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Young-age onset colorectal cancer in Brazil: Analysis of incidence, clinical features, and outcomes in a tertiary cancer center

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ABSTRACT

Background: Recent studies report increasing incidence of colorectal cancer (CRC) in the young-age population, but data concerning clinical behavior, pathologic findings, and prognosis are controversial for this group. Early recognition of CRC in young patients is a challenge and diagnosis at advanced stage is clearly associated with worse outcomes.
Materials and methods: We retrospectively reviewed medical records of 5806 patients diagnosed with CRC between January/2011 and November/2016 and identified 781 patients aged less than 50-years-old.
Results: We found an absolute increasing in the incidence of CRC in patients <50 years old of 1.88%–2.23% annually, with a relative increasing of 35.3% between 2011 and 2016. Median age was 42 years, 57.4% were female and 20.9% reported family history of CRC. Left-sided tumors were more frequent and the majority of patients were symptomatic. The most common stages at diagnosis were III (34.1%) and IV (37.3%). The median overall survival (OS) for stage IV was 25 months (95% CI 20.7-29.3) and was not reached for Stages I-III ($P < 0.001$). Family history of CRC was independently associated with better OS in stage IV($P = 0.02$). For stages I-III, wild-type KRAS, family history of CRC, and absence of angiolymphatic invasion were associated with better OS ($P = 0.02$, $P = 0.01$ and $P < 0.001$, respectively).
Conclusions: In our cohort, the incidence of early-onset CRC is increasing over the past years. Young patients were more likely to be diagnosed with metastatic disease, left-sided and/or rectum site and symptoms at presentation. These findings highlight the emerging importance of young-age onset CRC and the need to discuss strategies to early diagnosis.

Abbreviations: CRC, colorectal cancer; CEA, carcinoembryonic antigen; OS, overall survival; 95% CI, 95% confidence interval; dMMR, deficient mismatch repair.

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Introduction

Colorectal cancer (CRC) is the third most common cancer with nearly 1.4 million of new cases and 700,000 cancer-related deaths per year worldwide.[1] In Brazil, 36,360 new cases were estimated for 2018.[2] Age is an important risk factor for sporadic CRC with the highest incidence between the sixth and seventh decade of life.

Over the past years, a decrease in the global occurrence of CRC has been registered.[3,4] Apart from the treatment advances, this trend can be justified by screening programs developed since 1990, especially those including colonoscopy for patients over 45-50 years old.[5-7] In an analysis conducted from 1998 to 2006, a reduction in the CRC incidence of 3% per year among men and 2.4% per year among women was reported.[8] However, the incidence of CRC in the young population has been increasing worldwide. According to the *Surveillance, Epidemiology, and End Results Reporting (SEER)* database, the incidence of CRC in the population younger than 50 years old increased 2.1% per year from 1992 to 2012 in the United States.[9-12] Similarly, CRC incidence rates across Europe in adults aged 20 to 39 years increased by 6% every year between 2008 and 2016.[13] A remarkable incidence of young-onset CRC was also reported in series from Asia.[14,15]

Besides the well-known risk factors such as inflammatory bowel disease and hereditary syndromes related to CRC, other factors may be involved in the increasing incidence of early-onset CRC. Changes in lifestyle, alcohol consumption, sedentary lifestyle, red meat intake, obesity, and diabetes mellitus can partially explain this trend, but epidemiologic data are not strong enough to establish a definitive correlation.[16-23]

Once screening programs do not cover the population under 45-50 years old, the early recognition of CRC is a challenge. The diagnosis is frequently made in the metastatic setting, when curative treatment is less often successful. Additionally, clinical behavior and response to treatment seems to be different between the younger and the older population with sporadic CRC. Observational studies showed that sporadic tumors in the younger population are more often located in the left colon and rectum, are poorly differentiated and are diagnosed in more advanced stages.[10,11] Moreover, a comparison from historical cohort suggested that younger patients are less responsive to treatment and have poorer overall survival.[17]

In Brazil, the proportion of patients younger than 50 years old diagnosed with CRC is unknown. In the present study, we aim to evaluate the trend in the incidence of early-onset CRC among the patients referred to a tertiary cancer center and to describe clinicopathologic features of this group of CRC patients.

Materials and methods

Patients

A database of all patients with biopsy-proven diagnosis of CRC referred to Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, between January/2011 and November/2016 was analyzed and those patients who were diagnosed with less than 50 years old were included in the analysis. The study was approved by the local ethics committee.

