RESEARCH COMMUNICATION

Patterns of Survival for Anatomical Sites of Colorectal Cancer with Shift to Advanced Lesions in Iran

Manijeh Ghabeljoo[1*], Mohammad Asghari Jafarabadi[2], Seyede Momeneh Mohammadi[3], Ebrahim Hajizadeh[4], Anoshirvan Kazemnejad[5], Seyed Reza Fatemi[6]

Abstract

Background: With a background of disparities in colorectal cancer (CRC) incidences/mortality across countries due to differences in exposure to various prognostic factors, this study aimed to evaluate the site-specific pattern for the survival of colon and rectal patients. Methods: A total of 1,283 patients with CRC diagnosis according to the pathology report of cancer registry of RCGLD from 1 January 2002 to 1 October 2007, were entered into the study. Data were analyzed using univariate and multivariate competing risk survival analysis. Results: Survival proportion of patients showed a significant trend for 1, 3 and 5 year survival in colon cancer (P<0.001) but this wasn't significant for rectal cancer (P=0.078). Tumor grade and pathologic stage were the most important factors predicting the survival in colon and rectal cancers with stronger hazard in the rectal site for grade and stronger hazard in the colon site for stage. For colon site, in the well and moderate categories of tumor grade, shifting from early to advance stage and also shifting in tumor grade from well and moderate categories to poor tumor grade had a considerable effect in hazard ratios. For rectum site, well to moderate shifting in tumor grade increased the hazard of death and shifting from early to advance stage increased the hazard equal to 2.54 and 4.36 times within the well and moderate tumor differentiation, respectively. In shifting to advance CRC, colon site had generally worse hazard than the rectum. Conclusion: Due to the worse conditions of CRC patients as shifting to advance cancer, to improve the effectiveness of treatment and hence the survival of Iranian patients, we should pay more attention to early detection, in particular by implementing population based screening programmes.

Keywords: Colorectal cancer - survival patterns - stage - grade - Iran

Asian Pacific J Cancer Prev, **12**, 1225-1231

Introduction

Differences in exposure to various prognostic factors for CRC are the most likely reason for the wide disparity in worldwide incidence and survival among which clinico-pathological characteristics play a major role. The prognosis of patients with colorectal cancer is predicted mainly based on clinico-pathological staging; histological grading and the prognosis vary with morphology (Halvorsen and Seimt, 1988, Ciccolallo et al., 2005). In addition, the differences in colorectal cancer survival between patients are likely to be attributable to differences in these factors.

Stage at diagnosis is the most important predictor of survival for patients with colorectal cancer. It can be greatly helpful for prescription of appropriate treatment and meaningful evaluation of treatment outcome (Xue et al., 2008). Tumor grading is routinely determined by the degree of differentiation of the tumor tissue has generally been considered to reflect the grade of malignancy (Ciccolallo et al., 2005), and the morphology type is a key factor predicting survival (Gatta et al., 2003). Since timely identification and removal of precursor lesions potentially can prevent colorectal cancer (Winawer et al., 1993) and early stage tumors are curable (Chyke et al., 2007; American Cancer Society, 2008), then this makes it necessary to study the effect of these factors especially on the survival. There are many studies showed that tumor grade, tumor size pathologic stage and mucin production and histology behavior are significantly related to the survival of CRC patients (Halvorsen and Seimt, 1988; Roncucci et al., 1996; Boyle and Langman, 2000; Du et al., 2004; Li et al., 2007; Moghimi-Dehkordi et al., 2008, Asghari-Jafarabadi et al., 2009).

However, pathological features-specific survival comparisons would be confounded by the bowel segments (Ciccolallo et al., 2005) and the impact of these factors on survival is greatly depended on the anatomic site of the

*[1]Department of Nursing Management, Faculty of Nursing and Midwifery, Islamic Azad University, Karaj Branch, Karaj , [2]Department of Statistics and Epidemiology, Faculty of Health and Nutrition, [3]Imam Khomeini Hospital, Tabriz University of Medical Sciences, Tabriz, [4]Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, [5]Shahid Beheshti University of Medical Sciences, Gastrointestinal Research Center, Tehran, Iran *For correspondence: manijehghabeljoo@yahoo.com*

bowel. Differences between sub-sites of CRC have been reported by some studies (Wei et al., 2004; Li et al., 2007; Meguid et al., 2008; Asghari-Jafarabadi et al., 2009), But it remains unclear whether there is a site-specific pattern for the survival of colon and rectal patients as shifting to an advanced CRC, and whether the pattern in colon and rectal cancers is different. Up to our knowledge, the evaluation of synergy effect of these factors has not been studied on survival site-specifically; especially none of studies evaluate the trend of survival with shifting tumor grade and pathologic stage to worse condition.

