Microwave ablation with or without resection for colorectal liver metastases

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Accepted 25 April 2013
Available online 14 June 2013

Abstract

Background: Ablation with or without resection for colorectal liver metastases has been suggested as a potential method of improving survival if complete surgical resection is not possible. This study assessed the safety and efficacy of surgical microwave ablation (MWA) with or without resection for colorectal liver metastases.

Methods: A retrospective case series was reviewed. Data was extracted for all patients treated with open MWA with or without resection for colorectal liver metastases. Endpoints included postoperative 30-day morbidity and mortality, local treatment failure, disease free survival and overall survival.

Results: A total of 43 patients with technically irresectable disease were treated with MWA; 28 underwent combined MWA and resection, whilst 15 underwent MWA as the sole treatment modality. Overall post-operative morbidity was 35%, 30-day postoperative mortality 2%. At a median follow-up of 15 months, local treatment failure was observed in 4% of ablated lesions. 3-year OS was 36% for MWA group, compared to 45% for the combined ablate/resect group with 3-year DFS of 32% and 8% respectively.

Conclusion: Microwave ablation with or without resection is a safe and effective method of achieving local disease control. Ablation with or without resection is associated with good long-term outcomes, and may be a suitable treatment option for small non-resectable colorectal liver metastases.

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Keywords: Liver; Colorectal; Ablation; Microwave

Introduction

Colorectal cancer is the third leading cause of death from cancer in Europe with a lifetime risk of 2%.1,2 Over half of colorectal cancer patients will develop metastases, with one quarter presenting with stage IV disease.1 Surgical resection remains the only potentially curative option for these patients with reported 5-year survival after resection around 40%.1,2 However, surgery can be performed in only a minority of cases. Patients with synchronous disease, rectal primary, multiple diffuse metastases, metastases larger than 5 cm, disease-free interval of less than 1 year from the diagnosis of primary disease or a high serum CEA were previously considered unresectable and suitable only for palliative treatment.1,2 Modern surgical techniques and chemotherapeutic regimens mean none of these contra-indications now hold true and in 2013 resectability is defined as the ability to successfully remove all residual disease from the liver with clear surgical margins, whilst leaving adequate disease-free liver. Despite this change in approach, surgical resection with curative intent is only an option in around 20% of patients.1

In order to increase treatment options for patients with unresectable disease there is growing interest in ablative technologies for localised tumour destruction. However, there remains a lack of clarity surrounding the role of
Ablation in the treatment algorithm for metastatic colorectal cancer. Both the American Society of Clinical Oncology (ASCO) and UK National Institute for Health and Clinical Excellence (NICE) suggest that in the continued absence of high quality data, resection and not ablation should remain the gold standard treatment for resectable disease. However they support the use of ablation in cases where resection is not possible. For example, patients with small volume resectable metastases who are not sufficiently fit to undergo liver resection should be considered for ablation as should those with limited liver metastases who have insufficient liver volume to support resection. Ablation combined with resection has also been suggested as an option for patients in whom complete surgical resection is not possible. In patients with bilobar disease, dominant lesions can be resected whilst contralateral lesions that cannot be resected are ablated.

One reason for this lack of clarity is that published outcomes following ablation have been difficult to interpret, with many studies reporting recurrence on a per lesion basis and outcomes for heterogeneous patient populations with mixed tumour types. No large series of surgical open microwave ablations for colorectal liver metastases (CLM), either as sole treatment or adjunct to resection, have been published. We present early to midterm results of a consecutive single centre series of patients treated with microwave ablation (MWA) with or without resection for the treatment of colorectal liver metastases.

Methods

All patients treated with MWA between May 2005 and December 2012 were retrospectively analysed from a prospectively maintained database validated by case note review. Patients treated with percutaneous MWA were not included. Two groups were identified; MWA as the sole treatment modality and resection combined with MWA. All patients had pathological confirmation of colorectal liver metastasis. Prior to surgery, all patients were discussed at a supraregional multidisciplinary tumour board (sMDT) and considered technically unresectable at a single procedure. Standard preoperative assessment consisted of multidetector computed tomography (MDCT) of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) with hepatocyte specific contrast and positron emission tomography-CT (PET-CT). The ability to completely treat all identifiable tumours using a combination of resection and/or ablation defined the decision to proceed to surgery.

