Abbreviated Concurrent Chemo-Radiotherapy in Node-Negative Muscle-Invasive Bladder Cancer

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Abstract:

Background Bladder cancer represents a major economic burden in egypt, ranking as the second most common tumor in males 12.7%. Therefore, the goal of this research is to develop a hypofractionated treatment regimen that achieves a similar response at a lower cost and with less strain on the radiation machines.
Purpose: The aim of this study is to evaluate treatment outcome of hypofractionated concurrent chemo-radiotherapy using weekly cisplatin in muscle-invasive bladder cancer (MIBC).
Materials and methods: From September 2019 till February 2021, 40 patients with node-negative muscle-invasive transitional cell carcinoma of the bladder, stage T2-T3N0M0, underwent maximal transurethral resection of bladder tumor followed by 3-dimensional conformal radiotherapy to the bladder in 45 Gy in 15 fractions with a weekly cisplatin dose of 30mg/m2. Treatment outcome was assessed by response and toxicity.
Results: With a median follow-up time of 13 months (8-18 months), forty patients with a median age of 55.9 ± 8.4 years completed their treatment regimen. After 3 months of therapy, 26 patients (65%) had a complete local response, whereas 6 patients (15%) had progressive disease, 4 patients (10%) had local recurrence and 2 patients (5%) had with distant metastasis. Acute grade 3 gastrointestinal and genitourinary toxicities were 5% and 12.5% of all acute toxicities, respectively. 2.5% of patients had late grade 3 genitourinary toxicity. There were no reports of life-threatening complications or grade 4 toxicity.
Conclusions: In node-negative bladder cancer, concurrent chemo-radiotherapy is a feasible and well-tolerated alternative to surgery. In addition to lower morbidity, this regimen offers effective treatment with low cost. However, T2 masses which were completely resected yielded better results.
Recommendation: More advanced radiotherapy techniques as IMRT and VMAT can be experimented in further studies with larger number of patients and longer follow-up. Careful selection of patients with T2 completely resected masses and negative nodal status on MRI will yield better results.

Key words: Hypofractionation- node-negative- radiosensitizer

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Background:

Bladder cancer represents a worldwide health burden, ranking as the fourth most prevalent cancer in men, with a lifetime incidence of about 1 in 27, compared to 1 in 89 for women [1]. In Egypt, it is the third most common tumor in both sexes, accounting for 6.9% of all new cancer cases with a mortality rate of 2.1% [2], it compromises 3% of all new cancers cases with a mortality of 2.1% [3]. Bladder cancer has a predisposition for recurring after treatment thus the choice of the initial radical therapy is crucial. Due to this fact, bladder cancer is considered the most costly cancer from diagnosis to death [4] [5].

25% of all newly diagnosed bladder cancers are muscle invasive at presentation [6], with 1 in 3 cases presenting with muscle-invasive bladder-confined tumors at diagnosis [1]. Moreover, the 5-year survival

rate drops down to 69.5% in T2 tumors and further declines to 35% in the presence of nodal involvement [7] [8].

The gold standard treatment for non-metastatic muscle-invasive bladder cancer (T2-T4aN0M0) is radical cystectomy with pelvic lymph node dissection with resultant significant morbidity and mortality [9].

Since the α/β for bladder tumors often implies poor 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 considered [10]. In fact, hypofractionation appears to provide better local disease control than conventional fractionation [11]. From a cost-effectiveness perspective, an abbreviated regimen has the potential to lessen the financial load per patient in comparison to conventional treatments, with decreasing machine burden [12].

Trimodality therapies have proven to be an acceptable alternative to radical cystectomy, with several phase 3 studies reporting promising findings in terms of survival outcomes, with comparable efficacy in terms of response and toxicity [13].

Hammer et al employed a similar radiotherapy schedule but with fewer patients and with T4a [14], however, the standard guidelines recommend additional of radiosensitizer, especially cisplatin, in patients with good renal functions [15]. Therefore, this study recruited more patients with addition of weekly cisplatin and absence of T4 lesions.

Patients and Methods:

Forty patients with muscle-invasive bladder cancer (MIBC) were treated in Clinical Oncology and Medical oncology Departments, Zagazig University Hospitals. Patients with histologically and radiologically confirmed T2-3N0M0 transitional cell carcinoma (TCC) of the bladder, age older than 18 years, WHO performance status ≤ 2, serum creatinine < 1.5 times the upper limit of normal (ULN), creatinine clearance more than 70 were to be enrolled.

