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Original Article

Histomorphological Differences Between Right and Left Sided Colon Cancers

Danyal[1], Saria Saeed[2], Sarah Yousuf[3], Sara Ziaullah[4] and Fozia Rauf[5]
[1, 2,3,4,5] Department of Pathology, Peshawar Medical College, Peshawar, Pakistan

ABSTRACT
Introduction: Colorectal cancer (CRC) is third most common cancers of the world. Right and left sided colorectal cancers are different with respect to clinical, histological, and genetic aspects.
Objectives: The objective of the study was to analyze and compare right and left sided colorectal cancers regarding different clinic-pathologic parameters like grade, subtypes, stage of colorectal carcinoma.
Materials and Methods: A retrospective cross sectional comparative (Analytical) study was conducted at Department of Pathology, Peshawar Medical College during January 2022. Study included consecutive cases of CRC received at PMC Labs, Histopathology section from 2011 – 2021. Hematoxylin and Eosin slides were re-examined for Tumor Subtype, Grading, AJCC staging, Vascular Invasion, and Perineural Invasion. Cases do not have all the study para meters were excluded. Statistical analysis was performed using SPSS version 20.0. Chi Square test and Fisher's exact tests were performed for categorical variables.
Results: Left sided colorectal cancer cases were more common than left sided colorectal cancer cases. Mean age for right sided Colorectal Cancers (RSCRC) was 52.88 ±16.54 years and 44.03 ±13.81 for left sided colorectal cancers (LSCRC). Male to female ratio was 1.7:1 and 2:1 for Right and Left sided colorectal cancers respectively. Most common site for right sided CRCs was Cecum and that for left sided CRCs was Sigmoid Colon.
Adenocarcinoma (Mucinous type) was significantly associated with RSCCs although Adenocarcinoma NOS was the predominant Subtype for both sides. Right Sided CRCs exhibited greater (average diameter) tumor size, advanced stage and more lymph nodes harvest.
No difference was identified between right and left side regarding Tumor perforation, N stage, Tumor differentiation, lympho-vascular invasion and Perineural invasion.
Conclusion: Our study concluded that RSCC and LSCRC are quite diverse entities. RSCC is associated with older age, increased tumor size, Advanced T stage, Mucinous Subtype, and more lymph node harvest.
Keywords: CRC, Right Sided Colonic Carcinoma, Left Sided Colonic Carcinoma, Prognosis, Pakistan

Introduction

Colorectal cancer (CRC) is third in ranking among commonly diagnosed cancers of the world after breast and lung cancer, according to GLOBOCAN 2020 data with an incidence rate of 10% and 19.3 million new cases. It is also the 2nd leading cause of death worldwide with a mortality rate of 9.4 % [1].
Currently, the rate of colorectal cancers is 3 times higher in developed countries [2]. but the incidence rate of CRC is on rise in developing countries [3,4]. This change in developing countries is mainly attributed to two CRC associated risk factors i.e., increase in animal source food intake and sedentary lifestyle that leads to obesity [5].

CORRESPONDENCE AUTHOR
Dr. Danyal
Department of Pathology, Peshawar Medical College, Peshawar, Pakistan
Email: danyalkhattak91@gmail.com

In Pakistan, according to the data compiled by *Shaukat Khanum Memorial Cancer Hospital & Research Center* SKMH from Dec 1994 to Dec 2020, colorectal carcinoma stood 2nd among all cancers [6].
Based on embryological origin, blood supply and type of surgeries, colon is divided into right side and left side. Parts' originating from the midgut is right side of the colon, including cecum, ascending colon, transverse colon (proximal 2/3rd) and appendix. Parts originating from hindgut are considered left side of the colon. This includes transverse colon (distal 1/3rd), splenic flexure, descending colon, sigmoid colon and rectum. Hence, the RSCRC tumors arise from ascending colon, and proximal two thirds of the transverse colon and the LSCRCs arise from the descending and sigmoid colon, and distal one third of the transverse colon [7].
Several clinicopathologic parameters define the prognosis for colorectal carcinoma. According to American Joint Committee on Cancer (AJCC) the

