Sequential Chemotherapy Followed b y Radiotherapy Versus Concurrent Chemoradiotherapy in Muscle-Invasive Bladder Cancer

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Purpose: To date, data on survival and local control outcomes in patients with muscle-invasive bladder cancer who undergo sequential chemotherapy and radiotherapy after transurethral resection of bladder tumor, when they are unsuitable for concurrent therapy (trimodality treatment), are limited. Therefore, this study was designed to evaluate the feasibility and outcomes of sequential chemotherapy/radiotherapy compared with concurrent chemoradiotherapy in patients with muscle-invasive bladder cancer.

Materials and Methods: This retrospective study was conducted at the Shafa Radiotherapy Center in Kerman, Iran. The 2-, 3-, and 5-year overall survival and disease-free survival rates were estimated using the Kaplan-Meier method. The log-rank test was used to compare survival outcomes according to various factors, and Cox regression analysis was used to identify independent prognostic factors.

Results: Among 266 patients, the 2-year overall survival was 80% in the concurrent group and 74% in the sequential group. Disease-free survival was longer in the concurrent group according to the log-rank test (P = .024). Within 5 years, recurrence occurred in 71 patients, of whom 41 had received concurrent treatment and 30 had received sequential treatment.

Conclusion: Sequential chemotherapy and radiotherapy provide results comparable to those of concurrent chemoradiotherapy and better results than less-than-trimodality treatments.

Keywords: urinary bladder neoplasms; chemoradiotherapy; radiotherapy; drug therapy; survival analysis; disease-free survival

INTRODUCTION

In its latest report on the global cancer burden, GLOBOCAN estimated 573,278 new bladder cancer cases and 212,536 bladder cancer deaths worldwide in 2020.[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 an older age than 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 rate of 15% without treatment.[3] Radical cystectomy (RC) after neoadjuvant cisplatin-based combination chemotherapy is the gold standard of treatment for MIBC; however, some patients have medically inoperable disease or refuse cystectomy to preserve their bladder function. A representative bladder preservation therapy (BPT) that uses concurrent chemoradiotherapy (CCRT) following maximal transurethral resection of bladder tumor (TURBT) is termed trimodality therapy (TMT). TMT is considered an alternative curative treatment to RC for carefully selected patients with MIBC who desire bladder preservation (elective cases) and for those who are medically unfit for RC (imperative cases). According to the National Comprehensive Cancer Network (NCCN) guideline published in 2022, TMT is conditionally ranked as category 1 in the treatment of locally advanced MIBC, as it has resulted in outcomes comparable to those of RC in properly selected patients.[4] Chemotherapy is an important component of TMT, as the randomized BC2001 trial showed that chemoradiotherapy provides superior locoregional disease-free survival (DFS) compared with radiation alone.[5] A large proportion of patients with MIBC are elderly and have renal dysfunction; therefore, many could not receive a complete course of chemotherapy with cisplatin during BPT.[6] Studies show that older adults with MIBC tend to have poorer cancer-specific survival than younger patients, probably owing to lower rates of standard-of-care treatment (RC and TMT).[7]

According to the recent UpToDate guideline, radiation with or without chemotherapy is preferred for frail patients who are not surgical candidates or who elect a bladder-sparing treatment approach, and for patients who are ineligible for or decline radiotherapy, systemic therapy is a reasonable alternative.[8]

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Table 1. Patient characteristics and treatment information

Characteristics	Results
Age, mean (range; SD), years	66.4 (31-90; 10.58)
Gender, No. (%)	
Male	221 (83.1)
Female	45 (16.9)
T stage, No. (%)	
T2	234 (88)
T3	27 (10.2)
T4	5 (1.9)
Treatment modality, No. (%)	
Concurrent	107 (40.2)
Sequential	159 (59.8)
TURBT type, No. (%)	
Optimal	250 (94)
Suboptimal	16 (6)

Abbreviations: TURBT, transurethral resection of bladder tumor.

