

Definitive radiotherapy or chemoradiotherapy results and side effects in elderly bladder cancer patients

Yaşlı mesane kanseri hastalarında, definitif radyoterapi veya kemoradyoterapi sonuçları ve yan etkileri

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SUMMARY



Objective: Bladder cancer is most commonly observed in elderly patients. In these patients, it is not always possible to give the necessary treatment for the disease. In this study, definitive radiotherapy (RT) or chemoradiotherapy (CRT) results and side effects, as well as prognostic factors, were investigated in elderly bladder cancer patients.

Method: The results of 36 elderly patients who received definitive RT or CRT for bladder cancer between the years 2010–2018 in Sivas Oncology Center of Cumhuriyet University Medical Faculty were analyzed retrospectively.

Results: The median age of the patients was 75 (range, 65–84). Sixteen patients (44%) underwent RT without chemotherapy and 20 patients (56%) received CRT. Complete response was detected in 19 (53%) patients. The median survival was 18 months (range 3–102 months) and the overall 2-year survival rate was 37%. Treatment response ($p < .001$) and performance status of the patients ($p = .001$) were found to be statistically significant prognostic factors in patients' survival. However, sex, comorbidity, Charlson Comorbidity index, risk groups, treatment modality (RT vs. CRT), presence of in situ, grade, status of tumor foci (unifocal vs. multifocal), degree of tumor resection in transurethral resection of the bladder (TUR-B, complete vs. incomplete resection), chemotherapy after CRT, concurrent chemotherapy regimen (cisplatin vs. gemcitabine), RT dose (< 60 Gy vs. ≥ 60 Gy), and the device used in RT (linac vs. TomoTherapy) were not statistically significant.

Conclusions: Good performance and completed response to treatment in elderly bladder cancer patients positively affects survival.

Keywords: Bladder cancer, elderly patients, radiotherapy, chemoradiotherapy

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ÖZET

Amaç: Mesane kanseri en yaşlı hastalarda görülür. Bu hastalarda hastalık için gerekli tedaviyi vermek her zaman mümkün değildir. Bu çalışmada yaşlı mesane kanseri hastalarında definitif radyoterapi (RT) veya kemoradyoterapi (KRT) sonuçları ve yan etkileri ve prognostik faktörler araştırıldı.

Yöntem: Cumhuriyet Üniversitesi Tıp Fakültesi Sivas Onkoloji Merkezi'nde 2010-2018 yılları arasında mesane kanseri nedeniyle definitif RT veya KRT alan 36 yaşlı hastanın sonuçları retrospektif olarak incelendi.

Bulgular: Hastaların ortanca yaşı 75 (65-84) idi. On altı hastaya (% 44) kemoterapi olmadan RT uygulandı ve 20 hastaya (%56) KRT uygulandı. Tam cevap 19 (%53) hastada tespit edildi. Ortanca sağkalım 18 aydı (aralık: 3-102 ay) ve toplam 2 yıllık genel sağkalım oranı %37 idi. Tedavi yanıtı ($p < .001$) ve hastaların performans durumları ($p = .001$) hastaların sağkalımında istatistiksel olarak anlamlı prognostik faktörler olarak bulundu. Bununla birlikte, cinsiyet, komorbidite, Charlson Komorbidite indeksi, risk grupları, tedavi yöntemi (RT ve KRT), in situ varlığı, derecesi, tümör odaklarının durumu (unifokal ve multifokal), mesanenin transüretal rezeksiyonunda tümör rezeksiyonu derecesi (TUR-B, tam ve eksik rezeksiyon), KRT sonrası kemoterapi, eşzamanlı kemoterapi rejimi (siplatin vs. gemitabin), RT dozu (<60 Gy vs. ≥ 60 Gy) ve RT'de kullanılan cihaz (linak vs. TomoTherapy) istatistiksel olarak anlamlı değildi.

Sonuç: Yaşlı mesane kanseri hastalarında iyi performans ve tedaviye verilen cevap sağkalımı olumlu yönde etkilemektedir.

Anahtar sözcükler: Mesane Kanseri, yaşlı hastalar, radyoterapi, kemoradyoterapi

INTRODUCTION

Bladder cancer is the sixth most common cancer of all body cancers. It ranks fourth among males and eleventh among females ¹. In addition, bladder cancer is the second most common urologic malignancy ². Seventy percent of bladder cancer cases are observed as non-muscle invasive and 30% are observed as muscle invasive ³. However, 50–70% of non-muscle-invasive tumors are recurrent despite transurethral and intravesical treatments ^{4,5}.

