

COMPUTED TOMOGRAPHIC COLONOGRAPHY (CTC) FOR DIAGNOSIS OF EARLY CANCER AND POLYPS?

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ABSTRACT:

Computed tomographic (CT) colonography comprises thin-section CT scanning of the prepared, gas-distended colon, acquired in more than one patient position. The test is widely available internationally and is highly sensitive for colorectal cancer, including significant polyps and early colorectal cancers (SPECC). In this article, we will discuss the basic technique of CT colonography, its diagnostic performance, the challenge of detecting serrated polyps and handling of diminutive polyps. Since CT colonography permits a detailed assessment of polyp morphology, radiologists must communicate their descriptions of the CT appearances of larger polyps accurately and using widely-accepted terminology. This allows services to plan their resection strategy for these larger lesions in timely fashion and ensure availability of appropriate staff and equipment for that patient. Close collaboration between all members of the multi-disciplinary team will ensure that all patients have access to high-quality colonic imaging services.

INTRODUCTION:

Radiological techniques have been used to diagnose colorectal cancer (CRC) for over 100 years^{1,2}. With the advent of CT scanning,³ radiologists became able to both detect and stage CRC reliably, particularly by insufflating gas to distend the bowel and improve tumour visualisation.^{4,5} Yet it was a far more flamboyant display that truly ignited wider interest. Inspired by flight simulator computer games,⁶ Dr David Vining fused 3-dimensional data from newer helical CT scanners⁷ with virtual reality computer modelling to create a “virtual colonoscopy”, allowing radiologists to “fly through the body”. The resulting images (of a particularly tolerant colleague, Dr David Gelfand) were presented to the radiological and gastroenterological communities as a 3D rendered video to the sound of Wagner’s “Flight of the Valkyries”, and CT colonography (CTC) as recognised today was born.⁸ Accelerated by early reports of excellent diagnostic performance,^{9,10} the technique disseminated rapidly, driven by vast improvements to CT scanning hardware and image reconstruction software. Currently, over 100,000 CTC examinations are performed each year in England alone¹¹. In this article, we will describe the modern practice of CTC, what it entails for patients undergoing the test, its diagnostic performance, main benefits and downsides, and specific aspects relevant to early diagnosis of colonic neoplasia.

CTC TECHNIQUE

CTC comprises three key aspects: (a) some form of bowel “preparation” (not necessarily involving purgation); (b) colonic gas insufflation; and (c) image acquisition in more than one patient position.¹² Most would now regard oral contrast administration, to label or “tag” any residual stool, as an essential prerequisite for competent practice.¹² It is this aspect of CTC that precipitates more confusion among clinicians and patients than any other. Faecal tagging is a fundamental aspect of modern CTC, and must always be administered; whereas cathartics can be reduced or even omitted entirely in some cases (Figure 1)¹³. The confusion arises because the most commonly used faecal tagging agent, Gastrografin (sodium diatrizoate/meglumine diatrizoate, Bayer plc, Newbury, UK), also has a laxative effect, thereby providing a convenient and simple means to both cleanse and tag the colon using a single agent. Yet patients must still be warned that they may experience abdominal cramping and diarrhoea^{14,15}; and that a tube will be inserted into their rectum through which gas

(almost always carbon dioxide, at least in the UK¹⁶) will be machine-insufflated. Scans are performed with the patient supine and prone (or using decubitus positioning if preferred or limited by patient mobility) to allow redistribution of insufflated gas and any retained fluid or stool, thereby improving visualisation of the entire circumference of the colonic surface. Nonetheless, CTC can be employed reliably in the older, frailer patient; the average age of patients having CTC in England is over 70, and a quarter are over 80.¹¹ Despite this, serious complications are rare^{17,18} and the procedure is extremely well-tolerated^{19,20} and safe.

