

Peer Review File

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Reviewer Comments

Comment # 1: Editing for better English is desired

The two statements below are confusing if not contradictory. Please clarify if this is a retrospective study with waiver of consent obtained prior to publication or this was done with consent of subjects to participate in a research that would result in a publication?

“CONSENT TO PARTICIPATE: For this type of study formal consent 19 is not required. This study has obtained IRB approval from and the need for informed consent was waived.

CONSENT FOR PUBLICATION: Consent for publication was obtained for every individual person’s data included in the study”

Reply # 1: Thank you for bringing this statement to our attention. This has been fixed accordingly and is reflected in the manuscript.

Abstract

Comment # 2: Purpose:

- The statements here do not fully reflect current status of Thermal ablation is also indicated as a first line therapy ahead of surgery for small size HCC. Also Ablation is recommended in the Colon Cancer NCCN guidelines as a stand alone treatment or in combination with surgery in order to treat liver metastases, as long as all visible disease can be eradicated.

Reply #2:

Thank you for your wonderful feedback. We have incorporated the articles and guidelines you have recommended at the bottom of the comments into the manuscript, and the introduction part of both the abstract and manuscript reflect this included information now.

Comment # 3:

Materials and Methods:

- Wouldn't it be more relevant to include tumors within 1 cm from the heart rather than ablation zones within 5mm? The ablation zone depends on technique and sometimes can be off center. So a tumor that is 2 cm from the heart could have an ablation zone within 5 mm or even closer to the heart when in reality the tumor position was not qualifying it as a tumor proximal to the heart or diaphragm. Please revise

Reply # 3:

Thank you so much for providing us a different outlook for identifying lesions close to the heart. This is a very relevant question, and if you check some of the studies previously done (References: Flippidas 2017 and Carberry 2017), lesions next to the heart have been defined in different ways (We have now also included this in the methods section of the manuscript and discussion section as a limitation).

Lesions within 1 cm of the heart would have an issue however, the recommended ablation margin is from 0.5 to 1 cm, by ablating a mCRC within 1 cm lesion with a 1 cm ablation margin, the ablation zone would finish at the pericardium, which could raise safety issues. Instead we elected to emulate what has defined in the literature in animal and human studies (Carberry 2017) to add homogenous data that further strengthens the existing data on microwave ablation near the heart.

Using the tumor location as the relevant reference would introduce variability into the literature of how to define it, from the center of the mass versus from the periphery. From the closest periphery or make an average of all measured sides to the heart? Measurement from the closest final ablation margin visualized is not only backed by an existing study, but also has a safety relevance that is invariable considered during thermal ablation of lesions near the heart.

Comment # 4:

Results

- What is the range of tumor size?

- Stratification of outcomes by the ability to create ablation margins is needed. It seems that 13/17 patients progressed locally. This rate of local failure is high when compared to ablation papers. How is this explained?

Reply # 4:

Thank you for your wonderful feedback.

- Range of tumor size has been now included in the abstract
- 13/17 patients did not have local tumor progression, but rather a large (82%) of the patients had multifocal disease prior to ablation of target lesion. The definitions have been changed accordingly to avoid this confusion.

Comment # 5:

Introduction

- The statements about surgery and transplantation being the gold standard therapy for HCC do not fully reflect current status of recommendations. Thermal ablation is also indicated as a first line therapy ahead of surgery for small size HCC. Also Ablation is recommended in the Colon Cancer NCCN guidelines as a stand alone treatment or in combination with surgery in order to treat liver metastases, as long as all visible disease can be eradicated. The relevant NCCN, ESMO BCLC guidelines need be reviewed and discussed/cited.

- The impact of ablation margins is key to the success of ablation regardless of tumor location or ablation energy used. Papers establishing this information need be reviewed and cited accordingly both in introduction as well as the discussion

Reply # 5:

Thank you for your wonderful feedback. We have incorporated the articles and guidelines you have recommended at the bottom of the comments into the introduction section of the manuscript and into the discussion section of manuscript.

Comment # 6:

Methods

Patient Selection and Data Collection

- Local recurrence implies that the first imaging after ablation indicated complete tumor coverage by the ablation zone. Please use terminology as described in the relevant publication by Ahmed M et al. Currently reference 10.

- As indicated in prior comment it would be more desirable to mention the distance of the actual tumor rather than the ablation zone from the heart.

Reply # 6:

Thank you for your wonderful feedback. We have defined various terms of disease progression accordingly in the methods section. In addition, as discussed above we have addressed the rationale behind choosing ablation zone ≤ 5 mm in both the methods and discussion sections of the manuscript.

Comment # 7:

Technique

- What was the desired end point of each ablation zone with regards to tumor size? Was there an interest to cover the tumor with margins? What was the desired margins? How were these assessed?

- Figure 1 does not depict well the target tumor in CT.

- It would be useful to provide the actual distance of the tumor to the heart prior to ablation.

Reply # 7:

Thank you for taking the time to provide this feedback.

-The information regarding the technique, desired margins and the assessment are now addressed in the technique portion of the methods section

-The figures have been modified to provide increased clarity

-As discussed above, we have addressed the rationale behind choosing ablation zone \leq 5mm in both the methods and discussion sections of the manuscript.

Comment #8:

Results

- The distance of the ablation zone to the heart is useful mostly to establish safety however it is important to correlated these findings with the preablation tumor location and distance of each tumor to the heart and how this impacted not only the safety but also the ability to treat with margins and the subsequent local tumor control vs progression.

- What is the definition of the “technical Success Rate”? This was not mentioned in the methods. Since there was a case of residual disease the definitions according to terminology reporting standards need be stated in the methods for clarity.

