Systematic Review and Meta-Analysis

Medicine

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Prognostic value of circulating tumor cells in patients with recurrent and metastatic colorectal cancer

a systematic review and meta-analysis

Xia Liu, MD[a], Hui Lan, MD[a], Dongmei Yang, MD[a], Li Wang, MD[b], Liping Hu, MD[a,*]

Abstract

Background: The detection of circulating tumor cells (CTCs) has been employed in prognosticating the likelihood of recurrence and metastasis in colorectal cancer (CRC). Nonetheless, the findings remain enigmatic. This meta-analysis aims to systematically assess the predictive utility of CTCs detection in postoperative recurrence and metastasis among CRC patients.

Methods: A comprehensive search of PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Cochrane Library was conducted from inception to March 2023. Pooled estimates including sensitivity, specificity, positive and negative likelihood ratios, diagnostic odds ratio, and summary receiver operating characteristic curve were computed to gauge the predictive value. The QUADAS-2 tool was employed to appraise bias risks in individual studies. The assessment of publication bias in the included literature was performed using Deek's funnel plot.

Results: The study encompassed 16 articles and 2037 patients. After synthesizing the pertinent indices, CTCs monitoring demonstrated sensitivity and specificity of 0.71 (95% confidence interval [CI], 0.62–0.79) and 0.71 (95% CI, 0.55–0.83), respectively. The corresponding values for positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 2.4 (95% CI, 1.5–4.0), 0.41 (95% CI, 0.29–0.58), and 6 (95% CI, 3–13). The summary receiver operating characteristic curve yielded an area under the curve of 0.76 (95% CI, 0.72–0.80). Deek's funnel plot analysis revealed no significant evidence of publication bias (P = .42).

Conclusion: This investigation underscores the potential of CTCs detection as a noninvasive modality to efficaciously prognosticate postoperative recurrence and metastasis in CRC.

Abbreviations: AUC = area under the sROC curve, CRC = colorectal cancer, CTCs = circulating tumor cell, DOR = diagnostic odds ratio, FCM = flow cytometry, imFISH = immunofluorescence in situ hybridization, NLR = negative likelihood ratios, PLR = positive likelihood ratios, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2, RT-PCR = reverse transcription polymerase chain reaction, SEN = sensitivity, sROC = summary receiver operating characteristic.

Keywords: circulating tumour cells, colorectal cancer, meta-analysis, metastasis, postoperative, recurrence

1. Introduction

Colorectal cancer (CRC), ranking as the third most prevalent malignancy worldwide, harbors the second highest fatality rate among malignant tumors, constituting a pivotal contributor to human mortality. Notably, metastasis to the liver, accounting for approximately 70% of fatalities, emerges as the principal cause of CRC-related mortality. While surgical resection can address the primary tumors in most cases, the propensity of tumor cell dissemination prior to or during surgery often culminates in postoperative tumor recurrence. Alarmingly, post-radical resection, a substantial 30% to 50% of primary colon cancer patients succumb to tumor recurrence and metastasis, triggering in significant reduction as to the 5-year survival rate of patients.[1–4] Therefore, monitoring the recurrence and metastasis of CRC after surgery and selecting appropriate treatment plans can help improve the quality of life of patients and prolong their survival.

The onset of CRC remains insidious, lacking efficient prognostic measures for recurrence and metastasis. Clinical

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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employment of commonly utilized tumor markers underscores limited specificity and sensitivity. Traditional techniques such as colonoscopy and pathological biopsy, pivotal for CRC determination and diagnosis, amplify the risk of tumor dissemination. Currently, the innovative detection of circulating tumor cells (CTCs) emerged, encompassing liquid biopsy techniques characterized by attributes like non-invasiveness, sensitivity, convenience, and repeatability, with potential capacity in prognosticating colorectal cancer recurrence.[5] CTCs, rare malignant entities coursing through peripheral blood, primarily originate from primary tumors or metastatic foci.[6,7] Dislodging from solid primary tumors, CTCs infiltrate the bloodstream, surmounting obstacles like shear stress, hypoxia, immune surveillance, apoptosis, and more. Consequently, only a scant fraction of these cells endure. Surviving CTCs can coalesce and adhere, forming minute tumor thrombi that journey through the circulatory system. Once in hospitable microenvironments, these CTCs may proliferate and give rise to metastases, eluding immune scrutiny.[8,9] Some CTCs, evading immune clearance, metastasize to distant sites via the circulatory route, intricately linked to tumor recurrence and metastasis. The quantum of circulating tumor cells independently influences prognosis, escalating in tandem with lymph node and distant metastasis progression. CTCs levels intricately correlate with progression-free survival and overall survival, standing as pivotal indicators for appraising the risk of recurrence and metastasis.[10]

Progressing through decades of research, CTCs detection technologies have attained maturity. Given the minute presence of CTCs in peripheral blood, the detection procedure entails discrete phases: separation, enrichment, and identification analysis. Enrichment methods harness biological and physical tumor cell traits to segregate CTCs from blood cells, enhancing sensitivity. Non-marker-reliant enrichment strategies encompass technologies like Isolation by Size of Epithelial Tumor cells, density gradient centrifugation, and dielectric electrophoresis. Identification and analysis of CTCs involve discerning and studying their morphological attributes, surface antigens, genetic materials, and more.[11] Today, prevalent methods encompass immunofluorescence, immunofluorescence in situ hybridization (imFISH), reverse transcription polymerase chain reaction (RT-PCR), flow cytometry (FCM), and the CellSearch system, among others.

As comprehension of CTCs deepens, a plethora of studies unequivocally associate CTCs presence with postoperative recurrence and metastasis in CRC patients.[12–15] However, consensus on the value of CTCs in this field remains elusive. Thus, this meta-analysis and systematic review endeavor to assess the prognostic value of CTC detection concerning postoperative recurrence and metastasis in CRC, seeking to reconcile disparate viewpoints within this critical domain.

2. Methods

2.1. Study registration

This systematic review and meta-analysis protocol adheres to the Preferred Reporting Items for Systematic Reviews and