DIAGNOSTIC ACCURACY

Considerable research effort has been concentrated on establishing the diagnostic accuracy of CTC. Regarding detection of established colorectal cancer, the literature is relatively clear; two meta-analyses have shown that CTC is approximately 96% sensitive for CRC,^{21,22} not significantly different from colonoscopy (which was 95% sensitive in one of these analyses²²). In support, a recent further systematic review has shown that identification of (initially undetected) CRC in the three-year period following CTC is rare – only occurring in 4.4% of cases.²³ Since adenomas typically take many years or even decades to transition to carcinoma,²⁴ these are likely to be due to missed CRC at the index CTC examination, entirely consistent with approximately 95% sensitivity for cancer.

Regarding large (1cm+) polyps, CTC correctly identifies approximately 85-90% of individuals with at least one such polyp (i.e. per-patient sensitivity)^{21,25}; and approximately 75-80% of any given 1cm+ polyps (i.e. per-polyp sensitivity).^{8,25} The discrepancy is because individuals may have multiple 1cm+ polyps; finding only one of these is enough to define a CTC examination as positive, even if other polyps are missed – therefore, per-polyp sensitivity is (by definition) lower than per-patient. Small (6-9mm) polyps are more difficult to detect at CTC, with per-patient and per-polyp figures of 70-80%^{3,8} and 60-70%^{21,25} respectively. Clearly, the remit of the SPECC programme is to improve detection and management of significant polyps and early cancers – implying an emphasis on larger lesions, which are more likely to be histologically advanced. Therefore, it is particularly relevant that a UK pragmatic randomised trial, SIGGAR, found no significant difference in detection rates of a composite end point of colorectal cancer and large (1cm+) polyps between colonoscopy and CTC.²⁶

SPECIFIC ISSUES FOR SIGNIFICANT POLYPS AND EARLY COLORECTAL CANCERS (SPECC)

Although the diagnostic accuracy data outlined above show that CTC has excellent diagnostic sensitivity on average, early cancers may be harder to detect. This might mean that, for SPECC in particular, the performance of CTC might be poorer than the meta-analyses and randomised trial outlined above, which derive from “all-comers”. Perhaps the most pertinent data for early lesions derive from screening populations, since asymptomatic individuals have earlier stage tumours.²⁷ Both UK²⁸ and US²⁹ data show that screen-detected cancers are smaller, less bulky, and subjectively less conspicuous at CTC than those presenting with colorectal symptoms. Does this mean they are more likely to be missed at CTC? Most studies would suggest not. The largest cohort series from asymptomatic screenees found that CTC was again over 90% sensitive for 1cm+ polyps.^{30,31} Furthermore, in a Dutch randomised screening trial of CTC vs. colonoscopy³², initial screening colonoscopy detected more advanced neoplasia on a per-attendee basis (although the two were equal on a per-invitee basis, due to superior uptake of CTC), which was largely because small (6-9mm) polyps found at index CTC were not resected immediately, but instead kept under follow-up. Once these were included, CTC outperformed colonoscopy on a per-invitee basis and was its equal on a per-attendee basis.³³ Therefore, it is unlikely that SPECC lesions harbour a particular problem for detection by CTC.

DETECTION OF SERRATED NEOPLASIA

The serrated pathway is increasingly recognised as an important route to colorectal carcinogenesis, estimated to account for 20-30% of colorectal cancer.³⁴ Historically, flat or non-polypoid lesions have been regarded as an Achilles heel for CTC, which found fewer than half of them in some early studies.^{35,36} This is, at least partly, because of under-recognition of their existence and clinical importance during the early years of CTC development. Just as Western endoscopists had to adapt and improve detection of serrated neoplasia in response to the experience of Japanese endoscopists,³⁷ so must CTC radiologists. The issue is not purely due to obsolete technology – even with modern equipment, the recent Japanese National CTC trial reported only a 65% sensitivity for

1cm+ non-polypoid neoplasms³⁸ (versus 90% for 1cm+ neoplasia overall). Furthermore, there was a significantly lower detection rate of high-risk (large or histologically-advanced) serrated polyps in the Dutch randomised screening trial.³⁹ However, with optimised technique and image scrutiny, flat polyps can be depicted by CTC. For example, re-analysis of the images from the US multicentre ACRIN 6664 screening trial showed that most flat polyps were reliably visible in retrospect, with the same sensitivity as polypoid lesions.⁴⁰ There are clear cues to help detection of serrated neoplasms at CTC – in particular, surface coating by oral contrast tagging material.^{41,42} There is no doubt that serrated neoplasms can be extremely challenging for CTC, but with meticulous attention to patient preparation, colon distension and image scrutiny, they can be found (Figure 2).⁴³

