Original Article

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The Results and Outcomes of Rectal Cancer Treatment in the Era of Adjuvant Chemoradiation

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Abstract

Background: Colorectal cancer causes many deaths worldwide, with rectal cancer being responsible for a third of these mortalities. Surgical mesorectal excision along with preoperative neoadjuvant chemoradiotherapy is known as the standard treatment for rectal cancer. However, inaccurate preoperative staging is a main concern as it leads to a large number of patients not being treated with neoadjuvant therapy. Selection of the best treatment approach for these patients is controversial. Although some studies indicate significantly higher survival in patients who had received postoperative adjuvant chemoradiation compared with patients who had been treated with surgery alone, other studies have not found such results. Due to these contradictory findings, this study was designed to further evaluate the survival outcomes in rectal cancer patients who had received adjuvant chemoradiotherapy without neoadjuvant therapy.
Methods: Totally, 197 rectal cancer patients who had received adjuvant chemoradiation were included in this study. The demographic and clinico-pathological characteristics of the patients were evaluated by statistical analysis.
Results: Based on the univariate cox regression, poor disease free survival (DFS) was significantly associated with male sex and T3 stage. Poor overall survival (OS) was also associated with stage II/III, T3/T4, NI/NII, grade II/III, positive node number (>3), perineural invasion, lymphovascular invasion, and margin involvement. According to the multivariate cox regression, independent predictive factors for DFS were T3 and T4 stage; predictors for OS were T3/T4 stage, grade II/III, and lymphovascular invasion.
Conclusion: Taken together, the obtained results indicate that combined adjuvant chemoradiation contributes to improve survival outcomes in rectal cancer patients who do not receive neoadjuvant therapy.

Keywords: Rectal cancer, Adjuvant chemoradiation, Overall survival, Disease free survival

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Introduction

One of the most common causes of death worldwide is colorectal cancer. The rectum is involved in about one-third of all colorectal cancers. Cancerous lesions located within 12 cm of the anal verge are known as rectal cancer (1). Total mesorectal excision along with neoadjuvant (preoperative) chemoradiotherapy is the standard treatment for rectal cancer. However, due to inaccurate preoperative staging, a significant number of patients do not receive neoadjuvant therapy (2, 3). It has been estimated that in the USA, only about 55 % of patients with rectal cancer receive neoadjuvant therapy. Therefore, selection of the best treatment strategy for a significant population of patients without neoadjuvant therapy is questionable (4-6). According to the 2019 National Comprehensive Cancer Network (NCCN) recommendations, the best treatment for patients with stage II or III rectal cancer who do not receive neoadjuvant therapy is adjuvant chemoradiotherapy (7). However, according to the ESMO 2017 recommendations, adjuvant chemoradiotherapy should be applied only for patients with adverse histopathologic features, including a positive margin, perforation, T4b disease, or N1c disease (8). Some studies have indicated significantly better survival for patients with adjuvant therapy compared with patients with surgery alone (9); however, other studies found no such results (10, 11). Considering these contradictory results, the goal of this study was to assess the clinical features and survival outcomes in rectal cancer patients who had received adjuvant chemoradiotherapy without neoadjuvant therapy in Namazi Hospital of Shiraz University of Medical Sciences. These findings may be helpful for better evaluation of the adjuvant therapy efficacy for rectal cancer treatment.

Methods and Materials

Study Design and Data Collection

This study was a retrospective analysis of data collected from patients with a definitive diagnosis of rectal cancer who had undergone surgery between 2005 to 2011 at Shahid Faghihi Hospital in Shiraz, Iran. All patients had received postoperative adjuvant concurrent chemoradiation followed by adjuvant chemotherapy with FOLFOX regimen, and had been followed up until 2017. Neoadjuvant radiotherapy or chemotherapy was considered as the exclusion criteria. Finally, data from 197 rectal cancer patients were included in this study. The demographic and clinico-pathological characteristics of the patients including, age, sex, tumor size, stage, T stage and N stage, tumor grade, dissected node number, positive node number, operation type, relapse, perineural invasion (PNI), lymphovascular invasion (LVI) and margin involvement were recorded and evaluated.

