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RESEARCH ARTICLE
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CLINICAL OUTCOME OF MUSCLE INVASIVE BLADDER CANCER TREATED WITH DEFINITIVE RADIOTHERAPY

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ABSTRACT

BACKGROUND: The standard of care treatment approach for Muscle invasive bladder cancer (MIBC) at present is Radical Cystectomy. Organ preservation treatment is offered to patients with MIBC who are either not considered for surgery or patients who refuse surgical management. With this study we wanted to assess the clinical outcome of MIBC patients treated with organ preservation approach. **METODOLOGY**: This was a retrospective including MIBC patients treated at our centre with definitive raditherapy/ Chemoradiation.

RESULTS: Details of 18 patients were analysed. Majority of patients in our study were smokers (83%), males (94%) and had T3 as tumor stage. The most common histology was Urothelial carcinoma. Commonest RT schedule used was 60 Gy in 30 fractions (33%). Concurrent chemotherapy was given in six patients (33%). Only three patients (17%) had acute Grade 3 toxicity. Median OS in our study was 45 months. OS at 1 year,2 years and 5 years were 81.4%, 62.8% and 41.9% respectively. Median PFS of patients in this study was 39 months. PFS at 1 year,2 years,4 years were 69.8%, 59.9% and 44.9% respectively.

CONCLUSION: Our study showed that organ preservation approach for MIBC is a well tolerated treatment approach. PFS and OS in our study were slightly lesser compared to available literature. This could be due to the higher proportion of Stage III patients in our study and fewer patients

receiving concurrent chemotherapy due to multiple factors like multiple comorbidities and older age. Retrospective nature of study and the lesser number of patients are the limitations of this study.

INTRODUCTION

In India the annual incidence of Urinary bladder cancer is around 21,000 and worldwide it comprises 3% of all diagnosed new cases of cancer.(1)Transitional cell carcinoma (TCC) represents over 90% of bladder cancers and less common types include squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Muscle-invasive bladder cancer (MIBC) constitutes about 30% of newly diagnosed bladder cancers, with about 70% being non-invasive. About 15% of non-invasive bladder cancer cases progress to invasive cancer after transurethral resection of bladder tumor (TURBT).(2,3) Radical cystectomy with urinary diversion has long been considered the standard of treatment for Muscle invasive bladder cancer (MIBC).(4) Radiotherapy (RT) is an alternative treatment with comparatively good results for those who are too frail to undergo cystectomy or for those who refuse operation.(5,6) Radical RT with cystectomy for salvage is comparable with initial cystectomy and has the advantage of preserving normal bladder function.Studies have shown good survival rates with the approach of TURBT followed by concurrent chemoradiation.(7–9) To our knowledge there are only few studies which reported the outcome of organ preservation approach in MIBC from India.Hence with this study we intented to know the clinical outcome of organ preservation approach in MIBC.

METHODOLOGY

This was a study conducted in a tertiary cancer centre in India. This retrospective study aimed at assessing the clinical outcome of MIBC patients treated with definitive radiotherapy / chemoradiation and included patients treated during the period 1st January 2013 to 31st December 2022. The primary objectives of the study were to estimate the Overall survival (OS) and Progression free survival (PFS) of MIBC patients treated with definitive RT/ chemradiation. Secondary objective was to assess the acute toxicity profile of patients who underwent this treatment. Demographic details,treatment details and followup details will be recorded from case records and RT charts. Acute toxicities will be recorded as per CTCAE version 4.

Operational definition

- Overall survival(OS):Date of diagnosis to date of death/last followup
- PFS (Progression free survival) : Date of completion of treatment to date of locoregional recurrence or distant metastasis.

STATISTICAL ANALYSIS

The data was collected and recorded in the designed performa. All analysis were conducted using SPSS version 20.0. The data was expressed as frequencies, percentages,median (IQR),mean and standard deviation. Kaplan Meier method was used to estimate the OS & DFS. Log rank test was used to compare the survival between different composite stage, Neoadjuvant chemotherapy (NACT) usage and concurrent chemotherapy usage.

