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Review Article

Neoadjuvant Chemotherapy Followed By Conformal Hypofractionated Radiotherapy with Concurrent Gemcitabine in Muscle - Invasive Bladder Cancer

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Abstract:

Purpose: The aim of this prospective, phase II trial was to determine the response of muscle-invasive bladder cancer (MIBC) to concurrent chemoradiotherapy (CRT) of weekly gemcitabine with conformal hypofractionated radiotherapy after neoadjuvant chemotherapy.

Patients and Methods: Forty patients with transitional cell carcinoma, stage T2-4a, N0, M0 after magnetic resonance imaging were recruited. Transurethral resection was done and neoadjuvant chemotherapy with gemcitabine 1250 mg/m ^{2}on days 1 and 8 with cisplatin 100 mg/m2 on day1 repeated every three weeks was given. CRT phase included gemcitabine at 100 mg/m2 on days 1, 8, 15, and 22 of a 28-day RT schedule that delivered 52.5 Gy in 20 fractions. The end points were tumor response, toxicity, and survival.

Results: Thirty three patients (82.5%) completed treatment protocol. Twenty five patients (75.8%) achieved a complete endoscopic response. The remaining 8 patients (24.2%) had residual disease. At a median follow-up of 23.5 months (range, 11 to 33 months), 19 patients (57.6%) had a functional and intact bladder. Four patients (12.1%) had a loco regional recurrences and 2 patients (6.1%) developed distant metastasis. By using Kaplan-Meier analysis, 2-year disease free survival was 64%, and overall survival was 77.5%. Out of the 33 patients who entered the CCRT phase, only 6 patients (18.2%) had grade 3 acute rectal or bladder toxicity. No one developed G3 late toxicity. Overall, side effects were tolerable and manageable.

Conclusion: Concurrent gemcitabine-based CRT after neoadjuvant chemotherapy and TURBT is effective with high response rate, durable local control and acceptable toxicity, which allows patients to preserve their own bladder. However further investigations is needed to confirm these results in larger number in a phase III trial.

Keywords: Bladder cancer; Gemcitabine; Neoadjuvant chemotherapy; Concurrent radiotherapy

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Introduction

Cystectomy is the standard approach for the treatment of invasive bladder cancer [1]. However because the median age at diagnosis is 65 years; medical comorbidities are frequent consideration in patient management [2]. Furthermore, with RT the patients retains a functioning natural bladder and men are likely to retain sexual function suggesting that organ preservation may provide better quality of life [3].

So chemoradiotherapy (CRT) has emerged as an effective alternative to cystectomy. Surgery could be reserved for patients with an incomplete response or recurrence after CRT [4].

The result of radiotherapy alone is considered inferior to surgery and is only indicated for those who are unfit for surgery or cannot tolerate chemotherapy. However, the initial complete response and the long term bladder preservations rates are higher with combined CRT which makes it the preferred treatment [5]. In a randomized trial comparing RT alone with CRT in the National Cancer Institute of Canada, 99 patients underwent randomization to undergo RT alone or with concurrent cisplatin. The addition of cisplatin to RT increased the pelvic progression free survival rates at 5 years from 41% to 60 % [6]. Most chemoradiation regimens employ concurrent cisplatin in various doses and schedules. Studies combining cisplatin with 5fluorouracil (5-FU) have shown small additional benefits. However cisplatin is nephrotoxic, it requires pre and post infusion hydration, it often necessitates hospital admission and it is significantly myelosupressive and emetogenic [2]. So, observation of improved efficacy of CRT using combinations with novel drugs and altered fractionation is under investigation [7].

Gemcitabine is a nucleoside analogue that has been shown to be cytotoxic in a number of tumors including advanced transitional cell carcinoma (TCC) [8]. It has also been found to be radiosensitizing agent in preclinical studies and its efficacy has been demonstrated in various cancer cell lines including lines derived from bladder tumors [9].

Hypofractionated radiotherapy schemes may be more effective than conventional or low-daily-dose accelerated regimens especially for tumors with high clonogen repopulation ability (acceleration may counteract repopulation), intense hypoxia, or low intrinsic radiosensitivity (because large fractions may overcome the shallow shoulder of the dose response curves) [7]. The application of large radiotherapy fractions has been effectively used in clinical practice [10]. In a recent radiobiological analysis, however, an estimated median alpha/beta ratio of 10 Gy suggested no evidence to support the use of a short overall treatment time or hypofractionation [11]. However, the application of hypofractionated with or without chemotherapy has not been examined presumably because the expected early and late toxicity is high [7]. On the basis of the results of preclinical studies, a phase I study of hypofractionated conformal bladder radiotherapy with once weekly gemcitabine in muscle invasive bladder cancer (MIBC) was undertaken. The maximum recommended dose for gemcitabine was 100mg/m^2. It was given once weekly with concurrent hypofractionated conformal bladder radiotherapy [3].

