

# Colon capsule versus computed tomography colonography for colorectal cancer screening in patients with positive fecal occult blood test who refuse colonoscopy: a randomized trial

## Authors

Mathieu Pioche<sup>1,2</sup>, Christell Ganne<sup>3</sup>, Rodica Gincul<sup>1,4</sup>, Antoine De Leusse<sup>4</sup>, Julien Marsot<sup>5</sup>, Julien Balique<sup>5</sup>, Alain Fond<sup>5</sup>, Michel Bretagnolle<sup>5</sup>, Luc Henry<sup>6</sup>, Yann Billaud<sup>6</sup>, Romain Malezieux<sup>7</sup>, Marie-Georges Lapalus<sup>8</sup>, Christine Chambon-Augoyard<sup>1</sup>, Emilie Del Tedesco<sup>9</sup>, Olivia Scalone<sup>10</sup>, Jean-Charles Montoy<sup>11</sup>, Benoit Russias<sup>11</sup>, Antoine Detry<sup>11</sup>, Frédéric Veniat<sup>11</sup>, Jin Qiu<sup>12</sup>, Pierre-Jean Valette<sup>13</sup>, Annabel Taillandier<sup>14</sup>, Jean-Christophe Saurin<sup>1,2</sup>, Josiane Tomczyk-Ferrero<sup>15</sup>, Clémentine Gandilhon<sup>1,14</sup>, Léa Vecchiato<sup>14</sup>, Patricia Soler-Michel<sup>14</sup>, Thierry Ponchon<sup>1</sup>

## Institutions

- 1 Hepatogastroenterology department, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France
- 2 Lyon 1 University Claude Bernard, Lyon, France
- 3 Research and Medical Information Division, Hospices Civils de Lyon, Lyon, France
- 4 Hepatogastroenterology Department, Mermoz Hospital, Lyon, France
- 5 Radiology Department, Mermoz Hospital, Lyon, France
- 6 Radiology Department, Clinique du Val d'Ouest, Lyon, France
- 7 Radiology Department, Clinique du Parc, Saint-Priest en Jarez, France
- 8 Hepatogastroenterology Department, Hôpital Privé de L'est Lyonnais, Saint-Priest, France
- 9 Hepatogastroenterology Department, University Hospital Saint-Etienne, Saint-Priest en Jarez, France
- 10 Hepatogastroenterology Department, Nord Ouest Hospital, Villefranche-sur-Saône, France
- 11 Radiology Department, Clinique du Renaison, Roanne, France
- 12 Hepatogastroenterology Department, Public hospital, Roanne, France
- 13 Radiology Department, Hôpital Edouard Herriot, Hospices Civils de Lyon, Lyon, France
- 14 Departmental Screening Management Association Rhône ADEMAs 69, Lyon, France
- 15 Departmental Screening Management Association Loire Vivre 42, Saint-Etienne, France

submitted 11.8.2017

accepted after revision 19.12.2017

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DOI <https://doi.org/10.1055/s-0044-100721>

Published online: 27.2.2018 | Endoscopy 2018; 50: 761–769

© Georg Thieme Verlag KG Stuttgart · New York

ISSN 0013-726X

## Corresponding author

Mathieu Pioche, MD, Endoscopy Unit, Digestive Disease Department, L Pavillon – Edouard Herriot Hospital, 69437 Lyon Cedex, France  
 Fax: +33-4-72110147  
[mathieu.pioche@chu-lyon.fr](mailto:mathieu.pioche@chu-lyon.fr)

 Scan this QR-Code for the author's interview.



## ABSTRACT

**Objective** Some patients (10%–32%) with a positive guaiac fecal occult blood test (gFOBT) do not undergo the recommended colonoscopy. The aim of this study was to compare video capsule endoscopy (VCE) and computed tomography colonography (CTC) in terms of participation rate and detection outcomes when offered to patients with a positive gFOBT who did not undergo the recommended colonoscopy.

**Methods** An invitation letter offering CTC or VCE was sent to selected patients after randomization. Acceptance of the proposed (or alternative) procedure and procedure results were recorded. Sample size was evaluated according to the hypothesis of a 13% increase of participation with VCE.

**Results** A total of 756 patients were targeted. Following the invitation letter, 5.0% (19/378) of patients underwent the proposed VCE and 7.4% (28/378) underwent CTC, ( $P=0.18$ ). Following the letter, 9.8% (37/378) of patients in the VCE group underwent a diagnostic procedure (19 VCE, 1 CTC, 17 colonoscopy) vs. 10.8% in the CTC group (41/378: 28 CTC, 13 colonoscopy;  $P=0.55$ ). There were more potentially neoplastic lesions diagnosed in the VCE group than in the CTC group (12/20 [60.0%] vs. 8/28 [28.6%];  $P=0.04$ ). Thus, 15/20 noninvasive procedures in the VCE group (19

VCE, 1 CTC; 75.0%) vs. 10/28 in the CTC group (35.7%;  $P=0.01$ ) resulted in a recommendation of further colonoscopy, but only 10/25 patients actually underwent this proposed colonoscopy.

