

## Peer Review File

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### Reviewer Comments:

#### Introduction

1. An update on the status of locoregional therapy for colorectal liver metastases is needed according to NCCN guidelines, principles of surgery. These multidisciplinary guidelines recommend resection and image guided ablation either together or as monotherapies to the degree that all visible disease can be eradicated. Image guided radiotherapy is recommended only for non-resectable patients and in the context of a clinical trial. (NCCN 2022).

2. While historically thermal ablation has been used in patients that were deemed poor surgical candidates. Ablation is recommended as monotherapy or in combination with surgery even in resectable patients as long as all visible disease can be eradicated. Please revise to indicate that thermal ablation is not only recommended in non-surgical patients.

**Response:** Thank you for this comment. We have updated the introduction to address both points #1 and #2. Please see below:

*Hepatic resection is the preferred treatment for resectable CRLM [NCCN], offering a potentially curative option with an increase in overall survival (OS) and potential for long term disease control [7-9]; five-year OS ranges from 35% to 60% in patients who undergo surgery [3,7-9]. Ablative techniques [e.g. thermal ablation – radiofrequency ablation (RFA) or microwave ablation (MWA)] can be also be considered, either alone or in conjunction with resection, if all sites are amenable to treatment [NCCN, 10]. RFA or MWA may be considered in patients with three or less CRLM lesions, each with a diameter <3 cm and distant from vulnerable structures (e.g. major blood vessels, central biliary tract or gallbladder, just beneath the diaphragm) [12-14]. In a phase II randomized trial, the addition of RFA to systemic therapy for patients with <10 CRLM resulted in an improvement in 3-year progression-free survival (PFS: 27.6% vs 10.6%, p=0.025) [15].*

*Stereotactic body radiation therapy (SBRT) is another locally ablative therapy that enables the delivery of large radiation doses to a well-defined target, using image-guidance (IGRT), and motion management [16,17]. Steep dose gradients are created near the tumor edge, enabling the delivery of a high dose to the target while limiting the dose delivered to the surrounding organs-at-risk (OARs) [16,17]. Given the rationale for local therapy for the treatment of CRLM, unresectable CRLM was one of the first sites to be treated with SBRT. NCCN*

*guidelines state that SBRT may be considered in select cases and should not replace surgery in those patients who are potentially surgically resectable.*

### **Patient Selection**

1. While multidisciplinary discussion is encouraged and beneficial it should be clear that this is not a precondition for any recommended therapy within the standard of care and the NCCN guidelines. A mandatory multidisciplinary discussion should not be expected in every case undergoing liver directed therapy as this is not possible due to the number of patients in need for treatment. It should however, be reserved and completed for those complex cases where the role of local therapy is not established or there is more than one indicated therapy based on guidelines mentioned above.

**Response:** Thank you – we agree that it is not practically feasible for all patients to undergo MCC discussion and have updated this section as described below:

*Multidisciplinary case conference discussion is encouraged, where possible, for patients with CRLM. Although a mandatory discussion is not expected for every case undergoing standard management as per the NCCN guidelines, it should be strongly considered for complex cases where the role of local therapy is not established or where there are multiple therapeutic options based on the aforementioned guidelines.*

### **Treatment Planning**

1. It is desirable and would be clinically useful to define the safe distance of the target tumor from the central bile ducts and the gastrointestinal track in order to offer IMRT.

**Response:** Generally, there is no minimum distance – if there is overlap of the PTV with the central biliary tree or a luminal OAR, we would favor 5 fraction SBRT and might prescribe a lower dose to ensure safety.

*Dose fractionation can be individualized taking into account the strong dose response relationship for CRLM [39]. Technical considerations for dose selection include location within the liver, proximity to OARs, motion management technique, and type of on treatment image-guidance used. Single fraction or three fraction SBRT may be considered for lesions at least 1 cm away from the central biliary tract and away from luminal OARs. For lesions where the planning target volume (PTV) is in contact with or overlaps with the central biliary tract or a luminal OAR, five fraction SBRT is preferred.*

2. Are there any data stratified by the ability to create a margin over 5 and over 10 mm?

Margins have been extremely important to achieve tumor control in prior ablation as well as

radiation series. Please review and elaborate.

3. A discussion with reference to other local options such yttrium 90; Yttrium radiation segmentectomy and ablation could be of value.

4. At the minimum a discussion regarding the value of margins as discussed in paper by Shady et al (reference 14) could be usefull. Recommended references on ablation below could help the discussion further.

5. The impact of Tumor absorbed dose after Y90 for colorectal liver metastases has recently been documented (see references below), please comment how would this relate to IMRT.

*Response #2-4:* Thank you for providing these references and suggestions. Our understanding was that the focus of this series was specifically on SBRT and that is why the manuscript does not go into detail regarding other ablative therapies including RFA, MFA, nor Y90. In general, when planning SBRT, the gross tumor volume = clinical target volume (e.g. the margin is 0mm). To my knowledge, there are no data supporting larger clinical target volume (CTV) margins in SBRT. The concern with use of larger margins >5 or 10mm is that you are now treating larger volumes of liver and thus potentially increasing toxicity.

Internal target volume and planning target volume (ITV, PTV) margins are, however, extremely important. This is based on the motion management technique used and image guidance that is available. There is no minimum recommended margin – in fact, we generally try to reduce the ITV/PTV margins as much as possible based motion management and image guidance. For example, with real time MR guidance, where the lesion and relevant organs at risk are visible in real time, we might reduce our ITV margin to 0mm and PTV margin to only 5mm (This differs based on institutional standards).

*Response #5:* Although the references provided regarding margins in the setting of other types of ablation is quite interesting, however, I do not believe it applies in this setting.

## References

1. Add the NCCN guidelines and discuss principles of surgery as commented above:  
Benson AB, Venook AP, Al-Hawary MM, Arain MA, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Farkas L, Garrido-Laguna I, Grem JL, Gunn A, Hecht JR, Hoffe S, Hubbard J, Hunt S, Johung KL, Kirilcuk N, Krishnamurthi S, Messersmith WA, Meyerhardt J, Miller ED, Mulcahy MF, Nurkin S, Overman MJ, Parikh A, Patel H, Pedersen K, Saltz L, Schneider C, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Gregory KM, Gurski LA. Colon Cancer, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021 Mar 2;19(3):329-359. doi: 10.6004/jnccn.2021.0012. PMID: 33724754.

*Response:* Added.

2. Reference 7 has been updated by same group by a reference in 2018 on value of hepatectomy and factors affecting long term survival (creasy et al 2018):

Creasy JM, Sadot E, Koerkamp BG, Chou JF, Gonen M, Kemeny NE, Balachandran VP, Kingham TP, DeMatteo RP, Allen PJ, Blumgart LH, Jarnagin WR, D'Angelica MI. Actual 10-year survival after hepatic resection of colorectal liver metastases: what factors preclude cure? *Surgery*. 2018 Jun;163(6):1238-1244. doi: 10.1016/j.surg.2018.01.004. Epub 2018 Feb 15. PMID: 29455841; PMCID: PMC7439273.

*Response: Added.*

3. ESMO guidelines have an update since 2016 and should be reviewed and replaced.

*Response: Updated.*

4. Reference 10 is 14 years old and should be replaced with newer.

*Response: Updated.*