Operative technique

All patients underwent open surgical MWA or RMWA by an experienced hepatobiliary surgeon. Laparotomy was performed and extrahepatic abdominal disease excluded by careful intraoperative inspection. Intraoperative ultrasound (IOUS) was routinely performed to guide surgical planning. Low circulating volume anaesthesia was used, aiming for a central venous pressure (CVP) of below 5 mmHg. Liver parenchyma was transected with the Cavitron ultrasonic surgical aspirator (CUSA, Valleylab, Boulder, CO) or Kellyclasia, depending on operator preference. Use of intermittent vascular inflow occlusion was at the discretion of the operating surgeon, and was not used in patients who only underwent MWA. The 2.65 GHz Acculis MTA system (Microsulis Medical Ltd, UK) with a shaft-cooled Accu2i pMTA antenna was used for all ablations after 2008, before which antennas without cooled tip were used. IOUS was used to guide antenna placement in all cases. Standard energy delivery was 100 Watts for 90 s per lesion. Successful ablation was confirmed by IOUS 5 min after antenna removal. In all cases treatment was considered complete when a margin of 10 mm of healthy surrounding parenchyma had also been ablated in continuity with the tumour (except those close to major vessels where an ablation margin was not possible). In cases where it was not apparent on IOUS that complete tumour destruction had occurred, treatment was immediately repeated.

Recurrence, follow up and complications

Patients were assessed within 3 months of ablation by triple-phase MDCT and carcino-embryonic antigen (CEA) levels. This was repeated every three months during the first year and six monthly thereafter. Disease recurrences were divided into 4 groups based on imaging and sMDT consensus:

1. Local recurrence at the ablation site (within 10 mm of the ablation site).
2. Liver recurrence only at non-treated sites (with or without local recurrence at the ablation site).
3. General recurrence including liver and at least one other organ (with or without local recurrence).
4. Extrahepatic recurrence only.

Local recurrence was defined radiologically by increased contrast uptake within a solid lesion at or adjacent to a previous ablation site. If CT was suspicious for recurrence, positron emission tomography (PET-CT) and/or contrast magnetic resonance imaging (MRI) was used for confirmation. Post-operative complications were classified according to the Clavien Dindo five-point grading scale.

Statistical analysis

Data were expressed as median values and range. Statistical analysis was performed using SigmaStat v12 (Systat Software Inc, US) and Graph Pad Prism v5 (GraphPad Software Inc, US). Overall and disease-free survival were analysed using the Kaplan–Meier estimates, and the comparisons were performed using the log rank test.
dichotomous outcome the Mann–Whitney U or Fisher exact tests were used in univariate analysis. \( P < 0.05 \) was considered statistically significant.

**Results**

**Demographic and operative data**

Forty-three patients (11 females and 32 males) were analysed. Twenty-eight had combined liver resection and ablation, whilst 15 underwent ablation alone. The median length of hospital stay (LOS) for all patients was 7 days (range 4–80). Patient characteristics are shown in Table 1. Twenty-seven patients had synchronous disease at the time of initial diagnosis, with 3 having synchronous lung metastases. Data on the site of extrahepatic disease were not available for 2 patients.

Ablations were performed for 95 lesions with a median longest diameter of 15 mm (range 8–43). A median of 1 MWA (range 1–12) was performed per patient. Patients treated with MWA alone had significantly larger tumour diameter, significantly more lesions and a significantly lower number of treated tumours compared to the resection/MWA group. In the resection/MWA group, 3 patients had major hepatectomy (defined as more than 3 continuous Couinaud segments), 22 had minor non-anatomical resections and 3 had a combined major and minor resection. Thirty-one patients received preoperative systemic chemotherapy.

**Morbidity**

Fifteen complications occurred in 12 patients giving an overall morbidity of 35% (27% for MWA alone, 39% for RMWA). Re-intervention (grade 3 and 4 complications) was required in 4 cases, with one death on postoperative day 23 (30-day post-operative mortality 2%). This patient was excluded from disease recurrence analysis.

**Survival and patterns of recurrence**

Median overall survival was 28 months with a median follow up of 15 months (range 3–84). Twenty patients died during follow up. Combined 1-, 3- and 5-year overall survival rates were 82, 40 and 12% (Fig. 1) with estimated disease free survival (DFS) of 31, 22 and 6% (Fig. 2) respectively. Median DFS was 8 months. Estimated 1-, 3- and 5-year overall survival for the combined resection/MWA group was 82, 45 and 18%, compared to 1- and 3-year survival of 90 and 36% for the MWA only group (Log-Rank \( P = 0.969 \)). One and 3-year DFS for the ablated and resected group was 50 and 32% compared to 24 and 8% for the ablation only group (Log-Rank \( P = 0.465 \)).

At time of last follow up 31 patients had tumour recurrence. Five patients had diffuse hepatic only recurrence, all of whom were in the resection/MWA group, 17 had hepatic and extrahepatic recurrence, whilst 5 had extrahepatic recurrence only (one patient in the MWA and 4 in the resection/MWA group). Local recurrence at the ablation site was seen in 4 lesions in 4 separate patients within 7 months of ablation and was considered local treatment failure. All of these recurrences were located in segment 8 next to the middle or right hepatic veins.