prognostic factors for colorectal carcinoma can be divided into four different categories. The most important among them are TNM stage (**T**umor, **N**odes, **M**etastases), serum *CEA* (carcinoembryonic antigen), *Vascular invasion, Perineural invasion, Status of surgical margins and microscopic grade of CRC* [8]. However, tumor side has also come to attention for its significant role as an effective prognostic and predictive factor in the management of colorectal cancers. Studies have suggested that RSCCs have a poorer prognosis as compared to LSCRCs. Colon cancers of both sides responds to biological therapies differently [9].

Therefore, we examined 50 CRC cases received at our lab to determine the differences between right and left CRCs in our population.

Material and Methods

This Cross-Sectional analytical study was conducted at Department of Pathology, Peshawar Medical College, Peshawar. Study included all the consecutive cases of CRC received at PMC Labs, Histopathology Division from 2011 – 2021. Data was retrieved from electronic archives of PMC diagnostic Labs, Histopathology Division. Right and Left Hemi colectomy specimens were included in the study. Cases with incomplete information were excluded. Cases with cancer in cecum, ascending colon, hepatic flexure and transverse colon were considered RSCC and cases with cancer in splenic flexure, descending colon, sigmoid colon and rectum were considered LSCRC. Hematoxylin and Eosin slides were re-examined for Tumor Subtype, Grading, AJCC staging, Vascular invasion, and Perineural invasion

Variables included were age, gender, histological subtype, tumor grade, primary tumor and nodal stage, lymph vascular invasion and Perineural invasion. Data was entered in the statistical package for social sciences (SPSS) version 20.0 for Statistical analysis. Mean and standard deviation were calculated for quantitative variables (age), while frequencies and percentages were calculated for qualitative variables. Chi Square Test and Fisher Exact Test were used to analyze categorical variables. Probability value (P) ≤0.05 was considered statistically significant. This study was approved by the Institutional Review Board, Peshawar Medical College, Riphah International University.

Results

Study included 50 cases of CRC. Among 50 cases, 32 were male (64%) and 18 (44%) were female. Male to female ratio was 1.7:1. Mean age of all the cases was 47.04 ±15.233**.** Age range was 18 – 80 years. Majority of the cases were < 50 years of age (n=29, 58%) (Table 1). Tumor size (average diameter) was 5.6 cm. Tumor perforation was observed in 11 (22%) cases.

LSCRC cases (n=33/50, 66 %) were more as compared to RSCC cases (n=17/50, 34%). Most common subtype of CRC was 'Not otherwise specified' (NOS) n=38 (76%), followed by 'Mucinous type' (n=9, 18 %) and 3 cases (6 %) were 'Signet ring cell type'.

Most CRCs were Well Differentiated (n=33, 66%), followed by Moderately Differentiated (n=10, 20%) and Poorly Differentiated cases (n=7, 14%).Most common tumor invasion (T) category for RSCRC was 'T3' (n=30, 60%) followed by 'T4' (n=11, 22%), T2 (n=9, 18%) and T1 (n=0).Majority of the cases (n=27, 54%) showed absence of lymph node metastasis while a significant number of cases (n= 23, 46 %) showed involvement of lymph nodes by tumor. Stage N2 cases were more (n=12, 24%) than stage N1 cases (n=11, 22%). Average number of lymph nodes recovered per case was 11. Only 23 (46%) cases showed vascular invasion while 11 cases (22%) showed Perineural invasion.

