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Colon cancer as tow histopathological and molecular different type of cancer such as right and left

Mahlagha Zahedi[1*], Mansour Moghimi[1], Mahdi Yazdinejad[2]

1 Department of Pathology, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, mahlaghazahedi@yahoo.com

2 Department of urology, Azad Medical University of Medical Sciences and Health Services, Yazd, Iran.

Abstract

Background: Colon cancer is the second common cancer among men and the third among women, histopathological categories for anatomical assessment of colorectal carcinoma has not been defined properly. However, considering colon embryonic origination from mid- and hindgut, suggests the idea that there is histological and molecular differences between these two parts. Material & Method: From March, 2005 up to March, 2015, two hundred and ninety-one patient underwent curative surgery were included. Cases were studied for their age, gender, tumor location, site of tumor metastasis, tumor TNM classification, k-ras marker status and survival. Result: Right sided colon cancers were 100 cases and left sided were 129. Most of the patients with right sided cancers were young and female. Right sided tumors were significantly larger in size, presenting in higher grades than left sided tumors. However, the stages were the same in both sides. Right sided tumors K-ras mutant expression was approximately 1.5 times more than the left. Patients suffering from a right sided colon cancer had a less survival rate (RCC=22%, LCC=31.78%, P-value=0.001). Conclusion: It seems that there is clinical, histopathologic, and molecular difference between right and left sided colon tumors that they can be categorized in two separate groups. In our study, right sided tumors have more unfavorable characteristics rather than left sided ones. So, involved side (right side of tumor), older ages and stage of the tumor (higher stages) might be considered as independent poor prognostic factors of colorectal carcinoma.

Keywords: Colon cancer, Right, Left, Prognosis, Histopathology

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Introduction

Colorectal cancer is the second common malignancy among women and the third among men around the world, while the third and fourth among Iranian females and males, respectively (Bufill 1990; Torre et al. 2015).

The idea of epidemiologic, histopathologic, and cytogenetic differences between right and left sided colon cancers was suggested by Buffil, for the first time(Bufill 1990). Embryonic origins of the distal and the proximal colon are different; proximal colon including the cecum, ascending colon, and first 2/3 of transverse colon originates from midgut, supplied by the superior mesenteric artery, while distal which begins from splenic flexure and terminates to the superior part of anal canal originates from hindgut, supplied by the inferior mesenteric artery(Iacopetta 2002). Many studies have proved this category and mentioned the different clinical and histopathologic aspects of right and left sided colon cancers (Benedix et al. 2010; Price et al. 2015). Right-sided colon cancers which are more common among women, usually present as massive, bulky, and polypoid tumors growing into the lumen and causing anemia and weight loss. Moreover, mucinous adenocarcinoma and Microsatellite instability (MSI) have been reported to be present in the right side rather than the left. However, left-sided cancers infiltrate all around the lumen and may lead to its obstruction (Bufill 1990; Lee et al. 2015; Weiss et al. 2011).

Previous studies found that poorly differentiated, larger and high stage (stage III) tumors are more prevalent on the right side (Antúnez and Ganga, 2016, Benedix et al. 2010; Meguid et al. 2008; Weiss et al. 2011; Powell et al. 2012; Ishihara et al. 2012). In addition to clinical and histopathologic, there are also genetic differences between right and left-sided cancers. The 2 main genetic variations are MSI and chromosomal instability. MSI and CpG islands methylation have been reported more commonly in the right-sided cancers, while chromosomal instability, p53 and APC tumor suppressor genes inactivation, and KRAS oncogene activation are seen in the left-sided cancers more than the right (Pritchard and Grady 2011; Markowitz and Bertagnolli 2009; Gervaz, Bucher, and Morel 2004 and Nurgaliyeva et al., 2018).

Despite similar studies and results, the main reason for this category and its influence on the clinical outcome of the patients is controversial (Meguid et al. 2008; Suttie et al. 2011; Powell et al. 2012; Hemminki et al. 2010). We aim to compare the clinical, histopathologic and molecular features of right and left sided colon cancers and survival of the patients suffering from them in our retrospective study.

