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ORIGINAL ARTICLE

Curative Radiotherapy Outcomes in Elderly Bladder Cancer Patients: A Single-Center Experiences

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OBJECTIVE

In this retrospective research, it was aimed to evaluate results of radiotherapy (RT) in elderly bladder cancer patients.

METHODS

A total of 47 patients who receiving RT or chemoradiotherapy treatment for bladder cancer in elderly patient (>70 years) were included in the study.

RESULTS

In total 47 patients, 4 patients (8.5%) had Stage I, 38 patients (80.8%) had Stage II, and 5 patients (10.6%) had Stage III bladder cancer. About 76.9% of patients had invasive urothelial, 3.8% of patients had squamous and micropapillary carcinoma, and 19.2% of had other (adenocarcinoma) histopathological type. Gender, age, family cancer history, hematuria, smoking, bladder carcinoma type, Charlson CoMorbidity Index, RT dose, concurrent chemoradiotherapy, metastasis side, acute and late toxicity, and follow-up duration of patients showed insignificant differences according to stage ($p>0.05$). We found that overall survival and disease-free survival (DFS) were statistically significant according to the stages ($p<0.05$). DFS for Karnofsky Performance Status (KPS) >70 group (25.97±19.06) was higher than KPS <70 group (2.37±1.53) with statistically significant difference ($p<0.05$).

CONCLUSION

Curative RT and chemoradiotherapy can be safe regimen for older (>70 year) patients with bladder cancer. Nonetheless, KPS and geriatric assessments tools should be consideration before RT and chemoradiotherapy administration.

Keywords: Aged; bladder neoplasms; radiotherapy; stage.

Introduction

Bladder cancer is a type of cancer usually seen in older adults. Most of these patients are 65 years and older. The median age at diagnosis is 72 years.[1] Approximately 70% of bladder cancers are muscle non-invasive while 25-30% of bladder cancer are muscle invasive bladder cancer.[2] While frequent recurrences are seen in non-muscle-invasive bladder cancer (NMIBC) patients, intravesical treatments are insufficient for high-grade tumor (T1, high grade). In these patients and muscle-invasive bladder cancer (MIBC) patients although cystectomy is the standard treatment, it may not be possible in elderly patients because of comorbidity diseases, general condition, and surgery complication. Maximal transurethral resection (TUR) followed by concurrent

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chemotherapy and radiation (CRT) is similar effective to radical surgery.[3,4] Most of the time, alone radiotherapy (RT) is applied after TUR in the elderly (>80 years). These non-surgical treatments, called bladder-sparing treatment, are very important in the elderly patient group. The most important problem of bladder sparing treatment in elderly patients is treatment-related toxicities. Therefore, when deciding on bladder sparing treatments in elderly patients, advantages and disadvantages of these treatments should be take into consideration.

In this study, we aimed to investigate outcome of elderly patients with MIBC and NMIBC who taken curative RT and CRT after TUR.

Materials and Methods

In this retrospective study, we evaluated 47 patients over 70 years of age who were diagnosed with invasive bladder cancer after TUR, who were not eligible for radical surgery or who did not want to undergo radical surgery (T1 and high grade patients) and who were referred to Istanbul Training and Research Hospital Department of Radiation Oncology between 2011 and 2018. The study was approved by the local ethics committee of the University of Health Science, Istanbul Training and Research Hospital, Turkey, Human Research Ethics Committee (approval number: H: 2019-1859) according to Helsinki declaration, and informed consent was obtained from all patients after thorough explanation of the study. While all related laboratory and pathology results were obtained from hospital data, data related to treatment follow-up were obtained from clinical files. Patients had distant metastases, or received palliative dose RT were excluded from the study.

