RESEARCH ARTICLE

Colorectal Cancer Mortality in Shiraz, Iran

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Abstract

Background: Mortality among Iranian patients with colorectal cancer has not been fully examined and the factors associated with their survival are still controversial. This study aimed to determine the mortality rate and its related factors among the patients with colorectal cancer in southwestern regions in Iran. Materials and Methods: This prospective cohort study was conducted on 220 patients with colorectal cancer referred to Fahighi Hospital, Shiraz, Iran from 2009 to 2014. Data were collected from the patients' medical records and were analyzed using Cox regression analysis. Results: Over a median follow-up of 29.3 months, 56 out of the 220 patients (25.5%) died, 32 (14.5%) aged below 40 years, and 45.5% were female. Based on the results of multiple Cox regression analysis, family history of gastrointestinal cancer, stage III, former smoking, type of lesion (fungative and polypoid), and opium use were associated with a greater risk of colorectal cancer mortality (all P<0.05). Conclusions: This cohort study found that the mortality rate of colorectal cancer in Iran is lower than that in European countries. In addition, behavioral and clinical factors were significantly associated with the survival rate. Addressing the related factors would help healthcare providers and physicians provide the best care and improve the survival rate.

Keywords: Mortality - survival rate - colorectal cancer - Cox regression - Iran

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Introduction

Colorectal cancer is a major cause of morbidity and mortality throughout the world (Wiseman, 2008; Sinha et al., 2014). It is the third most common cancer worldwide and the fourth most common cause of death (Sarli et al., 2005). It is also the most common cancer in men over 75 years of age and the second leading cause of cancer-related mortality in the United State (Siegel et al., 2013). Colorectal cancer is one of the most important malignancies and the most frequent gastrointestinal (GI) cancer in the world. The incidence and mortality rates of this disease vary in different countries (Semmens et al., 2000). Although CRC is decreasing in the most western developed countries, the incidence of CRC is rapidly increasing in Asia (Poomphakwaen et al., 2014). It has been estimated that nearly 1.2 million individuals live in the United States with a previous diagnosis of colorectal cancer (Siegel et al., 2012). Countries with the highest incidence rates of colorectal cancer include Australia, New Zealand, Canada, the United States, and some European countries. On the other hand, countries with the lowest incidence rates include China, India, and some African and South American countries (Boyle and Langman, 2000). During the previous decade, in many Asian countries such as Iran, China and South Korea, colorectal cancer incidence was increasing (Zayeri et al., 2015).

In the 2010 report, colorectal cancer was the second most common cause of cancer death among men aged 40-79 years. It was also recognized as the third leading cause of cancer-related deaths among men and women (Siegel et al., 2014a; Siegel et al., 2014b).

The incidence rate of colon cancer is similar in both sexes, while rectal cancer is slightly more predominant among males. Worldwide, colorectal cancer comprises 9.4% and 10.1% of all the incidents of cancer in men and women, respectively. Colorectal cancer survival highly depends upon stage of disease at diagnosis, and typically ranges from a 90% 5-year survival rate for cancers detected at the localized stage and 70% for those detected at the regional stage to 10% for individuals diagnosed with distant metastatic cancer (Haggar and Boushey, 2009; Kohler et al., 2011; Newton et al., 2012).

The incidence rate of colorectal cancer in Iran is lower compared to European countries, such a way that it is the fifth and the third most common cancer among Iranian men and women, respectively. However, mortality rate of colorectal cancer in Iran is higher than that in American countries (Etemad et al.). For example, studies conducted in Iran have indicated that the 5-year survival rates of

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colorectal cancer were 47%, 41%, and 61% (O'Connell et al., 2004). In American countries, however, the overall 5-year survival rate was 65.2% (Ferlay et al., 2010).

