Editorial

Young Onset Colorectal Cancer

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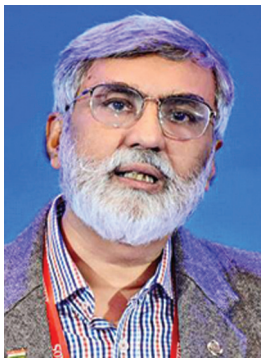
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Colorectal cancer (CRC) constitutes approximately 3% of all newly diagnosed cancers in India. The incidence of CRC is increasing in our country as opposed to the global trend of decreasing rates.[1,2]

Approximately a quarter to a third of these are identified in people in the prime of their most productive age (<40 years, also called young onset CRC [YO-CRC]) and at an advanced stage (III or IV).[3,4]

The global standardized incidence of YO-CRC increased from 3.05/100,000 population in 1990 to 3.85/100,000 population by 2019. The increase was higher in countries that had a higher socioeconomic level of living. There was especially a significance increase in the incidence of YO-CRC in Vietnam, Caribbean, and Saudia Arabia.[5]

The U.S. SEER database showed that between 2010 and 2015 YO-CRC accounted for 5,350 patients. This group had a higher incidence of mucinous/signet ring histology and was predominantly composed of non-Caucasian individuals. About a quarter of them (28.6%) were right-sided tumors.[6–8]

It is projected that by 2030 CRC will be the leading cause of death in the United States for people in the age group of 20 to 49 years.[9]

In India, their percentage remains unchanged from 2014 to 2021.[4] YO-CRC is characterized by being predominantly left sided (rectal) and with a signet ring histology.

YO-CRC has a greater percentage of high-risk features, a higher chance of recurrence, and a higher cancer-specific mortality.[10] Why this happens in the younger CRC patients is still to be understood.

A 10-year study included 4,758 consecutive patients, with 771 (16%) patients below the age of 50 years. Male YO-CRC patients had higher rectal cancer, were poorly differentiated, and were diagnosed at an advanced stage. Among female YO-CRC patients, left-sided tumors were more prevalent. Both relapse-free survival (RFS) and overall survival (OS) were worse in the YO-CRC group.[11]

In a 1-year Chinese study involving 991 YO-CRC patients and 3,581 older patients, the patients in the former group were found to be more educated, more aware, and willing for gene testing. They also had more extensive metastatic disease at presentation.[12]

Integrated multi-omics (combined datasets from genomics, epigenomics, proteomics, transcriptomics, and metabolomics) is likely to help unravel various complex biological mechanisms responsible for driving aggressiveness in YO-CRC.[13]

About 5% of all CRCs develop in the background of well-defined inherited syndromes. Another 30% show increased familial risk, probably also related to inheritance.[14] Common syndromes leading to higher risk include Lynch's syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC]) and familial adenomatous polyposis (FAP). There is some evidence that pathogenic germline variants are seen in approximately 20% of cases with YO-CRC.[15,16] The Ohio

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($N = 450$) and Michigan ($N = 403$) studies showed germline mutations associated with Lynch's syndrome (8.4 and 13.9%, respectively), FAP (1.1 and 2.5%, respectively), and MUTYH-associated polyposis (MAP; 0.9 and 0.5% respectively).

A study conducted between 2014 and 2021 included 100 YO-CRC cases. Only 31% underwent genetic testing, especially among those who were to receive chemotherapy or those with family history of cancer. Among them, the rate of pathologic germline genetic variants was higher as compared with the older CRC patients.[17]

Several genetic and clinical differences as compared with LO-CRC have been documented. YO-CRC presents at a more advanced stage and progresses more rapidly, suggesting that a young tissue environment is often more promotional.[18]

A prospective study performed molecular profiling of patients with CRC. They divided the patients into pediatric CRC ($N = 8$), YO-CRC (teenagers and young adults; $N = 30$), and late onset CRC (LO-CRC; $N = 56$). They found that pediatric patients showed mutations of RNF43 and amplification of CDK6. The molecular alterations in RAS, VEGF, mTOR, and AMPK pathways were found in the nonpediatric group and did not differ between YO-CRC and LO-CRC. They proposed that the pediatric CRC group has the potential to benefit from PI3K AKT and CDK6 inhibitors.[19]

Environmental risk factors and lifestyle choices considered important are obesity, type 2 diabetes mellitus (DM), decreased physical activity, and high intake of junk food.

