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Diagnostic Yield and Miss Rate of EndoRings in an Organized Colorectal Cancer Screening Program: the SMART (Study Methodology for ADR-Related Technology) Trial

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Abbreviations: E: Endorings; S: Standard; CRC: colorectal cancer; FIT: faecal immunochemical test; (A-) ADR: (Advanced-) adenoma detection rate; SSP: sessile serrated polyp; DR: detection rate

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ABSTRACT

Background and aims. The add-on EndoRings has been claimed to improve adenoma detection at colonoscopy, but available data are inconsistent. When testing a new technology, parallel and crossover methodologies measure different outcomes, leaving uncertainty on their correspondence. Aims of this study were to compare the diagnostic yield and miss rate of the EndoRings for colorectal neoplasia.

Methods. Consecutive subjects undergoing colonoscopy after a positive fecal immunochemical test (FIT) within organized screening program in 7 Italian centers, were randomized between a parallel (EndoRings or Standard) or a crossover (EndoRings/Standard or Standard/EndoRings) methodology. Outcomes measures were the detection rates of (advanced) adenomas (A-)ADR in the parallel arms and miss rate of adenomas in the crossover arms.

Results: Of 958 eligible subjects, 927 (317 EndoRings; 317 Standard; 142 EndoRings/Standard; 151 Standard/Endorings) were included in the final analysis. In the parallel arms (mean ADR: 51.3%; mean AADR: 25.4%), no difference between Standard and EndoRings was found for both ADR (RR, 1.10; 95% CI, 0.95-1.28) and A-ADR (RR, 1.16; 95% CI, 0.88-1.51), as well as for the mean number of adenomas and advanced adenomas per patient (EndoRings: 1.9±1.3 and 1.0±1.2; Standard 2.1±1.5 and 1.0±1.2; p=NS for both comparisons). In the crossover arms, no difference in miss rate for adenomas between EndoRings and Standard was found at *per-polyp* (RR, 1.43; 95% CI, 0.97-2.10), as well as at *per-patient* analysis (24% vs 26%; p=0.76).

Conclusions: No statistically significant difference in diagnostic yield and miss rate between EndoRings and Standard colonoscopy was detected in FIT+ patients. A clinically relevant correspondence between miss and detection rates was shown, supporting a cause-effect relationship.

INTRODUCTION

Improvement in adenoma detection rate (ADR) at screening colonoscopy has been associated with an additional long-term CRC prevention rate,[1] and this appears to be relevant in a population-based organized setting.[2,3]

Two different study designs are used to evaluate whether technological improvements increase adenoma detection. These are the randomized parallel design and the crossover randomized methodology, the latter also known as tandem or back-to-back study.[4] In the former, patients are randomized to undergo either the active intervention or the procedure but not both. In the crossover design patient undergoes both of the procedures in a randomized order. The main difference between the designs is the outcome measured, consisting of the additional diagnostic yield at per-patient (ADR) or per-polyp (adenomas per colonoscopy) analysis in the parallel design

and the decrease in the per-polyp miss rate in the tandem design. On one side, the parallel comparison favorably mimics the real clinical setting, but, on the other, it is hampered by the need of a much larger sample size and a higher risk of bias related to variability in underlying disease-prevalence, and provides less opportunity to explain the potential superiority of the new technique.[4] The crossover design mitigates all such limitations, but it represents a fully artificial design, and it is also at high risk of operator bias, as the unblinded endoscopist performing the first procedure is aware of the subsequent colonoscopy to be performed.[4] When validating the same innovations with different study methodologies, inconsistent results have been frequently reported,[5-9] generating uncertainty as to how well the 2 study designs actually correspond.

The add-on EndoRings (EndoAid Ltd, Caesarea, Israel) was developed to improve detection at colonoscopy by facilitating exploration of the proximal sides of folds. Haustral folds are flattened by the mechanical pressure of 2 circular layers of silicone-rubber rings. Previous studies with different methodologies led to different results.[6,10] On one hand, a crossover randomized trial showed a statistically significant decrease of polyp miss rate,[10] whereas, on the other, a parallel randomized trial failed to show any superiority in ADR.[6]

Population-based organized programs based on immunochemical fecal test (FIT) represent an ideal setting to evaluate colonoscopy innovations. The FIT-positive population is homogeneously-enriched for both advanced and nonadvanced neoplasia.[11] The actual miss rate of (advanced) adenomas in this setting is not yet known.

The aim of this study was to test whether the 2 different trial designs lead to similar results and conclusions by randomizing consecutive patients into an overall trial that employed both designs simultaneously. The active intervention tested was EndoRings and the study population was FIT positive subjects.

