RESEARCH ARTICLE

Right-Sided and Left-Sided Colon Cancers are Two Distinct Disease Entities: an Analysis of 200 Cases in Pakistan

Mudassar Hussain[1], Omer Waqas[1], Usman Hassan[1]*, Asif Loya[1], Noreen Akhtar[1], Sajid Mushtaq[1], Muhammad Aasim Yusuf[2], Aamir Ali Syed[3]

Abstract

Background: There is growing evidence that there are differences in histological and genetic characteristics along with clinical behavior between right- and left-sided colon carcinomas. We have compared various parameters of the two types and assessed associations of the results with prognosis in patients in Pakistan. Materials and Methods: We reviewed 200 cases from our institutional database; 100 cases of right-sided and 100 cases of left-sided colon cancer. Parameters including age, gender, TNM stage, histological features and clinical outcome were analyzed. Results: The patients with right-sided colon cancer were significantly older as compared to their counterparts with left-sided cancer. They presented with a lumbar mass rather than symptoms of obstruction and perforation as seen in left-sided colon cancers, and the histology showed higher percentage of poorly differentiated tumors with advanced pT stage. Moreover, Crohn's-like reactions, intra tumoral lymphocyte responses and other poor prognostic factors like lymph vascular invasion and perineural invasion were more common in right-sided cancers. Conclusions: We found that right- and left-sided colon cancers are different from each other in terms of clinical presentation, histology and clinical behavior. Right-sided colon cancers are more aggressive and are associated with poorer clinical outcome as compared to left sided colon cancers in our population.

Keywords: Colon cancer - right-sided - left sided - prognosis - Pakistan

Asian Pac J Cancer Prev, **17 (5)**, 2545-2548

Introduction

Colon cancer (CC) is the third most common cancer in the world with an estimated incidence of 72,090 cases for males and 70,480 for females in the USA annually. It is also the third most common cause of cancer-related death with an estimated 26,580 deaths of males and 24,790 deaths of females every year (Jemal et al., 2011). According to Pakistan Annual Cancer Registry Report 2012 by Shaukat Khanum Memorial Cancer Hospital & Research Centre, a total of 243 (5.01%) patients out of a total of 4,851 cancer patients were diagnosed with colorectal cancer and it is the second most common cancer in males and sixth most common in females in the year 2012 in Pakistan.

CC can present with a multitude of symptoms ranging from altered bowel habits and dragging sensation in the abdomen to feeling of abdominal mass and blood in stools. Certain demographic factors influence the prognosis, presentation and clinical behavior of the tumor including age, ethnic group, preexisting conditions and the type of tumor among many others. An interesting aspect is the site of involvement in CC, which may also have implications in addition to other features (Elnatan et al., 1996; Saltstein et al., 2007; Nawa et al., 2008; Weiss et al., 2011).

Recent studies have revealed that right-sided colon cancers (RSCC) pursue a different behavior in terms of epidemiology, clinical presentation, pathology and prognosis than the left-sided colon cancers (LSCC) (Papagiorgis et al., 2006; Meguid et al., 2008; Nawa et al., 2008; Banadix et al., 2010; Jess et al., 2013). Clinically the RSCCs are bulky, exophytic and polypoidal lesions projecting into the lumen and causing significant anemia, while LSCCs are infiltrating, constricting lesions encircling the lumen, often leading to obstruction and perforation (Lee et al., 2001; Cuffy et al., 2004; Lan et al., 2006; Gul et al., 2012; Ben-Ishay et al., 2013).

Several studies have shown that both cancers have different molecular pathways for carcinogenesis. High microsatellite instability (MSI-H) and CpG island methylation phenotype (CIMP) occur predominantly in the RSCCs while chromosomal instability (CIN) which is characterized by *K-Ras* and *p53* gene mutations along with loss of heterozygosity status (LOH) are more frequent in LSCCs (Bell et al., 1993; Bleeker et al., 2000; Soong et al., 2000; Toyota et al., 2000; Whitehall et al., 2001;

*[1]Department of Pathology, [2]Department of Internal Medicine, [3]Department of Surgery, Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan *For correspondence: drusmanhassan256@gmail.com,*

Buckowitz et al., 2005; Nakamura et al., 2005; Sugai et al., 2006; Ogino et al., 2009). Also the MSI-H which is associated with local lymphocyte infiltration seen in familial cancers syndrome is mostly seen in RSCCs (Peltomaki et al., 1997; Syngal et al., 2000; Terdiman et al., 2001; Percesepe et al., 2001; Potocnik et al., 2001; Jass et al., 2002; Umar et al., 2004; Terdiman et al., 2005).

