Advances in colonoscopic imaging and the approach to dysplasia in IBD

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CHAPTER 2

Diagnostic performance of narrowed spectrum endoscopy, autofluorescence imaging, and confocal laser endomicroscopy for optical diagnosis of colonic polyps: a meta-analysis

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ABSTRACT

Background

Novel endoscopic technologies could allow optical diagnosis and resection of colonic polyps without histopathological testing. Our aim was to establish the sensitivity, specificity, and real-time negative predictive value of three types of narrowed spectrum endoscopy (narrow-band imaging [NBI], image-enhanced endoscopy [i-scan], and Fujinon intelligent chromoendoscopy [FICE]), confocal laser endomicroscopy (CLE), and autofluorescence imaging for differentiation between neoplastic and non-neoplastic colonic lesions.

Methods

We identified relevant studies through a search of Medline, Embase, PubMed, and the Cochrane Library. Clinical trials and observational studies were eligible for inclusion when the diagnostic performance of NBI, i-scan, FICE, autofluorescence imaging, or CLE had been assessed for differentiation, with histopathology as the reference standard, and for which a 2×2 contingency table of lesion diagnosis could be constructed. We did a random-effects bivariate meta-analysis using a non-linear mixed model approach to calculate summary estimates of sensitivity and specificity, and plotted estimates in a summary receiver-operating characteristic curve.

Findings

We included 91 studies in our analysis: 56 were of NBI, ten of i-scan, 14 of FICE, 11 of CLE, and 11 of autofluorescence imaging (more than one of the investigated modalities assessed in eight studies). For NBI, overall sensitivity was 91.0% (95% CI 88.6–93.0), specificity 85.6% (81.3–89.0), and real-time negative predictive value 82.5% (75.4–87.9). For i-scan, overall sensitivity was 89.3% (83.3–93.3), specificity 88.2% (80.3–93.2), and real-time negative predictive value 86.5% (78.0–92.1). For FICE, overall sensitivity was 91.8% (87.1–94.9), specificity 83.5% (77.2–88.3), and real-time negative predictive value 83.7% (77.5–88.4). For autofluorescence imaging, overall sensitivity was 86.7% (79.5–91.6), specificity 65.9% (50.9–78.2), and real-time negative predictive value 81.5% (54.0–94.3). For CLE, overall sensitivity was 93.3% (88.4–96.2), specificity 89.9% (81.8–94.6), and real-time negative predictive value 94.8% (86.6–98.1).

Interpretation

All endoscopic imaging techniques other than autofluorescence imaging could be used by appropriately trained endoscopists to make a reliable optical diagnosis for colonic lesions in daily practice. Further research should be focused on whether training could help to improve negative predictive values.

INTRODUCTION

Colorectal cancer develops from precursor lesions called colorectal polyps, which can be detected during colonoscopy. Removal of these lesions can prevent the development of the disease.[1] Colorectal polyps can be neoplastic, adenomas, or non-neoplastic (e.g., serrated polyps and inflammatory polyps). Neoplastic lesions can become malignant, but the risk of non-neoplastic lesions other than serrated polyps becoming cancerous is negligible.[2,3] Accurate in-vivo differentiation between the types of lesions would assist decision making about endoscopic treatment, especially in the distal colon, where non-neoplastic diminutive polyps (≤5 mm) can be left in situ. Additionally, such differentiation would mean that the so-called resect and discard strategy could be implemented (ie, not all lesions would need histo-pathological tests after removal) and decisions about appropriate surveillance intervals could be made directly after colonoscopy.[4]

In 2011, the Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) statement about real-time endoscopic assessment of the histology of diminutive colorectal polyps[5] introduced two criteria for assessments of whether a technique or device could replace histopathological assessment (the gold standard). First, when the technology for optimum diagnosis is used to make an in-situ endoscopic diagnosis for diminutive polyps with high confidence, this technology should result in the same surveillance interval that would have been assigned after pathological assessment of polyps at least 90% of the time. Second, for a technology to be used to guide the decision to leave suspected rectosigmoid hyperplastic polyps of less than 5 mm in size in place (without resection), the technology should provide 90% or greater negative predictive value, when used with high confidence, for adenomatous histology. Practically, if an endoscopist uses a specific technology and achieves a negative predictive value of at least 90%, diminutive lesions in the rectosigmoid

colon could be left in situ if they are deemed to be non-adenomatous, other lesions could be resected but not sent in for pathology, and the surveillance interval could be established immediately.[5]

In the past two decades, several new endoscopic imaging techniques have been developed to improve endoscopic differentiation between neoplastic and non-neoplastic colonic lesions beyond standard white light assessment. Narrow-band imaging (NBI, Olympus, Japan), image-enhanced endoscopy (i-scan, Pentax, Japan), and Fujinon intelligent chromoendoscopy (FICE, Fujinon, Japan)—which are also all called virtual, digital, or electronic chromoendoscopy—are all built-in endoscopic imaging techniques. NBI is a blue light technology that highlights superficial mucosal vasculature and enhances surface patterns through illumination via narrowed bandwidth filters. Both i-scan and FICE use spectral-estimation technology to re construct images at different wavelengths on the basis of white light images.

Other new image enhanced techniques that are widely commercially available are confocal laser endomicroscopy (CLE) and autofluorescence imaging. CLE is a system that can provide highly magnified images of gastro intestinal epithelium that are similar to histopathological images through a miniaturised confocal laser endo-microscope, either integrated into the endoscope (Pentax, Japan), or via a probe introduced down the working channel of the endoscope (Mauna Kea Technologies, France). Autofluorescence imaging makes use of differences in mucosal blood flow and endogenous fluorophores (eg, collagen, flavins, and NADPH), which change the autofluorescence signal emitted after short wavelength illumination. The signal is processed to create a false-colour image to assist differentiation between neoplastic and non-neoplastic colonic lesions.

The diagnostic performance of these techniques has been widely studied both in single studies and in single-modality meta-analyses.[6–8] However, a comprehensive overview of the accuracy and precision for all available techniques has not been combined in one meta-analysis with standardised inclusion criteria, data extraction, and statistical approach. Our aim was to establish the sensitivity, specificity, and real-time negative predictive value of NBI, i-scan, FICE, autofluorescence imaging, and CLE for differentiation between

neoplastic and non-neoplastic colonic lesions, with histopathology as the reference standard.

METHODS

Search strategy and selection criteria

We did a meta-analysis in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[9] Under the supervision of a librarian at the University of Amsterdam (Amsterdam, Netherlands), we searched Medline from Jan 1, 1966, to Jan 14, 2013, Embase from Jan 1, 1986, to Jan 14, 2013, and PubMed from inception to Jan 14, 2013. We used the search term "'NBI' [Mesh] OR NBI [tiab] OR i-SCAN [tiab] OR FICE [tiab] OR confocal OR CLE [tiab] OR autofluorescence [tiab] OR AFI [tia] OR Fujinon intelligent chromo endoscopy [tiab] OR Flexible spectral imaging color enhancement [tiab] OR confocal [tiab] OR narrow band [tiab] OR real time histology [tiab] AND 'Colonoscopy' [Mesh] OR colonoscop* [tiab] OR colon imag* [tiab] OR intestinal imag* [tiab]". We also searched the Cochrane Library for any relevant additional review with data that was published before Jan 14, 2013. We used no language restrictions. We then selected suitable studies for inclusion in our analysis on the basis of the abstracts of the selected reports. We checked reference lists of the reports identified in the original search to identify studies that had been missed.

