Extracolonic Findings at Virtual Colonoscopy: An Important Consideration in Asymptomatic Colorectal Cancer Screening

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BACKGROUND: Virtual colonoscopy has been evaluated for use as a colorectal cancer screening tool, and in prior studies, it has been estimated that the evaluation of extra-colonic findings adds \$28-\$34 per patient studied.

METHODS: As an ancillary study to a prospective cohort study comparing virtual colonoscopy to conventional colonoscopy for colorectal cancer detection, the investigators retrospectively determined the number and estimated costs of all clinic visits, imaging and laboratory studies, and medical procedures that were generated as a direct result of extra-colonic findings at virtual colonoscopy.

RESULTS: We enrolled 143 subjects who underwent CTC followed by conventional colonoscopy. Data were available for 136 subjects, and 134 (98%) had at least one extra-colonic finding on CT. Evaluation of extra-colonic findings was performed in 32 subjects (24%). These subjects underwent 73 imaging studies, 30 laboratory studies, 44 clinic visits, 6 medical procedures, and 44 new or return outpatient visits over a mean of 38 months following the CTC. The most common findings causing further evaluation were lung nodules and indeterminate kidney lesions. No extra-colonic malignancies were found in this study. A total of \$33,690 was spent in evaluating extra-colonic findings, which is \$248 per patient enrolled.

CONCLUSIONS: The cost of the evaluation of extra-colonic findings following virtual colonoscopy may be much higher in actual practice than is suggested by prior studies. This will impact the cost-effectiveness of using virtual colonoscopy for asymptomatic colorectal cancer screening and underscores the importance of standardizing the reporting of extra-colonic findings to encourage appropriate follow-up.

KEY WORDS: colorectal cancer screening; colon cancer screening; virtual colonoscopy; computed tomography colonography; incidental findings; extracolonic findings.

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BACKGROUND

Computed tomographic colonography (CTC), more popularly referred to as virtual colonoscopy, is a radiologic technique that has shown promise as a tool for colorectal cancer screening.^{1,2} Recent guidelines incorporate CTC as an option for asymptomatic colorectal cancer screening.³ CTC is performed in the prepared colon using a low radiation dose CT technique in both prone and supine positions after gentle insufflation of the colon with room air or carbon dioxide. Software image reconstruction allows non-invasive two-dimensional and three-dimensional views of the colon. Results of studies looking at the performance of CTC to detect colon polyps are variable,⁴⁻⁶ but rapid improvement is likely in the face of development of improved imaging software, improvements in scanners, and other advances, such as stool-negating contrast.

A distinctive feature of CTC is the additional information obtained through imaging the entire abdomen and pelvis, and often the lower thorax. This attribute could potentially benefit patients by providing useful clinical information, but would have to be carefully weighed against the additional cost and potential harm to patients via morbidity incurred in working up findings ultimately found to be unimportant. The prevalence of these so-called extra-colonic findings (ECFs) has been evaluated in several studies, and some of those studies have also examined the additional costs associated with working up ECFs, though they have primarily examined expenses related to additional radiographic studies with a fairly brief follow-up period.⁷⁻¹²

The aims of our study were to determine the prevalence of ECFs in a population of largely asymptomatic patients appropriate for routine colon cancer screening, characterize the nature of these findings, and describe additional workup and the estimated cost of evaluating these findings.

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MATERIALS AND METHODS

Two CTC examinations, the first without oral contrast and the second with oral contrast, were performed at a large university medical center in 143 patients referred for conventional colonoscopy as part of a prospective study designed to evaluate the role of using oral contrast with CTC to detect colorectal polyps as compared to conventional colonoscopy (unpublished). The subjects were enrolled and the procedures performed between April 2002 and December 2003.

The study was approved by the institutional review board. Subjects were required to be 40 years of age or older, to be able to hold their breath for at least 20 s, to be non-pregnant/non-lactating, and to have an indication for conventional colonoscopy. Patients were excluded if there was a family history of familial adenomatous polyposis or hereditary non-polyposis colon cancer; a known allergy to iodine; renal insufficiency; inflammatory bowel disease or previous evaluation highly suggestive of inflammatory bowel disease; previous colon surgery; females who were pregnant or lactating; orthopedic metal prosthesis; partial or complete bowel obstruction. Patient characteristics are shown in Table 1.

