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Research article

Analysis of the impact of radiotherapy and surgical treatment regimens based on the SEER database on the survival outcomes of rectal cancer patients over 70 years

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Abstract: *Objective:* This study evaluates the impact of different combinations of treatment regimens, such as additional radiation, chemotherapy, and surgical treatments, on the survival of elderly rectal cancer patients ≥ 70 years of age to support physicians' clinical decision-making. *Methods:* Data from a sample of elderly rectal cancer patients aged ≥ 70 years diagnosed from 2005–2015 from the US surveillance, epidemiology, and end results (SEER) database were retrospectively analyzed. The best cut-off point was selected using the x-tile software for the three continuity indices: age, tumor size, and number of regional lymph nodes. All patients were categorized into either the neoadjuvant radiotherapy and surgery group (R_S group), the surgical treatment group (S group), or the surgery and adjuvant radiotherapy group (S_R group). The propensity score allocation was used to match each included study subject in a 1:1 ratio, and the restricted mean survival time method (RMST) was used to predict the mean survival of rectal cancer patients within 5 and 10 years. The prognostic risk factors for rectal cancer patients were determined using univariate and multivariate Cox regression analyses, and nomograms were constructed. A subgroup stratification analysis of patients with different treatment combination regimens was performed using the Kaplan-Meier method, and log-rank tests were used for between-group comparisons. The model's predictive accuracy was assessed by receiver operating characteristic (ROC) curves, correction curves, and a clinical decision curve analysis (DCA). *Results:* A total of 7556 cases of sample data from 2005 to 2015 were included, which were categorized into 6639 patients (87.86%) in the S group, 408 patients (5.4%) in the R_S group, and 509 patients (6.74%) in the S_R group, according to the relevant order

of radiotherapy and surgery. After propensity score matching (PSM), the primary clinical characteristics of the groups were balanced and comparable. The difference in the mean survival time before and after PSM was not statistically significant in both R_S and S groups (P value > 0.05), and the difference in the mean survival time after PSM was statistically substantial in S_R and S groups (P value < 0.05). In the multifactorial Cox analysis, the M1 stage and Nodes ≥ 9 were independent risk factors. An age between 70–75 was an independent protective factor for patients with rectal cancer in the R_S and S groups. The Marital_status, T4 stage, N2 stage, M1 stage, and Nodes ≥ 9 were independent risk factors for patients with rectal cancer in the S_R and S groups, and an age between 70–81 was an independent protective factor. The ROC curve area, the model C index, and the survival calibration curve suggested good agreement between the actual and predicted values of the model. The DCA for 3-year, 5-year, and 10-year survival periods indicated that the model had some potential for application. *Conclusions:* The results of the study showed no significant difference in the overall survival (OS) between elderly patients who received neoadjuvant radiotherapy and surgery and those who received surgery alone; elderly patients who received surgery and adjuvant radiotherapy had some survival benefits compared with those who received surgery alone, though the benefit of adjuvant radiotherapy was not significant. Therefore, radiotherapy for rectal cancer patients older than 70 years old should be based on individual differences in condition, and a precise treatment plan should be developed.

Keywords: colorectal cancer; SEER database; old patients; early death; analysis

1. Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths worldwide. In 2021, more than 50,000 patients have died from the 150,000 new cases of colorectal cancer diagnosed within the United States [1]. The prevalence of colorectal cancer in elderly patients has increased by more than 70% over the past 20 years. With asa trend of an aging population, the number of elderly patients with rectal cancer will continue to increase, and more and more studies are being conducted on the treatment modalities and efficacy of elderly patients with rectal cancer [2]. The median age of colorectal cancer is 70 years old, and about 60% of new cases are patients > 70 years old, while about 43% are patients > 75 years old [3]. Among the current treatment options, surgical treatment is the only radical treatment for patients with rectal cancer, and rectal cancer resection can be safely exhaustive in some elderly patients and does not increase the number of post-surgical complications. The study of the relationship between survival and the age of patients with rectal cancer in several high-income countries found that survival decreased with the increasing patient age. The difference between rectal cancer survival and age is even more significant for different cancer stages [4–6].

The concept of neoadjuvant therapy for rectal cancer was first proposed in the 2007 national comprehensive cancer network (NCCN) guidelines, in which locally progressive rectal cancer was preoperatively given a variety of radiotherapy and chemotherapy treatments. At present, a multidisciplinary treatment combining neoadjuvant therapy, radical surgery, and adjuvant chemotherapy has become the standard treatment for locally progressive low and intermediate rectal cancer cases.

However, the high risk of local and distant recurrence of rectal cancer complicates its treatment.

For elderly rectal cancer patients, the expected survival time and quality of life after surgery are essential factors to be considered. Relevant literature suggests that neoadjuvant chemotherapy (NCRT) can further preserve sphincter function and maximize the oncologic benefit [7]. Jiang et Al. demonstrated that older patients (>= 70 years) who underwent NCRT had a similar prognosis to younger patients with some oncologic benefit [8]. Several recent oncology studies have suggested that older patients may experience identical survival outcomes when treated according to standard guidelines as compared to younger patients [9].

However, some studies have also shown that the oncologic benefits of adjuvant chemotherapy are controversial. Rutten et Al. showed that no significant improvement in overall patient survival was seen in elderly rectal cancer patients treated with preoperative radiotherapy alongside total mesorectal excision (TME) surgery [10]. Maas et Al. showed that older patients who received preoperative radiotherapy had a lower local recurrence rate. However, due to the lower incidence of local recurrence in patients treated with radiotherapy and the increased incidence of postoperative complications, the absence of preoperative radiotherapy may be appropriate in older patients at the risk of complications or early death [11]. Shahir et Al. demonstrated a 14% increase in the rate of treatment-related complications in elderly patients with rectal cancer as compared to patients under 70 years of age [12]. Liu et Al. showed that little is known about the benefits of adjuvant chemotherapy in older patients with locally advanced rectal cancer and that older patients who underwent adjuvant chemotherapy experienced more chemotherapy-related toxicity [13].

Several large and randomized trials of rectal cancer patients have demonstrated that neoadjuvant radiotherapy can play a role in improving the local and regional status of patients with rectal cancer, though it does not significantly increase their long-term survival [14–17]. The benefits of radiation therapy should be carefully weighed against adverse events when considering its potential effects. Moreover, older patients are characterized by different clinicopathological features, increased comorbidities, and deficiencies in treatment intensity as compared with younger rectal cancer patients [18–20].

In the process of clinical treatment, it is important to fully understand the prognostic factors related to rectal cancer in the elderly and formulate individualized treatment plans, which will help to improve the prognosis of rectal cancer in the elderly. In summary, it is still controversial whether radiotherapy can increase the survival rate and improve the quality of life of elderly patients with rectal cancer before and after surgical treatment. Therefore, on the one hand, the purpose of this study is to investigate whether neoadjuvant and adjuvant radiotherapies can bring survival benefits to elderly rectal cancer patients before and after surgery; on the other hand, the purpose of this study is to identify which subgroups of elderly rectal cancer patients can benefit from radiotherapy, which will help doctors to conduct precision treatment for elderly rectal cancer patients.

The National Cancer Institute (NCI) established the U.S. Cancer, Epidemiology, and Outcomes (SEER) database in 1973. This study investigates the effect of neoadjuvant and adjuvant radiotherapies on the prognosis of elderly rectal cancer patients by retrospectively analyzing rectal cancer patients greater than 70 years of age in the SEER database between the period of 2005–2015 to improve the reference for the clinical application of radiotherapy in elderly rectal cancer patients.

2. Information and methods

2.1. General information

Data from the SEER database [Incidence-SEER Research Data, 12 Registries, Nov 2022 Sub [1992–2020], which contains information on patient demographics, tumor stage, treatment modalities, and survival status, were used in this study, and information on patients was obtained through SEER*State (version 8.4.1) to retrieve rectal cancer patients diagnosed from 2005–2015 and aged greater than or equal to 70 years. The patient information collected included age, race, marital status, gender, tumor size, tumor differentiation grade, tumor, node, and metastasis (TNM) stage, number of regional lymph nodes, radiotherapy information, chemotherapy information, surgery information, survival time, and survival status.

