Systematic Review and Meta-Analysis

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Diagnosis accuracy of Raman spectroscopy in colorectal cancer

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: The clinical significance of Raman spectroscopy (RS) in colorectal cancer (CRC) patients still remains underestimated. We performed this meta-analysis to elucidate the diagnostic value in CRC patients.

Methods: We systematically searched electronic databases for published articles. Fixed effect model and random effect model were used to calculate the pooled sensitivity, specificity, diagnostic accuracy, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and positive posttest probability (PPP) of CRC. Meta-regression and subgroup analysis were conducted to assess potential source of heterogeneity. We also used Egger linear regression tests to assess risk of publication bias.

Results: Thirteen studies had been included (679 patients: 186 with premalignant lesions and 493 with malignant lesions). The pooled sensitivity, specificity, diagnostic accuracy, PLR, NLR, DOR and PPP for CRC screening using RS were 0.94 (0.92–0.96), 0.94 (0.88–0.97), 0.96 (0.94–0.98), 16.44 (7.80–34.63), 0.062 (0.043–0.090), 263.65 (99.03–701.96) and 86%, respectively.

Conclusion: RS is a potentially useful tool for future CRC screening. It also offers potentially early detection for CRC patients.

Abbreviations: AUC = area under curve, CI = confidence intervals, CRC = colorectal cancer, DOR = diagnostic odds ratio, FN = false negatives, FP = false positives, NLR = negative likelihood ratio, PLR = positive likelihood ratio, PPP = positive posttest probability, QUADAS = Quality Assessment of Diagnostic accuracy Studies guidelines, RS = Raman spectroscopy, SERS = surface enhanced Raman spectroscopy, SROC = summary receptor operation characteristic, TN = true negatives, TP = true positives.

Keywords: colorectal cancer, early detection, meta-analysis, Raman spectroscopy

Key findings

- What is already known on this subject?
- Early detection awaited for better clinical apparatus or specific molecular biomarker rather than colonoscopic biopsy would be generalizable to a wild population instead of restricted for time and money-consuming.
- What are the new findings?
- RS is a rapid, nondestructive and highly accurate diagnostic tool applied to detect colorectal cancer. It also offers potentially early detection for CRC patients.
- How might it impact on clinical practice in the foreseeable future?
- We could diagnose the colorectal cancer at early stage by using RS with a high diagnostic authenticity and reliability. SERS could also be used to monitor the therapeutic effects of CRC patients after receiving chemotherapy treatment.

Editor: Amin Talebi Bazmin Abadi.

QZ and WK contributed equally to this work.

This work was supported by the Natural Science Research Projects at Higher Institutions in Anhui Province (KJ2018ZD017).

The authors have no conflicts of interest to disclose.

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Medicine (2019) 98:34(e16940)

Received: 26 November 2018 / Received in final form: 8 May 2019 / Accepted: 31 July 2019

http://dx.doi.org/10.1097/MD.0000000000016940

1. Introduction

Historically, detecting cancer at early stage and removing adenoma is a critical measure to reduce the incidence and mortality of colorectal cancer (CRC).[1,2] However, worldwide CRC is the second most common cancer in males (9%) and the third most common cancer in females (8%) with an estimated 1.2 million new cases per year, and ranks fourth in mortality with an approximately 0.5 million deaths annually[3–5] due to the lack of efficient diagnostic tools and effective therapy. Currently, colonoscopy based on biopsy or on endoscopic tissue characterization and classification in vivo using chromoendoscopy and Kudo classifications is main auxiliary examination for colorectal lesions. Biopsy or tumor histopathology after resection is used to

screen the precancerous and cancerous lesions of colorectum as the gold standard technique with gross limitations,[6–8] which is destructive, time-consuming and depends on the visual observation of pathologists, although it is cost-effective, well-targeted and high quality.[9] It is difficult to discriminate the subtle lesions (e.g., flat adenomas) from normal mucosa. Hence, an instant, non-destructive, objective and highly accurate diagnostic tool is urgently required in clinical works to detect CRC at early and curable stage. Besides, early detection awaited for better clinical apparatus or specific molecular biomarker rather than colonoscopic biopsy would be generalizable to a wild population instead of restricted for time and money-consuming.

