Selective bladder preserving treatment by radiation therapy concurrent with either paclitaxel and cisplatin or cisplatin alone following a transurethral surgery

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Abstract

Background: There is a debate regarding the optimal chemotherapeutic regimens that can be used concurrently with radiotherapy (Rth) in muscle invasive bladder cancer (MIBC). Taxanes started to be widely used with evidence of response rates improvement when compared to cisplatin. Our aims were to evaluate the tumor response, treatment toxicity, and disease outcome in MIBC patients who treated with concurrent chemo-radiotherapy (CCRTh) either with paclitaxel and cisplatin or cisplatin alone.

Methods: Between July 2007 and December 2010, sixty T2-4a N0 M0 bladder cancer patients were enrolled, of whom 55 were eligible for analysis. We randomized our patients into two groups; group I received CCRTh with weekly cisplatin (n=25) and group II received CCRTh with weekly paclitaxel and cisplatin (n=30). Kaplan-Meier curve used to estimate overall survival (OS) and recurrence free survival (RFS) with log rank test used to assess the significant difference between patients' subgroups.

Results: A durable complete response (CR) was achieved in 80% and 86.7% in group I and II respectively. The 2-year OS and recurrence free survival (RFS) were 76% and 61% for group I, and 85.6% and 67.2% for group II, respectively. Multivariate analysis showed that tumor stage was the only survival predictor (P<0.0001). In both groups, the majority of acute and late toxicities were grade 2 with no treatment-related mortality.

Conclusions: Achieving high initial durable CR rates, with acceptable toxicity in both groups; showed that addition of paclitaxel to cisplatin did not significantly add benefit to the treatment outcome.

Keywords: Bladder cancer, paclitaxel, cisplatin, bladder preservation, concurrent chemoradiotherapy

Introduction

Radical cystectomy (RC) with pelvic lymph node dissection may lead to significant morbidity and affects patients' quality of life (QOL); however it remains the standard treatment approach for muscle-invasive bladder cancer (MIBC) [1,2]. Trimodality bladder-sparing approach; consisting of transurethral resection

(TUR), chemotherapy (CTh) and radiotherapy (RT); induce 50-70% 5 years overall survival (OS) comparable to those of RC with better QOL [3]. Additionally, salvage cystectomy still an available option for local recurrent cases with acceptable operative complication rates, and excellent long-term disease control and survival outcomes [4].

Improvement in radiotherapy techniques such as intensity or volume modulated radiotherapy allow an interesting tumor dose escalation with better tumor control and lesser normal tissue morbidity [5]. Despite that, concurrent administration of chemotherapy with Rth decreased local recurrence rates. It didn't show any evidence of increasing survival, decreasing mortality, or improving in the quality of life [6]. The radiation sensitizing effects of cisplatin are well established and remain a standard of care with cystectomy-free survival rates between 42% and 55% at 5 years, depending on the initial tumor stage [7,8]. The opportunity to safely enhance this effect by simultaneous administration of a second radiation sensitizer such as fluorouracil or paclitaxel has been a goal [9].

Our study aims to evaluate the tumor response, treatment toxicity, and outcome of patients with muscle invasive bladder cancer treated with CCRth with weekly cisplatin and to assess if the addition of paclitaxel to cisplatin improves treatment outcomes for such patients. Additionally, to detect factors which may predict survival in both groups.

Patients and methods

Between July 2007 and December 2010, 60 muscle invasive bladder cancer patients were prospectively recruited and treated with CCRth with cisplatin (Platinol, Bristol-Myers Squibb company) with and without paclitaxel (Taxol, Bristol-Myers Squibb company) concurrently with Rth using linear accelerator 6-15 MV. The protocol was approved by the Institutional Review Board at Assiut University and a written consent was taken from all enrolled patients.

