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Biological and prognostic differences between symptomatic colorectal carcinomas and those detected by screening

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ABSTRACT

Introduction: Few studies have been conducted to establish the relationship between colorectal cancer screening programmes and survival adjusting by stage and, to determine whether there are differences, at a biological level, between the tumours of asymptomatic and symptomatic patients.
Accordingly, the aim of this study is to evaluate clinical, biological and survival differences between symptomatic colorectal tumours and those detected by screening.
Study method: A prospective cohort study was performed of patients subjected to surgical intervention during the period 2010–2012, at different hospitals in Spain. In every case, clinical, pathological, biological and survival-related variables were obtained.
Results: A total of 2634 patients from the CARESS-CCR cohort were analysed; of these, 220 were diagnosed through screening. The asymptomatic patients were younger, had a higher Body Mass Index (BMI), a lower degree of perineural invasion and a less advanced T stage and nodular stage, and the tumour was frequently located on the right side of the colon. All of these differences were statistically significant. The serum tumour marker carbohydrate antigen 19.9 (CA 19.9) was found more frequently in the symptomatic patients ($p < 0.05$). However, no significant differences were found regarding the markers of tumour biology: Ki67 (proliferation), CD105 (angiogenesis) and the Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling (TUNEL) assay (apoptosis). The patients with asymptomatic tumours had a lower mortality at five years than those diagnosed presenting symptoms.
Conclusions: The detection method employed influenced the survival of patients with colorectal cancer and there were no significant biological differences between the study groups.

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Introduction

Colorectal cancer (CRC) is a public health problem of the first magnitude, with a major impact on morbidity and mortality. In Europe there were 471,000 new cases and 228,000 deaths in 2012 [1]. In Spain, there were 22,128 cases of CRC and 14,303 deaths (13.3% of all cancer deaths) in 2008 [1].

The 5-year survival rate of patients with colon cancer in Spain is 57.1% and for rectal cancer it is 56.4% for patients diagnosed between 2000 and 2007. Both values are close to the European average for these conditions [2].

The diagnosis and early treatment of cancer is of fundamental importance, since most colorectal neoplasms emerge from adenomatous lesions, which are usually asymptomatic. Consequently, screening for CRC may help reduce its incidence, by detecting premalignant lesions before they progress to malignancy [3]. Randomised clinical trials have also reported that such screening can reduce mortality from the disease [4,5].

However, in contrast to the situation regarding breast cancer, there is surprisingly little research evidence on the influence made on survival by adjusting or stratifying by tumour stage [6–10]. Among these few studies, all except Wiegering et al. [6] reported finding a significant relationship in this respect.

To our knowledge, only one study [11] determined proliferation and microvessel density in a short series of screening cases (n = 71) and no previous study has explored apoptotic index between colorectal tumours detected by screening in comparison with those detected following the observation of symptoms. In another area, that of breast carcinomas, differences have been observed, in terms of biological characteristics, between screened patients and those with symptomatic carcinomas [12]. In other words, slow-growing tumours with a favourable prognosis have a high probability of being detected by screening.

Therefore, the detection method used is not considered important as regards stratifying the risk of recurrence, or in making treatment decisions. If the tumours detected by screening were associated with a lower degree of biological aggressiveness and better survival than tumours of a similar size but detected by other methods, perhaps patients with a low risk of recurrence would require less aggressive therapy.

The present study, thus, is the first to analyse the differences in tumour biology and survival between symptomatic and asymptomatic patients. In it, we seek to determine whether the detection method employed is a significant prognostic factor in the survival of patients with CRC, taking into account clinical, pathological and biological factors.

Study method

Patients

This study was conducted from 2010 to 2012, based on a multicentre prospective cohort, recruited at 22 hospitals belonging to the Spanish public health system and located in six regions, or Autonomous Communities (Andalusia, Canary Islands, Catalonia, Madrid, Valencia and Basque Country) [13].

The patients were divided into two groups:

1. Symptomatic: 2141 patients diagnosed following observation of suspicious signs and/or symptoms.
2. Asymptomatic: 220 patients, diagnosed as the result of a screening programme.

