

World Journal of *Gastrointestinal Surgery*

World J Gastrointest Surg 2023 December 27; 15(12): 2674-2961



Contents

Monthly Volume 15 Number 12 December 27, 2023

REVIEW

- 2674 Antimicrobial approach of abdominal post-surgical infections
Fiore M, Corrente A, Di Franco S, Alfieri A, Pace MC, Martora F, Petrou S, Mauriello C, Leone S

MINIREVIEWS

- 2693 Indocyanine green fluorescence in gastrointestinal surgery: Appraisal of current evidence
Kalayarasan R, Chandrasekar M, Sai Krishna P, Shanmugam D
- 2709 Post-cholecystectomy iatrogenic bile duct injuries: Emerging role for endoscopic management
Emara MH, Ahmed MH, Radwan MI, Emara EH, Basheer M, Ali A, Elfert AA

ORIGINAL ARTICLE

Case Control Study

- 2719 Multidisciplinary diagnosis and treatment nutritional support intervention for gastrointestinal tumor radiotherapy: Impact on nutrition and quality of life
Hui L, Zhang YY, Hu XD

Retrospective Cohort Study

- 2727 Association between the early high level of serum tacrolimus and recurrence of hepatocellular carcinoma in ABO-incompatible liver transplantation
Han JW, Choi JY, Jung ES, Kim JH, Cho HS, Yoo JS, Sung PS, Jang JW, Yoon SK, Choi HJ, You YK
- 2739 Determining the need for a thoracoscopic approach to treat a giant hiatal hernia when abdominal access is poor
Pérez Lara FJ, Zubizarreta Jimenez R, Prieto-Puga Arjona T, Gutierrez Delgado P, Hernández Carmona JM, Hernández Gonzalez JM, Pitarch Martinez M
- 2747 Predictive value of Hajibandeh index in determining peritoneal contamination in acute abdomen: A cohort study and meta-analysis
Hajibandeh S, Hajibandeh S, Evans L, Miller B, Waterman J, Ahmad SJ, Hale J, Higgi A, Johnson B, Pearce D, Helmy AH, Naguib N, Maw A

Retrospective Study

- 2757 Efficacy of pantoprazole plus perforation repair for peptic ulcer and its effect on the stress response
Leng ZY, Wang JH, Gao L, Shi K, Hua HB
- 2765 Application of electroacupuncture in the prevention of low anterior resection syndrome after rectal cancer surgery
Xu LL, Xiang NJ, Cheng TC, Li YX, Chen P, Jiang ZW, Liu XX

- 2774** Effects of remifentanyl combined with propofol on hemodynamics and oxidative stress in patients undergoing resection of rectal carcinoma
Huang J, Tian WJ
- 2783** Percutaneous microwave ablation and transcatheter arterial chemoembolization for serum tumor markers and prognostics of middle-late primary hepatic carcinoma
Lin ZP, Huang DB, Zou XG, Chen Y, Li XQ, Zhang J
- 2792** Novel invagination procedure for pancreaticojejunostomy using double purse string sutures: A technical note
Li J, Niu HY, Meng XK
- 2799** Laparoscopic resection and endoscopic submucosal dissection for treating gastric ectopic pancreas
Zheng HD, Huang QY, Hu YH, Ye K, Xu JH
- 2809** Prediction of the lymphatic, microvascular, and perineural invasion of pancreatic neuroendocrine tumors using preoperative magnetic resonance imaging
Liu YL, Zhu HB, Chen ML, Sun W, Li XT, Sun YS
- 2820** Impact of hepatectomy and postoperative adjuvant transarterial chemoembolization on serum tumor markers and prognosis in intermediate-stage hepatocellular carcinoma
Hu YD, Zhang H, Tan W, Li ZK

Observational Study

- 2831** Analysis of nutritional risk, skeletal muscle depletion, and lipid metabolism phenotype in acute radiation enteritis
Ma CY, Zhao J, Qian KY, Xu Z, Xu XT, Zhou JY

Randomized Controlled Trial

- 2844** Holistic conditions after colon cancer: A randomized controlled trial of systematic holistic care *vs* primary care
Wang J, Qiao JH

Basic Study

- 2855** Mutational separation and clinical outcomes of *TP53* and *CDH1* in gastric cancer
Liu HL, Peng H, Huang CH, Zhou HY, Ge J
- 2866** Hepatic vagotomy blunts liver regeneration after hepatectomy by downregulating the expression of interleukin-22
Zhou H, Xu JL, Huang SX, He Y, He XW, Lu S, Yao B

META-ANALYSIS

- 2879** Recent evidence for subcutaneous drains to prevent surgical site infections after abdominal surgery: A systematic review and meta-analysis
Ishinuki T, Shinkawa H, Kouzu K, Shinji S, Goda E, Ohyanagi T, Kobayashi M, Kobayashi M, Suzuki K, Kitagawa Y, Yamashita C, Mohri Y, Shimizu J, Uchino M, Haji S, Yoshida M, Ohge H, Mayumi T, Mizuguchi T

- 2890** Prognostic role of serum carcinoembryonic antigen in patients receiving liver resection for colorectal cancer liver metastasis: A meta-analysis

Tang F, Huang CW, Tang ZH, Lu SL, Bai T, Huang Q, Li XZ, Zhang B, Wu FX

- 2907** Significance of carcinoembryonic antigen detection in the early diagnosis of colorectal cancer: A systematic review and meta-analysis

Wang R, Wang Q, Li P

CASE REPORT

- 2919** Primary repair of esophageal atresia gross type C *via* thoracoscopic magnetic compression anastomosis: A case report

Zhang HK, Li XQ, Song HX, Liu SQ, Wang FH, Wen J, Xiao M, Yang AP, Duan XF, Gao ZZ, Hu KL, Zhang W, Lv Y, Zhou XH, Cao ZJ

- 2926** Portal vein embolization for closure of marked arteriportal shunt of hepatocellular carcinoma to enable radioembolization: A case report

Wang XD, Ge NJ, Yang YF

- 2932** Removal of a large rectal polyp with endoscopic submucosal dissection-trans-anal rectoscopic assisted minimally invasive surgery hybrid technique: A case report

Polese L

- 2938** Successful treatment of invasive liver abscess syndrome caused by *Klebsiella variicola* with intracranial infection and septic shock: A case report

Zhang PJ, Lu ZH, Cao LJ, Chen H, Sun Y

- 2945** Duodenojejunostomy treatment of groove pancreatitis-induced stenosis and obstruction of the horizontal duodenum: A case report

Zhang Y, Cheng HH, Fan WJ

- 2954** Awake robotic liver surgery: A case report

Delvecchio A, Pavone G, Conticchio M, Piacente C, Varvara M, Ferraro V, Stasi M, Casella A, Filippo R, Tedeschi M, Pullano C, Inchingolo R, Delmonte V, Memeo R

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Surgery*, Lapo Bencini, PhD, General Surgery Unit, AOUC, Department of Oncology and Robotics, Careggi University Hospital, Florence 350134, Italy. lapbenc@tin.it

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

INDEXING/ABSTRACTING

The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJGS as 2.0; IF without journal self cites: 1.9; 5-year IF: 2.2; Journal Citation Indicator: 0.52; Ranking: 113 among 212 journals in surgery; Quartile category: Q3; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Xu Guo, Editorial Office Director: Jia-Ru Fan.