Statistical Analysis

Data analysis was undertaken using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). Kaplan-Meier method was applied for analysis of overall survival (OS) and disease-free survival (DFS). Identification of the independent predictive variables for survival was also performed using Cox regression analyses. *P* values less than 0.05 were considered as statistically significant.

Table 1: Baseline characteristics of Rectal Cancer Patients

Characteristics	Number of Patients (%)
Sex	
Male	118 (59.9)
Female	79 (40.1)
Age (Year)	
≤50	59 (29.9)
>50	138 (70.1)
Tumor size (cm)	
≤5	138 (70.1)
>5	59 (29.9)
Stage	
I	33 (16.8)
II	87 (44.2)
III	77 (39.1)
T stage	
T1	3 (1.5)
T2	43 (21.8)
T3	147 (74.7)
T4	4 (2)
N stage	
N0	118 (59.9)
N1	53 (26.9)
N2	26 (13.2)
Grade	
I	102 (51.8)
II	62 (31.5)
III	33 (16.8)
Dissected node number	
≤12	141 (71.6)
>12	56 (28.4)
Positive node number	
≤3	176 (89.3)
>3	21 (10.7)
Operation	
VLAR	15 (7.6)
LAR	88 (44.7)
APR	94 (47.7)
Relapse	
Negative	116 (58.9)
Positive	81 (41.1)
PNI	
Negative	143(72.6)
Positive	54 (27.4)
LVI	
Negative	120 (60.9)
Positive	77 (39.1)
Margin involvement	
Negative	182 (92.4)
Positive	15 (7.6)

LAR: Low Anterior Resection, APR: Abdominoperineal Resection, VLAR: Very Low Anterior Resection, PNI: Perineural Invasion, LVI: Lymphovascular Invasion

Results

All rectal cancer patients including 118 (59.9%) men and 79 (40.1%) women with a mean age of 57.4 (range, 18-80 years) were analyzed. After a median follow up of 70 (range, 5-136) months, 77 patients had died due to disease, one patient had died without disease, 4 patients were alive with disease, and 115 patients were alive without disease. Among 81 patients who were identified with relapse (41.1%), disease-free survivals (DFSs) were estimated at less than 12 months in 22 patients (11.2 %), 12-36 months in 48 patients (24.4 %), 36-60 months in 9 patients (4.5 %) and more than 60 months in 2 patients (1 %). Among all 197 patients, overall survival (OS) was estimated at less than 12 months in 7 patients (3.6%), 12-36 months in 59 patients (29.9%), 36-60 months in 17 patients (8.6%) and more than 60 months in 114 patients (57.9%). Baseline characteristics of patients are illustrated in Table 1. Most of the patients were older than 50 years (70.1%) and identified with T2 and T3 stage (96.5%), N0 stage (59.9%) and grade I (51.8%). No relapse, PNI, LVI and margin involvement were observed in most of the patients (58.9%, 72.6%, 60.9% and 92.4%, respectively). As shown in Table 2, univariate Cox regression was applied to evaluate the potential association between baseline characteristics, DFS and OS. In this regard, poor DFS was associated with male sex (P=0.04) as well as the T2 (P=0.002) and T3

Table 2: Univariate Cox Regression Analysis of Disease Free Survival and Overall Survival

Parameters	DFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Sex						
Female	1		0.04	1		0.93
Male	1.62	1.02-2.57		1.02	0.65-1.6	
Age			0.35			0.41
≤50	1			1		
>50	1.27	0.77-2.1		1.23	0.74-2.03	
Tumor size (cm)			0.87			0.52
≤5	1			1		
>5	1.04	0.64-1.7		0.85	0.52-1.4	
Stage						
I	1			1		
II	2.67	0.62-11.22	0.19	6.41	1.97-20.8	0.002
III	3.24	0.76-13.61	0.11	8.12	2.5-26.34	<0.0001
T Stage			0.03			<0.0001
T1, T2	1			1		
T3, T4	3.23	1.14-9.1		5.16	2.24-11.88	
N Stage			0.15			0.009
N0	1			1		
N1, N2	1.39	0.89-2.16		1.81	1.16-2.82	
Grade						
I	1			1		
II	0.86	0.5-1.44	0.57	2.8	1.65-4.76	<0.0001
III	1.2	0.66-2.21	0.54	3.5	1.9-6.38	<0.0001
Dissected node Number			0.6			0.06
≤12	1			1		
>12	0.86	0.5-1.5		0.59	0.34-1.03	
Positive node Number			0.33			<0.0001
≤3	1			1		
>3	1.31	0.76-2.28		3	1.75-5.18	
Operation						
VLAR	1			1		
APR	0.94	0.42-2.12	0.88	0.91	0.41-2.01	0.82
LAR	0.81	0.33-1.98	0.55	0.53	0.22-1.5	0.14
PNI			0.82			<0.0001
Negative	1			1		
Positive	1.05	0.67-1.66		2.43	1.55-3.82	
LVI			0.38			<0.0001
Negative	1			1		
Positive	1.23	0.77-1.97		3.1	0.2-0.5	
Margin involvement			0.1			0.03
Negative	1			1		
Positive	1.83	0.89-3.76		2.19	2-4.99	