**Conclusion** Patients with a positive gFOBT result who do not undergo the recommended colonoscopy are difficult to recruit to the screening program and simply proposing an additional, less-invasive procedure, such as VCE or CTC, is not an effective strategy.

ClinicalTrials.gov

NCT02558881

TRIAL REGISTRATION: Randomized, controlled trial NCT02558881 at [clinicaltrials.gov](http://clinicaltrials.gov).

EU Clinical Trials Register

2012-A01294-39

TRIAL REGISTRATION: Randomized, controlled trial 2012-A01294-39 at [clinicaltrialsregister.eu](http://clinicaltrialsregister.eu).

## Introduction

The current colorectal cancer (CRC) screening strategy in many countries is based on a fecal occult blood test (FOBT) [1–3], yet participation is limited and varies from 7% to 67.7% between countries [1]. In France, a mass screening program was launched in 2002 and the screening experience reached 42% in 2006 [4]. For patients with a positive FOBT, colonoscopy is recommended. However, between 7% and 48.5% [5,6] of patients with positive FOBT do not undergo the recommended colonoscopy.

In France, the rate of patients with positive FOBT (either guaiac FOBT [gFOBT], or fecal immunochemical test) who refuse colonoscopy is 10%, despite a national reminder strategy [7]. This includes a postal reminder sent to the family doctor at 3 months, and then to the patient at 6 months and 1 year. These reminders contain information about CRC screening and the risk of CRC following a positive FOBT result. When the patient does not reply to any letter, or refuses to undergo the colonoscopy, no further action is taken. These patients are therefore lost to follow-up despite having a positive FOBT and a significant risk of CRC or adenoma.

With a view to reducing the number of such patients, the aim of the present study was to evaluate the benefits of proposing a less-invasive strategy than colonoscopy in order to recruit patients. The two options available were video capsule endoscopy (VCE) and computed tomography colonography (CTC). The latter is effective [6,8] in detecting CRC, and is recommended in France [9] in cases of contraindication or refusal of standard colonoscopy. VCE is another option [10] for CRC screening, and its superficial colonic lesion detection rate has been demonstrated to be superior to CTC [11]. However, the additional participation that could be obtained by proposing these procedures to patients who are unwilling to undergo colonoscopy despite positive FOBT in a screening program is not known. Participation in a strategy that is less invasive than colonoscopy but with high sensitivity/specificity [12,13] could improve patient selection by motivating otherwise reluctant patients to undergo colonoscopy if they have positive findings, but also avoid negative colonoscopy in patients without neoplastic findings on VCE or CTC. Therefore, the aim of this prospective randomized study was to compare VCE and CTC in terms of the additional participation obtained in patients with a positive gFOBT who did not undergo the further recommended colonoscopy.

## Methods

### Trial design

This was a randomized controlled trial with 1:1 allocation in two parallel groups. After selection and randomization, each patient received a letter of invitation to undergo either VCE or CTC.

### Registration

The study was conducted in accordance with the declaration of Helsinki and received approval from the South East French ethics committee (Comité de protection des personnes Sud-Est III) on 13 May 2013 (No.2013-001-B). The trial was registered at ClinicalTrials.gov (NCT 02558881) and EudraCT (2012-A01294-39).

### Participants

Patients were selected from the registry of two not-for-profit screening organizations (ADEMAS 69 and Vivre 42) in two French administrative departments (Rhône and Loire, respectively). Patients were included in the study if they were aged 50 years or more, had a positive gFOBT (Hemoccult II; Beckman Coulter, Villepinte, France) performed within the national screening program but without any result of colonoscopy received by the screening organization despite the reminder process being completed. Patients were excluded in cases of contraindication to the procedure proposed or when a colonoscopy was performed before patients had received the study letter.

### Interventions

After selection, the screening organizations sent the study letter to patients offering either a VCE or a CTC procedure, depending on group allocation. The letter proposed only one of the two procedures (VCE or CTC) without mentioning the other option. To accept or decline participation, patients had two options: they could either call the study manager or the not-for-profit screening organization (telephone numbers were provided in the letter) or make an appointment directly with one of the facilities performing VCE or CTC listed in the letter (telephone numbers provided in the letter). In parallel, a second letter was sent to the family physicians of each patient informing them about the study. Both the patient and family doctor were

blinded to the existence of a second group with another proposed procedure.

