

ORIGINAL PAPERS

Missed opportunities in early diagnosis of symptomatic colorectal cancer

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ABSTRACT

Objective: delays in diagnosis of symptomatic colorectal cancer are a reality in our context. This study aims at identifying missed diagnostic opportunities, describing events, clinical clues and most common mistakes, and quantifying delays.

Material and methods: an observational descriptive study was performed in order to review all case histories. Two experts reviewed the case histories of all the patients from the 4th Catchment Area of Asturias diagnosed with colorectal cancer in 2009. All data were analysed using bivariate and multivariate logistic regression.

Results: full information on 119 patients out of 143 patients was collected. 34.45% had a clinical missed opportunity –confidence interval (CI) 95%: 30.92-39.68–. Outcomes show an average of 2.41 missed opportunities and 2.61 diagnostic clinical clues per patient. The number of patients with missed opportunities was significantly higher. The total amount of co-morbidities was higher in patients with missed opportunities (2.7). This was the main determinant. The main diagnostic key was iron-deficiency anaemia (46.3%). It produced the longest delay (300 days). Not having requested diagnostic tests was the most common mistake (43.3%). Having at least one missed opportunity entailed an average delay of 235.8 days between the first visit to the office and the referral to a consultant.

Conclusions: in clinical practice, missed opportunities to start a diagnostic assessment in patients with presumptive diagnosis of colorectal cancer are common. The most significant clinical clue and the one generating the longest delay is iron-deficiency anaemia. The diagnostic delay is important and is caused mainly by not identifying symptoms.

Key words: Colorectal cancer. Delayed diagnosis. Quality.

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INTRODUCTION

In the developed world, colorectal cancer (CRC) has become the second most significant tumour location for both men and women. In Spain, its incidence is estimated at around 25,000 cases per year, with a mortality rate of around 50%; which in turn means 125,000 annual deaths due to CRC (11). From 2011 onwards, a change in dietary, environmental and life-style factors combined with an improvement in diagnostic methods has lead to a more favourable trend (2,3).

In Spain, screening in populations between 50 and 69 years of age, both sexes, is part of the national cancer-fighting strategy. However, most of the plans are still under development, and there are a few regions where they have not been implemented yet. Still, there are clinical guidelines describing the protocol to be deployed in case of symptoms (4).

The most frequent onset of CRC is sporadic: general or abdominal unspecific symptoms which sometimes are difficult to identify and connect to the aforementioned disease. Therefore, it is paramount to detect the symptoms and diagnose the patients, regardless of whether they belong or not to screening plans (5).

Iron-deficiency anaemia is amongst the most common signs and symptoms (6-8). Besides, rectal bleeding, change of bowel habit and abdominal pain are connected to CRC (9,10). Furthermore, the presence of an abdominal or rectal mass, weight loss, constitutional syndrome and/or bowel obstruction could be an indication of an advanced neoplastic process (8,11).

In the literature, abundant references to factors increasing the diagnostic delay of CRC were found: system-based errors (such as inadequate use of clinical guidelines), absence of follow-up in case of abnormal test results or other factors regarding the patient (5,11-13). Open error reporting could be very useful to analyse eventual delays and to, then, create and update a research framework (14).

In our context, there is probably a relevant amount of missed opportunities (MOs) in the diagnosis of CRC. Quantifying and describing those MOs would be the first step towards their prevention. Our main target is to identify the number of patients diagnosed with CRC who had at least one MO at the beginning of the diagnostic process, describe patients' characteristics, events, clinical clues and associated process types, and quantify the delay.

MATERIAL AND METHODS

A retrospective descriptive observational study including all patients from the 4th Catchment Area of Asturias diagnosed with CRC in 2009 was conducted.

Those patients belonging to other catchment areas, those who had some of their tests performed in private clinics (and therefore could not have access to the results themselves), and those with missing or unavailable information on their case histories were excluded.

Assuming a rate of 31.38% MOs from previous studies (5) and in order to analyse MO prevalence with a 95% confidence interval (CI) and a maximum error tolerance of 8%, 130 cases would be necessary. So it was decided to have all patients diagnosed with CRC in 2009 –a total number of 143– included in the study.