LKW and SEU reviewed the identified studies to assess whether they were eligible for inclusion. Clinical trials and observational studies were eligible for inclusion when the performance of NBI, i-scan, FICE, autofluorescence imaging, or CLE, or any combination of the five, had been assessed for differentiation between non-neoplastic and neoplastic lesions in the colon, with histopathology as the reference standard, and for which a 2×2 contingency table of lesion diagnosis could be constructed. We included conference abstracts when they contained relevant data. We approached authors of abstracts to receive relevant unpublished data. We excluded studies that were focused on surveillance in patients with inflammatory bowel diseases or polyposis syndromes, or on lesion detection only. We also excluded those for which inadequate data for histopathology were available. We examined studies for overlapping data and made contact with the relevant investigators when necessary.

Procedures

Because all the included studies were diagnostic in nature, we assessed their quality and risk of bias with QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies).[10] We measured overall sensitivity, specificity, and negative predictive value for real-time assessments of NBI, CLE, autofluorescence imaging, FICE, and i-scan to differentiate between neoplastic and non-neoplastic lesions. Additionally, we investigated heterogeneity by assessing sensitivity and specificity of NBI, i-scan, FICE, autofluorescence imaging, and CLE for real-time (in-vivo) diagnosis versus post-procedure image-based diagnosis, polyp size, use of high-definition technology, magnification, high confidence assessments, and type of colonoscopy system. LKW and SEU independently extracted relevant data from the selected studies. They solved discrepancies by discussion either with each other or with JEE and ED. For the core analysis, we constructed 2 × 2 contingency tables of true positives (neoplastic lesions predicted to be neoplastic), false positives (non-neoplastic predicted to be neoplastic), true negatives (non-neoplastic predicted to be non-neoplastic), and false negatives (neoplastic predicted to be non-neoplastic). When possible, we used raw data for numbers of lesions. Otherwise, we calculated the number in each category from the numbers of neoplastic and non-neoplastic lesions and the sensitivity and specificity.

Additionally, LKW and SEU extracted data from each trial for country of origin, study year, study design, number of patients, sex ratio, indication for colonoscopy, number of endoscopists and their experience, number of lesions, and features of the modalities used (including high definition, magnification, and type of endoscopy system for NBI [Exera ***vs*** Lucera]).

Statistical analysis

We did a random-effects bivariate meta-analysis using a non-linear mixed model approach to calculate summary estimates of sensitivity and specificity.[11] This approach models the sensitivity and specificity, while accounting for the correlation between the two because of threshold effects. We used the same approach to calculate summary estimates of positive predictive values and negative predictive values.[12] For all modalities, we plotted study estimates and a summary point with its 95% CIs in a summary receiver-operating characteristic plot. In this plot, all studies are presented, with the size of the study points representing the sample

size of the study. The summary point is represented by a dot, surrounded by a 95% confidence region (appendix).

For the overall analysis, we used both real-time and post-procedure studies. To estimate the negative predictive value, we used only real-time studies, because images used in post-procedure studies would have been selected for inclusion on the basis of quality, which would mean the ratio of neoplastic to non-neoplastic lesions in included images would not be representative of the ratio recorded in patients. Because the predictive values depend directly on this ratio, they cannot be estimated from these studies.

The correlation between sensitivity and specificity makes tests for heterogeneity difficult; most variation in sensitivity will be explained by variation in specificity, and vice versa.[13,14] Therefore, statistical tests and I^2 values as used in meta-analyses of interventions are not helpful. We assumed that heterogeneity was present in our data and planned to deal with it with random effects modeling and by investigation of the sources of heterogeneity. To investigate the potential sources, we assessed the effects of type of assessment (real-time ***vs*** post-procedure), magnification, high definition, type of endoscope, and polyp size (overall ***vs*** diminutive) on the summary estimates. We included these variables one by one as covariates in the bivariate model. We included covariates if at least three studies were available for each value of the covariate. The difference between a subgroup and the group without the feature is shown by a delta estimate. We did not assess publication bias, because no proven statistical method exists for this type of meta-analysis.[13] We used SAS (version 9.2) with NLMIXED for all statistical analyses.

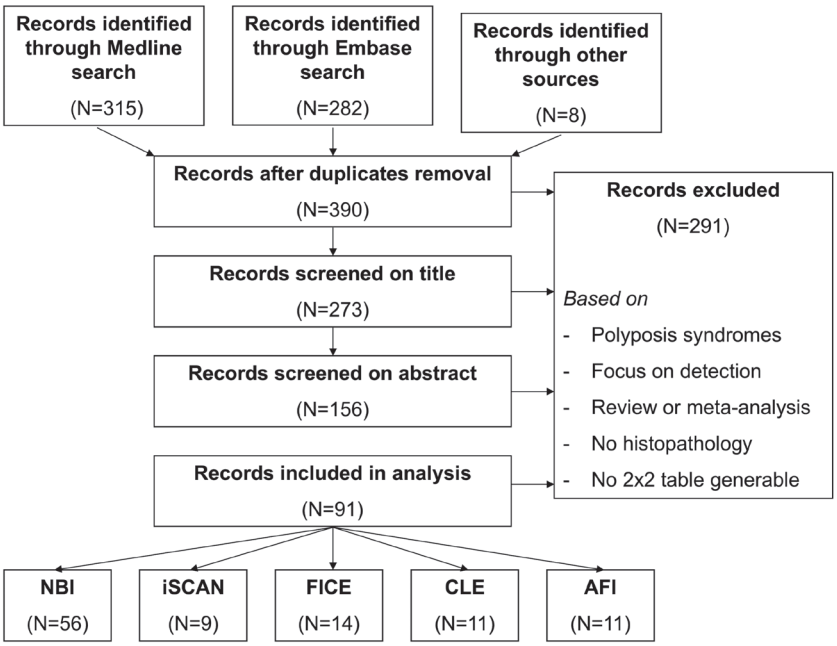
Role of the funding source

There was no funding source for this study. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.

RESULTS

From the initial keyword search, we identified 390 separate reports (figure 1). 91 studies were included in our analysis, of which 90[15–103] had been reported; details of another were provided by Arthur Hoff man (Johannes Gutenberg University of Mainz, personal communication). More than one imaging modality was assessed in some of the studies.[16,17,27,29,33,38,52,53]

Figure 1 Flow-chart literature search



The 56 included NBI studies[4,15–69] were mostly done in Asia, Europe, and the USA, and were generally reported between 2006 and 2013. We included 13 NBI studies that had been reported in abstracts; we obtained additional raw data directly from the investigators. A high proportion of NBI studies consisted of real-time assessments of colorectal lesions (table 1). Two studies consisted of both post-procedure and real-time assessments. 28 NBI studies (50%) were done with Exera series endoscopy systems, 24 (43%) with Lucera spectrum endoscopy systems, and four (7%) with unknown systems. Sensitivity for differentiation of colorectal lesions in all NBI studies varied from 60.0% to 100%, and specificity from 31.5% to 100%.