2.2. Inclusion and exclusion criteria

The inclusion criteria included the following: 1) the primary tumor location was confirmed in the rectum according to the International Classification of Diseases of Oncology (ICD-O), 3rd edition; 2) samples were confirmed as positive by histology; and 3) patients with complete follow-up information. The exclusion criteria included the following: 1) patients with unclear or unknown TNM staging; 2) patients with incomplete follow-up information; and 3) patients with less than four months of survival were excluded because radical surgery was usually performed at an interval of 5–12 weeks after the end of radiotherapy.

2.3. Study grouping

Three continuity indexes, including age, tumor size, and number of regional lymph nodes, were grouped using the x-tile software to select the optimal cut-off point. The optimal groupings for the present study were age (70–75, 76–81, and 82–90), tumor size (<= 34, 35–49, and >= 50), and number of regional lymph nodes (<= 2, 3–8, and >= 9). All included patients were divided into the following three groups according to the order of radiotherapy and surgery, and all patients received chemotherapy treatment: the surgical treatment group (Group S), the radiotherapy-surgery group (Group R_S), and the surgery-radiotherapy group (Group S_R).

2.4. Statistical analysis

Statistical analyses were performed using the R software (4.3.0); to control for the effect of confounding factors on the outcomes, the propensity scores were matched in a 1:1 ratio between the S and R_S groups, and between the S and S_R groups. PSM was calculated using the MatchIt program package (with a caliper value of 0.001). The restricted mean survival time function was used to estimate the mean survival of rectal cancer patients at 5 and 10 years. The relationship between clinical pathologic information and survival time was assessed by the Cox proportional risk regression modeling. Statistically significant clinical indicators at the screening were included in the multifactorial Cox regression analysis to construct a column-line graph disease-specific survival (DSS) prognostic model by a univariate Cox regression analysis. The accuracy and differentiation of

the prediction model were evaluated by the C index, the subjects' work characteristic curve (ROC), and the area under the curve (AUC). The consistency between the actual and predicted values of the prediction model was evaluated by a calibration curve, and the clinical utility of the model was evaluated by a decision curve analysis. Finally, the patient's survival was analyzed using the Kaplan-Meier method, the survival curves were compared using the log-rank test, and the P value of all the analyzed results was calculated using the P-rank test. The rank test and all analyzed P values were bipartite, and $P < 0.05$ was considered statistically significant in this study. The R language program packages included rms, foreign, survival, forest plot, and MatchIt.

3. Results

3.1. Matching of basic clinical information between included patients and different groups

Figure 1 describes the inclusion process of the samples in this study in detail. According to the inclusion and exclusion criteria and the relevant order of radiotherapy and surgery, a total of 7556 cases of sample data were included in this study, which was categorized into 6639 patients (87.86%) in the S group, 408 patients (5.4%) in the R_S group, and 509 patients (6.74%) in the S_R group.

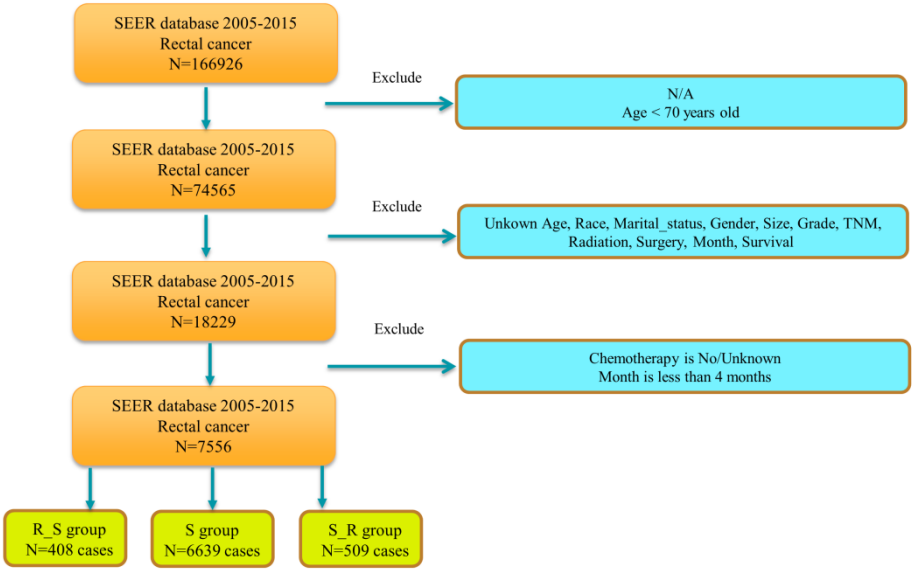


Figure 1. Flow chart for inclusion of patients with rectal cancer.

Based on the needs of the study in this paper, the PSM function selected surgery as the grouping variable, which was the key variable of the study, and age, race, and gender as additional confounding variables.

The basic clinical characteristics of rectal cancer patients in the R_S and S groups before and after PSM are shown in Table 1 and Table 2. After PSM, information from 408 patients was screened in each of the R_S and S groups. The basic clinical characteristics of rectal cancer patients in the S_R and S groups before PSM are shown in Tables 3 and 4. After PSM, information from 509 patients

was screened in each S_R and S group.

Table 1. Basic clinical characteristics of rectal cancer patients in the R_S and S groups before PSM.

Characteristics	Variables	R_S (N = 408)	S (N = 6639)	Total (N = 7047)	P value
Age	> 81	54 (13.2%)	1264 (19%)	3311 (47%)	.005
	70–75	217 (53.2%)	3094 (46.6%)	2418 (34.3%)	
	76–81	137 (33.6%)	2281 (34.4%)	1318 (18.7%)	
Race	Black	18 (4.4%)	439 (6.6%)	457 (6.5%)	.032
	ohter	72 (17.6%)	921 (13.9%)	5597 (79.4%)	
	White	318 (77.9%)	5279 (79.5%)	993 (14.1%)	
Marital_status	Married	241 (59.1%)	3966 (59.7%)	4207 (59.7%)	.829
	Unmarried	167 (40.9%)	2673 (40.3%)	2840 (40.3%)	
Gender	Female	167 (40.9%)	3455 (52%)	3622 (51.4%)	<.001
	Male	241 (59.1%)	3184 (48%)	3425 (48.6%)	
Size	<= 34	151 (37%)	1671 (25.2%)	1822 (25.9%)	<.001
	> 35–49	93 (22.8%)	1989 (30%)	2082 (29.5%)	
	> 50	164 (40.2%)	2979 (44.9%)	3143 (44.6%)	
Grade	I	17 (4.2%)	267 (4%)	284 (4%)	.005
	II	284 (69.6%)	4125 (62.1%)	4409 (62.6%)	
	III	99 (24.3%)	1935 (29.1%)	2034 (28.9%)	
	IV	8 (2%)	312 (4.7%)	320 (4.5%)	
T	T1	9 (2.2%)	173 (2.6%)	182 (2.6%)	<.001
	T2	36 (8.8%)	522 (7.9%)	558 (7.9%)	
	T3	321 (78.7%)	4436 (66.8%)	4757 (67.5%)	
	T4	42 (10.3%)	1508 (22.7%)	1550 (22%)	
N	N1	274 (67.2%)	3819 (57.5%)	4093 (58.1%)	<.001
	N2	134 (32.8%)	2820 (42.5%)	2954 (41.9%)	
M	M0	356 (87.3%)	5042 (75.9%)	5398 (76.6%)	<.001
	M1	52 (12.7%)	1597 (24.1%)	1649 (23.4%)	
Nodes	<= 2	224 (54.9%)	2992 (45.1%)	3216 (45.6%)	<.001
	>= 9	34 (8.3%)	902 (13.6%)	2895 (41.1%)	
	> 3–8	150 (36.8%)	2745 (41.3%)	936 (13.3%)	
Radiation	Yes	408 (100%)	4 (0.1%)	412 (5.8%)	<.001
	No	0 (0%)	6635 (99.9%)	6635 (94.2%)	
Month	Mean ± SD	64.92 ± 46.43	65.06 ± 48.04	65.06 ± 47.95	.953
Survival	Alive	99 (24.3%)	1947 (29.3%)	2046 (29%)	.033
	Dead	309 (75.7%)	4692 (70.7%)	5001 (71%)	

Table 2. Basic clinical characteristics of rectal cancer patients in the R_S and S groups after PSM.

