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The Survival Rate of Patients with Colorectal Cancer in Kerman Province of Iran from 2007 to 2016

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Abstract

Background: This paper presents the conditional relative survival rates of colorectal cancer (CRC) and associated prognostic factors in the Kerman province, the largest province in the south of Iran. Scince CRC is the fifth common cancer in this province, this study aimed to provide more detailed statistics on the survival rate of CRC patients.

Materials and Methods: This survival analysis study used the national population-based cancer registry data to estimate the survival rate in 1705 patients with CRC from 2007 to 2016. The Kaplan–Meier estimator and Log-rank test were used to plot survival curves and assess differences in survival rates. Univariate analysis and Cox proportional-hazards model were also used to determine association between CRC-related factors and patient survival.

Results: The 5-year survival rate for patients with CRC was 51.9%. This rate was significantly higher in the stage with localized lesions compared with those of regional and distant ($p<0.001$). The survival rate in patients undergoing surgical treatment was higher than that of patients receiving chemotherapy ($p<0.001$). Increased age, low tumor differentiation, the stage with distant tumors, and right-sided colon cancer (RCC) were associated with lower survival ($p<0.001$).

Conclusions: The tumor stage was significantly correlated with the survival rate of patients. Despite advances in the diagnosis and treatment of CRC in Iran and worldwide, the survival rate of patients in this study was low. Since many factors affect this rate, further studies are needed to identify its prognostic factors in Kerman.

Keywords: Colorectal Neoplasms, Survival Rate, Kaplan–Meier Estimate, Proportional Hazards Models, Confidence Interval (CI)

Introduction

Cancer is a major public health problem throughout the world. In recent years, it has become the second leading cause of death among chronic diseases in high-income countries (HICs) after cardiovascular disease; further, epidemiological evidence reveals a similar trend in low- and middle-income countries (LMICs) [1]. Of the long list of cancers, colorectal cancer (CRC) is among the most common worldwide [2]. CRC is the third common cancer in males after lung and prostate cancers and the second common cancer in females after breast cancer [3]. It is also the fourth and third leading cause of cancer deaths in

males and females globally, respectively [4]. In 2019 worldwide, CRC is also considered the second leading cause of cancer disability-adjusted life years (DALYs) [5].

Evidence suggests that incident cases of CRC are rising swiftly in LMICs due to the increased prevalence of changeable risk factors, including alcohol drinking, smoking, unhealthy eating behaviors, obesity, and sedentary lifestyle [1]. According to the latest statistics and epidemiological studies in Iran, CRC is the fourth common cancer in males and the second in females, as well as the fourth and third leading cause of cancer deaths in males and females, respectively [6].

Survival rates for CRC vary widely across the world [7]. Studies have shown that the survival rate in patients with CRC depends not only on the anatomical extent of the disease but also on many patient- and tumor-related factors [8]. Given the preventable nature of CRC, proper planning is essential to prevent and control this cancer [9]. Also, its timely diagnosis in the pre-symptomatic stage plays a vital role in improving the quality of life and survival rate in patients [10].

Kerman is the largest province of Iran located in the south. In this province, CRC is the fifth common cancer [11]. However, despite this relatively high prevalence, detailed statistics are not available on the survival rate in CRC patients in the province. Since the first principle in the prevention and control of CRC is to know its conditions at the local level, this study is carried out to examine the 5-year survival rate of CRC patients in Kerman Province. It is hoped that the current study results provide a basis for promoting CRC prevention and control programs in the province.

Materials and Methods

In this survival analysis study, data on all patients with CRC were collected using a checklist from four academic cancer registry centers in the provinces, including Kerman, Rafsanjan, Jiroft, and Bam. In the next step, extracted data for 1705 patients with a definite diagnosis of CRC, registered at those cancer registry centers, were examined from March 21, 2007, up to March 20, 2017, for their survival status. Mortality data of the patients, including the exact date and cause of death, were examined annually. Patients with uncertain death or survival status, as well as those who died from causes other than CRC (N=38), were excluded from further analyses. At the final stage, data, including age, gender, tumor location, degree of tumor differentiation, stage of the disease at the time of diagnosis, treatment modality (surgery/chemotherapy), and patient death, were used in the analysis.

