PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Can 18F-FDG PET/CT predict EGFR status in non-small cell lung cancer patients? A systematic review and meta-analysis
AUTHORS	Du, Bulin; Wang, Shu; Cui, Yan; Liu, Guanghui; Li, Xuena; Li, Yaming

VERSION 1 – REVIEW

REVIEWER	Zirpoli , Gary Boston University, Slone Epidemiology Center
REVIEW RETURNED	18-Nov-2020

GENERAL COMMENTS	In this study, a systematic review and meta-analysis of the use of F-FDG PET/CT to predict EGFR mutations in non-small cell lung cancer patients was conducted. The paper would be improved by addressing the following points. 1. The sentence starting “Although CT has…” on line 42 of page 5 of 28 is confusing to read and should be reworded. 2. SUV_max should be defined on its first use on line 29 of page 6 of 28. 3. WMD should be defined on its first use on line 50 of page 6 of 28. 4. The sentence starting “Additionally, 30…” on line 47 of page 7 of 28 should indicate the number of other language studies that were excluded. 5. The sentence starting “The pooled DOR…” on line 53 of page 8 of 28 lists 2 DORs, but only 1 is in figure 6. Please clarify what the other DOR is. 6. The paragraph starting on line 40 of page 10 of 28 argues against using F-FDG PET/CT for predicting EGFR mutations. One part of this argument is the low DOR, but as mentioned above, 2 DORs are presented in the text, but only the higher DOR is in figure 6. This paragraph should be updated to reflect the correct DOR, whichever it is. This also impacts the conclusion.

REVIEWER	Rolfo, Christian University of Maryland School of Medicine, Greenebaum Comprehensive Cancer Center
REVIEW RETURNED	06-Dec-2020

GENERAL COMMENTS	The manuscript entitled “Can 18F-FDG PET/CT predict EGFR status in NSCLC patients? A systematic review and meta-analysis” analyzed a possible correlation between high SUV and EGFR mutations in lung cancer nodules. - The manuscript may benefit from a language revision by an English native speaker.

	- The Authors should provide the extensive forms for all acronyms, including gene acronyms, through the text when they first appear. - Gene acronyms should be written in italics. - In the Introduction section “Therefore, identification of EGFR mutant has been considered a prognostic marker for TKI therapy in NSCLC.”, the Authors should modify considering that EGFR mutations have a predictive role for TKI administration. Please modify. - In the Introduction section “The standard approach to detecting EGFR status is genetic testing, which is based on tumor specimens captured by invasive needle biopsy.”, the Authors should mention less invasive approaches, such as fine needle aspiration and liquid biopsy. - In the Introduction section “However, this method does not reflect the status of the entire tumor.”, this problem of tissue based approaches may be overcome by liquid biopsy. - In the Introduction section “Although CT has been systematically analyzed to discover risk factors for EGFR mutations in NSCLC [12], 18F-FDG PET/CT was used to predict other biological features or other genetic mutations of certain malignancies through meta-analysis [13–15].”, the Authors should re-phrase. - In the Methods section the Authors should specify if only English article were evaluated and if the NSCLC stage (sec. TNM) was taking into account. In addition a third Authors assessed discordances between the two Authors? - The Authors should better discuss how EGFR analysis was performed. In particular, in the analyzed studies: all analysis were carried out on tissue? As far as molecular platforms and assays are concerned, the studies analyzed showed a similar limit of detection? The same PET procedures were carried out?

REVIEWER	Zhou, Shouhao Pennsylvania State University College of Medicine, Public Health Sciences
REVIEW RETURNED	12-Dec-2020

GENERAL COMMENTS	This is a study of systematic review and meta-analysis to examine the diagnostic significance of 18F-FDG PET/CT for predicting the presence of EGFR mutations in NSCLC patients. In general, the principle / standard procedure of meta-analysis were followed properly. My review and the following comments are with a particular emphasis on the study design and data analyses. 1. The authors need provide a better justification on the objective of the study regarding why PET/CT alone should be considered an alternative approach to genetic testing in assessing EGFR mutation. Even though genetic testing may not reflect the status of the entire tumor, it is still considered as the most accurate approach. For this reason, it is unclear why PET/CT alone should be used to predict EGFR mutational status, rather than as a supplementary approach to generic testing for better sensitivity/specificity. 2. The estimated overall 65% sensitivity and 62% specificity confirmed the concern above. It is worth to mention that the concern #1 was raised before any results were read or related. 3. Some abbreviations were either used without specification (e.g., SUV) or not specified when it was used for the first time (e.g. WMD).