This study aimed to evaluate two hypotheses using frailty competing risks survival analysis: First there would be a decreasing trend for survival in colon and rectal cancers with shifting stage and grade to worse conditions; Second there exist different pattern of survival for colon and rectal cancers.

Materials and Methods

Study participants

In this longitudinal prospective survival study, data were attained from the database of Research Center of Gastroenterology and Liver Disease (RCGLD), Shahid Beheshti University of Medical Sciences, 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, 1283 patients (802 (67.2%) of subjects with colon cancer, 392 (32.8%) of subjects with rectal cancer) were entered in the study.

Follow up

The follow up time was defined as the date of diagnosis up to the March 2008 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 number of CRC patients (2.1%) wherein no information about the cause of death was obtained, but only the dates of their death were known, which were excluded from the analysis.

Subjects characteristics and pathological features

Subject characteristics examined included age at diagnosis, sex, ethnicity, marital status, and education. Clinico-pathological features examined included tumor location, diameter in millimeters, American Joint Commission on Cancer (AJCC) stage, histological grade, mucin production and histology behavior.

Pathologic stage of tumor was defined as I, II, III, and IV according to American Joint Committee on Cancer (AJCC) TNM (Tumor, Node, and Metastasis) staging criterion which is based on the extent of bowel wall penetration (T-stage), involvement of the regional lymph nodes (N-stage) and spread of tumor to distant surfaces or organs (M-stage). Stage I (T1–2N0M0), tumors limited to the bowel wall; Stage II (T3– 4N0M0), tumors spread through the muscular wall into the surrounding tissues; Stage III (T1–4N1–2M0), metastasis in the lymph nodes are present; Stage IV (T1–4N0–2M1), refers to tumors with distant metastasis (usually liver and/or lung) (American Joint Committee on Cancer, 1988, World Health Organization, 2000). Finally, stage I together with stage II were considered as early pathologic stage and stage III together with stage IV were categorized as advanced pathologic stage.

Tumor grade was separated into three categories: grade I (well differentiated), grade II (moderately differentiated), and grades III to IV (poorly differentiated or undifferentiated). A total of 470 (38.59%) tumors could not be staged and graded, which prevented any further investigation; in the results, these cases have been excluded from analysis. In addition, morphology type of tumor was defined as adenocarcinoma, not otherwise specified (NOS) versus non-adenocarcinoma. Mucin production status determined as mucinus or nonmucinus. Based on site topography of the cancer, the colon and rectal segments were separated.

Statistical Analysis

Statistical analyses were performed using STATA 10 software (StataCorp, College Station, TX). Survival time was calculated in months and was represented as 1, 3 and 5 year survival and their 95% Confidence Interval (CI), person-time and Incidence Density Rate (IDR) for each category of Grade-Stage. Finkelstein and Esaulova (2008), to solve the problem of bivariate frailty competing risks models, showed that when the components of the system are independent conditionally on independent frailty terms, then the mixture failure rate of the system can be constructed by the sum of mixture failure rate of individual components (Finkelstein and Esaulova, 2008, Asghari-Jafarabadi et al., 2010b). Based on this idea, the Lunn-McNeil (L-M) competing risk approach implemented on parametric survival models had been introduced for modeling the prognostic factors in the analysis. Based on Weibul parametric model, cause-specific Hazard Ratios (HR) (and their 95% confidence intervals (CI)) was presented as the effect size of interest (Klein and Bajorunaite, 2004, Lunn and McNeil, 1995). The HR of difference and its 95% CI was also computed. The assumptions of the hazard proportionality have been tested by Shoenfield residuals ph-test (Kleinbaum and Klein, 2005). P-values less than 0.05 were considered as significant.

