

Trimodality Therapy with Maximal Transurethral Resection, Hypofractionated Irradiation with Concurrent Gemcitabine in Elderly Patients with Muscle Invasive Bladder Cancer

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Abstract: Background: Muscle invasive bladder cancer is a serious health problem. While radical cystectomy (RC) is the gold standard treatment, many patients are unfit or refuse cystectomy. Trimodality therapy with transurethral resection of the bladder tumor (TURBT), radiotherapy and chemotherapy is an attractive alternative with comparable results. Radiotherapy with concurrent gemcitabine may be a good alternative to cisplatin in elderly patients as many of them have comorbidities which render them unfit for cisplatin or prone to severe toxicities. **Aim:** We initiated this trial to assess the response rate, survival outcome and tolerability of trimodality therapy with gemcitabine as a radiosensitizer in elderly muscle invasive bladder cancer (MIBC) patients. **Methods:** This study was conducted at Tanta university hospital, urology and oncology department, during the period from January 2013 to September 2017. Thirty six patients with muscle invasive transitional cell carcinoma (TCC) of the bladder were enrolled. Eligible patients underwent maximal TURBT followed by hypofractionated radiation therapy with 52.5 Gy in 20 fractions with concomitant weekly gemcitabine. **Results:** The median age was 69.5 years. The median follow up time was 24 months. Most of the patients tolerated the treatment protocol with minimal toxicity. Twenty four patients achieved complete response (CR), 4 patients partial response (PR) and 8 patients with either stable disease (SD) or progressive disease (PD). Six patients developed disease recurrence, three with non-muscle invasive, two with muscle invasive transitional cell carcinoma and the last one with small cell carcinoma. Two year disease free survival (DFS) and overall survival (OS) was 66.6% and 76.8% respectively. **Conclusion:** Bladder preservation with maximal TURBT, concurrent chemotherapy with weekly gemcitabine is well tolerated and effective in older patients with muscle invasive bladder cancer.

[Amr Ghannam, Rasha Abd Elghany Khedr and Mohamed Hassan Radwa. **Trimodality Therapy with Maximal Transurethral Resection, Hypofractionated Irradiation with Concurrent Gemcitabine in Elderly Patients with Muscle Invasive Bladder Cancer.** *Cancer Biology* 2019;9(1):84-92]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). <http://www.cancerbio.net>. 11. doi:[10.7537/marscbj090119.11](https://doi.org/10.7537/marscbj090119.11).

Key words: bladder preservation, gemcitabine, radiotherapy.

1. Introduction

Bladder cancer (BC) is a serious health problem in Egypt. According to a population based registry in 2014, bladder cancer is the second common cancer in Egyptian males representing more than ten percent (10.7%), especially in upper Egypt (12.60%)[1].

Bladder cancer mortality is high; it represents the 13th cause of death worldwide in 2015. In the united states, in 2018, approximately eighty thousand new cases are estimated to be diagnosed [2]. Of the newly diagnosed bladder cancer cases, 25-30% are MIBC while the remaining are non MIBC or superficial[3, 4].

Unfortunately, approximately one third of the patients with non MIBC will progress and develop muscle invasive disease during their follow up in spite of undergoing complete TURBT and intravesical therapy[5].

The standard of care for curative treatment of MIBC is Radical cystectomy and pelvic lymph node dissection (PLND). The five year local control and OS rate reported in many studies is about 50% and 40-60% respectively[6-8]. For further improvement of the result of RC, neoadjuvant cisplatin-based

chemotherapy is used. A systematic review and meta-analysis included 11 studies reported a 5% and 9% absolute improvement in overall and disease free survival, respectively [9].

Radical cystectomy has significant morbidity and mortality. The mortality rate reported in clinical trials range from 0.8% to 2.7% [10, 11]. The trimodality therapy including maximal TURBT, definitive radiotherapy (RT) with or without chemotherapy is an alternative treatment modality for patients who are unfit or refuse radical cystectomy and wish to preserve their bladder [12]. It has been recently accepted that bladder sparing protocols have comparable survival outcomes to radical cystectomy with better quality of life due to preservation of the function of the bladder[13, 14].