Radical cystectomy with neoadjuvant chemotherapy is the standard recommended treatment for tumors with muscle invasion. In some bladder cancer patients, bladder-sparing treatment may be an alternative to radical cystectomy. In particular, bladder-sparing treatment may be considered in patients with unifocal T2–3 tumors, those with adequate renal function for cisplatin administration, and those without urethral obstruction and in situ disease ^{6–8}. In addition, chemoradiotherapy (CRT) may be a treatment option in medically inoperable patients who do not prefer radical cystectomy or in patients with comorbid diseases. In bladder-sparing treatment, maximal transurethral resection of the bladder (TUR-B) is performed first. After complete resection of the bladder, the patient is treated with CRT.

As a result of the growth of the global elderly population, there is an increase in cancer cases and in patients requiring continuous medical care. This is especially true in patients with cancers that have a long latency period, such as urothelial bladder carcinoma, in which the peak incidence is at an advanced age ⁹. Indeed, the median age of diagnosis of patients with bladder cancer is 73, and more than two-thirds of cases occur in people 65 years and older ¹. Amongst the elderly population, patients are often affected by multiple comorbidities, such as diabetes, hypertension and heart disease that limit tolerance to curative surgical treatment and other treatments. Often,

due to the low physiological reserves of older people, physicians will have difficulty in deciding whether the preferred treatment would be radical cystectomy. Therefore, alternative therapies for radical cystectomy may come to the fore in these patients, especially those with muscle-invasive tumors. Some elderly patients who would be candidates for CRT are considered not to be good candidates for this treatment due to medical problems.

In this study, treatment results and side effects of elderly patients treated with definitive radiotherapy (RT) or CRT for bladder cancer were investigated. In addition, prognostic factors affecting the survival of elderly patients were investigated.

MATERIAL AND METHODS

The results of 36 elderly patients who received definitive RT or CRT for bladder cancer between the years 2010–2018 in Sivas Oncology Center of Cumhuriyet University Medical Faculty were analyzed retrospectively. The study was approved by the Ethics Committee of Sivas Cumhuriyet University. Patients aged 65 years and over with bladder cancer, but without distant metastases, who underwent definitive RT or CRT and who did not accept radical cystectomy, or were not medical inoperable for cystectomy, were included in the study.

The staging of the disease was performed according to AJCC 8th TNM staging (2016) ^{10,11}. The performance status of the patients was evaluated according to The Eastern Cooperative Oncology Group (ECOG) performance criteria ¹².

For the patients, two risk groups have been described according to T stage, tumor size, tumor number, presence of in situ and presence of hydronephrosis. The first is the standard risk group: T1–3 tumor, tumor less than 5 cm, unifocal, in situ-free, and hydronephrosis-free. The second group is the high-risk group: T4 tumor, tumor larger than 5 cm, multifocal,

presence of in situ, and presence of hydronephrosis.

Radiotherapy was performed using linear accelerators (The Varian DHX device, N = 28, 78%) and TomoTherapy (N = 8, 22%) with standard fractionation. Eclipse (ver. 8.6; Varian Medical Systems, Inc. Palo Alto, CA, USA) was used as the three-dimensional conformal radiotherapy (3DRT) planning software program. VoLO planning system (Tomo HD VoLO planning system, Accuray Inc. Madison, WI, USA) was used as the intensity modulated radiotherapy.

First, the patients were given a total of 40–45 Gy RT from 1.8 Gy per day from the pelvic area (obturator, internal and external iliac lymph nodes, whole bladder), and a boost dose was planned considering the normal organ dose limitation. Radiotherapy-induced side effects were assessed according to The Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria¹³. Weekly cisplatin (35 mg/m²) or gemcitabine (400 mg/m²) was used as the concomitant chemotherapy agent.

Treatments

TUR-B was performed in 33 (92%) patients. Only 10 (30%) patients underwent complete resection of TUR. Four (11%) patients received intravesical therapy. Sixteen patients (44%) underwent RT without chemotherapy and only 20 patients (56%) were suitable to receive CRT. The median RT dose was 52.2 Gy (16.2–64.8 Gy). Simultaneous chemotherapy regimens were carried out; 9 (45%) patients received weekly gemcitabine and 11 (55%) patients received weekly cisplatin. After CRT, 9 (25%) patients received maintenance

chemotherapy. None of the patients underwent cystectomy after CRT.

