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Five year colorectal cancer outcomes in a large negative CT colonography screening cohort

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Abstract

Objectives—To assess the 5-year incidence of clinically presenting colorectal cancers following a negative CT colonography (CTC) screening examination, as few patient outcome data regarding a negative CTC screening result exist.

Methods—Negative CTC screening patients ($n=1,050$) in the University of Wisconsin Health system over a 14-month period were included. An electronic medical record (EMR) review was undertaken, encompassing provider, colonoscopy, imaging and histopathology reports. Incident colorectal cancers and other important GI tumours were recorded.

Results—Of the 1,050 cohort (mean $[\pm SD]$ age 56.9 ± 7.4 years), 39 (3.7%) patients were excluded owing to lack of follow-up within our system beyond the initial screening CTC. The remaining 1,011 patients were followed for an average of 4.73 ± 1.15 years. One incident colorectal adenocarcinoma represented a crude cancer incidence of 0.2 cancers per 1000 patient years. EMR revealed 14 additional patients with clinically important GI tumours including: advanced adenomas ($n=11$), appendiceal goblet cell carcinoid ($n=1$), appendiceal mucinous adenoma ($n=1$) and metastatic ileocolonic carcinoid ($n=1$). All positive patients including the incident carcinoma are alive at the time of review.

Conclusions—Clinically presenting colorectal adenocarcinoma is rare in the 5 years following negative screening CTC, suggesting that current strategies, including non-reporting of diminutive lesions, are appropriate.

Keywords

CT colonography; Gastrointestinal; Screening; Adenocarcinoma; Advanced Adenoma

Introduction

Computed tomography colonography (CTC) is a less invasive alternative method to colonoscopy. Several multicentre trials[1–4] have validated performance in large polyps and masses, leading to inclusion in the American Cancer Society colorectal cancer (CRC) screening guidelines.[5] CTC-based screening has been shown to be an efficient method for advanced neoplasia detection where yields equivalent to colonoscopy-based programmes are seen, despite substantially fewer polypectomies.[6]

On the other hand, critics contend that widespread screening by CTC may lead to interval cancers that could be avoided if screened by colonoscopy. They argue that the CTC selective polypectomy strategies where diminutive polyps are ignored and surveillance of isolated (one or two) 6- to 9-mm polyps is permissible result in many high-risk polyps and cancers that are not removed.[7] Furthermore, such proponents assert that CTC is unable to detect many flat lesions, which may hold higher rates of high grade dysplasia and invasive cancer. [8] Thus, if such hypotheses were correct, a negative result at CTC may lead to excessive numbers of cancers presenting symptomatically between routine screening intervals. The purpose of this study was to determine the rate of clinically presenting incident cancers over a 5-year follow-up in a large negative CT colonography screening cohort.

Materials and Methods

This Health Insurance Portability and Accountability Act (HIPAA)-compliant study was approved by the institutional review board at the University of Wisconsin School of Medicine and Public Health. The need for informed consent was waived.

Study group

Between April 2004 and May 2005, 1,209 consecutive individuals were enrolled in the University of Wisconsin (UW) CT colonography screening programme. Participation requires a physician/medical care provider referral; the programme is not yet an open access model. Individuals are generally at average risk of colorectal cancer and referred by their primary care provider for the purpose of colorectal cancer screening. Patients with a previous history of inflammatory bowel disease, colorectal cancer, or polyposis syndrome and those under surveillance for previous adenomas are not included. Most of the enrolled individuals are in the UW health system which covers Madison, WI, USA, and the surrounding regions. A small number enter the programme from outside the system (geographically out-of-state or from intrastate regions distant to the Madison area) because of its referral centre nature.