NAME OF JOURNAL

World Journal of Gastrointestinal Surgery

ISSN

ISSN 1948-9366 (online)

LAUNCH DATE

November 30, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Peter Schemmer

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

PUBLICATION DATE

December 27, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Significance of carcinoembryonic antigen detection in the early diagnosis of colorectal cancer: A systematic review and meta-analysis

Rui Wang, Qin Wang, Pan Li

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chourdakis M, Greece; Inoue H, Japan

Received: September 7, 2023

Peer-review started: September 7, 2023

First decision: September 20, 2023

Revised: September 30, 2023

Accepted: November 14, 2023

Article in press: November 14, 2023

Published online: December 27, 2023



Rui Wang, Pan Li, Department of Nuclear Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu 610072, Sichuan Province, China

Qin Wang, Delivery Room, Chengdu Women's and Children's Central Hospital, Chengdu 610000, Sichuan Province, China

Corresponding author: Pan Li, MBBS, Doctor, Department of Nuclear Medicine, Hospital of Chengdu University of Traditional Chinese Medicine, No. 39 Shi-er-qiao Road, Chengdu 610072, Sichuan Province, China. lp1759lp@163.com

Abstract

BACKGROUND

Colorectal cancer (CRC) is a prevalent malignant tumor involving adenomas that develop into malignant lesions. Carcinoembryonic antigen (CEA) is a non-specific serum biomarker upregulated in CRC. The concentration of CEA is modulated by tumor stage and grade, tumor site in the colon, ploidy status, and patient smoking status. This study aimed to evaluate current evidence regarding the diagnostic power of CEA levels in the early detection of CRC recurrence in adults.

AIM

To evaluate current evidence regarding the diagnostic power of CEA levels in the early detection of CRC recurrence in adults.

METHODS

A systematic search was performed using four databases: MEDLINE, Cochrane Trials, EMBASE, and the Web of Science. The inclusion criteria were as follows: Adult patients aged ≥ 18 years who had completed CRC curative treatment and were followed up postoperatively; reporting the number of CRC recurrences as an outcome; and randomized, clinical, cohort, and case-control study designs. Studies that were not published in English and animal studies were excluded. The following data were extracted by three independent reviewers: Study design, index tests, follow-up, patient characteristics, and primary outcomes. All statistical analyses were performed using the RevMan 5.4.1.

RESULTS

A total of 3232 studies were identified, with 73 remaining following the elimination of duplicates. After screening on predetermined criteria, 12 studies

were included in the final analysis. At a reference standard of 5 mg/L, CEA detected only approximately half of recurrent CRCs, with a pooled sensitivity of 59% (range, 33%–83%) and sensitivity of 89% (range, 58%–97%).

CONCLUSION

CEA is a significant marker for CRC diagnosis. However, it has insufficient sensitivity and specificity to be used as a single biomarker of early CRC recurrence, with an essential proportion of false negatives.

Key Words: Carcinoembryonic antigen; Colorectal cancer; Reference standard; Sensitivity and specificity; Curative carcinoembryonic antigen treatment

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Colorectal cancer (CRC) is a prevalent malignant tumor involving adenomas that develop into malignant lesions. Carcinoembryonic antigen (CEA) is a non-specific serum biomarker upregulated in CRC. The concentration of CEA is modulated by tumor stage and grade, tumor site in the colon, ploidy status, and patient smoking status. Overall, CEA remains an important diagnostic tool for CRC detection and management. When used in combination with other diagnostic tests, such as colonoscopy and imaging examinations, CEA can provide valuable information regarding the presence and progression of CRC and treatment effectiveness.

Citation: Wang R, Wang Q, Li P. Significance of carcinoembryonic antigen detection in the early diagnosis of colorectal cancer: A systematic review and meta-analysis. *World J Gastrointest Surg* 2023; 15(12): 2907-2918

URL: <https://www.wjgnet.com/1948-9366/full/v15/i12/2907.htm>

DOI: <https://dx.doi.org/10.4240/wjgs.v15.i12.2907>

INTRODUCTION

Colorectal cancer (CRC) is a prevalent malignant tumor involving adenomas that develop into malignant lesions. CRC can be detected through early screening and treated with surgery or colonoscopy, increasing the survival rate by 90%[1]. Carcinoembryonic antigen (CEA), commonly found in epithelial cells in the colon, stomach, prostate, or cervix, is a non-specific serum biomarker upregulated in CRC[2].

CEA is a glycoprotein with a molecular weight of 200 kDa. CEA is generally eliminated from the serum after birth, with small amounts retained in colonic tissues that are associated with chromosome 19q13.2[2]. CEA is a member of the CEACaM immunoglobulin family and is involved in cell adhesion, migration, and proliferation[3]. In normal cells, CEA is primarily located in the endoluminal section of the cell membrane, where it inhibits cell apoptosis and tumor pathogenesis[3].

Controversy surrounds CEA use in practice owing to variability in the measurement of CEA levels. Foremost, enzyme-linked immunosorbent assays, which are often used to test for the presence of CEA, can vary depending on the testing procedures, yielding inconsistent CEA levels. For example, using monoclonal antibodies against reactive isotopes of CEA produces significant errors in patients receiving secondary doses of monoclonal antibodies[2,4]. Moreover, in patients with CRC, the concentration of CEA is modulated by tumor stage and grade, tumor site, ploidy status, and patient smoking status. Because CEA is mainly metabolized in hepatic cells, dysfunction in biliary and hepatic function was associated with false positive detection due to increased levels of CEA[5]. Tumor differentiation also affects CEA levels, with higher levels implying appropriately differentiated tumors and vice versa. Lastly, Duffy[5] suggested that the isolation of CEA from liver metastases leaves a glycoprotein with 60% carbohydrate content and a relatively high molecular mass; therefore, CEA is heterogeneous because of significant variations in its carbohydrate side chains, consisting of mannose, galactose, and sialic acid.

CEA levels increase with CRC disease progression, with significantly differentiated CRCs being associated with higher levels of CEA per gram of protein than poorly differentiated CRCs[4,5]. Therefore, CEA testing has been suggested for CRC diagnosis, particularly for detecting disease recurrence and monitoring the response to therapy. However, the use of CEA in the screening of CRC in asymptomatic individuals remains controversial and, therefore, is not recommended in routine practice[6].

According to Lakemeyer *et al*[7] CEA testing can help detect early CRC recurrence in patients who have already been diagnosed with CRC. Increasing blood levels of CEA provides a biomarker of CRC recurrence, even before it appears in imaging tests[8]. Early detection of CRC recurrence can allow for early treatment of recurrent disease, improving patient outcomes. In addition to early detection, CEA testing can be used to determine treatment effectiveness and, therefore, the risk for CRC recurrence. Specifically, in patients with high pretreatment CEA levels, a decrease in CEA levels can indicate treatment effectiveness[9]. Conversely, a continued rise in CEA levels after treatment would suggest cancer recurrence. However, considering the inconsistencies in using CEA for CRC detection, this study aimed to evaluate current evidence regarding the diagnostic power of CEA levels in the early detection of CRC recurrence in adults.

MATERIALS AND METHODS

Information sources and search strategy

A systematic search was performed using three databases: MEDLINE, Cochrane Trials, EMBASE, and the Web of Science. The databases were searched from 1990 to 2022 using keywords such as "recurrence," "carcinoembryonic antigen," "colorectal cancer," "follow-up," and "curative." This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[10,11] and the Cochrane Handbook for Systematic Reviews [12,13]. The evidence from the findings of this study was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation procedure[14].

Eligibility criteria

This study adopted the Participants, Intervention, Comparison, and Outcomes model to determine the inclusion and exclusion criteria. The inclusion criteria were as follows: Adult patients, ≥ 18 years of age, who had undergone curative CRC treatment with postoperative follow-up; reporting of the number of CRC recurrences as an outcome; inclusion of sufficient information to calculate contingency tables for CEA, index tests, physical examinations, and echography; and randomized, clinical, and cohort and case-control study designs. Studies published in languages other than English, involving animal models, and not reporting CEA levels in CRC were excluded.

Study selection

Our study team included three reviewers who independently reviewed studies identified by our search. The titles and abstracts were screened using our predetermined inclusion and exclusion criteria. The reference list of selected publications was reviewed to identify other eligible studies. A full-text review was performed to confirm eligibility. Differences in opinions between independent reviewers were resolved through discussion and consensus before voting.

Data extraction

The data collection forms outlined by the standard Cochrane Library were used to extract data from eligible studies. The following data were extracted: Study design, index tests, follow-up, patient characteristics, CRC recurrent, and primary outcomes measured in each study.

