

Trimodality Bladder Preservation Therapy for Muscle-Invasive Bladder Cancer: Mansoura Experience

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Abstract: Background & objective: Bladder preservation therapy (BPT) using a trimodality approach represents an alternative option to cystectomy in muscle-invasive bladder cancer (MIBC) patients, also a treatment option in non-cystectomy candidates. The objective of this study was to evaluate BPT using a trimodality approach composed of maximum TURBT, neoadjuvant chemotherapy, followed by chemoradiotherapy, regarding the overall survival (OS), progression free survival (PFS), locoregional progression free survival (LPFS) and treatment toxicity. Patients & methods: This prospective study involved 47 patients with pathologically proven MIBC (T2-T4a N0M0). The study involved muscle invasive bladder cancer patients who refused or were not cystectomy candidates. Patients enrolled received neoadjuvant 3 cycles of Gemcitabine/Cisplatin, each cycle was every 21 days. Gemcitabine at 1000mg/m² on days 1&8 and cisplatin at 70mg/m² on day1, followed by Concurrent chemoradiotherapy with cisplatin weekly (40mg/m²). Radiation therapy included the whole bladder by 3D conformal planning to a dose of 64Gy/32Fxs. Results: Of the 47 patients, 25 (53.2%) patients expressed complete response (CR), while 22(46.8%) patients had incomplete response. The 4-year OS, PFS, and LPFS rates were 48%, 38%, and 42%, respectively. Acute genitourinary (GU) toxicity of Grade 1 and 2 occurs in 54% and 24% of patients, respectively, while acute gastrointestinal (GI) toxicity (colic & diarrhea) of Grade 1 and 2 occurs in 27.7% and 10.6 % of patients, respectively. Conclusion: For MIBC patients who are non-cystectomy candidates, or who are motivated to maintain their bladders, trimodality bladder preservation therapy (BPT) can be considered as an effective alternative to radical cystectomy.

Keywords: Bladder Cancer, Neoadjuvant Chemotherapy, Concurrent Chemoradiotherapy, Trimodality Treatment, Bladder Preservation

1. Introduction

Bladder cancer is the commonest malignancy of the urinary system, with 79,000 new cases and 17,000 deaths in the United States annually. Worldwide, bladder cancer accounts for approximately 540,000 new cases and 188,000 deaths [1]. In Egypt, it constitutes 6.94 % in both sexes in the period between 2008-2011 [2].

Nearly 75 percent of new bladder cancer diagnoses are early-stage and have not yet invaded the muscular layer of the bladder wall with the remaining 25 percent have muscle-invasive bladder cancer (MIBC) [3].

The gold standard for MIBC was radical cystectomy (RC)

with pelvic node dissection [4]. Radical cystectomy has an impact on patients' quality of life (QOL) with genitourinary or sexual dysfunction [5]. Outcomes of bladder function and QOL in patients who received bladder preserving treatment showed 75% of patients maintaining their native bladder function and 59% with satisfactory sexual life [4].

Modern oncologic therapies are increasingly driven towards organ preservation and maximizing functional outcomes while maintaining treatment efficacy. Although not the standard of care, BPT continued to evolve for patients refusing or considered as non cystectomy candidates [6].

BPT with trimodal approach is an alternative to RC for MIBC selected patients, and who are not considered as cystectomy candidates. It includes a maximum transurethral resection of the

bladder tumor (TURBT), followed by concurrent chemoradiotherapy, which offers patients a chance to maintain their bladders, and reduce the potential morbidity & mortality associated with RC [7].

The English National Comprehensive Cancer Network Guidelines include BPT with chemoradiotherapy after maximum TURBT as an alternative treatment to RC in MIBC [8]. The European Association of Urology Guidelines states that multimodal PBT can be an alternative option in selected, non cystectomy candidates [9].

No large randomized trials compared bladder preserving treatment & radical cystectomy in MIBC. However, available trials recorded comparable results between BPT and RC [10, 11].

