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Bladder Only Radiotherapy Concurrent with Chemotherapy Outcomes in Muscle Invasive Bladder Cancer Management: Our Institute Experience

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ABSTRACT

Background: Bladder only radiotherapy (RT) concurrent with chemotherapy emerged as a valid treatment option for patients with muscle invasive bladder cancer (MIIBC) with complete response to chemoradiotherapy, has been associated with better survival outcomes.

Objectives: Our study evaluates bladder only RT outcomes as regard locoregional and distant metastasis in negative lymph node MIBC and evaluates associations between patients, tumor characteristics, and treatment and complete response to chemoradiotherapy.

Patients and methods: This prospective study was conducted in Sohag University Hospital and Sohag Cancer Institute. This study was a part of study comparing bladder only RT versus whole pelvis RT. The study included 28 patients diagnosed as nonmetastatic negative lymph node MIBC. Patients underwent maximum transurethral resection of bladder tumor (TURBT) then received bladder only RT, concurrent with cisplatin then 4 cycles gemcitabine/cisplatin.

Results: Complete response was achieved in 75% of patients on cystoscopy assessment at 3 months post chemoradiotherapy. With median follow up of 3 years, locoregional recurrence free survival rate and distant metastasis free survival rate at 3 years were 85 % and 82 %, respectively. Complete TURBT, absence of carcinoma in situ (CIS) and concurrent chemotherapy were related to achieving complete response following bladder only RT concurrent with cisplatin but with no statistical significance, maybe due to small sample size.

Conclusion: Bladder only radiotherapy is an effective treatment option as a part of trimodality therapy for negative lymph node MIBC with complete TURBT, absence of CIS and concurrent chemotherapy is associated with complete response.

Keywords: Bladder only radiotherapy, Trimodality therapy, Complete response.

INTRODUCTION

Bladder cancer is the 10th most common cancer globally, with an estimated 573,000 new cases and 213,000 deaths in 2020. Bladder cancer is a significant burden on healthcare systems due to its high rate of morbidity and mortality. Over time, the incidence has not remained stable worldwide, and it is not expected to do so in near future [(1)].

Bladder cancer is still a serious health issue in Egypt. Despite evidence of schistosomiasis control, bladder cancer ranks third as most common cancer and cause of cancer death in 2020. According to GLOBACAN 2020, it is the second most frequent cancer among men in Egypt [(2)].

At presentation, approximately 70% of bladder cancer cases are non-muscle invasive and the remaining 25% are muscle-invasive. Although radical cystectomy with neoadjuvant chemotherapy is considered the standard treatment for MIBC, the associated morbidity and mortality remain substantial concerns result in growing interest in bladder preservation treatment. Trimodality therapy, which consists of maximum TURBT followed by concurrent chemoradiotherapy, now included in major guidelines. Trimodality therapy has comparable oncologic outcomes to radical cystectomy in carefully selected patients as demonstrated by meta-analysis and matched comparisons [(3,4)].

Optimizing radiation treatment volumes for trimodality therapy is still subject for further studies. The whole bladder irradiation without pelvic lymph node (LN) irradiation evolved as a feasible treatment option for patients with negative lymph node MIBC with favourable RT toxicity as shown in BC2001 trial [(5)].

Achieving treatment response is a serious issue during trimodality therapy. Studies showed that patients responding to trimodality therapy have better survival outcomes in comparison with non-responders. Factors affecting response include tumor size, tumor stage, multiplicity of tumor, the presence of hydronephrosis and/or CIS and maximum TURBT [(6)].

Our study evaluates outcomes of bladder only RT concurrent with cisplatin at our institute as regard locoregional and distant metastasis rates. Also, we evaluate patients, tumor characteristics and, treatment associated with complete response.

PATIENTS AND METHODS

Study design

This study is a prospective study, this study was a part of another study comparing bladder only versus whole pelvis RT, conducted in Sohag University Hospital and Sohag Cancer Institute. The study included 28 patients with non-metastatic negative lymph node MIBC enrolled

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between May 2020 till January 2021. 3D conformal bladder only RT was given concurrently with cisplatin then 4 cycles gemcitabine/cisplatin as adjuvant chemotherapy.