The facilities performing VCE or CTC were selected according to their expertise and their location in order to cover the whole of the two administrative departments. The total number of radiology centers for CTC was five (three in the Rhône department and two in the Loire department), and the number of gastroenterology centers for VCE was six (four in the Rhône department and two in the Loire department). According to the allocation arm, patients could choose their preferred center provided that it was located within their administrative department of residence. After making an appointment, radiologists (CTC group) or gastroenterologists (VCE group) informed the patients about the study and the procedure proposed in the letter (VCE or CTC, as appropriate), and collected patient's written informed consent.

### Data collection

All telephone calls to either accept or decline any further procedure made to the study manager or not-for-profit screening organization were recorded using a paper case report form. When patients accepted an appointment, the appointment report and procedure results were collected in the case report form and sent to the study manager. When the patient preferred to undergo a colonoscopy, the result was sent directly to the not-for-profit organization of the patient's administrative department of residence in accordance with usual screening program procedures.

### Procedures

CTC is usually performed in an outpatient setting. Bowel cleansing was necessary and involved a 4L polyethylene glycol (PEG; 4×64 g sachets or Fortrans; Ipsen, Boulogne, France) or sodium phosphate solution (Fleet phosphosoda; Ferring, Gentilly, France). Residual stool was marked with ingested contrast agent but without any injection of intravenous contrast agent. A rectal probe was then inserted to insufflate the bowel with air or carbon dioxide. A computed tomography scan was then performed with the patient first in the supine position and then in the prone position. After image acquisition, the software reconstructed the imaging data to reproduce a virtual 3-dimensional endoscopy of the colon.

For VCE, bowel preparation was standardized. Two days before the procedure the patient drank 10 glasses of water and ingested 4L of PEG (4×13.7 g of Movicol; Norgine, France). The day before the examination, the patient followed an exclusively liquid diet and ingested 3L of PEG solution. In the morning of the VCE examination, the patient ingested 1L of PEG solution (64 g of Fortrans; Ipsen) and then swallowed the capsule with 20 mg of domperidone (Motilium; Janssen Cilag, Val de Reuil, France), 30 mL sodium phosphate (Fleet phosphosoda; Ferring), and 1L of water, followed by 25 mL of sodium phosphate with 0.5L of water, and finally one bisacodyl suppository (Dulcolax; Boehringer, Paris, France). The patient was authorized to drink 2 hours after having swallowed the capsule and to eat 2 hours later, after capsule passage in the small bowel was verified. The PillCam Colon 2 capsule (Medtronic, Dublin, Ireland),

with two side cameras that obtain between 4 and 35 images/second, was used.

Lesions were described according to their relevance as adenomas or cancer, significant polyps (>5 mm) but without any presumed histology, and other bleeding lesions. In the VCE group, polyps under 5 mm in the rectosigmoid with hyperplastic appearance were not described and were considered to be hyperplastic polyps of no clinical relevance.

### Outcomes

The primary outcome was the participation rate for VCE and CTC. Participation was defined as the patient making an appointment and undergoing the procedure proposed (either VCE or CTC according to allocation) within a period of 3 months after sending the invitation letter.

Secondary outcomes were: participation rate for any diagnostic procedure after sending the invitation letter, including VCE, CTC, or colonoscopy; success rate of VCE and CTC; full review rate of colonic mucosa; diagnostic performance of VCE and CTC, defined as the proportion of patients with suspected colorectal neoplastic lesions; and the rate of achieving optical colonoscopy if a lesion was found, either by VCE or by CTC, in the 6 months following the positive result.