Patient selection

Patients with T2-4a urinary bladder cancer according to the American Joint Committee on Cancer (AJCC) stage [10] and Performance status <2 according to European Cooperative Oncology Group (ECOG) [11] enrolled in our study. Initial evaluation included complete blood count (CBC) and serum chemistry, and creatinine clearance, chest radiography, Abdomeno-pelvic computed tomography (CT) scan, and/or MRI and assessment of bladder capacity. Hemoglobin >10 gm/dl, white blood cells (WBC) >4000/mm³, platelets >100,000/mm³, serum creatinine <2.0 mg/dl, creatinine clearance >60ml/min, serum bilirubin of 2.0 mg%, and bladder capacity >350ml were mandatory. Small residual after second sitting of Maximum transurethral resection of bladder tumor (TURBT) were eligible. Patients were excluded if they have T4b stage, lymph node or distant metastasis, or previously treated with intravesical BCG, chemotherapy or pelvic irradiation.

Non contrast MRI imaging technique

Imaging was performed by using 1.5 Tesla super conducting image (Achieva Philips Health Care) using 16 channel array coil. *Special preparation:* The patient was advised to drink 2 litres of water before imaging by 2 hours to distend the bladder.

Sequences used: Non contrast coronal, axial, sagittal T2w and axial T1.

Treatment protocol

Maximal TURBT was performed in one or more attempts. Completeness of TURBT was assessed according to residual tumor status. Complete TURBT was defined as no residual tumor, whereas incomplete TURBT was defined as macroscopic residual tumor. Patients were randomly assigned into 2 groups; group I (n=25) and group II (n=30). All patients received combined chemoradiation within 4-6 weeks after the maximal TUR, in two phases.

During Phase I, patients received external radiotherapy in the form of 46 Gy/23 fractions/4½ weeks to whole pelvis; including bladder, the proximal urethra and the pelvic lymph nodes; with concurrent chemotherapy either cisplatin or cisplatin-paclitaxel in group I and II respectively. Subsequently, patients with >50% tumor response were shifted to phase II treatment, while Patients with <50% tumor response were considered for cystectomy. Thereafter, patients continue into phase II treated with 20 Gy/10 fractions/2 weeks radiation therapy to the bladder only with 1 cm margin concurrently with the same chemotherapy for each group. By the end of treatment, patients achieved complete response (CR) kept under follow up, while, those with residual tumor considered for radical cystectomy.

Regarding concurrent chemotherapy, in group I patients received weekly cisplatin 40 mg/m² slow I.V infusion over two hours. While, in group II patients received weekly Cisplatin 20 mg/m² and Paclitaxel 60 mg/m², both administered as a one-hour infusion. Paclitaxel was given before Cisplatin to avoid hematological toxicity and proper hydration and antiemetic were used before chemotherapy administration.

Radiotherapy technique

Position

Patients were treated in supine position checked by laser lights. Fixation with thermoplastic shells was used in obese patients and in patients having redundant abdomen. IV contrast was used to localize the bladder. For whole pelvic irradiation (phase I), treatment was given with full bladder to displace the small bowel out of the pelvis. For phase II treatment, the patient was instructed to empty the bladder immediately before the treatment session to ensure that the bladder is inside the target volume. The rectum should be as empty as possible before simulation (may use enema).

Localization

Field arrangement for the proposed target volume was done by computerized planning system or manual method taking in consideration homogeneous distribution shape to the target volume and the tolerance dose to the critical organs; rectum, small intestine, bilateral femoral head.

Bladder target volume

This volume included the whole bladder volume plus 1-1.5 cm margin beyond. This volume shaped using cerrobend blocks.

Pelvic target volume

This volume included the bladder, the prostate and the prostatic

urethra (in men) and the regional lymph nodes (perivesical lymph node, distal hypogastric, external iliac vessels and those within the obturator space). The field margins of planning target volume (PTV) in the cranio-caudal dimension extended from S1-S2 junction to the lower pole of the obturator foramen. In the anterior and posterior pelvic field, PTV widths extended 1.0 cm lateral to the bony margin of the pelvis at its widest point. The anterior border lies 1-2 cm in front of the anterior bladder wall and the posterior border at the mid-rectum. This volume shaped by using cerrobond blocks.

Radiation dose and energy

The radiotherapy course delivered 46 Gy to the pelvic fields, 66 Gy to whole bladder. All doses prescribed at the isocenter, using linear accelerator 6-15 MV. Total dose did not exceed 45 Gy and 50 Gy to the femoral heads and the posterior rectal wall respectively.

