Dear Editor

I am so glad that the reviewers evaluated our report titled “The early response of renal cell carcinoma to tyrosine kinase inhibitors evaluated by FDG PET/CT was not influenced by metastatic organ”. We believe that our information is very important for many clinical urologists.

We answered to each comment of reviewers point by point as below. I appreciate the reviewers for their important advices.

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Answer to Reviewer 1
Reviewer: Andrei Lagaru
Reviewer’s report:
Minor Essential Revisions
1. SUV is a semi-quantitative, not a quantitative tool.
   Answer)
   We changed “quantitative” to “semiquantitative” (p.3 l.5).

2. Reference #1 is old, the authors can use numbers from something more recent, such as Siegel R et al. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.
   Answer)
   The reviewer’s comment is reasonable, but most of recent epidemiological reports including the recommended paper analyzed the incidence of renal cell cancer and renal pelvic cancer collectively. We think that reference#1 reporting incidence of only renal cell carcinoma is better for our paper.

3. Range, average and SD of injected FDG dosage, as well as time from injection to imaging should be presented.
   Answer)
   We add the description about injected FDG Dosage in METHODS (p.7, l.12-13) and our hospital is punctual for the examination. We observe the “60 minute” rule strictly for all examinations in this study.

4. Range, average and SD of time between pre- and post-therapy scans should be presented, unless all patients had the follow-up exactly on 30th day.
   Answer)
   We agree to the reviewer’s advice that the details about of date when PET/CT was done (range, average and SD) should be described. We think that the time between TKI start and post-therapy scans was more important than the time between two PET/CT examinations. So we change the description to “We next analyzed the SUVmax assessed by FDG PET/CT performed 1 month after the TKI treatment initiation ( day 30±6; range 14 to 47).”(p.10, l.12)

5. Details on image analysis should be presented: how many readers, in what order, how were discrepancies solved, were the readers blinded to other studies etc.
   Answer)
   We added the description about details of image analysis in METHODS (p.8, l.5-10).

6. All PET and fused PET/CT images should be presented with a color scale.
   Answer)
   We added color scales in all fused PET/CT images in Fig 4.
Answer to Reviewer 2
Reviewer: Guido Davidzon
Reviewer's report:
Overall: I enjoyed reading the paper and although it does not touch upon a major
topic in nuclear medicine or molecular imaging, I think the findings of the authors
deserved publication after all revisions are made. Specifically, I think they have to
be more descriptive/detail on the technical aspects of the study. Also, authors
should acknowledge the limitations of a retrospective study and that these
findings should be confirm in a larger prospective study.
Comments
• Major Compulsory Revisions
1) Could you please thoroughly explain how ROIs (VOIs) were acquired (shape,
size, 3D or not, etc.). Did you choose this ROI based on established criteria? Also,
were ROIs acquired by a solo physician or multiple physicians? Which of the
authors worked on the ROIs?
Answer)
We added the description about details of image analysis in METHODS (p.8,
l.5-10).
2) The imaging section under methods mentioned SUV values were calculated
based on patient’s weight. Did you use total body weight or lean body weight? I
ask this because is well known that when lean body weight is used, SUV values
a more accurate for comparison among different patients and also within a same
patient between baseline and follow-up study. SUV values can me
underestimated in large patients since FDG doesn’t concentrate in fat as much
as it does in other tissues.
Answer)
We calculated SUV using total body weight in this study. We changed “per
weight” to “per total body weight” p.8, l.2)
3) It is interesting that SUVmax values were significantly different between lung
and non-lung metastases and that lung metastases showed lower FDG uptake.
Was this analysis adjusted for the size of the lung lesions? I’m curious to know if
there is something special about the lung metastases or if SUVmax values are
underestimated due to partial volume effects.
Answer)
There is no significant difference between the diameter of lung metastasis and
that of non-lung metastasis. So we speculated that the difference of FDG accumulation can result from the difference of biological characteristic between lung metastasis and non-lung metastasis. We added the description about the size of tumor (p.12. l.9-13) and speculation (p.12. l.13-19) in DISCUSSION.

4) On page 12 of the discussion you said: “it is well known that RCC patients with lung metastasis only show longer survival than other RCC patients”; were you implying that the patients in your cohort who have lung metastases also have lung only metastases? Do they?

Answer)

There was 23 patients with lung metastasis in our study. But, 2 patients of 23 have only lung metastasis. The difference of prognosis cannot be analyzed in our small sized study. The further study targeting large number patients is necessary. We add the description about this limitation in Discussions (p.12. l.20-22.)

5) I am impressed that all 96 PET/CTs (baseline and 1 month follow-up for 48 patients) were acquired at 60 minutes following the i.v administration of F18-FDG, given this is a retrospective (uncontrolled) study. Could you please clarify if this is the case or if 60 minutes is an approximation? If the latter, could you please provide the range for uptake time. As you probably know there are many variables affecting SUVmax values and uptake time is one of them. So if the range is large, meaning some patients were scanned at later than 70 minutes, ideally you should correct for this and/or acknowledge the limitation.

Answer)

Our hospital is punctual for the examination. We observe the “60 minute” rule strictly for all examinations in this study.

6) How did you work around the high background issue for ROIs on primary renal lesions and contralateral renal metastases? Did you encounter any problems? Is so, in how many lesions? –For e.g. patient F in Figure 4 has a large primary tumor in the left kidney. How did you assure that your SUV measurements weren’t affected by surrounding (and sometimes bleeding in) urine activity?

Answer)

We added the description about details of image analysis in METHODS (p.8, l.5-10).

• Minor Essential Revisions

1) Figures 2 and 3 have missing values in their Y and X axis.

Answer)

In the assessment of the SUVmax change ratio (Fig 2), the RCC metastases which pretreatment FDG accumulations were not detected were excluded. In the assessment of diameter change ratio (Fig 3), the RCC metastases which diameter could not be measured were excluded. We added the description in
METHOD (p.8. l.14-17).