Original Article

Chemoradiotherapy for elderly patients with rectal cancer: A single-institution study

ABSTRACT

Introduction: The incidence of cancer, particularly rectal cancer (RC), in older adults is gradually increasing. The aim of the present study was to evaluate radiotherapy (RT) and chemoradiotherapy (CRT) results, clinicopathological features, and survival factors in older patients with RC.

Methods: We evaluated patients aged ≥65 years with RC treated at a radiation oncology clinic. The demographic, clinical, and histopathological data of the patients were obtained by reviewing their medical records. The toxicity criteria of the Radiation Therapy Oncology Group were applied.

Results: Among 401 patients with RC, 183 (45.6%) were older adults (65–92 years). Furthermore, 122 (66.7%) patients had clinically stage 3 and above RC, and 183 and 91 patients received RT and neoadjuvant CRT, respectively. Surgical treatment was performed for 116 (63.4%) patients, 41 (34.4%) and 76 (65.6%) of whom underwent postoperative CRT and preoperative RT, respectively. Grade 3 or higher toxicity was observed in 22 (18.9%) patients during CRT. RT was performed in 64 patients (35%) at a 1–15-day interval. The mean follow-up duration was 34.7 (range, 1.4–149.0) months. The 2- and 5-year overall survival (OS) rates were 71.4 and 37.4%, respectively, and the 2- and 5-year disease-free survival (DFS) rates were 65.7 and 35.3%, respectively. OS was 49.4 and 34.9 months for patients aged 65–74 and ≥75 years, respectively. Survival was shorter in patients with the advanced geriatric disease ($p = 0.013$). In the multivariate analysis, factors affecting overall and DFS were age, distance from the tumor to the anal canal, and metastasis ($p < 0.05$).

Conclusion: The results of this study suggested that the selection of treatment modalities for older patients with RC should be based on performance status and not age. RT and CRT were safe treatment modalities for older patients with RC, particularly for those who could not undergo surgery.

KEY WORDS: Elderly patients, radiotherapy, rectal cancer

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INTRODUCTION

Human life expectancy has increased in recent years, leading to an increase in the number of older patients with cancer. Rectal cancer (RC) is the third most common cancer worldwide, accounting for 9.7% of all cancer cases.[1] This rate may gradually increase, and patients with high risks of comorbidity and fragility should be carefully evaluated and administered personalized treatment.[2,3] RC chemoradiotherapy (CRT) data are limited because the older patient group is less prone to receiving treatment in clinical practice and is underrepresented in clinical trials. Owing to heterogeneity, concerns regarding the treatment approach for these patients persist.[4] Since 2013, prospective studies involving patients aged ≥ 65 years and retrospective analyses of subgroups in previous studies have become prevalent.[5] The aim of the present study was to investigate the current status of patients with RC aged ≥65 years who underwent radiotherapy (RT) or CRT. Prognostic factors affecting survival were also evaluated.

MATERIALS AND METHODS

Eligibility criteria

The Ethics Committee of the Medical Faculty of our university approved the study protocol

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for collecting, evaluating, analyzing, and interpreting the data (decision no. 2022/77 on March 24, 2022). Data were retrospectively reviewed using the medical records of patients treated and followed-up at our university's radiation oncology clinic. Data from 401 patient records were analyzed. Demographic, clinical, and histopathological data were obtained for 183 patients aged ≥65 years. The tumor stage was determined based on the 2010 International Union against Cancer/American Joint Committee on Cancer TNM classification, and all patients were clinically staged according to the decision of a multidisciplinary oncology council. Magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography/CT were performed for staging.

Evaluation and follow-up

For postoperative neoadjuvant therapy, pelvic MRI was planned at 6 weeks postoperatively, and patients were scheduled for surgery. Subsequent radiologic and colonoscopic follow-ups were performed once every 3 months for 2 years, followed by once every 6 months.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 23 software. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the last follow-up. Disease-free survival (DFS) was calculated from the completion of RT to the date of local recurrence or progression. The normality of data distribution was examined using the Kolmogorov–Smirnov test. The Mann–Whitney *U*-test was used to compare nonnormally distributed quantitative data by sex, and the Chi-square test was used to compare categorical variables. Univariate and multivariate models were examined using Cox regression analysis. The log-rank (Mantel–Cox) test was used to compare OS and DFS according to these factors, and Cox regression analysis was used to examine the risk factors affecting OS and DFS. The results are expressed as frequency (percentage) for categorical data and mean ± standard deviation and median (minimum–maximum) for quantitative data. Statistical significance was set at $p < 0.05$.

