

Test-positive rate at CT colonography is increased by rectal bleeding and/or unexplained weight loss, unlike other common gastrointestinal symptoms

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Abstract

Purpose: We evaluated the rate of significant colonic and extra-colonic abnormalities at computed tomography colonography (CTC), according to symptoms and age.

Materials and methods: We retrospectively evaluated 7361 consecutive average-risk subjects (3073 males, average age: 60.3 ± 13.9 ; range 18–96 years) for colorectal cancer (CRC) who underwent CTC. They were divided into three groups according to clinical symptoms: 1343 asymptomatic individuals (group A), 899 patients with at least one “alarm” symptom for CRC, including rectal bleeding and unexplained weight loss (group C), and 5119 subjects with other gastrointestinal symptoms (group B). Diagnostic and test-positive rates of CTC were established using optical colonoscopy (OC) and/or surgery as reference standard. In addition, clinically significant extra-colonic findings were noted.

Results: 903 out of 7361 (12%, 95% confidence interval (CI) 0.11–0.13) subjects had at least one clinically significant colonic finding at CTC. CTC true positive fraction and false positive fraction were respectively 637/642 (99.2%, 95%CI 0.98–0.99) and 55/692 (7.95%, 95%CI 0.05–0.09). The pooled test-positive rate in group C (138/689, 20.0%, 95%CI 0.17–0.23) was significantly higher than in both groups A (79/1343, 5.9%, 95%CI 0.04–0.07) and B (420/5329, 7.5%, 95%CI 0.07–0.08) ($p < 0.001$). Aging and male gender were associated to a higher test positive rate. The rate of clinically significant extra-colonic findings was significantly higher in group C (44/689, 6.4%, 95%CI 0.04–0.08) versus groups A (26/1343, 1.9%, 95%CI 0.01–0.02) and B (64/5329, 1.2%, 95%CI 0.01–0.02) ($p < 0.001$).

Conclusion: Both test-positive and significant extra-colonic finding rates at CTC are significantly increased in the presence of “alarm” gastrointestinal symptoms especially in older patients.

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1. Introduction

Colorectal cancer (CRC) is the second cause of cancer-related death [1] and generally results from the transformation of clinically silent adenomas [2] that are sought by screening tests [3]. Persistence or sudden occurrence of various abdominal symptoms is often considered an indication to search or rule out colonic abnormalities, including CRC or precancerous polyps [4]. Literature suggests that the use of optical colonoscopy (OC) is warranted only for subjects with rectal bleeding and unexplained weight loss [5], whereas the other symptoms' specificity

remain questionable [6–8]. Meanwhile, the current diagnosis guidelines for individuals with average-risk for CRC only apply if there is no gastrointestinal symptom or complain [2], raising potentially important concerns. Indeed, as long as all symptoms are considered equivalent in terms of diagnostic yield, individuals with nonspecific gastrointestinal symptoms are evaluated, when needed, by OC, causing potential congestion of the facilities by low resection-rate procedures [9–11]. Second, patient compliance to current CRC screening guidelines is low. Almost 50% of asymptomatic subjects 50 years of age and older escape screening programs over a period of 10 years [12], while subjects with nonspecific gastrointestinal symptoms agree to undergo colonic explorations, for reassurance in a greater percentage [7].

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Computed tomography (CT) colonography (CTC) has emerged over the past decade as an accurate and less invasive alternative to OC in series of symptomatic patients [13,14]. Similarly good results were obtained in series of asymptomatic subjects [15]. To our knowledge, there are little data evaluating the test-positive rate according to gastrointestinal symptoms at CTC in the literature. This has implications for risk-stratification and potentially impacts CRC screening recommendation. We therefore evaluate in this study, the distribution of clinically significant colonic findings and extra-colonic at CTC, according to symptoms and age through a review of a 7-year experience in a single non-academic center.

2. Materials and methods

2.1. Patients

Our institutional review board approved the study and authorized this retrospective patient data analysis without further consent. We searched our hospital records for all subjects who completed a CTC procedure between June 2003 and August 2010. This search yielded 9122 subjects (3822 males, 5300 females, average age: 60.11 ± 13.75 years, range: 18–96 years). Indications for CTC included screening and direct referral ($n=8573$), secondary referral after incomplete OC ($n=285$), and Double Contrast Barium Enema (DCBE) referral change ($n=264$). This referral change was justified by the non-superiority of DCBE over CTC for colonic lesions in several studies [16,17].