A systematic review and meta-analysis of available trials assessing bladder preserving therapy using TURBT followed by chemoradiotherapy in MIBC patients, detected complete response in 78% of patients, with 5-year OS of 56% [12].

A case controlled study showed comparable results between RC and chemoradiotherapy in MIBC. Thirty three patients treated with chemoradiotherapy due to poor performance status for surgery were matched with patients treated with RC of similar age. The 5 year DFS & OS for RC and chemoradiotherapy were 63.2% vs 54% and 54.8% vs 56.6%, respectively [13].

Long term results of trimodality therapy (TMT) are very good and comparable to RC, with improving complete response rates with time (86% in 2010-2013). This has been shown by both the Princess Margaret hospital experience and the Massachusetts general hospital experience. There is similar disease specific survival (DSS) in both TMT and RC ranging from 66% in 5 years to 59% in 10 years. Overall survival (OS) is also similar with 57% 5 year and 39% 10 year [14, 15].

The objective of this study was to evaluate BPT using a trimodality approach composed of maximum TURBT, neoadjuvant chemotherapy, followed by chemoradiotherapy, regarding the overall survival (OS), progression free survival (PFS), locoregional progression free survival (LPFS) and treatment toxicity.

2. Patients & Methods

2.1. Study Design

After acceptance of the Mansoura Faculty of Medicine, institutional research board MFM IRB, this prospective trial was performed at the Clinical Oncology & Nuclear Medicine Department, Mansoura University, from Feb 2013 to June 2017, 47 patients with pathologically proven muscle invasive urothelial bladder carcinoma (T2-T4a N0M0) were enrolled. The study involved patients who refused radical cystectomy or were medically unfit for surgery or presented with unresectable disease.

2.2. Patients Selection and Eligibility

Eligibility criteria were; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2, T2-T4a Bladder

TCC, no hydronephrosis, those had solitary tumor with limited CIS. White blood cell count $\geq 3500/\mu\text{L}$; platelet count $\geq 100,000/\mu\text{L}$; hemoglobin $\geq 10 \text{ g/dl}$; hepatic function (AST, ALT $< 2 \times$ upper normal limit (UNL), total bilirubin $\leq 1.5 \times$ UNL; and renal function (serum creatinine $\leq 1.5 \text{ mg/dl}$, and creatinine clearance of at least 60 ml/min). Patients with major comorbidities, like active infection, significant arrhythmia, or heart failure, were not eligible. All expected benefits and side effects of treatment were explained to all patients and they signed informed consents before enrollment.

All patients underwent cystoscopic examination, biopsy from bladder mass, CT and or MRI abdomen & pelvis and CT chest. Bone scan was done only if there were symptoms or elevation of alkaline phosphatase. All patients underwent maximal TURBT.

Patients enrolled received neoadjuvant 3 cycles of Gemcitabine/Cisplatin, each cycle was every 21 days. Gemcitabine at 1000 mg/m^2 on days 1 & 8 and cisplatin at 70 mg/m^2 on day 1, followed by Concurrent chemoradiotherapy with cisplatin weekly (40 mg/m^2). CT simulation in the supine position, using 5 mm slice thickness was performed prior to planning, with empty bladder. The CTV included the GTV (primary tumor and extravesical spread) and the whole bladder, PTV included the CTV plus 1.5-2 cm around the bladder. Delineation of target volume and organs at risk was done. All patients were planned by 3D-Conformal radiotherapy (3D-CRT) with ELEKTA Linear Accelerator, and precise treatment planning software. The photon energy used was 6 MV and 15 MV. Dose was 64 Gy/32 Fx, with standard fractionation (2 Gy/Fraction/day). Chemotherapy Toxicity was assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.

