Peer Review File

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Reviewer A

This is a well written retrospective analysis by EA Knott and colleagues describing the local institutional series of microwave ablation for colorectal liver metastases. The authors demonstrate in this review significant rates of complete ablation, low rates of local tumor recurrences for a procedure that is overall well tolerated with a low rate of associated complications.

The article is excellent with good use of data analytics. I have the following comments.

Comment 1: Of the 19 provided authors listed, seven authors have listed conflicts of interest related to Ethicon for consulting or research support, the maker of the Neuwave microwave ablation system which was used in this study. A statement regarding whether Ethicon is sponsoring this work including payment for research publication is important to understanding the framework and context of this publication.
Reply 1: Thank you for the comment. The authors agree and have modified the text as advised.
Changes in the text: Page 5, lines 7-8 we added, "There was no industry support for this publication."

Comment 2: How did the authors decide to use US, contrast enhanced US or CT for guidance of microwave antenna placement? Was there a standard protocol or based on the choice of the treating physician?
Reply 2: Ultrasound is the modality of choice for placing antennas at our institution. CT fluoroscopy was only used when the tumor target was not visible by ultrasound. Rarely, contrast enhanced ultrasound assisted in visualizing the tumor prior to antenna placement, but was not used as a primary guidance modality.
Changes in the text: Added clarity as advised on page 6, lines 1-4.

Comment 3: Table 3 is not useful as there were really no significant predictors of overall survival on multivariate analysis. At the same time, one could argue you didn't include other variables in this table that could be related. As the authors did not find significant predictors of survival on multivariate analysis this table does not add much to the overall context of the paper.
Reply 3: Thanks for this comment. In table 3, we have tested the most common factors in the literature that are associated with OS. Given that our results differ from previous authors, we felt that including the multivariate regression analysis added value to the paper and the literature overall. Additionally, filtering results based on statistical significance is known to create a statistical bias towards non-replicable large effects (Vasishth et al 2018).

Shravan Vasishth, Daniela Mertzen, Lena A. Jäger, Andrew Gelman, The statistical significance filter leads to overoptimistic expectations of replicability, Journal of Memory and Language, 2018. https://doi.org/10.1016/j.jml.2018.07.004.

Comment 4: Does your institution have any surgeons who perform laparoscopic microwave ablation?
There are significant advantages to laparoscopic microwave ablation that should be addressed in the discussion of this article that specifically pertains to percutaneous ablation:
a) detection of occult peritoneal metastasis
b) identification of other lesions within the liver not detected on cross sectional imaging and or lesions not well detected by abdominal ultrasound secondary to patient body habitus
c) management of ablation related complications including bleeding or bile leak
d) other organs near lesions to be treated meaning, colon, stomach or duodenum
e) ability to reach lesions located at dome of the liver without need to traverse the pleural space or violate the diaphragm
Reply 4: Thank you for bringing up laparoscopic microwave ablation and the authors agree with the advantages you have discussed. We perform MW ablations in several ways: percutaneous, laparoscopic, open surgical, and ablation combined with resection. However, due to space constraints and the need to focus on a single uniform population, we have forgone a detailed discussion of other methods of performing ablation.

Comment 5: The top of Table 3 says that the tumor size is the largest tumor in the procedure see OS curves (Figure 4), but are you referring to the LTPF survival or the disease-free survival. What difference does it make in regard to the tumor size for this reference?
Reply 5: Thank you for pointing out this error in the figure caption. We intended to refer to Figure 2, which is the Kaplan-Meier analysis for predicting factors that influence OS and a supporting visualization for the Table 3 analysis.
Changes in the text: Fixed error and added clarity on table 3 caption (page 20, line 26-28)

Comment 6: Notably absent from this paper is a discussion regarding the synchronicity of the liver metastases? Were these lesions present at diagnosis? Metachronous lesions after chemo and primary treatment?
Reply 6: Thank you for the comment. The study population was a mix of both synchronous and metachronous tumors, but we have not further subdivided the population due to statistical considerations and the lack of prior ablation literature on this topic (i.e. this has not been definitely shown to be a predictor for ablation of LTP, OS, or PFS). However, as a surrogate we describe that 53% of the patients had prior liver-directed therapies for CRLM including hepatic resection, ablation, SBRT, and radioembolization (page 7, lines 22-23 and Table 1), and we evaluate prior treatment as a risk factor. We also found and fixed an error in the text (30/57 patients = 53%, not 47%).
Changes in the text: Error corrected on page 8, line 9.

