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Research Paper

Evaluation of treatment outcomes and tolerability in older patients with rectal cancer treated with radiotherapy accompanied by the G-8 geriatric score: TROD13–003 multicenter study

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A B S T R A C T

Introduction: The choice of treatment for rectal cancer often differs in older and younger patients, with the rate of radiotherapy use lower among older adults. In our daily practice, when evaluating a frail older patient with rectal cancer, we usually choose to give less treatment. This may be due to concern that the patient will not be able to tolerate radiotherapy. The Geriatric 8 score (G8GS) is a guide to evaluating treatment tolerability as it relates to frailty in older adults with cancer. The aim of this study was to evaluate treatment outcomes and tolerability in older patients with rectal cancer treated with radiotherapy (RT) accompanied by G8GS.
Materials and Methods: Patients aged 65 and older with stage I-III rectal adenocarcinoma who were treated with RT and had a G8 evaluation were included in this multicenter retrospective study. Prognostic factors related to G8GS were calculated using Chi-square and logistic regression tests and survival rates were calculated by the Kaplan–Meier test using the SPSS v24.0 software. All *p*-values $\leq$0.05 were considered statistically significant.
Results: A total of 699 patients from 16 national institutions were evaluated. The median age was 72 years (range 65–96), and the median follow-up was 43 (range 1-190) months. Four hundred and fifty patients (64%) were categorized as frail with G8GS $\leq$14 points. Frail patients had higher ages ($p = 0.001$) and more comorbidities ($p = 0.001$). Ability to receive concomitant and/or adjuvant chemotherapy rates were significantly higher in fit patients ($p = 0.002$ and $p = 0.001$, respectively). No significant difference was observed in terms of grade 3-4 early and late toxicity for both groups. Cancer-related death was higher ($p = 0.003$), and 5- and 8-year survival rates were significantly lower ($p = 0.001$), in the frail group. Age and being frail were significantly associated with survival.

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Discussion: Radiotherapy is a tolerable and effective treatment option for older adults with rectal cancer even with low G8GS. Being in the frail group according to G8GS and having multiple comorbidities was negatively associated with survival. Addressing the medical needs of frail patients through a comprehensive geriatric assessment prior to radiotherapy may improve G8GS, allowing for standard treatment and increased survival rates.

1. Introduction

Colorectal cancer (CRC) is the fourth most common cancer type and the second leading cause of cancer-related deaths. Patients 65 years and older account for 55% of newly diagnosed cases. The highest number of CRC-related deaths occurs in this age group (65 to 74 years) [1].

Despite the anticipated increase in the older adults with CRC in the future, older patients are still under-represented in many studies. This is due to a lack of sufficient data on oncological treatments for older adults and concerns that these patients might not tolerate the treatments. Therefore, less aggressive, personalized treatments are preferred [2–4].

The choice of treatment for rectal cancer differs in older and younger patients, and the rate of radiotherapy use is lower in older patients [5–9]. For this reason, the International Society of Geriatric Oncology (SIOG) recommends comprehensive geriatric assessment (CGA), which evaluates patients aged 65 and over with CRC for mental and physical competence, and determining the distinction between fit and frail patients [4]. By using objective measures of function, it is anticipated that patients are more likely to receive appropriate treatments that maximize effectiveness, minimize complications, and better meet individual patients' needs [4].

Today, performing a CGA before oncological treatments in older patients is considered the gold standard [4]. For this purpose, many screening tools, questionnaires, forms, and scoring systems are used to evaluate parameters such as nutritional status, neuropsychological status, medication use, age, and social support [10].