Patients with an infiltrating tumour were included, but those with a previous history of colon cancer, carcinoma in situ or interval cancer were excluded. Patients who had not received chemotherapy, due to associated comorbidity, were excluded from the survival analysis.

Ethical aspects of the study

The study was performed in accordance with the clinical practice guidelines of the Helsinki Declaration. Informed consent was obtained from all patients to take part in the study and for their clinical records to be reviewed. This project was approved by the ethics review board of each of the participating centres.

Variables

The following variables were considered:

A. - Sociodemographic: age, gender, education, current employment status, personal help required, social helper required, situation in the home, tobacco use.
B. -Clinical:
   (1) Patient data prior to diagnosis: personal history of polyps or adenomas, family history of CRC, and BMI (kg/m^2).
   (2) Data related to the tumour: diagnostic pathway (screening versus symptoms), histological diagnosis, location, size, presence of lymph nodes, metastasis, differentiation, vascular and perineural invasion, tumour type and tumour markers [CEA (Carcinoembryonic antigen) and CA 19.9].
   (3) Survival: data on patient deaths obtained from the hospitals and/or by contacting the patient's family.
C. - Markers of tumour biology: percentage of apoptotic cells, using the TUNEL assay; Ki67 antigen, as a marker of cell proliferation, and CD105, which measures the density of microvessels as a marker of angiogenesis.

Immunohistochemistry

Levels of Ki-67 (anti-Ki-67 (30–9) Rabbit Monoclonal Primary Antibody, Roche Diagnostics GmbH, Mannheim, Germany) and CD105 (Clone 4G11, Mouse Monoclonal Antibody, Leica Biosystems, United Kingdom) were determined by the streptavidin biotin enzyme assay. Ki-67 expression was calculated as the percentage of tumour cells positively stained by the antibody, with nuclear staining being the most common criterion of positivity. MIB1 is a monoclonal antibody that recognises the Ki-67 nuclear antigen in formalin-fixed paraffin-embedded tissue sections. Its reactivity is not affected by any delay in fixation. The cut-off point used was the median value in each tumour series.

The results of each case were evaluated independently (blind study with anonymised samples) by two pathologists in a semi-quantitative analysis in which the intensity and percentage of staining were determined. Cases that produced disagreement were re-evaluated by a third pathologist.

Detection of cellular apoptosis using the TUNEL assay

To detect apoptotic cells, the 3′-ends of the DNA fragments generated by apoptosis-associated endonucleases were labelled in situ using a commercial apoptosis detection kit (Roche Diagnostics GmbH, Mannheim, Germany). The sections were pre-treated with

DNase as a positive control, and absence of the enzyme was taken as a negative control. Cells were defined as apoptotic if the nuclear area was completely stained. Apoptotic bodies are defined as small globular bodies that are positively marked in the cytoplasm of the tumour cells, whether isolated or in groups. One thousand cells were counted for each sample. The cut-off point used was the median apoptosis value in each tumour series.

Statistical analysis of the results

The descriptive analysis was based on measures of central tendency and dispersion for the quantitative variables, and of frequency distribution for the qualitative ones. Taking as a variable of segmentation the presence of signs and symptoms in the presentation of the disease, the chi-square test was used to evaluate differences for independent quantitative variables, and the Student *t*-test for independent quantitative ones. For the outcome of the survival variable, the association between the presence of signs and symptoms and survival analysis was tested, using the Kaplan-Meier method and the SPSS v15 statistical package.

Results

The study included 2634 patients, of whom 220 (8.4%) were asymptomatic, diagnosed through different screening techniques, and 2414 (91.6%) were symptomatic. The characteristics of both groups are shown in Table 1. The results obtained show that symptomatic patients tend to be older, have a lower BMI, need more help in everyday activities and are less likely to be working than are patients diagnosed after screening. As well, asymptomatic patients are more likely to have a family history of CRC (Table 1).

No significant histological differences were observed, but mucinous adenocarcinoma was less common in the screening group, although the difference was not statistically significant. Perineural invasion was also less frequent in the asymptomatic patients, and this result was significant (Table 2). As well, the tumours in asymptomatic patients were of minor T stage and presented fewer lymph nodes than those in the symptomatic patients (Table 2).

