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ORIGINAL ARTICLE

Interval colorectal cancer after colonoscopy☆

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Abstract
Introduction and aims: Interval colorectal cancer (iCRC) can occur due to missed lesions or to a newly developed lesion. The present study aimed to assess the iCRC rate and its characteristics in our population and find possible explanations.
Materials and methods: A retrospective study was conducted on patients with colorectal cancer (CRC) diagnosed between January 2011 and January 2015 at our department. Demographics, endoscopic data, and tumor characteristics (location, histology, staging) were collected. We identified patients diagnosed with CCR who underwent colonoscopy at our department in the previous 10 years and presented the disease (iCRC) before the date of their next recommended exam. The cases of iCRC were characterized and compared with other CRC cases. Possible explanations for the appearance of iCRC were analyzed.
Results: A total of 266 patients presented with CRC, 61.7% were men, and mean patient age was 70.7 years. We identified 10 patients with iCRC: 6 were men, and mean patient age was 71.1 years. Mean time for iCRC diagnosis after index colonoscopy was 3.5 ± 1.84 years. Tumor was located in the right colon in 50% of the patients with iCRC and in 24.5% of the patients without iCRC ($P = .091$). More patients with iCRC had a family history of CRC (50%) than the patients with reference CRC (3.1%) ($P = .000$).
Conclusions: In our case series, 3.76% of all CRC were iCRC. There were no statistically significant differences between patients with or without iCRC, with the exception of family history of CRC.

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PALABRAS CLAVE
Cáncer colorrectal de intervalo;
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Cáncer colorrectal de intervalo después de colonoscopia

Resumen
Introducción y objetivos: El cáncer colorrectal de intervalo (CCRi) puede ocurrir debido a lesiones no detectadas o a una lesión recién desarrollada. El presente estudio tiene como objetivo la evaluación de la tasa de CCRi, de sus características en nuestra población y encontrar posibles explicaciones.
Material y métodos: Estudio retrospectivo que incluye cáncer colorrectal (CCR) diagnosticado entre enero de 2011 y enero de 2015 en nuestro departamento. Se han recogido datos endoscópicos y características tumorales (localización, histología y estadificación). Se identificaron los pacientes a quienes se les realizó una colonoscopia en nuestro departamento en los 10 años anteriores al diagnóstico del CCR y que presentaron el cáncer (CCRi) antes de la fecha del próximo examen recomendado. Se llevó a cabo caracterización del CCRi comparándolo con otros CCR y analizando las posibles explicaciones para el CCRi.
Resultados: Se incluyeron 266 pacientes con CCR, 61.7% varones; edad media de 70.7 años. Se identificaron 10 pacientes con CCRi: 6 varones, edad media de 71.1 años. El tiempo medio para el diagnóstico del CCRi después de la colonoscopia inicial fue de 3.5 ± 1.84 años, el tumor estaba en el colon derecho en el 50% de los pacientes con CCRi y en el 24.5% de los pacientes sin CCRi ($p = 0.091$). Un mayor número de pacientes con CCRi tenían antecedentes familiares de CCR (50%) en comparación con los pacientes con CCR de referencia (3.1%) ($p = 0.000$).
Conclusiones: En nuestra serie, el CCRi representa el 3.76% de todos los CCR. No hubo diferencias estadísticamente significativas entre los pacientes con o sin CCRi, excepto los antecedentes familiares de CCR.

Introduction and aims

Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cancer in Europe.[1] Colonoscopy screening has been proved effective in reducing CRC incidence by detecting and removing pre-malignant lesions.[2] Considering the recurrence of adenomatous polyps, patients should repeat colonoscopy to detect and excise further adenomas.[3] However, even with an appropriate colonoscopy surveillance program, CRC diagnosed shortly after a colonoscopy has been described. Interval CRC (iCRC) has increasingly been a focus of interest as a marker of colonoscopy quality,[4] and several studies have tried to determine the prevalence of iCRC and its causes. In a meta-analysis of population-based studies conducted by Singh et al.,[5] they described a pooled prevalence of iCRC of 3.7%.