The Geriatric 8 (G8) is a quick and reliable test that can be easily applied in daily practice [11]. It consists of eight questions and is derived from the Mini-Nutritional Assessment Short Form (MNA-SF). It has a sensitivity of 76.5% and a specificity of 64.4% in diagnosing fragility, which assesses patients' neurocognitive functions and question their personal health perception. The highest score a patient can get is 17, and patients who score above 14 points are considered fit and candidates for standard treatments. A score $\leq$ 14 is associated with decreased survival [12] and a more detailed geriatric examination is required [11]. It is worth noting that some older adults in this group may have other geriatric syndromes that can be managed, which may result in an increase in G8GS. For example, a patient with inadequate food intake and self-care to gain weight may be able to increase their scores in these areas by receiving nutritional support. Likewise, older adults with depression without dementia could see improvement with the use of antidepressants and the necessary social support. Likewise, scores of patients who receive physical therapy and rehabilitation support may increase, and they may then be included in the fit patient group. Older adults in the frail group are candidates for cancer treatments that will be completed in a shorter time and are the least toxic possible, by anticipating the risks of possible side effects.

In our retrospective multicenter cohort, we aimed to evaluate treatment outcomes and tolerability in older patients with rectal cancer treated with radiotherapy (RT) accompanied by the G-8 Geriatric Score (G8GS).

2. Patients and Methods

2.1. Study Design

The study was planned as a multicenter study by the Geriatric Oncology Study Group of the Turkish Radiation Oncology Association (TROD13–003). Patient records were collected from 16 centers. Patients aged 65 years and older with stage I-III rectal adenocarcinoma who received RT were evaluated retrospectively. Inclusion criteria included receiving at least three-dimensional conformal RT for neoadjuvant, definitive, or palliative intent and having had a pre-RT G8 test or available G8 data. Patients with stage IV disease and those receiving adjuvant RT were excluded. The study protocol was approved by the national ethics committee (approval number:2022/0 5-01).

The staging was performed according to the American Joint Committee on Cancer (AJCC) tumor, lymph nodes, and distant metastases (TNM) system (8th ed. 2017). The G8 geriatric screening tool form was used for geriatric assessment [11]. Early and late toxicities were evaluated according to the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer acute and late toxicity criteria [13].

The primary endpoint of the study was to evaluate treatments and survival in frail and fit patients. The secondary endpoint was toxicity evaluation.

2.2. Treatment Characteristics

Surgery $\pm$ adjuvant chemotherapy (CT) was planned following neoadjuvant RT/chemoradiotherapy (CRT) for locally advanced patients. Definitive RT was applied for patients who were not anticipated to undergo surgery after RT, and palliative RT was applied for more urgent conditions such as bleeding. All patients were planned using 3D conformal (3D-CRT) or intensity-modulated radiotherapy (IMRT)/volumetric arc therapy (VMAT) techniques. Concurrent CT was administered to patients with better performance status (Karnofsky Performance Status >70 or Eastern Cooperative Oncology Group performance status 0–1), sufficient blood cell count, and normal blood chemistry values. Treatment response and local recurrences were assessed both by imaging and clinical evaluation.

2.3. Statistical Analysis

All statistical analyses were performed using standard software (Statistical Package for the Social Sciences (SPSS) version 24.0; International Business Machines Corporation [IBM], Chicago, IL, USA). The Kolmogorov-Smirnov test was used for the analysis of normality distribution in the evaluation of age and total RT doses between frail and fit groups. The Mann–Whitney *U* test was used in the analysis and found not to fit a normal distribution. The Chi-Square Test and, when necessary, the Fisher Exact Test were used to evaluate sex, presence of comorbid diseases, hospitalization during RT, ability to receive concurrent CT, break during RT, the feasibility of surgery, ability to receive adjuvant CT, and early and late toxicity evaluations according to fit and frail groups. A logistic regression model was created for multivariate analysis.

Overall survival (OS) was calculated from the first day of biopsy-proven diagnosis to the last follow-up or death. Local recurrence and distant metastasis-free survival were calculated from the first day of biopsy-proven diagnosis to the respective recurrence or distant metastasis development. The OS, local recurrence-free survival (LRFS), and metastasis-free survival (MFS) rates were estimated using the Kaplan-Meier method. Prognostic factors such as age, stage, and frailty that could affect OS, LRFS, and MFS were evaluated. Univariate analysis was performed with the log-rank test. A Cox regression model was established for the multivariate analysis of survival. Using the R 4.3.1 software environment, survival (3.5–7) and survminer (0.4.9) R packages

were employed to compare the survival of groups, generate Kaplan-Meier plots, and create tables displaying the number at risk. All *p*-values≤0.05 were considered statistically significant.