Statistics

SPSS version 22 was used for statistical analysis. Descriptive tests (frequencies, descriptive, standard deviation) were used to describe the characteristics of the patients and the Kaplan Meiere test was used for survival analysis. P-values $p < 0.050$ were considered as significant.

RESULTS

When the data of 36 patients with bladder cancer were examined, it was found that 31 (86%) of the patients were male and 5 (14%) were female. The median age of the patients was 75 (range, 65–84). Twenty-seven patients (75%) had comorbidity. According to Charlson Comorbidity Scoring: there were 12 (34%) patients with 5 points; 13 (36%) patients with 6 points; 8 (22%) patients with 7 points; and 3 (8%) patients with 8 points¹⁴. All patients had histopathology of urothelial carcinoma and none had hydronephrosis. The characteristics of the patients are shown in Table 1. Treatment-related adverse events, acute and late side effects are shown in Table 2.

Complete response was detected in 19 (53%) patients. Complete response was observed in 8 (42%) patients who received RT without chemotherapy and in 11 (58%) patients who received CRT ($p = .515$). Local recurrence occurred in 8 (22%) patients and distant metastasis developed in 7 (19%) patients. The median survival was 18 months (range 3–102 months) and the overall 2-year survival rate was 37%.

Table 1: The patients characteristics.

	No of patients	%
Sex		
Male	31	86
Female	5	14
Comorbidity	27	75
Hypertension	16	44
Coronary artery disease	9	25
Diabetes mellitus	8	22
Renal disease	3	8
Charlson Comorbidity index		
5 point	12	34
6 point	13	36
7 point	8	22
8 point	3	8
Stage of initial daignosis		
Superficial stage (Ta, T1)	9	25
T2 and high	27	75
Stage		
Stage I	3	8
Stage II	25	70
Stage III	8	22
Grade		
Grade I	2	6
Grade II	2	6
Grade III	32	88
In situ		
No	28	78
Yes	8	22
The number of tumor		
Unifocal	19	57
Multifocal	17	43
Risk		
Standard risk	17	47
High risk	19	53

Table 2: Adverse events and toxicities.

	No of patients	%
The planned treatment incompleted	5	14
Interruption of treatment	7	19
Deterioration of performance status	13	36
Acute toxicities		
Lower gastrointestinal		
Grade 1-2	20	56
Genitourinary		
Grade 1-2	24	67
Grade 3-4	2	6
White blood cell		
Grade 1-2	11	32
Grade 3-4	2	6
Platelet		
Grade 1-2	2	6
Grade 3-4	3	8
Neutrophil		
Grade 1-2	4	11
Grade 3-4	2	6
Hemoglobin		
Grade 1-2	14	39
Hematocrit		
Grade 1-2	6	17
Late toxicites		
Lower Gastrointestinal [†]		
Grade 3-4	1	3

[†] Pathologically proven

Treatment response ($p < .001$) and performance status of the patients ($p = .001$) were found to be statistically significant prognostic factors in patients' survival. The survival curves of statistically significant prognostic factors are presented in Figure 1. However, sex, comorbidity, Charlson Comorbidity index, risk groups, treatment modality (RT vs. CRT), presence of in situ, grade, status of tumor foci (unifocal vs.

multifocal), degree of tumor resection in TUR (complete vs. incomplete resection), chemotherapy after CRT, concurrent chemotherapy regimen (cisplatin vs. gemcitabine), RT dose (<60 Gy vs. ≥ 60 Gy), and the device used in RT (linac vs. TomoTherapy) were not statistically significant. The prognostic factors in univariate analysis are shown in Table 3.

