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ORIGINAL ARTICLE

Full-spectrum (FUSE) versus standard forward-viewing colonoscopy in an organised colorectal cancer screening programme

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ABSTRACT

Objective Miss rate of polyps has been shown to be substantially lower with full-spectrum endoscopy (FUSE) compared with standard forward-viewing (SFV) colonoscopy in a tandem study at per polyp analysis. However, there is uncertainty on whether FUSE is also associated with a higher detection rate of colorectal neoplasia, especially advanced lesions, in per patient analysis.

Methods Consecutive subjects undergoing colonoscopy following a positive faecal immunochemical test (FIT) by experienced endoscopists and performed in the context of a regional colorectal cancer population-screening programme were randomised between colonoscopy with either FUSE or SFV colonoscopy in seven Italian centres. Randomisation was stratified by gender, age group and screening history. Primary outcomes included detection rates of advanced adenomas (A-ADR), adenomas (ADR) and sessile-serrated polyps (SSPDR).

Results Of 741 eligible subjects, 658 were randomised to either FUSE (n=328) or SFV (n=330) colonoscopy and included in the analysis. Overall, 293/658 and 143/658 subjects had at least one adenoma (ADR 44.5%) and advanced adenoma (A-ADR 21.7%), respectively, while SSP was the most advanced lesion in 18 cases (SSPDR 2.7%). ADR and A-ADR were 43.6% and 19.5% in the FUSE arm, and 45.5% and 23.9% in the SFV arm, with no difference for both ADR (OR for FUSE: 0.96, 95% CI 0.81 to 1.14) and A-ADR (OR for FUSE: 0.82, 95% CI 0.61 to 1.09). No difference in SSPDR or multiplicity was detected between the two arms. In the per polyp analysis, the mean number of adenomas and proximal adenomas per patient was 0.81±1.25 and 0.47±0.93 in the FUSE arm, and 0.85±1.33 and 0.48 ±0.96 in the SFV colonoscopy arm (p=NS for both comparisons).

Conclusions No statistically significant difference in ADR and A-ADR between FUSE and SFV colonoscopy was detected in a per patient analysis in FIT-positive patients.

Trial registration number ISRCTN10357435.

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Significance of this study

What is already known on this subject?

- Miss rate of neoplasia at colonoscopy is a relevant cause of postcolonoscopy interval cancer.
- (Advanced-)Adenoma detection rate represents a proxy for such miss rate, and it has also been related with interval cancer.
- Full-spectrum endoscopy (FUSE) is a technological innovation enlarging the field of view up to 330°. In a tandem study, such technology has been shown to significantly reduce the polyp miss rate.

What are the new findings?

- In this randomised trial, the use of FUSE did not increase the proportion of subjects with at least one adenoma and one advanced adenoma compared with standard forward-viewing endoscopy.
- Similarly, the number of adenomas and advanced adenomas per subject was not increased in a per polyp analysis.

How might it impact on clinical practice in the foreseeable future?

- Standard colonoscopy and FUSE in faecal immunochemical test-positive subjects showed a similar performance in adenoma as well as in advanced adenoma detection.

INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality.[1 2] CRC screening with biannual faecal immunochemical test (FIT) has been shown to reduce CRC mortality and incidence,[3 4] and population-based organised screening programmes based on FIT have already been implemented in Italy and the Netherlands.[5]

Colonoscopy represents the most accurate test for the detection of colorectal neoplasia, and it is recommended in FIT-positive subjects who are at high risk of advanced neoplasia (AN) and invasive cancer. However, the accuracy of colonoscopy is still suboptimal.[6] A substantial adenoma miss rate of 20–26% for any adenoma and of 2.1% for large

adenomas has been reported in a systematic review of tandem colonoscopy studies,[7] although it may have been recently lowered due to improved colonoscopy quality.