Table 1 Subgroup study characteristics by imaging modality

Modality		Subgroup proportion (%)								
		Real-time	MPP (range)	MAP (range)	Diminutive	+ High Confidence	Magnification	High-Definition	Type of endoscopy system	
	NBI	39/56 (69·6)	1·9 (0·9-2·9)	1·1 (0·5-1·5)	16/56 (28·6)	5/56 (8·8)	24/56 (42·9)	27/56 (48·2)	Exera 28/56 (50·0)	Lucera 27/56 (48·2)
	iSCAN	8/9 (88·9)	1·7 (0·9-2·1)	0·9 (0·6-1·3)	0/9 (0·0)	0/9 (0·0)	0/9 (0·0)	9/9 (100·0)	N/A	N/A
	FICE	13/14 (92·9)	1·6 (0·7-2·4)	1·1 (0·6-1·7)	5/14 (35·7)	0/14 (0·0)	10/14 (71·4)	11/14 (78·6)	N/A	N/A
	AFI	9/11 (81·8)	1·9 (1·4-2·1)	1·0 (0·9-1·4)	0/11 (0·0)	0/11 (0·0)	1/11 (9·1)	N/A	N/A	N/A
	CLE	6/11 (54·5)	2·6 (1·6-3·6)	1·2 (1·0-1·4)	0/11 (0·0)	0/11 (0·0)	11/11 (100·0)	N/A	iCLE 5/11 (45·5)	pCLE 6/11 (54·5)

MPP = mean polyps per patient, MAP = mean adenomas per patient, range = interval between 10% and 90% of study means. N/A = not applicable

Of the 56 NBI studies, seven had at least one item scored as high risk in QUADAS-2—all for selection of patients—suggesting a high risk of bias (appendix). The sensitivity and specificity values for real-time NBI assessments were not significantly different from those for post-procedure assessments (sensitivity: p=0.69; specificity: p=0.56; table 2). The negative predictive value was significantly lower in studies that included a higher proportion of neoplastic lesions (p=0.00026).

NBI had significantly lower sensitivity and specificity when high-definition assessments were done than when high definition was not used (p<0.0001 for both; table 2). Sensitivity did not vary according to whether magnification was used (p=0.24), but specificity increased significantly with magnification (p=0.032; table 2). High-definition technology was used in 20 of 33 studies in which magnification was not used, and five of 21 in which magnification was used (p=0.0082). This difference could have affected the effect of magnification on performance. To test this hypothesis, we included both magnification and high definition in the same model. We noted that magnification again had no significant effect on sensitivity (p=0.82) and no longer had a significant effect on specificity (p=0.42), but the effect of high definition on sensitivity (p=0.00017) and specificity (p=0.00013) was significant.

NBI studies in which only diminutive polyps were assessed and those in which all sizes of polyps were assessed did not differ significantly in terms of sensitivity (p=0.12) or specificity (p=0.98; table 2). Similarly, studies in which an Exera endoscopy system was used and those in which a Lucera system was used did not differ significantly in terms of sensitivity (p=0.18) or specificity (p=0.11; table 2).

The ten included i-scan studies—of which nine had been reported[37,70–76] and one communicated to us (Hoffman A, Johannes Gutenberg University of Mainz, personal communication)—were reported between 2009 and 2013. Four studies had been done in Germany, three of which were done by the same research group. Two generations of i-scan were compared in one study.76 Almost all i-scan studies were real-time assessments of colorectal lesions (table 1). Sensitivity in i-scan studies varied from 54.5% to 94.6%, and specificity from 64.0% to 100%.

None of the i-scan studies had a high-risk item in QUADAS-2 (appendix). The sensitivity and specificity values for real-time i-scan assessments were similar to those for all i-scan assessments (table 2). Because of the small number of i-scan studies, we could not do sub-analyses. All were done with high-definition colonoscopy; therefore the estimate of diagnostic performance of real-time i-scan is a high-definition estimate.

The 14 included FICE studies were reported between 2007 and 2012.[17,31,77–88] One study consisted of only post-procedure assessments, one of both post-procedure and real-time assessments, and the rest of only real-time assessments (table 1). Sensitivity in FICE studies varied from 73.9% to 100%, and specificity from 61.2% to 96.4%.

None of the FICE studies had a high-risk item in QUADAS-2 (appendix). The diagnostic performance of real-time assessments was similar to that in the overall analysis (table 2). Sensitivity increased significantly when magnification was used (p=0.0081), but specificity did not vary (p=0.64; table 2). Sensitivity (p=0.58) and specificity (p=0.12) did not vary according to whether high definition was used (table 2). Finally, assessment of only diminutive polyps did not significantly affect sensitivity (p=0.93) or specificity (p=0.17; table 2).

The 11 included studies of autofluorescence imaging were reported between 1998 and 2012.[15,29,33,38,52,53,89–93] Most consisted of real-time assessments (table 1). No studies were focused on differentiation of diminutive lesions alone (table 1). Sensitivity varied from 57.5% to 98.9%, and specificity from 7.5% to 90.9%.

Five studies of autofluorescence imaging had at least one item scored as high risk in QUADAS-2 for selection of patients, suggesting a high risk of bias (appendix). We also deemed one study to have a high risk for bias related to the interpretation of the index test (appendix). The sensitivity (p=0.31) and specificity (p=0.48) values for real-time AFI assessments were not significantly different from those for post-procedure assessments (table 2). Because of the small number of studies of autofluorescence imaging, we could not do sub-analyses.

The 11 included CLE studies were reported between 2004 and 2012.[17,94–103] Five consisted of only post-procedure assessments, one of both post-procedure and real-time assessments, and the rest of only real-time assessments (table 1). No studies were focused on differentiation of diminutive lesions alone (table 1). Five CLE studies (45%) were done with integrated techniques and six (55%) with probe-based techniques. Sensitivity in CLE studies varied from 76.0% to 100%, and specificity from 68.0% to 99.1%.

None of the CLE studies had a high-risk item in QUADAS-2 (appendix). Specificity increased significantly with real-time assessments when compared with post-procedure assessments (p=0.0048), but sensitivity did not (p=0.34; table 2). The only sub-analysis that we could do for CLE was the comparison between probe-based and integrated techniques. Specificity was significantly higher for integrated techniques than for the probe-based techniques (p=0.011), but no significant effect on sensitivity was recorded (p=0.34; table 2). However, when adjusted for real-time assessment, the difference was no longer significant (p=0.53).