The general status of the patients was evaluated by Karnofsky Performance Status (KPS) Scores range from 0 to 100 (<70 and ≥70). The status of comorbidities was determined using the Charlson Comorbidity Index.[5]

RT and Chemoradiotherapy Data

All patients received maximal TUR. All patients received external beam RT in 1.8-2.0 Gy daily fractions with 18 MV photon beams, 5 days a week. Pelvic lymph nodes were sometimes included and applied to the bladder or tumor to 65 Gy after 40-45 Gy. Radiation treatment was carried out using field-in field intensity-modulated radiation treatment and 4-field box three--dimension conformal technique. The clinical target volume (CTV) included gross tumor volume and covered any direct extension of the tumor. The planning treatment volume was the CTV with addition of a 1-1.5 cm margin. Almost all patients received a phase 2 boost to the tumor bed.

Chemotherapy protocol Cisplatin 35 mg/m^2, weekly to be administered by the Medical Oncology Clinic.

Treatment Toxicity and Follow-up

Treatment toxicity was evaluated with the Common Terminology Criteria for Adverse Events version 4.0.[6] During RT, patients were evaluated at least once a week with a clinical examination, and their blood counts and biochemistries were analyzed. The treatment responses were assessed using cystoscopy. Subsequent controls included physical examinations and cystoscopy and radiological imaging every 3 months. Follow-ups were conducted every 3 months for the first 2 years and every 6 months for years 3 through 5. During the follow-up period, a magnetic resonance imaging examination was requested in patients with suspected local or regional recurrence.

Statistical Analysis

Nominal and ordinal data were described with frequency analysis, whereas scale parameters were described with mean and standard deviations. Chi-square with likelihood ratio was used for differences between nominal and ordinal parameters. Kolmogorov-Smirnov test was used for normality of scale parameters. For normally distributed parameters, one-way ANOVA Test was used, and Kruskal-Wallis Test was used for non-normally distributed parameters. Kaplan-Meier analysis was used for disease-free survival (DFS) analysis for different patient groups. All analyses were performed at 95% confidence level with 0.05 significance level at SPSS 17.0 for windows program.

Results

Some baseline characteristics of patients and treatment features according to stage groups are given in Table 1. About 18.4% of Stage II patients, 20% of Stage III patients were females, and in total, 19.2% of patients were females with insignificant difference (p>0.05). Mean age was the highest in Stage III patients. Family CA history rate was 25.0% in Stage I, 10.5% in Stage II, and 20.0% in Stage III patients. About 25.0% of Stage I patients, 68.4% of Stage II patients, 80.0% of Stage III patients had hematuria. 25.0% of Stage I patients, 50.0% of Stage II patients, 20.0% of Stage III patients were smokers. 50.0% of Stage I patients, 78.9% of Stage II patients, and 80.0% of Stage III patients had invasive urothelial type. About 50.0% of Stage I patients, 15.8% of Stage II patients, and

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Table 1 Patients characteristics and treatment features of patients according to stage groups