Written informed consent was given by all subjects prior to procedures. 1761 subjects with a familial or personal history of polyps or colorectal cancer, genetic conditions, inflammatory bowel disease, who were at increased- or high-risk for colorectal cancer [2] were excluded. The remaining 7361 subjects, with average-risk [18] for CRC (general population) (3073 males, 4288 females, average age: 60.3 ± 13.9 years, range 18–96 years) were evaluated. Their clinical status with regard to the presence of the following gastrointestinal symptoms, prior to CTC was retrieved from the referral forms and/or gathered by patient's anamnesis and all other available patient data, including: (i) abdominal pain, (ii) constipation, (iii) diarrhea, (iv) irregular bowel movement, (v) bloating, (vi) melena, (vii) rectal bleeding, and (viii) unexplained weight loss. We retrospectively assigned the subjects to three main groups, according to the purported clinical importance of these symptoms regarding the level of specificity for CRC [5]: group A included the asymptomatic subjects; group B, the patients with one or more nonspecific symptom(s) (i–vii) in the absence of an established “alarm” symptom (vii and viii), who were assigned to group C.

2.2. CTC technique

All patients underwent the same standardized procedure that consisted into three steps including patient preparation, scanning and data interpretation. The preparation involved two steps including cathartic colonic cleansing and residual fluid tagging. For patients in good general condition, colonic cleansing

was achieved by a one-day clear liquid diet, one bottle of sodium phosphate preparation (Fleet-Phospho-soda[®], Wolfs, Zwijndrecht, Belgium) and 4 tablets of bisacodyl (Dulcolax[®], Boehringer Ingelheim, Ingelheim, Germany). For frail patients, cleansing consisted into 2 days of low-residue diet combined to 8 g of magnesium–sulphate on the examination day's morning, in addition to 2 tablets of bisacodyl and 100 ml of contrast agent (Gastrografin[®], Schering AG, Berlin, Germany) twice a day. In patients with renal insufficiency, cardiac failure or severe hypertension, preparation consisted in 3 days of low-residue diet with 2l of Moviprep[®] (Norgine, Heverlee, Belgium) (propylene-glycol + ascorbic acid) and 4 tablets of bisacodyl the day before the study. Residual fluid tagging was obtained by ingestion of 100 ml Gastrografin[®] the evening before the procedure and total colonic residual fluid volume was reduced by using a suppository of bisacodyl approximately 2 h before examination, except for patients who underwent CTC after incomplete OC. These patients drank 100 ml of Gastrografin and inserted a suppository of bisacodyl 1 h before the procedure. Before data acquisition, an iv injection of 20 mg/1 ml of Buscopan[®] (butylhyoscinebromid – Boehringer Ingelheim, Bruxelles, Belgium) was performed and a rectal cannula was inserted for colonic distension with an automatic carbon dioxide insufflator VMX-1010A (Vimap technologiesTM, Girona, Spain).

A 32-row (GE Lightspeed VCTTM, GE Healthcare, Milwaukee, WI) until 09/2010, then a 64-row (GE Discovery CT750 HDTM, GE Healthcare, Milwaukee, WI) multislice scanners were used for image acquisitions. Parameters consisted into 1.2 mm-thick slices with a 0.625 mm reconstruction interval, using a 50 mA s low-dose protocols with variable kV, adjusted to body-density for dose reduction, supplemented since 2010 by an adaptive statistical iterative reconstruction algorithm (ASIR) (GE Healthcare, Milwaukee, WI). Two acquisitions were performed: the first in supine position and the second, either in prone position, or right decubitus for unfit and obese patients. Immediate review of the images was performed by a radiologist in all cases. In 897 patients (10%), a third acquisition was ordered because of a segmental collapse preventing confident analysis.

Reading was performed offline on a workstation (Advantage Windows, GE Healthcare, Milwaukee, WI) with a software (Colon VCAR) allowing file-view, supplemented by “computer aided diagnosis” (CAD) assistance from January 2009, and electronic cleansing from June 2010. Reconstruction algorithms, image display preferences and reading principles used for interpretation are described elsewhere [19]. We used C-RAD reporting classification for all findings [20]. Each finding was assigned to both a colonic segment and a distance to the anal margin.

