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Long-term Outcomes Following Microwave Ablation for Liver Malignancies

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Abstract

Background—Microwave ablation has emerged as a promising treatment modality for liver malignancies, but there are scant long-term follow-up data. This study evaluates long-term outcomes with a comparison of 915MHz and 2.4GHz ablation systems.

Method—A retrospective review of patients with malignant liver tumors undergoing operative microwave ablation with or without liver resection between 2008 and 2013 was performed. Regional or systemic (neo)adjuvant therapy was given selectively. Local recurrence was analyzed using competing risk methods with clustering and overall survival was analyzed using Kaplan-Meier curves.

Results—One-hundred-and-seventy-six patients with 416 tumors were analyzed. Colorectal metastases (CRLM) comprised 81.0% of tumors, hepatocellular carcinoma 8.4%, primary biliary cancer 1.7%, and non-colorectal metastases 8.9%. Median follow-up was 20.5 months. Local recurrence occurred in 33 tumors (7.9%) in 31 patients (17.6%). Recurrence rates increased with tumor size, at 1%, 9%, and 33% for tumors <1cm, 1–3cm, and >3cm respectively. On univariable analysis, local recurrence was higher with larger tumors (hazard ratio 2.05 per cm, $p < 0.001$), perivascular (HR 3.71, $p = 0.001$) or subcapsular position (HR 2.71, $p = 0.008$), the 2.4GHz ablation system (HR 3.79, $p = 0.001$), and biliary or non-CRLM histology (HR 2.47, $p = 0.036$). On multivariable analysis, tumor size ($p < 0.001$) and perivascular position ($p = 0.045$) remained significant independent predictors. Regional chemotherapy was associated with decreased local recurrence (HR 0.49, $p = 0.049$). Overall survival at 4 years was 58% for CRLM and 79% for other pathology ($p = 0.36$).

Conclusion—Microwave ablation of liver malignancies, either combined or not combined with liver resection, and selective regional and systemic therapy resulted in good long-term survival. Local recurrence rates were low with tumors less than 3cm in diameter, and those remote from vessels.

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Keywords

ablation techniques; catheter ablation; microwaves; liver neoplasms; neoplasm metastasis

Introduction

Microwave ablation (MWA) has gained popularity in recent years as a local treatment for liver tumors including hepatocellular carcinoma (HCC) and colorectal liver metastases (CRLM). Radiofrequency ablation (RFA) has been used for some years with considerable data confirming its safety and efficacy. However, the reliance on passive heating, impedance from tissue desiccation, and the heat-sink effect limit the effectiveness of RFA, and local recurrence remains a problem.

Microwave ablation works by active heating of water molecules via an electromagnetic field and hence is less affected by tissue desiccation and heat-sink effect¹⁻³, creating larger, more homogenous ablation zones more rapidly^{4, 5}. Multiple antennae can also be used simultaneously to create larger ablation zones.⁶⁻⁸ There is considerable experience in the use of MWA in Asia for HCC, but in Western series there is relative paucity of evidence on the long-term survival after MWA, particularly for CRLM, which comprise the bulk of liver malignancies treated in the Western world.

Currently there are two microwave generator systems in use: a 915MHz system, and a 2.4GHz system. The 2.4GHz system has been in use in Asia and Europe for more than a decade, while in the US the 915MHz system was the only choice until FDA approval of the 2.4GHz system in 2006. The different wavelengths generated may alter the depth of penetration and the efficiency of energy delivery to the surrounding tissues. There are little data on the relative efficacy of the 915MHz and the 2.4GHz systems, with some experimental animal studies suggesting the 915MHz system may create larger ablation zones.⁹

In a previous study of thermal ablation of CRLM, Kingham et al showed local recurrence occurred in 11% of tumors.¹⁰ Microwave ablations comprised a relatively small proportion (13%) of that cohort. The aim of this study is to examine the local recurrence rate and long-term survival in a larger group of patients treated with MWA, and to perform a comparison between patients treated with the 915MHz and 2.4GHz systems.