Parameter	Stage I (n=4)	Stage II (n=38)	Stage III (n=5)	Total	p
Gender, n (%)					
Female	-	6 (18.4)	1 (20.0)	7 (19.2)	0.312[a]
Male	4 (100.0)	-	-	42 (80.8)	
Age, Mean±SD	73.50±1.73	75.42±6.12	78.40±3.85	75.54±5.63	0.164[b]
Family CA history, n (%)	1 (25.0)	4 (10.5)	1 (20)	6 (11.5)	0.322[a]
First complaint					
Hematuria	1 (25.0)	26 (68.4)	4 (80.0)	31 (76.5)	0.277[a]
Clottet hematuria	3 (75.0)	12 (31.6)	1 (20.0)	16 (34.0)	
Smoking n (%)					
None	2 (50.0)	7 (18.4)	1 (20.0)	10 (21.2)	
Smoker	1 (25.0)	19 (50.0)	1 (20.0)	21 (44.6)	0.480[a]
Ex-smoker	1 (25.0)	12 (31.6)	3 (60.0)	16 (34.0)	
Type, n (%)					
Invasive urothelial	2 (50.0)	30 (78.9)	4 (80.0)	36 (76.9)	0.656[a]
Squamos+micropap.	-	2 (5.3)	-	2 (0.4)	
Other	2 (50.0)	6 (15.8)	1 (20.0)	9 (19.2)	
KPS, n (%)					
>70	4 (100.0)	24 (63.2)	3 (60.0)	31 (65.9)	0.177[a]
<70	-	14 (36.8)	2 (40.0)	16 (34.0)	
Charlson Comorbidity Criteria					
0-1	-	-	-	-	
2-3	1(25.0)	22 (57.9)	5 (100.0)	32 (68.0)	0.110[a]
4-5	3(75.0)	12 (31.5)	-	15 (24.0)	
6-7	-	4 (10.6)	-	4 (8.0)	
RT dose (Gy)					
45	-	2 (5.2)	-	2 (4.2)	0.266[a]
60	4 (100.0)	35 (92.1)	3 (60.0)	42 (88.6)	
64	-	1 (2.7)	2 (40.0)	3 (6.3)	
RT break					
Yes	-	6 (15.8)	1 (20.0)	7 (14.8)	0.358[a]
No	4 (100.0)	32 (84.2)	4 (80.0)	40 (85.1)	
Concurrent cisplatin	2 (50.0)	18 (47.4)	3 (60.0)	23 (50.0)	0.726[a]
Metastasis, n (%)					
None	4 (100.0)	32 (84.2)	2 (40.0)	38 (80.8)	
Bone	-	1 (2.6)	2 (40.0)	3 (5.8)	
Lung	-	1 (2.6)	1 (20.0)	2 (3.8)	0.455[a]
Liver	-	3 (7.9)	-	3 (5.8)	
Brain	-	1 (2.6)	-	1 (1.9)	
Exitus, n (%)	1 (25.0)	28 (73.7)	5 (100.0)	34 (72.3)	0.066a
Follow-up, (month) Mean±SD	33.00±14.7	31.95±23.	11.60±5.2	29.40±23.3	0.231c
Acute Toxicity, n (%)					
Diarrhea					
Grade 1	-	-	-	-	
Grade 2	2 (50.0)	4 (10.5)	-	6 (12.7)	0.079a
Urinary Frequency, n (%)					
Grade 1	3 (75.0)	34 (89.5)	4 (80.0)	41 (87.2)	
Grade 2	1 (25.0)	4 (10.5)	1 (20.0)	6 (12.7)	0.525[a]
Hematologic, n (%)					
Grade 1	2 (40.0)	22 (57.8)	1 (20.0)	25 (48.0)	0.084[a]
Late toxicity, n (%)					
Cysitis					
None	1 (25.0)	14 (36.8)	1 (20.0)	16 (34.0)	
Grade 2	2 (50.0)	21 (55.3)	3 (60.0)	26 (55.3)	0.495[a]
Grade 3	1 (25.0)	3 (7.9)	1 (20.0)	5 (9.6)	

[a]: Chi-square (Likelihood ratio); [b]: One-way ANOVA (Welch); [c]: Kruskal-wallis test; SD: Standard deviation; RT: Radiotherapy; KPS: Karnofsky performance status; CA: Carcinoma

Table 2 Some clinical parameters of patients according to stage groups

	Stage I (n=4)	Stage II (n=38)	Stage III (n=5)	Total	p
Metastasis_time	-	2.21±8.50	5.80±6.38	2.17±7.60	0.040[b]
Local recurrence	-	1.16±6.21	1.60±3.58	1.19±5.55	0.436[b]

[b]: Kruskal–Wallis; SD: Standard deviation

20.0% of Stage III patients had non-urothelial (other) histopathological type. All of Stage I patients, 63.2% of Stage II patients, 60.0% of Stage III patients had KPS >70. Charlson Comorbidity Criteria, all of stage I patients had over 3 score, and 57.9% of patients II patients had 2-3 score, while rest of them had over 4 score. All of Stage III patients had score 2-3.

In terms of RT doses, all of Stage I patients received 60 Gy. About 92.1% of Stage II patients had 60 Gy, only one patient (2.7%) had 64 Gy. Half of the patients (21 patients) received RT alone while the other half received concomitant chemoradiotherapy with cisplatin (weekly). Six patients from Stage II (15.8%) and one patient from Stage III (20.0%) discontinued RT treatment.

