Study Protocol Systematic Review

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Diagnostic accuracy of endoscopic ultrasound, computed tomography, magnetic resonance imaging, and endorectal ultrasonography for detecting lymph node involvement in patients with rectal cancer

A protocol for an overview of systematic reviews

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Abstract

Background: Rectal cancer is one of the most common tumors and is the leading cause of cancer-related deaths in developed countries. Lymph node involvement remains the strongest prognostic factor associated with a worse prognosis in patients with rectal cancer. Several systematic reviews have investigated the accuracy of endoscopic ultrasound, computed tomography, magnetic resonance imaging, and endorectal ultrasonography for lymph node involvement of rectal cancer and compared the diagnostic accuracy of different imaging techniques, but there are considerable differences in conclusions. This study aims to assess the methodological quality and reporting quality of systematic reviews and to determine which diagnostic imaging techniques is the optimal modality for the diagnosis of lymph node involvement in patients with rectal cancer.

Methods: We will search PubMed, EMBASE, Cochrane Library, and Chinese Biomedicine Literature to identify relevant studies from inception to June 2018. We will include systematic reviews that evaluated the accuracy of diagnostic imaging techniques for lymph node involvement. The methodological quality will be assessed using AMASAR checklist, and the reporting quality will be assessed using PRISMA-DTA checklist. The pairwise meta-analysis and indirect comparisons will be performed using STATA V.12.0.

Results: The results of this overview will be submitted to a peer-reviewed journal for publication.

Conclusion: This overview will provide comprehensive evidence of different diagnostic imaging techniques for detecting lymph node involvement in patients with rectal cancer.

Ethics and dissemination: Ethics approval and patient consent are not required as this study is an overview based on published systematic reviews.

PROSPERO registration number: CRD42018104906.

Abbreviations: CI = confidence interval, CT = computed tomography, DOR = diagnostic odds ratio, ERUS = endorectal ultrasonography, EUS = Endoscopic ultrasound, MRI = magnetic resonance imaging, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

Keywords: computed tomography, diagnostic test, endorectal ultrasonography, endoscopic ultrasound, lymph node involvement, magnetic resonance imaging, overview, rectal cancer

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1. Introduction

Colorectal cancer is nowadays the third most common cancer in men and the second in women worldwide, accounting for 9% of new cancer cases and 9% of cancer-specific deaths.[1,2] Approximately 1 in 3 of these tumors are rectal cancers.[3] In the USA, rectal cancer is a major cause of mortality, and there were an estimated 39,220 new cases in 2016.[4] Risk factors for rectal cancer include familial polyposis syndromes (FAP, HNPCC), history of adenomatous polyps, diabetes mellitus, obesity, excessive alcohol, and cigarette smoking.[5–10] Because of the diffusion of screening programs, the incidence of this malignancy has gradually increased.[11,12]

As in most solid malignancies, lymph node involvement remains the strongest prognostic factor associated with a worse prognosis in patients with rectal cancer.[13,14] However, the prognosis of rectal cancer patients depends on the disease stage at the time of diagnosis; thus, accurate disease evaluation is necessary to properly treat rectal cancer.[15–17] Nowadays, treatment of rectal cancer with different locations and stages mainly includes transanal endoscopic microsurgery, anterior resection with total mesorectal excision, abdominoperineal resection, and neoadjuvant chemotherapy and radiotherapy.[2,18,19] Accurate preoperative assessment of lymph node involvement is essential for selecting patients to receive optimal treatment.[2,20]

Various modalities, endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), and endorectal ultrasonography (ERUS), for instance, have been used to assess the lymph node status. EUS is particularly effective for assessing the depth of tumor invasion into the rectal wall.[21] CT is a sensitive method for diagnosis of abdominal and pelvic diseases. It is used frequently to determine the stage of cancer and to follow progress.[14] MRI allows for comprehensive evaluation of disease stage including tumor infiltration degree, a precise assessment of the neoplasia distance by mesorectal fascia (circumferential margin) and an effective assessment of lymph nodes involvement and mesorectal infiltration.[22,23] ERUS is considered to be most accurate for small tumors (tumor stages 1 and 2).[24]

Recently, some meta-analysis has investigated the accuracy of EUS, CT, MRI, and ERUS for lymph node involvement of rectal cancer and compared the diagnostic accuracy of different imaging techniques,[3,25–27] but there are considerable differences in conclusions. Therefore, it is of great significance to re-evaluate these systematic reviews. The objectives of this overview are to assess the methodological quality and reporting quality of systematic reviews that evaluated the diagnostic value of index tests for lymph node involvement in patients with rectal cancer and to compare the diagnostic value of different diagnostic imaging techniques for lymph node involvement by reanalyzing the results of meta-analysis.

