Thieme

Implementation of real-time probe-based confocal laser endomicroscopy (pCLE) for differentiation of colorectal polyps during routine colonoscopy

Authors
Tim D. G. Belderbos[1], Martijn G. H. van Oijen[2], Leon M. G. Moons[1], Peter D. Siersema[1,3]

Institutions
1 Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands
2 Department of Medical Oncology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
3 Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands

submitted 31.1.2017
accepted after revision 16.6.2017

Bibliography
DOI https://doi.org/10.1055/s-0043-117948 |
Endoscopy International Open 2017; 05: E1104–E1110

ISSN 2364-3722

Corresponding author
T.D.G. Belderbos, MD, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands
Fax: +31-88-7555533
t.d.g.belderbos@umcutrecht.nl

ABSTRACT

Background and aims Probe-based confocal laser endomicroscopy (pCLE) is used to differentiate between neoplastic and non-neoplastic colorectal polyps during colonoscopy. We aimed to assess the accuracy of two endoscopists starting to use real-time pCLE for differentiation of colorectal polyps and to determine the negative predictive value (NPV) for neoplasia in polyps ≤ 5 mm.

Methods Patients undergoing colonoscopy in a tertiary hospital were included in this prospective trial. After a training session, two colonoscopists assessed 50 polyps between August 2012 and April 2014. They sequentially used narrow-band imaging (NBI) and real-time pCLE to differentiate non-adenomatous, adenomatous, and carcinomatous polyps during colonoscopy. Histologic diagnosis by a gastrointestinal pathologist was the gold standard. Results were compared to post-hoc pCLE by a panel of gastroenterologists and pathologists.

Results The accuracy of real-time pCLE was 76 %, compared to 73 % for NBI, and was not significantly different between the first 50 cases (74 %) and the last 50 cases (78 %, $P = 0.64$). The accuracy in polyps > 5 mm was 87 % versus 59 % in polyps ≤ 5 mm ($P = 0.04$) and increased from 45 % (13/29) in poor quality images to 86 % (44/51) in fair quality images and 95 % (19/20) in good quality images ($P < 0.01$). The post-hoc pCLE accuracy was 62 %. The NPV for polyps ≤ 5 mm was 58 % for real-time pCLE and 54 % for post-hoc pCLE.

Conclusion Although a fair accuracy of real-time pCLE for differentiation of colorectal polyps can be achieved within 50 cases, low NPV and difficulty in obtaining high-quality pCLE images hamper implementation in routine clinical practice.

Introduction

Colonoscopic removal of adenomatous, premalignant polyps is effective in preventing colorectal carcinoma and consequent death [1, 2]. In routine clinical practice, it is not possible to reliably distinguish adenomatous polyps from hyperplastic polyps, without malignant potential, using conventional white light colonoscopy [3 – 6]. The current standard is therefore to remove all colorectal polyps for histological examination [7]. As approximately one-third of all colonic polyps is hyperplastic [8 – 10], a considerable number of polypectomies is performed superfluously, unnecessarily increasing costs and risk of complications [11].

Reliable real-time differentiation of colonic polyps during colonoscopy could guide decisions to apply selective polypectomy or a resect-and-discard approach. These strategies, leaving small polyps in situ or discarding them after removal, require a high negative predictive value (NPV) of 90 % or higher, as misinterpretation might lead to inadequate surveillance recommendations or erroneously leaving adenomatous polyps in situ [12].

Previous studies have shown that probe-based confocal laser endomicroscopy (pCLE) could achieve a high post-hoc (i. e. after the endoscopic procedure) diagnostic accuracy when performed by expert pCLE endoscopists [13 – 16]. In order for pCLE to be broadly implemented, it is important that accurate real-time (i. e. during the endoscopic procedure) differentiation of colorectal polyps can be learned rapidly by endoscopists routinely performing screening and surveillance colonoscopies. A recent learning curve study indicated that a fair accuracy for post-hoc interpretation of pCLE images was achieved after a brief training of pCLE inexperienced endoscopists [17]. However, in that study, images obtained by a pCLE experienced endoscopist were used, thereby surpassing the notoriously difficult acquisition of interpretable images, probably due to difficulty in stabilizing the probe [15, 18].