To date, data on survival and local control outcomes for patients with MIBC undergoing sequential chemotherapy and radiotherapy when they are unsuitable 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 of observational studies valuable. Therefore, this study was designed to retrospectively evaluate the feasibility and outcomes of sequential chemotherapy/radiotherapy compared with CCRT in patients with MIBC after TURBT.

MATERIALS AND METHODS

This retrospective case series study was conducted at the Shafa Radiotherapy Center of Kerman. It was approved by the Ethics Committee of Kerman University of Medical Sciences (code: IR.KMU.REC.1401.949). Medical records of patients with bladder cancer were collected from April 22, 1994, to April 12, 2021. Patients were excluded if they had been co-diagnosed with any other cancer; had a history of prior malignancy; had non-urothelial cell carcinoma (non-transitional cell carcinoma or variant histology); had a multiple/unknown primary tumor; had node-positive disease or metastasis; had received a short radiotherapy schedule on request (for frail patients) or palliative-intent therapy; had extensive carcinoma in situ (CIS); or had missing clinical stage and treatment information. Clinical staging for all cases was assessed by abdominopelvic CT scan, cystoscopy, and TURBT. A single TURBT was considered standard; however, there were some exceptions, such as suboptimal TURBT, any T1 disease, and absence of muscle in the specimen. Suboptimal TURBT was considered incomplete resection of the mass on sonography.

Muscle-invasive cancer was defined as localized nonmetastatic bladder cancer (clinical stage T2-4N0M0). Among patients with MIBC, those treated with CCRT and those treated with sequential chemotherapy/radiotherapy were collected. There was no randomization between the groups. The selection of sequential chemoradiotherapy was based on the patient's condition, comorbidities, and the physician's choice. Medical comorbidities, age, gender, recurrence time, and TURBT type (optimal/suboptimal) were recorded, and hematologic and gastrointestinal toxicities were recorded according to the National Cancer Institute grading system, version 4.

Suboptimal TURBT was also defined as residual tumor on post-TURBT cystoscopy.

Survival data were collected by calling the patients' registered phone numbers. Radiotherapy dose and chemotherapy regimen were recorded. Local recurrence was defined as histologically proven urothelial carcinoma of the bladder, a papillary bladder tumor on cystoscopy, or urine cytology suspicious for high-grade urothelial carcinoma. Follow-up time was calculated from the first visit to the last visit by the physician. Patients were visited regularly during the follow-up period. The first documented recurrence was recorded as the recurrence time.

The total radiotherapy dose was 60 Gy (2 Gy/fraction) delivered to the bladder and pelvic lymph nodes in two phases (first, 44 Gy to the 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 (cisplatin 40 mg/m2 every week during radiotherapy). In the sequential group, the chemotherapy regimen was gemcitabine plus cisplatin (gemcitabine 1000 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 on day 1, repeated every 3 weeks) or gemcitabine plus carboplatin (gemcitabine 1000 mg/m2 on days 1 and 8 and carboplatin at an area under the curve of 5 on day 1, repeated every 3 weeks).

Patients with an incomplete response to concurrent or sequential chemoradiotherapy during follow-up were referred for RC. Data were analyzed using SPSS software, version 22. Descriptive statistics were used to present the baseline characteristics of the sequential and concurrent groups. Categorical variables were evaluated using the χ^2 test and continuous variables using ANOVA. The 2-, 3-, and 5-year overall survival (OS) and DFS rates were estimated using the Kaplan-Meier method. The log-rank test was used to compare survival outcomes according to various factors. Cox regression analysis was used to identify independent prognostic factors. The significance level for all tests was set at $P < .05$.

RESULTS

A total of 275 patients were enrolled in the present study, 9 of whom were excluded because of incomplete records. The mean follow-up time was 28 months (range, 1-890 months; SD, 61.7). Patient characteristics and treatment details are shown in **Table 1**.

The mean (SD) age of all patients was 66.4 (10.58) years, and there was no significant difference in age between the concurrent (65.18 years) and sequential (67.18 years) groups ($P = .216$). There was no significant difference in T stage between the treatment groups ($P = .629$).

