Optical diagnosis of malignant colorectal polyps: is it feasible?

Authors Manon van der Vlugt[1], Sascha Corrie van Doorn[1], Junfeng Wang[2], Barbara AJ Bastiaansen[1], Lowewijk AA Brosens[3], Paul Fockens[1], Evelien Dekker[1]

Institutions
[1] Academic Medical Center, Department of Gastroenterology and Hepatology Amsterdam, Netherlands
[2] Academic Medical Center, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam, Netherlands
[3] University Medical Centre of Utrecht, Department of Pathology, Utrecht, Netherlands

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Corresponding author
Evelien Dekker
Academic Medical Center
Department of Gastroenterology and Hepatology
Meibergdreef 9
Amsterdam 1105
Netherlands
e.dekker@amc.uva.nl

Background and study aims: As colorectal cancer screening programs are being implemented worldwide, an increasing number of early (T1) cancers are being diagnosed. These cancers should be recognized during colonoscopy because they require a specific therapeutic approach. Several studies have shown that Asian experts can reliably recognize T1 cancers during colonoscopy. In daily practice, however, accurate endoscopic diagnosis of T1 cancers still seems challenging. We evaluated the performance of optical diagnosis of T1 cancers by European colonoscopy experts, general gastroenterologists and gastrointestinal fellows.

Patients and methods: We collected endoscopic images of 43 colonic lesions: 19 T1 cancers (excluding intramucosal carcinoma) and 24 benign polyps ranging from 7 mm to 30 mm in size. Seven colonoscopy experts, 7 general gastroenterologists, and 14 gastrointestinal fellows assessed these images. We calculated sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) and their 95% confidence intervals for optical diagnosis of T1 cancers.

Results: Overall sensitivity for correct diagnosis of T1 cancers was 60% (95% CI;45–72). Sensitivity was highest for experts (67%: 95%CI; 48–81), when compared to general gastroenterologists (53%: 95%CI; 37–69) and gastrointestinal fellows (59%: 95%CI;45–72). The overall NPV was 75% (95%CI;60–86); NPV was lowest for general gastroenterologists 72% (95%CI;57–83) vs 78% (95%CI;63–89) for experts and 75% (95%CI;60–85) for gastrointestinal fellows.

Conclusions: In this image-based study, both sensitivity for the optical diagnosis of a T1 cancer and NPV for excluding a T1 cancer were insufficient. Experts performed best with a sensitivity of 67% and a NPV of 78%, while the performance of fellows in the last year of training was comparable to that of experts. Our study indicates that training for endoscopic diagnosis for T1 cancers is urgently needed to ensure optimal clinical practice for treatment of these lesions.

Introduction

Nearly 10% of all patients with colorectal cancer (CRC) are diagnosed in a polyp with early invasive growth: a T1 cancer (maximum depth of invasion into the submucosa). Due to the worldwide spread of CRC screening programs, the incidence of T1 cancers is gradually increasing [1,2]. These cancers can be cured by appropriately performed endoscopic treatment alone, if they are confined to the upper layer of the submucosa [3,4]. However, to select the optimal treatment strategy for T1 cancers, it is important that these lesions are recognized during endoscopy and not diagnosed as benign.

Adequate recognition of T1 cancers enables weighing the benefits and risks of endoscopic resection against the benefits and risks of surgical resection. Whereas endoscopic resection is less invasive, the risks include direct procedural risks (bleeding, perforation with the potential of seeding of malignant cells in the peritoneum) and the late risk of leaving residual malignant cells or positive lymph nodes in situ. For certain malignant lesions, however, endoscopic resection appears to be safe regarding both direct and late risks. This group includes T1 cancers that are resected en-bloc with clean resection margins, are well-differentiated, have a submucosal invasion depth less than 1000 µm, and do not show presence of tumor budding or lymphatic/vascular invasion [5,6]. When T1 carcinoma is suspected, piecemeal endoscopic mucosal resection (EMR) is not an appropriate treatment option as assessing completeness of the resection is difficult for both the pathologist and the endoscopist [10]. In those cases, endoscopic submucosal dissection (ESD) or other treatment options should be considered.

