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Simulated performance of flexible sigmoidoscopy-based screening for advanced neoplasia detection in a Greek population

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Abstract

Background Flexible sigmoidoscopy (FS) is resource-conserving and may increase adherence to colorectal cancer (CRC) screening compared to total colonoscopy. We investigated the diagnostic performance of FS-based screening for advanced colorectal neoplasia (ACN), including advanced adenomatous neoplasms (AANs), advanced serrated lesions (ASLs) and CRCs.

Methods Data from 2005 subjects undergoing average-risk screening colonoscopy in a single center in Greece were retrospectively reviewed. Sensitivities of FS-based screening for detecting AANs, ASLs, CRCs or any ACN were simulated on a per-lesion basis, assuming: 1) FS up to the sigmoid-descending junction (FS-1) or splenic flexure (FS-2); 2) colonoscopy referral criteria according to the 4 screening FS trials conducted in UK, Italy, Norway, and USA.

Results Overall, 114 ACNs (93 AANs, 17 ASLs, 4 CRCs) were detected in 102 (5.1%) subjects. The overall sensitivities of FS-1 and FS-2 alone for the detection of any ACN were 41.2% and 54.4%, respectively. Assuming different colonoscopy referral criteria, the estimated sensitivities for any ACN ranged from 48.2-50.9% for FS-1 and 60.5-64% for FS-2. The overall sensitivities were lower for ASLs (FS-1: 35.3-41.2%, FS-2: 41.2-52.9%) compared to those observed for AANs (FS-1: 48.4-51.6%, FS-2: 62.4-66.7%). The difference was particularly pronounced in women, in whom all 4 criteria led equally to a very low sensitivity for ASLs (30%).

Conclusions Implementation of FS-based screening in Greek subjects would have led to the detection of 48-64% of all ACNs. An alarmingly low detection of ASLs among women may call for gender-specific colonoscopy referral strategies.

Keywords Colorectal cancer, screening, flexible sigmoidoscopy, Greece

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Introduction

Colorectal cancer (CRC) is a worldwide public health concern with 1.4 million new cases and approximately 700,000 deaths/year, although CRC is largely preventable [1,2]. Over the past decades, several screening methods have been developed, aiming to detect and/or remove CRC precursor lesions [3,4]. These include direct endoscopic—colonoscopy and flexible sigmoidoscopy (FS)—or radiologic (e.g., computed tomography colonography) procedures and stool-based tests, including the fecal occult blood test and fecal immunochemical test (FIT). Despite a lack of randomized comparisons, colonoscopy is often referred to as the CRC screening "gold standard", because it has the potential to examine the whole colon and can remove precancerous lesions immediately [5]. However, several drawbacks may undermine its use as a primary screening test: it is expensive, it is invasive and can be uncomfortable to patients, and it has the potential for complications [6].

FS is a resource-conserving option, as it is less invasive and costly, it requires less bowel preparation and can be even performed without sedation by non-medical personnel. However, FS itself can only detect neoplasms in the rectum and sigmoid and, if possible, as far as the splenic flexure. To partly overcome this limitation, individuals with pathological

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distal findings are referred for colonoscopy, because they might be at risk for significant proximal pathology. To date, 4 large randomized trials (3 in Europe and 1 in the USA) determined that FS-based screening reduces CRC incidence and mortality [7-10]. Nevertheless, a mixture of different criteria were used to refer patients for colonoscopy, accounting for potential variations in the number of colonoscopies needed and the detection of proximal neoplasms. Furthermore, racial/ethnic disparities in the epidemiology of CRC may limit the generalizability of these findings to other countries, or even within a single country, while the benefit of CRC screening may not be uniformly distributed (e.g., between sexes). Last but not least, only conventional adenomas were considered, as these trials were mostly designed at a time when it was thought that the great majority of CRCs arose via the chromosomal instability pathway. However, nearly one third of CRCs are nowadays recognized to arise via serrated precursor lesions, which are challenging to detect and are predominantly located in the proximal colon [11,12].