This study aimed to assess the accuracy of real-time pCLE used by two experienced colonoscopists during their first 50 pCLE evaluations of colorectal polyps, to assess the NPV for detecting neoplasia in small polyps and to compare these results to post-hoc pCLE evaluation.

Methods

Study design, setting, and patients

We performed a single-center, prospective cohort study at the University Medical Center Utrecht, an academic hospital in the Netherlands. Patients aged 45 years or older with a high a priori risk for colorectal polyps undergoing colonoscopy between November 2012 and April 2014 were included. A high a priori risk was based on the indication for colonoscopy, including changed bowel habits, (occult) rectal blood loss, iron deficiency anemia, surveillance after previous colorectal polyps, and suspicion of colorectal polyps raised by PET- or CT-scan. Patients with inflammatory bowel disease, familial polyposis syndromes, fluorescein allergy or non-correctable coagulation disorders (including use of oral anticoagulants that could not be discontinued temporarily) were excluded. In addition, patients were excluded if bowel preparation was insufficient (Boston Bowel Preparation Scale (BBPS) score < 6) or if no colorectal polyps were detected. As characterization of sessile serrated adenomas/polyps (SSA/Ps) with pCLE needs further investigation, we chose to exclude SSA/Ps.

Based on two previous studies which indicated that maximum accuracy was already achieved before the 60th interpretation of pCLE images [15, 19], we decided to include patients until both endoscopists had interpreted self-obtained images of at least 50 polyps.

Outcome measures

Primary outcome measure was the diagnostic accuracy of real-time pCLE for differentiation of colorectal polyps and detection of neoplasia. For differentiation of polyps, a simplified classification was used, categorizing polyps as non-neoplastic, adenomatous or carcinomatous, including high grade dysplasia (HGD). Histopathologic evaluation performed by an expert gastrointestinal pathologist was considered to be the gold standard. Secondary outcome measures were the NPV of real-time pCLE for neoplasia in small colorectal polyps (≤ 5 mm) and the accuracy of post-hoc pCLE evaluation for differentiation of colorectal polyps and detection of neoplasia.

Study procedures and definitions

All patients provided informed consent to participate in the study. Bowel preparation was performed with a split dose polyethylene glycol (PEG) solution. Colonoscopies were performed under conscious sedation. Two staff endoscopists (PS and LM) performed all colonoscopies using a standard colonoscope. During withdrawal, all detected polyps were sequentially assessed with white light, narrow-band imaging (NBI), and pCLE. In the case of multiple rectal polyps with hyperplastic appearance, we included only the largest of these, like we do in routine clinical practice, where we send only one of these polyps for histopathologic evaluation to check whether it is adenomatous or not. Kudo pit pattern [20] and NICE classification [21] were used to classify polyps with NBI. After macroscopic evaluation, fluorescein (5 mL, 10 %) was administered intravenously and the pCLE probe (Cellvizio®, Mauna Kea Technologies) was inserted through the working channel of the colonoscope. Intravenous butyl-scopolamine was used at the discretion of the endoscopist to reduce colonic motility. We decided not to use a cap attached to the end of the colonoscope, as this is not standard practice in our center. Recording of pCLE images was performed by the coordinating investigator (TB) as demanded by the endoscopist. After use of pCLE, all polyps were removed for histopathologic evaluation.

The endoscopists were instructed on the use of the pCLE system and the interpretation of pCLE images in the colon according to the Miami classification system [18]. After obtaining and real-time interpreting pCLE images of 50 polyps per endoscopist, these images were interpreted post-hoc by a panel of gastroenterologists and gastrointestinal pathologists. The post-hoc panel also attended a training session on pCLE image interpretation. Four gastroenterologists and one pathologist interpreted all images of 50 polyps obtained by one endoscopist and an identical panel interpreted all images of 50 polyps obtained by the other endoscopist. Two gastroenterologists were in both panels, meaning they both interpreted pCLE images of 100 polyps in order to establish whether the maximization of accuracy occurred before or after 50 evaluations.