Eligibility criteria

Patients included in this study had the following criteria: age ≥18 years, operable patients with histologically proven invasive urothelial carcinoma of the bladder, localized MIBC by imaging (cT2-T3), glomerular filtration rate (GFR)≥ 60 ml/min, ECOG performance status ≤ 2 at the start of treatment, no evidence of distant metastasis or LN metastasis, no evidence of uncontrolled systemic disease which would preclude the patient from the study, no history of other malignancy within the previous 2 years (other than adequately treated basal cell carcinoma of the skin or adequately treated in situ carcinoma of the cervix), no inflammatory bowel disease and no history of previous pelvic RT. Evaluation of all patients before starting treatment included cystoscopy and tumour biopsy, physical examination and ECOG performance status assessment, estimation of GFR, MRI or CT Pelvis (MRI preferred when possible), CT chest and abdomen and bone scan if there was bone pain.

Treatment protocol

All patients underwent maximum TURBT before the initiation of radiotherapy. Radiotherapy began within 6 weeks following maximum TURBT. TURBT was considered complete if no visible residual tumor was present on cystoscopy.

1- Radiotherapy treatments

- **CT simulation for radiotherapy**

CT simulation was from L4 to midthigh with slice thickness 3-5 mm. Patients were in supine position with knee and feet support used for immobilization during CT simulation and treatment. Patients were asked to empty their bladder and rectum immediately prior to scan and before each treatment.

- **Radiotherapy technique**

Clinical target volume (CTV) included the whole bladder plus prostatic urethra then planning target volume (PTV) was created by expansion of CTV with 2 cm at the superior and anterior walls and 1.5 cm at all other walls with the radiotherapy dose was 64 Gy in 32 fractions.

- Organs at risk contouring included:

- Bowel contour: included the entire bowel in one bag starting 1.5 cm above the superior extent of PTV.
- Rectum: from the recto-sigmoid junction to the level of the ischial tuberosities.
- Bilateral femoral head and neck.

2- Chemotherapy included the following:

A. Concurrent chemotherapy: Cisplatin 40 mg/m^2 administered weekly.
B. 4 cycles adjuvant gemcitabine (1000 mg/m^2)/ cisplatin (70 mg/m^2) repeated every 3 weeks starting 4 weeks post concurrent chemoradiotherapy.

Response was assessed by cystoscopy, which was done after end of RT concurrently with cisplatin by 3 months. Complete response was considered if no macroscopic tumor and biopsy was negative at cystoscopy. For the first two years, evaluations were conducted every three months; after that, every six months, or more frequently as clinically indicated by physical examination, CT chest, abdomen, and pelvis, or MRI pelvis when possible, and cystoscopy.

Ethical approval

The Ethics Committee of Faculty of Medicine, Sohag University, approved this study and patient's informed written consent was obtained to participate in the study. Our study has been done in compliance with the World Medical Association's (Declaration of Helsinki) Code of Ethics for human subjects' research.

Statistical analysis

Data were analyzed using STATA version 17.0. Age was presented as mean ± standard deviant (SD), median, and range. Qualitative data were presented as number and percentage and were compared by Fisher's exact test. The Kaplan–Meier survival method with the log rank test was used to assess different categories on survival. P value was considered significant if it was < 0.05.

RESULTS

Patients and tumor characteristics

The mean age at diagnosis was 62 years (range: 49-67). Male patient constituted 86% of our patients with male to female ratio was 6:1. Initially, 64% of patients had performance status of 1. Most tumors were solitary with only 3 patients had multifocal tumor. Tumor greater than 3 cm was detected in 57% of patients. Most of our patients had T2 (57%) disease with 71.4% of tumors were grade 2. On pathological assessment 53.5% of patients had tumors with CIS while 39.3% had LVI.