CTC data were collected using a four-slice helical CT scanner (GE LightSpeed QX/i) with 5-mm collimation, 120 KVp, and 180 mA for the supine position and 80 mA for the prone position. Colonic distention for all CT scans was accomplished with a carbon-dioxide electronic insufflator. The raw data were reconstructed at 1-mm intervals. Following these scans, colonoscopy was performed the same day using segmental unblinding of the CTC results.

CTCs were initially read by one of three board-certified radiologists, all with previous CTC experience. Results were sealed in an envelope and provided for segmental unblinding during colonoscopies that were performed by one of two board-certified gastroenterologists.

Subsequently, a chart review was performed to determine the prevalence of ECFs. The results of all CTCs were included in their entirety in the subject's electronic medical record (EMR). ECFs were categorized as findings of high, moderate, or low importance in a manner similar to that in

Table 2. Extra-Colonic Findings of High Importance at Computed Tomography Colonography

Finding	No. of subjects
Lung nodules	23
Renal mass	1
Markedly thickened terminal ileum	1

previously published studies looking at extra-colonic findings at CTC.^{7,9-11}

Findings of high importance were those deemed very likely to be of high significance to the patient and the ones likely to require additional attention, either surgical or medical management, or mandating additional diagnostic tests. This category included lung nodules and other masses.

Findings of moderate importance were ones that had a lower, but significant likelihood of requiring additional workup or treatment and on a less urgent basis than those of high importance. Findings included in this category included indeterminate liver, pancreas, or kidney lesions, and adrenal lesions of 2 cm or less.

Findings of low importance were those considered to be unimportant and unlikely to require additional workup or treatment in the absence of any associated symptoms. There were numerous findings that were felt to be of low importance, and these included renal cysts, vascular calcifications, gallstones, and hiatal hernias.

Of the 143 patients enrolled, 136 had sufficient information in their EMR that allowed the investigators to conclude whether or not any additional evaluation or treatment of ECFs had been performed. Patients were not contacted directly during the course of this study to assess the possibility of evaluation outside our medical network. The subjects' EMRs were reviewed to determine what, if any, subsequent workup of ECFs had been performed through April 2006. In order for a study or procedure to be attributed to evaluation or management of an ECF, there had to be supporting evidence located in physician notes in the EMR indicating that the extra-colonic finding or findings were new ones and that additional evaluation or treatment was being ordered specifically for further evaluation or treatment of the ECF(s). All studies or interventions performed were categorized as diagnostic imaging studies, additional diagnostic tests, cognitive services, or invasive procedures or surgery. The costs of these interventions were determined using the 2006 Medicare Allowances for the state of North Carolina.¹³

RESULTS

The follow-up period after CTC ranged from 26 to 45 months (with a median of 38 months). Of the 136 patients with sufficient data in their EMRs, 134 (98%) had at least 1 ECF with a total of 423 ECFs. Twenty-five patients (17.5%) had a total of 25 ECFs of high importance (see Table 2). All but two of these patients had lung nodules; one patient with a thickened terminal ileum was eventually determined to have Crohn's ileitis, and one patient with a renal mass was eventually determined to have a complex cyst that was likely not neoplastic. Fourteen of these subjects (56%) received additional evaluation.

Table 1. Baseline Characteristics of the Subjects

Characteristic	No. (%)
Median age in years (range)	57 (44-83)
Gender	
% Male	48
Race	
White	123 (88%)
Black	17 (12%)
Family history of colorectal cancer	21 (15%)
Family history of colorectal polyps	11 (8%)
Symptoms	
Changes in bowel habits	9 (6)
Abdominal pain	11 (8)
Rectal bleeding	4 (3)
Weight loss	0 (0)
Iron deficiency	0 (0)
No. of symptoms/participant	
0	123 (87)
1	14 (10)
2	5 (4)

There were 53 ECFs of moderate importance present in 35 subjects (24.5%), and 15 of these subjects, or 43%, had additional evaluation or treatment. The most common ECF of moderate importance was indeterminate kidney lesions with a total of 11. Table 3 lists other findings of moderate importance.