From this initial group, the individuals who receive general medical care from health providers outside the UW system and whose only contact with the UW system was through a single CTC examination were excluded from consideration ($n=30$). Thus, the resultant group ($n=1,179$) represented asymptomatic screening individuals enrolled in the CTC programme who also receive their general care within the UW health network. From this group, patients with a positive examination result ($n=129$) were then excluded. A positive examination consisted of at least one detected soft tissue polyp 6 mm in size or greater. The resultant negative cohort consisted of 1,050 persons and represents the study population. This group consists of CRC-screened individuals with the result of a normal CTC examination and the recommendation of repeat routine screening examination in 5 years. Because CTC examination positivity is set at a 6-mm polyp threshold, individuals in this group may harbour diminutive polyps. Figure 1 outlines the study group determination.

CT colonography technique and polypectomy strategy

Standard CT colonography technique, which was state-of-the-art for 2004–2005, was undertaken. It has been previously described in detail.[9] Bowel preparation consisted of a clear liquid diet, cathartic administration and a tagging regimen that began one day before the scheduled examination. Catharsis was undertaken by either a single 45-mL dose of sodium phosphate, a double dose of magnesium citrate (300 mL per dose) or 1 L of polyethylene glycol. The tagging protocol included the administration of both 2.1% w/v barium sulphate (250 mL) and diatrizoate (60 mL).

Colonic distension was undertaken with an automated carbon dioxide delivery system (PROTOCO₂L; Bracco) and low-dose CTC was performed on either 8- or 16-section CT (LightSpeed Series; GE Medical Systems). The CTC technique consisted of 1.25 mm collimation, 1-mm reconstruction interval, 50–75 mAs and 120 kVp. All examinations were networked to a central reading area for post-processing and interpretation (V3D colon, Viatronix).

The polypectomy strategy was in compliance with the CT colonography reporting and data system (C-RADS) guidelines.[10] Any polyp detected that was 6 mm in size or greater was referred for therapeutic colonoscopy. For those individuals with isolated (one or two) 6- to 9-mm polyps, imaging surveillance was another option. Isolated diminutive polyps were neither identified nor reported. The routine screening interval for a negative examination was 5 years.

Determination of follow-up

The University of Wisconsin Health network is a vertically integrated system. It includes a tertiary referral hospital and local community-based hospital as well as local and regional primary care clinics in Madison and the surrounding regions. An electronic medical record (EMR) (EpicCare EMR, Epic) is integrated throughout the UW network.

The EMR for each patient was reviewed to assess for the interval development of colorectal cancer. Records are regularly reviewed as part of quality assurance measures for the CTC programme. Length of follow-up was established by the number of days between the date of the CTC examination and the date of the last comprehensive medical interaction recorded in the EMR. A comprehensive medical interaction was defined as a visit likely to record a history of colorectal cancer if present. These included any medical interaction (outpatient, emergency department, inpatient settings) where a complete history and physical was completed as well as office visits for the specific purpose of health maintenance (preventive care) discussion. Any medical interactions that did not fall specifically into one of these two visit types were reviewed to assess whether they would potentially capture an interval history of cancer. For example, a telephone encounter by a covering physician regarding an acute illness would not be counted while a focused subspecialty visit (i.e. dermatology, cardiology) may or may not depending on the nature of the recorded progress note. For the group of persons who underwent interval colonoscopy or CT colonography for whatever reason, the reports were reviewed for the presence of colorectal cancer. Any clinically significant neoplasms were also recorded. Advanced adenomas were defined as adenomas 10 mm in size or greater or adenomas that harboured high-grade dysplasia or ≥ 25% villous elements.