In our study 4 patients were found to have mild to moderate hydronephrosis. Percutaneous nephrostomy was needed in one patient of them. All patients underwent maximum TURBT before starting concurrent chemoradiotherapy with complete TURBT was achieved in 75% of patients. As regard chemotherapy, 89% of patients received cisplatin concurrently with RT while

78.6% ended 4 cycles adjuvant gemcitabine/cisplatin. Patients and tumor characteristic are shown in table 1.

Table 1. Patients and tumor characteristic

	Variable	Patients number =28
Age/year	Mean ± SD Median (range)	61.71±4.81 63 (49:67)
Age/year	≤60 year >60 year	10 (36%) 18 (64%)
Gender	Female Male	4 (14%) 24 (86%)
Performance status	0 1	10 (36%) 18 (64%)
History of bilharziasis	Absent Present	18 (64%) 10 (36%)
Smoking	Non-smoker or ex-smoker Current smoker	7 (25 %) 21 (75 %)
Site of tumors	Posterior wall Lateral wall Dome Trigone Anterior wall More than one site	5 (17.9%) 14 (50%) 5 (17.9%) 1 (3.6%) 1 (3.6%) 2 (7%)
Multiplicity	Solitary Multiple	25 (89%) 3 (11%)
Growth pattern	Papillary Solid	4 (14%) 24 (86%)
Tumor size (largest diameter)	≤ 3 cm > 3 cm	12 (43%) 16 (57%)
Grade	Grade 1 Grade 2 Grade 3	4 (14.3%) 20 (71.4%) 4 (14.3%)
Associated CIS	No Yes Not known	15 (53.5%) 1 (3.5%) 12 (43%)
LVI	No Yes Not known	11 (39.3%) 1 (3.6%) 16 (57.1%)
T stage	T 2 T 3	16 (57%) 12 (43%)
TURBT completeness	Complete Incomplete	21 (75%) 7 (25%)
Hydronephrosis	No Present	24 (85.7%) 4 (14.3%)
Radiotherapy	Complete	28(100%)
Concurrent Chemotherapy	Complete Incomplete	25 (89%) 3 (11%)
Adjuvant chemotherapy	Complete Incomplete	22(78.6%) 6 (21.4%)

Abbreviation:CIS-carcinoma in situ, LVI-lymphovascular invasion

Treatment outcomes

At intial cysoscopic assesment after concurrent chemoradiotherapy, 75% of patients achieved complete response. The seven patients who had either partial response or stationary disease, were offered salvage cystectomy. Unfortunately, five patients refused surgery and continued chemotherapy. One patient was unfit for surgery due to medical comorbidities and another patient delayed surgery then refused.

Follow up period ranged between 11 and 40 months. Four patients developed locoregional relapse during follow up with 3 patients developed local relapse in bladder and one patient developed bladder and regional pelvic LN relapse. Two patients developed locoregional relapse only proved by cystoscopic biopsy to be muscle invasive and by imaging to be non-metastatic while the other 2 patients developed locoregional relapse with distant metastasis. As for the patients with locoregional relapse only, one patient had salvage cystectomy and pelvic LN dissection with pathological assessment showed T2 N0 while the other patient didn't accept surgical intervention and missed follow up. Bone metastasis was detected in 2 patients and lung metastasis reported in 2 patients. Therefore, in our study bone and lung were the most common distant metastatic sites. These patients received 2nd line chemotherapy and palliative RT to bone in case of bone metastasis and bisphosphonates. These results are summarized in table 2.

Table 2. Outcome of studied population

Variable	Bladder only radiotherapy
Response to treatment Complete response Incomplete response	21(75%) 7 (25%)
Locoregional No Yes	N=28 26 (93%) 2 (7%)
Distant metastasis No Yes	N=28 23 (82%) 5 (18%)
Site of Relapse Locoregional Bone Lung Bone and locoregional Liver Lung and locoregional	N=7 2 (28.57%) 1 (14.29%) 1 (14.29%) 1 (14.29%) 1 (14.29%) 1 (14.29%)

With median follow up of 3 year, locoregional recurrence free survival rate and distant metastasis free survival rate at 3 years were 85% and 82%, respectively. This is shown in figure 1 and 2.

