

## COMPARATIVE CLINICOPATHOLOGICAL ANALYSIS OF RIGHT- AND LEFT-SIDED COLON CANCERS: A RETROSPECTIVE STUDY OF DEMOGRAPHIC, CLINICAL, AND HISTOLOGICAL DIFFERENCES

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**ABSTRACT**

**Background:** Colorectal cancer showed significant anatomical and molecular differences between the left and right sided tumors, which impacts the clinical implementation, histopathology, and prognosis. With the high global impact in case of well developed countries, the study aims to assess the clinicopathological and molecular variations between the left and the right sided colon cancer. **Materials and Methods:** This was a retrospective study to compare the right and left colon cancer, conducted at SSPM Medical College & Lifetime Hospital, Sindhudurg, among 110 patients. Demographic patterns, clinical and histopathological patterns as well as molecular data was analyzed. Tumors were classified as left sided and right sided. Statistical analysis was performed by SPSS, maintaining the  $p < 0.05$  for statistical significance. **Results:** The study showed no baseline difference between the two groups. Left sided tumours were more predominant, 64%. The study demonstrated that RCC had significantly higher anaemia (32.5% vs. 12.9%) and diabetes (22.5% vs. 8.6%), along with increased KRAS mutations (57.5% vs. 35.7%) and poorly differentiated tumours (45% vs. 20%). In contrast, LCC showed higher rectal bleeding (45.7% vs. 20.0%) and incomplete evacuation (25.2% vs. 5%). Although stage distribution was comparable, RCC exhibited greater T4 lesions (30%) and nodal involvement (N1: 50%), indicating relatively more aggressive disease characteristics. **Conclusion:** The Study concluded that right-sided colon cancers exhibit higher rates of anaemia, diabetes mellitus, KRAS mutations, and aggressive histopathological features including poor differentiation and mucinous subtype. In contrast, left-sided colon cancers predominantly present with rectal bleeding and incomplete evacuation, with a higher proportion of well-differentiated adenocarcinomas.

**INTRODUCTION**

Colorectal cancer (CRC) is a significant health problem worldwide, with an estimated incidence of 1.9 million and mortality of 0.94–0.935 million in 2020, placing it at number three for incidence and number two for mortality globally.<sup>[1,2]</sup> A Kerala tertiary hospital registry analysis (2010–2021) reported stable overall case trends but highlighted the role of lifestyle and dietary Westernization in driving CRC, consistent with global increases and improving survival where care systems strengthen.<sup>[3]</sup> Additionally, a multi centric Tamil Nadu survey (2021–2022) emphasized substantial rectal/rectosigmoid involvement and high proportions of overweight/obesity among newly diagnosed patients, supporting lifestyle contributions in developing settings.<sup>[4]</sup> CRC shows

anatomical heterogeneity between right- and left-sided cancers in terms of biology, epidemiology, and clinical outcomes.<sup>[1]</sup>

Colon cancers on the right and left are of different embryological origin, with the right colon being of midgut origin and the left colon of hindgut origin, with differences in pathways such as the serrated pathway on the right and the adenomatous pathway on the left.<sup>[5]</sup> Right-sided colon cancers are of the MSI-H and high tumor mutational burden with BRAF mutations, while left-sided colon cancers are of the chromosomal instability type with TP53, APC, and ERBB2 mutations, and KRAS and NRAS mutations with resistance to anti-EGFR therapy.<sup>[6]</sup> This affects the prognosis of the patients, with the prognosis being poor on the right and good on the left with good response to anti-EGFR therapy.<sup>[5,6]</sup>