The following data from the clinical records were retrospectively collected: age, gender, diagnostic date, primary tumor location, stage, histology, presence of angiolymphatic and perineural invasion, mismatch repair status, KRAS mutation, family history of cancer (first-degree relative), known genetic syndrome, symptoms at presentation, need of urgent surgery, prior screening,

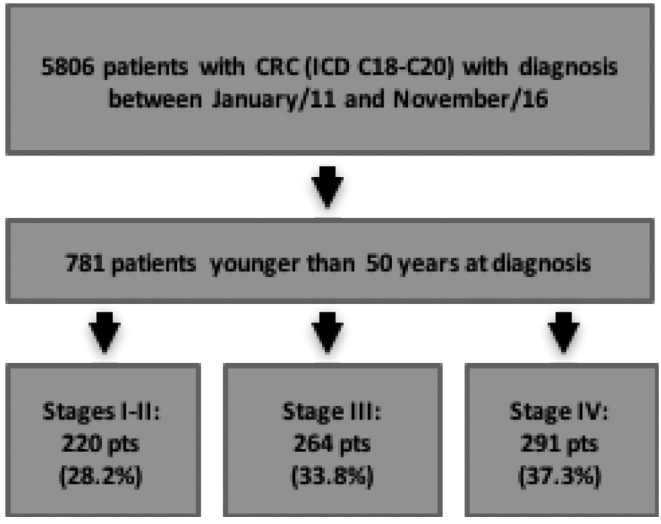

Fig. 1. Consort diagram of the study cohort.
CRC, colorectal cancer; ICD, International Classification of diseases.

carcinoembryonic antigen, treatment and outcomes. We considered as known genetic syndrome if a patient had a positive genetic test, a tumor sample with loss of immunohistochemical staining of MLH1, MSH2, MSH6 or PMS2, or any syndrome diagnosed by a Medical Genetics specialist.

Statistical analysis

Overall survival (OS) was defined as the time from diagnosis to death. Continuous variables were expressed as mean and ranges. Categorical variables were expressed as frequency and were compared using chi-square test. The Kaplan–Meier method was used to estimate OS and 95% confidence interval (95% CI). We analyzed pretreatment clinical and laboratorial characteristics potentially associated with outcome. Log-rank test was used in univariate analysis and Cox regression test in multivariate analysis. Variables were considered to be significant if two-sided P value was <0.05 on multivariate test. Data were evaluated using IBM SPSS software version 23.0 (SPSS Chicago, IL).

Results

Population characteristics

A total of 5806 patients diagnosed with CRC between January/2011 and November/2016 and 781 patients <50 years of age were identified (Fig 1). The median age of this cohort was 42 years (17-49 years), 57.4% were female and 42.6% were male. Baseline characteristics are summarized in Table 1.

At diagnosis, 93.9% of the patients were symptomatic and 28.3% underwent emergency surgery. The most common symptoms were abdominal pain (39.6%) and rectal bleeding (28.7%). The stage distribution was stage I 2.6%, stage II 25.6%, stage III 33.8%, and stage IV 37.3%. In our data, 73.4% of the patients presented with left-sided tumors (left colon 8.2%, sigmoid 33.7%, and rectum 31.5%), with only 19.4% patients with right-sided tumors. CRC family history was reported by 20.9% of the patients and 41.5% reported history of other primary cancers in the family. However, only 4% of the patients were diagnosed with a genetic syndrome (Table 1).

Most of the patients received the diagnosis between 40 and 49 years old (61.8%) and the incidence of patients younger than 30 years old was 9.7%.

Trends in annual incidence

In the biennial of 2011-2012, 11.6% (n = 255) of all the patients diagnosed with CRC (n = 2188) were younger than 50 years and this percentage increased to 13.5% in 2013-2014 (n = 269 / total of patients diagnosed with CRC = 1988) and then to 15.7% (n = 257; total of patients diagnosed with CRC = 1630) in 2015-1016, resulting in a difference between 1.88% and 2.23% annually (Fig 2). An absolute increase of 4.1% and a relative increase of 35.3% between 2011 and 2016 were detected.

Survival outcomes

Two hundred ninety-one (37.3%) patients were diagnosed with stage IV disease with a median OS of 25 months (95%CI 20.6-29.3 months). Patients with locoregional disease (stage I-III) corresponded to 67.4% of the cohort and the median OS for this group was not reached (NR) (95%CI NR-NR) (Fig 3).