	4. In the meta-analysis, three studies were excluded when 18F-FDG uptake was significantly lower in EGFR mutant group. In my opinion, this is unnecessary for diagnostic meta-analysis. A better approach is to conduct a sensitivity analysis by including those excluded studies and compare results. 5. In Figure 2, there were only 2 studies showing positive WMD. Why were three studies excluded? 6. In reporting of p-values in the results, the decimals should be consistent in the manuscript. In addition, a reporting like "p = 0.00" should be avoided.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Gary Zirpoli , Boston University
Comments to the Author:
In this study, a systematic review and meta-analysis of the use of F-FDG PET/CT to predict EGFR mutations in non-small cell lung cancer patients was conducted. The paper would be improved by addressing the following points.

1.The sentence starting “Although CT has…” on line 42 of page 5 of 28 is confusing to read and should be reworded.

Reply: Thank you for your suggestion. The sentence has been reorganized. See page 4 line 17.

2.SUV_max should be defined on its first use on line 29 of page 6 of 28.

Reply: Thank you for your suggestion. SUVmax (the maximum of standard uptake value) has been defined. See page 5 line 20.

3.WMD should be defined on its first use on line 50 of page 6 of 28.

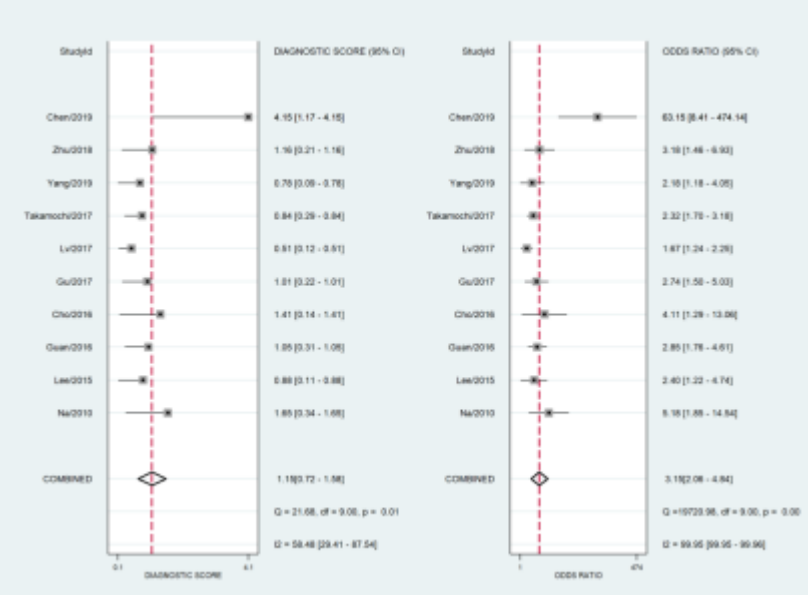
Reply: Thank you for your suggestion. WMD (weighted mean difference) has been defined. See page 6 line 4.

4.The sentence starting “Additionally, 30…” on line 47 of page 7 of 28 should indicate the number of other language studies that were excluded.

Reply: Thank you for your suggestion. The sentence has been rephrased. See page 4 line 17. See page 7 line 5.

5.The sentence starting “The pooled DOR…” on line 53 of page 8 of 28 lists 2 DORs, but only 1 is in figure 6. Please clarify what the other DOR is.

Reply: Sorry for this error. It should be one DOR. “1.15 (95% CI 0.72-1.58)” was the result of diagnostic score. We did not show this result in the end.



6.The paragraph starting on line 40 of page 10 of 28 argues against using F-FDG PET/CT for predicting EGFR mutations. One part of this argument is the low DOR, but as mentioned above, 2 DORs are presented in the text, but only the higher DOR is in figure 6. This paragraph should be updated to reflect the correct DOR, whichever it is. This also impacts the conclusion.

Reply: We are really sorry for the confusion caused by our negligence. As replied in #5, there should be only one DOR.

Reviewer: 2
Prof. Christian Rolfo, University of Maryland School of Medicine
Comments to the Author:
The manuscript entitled “Can 18F-FDG PET/CT predict EGFR status in NSCLC patients? A systematic review and meta-analysis” analyzed a possible correlation between high SUV and EGFR mutations in lung cancer nodules.

- The manuscript may benefit from a language revision by an English native speaker.

Reply: Thank you for your suggestion. The manuscript has been reviewed by an English native speaker.

