RESEARCH COMMUNICATION

Site-Specific Evaluation of Prognostic Factors on Survivial in Iranian Colorectal Cancer Patients: A Competing Risks Survival Analysis

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Abstract:

Background: Colorectal cancer (CRC) is one of the most malignant cancers, but prognosis varies in different parts of the world. Knowing the prognostic factors of the cancer is clinically important for prognosis and treatment application objectives. However, evaluation of these factors overall does not provide thorough understanding of the cancer. Therefore, this study aimed to evaluate prognostic factors of colon and rectal cancers site-specifically, via a competing risks survival analysis with colon and rectum as competing causes of death. Methods: A total of 1,219 patients with CRC diagnosis according to the pathology reports of our cancer registry, from 1 January 2002 to 1 October 2007, were entered into the study. Demographic and clinicopathological factors with regard to survival of patients were analyzed using univariate and multivariate competing risks survival analysis, utilizing STATA statistical software. Results: The results of univariate analysis showed that gender, body mass index (BMI), alcohol history, inflammatory bowel disease (IBD), tumor size, tumor grade and pathologic stage were significantly associated with colon cancer and BMI, personal history of cancer, pathologic stage and the kind of first treatment used were significantly related to rectal cancer. In the multivariate analysis, BMI, IBD, tumor grade and pathologic stage of the cancer were significant prognostic factors for colon cancer and BMI and the kind of first treatment used were significant prognostic factors of rectal cancer. Also 1, 2, 3, 4 and 5 year and overall adjusted survival of patients with rectal cancer was better than those of colon cancer. Conclusion: Based on our findings, CRC is not a single entity and its sub-sites should be evaluated separately to reveal hidden associations which may not be revealed under general modeling.

Key words: Colon cancer - rectal cancer - survival - prognostic factors - competing risks - Iran

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Introduction

Worldwide, CRC is the third most common malignancy; More than 1 million persons are diagnosed with the disease and half a million die from it each year (Wickham and Lassere, 2007). CRC is one of the most important causes of death in various part of the world (American Cancer Society, 2008, Ju et al., 2007, Toyoda et al., 2009). The incidence of CRC is lower in Iran than in Western countries, being the fifth and third most common cancer in men and women (Ministry of Health and Medical Education, 2006, Sadjadi et al., 2005). The total number of estimated CRC cases has increased since the 1990s (Capocaccia et al., 1997; Hayne et al., 2001; Payne, 2007; Toyoda et al., 2009), but the survival of CRC patients has been improving since the 1960s (Capocaccia et al., 1997, Hayne et al., 2001, Price et al., 2008, Söderlund et al., 2009). Incidence of CRC in Iran has increased recently (Hosseini et al., 2004), especially the incidence of the disease in young patients is higher than expected (Pahlavan and Jensen, 2005; Ansari et al., 2006, Foroutan et al., 2008) and this made the CRC an important public health problem in our country (Safaee et al., 2008).

Differences in exposure to various prognostic factors for CRC which may be modifiable or immutable are the most likely reason for the wide disparity in worldwide incidence and survival. Modifiable factors are obesity, diets high in processed or red meats (Willett et al., 1990; Sandhu et al., 2001; Bingham et al., 2003), as well as low consumption of fruits, vegetables, and fiber (Key et al., 2002), high alcohol consumption (Corrao et al., 2004), smoking, low physical activity and socioeconomic inequalities (Giovannucci, 2002; Kelsall et al., 2009). Non-modifiable risks include high age (2008), ethnicity, a familial history of colon or rectal cancer, inflammatory bowel disease (IBD), and hereditary predisposition (most notably familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC)) (American Cancer Society, 2008; Chan et al., 2008). Other studies showed that type of first treatment, body mass index (BMI), marital status, tumor grade, tumor size and pathologic stage of tumor are significantly related to the

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survival of CRC patients (Boyle and Langman, 2000; Moghimi-Dehkordi et al., 2008). As many as 70-80% of CRCs may owe their appearance to such factors; this clearly identifies CRC as one of the major neoplasm in which causes may be rapidly identified, and a large portion of the disease is theoretically avoidable by early diagnosis (Boyle and Langman, 2000; Cheah, 2009) and this emerged assessing about measures for reducing the risk of CRC.