In patients with locoregional disease, wild-type KRAS, family history and absence of angiolymphatic invasion were independently associated with better OS in the multivariate analysis ($P = 0.02$; $P = 0.01$ and $P < 0.001$ respectively) (Table 2).

In patients with stage IV, the univariate analysis for prognostic factors showed that family history of CRC, known genetic syndrome and absence of angiolymphatic invasion were associated with prolonged OS. In multivariate analysis, family history of CRC and absence of angiolymphatic invasion remained independently associated with OS ($P = 0.02$ and $P = 0.04$, respectively). (Table 2 and Fig 4)

Discussion

In the present cohort, a remarkable increasing in the incidence of early onset CRC over the last decade was observed. Additionally, the majority of patients presented with symptoms, had predominantly left-sided tumors and late stage disease at diagnosis.

This study was conducted in a large cancer center in the southeast Brazil. A noteworthy trend toward the adoption of a more westernized lifestyle and dietary habits is observed not only in this region but also in other regions of Latin America over the last decades.[24,25] This leads to an increasing in obesity rates, sedentarism, smoking habit, alcohol consumption, red meat intake and, probably, to changes in the age-incidence pattern of CRC.

We choose to analyze patients below the cut-off of 50-years old because this is the age in which screening starts to be recommended to the general population according to the US Preventive Services Task Force[26] and to the local practice. For this reason, 98.8% of our patients had not undergone screening tests. Nearly 70% of our cohort was diagnosed in the fifth decade of life. Other studies dedicated to early-onset CRC used different cut-off ages, such as 40[11,17] or 45 years old,[27] and this may impair the comparison among these data. The American Cancer Society currently recommends that adult aged 45 years and older with an average risk of CRC undergo regular screening. The recommendation to begin screening at age 45 was based on disease burden, new trend in young CRC, and the reasonable perception that screening will perform similarly in adults aged 45-50 years.[7] Once about one-third of the patients in our cohort were diagnosed between 45 and 50 years, the cut-off of 45 years would probably be appropriate in our context.

Several analyses showed a consistent fast-growing incidence of CRC in younger patients in the last decades. SEERS, a program that collects data from population-based cancer registries

Table 1
Baseline patient and tumor characteristics.

Baseline characteristics	n = 781 (%)
Median age (range)	42 years (17-49)
Age	
<30 y	76 (9.7%)
30–34 y	78 (10%)
35-39 y	144 (18.4%)
40-44 y	200 (25.6%)
45-50 y	283 (36.2%)
Sex	
Male	333 (42.6%)
Female	448 (57.4%)
Median BMI (Range)	23 (12-47)
Family history	
CRC	163 (20.9%)
Other primary malignancies	324 (41.5%)
Known genetic syndrome	31 (4.4%)
Symptoms	
Pain	309 (39.6%)
Obstruction	136 (17.4%)
Bleeding	224 (28.7%)
Weight loss	52 (6.7%)
Other	48 (6.1%)
Asymptomatic	12 (1.5%)
Urgent surgery	221 (28.3%)
T classification*	
1	12(1.5%)
2	52 (6.7%)
3	426 (54.5%)
4	167 (21.4%)
Unknown	124 (15.9%)
N status*	
0	256 (32.8%)
1	225 (28.8%)
2	162 (20.7%)
3	2 (0.3%)
Unknown	136 (17.4%)
M status*	
0	488 (62.5%)
1	292 (37.4%)
unknown	1 (0.1%)
Stage*	
I	20 (2.6%)
II	200 (25.6%)
III	264 (33.8%)
IV	291 (37.3%)
Unknown	6 (0.8%)
Site of primary tumor	
Left colon	64 (8.2%)
Sigmoid	262 (33.7%)
Rectum	246 (31.5%)
Right-sided tumor	151 (19.4%)
Transverse	40 (5.1%)
Synchronous	7 (0.9%)
Unknown	11 (1.4%)
Histology	
Well differentiated	58 (7.4%)
Moderately differentiated	584 (74.8%)
Poorly differentiated	38 (4.9%)
Mucinous	58 (7.4%)
Signet-ring	12 (1.5%)

(*continued on next page*)

Table 1 (*continued*)

