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Microwave ablation therapy for colorectal liver metastases

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Boston University
MICROWAVE ABLATION THERAPY FOR COLORECTAL LIVER METASTASES

by

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B.S., MUHLENBERG COLLEGE, 2012

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2016
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MICROWAVE ABLATION THERAPY FOR COLORECTAL LIVER METASTASES

JACQUELINE PRICE

ABSTRACT

Background: The gold standard treatment for colorectal cancer liver metastases (CRCLM) is surgical resection. Unfortunately, the majority of patients with colorectal hepatic metastases are not candidates for resection. In recent years, several alternatives have emerged for patients whom are not resection candidates including modern systemic chemotherapy, targeted biologic treatments, regional therapies and local tumor ablation options. Microwave ablation (MWA) therapy is one such treatment alternative, based on thermal tissue ablation. This modality in concert with the most recent published literature on its use for patients with CRCLM will be reviewed in this paper.

Literature review findings: A structured review of the literature on ablative technologies was performed. In recent years, there has been an evolution from radiofrequency ablation (RFA) to microwave ablation therapy for the treatment of CRCLM. RFA has several limitations to its use and MWA theoretically avoids such limitations making it the currently preferable treatment option. There are limited publications comparing the use of RFA to MWA and limited publications on the use of microwave ablation for CRCLM. This paper will focus on the most recent data on MWA for CRCLM. This data can then be compared to the already published data on RFA.

Proposed Methods: Given the relative novel status for MWA as a treatment option for CRCLM, a potential disadvantage for its use is the perceived lack of knowledge across
the medical professional spectrum. In an effort to expand the knowledge of MWA, the proposed outcomes for this study include creating a curriculum to be offered as a CME course focused for Primary Care Providers (PCPs) to provide a basis of clinical familiarity for its use. This effort will familiarize providers who may have patients diagnosed with CRCLM and also allow them to initiate the conversation about this therapy with their patients who may be candidates for this treatment.

**Conclusions:** MWA therapy is a safe and effective treatment modality for CRCLM. Due to this new development in treating liver lesions originating from colorectal cancer, it’s imperative for providers to become familiar with these new technologies especially considering the high incidence of CRCLM. Therefore, a curriculum for PCPs will allow for a better understanding of this new technology and foster better provider-patient relationships.
# TABLE OF CONTENTS

**TITLE** .................................................................................................................................................. i  
**COPYRIGHT PAGE** ................................................................................................................................. ii  
**READER APPROVAL PAGE** ....................................................................................................................... iii  
**ACKNOWLEDGMENTS** .............................................................................................................................. iv  
**ABSTRACT** .................................................................................................................................................. v  
**TABLE OF CONTENTS** ............................................................................................................................ vii  
**LIST OF TABLES** ....................................................................................................................................... ix  
**LIST OF ABBREVIATIONS** ....................................................................................................................... x  
**INTRODUCTION** ........................................................................................................................................ 1  
  Background ................................................................................................................................................ 1  
  Statement of the Problem ............................................................................................................................ 4  
  Hypothesis .................................................................................................................................................. 5  
  Objectives and specific aims ....................................................................................................................... 5  
**REVIEW OF THE LITERATURE** .............................................................................................................. 7  
  Overview .................................................................................................................................................... 7  
**METHODS** ............................................................................................................................................... 35  
  Study design ............................................................................................................................................... 35  
  Study population and sampling ............................................................................................................... 35
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>36</td>
</tr>
<tr>
<td>Curriculum</td>
<td>36</td>
</tr>
<tr>
<td>Curriculum Assessment</td>
<td>37</td>
</tr>
<tr>
<td>Study variables and measures</td>
<td>38</td>
</tr>
<tr>
<td>Data collection</td>
<td>38</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>38</td>
</tr>
<tr>
<td>Timeline and resources</td>
<td>39</td>
</tr>
<tr>
<td>Institutional Review Board</td>
<td>39</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>40</td>
</tr>
<tr>
<td>Discussion</td>
<td>40</td>
</tr>
<tr>
<td>Summary</td>
<td>41</td>
</tr>
<tr>
<td>Clinical and/or public health significance</td>
<td>41</td>
</tr>
<tr>
<td>LIST OF JOURNAL ABBREVIATIONS</td>
<td>43</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>44</td>
</tr>
<tr>
<td>VITA</td>
<td>47</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Summary of evidence-based recommendations by Garrean et al.(^1) for RFA in CRLM.</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>Studies evaluating RFA as a single therapy for CRLM by Garrean et al.(^1)</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>Studies evaluating MWA for CRLM</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Learning objectives of the curriculum</td>
<td>37</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>CME</td>
<td>Continuing medical education</td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
<td></td>
</tr>
<tr>
<td>CRCLM</td>
<td>Colorectal liver metastases</td>
<td></td>
</tr>
<tr>
<td>HAIP</td>
<td>Hepatic arterial infusion pump</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>MWA</td>
<td>Microwave ablation therapy</td>
<td></td>
</tr>
<tr>
<td>PAE</td>
<td>Percutaneous acetic injection</td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td>Primary care provider</td>
<td></td>
</tr>
<tr>
<td>PEI</td>
<td>Percutaneous ethanol injection</td>
<td></td>
</tr>
<tr>
<td>RFA</td>
<td>Radiofrequency ablation therapy</td>
<td></td>
</tr>
<tr>
<td>RFS</td>
<td>Recurrence free survival</td>
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</tr>
</tbody>
</table>
INTRODUCTION

Background

It is estimated that on an annual basis in the USA, colorectal cancer affects 125-150,000 persons. For patients diagnosed with colorectal cancer, approximately 25% will have synchronous metastases to the liver at the time of their original diagnosis, and up to 50% will develop them in the course of the disease. If patients diagnosed with CRCLM are untreated, their median survival can be less than 1 year. The gold standard for the treatment of liver metastases is surgical resection, with the 5-year survival rates as high as 58%; however, the majority of patients are not candidates for resection. Non-resectable patients can be grouped as such due to the anatomic location of the tumor, the number of tumors, the presence of extra-hepatic metastases or additional medical comorbidities. Taken as a whole, approximately 10% of patients will be candidates for resection and another 15-20% are candidates for other local liver directed therapies, with systemic chemotherapy continuing as the backbone of consolidation of treatment. It is for these patients whom are candidates for regional hepatic therapies that ablative modalities such as MWA therapy are important.

There are many options available for the treatment of unresectable liver tumors. These options include systemic chemotherapy, regional treatments and ablative therapies. Ablation of liver tumors is a widely accepted technology for the treatment of primary and secondary liver cancer. Tumor ablation is defined as the direct application of chemical or energy based therapies for the treatment of tumors. Chemical ablation includes percutaneous ethanol injections and percutaneous alcohol instillation. Energy based
ablation includes cryoablation, laser ablation, RFA and MWA. Due to the wide spectrum of alternative therapies to resection, this paper will focus on the energy based ablation techniques, specifically the utilization of RFA and MWA.

Initially, cryotherapy was used to treat unresectable primary and secondary liver tumors. Cryotherapy ablation kills tumor cells by cooling the tissue to at least -35 degrees and cell death occurs due to the ice crystal formation after rapid freezing of the tissue. Studies on cryotherapy ablation have shown high local recurrence rates in addition to many complications post procedurally such as cold injury to adjacent organs, coagulopathy, thrombocytopenia and intraoperative hemorrhage. Studies comparing cryotherapy ablation to RFA showed treatment with RFA resulted in less complications, lower overall mortality and a lower local recurrence rate. These publications prompted physicians to transition their treatment of hepatic tumors from cryotherapy ablation to RFA.

RFA is a widely accepted treatment option for unresectable liver disease. It achieves tumor necrosis by molecular friction secondary to the energy current applied to the liver parenchyma. The temperature of the ablated area rises due to the molecular friction and as a result causes tumor cell death; the degree of thermal transmission is limited in tumors in close proximity to major hepatic vessels which is known as the heat sink effect. Although this has been a successful option for patients, the literature published on RFA for hepatic tumors has revealed several shortcomings and prompted transition of care to an alternative ablation method. A common cause of treatment failure after RFA is attributed to the heat sink effect. In addition, intraoperative time of treating a patient with
RFA is long, especially when compared to other available modalities. Recently, MWA therapy has become another ablative option and has several theoretical advantages over RFA therapy. Prior to the transition in care to MWA, there was a lack of level 1 data published providing evidence that MWA therapy was at least equivalent to RFA therapy. Further studies are needed to gain a better understanding of the efficacy of MWA therapy in order to support the shift in this treatment paradigm.