Quality assessment

The Cochrane risk of bias (ROB) tool was used to assess the quality of the selected studies. The risk of blinding evaluators was discarded as a bias criterion as it is impossible to blind medical professionals to the measurement of CEA levels used in the diagnostic process. Therefore, ROB was evaluated based on patient selection, index tests, reference standards, flow, and timing.

Statistical techniques

Our meta-analysis assessed outcomes based on pooled odds ratios and their 95% confidence intervals using forest plots. All statistical analyses were performed using Review Manager 5.4.1 (RevMan, Copenhagen, The Cochrane Collaboration, 2014). The heterogeneity of studies was analyzed using statistic, with P values < 0.05 considered statistically significant. The effects of heterogeneity on CEA levels were assessed using the I^2 statistic, with scores between 0% and 40% regarded as insignificant inconsistencies in the measurement of CEA levels. The Mantel-Haenszel random effects model was used to evaluate the association between CEA levels and CRC recurrence as its assumptions were met. Clinical heterogeneity was examined to determine random effects on the association between CEA levels and CRC recurrence. Heterogeneity was explained based on sample size, sex, methodological quality, and study design. Moreover, differences in CRC subtypes, percentage of recurrences, testing frequency, tumor site, and follow-up parameters were examined. Sensitivity analyses were performed in various domains, including a validated CEA measurement.

RESULTS

In total, 3232 studies were identified, with 73 retained after eliminating duplicate records. After review, based on eligibility criteria, 12 studies were included in the final analysis[15-26] (Figure 1).

Characteristics of included studies

The 12 studies included in the final analysis reported on 3223 patients; 60% were men aged 25–95 years (Table 1). Of these, 569 patients were from secondary care facilities. Most patients were diagnosed with stage II or III CRC. Two studies included patients with stage IV CRC (Bhatti *et al*[16] and Shinkins *et al*[26]) with curative treatment, including resectioning liver metastases. The reported duration of follow-up ranged from 17 to 99 months, with a CRC recurrence rate of 20%.

Standards and index tests

Our study compared the diagnostic values of follow-up procedures used in detecting recurrence rates of CRC. Nine studies reported CEA as follow-up tests with 2 studies reporting ultrasound and 1 study involving a physical examination. In studies that reported CEA, a cut-off value of 5 micrograms per litre was used in all patients as the

Table 1 Characteristics of included studies

Ref.	Year of publication	Study design	Sample size	Age (yr)	Location of cancer	Stage of the tumour	Treatment therapy
Augestad <i>et al</i> [15]	2014	Randomized controlled trial	110	65.4 ± 8.1; males = 59.1%, females = 40.9%	Colon (110 patients)	I (24), II (55), III (32)	Surgical treatment for all patients
Bhatti <i>et al</i> [16]	2015	Prospective cohort study	569	70; males = 51%, females = 49%	Colon (336 patients) and rectum (233 patients)	0 (31), I (33), II (78), III (288), IV (137)	Surgical treatment (569 patients), neoadjuvant chemotherapy (106 patients) and adjuvant chemotherapy (204 patients)
Chang <i>et al</i> [17]	2017	Prospective cohort study	357	63.8 ± 11.5; males = 57.7%, females = 42.3%	Colon (259 patients) and rectum (98 patients)	I (97), II (125), III (135)	Surgical treatment (357 patients), neoadjuvant radiotherapy and chemotherapy (81 patients)
Gilardoni <i>et al</i> [18]	2015	Retrospective cohort study	196	70; males = 59.7%, females = 40.3%	Colon (196 patients)	I (65), III (131)	Surgical treatment (196 patients)
Guo <i>et al</i> [19]	2018	Retrospective cohort study	178	59.7 ± 10.6; males = 66.3%; females = 32.7%	Colon (79 patients) and rectum (42 patients)	0 (2), I (11), II (60), III (105)	Surgical treatment (178 patients) and chemotherapy (66 patients)
Hara <i>et al</i> [20]	2011	Prospective cohort study	127	63.4 ± 9.4; males = 55.1%, females = 44.9%	Colon (85 patients) and rectum (42 patients)	III (127)	Surgical treatment (127 patients), adjuvant chemotherapy (110 patients), adjuvant radiotherapy (1 patient)
Jones <i>et al</i> [21]	2015	Retrospective cohort study	118	N/A; males = 61.9%, females = 38.1%	Colon (66 patients) and rectum (52 patients)	I (26), II (47), III (45)	Surgical treatment (118 patients), adjuvant chemotherapy (73 patients)
Kim and Lee[22]	2013	Retrospective cohort study	336	60.4 ± 11.1; males = 60.7%, females = 39.3%	Colon (224 patients) and rectum (112 patients)	II (189 patients) and III (147 patients)	Surgical treatment for all patients
Moloney <i>et al</i> [23]	2019	Retrospective cohort study	138	67; males = 54.3%, females = 45.7%	Colon (90 patients) and rectum (48 patients)	I (58 patients), II (69 patients), III (11 patients)	Surgical treatment for all patients
Nicolini <i>et al</i> [24]	2010	Prospective cohort study	108	60	Colon (69 patients) and rectum (39 patients)	I (29 patients), II (41 patients), and III (38 patients)	Surgical treatment for all patients
Rodrigues <i>et al</i> [25]	2017	Prospective cohort study	404	64.6; males = 59.7%, females = 40.3%	Colon (199 patients) and rectum (205 patients)	II (177 patients) and III (227 patients)	Surgical treatment (404 patients), neoadjuvant chemotherapy in the rectum (175), adjuvant chemotherapy (196 patients) and adjuvant chemotherapy in the colon (86 patients)
Shinkins <i>et al</i> [26]	2017	Randomized controlled trial	582	65; males = 61.3%, females = 38.7%	N/A	I (110 patients), II (282 patients), III (166 patients) and U (24 patients)	Surgical treatment for all patients

standard threshold. The reference standard varied in various studies with histopathological and radiological examinations being widely used (see [Table 2](#))

ROB assessment

The ROB allowed us to assess the methodological quality of selected studies. We found four studies with a relatively high ROB regarding patient selection, while six studies had a higher ROB regarding reference standards.

ROB was assessed for patient selection, index tests used, reference standards for CEA levels, timing of CEA testing, and flow of patients through the study ([Figure 2](#)). As shown in [Figure 3](#), most studies had an unclear and low ROB across the four domains of patient selection, index test, reference standard, and flow and timing, with a high ROB observed in only four studies on various domains. The ROB for patient selection was unclear-to-low due to a lack of randomization, with patients selected based on specific features that could influence measured outcomes. Bias in index tests used in diagnostic studies can lead to under- or over-estimation of the diagnostic accuracy of a test and, thus, the selection and interpretation of a gold standard was low. The reference standard is often associated with a misclassification bias when it

Table 2 Diagnostic values of follow up duration and reference standards

Ref.	Year of publication	Sample size	Percent recurrence (%)	Duration of follow-up (mo)	Index test	Frequency (mo)	Standard of reference	True positive	False positive	False negative	True negative
Augestad <i>et al</i> [15]	2014	110	12.7	17	CEA reference threshold of 5 g/L	6	Colonoscopy, contrast-enhanced ultrasound, computed tomography scans, PET scans	3	6	4	97
Bhatti <i>et al</i> [16]	2015	569	26.2	6-50	CEA reference threshold of 5 g/L	6	CT and PET scans with or without biopsies	123	23	26	397
Chang <i>et al</i> [17]	2017	357	18.8	3-64	CEA reference threshold of 5 g/L	6	CT scan	44	59	23	231
Hara <i>et al</i> [20]	2011	127	36.2	N/A	CEA reference threshold of 5 g/L	6	Radiological examination	31	31	15	50
Guo <i>et al</i> [19]	2018	178	51.7	N/A	CEA reference threshold of 5 g/L	6	Radiological examination involving X-rays, CT scans	66	36	26	50
Kim and Lee[22]	2013	336	23.5	36-134	CEA reference threshold of 5 g/L	6	Biopsies and radiological examination	34	23	45	234
Moloney <i>et al</i> [23]	2019	138	4.3	25	N/A	6	CT scans, colonoscopy and ultrasound	2	5	4	127
Rodrigues <i>et al</i> [25]	2017	404	12.9	3-79	CEA reference threshold of 5 ug/L for smokers and a 3 g/L for non-smokers	6	Radiological examinations	23	36	29	316
Shinkins <i>et al</i> [26]	2017	582	17.9	N/A	CEA reference threshold of 5 g/L	6	CT scans, colonoscopy	51	12	53	466

CEA: Carcinoembryonic antigen; CT: Computed tomography; PET: Positron-emission tomography; N/A: Not applicable.

is not sensitive or sufficient to diagnose the desired medical condition. Bias in the timing of the index test and subsequent flow of patients through the study can further contribute to variability in the evaluation of diagnostic accuracy.