### Samples

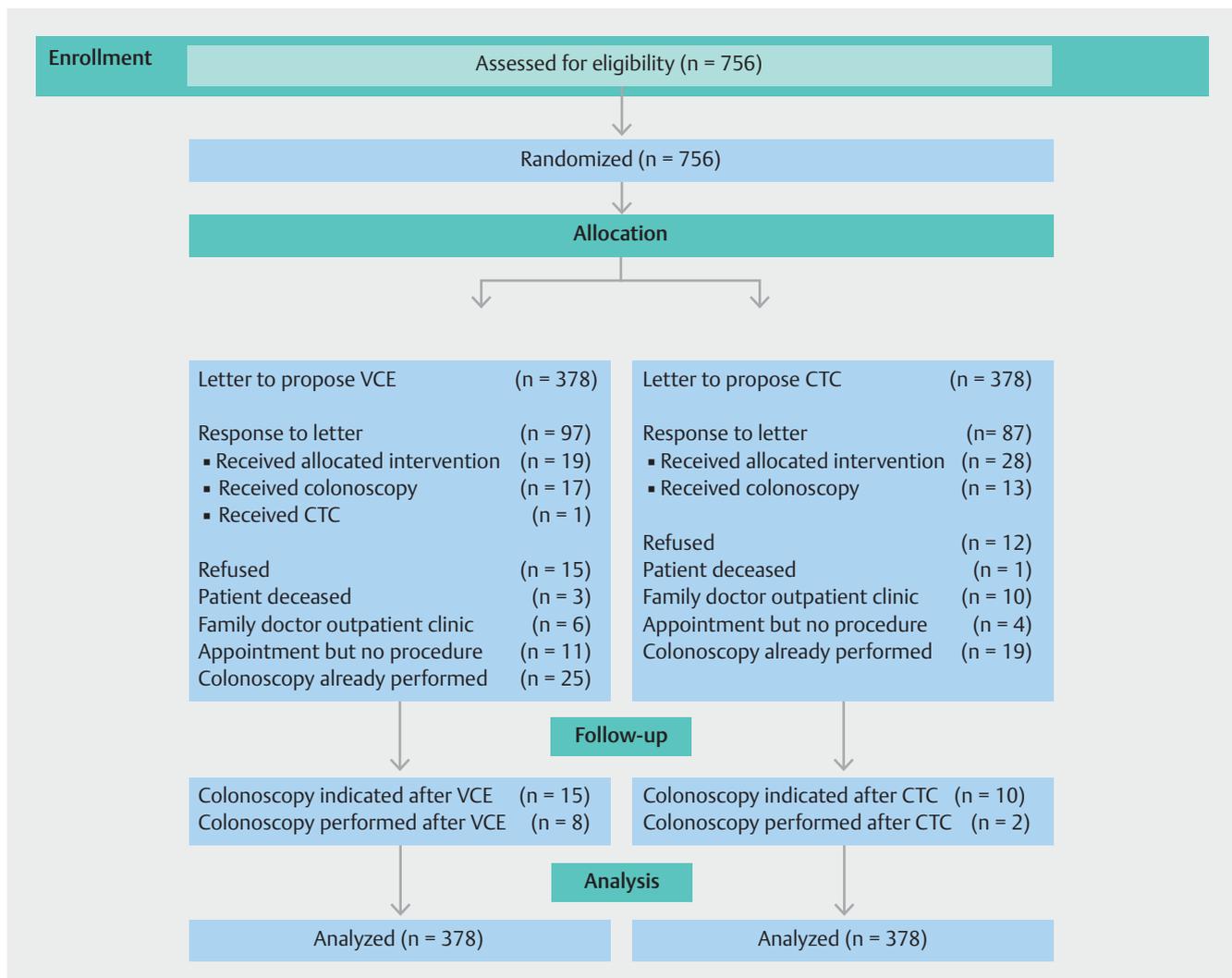
To the best of our knowledge there are no published data regarding VCE and CTC participation rates in a screening program. Therefore, the hypothesis for the study was based on expert opinion (members of the French national endoscopy society). With a statistical power of 90% and a two-sided alpha level of 0.05, using a hypothesis of 37% participation for CTC, the sample size needed to detect a statistically significant difference of 13% (50% participation in the VCE group) between CTC and VCE groups was 301 per group. Taking into account a 10% rate of loss to follow-up in each group, the estimated sample size needed was 332 per group.

### Randomization

After written informed consent was obtained, eligible patients were randomly allocated 1:1 to either VCE or CTC by a computerized randomization program without stratification by center or random blocks. The study manager generated the random allocation sequence and assigned participants to interventions. The invitation letter to enroll patients was sent by the not-for-profit screening organizations (ADEMAS 69 and Vivre 42).

### Statistical considerations

All data were collected using paper case report forms. Analyses were conducted according to intention-to-treat in which all randomized participants were analyzed. Categorical variables are presented as frequency (percentage). Quantitative variables were compared using the Wilcoxon test and qualitative ones were compared using the Pearson chi-squared test. A *P* value of <0.05 was regarded as statistically significant. All analyses were performed using SPSS Statistics version 19 (IBM Corp., Armonk, New York, USA).



► **Fig. 1** Study diagram. VCE, video capsule endoscopy; CTC, computed tomography colonography.

## Results

From June 2014 to June 2015, a total of 756 patients (387 females, 369 males) were sent an invitation letter; 378 were offered VCE and 378 were offered CTC (► **Fig. 1**). Baseline characteristics of invited patients were not different between the two groups (► **Table 1**). Among the letters sent, 21 were returned by the postal service for reason of wrong address (2.8%; 6 VCE and 15 CTC) (► **Table 2**).