A phase II study was done to evaluate the response rate and to address the data of acute and late toxicities of the treatment. The results were encouraging with high response rate, durable local control, acceptable toxicity and preservation of the bladder function [2].

However this treatment does not cover the pelvic lymph nodes, as it uses conformal radiotherapy on the bladder. Pelvic lymph nodes are known to be affected by microscopic metastatic disease in a proportion of clinically localized disease. So, it might be possible to consider combining concurrent CRT

with concomitant removal of the nodal risk areas by open or laparoscopic lymph node dissection. Also, addition of neoadjuvant chemotherapy reduces the risk of metastatic disease and improves the 5-year survival rates by 5% [2].

Patients and methods

40 patients with MIBC were included in this phase II trial; who presented to Clinical Oncology & Nuclear Medicine Department, Mansoura University Hospital during the period from the start of May 2011to the end of May 2013.

Patient Selection Criteria: Age ≥ 18 years, WHO performance status of ≤ 2, AJCC Stages II and III, Histologically and /or radiologically confirmed TCC of the bladder. Serum creatinine of less than 1.5 upper limit of normal Haemoglobin ≥10 g/dl, Platelets ≥100,000/L, WBCs ≥3000/L provided that absolute neutrophilic count (ANC) ≥ 1500/L.

Exclusion criteria: Previous administration of systemic chemotherapy or pelvic radiotherapy, Patients with prior malignancy, Current pregnancy.

Pre-treatment Evaluation: History was taken from all patients. Physical examination was done including weight, height and surface area. Performance status was assessed according to ECOG performance status scale. Laboratory studies (CBC, LFT, serum creatinine), radiological evaluation (chest x ray, abdominopelvic magnetic resonance imaging [MRI] and bone scan), endoscopic evaluation (cystoscopic examination, multiple punch biopsies and complete transurethral resection if possible) and pathological examination (pathological type, grade and depth of muscle invasion and urine cytology).

Treatment details: All patients entered the induction phase which consists of three cycles of chemotherapy (gemcitabine 1250 mg/m^2 on days 1and 8 and cisplatin 100 mg/m^2) repeated every three weeks.

The response was assessed following the completion of the induction chemotherapy by abdominopelvic MRI. Patients were subjected to complete transurethral resection of bladder tumor (TURBT) either before or after the induction phase of chemotherapy. Finally, patient entered the definitive phase of concurrent CRT except those who developed regional or distant metastasis after the chemotherapy phase or didn`t underwent TURBT.

Concurrent CRT consisted of gemcitabine 100 mg/m^2 given as 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. Radiotherapy was given by hypofractionation schedule aiming at a total dose of 52.5 Gy in 20 fractions over 26 days.

Radiotherapy technique: Radiotherapy was given using 6-15 MV linear accelerator (ELECTA) after CT simulation and conformal radiotherapy planning. A five-field arrangement with multileaf collimation was used. Treatment was given in a single phase using a once-daily fractionation regimen, treating 5 days a week. Fields were designed with the patient having 40 to 50 ml air contrast cystogram (20-30 ml dye + 20 ml air).

Target Volumes: In patients with radiological evidence of extravesical disease, the CTV comprised the outer bladder wall and the extravesical extension with a 10-mm margin. In patients with no evidence of

extravesical disease on CT scans, the CTV restricted to the outer bladder wall plus a 6-mm margin.

In expanding the CTV to the PTV, we added isotropic margins of 1.5 cm uniformly around the bladder in three dimensions. These margins incorporate internal margins, to account for variations in the size, shape and position of the bladder, and set-up margins, to account for uncertainties in patient positioning and beam arrangement.

However, as that most bladder motion occurs in the superior direction, the bladder dome, tumors lying in the cranial part of the bladder are most at risk of movement outside the target volume. Large movements are also seen in the anterior and posterior directions, with least motion at the inferior boundaries of the bladder. The superior, anterior and posterior margins are increased to 2 cm while the inferior direction remains 1.5 cm.

Radiotherapy dose specification: A daily fraction of 2.63-Gy through five fields directed to the whole bladder was used for a total of 20 fractions. A total physical dose of 52.5 Gy was delivered over 26 days. Thus acceleration with 21 days was achieved compared by the standard 2 phase technique which is given over 7 weeks; 47 days.