Fars province is a referral center for colorectal cancer in southern Iran. Nevertheless, limited evidence is available regarding the factors associated with this disease. Therefore, the present study aims to investigate the factors associated with colorectal cancer mortality using the data extracted from the medical records of the patients diagnosed with colorectal cancer referred to Faghihi hospital, Shiraz, Iran during 2009-2014.

Materials and Methods

This prospective cohort study was conducted from 2009 to 2014 on 220 patients with colorectal cancer who had complete information regarding the study factors at baseline in Shiraz, the largest city in southwest of Iran.

All the colorectal cancer cases presented to Faghihi hospital, Shiraz University of Medical Sciences were prospectively reviewed for 60 months. The colorectal cancer patients were identified through hospital discharge diagnostic code. The inclusion criteria of the study were having been diagnosed with colorectal cancer, having undergone surgery, and not having other cancers in other parts of the body. Overall, 220 patients with colorectal cancer fulfilled the inclusion criteria of the study.

The investigated variables in the present study were as follows: demographics, diagnosis and treatment, behavioral risk factors, and history of being exposed to risk factors. Type of disease was classified by colon and rectal cancer, tumor stage was categorized based on Tumor-Node-Metastasis (TNM), and type of lesion was categorized by an expert colorectal surgeon as ulcerative, fungative - polypoid, and diffuse infiltrative - napkin ring. This information was collected by standard questionnaires as well as by the hospital records provided by the Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. The routine follow-up was performed by the physician every 3 months. In case the patients did not attend the follow-up, they were called by phone to present and complete the follow-up.

In the present study, time-to-death (month) was the primary outcome variable. The survival time was considered as the interval between diagnosis by the physician and death if the patient had died and date of the last follow-up if the patient was still alive. The median follow-up was 29.3 months after diagnosis.

In this study, the relationship between the study variables and colorectal cancer death was explored using simple Cox proportional hazard regression analysis. Then, modeling was performed using multiple Cox proportional hazard regression analysis. All the covariates with significance level of less than 0.2 were entered into the final model. It should be noted that the proportional hazards assumption was checked globally as well as for individual covariates.

All the statistical analyses were performed using STATA software, version 12 assuming a two-sided test based on 5% level of significance. $P<0.05$ was considered to be statistically significant.

Results

This study was conducted on 220 patients suffering from colorectal cancer. The median follow-ups were 24.4 and 32.3 months for the patients with colon and rectal cancer, respectively. During the follow-up, 25.5% of the patients died. In fact, 32 patients (24.1%) with colon cancer and 24 ones (27.1%) with rectal cancer died during the study follow-up. The 1-, 3-, and 5-year survival rates were 95%, 87%, and 51%, respectively.

