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ORIGINAL ARTICLE

Does the prognosis of colorectal cancer vary with tumor site?

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ABSTRACT

Aim: The aim of this study was to compare prognostic factors between colon and rectal cancers.

Background: Prognosis of Colorectal Cancer (CRC) may depend on the anatomical site.

Patients and methods: A total of 1219 patients with CRC diagnosis according to the pathology report of RCGLD cancer registry, from 1 January 2002 to 1 October 2007, were entered into the study. Demographic and clinico-pathological factors were analyzed using survival analysis.

Results: From age at diagnosis, colon cancer had significantly better survival than rectal cancer (Multivariate Hazard Ratio (MVHR)=0.24; 95% Confidence Interval (CI) =(0.074-0.77)). Other factors, including marital status (MVHR =1.78; 95% CI =(0.33-9.62)), body mass index (BMI) (MVHR =1.21 and 1.54; 95% CI =(.30-4.85) and (.44-5.4) respectively for < 18.5 and >30 BMI groups), pathologic stage (MVHR =.64; 95% CI =(.21-1.98)) and alcohol history (MVHR =4.86; 95% CI =(.67-35.14)) were not significantly different between the two patient group but suggested a possible effect upon prognosis. Overall survival in rectum was better than that of colon.

Conclusion: Our findings support this hypothesis that prognosis of CRC varies with tumor site.

Keywords: Prognostic factors, Colorectal cancer, Survival analysis.

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Introduction

Worldwide, colorectal cancer (CRC) is the third most common malignancy (1) and is the fifth and third most common cancer in men and women in Iran (2). Worldwide, CRC rates are increasing (2-11). In Iran there has been a dramatic increase in CRC, especially in young patients (12-14) and this made the CRC an important public health problem in our country.

Factors that are known to predispose to CRC include age, gender, and race (3, 4, 15-23). Moderate to heavy alcohol consumption and raised BMI have all shown concordance with an increased formation of colorectal carcinoma and adenomas, known precursors to CRC (17, 24-31). Additional predisposing factors include a family history of colon or rectal cancer. Patient with inflammatory bowel disease (IBD), Familial Adenomatous Polyposis (FAP) or Hereditary non-Polyposis Colon

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Cancer (HNPCC) (9, 32-40) are also at increased risk of CRC.

Prognostic factors for patients with CRC include the anatomical site of the tumour (5, 19, 20, 39, 41). Therefore prognostic factors for colon or rectal cancer can be considered separately. Although the association of the site specific CRC with prognostic factors have been investigated through some studies (16, 19, 42-46), there are few studies that have made a comparison between colon and rectal cancers (39, 47). This study aimed to evaluate and to compare the prognostic factors of colon and rectal cancers through univariate and multivariate survival analysis.

Patients and Methods

Data were acquired from cancer registry center of Research Center of Gastroenterology and Liver Disease (RCGLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Patient information from ten public and private collaborative hospitals is provided for the cancer registry. All patients with CRC diagnosis according to the pathology report of the cancer registry were eligible for this study. Base on this criterion, a total of 1219 patients (802 (65.8%) with colon cancer and 392 patients (32.2%) with rectal cancer. 25 patients (2.1%), with cancer of unknown primary, were excluded in the analysis.

In this longitudinal survival analysis, 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. For a few patients, (2.1%), no information about the cause of death could be obtained and these patients were excluded from analysis.

For all patients' information, the demographic characteristics included age at diagnosis, gender, race, marital status, and education and clinico-pathological characteristics included BMI, alcohol history, FAP, HNPCC, IBD, familial history and pathologic stage which have been used in the analysis were obtained from hospital records. Pathologic stage of tumor was defined as early (including I and II) and advanced (including III and IV) according to American Joint Committee on Cancer (AJCC) (15). Based on site topography of the cancer, the colon and rectal were separated to define the sites of the cancer.