2.3. Treatment Evaluation & Follow Up

During treatment, weekly CBC, serum creatinine and clinical assessment for any side effects related to radiation or chemotherapy were performed, radiation reactions were reported and graded according to the Radiation Therapy Oncology Group (RTOG) toxicity criteria. After completion of chemoradiotherapy by 2 months, abdominopelvic MRI and cystoscopic examination were done for evaluation of treatment response. Patients were followed up by abdominopelvic MRI, cystoscopic examination and urine cytology every 3-6 months for 2 years, every 6 months for the subsequent 3 years and then annually. Bone scan and other radiologic investigations were done when clinically indicated. Salvage cystectomy was the treatment option for residual or recurrent disease.

2.4. Statistical Analysis

Data were entered and analyzed using SPSS software (version 21). Qualitative data were expressed as count and percent. Quantitative data were tested for normality using Kolmogorov-Smirnov and Shapiro-Wilk's test with data being normally distributed if $p > 0.050$. Quantitative data were expressed as mean \pm standard deviation (SD) if normally distributed or median if not. Progression free survival (PFS) and overall survival (OS) were analyzed by the Kaplan Meier curves and calculated from

the first day of treatment to tumor recurrence (PFS) or death or last visit (OS).

3. Results

A total of 47 patients with muscle-invasive bladder cancer were involved in this study. The patients and tumor characteristics are shown in Table 1.

There were 35 (74.5%) males and 12 (25.5%) females. The median age was 65 years (48–72). Most of patients were of ECOG performance status PS1 (44.7%), followed by PS 2 (31.9%). Tumor stage of T3b (21/44.7%) was the commonest followed by T4a (16/34%), also, grade III was the commonest grade (26/55.3%). All patients underwent maximum TURBT, 16 (34.04%) patients underwent complete TURBT, while 31 (65.96%) underwent incomplete TURBT.

The median follow-up period was 37 months (11–52). Of the 47 patients, 25 (53.2%) patients expressed complete response (CR), while 22 (46.8%) patients had incomplete response (PR). Patients with PR were referred to salvage cystectomy if they were operable & resectable.

Most of the patients have completed their radiotherapy course except 5 patients, who received 25–30 sessions.

The median number of chemotherapy cycles was 3 cycles.

The median duration of radiotherapy interruption was 4 days (3–8 days).

3.1. Toxicity

Acute toxicity was moderate with the hematological toxicity, was the main toxicity observed during induction chemotherapy, with Grade 2 and 3 toxicities were 42.6% and 17%, respectively (Table 2).

Chemoradiotherapy toxicity affected genitourinary (GU) and gastrointestinal (GI) systems, GU toxicity of Grade 1 and 2 occurs in 26 (55.3%) and 12 (25.5%) patients, respectively, while acute gastrointestinal (GI) toxicity (colic & diarrhea) of Grade 1 and 2 occurs in 27.7% and 10.6% of patients, respectively (Table 2).

Late toxicities were mostly of grade 1 & 2 with no grade 3 or 4 toxicity. Nine (19.2%) & 5 (10.6%) patients experienced Grade 1 & 2 chronic genitourinary toxicity, whereas grade 1 and 2 GI toxicity were detected in 5 (8.5%) and 2 (4.3%) patients, respectively.

3.2. Survival

The 4-year OS, PFS, and LPFS rates were 48%, 38%, and 42%, respectively (Figure 1, 2, 3).

On multivariate analysis, ECOG-PS was the independent prognostic factors for OS ($p = 0.03$), while tumor stage was the independent prognostic factors for PFS & LPFS ($p = 0.05$, $p = 0.02$).

Table 1. Patients characteristics.

Characteristics	No (%)
Age (years)	
Median	65
Range	(48 – 72)
Sex	
Male	35 (74.5%)
Female	12 (25.5%)
ECOG performance status	
0	11 (23.4%)
1	21 (44.7%)
2	15 (31.9%)
Tumor stage	
T2	10 (21.3%)
T3b	21 (44.7%)
T4a	16 (34%)
Tumor grade	
II	21 (44.7%)
III	26 (55.3%)
TURBT	
Complete	16 (34.04%)
incomplete	31 (65.96%)

Table 2. Treatment-related acute toxicity.