Materials and methods

From March, 2005 up to March, 2015, 291 patients with colorectal cancer treated with curative surgery were included in this retrospective study. This study has been confirmed by the ethics committee of Yazd Shahid Sadoughi University faculty of medicine numbered as

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ir.ssu.medicine.rec.1395.179. Written consent for research studies, a general policy of Shahid Sadoughi hospital as an educational and therapeutic center, was taken from all of the studied cases.

Patients with rectal cancer (N=36), those who catch other cancers (N=6), and cases with lack of complete follow up data (N=21) were excluded.

Remaining 229 primary colon cancer patients' data were arranged in a checklist including age, sex, location, size, histologic type, microscopic grading, tumor invasion depth, lymph node involvement, metastasis and it's site, TNM staging, diagnosis date, k-ras marker condition (from 2010), and patients phone number.

Right colon cancer was considered as cancers involving cecum, ascending colon, hepatic flexure, and transverse colon, while left colon cancer as splenic flexure, descending colon, and sigmoid based on previous studied (Distler and Holt 1997; Iacopetta 2002; McCashland et al. 2001; Gonzalez et al. 2001; Gervaz, Bucher, and Morel 2004).

TNM staging was done based on AJCC/UICC (Edge and Compton 2010).

All of the patients were followed up to 8/21/2017 by calling. Patients' average follow up period was 43.31±20.86 months (6m-144m). Cancer-specific survival is defined as the period of time from the diagnosis up to cancer-related death or last follow up date, while overall survival as the period of time from the diagnosis up to death due to any cause or last follow up date.

Statistical analysis

Statistical analysis was accomplished through SPSS 17 (SPSS INC. , Chicago , Il , USA). Chi-square test was used to assess the relation between histopathologic and demographic factors and tumor localization (right vs. Left colon) for nominal and sequential, and t-test for continuous variables. Overall survival and cancer-specific survival were assessed by Kaplan-Meier curve and survival difference was analyzed by Log-Rak test. Cox regression was applied to determine the effect of independent variables on prognosis.

Result

Patient's characteristics

Two hundred and twenty nine colorectal cancer patient were studied. The age average of these patients was 58.43±15.49 (14-88) years. One hundred (43.7%) of them had a right sided and 129 (56.3%) a left sided colon cancer. The difference of age average of patient in the 2 groups was studied with t-test analysis, that revealed no significant correlation between the involved side and the age of patients (P-value=0.151). Chi-square analysis was used to assess the sex distribution in relation to tumor localization and showed a significant correlation between these parameters (P-

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value=0.000). It means that right sided colon cancers are more common among women, while left sided in men.

Histopathologic characteristics

Out of 229 patients included, 181 (79%) patient had classic adenocarcinoma, 35 (15.3%) mucinous adenocarcinoma, and 13 (5.7%) were reported to have other types of carcinoma like neuroendocrine tumors and etc. classic adenocarcinoma is more common in the left side, while mucinous adenocarcinoma and other types are more common in the right side of colon(P-value=0.001). Tumor size average among all of the studied samples was 5.19±2.34 cm (SD=1-15 cm). Right sided tumors were larger in comparison to the left (6.35±2.56 cm (2-15) and 4.29±1.67 cm (1-9), respectively) (P-value=0.000). Fifty eight (25.3%) patients had a low grade (grade I), 156 (46.3%) medium grade (grade II), and 65 (28.4%) high grade (grade III) tumor. These findings demonstrate that high grade tumors were more common in the right side, while most of the left sided tumors were grade I and II (P-value=0.000) (detailed findings has been reported in table 1). There was 1 (0.4%) T_1 (tumor extension to submucosa), 13 (5.7%) T_2 (tumor extension to muscular layer), 132 (57.6%) T_3 (tumor extension beyond the muscular layer and to the pericolic tissues, such as pericolic fat), and 83 (36.2%) T_4 (tumor extension to visceral peritoneum and adjacent structures involvement, directly) tumor, considering both sides. There was not any significant correlation between depth of tumor invasion and tumor localization (P-value=0.613). One hundred and twenty seven patients presented lymph node involvement and the remaining 102 did not. Sixty two patient of those with right sided colon cancer and 56 of the left sided ones had lymph node involvement. These findings did not reveal any significant correlation between the lymph node involvement and tumor localization (P-value=0.079). Overally, 69 (30.1%) of patients presented distant metastasis. These findings indicated that the right sided colon cancers were more metastatic than those of the left side (37 and 32, respectively) (P-value=0.046) but there was not any significant difference between the right and left tumors for their site of metastasis (P-value=0.325) and tumor stage(P-value=0.069).