Hematologic toxicities were observed in 42.9% of the concurrent group (grade I-II: 40.18% [n = 43]; grade III-IV: 2.8% [n = 3]) and in 20.7% of the sequential group (grade I-II: 20.1% [n = 32]; grade III-IV: 0.6% [n = 1]).

Gastrointestinal toxicities were observed in 22.42% of the concurrent group (grade I-II: 21.49% [n = 23]; grade III-IV: 0.9% [n = 1]) and in 15.7% of the sequential group (grade I-II: 15.7% [n = 25]; grade III-IV: 0% [n = 0]).

The median survival time was 56 ± 17.68 months (CI, 21.34-90.65). The 2-, 3-, and 5-year OS rates for all patients were estimated to be 76%, 64%, and 48%, re-

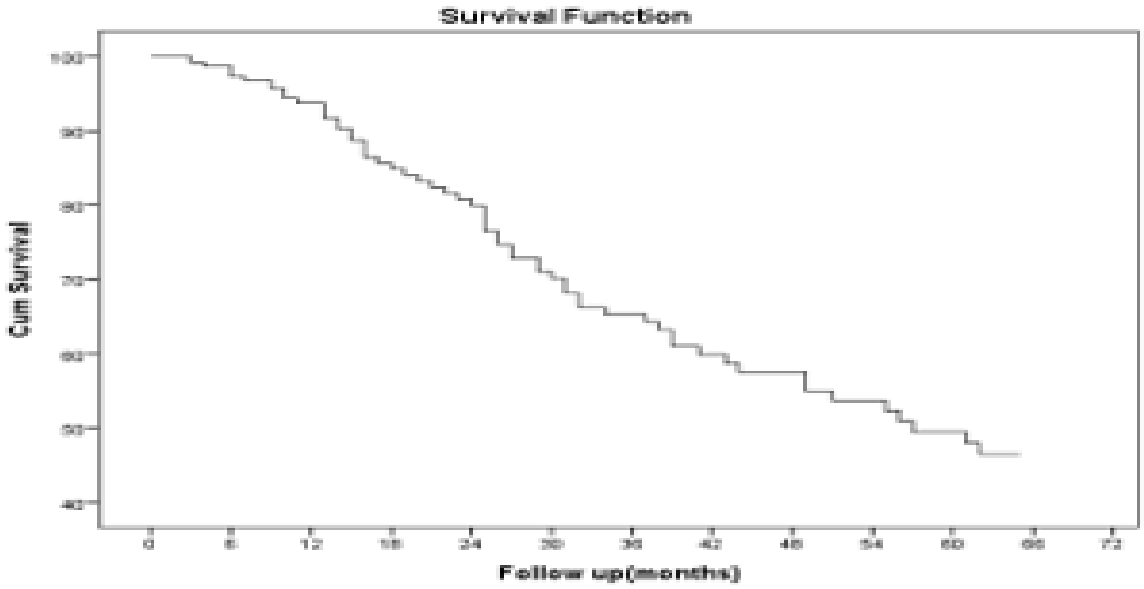

Figure 1. Overall survival (A) and recurrence-free survival (B) curves for all patients.

spectively (**Figure 1**). The survival curves according to T stage, treatment type, and TURBT type are shown in Figure 2. The log-rank test showed no significant difference in survival rates according to T stage (P = .5), treatment modality (P = .09), or TURBT type (P = .46). However, multivariate analysis showed that T stage had a statistically significant association with survival (P = .01), whereas treatment modality (P = .054) and TURBT type (P = .7) had no significant correlation.

The median survival times according to T stage for T2, T3, and T4 were 61.22, 41.91, and 17.6 months, respectively (P = .463). The 2-year OS was 77% in T2, 77% in T3, and 36% in T4. The 5-year OS was 50% in T2 and 49% in T3 (**Figure 2**).

The median survival time was 65 months in the CCRT group and 54.47 months in the sequential group (P = .93). The 2-year OS was 80% in the concurrent group and 74% in the sequential group. The 5-year OS was 57% in the concurrent group and 43% in the sequential group (**Figure 2**).