To address this unmet need, RS as a novel diagnostic technique, which is rapid, nondestructive and highly accurate, has been comprehensively investigated by many studies[10–14] demonstrating that could be potentially applied in clinical works. For instance, the acquisition times of Raman shift were 5 seconds in vivo.[15] In addition, a number of studies[16–19] were to develop a more valuable blood analysis based on surface enhanced Raman spectroscopy (SERS) system for fast and nondestructive detection of colorectal cancer patients, which can also surveille the treatment effects of receiving chemotherapy for long term follow up when compared with tissue samples.

Raman scattering is a kind of secondary radiation, including elastic and inelastic scattering. RS is a spectroscopic method to study molecular vibration, which relies on inelastic light scattering, and can achieve molecular chemicals fingerprint recognition. In terms of cancer detection, RS can detect tiny molecular level changes associated with cancerous lesions. By comparing the Raman spectra of cancer tissue and normal tissue, we can find the characteristic spectra which can reflect the information of tissue lesion. Therefore, RS is valuable of providing a unique spectroscopic fingerprint to differentiate the premalignant and malignant lesions from normal tissue at the level of molecular structure.[20–22] Clinicians could calculate Raman shift which transformed from colorectal tissues according to diagnostic algorithms, so that they can discriminate subtle lesions (e.g., flat adenomas that are difficult to be visually observed by using colonoscopy) from normal colorectal mucosa. Unfortunately, these studies were mono-centric, and employed different statistical analysis. Therefore, the objective of this paper was to present a meta-analysis of literatures calculating the diagnostic accuracy of RS for precancerous and cancerous lesions of CRC.

2. Materials and methods

2.1. Search strategy and selection criteria

We systematically searched electronic databases (PubMed, Web of Science, CNKI, CBM) for published studies up to June 1, 2018. Only Chinese and English studies were included. Search terms were containing "Raman spectroscope," "Raman spectroscopy," "Raman spectra," "Raman scattering," "Colon cancer," "colon carcinoma," "colon adenoma," "rectum cancer," "rectum carcinoma," "colorectal cancer," "colorectal carcinoma" combined with AND/OR.

Studies which had been recognized potentially eligible were screening through the title and abstract. Eligible full texts were analyzed afterwards. Two reviewers screened studies and analyzed eligibility of studies according to the selection criteria consisted of inclusion criteria:

1. Patients with premalignant lesions (colonic adenoma) and malignant lesions (colorectal cancer) were confirmed by histopathology.
2. RS was used or combined with other tools to diagnose CRC based on histopathology as the gold standard.
3. It contained a control group (healthy people or patients with colorectal polyps).
4. We could extract the sufficient data included true and false positives, true and false negatives (TP, FP, TN, FN) from the studies.

And the exclusion criteria are:

1. We excluded the studies after assessed for eligibility according to the result of the Quality Assessment of Diagnostic Accuracy Studies guidelines (QUADAS, the total score is less than 9 points).[23]
2. Studies not providing related data were letters and reviews. The third reviewer dealt with disagreements by discussion.

2.2. Data extraction and quality assessment

For each study, we included the first author, year of publication, nation, mean age of patients, sample type, pathological types, status of blind methods, Raman shift. We also extracted the fourfold table containing the data (TP, FP, TN, and FN). QUADAS list was used to assess the risk of bias and eligibility independently by 2 reviewers, which was verified by a third reviewer.

2.3. Statistical analysis

Statistical analysis was implemented using Stata 12.0, SPSS 17.0 and Meta-Disc 1.4, considering significant the $P < .05$. Continuous data was performed as mean. We assessed the heterogeneity as follows. First, fixed effect model[24] was used to assume that all studies have identical common effect by calculating Cochran Q test and I^2 index. Second, random effect model[25] was applied to assume that studies were random samples of hypothetical populations that were different from each other, in case of high between-study heterogeneity. We defined high heterogeneity as I^2 index value $> 50\%$ and a Q test P value $< .10$.[26] Finally, to explore potential source of heterogeneity, meta-regression and subgroup analysis were planned. Furthermore, the Spearman correlation coefficient was computed to explore the threshold effect.[27] Moreover, we used Egger linear regression tests to assess risk of publication bias with $P < .05$ for the coefficient slopes implying significantly asymmetry.[28]

