18-FDG PET/CT Predicts Microvascular Invasion in HCC with Promising Accuracy: Protocol for A Systematic Review and Meta-Analysis

Zhang, M1; Jin, H2.

Review question / Objective: Can 18-FDG PET/CT predict microvascular invasion in HCC patients?

Condition being studied: Hepatocellular carcinoma (HCC) is one of the severest malignancies in the world characterized by a comparatively high prevalence and disease-related burden due to high recurrence rate and inability to fulfill early diagnosis. With respect to cancer incidences, primary liver cancer ranked number seven among all cancer categories and even higher in abdominal cancer. Meanwhile, it ranked number 4 in cancer-related mortality worldwide in 2019 alone. Among all histological subtypes of primary liver cancer, HCC is regarded as the most common and relatively severe type, which accounts for about 75% of all cases reported. In recent years, despite the decreasing morbidity of old contributing factors like hepatitis B virus (HBV) infection and abnormally high alcohol intake, novel 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 30 November 2020 and was last updated on 30 November 2020 (registration number INPLASY2020110141).

INTRODUCTION

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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.

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**METHODS**

**Search strategy:** Relying on the guidelines for performing meta-analysis, we will search extensively acknowledged authenticated databases including PubMed/Medline, Web of Science, Cochrane Library, ClinicalTrials.gov (http://www.ClinicalTrials.gov), China National Knowledge Infrastructure (CNKI) for related articles published from January 2008 to November 2020. Articles we primarily searched and identified will be subsequently screened for their quality, relevancy and availability. No language restriction will be used. The keywords (query) of our primary search will be as follows: (((((((Hepatocellular carcinoma[Title/Abstract]) OR (HCC[Title/Abstract]) OR (Liver tumor[Title/Abstract])) OR (Liver mass[Title/Abstract])) AND (Microvascular invasion[Title/Abstract]) OR (MVI[Title/Abstract])) AND (PET-CT[Title/Abstract])) OR (18-FDG PET/CT[Title/Abstract])) OR (18-FDG PET/CT[Title/Abstract])).

**Participant or population:** We include patients pathologically diagnosed with HCC who simultaneously went through both the golden comparator (by liver puncture or biopsy after a radical surgery) and 18-FDG PET/CT.

**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 18-FDG PET/CT.

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

**Study designs to be included:** Randomized controlled trial or applying any kind of observational designs, including cross-sectional, case-control and cohort designs.

**Eligibility criteria:** Inclusion criteria: 1) reported the use of 18-FDG PET/CT 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 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.

**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 plan to independently analyze the final defined articles for primary parameters which indicate the diagnostic efficiency and secondary parameters concerning the basic information of the article. During the process, unexpected discrepancies are planned to be carefully
discussed and resolved. In general, a total of 9 important diagnostic efficiency related parameters will be extracted, including diagnostic sensitivity, specificity, accuracy, TP, TN, FP, FN values as well as spectra values. In addition, secondary parameters which reflect the baseline characteristics of the articles including title, first author, nationality, department, ethnicity, study design, sex and median age of the patients and enrollment year will also carefully be extracted.

Quality assessment / Risk of bias analysis: Standard quality evaluation of the included studies will be performed based on the Quadas-2 tool. Particularly, the risk of bias will be obtained by RevMan 5.3 (The Cochrane Collaboration). 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 outcome data (attrition bias), selective reporting (reporting bias) and others.

Strategy of data synthesis: Data will be extracted on either an article or study level when possible to reconstruct a 2×2 table, which we depend on to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratios (ORs) and diagnostic likelihood ratios (DLRs) with their 95% confidence intervals (CIs). The forest plots will be generated to display sensitivity and specificity estimates using Meta-Disc version 1.4 (Clinical Biostatistics Unit, UK). To summarize test performance, two methods for meta-analysis diagnostic accuracy test will be used: the bivariate model and the hierarchical summary receiver operating characteristic (HSROC) model. We choose to use these methods to respect the binomial structure of diagnostic accuracy data, thus jointly summarizing paired measures simultaneously, e.g. sensitivity and specificity or, positive and negative likelihood ratios (LRs). Meanwhile, as a random effects approach, the bivariate/HSROC meta-analysis allow pooling results in view of knowing that heterogeneity is commonplace across included studies due to different or implicit thresholds. 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).

Subgroup analysis: None.

Sensibility analysis: Not intend to do the sensitivity analysis.

Language: English.

Country(ies) involved: China.

Other relevant information: None.

Keywords: 18-FDG PET/CT; hepatocellular carcinoma; MVI.

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

Contributions of each author:
Author 1 - Man Zhang - The author came up with the plans of the research and did preliminary research. In the meantime, Man Zhang took charge of writing the original draft. Additionally, Man Zhang assisted Hongyu Jin in data processing and cross check the data extracted.
Email: zhangman60710@163.com
Author 2 - Hongyu Jin - The author took charge in reconfirming all data and check and correct the final manuscript.
Email: jinhongyu@stu.scu.edu.cn