Right-sided colon cancers are likely to present at a later stage with iron deficiency anemia, occult blood loss, weight loss, and vague abdominal complaints due to the lumen size and liquid stool consistency, which delay the obstruction and result in a more advanced tumor with a tendency towards mucinous or undifferentiated types.<sup>[7]</sup> On the contrary, left-sided colon cancers are likely to present with bowel habit change, colicky abdominal pain, visible rectal bleeding, and obstruction, which result in early detection and relatively more early-stage colon cancers.<sup>[7]</sup> Late detection of right-sided colon cancer may result in a poor outcome, although the survival rates are similar between the two locations after adjusting for the stages and comorbidity factors.<sup>[8]</sup> Detection of colon cancer with the help of screening methods like colonoscopy is possible, although the detection of right-sided colon cancer is difficult due to the proximal location of the tumor and flat morphology of the tumor, highlighting the importance of good quality of screening methods.<sup>[8]</sup> Right- and left-sided colon cancers demonstrate distinct histopathological features. Right-sided tumors are more frequently associated with mucinous histology, poor differentiation, higher T stage, and increased venous invasion, indicating a more aggressive phenotype, whereas left-sided tumors are typically well to moderately differentiated adenocarcinomas and often present at earlier stages.<sup>[9,10]</sup> Higher proportions of mucinous and undifferentiated tumors on the right further support this biological difference.<sup>[10]</sup> These variations influence prognosis, as right-sided cancers are generally linked to poorer outcomes, while left-sided stage III disease shows relatively better long-term survival; however, survival differences may diminish when adjusted for treatment and other clinical factors.<sup>[9,10]</sup> The lack of region-specific data also prompts the evaluation of clinicopathological variations, focusing on demographic, clinical, and histopathological variations; hence, this study aimed to retrospectively evaluate these characteristics in right- and left-sided colon cancers.

## MATERIALS AND METHODS

### Research design

This was a retrospective study to compare the clinicopathological evaluation of the right- and left-sided colon cancers, to investigate their demographic, clinical and histological differences. The study was conducted in the SSPM Medical College & Lifetime Hospital, Sindhudurg for a duration of 1 year, from February 2025 to January 2026. The study involved 110 patients who were diagnosed with colon cancer and had received chemotherapy. Data collected were systematically recorded and were analysed for comparing their demographic parameters, clinical presentations, and histopathological features between the right and left

colon cancer. Well written and verbal consent were taken from each of the patient for the study. Pre-defined inclusion and exclusion criteria were considered for the study for patient enrolment.

### Inclusion Criteria

Those patients were involved who were diagnosed with colon cancer.

Patients who had received chemotherapy were included.

Complete medical record was taken for the study.

Informed consent required for the study.

### Exclusion Criteria

Patients who were diagnosed with rectal cancer or other type of gastrointestinal malignancies were excluded.

Incomplete or duplicate medical records were excluded.

Any recurrent cases where information related to the initial diagnosis and the details of the treatment regimen absent, were not considered.

### Procedure

Patient approval was obtained from the Institutional Review Board of SSPM Medical College for the study and patients were recruited from the predefined criteria. Epidemiological data were collected, including age, gender and other related comorbidities during the diagnosis. other clinical parameters like the symptoms, performance status, stage of disease, primary tumour location (PTL), history of surgical intervention, and the location of the metastasis were also noted and recorded. Histopathological reports were investigated for the evaluation of certain features like the type of histopathology involved, tumour differentiation, the number of lymph nodes removed and involved, presence of necrosis, vascular and lymphatic invasion, and perineural infiltration. Also molecular profiling was performed, which mainly focussed on the significant biomarkers like KRAS and NRAS mutations, BRAF (V600E mutation), and mismatch repair genes, which were related with the microsatellite instability (MLH1, MSH2, MSH6, and PMS2). Apart from these, the comparative analysis was performed, which categorized the tumours on the basis of right-sided colon cancers which include the tumours, caecum, ascending colon, and transverse colon, while the left-sided colon cancers which included the tumours of the descending and sigmoid colon.

### Statistical Analysis

Statistical analysis was done by using SPSS version 27. Categorical variables were analyzed by the use of chi-square ( $\chi^2$ ) test and were expressed as the odds ratios (OR) along with the 95% confidence intervals (CI). The continuous variables were compared by the use of independent samples t-test. Time-to-event outcomes were evaluated by using the Kaplan–Meier survival curves and comparative analysis was done with log-rank test. Cox proportional hazards regression analysis was performed for the identification of the independent

prognostic factors. The p-value < 0.05 was maintained for the statistical significance.

## RESULTS

Table 1 demonstrated the baseline parameters for LCC (n = 70) and RCC (n = 40) without any significant difference across gender, age and BMI.

Females were predominant across both of the groups (LCC: 54.3%, RCC: 55.0%) and the gender distribution showed (P = 0.941). Comparable mean values were observed between LCC (64.8 ± 9.8 years) and RCC (65.9 ± 10.5 years), with p values 0.612, highlighted identical age profile. BMI is high in RCC (28.8 ± 5.9 kg/m<sup>2</sup>) than LCC (27.6 ± 4.2 kg/m<sup>2</sup>), non-significant differences with (P = 0.318).