Diagnostic accuracy of CEA

Forest plots were created to compare the diagnostic accuracy of the different follow-up tests (Figures 4 and 5). The sensitivity for detecting CRC recurrence overall ranged between 33% and 83%, with a specificity range from 58% to 97%.

As shown in Figure 6, the sensitivity and specificity of CEA in detecting CRC recurrence in high-quality studies ranged from 43% to 72%, with a specificity range from 58% to 94%.

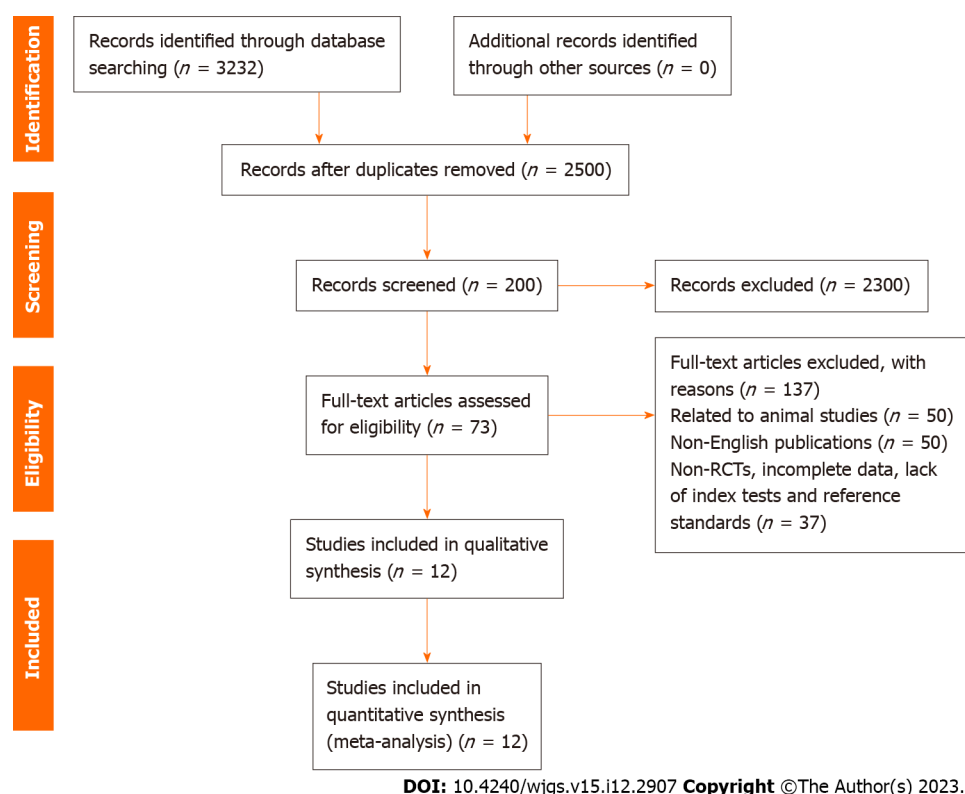


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. RCT: Randomized controlled trial.

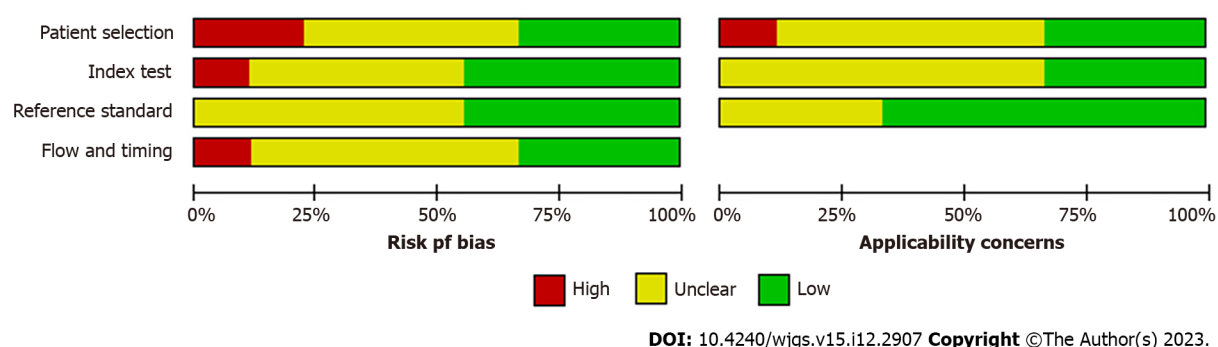


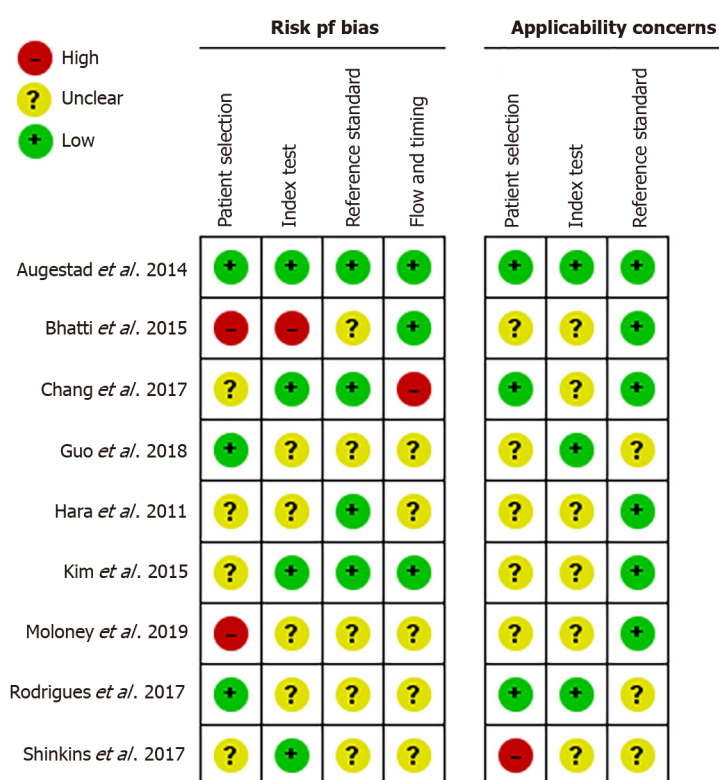
Figure 2 Risk of bias and applicability concerns of all studies.

DISCUSSION

Our findings revealed that using CEA at a reference level of 5 mg/L detected only approximately half of CRC recurrence, with CEA having neither the sensitivity nor specificity required to be used as a single test clinically. Although CEA can be useful for early identification of CRC recurrence, it must be combined with other tests, such as ultrasound or physical examination.