- It is not clear why the patient with residual disease as well as the one with LTP within 8 months from MWA were treated with TACE vs repeat MWA. An explanation is desired.

- Residual disease by definition does not develop but is what is left at same site of treatment after the first ablation. Please clarify data in table 1 accordingly

- Was there any death within 3 months from MWA?

Reply #8:

Thank you for providing us this wonderful feedback.

- As discussed above, we have addressed the rationale behind choosing ablation zone \leq 5mm in both the methods and discussion sections of the manuscript.

- We have included a statement regarding tumor margins from both literature and the technique used in the methods section.

- The term technical success rate has now been defined in the methods section

- We have defined various terms of disease progression accordingly in the methods section to avoid confusion regarding local tumor progression and residual disease.

- There were 3 deaths within 3 months of MWA, and is depicted in the table 1.

Comment # 9:

Discussion

- The information of how MWA works is not needed and is out of place here.
- The ability of MWA to overcome the heat sink effect is shown in animal models and only in very few papers in clinical practice. None of the cited papers 11, 13 or 14 is evidence to that. All 3 papers here are reviews. Please provide the papers with the direct evidence

Reply # 9:

Thank you for providing this feedback. I have deleted the paragraph on the technique of how MWA works which includes the heat sink effect statement.

Comment # 10:

- The continuous injection of fluid for organ protection does not necessarily maintain a space but has a cooling effect from flowing fluid.

Reply # 10:

Thank you for this feedback. I have also added the statement regarding cooling effect the hydrodissection and hydrothorax provide.

Comment # 11:

- The term partial response when ablation is used with local curative intent is not appropriate. The need to indicate range of tumor size and stratification of outcomes by margin size will address these issues and offer more objective information about the efficacy of ablation of dome tumors.
- The information that 82% of patients had multifocal disease need be presented in the materials and methods. This high rate of multifocal disease requires further explanation and justification of the use of thermal ablation to treat the dome tumor near the heart.
- The 6% LTP appear for first time in the discussion. I assume that this responds to 1/17 tumor LTP vs 1/12 that was reported in the results. This needs to be clarified in the results.

Reply # 11:

Thank you for pointing this out.

- The term partial response has been changed to incomplete response. We have included information about range of tumor size and the margin size in the manuscript.
- The information regarding local tumor progression and presence of multifocal disease has now been included in methods and results sections of the manuscript to avoid any confusion. The terms of disease progression have also been defined in the methods section.

Comment # 12:

References

The following references are relevant, and need be discussed in detail.

- Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. Benson AB 3rd, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS, Deming D, Engstrom PF, Enzinger PC, Fichera A, Grem JL, Grothey A, Hochster HS, Hoffe S, Hunt S, Kamel A, Kirilcuk N, Krishnamurthi S, Messersmith WA, Mulcahy MF, Murphy JD, Nurkin S, Saltz L, Sharma S, Shibata D, Skibber JM, Sofocleous CT, Stoffel EM, Stotsky-Himelfarb E, Willett CG, Wu CS, Gregory KM, Freedman-Cass D.J Natl Compr Canc Netw. 2017 Mar;15(3):370-398. doi: 10.6004/jnccn.2017.0036.PMID: 28275037

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- Benson AB 3rd, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, Saenz DA, Are C, Brown DB, Chang DT, Covey AM, Hawkins W, Iyer R, Jacob R, Karachristos A, Kelley RK, Kim R, Palta M, Park JO, Sahai V, Schefter T, Schmidt C, Sicklick JK, Singh G, Sohal D, Stein S, Tian GG, Vauthey JN, Venook AP, Zhu AX, Hoffmann KG, Darlow S. NCCN Guidelines Insights: Hepatobiliary Cancers, Version 1.2017. J Natl Compr Canc Netw. 2017 May;15(5):563-573. doi: 10.6004/jnccn.2017.0059. PMID: 28476736; PMCID: PMC5557008.

- The minimal ablative margin of radiofrequency ablation of hepatocellular carcinoma (> 2 and < 5 cm) needed to prevent local tumor progression: 3D quantitative assessment using CT image fusion. Kim YS, Lee WJ, Rhim H, Lim HK, Choi D, Lee JY. AJR Am J Roentgenol. 2010 Sep;195(3):758-65. doi: 10.2214/AJR.09.2954. PMID:20729457

- Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. Wang X, et al: Cardiovasc Intervent Radiol. 2013 Feb;36(1):166-75. doi: 10.1007/s00270-012-0377-1. Epub 2012 Apr 26.PMID: 22535243

- Radiofrequency ablation of liver metastases-software-assisted evaluation of the

ablation zone in MDCT: tumor-free follow-up versus local recurrent disease. Keil S, Bruners P, Schiffel K, Sedlmair M, Mühlenbruch G, Günther RW, Das M, Mahnen AH. *Cardiovasc Intervent Radiol*. 2010 Apr;33(2):297-306. doi: 10.1007/s00270-009-9681-9. Epub 2009 Aug 18. PMID:19688366

- Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (A0) Provides the Best Local Tumor Control. Shady W et al. *J Vasc Interv Radiol*. 2018 Feb;29(2):268-275.e1. doi: 10.1016/j.jvir.2017.08.021. Epub 2017 Dec 6. PMID:29203394

- Kaye, E. A. et al. Volumetric 3D assessment of ablation zones after thermal ablation of colorectal liver metastases to improve prediction of local tumor progression. *European radiology*, doi:10.1007/s00330-018-5809-0 (2018).

- Meijerink MR, Puijk RS, van Tilborg AAJM, Henningsen KH, Fernandez LG, Neyt M, et al. Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis. *CardioVascular and Interventional Radiology*. 2018;41(8):1189-204.

Reply # 12:

Thank you for providing us these references. These references have been discussed in detail in the manuscript