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IARC HANDBOOKS OF CANCER PREVENTION

3.5 Computed tomography colonography

3.5.1 Technique

The initial description of the use of computerized radiology for colon assessment dates back to the 1980s (Coin et al., 1983). However, it was not until more than a decade later that its full potential was better understood, because images to simulate the colon via three-dimensional (3D) fly-through techniques had been refined (Vining, 1996). The technology of computed tomography (CT) colonography enables a structural examination of the entire colon to be performed with a non-invasive method.

(a)   Equipment

(i)   Hardware

During the initial development of this technology, single-row helical CT scanners were used (Fenlon et al., 1999). Over time, the refinement of multidetector (or multirow) scanners has enabled the development of increasingly detailed images, and imaging times have become progressively shorter. For example, when a 64-slice multidetector scanner is used, the examination can be completed within a single breath hold of about 6–8 seconds (Lefere & Gryspeerdt, 2006). With multidetector scanners of at least 16 rows, submillimetre collimations are possible, enabling highly detailed 3D reconstructions (Cody & Mahesh, 2007).

Improvements in scanning technology continue. Currently, dual-source CT with 320 detector rows is in place at some centres. Automatic exposure control is also available (Kumar & Cash, 2017). This technology adjusts tube current continuously during the examination. Iterative reconstruction techniques are also being used. These improvements shorten the examination time and reduce radiation exposure. Nowadays, submillisievert examinations

are possible (Lubner et al., 2015; Lambert et al., 2016).

(ii)   Software

Software uses the cross-sectional image information obtained from the scanner to develop reconstructions of the colon for evaluation. Numerous developments in this area have enabled the image data to be manipulated in both two-dimensional (2D) and 3D formats (Kumar & Cash, 2017). Various types of 3D reconstructions are possible to facilitate reading. Examples of 3D reconstruction modes are fly-through, unfolded cube, and virtual dissection. The fly-through view develops colonoscopy-like images that can be examined in both antegrade and retrograde fashion, but it tends to have examination blind spots. Other reconstructions, such as unfolded cube and virtual dissection, "flatten" the colon more effectively and remove blind spots, but they introduce some distortion.

Data storage for the images can be a challenge. The use of a picture archiving and communication system (PACS) can facilitate both the storage and the retrieval of images when comparing examinations performed at different times and/or in separate venues.

(b)   Procedure

From the patient perspective, there are several important considerations to ensure the completion of a high-quality examination. For example, the colon needs to be prepared before the examination and distended during the examination. Some of the key elements to patient preparation are discussed here.

(i)   Colon preparation

As is the case for colonoscopy, the performance of CT colonography relies on adequate colon preparation to clear the colon of residual stool. Generally, dietary restriction (i.e. low-fibre diet) for at least a 24-hour period before the examination is recommended (Woodbridge &

Wylie, 2016). Laxatives are often used to induce catharsis, although they are not mandatory (see below). Multiple laxatives are available for colon preparation. The polyethylene glycol preparations that are commonly used for colonoscopy are the safest, because they are least associated with fluid shifts and electrolyte imbalance (Neri et al., 2013b). However, a relative disadvantage of polyethylene glycol is the high-volume "wet" nature of the preparation. This can lead to retained fluid in the bowel (Macari et al., 2001), which can be easily suctioned during conventional colonoscopy but is not effectively managed with CT colonography. For this reason, lower-volume preparations are often used (Laghi, 2014). This includes the use of osmotically active compounds such as sodium phosphate and magnesium citrate; however, some toxicity concerns remain about the administration of these types of agents in frail or elderly individuals. Acute phosphate nephropathy and the deposition of calcium phosphate within the renal tubules are particular concerns with sodium phosphate (Markowitz et al., 2005).

A separate consideration in colon preparation is faecal tagging, which uses the ingestion of high-density contrast agents to differentiate residual colonic contents from polyps. Tagging improves specificity by enabling the digital subtraction of stool after image collection, to better highlight colonic polyps (Fletcher et al., 2013). Barium and iodine-based agents (ionic and non-ionic), either alone or in combination, have been used for this purpose. When a contrast agent is used, the patient is asked to ingest the agent with each meal the day before the CT colonography examination (Neri et al., 2013b). Importantly, the iodine-based agents are hyperosmolar and therefore have inherent cathartic effects. These agents have facilitated the development of colon preparation protocols with a reduced dose of a conventional cathartic agent (Lefere et al., 2002) or even without such an agent (Zalis et al., 2012; Zueco Zueco et al., 2012). Although

the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus statement favours the use of faecal tagging (Neri et al., 2013a), there is no clear consensus about which agent to use. The American College of Radiology (ACR) also endorses tagging, recommending the use of soluble contrast, alone or combined with low-volume barium (American College of Radiology, 2014).