Molecular characteristic

There was 116 patients' documents for K-ras marker available, that 46 (39.7%) cases presented with mutant K-ras and 70 (6.3%) of them with wild type. Twenty nine (55.8%) patients of those with right sided colon cancer had mutant and 23 (44.2%) wild type K-ras. There was 17 patients with mutant and 47 wild type K-ras among the left sided colon cancers. Chi-square analysis revealed a significant difference between 2 groups (P-value=0.001). These findings demonstrated that K-ras mutant expression in the right-sided tumors is more common (1.5 times) than the left sided ones.

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Clinical outcome in relation to tumor localization

Survival average of the studied cases was 57.13±3.16 months (CI=95% [50.93-63.34]) and the 5-year survival was 27.51%. Survival average of the 100 right sided colon cancer patients was 42.07±2.32 months (CI=95% [37.53-46.61]) and 63.51+4.28 months (CI=95% [55.12-71.9]) for the 129 patients with left sided colon cancer. This finding were indicated the higher survival rate of the left sided colon cancers(P-value=0.0014).

Survival average of the patients with classic adenocarcinoma was 61.72±3.84 months (CI=95% [54.19-69.26]), and 39.84±2.79 months (CI=95% [34.38-45.30]) for those with mucinous adenocarcinoma . These findings demonstrated a significant correlation between the tumor histologic type and survival average as more survival of the classic adenocarcinoma type (P-value=0.0147).

Survival average of patients with stage I disease was 113.33±6.29 (CI=95% [101.01-125.65], and 70.43±5.20 (CI=95% [60.25-80.62]) for stage II, 49.21±1.9 (CI=95% [45.49-52.93]) for stage III, and 25.07±1.61 (CI=95% [21.91-28.24]) for patient with stage IV of disease. Cancer related deaths and survival rates for stages I to IV were 1 and 91.67%, 50 and 36.7%, 50 and 28.57%, and 65 and 4.41%, respectively. These findings demonstrated that higher the stage was, lower the survival average will be (P-value=0.000).

The patients with grade I survived 59.08±5.07 months as average (CI=95% [69.02-49.14]), and survival average of those with grade II and III was 60.25±4.95 (CI=95% [50.54-69.95]) and 41.60±2.61 (CI=95% [36.49-46.71]). Number of cancer related deaths and survival rates of the patients with grades I to III were 41 and 29.31%, 71 and 33.02, and 54 and 16.92, respectively. These findings showed that high grade tumors are associated with a lower survival average (P-value=0.035).

Survival average of patients aged 14-49 year was 78.15±7.26 months (CI=95% [63.92-92.3]). It was 56.62±4.15 (CI=95% [48.48-64.75]) and 36.53±1.84 months (CI=95% [32.91-40.15]) for 50-64 and 65-88 years old age groups, respectively. Number of cancer related deaths and survival rate in these age groups were 31 and 45.61%, 62 and 33.33%, and 73 and 7.59%, respectively. It means that survival average decreases in older ages (P-value=0.000).

Survival average for women and men was 61.40±4.70 (CI=95% [52.19-70.62]) and 52.01±3.34 (CI=95% [45.47-58-55]), respectively. Eighty four women died in this study and women survival rate was 30%. Men had 82 deaths and their survival rate was 24.77%. These findings demonstrated that men have lower survival rate than women (P-value=0.000).