A BBPS of ≥ 6 was considered sufficient; a BBPS ≥ 8 was considered a good bowel preparation. Locations of the polyps were either the right-sided colon (including the transverse colon and splenic flexure) or the left-sided colon. The macroscopic form of the polyps was categorized into (sub)pedunculated, sessile

or flat polyps. Image quality was scored by the endoscopist, based on the estimation whether the pCLE images were of sufficient quality to establish the right diagnosis. Image quality was categorized into 'good' (definite and clear crypt and vessel visualization during pCLE procedure), 'fair' (definite, but unclear, crypt and vessel visualization) and 'poor' (uncertain crypt and vessel visualization), as adapted from Kuiper et al. [22].

Statistical analysis

All statistical analyses were performed using Statistical Packages for Social Sciences version 22 (IBM Corp, Armonk, NY, United States).

Data are presented as mean with standard deviation or median with range and compared with chi-squared test or Student's *t* test, according to the nature of their distribution. Chi-squared test was used for comparison of accuracy between subgroups. To assess interobserver variability, we calculated Fleiss' Kappa for the post-hoc panel [23].

Medical ethics review

The study protocol was reviewed by the Medical Ethics Committee of the UMC Utrecht in accordance with the Medical Research Involving Human Subjects Act and was exempted from monitoring.

Results

After exclusion of 12 patients without polyps, we included 52 patients (▶ **Table 1**). Bowel preparation was good in 71 % of cases and sufficient in 29 % of cases. A mean number of two polyps per patient (range 1 – 8) were assessed with pCLE. A total of 113 polyps were evaluated with pCLE, of which 13 were excluded because of failure to obtain pCLE imaging (n = 2), failure to retrieve polyps for histopathologic evaluation (n = 10), or histologic diagnosis of SSA/P (n = 1). Of the 100 included polyps, 61 were smaller than 6 mm, and 47 polyps were located in the proximal colon. The majority (65 %) were sessile polyps, and 73 % of polyps contained neoplasia.

The accuracy of real-time pCLE for differentiation of polyps was 76 % (▶ **Table 2**) compared to 73 % for NBI. pCLE accuracy was 74 % in the first 50 cases and 78 % in the last 50 cases ($P = 0.64$). The accuracy of NBI was higher for left-sided polyps and for polyps ≥ 10 mm. Accuracy of pCLE increased with size and was 71 % in polyps < 10 mm (55/77) versus 91 % in polyps ≥ 10 mm (21/23, $P = 0.05$). Adenomas were correctly identified with pCLE in 53 of 68 cases (78 %) versus 19 of 27 non-neoplastic polyps (70 %, $P = 0.72$). Only five polyps containing HGD or carcinoma were included, of which four were identified with pCLE (80 %). The percentage correct diagnoses with pCLE was 45 % (13/29) for poor quality images, 86 % (44/51) for fair quality images, and 95 % (19/20) for good quality images ($P < 0.01$). For NBI, the accuracy was 62 % in polyps with poor quality pCLE images, 71 % in the case of fair quality, and 95 % in the case of good quality images ($P = 0.33$).

For the first 25 cases of both endoscopists, the image quality was poor in 32 % (16/50), fair in 48 % (24/50), and good in 20 % (10/50) of cases. During the second 25 cases, the image quality was poor in 26 % (13/50), fair in 54 % (27/50), and good in 20 % (10/50) of cases. This difference was not significant ($P = 0.78$). Image quality was better in 39 polyps > 5 mm (18 % poor, 51 % fair, 31 % good) than in 61 polyps ≤ 5 mm (36 % poor, 51 % fair, 13 % good, $P = 0.04$). For right-sided polyps, image quality was poor in 36 %, fair in 49 % and good in 15 %, whereas the image quality was poor in 23 %, fair in 53 % and good in 24 % of left-sided polyps ($P = 0.25$).

▶ **Table 1** Baseline characteristics.

Total patients, %	**52**
Age, mean ± SD, years	65.8 ± 9.1
Male gender, n (%)	34 (65.4)
Indication for colonoscopy, n (%)	
▪ Bowel symptoms	7 (13.5)
▪ Rectal (occult) blood loss	13 (25.0)
▪ Anemia	3 (5.8)
▪ Surveillance	19 (36.5)
▪ Abnormality found with other imaging	10 (19.2)
Endoscopist, n (%)	
▪ 1	26 (50.0)
▪ 2	26 (50.0)
Bowel preparation, n (%)	
▪ Good/excellent	37 (71.2)
▪ Sufficient	15 (28.8)
Median number of polyps assessed with pCLE (range)	2 (1 – 8)
Total number of polyps assessed with pCLE	113
Total number of polyps	100
Size	
▪ ≤ 5 mm	61
▪ 6 – 9 mm	16
▪ ≥ 10 mm	23
Localization	
▪ Right sided	47
▪ Left sided	53
Form	
▪ (Sub)pedunculated	24
▪ Sessile	65
▪ Flat	11
Histopathology	
▪ Non-neoplastic	27
▪ Adenoma	68
▪ Carcinoma/HGD	5

▶ **Table 2** Accuracy of real-time pCLE.

