CT Colonography

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Performance of CT Colonography for Detecting Small, Diminutive, and Flat Polyps

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KEYWORDS

- CT colonography • Virtual colonoscopy • Colorectal polyps
- Colorectal cancer screening • Flat lesions

The main goal of colorectal screening is to reduce the incidence, morbidity, and mortality of colorectal cancer (CRC). CRC is a deadly but preventable disease, which remains a major public health issue largely because of the low rates of effective screening.[1] The recently revised screening guidelines that were created by the American Cancer Society in conjunction with the major gastroenterology and radiology societies strongly emphasize the value of CRC prevention and detection rather than CRC detection alone.[2] In particular, tests that can provide full structural evaluation of the large intestine, such as optical colonoscopy (OC) and computerized tomography colonography (CTC), are likely to be favored in the future. CTC should not be viewed as a replacement for OC but as an additional effective parallel screening option that has the potential to substantially increase adherence rates, assuming that the test is eventually widely reimbursed by third-party payers.

CTC has several potential advantages relative to OC as a screening test, as well as some disadvantages. The primary advantages include that it is generally safer, more convenient, more cost-effective, provides a limited assessment of extracolonic organs, and is equally effective as OC for detecting large colorectal polyps and

cancers.[3–9] Perhaps the main drawback of CTC relates to its noninvasive nature; by itself it is a nontherapeutic test. Therefore, the determination of appropriate criteria for polypectomy referral for CTC-detected lesions is critical for clinical efficacy and cost-effectiveness considerations. There seems to be broad (albeit not universal) agreement that, in most circumstances, large polyps (defined as ≥10 mm) detected at CTC should be referred for polypectomy, whereas isolated diminutive lesions (defined as ≤5 mm) generally do not warrant colonoscopy.[5,7,9–15] The situation is less clear for small polyps (defined as 6–9 mm) detected at CTC,[2,7,14–17] because it is uncertain whether the benefits of polypectomy outweigh the risks and costs associated with the additive colonoscopy procedure. Another area of considerable controversy, not only for CTC but for CRC screening in general, is flat or nonpolypoid lesions.

This article explores the issues of small, diminutive, and flat colorectal polyps, focusing primarily on how they relate to CTC (and OC) screening. However, before delving into CTC-specific performance data, it is critical to understand and review what is known about the prevalence, histology, and natural history of polyps according to the various size categories. In particular, because advanced neoplasia represents the critical high-yield target of CRC prevention, this important subset of colorectal lesions is emphasized.

PREVALENCE, HISTOLOGY, AND NATURAL HISTORY OF POLYPS ACCORDING TO LESION SIZE

Based on a large number of clinical trials and experience, anywhere from 35% to 50% of adults more than 50 years of age may harbor at least 1 colorectal polyp.[4,5,7,18–20] This figure may increase even further with the implementation of more advanced endoscopic techniques. In most cases, the largest lesion will be diminutive. Because of the broad differences in the detection rates of diminutive lesions and their relative lack of clinical importance, polyp prevalence at the 6-mm and 10-mm size thresholds are much more reproducible and relevant values to consider. Recent colonoscopy screening studies have shown a remarkably narrow prevalence range for polyps greater than or equal to 6 mm of 13% to 16% (**Table 1**).[21] Similarly, the prevalence for large polyps is 5% to 6%, which results in about 8% of individuals in whom the largest polyp will lie within the 6- to 9-mm range. As a general rule, approximately one-third of diminutive lesions will be adenomatous (almost exclusively tubular adenomas) and two-thirds will be nonadenomatous, predominately consisting of nonneoplastic mucosal tags and hyperplastic polyps.[7,22] In polyps larger than 6 mm, the ratio of adenomatous to nonadenomatous polyps reverses, with neoplastic lesions representing approximately two-thirds of nondiminutive lesions.[4,7,22]

The ideal screening target for prevention of CRC is the advanced adenoma, which is defined as an adenoma that is large (≥10 mm) or contains histologic findings of high-grade dysplasia or a prominent villous component.[23] Although largely unproven, most experts believe that high-grade dysplasia is a more concerning feature than villous histology. The serrated polyp pathway, which is distinct from the classic adenoma-carcinoma sequence, may account for about 15% of CRC cases.[24] For this particular pathway, sessile serrated adenomas less than 10 mm without dysplasia should not be considered as histologically advanced lesions, but serrated adenomas that are large (≥10 mm) or exhibit dysplasia should also be categorized as advanced (Michael J. O'Brien, MD, personal communication, 2009). The term ''advanced neoplasia'' encompasses advanced (but still benign) adenomas and invasive adenocarcinoma. This term is useful for CRC screening because it combines the key features of prevention and detection.

Table 1
Relevant colorectal polyp data from modern screening cohorts

Variable	Typical Value (%)	Reported Range (%)	References
Screening prevalence of:			
All colorectal polyps ≥6 mm	14	13–16	4,5,7,18–20
Small 6- to 9-mm polyps	8	8–9	4,5,7,19,20
Large (≥10 mm) polyps	6	5–7	4,5,7,19,20
Advanced neoplasia (any polyp size)	3–4	3.3–7.1	5,7,18,20,25,92
Small 6- to 9-mm advanced adenomas	0.3	0.17–0.46	5,19,20
High-grade dysplasia in small polyps	0.05	0.048–0.064	5,20
Invasive cancer in small polyps	0.01	0–0.039	4,5,7,19,20,25
Rate of advanced histology in 6- to 9-mm adenomas	4	2.7–5.3	5,19,20,25,93
Rate of high-grade dysplasia in 6- to 9-mm adenomas	0.7	0.5–0.8	20,25
Rate of invasive cancer in 6- to 9-mm adenomas	0.1	0–0.49	4,5,7,19,20,25,93–95
Rate of invasive cancer in 1- to 2-cm adenomas	1	0.5–2.4	19,20,96

Data from Pickhardt PJ, Kim DH. Colorectal cancer screening with CT colonography: key concepts regarding polyp prevalence, size, histology, morphology, and natural history. AJR Am J Roentgenol 2009;193(1):40–6.