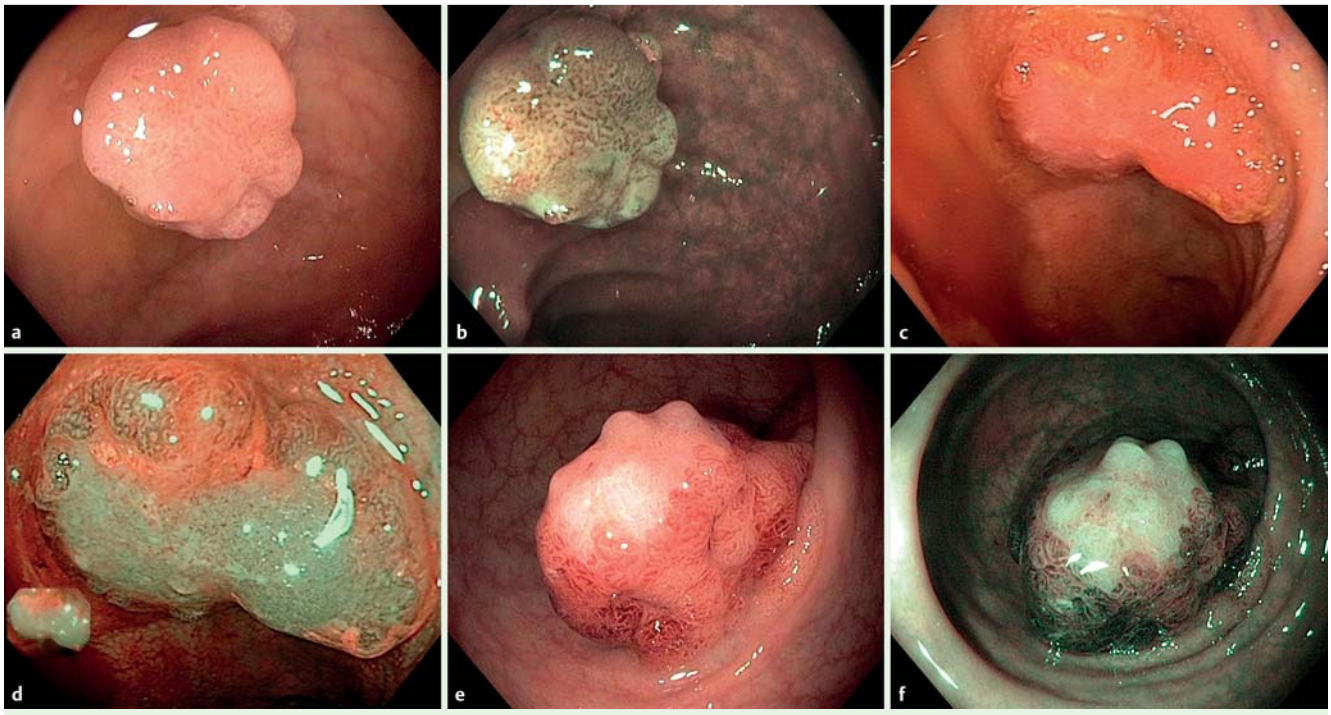

Fig. 1 Endoscopic images of T1 cancers selected for assessment. **a** White light and **b** NBI images of a 15-mm stage Is lesion. On the right edge the lesion has a small area of amorphous surface and an irregular contour. The lesion was radically resected en-bloc and marked by a tattoo. Histopathology showed a well-differentiated T1sm1 carcinoma without tumor budding or lymphatic/vascular invasion. **c** White light and **d** NBI images of a 20-mm stage Is lesion with retraction. The center is lacking a surface and vessel pattern. Surgical resection specimen showed a T1N0M0 carcinoma. **e** White light and **f** NBI images of a 30-mm stage Is lesion. At the top of the lesion the surface is patchy white/gray. The contour is atypical with small irregular protrusions on the top. Endoscopic piecemeal resection was performed. Histopathology showed a tubulovillous adenoma and focally a moderately differentiated adenocarcinoma with unclear margins. Additional surgical resection showed no residual tumor or positive lymph nodes.

