DOI:10.31557/APJCB.2024.9.3.301

RESEARCH ARTICLE

Colorectal Cancer in Patients Younger than 40 years -Analysis of Clinicopathological Profile and Treatment Patterns

Amogh P S, Geeta S Narayan, Sai Sanmathi B, Kiran Kumar BR

Vydehi Institute of Medical Sciences and Research Centre, India.

Abstract

Background: The incidence of colorectal cancer (CRC) is increasing among young adults. Cancer diagnosis in young adults leads to many challenges due to the impact of the disease on their fertility, career, and life expectancy. In the present study, we investigated the clinicopathological profile of colorectal cancer patients younger than 40 years. **Materials and Methods:** Retrospective analysis of all the biopsy proven CRC patients were collected over the period of 5 years, from January 2012 to December 2018. Clinicopathological data of patients under the age of 40 years were collected from their medical and pathological reports and analysed. **Results:** Out of 729 CRC, a total of 154 (21%) patients of colorectal cancer were younger than 40 years were registered during the study period. Among them, with 94 (61%) being male and 60 females (39%). Most of the patients were 30-35 years (37%) and less than 30 years (36%) age group. Adenocarcinoma was present in 97% patients and signet ring cell carcinoma in 3% patients The most common primary site was rectum (57 %), followed by ascending colon (17 %). Most of the patients presented with stage III (64 %) disease. The liver was the most common site of distant metastasis. **Conclusion:** The incidence of colorectal cancer is increasing among young adults. Most patients present in a locally advanced and non-metastatic stage and have the potential for curative treatment. Therefore, early detection by screening at a younger age may improve the survival of younger patients. Long term follow-up of these patients will provide insights on Treatment Outcomes.

Keywords: Colorectal Cancer- CRC- Young- Rectal Cancer- Radiation- Surgery

Asian Pac J Cancer Biol, **9 (3)**, 301-305

Submission Date: 05/23/2024 Acceptance Date: 07/09/2024

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated 1.9 million new cases (10.0 % of the total) in 2020 and the second leading cause of cancer deaths globally. With 19.29 million new cases and 9.96 million deaths, it accounts for 10% of the global cancer incidence and 9.4% of cancer deaths. CRC incidence rates show a varied geographical distribution with high age-standardized rate (ASR) of 16.9 in males and 8.9 in females of Eastern Europe as compared to only 2.8 in males and 1.9 in females of South and Central Asian countries, including India [1]. Although ranked 16th by incidence rate, India reported about 0.06 million new cases with 0.039 million deaths due to rectal cancer in 2020, which is further estimated to rise to 0.11 million new cases and 0.064 million deaths in 2040 [2].

In general, CRC incidence is rising in low- and middle-income countries but beginning to stabilize or decline in high-income countries, especially those that have implemented screening [2]. In India, colorectal cancer rates are rising and it is the sixth leading cause of cancer [3]. The risk of colorectal cancer increases with age, with 90% of cases being diagnosed in individuals 50 years of age and older. however, in India, there is increase in the incidence of CRC in young adults. The CRC incidence in younger adults in 2008 – 2012 was 3.5 -5% by Mathew et al and Seigel et al [4, 5], a relative increase of 30% over a decade. This rise in relative risk point to a rising trend in colorectal cancer burden in young adults in India. CRC usually begins with the non-cancerous proliferation of mucosal epithelial cells, which gradually evolve into pre neoplastic lesions, due to genetic or epigenetic mutations [6, 7].The cause could be genetic, but sporadic cases have

Corresponding Author:
Dr. Kiran Kumar BR
Vydehi Institute of Medical Sciences and Research Centre, India.
Email: drkiranbr@yahoo.com

been steadily rising worldwide, especially in developing countries that are adopting the 'western' way of life [8, 9]. Certain dietary and lifestyle factors, like obesity, sedentary lifestyle, red meat consumption, alcohol and tobacco, can promote intestinal inflammation and modify the intestinal microflora to promote an immune response, both of which can facilitate the process of carcinogenesis [10].