According to computerised simulation models of colonoscopy, adenomas are more likely to be missed when located behind folds, at flexures, or low in the rectum, and such miss rate may be minimised by increasing the optical field of view.[8–10] By adding two lateral lenses to the tip of the scope, full-spectrum endoscopy (FUSE) increases the maximum field of view by nearly twofold, from the previously ≤170° reported with standard forward-viewing (SFV) colonoscopy to 330° with FUSE colonoscopy. In an artificial model, higher detection rates of simulated polyps with FUSE compared with SFV were shown.[11] After a pilot study in human subjects,[12] a randomised back-to-back comparative study showed that there were significantly more adenomas detected (69% additional adenomas) and a lower adenoma miss rate (FUSE 7% vs SFV 41%, p<0.0001) with FUSE.[13] According to a simulation model, this miss rate reduction results in a substantial increase in the efficacy of primary colonoscopy screening that appears also cost-saving due to the simulated decrease in the CRC-associated costs.[14]

Back-to-back studies—which are based on the cumulative detection of two subsequent colonoscopies—represent an artificial deviation from clinical practice, generating uncertainty on the clinical relevance of the estimated miss rate. A more clinically orientated proxy for colonoscopy miss rate is represented by the adenoma detection rate (ADR). A suboptimal ADR is directly associated with an increased risk of postcolonoscopy interval cancer and its mortality.[15–20]

The primary aim of this randomised study was to evaluate whether—in the context of a population-based organised CRC screening programme—the use of FUSE colonoscopy increases the detection rate (DR) of any adenoma and advanced adenomas compared with SFV colonoscopy.

METHODS

We designed a parallel randomised controlled trial, conducted in seven endoscopy centres in northern and central Italy participating in the organised population CRC screening programme. The trial was registered on the International Standard Randomised Controlled Trials Number (ISRCTN) database (ISRCTN 10357435).

CRC organised screening programme in Italy

The organised screening programme with FIT in Italy is performed at a regional level. Screening centres in each region are responsible for inviting eligible subjects. Most regional programmes invite people aged 50–69 years to perform a single-sample FIT on a biennial basis. General practitioners are asked to exclude from invitation in the screening programme subjects with a recent (within 5 years) colonoscopy, a personal history of CRC, adenomas or IBD, severe comorbidity, including end-stage cardiovascular, pulmonary, liver or renal disease. Individuals with a positive result (cut-off=20 μg Hb/g faeces) are contacted by phone by the screening centre and they are offered an appointment date for a colonoscopy. All subjects accepting the invitation for colonoscopy are requested to visit the screening centre to receive the bowel preparation.

Study population

The target population included consecutive patients aged 50–69 undergoing their first colonoscopy following a positive FIT performed in the context of a regional mass screening programme. We excluded from the study (i) patients with previous colonic resection; (ii) patients on antithrombotic therapy, precluding polyp resection; (iii) patients at risk for inhalation; and (iv) patients who were not able to or refused to give informed written consent. These additional eligibility criteria were assessed at the time of subject's visit at the screening centre.

Randomisation

FIT-positive subjects were randomised within screening centre and endoscopist to undergo colonoscopy with either FUSE or SFV based on a computer-generated randomised blocks sequence. Randomisation was stratified by gender, age (50–59, 60–69 years) and screening history (first vs subsequent test). Only after entering in the online centralised study database the characteristics of each enrolled patient the endoscopist could visualise the randomisation arm assigned to that patient (ie, the technique to be used for that specific exam). As the characteristics of subjects undergoing screening could be expected to vary across participating centres, as a result of the local organisational constraints (number of previous rounds, age groups targeted during the study period), we planned to have a pre-fixed number of subjects in each randomisation stratum in each centre to ensure a balanced distribution of screenees' characteristics. After having achieved the maximum planned number of subjects in a specific stratum, no additional subject meeting those criteria in that centre could be enrolled in the study, even if eligible.