2.3. Data analysis

Clinically significant colonic findings were defined as either ≥ 6 mm polyps, masses or others requiring work-up or treatment [20]. Clinical files, and reports were searched for repeat CTC, OC and surgical procedures after the initial CTC, when applicable. A reviewer was requested to match CTC and the reference

standard findings, using available location by segment, and/or distance from the anal margin. We did not attempt to match using the size criteria because of known size discrepancies between OC and CTC polyp measurement [21]. Using an “intention to treat” algorithm, per-patient CTC diagnostic values for the diagnosis of clinically significant colonic findings were calculated. Patients with at least one matched finding were considered true-positive while patients with CTC findings unmatching the reference standard were considered as false-positive. Those with no finding at CTC and at least one positive finding on the reference standards were considered false-negative.

For patients with several colonic findings, two clinicians having access to all available data were requested to determine in consensus, the most significant with regard to CRC. For example, an individual with both a >6 mm colonic polyp and a non-neoplastic colonic mass accounted, for only the first. In addition, they were requested to establish a potential correspondence between the clinical symptoms and CTC colonic and significant extra-colonic findings (i.e.: E4 grade of the CTC Reporting and Data System, unrelated to a colonic disease).

2.4. Statistical analysis

Percentages are given with their 95% Confidence Intervals (CI). Continuous variables are compared using analysis of

variance, and two-tailed *t*-tests are used for direct comparison between two groups. Pearson chi-square tests are used to compare proportions and percentages. We used a regression analysis to evaluate the impact of the group of symptoms, age and gender on the test-positive rate. A *p*-value of less than 0.05 denotes a statistical significance.

3. Results

Fig. 1 summarizes the patient flowchart in this study. 903 out of the 7361 (12%, 95%CI 11–13%) subjects had at least one clinically significant colonic finding at CTC. Histopathological diagnoses and/or etiology for the confirmed findings are given in Table 1, showing that the abnormalities were most commonly of mucosal origin. Comparison of CTC to OC and/or surgery was possible for 692/903 (77%; 95%CI 0.074–0.79) of these subjects. CTC findings were confirmed in 637, while 55 patients were false-positive. In addition, repeat CTC, OC and/or surgery was performed within a range of 6–60 months in 1198 subjects with negative CTC findings for the following reasons: 656 patients underwent OC including programmed screening tests in 168, exacerbation of a “non-alarm” gastrointestinal symptom or occurrence of a new symptom in 443, and occurrence of an “alarm” symptom in 48. 527 patients underwent a second CTC including programmed screening tests in 287, new or

