Author’s response to reviews

Title: Changes in CT morphology can be an independent response marker for patients receiving regorafenib for colorectal liver metastases: retrospective pilot study

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Version: 2 Date: 07 Mar 2017

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All the revisions and additions are indicated in red in the revised manuscript.

Response to reviewer 1:

Re 1. The idea is interesting. But CT morphologic response maybe full of challenge to cancer patient and doctor.

Answer: The CT morphologic response criteria have initially been reported among patients who underwent chemotherapy with bevacizumab (Chun YS, et al, JAMA 2009) and later validated in several studies (Shindoh et al, JCO 2012; Yoshita et al, Digestion 2014; Nishioka et al JOGS 2015). Although the morphologic response criteria are rather subjective, good inter-observer agreement has been confirmed among independent radiologists in each study. The present population was reviewed by the radiologist (WG) who had experience of morphologic evaluation of >200 cases.
Re 2. If this article can show more data to compare to cancer cell morphologic response in vitro, that will be better.

Answer: We agree with the referee’s comment. Unfortunately, however, the current population are advanced cases treated with multiple lines of chemotherapy and not candidates for surgery. Therefore, pathologic specimens were not available. Nevertheless, significant correlation between the CT morphology and pathological viability of tumor has been confirmed in previous studies (Chun YS, JAMA 2009; Shindoh J, JCO 2012; Nishioka Y, JOGS 2015). Therefore, it would be plausible that optimal morphologic response is correlated with better pathologic response.

Response to reviewer 2:

Re 1: Some grammatical editing is necessary.

Answer: English language has been re-reviewed by a native speaker.

Re 2: Strictly speaking, "RECIST criteria" is redundant, since the "C" in "RECIST" stands for "criteria." A better phrase is "RECIST assessment" or simply "RECIST."

Answer: We appreciate the important correction. The wording was corrected in the revised version.

Re 3: It is heartening that the authors recognized the statistical limitation in determining whether morphologic response was an independent prognostic factor. However, an alternative would be to determine if there is a statistical difference between PFS/OS and: number of prior treatments, type of prior treatments, age, presence of toxicity, original tumor stage, and original tumor location. I would recommend the authors perform this analysis, and resubmit for review, including statistical analysis.

Answer: Thank you for the thoughtful comment. We have added the results of univariate analysis for the other potential prognostic factors in the revised version (see Method, paragraph 4).

Response to reviewer 3

Re 1: This is a very limited study of only 10 patients. The title should be modified to include: retrospective pilot study.

Answer: The title was changes in the revised version as suggested by the reviewer.

Re 2: The description of the CT morphologic assessment is rather vague. I strongly suggest to expand the description with a direct link with figures representing each of the three groups.

Answer: Thank you for the important comment. We have added supplemental figure presenting a typical images of CT morphology.
Re 3: How are the morphologic groups assessed, by one radiologists? A panel of radiologists, what is the variability among radiologists scoring patients?

Answer: As described in the original version, all the morphologic assessment was performed by one radiologist (WG) who was trained to adequately assess the morphology score with experience of >200 image readings. Very high inter-observer agreement has already been reported in several studies (Chun YS, JAMA 2009, Shindoh J, JCO 2012, Nishioka Y, JOGS 2015).

Re 4: It is unclear how there are three groups defined, but in the results only two groups are reported. Was one of the groups not present in the group of 10 patients?

“Morphology (group 1, 2 or 3)” and “Response (optimal/suboptimal)” (which is defined by the degree of changes in CT morphology) are different. Please refer to the description in the method section (see method, paragraph 2).