For the radiobiological analysis of the above scheme, the normalized total dose (NTD) was calculated using the formula proposed by Maciejewski *et al*, [12]. NTD = D [(α/β + d)/ (α/β + 2)], where 'D' is the total physical dose,'d' the dose per fraction and α/β is the tissue specific ratio. The NTD corrected for overall treatment time was calculated using a previously proposed formula, NTD (T) = D [(α/β + d)/(α/β+ 2)] + γ (Tc-To), where Tc is the number of days required for the delivery of the NTD using a conventionally fractionated scheme, To is the number of days required for the delivery of the current scheme, and 'γ' is the estimated daily dose consumed to compensate for rapid tumor repopulation. For cancer tissue an α/β ratio of 4 Gy was considered. We also assumed a median 'γ' value of 0.4 Gy for cancer cells and of 0.2 Gy for normal tissues. To the bladder, a total of 52.5 Gy of physical dose, equivalent to 58 Gy for α/β = 4 Gy, was delivered within 26 days (acceleration by 21days). Assuming a γ value of 0.2 Gy for normal bladder, the time corrected dose to the bladder was 62.2 Gy. Assuming a tumor γ value of 0.4 Gy, the estimated time-corrected biological dose to the bladder tumor was 66.4 Gy (for a tumor α/β = 4 Gy) and 63.66 Gy (for a tumor α/β = 10 Gy) (7). The minimum dose within the PTV was at least 95% of the protocol dose. The maximum dose did not exceed 107% of the protocol dose.

Normal tissue dose tolerance for hypofractionated radiotherapy is calculated using the linear quadratic (LQ) model to derive biologically effective doses (BED) according to Khaled *et al* [13].

Radiotherapy delays: Any grade 3 or higher toxicity (diarrhea, proctitis, or cystitis) was followed by treatment interruption, supportive medication (loperamide, analgesics, or antibiotics when necessary) and treatment restarted once symptoms regressed to grade 1.

Toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Toxicities occurred >90 days following the completion of RT were assessed according to the toxicity criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Patient's follow up: After end of treatment, patients were followed up every 3 months by clinical examination, abdomen and pelvis MRI and cystoscopy for the first two years. Late radiation effects were recorded after 3 months of radiation according to RTOG/EORTC late radiation morbidity scoring criteria. MRI, endoscopy and biopsy were done if recurrence was suspected.

Statistical analysis: Data entry and analyses were performed using SPSS statistical package version 10 **(SPSS, Inc., Chicago, IL, USA)**. The quantitative data were presented as a mean, median and range. The qualitative data were presented as number and percentage. The chi-square test ($\chi 2$) was used to find the association between variables of qualitative data. The P value of ≤ 0.05 and ≤ 0.001 indicate significant and highly significant results respectively at confidence interval 95%.

The disease free survival (DFS) was calculated in patients who achieved complete response, from the end of treatment till appearance of recurrence. The overall survival (OS) was calculated from the time of diagnosis till death or last follow up visit.

The primary end point was to evaluate response rate. The secondary end points were to evaluate the DFS, OS and treatment toxicity.

Results

This is a prospective phase II study in which 40 patients with MIBC; T2- T4a N0 M0; were enrolled. The patients presented to Clinical Oncology & Nuclear Medicine Department, Mansoura University Hospital from the start of May 2011to the end of May 2013.

Patient's characteristics are summarized in (Table 1). The median age was 69 years. There was male predominance. Males represented 72.5% with a male to female ratio of 2.6:1. T3 tumor was the most common followed by T2 and T4, they were (60%), (27.5%) and (12.5%) respectively. The majority of patients; 31 patients (77.5%); had grade III tumors. There was no significant correlation between the stage and the response rate. However there was a significant correlation between the stage and DFS. The grade shows no significant correlation with the response or with DFS. Most patients had a performance status (PS) of G1 (75 %) and the remaining 10 patients (25%) had PS GII. Comorbidities were encountered in 18 patients (45%) while the remaining 22 patients (55%) were free from any comorbidity. There was no significant correlation between the PS or the comorbidities and the chemotherapy completion, response rate or DFS. However, there was a significant correlation between the PS and OS. Hydronephrosis was detected in 11 patients (27.5 %) but it was mild and with normal serum creatinine. The other 29 patients (72.5%) had normal kidneys. However hydronephrosis showed no significant correlation with DFS or OS.

Of the 40 patients, 12 patients (30%) underwent complete TURBT before chemotherapy and the remaining 28 patients (70%) were unfit for the initial complete TURBT because of the age, comorbidities or the extent of the disease. However 21 patients (52.5%) became eligible and underwent TURBT after down staging of the tumor by neoadjuvant chemotherapy. Thus Complete TURBT was performed in 33 patients (82.5%) in one or more attempts.