2. Methods

2.1. Design and registration

We will conduct an overview of systematic reviews of diagnostic test accuracy. The protocol is registered in PROSPERO (CRD42018104906). We will follow the Preferred Reporting Items for Systematic Reviews and Meta-analysis[28] statements for reporting our overview.

2.2. Eligibility criteria

2.2.1. Type of study. Systematic reviews will meet the following criteria: diagnostic imaging techniques include EUS, CT, MRI, and ERUS or combinations; evaluate the diagnostic value of index tests for lymph node involvement in patients with rectal cancer. Systematic reviews for patients with colorectal cancer will be excluded.

2.2.2. Patients. We will include rectal cancer patients with lymph node involvement regardless of treatment. No limitations will be imposed on age, sex, or nationality.

2.2.3. Interventions. We will regard EUS, CT, MRI, or ERUS as index tests because these tests are usually used to predict lymph node involvement in patients with rectal cancer. In addition, other index tests for detecting lymph node involvement are also included.

2.2.4. Outcomes. The primary outcomes are sensitivity (SEN), specificity (SPE), positive predictive value, negative predictive value, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), area under the curve, and their respective 95% confidence intervals (CIs). The second outcomes are methodological quality score and reporting quality score.

2.3. Data sources

We will search PubMed, EMBASE, Cochrane Library, and Chinese Biomedicine Literature to identify relevant studies from inception to June 2018. Publication languages will be restricted to English and Chinese. In addition, we will check reference lists of included studies for additional references.

2.4. Search strategy

We will use search terms related to rectal neoplasm, SEN, SPE, receiver operating characteristic, meta-analysis, and systematic review. Search strategy of PubMed was as follows:

#1 "Rectal Neoplasms"[Mesh]
#2 "rect* neoplasm*"[Title/Abstract] OR "rect* canc*"[Title/Abstract] OR "rect* carcinom*"[Title/Abstract] OR "rect* adenocarc*"[Title/Abstract] OR "rect* tumor*"[Title/Abstract] OR "rect* tumour*"[Title/Abstract] OR "rect* sarcom*"[Title/Abstract]
#3 #1 OR #2
#4 "Sensitivity AND Specificity"[Mesh] OR "False Positive Reactions"[Mesh] OR "False Negative Reactions"[Mesh] OR "ROC Curve"[Mesh] OR "Predictive Value of Tests"[Mesh]
#5 sensitivity[Title/Abstract] OR specificity[Title/Abstract] OR receiver operating characteristic[Title/Abstract] OR receiver operator characteristic[Title/Abstract] OR predictive value*[Title/Abstract] OR roc[Title/Abstract] OR pre-test odds[Title/Abstract] OR pretest odds[Title/Abstract] OR pre-test probability*[Title/Abstract] OR pretest probability*[Title/Abstract] OR post-test odds[Title/Abstract] OR posttest odds[Title/Abstract] OR post test probabilit*[Title/Abstract] OR posttest probabilit* [Title/Abstract] OR likelihood ratio*[Title/Abstract] OR positive predictive value*[Title/Abstract] OR negative predictive value*[Title/Abstract] OR false negative*[Title/Abstract] OR false positive*[Title Abstract] OR true negative*[Title/Abstract] OR true positive*[Title/Abstract] OR fn[Title/Abstract] OR fp[Title/Abstract] OR tn[Title/Abstract] OR tp[Title/Abstract]
#6 #4 OR #5
#7 "Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh]

#8 Meta-Analysis[Title/Abstract] OR Meta-Analyses[Title/Abstract] OR Meta Analysis[Title/Abstract] OR Meta Analyses [Title/Abstract] OR gathering analysis[Title/Abstract]
#9 "Network Meta-Analysis"[Mesh]
#10 Network Meta-Analyses[Title/Abstract] OR Network Meta Analysis[Title/Abstract] OR Network Meta Analyses[Title/Abstract] OR Mixed Treatment Meta-Analysis[Title/Abstract] OR Mixed Treatment Meta-Analyses[Title/Abstract] OR Multiple Treatment Comparison Meta-Analysis[Title/Abstract] OR Multiple Treatment Comparison Meta Analysis[Title/Abstract]
#11 Systematic evaluation[Title/Abstract] OR Systematic assessment[Title/Abstract] OR Systematic review[Title/Abstract] OR Systematic reviews[Title/Abstract] OR System evaluation[Title/Abstract] OR System Assessment[Title/Abstract] OR Systemic review[Title/Abstract] OR Systemic reviews[Title/Abstract]
#12 #7 OR #8 OR #9 OR #10 OR #11
#13 #3 AND #6 AND #12