Methods

A waiver of consent for this retrospective study was granted by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC). Patients who had an operative microwave ablation with or without resection for liver malignancy between July 2008 and July 2013 were identified from a prospectively maintained database at MSKCC. Patients with at least 3 months follow-up were eligible. Tumor characteristics and ablation details were obtained from comprehensive synoptic operation notes, and medical records and radiological imaging were reviewed to obtain relevant clinical and pathological data and to examine follow-up and outcomes.

The indications of ablation with or without concomitant resection included 1) complete resection was contraindicated due to inadequate liver remnant, 2) a desire to spare parenchyma, e.g. when there were concerns regarding the quality of the non-tumorous liver, or in patients at high risk of occult metastases which may mandate repeated resection in the future, and 3) when a two-staged hepatectomy was planned. The choice of ablation between RFA and MWA was made at the discretion of the treating surgeon, although there had been a trend of moving away from RFA to MWA in recent years.

All patients had an open approach to ablation, with routine intraoperative ultrasound to identify lesions and monitor treatment effect. Two microwave ablation systems were used at the discretion of the surgeon: 915MHz (ValleyLab, Boulder, CO, USA; Covidien, Mansfield, MA, USA) or 2.4GHz (Microsulis, Hampshire, UK; NeuWave, Madison, WI, USA). The 915MHz system has been used since 2008. The newer 2.4GHz system became available in 2010 and has been the more frequently used system since. The ablation power settings and duration were determined by the surgeon on a case by case basis, guided by tumor size and by the manufacturers' specifications. For the 915MHz system, power was set at 45W; the 2.4GHz system was usually set at 60-95W but up to 140W was used.

A combination of ablation and resection was commonly performed for patients with extensive liver disease. Additional treatment including neoadjuvant or adjuvant systemic chemotherapy and hepatic-arterial pump infusion chemotherapy were given selectively with input from a multidisciplinary disease management team.

Complications were prospectively recorded and graded from 0 to 5 using a previously reported serious adverse events classification system.¹¹ Ninety-day morbidity and mortality were described for this study. Grade 3 and above were considered major complications. Frequency of follow-up imaging was individualized but typically patients underwent CT or MRI at 3 to 6 monthly intervals for the first 2 to 3 years, then annually.

Definitions

Local recurrence was defined as presence of a new tumor at or immediately adjacent to the margin of an ablation zone identified on follow-up imaging. This included patients with extrahepatic or new intrahepatic disease as part of their pattern of recurrence. Proximity to a major vessel was defined as a lesion within 10mm of the inferior vena cava, a hepatic vein or major tributary, or a segmental pedicle. Subcapsular location was defined as tumor lying within 10mm of the liver capsule.

Statistics

Patient and tumor characteristics were described by median and range for continuous variables and frequency and percentage for categorical variables. Categorical variables were compared using Fisher exact test. Kaplan Meier and the log-rank test were used to analyze overall survival, which was defined from the date of treatment to date of death or last follow-up. Patients alive at last follow-up were censored. Competing risk methods were used to analyze local recurrence. Distant recurrence and death without any recurrence were considered as competing events. Time to event was calculated as time from treatment to date of first event (local recurrence, distant recurrence, or death without recurrence) or last

follow-up. Patients alive without any event at last follow-up were censored. To account for the potential interaction between tumors from the same patient, a competing risk regression using the Fine-Gray proportional hazards model with clustering¹² was performed in the univariable and multivariable analysis of factors predicting local recurrence. Factors significant in the univariable analysis were included in the multivariable model and limited to the guideline of 10 events per coefficient estimated. A p-value of < 0.05 was considered significant. All analyses were done using R version 3.0.2 (<http://cran.r-project.org/>), including *survival*, *cmprsk*, and *crrSC* packages.

