Efficacy of Raman spectroscopy in the diagnosis of hepatocellular carcinoma: Protocol for a systematic review and meta-analysis

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Review question / Objective: What is the pooled sensitivity, specificity and accuracy of Raman spectroscopy on the diagnosis of hepatocellular carcinoma?

Condition being studied: Hepatocellular carcinoma (HCC) is one of the severest malignancies in the world with a comparatively high prevalence and disease-related burden. Primary liver cancer was proved to be the seventh with respect to cancer incidences and ranked number 4 in cancer-related mortality worldwide in 2016 alone. Among all histological subtypes of primary liver cancer, HCC is regarded as the most common type, which accounts for about 75% of all cases reported. Although in recent years, old contributing factors like hepatitis B virus (HBV) infection, abnormally high alcohol intake have been gradually controlled, new emerging factors are continuously being discovered. Thus, despite the constantly fluctuating epidemiology, the influence and disease burden of HCC are hardly cut down.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 November 2020 and was last updated on 20 November 2020 (registration number INPLASY2020110089).

INTRODUCTION

Review question / Objective: What is the pooled sensitivity, specificity and accuracy of Raman spectroscopy on the diagnosis of hepatocellular carcinoma?

Rationale: The pooled sensitivity, specificity and accuracy of Raman spectroscopy will be calculated based on the extracted values of true positive, true negative, false positive and false negative values in the clinical trials. The aforementioned data can be extracted based on the charts that
contain the primary data in the clinical trials.

**Condition being studied:** Hepatocellular carcinoma (HCC) is one of the severest malignancies in the world with a comparatively high prevalence and disease-related burden. Primary liver cancer was proved to be the seventh with respect to cancer incidences and ranked number 4 in cancer-related mortality worldwide in 2016 alone. Among all histological subtypes of primary liver cancer, HCC is regarded as the most common type, which accounts for about 75% of all cases reported. Although in recent years, old contributing factors like hepatitis B virus (HBV) infection, abnormally high alcohol intake have been gradually controlled, new emerging factors are continuously being discovered. Thus, despite the constantly fluctuating epidemiology, the influence and disease burden of HCC are hardly cut down.

**METHODS**

**Search strategy:** We will comprehensively and extensively search several widely authenticated databases according to the guidelines for performing meta-analysis, including Web of Science, PubMed/MEDLINE, Cochrane Library, China National Knowledge Infrastructure (CNKI) and ClinicalTrials.gov (http://www.ClinicalTrials.gov) for highly qualified and related articles published from January 2004 to December 2019. The keywords will contain (((((Hepatocellular carcinoma[Title/Abstract]) OR (HCC[Title/Abstract])) OR (hepatocellular cancer[Title/Abstract])) AND (Raman spectroscopy[Title/Abstract])) OR (RS[Title/Abstract])) OR (sensitivity[Title/Abstract]) OR (specificity[Title/Abstract])) OR (accuracy[Title/Abstract]).

**Participant or population:** We include patients pathologically diagnosed with hepatocellular carcinoma who simultaneously went through both the golden comparator (by liver puncture or biopsy after a radical surgery) and Raman spectroscopy.

**Intervention:** As far as we are concerned, our research is a diagnostic test. Therefore, the only intervention will be that the patients should undergo at least once Raman spectroscopy examination.

**Comparator:** The control will be those people who are disease-free or patients with other kinds of diseases other than hepatocellular carcinoma.

**Study designs to be included:** Inclusion criteria: 1) reported the use of RS in HCC diagnosis; 2) being a registered randomized controlled trial or applying any kind of observational designs, including cross-sectional, case-control and cohort designs; 3) reported at least the diagnostic sensitivity, specificity value, or other important parameters like true positive (TP), false positive (FP), true negative (TN) and false negative (FN) values, based on which sensitivity and specificity.

**Eligibility criteria:** Inclusion criteria: 1) reported the use of RS in HCC diagnosis; 2) being a registered randomized controlled trial or applying any kind of observational designs, including cross-sectional, case-control and cohort designs; 3) reported at least the diagnostic sensitivity, specificity value, or other important parameters like true positive (TP), false positive (FP), true negative (TN) and false negative (FN) values, based on which sensitivity and specificity values can be calculated. Meanwhile, we will particularly exclude studies which are letters, editorials, case reports, etc.