On univariate analysis age \( (p = 0.043) \), length of hospital stay \( (p = 0.035) \) and size of largest ablated tumour \( (p = 0.035) \) were predictive for overall survival. Number of lesions ablated, type of procedure, total number of lesions, preoperative chemotherapy and synchronous disease had no significant impact on overall survival. Using a Cox regression model for multivariate analysis, no significant factors influencing overall survival were identified.

**Treatment of recurrence**

The majority of patients whose disease recurred, and were deemed fit, were treated with palliative chemotherapy. Three patients with local lesonal recurrence were eligible.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>All ((n = 43))</th>
<th>MWA group A ((n = 15))</th>
<th>MWA + hepatectomy group B ((n = 28))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median years, range)</td>
<td>67 (40–84)</td>
<td>70 (58–83)</td>
<td>64 (40–84)</td>
<td>0.097</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>5</td>
<td>6</td>
<td>0.473</td>
</tr>
<tr>
<td>Synchronous disease</td>
<td>27</td>
<td>7</td>
<td>20</td>
<td>0.170</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>31</td>
<td>9</td>
<td>22</td>
<td>0.267</td>
</tr>
<tr>
<td>Median no. tumours ablated (range)</td>
<td>1 (1–12)</td>
<td>1 (1–12)</td>
<td>1 (1–3)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Median no. tumours treated (range)</td>
<td>4 (1–14)</td>
<td>1 (1–12)</td>
<td>4 (2–14)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Longest tumour diameter (mm)</td>
<td>43</td>
<td>43</td>
<td>40</td>
<td>0.004*</td>
</tr>
<tr>
<td>Median LOS (days, range)</td>
<td>7 (4–80)</td>
<td>7 (4–23)</td>
<td>6 (4–80)</td>
<td>0.462</td>
</tr>
<tr>
<td>Local recurrence</td>
<td></td>
<td></td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Per patient</td>
<td>4 (9.5%)</td>
<td>3 (7.1%)</td>
<td>1 (2.4%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Per lesion</td>
<td>4 (4.2%)</td>
<td>3 (3.2%)</td>
<td>1 (1.1%)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

* Indicates \( P < 0.05 \).
for further percutaneous ablative treatment. One patient developed local recurrence after 7 months and underwent successful percutaneous ultrasound guided radio frequency ablation (RFA) followed by drug eluting bead hepatic artery embolisation, and is currently recurrence free after 7 months follow up. An 83-year-old female patient who had a combined liver resection and ablation underwent a second open ablation with uneventful postoperative recovery, and is currently disease free after 3 months follow up. Only 1 patient who underwent an RMWA was deemed re-resectable, and underwent a hemihepatectomy with partial inferior vena cava resection 2 years after the primary liver resection and ablation.

Discussion

For patients with liver-limited metastatic colorectal cancer, resection offers the only chance of cure with 5-year survival approaching 40%. However, only a minority of patients are candidates for surgery. For patients in whom complete resection is not possible at a single procedure, ablation offers an opportunity for complete tumour destruction with possible benefits on long term outcome. In this study, patients underwent open MWA either because percutaneous approach was contra-indicated or the risk for resection seemed unexpectedly high during surgery (e.g. high central venous pressure not improvable by anaesthetic intervention, tumour location close to main hepatic outflow or poor quality liver parenchyma precluding safe resection). Five patients in the early study period (2005–2007) were recruited into a trial comparing MWA versus resection, explaining the high numbers of surgical ablations in this subgroup. This planned multicenter study was never finished.

Microwave ablation versus radio frequency ablation

The majority of reports concerning ablation have used radio frequency energy for local tumour destruction. Radio frequency ablation (RFA) relies on direct current transmission, with tissue desiccation and charring leading to an exponential increase in tissue impedance resulting in unpredictable ablation zones and a maximum theoretical size of ablation that can be achieved. MWA offers several advantages...
over RFA. Microwave energy causes polarised water molecules to oscillate or vibrate and this active heating mechanism means energy is not reduced by transmission through charred and desiccated tissue, leading to a more clearly defined histopathological ablation zone. This active heating mechanism also means that all tissue within the treatment zone is heated simultaneously, leading to reduced ablation times and more predictable ablation patterns, as well as avoiding the heatsink effect near large vessels.

