

COLORECTAL CANCER IN YOUNG INDIVIDUALS: AN OBSERVATIONAL STUDYMukesh Shanthilal¹, Sathya Maruthavanan²¹Assistant Professor, Department of Radiation Oncology, Mysore Medical College & Research Institute.²Associate Professor, Department of Radiation Oncology, Mysore Medical College & Research Institute.

ABSTRACT

INTRODUCTION

Colorectal cancer is the third most common cancer which can be detected early by implementation of cancer screening. This has led to decline in colorectal cancer related morbidity and mortality in elderly patients. However, there is increase in the incidence of this cancer in young individuals. This study was undertaken to study the characteristics of young colorectal cancer patients.

METHODS AND MATERIALS

The study was conducted from 2014 to 2016. All colorectal cancer patients attending the Department of Oncology, who were less than or equal to 50 years of age were included. Patients' demographic data as well as data regarding the colorectal cancer was collected. The data was entered into MS Excel worksheet and analysed using descriptive statistics.

RESULTS This study included 28 patients with a median age of 40 years and equal sex distribution. History of smoking in 85.7% (12/14) and alcohol (moderate) consumption in 64% (9/14) was present in male patients. There was no history of alcohol or smoking was present among female patients. However, tobacco chewing habit was present in 28% (4/14) of female patients. History of multiple sexual partners in 14% (4/28) of cases and 78% (22/28) were non-vegetarians. Nearly 85% (24/28) of patients presented with an advanced stage disease. The analysis showed involvement of left side of colon in 50% (14/28), rectum in 39% (11/28) and right side of colon in 11%(3/28). Except for two patients who were in stage - 1, all other patients received chemotherapy.

CONCLUSION

The incidence of colorectal cancer in young individuals is constantly rising. The reason for this increase is unclear and the relative contributions of genetic versus environmental factors remain relatively unexplored.

KEYWORDS

Colorectal Cancer, Genetics, Young Individuals.

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INTRODUCTION: The 1.3 million annual incidences is making colorectal cancer (CRC) as third most common cancer in males and the second most common cancer in females.⁽¹⁾ There is wide geographic, racial, and ethnic variation in incidence and patterns with 55% of cases occurring in high-resource nations. Higher proportions of colon cancers than rectal cancers (RC) and increased onset after age 50 are characteristics of CRC in developed countries.⁽²⁾ A recent analysis of End Results data for 3,93,241 patients with CRC seen between 1975 and 2010 showed an overall decreasing trend in the incidence and mortality rates in the United States.⁽³⁾ However, the incidence in younger adults showed an increasing trend with a striking rectal preponderance. In another analysis (1984-2005), the incidence of RC increased by 3.8% per year among people aged below 40.⁽⁴⁾ Data from the United States suggests that approximately 11% of colon cancers and 18% of RCs occur in individuals younger than age 50.⁽⁴⁾

These cancers are more likely to be poorly differentiated having mucinous and signet ring features, and with advanced stages of disease. Familial syndromes account for approximately 20% of these cases. Possible reasons for this disturbing trend is speculated to be lack of screening in young adults and lifestyle factors such as obesity, physical inactivity, diet rich in processed foods and red meat with a low intake of fruits and vegetables.⁽³⁾ This study was undertaken to study the characteristics of young colorectal cancer patients.

METHODS AND MATERIALS: The study included histopathologically proven colorectal cancer patients, with less than 50 years of age, attending the Department of Oncology between 2014 and 2016. Patients' demographic data as well as data regarding the colorectal cancer was collected. The data was entered into MS Excel worksheet and analysed using descriptive statistics. Informed consent was obtained from all patients.

RESULTS: Total of 28 patients seen between 2014 and 2016 were included in this study. Patient's characteristics of all 28 cases are given in Table - 1. Age ranged from 19 to 50 years with a Median age of 40 years. The male-female

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ratio was equal with 14 cases each. At the time of presentation, 85% (24/28) of patients presented with an advanced stage of disease. As per the stage of the disease: Stage-I two patients, stage IIA one patient, stage IIIA one patient, Stage IIIB 17 patients and Stage IIIC in four patients. Three patients presented with Stage IVA disease. There was no patient with Stage IVB disease. Site wise distribution of disease showed 50% (14/28) with left side of colon. This included transverse colon, descending colon, splenic flexure and sigmoid colon. Disease arising from rectum was seen in 39% (11/28) of cases, whereas in 11% (3/28) of cases showed involvement of the right side of colon which included ascending colon, hepatic flexure and caecum.