Results

Demographics, tumor, and treatment characteristics

Two hundred and fourteen patients were enrolled in this study. Thirty-eight patients were excluded due to the ablation system not being specified or inadequate follow-up. A total of 176 patients undergoing 188 episodes of ablation for 416 tumors were available for analysis. The median tumor size was 1cm (0.2-6cm), and median number of tumors treated per session was 2 (1-11). Eighty percent of patients had concomitant resection and ablation. Colorectal metastases comprised the majority of tumors (81%). Overall, 88% patients received systemic chemotherapy (neoadjuvant and/or adjuvant) and 48% received regional pump chemotherapy. Ninety-seven percent of patients with colorectal metastases received systemic chemotherapy and 58% received regional chemotherapy. For patients with pathologies other than colorectal metastases, 47% received systemic chemotherapy and 6% received hepatic artery infusion pump chemotherapy. Fifty six percent of tumors were in the right lobe, and 44% in the left. The 915MHz system was used in 226 lesions (54%) and the 2.4GHz system in 190 lesions (46%). Median ablation time was 5 minutes (2-50) per tumor for the 915MHz system, and 4 minutes (1-20) per tumor for the 2.4GHz system. These results are summarised in Tables 1 and 2.

Morbidity and Mortality

There were no mortalities in this cohort. Forty-five patients (25.6%) developed 70 complications. The most common complications were wound infections (12), intra-abdominal abscesses (12), non-infected intra-abdominal collections including bile leaks (9), gastrointestinal (6), respiratory (5), cardiac (4), bleeding (4), and venous thromboembolism (3); 15 patients had miscellaneous complications. Of the 70 complications, 10 (14%) were grade 1, 36 (51%) were grade 2, and 24 (34%) were grade 3. There were no grade 4 or 5 complications. For patients who had MWA alone without concomitant hepatectomy, 3 of 36 (8.3%) developed complications, compared with 42 of 140 patients (30%) who underwent MWA and resection (p=0.0091). Major complications occurred in 21 patients (12%), all of which had concomitant resection. No patients who had MWA alone developed a major complication.

Ablation System

Patients who were treated with the newer 2.4GHz system were compared with patients treated with the older 915MHz system. Patients treated with the 2.4GHz system had larger tumors (mean 1.6cm vs 1.1cm, p=0.001), a higher proportion of non-colorectal-metastases

(24% vs 15%, $p=0.017$), more subcapsular tumors (25% vs 9%, $p<0.001$), and were less likely to have received chemotherapy (81% vs 89%, $p=0.01$). The median number of tumors and proximity to major vessels were not significantly different.

Recurrence

Local recurrence occurred in 33 tumors in 31 patients (7.9% of tumors; 17.6% patients). For the entire cohort median follow-up was 20.5 months and median time to local recurrence was 7 months (range 1.1-41.6 months, with 3/33 tumors recurring after 18 months). Recurrence rates increased with tumor size, at 1%, 9%, and 33% for tumors $<1\text{cm}$ ($n=103$), 1-3cm ($n=301$), and $>3\text{cm}$ ($n=12$) respectively (Figure 1). When analyzed by tumor type, there was a statistically significant difference in local recurrence ($p<0.001$), highest in biliary carcinoma and non-colorectal metastases, and lowest in colorectal metastases and hepatocellular carcinoma (Figure 2). Biliary carcinoma in particular had a higher local recurrence rate, despite non-significantly different tumor sizes and perivascular or subcapsular positions compared to the other tumor types. The local recurrence rate for tumors treated with the 2.4GHz system was 24/190 (12.6%), compared with 9/226 (4%) for the 915MHz system (OR 3.8, $p<0.001$). New intrahepatic recurrence away from site of ablation occurred in 67/176 patients (38%) and 175/416 tumors (42%). Distant recurrence occurred in 62/176 patients (35.2%) and 138/416 tumors (33.2%).