Although large adenomas (≥10 mm) comprise about 90% of all advanced neoplasia in the screening setting,[5,20,25] approximately 4% of 6- to 9-mm adenomas will show advanced histology, with a reported range of 2.7% to 5.3% (see **Table 1**). Assuming an 8% screening prevalence of 6- to 9-mm polyps and a 4% frequency of advanced histology, the overall screening prevalence of small advanced adenomas is approximately 0.3%, with a reported range of 0.17% to 0.56% (see **Table 1**). The presence of high-grade dysplasia in 6- to 9-mm adenomas is even more uncommon, with an overall prevalence of about 0.05% (see **Table 1**). Although the overall prevalence of diminutive polyps is many times higher than small 6- to 9-mm polyps, the prevalence of diminutive advanced neoplasia is considerably lower than that for small polyps.[20]

One striking feature of the recent screening data is the lower rate of cancer according to lesion size compared with the high-risk, symptomatic, and/or surgical cohorts in the older literature. For example, a commonly quoted historical figure for the cancer rate among small 6- to 9-mm adenomas is 0.9%.[15,26–28] However, when the recent large screening studies are tallied, the frequency of cancer decreases to 0.1% or lower, ranging from 0% to 0.5% (see **Table 1**), with most of the reported small cancers concentrated within one Korean series.[19] The percentage falls even lower if all 6- to 9-mm polyps, and not just small colonomas, are considered in the denominator. We have yet to encounter a subcentimeter invasive cancer in our combined CTC and OC experience, including more than 1000 6- to 9-mm polyps.[29] Even for large 1- to 2-cm lesions, the cancer rate seems to be only about 1% (see **Table 1**), which is considerably lower than the commonly quoted historical range of 5% to 10%, which is again based on high-risk cohorts and not screening populations.[26,27] Given that

about 30% to 40% of large polyps are nonadenomatous[4,7,22] and that some large lesions detected at CTC may be false-positives,[4,30] the actual cancer risk for a 1- to 2-cm lesion detected at CTC is considerably less than 1%, lower than the frequency of significant complications at OC referral for therapeutic polypectomy.[31–34]

The natural history of small colorectal polyps has become an issue of critical importance in CRC screening. One reason for this is that CTC is an efficacious and cost-effective approach to population screening if only large polyps ($\geq$10 mm) were considered appropriate to trigger polypectomy.[11] If all small 6- to 9-mm CTC-detected polyps were to be referred to therapeutic colonoscopy for polypectomy, the usefulness of CTC as an intermediate filter would be diminished, but likely still useful.[5,7,9] Although CTC provides an ideal tool for in vivo surveillance of small unresected polyps, there are several older studies that have followed these lesions using other colorectal examinations, including endoscopy and barium enema. Contrary to the general perception, many of the data on polyp natural history already exist from these older longitudinal trials. As a group, these longitudinal studies have repeatedly shown the benign, indolent nature of unresected subcentimeter colorectal polyps, with no study showing that leaving 6- to 9-mm polyps in place is a harmful practice.

Most longitudinal polyp surveillance studies have focused more on small 6- to 9-mm polyps,[35–40] although some have focused on diminutive[41] or large[42] lesions. In Norway, Hofstad and colleagues[37] performed serial colonoscopy on unresected subcentimeter polyps and found that only 1 (0.5%) of 189 lesions eclipsed the 10-mm threshold after a 1-year time interval. At the 3-year follow-up, most polyps in this study remained stable or regressed in size, and there was an overall tendency to net regression among the 5- to 9-mm polyps.[38] The investigators of this endoscopic trial concluded that following unresected 5- to 9-mm polyps for 3 years was a safe practice. Longitudinal studies using flexible sigmoidoscopy have also shown the stability of smaller polyps over time.[35,36,39] In one study that used serial sigmoidoscopy to follow polyps measuring up to 15 mm over a 3- to 5-year period, Knoernschild[39] reported a significant increase in polyp size in only 4% of patients. In a longitudinal study using barium enemas to follow colorectal polyps, Welin and colleagues[40] showed slow growth rates by studying 375 unresected polyps over a mean interval of 30 months. The high observed adenoma detection rates at surveillance in the National Polyp Study, in conjunction with the low observed CRC incidence, was thought to be explainable only by regression of adenomas.[43] In a high-risk cohort of patients undergoing colonoscopy surveillance following CRC surgery, Togashi and colleagues[41] followed 500 polyps 6 mm or less over an average interval of 3.6 years. They concluded that this practice was safe even in the high-risk setting. In a classic barium enema study by Stryker and colleagues,[42] the cumulative 5-year and 10-year risk of cancer related to large colorectal polyps ($\geq$1 cm) left in place was less than 3% and 10%, respectively.

These reassuring longitudinal endoscopic and barium enema studies have done little to quell the current debate about the clinical management of small polyps detected at CTC screening.[44] Part of the problem may be a simple lack of awareness of these study results. CTC can now be used as the preferred instrument to follow unresected colorectal lesions. CTC provides superior polyp measurement capabilities compared with the other colorectal imaging examinations, including improved accuracy and reproducibility for linear size assessment.[45,46] In addition, CTC can assess polyp volume, which greatly amplifies interval changes in lesion size compared with linear measurement.