Greece is a financially constrained country with a relatively limited endoscopic capacity. In this country, colonoscopy screening is currently commenced at age 50 years with 10-yearly procedures. As there is no organized national screening program, colonoscopy screening is offered opportunistically, depending on requests from individuals or their health advisors. In a recent survey, the proportion of Greek healthy subjects aged 50-75 years who had undergone screening colonoscopy was disappointingly low (6.2%) [13], falling short of the >65% judged desirable by the European commission [14,15]. Thus, alternative policies, ideally in form of a government subsidized program, are urgently needed to increase the uptake of CRC screening in Greece. To this end, FS may be a reasonable option, since it is less resource-challenging and may achieve higher acceptance rates compared to total colonoscopy [15].

Using colonoscopy findings in a Greek population, we simulated the diagnostic performance of FS-based screening for advanced colorectal neoplasia (ACN) in men and women. For this purpose, we considered both advanced adenomatous and serrated lesions. Furthermore, we analyzed 4 different sets of colonoscopy referral criteria, proposed in 4 large randomized trials of screening FS conducted in the UK [7], Italy [10], Norway [8], and the USA [9].

Patients and methods

Study design and study population

This was a cross-sectional study conducted at the Endoscopy Unit of the "Konstantopoulio-Patision" General Hospital of Nea Ionia, Athens, Greece. The study protocol was in accordance with the principles of the Declaration of Helsinki and was approved by the local ethics committee. A prospectively-stored electronic database was retrospectively reviewed for all consecutive subjects ≥50 years old who underwent an average-risk screening colonoscopy between January 2014 and June 2018. The endoscopic database contains information regarding the indication for colonoscopy, patient demographics, and the number, location, size and shape of polyps. Data concerning the histology of all resected polyp specimens was obtained by retrospectively reviewing the pathology reports. Histopathological diagnoses were performed by 2 experienced pathologists, relying on the criteria of the World Health Organization [16]. Patients undergoing colonoscopy for an indication other than "screening" (evaluation of symptoms or occult bleeding, inflammatory bowel disease, hereditary polyposis or surveillance colonoscopy after polypectomy or CRC resection) were excluded (n=2618). To minimize the chance of missed neoplasms, we also excluded subjects with an incomplete colonoscopy (cecum not reached; n=169) or those with complete procedures in whom the bowel preparation was considered to be "inadequate" by the endoscopist (n=317). Finally, a total of 2005 participants were retained for the analyses.

Procedures and definitions

All procedures were performed by gastroenterologists from our department, all of whom generally perform >250 colonoscopies per year. Bowel preparation involved patients drinking a standard 4 L polyethylene glycol solution. Conscious sedation was provided in all the colonoscopies, using midazolam 1-5 mg, alone or in combination with fentanyl 25-50 μg. Cecal intubation was verified by identification of the appendiceal orifice and the ileocecal valve. The size of the polyps was estimated either with the use of open biopsy forceps or on the basis of clinical judgement. Diminutive, hyperplastic-appearing lesions from the rectosigmoid were not systematically removed, particularly in subjects with numerous such lesions.

Advanced adenomatous neoplasia (AAN) was defined as conventional adenoma with at least one of the following features: size ≥1 cm, tubulovillous or villous components, and high grade dysplasia. An advanced serrated lesion (ASL) was defined as a sessile serrated adenoma/polyp ≥1 cm and/or with cytological dysplasia, or traditional serrated adenoma. The term ACN was applied to any advanced lesion, grouping together AANs, ASLs, and invasive CRC. The histopathological findings were categorized according to the most advanced lesion, in the following order: no findings, hyperplastic polyps, non-advanced conventional adenomas/serrated lesions, and ACN. Lipomas, lymphoid aggregates, chronic nonspecific inflammation and inflammatory or juvenile polyps were categorized as "no findings".

Statistical analysis

Two definitions of FS were analyzed: up to the sigmoid-descending junction (FS-1) or the splenic flexure (FS-2). Overall sensitivities for detecting AANs, ASLs, CRCs or any ACN were estimated on a per-lesion basis, assuming that FS would detect the same neoplasms as colonoscopy within its

reach. Diagnostic performances of FS-based screening were investigated according to the colonoscopy referral criteria proposed in the 4 FS screening trials (Table 1). Sensitivities were calculated as the number of lesions correctly identified by FS itself or colonoscopy referral divided by the total number of such lesions detected during colonoscopy. Results were reported for the entire study population and stratified by sex. The number of colonoscopies needed according to each of the referral criteria was also derived.