In a study by James et al. [15], concurrent administration of chemotherapy and radio-therapy increased the 2-years loco-regional disease free survival (DFS) rates from 54% to 67%. The 5-years overall survival rates (OS) improved from 35% to 48%. As most of patients advised for definitive radiation therapy are elderly and many of them has

impaired renal function and poor performance status, cisplatin as a radiosensitizer, is not the ideal chemotherapeutic agent [15]. The synchronous use of radiotherapy and Gemcitabine as a radiosensitizer has been studied in multiple trials with good tolerability and effectiveness [16-18].

Elderly patients have much comorbidity with less tolerability to traveling and waiting. So, hypofractionation is a suitable and preferable choice for them. Hypofractionation is previously studied in many trials for radical treatment and for palliation [17, 19, 20].

We initiated this trial to assess the response rate, survival outcome and tolerability of trimodality therapy with gemcitabine as a radiosensitizer in those groups of elderly patients aiming for new and better alternative for those frail patients.

2. Methods

This is a prospective small phase II study conducted at Tanta University Hospital, Clinical Oncology and Urology departments during the period from January 2013 to September 2017 and included thirty-six patients. The protocol was approved by the ethical committee at Faculty of Medicine, Tanta University.

Eligible patients are ≥ 65 years old, had histologically confirmed transitional cell carcinoma (TCC) of the bladder, clinical T2-4a, N0, M0, ECOG (Eastern Cooperative Oncology Group) performance status of ≤ 2 , serum creatinine of less than 1.5 x upper limit of normal (ULN), hemoglobin greater than 10 g/dL; platelets greater than 100,000/ μ L; WCC greater than 2,000/ μ L, age older than 18 years, and ability to provide informed consent. Patients with TCC in whom biopsy had not demonstrated muscle invasion but in whom there was unequivocal evidence of deep muscle invasion on MRI were also accepted. Exclusion criteria were abnormal biochemistry (ie, bilirubin ≤ 1.3 xULN, alkaline phosphatase ≥ 5 xULN, AST/ALT ≥ 5 xULN), previous intravesical instillation of chemotherapy or immunotherapy, or previous administration of systemic chemotherapy or pelvic radiotherapy. Patients with prior malignancy (except basal cell carcinoma), current or recent pregnancy, or inability to use contraception during and for 3 months after completion of treatment were also excluded.

Treatment

Each cycle of concurrent chemotherapy comprised gemcitabine 100mg/m² given as a 30-minute intravenous infusion 2 to 4 hours before RT.

Gemcitabine was administered once per week during RT on days 1, 8, 15, and 22. Conformal radiotherapy, which used a four-field plan with multileaf collimators, was delivered to the whole

bladder plus a minimum 1.5 cm margin. A total dose of 52.5 Gy was given in 20 fractions within 28 days.

Evaluation of Treatment

Patients underwent transurethral resection of their bladder tumor before chemoradiotherapy. Preradiotherapy assessment included a full physical examination, routine hematologic and biochemical laboratory evaluation, magnetic resonance imaging (MRI) of the abdomen and pelvis (or computed tomography scan if MRI was not tolerated), and chest imaging at least 4 weeks after their diagnostic transurethral resection of bladder tumor.

Patients were observed at 3-month intervals for the first 3 years and every 6 months thereafter. Post-treatment follow-up consisted of medical history, physical examination, urine cytology, cystoscopy, and radiological evaluation as clinically indicated. Tumor response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) [21] both cystoscopically and radiographically (either CT or MRI) three months after treatment. Complete response (CR) was defined as the absence of detectable tumor as well as negative urine cytology. Among patients with less than CR, cystectomy was offered by the treating physicians. Salvage therapy for non-muscle invasive recurrences consisted of TUR-BT followed by intravesical therapy for non-muscle invasive recurrence and radical cystectomy for muscle-invasive recurrences. However, the final decision was determined at the discretion of urologist and patient's own will. Evaluation of late treatment-related toxicity was performed according to the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) [22].