Accuracy	NBI (%)	*P* value[1]	NBI + pCLE (%)	*P* value[2]
Total	73/100 (73.0)		76/100 (76.0)	
Endoscopist		0.822		1.00
▪ PS	37/50 (74.0)		38/50 (76.0)	
▪ LM	36/50 (72.0)		38/50 (76.0)	
Location		0.0017		0.202
▪ Right sided	29/47 (61.7)		33/47 (70.2)	
▪ Left sided	44/53 (83.0)		43/53 (81.1)	
Size		0.014		0.086
▪ 0 – 5 mm	39/61 (63.9)		42/61 (68.9)	
▪ 6 – 9 mm	12/16 (75.0)		13/16 (81.3)	
▪ ≥ 10 mm	22/23 (95.7)		21/23 (91.3)	
Form		0.036		0.232
▪ (Sub)pedunculated	21/24 (87.5)		21/24 (87.5)	
▪ Sessile	42/65 (64.6)		46/65 (70.8)	
▪ Flat	10/11 (90.9)		9/11 (81.8)	
Pathology		0.918		0.721
▪ Normal/hyperplastic	20/27 (74.1)		19/27 (70.4)	
▪ Adenoma	49/68 (72.1)		53/68 (77.9)	
▪ Carcinoma/HGD	4/5 (80.0)		4/5 (80.0)	
Image quality of pCLE		0.033		< 0.001
▪ Poor	18/29 (62.1)		13/29 (44.8)	
▪ Fair	36/51 (70.6)		44/51 (86.3)	
▪ Good	19/20 (95.0)		19/20 (95.0)	

[1] For NBI.
[2] For NBI + pCLE.

For real-time pCLE, overall accuracy for detecting neoplasia was 77 %, with a sensitivity of 88 %. Sensitivity in polyps < 10 mm was 71 % and sensitivity in polyps ≤ 5 mm was 65 %, meaning pCLE identified 24 of 37 neoplastic polyps ≤ 5 mm. The NPV in polyps ≤ 5 mm was 58 %, as only 18 of 31 polyps considered non-neoplastic with pCLE were actually non-neoplastic.

The mean accuracy amongst the six gastroenterologists and two pathologists in the post-hoc panel, blinded for endoscopic features, was 62 %, ranging from 58 % to 66 % (▶ **Table 3**). The accuracy was not different between pathologists (60 %) and gastroenterologists (62 %, $P = 0.68$). The accuracy for detecting neoplasia was 70 %, ranging from 62 % to 76 %. In polyps < 10 mm, the mean accuracy was 67 %. Two gastroenterologists evaluated pCLE images of all 100 cases. For both, the accuracy was similar during the first and last 50 cases (66 % vs. 66 % for gastroenterologist 1 and 62 % vs. 60 % for gastroenterologist 4, respectively). The accuracy in the post-hoc panel increased according to the quality of the images from 48 % in the case of poor quality to 63 % in the case of fair quality and 78 % in the case of good quality. Fleiss Kappa was 0.315 and 0.317 for images obtained by the first and second endoscopist, respectively, indicating fair interobserver agreement within the post-hoc panels. Mean sensitivity of post-hoc pCLE for detection of neoplasia was 69 % in polyps < 10 mm and 63 % in polyps ≤ 5 mm. The NPV in polyps ≤ 5 mm was 54 %.

Discussion

In their first 50 cases, two experienced colonoscopists using real-time pCLE achieved an accuracy of 76 % for differentiation of colorectal polyps and an accuracy of 77 % for detecting neoplasia. The NPV of real-time pCLE for detecting neoplasia in colorectal polyps ≤ 5 mm was only 58 %. The accuracy of post-hoc pCLE in a blinded panel of gastroenterologists and pathologists was 62 % for differentiation of polyps and 70 % for detec-

▶ **Table 3** Accuracy in the post-hoc panel.