MWA therapy achieves coagulation necrosis through a different ablation technique than RFA. MWA raises the temperature of the water molecules within the liver, causing oscillation and this agitation of water molecules results in necrosis of tumor cells. This therapy also produces a more homogeneous zone of ablation compared to RFA. MWA therapy utilizes generators at a higher frequency (2.45 GHz or 915MHz) when compared to the frequency of the RFA generators (<900 kHz).

MWA is a newer technology for treating unresectable CRCLM, and has been added to the ablation armamentarium. A limitation to the wide application of this therapy is providers’ lack of knowledge about the variety of options in treatment for CRCLM. A curriculum for PCPs about the background of ablative techniques and the efficacy and safety of MWA for CRCLM would allow for a more widespread understanding of this treatment modality. This report will provide a background on the topic of MWA therapy for the treatment of CRCLM and the efficacy of this treatment. The purpose of the study will be to formulate a curriculum for providers in order to educate them about this latest technology and its efficacy in treating unresectable CRCLM.
Statement of the Problem

Colorectal cancer is the third most commonly diagnosed malignancy and there are approximately 141,000 new cases diagnosed annually. The liver is the most common site of metastases in patients diagnosed with colorectal cancer. Ablation therapies have become more utilized in this patient population, as the majority of patients diagnosed with CRCLM are not candidates for resection. From the literature search conducted, there is adequate evidence to suggest that MWA therapy provides an effective option for treatment of patients diagnosed with unresectable CRCLM.

Although MWA is a promising therapy for this common disease, a problem for patients is certain provider’s unfamiliarity with this latest technology. There is a lack of current modalities in order for providers to learn more about these recently developed technologies. The diagnosis of colorectal cancer with unresectable liver metastases is a life changing diagnosis and carries much anxiety and emotions for these patients. Patients will commonly feel most comfortable discussing a treatment plan not only with providers who specialize in treating this disease, but also with providers with whom they have a long term relationship with. PCPs (MD, DO, PA-C, NP) have the ability to foster long-term relationships with their patients. In addition, patients feel comfortable with their primary care provider and value their opinion on their overall health.

In this scenario, it would be most beneficial for these providers to have a general understanding of the available treatment options for unresectable CRCLM. Patients would likely feel more comfortable knowing their PCP is familiar with their recommended treatment or if their provider is able to educate them more in depth about
MWA therapy. Providing a curriculum to PCPs to gain CME credits, or for providers interested in treating unresectable CRCLM, would allow for a better understanding of this technology, increased referrals for their patients and a better provider-patient relationship.

**Hypothesis**

PCPs will acquire an adequate understanding of MWA therapy as an option in the treatment of CRCLM in order to feel comfortable educating their patients and making appropriate referrals.

**Objectives and specific aims**

The purpose of this study will be to formulate a curriculum for PCPs on the background of MWA therapy and highlight the efficacy of this for treatment of CRCLM. The curriculum will be administered at CME conferences via a PowerPoint presentation after first assessing the pre-test knowledge of MWA of attendees with Turning Point clicker questions. Currently, providers who are not involved in the field of Surgical Oncology are most likely unfamiliar with the new developments and the various options for treating unresectable CRCLM. By assessing the pre-test knowledge of the attendees, we will compare it to the knowledge they’ve gained from the hour-long presentation in a second Turning Point session administered after the lecture. The results collected from the two tests will be compared in a paired t-test. At the end of the lecture, brochures highlighting the basics of the therapy will be provided to PCPs to assist in educating their patients.

1: Creating a CME curriculum to provide PCPs with a general understanding of MWA therapy.
2: To assess pre and post-test knowledge and understanding of MWA therapy in treating patients with CRCLM with questions and evaluate the data with a paired t-test.

3: To provide PCPs with a handout to assist educating patients about this alternative treatment for unresectable CRCLM.
REVIEW OF THE LITERATURE

Overview

In order to better understand the various thermoablative options available for treating liver lesions, this review will provide background knowledge on the options and logistics of the various techniques. RFA therapy was first used as a treatment modality for renal cell carcinoma, and was later utilized for unresectable hepatocellular carcinoma. This treatment method can be utilized as a stand-alone treatment for HCC or in conjunction with surgical resection or systemic treatments. RFA replaced percutaneous ethanol injections (PEI) for the treatment of HCC, which is supported by randomized trials. Lin et al.\textsuperscript{8} published a randomized controlled trial comparing RFA to PEI and percutaneous acetic injection (PAI) and found that long-term survival, local recurrence rates, and cancer free survival were superior when treated with RFA compared to treatment with PEI or PAI. Most importantly, RFA for HCC has comparable overall survival rates to surgical resection of HCC, the current mainstay of treatment for hepatic tumors.\textsuperscript{1}

According to this same study, surgical resection has longer local recurrence free survival rates compared to RFA, however, local recurrence rates did not affect overall survival.\textsuperscript{1} Measuring local recurrence rates in HCC after treatment with RFA is difficult to interpret as HCC can arise secondary to different types of viral hepatitis. The different viruses responsible for transformation to HCC represent different pathologies of liver disease. Due to this difference, HCC will not consistently demonstrate similar response rates or disease progression after treatment due to the different etiologies and pathologies for HCC and different stages of cirrhosis, which affects outcomes as well. In addition, HCC
is a vascular tumor and grows due to its parasitic activity of drawing in the arterial bloody supply from the liver. Treating HCC involves techniques, which induce ischemia to the liver thus resulting in tumor necrosis. This damage to the liver can have an impact on survival as well.

With the well-published evidence on RFA documenting its success for treatment of HCC, RFA became more frequently incorporated in the treatment of CRCLM. According to Saied et al.\textsuperscript{2} in 2013, the most common and widely accepted ablative therapy for treatment of CRCLM was RFA.

In 1999, Curley et al.\textsuperscript{4} published one of the first papers examining RFA for the treatment of CRCLM. A total of 123 patients with primary or secondary liver malignancy were treated with RFA, and 61 of these patients were treated for CRCLM. Curley et al.\textsuperscript{4} compared his findings of a 1.8\% local recurrence rate of all lesions after RFA to the published data on cryoablation for treatment of liver tumors. RFA of liver neoplasms had a much lower local recurrence rate of 1.8\%, whereas studies evaluating cryoablation showed a range of local recurrence rates from 10-15\%. The median survival in this study was 15 months. Out of the 123 patients, two tumors had a local recurrence, one HCC tumor and one CRLM tumor. Both tumors were documented as \( \geq \)6cm by the investigators. This data was not stratified to look specifically at CRCLM recurrence rate and there was no data from this study published on overall survival. However, being one of the first studies to publish data on RFA for the treatment of CRCLM, this low local recurrence rate coupled with a low rate of new metastatic disease, 27.6\% within 15
months, argued that RFA for both primary and metastatic liver tumors was safe and associated with adequate gross tumor control.\(^4\)

In 2000, data was published on RFA therapy for secondary liver malignancies. De Baere et al.\(^9\) had separated patients into two groups: one group receiving percutaneous RFA versus the second group treated with intraoperative RFA. The majority of patients, 58 out of 68 patients, in this study were treated for CRCLM. Out of the 54 patients diagnosed with metastatic disease, 16 patients experienced local recurrence over an average follow up period of 13.9 months. Comparing the two ablative methods, there was no difference between the percutaneous or intraoperative administration of RFA for tumor control rate. This study demonstrated a low local recurrence rate after RFA of secondary liver cancer and no difference in the administration of RFA. Overall, this data provided good evidence to support the use of RFA for treating CRCLM.\(^9\)

The most commonly used modality of RFA as treatment is administered using a monopolar electrode.\(^10\) With the continued use of monopolar radiofrequency electrodes, several shortcomings surfaced. Monopolar RFA causes an outward source of energy propelling outwards in all directions from the electrode resulting in a 1-1.5cm ablated area of liver parenchyma.\(^10\) Using one RFA electrode restricts the ablation diameter to a smaller area of coagulation necrosis. Surgeons treating tumors larger than 1.5 cm using this technique are required to administer several overlapping ablations in order to achieve necrosis of the entire hepatic tumor. The use of the monopolar ablation causes rapid heating of the electrode and liver tissue. It soon became evident that the rapid heating of the tissue caused premature charring of the tip of the electrode inserted into the liver and
limited the distance the radiofrequency waves could propagate through the parenchyma. In addition, the monopolar technology results in decreased heat convection if the tumor is adjacent to hepatic vessels, known as the heat sink effect. This is problematic because complete tumor necrosis is difficult to achieve depending on the anatomical location of the tumor. These limitations of the monopolar RFA coupled with the prolonged ablation time for surgeons to administer this treatment posed some setbacks; RFA has an average time for complete tissue necrosis of 21 minutes.\textsuperscript{11} This is especially limiting if the patient has multiple tumors or if the tumors are larger than 1.5 cm in size.

Yi et al.\textsuperscript{10} published the first study examining the use of laparoscopic bipolar RFA for treatment of liver tumors. In this publication, the investigators evaluated the bipolar RFA system and hypothesized it would yield shorter ablation times and limit the heat sink effect compared to the monopolar RFA system. The bipolar RFA electrode creates an energy wave that travels in one direction between the two electrodes strategically placed on either side of the tumor. This allows for a stronger energy density and reduces the time required for tumor ablation. The use of two electrodes should theoretically limit the heat sink effect as well. The study by Yi et al.\textsuperscript{10} included a total of 17 patients, 12 who were diagnosed with CRCLM. There were no complications post procedurally and complete tumor ablation was achieved in an average of 5 min and 58 seconds. The time of complete ablation was significantly shorter than the mean ablation time required for the monopolar RFA system. In addition, the bipolar system was found to have the ability to create larger zones of ablation compared to the zone of ablation caused by the monopolar RFA system. A drawback in this technology is that in order to ablate the desired tumor,
the surgeon must ensure the two electrodes are deliberately placed to outline the tumor. If the electrodes are placed at an angle, it can create an uneven zone of ablation and may not cause complete tumor cell death. Like monopolar RFA, bipolar RFA is operator dependent and familiarity and understanding of the use of two electrodes for administration of thermal ablation is paramount to confirm tumor necrosis. Despite the limitations of the bipolar system, overall bipolar RFA offered many advantages and limited disadvantages compared to the use of monopolar RFA. Studies continued to examine the use of RFA and improvements in technology for treatment of CRCLM. RFA used as an adjunct treatment with other therapies, such as systemic chemotherapy, became an option for patients with unresectable liver malignancies. Machi et al. evaluated the use of RFA for unresectable CRCLM in combination with chemotherapy. In this study, 100 patients were included and either received RFA as first line prior to chemotherapy or RFA as second-line treatment after completing a chemotherapy regimen. Comparing these two arms, the median survival in the first-line RFA group was 48 months and the median survival in the group who received RFA as a second-line treatment was 22 months, these different were found to be significant in this study. Overall median survival among all patients was 28 months and local recurrence rate was 6.7%. However, 87% of these patients developed new intrahepatic and extra-hepatic metastases. Overall survival in this study was related to tumor size, extra hepatic metastases, age of the patient, CEA level and if they had previously received chemotherapy prior to this study. Machi et al. concluded that RFA combined with systemic chemotherapy provides a clear survival benefit in patients with
unresectable CRCLM, particularly when chemo was administered prior to radiofrequency ablation.

Local recurrence rates are significantly lower when RFA is combined with chemotherapy than with RFA alone. Garrean et al. commented that in the published data, there is a wide range in local recurrence rates after patients received RFA. The likelihood of higher rates of local tumor recurrence associated with CRCLM treated with RFA therapy is attributed to the biology of the ablated tumor. Tumors greater than 3 cm in diameter treated with RFA are associated with higher rates of local recurrence.

In 2001, Solbiati et al. published long-term follow-up data after patients received treatment with percutaneous cooled-tip RFA for CRCLM. At the time, this was the first study examining long-term follow-up of patients treated with this particular type of RFA. Follow-up in this study ranged from 6-52 months. The investigators found that the size of the hepatic lesion was significantly associated to the time to and frequency of local tumor recurrence. Tumors less than 2.5 cm in diameter, demonstrated local tumor control in 78% of tumors. Smaller tumors were more easily ablated when compared to the ablation of larger tumors. Local tumor control was achieved in 47% of tumors ranging in size from 2.6 cm to 4 cm and local tumor control was achieved in only 32% of tumors larger than 4 cm. These results correlate with the study by Garrean et al. which stated that hepatic lesions larger than 3 cm in diameter are more susceptible to local tumor recurrence than tumors with a diameter smaller than 2.5-3 cm. Garrean et al. suggested this finding is attributed to the limits of RFA and its inability to achieve a complete zone of ablation for tumors larger than 3 cm.
Garrean et al.\textsuperscript{1} published a review of the use of RFA for treatment of both primary and secondary liver tumors in order to evaluate its success, measured in safety and efficacy. This review examined studies treating hepatocellular carcinoma with RFA therapy, studies treating CRCLM with RFA and studies evaluating use of RFA as an adjunct to surgery. For the purpose of this present literature review, this analysis of the RFA therapy review will focus on the evidence on RFA and CRCLM. From the data Garrean et al.\textsuperscript{1} collected, the overall complication rate ranged from 2.4-12\% and due to this low complication rate, the study declared RFA to be a safe technology for treatment of colorectal hepatic metastases. He summarized the evidence-based recommendations for RFA in CRCLM, which are located in table 1.

**Table 1. Summary of evidence-based recommendations by Garrean et al.\textsuperscript{1} for RFA in CRCLM.**

<table>
<thead>
<tr>
<th>Recommendation for unresectable CRCLM</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary therapy for tumors &lt;3cm</td>
<td>Level 2</td>
</tr>
<tr>
<td>Combination treatment with surgery</td>
<td>Level 2</td>
</tr>
<tr>
<td>Combination treatment with HAIP</td>
<td>Level 2</td>
</tr>
<tr>
<td>Combination treatment with systemic chemotherapy</td>
<td>Level 2</td>
</tr>
<tr>
<td>Locally recurrent or progressive hepatic disease</td>
<td>No evidence based data</td>
</tr>
</tbody>
</table>

Garrean et al.\textsuperscript{1} made several conclusions based on their literature review. Surgical resection remains the gold standard for patients presenting with CRCLM if the tumors are resectable and the patient is a surgical candidate. RFA therapy can be utilized for
complete ablation of tumors up to 3 cm in size. The use of RFA for CRCLM is associated with a low rate of complications and when treating unresectable CRCLM, using a multimodality approach has been found as superior to a single modality treatment approach. Overall the findings from this study support the use of RFA therapy and this therapy is a safe and effective means of treating CRCLM < 3cm in size. Garrean et al.\textsuperscript{1} also gathered the data in the form of a data table and posted the available data from each study including local recurrence per tumor, new liver or extra hepatic metastases and overall survival, located in Table 2.

**Table 2. Studies evaluating RFA as a single therapy for CRCLM by Garrean et al.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Approach</th>
<th>Tumor size (cm)</th>
<th>Follow up (mo)</th>
<th>Local recurrence per tumor</th>
<th>New metastases</th>
<th>Overall survival</th>
<th>Complications</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curley et al.</td>
<td>1999</td>
<td>123</td>
<td>Perc: 31 Ope n: 92</td>
<td>Median: 3.4 0.5-1.2</td>
<td>15</td>
<td>1.80 %</td>
<td>27.6%</td>
<td>1 y: N/A</td>
<td>2.4% minor</td>
<td>2</td>
</tr>
<tr>
<td>De Baere et al.</td>
<td>2000</td>
<td>68</td>
<td>Perc: 47 Ope n: 21</td>
<td>1.0-402</td>
<td>13.7</td>
<td>9%</td>
<td>14.8%</td>
<td>1 y: N/A</td>
<td>5.8% minor</td>
<td>4.4% major</td>
</tr>
<tr>
<td>Guilliams et al.</td>
<td>2001</td>
<td>69</td>
<td>Perc: All</td>
<td>1.0-8.0</td>
<td>27</td>
<td>N/A</td>
<td>50%</td>
<td>1y: 90% 2y: 60% 3y: 34% 4y: 22% Median 31</td>
<td>12% minor</td>
<td>3.2% major 1 death</td>
</tr>
<tr>
<td>Guilliams et al.</td>
<td>2005</td>
<td>73</td>
<td>Perc: All</td>
<td>Mean: 3.9 1.0-12</td>
<td>N/A</td>
<td>N/A</td>
<td>50%</td>
<td>1y: 91% 3y: 28% 5y: 25% Median : 36</td>
<td>6% minor</td>
<td>4% major</td>
</tr>
<tr>
<td>Solbiati et al.</td>
<td>2001</td>
<td>117</td>
<td>Perc: All</td>
<td>Median: 2.6 0.6-9.6</td>
<td>6-52</td>
<td>39%</td>
<td>57%</td>
<td>1y: 93% 2y: 69% 3y: 46%</td>
<td>1 minor 1 major</td>
<td>2</td>
</tr>
</tbody>
</table>
Although RFA is a widely accepted, widely available, safe and effective treatment for unresectable CRCLM, with the introduction of MWA therapy there was a transition of care for CRCLM in an effort to avoid the limitations presented with the use of RFA and because of the ease of use with MWA. In addition, there were multiple theoretical advantages MWA therapy encompassed that RFA therapy lacked. MWA therapy is the newest ablative modality available for treatment of liver tumors.

Ierardi et al. published a study to evaluate the success of treatment of MWA for unresectable metastatic liver malignancy. In addition to technical success, they also analyzed this treatment in terms of safety and efficacy. 25 patients with liver metastases were treated with MWA. A total of 31 liver metastases were treated, the most common etiology being CRCLM, which made up 21 of the 31 tumors. All metastases were >3 cm in diameter or were anatomically located in close proximity to hepatic vessels (>3 mm in diameter) because these characteristics of the tumors made them ineligible for RFA therapy. In this study, average disease free survival was 20.5 months. These results suggest that lesions > 3cm and located within close proximity to vessels can be treated with percutaneous MWA, allowing for a less invasive procedure than the current standard which is open RFA therapy for tumors with these classifications. The authors of this study did note that MWA therapy is less preferable for lesions > 3cm, within close proximity to large vessels or important structures, however, in this small series it remains a treatment option for patients with this form of complicated disease. An important point noted in this paper is that MWA therapy is able to offer the same endpoints as RFA.
therapy and potentially offers more advantages compared to RFA. Ierardi et al.\textsuperscript{13} highlights many advantages of MWA such as faster ablation times, an improved convection profile, higher temperatures and the ability to use multiple antennas for simultaneous treatment of multiple lesions. In addition, the limitations of RFA such as skin burns and the heat sink effect are less concerning when treating hepatic lesions with MWA.\textsuperscript{13} The investigators note that MWA therapy may have the ability to overcome the disadvantages of RFA and may potentially result in higher efficacy overall.\textsuperscript{13}

The use of MWA therapy has been thoroughly researched in Asia. One of the initial clinical trials performed in 2004 by Morita et al.\textsuperscript{14} treated 52 patients with unresectable CRCLM with MWA therapy. Twenty-five of these patients received hepatic resection with laparotomy MWA; otherwise the remainder of the patients received MWA administered percutaneously or via laparotomy. Five-year survival rates were compared between patients who received percutaneous MWA versus patients who received MWA with laparotomy versus patients who received hepatic resection and intraoperative microwave ablation. The five-year survival rates were 20\% in the percutaneous group, 24\% in the laparotomy group and 24\% in the hepatectomy group. There was no significant difference among these three groups. The conclusion of this study was that MWA is an effective ablative option for treatment of unresectable CRCLM.\textsuperscript{14}

MWA was first performed in the United States in 2003 using the 915-MHz system.\textsuperscript{15} Asia and Europe had utilized the 2.45-GHz system for decades before it became available in the United States. Lloyd et al.\textsuperscript{15} published preliminary results of the safety and efficacy of MWA for liver malignancies. A total of 36 international centers and 162 patients were
included in the study on MWA therapy administered with the 2.45 GHz system in this study. CRCLM made up 50.5% of the patients and were the most prevalent etiology of liver malignancy.

This study provided several advantages associated with the use of the 2.45 GHz system. There were a total of 299 tumors among these 162 patients. Follow up data was only provided for 68 patients. There was a limited follow up period in this population of 4 months. Twenty-four of these 68 patients were noted to have hepatic recurrence. Local recurrence was undetermined due to lack of detail about the location of the original ablation site. The average ablation time with the 2.45 GHz MWA system was 4 minutes per tumor. In addition to shorter ablation times, over 50% of tumors can be treated with one application of MWA and over 75% of tumors can be treated with two applications. Comparing MWA therapy to RFA therapy, RFA typically requires multiple treatment sessions because of limitations of the technology (i.e. heat sink effect). The data from the study by Lloyd et al. support the use of operative MWA with the 2.45 system. The findings of this data concluded that the use of this system resulted in short ablation times, low morbidity, low mortality and high rates of complete ablation.

A recent publication by Correa-Gallego et al. in 2014 is the only study comparing intraoperative MWA to RFA specifically for colorectal hepatic metastases. This study compared the difference in ablation site recurrence between the two modalities in a retrospective cohort analysis. 134 patients were included in the study and comprised a total of 254 tumors that were matched to create two similar groups. Ablation site recurrence was seen in 19% of patients. MWA local recurrence rate was 6%, whereas the
local recurrence rate for RFA was 20%, a statistically significant difference. This is a very important finding for effectiveness of these two therapies in terms of local tumor control. There was no significant difference in postoperative complications. This study noted that MWA has become a more utilized technique due to its ease of use and its several theoretical advantages. The results of this study were comparable to a phase II multi-institutional study with unresectable liver tumors who were treated with MWA and reported a local recurrence rate of 3%.\textsuperscript{17} This phase II trial was the first US clinical trial to analyze the use of MWA. Overall, the data from the Correa-Gallego et al.\textsuperscript{16} study suggests that MWA is a favorable alternative to RFA for treating CRCLM.

In 2011, Jones et al.\textsuperscript{18} conducted a literature search on the data from 2000-2009 on the use of MWA therapy for CRCLM. They found 15 papers, which met their inclusion criteria. They concluded that the initial use of animal studies assisted to determine the guidelines of ablative boundaries, such as time and power, and which settings were appropriate for ablation of liver lesions. One of the studies included in the review, by Shibata et al.\textsuperscript{19} found no significant difference between the survival of patients after treatment with MWA for CRCLM to patients who underwent hepatectomy for CRCLM. Jones et al.\textsuperscript{18} also concluded the many advantages MWA has over RFA including the low rates of complications and perioperative deaths. MWA is a feasible, realistic and effective treatment for liver tumors including patients with bilobar disease, multiple metastatic tumors or who are not candidates for surgical resection and is supported by the published literature from 2000-2009.\textsuperscript{18}
The data in table 3 represent the most recent literature, from 2011 to 2015, investigating the use of MWA for CRCLM in clinical trials. This table cumulates the primary endpoints of each study in an effort to measure the efficacy of MWA therapy for CRCLM. In addition, the data in this table will be used to compare the data published on RFA by Garrean et al.¹ Understanding the different modalities for treating the same disease will allow for an understanding of the efficacy of these two therapies.
Table 3. Studies evaluating MWA for CRCLM.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># of total patients</th>
<th>Disease</th>
<th>Frequency</th>
<th>Approach</th>
<th>Additional Treatment</th>
<th>Tumor size</th>
<th>Overall survival</th>
<th>Disease free survival</th>
<th>Recurrence-free survival</th>
<th>Patients local recurrence</th>
<th>Median Follow Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eng</td>
<td>2015</td>
<td>33</td>
<td>CRCLM: 33 patients</td>
<td>N/A</td>
<td>Intraoperative US guidance</td>
<td>Chemo, resection, radiation</td>
<td>&lt; or = to 3cm (14.3% are &gt;3cm)</td>
<td>4 yr: 35.2%</td>
<td>3.5 yr: 19.3%</td>
<td>N/A</td>
<td>7.80%</td>
<td>531 days</td>
</tr>
<tr>
<td>Groeschl</td>
<td>2012</td>
<td>72</td>
<td>HCC (10), CRLM (39), Carcinoid (29), other 14 total(GIST, anal squamous cell cancer, breast, cholangiocarcinoma, clear cell carcinoma, melanoma, ovarian, renal cell, sarcoma)</td>
<td>N/A</td>
<td>Open, Perc. and laparoscopic</td>
<td>Chemo, resection</td>
<td>Median size: 2.0 cm</td>
<td>1 yr: 92% 3 yr: 36%</td>
<td>N/A</td>
<td>1 yr: 47%, 3yr: 0%</td>
<td>6%</td>
<td>16 months</td>
</tr>
<tr>
<td>Stattner</td>
<td>2013</td>
<td>43</td>
<td>CRCLM: 43 patients</td>
<td>2.65 GHz</td>
<td>Open</td>
<td>Resection vs none</td>
<td>median longest diameter 1.5cm</td>
<td>3 yr: 36% for MWA 3 yr:45% for resection; Combined results 1yr: 82%, 3 yr: 40%, 5yr: 12%</td>
<td>1yr: 31, 3 yr: 22, 5year 6%</td>
<td>N/A</td>
<td>9.30%</td>
<td>15 months</td>
</tr>
<tr>
<td>Lorentzen</td>
<td>2011</td>
<td>39</td>
<td>CRCLM:31 Breast:6 Carcinoid:1 GIST:1</td>
<td>915 MHz</td>
<td>Perc. or Open US guided</td>
<td>Chemo, resection</td>
<td>median size 1.5cm</td>
<td>N/A (follow up too short)</td>
<td>N/A</td>
<td>N/A</td>
<td>23%</td>
<td>11 months</td>
</tr>
<tr>
<td>Alexander</td>
<td>2015</td>
<td>64</td>
<td>HCC 25 patients, CRLM 27 patients, other 12 patients</td>
<td>915 or 2450 MHz</td>
<td>Perc. with CT or US guided or Open with US guided</td>
<td>Chemo</td>
<td>mean size: 2.7 cm</td>
<td>median cancer specific survival: 36.3 months (predicted)</td>
<td>N/A</td>
<td>N/A</td>
<td>predicted 3yr: 45.7%</td>
<td>N/A</td>
</tr>
<tr>
<td>Groeschl</td>
<td>2014</td>
<td>450</td>
<td>HCC 139 patients, CRLM 198 patients, neuroendocrine tumor 61 patients, other (breast 14 patients, cholangiocarcinoma 10 patients, melanoma 8 patients)</td>
<td>915 MHz</td>
<td>Open, Perc. and laparoscopic</td>
<td>Chemo, resection</td>
<td>median size: 2.0</td>
<td>3 yr: 45%, 5 yr: 17%</td>
<td>N/A</td>
<td>3 yr: 34% 5 yr:9%</td>
<td>5%</td>
<td>19 months</td>
</tr>
<tr>
<td>Leung</td>
<td>2014</td>
<td>476</td>
<td>CRLM 81% of tumors, HCC 8.4% tumors, Primary biliary cancer 1.7% tumors, non- CRLM 8.9% of tumors</td>
<td>915 or 2450 MHz</td>
<td>Open</td>
<td>Chemo, resection</td>
<td>mean 1cm</td>
<td>4 yr: 58.3%</td>
<td>N/A</td>
<td>N/A</td>
<td>7.10%</td>
<td>20.5 months</td>
</tr>
<tr>
<td>Wang</td>
<td>2013</td>
<td>815</td>
<td>Colon cancer: 62 patients. Rectal cancer 53 patients</td>
<td>2.45 GHz</td>
<td>Perc. US guided</td>
<td>N/A</td>
<td>mean: 3.10 cm</td>
<td>Cumulative results: 1 yr: 98.1% 2 yr: 87.1% 3 yr:78.7%</td>
<td>N/A</td>
<td>N/A</td>
<td>colon: 1 year: 30%, 2 year: 48.1%, 3 year: 61.1%. Rectal: 1 year: 36%, 2 Year: 49.7%, 3 year: 57.5%</td>
<td>28 months</td>
</tr>
</tbody>
</table>
Visualization of the tumor via cross-sectional imaging is a crucial factor in order to achieve a successful and accurate ablation of liver lesions. Lorentzen et al.\textsuperscript{20} reported their use of contrast-enhanced ultrasound (CEUS) guided MWA of liver metastases. The primary endpoint in this study was to evaluate the efficacy of MWA with the use of ultrasound guidance. Out of the 39 patients who were retrospectively identified, 31 of these patients were treated for CRCLM. The method of MWA was either percutaneous MWA or intraoperative MWA. After treatment, depending on the method of MWA, patients were discharged from the hospital and followed a fixed regime of imaging and measurement of serologic markers. A contrast enhanced CT was performed 5 weeks post-ablation. The results of this study demonstrated 9 of 39 patients with CRCLM had a local recurrence (23%). Due to the short follow up period in this study, overall survival could not be determined.

Overall, Lorentzen et al.\textsuperscript{20} concluded that their results with MWA had many advantages over the use of RFA. These advantages include the ease of antenna application into the liver tumors, no requirement for grounding pads, which eliminates the risk of skin burns and a short overall average ablation time of 10 minutes per ablation. Additionally, multiple tumors could be ablated in one session with the use of multiple antennas. Lorentzen et al.\textsuperscript{20} provided an example of the faster application of MWA by documenting their experience with one patient who was scheduled for an intraoperative procedure. Prior to ablation, the use of CEUS found six smaller new metastases in the liver and during this same procedure, these new lesions could be treated with simultaneous ablation of the tissue. If this patient were to be treated with RFA, the time of treatment
would have taken at least 2 hours whereas treatment with MWA took only 40 minutes, a significantly shorter time period.

The primary endpoint of this study was to measure the efficacy of MWA with CEUS. From the previous example of diagnosing additional liver metastases, this demonstrates a clear advantage to the use of concurrent imaging modalities. Lorentzen et al. found that the use of ultrasound assisted in guiding their management and treating liver metastases with MWA, either percutaneously or in the intraoperative setting. Post-ablation, CEUS also assisted in visualizing the ablated lesion and documenting the site and size of inflammation. In addition, the use of CEUS can be applied while a MWA session is being carried out which speaks to the efficacy of MWA. During a RFA procedure, US visualization is affected and not possible to conduct simultaneously.

Of note, this study did report local recurrence rates that were higher than other clinical trials examining local recurrence rates of CRCLM or metastatic liver tumors after treatment with MWA. Lorentzen et al. explained that possible explanation for this finding is secondary to their patient population. Two thirds of the patients included in the study were status post chemotherapy, which qualified them as candidates for ablation. They hypothesized that the chemotherapy-induced tumor reduction could have altered the characteristics of the liver parenchyma and affected its response to MWA therapy. In addition, their definition of local recurrence included new tumors evolving from the rim of the ablation zone; therefore they included a wider area of tumor recurrence, which was classified as local recurrence. Overall, Lorentzen et al. proved several advantages with the use of MWA compared to other ablation options; however they recommended
continued studies to examine clinical outcome of MWA with longer follow up time. Out of the most recent studies included in this literature review, this paper did have the shortest follow up period of only 11 months.

In 2013, Stattner et al.\textsuperscript{21} published early to midterm results of consecutive single institution results of patients diagnosed with CRCLM who received MWA with or without hepatectomy. This publication highlighted the lack of clarity in terms of the previous research on MWA for treating metastatic liver tumors, especially from a colorectal malignancy origin. The primary endpoint in this study was to evaluate use of MWA for CRCLM as a stand-alone treatment or combined with surgical resection for bilobar metastases. They organized their data from patients who received MWA alone versus the patients who received MWA combined with surgical resection. The patients were all considered unresectable candidates for resection alone. Intraoperative ultrasound was performed to better visualize the desired tumors. Forty-three patients were included in this study and 31 patients received neoadjuvant chemotherapy. Patients who were treated with MWA alone had significantly larger tumor diameter, more lesions to ablate and a significantly lower number of treated tumors compared to the group who received MWA with resection. Median overall survival in this study by Stattner et al.\textsuperscript{21} was 28 months and the median follow up period was 15 months. The combined overall survival rates and disease free survival rates are reported in Table 3.

Stattner et al.\textsuperscript{21} like Lorentzen et al.\textsuperscript{20} discussed the advantages of MWA therapy for treatment of liver tumors that RFA therapy lacks. MWA therapy utilizes an active heating mechanism allowing for oscillation of polarized water molecules whereas RFA utilizes a
passive heating mechanism relying on direct current transmission and charring. The mechanism of coagulation necrosis by RFA results in an unpredictable ablation zone and potentially failure of the ablation. MWA allows for a more predictable ablation pattern and a reduced likelihood of a heat sink effect as well. Stattner et al.\textsuperscript{21} reported that MWA therapy is safe when conducted in the intraoperative setting, based on their report of a low complication rate of 10%. This study also reported a lower local recurrence rate, attributed to a better selection of tumors for ablation that were more adequately treated. In addition, to a better selection of tumors, the low local recurrence rate found in this study, posted in Table 3, may be attributed to MWA therapy conducting a more predictable and accurate ablation when compared treatment with RFA. The findings from this study suggest that combination of resection with MWA offers adequate outcomes comparable to the results after two-stage hepatic resection with curative intent.\textsuperscript{21} Overall, the findings from this study suggest that MWA provides good long-term outcomes with or without combined hepatic resection for small unresectable CRCLM. Stattner et al.\textsuperscript{21} suggested that the option of MWA alone or combined MWA with resection may be more cost effective, offers complete disease clearance in one operative session and has reduced post-operative morbidity when compared to the current two-stage hepatectomy offered to patients who are not surgical resection candidates. In addition, MWA offers a parenchyma sparing option to preserve functional liver volume whereas treatment with hepatectomy does not offer this benefit.\textsuperscript{21} The United States phase II trial performed by Ianittie et al.\textsuperscript{17} prompted Groeschl et al.\textsuperscript{22} to investigate the factors predisposing patients to tumor recurrence after receiving treatment
with MWA. The phase II trial confirmed successful tumor ablation in >90% patients after MWA; however, nearly half of these patients had tumor recurrence at remote hepatic and extra-hepatic sites.\textsuperscript{17} Due to the recent increase in utilization of MWA, it’s imperative to explore the features that correlate with a higher chance of recurrence rates. Groeschl et al.\textsuperscript{22} published results from a single-center retrospective review. The investigators in this study hypothesized that primary tumor histology was a significant predictor of early recurrence. The cancer histologies examined in this review included: HCC, CRCLM, metastatic carcinoid and the “other” category, listed in more detail in Table 3. Seventy-two patients were included, 39 of whom were diagnosed with CRCLM. The CRCLM category experienced a recurrence free survival of 47% after one year and an overall survival after one year of 92%. The remainder of the data regarding the CRCLM results is located in Table 3.

The important aspects of this study were the examination of the efficacy of MWA on different tumor types and how different histologies may be responsible for earlier tumor recurrence. The study found that timing of recurrence was not significantly different among the various histologies of the tumors. There was an association with patients who were younger and treated with neoadjuvant chemotherapy who were more likely to develop tumor recurrence. Prolonged recurrence free survival was associated with patients who received adjuvant chemotherapy. The results of this study were imperative to better understand if tumor biology was significant associated with shorter local recurrence, which was not found.\textsuperscript{22} Thus, treating CRCLM with MWA shows adequate tumor control and is a safe and effective method of treating CRCLM. A recommendation
was made to better understand the risks and long-term benefit of open, laparoscopic and percutaneous MWA.

Eng et al.\textsuperscript{23} presented outcomes and recurrence patterns after intraoperative MWA for CRCLM. In addition, these investigators attempted to determine which features of CRCLM are associated with higher rates of systemic and local recurrence, similar to the study performed by Groeschl et al.\textsuperscript{22} Thirty-three patients were retrospectively analyzed in this study and treated with intraoperative MWA. Almost all of these patients received neoadjuvant or adjuvant chemotherapy for their malignancy. Eighty-six percent of the tumors were less than or equal to 3 cm in size. The maximum size of tumors in this study treated with MWA was 5.5 cm. Only one of the patients in this study presented with a local recurrence in the liver. Approximately 23% of patients presented with distant disease alone. Overall survival in this cohort was 35.2% at 4 years.\textsuperscript{23} These investigators found the use of intraoperative MWA to be a safe and effective treatment technique for CRCLM.\textsuperscript{23} Only 1 in 7 tumors larger than 3 cm treated with MWA recurred indicating that MWA is effective for tumors up to 5.5 cm in size. This is the first study in the recent literature to demonstrate that survival after intraoperative MWA is not associated with the size of the tumor being ablated.\textsuperscript{23} In addition, the patients selected for this study compiled the highest percentage of patients with concomitant liver resection and the highest percentage of patients who received neoadjuvant chemotherapy. The results from this study are crucial to validate that MWA is a safe and effective treatment especially for patients who have received neoadjuvant chemotherapy prior to ablation or have undergone concomitant hepatectomy. A limitation
to this study was its inability to report long-term outcomes for these patients. Overall, the majority of the tumor recurrence experienced in this patient cohort was distant metastases indicating that intraoperative MWA therapy offers a reasonable approach for managing CRCLM in the liver.²³

Wang et al.²⁴ studied the clinical outcomes after percutaneous MWA for CRCLM. This study was conducted in order to generate more research on the use of MWA due to the lack of available studies examining MWA for treating liver metastases from a colorectal origin. Although MWA has many theoretical advantages over other ablative options, including RFA, the authors wanted to confirm the safety and efficacy of this technology for specifically CRCLM. One hundred and fifteen patients were enrolled in this study and treated with ultrasound-guided percutaneous MWA for CRCLM. The patients were separated based on the primary origin of disease: colon cancer versus rectal cancer. The cumulative recurrence rates and data from this study are located in Table 3. There were no significant differences in the recurrence data of colon versus rectal cancer patients. Currently, RFA therapy is the mainstay of treatment for unresectable CRCLM. Wang et al.²⁴ compared the recurrence rates of RFA published in the literature and noted a range of intrahepatic recurrence rates after treatment with RFA between 32-62.5%. In terms of survival, published data on RFA for CRCLM have reported a range of three-year survival between 37-77% and a five-year survival range of 27-36%. The study by Wang et al.²⁴ published a three-year survival rate of 78.7% for colon cancer and 78.6% for rectal cancer patients after treatment with MWA; cumulative recurrence rates in this population were reported as a one year 27.8%, two year 48.4% and three-year recurrence rate of
59.3% post ablation. It appears from these findings that MWA for CRCLM is at least equivalent to the data published on RFA in terms of survival after treatment with ablation. However, this data is somewhat limited as it only reports patient’s results from one center, had a short follow up period and did not directly compare MWA to RFA data in the same trial. Overall, the investigators suggest that percutaneous MWA is a safe and efficient way to treat unresectable CRCLM and recommend elucidation by a multicenter randomized controlled study to better evaluate the comparative data.\(^{24}\)

To evaluate the long-term outcomes of MWA, Leung et al.\(^{25}\) performed a retrospective review of patients who received MWA therapy with or without liver resection. This study not only evaluated the long-term data, but also compared the 915-MHz to the 2.4-GHz ablation system. The 915-MHz system has been utilized more commonly in the U.S. until 2006 when the FDA approved the use of the 2.4-GHz system, which is more popular for treatment in Asia. The difference between the two techniques is the altered wavelengths generated by each system, which may affect the depth of penetration of the energy instilled by the antennae. Local recurrence and long-term survival were the primary endpoints of this study and means of comparison between the 2 systems. An open approach was utilized for both systems and ablation was commonly combined with resection for the patients included in the study. A total of 176 patients were included in the study and collectively accounted for 416 tumors. CRCLM comprised 81% of the tumors treated in this study and the majority of these patients had previously received chemotherapy for this disease. Local recurrence rate for the patients with CRCLM was 7.1% and 4-year overall survival was 58.3%. Out of all tumor histologies, recurrence
rates were higher with the larger the tumor size and by tumor type, which differs from the results of the Groeschl et al. study. The highest rate of tumor recurrence was found in patients diagnosed with biliary carcinoma and lowest for patients treated for CRCLM and HCC.

Comparison of these two ablation systems found that tumors treated with the 2.45 GHz ablation system were larger, included a higher proportion of non-CRCLM tumors and were less likely to have been treated with chemotherapy. Local recurrence rate for tumors treated with the 2.45 GHz system was 12.6% and the local recurrence rate for tumors treated with the 915 MHz MWA was 4%, a statistically significant difference. There was no difference in overall survival between the two ablation systems. Tumor size is a significant factor associated with a higher rate of local recurrence according to Leung et al.; patients treated with MWA for tumors that were less than or equal to 3 cm in size rarely experienced a local recurrence. The results from Leung et al. suggest that MWA may achieve survival rates similar to patients treated for completely resectable disease with surgical resection. In terms of the comparison between the two MWA ablation systems, it appears from the data in this study that although the local recurrence rates were higher after treatment with the 2.45 GHz system, this data may have been confounded by differences between the two groups (i.e. tumor size). There was an inverse relationship between number of tumors treated with ablation and local recurrence. After treatment with RFA, the higher the number of tumors the more likely the tumors will recur, however the data from this study suggest the opposite is true after treatment with MWA. Leung et al. suggests that possibly this inverse relationship is attributed to
patients with a larger number of tumors were more likely to be candidates for MWA due to other favorable features of their disease. This study presented good quality data and analysis of a large series of MWA treatment procedures for liver malignancy. A key aspect from this study is the efficacy of MWA in terms in tumor control for CRLM tumors less than 3 cm in size.\textsuperscript{25}

To better understand the efficacy of MWA therapy and factors that affect recurrence-free survival, Groeschl et al.\textsuperscript{26} published a multiinstitutional analysis on the use of MWA for hepatic malignancies in 2014. The hypothesis in this study was that tumor size, number of tumors, surgical approach and tumor histology would have an effect on the efficacy of MWA therapy and recurrence free survival. The American Society of Clinical Oncology published a review on the use of RFA for CRCLM and determined that recurrence rates and survival after RFA were directly related to size, number and location of the tumors, surgical approach of the ablation and physical experience.\textsuperscript{27} This review stated that patients with CRCLM treated with RFA with tumors less than 3 cm in size, experienced the greatest success rates. Despite these findings in the use of RFA for CRCLM, there is no robust data on which factors may influence the efficacy of MWA for treating CRCLM. Groeschl et al.\textsuperscript{26} attempted to bridge this gap with the data from their multiinstitutional analysis. This analysis pooled data from 4 hepatobiliary centers familiar with treating patients with MWA.

All patients with hepatic metastases were participants in this study.\textsuperscript{26} One hundred ninety eight of these patients were treated for CRCLM. All three surgical techniques were included in the study: open, percutaneous and laparoscopic. Perioperative morbidity was
higher in open and laparoscopic groups when concomitant hepatectomy was performed with MWA. Regardless of the histology of the metastatic liver tumors, the most common site for recurrence of malignancy was a nonlocal intrahepatic location. Local recurrences occurred in 6% of total malignancies treated with MWA and the local recurrence rate for treatment of CRCLM was 5.2%. Treatment of liver tumors with the percutaneous MWA approach resulted in shorter times to local recurrence. Groeschl et al. explained that the finding of a higher rate of local recurrence with the percutaneous approach may be attributed to a selection bias. Patients selected for percutaneous MWA therapy may have more comorbid conditions reducing their opportunity for MWA ablation in the laparoscopic or laparotomy settings. Unlike the RFA published data, the surgical approach with MWA did not affect recurrence free survival or overall survival. More than 20% of patients with CRCLM had extra-hepatic recurrences. Recurrence free survival (RFS) in all malignant metastases in this study was most negatively affected by tumors larger than 3 cm in size. Although there is no specific data showing that CRCLM greater than 3 cm in size were negatively influencing the rate of RFS, all liver malignancies had a significant similarity in terms of median tumor size suggesting that this data applies to all liver malignancies treated in this study. Conclusively, this multiinstitutional analysis showed tumor size only had an effect on recurrence free survival and there were no differences in RFS or overall survival in the selected surgical approach. However, local recurrence rate was the highest for tumors that were percutaneously ablated. Overall, the use of MWA appears to be a safe and efficient treatment option for treating metastatic liver tumors, including those
originating from a colorectal primary neoplasm. The overall survival and local recurrence rate published in this study are similar to recently published data on CRCLM treated by MWA indicating that this is an effective modality for treating CRCLM.

Alexander et al. published a recent retrospective study to evaluate the safety and efficacy of MWA for hepatic malignancies with a long term follow up interval. The patient cohort included in this study consisted of patients treated with MWA for a single liver malignancy at a single institution and followed up over a 9-year period. Sixty-four patients were included in this study, 27 who were treated for liver metastases secondary to colorectal cancer. The majority of the MWA treatment sessions were performed by the percutaneous approach and the remainder of treatment sessions were performed intraoperatively. In this study, tumor size was not a significant predictor of time to tumor recurrence. This study also failed to show an association with tumor histology, adjuvant chemotherapy or cirrhosis to an earlier time to recurrence. Patients in this study with colorectal cancer had significantly longer survival times compared to other histological metastases to the liver. The median cancer specific survival for CRCLM patients was close to 3 years, 36.3 months. This data revealed that MWA is a safe, effective and minimally invasive treatment options for patients with a single, focal hepatic malignancy. Tumor size in this study did not impact local recurrence rates. In this data, there was no significant difference in cancer-specific survival among tumor histologies indicating that MWA is effective for treating both primary and metastatic liver neoplasms. The results of this study failed to demonstrate a relationship between tumor size and local recurrence which
differs from a plethora of previous data, such as the study published by Groeschl et al.,\textsuperscript{26} who published data stating that tumors greater than 3 cm in size are associated with a higher rate of local recurrence. In addition, study by Alexander et al.\textsuperscript{28} demonstrated that when a tumor was treated in the intraoperative setting, there was a lower rate of recurrence than when tumors were treated percutaneously. This result on the efficacy of percutaneous ablation was also shown in the Groeschl et al.\textsuperscript{26} article. Alexander et al.\textsuperscript{28} agreed with the reasoning provided in the Groeschl et al.\textsuperscript{26} study in that patients selected for treatment with percutaneous ablation typically have more comorbidities than those who are classified as suitable for an intraoperative ablation. Additionally, intraoperative ablation may provide the surgeon with the ability to better visualize the tumor with intraoperative surface ultrasound and may contribute to more successful ablations. This study concluded that MWA offers a minimally invasive technique for treatment of primary and metastatic liver tumors, including CRCLM, and may be effective for lesions of different sizes and different anatomical locations.\textsuperscript{28}

The evidence for treating unresectable CRCLM with MWA therapy is supported by the current literature. The transition in treatment of unresectable liver metastases from RFA to MWA was initially supported by the theoretical advantages of MWA. The hypothetical advantages that MWA has over RFA include: less of a heat sink effect, faster ablation times, larger ablation zones and simultaneous treatment of multiple tumors. The most recent literature on MWA has evidenced the safety and efficacy of this treatment for CRCLM. Based on the data of MWA and RFA, MWA is at least equivalent in managing local tumor control and overall survival. Due to the efficacy and safety of MWA therapy,
it’s imperative to educate health care professionals on this new accomplishment in order to offer this therapy to more patients with CRCLM.
METHODS

Study design

A lecture-based curriculum will be developed in order to educate PCPs on the utilization of MWA therapy to treat CRCLM. This curriculum will be presented at national CME conferences.

Study population and sampling

This curriculum will be presented at medical conferences and offered to PCPs for CME credits. All medical health care providers working in primary care or interested in learning more about the use of MWA therapy will be invited to attend this hour-long lecture on the background and basic application of MWA for CRCLM. This lecture can be presented at multiple conferences in an effort to spread the knowledge about this new technology in treating liver metastases. The lecture will be offered through the following organizations at national conferences in order to include all heath care professionals working in a variety of locations: American Academy of Physician Assistants (AAPA), American Academy of Family Physicians (AAFP) and American Association of Nurse Practitioners (AANP).

Based on the results of the pre and post-test and assuming an approximate 15% increase in scores after the lecture is predicted. In order to generate a 15% increase in scores to a passing score of 80% on the exam, a sample size of at least 28 persons is required. Thus, if we offer this lecture to at least three conferences (one per practitioner specialty) and have at least 10 attendees, this will meet the sample size criteria.
Recruitment

The providers who will be included in this study will be all attendees of the hour-long lecture offered at CME conferences who attend national medical conferences intended for health care providers in a primary care setting. The course will be advertised on CME websites and in emails to the providers registered for the respective conferences. Offering this lecture to multiple conferences in multiple locations will attempt to recruit a diverse population of PCPs in order to generalize the results and educate providers working in a wide variety of locations.

In exchange for attending the lecture, all providers will gain one hour worth of CME credits. The exchange of CME credits will provide an incentive for PCPs to attend the lecture, in addition to the high incidence of CRCLM, which also will provide incentive for these practitioners. Having the ability to learn more about a disease with a high incidence in our population will allow these providers to have a better patient-provider relationship and provide their patients with their knowledge on the multitude of treatment options for their new diagnosis, including MWA therapy.

Curriculum

The curriculum format will be a PowerPoint presentation discussing the epidemiology of the disease, background on alternative treatments to surgical resection, technology of thermoablative modalities and detail on MWA therapy itself. Learning objectives will be presented prior to the lecture; these learning objectives are listed in Table 4. The learning objectives will serve as an outline for the talk and will provide the attendees with the core aspects of the lecture we hope they will take away and learn from the curriculum.
Table 4. Learning Objectives of the curriculum

<table>
<thead>
<tr>
<th>Objective</th>
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<tbody>
<tr>
<td>1. Understand the spectrum of treatment options for patients diagnosed with CRCLM</td>
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<tr>
<td>2. Apply the indications for patients to receive treatment with MWA therapy for liver metastases.</td>
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<tr>
<td>3. Understand the logistics of MWA therapy and how it achieves tumor cell death.</td>
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<tr>
<td>4. Evaluate the risks versus benefits of thermoablative therapies, such as MWA therapy.</td>
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<tr>
<td>5. Create a provider-patient dialogue to educate patients about MWA therapy for CRCLM.</td>
</tr>
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</table>

Curriculum Assessment

In addition to the learning objectives, a pre and post-test will be administered to all attendees. The pre and post-tests will be used to assess the health care provider’s baseline understanding of MWA therapy and compare it to knowledge gained from the lecture. The pre and post-tests will be administered using the Turning Point clicker system and will be available to all PCPs attending the presentation. The content of the tests will include questions on the background of thermo ablation techniques, logistics of MWA, theoretical advantages MWA therapy has over RFA, the clinical importance of MWA, recent data published on MWA and follow up for patients and what to expect after the procedure.

In addition, a survey will be administered prior to the lecture to assess the demographics of the providers who will be included in this study. This survey will ask general questions about each provider’s age, gender, specialty and where they practice medicine. Lastly, all providers will receive an educational handout scripted for patient education.
Study variables and measures

The pre and post-tests will be the same exam consisting of 15 questions total. The questions of the exam will cover the learning objectives in addition to the following topics:

- Alternatives treatment to surgical resection for CRCLM
- Logistics of MWA therapy
- MWA therapy vs RFA therapy
- Complications of MWA therapy
- What to expect as a patient receiving MWA therapy

Data collection

The post-test will be administered directly after the lecture to retrieve results from every attendee of the presentation. If the post-test were to be mailed out to the providers who attended the lecture, it is unlikely that all providers would return the post-test and it would affect the data collection. Immediately after the lecture, the pre and post-test data from all lectures will be pooled together. The data will be collected from the Turning Point software and have separate attendee responses in order to collect each attendee’s answers from before and after the lecture. The tests will be graded with a passing score of greater than or equal to 80%.

Data Analysis

Once all of the lectures have been administered and the data has been collected, the paired t-test will be applied to the results of the pre and post-tests. The mean of the pre test and mean of the second test will be compared. In addition, we will perform an item
analysis to better categorize which aspects of the lecture the participants best
demonstrated an understanding. This will allow for an immediate understanding if the
presentation is a legitimate way to educate PCPs on the use of this therapy and the most
recent data explaining the efficacy and safety of this therapy as well.

**Timeline and resources**

In order to offer this lecture at a wide variety of conferences, first the lecture and
presenter of the talk needs to receive accreditation through the ACCME organization in
order to be presented at a CME supported conference. The accreditation process for first
time applicants can take anywhere from 12-18 months. The accrediting process will
ensure that the lecture is a high standard, effective method for providing education to
health care providers.

There are several conferences offered across the country throughout the year. Therefore,
as soon as the accreditation process is complete, we will select national conferences
offered either to all health care providers, or select national conferences for each health
care provider (AAFP, AAPA, AANP). Offering this lecture not only at several
conferences but also to a wide variety of PCPs will increase the data for our statistical
analysis and increase the amount of practitioners who will gain a better and more
thorough understanding of this technology for an alternative treatment of CRCLM.

**Institutional Review Board**

The study protocol will be submitted for IRB exemption for educational studies to the Boston
University Medical Campus IRB under 45 CFR 46.101 (b) criteria.
CONCLUSION

Discussion

Based on the most recent literature examining the efficacy and safety of MWA therapy for treatment of CRCLM, this technology is an effective tool, which can be added to the ablation armamentarium. Developing a curriculum directed at PCPs will allow for a better understanding of treating stage four colorectal cancer and hopefully increased referrals and better treatment of this disease.

The curriculum will be generalizable to all health care professionals working in a primary care setting or who are interested in learning more about MWA therapy for CRCLM. The same lecture will be administered to all providers (MD, PA, NP) assuming that all practitioners have the same core knowledge base. Some potential limitations of this curriculum may include if there are less than 28 providers who attend the CME conferences. In addition, the curriculum will only prove effective and educational if the providers have a desire to learn about this new technology. It will be imperative for the curriculum to address the epidemiology of CRCLM and how the use of alternative therapies for treating this disease is relevant to their practice.

An advantage to the design of a CME curriculum is that it provides an incentive for health care professionals to attend. Health care professionals are required to gain CME credits in order to maintain their accreditation and offering this lecture at these conferences will allow for the best attendance. In addition, presenting this lecture via the CME conferences will allow for a diverse population of practitioners to attend. This will allow for the material to be addressed to a more widespread group of health care
practitioners across the country. Overall, it appears that offering this lecture at a CME conference will allow for the best ability to spread the knowledge about this treatment option in an effort to provide treatment for more patients with unresectable CRCLM.

Summary

Colorectal cancer is one of the most prevalent malignancies in the United States. Most commonly, this disease metastasizes to the liver and unfortunately the majority of these patients are not surgical candidates for resection. Herein lies the requirement for an alternate therapy for these patients such as ablation modalities.

Based on the most current literature, the use of MWA therapy in treating CRCLM is a safe and effective treatment option for these tumors. Although RFA is currently the most commonly utilized ablation therapy, MWA appears to be at least equivalent in efficacy and safety to RFA therapy. Thus, the literature shows that MWA therapy is a legitimate option to consider when a patient presents with unresectable CRCLM.

Since this therapy is still in the beginning stages, there is no widespread educational forum about this technology available for practitioners. Thus, considering the most recent literature, presenting the literature and research on MWA therapy and its utilization to practitioners is a valuable and important considering the high incidence of unresectable CRCLM.

Clinical and/or public health significance

Given the high incidence of CRCLM in patients who are not candidates for surgical resection, there is a need for alternative treatments to surgical resection. MWA therapy has shown in the most recent literature to be a safe and effective alternative treatment.
option for these patients. Educating providers on this recent technology to treat this
unfortunately common disease will allow for better management of unresectable
colorectal liver disease and enhanced patient provider relationships and patient education
about MWA therapy.
# LIST OF JOURNAL ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tr>
<td>AJR Am J Roentgenol</td>
<td>AJR. American journal of roentgenology</td>
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<tr>
<td>Br J Surg</td>
<td>The British Journal of Surgery</td>
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<tr>
<td>Cancer J</td>
<td>Cancer Journal (Sudbury, Mass.)</td>
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<tr>
<td>Colorectal Dis</td>
<td>Colorectal Disease: The Official Journal of the Association of Coloproctology of Great Britain and Ireland</td>
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<tr>
<td>Eur J Radiol</td>
<td>European Journal of Radiology</td>
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<tr>
<td>Eur J Surg Oncol</td>
<td>European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology</td>
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<tr>
<td>Gan To Kagaku Ryoho</td>
<td>Gan to Kagaku Ryoho. Cancer &amp; Chemotherapy</td>
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<td>Gut</td>
<td>Gut</td>
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<td>Hepatobiliary Surg Nutr</td>
<td>Hepatobiliary Surgery and Nutrition</td>
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<tr>
<td>HPB (Oxford)</td>
<td>HPB: The Official Journal of the International Hepato Pancreato Biliary Association</td>
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<tr>
<td>J Surg Oncol</td>
<td>Journal of Surgical Oncology</td>
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<td>Oncol Lett</td>
<td>Oncology Letters</td>
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<td>Radiology</td>
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<td>Radiol Med</td>
<td>La Radiologia Medica</td>
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<tr>
<td>Surgeon</td>
<td>The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland</td>
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<td>Ultraschall Med</td>
<td>Ultraschall in Der Medizin</td>
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REFERENCES


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Bachelor of Science, Neuroscience
• Dean’s List
• Public Health Minor
• SIT Study Abroad: Global Health and Development Policy Program
• 4 year member of Muhlenberg Volleyball team
  • 3 year captain

Experience
Medical Assistant
Obtained histories from patients in Internal Medicine and Urgent Care settings. Performed vital signs, EKGs and pulmonary function tests. Interpreted laboratory results.

Certifications and Licensure
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National Commission on Certification of Physician Assistants, pending
Health Care Provider, Advanced Cardiac Life Support, American Heart Association, 2015
Health Care Provider, Basic Life Support, American Heart Association, 2014

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Student Member, The Massachusetts Association of PAs