Research Article

Post-Colonoscopy Colorectal Carcinomas (PostCRCs): Have we Improved Over Time?

María Lourdes Ruiz Rebollo¹* and María Fe Muñoz Moreno²

¹*Department of Digestive System, Hospital Clinico Universitario, Valladolid, Spain*
²*Department of Investigation Unit, Hospital Clinico Universitario, Valladolid, Spain*

Abstract

Background and Aim: There is an increasing concern on Post-Colonoscopy Colorectal Carcinomas (PostCRCs). Little is known about how these figures have evolved over time. We aim to compare the rates of PostCRCs in two periods of time and identify the risk factors.

Methods: Retrospective control-case study in our Endoscopic Unit. We studied two separate intervals (March 2004-September 2011 and October 2011 - December 2016). In both periods of time all patients diagnosed with CRC were identified. Patients with a previous colonoscopy performed 12 to 60 months before were retrieved (cases) and compared with those who did not have a previous procedure (controls).

Results: 712 and 743 patients diagnosed with CRC in both periods of time. 24 patients in the first period (3.6%) and 28 patients in the second one (3.8%) had a previous colonoscopy performed. PostCRCs were mainly located on the right side of the colon (63% *vs.* 35% *p=0.006* and 68% *vs.* 33% *p< 0.001)*, were smaller in size (3.17 *vs.*4.46 *p< 0.001* and 3.61 *vs.* 4.44 *p=0.086)*, with a tendency to host a better TNM stage. No differences in sex and age were found.

More than half of PostCRCs (58.3% and 60.7%) were attributed to procedure causes, meanwhile10 PostCRCs in both periods were considered new developed CRCs.

Conclusions: Despite what could be expected, we did not find a decrease in the rate of PostCRCs over time. A combination of preventable as much as biological factors would account for their etiology.

Introduction

Colorectal Carcinoma (CRC) is the second leading cause of cancer mortality in developed countries [1]. The prognosis depends on its early detection, or even better, on the endoscopic removal of the premalignant adenomatous polyps. Colonoscopy is the gold standard to detect early CRCs and remove precursor adenomatous polyps and so, reduce the incidence and mortality by CRC [2]. However, although colonoscopy is an effective tool, it is also imperfect. There is increasing recognition that CRC can arise soon after a previous normal colonoscopy, the so called Post Colonoscopy Colorectal Cancers (PostCRCs). Several reports have been published on this topic over the past decades [3-10] and some authors have even found a significant association between PostCRCs and measures of endoscopic quality [11]. Furthermore, PostCRCs rates are claimed to be considered as a colonoscopy quality marker which should be periodically measured in Endoscopy Units [12].

Possible explanations for PostCRCs have been divided into two groups: procedure, preventable factors, such as incomplete polyp removal or missed cancers, and biological factors, that is, a more aggressive tumor growth. [3,4].

However, it is not clear how the incidence of missed or early Colorectal Cancers (CRCs) has evolved over time. There are few studies that address this issue [13]. It is generally assumed that the rate of PostCRCs must have decreased over the years, mainly due to two situations: first, the more advanced equipment acquired in Endoscopy Units, and secondly, and most importantly, the great interest of endoscopists in adapting their procedures according to the quality indicators for colonoscopy [14,11], i.e. cecal intubation rate, withdrawal time and adequate bowel preparation. The risk of interval cancer in screening CRC programs is widely considered to be inversely related with the adenoma detection and the rate the cecal intubation [14,15] both matters related with a proper bowel preparation

The aim of the study was to assess and compare the rate of missed or early CRCs (PostCRCs) in our Institution in two periods of time: first period March 2004- September 2011 and second period from October 211 until December 2016. We also identified the possible risk factors that could be associated with their development.

Patients and Methods

Study design

Retrospective control-case study conducted in the Gastroenterology Department of our Institution, Hospital Clínico Universitarioin Valladolid (Spain). It is a tertiary, University Centre which serves a population around 250.000inhabitants.