HANDLING DIMINUTIVE POLYPS

Although rarely confused with a SPECC lesion, diminutive polyps (i.e. 5mm or less) nonetheless present a dilemma to both radiologists and referring clinicians. This is not usually problematic, as CTC has <50% sensitivity for these polyps. However, there is conflicting guidance regarding what to do when a diminutive polyp candidate has been identified by a meticulous radiologist. Some authorities recommend that radiologists should report diminutive lesions if they are seen with confidence (and particularly if multiple),¹² whereas others argue that they should be ignored.⁴⁴ One major difficulty with referring all patients with diminutive polyps for colonoscopy is that CTC has very poor specificity for neoplasia at this size – most such “polyps” will either be hyperplastic (and therefore clinically irrelevant) or complete false-positives,⁴⁵ meaning the patient is subjected to endoscopy for no ultimate benefit. For example, in one series the false-positive rate fell from 12% to only 4.2% when a 5mm+ reporting threshold was adopted.⁴⁶ It is important to recall that the clinical risk of diminutive polyps is small – indeed, the risk of advanced neoplasia in patients in whom their largest polyp is <5mm is below 4%,⁴⁷ little over half that of an average-risk screenee.⁴⁸ The risk of high-grade dysplasia or carcinoma, arguably the most important aspects of advanced neoplasia, is even smaller, at 0.7%.⁴⁷ Therefore, even if diminutive polyps are not reported, a normal CTC means that the patient has been successfully stratified as lower risk than a randomly selected member of the screening-age population. In our opinion, it makes no logical sense to refer these individuals for endoscopy – colonoscopic capacity is finite, and would be better used to improve its provision for higher risk

individuals (for example, those testing positive in the Bowel Cancer Screening Programme). We must avoid the perverse situation in which an endoscopist would have a greater chance of detecting advanced neoplasia in the person accompanying the patient to the hospital than in the patient themselves. Furthermore, such an over-conservative referral threshold hugely increases healthcare costs and has extremely poor cost-effectiveness, estimated at over \$460,000 per life-year gained in one US analysis⁴⁹ – well over commonly applied thresholds in the UK.⁵⁰

LESION CHARACTERISATION AND THERAPEUTIC STRATEGY

As the preceding paragraphs emphasise, CTC is primarily regarded as a tool for detection of colorectal neoplasia, rather than their characterisation. However, there are important morphological clues that may aid in therapeutic decision-making, beyond the obvious ability of CTC to depict remote metastases. For example, CTC can reliably determine when a carcinoma is *not* an early lesion – for example, transgressing the muscularis propria (denoting a T3 stage) and therefore unequivocally requiring full oncological resection (or palliation). Indeed, systematic review shows that studies in which the colon was distended with rectal contrast (whether using gas or positive iodinated contrast medium) reported more accurate T staging than those in which conventional, unprepared CT was performed.⁵¹ More subtly, the shape of a CTC-detected mass can help distinguish between T1 and T2 CRCs; the former being arc-shaped and the latter square or trapezoidal,⁵² although the reliability of this distinction is imperfect. Just as endoscopists recognise the importance of the Paris classification in their overall assessment of the risk of high-grade dysplasia or submucosal invasion (i.e. carcinoma) in any given lesion, CTC permits radiologists to provide useful morphological characterisation using the same descriptors. For example, a large Australian study identified polyp morphology (Paris Classification 0-IIa+IIc), non-granular surface and Kudo pit pattern type V as being risk factors for invasive cancer⁵³; of these three parameters, CTC can provide two (clearly being unable to resolve the pit pattern!), and radiologists should be encouraged to do so in their clinical reports (Figure 3).⁵⁴ Although management will ultimately be determined by the colonoscopic assessment, a detailed description at CTC permits the endoscopist to be forewarned of what they are likely to find, and so tailor their approach (for example, ensuring availability of an experienced interventional endoscopist

with access to sufficient time in the endoscopy room, their favoured equipment, and optimised patient preparation).