There were 345 ECFs of low importance identified in 74 subjects (51.7%), with only 3 of these (4%) getting additional evaluation. There were numerous extra-colonic findings in this category, which are listed in Table 4.

Evaluation of ECFs was performed in 32 patients, 24% of the patients for whom data were available (Table 5). Of the findings instigating further workup, 44% were findings of high importance, 47% were of moderate importance, and 9% were of low importance. These subjects underwent 73 imaging studies, including 37 CT scans with 22 of those being studies without intravenous contrast of the chest to evaluate lung nodules. Additionally, there were 16 ultrasound studies, with 11 of those being retroperitoneal studies to evaluate indeterminate kidney lesions. Six abdominal MRIs were performed to better characterize adnexal, kidney, and adrenal lesions. Also, four chest X-rays, eight KUBs, one hip X-ray, and one IVP were ordered to further evaluate various ECFs. The total estimated cost of the 73 imaging studies using 2006 Medicare reimbursement data for North Carolina was \$25,227. If that cost is averaged over the 136 subjects studied, then \$185 is spent for additional radiographic imaging per subject undergoing CTC.

Six subjects were further evaluated with a total of 30 laboratory studies, including basic metabolic panels, complete blood counts, serum prostate-specific antigen, CA-125, urine studies, and sputum studies, including culture and direct fluorescent antibody testing for *Legionella* and *Pneumocystis carinii*. The total estimated cost of these tests was \$1,080, which is \$8 per patient who underwent CTC in the study.

Five subjects underwent medical procedures as a direct result of findings at CTC, including two who had upper endoscopy for esophageal or gastric thickening with both of those endoscopies revealing no abnormalities. One non-smoking patient who had two 5-mm non-specific nodules in the lung bases on initial CTC with a focal area of ground-glass attenuation on subsequent chest CTs in the absence of any symptoms, such as cough, dyspnea, fever, or weight loss, eventually underwent fiberoptic bronchoscopy with trans-bronchial lung biopsy and cultures. This study revealed no abnormality, and these initial findings eventually resolved on subsequent CT scanning. One patient with large asymptomatic

Table 4. Extra-Colonic Findings of Low Importance at Computed Tomography Colonoscopy

Finding	No. of subjects
Vascular calcifications	73
Degenerative disease of spine	52
Probable renal cysts	32
Hiatus hernia	25
Probable liver cyst	21
Small renal calcification	19
Splenic granulomas	15
Lung or pleural scarring	11
Prostate calcifications	9
Coronary calcifications	8
Hepatic granulomas	8
Lung granulomas	7
Renal scar/stranding	7
Hepatic steatosis	7
"Shotty" adenopathy	7
Duodenal diverticulum	6
Uterine enlargement, calcification, or fibroid	6
Pericardial thickening or small effusion	5
Prostate enlargement	4
Calcified lymph node	4
Renal angiolipoma	3
Bony island	3
Hernia	3
Other	18

bladder stones found on CTC was referred to a urologist and eventually underwent cystoscopy. Because of the size of these stones, the patient received a transurethral dilation of the prostate and a urethral dilation to facilitate passage of these stones out of the bladder. Another patient with an adnexal mass with complex cystic features had several subsequent imaging studies, including MRI, and underwent laparoscopic oophorectomy with the pathology report indicating a benign ovarian cyst. The total cost of these five procedures was estimated at \$5,163, or \$38 per subject who underwent CTC. A sixth patient who was found to have terminal ileum thickening at CTC subsequently went on to have an additional colonoscopy with ileal intubation with biopsies suggesting Crohn's ileitis. Due to the presence of diarrhea going into the study, this subsequent diagnostic test was not attributed solely to the extra-colonic finding at CTC and not included in this analysis.