Table 1 Patient's characteristics

Patient Characteristic	(n=40)	
	No.	%
Age	Median age (Ys) 69	
(Years)	Range 45-82	
Sex		
M	29	72.5
F	11	27.5
Tumor stage		
T2	11	27.5
T3	24	60
T4a	5	12.5
Tumor grade		
G1	1	2.5
GII	8	20
GIII	31	77.5
Performance status		
0	30	75
1	8	20
2	2	5
Smoking		
Yes	16	40
No	24	60
Hydronephrosis		
Yes	11	27.5
No	29	72.5

Three patients developed persistent elevation of the serum creatinine and didn`t continue the full course of chemotherapy. Subsequently these patients were withdrawn from the study protocol.

Thirty seven patients were assessed by MRI abdomen and pelvis. Those who achieved complete response (CR) were 21 patients (56.8%), 10 patients (27%) achieved partial response (PR), 5 patients (13.5%) showed stable disease (SD) and the remaining 1 patient (2.7%) showed disease progression (DP).

Patient who developed DP on MRI, didn`t perform complete TURBT or didn`t complete the full course of induction chemotherapy were excluded from the concurrent CRT phase. So, out of the 40 eligible patients who entered the study, 33 patients (82.5%) were eligible to enter the concurrent CRT phase. All these patients completed the treatment protocol.

Response rate:

Thirty patients (90.9%) were assessed by cystoscopy. The remaining three patients (9.1%) were not

assessed by cystoscopy because of DP proved radiologically; 2 patients had pelvic failure and 1 had distant metastasis. The CR on check cystoscopy with tumor site biopsy following neoadjuvant chemotherapy and concurrent CRT was seen in 25 patients (75.8%). Of the 5 patients (15.1%), who did not achieve CR, 2 patients were lost follow up and 3 were treated with salvage chemotherapy. Results are summarized in Table (2).

Table 2 Summary of the results

Patients	Follow/up (months)	Patients finished CCRT	Initial CR	Initial failure	Follow up failure		Bladder preservation	DFS (2year)	OS (2 year)
					loco regional	Distant metastasis			
40	23.5	33	25	8	4	2	19	-	-
100%	-	82.5%	75.8%	24.2%	12.1%	6.1%	57.6%	64%	77.5%

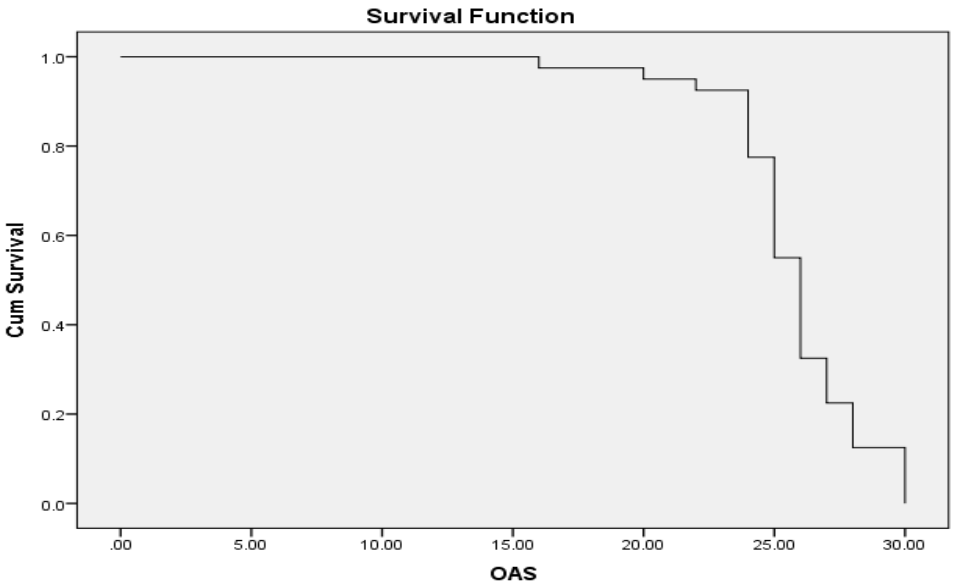

Figure 1 Kaplan-Meier survival curve showing OS

DFS and OS:

Out of the 25 patients (75.8%) who achieved CR, 4 patients (12.1%) had loco regional recurrence and treated with salvage chemotherapy as they were unfit or ineligible for surgery. The distant metastases in bones were seen in 2 patients (6%); and were treated with salvage chemotherapy, palliative radiotherapy and bisphosphonates. The remaining 19 patients (57.6%) remained free of disease and had an intact bladder. Using the Kaplan-Meier method, The 2 year DFS was 64% as shown in the Fig (1). The estimated 2 year OS was 77.5 % as shown in Fig (2).

