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Overview of Computed Tomographic Colonography for Colorectal Cancer Screening in an Average Risk Population

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

TECHNOLOGY OVERVIEW

HTA
Issue 47
December 2008
Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).


Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

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CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2008
National Library of Canada
ISSN: 1203-9012 (print)
ISSN: 1481-4501 (online)
O0474 – December 2008

PUBLICATIONS MAIL AGREEMENT NO. 40026386
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We thank Lisa Hum for her assistance in creating this overview from a longer report authored by Ho et al.

1 Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in men and women in Canada.\(^1\) Ontario Cancer Registry data show that the prevalence is 0.3%.\(^2\) CRC is the second leading cause of cancer death in men and women in Canada. In 2008, an estimated 21,500 (413 per week) Canadians will be diagnosed with CRC, and 8,900 (17 per week) will die of it.\(^3\)

Most cases of CRC arise from precancerous adenomatous polyps through the adenoma-carcinoma sequence.\(^4\) The purpose of screening is to identify earlier stage cancers with a resulting better prognosis and to prevent CRC through the removal of adenomatous polyps. Screening has been shown to reduce CRC-related mortality.\(^5-7\) Data show that the removal of polyps through colonoscopy reduces the incidence of CRC.\(^8\)

Most individuals are at average risk for CRC. In Canada, these individuals are 50 to 74 years old, are asymptomatic, and lack a personal or family history of adenomatous polyps or CRC.\(^9\) An individual’s risk status is used to determine when screening should occur, the tests to perform, and the frequency of tests.\(^10\) According to the National Cancer Institute of Canada, population-based screening is intended to detect cancer or precancerous conditions in asymptomatic individuals. The primary objectives of population-based screening are to reduce the cancer death rate and to increase the likelihood of successful treatment if cancer is detected early.\(^11\)

Canadian and American agencies have issued CRC screening recommendations.\(^12-21\) The agencies recognize fecal occult blood test (FOBT), sigmoidoscopy, a combination of FOBT and sigmoidoscopy, double contrast barium enema, and colonoscopy as acceptable screening modalities for use in asymptomatic adults of average risk. No published Canadian guidelines recommend computed tomographic colonography (CTC) for screening in asymptomatic adults with an average risk of developing CRC.

CTC (virtual colonoscopy) is a non-invasive colon cancer screening technique. The images that are generated during CT scanning are used to produce three-dimensional images of the colon and rectum. If a suspicious lesion is detected, the patient undergoes further testing through conventional colonoscopy. Although CTC requires bowel cleansing, no sedation or analgesia is needed. It is faster to perform CTC compared with conventional colonoscopy.\(^22\)

There is uncertainty about the clinical utility and impact of CTC compared with available screening tests. Alberta, Manitoba, and Ontario established provincial CRC screening programs in 2007. The primary screening method for all programs is FOBT. The recommended secondary screening method is colonoscopy when the FOBT is positive. The target population in Alberta and Manitoba are men and women between the ages of 50 and 74 years. In Ontario, the target populations are men and women older than 50 years of age with an average risk and all high risk individuals. In other jurisdictions, ad hoc opportunistic CRC screening is done. Provincial governments have launched more formalized pilot screening programs. The target population could be men and women between the ages of 50 and 74 years, with FOBT as the primary screening method.
The authors of one study performed an economic evaluation and found that CRC screening with CTC was more costly and less effective compared with colonoscopy. However, the time horizon was short, the patients’ time and travel costs were excluded, and the authors did not include other available strategies, such as FOBT. As jurisdictions across Canada develop guidelines for population-based screening, decision makers will need to determine if it is appropriate to include CTC as a substitute or as an adjunct to available screening tests. The evidence would have to suggest that CTC has comparable test performance characteristics for detecting cancers or adenomatous polyps at comparable stages, has the same or improved patient acceptability, and is associated with complication rates and costs that are comparable or lower than those of current screening tests.

2 Objectives

The objectives were to assess the clinical- and cost-effectiveness of CTC for CRC screening. The objectives were addressed by the following research questions:

- What are the demonstrated beneficial and harmful effects of CTC in individuals with an average risk, aged 50 to 74 years? What is the diagnostic accuracy of CTC in comparison with colonoscopy, based on polyp size?
- What are the economic consequences of various screening options in individuals with an average risk, aged 50 to 74 years?
- What are the known capital and human resources for health implications of implementing programs that involve CTC screening across Canadian jurisdictions?
- What is the impact of various screening modalities on access to screening for patients at average risk of CRC, aged 50 to 74 years?

3 Clinical Review

Methods

The results from the literature searches for the clinical review and economic evaluation were combined. For the clinical review, representatives from all provinces and territories were contacted about their CRC program.

