http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(6):515-9

Research Article Doi: 10.36472/msd.v7i6.386

Prognostic factors and curative radiotherapy results in patients with octogenarian bladder cancer

Berrin Inanc[1]*, Ozlem Mermut[1]

Abstract

Objective: In this retrospective research, we aimed to evaluate the survival outcomes and survival-related prognostic factors in octogenarian (>80 years) bladder cancer patients.

Material and Methods: A total of 17 patients receiving radiotherapy or chemoradiotherapy treatment for bladder cancer in octogenarian patients were included in the study.

Results: In total 17 patients, 13 patients (76.5%) had Stage II, 2 patients (11.8.%) had Stage III and stage IVa. Median follow-up was 23 months (6-72 months).While median overall survival (OS) was 14 months, median disease-free survival (DFS) was 13 months.Overall survival and disease-free survival rates for 6 months and 1st years were 70.6%, 35% and 64.3%, 24.1%, respectively. No prognostic factors were found in the univariate Cox regression analysis for overall survival. In multivariate Cox regression analysis, we found stage (hazard ratio [HR] = 3.009. 95% confidence interval [CI] = 1.003–9.029, p = 0.049), radiotherapy doses (HR = 241,226, 95% CI = 5.421–107.679, p = 0.005) and Charlson co-morbidity index (HR = 0.161 95% CI = 0.035–0.748, p = 0.020) as independent prognostic factors for overall survival.

Conlusion: Curative radiotherapy can be used for older (>80 years) patients with invasive bladder cancer. Nonetheless, the co-morbidity disease should be a consideration before radiotherapy and chemoradiotherapy administration.

Keywords: Urinary, bladder cancer, radiotherapy, 80 and over

Introduction

Bladder cancers are generally seen in older ages and are more aggressive in elderly patients (1). It is more common in men. Usually, 25-30% is non-invasive bladder cancer, while 75% is invasive bladder cancer at the time of diagnosis. The most crucial treatment option in invasive bladder cancer is maximal transurethral resection (TUR) and radical cystectomy (RC). Due to additional diseases, advanced age, and surgical complications, RC cannot be applied (2). In these patients, another treatment option, bladder-sparing treatment (curative chemoradiotherapy), is recommended. But, curative chemoradiotherapy cannot be applied in patients with elderly bladder cancer, which is generally not suitable for surgery, due to toxicity. Curative radiotherapy alone is preferred more frequently than chemoradiotherapy. The effect of this treatment on survival is lower than chemoradiotherapy in many studies (3-4). This is a significant challenge, especially in patients who are 80 years and above (octogenarian).

In this study, we examined the prognostic factors that affect survival and our curative radiotherapy results in patients with octogenarian bladder cancer.

Material and Methods

In this retrospective study, we evaluated 17 patients over 80 years of age who were diagnosed with invasive bladder cancer in Istanbul Training and Research Hospital, Department of Radiation Oncology between 2011 and 2018. TUR was applied to each patient for diagnosis and treatment purposes. After the TUR, we evaluated patients who were not eligible for surgery due to their additional diseases or did not want radical surgery for curative chemoradiotherapy (bladder preserving therapy). Before the treatment, all patients were given for hemogram and detailed biochemistry tests. The only radiotherapy was applied to patients who were not suitable for chemoradiotherapy (for bladder preservation therapy applied, small tumors (5 cm), unifocal disease, microscopic complete transurethral resection (R0-1), the absence of urethral obstruction or hydronephrosis, absence of lymph node metastasis, in situ and need not be carcinoma report). Patients were staged to the AJCC staging system (7th edition). According to the Helsinki declaration, the study was approved by the local ethics committee of The University of Health Science, Istanbul Training and Research Hospital, Turkey, and Human Research Ethics

Received 01-06-2019 **Accepted** 19-06-2020 **Available Online** 23-06-2020 **Published** 30-06-2020
1 University of Health Sciences, Istanbul Education and Research Hospital, Dept of Radiation Oncology, Istanbul, TR
*** Corresponding Author:** Berrin Inanc **E-mail:** byalcin77@hotmail.com

http://dx.doi.org/10.36472/msd.v7i6.386

Committee (approve number: 2020/ 2234). Informed consent was obtained from all patients after a thorough explanation of the study.

The Charlson comorbidity index was used to assess comorbidities (5). Curative chemoradiotherapy (CRT) or radiotherapy (RT) was decided according to the patients' Karnofsky Performance Status (KPS). This scoring is from 0 to 100, and we divided it as above 70 and below. Pathology and laboratory values were taken from hospital files and treatment and follow-up information from patient records.

Overall survival (OS) was defined as the time between the date of diagnosis and the last contact or death. Disease-free survival (DFS) was the period between the date of diagnosis and the time of local tumor recurrence and metastasis.

