Survival Rate of Colorectal Cancer and Its Effective Factors in Iran

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Abstract- Colorectal cancer is one of the most common cancers in Iran. Regarding the prevalence of this cancer and its mortality and morbidity, in this study, 5 Year Survival Rate and its Effective Factors of patients with colorectal cancer were investigated. This study was conducted using the retrospective cohort method. All patients diagnosed with colorectal cancer in Hamadan Imam Khomeini Clinic of Hematology and Oncology and Mahdieh Oncology Center between 2006 and 2011 were studied. Data were extracted from the patients' medical records, and to obtain extra information about them, telephone calls were made. The data were analyzed by SPPS version 16, and the assessment of survival rates was conducted using Kaplan-Meier methods and Cox regression method. A total number of 108 patients with colorectal cancer were studied. The status of 74 patients was determined at the end of the study by making follow-up phone calls. The one, two, three, four, and five survival rates were 77, 66, 50, 45, and 42%, respectively. The median overall survival was 46.8 months (1.3-135.6 months). Cox regression analysis showed that Metastatic tumor (P=0.001), lymphatic involvement (P=0.043), and is associated with underlying disease (P=0.025) was accompanied by increased risk. Multivariate cox regression test showed that metastasis was associated with an increase in the risk of death significantly (HR=2.83, P=0.013). According to the findings of the study, early screening is recommended for people with greater risk to increase the survival rate.

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Keywords: Survival rate; Colorectal cancer; Iran; Effective factors

Introduction

Colorectal cancer is the third and second most common cancer in terms of incidence and mortality in the world, respectively, accounting for 1.8 million new cancer cases and 881000 cancer deaths in 2018 (1).

Despite the increasing rate of cancer among economically transitioning countries (Eastern European countries, most parts of Asia, and some South American countries), incidence rates in the United States generally have been declining (2).

Age-standardized incidence rates are about 3 to 4 times higher in high/very high HDI versus low/medium HDI countries. However, there is less variation in mortality rates because of more fatality rates in lower HDI settings. Overall, the colorectal cancer incidence rate tends to rise with the increase in HDI (3-5).

Over the last two decades, trends of colorectal cancer in high-income countries have varied as reduction (United States), stabilization (France and Australia), or increasing (Finland, Norway, Spain) have all been witnessed (6). The reason for the decrease is the screening of people aged 50 years and older, as well as the removal of the precancerous lesion. There is wide variation among different geographic areas due to different environmental and dietary factors. Of course, genetic susceptibility is necessary for getting the process of cancer started (6).

However, CRC incidence rates are higher among males than females in different geographical areas (6,7). But male to female incidence rate ratio (MF IRR) is associated with anatomic sub sites of involvement and age. The ratio increases progressively across the colon

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from proximal to distal (7).

CRC incidence rate is not significantly different in people younger than 40 regardless of sex, but it is almost 1.5 times higher in men than women aged 55 to 74 years (8).

MF IRRs increase with age most rapidly for distal colon cancers; from <1.0 at ages <50 years to 1.4-1.9 at older ages. For rectal cancer, this increase is more than other sites (1 to 2). MF IRR for proximal cancer is not related to age and is consistently <1.5. The ratio is not associated to race, either (7). Reasons for higher rates in men may be differences in exposure to dietary- and lifestyle-related risk factors for CRC and sex hormones, complex interaction between environmental factors, and sex hormones, as well as more adherence to CRC screening in women (7,8).

Epidemiologic transition, reductions in physical activity and increases in sedentary behaviors, shifted dietary patterns towards increased intake of fat, sugar, and junk food have led to a rise in CRC in low- and middle-income countries (9-11).

Iran is situated in Southwest Asia and categorized as a high human development index (HDI=0.774). In 2012, ASR-ASMR of CRC were reported 10.5- 6.3 and 11.6-6.9 per 100000 among Iranian women and men, respectively. Colorectal cancer is the third (N=8131) highest 5-year prevalence in men and second (N=7298) in women. CRC is the fifth leading cause of cancer death in men (7.5%) and fourth in women (8.4%) (12).

Several studies have been done to measure the survival rate of colorectal cancer worldwide. In Asia, the overall rate of recovery has clearly not improved in the past decade, and the 5-year survival rate has remained around 60%. Survival duration has increased in recent years, but mortality rate is still high, and despite numerous factors predicting the survival rate after diagnosis, life expectancy has not changed a lot. It seems that the most important predictors of survival are those factors associated with the early detection of cancer (13).

