

Comparison of Neoadjuvant Chemotherapy and Bladder-Preserving Chemoradiation in Patients with Non-Metastatic, Muscle-Invasive Bladder Cancer: A Single-Center Experience

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ABSTRACT Objective: Approaches for curative treatment of muscle-invasive bladder cancer include radical cystectomy after neoadjuvant chemotherapy and chemoradiotherapy. We compared the results of these treatment modalities in our clinic. **Material and Methods:** A total of 43 patients with muscle-invasive bladder cancer, who underwent front-line cystectomy or received neoadjuvant chemoradiotherapy between 2010 and 2018, were compared retrospectively. **Results:** Twenty patients received definitive chemoradiotherapy, and 23 patients underwent surgery (cystectomy) after neoadjuvant treatment. The median age was 68 years, and 86% of the patients were male. The median age was higher in the chemoradiotherapy group, and the number of patients with an ECOG performance score above 2 was significantly higher in this group. In patients who underwent surgery after neoadjuvant treatment, median disease-free survival was 17.1 months (CI: 6.1-27.9) and overall survival (OS) was 22.2 months (CI: 10.3-34.1), whereas disease-free survival was 12.5 months (CI: 9.7-15.3) (p=0.93). The OS was 12.7 months (CI: 1.0-33.9) (p=0.74) in the group receiving definitive chemoradiotherapy. Survival was significantly longer (p=0.03) in patients who were treated with radical cystectomy, and pathological downstaging (T1 tumor and below) was achieved. In addition, the male gender, smoking above 40 pack-years, and alcohol remarkably reduced the OS. **Conclusion:** The OS and disease-free survival were similar between patients in the chemoradiotherapy and surgery groups. In contrast, patients with ECOG performance score below 2 and pathological downstaging after neoadjuvant chemotherapy had prolonged survival.

Keywords: Urinary bladder neoplasms; chemoradiotherapy; cystectomy

Bladder cancer is the sixth most common cancer, with an occurrence of 4.6%. It generally occurs in elderly people, with an average age of diagnosis to be 73 years. Fifty percent of the patients are diagnosed at the *in-situ* stage, whereas 34% at local and 5% at the metastatic stage. The average 5-year survival is 77%.^{1,2} Urothelial carcinoma is the most common subtype. Well-known risk factors include smoking, urinary tract diseases, family history, and occupational exposure.³

The gold standard treatment for advanced-stage bladder cancer includes radical cystectomy and pelvic lymph node dissection. However, the recurrence rate is significantly high after this treatment (56%).⁴ Moreover, performing radiotherapy after cystectomy in the treatment does not improve the outcomes.^{5,6} A study reported that the survival rate of bladder cancer increased by 5% after radical cystectomy following neoadjuvant chemotherapy.⁷

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Because the patient population is mostly geriatric, it is not always possible to use the gold standard treatment due to patient's reluctance. Therefore, organ preservation approaches have gained importance. The bladder-preserving approach consists of transurethral resection and a combination of chemotherapy and radiotherapy. Survival data are similar to those of standard radical surgery.⁸

Literature does not report any randomized controlled study that compares radical cystectomy following neoadjuvant chemotherapy with a bladder-preserving approach in patients with muscle-invasive bladder cancer. We retrospectively evaluated the data of patients with muscle-invasive bladder cancer who were treated in our clinic using the two treatment modalities: surgery following neoadjuvant chemotherapy and curative chemoradiotherapy.

MATERIAL AND METHODS

PARTICIPANTS

Data of 43 patients with muscle-invasive, non-metastatic bladder cancer, who were followed up and treated in our clinic between 2010 and 2018, were analyzed retrospectively. The patients were divided into two groups: those who underwent radical cystectomy following neoadjuvant chemotherapy and those who underwent curative chemoradiotherapy. Clinically pathological features, treatments and treatment outcomes, disease-free survival, and overall survival (OS) of patients were recorded. Chemoradiotherapy was performed using 55 Gy in 20 fractions over a 4-week period, with concomitant platin monotherapy, either cisplatin 40 mg/m² or carboplatin AUCx2 (for cisplatin-ineligible patients) for curative care. No patient received adjuvant chemotherapy after surgery.

ETHICS

The study was approved by the local ethics board (TUTF-BAEK 2019/305) and was conducted as per the good clinical practice and applicable laws, and the declaration of Helsinki.

STATISTICAL ANALYSIS

Quantitative data were calculated as the median (interquartile range) and compared with Student's *t*-test and Mann-Whitney test. Categorical data were

compared with Fisher's exact test. Disease-free survival was calculated as the time (months) between chemoradiotherapy/cystectomy date and progression date. Kaplan-Meier and long-rank tests were used in survival analysis. A *p*-value less than 0.05 was accepted as statistically significant.