From each collected or reconstructed fourfold table, we calculated estimated sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and positive posttest probability (PPP). The pretest probability of CRC is prevalence rate among special population in our study, which could be calculated or estimated.[29] Moreover, sensitivity, specificity and 95% CIs of each study for detecting premalignant and malignant lesions of colorectum were performed using forest plot. Additionally, summary sensitivity, specificity and diagnostic accuracy were assessed through calculating area under curve (AUC) of summary receptor operation characteristic (SROC) in order to avoiding heterogeneity from diagnostic threshold effect in our study.

2.4. Ethical review

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

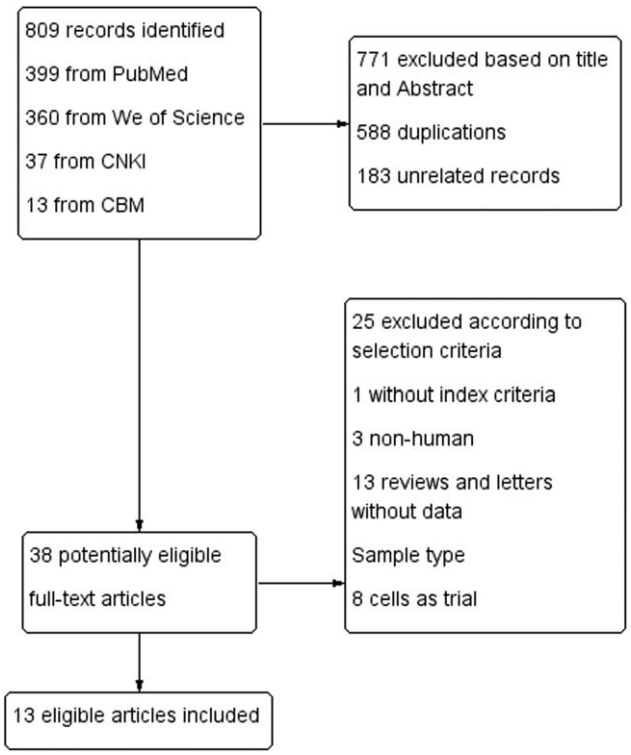

Figure 1. Study selection.

3. Results

3.1. Study identification and characteristics

During the literature search (Fig. 1), the initial 809 records were found, in which 588 duplications and 183 unrelated records were excluded based on reading tile and abstract. Then, we identified 38 potentially eligible full-text articles according to selection criteria. However, twenty-five articles were not eligible as they were not using index test, nonhuman studies and review articles. Ultimately, we included thirteen eligible studies.[16–19,30–38]

Detailed characteristics of included studies were showed in Table 1. All included studies fulfilled selection criteria and were published in English. There were a total of 679 patients (186 with premalignant lesions, 493 with malignant lesions). More than half of the included studies were from Asia. Partial least squares discriminant analysis (PLS-DA), principle component analysis integrated with linear discriminant analysis (PCA-LDA) and Cross-validation techniques were the common diagnostic algorithm used to analyze Raman shift among included studies. Only 3 studies were used blind methods, while the rest were unclear (Table 2). We defined blind methods as the investigators analyzing Raman spectrum without knowledge of the pathological results.[39] Raman shift is 800 to 1800 cm^{-1} in all included studies.

3.2. Risk of bias

The findings of study quality assessment according to the QUADAS composed of 14 items, which are used to assess eligibility of included studies, are shown in Table 2. All included studies were deserved high quality (total scores are equal to or greater than 9 points). In terms of publication bias, the Deeks' funnel plot asymmetry test demonstrated that there was statistically significant (bias = −39.96, $P = .037$), which was reported in Figure 2.

3.3. Meta-analysis findings

We used random effect model to estimate sensitivity, specificity, PLR, NLR and DOR for CRC screening using RS, which were 0.94 (0.92–0.96), 0.94 (0.88–0.97), 16.44 (7.80–34.63), 0.062 (0.043–0.090) and 263.65 (99.03–701.96), respectively, because of high heterogeneity ($P = .00$, $I^2 = 90.95\%$ in specificity) (Fig. 3). AUC of SROC was used to calculated summary diagnostic accuracy, which is 0.96 (0.94–0.98) (Fig. 4). The pretest probability of CRC was estimated as 27% among patients with CRC in our meta-analysis, and the corresponding PPP was 86% (Fig. 5).