The survival of colorectal cancer is associated with the stage of disease at the time of diagnosis, cultural beliefs, financial support (14), race and ethnicity (mortality in black people is 50% higher than whites which is due to the differences in socioeconomic status) (15), availability of screening services, timely appropriate treatment, and comorbidities (16).

In the United States, 5-year survival rate for local, regional, and metastatic tumors was reported to be 91.1, 71.1, and 13.3, respectively. Although colon cancer has a higher stage-specific survival rate than rectal cancer (8), the 5-year survival rate of rectal cancer is higher than colon cancer due to the further diagnosis rates of rectal cancer in the localized stage compared with colon cancer.

With a 5-year survival rate of about 90%, 39.5% of colon and rectal cancers are diagnosed in the local stage; with a survival rate of 70%, 36% in the regional stage; with a survival rate of 13%, 20% in the metastatic stage; and with a survival rate of 34.5%, 5% are diagnosed unstaged (17).

Age is an effective factor in the survival rate in the distal and rectal colon tumors so that the 5-year survival rate in patients under 65 is higher than older adults (68.9% versus 62%) (15). The highest mortality rate has been reported at the age of 75 to 84 years at 26.6%. The mortality rate for patients under 20 years old is zero percent, 20 to 34 years 0.7 percent, 35 to 44 years 2.5 percent, 45 to 54 years 9.3 percent, 55 to 64 years 17.9 percent, 65 to 74 years 22.1 percent, and higher than 84 years of age 21 percent. The median age of death is 73 (18).

In a study conducted in the Iranian population, the mortality rate in men and women was 96.9 and 83 per 100,000 people, respectively. After the diagnosis of cancer, 75, 50, and 25 percent of patients had survival rates of 2.72, 5.84, and more than 13 years, respectively (19). In several studies conducted in Iran, the 5-year survival rate is reported to be 27.2, 31, 46.7, and 56.8 (20-23).

In another study in Iran, the one- and five-year survival rate of colorectal cancer was 88% and 45% in women, and 86% and 39% in men. Totally, the 5-year survival rate is 41%. The worst survival rate has been reported in patients under 20 and over 80 years old. The median survival time in Iran is reported to be 3.5 years on average (3.8 to 3.2 years) (24).

In several studies conducted in Iran, the factors affecting survival rate included a race, marital status, family history of cancer and smoking, tumor characteristics including tumor grade and histological type of the tumor, stage of disease, and metastasis (13,20).

According to the importance of calculating the survival rate of colorectal cancer and the different survival rates observed in different treatment centers, this study aimed to determine survival rates and their effective factors in patients with colorectal cancer in the province of Hamadan.

Materials and Methods

This descriptive-analytic study is a retrospective cohort study that evaluated documents of all patients with

pathologic diagnosis of colorectal cancer who were admitted in the specialized center of hematology and oncology, as well as radiotherapy, of Hamadan city during the period of 2007 to 2011.

Tumors of the ascending, transverse, and descending colon, sigmoid, and rectum with confirmation of pathologic diagnosis were considered as colorectal cancer.

Under-studied variables, including gender, age, time of diagnosis, education, location of residence, comorbidities, smoking, grade, stage, history of malignancy in family, anatomical location of the tumor, tumor size, number of tumors, metastasis, location of metastasis, pathology of the tumor, lymph node involvement, and type of disease treatment, were collected based on patient records.

Telephone numbers and addresses of patients were extracted from their records. Afterward, full explanations about the research were given via phone calls. Observing the ethical points and respecting patient's family, after obtaining oral consent, the patients' status in terms of death or survival- and in case of death, the exact time and cause- were asked.

In this study, survival time was considered from the time of diagnosis to the time of death or the end of follow-up, and patients who could not be contacted or those who were alive were considered censored.