In literature, several endoscopic features suggestive of the presence of invasive growth (i.e., cancer) within a colonic lesion have been described. Among others, these features include presence of a depression or ulceration, irregular contour of a lesion, amorphous surface pattern of the epithelium, disrupted or missing vessels on the lesion's surface, and, in case of a stalked lesion, a short and immobile stalk [2,7]. An additional feature is the inability to elevate a sessile or flat lesion upon submucosal saline injection ("non-lifting sign"), although sensitivity of this feature is low [8].

Several Asian studies have demonstrated that experts in academic hospitals have a high degree of accuracy in diagnosing T1 cancers, including predicting depth of invasion, when using chromoendoscopy, high definition white light, non-magnified narrow band imaging or magnified NBI [7,9–13]. However, in the Western world, an accurate optical diagnosis of T1 cancers still seems challenging [14,15]. The aim of this study was to assess the accuracy of image-based optical diagnosis of T1 cancers by colonoscopy experts, general gastroenterologists, and gastrointestinal fellows in daily practice in the Western world.

Patients and methods

This study was retrospective and was performed at the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands. Review by the institutional review board was not required, as it conformed with the Medical Research Involving Human Subjects Act (WMO).

Collection of images

Endoscopic images of T1 cancers were collected from existing databases at Bergman clinics IZA and the endoscopy department at the Academic Medical Center in Amsterdam and were matched with endoscopic images of polyps, based on polyp size and morphology. We selected colorectal lesions ranging from 7 mm to 30 mm in size. Larger lesions were excluded because they are not routinely removed by general gastroenterologists. Polyps and T1 cancers detected between 2009 and 2014 were eligible to be included in this study. All colonoscopies were performed with endoscopes from Olympus: CF-H180DL, PCF-H180AL or CF-HQ190 L series variable-stiffness instruments (Olympus Medical Systems, Tokyo, Japan). Cases were selected if definitive histopathology was available. Images were selected if they were good quality (sharp and well-focused) white light and had Narrow Band Imaging (NBI); at least 1 white light and 1 NBI image per lesion, with a maximum of 3, were chosen when available. A second gastroenterologist expert, who specialized in colonoscopy and advanced polypectomy, verified that all images were of appropriate quality.

For all selected lesions, size, location, morphology and type of treatment were recorded. Location was considered proximal if proximal to the splenic flexure. Morphology was assessed according to the Paris classification: pedunculated, sessile, slightly elevated, flat, slightly depressed or excavated [16]. Adenomas with high-grade dysplasia (HGD) and intramucosal carcinomas were not included in this study, as they may both have a Kudo pit pattern type V, just as in an adenoma with superficial submucosal invasion (T1 cancer) and therefore, difficulty in endoscopic differentiation was expected [7].

Table 1 Endoscopic and histopathologic characteristics of the colorectal lesions

	Sessile serrated adenoma/ polyp	Tubular adenoma with low-grade dysplasia	Tubulovillous adenoma with low-grade dysplasia	T1 adenocarcinoma
Number	7	5	12	19
Mean size (± SD), mm	10.6 (± 4.3)	12.2 (± 5.2)	16.3 (± 7.6)	18.2 (± 6.6)
Location				
– proximal*	6	4	3	5
– distal colon	1	1	9	14
Morphology				
– pedunculated	0	0	7	4
– sessile	2	1	2	10
– slightly elevated	5	3	2	4
– flat	0	1	1	1

* colon proximal to the splenic flexure

The images were incorporated into a PowerPoint slideshow (Microsoft PowerPoint 2010: Microsoft, Redmond, WA, USA), with consecutive images of each lesion. In **Fig. 1** representative images are shown. A short training module was incorporated into the slideshow with detailed description of the Paris classification, Kudo classification, and the NBI international colorectal endoscopic classification (NICE-classification) [7,12,16].