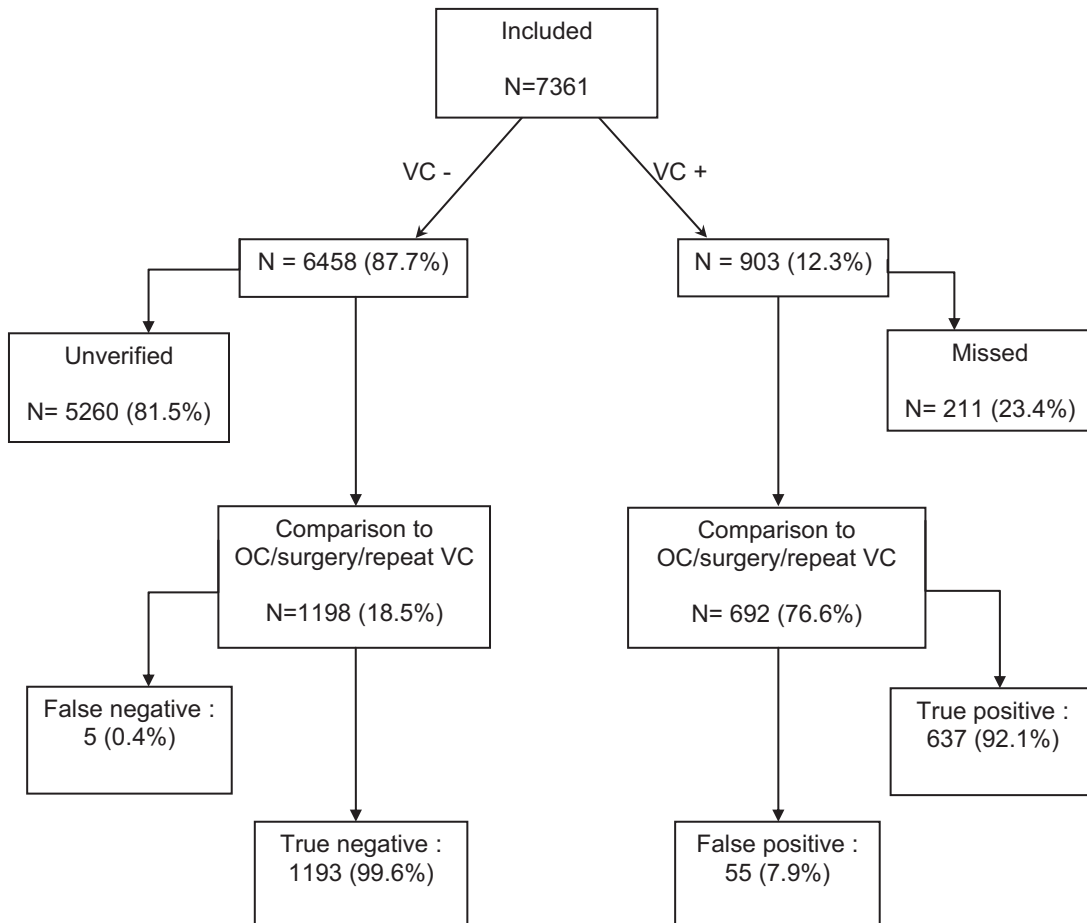


Fig. 1. Patient flowchart and diagnostic values of CTC. Between the parentheses are the percentages. Abbreviations as in the text.

Table 1
Histopathology and causes of confirmed CTC findings in 642 patients.

Causes of findings	Confirmed findings (N=642)	%	95%CI
Tumors and polyps			
Adenocarcinoma	97*	15.10	0.12–0.18
Carcinoid tumor	1	0.15	NA
Gastrointestinal stromal tumor	1	0.15	NA
Peritoneal metastasis	1	0.15	NA
Bladder cancer infiltration	1	0.15	NA
Villous	11	1.71	0.01–0.03
Tubulovillous	69	10.75	0.08–0.13
Tubular	70**	10.90	0.08–0.14
Hyperplastic	35**	5.45	0.04–0.07
Hamartomatous	1	0.15	NA
Fibrolipoma	1	0.15	NA
Lipoma	4	0.62	0.00–0.01
Post-hemorrhoid scar	1	0.15	NA
Others			
Diverticulitis	24	3.73	0.02–0.05
Ischemia	7	1.09	0.00–0.02
Endometriosis	7	1.09	0.00–0.02
Non-specific colitis	1	0.15	NA
Post-radiation colitis	1	0.15	NA
Leiomyoma	1	0.15	NA
Unknown (not recovered for analysis)	308	48.0	0.44–0.52

* Including 3 virtual colonoscopy false-negative.

** Including 1 virtual colonoscopy false-negative.

exacerbated “non alarm symptoms in 216 and “alarm symptoms” in 24. Twelve patients (all in group B) had surgical resection after acute diverticulitis.

Five patients were false-negative (2 with >6 mm polyps and 3 with cancers). All controlled cases, yield a 637/642 (99.2%, 95%CI 0.98–0.99) true-positive fraction and a 55/692 (7.95%, 95%CI 0.05–0.09) false-positive fraction.

The average number of symptoms per patient was 1.54 ± 0.35 (3800, 1524, 662, 29 and 3 patients had respectively 1, 2, 3, 4 and 5 symptoms). Abdominal pain and constipation were the most frequent, while unexplained weight loss was the least frequent symptom. Groups A, B and C included respectively 1343, 5329 and 689 patients; their demographic characteristics are given in Table 2. The average age in group C (64.37 ± 14.61 years) was significantly higher than in both groups A (60.96 ± 11.22 years) and B (59.43 ± 14.31 years) ($p < 0.001$). The male/female ratio was lower in group B (0.63) versus group A (1.03) ($p < 0.001$). The rate of E4 findings in the C-RAD reporting system was significantly higher in group C (44/689, 6.4%, 95%CI 0.04–0.08) versus groups A (26/1343, 1.9%, 95%CI 0.01–0.03) and B (64/5329, 1.2%, 95%CI 0.01–0.02) ($p < 0.001$). The regression analysis showed that the group of symptom (B < C), gender (F < M) and age all significantly impacted the test-positive rate at CTC. When pooling patients by age groups (Table 3), the test-positive rate in group C (138/689, 20.0%, 95%CI 0.17–0.23) was significantly higher than in groups A (79/1343, 5.8%, 95%CI 0.04–0.07) and B (420/5329, 7.8%, 95%CI 0.07–0.08) ($p < 0.001$), then, across all ages, except for patients younger

