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ORIGINAL ARTICLE

Comparison of colon and rectum cancer: survival and prognostic factors

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ABSTRACT

Aim: This study aims to investigate some clinical and pathologic factors associated with the prognosis of patients with colon and rectum cancers separately.

Background: Colorectal cancer is the most common cancer of the digestive system and also the fourth cause of cancer-related deaths around the world. Different studies indicate that survival of patients with colorectal cancer has improved in some areas of the world. However, it remains unclear which factors are involved in this improvement.

Patients and methods: Data for 1194 patients with colorectal cancer registered in the Cancer Registry Center of the Research Center of Gastroenterology and Liver Disease, Shahid Beheshti University of Medical Sciences were used in this study. Data analysis was performed using competing risks model. Software used for data analysis included STATA, Version11, and significance level was regarded as $p<0.05$.

Results: Body mass index (BMI), alcohol consumption, tumor site, inflammatory bowel disease, metastasis to lymph nodes and distant metastasis had a significant effect on death from colon cancer, while body mass index, distant metastasis and type of the first treatment had a significant effect ($p<0.05$) on death from rectum cancer. Also, median survival was 7.75 ± 1.118 and 3.917 ± 0.26 years for patients with colon cancer and rectum cancer, respectively.

Conclusion: According to the results of this study, some variables may have a different impact on colon and rectum carcinoma; therefore, the effects of these factors on different parts of the large bowel must be considered separately in future studies.

Keywords: Colon cancer, Rectum cancer, Survival, Competing risks.

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INTRODUCTION

Colorectal cancer is the third most common cancer around the world with an annual incidence of 1,200,000 new cases. It is the fourth cause of cancer mortality in the world. New cases for this disease have grown increasingly since 1975 (annually 500,000 new cases). It accounts for 10% of all kinds of cancer in men, and 9.4% in women around the world (1). Epidemiological characteristics of colorectal cancer are different in different parts of the world (2). Annual incidence of this cancer in North America and Europe is about 30-50% per 100,000 cases, while it is as estimated 3-7% per 100,000 cases in the Middle East (3, 4). Its incidence in Iran is lower than western countries. This cancer ranks fifth and third among all kinds of cancers, with an incidence of

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8.1 and 7.5 in every 100,000 men and women, respectively. However, its incidence is increasing, and consequently, it is a growing public health issue around the world (5).

Over the past years, debates have been raised on numerous variables related to patients' survival. The extent of tumor penetration to the bowel wall, adjacent lymph node metastases and distant metastasis are variables affecting patient survival. Although in most reports it is mentioned that there is a strong correlation between colorectal cancer stage and its prognosis (6-8), results of those studies suggest that the outcome for a patient with colorectal cancer depends not only on the anatomic extent of disease, but also on many other factors related to the patient and tumor (6, 9). In addition, it is well known that no one single factor can determine the prognosis of a disease. Furthermore there are differences between colonic and rectal cancers when comparing treatments, recurrence patterns and patient survival (6, 10-15). Furthermore, population survival rates vary according to geographical areas of the world, suggesting the influence of environmental factors.

Cancer mortality in different areas of the world varies for women and men, respectively (1). Thus, separate analysis of cancers of the large bowel according to patient gender and tumor site in the large bowel may provide accurate insight into the prognosis of disease. This study intends to investigate the influence of some clinical and pathologic factors on survival of patients with colon and rectum cancer in Iran.

PATIENTS and METHODS

Data for 1194 patients with colorectal cancer registered in the Cancer Registry Center of the Research Center of Gastroenterology and Liver Disease, Shahid Beheshti University of Medical Sciences from the period of January 2002 and January 2007 were used in this study. Subjects were followed until January 1, and their survival situation was identified. Death of subjects was confirmed via contact with their families and relatives. Cause of death in all subjects was due to colon or rectum cancer.

Factors in patients with colon and rectum cancer examined in this study included: sex, age, age at diagnosis, body mass index (BMI), diabetes disease history, current or past smoking and alcohol consumption, history of inflammatory bowel disease (IBD), family history of cancer, morphology type of tumor, histological grade of tumor, tumor size, extent of wall penetration of tumor, regional lymph nodes metastasis, distant metastasis, treatment type and pathological stage based on TNM measured in the form of stages I, II, III and IV.