Toxicities	Neoadjuvant chemotherapy				Conc chemoradiotherapy			
	I	II	III	IV	I	II	III	IV
Hematologic anemia	16 (34.04%)	9 (19.2%)	5 (10.6%)	0	13 (27.7%)	6 (12.8%)	3 (6.4%)	0
leucopenia	13 (27.7%)	6 (12.8%)	3 (6.4%)	0	10 (21.3%)	5 (10.6%)	0	0
thrombocytopenia	12 (25.5%)	5 (10.6%)	0	0	8 (17.02%)	4 (8.5%)	0	0
Non-hematologic GU toxicity	0	0	0	0	26 (55.3%)	12 (25.5%)	0	0
GI toxicity Nausea, vomiting	20 (42.6%)	8 (17.02%)	0	0	9 (19.2%)	4 (8.5%)	0	0
Colic, diarrhea	7 (14.9%)	3 (6.4%)	0	0	13 (27.7%)	5 (10.6%)	0	0

GU: genitourinary, GI: gastrointestinal.

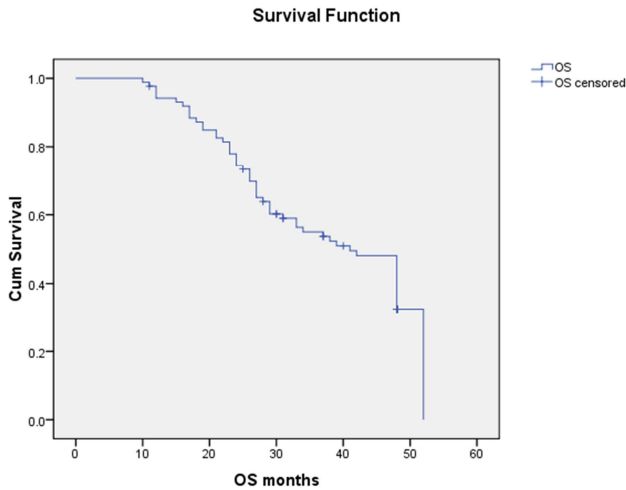


Figure 1. Overall survival curve.

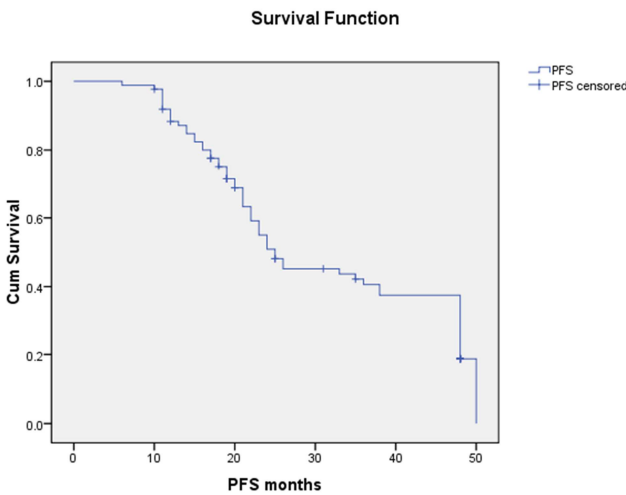


Figure 2. Progression free survival curve.

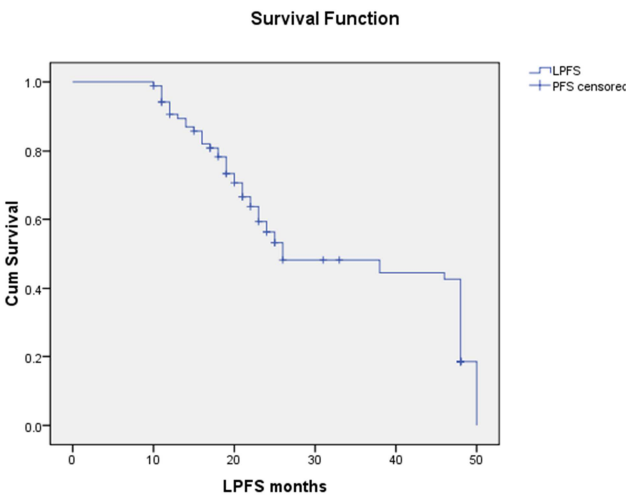


Figure 3. Local progression free survival curve.

