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Findings in the distal and proximal colon in colonoscopy screening after positive FIT and related pre-procedure factors

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ABSTRACT

Background: colonoscopy is the gold standard method for the early diagnosis and prevention of colorectal cancer (CRC). Screening programs include immune determination of blood in feces. Regardless of the method used, proximal colon lesions appear to be detected less frequently.

Objective: to analyze the characteristics of proximal and distal lesions and possible predisposing factors.

Methods: a cross-sectional study was performed of 692 patients from the CRC screening program with fecal immunological test (FIT) ≥ 100 ngHb/ml (October 2017-

October 2018). The right colon was examined twice as patients were participating in a randomized clinical trial to re-evaluate the right colon by forward-viewing endoscope or proximal retroflexion. The adenoma detection rate (ADR), advanced neoplasia (AN) and CRC in the proximal and distal colon, histological and morphological characteristics in each section were analyzed.

Results: in the study, 52.9 % of the patients were male, with a mean age of 59.5 years (standard deviation [SD]: 7.6); 1,490 polyps were found and the ADR was 57.7 % (distal 42 % and proximal 37 %). Detection rates were 45.8 % for AN, 40.9 % for advanced adenomas, 5.2 % for advanced sessile serrated lesions (SSL) and CRC was diagnosed in 4.8 % of patients. Males had more AN than females. The mean age of patients with AN was significantly higher. AN were associated with smoking and alcohol consumption ($p = 0.0001$). Globally, FIT levels were higher in patients with AN ($p = 0.003$). Sixty-six per cent of cancers were distally located and 61.3 % of CRC were diagnosed in the early stages.

Conclusions: in an average-risk asymptomatic population undergoing colonoscopy after positive FIT, AN were more common in the distal colon in males, older patients, smokers and those with alcohol intake.

Keywords: Advanced neoplasia. Advanced sessile serrated lesion, Colorectal cancer screening. Adenoma detection rate. Proximal colon. Distal colon.

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant tumor in males worldwide, and the second most common tumor in females. The incidence of CRC has increased in recent years, although mortality has fallen, possibly due to screening programs being introduced in many countries (1). Colonoscopy is the most effective method for the prevention and early diagnosis of CRC as it detects pre-neoplastic lesions and enables endoscopic resection. However, colonoscopy prevents proximal more than distal CRC (2), probably because the proximal colon has a suboptimal cleaning, flat lesions that are more difficult to distinguish from the normal mucosa (3) and some lesions are hidden behind the haustra, making their visualization difficult.

The fecal immunological test (FIT) is one of the screening methods recommended for CRC (4-6). Studies show that FIT is worse at detecting proximal colon cancers, increasing the proportion of right-sided colon interval cancers (7), although the results are conflicting (8-10).

The objective of the study was to analyze proximal and distal colon findings in patients with positive FIT in screening colonoscopies and possible related factors.

MATERIAL AND METHODS

Study design

Asymptomatic patients aged 50-69 years referred by the CRC screening program for colonoscopy after a positive FIT (≥ 100 ngHb/ml [20 µgHb/g feces]) were analyzed. Patients were recruited from the Gastroenterology departments of three Spanish hospitals (Hospital Río Hortega, Valladolid; Hospital del Mar, Barcelona; and Hospital Santos Reyes, Burgos) from October 2017 until October 2018. The study was approved by the Ethical Board of Hospital Río Hortega (6th June, 2017, CEIC: 62/16) and the respective ethics committees. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. In all patients, the right colon (up to the hepatic angle) was examined twice, using proximal retroflexion or forward view, as patients were participants in a randomized clinical trial to re-evaluate the right colon (NCT03041532) (11).

Procedure

The FIT kit used was the OC-Sensor (Eiken Chemical Co., Tokyo, Japan). A positive test was defined as a cut-off of 100 ngHb/ml, without specific dietary or medication restrictions. Colonoscopy was performed using a standard forward-view colonoscope (diameter 12.8 mm, working channel 3.7 mm) with a high-resolution Olympus Exera II and Exera III (H180 and H190 series, Olympus). Candidates for colonoscopy followed the colon cleansing protocols of each hospital. The Boston Bowel Preparation Scale (BBPS) was evaluated. Colonoscopy was performed under deep sedation with propofol and CO_2 insufflation and was carried out by four expert endoscopists, all with more than five years of experience who perform at least 200 colonoscopies per year.