METHODS

This randomized controlled study was conducted in 7 endoscopy centers in Northern and Central Italy participating in the organized CRC screening program. The protocol was approved by the Ethics Committee of the coordinating center (ASL RM1, Rome) and afterwards by all other participating institutions. Written and informed consent was obtained from all subjects enrolled in the study. The trial was registered on the ISRCTN data-base (ISRCTN: 56854419). All the authors had access to the study data and had reviewed and approved the final manuscript.

CRC organized screening program in Italy

Main features of the organized CRC screening program in Italy has already been detailed.[7]

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The target population is represented by 50 to 75 years eligible subjects who are invited for a biannual single sample FIT. Those with a positive result (cut-off=20 µg Hb/gr. feces) are invite to perform post-FIT+ colonoscopy.

Study population

Patients undergoing their first colonoscopy after a positive FIT were enrolled. We excluded from the study: (1) patients with previous colonic resection; (2) patients on anti-thrombotic therapy, precluding polyp resection; (3) patients who were not able or refuse to give informed written consent.

Randomization

FIT+-subjects were randomized in a 2:2:1:1 ratio within screening center and endoscopist to undergo colonoscopy with or without the EndoRings in a parallel or crossover design, based on a computer generated randomized blocks sequence, in 4 different arms:

1. **Parallel arm:** colonoscopy *without* EndoRings (ie, Standard colonoscopy, S)
2. **Parallel arm:** colonoscopy *with* EndoRings (E)

3. **Crossover arm:** colonoscopy *with* EndoRings (first) followed by Standard colonoscopy *without* EndoRings (second), E/S
4. **Crossover arm:** Standard colonoscopy *without* EndoRings (first) followed by colonoscopy *with* EndoRings (second) (S/E)

Randomization was stratified by gender, age (50-59, 60-75 years) and screening history (first versus subsequent round), as already detailed.[7]

Examination procedure

Experienced endoscopists each having performed ≥5000 standard colonoscopies and ≥5 EndoRings colonoscopies with unselected indication within the previous 6 months participated in the study. To minimize operator-related variability, only 2 endoscopists per center were included. For study procedures, each center was allowed to use the same scope that would have been used in daily clinical practice (Appendix 1), irrespective of the definition (standard vs high-definition), whereas the same scope`s models with the addition of EndoRings was used in the EndoRings arm. No chromo-endoscopy or light-modification technologies for polyp detection were allowed. Split-

based bowel preparation was performed according to the standardized protocol used in each study center with at least one day of low-fiber diet before the procedure. In the crossover arms, the same endoscopist performed both of the consecutive procedures in the same day. If either of the 2 was incomplete, the patient was excluded from the primary analysis.

Bowel preparation was evaluated and graded according to the Boston Bowel Preparation scale.[12] 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 cecal intubation was assessed by the endoscopist by the identification of the ileocecal valve and the appendix orifice via photo documentation. When the EndoRings was responsible for cecal intubation failure, the endoscopist was allowed to repeat the procedure without the EndoRings. The result of such repetition was considered in the primary analysis only for the parallel arms (in order to preserve an intention-to-treat approach). On the other hand, in the crossover arms, failure of cecal intubation in the first procedure did not prevent the second procedure, if considered appropriate by the investigator, but it was excluded from the primary analysis.

Polyps were classified according to their size, location, and morphology (pedunculated, sessile, and non-polypoid).[13] Location was considered proximal if proximal to the splenic flexure. Pathologist's measure, when available, was considered the reference standard, whereas endoscopist's measure was used in the remaining cases (ie, piecemeal resection). In the 2 crossover arms, all lesions detected in the first examination were resected at the time of observation. The second procedure was performed similarly.

-Assessing the duration of the examination

Intubation time was defined as the duration of the time from the entry of the colonoscope into the anal verge to the time when the colonoscope arrived in the cecum, as determined by the investigator. Withdrawal time was defined as the duration time between cecal intubation and the time when the colonoscope was withdrawn from the anus. Intubation time and all other times were measured using a stopwatch, pausing during therapeutic interventions and washing. Clean withdrawal time was targeted to a minimum of 6 minutes.

Histopathology

All resected lesions, either by forceps or snare, were sent to pathology in separate jars and were processed and stained for histopathology using standard methods and evaluated by expert pathologists (one in each center) according to the Vienna criteria.[7, 14] An advanced adenoma was defined as an adenoma ≥10 mm and/or with villous component > 20%, and/or high-grade dysplasia.