SUMMARY

CT colonography is widely-used, with excellent diagnostic accuracy for clinically-relevant polyps, and provides an alternative means of whole-colon investigation for many patients, particularly those less able to tolerate optical colonoscopy. Serrated polyps and diminutive lesions need careful handling, but with close dialogue between colonoscopists and radiologists, the two tests can be employed in complementary fashion. Radiologists should be encouraged to provide as much morphological information as possible, particularly for larger SPECC lesions, thereby helping assist pre-colonoscopy risk stratification and procedural planning.

FIGURE LEGENDS

Figure 1 – The importance of faecal tagging. Endoluminal three-dimensional image (A) shows only a pool of fluid and no polyp (arrow). The corresponding two-dimensional image (B) shows a 12mm pedunculated polyp (arrow) bathed in tagged (hyperdense) fluid (asterisks).

Figure 2 – Caecal sessile serrated lesion (SSL) with conventional type dysplasia depicted on supine (A) and prone (A) CTC, showing the characteristic coating with dense oral contrast medium. Corresponding endoluminal (C) and narrow-band imaging (NBI) colonoscopy (D) images.

Figure 3 – A proximal sigmoid 22mm granular type laterally-spreading tumour (LST-G) of the nodular mixed subtype with a dominant nodule shown by CTC (A) with colonoscopic correlation (B). Appropriate description of the lesion permitted this patient to be identified as having a complex lesion requiring careful scheduling for a specialist interventional endoscopist given its size and subtype.