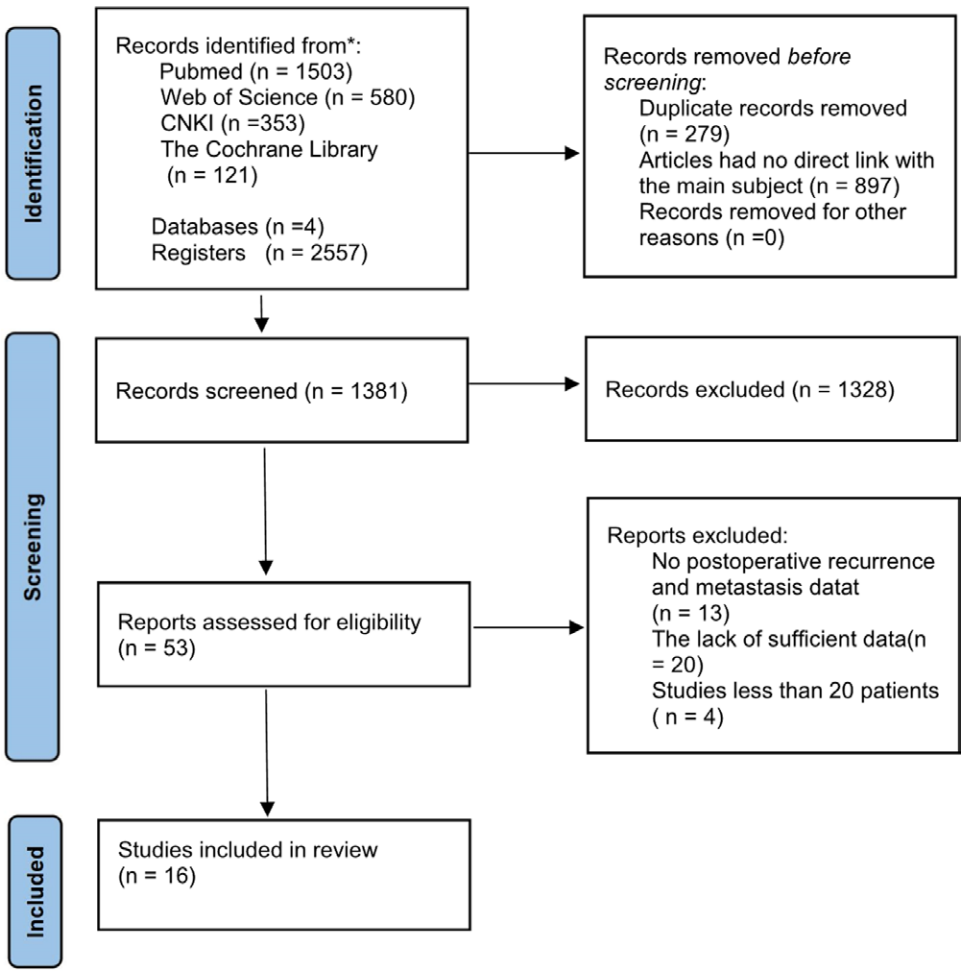

Figure 1. Flow diagram of study selection.

Table 1

Characteristics of included studies.

Study ID	Country	Study type	Study period	No. of patients	Age	Female, %	Tumor stage	Detection method	Sampling time	Mark	Treatment methods	Follow-up time, median (range)
Ito, 2002	Japan	R	1995–1997	99	NR	NR	I–III	RT-PCR	After surgery	CEA mRNA	Curative surgery	(1–59), mo
Bessa, 2003	Spain	P	1996–1999	66	>73, 31 (47%)	65	I–III	RT-PCR	24 h after radical surgery	CEA mRNA	"no-touch" surgery + post-operative adjuvant chemotherapy (II, III)	36 (14–73), mo
Allen-mersh, 2007	UK	P	1997–2003	147	67.4 ± 13.2	43.8	Dukes'A–C	RT-PCR	24 h and 1 wk after surgery	CEA or CK20	Surgical treatment + adjuvant chemotherapy	1393 (888–1769), days
Uen, 2007	Taiwan	P	2002–2005	194	64.9 (28–90)	45.9	II	Membrane-Arrays	1 wk after surgery	hTERT; CK-19; CK-20; CEA	Radical resection + adjuvant chemotherapy	40 (14–62), mo
Sadahiro, 2007	Japan	P	2000–2002	200	NR	43.5	I–III	RT-PCR	Between 7 and 10 d after surgery	CEA mRNA	Surgical treatment	52 (34–69), mo
Uen, 2008	Taiwan	P	2002–2005	438	65.6 ± 13.1	46.6	I–III	Membrane-Arrays	1 wk after operation	hTERT; CK-19; CK-21; CEA	Radical resection + adjuvant chemotherapy	41 (21–66), mo
Lu, 2011	Taiwan	R	2004–2008	141	64.1 ± 12.1	46.8	II–III	Membrane-Arrays	4 wk after operation	hTERT; CK-19; CK-20; CEA	Radical resection + adjuvant chemotherapy	40 (16–72), mo
Lu, 2013	Taiwan	R	2007–2010	90	63.1 ± 12.9	43.3	III	Membrane-Arrays	1 wk and 4 wk after completion of adjuvant chemotherapy	hTERT; CK-19; CK-20; CEA	Radical resection + adjuvant chemotherapy	36 (18–61), mo
Galizia, 2013	Italy	P	NR	69	NR	NR	II–III	CellSearch	1 mo after surgery	NR	Surgical treatment + adjuvant chemotherapy	8, mo
Lieto, 2015	Italy	P	2009–2012	72	NR	38.9	I–IV	FCM	1 mo after surgery	CD26/CD326	Curative resection + adjuvant chemotherapy	25 (3–42), mo
Kust, 2016	Croatia	P	NR	82	66 ± 9.6	60	I–III	RT-PCR	5–7 d after tumor resection	CK20	Surgical treatment	50 (1–60), mo
Pang, 2017	China	R	2014–2015	88	61 ± 14	46.6	II–IV	Second generation IF	1/6/12 mo after surgery	NR	Surgical treatment + adjuvant chemotherapy	12, mo
Wang, 2019	China	P	2015–2017	120	63	41.5	II–III	imFISH	3 d after operation	anti-CD45	Surgical treatment	Every 3 mo
Yao, 2019	China	R	2014–2017	72	63 (36–89)	36.1	I–III	CellSearch	After operation and before chemotherapy	anti-CD45	Curative resection + adjuvant chemotherapy	(1–12), mo
Yu, 2020	China	P	2015–2017	73	64.3(29–85)	54.8	II	imFISH	7th postoperative d	anti-CD45	Curative resectio + post-operative adjuvant chemotherapy	22.1 (3.5–25.9), mo
Fu, 2020	China	P	2012–2016	97	65.4 ± 4.9	50.5	I–IV	Second generation IF	After operation	NR	Curative resectio + post-operative adjuvant chemotherapy	(24–61), mo

FCM = flow cytometry, IF = immunofluorescence, imFISH = immunity fluorescence in situ hybridization, NR = no reported, P = prospective, R = retrospective, RT-PCR = reverse transcription polymerase chain reaction.

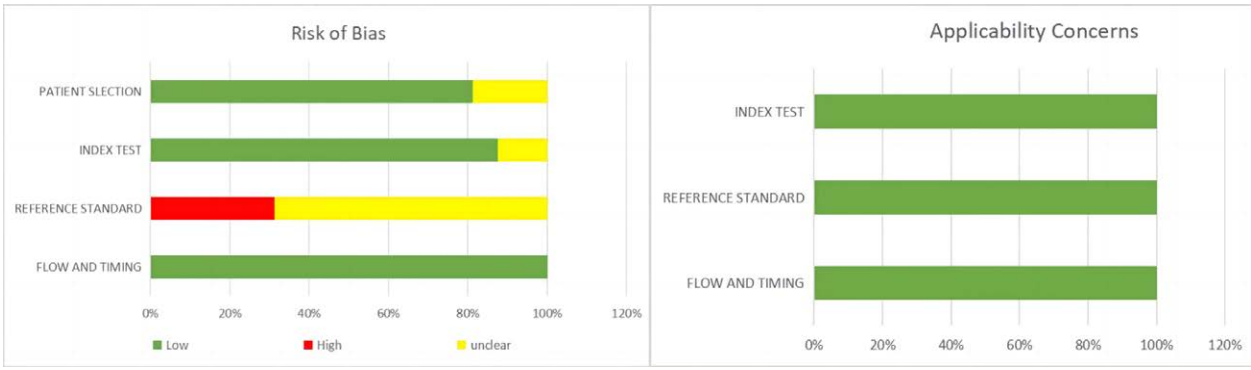

Figure 2. Risk of bias summary.

