PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Positron emission tomography (PET) for prediction of glioma histology: Protocol for an individual-level data meta-analysis of test performance.
AUTHORS	Trikalinos, Nikolaos; Nihashi, Takashi; Evangelou, Evangelos; Terasawa, Teruhiko

VERSION 1 – REVIEW

REVIEWER	Ramin Sadeghi Nuclear Medicine Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
REVIEW RETURNED	12-Nov-2017

GENERAL COMMENTS	Thank you for giving me the opportunity to perform a review for your journal again. The manuscript is a protocol of a meta-analysis on PET in glioma. I do not know the policy of your journal regarding the protocols. If you accept protocols, the following comments may help improving the manuscript. 1- the complete search strategy and list of databases should be mentioned in the current protocol. Mere citing another article is not acceptable. 2- The authors should mention if they use any language limits or studies in any language would be accepted. 3- A brief explanation regarding how authors would quantify threshold effect may be needed. A brief explanation on bivariate meta-analysis may also be helpful. 4- How do the authors address publication bias. This is not covered in the protocol.

REVIEWER	Valable Samuel ISTCT, CERVOxy group; France
REVIEW RETURNED	21-Nov-2017

GENERAL COMMENTS	The objective of the present protocole is very attracting and the selected tracers are also very pertinent for glioma. However, while the objective is well presented, the methodology is not clear. I'am confused about the way to perform imaging data extraction. It is hard to believe that data will be extracted drectly from the published papers and a low amount of papers renders raw data available? This point needs to be more clearly explained!

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1- the complete search strategy and list of databases should be mentioned in the current protocol. Mere citing another article is not acceptable. RESPONSE: Agree. Supplementary file (Appendix_literatureSearch) has been added and referenced in the body of the text.

2- The authors should mention if they use any language limits or studies in any language would be accepted.
RESPONSE: Updated in the Literature section. There was no language restriction (line 141)

3- A brief explanation regarding how authors would quantify threshold effect may be needed. A brief explanation on bivariate meta-analysis may also be helpful.

RESPONSE: We will use individual patient data, not the reported results calculated by a study-specific threshold like the regular meta-analysis. Thus, we can calculate sensitivity and specificity estimates at different cut-off values and formally meta-analyze summary ROC curves by synthesizing all individual ROC curves (easily constructed from the IPD) using the approach described in Hellmich M et al. Med Decis Making 1999.

The bivariate meta-analysis calculates a summary estimate of logit-transformed sensitivity and specificity, simultaneously taking account of the correlation between sensitivity and specificity. The mean of this bivariate distribution represents the test's expected operating characteristics. The uncertainty in the estimate is represented by an ellipse in two dimensions with contours representing bivariate quantiles, which is so-called the "elliptical" confidence region. The regression line of the logit-transformed sensitivity on the logit-transformed (1 -specificity) becomes the hierarchical summary ROC curve when transformed back to the regular ROC space of "sensitivity vs. (1 - specificity)" scale. The summary curve describes the tradeoff in sensitivity for specificity as the threshold changes.

4- How do the authors address publication bias. This is not covered in the protocol.

RESPONSE:Two reviewers (TN, NAT) will independently assess patient selection, index test, reference standard, and their flow and timing based on the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2). Discrepant ratings will be resolved by consensus. Methods to detect publication bias are not very reliable when used in diagnostic accuracy data especially in case of heterogeneity and therefore were omitted in the first version of the protocol. Following reviewer's request, we will use the method of Deeks et al that has been shown to be the least biased (Deeks JJ et al. JCE, 2005)

Reviewer: 2
The objective of the present protocole is very attracting and the selected tracers are also very pertinent for glioma. However, while the objective is well presented, the methodology is not clear. I'am confused about the way to perform imaging data extraction. It is hard to believe that data will be extracted drectly from the published papers and a low amount of papers renders raw data available? This point needs to be more clearly explained!

RESPONSE: Thank you for the comment. To clarify: We will extract published data such as visual assessment and quantitative assessment such as standard uptake values (SUVs) or tumor-to-normal uptake ratio (T/N ratio), alongside other survival and histology data. Eligible papers do publish these values in separate tables.

Including individual patient-level data (demographic and clinical data, together with quantitative data on tracer uptakes such as SUVs or T/N and etc.) and/or scatter plots (of SUVs and/or T/N, or other related indexes) in the papers is a common presentation practice in the field of nuclear medicine. We will also contact the authors if IPD are not presented. This statement has been added to the protocol.

VERSION 2 – REVIEW

REVIEWER	Ramin Sadeghi Mashhad University of Medical Sciences, Mashhad, Iran
REVIEW RETURNED	30-Dec-2017

GENERAL COMMENTS	The comments have been addressed. In my opinion the study is acceptable in the current format

REVIEWER	Valable Samuel ISTCT, CERVOxy group
REVIEW RETURNED	09-Jan-2018

GENERAL COMMENTS	None