Sequential Chemotherapy Followed by Radiotherapy Versus Concurrent Chemo-Radiation in Muscle Invasive Bladder Cancer

Mohammad hasan larizadeh[1], fateme arabnejad[2*], mohammad reza ebadzadeh[3]

1. Associate Professor of radiation oncology, Kerman medical university of Iran
2. assistant professor of radiation oncology, Kerman medical university of Iran
3. Associate Professor of urology, Kerman medical university of Iran

*corresponding author

Abstract:
Bladder cancer is diagnosed at older age compared to all other known cancer types. Radical cystectomy after neoadjuvant chemotherapy or tri-modality treatment (consist of TURB, concurrent chemo-radiation) are the standard treatments. Many of the patients cannot receive tri-modality treatment (concurrent chemo-radiation) because of medical comorbidities. The present study assessed the results of sequential use of chemotherapy and radiotherapy versus concurrent use of them in 266 muscle invasive bladder cancer patients. The results showed similar overall survival but lower disease-free survival in the sequential group. Recurrence rate was higher in the concurrent group. The results showed that sequential use of chemotherapy and radiotherapy provides comparable results to concurrent use of them and provides better results than less than tri-modality treatments.

INTRODUCTION:

The GLOBOCAN estimated 573,278 new bladder cancer cases and 212,536 bladder cancer deaths in 2020 worldwide in the latest report on the global cancer burden[(1)]. Evidence has shown that bladder cancer, the ninth most common type of cancer worldwide, and the most common urinary tract cancer is diagnosed at older age compared with all other known cancer types [(2)]. Nearly 25% of new cases are muscle-invasive bladder cancer (MIBC) (T2-T4 disease), which has a 5-year survival of 15% without treatment[(3)]. Radical cystectomy (RC) after neo-adjuvant cisplatin-based combination chemotherapy is the gold standard of treatment for muscle invasive bladder cancer, but some patients have medically inoperable disease or refuse cystectomy to preserve their bladder function. A representative bladder preservation therapy (BPT) that uses concurrent chemo-radiotherapy (CCRT) following maximal transurethral resection of the bladder tumor (TURBT) is named tri-modal therapy (TMT). It is considered as an alternative curative treatment to RC for carefully selected MIBC patients who desire bladder preservation (elective cases) and for those medically unfit for RC (imperative cases). TMT is ranked conditionally as category 1 in the treatment of locally advanced MIBC according to the National Comprehensive Cancer Network (NCCN) guideline published in 2022 which resulted in comparable outcomes to RC for properly selected patients [(4)].
Chemotherapy is an important component of TMT, as the randomized BC2001 trial showed that chemo-radiation provides superior loco-regional disease free survival compared to radiation alone [(5)]. A large proportion of patients with MIBC are elderly and with renal dysfunction; therefore, many could not receive a complete course of chemotherapy with cisplatin during bladder preservation therapy [(6)]. Studies show that older adults with MIBC tend to have poorer

cancer-specific survival compared with younger patients, probably due to a lower rate of standard-of-care (RC and tri-modality therapy) [7].
In the recent UPTODATE guideline, radiation with or without chemotherapy is preferred in the frail patients who are not surgical candidates or who elect bladder sparing treatment approach and for the patients who are ineligible for or decline radiotherapy, systemic therapy is a reasonable alternative [8].
To date, data on the survival and local control outcomes for MIBC patients undergoing sequential chemotherapy and radiotherapy in the setting of unsuitability for concurrent therapy are still limited, and the findings are inconsistent[5,9,10]. The absence of evidence from randomized clinical trials makes the results from observational studies valuable. So, the study was designed to retrospectively evaluate the feasibility and outcome of sequential chemotherapy/radiotherapy in comparison to concurrent chemo-radiation in MIBC patients after TURBT.