RESULTS

PATIENTS' CHARACTERISTICS

Data of 43 patients with muscle-invasive non-metastatic bladder cancer, who were followed up and treated in our clinic, were analyzed (Table 1). Twenty patients in the group received definitive chemoradiotherapy, and 23 patients underwent surgery after neoadjuvant treatment. The median age was 68 years, and 86% of the patients were male. The median age was 70 years in the chemoradiotherapy group and 63 years in the neoadjuvant group. The number of patients with an ECOG performance score above 2 was significantly higher in this group (*p*=0.02). A remarkable observation in the patients was heavy smoking (more than 20 pack-years), with a smoking rate of 80%. The median cigarette packet-year was 40 in the chemoradiotherapy group and 30 in the neoadjuvant group (*p*=0.04). Cisplatin-based chemotherapy was dominant in both neoadjuvant chemotherapy and concurrent treatment regimen (72%). The clinical stage was similar between the two groups (*p*=0.78).

SURVIVAL ANALYSIS

The median of disease-free survival was 17.1 months (confidence interval [CI:] 6.1-27.9) in the surgery group following neoadjuvant therapy, whereas it was 12.5 months (CI: 9.7-15.3) in the definitive chemoradiotherapy group (*p*=0.93) (Figure 1). No significant relationship was found between disease-free survival and advanced age, smoking, gender, and the chemotherapy regime. The disease-free survival of patients with a score of ECOG performance below 2 was significantly longer (*p*<0.001). Although statistically insignificant, the male gender and smoking above 40 pack-years reduced the disease-free survival (Table 2).

| TABLE 1: Demographic and clinical characteristics of the study subjects. | | | | |
|--|------------|-----------------------|--------------------|------|
| | All (n=43) | Definitive CRT (n=20) | Neoadjuvant (n=23) | p |
| Age, years | | | | |
| Median | 68 | 70 | 63 | 0.08 |
| Interquartile range | 61-72 | 65-76 | 58-71 | |
| ECOG-PS, n (%) | | | | |
| 0-1 | 21 (48.8) | 6 (30.0) | 15 (65.2) | 0.02 |
| ≥2 | 22 (51.2) | 14 (70.0) | 8 (34.8) | |
| Gender, n (%) | | | | |
| Male | 37 (86.0) | 19 (95.0) | 18 (78.3) | 0.19 |
| Female | 6 (14.0) | 1 (5.0) | 5 (21.7) | |
| Smoking, n (%) | | | | |
| | 34 (79.1) | 16 (80.0) | 18 (78.3) | 0.88 |
| Cigarette (packet-year) | | | | |
| Median | 40 | 40 | 30 | 0.04 |
| Interquartile range | 28.5-51.5 | 37.5-52.5 | 27.5-42.5 | |
| Alcohol consumption, n (%) | | | | |
| | 8 (18.6) | 5 (25.0) | 3 (13.0) | |
| Chemotherapy regimen, n (%) | | | | |
| Carboplatin-based | 12 (27.9) | 5 (25.0) | 7 (30.4) | 0.69 |
| Cisplatin-based | 31 (72.1) | 15 (75.0) | 16 (69.6) | |
| Clinical stage, n (%) | | | | |
| II | 13 (30.2) | 6 (30.0) | 7 (30.4) | 0.78 |
| III | 30 (69.8) | 14 (70.0) | 16 (69.6) | |

CRT: Chemoradiotherapy.

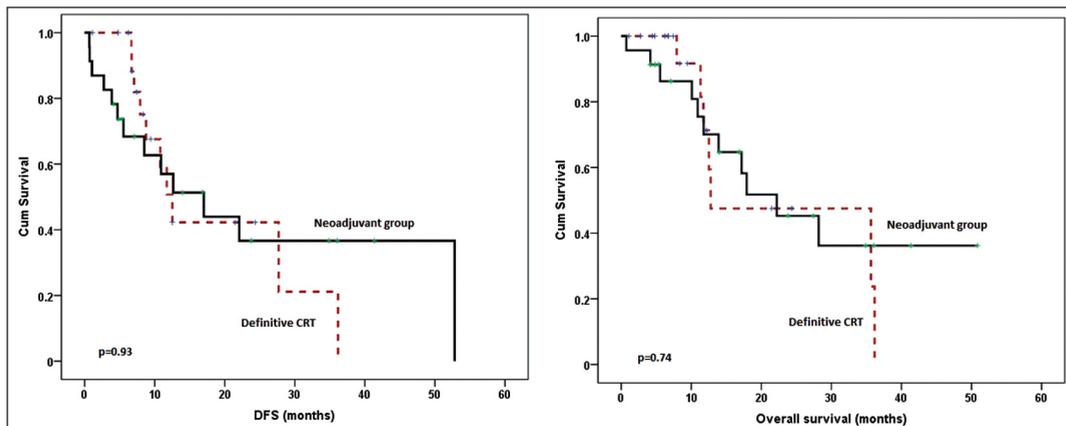


FIGURE 1: DFS and OS curves of the study subjects.