RESULTS

Patient and tumor characteristics

Table 1 shows patients' demographic, tumor, and treatment characteristics. Of the 401 patients with RC, 183 (45.6%) older patients, comprising 101 (55.2%) men and 72 (39.8%) women, were included in the analysis. Karnofsky Performance Scale (KPS) scores were ≤50, 51–70, and >70 in 60 (32.7%), 45 (21.8%), and 78 (42.6%) patients, respectively. The median patient age was 73 (range, 65–92) years, with 73 (38.9%) patients aged ≥75 years. Clinically, 61 (33.3%) patients had early-stage RC (stages 2A and 2B), and 122 (66.7%) patients had advanced-staged RC (stages 3 and 4). Furthermore, 176 (96.2%) patients had adenocarcinoma. A total of 108 (59.3%) patients had a tumor distance of ≤8 cm from the anal cavity. The RT dosage was ≤50 Gy in 38 (20.8%) patients and >50 Gy in 145 (79.2%) patients. Among the 116 (63.4%) patients who underwent surgical intervention, 40 (34.4%) underwent surgery after RT, while 76 (65.6%) underwent surgery before

Table 1: Patient and tumor characteristics

Characteristics	*n* (%)
Sex	
Male	101 (55.2)
Female	72 (39.8)
Age (years)	
65-74	110 (61.1)
≥75	73 (38.9)
TM distance from the anal wage (cm)	
<8	108 (59.3)
≥9	74 (40.7)
Pathological diagnosis	
Adenocarcinoma	176 (96.2)
Mucinouscarcinoma	6 (3.3)
Other	1 (0.5)
Stage	
2A+2B	61 (33.4)
3A	17 (9.3)
3B	82 (44.8)
3C	22 (12)
4A	1 (0.5)
Preoperative CRT	
No	92 (50.3)
Yes	91 (49.7)
RT	
Preoperative	97 (53)
Postoperative	74 (40.4)
Definitive	12 (6.6)
RT type	
3D-CRT	56 (30.6)
IMRT	41 (22.4)
VMAT	86 (47)
RT dose (Gy)	
≤50	28 (15.3)
>50	155 (84.7)
Metastasis	
Yes	26 (14.2)
No	157 (85.8)
Recurrence	
Yes	15 (8.2)
No	168 (91.8)
Surgery	
No	67 (36.6)
Postoperative CRT	40 (21.9)
Preoperative CRT	76 (41.5)
CT	
Preoperative with RT	91 (49.7)
Postoperative with RT	89 (48.6)
No	3 (1.7)
TM degree of regression	
Grade 0: no cancer cells	13 (31.7)
Grade 1: few cancer cells	12 (29.3)
Grade 2: fibrosis+residual cancer cell	5 (12.2)
Grade 3: dense residual cancer cells	11 (26.8)
GIS toxicity	
Yes	88 (48.1)
No	95 (51.9)
RT treatment break	
Yes	64 (35)
No	119 (65)

TM, tumor; CRT, chemoradiotherapy; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; CT, chemotherapy; GIS, gastrointestinal system

RT. A total of 67 (27.6%) patients were not treated surgically. Preoperative RT was planned for 55 (82.1%) patients who refused surgery or did not undergo surgery because of the morbidity risk. Twelve (17.9%) cases were surgically inoperable because of the lower rectal tumor location, and their treatment was completed with definitive CRT. Fifteen (27.2%) patients had cardiac abnormalities because of which anesthesia could not be administered, 25 (45.4%) patients or their relatives did not give consent for surgery, and 15 (27.2%) patients did not undergo surgery for unknown reasons. The follow-up showed 26 (14.2%) cases of metastasis and 15 (8.2%) cases of recurrence. At the last follow-up, 45 (24.6%) patients were alive, whereas 138 (75.4%) patients had died.

Table 2 shows the results of comparisons between men and women in the tumor stage, treatment-related gastrointestinal system (GIS) toxicity, treatment interruption, and tumor regression rates. Among categorical variables compared between sexes, the mortality rate differed significantly ($p = 0.027$). A total of 48 (66.7%) women and 90 (81.1%) men died. None of the other variables differed significantly between the sexes ($p > 0.050$). GIS toxicity occurred in 52.8% of women and 45% of men ($p = 0.306$). Most patients, including 66.7% of men and 62.5% of women, completed the treatment without interruption ($p = 0.564$). Thirteen (31.7%) patients showed a complete response (grade 0) to CRT with no pathological tumor cells. Grade 0 or 1 treatment response rate was found in 64.3% of men and 43.9% of women. Among those who underwent preoperative RT, grade 0–3 postoperative pathological tumor regression was found with no significant differences between the sexes [Table 2].

RT

A total of 127 patients were treated with intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT). For the 56 patients treated during the period in which IMRT could not be applied, three field techniques were used for three-dimensional conformal radiation therapy (3D-CRT). Furthermore, one patient received 25-Gy RT with a 5-Gy daily dose to the rectal mass with a 2-cm margin and a hypofractionated regimen, whereas other patients received 45-Gy RT for pelvic lymph nodes with a 0.3-cm margin. A booster dose of 50.4 Gy was applied to the rectal mass with a 2 cm margin in all directions. A definitive dose of 60 Gy was applied to each patient.