Table 1

Study characteristics.

Reference	Year	Nation	Age	N_1 679	N_2 186	N_3 493	Sample type	Diagnostic algorithm
Molckovsky[30]	2003	Canada	NR	44	44	0	tissue	PCA-LDA,#
WIDJAJA[31]	2008	Singapore	NR	59	0	59	tissue	PCA,SVM,#
Lopes[32]	2011	Portugal	NR	11	0	11	tissue	LDA, #
Chen[18]	2012	China	57.4	55	0	55	serum	LDA
Ashok[33]	2013	UK	NR	36	0	36	tissue	SVM, #
Short[34]	2013	Canada	NR	18	0	18	tissue	LDA, #
Wood[35]	2014	UK	NR	156	92	64	tissue	PCA-LDA,#
Wang[19]	2014	China	55.7	103	0	103	serum	PLS
Li[36]	2014	China	58.4	44	0	44	tissue	ACO-SVM, PCA-LDA,#
Bergholt[37]	2015a	Singapore	NR	50	0	50	tissue	PLS-DA,#
Bergholt[38]	2015b	Singapore	52	50	50	0	tissue	PLS-DA, #
Li[17]	2015	China	54	15	0	15	serum	PCA-LDA,#
Lin[16]	2016	China	55	38	0	38	serum	PCA-LDA

= cross-validation technique, ACO-SVM = ant colony optimization integrated with support vector machine, LDA = linear discriminant analysis, LS-SVM = least square integrated with support vector machine, N_1 = total number of patients, N_2 = number of patients with premalignancy, N_3 = number of patients with malignancy, NR = no report, PCA = principal component analysis, PCA-LDA = principle component analysis integrated with linear discriminant analysis, PLS-DA = partial least squares discriminant analysis, SVM = support vector machine.

Table 2

Study quality assessment.

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Molckovsky[30]	Y	N	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	N	9
WIDJAJA[31]	Y	N	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	N	10
Lopes[32]	Y	Y	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	N	10
Chen[18]	Y	N	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	Y	10
Ashok[33]	Y	N	Y	U	Y	Y	Y	Y	Y	U	U	Y	Y	N	9
Short[34]	Y	N	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	N	10
Wood[35]	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	11
Wang[19]	Y	N	Y	N	Y	Y	Y	Y	Y	U	U	Y	Y	N	9
Li[36]	Y	N	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	N	10
Bergholt[37]	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	12
Bergholt[38]	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	12
Li[17]	Y	N	Y	N	Y	Y	Y	Y	Y	Y	U	Y	Y	N	10
Lin[16]	Y	N	Y	Y	Y	Y	Y	Y	Y	U	U	Y	Y	N	10

Y = yes, N = no, U = unclear, 1 = Was the spectrum of patients representative? 2 = Was selection criteria detailedly introduced? 3 = Was reference standard reliable? 4 = Was the time interval between RS and histopathology short enough to finish the detection? 5 = Did all the samples or a random sample receive verification? 6 = Were patients detected by the same reference standard? 7 = Were the detection between reference standard and index text independent? 8 = Was the execution of RS described clearly? 9 = Was the execution of histopathology described clearly? 10 = Did the interpretation of RS blind from histopathology? 11 = Did the interpretation of histopathology blind from RS? 12 = Was the same clinical data available in the replicated test? 13 = Were uninterruptable outcomes of test existed? 14 = Were the explanation of withdrawals from the study reported?

3.4. Exploring heterogeneity

We applied a meta-regression to explore potential between-study heterogeneity. Year of publication [(2007–2013) or (2014–2016)], region (Asia or others), sample type (tissue or serum), type of RS [near-infrared Raman spectroscopy (NIRS) and high frequency Raman spectroscopy (HFRS), or others], diagnostic algorithms [(PLS-DA and PCA-LDA) or others], were considered as covariates. After meta-regression analyzing, we found all *P* value were greater than .05 showed in Table 3, which means none of these covariates were source of between-study heterogeneity.

