INPLASY PROTOCOL

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None declared.

Diagnostic performance of 18F-FDG PET/MR for primary central nervous system lymphoma: A protocol of systematic review and meta-analysis

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Review question / Objective: **The diagnostic efficacy of PET/MR in diagnosing PCNSL is still unknown, and there is no relevant systematic review and meta-analysis to provide evidence-based medical evidence for this topic. Therefore, the aim of this study is to evaluate the validity of PET/MR for the diagnosis of PCNSL by means of a meta-analysis.**
Information sources: **Electronic databases include Wanfang database, SinoMed, China National Knowledge Infrastructure (CNKI), the Cochrane Library, PubMed, and Embase will be searched for relevant candidate articles that reporting the diagnostic performance of 18F-FDG PET/MR in patients with PCNSL until December 2021. We will conduct an updated search before the study is completed. We will further evaluate additional candidate articles by hand searching references in the review or meta-analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 June 2021 and was last updated on 18 January 2022 (registration number INPLASY202160034).

INTRODUCTION

Review question / Objective: **The diagnostic efficacy of PET/MR in diagnosing PCNSL is still unknown, and there is no relevant systematic review and meta-analysis to provide evidence-based medical evidence for this topic. Therefore, the aim of this study is to evaluate the validity of PET/MR for the diagnosis of PCNSL by means of a meta-analysis.**

Condition being studied: **Primary central nervous system lymphoma (PCNSL) is a rare form of extra-nodal non-Hodgkin lymphoma (NHL) that is highly aggressive,**

often involving the brain, eyes, spinal cord and leptomeninges, without evidence of systemic lymphoma. PCNSL accounts for approximately 3-4% of all intracranial malignancies and 4%-6% of extra-nodal lymphomas. The prognosis for PCNSL is very poor compared to Hodgkin's lymphoma (HL), with an overall survival of only 1.5 months if left untreated. Early and rapid diagnosis of PCNSL is very important, but obtaining a rapid clinical diagnosis remains challenging because most lesions are located intracranially and do not have a specific clinical presentation. Stereotactic brain biopsy is the gold standard for the diagnosis of PCNSL. However, this operation is risky and does not apply to all patients. Imaging is the key to PCNSL and can play a crucial role in the non-invasive diagnosis of PCNSL. Enhanced magnetic resonance imaging (MRI) is the first line of recommended imaging for suspected intracranial tumors including PCNSL. Although MRI imaging features are suggestive of PCNSL, they cannot clearly distinguish PCNSL from other lesions with morphologically similar diseases, such as infectious diseases, metastases, and glioblastomas. In modern oncology diagnosis, 18F-flouro-deoxy-glucose positron emission tomography (18F-FDG PET) with or without computed tomography (CT) scan is the most commonly used functional imaging modality. PET with or without CT is also used in the diagnosis of PCNSL. A recent meta-analysis that included 29 original studies suggested that acceptably high diagnostic accuracy of pretreatment FDG-PET(CT) scan in patients with PCNSL. 18F-FDG PET/magnetic resonance (18F-FDG PET/MR) combines the advantages of high sensitivity and bioinformatic visualization of PET and high resolution and feature parameter diversification of MR imaging. PET/MR has advantages in the detection of muscle and soft tissue, parenchymal organs, and central neurological lesions and reduction of radiation dose. PET/MR is also recommended for the diagnosis of PCNSL and has shown good agreement with PET/CT in the diagnosis of PCNSL in some studies.

METHODS

Search strategy: #1 "primary central nervous system lymphoma" OR "primary CNS lymphoma" OR "Primary intracerebral lymphoma" #2 "Positron Emission Tomography Magnetic Resonance " OR "Positron Emission Tomography Magnetic Resonance Imaging" OR “PET-MR Scan” OR “PET-MR Scans” OR “Scan, PET-MR” OR “Scans, PET-MR” OR “PET MR Scan” OR “MR Scan, PET” OR “MR Scans, PET” OR “PET MR Scans” OR “Scan, PET MR” OR “Scans, PET MR” OR “MR PET” OR “Positron Emission Tomography- magnetic resonance” OR “PET-MR” OR “MR PET Scan” OR “MR PET Scans” OR “PET Scan, MR” OR “PET Scans, MR” OR “Scan, MR PET” OR “Scans, MR PET” OR PET/MR OR PET/MRI OR PETMRI OR PET-MRI #3 #1 AND #2.

Participant or population: Participants with untreated PCNSL, regardless of age, gender, or ethnicity.