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Based on the findings in Table 3, tumor localization (P-value= 0.026), age (P-value< 0.001), and tumor stage at diagnosis (P-value<0.001) are independent prognostic factors in colorectal cancer. The interesting finding was a poor prognosis for mucinous adenocarcinoma, when considered as univariable in cox regression analysis (table 2), while a better prognosis of that, when considered as multivariable in cox regression analysis (table 3). This might be due to the simultaneous tumor stage's effect on the analysis and must be interpreted carefully, because of the small number of patients in this study.

Table 1. Patient and tumor characteristics

Patients characteristics (229)	**Right sided (100) No. (%)**	**Left sided (129) No. (%)**
Age average	56.76±15.51 (14-86)	59.72±15.40 (17-88)
Gender		
Male	39 (39)	70 (54.3)
Female	61 (61)	59 (45.7)
Tumor histologic type		
Classic adenocarcinoma	68 (68)	113 (87.6)
Mucinous adenocarcinoma	22 (22)	13 (15.1)
Other	15(15)	3 (2.3)
Tumor size	6.35±2.56 cm (2-15)	4.29±1.67 cm (1-9)
Tumor microscopic grading		
I	22 (22)	36 (29.7)
II	33 (33)	73 (56.6)
III	45 (45)	20 (15.5)
Tumor depth of invasion		
T_1	0 (0)	1 (0.8)
T_2	4 (4)	9 (7)
T_3	58 (58)	74 (57.4)
T_4	38 (38)	45 (34.9)
Lymph node involvement	62 (62)	65 (50.4)
Distant metastasis	37 (37)	32 (24.8)
Distant metastasis site		
Lung	5 (13.5)	9 (28.1)
Liver	13 (35.1)	9 (28.1)
Other organs	4 (10.8)	1 (3.1)
Multiple organs	15 (40.5)	13 (40.6)
Stage at diagnosis		
I	2 (2)	10 (7.8)

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II	30 (30)	49 (38)
III	32 (32)	38 (29.5)
IV	36 (36)	32 (24.8)
K-ras mutant (116 patients)	29 (55.8)	17 (26.6)

Table 2. Univariable cox regression analysis. Determining different variables HRs on survival of patients with right- and left sided colon cancers.

Variable	HR	95% CI	P-value
Side			
Left	1		
right	1.59	1.17-2.17	0.003
Age	1.03	1.02-1.04	<0.001
Gender			
Male	1		
Female	0.96	0.71-1.30	0.809
Stage at diagnosis			
I	1		
II	11.32	1.55-82.43	0.017
III	17.68	2.41-129.39	0.005
IV	82.02	11.19-601.15	<0.001
Tumor histologic type			
Classic adenocarcinoma	1		
Mucinous adenocarcinoma	1.59	1.07-2.36	0.021
Other	1.18	0.64-2.20	0.583
Tumor microscopic grading			
I	1		
II	1.032	0.70-1.51	0.873
III	1.522	1.01-2.28	0.044

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Table 3. Multivariable cox regression analysis. Determining independent variables' HRs on survival of patients with right- and left sided colon cancers.

Variable	HR	95% CI	P-value
Side			
Left	1		
right	1.47	1.04-2.07	0.026
Age	1.05	1.04-1.06	<0.001
Gender			
Male	1		
Female	0.99	0.72-1.35	0.96
Stage at diagnosis			
I	1		
II	9.24	1.22-69.59	0.031
III	20.91	2.75-158.77	0.003
IV	123.34	15.89-957.11	<0.001
Tumor histologic type			
Classic adenocarcinoma	1		
Mucinous adenocarcinoma	0.47	0.25-0.86	0.015
Other	1.17	0.54-2.56	0.684
Tumor microscopic grading			
I	1		
II	0.76	0.50-1.15	0.201
III	1.13	0.62-2.07	0.683