Reference standard

Histopathology was used as reference standard. Histopathology of all colorectal lesions was revised by 2 dedicated gastrointestinal pathologists, according to the Vienna criteria [17].

Observers

International colonoscopy experts, general gastroenterologists, and gastrointestinal fellows were invited to participate in this study. Experts were defined as NBI-experienced colorectal endoscopists who regularly resect large colonic polyps (>20 mm) and have published on colorectal polyps, colonoscopy techniques and/or imaging. General gastroenterologists were defined as endoscopists working in our academic center who do not specialize in optical imaging of colorectal polyps and who do not routinely perform large polypectomies. Gastrointestinal fellows with varying levels of experience were asked to participate. In our country, a gastrointestinal fellowship is a program of 4 years at the Department of Gastroenterology and Hepatology, preceded by 2 years of general Internal Medicine. Fellows in their first year of training do not perform endoscopies. Second- and third-year fellows perform supervised endoscopies, and fourth-year fellows perform unsupervised polypectomies for polyps up to 10 mm and perform supervised advanced endoscopies including the removal of large polyps.

Assessment of images

The slideshow was presented in a meeting at the Department of Gastroenterology and Hepatology at the Academic Medical Center in Amsterdam. Five international experts received the slideshow via email transfer. All observers were requested to provide their optical diagnosis per lesion. Options were: hyperplastic polyp, sessile serrated adenoma/polyp, adenoma or adenocarcinoma.

Statistical analysis

The primary endpoint was assessment of accuracy of optical diagnosis of T1 cancers by colonoscopy experts, general gastroenterologists, and gastrointestinal fellows.

Normally distributed data were described with the mean and standard deviation. Sensitivity and specificity and their 95 % confidence intervals (CI) were calculated from the cases with benign/malignant histopathology results separately. Test results for optical diagnosis were used as a dependent variable and level of experience (experts, generals gastroenterologists and GI fellows) was used as a covariate as dummy variables. The positive predictive value (PPV) and negative predictive value (NPV) and their CI were calculated for cases with benign/malignant optical diagnosis separately. Results of histopathology were used as a dependent variable and level of experience was used as a covariate as dummy variables. For fellows, this was also described according to their level of experience (in years of training). The calculation was done by using logistic regression parameter estimates from generalized estimating equation (GEE) with exchangeable correlation structure [18]. SPSS for Windows software version 22 (SPSS Inc, Chicago, Ill) and STATA/IC V12 (Statacorp: College Station, Texas, USA) were used for analysis.

Results

Characteristics of colorectal lesions

In total 43 colorectal lesions were selected and included in a slideshow consisting of 126 images. Nineteen T1 cancers and 24 benign polyps (7 sessile serrated adenomas and 17 adenomas with low-grade dysplasia) were selected. Mean size of T1 cancers was 18.2 mm (SD ±6.6 mm) and 13.8 mm (SD ±6.6 mm) for benign polyps (**Table 1**). Most T1 cancers were located in the distal colon (74 %); the benign lesions were distributed evenly across the colon. Most included lesions were sessile or slightly elevated according to the Paris classification [16].

Observers

A total of 28 observers (7 international colonoscopy experts, 7 general gastroenterologists, and 14 fellows) participated in the study and assessed the slideshow. Two of the fellows were in the first year of their fellowship (and had not performed any colonoscopies yet), 3 in the second, 3 in the third and 6 in the fourth year.