Moreover, we conducted subgroup analysis by considering these covariates as confounding factors. The results of subgroup analysis were performed in Table 4. Additionally, there was no statistically significant about diagnostic threshold effect (Spearman correlation coefficient = −0.26, *P* = .45).

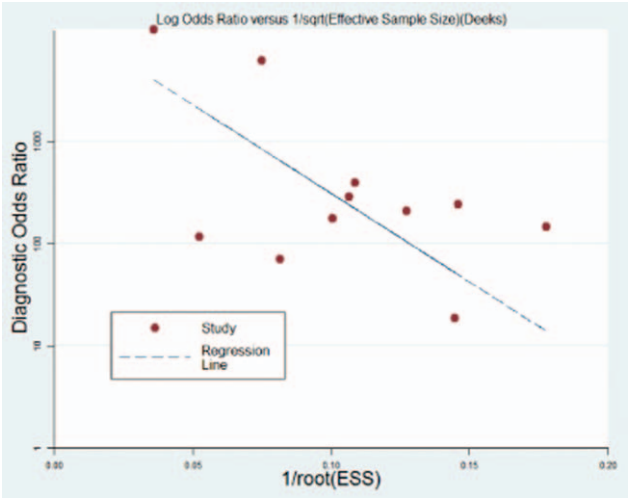

Figure 2. Linear regression test of funnel plot asymmetry demonstrated statistically significant (bias = −39.96, *P* = .037).

4. Discussion

Colorectal cancer remains a significant threat to human health because of the lack of awareness of physical examination or the limitations of early diagnostic level. Although colonoscopy biopsy is currently the primary method for the early diagnosis of colorectal cancer, which requires a high level of the operator and pathologist, biopsy is difficult to detect subtle lesions and carries risk of visceral perforation. In order to overcome the problem, more and more studies focus on the tumor biomarkers and clinical instruments. Raman spectroscopy as a new technique for cancer detection is easy to implement, no special staining or preparation.[40] Besides, RS which is characterized by rapidity, molecular specificity and high accuracy, has attracted the attention of more and more researchers.[41–43]

The purpose of this study was to illustrate the diagnostic accuracy of Raman spectroscopy in colorectal cancer. Avoiding diagnostic threshold effect and high between-study heterogeneity, random effect model was conducted to pooled effect index, and fixed effect model was used to recalculate the data that have heterogeneity for verifying stability of result in this meta-analysis. The pooled sensitivity and specificity were 0.94 (0.91–0.96) and 0.94 (0.86–0.97), respectively. It indicated that 94% of people were identified correctly among patients with CRC and 94% of people were diagnosed without CRC among healthy people, respectively. Therefore, RS could be considered to have high sensitivity and specificity. AUC was 0.96 (0.94–0.98). SROC curve can be described, which can be used to assess summary diagnostic accuracy, based on the weight of several diagnostic odds ratios meta-analyzed multiple different trails that researched one diagnostic index. When the AUC is closer to 1.00, the better diagnostic authenticity is reliable.[44] Therefore, all these 3 parameters implied that RS could discriminate colorectal cancer form normal tissues with a high diagnostic accuracy. The pooled DOR value that ranges from 0 to infinity with a higher value implying better differentiating effect,[45] was 263.65 (99.03–701.96) in this study. However, DOR probably is conducted as a single pooled measurement with the caveat that some DOR is possibly calculated by several different combinations of sensitivity and specificity, which could reduce the