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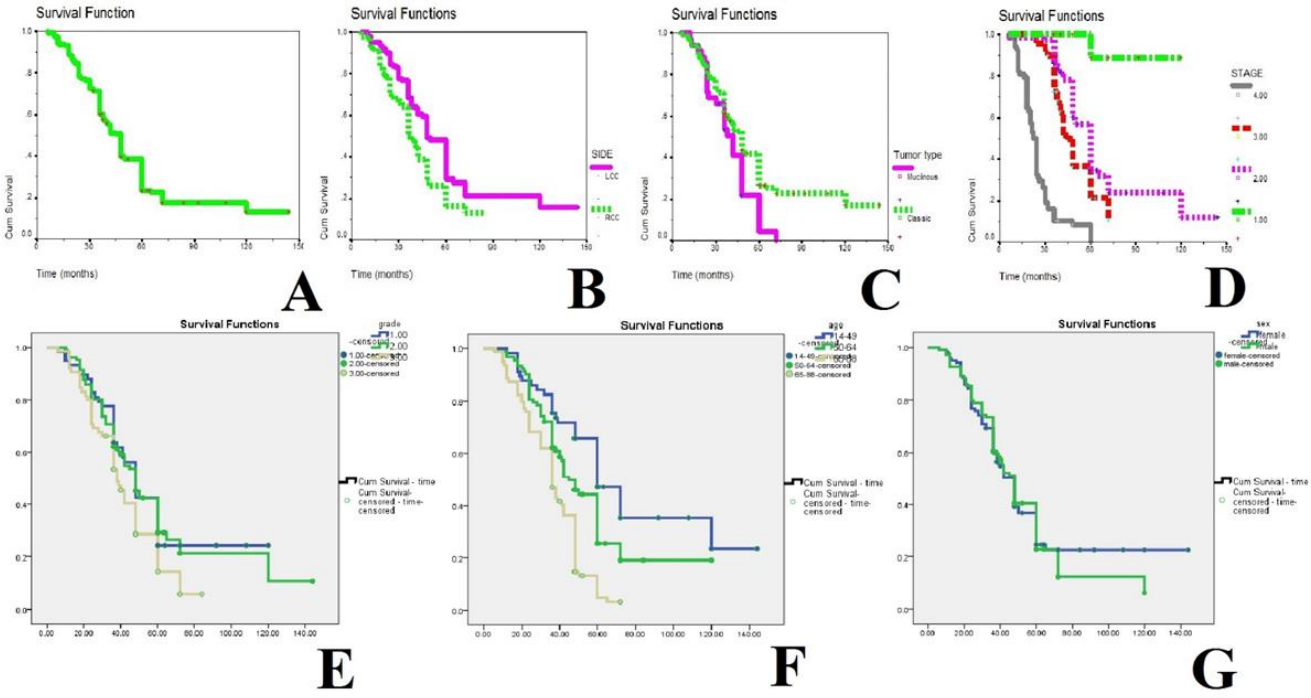

Figure 1. A- Survival average. B- Survival average in relation to tumor localization. C- Survival average in relation to tumor histologic type. D- Survival average in relation to stage at diagnosis. E- Survival average in relation to tumor microscopic grading. F- Survival average in relation to patients' age. G- Survival average in relation to patients' gender.

Discussion

In this study, there are 100 (43.7%) patients with right-sided colon cancer and 129 (56.3%) patients with left-sided colon cancer. Cancer-specific survival of right-sided colon cancers is less than left-sided colon cancers, which is an independent poor prognosis predictable factor. Large bowel divided into two parts: proximal (cecum, ascending and transverse colon) and distal (splenic flexure, descending colon, and sigmoid) that is because of their different embryonic origin. Many studies affirm this categorization, and consider different clinical, histopathological, and molecular differences.

The mean age prevalence of left-sided colon cancers (59.72±15.40) is 3 years more than right-sided colon cancers, but it is not statistically significant. However, other studies reported the old ages of right-sided colon cancers involvement (Zahir et al. 2016; Nitsche et al. 2016).