Hypothesis

The improvement in colonoscopy training, the refinement in technology equipment and the awareness of colonoscopy quality indications by colonoscopists have led to a decrease in Post-colonoscopy colorectal carcinomas over time.

Data Sources and patients

We retrieved patients diagnosed with "Malignant Colorectal Carcinoma" from our electronic data base of the Endoscopy Unit (Endobase, Olympus) for both periods of time studied: March 2004-September 2011 and October 2011-December 2016. As in our former study [16], patients who had undergone a colonoscopy between 1 and 5 years previously were identified (this first colonoscopy was called "index colonoscopy") and were considered the case group. As we previously stated, a period of 5 years was chosen because the risk of development of CRC or advanced adenoma within this period of time is low, a trend that has also been proven in cost-effectiveness studies on CRC screening strategies which recommend that screening colonoscopies be performed at intervals of at least 5 years [17]. We also considered that colonoscopies carried out in a period of time less than 12 months should have been performed in order to fulfill quality standards (i.e. poor bowel prep, incomplete colonoscopy or incomplete polyp removal) and so, were not considered. Patients with sporadic CRC were included in both groups as the control group, i.e. patients diagnosed in the first recorded colonoscopy in our data base during the same period.

For both periods of time, PostCRC rate was calculated as the number of CRCs diagnosed with a previous clear colonoscopy divided by the total number of CRCs detected.

Patient demographic data: age, sex, comorbilities according to Charlson comorbidity index [18], colonoscopy indication (index and diagnostic), quality of bowel preparation, extension of the examination and findings in index colonoscopy and diagnostic colonoscopies were recorded.

Patient exclusion

Patient who developed anastomotic recurrence of a previous CRC, those with familial polyposis syndromes or inflammatory bowel disease were excluded along with those aged <18 years or whose index colonoscopy was performed in another center.

Procedures and definitions

In the first period of time (March 2004-September 2011) all colonoscopies were carried out by 7 experienced staff endoscopists who performed a mean of 800-1000 colonoscopies annually. In the second period (October 2011-December 2016) the procedures were performed by 6 of the previous gastroenterologists and 4 other endoscopists with less experience. All procedures executed by a

trainee were supervised by a staff endoscopist. Patients underwent conscious sedation with midazolam and petidine or propofol given by specialized nursing staff. Olympus white light endoscopes with video processors from the EvisExera CV160-CLE145, EvisExera II CV 180 and EvisExera II CV165 series were used. Bowel preparation regimens consisted on diet and either oral sodium phosphate solution or polyethylene glycol 3350-electrolyte solution (PEG-ELS); split dose was implemented on July 2013. Colon cleanliness was classified as "good/adequate" or "poor/inadequate" according to the endoscopists impression; however, from 2013 onwards the quality of the endoscopic preparation was assessed according to the Harefield cleansing scale [19]. The procedure was considered complete if the caput cecum was reached, a picture from the area was taken and all visible polyps removed. The colon was divided into 8 segments; however, in order to facilitate analysis they were cut down into 2 categories: proximal colon (cecum, ascending colon, hepatic flexure and transverse colon) and distal colon (left colon, splenic flexure, sigmoid colon and rectum).

Data from tumor collected were size, location, histological grade and TNM stage [20].Tumor location was estimated using anatomical landmarks and the distance on withdrawal. Size of CRCs was measured routinely and documented in the pathology report. Polyps were classified as hyperplastic and adenomatous. Advanced adenoma was defined as an adenomatous polyp of more than 10 mm in size and/or with villous component and/or high grade dysplasia.