**Table 1: Representation of the baseline, demographic and clinical features of patients with Left-Sided Colon Cancer (LCC) and Right-Sided Colon Cancer (RCC)**

Variable	LCC (n = 70)	RCC (n = 40)	P value
Male	32 (45.7%)	18 (45.0%)	P = 0.941
Female	38 (54.3%)	22 (55.0%)	
Age (mean ± SD) (yr)	64.8 (± 9.8)	65.9 (± 10.5)	P = 0.612
BMI (mean ± SD) (kg/m <sup>2</sup> )	27.6 (± 4.2)	28.8 (± 5.9)	P = 0.318

Table 2 showed the distribution of the location of the primary tumour which indicated the predominance of distal colorectal involvement. The sigmoid colon is the highest cases 35.0%, which was followed by the rectum 29% and altogether comprises of two-thirds (64.0%) of the total tumour. Contrastingly, the proximal sites like the ascending

colon were 10.5% and caecum (11.5%). The transverse (6.0%) and descending colon (5.5%) were frequently observed, while appendix is the rare site, showed 2.5%. Thus the data demonstrated the dominance of the left-sided tumour, suggested for high burden of distal segments rather than the proximal colon regions.

**Table 2: The distribution of primary location of tumour among colon cancer patients**

Tumour Location	Percentage (%)
Rectum	29.00%
Sigmoid colon	35.00%
Descending colon	5.50%
Transverse colon	6.00%
Ascending colon	10.50%
Caecum	11.50%
Appendix	2.50%
<b>Total</b>	<b>100%</b>

Table 3 showed the comparative analysis of the clinical patterns between LCC and RCC patients. The most prevalent is Anaemia observed among RCC with 32.5% compared with LCC 12.9%, which highlighted the strong association with the right-sided tumours. Contrastingly, the rectal bleeding (45.7% vs. 20.0%, P = 0.005) and the incomplete evacuation is 25.2% vs. 5.0%, P = 0.007, are

commonly observed in LCC, which reflected the distal tumour. The comorbidities, diabetes mellitus showed high prevalence among RCC 22.5% rather than LCC (8.6%), which suggested the relation with the right-sided disease. Coronary heart disease is frequently observed among RCC with the statistical significance P = 0.061.

**Table 3: The comparative analysis of the features and the Comorbidities between Left-Sided (LCC) and Right-Sided Colon Cancer (RCC) among patients**

Variable	LCC (n = 70), n (%)	RCC (n = 40), n (%)	P value
Anaemia	9 (12.9%)	13 (32.5%)	aP = 0.010
Rectal bleeding	32 (45.7%)	8 (20.0%)	aP = 0.005
Feeling of incomplete evacuation	17 (25.2%)	2 (5%)	aP = 0.007
Coronary heart disease	6 (8.6%)	8 (20.0%)	bP = 0.061
Diabetes mellitus	6 (8.6%)	9 (22.5%)	aP = 0.018

Table 4 presented the patient at advanced stages, which showed that Stage IV is the most common stage, which was followed by the Stage III. Non-significant relationship was observed between the LCC and RCC with (P = 0.248). T3 tumour is predominating for both of the groups, while T4

lesions are higher in RCC, which indicated the local advanced disease. Nodal involvement showed significant difference, while RCC showed high proportion of N1 cases. The distant metastasis (M classification) is comparable between the groups.

**Table 4: Comparative analysis of the Tumour Stage and TNM Classification between Left-Sided (LCC) and Right-Sided Colon Cancer (RCC)**

Variable	LCC (n = 70), n (%)	RCC (n = 40), n (%)	P value
<b>Stage</b>			
Stage I	5 (7.1%)	1 (2.5%)	P = 0.248
Stage II	9 (12.9%)	7 (17.5%)	
Stage III	18 (25.7%)	13 (32.5%)	
Stage IV	38 (54.3%)	19 (47.5%)	
<b>T classification</b>			
T1-T2	8 (11.4%)	3 (7.5%)	bP = 0.092
T3	42 (60.0%)	22 (55.0%)	
T4	9 (12.9%)	12 (30.0%)	
TX	11 (15.7%)	3 (7.5%)	
<b>N classification</b>			
N0	20 (28.6%)	8 (20.0%)	aP = 0.042
N1	23 (32.9%)	20 (50.0%)	
N2	16 (22.9%)	5 (12.5%)	
NX	11 (15.7%)	7 (17.5%)	
<b>M classification</b>			
M0	32 (45.7%)	19 (47.5%)	P = 0.458
M1a	27 (38.6%)	12 (30.0%)	
M1b	11 (15.7%)	9 (22.5%)	