Table 2 Diagnostic performance of optical diagnosis of NBI, iSCAN, FICE, CLE and AFI

Modality	Study characteristics	No. of studies (lesions)	Summary estimates (95% CI)			Delta per subgroup in percentage (95% CI)	
			Sensitivity	Specificity	NPV	Sensitivity	Specificity
NBI	Overall	56 (18,051)	91·0 (88·6 to 93·0)	85·6 (81·3 to 89·0)	-		
	Real-time	39	91·5 (88·2 to 93·9)	85·2 (80·0 to 89·3)	82·5 (75·4 to 87·9)	1·0 (-3·9 to 5·9)	-2·4 (-10·5 to 5·6)
	Polyps < 6mm	16	86·9 (81·0 to 92·8)	84·4 (76·7 to 92·1)	-	-4·6 (-10·9 to 1·8)	0·0 (-8·9 to 9·0)
	+ high confidence	5	87·1 (77·8 to 92·9)	85·3 (74·2 to 92·1)	-	-	-
	Magnification	24	92·0 (89·0 to 95·0)	89·0 (84·3 to 93·7)	-	2·6 (-1·7 to 7·0)	8·1 (0·9 to 15·3)
	No magnification	35	89·4 (86·3 to 92·6)	80·9 (75·4 to 86·4)		-	-
	High Definition	27	85·2 (81·1 to 89·4)	74·6 (68·0 to 81·3)	-	-8·4 (-13·0 to 3·9)	-15·7 (-23·1 to -8·3)
	Exera	28	89·4 (86·0 to 92·8)	85·7 (80·9 to 90·4)	-	-1·4 (-6·1 to 3·3)	6·1 (-2·3 to 14·5)
	Lucera	24	90·8 (87·6 to 94·0)	79·6 (72·6 to 86·5)	-	-	-
iSCAN	***Overall***	***9 (1,143)***	***89·3 (83·3 to 93·3)***	***88·2 (80·3 to 93·2)***	-	-	-
	Real-time	8	89·5 (82·7 to 93·8)	89·3 (81·0 to 94·2)	86·5 (78·0 to 92·1)	-	-
FICE	***Overall***	***14 (4,824)***	***91·8 (87·1 to 94·9)***	***83·5 (77·2 to 88·3)***	-	-	-
	Real-time	13	92·5 (87·6 to 95·6)	85·1 (78·7 to 89·8)	83·7 (77·5 to 88·4)	-	-
	Polyps < 6mm	5	83·6 (72·8 to 94·4)	86·5 (79·4 to 93·6)	-	-1·7 (-12·0 to 8·8)	5·6 (-2·1 to 13·3)
	Magnification	10	93·7 (90·6 to 96·8)	82·6 (76·9 to 88·2)	-	8·5 (1·4 to 15·6)	1·7 (-6·3 to 9·7)
	High Definition	10	92·6 (88·2 to 97·0)	79·8 (72·2 to 87·4)	-	2·2 (-6·0 to 10·3)	-7·7 (-17·4 to 2·0)
AFI	***Overall***	***11 (1,670)***	***86·7 (79·5 to 91·6)***	***65·9 (50·9 to 78·2)***	-	-	-
	Real-time	9	88·0 (80·5 to 92·8)	69·2 (51·7 to 82·4)	81·5 (54·0 to 94·3)	8·5 (-10·2 to 27·3)	12·9 (-24·0 to 49·7)
CLE	***Overall***	***11 (1,372)***	***93·3 (88·4 to 96·2)***	***89·9 (81·8 to 94·6)***	-	-	-
	Real-time	6	94·3 (88·1 to 97·3)	94·8 (87·3 to 98·1)	94·8 (86·6 to 98·1)	5·1 (1·5 to 8·7)	12·7 (6·0 to 19·4)
	iCLE	5	94·8 (90·6 to 98·9)	94·4 (90·7 to 99·2)	-	-	-
	pCLE	6	91·5 (86·0 to 97·0)	80·9 (69·4 to 92·4)		5.2 (1.9 to 8.4)	11.1 (5.1 to 17.2)

CI: confidence interval, NPV: Negative Predictive Value, Delta: difference between subgroup and non-subgroup

DISCUSSION

We have shown that built-in endoscopic imaging techniques have overall negative predictive values of greater than 80% in the differentiation between neoplastic and non-neoplastic lesions. NBI, i-scan, FICE, and CLE have similar sensitivity and specificity overall. Autofluorescence imaging had a sensitivity of more than 85%, but had a much lower specificity than did the other investigated modalities. In the overall analysis, only CLE had a negative predictive value of more than 90%.

To our knowledge, ours is the first meta-analysis to give an overview of the accuracy of all available built-in image-enhanced techniques for optical diagnosis of colorectal lesions. The diagnostic performance of NBI and CLE have been assessed separately in meta-analyses, 6–8 although fewer studies were included. Our analysis provides an overview of optical diagnosis with all available techniques, analysed with a standardised approach. We hope that the outcomes reported here will support future guidelines and research.

With the results of our meta-analysis, we can compare the real-time negative predictive values of the different modalities with the criteria in the PIVI statement. However, we calculated the overall negative predictive value, not just that for diminutive rectosigmoid lesions as in the PIVI statement. Because the prevalence of non-neoplastic lesions is increased in the rectosigmoid area, studies of only rectosigmoid negative predictive value are likely to show a good diagnostic performance.

To provide a complete overview of all data available for differentiation of colonic lesions and to maximise the precision of estimates, we did an overall analysis of both real-time and post-procedure assessments for all five modalities. Real-time assessment is the optimum situation to investigate performance, because it avoids bias of photographic selection, simulates an in-vivo optical diagnosis, and allows calculation of a negative predictive value on the basis of the real-life lesion prevalence. However, if we were to have included only real-time assessments, the number of included studies and reports would have substantially reduced and potentially important data would have been missed. Studies with real-time data could be analysed separately from post-procedure photographic studies, rather than using real time in the analysis. In most studies, either

a real-time or post-procedure approach was used, but not both. We did not expect characteristics of real-time studies to be different from those of post-procedure studies, and almost all real-time analyses were similar to the overall analyses. The only significant difference was that real-time specificity of CLE was significantly better than the overall specificity (p=0.0048). Stratification for real time would have reduced numbers, making investigation of other sources of heterogeneity (e.g., magnification) more difficult. When we had enough data, we did extra subgroup analyses. However, because the number of NBI studies was more than three times that of any other modality, most subgroup analysis was restricted to this technique.

Of all advanced imaging techniques, NBI is the most studied. McGill and colleagues[7] reported that real-time assessment of colorectal lesions had a sensitivity of 91.0% (95% CI 87.6–93.5) and a specificity of 82.6% (79.0–85.7)—i.e., similar values to those in our analysis. However, the CIs reported by McGill and colleagues are wider than ours were, presumably because they used a smaller sample (28 studies).[7]

Counter intuitively, we recorded that high definition significantly decreased the performance of NBI. A possible explanation is that high-definition techniques are used by endoscopists who are less experienced than are those who use magnification. Before high-definition technology was widely available, standard-definition colonoscopes incorporated magnification to allow detailed examination of minute mucosal structures, and were mainly used by experts; the image is more detailed than with high definition but no magnification. However, we could not test this hypothesis with additional analyses.