Characteristics	Variables	R_S (N = 408)	S (N = 408)	Total (N = 816)	P value
Age	> 81	54 (13.2%)	132 (32.4%)	410 (50.2%)	<.001
	70–75	217 (53.2%)	193 (47.3%)	220 (27%)	
	76–81	137 (33.6%)	83 (20.3%)	186 (22.8%)	
Race	Black	18 (4.4%)	21 (5.1%)	39 (4.8%)	<.001
	ohter	72 (17.6%)	141 (34.6%)	564 (69.1%)	
	White	318 (77.9%)	246 (60.3%)	213 (26.1%)	
Marital_status	Married	241 (59.1%)	259 (63.5%)	500 (61.3%)	.222
	Unmarried	167 (40.9%)	149 (36.5%)	316 (38.7%)	
Gender	Female	167 (40.9%)	155 (38%)	322 (39.5%)	.431
	Male	241 (59.1%)	253 (62%)	494 (60.5%)	
Size	<= 34	151 (37%)	97 (23.8%)	248 (30.4%)	<.001
	> 35–49	93 (22.8%)	126 (30.9%)	219 (26.8%)	
	> 50	164 (40.2%)	185 (45.3%)	349 (42.8%)	
Grade	I	17 (4.2%)	27 (6.6%)	44 (5.4%)	.054
	II	284 (69.6%)	251 (61.5%)	535 (65.6%)	
	III	99 (24.3%)	115 (28.2%)	214 (26.2%)	
	IV	8 (2%)	15 (3.7%)	23 (2.8%)	
T	T1	9 (2.2%)	6 (1.5%)	15 (1.8%)	<.001
	T2	36 (8.8%)	34 (8.3%)	70 (8.6%)	
	T3	321 (78.7%)	284 (69.6%)	605 (74.1%)	
	T4	42 (10.3%)	84 (20.6%)	126 (15.4%)	
N	N1	274 (67.2%)	244 (59.8%)	518 (63.5%)	.035
	N2	134 (32.8%)	164 (40.2%)	298 (36.5%)	
M	M0	356 (87.3%)	295 (72.3%)	651 (79.8%)	<.001
	M1	52 (12.7%)	113 (27.7%)	165 (20.2%)	
Nodes	<= 2	224 (54.9%)	183 (44.9%)	407 (49.9%)	.016
	>= 9	34 (8.3%)	44 (10.8%)	331 (40.6%)	
	> 3–8	150 (36.8%)	181 (44.4%)	78 (9.6%)	
Radiation	Yes	408 (100%)	1 (0.2%)	409 (50.1%)	<.001
	No	0 (0%)	407 (99.8%)	407 (49.9%)	
Month	Mean ± SD	64.92 ± 46.43	62.91 ± 51.25	63.92 ± 48.88	.558
Survival	Alive	99 (24.3%)	89 (21.8%)	188 (23%)	.454
	Dead	309 (75.7%)	319 (78.2%)	628 (77%)	

Table 3. Basic clinical characteristics of rectal cancer patients in S_R and S groups before PSM.

Characteristics	Variables	S_R (N = 509)	S (N = 6639)	Total (N = 7148)	P value
Age	> 81	81 (15.9%)	1264 (19%)	3343 (46.8%)	.214
	70–75	249 (48.9%)	3094 (46.6%)	2460 (34.4%)	
	76–81	179 (35.2%)	2281 (34.4%)	1345 (18.8%)	
Race	Black	36 (7.1%)	439 (6.6%)	475 (6.6%)	.321
	ohter	82 (16.1%)	921 (13.9%)	5670 (79.3%)	
	White	391 (76.8%)	5279 (79.5%)	1003 (14%)	
Marital_status	Married	307 (60.3%)	3966 (59.7%)	4273 (59.8%)	.835
	Unmarried	202 (39.7%)	2673 (40.3%)	2875 (40.2%)	
Gender	Female	230 (45.2%)	3455 (52%)	3685 (51.6%)	.003
	Male	279 (54.8%)	3184 (48%)	3463 (48.4%)	
Size	<= 34	166 (32.6%)	1671 (25.2%)	1837 (25.7%)	.001
	> 35–49	137 (26.9%)	1989 (30%)	2126 (29.7%)	
	> 50	206 (40.5%)	2979 (44.9%)	3185 (44.6%)	
Grade	I	19 (3.7%)	267 (4%)	286 (4%)	.045
	II	348 (68.4%)	4125 (62.1%)	4473 (62.6%)	
	III	122 (24%)	1935 (29.1%)	2057 (28.8%)	
	IV	20 (3.9%)	312 (4.7%)	332 (4.6%)	
T	T1	22 (4.3%)	173 (2.6%)	195 (2.7%)	<.001
	T2	63 (12.4%)	522 (7.9%)	585 (8.2%)	
	T3	318 (62.5%)	4436 (66.8%)	4754 (66.5%)	
	T4	106 (20.8%)	1508 (22.7%)	1614 (22.6%)	
N	N1	302 (59.3%)	3819 (57.5%)	4121 (57.7%)	.454
	N2	207 (40.7%)	2820 (42.5%)	3027 (42.3%)	
M	M0	451 (88.6%)	5042 (75.9%)	5493 (76.8%)	<.001
	M1	58 (11.4%)	1597 (24.1%)	1655 (23.2%)	
Nodes	<= 2	238 (46.8%)	2992 (45.1%)	3230 (45.2%)	.735
	>= 9	69 (13.6%)	902 (13.6%)	2947 (41.2%)	
	> 3–8	202 (39.7%)	2745 (41.3%)	971 (13.6%)	
Radiation	Yes	509 (100%)	4 (0.1%)	513 (7.2%)	<.001
	No	0 (0%)	6635 (99.9%)	6635 (92.8%)	
Month	Mean ± SD	67.08 ± 50.73	65.06 ± 48.04	65.21 ± 48.24	.364
Survival	Alive	122 (24%)	1947 (29.3%)	2069 (28.9%)	.012
	Dead	387 (76%)	4692 (70.7%)	5079 (71.1%)	

Table 4. Basic clinical characteristics of rectal cancer patients in the S_R and S groups after PSM.

Characteristics	Variables	S_R (N = 509)	S (N = 509)	Total (N = 1018)	P value
Age	> 81	81 (15.9%)	509 (100%)	249 (24.5%)	<.001
	70–75	249 (48.9%)	0 (0%)	179 (17.6%)	
	76–81	179 (35.2%)	0 (0%)	590 (58%)	
Race	Black	36 (7.1%)	29 (5.7%)	65 (6.4%)	<.001
	ohter	82 (16.1%)	4 (0.8%)	867 (85.2%)	
	White	391 (76.8%)	476 (93.5%)	86 (8.4%)	
Marital_status	Married	307 (60.3%)	163 (32%)	470 (46.2%)	<.001
	Unmarried	202 (39.7%)	346 (68%)	548 (53.8%)	
Gender	Female	230 (45.2%)	509 (100%)	739 (72.6%)	<.001
	Male	279 (54.8%)	0 (0%)	279 (27.4%)	
Size	<= 34	166 (32.6%)	0 (0%)	166 (16.3%)	<.001
	> 35–49	137 (26.9%)	204 (40.1%)	341 (33.5%)	
	> 50	206 (40.5%)	305 (59.9%)	511 (50.2%)	
Grade	I	19 (3.7%)	24 (4.7%)	43 (4.2%)	<.001
	II	348 (68.4%)	243 (47.7%)	591 (58.1%)	
	III	122 (24%)	212 (41.7%)	334 (32.8%)	
	IV	20 (3.9%)	30 (5.9%)	50 (4.9%)	
T	T1	22 (4.3%)	2 (0.4%)	24 (2.4%)	<.001
	T2	63 (12.4%)	21 (4.1%)	84 (8.3%)	
	T3	318 (62.5%)	342 (67.2%)	660 (64.8%)	
	T4	106 (20.8%)	144 (28.3%)	250 (24.6%)	
N	N1	302 (59.3%)	248 (48.7%)	550 (54%)	<.001
	N2	207 (40.7%)	261 (51.3%)	468 (46%)	
M	M0	451 (88.6%)	369 (72.5%)	820 (80.6%)	<.001
	M1	58 (11.4%)	140 (27.5%)	198 (19.4%)	
Nodes	<= 2	238 (46.8%)	193 (37.9%)	431 (42.3%)	.010
	>= 9	69 (13.6%)	93 (18.3%)	425 (41.7%)	
	> 3–8	202 (39.7%)	223 (43.8%)	162 (15.9%)	
Radiation	Yes	509 (100%)	0 (0%)	509 (50%)	<.001
	No	0 (0%)	509 (100%)	509 (50%)	
Month	Mean ± SD	67.08 ± 50.73	50.16 ± 42.23	58.62 ± 47.41	<.001
Survival	Alive	122 (24%)	85 (16.7%)	207 (20.3%)	.005
	Dead	387 (76%)	424 (83.3%)	811 (79.7%)	