Chemotherapy and concurrent CRT

A total of 91 patients received concurrent CRT. The oldest patient was 92 years old, and 61 patients were administered 875 mg/m^2 capecitabine twice daily. Other patients were administered 400 mg/m^2 fluorouracil for 5 days, followed by 4 days of RT. All patients completed the chemotherapy charts with no serious toxic reactions requiring discontinuation. Of the 89 patients scheduled for postoperative chemotherapy, 6 were treated with folinic acid and fluorouracil and 28 were treated with capecitabine. Additionally, three patients did not receive chemotherapy because of their poor performance capacity. Of the 41 patients who underwent surgery after CRT, 13 (31.7%) did not undergo adjuvant postoperative chemotherapy because no tumor cells were observed (grade 0).

Overall survival

Table 3 shows the factors affecting OS. The mean follow-up duration was 34.7 (1.4–149.0) months. The 2- and 5-year OS rates were 71.4 and 37.4%, respectively. Significant parameters affecting OS were age, distance from the tumor to the anal verge, clinical stage, and presence of metastasis. OS was 49.4 months for patients aged 65–74 years and 34.9 months for those aged ≥75 years. Survival duration was significantly shorter in patients with advanced geriatric disease ($p = 0.013$).

OS was 35.8 months in patients with a tumor distance from the anal wall of ≤8 cm and 59.3 months in those with a tumor distance of ≥9 cm ($p = 0.034$). It did not differ significantly between preoperative and postoperative RT cases (41.6 and

Table 2: Comparison of data by sex

	Female *n* (%)	Male *n* (%)	Total *n* (%)	*P**
Stage				
Early stage (IIA and IIB)	18 (25)	43 (38.7)	61 (33.3)	
Advanced stage (III and IV)	54 (75)	68 (61.3)	122 (66.7)	0.054
GIS toxicity				
Yes	38 (52.8)	50 (45)	88 (48.1)	
No	34 (47.2)	61 (55)	95 (51.9)	0.306
RT treatment break				
Yes	27 (37.5)	37 (33.3)	64 (35)	
No	45 (62.5)	74 (66.7)	119 (65)	0.564
TM degree of regression				
Grade 0: no cancer cells	2 (15.4)	11 (39.3)	13 (31.7)	0.490
Grade 1: few cancer cells	5 (38.5)	7 (25)	12 (29.3)	
Grade 2: fibrosis + residual cancer cell	2 (15.4)	3 (10.7)	5 (12.2)	
Grade 3: dense residual cancer cells	4 (30.8)	7 (25)	11 (26.8)	
Death				
No	24 (33.3)	21 (18.9)	45 (24.6)	0.027
Yes	48 (66.7)	90 (81.1)	138 (75.4)	

*Chi-square test, *n* (%). TM, tumor; GIS, gastrointestinal system; RT, radiotherapy