Publications were included in the clinical review if they were randomized controlled trials or observational studies, compared CTC with colonoscopy, involved individuals of average risk for CRC, and reported at least one of the following outcomes: detection of small, medium, or large polyps or carcinomas; sensitivity, specificity, positive predictive value, or negative predictive value of CTC and colonoscopy; and adverse events that were the direct results of using screening methods.

Two reviewers extracted data independently. Quality assessment was performed using the Jadad scale and an appraisal form that considers study design and performance that was modified from Hailey et al. Studies with an overall score of 11.5 to 15.0 were considered to be studies of high quality, whereas scores of 1.0 to 5.0 indicated poor-quality studies. There was no validated
cut-off score to distinguish between low-quality and high-quality studies. Instead, reviewers subjectively assessed quality by evaluating the reasons given for not using accepted methods.

**Results**

The literature search identified 1,461 citations. Of these, 512 were retrieved in full text, and eight reports met the inclusion criteria. Seven of the eight studies were prospective studies originating in the US or Australia. One was a retrospective study conducted in South Korea. The number of patients screened ranged from 46 to 2,531. Five studies included men and women, one study included men only, and gender was not reported in two studies. Six trials were conducted in 2001 or later, one was conducted in 1995, and one did not indicate the date. The trial quality scores ranged from 8 to 11.

a) **Sensitivity of CTC**

One study reported that CTC was used to correctly identify 25% of patients having polyps of 5 mm or less. Among three studies, the sensitivity of CTC to correctly detect polyps of 5 mm or less ranged from 11.5% to 38.5% to 43%.

Seven studies reported the sensitivity of CTC with respect to polyps that were 6 mm to 9 mm or greater. With the use of CTC, 75% to 100% of patients with polyps in this range were correctly identified. In addition, 75% to 100% of polyps that were 6 mm to 9 mm or greater were correctly detected using CTC.

Six studies reported the sensitivity of CTC for polyps that were 10 mm or greater. CTC was used to correctly identify 80% to 100% of patients with polyps in this range. Moreover, detection was accurate for 50% to 100% of polyps that were 10 mm or greater.

One study found that CTC could be used to correctly identify 62% of patients having polyps of any size. In three studies, CTC was used to correctly detect 21% to 50% of polyps of any size.

b) **Specificity of CTC**

Two studies reported the specificity of CTC to detect polyps that were 6 mm to 9 mm. In these studies, CTC was used to correctly identify 80% to 100% of patients who did not have polyps of this size. With respect to polyps of greater size, five studies reported that 89% to 100% of patients who did not have polyps that were 10 mm or greater were accurately identified by using CTC.

c) **Sensitivity of Colonoscopy**

One study reported the sensitivity of colonoscopy. With the use of colonoscopy, 91% to 92% of patients with polyps that were less than 10 mm and 87% of patients with polyps that were 10 mm or greater were correctly identified. In addition, 89% to 90% of polyps less than 10 mm and 88% of polyps that were 10 mm or greater were correctly detected by using colonoscopy.
4 Economic Review

Methods

Full economic studies (cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis) and partial economic studies (cost analysis, cost-comparison analysis, and cost-consequence analysis) were included. To be included, studies had to involve individuals of average risk for CRC; compare CTC with no screening, annual FOBT, or colonoscopy; and report at least one of the following outcomes: cost per quality-adjusted life-year (QALY), life-year saved, cost per cancer detected, health care resources use, and lost time from work. Preference was given to Canadian studies.

Two reviewers independently screened all titles, abstracts, and keywords and applied the selection criteria to full-text articles. Disagreements were resolved by consensus or by a third reviewer if consensus could not be achieved.

Results

Of 85 citations identified, six economic studies met the inclusion criteria. One study was conducted in Canada. The perspectives of the studies were not indicated in three reports. One study examined a population at high risk of CRC, and one studied individuals with positive FOBT. Three studies did not consider the costs that were associated with perforation and bleeding complications.

Four evaluations found CTC to be cost-ineffective. The Canadian study reported that CTC was more costly and less effective than colonoscopy, with an incremental budget of $2.27 million to screen 100,000 individuals.

5 Economic Evaluation

Methods

An incremental cost-utility analysis comparing CTC, colonoscopy, and FOBT with no screening in individuals with an average risk of developing CRC was performed. Outcomes included costs, QALYs, life-years gained, number of cancers and cancer deaths, and the cost per QALY gained. The primary perspective was that of a publicly funded health care system, with relevant costs including direct health care costs, patient time costs, and transport costs. A lifetime analytic horizon was used, and costs and effects were discounted at 5%.

