ELSEVIER

European Journal of Cancer 40 (2004) 245–252

European Journal of Cancer

www.ejconline.com

Predictive value of rectal bleeding for distal colonic neoplastic lesions in a screened population

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Received 3 February 2003; received in revised form 30 May 2003; accepted 5 August 2003

Abstract

The aim of this study was to determine the diagnostic value of rectal bleeding for distal colorectal cancer (CRC), or large (⩾10 mm) adenomas among an average-risk population. A cross-sectional survey was conducted among individuals aged 55–64 years, who attended sigmoidoscopy (FS) screening in the context of a multicentre randomised trial of FS screening for CRC. Sensitivity, specificity and positive predictive value (PPV) of rectal bleeding for large distal adenomas or CRC were calculated. Rectal bleeding was reported by 8.8% of 8507 patients examined (15% of those with large adenomas and 29% of those with CRC). The risk of CRC was increased when bleeding was associated with an altered bowel habit: odds ratio (OR) = 10.42; 95% Confidence Interval (CI): 4.08–26.59; the corresponding OR for isolated bleeding was 5.29 (95% CI: 2.28–12.30). Rectal bleeding carries an increased risk of distal neoplastic lesions. However, most lesions are detected among asymptomatic subjects. This finding suggests that screening represents the optimal strategy to detect CRC or large adenomas in the distal colon in the targeted age range.

Keywords: Colorectal neoplasm; Rectal bleeding; Predictive value; Screening

1. Introduction

Rectal bleeding is usually considered to be a suspicious symptom for colorectal cancer (CRC) [1–3]. However, it is a fairly common symptom in the general population, with a reported prevalence of approximately 15% [4,5]. In studies conducted among hospital patients undergoing investigation for lower abdominal symptoms, the reported prevalence of polyps or CRC varied between 19 and 35% [6–10]. Lower prevalence figures have been reported among primary care patients seeking care for rectal bleeding [4,11–14]. Since only a few (approximately 15–20%) of patients with rectal bleeding seek medical advice [4,5,15], these figures may represent an overestimate of the predictive value of the symptom in the population. The positive predictive value (PPV) of rectal bleeding for distal polyps or CRC was 8% in a small prospective study of a randomly selected group of healthy men, who had not consulted their physician for this symptom and underwent sigmoidoscopy (FS) to at least 30 cm [16].

We assessed the predictive value of rectal bleeding in identifying distal neoplastic lesions among average-risk individuals, aged 55–64 years, enrolled in a multicentre trial of efficacy of FS screening for CRC [17]. As all screenees had FS independent of their symptoms, we could obtain an unbiased estimate of the predictive value of bleeding among people attending screening. We also assessed the predictive value of other symptoms, such as abdominal pain and altered bowel habit, which are also considered to be symptoms of colorectal cancer

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doi:10.1016/j.ejca.2003.08.002

[1,3]. Since smaller lesions are rarely the cause of rectal bleeding [18], the present study focused on distal large ($\geqslant$10 mm) adenomas and CRC.

2. Patients and methods

2.1. Study population

The study was conducted in the context of a multicentre randomised trial of 'once only' FS screening for CRC (SCORE) [17], carried out in six centres in Italy, as a parallel study to the UK trial co-ordinated by W.S. Atkin [19]. The protocol of the trial was approved by the local Ethics Committee in each centre.

The recruitment procedure has been described elsewhere in Ref. [17]. Briefly, all individuals who responded to a questionnaire mailed to a random sample of men and women aged 55–64 years, drawn from the general population register, were enrolled, if eligible and interested in undergoing screening. Exclusion criteria included a previous diagnosis of CRC, polyps, inflammatory bowel disease, life-threatening disease, two or more first-degree relatives with CRC, and a large bowel endoscopy within the previous two years. Individuals allocated to the screening arm who took up the invitation for screening were included in the study.

2.2. Test procedure

Bowel preparation was limited to a single enema (133 ml sodium phosphate) self-administered at home 2 h before the test. Written informed consent was obtained before undergoing FS. All participants were also administered a questionnaire asking about gastrointestinal symptoms during the month preceding FS.

