Peer Review File

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Reviewer A

The authors propose a narrative review on the utility of SIRT Y90 in the surgical line of care of patients bearing colorectal liver mets.

Considerations:
1. Why a narrative review? This in some instances (not this one) might be a pleasant and logical text to read, but is clearly biased by the intention and bibliographic selection of the authors. Is there is enough scientific evidence to support a consensus, that should be translated in a systematic review or meta-analytic paper.
Reply: Thank you very much for taking the time to review our manuscript. We were comprehensive in our literature search to provide the best available evidence. There has been a meta-analysis of the FOXFIRE, SIRFLOX, and FOXFIRE-Global randomized studies that was published in 2017 (Ref 56) and addressed the clinical value of adding SIRT to chemotherapy in 1103 chemotherapy-naïve patients with unresectable or ablatable liver-dominant CRLMs. In the authors' opinion and despite the other trials published in the role of Y-90 SIRT in other disease processes (MISPHEC trial etc..), there has been no new randomized trials or major chart reviews to adequately perform another systematic review or meta-analytic for resectable CRLMs. We think that this review will shed the light on the benefit of this modality and encourage further trials as we mentioned in our summary section. Moreover, there is limited data on the utility of SIRT with Y90 in the setting of surgical treatment. This novel aspect is the main emphasis of this paper and is based on the available data.

2. The goal of the article is confusing. It proposes to discuss the applicability of SIRT Y90 in the surgical management of CRLMs. But also considers treatment of liver dominant disease. Those are different scenarios.
Reply: Y-90 SIRT has been less used in the setting of resectable CRLM disease. Most of the trials and chart reviews that addressed the benefit of SIRT have included patients with extrahepatic disease dissemination, as in the SIRFLOX trial. Therefore, the authors felt that it is important to stratify the role of this modality in different disease burden scenarios. As well, this paper builds on the published work of this group in this journal that delineated the role of SIRT in a surgical algorithm (Jeyarajah DR, et al. Role of yttrium-90 selective internal radiation therapy in the treatment of liver-dominant metastatic colorectal cancer: an evidence-based expert consensus algorithm. J Gastrointest Oncol. 2020;11:443-460.). Therefore, this paper is a natural follow up to the prior publication.

3. Methodology mentions the inclusion of phase 1 and phase 2 studies to aid the consensus, this lacks clinical evidence to support the use of any therapy. "Old" studies, previous to 2009 were

dismissed, without any apparent reason. Another point for the systematic review.
Reply: The reason why we excluded studies prior to 2009 is that SIRT with Y-90 was considered a salvage option prior to that year, which brings the necessity of this review to highlight its benefit in resectable CRLM disease as a first line modality. In addition, prior data was referenced and reviewed in the paper on which this material was built (Jeyarajah DR, et al. Role of yttrium-90 selective internal radiation therapy in the treatment of liver-dominant metastatic colorectal cancer: an evidence-based expert consensus algorithm. J Gastrointest Oncol. 2020;11:443-460.).

4. Still in the methods: liver dominant disease was classified in resectable, borderline and unresectable. Classic concept, but no criteria described. We all know this is highly variable between surgeons and institutions, but when dealing with a scientific report, it needs to be clear which kind of patient would fit into each category. Moreover, this stratification has no further impact on the continuity of the review.
Reply: This is a very debatable subject in surgical oncology, thus the role of multidisciplinary conference is essential. What may be resectable to a surgeon might not be the case to another one. In the authors' opinion, margins and future liver remnant are the major driving forces of respectability of CRLM. One of the critical benefits of SIRT is margin accentuation and radiation lobectomy with contralateral hypertrophy as we alluded to in our discussion. If margins are threatened due to vicinity to major vasculobiliary structures or inadequate FLR, we consider the disease as borderline resectable. Definitive unresectability happens when clearing both lobes of the liver is impossible even after utilization of current systemic regimens. This concept has already been published and referenced in this paper (Jeyarajah DR, et al. Role of yttrium-90 selective internal radiation therapy in the treatment of liver-dominant metastatic colorectal cancer: an evidence-based expert consensus algorithm. J Gastrointest Oncol. 2020;11:443-460.). This paper was peer reviewed and published in this journal and would provide the rationale for this delineation.
Change in the text: We expanded the text in the methodology (please see page 6, lines 89-94).