Our sub-analysis of high confidence assessments did not improve diagnostic performance for diminutive lesions. Although it is recommended in the PIVI statement that only assessments made with high confidence should be used to make optical diagnoses, confidence is subjective and could be less important than has been previously supposed. Several studies of how individuals learn to differentiate with NBI have been done.[22,30,35,44,51,58] Three studies[22,44,58] of the accuracy before and after training showed that gastroenterology trainees and less experienced endoscopists (e.g., community-based endoscopists) can learn to predict histology with an accuracy of at least 90%. Therefore, an endoscopist

needs to be trained before he or she can implement the resect and discard strategy in daily clinical practice. Nevertheless, results from community based studies of NBI or i-scan suggest that training in community clinical practice could be substantially more difficult than would be assumed from training studies.[34,35,104]

Several classification methods for differentiation of colorectal lesions have been developed to guide endoscopists in optical diagnosis of colorectal lesions, most commonly for NBI. One of the most recently developed is the NBI international colorectal endoscopic classifi cation, which uses colour, vessels, and surface pattern to help endoscopists to distinguish between hyperplastic and adenomatous lesions.[27]

FICE and i-scan have similar diagnostic performance to NBI, although their confidence regions are notably larger than for NBI, because of the small number of studies. CLE had a high sensitivity and specificity for real-time diagnosis of colorectal lesions. Integrated techniques had a significantly better diagnostic performance than did probe-based techniques in our initial analysis, but the difference was no longer significant after adjustment for real time. The studies of probe-based CLE could have assessed patients or lesions that were different from those of integrated CLE—i.e., spectrum bias might have been an issue. The outcome for real-time CLE is similar to the results of Su and colleagues' meta-analysis,[8] which showed a pooled sensitivity of 0.94 (95% CI 0.88–0.97) and a pooled specificity of 0.95 (0.89–0.97). However, CLE can only be done by highly specialized endoscopists with expensive and fragile equipment—factors that might have caused the high accuracy in our analysis and make CLE less suitable for daily clinical practice than the other modalities. Nevertheless, CLE might be an interesting technique to use for specific indications in tertiary referral centres.

Autofluorescence imaging had a fairly good sensitivity, but a substantially lower specificity than did the other modalities. Autofluorescence imaging differentiates between neoplastic and non-neoplastic lesions by colour of the lesion when compared with the surrounding mucosa. This technique is accurate when the colour is either clear green or purple, but difficulties arise when the colour is not clear enough to distinguish. The fairly low specificity of autofluorescence imaging might be explained by the fact that endoscopists prefer not to misinterpret neoplastic lesions and therefore are more likely to classify lesions as

neoplastic than non-neoplastic when uncertain. However, none of the included studies of autofluorescence imaging incorporated measures of confidence in their study design. Initially, autofluorescence imaging was studied as a technique on its own for optical diagnosis, but in most studies in the past 2 years, autofluorescence imaging was combined with NBI and high-definition white light endoscopy—the so-called endoscopic trimodal imaging approach. Rotondano and colleagues' study[52] indicated that autofluorescence imaging is of additional value to NBI for both the detection and the differentiation of colorectal lesions.

Every meta-analysis has limitations due to the extraction of data from many different reports. A major limitation of our study was that we could often make no clear distinction between experts and non-experts. There is no unambiguous definition of expert; in some studies, an endoscopist was defined as an expert after a specific number of colonoscopies, but in others, individuals had to have had specific training. Generally, experts did most of the studies, which reduces the value of the outcomes for daily practice. Besides the inequality of expertise and the absence of a validated training programme, several classification systems were used in the included studies, reducing the generalisability of the overall performance. Levels of confidence, and especially whether assessments were made with high confidence, were available in only five studies. The PIVI statement5 specifies that high confidence should be necessary before a method of optical diagnosis can be applied in daily practice. Gupta and colleagues[105] showed that, besides confidence, how long it takes someone to make a diagnosis affects the accuracy; they advised a wait of 5 s before a diagnosis is made.

Other limitations are that polyp size and location were most commonly not clearly described in individual studies, and serrated lesions were subsequently not sub-classified as sessile serrated adenomas or polyps, traditional serrated adenomas, or hyperplastic lesions. Therefore, sessile serrated adenomas or polyps might have previously been put in non-neoplastic groups, whereas nowadays most clinicians deem these lesions to be neoplastic according to the serrated neoplasia pathway, especially outside the rectosigmoid.[2] Potential bias also exists when specific populations of patients were excluded. Studies that included patients with either inflammatory bowel disease or polyposis syndromes were excluded from our analysis because lesions in these disorders are fundamentally different in phenotype—e.g., dysplasia-associated lesions or masses in colitis

or hamartomatous polyps in polyposis syndromes. Studies in patients with hereditary non-polyposis colorectal cancer were included in the analysis because there is no reason to suspect that the endoscopic characteristics of polyps in these patients are different from those of patients with an average risk for polyps.

Another limitation is that we did not formally compare the differences between the five modalities assessed. The use of network meta-analyses for diagnostic accuracy data is not yet reliable. As yet, only one method has been reported that combines both direct and indirect comparisons; a real network meta-analysis of diagnostic accuracy has not yet been reported, although such an analysis could be possible in the future.[106] If formal comparisons are to be made, studies that assess all (or at least two) modalities against the same reference standard in the same patients or in a randomised design would be ideal.[13] However, these studies are rare; we identified eight, which were all about different pairs of modalities.[16,17,27,29,33,38,52,53] Without these so-called direct comparisons, comparisons of the accuracy of one modality with the accuracy of another could result in biased conclusions, because both modalities could be assessed in a different population. This source of bias (spectrum bias) is the reason that we did not make formal comparisons between the investigated modalities.[107] We did create a table with the proportions by subgroup per modality, but comparisons of the different modalities should be approached with caution.

In our meta-analysis, we calculated negative predictive values for all modalities, but negative predictive values are strongly dependent on the ratio between neoplastic lesions and non-neoplastic lesions in the patients. Care should be taken in comparisons of the accuracy of these modalities against each other and when the negative predictive values from our review are applied in practice.

In conclusion, all endoscopic imaging techniques other than autofluorescence imaging could be used by appropriately trained endoscopists to make a reliable optical diagnosis for colonic lesions in daily practice. Further research should be focused on whether training in narrow-spectrum endoscopy (ie, NBI, i-scan, and FICE) will help community-based gastroenterologists to reach a negative predictive value of at least 90% for diminutive rectosigmoid adenomas and maintain that value.