Examination procedure

Experienced endoscopists (>5000 standard colonoscopies and ≥10 FUSE colonoscopies within the previous 6 months) participated in the study. A centralised 1-day FUSE retraining was conducted before starting recruitment, involving one endoscopist from each participating centre. The retraining included a 2 hour presentation of the FUSE technology and of the examination technique with FUSE colonoscopy by a FUSE expert participating in the previous validation and tandem studies,[12 13] followed by a hands-on session: each endoscopist performed two FUSE examinations under supervision of the FUSE expert (PS). In addition, participating endoscopists in each centre were required to perform routine examinations with FUSE over a period of at least two days before starting recruitment. In order to reduce operator-related variability, only two endoscopists in each centre were involved in the study. Each endoscopist was required to perform a minimum of 25 examinations in each arm (i.e. at least 50 examinations in the study). For study procedures, in the SFV arm, each centre was allowed to use the same scope that would have been used in daily clinical practice (online supplementary appendix 1), while FUSE (FUSE EndoChoice, Alpharetta, Georgia, USA) was used for the FUSE arm. No chromoendoscopy or light-modification technologies for polyp detection were allowed. Four-litre polyethylene glycol bowel preparation in split regimen and at least one day of low fibre diet was used; procedures were performed after 10:00 a.m. to favour the split regimen. Bowel preparation was evaluated and graded according to the Boston Bowel Preparation scale.[21] The endoscopist and facility staff used their standard procedures for subject management and monitoring, including use of conscious sedation according to endoscopist's and patient's preferences. The success of caecal intubation was assessed by the endoscopist by the identification of the ileocecal valve and the appendix orifice via photo documentation. According to the study protocol, all polyps were removed irrespective of size, colour or subjective interpretation, with the possible exception of very small (1–5 mm) polyps located in the rectum and—according to the judgement of the endoscopists—not clinically significant. Polyps

were classified according to their size, location and morphology (pedunculated, sessile and non-polypoid). Non-polypoid (flat and depressed) lesions were defined as lesions endoscopically high less than half wide, according to Paris classification. Location was considered proximal if proximal to the splenic flexure. Pathologist's measure, when available, was considered the reference standard, while endoscopist's measure was used in the remaining cases (ie, piecemeal resection). Endoscopists were required to be compliant with a minimum of 6 min for the withdrawal time. Withdrawal time was recorded by a member of the research staff, or by an endoscopy nurse, using a stopwatch. Only negative examinations were considered when comparing the mean withdrawal time in the two arms.

Histopathology

All resected lesions, either by forceps or snare, were sent to pathology in separated jars and were processed and stained for histopathology using standard methods and evaluated by expert pathologists (one in each centre) according to the Vienna criteria. All lesions were classified as inflammatory/normal mucosa, or adenoma, or serrated (hyperplastic, sessile-serrated polyp (SSP), traditional-serrated adenoma (TSA)). An advanced adenoma was defined as an adenoma ≥10 mm and/or with villous component >20%, and/or high-grade dysplasia.[22] Pathologists were blinded to the endoscopic technique.

Sample size and statistical analysis

Based on the observed prevalence of adenomas (40%), advanced adenomas (25%) and non-polypoid lesions (4%) among patients with a positive FIT in the regional screening programme, a sample size of 300 subjects per arm could allow for a 80% power to detect as statistical significant ($\alpha=0.05$; two-sided test) a 11.5%, 10.5% and 6% absolute increase in the detection rate of adenomas, advanced adenomas and non-polypoid lesions respectively in the FUSE arm. Assuming superiority of FUSE compared with SFV, the expected increase in the ADR in the FUSE arm is consistent with the initial data from previous studies comparing SFV and FUSE in primary screening setting.[13]

χ^2 test and t-test were used for categorical and continuous variables in the univariate analysis. To estimate DRs adjusted for patients' characteristics and screening centre, we fitted a logistic regression model. Also, based on available evidence, we assumed that the ADR could be related not only to a set of individual characteristics, but also to the endoscopists' attributes, such as endoscopy technique. As we included several endoscopists in the study, we fitted a multilevel (random-intercept) logistic regression model (two hierarchical levels: the patient and the endoscopist; centres entered as fixed effects) to investigate the influence of several covariates on the observed DRs of adenomas (any adenoma and advanced adenomas only) and AN (advanced adenoma+CRC). The set of patient-related fixed covariates included gender, age (50–59, 60–69) and screening history (first test in the programme; at least one previous negative FIT). We used the same age strata as in the randomisation procedure: given the relatively small size of the study groups, a dichotomous classification could favour at the same time comparability with other similar reports while allowing to get more precise estimates of effect. Available data from subjects with a positive FIT tests in the context of population-based screening programmes show a higher prevalence of neoplasia among men and among subjects performing their first test in the programme compared with women and with those with previous negative tests.[5] Endoscopist's characteristics included withdrawal time (calculated over negative exams only), proportion of incomplete tests and ADR, classified into two groups (low/high), based on the median of the observed distribution.