Sample size and statistical analysis

Based on the observed prevalence of adenomas (40%), advanced adenomas (25%), adenomas (33%) and flat lesions (4%) among FIT+-patients, an overall sample size of 900 patients divided between the parallel (600 patients; 300 per each of the 2 arms) and the crossover (300 patients; 150 per each arm) methodology could allow for a 80% power to detect as statistical significant (α=0.05; 2-sided test) a 11.5%, 10.5% and 6% absolute increase in the detection rate of adenomas, advanced adenomas and flat lesions respectively when comparing colonoscopy with and without EndoRings arms (parallel arms). In the crossover colonoscopy a 14% absolute difference in the miss rate with standard as compared to EndoRings examination could be detected as statistically significant, assuming a 15% miss rate with EndoRings (per-patient analysis). Also, in the per-polyp analysis (advanced) adenoma miss rate was defined as the number of (advanced) adenomas detected in the second procedure/total number of (advanced) adenomas detected in the first and second procedures, both at per-polyp and per-patient analysis. Assuming a 45% ADR at the first examination, with an average number of 2 adenomas, the planned sample size could allow to detect as statistically significant a 10% absolute difference (from 15% to 25%) in the proportion of adenomas detected at the second procedure over the total number of adenomas detected at the 2 procedures.

The expected increase in the ADR in the EndoRings arm is consistent with the initial data from previous studies comparing colonoscopy with and without EndoRings in primary screening setting.[10] Chi-square test and t-test were used for categorical and continuous variables in the univariate analysis. Based on available evidence, we can assume that the ADR can be related not only to a set of individual characteristics, but also to the examiner's attributes, such as skills, training, volume of activity and specialty, and to the characteristics of the endoscopy unit, including the pathology department classifying the excised lesions. Thus, a multilevel (random-intercept) logistic regression analysis (3 hierarchical levels: the patient, the endoscopist and the endoscopy unit) was performed, selecting the observed prevalence rates of adenomas (any adenoma and advanced adenomas only) and advanced neoplasia (AN -advanced adenoma + CRC) as main outcomes, as already detailed.[7]

RESULTS

In the study period (28 July 2016 – 21 Aug 2017), 958 eligible subjects were randomized to the parallel arms of colonoscopy with (E: 319) and without (S: 318) EndoRings, or to the crossover arms, with (ES: 160) or without (SE: 161) EndoRings, at the first of the 2 examinations, respectively (**Figure 1**). After excluding 9 (2 E; 4 ES; 1 S; 2 SE) subjects who did not attend the planned appointment (they had been randomized at the time of the encounter to fix the colonoscopy, but they did not show up thereafter), 7 (2 ES; 5 SE) who refused to have the second exam and 15 (12 ES; 3 SE) with an incomplete procedure at the first of the 2 sequential colonoscopies in the crossover arms, 927 subjects 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 (1° versus ≥2°subsequent FIT rounds).

Quality of the examinations was also similar across the study groups **(Table 1).** Cecal intubation in the parallel arms was achieved in 309 out of 317 (97.4%) and 311 of 317 (98.1%) cases with and without EndoRings, respectively, whereas it was achieved in 142 of 154 (92.2%) and 151 of 154 (98.1%) cases at the first procedure with and without EndoRings in the crossover arms. Bowel preparation was considered inadequate (ie, BBPS <2 in one of 3 segments) in 55 of 927 (5.9%) subjects with no difference across the groups. Mean insertion time and withdrawal times were similar across the study arms. One patient reported a minor, self-limiting adverse event (vagal reaction).

Parallel arms

-Per-patient analysis

Overall, 324 of 634 (51.1%) and 162 of 634 (25.6%) patients had at least one adenoma and one advanced adenoma in the study population, whereas SSP/TSA was the most advanced lesion in 13/634 (2.1%). The distribution of the most advanced lesion across Standard and EndoRings arms is shown in **Table 2**. The proportion of subjects with at least one adenoma (ADR) was similar between the Standard and EndoRings arms (53.6% vs 48.6% vs RR, 1.10; 95% CI, 0.95-1.28); the corresponding figures for advanced adenomas were 27.4% versus 23.7% versus (RR, 1.16; 95% CI, 0.88-1.51). No differences according to site (proximal/distal) or dimension (<10 mm/≥10 mm) for the most advanced lesion was detected between the 2 arms (**Table 2**). Distribution of SSP/TSA was also similar between the 2 groups (**Table 2**).

The same differences between the EndoRings and the Standard colonoscopy were maintained after adjusting (**Table 3**) for gender, age, screening history, and screening center; both ADR and AADR were higher among men than among women, with a trend toward an increase with age, which was statistically significant for AADR. The AADR, but not the ADR, was decreased among subjects having performed previous FIT examinations; the ADR was increased when the bowel preparation was rated as adequate (BBPS≥2 in all segments) and in those centers where withdrawal time for negative TCs was longer than 6 minutes in more than half of the cases.