In this study, cases of RSCC and LSCC were analyzed for age, gender, clinical presentation, primary tumor and nodal stage, histological features and prognostic factors. The aim of our study was to describe differences in the characteristics of LSCC and RSCC in our population.

Materials and Methods

This was a retrospective descriptive cross-sectional study carried out at Pathology Department of Shaukat Khanum Memorial Cancer Hospital & Research Center (SKMCH&RC). We reviewed and selected cases of RSCC and LSCC from January 1st 2001 to December 31st 2010. Only resection specimens were included. The cases with cancer of appendix and rectum and the cases with recurrent disease were excluded. The cases with cancer in cecum, ascending colon, hepatic flexure and transverse colon were considered RSCC and the cases with cancer in splenic flexure, descending colon and sigmoid colon were considered LSCC. The parameters analyzed were age, gender, clinical presentation, histological subtype, tumor grade, primary tumor and nodal stage, presence of Crohn's like reaction (CLR), presence of intra tumoral lymphocyte response (TIL), lymph vascular invasion and perineural invasion and clinical outcome. Mean, mode and median were calculated for quantitative variables (age), while frequencies and percentages were calculated for qualitative variables.

Results

A total of 200 cases including 100 cases each of RSCC and LSCC were analyzed. Both RSCC and LSCC showed almost equal distribution in males (52% for RSCC and 49% for LSCC) and females (48% for RSCC and 51% for LSCC) . Median age for both cancers in males and females were 53 years and 50 years respectively. Abdominal mass was the most common clinical presentation followed by anemia and weight loss in RSCCs and the majority of tumors were located in cecum and ascending colon. Descending colon and sigmoid colon were the frequent sites in LSCCs and these mostly presented in emergency with symptoms of obstruction and perforation. The site distribution and various parameters of CC are summarized in Figure 1 and Table 1.

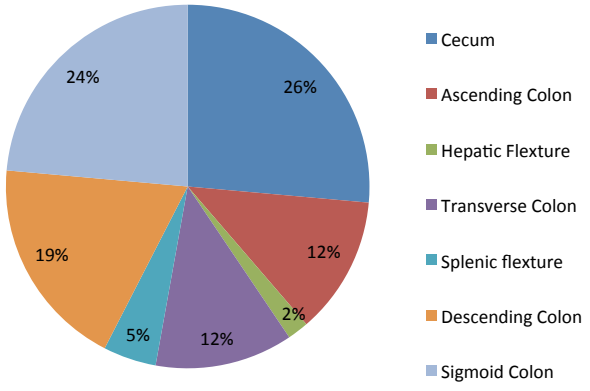

Figure 1. Anatomic Site Distribution of CCs

Pathological assessment showed higher proportions of poorly differentiated tumors (61%) in RSCCs than LSCCs (19%). Mucinous and signet ring cell features, lymph vascular invasion and perineural invasion were more common in RSCCs as compared to LSCCs. Crohn's like reaction and tumor infiltrating lymphocytes were more frequent in RSCCs. RSCCs also presented at higher pT and pN stages when compared with LSCRCs (Table 2).

Out of a total 100 cases of RSCC, only 47 patients showed up for follow up visits and 20 of them died within one year, 24 showed survivals between 2 to 3 years, while only 4 patients showed 3 year survival. Majority of the patients left the follow up after first year. In LSCCs, 49 out of total 100 cases came to follow up clinics, 9 patients with high clinical stage and high grade tumors died within

Table 1. Clinical Parameters, Tumor Grade (Differentiation) and Poor Prognostic Features Of Patients with RSCC and LSCC

Column1	RSCC	LSCC
Gender distribution		
Male	52	49
Female	48	51
Median Age (years)		
All	53	50
Male	46	50
Female	50	54
Clinical presentation		
Anemia and weight loss	17	1
Constipation	9	22
Mass abdomen	65	11
Bleeding per rectum	1	17
Emergency (perforation, ileus)	8	23
Tumor grade		
Low grade		
Well differentiated	0	12
Moderately differentated	39	69
High grade		
Poorly differentiated	61	19
Poor prognostic factors		
Mucinous differentiation	63	27
Signet ring cell features	35	10
Lymphovascular invasion	40	17
Perineural invasion	9	3
CLR	62	31
TIL	65	33

Table 2. pT and pN Staging of CCs

	RSCC (%)	LSCC (%)
pT		
pT1	0	0
pT2	6	13
pT3	67	71
pT4	27	16
pN		
pN0	40	64
pN1	22	19
pN2	38	17

the first year, 24 showed disease free survival of more than five years and remaining 16 showed survivals up to 3 years. All of them had early stage tumors, diagnosed on the endoscopic biopsy and underwent an elective surgery.