We performed also sensitivity analyses, excluding subjects with a Boston Bowel Preparation Score (BBPS)<2 in any one of the three segments (ie, left, transverse and right colon), and/or incomplete examinations, or exams with withdrawal times of <5 min. All the analyses were conducted using the intention-to-screen approach.

RESULTS

In the study period (September 2014–April 2015), 741 eligible subjects were examined in the study centres and 672 (males: 51.1%; mean age: 60.3±6.1) were randomised to FUSE or SFV; the remaining 79 subjects were not randomised as the planned number of subjects in their randomisation stratum had already been achieved in that centre. After excluding 14 subjects (8 FUSE group and 6 SFV group) who did not attend the planned appointment (they had been randomised at the time of the encounter to fix the colonoscopy, but they did not show up thereafter), 658 subjects (FUSE: 328; SFV: 330) were included in the analysis. Subject flow is represented in figure 1. Groups were comparable (table 1) with respect to age, gender and screening history (first vs subsequent FIT rounds).

Quality of the examinations was also similar in the two groups (table 1). Caecal intubation was achieved in 302/328 subjects (92.1%) in the FUSE and in 307/330 (93.3%) in the SFV arm (p=0.64); bowel preparation was considered inadequate (ie, BBPS<2 in 1 of 3 segments) in 64/328 (19.5%) subjects in the FUSE and in 60/330 (18.2%) in the SFV arm (p=0.66); conscious sedation was used in 86.9% of the subjects allocated to the FUSE and in 87.0% of those allocated to the SFV arm (p=0.98); withdrawal time for negative examinations was similar between the two arms (SFV: 10–90 percentile: 6–11; mean: 8.1 SD: 3.8 min; FUSE: 10–90 percentile: 5–15; mean: 8.4 SD: 4.5 min). A total of six minor adverse events occurred: self-limited bleeding following polypectomy was reported for two patients in the SFV and for one in the FUSE group; one patient in the SFV group reported severe pain and two in the FUSE arm suffered from vagovagal reactions.

Detection rates of adenomas, advanced adenomas and SSP/TSA (per patient analysis)

Overall, 293/658 (44.5%) and 143/658 (21.7%) patients had at least one adenoma and one advanced adenoma in the study population, while SSP/TSA was the most advanced lesion in 18/658 (2.7%). The distribution of the most advanced lesion across FUSE and SFV according to histology and localisation is shown in table 2. The proportion of subjects with at least one adenoma (ADR) was similar between the FUSE and SFV arms (43.6% vs 45.5%, RR 0.96, 95% CI 0.81 to 1.14); the corresponding figures for advanced adenomas were 19.5% vs 23.9% (relative risk (RR) 0.82, 95% CI 0.61 to 1.09). Distribution of SSP/TSA was also similar between the two groups. The lack of statistical difference between the two arms was consistent among all the seven study centres (data not shown). The number of patients with ≥3 adenomas was 10.4% (34/328) and 7.4% (25/330) in the FUSE and SFV arms, respectively (RR 1.37, 95% CI 0.84 to 2.24). The most advanced lesion was located proximally to the splenic flexure in 19.8% (10.7% LR adenoma; 9.1% advanced adenoma) of the patients in the FUSE and in 22.4% (13.9% LR adenoma; 8.5% advanced adenoma) in the SFV group.