The median survival time was 56.49 months in optimal and 61.31 months in suboptimal TURBT cases (P = .463) (**Figure 2**). The 2-year OS was 77% and 74% in optimal and suboptimal TURBT cases, respectively. The 5-year OS was 48% and 56% in optimal and suboptimal TURBT cases, respectively.

Within 5 years, recurrence occurred in 71 patients, of whom 41 had received concurrent treatment and 30 had received sequential treatment. Of the 71 recurrences, 13 were metastatic, 26 were muscle invasive, and 32 were non-muscle-invasive bladder cancer (NMIBC). Recurrent MIBC and NMIBC were treated with chemotherapy, TURBT, intravesical chemotherapy, or intravesical BCG. No salvage cystectomy was performed, possibly because of comorbidities. The median DFS was 15 months (10.01-19.98; SD, 2.5) in all patients, 26 months (10-91.9; SD, 8.1) in the concurrent group, and 12 months (8.2-15.7; SD, 1.9) in the sequential group. The 2-, 3-, and 5-year DFS rates were 50%, 42%, and 27%, respectively, for the concurrent group and 37%, 33%, and 20%, respectively, for the sequential group. DFS was longer in the concurrent group according to the log-rank test (P = .024). In the Cox regression analysis, treatment modality was the only variable that had a significant association with DFS (P = .04). Other variables did not have a significant association, including T stage (P = .9), TURBT type (P = .2), gender (P = .9), and age (P = .1). The recurrence rate was significantly lower in the sequential group (P < .0001) (Figure 6). The median time to recurrence was 29.04 ± 34.26 months overall, 34.16 ± 42.26 months in the concurrent group, and 25 ± 26.31 months in the sequential group, and there was no significant difference in the time to recurrence between the concurrent and sequential groups (P = .299). There was no difference in recurrence time according to gender (P = .51).

DISCUSSION

To the best of our knowledge, this is one of the largest retrospective studies reporting the outcomes of bladder-sparing concurrent and sequential chemotherapy/radiotherapy in patients with MIBC.

RC after neoadjuvant cisplatin-based combination chemotherapy is the gold standard of treatment for MIBC, and CCRT following maximal TURBT, termed TMT, is considered an alternative curative treatment. Sequential Versus Concurrent Chemoradiotherapy in a

Trimodality Manner

Chemotherapy is an important part of TMT, as the randomized BC2001 trial showed that chemoradiotherapy provides superior locoregional DFS compared with radiation alone.[5] Chemotherapy can potentially improve locoregional control, as up to 50% of patients with MIBC may have occult metastasis. Omitting chemotherapy from chemoradiotherapy in frail patients will compromise oncologic outcomes.[11] In circumstances in which the patient cannot receive sufficient concurrent chemotherapy because of comorbidity or poor medical condition, the patient will be deprived of these clinical