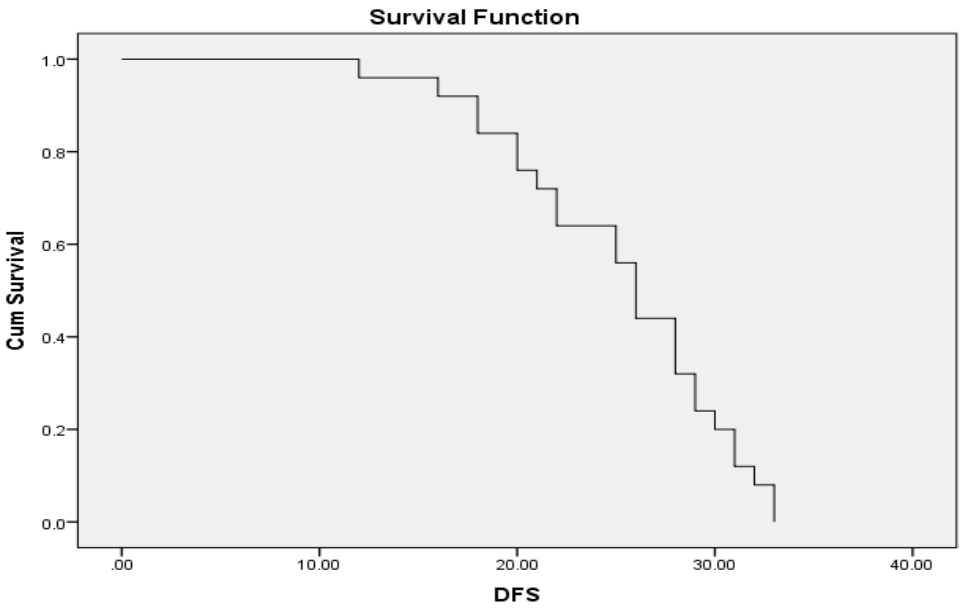

Figure 2 Kaplan-Meier survival curve showing DFS

Treatment toxicity:

Chemotherapy toxicity:

During the induction phase of chemotherapy and regarding the hematological toxicity, no patient developed toxicity more than G2. A majority of the patient; 17 patients (42.5%) had G1 hematological toxicity and 8 patients (20%) developed G2 toxicity during the course of the treatment. The remaining 15 patients (37.5%) had no toxicity.

Regarding the non hematological toxicity, 3 patients (7.5%) didn`t complete the full course of chemotherapy. They developed G3 nephrotoxicity with persistent elevation of the serum creatinine and did not continue the full course of chemotherapy. Regarding the nausea and vomiting, most patients had GI or GII toxicity and no patients developed G3 toxicity.

Early radiation toxicity:

Acute radiation toxicities are summarized in Table (3). Of the 33 patients who entered the concurrent CRT phase, 6 patients (18.2%) had treatment interruption because of G3 rectal or bladder toxicity. The remaining 27 patients (81.8%) completed the full course of concurrent CRT without interruption. Overall, side effects were tolerable and manageable. Dysuria & frequency were the most frequently observed non-hematologic toxicities followed by diarrhea. Four patients (12.1%) experienced G3 cystitis, sixteen patients (48.5%) developed G2 cystitis and 5 patients (15.2%) had G1 toxicity. The remaining 8 patients (24.2%) had no cystitis. Gastrointestinal (GI) complications were a major concern. Regarding the diarrhea, 10 patients (30.3%) developed G2 toxicity. Fifteen patients (45.5%) developed G1 toxicity. The remaining 8 patients (24.2%) did not develop any diarrhea during the course of concurrent CRT or 90 days after.

Regarding proctitis, there was a large variation in the rectal toxicity. Three patients (9.1%) developed G3 rectal toxicity, 11 patients (33.3%) had G2 toxicity and 14 patients (42.4%) developed only G1 toxicity. Only 5 patients (15.2%) had no rectal toxicity.

Table 3 acute radiation toxicity during the concurrent CRT phase

	0	Grade 1	Grade 2	Grade 3	Grade 4
Cystitis	24.1%	15.2%	48.5%	12.1%	0
Diarrhea	24.1%	45.6%	30.3%	0	0
Proctitis	15.2%	22.4%	33.3%	9.1%	0
Hematologica	72.7%	27.3%	0	0	0

No major hematologic toxicity was encountered. Only 9 (27.3%) patients had G1 hematological toxicity. The remaining 24 patients (72.7%) had no hematological toxicity.