The University of Wisconsin School of Medicine and Public Health and the National Naval Medical Center (NNMC) in Bethesda, Maryland, are currently collaborating on

a small-polyp natural history trial that commenced in 2004. The early interim results of CTC surveillance in 128 small colorectal polyps from the initial 100 patients has largely recapitulated the findings from the older endoscopic and barium enema trials.[47] With an average CTC follow-up interval of about 1.5 years, 12 (9.4%) of the small polyps showed interval growth, including 11 proven adenomas (1 polyp was removed but not retrieved at OC). There were no cancers that developed during this short interval, and none of the lesions grew past the 10-mm threshold. Five of the adenomas represented advanced lesions, corresponding to 4% of the total polyp cohort (ie, the expected number of advanced lesions from the entire group of 6- to 9-mm polyps). The remaining 116 polyps (90.6%) did not increase in size at CTC follow-up, and some of them had regressed. These findings suggest that interval growth can predict important histology, allowing for noninvasive identification of the small fraction of polyps for which polypectomy is clearly of benefit.

CTC DETECTION OF SMALL 6- TO 9-MM COLORECTAL POLYPS

The accuracy of CTC for detecting large polyps (≥ 10 mm) and masses (≥ 3 cm) has been well established, with most studies reporting sensitivity and specificity values of 90% or higher.[4,7,48–53] CTC performance tends to be more robust when three-dimensional (3D) polyp detection is used alongside two-dimensional (2D) evaluation, when oral contrast tagging has been applied, and when automated carbon dioxide delivery is used for colonic distention. When state-of-the-art CTC is undertaken, there is evidence to suggest that CTC sensitivity for large polyps and cancers may exceed that of OC.[5,7,54] However, there are a few notable exceptions in which the CTC sensitivity for large-polyp detection was in the 50% to 60% range,[55–57] but none of these studies used primary 3D detection, oral contrast tagging, or carbon dioxide.

The CTC performance for small 6- to 9-mm polyps is more variable (**Fig. 1**). One problem is the lack of a reliable reference standard, because the miss rate for small lesions at OC can be 10% or higher when tandem (back-to-back) colonoscopy studies are performed.[58–60] In addition, several published studies have reported by-patient results at the 6-mm and 10-mm thresholds, but not specifically for the 6- to 9-mm range. Although such results can generally be inferred, the conversion is imperfect related to the use of different polyp-matching algorithms. The patient populations are also somewhat heterogeneous, representing screening and nonscreening cohorts. For most CTC studies that have evaluated at least 100 patients, the per-patient sensitivity for small 6- to 9-mm polyps lies somewhere within the range of 50% to 95% (**Fig. 2**, **Table 2**).[4,7,48–53,55–57,61–65] The only outlier was the study by Cotton and colleagues,[55] in which the per-patient sensitivity was only 30%.

More recent data from the clinical CTC screening programs at the University of Wisconsin (UW) and the NNMC suggest that the performance for state-of-the-art CTC for 6- to 9-mm polyps is now approaching that for larger lesions (see **Fig. 1**). An ongoing CTC trial at NNMC continues to show sensitivity for small polyps of about 90% (Brooks Cash, personal communication, 2009). At UW, the positive predictive value of 6- to 9-mm CTC-detected polyps is more than 90%, significantly higher than results from the published clinical trials.[66] In routine clinical practice, the positive predictive value is an important quality measure, along with the overall yield of advanced neoplasia, because performance assessments by sensitivity, specificity, and accuracy cannot be measured when negative CTC cases do not go on to OC. The common CTC methodology used at UW and NNMC provide further support for primary 3D interpretation, which has also been shown to improve small-polyp detection compared with 2D detection alone in a phantom study.[67]
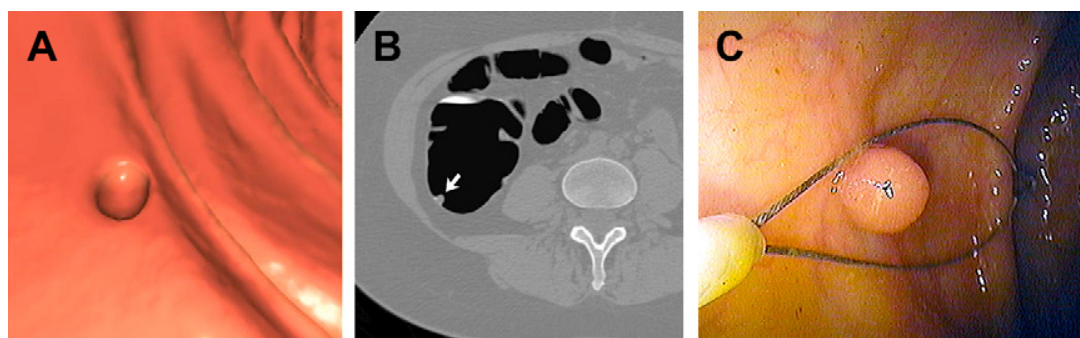
Fig. 1. Small 6-mm tubular adenoma detected at CTC screening. 3D endoluminal (*A*) and 2D transverse (*B*) CTC images show a well-circumscribed 6-mm sessile polyp (*arrow*) in the ascending colon, which proved to be a tubular adenoma after resection at same-day OC (*C*). With state-of-the-art CTC technique, the diagnostic performance for detecting small 6- to 9-mm polyps likely approaches that for larger lesions. (*From* Pickhardt PJ. The colon and rectum. In: Pickhardt PJ, Arluk GM, editors. Atlas of gastrointestinal imaging: radio-logic-endoscopic correlation. Philadelphia: Saunders; 2007. p. 212; with permission.)