Adequate distension of the colon is a requirement for CT colonography. To accomplish this, the physician or technician performing the procedure inserts a small, flexible catheter. Options for insufflation of the colon include air and carbon dioxide. Carbon dioxide is absorbed through the bowel wall and exhaled, making overdistension and discomfort less likely. Carbon dioxide has been shown to be more effective in reducing abdominal pain, both for CT colonography (Shinners et al., 2006) and for colonoscopy (Memon et al., 2016).

(ii)   Patient positioning

Generally, images are obtained in both the supine and the prone positions. Imaging in two positions has several advantages: it enables redistribution of fluid and stool and improves segmental distension (Tewari et al., 2013).

(iii)   Image interpretation

There is no consensus about the best approach to image interpretation and whether starting with the 2D or 3D images affects the findings. Generally, a 2D read is considered to be faster than a primary 3D read (de Haan et al., 2015). The performance of the two approaches has been compared. A large study by Pickhardt et al. (2007a) demonstrated that for the detection of adenomas 6 mm or larger, primary 2D CT colonography was less sensitive (44.1%) than 3D CT colonography (85.7%). However, in the large (*n* = 2600) ACR Imaging Network (ACRIN) study, no significant difference was seen between the two approaches in the detection of large lesions (Johnson et al.,

2008). The ESGAR consensus statement included statements about this topic (Neri et al., 2013a). There was strong consensus that interpretation should include both 2D and 3D visualization, and that the choice of the primary approach should be based on factors such as personal preference.

The time it takes to read a scan varies greatly, depending on experience and technique. In the multicentre study by Pickhardt et al. (2003), reading times were, on average, about 20 minutes. In a large, multicentre European investigation, somewhat shorter interpretation times were observed (~14 minutes) (Burling et al., 2006). The technique used is an important factor here. Although the 2D images have shorter interpretation times, there are multiple 3D approaches, which can vary in terms of time required for evaluation.

A separate but related issue for reading times is the use of a second reader to evaluate the scans. Computer-aided detection may facilitate the reading process; it uses software algorithms to highlight potential abnormalities that can be reviewed by the radiologists (Kumar & Cash, 2017).

A standard reporting format for CT colonography is now available. The CT Colonography Reporting and Data System (C-RADS) (Zalis et al., 2005) places studies into one of five categories of findings (C0–C4), depending on the interpretability of the scan and the severity of the findings. The categorization also outlines a suggested follow-up for each category. For findings in the categories C2 (intermediate polyp or indeterminate finding) and C3 (polyp, possibly advanced adenoma), colonoscopy is often the follow-up recommendation, and ideally systems are in place to move the patient to colonoscopy on the same day, so that a separate colon preparation is not required (Pickhardt, 2005). In addition to standard reporting of target findings within the colon, the C-RADS document also outlines standard reporting for extracolonic findings using a similar system of five categories (E0–E4).

(c)   Quality control, including training

There is no single national or international standard on the performance of CT colonography. ACR (American College of Radiology, 2014) and ESGAR (Neri et al., 2013a) have issued guidance statements that cover the practical application issues discussed above.

The ACR document includes statements that preparation and distension should be adequate to detect large (≥ 10 mm) polyps, and that the examination should be a complete anatomical coverage (colon and rectum), with luminal surface views of each segment of the colon. The determination of detection rates for polyps 10 mm or larger is encouraged, as is the use of a registry to track performance. Guidance about interpretation includes outlining the need to have access to both 2D and 3D representations of the bowel, and to report polyp measurement in the largest dimension. ACR endorses the reporting of all polyps 6 mm or larger, and considers that reporting polyps smaller than 6 mm is not necessary. Significant extracolonic findings should be reported, and a "balanced approach" should be taken to recommending further workup of extracolonic findings, considering a host of factors (e.g. the clinical importance of the finding, cost, and patient anxiety) (American College of Radiology, 2014).

The approach of ESGAR to developing recommendations is slightly different to that of ACR. A panel of nine delegates from six European Union countries used a modified Delphi process to establish consensus. The panel was asked to evaluate 86 statements about all aspects of the CT colonography procedure, including patient preparation, image acquisition, and interpretation. After four rounds, the panel reached full consensus on 82% of the statements (Neri et al., 2013a).