Interval cancers may result from missed lesions or incomplete polyp resections or they can be new cancers with aggressive biologic behavior and rapid growth.[6,7] Improving bowel preparation, increasing cecal intubation, improving adenoma detection rates, and defining the proper surveillance for each patient have been signaled as ways of decreasing iCRC.[8] In our study, we analyzed CRC patients diagnosed over a 4-year period, determined the iCRC rate, and attempted to provide explanations for iCRC development.

Materials and methods

A retrospective study was conducted on consecutive patients diagnosed with colorectal adenocarcinomas between January 2011 and January 2015 at a Portuguese hospital. Demographics and endoscopic data were obtained. Charts were reviewed and family history of first-degree relatives with CRC was recorded. During the present study period, the Boston Bowel Preparation Scale was not utilized to classify preparation quality, and so it was categorized as adequate or inadequate. Tumor location, histology, and staging were the cancer characteristics reviewed. We identified the patients that had a colonoscopy at our institution within a 10-year period prior to colorectal cancer diagnosis. We used the definition of iCRC as proposed by the Expert Working Group on Interval Cancers of the Colorectal Cancer Screening Committee, WEO: [4] CRC diagnosed after a colonoscopy in which no cancer was detected and before the date of the next recommended exam. Non-interval cancers were termed reference cancers.

According to family history of CRC, age, and number of polyps and their histology in the index colonoscopy, we retrospectively determined the ideal screening interval according to the post-polypectomy colonoscopy surveillance ESGE guidelines[9] and identified interval colorectal cancers. We named the colonoscopy performed before the development of the interval cancer as the index colonoscopy. The

proportion of iCRC was calculated as: iCRC/total number of CRC.

Interval cancers were divided into those of the right colon (cecum, ascending colon, and hepatic flexure) and the left colon (transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum). Patients with familial adenomatous polyposis, inflammatory bowel disease, or Lynch syndrome were excluded.

Potential iCRC causes were grouped into three etiologies, following the algorithm of Pabby et al.:[6]

1) *Incomplete removal:* interval cancer occurred at the site of the resected adenomas at initial baseline colonoscopy.
2) *Missed cancer*: cancer was detected at a location different from a previous adenoma site and was diagnosed $\leq$ 36 months after polypectomy of the most recent colonoscopy (regardless of size or stage), or cancer that was diagnosed > 36 months after a baseline colonoscopy and had features of advanced cancer (size $\geq$ 2 cm and advanced stage III or IV).
3) *New cancer:* cancer that occurred at a location different from the previous adenoma site, and was detected > 36 months after a colonoscopy, and had no features or only one feature of advanced cancer (large size or advanced stage).

The statistical analysis was performed with the SPSS 21 program. Differences in the dichotomous variables were tested using the $\chi 2$ test or Fisher's exact test, where appropriate. Differences in the numerical variables were examined through the independent-samples t test. The categorical variable analyses were compared using $\chi 2$ tests.

The present study protocol followed the guidelines of the Declaration of Helsinki and was approved by the local ethics committee. The requirement for individual informed consent was waived.

Results

We identified 266 patients with CRC, 164 (61.7%) were men, and mean patient age was 70.7 $\pm$ 11.0 years. The main indications for diagnostic colonoscopy were hematochezia (29.7%), a positive fecal occult blood test (20.7%), and anemia (20.3%). We identified 10 patients with iCRC, representing 3.76% of all the CRC cases.

The demographic data of patients with iCRC (iCRC group) and without iCRC (reference group) are presented in Table 1. Regarding sex distribution, 60% of the patients in the iCRC group and 61.7% in the reference group were men, with no statistical difference (p = 0.913). In the iCRC group the mean age was 71.1 $\pm$ 11 .7 years and in the reference group, 70.51 $\pm$ 11.0 years. The difference was not statistically significant (p = 0.248).

There was a higher prevalence of family history of CRC in the iCRC group (50%) than in the reference group (3.1%) (p < 0.001). Fifty percent of the cancers were in the right colon in the iCRC group, whereas only 24.5% were right-sided in the reference group, but that difference did not reach statistical significance (p = 0.091).