Table 3: Results of the log-rank univariate analysis of overall survival

	Median survival (95% CI)	2-year overall survival, mean (±SE)	5-year overall survival, mean (±SE)	*P*
Sex				
Male	43.9 (25.0-62.7)	68.9% (0.057%)	42.1% (0.065%)	0.322
Female	38.6 (29.8-47.5)	72.9% (0.043%)	34.5% (0.049%)	
Age (years)				
65-74	49.4 (33.0-65.8)	74.2% (0.043%)	43.7% (0.052%)	0.013
≥75	34.9 (31.0-38.8)	67.1% (0.056%)	28% (0.059%)	
TM distance from the anal wage (cm)				
≤8	35.8 (31.9-39.7)	66.7% (0.047%)	28.9% (0.049%)	0.034
>9	59.3 (35.4-83.1)	77.6% (0.05%)	48.4% (0.063%)	
Time between the diagnosis and the operation (months)				
≤3	42.6 (24.1-61.1)	74.2% (0.05%)	41.8% (0.057%)	0.341
>3	47.8 (27.8-67.8)	72.1% (0.075%)	40.9% (0.091%)	
Time between the diagnosis and RT (months)				
≤3	38.1 (30.7-45.6)	66.6% (0.042%)	36.9% (0.046%)	0.361
>3	45.4 (27.8-63.1)	84.7% (0.054%)	39.4% (0.076%)	
RT period				
Preoperative	41.6 (27.1-56.1)	71.2% (0.073%)	34.8% (0.083%)	0.255
Postoperative	41.2 (31.3-51.1)	72.1% (0.039%)	38.4% (0.046%)	
Time between RT and the operation (weeks)				
≤8	45.4 (26.4-64.5)	68.2% (0.099%)	33.1% (0.106%)	0.539
>9	35.8 (24.5-47.0)	75.3% (0.107%)	38% (0.131%)	
C type				
APR	34.3 (16.4-52.3)	64.3% (0.083%)	33.7% (0.082%)	0.083
LAR	53.6 (33.7-73.5)	77.2% (0.047%)	45.1% (0.059%)	
Stage				
Early stage	60.0 (30.1-89.8)	69.9% (0.063%)	48.9% (0.071%)	
Advanced stage	34.2 (28.4-40.1)	61% (0.046%)	27.9% (0.048%)	0.019
Preoperative CRT				
No	42.6 (25.9-59.4)	72.6% (0.047%)	42% (0.053%)	0.145
Yes	38.4 (32.4-44.3)	70.2% (0.05%)	30.2% (0.06%)	
RT type				
3D-CRT	56.8 (33.5-80.2)	76.8% (0.056%)	48.1% (0.067%)	0.103
IMRT	34.7 (33.1-36.3)	63.4% (0.075%)	27.8% (0.072%)	
VMAT	39.3 (32.5-46.1)	71% (0.053%)	32.4% (0.065%)	
RT dose (Gy)				
≤50	41.2 (26.7-55.7)	69.7% (0.077%)	32.6% (0.088%)	0.264
>50	41.2 (31.8-50.6)	71.8% (0.038%)	38.5% (0.044%)	
Metastasis				
No	49.4 (38.1-60.7)	75.8% (0.035%)	43.1% (0.044%)	<0.001
Yes	21.8 (12.6-31.0)	46.2% (0.098%)	7.7% (0.052%)	
Recurrence				
No	42.6 (31.7-53.5)	71.8% (0.036%)	38.4% (0.042%)	0.760
Yes	34.3 (22.8-45.9)	66.7% (0.122%)	26.7% (0.114%)	
CS (mm)				
>10 Tm-	47.8 (34.0-61.7)	73.6% (0.045%)	44% (0.053%)	0.368
Tm+	56.8 (32.5-81.2)	100%	0% (0%)	
≤10	34.7 (0.0-85.4)	71.4% (0.121%)	41.7% (0.135%)	
C				
No	37.6 (30.2-45.0)	67.6% (0.06%)	27.4% (0.068%)	0.133
Yes	47.8 (33.6-62.0)	73.4% (0.042%)	41.7% (0.048%)	
GIS Toxicity				
Yes	41.6 (26.1-57.1)	68.5% (0.05%)	38.8% (0.055%)	0.779
No	39.5 (31.5-47.6)	74.1% (0.047%)	36.2% (0.057%)	
RT treatment break				
Yes	41.6 (26.4-56.8)	68.4% (0.059%)	37.7% (0.063%)	
No	37.6 (30-45.1)	73% (0.042%)	37.6% (0.051%)	0.788

TM, tumor; RT, radiotherapy; C, surgery; APR, abdominoperineal resection; LAR, low anterior resection; CRT, chemoradiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; CS, surgical; GIS, gastrointestinal system; CI, confidence interval; SE, standard error

41.2 months, respectively; $p = 0.255$). It was 21.8 months in the presence of metastasis and 49.4 months in the absence of metastasis ($p < 0.001$). It did not differ with respect to the other variables or between abdominoperineal resection (APR) and low anterior resection (LAR) [Table 3].

Disease-free survival

The mean follow-up duration was 32.7 (range, 2.0–137.1) months. The 2- and 5-year DFS rates were 65.7 and 35.3%, respectively. Table 4 shows the results of DFS. Significant parameters affecting DFS were age, distance between the