Explaining post colonoscopy colorectal carcinomas

In order to determine the most possible etiology of the PostCRCs, we followed the algorithm drawn up by Pabby et al [3]. According to it, PostCRCs are assigned to 4 possible categories: 1. "Incomplete removal" for those cancers arising at the same anatomic segment of a previously resected adenoma, 2. "Failed biopsy detection" which included lesions suspected by the endoscopist to be neoplastic with negative pathological results, 3. "Missed cancers" were considered those cancers in a different location from the site of a previous adenoma diagnosed within 30 months or less after the previous colonoscopy (regardless size or stage) or diagnosed more than 30 months and were advanced cancers (stage II or IV), and 4. "New cancers" were those occurring at a different site from that of the previous adenoma, or those detected more than30 months after the previous colonoscopy without features of advanced cancer. Categories 1-3 were considered procedural related factors and so, potentially preventable; on the other hand, category 4 was considered true "new cancers" with probably a biologically aggressive behavior.

Statistical analyses

For statistical analysis, quantitative variables are presented as the mean and standard deviation and qualitative variables as frequency distribution. Using the Chi-square test, we analyzed the association between qualitative variables. In the event that the number of cells with expected values less than 5 was greater than 20%, we used the Fisher exact test or likelihood ratio test for variables with more than two categories. A comparison of quantitative values was performed using Student's t test for independent samples or the Mann Whitney U test as appropriate. Data were analyzed using SPSS version 19.0 for Windows. Those values of p <0.05 were considered statistically significant.
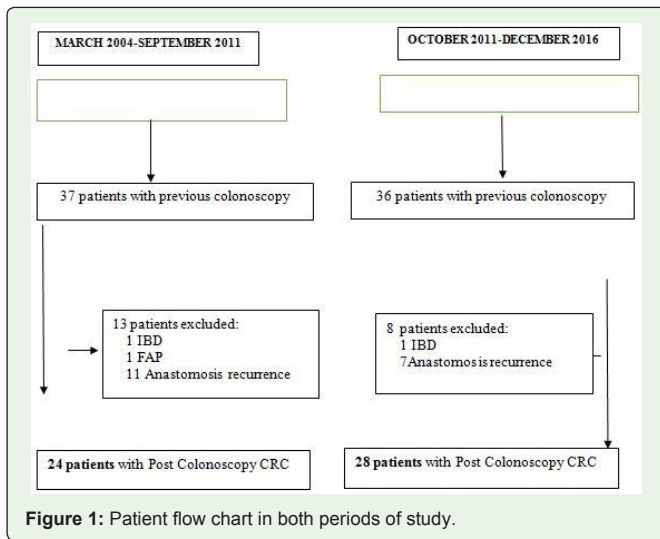
Figure 1: Patient flow chart in both periods of study.

compare the clinicopathologic characteristics of sporadic CRCs and Postcolonoscopy CRCs and describe the most possible etiology of the PostCRCs.

Results

Study Population and tumor characteristics

The total number of patients diagnosed with sporadic CRC and PostCRC in both periods of study is shown in figure 1. The characteristics of cases and controls are shown in table 1. There were no differences either in patient age (*p=0.134*) or sex (*p=0.102)* between years; however, patients in the second period had a higher Charlson comorbidity index score *(p>0.005).* A slight increase in PostCRCs along time was observed: 24 patients (3.6%) in the first period studied and 28 patients (3.8%) in the second one. Tumor TNM stage and distribution can be seen in Table 2. PostCRCs were manly located in proximal colon in both periods (63% *vs.*35% *p=0.006* and 68% *vs.* 33% *p< 0.001)* and were smaller in size (3.17 *vs.* 4.46 *p< 0.001* and 3.61 *vs.*4.44 *p=0.086)* The histological grade was similar for cases and controls in both periods of time; nevertheless, there was a tendency toward an earlier TNM stage in the first period studied (*p= 0.053)* which was not found in the second one.

Median time of diagnosis of PostCRCs was 36 months in both periods (range 15-57 and 12-58 months respectively). The main indications for performing the diagnostic colonoscopy were rectal bleeding (30%) and anemia (22%) in the first period whereas in recent years surveillance after polypectomy or CRC surgery accounted for 37.5% of the colonoscopies and 25%of them were performed for anemia.

