

Factors Affecting Survival in Elderly Rectum Cancer Patients Undergoing Neoadjuvant Chemoradiotherapy

Neoadjuvan Kemoradyoterapi Uygulanan Yaşlı Rektum Kanseri Hastalarda Sağkalımı Etkileyen Faktörler

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ÖZET

Amaç: Tüm dünyada yaşlı nüfusun artmasıyla rektum kanserli yaşlı hastaların sağkalımına etkileyen faktörlerin incelenmesi amaçlandı.

Gereçler ve Yöntem: Aralık 2009- Haziran 2021 tarihleri arasında, 65 yaş üstü ve neoadjuvan KRT (nKRT) uygulanmış 171 hastanın verileri retrospektif olarak incelendi.

Bulgular: Çalışmaya dahil edilen hastaların 117 si erkekti ve median yaş 72 idi. Median izlem süresi 40,5 aydı. Hastaların %63 ü nKRT sonrası opere edildi. Ortalama genel sağkalım (GS) opere olanlarda 109 ay, opere olmayanlarda 29 ay idi ($p<0,001$). Kaplan Meier tek değişkenli analizlerde; yaş (<75 vs >75 , $p<0,00$), Karnofsky Performans skalası (KPS, <70 vs >70 , $p=001$), tanı anında lenf nodu durumu (LN+ vs LN-, $p<0,001$), opere olanlarda lenfovasküler invazyon durumu (LVI+ vs -, $p<0,001$) GS etkileyen faktörler olarak bulundu. Yaş gruplarına göre bakıldığında <75 yaşta operasyonun sağkalıma anlamlı katkısı varken ($p<0,001$), 75 yaş üstü hastalarda opere olup olmamanın sağkalıma katkısı gösterilemedi. Benzer şekilde >75 yaşta KPS nin anlamlı katkısı gösterilemedi.

Sonuç: Yaş ilerledikçe komorbid hastalıkların sık ve ağır seyretmesi ve performansı etkileyeceğinden operasyon durumunun sağkalıma etkisinin saptanamamış olabileceği düşünüldü.

Anahtar Kelimeler: Rektum kanseri, radyoterapi, sağkalım

ABSTRACT

Purpose: As the elderly population increases all over the world, it was aimed to examine the factors affecting the survival of elderly patients with rectal cancer.

Materials and Methods: Between December 2009 and June 2021, the data of 171 patients over the age of 65 who underwent nCRT were examined retrospectively.

Results: 117 of the patients included in the study were male and the median age was 72. The median follow-up time was 40.5 months. 63% of the patients were operated after nCRT. Median overall survival (OS) was 109 months in those who were operated on and 29 months in those who were not operated on ($p<0.001$). In Kaplan Meier univariate analyses; age (<75 vs >75 , $p<0.00$), Karnofsky Performance scale (KPS, <70 vs >70 , $p=001$), lymph node status at diagnosis (LN+ vs LN-, $p<0.001$), lymphovascular invasion in operated patient status (LVI+ vs -, $p<0.001$) were found to be factors affecting OS. When looked at by age groups, surgery at age <75 had a significant contribution to survival ($p<0.001$), whereas in patients over 75 years of age, whether or not being operated on had a significant contribution to survival. Similarly, no significant contribution of KPS was shown at the age of >75 .

Conclusion: It was thought that the effect of the operation status on survival may not have been detected, as comorbid diseases become more frequent and severe with age and affect performance.

Key words: Rectal cancer, Radiotherapy, Survival

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in both women and men. The median age of diagnosis is 68 for men and 72 for women (1). With the increasing life expectancy all over the world, the number of elderly cancer patients is increasing steadily. In CRC patients, 58% of new cases are ≥ 65 years and 19% are ≥ 80 years. Rectal cancer is the tenth deadliest cancer and accounts for 3.2% of all cancer deaths. (2).

Neoadjuvant chemoradiotherapy (nCRT) followed by curative total mesorectal excision (TME) is the standard treatment and may improve locoregional tumor control, sphincter-saving rates, and survival in locally advanced rectal cancer patients (3,4). Especially preoperative radiotherapy and chemotherapy regimens are better tolerated (5). However, when evaluating current treatment for rectal cancer, elderly patients are not included in large clinical trials. The German CAO/ARO/AIO-94 study included patients under 75 years of age, and the mean age of patients who received preoperative CRT and underwent surgery was 62 years (6). The FFCD 9203 trial evaluated nCRT in ≤ 75 years patient (7). There is little clinical trial evidence describing the benefits and risks of all aspects of rectal cancer care in older adults. (8). Due to the lack of sufficient clinical data for elderly rectal cancer patients, clinicians have difficulty applying standard three-modality treatments to these patients.