Results were expressed as mean and standard deviation (SD) for continuous variables or as percentages for categorical data. For sensitivities, 95% confidence intervals (CI) were calculated using the adjusted Wald method [17]. Analyses were performed using SPSS version 24 for Macintosh (IBM, SPSS, Chicago, IL, USA).

Results

Study population

The study cohort comprised 2005 average-risk subjects (mean age: 61.9±8.1 years), of whom 1147 (57.2%) were female. Overall, 229 (11.4%) had non-advanced adenomas and/or non-advanced serrated lesions as the most advanced finding at screening colonoscopy, and 102 (5.1%) had ACNs including 4 (0.2%) patients with invasive CRC (Table 2). The subcategories of patients with ACNs detected in the study are listed in Table 3. There were 91 (4.5%) patients with a single ACN (AAN: n=76, ASL: n=12, CRC: n=3), whereas 11 (0.6%) patients had 2 or more synchronous ACNs. In total, 114 ACNs were detected, comprising 93 AANs, 17 ASLs, and 4 CRCs.

Table 1 Colonoscopy referral criteria proposed in 4 large randomized trials of screening flexible sigmoidoscopy (FS)

Trial/Country [Ref]	Colonoscopy referral criteria
UK FS screening trial/UK [7]	CRC, one distal polyp or adenoma >1 cm, (tubulo)villous histology, HGD, ≥3 adenomas or ≥20 hyperplastic polyps above the rectum
SCORE/Italy [10]	Distal polyp(s) >5 mm, (tubulo) villous histology, HGD, ≥3 adenomas or CRC
NORCCAP/Norway [8]	CRC, one distal polyp ≥1 cm or any adenoma
PLCO trial/USA [9]	Score ≥4 [age (50-54: 0, 55-59: 1, 60-64: 2, 65-70: 3) + sex (female: 0, male: 1) + most advanced distal finding (no polyps: 0, hyperplastic: 1, tubular adenoma <10 mm: 2, advanced lesion (tubular adenoma ≥10 mm, villous histology, HGD, CRC): 3)]

SCORE, screening for colon rectum; NORCCAP, Norwegian colorectal cancer prevention; PLCO, prostate, lung, colorectal and ovarian cancer; HGD, high-grade dysplasia; CRC, colorectal cancer

Diagnostic performance of FS alone

The estimated diagnostic performances of FS without any colonoscopy referral are summarized in Table 4. The overall sensitivity of FS-1 for the detection of any ACN was 41.2% (95%CI 32.6-50.4%), estimated as 40.4% (95%CI 27.6-54.5%) in women and 41.8% (95%CI 30.7-53.7%) in men. Consistently higher sensitivities were observed for FS-2 compared to FS-1. The overall FS-2 sensitivity for any ACN was estimated as 54.4% (95%CI 45.2-63.2%); 57.4% (95%CI 43.3-70.5%) in women and 52.2% (95%CI 40.5-63.7%) in men. The overall sensitivities for ASLs (FS-1: 23.5%; FS-2: 29.4%) were consistently lower than the respective sensitivities observed for AANs (FS-1: 43%; FS-2: 57%). The vast majority of ASLs (12/17; 70.6%) were indeed located proximal to the splenic flexure, thus would be expected to be missed by FS. In subanalyses according to sex, the sensitivity of FS for ASLs appeared to be particularly low among women (20% for both FS-1 and FS-2). Finally, 3/4 and 4/4 cases of invasive CRC (all detected in men) were located within the reach of FS-1 and FS-2, respectively.