Even if CTC has high accuracy for detecting small polyps, it remains unclear whether all such lesions warrant immediate polypectomy. Evaluating the potential benefit (ie, preventing CRC) against the potential risks (eg, perforation, bleeding, seda-tion-related events) and costs (eg, OC procedure, pathology charges), it becomes clear that the conclusion will be largely driven by the input assumptions. Given the low risk (approximately 4%) that a 6- to 9-mm polyp will be an advanced adenoma and the extremely low risk (<0.1%) of CRC, deferring polypectomy may be an attrac-tive option for individuals who have already decided to undergo a less invasive

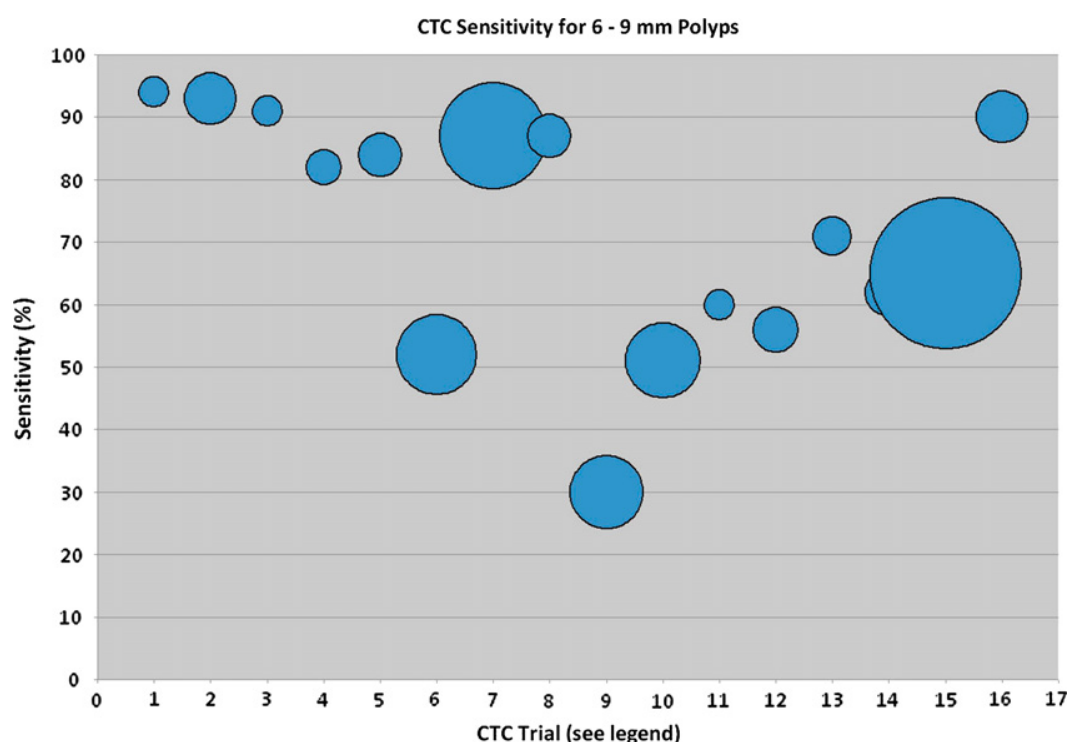**Fig. 2.** Bubble graph showing CTC by-patient sensitivity for detecting 6- to 9-mm polyps for published trials that involved 100 or more patients and used OC as the reference standard. The bubble sizes correspond to the size of the patient cohorts. The studies are displayed in chronologic order, with the oldest on the left (see **Table 2**). Note the 1 outlier where the CTC sensitivity decreases to less than 50%.

Table 2			
Reported per-patient sensitivities for small 6- to 9-mm polyps			
Trial	Author, Year	Sensitivity	No. of Patients
1	Fenlon et al, 1999[48]	94	100
2	Yee et al, 2001[51]	93	300
3	Lefere et al, 2002[61]	91	100
4	Ginnerup Pedersen et al, 2003[97]	82	144
5	Pineau et al, 2003[50]	84	205
6	Johnson et al, 2003[56]	52	703
7	Pickhardt et al, 2003[7]	87	1233
8	Innaccone et al, 2004[98]	87	203
9	Cotton et al, 2004[55]	30	600
10	Rockey et al, 2005[57]	51	614
11	Arnesen et al, 2005[63]	60	100
12	Arnesen et al, 2007[64]	56	231
13	Jensch et al, 2008[62]	71	168
14	Kim et al, 2008[53]	62	241
15	Johnson et al, 2008[4]	65	2531
16	Graser et al, 2009[49]	90	307

screening route. To coincide with current standard of care, the current protocol at UW is to offer all patients with any CTC-detected polyp that is larger than or equal to 6 mm same-day OC for polypectomy (see **Fig. 1**). However, individuals with one or two 6- to 9-mm lesions, corresponding to a C-RADS C2 classification,[12] are also offered the option of short-term CTC follow-up in 2 to 3 years. Preliminary results with CTC surveillance (described earlier) suggest that this approach may effectively identify the small subset of lesions for which polypectomy is indicated and avoid the need for colonoscopy in most other cases. However, more data are needed before drawing firm conclusions. Given the published data establishing the risk of future advanced neoplasia related to finding multiple adenomas at the index colonoscopy,[68,69] the policy at CTC is that patients with 3 or more small polyps are referred for polypectomy. This approach corresponds with a C-RADS C3 categorization, placing 3 or more small polyps detected at CTC at the same level as 1 or more large ($\geq$ 10 mm) polyps.