Based on extracted data, the stage of the disease at diagnosis was classified as local (tumor confined to the primary site), regional (tumor expanded to adjacent tissues and/or to regional or distant lymph nodes), and distant (tumor spread to distant organs). Tumor location was divided into right-sided colon cancer (RCC), left-sided colon cancer (LCC), and rectal cancer (RECC). RCC includes parts from the cecum to the transverse colon. LCC comprises the splenic flexure to the sigmoid. Finally, RECC consists of the rectum, rectosigmoid, anus, anal canal, and anorectal area. The degree of tumor differentiation was classified as low-grade (well- and moderately-differentiated) and high-grade (poorly differentiated /anaplastic) [9].

For analyzing the data, the chi-square test was used to determine the relationship of each factor with the patient status (death, survival). The Kaplan–Meier estimator was used to estimate the survival rate and plot its curves. The Log-rank test was utilized to assess differences in the survival rate among the groups studied. Given that the tumor staging system is the proper guide for predicting disease progression and making decisions about therapeutic strategies in patients with cancer [12], the relationship of each tumor-specific variable with patient survival was assessed based on the diagnostic stage of the disease. Finally, univariate analysis and Cox proportional-hazards model were used to determine relationships between CRC-related factors and patient survival. Data were analyzed using standardized methods in SAS-9.1 software. The significance level was set at $P<0.05$.

Ethical approval was obtained from the Rafsanjan University of Medical Sciences Ethics Committee (No. IR.RUMS.REC.1396.189).

Results

In this study, 929 patients (54.5%) were male and 776 (45.5%) female. The mean and standard deviation of patients' age was 60.71±15.39 years (range: 10-100 years). Of them, 916 (53.7%) died, and 789 (46.3%) were still alive by the end of this study. Table 1 provides the frequency distribution of patients' characteristics based on their status (dead, alive).

Table 1. Frequency distribution of the characteristics of patients with CRC based on status (dead, alive) from 2007 to 2016

Variable		Dead (n=916)	Alive (n=789)	All (n=1705)	χ^2	df	P-value
Stage	Local	283(30.9)	549(69.6)	832(48.8)	312.077	2	**<0.001**
	Regional	444(48.5)	233(29.5)	677(39.7)			
	Distant	189(20.6)	7(0.9)	196(11.5)			
Tumor location	Right colon	330(36.0)	198(25.1)	528(31.0)	90.096	2	**<0.001**
	Left colon	193(21.1)	336(42.6)	529(31.0)			
	Rectal	393(42.9)	255(32.3)	648(38.0)			
Grade	Low grade	373(48.1)	632(82.2)	1005(58.9)	279.870	2	**<0.001**
	High grade	403(51.9)	137(17.8)	540(31.7)			
	Unknown	140(15.3)	20(2.5)	160(9.4)			
Treatment	Surgery	458(50.0)	614(77.8)	1072(62.9)	140.544	1	**<0.001**
	Chemotherapy	458(50.0)	175(22.2)	633(37.1)			
Age	45>	74(8.1)	170(21.5)	244(14.3)	112.787	4	**<0.001**
	45-54	142(15.5)	159(20.2)	301(17.7)			
	55-64	218(23.8)	207(26.2)	425(24.9)			
	65-74	239(26.1)	160(20.3)	399(23.4)			
	75≤	243(26.5)	93(11.8)	336(19.7)			
Sex	Male	505(55.1)	424(53.7)	929(54.5)	0.331	1	0.565
	Female	411(44.9)	365(46.3)	776(45.5)			

According to the chi-square test, diagnostic stage, tumor location, tumor grade, treatment type, and the age group showed a significant relationship with patient status (dead, alive) ($p<0.001$).

Survival rates: In this study, the median 5-year survival for patients with CRC was 61.0 months, and the overall survival rate was 51.9%. Table 2 presents 0- to 5-year survival rates based on tumor stage, tumor grade, tumor location, treatment type, age, and sex.