- The Authors should provide the extensive forms for all acronyms, including gene acronyms, through the text when they first appear.

Reply: Thank you for your suggestion. The extensive forms for all acronyms were renewed.

- Gene acronyms should be written in italics.

Reply: Thank you for your suggestion. The gene acronyms were written in italics.

- In the Introduction section “Therefore, identification of EGFR mutant has been considered a prognostic marker for TKI therapy in NSCLC.”, the Authors should modify considering that EGFR mutations have a predictive role for TKI administration. Please modify.

Reply: Thank you for your suggestion. We have reworded the sentence “it was considered that *EGFR* mutations have a predictive role for TKI administration in NSCLC”. See page 4 line 10.

- In the Introduction section “The standard approach to detecting EGFR status is genetic testing, which is based on tumor specimens captured by invasive needle biopsy.”, the Authors should mention less invasive approaches, such as fine needle aspiration and liquid biopsy.

Reply: Thank you for your suggestion. The related statements were added as “However, this method does not reflect the status of the entire tumor, and usually results in failure or poor reproducibility due to insufficient materials. Liquid biopsy can identify target mutant gene in circulating cell-free tumor DNA, which is sometimes inconsistencies with specimens biopsy, limiting it clinical application.” See page 4 line 13.

- In the Introduction section “However, this method does not reflect the status of the entire tumor.”, this problem of tissue based approaches may be overcome by liquid biopsy.

Reply: Thank you for your suggestion. The related statements were added as “Liquid biopsy can identify target mutant gene in circulating cell-free tumor DNA, which is sometimes inconsistencies with specimens biopsy, limiting it clinical application.” See page 4 line 14.

- In the Introduction section “Although CT has been systematically analyzed to discover risk factors for EGFR mutations in NSCLC [12], 18F-FDG PET/CT was used to predict other biological features or other genetic mutations of certain malignancies through meta-analysis [13–15].”, the Authors should re-phrase.

Reply: Thank you for your suggestion. These sentences have been rephrased. See page 4 line 17.

- In the Methods section the Authors should specify if only English article were evaluated and if the NSCLC stage (sec. TNM) was taking into account. In addition a third Authors assessed discordances between the two Authors?

Reply: Thank you for your suggestion. The related statements were added. Only English article were evaluated. The information about NSCLC stage was not taken into account for exclusion or inclusion. When there were disagreements between authors, a consensus was reached through a third author was consulted. See page 5 line 29.

- The Authors should better discuss how EGFR analysis was performed. In particular, in the analyzed studies: all analysis were carried out on tissue? As far as molecular platforms and assays are concerned, the studies analyzed showed a similar limit of detection? The same PET procedures were carried out?

Reply: All analysis was carried out on tissue specimens obtained from resection, aspiration or biopsy. Related statements were added. The dose of injected ^{18}F-FDG was shown in Table 1. Different PET/CT equipment with different acquisition parameters can affect SUV_{max}. Related statements were added in limitation section. See page 7 line 16, page 11 line 7.

Reviewer: 3
Dr. Shouhao Zhou, Pennsylvania State University College of Medicine
Comments to the Author:

This is a study of systematic review and meta-analysis to examine the diagnostic significance of 18F-FDG PET/CT for predicting the presence of EGFR mutations in NSCLC patients. In general, the principle / standard procedure of meta-analysis were followed properly. My review and the following comments are with a particular emphasis on the study design and data analyses.

1. The authors need provide a better justification on the objective of the study regarding why PET/CT alone should be considered an alternative approach to genetic testing in assessing EGFR mutation. Even though genetic testing may not reflect the status of the entire tumor, it is still considered as the most accurate approach. For this reason, it is unclear why PET/CT alone should be used to predict EGFR mutational status, rather than as a supplementary approach to generic testing for better sensitivity/specificity.

Reply: Thank you for your suggestion. Genetic testing is the gold standard for EGFR mutation evaluation. PET/CT is a molecular imaging technique that may be helpful in some clinical situations, especially when samples are not easily available. It should be a supplementary approach to genetic testing.

2. The estimated overall 65% sensitivity and 62% specificity confirmed the concern above. It is worth to mention that the concern #1 was raised before any results were read or related.