Outcome and definitions

The main objectives were to assess the detection rate of advanced neoplasia (AN) (advanced adenomas [AA] and CRC) in the proximal and distal colon and to analyze FIT levels and possible pre-procedure factors associated with AN. A secondary objective was to determine whether a second right colon examination resulted in modifications in the detection rate of adenomas and/or advanced CRC between the distal and proximal colon.

The size, shape and location of polyps resected were collected. The morphology was described according to the Paris classification. The size was estimated by the open biopsy forceps prior to resection. Polyps < 5 mm were resected with cold forceps, pedunculated polyps ≥ 5 mm with a hot snare polypectomy and non-pedunculated polyps by mucosectomy.

The proximal colon (PC) was defined as the cecum, ascending colon and transverse colon, and the distal colon (DC) was defined as the splenic flexure, descending colon, sigmoid colon and rectum. AA was defined as adenomas ≥ 10 mm, villous component or high grade dysplasia (HGD) or dysplasia in sessile serrated adenoma or ≥ 3 tubular adenomas without advanced features (12). Advanced sessile serrated lesion (SSL) was defined as SSL with dysplasia, without dysplasia ≥ 10 mm or right-side hyperplastic lesion ≥ 10 mm. CRC was defined as invasion beyond the muscularis mucosae. Tumor staging was established according to the TNM colon cancer 8th edition, 2017 (13). AN was defined as CRC and AA. Non-advanced adenoma was defined as an adenoma < 10 mm without high grade dysplasia or villous histology and < 3 adenomas (10,14). Distal hyperplastic polyps < 10 mm were excluded. Proximal hyperplastic polyps ≥ 10 mm were included in the analysis.

Adenoma detection rate (ADR) was defined as the number of colonoscopies with ≥ 1 adenoma divided by the number of total colonoscopies and median adenoma rate (MAR), as the median number of adenomas per colonoscopy.

Patients included

Consecutive asymptomatic patients aged 50-69 years with a positive FIT referred by the CRC screening program who gave signed informed consent were included. A BBPS score of ≥ 2 in each segment was required. Stenosing malignant tumors of the colon and rectum were counted as CRC.

Exclusion criteria were: lack of informed consent, colorectal hereditary syndrome or familial colorectal cancer (≥ 2 first degree relatives with colorectal cancer or one in whom the disease was diagnosed before 60 years), symptomatic patients, inadequate preparation or pathological findings (diverticulitis or inflammatory bowel disease) or colonoscopy in the previous five years.

Statistical analysis

Qualitative variables were described using absolute and relative frequencies (percentages). Percentages were compared using the Chi-squared test or Fisher's exact test, as required. Non-conditional logistic regression was used to adjust for other variables of interest. In the bivariate analyses, contingency tables and the Chi-squared test were used to detect relationships between qualitative variables. The Student's t-test or non-parametric alternatives were used to compare quantitative variables, whose normality was established using the Kolmogorov-Smirnov test. Variables with a normal distribution were described using means and standard deviation (SD). Differences in the number of adenomas detected and pre-procedure factors were studied using a Poisson regression model. The measures of accuracy for FIT value were sensitivity, specificity and the ROC curve was used for the area under the curve (AUC) analysis. The level of statistical significance was established as 5 % and 95 % confidence intervals were calculated. The analysis was made using the R Core Team (R package version 2018.04.17) program with the RStudio interface and the IBM SPSS 26.0 statistical program.

RESULTS

Six hundred and ninety-two patients were included and 36 patients were finally excluded due to: incomplete colonoscopy (n = 5), inadequate bowel preparation (n = 26) and findings of inflammatory bowel disease (n = 5). The mean age was 59.5 years

(SD 7.6), 52.9 % were male, 29.6 % were smokers and 34 % consumed > 20 g of alcohol/day. The mean body mass index (BMI) was 27.4 (SD 4.6). The global results were ADR 57.7 % (376/656); proximal ADR 39 % (259/656) and distal ADR 42 % (276/656). The MAR per procedure was 1.8 ± 2.7 and the proximal MAR was 1.04 ± 2.02 *vs* distal MAR 0.8 ± 1.12 (p = 0.001). The polyp detection rate (PDR) was 69 %, the polyp retrieval rate (PRR) was 94 % and the cecal intubation rate, 97 %. The mean examination time from the cecum to the anus was 9.17 minutes and 99.6 % of patients had an adequate bowel preparation.