Materials and Methods

The present retrospective case series study was conducted at the Shafa radiotherapy center of Kerman. It has been approved in Kerman medical university ethics committee by the code: IR.KMU.REC.1401.949 Medical records of the patients with bladder cancer were collected from April ٢٢, ١٩٩٤, to April 12, 2021. Patients co-diagnosed with any other cancers, a history of prior malignancy, non-urothelial cell carcinoma (non-transitional cell carcinoma, or variant histology), multiple/unknown primary, node positive, metastasis present, short RT schedule on request for fragile patients or received palliative intent therapy, presence of extensive carcinoma in-situ (CIS) and missing clinical stage and treatment information were excluded. Clinical staging for all cases has been assessed, by abdomino-pelvic CT scan, cystoscopy and TURB. One TURB was considered as standard, but there was some exceptions such as suboptimal TURB, any T1 ang absence of muscle in the specimen. Suboptimal TURB was considered as incomplete resection of the mass in the sonography.
Muscle-invasive cancer was defined as localized non-metastatic bladder cancer (clinical stage T2-4N0M0). From MIBC patients, concurrent chemo-radiation treated and sequential chemotherapy/radiotherapy treated patients were collected. There was no randomization between the groups. Selection of the sequential use of chemo-radiation has been based on the patient condition, comorbidities and the physician's choice. Medical comorbidities, age, gender, recurrence time and TURB type (optimal/suboptimal), hematologic and gastrointestinal toxicities were recorded by the NCI version 4 grading system.
Suboptimal TURB was defined as reside in the post cystoscopy TURB.
The survival data was collected by calling the patient registered phone number. Radiotherapy dose and chemotherapy regimen were recorded. Local recurrence was defined as a histologically proven urothelial carcinoma of the bladder or a papillary bladder tumor on cystoscopy or urine cytology that showed a suspicion of high-grade urothelial carcinoma. Follow-up time was calculated from the first visit to the last visit by the physician. The patients were visited regularly during the follow up time. The first documented recurrence was noted as the recurrence time. Radiotherapy total doses was 60 Gy (2 Gy/fraction) delivered to the bladder and pelvic lymph nodes, in two phases (first 44 Gy to whole pelvis and then up to 60 Gy as a boost to the bladder), using a four-field box three-dimensional conformal radiotherapy technique. In the concurrent group the chemotherapy regimen was 5-fluorouracil alone or cisplatin alone (40 mg/m^2 cisplatin every week during radiotherapy). In the sequential group, the chemotherapy regimen was

gemcitabine and cisplatin (1000 mg/m2 gemcitabine on day 1, 8 and 75 mg/m^2 cisplatin on day 1 repeated every three weeks) or gemcitabine and carboplatin (1000 mg/m2 gemcitabine on day 1, 8 and 5 AUC carboplatin on day 1 repeated every three weeks).

Incomplete response to concurrent or sequential chemo-radiotherapy in the follow up was referred for radical cystectomy. Data was analyzed by SPSS 22 software. Descriptive statistics presented the baseline characteristics in the sequential and concurrent groups. Categorical variables were evaluated via Chi-square tests and continuous variables by ANOVA. The 2-year, 3-year and 5-year overall survival and disease-free survival rates were estimated using the Kaplan-Meier method. Log-rank test was used to compare survival outcomes according to various factors. To define independent prognostic factors Cox regression analysis was used. Significance level for all tests was set at p-value< 0.05.

Results:

In the present study, 275 patients were enrolled. 9 of them were excluded because of incomplete recordings. The mean follow-up time was 28 months (Range: 1-890 months, SD: 61.7). The patient's characteristics and treatment details have been shown in Table 1.
Median age in all the patients was 66.4±10.58 years and there was no significant difference between the age of concomitant (65.18 years) and sequential (67.18 years) group, (P-value: 0.216). There was no significant difference in the T-stage between the treatment groups (P-value: 0.629).

Hematologic toxicities was seen in 42.9% of the concurrent group (grade I, II: 40.18%(n=43), grade III, IV: 2.8%(n=3)) and 20.7% of the sequential group (grade I, II: 20.1%(n=32), grade III, IV: 0.6%(n=1)) .
Gastro-intestinal toxicities was seen in 22.42% of the concurrent group (grade I, II: 21.49%(n=23), grade III, IV: 0.9%(n=1)) and 15.7% of the sequential group (grade I, II: 15.7%(n=25), grade III, IV: 0%(n=0)) .