Curative treatment of elderly patients can be challenging due to risks of treatment toxicity and underlying comorbidities. The main risk is under- or over-treating them because of their chronological age or degree of frailty. In clinical practice, the rate of receiving any cancer treatment in elderly patients is significantly lower than in younger patients (9). With the rapid increase in the number of elderly cancer patients, the failure of this group of patients to receive standard treatments results in a significant number of undertreated patients. To provide more clinical data regarding treatment outcomes of elderly rectal cancer patients, the data of this group of patients should be investigated in more detail. Thus, studies specific to elderly patients may be more effective and result in similar effects and survival with fewer side effects. The aim of this study is to evaluate the factors affecting the prognosis in patients over 65 years of age who were diagnosed with rectal cancer and received standard treatment.

MATERIALS AND METHODS

Informed consent was obtained from all of the patients before the treatments.

Patients characteristics

We analyzed the medical records of 171 newly diagnosed rectal cancer patients ≥ 65 years who were treated with standard nCRT between November 2009 and June 2021. The patients

who were enrolled in this study had the following inclusion criteria: 1) locally advanced rectal cancer without metastasis at the time of diagnosis; 2) ≥ 65 years of age at diagnosis; 3) patients treated with standard nCRT; 4) available and consistent data from histopathological sections and patient files. The following data were obtained using patient records and electronic records: demographics (sex, age, Karnofsky performance status (KPS) before treatments), radiotherapy techniques and doses, clinical tumor stage, nCRT schedule, surgical status, side effects, post-nCRT pathological and radiological response, date of metastasis or recurrence, death or last follow up and survival time.

Pre-treatment assessment

In the first evaluation, pathological confirmation for all patients was done by tissue biopsy from the primary lesion. Physical examination, digital rectal examination (DRE), thorax, and abdomen computed tomography (CT) were performed. Magnetic resonance imaging (MRI) of the pelvis to stage the nodal status and local transmural extension was performed for all patients. If possible image-guided biopsy and/ or positron emission tomography - computed tomography (PET-CT) and was performed on patients with suspected distant metastasis. According to the AJCC Staging System, seventh edition, clinical stages were recorded (10).

Neoadjuvant treatment protocol

Pelvic radiotherapy (RT) was applied to all patients with clinical or radiological stage T2-T4, with or without positive lymph nodes. RT doses were 45 -54 Gy at 1.8-2 Gy per fraction and were delivered for five sessions per week with three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT) techniques. During RT, patients received concurrent chemotherapy for approximately 6 weeks. The chemotherapy regimens used were 5-fluorouracil (5-FU) and leucovorin or oral capecitabine. 5-FU and leucovorin at 1000 mg/m²/day on days 1-5 and 29-33. It was given as a continuous infusion for days. Capecitabine was given at 1650 mg/m²/day, started on the same day as RT, and stopped on the last day of RT (11). Weekly hematology and biochemistry tests and physical examinations were performed.

Treatment response to nCRT

An average of 8 weeks after nCRT, all patients underwent MRI to evaluate response. Radiological response to treatment was recorded according to Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Evaluation of efficacy and Follow-up

Follow-up of the patients was done every 3 months for two years, every 6 months for the next 3 years, and then annually. At each control, serum hematology and biochemistry, serum CEA, 19.9 levels, chest radiography, and abdominal ultrasound or CT and MRI were performed, depending

on necessity. Colonoscopy was performed at 1 and 3 years. Treatment-related toxicities were retrospectively graded using the Common Terminology Criteria for Adverse Events v4.0 (CTCAEv4.0) (13).

Statistical analysis

Overall survival (OS) was defined as the time interval from diagnosis time to any cause of death or the last follow-up. Median time to local recurrence (LR) was defined as the time interval from nCRT to any recurrence, clinical, and/or radiological progression. The median time to metastases was defined as the time from the date of RT completion to the date of any distant metastases. Lesions on the anastomosis line or in the pelvic region were considered as LR, and other regions were considered as distant metastases. OS, LR, and metastasis time were estimated with the Kaplan–Meier method. Comparisons of median survival were performed using a Log-rank test. Median values were given with the range (min–max). The Fisher test or chi-2 test or was performed to compare the distribution of patient characteristics. The multivariate analysis was performed using a Cox multivariate analysis. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) (Windows software program, version 22; Chicago, USA).