Finally, 1,619 lesions were found: 1,301 (80 %) were adenomas, 35 (2,2 %) had normal histology and 60 were not recovered (4.7 %) (Table 1; percentages have been calculated for the total lesions recovered). Eight hundred and ninety-two lesions (55.1 %) were found in the PC and 727 (44.9 %) in the DC (p = 0.0001). The distribution was 597 in the right colon (36.9 %), 295 (18.2 %) in the transverse colon, 64 (4 %) in the splenic colon, 167 (10.3 %) in the left colon, 291 (18 %) in the sigmoid colon and 205 (12.7 %) in the rectum. Twenty-three percent (n = 159) of patients had proximal and distal lesions simultaneously and there was a significant correlation between the number of proximal and distal adenomas (p = 0.01). The colonoscopy was normal in 42.7 % (n = 280) of patients. Thirty-four patients (5.2 %) had ≥ 1 advanced SSL (advanced SSL detection rate). There were no differences between males and females and there was a non-significant trend to a greater frequency with age (p = 0.07).

AN was found in 300 patients (44 %), proximal in 66 (10 %) *vs* distal in 132 (20 %) cases (p = 0.001); and AA in 268 patients (41 %), with significant differences between the proximal location of the colon (n = 96, 35.8 %) *vs* distal (n = 172, 64.2 %), p = 0.001. According to the multivariate analysis, there were associations between the presence of advanced adenomas and older age, male sex, alcohol consumption and smoking. The presence of CRC was associated with higher BMI values and alcohol consumption (Table 2).

Globally, FIT levels were higher in patients with CRC (p = 0.002) and the association was significant for distal AA (p = 0.001) but not for proximal AA. The polyp mean size was greater for distal lesions (proximal: 6.6 mm [SD 6.4] *vs* distal mean size: 9.6 mm [SD 8.4]) (p = 0.0001). FIT levels tended to be higher the larger the size of the polyp

and whether polyps were located in the left colon (p = 0.02), rectum (p = 0.007) and right colon (p = 0.001). There were no significant correlations between the FIT level and the number of adenomas.

CRC was diagnosed in 32 patients (4.8 %); 68.8 % were male and the BMI was 29.6 (SD 4.5). Alcohol consumption was > 20 g ethanol/day in 56.3 % and 43.8 % were smokers. A total of 65.6 % of CRC were distally located. There was no relationship between FIT levels and CRC location. FIT > 100 ng/ml had a positive predictive value (PPV) of 0.05 for the diagnosis of CRC. A total of 61.3 % of infiltrating CRCs were diagnosed in early stages (I and II). The percentages by stage were: stage I 38.7 % (n = 12); stage II-IIA 22.6 % (n = 7), stage IIIA-IIIB 25.8 % (n = 8) and stage IV 3.1 % (n = 1). There was an association between a diagnosis of CRC and FIT levels (p = 0.002), alcohol intake (p = 0.0001) and BMI (p = 0.04). No patients presented CRC simultaneously with advanced SSL (p = 0.5)

Sensitivity (Sen) and specificity (Spe) were analyzed in our population. The FIT cut-off level of 100 ngHb/ml for the detection of AA had a Sen of 98 % and Spe of 3 % (AUC: 0.57, p = 0.006, CI 0.5-0.6). For the detection of CRC, the AUC is 0.68 (p = 0.0001; CI 0.57-0.8), with 92 % Sen and 2 % Spe. For the detection of AN, the AUC is 0.6 (p > 0.0001; CI: 0.5-0.6), with a 97 % Sen and 3 % Spe.