In a recent update, the U.S. Multi-Society Task Force suggested that an average-risk CRC screening should begin at the age of 45.This recommendation is based on the increasing disease burden among individuals under the age of 50 years [5]. The ACS (American Cancer Society) also updated their guidelines in 2018 with recommendations that colorectal screening should be done for everyone, not merely for those at increased risk for colon cancer, and should begin at age 45. They based their recommendation on a decision analysis demonstrating an increase in life years gained when beginning screening at an earlier age [6]. Due to the paucity of data, the recommendation and effectiveness of systematic or community-based screening of colorectal cancer remain unsolved. In the current study, we investigated the clinicopathological profile of colorectal cancer patients younger than 40 years.

Materials and Methods

This retrospective study investigates the clinicopathological profile of colorectal cancer patients younger than 40 years. Ethical Committee approval taken from the Institutional Ethical Committee. Data from patients diagnosed with colorectal cancer between January 2012 and December 2018 were collected from the medical and pathological reports and analysed. All the patients with the Biopsy proven CRC who were the age of 40 years and below were included in the study and the patients above 40 years were excluded. Demographic information such as age, gender, and primary disease site (colon or rectum) were collected. Additionally, data regarding the patients' complaints at presentation, histology, and stage at diagnosis and treatment details were recorded. The collected data were stratified based on gender (male/female), different age groups (35-39 tears 30 – 35 years, and <30 years of age), and primary site of disease (colon or rectum). Furthermore, the data were analysed to determine the distribution of complaints at presentation, histological types of colorectal cancer, and stage at diagnosis and treatment details.

Data was entered in MS Excel and analysed by using SPSS software version 21. Categorical variables were expressed as percentages and analysed using the Chi-square test or Fisher's exact test. Continuous variables were expressed as mean or median and analysed using the

Mann-Whitney test. Demographic factors and clinical characteristics were summarized with percentages for categorical variables and median for continuous variables.

Results

A total of 154 patients of the age with less than 40 years with colorectal cancer were registered during the study period. Out of which, 94 (61%) being male and 60 females (39%). Most of the patients were 30-35 years (37%), followed by the less than 30 years (36%) age group. Demographic details are given in Table 1.

The commonest presentation was abdominal pain and distension in 49% patients, bleeding per rectum in 35% patients, and obstructive symptoms in 16% patients.

The most common primary site was the rectum (107 patients), followed by ascending colon (22 patients). Most of the patients presented with stage III (71 patients), followed by stage II (55patients). The liver was the most common site of distant metastasis in stage IV patients. Histologically, Adenocarcinoma was present in 97% patients and signet ring cell carcinoma in 3% patients. Moderately Differentiated Adenocarcinoma was a predominant type. Tumour Characteristics are given in Table 2.

Surgery was the main modality of treatment in all the patients without distant metastasis. Colectomy was done in the patients with Colon Cancer (35.6%). Low anterior resection (33.5%) was done in the patients with upper and mid rectal tumours whereas Abdominoperineal resection(30.7%) in lower rectal cancers.

Neoadjuvant Chemoradiotherapy was received by 60 patients in rectal cancer patients, whereas adjuvant chemotherapy by 44 patients with colon cancer. Palliative Chemotherapy was received by 7 patients. Treatment details are given in Table 3.

Discussion

CRC is a major cause of morbidity and mortality worldwide with wide geographical variation in incidence and clinical presentation [11]. Although CRC is more likely to occur at old age, nowadays, younger patients are increasingly affected by different types of CRCs [12].