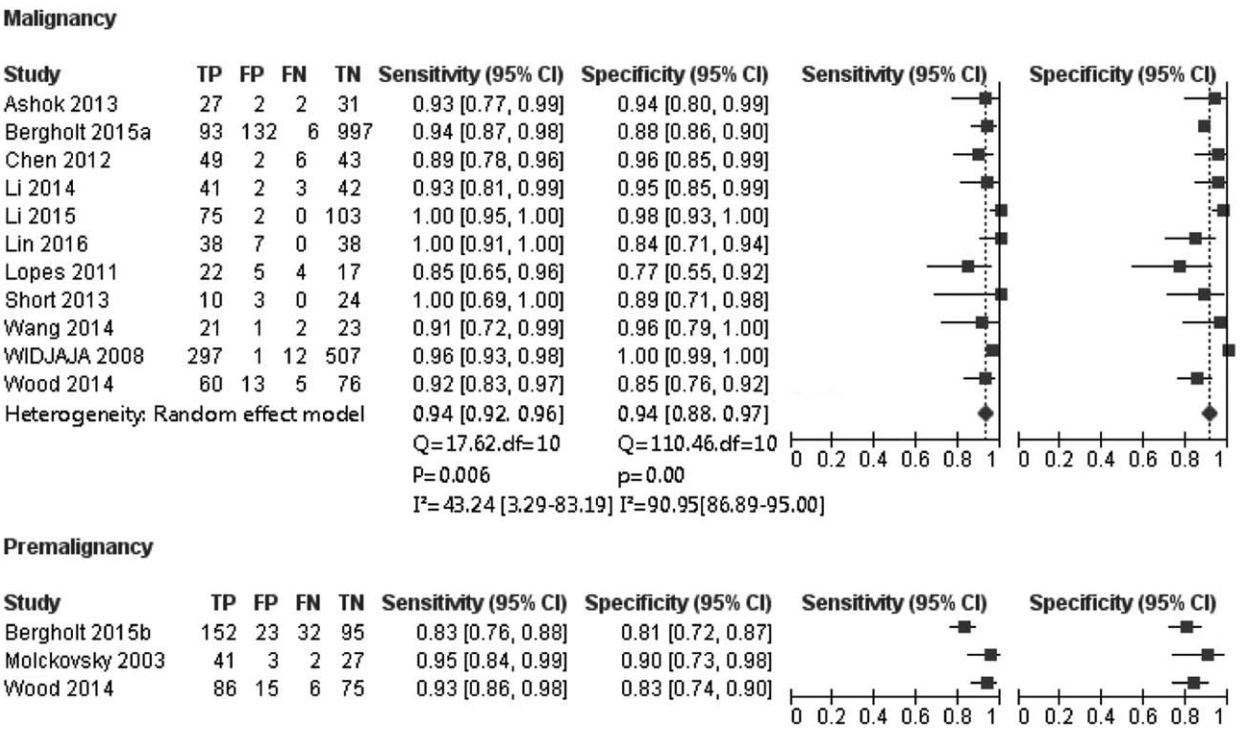

Figure 3. Forest plot for detecting colorectal cancer at premalignant and malignant stage.

authenticity of final results.[46] By contrast, likelihood ratio and posttest probability were more likely used in clinical decision-making. When PLR is greater than 10, we consider it has value of confirmed diagnosis of disease. While NLR is less than 0.10, it has value of negative test results.[47] Furthermore, patients with 27% pretest probability, was corresponding 86% posttest probability. It demonstrated that patients with probability of CRC were increased from 27% to 86% through utilizing Raman spectroscopy system. Taken together, these data suggested that RS was very authentic and reliable in the diagnosis of colorectal cancer.

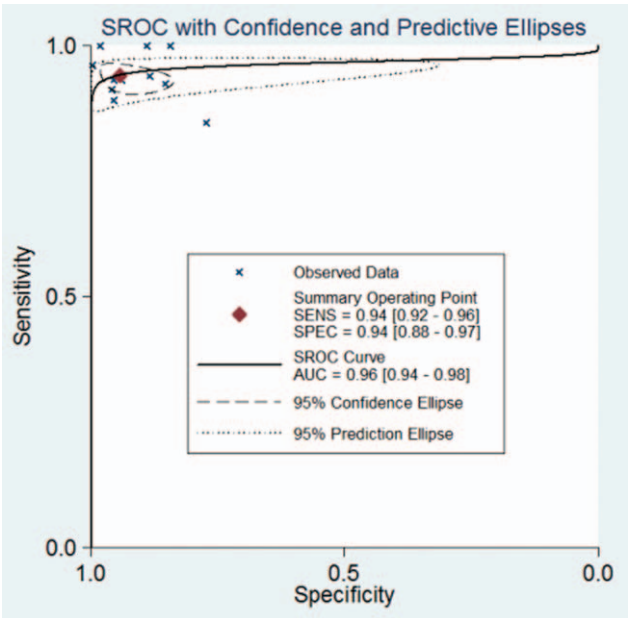

Figure 4. Summary receiver operating characteristic (SROC) plot of RS imaging was used to predict colorectal cancer based on combination of sensitivity and specificity weighted for sample size of each data.