Late Radiation Toxicity:

Within a median follow-up of 23.5 months (range 11 to 33), the patients showed low incidence of severe late complication. Of 33 patients who completed the concurrent CRT phase, no one developed G3 toxicity. The major complications were related to the GU system with 8 patients (24.3%) had G2 toxicity and 15 patients (45.5%) had G1 toxicity. Two patients (6.1%) complained of G2 dysuria, 3 patients (9.1%) of G2 frequency and 3 patients (9.1%) of G2 incontinence. All the remaining patients experienced minimal grade 0 to 1 toxicity. Regarding rectal toxicity, 2 patients (6.1%) complained of G2 toxicity, but no case of bleeding, ulceration, or stricture developed.

Discussion

Urinary bladder cancer is a common malignancy. It is the 9th most frequent cancer worldwide, accounting for 2.1% of all cancer deaths [14]. Three hundred and fifty seven thousands new cases of bladder cancer were diagnosed, while 145,000 patients died from the disease [15].

Fifty five thousands new cases were diagnosed and 12,000 cancer-related deaths per year were reported in United States. It is ranked as the 5th most common cancer in United States (US) and the 4th leading cause of cancer deaths [16]. In Europe an estimated 110,500 new cases of bladder cancer were diagnosed, leading to 38,000 cancer deaths. The median age at diagnosis is 65 years, and 70% of patients with bladder cancer are >60 years of age [14].

In Egypt, bladder cancer is the most prevalent malignancy among males (16%), producing >7900 deaths annually, which is strikingly higher than most other parts of the world [17]. According to International Agency for Research on Cancer (IARC), the world age adjusted incidence rate (IR) for Egyptian males is an estimated 27.9/ 100,000 per year (PY) [18]. Countries geographically close to Egypt have much lower rates of bladder cancer: for example, the age-adjusted male IR is for Jordan, Saudi Arabia, Lebanon and Morocco are 7.2, 7.9, 17.5, and 9.7 per 100,000 PY, respectively [19].

There is large geographical variation in the histology of urinary bladder cancer. In the Western world,

approximately 90% of the cases are TCC. In Egypt and parts of the Middle East, where *Schistosoma haematobium* infections are frequent, 55–80% of the bladder cancers are squamous cell carcinomas [20]**.** However, with the government's efforts to eradicate *S. haematobium* and treat infected individuals over the past 3 decades, a shift from SCC to TCC and an increase in the mean age at diagnosis have been reported. However, the incidence of bladder cancer in Egypt has not decreased due to an increase in TCC over the past 30 years; this malignancy remains the most commonly diagnosed in men [13]**.** An additional source of tobacco exposure is from smoking with a water pipe or ‘‘shisha,’’ which is prevalent in Egypt with 15.3% of rural males and 10.9% of urban males reporting regular, current ‘‘shisha’’ use [21].

The treatment of patients with MIBC is undergoing dramatic changes, incorporating many potentially effective and complementary therapies from several disciplines, including TURBT, systemic chemotherapy, radiotherapy with new techniques and advanced methods of surgical construction of a substitute bladder [22].

New chemotherapeutic agents, particularly gemcitabine and taxanes, have been shown to be potent radiation sensitizers. Furthermore, many modern studies have established that gemcitabine in combination with radiotherapy is a feasible regimen for bladder sparing treatments [23].

The patients studied were in age range of 45-82 years with a median age of 69 years. This median age is matched to the worldwide reported median age. Khosravi-Shahi and Cabezón-Gutiérrez [14] reported that median age at diagnosis was 65 years, and 70% of patients with bladder cancer were >60 years of age.

Our study showed male predominance with male to female ratio 2.6:1. This ratio is matched with the reported worldwide ratio which is about 3:1 [14].

In the current study, the final assessment of patients with MIBC after the CRT showed that complete response rate (CR) was achieved in 75.8% of patients (25 Patients) after maximum TURBT, neoadjuvant chemotherapy and concurrent CRT. Our results are comparable with the studies conducted by Sabaa *et al*. [24], Khader *et al*. [25] & Efstathiou *et al*. [26] and are better than those reported in other studies done by Gamal El Deen [27], Ibrahem *et al*. [28], and Nowak-Sadzikowska *et al*. [29].