Discussion

Emerging amount of data regarding biological behavior of the tumor with respect to the location within the colon suggests that RSCC (cecum, ascending colon, hepatic flexture and transverse colon) pursue a different clinical course when compared to LSCC (splenic flexture, descending colon and sigmoid colon) (Nawa et al., 2008). A number of studies have been carried out in different regions of the world to describe the differences between the two cancers (Saltstein et al., 2007; Weiss et al., 2011; Jess et al., 2013). The incidence of RSCC and LSCC is different in different regions of the world. These cancers are shown to relate with age and gender. It has been found that RSCCs are found more frequently in older age group than LSCCs and RSCCs show female predisposition. RSCCs are known to present with the sign and symptoms of weight loss, anemia or abdominal mass and usually show advance stage at the time of presentation, while LSCCs present with acute abdomen (usually due to intestinal obstruction and perforation) in the emergency and bleeding per rectum (Lee et al., 2001; Cuffy et al., 2004; Lan et al., 2006; Gul et al ., 2012; Ben-Ishay et al., 2013). RSCCs are found to be bulky, exophytic and polypoidal lesions while LSCCs are mostly infiltrative and constricting lesions. RSCCs usually show high histological grade, pathological stage (pT) and poor prognostic features like mucinous differentiation and signet ring cell components. They are usually more resistant to chemotherapy as compared to LSCCs (Sargent et al., 2010; McGee et al., 2014).

In the present study, the incidence of RSCCs was more in males which is in contrast to what is seen in other regions of the world. The median ages for RSCCs and LSCCs were lower as compared to the studies carried out in the Western world which show median ages of 71 years and 68.5 years for RSCCs and LSCCs respectively (Saltzstein et al., 2007; Nwa et al., 2008; Weiss et al., 2011). In our study, RSCCs mostly presented with abdominal mass, anemia and weight loss while LSCCs presented with obstruction and bleeding per rectum. The clinical presentation for these cancers in our population was comparable with the available literature (Lee et al., 2001; Lan et al., 2006;Meguid et al., 2008; Nawa et al., 2008;Benedix et al., 2010; Jess et al., 2013). The frequent locations in RSCCs were cecum and ascending colon, and in LSCCs, were sigmoid colon and descending colon; this site distribution is similar to the results of a study by Papagiorgis et al (Papagiogis et al., 2006). We found that higher grade histology (poorly differentiated adenocarcinoma including mucinous and signet ring cells adenocarcinoma), advance pT & pN stages and lymph vascular invasion / perineural invasion were seen more commonly in RSCCs as compared to LSCCs. These findings are consistent with the findings of studies carried out in other regions (Lee et al., 2001; Cuffy et al., 2004; Lan et al., 2006; Ben-Ishay et al.. 2013).

In this era of molecular genetics, a number of researches have been focused on determining the molecular pathways leading to both RSCCs and LSCCs. High microsatellite instability (MSI-H) which is reflected by local lymphocyte reaction (CLR and TIL) has been seen mostly in RSCCs ((Bell et al., 1993; Bleeker et al., 2000; Soong et al., 2000; Whitehall et al., 2001; Buckowitz et al., 2005; Nakamura et al., 2005; Sugai et al., 2006; Ogino et al., 2009). This characteristic pathway is also implicated in HNPCC syndrome, a condition which is found in 2-5 % of all colorectal cancer patients. In addition to MSI-H, CpG methylation island phenotype (CIMP) has been suggested to contribute to the RSCC carcinogenesis. On the other hand, mutations in the *p53* and *K-Ras* gene which correspond to chromosomal instability (CIN) along with loss of heterozygosity (LOH), are reported to occur frequently in LSCCs RSCCs (Peltomaki et al., 1997; Syngal et al., 2000; Terdiman et al., 2001; Percesepe et al., 2001; Potocnik et al., 2001; Jass et al., 2002; Umar et al., 2004; Terdiman et al., 2005). Our results are in concordance with the above mentioned findings. We also found that the poor prognostic parameters including Crohn's like reaction (CLR) and Tumor infiltrating lymphocytes (TIL) were mostly seen in RSCCs.

