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), 0.96 (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 colonooscopic 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.

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).	extsuperscript{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 textsuperscript{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, which is destructive, time-consuming and depends on the visual observation of pathologists, although it is cost-effective, well-targeted and high quality. 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 colonscopic 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 demonstrating that could be potentially applied in clinical works. For instance, the acquisition times of Raman shift were 5 seconds in vivo. In addition, a number of studies 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. 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 colonscopy) 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 spectroscopy," "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).
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, 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 was used to assume that all studies have identical common effect by calculating Cochran Q test and I² index. Second, random effect model 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 I² index value > 50% and a Q test P value < .10. 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. Moreover, we used Egger linear regression tests to assess risk of publication bias with P < .05 for the coefficient slopes implying significantly asymmetry.

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. 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.
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 title 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.\[19\] R a m a n s h i f t 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).

![Figure 1. Study selection.](image)

| Reference    | Year | Nation   | Age   | \(N_1\) | \(N_2\) | \(N_3\) | 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\[36\]    | 2014 | China    | 55.7  | 103    | 0      | 103    | serum      | PLS                |
| L\[36\]      | 2014 | China    | 58.4  | 44     | 0      | 44     | tissue     | LDA                |
| Bergho\[37\]  | 2015a| Singapore| NR    | 50     | 0      | 50     | tissue     | PCA-LDA            |
| Bergho\[38\]  | 2015b| Singapore| NR    | 50     | 0      | 50     | tissue     | PCA-LDA,          |
| L\[17\]      | 2015 | China    | 54    | 15     | 0      | 15     | serum      | PCA-LDA,          |
| L\[17\]      | 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.
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 = \( -0.26, P = .45 \)).

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. Besides, RS which is characterized by rapidity, molecular specificity and high accuracy, has attracted the attention of more and more researchers.

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). ROC 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. 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 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...
authenticity of final results.\textsuperscript{[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.\textsuperscript{[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.

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 investigation.
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. Nonetheless, multicenter studies on premalignant lesions of colorectum are still needed to improve the diagnostic authenticity and reliability.

Figure 5. Posttest probability of RS for detecting CRC

| 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.
| 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) | 0.94 (0.92–0.96) | 0.94 (0.92–0.96) |
| Year of pub.            | 0.95 (0.92–0.97)           | 0.95 (0.96–0.98) | 0.95 (0.96–0.98) | 0.96 (0.93–0.97) |
| 2007–2013               |                           | 0.95 (0.92–0.97) | 0.95 (0.96–0.98) | 0.96 (0.93–0.97) |
| 2014–2016               |                           | 0.95 (0.92–0.97) | 0.95 (0.96–0.98) | 0.96 (0.93–0.97) |
| Region                  |                           | 0.96 (0.94–0.97) | 0.96 (0.94–0.97) | 0.96 (0.94–0.97) |
| Asia                    | 0.96 (0.94–0.97)           | 0.96 (0.94–0.97) | 0.96 (0.94–0.97) | 0.96 (0.94–0.97) |
| DA                      |                           | 0.97 (0.96–0.98) | 0.97 (0.96–0.98) | 0.97 (0.96–0.98) |
| PLS-DA and PCA-LDA      |                           | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) |
| Others                  |                           | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) | 0.98 (0.97–0.99) |
| Sample type             |                           | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) |
| Tissue                  |                           | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) |
| Serum                   |                           | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) |
| RS                      |                           | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) |
| NIRS and HFRS           |                           | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) |
| Others                  |                           | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) | 0.99 (0.99–1.00) |

CI = confidence interval, DA = diagnostic algorithms, DOR = diagnostic odds ratio, HFRS = high frequency Raman spectroscopy, NIRS = near-infrared Raman spectroscopy, PCA-LDA = principle component analysis integrated with linear discriminant analysis, PLS-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.

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