Patients who had another malignancy along with colorectal cancer or who were not satisfied with the treatment were excluded from the study. Data analysis was performed using SPSS software. Kaplan-Meier test was used to determine the survival rate. Cox regression test was applied to assess the affective survival factors, and log-rank was used to evaluate the differences in survival of different groups. The significance level was considered to be 5% in all cases. The calculation of 1 to 5 years of survival was investigated in three cases: 1) Evaluation of the survival of all patients (108 patients), considering the best situation for patients who have not responded to the follow-up; 2) Evaluation of the survival of all patients (108 patients) considering the worst situation for patients who have not responded to the follow-up; 3) Survival assessment of patients who have responded to the follow-up (74 patients). The risk-based analysis was performed based on various factors in 74 patients, and the survival difference was evaluated.

Results

In this study, the records of 108 patients with colorectal cancer were evaluated following the objectives of the study. At the end of the study, in July 2016, among these 108 cases, the status of 74 (68.5%) patients were specified, and the status of 34 (31.5%) patients remained unspecified (because of unresponsiveness, change of location, or not having contact information). Of the 74 patients whose status was specified to the researcher at the end of the study, 44 patients (59.5%) died (expected event), and 30 patients (40.5%) survived to the end of the study. The mean age of the patients at the time of diagnosis was 55.1±14.4 years with the range of 15 to 83-year-old. The description of the sample is shown in Tables 1 and 2.

Table 1. Describing the basic variables of patients participating in the study

Variable		Frequency	Percent
Sex	Female	57	52.8
	Male	51	47.2
Residence	Urban	80	74.1
	Rural	28	25.9
Education	Low literacy, illiterate	68	63.0
	Diploma and higher	11	10.2
	Unknown	29	26.8
Smoking	No	51	47.2
	Yes	29	26.9
	Unknown	28	25.9
Family background	No	57	52.8
	Yes	16	14.8
	Unknown	35	32.4
Family background (n=16) Positive	Grade 1	12	75.0
	Grade 2	3	18.7
	Other	1	6.3
Underlying disease	No	33	30.6
	Yes	43	39.8
	Unknown	32	29.6

Table 2. Tumor characteristics in subjects in the study (108 patients)

Variable		Frequency
Location of the tumor	Right colon	16 (14.8)
	Left colon	92 (85.2)
Differentiation	Well	52 (48.1)
	Moderate	50 (46.3)
	Poor	6 (5.6)
Metastasis	No	72 (66.7)
	Yes	36 (33.3)
Stage	One	6 (5.6)
	Two	55 (50.9)
	Three	10 (9.3)
	Four	37 (34.2)
Size	<5	64 (59.3)
	>=5	44 (40.7)
Lymph node	No	31 (28.7)
	Yes	77 (71.3)
Treatment	Chemotherapy and Surgery	48 (44.4)
	Chemotherapy + Radiotherapy and Surgery	56 (51.8)
	Others	4 (3.8)
Age category	Less than 65-year-old	75 (69.4)
	More than 65-year-old	33 (30.6)

One, two, three, four, and five-year survival rates were 77, 66, 50, 45, and 42 percent, respectively.

The worst possible situation for the 34 people whom the researcher did not know about would be dead before the end of the study. With this assumption, the one, two, three, four, and five-year survival rates in the participants would be 53, 45, 34, 31, and 29 percent, respectively.

On the other hand, the best possible situation for those whose information was not known to the researcher would be the non-occurrence of death. With this assumption, the one, two, three, four, and five-year survival rates in the participants would be 84, 76, 65, 62, and 60 percent, respectively. Based on the above-mentioned assumptions, the 5-year survival rate cannot be more than 60% and less than 29%.

The median survival time in survived patients is significantly more in comparison with the people who died (99.6 months vs. 24.6 months). The median survival time for those who survived was 99.6 months compared to 24.6 months in the people who died, which was significant. The median survival time in 74 patients whose status was clear in the follow-up was 46.8 months (3.1-135.6 months). The comparison of median survival time according to different variables has been shown in Table 3.

Table 3. Median survival time based on variables in patients (n=74)

Variable		Median survival time (month)
Sex	Female	54.6
	Male	40.2
Residence	Urban	45.6
	Rural	48
Metastasis	No	69
	Yes	24.6
Size	<5	48
	>=5	36
Smoking	No	61.2
	Yes	36
Treatment	Chemotherapy and Surgery	36
	Chemotherapy + Radiotherapy and Surgery	55.8
Differentiation	Well	63
	Moderate&Poor	36
Age	<65	63.6
	≥65	36
Colon	Right	63.6
	Left	40.8
Stage	1	50.4
	2	74.4
	3	55.2
	4	24
Lymph node involvement	No	69
	Yes	36

According to the findings of this study, the median survival time was higher in women, people under 65-year-old, rural residents, patients with no history of smoking, no lymph node involvement, smaller tumor size, early-stage tumor, lack of metastasis, well differentiation, and right colon involvement.