than 50 years of age whose test-positive rate in groups C, A and B were respectively (6/96, 6.25%, 95%CI 0.01–0.11), (5/173, 2.9%, 95%CI 0.00–0.05) and (47/1241, 3.8%, 95%CI 0.02–0.04) ($p = 0.412$). Diagnostic values of CTC within the three groups are given in Table 4. Both the true-positive fraction that was consistently above 97% in all groups ($p = 0.991$) and the false-positive fraction did not differ among all groups ($p = 0.240$).

4. Discussion

In a recent meta-analysis evaluating the value of various symptoms for CRC in primary care, Jellema et al. found large heterogeneities in the sensitivity and specificity of most symptoms [6]. Rectal bleeding and unexplained weight loss have consistently higher specificity than the others, according to another recent meta-analysis [5]. Similarly to studies using OC, the test-positive rate at CTC in our study was higher in patients with these “alarm” symptoms than in asymptomatic subjects and those with minor gastrointestinal symptoms ($p < 0.05$). Although the average age was also significantly higher in the “alarm” symptoms group ($p < 0.05$), age was not a key determinant, since similar differences were observed in all age groups above 50 years. In terms of CRC diagnostic recommendations, a test-positive rate around 20% makes OC the procedure of choice in patients with “alarm” symptoms, owing to the high resection-rate. An exception to this rule, though requiring stronger evidence, may be patients aged less than 50 years. Their findings prevalence was 6/96 (6.25%; 95%CI 0.01–0.11), i.e.: higher than in age-matched patients, but comparable to the overall prevalence in the other groups.

Due to the low specificity of the remaining gastrointestinal symptoms (alone or in combination), diagnostic recommendations currently fails to avoid OC facilities congestion by procedures yielding low rates of resection [9–11,22,23]. Exception made of melena and hemorrhoids, the “non-alarm” symptoms evaluated in this study are commonly described in patients with irritable bowel syndrome (IBS) which is a functional bowel disorder affecting 7–15% of the general population in the USA, women being twice more often afflicted than men [24,25]. Its diagnosis nicely illustrates the dichotomy between the daily management of gastrointestinal symptoms and evidence-based diagnostic recommendations. Indeed, the diagnosis of IBS is based exclusively on clinical criteria [26], but, up to 75% of clinicians believe that it should be ascertained by exclusion of organic disease [27]. For this purpose, approximately half of the patients with known or suspected IBS have undergone at least one diagnostic OC procedure [28]. Lastly, it has been estimated that 25% of the OC procedures performed in the USA are for patients with “non-alarm” gastrointestinal symptoms, although the actual risk of CRC in these patients is not higher than in asymptomatic individuals in several studies reporting very close ranges of test-positive rate at OC among IBS (range 1.9–9.3%) and asymptomatic individuals (range 4.5–12.1%) [29,30]. Several reasons could be advocated for this dichotomy, including physicians and patient’s anxiety,

Table 2
Patient groups demographics.

	Age \pm SD (years)	Age range (years)	Sex ratio	C-RAD reporting classification					
				C0	C1	C2	C3	C4	E4
Group A (N=1343)	60.96 \pm 11.22	21–91	683M/660F (1.03)	11	1179 (87%)	58 (4%)	55 (4%)	40 (3%)	26 (2%)
Group B (N=5329)	59.43 \pm 14.31	18–96	1975M/3144F (0.63)	21	4587 (86%)	269 (5%)	287 (5%)	165 (3%)	64 (1%)
Group C (N=689)	64.37 \pm 14.61	20–95	318M/371F (0.86)	0	594 (86%)	34 (5%)	38 (5%)	23 (3%)	44 (6%)
p-value	<0.0001*	NA	<0.0001**	NA	0.906	0.573	0.174	0.916	<0.001*

* Significantly higher ($p < 0.05$) in group C versus group B and group C versus group A.

** The proportion of males is significantly higher in group A versus group B ($p < 0.0001$).

NA = not applicable.

C-RAD reporting and data system.

- C0 = inadequate study.
- C1 = normal colon/benign lesion.
- C2 = polyps 6–9 mm in diameter or <3 in number.
- C3 = polyp >10 mm in diameter or >3 polyps with each 6–9 mm.