However, the survival of a patient with CRC is depended on the anatomic site due to possible heterogeneity between sub-sites of CRC. Although, over recent decades, the site-specific incidence and the effect of prognostic factors in the large bowel has been investigated (Wei et al., 2004; Fukatsu et al., 2007; Li and Lai, 2009), but few studies have considered site-specific prognostic factors for colon or rectal cancer, especially up to our knowledge there is no study that consider colon and rectum as competing causes of death. Therefore, to further understanding of similarities and differences between colon and rectal cancers, it is necessary to evaluate the prognostic factors of CRC by sub-sites. This study aimed to model the specific prognostic factors of colon and rectal cancers through univariate and multivariate competing risks survival analysis. The results may be helpful in diagnosis, planning appropriate therapy and possible screening programs.

Materials & Methods

Data were acquired from cancer registry of the Research Center of Gastroenterology and Liver Disease (RCGLD), Shahid Beheshti Medical University, Tehran, Iran. The patients from ten public and private collaborative hospitals were treated and referred to the cancer registry. All patients with CRC diagnosis according to the pathology report of cancer registry were eligible for this study. Based on this criterion, a total of 1219 patients (802 (65.8%) of subjects with colon cancer, 392 (32.2%) of subjects with rectal cancer and 25 (2.1%) with unknown cause) were entered in the study. The follow up time was defined as the date of diagnosis up to the 1 October 2007 as the time of the death from the disease (as the exact failure time) or survival (as the censoring time). The start time of the study was considered as 1 January 2002. Deaths were confirmed through the telephonic contact to relatives of patients. We encounter a few numbers (about 2.1%) of CRC patients wherein no information about the cause of death was obtained, but only the dates of their death were known, which exclude from analysis.

For all the patients and based on hospital document information, the demographic included age at diagnosis, sex, race, marital status, and education and clinico-pathological characteristics included BMI, smoking, alcohol history, FAP, HNPCC, IBD, personal and familial history, mucin production, tumor grade, tumor size, pathologic stage and the kind of first treatment used which have been recorded in the database of center, were used in the analysis. Pathologic stage of tumor was defined as I, II, III, and IV according to American Joint Committee on Cancer (AJCC) on TNM staging criterion (1988). Based on site topography of the cancer, the colon and rectum sites were separated to define the site specific cancers. Tumor grade was obtained as stated in the pathology reports, which was reported on a three-grade scale (well differentiated, moderately differentiated, and poorly differentiated). Mucin production status determined as mucinus or nonmucinus.

Survival time was calculated in months and was represented as mean (±standard deviation). The survival probabilities were compared in groups by the cause-specific Log-rank test procedure, separately for each of competing events (Balakrishnan and Rao, 2004). Significant factors ($p<0.1$) in the univariate analysis were candidate as to enter in the multivariate analysis. Cause specific Cox proportional hazard (PH) model, as a multivariate procedure, was used to analyze the data in the presence of competing risks. Hazard ratios (and their 95% confidence intervals) were estimated as the effect size of interest. In this step, p-values less than 0.05 were considered as significant. The assumptions of the hazard proportionality have been tested by Shoenfield residuals ph-test (Kleinbaum and Klein, 2005). Also Harrell's C index has been computed, as a measure of concordance between model predictions and real outcomes (Harrell et al., 1984). Data were analyzed using Stata (version 10) Statistical software.

Results

The mean follow up time (± SD) for patients with colon and rectal cancers was 26.35 (±25.27) and 23.88 (± 20.56), respectively. The mean age at diagnosis (± SD) was 53.56 (±14.21) in colon cancer patients and 55.03 (±37.63) in rectal cancer patients. In these patients, 1, 2, 3, 4, and 5 year survival probability were 91.7%, 83.7%, 75.9%, 69.0% and 63.3%, respectively. The mean survival time (95% confidence interval) of these patients was 111.82 (102.25 – 121.39). Also in patients with rectal cancer, 1, 2, 3, 4, and 5 year survival probability were 96.0%, 91.2%, 84.0%, 78.2% and 76.0%, respectively. The mean survival time (95% confidence interval) of these patients was 135.95 (126.20 – 145.70). Demographic and clinico-pathological characteristics of the study participants and the results of log-rank test are shown in the Tables 1 and 2, respectively.

