Concurrent chemoradiotherapy with weekly cisplatin in muscle-invasive bladder cancer

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Abstract: Background and aim: Bladder cancer is the 7th most common cancer in men and the 17th most common in women worldwide; the aim of our study was evaluation of the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) with weekly cisplatin in muscle-invasive bladder cancer patients (MIBC). **Patients and Methods:** Twenty five patients with **MIBC** were treated by CCRT with weekly cisplatin at Assiut University Hospital Between (2012 and 2014). The dose of cisplatin was set at 40 mg/m^2**. Results**: The patients range in age from (40-73) years, median age was 57 years and 48% of them ≥ 60 years. Male is significantly affected more than female (23 males and 2 females). Transitional cell carcinoma TCC was the most predominant histological type in 92% of patients; 56% of patients were grade II and 72% of patients were stage III**.** Response to treatment was assed in 23 patients with complete response rate in 65% of patients while partial response and disease progression in 26% and 9% of patients respectively and the 2-year disease free survival was 68%. Acute treatment toxicity mainly Grade 3 hematological and, genitourinary side effects in 13% and 8% of patients respectively. **Conclusions**: chemoradiation with weekly cisplatin seams to be a good treatment option especially in elderly patients with acceptable response rate and limited GU and hematological toxicity.
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Key words: chemoradiotherapy, weekly cisplatin, muscle-invasive bladder cancer

1. Introduction:

Bladder cancer is the 7th most common cancer in men and the 17th most common in women worldwide [(1).] Radical cystectomy is the standard therapy for these patients with an expected 5-year survival of 45–60%. However, radical surgery comes at the cost of long-term morbidity secondary to urinary diversion techniques [(2)].

As an organ-preserving treatment alternative to radical surgery for muscle-invasive bladder cancer, a trimodality therapy (TMT) approach that includes initial maximal transurethral tumor resection of the bladder tumor (TURBT) followed by radiotherapy combined with various forms of neoadjuvant, concurrent, and adjuvant chemotherapy protocols has been tested in series at single institutions and in prospective clinical trials by cooperative groups, such as the Radiation Therapy Oncology Group (RTOG), over several decades. With this approach, radical cystectomy is reserved as a salvage option for patients with incomplete responses to (induction) chemoradiotherapy or with invasive local recurrence [(3)].

A recent systematic review of all available retrospective and prospective series and studies of TMT for muscle-invasive bladder cancer confirmed cancer-specific and overall survival rates in the range of 50% to 82% and 36% to 74%, respectively, with salvage cystectomy restricted to 25% to 30% of patients [(4)].

Mak *et al.* showed that patients age 75 years and older had excellent compliance with radiotherapy and similar bladder-preservation and disease-free survival rates compared with younger patients, indicating that elderly patients, who are often not well suited for radical surgery, are excellent candidates for a curative bladder-preservation approach [(5)].

Inclusion of molecular markers that predict response and diffusion-weighted magnetic resonance imaging, to monitor response to TMT may also help to improve patient selection and management [(6, 7)].

To date, the current radiation protocol for bladder preservation includes external-beam RT (either once daily or twice daily) to the bladder and limited pelvic lymph nodes to an initial of 40 Gy and a further to 54 Gy to the whole bladder with a further boost (which incorporates all TUR and radiographic information) to a total dose of 64–65 [(8)].

New treatment techniques, such as image-guided and intensity-modulated radiotherapy as well as interstitial radiotherapy in selected patients (with unifocal, small bulk disease) may allow dose escalation with the expectation of further reducing toxicity and improving tumor response and long-term local control [(9, 10)].

Concurrent cisplatin is currently used in most protocols as a radiosensitizing drug in those with adequate renal function. Recently, a regimen using concurrent fluorouracil and mitomycin in addition to radiotherapy demonstrated benefit in a randomized phase III trial [(11)].

Multimodal treatment for bladder preservation can be offered to patients with an acceptable toxicity. Except in studies using neoadjuvant or adjuvant chemotherapy, where toxicity seems higher, the rate of acute grade 3-4 toxicities are ranged from 10% to 36%, while the majority (80-90%) of patients did complete the entire course of treatment. The main toxicities are haematologic, GI, and genitourinary (GU). Neuropathy may be reported in cases of cisplatin-based concurrent chemotherapy. The BC2001 trial reported neither an increase in grade 3-4 toxicity with concurrent chemotherapy compared with RT alone nor a decrease in RT completion rates caused by toxicity [(12)].

No treatment concept in oncology is without risks and limitations. Patients who achieve an initial complete response should be encouraged to undergo lifelong surveillance cystoscopies with prompt salvage therapy on recurrence of disease. Most patients will in fact remain free from muscle-invasive recurrences; however, non-muscle-invasive recurrences in the retained bladder occurred in up to 36% of patients after 10 years in the pooled analysis of the RTOG trials [(3)].