This study investigated the clinicopathological characteristics of CRC patients under the age of 40 years. Our study population showed a male predominance with a male to female ratio of 1.5:1. This is in accordance to other studies reporting a higher incidence rate of CRC among males than females [13]. The male-to-female incidence rate ratio increases progressively across the colon from the caecum to the rectum from close to unity for cecal cancers to two for rectal cancers [14]. Although the reason

Table 1. Demographic Characteristics

Age	Number	Percentage	p Value
Less than 30	56	36	0.04
30-35	58	37.6	
35-40	40	26.4	
Gender			
Male	94	61	0.2
Female	60	39	

Table 2. Tumour Characteristics

Staging	Number	Percentage	p Value
I	11	7	0.06
II	55	36	
III	71	46	
IV	17	11	
Site			
Rectum	107	69.4	0.3
Ascending colon	22	14.2	
Sigmoid colon	11	7	
Descending colon	10	6.4	
Caecum	4	3	
Histology			
Well differentiated adenocarcinoma	23	15	0.05
Moderately differentiated adenocarcinoma	123	80.0	
Poorly differentiated adenocarcinoma	6	3.8	
Undifferentiated adenocarcinoma	2	1.2	
Total	154	100	

Table 3. Treatment Characteristics

Surgery	Number	Percentage	p Value
Abdominoperineal resection	44	30.7	0.45
Colectomy	51	35.6	
Lower anterior resection	48	33.5	
Chemotherapy			
Neoadjuvant Chemoradiotherapy	60	19.4	0.3
Adjuvant chemotherapy	44	28.5	
Palliative chemotherapy	7	4.5	

for this is not completely understood, a study by Murphy et al [15] suggests that differential exposure to dietary and lifestyle-related risk factors like alcohol, consumption of red meat as well as a differential expression of hormonal and other receptors across the length of the colon and rectum could be the probable cause.

We observed that most of the patients were in the group of 30-35 years of age (37.6 %), and the most common site of cancer was rectum (69.4%). In a study by Jones et al. [16], rectal cancer was more frequent among patients younger than 50 years of age compared to the older group.

CRC has been long considered a disease of the elderly [17]. However, the recent studies have reported that the incidence of CRC is increasing among young individuals in the Middle East and other regions in the world [18, 19]. A single-centre audit of CRC in India by Patil et al [20] concluded that CRC in India differs from that described in the Western countries and we have a higher proportion of young patients. However, there is a controversy over the effects of age on the presentation and survival of CRC patients. The cut-off ages 30, 35, 40, 45, and 50 years have been used in different studies [16, 21-23]. We chose the cut-off age of 40 years.

Twenty One Percent of the patients in our study were under the age of 40 years which is similar to the study done by Prachi S. Patil, et al.[20]. They found that 35% of patients in their study were under the age of 40 years. In another study from central India, on 233 patients over 8 years, the median age at diagnosis was 43 years with 39% of CRC patients being diagnosed at the age of 40 or younger [24]. Other studies from India though on a small number of patients show similar results which elicits the question whether CRC occurs at a younger age in India [25, 26].

Rising incidence in young age signals changes in early lifestyle modifications that adversely influence CRC risk. [27] Reduction in the prevalence of protective factors such as physical activity (for colon cancer) and insufficient intake of a high-fibre diet, dairy, and fruits and vegetables may play a role, as well as increased prevalence of obesity, smoking, red and processed meat consumption, and excess alcohol consumption [27]. Obesity was recently found to be associated with a 20% excess risk of early-onset colorectal cancer, and prevalence has risen most rapidly in young adults [28].

In our study, most of the patients presented in stages II and III. The presence of a higher cancer stage in young patients may be due to a delay in diagnosis. Various studies have reported that CRC in young patients is more likely to have poor histological features and present in an advanced stage than in the older age group [29, 30]. These

findings do suggest that CRC in young patients could be a different biological entity requiring aggressive treatment [31, 32]. Further, colorectal screening programs might increase the likelihood of diagnosis at earlier stages among older patients in other countries. Colorectal screening programs have mostly emerged over the past two decades and likely contributed to the decline in incidence among older adults in Western countries. However, systematic or community-based screening of colorectal cancer does not exist in India. We do not know the impact of an organized screening program as recommended in Western countries [33].