Table 4: Results of the log-rank univariate analysis of disease-free survival

	Disease-free survival			
	Median (95% CI)	2-year, mean (±SE)	5-year, mean (±SE)	*P*
Sex				
Male	41.6 (26.1-57.1)	64.7% (0.058%)	38.8% (0.065%)	0.294
Female	34.9 (30.0-39.8)	66.3% (0.046%)	33.1% (0.049%)	
Age (years)				
65-74	42.6 (26.5-58.7)	68.4% (0.046%)	41% (0.052%)	0.023
≥75	34.9 (27.0-42.8)	61.6% (0.058%)	26.6% (0.058%)	
TM distance from the anal wage (cm)				
≤8	33.6 (25.7-41.6)	58.9% (0.049%)	27.1% (0.048%)	0.032
>9	49.4 (28.2-70.6)	75% (0.051%)	45.8% (0.063%)	
Time between the diagnosis and the operation (months)				
≤3	41.6 (27.2-56.0)	66.4% (0.054%)	39.3% (0.057%)	0.423
>3	47.8 (25.0-70.6)	69.1% (0.078%)	38% (0.09%)	
Time between the diagnosis and RT (months)				
≤3	37.6 (30.7-44.4)	62.1% (0.043%)	36.5% (0.046%)	0.842
>3	39.3 (24.6-54.0)	75.9% (0.064%)	32.9% (0.073%)	
RT period				
Preoperative	35.8 (26.7-44.8)	68.6% (0.075%)	32.2% (0.082%)	0.261
Postoperative	39.3 (30.0-48.5)	66.8% (0.041%)	37.2% (0.045%)	
Time between RT and operation (weeks)				
≤8	34.2 (18.9-49.6)	63.6% (0.103%)	28.4% (0.102%)	0.754
>9	35.8 (24.5-47.0)	75.3% (0.107%)	38% (0.131%)	
C type				
APR	26.4 (14.2-38.6)	58.7% (0.085%)	34% (0.083%)	0.118
LAR	47.8 (32.1-63.5)	70.9% (0.051%)	41.2% (0.058%)	
C stage group				
Early stage	60.0 (30.1-89.8)	69.9% (0.063%)	48.9% (0.071%)	
Advanced stage	34.2 (28.4-40.1)	61% (0.046%)	27.9% (0.048%)	0.019
Preoperative CRT				
No	34.8 (19.3-50.3)	62.8% (0.051%)	37.7% (0.052%)	0.504
Yes	38.1 (32.3-43.9)	69.4% (0.05%)	30.8% (0.061%)	
RT technique				
3D-CRT	46.1 (27.7-64.4)	67.9% (0.062%)	42.8% (0.066%)	0.287
IMRT	34.2 (22.3-46.0)	58.5% (0.077%)	27.8% (0.072%)	
VMAT	37.6 (30.6-44.5)	67.2% (0.054%)	31.5% (0.065%)	
RT dose (Gy)				
≤50	35.8 (23.3-48.3)	62.2% (0.08%)	26.1% (0.087%)	0.145
>50	37.6 (31.6-43.5)	66.7% (0.04%)	37.4% (0.044%)	
Metastasis				
No	46.1 (33.5-58.6)	71.8% (0.037%)	41.1% (0.044%)	<0.001
Yes	15.6 (2.9-28.3)	30.8% (0.091%)	3.8% (0.038%)	
Recurrence				
No	41.2 (31.1-51.3)	69.4% (0.037%)	38% (0.042%)	<0.001
Yes	15.0 (4.9-25.1)	26.7% (0.114%)	6.7% (0.064%)	
SM (mm)				
>10 Tm-	42.6 (25.8-59.4)	68.4% (0.048%)	---	0.367
Tm+	49.9 (36.6-63.1)	100%	0% (0%)	
≤10	24.4 (0.0-56.6)	57.1% (0.132%)	34.3% (0.131%)	
C				
No	34.9 (22.6-47.2)	63.5% (0.061%)	26.3 (0.068%)	0.166
Yes	41.6 (28.0-55.2)	67.3% (0.044%)	39.1% (0.048%)	
GIS toxicity				
Yes	37.4 (23.3-51.5)	62.2% (0.054%)	37.3% (0.056%)	0.828
No	34.2 (25.3-43.2)	65.6% (0.052%)	33.2% (0.06%)	
RT treatment break				
Yes	36.9 (12.8-61.1)	57% (0.064%)	36.8% (0.064%)	
No	34.5 (26.9-42.1)	67.9% (0.046%)	34.7% (0.053%)	0.902

TM, tumor; RT, radiotherapy; C, surgery; APR, abdominoperineal resection; LAR, low anterior resection; CRT, chemoradiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; SM, surgical margin; GIS, gastrointestinal system; CI, confidence interval; SE, standard error

tumor and the anal canal, presence of metastasis, and recurrence. DFS was 42.6 months in patients aged 65–74 years and 34.9 months in those older than 75 years ($p = 0.023$). It was 33.6 and 49.4 months in patients with a distance of ≤8 and ≥9 cm between the tumor and the anal canal, respectively ($p = 0.032$). The proximity of the tumor to the anal canal negatively affected DFS. The presence of metastasis and recurrence also negatively affected DFS ($p < 0.001$). Survival showed no relationship with parameters, such as sex, time between the diagnosis and the operation, time between the

diagnosis and RT, time between the diagnosis and RT, RT period (preoperative or postoperative), type of surgery (APR or LAR), preoperative CRT status, RT technique (3D-CRT, IMRT, or VMAT), RT dose (≤50 Gy or >50 Gy), surgical margin, GIS toxicity, or RT treatment break [Table 4].