### Patient response to invitation

Among the 756 patients, information was collected for 97 patients who were invited to a VCE appointment (25.7%) and 87 patients who were invited to a CTC appointment (23.0%;  $P = 0.35$ ) (► **Table 2**). Among these 184 patients, 92 (49 VCE, 42 CTC) declined the invitation for various reasons (► **Table 2**). A total of 44 of the 184 responders (23.9%) had already undergone a colonoscopy without any information provided to the not-for-profit screening organization.

► **Table 1** Baseline characteristics.

	VCE group n = 378	CTC group n = 378
Sex, n		
▪ Female	197	190
▪ Male	181	188
Age, mean (SD), years	62.5 (7.4)	62.7 (7.4)
▪ Female	63.7 (7.4)	63.3 (7.3)
▪ Male	63.0 (7.6)	62.0 (7.5)
Delay after positive gFOBT, mean (SD), years	3.6 (1.1)	3.7 (1.2)

VCE, video capsule endoscopy; CTC, computed tomography colonography; gFOBT, guaiac fecal occult blood test.

► **Table 2** Information received following distribution of study letter.

	VCE group n = 378	CTC group n = 378	P value
Information received, n (%)	97 (25.7)	87 (23.0)	0.35
▪ Participation to a diagnostic procedure	37 (9.8)	41 <sup>1</sup> (10.8)	0.19
▪ Appointment but no procedure performed	11 (2.9)	4 (1.1)	0.07
▪ Colonoscopy already performed	25 (6.6)	19 (5.0)	0.35
▪ Refusal	15 (4.0)	12 (3.2)	0.56
▪ Family physician consultation preferred	6 (1.6)	10 <sup>1</sup> (2.6)	0.31
▪ Patient had died	3 (0.8)	1 (0.3)	0.32
No information received, n (%)	275 (72.8)	276 (73.0)	0.94
Wrong address, n (%)	6 (1.6)	15 (4.0)	0.046

VCE, video capsule endoscopy; CTC, computed tomography colonography.

<sup>1</sup> One patient called to say he wanted to meet his family doctor and then he underwent colonoscopy independently (so he is counted only once as a participant to a diagnostic procedure).

► **Table 3** Participation.

	VCE group n = 378	CTC group n = 378	P value
VCE/CTC study appointment, n (%)	36 (9.5)	33 (8.7)	0.19
Procedure declined after study appointment, n (%)	11 (2.9)	4 (1.1)	0.07
Procedure performed following study appointment, n (%)	25 (6.6)	29 (7.7)	0.67
▪ <b>Procedure performed according to allocation<sup>1</sup></b>	<b>19 (5.0)</b>	<b>28 (7.4)</b>	<b>0.18</b>
▪ VCE proposed but CTC performed	1 (0.3)	N/A	N/A
▪ CTC proposed but VCE performed	N/A	0 (0)	
▪ Colonoscopy performed	5 (1.3)	1 (0.3)	0.01
Colonoscopy performed without VCE/CTC outpatient clinic appointment (spontaneous participation), n (%)	12 (3.2)	12 (3.2)	0.84
<b>Total number of diagnostic procedures performed following the study letter, n (%)</b>	<b>37 (9.8)</b>	<b>41 (10.8)</b>	<b>0.55</b>

VCE, video capsule endoscopy; CTC, computed tomography colonography; N/A, not applicable.

<sup>1</sup> Primary outcome: rate of patients who went to the appointment and underwent the proposed procedure according to the allocation.

Among the 184 patients who replied, 104 (56.5%) were women, with a mean age of 62.6 years; there was no significant difference in reply rate according to sex ( $P=0.41$ ), age ( $P=0.39$ ), or between younger (50–62 years), middle aged (63–74 years) and older (> 74 years) patients ( $P=0.71$ ).

Following the invitation letter, 36 patients in the VCE group (36/378, 9.5%) and 33 patients in the CTC group (33/378, 8.7%) attended the proposed outpatient clinic appointment ( $P=0.19$ ; ► **Table 3**). After the gastroenterologist outpatient appointment in the VCE group, 19 of the 36 patients underwent VCE, 5 underwent colonoscopy, 1 preferred to undergo a CTC examination, and 11 refused any procedure. After the radiologist outpatient appointment in the CTC group, 28 of the 33 patients underwent CTC, 1 patient underwent colonoscopy, and 4

refused any procedure. Thus, 5.0% of patients (19/378) in the VCE group and 7.4% of patients (28/378) in the CTC group underwent the proposed procedure ( $P=0.18$ ; primary outcome). Similarly, 6.6% of patients (25/378) in the VCE group and 7.7% of patients (29/378) in the CTC group underwent any diagnostic procedure (i.e. the one proposed or another diagnostic procedure;  $P=0.67$ ), with no significant difference according to sex ( $P=0.51$ ). Among the 36 patients who met a gastroenterologist, 13.9% finally underwent a colonoscopy (5/36) vs. 3.0% after meeting a radiologist (1/33;  $P=0.01$ ).

