4.461	0.681	0.457-9.619	0.340
N stage	0.177-4.058	0.835	0.006-2.220	0.152	0.191-4.571	0.933	0.103-4.672	0.760
Chemotherapy	0.152-0.835	**0.018***	0.098-1.056	0.061	0.119-0.823	**0.019***	0.066-0.814	**0.023***

CI: confidence interval, UTI: urinary tract infection, *Significant difference ($p \leq 0.05$)

Fig.1 Kaplan Meier curve showing progression free survival for both groups

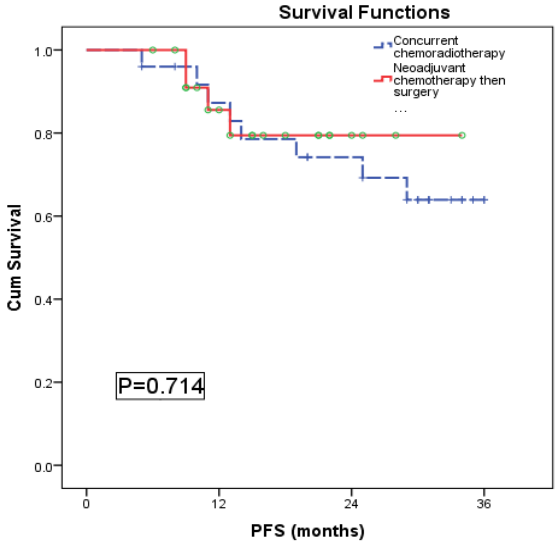


Table.4 Progression, mode of progression, and deaths

	BST(n=25)	RC(n=24)	Odd Ratio (95% CI)	P value
	N(%)			
Progression **No** **Yes**	17(68%) 8(32%)	20(83.3%) 4(16.7%)	0.425(0.11-1.66)	0.212
Mode of progression				
Local recurrence	4	4		
LN recurrence	1	0		
Distant metastasis	4	2		
Bone metastasis	2	2		
Brain metastasis	1	0		
Lung metastasis	1	0		
Deaths				
NO	18(72%)	20(83.3%)		0.342
Yes	7(28%)	4(16.7%)	0.514(0.13-2.05)	
Due to disease	4	2		
Complication of treatment	2	2		
Unrelated cause	1	0		

CI: Confidence Interval; The patients may develop more than one site of progression.

Fig.2 Kaplan Meier curve showing overall survival of both groups

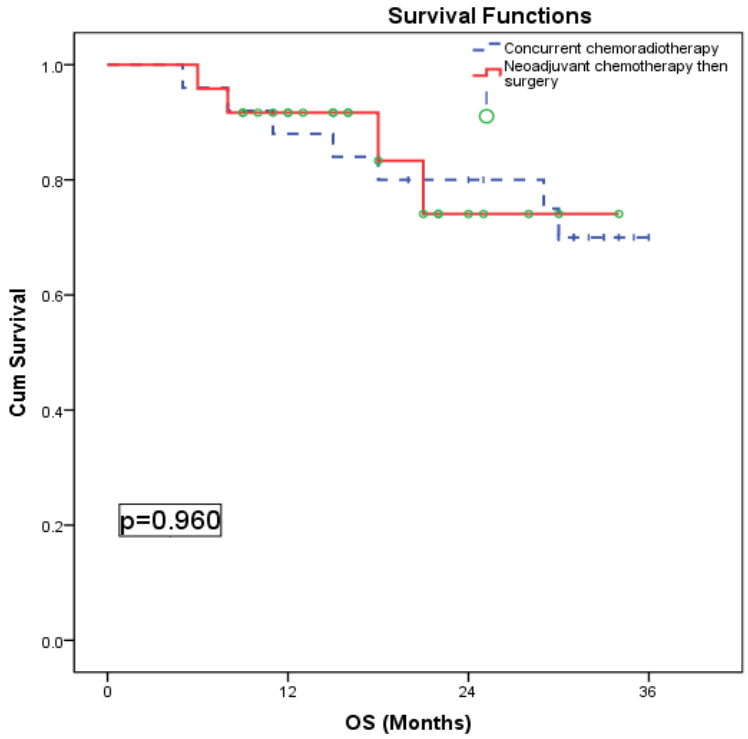
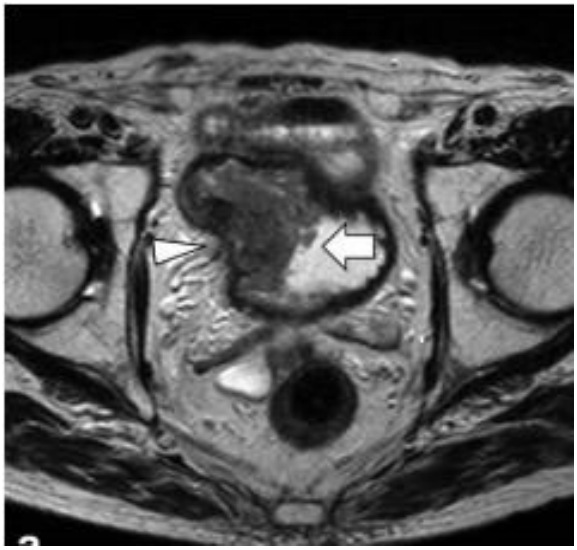
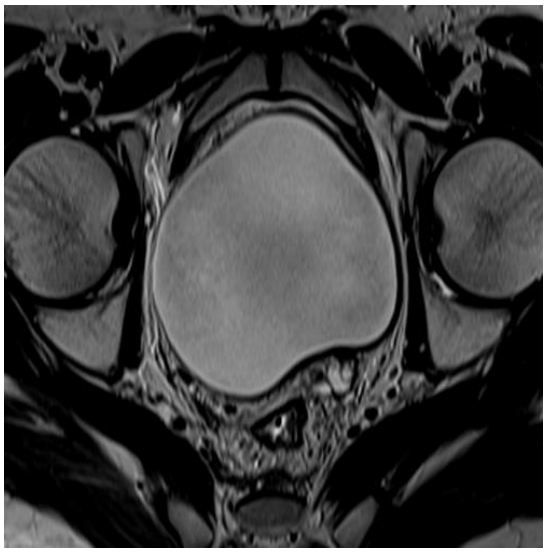