RESULTS

Total of details of 18 patients who received Definitive RT/ Chemoradiation were analysed. Clinicodemographic features of the patients included in the study are shown in Table1.

Treatment details of patients included in the study are shown in Table 2. NACT was given in three patients. One patient received Gemcitabine-Cisplatin combination, one patient received Gemcitabine-Carboplatin combination and one patient received Cisplatin-Etoposide combination. Among the six patients who were given concurrent chemotherapy, five received 40mg/m2 weekly Cisplatin as concurrent and one patient with small cell carcinoma received Cisplatin & Etoposide combination.

OS & PFS

Median Overall survival of all patients was 45 months. OS at 1 year,2 years and 5 years were 81.4%, 62.8% and 41.9% respectively. Kaplan Meier curve of overall survival is shown in Figure 1. Overall survival of patients with different composite stages were compared using logrank test, but there was no significant difference (p value 0.333). There was no significant difference in OS with and without Neoadjuvant chemotherapy (p value 0.064). There was no significant difference in survival with and without concurrent chemotherapy (p value 0.140) Median PFS of patients in this study was 39 months. PFS at 1 year,2 years,4 years were 69.8%, 59.9% and 44.9% respectively. Kaplan Meier curve of PFS is shown in Figure 2. There was no significant difference in PFS in different composite stages (p value 0.212). There was no significant difference in PFS with and without NACT usage (p value 0.47). There was no significant difference in PFS with and without concurrent chemotherapy (p value 0.298).

DISCUSSION

Median age of the patients in our study was 72 years, it was similar in other studies.(8,10) In usual clinical practice patients refusing surgery or who are not considered for surgery are given definitive RT / Chemo RT and incidence of bladder cancer increases with increasing age and these may be the reasons for an elderly population in our study. As it is already known, the patients were predominantly males in our study.(11) Since our patient group was elderly, almost 90% had comorbidities.Smoking is a well known etiological factor, and 83% of our patient group were smokers.(12,13) The most common histology was Urothelial carcinoma and there were two cases (11%) of small cell carcinoma among the patients. As per available literature the incidence of small cell carcimoma is less than 1%.(14) Predominant tumour stage was T3 (61%) in our patients and it was T2 (66%) in a large similar study.(15) Past history of Non muscle invasive bladder cancer (NMIBC) was observed in two (11%) patients. As per a meta analysis around 50% of high risk NMIBC can later on surveillance develop MIBC.(16) Incidence of MIBC in radical cystectomy specimen is around 57%.(17) In our study three (17%) patients received neoadjuvant chemotherapy, two of them had Gemcitabine & platinum based combination and one small cell carcinoma received Cisplatin & Etoposide combination. Before radical radiotherapy in NACT was given around 25% of patients in similar study.(15) Different radiotherapy schedules were used in our study since it is a retrospective study done over a period of 8 years and protocols might have changed over this period. All our patients were treated with conformal Radiotherapy technique and three dimensional conformal radiotherapy (3DCRT) being the commonest (67%) followed by Volumetric modulated arc therapy (33%). Patients have previously successfully treated with both 3DCRT and IMRT technique.(18,19) Concurrent chemoradiation was given in 7 (38%) of our patients and the chemotherapy given was weekly Cisplatin in six patients, as in similar studies and the proportion of patients receiving were lesser in our study.(8,9) Acute Grade III toxicities were observed in three (17%) patients and there were no Grade IV toxicities and toxicity rate was similar in a published study.(15) Clinical outcome in our study was assessed in our study in terms of OS & PFS. OS in our patients were 1 year,2 years and 5 years were 81.4%, 62.8% and 41.9% respectively. Available literature showed a slightly higher OS rates.(15,20) In our study 4 patients had disease progression during follow up period and among them two had local disease progression, while two had distant metastasis. PFS of our patients at 1 year,2 years,4 years were 69.8%, 59.9% and 44.9% respectively and this was also lesser compared to literature.(15,20) We could not find any difference in treatment outcome with factors like stage disease, NACT and concurrent chemotherapy, but these factors were associated with better outcome in a similar study.(20) Outcome in our study might have been influenced by the larger proportion of Stage III patients and lesser number of patients receiving neoadjuvant and concurrent chemotherapy.There are many limitations for this study. Retrospective nature and lesser number of patients being the major limitation. Prospective randomised studies comparing surgical and organ preservation approach in bladder carcinoma is needed in future for definitive answers.