Results

Study participants

Of all patients identified in the RCGLD database, a number of 470 (38.59%) tumors could not be staged and graded, therefore a total of 748 patients included in the analysis, from them 530 patients (70.86%) had colon cancer and 218 patients (29.14%) had rectal cancer. The median time at risk (± IQR) in month for patients with colon and rectal cancers was 21.1 (±24.8) and 20.27 (± 21.00), respectively. The mean (± SD) of age at diagnosis was 53.56 (±14.21) years in colon cancer and 55.03 (±37.63) years in rectal cancer patients. In patients with

Table 1. Multivariate Analysis of Survival with Reference to Clinico-Pathological Characteristics of Study Participants

Characteristic Categories		Colon Cancer		Rectal Cancer		Colon/ Rectum Comparison	
		HR (95% CI)	P-value[a]	HR (95% CI)	P-value[a]	HR (95% CI)	P-value[a]
BMI	18.6 - 24.9	1	-------	1	-------	1	-------
	<18.5	2.22 (1.06-4.24)	.034	1.20 (.44-3.29)	.724	1.85 (.52-6.55)	.340
	25-29.9	0.24 (.12-.50)	.000	0.37 (.17-.81)	.013	0.66 (.23-1.88)	.434
	>30	0.73 (.29-1.81)	.497	0.34 (.07-1.76)	.197	2.16 (.33-14.05)	.421
Tumor Grade (differentiation)							
	well	1	-------	1	-------	1	-------
	moderately	.61 (.34-1.10)	.101	2.10 (1.10-4.02)	.024	0.29 (.12-.69)	.005
	poorly	3.13 (1.02-9.56)	.045	0.93 (.19-4.56)	.930	3.36 (.55-20.56)	.190
Size	<20mma	1	-------	1	-------	1	-------
	>20mm	.88 (.25-3.13)	.840	1.97 (.35-11.07)	.442	0.45 (.05-3.81)	.460
Pathologic stage							
	I	1	-------	1	-------	1	-------
	II	1.92 (.56-6.59)	.301	0.36 (.10-1.24)	.105	5.40 (.93-31.44)	.061
	III	3.14 (.84-11.77)	.090	1.69 (.58-4.97)	.337	1.85 (.35-9.83)	.469
	IV	8.42 (2.09-33.93)	.003	4.00 (1.13-14.19)	.032	2.11 (.34-13.24)	.427
Grade-Stage Category							
	Well -early	1	-------	1	-------	1	-------
	Well -advanced	3.08 (1.65-5.77)	.000	2.54 (1.22-5.28)	.013	1.21 (0.48-3.07)	.682
	Moderate -early	1.18 (0.56-2.46)	.664	0.98 (0.38-2.55)	.963	1.21 (0.36-4.03)	.763
	Moderate -Advanced	2.51 (1.23-5.11)	.011	4.17 (1.88-9.25)	.000	0.60 (0.22-1.68)	.334
	Poor -early	6.08 (2.33-15.9)	.000	1.60 (0.36-7.18)	.593	3.80 (0.64-22.6)	.142
	Poor - Advanced	8.61 (0.83-89.3)	.071	0.47 (0.04-5.18)	.537	18.4 (0.65-517.4)	.088

[a]Based on Multivariate L-M or adjusted L-M model

colon cancer, 1, 3, and 5-year survival probability were 91.7%, 75.9%, and 63.3%, resp In well-early category of grade-stage, there were 184 patients (34.7%) in colon site with 1, 3 and 5 year survival equal to 0.94, 0.83 and 0.71 respectively with an IDR of 0.0055, and there were 61 patients (28.0%) in rectal site with 1, 3 and 5 year survival equal to 0.96, 0.73 and 0.47 respectively with an IDR of 0.0087. For well-advanced category, 184 (22.8%) patients with colon cancer had 1, 3 and 5 year survival equal to 0.86, 0.59 and 0.47 respectively and had an IDR of 0.0135, while 53 (24.3%) patients with rectal cancer had 1, 3 and 5 year survival equal to 0.88, 0.54 and 0.39 respectively and had an IDR of 0.0160.