Comment 7: The authors mention that the decision for ablation was made in a

multidisciplinary fashion at a tumor board. Were lesions chosen for microwave ablation only those lesions that were deemed unresectable by hepatobiliary surgeons? How was the choice made to use microwave ablation? Also, in patients who were previously treated with hepatectomy and had recurrence that then went on to have ablation, was this disease recurrence of the initially resected lesion or disease recurrence remote from the primary site?
Reply 7: The authors agree that the selection process could have been written more clearly and we have made modifications to the text. Patients were chosen for MW ablation by the multidisciplinary tumor board and were generally those that were technically unresectable or were poor surgical candidates. There were other individual cases where the patients underwent ablation + resection in a staged manner. MW ablation has been the thermal modality of choice at our institution since 2011. In terms of site of recurrence, the vast majority of the cases were new tumors elsewhere in the liver, but since this has not been previously established as an important factor for OS, LTP, or LTPFS we did not further analyze this metric.
Changes in text: Added clarity around patient selection process as advised (page 5, lines 15-20)

Reviewer B

Summary

Comments
This report by Knott and colleagues represents a single center retrospective analyses of outcomes following MWA for colorectal cancer metastasis to the liver. Overall, the study is well written and the data provide good evidence for the safety and application of MWA for treating hepatic CRLM. The strengths of the study lie with data consistency derived from the single center, multi-disciplinary approach to treating CRLM, and the use of a single MWA device (NeuWave Microwave Ablation System [Ethicon]) for all of the MWAs performed. The authors report a comprehensive listing of patient and tumor characteristics and the statistical analyses are appropriate for the data. In addition, the authors identify the limitations of the study design and interpretation of their data relative to prior reports from other investigators. In as much as the data interpretation allows, the authors present a reasonable conclusion that MWA can be successfully used for the treatment of CRLM with a high rate of clinical success and low perioperative complication rate. [As highlighted by the authors] the most significant drawback to the study is the absence of a non-MWA treated cohort for comparison and thus, the inclusion of discussion to other published studies is important. While I do not have any major points to raise regarding study design, data analyses/presentation or interpretation, I do have some suggestions the authors may want to consider.
Comment 1: The authors should consider including discussion of the recent study by Tinguely and colleagues (Eur J. Surg Oncol) in which MWA and resection for CRLM are compared and [when appropriate adjustments are made] demonstrate equivalent overall survival between the cohorts.

Reply 1: Thank you for this comment and your review of our manuscript. We have added this citation to the paper.
Changes in text: We have added discussion of this manuscript to the paper (page 4, lines 16-17 and page 12, line 11-12)

Comment 2: It would be of interest to provide data regarding the number of MWAs performed each year within the study group to allow the reader to better evaluate the outcome data. As the authors indicate, relative to RFA, MWA is a newer technology and one would presume that fewer MWA were performed during the earlier times of the study period than the latter.
Reply 2: The authors agree. We are a highly experienced center that has used MW ablation almost exclusively since 2011. Interestingly, all of the LTP's in this study occurred within the first 4 years of this study, corroborating the reviewer's point that there may be a learning curve for MW (page 11, lines 22-23). However, we are concerned about adding new data (numbers of cases per year) at this stage which would require further data analysis and discussion and decrease focus on the other endpoints in the manuscript.