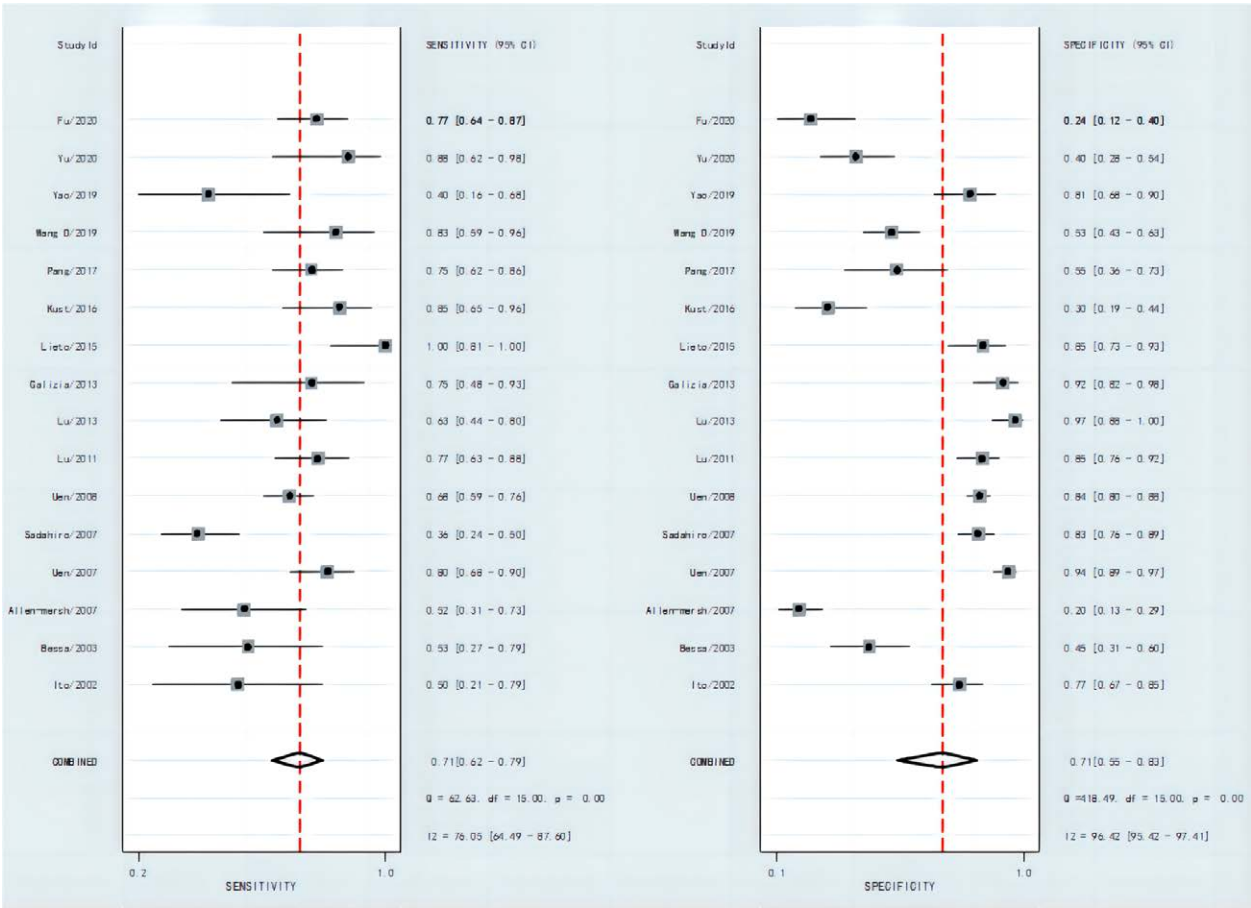

Figure 3. Forest plots of the sensitivity and specificity with corresponding heterogeneity statistics.

Meta-Analyses Protocols (PRISMA-P) guidelines. The protocol has been registered on the international prospective register of systematic reviews under registration number CRD42023409866.

2.2. Ethical review

As this meta-analysis constitutes a secondary analysis based on previously published data, no ethical approval or informed consent is necessary.

2.3. Literature search

Conforming to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a comprehensive literature search will be conducted across PubMed, Web of Science, China National Knowledge Infrastructure, and the Cochrane Library. The search will encompass the period from inception to March 2023. Supplementary to this, reference lists of relevant systematic reviews and meta-analyses will be scrutinized for additional eligible studies.

2.4. Search strategy

The search strategy will be devised collaboratively based on the guidelines provided in the Cochrane handbook. Employing a strategic selection of search terms, including "colorectal cancer," "CRC," "colorectal neoplasm," "colorectal tumor," "metastatic," "postoperative recurrence," "postoperative metastatic,"