Table 5 showed the histopathological analysis highlighted the significant differences observed between the two groups. The most predominant type is Adenocarcinoma and frequently observed in LCC 94.3% rather than the RCC 82.5%. The mucinous histology is high in RCC 17.5%. Significant

difference was observed for Tumour differentiation, with poorly differentiated tumours was most commonly observed in RCC, 45.0% and LCC (20.0%). Contrastingly, the necrosis, vascular emboli, and perineural infiltration was comparable between the groups.

**Table 5: The comparative analysis of the Histopathological parameters between the Left-Sided (LCC) and Right-Sided Colon Cancer (RCC) Patients**

Variable	LCC (n = 70), n (%)	RCC (n = 40), n (%)	P value
<b>Histology</b>			
Adenocarcinoma	66 (94.3%)	33 (82.5%)	aP = 0.048
Mucinous	3 (4.3%)	7 (17.5%)	
Neuroendocrine	1 (1.4%)	0 (0%)	
<b>Differentiation</b>			
Low	14 (20.0%)	18 (45.0%)	aP = 0.006
Moderate/High	56 (80.0%)	22 (55.0%)	
<b>Necroses</b>			
No	44 (62.9%)	25 (62.5%)	P = 0.962
Yes	26 (37.1%)	15 (37.5%)	
<b>Emboli</b>			
No	58 (82.9%)	35 (87.5%)	P = 0.588
Yes	12 (17.1%)	5 (12.5%)	
<b>Perineural infiltration</b>			
No	61 (87.1%)	37 (92.5%)	P = 0.528
Yes	9 (12.9%)	3 (7.5%)	

Table 6 showed the analysis of the significant difference in association with the KRAS mutation status with (P = 0.036). Mutations in RCC is more common and the wild type is more predominant in LCC, which indicated strong relation of the KRAS mutations with right-sided tumour. The NRAS mutations were rarely observed and the overall RAS

and BRAF mutations were highly seen in RCC. Both of the groups were microsatellite stable (MSS ~93–94%), while no significant variation was noted in minimal MSI-H. This highlighted the KRAS as the crucial molecular discriminator between the RCC and LCC.

**Title 6: The comparative analysis of the RAS Pathway Mutations and Microsatellite Instability for both of the groups**

Variable	LCC (n = 70), n (%)	RCC (n = 40), n (%)	Total, n (%)	P value
<b>KRAS wild type</b>	45 (64.3%)	17 (42.5%)	62 (56.4%)	aP = 0.036
<b>KRAS mutant</b>	25 (35.7%)	23 (57.5%)	48 (43.6%)	
<b>NRAS wild type</b>	67 (95.7%)	40 (100.0%)	107 (97.3%)	P = 0.571
<b>NRAS mutant</b>	3 (4.3%)	0 (0%)	3 (2.7%)	
<b>RAS wild type</b>	42 (60.0%)	17 (42.5%)	59 (53.6%)	P = 0.104
<b>RAS mutant</b>	28 (40.0%)	23 (57.5%)	51 (46.4%)	
<b>BRAF wild type</b>	66 (94.3%)	33 (82.5%)	99 (90.0%)	P = 0.125
<b>BRAF mutant</b>	4 (5.7%)	7 (17.5%)	11 (10.0%)	

<b>MSS</b>	66 (94.3%)	37 (92.5%)	103 (93.6%)	P = 1.000
<b>MSI-H</b>	4 (5.7%)	3 (7.5%)	7 (6.4%)	

## DISCUSSION

A large study conducted by Ulanja et al. (2024) based on SEER data for 227,637 patients between 1975 and 2019 confirmed that right-sided colon cancer was more common among older individuals (>65 years: 51.4%) and females (50.4%), while left-sided colon cancer was more common among younger individuals and males, with overall survival rates being better for left-sided disease at all time periods.<sup>[11]</sup> In another study conducted by Yilmaz et al. (2026) based on a cohort of patients treated at a tertiary center between 2010 and 2020, it was confirmed that right-sided colon cancer was diagnosed at an older age on average ( $62.6 \pm 14.8$  vs.  $59.3 \pm 14.4$  years) and was more common among females (48.1% vs. 37.0%) than left-sided disease, and right-sided disease was an independent predictor of poorer survival.<sup>[12]</sup>