For demographic characteristics, only the gender of the patients with colon cancer was the candidate variable to enter in multivariate analysis ($p < 0.1$), but this variable wasn't significant for rectal cancer ($p > 0.1$). Other factors i.e. age at diagnosis, marital status, race and education, in both of colon and rectal cancer patients weren't significant to enter in the multivariate analysis ($p > 0.1$).

The results of the test for clinico-pathological variables showed that for patients with colon cancer, the variables BMI, alcohol history, IBD, tumor grade, tumor size and pathologic stage of cancer were significant ($p<0.1$), but other clinical variables such as tobacco smoking, FAP, HNPCC, personal and familial history of cancer, histology type, mucin production and the kind of first treatment used weren't significant ($p> 0.1$).Also the results showed that for patients with rectal cancer, BMI, personal history of

Table 1. Demographic Characteristics of the Study Participants and the Results of Cause Specific Log-Rank Test

Characteristic	Colon Cancer N (%)	P-value	Rectal Cancer N (%)	P-value
Age at Diagnosis				
<45	241 (30)		118 (30)	
45-65	373 (47)	0.32	176 (45)	0.20
>65	188 (23)		98 (25)	
Gender				
Male	472 (59)	0.09	248 (63)	0.12
Female	330 (41)		144 (37)	
Marital Status				
Single	32 (4)	0.14	22 (6)	0.31
Married	729 (96)		344 (94)	
Race				
Fars	367 (51)		180 (53)	
Kurdish	59 (8)		26 (8)	
Lourish	56 (8)	0.42	23 (7)	0.53
Turkish	158 (22)		69 (20)	
other	79 (11)		44 (13)	
Education				
Illiterate	157 (25)		81 (29)	
Primary school	208 (33)	0.30	85 (30)	0.58
High school	155 (25)		67 (24)	
University	104 (17)		50 (18)	

cancer, pathologic stage of cancer and the kind of first treatment used were significant (p<0.1), but other clinico-pathological variables such as tobacco smoking, alcohol history, FAP, HNPCC, IBD, familial history of cancer, histological type, mucin production, tumor grade and tumor size weren't significant (p > 0.1).

In the next step, significant variables in the univariate test were entered in the multivariate analysis. The results of the multivariate PH Cox regression for patients with colon and rectal cancers are shown in Table 3. For patients with colon cancer, total time at risk was 6906.73 for 239 subjects entered in the analysis.

Likelihood ratio test showed a significant contribution of the variables entered in the model (Wald Chi Square = 50.22, df= 12 (AIC=395.61) and p < 0.0001). For patients with rectal cancer, total time at risk was 8231.53 for 291 subjects entered in the analysis. Likelihood ratio test showed a significant contribution of the variables entered in the model (Wald Chi Square = 45.26, df= 9 (AIC=301.91) and p < 0.0001).

The proportional hazard assumption of both models was assessed by Schoenfeld residuals ph-test; the results showed that all the variables contributed in each model satisfied the PH assumption of the Cox regressions (all p >0.05). Also Harrell's C indexes for first and second model were equal to 0.76 and 0.73 respectively, which

Table 2. Clinical Characteristics of the Study Participants and the Results of Cause Specific Log-Rank Test