Baseline characteristics	n = 781 (%)
Small cells	1 (0.1%)
Other	30 (3.8%)
Angiolymphatic invasion	
Present	270 (34.6%)
Absent	152 (19.5%)
Unknown	359 (45.9%)
Perineural invasion	
Present	226 (28.9%)
Absent	299 (38.3%)
Unknown	256 (32.8%)
Mismatch-repair status	
Deficient	78 (10%)
Proficient	388 (49.7%)
Unknown	315 (40.3%)
KRAS status	
Mutated	115 (14.7%)
Wild-type	192 (24.6%)
Unknown	474 (60.7%)
Screening prior to diagnosis	
Yes	9 (12%)
No	772 (98.8%)
Adjuvant chemotherapy	394 (50.4%)
Median CEA at diagnosis (range)	6 (0.4-50.000)

BMI, body mass index; CRC, colorectal cancer; CEA, carcinoembryonic antigen.
* Based on the 8th *edition* of the *TNM* Classification of Malignant tumors.

Table 2
Independent prognostic factors in the cohort of patients with colorectal cancer < 50 years.

	Median overall survival, months (95% CI)	Multivariate *P* value
Stage I-III		
Angiolymphatic invasion (yes vs no)	NR (NE-NE) vs NR (NE-NE)	<0.001
Family history of CRC (yes vs no)	NR (NE-NE) vs NR (NE-NE)	0.01
Wild-type KRAS (no vs yes)	40 months (29.3-50.6) vs NR (NE-NE)	0.02
Stage IV		
Family history of CRC (yes vs no)	40.0 months (27.9-52.1) vs 21.0 months (16.8-25.2)	0.02
Angiolymphatic invasion (yes vs no)	24.0 months (19.6-28.4) vs 34.0 months (23.8-44.2)	0.04

CRC, colorectal cancer; NR, not reached; NE, not estimable.

covering around one-third of the US population, showed a stable incidence of CRC in older patients, whereas the incidence increased 17% among young between 1973 and 1999.[11] The National Cancer Database, a hospital-based cancer registry sponsored by the American College of Surgeons and American Cancer Society that captures more than 70% of newly diagnosed cancer cases in US, observed an increase for young-onset disease since 2001, more relevant for rectal than colon cancers. Recently presented data on age-related incidence of CRC retrieved from national European cancer registries in 20 countries also confirmed this trend.[13] However, different trends were reported by two population-based studies in Australia[28,29] and data from Hong Kong[30] and Korea[31] did not a find an increase in the incidence of young-onset CRC. There is no clear explanation for this phenomenon. Possible reasons may be related to changes in diet, sedentary lifestyle, and general lifestyle changes in the western population over the last decades. We observed that the majority of our patients were diagnosed with advanced disease at the time of presentation, which is consistent with other reports in the literature.[10,11,17] Additionally, there was a significant percentage who underwent urgent surgery at diagnosis. As expected, only 1.2% of the patients were submitted to a screening test, probably because they had a known predisposing factor that encouraged the screening. The high incidence of late-stage presentation

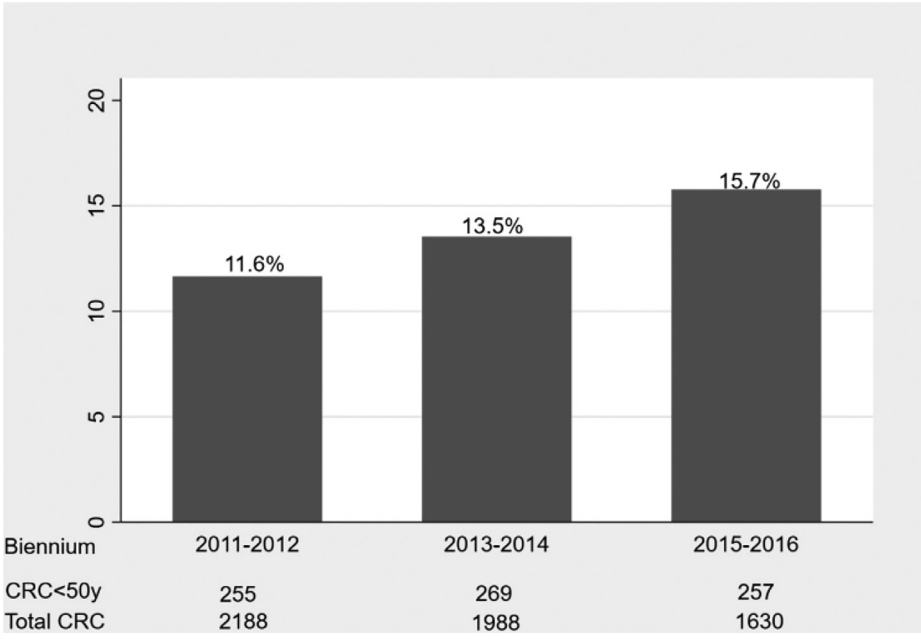

Fig. 2. Evolutionary percentages of colorectal cancer in patients <50 years across the total of colorectal cancer in each biennium from 2011 to 2016.
CRC, colorectal cancer.