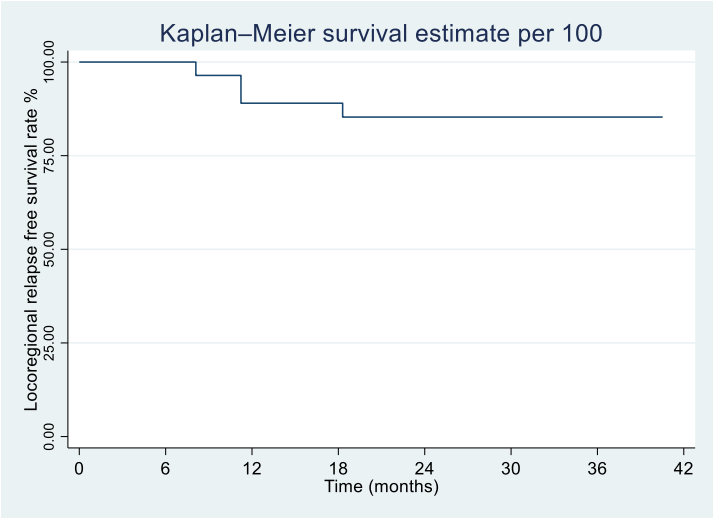

Figure 1. Locoregional relapse free survival rate.

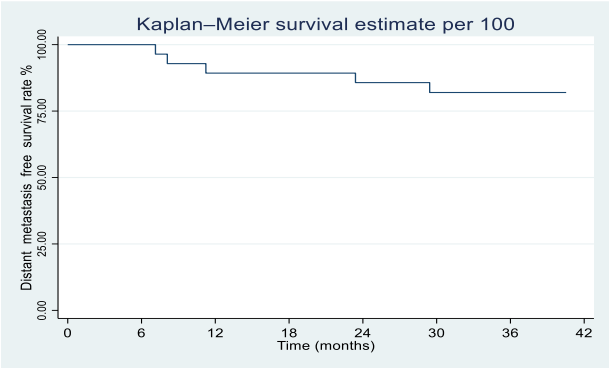

Figure 2. Distant metastasis free survival rate

As regard factors associated with complete response, our study results show that patients characteristics including age, gender, performance status and smoking were not significantly associated with complete response as shown in table 3.

Table 3. Response pattern as regard patients' characteristics of the studied patients

Variable	CR	PR	SD	P value
Age/year				
≤60 year	9 (42.9%)	0	1 (33.3%)	0.29
>60 year	12 (57.1%)	4 (100)	2 (66.7%)	
Gender				
Female	3 (14.3%)	1 (25%)	0	0.71
Male	18 (85.7%)	3 (75%)	3 (100%)	
Performance status				
0	7(33.3%)	3 (75%)	0	0.13
1	14(66.7%)	1 (25%)	3 (100%)	
History of bilharziasis				
Absent	13(61.9%)	4 (100%)	1 (33.3%)	0.17
Present	8(38.1%)	0	2 (66.7%)	
Smoking				
Non-smoker or ex-smoker	4(19%)	3 (75%)	0	0.09
Current smoker	17(81%)	1 (25%)	3 (100%)	

Regarding tumor characteristics as tumor grade, site, size, growth pattern and multiplicity, neither of these factors were associated with complete response. Our results show that complete TURBT, absence of CIS and concurrent chemotherapy were associated with complete response with reported p value that is highly suggestive of significance. Eighty five percent of patients who underwent complete TURBT achieved complete response (p=0.06). Patient achieved complete response had tumors with absent CIS in 62% of patients (p=0.07). Concurrent chemotherapy was received by 95% of patients who achieved complete response (p=0.07). These results are summarized in table 4.