	Accuracy (%)	Accuracy for neoplasia (%)
Images obtained by endoscopist 1		
Gastroenterologist		
▪ 1	66	74
▪ 2	58	72
▪ 3	58	62
Gastroenterologist 4, 2nd round	60	68
Pathologist 1	58	66
Overall panel 1	60	68
Images obtained by endoscopist 2		
Gastroenterologist		
▪ 4	62	70
▪ 5	66	72
▪ 6	60	66
Gastroenterologist 1, 2nd round	66	76
Pathologist 2	62	72
Overall panel 2	63	71
Total	62	70

tion of neoplasia. Both for real-time and post-hoc pCLE, the accuracy depended significantly on the quality of the images.

Only one previous study has described results of real-time pCLE, as performed by an expert user. Shahid et al. [24] found an accuracy of 79 % and a sensitivity of 81 % for detecting neoplasia in 154 polyps, of which 52 % contained neoplasia. We found similar accuracy for two non-expert pCLE users. Factors that might have increased the accuracy of real-time pCLE in our study, were the high rate of neoplasia (73 %) and the use of NBI, possibly facilitating a preliminary diagnosis based on macroscopic polyp appearance. In addition, the endoscopists were allowed to review the pCLE images during colonoscopy, which probably contributed to a more accurate diagnosis.

We found post-hoc pCLE to be less accurate and sensitive than real-time pCLE. Shahid et al. reported the accuracy and sensitivity of blinded, post-hoc pCLE to be comparable to their real-time results. In their study, post-hoc pCLE was more accurate and sensitive than real-time pCLE for polyps < 10 mm [24]. We did not find such an effect, although real-time and post-hoc accuracy and sensitivity were more similar in polyps < 10 mm than in larger polyps. Shahid et al. speculated that the higher accuracy for post-hoc pCLE is explained by the possibility to perform a more detailed review of the images, without having to stabilize the probe, which is especially difficult in small polyps [24]. As a review of the images was possible during colonoscopy in our study, we think that the size-dependent difference in accuracy between real-time and post-hoc pCLE is mainly a consequence of the blinding for endoscopic polyp features. The macroscopic appearance of the polyps undoubtedly contributed to the real-time diagnoses, especially for larger polyps with a higher a priori likelihood of neoplasia.

The quality of the pCLE images in our study was low in 29 % of all polyps and in 36 % of polyps ≤ 5 mm, for which pCLE could be relevant with regard to a resect-and-discard strategy. Although objective definition of image quality is difficult, the quality was probably lower than in the study by Shahid and colleagues and other previous studies, in which experts obtained the images [14 – 16, 24 – 26] (▶ **Table 4**). As a consequence, post-hoc sensitivity and accuracy were higher in previous studies than in our study, apart from the study by Kuiper et al. [22], in which the endoscopists were as inexperienced in obtaining pCLE images as in our study. As expected, the difference in NBI accuracy between polyps with poor and fair pCLE image quality was smaller (62 % and 72 %, respectively) than the difference in accuracy of pCLE in polyps with poor and fair image quality (45 % and 86 %, respectively). However, the accuracy of NBI in polyps with good quality pCLE images was as high as the accuracy of pCLE (95 %). Possibly, these polyps were more easily assessed with NBI as well. Another explanation might be that judgment of the quality of the images by the endoscopist was biased by the certainty of the diagnosis with NBI, which aided a correct pCLE diagnosis.

The accuracy of real-time pCLE in this study was only slightly higher than for NBI, although pCLE was always performed after NBI, both performed by the same operator. This suggests that pCLE has no or only limited benefits to NBI. In addition, both experienced colonoscopists in this study were not able to meet the recommended sensitivity and NPV thresholds for detecting neoplasia in colorectal polyps [12]. This might be due to their ongoing learning curve, but a previous study has shown a short learning curve for pCLE interpretation [17]. In addition, accuracy was not different between the first 50 and the last 50 of 100 cases evaluated by two post-hoc panel members in our study. Therefore, it is unlikely that insufficient pCLE interpretation caused the low sensitivity. As Shahid et al. and Kuiper et al. previously suggested [22, 24], obtaining high-quality images is crucial for the accuracy of pCLE. The association we found between image quality and pCLE accuracy, both real-time and post-hoc, supports this hypothesis.

