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Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 20104

Manuscript Type: ORIGINAL ARTICLE

Plain text: our response
Hightlighted text: correction in the manuscript

1) Well written paper. Good image analysis. Concern: Follow-up is used as a surrogate of histology = this is a major critical endpoint. Tables should provide the patients follow-up data. Should explicitly details which patients experienced one or the other reference criteria.
Thank You. This is an important point. We agree with the reviewer that the present reference standard can be questioned. Histological confirmation of metastases was not obtained in the large majority of patients. The lack of an accepted gold standard for diagnostic tests and the possibility of false results on functional images should be acknowledged. For these reasons, 12-month clinical radiological follow-up findings may not reflect the real disease state. However, radiological follow up (and in particular CT) still represents a common standard in clinical practice and it is routinely used in the follow-up of high-risk breast cancer. Accordingly, many studies on metastatic bone involvement have been based on the clinical course and comparative imaging modalities, with only a minority of patients undergoing biopsy. However we do believe that the reviewer's remark is meaningful and thus, this issue was clearly stated in the limitation paragraph of the manuscript. According to the reviewer's remark, we have now added details about the number of patients with available histological data in the results section, "*Overall diagnostic accuracy and patient-based analysis*" paragraph: Histology was used as standard references in two patients (specifically in one patient true positive for bone marrow involvement at 18F-FDG PET and in one patient true positive for the presence of an osteosclerotic lesion in the ribs detected by 18F-NaF only).
Finally, follow up time (mean and range) and follow up data have been added to table 1.

2) For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies.
We submitted the text to the attention of a native English speaker. Accordingly, on the basis of his considerations, we made the suggested corrections that we reported in yellow in the text. Personal guarantee has been added in our own handwriting and sent as PDF format.

3) Authors' full names should be given first, then the complete name of institution, country, city, province and postcode..
These information have been added as follows:

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Cecilia Marini has been removed from authors' list.

4) We explicitly added informed consent statement in the title page together with Institutional review board statement, Biostatistics and Data Sharing Statement, as You requested. We didn't reported any patient personal information so they were not identifiable.
Institutional review board statement: The Internal Review Board (Comitato Etico Regionale della Liguria) evaluated and approved this retrospective study.
Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment. We didn't report any detail that might disclose the identity of the subjects under study.
Biostatistics: The statistical methods of this study were reviewed by Campus Claudio from Istituto Italiano di Tecnologia, 16163 Genoa, Italy
Data Sharing Statement: No additional data are available.

   We also added in the materials and methods section, Statistical analysis paragraph, this sentence: "The statistical methods of this study were reviewed by a biomedical statistician."

5) We modified corresponding address adding all required information.
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6) We added the audio core tip in .mp3 format
7) We check reference format as You requested.
8) We added Comments (Background, Research frontiers, Innovations and breakthroughs, Applications, Terminology and Peer-review) as it follows:
Comments:
Background

Early detection of bone metastases is of pivotal importance in breast cancer patients.
To this purpose, besides conventional bone scintigraphy, Positron Emission Tomography has become an established imaging modality with a better spatial resolution and a superior image quality. Among PET tracers, 2-(fluoro-18)-2-deoxy-Dglucose represents the most widely used tracer in clinical routine and can provide information about the presence/absence of disease in the skeleton as well as in non-skeletal districts. However, characterization of bone metastases is also possible with 18F-NaF. In this context, it has not been clearly investigated whether 18F-NaF PET/CT can provide incremental information concerning breast cancer patients that have already been evaluated by means of FDG PET/CT.
Research frontiers
To date, controversial results have been reported about the accuracy of the two PET tracers in breast cancer patients and some authors have even proposed their combined use. This work aim to clarify whether, at least in specific conditions, these two tracers could be complemental in order to improve diagnostic accuracy in bone lesion characterization.
Innovations and breakthroughs
This work aims to compare the role of 18F-FDG and 18F-NaF PET/CT in restaging breast cancer patients with bone lesions through a patient-, density- and site-based analyses. Actually, a more prompt and accurate characterization of bone alterations could lead to a more accurate patient management.
Applications
Besides 18F-FDG, 18F-NaF PET/CT emerges as a powerful "second-line" functional imaging tool, which may be useful in selected patients on the bases of their specific clinical history.
Terminology
Glucose analogue 2-(fluoro-18)-2-deoxy-Dglucose (18F-FDG) PET enables the detection of neoplastic lesions on the basis of their increased glucose metabolism directly reflecting tumor cell viability allowing a characterization of skeletal and extra-skeletal lesions.
On the other hand, 18F-Sodium Fluoride (18F-NaF) reflects the increased regional blood flow and osteoblastic bone reaction being irreversible incorporated into the bone matrix as fluoroapatite.
Peer-review
An agreement on which is the best PET tracer in the characterization of bone lesions has not been reached yet. In this study we compared 18F-FDG and 18F-NaF PET/CT accuracy in the restaging of breast cancer patients. We observed that, despite 18F-FDG PET/CT could be considered as the most reliable tool in the general population of breast cancer patients, 18F-NaF PET/CT can exploit its diagnostic potential in specific clinical settings. These results were interesting and provided important information concerning the most appropriate management of breast cancer patients with suspected bone metastases.

9) Reference format has been revised according to BPG's Revision Policies, we added the corresponding PMID number and DOI. However, for few references, PMID and DOI citation were not available.
10) We provided the decomposable figures and tables in ppt format as You requested.

We do hope that you can find our manuscript suitable for publication.
Looking forward for hearing from you soon

Regards
Silvia Morbelli

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