4. Discussion

Platinum based neoadjuvant chemotherapy followed by radical cystectomy is the gold standard therapy for MIBC.

Patients with bladder cancer are older and are often frail, with comorbidities. As a greater percentage of the worldwide population ages, bladder cancer patients will continue to present at advanced age and may no longer be considered ideal candidates for RC, bladder preservation therapy represents a treatment option for non-cystectomy candidates patients [16].

In the current study, Of the 47 patients, 25 (53.2%) patients expressed complete response (CR), while 22(46.8%) patients had incomplete response. The 4-year OS, PFS, and LPFS rates were 48%, 38%, and 42%, respectively. Acute GU toxicity of Grade 1 & 2 occurred in 54% and 24% of patients, respectively, while acute GI toxicity (colic & diarrhea) of Grade 1 & 2 was detected in 27.7% and 10.6 % of patients, respectively.

In the BC2001 trial, they targeted by radiotherapy the bladder only. Pelvic lymph node relapse rate was 5% in the chemoradiotherapy group, which is comparable to a large RC series [17], local relapse in lymph node negative disease was 6% & 13% for localized and extravesical tumors, respectively. Unplanned involvement of pelvic lymph nodes in the planning target volume may give an explanation of the low incidence of lymph node recurrence. Also, concomitant chemotherapy may have a role in targeting nodal micrometastatic disease [18].

In a randomized study that compared pelvic lymph nodes irradiation (45Gy plus 20Gy bladder boost) to localized bladder irradiation (65Gy), the incidence of lymph node recurrence in patients who achieved complete response was comparable in both arms (15.8% versus 17.6%) [39]. Similarly, OS was 51% versus 52.9%. Higher incidence of pelvic lymph nodes recurrence in comparison to BC2001 is mostly because half of the patients were of stage T3 but in BC2001 trial, it was only 15% [19].

From this evidence, there is no strong support for pelvic nodal irradiation in clinically node negative disease, so in the current trial, we targeted only the bladder without pelvic lymph nodes involvement depending upon the use of neoadjuvant systemic chemotherapy and concurrent chemoradiotherapy.

In several prospective trials, trimodality therapy demonstrated 5-year OS rates of 48% - 65%, similar to that registered in RC trials, with approximately 75%- 80% of patients maintained their bladders, with good function and better quality of life [20].

A meta-analysis of clinical trials assessing trimodal therapy composed of TURBT followed by chemoradiotherapy in treatment of MIBC, recorded a complete response in 78% of patients, with 56% 5-year OS [12].

Analysis of Radiation Therapy Oncology Group protocols of bladder preserving therapy using TURBT and concurrent platinum-based chemoradiotherapy revealed a complete response in 69% of patients, with 5- & 10-year OS of 57% and 36%, respectively [11].

At the Massachusetts General Hospital between 1986 and

2013, 475 patients with cT2–T4a MIBC underwent TURBT followed by concurrent chemoradiotherapy. The 5 and 10-yr DSS were 66% and 59%, respectively, while the 5- and 10-yr OS were 57% and 39%, respectively. Salvage cystectomy rates were 29% at 5 year [15].

In multiple series, the 5 & 10-year OS for RC was 45%- 60% and 37% - 45%, respectively [2-7] while, the 5-year OS for BPT utilizing trimodal therapy was 36-74% [21-26].

