Comments to the original manuscript (Manuscript NO:27497)

Reviewers' comments are quoted "verbatim" → followed by our response.

" Comments To Authors:

Reviewed by 02510765

" The paper is well written, interesting and worthy of publication. I would suggest few corrections: Abstract: Please, replace "less invasive" at line 1 with "not invasive"; "

→ We thank the Reviewer for the positive comment. As requested by the Reviewer, we have replaced the wording in the revised manuscript (p.2, lane 3).

" please, replace also the term "prognostication" with "prognosis" in the abstract and the text. "

→ As requested by the Reviewer, we have replaced the wording in the revised manuscript (p.2, lane 5, and p.4, lane 4).

" Page 10: Are you sure that "independent of all variables tested" is it correct? Would you consider to change this part as follows: "not dependent on all variables tested" ? It sounds better. "

→ As requested by the Reviewer, we have replaced the wording in the revised manuscript (p.11, lane 7).

Reviewed by 02665693

" GENERAL COMMENTS

Albeit 18F-FDG has been widely used for clinical diagnosis in colorectal cancer (CRC), the mechanisms underlying 18F-FDG accumulation in CRC haven't been fully elucidated yet. In this review, the references related to 18F-FDG uptake in CRC are summarized. The review focuses on the potential of FDG-PET/CT scans in predicting mutational status (e.g., KRAS gene mutation) and its role in clinically determining therapeutic strategies by non-invasively assessing tumor response to anti-epidermal growth factor receptor (EGFR) therapy. This manuscript is recommended for publication after the following comments are appropriately addressed. "

→ We thank the Reviewer for the positive comment.

" SPECIFIC COMMENTS:

1. The cited literatures are not up-to-date except for those in the section of KRAS gene mutation. Citing recent publications is strongly recommended in other sections. "

→ As requested by the Reviewer, we have added 5 references (reference #15, #36, #49, #52 and #57) in the revised manuscript. All references were recently published in a few years.

“ 2. No any figures in the manuscript? ”
→ We suppose that there is no necessary figure in this review article. Please consider this situation.

“ 3. TITLE: The title is not clear enough to outline the content. A better title would be “Mechanisms underlying 18F-FDG accumulation in colorectal cancer”. ”
→ As requested by the Reviewer, we have modified the TITLE in the revised manuscript.

“ 4. ABSTRACT: In the last sentence of ABSTRACT, please emphasize that this review only focuses on the underlying molecular mechanisms of 18F-FDG accumulation in colorectal cancer. ”
→ As requested by the Reviewer, we have modified the last sentence of ABSTRACT (p.2, lanes 15–16).

“ 5. INTRODUCTION: The definition of SUVmax, SUVmean, SUVpeak, TLR and TW40% must be provided in their first time occurrence. Please specify that these parameters are the key indicators for quantitative measurement of 18F-FDG accumulation. ”
→ As requested by the Reviewer, we have added the definition of these FDG-related parameters in INTRODUCTION (p.4, lanes 11–14).

“ 6. Section of “Glucose transporters (GLUT) and Hexokinases (HXKs)”: This paragraph seems very weak to introduce the contribution of GLUT1 and HXK to the 18F-FDG accumulation in the CRC. More recent references and better elaboration are needed. ”
→ As noted above, we have added one reference (reference #15) in this section. This new reference was published in 2015. Only a few reports have been recently published regarding the role of GLUT and HXKs in FDG accumulation, because this point is a becoming common sense in this field. Therefore, we suppose that it is difficult to cite many recent references in this section. Please consider this situation.

“ 7. Section of “KRAS (V-Ki-Ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog)”: It’d better organize this section as follows: 1) Mutations in the KRAS gene in CRCs; 2) the association between the KRAS mutations and enhanced GLUT1 expression; 3) 18F-FDG accumulation reflecting KRAS mutational status of the primary CRC; 4) Relationship between KRAS mutations and 18F-FDG

accumulation in metastatic CRC; 5) FDG-PET/CT scans for predicting tumor response to anti-EGFR therapy. ”

→ As requested by the Reviewer, we have modified the section of “KRAS (V-Ki-Ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog)”. However, 5 subparts are too much, considering the total flow of this manuscript. Therefore, we have divided this part into 2 subparts: 1) Mutations in the *KRAS* gene in CRCs and 2) Association between *KRAS* mutations and ^{18}F-FDG accumulation. We suppose that this form is best.

“ 8. Section of “KRAS (V-Ki-Ras2 Kirsten Rat Sarcoma Viral Oncogene Homolog)”: It’s unclear why 18F-FDG uptake in NSCLC is described here. It’d better focus on the theme of “18F-FDG in CRC. ”

→ *KRAS* mutations occur in a variety of human malignancies, most frequently in pancreatic cancer, non-small cell lung cancer (NSCLC) and CRC. Therefore, we suppose that it is important to note that there is a significant association between *KRAS* mutations and ^{18}F-FDG accumulation in human *KRAS*-related malignancies including CRC. Therefore, we have modified the sentence of this part (p.6, lanes 7–10, and p.9, lanes 18–20).