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Cost-effectiveness of CT Colonography

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Abstract

Simulation modelling has been extensively applied to CT colonography (CTC) in order to define its long-term efficacy and cost-effectiveness in the setting of colorectal cancer (CRC) screening. The available models indicate that CTC is effective in reducing both CRC incidence and mortality, ranging from 40% to 77% for CRC incidence prevention and from 58% to 84% for CRC mortality reduction.[15–22] Several factors may explain this inter-study variability, such as the assumed rate of de novo CRC, the type and prevalence of polyp size classes, the simulated stages of CRC, the progression through the different types of polyps and CRC stages, CTC accuracy, and extra-colonic findings. CTC has been consistently shown to be cost-effective as compared with no screening, indicating that it represents at the very least an attractive test for individuals who are non-compliant with the available options. According to the majority of the simulation models, CTC needs to achieve a higher attendance rate or cost less than colonoscopy in order to be cost-effective relative to colonoscopy.

Keywords

Colorectal cancer screening; colonoscopy; CT colonography

Introduction

There are two main motivations for applying computer micro-simulation to colorectal cancer (CRC) screening: to estimate the long-term efficacy of a new test and to extrapolate the results of clinical trials.

Modelling can be exploited to assess the potential long-term efficacy of a new screening technique. Innovative techniques are usually validated through head-to-head comparisons with colonoscopy or other established reference standards. Although such comparisons can define the accuracy of new techniques for relevant targets, such as advanced neoplasia, they fail to assess the potential impact of these tests on the natural history of colorectal neoplasia. Consequently, the actual long-term reductions in both incidence and mortality of colorectal cancer – which represents the relevant target for society at large – are not addressed by such

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studies. Ultimate reduction in CRC incidence and mortality can be measured through long-lasting randomized/cohort studies – as has already been performed for guaiac-based faecal tests or sigmoidoscopy.[1–5] However, if this were to be required for every new screening modality, it would significantly delay implementation of a potentially useful new technique for a decade or more while awaiting trial results. Simulation modelling allows for estimation of long-term impact on the natural history of colorectal neoplasia by any new technique by converting the comparison in accuracy with the reference standard techniques (i.e. colonoscopy) into estimates of long-term CRC incidence or mortality reduction. Although these estimates may be weakened by the incomplete knowledge of the characteristics of the test, the interaction between the test and the natural history of the disease, or the correctness of the model structure, such uncertainty may be fully explored by a proper sensitivity analysis, substantially reducing the risk of error in the decision-making process.

The second reason in support of utilizing computerized simulation in CRC screening is to project the results of relatively small controlled trials assessing a novel technique onto the general population that would be expected to potentially undergo such a technique. In distinction from the clinical setting for symptomatic conditions – in which only a very small percentage of the population is affected by a technological innovation – novel techniques applied to CRC screening programs may potentially involve millions of individuals in a given country, raising concern for both medical and non-medical issues that are not necessarily addressed within the smaller clinical studies on diagnostic accuracy. The most relevant output of population modelling is represented by the cost-effectiveness ratio, which is the relationship between test efficacy in terms of CRC incidence and mortality reduction – usually expressed as years of years saved (with/without correction for the quality of life) – estimated for the new technique and the cost of an eventual screening program based on the same technique. Although this parameter is usually expressed as the amount of money spent in order to save one additional year of life, its meaningfulness is only apparently limited to financial considerations. Indeed, the estimate of cost not only involves the cost of the new test itself, but also takes into account several other economic variables, such as the exploitation of human, technological, and logistic resources, as well as the potential loss of productivity due to the screening test itself or the induced harm.

CT colonography (CTC), also referred to as virtual colonoscopy, is a minimally invasive imaging examination of the entire colon and rectum that is capable of assessing for the presence or absence of structural lesions, most notably large colorectal polyps and cancer. In clinical studies, CTC has been shown to be highly effective for detecting advanced neoplasia,[6–8] which is the critical target for colorectal cancer screening and prevention. Given this high level of performance, CTC has been recommended for CRC screening by the American Cancer Society, working in conjunction with the major gastroenterology and radiology societies.[9] Micro-simulation modelling has been extensively applied to CTC in order to anticipate its potential impact on the CRC screening field. For the remainder of this review, we will focus on the following issues, which have all been systematically addressed in the literature:

1. Can CTC reduce CRC incidence and mortality?
2. Is CTC cost-effective compared with no screening?

3. Is CTC cost-effective compared with previously established tests?

Can CTC reduce CRC incidence and mortality?