3. Results

3.1. Patients

A total of 711 patients treated between August 2004 and October 2022 from 16 radiation oncology centers participated in the study. Of these patients, 699 with accessible G8 scores were included in the study. Patients with G8 scores >14 and ≤ 14 were considered fit and frail, respectively. The median age at diagnosis was 72 years (range 65–96). The male/female ratio was 61%/39%, and 74% of the patients had a history of at least one comorbidity. Forty-four patients had a history of secondary cancer. The most common baseline complaint was rectal bleeding (47%), followed by constipation (15%), diarrhea (7%), rectal pain (6.5%), obstruction (1.5%), and other (3%). The upper, middle, and lower rectal tumor localisation rates were 20%, 39%, and 39%, respectively. Stage I, II, and III disease rates were 1%, 20%, and 79%, respectively.

Neoadjuvant RT was administered to 671 patients (96%) at a median dose of 47.8 Gy (range 9-69 Gy). The patient who received 9 Gy discontinued RT by his own choice, while the patient who received 69 Gy was treated with a definitive dose because surgery was not expected to be feasible. Two hundred fifty-four (36%) patients were treated with IMRT, 297 (42%) with VMAT, and 148 (21%) with 3D conformal radiotherapy. Fifty-nine patients received short-course neoadjuvant RT (5 × 5 Gy), with 38 being frail (64%), and 21 being fit. No patient received brachytherapy. Five-hundred sixty-three patients (80%) were able to receive concurrent CT. Standard-dose capecitabine (1650 mg/m2/day) was administered to 414 patients (59%), 57 patients (8%) received a dose below the standard dose, and 92 patients (13%) received intravenous 5-fluorouracil. Forty-four patients had a break in the radiotherapy schedule, and 22 patients (3%) were hospitalized during RT. One of the hospitalized patients died because of a general condition disorder, one developed tumor perforation, and one discontinued RT at his request. One patient died due to cancer progression and another due to postoperative complications during the first 30 days following RT. Surgery was performed in 566 patients (81%). The most common surgical procedure was abdominoperineal resection (57%). Complete pathological response was achieved in 63 (11%) patients who underwent neoadjuvant RT. Eight patients (1%) died due to postoperative complications. In the group of patients who did not undergo surgery, 54% did not want surgery after RT, 32% had insufficient tumor shrinkage with RT, 11% had metabolic problems, and 3% did not undergo surgery due to RT-related side effects. Adjuvant CT was administered to 341 patients (49%) with suitable performance scores. CT was not administered to 309 patients (42%). Adjuvant CT information for 49 patients could not be obtained. The median duration of follow-up was 43 months (range 1-190 months). Patient characteristics classified by G8 score are indicated in Table 1.

During follow-up, local recurrence was detected in 57 patients (12%) and distant metastasis in 145 patients (21%). It was determined that 18% of patients ($n = 127$) died due to cancer. The most common cause of non-rectal cancer deaths was secondary cancer. Local recurrence, distant metastasis, and cancer-related death data for fit and frail patient groups are shown in Table 2.

In the analysis evaluating the independent variables, age was associated with an increase in the risk of death by 1.04 times with $p = 0.013$, odds ratio (OR):1.04 (1.01–1.09 confidence interval [CI] 95%), and being frail was associate with an increase in the risk of death by 1.66 times with $p = 0.026$, OR: 1.66 (1.06–2.60 CI 95%).

Table 1
Patient and treatment characteristics.