The accuracy of CTC and colonoscopy was determined in the clinical review. Data on the occurrence of complications associated with colonoscopy and CTC were obtained from the literature. The accuracy of FOBT was taken from two studies that examined the use of FOBT and colonoscopy by patients who had an average risk of developing CRC. The prevalence of polyps and CRC was determined from a systematic review among North American patients with an average risk of CRC.
The CRC stage distributions for unscreened individuals and for individuals undergoing screening with FOBT were estimated from the control and treatment arms respectively in the randomized controlled trials that evaluated FOBT. The stage distributions for individuals who were screened using colonoscopy were calculated from data based on three cohorts. It was assumed that individuals who were screened using CTC and individuals who were screened using colonoscopy benefit from the same improved stage distribution. The five-year risk of mortality according to the stage of CRC was taken from a recent study. The costs of screening, including indirect costs, were taken from Canadian studies. The cost of CRC management was taken from contemporary North American studies.

Modelling was performed using Markov analysis and an annual cycle. Base-case analyses were performed using cohort simulation, with alternative modelling strategies (first order Monte Carlo simulation) used to assess cancer rates and number of colonoscopies. The internal and external validity of the model and calibration to existing datasets were established before conducting the economic evaluation. Scenario and sensitivity analyses were conducted to explore the assumptions and uncertainties in the model. Details about the clinical events, costs, estimates used in the model, assumptions, and potential limitations appear in the full report.

Results

In the base-case analysis, when compared with no screening, colonoscopy, FOBT, and CTC were each associated with small incremental gains in quality-adjusted life-expectancy (additional QALYs of 0.04, 0.02, and 0.03 respectively). The no screening strategy was the least expensive ($1,690), followed by FOBT ($2,000), colonoscopy ($2,040), and CTC ($2,110). Although FOBT was less expensive than colonoscopy, QALYs can be obtained with colonoscopy at a lower rate by paying an extra $40 per patient. (Table 1)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost of Screening &amp; CRC Management (95% CI)</th>
<th>Incremental Cost</th>
<th>QALY (95% CI)</th>
<th>QALY Gained</th>
<th>Incremental Cost / QALY Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>$1,690 (1,150; 2,184)</td>
<td></td>
<td>11.25 (11.22, 11.27)</td>
<td>0.04†</td>
<td>$7,940†</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>$2,040 (1,764; 2,642)</td>
<td>350†</td>
<td>11.29 (11.28, 11.30)</td>
<td>0.02†</td>
<td>Eliminated by extended dominance‡</td>
</tr>
<tr>
<td>FOBT</td>
<td>$2,000 (1,626; 2,394)</td>
<td>$310†</td>
<td>11.27 (11.27, 11.31)</td>
<td>0.03†</td>
<td>(Dominated)§</td>
</tr>
<tr>
<td>CTC</td>
<td>$2,110 (1,813; 2,479)</td>
<td>$420†</td>
<td>11.28 (11.27, 11.30)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI=confidence interval; CRC=colorectal cancer; CTC=computed tomographic colonography; FOBT=fecal occult blood test; QALY=quality-adjusted life-year

*Numbers rounded to nearest $10
†Each incremental value compares value of that strategy to common baseline (no screening)
‡Compared with “no screening,” FOBT was associated with cost per QALY of $14,290, while colonoscopy, compared with FOBT, was associated with cost per QALY of $1,810. FOBT is therefore eliminated by extended dominance, and colonoscopy becomes next most attractive strategy in comparison to “no screening.” Based on 95% CIs observed in baseline probabilistic sensitivity analysis
§“dominated” means that CTC was equal or less effective than less costly strategy (colonoscopy)
When compared with colonoscopy, CTC was associated with worse clinical outcomes and higher costs. Compared with no screening, colonoscopy was associated with a cost per QALY gained of $7,937. If colonoscopy was not a screening option (and thus, did not dominate CTC), then compared with no screening, CTC would be associated with a cost per QALY of $11,900.

In a hypothetical cohort of 100,000 patients, when compared with no screening, the expected number of cancers was reduced in each screening strategy, with the greatest reduction observed with colonoscopy. The number of cancers was reduced from 5,224 with no screening to 1,949 with colonoscopy; 2,670 with CTC; and 3,371 with FOBT. The number of cancer deaths was also reduced in each screening strategy, with the largest reduction observed with colonoscopy. The number of cancer deaths was reduced from 1,925 with no screening to 660 with colonoscopy; 935 with CTC; and 1,229 with FOBT.