3.2. Survival analysis

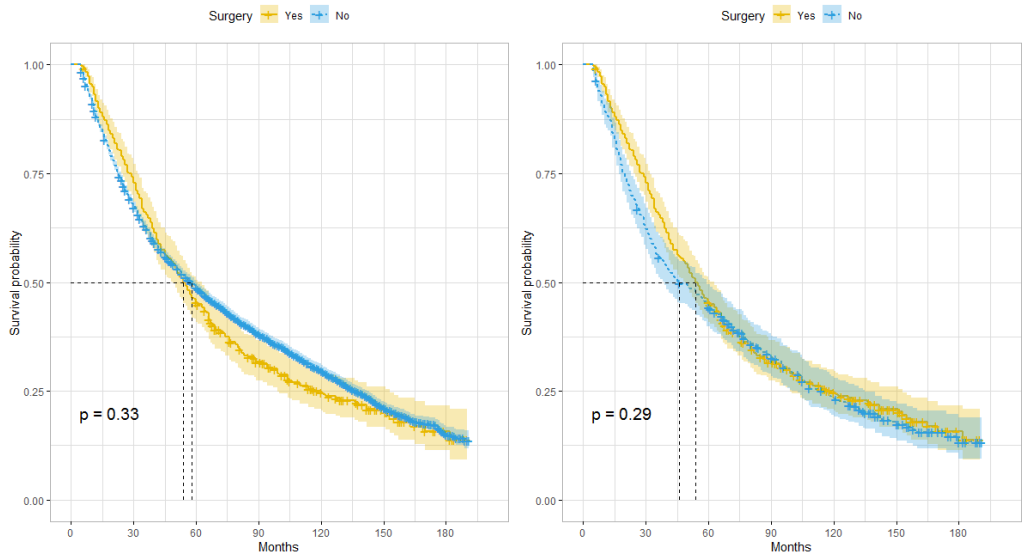
As shown in Table 5, the median survival time before PSM was 54 months for the R_S group and 58 months for the S group. The median survival time after PSM was 54 months for the R_S group and 46 months for the S group. The survival time at 5 years were 44 months and 42.6 months for the R_S and S groups, respectively, and 60.2 months and 60.5 months at 10 years for the R_S and S groups before PSM. The results of RMST analysis showed that the survival times at 5 years were 44

months and 40.4 months for the R_S and S groups, respectively, and 63.8 months, and 60.4 months at 10 years for the R_S and S groups, respectively.

The difference in mean survival time between R_S and S groups before and after PSM was not statistically significant (P value > 0.05), as shown in Table 5. Figure 2A,B show that before and after PSM, the R_S and S group's survival curves largely overlap, and it is impossible to differentiate the survival benefits from different surgical approaches.

Table 5. Survival of rectal cancer patients in R_S and S groups before and after PSM.

Test model	**Before PSM**			**After PSM**		
	R_S group (95% *CI*)	**S group (95% CI)**	***P* value**	**R_S group (95% *CI*)**	**S group (95% CI)**	***P* value**
Log-rank						
Median	54 (49–63)	58 (55–61)	0.33	54 (49–63)	46 (39–59)	0.29
RMST						
60 months survival time	44.0(42.2–45.8)	42.6(42.2–43.1)	0.153	44.0(42.2–45.8)	40.4(38.4–42.4)	0.009
120 months survival time	60.2(56.6–63.8)	60.5(59.6–61.5)	0.861	63.8(59.8–67.7)	60.4(56.1–64.6)	0.25



A. Survival curves of R_S and S groups before PSM B. Survival curves of R_S and S groups after PSM

Figure 2. The survival curves of R_S and S groups.

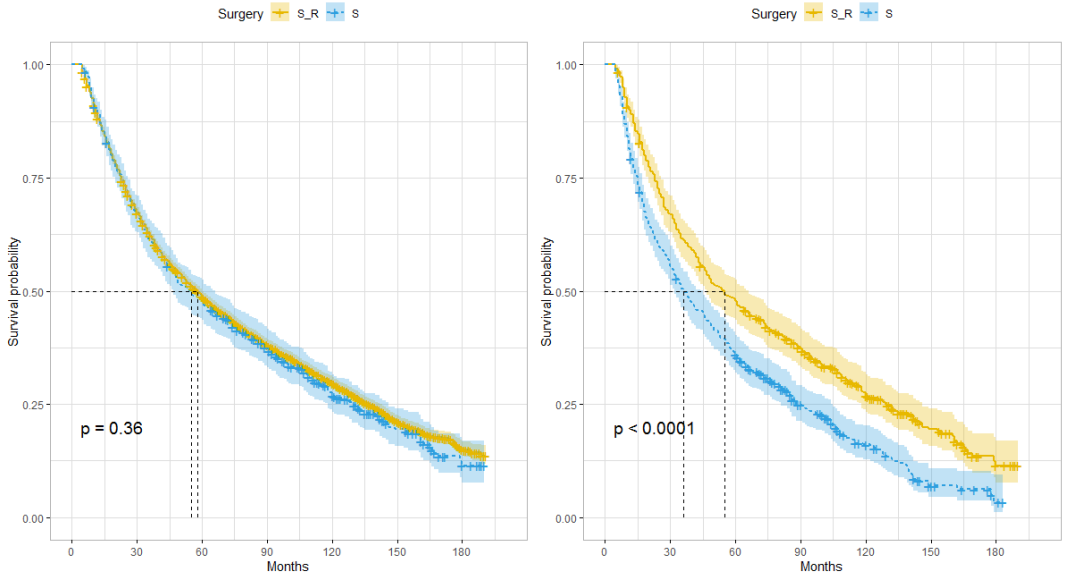
As shown in Table 6, the median survival time before PSM was 55 months for the S_R group and 58 months for the S group. The median survival time after PSM was 55 months for the S_R group and 36 months for the S group.

Table 6 and Figure 3A show that the difference in the mean survival time between the S_R and S groups before PSM was not statistically significant (P value > 0.05). The survival time at 5 years were 42.3 months and 42.7 months for the S_R and S groups, respectively, and 64.8 months and 65.9 months at 10 years for the S_R and S groups before PSM. The results of RMST analysis showed that the survival times at 5 years were 42.3 months and 36.7 months for the S_R and S groups,

respectively, and 64.8 months, and 51.9 months at 10 years for the S_R and S groups, respectively. The difference in the survival time between the S_R and S groups after PSM was statistically significant (P value < 0.05), as shown in Table 6. From Figure 3A,B, it was found that after PSM matching, the short-term prognosis (5 years) and long-term prognosis (10 years) of the S_R group were significantly better than that of the S group, thus indicating that postoperative adjuvant radiotherapy improved the prognosis of patients.

Table 6. Survival of rectal cancer patients in S_R and S groups before and after PSM.