2.5. Study selection and data extraction

Literature search records will be imported into ENDNOTE X7 literature management software. Two independent reviewers will screen out possibly relevant studies independently based on the title and abstract. Then, the same 2 reviewers will retrieve the full text of all possibly relevant studies to screen out the studies that meet the inclusion criteria. We will extract study characteristics from systematic reviews including the following items: author name, year of publication, country of first author, number of author, journal name, country of journal, funding, disease, number and name of index test, number and name of reference test, outcomes; methodological characteristics of systematic reviews such as types of included studies, number of included studies, samples, number and name of databases retrieved, supplemental literature search; and results of statistical analysis including SEN, SPE, likelihood ratio, predictive value, DOR, and area under curve. Disagreements will be resolved by consensus or by discussion with a third reviewer.

2.6. Quality assessment

We will assess the methodological quality of included systematic reviews using the Assessment of Multiple Systematic Reviews checklist. This checklist includes 11 items with scores ranging from 0 to 11.0. Based on previous overviews, we will consider studies with a score between 0 and 4.0 to be of low quality, 5.0 and 8.0 to be of moderate quality, and 9.0 and 11.0 to be of high quality.[29,30]

The reporting quality of included systematic reviews will be assessed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis diagnostic test accuracy (PRISMA-DTA) checklist. The PRISMA-DTA statement is an expanded checklist of original PRISMA, which aims to improve the completeness and transparency of reporting of systematic reviews of diagnostic test accuracy studies.[31] This checklist consists of 27 items. The maximum score on the PRISMA-DTA is 27. The review will be considered to have major flaws if it receives a total score of $\leq$15.0, minor flaws if it receives a total score of 15.5 to 21.0, and minimal flaws if it receives a total score 21.5 to 27.0.[32] The quality assessment of the included systematic reviews will be performed independently by the 2 authors and the differences will be resolved through discussion to reach a consensus.

2.7. Statistical analysis

2.7.1. Pairwise meta-analysis. We will perform pairwise meta-analysis with the data of pooled SEN, SPE, DOR, PLR, NLR, and their 95% CI lower limit, 95% CI upper limit using bivariate mixed-effects regression modeling with STATA V.12.0 (Stata). The between-study variance will be calculated var logitSEN and logitSPE.[33,34] The proportion of heterogeneity due to the threshold effect among the included studies will be calculated by the squared correlation coefficient estimated from the between-study covariance variable in the bivariate model.[35] The heterogeneity between each study will be estimated using the Q value and the inconsistency index (I^2) test, and the values of 25%, 50%, and 75% for the I^2 will be indicative of low, moderate, and high statistical heterogeneity, respectively.[36]

2.7.2. Indirect comparisons between competing diagnostic tests. We will calculate relative diagnostic outcomes between index tests including relative SEN, relative SPE, relative DOR, relative PLR, and relative NLR. Then, we will conduct indirect comparisons using the relative diagnostic outcomes. All analysis will be performed using Stata software (version 12.0).

2.7.3. Assessment of reporting bias. If there are 10 or more studies in the network meta-analysis, we will use the funnel plot to evaluate the potential publication bias.[37]

2.7.4. Subgroup analysis. Subgroup analysis will be conducted according to the difference of time period of index tests, treatment of rectal cancer, MRI field strength, types of EUS, and CT if the necessary data are available.

3. Discussion

It is not uncommon to have several systematic reviews under the same topic published evaluating the same interventions, yet without consistent conclusions.[38] However, no overviews summarize evidence for systematic reviews of the diagnostic test for patients with rectal cancer. According to our knowledge, this will be the first overview to assess the methodological quality using AMASAR checklist and the reporting quality using PRISMA-DTA checklist of systematic reviews evaluating the diagnostic value of index tests for lymph node involvement in patients with rectal cancer. Moreover, we will perform indirect comparisons between different diagnostic imaging techniques, which can clearly show the differences between different modalities. We hope that the results of this overview will help clinicians and patients to select an appropriate diagnostic test for rectal cancer.

Author contributions

XW, YG, and JW planed and designed the research. JL, JW, and BW tested the feasibility of the study. JT, MS, and JW provided methodological advice, polished, and revised the manuscript. XW and YG wrote the manuscript. All authors approved the final version of the manuscript.

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