Bladder preservation with conformal radiotherapy using a simultaneous boost with concurrent cisplatin in patients with muscle-invasive bladder cancer

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Abstract:

Background: The estimated annual incidence of bladder cancer in Egypt is 10,655 cases, accounting for 7.9% of all newly diagnosed cancers. Sharkia population exceeds 8 million with only a few radiotherapy machines available, in addition, the global coronavirus (COVID-19) pandemic, therefore, shorter overall treatment duration would be more convenient for the patient quality of life.

Purpose: The aim of this study is to evaluate treatment outcome of bladder preservation with conformal radiotherapy using a simultaneous boost with concurrent cisplatin in patients with muscle-invasive bladder cancer (MIBC).

Materials and methods: From May 2021 to April 2022, 34 patients with muscle-invasive transitional cell bladder cancer, T2–3 N0 M0 were treated with maximum transurethral resection of bladder tumor (TURBT), followed by conformal hypofractionated radiotherapy in a dose of 2.4 Gy to the pelvis in the morning and a simultaneous radiotherapy boost in the evening in a dose of 1.33 Gy to the whole bladder for all 15 days of treatment (36 Gy to the pelvis and 20 Gy to whole bladder) with a weekly Cisplatin dose of 30 mg/m^2. Treatment outcome was assessed by response and toxicity.

Results: All 34 patients with a median age of 57 ± 6.64 years completed their treatment regimen. After 3 months of therapy, 26 patients (76.5%) had an overall response, whereas 8 patients (23.5%) showed no response. Grade 3 anemia was prominent in 3 patients (8.8%), whereas, acute grade 3 cystitis persisted in 5 patients (14.7%). There were no reports of life-threatening complications or grade 4 toxicity.

Conclusions: Conformal radiotherapy using a simultaneous boost with concurrent cisplatin in patients with muscle-invasive bladder cancer is a shortened and acceptable alternative to the prolonged 6-6.5 weeks radiotherapy protocol in T2–3 N0 M0 bladder cancer. Absence of hydronephrosis and complete TUR are of better outcome.

Recommendation: Other radiosensitizers can be experimented and enrollment of larger number of patients can be of better significance. In addition, new protocols using node-positive disease could be further studied over extended periods with documentation of local control and survival.

Key words: Bladder preservation- simultaneous boost- cisplatin

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Introduction:

In Egypt, bladder cancer is the third most common cancer and the third most leading cause of cancer death in 2020. The estimated annual incidence of bladder cancer in Egypt is 10,655 cases, accounting for 7.9% of all newly diagnosed cancers. The estimated annual deaths in Egypt of 6,170 cases, accounting for 6.9% of all cancer deaths [1]. In Egypt, over 90% of cancers

arising in the bladder are transitional cell carcinomas (TCCs) [2]. Hematuria and burning micturition are the most common presenting complaints seen in > 80% of the patients [3].

Although radical cystectomy with bilateral pelvic lymph node dissection has been the gold standard management for muscle invasive bladder cancer (MIBC), organ preservation regimen using selective trimodality therapy are emerging as feasible proven alternative in a subset of patients. Selective trimodality therapy has been developed to improve quality of life (QOL) of patients who want to maintain urinary function without a diversion and those who are not candidates for surgery [4].

Since the α/β for bladder cancers generally indicates low fractionation sensitivity (mostly, α/β = 10 Gy), hypo-fractionated radiotherapy approaches using larger dose per fraction than the conventional 1.8-2 Gy have been investigated [5]. Hypofractionated chemoradiation is an effective and well-tolerated treatment for bladder cancer. In fact, hypofractionation appears to provide better local disease control than conventional fractionation [6].

Sharkia population exceeds 8 million with only a few radiotherapy machines available [7], in addition, the global coronavirus (COVID-19) pandemic had profound and difficult implications for the practice of radiation oncology. Hence, shorter overall treatment duration would be more convenient for the patient quality of life, which could be even more important for the typical bladder cancer population which can be frail and/or elderly. Moreover, from a cost-effectiveness perspective, a shorter regimen has the potential to decrease the cost per episode of care, relative to conventional treatments [8].

We aimed to assess treatment outcome, in terms of toxicity, of transurethral resection of bladder tumor (TURBT) followed by hypofractionated radiotherapy using a simultaneous boost with weekly cisplatin as a radiosensitizer in an attempt of selected bladder preservation for patients with muscle invasive bladder cancer.