Comment 3: As points of discussion it would be of interest to the readership to include reference to emerging technology for "targeting" tumors for MWA and use of integrated software to determine power settings deployed (e.g. Emprint SX with Thermosphere [Medtronic]. This may be particularly relevant to readers who may not have the same level of technology available to the study group for tumor localization/antenna placement. Similarly, mention/discussion of other emerging surgical technologies/techniques (HIFU, IRE, MWA + resection) would be beneficial.
Reply 3: Thank you for bringing this to our attention. We have added discussion of emerging technologies and software that will likely improve future MW procedures.
Changes in text: Discussion of emerging software added to pages 11 lines 23-24, page 12 lines 1-7.

Reviewer C

MWA CLM

Abstract
Purpose
OK
Methods

Comment 1: Further clarification is needed for the pattern of referrals to ablation. Especially the treatment especially after radiation and radioembolization. These treatments are not indicated prior to thermal ablation according to NCCN guidelines. A detailed explanation is thus necessary

Reply 1: Thank you, we have added clarity and further explained the referral pattern in the methods of the paper under "Patient selection." We have not added the referral process to the abstract due to word count limitations.
Changes in text: Added clarity around patient selection process as advised (page 5, lines 15-20)

Results

Comment 2: Is the 100% success rate accounts for the ability to treat with margins?
Reply 2: Yes, technical success is defined as the ablation zone completely overlaps or encompasses target tumor plus an ablative margin as determined by the operating physician as previously described (28). We have clarified this in the text of the manuscript.

Changes in text: Added clarity in methods of manuscript on page 6, line 19-20.

Comment 3: Is the LTP rate of 2 and 4% reported within the entire study follow-up period?
Reply 3: Thank you for pointing this out. We have clarified it in the abstract.
Changes in text: Revised as discussed (page 3, line 19)

Comment 4: It is desirable to report LTPFS by margin size. A 58% and 39% LTPFS at 3 and 5 years may ne very different for tumors that were treated with margins > or under 5 mm as shown by many prior similar papers (many of which are missing and need be included and reviewed/discussed).
Reply 4: This is an excellent comment. We agree that ablation margin size is an important factor when considering LTPFS. If we had more recurrences or a larger dataset, this is certainly a variable we would analyze. Unfortunately, because we only had four cases of LTP, any analysis involving covariates with tumor recurrence as the response variable would be far too underpowered. Using the sample size formula derived by Schoenfeld (1983) in regard to a proportional hazards regression model, with only four events we would only be able to detect a relative hazard ratio of 15 or more, and that's under the best-case scenario that there would be an equal distribution of tumors over/under 5mm (an equal distribution reduces the number of events necessary). Given that the *true* relative hazard ratio is likely *far* smaller than 15, we felt that our data didn't put us in a strong position to accurately assess the role of tumor margin size in our patient population (i.e. we would likely have to conclude that margin size is not a significant predictor of LTPFS-a conclusion that we don't truly believe), and thus defer to other manuscripts which have the statistical power to more convincingly make the argument that margins are important.
Changes in text: Added text as discussed on page 13, lines 6-8

Conclusions

Comment 5: Since there is no comparison group I am not sure it is justified to declared "prolonged" survival unless if there is an internal comparison group.

Reply 5: Thank you for pointing this out. We agree and have adjusted the text to include "prolonged survival compared to historical controls"
Changes in text: Added to page 3, line 26

Introduction.

Comment 6: Please indicate that thermal ablation is indicated as a sole treatment or in combination with surgery for CLM according to the NCCN guidelines that need be included and discussed.
Reply 6: The authors agree that this strengthens the paper and have added it to the introduction.
Changes in text: Added citation to NCCN guidelines on page 4, line 10.

Comment 7: Please clarify the direct role of margins on local tumor control and LTPFS. This has been validated in many studies that need be included and discussed.
Reply 7: Thank you, the authors agree. We have added more citations in the discussion that clarify this point.
Changes in text: Added citations to margin studies (page 13, lines 6-8)

Comment 8: There are more papers describing MWA for CRC liver metastases that need be included and discussed.
Reply 8: Thank you for providing these below. We have incorporated them throughout the entire paper.