Statistical analysis

The crude cancer incidence rate was obtained by dividing the number of people in the cohort with observed colorectal cancer events by the total time at risk, in person years. A 95% confidence interval was calculated by assuming the numbers of events to be Poisson-distributed and using an exact method.[11]

Results

At a 6-mm threshold for a positive examination, individuals with a negative CTC result accounted for 89.1% (1,050/1,179) of the total CTC screening population. The mean age for the negative CTC study population was 56.9 years of age with a standard deviation of 7.4 years. There was a female predominance of 54.0% (567/1,050). Table 1 shows the negative CTC demographics including those of the two major subcohorts. A positive family history

was defined in accordance with the American Cancer Society guidelines, which includes a first-degree relative with CRC before the age of 60 or two or more first-degree relatives with CRC of any age.[5]

Of the 1,050 negative examinations, there were 39 examinations (3.7%) with a lack of follow-up within the EMR where the only record was the CTC examination for the in-network individual. This group was excluded from consideration. The remaining 1,011 patients had a documented average follow up of 4.73 years (SD 1.15 years) with a total of 4,786 patient years of follow-up. 595/1011 (58.9%) had at least 5 years of documented follow-up, which corresponds to the recommended interval for repeat examination for negative CTC screening. Luminal colorectal evaluation by interval colonoscopy or CT colonography was performed in 368/1011 (36.4%).

In the negative cohort, there was one incident colorectal adenocarcinoma that presented during the routine screening interval, leading to a rate of 0.1% (1/1,011). The crude incidence rate was 0.2 cancers per 1000 person-years (95% confidence interval 0.00529 to 1.16421 per 1000 person-years). With regard to the incident cancer, the patient presented 35 months after a negative CTC examination with increased rectal urgency and altered stool habits. Diagnostic work-up revealed a Stage II (T3, N0) low rectal adenocarcinoma. In retrospect, a questionable area of abnormality was present on the index CTC examination although the area is difficult to assess due to adjacent redundant tissues and the rectal balloon (Fig. 2). The patient underwent neoadjuvant chemoradiation with complete surgical resection. He remains disease free to date.

For those who underwent luminal examination, 14 patients had clinically significant lesions (14/368; 3.8%). 11 patients had an advanced adenoma. All advanced lesions met the criteria by large size ($n=11$) alone; 5/11 were also of tubulovillous histology. None harboured high-grade dysplasia. No subcentimetre advanced adenomas were seen. Overall, the per-patient advanced adenoma rate was 3.0% (11/368). The average time period between the index CTC and interval colonoscopy for this group was 5.1 years (SD 0.5 years). There were 5 patients with 6 polyps of unknown histology 6-9 mm in size detected at subsequent CT colonography at which the patient elected for imaging surveillance.

The remaining 3 patients harboured significant pericolic gastrointestinal lesions including an appendiceal goblet cell carcinoid, an appendiceal mucinous tumour and an ileocecal carcinoid with metastases to the liver. All 3 patients presented symptomatically from 1 to 5 years from the index CTC. Surgical resection was performed during the course of care in all cases. All patients are alive at the time of review.

Discussion

Our study addresses the current paucity of data regarding longitudinal colorectal outcomes in the CTC-screened population with a negative result and directly addresses the hypothetical concern that large numbers of incident cancers may present clinically between negative CTC screening examinations. Such concern has arisen for two major reasons.

First, CTC-based screening differs from colonoscopy with regard to the management of subcentimetre polyps. The positivity threshold for the examination is set at 6 mm in which isolated diminutive lesions are neither identified nor resected. The rationale for this alternative strategy is that these tiny polyps are very common (representing up to 76% of all polyps)[12] yet most never progress to cancer nor harbour cancer (0.03% of diminutive polyps).[12] The few potentially important polyps in this group can be identified by demonstrating interval growth as they pass the 6-mm threshold on future routine screening examinations set at 5-year intervals. The benefit of this particular screening methodology is

that it markedly decreases the number of polypectomies and procedure-related therapeutic complications yet maintains programmatic advanced neoplasia yields.[6] Critics to this selective polypectomy approach suggest that too many tiny cancers as well as high-risk polyps with the potential to develop into incident cancers may be left in vivo. Rex et al reported that 5% of CTC-negative screening patients may harbour high-risk adenoma findings.[7] However, it is important to realise that over 90% of these cases will consist of patients with only three or more diminutive tubular adenomas, which are of uncertain but doubtful importance.[13] Only a very small fraction would harbour diminutive advanced adenomas.