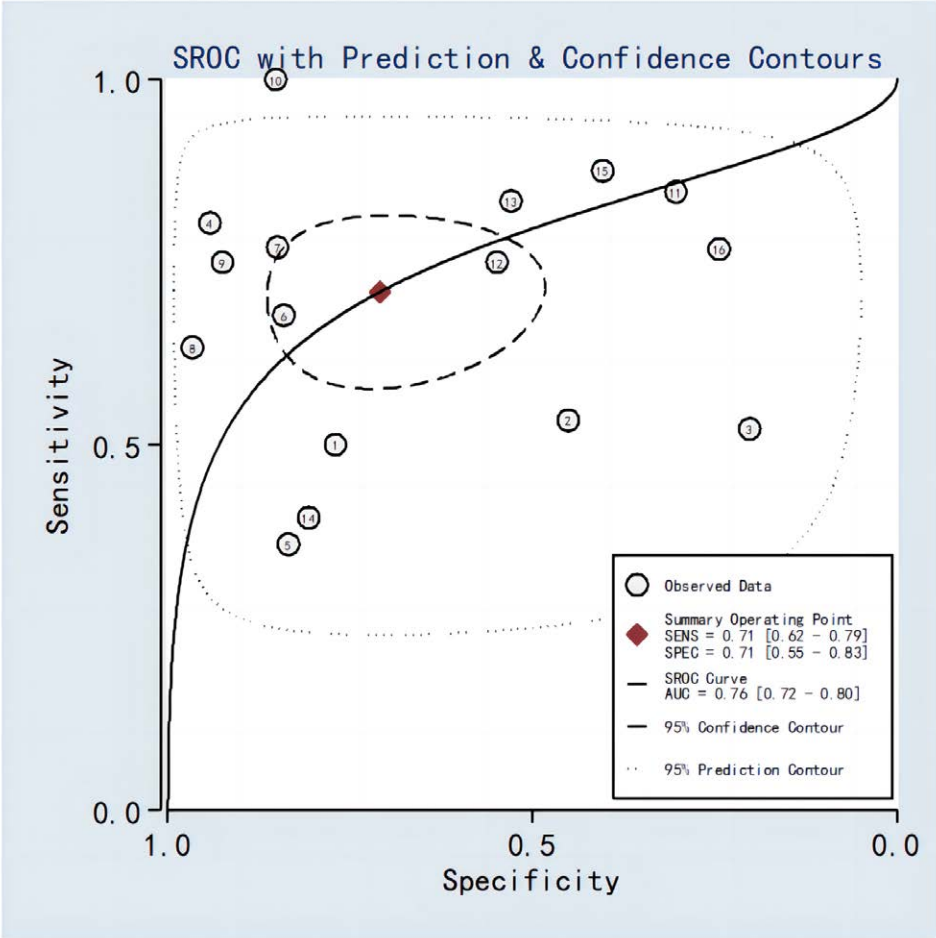

Figure 4. Summary receiver operating characteristic (SROC) curve of the predictive accuracy of CTCs detection. CTCs = circulating tumor cell.

and "circulating tumor cells" or "CTCs," the retrieval strategy will be tailored to ensure comprehensive coverage. No temporal or linguistic restrictions will be imposed (Table S1, Supplemental Digital Content, http://links.lww.com/MD/L264).

2.5. Eligibility criteria

The studies enrolled in this meta-analysis consisted of both prospective and retrospective studies. We applied the following inclusion criteria: Patients diagnosed with CRC through pathological examination and aged 18 years or older; Studies must encompass post-radical surgery CTC testing with well-described detection methods; Research with sample size more than 20; Studies with complete follow-up data; and Studies reporting or providing sufficient information to calculate true positive, false positive, true negative, and false negative values. There were no restrictions based on language, publication year, publication status, or severity of kidney injury. The exclusion criteria were as follows: Patients who have not undergone curative surgery; Studies with fewer than 20 patients; Studies with insufficient data integrity; and Studies with duplicated data, letters, editorials, case reports, or case series.

2.6. Data extraction

Two independent reviewers will meticulously assess titles, abstracts, and full texts to identify potential eligible studies. Discordances will be resolved through consensus or third-party arbitration. For each study, the following information was recorded: author's name, publication year, country, study period, number of patients, age, sex, tumor stage, detection method, sampling time, mark, treatment methods, follow-up time, and results (including true positive, false positive, true negative, and false negative values).

2.7. Quality assessment

Quality appraisal will be conducted independently by 2 researchers according to standardized criteria, with disagreements resolved through consensus or third-party mediation. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) scale will be employed for this purpose.

2.8. Statistical analyses

Utilizing a bivariate regression model, a summary receiver operating characteristic (sROC) curve will be constructed. Pooled estimates of sensitivity (SEN), specificity, positive likelihood ratios (PLR), negative likelihood ratios (NLR), and diagnostic odds ratio (DOR) will be computed. The area under the sROC curve (AUC) will gauge overall diagnostic accuracy. Heterogeneity assessment will be conducted using Stata (version 14.2) software, employing both the Cochran Q test and I^2 statistic. Based on the degree of heterogeneity, a fixed-effects or random-effects model will be applied. Sensitivity analyses will ensure result robustness, while potential publication bias will be evaluated through Deeks' funnel plot asymmetry tests. Statistical significance will be defined as $P < .05$.

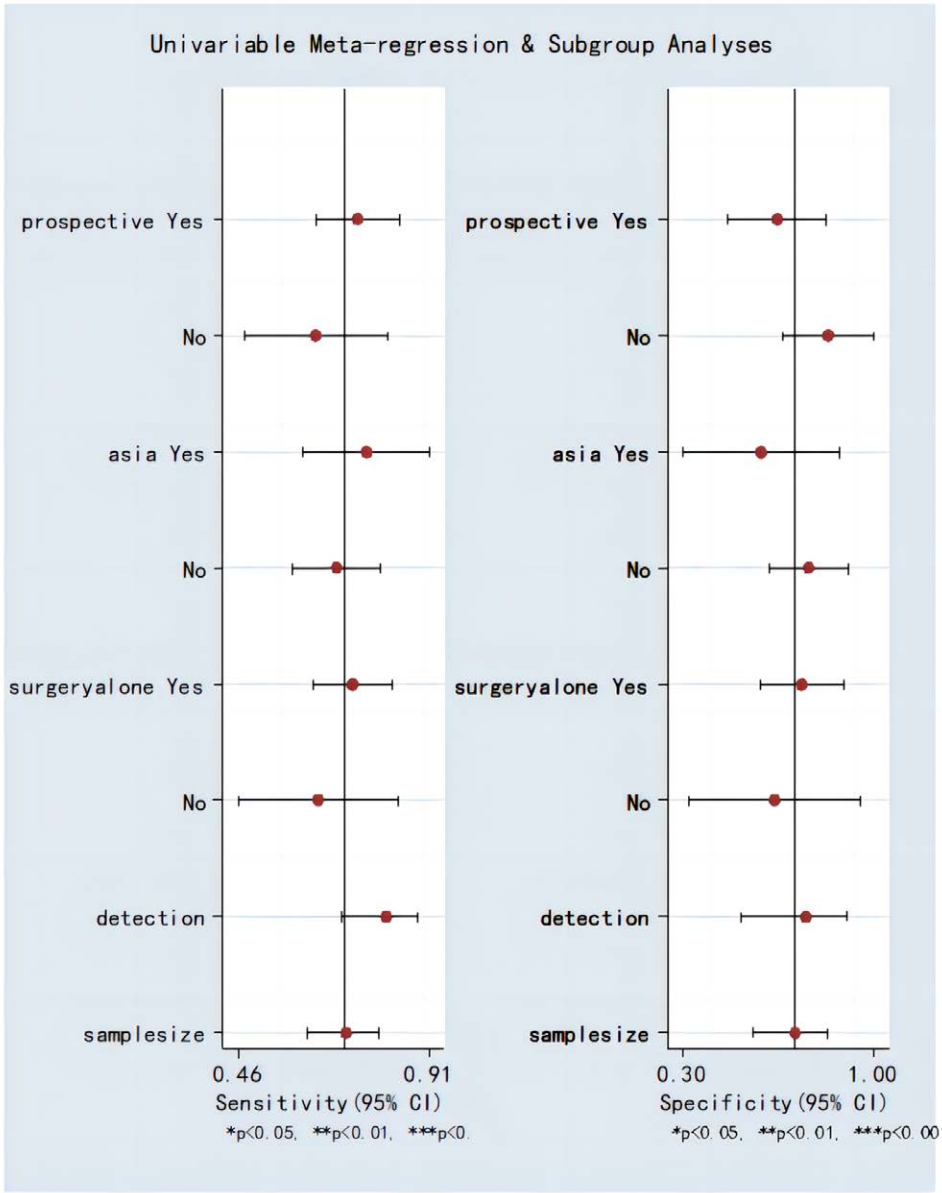

Figure 5. Forest plot of multiple univariable meta-regression and subgroup analyses for SEN and SPE. SEN = sensitivity, SPE = specificity.