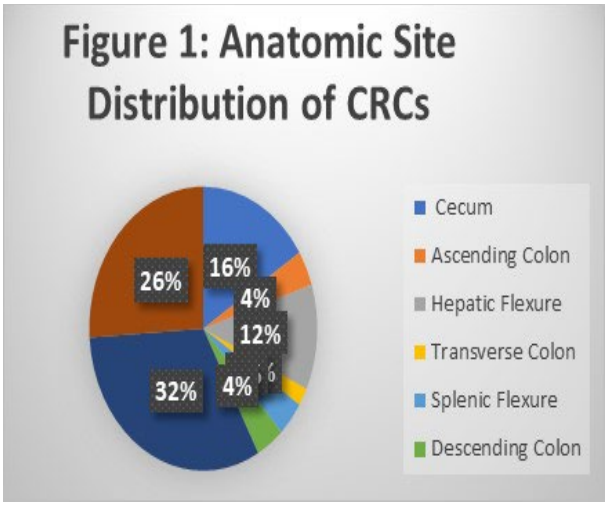
Clinicopathologic Parameters of Right-side Colorectal Cancers

Among 17 RSCRC cases, 10 were male (58.82%) and 7 (41.17%) were female. Male to female ratio was 1.7:1. Mean age of RSCR cases was 52.88 ±16.54. Age range was 18 – 80 years. Majority of the RSCRC were ≥ 50 years of age (n 10=, 58.82%) (Table 1). Tumor size (average diameter) was 7.2 cm. Tumor perforation was observed in 3 (17.64%) cases. Most common site for RSCRC was Cecum. Most common subtype of RSCC was 'Not Otherwise Specified' (NOS) n=10 (58.82%), followed by 'Mucinous Type' (n=7, 41.17%).

Most RSCRCs were Well Differentiated (n=11, 64.7%), followed by Moderately Differentiated (n=4, 23.52%) and Poorly Differentiated Cases (n=2, 11.76%). Most common tumor invasion (T) category was 'T3' (n=11, 64.7%) followed by 'T4' (n=6, 35.29%). Majority of the RSCRC cases (n=8, 47.05%) were N0 followed by N2 cases (n=5, 29.41%) and N1 cases (n=4, 23.52%). The average number of lymph nodes recovered per case was 14. Only 8 (47.05%) cases showed vascular invasion while 3 cases (17.64%) showed perineural invasion.

Clinicopathologic Parameters of Left Colorectal Cancers

Among 33 cases of LCRCs, 22 were male (66.66%) and 11 (33.33%) were female. Male to female ratio was 2:1. Mean age of LSCRC cases was 44.03 ±13.81. Age range was 20 – 70 years. Majority of the LSCRC cases were < 50 years of age (n=22, 69.66%) (Table 1).Tumor size (average diameter) was 4.8 cm. Tumor perforation was observed in 8 (24.24) cases. Most common site was Sigmoid Colon. Most common subtype of CRC was 'Not Otherwise Specified' (NOS) n=28 (84.84%), followed by 'Signet Ring Cell Type' (n=3 cases, 9.09%) and 'Mucinous Type' (n=2, 6.06%).