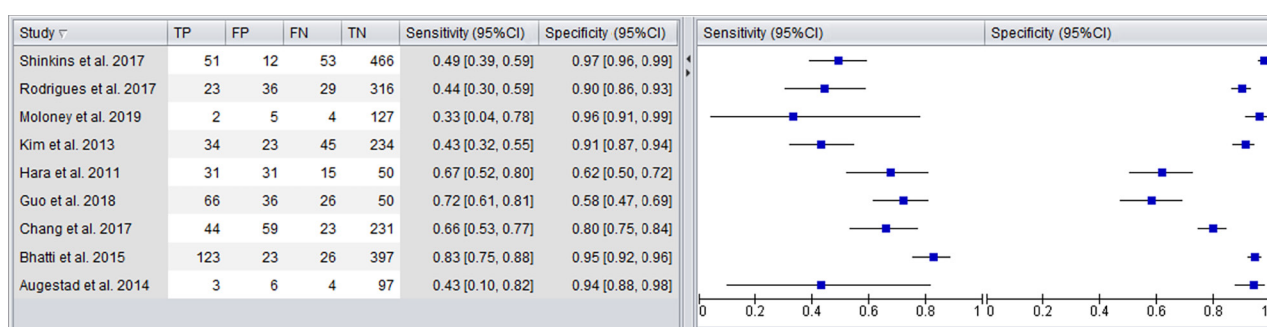
The recommended reference standard for CEA testing is 5 mg/L, with levels > 5 mg/L considered abnormal. However, it is essential to note that not all patients with CRC have elevated CEA levels and that some patients with other conditions may also have elevated CEA levels. The significance of CEA detection in the early diagnosis of CRC lies in its ability to detect cancer in its early stages before symptoms appear. CEA testing is often used with other diagnostic tests, such as colonoscopy or biopsy, for early CRC diagnosis. This is important as early diagnosis can optimize treatment and, thus, patient outcomes and survival.

Our findings are similar to Hung *et al* [27], who identified elevated serum CEA levels > 5 mg/L in 63.6% of patients with recurrent CRC. For patients with low serum CEA levels (2 mg/L), suspected CRC recurrence was assessed based on symptomatology and radiological examination. Repeated measurement of postoperative CEA levels is recommended to improve the detection of CRC recurrence for early treatment, with monitoring at 3 and 6 mo recommended for five years after initial diagnosis. In addition, annual computed tomography (CT) imaging is recommended to enhance CRC recurrence detection. Before curative treatment, patients with high CEA levels are expected to exhibit decreased or normal levels postoperatively. Persistently high or increased levels during routine postoperative monitoring suggest CRC



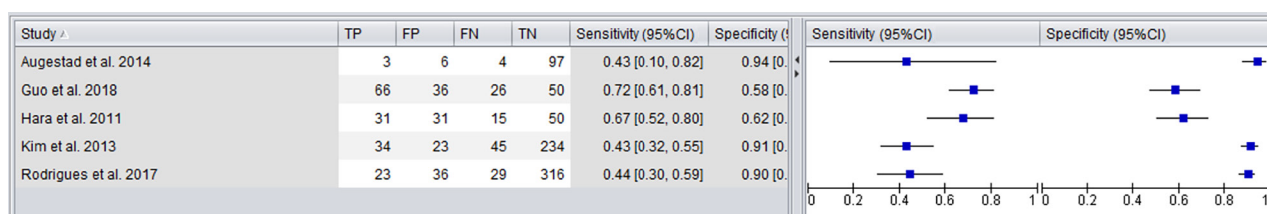
DOI: 10.4240/wjgs.v15.i12.2907 Copyright ©The Author(s) 2023.

Figure 3 Risk of bias assessment of every study.



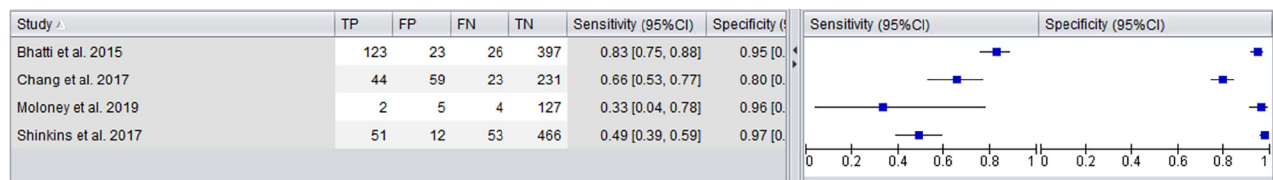
DOI: 10.4240/wjgs.v15.i12.2907 Copyright ©The Author(s) 2023.

Figure 4 Forest plot of sensitivity of carcinoembryonic antigen. TP: True positive; FP: False positive; FN: False negative; TN: True negative; 95%CI: 95% confidence interval.



DOI: 10.4240/wjgs.v15.i12.2907 Copyright ©The Author(s) 2023.

Figure 5 Forest plot of sensitivity and specificity of carcinoembryonic antigen. TP: True positive; FP: False positive; FN: False negative; TN: True negative; 95%CI: 95% confidence interval.



DOI: 10.4240/wjgs.v15.i12.2907 Copyright ©The Author(s) 2023.

Figure 6 Forest plot of the sensitivity and specificity of carcinoembryonic antigen in high-quality trials. TP: True positive; FP: False positive; FN: False negative; TN: True negative; 95%CI: 95% confidence interval.

recurrence and are an indication for follow-up imaging examination, including radiography, CT, and positron-emission tomography (PET)[27]. Therefore, the monitoring of CEA levels should be considered as one component of a comprehensive postoperative follow-up for early diagnosis of CRC recurrence.

Despite advancements in surgical procedures, care, and adjuvant and neoadjuvant chemotherapy[28], postoperative follow-up is recommended for CRC recurrence for early treatment to improve patient outcomes and survival. Our analysis included studies with a postoperative follow-up duration of at least six months for CRC recurrence detection. Our findings indicate the possibility of missed diagnosis of CRC recurrence, including false negatives, when using only CEA levels due to its lower-than-needed diagnostic sensitivity and specificity. Therefore, CEA levels should not be used as a single technique for CRC follow-up.

The incorporation of imaging examinations in CRC follow-up has been inconsistent and lacks predefined standards. Locker *et al*[29] suggested that shorter follow-up intervals and precise radiological examination improved the detection of CRC recurrence, increasing patient survival by allowing for early intervention. In contrast, Primrose *et al*[30] suggested that shorter follow-up intervals and detailed procedures after curative CRC treatment did not yield a survival advantage. Moreover, they reported a higher risk of recurrence in patients who underwent CT and CEA measurements than in those who were followed-up only using CEA or CT imaging, but with no statistical difference in overall survival between the two groups. Based on these results, the combination of CEA and CT imaging may be significant only during the early stages of follow-up and not the later stages. Our findings indicated that follow-up should be more intensive during the first three years after curative CRC treatment, with the inclusion of imaging and physical examination recommended considering the 30% CRC recurrence rate within the first three years postoperatively and that > 70% of recurrent CRCs were not detected by CEA levels. In addition, we propose that adoption of PET imaging over other imaging modalities could be significant for detecting metastasis. We recognize that although PET imaging provides high sensitivity and specificity for CRC recurrence compared to CEA, it is relatively expensive, and its availability is limited in some regions of the world[28]. As a rule, medical professionals should incorporate PET or CT as secondary diagnostic tools when an elevation in CEA is detected.

Our findings indicated a higher rate of CRC recurrence among patients with higher preoperative CEA levels. However, frequent radiological examination was associated with a good prognosis and delayed detection of CRC recurrent among patients with low preoperative CEA levels. In their study of 106 patients with CRC recurrence after surgical treatment, Saito *et al*[31] reported that 56% of patients had normal CEA levels at the time of diagnosis and serum CEA concentrations > 5 mg/L at the time of CRC recurrence. Using a cutoff CEA level of 5 mg/L lowers the sensitivity of detecting recurrent CRC, with 80% of patients with CEA levels > 5 mg/L reporting abnormal symptoms at the time of diagnosis of CRC recurrence. In comparison, among patients with CEA levels < 5 mg/L, 42% of the patients reported abnormal symptoms at the time of diagnosis of recurrent CRC. Therefore, surveillance of recurrent CRC using CEA levels alone is insufficient and risky due to its low diagnostic accuracy for CRC recurrence.

Incorporating other tumor markers, such as carbohydrate antigen 19 and cancer antigen 125, is essential in determining CRC recurrence rates, particularly in patients who do not exhibit elevated levels of CEA before surgery or during follow-up. We propose that adoption of other tumor markers could increase the specificity and precision of early detection of CRC. Several studies have proposed that a CEA cutoff value of 5 mg/L should be adopted for CRC recurrence detection in follow-up studies. However, we propose that this cutoff value should be slightly lowered for patients with low CEA levels to permit the early detection of recurrent CRC, such as 10 µg/dL.