DFS: Disease-free survival; OS: Overall survival.

The OS was 22.2 months (CI:10.3-34.1) in the neoadjuvant chemotherapy + cystectomy group, whereas it was 12.7 months (CI: 1.0-33.9) in the definitive chemoradiotherapy group (p=0.74). The survival was significantly longer (p=0.03) in patients who underwent radical cystectomy, and pathological downstaging (T1 tumor and below)

was achieved (Figure 2). No significant relationship was found between OS and advanced age, smoking, alcohol consumption, gender, and chemotherapy regimen. Although statistically insignificant, the male gender, smoking above 40 pack-years, and alcohol consumption remarkably reduced the OS (Table 3).

| TABLE 2: DFS of the study subjects. | | | |
|-------------------------------------|--------|---------------------|--------|
| | Median | 95%CI (Lower-Upper) | p |
| Age, years | | | |
| <65 | 10.7 | 3.9-17.6 | 0.95 |
| ≥65 | 17.1 | 7.7-26.2 | |
| ECOG-PS | | | |
| 0-1 | 37.5 | 24.5-50.6 | <0.001 |
| ≥2 | 7.9 | 5.2-10.5 | |
| Gender | | | |
| Male | 12.5 | 9.9-15.1 | 0.86 |
| Female | 22.1 | 1.0-56.1 | |
| Smoking, yes | | | |
| | 12.6 | 4.6-20.6 | 0.92 |
| Cigarette (packet-year) | | | |
| <40 | 27.6 | 1.0-57.3 | 0.17 |
| ≥40 | 10.7 | 7.1-14.4 | |
| Alcohol consumption, yes | | | |
| | 12.5 | 5.7-19.2 | 0.33 |
| Chemotherapy regimen | | | |
| Carboplatin-based | 22.0 | 1.0-48.4 | 0.56 |
| Cisplatin-based | 12.5 | 9.9-15.1 | |

DSF: Disease free survival CI: Confidence interval.

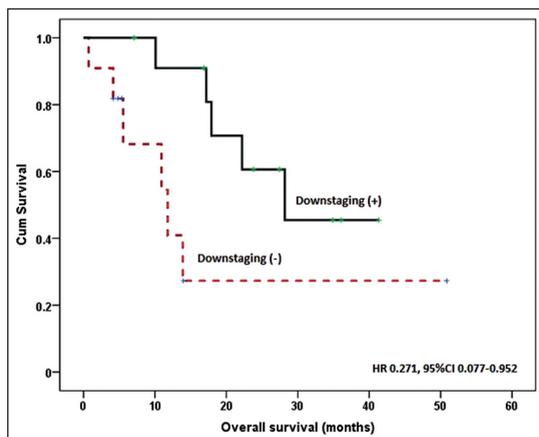


FIGURE 2: Overall survival curve of the patients who underwent neoadjuvant treatment.

DISCUSSION

Although radical cystectomy is accepted as the gold standard treatment for muscle-invasive bladder cancer, bladder-preserving approaches have become popular over time with an aim to increase the quality of life. In the present study, we compared patients who underwent curative chemoradiotherapy with those who underwent radical cystectomy following neoadjuvant chemotherapy. We observed no signifi-

cant difference between these groups in terms of disease-free survival and OS.

Literature does not report any randomized controlled study that compares radical cystectomy with curative chemoradiotherapy in muscle-invasive bladder cancer. We did not find any differences in survival between the two groups. Outcomes of chemoradiotherapy were as effective as radical cystectomy in older patients with poor performance scores and comorbidities. These results were similar to other retrospective analyses. Moreover, no difference in OS between patients undergoing radical cystectomy and chemoradiotherapy has been reported in two previous large population-based analyses.^{9,10} Five-year OS rate was 41.4% in the radical cystectomy group, whereas it was 34.6% in the chemoradiotherapy group (p=0.39).⁹ Munro et al. reported 10-years OS rates as 21.6% and 24.1%, respectively (p=0.77) for the two treatment approaches.¹⁰ In the analysis performed by Booth et al., no cancer-specific survival difference was found in older patients