APPENDIX A SROC-plots

Summary receiver-operating characteristic (SROC) plots of overall performance per modality

Figure 2 NBI

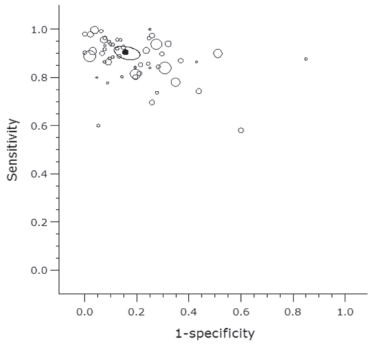


Figure 3 iSCAN

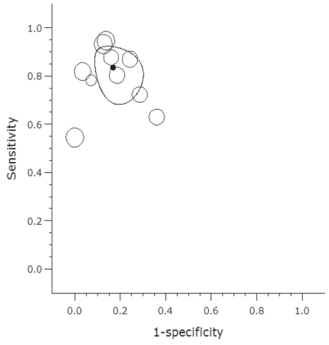


Figure 4 FICE

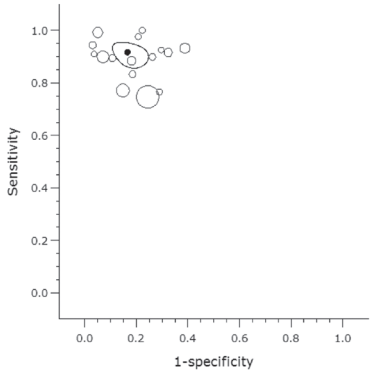


Figure 5 AFI

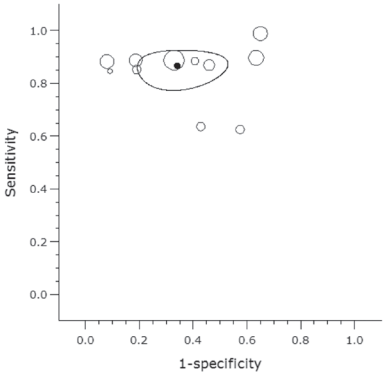
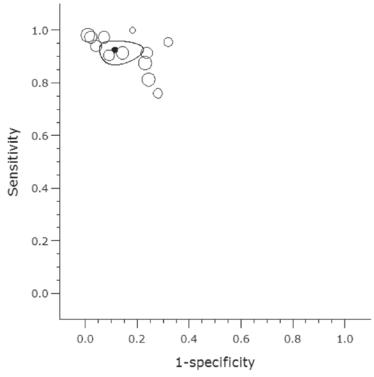


Figure 6 CLE



∘ *Study estimate*

● *Summary point with 95% confidence re*

Table 3 Study characteristics NBI, iSCAN, FICE, CLE and AFI

NBI

	Author	Year	Country	Publication	Patients	Neo-plasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
1	*Broek vd* [15]	2009	Netherlands	Full text	100	22	28	no	yes	PP	no	Lucera
2	*Broek vd* [16]	2009	Netherlands	Full text	107	88	118	no	yes	RT	no	Lucera
3	*Buchner* [17]	2010	USA	Full text	28	25	16	no	yes	PP	no	Exera
4	*Canales* [18]	2011	Peru	Full text	134	76	43	yes	-	RT	no	Exera
5	*Chang* [19]	2009	Taiwan	Full text	104	82	81	yes	no	PP	no	Lucera
6	*Chiu* [20]	2012	Taiwan	Full text	133	141	39	yes	no	PP	no	Lucera
7	*Coe* [21]	2012	USA	Full text	654	467	307	no	yes	RT	no	Exera
8	*Dai* [22]	2012	China	Full text	326	30	10	yes	yes	RT	no	Lucera
9	*East* [23]	2008	UK	Full text	62	50	66	yes	yes	RT	yes	Lucera
10	*Gross* [24]	2011	Germany	Full text	214	120	135	yes	no	RT	yes	Exera
11	*Heller* [25]	2011	-	Abstract	100	27	23	no	-	PP	yes	UK
12	*Henry* [26]	2010	USA	Full text	52	67	59	no	yes	PP	yes	Exera
13	*Hewett* [27]	2012	USA	Full text	31	39	197	no	no	RT/PP	no	Exera
14	*Hirata* [28]	2007	Japan	Full text	99	132	16	yes	no	RT	no	Lucera
15	*Ignjatovic* [4]	2009	UK	Full text	130	198	80	no	yes	RT/PP	yes	Lucera
16	*Ignjatovic* [29]	2011	UK	Full text	48	40	40	both	yes	PP	no	Lucera
17	*Ignjatovic* [30]	2011	UK	Full text	-	15	15	no	no	PP	no	Lucera
18	*Kang* [31]	2012	Korea	Abstract	821	943	667	no	no	PP	no	Lucera
19	*Katagiri* [32]	2008	Japan	Full text	104	134	5	yes	no	PP	no	Lucera
20	*Kuiper* [33]	2011	Netherlands	Full text	118	115	122	no	yes	RT	no	Exera
21	*Kuiper* [34]	2012	Netherlands	Full text	108	141	167	no	yes	RT	no	Exera
22	*Ladabaum* [35]	2013	USA	Full text	-	1541	1055	no	yes	RT	yes	Exera
23	*Lau* [36]	2012	China	Abstract	441	341	178	yes	-	RT	no	Exera
24	*Lee* [37]	2011	Korea	Full text	70	80	76	no	yes	RT	yes	Lucera
25	*Lin* [38]	2013	Taiwan	Abstract	66	84	37	yes	yes	RT	no	Lucera

Table 3 Continued

NBI

	Author	Year	Country	Publication	Patients	Neo-plasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
26	*Lopata* [39]	2012	USA	Abstract	482	405	401	no	yes	RT	no	Lucera
27	*Machida* [40]	2004	Japan	Full text	34	34	9	no	no	RT	no	Lucera
28	*Occhipinti* [41]	2012	Italy	Abstract	93	120	100	yes	no	PP	no	Exera
29	*Oka* [42]	2011	Japan	Full text	-	645	53	yes	no	RT	no	UK
30	*Paggi* [43]	2012	Italy	Full text	286	350	161	no	yes	RT	yes	Exera
31	*Patel* [44]	2013	USA	Full text	-	52	28	no	yes	PP	yes	Exera
32	*Pohl* [45]	2012	Germany	Abstract	608	616	883	no	no	RT	yes	Exera
33	*Ramirez* [46]	2009	USA	Abstract	56	5	22	no	-	RT	no	UK
34	*Rastogi* [47]	2008	USA	Full text	40	43	28	no	yes	RT	yes*	Exera
35	*Rastogi* [48]	2009	USA	Full text	100	143	93	no	yes	RT	yes*	Exera
36	*Rastogi* [49]	2011	USA	Full text	210	147	237	no	yes	RT	yes*	Exera
37	*Rex* [50]	2009	USA	Full text	136	230	221	yes	no	RT	yes	Exera
38	*Rogart* [51]	2008	USA	Full text	131	131	134	yes	yes	RT	no	Exera
39	*Rotondano* [52]	2011	Italy	Full text	94	141	140	yes	yes	RT	no	Lucera
40	*Sato* [53]	2011	Japan	Full text	183	339	85	no	no	PP	no	Lucera
41	*Sakamoto* [54]	2012	Japan	Full text	151	52	42	yes	no	RT	no	Lucera
42	*Sano* [55]	2008	Japan	Full text	92	111	39	yes	no	RT	no	Exera
43	*Shahid* [56]	2011	USA	Full text	65	58	72	no	yes	RT	yes	Exera
44	*Sikka* [57]	2008	USA	Full text	63	49	31	no	no	PP	no	Exera
45	*Singh* [58]	2010	Australia	Full text	32	30	20	no	yes	PP	yes	Exera
46	*Soto* [59]	2012	Venezuela	Abstract	85	60	66	no	no	RT	no	Exera
47	*Su* [60]	2006	Taiwan	Full text	78	65	40	no	no	RT	no	Lucera
48	*Takemura* [61]	2012	Japan	Full text	-	324	47	yes	no	PP	no	Lucera
49	*Tischendorf* [62]	2007	Germany	Full text	52	63	37	yes	no	RT	no	Exera
50	*Tischendorf* [63]	2010	Germany	Full text	131	121	79	both	yes	PP	no	Exera