The characteristics of the study subjects have been

Table 1. Characteristics of the 220 Study Subjects

Variable	Alive N (%)	Dead N (%)	Total (%)
Disease			
Colon cancer	101 (61.6)	32 (57.1	133 (60.45)
Rectal cancer	63 (38.4)	24 (42.9	77 (39.5)
Age (year)			
<40	24 (14.6)	8 (14.3)	32 (14.50)
40-60	78 (47.6)	24 (42.9)	102 (46.36)
>60	62 (37.8	24 (42.9)	86 (39.09)
Sex			
Female	75 (45.7)	25 (44.6)	100 (45.45)
Male	89 (54.3)	31 (55.4)	120 (54.55)
BMI			
Underweight	27 (16.5)	16 (28.6)	43 (19.54)
Normal	73 (44.5)	19 (33.9)	92 (41.81)
Overweight	46 (28)	17 (30.4)	63 (28.63)
Fat	14 (8.5)	3 (5.4)	17 (7.72)
Education			
Illiterate	103 (62.8)	44 (78.6)	147 (66.81)
Primary	40 (24.4)	6 (10.7)	46 (20.90)
Academic	21 (12.8)	6 (10.7)	27 (12.72)
Ethnicity			
Fars	139 (84.80)	45 (80.40)	134 (87.7)
Non-Fars	25 (15.50)	11 (19.60)	36 (16.3)
Family history of GI cancer			
No	112 (68.30)	50 (89.30)	162 (73.63)
Yes	52 (31.70)	6 (10.70)	58 (26.36)
Family history any cancer			
No	109 (66.5)	45 (80.40)	154 (70)
Yes	55 (33.5)	11 (19.60)	66 (30)
Family history colon and rectal cancer			
No	137 (83.5)	53 (94.6)	190 (86.36)
Yes	27 (16.5)	3 (5.4)	30 (13.64)
Stage			
1	35 (21.3)	4 (7.1)	39 (17.73)
2	44 (26.8)	4 (7.1)	48 (21.81)
≥3	85 (51.8)	48 (85.7)	133 (42.30)
Smoking			
No	110 (67.1)	24 (42.9)	134 (60.90)
Former smoker	26 (15.9)	18 (32.1)	44 (20)
Current smoker	28 (17.1)	14 (25)	42 (19.09)
Type of lesion			
Ulcerative	86 (52.4)	21 (37.5)	107 (48.63)
Fungative and polypoid	49 (29.9)	19 (33.9)	68 (30.90)
Diffuse infiltrative - napkin ring	28 (17.1)	16 (28.6)	44 (20.00)
Occupation			
Manual	50 (30.5)	16 (28.6)	66 (30.00)
Non-manual	38 (23.2)	13 (23.2)	51 (23.18)
Unemployed	76 (46.3)	27 (48.2)	103 (46.82)
Monthly income (Rial)			
<5000000	92 (56.1)	31 (55.4)	105 (47.73)
5000000- 10000000	55 (33.5)	22 (39.3)	77 (35)
>10000000	17 (10.4)	3 (5.4)	20 (9.09)
Opium use			
No	150 (91.5)	54 (96.4)	204 (92.72)
Yes	14 (8.5)	2 (3.6)	16 (7.28)

presented in Table 1. Accordingly, 45.5% of the patients were female, 14.5% were below 40 years old, and 39.0% were over 60 years of age. Additionally, 73.5% of the patients did not have formal education.

The association between the study variables and colorectal cancer death using simple Cox proportional hazard model based on a 60-month follow-up has been presented in Table 2. As the table depicts, colorectal cancer death was significantly associated with education level [Hazard Ratio (HR): 0.42, 95% Confidence Interval (CI): 0.18 - 0.99, P(value)= 0.04], family history of GI cancer [HR: 0.26, 95% CI: 0.11 - 0.61, P(value)= 0.002], opium use [HR: 2.49, 95% CI: 1.41- 4.42, P(value)=0.001], current smoking [HR: 2.77, 95% CI: 1.50 - 5.12, P(value)= .001], former smoking [HR: 1.92, 95% CI: 1.00 - 3.71, P(value)= 0.05], type of lesion [HR: 2.10, 95% CI: 1.12 - 4.07, P(value)=0.02], and stage III [HR: 3.09, 95% CI: 1.11 - 8.60, P(value)=0.03].

Table 2. Relationships between Study Variables and Colorectal Mortality Using Univariate Cox Regression Analysis and Multivariate Analysis