Different variates were studied: demographic (age and gender), clinical (hypertension, diabetes, coronary artery disease, chronic obstructive pulmonary disease, depression, dyslipidemia, atrial fibrillation, benign prostatic hypertrophy, heart failure), clinical diagnostic clue (5) (iron-deficiency anaemia, rectal bleeding, abdominal or rectal mass on clinical examination and image-guided tests, intestinal obstruction, changes of bowel habit, new-onset abdominal pain, constitutional syndrome and melena) presence or absence of MOs, time-related (dates of: first visit to GP, referral to consultant, first visit to consultant, diagnostic tests), and physicians involved (primary care, digestive, general surgery, internal medicine, emergency dpt. and others).

In order to identify the first symptom/sign which is most frequently connected to MOs, clinical clue were pooled into "main" (first clinical key suggesting CRC and which triggers the diagnostic process) or "secondary" (symptoms added during the events associated to MOs).

As to classify the data identifying MOs according to the medical process (case history, physical examination, specialist consultation for differential diagnosis) and the diagnostic tests (non-performed or misinterpreted test results, lack of follow-up in case of abnormal results), data were adjusted from the data pool. The aim was to study diagnostic targets according to "*Malpractice insures medical error prevention study*" (15) and Schiff's taxonomy (16).

With the authorization of the Ethical Committee, case histories of patients with established diagnosis of CRC in 2009 from the Tumour Registry of Anatomical Pathology were reviewed. Histories came from both hospital (from Hospital Universitario Central de Asturias) and primary-

care services. Two experts reviewed the histories in order to identify the presence or absence of MOs in each patient. In case of disagreement, the history would be discussed with a third expert and a joint decision would be made.

The concept "clinical missed opportunity" has been defined as any physician-patient meeting where despite presumptive CRC symptoms, the CRC diagnostic process is not started by referring the patient to a consultant or by image-guided tests. This definition has been adapted from existing literature (5). Likewise, "physician-patient meeting" has been defined as any consultation event with presumptive CRC symptoms, including clinical visit or one-time events during hospitalization.

If, according to the case history, there was an intentional decision not to perform a differential diagnosis for any given reason, it was not considered a missed opportunity. Similarly, in case of lack of new tests for a recurring symptom, it was not considered missed opportunity if the diagnostic process had already been started.

Delays were divided into 4 waiting times, according to the number of days:

- From the first physician-patient meeting to the date on which the patient was referred to the consultant.
- From the referral date to the first visit to consultant.
- From the first visit to the consultant to the request of diagnostic tests.
- From the request of diagnostic tests to the test performance or the final diagnosis.

A descriptive study of the data with 95% CI was performed. Patients with MOs and patients without MOs were compared by means of the Student's *t* test (or nonparametric tests such as Mann Whitney's "U" in case of data abnormality, measured using the Kolmogorov-Smirnov test) and the Chi-square test (or Fisher's exact test in case of missing implementation conditions) depending on whether they were quantitative or qualitative variates. The average and the median for deadlines were estimated. Finally, a logistic regression multivariate analysis was conducted using the "introduction" method in order to include all variates and, hence, study an eventual confusion of variates in the bivariate analysis.

RESULTS

Twenty four patients were excluded because they belonged to another catchment area and/or their medical histories were not available. There was disagreement regarding to the presence or absence of MO only in 5 cases. These cases were discussed with a third reviewer reaching a joint resolution. Definitely, from 119 patients of CRC identified during the period of current study, there was at least one clinic MO in 41 cases (34.45% of the population, CI 95% 30.92-39.68). There was an average of 2.41 MOs and 2.61 clues per patient.

Demographic characteristics are shown in table I. Patients with MOs were older, 74 years vs. 69. There were

Table I. Demographic characteristics and comorbidities of patients with and without missed opportunity

	<i>Missed opportunity</i>	<i>No missed opportunity</i>	<i>p</i>
Age	Mean (SD) 74.85 (10.6)	Mean (SD) 69.2 (11.6)	0.009
Gender	N.º (percentage)	N.º (percentage)	0.344
Male	21 (51.2%)	47 (60.3%)	
Female	20 (48.2%)	31 (39.7%)	
Comorbid medical diseases	Mean (SD) 2.76 (1.55) N.º (percentage)	Mean (SD) 1.69 (1.18) N.º (percentage)	< 0.001
Hypertension	24 (58.5%)	33 (42.3%)	0.092
Diabetes	11 (26.8%)	16 (20.5%)	0.434
CAD	9 (22%)	7 (9%)	0.049
COPD	5 (12.2%)	4 (5.1%)	0.166
Depression	13 (31.7%)	11 (14.1%)	0.023
Dyslipemia	12 (29.3%)	13 (16.6%)	0.109
AF	4 (9.8%)	5 (6.4%)	0.512
CHF	3 (7.3%)	3 (3.8)	0.411
BPH	3 (7.3%)	3 (3.8)	0.411
Others*	17 (41.5%)	15 (19.2%)	0.009