In our analysis, we included studies that adopted colonoscopy[32] as a reference standard for CRC recurrence detection in addition to CEA levels. Colonoscopy refers to medical tests performed inside the bowel to detect abnormalities. It involves a long, flexible tube with a tiny camera placed at the tip of the rectum to visualize any changes. According to the American Cancer Society, individuals with a high risk of CRC should begin screening at the age of 45 years, and individuals with a family history of CRC or predisposition should undergo regular screening. A colonoscopy permits doctors or cancer professionals to analyze the rectum and colon for abnormalities, such as polyps or growth, which can be biopsied for further examination. Colonoscopy is considered the gold standard for CRC detection; combined with CEA testing, it is highly effective for detecting early-stage CRC. In addition to its effectiveness in detecting CRC, polyps and other growths can be removed during the procedure to prevent CRC development[32]. Although colonoscopy is generally a safe and effective procedure, it does carry some risks, such as bleeding or perforation of the colon. However, these risks are rare, and the benefits of early detection and prevention of CRC far outweigh the risks associated with the procedure.

Our analysis included studies that adopted contrast-enhanced ultrasound (CEUS) and CEA for CRC detection. CEUS is an imaging technique that uses contrast agents, such as microbubbles, to improve the clarity and visualization of images

in the rectum and colon. It permits the visualization of functional and structural systems of the rectum and colon to offer a complete image of abnormalities or growths[33,34]. Contrast agents represent areas of higher blood flow, indicating the presence of tumors. CEUS is more robust than CT or magnetic resonance imaging (MRI) as it does not involve ionizing radiation and is highly safe for patients who require frequent medical examinations. The high effectiveness of CEUS for early-stage CRC detection has been reported, with a sensitivity of 92% and specificity of 89%[35]. Therefore, CEUS may be a valuable tool for the early detection of treatable CRC. However, CEUS has not been widely adopted in clinical practice, and further research is required to comprehend its effectiveness and limitations compared with other imaging techniques.

CT imaging for CRC detection and staging involves numerous radiographs to create clear and detailed images of the colon and rectum to reveal tumors or enlarged lymph nodes. CT imaging is highly effective for early CRC detection, which improves treatment outcomes and overall survival rates[36,37]. Moreover, CT imaging can be used to monitor disease progression, assess treatment effectiveness, measure tumor size, and monitor change over time. Combining CT images and CEA measurement increases the sensitivity and specificity of detecting early CRC by identifying abnormal growth or lesions within the colon and rectum and determining the cancer stage. CT can also detect the presence of cancerous cells in other parts of the body, such as the liver, indicating whether the cancer has metastasized. However, CT imaging is associated with high exposure to ionizing radiation, which increases cancer risk, particularly in young patients. However, the benefits of early detection and treatment of CRC generally outweigh the risks associated with CT imaging.

Our findings indicate that combined radiological examinations, including CT, MRI, and CEUS, are adequate for early CRC detection. Radiographs can detect abnormalities in the colon and rectum, such as growth or blockage[28,38]. However, radiography alone is insufficient for CRC detection as it does not provide a detailed image of the colon and rectum. In this regard, CT or MRI is recommended over plain radiography. Moreover, because MRI provides detailed images of the colon and rectum, similar to CT, but without radiation exposure, it should be considered over CT.

The diagnostic accuracy of CEA for detecting CRC recurrence is influenced by various factors, such as cancer stage of cancer, CEA test sensitivity and specificity, and other factors that can affect CEA levels, such as smoking and other medical conditions. For example, smoking may have elevated CEA levels even without CRC. Furthermore, inflammatory bowel disease or liver disease can yield an elevation in CEA levels owing to inflammation in the body. Our findings indicate a sensitivity of 40%–70% CEA and a specificity of 80%–90%, suggesting that CEA can correctly identify the presence of CRC in 40%–70% of cases and the absence of CRC in 80%–90% of cases.

The limitations of our systematic review and meta-analysis must be acknowledged in applying the findings for practice. First, few studies were identified in which CEA was solely used as the follow-up test, without including imaging examination or colonoscopy. Therefore, further studies should be performed on a larger prospective and randomized basis to examine CEA's diagnostic accuracy in terms of patient outcomes, quality of life, and the cost of care or treatment. Second, we excluded studies not published in English, which may have limited the findings. The presence of patient selection bias and applicability concerns have significant implications for the validity and generalizability of the study findings. For example, studies that only included patients at a particular stage of CRC or those who had undergone a specific type of treatment may not represent the broader population of patients with CRC. This may have led to incorrect conclusions regarding diagnostic accuracy or the effectiveness of specific tests and treatments.

The strengths of our study also need to be specified. First, we adhered to the methodology of the Cochrane Handbook for Systematic Reviews and PRISMA guidelines. Second, we adopted a robust and broad search strategy that retrieved articles from all databases up to 2022. Most of the included studies reported a CEA level of 5 mg/L as the index test alongside other reference standards, such as imaging techniques.

Overall, CEA remains an essential diagnostic tool for CRC detection and management. CEA can provide valuable information regarding the presence and progression of CRC and treatment effectiveness when combined with other diagnostic tests, such as colonoscopy and imaging examinations.

CONCLUSION

CEA is a significant marker for CRC diagnosis. However, it has insufficient sensitivity and specificity to be used as a single biomarker of early CRC recurrence, with an essential proportion of false negatives.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is a prevalent malignant tumor involving adenomas that develop into malignant lesions. CRC can be detected through early screening and treated with surgery or colonoscopy, increasing the survival rate by 90%. Therefore, carcinoembryonic antigen (CEA) testing has been suggested for CRC diagnosis, particularly for detecting disease recurrence and monitoring the response to therapy. However, the use of CEA in the screening of CRC in asymptomatic individuals remains controversial and, therefore, is not recommended in routine practice. Controversy surrounds CEA use in practice owing to variability in the measurement of CEA levels.

Research motivation

Controversy surrounds CEA use in practice owing to variability in the measurement of CEA levels. Foremost, enzyme-linked immunosorbent assays, which are often used to test for the presence of CEA, can vary depending on the testing procedures, yielding inconsistent CEA levels.

Research objectives

However, considering the inconsistencies in using CEA for CRC detection, this study aimed to evaluate current evidence regarding the diagnostic power of CEA levels in the early detection of CRC recurrence in adults.

Research methods

Our research methods were a systematic review and meta-analysis significance of CEA detection in the early diagnosis of CRC.

Research results

CEA testing is often used with other diagnostic tests, such as colonoscopy or biopsy, for early CRC diagnosis. This is important as early diagnosis can optimize treatment and, thus, patient outcomes and survival. Therefore, the monitoring of CEA levels should be considered as one component of a comprehensive postoperative follow-up for early diagnosis of CRC recurrence.

Research conclusions

We concluded that the CEA detection was significant in the early diagnosis of CRC.

Research perspectives

Our research perspectives involved investigating the sensitivity and specificity of CEA as a diagnostic marker for CRC. Also, we sought to examine the possibility of early detection of CRC and how it improves the possibility of early treatment.

FOOTNOTES

Author contributions: Wang R, Wang Q and Li P jointly designed this study; Wang R, Wang Q, wrote the paper; Wang R and Li P were responsible for collating the data and reviewing the articles.

Conflict-of-interest statement: Dr. Li has nothing to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Rui Wang [0009-0005-3163-1723](https://orcid.org/0009-0005-3163-1723); Pan Li [0009-0007-5192-1204](https://orcid.org/0009-0007-5192-1204).