Toxicity

Toxicity in 183 patients was evaluated according to the Radiation Toxicity Oncology Group criteria. During RT, 88 (48.1%) patients developed GIS toxicity, including 66 patients (36.1%) with grade 1–2 toxicity and 22 patients (12%) with grade 3 toxicity. In 64 (35%) patients, treatment was suspended for a minimum duration of 1 day and a maximum duration of 15 days. These treatment breaks did not affect OS or DFS [Tables 3 and 4]. Of all the patients with KPS <60, 56 (30.6%) developed grade 2–3 hematological toxicity. Twenty (10.9%) patients developed grade 4 hematological toxicity requiring treatment interruption. Genitourinary system toxicities were grades 1–2 in 150 (81.9%) patients. No treatment interruption was required.

Proportional-hazards analysis

Multivariate and univariate analyses were performed to obtain quantitative estimates of the association between the 13 clinical and pathological tumor factors and OS and DFS. Table 5 shows the results of the multivariate and univariate analyses of the risk factors affecting OS and DFS. Risk factors affecting OS and DFS were age, tumor location, time from the diagnosis to the surgery, time from the diagnosis to RT, timing of RT (preoperative/postoperative), sex, RT type, metastasis, recurrence, RT dose, CRT, clinical stage, and number of lymph nodes removed.

Univariate and multivariate analyses identified age ($p < 0.001$), tumor localization ($p = 0.008$), and presence of metastasis ($p < 0.001$) as prognostic factors affecting OS and DFS. Recurrence ($p = 0.001$) was a factor affecting DFS. The clinical stage was a factor affecting OS ($p = 0.011$). The mortality risk appeared to be higher in patients who underwent IMRT because of the large sample size of the IMRT group ($p = 0.040$). None of the other risk factors significantly affected OS or DFS [$p > 0.050$; Table 5].

DISCUSSION

With increasing life expectancy in recent years, older adults have become the largest patient group in oncology. Owing to their advanced age, they are ineligible for many treatments and clinical trials. For older patients, treatments are often terminated without completion. Further, they are often not eligible for clinical trials or are required to fulfill several additional criteria.[6] Age alone is not a criterion for deciding the administration of adjuvant, neoadjuvant, or palliative treatment in RC.[7,8]

Surgery is the standard treatment for early-stage RC.[9,10] In clinical practice, the number of patients with surgery alone as an indication is small. Older patients cannot undergo surgery because of additional morbidities. Therefore, neoadjuvant therapies and their results should be updated, and further research should be performed.[11] In standard RC treatments, T3, T4, and N+ lesions carry a high risk of locoregional recurrence, and preoperative/postoperative RT is required. Chemotherapy reduces the risk of distant metastases and enhances the

Table 5: Risk factors affecting overall and disease-free survival

	Overall survival				Disease-free survival			
	Univariate				Multivariate			
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)	1.047 (1.019-1.075)	0.001	1.035 (1.005-1.065)	0.023	1.046 (1.018-1.074)	0.001	1.033 (1.003-1.064)	0.032
TM localization	0.944 (0.904-0.985)	0.008	0.931 (0.888-0.975)	0.003	0.942 (0.903-0.983)	0.006	0.937 (0.894-0.981)	0.006
Time from the diagnosis to the surgery	1.003 (0.956-1.053)	0.890			1.022 (0.969-1.078)	0.426		
Time from the diagnosis to RT	0.991 (0.961-1.021)	0.546	0.99 (0.949-1.032)	0.633	1.009 (0.98-1.038)	0.555	0.983 (0.944-1.023)	0.398
Preoperative RT	0.998 (0.969-1.028)	0.910			0.993 (0.962-1.025)	0.673		
Postoperative RT	1 (0.993-1.008)	0.912			1.004 (0.997-1.011)	0.239		
Sex	1.195 (0.839-1.701)	0.323	1.318 (0.905-1.921)	0.151	1.207 (0.849-1.717)	0.295	1.24 (0.849-1.81)	0.265
Chemoradiotherapy	1.301 (0.913-1.853)	0.146	1.055 (0.558-1.995)	0.869	1.127 (0.793-1.604)	0.505	0.936 (0.494-1.774)	0.840
RT type (reference: 3D-CRT)								
IMRT	1.598 (1.022-2.497)	0.040	2.235 (1.326-3.768)	0.003	1.428 (0.915-2.228)	0.116	2.27 (1.344-3.833)	0.002
VMAT	1.367 (0.893-2.093)	0.150	1.682 (0.996-2.839)	0.052	1.198 (0.783-1.832)	0.406	1.59 (0.952-2.655)	0.077
RT dose	0.782 (0.508-1.205)	0.265	0.918 (0.549-1.533)	0.743	0.725 (0.47-1.12)	0.147	0.924 (0.552-1.548)	0.765
Metastasis	2.608 (1.686-4.035)	<0.001	3.634 (2.215-5.965)	<0.001	3.509 (2.255-5.46)	<0.001	5.538 (3.289-9.326)	<0.001
Recurrence	1.091 (0.623-1.912)	0.761	1.019 (0.393-2.639)	0.969	2.567 (1.49-4.424)	0.001	2.442 (1.01-5.901)	0.047
C stage group (reference: early stage)	1.621 (1.118-2.349)	0.011	0.958 (0.576-1.594)	0.869	1.585 (1.075-2.338)	0.020	0.851 (0.491-1.475)	0.566
Number of lymph nodes removed	0.997 (0.97-1.024)	0.803	1.003 (0.973-1.034)	0.839	1.002 (0.974-1.03)	0.909	1.01 (0.979-1.043)	0.524
RT treatment break	1.048 (0.744-1.477)	0.788	1.83 (0.901-3.719)	0.095	1.023 (0.715-1.462)	0.902	2.033 (0.992-4.168)	0.053