Table 3 Continued

NBI

	Author	Year	Country	Publication	Patients	Neo-plasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
51	*Valiante*[64]	2011	Italy	Abstract	65	57	47	no	yes	RT	no	Exera
52	*Wada*[65]	2012	Japan	Abstract	495	1420	53	yes	no	RT	no	Lucera
53	*Wang*[66]	2009	USA	Abstract	15	15	10	no	no	RT	no	-
54	*Yague*[67]	2011	Spain	Abstract	75	107	108	no	yes	RT	no	Exera
55	*Yoo*[68]	2011	Korea	Full text	68	89	18	yes	no	RT	no	Lucera
56	*Zhou*[69]	2011	China	Full text	118	118	109	both	no	RT	no	Lucera

iSCAN

	Author	Year	Country	Publication	Patients	Neo-plasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
1	*Chan*[70]	2012	USA	Full text	43	54	49	no	yes	RT	no	Pentax
2	*Han*[71]	2012	Taiwan	Full text	54	57	44	no	yes	RT	no	Pentax
3	*Hoffman*[72]	2010	Germany	Full text	100	11	117	no	yes	RT	no	Pentax
4	*Hoffman*[73]	2010	Germany	Full text	69	82	63	no	yes	RT	no	Pentax
5	*Hoffman*[74]	2013	Germany	Abstract	-	23	28	no	yes	RT	no	Pentax
6	*Hong*[75]	2012	Korea	Full text	115	81	25	no	yes	RT	no	Pentax
7	*Hong**[76]	2012	Korea	Full text	118	66	43	no	yes	RT	no	Pentax
8	*Lee*[76]	2011	Korea	Full text	72	74	66	no	yes	RT	no	Pentax
9	*Neumann*[77]	2013	Germany	Full text	-	77	33	no	yes	PP	no	Pentax
10	*Pigo*[78]	2012	Italy	Full text	78	118	32	no	yes	RT	no	Pentax

Table 3 Continued

FICE

	Author	Year	Country	Publication	Patients	Neoplasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
1	*Buchner*[17]	2010	USA	Full text	47	81	38	no	yes	PP	no	Fujinon
2	*Kang*[31]	2012	Korea	Abstract	821	943	667	yes	-	RT	no	Fujinon
3	*Kim*[79]	2011	Korea	Full text	361	325	210	both	yes	RT	yes	Fujinon
4	*Liu*[80]	2008	China	Full text	223	209	242	yes	no	RT	no	Fujinon
5	*Longcroft*[81]	2011	UK	Full text	89	155	77	no	no	RT	yes	Fujinon
6	*Longcroft*[82]	2012	UK	Full text	170	96	54	no	both	RT	no	Fujinon
7	*Pohl*[83]	2008	Germany	Full text	63	89	61	both	yes	RT	no	Fujinon
8	*Pohl*[84]	2009	Germany	Full text	368	236	85	yes	yes	RT	no	Fujinon
9	*Santos*[85]	2009	Brazil	Full text	75	124	33	yes	yes	RT	no	Fujinon
10	*Santos*[86]	2010	Brazil	Full text	72	82	29	yes	yes	RT	no	Fujinon
11	*Santos*[87]	2012	Brazil	Full text	65	67	28	yes	yes	RT	yes	Fujinon
12	*Teixeira*[88]	2009	Brazil	Full text	148	250	59	yes	no	RT	yes	Fujinon
13	*Togashi*[89]	2009	Japan	Full text	133	80	27	yes	both	RT	yes	Fujinon
14	*Yoshida*[90]	2011	Japan	Full text	-	114	9	yes	yes	RT	no	Fujinon

Table 3 Continued

AFI

	Author	Year	Country	Publication	Patients	Neoplasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
1	*Broek vd* [15]	2009	Netherlands	Full text	50	88	118	no	yes	RT	no	Olympus
2	*Ignjatovic* [29]	2011	UK	Full text	48	40	40	no	yes	PP	no	Olympus
3	*Kuiper* [33]	2011	Netherlands	Full text	118	116	123	no	yes	RT	no	Olympus
4	*Lin* [38]	2011	Germany	Full text	66	84	37	yes	yes	RT	no	Olympus
5	*McCallum* [91]	2008	UK	Full text	107	54	21	no	no	RT	no	Olympus
6	*Mycek* [92]	1998	USA	Full text	17	13	11	no	no	RT	no	Xillix
7	*Nakaniwa* [93]	2005	Japan	Full text	-	125	43	no	no	RT	no	Superguide
8	*Rotondano* [52]	2012	Italy	Full text	47	66	7	no	yes	RT	no	Olympus
9	*Sato* [53]	2011	Japan	Full text	183	339	85	no	yes	PP	no	Olympus
10	*Shao* [94]	2011	Singapore	Full text	96	34	164	no	no	RT	no	Olympus
11	*Uedo* [95]	2007	Japan	Full text	32	26	32	no	no	RT	no	Olympus

CLE

	Author	Year	Country	Publication	Patients	Neoplasia	Non-neoplasia	Magnification	High Definition	Evaluation	<6mm	Colonoscope
1	*Andre* [96]	2012	France	Full text	71	93	42	yes	yes	PP	no	Mauna Kea
2	*Buchner* [17]	2010	USA	Full text	-	81	38	yes	yes	PP	no	Mauna Kea
3	*Buchner* [97]	2011	USA	Full text	54	44	25	yes	yes	PP	no	Mauna Kea
4	*Gomez* [98]	2010	USA	Full text	53	50	25	yes	no	PP	no	Mauna Kea
5	*Hurlstone* [99]	2008	UK	Full text	40	55	107	yes	no	RT	no	Pentax
6	*Kiesslich* [100]	2004	Germany	Full text	42	38	96	yes	no	RT	no	Pentax
7	*DePalma* [101]	2010	Italy	Full text	20	21	11	yes	no	PP	no	Mauna Kea
8	*Sanduleanu* [102]	2010	Netherlands	Full text	72	74	42	yes	no	RT	no	Pentax
9	*Shahid* [103]	2012	USA	Full text	74	80	74	yes	yes	RT/PP	no	Pentax
10	*Singson* [104]	2012	-	Abstract	30	63	44	yes	yes	RT	no	Mauna Kea
11	*Xie* [105]	2011	China	Full text	115	66	49	yes	no	RT	no	Pentax