Characteristic	Categories	Colon Cancer N (%)	Colon Cancer Log-Rank P-value	Rectal cancer N (%)	Rectal cancer Log-Rank P-value
BMI	18.6 - 24.9	252 (49)	0.0001	151 (55)	< 0.0001
	<18.5	45 (9)		27 (10)	
	25-29.9	170 (33)		77 (28)	
	>30	46 (9)		21 (8)	
Tobacco Smoking	never used	566 (74)	0.3849	266 (75)	0.1729
	past or current use	194 (26)		90 (25)	
Alcohol History	never used	684 (91)	0.0661	331 (92)	0.1939
	past or current use	71 (09)		27 (8)	
FAP	No	255 (99)	0.4406	73 (97)	0.8707
	Yes	3 (1)		2 (3)	
HNPCC	No	136 (83)	0.8619	51 (91)	0.1076
	Yes	28 (17)		5 (9)	
IBD	No	296 (97)	0.0098	102 (98)	0.7621
	Yes	10 (3)		2 (2)	
Personal History	No	304 (89)	0.3672	133 (94)	0.0204
	Yes	37 (11)		9 (6)	
Familial History	No	466 (60)	0.3782	255 (69)	0.5267
	Yes	308 (40)		114 (31)	
Mucin Production	Mucinous	65 (8)	0.7065	36 (09)	0.9969
	Non mucinous	737 (92)		356 (91)	
Tumor Grade	well	326 (57)	0.0145	143 (52)	0.2522
(differentiated)	moderately	195 (34)		112 (41)	
	poorly	55 (10)		20 (7)	
Tumor size	<20mm	43 (5)	0.0434	29 (7)	0.2643
	>20mm	757 (95)		363 (93)	
AJCC Pathologic stage	I	48 (8)	< 0.0001	36 (14)	0.0002
	II	265 (44)		82 (32)	
	III	220 (36)		113 (44)	
	IV	70 (12)		28 (11)	
First treatment used	Surgery	604 (81)	0.1279	248 (69)	< 0.0001
	Chemo, radio & immune	50 (7)		64 (18)	
	Biopsy	89 (12)		45 (13)	

show reasonable agreement between observed outcome and those predicted by the models.

Based on the results of multivariate analysis, BMI, IBD, tumor grade and the pathologic stage were significant prognostic factors of colon cancer ($p < 0.05$), but sex, alcohol history and tumor size weren't significant ($p > 0.05$). Also for rectal cancer patients, BMI and the kind of first treatment used were significant prognostic factors ($p<0.05$) but personal history of cancer and pathologic stage were not significant in this case ($p > 0.05$).

Colon and rectum specific survival curves adjusted for prognostic factors in each multivariate analysis are shown in Fig. 1. As can be seen, adjusted survival of colon cancer patients fell down at about 0.25 in 100 months and continued up to end of study time with a straight line, but this occurred at about 0.82 survival probability in 50 months for rectal cancer. So the adjusted survival of patients with rectal cancer is better than those of colon cancer.

Table 3. Results of Specific Cox Regression Models

Variables	HR[b]	95% CI[c]	P-value
Colon			
Sex			
Male	1[a]	----------	-----
Female	0.68	0.32-1.43	0.31
BMI			
18.6 - 24.9	1[a]	----------	-----
<18.5	2.74	1.17-6.45	0.02
25-29.9	0.32	0.14-0.73	0.01
>30	0.71	0.25-2.03	0.52
Alcohol History			
never used	1[a]	----------	-----
past or current	1.84	0.89-3.81	0.10
IBD			
No	1[a]	----------	-----
Yes	9.98	3.33-29.9	0.00
Tumor Grade (differentiated)			
well	1[a]	----------	-----
moderately	0.53	0.22-1.29	0.16
poorly	2.67	1.31-5.44	0.01
Tumor Size			
<20mm	1[a]	----------	-----
>20mm	1.45	0.33-6.43	0.62
AJCC Stage			
I	1[a]	----------	-----
II	1.38	0.29-6.51	0.69
III	1.87	0.39-8.90	0.43
IV	4.54	0.98-21.0	0.05
Rectum			
BMI			
18.6 - 24.9	1[a]	----------	-----
<18.5	2.79	1.11-6.99	0.03
25-29.9	0.40	0.16-0.97	0.04
>30	0.76	0.16-3.57	0.73
Personal History of Cancer			
No	1[a]	----------	-----
Yes	0.29	0.04-2.06	0.22
Kind of First Treatment Used			
Surgery	1[a]	----------	-----
Chemo etc	3.49	1.47-8.13	0.01
Biopsy	0.83	0.19-3.61	0.81
AJCC Pathologic Stage			
I	1[a]	----------	-----
II	0.31	0.08-1.23	0.10
III	0.98	0.31-3.09	0.98
IV	1.69	0.53-5.38	0.37

[a]Reference category; [b]Hazard Ratio; [c]95% Confidence Interval

Discussion

The importance of CRC as a threat of public health and its increasing rate in our country especially in youth through recent decades (Hosseini et al., 2004, Pahlavan and Jensen, 2005), make it necessary to study this kind of cancer. Also, for further understanding and more exact study of the cancers in different anatomic locations within colo-rectum, this study was conducted on 1219 Iranian CRC patients in order to evaluate the effect of specific prognostic factors of colon and rectal cancers using univariate and multivariate analyses by competing risk approach.