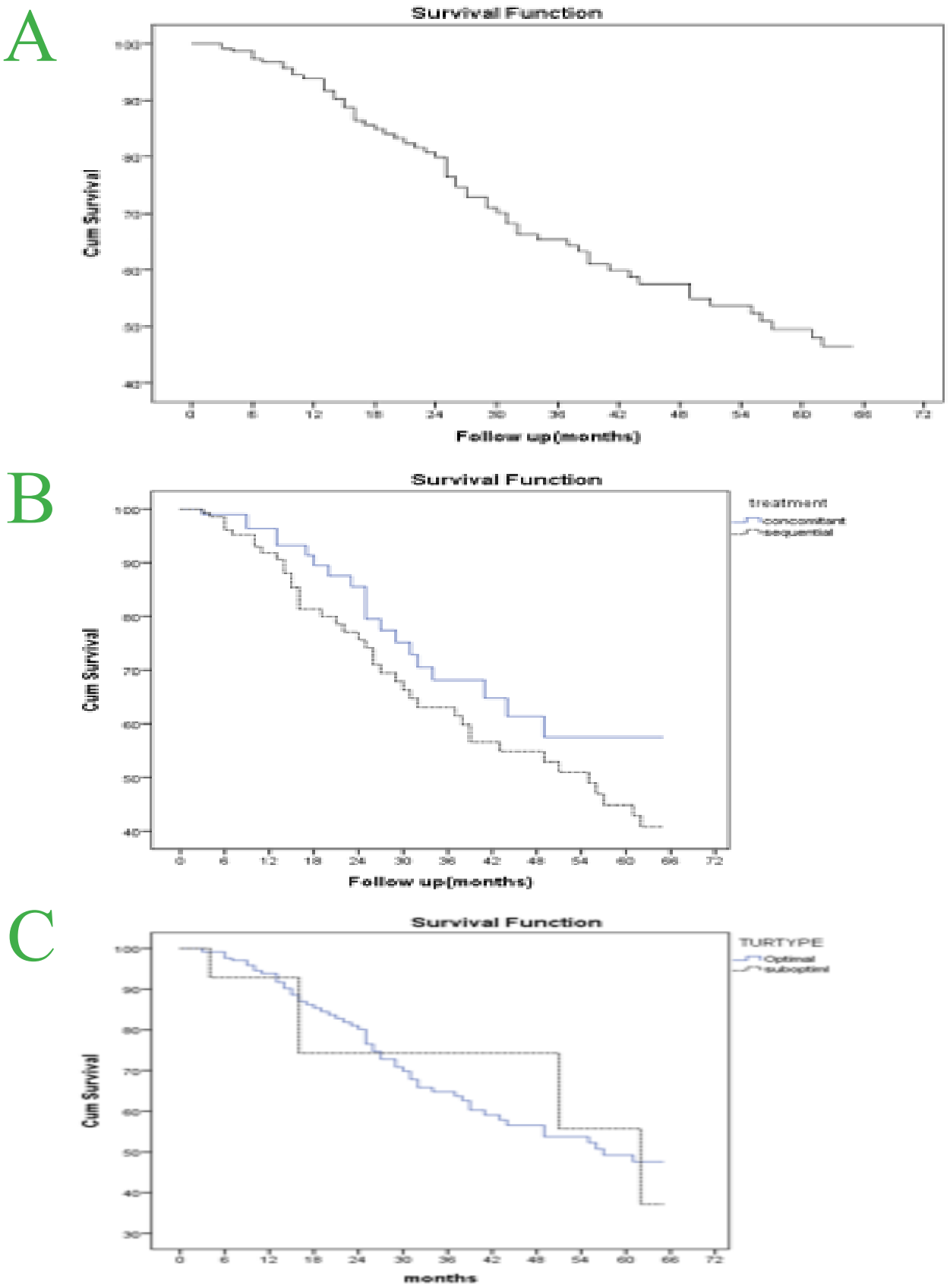

Figure 2. Overall survival curves according to T stage (A), treatment type (B), and TURBT type (C).

benefits; therefore, we aimed to assess the feasibility and results of the sequential use of chemotherapy and radiotherapy (to reduce toxicity and treatment interruptions) compared with concurrent use.

In terms of median survival, the present study showed comparable results between concurrent and sequential chemoradiotherapy. The median survival time was 65 months, and the 5-year OS was 57% in the concurrent group, which is comparable to the literature showing that localized MIBC (stage ≥T2) has a 5-year OS of 40%-60% with CCRT.(12,13) The 2-year survival was 74% and the 5-year survival was 43% in the sequential group. There are only a few articles that report the results of the sequential use of chemotherapy and radiotherapy, in which the estimated 5-year OS is 52%[10]; however, comparing our results for sequential chemoradiotherapy with the data for definitive radiotherapy in the literature shows the superiority of sequential therapy in terms of OS and local control (5-year survival of 27.6% and 2-year local control of 67% for radiotherapy alone).[9-14]

The median DFS was 15 ± 2.54 months in our study. The 3- and 5-year DFS rates for the concurrent group were estimated to be 50% and 42%, respectively, which are comparable to, and even better than, the DFS reported for TMT in some other studies, in which the 3- and 5-year DFS rates were 44% and 29.1%, respectively.[15] DFS was longer in the concurrent group. The recurrence rate was significantly lower in the sequential group in our study, which might be due to fewer interruptions during treatment.