In parallel, the letter led to a direct gastroenterologist consultation to undergo a colonoscopy for 12 patients in each group (3.2%;  $P=0.84$ ) outside of the framework of the study. Among the patients targeted by a letter inviting them to un-

► **Table 4** Results of video capsule endoscopy and computed tomography colonography procedures.

	VCE group n = 20 (19 VCE, 1 CTC)	CTC group n = 28	P value
Success rate of the procedure <sup>1</sup> , n (%)	8 (40.0)	26 (92.9)	0.40
Positive findings, n (%)	16 (80.0)	13 (46.4)	0.04
▪ Normal	4 (20.0)	15 (53.6)	0.04
▪ Adenomas or cancer	6 (30.0)	3 (10.7)	0.07
▪ Clinically significant polyps without histology predicted	6 (30.0)	5 (17.9)	0.49
▪ Diverticulas	4 (20.0)	5 (17.9)	>0.99
Further colonoscopy recommended, n (%)	15 (75.0)	10 (35.7)	0.01
▪ Further colonoscopy finally performed	8 (53.3)	2 (20.0)	0.21

VCE, video capsule endoscopy; CTC, computed tomography colonography.  
<sup>1</sup> Success rate was defined by the rate of complete procedure with full review of the colonic mucosa.

dergo VCE or CTC, 13.3% (37/278: 19 VCE, 1 CTC, 17 colonoscopies) and 10.8% (41/378: 28 CTC and 13 colonoscopies;  $P=0.55$ ), respectively, underwent a diagnostic procedure (► **Fig. 1**). Considering the whole study population, the invitation letter led to a total of 78 (10.3%, 78/756) diagnostic procedures performed (19 VCE, 29 CTC, and 30 colonoscopies).

## Results of VCE and CTC

Among the 19 VCE and 29 CTC (including 1 in the VCE group) procedures performed, the success rate of procedures, defined by a full review of the colonic mucosa, was 40.0% in the VCE group (8/20, 19 VCE and 1 CTC) and 92.9% in the CTC group (26/28) CTC ( $P=0.40$ ; ► **Table 4**). Seven procedures (five VCE, two CTC) showed poor bowel preparation, and six capsules were not excreted at the end of the recording.

In total, 80% of the procedures performed in the VCE group (16/20; 19 VCE, 1 CTC) and 46.4% (13/28; 28 CTC) in the CTC group were positive ( $P=0.04$ ).

In the VCE group, 84.2% of the VCE procedures were positive (16/19) and the CTC procedure was negative. Positive findings were 12 potentially neoplastic lesions (60.0%; 6 adenomas or cancers, 6 clinically significant polyps) and 4 potentially bloody lesions (diverticulas).

In the CTC group, 46.4% of the CTC procedures were positive (13/28), with 8 potentially neoplastic lesions (28.6%; 3 adenomas or cancer, 5 polyps) and 5 potentially bloody lesions (diverticulas). There were more potentially neoplastic lesions diagnosed in the VCE group ( $P=0.04$ ).

Examples of lesions detected are presented in ► **Fig. 2**.

## Colonoscopy indications

Taking into account the diagnosis of potentially neoplastic lesions and the incomplete procedures, 15/20 procedures (75.0%; 19 CCE and 1 CTC) in the VCE group and 10/28 procedures (35.7%; 28 CTC) in the CTC group ( $P=0.01$ ) resulted in the recommendation for further colonoscopy (► **Table 4**). Thus, this strategy allowed 5/20 (25.0%) colonoscopies in the VCE group and 18/28 (64.3%) in the CTC group to be avoided.