Methods

Comment 9: Please describe "vulnerable" structures.
Reply 9: Added clarity in text.
Changes in text: Page 6, lines 8-9.

Comment 10: Was margin assessed only by US? This is usually suboptimal since the posterior ablation zone (AZ) interface is obscured by artifact. Please explain.
Reply 10: Thank you for the comment. During the ablation procedure, US was used to place the antennas and monitor the progress of the ablation in real-time including a limited evaluation of margins. After the ablation an immediate CECT was performed where margins were more thoroughly assessed by the treating physician.

Ziemlewicz TJ, et al. (2020) Radiofrequency and microwave ablation in a porcine liver model: non-contrast CT and ultrasound radiologic-pathologic correlation, International Journal of Hyperthermia, 37:1, 799-807, DOI: 10.1080/02656736.2020.1784471

Comment 11: Also it seems that all patients were assessed by CECT at the end of ablation. Please use this to stratify outcomes by the ability to create margins. To allow comparisons to prior similar papers a classification of margin as 0, 1-5, 6-10 and over 10 mm is desired.

Reply 11: Please see reply above (Reply 4).

Comment 12: The definition of complete ablation needs more clarification as most CRC liver metastases are not enhancing.
Reply 12: Thank you for pointing this out. We agree and the definition of technical success has been modified to reflect Ahmed et al. 2014 reporting standards.

Changes in text: page 6, lines 19-20.

Comment 13: The clinical Risk score modified for ablation has been shown to be a strong predictor of oncologic outcomes similar to hepatectomy. This is relevant to this study. Please review these studies (current references 7 and 31).
Reply 13: Clinical risk score modified for ablation is an interesting concept that we agree can have prognostic value. We elected not to add this to the manuscript due to adherence to word limits.

Comment 14: Competing Risk analysis may be indicated to account for patients that died prior to LTP. A statistical review is indicated.
Reply 14: The reviewer is correct that in this setting, death is a competing risk for tumor recurrence. For this reason, in our Kaplan Meier analysis, we decided *not* to censor patients who died, but instead we used a composite endpoint which was tumor recurrence *or* death. We considered different statistical methods to model the competing risks directly but given that we only had four local tumor recurrences, we ultimately decided that the added value of these methods didn't merit the increase in statistical complexity. Moreover, because we chose not to model LTPFS in a multivariate, regression setting, there would be no distinct risk sets to report (as there would be no covariate stratification).

Results.
Comment 15: The inclusion of the patient with over 3 and certainly over 4 metastases seems to be beyond standard recommendations for ablation with local curative intent. The same applies for those patients that had multiple tumors subsequently treated with resection. An exclusion of these papers seems appropriate or at the very minimum an explanation is needed.
Reply 15: The intent of the study was to report the results of MW for CRC metastases, not to report the results of MW for CRC metastases limited to within a specific guideline. The patients in this study were all of those referred through multidisciplinary hepatobiliary conference that subsequently underwent percutaneous MW ablation. There was general adherence to known recommendations, but exceptions were made for individual patients because treatment plans were tailored as is typical at most cancer centers. Interestingly, we found that the number of tumors and the size of the tumor did not significantly influence OS on multivariate analysis.

Comment 16: It appears that the squamous cell pathology should be excluded.

Reply 16: Even though these patients had worse results and are rarely treated, we would like to include them in the manuscript for informational purposes for the readers-even though their exclusion would improve our results. We did consider results of atypical cell types separately on page 10, lines 13-14.

Comment 17: A very detailed explanation about treatment with ablation after SBRT and radioembolization is needed. Guidelines recommend thermal ablation as a treatment offered with surgery or alone and certainly before SBRT or radioembolization (NCCN guidelines 2020).
Reply 17: Please see reply 15 above. The patients (4 SBRT; 1 Y90) had been referred to us after they had already undergone these therapies or as a combination treatment plan for separate metastases, both at the recommendation of a multidisciplinary tumor board. Individual treatment plans were considered for each patient as described above.