There were a number of 90 patients (17.0%) in moderate-early category of grade-stage for colon cancer, whose 1, 3 and 5 year survival proportion were equal to 0.99, 0.73 and 0.61 respectively and their IDR was 0.0070, compared to a number of 37 patients (17.0%) in this category for rectal cancer, whose 1, 3 and 5 year survival proportion were equal to 0.91, 0.80 and 0.54 respectively, and their IDR was 0.0071. Moderate-advanced tumor grade-stage category of colon site had 90 (17.0%) patients who had 0.91, 0.59 and 0.45 as their 1, 3 and 5 year survival respectively, and an IDR of 0.0131, in contrast this category in rectal site had 55 (25.2%) patients who had 0.86, 0.48 and 0.36 as their 1, 3 and 5 year survival respectively, and an IDR of 0.0170.

Also for poor-early tumor grade-stage category, there were 16 (3.0%) colonic patients with 0.87, 0.42 and 0.14 as their 1, 3 and 5 year survival respectively, and an IDR of 0.0243, while there were only 4 (1.8%) patients with rectal cancer who had 1.00, 0.67 and 0.33 as their 1, 3 and 5 year survival respectively, and an IDR of 0.0170. Finally poor- advanced category consisted of 29 (5.5%) patients with colon cancer whose 1, 3 and 5 year survival proportion were 0.71, 0.56 and 0.56 respectively, and their IDR was 0.0139, in comparison this category consisted of 8 (3.7%) patients with colon cancer whose 1 and 3 year survival proportion were 1.00 and 0.80 respectively, and their IDR was 0.0062. In this category 5 year survival was not computed because there were no patient after 3 years to have an event after 3 years.

Univariate and Multivariate Analyses

It should be noted that a series of univariate L-M model were fitted for sex, age at diagnosis, marital status, educational level, ethnicity, BMI, histology behavior, morphology type, tumor size, tumor grade and pathological stage and the significant variables from this analysis including BMI, Tumor size together with Tumor grade and pathological stage were candidate to enter in the multivariate model.

For this model the frailty terms and the shape parameters of Weibul regression were significant ($p<0.05$). In addition, Shoenfield residual PH-test confirmed the fulfillment of PH assumption for all variables included in the model (all $P>0.05$).

Results for colon site*:* In this analysis, BMI, tumor grade and pathologic stage were significantly related to the survival probability for patients with colon cancer (all $P<0.05$), but tumor size showed no significant relationship with survival ($P>0.05$) (Table 1). Colonic patients with BMI category of <18.5 had 2.22 (95% CI= (1.06-4.24)) times more hazard than those patients in the reference category of 18.6- 24.9, while patients with BMI category of 25-29.9 had 76% (HR = 0.24, 95% CI= (0.12-0.50)) times less hazard than those patients in the reference

category.

Colonic patients with poorly differentiated tumor grade had 3.13 (95% CI= (1.02-9.56)) times more hazard than those patients in the reference category of well differentiated tumors. Also stronger hazard of death were observed for stage IV (HR = 8.42, 95% CI= (2.09-33.93)) compared to reference category of stage I tumor. In addition, the results for stage III, though not significant, but was considerable (HR = 3.14, 95% CI= (0.84-11.77), P=0.090) (Table 1).

Results for rectum site: BMI, tumor grade and pathologic stage were significantly related to the survival probability (all P<0.05), however tumor size showed no significant relationship (P>0.05) (Table1). Patients with rectal cancer and in the BMI category of 25-29.9 had 63% hazard less than those patients in the reference category (HR = 0.37, 95% CI= (0.17-0.81)).

Patients with moderately differentiated tumor grade had 2.10 (95% CI= (1.10-4.02)) times more hazard than those patients in the reference category of well differentiated tumors. Also stronger hazard of death were observed for stage IV (HR = 4.00, 95% CI= (1.13-14.19)) compared to reference category of stage I tumor (Table 1).

Colon versus rectum site: The difference between colon and rectum in survival probability was significant for tumor grade with better survival in colon site (Colon/Rectum (C/R) HR= 0.29, 95% CI = (0.12-0.69) and P<0.05) and it was suggestive (though not significant) for pathologic stage II with stronger hazard ratios in colon site (HR(C/R) = 5.40, 95% CI = (0.93-31.44) and P=0.061). However, there were no significant differences between colon and rectal cancers for BMI and tumor size (all P > 0.05). Therefore, from these variables pathologic stage and tumor grade were considered in subsequent analyses (Table 1).