In a multicenter Portuguese study conducted by Goncalves et al. (2023), it was shown that anemia was more common in patients with right-sided colon cancers, while intestinal obstruction was more common in patients with left-sided tumors (anemia  $p < 0.01$ , obstruction  $p < 0.001$ ) and thus reflected different clinical features, including delayed presentation with occult blood loss in patients with right-sided tumors, compared with features associated with left-sided tumors, such as obstruction.<sup>[13]</sup> This was reinforced in a 2023 review, where it was noted that patients with right-sided tumors tend to present with iron deficiency anemia, whereas patients with left-sided tumors tend to have obstruction, which is a major emergency symptom in patients with colorectal cancer.<sup>[6]</sup>

Colon cancers on the right side are more likely to have mucinous histology and poor differentiation compared to cancers on the left side. These are due to the difference in the embryologic origin of the two sides. A study conducted by Lansom et al. (2024) based on pathology-based sidedness on a large Australian cohort found that cancers on the right side were significantly associated with features such as tumor-infiltrating lymphocytes, mismatch repair deficiency, and BRAF mutations, thus supporting the link with adverse grade and mucinous types.<sup>[14]</sup> Another study conducted by Wismayer et al. (2023) based on regional data from Ugandan cancers found that cancers on the right side had a higher prevalence of poorly differentiated and mucinous types with high rates of lymphovascular invasion, thus supporting globally observed aggressive histopathological features.<sup>[15]</sup>

Colon cancers on the right and left sides have been shown to have different embryologic origins, with midgut and hindgut derivatives, respectively. These have been linked to different microenvironments and pathways. The microenvironments of right-

sided colon cancers have been linked to immune secretory activity, hypoxia, immune evasion, mismatch repair deficiency, and BRAF V600E.<sup>[16]</sup> On the contrary, the microenvironments of left-sided colon cancers have been linked to proliferation-stemness, RAS/RAF wild-type status, and better response to anti-EGFR therapy. These have been shown to influence the prognosis and treatment outcomes.<sup>[16,17]</sup> The presentation of colon cancers on the two sides is also different. Colon cancers on the right side are diagnosed at an advanced stage with anemia and vague symptoms due to the larger lumen. On the contrary, colon cancers on the left side are diagnosed due to bowel changes or obstruction, which leads to early detection.<sup>[17]</sup>

Tumor sidedness is an important factor in the presentation and prognosis of colon cancer, as the prognosis is generally poorer in the case of right-sided colon cancer, although the difference might not be significant after stage and treatment adjustment.<sup>[10,17]</sup> The prognosis is likely to be improved by the implementation of screening, and the sidedness is taken into consideration while making the decision, as left-sided colon cancer is likely to respond better to anti-EGFR therapy, while histopathological examination is important in the risk stratification and prognosis of the two sides.<sup>[10,17]</sup>

## CONCLUSION

The Study concluded that right-sided colon cancers (RCC) are characterized by a higher prevalence of anaemia, diabetes mellitus, and KRAS mutations, along with more aggressive histopathological features such as poor differentiation and mucinous subtype. In contrast, left-sided colon cancers (LCC) predominantly present with rectal bleeding and incomplete evacuation, reflecting distal tumor localization with a higher proportion of well-differentiated adenocarcinomas. Although overall stage distribution and metastasis were comparable, RCC demonstrated greater nodal involvement and a higher proportion of T4 lesions, indicating more advanced local disease. LCC was related with the rectal bleeding, which reflected in the site-specific symptomatology. Tumour distribution was mostly observed in left side, along with major cases of sigmoid colon and rectum accounting. Both of the groups showed advanced stages, while more aggressive features were observed in RCC, which include the high T4 lesions and the involvement of nodes. The mucinous type and poor differentiation were frequently seen in case of RCC, which indicated the prognosis. Molecular analysis revealed that KRAS mutation is high in RCC, and considered as the key discriminator. There is not significant difference between the NRAS, BRAF, and MSI.

RCC is more aggressive and showed distinctive molecular pattern in comparison to LCC.

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