Second, flat polyps have been argued to be a clinically significant lesion, more prevalent in the US population than previously realised. Soetikno et al reported that flat polyps had a greater association with cancer than polypoid lesions regardless of size with a prevalence of nearly 6% in a screening population and nearly 10% in a mixed population.[8] It has been argued that CTC has difficulty in detecting these lesions given their minimally raised, plaque-like nature. However, in our experience, these lesions are often detectable at CTC, and their histology is significantly less aggressive than polypoid and mass-like lesions.[14]

The results of our study strongly argue against the clinical relevance of these debated concerns and suggest that the 5-year interval between negative CTC screening examinations is a safe practice. In a large negative screening cohort, there was only a single incident symptomatic cancer that presented in nearly 5 years of follow-up. This colorectal cancer outcome mirrors the results seen at colonoscopy screening despite the markedly different polyp harvesting strategies and the underlying difference in technique. In a large cohort of 1,256 individuals with a negative colonoscopic examination, Imperiale et al reported no cancers in the intervening 5 years.[15] Given the substantial fraction ($n=865$; 35.5% of the original group of 2,436) where neither colonoscopic nor follow-up information was available in the Imperiale series, the result of one incident cancer in our study compares favourably with the outcome seen in the colonoscopic study. Other small negative colonoscopic series have also demonstrated similar results at 5-year follow-up.[16–18]

The observed crude cancer incidence rate of our CTC-negative cohort (0.2 cancers/1000 person years) is substantially lower than the rates observed in colonoscopic surveillance cohorts where rates range from 1.7–2.4 cancers per 1000 person years.[19–21] Colonoscopic surveillance groups comprise individuals with positive index examinations (i.e. at least one adenoma identified and removed) who undergo clearing colonoscopy and are then followed for the interval development of additional adenomas. The marked difference in cancer incidence between these groups argues that the negative CTC population remains a low risk group and is distinctly different from these colonoscopic surveillance cohorts. In other words, the situation where a CTC-negative screen may actually be similar to a colonoscopic positive examination in surveillance is not likely. If a CTC-negative screen harboured clinically important adenomas that would have been detected if screened by colonoscopy (i.e. the debated significance of a diminutive adenoma), then the crude cancer incidence rate would presumably be much higher to echo the published colonoscopic surveillance series.

An argument may be raised that the lack of interval luminal examination of all study participants in this series diminishes the study results and conclusions. However, it is important to consider the following line of reasoning why these study outcomes remain valid. The purpose of the study is to provide evidence that the concerns of cancers and high-risk polyps left in situ at negative CTC screening are overstated. If such lesions were present at the index examination, it would seem logical that these cancers would present symptomatically in the intervening years. Moreover, our study suggests that it is highly likely that the incident cancer rate to include asymptomatic cancers that have not yet

presented clinically remains very low despite the lack of follow-up colonoscopy of the entire study population. In the sizeable cohort ($n=368$) that did undergo interval luminal evaluation, *no cancers or adenomatous polyps with high-grade dysplasia* were present. Thus, although it is possible that additional clinically silent cancers are present in the remainder of the population with clinical follow-up only ($n=643$), it is likely to be few to none in number as this subgroup is statistically similar to the first group with regard to the major demographic determinants of adenoma and cancer prevalence (Table 1).[22–23] Between the two groups, there was no statistical difference seen in the gender proportions or percentage with a positive family history. A statistically significant difference was seen in the mean ages of the groups. However, such a difference of 1 year is of doubtful clinical relevance. Even in the unlikely circumstance that several silent cancers are present in this group; the routine screen interval should detect these cancers at an earlier stage with improved future outcomes, arguing against the true clinical impact of the concerns outlined in the previous paragraphs.