Patients and Methods:

Patient Selection

This prospective study enrolled 34 patients with muscle-invasive transitional cell bladder cancer, over a period of 12 months from May 2021 to April 2022. All patients underwent maximal transurethral resection of bladder tumor (TURBT) and cystoscopic assessment in urology department then sent for histopathology in pathology department. Patients received conformal hypofractionated radiotherapy using a simultaneous boost with concurrent weekly cisplatin as a radiosensitizer at the Clinical Oncology and Medical Oncology Departments, Zagazig University Hospitals.

In our study, we recruited patients with primary carcinomas of the bladder and histological evidence of muscularis propria invasion, AJCC clinical stages T2–3, N0 M0 [9]. Previous systemic chemotherapy, pelvic radiotherapy, and those with poor bladder function were not permitted in the study. The protocol was approved by institutional review boards before starting the study.

Each patient was evaluated by chest radiograph, abdomen-pelvic magnetic resonance imaging (MRI), bone scan, and performance status ≤ 2 according to ECOG scoring system. Patients underwent complete blood count, and kidney and liver function tests, and those with hemoglobin ≥ 10 mg/dl, and absolute neutrophil count of ≥1500/ml, a platelet count of > 100,000/mm^3, a serum creatinine of 1.5 mg% or less, a serum bilirubin 1.3 time of ULN, were included in current study.

Radiation Therapy

All patients were planned through CT simulator based planning with isocentric technique. Treatment began within 8 weeks after transurethral resection and endoscopic assessment. Patients were treated with 3-D conformal hypofractionated radiotherapy in a dose of 2.4 Gy to the pelvis in the morning and a simultaneous radiotherapy boost in the evening in a dose of 1.33 Gy to the whole bladder for all 15 days of treatment (36 Gy to the pelvis and 20 Gy to whole bladder). The minimal interval between treatment sessions was 6 hours. Weekly Cisplatin (30 mg/m^2) was administered to all patients. Complete blood cell counts and renal function tests were performed weekly.

Response and Toxicity Assessment

All patients were evaluated four weeks after completion of therapy with cystoscopy, contrast-enhanced abdomen/pelvis CT, and chest X-ray. Assessment of response to the treatment was done using the new response evaluation criteria in solid tumors, revised RECIST guidelines version 1.1 [10].

Treatment-related acute toxicities in the form of hematological (anemia, neutropenia, and thrombocytopenia) and non-hematological toxicities was assessed weekly during treatment, on the final day of treatment, and for the first three months after completion of treatment. Acute toxicities were expressed by using the RTOG acute radiation scoring criteria.

Results:

34 patients with a median age of 57 ± 6.64 years completed their treatment regimen. 29 (85.3%) patients were >50 years, supporting the evidence of elderly predisposition in bladder cancer, with 28 (82.4%) male patients. Grade 3 tumors ranked the most with 16 (47.1%). The majority of patients had tumor size of <=3cm, cT2, absent hydronephrosis, 18 (52.9%), 21 (61.8%) and 26 (76.5%) respectively. Complete TUR was endoscopically done in 20 (58.8%) of patients (Table 1).

After 3 months of therapy, 26 patients (76.5%) had an overall response, whereas 8 patients (23.5%) showed no response. 5 (14.7%) showed stable disease, whereas, 3 (8.8%) showed progressive disease in the form of 2 local progression and 1 bone metastasis (Table 2). 22 patients of the 26 responders were >50 years and the

same number were males; however, both were unsignificant. 20 patients of the 26 responders were cT2 tumors with statistical significance of 0.002. Statistical significance was, as well, correlated to hydronephrosis and extent of TUR, with 0.009 and <0.001, respectively (Table 3).

Hematological toxicity recorded after 3 months was grade 3 anemia, leukopenia, thrombocytopenia in 3 (8.8%), 2 (5.9%) and 1 (2.9%) of patients, respectively. Thus revealing that the low-dose cisplatin caused no toxicity (Table 4).

Non-hematological toxicity documented was local grade 3 dermatitis in only 2 (5.9%) patients. In addition, persistent grade 3 cystitis in 5 patients (14.7%). Grade 3 enteritis and proctitis were 3 (8.8%), 2 (5.9%) and 1 (2.9%) of patients, respectively. There were no reports of life-threatening complications or grade 4 toxicity (Table 5).