The same differences between SFV and FUSE colonoscopy were maintained after adjusting (table 3) for gender age,

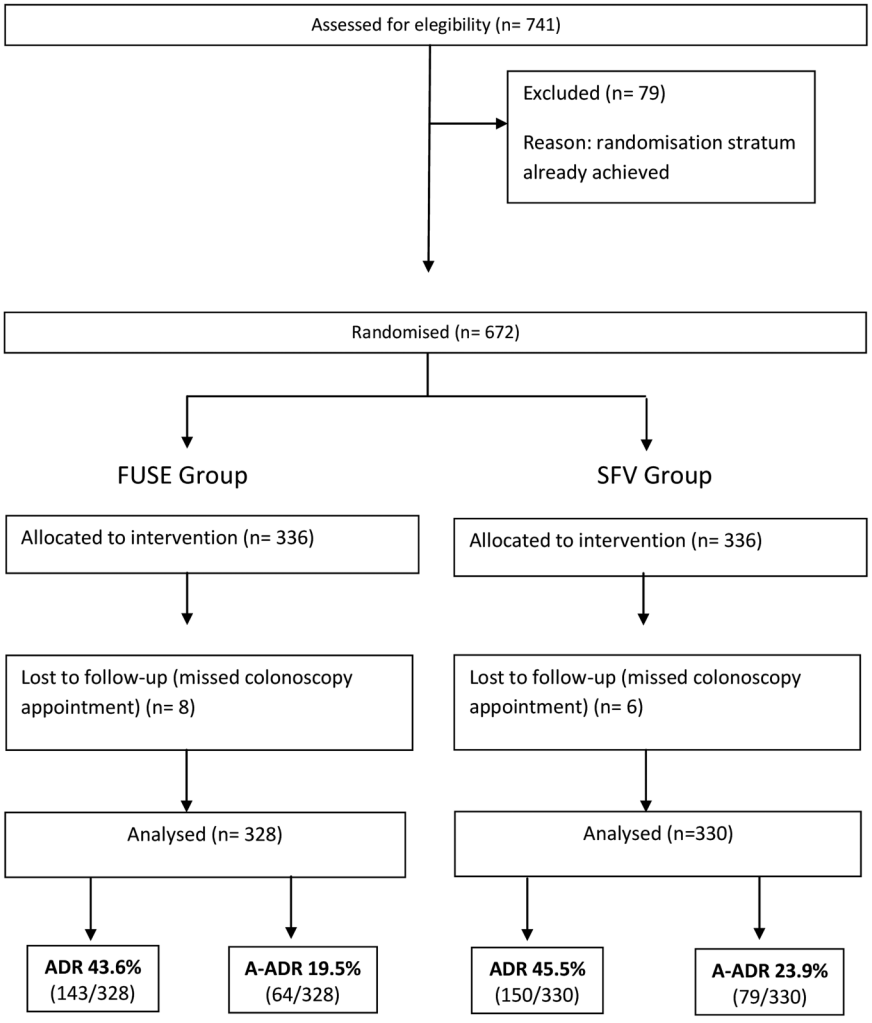

Figure 1 Subjects' flow. (A-)ADR, (advanced-)adenoma detection rate; FUSE, full-spectrum endoscopy; SFV, standard forward-viewing.

Table 1 Patients' characteristics and quality of colonoscopy by intervention arm

	FUSE (N=328)	SFV (N=330)
Age (years)		
Mean (SD)	60.1 (6.16)	60.4 (6.06)
Gender		
Male, N (%)	166 (50.6)	170 (51.5)
Female, N (%)	162 (49.4)	160 (48.5)
Number of previous FIT		
None, N (%)	132 (40.2)	126 (38.2)
1, N (%)	71 (21.6)	64 (19.4)
≥2, N (%)	125 (38.2)	140 (42.4)
Colonoscopy competed		
No, N (%)	26 (7.9)	22 (6.7)
Yes, N (%)	302 (92.1)	308 (93.3)
BBPS		
<6, N (%)	64 (19.5)	60 (18.2)
≥6, N (%)	264 (80.5)	270 (81.8)

BBPS, Boston Bowel Preparation Score; FIT, faecal immunochemical test; FUSE, full-spectrum endoscopy; SFV, standard forward-viewing.

screening history and screening centre; both ADR and A-ADR were higher among men than among women and a trend towards an increase with age and a decrease with increasing number of previous negative exams was observed.

These estimates were not changed when running the multilevel model including also endoscopist's ADR, completion rate and withdrawal time: OR (any adenoma): 0.96; 95% CI 0.69 to 1.33; OR (advanced adenoma): 0.85; 95% CI 0.58 to 1.25.