The ACR document also establishes some training parameters for CT colonography. For physicians with prior qualifications in reading

abdominal and pelvic CT scans, education and hands-on experience with at least 50 CT cases is generally recommended. For physicians without prior experience in interpreting abdominal and pelvic CT scans (e.g. non-radiologists, such as gastroenterologists), completion of more than 200 hours of continuing medical education in the performance and interpretation of abdominal and pelvic CT scans and supervised review of at least 500 CT cases are needed before addressing CT colonography-specific training (American College of Radiology, 2014).

The American Gastroenterological Association released its own set of standards for gastroenterologists performing CT colonography (Cash et al., 2011). The guidance suggests that non-radiologists could perform colon-only interpretation (i.e. avoiding extracolonic CT images) after a period of fairly extensive training including more than 200 case reads with close mentorship.

(d) Screening performance

Several meta-analyses and systematic reviews have been conducted on the screening performance of CT colonography in terms of sensitivity and specificity (Mulhall et al., 2005; Whitlock et al., 2008; Martín-López et al., 2011; Pickhardt et al., 2011; Martín-López et al., 2014).

Most recently, the USPSTF performed a detailed evidence review (Lin et al., 2016a,b). Nine studies (Pickhardt et al., 2003; Macari et al., 2004; Johnson et al., 2007, 2008; Kim et al., 2008; Graser et al., 2009; Zalis et al., 2012; Fletcher et al., 2013; Lefere et al., 2013) of fair or good quality (*n* = 6497) assessed the screening performance of CT colonography. In seven studies (Pickhardt et al., 2003; Macari et al., 2004; Johnson et al., 2007, 2008; Kim et al., 2008; Graser et al., 2009; Lefere et al., 2013) colon preparation was used, and in two studies (Zalis et al., 2012; Fletcher et al., 2013) it was not. Colonoscopy was the standard reference for the assessment of test characteristics. When the seven studies that used colon preparation were considered, the per-person sensitivity of CT colonography for lesions 10 mm or larger was 67–94% and the per-person specificity was 96–98%. When lesions 6 mm or larger were considered, the per-person sensitivity was 73–98% and the per-person specificity was 89–91%.

An earlier meta-analysis also summarized evidence on the sensitivity of CT colonography for the detection of polyps (de Haan et al., 2011). It included four studies (Pickhardt et al., 2003; Johnson et al., 2008; Kim et al., 2008; Graser et al., 2009) that reported the sensitivity of CT colonography for adenoma detection at the 6 mm threshold and the 10 mm threshold. The per-patient sensitivity of CT colonography was 82.9% for adenomas 6 mm or larger and 87.9% for adenomas 10 mm or larger. No cancers were missed in any of these studies.

(e) Host factors that affect performance

Although there are several contraindications to the performance of CT colonography, most are not relevant to screening examinations. For example, there is an increased risk of perforation with CT colonography in those who have had recent colonoscopy or deep mucosal biopsies (American College of Radiology, 2014) (see also Section 3.5.3). One patient-related factor of some concern may be obesity. Radiological imaging generally requires higher doses of radiation in such circumstances (Yanch et al., 2009), and therefore the risk of inducing secondary cancer may be incrementally higher in obese individuals.

3.5.2 Preventive effects

There are no RCTs or observational studies that have reported CRC incidence or mortality outcomes associated with screening with CT colonography. Early evaluation of the effectiveness of CT colonography for the detection of advanced neoplasia was typically measured by tandem studies of CT colonography and colonoscopy in

a single group of patients (i.e. one-time screening with CT colonography followed by colonoscopy as the reference standard). These studies often included both asymptomatic individuals and individuals at higher risk (because of symptoms, family history, or history of colonic lesions), and therefore could not be interpreted as providing evidence related to test performance in a screening cohort.

Current evidence of the effectiveness of CT colonography comes from tandem studies, RCTs, and modelling studies in which detection rates of adenomas and cancer with CT colonography are compared with those with an established CRC screening test.

(a)   Tandem studies

The tandem studies of CT colonography screening in asymptomatic adults in which the ADR and cancer detection rate (CDR) were reported or could be calculated are presented in Table 3.5.1. In 2003, Pickhardt et al. (2003) evaluated a cohort of 1233 asymptomatic adults who underwent same-day CT colonography and colonoscopy and observed slightly better performance with CT colonography in the detection rate of adenomas 10 mm or larger and of cancer compared with colonoscopy. The ADR for colonoscopy was superior to that for CT colonography for adenomas 6 mm or larger, but this was principally due to the subset of adenomas 6 mm in size. Kim et al. (2007) compared the performance of CT colonography and colonoscopy in two separate groups of consecutive adults undergoing screening with each test and observed similar detection rates for advanced neoplasia.