**Survival after microwave ablation**

Outcomes for patients with unresectable stage IV disease are constantly improving. In 2000, fewer than 2% of patients treated with systemic chemotherapy would survive 5 years. Updated results of the CRYSTAL study of systemic FOLFIRI with Cetuximab showed that in 2011, nearly 15% of patients with unresectable stage IV disease were alive 5 years after diagnosis. This constant improvement in outcomes for medically treated patients makes meaningful comparison of survival from historical case series difficult. Despite this observation, the positive impact of ablation on long-term outcomes has been independently demonstrated by 2 high quality prospective studies. EORTC 40004 compared systemic chemotherapy vs. systemic chemotherapy plus ablation for patients with technically unresectable liver limited disease. 3-year DFS was improved in the combined ablate and chemotherapy arm (27.6% vs. 10%, \( p = 0.025 \)) with a trend towards improved OS (median 45.3 months vs. 40.5, \( p = 0.22 \)). In the French ARF2003 single arm phase II study, 52 patients with unresectable liver limited disease were treated with a combined ablate and resect strategy using RFA. One year local DFS was 46% (95% CI 32–59) whilst 5 year OS was 43% (21–64), demonstrating that ablation and resection can lead to good long-term survival. The evidence now points towards managing stage IV colorectal cancer as a chronic disease condition, where surgery or ablation is performed in the expectation of potentially treatable disease recurrence rather than a single entity which can only be surgically treated once with curative intent or not. Sixty five percent of patients who survive to 5-years after liver resection will develop hepatic recurrence, which can now be treated with further interventions including surgery or ablation. Parenchyma sparing techniques (such as ablation) preserve functional liver volume, thereby maximising the opportunity for further liver directed interventions.

**Safety and efficacy of microwave ablation**

This study clearly demonstrates the safety of performing open MWA in a specialist unit for patients with disease that was technically unresectable at a single procedure. Complication rates were low, with fewer than 10% grade 3/4 complications, comparing very favourably with other ablation modalities. Operative mortality was also low (2%), and comparable with published series for resection alone. Ablation offered excellent local disease control, with only 4% lesional recurrence - comparable with resection margin recurrence rates reported after hepatectomy. In contrast, EORTC 40004 reported a 9% lesion recurrence rate. The lower rate reported in the present series likely reflects better selection of lesions suitable for ablation (small size and so more likely to be adequately treated), the requirement for 10 mm ablation margin, low threshold for immediate repeat ablation and the open approach. It may also reflect more predictable ablations achieved with MWA compared to RFA. Previous data from our group have clearly demonstrated that ablated tissue is non-viable, and so local recurrence is likely to be due to inaccurate probe placement. The current technique relies on the operating surgeon positioning the probe within a lesion using hand held IOUS. This is hugely operator dependent and relies on 2-D imaging to interpret a 3-D lesion. Improvements in intraoperative imaging, and novel probes that are able to differentiate between tumour and normal tissue will improve the accuracy of probe placement and hopefully lead to even lower local recurrence rates. This series demonstrates promising long-term outcomes after MWA, with 5-year survivors achieved in both groups. Although the OS and PFS reported in this series are inferior to those achieved by EORTC 4004, this may reflect the unselected treatment population at the start of the study period and the lack of biologic agents for the treatment of stage IV disease in the UK during that period.

**Microwave ablation as an adjunct to surgical resection**

Patients require around 25% of their liver volume for a functional post-resection future liver remnant (FLR), and it is accepted wisdom that patients treated with preoperative chemotherapy, who may have chemotherapy associated liver injury, require a larger FLR of around 30%. These requirements limit the potential for formal resection in patients with extensive bilobar disease. One option is to perform two-stage hepatectomy, where the initial operation removes the minority of disease from what will become the FLR. Simultaneous portal vein embolisation of the contralateral segment results in FLR hypertrophy, after which a larger resection for the remaining disease can be performed. However, around 25% of these patients do not proceed to the planned second hepatectomy because of disease progression or inadequate remnant hypertrophy. A large series reported operative morbidity for first and second stage as 14 and 54% respectively, and 1-, 3- and 5-year survival for those who completed two-stage hepatectomy were 97, 59 and 32% respectively. However, there were no long term survivors in the incomplete resection group who did not proceed to second stage. The current study demonstrates good long term outcomes from an unselected cohort, with reduced post-operative morbidity for patients who underwent complete clearance of liver disease using a
combined single stage MWA/resection + MWA approach, with the additional benefit of offering complete disease clearance in one operative session thus avoiding the lost opportunity to treat all identifiable disease because of progression or inadequate hypertrophy of the FLR. This approach may also be more cost effective, as second liver resection can be avoided.

Conclusions

The present study suggests that in expert hands MWA is a safe and effective method of achieving disease control for unresectable colorectal liver metastases. Combination of resection and ablation offers good medium term outcomes, which are comparable to that seen after two-stage resection on an intention to treat basis.

Funding

The authors have no commercial interests, no financial support was given.

Conflict of interests

The authors declare no conflict of interests.

References