Re-evaluation and Follow up

During treatment, weekly evaluation by Complete blood counts was performed before each chemotherapy administration. Additional laboratory investigations were done every 3 weeks included electrolytes, liver function, and kidney functions.

Re-evaluation after phase I and 3-4 weeks after phase II was done by pelvic CT and/or MRI, urine cytology, and TURBT. Patients were considered to have achieved CR if there was no evidence of visible tumor on cystoscopy and both biopsy and urine cytology showed no malignancy. Patients with any residual tumor at the original tumor site or muscle-invasive tumor $\geq$ T2 at a new site were considered candidates for salvage cystectomy.

During CCRT, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 was used for acute toxicity grading [12]. While, for late toxicity The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria was used for assessment. After completing the treatment protocol monthly follow-up visit was done during the first 6 months, then every 2 month during the rest of the first year then every 3 months thereafter. History and physical examination were done at each visit, chest x-ray and abdominal pelvic CT and/ or MRI every 3 months or when indicated, and cystoscopy every 6 months or when indicated.

Statistical methods of analysis

We used IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY) for data management and statistical analysis. Univariate analysis was done using chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis test for continuous variables. The Kaplan-Meier method was used to estimate the median overall survival (OS); which was defined as the time interval between the date of diagnosis and the date of death or last follow-up, disease free survival (DFS); which was defined as the time between treatment end date and the date of documented disease recurrence, death from cancer and/or last follow-up (censored). The comparisons for various endpoints were performed using log rank test and Cox regression analysis

was used to detect predictors of survival.

Results

Among 60 muscle invasive bladder cancer patients, 55 patients (25, group I; 30, group II) were evaluable for response (2 patients died of non-cancer comorbidities shortly after starting treatment, and 3 patients refused to complete treatment). **Table 1** highlights the statistically significant variations in patient characteristics between the two cohorts. Notably, 80% of group I patients were smokers compared to only 33.3% in group II with P value 0.001. Additionally, in group I 64% had 3-5cm tumor size and 40% had stage T2b compared to 60% had <3 cm tumor size and 50% presented with stage T2a in group II with P value 0.003 and 0.04 respectively. Furthermore, completed TUR was achieved in 18 patients (72%) in group I and 20 patients (66.7%) in group II.

Tumor response and salvage treatment

Urologic evaluation after phase I revealed CR in 16 patients (64%) and 23 patients (76.7%) and partial response (PR) in 5 patients (20%) and 5 patients (16.7%) in group I and II respectively. Four patients (16%) and 2 patients (6.7%) had Stable disease (SD) or Progressive disease (PD) in group I and II respectively. Patients achieved CR and PR continue phase II and reevaluation at the end of phase II. At end of treatment; 20 patients (80%) and 26 patients (86.7%) had CR and 1 patients (4%) and 2 patients (6.7%) had PR, in group I and II respectively (**Table 2**) and (**Figures 7** and **8**).

Radio-chemotherapy related toxicity **Table 3**

Early radiation toxicity

Notably, side effects were tolerable, manageable and most of them were hematological, genitourinary (GU) and gastrointestinal (GI) with no life threatening toxicities detected in both groups. Among 55 patients there were no significant difference between group I and II either in the G1/2 or G3/4 acute toxicity. Regarding the hematological toxicity, 15 patients (60%), 20 patients (66.7%) experienced G1/2, while 1 patient (4%), 3 patients (10%) experienced G3/4 in group I and II respectively. Dysuria and frequency were the most frequently observed non hematological toxicities followed by diarrhea. Nine patients (36%) and 11 patients (36.7%) experienced G1/2 and 3 patients (12%), 5 patients (16.7%) experienced G3/4 GU toxicity in group I and II respectively. Additionally, G1/2 GI toxicity developed in 20 patients (80%), 22 patients (73.3%), while 1 patients (4%), 2 patients (6.7%) developed G3/4 in group I and II respectively.