Table 1: Patient Demographics

Age (years)					
N	**Mean**	**Std. Deviation**	**Median**	**Minimum**	**Maximum**
34	57.0000	6.64238	57.0000	43.00	71.00
Variable	**Frequency**	**Percent**		**Cumulative Percent**	
Age group					
<=50 years	5	14.7		14.7	
>50 years	29	85.3		100.0	
Total	34	100.0			
Sex					
Male	28	82.4		82.4	
Female	6	17.6		100.0	
Total	34	100.0			
Tumor grade					
G1	4	11.8		11.8	
G2	14	41.2		52.9	
G3	16	47.1		100.0	
Total	34	100.0			
ECOG PS					
ECOG 0	12	35.3		35.3	
ECOG 1	16	47.1		82.4	
ECOG 2	6	17.6		100.0	
Total	34	100.0			
Tumor size					
<=3cm	18	52.9		52.9	
>3cm	16	47.1		100.0	
Total	34	100.0			
cT					
cT2	21	61.8		61.8	
cT3	13	38.2		100.0	
Total	34	100.0			
Hydronephrosis					
Absent	26	76.5		76.5	
Present	8	23.5		100.0	
Total	34	100.0			
TUR					
Complete	20	58.8		58.8	
Incomplete	14	41.2		100.0	
Total	34	100.0			

Table 2: Response

Variable	Frequency	Percent	Cumulative Percent
Response			
OAR	26	76.5	76.5
NR	8	23.5	100.0
Total	34	100.0	
Response			
CR	20	58.8	58.8
PR	6	17.6	76.5
SD	5	14.7	91.2
PD	3	8.8	100.0
Total	34	100.0	

Table 3: Response according to patient demographics

Variable	Response (number, %)		Total	P value
	OAR	NR		
Age group				
<=50 years	4 (80)	1 (20)	5 (100)	1.000
>50 years	22 (75.9)	7 (24.1)	29 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
Sex				
Male	22 (78.6)	6 (21.4)	28 (100)	0.609
Female	4 (66.7)	2 (33.3)	6 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
Tumor grade				
G1	4 (100)	0 (0)	4 (100)	0.163
G2	12 (85.7)	2 (14.3)	14 (100)	
G3	10 (62.5)	6 (37.5)	16 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
ECOG PS				
ECOG 0	10 (83.3)	2 (16.7)	12 (100)	0.143
ECOG 1	10 (62.5)	6 (37.5)	16 (100)	
ECOG 2	6 (100)	0 (0)	6 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
Tumor size				
<=3cm	16 (88.9)	2 (11.1)	18 (100)	0.110
>3cm	10 (62.5)	6 (37.5)	16 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
cT				
T2	20 (95.2)	1 (4.8)	21 (100)	0.002
T3	6 (46.2)	7 (53.8)	13 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
Hydronephrosis				
Absent	23 (88.5)	3 (11.5)	26 (100)	0.009
Present	3 (37.5)	5 (62.5)	8 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	
TUR				
Complete	20 (100)	0 (0)	20 (100)	<0.001
Incomplete	6 (42.9)	8 (57.1)	14 (100)	
Total	26 (76.5)	8 (23.5)	34 (100)	

Table 4: Hematological Toxicity

Variable	Frequency	Percent	Cumulative Percent
Anemia			
Grade 0	8	23.5	23.5
Grade 1	20	58.8	82.4
Grade 2	3	8.8	91.2
Grade 3	3	8.8	100.0
Total	34	100.0	
Leukopenia			
Grade 0	14	41.2	41.2
Grade 1	14	41.2	82.4
Grade 2	4	11.8	94.1
Grade 3	2	5.9	100.0
Total	34	100.0	
Thrombocytopenia			
Grade 0	10	29.4	29.4
Grade 1	15	44.1	73.5
Grade 2	8	23.5	97.1
Grade 3	1	2.9	100.0
Total	34	100.0	

Table 5: Non-hematological Toxicity

Variable	Frequency	Percent	Cumulative Percent
Dermatitis			
Grade 0	7	20.6	20.6
Grade 1	20	58.8	79.4
Grade 2	5	14.7	94.1
Grade 3	2	5.9	100.0
Total	34	100.0	
Enteritis			
Grade 0	8	23.5	23.5
Grade 1	15	44.1	67.6
Grade 2	8	23.5	91.2
Grade 3	3	8.8	100.0
Total	34	100.0	
Proctitis			
Grade 0	5	14.7	14.7
Grade 1	17	50.0	64.7
Grade 2	10	29.4	94.1
Grade 3	2	5.9	100.0
Total	34	100.0	
Cystitis			
Grade 1	23	67.6	67.6
Grade 2	6	17.6	85.3
Grade 3	5	14.7	100.0
Total	34	100.0	

Discussion:

Several studies adapted hypofractionated doses of 50 to 55 Gy in 4 weeks ranging from 2.25Gy/fraction to 2.75 Gy/fraction over 4 weeks after TUR in T1-4a N0 M0 with results showing better complete response and survival rate, in addition to favorable toxicity profiles in comparison to the standard conventional 6-week schedule [11,12], however, some reserved this regimen for elderly, unfit or those with poor performance status [13]. Addition of radiosensitizers to hypofractionated radiotherapy protocols in muscle-invasive bladder cancer, allowed bladder preservation with acceptable response, local control and toxicity [14-16].