raises a question about why diagnosis is not made earlier. Our data did not address specifically this issue. However, the reluctance of young patients to seek for medical care, the low clinical suspicious of minimal intestinal symptoms, and lack of access may explain the delay in diagnosis in primary and secondary care. Another finding of our study was a slight majority of women in comparison to men, what is consistent with Brazilian cancer statistics on CRC incidence.[2]

Patients with family history of CRC may have a better prognosis, as was reported in the present study. It is becoming clearer that deficient mismatch repair genes, that is the hallmark of Lynch syndrome, is associated with high rate of somatic mutations and neoepitope formation. This could contribute to enhanced host immune response against the tumor. Deficient MMR tumors are also associated with improved prognosis in early stage disease.[32-34] Perea et al analyzed MMR and CpG island methylator phenotype-high in early and late-onset CRC and found correlation between *BRAF* mutations and deficient mismatch repair/CpG island methylator phenotype-high, as well as differences according to primary tumor location and stages.[27] This suggests that the age of onset of the CRC can be influenced by molecular features and carcinogenetic pathways.[35,36] The understanding of these features is fundamental to improve diagnosis and treatment methods. Angiolymphatic invasion is a well-known risk factor for recurrence. In the present study, absence of angiolymphatic invasion was associated with better OS in patient with stages I-III, reflecting what was also observed in other studies.[37,38]

Our analysis did not have sufficient patient information to investigate potential risk factors due to the retrospective nature of the study. Moreover, we did not have available a wide-ranging genomic test to investigate the presence of genetic syndromes.

Another limitation of our study is that our center is a tertiary cancer hospital for which patients are referred from primary care or secondary hospitals. Patients with strong family history or polyposis syndromes are more likely to be referred to tertiary hospitals, what may overestimate the incidence of young-onset CRC. Besides, we probably deal with a more complex and symptomatic subset of patients, what may not reflect exactly the community patients with