The T stage findings were also grouped into those presenting a smaller or larger local extension. The asymptomatic patients, in general, presented a smaller tumour extension (Table 3). In addition, we examined the location of the tumour, to see whether there was any difference in this respect, and found that more cancers were located on the right side of the colon than on the left in asymptomatic patients, a difference that was significant. In contrast, rectal cancer was more commonly found in the symptomatic patients (Table 3).

Serum tumour markers CEA and CA 19.9 were less frequently observed in the asymptomatic patients (Table 4). The markers of tumour biology (Ki67, CD105 and the TUNEL assay) did not vary significantly between the two groups of patients (Fig. 1,Table 4).

Significant differences were found between asymptomatic and symptomatic patients regarding survival, which was longer for the asymptomatic patients: 42.2 months (95% CI 39.37–45.20) versus 37.47 months (95% CI 36.80–38.15) for the symptomatic patients (Fig. 2).

Discussion

The main objective of CRC screening is to reduce mortality, by early detection of the tumour. It is generally accepted that screening programmes, properly applied, can reduce the incidence of cancer and hence mortality [14]. Our study hypothesis was that an appropriate screening programme can achieve the early detection of asymptomatic tumours, which present a more benign pattern of behaviour than symptomatic ones.

In our series no significant differences were observed between male and female patients as regards the presence or absence of symptoms. However, asymptomatic patients tend to be younger and have a higher BMI as was reported previously [6,7,15].

In addition, a higher proportion of asymptomatic than

Table 1
Sociodemographic and clinical differences between asymptomatic and symptomatic colorectal cancer patients.

		Patients		$p < 0.05$
		Asymptomatic %(N)	Symptomatic %(N)	
Sex	Male	9% (151)	91% (1522)	Chi square
	Female	7,2% (69)	92.8% (892)	NS
Age	Total:	64.85 ± 8.31	68.84 ± 11.17	Student *t*-test <0.001
BMI	Total:	28.31 ± 4.4	27.63 ± 4.85	Student *t*-test 0.098
Education qualifications	None-primary	8.2% (137)	91.8% (1536)	Chi square
	Secondary-University	10.1% (51)	89.9% (452)	NS
Currently working	No	7.4% (121)	92.6% (1518)	Chi square
	Yes	11.4% (58)	88.6% (452)	0.006
Need help for everyday activities	No	11.6% (96)	88.4% (733)	Chi square
	Yes	7.1% (88)	92.9% (1159)	0.001
Social assistant	No	9% (161)	91% (1622)	Chi square
	Yes	6.4% (20)	93.6% (291)	NS
Home status	Living alone	6.4% (19)	93.6% (277)	Chi square
	Sharing home	9.1% (166)	90.9% (1650)	NS
	Other situation	6.5% (3)	93.5% (43)	
Tobacco use	Non smoker	7% (84)	93% (1120)	Chi square
	Smoker	10.7% (36)	89.3% (299)	0.075
	Ex- smoker	8.1% (78)	91.9% (889)	
Family history of neoplasia	No	8.3% (122)	91.7% (1355)	Chi square
	Yes	8.6% (75)	91.4% (799)	NS
Family history of CRC	No	7.9% (113)	92.1% (1323)	Chi square
	Yes	12.3% (26)	87.7% (185)	0.041

NS: Non significant.

Table 2
Pathological differences between asymptomatic and symptomatic colorectal cancer patients.

		Patients		Patients
		Asymptomatic %(N)	Symptomatic %(N)	
Presence of ganglia	No	9.1% (142)	90.9% (1423)	Chi square
	Yes	7.3% (68)	92.7% (865)	NS
Histological diagnosis	Adenocarcinoma	8.7% (203)	91.3% (2136)	Chi square
	Mucinous or other adenocarcinoma	5.9% (15)	94.1% (241)	NS
Metastasis	Absent	9% (200)	91% (2026)	Chi square
	Present	6.4% (13)	93.6% (189)	NS
Differentiation	Low grade	8.6% (164)	91.4% (1732)	Chi square
	High grade	7.3% (22)	92.7% (279)	NS
Vascular invasion	No	8.2% (156)	91.8% (1756)	Chi square
	Yes	6.3% (19)	93.7% (283)	NS
Perineural invasion	No	8.8% (156)	91.2% (1625)	Chi square
	Yes	4% (15)	96% (364)	0.02
T stage	T0	8.8% (5)	91.2% (52)	Chi square
	T1	15.5% (34)	82.5% (160)	0.000
	T2	13.6% (64)	86.4% (407)	
	T3	6.4% (95)	93.6% (1390)	
	T4	3.7% (13)	96.3% (335)	
Lymph node	N0	9.2% (143)	90.8% (1416)	Chi square
	N1	7.7% (52)	92.3% (622)	0.041
	N2	5.4% (17)	94.6% (298)	
Metastasis	M0	9.7% (176)	90.3% (1637)	Chi square
	M1	6.4% (13)	93.6% (189)	NS