3. Result

3.1. Literature search

The exhaustive initial search yielded a total of 2557 potentially relevant studies. Subsequent review of titles and abstracts led to the exclusion of 2504 articles. Upon retrieval of 53 full manuscripts for meticulous scrutiny, 37 studies were subsequently excluded for reasons such as insufficient data (n = 20), absence of postoperative recurrence and metastasis data (n = 13), and studies with fewer than 10 patients (n = 4). This rigorous filtration process culminated in the inclusion of a final set of 16 studies[16–31] that met the established inclusion and exclusion criteria (Fig. 1).

3.2. Characteristics of the included studies

The included studies exhibited sample sizes ranging from 66 to 438 participants, collectively encompassing a total of 2037 individuals. Geographically, these studies predominantly emanated from Europe and Asia, with 11 conducted in Asia (1163 participants, 57.1%) and the remaining 5 in Europe (1245 participants, 42.9%). Among the publications, 3 were in Chinese (19%), with the remaining 13 being in English. Of these studies, 11 were prospective trials, while the remainder adopted retrospective designs. Analysis of the included studies revealed that 8 of them sampled within 7 days post-surgery, with the remainder collecting samples beyond this timeframe. CTC detection methodologies exhibited diversity, with 5 studies employing RT-PCR (584 participants, 28.7%), 4 utilizing Membrane-Arrays (863 participants, 42.4%), 2 applying CellSearch (141 participants, 6.9%), 1 adopting FCM (71 participants, 3.5%), 2 incorporating imFISH (193 participants, 9.5%), and 2 integrating second-generation fluorescence development technology (184 participants, 9.0%) (Table 1).

3.3. Quality assessment

Utilizing the QUADAS-2 tool, quality assessment was concisely presented via a bar graph. The collective quality of the included

Table 2

Pooled results of the meta-analysis of the prognostic value of CTCs detection in colorectal cancer.

Analysis (n)	Senstivity	I^2 (%)	Specificity	I^2 (%)	PLR	I^2 (%)	NLR	I^2 (%)	DOR	I^2 (%)	Heterogeneity	
Study type												
Retrospective (5)	0.66 [0.53, 0.77]	60.6	0.82 [0.67, 0.9]	84.8	3.7 [1.9, 7.1]	81.6	0.42 [0.29, 0.59]	65.4	9 [4, 21]	75.4	Q = 10.387	*P* = .003
Prospective (11)	0.74 [0.62, 0.84]	82.3	0.64 [0.43, 0.81]	97.2	2.1 [1.2, 3.7]	94.8	0.40 [0.23, 0.69]	87.9	5 [2, 15]	90.9	Q = 116.533	*P* = .000
Area												
Asia (11)	0.69 [0.59, 0.78]	77.8	0.76 [0.60, 0.87]	94.7	2.8 [1.7, 4.8]	93.7	0.41 [0.30, 0.55]	80.8	7 [3, 14]	83.9	Q = 96.194	*P* = .000
Europe (5)	0.78 [0.55, 0.91]	80.5	0.59 [0.27, 0.84]	96.9	1.9 [0.7, 4.7]	92.8	0.38 [0.11, 1.27]	89.2	5 [1, 40]	90.9	Q = 7.642	*P* = .011
Detection method												
RT-PCR (5)	0.56 [0.39, 0.71]	77.5	0.52 [0.28, 0.75]	97.2	1.2 [0.8, 1.8]	77.4	0.85 [0.58, 1.26]	75.2	1 [1, 3]	78.6	Q = 64.706	*P* = .000
Membrane-Arrays (4)	0.73 [0.66, 0.79]	39.1	0.90 [0.83, 0.95]	82.0	7.5 [4.2, 13.5]	78.7	0.30 [0.23, 0.39]	43.3	25 [11, 4]	76.0	Q = 1.959	*P* = .188
Others (7)	0.79 [0.65, 0.89]	70.8	0.65 [0.44, 0.82]	93.2	2.3 [1.3, 4.1]	88.9	0.32 [0.17, 0.61]	66.9	7 [2, 22]	75.0	Q = 25.289	*P* = .000
Sampling time												
≤7 days after surgery (8)	0.74 [0.66, 0.81]	57.0	0.56 [0.33, 0.77]	97.7	1.7 [1.0, 3.0]	95.4	0.46 [0.28, 0.77]	86.3	4 [1, 11]	91.9	Q = 80.495	*P* = .000
>7 days after surgery (8)	0.68 [0.50, 0.81]	84.6	0.82 [0.69, 0.90]	89.2	3.8 [1.9, 7.3]	85.9	0.39 [0.24, 0.66]	82.6	10 [3, 28]	83.2	Q = 27.998	*P* = .000

CTCs = circulating tumor cell, DOR = diagnostic odds ratio, NLR = negative likelihood ratios, PLR = positive likelihood ratios, RT-PCR = reverse transcription polymerase chain reaction.

studies was notably high, reflecting meticulous adherence to methodological rigor (Fig. 2 and Table S2, Supplemental Digital Content, http://links.lww.com/MD/L265).

3.4. Meta analysis results

Pooling the outcomes, the sensitivity, specificity, PLR, NLR, and DOR of peripheral blood CTCs in detecting CRC recurrence or metastasis were computed. The sensitivity and specificity were estimated at 0.71 (95% CI, 0.62–0.79) and 0.71 (95% CI, 0.55–0.83) respectively. PLR, NLR, and DOR were calculated as 2.4 (95% CI, 1.5–4.0), 0.41 (95% CI, 0.29–0.58), and 6 (95% CI, 3–13) (Fig. 3). The sROC curve, depicted in Figure 4, showcased an AUC of 0.76 (95% CI, 0.72–0.80).

3.5. Heterogeneity and subgroup analysis

Threshold effect analysis indicated minimal impact (2.5%, $P = .927$), while non-threshold effect-related heterogeneity analysis revealed significant heterogeneity (Q = 93.34, $P = .00$, $I^2 = 88.8\%$) among the studies (Fig. 5). Subgroup analyses were conducted based on CTC detection methods, region, study design, and sampling timing, yielding insights into factors potentially influencing the observed heterogeneity (Table 2).

3.6. Predictive assessment and likelihood ratios

Utilizing the informative Fagan plot, this meta-analysis succinctly illustrates the clinical implications. Given a pretest probability of colorectal cancer set at 20%, the Fagan plot clarifies that a negative CTCs detection outcome is associated with a post-test probability of colorectal cancer at 9%. In contrast, a positive CTCs detection outcome elevates the post-test probability to 38%, thereby highlighting the diagnostic impact of CTC assessment within the context of colorectal cancer (Fig. 6). Moreover, the likelihood ratio scattergram captures a consolidated depiction of likelihood ratios plotted as a function of mean SEN (Fig. 7). This discerning visualization accentuates the relationship between the diagnostic accuracy metrics, thereby furnishing a comprehensive insight into the test's diagnostic potential within this meta-analysis.

3.7. Publication bias and sensitivity analysis

Publication bias assessment via Deek's funnel plot asymmetry test revealed insignificance ($P = .42$), implying a lack of substantial publication bias (Fig. 8). Additionally, sensitivity analysis, post-removal of the outlier study,[20] affirmed the stability of results, underlining the robustness of the pooled outcomes.