In reviewing these subjects' electronic medical records, it was clear that several outpatient physician encounters were initiated solely to address ECFs identified at CTC. These included new referrals to specialists, including pulmonologists, urologists, gastroenterologists, gynecologists, and surgeons, for newly identified findings such as lung nodules, indeterminate kidney and liver lesions, and adnexal lesions as well as return visits to specialists that patients had already seen for other reasons and return visits to primary care physicians to further discuss and evaluate findings. There

Table 3. Extra-Colonic Findings of Moderate Importance at Computed Tomography Colonography

Finding	No. of subjects
Indeterminate kidney lesions	11
Indeterminate gastric mass or thickened stomach	4
Lung interstitial disease or fibrosis	4
Lung cysts or emphysema	4
Adenopathy (>1 cm)	4
Indeterminate liver lesions	3
Adrenal adenoma (<2 cm)	3
Thickened gastroesophageal junction or esophagus	3
Lytic or sclerotic bone lesions	3
Solitary kidney or renal agenesis	2
Pancreatic calcifications	2
Other	10

Table 5. Summary of Extra-Colonic Findings

Importance	Number of patients (%)	Patients with subsequent workup
High	25 (17.5%)	14 (56%)
Moderate	35 (24.5%)	15 (43%)
Low	74 (51.7%)	3 (4%)
No ECFs	2 (1.4%)	0

were 11 new referrals and 33 return visits to specialists or primary care physicians that were clearly a result of ECFs at CTC with an estimated total cost of \$2,279 or \$17 per patient enrolled in the study.

The combined cost of the additional radiographic studies, laboratory studies, medical procedures, and outpatient care rendered solely to address extracolonic findings at CTC is \$33,690. Averaged over the 136 subjects evaluated, this gives a cost of \$248 per patient who underwent CTC, with subsequent radiographic imaging representing the largest component of this cost (75%). While the diagnosis of one case of Crohn's ileitis was made with the assistance of CTC, there were no extracolonic malignancies or any aortic aneurysms identified in this cohort.

DISCUSSION

Our finding of an additional estimated cost of \$248 spent for every patient who undergoes CTC for colon cancer screening varies by an order of magnitude from figures cited in the previously published studies looking at the cost of evaluating ECFs at CTC.^{7,9,12} This figure is even more striking considering that none of the patients in this cohort had any extracolonic malignancies or significant abdominal aortic aneurysms identified; proponents of this modality of colorectal cancer screening often cite identification of these entities as a benefit of CTC. It is not clear to us that anyone experienced health benefits from the \$33,690 spent on evaluation of ECFs. There are several reasons why our results may vary so much compared to some other studies. Table 6 summarizes the results of these other studies.

A key difference among these studies is how clinicians were notified of the presence of ECFs in the CTC. In the study by Yee, only ECFs of high importance were reported to the clinicians, and other findings were not revealed. This minimized the follow-up of unimportant ECFs, but does not match real-life clinical practice; thus, the finding of \$28 per patient to work up ECFs may not be comparable to actual clinical practice. Our study matched the use of CTC in clinical practice. The entire report with all ECFs was entered into the patient's EMR and sent to the patient's primary care physician. All follow-up was at the discretion of the primary care physician. Our study also included costs for physician visits and other studies, not just radiologic follow-up. For these reasons, we believe that our results would more closely match the results obtained during routine clinical practice outside of a clinical trial. Different reporting techniques were used in the other trials

in Table 6, and these differences would limit the validity of a meta-analysis.

All but 2, or 98%, of the 136 patients evaluated in our study had at least one extracolonic finding, and there was an average of 3.2 ECFs for each patient who underwent CTC. This is compared to the six previously published trials where there was a range from 15% of subjects having ECFs in the study by Edwards to 85% of subjects in Hellstrom's trial. There are likely several reasons why our cohort had a higher percentage of ECFs. It would not appear that our cohort would be expected to have more extra-colonic abnormalities given the younger average age compared to other trials and the fact that this was largely a population undergoing average risk screening for colorectal cancer in comparison to other trials, which often had large percentages of symptomatic patients.