History of smoking in 85.7% (12/14) and Alcohol (moderate) consumption in 64% (9/14) was present in male patients. There was no history of alcohol intake or smoking among female patients. Tobacco chewing habit was present in 28% (4/14) of female patients. History of multiple sexual partners in 14% (4/28) of cases and 78% (22/28) were non-vegetarians. There was no family history of colorectal cancer, Lynch syndrome or hereditary polyposis colorectal cancer in any of the patients in the group.

Except for two patients who were in stage I, all other patients received chemotherapy (26/28). The most common regimen used was modified FOLFOX 6. This included fluorouracil 400 mg/m² bolus and 1200 mg/m² 46 hours infusion, leucovorin 400 mg/m² and oxaliplatin 85 mg/m². This was used in 17 cases. Next common regimen was CAPEOX which included oxaliplatin 130 mg/m² and Tab capecitabine 850 to 1000 mg/m² twice a day for 14 days. This regimen was used in seven cases. One each patient received FOLFIRI (fluorouracil 400 mg/m² bolus and 1200 mg/m² 46 hours infusion, leucovorin 400 mg/m² and irinotecan 180 mg/m²) and modified FOLFOX with bevacizumab 5 mg/kg.

Characteristics	Values
Age Range	19 – 50
Stage	
Stage 1	2
Stage IIA	1
Stage IIIA	1
Stage IIIB	17
Stage IIIC	4
Stage IVA	3
Site of Tumour	
Rectum	11
Left side of Colon	14
Right side of Colon	3
Chemotherapy	
mFOLFOX6*	17
CapeOx**	7
FOLFIRI†	1
mFOLFOX+bevacizumab	1

Table 1: Patients Characteristics

*5- fluorouracil, leucovorin and oxaliplatin, † 5- fluorouracil, leucovorin and irinotecan, ** Oxaliplatin and capecitabine.

DISCUSSION: Very low incidence rates of CRC, 4.2 and 3.2 per 100,000 in males and females, respectively were reported from India, compared to 25-44 per 100,000 from developed countries.^(1,5) The highest estimated rates have been reported from Australia and New Zealand with age-adjusted rates of 44.8 and 32.2 per 100,000 in males and females respectively. The traditional Indian diet, consisting predominantly of plant-based, fibre-rich foods and antioxidant-rich spices, has been postulated to be protective for colorectal cancers.⁽⁶⁾ Recent available data; however, indicate a steady increase of colorectal cancer incidence in India, presumably a result of increasing urbanisation and changing lifestyles and dietary patterns.⁽⁷⁾ These factors still do not sufficiently explain the striking differences that have been noted in the clinicopathologic profile of CRCs occurring in India compared to western counterparts. Among these differences significantly lower median age incidence and a rectal preponderance are the important ones.^(8,9) This study showed predominance of left-sided colon cancer (50%) followed by rectal cancer (39%) in contrast to other studies from India where rectal cancer was predominant.^(8,9) When we look at the diet most of them (78%) followed a non-vegetarian diet. The incidence of cancer had equal sex distribution. History of smoking was seen 85% and alcohol intake in 64% of male patients. None of the female patients had any history of smoking or alcohol intake but tobacco consumption was seen in 14% of female patients. Although many studies have suggested an aetiological role for tobacco, alcohol, and HPV, little attention has been paid to factors such as occupational exposures, environmental and industrial pollution and risk factors that have evolved in parallel to the incidence of these tumours.⁽¹⁰⁻¹³⁾