Bone metastasis was dominant in Stage III patients. Follow-up duration mean was the highest in Stage I patients (33 month). All patients in the Stage III were died. Mortality rate was 25.0% in Stage I and 73.7% in Stage II patients.

RT and CRT treatment was well tolerated. It was seen in 4 (10.5%) patients with Grade 2 diarrhea Stage II. Urinary frequency was most common in Stage II patients. In terms of late toxicity, three patients (7.9%) had Grade 3 cystitis in Stage II and one patient (20.0%) had Grade 3 cystitis in Stage III. One patient in Stage III, two patients in Stage II required hospitalization due to late side effects. According to difference analysis results, all differences between stage groups were not statistically significant (p>0.05).

Some clinical parameters of patients according to stage groups are given in Table 2. Metastasis time was the highest in the Stage III patients and metastasis time showed significantly difference between stage groups (p<0.05).

Kaplan-Meier results for stage and KPS groups are given in Figures 1 and 2. Cumulative DFS was the highest in Stage II (19.58±20.35) patients, followed by Stage I (13.25±8.84) and Stage III (7.60±5.18), respectively. Overall survival (OS) was highest in Stage I (33±14.7) patients, followed by Stage II (31.9±23) and Stage III (11.6±34), respectively. We found that OS and DFS were statistically significant according to the stages (p=0.08

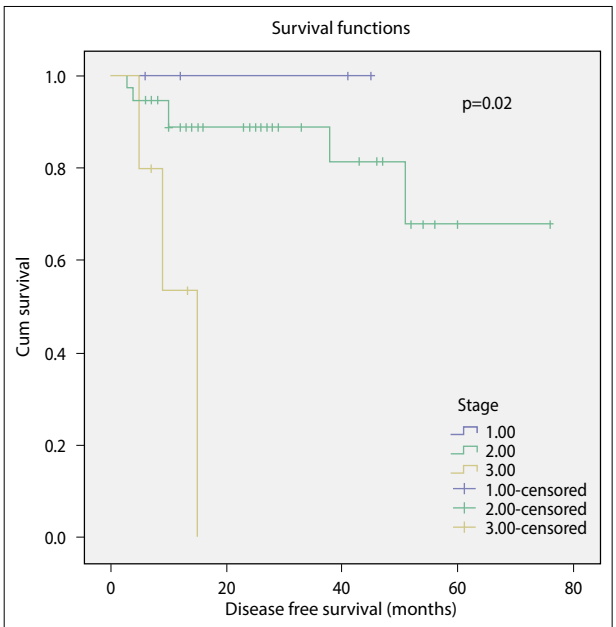

Fig. 1. Disease free survival results for stage.

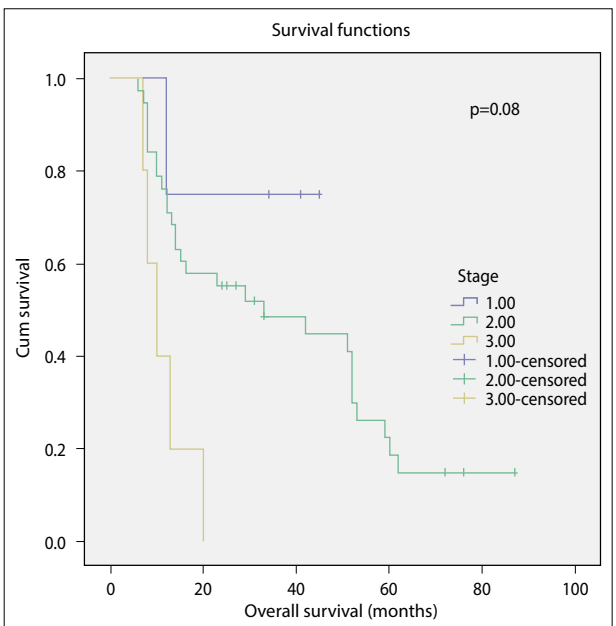

Fig. 2. Overall survival results for stage.

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and p=0.02). Mean DFS for KPS >70 group (25.97±19.06) was higher than KPS <70 group (2.37±1.53) with statistically significant difference (p<0.05).