Late Radiation Toxicity

Within a median follow-up of 26 months (range 12 to 28), the patients showed low incidence of severe late complications. Only one patient in each group had late G3 toxicity and no cases reported G4 toxicity. The major complications were related to the GU system where 16 patients (64%) in group I and 13 patients (43.3%) in group II had grade 1/2 toxicity. Notably, there were no treatment-related deaths, and no cystectomies performed

Table 1. Variations in the epidemiological, risk factors, and clinicopathological characteristics between group I (cisplatin treated patients) and group II (cisplatin with paclitaxel treated patients).

Patient characteristic	Parameter	Group I N=25 (%)	Group II N=30 (%)	P-value
Age (years)	Mean	58.8	55.6	--
	≤60	14 (56%)	20 (66.7%)	0.6
	>60	11 (44%)	10 (33.3%)	
Sex	Male	20 (80%)	22 (73.3%)	0.8
	Female	5 (20%)	8 (26.7%)	
Smoking	Smoker	20 (80%)	10 (33.3%)	0.001
	Non-smoker	5 (20%)	20 (66.7%)	
Bilharzias	Positive	16 (64%)	11 (36.7%)	0.08
	Negative	9 (36%)	19 (63.3%)	
Complaint	Hematuria	17 (68%)	24 (80%)	0.9
	Noctnuria	3 (12%)	11 (36.7%)	
	Dysuria	3 (12%)	19 (63.3%)	
	Burning Micturition	8 (32%)	4 (13.3%)	
	Increase Frequency	3 (12%)	13 (43.3%)	
	Pelvic pain	2 (8%)	10 (33.3%)	
ECOG *	PS_0	21 (84%)	25 (83.3%)	0.8
	PS_1	4 (16%)	5 (16.7%)	
Tumor site	Anterior wall	6 (24%)	1 (3.3%)	0.9
	Posterior wall	0 (0%)	4 (13.3%)	
	Lt. Lateral wall	7 (28%)	4 (13.3%)	
	Rt. Lateral wall	5 (20%)	13 (43.3%)	
	Bladder dome	0 (0%)	3 (10%)	
	Bladder neck	1 (4%)	2 (6.7%)	
	Multiple lesions	6 (24%)	3 (10%)	
Tumor size	<3 cm	4 (16%)	18 (60%)	0.003
	3-5 cm	16 (64%)	10 (33.3%)	
	>5 cm	5 (20%)	2 (6.7%)	
Histopathology	TCC*	12 (48%)	14 (46.7%)	0.7
	Sq. C. C.*	8 (32%)	6 (20%)	
	TCC with Sq. differentiation	2 (8%)	8 (26.7%)	
	TCC with glandular differentiation	0 (0%)	2 (6.7%)	
	Adenocarcinoma	2 (8%)	0 (0%)	
	Anaplastic cell carcinoma	1 (4%)	0 (0%)	
Stage	T2a	4 (16%)	15 (50%)	0.04
	T2b	10 (40%)	7 (23.3%)	
	T3a	5 (20%)	6 (20%)	
	T3b-4	6 (24%)	2 (6.7%)	

Continuation of Table 1.

Patient characteristic	Parameter	Group I N=25 (%)	Group II N=30 (%)	P-value
Tumor differentiation	Well differentiated	3 (12%)	4 (13.3%)	0.9
	Moderately differentiated	13 (52%)	14 (46.7%)	
	Poorly differentiated	9 (36%)	12 (40%)	
Previous surgery	TUR	24 (96%)	30 (100%)	0.9
	Partial cystectomy	1 (4%)	0 (0%)	
TUR	Complete	18 (72%)	20 (66.7%)	0.9
	Incomplete	7 (28%)	10 (33.3%)	

ECOG: Eastern Cooperative Oncology Group; TCC: Transitional Cell Carcinoma; Sq.C.C: Squamous cell carcinoma; TUR: Transurethral resection

Table 2. Treatment responses after phase I and II of concurrent chemoradiotherapy among group I (cisplatin treated patients) and group II (cisplatin with paclitaxel treated patients).

	Group I N=25 (%)		Group II N=30 (%)	
	Phase I	Phase II	Phase I	Phase II
CR	16 (64%)	20 (80%)	23 (76.7%)	26 (86.7%)
PR	5 (20%)	1 (4%)	5 (16.7%)	2 (6.7%)
SD and PD	4 (16%)	--	2 (6.7%)	--

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

due to treatment-related toxicity.