Test model	**Before PSM**			**After PSM**		
	S_R group (95% *CI*)	**S group (95% CI)**	***P* value**	**S_R group (95% *CI*)**	**S group (95% CI)**	***P* value**
Log-rank						
Median	55 (47–66)	58 (55–61)	0.36	55 (47–66)	36 (32–45)	<0.0001
RMST						
60 months survival time	42.3(40.6–44.0)	42.7(42.2–43.1)	0.691	42.3(40.6–44.0)	36.7(34.8–38.5)	0.000
120 months survival time	64.8(60.9–68.6)	65.9(64.8–67.0)	0.579	64.8(60.9–68.6)	51.9(48.3–55.6)	0.000



A. Survival curves of S_R and S groups before PSM **B.** Survival curves of S_R and S groups after PSM

Figure 3. The survival curves of S_R and S groups.

3.3. Prognostic analysis after PSM matching

3.3.1. Unifactorial and multifactorial analysis

After PSM in the R_S and S groups, the unifactorial Cox analysis showed that age,

marital_status, size, N, M, and Nodes significantly affected the survival status. Covariates with P < 0.05 were included in the multifactorial Cox analysis, in which the M1 stage and Nodes >= 9 were independent risk factors for rectal cancer patients, and an age between 70–75 was an independent protective factor, as shown in Table 7.

Table 7. Univariate and multivariate Cox regression analysis of rectal cancer patients in group R_S and group S.

Characteristics	**Variables**	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age	> 81	Reference	Reference	Reference	Reference
	70–75	0.58(0.46–0.74)	0.000	0.56 (0.44–0.72)	0.0000
	76–81	0.84(0.66–1.08)	0.172	0.79 (0.61–1.01)	0.0564
Race	Black	Reference	Reference	Reference	Reference
	ohter	0.87(0.56–1.36)	0.539		
	White	1.06(0.7–1.6)	0.780		
Marital_status	Married	Reference	Reference	Reference	Reference
	Unmarried	1.20(1.02–1.42)	0.028	1.17 (0.99–1.38)	0.0632
Gender	Female	Reference	Reference	Reference	Reference
	Male	1.02(0.86–1.2)	0.853		
Size	<= 34	Reference	Reference	Reference	Reference
	> 35–49	1.32(1.07–1.64)	0.010	1.13 (0.91–1.41)	0.2682
	> 50	1.31(1.08–1.59)	0.006	1.11 (0.91–1.35)	0.3133
Grade	I	Reference	Reference	Reference	Reference
	II	1.06(0.71–1.59)	0.779	0.93 (0.61–1.39)	0.7098
	III	1.61(1.06–2.45)	0.025	1.3 (0.85–1.98)	0.2309
	IV	1.26(0.7–2.26)	0.446	0.97 (0.54–1.77)	0.9335
T	T1	Reference	Reference	Reference	Reference
	T2	0.61(0.33–1.11)	0.105		
	T3	0.79(0.47–1.35)	0.396		
	T4	1.20(0.69–2.1)	0.519		
N	N1	Reference	Reference	Reference	Reference
	N2	1.39(1.18–1.63)	0.000	0.96 (0.75–1.24)	0.7735
M	M0	Reference	Reference	Reference	Reference
	M1	3.08(2.54–3.73)	0.000	3.06 (2.51–3.74)	0.0000
Nodes	<= 2	Reference	Reference	Reference	Reference
	>= 9	2.64(2.05–3.41)	0.000	2.07 (1.46–2.94)	0.0000
	> 3–8	1.18(1–1.41)	0.057	0.99 (0.77–1.27)	0.9299
Radiation	Yes	Reference	Reference	Reference	Reference
	No	0.90(0.77–1.06)	0.225		
Surgery	S	Reference	Reference	Reference	Reference
	R_S	1.13(0.94–1.3)	0.225		

Table 8. Univariate and multivariate Cox regression analysis of rectal cancer patients in group S_R and group S.

Characteristics	**Variables**	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age	> 81	Reference	Reference	Reference	Reference
	70–75	0.52(0.43–0.63)	0.00	0.45 (0.37–0.55)	0.000
	76–81	0.58(0.47–0.71)	0.00	0.52 (0.42–0.64)	0.000
Race	Black	Reference	Reference	Reference	Reference
	ohter	0.86(0.62–1.2)	0.0384	0.84 (0.6–1.17)	0.3058
	White	1.01(0.76–1.33)	0.972	1.01 (0.75–1.35)	0.9685
Marital_status	Married	Reference	Reference	Reference	Reference
	Unmarried	1.25(1.08–1.44)	0.0003	1.25 (1.07–1.45)	0.0041
Gender	Female	Reference	Reference	Reference	Reference
	Male	1.14(0.99–1.32)	0.078		
Size	<= 34	Reference	Reference	Reference	Reference
	> 35–49	1.23(1.02–1.48)	0.0032	0.95 (0.78–1.15)	0.5842
	> 50	1.46(1.23–1.73)	0.000	1.03 (0.86–1.24)	0.7152
Grade	I	Reference	Reference	Reference	Reference
	II	1.22(0.84–1.78)	0.290		
	III	1.39(0.94–2.05)	0.096		
	IV	1.46(0.89–2.38)	0.136		
T	T1	Reference	Reference	Reference	Reference
	T2	1.10(0.69–1.76)	0.689	0.94 (0.58–1.51)	0.7988
	T3	1.68(1.11–2.56)	0.015	1.21 (0.78–1.88)	0.4019
	T4	2.72(1.76–4.2)	0.000	1.73 (1.09–2.75)	0.0193
N	N1	Reference	Reference	Reference	Reference
	N2	1.59(1.38–1.84)	0.000	1.28 (1–1.63)	0.0494
M	M0	Reference	Reference	Reference	Reference
	M1	3.67(3.07–4.38)	0.000	3.25 (2.7–3.91)	0.0000
Nodes	<= 2	Reference	Reference	Reference	Reference
	>= 9	2.32(1.87–2.87)	0.000	1.53 (1.12–2.1)	0.0085
	> 3–8	1.31(1.12–1.53)	0.001	1.05 (0.83–1.32)	0.7062
Radiation	Yes	Reference	Reference	Reference	Reference
	No	0.91(0.79–1.05)	0.218		
Surgery	S	Reference	Reference	Reference	Reference
	S_R	1.09(0.95–1.26)	0.218		

A univariate Cox analysis of the S_R and S groups after PSM showed that age, rRace, marital_status, size, T, N, M, and Nodes had significant effects on the survival status. Covariates with $P < 0.05$ were included in the multifactorial Cox analysis, in which marital_status, T4 stage, N2 stage, M1 stage, and Nodes >= 9 were independent risk factors for rectal cancer patients, and an age between 70–81 was an independent protective factor, as shown in Table 8.

3.3.2. Construction and validation of nomograms

According to the results of the multifactorial Cox regression, the nomograms to predict the survival status of patients in the R_S, S, S_R, and S groups for 5 and 10 years were constructed, as shown in Figure 4, and the corresponding ROC curves of the nomograms were established, as shown in Figure 5.

The Cox proportional risk model-predicted AUC values corresponding to one year, three years, and five years for ROC curves of patients in the R_S and S groups were 0.71, 0.69, and 0.73, respectively; the Cox proportional risk for ROC curves of patients in S_R and S groups and the corresponding AUC values predicted by the model for one, three, and five years were 0.74, 0.75, and 0.75, respectively. This indicates that the survival prediction model established in this study has a good predictive ability. The C-index of the R_S and S group's nomogram was 0.648 (95% CI: 0.626~0.671), and the C-index of the S_R and S group's nomogram was 0.679 (95% CI: 0.659~0.699), which suggests that the model has a good discriminative ability; the present study further used the bootstrap model (iterations = 1000) to predict the survival of the group. The study further used the bootstrap method (iterations = 1000) to establish the calibration curves of the nomogram to predict the survival at 3, 5, and 10 years (Figure 6A,B); the results showed that the actual values were in good agreement with the predicted values. Finally, a decision curve analysis (DCA) of the nomograms at 3, 5 and 10 years was produced to validate the model's clinical practice ability. The DCA curves suggested that the predictive model of the present study had a wide range of threshold probabilities and certain clinical net benefits, as shown in Figure 7A–F.