Diagnostic performance of FS with colonoscopy referral

A steady increase in the overall sensitivities of approximately 6-10 percentage points was observed when assuming FS with colonoscopy referral (Table 5). According to the different colonoscopy referral criteria, the overall sensitivity of FS-1-based screening ranged between 48.2-50.9%, whereas the overall sensitivity of FS-2-based screening was consistently higher, ranging between 60.5% and 64%. Up to 62.5% of AANs would have been detected in men and 73% in women, assuming FS-2 followed by colonoscopy referral. For ASLs, the sensitivities of FS-based screening appeared to differ substantially between sexes. In men, up to 57.1% (4/7) and 85.7% (6/7) of ASLs would have been detected assuming FS-1 and FS-2, respectively, followed by colonoscopy referral. The rate among women was 30% (3/10) for both FS-1 and FS-2, showing no change when assuming different colonoscopy referral criteria. More specifically, all 4 colonoscopy referral criteria equally led to the additional detection of only 1 of 8 proximal (i.e., FS-unreachable) ASLs among women, indicating a poor association between distal findings and proximal ASL.

Discussion

This is the first study to simulate the performance of once-only FS-based screening for the detection of advanced colorectal neoplasia, assuming different colonoscopy referral criteria, in a Greek CRC screening population. Without colonoscopy referral, FS would detect 40.4% (FS-1) to 57.4% (FS-2) of all ACNs in women and 41.8% (FS-1) to 52.2% (FS-2) in men. At its best, an FS-based screening strategy with FS up to the splenic flexure followed by colonoscopy according to the less restrictive US (PLCO) criteria would detect 63.8% of all

Table 2 Characteristics of the study population according to age and most advanced finding at screening colonoscopy

Characteristic	Total (n=2005)		Men (n=858)		Women (n=1147)	
	n	%	n	%	n	%
Age (years)						
50-59	838	41.8	320	37.3	518	45.2
60-69	772	38.5	340	39.6	432	37.7
≥70	395	19.7	198	23.1	197	17.2
Most advanced finding at screening colonoscopy						
No findings	1533	76.5	611	71.2	922	80.4
HP	141	7	75	8.7	66	5.6
Non-advanced adenoma and/or non-advanced serrated lesion	229	11.4	112	13	117	10.2
Non-advanced adenoma	207	10.3	104	12.1	103	9
Non-advanced serrated	16	0.8	6	0.7	10	0.9
Non-advanced adenoma+non-advanced serrated	6	0.3	2	0.2	4	0.3
ACN	102	5.1	60	7	42	3.7
AAN	83	4.1	50	5.8	33	2.9
ASL	13	0.6	5	0.6	8	0.7
AAN+ASL	2	0.1	1	0.1	1	0.09
AAN+cancer	1	0.05	1	0.1	0	0
Cancer	3	0.1	3	0.3	0	0

HP, hyperplastic polyps; ACN, advanced colorectal neoplasia; AAN, advanced conventional adenomatous neoplasia; ASL, advanced serrated lesion

Table 3 Subcategories of patients with advanced colorectal neoplasia

76 patients with a single AAN
7 patients with 2 AANs
12 patients with a single ASL
1 patient with 2 ASLs
1 patient with 1 AAN and 1 ASL
1 patient with 1 AAN and 2 ASLs
1 patient with 1 AAN and a synchronous invasive CRC
3 patients with invasive CRC

AAN, advanced conventional adenomatous neoplasia; ASL, advanced serrated lesion, CRC, colorectal cancer

ACNs in women and 64.2% in men (overall sensitivity: 64%). However, under this assumption, a substantial proportion (187/2005; 9.1%) of the study subjects would undergo colonoscopy. Interestingly, by using the most restrictive UK criteria the overall sensitivity of FS-2-based screening would be only slightly decreased (60.5%), although at a much lower colonoscopy referral rate (56/2005; 2.8%). These data appear to favor the use of the more restrictive UK criteria for FS-based CRC screening in the Greek population. Accordingly, in a *post-hoc* analysis of a Spanish trial (COLONPREV study), the UK criteria appeared to be more resource-saving compared to the less stringent NORCCAP and SCORE criteria, benefiting from lower colonoscopy referral rates and higher specificity for proximal ACN [18]. Three other comparative studies of existing FS-based colonoscopy referral strategies also confirmed that the UK criteria achieve the best specificity and lowest number of subjects needed to refer for colonoscopy [19-21].