5. Discussion: this topic comes too early, hard to discuss based on no information, no results…
Reply: We appreciate the reviewer's point of view. We would ask the editors to examine this concern in light of the fact that the reviewer is not familiar with the published work in this area as outlined in (4) above. The authors feel that this surgical approach to SIRT with Y90 will add to the existing literature.
Change in the text: Per the narrative review checklist provided by the Journal, there is no results section. We are happy to change the text and add a result section if deemed necessary.

6. Still in the discussion: authors should clear that there is no scientific and clinic background to support the use of pre-operative chemotherapy for resectable low risk CRLMs. Would be very useful to establish the concept of high and low risk mets. And please omit the "authors prefer" statement, including the evidence and practice that would make the authors and readers to be informed and to assume that same preference.
Reply: We appreciate you comment and agree with your statement as we mentioned in page 7, lines 108-116. We have alluded to the difference between low risk and high risk CRLMs in the

introduction section (please see page 4-5, lines 69-76). We have changed our text per your request.
Change in the text: please see changes in page 7, lines 108-109 and page 7, line 111.

7. Continuing in the discussion: there are many well designed papers on the role of chemotherapy and how it can be harmful to the liver. Needs improvement, from the creation of effective drugs (oxali/irino) through combined treatments and the addition of biologics.
Reply: We agree as we mentioned in the introduction and page 8. We expanded the text per your request.
Change in the text: changes were made to the text (please see page 8, lines 122-123)

8. Throughout the paper there are some phrases that mention the need for a "multidisciplinary tem approach". With one exception, all of them lack reference.
Reply: We apologize. A reference has been added. Thank you for pointing this out.
Change in the text: please see page 12, line 226, subsequent changes in reference numbers have been assured.

9. Liver directed topic: mentions the "exclusive" hepatic arterial supply for mets. That is also a classic concept, but "exclusive" may be too optimistic. Needs better wording, specially when we know that CRLMs are predominantly hipovascular.
Reply: We have changed the word from exclusive to main. Thank you for pointing this out.
Change in the text: Please see page 8, line 139.

10. Mentions the 2 commercial versions available of the Y90 SIRT. That's honest. Well done.
Reply: Thank you

11. Role of Y90 SIRT is divided in three possibilities. (1) as a definitive treatment for CRLMs. But this is only true if the tumor is resected or ablated, so the definitive treatment is surgery and/or ablation. It is not clear, from the evidence offered in this review, why should Y90 be employed as definitive treatment. Moreover there is extensive citation of papers that employed Y90 on the palliative setting. This breaks the 3 roles to 2. (2) Margin accentuation: theoretically an interesting indication, but a very economic discussion, no evidence, no confrontation with current concepts on the role of surgical margins, the role of systemic treatment on margins and how we evolved to concepts such and R1 vascular resection. According the information cited on the review, this breaks the 3 roles down to only one. (3) Radiation lobectomy: another theoretical reasonable indication, but one might say, a costly one and largely unavailable outside wealthy countries. Moreover, there is no clear advantage over portal vein embolization, especially if systemic treatment is to be kept during liver hypertrophy. The remaining third and only role seems to fade. After reading this topic I was not convinced that SIRT Y90 has any specific or advantageous role in managing CRLMs.
Reply: In the setting of resectable CRLM, we believe that definitive treatment is multimodality that includes but not limited to chemotherapy, surgery or local destructive interventions and SIRT (to increase R0 resection). Definitive treatment happens when R0 resection is assured where the role of SIRT comes. We have mentioned a small phase II randomized trial that

compared systemic fluorouracil/leucovorin chemotherapy with and without single administration of SIRT in 21-patient with metastatic CRC.(Ref 55) There was a significant improvement in time to progressive disease (18.6 months versus 3.6 months, $P < 0.0005$) and median survival (29.4 months versus 12.8 months, $P = 0.02$) in the combination therapy group. Although we agree that this is different from the current regimens used, which is related to literature deficiency and needs for more trials to address the role of Y-90 in resectable CRLM as we concluded in our summary. In addition, we are not saying it is the only option, but it is an available one to patients who have access to it. Not every hospital in the US would provide Y-90 either. The reviewer brings up economic discussion which is not within the scope of this paper. The aim of this work is to outline what is available rather than discuss the finances of SIRT with Y90. The reviewer appears to have missed the point of definitive management of CRLM rather than palliative treatment. Moreover, this reviewer has not read the detailed reasoning offered for SIRT with Y90 over portal vein embolization - see page 15 lines 278-288, The authors would put forward that all these concerns are answered with careful reading of the text of the paper.