The first prospective, tandem study of significant size comparing CT colonography and colonoscopy in asymptomatic adults was the National CT Colonography Trial (ACRIN 6664), reported in 2008 (Johnson et al., 2008). The trial recruited about 2600 asymptomatic adults 50 years or older who underwent CT colonography followed by colonoscopy, which served as

the reference standard. The primary end-point was detection by colonoscopy of large adenomas (≥ 10 mm) and adenocarcinomas, although radiologists reported all detected lesions 5 mm or larger, which enabled comparative measures of sensitivity per millimetre of size of adenomas and cancers. Per-polyp sensitivity was expressed as the proportion of lesions detected by colonoscopy that were also detected by CT colonography, which increased with increasing lesion size, from 0.59 for polyps 5 mm or larger to 0.84 for polyps 10 mm or larger (Johnson et al., 2008) Separate per-patient ADR and CDR were not reported. Graser et al. (2009) evaluated the performance of gFOBT, FIT, sigmoidoscopy, CT colonography, and colonoscopy in a group of 307 asymptomatic adults who underwent each of these tests consecutively, with colonoscopy as the reference standard. CT colonography and colonoscopy had a nearly equivalent performance in the detection of advanced adenomas (7.5% vs 8.1%) and of advanced neoplasia (9.4% vs 9.8%), and both CT colonography and colonoscopy identified the one case of cancer in the study group.

(b)   Randomized controlled trials

In the Netherlands, the Colonoscopy or Colonography for Screening (COCOS) trial was initiated in 2009 to compare the participation rate and the detection rates between a CT colonography arm (n = 982 of 2920 CT colonography invitees) and a colonoscopy arm (n = 1276 of 5924 colonoscopy invitees) and to eventually link participants to the national cancer registry 10 years after invitation, for follow-up on CRC incidence and mortality (de Wijkerslooth et al., 2010; Stoop et al., 2012). Participants in the CT colonography arm who had one or more lesions 10 mm or larger were offered immediate colonoscopy; participants with three or more lesions of 6–9 mm were scheduled for colonoscopy in 1.5 years, and participants with one to two lesions of 6–9 mm were offered surveillance CT colonography in 3 years. The two primary outcomes were

Table 3.5.1 Detection rates of neoplastic lesions with CT colonography and colonoscopy in randomized controlled trials and tandem studies of colorectal cancer screening in asymptomatic adults

Study	Study type	Age at enrolment (years)	No. of participants	Detection rate of adenomas ≥ 10 mm (%) CTC/OC	Detection rate of cancer (%) CTC/OC	Detection rate of advanced neoplasia[a] (%) CTC/OC	Comments
Pickhardt et al. (2003)	Single cohort, TS	40–79	1233	3.6/3.4[b]	0.16/0.08[b]	4.1/4.0[c]	All patients underwent same-day CTC and OC
Kim et al. (2007)	Parallel CTC and OC studies of consecutive adults undergoing screening	CTC: 57 (7.2)[d] OC: 58 (7.8)[d]	CTC: 3120 OC: 3163	3.3/3.3[c]	0.45/0.13[c]	3.9/3.8[c]	Patients with polyps ≥ 6 mm detected by primary CTC were offered same-day OC
Johnson et al. (2008)	Single cohort, TS	≥ 50	2531	—	—	3.9/4.3[b]	
Graser et al. (2009)	Single cohort, TS	50–81	307	7.5/8.1[b]	0.3/0.3[b]	9.4/9.8[b]	Parallel comparison of CTC, OC, FS, FIT, and gFOBT
Stoop et al. (2012)	RCT (COCOS trial)	50–75	CTC: 982 OC: 1276	5.4/6.3[b,e]	0.5/0.5[b]	6.1/8.7[b]	Patients with ≥ 1 lesions ≥ 10 mm detected by CTC were referred for OC
Sali et al. (2016)	RCT (SAVE trial)	54–65	CTC: 1286 OC: 153	2.6/2.0[b,e]	0.5/0[b]	5.2/7.2[b]	CTC arm divided into reduced cathartic preparation and full cathartic preparation. In the CTC groups, participants with a colonic mass or ≥ 1 polyps > 6 mm were referred for OC
Regge et al. (2017)	RCT (Proteus trial)	58–60	2595	3.8[b,e]	0.4[b]	5.1[b]	CTC with non-cathartic preparation The aim of this trial was to compare participation rates and detection rates between FS and CTC in a screening setting

COCOS, Colonoscopy or Colonography for Screening; CT, computed tomography; CTC, CT colonography; gFOBT, guaiac faecal occult blood test; FIT, faecal immunochemical test; FS, flexible sigmoidoscopy; OC, optical colonoscopy; RCT, randomized controlled trial; TS, tandem study or studies.