Comment 18: Prior papers have shown that KRAS mutant CRC liver metastases require larger margins to achieve reasonable local tumor control. I wonder if this is the case in this series. Please assess and report.
Reply 18: In this study, KRAS mutant CRC liver mets had no effect on OS (Table 3) and we did not observe any noticeable correlation with KRAS mutant CRC mets that developed an LTP (Table 4). Only 1 of the patients that had an LTP had a KRAS mutation, making any inference about local control and KRAS statistically underpowered.

Comment 19: Were there overlap ablations offered/required to achieve complete ablation with desired margins.
Reply 19: Overlap ablations were very rare as we performed multiprobe ablations for the majority of ablations (80% of the tumors) to take advantage of the known thermal and electric synergy of MW.

Comment 20: Why was additional ablation not offered to manage the initial 2 failures?
Reply 20: Thank you for pointing this out. The first failure was in the setting of extrahepatic disease (lung nodules) and the patient was subsequently treated with SBRT and chemotherapy. The second lesion recurred in an area that was inaccessible to ablation, so this patient was offered surgery. We have modified this in the text.
Changes in text: Added detail on page 8, lines 22-23

Comment 21: Regarding the biliary complications, did they occur to background of high risk, such as prior biliary intervention or other biliary issue?
Reply 21: Thank you, the patient that had a bile leak and abscess which resolved with drainage had a history of cholecystectomy only (but no common bile duct interventions).
Changes in text: page 13, line 15-17

Comment 22: It seems that high percentage of patients had extrahepatic disease. Was this the main reason that chemotherapy was administered after ablation?

Reply 22: Yes, MW was performed as a part of a multidisciplinary approach to the disease. In general, it has been shown that adjuvant chemotherapy is beneficial, and it is now a part of our institutional standard.

Gillams, A., Goldberg, N., Ahmed, M. *et al*. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, the interventional oncology sans frontières meeting 2013. *Eur Radiol* **25,** 3438–3454 (2015). https://doi.org/10.1007/s00330-015-3779-z

Comment 23: It is very interesting that the LTP was so low in the face of relatively low DFS. Any explanation for this?
Reply 23: This is the result of our patient population. A high percentage of patients in this study had extra-hepatic disease (26% total with 7% having more than 1 site), and a high proportion of patients had undergone prior liver-directed procedures for prior metastases (53%), reflecting our fairly advanced patient population. Most of the disease progression therefore came from new tumors in the liver or elsewhere.

Conclusions
Comment 24: Paper 21 as well as recent 2020 paper (Kurilova et al) have used mostly the same system and reported no LTP for margins over 10 mm and with LTP roughly around 75% for those treated with margins 6-10 mm. It is desirable to know if your data further support this findings.
Reply 24: We find the margin data in both of these studies highly interesting and have considered it for our work. With only 4 cases of LTP in our study, we would have had difficulty drawing any statistical significance from such a limited sample size (please see reply 4). An important difference between this study and the earlier referenced studies is the higher frequency of use of multiple MW antennas.
Changes in text: page 13, lines 6-8

Comment 25: The information about re-ablation for treating those with close margins is indeed a factor that can explain the superior local control in this cohort. This information was not mentioned in the methods and results. It is of paramount importance to indicate the number of ablation overlaps as well as the need to offer additional ablation after initial assessment of the ablation zone.
Reply 25: The need for re-ablation is rare in our practice because of the use of multiple probes that provide substantial electrical and thermal synergy. Re-ablation within the same session and anesthesia is rare, but the exact number of retreatments is not obtainable on a retrospective basis.