Statistical Considerations

The primary study end point was to determine the tumor response rate to chemoradiotherapy by using gemcitabine and conformal radiotherapy in the treatment of patients with muscle-invasive TCC of the bladder, as assessed by cystoscopy 3 months after completion of treatment. For patients with complete response, the duration of the response was also determined.

Secondary end points included measurement of the severity of acute and late toxicities after chemoradiotherapy and overall survival and disease-specific survival rates. Survival was estimated by using the Kaplan Meir method. Univariate and multivariate analysis by Cox proportional hazards model were performed to determine clinic-pathological factors with prognostic value for OS. A p-value < 0.05 (two-sided) was considered significant in all of the statistical testing. The statistical analysis was performed using Statistical Package for Social

Sciences software for Windows version 21.0(SPSS, Inc, Chicago, IL).

3. Results

Patient Characteristics

The patient characteristics in our study are represented in table 1. The age range from 60 to 78 years old with a median age of 69.5year. Male were more common than females which represent only about 8.3% of patients. Most patients has ECOG performance status of one (64%), the most common tumor grade were grade II (64%) and most patients (52.8) were either current or former smokers. Frequency was the commonest complain (64%) followed by haematuria. Mixed Transitional and squamous cell carcinoma was present in four patients. T2 was the most frequent tumor stage (52.8%). About one fourth of patients have hydronephrosis.

Treatment response

The response rate assessed three months after treatment was represented in table 2. Complete pathological response was achieved in 24 (66.7%) patients and partial response in 4 patients. Either stable or progressive disease was seen in about 8 patients. Seven out of 12 patients with incomplete response or progression underwent cystectomy for residual disease; the other five refused cystectomy and received palliative chemotherapy with subsequent development of distant metastases.

With a median follow up period of 24 months (range 15-60), six patients out of 24 patients with CR had recurrent disease, three are non muscle invasive and was managed by transurethral resection and intravesical therapy and two was muscle invasive with pelvic nodal recurrence required cystectomy, the last recurrence was small cell carcinoma with metastases in the liver and the abdominal lymph nodes and received palliative chemotherapy.

Toxicity

Most patients tolerated the treatment protocol without significant complications. Complete transurethral resection was achieved in 20 patients with minimal tumor residual in 16 patients especially in those with advanced T stage. All patients completed their radiation therapy course without significant delay (range 26-45day). The most frequent complain during radiation therapy was cystitis and frequency which required strong analgesics up to mild opioids. Diarrhea, as a small bowel toxicity was frequent and required delayed treatment in three patients for a period of 7-10 days. Tenesmus was a common rectal complication but without affecting the treatment course. No significant grade 4 adverse event was seen.

The chemotherapy sensitizer gemcitabine was well tolerated. The most common haematological

toxicity was thrombocytopenia necessitating treatment delay in five patients. No significant grade IV haematological toxicity seen.

The late bladder toxicity was tolerable in most patients with bladder contracture in five patients necessitating cystectomy in two of them due to frequent micturition with intermittent catheterization in the other three patients. No grade III or IV rectal toxicity was seen.

Survival

The median survival was not reached. The mean disease free and overall survival was 24.5 and 30.4 months respectively. The two years disease free and overall survival was 66.6% and 76.8% respectively. In a univariate analysis, the presence of hydronephrosis was a negative prognostic factor for disease free survival, while incomplete transurethral resection was a negative prognostic factor for both disease free and overall survival.

Table [1]: Main characteristics of 36 patients with muscle invasive bladder cancer.

