Original Article

Outcome of Concurrent Chemoradiation in Inoperable Muscle Invasive Urothelial Carcinoma of Urinary Bladder in terms of Locoregional Response and Toxicities — A Longitudinal Study in a Tertiary Care Hospital

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Background : The presenting study was performed to assess the efficacy in terms of tumour response and toxicity profile of a curative intent organ preservation approach in Inoperable Non-metastatic Muscle-Invasive Urinary Bladder Carcinoma.

Materials and Methods : Prospective Interventional Single-Arm, Single Center study with a duration of one and half year in which 47 patients with Muscle-invaded Bladder Cancer were treated with Radiotherapy with 64 Gy in 32# along with Concurrent Chemotherapy with three weekly injection Cisplatin in dose of 70 mg/m^2. Response evaluation was done using both Clinical and Radiological means and categorized using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. For adverse events measurement: NCI CTCAE (Common Terminology Criteria for Adverse Events, v4.1) and RTOG/EORTC Acute and Late Morbidity criteria was used.

Results : Of the 47 patients who completed chemoradiation, complete treatment response was seen in 25 patients (53.2%), 17 patients (36.2%) had partial response on initial assessment and one patient had disease progression both in form of locoregional and distant (lung) metastasis. Stable disease found in 4(8.5%). Patients with residual disease were advised to undergo salvage treatment. Grade 3 Nephrotoxicity reported in one patient, Grade 2 Cystitis in 32 patients (68.1%), while Grade 2 Diarrhoea occurred in four patients (8.5%). Hematological toxicity attributable to Chemoradiotherapy included Grade 2, Grade 3 Neutropenia seen in 6.4% and 2.1% respectively and Grade 2 Anaemia in 4.3% patients.

Conclusion : Concurrent Chemoradiotherapy is well-tolerated, effective and convenient curative treatment option for patients with Inoperable Non-metastatic Muscle Invasive Carcinoma of Urinary Bladder.

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***Key words* : Urinary Bladder Urothelial Carcinoma, Chemoradiation, Toxicities, Local control.**

Urinary Bladder Malignancy is the 10th most commonly presenting malignancy Worldwide[1]. It is the second most common malignancy of genitourinary system. The incidence of Bladder Cancer has been steadily rising over the past three decades. Urothelial carcinoma is the most common histologic type of Bladder Cancer (approximately 90%). Approximately 75% of diagnosed Tumors are superficial and about 25% of new diagnoses are Muscle-Invasive Bladder Cancer (MIBC)[2], which carry a worse prognosis compared to Non-Muscle Invasive disease with higher rates of metastasis and cancer mortality in 6 months if remain untreated. About one third of Non-MIBC (NMIBC) eventually progress to muscle-invasive disease[2,3]. Neoadjuvant Chemotherapy (NAC) followed by Radical Cystectomy (RC) with bilateral Pelvic Lymphadenectomy is considered as the gold-standard for MIBC. It has been shown to offer good pelvic control rates (85-90%) and acceptable cancer-specific survival [5-year Overall Survival (OS): 40-60%][4]. Radical Cystectomy comprises of resection of bladder, regional Pelvic Lymph Nodes (extended Lymph Node dissection) and adjacent organs like Uterus or Prostate gland with various modes of urinary diversion[5]. This procedure is associated with postoperative morbidity rates of up to 30% and, moreover, Urinary diversion has a great impact on long term Urinary, Metabolic, Gastrointestinal and Sexual function, significantly affecting the patient's Quality of Life (QOL)[6].

Editor's Comment :

- Incidence of Urinary Bladder Cancer is steadily increasing in last few years.
- Different treatment options available to combat this cancer should be evaluated and awareness about these options is important.

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Due to the morbidity associated with surgical approach, many patients are not candidates to undergo surgery due to poor performance status or older age or they simply choose to undergo alternative less invasive modality. Over the past decades, there is gradually increasing trends and evidences to support bladder preserving conservative options. Two groups of patients can benefit from this approach: patients with organ-confined disease who have a strong preference to avoid aggressive surgery and comorbid patients who are not candidates for surgical intervention. Single modality Bladder-preservation consisting of only Transurethral Resection of Bladder Tumour (TURBT), Chemotherapy alone or Radiotherapy yield poorer outcome in terms of locoregional tumour control and long-term survival[7]. Multimodal Bladder preservation protocol consists of Maximal Transurethral Resection of the Bladder Tumor (TURBT) followed by Chemoradiotherapy (CRT), known as Trimodal Therapy (TMT). Survival outcomes after TMT for carefully selected patients are comparable to RC but without the risks of perioperative mortality and morbidity[8].