Additionally, Cox regression showed that a relationship exists between increasing age, tumor in the left colon, tumor with the size of greater than 5 cm, higher stage of the tumor, male gender, smoking, poor differentiation, comorbidities, and positive family history and increase in risk in patients, although the relationship was not statistically significant.

Tumor metastasis, lymph node involvement, and comorbidities were significantly associated with increased risk in patients. Combined therapy and living in rural areas were associated with a reduction in risk in patients, although it was not statistically significant (Table 4).

After performing the univariate analysis, the significant variables in the results, as well as those variables were not significant but, with very little difference, were entered into the final regression model. The presence of metastasis in patients is the only variable in multivariate analysis which has significantly increased the Hazard Ratio. The mortality rate in the metastatic patient was 2.83 times higher than non-metastasis ones (Table 5).

Table 4. Cox Proportional Hazard coefficients for patients with colorectal cancer (Univariate Analysis)

Variable		Hazard Ratio	*P*
Sex (male)		1.28	0.410
Age		1.01	0.077
Residence (rural)		0.90	0.769
Smoking		1.18	0.594
Family background (yes)		1.07	0.71
Distinction	**Medium**	1.41	0.269
	Weak	1.47	0.530
Metastasis		3.37	0.001
stage	**2**	0.64	0.565
	3	1.02	0.974
	4	2.67	0.185
Size=> 5		1.09	0.768
Underlying disease		2.09	0.025
Treatment (combined)		0.70	0.241
Along with other cancer		3.03	0.278
Lymph node		2.07	0.043
Left colon		2.88	0.144

Table 5. Cox Proportional Hazard coefficients for patients with colorectal cancer (Multivariate Analysis)

Variable	Hazard Ratio	*P*
Age	1.00	0.48
Metastasis	2.83	0.013
Underlying disease	1.61	0.282
Lymph node	1.07	0.878
Along with other cancer	2.13	0.475

Discussion

Today, cancer is one of the main health problems in societies and takes a significant share of resources and health facilities in developing countries. Gastrointestinal cancers are among the most common malignancies with high mortality rates in many countries, including Iran. Colorectal cancer is the third most common cancer in the world, with 1.4 million new cases in 2012, and it is one of the most common gastrointestinal cancers in Iran (22,25). It is considered to be the second most lethal cancer in the United States (8). Therefore, it is important to study the factors influencing the prediction of the survival time of the patients.

In the present study, the 1- to 5-year survival rate of patients were 0.77, 0.66, 0.50, 0.45, and 0.42, respectively. The data of 34 patients were unavailable for the reasons previously mentioned in the results. Two fates were conceivable for these patients: Death or survival at the end of the study. If survived, the probability of a five-year survival was 60%, and assuming death for all 34 patients; survival was estimated to be 29%. In the study

of Mohammad Reza Akhoond *et al*., the survival rates of one, two, three, four, and five years for colon cancer were 88.7%, 77.9%, 68.5%, 61.4%, and 56.8%, respectively, which is almost consistent with the results of the present study (23). In the study of Asghari Jafarabadi *et al*., (26), the survival time of 1-5 years was 91.9%, 73.7%, 75.9%, 69%, and 63.6%, respectively, which is not in conflict with the results of the present study. In their study in Shiraz, during 2003 to 2008, Davood Mehrabani *et al.*, (21) reported the 1-, 3-, and 5-year survival rates of colorectal cancer to be 93.9%, 50.3%, and 27.2%, respectively, which is less than the survival rates obtained in present study. These differences may be due to the improvements in care and treatment, as well as the diagnosis of cancer in the recent years. Thus, it is expected that studies conducted in recent years show a better survival rates than those conducted previously. Another explanation for the different results among studies is that survival rate in rectal cancer is different from colon cancer, so the studies that examine these two cancers simultaneously in patients, offer a lower survival rate compared to the studies only examine colon cancer. However, some studies have reported different results (27,28). Ghodratollah Roshanaie *et al*.,'s study, from 2005 to 2013, in Hamadan, showed that the probability of 1-, 3-, and 5-year survival in patients with colorectal cancer is 89%, 54%, and 31%, respectively (20), which is less than the survival rates obtained in present study. One possible reason, in addition to time differences mentioned above, is simultaneous examination of colon and rectal cancer survival in that study. Another reason for the different results of survival rate between studies is the variables which have been included in some studies and not in others.