Sabaa *et al*. [24] studied 104 patients with MIBC that were treated by complete TURBT followed by CRT in the form of gemcitabine and cisplatin and conventional radiotherapy. CR was shown by 78.8 % of their patients. Khader and his colleagues at [25] studied 14 patients with MIBC. Initial therapy consisted of TURBT followed by induction chemotherapy, then irradiation with concurrent platinum-based agents. The bladder and pelvic lymph nodes were treated via a four-field box technique to a total dose of 4500 cGy. Additional therapy with irradiation (up to 6400 cGy) was delivered to the bladder with safety margin to complete responders. They achieved 73% CR and this is much near to CR obtained in our results**.**

Efstathiou *et al*. [26] reported the Massachusetts General Hospital (MGH) experience with selective bladder preservation in the treatment of 348 patients with MIBC (T2-T4a). Patients underwent concurrent cisplatin-based CRT after maximal TURBT plus neoadjuvant or adjuvant chemotherapy. CR was achieved in 72% of patients**.** This agrees with our results as they used multidrug regimen with

platinum-based agents concomitant with radiotherapy.

On the other hand, the results obtained in our series are better than Gamal El Deen [27], Ibrahem *et al*., [28] and Nowak-sadzikowska *et al*., [29] studies. CR was achieved by Gamal El Deen [27] in 67.3% of 55 patients with MIBC treated with complete TURBT, followed by induction chemotherapy, followed by irradiation aiming at 4500 cGy with concurrent cisplatin administration. Patients who had incomplete response were subjected to radical cystectomy. Those who had CR received additional chemotherapy and radiotherapy up to 6480 cGy. Our results were slightly higher and this may be due to the use of unconventional fractionation.

Ibrahim *et al*. [28] reported that 40 patients with MIBC presented to the Radiation Oncology and Urosurgery departments - Ain Shams University hospitals were enrolled in a prospective phase II study. Patients were treated using concurrent cisplatin and 45Gy radiotherapy (induction phase) after maximal TURBT. Those with CR received consolidation CRT to 64.8Gy. Patients with less than CR were advised to undergo radical cystectomy. Four cycles of adjuvant gemcitabine and cisplatin, repeated every 3 weeks, were given following definitive therapy. They found that 24 patients (60%) achieved CR after initial 45Gy CRT. Similarly, this study showed lower results than ours which may also be attributed to the use of multidrug regimens and unconventional fractionation schedules of radiotherapy in our study. Nowak-Sadzikowska *et al*. [29] found only 67% CR rate of their studied patients which is lower than our study results.

Treatment protocol completion is an important issue when investigating multimodality treatment for studying bladder preservation protocols. It is important to study how far it is safe to replace radical cystectomy in treatment of bladder cancer with these protocols and how they will affect quality of life of the patients. Ibrahem and his colleagues [28] reported that 75% of their patients completed treatment. Also, Nowak-Sadzikowska *et al*. [29] showed 78% completion treatment rate. They studied 27 patients with MIBC who were fit for CRT and refused radical surgery. Kaufman *et al*. [30] reported that their treatment protocol completion rate was 70% after studying 80 patients with MIBC. Twice-daily radiotherapy with paclitaxel and cisplatin chemotherapy (TCI) was administered. Then consolidation with TCI was given. Adjuvant gemcitabine and cisplatin were given to all patients.

In our study, 33 patients (82.5%) from the 40 eligible patients who entered the study completed the treatment protocol. Our results are higher than these results and this could be attributed to the conformal technique used to irradiate small target volume; whole bladder; compared to the large target volume; whole pelvis.

Treatment failure is an important issue that must be investigated to decide the efficacy of this protocol in the treatment of bladder cancer. Ibrahem *et al*. [28] reported that local failure and distant metastasis were recorded in 40% and 25% of the patients respectively. Kaufman *et al*. [30] reported loco-regional failure rate as 27.5% and distant failure rate of 31.25%. Sabaa *et al*. [24] found that local failure rate in their study was 16.2% out of the evaluable 74 patients and distant failure rate was 24.3%. Zapatero *et al*. [31] reported that 18 patients (24.5%) experienced local bladder relapse and 11 patients (15%) developed distant metastasis. Efstathiou *et al*. [26] reported that among patients achieving CR to induction CRT, 10-yr rates of non-invasive, invasive, pelvic (nodal or sidewall), and distant recurrences were 29%, 16%, 11%, and 32%, respectively.

In our study, after a median follow up of 19 months the local failure rate for the whole studied patients was 16%. Four out of 25 patients who achieved CR developed local recurrence. On the other hand, distant failure rate was (8%); 2 out of 25 patients. The relative difference between treatment failure rates of our study and other series could be explained by the relatively shorter follow-up period in our study compared to other series and the larger sample size in other studies. Also, the use of neoadjuvant chemotherapy in our protocol may contribute in lowering distant failure rates.