Treatment outcome and patterns of failure Table 4

Of the 46 patients who had CR after completion of treatment, 4 patients (20%), 2patients (7.7%) experienced superficial bladder relapse, 3 patients (15%), 2 patients (7.7%) developed muscle-invasive relapse, 2 patients (10%),1 patient (3.8%) developed pelvic recurrence and1 patient(5%),1 patient (3.8%) developed distant metastases in group I and group II respectively. The median time to bladder relapse was 11 and 13 months for group I

Table 4. Different patterns of Failure with concurrent chemoradiotherapy among complete responders of group I (cisplatin treated patients) and group II (cisplatin with paclitaxel treated patients).

Variables	Group I N=20 (%)	Group II N=26 (%)	P-value
Superficial recurrence	4 (20%)	2 (7.7%)	0.9
Muscle invasive recurrence	3 (15%)	2 (7.7%)	
Pelvic recurrence	2 (10%)	1 (3.8%)	
Distant metastasis	1 (5%)	1 (3.8%)

Figure 7. 55 years old patient presented with a malignant bladder mass seen at the left posterolateral wall on MRI axial T2w images (A&B) which proved to be transitional cell carcinoma. First phase CCRT showed partial response on MRI axial T1w image (C) and axial T2w image (D). After the end of treatment there was complete response as seen at axial T2w (E) and T1w (F). The wall thickening seen is post irradiation effect.

Figure 8. 49 years old patient presented with hematuria. On MRI imaging (A&B) coronal and sagittal T2w, a hypo-intense right posterolateral bladder mass is seen compressing and evolving the right ureter resulting in proximal dilatation. After CCRT there was partial remission of the mass as seen on T2w coronal image (C) and T2w sagittal image (D).

and group II, respectively. The median time to distant metastasis was 11 and 12 months for group I and group II, respectively.

There were no significant differences regarding the incidence of superficial recurrences, muscle-invasive relapses, pelvic recurrence and distant metastasis for patients of both groups.

Survival and bladder preservation

The 2-year overall survival was 76% and 85.6% ($P=0.0319$), while the 2-year recurrence free survival was 61% and 67.2% ($P=0.134$) for group I and group II respectively. Subclassifying patients according to the TNM stage showed that patients who have clinical stage T2, the 2-year overall survival rate was 85.7% and 89.2% ($P=0.642$) and the 2-year recurrence free survival rate was 63.5% and 71.3% ($P=0.173$) for group I and group II respectively. For clinical stage T3, the 2-year overall survival rate was 61.4% and 66.7% ($P=0.640$), and the 2-year Recurrence free survival rate was 59.7% and 58.3% ($P=0.624$) for group I and group II respectively (Figures 1-6).

Table 5 showed that however performance status ($P=0.05$), tumor stage ($P<0.0001$), completeness of TUR ($P=0.04$), and response to induction treatment ($P=0.02$) were the factors significantly correlated with a superior OS. Multivariate analysis (MVA) showed that tumor stage was the only factor significantly associated with OS ($P<0.0001$).

Discussion

Both induction regimens either cisplatin alone or in combination with paclitaxel had high response rate, high rate of bladder preservation, and acceptable toxicity, however the addition of paclitaxel to cisplatin did not add significantly to the treatment outcome.

Tri-modality therapy (TMT) approach including maximal TUR followed by concurrent chemo-radiotherapy is the most studied bladder-sparing modalities. The rationale for CCRT is that certain cytotoxic agents have the ability to sensitize cancer cells to radiation and inhibit its repopulation during radiotherapy, thus increasing local cure rates. Furthermore, since approximately 10% of superficially infiltrating tumors and 50% of muscle-invasive tumors already develop occult metastases, systemic chemotherapy may help to eradicate them [13].

Figure 1. Overall survival for both groups.

Table 3. Reported toxicities with concurrent chemoradiotherapy among group I (cisplatin treated patients) and group II (cisplatin with paclitaxel treated patients).