Between 1998 and 2018, a total of 1,087 YO-CRC and 2,554 older-onset CRC patients were studied. YO-CRC patients had lower intake of vegetables and higher consumption of processed meat and spicy food.[20]

Increase incidence of YO-CRC is following the global increasing trend of type 2 DM (which increased from 30 million cases in 1964 to 171 million cases by 2004). In fact, a Swedish study quantifies that those younger than 50 years and diagnosed with type 2 DM have a 3.5-fold higher risk of YO-CRC.[21]

Change in colonic microbiota has also been linked with use of antibiotics. In the Nurses' Health Study (16,642 individuals who underwent screening colonoscopy after the age of 60 years and had extensive medical records going back decades),[22] 1,195 had colonic adenomas (considered premalignant lesions). Exposure to antibiotics at least 10 years earlier was significantly associated with the presence of this premalignant lesion, with a strong dose–response correlation. The six-study meta-analysis supports this association, it being stronger for colon (as compared with rectal) cancer and use of penicillin or cephalosporin.[23–26]

Fusobacterium nucleatum, *Bacteroides fragilis*, and *Escherichia coli* are the most common gut bacteria that are related to LO-CRC,[27] and below we discuss their involvement in YO-CRC.[28]

In a study, 170 samples from 66 YO-CRC and 104 LO-CRC patients were compared with those from 49 non-CRC controls. YO-CRC patients showed more disruption involving the citrate cycle and arginine biosynthesis pathways.[29]

An interesting microbiome study looked at samples from 276 patients with CRC. This included 136 samples from YO-CRC patients and 140 from LO-CRC patients. The bioinformatic analysis included the use of PhyloSeq, MicrobiomeSeq, MetagenomeSeq, and NetComi. The YO-CRC group had higher left-sided, rectal, and stage IV cancers. They also had higher microbial α diversity and were enriched for *Akkermansia* and *Bacteroides* species. Interestingly patients expressing *Akkermansia* had smaller tumor sizer and better OS, whereas those expressing *Fusobacterium* correlated with bigger tumor size and shorter OS.[30]

Another study found no difference in the gut microbiome spectrum between the two groups.[31]

The impact of treatment is more profound among the YO-CRC patients. Surgery-related factors include permanent bowel dysfunction, low anterior resection syndrome, sphincter loss, and permanent ostomy.[32] In addition, they can develop urinary dysfunction, perianal/peristomal disorders, stricture formation, and sexual dysfunction. They, in turn, lead to problems related to diet, clothing, professional work, travel, sports, and other social activities. No wonder YO-CRC patients face anxiety, body image issues, and embarrassment about bowel movements—existing for up to 10 years after diagnosis.[33,34] Challenges with financial toxicity and oncofertility cannot be overemphasized. YO-CRC patients face more out-of-pocket expenses and medical debt for prolonged periods.[35] It often leads to skipping medication or meals, compromising treatment outcomes.

Young patients are frequently underinsured and may suffer significant disruptions to professional and financial growth. A survey included patients between 2019 and 2021 was conducted among patients diagnosed earlier with CRC. As compared with age-matched controls, YO-CRC patients had a higher composite financial toxicity score (higher for females, food insecurity, delays in essential medical care, greater need for mental health counseling, out-of-pocket cost of filling prescriptions).[36]

In view of the central and state government schemes in India, management of cancer patients is largely supported by public funding. It is therefore interesting to look at direct medical spending as a method of evaluating cost to the government health department. A study from Canada compared this between 1,058 YO-CRC patients and 12,619 LO-CRC patients. Their findings are shown in ►Table 1. Interestingly the YO-CRC group's total cancer-related cost was higher by 39% (C$144,702 vs. C$104,368), mainly due to the more aggressive use of targeted therapy, chemotherapy, and radiation therapy—factors that have not improved the OS.[37]

The psychosocial impact of financial toxicity, in turn, affects quality of life.[34] Options for sperm, embryo, and/or oocyte preservation need to be discussed.[38] So also the likelihood of successful fertility preservation and pregnancy outcome.[39]

In conclusion, the management of YO-CRC needs special attention. A multidisciplinary proactive approach to anticipate and address the entire spectrum of needs will go a long way in providing optimal outcome in this group.

International guidelines clearly specify that management of CRC should not differ between YO-CRC and older CRC patients. A retrospective, population-based, cohort study included 32,363 patients with CRC diagnosed from 2010 to

Table 1 Direct medical spending (by government) for CRC patients (Canadian data; in Canadian dollars; 1 Canadian dollar = 61 INR)[37]

	Parameter	YO-CRC	LO-CRC
1	Before diagnosis of cancer (1 year)	6,711	8,056
2	**Cancer related**		
A	Initial (diagnosis + treatment)	50,216	37,842
B	Continuing after completion of cancer treatment	8,361	5,014
C	End of life cancer related	86,125	61,512
D	Total CRC related	1,44,702	1,04,368
3	Non-cancer-related end of life	77,273	23,316

2021. This group comprised 130 YO-CRC patients and 668 LO-CRC patients. The YO-CRC patients were more likely to be offered adjuvant chemotherapy (even in stage II; $p = < 0.001$) or multi-agent therapy (stages II and III; $p = < 0.01$) without any associated increase in survival.[40] Unfortunately, this trend of using more aggressive treatment in YO-CRC persists, without any evidence of a survival benefit.

The application of artificial intelligence and deep learning algorithms can accelerate the process, perhaps even identify novel markers to guide personalized management of CRC.[41]

Having said that, we have access to a simple fecal immunohistochemical screening test that has been demonstrated to be sensitive (97%) and specific (99.8% negative predictive value).[42] Also, there are data to indicate the screening benefit of using next-generation multitarget stool DNA test.[43] Is it time for mass screening in India, at least in the high-risk population?

Conflict of Interest

None declared.

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