SD: standard deviation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; CHF: congestive heart failure; BPH: hyperplasia benign prostatic. *Different diseases with a percentage below 4%.

no significant differences in gender. Total number of comorbid medical diseases was higher in patients with MOs, with an average of 2.76. Coronary artery disease, as well as depression, was the most important pathology associated with MOs. Rest of comorbid medical diseases distribution was similar in both groups.

Table II shows the frequency of predefined clinical clues. The most common one was iron deficiency anaemia, representing 46.3% of the population. The second main clue was rectal bleeding, with 26.8% of MO patients. On the other hand, clinical clues that usually involved hospitalization, urgent surgery or colonoscopy, like obstruction or CRC imaging suspicious, were not associated with MOs.

Secondary symptoms after the main clinical clue are described in table III. The most common one was the change of bowel habit (24.5%). There was similar frequency in rectal bleeding (16.6%), iron deficiency anemia (18%), abdominal pain (15%) or constitutional syndrome (15%).

The most common errors which involved delays and missed diagnostic opportunities are presented in table IV. The main one was the lack of request for diagnostic tests in 43.3% of the cases, followed by the fact of not having referred the patient to a consultant in 34.4% of the cases.

Primary Care physicians were usually involved in MO process; with 33 cases; (55.9% of the population). Other medical specialties involved in the process were: Internal Medicine 3 (5%); Emergency 7 (11.8%); General Surgery 1 (6%) Digestive 6 (10.1%); and others 9 (15.2%).

The waiting times are shown in table V. The waiting time between the first physician-patient meeting and the date when the patient was referred to the consultant, was the longest one in every cases. Having at least one MO, represented an average of 235.8 days of delay compared to 8.7 days in the group that had no MO.

Delays presented in table VI were classified according to the symptoms. Iron deficiency anemia was the main clinical key related to the increasing delay, which had an average of 300 days in the first time range.

We used multivariable logistic regression model. Only the number of co-morbid medical diseases was associated with the presence of MO when we controlled gender and age (OR: 1.66; CI 95% 1.8-2.35; $p = 0.004$).

DISCUSSION

In this study a total of 34.45% of patients with clinical signs presumptive of CRC presented at least one MO at the beginning of diagnosis, which meant that approximately 1 out of 3 of the 119 cases of CRC could have received an earlier diagnosis. This figure is somewhat greater than the 31.38% found in previous studies that used comparable methodologies (5). An average of 2.4 MOs was obtained per patient. Unlike other studies, we did not take into account the group of patients with a family history positive for CRC who were asymptomatic and had a MO due to lack of screening when recommended in the guidelines (17,18). The decision to separate both groups lies in the fact that these patients had a MO when asymptomatic, and our aim

Table II. Main diagnostic clues in patients with MOs

	<i>Frequency</i>	<i>Percentage</i>
Anemia	19	46.3%
Rectal bleeding	11	26.8%
Change of bowel habit	6	14.6%
Abdominal pain	3	7.3%
Suspected mass on physical exam	1	2.4%
Constitutional syndrome	1	2.4%
Total	41	100%

Table III. Secondary clinical clues in patients with MOs

<i>Clinical clues</i>	<i>Frequency</i>	<i>Percentage</i>
Change of bowel habit	25	24.5%
Anemia	19	18.6%
Rectal bleeding	17	16.6%
Abdominal pain	16	15.6%
Constitutional syndrome	16	15.6%
Imaging suspicious of CRC	3	2.9%
Intestinal obstruction	3	2.9%
Melena	3	2.9%
Total	101	100%

is to analyse the signs and symptoms of CRC; in addition, the lack of screening poses a different type of error.

As to associated characteristics, the oldest patients and with more pathologies are most likely to be associated with MOs; if we analyse age in conjunction with the number of co-morbidities, the latter is the determining factor. These results reflect the current tendency not to request diagnostic tests, based primarily on the presence of multiple concomitant pathologies, and secondarily on age. In the future, it would be advisable for studies to focus more on the impact of specific co-morbidities on the request of diagnostic tests in CRC.