Table 2. Five-year survival (%) by prognostic factors for patients with colorectal cancer

Variable		12 months	24 months	36 months	48 months	60 months	Median Survival (month)	P-value
Stage	Local	99.3	95.7	90.0	82.8	73.9	65.0	**<.001**
	Regional	95.1	75.1	62.0	49.3	41.9	48.0	
	Distant	47.3	24.4	14.9	9.6	3.7	12.0	
Grade	Low	99.2	92.6	85.4	76.9	69.0	63.0	**<.001**
	High	75.1	51.1	37.8	27.8	20.2	25.0	
Tumor location	RCC	86.9	75.0	65.0	57.0	49.1	60.0	**<.001**
	LCC	94.9	85.0	76.9	68.9	62.2	62.0	
	RECC	92.2	76.8	67.2	55.7	46.4	51.0	
Treatment	Surgery	93.9	86.7	80.9	74.0	66.9	63.0	**<.001**
	Chemotherapy	87.3	66.0	51.5	38.5	28.8	37.0	
Age	<45	96.4	93.8	91.5	89.6	84.4	87.0	**<.001**
	45-54	96.2	92.4	88.9	82.5	73.6	62.0	
	55-64	94.7	87.3	81.4	70.2	61.2	61.0	
	65-74	91.1	74.3	61.9	50.3	38.1	49.0	
	≥75	80.4	42.9	29.4	16.1	10.9	24.0	
Sex	Male	90.0	76.6	67.3	58.4	50.7	61.0	.054
	Female	93.1	81.5	72.3	62.3	53.3	61.0	

Survival rate based on tumor stage: The survival rate in patients with CRC was evaluated using the tumor staging system. The 5-year survival rate in the local, regional, and distant stages was 73.9%, 41.9%, and 3.7%, respectively. Comparison of survival rates showed a significant difference between stages of the disease ($p<0.001$) (Fig. 1), such that the survival rate was significantly higher in the local stage than that in regional and distant stages ($p<0.001$). Also, the survival rate in the regional stage was significantly higher than that in the distant stage ($p<0.001$).

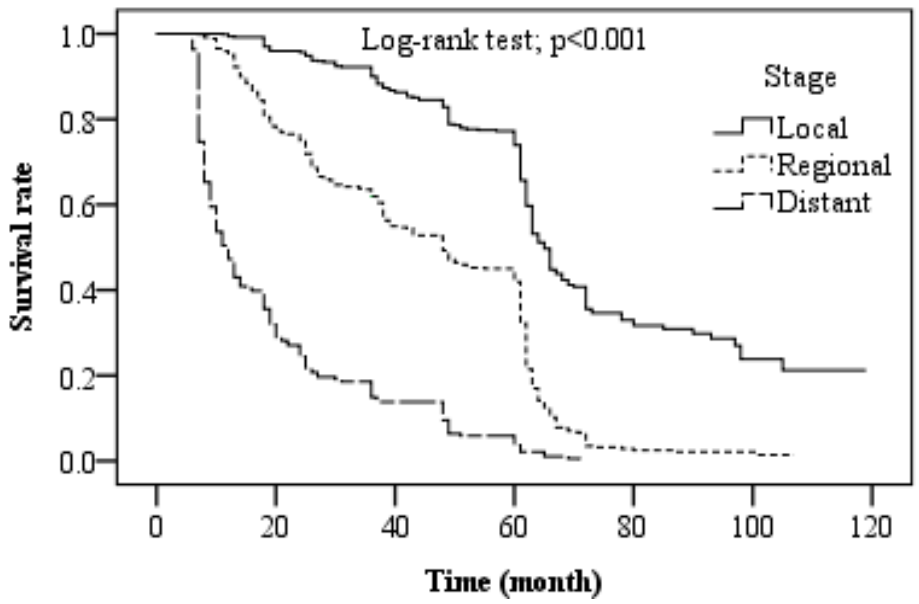

Fig. 1. Five-year survival rate (%) by stages (Local, Regional, Distant)

Survival rate based on tumor grade: The Log-rank test showed a statistically significant difference in the survival rate in patients during the follow-up period based on the tumor grade (p<0.001). Survival was higher in low-grade tumors than that in high-grade ones. Survival was then evaluated for tumor grade based on defined clinical stages. Survival curves in all three stages of CRC showed higher survival in low-grade than that in high-grade tumors (Fig. 2).