Till date, no randomised study directly compared Radical Cystectomy with the bladder-sparing approach. Several studies presented TMT oncologic outcomes comparable to RC, with 5-year and 10-year overall survival at 57% and 39%, respectively[8]. Long-term data as given by the Radiation Therapy Oncology Group (RTOG), has established selective bladder-preserving treatments as a safe and effective alternative to Cystectomy. As a result, Multimodal Bladder preservation therapy is now approved as an option by the Major Scientific Societies Guidelines (National Comprehensive Cancer Network, European Association of Urology EAU) for selective patients[9].

However, the existing studies do not unanimously support the use of bladder preservation modalities. A study in 2018, claimed that TMT resulted significantly decreased OS and Cancer-Specific Survival (CSS) and more burden of expenditure in 2011[10]. As a result of still conflicting evidence, more research is needed to better understand the efficacy of TMT as an alternative treatment option for MIBC.

The patients who are surgically or medically not fit for Cystectomy, comprise a poor cohort for any curative mode of treatment and in more need of this conservative management.

Our purpose, at a Tertiary Care Hospital, was to assess the achievability, toxicity profile and locoregional response of tumor following treatment with the Concurrent Chemoradiotherapy in Inoperable locally advanced Muscle Invasive Urinary Bladder Urothelial Carcinoma.

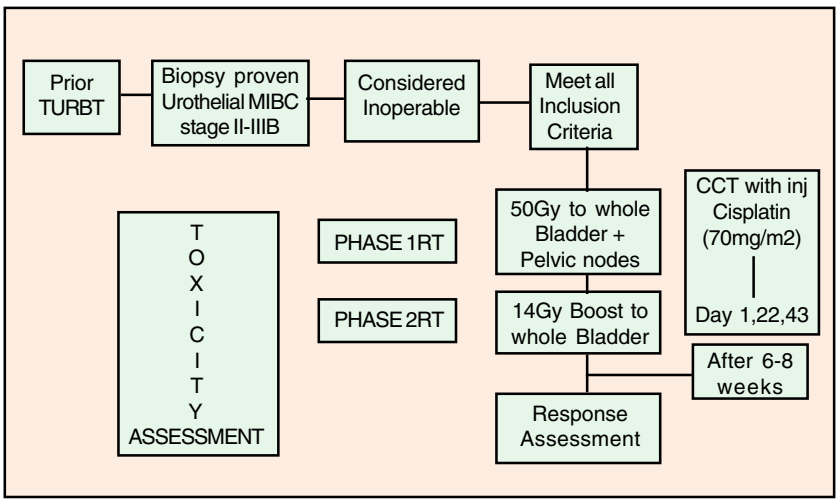
Materials and Methods

Selection of Patients :

This Prospective, Interventional Single-arm study was conducted at the Radiotherapy Department of R G Kar Medical College & Hospital, Kolkata, over a period of 18 months. Fiftytwo patients with a primary non-metastatic Muscle Invasive Urothelial Carcinoma of Urinary Bladder presenting with the Eastern Cooperative Oncology Group (ECOG) performance status ≤2, staged T2-T4aN0-2M0, age 18-75 years, were recruited from January, 2020 to January, 2021 with written informed consent. Cancer staging was done according to the American Joint Committee on Cancer 8th edition TNM Staging and patients were considered inoperable either surgically or medically. Exclusion criteria were any other malignancy, evidence of distant metastasis, uncontrolled morbidity, psychiatric illness, informed consent not granted and patients with any contraindication to chemoradiotherapy. Accrual was started only after getting ethical clearance certificate from Institutional Ethics Committee.

After the Baseline assessment, Radiological pre-treatment Metastatic Work-up was done as inclusion pre-requisites. After the attempt of Maximal TURBT, biopsy proved Muscle Invasive Urothelial Bladder Cancer (T2-T4a) patients were treated by External Beam Radiotherapy + Concomitant Chemotherapy.

Study Schema :



Treatment :

After initial work up, Treatment Planning Computed Tomography (CT) simulation was performed and Three-Dimensional Conformal RT planning was done. Two phase Radiotherapy (RT) was given using a Linear Accelerator with 6-20 MV photons with shrinking field technique. The 1st Phase included RT of 50 Gy/ 25 fractions to the whole pelvic field encompassing the whole Urinary Bladder with local extension and draining pelvic lymph nodes, planned in empty Bladder. In the 2nd Phase, planned in full Bladder, field was reduced to cover the whole Bladder volume with 1-2.5 cm anisotropic margin and the boost dose given was 14 Gy in 7 fractions to a total dose of 64 Gy. There was no mid-treatment break for Intermediate Cystoscopic evaluation. During radiation, Complete Blood Counts and Serum Creatinine Levels were evaluated every week.