The colonoscopy strategy was associated with the highest colonoscopy demand. Although the use of CTC reduced the number of colonoscopies to 0.46 per person, it also entailed an average of 1.35 CTCs over a person’s lifetime. In probabilistic sensitivity analyses, when compared with no screening, colonoscopy was associated with a cost per QALY of less than $10,000 nearly 99% of the time, whereas colonoscopy was cost saving in comparison to CTC 91% of the time. If decision makers were willing to pay $30,000 per QALY, then colonoscopy would be cost-effective 100% of the time.

The results from scenario analyses showed that screening patients aged 50 to 74 years with colonoscopy, with ongoing surveillance after age 64 years in those found to have polyps, reduced the number of colonoscopies by 45%. The number of cancers that were missed increased by 37% compared with the base-case strategy.

6 Limitations

Because most studies evaluated the accuracy of CTC in symptomatic or high-risk patient cohorts, the clinical review included only a few trials that compared the accuracy of CTC and colonoscopy in average risk populations. Moreover, because the clinical findings from the eight included studies were heterogeneous, they were summarized qualitatively.

The cost of CTC is unknown in Canada. For this analysis, the cost of CTC was estimated by comparing it with that of other radiology services. The true cost of CTC will likely be higher than that modelled. The sensitivity and specificity of CTC were modelled from large studies that used the latest technology. Given that many centres in Canada may not have the latest technology, this evaluation may overestimate the accuracy of CTC. Lower cost and higher accuracy would bias the analysis in favour of CTC.

The economic evaluation did not model any “disutilities” that were associated with CTC (for example, exposure to ionizing radiation) or colonoscopy (for example, bowel perforation). This was unlikely to have affected the results because screening with these modalities occurs infrequently, both require bowel preparation and colonic insufflation, and the expected average impact of each on the quality of life is small.
The additional costs and potential benefits of identifying extra-colonic findings through CTC were not considered. One study\textsuperscript{66} reported that CTC is less expensive and more effective than colonoscopy when the impact of extra-colonic findings, including the identification of unsuspected abdominal aortic aneurysms, is considered.

The probabilistic sensitivity analysis did not model any variability in sensitivity or specific results for the three CRC screening modalities, because the data required were unavailable from the included studies.

7 Health System Implications

Without screening for CRC in eligible Canadians who are 50 to 74 years old, there would be approximately 268,000 CRC cases and 99,000 deaths over the lifetime of the screening population. With the colonoscopy strategy, the demand would be approximately 8 million colonoscopies and 1.1 million polypectomies. The projection for CTC, colonoscopies, and polypectomies with the CTC strategy is approximately 7 million, 2.3 million, and 792,000 respectively. With the FOBT strategy, the demand would be approximately 45 million FOBTs, 1.3 million colonoscopies, and 539,000 polypectomies.

When indirect costs are not considered, the undiscounted budget impact analysis from the health care payer’s perspective shows that the no screening strategy is the most expensive strategy (C$15.8 billion) and FOBT is the least expensive strategy (C$11.7 billion). Screening the eligible population with colonoscopy would require C$12.8 billion, and screening with CTC would cost C$14.1 billion. Screening with FOBT is the cheapest strategy, but it reduces the number of CRC cases only by a third (net reduction of 94,960 cases).

If Canadians who are eligible were to undergo CRC screening, there would be an acute shortage of radiologists and gastroenterologists. To screen efficiently with colonoscopy, the number of gastroenterologists would have to be 12 times higher. With the CTC strategy, the number of radiologists would have to increase by five times, and the number of gastroenterologists would have to increase by 2.5 times. The FOBT strategy would require three times the number of gastroenterologists and approximately 580 additional full-time general practitioners or family physicians.

8 Conclusions

Based on the available evidence, CTC appears comparable to colonoscopy in sensitivity and specificity for detecting polyps that are 10 mm or larger, and CRC. CTC appears to have lower sensitivity and specificity for detecting polyps that are smaller than 10 mm. QALYs can be purchased at the lowest rate with colonoscopy or no screening. Screening with CTC produced less health at higher costs compared to colonoscopy in all plausible scenarios that are considered. Compared with no screening, screening with colonoscopy is associated with a cost per QALY of less than $10,000 in almost all scenarios that are considered. Screening all Canadians aged 50 to 74 years using colonoscopy is resource intensive and likely to be unfeasible given the current
CRC screening infrastructure. In the short term, or if health ministries cannot commit resources to additional colonoscopy units, then screening with CTC is the next most cost-effective strategy for detecting CRC. The use of CTC introduces similar infrastructure and human resource concerns. If neither colonoscopy nor CTC are options for first-line screening, FOBT is an alternative strategy. While it is less effective, it is less expensive and less resource-intensive than colonoscopy. CRC screening with FOBT or colonoscopy is associated with a cost per QALY of less than $20,000 compared to the most common management of average risk Canadians (no screening).

9 References