The onset of CRC clinical signs in patients often presents with diversified symptoms. By pooling clinical clues into two categories, the main symptom for which the patient

Table IV. Mistakes in the diagnostic process

<i>Mistakes</i>	<i>Frequency</i>	<i>Percentage</i>
Medical history exam (15,16)	6	6.6%
Insufficient physical examination (15,16)	8	8.8%
Not ordered diagnostic test	39	43.3%
Not requested consult	31	34.4%
Incorrect test interpretation (15,16)	6	6.6%

consulted and from which the diagnostic process should have been initiated was identified. The result is an average of 2.6 clinical clues per patient.

The main diagnostic clue most often associated with MOs was iron-deficiency anaemia. In our study, this clue was not classified in specific ranges as it was the case in other studies (19). Iron-deficiency anaemia was present in 46% of all patients, and this is similar to the outcomes of other authors (20). This shows the lack of recognition of iron-deficiency anaemia as indicator of CRC, despite of the fact that the guidelines recommend patient referral in order to study eventual digestive losses (17,18,21). Besides, many studies confirm the association between anaemia and CRC (8,19,22,23). The problem arises when iron-deficiency anaemia appears unexpectedly in the daily clinical practice and the consultant has to decide the probability of CRC. To resolve this question it should be studied as a separate variate and more than one diagnosis should be weighed when this key is present (21).

Another symptom associated with MOs was rectal bleeding, and this occurred in 26.8% of patients. Nevertheless, in other studies this symptom appears as the main symptom (24). Due to the limited number of cases, we could not analyze the influence of perianal symptoms associated with these MOs caused by rectal bleeding. It should be pointed out that rectal bleeding might be controversial in terms of deciding if it requires a quick evaluation as isolated symptom, probably due to its high prevalence in the general population and its low sensitivity when it occurs as an isolated symptom (20,23).

Table V. Waiting times and delays in different ranges

	<i>Missed opportunity</i>			<i>No missed opportunity</i>			<i>p</i>
	<i>Mean</i>	<i>SD</i>	<i>Median</i>	<i>Mean</i>	<i>SD</i>	<i>Median</i>	
Days: the 1 st physician-patient meeting -first referred to the consultant	235.8	277.6	131	8.7	25.2	0	< 0.001
Days: the referral date - first visit to consultant	16.2	25.3	2	15.8	24.7	2.5	0.793
Days: first visit to consultant - the request of diagnostic tests	9.1	28.7	0	2.7	10	0	0.423
Days: the request of diagnostic tests - performed tests	15.8	21.7	7	22.8	33.1	7.1	0.393

SD: standard deviation.

Table VI. Waiting times and main clinical clues

Main clinical clues	1 st meeting-referral date (days)	Referral date-first visit to consultant (days)	First visit to consultant –the request of test (days)	The request of test –performed test (days)
<i>Anemia: Total</i>	19			
Mean (SD)	300.6 (196.3)	16.2 (29.2)	15.0 (21.2)	14.3 (40.2)
Median	275.0	0.0	6.0	0.0
<i>R. bleeding: Total</i>	11			
Mean (SD)	155.4 (293.7)	18.4 (21.0)	18.0 (25.5)	5.1 (14.4)
Median	59.0	9.0	7.0	0.0
<i>Change in bowel: Total</i>	6			
Mean (SD)	144.8 (198.0)	7.3 (11.6)	6.5 (7.6)	7.8 (12.2)
Median	40.5	0.0	5.0	0.0
<i>Abd. pain: Total</i>	2			
Mean (SD)	84.5 (23.3)	50.0 (43.8)	29.0 (29.6)	0.0 (0.0)
Median	84.5	50.0	29.0	0.0
<i>Constitutional syndrome: Total</i>	1			
Mean (SD)	189.0 (189.0)	10.0 (10.0)	59.0 (59.0)	0.0 (0.0)
Median	189.0	10.0	59.0	0.0
<i>Mass on physical exam: Total</i>	1			
Mean (SD)	93.0 (93.0)	3.0 (3.0)	12.0 (12.0)	0.0 (0.0)
Median	93.0	3.0	12.0	0.0

SD: standard deviation.