Characteristics	Frail n (%)	Fit n (%)	p
	450 (64%)	249 (36%)	
Age, years (median)	73 (65–96)	70 (61–86)	<0.001(MWU)
Sex			
Male	265 (62.1%)	162 (37.9%)	0.11
Female	185 (68.0%)	87 (32.0%)	
≥1 Comorbid disease	356 (80.5%)	164 (67.2%)	<0.001
G8 score (median)	10 (3-14)	16 (15-17)	NA
Stage			
I	3	2	
IIA	83	36	
IIB	5	4	
IIC	10	4	N A
IIIA	15	15	
IIIB	273	150	
IIIC	60	37	
Tx/Nx	1	1	
Intent of treatment			
Neoadjuvant	427	244	NA
Definitive	17	4	
Palliative	6	1	
RT total dose Gy (median)	50.4 (9-63)	50.40 (21. 8-65)	0.49
Hospitalization during RT	15(3.3%)	7 (2.9%)	0.77
Concurrent CT	346 (77.1%)	215 (86.7%) *	0.002
Interruption of RT	32 (7.1%)	12 (4.8%)	0.23
Surgery	355 (78.9%)	211 (84.7%)	0.059
Adjuvant chemotherapy	181(43.7%)	160 (67.8%)*	0.001

Abbreviations: MWU, Mann-Whitney *U* test; RT, radiotherapy; CT, chemotherapy.
* colon values read.

Table 2
Local recurrence, distant metastasis, and cancer-related mortality according to G8 score.

	Frail n (%)	Fit n (%)	*p* value
Local recurrence	31 (54.4%)	26 (45.6%)	0.08
Distant metastasis	96 (66.2%)	49 (33.8%)	0.70
Cancer-related death	92 (71.3%)	37 (28.7%)	0.003

3.2. Assessment of Survival

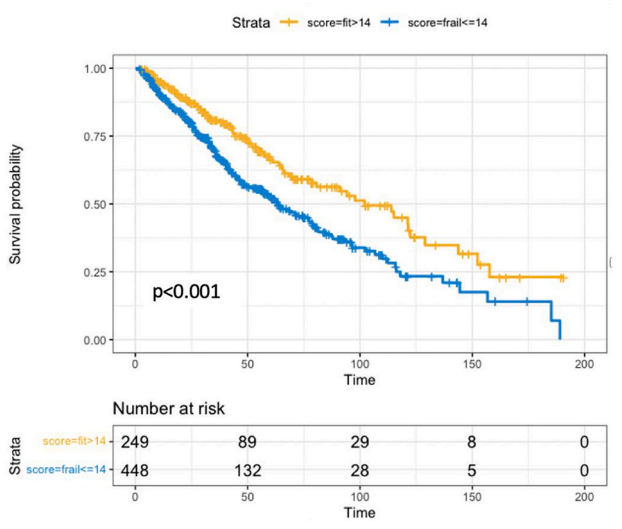
The 5-year and 8-year OS, LRFS, and MFS rates were 58% and 50%, 87% and 86%, and 72% and 69%, respectively. It was determined that adjuvant chemotherapy was associated with longer overall survival ($p = 0.004$) and a reduction in the development of distant metastasis ($p = 0.016$) but had no association with local control. Table 3 and Fig. 1 display the data and graphs for OS, LRFS, MFS in fit and frail patient groups, respectively.

A statistical model was created for factors that could affect prognosis,

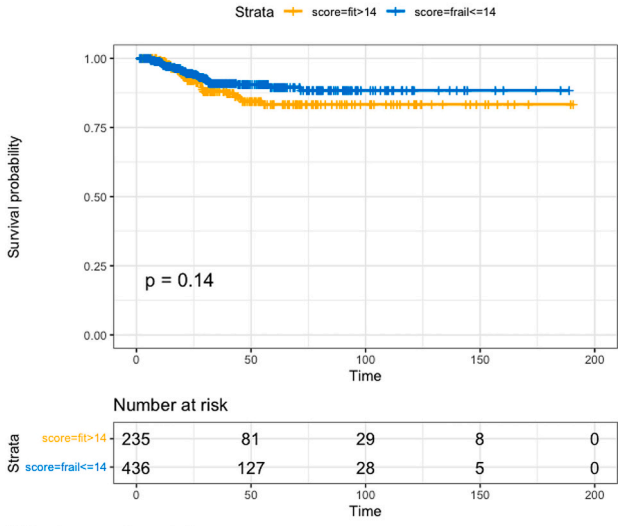
Table 3
Overall survival, local recurrence-free survival, and metastasis-free survival according to G8 score.