Comment 26: Prior studies have shown that 3D assessments of the ablation zone can better depict the ablation margin and predict LTP. Have you used such method for the assessment of the ablation zone prior to offering additional ablation?
Reply 26: We agree that automated methods of 3D ablation assessment are an interesting and useful emerging technology, and we have recently started using this technology in our

practice. However, it was not standard practice during the study period, and few if any patients in this cohort were assessed with ablation confirmation software. Therefore, we defer any broader conclusions about its usefulness to other studies that are adequately powered to do so. Because of the increasing importance of these tools and obvious benefits of standardizing margin analysis, we have added text in the Discussion.
Changes in text: page 11 lines 23-24, page 12 lines 1-7

Comment 27: Several studies have used biopsy immediate after ablation, special markers and methods to assess whether there is residual viable tumor or complete tumor cell death. Margins of 5-10 mm with biopsy approved complete tumor cell death were associated with Local tumor PFS of 97% at 30 months. Please discuss.
Reply 27: Biopsy immediately after ablation is not standard of care at our institution. The authors feel that a discussion of this is important but outside the scope of this manuscript which is to report results at a single academic medical center.
Changes in text: Added citation to biopsy and ablation margins page 13, line 6

Comment 28: Discussions regarding patient survival are very difficult especially in view of the chemotherapy treatments after ablation.
Reply 28: The authors absolutely agree and have addressed this limitation in the discussion section (page 12, lines 15-18; page 14, lines 13-15)

Comment 29: A better survival assessment could be achieved by reporting survival not only from ablation but also from initial diagnosis and the detection of liver metastasis.
Reply 29: Thank you, we agree with your comment, but in the interest of a concise discussion of OS, we have deferred to the ablation terminology and reporting standards (Ahmed et al. (28)) which state that OS should be calculated from the start of ablation treatment.

Comment 30: Several methods of intraop assessmengt of the ablation zone have been described. please discuss.
Reply 30: Thank you. We have added text to the Discussion of emerging technologies that are available for ablation targeting and assessment.
Changes in text: page 11 lines 23-24, page 12 lines 1-7

Comment 31: Kras, Ki67 and primary tumor site have been shown to impact outcomes. please discuss.
Reply 31: We agree, the manuscripts discussing KRAS, Ki67, and primary tumor site impacting outcomes are highly interesting. We were able to do multivariate analysis on the KRAS patients. We have displayed the primary tumor site in Table 1, but in the interest of space have decided not to include this in our analysis. Ki67 was not routinely reported at our institution during the study period.

References

Comment 32: The following relevant references need be reviewed and discussed:
Reply 32: Thank you for the additional resources. We have incorporated many of these into the manuscript.

1. 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.

2. Kurilova I, Bendet A, Petre EN, Boas FE, Kaye E, Gonen M, Covey A, Brody LA, Brown KT, Kemeny NE, Yarmohammadi H, Ziv E, D'Angelica MI, Kingham TP, Cercek A, Solomon SB, Beets-Tan RGH, Sofocleous CT. Factors Associated With Local Tumor Control and Complications After Thermal Ablation of Colorectal Cancer Liver Metastases: A 15-year Retrospective Cohort Study. Clin Colorectal Cancer. 2020 Oct 24:S1533-0028(20)30134-1. doi: 10.1016/j.clcc.2020.09.005. Epub ahead of print. PMID: 33246789

3. 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, Schiffl K, Sedlmair M, Mühlenbruch G, Günther RW, Das M, Mahnken AH.Cardiovasc Intervent Radiol. 2010 Apr;33(2):297-306. doi: 10.1007/s00270-009-9681-9. Epub 2009 Aug 18.PMID:19688366

4. Sotirchos VS, Petrovic LM, Gönen M, Klimstra DS, Do RK, Petre EN, Garcia AR, Barlas A, Erinjeri JP, Brown KT, Covey AM, Alago W, Brody LA, DeMatteo RP, Kemeny NE, Solomon SB, Manova-Todorova KO, Sofocleous CT. Colorectal Cancer Liver Metastases: Biopsy of the Ablation Zone and Margins Can Be Used to Predict Oncologic Outcome. Radiology. 2016 Sep;280(3):949-59. doi: 10.1148/radiol.2016151005. Epub 2016 Mar 24. PMID: 27010254; PMCID: PMC5006720. https://pubmed.ncbi.nlm.nih.gov/27010254/