Colonoscopy has been consistently shown to be effective in reducing CRC incidence and mortality by two main mechanisms. Endoscopic polypectomy has been reported to reduce CRC incidence by 30–80% in randomized and cohort studies,[1,2,10–14] while the early identification of already developed CRC has been shown to reduce CRC mortality by 20% in randomized studies through the initial use of guaiac-based faecal occult blood testing.[3–5] By comparing CTC accuracy for the different sizes of polyps [i.e. diminutive (≤5 mm), small (6–9 mm), and large (≥10 mm)] and for the different stages of CRC (i.e. localized, regional, and distant) with those of colonoscopy, all the available simulation models available in the literature (see Table 1) consistently indicate the efficacy of CTC in reducing both CRC incidence and mortality, ranging from 40% to 77% for reduction in CRC incidence (prevention) and from 58% to 84% for CRC mortality reduction.[15–22] Several factors may explain this inter-study variability:

a. The rate of de novo CRC versus benign polyp precursor

b. The type and prevalence of polyp size classes

c. The simulated stages of CRC

d. The rate of progression through the different types of polyps and CRC stages

e. Input assumptions of CTC accuracy

f. The impact of extra-colonic findings.

a) Assumptions regarding the de novo CRC rate (versus CRC development through a benign precursor polyp) directly affect the percentage of incident CRC that are potentially preventable through polyp detection and removal (via endoscopic polypectomy). The higher the de novo CRC rate, the less effective all techniques will be that mainly exploit polypectomy to reduce CRC incidence and mortality. In theory, such a mechanism should affect both CTC and colonoscopy equally. However, the higher frequency of repetition recommended for CTC screening as compared with colonoscopy (5 years versus 10 years)[9] doubles the opportunity for CTC to down-stage de novo CRC, thereby increasing the relative efficacy of CTC in reducing CRC mortality.

b) Because of the relatively poor knowledge on the progression of colorectal neoplasia through the different sizes of polyps (i.e., diminutive, small, and large), some models assume only two size classes (i.e. small and large), while other models simulate all the three classes. Moreover, some models allow only large polyps to progress to early stage CRC, whereas others also simulate the progression of small or diminutive polyps directly to CRC. Presumably, this structural heterogeneity amongst the different models would affect the various colorectal screening tests to the same extent, without generating uncertainty on the model outputs. However, this does not appear to be the case for CTC, mainly because of the different management strategies between CTC and the endoscopic tests. Unlike endoscopy, in which all visualized polyps are generally removed, only polyps 6 mm or larger constitute a positive CTC and trigger referral to endoscopic polypectomy. Furthermore, CTC practice

may also allow for in vivo surveillance of small 6–9 mm polyps, resulting in a more complex situation to model.(6–9mm refs) As such, any variability in polyp size distribution across the models may impact CTC and endoscopy differently, accounting for some of the heterogeneity in results across the studies.

c) Although the progression of invasive CRC across stages has been clarified in screening studies, different models tend to classify CRC stages in different ways. For instance, some model simplify CRC progression in only two stages (i.e. localized and metastatic), other models in three stages (i.e. localized, regional, and metastatic), while still other models adopt a TNM or Dukes staging approach. Such variability is at least partially explained by the different sources of data input (e.g, the Surveillance Epidemiology and End-Result (SEER) database provides a 3-stages classification) among different models. Although such model heterogeneity is unlikely to affect the relative efficacy between CTC and colonoscopy because of the very high CRC sensitivity for each technique,[8] it may affect the yearly rate of progression from curable to non-curable CRC, which would affect tests with different frequencies of repetition differently, such as CTC versus colonoscopy.

d) The rate of progression through the different types of polyps and CRC stages indicates how many lesions transition from one class to the next each year (e.g., from diminutive to small adenoma), and it actually represents the real core of the model structure. Indeed, such rates are the main determinant of the natural history of colorectal neoplasia simulated by any model. Unfortunately, because of the poor knowledge of the natural history of colorectal neoplasia, there is a substantial inter-model variability in these transition rates, due to the fact that any difference in assumption in the adenoma-carcinoma sequence will be eventually reflected in these transition rates. For instance, when assuming the possibility of a de novo CRC pathway (see above), the transition rates underlying the progression among different classes of polyps should be necessarily decelerated, in order to result in the same incidence of CRC. Similarly, when simulating the possibility of progression through 3 (diminutive, small, and large) rather than just 2 classes of polyps, the transition rates should be accelerated, in order to sustain the same CRC incidence. Of note, transition rates may also be changed, in order to simulate different degrees of population risk for CRC. For instance, such rates are usually 2-fold increased in order to simulate the CRC incidence in first-degree relatives of CRC patients or the higher incidence of CRC in those with a previous polypectomy. Moreover, models adapted to regions with different CRC risk (e.g., Europe vs. USA) would have different transition rates to simulate the difference in the natural history of colorectal neoplasia. The impact of this variability in the assumptions of the polyp-transition rates over the efficacy of screening techniques is large. Any increase in the transition rates will reduce the ‘window of opportunity’ of CRC screening, exponentially reducing the efficacy of techniques that mainly exploit prevention with polypectomy (CTC, colonoscopy) rather than just CRC detection and down-staging (faecal tests) as the mechanism of action. On the other hand, any reduction in such transition rates will exponentially increase the efficacy of CRC screening. As already outline, although these assumptions should affect both CTC and its reference standard (colonoscopy) to the same extent, the different strategies of the two programs (e.g., 5-year vs 10-year interval, non-referral for diminutive