	Frail (%)	Fit (%)	p value
OS			
5 year	54%	67%	<0.001
8 year	36%	53%	
LRFS			
5 year	90%	83%	0.14
8 year	88%	83%	
MFS			
5 year	71%	72%	0.45
8 year	69%	72%	

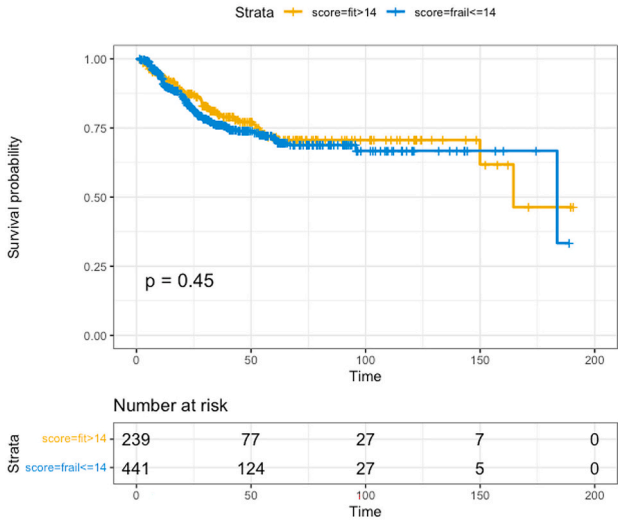
OS: overall survival, LRFS: Local recurrence-free survival, MFS: Metastasis-free survival.



(a): Overall survival



(b): Local recurrence-free survival



(c) Metastasis-free survival

Fig. 1. Survival curves with number at risk data stratified by G8 score.

such as age, sex, stage, comorbid disease, being frail or fit, breaks during RT, surgery, adjuvant CT, concurrent CT, toxicity and the need for hospitalization in the multivariate analysis. Not having surgery and not receiving adjuvant chemotherapy were negatively associated with survival. Table 4 shows the prognostic factors assessed in the univariate and multivariate analyses.

When the 108 patients who scored 14 points were compared with patients who scored above and below 14 points, no differences were found regarding local recurrence, distant metastasis, and treatment-related early and late toxicity. Cancer-related death was significantly higher in patients with a score below 14 (32% for >14 points, 37% for 14 points, and 57% for <14 points; $p = 0.02$). The 5-year OS in patients with a score below 14 was 63% and the 8-year OS was 44%.

3.3. Assessment of Toxicity

Treatment-related early and late toxicity data were accessible in 602 (86%) and 444 patients (63.5%), respectively. Twenty-four patients (3.4%) experienced acute grade 3-4 toxicity and 13 patients (1.9%) exhibited late grade 3-4 toxicity. The most frequent acute toxicity was cystitis, and the most common late toxicity was proctitis. No statistical significance was found between G8GS and acute or late toxicity ($p = 0.84$ for acute toxicity, and $p = 0.25$ for late toxicity). Toxicity rates observed in patients classified according to the G8 score are presented in Table 5.

4. Discussion

In this multicenter study we found that older age and comorbid diseases were more common in the frail group. The use of concurrent and adjuvant CT was higher in the fit group. In the frail group cancer-related deaths were higher and OS was lower. It was observed that the use of surgery and adjuvant CT were among the important parameters associated with survival. There was no difference between the two groups in terms of early and late side effects, and grade 3-4 toxicities were rare.

In daily practice, when evaluating a frail older adult with rectal cancer, clinicians usually choose giving less treatment. They may not give the full treatment due to concerns that patients will not be able to tolerate RT and CT [14]. However, in our study population, which mainly consists of frail patients, we observed that RT and CT can be safely administered. Contrary to expectations, standard RT doses were given to both groups, with a low need for hospitalization during RT and a limited number of patients requiring a break in RT. Although the rate of receiving concurrent and adjuvant CT is significantly higher in the fit group, the rate of receiving concurrent and adjuvant CT in the frail group is considerable. After all these treatments, grade 3-4 toxicity was detected in a small number of patients.