Few earlier studies evaluated the diagnostic performance of FS-based CRC screening with different colonoscopy referral criteria using datasets of patients who had undergone colonoscopy [19-22]. The reported prevalence of ACN ranged between 3.3% and 6.3%, including 0.4-1.4% of CRCs, consistent with the respective rates (ACN: 5.1%, CRC: 0.2%) observed in the current study. In a German study, 62% of AANs in men and 59% in women would be detected by FS visualizing the sigmoid and rectum [20]. Assuming colonoscopy referral, a gradual increase in sensitivities was observed by applying gradually less restrictive referral criteria, reaching a highest overall sensitivity of 85% with the US-PLCO criteria. Interestingly, in the German study, as in 2 Asian studies [19,21], sex-specific differences have been reported in terms of diagnostic performance, outlining higher sensitivities in men than in women. Sex differences in sensitivity were approximately 7-10% within the UK, NORCCAP and SCORE criteria in the German study, whereas they were more pronounced (approximately 20%) for the US-PLCO criteria. However, as regards AANs, we could not confirm a lower sensitivity of FS in women compared to men. On the contrary, an opposite numerical trend was observed. For instance, at its upper end, FS-2 followed by colonoscopy would detect 73% of AANs in women compared to 62.5% in men. Obviously, comparisons should be interpreted cautiously, as potential ethnic/racial background differences and age imbalances may have affected the reported sensitivities. A unique contribution of the present study is that we analyzed

Table 4 Estimated sensitivities of FS for advanced colorectal neoplasia in the total population and stratified by sex

Sex	FS-1		FS-2	
	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [%(95%CI)]
Total				
AAN (n=93)	40	43 (33.4-53.2)	53	57(46.8-66.6)
ASL (n=17)	4	23.5 (9.1-47.8)	5	29.4 (13-53.4)
Cancer (n=4)	3	75 (29.8-96.6)	4	100 (45.2-100)
ACN (n=114)	47	41.2 (32.6-50.4)	62	54.4 (45.2-63.2)
Men				
AAN (n=56)	23	41.1 (29.2-54.1)	28	50 (37.3-62.7)
ASL (n=7)	2	28.6 (7.6-64.8)	3	42.9 (15.8-75)
Cancer (n=4)	s3	75 (29.8-96.6)	4	100 (45.2-100)
ACN (n=67)	28	41.8 (30.7-53.7)	35	52.2 (40.5-63.7)
Women				
AAN (n=37)	17	45.9 (31-61.6)	25	67.6 (51.4-80.4)
ASL (n=10)	2	20 (4.6-52.1)	2	20 (4.6-52.1)
Cancer (n=0)	-	-	-	-
ACN (n=47)	19	40.4 (27.6-54.5)	27	57.4 (43.3-70.5)

AAN, advanced conventional adenomatous neoplasia; ASL, advanced serrated lesion; ACN, advanced colorectal neoplasia

a broader definition of ACN, allowing for distinct evaluation of the predictive performances of FS-based screening for AANs and ASLs. Our data suggest that the ability of FS-based screening to detect ASLs is lower compared to its ability to detect AANs. This was valid for both sexes; however, the difference was particularly pronounced in women, in whom all 4 criteria equally led to a particularly low sensitivity for ASLs (30%). In a *post-hoc* analysis of the ColonPrev study, the authors evaluated the diagnostic performance of FS visualizing the rectosigmoid followed by colonoscopy (UK referral criteria), focusing on detection of proximal serrated neoplasms [23]. In keeping with our findings, they determined that such a strategy would have detected 86% fewer individuals with proximal serrated polyps compared to total colonoscopy (odds ratio 0.13, 95%CI 0.10-0.18), with the performance being particularly low among women. Strikingly, only 6/131 women with proximal serrated polyps and none of 29 women with at-risk proximal serrated polyps would have been identified by FS-based screening. Apparently, these findings could largely explain the contrasting evidence arising from FS screening trials. Indeed, in a pooled analysis of the PLCO, SCORE and NORCCAP trials, the incidence of proximal CRCs was significantly reduced in men but not in women (27% vs. 9%, respectively) [24]. Moreover, the extended follow up, through a median of 17 years, of the UK Flexible Sigmoidoscopy Trial determined a 56% reduction in the incidence of distal CRCs, but only a 5% nonsignificant effect on proximal CRC incidence [25]. In support of this notion, epidemiological studies have shown a rightward shift in the distribution of CRCs over time, with patients having fewer distal but more proximal colorectal neoplasms [26,27]. Moreover, a cross-sectional study of 1910 individuals conducted in the USA showed that only 48% of average-risk subjects ≥50 years old with proximal ASLs had concurrent distal polyps [28]. Thus, to the extent that detection of proximal ASLs is important to CRC prevention, these data may call into question the use of primary FS screening, outlining a dramatically low performance in detecting these lesions, particularly in women. Nevertheless, It should be emphasized that even total colonoscopy appears to offer imperfect protection against right-sided CRC; this is at least partly attributable to failed detection and/or inadequate resection of serrated lesions [29,30].