The advanced adenoma rate in this longitudinal study was approximately 3% and all incident lesions were 10 mm or larger in size. Despite the fact that theoretically a few of these lesions were potentially present for several years, neither high-grade dysplasia nor asymptomatic cancers were identified. At first glance, the advanced neoplasia incidence in this study appears slightly elevated in comparison with colonoscopic series (reported rates of 1.3–1.4% at follow-up).[15–17] However, this rate is in line with these studies if it is considered that the rate in the CTC-negative cohort represents the combination of advanced adenomas present in the diminutive group at the index examination as well as ones that developed during the follow-up period. Large colonoscopic studies suggest that the prevalence of advanced neoplasia may be 0.87–1.7% in the diminutive group.[7, 12] Added to the percentage of advanced lesions seen over a 5-year follow up after clearing colonoscopy, the number in the CTC-negative cohort is very similar to the colonoscopic side. The lack of high-grade dysplasia (or malignant foci) among these advanced lesions in our study adds to the mounting evidence that transformation of these lesions occurs over the span of many years. These findings reinforce the relative indolent nature of diminutive adenomas. However, the outcomes do point out that programmatic screening compliance is required in order to detect these lesions. Screening at regular intervals would help to detect these few important polyps in the diminutive group as they grow to larger sizes before malignant transformation.

Regarding the limitations of this study, there were a small number of individuals without follow-up information in the EMR. In addition, patients entered screening on referral from their primary care provider. Although they were generally at average risk, the exact reasons leading to CTC screening are unknown and selection bias cannot be completely excluded. Finally, as discussed previously, it is also possible that tumours may not become clinically apparent during the 5-year study window. However, this interval does represent the recommended routine screening interval for CT colonography and as discussed previously, compliance with routine screening would presumably identify these clinically silent lesions, leading to earlier intervention and improved outcomes compared with later symptomatic presentation.

In conclusion, the clinical presentation of an incident colorectal cancer is a rare event following a negative result at CTC screening. The results of this large negative cohort at follow-up suggest that the practice of setting a threshold of 6 mm for examination positivity and a routine screen interval of 5 years is a safe practice despite the theoretical concerns that too many high-risk polyps and cancers are left behind. The low, but non-negligible incidence of advanced adenomas reinforces the necessity for programmatic compliance with regular routine screening.

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Key Points

1. CT colonography (CTC) screening is increasingly used to identify potential colorectal cancer.
2. Clinically presenting cancers are rare for 5 years following negative CTC screening.
3. The practice of setting a 6 mm polyp size threshold seems safe.
4. An interval of 5 years for routine CTC screening is appropriate.

Fig. 1.
Flowchart for study cohort inclusion

Fig. 2.

A 69-year-old man who presented with an incident colorectal cancer 35 months after negative CTC screening (the only incident cancer in this CTC-negative cohort). A lesion or polyp in this area is questionably seen on the index examination.

a, 3D endoluminal image at index CTC demonstrates an undulating longitudinal fold (*arrow*) adjacent to the rectal catheter tip. There is a questionable minimally raised area (*arrowheads*) versus redundant tissues in this area.

b, Translucency rendering demonstrates a homogeneous latticework appearance to the area arguing against a focal lesion (*arrowheads, arrow*) in the distal rectum

c, 2D coronal reconstruction in the prone position shows the rectal fold (*arrow*) without definite lobulated borders adjacent to the rectal catheter

Table 1

Demographic characteristics of the patients

	Entire study population	Luminal examination cohort (<i>n</i> =368)	Clinical follow- up only cohort (<i>n</i> =643)	<i>P</i> value *
Mean age (years)	56.9±7.4	56.3±6.7	57.3±7.6	0.036
Male:female ratio	483:567	174:194	285:358	0.394
Positive family hx	17	5	12	0.621

*
For comparisons between luminal and clinical follow-up only cohorts