In survival data, the respective event (death in this case) may occur due to different causes. For example, if we are interested in the analysis of data until death occurrence due to heart disease, some subjects in the study may die due to causes other than heart disease. These different causes of death are called competing risks. In this study, since death of subjects may be due to colon cancer or rectum cancer, the competing risks model is used to analyze data (16-18). Data analysis was performed using the competing risks model. Software used for data analysis was STATA, Version11, and the significance level was regarded as $p<0.05$ in all tests.

RESULTS

Among 1194 subjects in the study, 720 (60.3%) were male and 474 (39.9%) were female. The average age of subjects at diagnosis age was 53.59±14.34 years (age range: 14-94). 25.9% had a history of smoking, and 88.8% had a history of alcohol consumption. 36.9% had a family history of cancer (Table1).

Table1. Clinical characteristics of patients and their influence on survival of patients with colon and rectum cancer

		Colon cancer		Rectum cancer	
		Number (%)	p-value	Number (%)	p-value
Age at diagnosis (Years)			0.49		0.35
	<45	241(30)		118(30.1)	
	45-65	373(46.5)		176(44.9)	
	>65	188(23.4)		98(25)	
Body mass index (Kg/m2)			0.003		< 0.001
	≤18.5	45(8.8)		27(9.8)	
	18.6-24.9	252(49.1)		151(54.7)	
	25-29.5	170(33.1)		77(27.9)	
	≥30	46(9)		21(7.6)	
Sex			0.13		0.16
	Male	472(58.9)		248(63.3)	
	Female	330(41.1)		144(36.7)	
Diabetes mllitus			0.29		0.35
	No	575(91.3)		304(92.7)	
	Yes	55(8.7)		24(7.3)	
Inflammatory bowel disorders			0.048		0.92
	No	296(96.7)		102(98.1)	
	Yes	10(3.3)		2(1.9)	
Smoking			0.45		0.2
	Never use	566(74.5)		266(74.7)	
	Past or current user	194(25.5)		90(25.3)	
Alcohol usage			0.045		0.16
	Never use	684(90.6)		331(92.5)	
	Old user	71(9.4)		27(7.5)	
Family history of cancer			0.47		0.65
	Yes	466(60.2)		255(69.1)	
	No	308(39.8)		114(30.9)	
Type of first treatment			0.19		< 0.001
	Surgery	604(81.3)		248(69.5)	
	Chemotherapy radiotheraphy	50(6.7)		64(17.9)	
	Biological therapy	89(12)		45(12.6)	

Tumor morphology was of the adenocarcinoma type in 86.9%, and of the non-adenocarcinoma type in 13.1%. There w ere distant metastases in 15.4% of subjects. Stage I, II, III, and IV disease were observed in 9.7%, 40.3%, 38.6%, and 11.4% of cases, respectively (Table 2).

The primary site of tumor for 802 patients (67.2%) was in the colon, while 392 (32.8%) was in the rectum.

Among 1194 subjects, 223 (18.7%) died due to colon cancer, 125 (10.5%) died due to rectum cancer, and 894 (70.9%) survived until the end of study.

Median survival for subjects with colon cancer was 7.75±1.12 years (95% CI 5.6-9.9), while it was 3.92±0.3 years (95% CI 3.4-4.4).

One-, 2-, 3-, 4-, and 5-year survival rates for colon cancer were 88.7%, 77.9%, 68.5%, 61.4%, and 56.8%, respectively, while they were 89.1%, 74.2%, 60.7%, 47.1%, and 41.9% for rectum cancer, respectively.