-Per-polyp analysis

The average number of adenomas and proximal adenomas per patient (with adenomas) was 1.9±1.3 and 1.0±1.2 in the EndoRings and 2.1±1.5 and 1.0±1.2 in the Standard arm, respectively (p=NS for both comparisons); the corresponding figures for SSP/TSA were 1.6 (±1.2) and 1.6 (±1.2) for total SSP/TSA and 1.2 (±1.2) and 1.5 (±1.3) for proximal SSP/TSA. The proportion of non-polypoid lesions was 5.0% (81/510) and 18.4% (98/532) in the EndoRings and in the Standard arms respectively (p=0.315).

Crossover arms

A total of 279 completed both of the crossover procedures, 139 in the EndoRings/Standard group and 140 in the Standard/EndoRings group (**Figure 1**). The distribution of the most advanced lesion across each of the 2 crossover arms for each of the 2 individual procedures according to histology and localization is shown in **Appendix 2**. No difference in ADR between each of the first procedures in each arm (EndoRings first: 53%; Standard first: 50%) and the corresponding parallel arms (see above) was detected (**Table 2**).

-Per-polyp analysis

Among the 304 and 291 polyps detected in the EndoRings/Standard and Standard EndoRings arms, respectively, 61 and 70 were missed, corresponding to a miss rate of 20% and 24% for Endorings and Standard colonoscopy, respectively (RR, 1.20; 95% CI, 0.89-1.62).

Among the 410 and 122 detected adenomas and advanced adenomas, 212 and 63 were removed in the EndoRings/Standard arm, and 198 and 59 in the Standard/EndoRings arm (**Table 4**). The EndoRings appeared to miss 36 out of 212 adenomas, corresponding to a miss rate of 17.0%, whereas the Standard missed 48 out of 198 adenomas, corresponding to a miss rates of 24.2% (RR,

1.43; 95% CI, 0.97-2.10). For advanced adenomas, the EndoRings appeared to miss 2 out of 63 lesions, corresponding to a miss rate of 3.2%, whereas the Standard missed 5 out of 59 advanced adenomas, corresponding to a miss rates of 8.5% (p=0.38). Most of missed lesions (80/84; 95.2%) were <10 mm adenomas with similar distribution between proximal (46/84; 54.8%) and distal location (**Table 4)**. Similar miss rates for SSA/TSA were also observed (**Table 4**).

-Per-patient analysis

Miss rate

At least one adenoma was missed in overall 69 out of 279 patients (**Table 4**), corresponding to a miss rate of 24.7%, without difference between the 2 techniques (miss rate EndoRings, 24% vs miss rate Standard, 26%; p=NS). Overall, advanced adenomas were missed in 6 out of 279 patients (2.2%) with no difference between the 2 techniques (**Table 4**). No other differences at per-patient analysis were detected (**Table 4**).

False negative rate and incorrect surveillance interval

An adenoma and advanced adenoma was detected at second examination in those without any (advanced) adenoma at the first examination in 16 and 1 patient, respectively, corresponding to a false negative rate of 5.7% and 0.4%, respectively, with no difference between the 2 techniques (**Table 4**). This would have resulted in a difference surveillance strategy in 11 out of 279 (3.9%) patients, corresponding to a 3-year colonoscopy for multiplicity (10 cases) or advanced adenoma (1 case) instead of FIT repetition (**Table 4**).

DISCUSSION

The lack of superiority of the EndoRings in (advanced) adenoma detection rate in the parallel arms corresponded to the lack of inferiority of the miss rate of adenomas in the crossover arms, supporting a cause-effect relationship between miss and detection rates. In addition, these results also corresponded to similar values between the 2 techniques in the mean number of adenomas per patient, on one side, and the miss rate at *per-patient* level, on the other.

Our study clearly excluded any significant utility for EndoRings in the detection of both non-advanced and advanced lesions, as well as for proximal and small (<10 mm) lesions in FIT+ subjects. Similarly, EndoRings did not reduce the miss rate for adenomas both at per-polyp and per-patient analysis. These findings are clinically relevant as this was the first study with the EndoRings designed with ADR as primary end-point. The enriched-disease FIT+ setting provided a

sufficient number of advanced adenomas to detect a possible increase in the detection rate of these lesions, which was also not achieved. From a clinical perspective, our result is in line with a recent 4-arm parallel comparison among different technologies to improve detection of colorectal neoplasia in a primary colonoscopy setting, showing an equivalence in the mean number of adenoma per patient between EndoRings and standard colonoscopy.[6] On the other hand, our study failed to confirm a reduced miss rate of adenomas with the EndoRings, as recently shown by a tandem study.[10] This may be at least in part related with a much higher ADR when using standard colonoscopy as first pass in our study compared with the previous study – 50% versus 28% – and in a much lower miss rate of adenomas – 24% versus 48.3% – of standard colonoscopy.[10]