Radiotherapy and Chemoradiotherapy Data

All patients received TUR. All patients received external beam RT in 1.8 to 2.0 Gy daily fractions with 18 MV photon beams, five days a week. Radiation doses were applied to the bladder or tumor to 60 Gy after 40-45Gy. Radiation treatment was carried out using field-in field IMRT and 4- field box 3-Dimension conformal technique.

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 (CTCAE) version 4.0 (6). During RT, patients were assessed at least once a week with a clinical examination, and their blood counts and biochemistries were analyzed. The treatment responses were evaluated by using cystoscopy. Subsequent controls included physical examinations and cystoscopy and radiological imaging every three months. Follow-ups were conducted every three months for the first two years and every six months for years 3 through 5. During the follow-up period, a magnetic resonance imaging (MRI) 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. Kaplan Meier analysis was used for OS and DFS analysis. A Cox proportional hazard model was applied for multivariate analysis to determine independent prognostic factors. All analyses were performed at 95% confidence level with a 0.05 significance level at SPSS 17.0 for windows program.

Results

Table 1 presents some baseline characteristics of patients and treatment features.

The mean age of the patients was 82.1 (range 80-89) years. 12 (70.6%) of the patients were male, and 5 (29.4%) were female. All patients had a history of smoking. While 47.1% (8) patients were still smoking, 52.9% (9) had ex-smoker.In our hospital, 76.5% (13) of the patients had invasive urothelial carcinoma and 23.5% (4) other histopathology. In terms of stage, 76.5% (13) of patients were stage II, and 11.8% (2) were stage III and IV. Karnofsky performance status was 61.1% (10) patients ⩾70, 38.9% (7) patients had a <70 KPS. Considering the co-morbidity index of Charlson according to additional diseases, the score was 2-3 in 55.6% (9) patients, 4-5 in 33.3% (6) patients, and 6-7 in 11.1% (2) patients. Almost all of the patients received 88.2% only curative radiotherapy, while only 11.2% (2) received chemoradiotherapy. Radiotherapy doses were different. Therapeutic radiotherapy doses (60 Gy) were taken by 77.8% (14) of patients. Three patients discontinued the treatment after 40 to 45 Gy. Recurrence was observed in 3 patients (56.6%), distant metastasis detected in 4 patients (42.5%). RT and CRT treatments were well tolerated. It was seen in 4 (32.5%) patients with grade 2 diarrhea stage II. Urinary frequency was most common in stage II and stage III patients. Two patients in stage II required hospitalization due to late side effects.

Table 1: Patients and treatment characterics

	Patient (n)	%
Age, Mean ± SD (years)	82.12 ± 2.64(80-89)	
Sex		
Male	12	70.6
Female	5	29.4
Smoking Status		
Smoker	8	47.1
Ex-smoker	9	52.9
Histopathology		
Invasive urothelial Ca.	13	76.5
Other	4	23.5
Stage		
II	13	76.5
III	2	11.8
Iva	2	11.8
Karnofsky Performance Status		
≥70	10	61.1
<70	7	38.9
Charlson Co-morbidity Index		
2-3	9	55.6
4-5	6	33.3
6-7	2	11.1
Radiotherapy doses		
40 Gy	1	5.6
45 Gy	2	11.1
60 Gy	14	77.8
Chemoradiotherapy	2	11.8
Radiotherapy (alone)	15	88.2
Metastasis	4	68
Recurrence	3	56.6
Follow-up, Mean±SD (month)	23 ± 20.48 (6-72)	
Exitus	14	
Alive	3	

SD: Standart deriviation

Median follow-up time was 23 months (6-72 months). Median OS was 13 months, OS rates were 70.6% for six months, while 1-year survival was 35%. Overall survival, according to the stage, is showed in Figure-1. Median DFS was 14 months, DFS rates were 64.3% for six months, and 1-year DFS was 24.1%. At the time of analysis, three patients were alive, and 14 patients died.

http://dx.doi.org/10.36472/msd.v7i6.386

No factor affecting survival was found statistically significant in univariate analysis. According to the multivariate analysis, stage (p=0.049), RT doses (p=0.005), and Charlson co-morbidity index (p=0.020) were determined to be an independent prognostic factor for OS (Table-2). There was a threefold increase in mortality in patients stage III and IV as compared with the patient's stage II.

Similarly, RT doses were found independent prognostic factor for overall survival, and mortality was increased by 214 fold in received 60 Gy compared 40 Gy in patients. Charlson co-morbidity index also was found independent prognostic factor for death and overall survival. It was increased by 0.1 fold score 2-3 compared 6-7 score.