Although we could not retrieve the follow-up data of all the patients but the limited available information revealed that death rates were more in RSCCs than LSCCs. All of these RSCC cases showed advanced stage disease along with high grade histology (poorly differentiated) and additional poor prognostic parameters (signet ring cell features, mucinous features, lymph vascular invasion and perineural invasion). LSCCs patients, in our study, showed better five year survival rate when compared with LSCCs. Other studies depict similar results indicating that the long term survival was better in LSCCs than RSCCs and depends upon the stage, histology and associated poor prognostic features (Elnatan et al., 1996; Weiss et al., 2011; Hemminki et al., 2010; Hansen et al., 2012; Jess et al., 2013).

We have described the characteristics of RSCCs and LSCCs in our patients and have found that these two disease entities are distinctly different. Our findings are no different from the data of other regions of the world and highlights the importance of considering and managing these two cancers in different and purposeful manner.

In conclusion, RSCCs and LSCCs show distinctively different characteristics in terms of presentation and prognostic features. It appears that the site of tumor is helpful in determining the behavior and the prognostic implication. Demographic features may affect the characteristics of tumor but generally LSCC and RSCC show similar pattern in different ethnic groups. Further studies on a larger scale are required in order to determine distinct management and treatment plans for these separate entities.

References

Jemal A, Bray F, Center M, Ferlay J, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.

Kawamoto H, Kato J, Nawa T, et al (2008). Differences between right and left-sided colon cancer in patient characteristics, cancer morphology and histology. *J Gastroenterol Hepatol*, **23**, 418-23.

Kennedy G, Weiss JM, LoConte N, et al (2011). Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results–medicare data. *JCO*, **29**, 4401-9.

Smith DR, Goh HS, Elnatan J (1996), Activation and the biological behavior of proximal and distal colonic adenocarcinomas. *Eur J Cancer*, **32**, 491-7.

Behling CA, Saltzstein SL (2007). Age and time as factors in the left-to right shift of the sub site of colorectal adenocarcinoma: a study of 213,383 cases from the california cancer registry. *j clin gastroenterol*, **41**, 173–7.

Karapanagiotou I, Oikonomakis I, Papagiorgis P, et al (2006). The impact of tumor location on the histopathologic expression of colorectal cancer. *J BUON*, **11**, 317-21.

Hansen IO, Gamborg M, Jess P, Jess T (2013). A nationwide Danish cohort study challenging the categorization into right-sided and left-sided colon cancer. *BMJ*, **3**, 2608

Benedix F, Meyer F, Lippert H, Gastinger I, Kube R, Schmidt U, (2010). Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology and survival, *Dis Colon Rectum*, **53**, 57-64.

Wolfgang CL, Chang DC, Slidell MB, Ahuja N, Meguid RA (2008). Is there a difference in survival between right-versus left-sided colon cancers? *Ann Surg Oncol*, **15**, 2388–94.

Kawamoto H, Kohno H Kato J, Nawa T, et al (2008). Differences between right- and left-sided colon cancer in patient characteristics, cancer morphology and histology. *J Gastroenterol Hepatol*, **23**, 418-23.

Jiang J, Lin J, Chen W, Yang S, Lin T, Lan Y, et al (2006). Obstructive left-sided colorectal cancer: a comparison between primary resection and delayed resection. *J Soc Colon Rectal Surgeon*, **51**, 306-11

Chu KW, Poon RT, Law WL, Lee YM (2001). Emergency surgery for obstructing colorectal cancers: a comparison between right-sided and left-sided lesions. *J Am Coll Surg*, **192**, 719-25.

Abir F, Cuffy M, Audisio RA, Longo WE (2004). Colorectal cancer presenting as surgical emergencies. *Surg Oncol*, **13**, 149-57.

Othman A, Brauner E, Ben-Ishay O, Kluger Y, Peled Z (2013). Clinical presentation predicts the outcome of patients with colon cancer. *World J Gastrointest Surg*, **5**, 104-9.

Gul A, Gul Sharif G, Alam SI (2012). Clinical presentations of colorectal carcinoma in patients below 40 years of age presenting to a tertiary care level hospital. *J Med Sci*, **20**, 67-7

Fuchs CS, Nosho K, Ogino S (2009). Lymphocytic reaction to colorectal cancer is associated with longer survival, independent of lymph node count, Msi and CpG island methylator phenotype. *Clin Cancer Res*, **15**, 6412-20.