Median survival time was 56±17.68 (CI: 21.34-90.65) months. The 2- year, 3- year and 5- year overall survival rates for all the patients were estimated to be 76%, 64% and 48%, respectively (Figure 1). The survival curves according to T stage, Treatment type and TUR type has been shown in Figure 2. Log-Rank test showed no significant difference in survival rates according to T-stage (p=0.5), treatment modality (p=0.09) and TUR type (p=0.46). However, multivariate analysis showed that T stage had a statically significant relation with survival (p=0.01). Treatment modality (p=0.054) and TUR type (p=0.7) had no significant correlation.
Median survival time according T stage for T2, T3 and T4 was 61.22, 41.91 and 17.6 months respectively (P-valve: 0.463). Two-year overall survival was 77% in T2, 77% in T3 and 36% in T4. Five-year overall survival was 50% in T2 and 49% in T3, (Figure 2).
Median survival time was 65 months in concurrent CRT group and 54.47 months in sequential group (P-valve: 0.93). Two-year overall survival was 80% in concurrent group and 74% in sequential group. Five-year overall survival was 57% in concurrent group and 43% in sequential group (Figure 2).

Median survival time was 56.49 month in optimal and 61.31% in suboptimal cases (P-valve: 0.463) (figure 2). Two-year overall survival was 77% and 74% in optimal and suboptimal TURB cases, respectively. Five-year overall survival was 48% and 56% in optimal and suboptimal TURB cases, respectively.

Recurrence was experienced in 71 cases of all the patients within 5 years that 41 of them had received concurrent and 30 of them received sequential treatment. From 71 recurrences, 13 had metastasis, 26 were muscle invasive and 32 were non-muscle invasive. MIBC and NMIBC were treated by chemotherapy, TURB, intravesical CTX or intravesical BCG. No salvage cystectomy was done possibly because of comorbidities. Median disease-free survival was 15 (10.01-19.98, SD: 2.5) months in all the patients, 26 (10-91.9, SD: 8.1) months in the concurrent group and 12(8.2-15.7, SD: 1.9) in the sequential group. The 2- year, 3- year and 5- year disease free survival rates for the concurrent group were 50%, 42% and 27% and was 37%, 33% and 20% for the sequential group respectively. Disease free survival was more in the concurrent group in the logrank test (p-value: 0.024). On the cox regression analysis treatment modality was the only variable that had significant relation with disease free survival (p-value: 0.04). Other variables did not have a significant relationship, T-stage (p-value: 0.9), TUR type (p-value: 0.2), gender (p-value: 0.9) and age (p-value: 0.1). Recurrence rate was significantly lower in the sequential group (P-value<0.0001), (figure 6). Median time to recurrence was 29.04±34.26 months, 34.16±42.26 months in concurrent group and 25±26.31 months in sequential group and there was no significant difference in the time to recurrence in concurrent and sequential group (P-value=0.299). There was no difference in recurrence time according the gender (P-value=0.51).

Table1. Patient characteristics & Treatment information

Characteristics	Results
Age: Mean (Range, SD)	66.4 (31-90,10.58)
Gender: Number (%) Male Female	 221(83.1) 45(16.9)
T stage: Number (%) T2 T3 T4	 234(88) 27(10.2) 5(1.9
Treatment modality Concomitant Sequential	 107(40.2) 159(59.8)
TUR type Optimal Suboptimal	 250(94) 16(6)