Variables	Group I N=25 (%)				Group II N=30 (%)			
	G1	G2	G3	G4	G1	G2	G3	G4
Early toxicity								
Anemia	3 (12%)	5 (20%)	0 (0%)	0	6 (20%)	5 (16.7%)	1 (3.3%)	1 (3.3%)
Leucopenia	4 (16%)	2 (8%)	1 (4%)	0	3 (10%)	2 (6.7%)	1 (3.3%)	0
Thrombocytopenia	1 (4%)	1 (4%)	0 (0%)	0	3 (10%)	2 (6.7%)	0	0
Diarrhea	10 (40%)	3 (12%)	1 (4%)	0	11 (36.7%)	5 (16.6%)	1 (3.3%)	0
Vomiting	12 (48%)	5 (20%)	0	0	13 (43.3%)	7 (23.3%)	2 (6.7%)	0
Proctitis	15 (60%)	3 (12%)	0	0	10 (33.3%)	2 (6.7%)	0	0
Dysuria	8 (32%)	8 (32%)	2 (8%)	0	9 (30%)	8 (26.6%)	3 (10%)	0
Frequency/urgency	6 (24%)	5 (20%)	2 (8%)	1 (4%)	10 (33.3%)	7 (23.3%)	4 (13.3%)	1
Radiation dermatitis	5 (20%)	1 (4%)	0	0	4 (13.3%)	1 (3.3%)	0	0
Increased creatinine	5 (20%)	1 (4%)	0	0	3 (10%)	1 (3.3%)	0	0
Increased bilirubin	0	0	0	0	0	0	0	0
Increased liver enzymes	0	0	0	0	0	0	0	0
Allergy	1 (4%)	0	0	0	2 (6.7%)	0	0	0
Hearing impairment	1 (4%)	0	0	0	1 (3.3%)	0	0	0
Cardiovascular arrhythmia	0	0	0	0	1 (3.3%)	1 (3.3%)	0	0
Late Toxicity								
Proctitis	4 (16%)	1 (4%)	0	0	3 (10%)	1 (3.3%)	0	0
Dysuria	6 (24%)	4 (16%)	1 (4%)	0	6 (20%)	3 (10%)	1 (3.3%)	0
Frequency/urgency	15 (60%)	2 (8%)	0	0	9 (30%)	2 (6.7%)	0	0
Increased creatinine	2 (8%)	1 (4%)	0	0	1 (3.3%)	1 (3.3%)	0	0

Table 5. Univariate and multivariate cox regression analysis for estimation of survival predictors.

Variable	Univairant HR (95% CI)	P-value	Multivariant HR (95% CI)	*P-value
Age >60 vs. ≤ 60y	1.2 (0.6-2.3)	0.6	0.9 (0.7-1.6)	0.3
Female vs. Male	0.98 (0.5-2)	0.97	0.85 (0.5-1.6)	0.4
ECOG 1 vs. 0	2.4 (1-5.9)	0.05	2.3 (0.9-4.8)	0.1
TNM Stage T3-4 vs. T2	15.4 (9.4-22.7)	<0.0001	17.2 (10.2-25.7)	<.0001
TUR incomplete vs. complete	2.3 (1.2-4.7)	0.02	1.4 (0.6-3)	0.6
Induction response	2 (1.2-3.2)	0.04	1.2 (0.8-2.1)	0.2
Incomplete vs. complete				

ECOG: Eastern Cooperative Oncology Group; TUR: Transurethral resection

Cisplatin is the main chemotherapeutic agent used in bladder preservation protocols [14]. Notably, cisplatin induced good results in terms of cancer control and bladder preservation. Over the years, the researchers started to use combination therapy instead of single agent cisplatin with noticed significantly higher CR rate and longer overall survival rates. The optimum combination of chemotherapeutic drugs needs to be identified not only to improve efficacy but also to minimize toxic effects related to treatment [9].

In our study the rate of CR in group I and II was 80% and 86.7% respectively which is comparable to previous studies [15-24], while, other studies showed lower CR rate and this is explained by that the majority of our patients were T2. [9,25-31].