Patients underwent maximal transurethral resection of their bladder tumor (TURBT) before chemoradiotherapy. Pre-radiotherapy assessment included a full physical examination, hematological and biochemical laboratory evaluation, urine analysis, urine culture and sensitivity, CT (computed tomography) of chest, MRI (magnetic resonance imaging) of the abdomen and pelvis to conclude negative pelvic nodes and bone scan if indicated (if there is bone pain or bone aches).

All MRI data were transferred to the workstations, and image analysis was performed using a dedicated platform Extended Brilliance Workstation (Philips Medical System, Best, The Netherlands). Images taken on the pelvis was assessed firstly by T2WI regarding the masses' site, size, signal intensity (SI), growth pattern, as well the integrity of outer low SI muscle layer, and extra-vesical extension. Followed by the DWI and ADC map were interpreted regarding the SI and extension of the mass and integrity of detrusor muscle layer. Lastly, DCE was evaluated regarding the enhancement of mass lesion, and detrusor muscle layer. Assessment of nodal enlargement, abnormal morphology, and pericapsular stranding was done at level of abdomen and pelvis.

By referring to tattoos on the skin and bone landmarks at the level of the L5 vertebra, the patient is brought up in the supine posture with both arms on both sides and both legs laying straight. The patient was CT scanned at 5 mm intervals in the treatment position as part of the CT-based planning. The simulation was carried out with a full bladder in order to keep as much of the intestine out of the radiation area as possible. With high-energy photons, a linear accelerator was used (15 MV X-ray). A four-field plan with multileaf collimators was adopted for all patients' 3D conformal radiotherapy. Total dose of 45 Gy was delivered to the whole bladder with 1.5 cm margin in 15 fractions. Contouring of normal organs at risk was carried out to not exceed 45 Gy to the femoral heads. The volume of the femoral head receiving 50Gy was less than 10%. The volume of the small and large bowel receiving 50Gy was less than 5%. The volume of the rectum that received 30Gy was less than 50%. Cisplatin 30 mg/m2 was administered once per week as a 30-minute intravenous infusion, 30 minutes before radiotherapy on days 1, 8 and 15. During treatment, evaluation was done by weekly hematological evaluation with creatinine clearance.

CT chest scans and MRI of the abdomen and pelvis were used for post-therapy evaluation after one month of treatment completion, and after three months. If necessary, bone scan was done. A clinical complete response was confirmed by cystoscopy and biopsy. Patients who showed residual, recurrent or progressive disease were deemed to have experienced treatment failure and were planned to shift to salvage cystectomy or chemotherapy according to protocols used in Clinical Oncology Department, Zagazig University Hospitals.

Response criteria: was established via MRI, cystoscopy and biopsy [16] and included: (1) Complete response (CR): absence of visible tumor cystoscopically and the absence of histological and radiological evidence of disease. (2) Partial response (PR): residual after maximal TUR shows more than 50% decrease in tumor size with a positive biopsy. There should be no appearance of new lesions or progression of any lesions. (3) Stable disease (SD): residual after maximal TUR shows less than 50% decrease in tumor size with a positive biopsy. (4) Progressive disease (PD): residual after maximal TUR shows increase in the size of lesion or the appearance of new lesion(s) with a positive biopsy.

Toxicity was assessed by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) radiation scoring criteria [17]. Acute toxicity was assessed after 3 months of completing the treatment. Late toxicity was defined as toxicity occurring or persisting after 3 months following completion of treatment.

Statistical analysis

Data entry, processing and statistical analysis was carried out using MedCalc ver. 20 (MedCalc, Ostend, Belgium). Tests of significance (Student's t, Chi square tests, logistic and multiple regression analysis, Pearson's correlation) were used. P-values less than 0.05 (5%) was considered to be statistically significant.

Results:

This was a prospective case control study conducted on 40 MIBC patients to evaluate response and toxicity after implementation of hypofractionated radiotherapy for 3 weeks with weekly cisplatin as a radiosensitizer.