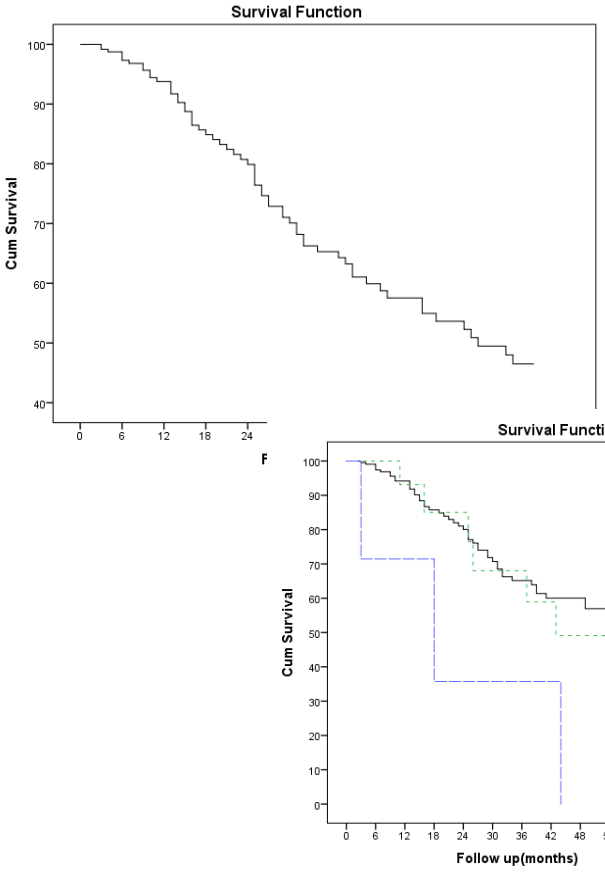

Figure1. Overall survival (A) & Recurrence free survival (B) curves for all the patients

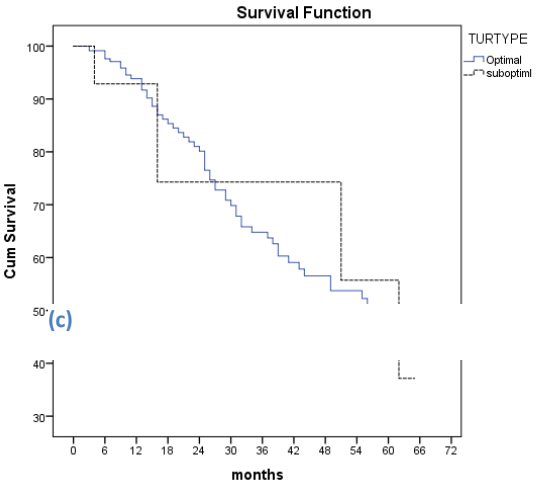

Figure2. Overall survival curves according to T stage (A), Treatment type (B) & TUR type(C)

Discussion:

To our best knowledge, this is one of the largest retrospective studies reporting outcomes of bladder-sparing concurrent and sequential chemotherapy/radiotherapy in MIBC patients. Radical cystectomy after neo-adjuvant cisplatin-based combination chemotherapy is the gold standard of treatment for muscle invasive bladder cancer and concurrent chemo-radiotherapy following maximal transurethral resection of the bladder tumor named tri-modal therapy is considered as an alternative curative treatment.

Sequential versus concurrent chemo-radiation in a tri-modality manner:

Chemotherapy is an important part of tri-modality therapy, as the randomized BC2001 trial showed that chemo-radiation provides superior loco-regional disease free survival compared to radiation alone.(5) Chemotherapy can potentially improve loco-regional control, as up to 50% of patients with MIBC may have occult metastasis. Omitting the chemotherapy from chemo-radiation therapy in fragile patients will compromise the oncologic outcomes [(11)]. In the circumstances that the patient cannot receive sufficient concurrent chemotherapy because of comorbidity or poor medical condition, the patient will be deprived of these clinical benefits, and we aimed to assess the feasibility and results of the sequential use of chemotherapy and radiotherapy (to reduce the toxicity and treatment interruptions) as compared to the concurrent use.

In terms of median survival, the present study showed comparable results between concurrent CRT and sequential CRT. Median survival time was 65 months and five-year overall survival was 57% in concurrent group, which is comparable to the literature that shows localized muscle invasive bladder cancer (MIBC, stage ≥T2) has a 5-year overall survival of 40–60% with concurrent chemo-radiation[(12,13)]. Two-year survival was 74% and five-year survival was 43% in the sequential group. There are just few articles that report the results of sequential use of chemotherapy and radiotherapy, in which the estimated 5 year overall survival is to be 52% [(10)], but comparing our results for sequential chemo-radiotherapy with the data for definitive radiotherapy in the literature shows superiority of sequential therapy in terms of overall survival and local control (27.6% five year survival and 67% two year local control for radiotherapy alone)[(9-14)].

Median disease-free survival was 15±2.54 months in our study. The 3- year and 5- year disease free survival rates for the concurrent group were estimated to be 50% and 42% respectively, which are comparable and even better that the reported disease free survival (DFS) for tri-modality therapy in some other studies, in which 3 year and 5 year DFS has been 44% and 29.1% respectively [15] .
Disease free survival was more in the concurrent group. Recurrence rate was significantly lower in the sequential group in our study that might be due to lower interruptions during the treatment.