The present study is not free of limitations. Firstly, the histological diagnoses in this study were not centrally reviewed, leaving open the possibility of incorrect assessments of the nature and distribution of resected neoplasms. This applies particularly to serrated lesions, as the pathological features required to diagnose these lesions vary among guidelines and may be subject to significant interobserver disagreement [31]. Moreover, the definition we used for ASLs was arbitrary and was based on current recommendations for more intense surveillance after resection of serrated lesions ≥10 mm or with dysplasia [32,33]; clearly, this definition has not yet been supported by such robust evidence as exists for AANs. Secondly, by design, the present retrospective simulation might not accurately reflect the real-life performance of FS-based screening. Indeed, reaching the splenic flexure (FS-2) may not be feasible in a substantial proportion of patients undergoing FS in practice, because of inadequate enema preparation (vs. oral bowel cleansing administered for colonoscopy) and the absence of intravenous sedation. According to our data, limiting the insertion depth of FS to the sigmoid-descending

Table 5 Estimated sensitivities of flexible sigmoidoscopy-based screening for advanced colorectal neoplasia assuming different colonoscopy referral criteria in the total population and stratified by sex

	UK criteria [6]				Source criteria [9]				NORCCAP criteria [9]				PLCO criteria [8]			
	F S-1		F S-2		F S-1		F S-2		F S-1		F S-2		F S-1		F S-2	
No. colonoscopies	42		56		99		127		131		174		157		187	
	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]	N detected	Sensitivity [% (95%CI)]
Total																
AAN (n=93)	45	48.4 (38.5-58.4)	58	62.4 (52.2-71.6)	46	49.5 (39.5-59.4)	59	63.4 (53.3-72.5)	47	50.5 (40.6-60.5)	61	65.6 (55.5-74.5)	48	51.6 (41.6-61.5)	62	66.7 (56.6-75.4)
ASL (n=17)	6	35.3 (17.2-58.8)	7	41.2 (21.6-64.1)	7	41.2 (21.6-64.1)	9	52.9 (31-73.8)	6	35.3 (17.2-58.8)	8	47.1 (26.2-69)	6	35.3 (17.2-58.8)	7	41.2 (21.6-64.1)
Cancer (n=4)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)
ACN (n=114)	55	48.2 (39.3-57.3)	69	60.5 (51.3-69)	57	50 (41-59)	72	63.2 (54-71.5)	57	50 (41-59)	73	64 (54.9-72.3)	58	50.9 (41.8-59.9)	73	64 (54.9-72.3)
Men																
AAN (n=56)	26	46.4 (34-59.3)	31	55.4 (42.4-67.6)	27	48.2 (35.7-61)	32	57.1 (44.1-69.2)	28	50 (37.3-62.7)	34	60.7 (47.6-72.4)	29	51.8 (39-64.3)	35	62.5 (49.4-74)
ASL (n=7)	3	42.8 (15.8-75)	4	57.1 (25-84.2)	4	57.1 (25-84.2)	6	85.7 (46.6-99.5)	3	42.8 (15.8-75)	5	71.4 (35.2-92.4)	3	42.8 (15.8-75)	4	57.1 (25-84.2)
Cancer (n=4)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)	4	100 (45.4-100)
ACN (n=67)	33	49.2 (37.6-60.9)	39	58.2 (46.2-69.3)	35	52.2 (40.5-63.7)	42	62.7 (50.7-73.3)	35	52.2 (40.5-63.7)	43	64.2 (52.3-74.6)	36	53.7 (41.9-65.1)	43	64.2 (52.3-74.6)
Women																
AAN (n=37)	19	51.3 (35.9-66.5)	27	73 (56.9-84.8)	19	51.3 (35.9-66.5)	27	73 (56.9-84.8)	19	51.3 (35.9-66.5)	27	73 (56.9-84.8)	19	51.3 (35.9-66.5)	27	73 (56.9-84.8)
ASL (n=10)	3	30 (10.3-60.8)	3	30 (10.3-60.8)	3	30 (10.3-60.8)	3	30 (10.3-60.8)	3	30 (10.3-60.8)	3	30 (10.3-60.8)	3	30 (10.3-60.8)	3	30 (10.3-60.8)
Cancer (n=0)	0	-	0	-	0	-	0	-	0	-	0	-	0	-	0	-
ACN (n=47)	22	46.8 (33.3-60.8)	30	63.8 (49.5-76.1)	22	46.8 (33.3-60.8)	30	63.8 (49.5-76.1)	22	46.8 (33.3-60.8)	30	63.8 (49.5-76.1)	22	46.8 (33.3-60.8)	30	63.8 (49.5-76.1)