Evaluation of Survival with Shift to Advanced CRC

For combination levels of pathologic stage and tumor grade, the trend test showed a significant increasing trend for hazard in colon cancer (HR for trend = 1.22, 95% CI = (1.13 – 1.33) and P < 0.001) but it wasn't significant in rectal cancer (HR for trend = 1.02, 95% CI = (.94 – 1.11) and P= 0.626). In addition the hazard in colon cancer was 1.20 (95% CI = (1.11 – 1.29)) times of it in rectal cancer (P < 0.001) (Table 3).

Colon site: In this analysis, well-early category of grade-stage considered as reference category (Table 1). Hazard of death for patients in well- advanced category was 3.08 (95% CI= (1.65 – 5.77)) times than reference category. There was a significant difference between moderate-advanced category and reference category (HR = 2.51, 95% CI = (1.23 – 5.11)). Hazard of patients with poor-early category was 6.08 (95% CI = (2.33 - 15.90)) times higher than those patients in reference category. Finally, in the poor-advance category, patients experienced the death followed by colon cancer 8.61 (95% CI = 0.83 – 89.37) times more than patients in reference category. Although in the latter case the result was non-significant,

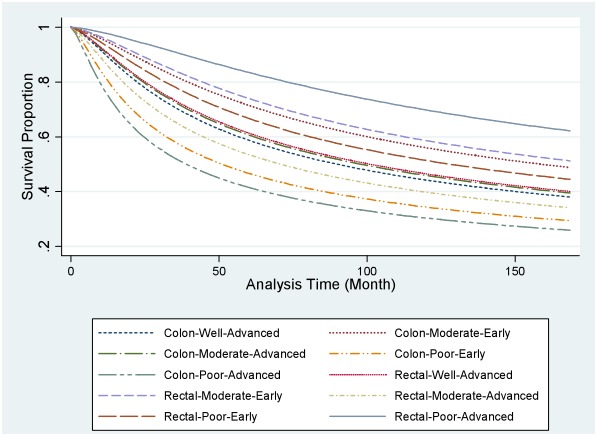

Figure 1. Adjusted Survival Curves for Colon and Rectal Cancers in Various Levels of Tumor Grade and Pathologic Stage

but a considerable HR was observed; it seems that this was highly related to the low number of events in this category. Also, the wide interval of HR was in the line of this problem. Moderate-early tumor grade -stages had no significant differences in hazard compared to reference category (P>0.05).

Rectum site: Patients in well- advanced tumor grade-stage had a hazard of 2.54 (95% CI= (1.22 – 5.28)) times higher than patients in reference category of well-early and the value of hazard was 4.17 (95% CI= (1.88 – 9.25)) times for moderate- advance category compared to reference category(Table 1). Other tumor grade – stages had no significant differences in hazard compared to reference category (All P>0.05).

Colon versus rectum site: There were no significant differences between colon and rectum sites within each category of grade-stage (Table 1). However an overall test showed that the colon site had generally worse hazard then the rectum site (HR(C/R) = 1.39, 95% CI = (1.21-1.58) and P<0.001).

Survival curves

The adjusted survival curves for colon and rectal cancers by grade-stage categories showed that was there better survival for patients with rectal cancer within poor-advance and moderate-early grade-stage tumors and the worst for colon in poor-advance grade-stage (Figure 1).

Discussion

The importance of CRC as a threat of public health and its increasing rate in our country, especially in youth through three recent decades (Hosseini et al., 2004; Pahlavan and Jensen, 2005; Ansari et al., 2006; Foroutan et al., 2008), make it necessary to study the prognostic factors of this cancer, especially pathologic stage, tumor grade and those which have a major role, for better decision making in the field of screening and control. Recently CRC in Iran was the concern of many epidemiological and clinical studies (Safaee et al., 2008; Fatemi et al., 2009; 2010; Hodadoostan et al., 2010).