Table 1 Population data.

	iCRC	Reference CRC
Number	10	256
Age, years $\pm$ *SD*	71.1 $\pm$ 11 .7	70.5 $\pm$ 11 .0
Men, n (%)	6 (60)	158 (61.7)
Family history of CRC, n (%)	5 (50)	8 (3.1)
Right colon CRC, n (%)	5 (50)	63 (24.5)
Staging, n (%)		
I	2 (20)	67 (27.3)
II	2 (20)	65 (26.5)
III	4 (40)	71 (29.0)
IV	2 (20)	42 (17.2)

Staging data were unavailable in 11 patients (4.3%) in the reference group.

At the time of diagnosis, there was no difference in staging between patients with iCRC and with reference CRC (60 vs. 46.2%; p = 0.852).

Regarding the iCRC patients, the mean time for CRC diagnosis after index colonoscopy was 3.5 $\pm$ 1.84 years. Index colonoscopy was performed due to hematochezia in 40% of the patients, family history in 20%, anemia in 20%, polyp screening in 10%, and fecal occult blood test in 10%. The indications for diagnostic colonoscopy were anemia (40%), hematochezia (30%), and surveillance (30%).

All index colonoscopies of iCRC reported cecal intubation and bowel preparation quality was reported as good (30%), reasonable (30%), inadequate in the right colon (30%), and globally inadequate (10%). Findings included one normal examination and 1 patient with colonic angioectasia. In addition, polyps were removed from 8 patients: 7 patients with adenomas (median number of polyps per patient 1.43; range 1-3) and one patient had hyperplastic polyps. Polyp characteristics are described in Table 2.

Possible explanations for iCRC were inferred from the individual analyses of patient characteristics, index colonoscopy findings, and bowel preparation and are described in Table 3.

Polypectomy may have been incomplete in 3 patients, given that CRC was identified in the same segment as previously resected polyps.

In accordance with our definition, missed lesions were found in 4 patients with possible explanations in 3 of them: in one patient, the missed lesion could have been the result of inadequate bowel preparation in the right colon in the index colonoscopy; in 2 patients the tumors were small and identified behind intestinal folds; we consider that the location may have hindered previous visualization of lesions at index colonoscopy.

Three iCRCs were considered new lesions, since the colorectal cancers were detected > 36 months after index colonoscopy, they were not located in a previous polypectomy site, and they did not have all the features of advanced-stage disease.

Discussion and conclusion

Previous reports of iCRC vary in definition and include colorectal cancers diagnosed< 3 years,< 5 years, or< 10 years

Table 2 Polyp characteristics at index colonoscopy.

Patient	Polyp number and size	Histology
1	1 sessile polyp, 5 mm	Tubular adenoma with low-grade dysplasia
2	1 sessile polyp, 8 mm	Villous adenoma with low-grade dysplasia
3	2 pedunculated polyps, 8 mm	Tubular adenoma with low-grade dysplasia
4	1 sessile polyp, 3 mm	Tubular adenoma with low-grade dysplasia
	2 pedunculated polyps, 10 mm	Tubular adenoma with low-grade dysplasia
5	1 pedunculated polyp, 8mm	Tubular adenoma with low-grade dysplasia
6	1 sessile polyp, 3 mm	Hyperplastic polyp
7	1 sessile polyp, 2 mm	Tubular adenoma with low-grade dysplasia
8	No polyps	-
9	1 sessile polyp, 3 mm	Tubular adenoma with low-grade dysplasia
10	No polyps	-

Table 3 Characteristics of iCRC detected at follow-up colonoscopy.

Patient	Bowel preparation quality at index colonoscopy	Time interval (months)	Indication	Location	Stage	Assessment
1	Adequate	4	Bloody stools	Sigmoid colon	II	Missed lesionDifficult visualization
2	Adequate	14	Anemia	Ascending colon	III	Missed lesionDifficult visualization
3	Inadequate	42	Surveillance	Sigmoid colon	III	Incomplete resection
4	Adequate	26	Bloody stools	Sigmoid colon	IV	Incomplete resection
5	Inadequate right colon	43	Bloody stools	Sigmoid colon	IV	Incomplete resection
6	Inadequate right colon	40	Anemia	Ascending colon	I	New lesion
7	Inadequate right colon	56	Surveillance	Cecum	III	Missed lesion Preparation
8	Adequate	58	Surveillance	Sigmoid colon	III	Missed lesion
9	Adequate	37	Anemia	Ascending colon	II	New lesion
10	Adequate	84	Anemia	Ascending colon	I	New lesion

after index colonoscopy.[10–12] Bressler et al.[13] and Singh et al.[14] studied patients that underwent colonoscopy 6-36 months prior to CRC diagnosis and reported iCRC rates of 3.4 and 5.4%, respectively. Farrar et al., [15] and Samadder et al.[16] evaluated patients with colonoscopy 6-60 months prior to CRC diagnosis and described 5.4 and 6% iCRC rates, respectively.