UK = United Kingdom, USA = United States of America, PP = post-procedure, RT = real-time

APPENDIX C Quality assessment

Table 4 Quality assessment of diagnostic accuracy studies (QUADAS) – 2 tool, for quality assessment of the included studies

NBI

Study	Risk of bias				Applicability concerns		
	Patient selection	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index test*	*Reference standard*
Broek vd [54]	Intermediate	Intermediate	Low	Low	No	Yes	No
Broek vd [16]	Yes	Low	Low	Low	No	No	No
Buchner [17]	Low	Low	Low	Low	No	No	No
Canales [18]	Intermediate	Low	Low	Low	UK	No	No
Chang [19]	High	Low	Low	Low	Yes	No	No
Chiu [20]	High	Low	Low	Low	Yes	No	No
Coe [21]	Low	Low	Low	Low	No	No	No
Dai [22]	Low	Low	Low	Low	No	No	No
East [23]	Intermediate	Low	Low	Low	UK	No	No
Gross [24]	Low	Low	Low	Low	No	No	No
Heller [25]	UK	UK	Low	Low	UK	UK	No
Henry [26]	Low	Low	Low	Low	No	No	UK
Hewett [27]	UK	Low	Low	Low	UK	No	No
Hirata [28]	High	Low	Low	Low	Yes	No	No
Ignjatovic [4]	Low	Low	Low	Low	No	No	No
Ignjatovic [29]	Low	Low	Low	Low	No	No	No
Ignjatovic [30]	High	Low	Low	Low	Yes	No	No
Kang [31]	UK	Low	Low	Low	UK	No	No
Katagiri [32]	High	Low	Low	Low	Yes	No	No
Kuiper [33]	Low	Low	Low	Low	No	No	No
Kuiper [34]	Low	Low	Low	Low	No	No	No
Ladabaum [35]	UK	Low	Low	Low	UK	No	No
Lau [36]	UK	Low	Low	Low	UK	No	No
Lee [37]	Low	Low	Low	Low	No	No	No
Lin [38]	UK	Low	Low	Low	No	No	No
Lopata [39]	UK	Low	Low	Low	No	No	No
Machida [40]	UK	Low	Low	Low	No	No	No
Occhipinti [41]	UK	Low	Low	Low	No	No	No
Oka [42]	Low	Low	Low	Low	No	No	No
Paggi [43]	Low	Low	Low	Low	No	No	No
Patel [44]	Low	Low	Low	Low	No	No	No
Pohl [45]	Low	Low	Low	Low	No	No	No
Ramirez [46]	UK	UK	Low	Low	UK	UK	No
Rastogi [47]	Low	Low	Low	Low	No	No	No
Rastogi [48]	Low	Low	Low	Low	No	No	No
Rastogi [49]	Low	Low	Low	Low	No	No	No
Rex [50]	UK	Low	Low	Low	UK	No	No

Table 4 Continued

NBI

Study	Risk of bias				Applicability concerns		
	Patient selection	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index test*	*Reference standard*
Rogart [51]	Low	Low	Low	Low	No	No	No
Rotondano [52]	Low	Intermediate	Low	Low	No	No	No
Sato [53]	UK	Low	Low	Low	UK	No	No
Sakamoto [54]	Low	Low	Low	Low	No	No	No
Sano [55]	Low	Low	Low	Low	No	No	No
Shahid [56]	Low	Low	Low	Low	No	No	No
Sikka [57]	Low	Low	Low	Low	No	No	No
Singh [58]	UK	Low	Low	Low	UK	No	No
Soto [59]	UK	Low	Low	Low	UK	No	No
Su [60]	UK	Low	Low	Low	UK	No	No
Takemura [61]	High	Low	Low	Low	Yes	No	No
Tischendorf [62]	Intermediate	Low	Low	Low	No	No	No
Tischendorf [63]	High	Low	Low	Low	Yes	No	No
Valiante [64]	Low	Low	Low	Low	No	No	No
Wada [65]	UK	Low	Low	Low	UK	No	No
Wang [66]	UK	Low	Low	Low	UK	No	No
Yague [67]	UK	Low	Low	Low	UK	No	No
Yoo [68]	UK	Low	Low	Low	UK	No	No
Zhou [69]	Low	Low	Low	Low	No	No	No

iSCAN

Study	Risk of bias				Applicability concerns		
	Patient selection	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index Test*	*Reference Standard*
Chan [70]	Low	Low	Low	Low	No	No	No
Han [71]	Intermediate	Low	Low	Low	No	No	No
Hoffman [72]	Low	Low	Low	Low	No	No	No
Hoffman [73]	Low	Low	Low	Low	No	No	No
Hoffman [74]	Low	Low	Low	Low	No	No	No
Hong [75]	Low	Low	Low	Low	No	No	No
*Hong** [75]	Low	Low	Low	Low	No	No	No
Lee [76]	Low	Low	Low	Low	No	No	No
Neumann [77]	Low	Low	Low	Low	No	No	No
Pigo [78]	Low	Low	Low	Low	No	No	No

Table 4 Continued

FICE

Study	Risk of bias				Applicability concerns		
	Patient selection	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index Test*	*Reference Standard*
Buchner [17]	Low	Low	Low	Low	No	No	No
Kang [31]	UK	Low	Low	Low	UK	No	No
Kim [79]	Low	Low	Low	Low	No	No	No
Liu [80]	Low	Low	Low	Low	No	No	No
Longcroft [81]	Low	Low	Low	Low	No	No	No
Longcroft [82]	Low	Low	Low	Low	No	No	No
Pohl [83]	Low	Low	Low	Low	No	No	No
Pohl [84]	Low	Low	Low	Low	No	No	No
Santos [85]	Low	Low	Low	Low	No	No	No
Santos [86]	Low	Low	Low	Low	No	No	No
Santos [87]	Low	Low	Low	Low	No	No	No
Teixeira [88]	Low	Low	Low	Low	No	No	No
Togashi [89]	Intermediate	Low	Low	Low	Intermediate	No	No
Yoshida [90]	Intermediate	Low	Low	Low	Intermediate	No	No

AFI

Study	Risk of bias				Applicability concerns		
	Patient selection	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index Test*	*Reference Standard*
Broek vd [15]	Intermediate	Intermediate	Low	Low	No	Yes	No
Ignjatovic [29]	High	Intermediate	Low	Low	Yes	No	No
Kuiper [33]	Low	Intermediate	Low	Low	No	No	No
Lin [38]	Low	Low	Low	Low	No	No	No
McCallum [91]	Intermediate	Low	Low	Low	Yes	No	No
Mycek [92]	High	High	Low	Low	Yes	Yes	No
Nakaniwa [93]	High	Low	Low	Low	Yes	No	No
Rotondano [52]	Low	Intermediate	Low	Low	No	No	No
Sato [53]	Intermediate	Low	Low	Low	UK	No	No
Shao [94]	High	Low	Low	Low	UK	No	No
Uedo [95]	High	Intermediate	Low	Low	Yes	UK	No

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