Survival time was calculated in months and was represented as mean (±Standard deviation) survival time. Significant factors ($p<0.1$) from univariate analysis were candidate as to enter in the multivariate analysis. Cause-specific Hazard Ratio (HR) (and its 95% CI) was considered as the effect size of interest. In this step, p-values less than 0.05 were considered as significant. The HR of difference and its 95% CI was computed by the "lincom" function of STATA software. The assumptions of the hazard proportionality have been tested by Shoenfield residuals ph- test (48). Also Harrell's C index has been computed, which is defined as a measure of concordance between the predictions and outcomes, and higher (> 0.5) values of this index reveals the adequacy of data modeling (49). Data were analyzed using STATA 10 Statistical software (StataCorp, College Station, Texas 77845 USA).

Results

A total of 508 subjects were studied for a total of 14407 months.

Table 1- Demographic and clinico-pathological characteristics of the study participants and results of univariate analysis by colon and rectum

Characteristic		Colon Cancer			Rectal Cancer		
		N(%)	IDR ×1000	P-value [b]	N(%)	IDR ×1000	P-value [b]
Age at Diagnosis	<45 [a]	241 (30)	6.8	-------	118(30)	3.4	-------
	45-65	373 (47)	6.9	0.933	176(45)	4.1	0.408
	>65	188 (23)	9.1	0.195	98(25)	5.4	0.065
Gender	Male [a]	472 (59)	8.1	-------	248(63)	4.6	-------
	Female	330 (41)	6.2	0.077	144(37)	3.3	0.098
Marital Status	Single [a]	32 (4)	12.2	-------	22(6)	6.6	-------
	Married	729 (96)	7.0	0.058	344(94)	3.9	0.175
Ethnicity	Fars [a]	367 (51)	7.7	-------	180(53)	4.4	-------
	Kurd	59 (8)	9.3	0.524	26 (8)	5.6	0.473
	Lor	56 (8)	7.1	0.824	23 (7)	2.1	0.121
	Turk	158 (22)	6.1	0.232	69 (20)	3.9	0.794
	Other	79 (11)	9.5	0.283	44 (13)	4.6	0.856
Education	Illiterate [a]	157 (25)	9.0	-------	81 (29)	5.2	-------
	Primary school	208 (33)	7.9	0.428	85 (30)	4.2	0.459
	High school	155 (25)	6.0	0.054	67 (24)	3.4	0.198
	University	104 (17)	7.0	0.256	50 (18)	3.6	0.258
BMI	18.6 - 24.9 [a]	252 (49)	8.3	--------	151(55)	6.2	--------
	<18.5	45 (9)	12.3	0.119	27 (10)	8.4	0.285
	25-29.9	170 (33)	3.7	< 0.001	77 (28)	2.0	< 0.001
	>30	46 (9)	6.6	0.431	21 (8)	2.4	0.054
Alcohol History	never used [a]	684 (91)	6.9	--------	331(92)	4.1	--------
	past or current [a]	71 (9)	10.5	0.060	27 (8)	2.5	0.208
FAP	No [a]	255 (99)	7.0	--------	73 (97)	2.9	--------
	Yes	3 (1)	5.0	0.670	2 (3)	4.7	0.597
HNPCC	No [a]	136 (83)	8.8	--------	51 (91)	5.0	--------
	Yes	28 (17)	7.7	0.789	5 (9)	1.1	0.138
IBD	No [a]	296 (97)	6.8	--------	102(98)	3.2	--------
	Yes	10 (3)	21.5	0.047	2 (2)	4.3	0.775
Familial History of Cancer	No [a]	466 (60)	7.3	--------	255(69)	4.3	--------
	Yes	308 (40)	5.0	0.346	114(31)	5.0	0.490
Pathologic stage	Early [a]	313 (52)	7.6	--------	118(46)	4.3	--------
	Advanced	290 (48)	6.4	< 0.001	141(55)	3.6	0.001