Fig.3(A) MRI before treatment showed bladder mass infiltrating the muscles with no infiltration of perivesical fat (T2 N0)
Fig.3(B) MRI after treatment showed disappearance of the bladder mass

A **B**





In the present study patients tolerated NAC better than patients in Herchenhorn's study where a similar NAC regimen was used with reported incidence of 33% grade III and 4% grade IV [14].

In the present study BST group toxicity results were more or less equivalent to Rashed et al., study. In this study patients were randomized into two groups, (group I) received BST with concomitant cisplatin - paclitaxel, while (group II) received cisplatin - 5. FU with RT, all patients who showed CR after induction and consolidation phases were given adjuvant chemotherapy 4 cycles every 3 weeks. Side effects were tolerable and manageable; cystitis and diarrhea also were the most non-hematologic toxicities [29].

We did not compare between patients received CRT versus RT alone as regard treatment related toxicity due to very small sample size (19 & 6 patients respectively). Hall et al. reported higher grade 3 and 4 toxic effects in CRT vs. RT group (36% vs. 27.5%, P=0.07). These events were gastrointestinal toxic effects, with 17 events (9.6%) in the CRT group versus 5 events (2.7%) in the RT group (P=0.007) [30]. Contrarily, Majewski et al. reported higher toxicity with RT alone than with CCRT or NAC and radiation (neoCRT). The incidence of acute grade 3 or more genitourinary toxicity was (25%, 11% and 19%) in the RT, CCRT and neoCRT groups respectively (p=0.029) [31].

In the present study; the median follow-up period was 22 months (range 5-36 months). For RC group; the mean PFS was 29.21 months (95% CI. 24.99-33.43). The one and two –year PFS were (74%, 77%). The mean OS was 29.21 months. (95% CI, 25.06-33.37), the one-year OS was 91%, while two- years OS was 76%. However; for BST group; the mean PFS was 28.91 months, the mean OS of was 30.43 months, the one and two –year PFS was (88 %, 86%) and the one-year OS was 88%, while two- years OS was 80%.

In the present study results were better than data of Rashed's study. In which, 1-year and 2-years PFS were (78.26% and 78.26%) for group I and (73.68% and 68.42%) for group II. However, 1-year and 2-years OS were (69.57 % and 65.22%) for group I and (78.95% and 68.42%) for group II [29]. The age ranged from 48-78 years, most of patients aged ≥ 60 years and this may be the cause of lower PFS and OS in Rashed's study. Also, Polineni et al. included 32 patients who received cisplatin concurrently with RT. The mean follow up was 36 month (range 6-213). Overall survival and DFS were (84%, 61%& 84% and 61%) at 1 year and 5 year respectively [32]. In the present study results are better than Polineni attributed to inclusion of patients with associated CIS (31%), hydronephrosis (25%) and lack of visibly complete TURBT.