This is the first crossover study performed in a purely FIT+ setting. Irrespective of the technical comparison, our study also allowed observation of the very clinically relevant risk of missed lesions, ie, advanced adenomas, in a FIT + population. We found this miss rate to be very low at 3.2%, and similarly found a very low number of entirely false negative subjects (subjects with a missed adenoma without any other detected lesion). These results are very reassuring given the potential for large differences in the recommended time interval for next colonoscopy between persons with advanced adenomas (colonoscopy at 3 years) versus persons without (FIT at 5-10 years). The very low rate of clinically relevant lesions missed in our study, as well as the lack of benefit of EndoRings, may be the result of other recent improvements in colonoscopy including high-definition, improved maneuverability, and split-dose cleansing. In this regard, a recent crossover trial showed a substantial reduction in adenoma miss rate when skipping 2 generation of colonoscopy system.[15]

From a methodology perspective, our study showed a favorable correspondence between the detection and miss rates in the parallel and crossover arms, respectively, and also a somewhat unexpected coherence across all the secondary end-points at both the *per-patient* and *per-polyp* level. This result is to be related with a uniform performance of the study endoscopists in the 2 methodological arms, as clearly supported by the similar values in ADR between the 2 parallel arms, on one side, and the 2 crossover arms (first pass), on the other. These findings are reassuring with regard to validation studies on any technology innovation for improving detection, irrespective of which of the 2 methodologies is adopted. When considering that crossover studies, albeit requiring a smaller sample size, are technically more demanding and less patient-friendly, parallel studies should be trusted as an adequate methodology to validate new technologies.

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The main strength of our study is represented by the double randomization between the study design, ie, parallel and crossover, and within each study design, by the lack of intercenter variability in the main study outcomes, and by the similar estimates of ADR between the parallel and the crossover arms. The main limitation is represented by the role of ADR as intermediate end-point in CRC prevention, as compared with interval cancer, and by the uncertain role of miss rate in the degree of CRC prevention.

While excluding a clinically relevant effect of the EndoRings in the FIT+ setting, our study supports an equivalence between parallel and crossover studies when validating new technologies for ADR improvement.

Figure Legend

Figure 1 – Study flowchart.

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

	Parallel EndoRing N=317	**Parallel Standard N=317**	**Crossover (EndoRing first) N=142**	**Crossover (Standard first) N=151**
Age (years) mean (SD)	62.9 (7.2)	61.8 (6.9)	61.8 (6.6)	62.3 (7.1)
Gender				
Male N (%)	159 (50.2)	161 (50.8)	73 (51.4)	75 (49.7)
Female N (%)	158 (49.8)	156 (49.2)	69 (48.6)	76 (50.3)
Number of previous FIT				
None N (%)	110 (34.7)	111 (35.0)	49 (34.5)	50 (33.1)
1 N (%)	96 (30.3)	88 (27.8)	37 (26.1)	44 (29.1)
≥ 2 N (%)	111 (35.0)	118 (37.2)	56 (39.4)	57 (37.8)
Colonoscopy competed				
No N (%)	8 (2.6)	6 (1.9)	12 (7.8)	3 (1.9)
Yes N (%)	309 (97.4)	311 (98.1)	142 (92.2)	151 (98.1)
			3 (2.1)	11 (7.3)
			139 (97.9)	140 (92.7)
BBPS*				
< 6 N (%)	16 (5.1)	21 (6.6)	5 (3.5)	13 (8.6)
≥ 6 N (%)	301 (94.9)	296 (93.4)	137 (96.5)	138 (91.4)
Insertion time (mean±SD)**	5.5 (2.8)	5.5 (3.9)	5.4 (2.7)	6.0 (4.0)
			3.8 (1.9)	4.6 (2.8)
Withdrawal time All TCs (mean±SD) ***	7.8 (3.9)	8.3 (4.8)	7.2 (3.1)	7.8 (6.7)
			6.2 (1.8)	6.4 (4.9)

* Boston Bowel Preparation Score

** Information missing for: 8 pts. Group E; 9 pts. Group S; 2 pts. Group ES 1 and 8 pts Group ES 2; 2 pts. Group SE 1 and 10 pts. Group SE 2;

*** Information missing for: 10 pts group E; 9 pts group S; 2 pts. Group ES 1 and 6 pts Group ES 2; 3 pt. Group SE 1 and 12 pts. Group SE 2;

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Table 2. A, Most advanced lesion by intervention arm and colonic site. **B,** Statistical comparison across the 4 arms by using the parallel arm with standard colonoscopy (i.e. without EndoRings) as reference standard.