[a] Advanced neoplasia may include adenomas ≤ 10 mm with prominent villous components or high-grade dysplasia.

[b] Per participant or patient.

[c] Per polyp.

[d] Mean age (standard deviation).

[e] Advanced adenomas ≥ 10 mm.

the participation rate, defined as the number of invitees undergoing the examination relative to the total number of invitees, and the detection rate, defined as the number of participants with advanced neoplasia relative to the total number of invitees. The CDR per 100 participants was equivalent in the CT colonography and colonoscopy arms (both 0.5%; P = 0.91), and the CDR per 100 invitees was 0.1 in the CT colonography arm and 0.2 in the colonoscopy arm (P = 0.50). The overall advanced ADR per 100 participants was higher in the colonoscopy arm (8.2%) than in the CT colonography arm (5.6%) (P = 0.02), and the advanced ADR per 100 participants for adenomas 10 mm or larger was also higher in the colonoscopy arm (6.3%) than in the CT colonography arm (5.4%), although the difference was not statistically significant (Stoop et al., 2012). [Because enrolment was considerably lower than initial targets, the Working Group expressed concerns that the study had insufficient statistical power.]

Two RCTs in Italy compared the detection rate and the participation rate between CT colonography and other CRC screening methods. The SAVE trial randomized adults to CT colonography, FIT, and colonoscopy to compare the participation rate, detection rate, and screening costs (Sali et al., 2013, 2016). A cohort of approximately 16 000 adults aged 54–65 years with no history of CRC screening was randomized into three groups. Group 1 (n = 1286 of 4825 eligible invitees) was invited to undergo CT colonography, and the CT arm was divided into reduced cathartic preparation and full cathartic preparation groups. Group 2 (n = 4677 of 9288 eligible invitees) was invited to undergo three rounds of biennial FIT. Group 3 (n = 153 of 1036 eligible invitees) was invited to undergo colonoscopy. Adults in the CT colonography arm with one or more polyps 6 mm or larger or with a colonic mass were invited to undergo colonoscopy, and adults with no lesions or with polyps smaller than 6 mm were classified as having negative

results and were invited to undergo FOBT after 5 years. The advanced ADR was 4.7% in the CT colonography arm versus 7.2% in the colonoscopy arm, and the detection rate for all advanced neoplasia was 5.2% in the CT colonography arm versus 7.2% in the colonoscopy arm. [The investigators considered the smaller size of the colonoscopy arm (n = 153) as a limitation of the study and emphasized that the principal interest in comparing the CT colonography arm (n = 1286) and the colonoscopy arm related to participation rate and not detection rate.] CT colonography detected more CRC compared with FIT (0.5% vs 0.1%) and more advanced adenomas (4.7% vs 1.6%) per participant (Sali et al., 2016). [The Working Group noted the difference in the size of the arms as a limitation.]

The second RCT in Italy, the Proteus trial, included two RCTs comparing the acceptability and detection rate between CT colonography and sigmoidoscopy within a population-based screening programme: a pragmatic RCT comparing participation rates (Proteus 1) and an efficacy RCT comparing advanced ADR and CDR (Proteus 2) (Regge et al., 2014, 2017). The target population comprised adults aged 58 years residing in the Piedmont region and adults aged 60 years residing in Verona. Adults who agreed to participate were randomized to either sigmoidoscopy or CT colonography with non-cathartic preparation. Participants in the CT colonography arm with no lesions or with lesions smaller than 6 mm were interpreted as having negative results; participants with lesions 6 mm or larger were invited to undergo colonoscopy. In the sigmoidoscopy arm, polyps smaller than 10 mm detected during sigmoidoscopy were removed and sent for histological evaluation, and participants with polyps 10 mm or larger or with "high-risk polyps" (at least one advanced adenoma < 10 mm, or more than two small tubular adenomas with low-grade dysplasia) were referred for colonoscopy. In Proteus 2, comparable CDRs and ADRs were

reported for CT colonography and sigmoidoscopy. The CDR was 0.4% for CT colonography and 0.3% for sigmoidoscopy, and the advanced ADR for lesions 10 mm or larger was 3.8% for CT colonography and 3.5% for sigmoidoscopy. The detection rate for proximal advanced neoplasia for CT colonography (2.7%) was double that for sigmoidoscopy (1.3%); the detection rate for distal advanced neoplasia was 2.9% for CT colonography and 4.1% for sigmoidoscopy. [The investigators speculated that quality issues, such as the non-cathartic preparation, suboptimal distension, and a new computer-aided detection reading algorithm, may have contributed to the lower than expected detection rates in the distal colon (Regge et al., 2017).]