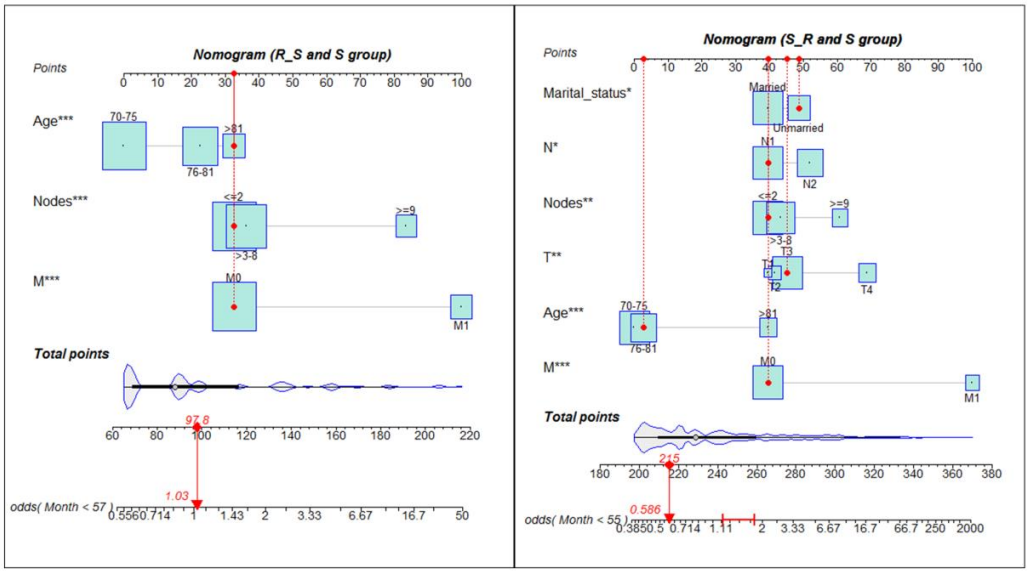


Figure 4. Nomograms of patients in group R_S, group S and group S_R, group S.

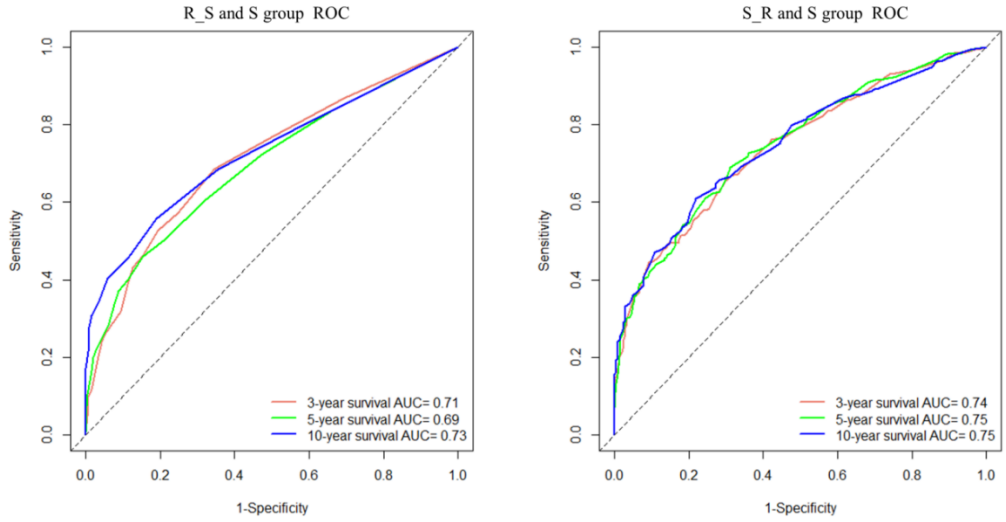


Figure 5. ROC curves of patients in group R_S, group S, and group S_R, group S.

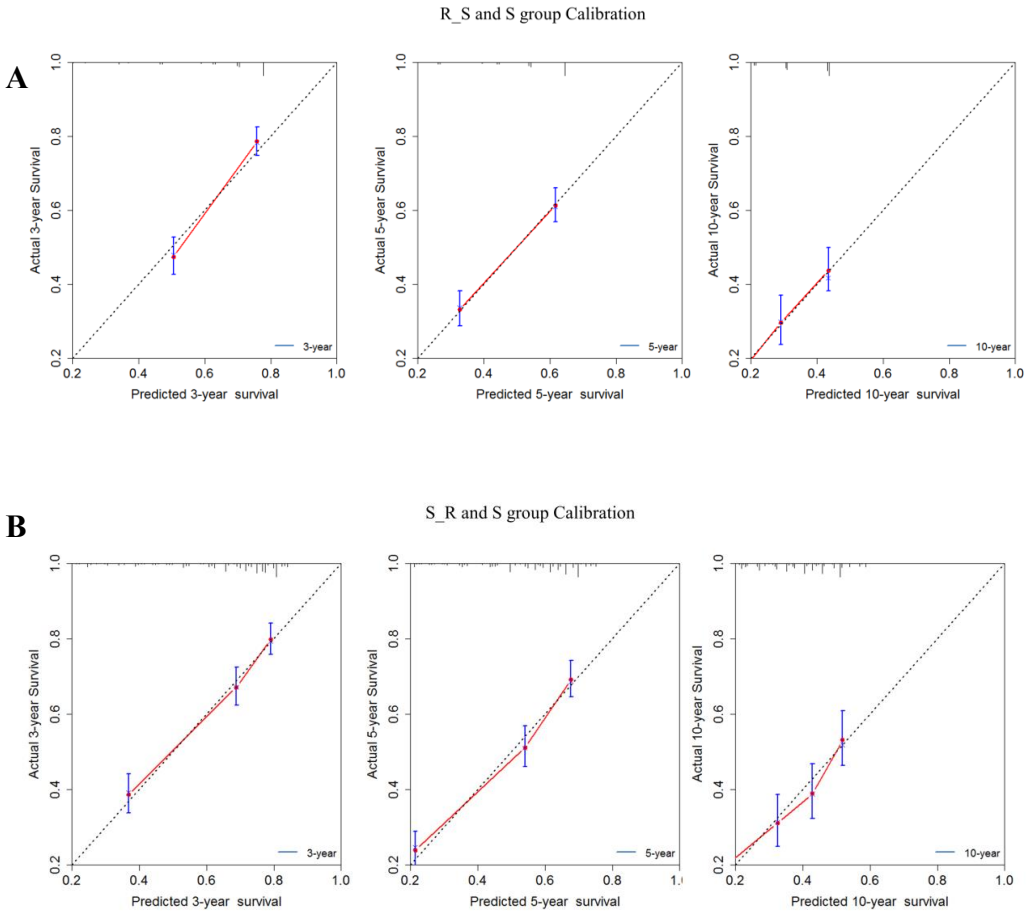


Figure 6. Calibration curves for different groups. **A.** Calibration curves for patients in group R_S and group S. **B.** Calibration curves for patients in group S_R and group S.