[a] Reference category; [b] Based on unadjusted model; IDR: Incidence Density Ratio

The mean follow up time (± SD) in months for patients with colon and rectal cancers was 26.35 (±25.27) and 23.88 (± 20.56), respectively. The mean age at diagnosis (± SD) in month was 53.56 (±14.21) in colon cancer patients and 55.03 (±37.63) in rectal cancer patients. A total of 223 (19.7%) subjects died during the study period. For all patients, 1, 2, 3, 4 and 5 year survival was 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) months. 124 (11.4%) patients

Table 2. Results of multivariate model for significant prognostic factors from univariate analysis by colon and rectum

Characteristic		Colon Cancer			Rectal Cancer		
		HR[b]	95% CI	P-value[c]	HR[b]	95% CI	P-value[c]
Age at Diagnosis	<45	1[a]	-----	-----	1[a]	-----	-----
	45-65	0.83	0.43- 1.57	0.56	3.44	1.29-9.16	0.01
	>65	1.00	0.45- 2.26	0.99	1.52	0.34 - 6.75	0.59
Marital Status	Single	1[a]	-----	-----	1[a]	-----	-----
	Married	0.71	0.21-2.36	0.57	0.40	0.12-1.30	0.13
BMI	18.6 - 24.9	1[a]	-----	-----	1[a]	-----	-----
	<18.5	2.67	1.12-6.34	0.03	2.20	0.74-6.50	0.15
	25-29.9	0.41	0.20-0.83	0.01	0.26	0.09-0.74	0.01
	>30	0.62	0.19-2.05	0.44	0.62	0.15-2.54	0.50
Alcohol History	never used	1[a]	-----	-----	1[a]	-----	-----
	past or current use	2.30	1.14-4.67	0.02	0.47	0.07-3.00	0.43
IBD	no	1[a]	-----	-----	1[a]	-----	-----
	yes	9.97	2.82-35.28	0.00	8.50	1.31-55.32	0.03
Pathologic Stage	early	1[a]	-----	-----	1[a]	-----	-----
	advanced	1.94	1.06-3.54	0.03	3.03	1.17-7.89	0.02

[a] Reference category; [b] Multivariate Hazard Ratio; [c] Based on adjusted model

with rectal cancer died during the study period. In these patients, 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) months.

Based on univariate analysis for demographic characteristics (table 1), age at diagnosis, gender, marital status and education were significantly related to the survival in patients with colon cancer ($P < 0.1$), but ethnicity wasn't significant ($p > 0.1$). Also age at diagnosis and gender were significantly related to the rectal cancer ($P < 0.1$), but marital status, education and ethnicity weren't significant ($P > 0.1$).

The results of the test for clinico-pathological factors (table 1) showed that for patients with colon cancer, BMI, Alcohol history, IBD and pathologic stage were significant ($P<0.1$), but other factors including FAP, HNPCC and familial history of cancer weren't significant ($P> 0.1$). Also the results showed that for patients with rectal cancer, BMI and pathologic stage were significant ($P<0.1$), but other clinico-pathological variables including alcohol history, FAP, HNPCC, IBD, familial history of cancer weren't significant ($P > 0.1$). In the next step, significant variables in the univariate analysis were entered in the multivariate analysis.

Likelihood ratio test showed a significant contribution of the variables entered in the model (Wald Chi Square = 64.74, df= 18 (AIC=684.38) and $P < 0.001$). The results of Schoenfeld residuals ph-test showed that all the variables contributed in the model satisfied the PH assumption of the Cox regressions (all $P > 0.05$). Harrell's C index for model was equal to 0.74, suggesting a reasonable agreement between observed outcome and that predicted by the model.