Given the limited health care dollars available for expensive resources, it is critical to also consider costs alongside the anticipated health consequence for the various screening strategies. We have studied the theoretical cost-effectiveness of immediate polypectomy versus 3-year CTC surveillance for small 6- to 9-mm polyps detected at CTC screening.[17] Without any intervention, the estimated 5-year CRC death rate for patients with unresected 6- to 9-mm polyps was 0.08%, which already represents a sevenfold decrease from the 0.56% 5-year CRC death rate in the general (unscreened) population, most of whom do not harbor polyps. Therefore, for patients with 6- to 9-mm polyps detected at CTC screening, the exclusion of large polyps ($\geq$ 10 mm) and masses already confers a low CRC risk. Focusing on a concentrated cohort with only small 6- to 9-mm polyps, the death rate was further reduced to 0.03% with the CTC surveillance strategy and to 0.02% with immediate colonoscopy referral. However, for each additional cancer-related death prevented with immediate polypectomy versus CTC follow-up, 10,000 additional colonoscopy referrals would be needed, resulting in an expected 10 additional perforations and an exorbitant

incremental cost-effectiveness ratio (ICER) of $372,853. We therefore concluded that the high costs, additional complications, and low incremental yield associated with immediate polypectomy of 6- to 9-mm polyps support the practice of 3-year CTC surveillance, which allows for selective noninvasive identification of small polyps at risk (as described earlier). CTC surveillance of small unresected polyps should only be undertaken in the context of a dedicated CTC program, in which a reliable mechanism for follow-up is in place and in which the patient understands the relative risks and benefits involved.

CTC DETECTION OF DIMINUTIVE (≤5 MM) COLORECTAL POLYPS

Few data exist for the performance of CTC in detecting diminutive lesions that measure 5 mm or less (**Fig. 3**). By design, most large CTC trials have not reported diminutive lesions. Without a reliable reference standard, the performance for diminutive lesions is difficult to establish. All the issues that complicate the performance evaluation for small 6- to 9-mm polyps are greatly amplified for diminutive lesions (≤5 mm). Among the studies that have attempted to assess CTC detection of diminutive polyps relative to OC, the by-polyp sensitivity has varied widely but averages to approximately 50% in systematic reviews.[70,71] One recent study carefully assessed CTC-OC correlation for diminutive adenomas using high-quality CTC and found a by-polyp sensitivity of 59% (84 of 147).[49] This value probably approaches the current best-case scenario of expected yield for diminutive lesions.

If the case can be made for the nonaggressive management of small 6- to 9-mm polyps detected at CTC, the appropriate handling of potential diminutive lesions becomes even more apparent. Even at OC, the need to remove or take biopsies of all diminutive lesions is individualized. Because of the high costs of polypectomy and pathologic assessment, as well as the limited yield in terms of important histology, some have suggested that diminutive lesions at colonoscopy could simply be ablated or resected but not sent for pathologic assessment. For several reasons, we believe it is prudent to go one step further for CTC and not report potential diminutive lesions in isolation. The likelihood of a false-positive finding is greatly increased over nondiminutive lesions (see **Fig. 3**). However, even if an isolated diminutive polyp is real, it is almost certainly just a nonneoplastic lesion (eg, hyperplastic polyp or normal mucosa) or nonadvanced tubular adenoma, neither of which has enough clinical importance to warrant polypectomy referral. The rare diminutive advanced adenoma will likely grow to a relevant size at follow-up if truly important, allowing for more selective polypectomy. The current CTC screening interval of 5 years should effectively allow for this determination. Invasive cancer in the diminutive size range is so rare that it can be assumed to be nonexistent in terms of population screening. Although the future risk related to finding multiple adenomas at OC is well established,[69] this has not been stratified by lesion size. The risk related to multiple diminutive-only lesions is unknown but probably much lower. CTC detection of at least 1 nondiminutive polyp would presumably identify most patients at increased risk, although this needs to be proven. It is also important to note that OC detection of diminutive lesions and attempted matching with CTC findings can be highly problematic, incurring additional time, costs, and complications. Therefore, a CTC study without any polyps of 6 mm or larger is considered a negative study, corresponding to C-RADS category C1.[12] However, when larger polyps are present, we often incidentally note the presence of high-confidence diminutive lesions for the endoscopist.