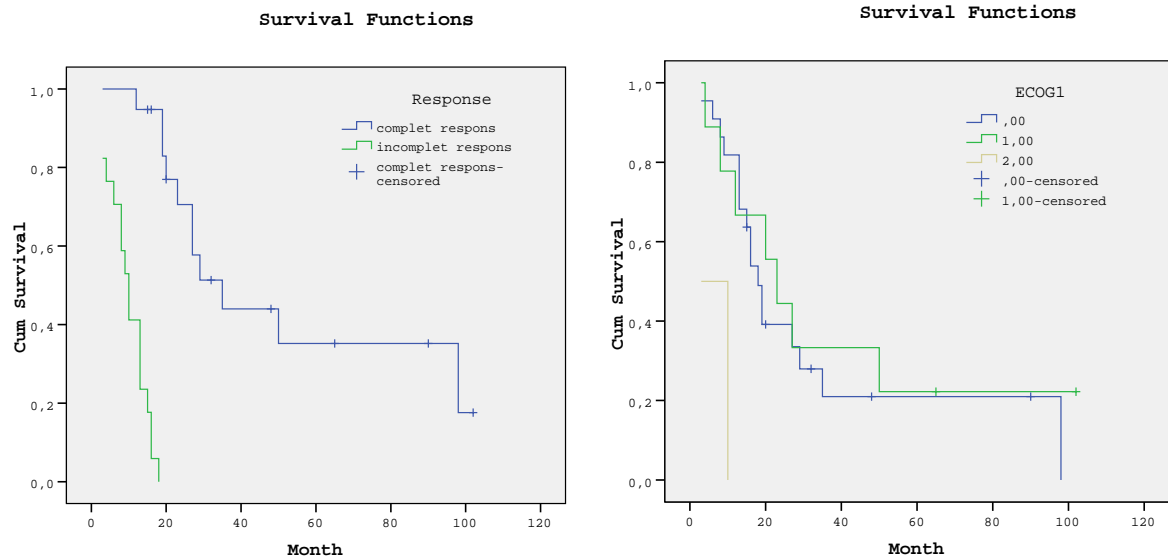


Figure 1: The survival curves according to treatment response and performance status (ECOG).

Table 3: The prognostic factors in univariate analysis.

	No of patients (%)	The 2 years overall survival	The median survival	P value
RT [†] /CRT [‡] response				
Complet response	19 (53)	71	35	<0.001
Incomplet response	17 (47)	-	10	
ECOG				
ECOG 0	22 (61)	34	18	0.001
ECOG 1	9 (23)	33	23	
ECOG 2 and high	4 (11)	-	3	
Treatment				
RT	16 (44)	31	15	0.350
CRT	20 (56)	35	19	
RT dose				
<60 Gy	21	20	16	0.562
≥60 Gy	15	37	19	
Radiotherapy devices				
Lineer accerator	28 (78)	32	16	0.197
TomoTherapy	8 (22)	54	NR [§]	
Risk				
Standard risk	17 (47)	37	18	0.751
High risk	19 (53)	29	16	

[†]RT: Radiotherapy, [‡]CRT: Chemoradiotherapy, [§]NR: Not reached.

DISCUSSION

Although radical cystectomy is the standard treatment for muscle-invasive bladder cancers and frequently recurrent superficial tumors, some of the patients do not want to lose their bladder. In some patients, especially elderly people with comorbid disease, their physiological reserves are not suitable for surgery. Therefore, alternative therapies for radical cystectomy are being investigated especially in selected patients. CRT may be an alternative treatment for these patients. RTOG The Radiation Therapy Oncology Group (RTOG) has been investigating treatments that protect the bladder since the 1980s¹⁵⁻²¹. The group has undertaken a number of CRT studies with various chemotherapy agents. In these studies, 5-year overall survival rates were found to be 49.5–71.75%¹⁶⁻²¹. Massachusetts General Hospital published the data of 475 bladder cancer patients treated with TUR-B + CRT (simultaneous cisplatin, 5FU, paclitaxel, gemcitabine, median RT dose 64 Gy) between 1986 and 2013. The Median follow-up was 7.21 years: complete response was 75%, 5 and 10-year overall survival were 57% and 39%, 5 and 10-year disease-specific survival were 66% and 59%, respectively. The patients in this study were selected for bladder-sparing therapies and survival rates of elderly patients were not indicated. However, advanced age at diagnosis has been reported to be a poor prognostic factor for overall survival²².