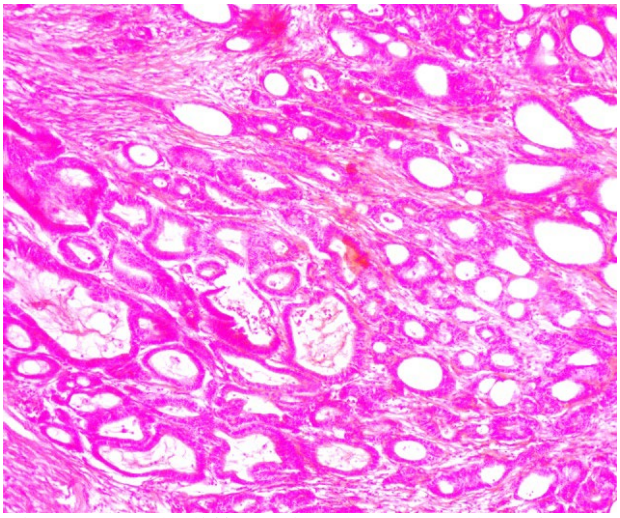


Figure 2: Well differentiated Colorectal carcinoma (H&E stain; 4x magnification

. Most LSCRCs were Well Differentiated (n=22, 66.66%), followed by Moderately Differentiated (n=6, 18.18%) and Poorly Differentiated Cases (n=5, 15.15%). Most common tumor invasion (T) category for LSCRC was 'T3' (n=19, 57.57%) followed by 'T2' (n=9, 27.27%) and T4 (n=5, 15.15%). Majority of the cases (n=19, 57.57%) showed absence of lymph node metastasis while a significant number of cases (n= 14, 42.42 %) showed involvement of lymph nodes by tumor. N1 cases (n=7, 21.21%) were equal to N2 cases (n=7, 21.21%). Average number of lymph nodes recovered per case was 10. Only 15 cases (45.45%) showed vascular invasion while 8 cases (24.24%) showed Perineural invasion

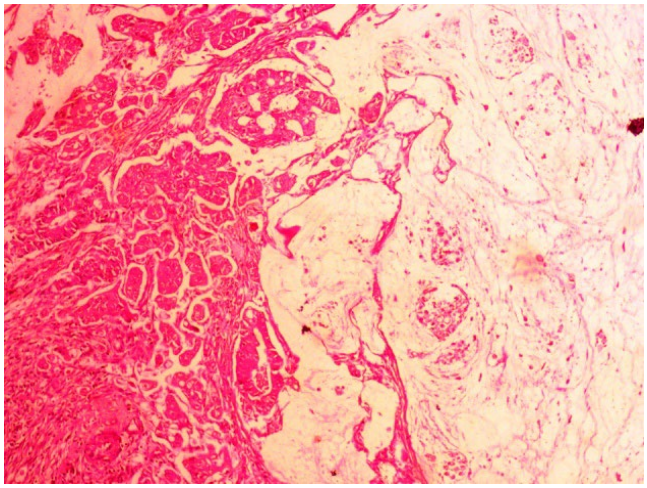


Figure 3: Moderately Differentiated Mucinous Type Colorectal Carcinoma (H&E stain; 10x magnification)