Sequential Chemoradiotherapy Versus Less-Than-Trimodality Therapy

For patients with MIBC who are ineligible for RC or TMT, radical TURBT alone, partial cystectomy with or without lymphadenectomy, chemotherapy alone, or maximal TURBT plus radiotherapy alone can be potential alternatives.[15]

Evidence has shown that such palliative treatments result in inferior OS compared with TMT. Therefore, aggressive treatment should be provided as much as possible.[16,17] However, some recent studies have investigated the role of radiotherapy alone in patients who are not suitable for chemotherapy and have reported that external beam radiotherapy (EBRT) without chemotherapy could still be a feasible alternative treatment to maintain quality of life and achieve acceptable local control rates, although these rates are still lower than those of combined-modality treatments.[14,18-21] In addition, accelerated hypofractionated radiotherapy alone has shown good local control in elderly patients unfit for chemoradiotherapy.[22,23]

On the other hand, neoadjuvant chemotherapy has been shown to lead to downstaging in some patients, such that 30% to 40% of patients have no residual disease at the time of RC, which shows the inevitable and significant role of chemotherapy alone.[24] The addition of neoadjuvant chemotherapy to definitive radiation alone provides a 6% OS benefit,[10] even in elderly patients.[11] A study of 976 patients with bladder cancer showed that three cycles of CMV (cisplatin, methotrexate, and vinblastine) chemotherapy before radiotherapy or cystectomy resulted in a 16% reduction in the risk of death, corresponding to an increase in 3-year survival from 50% to 56%, an increase in 10-year survival from 30% to 36%, and an increase in median survival time of 7 months (from 37 to 44 months). The reduction in the risk of death with CMV was 20% for the radiotherapy-alone groups, and for locoregional DFS, chemotherapy given before radiotherapy caused a 9% reduction in risk.[10] Although this study shows a significant effect of chemotherapy before local therapy, its results could not be compared with ours because RC was included in the local therapy group in the final analysis. In a cohort of 63 patients who refused RC after a 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 recurrences being muscle invasive. The median time to recurrence was 16 months, which is much shorter than the median time to recurrence in the sequential group of our study (29 months), and this shows the inadequacy of single-modality treatment even in the presence of a pathologic complete response.[25]

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 the 5-year OS is only 20%-30%, which is significantly lower than the 5-year survival in the sequential group of our study (43%).[26]

When comparing recurrence between the concurrent and sequential chemotherapy/radiotherapy groups, our data showed an equal time to recurrence but a lower recurrence rate in the sequential group, which might be due to more comorbidities in the sequential group and a lack of adequate referral for follow-up. In the univariate analysis, there was no significant difference in survival according to T stage; however, in the multivariate analysis, T stage was a predictive factor for survival, which could be due to the small number of cases in the T4 group.

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 option for frail patients, a hypothesis that is supported by the results of the present study, which show comparable outcomes between the sequential and concurrent use of chemotherapy and radiotherapy.

Limitations

There are several limitations to our study. First, frail patients were often seen only when they had complaints and did not always undergo follow-up cystoscopy. This may have affected the reported local control rates in this group.

Second, owing to the retrospective design of the study, the cases could not be well matched, and there was no randomization between the groups; therefore, the sequential group probably had more medical complications and was frailer.

CONCLUSIONS

The results of our study showed that sequential chemotherapy and radiotherapy provide results comparable to those of concurrent chemoradiotherapy and better results than less-than-trimodality 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 for CCRT in special circumstances in which concurrent use is not possible.

SUMMARY

Some patients with bladder cancer cannot receive chemotherapy and radiation together. In our study, giving these treatments one after the other led to similar survival and may be a good option for frail patients.

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