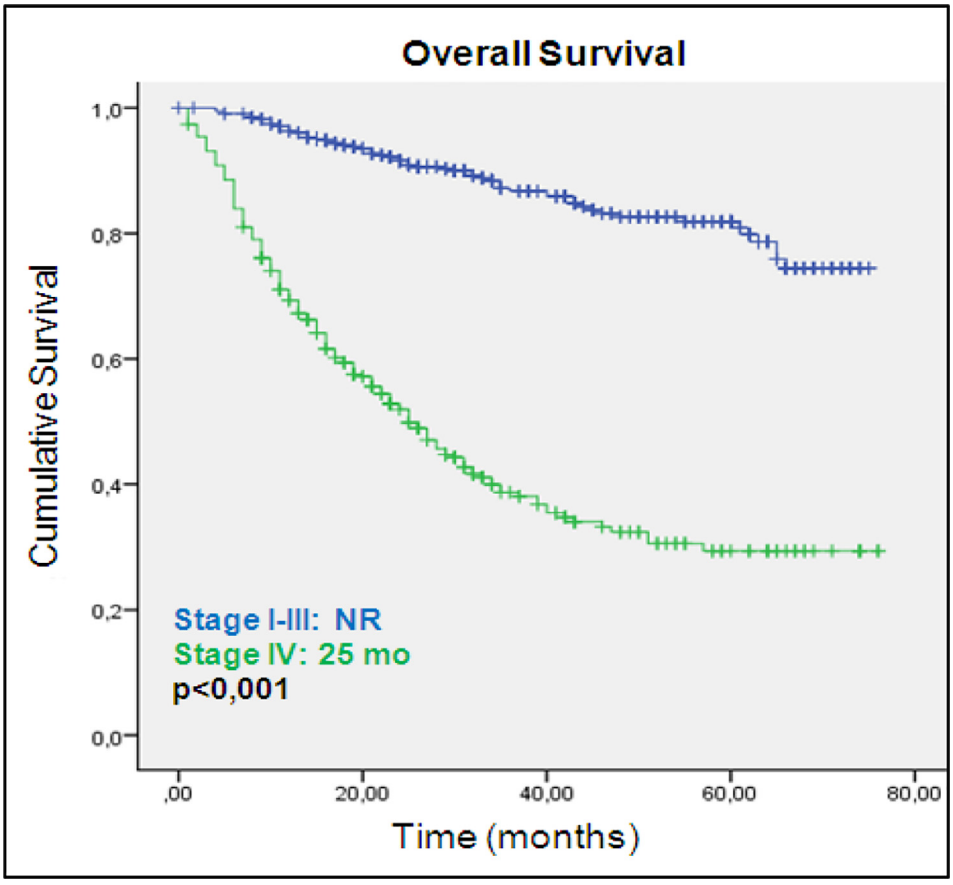

Fig. 3. Survival curves of colorectal cancer patients < 50 years according to TNM stages I-III vs IV.

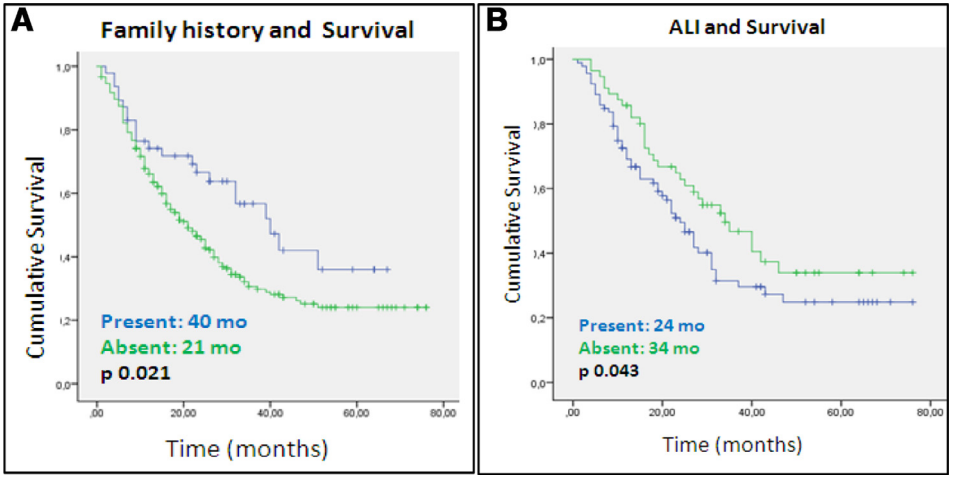

Fig. 4. Survival curves of stage IV patients according to: (A) family history (present vs absent) and (B) angiolymphatic invasion (ALI) (present vs absent).

CRC. It is likely that secondary hospitals have been able to manage some asymptomatic and early-stages tumors among young patients, thus resulting in an overestimated incidence of late-stage and symptomatic tumors and a significant rate of urgent surgeries in our cohort. Another possible source of selection bias is that left-sided tumors are more commonly associated with symptoms, such as obstruction, pain or bleeding, what may have selected this subgroup of CRC patients to our center. However, we do not consider that these factors varied along the years analyzed in the present study because no major changes in the local public health system organization was implemented during this period. A prospective collection of data beginning in the primary care units could be more informative in terms of practice changing recommendations.

Conclusion

To sum up, this retrospective study reinforces that an alarming rise in the incidence of CCR in young patients and that the diagnosis in this population is often made when treatment with curative intention is less likely to be successful. Efforts in identifying high-risk cohorts for target screening should be warranted. Moreover, health care professionals should need to be aware of this trend and keep an adequate clinical suspicion. Strategies to improve early detection and prevention in the patients under 50 years of age are required and would certainly improve survival.

Clinical practice points

Recent database studies noticed a rising incidence in colorectal cancer among young people, finding that is also observed in daily practice. Our study confirmed this suspect in a tertiary public hospital and found a relative increasing of 35.3% between 2011 and 2016 among people with less than 50 years old. The majority of patients were symptomatic and 37.3% were metastatic at diagnosis, finding that make us aware that we need to anticipate the diagnosis in this age group. These results reinforce that we shall pay more attention in young people symptoms and develop preventive, screening, and diagnostic strategies concerning early-onset colorectal cancer.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.01.009.

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