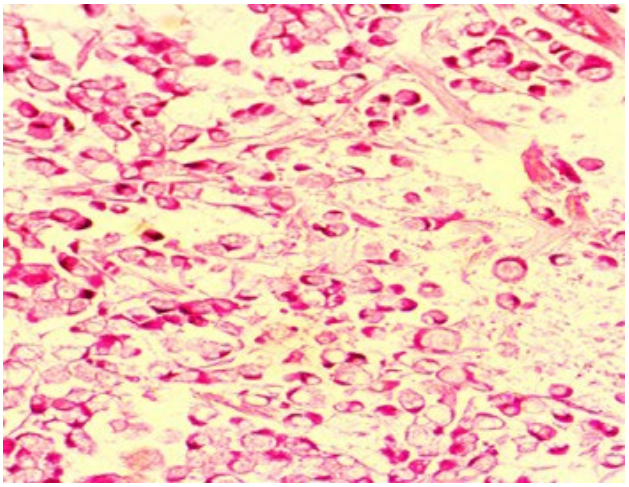


***Figure* 4: Poorly Differentiated Signet Ring Cell Type Colorectal Carcinoma (H&E stain; 10x magnification**

Table 1: Comparison of RSCC Cases and LCRC Cases with Clinicopathologic

Feature		Combined	Right colon	Left colon	p Value
TOTAL NUMBER		**50 (100%)**	**17 (100%)**	**33 (100%)**	
AGE	**<50**	29 (58%)	7 (41.17%)	22 (69.66%)	0.8
	≥50	21 (42%)	10 (58.82%)	11 (33.33%)	
MEAN AGE		47.04 ±15.233	52.88 ±16.549	44.03 ±13.817	
GENDER	Male	32 (64%)	M= 10 (58.82%)	M=22 (66.66%)	0.58
	Female	18 (44%)	F= 7 (41.17%)	F=11 (33.33%)	
	Ratio	1.7:1	1.4:1	2:1	
TUMOR SIZE (AVERAGE DIAMETER)		5.6 cm	7.2 cm	4.8 cm	
TUMOR PERFORATION	Yes	11	3	8	0.28
	No	39	14	25	
SUBTYPE	Adenocarcinoma Not Otherwise Specified (NOS)	38 (76%)	10 (58.82%)	28 (84.84%)	**0.004**
	Adenocarcinoma (Mucinous Subtype)	9 (18%)	7 (41.17%)	2 (6.06%)	
	Adenocarcinoma Signet Ring Cell Subtype	3 (6%)	0	3 (9.09%)	
GRADING	Well Differentiated	33 (66%)	11 (64.70%)	22 (66.66%)	0.88
	Moderately Differentiated	10 (20%)	4 (23.52%)	6 (18.18%)	
	Poorly Differentiated	7 (14%)	2 (11.76%)	5 (15.15%)	
TUMOR INVASION (T)	T1	0	0	1 (3%)	**0.01**
	T2	9 (18%)	0	8 (24.2%)	
	T3	30 (60%)	11 (64.7%)	19 (57.57%)	
	T4	11 (22%)	6 (35.29%)	5 (15.15%)	
LYMPH NODE METS (N)	N0	27 (54%)	8 (47.05%)	19 (57.57%)	0.47
	N1	11 (22%)	4 (23.52%)	7 (21.21%)	
	N2	12 (24%)	5 (29.41%)	7 (21.21%)	
LYMPHO VASCULAR INVASION	Yes	23 (46%)	8 (47.05%)	15 (45.45%)	0.91
	No	27 (54%)	9 (52.94%)	18 (54.54%)	
PERINEURAL INVASION	Yes	11 (22%)	3 (17.64%)	8 (24.24%)	0.59
	No	39 (78%)	14 (82.35%)	25 (75.75%)	
LYMPH NODES RECOVERED (AVERAGE)		11	14	10	

Discussion

Right sided colon cancer is associated with older age [9], female gender [10], a more advanced T stage [11], more advanced N stage [12], higher grade [11], mucinous subtype and vascular invasion [13]. RSCC is associated with more lymph nodes harvest [12].

RSCCs are usually associated with MSI-high, mismatch repair deficient tumors [14] and HNPCC Syndrome [15] while LSCRCs are associated with CIN Pathway [14] most of which are sporadic [16].

In our study group left sided CRC cases (n=32, 60.37%) were more as compared to right sided cases (n=21, 39.6 %) which is in accordance with Qayyum et al., 2016 from Pakistan [17], Hashmi et al., 2017 from Pakistan [18], Gomez et al., 2004 from UK [19], Calik et al., 2019 from Turkey [20]. Contrary to our study Ulanja et al., 2019 from USA [21], Janssens et al., 2018 from Belgium [22] and Yoon et al., 2020 from Canada [23] which showed right side to be the more common site for colorectal carcinoma.

Male was the dominant gender in both right and left sided colon cases i.e., 58.82% and 66.66% respectively. For RSCC our observation contrasts with the general trend throughout the world [24, 25, 19]. The median ages for RSCCs and LSCRCs were lower as compared to the studies carried out in the Western world [21,26,27].

Mean age in our population was quite low for left sided colon cancers as compared to right sided CRCs. This is in accordance with studies like Zhao et al., 2020 from China [28], Ulanja et al., 2019 from USA [21], Karim et al., 2017 from Canada [25] and Hussain et al., 2016 from Pakistan [29]. However, Khan & Fatima 2019 from Pakistan [30] reported a lower Mean age for right sided colorectal cancers as compared to LSCRC. Lim et al., 2017 [27] reported almost the same age for right and left colorectal cancers.

Common site of involvement for RSCRCs was cecum and ascending colon, and in LSCRCs, was sigmoid colon; this site distribution is in accordance with Hussain et al., 2016 [29]. We found RSCRCs presented with advanced pT as compared to LSCRCs. These findings are consistent with the findings of studies by Hussain et al., 2016 [29] and Ulanja et al., 2019 [21].