Seventy patients with T2–N0M0 MIBC received trimodality BPT involving maximum TURBT, small pelvis radiotherapy by proton beam and intra-arterial chemotherapy. The 5-year OS, PFS were 82% and 77%, respectively. By uni & multivariate analysis, tumor multiplicity and tumor size larger than or equal to 5 cm were significant prognostic factors for progression. Regarding toxicity, 26 (18%) patients expressed G 3 & 4 acute hematologic toxicity and 2 (3%) patients had G 3 late GU toxicity [27].

Patients with MIBC T2-3, N0 M0 were randomly assigned to two arms: Arm 1: patients underwent RC alone; and Arm 2, patients underwent maximum TURBT, followed by concomitant chemoradiotherapy. Complete response was found in 62 patients (83.8%) and residual disease was found in 12 patients (16.2%). The 3-year OS for the trimodality group and the RC group were 61 & 63%, respectively ($p = 0.425$), while the DSS were 69 & 73%, respectively ($p = 0.714$). The 3-year OS with intact bladder was 50% [28].

A total of 112 patients (56 received TMT while 56 underwent RC), TMT had survival outcomes similar to RC. The 5-year disease specific survival was 73.2% & 76.6% in the RC and TMT arms, respectively ($P = 0.49$). Cystectomy was done in 10.7% of patients in the TMT arm [14].

A retrospective analyses published by 2 English cancer centers showed comparable outcomes for RC & bladder preserving therapy in MIBC patients. Munroe et al showed 10-year OS of 21.6% for radiotherapy versus 24.1% for RC in MIBC [29]. Also, Kotwal et al registered 5-year OS for radical radiotherapy and RC of 34.6% and 41.3%, respectively [30].

A case controlled study showed comparable results between RC & chemoradiotherapy for MIBC [17], 33 patients received chemoradiotherapy because of poor performance for RC were matched with patients of comparable age who underwent RC. The 5- year DFS for RC and chemoradiotherapy were 63.2% and 54% respectively, whereas the 5 year OS were 54.8% & 56.6% for RC & chemoradiotherapy, respectively [13].

A database of 3,024 consecutive patients with clinical T2–T4aN0M0 MIBC, from 29 international centers from 2005 to 2013 were enrolled, where 265 patients received bladder preserving therapy (BPT) compared to 1,447 patients who underwent RC, BPT patients were older with worse performance status, and more comorbidities ($p < 0.01$). The median OS for BPT and RC were 41 vs 46 months, $p = 0.33$, respectively. Only 4% of BPT patients underwent salvage cystectomy [31].

Patients who are candidates for bladder preserving therapy

(BPT) are usually older, with worse performance status, and more comorbidities than patients who underwent RC. These conditions greatly direct the treatment decision towards BPT due to lack of ideal candidacy for radical cystectomy. Prior findings similarly showed that non cystectomy candidates have poorer OS when treated with BPT than cystectomy candidates treated with BPT [32].

The survival outcomes in our study and the incidence of complete response were somewhat lower than other trials, which may be explained by the increased incidence of T 3b (44.7%) & T 4a (34%) with decreased incidence of complete TURBT (34.04%) in our study.

Radical cystectomy (RC) affects quality of life (QOL) significantly despite great advance in surgical techniques because of the presence of a stoma and reduced sexual function [5]. Bladder function and QOL in patients who underwent BPT after 6.3 years of follow up showed 75% of patients survived with their native bladders and 59% had satisfactory sexual activity [33].

Another multi-institutional study involved 173 MIBC patients compared QOL in patients treated with BPT and RC, BPT treated patients was associated with better QOL and bowel function compared to RC, while urinary toxicity was comparable between the 2 treatment modalities [34].

Randomized trials comparing trimodality BPT and RC are needed with comparison of tumor control and QOL.

5. Conclusion

For MIBC patients who are non-cystectomy candidates, or who are motivated to keep their native bladders, trimodality bladder preservation therapy (BPT), including a maximum transurethral resection of the bladder tumor (TURBT), followed by concurrent chemoradiotherapy can be considered as an effective alternative approach.

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