In the present study; there was no statistically insignificant difference in OS and PFS between both groups (P=0.714 for PFS, 0.960 for OS). In agreement with this study; an Egyptian study retrospectively compared between RC without NAC and BST with concurrent platinum based chemotherapy, this study reported no statistically significant differences between both groups. For patients treated by RC and BST, the 5-year OS was 39.6% and 58.9 (p = 0.273), and the 5-year DFS was 86.8% and 91.6% % (p =0.6) [33]. Vice versa; Nagao et al., retrospectively reported significant survival advantage conferred by BST over RC, this study compared between patients with MIBC treated with RC (n=205) and patients treated by TURBT followed by BST with cisplatin (n=50). The 2 year OS rates after BST and RC were 90.5% and 71.8% respectively .The 2 year and 5 year PFS for BST were 70.8% and 63.9% respectively [34]. This result was higher than this results may be due to larger sample size and longer follow up period in Nagao's study.

There are no RCTs comparing patients treated with BST with those underwent RC. The best data comparing both treatment modalities come from retrospective studies, a systematic review and meta-analyses [35]. In the present study results are consistent with data reported from multiple trials. A recent retrospective study by Kulkarni et al. at 2017 at the Princess Margaret Hospital reported that no significant difference in OS (64.3 versus 70.7%, P=0.84) or DFS (73.2 versus 76.6%, P=0.49) [36]. Vashistha et al. at 2017 performed a meta-analysis of 19 retrospective studies comparing RC and TMT. There was no difference in OS or PFS at 5 or 10 years [8]. Fahmy et al. at 2018 performed a meta-analysis of 57 studies. The mean 10-year OS was (30.9% and 35.1%) for TMT and RC respectively (P = 0.32). The mean 10-year DSS was (50.9% and 57.8%) for TMT and RC respectively (P = 0.26) [37].

The association between DM and survival was reported in multiple trials. Hong et al., showed a statistically positive association between presence of DM and poorer OS (p = 0.03) and cancer-specific survival (CSS) (p = 0.01) [38]. Oh et al. also observed that after RC, bladder cancer patients with DM displayed worse CSS and OS than non-DM patients [11]. Contrarily, Goossens conducted a retrospective cohort study using data from the UK Clinical Practice Research Data link (CPRD) and showed that neither the risk, nor the mortality from BC was increased in patients with DM [12].

Impact of tumor stage on survival was reported in multiple trials. In consistent with this results; Stein et al., reported that increasing pathologic stage and lymph node–positive disease were associated with significantly higher recurrence rates and worse OS (P < 0.001) [39]. Dalbagni et al. followed up 300 patients after RC for about 65 months. A significant difference was seen in the OS and DSS between patients with organ confined (≤T2) and non-organ confined tumors [40].

In the present study, during the follow up period, eight patients (32%) in the BST group and four patients (16.7%) in the RC group had progression with no statistically significant difference (p value=0.212). Four patients in each group developed local tumor progression (total 8 patients). The present study results are different from Huddart *et al.*, study. Local recurrence rate was higher than ours; (68.9% and 15.3% for BST and RC respectively) (41). Many patients received no radiosensitizers thus might be the cause of high failure rate. The present study results also better than Hong *et al.*, study that retrospectively compared between patients underwent RC and BST. A 5-year local recurrence rate was (41% vs. 30%, p = 0.35) (35). That high local recurrence rate might be attributed that only 28% of the patients received RT alone, only 24% received NAC and presence of hydronephrosis that significantly associated with tumor recurrence (p = 0.04).

Due to small patient number; results of the present study were different from multiple trials evaluated concurrent CRT versus pelvic RT alone. Concurrent chemotherapy with radiation was also supported over RT alone by Radiation Therapy Oncology Group (RTOG). Analysis of six RTOG studies reported a survival benefit at 5 and 10 years (26). RTOG 0712 study also evaluated CCRT versus RT alone, 66 patients were treated with either low-dose gemcitabine with daily RT or cisplatin plus 5-F U with twice-daily RT. The 3-year distant metastasis-free survival rate was 84% and 77.8%, respectively (42).

In Conclusion, BST is an emerging procedure with tolerable toxicities and similar oncologic outcomes to cystectomy for patients with MIBC. In selected patients, TMT should be considered as an alternative option to RC and in patients who are not candidate or refusing cystectomy.

Platinum based NAC should be the mainstay of treatment before RC. Gemcitabine-cisplatin is well tolerated regimen with promising outcomes.

There were many limitations for the trial, being small number of patients with short follow up period.

Multicentric larger randomized controlled trials with long-term follow up are warranted to define best candidates, regimen for TMT and RC.

Ethical considerations

Study protocol was submitted for approval by the Institutional Research Board (IRB), Faculty of Medicine at Mansoura University. Informed written consent was obtained from each participant patient after assuring confidentiality.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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