Author's response to reviews

Title: Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach.

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Author's response to reviews: see over
Reviewer: Hee Chul Park
Reviewer's report:
This is well written paper and the included data supports the conclusion of this study.
We thank the reviewer for the kind revision. Below our detailed answer to the comments.

1) There are no aspects which needs major revision.
Thanks.

2) In lung metastatic cases, the lesions received more than 60 Gy is less than 2 cm. So, I believe that only with the material included in this study, the authors can not draw that the dose escalation have been translated into better local control. Because the lesions treated with 48 Gy/4 Fx was larger in its size. Of course, in the liver cases, there were no size dependency in local control which were treated with higher dose of 75 Gy/3 Fx. It gives us the impression that with sufficiently higher dose, even the lesion larger than 2 cm can be treated successfully. It needs to be clarified more precisely in the discussion section.

As recommended, we added some clarification in the discussion pointing to the relevant publications. Thanks.

3) There are some typographical errors in line 112, 134, 146.

Fixed. Thanks.
Reviewer: Yuan Zhiyong
We thank the reviewer for the kind revision. Below our detailed answer to the comments.

Reviewer's report:
Major revise:
1. The follow-up time of some patients was a little shorter. And it is maybe influence the analysis of survival time.
In our data 5 patients have a FU shorter than 6 months but these are the patients who died really early. The median FU is 24 years. We believe that this is not really biasing the OS since all cases are properly censored or accounted for. We clarified this better in the new text.

2. Some factors, for example, chemotherapy, need included in the univariate analysis for the LC, PFS and OS.
CT has been included in the univariate analysis as a prognostic factor but it was not influencing OS and other parameters. We have to consider that 95% of patients received CT before SBRT (as from table 1) and for this reason there is little that can be derived from this. We have clarified this in the revised manuscript.

3. Why did the authors decide the dose regime 75Gy/3F(it is hardly reported in other papers) for the liver lesions while 48/4f or 60Gy/3f for lung lesions? Did the author really believe 75Gy/3F is needed for the treatment.

The scope of increasing the dose to the level of 3x25Gy was to try to improve local control in general and in particular for the larger lesions. In fact, earlier studies confirmed that LC was decreased for lesions > 3cm. As an example, Rusthoven (ref 16) showed LC ~100% for the smaller lesions and ~70% for the greater (3 to 6cm) with a fractionation of 3x20Gy. Also studies like the Lee et al. one (ref 17), confirmed that LC is correlated with the prescription dose. Our data shows that with the 3x25Gy scheme, LC is not influenced by the size of the lesions.
75Gy/3Fr in the liver is the standard prescription for liver mets in our institute after the results of a phase II trial (ref 18 and final data currently submitted for publication) which demonstrated the safety of the approach with good outcome. The lung fractionation follows the NCCN guidelines and institutional risk adaptive fractionation scheme. We better clarified this in the manuscript.

4. The paper should provide the details of prescription dose distributions for different volume. For example, how about the dose for liver lesions which PTV volume more than 500ml, which got similar excellent LC as the small tumor.
In the case of the liver lesions, the dose prescription was irrespective of the target size (as described in the ref. 18) but was depending on the possibility to respect the dose constraints. In addition, no correlation was observed between LC and target coverage also for the patients with a low minimum dose to PTV. The minimum dose to PTV for
the 5 recurrent patients ranged from 65 to 68Gy. We amended the revised text to clarify this aspect.

5. The definition of unresectable is not really unresectable, because most patients only have one metastases lesion, and the mean age is 68 (not too aged), the most important factor maybe that the operation could not have the patients get curative treatment results for most of the patients will have new mets disease in the future, while SABR could provide similar LC compare operation with less damage to the patients body. For example, the lung lesion in figure 1 could be easily resected. The definition of unresectable here derives from not only technical surgical challenges but also due to concomitant comorbidities (e.g. cardiac) suggesting to avoid surgery. We better clarified the definition in the revision.

6. I suggest do further analysis tumor special-survival and draw the survival curve.

We have seriously considered the proposal of the referee. The fact is that most of patients died because of the disease (we added the data in the revised text) and the diseases specific OS does not differ significantly from the overall OS. To keep the economy of the manuscript and not dilute the message, we preferred to avoid the duplication of the figure and just amend the text.