Survival rate based on tumor location: Survival curves showed a significant correlation between the survival rate and tumor location (Fig. 2). The survival rate of patients with LCC showed a statistically significant difference from those of cases with RCC and RECC (p<0.001). Generally, LCC had a higher survival rate than RCC and RECC (p<0.001). There was no statistical difference between the survival rates of RCC and RECC. In the next step, the survival rate in patients was estimated based on tumor location in terms of the clinical stage, where survival curves at each stage showed different trends. For instance, in the local stage, the survival rate in LCC was higher than that in RCC (p<0.001). Also, the survival rate in RCC was significantly higher than that in RECC (p<0.001).

Survival rate based on the treatment type: Survival curves showed a significant correlation between the survival rate in patients with CRC and their treatment type (Fig. 2). There was a statistically significant difference in the survival rate between patients treated by surgery and those treated by chemotherapy (p<0.001); those treated by surgery had a higher survival rate. In the next step, the survival rate of patients was estimated based on the treatment type in terms of the clinical stage, where survival curves at different stages showed different trends. The survival rate in the distant stage was significantly higher in patients undergoing chemotherapy than that in those undergoing surgery (p<0.001).

Survival rate based on age groups and sex: Patients in this study were divided into five age groups of <45, 45-54, 55-64, 65-74, and ≥75 years. Survival curves by age groups showed a significant difference in 5-year survival rates. The highest survival rate was that of the <45 years age group, which decreased by age, and the lowest survival rate was that of the age group ≥75 years (p<0.001). In survival rate evaluation based on sex, survival curves did not show a significant difference (p=0.054). Fig. 3 shows the survival curves of age and sex variables.