One difference between our study and others is the fact that subjects had two CTCs serially - one with and one without oral contrast. For each subject, both studies were read sequentially by the same radiologist with the non-contrasted study being read first. While we don't feel that undergoing two studies increased the number of ECFs, the radiation dose at 180 mA for supine images and 80 mA for prone was higher in our study than in the others. For example, in Hara's and Edward's studies where only 41% and 15% of subjects respectively had ECFs, the radiation doses used were 70 mA to 80 mA for both supine and prone images. Conversely, the study by Hellstrom where 85% of subjects had ECFs used a radiation dose more comparable to that used at our center at 150 mA.

In the study by Edwards and colleagues, the authors note that, by using scout views and single breath-hold acquisition, minimal lung parenchyma was visualized, and thus no pulmonary lesions were detected. In our cohort indeterminate lung lesions were the single most important group of findings leading to further testing and were very important in other studies as well. Another factor may be which findings warrant being reported by the radiologist. For example, degenerative disease of the spine was the second most common finding in our cohort, being identified in 52 subjects, whereas this finding wasn't reported in any subjects in other studies. The local training and practice of the radiologists may significantly alter the frequency of findings. Also, it is possible that the perceived risk of litigation regarding missed lesions may lead to differences in reporting.

Not only were there more extra-colonic findings in our study, but compared to most of the previously published studies, a higher percentage of subjects, 24%, had additional investigation of these findings. An exception is the Edwards study,⁸ where 11 of 15 (73%) subjects with ECFs underwent additional workup, but this study had the smallest percentage

Table 6. Summary of Studies Evaluating Extra-Colonic Findings

Study lead author	No.	No. with ECF (%)	No. of high importance ECFs (no. of patients)	No. of moderate importance ECFs (no. of patients)	No. of low importance ECFs (no. of patients)	% of ECF patients with workup	Cost of ECF workup per CTC performed
Hara ⁷	264	(41%)	34 (30)	49 (46)	68 (55)	18%	\$28
Edwards ⁸	100	(15%)	Findings	Not	Stratified	73%	–
Glueker ⁹	681	(69%)	88 (71)	196 (183)	574 (341)	–	\$34
Hellstrom ¹⁰	111	(85%)	37 (26)	83 (58)	120 (72)	–	–
Rajapaska ¹¹	250	(33%)	17 (17)	53	66	14%	–
Yee ¹²	500	(63%)	50 (45)		546 (270)	8%	\$28
Kimberly	136	(98%)	25 (25)	53 (35)	345 (74)	24%	\$248

of subjects with ECFs. In the study by Yee and colleagues,¹² while 63% of subjects had ECFs, the only ECFs reported to treating physicians were in the 9% of subjects deemed to have important findings, and thus only 8% of subjects with ECFs had additional evaluation. In Rajapaska's study conducted in a New York Veteran's Administration facility,¹¹ 14% of subjects with ECFs underwent subsequent workup. In the two remaining studies by Hellstrom and Glueker, it wasn't clear what percentage of patients with ECFs underwent additional evaluation. Just as litigation concerns may lead to differences in reporting, the same concerns may drive additional workup of those findings in patients, despite a low yield of further testing. It is also clear that specific radiologist recommendations may encourage or discourage further testing. For example, in our study, recommendations regarding pulmonary nodules were done in the usual practice of the specific radiologist, and a standardized protocol was not utilized. Some follow-up imaging of the chest was done at the recommendation of the radiologist, and some was done at the recommendation of the primary care physician without specific radiologist recommendations. It is unknown if other studies utilized a protocol such as "Guidelines for the Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society."¹⁴

In conclusion, extra-colonic findings will be an important consideration as CTC is championed as a colorectal cancer screening tool. As with other radiologic evaluations, including chest CT for lung cancer screening in high-risk populations and whole body CT, it is not clear that the benefits of uncovering previously undetected and asymptomatic lesions outweigh the risks and costs of additional studies and treatments done for findings that are often ultimately found to be unimportant. In the future, it will be important for radiologists to risk stratify lesions that are found at CTC and to provide guidance to clinicians for subsequent workup for the broad array of extra-colonic findings uncovered. Since our study was completed, a consensus proposal for CTC reporting called C-RADS (CT Colonography Reporting and Data System) has been proposed and includes categorization of ECFs in a format that may ease management decisions.¹⁵

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