Our study is the first to investigate the use of real-time pCLE for differentiation of colorectal polyps in non-expert users, closely resembling the way the technique should ideally be implemented in routine clinical practice. We evaluated pCLE as an additional technique to NBI for detection of neoplasia in colorectal polyps, allowing immediate revision of pCLE images. The comparison with results of the post-hoc panel allowed estimation of the contribution of endoscopic features to the accuracy of pCLE.

The small sample size is a limitation of our study and the results should therefore be interpreted with caution. As mentioned above, the learning curve for the interpretation of pCLE images was probably already completed within the sample size of this study, but the learning curve to obtain pCLE images might not. This is however not just a limitation of our study,

▶ **Table 4** Comparison of the current study with previous studies evaluating pCLE.

Study	Year	pCLE-expert	Blinded	Number	Mean/median size (mm)	Neoplastic (%)	Accuracy for neoplasia (%)	Sensitivity for neoplasia (%)	Sensitivity in polyps ≤5 mm (%)
Real-time pCLE									
Current	2016	No	No	100	8	73	77	88	65
Shahid et al. [24]	2012	Yes	No	154	10	52	79	81	Unknown
Post-hoc pCLE									
Current	2016	No	Yes	100	8	73	70	72	63
De Palma et al. [14]	2010	Yes	Unknown	32	13	66	92	100	Unknown
Buchner et al. [15]	2010	Yes	Yes	119	10	68	87	91	Unknown
Gomez et al. [25]	2010	Yes	Yes	75	Unknown	67	75	76	Unknown
André et al. [26]	2012	Yes	Yes	135	8	69	90	91	Unknown
Kuiper et al. [22]	2012	No[1]	Yes	135	5	40	69	58	Unknown
Shahid et al. [16]	2012	Yes	Yes	130	5	45	82	86	84
Shahid et al. [24]	2012	Yes	Yes	154	10	52	88	83	Unknown

[1] Experts for interpretation, not for obtaining images.

but it is also an outcome, reflecting a difficulty of the technique. Of note, the long inclusion period might have prolonged the learning curve and is therefore a limitation of our study. In addition, the brief hands-on training that was provided to both endoscopists might have been insufficient, although it was performed in accordance with the standard Cellvizio® instruction. Based on this, it may well be that the requirement of a longer training period is a potential limitation of pCLE implementation. In this study, we did not use a cap attached to the colonoscope, which may help to stabilize the probe. Another limitation of our study is the relatively large sizes and high rate of neoplasia of the polyps, which probably affected the accuracy of real-time diagnoses. To assess the use of pCLE in a resect-and-discard strategy, investigation of small polyps is necessary. This was not the primary aim of our study, but we included more than 60 % small polyps. Sensitivity and NPV for detecting neoplasia in small polyps were quite low and a larger sample size probably would not have contributed essentially to the outcome.

In conclusion, the accuracy of real-time pCLE was comparable to NBI and not sufficiently high to reliably differentiate colorectal polyps. The NPV was well below the 90 % that is required to use pCLE in a 'resect-and-discard' strategy. In the current era of high definition endoscopes and digital chromoendoscopy, we estimate that the additional value of using pCLE in the colon is likely to be limited. Difficulty in obtaining high-quality pCLE images hampers straightforward implementation in routine clinical practice.

Competing interests

None

References

[1] Muto T, Bussey HJ, Morson BC. The evolution of cancer of the colon and rectum. Cancer 1975; 36: 2251 – 2270

[2] Zauber AG, Winawer SJ, O'Brien MJ et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. NEJM 2012; 366: 687 – 696

[3] Schachschal G, Mayr M, Treszl A et al. Endoscopic versus histological characterisation of polyps during screening colonoscopy. Gut 2014; 63: 458 – 465

[4] Vu HT, Sayuk GS, Hollander TG et al. Resect and discard approach to colon polyps: real-world applicability among academic and community gastroenterologists. Dig Dis Sci 2015; 60: 502 – 508