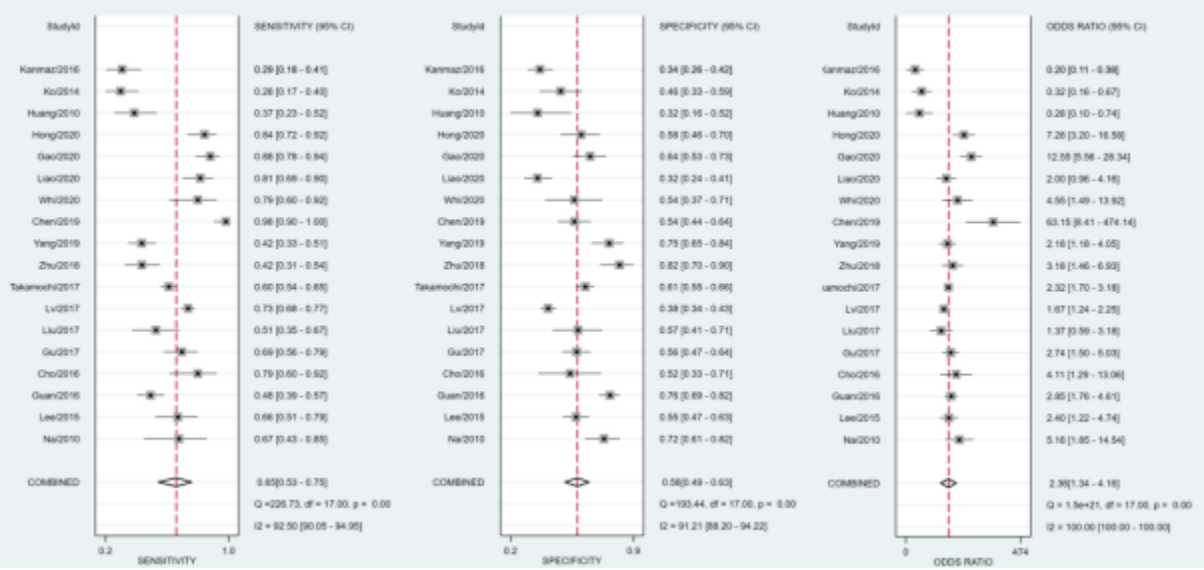
Reply: Thank you for your suggestion. Genetic testing is the gold standard for EGFR mutation evaluation. PET/CT is a molecular imaging technique that may be helpful in some clinical situations, especially when samples are not easily available. It should be a supplementary approach to generic testing. Related researches about other parameters (not only for SUVmax, but also for MTV or TLG) or technique (Radiomics) based on PET/CT imaging are ongoing and promising

3. Some abbreviations were either used without specification (e.g., SUV) or not specified when it was used for the first time (e.g. WMD).

Reply: Thank you for your suggestion. The extensive forms for all acronyms were renewed.

4. In the meta-analysis, three studies were excluded when 18F-FDG uptake was significantly lower in EGFR mutant group. In my opinion, this is unnecessary for diagnostic meta-analysis. A better approach is to conduct a sensitivity analysis by including those excluded studies and compare results.

Reply: Three studies were excluded when ^{18}F-FDG uptake was significantly higher in EGFR mutant group. The results of the sensitivity, specificity and DOR obtained from the three studies included are shown below (The results were added in the supplementary file Figure S1). See page8 line 13.



5. In Figure 2, there were only 2 studies showing positive WMD. Why were three studies excluded?

Reply: Thank you for your review. For WMD analysis, the 2 studies showing positive WMD were reference 9 and 10. For DOR analysis excluded is reference 9, 10 and 11. Reference 11 was not included for WMD analysis.

6. In reporting of p-values in the results, the decimals should be consistent in the manuscript. In addition, a reporting like "p = 0.00" should be avoided.

Reply: We have amended the p value to <0.05.

VERSION 2 – REVIEW

REVIEWER	Zirpoli , Gary Boston University, Slone Epidemiology Center
REVIEW RETURNED	11-Mar-2021

GENERAL COMMENTS	The authors have addressed my comments and the manuscript is much improved.

REVIEWER	Zhou, Shouhao Pennsylvania State University College of Medicine, Public Health Sciences
REVIEW RETURNED	09-Mar-2021

GENERAL COMMENTS	The overall quality of the manuscript is much improved in the revision. I have no more concerns.

VERSION 2 – AUTHOR RESPONSE

Reviewer Reports:

Reviewer: 3

Dr. Shouhao Zhou, Pennsylvania State University College of Medicine
Comments to the Author:
The overall quality of the manuscript is much improved in the revision. I have no more concerns.
Reply: Thanks a lot.

Reviewer: 1
Dr. Gary Zirpoli , Boston University
Comments to the Author:
The authors have addressed my comments and the manuscript is much improved.
Reply: Thanks a lot.