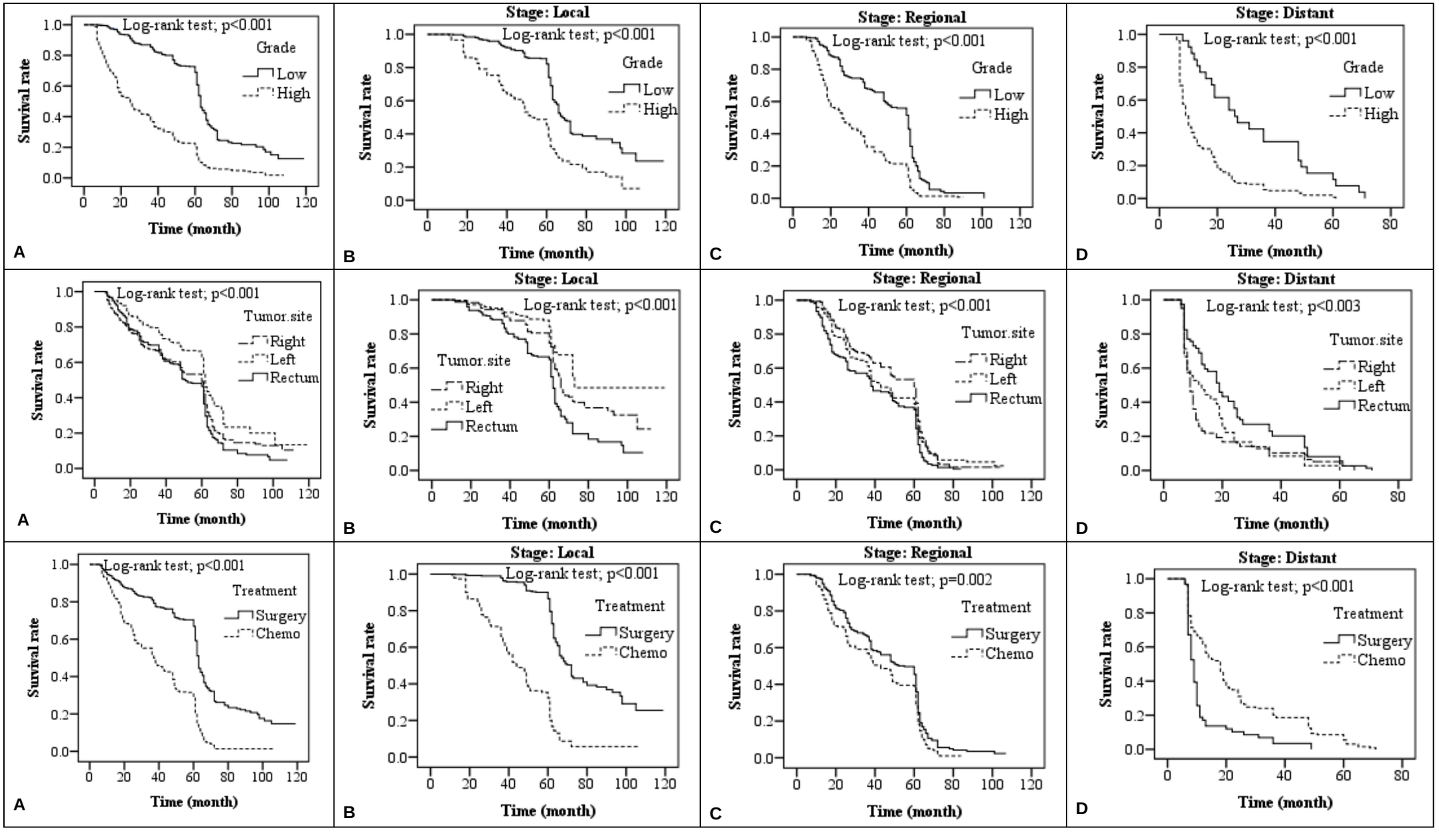

Fig. 2. Kaplan-Meier survival: (A) Overall survival by grade, tumor site, treatment; (B) Survival rate by local stage; (C) Survival rate by regional stage; (D) Survival rate by distant stage

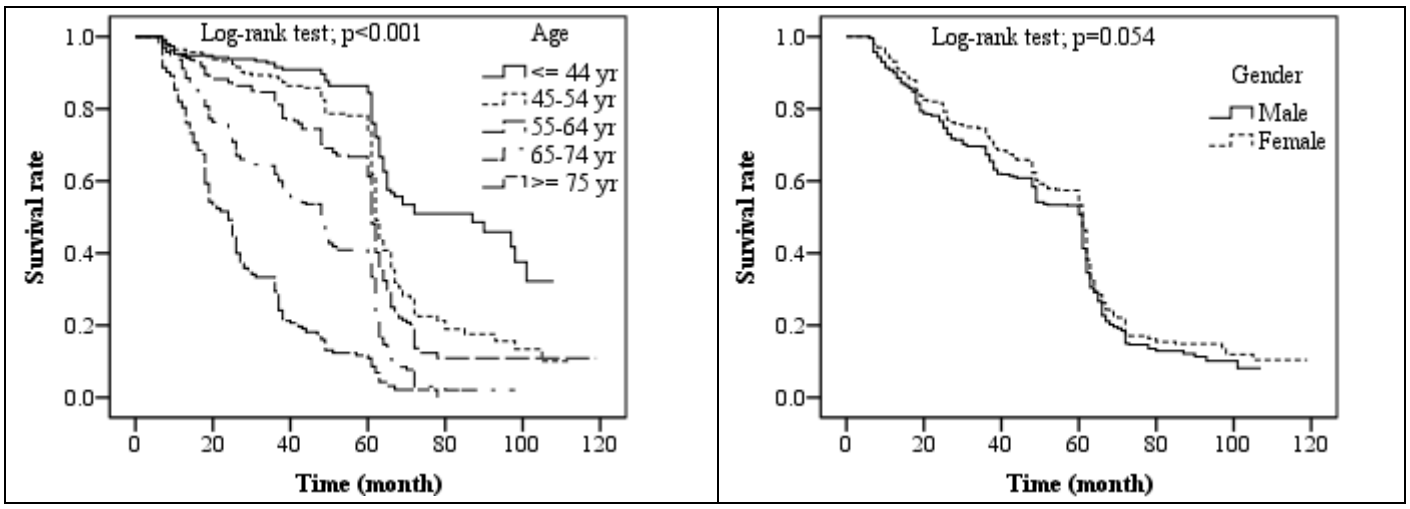

Fig. 3. Kaplan-Meier survival rate by age and sex of patients with colorectal cancer

Finally, the correlation of each variable with the survival rate of CRC patients was evaluated through Cox proportional hazards regression model (Table 3). In the Adjusted Regression Model, the risk increased significantly with age. The risk of death in the age group of ≥75 years was 7.660 times higher than that in the age group of <45 years (p<0.0001). Moreover, the risk of death in female patients with CRC was lower than that in males (Hazard Ratio; HR=0.689, p<0.0001). The risk of death in patients with high tumor grades was 3.390 times higher than that in patients with low tumor grades (p<0.0001). Type of treatment, after adjustments in the model, showed no significant difference in the risk level; however, the survival rate in patients undergoing chemotherapy was lower than that in patients treated by surgery (HR = 1.081, p= 0.3637).