The reported results were not changed when restricting the analysis to subjects with complete examinations and/or adequate bowel preparation (data not shown).

We also assessed whether the ADR had improved in the second half of cases included compared with the first half, but we did not find any evidence of a learning curve effect: the same ADR was observed in each centre in the first as in the second set of examinations in both arms (data not shown).

Detection rates of adenomas, advanced adenomas and SSP/TSA (per polyp analysis)

A total of 930 polypoid (N=846) or non-polypoid (N=84) lesions were detected: of them, 570 were adenomas and 47 serrated polyps (30 SSP, 17 TSA).The average number of adenomas and proximal adenomas per patient was 0.81±1.25 and 0.47 ±0.93 in the FUSE and 0.85±1.33 and 0.48±0.96 in the SFV arm, respectively (p=0.346 and 0.446). Considering only subjects with at least one adenoma, the average number of adenomas per person was 1.84 (±1.26) in the FUSE and 1.91 (±1.56) in the SFV arm (p=0.332); the corresponding figures for SSP/TSA (14 people in the FUSE and 14 in the SFV arm) were 1.43 (±0.76) and 1.92 (±1.38) (p=0.128). The proportion of non-polypoid lesions was 8% (37/461) and 10%

Table 2 Most advanced lesion by intervention arm and colonic site

	Hyperplastic polyp	LR adenoma <10 mm	SSP <10 mm	Advanced adenoma <10 mm	SSP/TSA <10 mm with dysplasia	Tubular adenoma ≥10 mm	SSP/TSA ≥10 mm	Adenoma TV-V ≥10 mm	CRC
FUSE									
Distal	18	44	1	5	3	13	0	24	4
	5.5%	13.4%	0.3%	1.5%	0.9%	4.0%	0.0%	7.3%	1.2%
Proximal	10	35	0	3	2	10	5	9	2
	3.0%	10.7%	0.0%	0.9%	0.6%	3.0%	1.5%	2.7%	0.6%
Total	28	79	1	8	5	23	5	33	6
	8.5%	24.1%	0.3%	2.4%	1.5%	7.0%	1.5%	10.1%	1.8%
SFV									
Distal	22	33	0	14	2	14	1	30	5
	6.7%	10.0%	0.0%	4.2%	0.6%	4.2%	0.3%	9.1%	1.5%
Proximal	6	38	1	6	1	8	2	7	5
	1.8%	11.5%	0.3%	1.8%	0.3%	2.4%	0.6%	2.1%	1.5%
Total	28	71	1	20	3	22	3	37	10
	8.5%	21.5%	0.3%	6.1%	0.9%	6.7%	0.9%	11.2%	3.0%

CRC, colorectal cancer; FUSE, full-spectrum endoscopy; LR adenoma, low-risk adenoma (tubular with low-grade dysplasia); SFV, standard forward-viewing; SSP, sessile-serrated polyp; TSA, traditional-serrated adenoma; TV-V, tubulo-vollous / villous.

Table 3 Factors associated with adenoma detection rate at multivariable analysis

	Any adenoma		Advanced adenoma	
	OR*	95% CI	OR*	95% CI
Gender				
Men	1		1	
Women	0.58	0.42 to 0.81	0.58	0.40 to 0.84
Age				
50–59	1		1	
60–69	1.28	0.90 to 1.84	1.16	0.77 to 1.75
Number of previous FITs				
None	1		1	
1	0.87	0.55 to 1.36	0.85	0.50 to 1.43
≥2	1.12	0.64 to 1.69	0.96	0.59 to 1.57
TC completed				
No	1		1	
Yes	3.14	1.49 to 6.59	2.27	0.93 to 6.81
BBPS				
<6	1		1	
≥6	1.24	0.78 to 1.96	1.38	0.79 to 2.41
Colonoscopy arm				
SFV	1		1	
FUSE	0.96	0.69 to 1.32	0.84	0.58 to 1.21

*OR adjusted for screening centre and for all other variables in the model.
BBPS, Boston Bowel Preparation Score; FIT, faecal immunochemical test; FUSE, full-spectrum endoscopy; SFV, standard forward-viewing; TC, total colonoscopy.