Characteristic	No. patients (%)
Age (years)	
Median	69.5
Range	65-78
Sex	
M	33 (91.7)
F	3 (8.3)
ECOG	
1	23(64)
2	13(36)
Tumor grade	
G2	24(66.6)
G3	12(33.3)
Smokers	
Yes	17 (47.2)
no	19 (52.8)
Symptoms	
Haematuria	9(25)
Dysuria	2(5.5)
Frequency	23(64)
Suprapubic pain	2(5.5)
T stage	
T2	19(52.8)
T3	11(30.6)
T4a	6(16.6)
Hydronephrosis	
Present	10 (27.8)
Absent	26 (72.2)
TUR	
Complete	20(55.5)
partial	16(44.5)

Table [2]: The treatment response three months after initial treatment.

Response	Treatment group No. (%)
CR	24 (66.7)
PR	4 (11.1)
SD & PD	8(22.2)

Table [3]: Acute treatment toxicity in treatment group.

	Grade 0 No (%)	Grade 1 No (%)	Grade 2 No (%)	Grade 3 No (%)
Skin	0(0)	19(53)	13(36)	4(11)
Diarrhea	12(33.3)	11(30)	7(19)	6(17)
Nausea/Vomiting	22(61)	12(33.3)	2(5.5)	0(0)
Bladder	18(50)	30(83.5)	12(33.3)	6(17)
Rectal	15(42)	10(28)	7(19)	4(11)
Renal	28(78)	7(19)	1(3)	0(0)
Hematological				
Anemia	14(39)	17(47)	5(14)	0(0)
Leucopenia	16(44)	14(39)	6(17)	0(0)
Thrombocytopenia	9(25)	16(44)	9(25)	2(5.5)

Table [4]: Late treatment toxicity in treatment group.

	Grade 0 No (%)	Grade 1 No (%)	Grade 2 No (%)	Grade 3 No (%)
Skin	8(22.5)	20(55)	6(17)	2(5.5)
Bladder	21(58.7)	7(19)	3(8.3)	5(14)
Rectal	30(83.5)	4(11)	2(5.5)	0(0)

Table [5] Univariate analysis of prognostic indicators of two years OS and DFS for the 31 bladder cancer patients

	Disease free survival		Overall survival	
	Estimate (%)	P value	Estimate (%)	P value
Smoking				
Yes	69	0.24	65	0.17
no	71		86	
PS				
1	80	0.18	80	0.93
2	75		74	
Grade				
II	67	0.22	85	0.47
III	64		73	
TUR				
Complete	80	0.01	89	0.01
incomplete	26		56	
Hydronephrosis				
Present	28	0.02	59	0.21
Absent	82		86	
Tumor stage				
T2	90	0.06	93	0.56
T3	61		80	
T4a	53		75	

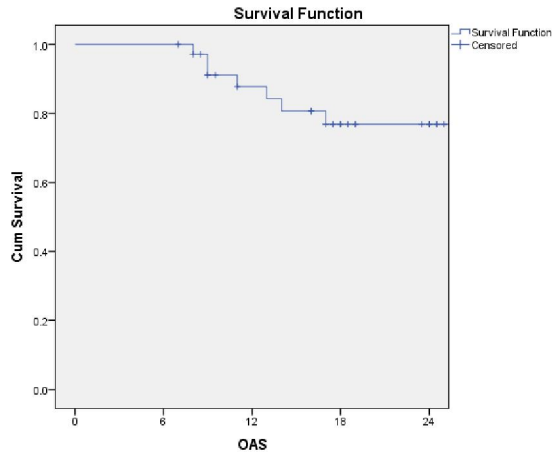


Figure 1: Kaplan-Meier Overall survival curves for all patients.