DFS: Disease Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, LAR: Low Anterior Resection, APR: Abdominoperineal Resection, VLAR: Very Low Anterior Resection, PNI: Perineural Invasion, LVI: Lymphovascular Invasion

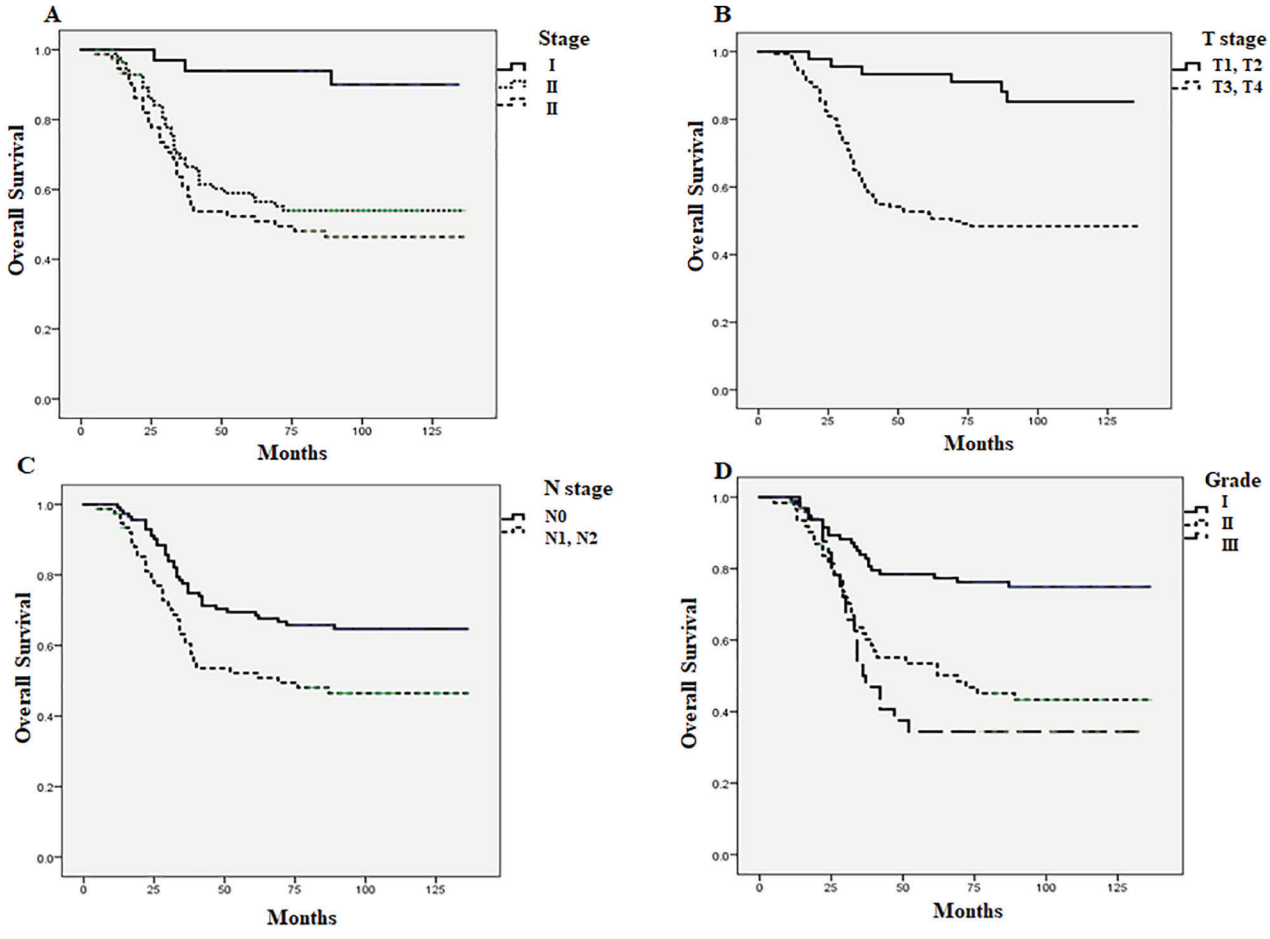

Figure 1: Kaplan-Meier survival curves for rectal cancer patients categorized based on stage (A), T stage (B), N stage (C) and grade (D) with P<0.05.

Table 3: Multivariate Cox Regression Analysis of Disease Free Survival and Overall Survival

Parameters	OS			DFS		
	HR	95% CI	P value	HR	95% CI	P value
T Stage						
T1, T2	1		0.006	1	1.14-9.09	0.03
T3, T4	3.37	1.41-8.04		3.23		
Grade						
I	1					
II	1.82	1.05-3.17	0.03	-	-	-
III	2.45	1.31-4.56	0.005			
LVI						
Negative	1		0.003	-	-	-
Positive	2.07	1.27-3.36				

OS: Overall Survival, DFS: Disease Free Survival, HR: Hazard Ratio, CI: Confidence Interval, LVI: Lymphovascular Invasion

(P≤0.0001) stages. Poor OS was also associated with stage II (P=0.002), stage III (P≤0.0001), T3 and T4 stages (P≤0.0001), NI and NII stages (P=0.009), grade II (P≤0.0001), grade III (P≤0.0001), positive node number (>3, P≤0.0001), PNI (P≤0.0001), LVI (P≤0.0001), and margin involvement (P=0.03) (Figures 1 and 2). Variable interactions that could affect survival were determined using multivariate Cox regression analysis. Based on these steps, independent predictive factors for DFS were T3/T4 stage (P=0.03); predictors for OS were T3/T4 stage (0.006), grade II (P=0.03), grade III (P=0.005) and LVI (P=0.003) (Table 3).

Discussion

In order to improve the survival rates of rectal cancer patients, a multidisciplinary team is essential to propose combination treatment strategies of radical surgery as well as pre- or post-operative radiotherapy and chemotherapy (12). More than 70% of patients with non-metastatic rectal cancer identified as T3