(c)   Modelling studies

Simulation modelling of different screening strategies provides an opportunity to estimate their comparative effectiveness and to estimate conventional end-points such as CRC incidence, mortality, and LYG associated with screening.

Lucidarme et al. (2012) used a simulation model to assess the outcomes and cost–effectiveness of colonoscopy, CT colonography, and gFOBT (without rehydration) based on varying rates of attendance over a 10-year period. The screening intervals for colonoscopy, CT colonography, and gFOBT were 10 years, 5 years, and 2 years, respectively, with colonoscopy surveillance intervals of 3–5 years, depending on the nature of positive findings at screening. An unconventional, but practical, end-point was used: the rate of remaining CRC, defined either as screened and undetected disease or as unscreened and undetected disease (in keeping with simulated attendance rates), to estimate the cost per CRC avoided over 10 years. For example, with no screening, the remaining CRC rate per 10 000 people was estimated to be 123 cancers per 10 000 adults older than 50 years, equivalent to the expected cumulative incidence over the 10-year period. With 100% participation in

screening, which represents one screening colonoscopy or two screening CT colonographies over the 10-year period, the model estimated that the remaining CRC rate per 10 000 adults was 17 in the colonoscopy arm and 2 in the CT colonography arm (Lucidarme et al., 2012). [The Working Group noted that in the CT colonography arm there were two opportunities to diagnose a CRC, compared with one opportunity in the colonoscopy arm, consistent with a 5-year screening interval for CT colonography compared with a 10-year screening interval for colonoscopy.] Overall, for any participation rate in the simulation, CT colonography screening was the most effective but not always the most cost-effective strategy; gFOBT was the least effective but most cost-effective strategy, and colonoscopy had an intermediate effectiveness and was the least cost-effective strategy (Lucidarme et al., 2012).

The Cancer Intervention and Surveillance Modeling Network (CISNET) recently estimated the long-term effectiveness of CT colonography for the USPSTF's update of its 2008 CRC screening recommendations (Bibbins-Domingo et al., 2016); modelling conducted for the 2008 update did not include CT colonography (Zauber et al., 2008). The modelling was conducted with three separate microsimulation models (SimCRC, MISCAN, and CRC-SPIN) and was used to simulate the effects of different ages at the start of screening and the end of screening, and of different screening intervals, on life years lost and LYG as a measure of benefit, and the number of lifetime colonoscopies as a measure of the burden of screening for an individual aged 40 years at average risk beginning screening at various ages in the simulations (Knudsen et al., 2016). Screening strategies included annual HSgFOBT and FIT, mt-sDNA, sigmoidoscopy every 10 years with annual FOBT or sigmoidoscopy every 5 years without FOBT, CT colonography, and colonoscopy. In all three microsimulations, CT colonography test characteristics were derived from the ACRIN 6664 trial (Johnson et al., 2008). For

comparisons within CT colonography strategies and between simulations of all CRC screening tests, the incremental number of colonoscopies (ΔCOL), the incremental LYG (ΔLYG), and the efficiency ratio (i.e. ΔCOL/ΔLYG) relative to the next-less-effective efficient strategy were calculated for the efficient and near-efficient strategies. The study simulated 15 unique CT colonography screening strategies representing different ages at the start of screening (45, 50, or 55 years), ages at the end of screening (75, 80, or 85 years), and screening intervals (5 years or 10 years). In the analyses, across all three models, the estimated median reduction in the lifetime risk of dying from CRC associated with screening with CT colonography every 5 years between age 50 years and age 75 years was 72–85%. In comparison, the median reduction in the lifetime risk of dying from CRC associated with screening was 72–81% with annual FIT, 77–85% with annual FIT plus sigmoidoscopy every 10 years, and 79–90% with colonoscopy every 10 years (Knudsen et al., 2016).

Barzi et al. (2017) used a Markov model to simulate CRC screening with 13 strategies (gFOBT, FIT, mt-sDNA, sigmoidoscopy, colonoscopy, and CT colonography), including CT colonography every 10 years, on a cohort of 100 000 adults aged 50–75 years in the USA followed up for 35 years or until death. The outcome measures included discounted LYG and prevented cases of CRC. In the base case model, there was no difference between CT colonography and colonoscopy in terms of discounted LYG (15.225 vs 15.227 LYG). CT colonography detected more cancers (3594 vs 3462) but prevented fewer cancers (1068 vs 930) and fewer CRC deaths (922 vs 863). The corresponding reduction in the risk of CRC was 23% with colonoscopy and 20% with CT colonography; the corresponding reduction in the risk of CRC death was 34% for colonoscopy and 30% for colonoscopy. CT colonography was the second most efficient strategy among the 13 strategies compared in the simulation (Barzi et al., 2017).