E4 = potentially important finding: communicate to referring physician.

symptoms severity and the lack of evidence that other diagnostic procedures may be as accurate or cost-effective than OC.

To our knowledge, our study is the first evaluating colonic findings according to gastrointestinal symptoms using CTC. This was possible as, since 2002, CTC has progressively become a routine procedure in our institution, acknowledged both by

our gastroenterologists, general practitioners and patients. The ranges of test-positive rate in asymptomatic individuals and those with “non-alarm” symptoms were low and comparable to those reported using OC. In both groups, the test-positive rate increased roughly linearly with aging ($p < 0.05$). Given their relatively low test-positive rate, patients with “non-alarm”

Table 3
CTC test-positive rate by age in all groups.

Age (years)	Group A	Group B	Group C	Total	p-value*
<50	5/173 (2.89%) 95%CI 0.00–0.05	47/1241 (3.78%) 95%CI 0.02–0.04	6/96 (6.25%) 95%CI 0.01–0.11	58/1510 (3.84%) 95%CI 0.02–0.05	0.412
50–59	23/441 (5.21%) 95%CI 0.03–0.07	91/1362 (6.68%) 95%CI 0.05–0.08	22/159 (13.83%) 95%CI 0.08–0.19	136/1962 (6.93%) 95%CI 0.05–0.08	0.003*
60–69	30/420 (7.14%) 95%CI 0.04–0.09	107/1251 (8.55%) 95%CI 0.07–0.10	42/151 (27.81%) 95%CI 0.21–0.35	179/1822 (9.82%) 95%CI 0.08–0.11	<0.0001*
70–79	14/244 (5.73%) 95%CI 0.02–0.08	134/1077 (12.44%) 95%CI 0.10–0.14	42/180 (23.33%) 95%CI 0.17–0.29	190/1501 (12.65%) 95%CI 0.10–0.14	<0.0001*
>80	7/65 (10.77%) 95%CI 0.03–0.18	41/398 (10.30%) 95%CI 0.07–0.13	26/103 (25.24%) 95%CI 0.17–0.33	74/566 (13.07%) 95%CI 0.10–0.16	0.003**
Total	79/1343 (5.88%) 95%CI 0.04–0.07	420/5329 (7.88%) 95%CI 0.07–0.08	138/689 (20.02%) 95%CI 0.17–0.23	637/7361 (8.65%) 95%CI 0.08–0.09	<0.0001*
p-value	0.176	<0.0001	=0.002	<0.0001	NA

* Significant difference between group C versus groups A and B.

** Significant difference between group C versus groups B.

Table 4
Diagnostic values of CTC versus OC and/or surgery in groups A, B and C. Abbreviations as in the text.

	True-positive fraction	False-positive fraction
Group A	79/79 (100%) (95%CI=NA)	10/89 (11%) (95%CI 0.04–0.17)
Group B	420/422 (99.5%) (95%CI 0.98–1.00)	38/458 (8%) (95%CI 0.05–0.11)
Group C	138/141 (97.9%) (95%CI 0.95–1.00)	7/145 (5%) (95%CI 0.01–0.08)
<i>p</i> -value	0.991	0.240

symptoms may indeed benefit from accurate noninvasive diagnostic procedures. In our series of 5329 patients with “non-alarm” symptoms, 4088 were older than 50 years of age: it may thus be emphasized that these symptoms were an incentive to comply with screening guidelines and should therefore be carefully sought. Although patients under 50 years of age and suspected of IBS should not undergo any colonic exploration, many of them unfortunately do in most institutions, including ours. In our series, this malpractice applies to 1241 patients (23% referred by gastroenterologists) for whom CTC has a low test-positive rate in good correlation with other series, but represent the most comprehensive and the less harmful option as compared to OC, the standard of reference.

In this setting, our study confirmed that CTC has a high true-positive fraction and a low false-positive fraction for polyps and CRC in all groups [15,31] clearly advocating for its recommendation in patients with “non-alarm” gastrointestinal symptoms.