With regard to 1) evaluate the trend for survival in colon and rectal cancers by shifting stage and grade to worse conditions and 2) to compare the pattern of survival between colon and rectal cancers, this study was conducted on Iranian CRC patients using frailty competing risk survival analysis. In addition, to achieve the unbiased estimate of the parameters, we used the gamma frailty correction in the Weibul hazard regression (Asghari-Jafarabadi et al., 2010a) based on the results of Finklestein and Esaulova (2008) (Finkelstein and Esaulova, 2008).

Survival proportion of patients showed a significant trend for 1, 3 and 5 year survival in colon cancer (Chi2 (5) = 26.20, P<0.001) but this trend wasn't significant for rectal cancer (Chi2 (5) = 9.91, P=0.078), though it seems considerable (table 1). Therefore, to address the first hypothesis of this study, survival proportion had a decreasing trend as shifting to advance CRC. In addition there was a considerable decrease in survival proportion as shifting from early to an advance stage within each level of tumor differentiation, except for poor differentiation in rectal site which could be explained by low number of patients in these categories. The same pattern of shifting was also observed for IDR. Results showed lower proportion of survival in rectal site for well and moderate differentiation and for both early and advance stage, except for 1 year survival in well- advance category. However, the reverse results were observed for poor differentiation. The same pattern of results could be inspected for IDR, so that the values of this quantity were lower in colon cancer for the first four categories of grade-stage (table 1), while the values were higher in colon site for poor-early and poor-advance categories.

The same results were observed by Kobayashi et al. (2006). In their study, patients were categorized into 4 groups of stages and in the colon cancer arm, the 5-year survival rates of the patients in groups 1 to 4 were 74%, 51%, 52%, and 54%, respectively. There was a significant difference in survival rate between groups 1 and 3 (P = .0002). In the rectum cancer arm, the 5-year survival rates of the patients in each group were 65%, 39%, 60%, and 32%, respectively. Similar to our case there are inconsistencies of survival rate by shifting within stage categories in both sites.

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 (Wei et al., 2004). Also similar with our findings, Sriamporn et al. (2007) reported lower risk of colorectal cancer (OR=0.5 95%CI=0.3-0.8) for subjects with higher BMI (Sriamporn et al., 2007), but some controversies exist for our results (Gerhardsson-deVerdier et al., 1990; Chyou et al., 1996, Colditz et al., 1997, Potter, 1999, Slattery et al., 2003, Adams et al., 2007).

Opposing to our findings for tumor size, in a study by Meguid et al, a significant difference in tumor size has been reported between sub-sites of CRC (Meguid et al., 2008). There is one study in the line with of our findings (Li et al., 2007).

Tumor g rade was an independent prognostic factor of colon cancer and in the multivariate analysis it was significantly related to the survival for patients with rectal cancer with better survival for colonic patients. There are some contrary findings (Roncucci et al., 1996; Takahashi et al., 2000), but a study reached to similar findings to those of us (Li et al., 2007; Hotokezaka et al., 2008).

The findings of our study confirmed this fact that the stage at diagnosis is the most important predictor of survival for patients with colorectal cancer. Pathologic stage was an independent prognostic factor for both colon and rectal cancers with higher hazard ratios in colon site (about 4.26 to 7.22 in the univariate analysis and 1.85 to 5.44 in the multivariate analysis). Finding of some studies are in the line with of our results (Hall et al., 2000). In the other hand, some negotiations exist with regard to our findings (Cheng et al., 2001, Haidinger et al., 2006, Li and Lai, 2009).

By shifting to advance CRC for colon site, in the well and moderate categories of tumor grade, shifting from early to advance stage had a considerable effect in hazard ratio, so that the hazard ratio prompted to a value of approximately 3 and 2 times for well and moderate tumor grade respectively. However, within the poor grade tumors this proportion was about 1.5 (8.61 divided by 6.08). In addition shifting in tumor grade from well and moderate categories to poor tumor grade had a great effect on hazard ratios; it forced a maximum shift in hazard ratios equal to 2.80 (= 8.61 / 3.08) and 6.08 (= 6.08 / 1), approximately for early and advanced stages respectively. By shifting to advance CRC for rectum site, well to moderate shifting in tumor grade increased the hazard of death 1.68 (= 4.27 /2.54) times within advance stage, however no significant changes was observed as shifting to poor grade within the advance stage and there were no significant changes as shifting in the grade categories from well to poor tumors within early stage. Also, shifting from early to advance stage had an effect of increasing the hazard equal to 2.54 (=2.54 / 1) and 4.36 (=4.27 / 0.98) times within the well and moderate tumor differentiation, respectively and the value of change in the poor grade was unexpected and in the reverse direction (a decrease in hazard was observed about 3 times). For colon – rectum comparison in the shifting to advance CRC, only for poor-advance category the difference was considerable so with worse condition in the colon site (HR (C/R) = 18.35, 95% CI = (0.65-517.47) and P=0.088), tough it was not statistically significant. The wide CI is a sign of instability for this category and unexpected results (as have been observed for individual evaluation of colon and rectum). As mentioned earlier, it might be due to low number of events in these categories. However the colon site had generally worse hazard than the rectum. In addition, it was just in advanced CRC (poor grade and advance stage) that the colon site showed worse condition than the rectum.