When analyzing the cut-off point by age groups and sex, the greatest discriminative power of the FIT cut-off level of 100 ngHb/ml in our population was found for the detection of CRC in individuals under 60 years of age, with a Sen of 100 % and Spe of 3 % (females: AUC 0.8, p = 0.001, CI 0.7-0.9; and males: AUC 0.8, p = 0.01, CI 0.7-0.9). The group that were under 60 years of age also had a moderate discriminative capacity for the detection of AN with a 96 % Sen, 2 % Spe (males: AUC 0.66, p = 0.002, CI 0.5-0.7; and females: AUC 0.67, p = 0.001, CI 0.5-0.7). There was no significant discriminative capacity for the detection of AA, CRC or AN in people older than 60 years nor for the detection of AA in patients under the age of 60. For distal AA, there was a significant discriminative capacity (AUC: 0.62, p: 0.0001) and the FIT did not have a discriminative capacity for the detection of proximal AA.

In both men and women under 60 years of age, the cut-off point could be increased to 158 ngHb/ml, with a higher Spe of 25 %, maintaining Sen at 93 % for the detection of

AN. In our sample, 50 patients (7.6 %) were under 60 years of age with FIT < 158 ngHb/ml (20 men and 30 women), with AA in nine patients (1.3 %) and no CRC.

DISCUSSION

Our results showed that ADR was higher in the DC (8,15), which is similar to the results of screening programs with direct colonoscopy (16). The differences between the PC and DC do not seem to be related to the screening method but rather to the intrinsic characteristics of the average risk population. It has been suggested that colonoscopy screening protects less against proximal cancer, partly due to a higher rate of undetected right colon adenomas and probably because proximal colon adenomas frequently progress to more advanced lesions, as a result of the different pathways of development (17,18). A second examination of the right colon increased the number of AN significantly, although the differences between the PC and DC were still apparent (11). There was a significant correlation between the number of proximal and distal adenomas, as demonstrated in a metanalysis (19).

Histologically, serrated lesions were mainly observed in the proximal colon: 13 % were SSL (0.3 % advanced SSL). Studies in screening populations have shown an SSL detection rate of 3 % (20), compared with an advanced SSL detection rate of 5.2 % in our patients. The second visualization of the proximal colon detected nine new advanced SSL and six SSL without dysplasia < 10 mm, which justifies the higher percentage of SSL in our study. A total of 43 % patients had a normal colonoscopy, which is somewhat lower than previously reported studies (9), while 24 % had non-advanced adenomas, which is higher than the results shown by other studies (21).

Reported AN results in CRC screening populations vary widely, depending on the FIT cut-off level, with the highest PPV for higher cut-off levels. AN percentages in studies vary between 37-38 % for cut-off levels between 10-50 ngHb/ml (9,22) and 52 % when FIT was 100 ngHb/ml (9). In our cohort, the PPV for AN was 44 % with a FIT cut-off level of 100 ngHb/ml, which is similar to those of other Spanish studies when calculated in colonoscopies performed in patients with positive FIT (21,23). A Swedish study found a PPV for AN of 29 % for a cut-off 20 µgHb/g (24) and the PPV for proximal AN was between 2-6 % for all FIT cut-offs, while it was 13.4 % in our cohort. The higher number

of AN in the right colon in our series compared with other reports may be because our patients were included in a study that evaluated the right colon and, therefore, endoscopists may have been more alert during the PC examination. In addition, we included cases with ≥ 3 adenomas < 10 mm as AA, which may justify the higher number of AA. With the new recommendations of the European Society of Gastrointestinal Endoscopy (ESGE) (25), these polyps are no longer considered as high risk and therefore, the number of colonoscopies with the conclusion of AA would decrease. Thus, it is even more important to adjust their indications to avoid the unnecessary ones. We found that AA were more common in older males (16), smokers and patients that consume > 20 g ethanol/day.

Our PPV for CRC for the same level of FIT was similar to that of other studies (9,21,24,26,27). Quintero et al. found similar results after taking into account the number of colonoscopies performed after positive FIT (663) and diagnosed 36 patients with CRC. This is consistent with our results, which were somewhat lower than those of the PROCOLON group (23), possibly due to the number of patients included in the first round of screening, as our patients were in the second and third rounds. In other studies with similar FIT cut-off levels, the CRC detection was much lower, ranging between 0.3 and 1.7 % (9,22,28,29). In the study recently published by the Working Group of the Galician Colorectal Cancer Early Detection Program, during the COVID-19 pandemic, the delay in performing diagnostic tests did not increase the diagnosis of CRC (30). However, the number of high-risk adenomas described is higher than in our population. This study found 2.2 % CRC, 43.9 % high-risk adenomas and 20.4 % low-risk adenomas.