AAN, advanced adenomatous neoplasia; ASL, advanced serrated lesion; ACN, advanced colorectal neoplasia

Summary Box

What is already known:

- Flexible sigmoidoscopy (FS) is a resource-conserving screening option compared to total colonoscopy, as it is less invasive and costly
- To date, 4 randomized controlled trials conducted in UK, Italy, Norway and the USA determined that once-only FS-based screening reduces the incidence and mortality of colorectal cancer
- However, different criteria were used to refer patients for colonoscopy, exclusively focusing on conventional adenomas

What the new findings are:

- Assuming different colonoscopy referral criteria, implementation of once-only FS-based screening in Greek subjects would have led to the detection of 48-64% of all advanced colorectal neoplasms
- The overall sensitivities of FS-based screening for advanced serrated lesions are lower compared to those for advanced conventional adenomas
- An alarmingly low (30%) detection of advanced serrated lesions in women may call for sex-specific colonoscopy referral strategies

junction (FS-1) would diminish the overall sensitivity of FS-based screening by approximately 12-13 percentage points. Thirdly, the overall detection rate of adenomas in this study was apparently low, falling short of the recommended 25% threshold [34]. This could potentially be attributed to a variety of factors, including a demographic mix predominantly comprising younger (50-59 years) women, exclusive use of standard-definition colonoscopes in years 2014-2016, and the inclusion of procedures with suboptimal bowel preparation, as we did not use a validated scale to rate colonic cleanliness. Moreover, although all of the study subjects appeared to be screening-naïve based on our endoscopy records, a prior history of colonoscopy with polyp removal performed at another institution cannot be precluded. Fourthly, although we extensively analyzed data with respect to sex, depth of FS insertion and colonoscopy referral criteria, the relatively small number of "events" prevented us from undertaking age analyses; thus, important age-specific associations may have been missed. Lastly, our study did not primarily aim to compare the differential impact of colonoscopy referral criteria; thus, relevant subanalyses, such as the calculation of the number of colonoscopies needed to detect one proximal ACN, were not performed.

In conclusion, this is the first study to simulate the diagnostic performance of FS-based screening using a relatively large, hospital-based, dataset of Greek subjects who had undergone screening colonoscopy. In the light of our findings, implementation of FS-based screening in the Greek population would have led to the detection of 48-64% of all ACNs. Interestingly, the sensitivities for ASLs appear to be lower compared to those observed for AANs, and this difference appears to be influenced by sex. Detection of ASLs was indeed found to be lowest among women (only 30%), indicating that sex-specific colonoscopy referral strategies may be warranted to enhance the sensitivity of FS-based screening. Obviously, colonoscopy identifies more advanced proximal neoplasia than all other tests, although at a cost of a large number of negative exams, which are expensive, inconvenient, and entail a small, but not insignificant, risk of complications. To this end, combining less resource-challenging and less invasive tests (e.g., FS and FIT, both insufficiently effective when used alone [22,35]) may be worthwhile in order to increase the detectability of proximal advanced neoplasia, save resources, and optimize adherence to screening. Future comparative studies with cost-effectiveness analyses are awaited to establish the optimal approach to organized CRC screening in Greece.

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