Wujanto et al. analyzed the survival of 45 bladder cancer patients treated between 2002 and 2017 with a median age of 77 (range 65–95). In this study, the median RT dose was 65 Gy (range 50–69.8 Gy). CRT was administered to 21 (47%) patients and RT was administered to 24 (53%) patients. Forty-two patients (93%) completed the planned treatment. The 2-year overall survival was 64%. In this study, the performance of patients was identified as a prognostic factor affecting survival²³. Forty-four percent of our patients did not receive concomitant chemotherapy and 14% did not complete the planned treatment. In addition, 36% of patients' performance status deteriorated during treatment.

Lee et al. investigated CRT in elderly bladder cancer patients. Nineteen patients with a median age of 79.5 were included in the study. Median RT dose was 58.6 Gy (range 54–62.8). Chemotherapy agent gemcitabine or carboplatin was used and grade 3–4 neutropenia was observed in 53% of the patients as a major adverse event. In the study, 2-year overall survival was reported as 74% and 3-year overall survival as 60%²⁴.

In 2014, Turgeon et al. investigated hypofractionated RT in 24 bladder cancer patients age 70 years and over (median 79 years). A total of 40 Gy RT was administered to the pelvic area from 2 Gy daily to the patient and 2.5 Gy to 2.5 Gy daily to the bladder. All patients were taken to RT by Intensity Modulated Radiotherapy (IMRT) technique. Simultaneously, cisplatin or gemcitabine or gemcitabine + everolimus was administered to RT. Complete response was achieved in 83% of the patients. The 3-year overall survival was 61%. Acute grade 3 gastrointestinal or genitourinary toxicities occurred in only 4% of patients and acute grade 3–4 hematologic toxicity occurred in 17%²⁵. Compared with the study of Turgeon et al., the treatment response of our study was found to be quite low (53%). Furthermore, the addition of chemotherapy to radiotherapy did not alter this outcome in our study. Complete response was observed in 42% patients who received RT without chemotherapy and in 58% patients who received CRT ($p = .515$).

Hsieh et al. evaluated the results of 19 elderly patients with bladder cancer irradiated with IMRT (N = 9) and Helical Tomo Therapy (N = 10). The median age of the patients was 80 years (range 65–90 years). Median 64.8 Gy RT was administered to patients whether or not they received concurrent chemotherapy. The median survival of all patients was 21 months (5–26 months). The actuarial 2 years overall survival was 26.3% in IMRT and 37.5% in Helical Tomo Therapy, respectively²⁶. In contrast to the above study, we did not statistically find any difference in survival in terms of 3DRT and TomoTherapy irradiation in our study. The 2-year overall survival was 32% and 54% in 3DRT and TomoTherapy, respectively. Furthermore, in the present study, patients' 2-year overall survival rates were slightly higher than in the study of Hsieh et al.

Korpics et al. compared RT vs. CRT in elderly bladder cancer patients. In this study, the researchers used the National Cancer Data Base. The data of 1369 bladder cancer patients who were clinically T2–4, N0–3, M0 were examined. The median age of the patients was 84 (range 80–90). Seventy-nine (54%) of the patients received RT without chemotherapy and 630 (46%) received CRT. The RT dose used was 60–70 Gy. The 2-year overall survival of all patients was 48%. The two-year overall survival of patients receiving RT without chemotherapy and patients receiving CRT was 42% and 56%, respectively ($P < .0001$). The authors concluded that the addition of chemotherapy to RT increases survival in

elderly patients²⁷. However, in our present study, the addition of chemotherapy to radiotherapy did not cause a difference in survival.

In our study, the 2-year overall survival was 37% and the median survival was 18 months. These results are lower than in most, but not all, other studies in older patients with bladder cancer^{26,27}. When the general characteristics of the patients included in the study were examined, it was observed that it was a very fragile group. Due to the high rate of comorbidity, the majority of patients being at high risk for bladder-sparing treatment, and almost half of the patients failing to receive concomitant chemotherapy, patients could not complete their treatment optimally. The reasons listed above may explain why our patients' survival rates are low. However, in our study, when the side effects of treatments were examined, we obtained similar results to other studies. In the acute phase, grade 3–4 toxicity was around 2% for the genitourinary and 6–8% for the hematologic toxicities. In the late period, only one patient had gastrointestinal side effects with biopsy proven. There may be a need to step out of routine practice when making treatment decisions of elderly patients. In most cases, the lack of optimal treatment may adversely affect treatment outcomes in this patient group.

The limitations of this study are the retrospective nature of the study, the small number of patients, and the fact that most patients were not good candidates for bladder-sparing treatment.

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