Table 3. Comparison of unadjusted and adjusted Hazard ratios between colon and rectal sites for demographic and clinical characteristics

Characteristic	Unadjusted		Adjusted	
	HR [a] (C/R)[b]	95% CI (C/R)[c]	HR[c] (C/R)[c]	95% CI (C/R)[c]
Age at Diagnosis				
45-65	.83	.50-1.39	.24	.074- .77
>65	.81	.45-1.47	.66	.12- 3.63
Gender (Female)	1.07	.67- 1.70	-----	-----
Marital Status (Married)	.98	.40- 2.41	1.78	.33- 9.62
Ethnicity				
Kurd	.92	.37- 2.27	-----	-----
Lor	1.98	.67- 5.86	-----	-----
Turk	.85	.46- 1.55	-----	-----
Other	1.17	.59- 2.32	-----	-----
Education				
Primary school	1.04	.54- 1.98	-----	-----
High school	.95	.46-1.99	-----	-----
University	1.10	.52- 2.35	-----	-----
BMI				
<18.5	1.07	.50- 2.28	1.21	.30 -4.85
25-29.9	1.35	.66- 2.77	1.54	.44 - 5.4
>30	2.15	.64- 7.28	1.01	.16 - 6.45
Alcohol History (past or current use)	2.53	.999-6.43	4.86	.67- 35.14
FAP (Present)	.38	.022-6.65	-----	-----
HNPCC (Present)	4.23	.47- 38.42	-----	-----
IBD (Present)	2.30	.27- 22.32	1.17	.12- 11.23
Familial History of Cancer (Present)	1.00	.62- 1.60	-----	-----
Pathologic stage (Advanced)	.86	.49- 1.50	.64	.21- 1.98

[a] Univariate Hazard Ratio based on unadjusted model; [b] Colon with respect to Rectum; [c] Multivariate Hazard Ratio based on adjusted model

From those significant factors from univariate analysis, gender and education could not enter in the multivariate analysis since their presence along with other variables made co linearity problem and they automatically removed from analysis. Based on the results of multivariate analysis (table 2), BMI, alcohol history, IBD and the pathologic stage of cancer were significant prognostic factors of colon cancer ($P < 0.05$), but age at diagnosis and marital status weren't significant for this cancer ($P > 0.05$). Also for rectal cancer, age at diagnosis, BMI, IBD and the pathologic stage of cancer were significant prognostic factors ($P < 0.05$), but marital status and alcohol history weren't significantly associated with survival of this cancer ($P > 0.05$).

Albeit in univariate analysis there were no statistically significant difference between colon and rectal cancers (table 3), but some substantial effect has been observed for BMI, alcohol history, FAP, HNPCC and IBD. Also in the adjusted analysis, age at diagnosis was significantly different between two sub-sites of colon and rectum (CI didn't include 1), but other factors weren't significantly different between these two sub-sites. Though not statistically significant,

there were some suggestive effect sizes in marital status, BMI, alcohol history and pathologic stage in the comparison of survival between colon and rectal cancers.

Colon and rectal specific survival curves based on adjusted analysis is showed that (Figure 1), adjusted survival of colon cancer patients fell down at about 0.3 in 100 month and continued up to end of study time with a straight line, but this occurred at about 0.7 in 100 month for rectal cancer. So, in total the adjusted survival of patients with rectal cancer is better than those of with colon cancer.

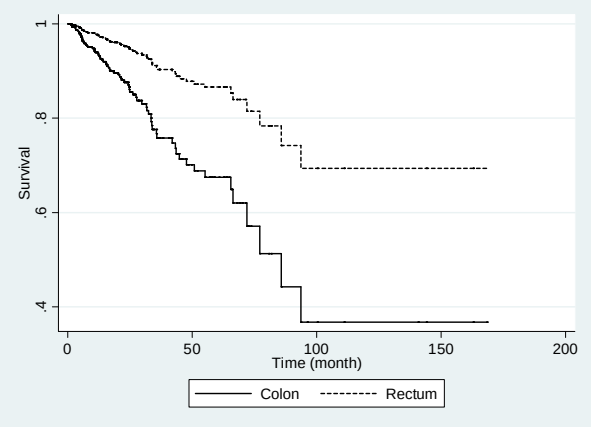

Figure 1. Adjusted survival probability for colon and rectal cancers

Discussion

CRC is a significant public health concern and its increasing rate in Iran (11-14). Heterogeneity of CRC by anatomical site necessitates analysis of mortality rates by tumor location. This study was conducted on 1219 Iranian CRC patients to evaluate the effect of specific prognostic factors of colon and rectal cancers.