Based on the results of this study, we could foresee the future developments in RS of colorectal cancer.

1. RS could be used wildly in clinical practice rather than tentative research.
2. We could diagnose the colorectal cancer at early stage by using RS with a high diagnostic authenticity and reliability.
3. RS could be applied to determine the range of resection in colorectal cancer operation.
4. SERS might also be used to monitor the therapeutic effects of CRC patients after receiving chemotherapy treatment.

However, there are several limitations. First, the research has not been registered and there may be some bias, but we still follow the steps of systematic reviews strictly. Second, failure to publish negative results of studies is a common phenomenon and only published studies are included in our meta-analysis which is likely to overestimate summary diagnostic accuracy. Third, all included studies were published in English. Thus, language bias cannot be thoroughly avoided. In order to reduce the risk of publication bias, we systematically searched electronic databases by using self-made search strategy. Finally, the Deeks' funnel plot asymmetry test showed that there was statistically significant of publication bias. Considering high heterogeneity existed in our study, we used meta-regression and subgroup analysis (using the following covariates: region, the year of publication, sample type, the type of RS, diagnostic algorithms) to explore potential sources of between-study heterogeneity which may not be measured because of insufficient information and merit further

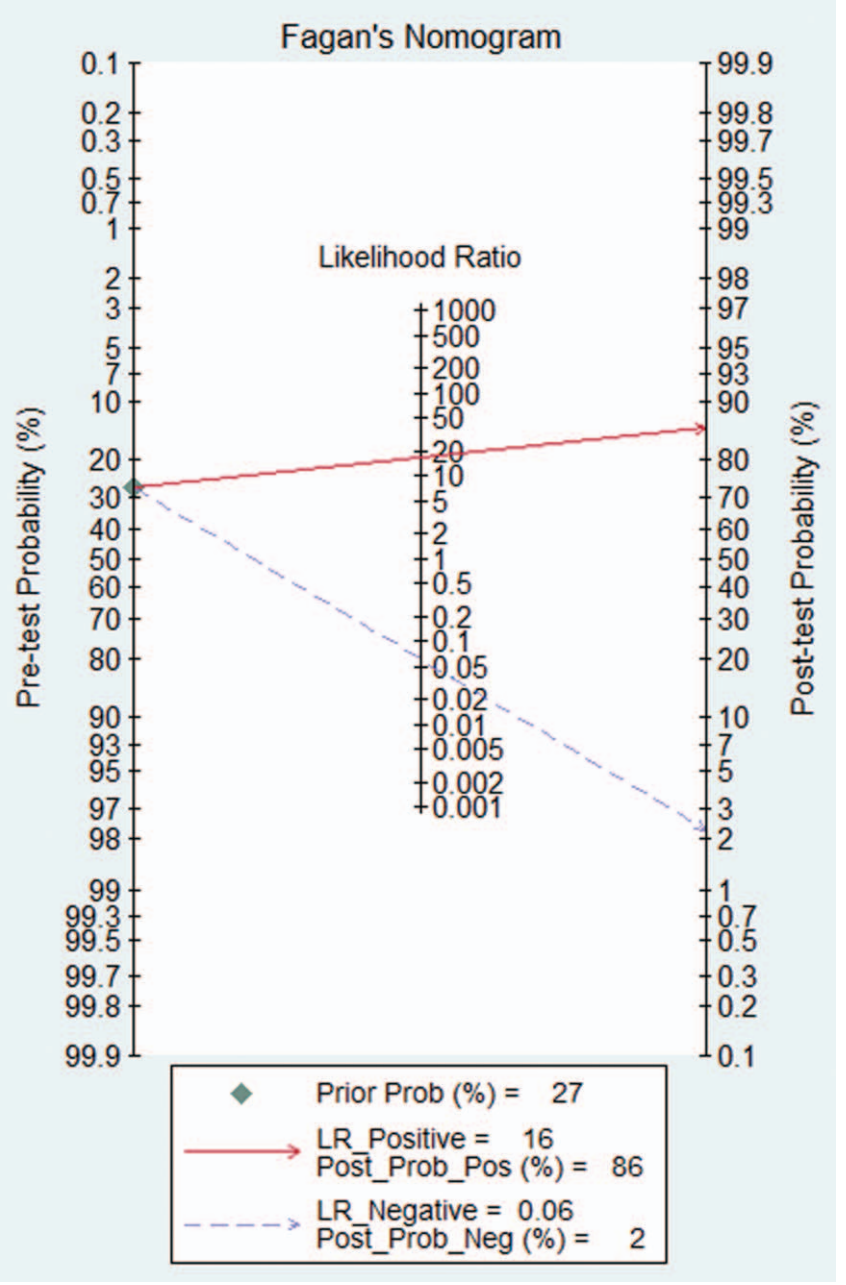

Figure 5. Posttest probability of RS for detecting CRC

investigation. In terms of diagnostic threshold effect, SROC curve was conducted to control influence of heterogeneity. As for early detection of CRC by using RS, there are only 3 included studies which were focused on differentiating colorectal adenomas from normal or polyps tissues with a sensitivity of 83%, 93%, and 95%, respectively.[30,38,35] Nonetheless, multicenter studies on premalignant lesions of colorectum are still needed to improve the diagnostic authenticity and reliability.