Study oversight

The study was conducted after obtaining ethical approval from the Hospital Clinical Research Ethics Board.

Study endpoints

The primary endpoint was to estimate and compare the proportion of PostCRCs in to separate periods of time: March 2004/September 2011 and October 2011/December 2016. Secondary outcomes were to

Table 1: Characteristics of PostCRCs.

		1st Period			March 2004-September 2011			2nd Period			October 2011-December 2016		
		Control Group N=675	IC 95%		Post-CCR N=24	IC 95%		*P*	Control Group N=707	IC 95%		Post-CCR N=28	IC 95%		*P*
Localization	Distal Colon	438 (64.9%)	61.30	68.50	9 (37.5%)	18.13	56.87	0.006	470 (66.5%)	63.02	69.98	9 (33.3%)	15.84	50.76	<0.001
	Proximal Colon	237 (35.1%)	31.50	38.70	15 (62.5%)	43.13	81.87		237 (33.5%)	30.02	36.98	18 (66.7%)	49.24	84.16	
Histological Differentiation	Good	637 (94.8%)	93.13	96.47	21 (87.5%)	74.27	100.73	0.125	564 (80.1%)	77.16	83.04	23 (82.1%)	67.90	96.30	1.000
	poor	35 (5.2%)	3.53	6.87	3 (12.5%)	0.00	25.73		140 (19.9%)	16.96	22.84	5 (17.9%)	3.70	32.10	
TNM Stage	0-I-II	428 (67%)	63.45	70.55	12 (50%)	30.00	70.00	0.053	485 (71.5%)	68.17	74.83	22 (81.5%)	67.12	95.88	0.259
	III-IV	211 (33%)	29.45	36.55	12 (50%)	30.00	70.00		193 (28.5%)	25.17	31.83	5 (18.5%)	4.12	32.88	
Tumour Size (cm)		4.46	4.29	4.62	3.17	2.69	3.66	<0.001	4.44	4.27	4.63	3.613	2.92	4.31	0.086
Patient Age		71.2	69.63	71.52	72.38	66.47	78.75	0.604	71.39	70.53	72.24	72,96	67.76	78.16	0.311
Gender		F 268 (39.8%)	36.11	43.49	F12 (50%)	30.00	70.00	0.315	F 455 (64.4%)	60.87	67.93	F 16 (57.1%)	38.77	75.43	0.435
		M 406 (60.2%)	56.5	63.89	M 12 (50%)	30.00	70.00		M 252 (35.6%)	32.07	39.13	M12 (42.9%)	24.57	61.23	
Comorbilities	0-1-2	640 (94.4%)	92.67	96.13	24 (100%)	100	100	0.622	653 (92.4%)	90.4	94.4	22 (78.6%)	63.41	93.79	0.021
	>=3	38 (5.6%)	3.87	7.33	0 (0%)	0	0		54 (7.6%)	5.65	9.55	6 (21.4%)	6.21	36.59	

Distal Colon: left colon, sigmoid and rectum

Proximal Colon: cecum, ascending and transverse colon

Good differentiation includes G1 and G2.

Poor differentiation includes G3

F: female   M: male

Table 2: Distribution and tumor stage of PostCRCs.

	March 2004-September 2011 (N=24)	October 2011-December 2016 (N=28)*
Distribution		
Rectum	3 (12.5%)	6 (22.2%)
Left and sigmoid colon	6 (25%)	4 (14.8%)
Transverse colon	2 (8.3%)	1 (3.7%)
Ascending colon and hepatic flexure	5 (20.8%)	12 (44.4%)
Cecum and ileocecal valve	8 (33.3%)	5 (18.5%)
TNM Tumor Stage		
0	1 (4.2%)	2 (7.4%)
I	8 (33.3%)	4 (14.8%)
II	3 (12.5%)	9 (33.3%)
III	6 (25%)	7 (26%)
IV	6 (25%)	5 (18.5%)

*1 case not classified

Table 3: Possible etiology of Post colonoscopy CRC.