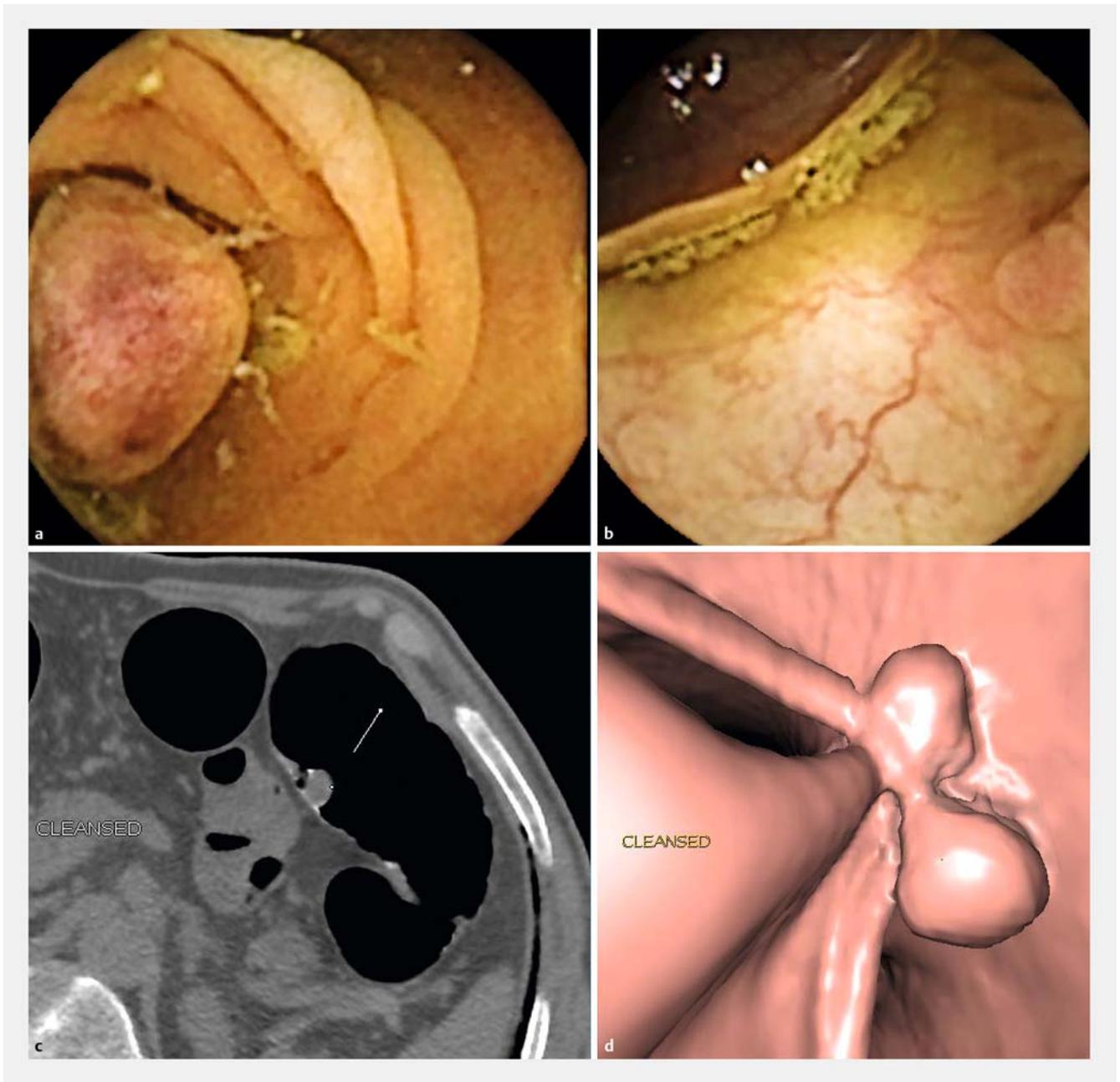
## Findings on colonoscopy

Six months after the recommendation of further colonoscopy (VCE or CTC), 8 patients (8/15, 53.3%) in the VCE group and 2 (2/10, 20.0%) in the CTC group underwent colonoscopy. Only four colonoscopies detected neoplastic lesions (one superficial adenocarcinoma and three adenomas; ► **Table 5**).

## Discussion

Proposing a VCE or CTC examination was not very effective in recruiting patients with a positive gFOBT result who did not undergo the recommended colonoscopy. In our work, there was no significant difference between VCE or CTC, with only 5.0% and 7.4% ( $P=0.18$ ) of patients, respectively, undergoing the proposed procedure. However, the lack of statistically significant difference is probably related to the small number of participants and the fact that CTC could be slightly more attractive to patients than VCE. This low participation rate is an important limitation of the study. Thus, the additional value of proposing a less-invasive procedure (VCE or CTC) was low, as only 6.3% (48/756) of targeted patients actually underwent a less-invasive procedure. In total, 78 patients (78/756, 10.3%) were recruited to the screening strategy when including the 30 additional patients who preferred a colonoscopy instead of the VCE or CTC. Among these, 24 did so without any contact with the study, but the remaining 6 met a study gastroenterologist or radiologist first. Meeting a gastroenterologist led to a colonoscopy being performed more frequently than meeting a radiologist (13.9% vs. 3.0%;  $P=0.01$ ). This result seems understandable, as gastroenterologists can schedule both examinations easily, unlike radiologists who perform only CTC for CRC screening.