All polyps $\leqslant$5 mm were removed during FS. Patients were referred for colonoscopy (TC) if they were found to have polyps $>$5 mm, or CRC, or 'high-risk' small ($\leqslant$5 mm) adenomas (villous component $>$20% or severe dysplasia, $\geqslant$3 tubular adenomas). The endoscopist recorded on a standard form information about the adequacy of the bowel preparation, reach of the scope, characteristics of detected lesions, or visualisation of other findings, such as haemorrhoids or diverticula.

The histopathology of polyps and cancers was classified according to the World Health Organization (WHO) criteria [20].

2.2.1. Analysis

For the purposes of this analysis, only people who had the rectum and sigmoid colon examined, either at FS or at a subsequent TC, were considered. Polyp size was classified according to the measure recorded by the endoscopist. If multiple polyps were detected, the largest one was considered.

Positive history for rectal bleeding was defined as a self-report of any visible bleeding from the anus over the month preceding the FS at the interview administered before the screening. Based on the findings of previous reports, indicating that the predictive value of rectal bleeding increases when it occurs in association with a change in bowel habit [8,21], we considered four symptom groups: (1) rectal bleeding associated with changes in bowel habits, (2) rectal bleeding (isolated or with other abdominal symptoms), (3) changes in bowel habit (isolated or with other abdominal symptoms), (4) other abdominal symptoms only. The absolute risk of large adenomas and CRC was calculated for each symptom group. The diagnostic value—sensitivity (Se), specificity (Sp), PPV, negative predictive value (NPV)—of these symptom groups in predicting the presence of distal neoplasia was considered. The 95% confidence intervals (95% CI) were calculated by the exact methods for binomial data [22]. Likelihood ratios (LR) were derived to calculate the posttest probability associated with the different symptom categories, assuming the prevalence of large adenomas and CRC observed in our study population as the pretest probability of disease [23]. Logistic regression was used to estimate odds ratios (OR), adjusted for gender, age, presence of haemorrhoids, family history and history of previous colorectal endoscopy. Multivariate ORs were also adjusted for trial centre to allow for variability in adenoma detection rates. The Statistical Analysis System (SAS) statistical package [24] was used for the analysis.

3. Results

We contacted 236 568 people and received 56 532 replies (23.9%). Among the responders, 6082 (10.8%) were not eligible and 16 158 (28.6%) were not interested in undergoing FS. Out of 17 148 subjects allocated to the screening arm, 9999 (58.3%) attended.

The large bowel was examined up to at least the distal descending colon in 8668 patients. The presence of symptoms was not recorded for 62 (0.7%) of these subjects, and information about polyp histology was unavailable for a further 99 (1.1%): 11 patients refused to undergo TC, while in a further 88 cases, the polyp was either lost after resection or not detected at TC. The proportion of incomplete procedures was 16.3% among women and 9.2% among men ($P<0.001$). No other difference was observed between patients with incomplete exams or missing information and those included in the analysis, with respect to age, symptoms, report of other findings at endoscopy, family history of CRC, or history of previous endoscopies.

Of the 8507 patients included in the study, 747 (8.8%) reported rectal bleeding: in 275 cases (36.8%) bleeding was associated with changes in their bowel habit

(Table 1). The prevalence of bleeding was similar in both genders and decreased from 9.5% among subjects aged 55–59 years, to 7.9% in the older age group (OR = 0.81; 95% CI: 0.70–0.95). Women reported bowel-related symptoms other than bleeding more frequently than men (OR = 1.71; 95% CI: 1.55–1.89).

Overall, rectal bleeding was reported by 39 (15.1%) of the 258 subjects with a distal large adenomas and by 15 (31.9%) of 47 who had a distal CRC (Table 2). The prevalence of bleeding (which corresponds to the sensitivity of this symptom) was similar among subjects with adenomas <10 mm (tubular adenomas: 8.3%; adenomas with villous component: 9.1%), among those harbouring only hyperplastic polyps (9.0%) and among patients with a negative test (8.4%). In this latter group, bleeding was reported more often by patients with haemorrhoids, but no association with the presence of diverticula was observed.