S-Editor: Lin C

L-Editor: A

P-Editor: Yu HG

REFERENCES

- 1 Mo S, Dai W, Wang H, Lan X, Ma C, Su Z, Xiang W, Han L, Luo W, Zhang L, Wang R, Zhang Y, Zhang W, Yang L, Lu R, Guo L, Zheng Y, Huang M, Xu Y, Liang L, Cai S, Cai G. Early detection and prognosis prediction for colorectal cancer by circulating tumour DNA methylation haplotypes: A multicentre cohort study. *EClinicalMedicine* 2023; **55**: 101717 [PMID: [36386039](https://pubmed.ncbi.nlm.nih.gov/36386039/) DOI: [10.1016/j.eclinm.2022.101717](https://doi.org/10.1016/j.eclinm.2022.101717)]
- 2 Kankanala VL, Mukkamalla SKR. Carcinoembryonic Antigen. 2023 Jan 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. [PMID: [35201700](https://pubmed.ncbi.nlm.nih.gov/35201700/)]
- 3 Zi-Yang Y, Kaixun Z, Dongling L, Zhou Y, Chengbin Z, Jimei C, Caojin Z. Carcinoembryonic antigen levels are increased with pulmonary output in pulmonary hypertension due to congenital heart disease. *J Int Med Res* 2020; **48**: 300060520964378 [PMID: [33203284](https://pubmed.ncbi.nlm.nih.gov/33203284/) DOI: [10.1177/0300060520964378](https://doi.org/10.1177/0300060520964378)]
- 4 Wang WS, Lin JK, Chiou TJ, Liu JH, Fan FS, Yen CC, Lin TC, Jiang JK, Yang SH, Wang HS, Chen PM. Preoperative carcinoembryonic antigen level as an independent prognostic factor in colorectal cancer: Taiwan experience. *Jpn J Clin Oncol* 2000; **30**: 12-16 [PMID: [10770562](https://pubmed.ncbi.nlm.nih.gov/10770562/)]

DOI: [10.1093/jjco/hyd003](https://doi.org/10.1093/jjco/hyd003)]

- 5 **Duffy MJ.** Carcinoembryonic antigen as a marker for colorectal cancer: is it clinically useful? *Clin Chem* 2001; **47**: 624-630 [PMID: [11274010](https://pubmed.ncbi.nlm.nih.gov/11274010/)]
- 6 **Siregar GA, Sibarani H.** Comparison of Carcinoembryonic Antigen Levels Among Degree of Differentiation and Colorectal Cancer's Location in Medan. *Open Access Maced J Med Sci* 2019; **7**: 3447-3450 [PMID: [32002071](https://pubmed.ncbi.nlm.nih.gov/32002071/) DOI: [10.3889/oamjms.2019.442](https://doi.org/10.3889/oamjms.2019.442)]
- 7 **Lakemeyer L, Sander S, Wittau M, Henne-Bruns D, Kornmann M, Lemke J.** Diagnostic and Prognostic Value of CEA and CA19-9 in Colorectal Cancer. *Diseases* 2021; **9** [PMID: [33802962](https://pubmed.ncbi.nlm.nih.gov/33802962/) DOI: [10.3390/diseases9010021](https://doi.org/10.3390/diseases9010021)]
- 8 **Minato T, Ito S, Li B, Fujimori H, Mochizuki M, Yamaguchi K, Tamai K, Shimada M, Tokunaga H, Shigeta S, Sato I, Shima H, Yamada H, Yaegashi N, Yasuda J.** Liquid biopsy with droplet digital PCR targeted to specific mutations in plasma cell-free tumor DNA can detect ovarian cancer recurrence earlier than CA125. *Gynecol Oncol Rep* 2021; **38**: 100847 [PMID: [34557579](https://pubmed.ncbi.nlm.nih.gov/34557579/) DOI: [10.1016/j.gore.2021.100847](https://doi.org/10.1016/j.gore.2021.100847)]
- 9 **AL-Nafakh ZM, AL-Dujaili AN, Rudha AR.** Assessment of cancer embryonic antigen (CEA) biomarker in women with breast cancer disease. *AIP Conference Proceedings* 2020; **2290**: 020042 [DOI: [10.1063/5.0029114](https://doi.org/10.1063/5.0029114)]
- 10 **Selçuk AA.** A Guide for Systematic Reviews: PRISMA. *Turk Arch Otorhinolaryngol* 2019; **57**: 57-58 [PMID: [31049257](https://pubmed.ncbi.nlm.nih.gov/31049257/) DOI: [10.5152/tao.2019.4058](https://doi.org/10.5152/tao.2019.4058)]
- 11 **Sarkis-Onofre R, Catalá-López F, Aromataris E, Lockwood C.** How to properly use the PRISMA Statement. *Syst Rev* 2021; **10**: 117 [PMID: [33875004](https://pubmed.ncbi.nlm.nih.gov/33875004/) DOI: [10.1186/s13643-021-01671-z](https://doi.org/10.1186/s13643-021-01671-z)]
- 12 **Tarsilla M.** Cochrane handbook for systematic reviews of interventions. *Journal of Multidisciplinary Evaluation* 2010; **6**: 142-148 [DOI: [10.56645/jmd.e.v6i14.284](https://doi.org/10.56645/jmd.e.v6i14.284)]
- 13 **Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J.** Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* 2019; **10**: ED000142 [PMID: [31643080](https://pubmed.ncbi.nlm.nih.gov/31643080/) DOI: [10.1002/14651858.ED000142](https://doi.org/10.1002/14651858.ED000142)]
- 14 **Santesso N, Carrasco-Labra A, Langendam M, Brignardello-Petersen R, Mustafa RA, Heus P, Lasserson T, Opiyo N, Kunnamo I, Sinclair D, Garner P, Treweek S, Tovey D, Akl EA, Tugwell P, Brozek JL, Guyatt G, Schünemann HJ.** Improving GRADE evidence tables part 3: detailed guidance for explanatory footnotes supports creating and understanding GRADE certainty in the evidence judgments. *J Clin Epidemiol* 2016; **74**: 28-39 [PMID: [26796947](https://pubmed.ncbi.nlm.nih.gov/26796947/) DOI: [10.1016/j.jclinepi.2015.12.006](https://doi.org/10.1016/j.jclinepi.2015.12.006)]
- 15 **Augustad KM, Norum J, Rose J, Lindsetmo RO.** A prospective analysis of false positive events in a National Colon Cancer Surveillance Program. *BMC Health Serv Res* 2014; **14**: 137 [PMID: [24674307](https://pubmed.ncbi.nlm.nih.gov/24674307/) DOI: [10.1186/1472-6963-14-137](https://doi.org/10.1186/1472-6963-14-137)]
- 16 **Bhatti I, Patel M, Dennison AR, Thomas MW, Garcea G.** Utility of postoperative CEA for surveillance of recurrence after resection of primary colorectal cancer. *Int J Surg* 2015; **16**: 123-128 [PMID: [25771102](https://pubmed.ncbi.nlm.nih.gov/25771102/) DOI: [10.1016/j.ijsu.2015.03.002](https://doi.org/10.1016/j.ijsu.2015.03.002)]
- 17 **Chang YT, Yeh YS, Ma CJ, Huang CW, Tsai HL, Huang MY, Cheng TL, Wang JY.** Optimization of a multigene biochip for detection of relapsed and early relapsed colorectal cancer. *J Surg Res* 2017; **220**: 427-437 [PMID: [2925530](https://pubmed.ncbi.nlm.nih.gov/2925530/) DOI: [10.1016/j.jss.2017.06.030](https://doi.org/10.1016/j.jss.2017.06.030)]
- 18 **Gilardoni E, Bernasconi DP, Poli S, Garancini M, Luperto M, Zucchini N, Bovo G, Totis M, Bugatti A, Gianotti L.** Surveillance for early stages of colon cancer: potentials for optimizing follow-up protocols. *World J Surg Oncol* 2015; **13**: 260 [PMID: [26311420](https://pubmed.ncbi.nlm.nih.gov/26311420/) DOI: [10.1186/s12957-015-0674-7](https://doi.org/10.1186/s12957-015-0674-7)]
- 19 **Guo Y, Chen F, Cui W.** Usefulness of plasma D-dimer level for monitoring development of distant organ metastasis in colorectal cancer patients after curative resection. *Cancer Manag Res* 2018; **10**: 4203-4216 [PMID: [30323676](https://pubmed.ncbi.nlm.nih.gov/30323676/) DOI: [10.2147/CMAR.S177274](https://doi.org/10.2147/CMAR.S177274)]
- 20 **Hara M, Sato M, Takahashi H, Takayama S, Takeyama H.** Accuracy of monitoring serum carcinoembryonic antigen levels in postoperative stage III colorectal cancer patients is limited to only the first postoperative year. *Surg Today* 2011; **41**: 1357-1362 [PMID: [21922357](https://pubmed.ncbi.nlm.nih.gov/21922357/) DOI: [10.1007/s00595-010-4519-2](https://doi.org/10.1007/s00595-010-4519-2)]
- 21 **Jones RP, McWhirter D, Fretwell VL, McAvoy A, Hardman JG.** Clinical follow-up does not improve survival after resection of stage I-III colorectal cancer: A cohort study. *Int J Surg* 2015; **17**: 67-71 [PMID: [25827817](https://pubmed.ncbi.nlm.nih.gov/25827817/) DOI: [10.1016/j.ijsu.2015.03.017](https://doi.org/10.1016/j.ijsu.2015.03.017)]
- 22 **Kim HS, Lee MR.** Diagnostic Accuracy of Elevated Serum Carcinoembryonic Antigen for Recurrence in Postoperative Stage II Colorectal Cancer Patients: Comparison With Stage III. *Ann Coloproctol* 2013; **29**: 155-159 [PMID: [24032116](https://pubmed.ncbi.nlm.nih.gov/24032116/) DOI: [10.3393/ac.2013.29.4.155](https://doi.org/10.3393/ac.2013.29.4.155)]
- 23 **Moloney J, Partridge C, Delanty S, Lloyd D, Nguyen MH.** High efficacy and patient satisfaction with a nurse-led colorectal cancer surveillance programme with 10-year follow-up. *ANZ J Surg* 2019; **89**: 1286-1290 [PMID: [31280494](https://pubmed.ncbi.nlm.nih.gov/31280494/) DOI: [10.1111/ans.15333](https://doi.org/10.1111/ans.15333)]
- 24 **Nicolini A, Ferrari P, Duffy MJ, Antonelli A, Rossi G, Metelli MR, Fulceri F, Anselmi L, Conte M, Berti P, Miccoli P.** Intensive risk-adjusted follow-up with the CEA, TPA, CA19.9, and CA72.4 tumor marker panel and abdominal ultrasonography to diagnose operable colorectal cancer recurrences: effect on survival. *Arch Surg* 2010; **145**: 1177-1183 [PMID: [21173292](https://pubmed.ncbi.nlm.nih.gov/21173292/) DOI: [10.1001/archsurg.2010.251](https://doi.org/10.1001/archsurg.2010.251)]
- 25 **Rodrigues RV, Pereira da Silva J, Rosa I, Santos I, Pereira N, Soares C, Pereira AD.** Intensive Follow-Up After Curative Surgery for Colorectal Cancer. *Acta Med Port* 2017; **30**: 633-641 [PMID: [29025530](https://pubmed.ncbi.nlm.nih.gov/29025530/) DOI: [10.20344/amp.7889](https://doi.org/10.20344/amp.7889)]
- 26 **Shinkins B, Nicholson BD, Primrose J, Perera R, James T, Pugh S, Mant D.** The diagnostic accuracy of a single CEA blood test in detecting colorectal cancer recurrence: Results from the FACS trial. *PLoS One* 2017; **12**: e0171810 [PMID: [28282381](https://pubmed.ncbi.nlm.nih.gov/28282381/) DOI: [10.1371/journal.pone.0171810](https://doi.org/10.1371/journal.pone.0171810)]
- 27 **Hung H, You J, Chiang J, Hsieh P, Chiang S, Lai C, Tasi W, Yeh C.** Why recurrence was initially suspected during colorectal cancer postoperative surveillance?: A retrospective analysis. *Medicine (Baltimore)* 2020; **99**: e22803 [PMID: [33120800](https://pubmed.ncbi.nlm.nih.gov/33120800/) DOI: [10.1097/MD.00000000000022803](https://doi.org/10.1097/MD.00000000000022803)]
- 28 **Young PE, Womeldorph CM, Johnson EK, Maykel JA, Brucher B, Stojadinovic A, Avital I, Nissan A, Steele SR.** Early detection of colorectal cancer recurrence in patients undergoing surgery with curative intent: current status and challenges. *J Cancer* 2014; **5**: 262-271 [PMID: [24790654](https://pubmed.ncbi.nlm.nih.gov/24790654/) DOI: [10.7150/jca.7988](https://doi.org/10.7150/jca.7988)]
- 29 **Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, Somerfield MR, Hayes DF, Bast RC Jr, ASCO.** ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol* 2006; **24**: 5313-5327 [PMID: [17060676](https://pubmed.ncbi.nlm.nih.gov/17060676/) DOI: [10.1200/JCO.2006.08.2644](https://doi.org/10.1200/JCO.2006.08.2644)]
- 30 **Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, George S, Mant D, FACS Trial Investigators.** Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial. *JAMA* 2014; **311**: 263-270 [PMID: [24430319](https://pubmed.ncbi.nlm.nih.gov/24430319/) DOI: [10.1001/jama.2013.285718](https://doi.org/10.1001/jama.2013.285718)]
- 31 **Saito G, Sadahiro S, Kamata H, Miyakita H, Okada K, Tanaka A, Suzuki T.** Monitoring of Serum Carcinoembryonic Antigen Levels after Curative Resection of Colon Cancer: Cutoff Values Determined according to Preoperative Levels Enhance the Diagnostic Accuracy for Recurrence. *Oncology* 2017; **92**: 276-282 [PMID: [28178692](https://pubmed.ncbi.nlm.nih.gov/28178692/) DOI: [10.1159/000456075](https://doi.org/10.1159/000456075)]
- 32 **Stark UA, Frese T, Unverzagt S, Bauer A.** What is the effectiveness of various invitation methods to a colonoscopy in the early detection and