	Parallel EndoRing N=317		**Parallel Standard N=317**		**Crossover EndoRing first (1° colonoscopy) N=142**		**Crossover Standard first (1° colonoscopy) N=151**	
No. patients with any polyp	192	(61%)	199	(63%)	94	(66%)	92	(61%)
No. patients with CRC	8	(3%)	12	(4%)	5	(4%)	1	(1%)
No. patients with adenoma	154	**(49%)**	170	**(54%)**	75	**(53%)**	75	**(50%)**
- No. patients with Non-advanced adenoma	79	(25%)	83	(26%)	40	(28%)	35	(23%)
- No. patients with Advanced adenoma	75	**(24%)**	87	**(27%)**	35	**(25%)**	40	**(26%)**
- No. patients with distal adenoma	93	**(29%)**	122	**(39%)**	36	**(25%)**	52	**(34%)**
- No. patients with proximal adenoma	61	**(19%)**	48	**(15%)**	39	**(27%)**	23	**(15%)**
- No. patients with <10 mm adenoma	93	**(29%)**	99	**(31%)**	50	**(35%)**	46	**(30%)**
- No. patients with ≥10 mm adenoma	61	**(19%)**	71	**(22%)**	25	**(18%)**	29	**(19%)**
No. patients with SSP/TSA	7	**(2%)**	6	**(2%)**	3	**(2%)**	3	**(2%)**
Mean number of adenomas per patient with adenomas (mean±SD)	**1.9 (1.3)**		**2.1 (1.5)**		**2.3 (1.7)**		**2.0 (1.2)**	

A

Most advanced lesion per patient	Relative Risk – 95%CI
Any adenoma	
Standard vs EndoRing	1.10 - 0.95-1.28
Standard vs Crossover (Standard first)	1.08 – 0.89-1.31
Standard vs Crossover (EndoRing first)	1.02 – 0.84-1.22
Advanced Adenoma	
Standard vs EndoRing	1.16- 0.88-1.51
Standard vs Crossover (Standard first)	0.99 – 0.63-1.57
Standard vs Crossover (EndoRing first)	1.11 – 0.79-1.56
Proximal Adenoma	
Standard vs EndoRing	0.79 - 0.56-1.11
Standard vs Crossover (Standard first)	1.04 – 0.65-1.66
Standard vs Crossover (EndoRing first)	0.55 – 0.35-0.80
Adenoma ≥10 mm	
Standard vs EndoRing	1.16 - 0.86-1.58
Standard vs Crossover (Standard first)	1.17 – 0.79-1.72
Standard vs Crossover (EndoRing first)	1.27 – 0.84-1.38

B

Table 3. Factors associated with ADR at multivariable analysis (Parallel arms).

	Any adenoma		Advanced adenoma	
	OR*	**95% CI**	**OR***	**95% CI**
Gender				
Men	1		1	
Women	0.65	0.47-0.90	0.64	0.44-0.92
Age				
50-59	1		1	
60-74	1.39	0.99-1.94	1.64	1.11-2.42
Number of previous FITs none				
≥1	1		1	
	0.80	0.55-1.15	0.47	0.31-0.70
BBPS				
< 6	1		1	
≥ 6	5.04	2.23-11.38	2.54	0.95-6.76
Withdrawal time (centers)				
≤ 6 minutes in ≤ 50% negative TCs	1		1	
>6 minutes in > 50% negative TCs	1.49	1.03-2.15	1.14	0.74-1.76
Colonoscopy arm				
S	1		1	
E	0.80	0.58-1.10	0.79	0.55-1.14
*OR = Odds ratio adjusted for all the variables in the model				

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Table 4. Miss rate at per-polyp and per-patient analysis

Miss rate at per-polyp level	**EndoRing first**		**Standard first**		***P* value**
All adenomas (ES:212 – SE 198)	**36**	**(17.0%)**	**48**	**(24.2%)**	0.09
Non-advanced adenomas (ES:149 – SE 139)	34	(22.8%)	43	(30.9%)	0.15
Advanced adenomas (ES:63 – SE 59)	**2**	**(3.2%)**	**5**	**(8.5%)**	0.38
Distal adenomas (ES:123 – SE 104)	13	(10.6%)	25	(24.0%)	**0.01**
Proximal adenomas (ES:89 – SE 94)	23	(25.8%)	23	(24.5%)	0.96
<10 mm adenomas (ES:183 – SE 156)	36	(19.7%)	44	(28.2%)	0.08
≥10 mm adenomas (ES:29 – SE 42)	0	(0.0%)	4	(9.5%)	NS
SSA/TSA (ES:13 – SE 20)	4	(30.8%)	5	(25.0%)	0.98
Miss rate at per-patient level (pts. with at least one adenoma at 2° colonoscopy / all patients)	**N=139**		**N=140**		***P* value**
All adenomas	33	(24%)	36	(26%)	0.76
Non-advanced adenomas	32	(23%)	31	(22%)	0.86
Advanced adenomas	1	(1%)	5	(4%)	0.21
Distal adenomas	13	(9%)	21	(15%)	0.20
Proximal adenomas	20	(14%)	15	(11%)	0.35
<10 mm adenomas	33	(24%)	32	(23%)	0.86
≥10 mm adenomas	0	(0%)	4	(3%)	NS
SSA/TSA	0	(0%)	3	(2%)	NS
False negative at per-patient level (All pts. with at least one adenoma at 2° colonoscopy and no adenoma at 1° colonoscopy / all patients)**	EndoRing first N=139 ***		Standard first N=140 **		*P* value
All adenomas	6	(4%)	10	(7%)	0.31
Non-advanced adenomas	6	(4%)	9	(6%)	0.43
Advanced adenomas	0	(0%)	1	(1%)	NS
Distal adenomas	1	(1%)	4	(3%)	0.37
Proximal adenomas	5	(4%)	6	(4%)	0.77
<10 mm adenomas	6	(4%)	9	(6%)	0.43
≥10 mm adenomas	0	(0%)	1	(1%)	NS
SSA/TSA	0	(0%)	2	(1%)	NS