	March 2004-September 2011 (N=24)	October 2011-December 2016 (N=28)*
Incomplete polyp resection	4	5
Incomplete colonoscopy	1	0
Failed biopsy	1	0
Missed CRC	8	12
New CRC	10	10

*1 case not classified

Preventable etiologies: Incomplete polyp resection incomplete colonoscopy, failed biopsy, and Missed CRC

Possible etiology of postCRCs

According to the algorithm designed by Pabby et al. [3] PostCRCs were ascribed to either missed CRCs or early onset-new CRCs as shown in (Table 3). More than half of them in both periods of time (58.3% and 60.7%) were attributing to preventable causes (incomplete polyp resection, incomplete colonoscopy, failed biopsy and truly missed CRC). Only 10 PostCRCs were considered to be really new CRCs with a probable or aggressive biology.

Discussion

Our study shows that, despite what could be expected, the rate of PostCRCs has slightly increased over time in our Institution, going from 3.6% in 2004-2011 to 3.8% in recent years. Even more, despite better technology and improvement in the quality of colonoscopies, we found that procedural factors account for a great majority of PostCRCs in both periods of time (58% and 61% respectively).

Few studies in literature have examined the rate of PostCRCs over time. Pullens et al. [13] performed an interesting comparison over a 10-year period time in The Netherlands and they also found an increase in the incidence of PostCRCs; as stated in the limitations of their research, they could only consider patients who had a previous colonoscopy performed with polyp removal; patients without

histological exam in their previous colonoscopy were not included, so we can speculate that their figures could be even higher. On the other hand, another preliminary study also from The Netherlands [21] showed a considerable reduction in the number of PostCRCs when endoscopists followed a training period on the detection of proximal colonic flat lesions. In this line, a recently published nation-wide Swedish [22] study found a 12% decrease in their PostCRCs in the recent years which they consider to be related to better equipment and better bowel preparation.

Published rates of PostCRCs vary greatly: 1.7-2.3 % [13], 5.4% [4] or as high as 12% [12]. Although this variation can be attributed in part to the time frame considered for the index colonoscopy and differences in the registration data, the methodology used to calculate the rate of PostCRCs explains, undoubtedly, much of this variation, as demonstrated by Morris et al. [23] In their study, the application of four different methods in their analysis led to rates ranging from 2.5% to 7.7%, using the same data.

Our study identified several factors associated with the development of PostCRCs. According to practically all previous publications on this topic [4,6,8,12] our PostCRCs were mainly located in right colon in both periods studied (Table 1). The reasons for this right-sided predominance remains unclear and is likely to be multifactorial: first, as stated by Singh et al. [5], caput cecum is not always properly in tubated as sometimes landmarks are unclear; secondly, this portion of the colon is more difficult to be adequately cleaned and thirdly, right side adenomas are sometimes flat and depressed lesions, not always easily detected and completely resected. Even more, several authors propose differences between CRCs from right and left colon, as their embryological origins are different (midgut and hindgut, respectively). As Iacopetta asserts [24], right colonic mucosa secretes neutral mucins, meanwhile those secreted by left colonic mucosa are acidic. The apoptotic index is lower in the right colon where fermentation reactions, bacterial enzymes and levels of promutagenic N-nitroso compounds are higher. Finally, it is argued that, unlike left CRCs which are developed through the classical way of genomic instability [25,26], a great proportion of CRCs on the right side of the bowel would be related with the microsatellite instability [27] and CpG island methylator phenotype pathways [28]. Such tumors are thought to be fast growing ones and associated with sessile serrated precursors that can be difficult to detect on colonoscopy. All these factors may, therefore, lead to a predominance of right-sided PostCRCs. However, some other authors do not find a special location in their studies [29].