- prevention of colorectal cancer? Protocol of a systematic review. *Syst Rev* 2020; **9**: 49 [PMID: [32143683](#) DOI: [10.1186/s13643-020-01312-x](#)]
- 33 **Hwang M**, Back SJ, Didier RA, Lorenz N, Morgan TA, Poznick L, Steffgen L, Sridharan A. Pediatric contrast-enhanced ultrasound: optimization of techniques and dosing. *Pediatr Radiol* 2021; **51**: 2147-2160 [PMID: [32955599](#) DOI: [10.1007/s00247-020-04812-z](#)]
- 34 **Badea R**, Socaciu M, Ciobanu L, Hagiuc C, Golea A. Contrast-enhanced ultrasonography (CEUS) for the evaluation of the inflammation of the digestive tract wall. *J Gastrointest Liver Dis* 2010; **19**: 439-444 [PMID: [21188338](#)]
- 35 **Barr RG**, Huang P, Luo Y, Xie X, Zheng R, Yan K, Jing X, Xu H, Fei X, Lee JM. Contrast-enhanced ultrasound imaging of the liver: a review of the clinical evidence for SonoVue and Sonazoid. *Abdom Radiol (NY)* 2020; **45**: 3779-3788 [PMID: [32424608](#) DOI: [10.1007/s00261-020-02573-9](#)]
- 36 **Bruening W**, Sullivan N, Paulson EC, Zafar H, Mitchell M, Treadwell J, Schoelles K. Imaging Tests for the Staging of Colorectal Cancer [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Sep- [PMID: [25340228](#)]
- 37 **Kijima S**, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. *World J Gastroenterol* 2014; **20**: 16964-16975 [PMID: [25493009](#) DOI: [10.3748/wjg.v20.i45.16964](#)]
- 38 **Nicholson BD**, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, Perera R, Primrose JN, Mant D. Blood CEA levels for detecting recurrent colorectal cancer. *Cochrane Database Syst Rev* 2015; **2015**: CD011134 [PMID: [26661580](#) DOI: [10.1002/14651858.CD011134.pub2](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