In terms of cost-effectiveness, the initial published analyses assumed that all CTC-detected diminutive lesions would automatically be referred to colonoscopy.[72–75] This
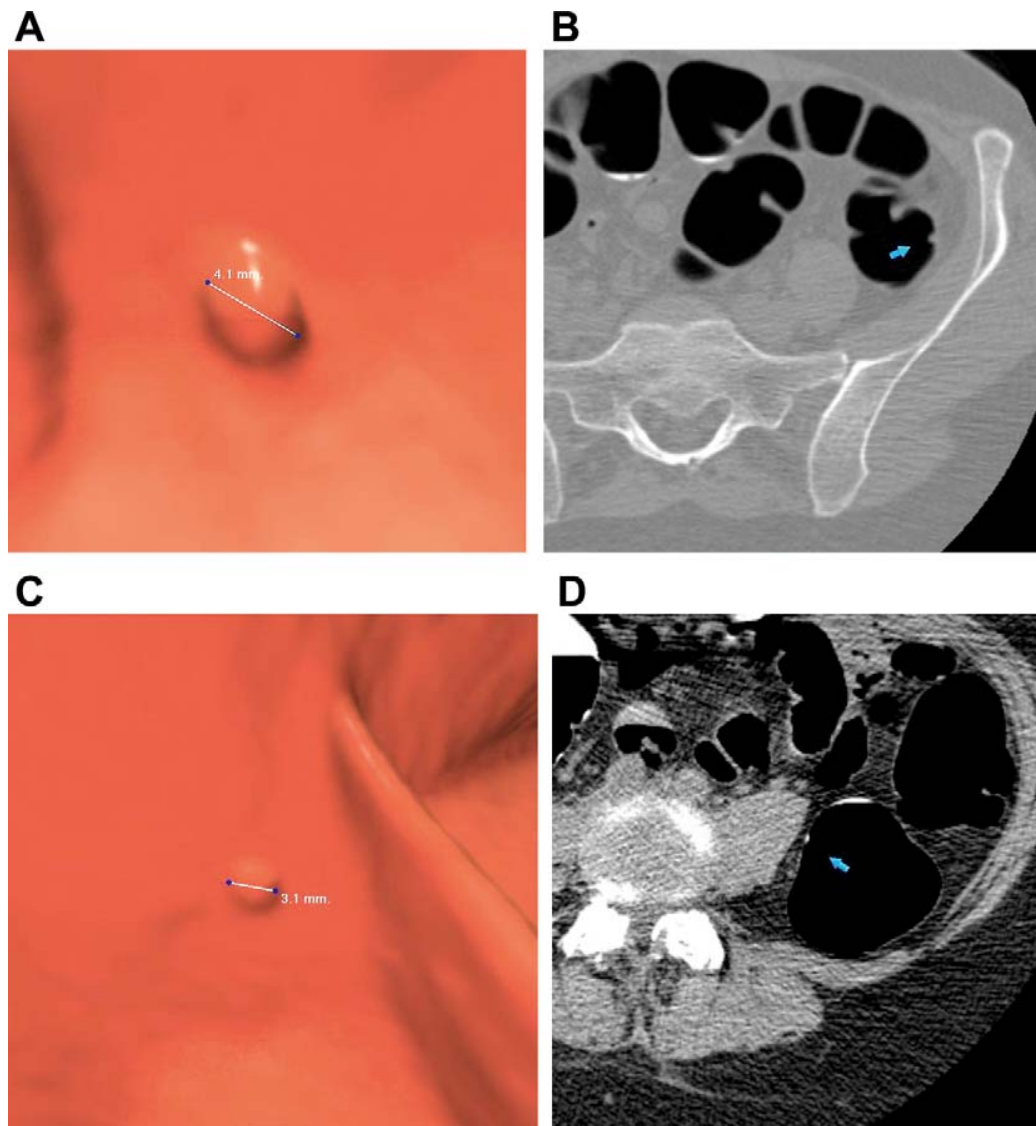
Fig. 3. Diminutive lesions at CTC screening. 3D endoluminal CTC image (*A*) shows a diminutive 4-mm lesion, which appears to be composed of soft tissue at 2D correlation (*B, arrow*). However, most diminutive lesions (*C*) will represent residual adherent stool, which will show internal tagging if oral contrast has been applied (*D, blue arrow*). Regardless of whether these lesions are true polyps or pseudolesions, we believe they should not be reported in isolation at CTC. (*From* Pickhardt PJ, Kim DH. Potential pitfalls at CTC interpretation. In: CT colonography: principles and practice of virtual colonoscopy. Philadelphia: Saunders; 2010. p. 287; with permission.)

not only fails to represent actual clinical practice but also greatly diminishes the theoretical cost-effectiveness of CTC. By using a 6-mm reporting threshold at CTC screening in a hypothetical cohort of 100,000 adults, our Markov analysis showed that CTC is a safer and more cost-effective screening option than OC.[9] CTC screening resulted in a 78% reduction in invasive endoscopic procedures compared with primary OC screening (39,374 vs 175,911), as well as more than 1000 fewer OC-related complications from perforation or bleeding. Reporting of diminutive lesions at CTC increased the CRC prevention rate by about 1%, with an ICER of more than $100,000 per life-year gained. We concluded that removal of diminutive lesions carries an unjustified burden of costs and complications relative to the minimal gains in CRC prevention.

To further evaluate the effect of sending diminutive CTC-detected polyps to OC, we constructed a decision analysis model incorporating the expected polyp distribution, advanced adenoma prevalence, CRC risk, CTC performance, and costs related to CRC screening and treatment.[11] The model conservatively assumed that CRC risk was independent of advanced adenoma size, which clearly overestimates the risk of subcentimeter polyps. For example, a 3-mm tubulovillous adenoma would carry the same cancer risk as a 3-cm villous adenoma with high-grade dysplasia. We found that the number of diminutive polyps that needed to be removed to avoid leaving behind 1 advanced adenoma was 562, and that 2352 diminutive polypectomies would be needed to prevent 1 CRC in 10 years. The ICER for removing all diminutive CTC-detected polyps was $464,407, compared with a cost saving for removal of large polyps only. We again concluded that the low likelihood of advanced neoplasia and the high costs associated with polypectomy argue against colonoscopic referral for diminutive polyps, whereas removal of large CTC-detected polyps was effective.

A nonaggressive approach regarding diminutive lesions detected at CTC has also been favored by several gastrointestinal experts outside radiology. An American Gastroenterological Association future trends report from 2004 noted that "polyps ≤ 5 mm in size do not appear to be a compelling reason for colonoscopy and poly-pectomy."[15] In an editorial from 2005, Ransohoff[13] remarked that "few clinicians would likely argue that colonoscopy is justified" for diminutive lesions, adding that "the overwhelming majority cannot possibly represent an important near-term health threat."[13] In an insightful editorial from 2001, Bond[10] remarked that "a large volume of scientific data indicates that clinicians need to shift their attention away from simply finding and harvesting all diminutive colorectal adenomas toward strategies which allow the reliable detection of the much less common, but much more dangerous advanced adenoma." Although a some gastroenterologists have suggested that colonoscopy referral should be considered for isolated CTC-detected diminutive lesions,[44] the real controversy regarding the clinical management of polyps detected at CTC relates more to the handling of small 6- to 9-mm colorectal polyps.