Performance of optical diagnosis

Overall sensitivity for an accurate diagnosis of T1 cancer was 60 % (95 %CI;45 – 72) (**Table 2**). **Fig. 1** and **Fig. 2** show some representative examples assessed of which **Fig. 1a** and **Fig. 1b** were correctly recognized as a T1 cancer by 6 of 28 observers (21 %). **Fig. 1c**, **Fig. 1d**, **Fig. 1e** and Fig. **1f** were correctly

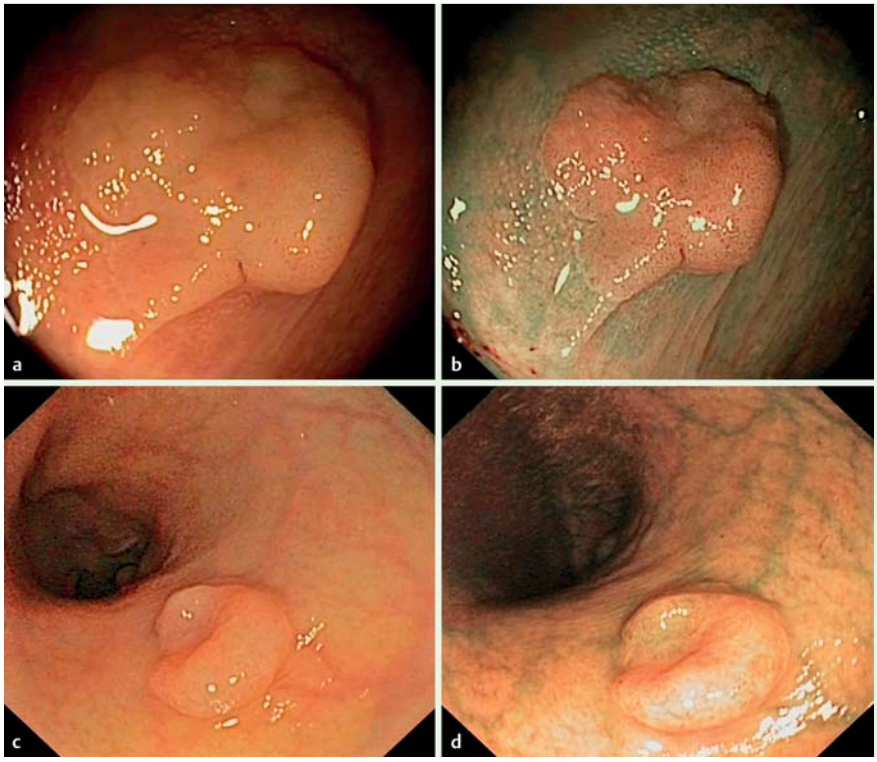

Fig. 2 Endoscopic images of benign colorectal lesions selected for assessment. **a** White light and **b** NBI images of a 12-mm stage IIa + Is lesion with a regular contour and regular surface and vascular pattern. Histopathology showed a tubulovillous adenoma with low-grade dysplasia. **c** White light and **d** NBI images of an 8-mm stage IIa + IIc lesion with a regular contour and surface with a NICE I aspect with dark spots inside the crypts. Histopathology showed a sessile serrated adenoma/polyp without dysplasia.

Table 2 Endoscopic diagnosis according to level of experience

	Sensitivity %, (95 %CI)	Range	Specificity %, (95 %CI)	Range	Positive predictive value %, (95 %CI)	Range	Negative predictive value %, (95 %CI)	Range
All observers (n = 28)	60 (45 – 72)	26 – 90	95 (89 – 98)	79 – 100	91 (77 – 97)	72 – 100	75 (60 – 86)	62 – 92
Experts (n = 7)	67 (48 – 81)	42 – 90	95 (84 – 99)	79 – 100	92 (74 – 98)	72 – 100	78 (63 – 89)	67 – 92
General endoscopist (n = 7)	53 (37 – 69)	32 – 74	96 (84 – 99)	83 – 100	91 (71 – 98)	78 – 100	72 (57 – 83)	64 – 80
Gastrointestinal fellow (n = 14)	59 (45 – 72)	26 – 90	95 (88 – 98)	88 – 100	90 (76 – 96)	73 – 100	75 (60 – 85)	62 – 92
1st year training (n = 2)	37 (21 – 56)	26 – 47	94 (90 – 96)	92 – 96	82 (74 – 88)	82 – 83	65 (53 – 76)	62 – 69
2nd year training (n = 3)	58 (44 – 70)	42 – 68	93 (82 – 97)	88 – 100	87 (66 – 96)	73 – 100	74 (60 – 84)	66 – 79
3rd year training (n = 3)	60 (43 – 74)	47 – 74	93 (82 – 97)	88 – 100	87 (68 – 96)	75 – 100	74 (60 – 85)	68 – 81
4th year training (n = 6)	67 (48 – 81)	42 – 90	97 (89 – 99)	92 – 100	94 (80 – 98)	82 – 100	79 (63 – 89)	69 – 92