Based on univariate analysis of data, the following factors had an effect on time of death due to colon cancer: body mass index, inflammatory bowel disease, alcohol usage, grade of tumor, lymph nodes metastasis, extent of wall penetration, distant metastasis and pathologic stage, whereas the body mass index, type of first treatment, lymph nodes metastasis, distant

Table 2. Pathologic charactersitics of patients and their influence on survival of patients with colon and rectum cancer

variable		Colon cancer		Rectum cancer	
		Number (%)	p-value	Number (%)	p-value
Grading			0.03		0.239
	Well differentiated	326 (56.6)		143 (52)	
	Moderately differentiated	195 (33.9)		112 (40.7)	
	Poorly differentiated	55 (9.5)		20 (7.3)	
Tumor size			0.058		0.41
	< 20mm	43 (7.4)		29 (5.4)	
	≥ 20mm	757 (92.6)		363 (94.6)	
Type			0.3		0.22
	Adenocarcinoma	643 (87.8)		301 (85)	
	Non- adenocarcinoma	89 (12.2)		53 (15)	
Tumor*			0.001		0.49
	T1	9 (1.5)		4 (1.6)	
	T2	55 (9.2)		44 (17.3)	
	T3	446 (75)		178 (70.1)	
	T4	85 (14.3)		28 (11)	
Lymph nodes*			0.02		< 0.001
	N0	438 (53.7)		136 (45.5)	
	N1	269 (42.8)		139 (46.5)	
	N2	22 (3.5)		24 (8)	
Metastasis*			< 0.001		0.02
	M0	365 (84.5)		150 (84.7)	
	M1	67 (15.5)		27 (15.3)	
Staging			< 0.001		0.003
	I	48 (8)		36 (13.9)	
	II	265 (43.9)		82 (31.7)	
	III	220 (36.5)		113 (43.6)	
	IV	70 (11.6)		28 (10.8)	

* TNM Classification of Malignant Tumors

metastasis and pathologic stage were factors influencing the time of death due to rectum cancer (Table 1 and 2).

In the next stage, a multivariate model was fitted to data using a forward approach, entering variables in the order of descending significance level (19, 20). Variables such as BMI, alcohol consumption, inflammatory bowel disease, tumor grade, lymph node metastasis and distant metastasis had a significant influence on survival

Table 3. Prognostic variables in patients with colon and rectum cancer using competing risks model

		Hazard ratio	95% confidence interval	p-value
Colon				
Body mass index				
	18.6-24.9	-		-
	≤18.5	1.302	(0.425- 3.985)	0.64
	25-29.9	0.381	(0.171- 0.845)	0.02
	≥30	0.901	(0.318-2.549)	0.45
Inflammatory bowel diseases				
	No	-	-	-
	Yes	8.898	(3.13-25.81)	< 0.001
Alcohol use				
	Never use	-	-	-
	Current or past user	2.303	(1.168-4.541)	0.02
Grading				
	Well differentiated	-	-	-
	Moderately differentiated	0.473	(0.169- 1.32)	0.15
	Poorly differentiated	3.895	(1.635, 9.277)	0.002
Lymph node*				
	N0	-	-	-
	N1	0.710	(0.336-1.496)	0.39
	N2	6.287	(2.8-14.115)	< 0.001
Metastasis*				
	M0	-	-	-
	M1	3.577	(1.572- 8.143)	0.002
Rectum				
Body mass index				
	18.6-24.9	-	-	-
	≤18.5	1.071	(0.418- 2.741)	0.89
	25-29.9	0.396	(0.18-0.874)	0.02
	≥30	0.598	(0.173-2.067)	0.42
Type of first treatment				
	Surgery	-	-	-
	Chemotherapy,radiotheraphy	2.674	(1.261-5.669)	0.01
	Biological therapy	1.026	(0.301- 3.491)	0.97
Metastasis*				
	M0	-	-	-
	M1	2.646	(1.387-5.078)	0.003

* TNM Classification of Malignant Tumors

of colon cancer (Table 3).

In regards to hazard ratios, it was found that people with a BMI less than 18.6 were more susceptible to death from colon and rectum cancer than people with a BMI between 18.6 and 24.9. Also, people with a BMI between 25 and 29.9 were significantly less susceptible to death from colon and rectum cancer compared to people with BMI between 18.6 and 24.9 ($p<0.05$). People with a BMI higher than 30, though being less susceptible than those with a BMI between 18.6 and 24.9 were more susceptible to death from colon and rectum cancer than those with a BMI between 25 and 29.9.