Considering the recommendations guidelines for CRC, the main disadvantage of CTC, namely the inability to perform polypectomy, may raise cost-effectiveness issues. In our study, at least 420 additional OC were performed in the group of patients with “non-alarm” symptoms, while approximately 5000 potential diagnostic OC procedures were replaced by less expensive CTC procedures, putting obviously the cost-effectiveness balance in favor of a primary diagnostic procedure by CTC in our institution. In addition, offering a same-day OC after positive CTC scenario currently prevent the need for a second bowel preparation in most institutions including ours [32]. The ability to detect clinically significant extra-colonic abnormalities (E4) may also impact CTC cost-effectiveness. A total number of 134 individuals had E4 findings, which represent an asset for CTC. Interestingly, the rate of E4 findings distribution *per group* was quite similar to the test-positive rate distribution, prevailing thus in older patients. This indicates that E4 findings rate are not either increased by nonspecific gastrointestinal symptoms. Lastly, the concern of exposure to ionizing radiation during CTC, has dropped significantly with the latest generation of scanners [33]. In our institution, the combined dose for supine and prone acquisitions of an average-sized subject is approximately 3 mSv (i.e.: levels comparable to the annual environmental scatter doses).

Some limitations may be applied to this study and its conclusions, the first of which is its retrospective nature that resulted into several patients lost to follow-up and clinical data missing.

Histopathological data were also missing in several patient from mis-retrieved polypectomies that are, however, not uncommon [33]. Reported symptoms were not based on a checklist of all gastrointestinal symptoms. The same design forced us to pool symptoms in two groups, resulting into potential masking of the effect of one or several underrepresented individual symptom(s) on the CTC test-positive rate. Moreover, age of symptoms onset, their intensity and duration lacked, preventing a better detailed relationship between symptoms and test-positive rate. Reported diagnostic values of CTC, though comparable with previously reported studies, are subject to verification bias, since OC was mostly performed when CTC was positive. In addition, most of the unverified CTC positive cases were small polyps, which probably decreased artificially the false-positive rate. Lastly, patients with at least one gastrointestinal symptom largely outnumbered asymptomatic subjects in our study, with 6929 out of the 7361 average-risk subjects for CRC having at least one symptom. This selection bias was caused by a progressive referral replacement of DCBE by CTC during the study period.

5. Conclusion

In conclusion, asymptomatic subjects, patients with “non-alarm” gastrointestinal symptoms and even young patients with “alarm” symptoms for CRC have nearly similarly low test-positive rates at CTC. Overall, the rate of colonic and extra-colonic findings increased with age, male gender and the presence of “alarm” symptoms for CRC. The high diagnostic value of CTC in all patient groups makes it the examination of choice in low-yield patients; who include asymptomatic subjects and those with “non-alarm” gastrointestinal symptoms.

Conflict of interest

The authors declare that there is no conflict of interest.

References

- [1] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49(6):1374–403.
- [2] Levin B, Lieberman DA, McFarland B, Smith RA, Brooks D, Andrews KS, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58(3):130–60.
- [3] McFarland EG, Levin B, Lieberman DA, Pickhardt PJ, Johnson CD, Glick SN, et al. Revised colorectal screening guidelines: joint effort of the American Cancer Society, U.S. Multisociety Task Force on Colorectal Cancer, and American College of Radiology. *Radiology* 2008;248(3):717–20.
- [4] Arditi C, Peytremann-Bridevaux I, Burnand B, Eckardt VF, Bytzer P, Agreus L, et al. Appropriateness of colonoscopy in Europe (EPAGE II). Screening for colorectal cancer. *Endoscopy* 2009;41(3):200–8.
- [5] Adelstein BA, Macaskill P, Chan SF, Katelaris PH, Irwig L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. *BMC Gastroenterol* 2011;11:65.
- [6] Jellema P, van der Windt DA, Bruinvels DJ, Mallen CD, van Weyenberg SJ, Mulder CJ, et al. Value of symptoms and additional diagnostic tests for colorectal cancer in primary care: systematic review and meta-analysis. *BMJ* 2010;340:c1269.