Variable	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Disease						
Colon cancer	1	-	-	-	-	-
Rectal cancer	1.21	0.71 - 2.07	0.46			
Age						
<40 years	1	-	-	-	-	-
40-60 years	1.12	0.50 - 2.50	0.77			
>60 years	1.17	0.52 - 2.61	0.69			
Sex						
Female	1	-	-	-	-	-
Male	0.89	0.52 - 1.51	0.67			
BMI						
Underweight	1.59	0.82 - 3.07	0.16	-	-	-
Normal	1	-	-			
Overweight	1.11	0.33 - 3.76	0.85			
Fat	1.39	0.72 - 2.66	0.31			
Education				-	-	-
Illiterate	1	-	-			
Primary	0.42	0.18 - 0.99	0.04			
Academic	0.73	0.31 - 1.71	0.47			
Ethnicity						
Fars	1	-	-	-	-	-
Non-Fars	1.15	0.59 - 2.23	0.66			
Family history of GI cancer						
No	1	-	-	1	-	-
Yes	0.26	0.11 - 0.61	0.002	0.27	0.11 - 0.65	0.004
Family history of any cancer						
No	1	-	-	-	-	-
Yes	0.56	0.29 - 1.08	0. 08			
Family history of colon and rectal cancer						
No	1	-	-	-	-	-
Yes	0.35	0.11 - 1.14	0.08			
Stage						
1	1	-	-	1	-	-
2	0.62	0.15 - 2.51	0.51	0.74	0.18 - 3.06	0.65
≥3	3.09	1.11 - 8.60	0.03	3.05	1.08 - 8.61	0.03
Smoking						
No	1	-	-	1	-	-
Current smoker	2.77	1.50 - 5.12	0.001	2.43	1.28 - 4.36	0.006
Former smoker	1.92	0.99 - 3.71	0.05	1.82	0.93 - 3.57	0.07
Type of lesion						
Ulcerative	1	-	-	1	-	-
Fungative and polypoid	1.52	0.81 - 2.83	0.18	1.5	0.80 - 2.82	0.19
Diffuse infiltrative - napkin ring	2.1	1.12 - 4.07	0.02	2.38	1.22 - 4.63	0.01
Occupation						
Manual	1	-	-	-	-	-
Non-manual	1.58	0.76 - 3.31	0.21			
Unemployed	1.21	0.65 - 2.24	0.54			
Monthly income (Rial)						
<5000000	1	-	-	-	-	-
5000000-10000000	1.11	0.64 - 1.92	0.69			
>10000000	0.54	0.16 - 1.79	0.32			
Opium use						
No	1	-	-	1	-	-
Yes	2.49	1.41 - 4.42	0.001	2.8	1.50 - 4.63	0.001

The results of the modeling using multiple Cox proportional hazard model have been shown in Table 3. Based on this table, clinical factors, including stage III [HR: 3.05, 95% CI: 1.08 -8.61, P (value)=0.03] and diffuse infiltrative and napkin ring type of lesion [HR: 2.36, 95% CI: 1.22 - 4.63, P(value)= 0.01], were significantly associated with a greater risk of colorectal cancer death.

Among the demographic factors, family history of GI cancer [HR: 0.27, 95% CI: 0.11 - 0.65, P(value)=0.004], former smoking [HR: 2.43, 95% CI: 1.28 - 4.63, P(value)=0.006], and opium use [HR: 2.80, 95% CI: 1.50 - 5.25, P(value)=0.001] were significantly associated with colorectal cancer death.

According to the modeling of the association between the study variables and colorectal cancer mortality using multivariate analysis, stage III of colorectal cancer was positively associated with colorectal cancer mortality [HR: 3.05, 95% CI: 1.08 -8.61, P(value)=0.03]. Former smoking [HR: 2.43, 95% CI: 1.28 - 4.63, P(value)=0.006] and opium use [HR: 2.80, 95% CI: 1.50 - 5.25, P(value)=0.001] were also significantly associated with a higher risk of colorectal cancer mortality.

Discussion

Colorectal cancer is one of the most important malignancies and the most common GI cancer in the world. The incidence rate and mortality of this disease vary in different countries (Semmens et al., 2000). The most important finding of the present study was that some clinical and behavioral factors could influence colorectal cancer mortality.

The results of this prospective cohort study indicated that demographic factors, including family history of GI cancer, former smoking, and opium use, were significantly associated with colorectal cancer death. Stage III of colorectal cancer was also positively associated with colorectal cancer mortality.