Range = minimum and maximum score among observers; CI, confidence interval

assessed as T1 cancers by 89 % and 39 % of the observers, respectively. **Fig. 2a**, **Fig. 2b**, **Fig. 2c** and **Fig. 2d** were correctly recognized as benign lesions by 89 % and 61 % of the observers, respectively. Experts recognized T1 cancers most often correctly when compared to general gastroenterologists and fellows: sensitivity was 67 % (95 %CI;48 – 81), 53 % (95 %CI;37 – 69) and 59 % (95 %CI;45 – 72), respectively. Compared to first-year fellows, sensitivity increased from 37 % to 67 % for fellows in their fourth year of training. The ability to correctly exclude presence of an invasive cancer (T1 cancers) was comparable among the different endoscopist groups, but was highest for fellows in their fourth year of training, with a specificity of 97 %.

NPV for optical diagnosis of T1 cancers was lowest for general gastroenterologists. Of all endoscopists, 2 of 28 (1 expert and 1 fellow) reached a NPV of ≥ 90 %. For fellows, overall PPV was 90 % (95 %CI;76 – 96) and increased with years of training.

Discussion

To determine the best treatment strategy during colonoscopy, it is of great importance to identify lesions that are suspicious for cancer. Therefore, achieving a high sensitivity in combination with a high NPV for the optical diagnosis of T1 cancers should be prioritized. Our study demonstrated an overall sensitivity for T1 cancers that was disappointingly low at 60 % (95 %CI; 45 – 72) and a NPV of 75 % (95 %CI;60 – 86), which is clearly insufficient for relying on an optical diagnosis for decision-making in therapy. The low performance of general gastroenterologists and experts, in particular, is unsatisfactory because both groups regularly perform colonoscopies with a high incidence of colorectal lesions and both provide supervision to gastrointestinal fellows. Given the widespread implementation of bowel cancer screening programs in the Western world, we expect that the incidence of T1 cancers will gradually increase, hence making this an issue of great importance.

Our study has several strengths. First, we collected a unique set of images of T1 colorectal cancers and benign lesions of appropriate quality. To the best of our knowledge, this is the first study performed in the Western world to assess the performance of optical diagnosis of T1 cancers with the use of the NICE classification among experts and general gastroenterologists [7,19]. Most previous optical diagnosis studies for T1 cancers have been performed in Japan and other Asian countries. We invited various European experts to participate in this study and all were willing to participate.

Our study also has some limitations. First, because T1 cancers are uncommon and we do not routinely make videos during endoscopy, we only were able to retrieve still images from our structured databases, and no high-definition videos. We are aware that the use of still images differs considerably from in vivo endoscopic assessments, excluding the possibility of direct examination (e.g., at close up or from other angles, as long as needed). The images also were selected by a single gastroenterologist and confirmed by a second expert colonoscopist, based on the size of the lesion and the quality of the image. Selection of only good quality images may have led to selection bias. However, an image-based study strategy is often applied for optical diagnosis studies and seems the most feasible method for such rare cases as T1 cancers [7,13,20,21].