Our findings agree with previous research [7-9] showing that PostCRCs are smaller in size in both periods studied (Table 1). Although some publications have suggested that rates of PostCRCs may be higher for women than men [12], we could not find those differences in neither of the periods analyzed, in line with some other research [30-32]. Patient age claimed by some authors [5,8,30,32] did not differ in our study. In agreement to several publications [5,8,9] a tendency towards a better histological differentiation and earlier tumor stage was found in the first period studied; however, we did not reach those figures in the recent years.

Possible explanations for PostCRCs have also been widely studied. Most authors show a great proportion of them being related to procedural factors, mainly missed lesions and incomplete polyp

removal [3,8,31]. Our results are in the same line, as more than half of our PostCRCs were classified as avoidable according to Pabby´s classification (58.4% and 64.3%). However, even applying this structured algorithm to estimate the underlying etiology is not easy to differentiate missed PostCRCs from new onset ones, since it is impossible to prove that a precursor adenoma was present or not and could not be initially detected.

Nevertheless, our understanding of the true prevalence and the causes of PostCRCs remains limited. It is discouraging that despite better technology and greater awareness of the measures of quality in colonoscopies, our figures have not decreased over time. It is therefore reasonable to assume that not all related with PostCRCs is a consequence of an inadequate technique, so raising the issue of possible distinct biological features of these tumors. There is indeed increasing evidence that PostCRCs could harbor a different cell biology, with a more aggressive and rapid growth [27,28,30]. Arain et al. found that interval colorectal cancer were 2.5 and 2.7 times more likely to demonstrate CpG island methylator phenotype and microsatellite instability respectively than sporadic CRCs. Stoffel et al. in Denmark observed that 1 out of 5 PostCRCs were *BRAF*-mutated and had a DNA mismatch repair deficiency.

Whether this apparent inability to reduce PostCRCs rates are attributed to endoscopist- related factors or to a different biological tumor behavior is an issue of great concern and a matter that remains to be established.

We agree with several authors [11,33] which claim PostCRCs to be considered as a new quality indicator for colonoscopy. The goal of the colonoscopy is to prevent and provide early detection of CRCs and, therefore every Endoscopic Unit should periodically measure their figures on PostCRCs, and improve them over time.

On the other hand, as stated by Sanduleanu et al. [34] the process of bench marking PostCRCs is neither quick nor simple. The first step would be to establish a standardized definition and time frame for PostCRCs, which has yet to be established (6-36 months, 12-60 months…) [35]. Another challenging issue brought up by Morris et al. [23] is that the rate of PostCRCs varies considerably in relation to the method used to calculate it. Hence, a similar framework is needed to enable the results to be compared. (Cohort of CRC patients vs. cohort of patients undergoing a colonoscopy). And finally, the different pathways of carcinogenesis of PostCRCs must be investigated.

Our study has several notable strengths. The sample size and the tertiary teaching hospital setting support the importance of this study so our results could be easily generalized to other similar populations in the US and Europe. It is noteworthy that both, index and diagnostic colonoscopies were performed by mainly the same group of endoscopists in both periods of time and so, performance bias was avoided.

Unlike some other studies, we had access to indication of colonoscopies (index and diagnostic) as well as quality of bowel preparation and cecal in tubation. However, we did not know our figures on adenoma detection rate which are also considered an important marker for quality of colonoscopies.

The main limitation of our research is that we included data collected from our endoscopic register, not from a histopathological database. Thus, patients who underwent emergency surgery or were referred to palliative care without colonoscopy were not included. Secondly, since we did not have a detailed family history of patients with PostCRCs, we could not know if any of them met clinical criteria for suspecting hereditary non-polyposis CRC (Lynch or FAP); however, these syndromes account for less than 3% of all cancers.

Conclusions

In summary, in our experience rates of PostCRCs did not decrease over time. These tumors are mainly located in the right side of the colon and are smaller in size

We could hypothesize an unifying explanation for Post CRCs that would combine procedural avoidable factors together with biological behavior differences in these particular tumors.

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