Although these recurrences can be managed conservatively with TURBT and intravesical therapy, patients remain at risk of requiring delayed cystectomy [(13)]. (Another concern is that orthotopic neobladder reconstruction (although feasible) after pelvic radiotherapy is often not advocated by surgeons because of a higher risk of functional complications [(14)].

2. Patients and methods:

Eligibility criteria:

Eligible patients had histologically confirmed T2-3, N0, M0 transitional cell carcinoma (TCC) of the bladder, WHO performance status of ≤ 2, serum creatinine of less than 1.5 × upper limit of normal (ULN), hemoglobin greater than 10 g/dL; platelets greater than 100,000/μL; WCC greater than 2,000/μL, 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:

Patients with poor bladder function (defined as any WHO bladder symptom score of 3, as two or more bladder symptom scores of 2, or as a documented bladder capacity of less than 200 mL) were excluded from the study. Other exclusion criteria were abnormal biochemistry (i.e., bilirubin > 1.3 × ULN, alkaline phosphatase > 5 × ULN, AST/ALT > 5 × ULN), more than one intravesical instillation of chemotherapy or immunotherapy, or previous administration of systemic chemotherapy or pelvic radiotherapy. Patients with prior malignancy current or recent pregnancy, or inability to use contraception during and for 3 months after completion of treatment were also excluded. Patients underwent transurethral resection of their bladder tumor before chemo-radiotherapy. Pre radiotherapy 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.

Treatment:

Twenty five patients with MIBC were treated by (CCRT) with cisplatin at Assiut University Hospital Between (2012 and 2014). The dose of cisplatin was set at 40 mg/m^2. Serum creatinine greater than140 micromol/L Delay chemotherapy, recheck in 1 week, if Serum creatinine still greater than140micromol/L after one week chemotherapy delay Discontinue protocol.

Radiation therapy was delivered via 15 MV linear accelerator, bladder and pelvic lymphatics were treated via a four-field box technique to a total dose of 4500 cGy given over a period of 5 weeks (180cGy daily fractions in 5 consecutive days). Planned target volume (PTV) consisted of the bladder and tumor with 2-cm margin. Re-staging cystoscopy performed 4 weeks after the completion of CCRT directed additional therapy with delivery of irradiation (up to 6400 cGy) in a proportion of patients who had CR. A complete pathological response required absence of any macroscopically and microscopically viable tumor in addition to negative urine cytology. Empty bladder was a mandatory condition for each fraction. Physical examination, total blood counts, kidney function tests were done weekly and side effects were recorded once a week according to the common toxicity criteria (CTC) v2.0.

Evaluation and follow-up:

The first cytoscopic and radiological evaluation was done3 months after the end of chemoradiotherapy. Cystoscopy was performed every 4–6 months in the first 2 years, thereafter every 6 months for an additional 3 years and if clinically indicated. Radiological evaluation was done every 3 months for the first 2 years and thereafter every 6 months or if clinically indicated.

Statistical analyses:

The therapeutic efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 every two cycles. The efficacy was evaluated as complete remission (CR), partial responses (PR), stable disease (SD), and progressive

disease (PD). The progression-free survival (PFS) was defined as the time elapsed between combined treatment initiation and tumor progression, loss to follow-up, or death during the combination therapy or maintenance therapy. The National Cancer Institute's Common Terminology Criteria for Adverse Events was applied in this study.

Design of the study:

This study was a prospective; single institution study. The Ethics Committee in Faculty of Medicine, Assiut University, granted protocol approval and all patients signed an informed consent before the initiation of any treatment.

3. Results:

Twenty five patients of histological proven primary urinary bladder tumor were managed during the period from (2012- 2014) by concurrent chemoradiotherapy at Assiut University Hospital. The patients range in age from (40-73) years and median age was 57years. There were 23 males and 2 females, male: female ratio was11.5:1(male is significantly affected more than female). As regard pathology: transitional cell carcinoma TCC was the most predominant histological type 92% and 8% squamous cell carcinoma; 36% of patients were grade III, 56% of patients were grade II and unknown grade in 8% of patients. As regard stage; 28% of patients were stage II while 72% of patients were stage III **Table (1).** Response to treatment was assed in 23 patients with complete response rate in 65% of patients while partial response and disease progression in 26%and 9% of patients respectively **Figure (1)** and the 2-year disease free survival was 68%.