3.5.3 Adverse effects

The potential adverse effects of CT colonography include perforation, non-serious adverse events associated with colon preparation (such as abdominal pain), and examination-related pain, vasovagal syncope, and presyncope. Other potential harms are an increased risk of radiation-induced cancer from a single examination or multiple examinations, and extracolonic findings.

Perforation during CT colonography screening is very rare and is typically associated with insufflation. A common finding in most reports of perforation during CT colonography is the presence of symptoms such as inflammatory bowel disease, ulcerative colitis, and cancer. Lin et al. (2016a) identified 15 studies that addressed serious adverse events associated with CT colonography in screening and mixed populations (screening and diagnostic examination). The risk of perforation during CT colonography was less than 0.02% overall (2 per 10 000 CT colonography procedures); in 11 prospective studies restricted to screening populations (n = 10 272), no perforation events were reported (Lin et al., 2016a). In another systematic review and meta-analysis of 11 studies including more than 100 000 patients (including 7 among the 15 studies from Lin et al., 2016a), 28 colon perforations were reported, for an estimated perforation rate of 0.04% overall and 0.02% in asymptomatic patients (Bellini et al., 2014).

Although only low-dose, non-enhanced multidetector CT protocols are recommended for screening asymptomatic adults at average risk, there is still concern about the estimated risk of radiation-induced cancer from a single examination and multiple examinations, and the cumulative dose that may be accrued from examinations for other conditions (Brenner & Hall, 2007). The systematic review by Lin et al. (2016a) of CT colonography screening studies revealed few studies that reported average exposures and

dose levels, but the evidence reflected a decrease in exposures over time with newer multidetector scanners and greater attention to dose-reducing protocols. For example, in the ACRIN 6664 study, which enrolled participants in 2005–2006, the estimated mean effective dose per CT colonography screening study was 8 mSv for women and 7 mSv for men, whereas more recent data from a 2011 survey of practices in the USA revealed that the mean effective radiation dose for CT colonography screening had declined to 4.4 mSv (Boellaard et al., 2012). This effective dose level is greater than that of a chest X-ray (0.4 mSv) and a mammogram (0.4 mSv) but less than that of most diagnostic CT procedures (American College of Radiology, 2017) and is estimated to be equivalent to about 16 months of natural background radiation.

Berrington de González et al. (2011) estimated the radiation-related risk of cancer using risk projection models based on the report of the Biological Effects of Ionizing Radiation (BEIR) VII committee (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, 2006) and screening protocols from the ACRIN 6664 trial (Berrington de González et al., 2011). A single CT colonography examination at age 50 years would result in a slightly higher risk (0.06%) than a single screening examination at age 70 years (0.03%). A series of CT colonography examinations every 5 years from age 50–80 years, which include additional radiation exposure from follow-up CT examinations for incidental, extracolonic findings, were estimated to result in a 0.15% risk of radiation-induced cancer (Berrington de González et al., 2011). The estimated benefit of screening in avoiding a CRC death was estimated to be considerably higher than the estimated risk of radiation-induced death from CRC screening, with a ratio ranging from 35:1 to 47:1 (Berrington de González et al., 2011).

Extracolonic findings represent potential harms, but in some instances the detection of an extracolonic finding may be beneficial. Extracolonic findings were reported in 27–69% of CT colonography examinations (Lin et al., 2016a) and included small masses, suspected cancers, aneurysms, and adenopathy. Detection of unsuspected, clinically significant findings, such as extracolonic cancers, which are uncommon, and abdominal aortic aneurysms, may represent a benefit to the patient. However, some extracolonic findings may be insignificant, requiring no further evaluation, whereas others are judged to be potentially serious enough to warrant additional imaging, which may prove to be unproductive and result in an increased radiation dose and in diagnostic and therapeutic procedures that may also result in serious complications. On the C-RADS scale ranging from E0 to E4 (where E0 is a compromised examination and E1 or E2 represents no or insignificant extracolonic findings), E3 is judged as likely unimportant but may warrant additional workup, and E4 is a potentially important finding that requires follow-up (Zalis et al., 2005).