In the univariate analysis, patient gender and BMI were significantly related to mortality for colon and rectal cancers. In the study by Wei et al. (2004), there was no significant correlation between colon and rectal cancer mortality and patient age, (39). Meguid et al (2008) reported a significant difference between colon and rectum in the age (47). Other studies have reporteded that the left-to-right shift in tumor location increases significantly with increasing age and year of diagnosis (16, 43, 45, 50), Roncucci et al (1996) showed reverse relationship (51). Studies comparing outcome for CRC and patient gender Wei et al (2004) reported no difference between colon and rectum (39). Other studies showed that men have more distal colon and rectal cancers, while women have more proximal colon cancers (16, 21, 43, 45, 47). Further studies have alluded to other patient factors such as educational achievement as factors associated with tumour locations and outcome, but the evidence for such associations remains controversial (16, 19, 23, 43, 44, 47, 52, 53).

BMI was an independent prognostic factor for both colon and rectum with slightly stronger hazard in colon site (although not significant). In the line with our study, there was no significant difference between colon and rectum in study by Wei et al (2004), but they reported BMI as a prognostic factor just for colon cancer (39). Le Marchand et al (1992) found associations of BMI with both proximal (caecum, ascending colon, transverse colon) and distal colon (descending colon, sigmoid colon and rectum) cancers (27, 17, 26, 29, 54, 55).

Although alcohol history was not significantly different between colon and rectal cancers, a substantial effect size of difference has been observed with stronger hazards in colon site (Univariate (U)HR (colon/rectum) =2.53, MVHR (colon/rectum) = 4.86)). Alcohol history was significant for colon cancer based on univariate and multivariate analysis (MVHR=2.3), but the association wasn't significant for rectum. This suggests that alcohol history may be an independent prognostic factor for just colon cancer. Like our findings, Wei et al. didn't observe any significant difference between these

sub-sites (39). Also, a review of 27 epidemiological studies showed that cohort studies reported risk estimates of 1.0–1.7 for colon cancer and the same for rectal cancer (56), but no comparison has been done between these two parts. Meta-analysis of cohort and case-control studies combined has reported moderately increased risks of CRC, with a dose-response relation for rising alcohol consumption (57, 58), but did not detect any differences in risk of colon cancer versus that for rectal cancer (58). High alcohol consumption has been associated with modest elevations of CRC risk in several recent studies with an excess of colon cancer (25, 28) has been noted among persons with chronic IBD (24). On the other hand, results of some other studies showed that alcohol was associated with tumors of the distal colon and Rectal (17, 57, 59). Different grouping of sub-sites characterization by different patterns of exposure, for example race and genotypes may be possible reasons for the apparently inconsistent findings (57).

IBD was highly significant for both colon and rectum (HR (colon) = 9.97 and HR (rectum) = 8.50), with slightly stronger association for colon site (HR (colon/rectum) = 2.3). CRC is the most common site of cancer in IBD (Ulcerative colitis (UC) and Crohn's disease (CD)) (40). In a population-based study, it was found that the risk for colon cancer among patients with both UC and CD is approximately 2-3 folds greater than the general population and that the risk of rectal cancer is increased 2-fold in UC but not CD (32). The effect of UC or CD on colon or rectal cancers was confirmed by other studies (60-67). In this study we made no separation between UC and CD, since colorectal carcinoma complicating UC is quite similar clinico-pathologically to that complicating CD and colorectal carcinoma associated with CD shared a 5-year survival rate similar to colorectal carcinoma occurring in UC (46% vs. 50%) (68).