NS: Non significant.

Table 3
Local extension and localization of colorectal tumours.

		Patients		Patients
		Asymptomatic %(N)	Symptomatic %(N)	
T stage	Small local extension (T0-T1-T2)	14.2% (106)	85.8% (641)	Chi square
	Large local extension (T3-T4)	5.9% (108)	94.1% (1725)	<0.001
Tumour location	Colon: right side	10.5% (80)	89.5% (683)	Chi square
	Colon: left side	8.6% (94)	91.4% (995)	0.006
	Rectum	5.9% (43)	94.1% (685)	
Combination of tumour locations	Colon: right side	10.5% (80)	89.5% (683)	Chi square
	Colon left side + Rectum	7.5% (137)	92.5% (1680)	0.017

Table 4
Serum and tissue tumour markers in colorectal tumours.

			Patients		Patients
			Asymptomatic	Symptomatic	
Tumour markers	CEA	Normal (0–5)	7.7% (107)	92.3% (1289)	Chi square
		Abnormal (>5)	5.3% (35)	94.7% (628)	0.057
	CA 19-9	Normal (1-37)	6% (57)	94% (887)	Chi square 0.035
		Abnormal (>37)	1.7% (3)	98.3% (169)	
Biological tumour markers (quantitative variable)	TUNEL %		1.35 ± 0.63 (41)	1.34 ± 0.68 (433)	Test of independent samples
	CD105		11.80 ± 4.93 (41)	11.14 ± 4.48 (446)	NS
	ki67		32.05 ± 21.75 (43)	34.13 ± 22.51 (498)	
Biological tumour markers (qualitative variable)	**TUNEL %**	≤1.4*	8.2% (21)	91.8% (234)	Chi square
		<1.4	9.1% (20)	90.9% (199)	NS
	CD105%	≤10.66	8.1% (20)	91.9% (228)	Chi square
		<10.66	8.8% (21)	91.2% (218)	NS
	Ki67%	≤29	8.7% (24)	91.3% (253)	Chi square
		<29	7.2% (19)	92.8% (245)	NS

NS: Non-significant; * Mean (%).

symptomatic patients are currently in work. This may be related to their age, as the former are both younger and require less personal assistance. Another interesting finding is that symptomatic patients are more likely to be non-smokers, which could be related to the severity of their pathology and the associated morbidity.

Analysis of the tumour-related data showed that the asymptomatic patients had less perineural invasion, a lower T stage and a lower nodular stage. In every case, the differences were significant. However, no such statistical significance was obtained with respect to metastases, although these were slightly more common among