CONCLUSION

This study showed that organ preservation approach with definitive RT/ Chemoradiation is a well tolerated approach for patients with MIBC who are either not considered for surgery or refuses surgery. Clinical outcome in terms of PFS and OS in our study slightly lower compared to available literature. In our patients majority had multiple comorbidities, they belonged an older age group hindering the use of concurrent chemotherapy and this could be the reason for lower PFS and OS. This retrospective study with less number of patients cannot definitively answer organ preservation approach as an alternative to radical cystectomy.Randomised prospective well conducted studies in future can definitively answer regarding the non inferiority of organ preservation approach. However the results of this study ascertain the fact that Organ preservation approach with definitive RT/ Chemoradiation is still a reasonable treatment option for patients with MIBC in whom radical cystectomy is not an option.

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Table 1 shows the clinicodemographic features of the patients .

Variable	**Values**
Age	Median : 72 years Range : 58-86 years
Gender	Males : 17 (94%) Females : 1 (6%)
Smokers	Yes : 15 (83%) No : 3 (17%)
ECOG Performance Status	I : 12 (67%) II: 6 (33%)
Comorbidities	Yes : 16 (89%) No : 2 (11%)
T stage	T2 : 6 (33%) T3: 11 (61%) T4 : 1 (6%)
Composite Stage	II (33%) III (67%)
Histology	Urothelial carcinoma : 15 (83%) Small cell carcinoma : 2 (11%) Adenocarcinoma : 1 (6%)
History of NMIBC	Yes : 2 (11%) No : 16 (89%)

Table 2 shows the treatment details of patients

Variable	Values
Neoadjuvant Chemotherapy	No : 15 (83%) Yes : 3 (17%)
RT technique	3DCRT : 12 (67%) VMAT : 6 (33%)
Different RT dosage schedules	60 Gy in 30 fractions : 6 (33%) 64 Gy in 32 fractions : 3 (17%) 66 Gy in 33 fractions : 2 (11%) 64.8 Gy in 36 fractions: 2 (11%) 59.4 Gy in 33 fractions: 3 (17%) 55 Gy in 20 fractions : 2 (11%)
Concurrent Chemotherapy	No : 12 (67%) Yes : 6 (33%)
Grade III/IV acute toxicity	Yes : 3 (17%) No : 15 (83%)

