

Name of journal: World Journal of Radiology

Manuscript NO: 34107

Title: Preoperative ¹⁸F-DG-PET/CT in early stage breast cancer.

Revised title:

Preoperative ¹⁸F-DG-PET/CT in early stage breast cancer: Rates of distant metastases.

Response to reviewers.

Dear Editor,

We are most grateful for the reviewers, to whom we address our response.

Reviewer #1:

A nice review article.

Response to reviewer #1:

We particularly appreciate the encouragement.

As corresponding author, I wish to share the praise and acknowledge the students who participated in this study.

Reviewer #2:

Dear Editor, Hung et al. presented a review title as "Preoperative ¹⁸F-DG-PET/CT in early stage breast cancer" The topic is clinically important and developing because of predicting value of PET scan. The authors discussed only percentages of the PET scan positivity in stage I and IIA/B and some additional information such as grade, TNBC and age. We also well know that breast cancer is a heterogen status, include many prognostic and predictive parameters, authors did not state these data. When I red the topic, I wanted to learn what is the negative and positive predictive values of PET scan especially lymph nodes status, how they changes following the neoadjuvant treatment and comparison with other standart radiologic examination especially MRI. Additionally they did not define SUV parameters as well as Ki-67 status, HER 2 status and hormonal status (not only Triple negative patients data). My major concerns are, 1- How PET CT parameters (SUV max and others) changes with neoadjuvant treatment in early stage because this is the main topic can explain how PET CT are prognostic 2- If we compare the MRI and PET CT what are the difference in early BC 3- What are the difference between ER/PR positive and HER 2 positive patients with TNBC according to PET scan parameters in early BC.

Response to reviewer #2:

We agree with Reviewer #2's comments.

The original title was misleading. It suggested that the review would be all-encompassing. As corresponding author, I bear the responsibility of the original title that caused misunderstanding and acknowledge the critic.

We have revised the manuscript to correct the shortcoming. The changes are highlighted below in bold. The corresponding author (CA)'s comments are in italics.

1) Revised title:

"Preoperative ¹⁸FDG-PET/CT in early stage breast cancer: Rates of distant metastases."

CA: three Google Scholar searches indeed show that the issue has been scantily explored.

2) Revised Abstract:

AIM: To investigate rates of distant metastases (DM) detected with [18]fluorodeoxyglucose-positron emission tomography...

RESULTS: ... the rate of occult metastases diagnosed by 18FDG-PET/CT was 7.2% (range, 0%-19.6%) for stage IIA and 15.8% (range, 0%-40.8%) for stage IIB...

CA: identifying the rates is not a trivial issue. The rates are not only important for the information and the management of patients, but they are also of critical importance in the current era of restricted health care funding. Economic studies of QALY to recommend reimbursements are based on economic models that use misleading rates based on studies of 10-15 years ago. The revised abstract provides a take home message that others might use.

3) Revised DISCUSSION:

First paragraph:

This article reviews the role of 18FDG-PET/CT scan in the detection of DM in patients with early stages (i.e. I and II) of invasive breast cancer. The findings might represent important information applicable to discussions with patients about the utility of the scan...

Ninth paragraph:

Our study was restricted by the limited availability of the data correlating

clinical stages and biology with the risk of DM diagnosed with 18FDG-PET/CT scan in patients with early stage breast cancer. Ki-67 is a known prognostic marker[46] but was not reported in any of the recent and largest studies[31-34]. Most studies were retrospective. The classification of patients into stages was usually done after the 18FDG-PET/CT image acquisition, which might have affected the selection of patients. Some studies included the more advanced stages, stage III and IV, and a few studies included post-operative patients. Many issues of importance are relevant for breast cancer, notably the emerging role of PET/MRI and its comparison with PET/CT[47], the use of PET in the monitoring of neoadjuvant therapy[48], the use for staging and restaging[49], the standardized uptake values (commonly known as SUVs) and how they relate to lymph node status[50], the prognostic role of FDG-PET[51] and the suitability for treatment planning[52]; all these represent immensely exciting domains of breast cancer research, but would have confused the scope of the present study, ~~namely the rates of DM.~~

CA: the paragraph agrees with the remarks of Reviewer #2.

Reviewer #3:

This is a clear, well written and documented systematic review, and I suggest to accept and publish the article after minor revisions. I have no specific comments.

Response to Reviewer #3:

Reviewer #3's comment was most important to us. It spotlighted how the revision should proceed, that it should maintain the clarity of the original submission.

Additional changes:

- 1) We noticed an error regarding the original manuscript's reference "Aukema", the publication year was 2010, which did not match the selection criteria. That reference has been removed.
- 2) We updated the review with an additional reference, Ulaner 2017.
- 3) Table 2 has been updated. It adds the reference Ulaner 2017. It inserts the reference Cochet 2014, inadvertently omitted in the original manuscript. A bottom row has been added to facilitate the reading of the overall rates.
- 4) Language was edited with the help of a professional language editing service.