**Information sources:** We will comprehensively and extensively search several widely authenticated databases according to the guidelines for performing meta-analysis, including Web of Science, PubMed/MEDLINE, Cochrane Library, China National Knowledge Infrastructure (CNKI) and ClinicalTrials.gov (http://www.ClinicalTrials.gov) for highly qualified and related articles published from January 2004 to December 2019. Furthermore, we also plan to reach out to the authors if necessary. Meanwhile, online resources of
trial registration websites are also intended to be searched.

**Main outcome(s):** The diagnostic sensitivity, specificity and accuracy.

**Additional outcome(s):** The positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio.

**Data management:** Two experienced investigators will subsequently be assigned to extract important data. Primary parameters indicating the diagnostic efficiency and basic information of the articles will be extracted. Generally, these include 9 diagnostic efficiency related parameters including sensitivity, specificity, corresponding TP, TN, FP, FN values, accuracy and spectra data. Meanwhile, parameters concerning the basic characteristics of the studies, including article title, first author, publication year, nationality, department, ethnicity, study design, sex and median age of the patients, enrollment year will also be carefully extracted.

**Quality assessment / Risk of bias analysis:** Two independent reviewers will simultaneously evaluate the methodological quality of each study via the QUADAS guidelines. All QUADAS items will be applied to evaluate eligible studies. The articles will be evaluated in the following processes: sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and others.

**Strategy of data synthesis:** The minimum number of studies required for synthesis will be set at 6. Meanwhile, the level of consistency of the included studies should be medium to high. If the aforementioned criteria can be met, based on the extracted data, we will calculate the sensitivity, specificity, PPV, NPV, OR and DLR with their 95% CIs. The forest plots will be generated in order to display sensitivity and specificity estimates through Meta-Disc version 1.4 (Clinical Biostatistics Unit, UK). To summarize test performance, two meta-analyzing diagnostic accuracy tests will be used: the bivariate model and the hierarchical summary receiver operating characteristic (HSROC) model. We will use these methods to reflect the binomial structure of diagnostic accuracy data, thus jointly summarizing paired measures simultaneously, e.g. sensitivity and specificity or, positive and negative LRs. The said approach will be carried out by metandi (Meta-analysis of diagnostic accuracy using hierarchical logistic regression) command in Stata 14.2 (StataCorp, USA). Meanwhile, summary receiver operator characteristics (SROC) curves will be generated to determine the relationship between sensitivity and specificity. The area under curve (AUC) will be simultaneously calculated to evaluate the overall performance. The SROC curve will be made through Meta-Disc version 1.4 (Clinical Biostatistics Unit, UK). Two researchers (Dr. Hongyu Jin, Department of Liver Surgery, Liver Transplantation Center, West China Hospital, Sichuan University; Dr. Man Zhang, Department of Gynecology and Obstetrics, West China Second University Hospital, Sichuan University) will take part in the aforementioned process. If a discrepancy should occur, another more experienced third-party researcher (Prof. Hui Zhou, Chengdu Women’s and Children’s Central Hospital, School of Medicine, University of Electronic Science and Technology) will take part into the data synthesis process to resolve the disagreement.

**Subgroup analysis:** None.

**Sensibility analysis:** Not intended to do the sensibility analysis.

**Language:** English.

**Country(ies) involved:** China.

**Other relevant information:** None.

**Keywords:** Hepatocellular carcinoma;
Raman spectroscopy; sensitivity; specificity; accuracy.

**Dissemination plans:** We intend to publish the protocol, which will be the main dissemination plan.

**Contributions of each author:**
Author 1 - Hongyu Jin came up with the plans of the research and did the preliminary research. In the meantime, Hongyu Jin took charge of writing the original draft. Additionally, Hongyu Jin assisted Man Zhang in data processing and cross check the data extracted.
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Author 2 - Man Zhang is responsible to research relevant clinical trials published so far and extract the original data.
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