RESULTS

Data of 171 patients above 65 years old at the time of initial diagnosis and histologically proven rectal cancer, undergoing nCRT between 2009 and 2021 were analyzed. Of the 171 patients included in the study, 117 were male (68%), 54 were female, and the median age was 72 (65-90 years). A total of 114 patients (66%) were > 75 years. Patients were in good condition, with 157 patients (91.8%) with KPS between 80-100. Patient characteristics (Table 1), complications, and grades (Table 2) are shown in tables.

Median follow-up was 40.5 months (3-156 months). While 94.7% of the patients could receive the planned nCRT, chemotherapy could not be given to only 9 patients. While 109 (64%) patients were operated after nCRT, 62 patients were not operated for various reasons. Low anterior resection was performed in 83 and abdominoperineal resection in 26 of 109 patients who were operated on. Analysis of data after nCRT is shown in Table 3. The median OS was 109 months (74-144 months) in operated patients and 29 months in non-operated patients ($p < 0.001$). Median OS was 89 months (38-140 months) for < 75 years, and 28 months (23-33 months) for above 75 years ($p < 0,001$). And 59 months (43-76 months) for KPS 80- 100, 23,3 months for KPS 70 and under ($p = 0,001$).

Considering the radiological lymph node involvement at the time of diagnosis, the median OS was 46 months in patients with lymph node involvement and 129 months in

Table 1. Patient characteristics

| Characteristics | n=171 | % |
|--|----------|-------|
| Sex | | |
| Male | 117 | 68% |
| Female | 54 | 32% |
| Age (Years) | | |
| Median | 72 | |
| Range | 65-90 | |
| Patients performance at diagnosis (KPS) | | |
| Median | 90 | |
| Range | 70-100 | |
| Tumor location | | |
| Distal rectum (0-4. Cm) | 63 | 37% |
| Mid rectum (5-9. Cm) | 68 | 40% |
| Proximal rectum (>10 . Cm) | 40 | 23% |
| Clinical TNM stages at diagnosis | | |
| T2 | 6 | 3.5% |
| T3 | 88 | 51.5% |
| T4a | 62 | 36% |
| T4b | 13 | 13% |
| Lymph node at diagnosis | | |
| Positive | 123 | 72% |
| Negative | 48 | 28% |
| Radiotherapy dose | | |
| Median | 50 Gy | |
| Range | 25-54 Gy | |
| Radiotherapy technic | | |
| IMRT | 127 | 74% |
| 3D-CRT | 44 | 26% |

Table 2. Complications during nCRT

| | n (%) |
|-------------------------|----------|
| Leukopenia | |
| Grade 1 | 26 (15%) |
| Grade2 | 8 (5%) |
| Grade 3 | 1 (<1%) |
| Neutropenia | |
| Grade 1 | 14 (8%) |
| Grade2 | 5 (3%) |
| Grade 3 | 1 (<1%) |
| Thrombocytopenia | |
| Grade 1 | 10 (6%) |
| Grade 2 | 5 (3%) |
| Grade 3 | 1 (<1%) |
| Diarhea | |
| Grade 1 | 21 (12%) |
| Grade 2 | 21(12%) |
| Grade 3 | 8 (5%) |
| Proctitis | |
| Grade 1 | 41(24%) |
| Grade 2 | 28 (16%) |
| Dermatitis | |
| Grade 1 | 68 (40%) |
| Grade 2 | 49 (29%) |
| Grade 3 | 2 (1%) |
| Cystitis | |
| Grade 1 | 15 (9%) |
| Grade 2 | 8 (5%) |
| Grade 3 | 1 (<1%) |

Table 3. Analysis of data after nCRT

| | n=171 | % |
|---|-------|-------|
| Type of operation | | |
| LAR | 83 | 48.5% |
| APR | 26 | 15% |
| No Operation | 62 | 36.5% |
| Response to treatment, radiological | | |
| Complete | 28 | 16% |
| Partial | 120 | 71% |
| No response | 23 | 13% |
| Response to treatment, clinical or pathological | | |
| Complete | 33 | 20% |
| Moderate | 63 | 37% |
| Minimal | 24 | 14% |
| No response | 2 | 1% |
| Missing | 49 | 29% |
| Lymphovascular invasion | | |
| Negative | 82 | 48% |
| Positive | 27 | 15.5% |
| Perineural invasion | | |
| Negative | 77 | 45% |
| Positive | 32 | 18.5% |
| Pathologic lymph node involment | | |
| Positive | 82 | 48% |
| Negative | 27 | 16% |

patients without lymph node metastasis ($p < 0.001$). When the pathology results of the patients who were operated on after the treatment were examined, the OS was 42.5 months in patients with positive LVI and 129.5 months in negative LVI ($p < 0.001$). Similarly, when the presence of PNI was considered, the OS was 31 months in patients with positive PNI and 77 months in patients with negative PNI, but there was no statistically significant difference between the two groups ($p = 0.06$).