Moreover, recent studies emphasized that addition of a simultaneous boost not only provides higher local control with acceptable toxicity, but as well, condenses the overall treatment time [17,18].

26 (76.5%) patients presented with no hydronephrosis whereas Lotte enrolled 97 (82%) patients thus giving higher complete response 87% in contrast to 58.8% in this study, in addition to 9 (8%) node-positive and 10 (9%) T4 patients (17). 3-D conformal radiotherapy was delivered to all 34 patients in a total dose of 56 Gy in this study, despite 3-D conformal radiotherapy, IMRT and VMAT 67 (57%), 43 (36%) and 8 (7%) respectively in a total dose of 55 Gy in 61 (52%) and 60 Gy in 57 (48%) patients in other studies [17].

All patients in this study received cisplatin as a radiosensitizer and completed their radiotherapy course, in contrast to Mitin where only 85% completed induction and consolidation radiotherapy in the paclitaxel group and 83% in the 5-fluorouracil group [15]. 1 patient (in the fluorouracil group) died during follow-up, whereas, 6 (13%) patients in the paclitaxel group and 3 (6%) patients in the fluorouracil group discontinued due to treatment-related toxicity [15].

Cisplatin was concurrently used once weekly in this study, Jadwiga added cisplatin daily in the last 2 weeks of radiotherapy in 42/73 (58%) patients, with complete remission in 66% and partial remission in 23%, in contrast to 58.8% and 17.6%, respectively [16]. Acute genitourinary toxicity of G3 was scored in 2/31 (6%) patients, while cystitis in this study was present in 5 (14.7%) of patients. In addition, no grade 3 gastrointestinal toxicity was reported and grade 2 was 4 (12%), whereas, in this study grade 3 and grade 2 enteritis were 3 (8.8%) and 8 (23.5%), respectively, mostly owing to absence of cisplatin and localized radiotherapy to the whole bladder with 2-3 cm margin [16].

70% of patients showed complete remission while 15% partial remission with 1 (5%) patient showing grade 3 gastrointestinal and 1 (5%) showing urinary toxicity, which may be contributed to the low dose per fraction, 40 Gy delivered to the pelvis in 2 Gy per fraction, whereas, in this study, 36 Gy were delivered to the pelvis in 2.4 Gy, in addition to, 15 Gy delivered in 0.75 Gy per fraction to the bladder, despite, 20 Gy in 1.33 Gy in this study [18]. In this study, enteritis of grade 3 severity was noted in 3 (8.8%) patients. In this study, complete TUR was performed in 20 (58.8%) patients and cT2 were 21 (61.8%) patients, despite 14 (70%) and 12 (60%) with Nada et al [18].

Conclusion:

Conformal radiotherapy using a simultaneous boost with concurrent cisplatin in patients with muscle-invasive bladder cancer is a shortened and acceptable alternative to the prolonged 6-6.5 weeks radiotherapy protocol in T2–3 N0 M0 bladder cancer. Absence of hydronephrosis and complete TUR are of better outcome. Shortened courses will allow larger number of patients to receive radiotherapy, decrease machine burden and total cost. In addition, bladder preservation is an acceptable alternative with better quality of life in contrast to morbidity resulting from cystectomy.

Recommendations:

Other radiosensitizers can be experimented and enrollment of larger number of patients can be of better significance. In addition, new protocols using node-positive disease could be further studied over extended periods with documentation of local control and survival. The use of more advanced radiotherapy techniques as IMRT and VMAT can yield promising results in terms of local control and toxicity.

List of abbreviations:

MIBC- muscle-invasive bladder cancer
Gy- gray
CT- computed tomography
MRI- magnetic resonance imaging
RTOG- Radiation Therapy Oncology Group
EORTC- European Organization for Research and Treatment of Cancer
CR- Complete response
PR- Partial response
SD- Stationary disease
PD- Progressive disease
TCC- transitional cell carcinoma
TURBT- transurethral resection of bladder tumor

Conflict of interest: None

Authors' contributions:

All the authors helped in collecting the cases. RB, AA and SB delivered radiotherapy and chemotherapy and follow-up. OF assisted in delivering chemotherapy and follow-up for toxicity. MK and ME were the urologists who performed TUR and cystoscopy to all patients, pre and post-treatment. MA performed all histopathological assessment. EA helped in physics calculation and dosage distribution. RB (the corresponding author) and SB were the principal investigators who designed the subject and drafted the manuscript. All the authors read and approved the final manuscript.

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