CTC DETECTION OF FLAT COLORECTAL POLYPS

Colorectal polyps are generally divided into 3 major morphologic categories: sessile, pedunculated, and flat. Sessile polyps have a broad base of attachment, whereas pedunculated polyps have a defined lesion head and a polyp stalk that connects the lesion head to the adjacent colonic surface. The term "polypoid" can then refer to sessile and pedunculated polyps. Polypoid lesions account for most findings, including most advanced adenomas and cancers.[5,25] Flat lesions represent a subset of sessile polyps that, as the name implies, have a nonpolypoid or plaquelike morphology. A polyp height that is less than half its width has been commonly used as a morphologic descriptor.[76,77] However, this definition is too forgiving and could theoretically include lesions that would be more suitably labeled as sessile. For smaller flat polyps less than 1 to 2 cm, lesion elevation above the surrounding mucosal surface is typically 3 mm or less.[12] Categorization of large, superficially elevated lesions that are clearly flat in morphology but which may exceed a maximal height of 3 mm is less uniform. The term "carpet lesion," also referred to as a laterally or superficially spreading tumor, best applies to this important nonpolypoid subset that tends to be large in cross-sectional area but not bulky in appearance (**Fig. 4**).[78]

The prevalence and clinical significance of flat (nonpolypoid) lesions have been the source of recent debate. Endoscopic detection of nonpolypoid lesions may be increased by the use of advanced endoscopic techniques such as chromoendoscopy

and narrow-band imaging. However, unlike the case for East Asia,[79] there is little evidence to suggest that small, flat, aggressive lesions represent a major problem in the screening population in the United States. Although a single-center Veterans Administration study by Soetikno and colleagues[77] suggested that important nonpolypoid lesions may be more common in the United States than was previously believed, a closer analysis of this work reveals that the conclusions are not well supported by the findings.[80] First, a clear distinction must be made between the flat lesions described in this study (defined as elevated lesions with a height less than half the diameter), and completely flat or depressed lesions. The investigators clearly state in this paper that "completely flat lesions are exceedingly rare" and it seems they were completely absent in this study. Furthermore, depressed lesions comprised less than 1% of all colorectal lesions (18 of 2770), only 4 of which were identified at screening. Most of these depressed lesions presumably had a raised edge, but this information was not provided. Therefore, all or nearly all of the nonpolypoid lesions in this study were elevated from the surrounding mucosa, a critical distinction that favors detection at OC and CTC. In addition, the investigators included carcinoma
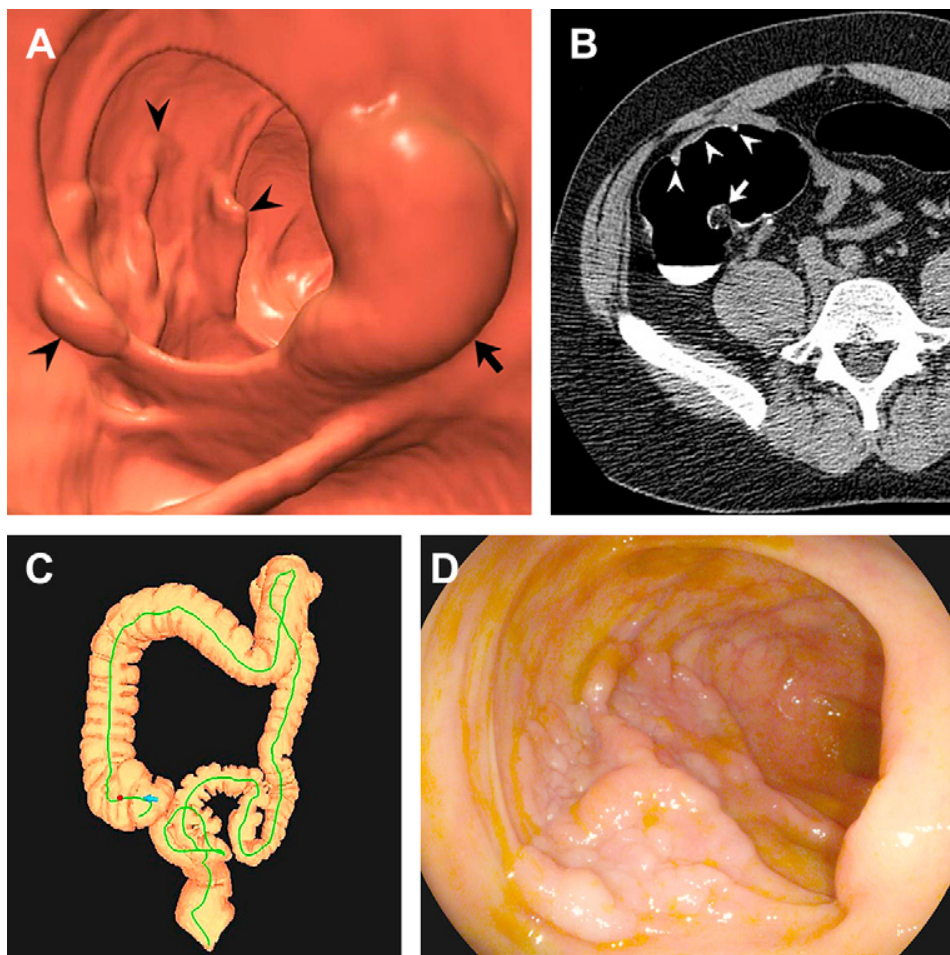

Fig. 4. Cecal carpet lesion detected at CTC screening. 3D endoluminal (*A*) and 2D transverse (*B*) CTC images show a large 4-cm laterally spreading tumor (carpet lesion) within the cecum (*arrowheads*), opposite the ileocecal valve (*arrow*). 3D colon map (*C*) shows the precise location of the lesion (*red dot*) for the endoscopist. With good CTC technique, these flat lesions can be detected with high confidence. A biopsy was taken of the lesion at OC (*D*), but could not resected endoscopically. Multiple biopsies showed tubular adenoma without high-grade dysplasia. The patient underwent laparoscopic right hemicolectomy for definitive treatment.

in situ, which is more appropriately termed "high-grade dysplasia," with invasive cancer.[81] As such, most (11 of 15) nonpolypoid cancers in this study were noninvasive advanced adenomas. The average size of advanced nonpolypoid lesions was large (1.6 cm) and similar in size to their polypoid counterparts (1.9 cm), which is also reassuring for detection at CTC (or standard OC).