In the analysis of the secondary symptoms in case of MOs, change of bowel habit was the most frequent symptom, and this occurred in 24.5% of patients. The rest of the symptoms were relatively low in frequency, in all patients. These results reflect the fact that when any of these symptoms occur as added symptoms to a different initial symptom already consulted for, the probability of an underlying cancer doubles (6).

Finally, the signs and symptoms that were hardly associated with MOs were melena (2.9%), intestinal obstruction (2.9%) and a mass on clinical examination (2.9%). These symptoms appear at more advanced stages and are associated with a severe or sometimes an emergency situation that requires immediate action (18). Therefore, it is less likely that they are associated with MOs. Waiting times were significantly shorter.

The factors that contribute to delays and missed diagnostic opportunities show that the most common mistake was not having requested diagnostic tests in 43.3% of the cases, and not having referred the patient to a consultant in 34.4% of the cases. One of the reasons that could explain these results may be that diagnostic colonoscopy is an invasive test that requires a more rigorous evaluation of its relevance; moreover, acceptance is often low (21,25-27). Besides, it was not available in primary health care in 2009. As to lack of referrals, this may be associated with the high

frequency of symptoms such as anaemia, rectal haemorrhage and abdominal pain in the general population (20). Nevertheless, in the future it would be interesting to describe the cognitive processes that trigger the decision to refer the patient, systematize them and therefore reduce professionals' bias.

Contrary to previous studies (5,12), and by applying the definitions proposed in the literature (15,16) it was found that the case histories failed in only 6.6% of the cases, 8.8% of patients did not receive a correct clinical examination, and all the abnormal results were followed up.

Delays were divided into 4 waiting times, according to the number of days from the first visit due to the onset of symptoms to the final diagnosis; unlike other studies that quantify delays once the patient had been referred to a consultant (28). There was an average delay of 235 days, and this is similar to the outcomes of previous studies (24). Moreover, delays were classified according to the symptoms occurring at the beginning of the diagnosis. Iron-deficiency anaemia was the clinical clue associated with the longest delay, with an average of 300 days. Of the total waiting times regardless of the symptoms, the longest delay was in the number of days from the first physician-patient meeting after onset to the date on which the patient was referred to the consultant. That is when symptoms presumptive of CRC are recognized and a decision is made to refer

the patient. Such a great difference between the first waiting time and the other three is due to several reasons: one of them is that following a high suspicion of CRC in our context a preferential diagnosis sequence begins so as to obtain a final diagnosis in a short period of time. Moreover, in cases where delays are foreseen, patients decide to go to private clinics for diagnostic tests, or directly to the emergency department and thus waiting times are shortened. Therefore, it is possible to say that delays in the diagnosis of this pathology fundamentally depend on the recognition of presumptive CRC symptoms, within a multifactorial problem such as the delay in the diagnosis of CRC (13).

Regarding the limitations of our study, the subjectivity of the concept "missed opportunities" should be pointed out. In order to reduce this subjectivity the definition was adapted from the literature, the clinical keys that justify the differential diagnosis of CRC were defined and two experts contributed to the process. Despite all that, the digressions resulting from the clinical process of each patient hinder the decision to consider if an action corresponds to the definition previously established. Likewise, we found limitations in terms of methodology. Data reviewed covered 2 years before diagnosis, so it is likely that in some cases a greater number of MOs per patient might not have been registered. As for the outcomes obtained, it has not been possible to analyze the probability of MOs when a specific symptom occurs, or what combination of symptoms is most often associated with MOs due to the limited sample size of the study. Likewise, the limitation from the retrospective nature of the study should be highlighted.

To conclude, missed clinical opportunities to start a diagnostic assessment of patients with presumptive colorectal cancer are common (34.45%). The number of co-morbidities is the most important factor associated with MOs, above age; and the main clinical key is iron-deficiency anaemia. The types of processes associated with mistakes at the beginning of diagnosis are the decision not to request a diagnostic test and the non-referral to a consultant. The delay when a MO occurs at the beginning of diagnosis of CRC is significant, if compared to the non-occurrence of a MO. The time to identify symptoms is the factor that generates the longest delay. Therefore, it is necessary to continuously screen for symptoms in order not to miss diagnostic opportunities in symptomatic patients, regardless of whether they belong or not to screening plans. The efforts to improve the quality of the healthcare services in the fight against this pathology should focus on key signs and symptoms, as well as on completing the necessary implementation of medium and high risk screening programs.

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