In this study, the mean survival rate for patients was 69.3±4.40 months and their median survival was 75.6 months. In the study of Ali Ahmadi *et al*., the median survival of colorectal cancer patients was approximately 70 months, (19) which is consistent with the findings of this study.

The findings of this study showed that the presence or absence of metastasis has a significant correlation with survival in both the univariate and multivariate regression method, in a way that the risk of death in people who had metastasis was 3.35 and 2.83 times higher than those who only had colon involvement, respectively in the single-variable and multivariate methods. With regard to the sample size of the study, the median of survival was also an important factor, so that 60% of patients who did not have metastasis survived at the end of the study, while less than 10% of those who had metastasis had a 5-year survival. Other studies have confirmed these findings (19,21,23). The reduction in morbidity rate in the final regression model shows that the studied variables have had a positive effect on metastasis patients, which by adapting these variables in the final model, the risk of mortality has been reduced.

As expected, the variable of tumor distinction grade was recognized as an effective factor of survival in colon cancer in this study so that patients with a good distinction stage at the time of diagnosis had a lower risk of death. On the contrary, those with moderate and weak distinction stages at the time of diagnosis had a mortality risk of 1.41 and 1.47 times more than those with a good degree of distinction. Studies have confirmed these findings, as well (20,26,29). It seems that with a larger sample, this risk ratio could be statistically significant.

The results of the single-variable model showed that patients with left colon cancer had significantly lower survival rates than those whose colon cancer is in the right or other parts of the body. The justification for this finding is that the diagnosis of right colon tumor is faster and easier than left colon tumor so that patients with left colon tumor may be diagnosed in the final stages and at higher grades, leading to worse prognoses and lower survival rates in patients (30). However, given that few patients had right colon cancer, accurate judgment is difficult.

In this study, as expected, the median survival rate for patients who received combination therapy was 48 months, while this rate in patients receiving monotherapy was 36 months. In a study by Cunningham *et al*., the mortality rate of patients with combined therapy was 22.24%, compared to 56.67% in patients who received monotherapy (31).

The findings of this study indicate that patients with positive family backgrounds had higher mortality rates in the single-variable model. Therefore, these patients require early-stage interventions and regular screening tests.

Among the demographic variables in this study, age and male gender were associated with a lower survival rate, so that the survival rates of younger people were about 40 months higher than older people. This may be due to lower disease progression in younger people or better physical conditions in them. Because women usually come for treatment earlier than men, it is expected to have more survival times. Some studies have confirmed the effects of gender on colon cancer, while others have not found such effects. In a study by Artes and Depont, the survival time for women with colon cancer was more than men (32,33). This finding could be

explained in terms of how hormonal and immune agents are responsible for different levels of colon and rectum in men and women; therefore, secretion of steroids in women makes them more protected against these two types of cancers and leads to higher survival in women (28). Agah *et al*., concluded that age and male gender are two risk factors for this cancer, which is consistent with the findings of our study (34). In the study of Molaei, the age of patients at the time of diagnosis was a significant variable in their survival (33,35).

This study, as well as previous studies, suggests that the correct prediction of outcomes in patients with colon cancer be a complicated and complex problem. Despite the extensive studies performed in this field all around the world, the validity of the identified factors remains uncertain and further studies are required.

Among the strength points of this study is statistical modeling using the Cox model- in addition to univariate methods- in order to analyze survival in patients, which can eliminate the effects of confounding variables.

One of the factors that may affect survival studies is the change in diagnosis and treatment methods over time (secular trends). Thus, long-term studies may indicate different survivals over time, but given the fact that this study examines the five-year survival rate, the occurrence of such a problem is unlikely and the results of this study are not likely to be affected by this.

Based on the findings of this study, the diagnosis of cancer in early stages- when the tumors has not yet invaded other organs- and at early ages in at-risk individuals- including men- is necessary by using screening and diagnostic methods to increase survival in patients.

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