Reviewer B

Thank You very much for providing such an elaborate overview over the potential therapeutic fields of Y-90-SIRT in the context of oncological surgery of CRLMs.

As you mentioned correctly, SIRT has been underestimated in resectable CRLM throughout the years, as it was regarded as an end-of-line therapy, if not even less than that. For oncological and hepatobiliary surgeons this manuscript might be truly helpful, in order to have scientifically well-founded arguments at hand when it comes to a multidisciplinary treatment decision; especially in the light of borderline resectable tumor lesions.

The only minor change that I would suggest would be a more precise description of the "definitive treatment of low-volume liver metastases"-situation: When reading the respective headline and abstract for the first time, one could be mislead, that SIRT itself represents a definitive (oncologically satisfying) treatment strategy for up to 6 hepatic tumor lesions. In the manuscript itself it says that SIRT in these situations is rather used as a supportive treatment prior to subsequent resetion or ablation. Maybe these situations should be clarified a bit more precisely. Additionally, maybe the authors could comment on the situations in which a SIRT-enhanced treatment sequence should be applicable (i.e. primarily resectable vs. borderline resectable vs. primarily unresectable), in the context of the sole use of surgery.

Overall, I would to congratulate you for this very well structured manuscript which is indeed quite enjoyable to read.

Reply: Thank you for taking the time to review our work and for your comments. We appreciate your acknowledgement of the potential underuse of this therapy. Yes, we agree that Y-90 by itself is not a definitive treatment, rather an element of multidisciplinary treatment, especially in the setting of low-volume liver metastases. We made the appropriate changes in the text to reflect our mutual opinion. In addition, we do agree that SIRT has a valid role in margin accentuation, especially in the setting of resectable disease with threatened margins or borderline-resectable disease with involved margins and low FLR.

Change in the text: Please see page 12, line 229&232, and page 17, line 309

Reviewer C

A first-line treatment for colorectal liver metastasis alone or in combination 38 with systemic chemotherapy- This role has not been supported. Please remove the sentence or provide references.
Reply: Thank you for taking the time to review our manuscript. Please see reference 26 and 46 as mentioned in the text in page 12 lines 212-214.

Line 38 abstract "adjacent" should be adjunct?
Reply: We thank the reviewer and have changed this – see page 3 line 38.

Page 7 line 111 should be "improvement" as opposed to "improve"?
Reply: This has been changed.

Line 122 page 8 "TRIBE trial to associated with" as opposed to "TRIBE trial to associate "
Reply: This has been changed.

Not sure what the paragraph in page 10 adds, why do you want to discuss Y90 in cholnagio and HCC when the topic of discussion is role of Y90 in CRC
Reply: we wanted to point that Y-90 SIRT has been proved to have a significant role in other liver malignancies such as cholangiocarcinoma, while it is still under-utilized in CRLM. Radio-embolization uses radiation-induced treatment effect which should have no different effects on various radiosensitive malignances in the liver.

Lines 195-197 is the same as 210-212 is there any value in repeating.
Reply: We agree. We have incorporated the second paragraph within the first one.

1. definitive treatment of low-volume liver metastases What does this mean? Most of this is palliation, unless you are talking about segmentectomy kind of doses (which is predominantly for HCC). The discussion under that heading sounds like palliative treatment not definite treatment. The heading is a little misleading.
Reply: As we answered to reviewer#2, we changed it to element in the multidisciplinary treatment of low-volume liver metastases:

What does clearing the left lobe mean? Line 279 page 15 By ablation etc? why do you need hybrid operation/IR suites for this as the surgery is 4-12 weeks later after the Y90 and can be done in a regular OR, what is the point in emphasizing on the innovation of hybrid rooms.
Reply: the word clearing was changed to resection. Hybrid procedures has anecdotally shown to lessen the burden on patients, decrease interruption of chemotherapy, increase compliance, reduce multiple admission rate, and enhance multidisciplinary approach. In addition, the operative suite is the best place to manage procedural complications.
Change in the text: Please see page 15, line 282.

In the summary line line 312 should be adjunct not adjacent.

Reply: Thank you for noting this, It has been changed.