- [7] Lieberman DA, Williams JL, Holub JL, Morris CD, Logan JR, Eisen GM, et al. Colonoscopy utilization and outcomes 2000 to 2011. *Gastrointest Endosc* 2014;80(1):133–43.
- [8] Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. *Br J Gen Pract* 2011;61(586):e231–43.
- [9] Rex DK, Lieberman DA. Feasibility of colonoscopy screening: discussion of issues and recommendations regarding implementation. *Gastrointest Endosc* 2001;54(5):662–7.
- [10] Hoffman RM, Espey D, Rhyne RL. A public-health perspective on screening colonoscopy. *Expert Rev Anticancer Ther* 2011;11(4):561–9.
- [11] Levin TR. Colonoscopy capacity: can we build it? Will they come? *Gastroenterology* 2004;127(6):1841–4.
- [12] Shapiro JA, Seeff LC, Thompson TD, Nadel MR, Klabunde CN, Vernon SW. Colorectal cancer test use from the 2005 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev* 2008;17(7):1623–30.
- [13] Halligan S, Wooldrage K, Dadswell E, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. *Lancet* 2013;381(9873):1185–93.
- [14] Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013;381(9873):1194–202.
- [15] Pickhardt PJ, Choi JR, Hwang I, Butler JA, Puckett ML, Hildebrandt HA, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003;349(23):2191–200.
- [16] Johnson CD, MacCarty RL, Welch TJ, Wilson LA, Harmsen WS, Ilstrup DM, et al. Comparison of the relative sensitivity of CT colonography and double-contrast barium enema for screen detection of colorectal polyps. *Clin Gastroenterol Hepatol* 2004;2(4):314–21.
- [17] Sosna J, Bar-Ziv J, Libson E, Eligulashvili M, Blachar A. Critical analysis of the performance of double-contrast barium enema for detecting colorectal polyps ≥ 6 mm in the era of CT colonography. *AJR Am J Roentgenol* 2008;190(2):374–85.
- [18] Summaries for patients. Screening for colorectal cancer: recommendations from the United States Preventive Services Task Force. *Ann Intern Med* 2002;137(2):138.
- [19] Hock D, Ouhadi R, Materne R, Aouchria AS, Mancini I, Broussaud T, et al. Virtual dissection CT colonography: evaluation of learning curves and reading times with and without computer-aided detection. *Radiology* 2008;248(3):860–8.
- [20] Zalis ME, Barish MA, Choi JR, Dachman AH, Fenlon HM, Ferrucci JT, et al. CT colonography reporting and data system: a consensus proposal. *Radiology* 2005;236(1):3–9.
- [21] de Vries AH, Bipat S, Dekker E, Liedenbaum MH, Florie J, Fockens P, et al. Polyp measurement based on CT colonography and colonoscopy: variability and systematic differences. *Eur Radiol* 2010;20(6):1404–13.
- [22] Brown ML, Klabunde CN, Mysliwiec P. Current capacity for endoscopic colorectal cancer screening in the United States: data from the National Cancer Institute Survey of Colorectal Cancer Screening Practices. *Am J Med* 2003;115(2):129–33.
- [23] Seeff LC, Manninen DL, Dong FB, Chattopadhyay SK, Nadel MR, Tangka FK, et al. Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? *Gastroenterology* 2004;127(6):1661–9.
- [24] Meleine M, Matricon J. Gender-related differences in irritable bowel syndrome: potential mechanisms of sex hormones. *World J Gastroenterol* 2014;20(22):6725–43.
- [25] Khan S, Chang L. Diagnosis and management of IBS. *Nat Rev Gastroenterol Hepatol* 2010;7(10):565–81.
- [26] Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006;130(5):1480–91.
- [27] Spiegel BM, Farid M, Esrailian E, Talley J, Chang L. Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, gastroenterologists, and IBS experts. *Am J Gastroenterol* 2010;105(4):848–58.
- [28] Talley NJ, Boyce P, Owen BK. Psychological distress and seasonal symptom changes in irritable bowel syndrome. *Am J Gastroenterol* 1995;90(12):2115–9.
- [29] Lieberman DA, Holub J, Eisen G, Kraemer D, Morris CD. Prevalence of polyps greater than 9 mm in a consortium of diverse clinical practice settings in the United States. *Clin Gastroenterol Hepatol* 2005;3(8):798–805.
- [30] Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: a systematic review. *Am J Gastroenterol* 2002;97(11):2812–9.
- [31] Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008;359(12):1207–17.
- [32] Pickhardt PJ, Taylor AJ, Kim DH, Reichelderfer M, Gopal DV, Pfau PR. Screening for colorectal neoplasia with CT colonography: initial experience from the 1st year of coverage by third-party payers. *Radiology* 2006;241(2):417–25.
- [33] Berrington de Gonzalez A, Kim KP, Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Smith-Bindman R, et al. Radiation-related cancer risks from CT colonography screening: a risk-benefit analysis. *AJR Am J Roentgenol* 2011;196(4):816–23.