Bladder cancer is a disease of elderly so treatment toxic effects are a concern. The treatment was tolerable with no need for cystectomy subsequent to treatment related toxicities in both groups. The acute toxicities were usually self-limiting or manageable. However, G3/4 acute toxicities reported among both groups were comparable to previous studies [16,21,24]. G3/4 toxicities reported in cisplatin-paclitaxel group were lower than the studies that used twice-daily radiotherapy with adjuvant chemotherapy [31,32]. Additionally, we reported a low incidence of late pelvic toxicity which is similar to previous studies. Notably, G3 late toxicity in cisplatin-paclitaxel group was lower than that reported by Mitin and his colleague. However this is explained by using hyper fractionated radiotherapy technique [9].

Figure 2. Recurrence free survival for both groups.

Figure 5. Recurrence free survival for T2 for both groups.

Figure 3. Overall survival for T2 for both groups.

Figure 6. Recurrence free survival for T3 for both groups.

Figure 4. Overall survival for T3 for both groups.

The 5-year survival rate for definitive radiation therapy for muscle invasive bladder cancer was ranging from 30% to 40%. However, increasing patients' survival is the primary goal of the bladder-sparing approach. Concomitant administration of chemotherapy with radiation therapy only reduce local relapse rates without evidence of increasing survival, decreasing mortality, or improving in the quality of life [6]. Among our groups both OS and RFS results was similar to previously published

studies [7,19,33-35]. Additionally, the OS of cisplatin-paclitaxel group was comparable to the early reports of RTOG-99-6 [36].

The risk of local recurrence after achievement of CR ranging from 14% to 43% at 5 years. Approximately 60% of local failures are superficial and 40% are muscle invasive [14,21,24,25,34,37-40]. The rate of local recurrence in our study was within the same range of the previously reported studies. Although, it was reported that the majority of patients developed local recurrences within the first 12-24 months after treatment completion and so patients need to be closely monitored with repeated cystoscopies during this period [15,30,37,39,41]. Follow-up should not be limited to the first 2 years as some series reported local recurrences as late as 5-10 years after treatment and some of these patients still had the chance for salvage surgery [15,39,42].

Selection of ideal candidates and the optimal regimens are main concern in bladder-preserving approach. Thus, several studies were done to identify the predictors for ideal candidates for tri-modality treatment. Similar to previous studies [13-15,18,21,24,33,43,44], our study showed that completeness of TUR, PS, response to induction treatment and TNM stage were the main factors affecting survival. However, multivariate analysis showed that TNM staging was the main survival predictor. According to The International Consultation on Urological Diseases, European Association of Urology International, and Consultation on Bladder Cancer, patients with early-stage T2

disease without any evidence of hydronephrosis, carcinoma in situ (CIS), and tumor invasion into the prostatic stroma are the best candidate for bladder preservation [1]. Regarding the optimal chemotherapeutic regimens, cisplatin and 5-FU still recommended by many physicians based on its radio-sensitizing activities and acceptable toxicities [38]. Recently, taxanes and gemcitabine in combination with platinum are widely used as a neoadjuvant, concurrent or adjuvant settings with evidence of improvement in response rates compared with platinum monotherapy [45].

Conclusion

Up to our knowledge this is the first randomized study that compared cisplatin with or without taxanes among Egyptian urinary bladder patients. Currently, according to our study in addition to previously published studies, there is no clear clue support one chemotherapy agent over the other with no definite recommendations for the best combination chemotherapy in TMT. However, cisplatin still the cornerstone in treating muscle invasive bladder cancer patients outside clinical trials, biological agents such as trastuzumab are currently under evaluation to be used concurrently with radiation therapy. Further phase III trials should be done to compare between different bladder preservation protocols to achieve longer patients' survival and higher quality of life.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors shared in research design and conduction and analysis of data. The corresponding author (Essa HH) wrote the paper and had primary responsibility for final content. All authors read and approved the final manuscript.

Acknowledgement

The authors thank the patients who consented to participate in this study and their families and carers. We also thank all the colleagues who have collaborated in this study and are not included in the list of authors.

Publication history

Editors: Jianxun Song, Penn State University, College of Medicine, USA. Satyendra Kumar, University of Illinois at Chicago, USA.

Received: 06 April 2016 Revised: 04 May 2016

Accepted: 02 June 2016 Published: 07 June 2016

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Citation:

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