The sensitivity of bleeding for large adenomas and CRC considered together was 17.7%; the specificity was 96.9% when bleeding was associated with an altered bowel habit and 94.7% when bleeding was not associated with other symptoms; the corresponding figures for PPV were 7.3 and 7.2% (Table 3). Among men

Table 1
Prevalence of symptoms by gender and age

	No symptoms *N* (%) (95% CI)	Changes in bowel habit *N* (%) (95% CI)	Other abdominal symptoms *N* (%) (95% CI)	Rectal bleeding[a] *N* (%) (95% CI)	Rectal bleeding + changes in bowel habit *N* (%) (95% CI)	Total
Females	2244 (58.8) (57.2–60.3)	950 (24.9) (23.5–26.3)	290 (7.6) (6.8–8.5)	172 (4.5) (3.9–5.2)	163 (4.3) (3.7–5.0)	3819
Males	3250 (69.3) (68.0–70.6)	681 (14.5) (13.5–15.6)	345 (7.4) (6.7–8.2)	300 (6.4) (5.7–7.2)	112 (2.4) (2.0–2.9)	4688
55–59 years	2943 (64.9) (63.5–66.2)	820 (18.1) (17.0–19.2)	342 (7.5) (6.8–8.3)	278 (6.1) (5.5–6.9)	155 (3.4) (2.9–4.0)	4538
60–64 years	2551 (64.3) (62.8–65.8)	811 (20.4) (19.2–21.7)	293 (7.4) (6.6–8.3)	194 (4.9) (4.3–5.6)	120 (3.0) (2.5–3.6)	3969
Total	5494 64.6 (63.6–65.6)	1631 (19.2) (18.3–20.0)	635 (7.5) (6.9–8.1)	472 (5.5) (5.1–6.1)	275 (3.2) (2.9–3.6)	8507

95% CI, 95% Confidence Interval.
[a] 41 patients reported rectal bleeding (RB) associated with abdominal pain or other non-specific gastrointestinal symptoms.

Table 2
Prevalence of symptoms by distal finding

Distal findings	Rectal bleeding + changes in bowel habit *N* (%) (95% CI)	Rectal bleeding[a] *N* (%) (95% CI)	Changes in bowel habit *N* (%) (95% CI)	Other abdominal symptoms *N* (%) (95% CI)	No symptoms *N* (%) (95% CI)	Total
CRC	7 (14.9) (6.7–28.9)	8 (17.0) (8.1–31.4)	6 (12.8) (5.3–26.4)	4 (8.5) (2.8–21.3)	22 (46.8) (32.4–61.8)	47 100.0
Adenoma ⩾10 mm	13 (5.0) (2.8–8.7)	26 (10.1) (6.8–14.6)	36 (14.0) (10.1–18.9)	11 (4.3) (2.3–7.7)	172 (66.7) (60.5–72.3)	258 100.0
Tubulo-villous/villous adenomas <10 mm	4 (5.2) (1.7–13.5)	3 (3.9) (1.0–11.7)	11 (14.3) (7.7–24.6)	7 (9.1) (4.0–18.4)	52 (67.5) (55.8–77.5)	77 100.0
Tubular adenomas <10 mm	21 (3.0) (1.9–4.7)	37 (5.3) (3.8–7.3)	97 (13.9) (11.5–16.8)	73 (10.5) (6.4–13.1)	469 (67.3) (63.7–70.7)	697 100.0
Hyperplastic polyps	8 (2.2) (1.0–4.4)	25 (6.8) (4.6–10.1)	77 (21.0) (17.1–26.7)	18 (4.9) (3.0–7.8)	238 (65.0) (59.5–69.9)	366 100.0
Negative	222 (3.1) (2.8–3.6)	373 (5.3) (4.8–5.8)	1404 (19.9) (19.0–20.8)	522 (7.4) (6.8–8.0)	4541 (64.3) (63.2–65.4)	7062 100.0
Total	275	472	1631	635	5494	8507

CRC, colorectal cancer; 95% CI, 95% Confidence Interval.
[a] Isolated bleeding or bleeding + other abdominal symptoms.

reporting bleeding, 2.7% had CRC and 7.5% had large adenomas; the corresponding figures for women were 1.2 and 2.4%, respectively (data not shown). The prevalence of CRC was higher among men who also reported a change in their bowel habit (4.4%), compared with those with bleeding, isolated or associated with other abdominal symptoms (2.2%). The PPV for large adenomas was not different, either among men or women, when bleeding was associated with an altered bowel habit. The likelihood ratio for CRC of bleeding was 4.7 when associated with a change in bowel habit and 3.1 when it was isolated or associated with other symptoms, shifting the probability of CRC from 0.55% (observed CRC prevalence) to 2.6% and 1.7%, respectively. The corresponding LRs for changes in bowel habit, other abdominal symptoms and absence of symptoms were 0.7, 1.1 and 0.7, respectively.