Concurrent Chemotherapy was given every 3 weeks with intravenous Cisplatin dose of 70 mg/m^2. In total, three cycles of chemotherapy were planned during RT.

Every patient was evaluated 6-8 weeks after completion of therapy with MRI Pelvis, Cystoscopy, Contrast-Enhanced CT scan of Abdomen and Thorax. Assessment of tumor response to the treatment was done according to revised RECIST guidelines version 1.1. Treatment-related Acute Hematological Toxicities (Anaemia, Neutropenia, and Thrombocytopenia) and non-hematological toxicities (Vomiting, Diarrhoea, and cystitis) were scored and reported using Common Terminology Criteria for Adverse Events version 4.0.

Management of Data and Statistical Analysis :

Software SPSS version 25.0 for Mac was used for interpretation and analysis of data recorded. Categorical variables were expressed as numbers and percentages, whereas comparisons were done using paired samples t-test. Cross tabulation was done to check associations as significance level, p-value <0.05.

Results

A total of 52 patients were recruited in the study. Among them, for 1 patient, treatment was stopped midway due to sudden aggravation of cardiological problem. 3 more patients were lost to treatment during EBRT. 1 patient completed full course of treatment but did not turn up for response assessment and follow up. Those total 5 patients were excluded from analysis. So, total 47 patients were analysed in this study (Tables 1 & 2).

Within the full period of this study, every patient was evaluated during RT in each week with blood for Hb, TC, DC, Platelet, Urea, Creatinine. Two patients (4.3%) had Grade 2 Anaemia, one patient had Grade 3 Neutropenia during Chemoradiotherapy course and managed conservatively (Table 3).

Table1 — *Distribution of study population according to clinico-pathological profile (n=52)*

Attributes	Category	Number	Percentage
Age	<60 years	18	34.6
	≥ 60 years	34	65.4
Gender	Male	45	86.5
	Female	7	13.5
Family History	Present	2	3.8
	Absent	50	96.2
Smoking Habit	Present	34	65.4
	Absent	18	34.6
Occupational exposure	Present	11	21.2
	Absent	41	78.8
Comorbidity	Present	28	53.8
	Absent	24	46.2
ECOG PS at presentation	0	7	13.5
	1	18	34.6
	2	27	51.9

Table 2 — *Tumor Related Factors (n=52)*

Variables		Number	Percent
T stage	T2	36	69.2
	T3	13	25
	T4	3	5.8
N stage	N0	39	75
	N1	5	9.6
	N2	8	15.4
Clinical TNM stage	Stage II	33	63.5
	Stage IIIA	11	21.1
	Stage IIIB	8	15.4
Multiplicity	Solitary	34	65.4
	Multiple/Diffuse	18	34.6
Completeness of TURBT :			
No visible tumor after TURBT		33	63.5
visible tumor after TURBT		19	36.5

With Concurrent use of injection Cisplatin,13 recent (27.7%) patients had G1 nausea and vomiting during radiation period. Acute GI toxicity in form of Diarrhoea was seen in 20 patients (42.6), 4 patients (8.5%) had G2 Diarrhoea. Proctitis G1 was present in 8 patients (17.0%), while 1 patient (2.1%) had G2 proctitis in form of rectal discomfort, tenesmus and minor intervention required.

Cystitis is the m/c acute toxicity observed in the study population in form of increased urinary frequency, urgency, dysuria, incontinence, nocturia and haematuria. 14(29.8%) patients had G1 and 32(68.1%) had G2 Cystitis. 6 patients (12.8%) had only haematuria G2 and managed conservatively. G1 Nephrotoxicity was found in 20(42.6%), G2 in 2(4.3%) patients. One (2.1%) patient had G3 toxicity and this patient and other one developed bilateral

Table 3 — *Acute and late toxicities of definite chemoradiation in the study population (Grading by CTCAE version 4.0) (n=47)*