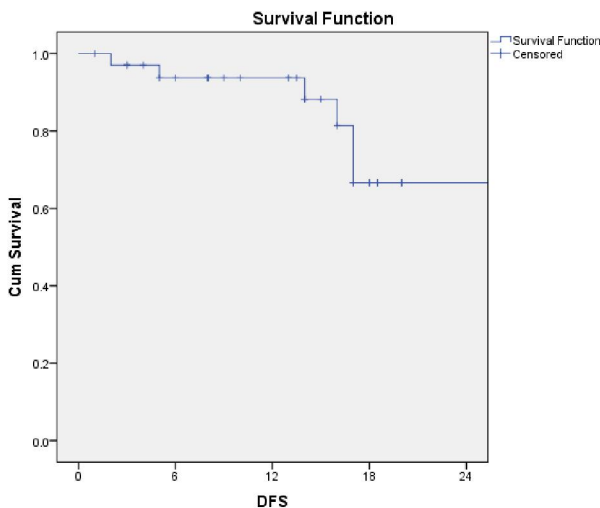


Figure 2: Kaplan-Meier disease free survival curves for all patients.

4. Discussion

Bladder preserving therapy with trimodality treatment seems to be comparable to radical cystectomy. A recent study published at 2018 based on the national cancer database in the united states compared the overall survival rates between patients who underwent radical cystectomy/chemo and those who were treated by chemoradiotherapy found no significant OS difference between both modalities[23].

A recent meta-analysis published also in the same year and included 11 cohort studies with 1735 patients concluded that bladder preservation is a superior treatment modality in comparison to radical cystectomy, particularly in elderly patients and T1G3 or lower grade tumors. However, RC could be a better option for younger patients[24].

We designed this study to include elderly patients because this group of patients needs a less toxic approach of treatment due to comorbidities associated with increased age and less tolerability to cisplatin. The definition of elderly population as over 65 is chosen by many studies, so we choose the same age for better comparison[17, 25]

Hypofractionation is an attractive option for older populations due to shortened treatment time and infrequent travelling compared to standard fractionation.

We enrolled 36 patients in our trial with 67.7 complete response rate at first cystoscopic examination, three months after treatment. This is consistent with that reported by Pos et al, where they demonstrated a CR rate of 74% in a similar study design with the same tumor dose and fractionation as our study[26]. In a literature review which included 496 elderly patients who were treated by trimodality therapy for muscle invasive bladder cancer that included 9 retrospective analysis, two case series from prospective studies and one prospective comparative phase II study, Turgeon et al. reported a 72% complete response rate [27]. The median age in this review was 78 years. Also our results compare favorably with that reported by the Christie group where they randomized sixty patients to a similar protocol with reported CR rate of 75%.[28]. However, our results is inferior to that reported by Choudhury et al., where they reported a 88% complete response rate in a similar design study, however, they included younger patients (48-84year, median 67 year) and no T4 tumors were included in their study[18].

Unlike radical cystectomy, the in-bladder recurrence is a common distress in bladder sparing protocols particularly the MIBC recurrence. In our study, six out of 24(25%) with CR have local recurrence within the bladder. Tunio et al. [29], reported that 21% of patients who achieved initial complete response after bladder preservation protocol had MIBC, of which 69% were within the primary tumor site. Formal studies showed in-bladder recurrence rate of 19-58% with about half of them were muscle invasive. This is consistent with our results as three patients (50%) of in-bladder recurrence had MIBC [30-32].

Complete TUR should be the goal whenever it is feasible, as residual tumor has a significant adverse effect on survival. Salvage cystectomies are necessary in about 25% of patients, which is similar to other studies [17, 33, 34].

Fifty three percent of our patients have intact bladder at two years after treatment. This results are consistent with that demonstrated in the RTOG 8903 trial who reported two year bladder free survival rate of 64.2%[35]. However, our results are inferior to that

reported by Choudhury, et al.[18] who showed that 89% percent of patients in his study has intact bladder. This may be due to the difference of patient population between our study and this study as our patients are older with less tolerability to treatment and also we included patients with T4a which is more advanced than the previous study which enrolled patients with T2-3 only with less local recurrence.

Our treatment protocol was well tolerated with no major treatment interruption. No reported acute or late grade IV toxicity. The grade III acute toxicity was reported in 39% of patients and late toxicity in 19% of patients. This is consistent with that stated by James et al [15] which reported acute grade III/IV toxicity in one third of patients with grade III/IV in 10%. Also this result compare favorably with the acute and late toxicities reported in a recent trial [17] and in the RTOG study[6].