Buckowitz A, Benner A, Bläker H, et al (2005). Microsatellite instability in colorectal cancer is associated with local lymphocyte infiltration and low frequency of distant metastases. *British J Cancer*, **92**, 1746-53.

Sugai T, Habano W, Jiao Y, et al (2006). Analysis of molecular alterations in left- and right-sided colorectal carcinomas reveals distinct pathways of carcinogenesis. *J Molecular Diagnostics*, **8**, 193-201

Blair GE, Cross D, Lewis FA, Bell SM, et al (1993). Prognostic value of *p53* overexpression and *K-Ras* gene mutations in colorectal cancer. *Gastroenterol*, **104**, 57-64.

Nakamura S (2005). Analysis of allelic imbalances at multiple cancer related chromosomal loci and microsatellite instability within the same tumor using a single tumor gland from colorectal carcinomas. *Int J Cancer*, **114**, 337-45.

Leggett BA, Young J, Walsh MD, Jass JR, Whitehall VL (2001). Methylation of O-6-methylguanine DNA methyltransferase characterizes a subsetof colorectal cancer with low- low-level DNA microsatellite instability. *Cancer Res*, **61**, 827-30.

Karrenbeld A, Hayes VM, Bleeker WA, et al (2000). Impact of KRAS and T*P53* mutations on survival in patients with left and right-sided Dukes' C colon cancer. *Am J Gastroenterol*, **95**, 2953-7.

Powell B, Elsaleh H, Soong R, et al (2000). Prognostic significance of T*P53* gene mutation in 995 cases of colorectal carcinoma. Influence of tumor site, stage, adjuvant chemotherapy and type of mutation. *Eur J Cancer*, **36**, 2053-60.

Issa JP, Ohe-Toyota M, Toyota M, Ahuja N, (2000). Distinct genetic profiles in colorectal tumors with or without the CpG island methylator phenotype. *Proc Natl Acad Sci*, 97, 710-15.

Terdiman JP (2005). Is time to get serious about diagnosing Lynch syndrome (HNPCC with defective DNA mismatch repair) in the general population? *Gastroenterol*, **129**, 741-74.

Umar A, Chapelle A, Boland CR, Terdiman JP, Syngal S, et al (2004). Revised Bethesda guidelines for Lynch Syndrome and MSI. *JNCI*, **96**, 261-68.

Leggett BA, Jass JR, Young J, Simms LA, Walsh MD, (2002). Distinction between familial and sporadic forms of colorectal cancer showing DNA microsatellite instability. *Eur J Cancer*, **38**, 858-66.

Glavac D, Ravnik-Glavac M, Golouh R, Potocnik U (2001). Causes of microsatellite instability in colorectal tumors: implications for hereditary non-polyposis colorectal cancer screening. *Cancer Genet Cytogenet*, **126**, 85-96.

Vasen HF, Peltomaki P (1997). Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. *Gastroenterol,* **113**, 1146-58.

Miller GA, Terdiman JP, Gum JR Jr, Conrad PG, Crawley SC, Weinberg V, et al (2001). Efficient detection of hereditary non-polyposis colorectal cancer gene carriers by screening for tumor microsatellite instability before germline genetic testing. *Gastroenterol*, **120**, 21-30.

Eng C, Fox EA, Garber JE, Kolodner RD, Syngal S (2000). Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. *J Med Genet*, **37**, 641-5.

32.Percesepe A, Di Gregorio C, Borghi F, Losi L, Foroni M, Menigatti M, et al (2001). Molecular screening for hereditary non-polyposis colorectal cancer: a prospective, population-based study. *J Clin Oncol*, **19**, 3944-50.

Benson AB, McGee MF (2014). Adjuvant chemotherapy for stage II colon cancer: everyone still needs a tailor. *Ann Surg Oncol*, **21**, 1765-67

Sargent DJ, Monges G, Marsoni S, et al (2010). Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil based adjuvant therapy in colon cancer. *J Clin Oncol*, **28**, 3219-26.

Hansen IO, Jess P (2012). Possible better long-term survival in left versus right-sided colon cancer - a systematic review. *Dan Med J*, **59**, 4444

Santi I, Hemminki K, Weires M, et al (2010). Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes. *BMC Cancer*, **10**, 688.