Table 4. Response pattern as regard tumor characteristics of the studied patients and treatment

Variable	CR	PR	SD	P value
Site of tumors				
Posterior wall	4(19%)	0	1(33.3%)	
Lateral wall	9(42.9%)	3(75%)	2(66.7%)	
Dome	4(19%)	1(25%)	0	0.96
Trigone	1(4.8%)	0	0	
Anterior wall	1(4.8%)	0	0	
More than one site	2(9.5%)	0	0	
Multiplicity				
Solitary	19(90.5%)	3(75%)	3(100%)	0.59
Multiple	2(9.5%)	1(25%)	0	
Growth pattern				
Papillary	3(14.3%)	1(25%)	0	1
Solid	18(85.7%)	3(75%)	3(100%)	
Tumor size (largest diameter)				
≤ 3cm	10(47.6%)	1(25%)	1(33.3%)	0.83
> 3cm	11(52.4%)	3(75%)	2(66.7%)	
Grade				
Grade 1	4(19.0%)	0	2(66.7%)	0.5
Grade 2	14(66.7%)	4(100%)	1(33.3%)	
Grade 3	3(14.3%)	0	0	
Associated CIS				
No	13(62%)	1(25%)	1(33.3%)	0.07
Yes	0	0	1(33.3%)	
Not known	8(38%)	3(75%)	1(33.3%)	
LVI				
No	9(42.9%)	1(25%)	1(33.3%)	0.1
Yes	0	0	1(33.3%)	
Not known	12(57.1%)	3(75%)	1(33.3%)	
T stage				
T 2	14(66.7%)	1(25%)	1(33.3%)	0.25
T 3	7(33.3%)	3(75%)	2(66.7%)	
TURBT completeness				
Complete	18(85.7%)	2(50%)	1(33.3%)	0.06
Incomplete	3(14.3%)	2(50%)	2(66.7%)	
Hydronephrosis				
No	19(90.5%)	2(50%)	0	0.12
Present	2(9.5%)	2(50%)	3(100%)	
Concurrent chemotherapy				
Complete	20(95.2%)	2(50%)	0	0.07
Incomplete	1(4.8%)	2(50%)	3(100%)	

DISCUSSION

The pelvic LN may not be targeted in curative bladder RT for patients with cN0 disease because the clinical benefit of elective nodal RT has been uncertain. Bladder only RT has emerged as a valid treatment option as a part of trimodality therapy of MIBC aiming to minimize bowel toxicity [7].

Our study examined bladder only RT concurrent with cisplatin followed by adjuvant gemcitabine/cisplatin to evaluate outcomes of this approach in non-metastatic negative lymph node MIBC.

Complete response was achieved in 75% of our patients on cystoscopic assessment done 3 months post concurrent chemoradiotherapy, this is consistent with the previous results showing that 70-80% of patients receiving trimodality therapy achieve complete response [8].

With median follow up of 3 years, distant metastasis free survival rate was 82 %. These results are comparable to those reported from pooled analysis of RTOG trials in which RT field included the whole bladder, prostate in men, and pelvic LNs showing that 3-year distant metastasis free survival was 78-84% [9].

As regard relapse, distant metastasis was detected in 18% of patients and 7% developed locoregional recurrence with only one patient (3.5%) developed pelvic nodal relapse. Findings from previous studies reported LN relapse rate in patients receiving radical bladder RT to range between 4% and 14% regardless pelvic LN was included in RT field or not. Data from pooled RTOG analysis showing that the rate of 5-year distant metastasis is 32% while locoregional recurrence rate varies between 12 and 16% [10,11].

Data report that the most common sites of distant metastasis were bone (48%), then lung (46%), liver (29%), distant LN (8%), and brain (3%) [12]. In our study, bone and lung were the most common site of distant metastasis.

The 5-year overall survival rates for responders to trimodality therapy was approximately 60% versus 40% in non-responders indicating that response to trimodality therapy is an important predictor of survival. Maximum TURBT is an important predictor of oncologic control and TMT effectiveness, according to several studies. Complete TURBT is associated with 20% improvement in rates of complete response and long-term bladder preservation, which result in improving overall and disease-specific survival in patients who underwent complete TURBT [13]. These results are consistent with our results showing that complete TURBT was associated with complete response with high suggestion of statistical significance (P=0.06).