Hazard ratios of death from colon cancer in people with a current or past record of alcohol consumption was 2.3 times greater than those who never used it (95% CI 1.2 - 4.5; $p=0.016$). People with a history of inflammatory bowel disease were significantly more susceptible to death from colon cancer in such a way that the hazards ratio of death from colon cancer for these people was 8.99 times more than others (95% CI 3.1-25.8; $p<0.001$). Also tumor grade had a significantly reversed relationship for death from colon cancer, and the hazards ratio of poorly differentiated colon cancer was 3.9 times more than well differentiated colon (95% CI 1.6-9.3; $p=0.002$). Hazards ratio of death hazard for those with distant metastasis was 3.6 times more than those without metastasis (95% CI 1.6-8.1; $p=0.002$). Lymph node metastasis was another variable affecting death from colon cancer significantly. Hazard ratio for death in people with more than three cancerous lymph nodes was 6.3 times more than those without cancerous lymph nodes. BMI, distant metastasis, and type of first treatment were also recognized as significant variables in rectum cancer. Hazards ratio for death from rectum cancer in people with distant metastasis was 2.6 times more than others (95% CI 1.4-5.1; $p<0.003$). Type of first treatment had a significant effect on the hazards ratio for death from rectum cancer, and hazards ratio of death in patients with chemotherapy and/or radiotherapy as a first treatment was 2.7 times more than those experiencing surgery as a first treatment (95% CI 1.3-5.7; $p<0.010$).

DISCUSSION

In previous studies, Cox regression has been used for data analysis; however, in this study, a competing risks model was used for data analysis. According to Huang and Zhang (2008) and Chen (2010), considering independence between dependent censored times may lead to biased estimates and misleading results (21, 22).

Colorectal cancer, with more than 1,200,000 new cases every year and over 600,000 annual deaths, is regarded as a serious public health issue around the world (23). The increasing age pace in non-industrial countries has contributed to its increased incidence. Colorectal cancer incidence in Iran have has also increased over the past three decades (23).

Our results show that patients with colon cancer had worse one-year survival rates and better 2-, 3-, 4-, and 5-year survival rates than those with rectum cancer, which is consistent with reports from Labianca et al. (2004) and Zampino et al. (2004) (24, 25). Some studies suggest that patients with colon cancer have better 1- to 5-year survival rates than those with rectum cancer (14, 26-28).

Among clinical characteristics, BMI had a significant relationship with death from colon and rectum cancer. People with BMI less than 18.5 were more susceptible to death from colon and rectum cancer than those with BMI between 18.6 and 24.9. Also, people with BMI between 25 and 29.9 were significantly less susceptible to death from colon and rectum cancer compared to people with BMI between 18.6 and 24.9 ($p<0.05$). People with BMI higher than 30 were less susceptible to death than those with BMI between 18.6 and 24.9,

and more susceptible to death from colon and rectum cancer than those with BMI between 25 and 29.9. Overall, people with BMI between 25 and 29.9 had the lowest hazards ratio of colon and rectum cancer. Those with BMI less than 18.5 had the highest death hazard. Findings from different studies on the role of BMI in death due to colorectal cancer are inconsistent. Murphy et al. (2000) argued that being overweight increases hazards ratio of death from colon cancer, especially in men (29). Shibakita et al. (2010) indicated that BMI lower than 21 and higher than 24 is related to an increase of death due to colorectal cancer (30). In another study by Sinicrope et al. (2010), they indicated that men with BMI between 30 and 34 and more than 35 are more susceptible to death (31). Also they showed that women with BMI between 30 and 34 in stages II and III are more susceptible to death due to colon cancer. However, men with BMI between 25 and 30 had better overall survival rates, while underweight women had the worst survival rate. However in another study, it is found that underweight patients with colon cancer had increased rates of death and overweight people had decreased rates of death (32). The inconsistency of these findings might be because of the difference in number clinical and pathologic factors related to survival in statistical analysis and types of population. Also, defining different levels for BMI have influenced the different findings. Time of measuring BMI can also have an effect on the difference in findings since, for example, if the BMI of someone who is overweight is measured after surgery, it leads to errors in evaluating BMI effect on one's survival. The other reason for the different results may be because the colon is considered the large bowel in all the above mentioned studies, except in Shibakita et al. which used subjects with colorectal cancer. Shibakita et al. found that BMI less than normal is related to increasing death rate (30). Similarly, the lowest hazards ratio was estimated for those with BMI between 25 and 30, which is consistent with the findings of this study.