The results of univariate analysis for demographic characteristics showed that only the gender of the subject was of prognostic significance for patients with colon cancer. Although, the gender wasn't significant in multivariate analysis, it seems the male patients were more susceptible (about 1.5 (1/0.68) times) for dying from colon cancer. Although finding of some studies confirm this results (Capocaccia et al., 1997, Li et al., 2007), there are some controversies (Cheng et al., 2001, Ji et al., 1998 , Svensson et al., 2002). It has been hypothesized that hormonal factors and immune function are responsible for the different rates of CRC in men and women (Hayne et al., 2001), where female sex steroids offer women protection both from the disease and in terms of survival (Payne, 2007). Other demographic characteristics i.e. age at diagnosis, race, marital status and education weren't of significant prognostic factors for each cause of colon and rectal cancers. There are some negotiations in this setting; significant differences of CRC rates are reported in various race groups, marital status and education site-specifically by some of studies(Charles and Thomas, 1992, Cheng et al., 2001, Li et al., 2007, Tavani et al., 1999, Troisi et al., 1999 , Wu et al., 2004).

Of clinical characteristics, BMI was significant prognostic factor of colon and rectal cancers, based on the results of univariate and multivariate analysis. Patients with BMI group of <18.5 had worse outcome and those patients with BMI groups of 25-29.9 and >30 had better outcome than the patients with reference group of 18.6 – 24.9. There is a finding in line with our study (LeMarchand et al., 1992). But some controversies exist (Gerhardsson-deVerdier et al., 1990, Slattery et al., 2003).

Alcohol history was significant prognostic factor of colon cancer and not for rectal cancer in univariate analysis. Though it wasn't statistically significant in multivariate analysis, however a suggestive effect of this variable has been observed so that alcohol past or current users develop colon cancer .84% more than those who never used alcohol. Some studies confirm our results (Cho et al., 2004, Erhardt et al., 2002, Giovannucci et al., 1995 , Mizoue et al., 2006). On the other hand, there some unfavorable findings (Akhter et al., 2007, Chyou et al., 1996, Corrao et al., 2004,

Franceschi and La-Vecchia, 1994). Different patterns of exposure, for example race and genotypes may be possible reason for this heterogeneity (Akhter et al., 2007).

IBD was significant prognostic factor of colon cancer and not for rectal cancer in univariate and multivariate analysis. Patients with a history of IBD develop colon cancer about 10 times more than patients without a history of IBD. CRC in patients with IBD (ulcerative colitis (UC) and Crohn's colitis) has long been recognized. CRC is the most common site of cancer in IBD (Xie and Itzkowitz, 2008) with similar effects in colon and rectum (Bernstein et al., 2001).

Tobacco smoking wasn't significant prognostic factor of either colon or rectal cancer. Contrary to our findings, some studies suggest that long-term tobacco smoking increases the risk of CRC by colon and rectum sub-sites (Giovannucci et al., 1994, Chao et al., 2000; Giovannucci, 2001; Terry et al., 2002). It is hypothesized that smoking acts as an initiator of colorectal neoplasia (Giovannucci et al., 1994). But, in line in our results, neither the International Agency for Research on Cancer nor the Surgeon General has classified smoking as a cause of CRC (US Department of Health and Human Services, 2004).

Tumor grade was a significant prognostic factor of colon cancer based on the results of univariate and multivariate analysis but not for rectal cancer. Colonic patients with poorly differentiated tumors had 2.7 times worse outcome than well differentiated patients. There are some contrary findings (Roncucci et al., 1996 , Takahashi et al., 2000), but a study reached similar results to those of us (Li et al., 2007).