Another discrepancy among the studies involves the calculation of the iCRC rate: some authors calculate the proportion of interval CRC as the number of iCRC/total number of persons with CRC,[13,17] whereas others compute the rate as the number of persons with iCRC/total number of colonoscopies. Therefore, given the different methodologies and definitions, the iCRC rates reported vary widely.

In our case series, we selected all patients with a colonoscopy prior to CRC diagnosis and identified iCRC according to the ideal surveillance time for each individual. We also followed the indication presented by Sanduleanu et al.[4] and considered the proportion in relation to the total number of CRCs. According to our definition, iCRC accounted for 3.75% of all colorectal cancers diagnosed.

When evaluating interval cancer, missed lesions and newly developed cancers with an aggressive biologic behavior are not easily distinguishable. Missed lesions are thought to be responsible for over 50% of iCRCs.[7] Many studies consider cancers diagnosed > 36 months following a colonoscopy as newly developed cancers, especially if they do not present with features of advanced disease, such as large dimensions or advanced stage.[17] Microsatellite instability[18] and methylation abnormalities (CpG island methylator phenotype) may contribute to rapid iCRC progression.[19]

Several studies have found that procedure factors, such as inadequate bowel preparation, incomplete colonoscopy, and missed or incompletely resected lesions, contribute to iCRC.[17]

In our study, inadequate bowel preparation played a role in iCRC development in at least one patient and may have contributed to an incomplete resection in another.

Incomplete polypectomy was assumed to be responsible for 30% of our iCRCs, which is in line with data from other studies. Farrar et al.[15] and Robertson et al.[7] found that 12 of 45 and 7 of 19 cases of iCRC, respectively, developed at the site of a previously resected polyp. Huang et al.[20] concluded that among patients undergoing surveillance colonoscopy within a 5-year period after polypectomy, 50% of iCRCs were due to incomplete polypectomy.

In our study, iCRC predominated in the right colon, compared with CRC in the control group, albeit without statistical significance. Other studies have shown that it is more

common for iCRCs to have a proximal location than it is for other CRCs.[13,15,17]

Several studies have assessed other patient characteristics as risk factors for iCRC. Older age and diverticular disease were described as risk factors for iCRC in some studies,[13] whereas others reported no differences.[15] We found no significant difference regarding age between the two groups.

We also found no differences in iCRCs in relation to sex, coinciding with results of previous studies.[21] However, other studies showed a greater trend toward iCRC in women, probably due to a higher colonoscopy incompleteness rate.[12,22]

In line with other studies, we found that iCRC was associated with family history of CRC.

Unlike other studies in which there tended to be earlier-stage iCRC, our analysis produced no differences with respect to the reference CRC.

All our colonoscopies were performed by gastroenterologists at a hospital facility. Studies have reported an association with increased risk of iCRC with colonoscopies carried out by physicians other than gastroenterologists and performed in an office.[13,14]

Our study has several limitations. First, the retrospective study design assumes reliable data registration across the study period for the results and conclusions. Second, due to said study design the adenoma detection rate could not be calculated. Several studies have found an inverse association between the adenoma detection rate and interval cancers.[23,24] Third, colonoscope withdrawal time, which is inversely associated with iCRC,[25] could not be measured, given the retrospective study design.[25] Finally, the Boston Bowel Preparation Scale was not utilized during the study period, limiting the evaluation of preparation quality and making it difficult to analyze whether some of the follow-up colonoscopies should have been performed earlier.

In conclusion, we found a 3.76% iCRC rate. The quality of bowel preparation and incomplete resection played an important role in iCRC etiology, underlying the importance of optimizing colonoscopy procedures.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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