Lin et al. (2016a) summarized the challenges of obtaining clear estimates of the burden of extracolonic findings from studies that often include heterogeneous patient samples (asymptomatic vs mixed populations), variations in reporting extracolonic findings (all vs suspected malignancies only), variable age ranges in the study group (the risk of extracolonic findings increases with age), variations in reporting medical follow-up including treatment, and variations in duration and completeness of follow-up. In a review of 21 studies ranging in size from 75 patients to 10 286 patients, Lin et al. (2016a) reported that the frequency of E3 and E4 findings ranged from 5% to 37%, and the frequency of E4 findings ranged from 1.7% to 12%. In studies that reported medical follow-up, 1.4–11% of patients were referred for further evaluation, but only 3% or less underwent treatment. In a report from a large single practice (Pooler et al., 2016), 88.3% of the patients with extracolonic findings had

category E1 and E2 extracolonic findings (not clinically relevant), 9.1% had E3 findings (likely unimportant), and 2.5% had E4 findings (potentially important). The potential benefit of extracolonic findings was higher in the E4 group, with 68% of patients receiving a diagnosis of clinically significant disease (malignancies, abdominal aortic aneurysms, etc.), whereas patients with an E3 finding were very unlikely to have clinically significant extracolonic disease (8.3%).

3.5.4 Benefit–harm ratio and cost–effectiveness

The benefits of CT colonography include high sensitivity for advanced adenomas and cancer, and the possibility that some extracolonic findings represent important occult disease. Harms associated with CT colonography include perforation (for which the risk is lower than that with colonoscopy), radiation-induced cancer, the need to undergo a second colon preparation if the findings are positive and same-day colonoscopy is not feasible, and the downstream effects of the detection of extracolonic findings that warrant further investigation and are determined to be benign. The existing evidence indicates that CT colonography has a favourable benefit–harm ratio.

The cost–effectiveness of CT colonography can be estimated relative to no screening or relative to other screening tests (de Haan et al., 2015). The costs of CT colonography include costs associated with the initial examination, costs associated with follow-up colonoscopy, and costs associated with the evaluation and treatment of extracolonic findings. The review of the studies of cost–effectiveness of CT colonography relative to no screening found that in all studies CT colonography screening, at different intervals, was cost-effective relative to no screening (Hassan & Pickhardt, 2013). Knudsen et al. (2010) also estimated that CT colonography screening every 5 years was cost-beneficial (i.e. less costly) relative

to no screening in the Medicare population in the USA, and Heresbach et al. (2010) showed that CT colonography screening easily meets conventional criteria for cost–effectiveness compared with no screening.

Comparative cost–effectiveness, when CT colonography is compared with other screening tests, is sensitive to model parameters, i.e. the cost of the tests, additional programme costs, testing intervals, test accuracy, downstream costs, and assumptions about the natural history of the disease. Although model assumptions, including test performance, intervals, and participation rates, vary considerably in existing models, most comparisons have been with colonoscopy and have shown that colonoscopy every 10 years is more cost-effective than CT colonography is (Knudsen et al., 2010; Lee et al., 2010). However, cost–effectiveness is significantly influenced by the cost and the estimated accuracy of the tests being compared and, in particular, the participation rate. CT colonography has been shown to be more cost-effective than colonoscopy when the participation rate of CT colonography exceeds that of colonoscopy (Pickhardt et al., 2007b; Knudsen et al., 2010; Hassan & Pickhardt, 2013). For example, assuming 100% participation in screening in the Medicare population in the USA, Knudsen et al. (2010) showed that the LYG from 5-yearly CT colonography was similar to the LYG from 10-yearly colonoscopy but that the programme costs of CT colonography were higher. However, if the relative participation in CT colonography screening was 25% higher than participation in other tests, then CT colonography could be cost-effective if reimbursed at US$ 488 per examination (Knudsen et al. 2010).

In a recent simulation of CRC screening in the Netherlands, van der Meulen et al. (2018) compared the cost–effectiveness of CT colonography versus colonoscopy in a microsimulation model (MISCAN) using data from the COCOS trial. In the comparison of 10-yearly screening with colonoscopy and CT colonography in 1000

adults aged 50–70 years with 100% participation, screening with colonoscopy resulted in fewer CRC deaths and more QALYs gained (106 vs 81) compared with CT colonography. The costs of the colonoscopy programme were higher than those of the CT colonography programme, but treatment costs were lower, which resulted in lower total programme costs for colonoscopy. In contrast, when observed CT colonography participation rates from the COCOS trial were used, which were higher than colonoscopy participation rates, CT colonography screening had higher costs but was associated with a higher reduction in CRC deaths and more QALYs gained (29 vs 22). Based on observed participation rates, the simulation showed that colonoscopy screening with more than two lifetime screens would be less cost-effective than CT colonography screening.

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