Table 2. Univariate and multivariate analyses of factors for prediction of overall-survival

	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value
Sex				
Male	1		1	
Female	0.685(0.204-2.299)	0.541	1.101(0.008-1.365)	0.084
Smoking Status				
Smoker	1		1	
Ex-smoker	1.440(0.447-4.643)	0.641	0.324(0.031-3.393)	0.347
Histopathology				
Invasive Urothelial	1		1	
Others	1.239(0.374-4.109)	0.726	0.921(0.185-4.584)	0.920
Stage				
II	1		1	
III	1.909(0.874-7.973)	0.105	3.009(1.003-9.029)	0.049
Iva	0.151(0.151-2.034)	0.154	2.873(0.986-8.374)	0.053
KPS				
≥70	1		1	
<70	1.803(0.573-5.677)	0.314	2.432(0.433-13.653)	0.313
Charlson Co-morbidity Index				
2-3	1		1	
4-5	0.546(0.230-1.283)	0.165	0.203(0.049-8.826)	0.057
6-7	0.674(0.231-4.726)	0.178	0.161(0.035-0.748)	0.020
Radiotherapy doses				
60 Gy	1		1	
45 Gy	1.468(0.456-5.246)	0.678	7.834(0.694-88.429)	0.096
40 Gy	1.791(0.500-6.4169	0.371	241.22(5.421-107.679)	0.005
Chemoradiotherapy				
Present	1		1	
Absent (Radiotherapy alone)	1.791(0.370-7.973)	0.491	2.039(0.241-17.226)	0.513

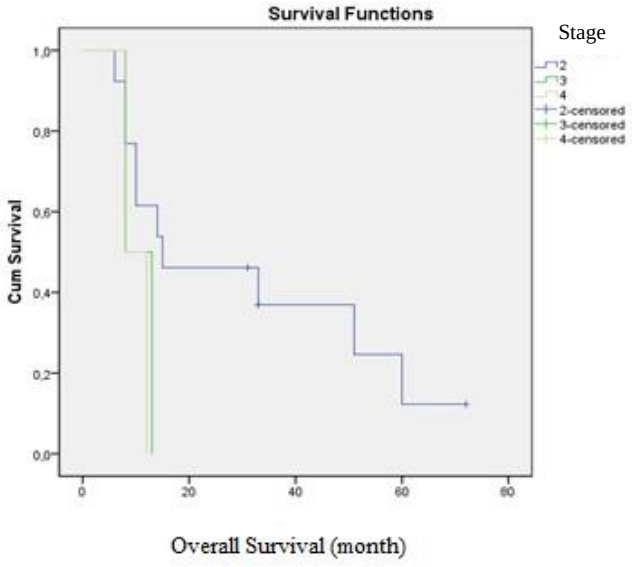

Figure 1: Overall survival according to the stages.

Discussion

Bladder cancer is more common in older adults. The average age of diagnosis is 72 years. Today, with increasing life expectancy, the curative treatments to be more critical in octogenarians.

Maximal TUR and radical cystectomy is a primary curative treatment in bladder cancer. Despite the improvements in surgical techniques, sometimes it is not possible due to additional diseases. Bladder-conserving treatment (TUR and after chemoradiotherapy) is the preferred treatment option for invasive bladder cancer patients. The European Association of Urology Guidelines consider it appropriate to add radiotherapy alone or in combination with chemotherapy after the maximum TUR in patients who are not eligible for radical cystectomy (7). While 5-year overall survival was 36-74%, 5-year disease-free survival was 50-82%. Similarly, in the study conducted by Erlangen University, the five and 10-year survival rates of patients receiving bladder-sparing treatment were 51% and 31%, respectively (8).

However, in these studies, the patient's age is younger than our research. Studies with Octogenarian are generally very few. In these studies, patients received a TUR alone as primary treatment (9). The patients were then followed up. In our study, we applied radiotherapy or chemoradiotherapy after TUR.

Fischer-valuck et al. compared treatment modalities in an octogenarian with muscle-invasive bladder cancer patients (10). They found the OS for 14 month. The 3-year and 5-year survival rates were 26.3% and 14.5%. They found that the survival of CRT and radical surgery is equal to each other, but CRT has a superior treatment modality than radiotherapy alone. In our study, the median OS was 13 months and similar to Fischer-valuck et al. study.

However, our patients do not have three and 5-years of survival. Moreover, only three patients took CRT. Almost all patients received RT alone. Charlson's co-morbidity index is to use geriatric oncology patients. Our patients

were generally found to be 2-3 points. We found that this score was an independent prognostic factor in multivariate analysis. Similar, other studies found Charlson's co-morbidity score was an independent prognostic factor in octogenarians (10-11).

Stage of bladder cancer is an essential factor that affects the course of the disease and survival rate. Studies conducted in the literature regarding the stage and progression of the disease, and different results have been reported (12-13-14). We found that stage II was an independent prognostic factor for OS in octogenarians.