Most early-stage CRC are asymptomatic, and these may be diagnosed at the time of screening. Symptomatic patients can present with pain, bleeding, or obstructive symptoms, or rarely in an emergency setting with obstruction or perforation. In our study most common symptoms were abdominal pain and rectal bleeding. In our study, adenocarcinoma was the predominant histology in both the groups as has been reported in other studies [25, 34].

The intent of treating with radiotherapy was neoadjuvant in 56% of patients with Rectal Cancer. Neoadjuvant therapy comprises a combination of radiotherapy and chemotherapy and is used to downsize or downstage the tumour in anticipation of surgical resection. In rectal cancer involving the anal sphincters, neoadjuvant therapy can potentially downsize a tumour to allow for the creation of a safe resection margin, thereby preserving the anal sphincters and maintaining anal continence [35]. Radiotherapy has been established as a mainstay of treatment alongside surgery in locally advanced rectal cancer and provides good symptomatic relief in these patients [36]. An analysis by the National Cancer Database in 2017 showed a pathologic complete response rate of 13% in an overall patient cohort of 27,532 receiving neoadjuvant therapy [37].

Before we conclude, it is important to describe the limitations of this study. Being a retrospective analysis, only documented details were available for evaluation. Many relevant data like prognostic markers, pre-treatment CEA level, MSI, and RAS status, which were largely unknown. Nonetheless, this study provides relevant data regarding the clinicopathological profile colorectal cancer burden in young adults in South India. Rectal bleeding in any patient should not be ignored but evaluated further with at least a digital rectal examination and a sigmoidoscopy.

In conclusion, the colorectal cancer incidence rate has been increasing in young adults, which is likely to continue. Our study revealed a significant number of young patients are among rectal cancer patients. The younger age group had more patients presenting with an advanced stage. Rectal bleeding in any patient should not be ignored but evaluated further with at least a digital rectal examination and a sigmoidoscopy. Screening Programmes should be implemented at all the healthcare centres to identify these patients. Early diagnosis and appropriate treatment of colorectal cancer in young adults represent a critical unmet clinical need.

Acknowledgements

Nil

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests

There was no conflict of interests

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021 05;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Translational Oncology. 2021 Oct;14(10):101174. https://doi.org/10.1016/j.tranon.2021.101174
3. https://gco.iarc.who.int/media/globocan/factsheets/populations/356-india-fact-sheet.pdf.
4. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, Jemal A. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019 Dec;68(12):2179-2185. https://doi.org/10.1136/gutjnl-2019-319511
5. Mathew A, Baby B, Wang K, Sirohi B, Lei F, Chen Q, Huang B. Colorectal cancer incidence in younger adults in India. Gut. 2020 Oct;69(10):1899-1900. https://doi.org/10.1136/gutjnl-2019-320271
6. Leslie A, Carey FA, Pratt NR, Steele RJC. The colorectal adenoma-carcinoma sequence. The British Journal of Surgery. 2002 07;89(7):845-860. https://doi.org/10.1046/j.1365-2168.2002.02120.x
7. Grady WM, Markowitz SD. The molecular pathogenesis of colorectal cancer and its potential application to colorectal cancer screening. Digestive diseases and sciences. 2015 03 01;60(3):762-772. https://doi.org/10.1007/s10620-014-3444-4
8. Stoffel EM, Koeppe E, Everett J, Ulintz P, Kiel M, Osborne J, Williams L, et al. Germline Genetic Features of Young Individuals With Colorectal Cancer. Gastroenterology. 2018 03;154(4):897-905.e1. https://doi.org/10.1053/j.gastro.2017.11.004
9. Carethers JM, Jung BH. Genetics and Genetic Biomarkers in Sporadic Colorectal Cancer. Gastroenterology. 2015 Oct;149(5):1177-1190.e3. https://doi.org/10.1053/j.gastro.2015.06.047
10. O'Sullivan DE, Sutherland RL, Town S, Chow K, Fan J, Forbes N, Heitman SJ, Hilsden RJ, Brenner DR. Risk Factors for Early-Onset Colorectal Cancer: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association. 2022 06;20(6):1229-1240.e5. https://doi.org/10.1016/j.cgh.2021.01.037
11. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. CA: a cancer journal for clinicians. 2009;59(6):366-378. https://doi.org/10.3322/caac.20038
12. Nelson RL, Dollear T, Freels S, Persky V. The relation of