A number of additional factors have also been shown to be related to poor response as hydronephrosis. Data suggest that the response rate of patients with hydronephrosis was 1.5 times lower than that of patients without hydronephrosis. Consequently, since 1993, hydronephrosis has been a criterion for exclusion in RTOG protocols [14].

In our study hydronephrosis was not associated with response (p=0.1). This may be due to small sample size and hydronephrosis detected in our patients was mild to moderate with only one patient needed percutaneous nephrostomy.

Poor response rates were also shown by earlier RT series in patients with multifocal disease, CIS, and T4 disease. Furthermore, high-risk histologic characteristics as lymphovascular invasion, variable histology, and tumor grade are probably prognostic in trimodality therapy [3]. Our results show that absence of CIS was associated with complete response but small sample size may make it statistically insignificant (p=0.07).

While complete TURBT confers a significant survival benefit, the role of concurrent chemoradiotherapy to further reduce disease burden by eliminating microscopic disease is a crucial component of trimodality therapy and is suggestive of integration between these different modalities. So, concurrent cisplatin with RT and adjuvant 4 cycles gemcitabine/cisplatin received in our study may play a role in eradication of micrometastasis resulting in improved local disease control, lower rate of distant recurrence, and long-term survival rates.

An updated analysis of patients treated within the BC2001 trial confirms that chemoradiotherapy resulted in improvement of locoregional control. This benefit translated into nonsignificant improvement of disease free survival (P=0.06), metastasis free survival (P = 0.08) and overall survival from 2 year onwards (P=0.3) [5].

Several radiosensitizing chemotherapy for trimodality therapy have been developed with lack of evidence to recommend an optimal choice of a radiosensitizer, as they have not been compared in randomized trial. Cisplatin is a reasonable option for patients fit for cisplatin [11]. Most of our patients (89%) received cisplatin concurrent with RT with the remaining (11%) received cisplatin with reduction due to toxicity.

Regarding adjuvant chemotherapy, there are no published phase 3 trial survival data in the trimodality therapy context. In phase 1 and 2 trials, tolerability was shown to be lower, with only 45–70% of patients completing treatment. Additionally, it appeared that severe toxicity (grade 3 or 4) was more common than in the neoadjuvant context [15]. Recently, meta-analysis of ten randomized controlled trials demonstrated that cisplatin-based adjuvant chemotherapy in MIBC patients resulted in an absolute improvement in survival at 5 year indicating that cisplatin based adjuvant chemotherapy is a

valid option for improving outcomes for MIBC [16]. So, although there exists clinical rationale to use neoadjuvant or adjuvant chemotherapy with trimodality therapy, well-designed large randomized controlled trials are required to demonstrate their role with trimodality therapy. The benefit of adjuvant chemotherapy was out of scope of our goals and further data are needed to specify its benefit but we report that adjuvant gemcitabine/cisplatin is tolerated and 78.6% of patients completed 4 cycles gemcitabine/cisplatin.

Further studies are needed as validated biomarkers that predict the tumor response to chemoradiotherapy are currently lacking. Numerous biomarkers have been examined. Unfortunately, even MER11, which was the most promising biomarkers, have failed to result in reproducible data [17].

CONCLUSION

Our study addresses bladder only radiotherapy concurrent with chemotherapy and demonstrates its effectiveness in patients with non-metastatic negative lymph node muscle invasive bladder cancer based on oncologic outcomes as regard response rate, locoregional relapse free survival, distant metastasis free survival with complete TURBT, absence of CIS and concurrent chemotherapy, which are important factors for achieving complete response.

LIMITATIONS

Our most obvious limitation of this study was small sample size, which may affect statistical significance of our results. In addition, longer follow up period was needed for better assessment of outcomes.

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Conflict of Interest: The authors had nothing to declare.

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