Regarding patient characteristics, the mean age of all patients was 55.9 ± 8.4 years, where 77.5% were older than 50 years, with the majority presenting as males 85% (Table 1). All patients were categorized as T2 (60%) or T3 (40%). Patients with grades 1 and 2 resembled 10% and 20%, respectively whereas grade 3 dominated in 70% of patients. TUR was done for all 40 patients, where 62.5% underwent complete resection, in contrast to 37.5% with partial resection. Overall responders (CR and PR) presented 29 patients, 72.5%, of which 24 were T2 while only 5 were T3, 82.8% and 17.2%, respectively. Furthermore, the non-responders (SD and PD) presented 11 patients, 27.5%, which were T3 extravesical masses, however, not infiltrating adjacent structures, thus complete resection was difficult.

Post-treatment evaluation was done after 1 month of completion of treatment and repeated after 3 months by MRI of the abdomen and pelvis to assess lymph nodes, CT chest scans to detect any distant metastasis, cystoscopy and biopsy were to assess the bladder status with any local recurrence or progression (Table 2). 65% of patients showed complete response, whereas, 6 patients (15%) showed progressive disease, 4 with local recurrence (10%) and 2 with distant metastasis (5%).

Comparative study between the 2 groups of responders and non-responders revealed highly significant decrease in ECOG (Performance Status) in overall-responders group; compared to non-responders' group ($p = 0.002$) (Table 3). In addition, there was a highly significant difference of < 0.01 in favor of T2 bladder lesions and especially those with complete tumor resection.

Acute toxicity was recorded after 3 months of completion of therapy. Acute grade 3 gastrointestinal and genitourinary toxicities were 5% and 12.5%, respectively. No life-threatening or grade 4 toxicity was recorded (Table 4). Late toxicity was that occurring or persisting after 3 months following completion of treatment. Late grade 3 genitourinary toxicity was 2.5%.

Table 1: Patient Demographics

Variables		Frequency (%) / Mean ± SD
Age (years)		55.9 ± 8.4
Age groups	Old > 50	31 (77.5%)
	Young < 50	9 (22.5%)
Gender	Female	6 (15%)
	Male	34 (85%)
ECOG (Performance Status)	PS 0	11 (27.5%)
	PS 1	21 (52.5%)
	PS 2	8 (20%)
Tumor grade	G1	4 (10%)
	G2	8 (20%)
	G3	28 (70%)
Tumor classification	T2	24 (60%)
	T3	16 (40%)
Lesion after TUR	Complete Resection	25 (62.5%)
	Partial Resection	15 (37.5%)

Table 2: Response data

Variables		Frequency (%)
Response	Non-Responders	11 (27.5%)
	Overall-Responders	29 (72.5%)
Degree of Response	CR	26 (65%)
	PR	3 (7.5%)
	SD	5 (12.5%)
	PD	6 (15%)

Table 3: Response data according to patient demographics

Variable		Non-responders group (11) Mean ± SD	Overall-responders group (29) Mean ± SD	Chi square test P value
Age (years)		58.45 ± 9	55 ± 8.2	= 0.258 (Student's *t* test)
Gender	Female	2 (18.2%)	4 (13.8%)	
	Male	9 (81.8%)	25 (86.2%)	= 0.7318
ECOG (Performance Status)	PS 0	3 (27.3%)	8 (27.6%)	
	PS 1	2 (18.2%)	19 (65.5%)	= 0.002**
	PS 2	6 (54.5%)	2 (6.9%)	
Tumor grade	G1	1 (9.1%)	3 (10.3%)	
	G2	3 (27.3%)	5 (17.2%)	= 0.7782
	G3	7 (63.6%)	21 (72.4%)	
Tumor classification	T2	0 (0.0%)	24 (82.8%)	
	T3	11 (100.0%)	5 (17.2%)	<0.0001**
Lesion after TUR	Complete Resection	0 (0.0%)	25 (86.2%)	
	Partial Resection	11 (100.0%)	4 (13.8%)	< 0.0001**

Table 4: Acute and Late toxicity

Variables		Frequency (%)
Early Gastro-intestinal	Normal	26 (65%)
	Grade-1	8 (20%)
	Grade-2	4 (10%)
	Grade-3	2 (5%)
Early Genito-urinary	Normal	18 (45%)
	Grade-1	14 (35%)
	Grade-2	3 (7.5%)
	Grade-3	5 (12.5%)
Late Gastro-intestinal	Normal	30 (75%)
	Grade-1	8 (20%)
	Grade-2	2 (5%)
Late Genito-urinary	Normal	28 (70%)
	Grade-1	9 (22.5%)
	Grade-2	2 (5%)
	Grade-3	1 (2.5%)