4. Discussion

Significant strides have been achieved in the investigation of circulating tumor cells; however, the link between their presence and the subsequent recurrence and metastasis in colorectal cancer patients remains a subject of dispute. Our findings underscore the utility of CTCs detection in discerning the presence of CRC, identifying recurrent and metastatic CRC patients with the sensitivity and specificity of more than 70%. The calculated results of PLR, NLR, DOR and AUC collectively underscore CTC detection's favorable predictive accuracy. This holds significance as disseminated tumor cells represent a pivotal precursor to distant metastases.

In a comprehensive meta-analysis conducted by Yang et al,[32] the identification of CTCs in Peripheral Blood (PB) using Reverse Transcription-Polymerase Chain Reaction (RT-PCR) emerged as a prognostic factor for non-metastatic CRC patients. Positive CTC status correlated with unfavorable prognoses and adverse clinicopathological indicators. Notably, Cohen's investigation revealed that 26% of subjects exhibited adverse CTC counts (3 CTCs per 7.5 mL of blood).[33] Elevated baseline CTC levels were observed in patients with hepatic metastases and impaired performance status.[34] Further insights from Bork's work unveiled distinct CTC detection rates between non-metastatic (3 CTCs, 4.9%) and metastatic (9 CTCs, 10.5%) cohorts, suggesting diagnostic potential.[35]

Among the various Polymerase Chain Reaction (PCR)-based markers for CTC detection, identifying specific mRNAs remains prominent due to its focus on viable CTCs. This approach employs RT-PCR to detect tumor-related genes or epithelial antigens like CK19, CK7, and HER-2, indicative of active CTC presence.[36] Remarkably, Pantel's study showcased the robustness of RT-QCPR in detecting CK19 mRNA in breast cancer patients' blood, albeit its efficacy may be limited by post-EMT gene expression changes.[37] The small number of detectable tumor cells through CTC detection verifies micro-metastasis in peripheral blood, an arduous task for pathology or radiology.

This meta-analysis's core focus pertains to the prognostic implications of CTC detection concerning postoperative CRC recurrence and metastasis. However, the challenge

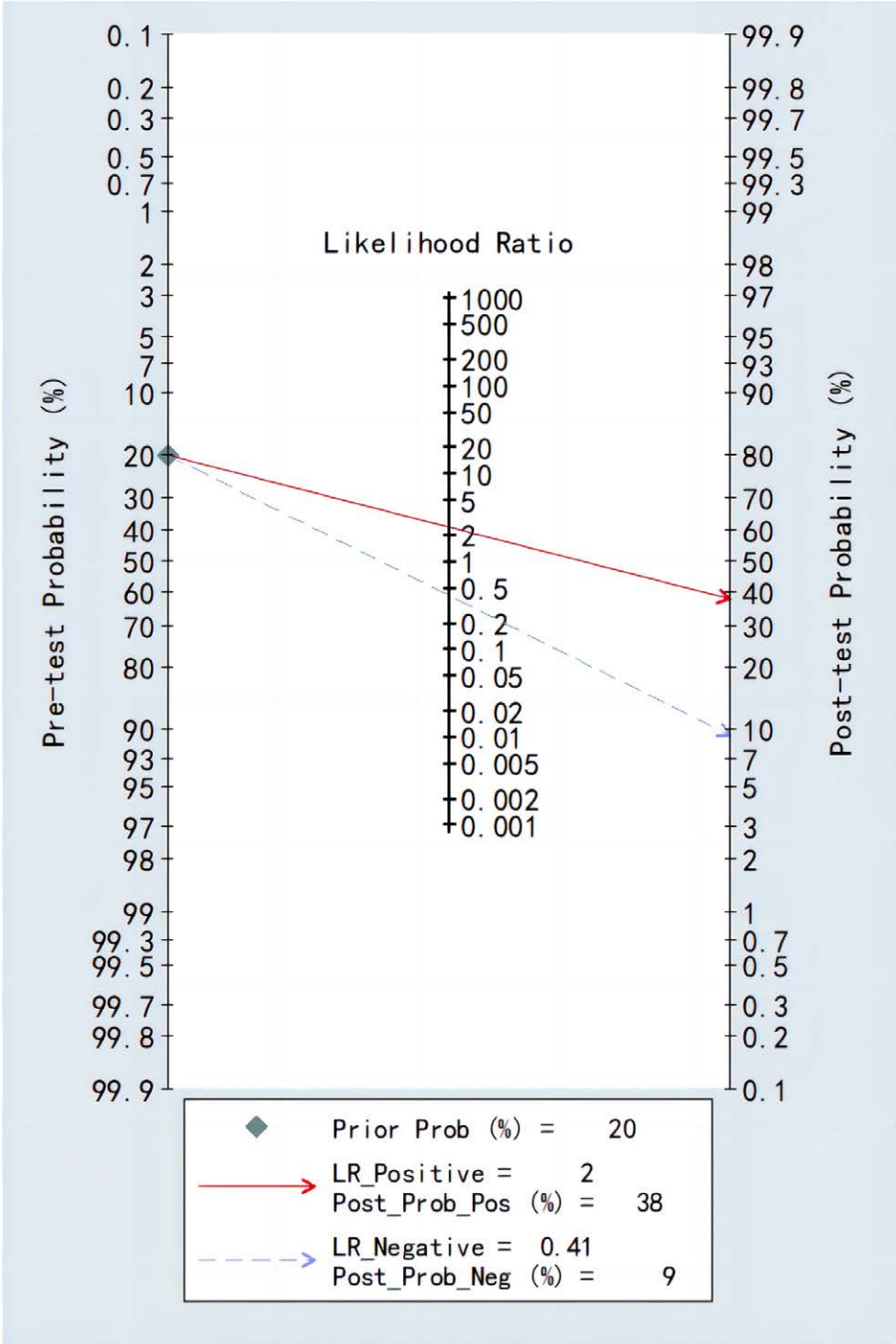

Figure 6. Fagan plot presents the clinical utility of circulating tumor cells.

of isolating cells from low-concentration CTC blood samples underscores the methodological imperative in CTC detection selection. Heterogeneity looms as a potential concern, as divergent methods might exacerbate its presence. Accordingly, subgroup analysis has proven essential. The analysis demonstrated that prospective studies yielded a SEN of 0.74, surpassing the retrospective group's 0.66. Geographical stratification unveiled SEN scores of 0.69 (Asia) and 0.78 (Europe), and CTC detection methods including RT-PCR, Membrane-Arrays, and others demonstrated distinct SEN values of 0.56, 0.73, and 0.79, respectively. Membrane-Arrays exhibited promise, combining time-efficiency, cost-effectiveness, and high-throughput capacity,[38] albeit with concerns raised by Wu's analysis.[39] The value-added of our study lies in the integration of the China National Knowledge Infrastructure database, augmenting our research with additional subgroup analyses stratified by study design and research region. This methodological refinement enhances the depth and breadth of our investigation, ultimately yielding a more comprehensive body of evidence. Furthermore, Gervasoni's work highlighted RT-PCR's superiority in detecting tumor-associated markers,[40] lending credence to its value in CRC prognosis. Subgroup analysis based on post-surgery duration indicated