By comparison, data from the National Polyp Study showed that flat adenomas were less likely to harbor high-grade dysplasia compared with sessile or pedunculated adenomas.[82] Patients with flat adenomas in this trial were not found to be at greater risk for advanced adenomas at subsequent surveillance colonoscopy. If aggressive flat lesions had somehow been missed at the index colonoscopy in the National Polyp Study, more incident cancers would presumably have developed in the course of longitudinal evaluation.[80,83]

Our own experience with flat lesions detected at CTC screening has also shown a pattern of nonaggressive lesions.[84] Of 92 flat CTC-detected lesions measuring less than 3 cm evaluated at subsequent OC, 23 (25.0%) were neoplastic, 5 (5.4%) were histologically advanced, and none was malignant. In comparison, polypoid lesions measuring less than 3 cm were more likely to be neoplastic (60.3%; 363 of 602), histologically advanced (12.1%; 73 of 602), and malignant (0.5%; 3 of 602). Most of these flat lesions measured less than 3 mm in maximal height at CTC, suggesting that this represents a suitable criterion. Of the 9 flat lesions missed at CTC but seen at colonoscopy in this screening cohort, none was histologically advanced and only 2 were neoplastic (tubular adenomas). In contrast, all 10 carpet lesions (defined as flat, laterally spreading tumors ≥3 cm) were neoplastic and 9 were histologically advanced. These findings suggest that flat lesions less than 3 cm are probably not a major concern compared with polypoid lesions of similar size, and that large carpet lesions represent the subset of polyps with flat morphology of most clinical relevance.

Considering colorectal lesions of similar (linear) size, flat lesions will be less conspicuous than polypoid lesions at CTC and OC. However, reasonable sensitivity at CTC can nonetheless be achieved with oral contrast tagging and combined 3D and 2D polyp detection methods at CTC.[76] Phantom and clinical studies have shown that the 3D endoluminal display improves the sensitivity of CTC for detecting flat lesions.[76,79,85] The 2D multiplanar images remain critical for lesion confirmation. Continued improvements in CTC interpretation and computer-aided detection software have resulted in further increases in sensitivity for detection.[86] In our recent clinical experience, more large, flat, advanced adenomas were detected at primary CTC screening compared with parallel primary OC screening, although such lesions were uncommon in either screening arm.[5] Perhaps a more legitimate concern is the increased rate of discordant findings between CTC and OC, in which flat lesions called at CTC cannot be found at subsequent OC.[66] Some of these discordant cases undoubtedly represent CTC false-positive interpretations, but we have also found several OC false-negative results where a discordant flat lesion is ultimately proved to be real on subsequent CTC and OC.

Histologically advanced or depressed small flat lesions seem to be rare in our screening population. Most flat lesions detected (or missed) at CTC are hyperplastic.[22,87] This is likely due in part to the tendency of hyperplastic polyps to flatten when the colonic lumen is distended.[88] In comparison, large serrated polyps tend to be more conspicuous at CTC in our experience. In the Mayo Clinic experience, most occult polyps at CTC (ie, missed lesions that could not be identified even retrospectively) were flat hyperplastic polyps ranging in size from 6 mm to 2.1 cm.[89] This mirrors our own clinical experience with occult lesions at CTC.[22,90] Given these

collective findings, we believe that flat lesions measuring less than 3 cm remain a diagnostic challenge but do not represent a major drawback to widespread CTC screening.

Carpet lesions are an important subset of flat lesions that, despite their large surface area, can be subtle on CTC because of the paucity of raised tissue. These lesions have a strong predilection for the rectum and cecum (see **Fig. 4**).[91] Despite their large linear size, carpet lesions have a low rate of malignancy but frequently show villous features, with or without high-grade dysplasia.[78,91] Although classic carpet lesions are less conspicuous than large sessile or pedunculated polyps, they are nonetheless detectable at CTC in our experience, because of the fixed fold distortion and the raised edges that often have a rolled-up or polypoid appearance (see **Fig. 4**). Optimal preparation and distention, as well as a hybrid 3D-2D detection strategy, allow for confident detection of carpet lesions. In some cases, endoscopic mucosal resection can serve as the definitive treatment, whereas others will require more aggressive surgery.[78]

SUMMARY

With the advent of less invasive, nontherapeutic colorectal screening tests such as CTC, strict adherence to a "leave no polyp behind" approach loses its validity on clinical and economic grounds, and from a patient safety standpoint. We must remain open-minded about novel approaches to colorectal screening that will safely and effectively increase compliance rates beyond OC screening alone. All cancers presumably arise from smaller benign polyps, but this does not imply that polypectomy is indicated for every small benign lesion. The mindset of universal polypectomy has long been applied to primary OC screening, although even this may be changing because of the limited clinical yield related to diminutive polypectomy, which is also associated with significant costs and complications. An aggressive management approach to smaller polyps makes even less sense when applying safer nontherapeutic tests such as CTC that provide a filter between polyp detection and invasive therapy. More recent screening data on the low prevalence rates of important histology in small and diminutive lesions further support a nonaggressive approach. The current concepts and existing data surrounding flat (nonpolypoid) lesions also support the parallel use of CTC screening alongside primary OC screening to increase overall adherence rates.

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