We observed greater tumor size (average diameter) for RSCRCs as compared to LSCRCs. This observation is in accordance with Zenger et al., 2020 [31] and Mik et al., 2017 [7]. In our study, right sided colorectal cancers were significantly associated with mucinous subtype adenocarcinoma which is in concordance with Lim et al., 2017 [27] & Hu et al., 2015[32]. Right sided colorectal cancers were associated with more lymph node harvest which is in accordance with Lim et al., 2017 [27].

Although in our study, the difference between right and left sided CRCs was not statistically significant but studies have reported RSCRC to exhibit more advanced N stage [21], poor differentiation [25] and more positivity for lympho-vascular invasion than LSCRC [27]. However, Zahir et al., 2014 from Pakistan [33] in accordance with our study showed no statistical difference for right and left sided colorectal cancers regarding N stage, grade, perineural Invasion and lympho-vascular invasion.

Combined mean age was 47.04 ±15.233 which is below 50 years. This observation is supported by Ahmad et al., 2015 [34], Amini et al., 2013 [35] & Rex et al., 2017 [36]. This presentation of CRC in younger age group in our population is a point of great concern suggesting a possible hereditary etiology or earlier and persistent exposures to known risk factors like physical inactivity, improper diet and smoking, therefore requires in depth investigation [30, 33].

We observed that majority of the cases were in advanced stage and not being detected in early stages, it is only when they cause signs of obstruction that they come into notice, primarily due to lack of adequate referral systems and timely access to oncology care along with the total unavailability of a screening program at population-level [30]

Importance of screening for colorectal cancer has been highlighted in many studies [37,38,39] with a special focus on colonoscopy; considered as gold standard for CRC screening because of its high sensitivity and specificity in early detection and prevention of development of later stage disease. [37,40,41,42]. The US preventive services task force now recommends Colonoscopy for adults aged 45 years old and onwards [43]. Fecal Occult Blood testing have also shown good results in screening for colorectal lesions. It being economical and easily available adds to its value [44, 45, 46].

Unfortunately, in Pakistan, CRC screening is not done routinely and due to high illiteracy rate in rural areas, people are unaware of its importance. Even in urban areas, where people have more access to specialized centers, they are not checked routinely and are diagnosed only at a very late stage [35]. Therefore, with colonoscopy as a regular screening test, we may be able to detect early CRC [47]. We suggest age 40 years and above for screening in our population based on our findings and supportive studies from Pakistan. Occult blood test, as non-invasive screening technique may also play a positive role in CRC screening.

Public Awareness in this regard is very important and it can be done in multiple ways for example convincing the public via media and publications to take screening tests, making screening tests a part of routine workup, or making screening facilities easily available to the community [48].

The younger age and late diagnosis suggest that we need to have a cancer registry in our country to determine the exact situation with regards to colorectal carcinoma in our population and to take preventive steps accordingly.

Conclusion

We observed LSCRC to be more common than RSCRC. In our population RSCRC is associated with older age, increased tumor size, advanced T stage, mucinous subtype and more lymph node harvest as compared to LSCRC. There is no difference between right and left side regarding tumor perforation, N stage, differentiation, lympho-vascular invasion and perineural invasion.

Limitations:

Due to limited time, and financial resources, our study could not consider a larger sample size.

Recommendations:

Colonoscopy as a regular screening test at 40 years and above should be added to protocols to detect early CRC.

Multi-Institutional Studies are required for better representation of our population's demographics of CRCs in short term. A National level cancer registry accommodating all provinces is needed for better long-term results.

Follow up studies can be conducted to compare patient survival in RSCRC and LSCRC.

Further case control studies will add to our knowledge on risk factors exposure.

Molecular characteristics and Immunotherapy responses can also be studied that can aid in assessing RSCRCs and LSCRCs differences on molecular levels and their responses to Immunotherapy agents.

Conflict of Interest: Authors declare no conflict of interest.

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CONTRIBUTION OF AUTHORS	
Author	**Contribution**
Danyal	A,B,C
Saria Saeed	B,C
Sarah Yousaf	B,C
Sara Ziaullah	A
Fozia Rauf	A,C

KEY FOR CONTRIBUTION OF AUTHORS:

A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion