

**Peer Review File**

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**Reviewer A**

Dear authors, your manuscript required a major revision in order to be suitable for publication.

**Comment 1:** Why do you define high volume liver disease by presence of 5 or more CRLM? It's not reference. I am not aware of this definition.

**Reply 1:** Thank you for your comment, which brings up an important issue. The term "high volume disease" as used in our title was not based on any official definition. We used it in a subjective manner, based on our institutional experience. We would be happy to change our title to "Surgical Microwave Ablation for Multifocal Non-Resectable Liver Metastases: A Single Institution Experience Treating Five or More Lesions".

**Changes in the text:**

Changed title to Surgical Microwave Ablation for Multifocal Non-Resectable Liver Metastases: A Single Institution Experience Treating Five or More Lesions

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**Comment 2:** Why patients who had bowel cancer with liver metastases were not considered for staged resection (liver first or bowel first approach) to reduce the risk of morbidity. This is a conventional approach nowadays.

**Reply 2:** Thank you for your comment. At our institution, our preference is to always do combined procedures as it saves a second operation and usually aligns with patient preference. We do routinely use stage resections when necessary, and three of our seven patients did have bowel resection prior to their ablation procedure. Of the seven who did not, five had colon resection at the time of their ablation and two had a complete clinical response to upfront clinical therapy and therefore are on a "Watch and Wait" protocol for their rectal cancer primary. We agree with the editor that staged resections can be used to reduce the risk of morbidity however in this small group of patients we were able to accomplish liver directed therapies at the same time as the resection of their primary tumor in a very safe fashion. We will add a sentence in the text to reflect that staged procedures could have been performed in lieu of combined procedures.

**Changes in the text:**

To the methods: "Staged resections were considered but felt to be unnecessary in the majority of this cohort due to the ability to safely performed combined liver directed therapy with colectomy. Staged resections should be considered in cases where operative morbidity is a concern." Page 6 Lines 135-137.

To table 1: Added a row for prior colon/rectal resection.

To table 2: Added a row for concurrent bowel/rectal resection.

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**Comment 3:** Did all patients have MRI liver on day one after surgery?

**Reply 3:** Thank you for your question. Our patients typically had an MRI within 2 weeks of operation. This is due to our institutional experience. Early on in our experience with ablation, imaging was performed shortly after treatment. However, after several hundred ablations, we observed zero primary treatment failures and therefore our current practice is to evaluate ablation at the time of post-operative assessment two weeks after surgery.

**Changes in the text:**

To methods: “Within two weeks of surgery, all patients had repeat MRI to assess for primary treatment failure (incomplete ablation) or missed lesions.” Page 6 Line 151.

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**Comment 4:** Overall survival is defined as time from diagnosis of bowel cancer or liver metastases? Does it mean all patients had synchronous liver metastases? It’s not clear, could you please define overall survival clearer?

**Reply 4:** Thank you for the observation. All of our patients had synchronous liver metastases. Therefore, overall survival was defined as time from diagnosis of bowel/rectal cancer and liver metastases to last follow up or death.

**Changes in the text:**

In the methods: “The median overall survival (OS) was defined as time from diagnosis (all patients had synchronous liver lesions) to last follow up or death.” Page 7 Line 159-161.

In the results: “All had synchronous liver lesions.” Page 7 Line 173.

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**Comment 5:** Could you please review and elaborate more on statistical analysis section?

**Reply 5:** Thank you for your comment. We have edited and amended our methods section to reflect our methodologic approach and analyses.

**Changes in the text:**

“Median and range or number and percent were calculated and reported for relevant outcomes.” Page 7 Line 161-162.

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**Comment 6:** In the results section you largely repeated the information provided by you tables.

**Reply 6:** Thank you for the observation. We have removed redundant text in the results section and referenced the tables. We removed table 4 per other reviewer’s request but kept the results in the text.

**Changes in the text:**

Removed text in the results section. Page 7 Line 173-199.

Removed Table 4.

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**Comment 7:** Half of the patients didn't have prior abdominal surgery, does it mean they had primary tumour unreserved. When was the primary resected then?

**Reply 7:** Thank you for your comment. Three of our seven patients did have bowel resection prior to their ablation procedure. Of the seven who did not, five had colon resection at the time of their ablation and two had a liver first approach with complete clinical response to upfront clinical therapy and therefore are on a "Watch and Wait" protocol for their rectal cancer primary.

**Changes in the text:**

To table 1: Added a row for prior colon/rectal resection.

To table 2: Added a row for concurrent bowel/rectal resection.

To results: "Three of our seven patients did have bowel resection prior to their ablation procedure. Of the seven who did not, five had colon resection at the time of their ablation and two had a liver first approach with complete clinical response to upfront clinical therapy and therefore are on a "Watch and Wait" protocol for their rectal cancer primary." Page 8 Line 199-202.

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**Comment 8:** All patients had stage IV disease, so it means all patients had synchronous liver mets?

**Reply 8:** We apologize for the confusion. We defined stage IV disease as any evidence of metastatic disease. Therefore, any patient with liver disease is considered to have stage IV disease, regardless of when the liver lesions were detected.

**Changes in the text:**

None

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**Comment 9:** Can you present the clear data on how many patients had simultaneous bowel resection and why it wasn't done in a stages manor to reduce the risk of complications.

**Reply 9:** Thank you for your comment. Three of our seven patients did have bowel resection prior to their ablation procedure. Of the seven who did not, five had colon resection at the time of their ablation and two had a liver first approach with complete clinical response to upfront clinical therapy and therefore are on a "Watch and Wait" protocol for their rectal cancer primary.

**Changes in the text:**

To table 1: Added a row for prior colon/rectal resection.

To table 2: Added a row for concurrent bowel/rectal resection.

To results: “Three of our seven patients did have bowel resection prior to their ablation procedure. Of the seven who did not, five had colon resection at the time of their ablation and two had a liver first approach with complete clinical response to upfront clinical therapy and therefore are on a “Watch and Wait” protocol for their rectal cancer primary.” Page 8 Line 199-202.

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**Comment 10:** Did patients receive postoperative adjuvant chemotherapy and were there any difference in DFS and OS?

**Reply 10:** Thank you for your comment. Our institutional practice is that all patients receive adjuvant chemotherapy before and after surgery. Therefore, we do not have a comparative group for survival outcomes. We have added a clarifying statement to the text.

**Changes in the text:**

In the results: “All patients received post-operative chemotherapy.” Page 9 Line 236.

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**Comment 11:** What’s the point of the Kaplan-Meier curve? It doesn’t compare any groups of patients?

**Reply 11:** Thank you for your comment. We have removed the Kaplan-Meier curve.

**Changes in the text:**

Removed Kaplan Meier curve.

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**Comment 12:** In figure 2 it’s probably better to demonstrate post ablation/resection scans than just scans of liver metastases.

**Reply 12:** Thank you for your comment. We have removed Figure 2.

**Changes in the text:**

Removed Figure 2.

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**Comment 13:** In table 1 neoadjuvant chemo was for bowel cancer or liver mets or both in case all patients had synchronous liver mets?

**Reply 13:** Thank you for your comment. For the purpose of this study, neoadjuvant chemotherapy refers to systemic chemotherapy given prior to liver directed therapy and, in some cases, where a synchronous colon resection was performed neoadjuvant was included for the primary tumor.

**Changes in the text:**

None

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**Comment 14:** Can you calculate Clinical Risk score (Fong) for all patients please to see if they were high risk or low risk for liver recurrence.

**Reply 14:** Thank you for your comment. We have calculated and added Fong clinical risk score to Table 1b. The median was 3, indicating high risk of recurrence.

**Changes in the text:**

Added to Table 1b.

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**Comment 15:** What was median CEA?

**Reply 15:** Thank you for your comment. The median CEA was 2.2. This was added to the text.

**Changes in the text:**

To the results: “All patients were stage IV at diagnosis and median CEA was 2.2. Page 8 Line 192.

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**Comment 16:** How did you manage disappearing CRLM?

**Reply 16:** Thank you for your comment. Disappearing liver lesions were common in this group of patients because many patients had tumors that were quite small despite being multifocal. The text has been changed to reflect our management strategy.

**Changes in text:**

To results: “For patients that had disappearing liver lesions we used ultrasound to assess intraoperatively. In some cases, residual lesions could be identified and treated. However, in other cases, despite the use of intraoperative ultrasound, no lesion could be identified and thus no treatment was performed in that area. These patients were surveilled with imaging every 3 months and any lesion that reappeared was treated immediately either with minimally invasive resection or ablation.” Page 8 Line 207-212.

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**Comment 17:** You had 10 patients in 10 years? Doesn't appear to be a huge number? Why is that. It's not rare to have multiple liver mets. Why don't you use this strategy more often?

**Reply 17:** Thank you for your comment. One patient was in 2012, the rest were 2016-2018. Therefore the range is 10 years but the number of patients appears small. In general, we have been much more aggressive with surgical resection for metastatic disease and only more recently have started using ablation to treat patients with a high number of lesions. These cases, although rare, demonstrate an ability to treat non-resectable disease with potential for curative therapy. It is not common to have this many liver lesions, and it is even less common to find more than five liver lesions without any other systemic disease. Additionally, this study details our early experience and additional cases have been performed that were not included in this study due to lack of long-term data.

**Changes in text:**

None

**Reviewer B**

**Comment 18:** Introduction: 50% of colorectal cancer patients do NOT develop liver metastases, population-based studies indicate 30-35%. Ref 3+4 are not studies of metastatic patterns of colorectal cancer and are not appropriate. Otherwise adequate.

**Reply 18:** Thank you for your comment. We have removed these references and changed the text to reflect the current literature more accurately.

**Changes in text:**

Changed citations. Page 4 Line 84-85.

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**Comment 19:** Methods: Surely an exclusion criteria for thermal ablation was proximity to central bile ducts and not only within 1cm of the hilum. How were tumors targeted? (visually, tactically, ultrasound (what kind of equipment?))

**Reply 19:** Thank you for your comment. Proximity to central bile ducts was also a reason not to proceed with ablation. We have changed the text to reflect this. Tumors were targeted via laparoscopic ultrasound (BK Medical, Peabody, MA, USA). These methods are described in our previous paper:

McEachron K, Ankeny J, Robbins A, et al. Surgical microwave ablation of otherwise non-resectable colorectal cancer liver metastases: Expanding opportunities for long term survival. Surg Oncol 2021;36:61-64.

**Changes in text:**

In methods: "Tumors <3 cm in size located at least 1 cm from the hilum and the central bile ducts were considered candidates for ablation." And "All patients were treated by a single surgeon with a Certus 140 2.45GHz ablation system (Neuwave Medical, Madison, WI, USA) with laparoscopic ultrasound (BK Medical, Peabody, MA, USA) as previously reported by our group (10)." Page 6 Line 131 and 150-151.

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**Comment 20:** Over the 10-year period only ten patients were included which constitutes a very small material for further study. It is not meaningful to talk of complications of four patients that had only ablation done and 6 with combined resection. The material indicates feasibility, not safety or efficacy for which the material is much too small.

**Reply 20:** Thank you for your comment. We agree with the reviewer that this is a very small study. Although we included patients with as few as 5 lesions, we ablated as many as 15. We believe it is important to report outcomes and complications, which could be used in future

meta-analysis and systemic reviews. We have altered our text to decrease language with conclusions about safety and efficacy.

**Changes in text:**

Changed language throughout discussion. Page 10-11, lines 268-342

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**Comment 21:** Conclusions: The discussion is too long. The CLOCC-study is in it's way groundbreaking but it has several problems with selection of patients and cross-overs making it difficult to draw clear conclusions from todays perspective.

**Reply 21:** Thank you for your comment. We have decreased the length of the discussion.

**Changes in text:**

Decreased length of discussion. Page 10-11, lines 268-342

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**Comment 22:** Figure 1. Please make a proper Kaplan curve with steps and ticks for censored data. A table below the x-axis should list the number of patients.

**Reply 22:** Thank you for your comment. We have removed the Kaplan Meier curve at the request of another reviewer.

**Changes in the text:**

Removed Figure 1.

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**Comment 23:** Figure 2 doesn't add value to an audience that is involved with treating colorectal liver mets.

**Reply 23:** Thank you for your comment. We have removed Figure 1.

**Changes in the text:**

Removed Figure 2.

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**Comment 24:** Table 3. Range data is missing for Medians

**Reply 24:** Thank you for your comment. We have included range data in the revision.

**Changes in text:**

Added range data to Table 3.

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**Comment 25:** Table 4. number treated is too low to make this meaningful

**Reply 25:** We appreciate your comment. We have removed the table.

**Changes in text:**

Removed Table 4.

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**Comment 26:** The benefits of microwave treatment of colorectal liver mets has been proven in many previous studies including excellent survival and low complication rates. Larger studies on multiple ablations for crlm:s have been published. The present paper adds very little to what has already been published.

**Reply 26:** Thank you for your comment. Although the benefits of ablation have been demonstrated in larger studies, this effort was to help define outcomes for patients who had as many as 18 lesions treated. The benefit of such an aggressive approach remains unclear/has not been well defined. We believe it is important to continue to contribute to existing literature as this treatment approach for high volume disease continues to evolve.

**Changes in text:**

None