lesions, etc.) results in divergent estimates when changing these transition rates, explaining the heterogeneity in the estimates of CTC efficacy in the literature.

e) The estimate of efficacy of CTC is heavily affected by the assumptions of CTC sensitivity for each of the precancerous and malignant lesions. Since modeling extracts CTC accuracy data from the literature, these estimates could, in theory, be expected to be equal across the different models, reducing the heterogeneity in the model outputs. Unfortunately, this did not occur, as different models adopt different accuracy values for the same technique. This is mainly explained by the fact that CTC modeling has evolved over a decade or more, such that some authors had only the initial studies on CTC available, which may not be representative of what is considered today as state-of-the-art technique (e.g., faecal tagging, combined 3D/2D evaluation, etc.). Alternatively, some models have been purposely based on just one or a few studies in order to assess the impact of such a study on CRC screening with CTC. Because of the direct relationship between efficacy in CRC incidence/mortality reduction and sensitivity for precancerous lesions, any change in CTC sensitivity may be expected to result in a substantial inter-model variability.

f) Although the potential detection of extra-colonic findings has been mainly portrayed as an undesirable outcome of CTC screening, recent evidence would support its efficacy in reducing general mortality by the early detection of abdominal aortic aneurysms (AAA) and extra-colonic malignancies. Regarding the former, AAA screening in high-risk subjects (e.g., male smokers) has already been shown to be clinically effective and cost-effective in the general population.[23] Therefore, it is likely that, at least in these high-risk subjects, the detection of AAA would increase the overall efficacy of CTC. Regarding the latter, a recent study has shown that most of the extra-colonic CTC-detected carcinomas have been detected in early stages, allowing a potentially curable surgical treatment.[24] Although there is no direct evidence that such a down-staging may increase overall survival, this would be supported by previously established efficacy seen with other tumors.[25] According to one model, the simultaneous detection of AAA and early extra-colonic carcinomas added a substantial advantage to CTC as compared with other tests that are unable to visualize extra-colonic structures.[19]

Taking all these considerations into account, CTC appears to be able, according to simulation modeling, to substantially reduce CRC incidence and mortality when applied in the CRC screening field at the population level. Although the wide range of variation in model estimates may cause some uncertainty on the exact benefit from CTC screening, it provides a robust interval beyond which it is extremely unlikely such efficacy would not exist.

Is CTC cost-effective compared with no screening?

Nearly half of the eligible American population has not been screened for CRC in the last 10 years, and this figure is likely to be substantially higher in European countries.[26,27] This would indicate that a large part of the eligible population has not been compliant with the tests which were already available to them, such as endoscopy or faecal tests. CTC may be expected to convince at least part of this non-compliant population to undertake CRC

screening, because it couples the possibility to image the entire colorectum without the discomfort and risk of colonoscopy. When considering the offer of a new screening test to subjects who were noncompliant with the previous tests, it is necessary to assess whether the new test is not only effective, but also cost-effective as compared with the current 'no screening' scenario, that well represents the non-compliant subjects.

Cost-effectiveness not only depends upon efficacy, but also on costs. The main cost variables in any screening program are represented by the intrinsic/actual cost of the test itself, the cost of any post-test work-up/follow up, and the cost of treatment for CRC (e.g., surgery, chemotherapy, and palliative care). It has been customary that any diagnostic, therapeutic, or operative procedure within a given health care system is cost-effective when the amount of money spent to save one year of life is inferior to an arbitrary threshold that is usually set between $50,000 and $100,000, according to the financial status of the different health systems.[28] Most of the currently available CRC screening tests – such as faecal tests or endoscopy – have been shown to be extremely cost-effective as compared with no screening, with cost-effectiveness ratios much lower than $50,000.[29] Such a favorable profile has been related, on one hand, with the efficacy of CRC screening tests in reducing CRC mortality (i.e. gain of life-years), and on the other, with the substantial reduction of CRC-related treatment costs related to reduction in CRC incidence. The latter has recently gained even more attention because of the abrupt increase in the cost of metastatic CRC treatment following the introduction of novel but extremely costly chemotherapy agents.[30]