Discussion

Bladder cancer is a type of cancer that is more common in advanced years of life, especially in women than in men. In men, it has 9.6 incidences and 3.2 prevalence per 100,000 people, more than women.[1] In our study, 19.2% of the sample was female and 80.8% was male. Bladder cancer is more common in older adults. The average age of diagnosis is 72 years.[1] When we look at the average age by stage, similar results were found.

Gross hematuria and painless bleeding are most important sign in bladder cancer.[7] Especially in Stage 2, hematuria and clotting hematuria were the most common symptoms in our study (68.4% and 31.6%).

Smoking is one of the important risk factors in bladder cancer. Studies in the literature show that smoking is one of the most important factors.[8-10] Barbosa et al.[8] reported that 17.4% of bladder cancer patients had never smoked, 46.8% had previously smoked, and 33.9% had still smoked. Jiang et al.[11] reported that smoking not only increases the risk of bladder cancer but also adversely affects stage and disease progression. On the other hand, Castelao et al.[12] reported that women who smoke have a higher risk of bladder cancer than men who smoke. In our study, 21.2% of the patients were non-smokers, 42.3% were smokers, and 36.5% had previously smoked.

KPS is an parameter used in bladder cancer and other cancer. While making the treatment decision, the general condition of the patient is evaluated with this parameter. In the study conducted by Wujanto et al.,[13] performance of patients was prognostic factor affecting survival. In our study, the survival rate was higher in patients with KPS ≥70.

Charlson Comorbidity Index is use geriatric oncology patients. The patient is given points according to the additional diseases. Our patients were generally found to be 3 points or more.

In many studies on elderly bladder cancer, RT dose was applied over 60 Gy. Median 58.6 Gy (range 54-62.8) was used in the study of Lee et al.,[14] The median 64.8 Gy was used in the study of Hsieh et al.(15) and 60-60 Gy received in the study of Korpics et al .(16) Similar to the above studies, we applied median 60 Gy and 64 Gy to pelvic area and bladder. We did not find statistical difference between 60 and 64 Gy when compared by stages. In our study, 26 patients received CRT, while 21 patients received RT only. Patients who break the treatment were generally Stage 2 (six patients) and CRT used patients. CRT and RT was well tolerated all patients. Diarrhea, urinary frequency, and hematologic side effects were most common in Stage II patients. In the late period, three patients (7.9%) had Grade 3 cystitis. Our side effect results were similar to other studies.[14-17]

Metastasis was most common in the liver after treatment. Follow-up time was at least 11 months with Stage III. In other stages, the follow-up period was approximately 30 months.

Stage of bladder cancer is an important factor that affects both the course of the disease and survival rate. Studies have been conducted in the literature regarding the stage and course of the disease and different results have been reported.[18-20]

In our study, clinical, treatment, toxicity, demographic parameters did not differ significantly according to the stages. OS and DFS are significantly difference between stage groups (p=0.08 and p=0.02). DFS and OS were observed at the lowest Stage III. The reason for this is that patients are lost due to additional diseases or they are receiving alone RT. DFS and OS were found at the highest Stage II. Because, almost all of these patients received CRT.

A limitation of our study was almost all patients Stage II. According to the stages, the number of patients was not homogeneously distributed. It was not clear whether the cause of death was due to the additional disease. Bladder cancer is mostly diagnosed in older patients; a comprehensive assessment is required when deciding on the options for curative treatment.

Conclusion

According to the results of the study, RT alone or CRT can be safely performed at all stages in patients over 70 years of age. Longer life expectancy and "KPS over 70" older bladder cancer patients, RT and CRT treatment should be taking into consideration. When making treatment decision, performance status most important than the patients chronological age and stage.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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Authorship contributions: Concept – B.İ.; Design – B.İ., Ö.M.; Supervision – Ö.M.; Funding – B.İ.; Materials – B.İ., Ö.M.; Data collection and/or processing – B.İ.; Data analysis and/or interpretation – B.İ., Ö.M.; Literature search – Ö.M.; Writing – B.İ.; Critical review – B.İ.

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