Self-reported bleeding was significantly associated with the presence of both large adenomas and CRC whereas no association with the other symptoms was found (Table 4). After adjusting for the history of colorectal endoscopy, family history of CRC, presence of haemorrhoids, age and trial centre, the risk of distal CRC or large adenomas was increased among patients who reported bleeding associated with a change in bowel habits (Table 4), but the diagnostic value of this combination of symptoms was more marked for CRC (OR = 10.42; 95% CI: 4.08–26.59) than for large adenomas (OR = 2.49; 95% CI: 1.36–4.57). In addition, the predictive value was dependent on the stage of CRC (data not shown). A nearly 3-fold increase in the risk of detecting an advanced cancer (Dukes' B2 or more advanced: $N = 21$) was observed among patients who also reported a change in their bowel habit (OR = 13.28; 95% CI: 4.36–40.33), compared with those with isolated rectal bleeding, or bleeding associated with abdominal pain (OR = 4.92; 95% CI: 1.51–16.07). In contrast, the risk was similar for early stage CRC ($N = 26$), both for patients with isolated bleeding (OR = 3.52; 95% CI: 0.74–16.75) and for those who also reported a change in their bowel habit (OR = 3.51; 95%CI: 1.12–11.06). Men were approximately twice as likely as women to harbour large adenomas or CRC, after adjusting for self-reported bleeding and the other factors included in the multivariate model (Table 4).

When considering patients referred for TC, the prevalence of rectal bleeding was 13.7% (44/322) among those with a large distal adenoma and 7.9% (30/378) among those with smaller lesions in the distal colon. The prevalence of large adenomas or CRC in the proximal colon among those who harboured a large distal adenoma was 11.4% (5/44) when bleeding was present and 5.0% (14/278) among those who did not report bleeding. The corresponding figures among those who did not have a large distal adenoma were 3.3% (1/30) and 2.3% (8/348), respectively.

4. Discussion

Our findings confirm that patients reporting rectal bleeding carry an increased risk of distal neoplasia. CRC and large adenomas were detected in 2.0% and in 5.2% of people undergoing FS screening, who complained of rectal bleeding. A 5-fold increase in the risk of CRC, was observed when bleeding was not associated with an altered bowel habit; the combination of bleeding with a change in bowel habit was associated with a 10-fold increase in the risk of CRC, although, compared with the risk associated with the presence of isolated bleeding, the observed increase in the predictive value of this symptom did not reach statistical sig-

Table 3
Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and Likelihood Ratio (LR) of abdominal symptoms in predicting large distal adenomas and CRC

	Rectal bleeding + changes in bowel habit		Rectal bleeding[a]		Altered bowel habits		Other abdominal symptoms	
	Large adenomas + CRC	CRC	Large adenomas + CRC	CRC	Large adenomas + CRC	CRC	Large adenomas + CRC	CRC
Se (%)	6.6	14.9	11.1	17.0	13.8	12.8	4.9	8.5
95% CI (%)	4.2–10.1	6.7–28.9	8.0–15.4	8.1–31.3	10.2–18.3	5.3–26.4	2.9–8.2	2.8–21.3
Sp (%)	96.9	96.8	94.7	94.5	80.6	80.8	92.5	92.5
95% CI (%)	96.5–97.3	96.4–97.2	94.2–95.1	94.0–95.0	79.8–81.5	79.9–81.6	91.8–93.0	92.0–93.1
PPV (%)	7.3	2.5	7.2	1.7	2.6	0.4	2.6	0.6
95% CI (%)	4.6–11.2	1.1–5.4	5.1–10.0	0.8–3.5	1.9–3.5	0.2–0.8	1.4–4.0	0.2–1.7
NPV (%)	96.5	99.5	96.6	99.5	96.2	99.4	96.3	99.4
95% CI (%)	96.1–96.9	99.3–99.7	96.2–97.0	99.3–99.7	95.7–96.6	99.2–99.6	95.9–96.7	99.3–99.6
LR +	2.1	4.7	2.1	3.1	0.7	0.7	1.1	0.7

[a] Isolated bleeding or bleeding + other abdominal symptoms.