When dealing with CTC, cost-effectiveness not only depends upon its efficacy, which related to CTC sensitivity, but also on CTC-related costs. Such costs are represented by the cost of CTC itself and by the cost of colonoscopies induced by the screening (i.e. post-CTC polypectomy) or by the post-polypectomy/post-surgical surveillance program. In contrast to colonoscopy, in which polypectomy is a part of the same diagnostic procedure (albeit with increased costs), the detection of "significant" lesions at CTC will require the additional cost of the post-CTC colonoscopy. Of note, such cost will not only depend on the sensitivity of the procedure (i.e. true positive), but also on the specificity (i.e. false positive). In other words, a suboptimal CTC specificity would result in the waste of considerable financial and medical resources for overcalls leading to post-CTC colonoscopies, potentially undermining the cost-effectiveness of the technique. A further distinct characteristic of CTC is represented by the cost entailed in the work-up of extra-colonic findings, such as renal/ovary/liver/pancreatic masses or vascular abnormalities (i.e. aortic aneurysm). However, such costs have consistently been shown to be quite small, accounting only for a small fraction of the initial cost of CTC.[15–22,31–34]

Similar to endoscopic and fecal screening tests, CTC has been consistently shown to be cost-effective as compared with no screening by all the available models (Table 2).[15–22] This would indicate that CTC should be always regarded as an effective and convenient tests at least in all those persons who did not adhere to the competitive options (i.e. colonoscopy). In other words, for society it would seem prudent to reimburse for CTC screening test rather than to have eligible persons non-compliant.

Is CTC cost-effective compared with previously established tests?

Microsimulation allows long-term comparisons of costs and efficacies among multiple competitive options that would require too many resources to be performed within clinical setting. The output of these simulations is usually represented by a rank of the different options according to the overall cost of the program, with the computation of the relative cost-effectiveness ratios between the more costly and effective strategies with the less costly and effective strategies. Similar to the comparison between any screening program with no screening, the relative cost-effectiveness between two tests depends on several characteristics, such as the test accuracy, the frequency of repetition, the assumptions on the natural history of colorectal neoplasia (see above), the relative cost among the different procedures, and the CRC treatment cost.

When considering the uncertainty surrounding most of these estimates, it is not surprising that different models may lead to different ranking lists of the available options, so that some strategies that appear to be cost-effective under some assumptions on the natural history or cost may not be under different circumstances. However, this does not necessarily indicate that the conclusions of different models are incompatible, since variations in the model-specific inputs at sensitivity analysis are often able to reproduce similar results across the apparently discordant models.

Regarding CTC, most of the available models have mainly focused on its cost-effectiveness when compared with colonoscopy. Such cost-effectiveness would depend on two main theoretical assumptions:

1. When assuming the same frequency of repetition (i.e. every 10 years), the efficacy of CTC is likely to be slightly lower as compared with colonoscopy, because of the lower sensitivity for smaller polyps and the non-referral for diminutive lesions. This may also result in a higher expenditure for treatment of unprevented CRC.
2. When assuming the same cost between the two procedures, the cost of CTC screening is likely to be higher than that of colonoscopy, because CTC implies a duplication of cost for the 10–20% of CTC-positive subjects who need a post-CTC colonoscopy for true- or false-positive results.

In order to reverse this theoretical cost-ineffectiveness for CTC, several possibilities exist:

a. According to official guidelines,[9] CTC needs to be repeated more frequently than colonoscopy. When considering the very high sensitivity of CTC for large polyps and already developed CRC – which represents over 90% of the all advanced neoplasia –, it is extremely likely that 5-year CTC is equal – if not more effective – than 10-year colonoscopy in preventing CRC incidence/mortality.

b. When simulating a screening program, the overall efficacy not only depends upon the actual detection rate of advanced neoplasia in those undertaking the screening procedure, but also on the actual participation rate. In other words, if CTC is able to convince more people to undertake the screening procedure than colonoscopy, the gap of compliance would immediately result into an equivalent

increase of the relative efficacy of CTC versus colonoscopy. Of note, this has been recently shown to be the case in a randomized study comparing the adherence and detection rate between CTC and colonoscopy.[35–37]

c. CTC cost is substantially less than that of colonoscopy in several health systems. This is related with the reduced exploitation of logistic and medical/non-medical resources when performing a CTC as compared with colonoscopy. CTC also reduces the costs for colonoscopy-related complications (i.e. perforation) and productivity loss (i.e. working-days lost for CRC screening). Of note, by progressively reducing the CTC cost, virtually any model would indicate the potential efficacy and cost-effectiveness of CTC.[15–22] This would indicate that the adoption of different reimbursement policies between the clinical and screening settings – as has been widely implemented with endoscopic or faecal tests – would substantially reduce, if not eliminate, the residual uncertainty over the affordability of a CTC screening program.