** Including 1 patient with LR adenoma at first TC detected with an HR adenoma at second TC: in addition 6 patients would have received an incorrect indication for surveillance (ie, ≥3 adenomas after II TC)
*** 4 patients would have received an incorrect indication for surveillance (ie, ≥3 adenomas after II TC)

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Appendix 1. Colonoscopes used within this study for the standard colonoscopy arm across the different centers.

- Olympus, CF-165/HQ180/HQ185/HQ190, PCF-H180AL series
- Fujifilm Eluxeo 760 series
- Pentax i10 series

Appendix 2.

Most advanced lesion by intervention arm and colonic site
Parallel arms

EndoRing	Hyperplastic polyp	LR adenoma < 10 mm	SSP LG < 10 mm	Advanced adenoma < 10 mm	SSP HG/ TSA < 10 mm	LG Tubular adenoma ≥ 10 mm	SSP/TSA ≥ 10 mm	HG T + LG/HG TV-V adenoma ≥ 10 mm	CRC
Distal	18	36	1	11	1	11	1	32	5
	5,7%	11,4%	0,3%	3,5%	0,3%	3,5%	0,3%	10,1%	1,6%
Proximal	13	45	2	3	1	8	0	9	3
	4,1%	14,2%	0,6%	0,9%	0,3%	2,5%	0,0%	2,8%	0,9%
Total N=317	31	81	3	14	2	19	1	41	8
	9,8%	25,6%	0,9%	4,4%	0,6%	6,0%	0,3%	12,9%	2,5%
Standard	**Hyperplastic polyp**	**LR adenoma < 10 mm**	**SSP LG < 10 mm**	**Advanced adenoma < 10 mm**	**SSP HG/TSA < 10 mm**	**LG Tubular adenoma ≥ 10 mm**	**SSP/TSA ≥ 10 mm**	**HG T + LG/HG TV-V adenoma ≥ 10 mm**	**CRC**
Distal	18	59	1	10	1	17	0	36	10
	5,7%	18,6%	0,3%	3,2%	0,3%	5,4%	0,0%	11,4%	3,2%
Proximal	5	24	1	6	0	8	3	10	2
	1,6%	7,6%	0,3%	1,9%	0,0%	2,5%	0,9%	3,2%	0,6%
Total N=317	23	83	2	16	1	25	3	46	12
	7,3%	26,2%	0,6%	5,0%	0,3%	7,9%	0,9%	14,5%	3,8%

Most advanced lesion by intervention arm and colonic site
Crossover arms – first TC

EndoRing *	Hyperplastic polyp	LR adenoma < 10 mm	SSP LG < 10 mm	Advanced adenoma < 10 mm	SSP HG/ TSA < 10 mm	LG Tubular adenoma ≥ 10 mm	SSP/TSA ≥ 10 mm	HG T + LG/HG TV-V adenoma ≥ 10 mm	CRC
Distal	6	18	0	3	1	7	1	8	4
	4.2%	12.7%	0.0%	2.1%	0.7%	4.9%	0.7%	5.6%	2.8%
Proximal	5	22	1	7	0	6	0	3	1
	3.5%	15.5%	0.7%	4.9%	0.0%	4.2%	0.0%	2.1%	0.7%
Total	11	40	1	10	1	13	1	11	5
	21.8%	28.2%	0.7%	7.0%	0.7%	9.2%	0.7%	7.7%	5.6%
Standard **	**Hyperplastic polyp**	**LR adenoma < 10 mm**	**SSP LG < 10 mm**	**Advanced adenoma < 10 mm**	**SSP HG/TSA < 10 mm**	**LG Tubular adenoma ≥ 10 mm**	**SSP/TSA ≥ 10 mm**	**HG T + LG/HG TV-V adenoma ≥ 10 mm**	**CRC**