In our study, a second visualization of the right colon increased the number of lesions detected, mainly low-grade sessile adenomas and sessile serrated lesions. Therefore, it could be interesting to include this maneuver in screening colonoscopies to improve the quality of the examination. An attempt should be made to establish cut-off levels with greater specificity but without losing sensitivity to optimize screening for CRC. This will avoid a significant number of colonoscopies in which no pathology is found (44 % in our series) and where the patient is exposed to unnecessary risk, which also saturates the endoscopy units. In our setting, this cut-off level was established at 158

ng/ml, at least for those under 60 years of age, maintaining an adequate sensitivity of 93 % and increasing specificity to 25 %.

In addition, other risk factors for CRC, such as gender, BMI and toxic habits, among others, could be taken into account in order to design a more personalized screening program. In this way, we found that there was a relationship between age, alcohol consumption and being overweight. Furthermore, males with a higher BMI had more adenomas, as found by other studies (31). FIT levels are significantly higher in individuals with AN and CRC, allowing these lesions to be differentiated from other non-relevant findings in the colonoscopy screening (23,24). The Florence colorectal screening program (32) found that FIT levels were significantly higher in individuals with advanced distal colon adenomas, which is similar to our data. In our population, the FIT level also increased in relation to the size and location of the lesions, which differs from other studies (24,26).

Our study has some limitations, such as the fact that it was an observational, cross-sectional study and patients with negative FIT were not analyzed, to better understand the sensitivity and specificity of FIT in our population. Furthermore, we take into account the influence of medication on the FIT results (33).

CONCLUSIONS

In asymptomatic patients at average risk of colorectal cancer after a positive FIT, 44 % of patients had AN, which was more frequent in the DC. AN were more common in older males, smokers and individuals with an alcohol intake > 20-40 g/day. FIT levels were higher in patients with AN, especially when located in the DC and associated with CRC, regardless of the location. Increasing the FIT cut-off value in those under 60 years of age could be considered.

REFERENCES

1. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. Gut 2017;66:683-91. DOI: 10.1136/gutjnl-2015-310912

2. Brenner H, Hoffmeister M, Arndt V, et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. J Natl Cancer Inst 2010;102:89-95. DOI: 10.1093/jnci/djp436

3. Soetikno RM, Kaltenbach T, Rouse RV, et al. Prevalence of nonpolypoid (flat and depressed) colorectal neoplasms in asymptomatic and symptomatic adults. JAMA 2008;299:1027-35. DOI: 10.1001/jama.299.9.1027

4. Provenzale D, Gupta S, Ahnen DJ, et al. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1.2018. J Natl Compr Canc Netw 2018;16:939-49. DOI: 10.6004/jnccn.2018.0067

5. Navarro M, Nicolás A, Ferrández A, et al. Colorectal cancer population screening programs worldwide in 2016: an update. World J Gastroenterol 2017;23:3632-42. DOI: 10.3748/wjg.v23.i20.3632

6. Gies A, Cuk K, Schrotz-King P, et al. Direct comparison of diagnostic performance of 9 quantitative fecal immunochemical tests for colorectal cancer screening. Gastroenterology 2018;154:93-104. DOI: 10.1053/j.gastro.2017.09.018

7. De Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. DOI: 10.1038/ajg.2012.249

8. Ribbing Wilen H, Blom J, Hoijer J, et al. Fecal immunochemical test in cancer screening - Colonoscopy outcome in FIT positives and negatives. Scand J Gastroenterol 2019;54:303-10. DOI: 10.1080/00365521.2019.1585569

9. Lee JK, Liles EG, Bent S, et al. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med 2014;160(3):171. DOI: 10.7326/M13-1484

10. Iovanescu D, Frandes M, Lungeanu D, et al. Diagnosis reliability of combined flexible sigmoidoscopy and fecal-immunochemical test in colorectal neoplasia screening. Onco Targets Ther 2016;9:6819-28. DOI: 10.2147/OTT.S122425

11. Haug U, Kuntz KM, Knudsen AB, et al. Sensitivity of immunochemical faecal occult blood testing for detecting left- vs right-sided colorectal neoplasia. Br J Cancer 2011;104:1779-85. DOI: 10.1038/bjc.2011.160

12. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-57. DOI: 10.1053/j.gastro.2012.06.001

13. Núñez Rodríguez MH, Díez Redondo P, Riu Pons F, et al. Proximal retroflexion versus second forward view of the right colon during screening colonoscopy: a multicentre randomized controlled trial. United European Gastroenterol J 2020;8(6):725-35. DOI: 10.1177/2050640620924210

14. American Joint Committee on Cancer (AJCC). TNM Staging System for Colorectal Cancer. 8th Edition. 2017.

15. Mangas-Sanjuán C, Jover R, Cubiella J, et al. Endoscopic surveillance after colonic polyps and colorrectal cancer resection. 2018 update. Gastroenterol Hepatol 2019;42:188-201. DOI: 10.1016/j.gastrohep.2018.11.001

16. Schramm C, Mbaya N, Franklin J, et al. Patient- and procedure-related factors affecting proximal and distal detection rates for polyps and adenomas: results from 1603 screening colonoscopies. Int J Colorectal Dis 2015;30:1715-22. DOI: 10.1007/s00384-015-2360-1

17. Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol 2011;42:1-10. DOI: 10.1016/j.humpath.2010.06.002

18. Erichsen R, Baron JA, Hamilton-Dutoit SJ, et al. Increased risk of colorectal cancer development among patients with serrated polyps. Gastroenterology 2016;150:895-902e895. DOI: 10.1053/j.gastro.2015.11.046

19. Morikawa T, Kato J, Yamaji Y, et al. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. DOI: 10.1016/j.gastro.2005.05.056

20. Dodou D, De Winter JC. The relationship between distal and proximal colonic neoplasia: a meta-analysis. J Gen Intern Med 2011;27:361-70. DOI: 10.1007/s11606-011-1919-y

21. Kahi CJ, Vemulapalli KC, Snover DC, et al. Findings in the distal colorectum are not associated with proximal advanced serrated lesions. Clin Gastroenterol Hepatol 2015;13:345-51. DOI: 10.1016/j.cgh.2014.07.044

22. Hamoudah T, Ma K, Esteban M, et al. Patients with small and diminutive proximal hyperplastic polyps have higher rates of synchronous advanced neoplasia compared with patients without serrated lesions. Gastrointest Endosc 2018;87:1518-26. DOI: 10.1016/j.gie.2017.12.028

23. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. DOI: 10.1056/NEJMoa1108895

24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. DOI: 10.1038/ajg.2010.179

25. Auge JM, Pellise M, Escudero JM, et al. Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. Gastroenterology 2014;147:628-36e621. DOI: 10.1053/j.gastro.2014.06.008

26. Cubiella J, Castro I, Hernández V, et al. Diagnostic accuracy of fecal immunochemical test in average- and familial-risk colorectal cancer screening. United European Gastroenterol J 2014;2:522-9. DOI: 10.1177/2050640614553285

27. Digby J, Fraser CG, Carey FA, et al. Faecal haemoglobin concentration is related to severity of colorectal neoplasia. J Clin Pathol 2013;66:415-9. DOI: 10.1136/jclinpath-2013-201445

28. Grazzini G, Visioli CB, Zorzi M, et al. Immunochemical faecal occult blood test: number of samples and positivity cutoff. What is the best strategy for colorectal cancer screening? Br J Cancer 2009;100:259-65.

29. Sohn DK, Jeong SY, Choi HS, et al. Single immunochemical fecal occult blood test for detection of colorectal neoplasia. Cancer Res Treat 2005;37:20-3. DOI: 10.4143/crt.2005.37.1.20

30. Nakama H, Kamijo N, Abdul Fattah AS, et al. Validity of immunological faecal occult blood screening for colorectal cancer: a follow up study. J Med Screen 1996;3:63-5. DOI: 10.1177/096914139600300203

31. Kapidzic A, van der Meulen MP, Hol L, et al. Gender differences in fecal immunochemical test performance for early detection of colorectal neoplasia. Clin Gastroenterol Hepatol 2015;13:1464-71e1464. DOI: 10.1016/j.cgh.2015.02.023

32. Ciatto S, Martinelli F, Castiglione G, et al. Association of FOBT-assessed faecal Hb content with colonic lesions detected in the Florence screening programme. Br J Cancer 2007;96:218-21. DOI: 10.1038/sj.bjc.6603534