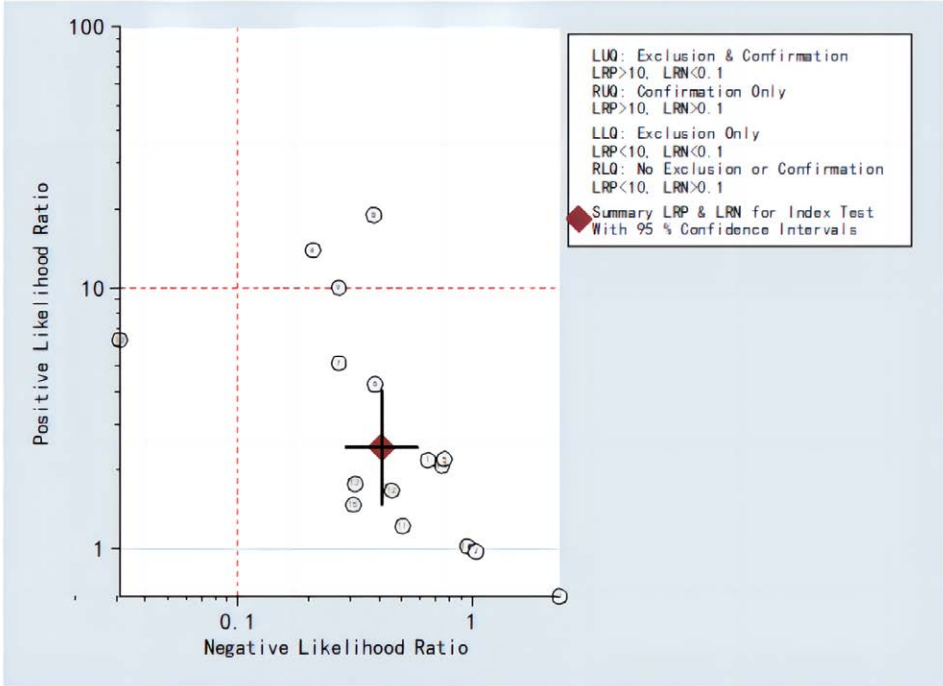

Figure 7. Negative likelihood ratio scattergram.

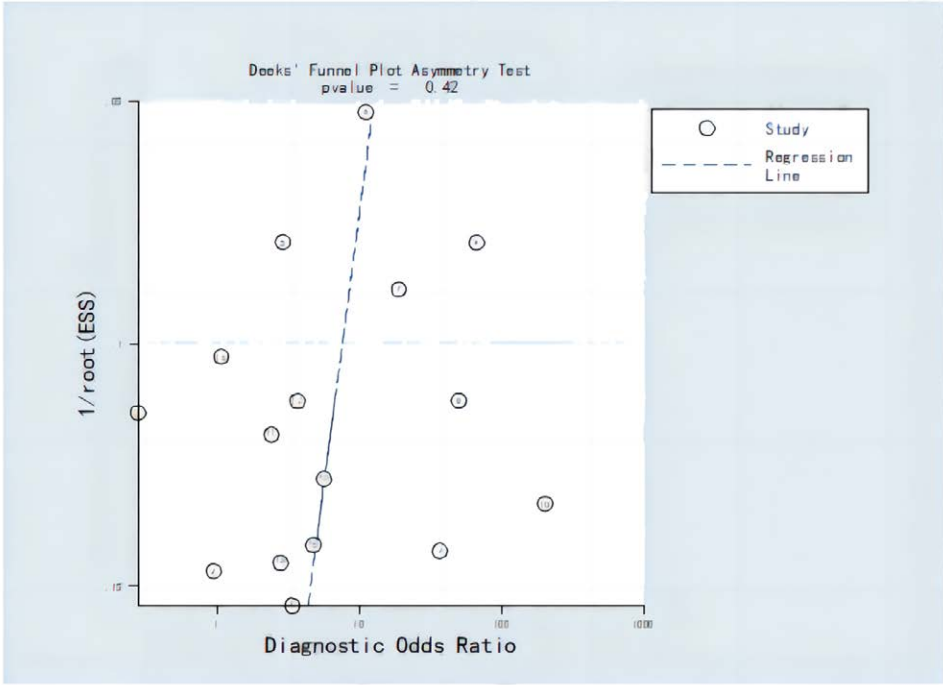

Figure 8. Deek's Funnel Plot for assessment of publication bias.

that CTC detection 7 days post-surgery exhibited a stronger correlation with CRC recurrence and metastasis.

Nonetheless, limitations temper the findings. Heterogeneity stemming from dissimilar study attributes, such as sampling times, demands consideration. Surgery-induced CTC entrance may inflate SEN, while chemotherapy could eliminate CTCs. Unpublished data's absence could impact results, and incomplete treatment documentation obscures further analysis. Substantiation and quantification of CTC detection's prognostic value warrant continued research.

5. Conclusions

In summary, this study underscores CTC detection's potential as a noninvasive prognostic tool for metastatic CRC recurrence and metastasis. The promising membrane array method emerges as an asset in predicting postoperative CRC outcomes, particularly when applied 7 days post-surgery. This investigation's significance is underscored by its potential to guide clinical practice in managing CRC patients' postoperative trajectory.

Author contributions

Conceptualization: Liping Hu.
Data curation: Hui Lan, Xia Liu.
Formal analysis: Hui Lan.
Investigation: Xia Liu.
Methodology: Liping Hu.
Project administration: Xia Liu, Li Wang, Liping Hu.
Software: Dongmei Yang.
Supervision: Liping Hu.
Validation: Xia Liu.
Visualization: Dongmei Yang.
Writing – original draft: Xia Liu.
Writing – review & editing: Hui Lan, Dongmei Yang, Li Wang, Liping Hu.