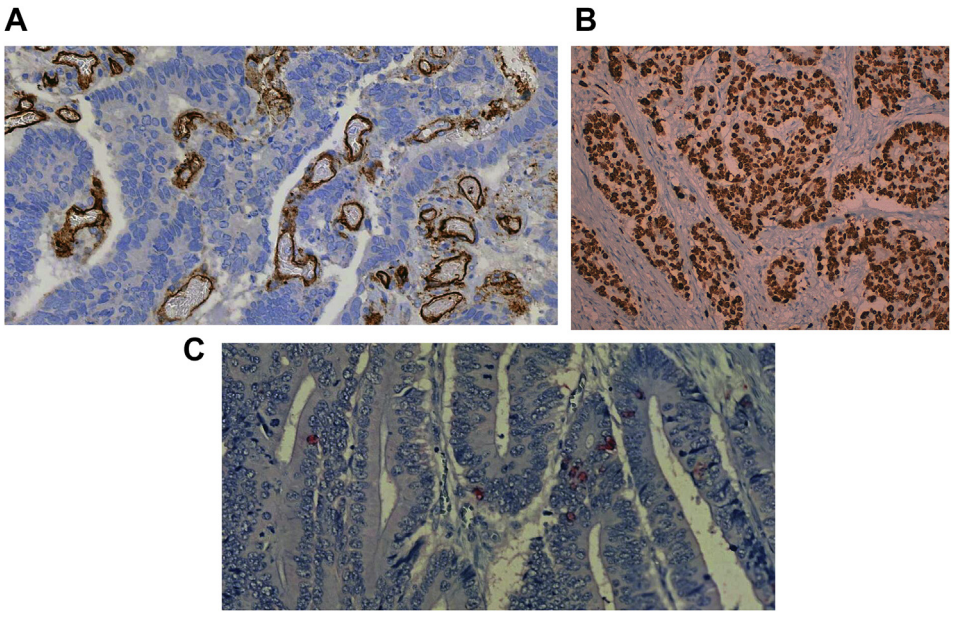

Fig. 1. Markers of tumour biology
a).CD105: Tumour neovascularization in a moderately differentiated colonic adenocarcinoma; 20x.
b) KI67: Proliferative index in a colonic adenocarcinoma, moderately differentiated; 20x.
c) Tunnel: apoptotic cells in a colonic adenocarcinoma, moderately differentiated; 20x.

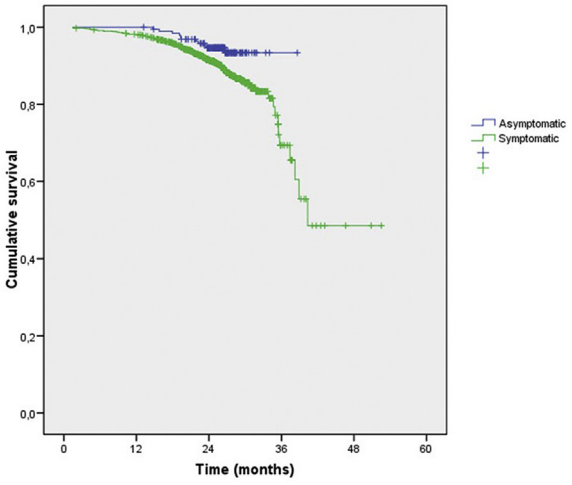

Fig. 2. Kaplan-Meier survival curve: symptomatic vs. asymptomatic.

patients with symptomatic tumours.

Our finding that asymptomatic patients present a less advanced T stage corroborates previous reports [6,7,10,16]. This was also the case with the nodular stage [6].

We found that screening tumours were located frequently on the right side of the colon and rectal cancer was more commonly found in the symptomatic patients (Table 3). Tumours in the right side are known to have a worse prognosis than those on the left and in the rectum [17]. It is possible that asymptomatic tumours represent the only subgroup with good prognosis located in this side of the colon.

We also found differences between both groups in preoperative levels of CEA and CA19.9. A more elevated preoperative levels of CEA and CA19.9 were found in symptomatic patients. A previous work [18] showed that preoperative CEA was a predictor of decreased survival.

Studies on survival by adjusting for tumour stage are surprisingly scarce. Our analysis showed the asymptomatic patients to have a higher proportion of long-term survivors. This fact is not explained by the more favourable stage distribution of patients with screening detected cancers, as these patients had a better prognosis for a comparable tumour stage. These are similar results to those reported by other groups [7–9,19,20]. This fact could be due to that the slower growing tumours could have more possibilities of being detected by screening (length time bias). However, we have not detected differences when we have studied the processes of proliferation, apoptosis or angiogenesis. Similar results were found by Walsh et al. when they study proliferation and microvessel density in a short series [11]. Perhaps other possibilities such as greater awareness and adherence to the treatment of these patients may be relevant although the level of studies has not influenced the outcome in our series.

We conclude that the detection method clearly influenced the survival of patients with CRC, and the difference observed with symptomatic patients is not explicable by marked changes in the biological properties such as the apoptosis, proliferation and neoformation of blood vessels.

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Conflict of interest

None.

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