REFERENCES

1. Haenisch GF. The value of the roentgen ray in the early diagnosis of carcinoma of the bowel. *Am Q Roentgenol* 1911; **3**: 175-81.
2. Haenisch GF. Die Röntgenuntersuchung bei Verengungen des Dickdarms. Röntgenologische Frühdiagnose des Dickdarmkarzinoms. *Munch Med Wochenschr* 1911; **45**: 2375-81.
3. Hounsfield GN. Computerized transverse axial scanning (tomography). 1. Description of system. *Br J Radiol* 1973; **46**(552): 1016-22.
4. Hamlin DJ, Burgener FA, Sischy B. New technique to stage early rectal carcinoma by computed tomography. *Radiology* 1981; **141**(2): 539-40.
5. Balthazar EJ, Megibow AJ, Hulnick D, Naidich DP. Carcinoma of the colon: detection and preoperative staging by CT. *AJR Am J Roentgenol* 1988; **150**(2): 301-6.
6. Vining DJ. Virtual Colonoscopy: The Inside Story. In: Dachman A, ed. *Fundamentals of Virtual Colonoscopy*. New York: Springer; 2005: xii, 112 p.
7. Kalender WA, Seissler W, Klotz E, Vock P. Spiral volumetric CT with single-breath-hold technique, continuous transport, and continuous scanner rotation. *Radiology* 1990; **176**(1): 181-3.
8. Vining DJ, Gelfand DW, Bechtold RE, Scharling ES, Grishaw EK, Shifrin R. Technical feasibility of colon imaging with helical CT and virtual reality (abstr). *American Journal of Roentgenology* 1994; **162**: 104.
9. Fenlon HM, Nunes DP, Schroy PC, 3rd, Barish MA, Clarke PD, Ferrucci JT. A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps. *N Engl J Med* 1999; **341**(20): 1496-503.
10. Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR. Colorectal neoplasia: Performance characteristics of CT colonography for detection in 300 patients. *Radiology* 2001; **219**(3): 685-92.
11. Diagnostic Imaging Dataset. *Health and Social Care Information Centre*; <https://did.hscic.gov.uk/>.
12. Neri E, Halligan S, Hellstrom M, et al. The second ESGAR consensus statement on CT colonography. *Eur Radiol* 2013; **23**(3): 720-9.
13. Iannaccone R, Laghi A, Catalano C, et al. Computed tomographic colonography without cathartic preparation for the detection of colorectal polyps. *Gastroenterology* 2004; **127**(5): 1300-11.
14. Slater A, Betts M, D'Costa H. Laxative-free CT colonography. *Br J Radiol* 2012; **85**(1016): e410-5.
15. Campanella D, Morra L, Delsanto S, et al. Comparison of three different iodine-based bowel regimens for CT colonography. *Eur Radiol* 2010; **20**(2): 348-58.
16. Plumb AA, Halligan S, Taylor SA, Burling D, Nickerson C, Patnick J. CT colonography in the English Bowel Cancer Screening Programme: national survey of current practice. *Clin Radiol* 2013; **68**(5): 479-87.
17. Bellini D, Rengo M, De Cecco CN, Iafrate F, Hassan C, Laghi A. Perforation rate in CT colonography: a systematic review of the literature and meta-analysis. *Eur Radiol* 2014; **24**(7): 1487-96.
18. Pendse DA, Taylor SA. Complications of CT colonography: A Review. *European Journal of Radiology* 2013; **82**(8): 1159-65.
19. Von Wagner C, Ghanouni A, Halligan S, et al. Patient acceptability and psychologic consequences of CT colonography compared with those of colonoscopy: Results from a multicenter randomized controlled trial of symptomatic patients. *Radiology* 2012; **263**(3): 723-31.
20. von Wagner C, Smith S, Halligan S, et al. Patient acceptability of CT colonography compared with double contrast barium enema: results from a multicentre randomised controlled trial of symptomatic patients. *European radiology* 2011; **21**(10): 2046-55.
21. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. *Radiology* 2005; **237**(3): 893-904.
22. Pickhardt PJ, Hassan C, Halligan S, Marmo R. Colorectal cancer: CT colonography and colonoscopy for detection--systematic review and meta-analysis. *Radiology* 2011; **259**(2): 393-405.
23. Obaro A, Plumb AA, Fanshawe TR, et al. Post-imaging colorectal cancer or interval cancer rates after computed tomographic colonography: A systematic review and meta-analysis. *The Lancet Gastroenterology and Hepatology* 2018.
24. Rutter CM, Knudsen AB, Marsh TL, et al. Validation of Models Used to Inform Colorectal Cancer Screening Guidelines: Accuracy and Implications. *Med Decis Making* 2016; **36**(5): 604-14.
25. Chaparro M, Gisbert JP, Del Campo L, Cantero J, Maté J. Accuracy of computed tomographic colonography for the detection of polyps and colorectal tumors: a systematic review and meta-analysis. *Digestion* 2009; **80**(1): 1-17.

