Author's response to reviews

Title: Integrated FDG-PET/CT Imaging Is Useful In The Approach To Carcinoid Tumors Of The Lung

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Version: 2
Date: 11 November 2013

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REVIEWER 1.

Major compulsory revisions
We agree with the comment of the reviewer and we removed patients’ initials from table 1, for confidentially purposes. Patients are now identified with consecutive numbers.

Minor essential revisions.
1) We apologize for the mistake and we thank the reviewer for the correction, that we added in the text
2) We apologize for the mistake and we thank the reviewer for the correction, that we added in the text
3) We changed the sentence in order to make it clearer:” When the tumor was visible on bronchoscopy an endoscopic biopsy of the lesion was undertaken” is the new sentence we added.

Discretionary revisions
1) We agree with the reviewer, therefore we changed the sentence which defines the SUVmax in the Methods section. “The SUVmax is a semiquantitative measurement of tissue metabolic rate and represents the maximum measured activity at the region of interest (ROI), placed manually over the most intense area of FDG accumulation, on the axial attenuation corrected PET images”. This is the new sentence we added.
2) We used the longest diameter to describe the tumor size because it is easier
to measure and because it is more intuitive to understand and immediate to consider when thinking about an SPN in the common clinical practice. Many of these lesions are small, with largest diameters less than 20mm and ovoid, therefore if the shortest diameter was considered we had obtained many lesions smaller than 1 cm. This would contrast with the statement that PET frequently obtains false-negative results for lesions smaller than 1 cm. This statement however refers to the largest diameter of the lesions and not to the smaller. Thus, to maintain an adequate comparison between CT dimensions and FDG uptake, we chose to express the dimensions of the nodules by the largest diameter.

3) We apologize but we did not understand the meaning of this comment.

REVIEWER 2.

Major point

1) As noted by the reviewer, we acknowledge that a comparison with the SUV max of lesions such as hamartomas, metastases or infectious/inflammatory lesions is lacking in our study. Unfortunately, this is an unavoidable limit of this study, that has been conceived to analyze the FDG uptake in a population of carcinoids only. This limitation was already clearly discussed in the final part of the Discussion section, when the various differential diagnoses were investigated. Moreover, to further stress this concept, in the revision version we added the discussion about the differential diagnosis with infectious/inflammatory lesions and we concluded that, however, “further studies comparing the PET/CT findings of carcinoids, hamartomas, low-grade adenocarcinomas and infectious/inflammatory lesions should be advocated”.

Finally, as suggested by the reviewer, we changed the final sentence in the conclusion part of the abstract.

2) As suggested by the reviewer, we shortened the discussion, especially removing the speculative sentences. The discussion section was reduced from 1664 to 1372 words.

Minor point

1) We apologize for the mistake and we thank the reviewer for the correction, that we included in the text

2) We agree with the comment of the reviewer and we removed patients’ initials from table 1, for confidentially purposes. Patients are now identified with consecutive numbers.

REVIEWER 3

We thank the reviewer for his interesting comment. The question whether is it better to perform FDG-PET rather than octreotide scan in the approach to pulmonary carcinoids is an important point to stress.

However, this study has not been conceived to investigate the role of octreotide or dotatoc imaging in the approach to lung carcinoids. First, these imaging
techniques are rarely performed in our Institution and we do not have an adequate experience to include those imaging examinations in our study. Second, our study focused on the clinical setting of an SPN which has been detected on CT scan. Irrespective to the shape and margins of the nodule, no one knows for sure that the nodule is a carcinoid. Thus, the SPN remains an SPN until further examinations are performed. And at present the further examination of choice for SPN, even in the case of oval shape and regular margins, is FDG-PET/CT. In fact, FDG-PET is useful not only to help the diagnosis of carcinoids (question addressed in the study) but also for hamartomas, infectious/inflammatory lesions, metastases, low-grade adenocarcinomas and so on...that is all the lesions that can present with oval/round shape and regular margins. On the contrary, octreotide–dotatoc scan are useful only for typical carcinoids. In fact, the role of these techniques is for the staging rather than for the diagnosis of carcinoids.

In other words, our study did not try to answer the question “should we perform an FDG or an octreotide imaging in the approach of an SPN, because the answer is widely accepted: we should perform an FDG-PET. Our study try to answer the following question: “The FDG-PET we commonly perform as further study for SPN is also useful in case this SPN is a carcinoid?” However, we accepted the suggestion of the reviewer and we changed the title of the manuscript (“in the approach to” in the place of “in the diagnosis of”).

Regarding the second comment, the correlation between FDG uptake and shape/margins of the lesions was done, as reported in the Methods section (in the statistical analysis paragraph) and in the Results section: “No further correlations were found between the SUVmax and the other clinical, radiological and pathological variables”.

Our study primarily suggests a role of FDG-PET/CT in the approach to pulmonary carcinoids when they presents as SPN. Because in many cases pulmonary carcinoids presents as nodules with ovoid/round shape and smooth margins on the CT scan, we can infer that FDG-PET may help in the diagnosis of these kind of nodules.

Regarding the amperage, we used an amperage of 80-250 mA, modulated to maintain a noise index of 30, in free breath. We added this note in the text of the Methods section of the revised version.

We agree with the reviewer that this low amperage is not adequate for a careful assessment of the nodule characteristics. However, all our patients had performed an enhanced helical CT scan before integrated FDG-PET/CT. The indication to perform the FDG-PET was based on the results of previous enhanced CT scan. The assessment of the nodule characteristics was done analysing the images of the enhanced helical CT scan rather than the images of the CT scan integrated with the FDG-PET. In this way we was able to adequately recognize features of the nodules such as necrotic areas, margins, shape.

We added some sentences in the Method and in the Discussion section of the revised version to clearly explain these issues.
The analysis lack of the calculation of sensitivity and specificity because we did not establish any cut-off to evaluate the accuracy of PET. The aim of the study was to investigate the FDG uptake of carcinoids and we demonstrated that all lesions had an FDG uptake, in all cases >1.4. As reported in the discussion, when a visual assessment or a SUVmax cut-off of 2.5 were considered, the accuracy of FDG-PET might be very low (see references). This is not an adequate method of assessment for lung carcinoids. We believe that it may be more appropriate to compare the nodule activity with the normal lung and not with the mediastinal blood pool activity, so that the majority of the nodules can be easily visualized. In this way all the lesions in our series have been visualized at FDG-PET. Thus, without a cut-off to define a positive or a negative result, nor sensitivity neither specificity can be expressed.

The 4 patients who received preoperative diagnosis by bronchoscopic biopsy undergone FDG-PET before the fiberoptic bronchoscopy.

This was explained in the Discussion section of the original manuscript.