age, race, and gender to the subsite location of colorectal carcinoma. Cancer. 1997 07 15;80(2):193-197. https://doi.org/10.1002/(sici)1097-0142(19970715)80:2<193::aid-cncr4>3.0.co;2-v
13. Patra T, Mandal S, Alam N, Murmu N. Clinicopathological trends of colorectal carcinoma patients in a tertiary cancer centre in Eastern India. Clinical Epidemiology and Global Health 2213-3984. 2017 04 22;6. https://doi.org/10.1016/j.cegh.2017.04.003
14. Perdue DG, Perkins C, Jackson-Thompson J, Coughlin SS, Ahmed F, Haverkamp DS, Jim MA. Regional differences in colorectal cancer incidence, stage, and subsite among American Indians and Alaska Natives, 1999-2004. Cancer. 2008 09 01;113(5 Suppl):1179-1190. https://doi.org/10.1002/cncr.23726
15. Murphy G, Devesa SS, Cross AJ, Inskip PD, McGlynn KA, Cook MB. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. International Journal of Cancer. 2011 04 01;128(7):1668-1675. https://doi.org/10.1002/ijc.25481
16. Jones HG, Radwan R, Davies M, Evans M, Khot U, Chandrasekaran TV, Williams N, et al. Clinicopathological characteristics of colorectal cancer presenting under the age of 50. International Journal of Colorectal Disease. 2015 04;30(4):483-489. https://doi.org/10.1007/s00384-015-2166-1
17. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: a cancer journal for clinicians. 2018 01;68(1):7-30. https://doi.org/10.3322/caac.21442
18. You YN, Xing Y, Feig BW, Chang GJ, Cormier JN. Young-onset colorectal cancer: is it time to pay attention?. Archives of Internal Medicine. 2012 02 13;172(3):287-289. https://doi.org/10.1001/archinternmed.2011.602
19. Kasi PM, Shahjehan F, Cochuyt JJ, Li Z, Colibaseanu DT, Merchea A. Rising Proportion of Young Individuals With Rectal and Colon Cancer. Clinical Colorectal Cancer. 2019 03;18(1):e87-e95. https://doi.org/10.1016/j.clcc.2018.10.002
20. Patil PS, Saklani A, Gambhire P, Mehta S, Engineer R, De'Souza A, Chopra S, Bal M. Colorectal Cancer in India: An Audit from a Tertiary Center in a Low Prevalence Area. Indian Journal of Surgical Oncology. 2017 Dec;8(4):484-490. https://doi.org/10.1007/s13193-017-0655-0
21. Kam MH, Eu KW, Barben CP, Seow-Choen F. Colorectal cancer in the young: a 12-year review of patients 30 years or less. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland. 2004 05;6(3):191-194. https://doi.org/10.1111/j.1463-1318.2004.00596.x
22. Fu J, Yang J, Tan Y, Jiang M, Wen F, Huang Y, Chen H, et al. Young patients (≤ 35 years old) with colorectal cancer have worse outcomes due to more advanced disease: a 30-year retrospective review. Medicine. 2014 Nov;93(23):e135. https://doi.org/10.1097/MD.0000000000000135
23. Chan KK, Dassanayake B, Deen R, Wickramarachchi RE, Kumarage SK, Samita S, Deen KI. Young patients with colorectal cancer have poor survival in the first twenty months after operation and predictable survival in the medium and long-term: analysis of survival and prognostic markers. World Journal of Surgical Oncology. 2010 09 15;8:82. https://doi.org/10.1186/1477-7819-8-82
24. Sudarshan V, Hussain N, Gahine R, Mourya J. Colorectal cancer in young adults in a tertiary care hospital in Chhattisgarh, Raipur. Indian Journal of Cancer. 2013;50(4):337-340. https://doi.org/10.4103/0019-509X.123621