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Distal	4	24	0	7	1	9	0	11	1
	2.6%	15.9%	0.0%	4.6%	0.7%	6.0%	0.0%	7.3%	0.7%
Proximal	7	11	1	3	0	5	1	3	0
	4.6%	7.3%	0.7%	2.0%	0.0%	3.3%	0.7%	2.0%	0.0%
Total	11	35	1	10	1	14	1	14	1
	7.3%	23.2%	0.7%	6.6%	0.7%	9.3%	0.7%	9.3%	0.7%

Most advanced lesion by intervention arm and colonic site
Crossover arms – second TC

EndoRing 139 completed TCs / 142	**Hyperplastic polyp**	**LR adenoma < 10 mm**	**SSP LG < 10 mm**	**Advanced adenoma < 10 mm**	**SSP HG/ TSA < 10 mm**	**LG Tubular adenoma ≥ 10 mm**	**SSP/TSA ≥ 10 mm**	**HG T + LG/HG TV-V adenoma ≥ 10 mm**	**CRC**
Distal	4	19	0	0	0	0	0	2	0
	2.9%	13.6%	0.0%	0.0%	0.0%	0.0%	0.0%	1.4%	0.0%
Proximal	5	12	3	1	0	1	0	1	0
	3.6%	8.6%	2.1%	0.7%	0.0%	0.7%	0.0%	0.7%	0.0%
Total	9	31	3	1	0	1	0	3	0
	6.4%	22.1%	2.1%	0.7%	0.0%	0.7%	0.0%	2.1%	0.0%
Standard (140 completed TCs / 151)	**Hyperplastic polyp**	**LR adenoma < 10 mm**	**SSP LG < 10 mm**	**Advanced adenoma < 10 mm**	**SSP HG/TSA < 10 mm**	**LG Tubular adenoma ≥ 10 mm**	**SSP/TSA ≥ 10 mm**	**HG T + LG/HG TV-V adenoma ≥ 10 mm**	**CRC**
Distal	3	12	0	1	0	0	0	0	0
	2.2%	8.6%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%
Proximal	5	20	0	0	0	0	0	0	0
	3.6%	14.4%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Total	8	32	0	1	0	0	0	0	0
	5.8%	23.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%

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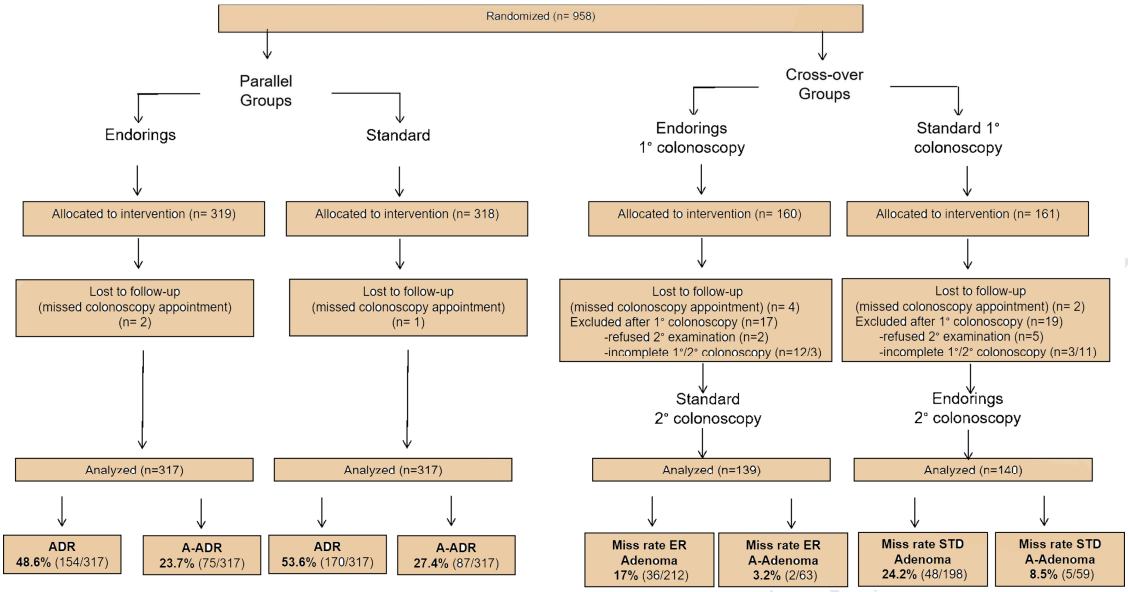

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Acronyms

E: Endorings;

S: Standard;

CRC: colorectal cancer;

FIT: faecal immunochemical test;

(A-) ADR: (Advanced-) adenoma detection rate;

SSP: sessile serrated polyp;

DR: detection rate

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Proof of Human Trial Registration

The trial was registered on the ISRCTN data-base (ISRCTN: 56854419).

https://doi.org/10.1186/ISRCTN56854419

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