While the risk was not significantly different for different tumor locations, there was a higher survival rate in patients with tumors in LCC (HR = 0.849, p= 0.1053). Furthermore, based on the tumor stage, the risk was 3.147 times higher in the regional stage and 9.412 times higher in the distant stage than that in the local stage (p<0.0001).

Table 3. Multivariate analysis of prognostic factors influencing survival of colorectal cancer patients in Cox regression analysis

Variable		Unadjusted hazard ratio	Unadjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio	Adjusted hazard ratio (95% CI)	P-value
Age	45>	1(Ref)	-	-	1(Ref)	-	-
	45-54	1.936	1.461-2.565	<.0001	1.808	1.250-2.613	**.0016**
	55-64	2.615	2.005-3.411	<.0001	2.212	1.514-3.210	**<.0001**
	65-74	4.668	3.579-6.088	<.0001	3.760	2.484-5.690	**<.0001**
	75≤	11.327	8.621-14.881	<.0001	7.660	4.854-12.087	**<.0001**
Sex	Male	1(Ref)	-	-	1(Ref)	-	-
	Female	0.880	0.772-1.003	.0552	0.689	0.570-0.835	**.0001**
Grade	Low grade	1(Ref)	-	-	1(Ref)	-	-
	High grade	3.877	3.360-4.474	<.0001	3.390	2.878-3.994	**<.0001**
Treatment	Surgery	1(Ref)	-	-	1(Ref)	-	-
	Chemotherapy	2.912	2.546-3.330	<.0001	1.081	0.914-1.277	.3637
Tumor location	RCC	1(Ref)	-	-	1(Ref)	-	-
	LCC	0.658	0.573-0.820	<.0001	0.849	0.697-1.035	.1053
	RECC	1.138	0.982-1.319	.0848	1.120	0.944-1.330	.1942
	Local	1(Ref)	-	-	1(Ref)	-	-
Stage	Regional	3.142	2.700-3.656	<.0001	3.147	2.637-3.756	**<.0001**
	Distant	12.955	10.688-15.734	<.0001	9.412	7.387-11.993	**<.0001**

After determining predictor variables of death in patients with CRC, the interaction between these variables was investigated in the Cox proportional hazards regression model. Statistical analysis results showed that the interaction between predictor variable pairs was not statistically significant. Therefore, only the main effect of predictor variables of death remained in the Cox proportional hazards model, and all interactions between the variable pairs were excluded from the regression model. Time-independent covariates of death in patients with CRC were also evaluated. Statistical analysis showed none of the predictor variables to be time-dependent.

Discussion

This study evaluated the effect of factors potentially associated with the survival rate in CRC patients. The effects of specific variables, including clinical stage, tumor grade, tumor location, and treatment type, on survival rate were evaluated. Given the crucial role of the tumor stage in predicting patient survival, selecting treatment strategies, and evaluating control programs, the effect of each specific factor on patient survival was evaluated separately based on that [13].

The results showed a 5-years survival rate of 51.9% in CRC. Various studies have been conducted worldwide to estimate cancer survival rates. In 2019, WHO reported the results of the global surveillance of cancer survival rates based on the CONCORD3 program [14]. According to these results, CRC survival varied widely in different parts of the world. The highest 5-year survival rate was about 70% in Israel, Jordan, South Korea, and Australia, while the survival was reported less than 50% in Ecuador, Thailand, Russia, and India.

Studies have shown that the CRC survival rate is affected by many factors dependent on patient and tumor characteristics [15]. Differences in CRC survival rates in different countries can be due to differences in access to medical attention and delays in diagnosis and treatment, as well as environmental or lifestyle factors [16]. Also, geographical conditions, as well as cultural, economic, and social factors, influence the distribution of the disease and differences in survival rates [17].