In the Cox Regression multivariate analysis, all variables except KPS were found to be statistically significant. When the subgroup analysis according to age was performed, although OS was statistically significantly longer in patients under 75 years of age in the operated group ($p < 0.001$), the operation could not show any contribution to overall survival in patients over 75 years of age. ($p = 0.3$). Similarly, while KPS made a statistically significant contribution to OS in patients under 75 years of age ($p < 0.001$), no statistically significant contribution of KPS on OS could be demonstrated in patients over 75 years of age ($p = 0.1$).

The median time to LR was 21.9 months (8.6-66.7 months). LR occurred in 14 patients (8%). The most LR occurred in distally located tumors (7 patients). Of the patients with LR, 10 had positive lymph nodes. The median time between diagnosis and metastases was 16.7 months (range 1-66.7 months). distant metastasis developed in 35 patients (20.5%). Liver metastases (25 patients, 14.6%) and lung metastases (16

patients, 9.4%) were the most common ones. Brain, bone, abdomen, and adrenal gland metastases were observed less frequently.

DISCUSSION

The results of our study showed that nCRT and curative TME were well tolerated in elderly rectal cancer patients undergoing surgery. The oncological outcomes of elderly patients were similar to younger patients. It has been shown that surgery has a significant contribution to survival after curative treatments, especially in patients aged 65-75 years. Especially in this patient group, who avoided curative treatments due to their age and were not forced to surgery, it was observed that they could tolerate the treatments well. However, the effect of surgery on overall survival after curative treatments could not be demonstrated due to the presence of comorbid diseases and progressive deterioration in performance, especially in the patient group over 75 years of age. Despite this, this patient group was also able to complete curative radiotherapy and chemotherapy without any serious side effects. Standard treatment in fit elderly patients consists of neoadjuvant 5-FU-based CRT followed by TME. (14). In our study, 94.7% of the patients were able to receive the planned simultaneous CRT, chemotherapy could not be given to only 9 patients. This rate was only 19.7% of patients in another study (15). Although TME with or without preoperative CRT is the standard treatment for rectal cancer, the risk of surgical complications and postoperative mortality increases with age and comorbidities. Analysis of two Dutch databases showed that postoperative complications occurred in approximately 50% of patients over the age of 75 (14). In Badic et. al. (15) studies, 1 and 6-month mortality was 3.3% and 22% respectively.

Recent data show improved long-term survival of older patients compared with younger patients (relative 5-year survival 55% in 2000-2004 vs 64% in 2010-2014) and a greater improvement in survival. (16). In a study of 2992 patients with rectal cancer, the relative survival of patients aged 75 years and older was similar to that of younger patients, provided they survived 1 year after surgery (17). In our study, the median OS was 89 months (38-140 months) for <75 years, and 28 months (23-33 months) for above 75 years. For elderly patients who achieve a complete clinical response after nCRT, a watch-and-wait strategy is also an option to avoid the risks of major surgery. Van de Valk et.al. (18) showed in their study of more than 1000 patients (mean 63.3 years old), with nCRT and then a watch-and-wait approach, 2-year local regrowth was determined as 25%, 5-year OS was 85%, and 5-year disease-specific survival was 94%. In our study, 62 patients were not operated for various reasons and the mean overall survival was 109 months (74-144 months) in operated patients and 29

months in non-operated patients. Results from a multicenter study showed that nCRT and curative TME for rectal cancer were well tolerated in elderly (over 70 years old) rectal cancer patients. Oncological outcomes were similar to younger patients. The 5-year OS rate in the entire cohort was 81.3% and 79.5 percent in the elderly (19).

As a conclusion, In the elderly patient group, curative treatment protocols were generally avoided because of fear of possible complications related to treatments. However, in recent studies, post-surgical survival of patients who had good performance and could tolerate neoadjuvant treatments was found to be similar to the younger group. It has also been shown that surgery has a significant contribution to survival in the elderly patient group. With the help of today's developing treatment methods and imaging techniques, curative treatment protocols can also be applied to elderly patients with good performance.

Etik Kurul: The design of the study was approved by the Ethics Committee and Institutional Review Board of the local ethics committee, where the study was conducted (01.03.2024/2024/4845).

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