Sequential chemo-radiation versus less than tri-modality therapy:
For patients with MIBC who are ineligible radical cystectomy or tri-modality therapy, radical TURBT alone, partial cystectomy with or without lymphadenectomy, chemotherapy alone or maximum TURBT + radiotherapy alone can be potential alternatives [15].
Evidence has shown that such palliative treatments showed inferior OS than tri-modality therapy. Therefore, aggressive treatment should be provided as much as possible [16,17].
However recently some studies have investigated the role of radiotherapy alone in the patients who are not suitable for chemotherapy and have reported that EBRT without chemotherapy could still be a feasible alternative treatment to maintain quality of life and achieve acceptable local control rates, but still lower than combined modality treatments[14, 18-21]. Also, accelerated hypo-fractionated radiotherapy alone has shown good local control in elderly patients unfit for chemo-radiotherapy [22,23].
On the other hand neo-adjuvant chemotherapy was shown to lead to down-staging in some patients, in a way that 30% to 40% of patients having no residual disease at time of radical cystectomy which shows the inevitable and significant role of chemotherapy alone [24]. The addition of neo-adjuvant chemotherapy to definitive radiation-alone provides a 6% overall survival benefit (10) , even in the elderly patients (11). A study on 976 bladder cancer patients showed that three cycles of CMV (cisplatin, methotrexate, vinblastine) chemotherapy before radiotherapy or cystectomy results in a 16% reduction in the risk of death, corresponding to an increase in 3-year survival from 50% to 56%, 10-year survival from 30% to 36%, and median survival time of 7 months (from 37 to 44 months). The reductions in the risk of death with CMV were 20% for the radiotherapy alone groups, and for loco-regional disease-free survival, chemotherapy given before radiotherapy caused a 9% reduction in risk (10). Although, this study shows a significant effect of chemotherapy before local therapy but the results could not be compared to ours because of the inclusion of radical cystectomy in the local therapy group in the final analysis. In a cohort of 63 patients who refused RC after complete response following neoadjuvant chemotherapy. The 5-year OS was 64%; however, the relapse rate was relatively high at 64%, with 38% (24 patients) of recurrence being muscle-invasive. The median time to recurrence was 16 months, which is much shorter than the results of our study for median time to recurrence in the sequential group that was 29 months which shows the inadequacy of single modality treatment even in the presence of pathologic complete response [25].
External beam radiotherapy (EBRT) has been shown to lead to complete regression of MIBC in up to 70% of patients, however, more than 50% of individuals will develop metastatic disease and 5-year OS is only 20–30% which is significantly lower than 5 year survival in the sequential group of our study that was 43%[26].
Comparing recurrence in concurrent and sequential chemotherapy radiotherapy groups, our data showed equal time to recurrence but lower recurrence rate in the sequential group which might be due to more comorbidity in the sequential group and lack of adequate referral for follow-up.

On the uni-variant analysis, there was no significant difference in the survival according T-stage but in the multi-variant analysis T-stage was a predictive factor for survival that could be due to small number of cases in the T4 group.

By considering the significant but inadequate response to chemotherapy alone or radiotherapy alone after TURBT, it seems that combining these modalities in a sequential order would be a reasonable offer for the fragile patients, a hypothesis which is powered by the results of the present study that shows comparable outcomes between sequential and concurrent use of chemotherapy and radiotherapy.

Conclusion:
The results of our study showed that sequential use of chemotherapy and radiotherapy provides comparable results to concurrent use of them and provides better results than less than tri-modality treatments. These results are important because they fill an existing gap in the literature regarding whether the sequential use of chemotherapy and radiotherapy can be a suitable substitute to concurrent chemo-radiation in special circumstances that the concurrent use is not possible.

Limitations:
There are several limitations to our study. First, Frail patients were often only seen in case of complaints and did not always undergo follow-up cystoscopy. This may have impacted the reported local control rates in this group.
Second, by considering the retrospective design of the study, the cases could not be well-matched and there was no randomization between the groups, so the sequential group probably had more medical complications and had been more frail.

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