In locally advanced rectal cancer, total neoadjuvant therapy is the standard treatment [15]. Adjuvant CT is added in locally advanced patients. However, few older patients can receive preoperative CRT, and some are alternatively given palliative RT. Nonoperative management (NOM) is recommended for patients with poor indication for surgery [16]. According to the extrapolation of data from several retrospective studies on CRT/RT in rectal carcinoma, it is an effective treatment modality for older patients [17]. In a retrospective study conducted at the Mayo Clinic on patients aged 75 and older, it was found that neoadjuvant RT in patients with stage III disease was associated with increased survival, as was adding any adjuvant treatment (neoadjuvant/adjuvant) to surgery compared to surgery alone (58 months vs. 30 months; $p = 0.007$) [18]. In the Surveillance, Epidemiology, and End Results (SEER) database analysis of 4121 patients aged 75 and older by Wan and colleagues, it was found that the five-year cancer-specific survival rate with CRT was higher than that of patients receiving adjuvant RT or surgery alone or RT alone (70.4%, 60.4%, 52.1%, and 27.7%, respectively) [19]. In a French study, NOM was applied after CRT in

Table 4
The univariate and multivariate analyses assessing prognostic factors.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.04	1.02–1.06	<0.001	1.02	0.99–1.051	0.27
Sex	1.19	0.93–1.52	0.167	1.18	0.85–1.64	0.32
Comorbid disease	1.08	0.82–1.43	0.60	0.88	0.60–1.29	0.50
G8 status	1.65	1. 27-2.15	<0.001	1.35	0.92–1.98	0.13
Hospitalization during RT	0.321	0. 17-0.56	<0.001	0.87	0.298–2.54	0.80
Concurrent CT	1.70	1. 27-2.27	<0.001	1.41	0.96–2.06	0.81
Interruption of RT	1.22	0.77–1.92	0.40	1.07	0.52–2.20	0.85
Surgery	2.51	1.86–3.40	<0.001	3.98	2.54–6.24	<0.001
Adjuvant CT	1.78	1.39–2.30	<0.001	1.71	1.21–2.43	0.002
Acute toxicity	0.68	0.301–1.53	0.35	0.83	0. 26-2.63	0.75
Late toxicity	1.98	0.97–4.0	0.60	0.007	0.72–5.6	0.18

Table 5
Evaluation of grade 3-4 toxicity according to G8 score.

Toxicity	Frail n (%)	Fit n (%)	p value
Acute grade 3-4 toxicity	15 (3.3%)	9 (3.6%)	0.84
Late grade 3-4 toxicity	6 (1.3%)	7 (2.8%)	0.24

patients aged 85 and older. The five-year overall and disease-free survival rates were 45% and 65%, respectively [20]. Although our study population had a more heterogeneous patient group compared with other studies, the survival data are consistent with the literature. Additionally, in multivariate analyses, being excluded from surgery due to frailty status and not receiving adjuvant chemotherapy were significantly associated with an increased risk of death, highlighting the importance and necessity of providing standard treatment in this age group.

Conflicting data exist regarding the use of RT in rectal cancer patients based on age. The Swedish data states that the benefit of RT decreases in patients over 75 years of age [6], while in the study by Marthjin and colleagues, it has been reported that RT increases the local control rate in patients aged 70 and older [21]. Our study did not determine any such cut-off value. However, we found that the age of the patients in the frail group was significantly higher, and age is a prognostic factor associated with an increased risk of death.

The toxicity rates reported for rectal cancer patients treated with CRT are somewhat low. In the study by Rosa and colleagues, late toxicity was evaluated in 94 of the 117 patients. Grade $\geq$ 3 side effects were detected in one patient for the skin and in three patients for the gastrointestinal system [22]. In the study by Liu and colleagues, the rates of grade $\geq$ 3 toxicity was 3% for diarrhea and 9% for hematological toxicities [23]. Middelburg et al. performed a toxicity assessment for 70 patients with rectal cancer on a scale of 1-5 points, and detected grade 4 toxicity in one patient, whereas grade 5 toxicity was not observed [24]. VanderWalde et al. evaluated patients with lower gastrointestinal tumors in the NRG studies and reported that older patients had more grade $\geq$ 3 gastrointestinal toxicity than younger patients (36% vs 23%; $p < 0.001$), and less grade $\geq$ 3 skin toxicity (8% vs 14%; $p = 0.002$) [25]. In our study, the rates of acute and late side effects were quite low, like the literature, and there was no difference between the two groups. The fact that the study population was composed of patients with good enough performance levels to receive RT, the low rate of toxicity may have led to the lack of statistically significant results. Other factors could be that some patients were lost before late toxicity developed and older patients may not have followed-up regularly. A more promising theory is that modern RT technologies have reduced the frequency of side effects. In our study, 79% of the patients were treated with IMRT/VMAT techniques. As stated in SIOG guidelines, the use of IMRT and VMAT is not only associated with low toxicity but also may facilitate increased use of CT [4].