[5] Ladabaum U, Fioritto A, Mitani A et al. Real-time optical biopsy of colon polyps with narrow band imaging in community practice does not yet meet key thresholds for clinical decisions. Gastroenterology 2013; 144: 81 – 91

[6] Butterly LF, Chase MP, Pohl H et al. Prevalence of clinically important histology in small adenomas. Clin Gastroenterol Hepatol 2006; 4: 343 – 348

[7] Levin B, Lieberman DA, McFarland B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008; 58: 130 – 160

[8] Huang CS, O'Brien MJ, Yang S et al. Hyperplastic polyps, serrated adenomas, and the serrated polyp neoplasia pathway. Am J Gastroenterol 2004; 99: 2242 – 2255

[9] Coode PE, Chan KW, Chan YT. Polyps and diverticula of the large intestine: a necropsy survey in Hong Kong. Gut 1985; 26: 1045 – 1048

[10] Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. Gut 1982; 23: 835 – 842

[11] Pox CP, Altenhofen L, Brenner H et al. Efficacy of a nationwide screening colonoscopy program for colorectal cancer. Gastroenterology 2012; 142: 1460 – 1467

[12] Rex DK, Kahi C, O'Brien M et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. Gastrointest Endosc 2011; 73: 419 – 422

[13] Meining A, Saur D, Bajbouj M et al. In vivo histopathology for detection of gastrointestinal neoplasia with a portable, confocal miniprobe: an examiner blinded analysis. Clin Gastroenterol Hepatol 2007; 5: 1261 – 1267

[14] De Palma GD, Staibano S, Siciliano S et al. In vivo characterization of superficial colorectal neoplastic lesions with high-resolution probe-based confocal laser endomicroscopy in combination with video-mosaicing: a feasibility study to enhance routine endoscopy. Dig Liver Dis 2010; 42: 791 – 797

[15] Buchner AM, Shahid MW, Heckman MG et al. Comparison of probe-based confocal laser endomicroscopy with virtual chromoendoscopy for classification of colon polyps. Gastroenterology 2010; 138: 834 – 842

[16] Shahid MW, Buchner AM, Heckman MG et al. Diagnostic accuracy of probe-based confocal laser endomicroscopy and narrow band imaging for small colorectal polyps: a feasibility study. Am J Gastroenterol 2012; 107: 231 – 239

[17] Buchner AM, Gomez V, Heckman MG et al. The learning curve of in vivo probe-based confocal laser endomicroscopy for prediction of colorectal neoplasia. Gastrointest Endosc 2011; 73: 556 – 560

[18] Wallace M, Lauwers GY, Chen Y et al. Miami classification for probe-based confocal laser endomicroscopy. Endoscopy 2011; 43: 882 – 891

[19] Buchner AM, Shahid MW, Wallace M. The learning curve of probe based CLE for detection of neoplasia in colon polyps. Gastroenterology 2010; 138: S95

[20] Kudo S, Tamura S, Nakajima T et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc 1996; 44: 8 – 14

[21] Hewett DG, Kaltenbach T, Sano Y et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. Gastroenterology 2012; 143: 599 – 607

[22] Kuiper T, van den Broek FJ, van Eeden S et al. Feasibility and accuracy of confocal endomicroscopy in comparison with narrow-band imaging and chromoendoscopy for the differentiation of colorectal lesions. Am J Gastroenterol 2012; 107: 543 – 550

[23] Geertzen J (2012). Inter-Rater Agreement with multiple raters and variables. https://nlp-ml.io/jg/software/ira/ [last accessed 18 March 2016]

[24] Shahid MW, Buchner AM, Raimondo M et al. Accuracy of real-time vs. blinded offline diagnosis of neoplastic colorectal polyps using probe-based confocal laser endomicroscopy: a pilot study. Endoscopy 2012; 44: 343 – 348

[25] Gomez V, Buchner AM, Dekker E et al. Interobserver agreement and accuracy among international experts with probe based confocal laser endomicroscopy in predicting colorectal neoplasia. Endoscopy 2010; 42: 286 – 291

[26] André B, Vercauteren T, Buchner AM et al. Software for automated classification of probe-based confocal laser endomicroscopy videos of colorectal polyps. World J Gastroenterol 2012; 18: 5560 – 5569