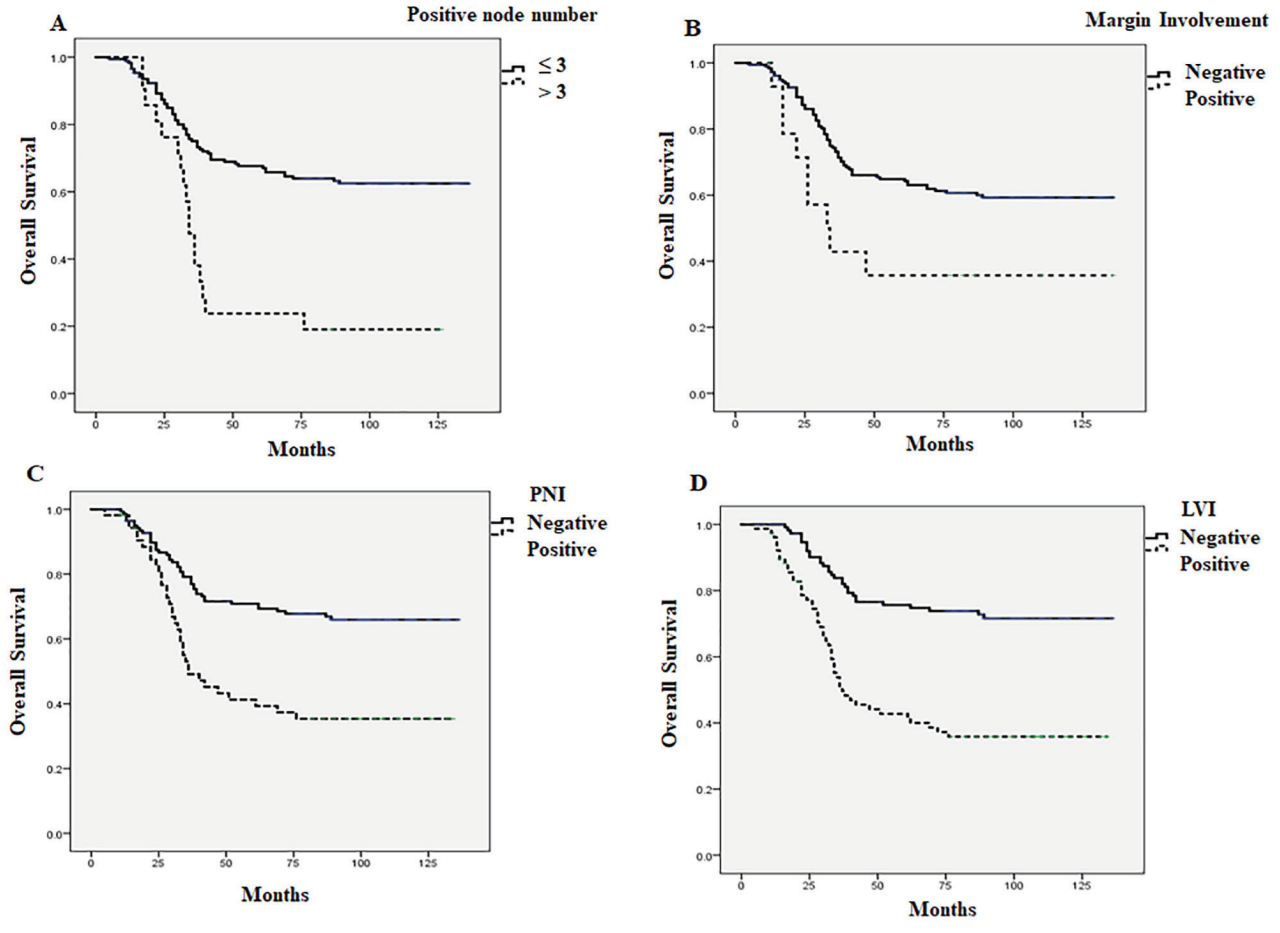

Figure 2: Kaplan-Meier survival curves for rectal cancer patients categorized based on positive node number (A), margin involvement (B), PNI (C) and LVI (D) with P<0.05.

or N positive disease. Therefore, the highest amount of focus should be on the application of aggressive treatment plans and achievement of cure for advanced rectal cancer (13).

Strong evidence indicates that preoperative neoadjuvant therapy is more effective than postoperative adjuvant therapy (1, 14). Therefore, the standard clinical practice for rectal cancer patients is radical surgery along with neoadjuvant chemoradiation (15-17). However, a large number of patients do not have access to magnetic resonance imaging (MRI) with rectal protocol; MRI also fails to differentiate between T2 and T3 tumors in some cases. For the detection of the mesorectal nodal metastasis, the overall accuracy, sensitivity and specificity of MRI are 95%, 80% and 98%, respectively (18). Therefore, inaccurate preoperative staging leads to a significant number of rectal cancer patients failing to receive neoadjuvant therapy (2, 3). The best strategy for the treatment of this patient population is controversial. Although most of the evidence shows that postoperative radiotherapy does not improve survival of rectal cancer patients, survival gain has been reported for combined radiotherapy and chemotherapy in some postoperative trials (19-21).

In a seminal trial, preoperative neoadjuvant and postoperative adjuvant chemoradiation were also compared in rectal cancer patients. Although, significantly better local control and lower systemic toxicity were observed in patients who received preoperative neoadjuvant chemoradiation, overall survival was similar in both treatment approaches (22). In this study, the survival outcomes in rectal cancer patients who had received postoperative adjuvant chemoradiotherapy were evaluated. Our findings are consistent with previous studies, indicating that combined adjuvant radiotherapy and chemotherapy are effective in rectal cancer patients (7, 19-22).

Conclusion

Taken together, our findings confirm that adjuvant radiotherapy combined with chemotherapy improves the survival of rectal cancer patients who fail to receive neoadjuvant therapy.

Conflict of Interests: None declared.

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