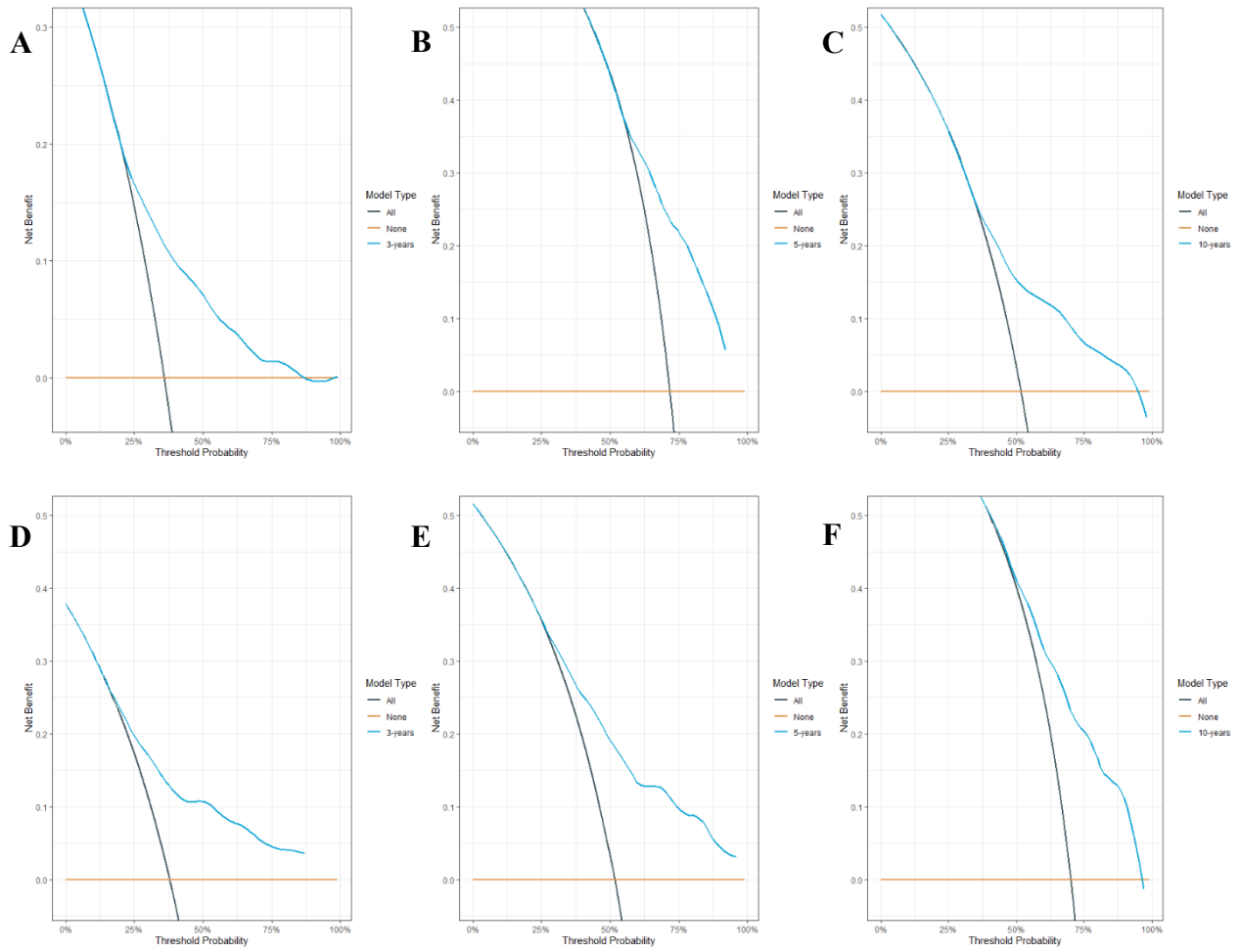


Figure 7. DCA curves for different subgroups at 3,5,10 years. **A.** DCA curves in group R_S and group S (3-years). **B.** DCA curves in group R_S and group S (5-years). **C.** DCA curves in group R_S and group S (10-years). **D.** DCA curves in group S_R and group S (3-years). **E.** DCA curves in group S_R and group S (5-years). **F.** DCA curves in group S_R and group S (10-years).

3.4. Subgroup analysis

The patient's characteristics will affect the final efficacy. Therefore, to further explore whether rectal cancer patients who receive radiotherapy and chemotherapy before and after surgery will produce clinical benefits, we conducted a subgroup analysis between the R_S and S groups, and the S_R and S groups, and the subgroup analysis forest diagrams are shown in Figures 8 and 9. Through the subgroup analysis of the forest plots, we found that radiotherapy and chemotherapy did not improve the long-term prognosis of rectal cancer patients after surgical treatment for elderly patients over 70 years old.

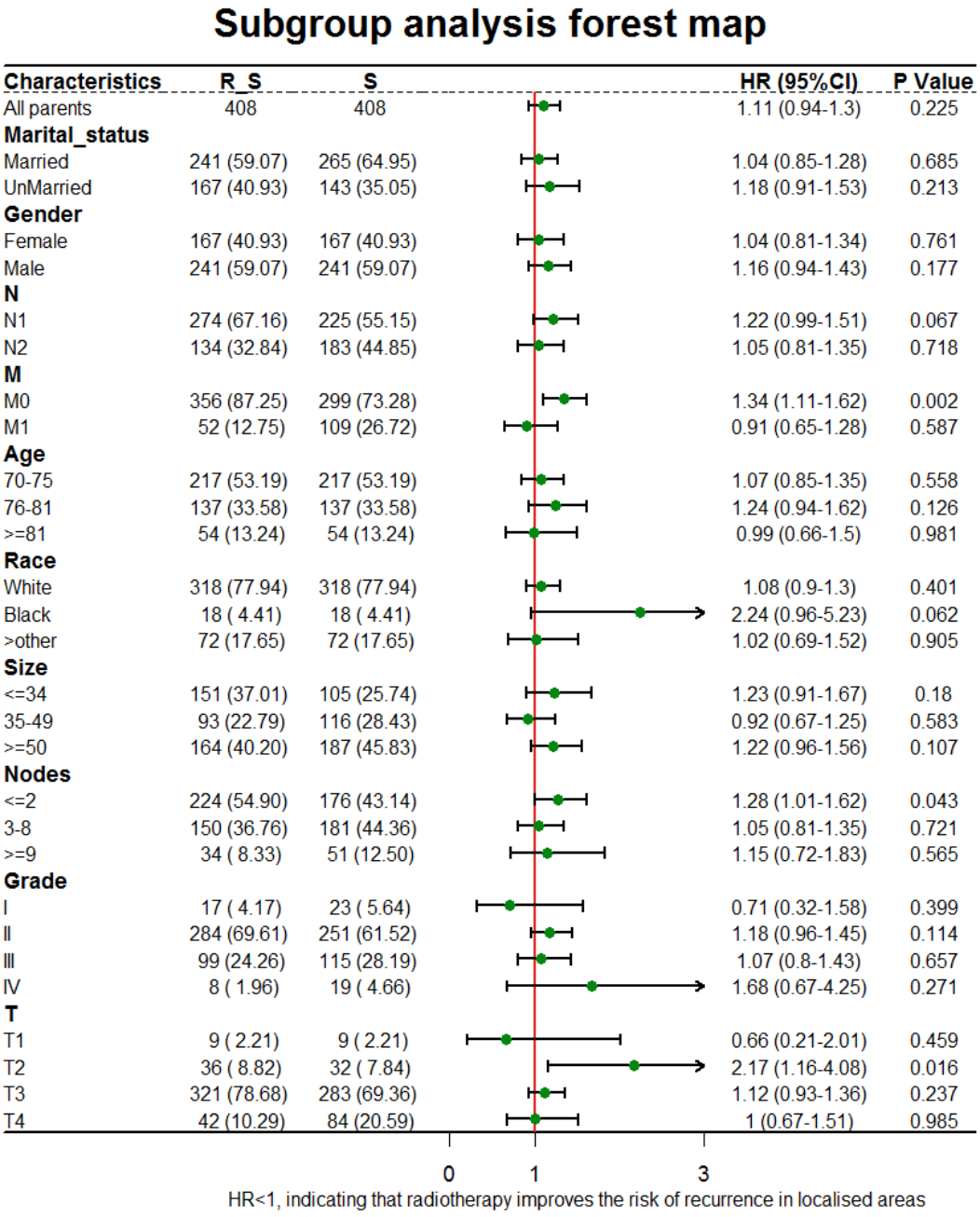


Figure 8. Forest plot for subgroup analysis of group R_S and group S.