Acute treatment toxicity (assessed by NCI criteria) mainly grade 1/2 toxicities while grade 3 adverse events were primarily hematological and, genitourinary side effects in 13% and 8% of patients respectively **Table (2).**

Table (1): Patients characteristic

	No. (n= 25)	**%**
Age range:	Median age 57 years	
< 60	13 (52.0%)	
≥ 60	12 (48.0%)	
Gender:		
Male	23	92%
Female	2	8%
Performance status:		
0-1	9	36%
2	16	64%
Stage:		
T2a-bN0M0	7	28%
T3a-bN0M0	18	72%
Tumor Histology:		
Transitional cell	23	92%
Squamous cell	2	8%
Tumor grade:		
Grade II	14	56%
Grade III	9	36%
Unknown	2	8%

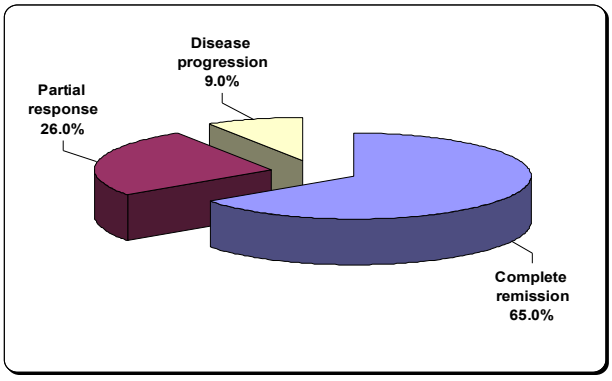

Figure (1): Treatment response in bladder cancer

Table (2): Acute toxicities after concurrent chemoradiotherapy for bladder

Toxicity	**G1**	**G2**	**G3**
Neutropenia	0 (0%)	3 (13%)	2 (9%)
Anemia	2 (9%)	3 (13%)	1 (4%)
Vomiting	6 (26%)	3 (13%)	0 (0%)
Diarrhea	6 (26%)	2 (9%)	0 (0%)
Proctitis	5 (22%)	2 (9%)	0 (0%)
Dysuria	5 (22%)	9 (39%)	1 (4%)
Frequency/ Urgency	3 (13%)	4 (17%)	1 (4%)

4. Discussion:

Bladder preservation appears to be a viable alternative to radical cystectomy in patients who may be poor surgical candidates or in those who may opt not to undergo radical cystectomy [15].

The complete response rate in our study was slightly higher than that reported by Aboziada [16] who reported a response rate of 60% with concurrent chemoradiotherapy with weekly Cisplatin while it was lower than that reported with other studies with concurrent weekly Gemcitabine, Cisplatin + 5-FU or Cisplatin + paclitaxel [17-19] and this could be attributed to a higher percentage of T3 stage in our study , differences in chemotherapy and radiation regimens and the use of newadjuvant and adjuvant chemotherapy in the comparative studies **Table (3)**.

Table (3): Published series of trimodality therapy for bladder preservation

Study	Design and follow-up	Stage	No. of patients	Concomitant chemotherapy	RT	CR rate
Zapatero *et al.,* 2012 [17]	Split Retrospective (60 mo)	T2–T4a N0	39	Cisplatin weekly (paclitaxel: *n*5) =	64.8 Gy ST BID: *n*24 =	80%
Choudhury *et al.,* 2011 [18]	Continuous Phase 2 (36 mo)	T2–T3 N0/Nx	50	Gemcitabine weekly	52.5 Gy in 20	82% (88%)
Aboziada *et al.,* 2009 [16]	Split Retrospective (18 mo)	T2–T3b N0	50	Cisplatin weekly	66 Gy ST	60%
Peyromaure *et al.,* 2004 [19]	Split Retrospective (36.3 mo)	T2N0/ Nx	43	Cisplatin + 5-FU x2	24 Gy in 8 BID	74.4%
In our study	Split Retrospective (24 mo)	T2–T3b N0	25	Cisplatin weekly	64 Gy	65%

Acute grade 3 adverse events were primarily hematological and, genitourinary side effects in 21% of patients and this agree with what reported in cisplatin-based CCRT which ranged between 20% to 25 % and lower than studies using neoadjuvant or adjuvant chemotherapy, where toxicity seems higher [20-26].

CCRT with weekly cisplatin seams to be a good treatment option especially in elderly patients (as 48% of patients in our study ≥ 60 years) with acceptable response rate and limited GU and hematological toxicity.

Based on the fact that no treatment concept in oncology is without risks and limitations so patients who achieve an initial complete response should be encouraged to undergo lifelong surveillance cystoscopies with prompt salvage therapy on recurrence of disease. Recurrences can be managed conservatively with TURBT and intravesical therapy, but patients remain at risk of requiring delayed cystectomy and the orthotopic neobladder reconstruction (although feasible) after pelvic radiotherapy is often not advocated by surgeons because of a higher risk of functional complications.

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