Second, we decided to select a series of benign and malignant colorectal lesions that would be feasible to assess within 30 to 45 minutes. Therefore, the ratio of T1 cancers in our image set was over-represented and not comparable according to the prevalence in daily practice. Although the observers were not aware of the aim of the study other than an assessment of accuracy of optical diagnosis, that might have caused bias. All participants assessed the slide show during a meeting at our department in the Academic Medical Center, except for 5 of 7 experts who assessed the slide shows individually. We were not informed about the circumstances under which those 5 assessments were performed and it is not possible to rule out that specific circumstances could have affected the outcomes.

The NICE classification system [19], used in this study, is designed to distinguish between superficial and deep submucosal invasion and is not helpful for diagnosis of early T1 (sm1) cancers. Still, we believe that NICE and Kudo pit-pattern could help the endoscopist to better *recognize* invasive lesions and differentiate them from adenomas with low-grade dysplasia. In addition, for the purpose of this study, we excluded adenomas with high-grade dysplasia and intramucosal carcinoma because we know that differentiating superficial submucosal invasion from intramucosal carcinoma and high-grade dysplasia may be difficult. As a consequence, our dataset does not resemble real life. Finally, in contrast to some studies in benign lesions, we did not include a level of confidence for the endoscopic prediction because our aim was to *recognize* and thus *suspect* a malignancy. We also avoided bias by asking for depth of invasion in case of an optical diagnosis of cancer.

In this study we showed that fellows in their last year of training performed comparable to experts in their assessment of T1 cancers. In recent years there has been more awareness of optical diagnosis of colonic lesions in our gastroenterology and endoscopic society and in gastrointestinal fellowship. During the fourth year of training, fellows in the Academic Medical Center are frequently exposed to optical diagnosis according to the Kudo classification [12] and NICE classification [7,19] and polypectomy techniques. Training tools have been developed and are accessible on the Internet [22] and additional teaching takes place during advanced endoscopies, supervised by colorectal experts. That may explain the relatively high scores of the fourth-year gastrointestinal fellows. That result is encouraging as it suggests that optical diagnosis of T1 cancers can be improved by training, but that topic should be addressed in future studies.

Kudo et al. proposed a classification system for colonic pit patterns to predict histology of colorectal lesions [12]. In that system, lesions with a type I or II pit pattern are nonneoplastic, whereas lesions with types IIIs, IIIL, IV, and/or V pit patterns are neoplastic. Fifty percent of lesions with a type V pit pattern were found to be invasive cancers with involvement of the submucosal layer, thus a T1 cancer [12]. In addition, Hayashi *et al.* developed and validated an endoscopic classification system using high-definition endoscopes with NBI without optical magnification: the NICE classification. They expanded the original NICE classification by adding a category representing deeply invasive submucosal carcinoma ("type 3 lesion"), whereas adenomas, high-grade dysplasia or superficial invasive carcinoma are all classified as type 2 lesions [7]. They reported an overall sensitivity and NPV for deep submucosal invasive carcinoma of 92 % for both for high confidence predictions [7]. However, the NICE classification system makes no distinction between adenomas or superficial invasive carcinoma. We believe that correct recognition of malignant colonic lesions is of utmost importance for decision-making on therapy in daily practice, ideally also enabling correct prediction of the level of depth of invasion (e.g., differentiation between NICE type 2 and type 3 lesions). Piecemeal resection of superficial invasive carcinomas hinders the endoscopist in determining the completeness of resection and the pathologist in making a correct histopathologic diagnosis, which may lead to additional surgery that otherwise could have been prevented [10]. Deeply invasive carcinomas require surgery [5,6] and endoscopic attempts for resection may lead to unnecessary risks of bleeding and perforation [23].

Because we demonstrated that optical diagnosis of T1 cancers was insufficient, we suggest: 1) offering training in optical diagnosis; 2) providing systematic feedback on optical diagnosis of cancers to facilitate a learning curve; and 3) in case of doubt on the invasiveness of a lesion, marking it with a tattoo, making a video and/or several still images, and discussing the case in a multidisciplinary meeting including at least 1 expert colonoscopist.

Competing interests: None

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