TM, tumor; RT, radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; C, surgery

locoregional control of RT. Neoadjuvant CRT is the standard treatment for locally advanced RC.[12] However, these previous studies were conducted in heterogeneous age groups. The same CRT treatment can be administered to older patients with vulnerable RC.[13] However, in these patients, particularly those aged >70 years, CRT may be interrupted and cause toxicity. Therefore, short fractional schemes without chemotherapy should be administered depending on the condition of the patient.[14] In the present study, only one patient received a 25-Gy hypofractionated regimen.

Additional therapy (RT or chemotherapy) following surgery was performed for only 24% of patients aged ≥65 years[15] and for 44% of those aged <60 years. Moreover, CRT was administered to only 8% of patients aged >80 years.[16,17] In the present study, only 40 patients who received neoadjuvant CRT underwent surgery. Furthermore, 63.4% of all the patients underwent surgery.

The depth of RC tumor invasion, number of involved regional lymph nodes, and presence of distant metastasis are parameters affecting survival. Owing to the anatomical features of the rectum, distal tumors often metastasize, and their prognosis is poor.[18,19] Similar conditions are found in older patients with RC. In the present study, both OS and DFS of distal tumors were shorter in patients with tumors located <8 cm from the anal canal. In one study, young and older patients with RC who underwent surgery and completed all CRT treatments were compared. This study included 103 older and 292 nonolder patients, with treatment completion rates of 95.37 and 95.42% and RT toxicity in 37 and 22 patients, respectively.[20] In the present study, 116 patients completed all treatments (preoperative CRT+ surgery or surgery + postoperative CRT), 22 of whom had grade 3 or higher RT toxicity.

Surgery is the most life-saving treatment option for RC. Positive radial surgical margins are independent prognostic factors for local recurrence.[21] In the present study, the surgical margin was not a prognostic factor, possibly because of the small number of older patients eligible for surgery. At least 12–15 perirectal and pelvic lymph node dissections are recommended for accurate staging. Although the number of lymph nodes removed from the older patients with RC alone did not affect the prognosis, the clinical stage was identified as a significant factor affecting survival. Although determined subjectively, the degree of tumor regression, which indicates the response to neoadjuvant therapy, also provides information about the prognosis and should be noted in pathology reports.[12] The regression scoring system developed by Dworak *et al*.[22] (1997) was used for this purpose. In the present study, 40 patients underwent surgery after neoadjuvant therapy. No significant prognostic factors were observed when the tumor regression scores were examined. The surgical chances in older patients with RC are lower than those in younger patients, and RT and CRT treatment schemes should be planned according to the unique conditions of each patient. Although our patients could not undergo surgery, RT and CRT were well-tolerated. In other studies, local recurrence and OS rates in T3–T4/N+ patients were 25 and 40–50% with surgery alone, respectively. Local recurrence decreased to 10–15%, and OS improved to 50–60% with the addition of postoperative RT and CT to the treatment.[23] In the present study, the 2- and 5-year OS rates were 71.4 and 37.4%, respectively. The age groups of the patients were similar to those in other studies, with heterogeneity.

In the Intergroup 0114 study, RT (50.4Gy–54 Gy) and RT combinations with bolus fluorouracil alone and other drugs showed no significant differences in OS or DFS rates. However, toxicity was greater in the combined chemotherapy arm.[24] In contrast, older patients were less likely to receive RT or chemotherapy in combination with surgery than younger patients. The standard treatment paradigm for RC is often not applicable to patients aged 80–85 years owing to morbidity. Information and treatment guidelines to assist in the direct treatment of these patients are limited, and further retrospective studies are required.[25]

This study had some limitations. First, the sample size was small, reducing the robustness of the result. Second, the study design was retrospective, inducing the possibility of bias.

CONCLUSIONS

The results of this study suggested that in older patients with RC, the possibility of surgery and the presence of comorbidities preventing surgery should be evaluated at presentation. Compared to younger patients, older patients better tolerated CRT protocols and showed similar survival rates; therefore, surgeons and radiation oncologists should formulate a treatment plan using a patient-specific multidisciplinary approach. Older patients with RC should be treated using definitive CRT or hypofractionated RT protocols.