Studies indicating the prognostic importance of nutrition in the treatment of rectal cancer in older patients have been published recently [26,27]. The G8 aims to standardize evaluation of older adults with cancer not only in terms of nutrition but also physical and mental health, categorizing patients as fit or frail. Most of our study population was considered frail. The age and comorbidity rates were higher in the frail group, which could be one of the reasons that there were fewer frail patients receiving concomitant and adjuvant CT in our study.

A low G8 score is among the significant factors associated with mortality in all types of cancer, including rectal cancer [24,28]. In our study, like in the literature, the cancer-related death rate was higher in the group with a low G8 score, and the OS was significantly lower. We believe this could be due to the high age, comorbid diseases, and potential ineligibility for administer standard treatments such as surgery and adjuvant chemotherapy.

According to the original G8 test, patients who score 14 points are in the frail group. Various cut-off values appear in the literature [28,29]. However, these patients have been evaluated as a gray zone because they are at the transition point from the fit group to the frail group. In our study, the fact that patients with 14 points show similar results to the group below 14 points in terms of local recurrence, distant metastasis, and toxicity and better results in terms of cancer-related death encourages us to consider these patients as fit patients and give standard treatment.

The postoperative complication rate of older adults is higher compared with younger patients [30]. This could have had a negative impact on the G8 score. Therefore, we think it would be more appropriate to evaluate the G8GS before surgery, and we excluded adjuvant radiotherapy cases from the study. On the other hand, to reveal national data, we preferred to evaluate the patients who received radiotherapy (RT) for radical and palliative purposes, despite their small number.

Our study has inherent limitations due to its retrospective nature. The literature recommends CGA for frail patients and initiating oncological treatments with supportive care before treatment. However, in our study, it was not investigated whether CGA and additional supportive care were performed for these patients after the G8 test. Conducting the study with older adults is another issue that shortens the follow-up period after treatment. Some patients may be lost before the development of late side effects. Additionally, death due to age-related factors is another competing factor that could affect follow up and cancer related survival.

There are numerous studies evaluating heterogeneous patient groups with various cancer diagnoses using the G8 scoring system [12,28,31,32]. We believe our study is the first analyzing radiotherapy in older adults with rectal cancer accompanied by the G8 test, investigating treatment tolerability, and revealing differences in treatment and survival between fit and frail patient groups.

Despite the inherent limitations, our study is notable for its high number of patients from multiple centers, and high availability of G8 test results. Another strength of our study is the long follow-up period, although it was designed for the older population. Furthermore, the

evaluation of patients who scored 14 points on the G8, which we have not seen in any other study, and is considered a gray zone in the clinic, is another strong aspect of this study.

In conclusion, radiotherapy is an effective treatment option that may be tolerated even by frail older adults with rectal cancer. Being in the vulnerable group according to G8GS and having multiple comorbidities are associated with worse survival. CGA before radiotherapy may help to address the medical needs of frail patients, improve G8GS with supportive treatment, increase access to standard treatment, and improve survival rates.

Author contributions

Conception and Design: ZG, EM, GA. Data Collection: ZG, İBG, BA, FS, DY, MP, GGA, PA, HH, ŞAE, ZA, EÖ,YG,DK, NK, MD,MA, BU. Analysis and Interpretation of Data: ZG, EM, HE. Manuscript Writing: all authors. Approval of Final Article: all authors.

Declaration of Competing Interest

The authors declared that they have no conflict of interest.

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