Table 3

Results of meta-regression.

Covariate	Coefficient	SD	*P* value	DOR	95%CI
Year	−1.64	2.56	.56	0.19	(0.00–248.24)
Nation	1.52	4.02	.72	4.59	(0.00–323477.97)
DA	−3.16	3.30	.39	0.04	(0.00–411.07)
ST	3.88	4.23	.41	48.58	(0.00–6176260.90)
RS	−2.16	2.90	.50	0.12	(0.00–367.12)

DA = diagnostic algorithms, DOR = diagnostic odds ratio, RS = the type of Raman spectroscopy, SD = standard deviation, ST = simple type.

Table 4

Results of subgroup analysis.

Factors	Pooled sensitivity (95% CI)	*P* value	Pooled specificity (95% CI)	*P* value
Overall studies	0.94 (0.88–0.97)	–	0.94 (0.92–0.96)	–
Year of pub.		.44		.053
2007–2013	0.95 (0.92–0.97)		0.89 (0.88–0.91)	
2014–2016	0.95 (0.92–0.97)		0.97 (0.96–0.98)	
Region		.55		.13
Asia	0.96 (0.94–0.97)		0.92 (0.91–0.93)	
Others	0.92 (0.85–0.96)		0.87 (0.81–0.91)	
DA		.24		.66
PLS-DA and PCA-LDA	0.96 (0.93–0.98)		0.890 (0.87–0.91)	
Others	0.94 (0.92–0.96)		0.98 (0.97–0.99)	
Sample type		.63		.41
Tissue	0.95 (0.92–0.96)		0.92 (0.90–0.93)	
Serum	0.96 (0.92–0.98)		0.95 (0.91–0.97)	
RS		.29		.49
NIRS and HFRS	0.96 (0.93–0.97)		0.92 (0.91–0.93)	
Others	0.94 (0.91–0.96)		0.91 (0.88–0.94)	

CI = confidence interval, DA = diagnostic algorithms, DOR = diagnostic odds ratio, HFRS = high frequency Raman spectroscopy, NIRS = near-infrared Rama spectroscopy, PCA-LDA = principle component analysis integrated with linear discriminant analysis, PS-DA = partial least squares discriminant analysis, RS = the type of Raman spectroscopy, SD = standard deviation, ST = simple type,

5. Conclusion

In conclusion, RS is a potentially useful tool for future CRC screening applied to help clinicians make decisions instantly, objectively, and unambiguously. It also offers potentially early detection for CRC, which might have a significant impact on reducing the incidence and improving the survival rates of colorectal cancer.

Acknowledgments

Thanks for the authors of all included studies. .

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Writing – original draft: Qiang Zheng.
Writing – review & editing: Weibiao Kang, Changjun Yu.

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