

Peer Review File

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Reviewer comments

General comments: This editorial provides commentary on the recent CAMINO trial and advocates for the routine performance of MRI in the evaluation of patients with CRCLM undergoing evaluation for locoregional treatments. MRI with hepatobiliary contrast agents offers an improved assessment for the extent of disease in the liver, which is extremely important when considering invasive treatments. Surgery and ablation, in order to achieve local cure, require adequate margins (R0 or A0, respectively). Especially with ablation, MRI provides important anatomic detail to ensure that margins (at minimum >5 mm, ideally >10 mm) can be achieved safely. The performance of MRCP and/or delayed biliary excretion phase imaging can assess the risk for biliary injury with ablation. I think that the importance of adequate treatment margins and how MRI can assist with this assessment should be added to the editorial. Finally, I think that it is important to consider the performance of PET/CT prior to locoregional treatments, as mentioned by the NCCN guidelines. This assessment complements the limitations of MRI (more global assessment, detection of distant and nodal metastases) and offers a baseline prior to arterially-directed locoregional treatments (i.e. TACE and Y90), as RECIST response tends to lag behind metabolic changes in the treatment volume.

General comments:

Reply: We have added sentences respectively to these different points, most will be detailed in the specific comments paragraph. Considering the first point on the added value of MRI in margins assessment, we added the recommended paragraph (see page1, line 30)

Changes in the text: “Moreover, surgery and ablation, in order to achieve local cure, require adequate margins (R0 or A0, respectively). Especially with ablation, MRI provides important anatomic detail to ensure that margins (at minimum >5 mm, ideally >10 mm) can be achieved safely. MRCP and/or delayed biliary excretion phase imaging can also assess the risk for biliary injury with ablation and the relationship between the metastases and the biliary tree prior to surgery.”

Specific comments:

P1, L8: Consider “Over the past decades” vs. “since”

Reply 1: The text has been modified as suggested (see page 1, line 8)

Changes in the text: Over the past decades, locoregional treatments (ablation with or without surgery) for unresectable CRCLM (4,5) have been shown to significantly prolong survival, as long as all disease can be addressed

P1, L8: Comment: I disagree with the characterization of locoregional treatments as “aggressive”. Some are more invasive than others, with ablation being a minimally invasive treatment evolving into an acceptable alternative to surgery for small volume disease. I am aware that Ruers et al. used the term aggressive in their CLOCC trial publication. I would

recommend rephrasing sentence to: “Locoregional treatments (ablation with or without surgery) for unresectable CRCLM have been shown to significantly prolong survival, as long as all disease can be addressed.”

Reply 2: The text has been modified as suggested (see page 1, line 8)

Changes in the text: “Over the past decades, locoregional treatments (ablation with or without surgery) for unresectable CRCLM (4,5) have been shown to significantly prolong survival, as long as all disease can be addressed”

P1, L13: I would add: treatment related questions (i.e. can all disease be treated safely with adequate surgical and/or ablative margins)

Reply 3: The text has been modified as suggested (see page 1, line 13)

Changes in the text: “tumor oriented questions (i.e. can all disease be treated safely with adequate surgical and/or ablative margins).”

P1, L20: I think it is worth mentioning that (1) PET/CT offers the benefit of detection of distant metastases (2) has been shown to change management in 24% of patients (Maffione et al meta-analysis) and (3) is mentioned in the latest NCCN guidelines, as a consideration prior to minimally invasive liver-directed therapies. The current landscape of imaging modalities for CRCLM prior to and after locoregional treatments is reviewed by Chlorogiannis et al 2024, demonstrating the benefits of metabolic and MR imaging in assessment of these patients.

Reply 4: The paragraph has been added as suggested to underline the added benefit of PET/CT (see page 1, line 20)

Changes in the text: “It must be noted that PET/CT offers the benefit of detection of distant metastases, has been shown to change management in 24% of patients (9) and should be considered prior to minimally invasive liver-directed therapies”

P1, L33: This abbreviation (HBP) has not been defined previously.

Reply 5: The abbreviation is defined here as suggested (see page 1, line 41)

Changes in the text: “adding MRI with hepatobiliary (HPB) agents to CT”

P2, L72: IOUS is very operator dependent. Moreover, many of the intrahepatic changes that occur with prolonged exposure to chemotherapy can generate false-positive IOUS findings. Even though IOUS is not performed with ablation, other imaging assessments performed at the time of ablation (particularly when performed with CECT and PET/CT guidance) significantly overcome this limitation.

Reply 6: The limitations of IOUS have been added (see page 2, line 85) as well as the way to overcome the lack of IOUS during ablation (see page 2, line 90)

Changes in the text: “as well as IOUS, which is also operator dependent” and “although imaging assessments performed at the time of ablation (particularly when performed with CECT and/or PET/CT guidance) significantly overcome this limitation”

P3, L92: Nevertheless, a subset of patients with CRCLM and extrahepatic disease involving the lungs or lymph nodes appear to benefit from local CRCLM treatment (Schultz et al, AmCORE registry Cancers 2024).

Reply 7: The paragraph has been added as suggested (see page 3, line 112)

Changes in the text: “Interestingly, it must be noted that a subset of patients with CRCLM and

extrahepatic disease involving the lungs or lymph nodes appear to benefit from local CRCLM treatment (20).”

P3, L99: IOUS is misspelled.

Reply 8: IOUS is now correctly spelled (see page 3, line 121)

Changes in the text: “IOUS”