Toxicities	Grading	Number	Percentage
Anaemia	None	16	34.0
	G1	29	61.7
	G2	2	4.3
Neutropenia	None	27	57.5
	G1	16	34
	G2	03	6.4
	G3	01	2.1
Thrombocytopenia	None	25	53.2
	G1	22	46.8
Fatigue	None	28	59.6
	G1	18	38.3
	G2	1	2.1
Nausea / Vomiting	None	34	72.3
	G1	13	27.7
Diarrhoea	None	23	48.9
	G1	20	42.6
	G2	4	8.5
Proctitis	None	38	80.9
	G1	8	17
	G2	1	2.1
Haematuria	None	41	87.2
	G2	6	12.8
Cystitis	None	1	2.1
	G1	14	29.8
	G2	32	68.1
Nephrotoxicity	None	24	51.1
	G1	20	42.6
	G2	2	4.3
	G3	1	2.1
Hydronephrosis	No	45	95.7
	Yes	2	4.3

hydroneprosis, 2(4.3%) which is a late toxicity. One patient with hydronephrosis died in spite of having CR (Complete Response) (Tables 4 & 5).

Table 4 — *Assessment of the Locoregional Response of Definitive Chemoradiation in study population by using RECIST v 1.1. (n=47)*

Response	Status	Number	Percentage
RECIST v1.1	CR (Complete Response)	25	53.2
	PR (Partial Response)	17	36.2
	SD (Stable Disease)	4	8.5
	PD (Progressive Disease)	1	2.1
	Total	47	100

Table 5 — *Patterns of Failure in the study population till the last reported follow-up (n=45)*

Patterns of Failure	Status	Number	Percentage
Loco-regional Recurrence	Yes	5	11.1
	No	40	88.9
	Total	45	100
Distal Metastasis	Yes	4	8.9
	No	41	91.1
	Total	45	100

Discussion

Radical Cystectomy is still being considered as the gold standard for treatment of Muscle Invasive Urinary Bladder Cancer. However, it is an inherently morbid intervention with subsequent compromise of QOL with urinary diversion. This dilemma is more evident in elderly patients, where perioperative mortality is significantly higher as compared to younger patients. Many patients with MIBC have age-related comorbidities, such as renal function impairment, and cardiovascular or respiratory diseases which disqualify them from surgery. Given the increased life expectancy, the demand for alternative curative treatment for MIBC patients who are unfit for RC is increasing. With these considerations, Bladder Sparing conservative approach to Radical Cystectomy are attractive for both patients and clinicians.

Existing literature have opined Bladder Preservation Therapy as a convenient, safe, and effective approach with tolerable toxicities when compared with Radical Cystectomy along with a comparable Disease-Free and Overall Survival. Majority of patients treated under this protocol maintained good QOL, retained functional Bladder and preserved sexual function without compromising survival outcome.

Our study purposed to evaluate the tumor outcome and toxicities of Concurrent Chemoradiotherapy in Muscle Invasive Urinary Bladder Carcinoma, who are medically or surgically not fit for Cystectomy. A total of 52 patients were recruited in the study and were treated with curative intent by Concurrent Chemoradiation.

The baseline attributes in this study were congruent with the recent evidences. 65.4% (34) patients are above the age of 60 years with median age of the patients are 61.75 years. 86.5% patients are male with Male:Female ratio 6.4:1. Hafeez *et al*[11], reported in a pivotal study, the median age of the patients was 65 years with male preponderance (87.23%). Similar Male:Female ratio of 7.3:1 was seen in a study of Mitin *et al*[12].

Majority of the patients presented with T2 (69.2%) and T3 (25%) disease in our study, 63.5% patients had Clinical TNM stage II, 21.1% had stage IIIA and 15.4% had stage IIIB at presentation. Sang Jun *et al*[13]. in a Korean retrospective study (KROG14-16) reported 47.4%, 32.2% and 20.4% of stage II, stage III and stage IV respectively. This study also reported 63.8% patients presented with solitary tumour and 30.3% had multiple tumors, comparable to our study where solitary tumour and multiple tumor at presentation were 65.4% and 34.6% respectively. In all our 52 patients,

TURBT was attempted but Maximal TURBT, ie, no visible tumour after TURBT was seen in 63.5% and incomplete TURBT in 36.5% of patients. In GETUG 97-015 study with 53 patients Maximal TURBT was attempted for all patients but esteemed complete for only 33 (66%) patients[14].

As in our study, majority of patients are inoperable, continuous course of radiation was planned in protocol as done in the ERLANGEN protocol[15]. The conventional and mostly used radiotherapy fractional schedule with a dose of 64 Gy in 32 fractions over 6·5 weeks was delivered to the patients as done in the largest phase III UK BC2001 trial[16].