Discussion:

Bladder cancer is chiefly a disease of elderly, thus the choice of therapy mainly relies on maintaining quality of life without compromising local control, hence, the need for bladder preservation and trimodality therapies arose [18] [19] [20]. In patients unfit for radical cystectomy, or in cases where bladder preservation is desired, trimodality therapy (TMT) can be considered. This incorporates maximal transurethral resection of bladder tumor (TURBT) followed by radiation therapy with concurrent chemotherapy [18]. Results with radiotherapy alone are suboptimal, thus addition of concurrent chemotherapy with radiation therapy has improved bladder-intact disease-free survival. Most chemoradiation regimens for MIBC employ concurrent cisplatin with significant remissions and better survival [21]. Survival rates are similar to those achieved by primary cystectomy [22] and have proven superior for T3b and T4 tumors [23].

Radiation technique delivered was 3-dimensional conformal radiotherapy in contrast to other studies using intensity modulated radiotherapy and volumetric modulated arc therapy [14] [24]. Several studies experimented hypofractionated radiotherapy alone, yet others administered an additional concomitant radiosensitizer as fluorouracil and mitomycin C [13].

Two large multicentre, phase 3 trials (BC2001 and BCON) concluded that patients who received 55 Gy in 20 fractions showed better local control than those who received 64 Gy in 32 fractions, with comparable morbidity. These studies enrolled 782 patients with median age more than 80 years, with an excess of male participants, however, only 40 patients were employed in this study with a mean age of 55.9 ± 8.4 years [13]. On the contrary, HYBRID trial implemented weekly hypofractionated radiotherapy schedule of 36 Gy/6 fraction with 81.3% local control, followed by 69% down to 65% showing complete response in this study [14] [25].

The incidence of lymph node involvement in bladder cancer occurs in approximately 30% of T2 cases and 60% of T3 or greater [26] [27], therefore patients selected were of T2-3 tumors only whereas other studies which employed T1G3 (high-grade non-muscle invasive) and T4 cases thus clarifying that 6 patients (15%) showed progressive disease, 10% with

local recurrence and 5% with distant metastasis against 35% local recurrence and 11.7% distant metastases in the other studies [14]. This can be supported, as well, with 37.5% partial transurethral resection of the bladder mass in contrast to 65% with Hammer et al [14]. This finding may, however, stand with the short follow-up period of 13 months (8-18 months).

Localization of radiotherapy to bladder only from the start was a strong predictor for absence of life-threatening or grade 4 toxicity. In addition, acute grade 3 gastrointestinal and genitourinary toxicities were only 5% and 12.5% versus, 6% and 24%, respectively [14]. Higher toxicity rates were reported with Symon et al with grade 3 gastrointestinal and genitourinary toxicity of 4.5% and 18%, respectively [24].

Late grade 3 genitourinary toxicity was 2.5%, whereas, Amestoy et al documented between 4 to 46% grade $\geq$ 3 genitourinary toxicity and less than 12% grade $\geq$ 3 gastrointestinal toxicity [28].

Conclusion:

Bladder preservation is considered a preferable alternative to immediate cystectomy in selected patients with bladder cancer, in addition to, providing a better quality of life by avoiding the undesirable effects of urine diversion. Conformal hypofractionated radiotherapy with cisplatin as a radiosensitizer is considered an applicable treatment with low financial burden for treatment of T2-3N0M0 patients after performing complete TUR. Shorter treatment protocols have numerous socioeconomic advantages in any health-care system. Accurate selection of T2 completely resected lesions will yield better response. Therefore, if evidence of superiority of treatment can be provided, with no difference in toxicity then this protocol should be preferably adopted.

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:

RB, RH and DM collected the cases and delivered radiotherapy and chemotherapy. SE assisted in collecting the cases and delivering chemotherapy. MI was responsible for performing and diagnosing all CT scans and MRI done. MM was the urologist who performed all TURBT pre and post-treatment. RB (the corresponding author) was the principal investigator who designed the subject and drafted the manuscript. All the authors read and approved the final manuscript.

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