5. Embryonic origin of primary colon cancer predicts survival in patients undergoing ablation for colorectal liver metastases.Yamashita S, Odisio BC, Huang SY, Kopetz SE, Ahrar K, Chun YS, Conrad C, Aloia TA, Gupta S, Harmoush S, Hicks ME, Vauthey JN. Eur J Surg Oncol. 2017 Jun;43(6):1040-1049. doi: 10.1016/j.ejso.2017.01.007. Epub 2017 Jan 29. PMID: 28187878

6. Tanis E, Nordlinger B, Mauer M, Sorbye H, van Coevorden F, Gruenberger T, Schlag PM, Punt CJ, Ledermann J, Ruers TJ. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. Eur J Cancer. 2014 Mar;50(5):912-9. doi:

10.1016/j.ejca.2013.12.008. Epub 2014 Jan 7. PMID: 24411080.

7. Tanis E, Spliethoff JW, Evers DJ, Langhout GC, Snaebjornsson P, Prevoo W, Hendriks BH, Ruers TJ. Real-time in vivo assessment of radiofrequency ablation of human colorectal liver metastases using diffuse reflectance spectroscopy. Eur J Surg Oncol. 2016 Feb;42(2):251-9. doi: 10.1016/j.ejso.2015.12.005. Epub 2015 Dec 23. PMID: 26746090.

8. Sotirchos VS, Fujisawa S, Vakiani E, Solomon SB, Manova-Todorova KO, Sofocleous CT. Fluorescent Tissue Assessment of Colorectal Cancer Liver Metastases Ablation Zone: A Potential Real-Time Biomarker of Complete Tumor Ablation. Ann Surg Oncol. 2019 Jun;26(6):1833-1840. doi: 10.1245/s10434-018-07133-6. Epub 2019 Mar 4. PMID: 30830537; PMCID: PMC6839687.

9. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer. 2003 Jun 15;97(12):3027-35. doi: 10.1002/cncr.11426. PMID: 12784338.

10. Sofocleous CT, Garg S, Petrovic LM, Gonen M, Petre EN, Klimstra DS, Solomon SB, Brown KT, Brody LA, Covey AM, Dematteo RP, Schwartz L, Kemeny NE. Ki-67 is a prognostic biomarker of survival after radiofrequency ablation of liver malignancies. Ann Surg Oncol. 2012 Dec;19(13):4262-9.

11. Han K, Kim JH, Yang SG, Park SH, Choi HK, Chun SY, Kim PN, Park J, Lee M. A Single-Center Retrospective Analysis of Periprocedural Variables Affecting Local Tumor Progression after Radiofrequency Ablation of Colorectal Cancer Liver Metastases. Radiology. 2021 Jan;298(1):212-218. doi: 10.1148/radiol.2020200109. Epub 2020 Nov 10. PMID: 33170105.

12. Odisio, B. C. et al. Local tumour progression after percutaneous ablation of colorectal liver metastases according to RAS mutation status. The British journal of surgery 104, 760-768, doi:10.1002/bjs.10490 (2017).

13. Calandri, M. et al. Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. Europeanradiology 28, 2727-2734, doi:10.1007/s00330-017-5273-2 (2018).

14. Livraghi, T., Meloni, F., Solbiati, L. & Zanus, G. Complications of microwave ablation for liver tumors: results of a multicenter study. Cardiovascular and interventional radiology 35, 868-874, doi:10.1007/s00270-011-0241-8 (2012).

15. Lahat, E. et al. Complications after percutaneous ablation of liver tumors: a systematic review. Hepatobiliary surgery and nutrition 3, 317-323, doi:10.3978/j.issn.2304-3881.2014.09.07 (2014).

16. 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).

17. Laimer G, Bale R et al. Volumetric assessment of the periablational safety margin after thermal ablation of colorectal liver metastases. Eur Radiol. 2021 Jan 14. doi: 10.1007/s00330-020-07579-x. Epub ahead of print. PMID: 33447860.

Need significant revision after accounting for many relevant refernces that have been ignored. A stratification of outcomes by ablation margins is needed. Statistics need be reviewed by statisticians.