In our study, we use intravenous inj Cisplatin for its proven potent radiosensitizer properties in a dose of 70mg/meter^2 on days 1,21,43. This dose of cisplatin was validated in RTOG 88-02 trial[17]. Considering the compromised renal function in Bladder cancer patients a lower dose of Cisplatin instead of conventional 3 weekly dose (100mg/meter^2) was considered. Most of the patient tolerated this reduced dose cisplatin well.

Of the 47 patients who underwent full course of Chemoradiation, Complete Response (CR) was achieved in 25 patients (53.2%), Partial Response (PR) seen in 17 patients (36.2%) on initial assessment and one patient developed Progression of Disease (PD), both in form of locoregional and distant (lung) metastasis. Stable Disease (SD) found in 4(8.5%). All the patients with the residual disease were advised to undergo salvage treatment. Two patients were planned for salvage Cystectomy and thirteen patients for Palliative Chemotherapy, owing to inoperability. Two patients refused any further treatment. This is very similar to SWOG 9312 trial where out of the 53 total patients, 26 (49%) reported a Complete Response[18]. Recently RTOG 0524 included 66 patients with T2-T4 NXM0 disease who were considered medically inoperable and reported Complete Response rates at 1year 67.6% to 72.2%[19].

Hematological toxicity attributable to Chemo-radiotherapy included Grade 1, Grade 2, Grade 3 Neutropenia seen in 34%, 6.4% and 2.1% respectively. Grade 2 Anaemia occurred in 4.3% patients and Grade 1 Thrombocytopenia in 46.8%, Grade 2 Thrombo-cytopenia in none of patients. Hussain *et al* reported alike hematological profile in their study[20].

The most common toxicity recorded in present study was Cystitis followed by Diarrhoea. Grade 2 Cystitis was seen in 32 patients (68.1%), while Grade2 Diarrhoea occurred in 8.5% cases. Sabaa *et al*[21] reported Grade 1 or 2 Cystitis in 51.9% of patients and Grade 1 or 2 Diarrhoea in 35.6% of patients. Late toxicity in form of hydronephrosis developed in 2(4.3%), one of them died in spite of having initial CR.

In contrast to RC, treatment failure is a common concern for MIBC in the preserved Bladder. In our study, 3 patients (6.7%) with CR later developed in-bladder recurrence. In 2 patients with PR later developed locoregional recurrence (in-bladder and nodes) and distant(bone) progression, local (in-bladder) and distant(lung) progression. 1 patient with Stable Disease later developed bone only metastasis. Overall local recurrence till the last follow-up in the study was seen in 5 patients (11.1%). Previous studies reported in-bladder recurrence rates ranging from 19% to 58%, and muscle invasive recurrence was approximately half of non-muscle invasive recurrence. As reported by Rodel *et al*[15]. 5-year cumulative Bladder malignancy recurrence and MIBC recurrence rates was 41% and 28%, respectively. Regarding in-bladder recurrence sites, Tunio *et al*[22]. reported that 21% of patients having initial CR in tri-modality therapy showed MIBC recurrence, of which 69% were within the original MIBC site. Considering very short follow-up period of our study compared to these studies, these results are considerable.

Our results identified several prognostic factors related to response outcome, including patient age, T Stage, N Stage, multiplicity of tumor, Treatment time, Complete TURBT. Only Complete TURBT was associated with Complete Response and it was statistically significant. All other variables were found to be statistically insignificant, may be due to small sample size.

Presenting these findings, we opine that Concurrent Chemoradiotherapy with prior TURBT is well-tolerated with an acceptable rate of toxicities with good locoregional response and should be recommended in patients who are not candidates for surgery.

Limitation :

In the present study, there are several limitations. It was Single Institutional with a smaller sample size. It had a short median follow up to evaluate oncological outcome. We tried to identify associated variables as significant predictors of complete tumor response. However, there were few statistically significant predictors, likely due the lesser enrolment. With a Multi-Institutional study with larger sample size, significant predictors of tumor response could be identified.

Conclusion :

In patients with Muscle-Invasive Non-Metastatic Urinary Bladder Cancer who are unfit for surgery,

Concurrent Chemoradiotherapy could be considered as a effective and convenient therapeutic option with a high probability of local response, and tolerable toxicity profile.

More and more prospective multicentric researches with larger sample size and long term follow up are needed to confirm the results of our Single Institution study.

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Conflicts of Interest : None declared.

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