Table 4

	N	Large adenomas				CRC			
			Univariate analysis				Univariate analysis		
		N	% 95% CI	OR 95% CI	OR[a] 95% CI	N	% 95% CI	OR 95% CI	OR[a] 95% CI
No symptoms	5494	172	3.1 2.7–3.3	1	1	22	0.4 0.3–0.6	1	1
Other abdominal symptoms	635	11	1.7 0.9–3.2	0.55 0.30–1.01	0.71 0.44–1.45	4	0.6 0.2–1.7	1.58 0.54–4.59	1.54 0.53–5.51
Changes in bowel habit	1631	36	2.2 1.6–3.1	0.70 0.49–1.01	0.94 0.63–1.40	6	0.4 0.2–0.8	0.92 0.37–2.27	1.34 0.52–3.45
Rectal bleeding[b]	472	26	5.5 3.7–8.1	1.80 1.18–2.76	2.09 1.33–3.29	8	1.7 0.8–3.5	4.29 1.90–8.69	5.29 2.28–12.30
Rectal bleeding + changes in bowel habit	275	13	4.7 2.7–8.1	1.54 0.86–2.74	2.49 1.36–4.57	7	2.6 1.1–5.4	6.50 2.75–15.34	10.42 4.08–26.59
Females	3819	76	2.0 1.6–2.5	1	1	13	0.3 0.2–0.6	1	1
Males	4688	182	3.9 3.4–4.5	1.99 1.51–2.63	1.97 1.49–2.62	34	0.7 0.5–1.0	2.14 1.09–4.27	2.30 1.19–4.44
55–59 years	4538	121	2.7 2.2–3.2	1	1	25	0.6 0.4–0.8	1	1
60–64 years	3969	137	3.5 2.9–4.1	1.31 1.01–1.69	1.29 0.99–1.67	22	0.6 0.4–0.9	1.01 0.55–1.85	1.04 0.58–1.87

OR, Odds Ratio; CRC, colorectal cancer.

[a] ORs are adjusted for all the other variables in the model, and for the history of colorectal endoscopy, family history of CRC, presence of haemorrhoids and trial centre.

[b] Isolated bleeding or bleeding + other abdominal symptoms.

nificance, due to the low number of cases. Self-reported bleeding was also associated with a 2-fold increase in the risk of harbouring a large distal adenoma.

However, only 15% of patients with large adenomas and 32% of those with CRC reported bleeding. Thus, the absence of rectal bleeding did not exclude the presence of CRC: compared with the 0.55% prevalence in the whole study population (pretest probability of CRC), 0.40% of asymptomatic subjects were found to have CRC.

The finding of a similar prevalence of self-reported bleeding among people with a negative exam and among those with polyps <10 mm confirms that this symptom has no diagnostic value for these lesions. The higher PPV of hyperplastic polyps and small tubular adenomas, compared with larger neoplasms, is explained by their higher prevalence.

Our results are consistent with the findings from other studies indicating that the prevalence of CRC is increased among patients reporting bleeding associated with an altered bowel habit [8,21].

A higher PPV of rectal bleeding for CRC has been reported in follow-up studies of patients presenting with rectal bleeding in general practice or primary care clinics (range 3–15%) [11–14] and among patients referred to specialist gastroenterologists for lower abdominal symptoms (range 10–33%) [6–10]. However, selection and referral bias may hamper the generalisability of these findings. Indeed, the clinical relevance of the symptom (i.e. first onset of bleeding and/or association with other symptoms) may have influenced the general practitioner's (GP's) decision to refer the patient for further investigation, as well as the patient's decision to seek medical care [25].

In addition, in previous studies, endoscopic investigations were not performed in patients without bleeding. The prevalence of CRC and large adenomas in our study is similar to the figure reported from another small survey of a sample of healthy men who underwent sigmoidoscopy, independent of any self-reported symptoms [16].

As in our trial, the decision to perform a TC was based on the characteristics of the distal polyps, only approximately 14% of the patients reporting bleeding from the anus had the whole colon examined. Therefore, we can assess the diagnostic value of bleeding for distal lesions only. However, previous studies have shown a clear difference between the mode of presentation of cancers of the rectum and sigmoid, compared with more proximal cancers. Although bleeding may

come from lesions above the reach of FS, this seems to be relatively uncommon [16], while approximately 80% of distal cancers present with rectal bleeding [26].