Author contribution

Conceptualization, GHU and SYR; formal analysis, SYR and GHU; investigation, GHU and SYR; resources, GHU; data curation, GHU; writing—original draft preparation, SYR; writing—review and editing, SYR; supervision, SYR. All authors have read and agreed to the final version of the manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Available from: http://seer.cancer.gov/csr/1975_2004/results.
2. Aarts MJ, Lemmens VE, Louwman MW, Kunst AE, Coebergh JW. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. Eur J Cancer 2010;46:2681-95.
3. Van Leersum NJ, Janssen-Heijnen ML, Wouters MW, Rutten HJ, Coebergh JW, Tollenaar RA, *et al*. Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995–2010. Int J Cancer 2013;132:2157-63.
4. Martijn H, Vulto JCM. Should radiotherapy be avoided or delivered differently in elderly patients with rectal cancer? Eur J Cancer 2007;43:2301-6.
5. Papamichael D, Audisio RA, Glimelius B, de Gramont A, Glynne-Jones R, Haller D, *et al*. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2015;26:463-76.
6. Popescu RA, Norman A, Ross PJ, Parikh B, Cunningham D. Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. J Clin Oncol 1999;17:2412-8.
7. Chiara S, Nobile MT, Vincenti M, Lionetto R, Gozza A, Barzacchi MC, *et al*. Advanced colorectal cancer in the elderly: Results of consecutive trials with 5-fluorouracil-based chemotherapy. Cancer Chemother Pharmacol 1998;42:336-40.
8. Lyman GH, Kuderer NM, Balducci L. Cost-benefit analysis of granulocyte colony-stimulating factor in the management of elderly cancer patients. Curr Opin Hematol 2002;9:207-14.
9. Kodner IJ. Rectal cancer. In: Zinner MJ, Schwartz SI, Ellis H, editors. Maingots Abdominal Operations. Stamford, CT: Appleton & Lange; 1997. p. 1455-502.
10. Mohiuddin M, Marks G, Bannon J. High-dose preoperative radiation and full thickness local excision: A new option for selected T3 distal rectal cancers. Int J Radiat Oncol Biol Phys 1994;30:845-9.
11. Pasetto LM, Pucciarelli S, Agostini M, Rossi E, Monfardini S. Neoadjuvant treatment for locally advanced rectal carcinoma. Crit Rev Oncol Hematol 2004;52:61-71.
12. Li Y, Wang J, Ma X, Tan L, Yan Y, Xue C, *et al*. A review of neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Int J Biol Sci 2016;12:1022-31.
13. Pasetto LM, Friso ML, Pucciarelli S, Basso U, Falci C, Bortolami A, *et al*. Rectal cancer neoadjuvant treatment in elderly patients. Anticancer Res 2006;26:3913-23.
14. Servagi Vernat S, Guilbert P, Bouché G, Ramiandrisoa F, Bellefqih S. Hypofractionated radiotherapy in rectal cancer for elderly patients. Cancer Radiother 2018;22:644-6.
15. Walter LC, Covinsky KE. Cancer screening in elderly patients: A framework for individualized decision making. JAMA 2001;285:2750-6.
16. Jessup JM, McGinnis LS, Steele GD, Menck HR, Winchester DP. The national cancer data base. Report on colon cancer. Cancer 1996;78:918-26.
17. Köhne CH, Grothey A, Bokemeyer C, Bontke N, Aapro M. Chemotherapy in elderly patients with colorectal cancer. Ann Oncol 2001;12:435-42.
18. Spratt JS, Spjut HJ. Prevalence and prognosis of individual clinical and pathologic variables associated with colorectal carcinoma. Cancer 1967;20:1976-85.
19. Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1997;38:785-90.
20. Liu H, Li C, Zhao Z, Guan X, Yang M, Liu Z, *et al*. Safety and long-term effect assessment of neoadjuvant chemoradiotherapy for elderly patients with locally advanced rectal cancer: A CHN single-center retrospective study. Technol Cancer Res Treat 2020;19:1533033820970339. doi: 10.1177/1533033820970339.
21. Adam IJ, Mohamdee MO, Martin IG, Scott N, Finan PJ, Johnston D, *et al*. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994;344:707-11.
22. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 1997;12:19-23.
23. Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, *et al*. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 1991;324:709-15.
24. Stockholm Colorectal Cancer Study Group. Randomized study on preoperative radiotherapy in rectal carcinoma. Ann Surg Oncol 1996;3:423-30.
25. Wang SJ, Hathout L, Malhotra U, Maloney-Patel N, Kilic S, Poplin E, *et al*. Decision-making strategy for rectal cancer management using radiation therapy for elderly or comorbid patients. Int J Radiat Oncol Biol Phys 2018;100:926-44.