We also found that there is a significant relationship between alcohol consumption and death from colon cancer. In a prospective study by Yi et al. (2010), in a period from 1985 to 2005 in 6291 subjects, they reported that death in men with colorectal cancer and alcohol consumption is more than those not using it (33). They found that the greater usage of alcohol, the higher risk of death. In the sub-group with alcohol usage, there was a significant difference compared to those not using alcohol ($p=0.04$), and the rate of increase was 4.9 times. However, such significant difference was not observed in women using alcohol. In their study, subjects were above 55 years old, while in our case, there was no age limitation. An advantage of their study was classifying alcohol usage into three groups (low, normal, high), which was not possible in this study due to lack of access to data. Yi et al. found a significant relationship between alcohol consumption and colon cancer; they did not observe such a significant relationship for rectum cancer, which is consistent with our findings (33).

A significant relationship was seen between history of inflammatory bowel disease and hazards ratio of death from colon cancer. Larsen et al. (2007) also found a significant relationship between hazards ratio of death from colorectal cancer and Crohn's disease (CD) (34). They studied all patients with/without CD in the period of 1977 and 1999 and compared 1 and 5 year survival rates between these two groups. They concluded that patients with CD had a higher death rate from colorectal cancer. The increased rate of death in this group might be related to treatment outcomes, imperfect surgery, and/or the coincidence of cancers such as small bowel cancer. It is reported that there is no difference in survival rates of patients within the normal population with colorectal cancer except in patients with comorbidities such as sclerosing

cholangitis (35). The insignificance of results on rectum cancer can be related to low number of subjects with rectum cancer and a history of inflammatory bowel disease, which requires further research. The probability of rectum involvement and its infection with cancer in inflammatory bowel disease is low.

The relationship between pathologic stage and survival rate was seen in evaluation of pathologic factors in univariate analysis, while in multivariate analysis, no significant relationship with prognosis of patients was seen. Park et al. (1999) reported a significant relationship between survival rate of patients with colon and rectum cancer and pathologic stage in univariate mode. However, they found no such significant relationship in the multivariate mode (36). There was no significant relationship between pathologic stage and survival rate in multivariate mode. Similarly, tumor grade had a significant relationship with survival rate of patients with colon cancer. However, there was no significant relationship between tumor grade and death hazard of rectum cancer. In a study by Liang et al. (2006) they observed a significant relationship between survival rate of patients with colon cancer and tumor grade (37). Though in a study by Park et al. (1999), there was a stronger relationship between tumor grade and rectum cancer, such significant relationship between tumor grade and rectum caner was not found in our case (36).

Lymph nodes metastasis had a significant relationship with death hazard of colon and rectum cancer in univariate mode; however, in multivariate mode it had a significant relationship with only death hazard of colon cancer. Adjacent lymph node metastasis in most studies is considered an independent variable related to survival of patients with colorectal cancer (38-40). Similarly, in Liang et al.'s study, adjacent lymph node metastasis had an effect on the survival rate of patients with colon cancer (37). Also, Park et al. reported adjacent lymph node metastases as a factor influencing in colon and rectum cancer (36).

As multivariate analysis indicated, patients with distant metastasis had 3.577 and 2.646 times more death hazard from colon cancer and rectum canver, respectively, compared to cases without metastasis. There are several reports consistent with these findings (36, 37, 41, 42).

In addition, the type of treatment had a significant relationship with survival rate of patients with rectum cancer, which has been mentioned in other studies (40, 43-45).

Some limitations of this study include lack of access to such information, such as the number of removed ganglions, metastasis site, and type of surgery, etc, which can have important effects on the survival rate of patients with colorectal cancer. Changing address and phone numbers for follow up were other limitations of this study.

This study and past reports indicate that appropriate predictions of outcome in patients with colorectal cancer is clinically a complex issue. Despite numerous studies done on this issue around the world, authenticity of determining factors is still in doubt. As observed in the above mentioned results, there are various studies reporting factors influencing survival of patients with colon and rectum cancer differently. Thus, performing research regarding the primary site of tumor seems necessary in order to determine the role of different clinical and pathologic factors involved in the prognosis of cancers in different parts of the colon.

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