Intervention: PET/MR will be the index test.

Comparator: This study will evaluate the diagnostic accuracy of PET/MR for PCNSL. Other comparator tests (not the reference standard) are not mandatory, and single arm studies that have evaluated the diagnostic accuracy of PET/MR for PCNSL could be included.

Study designs to be included: This study does not impose any restrictions on the study design, studies that evaluate the diagnostic performance of PET/MR for the diagnosis of PCNSL may be included, whether they are retrospective or case-control studies.

Eligibility criteria: Full text accessible original researches that assessed the PET/MR for the diagnosis of PCNSL will be included. The original study used the reference standard applied in this study protocol. True positive (TP), false positive (FP), false negative (FN), and true negative (TN) values for PET/MR diagnosis of PCNSL will be reported directly in the included original studies or will be available

by calculating. Studies without full TP, FP, FN, TN values, studies reported in languages other than English and Chinese, conference abstracts not available in full text, and case reports will be excluded.

Information sources: Electronic databases include Wanfang database, SinoMed, China National Knowledge Infrastructure (CNKI), the Cochrane Library, PubMed, and Embase will be searched for relevant candidate articles that reporting the diagnostic performance of 18F-FDG PET/MR in patients with PCNSL until June 2022. We will conduct an updated search before the study is completed. We will further evaluate additional candidate articles by hand searching references in the review or meta-analysis.

Main outcome(s): The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic odds ratio (DOR), and the areas under summary receiver operating characteristic (SROC) curves (AUC) of the PET/MR for the diagnosis of PCNSL will be considered as the main outcomes.

Data management: We will import the articles searched from each electronic database into Endnote (Version 9.2) for literature management. We will conduct literature screening based on the inclusion and exclusion criteria identified in this study protocol. Two investigators (Xiaohui Zhu and Shijun Shi) will screen the literature independently, they will cross-check and if there is a dispute, the decision will be discussed with a third investigator (Hong Zheng). The two investigators will confirm whether the study meets the inclusion criteria by reading the title, abstract and then the full text.

Quality assessment / Risk of bias analysis: Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) will be used to assess the methodological quality of each individually included study. This revised assessment tool includes 4 domains (patient selection, index test, reference standard, and flow and timing). The same two investigators will evaluate the risk of bias and applicability for each included study independently. Disputes will be resolved through discussion with a third investigator, just as in the literature screening and data extraction phase.

Strategy of data synthesis: TP, FP, FN, TN values for PET/MR diagnosis of PCNSL extracting from each individually included study will be used to estimate the pooled sensitivity, specificity, PPV, NPV, DOR and their 95% confidence interval (CI). We will use I2 statistics to assess heterogeneity between studies. An I2 of 0% will indicate no heterogeneity between studies, and an I2 greater than 50% will indicate significant heterogeneity between studies. AUC with 95% CI will subsequently be calculated. Threshold effect will be assessed using spearman's correlation between sensitivity and specificity. Stata version 15.0 (Stata Corp., College Station, TX, USA) with the midas command and Meta-Disc software (version 1.4, Clinical Biostatistics Ramón y Cajal Hospital, Madrid, Spain) will be used for perform meta analyses. A p-value less than 0.05 will be considered statistically significant for the analysis.

Subgroup analysis: When significant heterogeneity is indicated, we will explore the sources of heterogeneity through subgroup analysis and meta-regression analysis. Subgroup analysis and meta-regression analysis will be performed on pre-defined parameters, as we determined during the data extraction phase, such as different study design, method of patient selection, type of lesion; type of sample.

Sensitivity analysis: The robustness of analyses will be checked by sensitivity analyses.

Language: No restriction.

Country(ies) involved: China.

Other relevant information: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline will be used to evaluate the quality of evidence. According to this guideline, the quality of evidence will be

classified into four levels: high, moderate, low, and very low. Factors (such as study design, patient populations, outcomes, risk of bias) that can determine and decrease the quality of the evidence will be evaluated to confirm the level of evidence.

Keywords: primary central nervous system lymphoma, diagnostic accuracy, PET/MR, sensitivity, meta-analysis.

Contributions of each author:

Author 1 - Xiaohui Zhu - The author will search databases, select literatures, manage data, assesse quality, feedback and approve the final manuscript.
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Author 2 - Shijun Shi - The author will search databases, select literatures, manage data and evaluate quality.
Author 3 - Xiaowei Qiu - The author will draft and revise the manuscript.
Author 4 - Hong Zheng - The author will provide statistical expertise, read, drafte and revise the manuscript.
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