25. Laskar RS, Talukdar FR, Mondal R, Kannan R, Ghosh SK. High frequency of young age rectal cancer in a tertiary care centre of southern Assam, North East India. The Indian Journal of Medical Research. 2014 02;139(2):314-318. https://doi.org/5555
26. Nath J, Wigley C, Keighley MRB, Perakath B. Rectal cancer in young adults: a series of 102 patients at a tertiary care centre in India. Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland. 2009 06;11(5):475-479. https://doi.org/10.1111/j.1463-1318.2008.01607.x
27. Araghi M, Soerjomataram I, Bardot A, Ferlay J, Cabasag CJ, Morrison DS, De P, et al. Changes in colorectal cancer incidence in seven high-income countries: a population-based study. The Lancet. Gastroenterology & Hepatology. 2019 07;4(7):511-518. https://doi.org/10.1016/S2468-1253(19)30147-5
28. Liu P, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, He X, et al. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. JAMA oncology. 2019 01 01;5(1):37-44. https://doi.org/10.1001/jamaoncol.2018.4280
29. McMillan DC, McArdle CS. The impact of young age on cancer-specific and non-cancer-related survival after surgery for colorectal cancer: 10-year follow-up. British Journal of Cancer. 2009 08 18;101(4):557-560. https://doi.org/10.1038/sj.bjc.6605222
30. Mäkelä JT, Kiviniemi H. Clinicopathological features of colorectal cancer in patients under 40 years of age. International Journal of Colorectal Disease. 2010 07;25(7):823-828. https://doi.org/10.1007/s00384-010-0914-9
31. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The Rising Incidence of Younger Patients With Colorectal Cancer: Questions About Screening, Biology, and Treatment. Current Treatment Options in Oncology. 2017 04;18(4):23. https://doi.org/10.1007/s11864-017-0463-3
32. Ballester V, Rashtak S, Boardman L. Clinical and molecular features of young-onset colorectal cancer. World Journal of Gastroenterology. 2016 02 07;22(5):1736-1744. https://doi.org/10.3748/wjg.v22.i5.1736
33. Mathew A. Cancer trends and burden in India. The Lancet. Oncology. 2018 Dec;19(12):e662. https://doi.org/10.1016/S1470-2045(18)30755-1
34. Suryadevara S, Kumar K, Pampanagouda S, Arjun R, Deshmani V, Mukherjee G. Colorectal Cancer Profile in a Tertiary Care Centre, Bangalore, India. Online Journal of Health and Allied Sciences. 2014 05 01;13.
35. Feeney G, Sehgal R, Sheehan M, Hogan A, Regan M, Joyce M, Kerin M. Neoadjuvant radiotherapy for rectal cancer management. World Journal of Gastroenterology. 2019 09 07;25(33):4850-4869. https://doi.org/10.3748/wjg.v25.i33.4850
36. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, Arnold D. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2017 07 01;28(suppl_4):iv22-iv40. https://doi.org/10.1093/annonc/mdx224
37. Lorimer PD, Motz BM, Kirks RC, Boselli DM, Walsh KK, Prabhu RS, Hill JS, Salo JC. Pathologic Complete Response Rates After Neoadjuvant Treatment in Rectal Cancer: An Analysis of the National Cancer Database. Annals of Surgical Oncology. 2017 08;24(8):2095-2103. https://doi.org/10.1245/s10434-017-5873-8

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.