It seems that it would be an explanation for our previous results for better condition of rectal cancer in general (Asghari-Jafarabadi et al., 2009), which have been confounded by the overall test and have been illustrated now by separate evaluation of grade-stage tumors. Hall et al. (2000) opposing to our results, found that the disease-

free survival and mortality from cancers situated in the rectum appear to be no worse than for colonic cancers (Hall et al., 2000).

Unfortunately, a large percent of patients have advanced disease at the time of presentation (Radzniwan et al., 2009) in our study it was 48% for colon cancer and 54% for rectal cancer) and the reported 5-year survival rates for this stage colon and rectal cancer were low (Table 1). It was found that advance stages make the risk of deaths of cancers about 9 and 4 times more, respectively in colon and rectal cancers and this especially was considerable in poor grades of tumor, which in turn may affect the overall optimal outcome (Bethesda, 2007; Hotokezaka et al., 2008).

As results showed (Figure 1), there was no general rule for stating which colorectal site has better survival than the other and therefore, the anatomical sites should be separated and they should be compared within the categories of tumor grade and stage. Of note, poor-advance and moderate-early categories of rectal cancer showed unexpected results in the individually evaluation of it and as explained before it may be due to low number of event in these categories. However, other studies by evaluation total survival showed worse result for rectal cancer than colon cancer (Boyle and Langman, 2000, Gatta et al., 1998, LI and LAI, 2009, Steinberg et al., 1986, Xu et al., 2006, Roncucci et al., 1996)}. In one study the risk of death in patients with colonic cancer was estimated to be about one half (0.44) of the risk in those with rectal cancer (Halvorsen and Seimt, 1988). There are some arguments too (Berrino et al., 2007, Capocaccia et al., 1997, Hayne et al., 2001, Wilkes and Hartshorn, 2009, Zampinoa et al., 2004).

Finally, the hypothesis presented in this study was confirmed so that: First there was a decreasing trend for survival in colon and rectal cancers with shifting stage and grade to worse conditions; Second there existed different pattern of survival for colon and rectal cancers in the shifting to advance CRC.

This study has a strength compared with other follow-up studies of colorectal cancer; by examining survival for cancer of the colon and rectum in the various levels of stage and grade it has been possible to provide a fair comparison of outcome between tumors in these two segments of the bowel. These findings need to be updated with more recent data as they become available. Additional studies that include adequate samples and number of events within these categories especially in the advanced CRC (which was a limitation of our study) are required to support these results efficiently. Also, etiologic distinctions between the proximal and distal colon may exist (LI and LAI, 2009, Wei et al., 2004), which is our suggestion for another study.

In conclusion, this study confirms the paramount importance of stage at diagnosis and histological grade in the management of colorectal cancer. Since accurate staging together with histological grade are critical for appropriate treatment and meaningful evaluation of treatment outcome, this is an important part of our finding that each of these factors separately themselves and their combination levels especially in colon site showed a significant relationship with survival, so that there was a significant trend in colon site. These suggest that timely identification with regard to stage and grade and removal of precursor lesions especially in colon cancer potentially can prevent the cancer and early stage tumors are curable. The usual delay in presentation reinforces to use this evidence to initiate a screening program. In the exact words, to improve the effectiveness of treatment and hence the survival of Iranian patients with CRC, we should pay more attention to early detection, in particular by implementing population based screening programmes.

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