In the Western world, there have been major advances in knowledge of molecular mechanisms involved in CRC carcinogenesis, particularly regarding cytogenetic and epigenetic events. It is now recognised that there are at least three major pathways that lead to colorectal carcinogenesis: The chromosomal instability pathway (CIN), the microsatellite instability pathway (MSI), and the cytosine-phosphate-guanine island methylator phenotype pathway (CIMP).^(14,15) CIN accounts for approximately 70%-85% of all sporadic CRCs in the Western population. These cancers are often distal in location and are associated with poorer outcomes, regardless of stage.⁽¹⁵⁾ MSI results from point mutations in defect mismatch repair genes and are associated with approximately 15%-20% of sporadic CRCs. These tumours are usually proximally located with mucinous histology, poor differentiation, and a dense lymphocytic infiltration. CIMP, the third most commonly involved event, is characterised by widespread methylation of cytosine-phosphate-guanine islands of suppressor promoters. Sporadic MSI tumours are usually CIMP-positive and are predominantly located in the proximal colon (up to 40%). Activating mutations in BRAF occur almost exclusively in

MSI- and CIMP-positive CRC. Mutations in KRAS are more commonly seen CIMP-low tumours.⁽¹⁵⁾ In contrast, very little is known about the genetic and epigenetic alterations in CRC from resource-constrained countries. Emerging data seem to suggest that these cancers have distinct characteristics that are substantially different from their Western counterparts. An analysis of one of the first studies on genetic, epigenetic, and clinical profiles of RC from India revealed that 52% of patients were younger than age 45, with a higher percentage of low-rectal, advanced-stage, and aggressive tumours (poorly differentiated/mucinous).⁽¹⁶⁾ MSI and BRAF mutations were uncommon and seen in 5.0% and 2.5% of samples, respectively, but high frequencies of overall KRAS mutations (67.5%) were seen. The younger patients exhibited higher codon 15 and 18 KRAS mutations as compared to the older patients, who showed mutations more commonly in codon 12 or 13, similar to their Western counterparts. This study also revealed a novel KRAS G15S mutation with concomitant RASSF1 methylation in early-onset cases, findings that have not been previously reported. The investigators noted that the early-onset subgroup showed the most unfavourable disease characteristics, including advanced stage, poorly differentiated tumours, and the poorest survival outcomes. A few previous studies from early-onset Indian and Bangladeshi patients with CRC also reported similar findings.^(17,18)

Although many studies have suggested an aetiological role for tobacco, alcohol, and HPV, little attention has been paid to factors such as occupational exposures, environmental and industrial pollution, and risk factors that have evolved in parallel to the incidence of these tumours. Though it was not analysed in this study, there is growing evidence which suggests its link in carcinogenesis of colorectal cancer. Publications on the topic are few and, in many cases, rather inconclusive. Pesticide remains and nitrate pollutants can easily contaminate surface water, and various studies have demonstrated a positive correlation to CRC. An epidemiologic study from China demonstrated that populations drinking surface and well water have higher RC and colon cancer risk than those using municipal groundwater.⁽¹⁹⁾ The consumption of pesticides in India has increased several hundred-fold, from 154 metric tons in 1954 to 41,822 metric tons in 2009-2010.⁽²⁰⁾ Pesticides enter surface and groundwater primarily as runoff from crops and are most prevalent in agricultural areas. In most low-income countries, including India, it is estimated that approximately 10% of the contaminated water generated from various sources is treated; the rest is discharged as such into water bodies. Such water, which ultimately ends up being used in households, is often highly contaminated with chemicals and pesticides and can potentially cause various adverse health effects, including cancer.⁽²¹⁾

The growing magnitude and aggressive behaviour of these tumours warrant a comprehensive exploration of potential risk factors, including water and air pollution, initiation of preventive strategies, and screening programs. This study is limited in terms of less number of cases and

lack of genetic testing. Further studies are needed which would study the genetic makeup of these cancers.

CONCLUSION: The incidence of colorectal cancer in young individuals continues to rise. The reason for this increase is unclear, and the relative contributions of genetic versus environmental factors remain relatively unexplored. The growing magnitude and aggressive behaviour of these tumours warrant a comprehensive exploration of potential risk factors and initiation of preventive strategies, and screening programs.

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