References

[1] Hinoi T, Akyol A, Theisen BK, et al. Mouse model of colonic adenoma-carcinoma progression based on somatic Apc inactivation. Cancer Res. 2007;67:9721–30.
[2] Kanthan R, Senger JL, Kanthan SC. Molecular events in primary and metastatic colorectal carcinoma: a review. Patholog Res Int. 2012;2012:597497.
[3] Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012 [published correction appears in CA Cancer J Clin 2012 Sep-Oct;62(5):348]. CA Cancer J Clin. 2012;62:220–41.
[4] Tauriello DV, Calon A, Lonardo E, et al. Determinants of metastatic competency in colorectal cancer. Mol Oncol. 2017;11:97–119.
[5] Klein CA. Parallel progression of primary tumours and metastases. Nat Rev Cancer. 2009;9:302–12.
[6] Kim MY, Oskarsson T, Acharyya S, et al. Tumor self-seeding by circulating cancer cells. Cell. 2009;139:1315–26.
[7] Allard WJ, Matera J, Miller MC, et al. Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. Clin Cancer Res. 2004;10:6897–904.
[8] Pantel K, Speicher M. The biology of circulating tumor cells. Oncogene. 2016;35:1216–24.
[9] Lin D, Shen L, Luo M, et al. Circulating tumor cells: biology and clinical significance. Signal Transduc Targeted Ther. 2021;6:404.
[10] Praharaj PP, Bhutia SK, Nagrath S, et al. Circulating tumor cell-derived organoids: current challenges and promises in medical research and precision medicine. Biochim Biophys Acta Rev Cancer. 2018;1869:117–27.
[11] Asante DB, Morici M, Mohan GRKA, et al. Multi-marker immunofluorescent staining and PD-L1 detection on circulating tumour cells from ovarian cancer patients. Cancers (Basel). 2021;13:6225.
[12] Osumi H, Shinozaki E, Yamaguchi K, et al. Clinical utility of circulating tumor DNA for colorectal cancer. Cancer Sci. 2019;110:1148–55.
[13] Seeberg LT, Brunborg C, Waage A, et al. Survival impact of primary tumor lymph node status and circulating tumor cells in patients with colorectal liver metastases. Ann Surg Oncol. 2017;24:2113–21.
[14] Lu Y, Wang P, Peng J, et al. Meta-analysis reveals the prognostic value of circulating tumour cells detected in the peripheral blood in patients with non-metastatic colorectal cancer. Sci Rep. 2017;7:905.
[15] Aggarwal C, Meropol NJ, Punt CJ, et al. Relationship among circulating tumor cells, CEA and overall survival in patients with metastatic colorectal cancer [published correction appears in Ann Oncol 2013 Oct;24(10):2708–10] [published correction appears in Ann Oncol 2013 Oct;24(10):2708–10]. Ann Oncol. 2013;24:420–8.
[16] Allen-Mersh TG, McCullough TK, Patel H, et al. Role of circulating tumour cells in predicting recurrence after excision of primary colorectal carcinoma. Br J Surg. 2007;94:96–105.
[17] Bessa X, Piñol V, Castellví-Bel S, et al. Prognostic value of postoperative detection of blood circulating tumor cells in patients with colorectal cancer operated on for cure. Ann Surg. 2003;237:368–75.
[18] Fu Y, Lu W, Li H. Correlation between the levels of serum CTCs, CA125, CEA and CA19-9 and recurrence or metastasis after colorectal cancer surgery. Chinese J Coal Industry Med. 2020;23:143–8.
[19] Gazzaniga P, Gianni W, Raimondi C, et al. Circulating tumor cells in high-risk nonmetastatic colorectal cancer. Tumour Biol. 2013;34:2507–9.
[20] Lieto E, Galizia G, Orditura M, et al. CD26-positive/CD326-negative circulating cancer cells as prognostic markers for colorectal cancer recurrence. Oncol Lett. 2015;9:542–50.
[21] Ito S, Nakanishi H, Hirai T, et al. Quantitative detection of CEA expressing free tumor cells in the peripheral blood of colorectal cancer patients during surgery with real-time RT-PCR on a LightCycler. Cancer Lett. 2002;183:195–203.
[22] Kust D, Šamija I, Kirac I, et al. Cytokeratin 20 positive cells in blood of colorectal cancer patients as an unfavorable prognostic marker. Acta Clin Belg. 2016;71:235–43.
[23] Lu CY, Uen YH, Tsai HL, et al. Molecular detection of persistent postoperative circulating tumour cells in stages II and III colon cancer patients via multiple blood sampling: prognostic significance of detection for early relapse. Br J Cancer. 2011;104:1178–84.
[24] Lu CY, Tsai HL, Uen YH, et al. Circulating tumor cells as a surrogate marker for determining clinical outcome to mFOLFOX chemotherapy in patients with stage III colon cancer. Br J Cancer. 2013;108:791–7.
[25] Pang M, Luo K, Ttou N, et al. Colorectal Cancer Patients with Peripheral Circulating Tumor Cells of the Change and Clinical Significance. Chengdu: Department of Gastrointestinal JsMrgew, Siehuan Academy of Medical Science; 2017;34:35–7.
[26] Sadahiro S, Suzuki T, Maeda Y, et al. Detection of carcinoembryonic antigen messenger RNA-expressing cells in peripheral blood 7 days after curative surgery is a novel prognostic factor in colorectal cancer. Ann Surg Oncol. 2007;14:1092–8.
[27] Uen YH, Lin SR, Wu DC, et al. Prognostic significance of multiple molecular markers for patients with stage II colorectal cancer undergoing curative resection. Ann Surg. 2007;246:1040–6.
[28] Uen YH, Lu CY, Tsai HL, et al. Persistent presence of postoperative circulating tumor cells is a poor prognostic factor for patients with stage I-III colorectal cancer after curative resection. Ann Surg Oncol. 2008;15:2120–8.
[29] Wang D, Yang Y, Jin L, et al. Prognostic models based on postoperative circulating tumor cells can predict poor tumor recurrence-free survival in patients with stage II-III colorectal cancer. J Cancer. 2019;10:4552–63.
[30] Yao P. The clinical significance of circulating tumor cells and inflammatory parameters in patients with colorectal cancer. J Dalian Med Univ. 2020;4:734–35.
[31] Yu JH, Wang D, Jin L, et al. Utility of circulating tumor cells in stage II colorectal cancer patients undergoing curative resection. Transl Cancer Res. 2020;9:1487–94.
[32] Yang C, Zou K, Zheng L, et al. Prognostic and clinicopathological significance of circulating tumor cells detected by RT-PCR in non-metastatic colorectal cancer: a meta-analysis and systematic review. BMC Cancer. 2017;17:725.
[33] Cohen SJ, Punt CJ, Iannotti N, et al. Relationship of circulating tumour cells to tumour response, progressionfree survival, and overall survival in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26:3213–21.
[34] Tan Y, Wu H. The significant prognostic value of circulating tumor cells in colorectal cancer: a systematic review and meta-analysis. Curr Probl Cancer. 2018;42:95–106.
[35] Bork U, Rahbari NN, Schölch S, et al. Circulating tumour cells and outcome in non-metastatic colorectal cancer: a prospective study. Br J Cancer. 2015;112:1306–13.
[36] Ignatiadis M, Xenidis N, Perraki M, et al. Different prognostic value of cytokeratin-19 mRNA positive circulating tumor cells according to estrogen receptor and HER2 status in early-stage breast cancer. J Clin Oncol. 2007;25:5194–202.
[37] Pantel K, Brakenhoff RH, Brandt B. Detection, clinical relevance and specific biological properties of disseminating tumour cells. Nat Rev Cancer. 2008;8:329–40.
[38] Wang JY, Yeh CS, Chen YF, et al. Development and evaluation of a colorimetric membrane-array method for the detection of circulating tumor cells in the peripheral blood of Taiwanese patients with colorectal cancer. Int J Mol Med. 2006;17:737–47.
[39] Wu J, Li Z, Zou J, et al. A meta-analysis of the value of circulating tumor cells in monitoring postoperative recurrence and metastasis of colorectal cancer. PLoS One. 2022;17:e0274282.
[40] Gervasoni A, Sandri MT, Nascimbeni R, et al. Comparison of three distinct methods for the detection of circulating tumor cells in colorectal cancer patients. Oncol Rep. 2011;25:1669–703.