In many studies on elderly bladder cancer, radiotherapy dose was applied over 60 Gy. Median 58.6 Gy (range 54-62.8) was used in the study of Lee et al., 60-70 Gy was received in the study of Korpics et al., and a median 64.8 Gy was used in the study of Hsieh et al. (15, 16, 17). Similar to the above studies, we applied a median of 60 Gy to the bladder. Curative radiotherapy dose is also an essential prognostic factor in elderly bladder cancer patients. RT was well tolerated by all patients. In our study, three patients received CRT, while 14 patients received radiotherapy alone. Patients who break the treatment were CRT used patients. Diarrhea and urinary frequency were the most common side effect. Our side effect results were similar to other studies (15, 16, 17, 18).

A limitation of our study was almost all patients stage II. The number of patients receiving RT alone or CRT is minimal in terms of which one is more effective. It was not clear whether the cause of death was due to the additional disease.

Conclusion

According to the study results, radiotherapy alone or CRT can be performed in octogenarians who have longer life expectancies.When deciding curative treatment in patients with invasive bladder cancer over 80 years of age, we should be highly selective, especially with co-morbidity diseases, and we comprehensive assessment is required

Acknowledgement, Funding: None.

Author's contributions: BI, OM; Project design, Patient examination, Treatmen, Statistical Analyses **BI;** Article preparation and revisions

Conflict of interest: The authors declare that they have no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68(6):394–424.

2. Zakaria AS, Santos F, Tanguay S, Kassouf W, Aprikian AG. Radical cystectomy in patients over 80 years old in Quebec: a population-based study of outcomes. J Surg Oncol. 2015;111:917–922.

3. Mak RH, Hunt D, Shipley WU, Efstathiou JA, Tester WJ, Hagan MP, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder- preserving combined-modality therapy: a pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, 0233. J Clin Oncol 2014;32: 3801–9.

4. Lin HYD, Ye H, Krauss DJ. Muscle invasive bladder cancer survival after radical cystectomy or definitive chemoradiation: a national cancer database matched pair analysis. Int J Radiat Oncol Biol Phys 2017;99:E252.

5. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted inhospital mortality. J Clin Epidemiol 2004;57:1288–94.

6. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events(CTCAE).http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf Date last updated: June 14, 2010.

7. Witjes JA, Compérat E, Cowan NC, Santis MD, Gakis G, Lebret T, et al.European Association of Urology: EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol 2014;65:778–792.

8. Rödel C, Grabenbauer GG, Kühn R, Papadopoulus T, Dunst J, Meyer M, et al.Combined- modality treatment and selective organ preservation in invasive bladder cancer: Long-term results.J Clin Oncol 2002;20:3061-3071.

9. Hollenbeck BK, Miller DC, Taub D, Dunn RL, Underwood W 3rd, Montie JE, et al:Aggressive treatment for bladder cancer is associated with improved overall survival among patients 80 years old or older. Urology 2004; 64:292–297.

10. Fischer-Valuck BW, Rao YJ, Rudra S, Przybysz D, Germino E, Samson P, et al. Treatment patterns and overall survival outcomes of octogenarians with muscle invasive cancer of the bladder: an analysis of the National Cancer Database. J Urol. 2018;199:416–423.

11. Ha MS, Chang IH. Significance of age and comorbidity as prognostic indicators for patients with bladder cancer. Asian J Androl. 2010;12:766–774.

12. Guo CC, Czerniak B. Bladder cancer in the genomic era. Archives of Pathology and Laboratory Medicine 2019; 143(6):695–704.

13. Zhu C Z, Ting HN, Ng KH, Ong TA. A review on the accuracy of bladder cancer detection methods. Journal of Cancer 2019;10(17):4038–4044.

14. Kim WJ. Changing landscape of diagnosis and treatment of bladder cancer. Investigative and Clinical Urology 2016; 57: S1–S3.

15. Lee YT, Wu YT, Yen CC, Chang MH, Chang YH, Chung HJ, et al. Concurrent chemoradiotherapy in elderly patients with muscle-invasive bladder cancer: A single-center experience. Journal of Cancer Research and Practice 2016;3(3):73-6.

16. Hsieh CH, Chung SD, Chan PH, Lai SK, Chang HC, Hsiao CH, et al. Intensity modulated radiotherapy for elderly bladder cancer patients. Radiation Oncology 2011;6(1):75.

17. Korpics MC, Block AM, Martin B, Hentz C, Gaynor ER, Henry E, et al. Concurrent chemotherapy is associated with improved survival in elderly patients with bladder cancer undergoing radiotherapy. Cancer 2017;123(18):3524-31.

18. Turgeon GA, Souhami L, Cury FL, Faria SL, Duclos M, Sturgeon J, et al. Hypofractionated intensity modulated radiation therapy in combined modality treatment for bladder preservation in elderly patients with invasive bladder cancer. International Journal of Radiation Oncology Biology Physics 2014;88(2):326-31.