(47/469) in the FUSE and in the SFV arm, respectively (p=0.305).

DISCUSSION

In a randomised trial based in an organised CRC screening programme, FUSE showed a similar performance as standard endoscopy in the detection of adenomas and advanced adenomas at *per patient* analysis. The clinical implications of our data are relevant. ADR represents the main proxy of the efficacy of colonoscopy in reducing CRC incidence and mortality.[15–20] In addition, AN represents the main target of FIT-based organised screening programmes due to the very high prevalence of these lesions in FIT-positive subjects and the high risk of progression of advanced adenomas in invasive cancer.[23–25] When considering the similar detection rates between FUSE and SFV for both types of lesions, the implementation of FUSE may not substantially affect the main outcomes of an organised programme in terms of morbidity and mortality from CRC compared with SFV endoscopy. Despite the role of clinically relevant serrated lesions—such as SSP and TSA—in CRC carcinogenesis is still unclear, we also showed similar detection rates for SSP/TSA rates between FUSE and SFV colonoscopy, further substantiating their equivalence in CRC prevention. This was not unexpected due to the strict relationship between the detection rate of adenomas and that of clinically relevant serrated lesions recently shown in the same Italian screening programme setting.[26] It could be argued that ADR —as proxy of miss rate—underestimates the limitations of colonoscopy since patients with multiple adenomas may be correctly classified by the mere detection of the most severe lesion. However, we also showed an equivalence in the mean number of adenomas between the two arms, as well as on multiplicity—that is, patients with ≥3 adenomas—reassuring on the equivalent CRC prevention efficacy between the two techniques.

Efficacy of colonoscopy in CRC prevention appears to be reduced in the proximal colon.[18 27] This likely depends on its suboptimal accuracy in exploring both sides of the folds, the more frequent non-polypoid morphology of proximal lesions and the higher prevalence of subtle serrated lesions. To avoid this, dedicated modifications of the colonoscopy technique, such as retroflexion in the proximal colon or segmental repetition of the withdrawal phase, have been recommended.[28–30] According to computerised simulations, a wider field of view should be effective in increasing the detection rate of proximal lesions, simplifying the exposure of the mucosa behind the folds.[10] However, we found similar detection rate between FUSE and SFV for both proximal and non-polypoid neoplasia, indicating that a wider field of view may not represent the main determinant of proximal ADR.

This is the first randomised trial comparing DR of FUSE and SFV examinations. The discrepancy between our results and the lower miss rate with FUSE previously shown in a back-to-back study[13] has a variety of potential explanations. First, because of