| TABLE 3: OS of the study subjects. | | | |
|------------------------------------|--------|---------------------|-------|
| | Median | 95%CI (Lower-Upper) | p |
| Age, years | | | |
| <65 | 17.1 | 9.7-24.5 | 0.70 |
| ≥65 | 28.1 | 9.0-47.3 | |
| ECOG-PS | | | |
| 0-1 | 39.6 | 29.1-50.2 | 0.002 |
| ≥2 | 12.8 | 10.8-14.6 | |
| Gender | | | |
| Male | 17.9 | 6.1-29.7 | 0.54 |
| Female | 24.8 | 13.4-36.2 | |
| Smoking, | | | |
| Yes | 22.2 | 12.8-31.5 | 0.98 |
| No | 22.9 | 12.8-33.1 | |
| Cigarette (packet-year) | | | |
| <40 | 35.6 | 9.3-61.9 | 0.35 |
| ≥40 | 17.1 | 8.9-25.3 | |
| Alcohol consumption | | | |
| Yes | 22.2 | 9.2-35.1 | 0.70 |
| No | 35.1 | 17.1-53.1 | |
| Chemotherapy regimen | | | |
| Carboplatin-based | 36.5 | 22.9-50.1 | 0.46 |
| Cisplatin-based | 17.9 | 6.9-28.8 | |

OS: Overall survival; CI: Confidence interval.

with comorbidities.¹¹ In a systemic review, including 13,396 patients, 5-year survival data were analyzed, and no difference was found between the two treatment modalities.¹² In contrast, Ritch et al. showed that as an initial treatment for muscle-invasive bladder cancer, the risk of mortality was lower with chemoradiotherapy compared to surgery.¹³ We found numerically different OS between the two groups; however, it was statistically insignificant.

The OS in the radical cystectomy group was 22.2 months, similar to that reported in the literature. The median survival was 23.8 months in a retrospective analysis performed by Boutani et al.¹⁴ The median survival of patients undergoing chemoradiotherapy was 23.6 months in the same study, whereas it was 12.7 months (shorter) in our study. In a prospective study performed by Grosman et al., the 20-year survival of patients who underwent radical cystectomy following the neoadjuvant chemotherapy was 77 months.¹⁵ Longer follow-up duration, a better performance score of patients in the study group, and different chemotherapy regimens can explain the results in a better manner.

The complete pathological response was detected in the radical cystectomy material of five patients (21.7%) in the neoadjuvant chemotherapy group. All patients were treated with a platin-based double regime. In a randomized study, a 38% complete pathological response rate was detected with the triplet chemotherapy regime.¹⁵ In another meta-analysis, the complete pathological response rate following neoadjuvant chemotherapy with a double regimen was 25.6%, whereas the rate was 24.2% with a triple regimen in the same study ($p=0.2$).¹⁶ Achieving a complete response with platin-based neoadjuvant chemotherapy is a significant predictive marker for disease-specific survival.¹⁷ In our study, survival data of patients in whom downstaging was achieved was remarkably better.

Patient's age and performance status may determine their clinical management. Elderly patients who had multiple comorbidities may be feasible for chemoradiotherapy. Hong-Yiou et al. demonstrated that younger and healthier patients underwent surgery rather than chemoradiotherapy.¹⁸ An adjusted analysis using the clinical-stage revealed no significant OS between the chemoradiotherapy and surgery groups. In our

study, although a small patient group was analyzed, no statistically significant difference was observed between the treatment groups with respect to mortality.

Limitations of our study include fewer patients due to being a single-center, nonhomogenous patient group; inability to state the toxicity findings due to lack of data; and inadequate pathological findings. Because the number of patients taking carboplatin was low, there was a possibility of error in survival analysis. More randomized controlled studies are required to compare these two treatment regimens.

CONCLUSION

The present study showed that the outcomes of curative chemoradiotherapy are close to those of cystectomy, the gold standard treatment for patients. Thus, chemoradiotherapy can be used for patients not eligible for cystectomy. Although OS and disease-free survival were similar between patients in the chemoradiotherapy and surgery groups, the ECOG performance score below 2 and pathologic downstaging were observed in patients after neoadjuvant treatment, and the OS was longer. Further studies are required to further study these aspects.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Ali Gökyer, İrfan Çiçin; **Design:** Ali Gökyer, Osman Köstek, İrfan Çiçin; **Control/Supervision:** İrfan Çiçin, Bülent Erdoğan; **Data Collection and/or Processing:** Ahmet Küçükarda, Talar Özler, Gökhan Çevik, Kubilay İşsever, Osman Köstek, Ali Gökyer; **Analysis and/or Interpretation:** Osman Köstek, Ali Gökyer; **Literature Review:** Ali Gökyer, Sernaz Uzunoğlu; **Writing the Article:** Ali Gökyer, Osman Köstek; **Critical Review:** Osman Köstek, İrfan Çiçin; **References and Fundings:** Ali Gökyer, İrfan Çiçin; **Materials:** Ali Gökyer, İrfan Çiçin.

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