Due to the low response rate to the initial mail questionnaire aimed at assessing eligibility and interest in screening, and to the choice of randomising only eligible interested responders, approximately 14% of the subjects who received the mailing questionnaire actually had a FS exam. Therefore, a self-selection of subjects who might show a risk of CRC different from the general population targeted for screening cannot be excluded.

The proportion of subjects mentioning one first-degree relative with CRC was approximately twice as high in our trial, compared with the prevalence reported in case–control studies conducted in the study areas (range 5.0–7.0%) [27,28]. However, misclassification may partially account for this finding, as the prevalence of a positive family history was 9.5% in the only centre where self-reported information was verified by the GP.

In Turin and Genova, the response rate was higher among better educated subjects, who have been shown to have a higher incidence of CRC, compared with those with a lower educational level [29].

As the observed prevalence of self-reported bleeding was not associated with either the educational level or family history, the overrepresentation of these two subgroups at increased risk of CRC would lead to an overestimate of the PPV for this symptom, which might be lower in the population in the same age group attending general practices or outpatients clinics.

Also, overrepresentation of symptomatic individuals can be excluded.

The proportion of people reporting other abdominal symptoms (diarrhoea, constipation, pain) was 27% in our trial and 15–25% in population-based surveys [30–32]. In addition, the prevalence of 8.8% for rectal bleeding is actually lower than that reported in other studies [5,8]. The inclusion in these studies of a substantial proportion of patients younger than 55 years of age might partially explain this difference, as rectal bleeding has been shown to be less frequent in older people [5] (a trend towards a reduction in the prevalence with age was also observed in our study). Moreover, we chose to include only symptoms experienced during the month preceding the test, while in previous studies, patients were asked to report symptoms noted over a longer period (between 3 and 6 months) [7,11,16]. We adopted more restrictive criteria in order to achieve greater accuracy in the patients' reports and because it has been suggested that the risk of CRC may be higher when bleeding has been present for less than 2 months [11,13].

We made no attempt to classify rectal bleeding according to its characteristics (i.e. colour, blood seen on the toilet paper or in the toilet bowl), because it has been suggested that this does not influence its diagnostic value [5,9,33,34].

It is usual to emphasise the importance of a prompt and careful evaluation of patients presenting with lower gastrointestinal symptoms, in order to reduce any delay in diagnosis and treatment [3]. However, in a population targeted for screening, lower gastrointestinal symptoms showed a low sensitivity. Abdominal pain or an altered bowel habit did not discriminate patients at an increased risk of CRC or large adenomas. Rectal bleeding was associated with a higher risk of distal neoplasms, but most subjects with these lesions did not report rectal bleeding. In addition, while other studies suggest that bleeding is a symptom of early rather than late cancer [35], we found that it was mainly associated with the presence of advanced cancer and it was a poor predictor of early neoplastic lesions, such as early cancer or large adenomas.

In conclusion, our findings suggest that screening represents the most effective strategy to detect early-stage CRC or advanced adenomas in the distal colon in the targeted age range, as most people with these lesions were asymptomatic. The choice of screening strategies should be based on a careful evaluation of the balance between side-effects and the yield of advanced neoplastic lesions from the available tests. In the context of a screening programme, obtaining a history of symptoms is of little extra value.

In the absence of a screening programme, rectal bleeding is moderately helpful in identifying individuals at an increased risk of neoplasia. Among patients younger than 65 years who report this symptom, FS may be a safe and efficient mode of investigation. In a recent study [36] of over 8000 patients with lower gastrointestinal symptoms attending a surgical outpatient clinic, diagnosis of virtually all the significant large bowel pathology was achieved by FS. Given the diagnostic yield of large adenomas among these patients, this strategy may also have an important impact on the CRC incidence.

The diagnostic value of bleeding might be increased among subjects older than 64 years. Indeed, the PPV of bleeding increases with age, as a result of the observed parallel decrease in the prevalence of bleeding [5] and of the increase in the risk of CRC [14,37]. Given the higher prevalence of right-sided neoplasms in this age group [37], visualisation of the entire colon in these patients is recommended.

Acknowledgements

The SCORE trial was supported by grants from the Italian Association for Cancer Research (AIRC), the Italian National Research Council (CNR—grant, no. 95.00539.PF39; no. 96.00736.PF39) and the Istituto Oncologico Romagnolo (Rimini). SOFAR s.p.a. provided the enema supply for the patients enrolled in the study.

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