Right-sided colon cancers are more common in women (RCC: 61%, LCC: 45.7%, P-value= 0.000) which is also showed in Lee GH et al (Lee et al. 2015) and Weiss JM et al (Weiss et al. 2011) articles. The size of the right-sided colon cancer (6.35±2.56) is larger than left ones (4.29±1.67) that also indicate the previous studies results.

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The incident of grade III tumors are common in the right-sided colon; this histopathologic feature is also emphasized in other articles (Pritchard and Grady 2011; McCashland et al. 2001; Lee et al. 2015; Markowitz and Bertagnolli 2009; Gonzalez et al. 2001; Powell et al. 2012; Ishihara et al. 2012).

The right-sided mucinous adenocarcinoma frequency (22%) is approximately1.5 times more than the left side (15.1%); the same as Lacopetta B study in 2002 (Iacopetta 2002) and Benedix et al study in 2010 (Benedix et al. 2010).

Invasion depth (P-value = 0.613), lymph node involvements (P-value = 0.079), and metastasis sites, for example liver, lung, etc. (P-value= 0.0325) are not significantly different between two sides of the colon, the same as Nitsche et al (Nitsche et al. 2016) study. However, Benedix et al (Benedix et al. 2010) and Hussain et al (Hussain et al. 2016) studies showed more invasion depth and lymph node involvement in right-sided tumors.

Metastasis frequency of right-sided colon cancers (37%) in comparison with left side (24.8%) are significantly more common (P-value= 0.046). These data are not similar to Nitsche et al (Nitsche et al. 2016) study; this difference seems to be as a result of late diagnosis of right side tumors due to failure of cancer screening and prevention program (total colonoscopy) which begins at the age of 40. Based on the evidence of our study, low stages (I and II) tumors are common on left side of colon and stages III and IV are common in the right colon. This difference is not statically significant (P-Value= 0.069). Most of the prior studies such as: Meguid et al (Meguid et al. 2008), Benedix et al (Benedix et al. 2010), Weiss et al (Weiss et al. 2011), and Nitsche et all (Nitsche et al. 2016), stage II and III tumors were common in right side and stage I in left. Nitsche study also reported the same prevalence of stage IV tumors on both sides of the colon.

Oncogenic K-ras mutation is a prominent factor in metastatic colon cancer, because it makes anti epidermal growth factor therapy ineffective (Rosai 2011). It was found in 55.8% of right-sided colon cancers, that is approximately 2times more than of those of left side with the 26.6% frequency (P-value=0.001). These findings are accordant to previous studies (Zahir et al. 2016; Gonzalez et al. 2001). Five-year survival of right-sided tumors is 9% less than the left side. This result that right-sided colon tumors prognosis is poorer than left side has been reported in many similar studies, but the difference between the 5-year survival percentage varies: 3.4% (Meguid et al. 2008), 4% (Benedix et al. 2010), and 9% (Huang et al. 2015; Nitsche et al. 2016) which is the same as our study. However, some other articles declared that there is no difference between the 5-year survivals of both side cancers (Weiss et al. 2011; Powell et al. 2012). It has been suggested that better prognosis of left-sided colon cancer is due to colonoscopy leading to the early diagnosis (Meguid et al. 2008).

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Our study shows that site of involvement (right side of colon), old ages and high stages are an independent poor prognosis factor, which is similar to Nitsche et al (Nitsche et al. 2016) study except the type of tumor histology that is seems to be as a result of less samples of left-sided mucinous adenocarcinoma. Eventually, some other articles declared the poor prognosis of mucinous adenocarcinoma, due to its more rectal incidence and higher stages (Rosai 2011).

Conclusion

Colon cancer is divided into two groups:right and left.These two groups have different histopathologic,molecular and prognostic features.Worse prognosis and less survival occur in right colon cancer which is associated with clinical (anemia,weigh loss,…),histopathological (high microscopic grade,high percentage of mucinous adenocarcinoma) and molecular (more expression of mutant k-ras) characteristics.

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