When considering all these pros and cons of CTC as compared with colonoscopy, it is not surprising that models based on different assumptions or structures reach divergent results on the relative cost-effectiveness of CTC as compared with colonoscopy, as summarized in Table 2. Irrespective of the model output with the baseline inputs, however, most of the models also show at sensitivity analysis that the reversed situation may not be excluded when the main input assumptions are changed. Such uncertainty underlines how further clinical research on all the aspects dealing with the relative cost-effectiveness between these two techniques is needed. In particular, a recent article – exploiting modeling to define the priority in clinical research –[38] has indicated adherence to screening test as the most influential variable to be addressed in a research setting on the relative cost-effectiveness between the two procedures.

Conclusions

Microsimulation modeling has been widely applied to CTC, in order to anticipate the potential benefit and costs on the general population. These simulations overall suggest that society may expect a substantial benefit when implementing a mass screening program with CTC that would appear affordable as compared with other medical procedures both within and outside the CRC screening field. This clearly indicates that CTC should at least be immediately offered to all eligible subjects who are not compliant with other screening options, such as colonoscopy or faecal tests. On the other hand, there is a residual uncertainty over the cost-effectiveness of CTC as compared with a primary colonoscopy screening that should be addressed by further research.

Abbreviations

CTC	CT colonography
CRC	colorectal cancer

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Table 1

Main characteristics and estimates on CTC long-term efficacy of the simulation models on CTC available in the literature.

Author, year*	Country	Simulation of de novo pathogenesis	Polyp types simulated	CRC stages simulated	Yearly progression from large polyp to CRC	CTC accuracy for large polyps	Frequency of CTC repetition	CTC-related CRC incidence prevention	CTC-related CRC mortality prevention
Sonnenberg et al., 1999	USA	No	Adenomas§	1 stage	NA	80%	10 yrs	40	NA
Ladabaum et al., 2004	USA	Yes	Small/Large	Loc/Reg/Dis	5%	60%–94%°	10 yrs	51–70	58–79
Heitman et al., 2005	Canada	No	Small/Large	1 stage	NA	71%	NA	NA	NA
Vijan et al., 2007	USA	No	Low-/High-risk	Loc/Reg/Dis	NA	82%–91%°	5–10 yrs	71–77	76–81
Hassan et al., 2008	USA	Yes	Dim./Small/Large	Loc/Reg/Dis	3%–4%	90%	10 years	62	NA
Lee et al., 2010	UK	No	Small/Large	Dukes A–D	3%	90%	10 years	77ς	84ς
Knudsen et al., 2010**	USA	No	Dim./Small/Large	AJCC Stages 1–4	NA	84%–92%	5 years	48	NA
Heresbach et al., 2010	France	No	Low-/High-risk	NA	NA	NA	NA	36–38	42–46

*In the case of multiple publications, the most recent was included.

§Without further classification.

°Two different scenarios were simulated.

ςAs compared with colonoscopy. occult blood test.

**MISCAN model

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Table 2

Cost-effectiveness of CTC as compared with no screening and colonoscopy.

Author, year*	CTC specificity	CTC/colonoscopy cost ratio	CTC cost-effective as compared with no screening	CTC cost-effective as compared with colonoscopy	If not cost-effective vs colonoscopy, CTC may reverse when varying
Sonnenberg et al., 1999	95%	0.65	Yes	No	Cost/adherence
Ladabaum et al., 2004	85%	1	Yes	No	Cost
Heitman et al., 2005	84%	0.8	NA	No	Cost/adherence/CTC accuracy/natural history
Vijan et al., 2007	91%	0.8	Yes	No	Accuracy/cost
Hassan et al., 2008	86%	0.8	Yes	Yes	-
Lee et al., 2010	88%	0.3	NA	No	NA
Knudsen et al., 2010**	80%–88%	1	Yes	No	Cost/adherence
Heresbach et al., 2010	NA	NA	Yes	NA	NA

*In the case of multiple publications, the most recent was included.

§Without further classification.

**MISCAN model

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