In the present study, the prevalence of CRC was higher in males than females. It should be noted that most studies on the CRC survival rate have shown a higher prevalence in males [18,19]. The mean age of patients in this study was 60.71±15.39 years, and 14.3% were younger than 40 years at the time of diagnosis. In HICs, only 2%- 8% of CRC cases occurred in people under the age of 40 [20,21]. However, the incidence of CRC in the young population is increasing in most LMICs [22]. In addition to numerous indicators related to the development level of the country, environmental factors, and changes in effective behavioral patterns, another major reason for the high incidence rate of CRC among young people in LMICs, including Iran, can be their young age structure [23]. The older age structure in Western countries has made CRC a disease of old age.

This study also evaluated the relationship between tumor-related characteristics and the survival rate. The first specific factor examined was the clinical stage and its effect on survival. According to the results and consistent with previous studies, the clinical stage of the disease significantly affected the 5-year survival rate [24]. Significant changes in 5-year survival rates were observed among different stages of the disease.

Another specific variable was tumor grade. The effect of this factor on the survival rate of patients with CRC was studied. According to the findings, there was a significant difference between the survival rate of patients with high-grade tumors and those with low-grade tumors. These differences were evident at all stages of the disease, being confirmed by numerous studies [25].

The relationship between tumor location and survival rate was also evaluated, which showed the overall survival in patients with LCC to be better than that in those with RCC and RECC [26]. After examining the effect of tumor location on survival, different behaviors were observed in regional and distant stages. Patients with RCC in the regional stage and those with RECC in the distant stage showed higher survival rates.

Patients undergoing surgery had a better survival rate than patients undergoing chemotherapy, except for those in the distant stage [27]. This difference can be explained by the fact that the type of treatment is chosen based on the disease stage in CRC. Chemotherapy is the treatment of choice in the distant stage, in which patients have clearly a lower survival rate due to the disease spread, while surgery is the treatment of choice for the local stage and many cases in the regional stage. In these two stages, especially that of local, patients have a higher survival rate. Another reason is the influence of age on treatment choice. Younger patients are more suitable candidates for surgical treatment compared to others, while surgery is selected for older patients cautiously [28]. In line with previous studies, the present study showed that the survival rate significantly decreased in all diagnostic stages by age [29,30].

In this study, females had a higher survival rate than males, and males had a higher risk of dying from colon and rectal cancer than females. This finding is supported by many studies that have evaluated the effect of sex on the CRC survival rate [31]. It can be attributed to the social support and greater acceptance of health-centered programs in females and the negative attitude toward screening programs and less attention to medical advice in males. Other factors may also influence this difference, thus requiring further studies.

In this study, specific and diagnostic data and demographic characteristics of patients with CRC were used as the information source to estimate

survival rates. It is worth noting that even though this study was based on a large population, it had potential limitations. First, despite careful review of the measurements at cancer registry centers to prevent inaccurate data recording, as well as data re-evaluation at the Central Cancer Registry for accuracy and quality, a few cases of data miscoding were observed. These discrepancies were largely resolved by obtaining reports from the diagnosis and pathology centers where the patients were registered. Second, studied cancer registration systems contained treatment information on surgery and chemotherapy, but adjuvant treatment information was not available.
The results can also be used to devise effective strategies for CRC screening programs and develop effective educational programs to raise public awareness about disease symptoms and the importance of participating in screening programs for early detection.

Conclusion

Using population-based cancer registry information, we analyzed data from patients with CRC and estimated their survival rates according to the clinical stage. The overall 5-years survival rate was 51.9%. The tumor stage at diagnosis, as the most important determinant of survival, was significantly correlated with the survival rate of patients; this rate was significantly higher in the local stage patients than in others. Consistent with our findings, studies on CRC survival rates worldwide have reported a statistically significant relationship between the tumor stage and the survival rate. In the present study, increased age, low tumor differentiation, distant stage of the tumor, and RCC were associated with lower survival. CRC is preventable cancer, and patients' survival rate increases significantly with the diagnosis of the tumor in an early stage. Despite advances in the diagnosis and treatment of CRC in Iran and worldwide, the 5-year survival rate of patients in this study was lower than that of HICs. Since many factors affect this rate, further studies are required to identify prognostic factors of survival rate. The implementation of targeted screening strategies is also essential for the timely diagnosis and treatment of patients to improve colorectal cancer survival rates in the Iranian population.

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Conflict of interest: None declared.

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