33. Rodríguez-Alonso L, Rodríguez-Moranta F, Arajol C, et al. Proton pump inhibitors reduce the accuracy of faecal immunochemical test for detecting advanced colorectal neoplasia in symptomatic patients. PLoS One 2018;13:e0203359. DOI: 10.1371/journal.pone.0203359

Table 1. Description of the lesion findings

	Lesions	*Total*	*Proximal standard examination*	*Proximal second-look*	*p (proximal standard/proximal second look)*	*Distal*	*p (colon proximal/colon distal)*
Total	1,545	1,545	737 (51.2 %)	892 (56.3 %)	0.29	693 (43.7 %)	0.0001
Non-advanced adenoma (< 10 mm)	710	45 %	*424 (28.9 %)*	488 (30.9 %)	0.04	222 (14 %)	0.0001
Advanced adenoma	431	29 %	138 (9.4 %)	156 (9.9 %)	0.02	*275 (17.4 %)*	0.0001
Advanced SSL	52	3.4 %	*35 (2.4 %)*	*44 (2.8 %)*	0.01	8 (0.5 %)	0.5
SSL without dysplasia < 10 mm	76	5 %	35 (2.4 %)	*41 (2.6 %)*	0.07	35 (2.2 %)	0.3
CRC	32	2.2 %	9 (0.6 %)	9 (0.6 %)	0.3	*23 (1.6 %)*	0.7
Morphology of the lesions:							
LST (G and NG)							
Ip	21	1.2 %	7	0	0.73	14	0.8
Is	202	13 %	20	20	0.39	182	0.1
II (a,b,c)	1,084	69 %	579	672	0.0001	409	0.0001
	293	17 %	175	198	0.01	95	0.001

SSL: sessile serrated lesions; CRC: colorectal cancer; LST: laterally spreading lesions; G: granular; NG: non granular. p-values are χ^2 test.

Table 2. Advanced neoplasia, CRC and advanced-SSL findings and related pre-procedure factors

n = 656		***AN*** ***n = 268***			***CRC*** ***n = 32***			***Advanced-SSL*** ***n = 34***		
		Yes	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**
Location (n, %) (proximal/distal)		Proximal n = 96 (35.8 %) Distal n = 172 (64.2 %)		0.001*	Proximal n = 11 (34 %) Distal n = 21 (66 %)		0.002	Proximal n = 19 (56 %) Distal n = 15 (44 %)		0.07*
Age (mean ± SD)		60.8 ± 5.6	59.2 ± 5.8	0.0001†	61.7 ± 5.4	59.7 ± 5.8	0.07†	60.5 ± 5	59.8 ± 5.8	0.4†
Gender (male/female) n (%)		176 (65.7 %)/92 (34.3 %)		0.0001*	Male 22 (69 %): distal 13 Female 10 (31 %): distal 8		0.2*	18/16		0.9*
BMI (mean ± SD)		27.5 ± 4.5	27.4 ± 4.7	0.8†	29 ± 4.5	27.3 ± 4.6	0.04†	27.4 ± 4.5	27.4 ± 4.6	0.9†
Alcohol consumption (≥ 20 g/per day)		194 (72.4 %)	73 (27.2 %)	0.01*	18 (56.3 %)	14	0.0001*	9	25	0.9*
Smokers		*109 (40.7 %)*	*159 (59.3 %)*	0.001*	13 (43.8 %)	19	0.4*	15	19	0.1*
FIT (ngHb/ml) (n = 530)	Global	677.3 ± 838	565.6 ± 782.3	0.1†	1,077 (± 890)	585.17 ± 774	0.002†	470 ± 555	615 ± 800	0.4†
	Proximal	565 ± 848	612.3 ± 787.5	0.8†	1,607.5 ± 1,463	1,338.6 ± 1302.4	0.3†			
	Distal	832.6 ± 905	552 ± 751.5	0.001†	988.6 ± 839.9	939.6 ± 810.4	0.3†			

*p-values are χ^2 test; †Student's t test. SD: standard deviation; AN: advanced neoplasia; CRC: colorectal cancer; SSL: sessile serrated lesion; BMI body mass index; FIT: fecal immunological test only available in 530 subjects.