The two years disease free and overall survival in our study was 66.6% and 76.8% respectively. This is consistent with another studies with a similar design [17, 18]. Choudhury et al. reported three year OS of 75% and DFS of 82%[18]. In the above mentioned study by the Christie group, the reported 5 years OS and DFS was 61% and 69%, respectively[28].

In a univariate analysis, the presence of hydronephrosis was a negative prognostic factor for disease free survival, while incomplete transurethral resection was a negative prognostic factor for both disease free and overall survival.

Hydronephrosis is known to be one of the negative prognostic factors in bladder preservation protocols[36]. However, hydronephrosis may not be a contraindication to trimodality treatment. In our study, there were a substantial number of patients (27.8%) who had hydronephrosis, however, the CR rate was consistent with that reported in the most published studies as previously clarified.

Our results showed excellent local control rates, in spite of the pelvic lymph nodes was not included in the radiation field. This may not be appropriate for some patients as pelvic lymph nodes may harbor a microscopic metastatic disease [37]. The pelvic recurrence rate in our study was 8.3% (2/24).

There are no data to support the routine irradiation of radiologically negative lymph nodes. Pelvic irradiation was used routinely in RTOG (Radiation Therapy Oncology Group) protocols [35, 38-40], however, Tunio et al.[29] randomized the patient with T2-4 tumors to receive either bladder only irradiation or pelvic irradiation with bladder boost and reported comparable rates of failure in the pelvic lymph nodes. The BC2001 study [41] gives a good demonstration of patterns of failure. The low rate of nodal recurrence in BC2001 (only 3% in the chemoradiotherapy arm and 6% with radiotherapy

only arm) is also of interest, as no attempt was made to include pelvic nodes in the field, although lymph nodes in the lower pelvis would have been irradiated in the treated volume.

These results imply that RT fields including bladder only could be feasible in selected patients and concurrent chemotherapy might also have targeted microscopic lymph nodal disease.

However, the dose of gemcitabine used in our trial is 1/10 of the usual dose used either in neoadjuvant treatment or used for treating metastatic disease. Thus, the effect of gemcitabine on response rate in our study is likely due to its role as a radiosensitizer, for which the improvement in survival may be due to increased local control rather than treatment of micrometastatic disease. To cover this issue, the surgical excision of high risk lymph node areas through open or laparoscopic surgery may be considered. Also the use of neoadjuvant or adjuvant chemotherapy with concomitant chemoradiation should be studied carefully for its effect on nodal failure. This combination may be a better option as irradiation of pelvic lymph nodes with essentially increase the late gastrointestinal toxicity.

Surely, RC will be the preferred option for some patients (those with small bladder capacity, marked hydronephrosis or extensive carcinoma in situ). However, if proper selection of patients occurred, a percentage of patients can be cured while retaining their well-functioning bladder and good sexual function. So, every effort should be done for better identification of clinic-pathological factors associated with better prognosis and better predication of response to treatment.

Hypofractionation cannot be considered the most appropriate protocol as the α/β ratio of the bladder is 10 Gy, thus shortened treatment times and larger fraction sizes have no potential therapeutic gain [42]. However, with studies using modern radiation techniques such as IMRT (Intensity Modulated Radiation Therapy), IGRT (Image Guided Radiation Therapy) or tomotherapy which allowed dose escalation and a reduction in toxicity, this concept has been changed [43].

Although our results may be a promising new alternative for elderly populations, they should be taken with cautious due to the limited number of participants'. Also, we reported only the 2-years DFS, as done in some phase II studies[44]; however, the 5-years will be more explanatory with more patients included and an extended follow-up time. Hypofractionation with concurrent gemcitabine has a tolerable toxicity profile with good response rate and DFS. Hypofractionated approach has better therapeutic ratio if done through whole course IMRT to spare normal organ at risk as much as possible.

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2/25/2019