Treatment toxicities are important issues to be investigated as they may lead to stoppage of the protocol if they are not controlled or managed well by the investigators. Our study showed comparable treatment complications with other series. Treatment was generally well tolerated with no treatment-related deaths.

Ibrahem *et al*. [28] reported that (20%) and (13.7%) of patients experienced at least one severe G3 toxicity during induction and consolidation phase of CRT, respectively, mainly neutropenia, cystitis and proctitis. These are more than our results during the induction phase that report only (7.5%) of patients who experienced G3 toxicities; nephrotoxicity; and less than our results in concurrent CRT phase that report (27%) of the patients (9 patients; 6 with G3 cystitis and 3 with G3 proctitis) experienced at least one G3 toxicity. These results could be attributed to the hypofractionation protocol with chemotherapy sensitizer.

Nowak-Sadzikowska *et al*., [29] treated 27 patients with CRT. Hematological toxicities were mainly of G1 occurred in 13 patients (48%) and of G3 in 6 patients (22%). GI complications of G1 occurred in 12 patients (44%) and G2 in 4 patients (15%). The total GI complication rate was 59%. The overall GU toxicities that happened were 77% with G1 in 9 patients (33%) and GII in 12 patients (44%). These results are much more comparable with our results which revealed GI complication in (75.8%) of the patients with (45.5%) had G1 and (30.3%) had G2. Also, GU complications in our results were noticed in (75.8%) of the patient with G1 in (15.2%), G2 in (48.5%) and G3 in (12.1%). However they gave only 2 cycles of neoadjuvant chemotherapy with (22%) of the patients received only one cycle. Also, they gave cisplatin radiosensitizer in only (33%) of the patients.

Kaufman *et al* [30] reported acute treatment-related toxicities that resulted from the combination of radiotherapy and chemotherapy during induction and consolidation. During induction twice daily irradiation with paclitaxel - cisplatin was administered (TCI). TCI resulted in 26% developing grade 3-4 acute toxicity, mainly GI (25%). The G4 acute toxicities were leucopenia. During the consolidation TCI, 8% of the patients had grade 3-4 acute toxicity. This protocol in which paclitaxel was added to the induction and consolidation regimen resulted in a greater percentage of G3 and G4 toxicities. Our results showed much better toxicity profile with majority of the patients had G1 and G2 complications and were managed conservatively well and completed their protocol without serious toxicities threatening their life.

Zapatero *et al*. [31] recorded toxicities encountered after treating their patients with the bladder sparing trimodality therapy in two arms. Grade 3 late GU and GI complications were 5% and 1.3%, respectively. In our study, there was no G3 late toxicities were detected. Khader *et al*. [25] reported 9 out of 14 patients (64.5%) treated by TURBT followed by induction chemotherapy, then irradiation with concurrent platinum-based agents exhibited G1 and/or G2 hematological, GI and GU toxicity.

The survival rates including DFS and OS are important issues when comparing our study results and

those of other series. At a median follow up period of 23.5 months (range 11 to 33), the 2 year DFS was 64% and the estimated 2 year OS was 77.5 %. Ibrahim and his colleagues **[**28] recorded that the 2-year OS and progression free survival (PFS) rates were 67% and 58%, respectively which is less than our study results.

Of the 80 patients studied by Kaufman *et al*. [30], 44 survived, with an OS rate of 67% at 36 months and 56% at 60 months. DFS rate was 73% at 36 months and 71% at 60 months which is comparable with our results. Zapatero *et al* reported at [31] that the 5-year OS were 72% and 60% for the arm I and arm II protocols respectively. The corresponding figures for DFS were 80% and 88%. We must put in consideration the little difference in the design of the Zapatero's study from ours. They excluded patients who did not achieve CR after neoadjuvant chemotherapy.

The 5-year DFS and OS rates for all available patients in the study of Sabaa *et al*. [24] were 68.8% and 59.4%, respectively. Efstathiou and his colleagues [26] reported that the 5, 10, and 15-yr DFS rates were 64%, 59% and 57%, respectively. Five, 10, & 15-yr OS rates were 52%, 35% & 22% respectively. Also, Khosravi-Shahi and Cabezón-Gutiérrez [14] reported that the 5-year OS rates range from 50 to 67% with trimodality treatment.

Conclusion

Concurrent gemcitabine-based CRT after neoadjuvant chemotherapy and TURBT is effective with high response rate, durable local control and acceptable toxicity, which allows patients to preserve their own bladder. However further investigations is needed to confirm these results in larger number in a phase III trial.

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