Tumor size was significant for colon cancer in univariate analysis but it wasn't significant in multivariate analysis. However, colonic patients with > 20mm tumor size had .45% worse outcome than those patients with < 20mm tumor size. In a study by Meguid et al (2008), a significant difference in tumor size has been reported between sub-sites of CRC. There is one study in contrast with our findings (Li et al., 2007).

Personal history of cancer was significant for rectal cancer in the univariate analysis, but it wasn't significant in the multivariate analysis. American Cancer Society has introduced this factor as prognostic factor of CRC; People who have had colorectal cancer are more likely to develop new cancers in other areas of the colon and rectum (American Cancer Society, 2008).

Although in our study familial history of the cancer was not a significant prognostic factor of colon or rectal cancers, there have been many studies which have demonstrated that familial history of CRC appears to affect relative risk (RR) of colon cancer more strongly than RR of rectal cancer (Fuchs et al., 1994; Mahdavinia et al., 2005).

Based on our findings, HNPCC and FAP were significantly related to neither colon cancer nor rectal cancer, but other studies reported that the HNPCC and FAP predispose cancers of the colon and rectum (Watson and Lynch, 1993). FAP and HNPCC arise first in different sections of the colo-rectum (FAP: rectum and distal colon, HNPCC: proximal colon) (Iacopetta, 2002 , Lynch et al., 1988). These differences suggest that each may arise through different patho-genetic mechanisms (Bufill, 1990 ,Wei et al., 2004).

Although some studies had reached to similar finding of us, which the mucin production wasn't significant prognostic factor of either colon or rectal cancer (Li et al., 2007), but there are some adverse findings (Du et al., 2004; Papadopoulos et al., 2004)

From pathological features, pathologic stage of cancer was of prognostic significance for colon and rectal cancers, in univariate analysis. However, it was significant just for colon cancer in the multivariate analysis. Based on the results, advanced stage of disease had higher effect in patient's survival; so that, the stage V was significantly different from stage I and patients in this stage experienced the death about 4.5 times more than patients in stage I. Finding of some studies are in the line with of our results (Cheng et al., 2001). However, some discrepancies exist (Hall et al., 2000; Haidinger et al., 2006; Meguid et al., 2008).

The kind of first treatment used, was significant prognostic factor just for rectal cancer based on univariate and multivariate analysis; so that patients with chemotherapy, radio and Immunotherapy had 2.3 times worse outcome than patients with surgery. There are some arguments (Casillas et al., 1997 , Taal et al., 2001); such differences are probably related to the molecular characteristics of the tumors (Moertel et al., 1995).

Overally adjusted survival and 1, 2, 3, 4 and 5 year survival of patients with rectal cancer were better than those of colon cancer. This shows the better overall and year by year condition of patients with rectal cancer. Other studies confirm this result too (Meguid et al., 2008; Toyoda et al., 2009). However, there have also been some arguments to the contrary (Hayne et al., 2001: Zampinoa et al., 2004; Berrino et al., 2007).

Finally, the dispute about the inconsistency of data concerning the site-specific mechanism of colorectal carcinoma does exist, and more evidence about the specific characteristics of these cancers needs to be collected to definitely confirm the conception. Our study had some limitations; we did not have access to part of the important data, such as type of treatment, because we have to use first treatment. Unknown cause of death in a few of cases was another limitation. Generally, we encounter defective data for the reason that registration of data on cancer in our center was incomplete. Etiologic distinctions between the proximal and distal colon may exist (Wei et al., 2004; Li and Lai, 2009), but this needs more cases.

It is more rational to divide the colo-rectum into sub-sites rather than to consider CRC as a whole, between which heterogeneity exists. Epidemiological, etiological and genetic factors all suggest that CRC is not a single entity and that the colon and rectum should be evaluated separately, in order to reveal the associations that may otherwise remain hidden. Especially, in our country the increasing rate of CRC is mostly due to colon cancer therefore, a more appropriate classification will avoid neglecting useful information and will be beneficial for the study of the molecular mechanism, prognosis, treatment application, designing clinical trials and develop appropriate treatments and screening programs.

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