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Circulating tumor DNA as a biomarker in selected Solid Tumors: An Evidence Mapping

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Review question / Objective: **Population: Solid tumors (stomach cancer, liver cancer, biliary cancer, esophageal cancer, head and neck cancer, pancreatic cancer, ovarian cancer, cervical cancer, endometrial cancer, bladder cancer, urothelium carcinoma). Predictive factors: ctDNA detected; Intervention/comparator: No limitation. Outcomes: Primary outcomes: Progression-free survival (PFS); Include Relapse-free survival (RFS)、Disease free survival (DFS)、DMFS (Distant Metastasis-Free Survival)、Event-free survival(EFS). Overall survival (OS). Secondary outcome: MRD positive rate; Recurrence/relapse rate; Lead time; positive and negative predictive values(NPV/PPV). Study design: RCT(randomized controlled trial), CCT(clinical controlled trial), cohort study, and case control studies. Publication year: 2017-2022.04.02.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 October 2022 and was last updated on 12 October 2022 (registration number INPLASY2022100047).

INTRODUCTION

Review question / Objective: **Population: Solid tumors (stomach cancer, liver cancer, biliary cancer, esophageal cancer, head and neck cancer, pancreatic cancer, ovarian cancer, cervical cancer, endometrial cancer, bladder cancer, urothelium carcinoma). Predictive factors: ctDNA detected; Intervention/comparator: No limitation. Outcomes: Primary outcomes: Progression-free survival (PFS); Include Relapse-free survival (RFS)、Disease free survival (DFS)、DMFS (Distant Metastasis-Free Survival)、Event-free survival(EFS). Overall survival (OS). Secondary outcome: MRD positive rate;**

Recurrence/relapse rate; Lead time; positive and negative predictive values(NPV/PPV). Study design: RCT(randomized controlled trial), CCT(clinical controlled trial), cohort study, and case control studies. Publication year: 2017-2022.04.02.

Background: With the rapid progress of high-throughput sequencing and liquid biopsy approach, plasma-based circulating tumor DNA (ctDNA) analysis has emerged as a potential prognostic or predictive biomarker for many solid tumors. Studies have shown that ctDNA levels generally correlate with tumor burden and can be used to monitor all stages of tumor development1-3. For patients eligible for definitive therapy, some studies have measured ctDNA levels to assess the existence of minimal residual disease (MRD), which often leads to disease recurrence. Single or dynamic blood sampling for ctDNA level detection after definitive therapy can detect disease recurrence earlier than radiographic imaging, and improve the chance of cure through timely intervention4-8. For patients with non-definitive therapy, some studies have shown that ctDNA detection was consistently associated with prognosis, and ctDNA dynamic detection can also predict drug treatment response9-12. Few systematic reviews explored the association of ctDNA with prognosis in patients with different solid tumors. We hoped to present the correlation between ctDNA level detection and prognosis in selected Solid Tumors using a systematic review.

Rationale: This study aims to perform a scoping review to assess the current evidence for an association between ctDNA level and survival endpoints in patients with selected solid tumors. The selected solid tumors of interest include stomach cancer, liver cancer, biliary cancer, esophageal cancer, head and neck cancer, pancreatic cancer, ovarian cancer, cervical cancer, endometrial cancer, bladder cancer, and urothelium carcinoma.

METHODS

Strategy of data synthesis: Terms: stomach cancer, liver cancer, biliary cancer, esophageal cancer, head and neck cancer, pancreatic cancer, ovarian cancer, cervical cancer, endometrial cancer, bladder cancer, urothelium carcinoma; and circulating tumor DNA. PubMed, Embase and Cochrane library will be searched.

Eligibility criteria: Population：Solid tumors (stomach cancer, liver cancer, biliary cancer, esophageal cancer, head and neck cancer, pancreatic cancer, ovarian cancer, cervical cancer, endometrial cancer, bladder cancer, urothelium carcinoma). Predictive factors: ctDNA detected; Intervention/comparator： No limitation. Outcomes： Primary outcomes: Progression-free survival (PFS); Include Relapse-free survival (RFS)、Disease free survival (DFS)、DMFS (Distant Metastasis-Free Survival)、Event-free survival(EFS). Overall survival (OS). Secondary outcome: MRD positive rate; Recurrence/relapse rate; Lead time; positive and negative predictive values(NPV/PPV). Study design: RCT(randomized controlled trial), CCT(clinical controlled trial), cohort study, and case control studies. Publication year: 2017-2022.04.02.

Source of evidence screening and selection: Two reviewers will independently assess eligible studies' inclusion on the basis of the title, abstract, and keywords. Then, full articles will be obtained for a final decision. Detailed reasons for exclusion of any study considered relevant were clearly stated. A PRISMA flow diagram will be constructed to show the full study-selection process. We will include RCT, CCT, prospective cohort, retrospective cohort, and case-control studies that investigated the association between ctDNA level and survival endpoints in selected solid tumors patients. Review, case series and case reports, will be excluded.

Data management: Two reviewers will extract the data independently using a standardized data extraction form. Any disagreements will be resolved by discussion with a third consultant. Where more information relating to a potentially included study is lacking, we will contact study authors and request further information. A PICOS structure will be used to formulate the data extraction, as follows : We plan to data-extract all relevant characteristics of all included studies, including: 1. General study characteristics (first author name and publication years, country); 2. Methods (study design: prospective cohort, retrospective cohort, case control studies, or RCT (randomized controlled trial), CCT (clinical controlled trial)); 3. Participants (diagnosis, age, gender, total sample size, cancer type, follow-up time, resectable/ unresectable, stage of cancer etc.); 4. ctDNA detection information (Definition of ctDNA+ and ctDNA-, detection technology and sensitivity, detection time, sampling site, sample type, gene panel, etc.); 5. Adjusted factors involved in models to evaluate the association between ctDNA testing and predefined outcomes; 6. Characteristic of predefined outcomes (length of follow-up, definition, and conclusions (Risk ration, Hazard ratio, etc.))

Presentation of the results: Where possible, we will summarize study characteristics and outcome information by using tables and bubble plots. Included studies will be coded according to cancer type, number of studies, total sample size, treatment stage,different outcomes and outcome findings. We will accompany the tables and bubble plots with narrative syntheses of extracted data. The narrative syntheses will also present any limitations of studies included, knowledge gaps identified and highlight areas that need further research.

Language restriction: English or Chinese.

Country(ies) involved: China.

Keywords: ctDNA; MRD; Prognosis; Gastric cancer; Pancreatic cancer; Esophageal cancer; Liver cancer; urothelium carcinoma; head and neck cancer; Ovarian cancer.

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Conflicts of interest: Yaqian Li,Ke Ma,Yexian Yu,Yawei Chen,Jiaxing Sun,Fenghuan Zhang,Zhishou Dong are employees of Genecast Biotechnology Co., Ltd. The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.