In this study, the mean age of men and women was 58.28 and 55.27 years, respectively. Besides, most of both male and female patients were in the 40-60 years age group. In addition, 62 patients (28.2%) were below 50 years old. However, European studies showed that less than 20% of colorectal cancer cases were related to below-50-year-old individuals (Mousavi et al., 2009). In the United States also, only 5% of the patients with colorectal cancer aged below 50 years and their median age at diagnosis was 67 years in men and 71 years in

women (Wiseman, 2008).

The findings of the current study demonstrated that colorectal cancer mortality was increasing among the youth. Similar results have also been obtained in the previous studies (O'Connell et al., 2003; O'Connell et al., 2004). For instance, colorectal cancer was known as one of the 10 most common cancers diagnosed in men and women between 20 and 49 years old in the United States in 2006 (Fairley et al., 2006). Rebecca also performed a study in the United States and revealed the increasing incidence rate of colorectal cancer in young people between 20 and 49 years old (Siegel et al., 2009). Our study showed similar results, too. Because of social beliefs and stigma resulting from colorectal cancer, people think that this disease can influence their dignity in the society and they feel ashamed. Therefore, it seems that prevention measures, especially screening at early ages, health education, and public awareness, should be taken seriously in Iran. It is evident that using the recommended colorectal cancer screening tests can both detect the cancer earlier and prevent it by removal of precancerous polyps (Siegel et al., 2012). In fact, early detection by screening can significantly contribute to finding the high-risk population and taking the necessary measures (Taheri-Kharameh et al., 2014).

The results of the present study indicated that the 60-month survival rate of colorectal cancer was 51%, which is lower compared to European countries. This can be due to delay in referral, diagnosis at end stage of the disease, and lack of awareness about the disease symptoms to seek for clinical support.

In this study, history of smoking was significantly associated with colorectal cancer survival. This implies that smoking is one of the important factors that increase the risk of mortality in patients with colorectal cancer(Morrison et al., 2013). The study performed by Edward Giovannucci also came to similar results (Liang et al., 2009). In the same line, other studies suggested that history of smoking was significantly related to colorectal cancer survival (Morrison et al., 2011; Phipps et al., 2011).

Additionally, the results of the present study showed that the mortality rate of colorectal cancer had a significant relationship with family history of the disease. Several studies worldwide have also examined this relationship and stated that colorectal cancer mortality was directly related to family history of the disease (Johns and Houlston, 2001; Lynch et al., 2003; Azadeh et al., 2008).

The results of Cox multivariate analysis demonstrated that stage of the disease, based on TNM categories, was an important factor in colorectal cancer mortality. Accordingly, as the disease stage increased, the survival rate reduced. This could be due to the subjects' low awareness of the early symptoms and preventive care and referral at end stage of the disease when the process is more complicated for healthcare providers. These findings were consistent with those obtained by Jessica O'Connell et al.(O'Connell et al., 2004). Overall, the lower the stage of the disease, the more comfortable the treatment and the better the survival will be (Wang et al., 2003).

Among the clinical factors, type of lesion showed a strong significant relationship with the survival of colorectal cancer. In comparison to ulcerative lesions, diffuse infiltrative - napkin ring was significantly related to colorectal cancer survival. This suggests that pathology reports should be taken seriously by physicians and healthcare providers.

One of the strong points of this study was that it was undertaken based on colorectal cancer registry. Besides, all the patients were routinely followed up by the physician. Finally, it was a prospective study where we could collect the factors we needed. However, this study had some drawbacks. Firstly, the required information about the patients' last status was collected by phone and unfortunately, some patients did not answer. In addition, old cases were excluded from the study due to lack of information.

In conclusion, the present study results showed that colorectal cancer survival was affected by some modifiable factors, including smoking and opium use, some clinical factors, such as disease stage and type of lesion, and family history of GI cancer. These findings could help us determine the factors related to colorectal cancer mortality. In addition, health education is of great importance for at-risk populations, because detection at early stages can result in better survival. Moreover, increasing public awareness regarding the impact of opium use on colorectal cancer mortality can also play a key role in this respect.

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