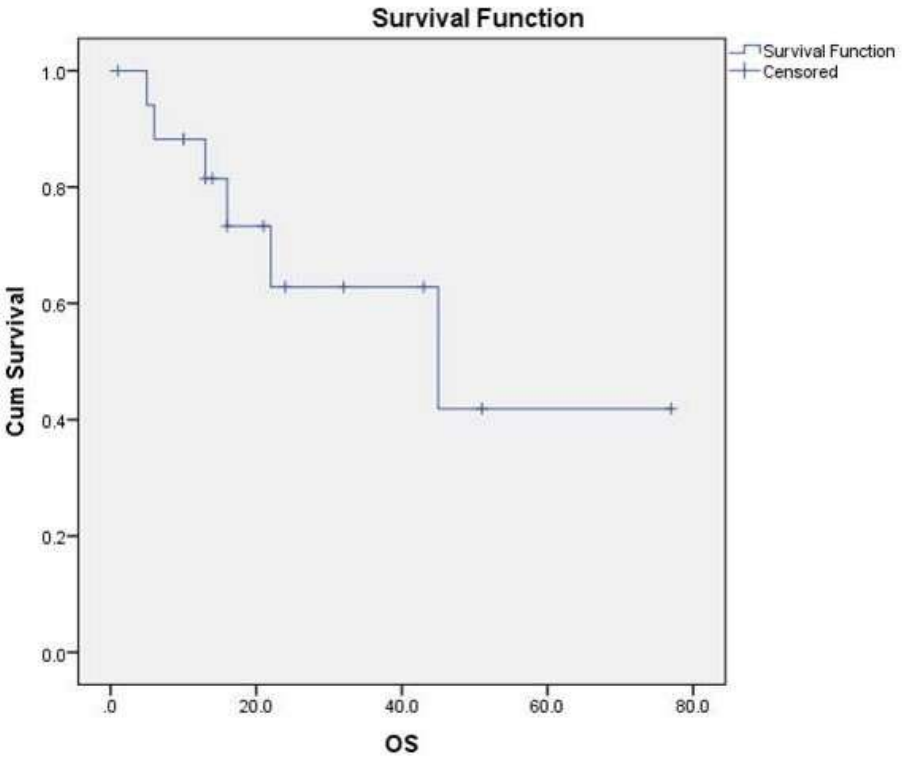

Figure 1 shows Overall survival Kaplan Meier Plot

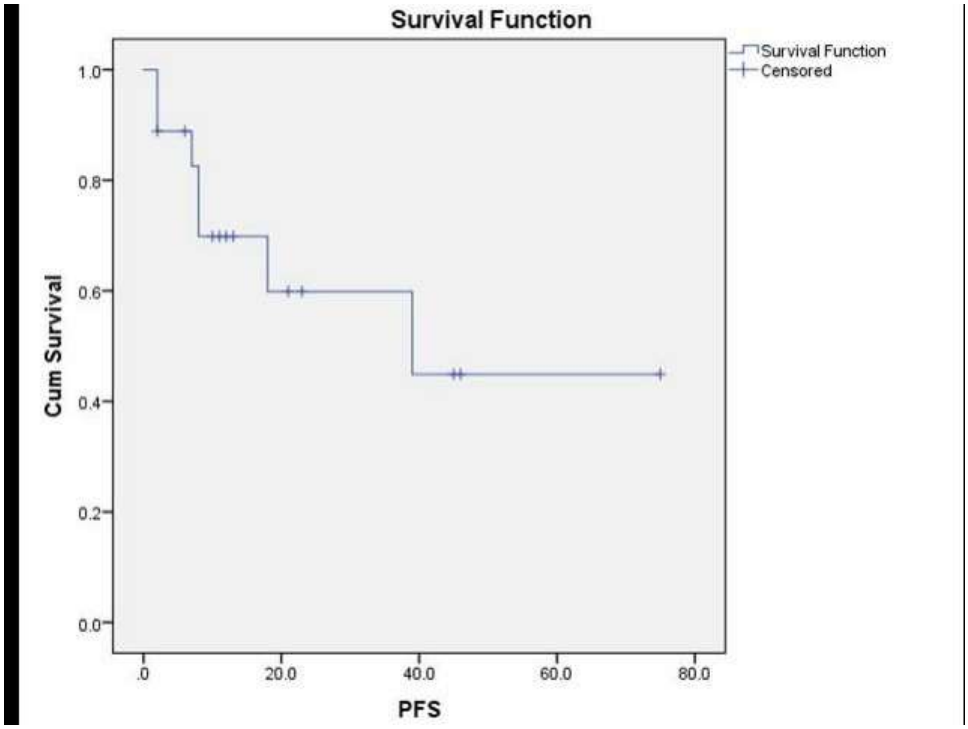

Figure 2 shows the PFS Kaplan Meier Plot