In France, 10% of patients with a positive gFOBT [7] are reported to never undergo the further colonoscopy recommended, and this rate reaches 16.9% in the Dutch cancer screening program [14] and 32% in Taiwan [15]; Thus, recruiting patients with a high risk of neoplastic lesions who do not undergo the



► **Fig. 2** Example of lesions seen in video capsule endoscopy (VCE' **a, b**) and computed tomography colonography (CTC; **c, d**). **a** Polypoid lesion. **b** Diminutive flat polyp. **c** CTC native picture of a detected polyp. **d** CTC reconstructed picture of the same detected polyp.

recommended colonoscopy should become a target for a screening strategy. Different strategies have already been proposed to recruit those patients: patient navigators or giving healthcare providers reminders or performance data appeared to help, but data on system-level interventions were considered insufficient and are required [16]. One of the reasons patients refuse colonoscopy is the invasive nature of the procedure [17].

In France, three reminders are systematically sent to the patients (and their family doctor) following the positive FOBT result, and the current study aimed to recruit the refractory patients who do not undergo the recommended colonoscopy despite the reminders. Taken together, proposing VCE or CTC

after a positive FOBT seems of little additional value for refractory patients and different strategies should be tested, such as tailored telephone counseling, dedicated screening consultation with family doctor, or television advertisement. There have been more reports of investigations that aimed to improve participation to FOBT screening. For instance, tailored telephone counseling is reported to be not more effective than FOBT kit mailing [18], but the latter has been found to be more effective than an invitation letter [19]. Although currently no diagnostic kit can be sent directly to patients, it would be of interest in future studies targeting the population refractory to colonoscopy to investigate tailored telephone counseling.

► **Table 5** Results of colonoscopy recommended after video capsule endoscopy or computed tomography colonography.

	VCE group n=15	CTC group n=10
Colonoscopy performed, n (%)	8 (53.3)	2 (20.0)
Results, n		
▪ Cancer	1	0
▪ Adenomas	3	0
▪ Hyperplastic polyp	3	1
▪ Normal	1	0
▪ Result missing	0	1

VCE, video capsule endoscopy; CTC, computed tomography colonography.

From a diagnostic point of view, the number of potentially neoplastic lesions detected by VCE (60.0%) was significantly higher than the number detected by CTC (28.6%;  $P=0.04$ ). This may suggest capsule overdetection, which has been demonstrated in a prospective comparative study in which twice as many adenomas were detected by VCE than by CTC [20]. These results should be confirmed by other prospective studies before any conclusion can be drawn on a possible superiority of VCE as a less-invasive strategy [10]. Furthermore, CTC also requires good-quality bowel preparation [21] but also, if possible, additional stool tagging [22] and air insufflation to improve colon stretching [23]. Therefore, the tolerance of CTC approaches that of VCE, leaving the choice to be made on the basis of effectiveness; however, it is of note that the duration of the CTC procedure (less than 1 hour) is shorter than that of VCE (half a day or more), which depends on the colon transit time (mean 208 minutes [10]).

Positive VCE led to a colonoscopy indication in 15/19 cases and so colonoscopy was avoided in only 21.1% of patients. Furthermore, only 10 patients in total accepted to undergo the recommended colonoscopy. However, the results do suggest that a fourth reminder offering an outpatient clinic appointment with a gastroenterologist could lead to the recruitment of about 10% of refractory patients.

A major limitation of this work is the low rate of replies to the invitation letter; however, this reflects the real-life situation in this particularly challenging population who refuse any further diagnostic procedure despite a positive FOBT and a full sequence of reminders. Other strategies will be tested in the near future, such as dedicated motivational phone calls to attempt a more personalized approach (NCT 03276091). A second limitation is the lack of an exhaustive national screening database; nearly a quarter of the patients who were identified as not having undergone colonoscopy despite a positive gFOBT result did in fact undergo the procedure. This suggests that the effectiveness of the screening program may be underestimated.

To summarize, patients with a positive gFOBT result who do not undergo the recommended colonoscopy after postal reminders are difficult to recruit to the screening program, and simply proposing an additional, less-invasive procedure such as VCE or CTC, is not an effective strategy.

## Acknowledgments

We thank the two screening organizations, Vivre 42 and ADE-MAS 69, for their participation, and Philip Robinson for help in manuscript preparation.

## Competing interests

None

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