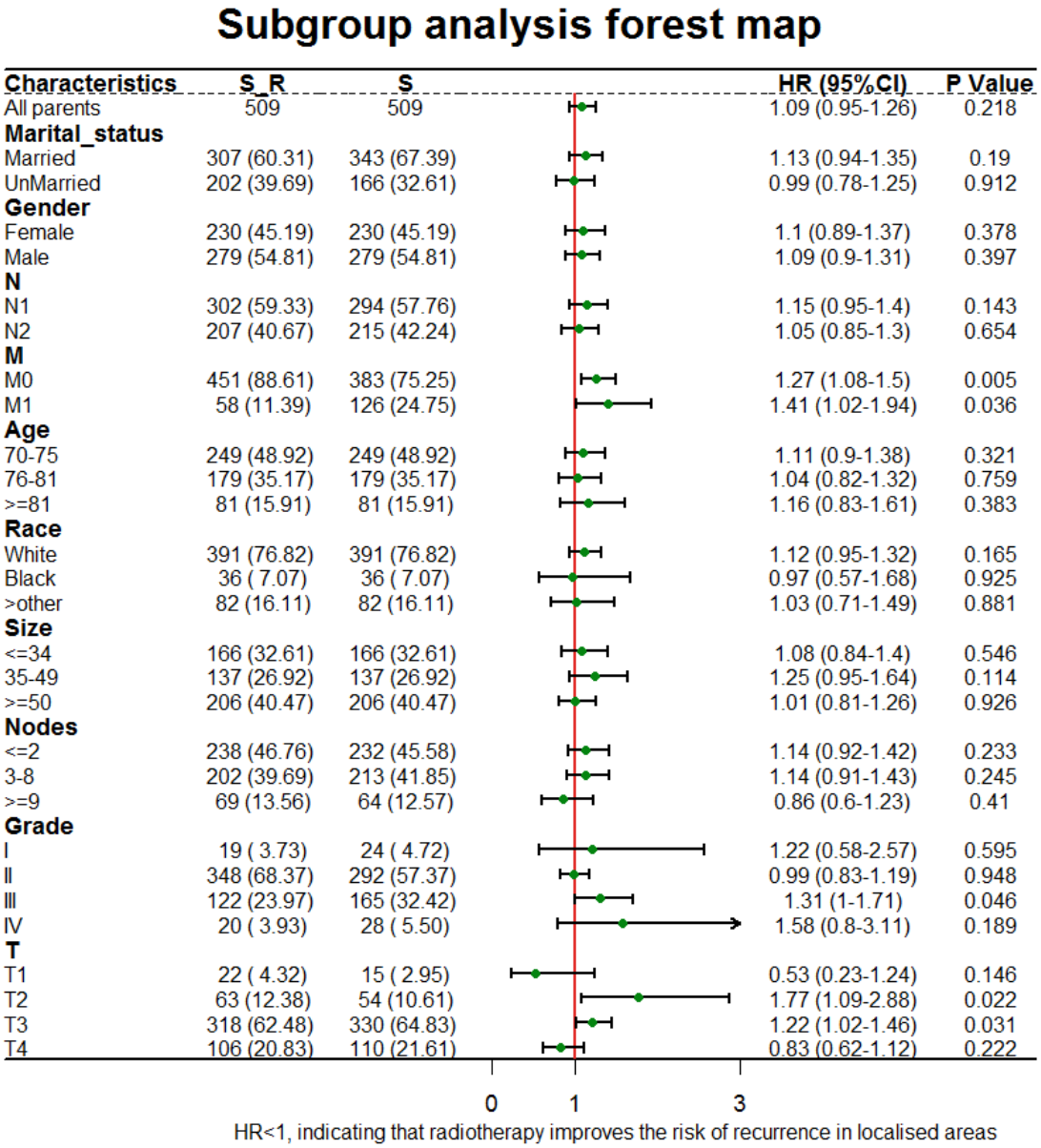


Figure 9. Forest plot for subgroup analysis of group S_R and group S.

4. Discussion

Radiotherapy is currently one of the primary means of local control and treatment for many tumor diseases. However, there is still some controversy about radiotherapy for elderly rectal cancer patients, mainly focusing on the clinical benefits of radiotherapy and its impact on the quality of life of the elderly. Elderly rectal cancer patients are prone to develop more complications as compared to younger patients. For elderly rectal cancer patients who agree to undergo chemotherapy and surgery, the question of whether to combine radiotherapy and the sequence of radiotherapy, as well as which part of the patients can benefit from radiotherapy, needs to be discussed. The log-rank test, which analyzes the overall survival, requires the proportional hazard (PH) assumption to hold and does not

allow for a direct comparison of future prognosis. The RMST method does not rely on the PH assumption, and its results are robust in both proportional and nonproportional risk survival models [21]. In this paper, the results of the RMST showed that after PSM (S_R group), adjuvant radiotherapy prolonged the mean survival time of the patients within 5 and 10 years, which was consistent with the log-rank test results. Therefore, we conclude that adjuvant radiotherapy in patients with rectal cancer who underwent chemotherapy and surgical resection could provide a survival benefit, although not in all populations. Neoadjuvant radiotherapy (R_S group) did not significantly improve the 5- and 10-year survival benefit in elderly rectal cancer patients.

Although adjuvant radiotherapy in line with chemotherapy and surgery has some protective factors for elderly patients with rectal cancer, the use of neoadjuvant radiotherapy for all patients is not justified. A subgroup analysis was performed to identify subgroups that benefited more from radiotherapy to avoid overtreatment of patients with limited survival benefits. From the subgroup forest plot results, patients with smaller tumor diameters, well-differentiated tumors, and earlier TNM staging may not need adjuvant radiotherapy. The study [22] showed that metastasis of the primary tumor and postoperative adverse effects were the main reasons why adjuvant radiotherapy did not improve OS. Therefore, we hypothesized that the adverse effects of radiotherapy may offset the survival benefit of neoadjuvant radiotherapy in patients with small tumor diameter, good differentiation, and an early TNM stage. For metastatic rectal cancer, mainly stage IV rectal cancer, the treatment guidelines vary considerably, and a study by Logan et al. [23] found that surgery combined with radiotherapy prolonged survival in patients with stage IV CRC, especially rectal cancer, as compared with either surgery or radiotherapy alone.

However, some literature suggests that reasonable control can be achieved by surgical treatment for patients with early-stage rectal cancer, and neoadjuvant radiotherapy may not be necessary for these patients. Neoadjuvant radiotherapy can reduce the risk of local recurrence of rectal cancer. Still, radiotherapy may bring a series of side effects, such as urinary disorders, rectal damage, urinary incontinence, etc., and these complications have an impact on the quality of survival of patients. Therefore, there is still a certain degree of clinical controversy as to whether the local control effect produced by neoadjuvant radiotherapy can offset the side effects brought about by radiotherapy in the treatment regimen of elderly rectal cancer patients. Relevant population-level data from other countries have shown that elderly patients are not highly motivated to radiotherapy. For example, in Spain, 24% of colorectal cancer patients less than 75 years of age and 11% of colorectal cancer patients aged 75 years and older received radiotherapy [24].

In Sweden, the utilization of preoperative radiotherapy decreased from 64% in patients less than 65 years of age to 15% in patients over 80 years of age [25]. According to a review by Faivre [26], the rates of preoperative and postoperative radiotherapy in different registries in Europe and the United States ranged between 20% to 50%. The results of our study showed that there was no significant difference in OS between patients who received neoadjuvant CRT + surgery and those who received surgery alone. Therefore, our study concludes that neoadjuvant CRT + surgery and surgery + adjuvant radiotherapy are not effective to improve long-term survival in elderly rectal cancer patients.

Additionally, we performed subgroup analyses to investigate the effects of neoadjuvant and adjuvant therapies in different risk groups. The results showed that neoadjuvant CRT + surgery + chemotherapy did not significantly improve OS in elderly patients, regardless of preoperative risk factors. Due to a lack of data from prospective studies, the safety and efficacy of neoadjuvant radiotherapy in elderly patients are controversial, and the individualized principle should be followed

when choosing neoadjuvant radiotherapy. However, we still encourage radiotherapy for elderly patients with good general conditions. The SEER database is a large, population-based cancer registry dataset that contains patient-level data, so results can be better extrapolated to the general population than in single-center studies. The strengths of this study are the large sample size obtained from the SEER database, which contains a wide range of information on the neoadjuvant and adjuvant therapies to be analyzed and compared, and the application of PSM to reduce the effect of confounding factors, which increases the persuasiveness of this study.

However, our study has some unavoidable limitations. First, our study should have included information on the order of chemotherapy. Although all included patients took chemotherapy, neoadjuvant and adjuvant chemotherapies may have some bias in our group. Second, the use of different chemotherapeutic agents is one of the critical factors that affects a long-term prognosis. Finally, we did not differentiate the modality and dose of radiotherapy, which is also an essential confounding factor affecting prognosis. As our findings may provide some lessons for clinical personalized treatment, further validation by multi-center and large sample-size clinical trials is still needed.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there is no conflict of interest.

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