26. Atkin W, Dadswell E, Wooldrage K, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013; **381**(9873): 1194-202.
27. Morris EJA, Whitehouse LE, Farrell T, et al. A retrospective observational study examining the characteristics and outcomes of tumours diagnosed within and without of the English NHS Bowel Cancer Screening Programme. *Br J Cancer* 2012; **107**(5): 757-64.
28. Plumb AA, Pathiraja F, Nickerson C, et al. Appearances of screen-detected versus symptomatic colorectal cancers at CT colonography. *Eur Radiol* 2016; **26**(12): 4313-22.
29. Lee MH, Hinshaw JL, Kim DH, Pickhardt PJ. Symptomatic Versus Asymptomatic Colorectal Cancer: Predictive Features at CT Colonography. *Acad Radiol* 2016; **23**(6): 712-7.
30. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003; **349**(23): 2191-200.
31. Johnson CD, Chen M-H, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008; **359**(12): 1207-17.
32. Stoop EM, de Haan MC, de Wijkerslooth TR, et al. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: A randomised controlled trial. *Lancet Oncol* 2012; **13**(1): 55-64.
33. Tutein Nolthenius CJ, Boellaard TN, de Haan MC, et al. Computer tomography colonography participation and yield in patients under surveillance for 6-9 mm polyps in a population-based screening trial. *European Radiology* 2016; **26**(8): 2762-70.
34. East JE, Vieth M, Rex DK. Serrated lesions in colorectal cancer screening: Detection, resection, pathology and surveillance. *Gut* 2015; **64**(6): 991-1000.
35. Fidler JL, Johnson CD, MacCarty RL, Welch TJ, Hara AK, Harmsen WS. Detection of flat lesions in the colon with CT colonography. *Abdom Imaging* 2002; **27**(3): 292-300.
36. Gluecker TM, Fletcher JG, Welch TJ, et al. Characterization of lesions missed on interpretation of CT colonography using a 2D search method. *AJR American Journal of Roentgenology* 2004; **182**(4): 881-9.
37. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology* 2001; **120**(7): 1657-65.
38. Nagata K, Endo S, Honda T, et al. Accuracy of CT Colonography for Detection of Polypoid and Nonpolypoid Neoplasia by Gastroenterologists and Radiologists: A Nationwide Multicenter Study in Japan. *Am J Gastroenterol* 2017; **112**(1): 163-71.
39. Ijspeert JEG, Tutein Nolthenius CJ, Kuipers EJ, et al. CT-Colonography vs. Colonoscopy for Detection of High-Risk Sessile Serrated Polyps. *American Journal of Gastroenterology* 2016; **111**(4): 516-22.
40. Fidler JL, Zhang Z, Herman BA, et al. CT colonography for the detection of nonpolypoid adenomas: sensitivity assessed with restricted national CT colonography trial criteria. *AJR Am J Roentgenol* 2014; **203**(6): W614-22.
41. Kim DH, Hinshaw JL, Lubner MG, Munoz del Rio A, Pooler BD, Pickhardt PJ. Contrast coating for the surface of flat polyps at CT colonography: a marker for detection. *Eur Radiol* 2014; **24**(4): 940-6.
42. Kim DH, Matkowskyj KA, Lubner MG, et al. Serrated Polyps at CT Colonography: Prevalence and Characteristics of the Serrated Polyp Spectrum. *Radiology* 2016; **280**(2): 455-63.
43. Kim DH, Lubner MG, Cahoon AR, Pooler BD, Pickhardt PJ. Flat Serrated Polyps at CT Colonography: Relevance, Appearance, and Optimizing Interpretation. *Radiographics* 2018; **38**(1): 60-74.
44. Zalis ME, Barish MA, Choi JR, et al. CT colonography reporting and data system: a consensus proposal. *Radiology* 2005; **236**(1): 3-9.
45. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. *Gut* 2009; **58**(2): 241-8.
46. Edwards JT, Mendelson RM, Fritschi L, et al. Colorectal neoplasia screening with CT colonography in average-risk asymptomatic subjects: community-based study. *Radiology* 2004; **230**(2): 459-64.
47. Kolligs FT, Crispin A, Graser A, Munte A, Mansmann U, Goke B. Risk factors for advanced neoplasia within subcentimetric polyps: Implications for diagnostic imaging. *Gut* 2013; **62**(6): 863-70.
48. Kolligs FT, Crispin A, Munte A, Wagner A, Mansmann U, Goke B. Risk of advanced colorectal neoplasia according to age and gender. *PLoS One* 2011; **6**(5): e20076.
49. Pickhardt PJ, Hassan C, Laghi A, et al. Small and diminutive polyps detected at screening CT colonography: a decision analysis for referral to colonoscopy. *AJR Am J Roentgenol* 2008; **190**(1): 136-44.
50. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013.

51. Dighe S, Purkayastha S, Swift I, et al. Diagnostic precision of CT in local staging of colon cancers: a meta-analysis. *Clin Radiol* 2010; **65**(9): 708-19.
52. Utano K, Endo K, Togashi K, et al. Preoperative T staging of colorectal cancer by CT colonography. *Dis Colon Rectum* 2008; **51**(6): 875-81.
53. Moss A, Bourke MJ, Williams SJ, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011; **140**(7): 1909-18.
54. Ignjatovic A, Burling D, Ilangovan R, et al. Flat colon polyps: what should radiologists know? *Clin Radiol* 2010; **65**(12): 958-66.