lack of blinding, there could have been overt bias in favour of or against FUSE in one or some of the investigators in one or both studies. Second, by using (advanced-) ADR as indirect proxy for colonoscopy miss rate in our study, endoscopists were randomised to use only one technique in each patient. It is likely that they maximised the diagnostic accuracy of each single technique in order to avoid clinically relevant false negative results, especially when considering the very high prevalence of AN in FIT-positive subjects. On the other hand, in back-to-back studies, the relevant result for patient management is represented by the cumulative detection of the tandem procedures. In this artificial setting, there might be less pressure on the endoscopist to maximise the accuracy of each technique since a potential false negative of the first procedure may still be detected by the second examination. The hypothesis of a lower risk of bias in our series is supported by the equivalence in the observed ADR with that reported in a retrospective series of 72 000 patients included in the same Italian organised screening setting.[26] Third, our study was performed in an enriched-disease population, while the previous back-to-back study was based on an unselected colonoscopy population, the mean ADR being 44% and 34% (considering the cumulative ADR with both of the techniques) in the two studies, respectively.[13] Perhaps the additional diagnostic value of FUSE was hampered by the very high value of ADR in the control group, the opposite being true in a non-FIT-positive population. In the same FIT-positive population, however, we have recently shown the efficacy of a split regimen in significantly increasing the mean ADR,[31] suggesting the validity of this setting to test the additional efficacy of any improvement in the technique of colonoscopy. Fourth, the relationship between polyp miss rate in back-to-back studies and stratification of results by patient is unclear. It is possible that the additional polyps detected with back-to-back methodology would fail—at least in some cases—to upstage the *per patient* classification according to the most advanced lesion. For instance, the additional detection of one or two non-advanced adenomas or non-neoplastic polyps may be considered clinically meaningless in a patient already classified by an advanced adenoma. Finally, we cannot exclude the possibility that the learning curve for optimal use of FUSE is longer than currently expected, or understood, even for experienced endoscopists, and thereby FUSE did not reach its full potential in this study. No training was advised at the time our study was launched, but we preferred to have our endoscopists to get familiar with the new platform as colonoscopy is a complex procedure based on the manoeuvrability, optical system, electronic interface, and so on. Thus, our study was the first with this system to have included a formal training, which was however limited to a 1-day course and a 2-day run-in period. The lack of any difference in the ADR when comparing the first with the second half of the study would suggest that the short FUSE training period did not critically affect the performance of FUSE in our trial. However, we acknowledge that the learning curve for reaching optimal performance with FUSE has not been fully investigated or characterised. The biological plausibility of the equivalence between two different degrees of field view is related to the possibility that rotating the instrument tip can allow a scope with a narrower angle of view to cover the mucosal surfaces as well as the wider angle of view. Thus, it seems reasonable to suspect that tip movement using an end-viewing instrument, perhaps combined with in–out movements of the insertion tube, could compensate for most, or all, of the increased angle of view provided by FUSE. Additional study of this issue is warranted. Further, it must be remembered using FUSE that the wide angle of view pertains only to the right-left direction and not the up-down directions. FUSE endoscopists must still deflect the tip widely in the up-down direction or rotate the insertion tube to rotate the wide angle of view to see effectively in both the horizontal and vertical directions. Although our endoscopists were aware of this feature of FUSE imaging, we did not monitor the extent to which they effectively visualised mucosa in the vertical directions. Further, our study design did not assess all potential advantages of FUSE. Thus, while our result indicates that effective tip movement of an SFV instrument compensates for the relatively narrower angle of view compared with FUSE, it is possible that with the wide angle of view FUSE instrument can effectively expose all the colonic mucosa faster and more efficiently than an SFV instrument. Demonstrating an efficiency advantage for FUSE or wide-angle imaging in general would require a different study design. Finally, it is our impression that not all aspects of optimal use of FUSE have been clarified. For example, there is uncertainty on whether all endoscopists can effectively monitor three screens for exposed polyps without help from others. We acknowledge that additional work may clarify elements of optimal FUSE use that might enhance its performance and may not have been fully captured in this study.

Our study has other limitations. We used the first generation of FUSE, while a second generation has been released, and we cannot exclude different results with such updated platform. However, we used the same equipment as in the previous back-to-back study.[13] We recommended a ≥6 min withdrawal time, which was achieved in >90% of negative examinations in both arms. Even if we observed in the multilevel analysis a trend towards an increase in the ADR among endoscopists with a longer withdrawal time (9–12 min compared with 6–8 min), the difference did not reach the level of statistical significance, which would suggest that differences in the examination technique did not have a major impact on the ADR. Even restricting the analysis to complete exams with adequate bowel preparation did not change the observed results.

The study was powered to detect as statistical significant a fairly large difference in the ADR with the two methods, based on available evidence from the tandem study published before starting our trial. However, the observed estimates of effect are suggestive of a similar performance of FUSE and SFV rather than of a superiority of FUSE.

Although we failed to show its superiority, the performance of FUSE and SFV colonoscopy in an organised screening programme, in terms of main quality indicators, was similar, which would indirectly support the use of FUSE as an alternative to SFV endoscopy in this setting. Future trials designed to test equivalence of the two methods could confirm this hypothesis.

In conclusion, in a randomised trial within the context of an organised screening programme, we showed similar detection rates of adenomas and advanced adenomas between FUSE and standard colonoscopy.

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Ethics approval IRB Torino. The protocol was approved by the ethics committee of the coordinating centre (AOU Città della Salute e della Scienza—CPO, Turin, Italy) and afterwards by all other participating institutions.

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Full-spectrum (FUSE) versus standard forward-viewing colonoscopy in an organised colorectal cancer screening programme

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