Familial history was neither significantly nor suggestively different between these two sites of colo-rectum and it wasn't significantly related to colon or rectal cancers. However in a study by Wei et al (2004), it has demonstrated that familial history of CRC appears to affect relative risk (RR) of colon cancer (RR= 1.94 (1.80, 2.10)) more strongly than RR of rectal cancer (1.27 (1.08, 1.50)) (39) and in their study, Fuchs et al reported relative risk (RR) of 1.99 (95% confidence interval (CI): 1.50 –2.63) for colon cancer and a relative risk of 0.86 (95% CI: 0.43–1.70) for rectal cancer among those who reported a family history of colon or rectal cancer (35,38).

FAP and HNPCC weren't significantly different between colon and rectum, however a considerable effect size was observed in the univariate analysis; FAP produced stronger hazard in rectal cancer however HNPCC in colon cancer (FAP: HR (colon/rectum) = 0.378, HNPCC: HR (colon/rectum) = 4.23). Also, both FAP and HNPCC 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 rectal (69). However in the line with our findings, other studies reported that there is very strong preference for FAP individuals to develop CRC in the left colon while there is strong preference for HNPCC individuals to develop CRC in the right colon (36, 37, 41, 70). It has been hypothesized that different patho-genetic mechanisms can explain such differences (33, 39, 41). In addition based on a study done by Molaei et al. (2010) the estimation of prevalence of HNPCC in Iran was 5.5% of the total colorectal cancers (70), while in our study it was 9% in the line with another study (71).

The difference between colon and rectum was not significant for pathologic stage of cancer in univariate analysis and multivariate analysis but patients with colon cancer had better survival than patients with rectal cancer, suggestively (UHR (colon/rectum) = 0.86, MVHR (colon/rectum) = .639). Also,

pathologic stage of cancer was significantly associated with survival in colon and rectal cancers based on both univariate and multivariate analyses (Colon: HR = 1.94, Rectum: HR = 3.03). Therefore, pathologic stage is an independent prognostic factor of survival in both colon and rectum with a stronger association with mortality for rectal cancers. Finding of some studies are in the line with of our results (72). However, in a study by Meguid et al (2008), pathologic stage was significantly different between right and left colon (47) but they have just compared the frequency of the events but not the survival. Also they used large number of cases which provided more statistical power to detect the discrepancy significantly. In the other hand, some negotiations exist with regard to our findings (16, 41, 73).

Overall 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 status of patients with rectal cancer. However, other studies showed the reverse results (41, 42, 74, 75). There are some arguments too (3, 5, 9, 76, 77).

This study has a strength compared with other follow-up studies of colorectal cancer; by examining survival for cancer of the colon and rectum across prognostic factors, it has been possible to provide a fair comparison of outcome between tumors in these two segments of the bowel. However, with 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. Especially larger number of cases is needed to achieve higher statistical power to detect significant differences that have been asserted as suggestive or substantial. This was a limitation of our study. As another limitation, we didn't have access to part of the important data such as physical activity, diet and some genetic markers. Unknown cause of death in a few of cases was another limitation. Etiologic distinctions between the proximal and distal colon may exist (39, 41), which is our suggestion for another study.

In Conclusion, based on our findings there are differences between two sub-sites of colo-rectum. Albeit, only for age at diagnosis there was a statistically significant difference between colon and rectum, but for other factors including marital status, BMI, alcohol history and pathologic stage, some suggestive to substantial (though statistically non-significant) effect size of discrepancies were observed. Our findings support this hypothesis that some prognostic factors have different effect on colon and rectum. Therefore CRC is not a single entity and colon and rectum should be evaluated separately, in order to avoid neglecting useful information that will be beneficial for the study of the molecular mechanism, prognosis, and treatment application, designing clinical trials and developing appropriate treatments and planning screening programs.

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