On univariable analysis (Table 3), significant factors associated with an increased rate of local recurrence were increasing size, 2.4GHz system, subcapsular location, proximity to major vessels, and biliary or non-colorectal metastasis histology. Concomitant resection, number of tumors, and use of hepatic artery pump chemotherapy were associated with a lower rate of local recurrence. Age, sex, and systemic chemotherapy were not significant factors. Given 33 events, the 3 factors with the most significant p-values on univariable analyses were entered into a multivariable analysis. On multivariable analysis (Table 4), there was a non-significant trend towards a higher local recurrence with the 2.4GHz system, while size of tumor and proximity to a vessel retained significance.

Overall Survival

The median survival following MWA for the entire cohort was 57 months, equating to a 4-year overall survival of 58% with 9 actual 4-year survivors. The median follow-up for the survivors was 56 months. For patients with colorectal metastases, the overall 4-year survival was 58%, compared with 79% for patients with other pathological diagnoses. The difference in survival by log-rank test was not statistically significant ($p=0.36$) (Figure 3). There was no difference in survival between patients treated with 2.4GHz and 915MHz systems ($p=0.226$).

Discussion

This study shows that microwave ablation for liver tumors is a safe treatment, and local recurrence is uncommon for small tumors $<3\text{cm}$ in size. As only 10-20% of patients with primary or secondary liver malignancies have surgically resectable disease, ablation has potential to expand the proportion of patients that may be potentially cured or achieve long

term survival.^{13–16} These results also suggest that with appropriate selection, the use of ablation with or without concomitant resection and/or chemotherapy may achieve survival rates similar to patients with completely resectable disease.

Microwave ablation is a relatively new ablation modality and there is less available data on its efficacy than radiofrequency ablation. Data from Asia suggest that MWA can result in local recurrence rates ranging from 0–24% and 5-year survival of 51%.^{17, 18} The sole randomized trial comparing MWA and resection was done by Shibata et al who randomized 30 patients with resectable CRLM to resection or MWA and found equivalent 3 year survival of 14% and 23%, and median survival of 27 months and 25 months, respectively. However, their 3-year survival post-resection is considerably lower than what can be achieved by modern standards. In addition, this study was powered to detect a 50% difference in survival, much higher than one may reasonably expect, hence smaller differences cannot be excluded.¹⁹ More recently data have emerged from the Western world regarding the efficacy of MWA, with local recurrence rates ranging from 2% to 19%.^{20–24} Lloyd et al reported a morbidity of 17.6% (8.3% major) and in-hospital mortality of 1.9% in a multi-center prospective study with 140 patients from USA, Europe, Asia, and Australia.²⁰ Stattner et al studied patients with unresectable CRLM and reported a 3-year overall survival of 36% for those treated with MWA only.²⁵

Most studies on MWA are small (<50 patients) and tend to focus on hepatocellular carcinoma with small numbers of patients with CRLM. In the present study, 7% of patients with CRLM experienced local recurrence, comparable with the literature. It has been previously reported that for CRLM, a combined approach of RFA with liver resection yields good long-term outcomes for patients who otherwise have unresectable disease.²⁶ The current data showed that MWA can be effectively combined with resection for good results as well.

Due to potential differences between the 2.4GHz and 915MHz ablation systems, a comparison was performed in this study. Although the longer wavelengths of the 915MHz system may have better tissue penetration, the 2.4GHz system has a higher power output and may be more efficient in energy delivery due to a lower impedance mismatch.²⁷ In the present study, local recurrence rates in the 2.4GHz group appeared to be higher than the 915MHz group but results may have been confounded by baseline differences between the two groups. In the multivariable analysis, the difference in local recurrence rates became statistically insignificant.

Traditionally, subcapsular tumors were less commonly treated with ablation due to technical difficulties with probe placement, and ready accessibility for surface wedge resection. On the other hand, deep isolated lesions benefit from ablation by avoiding sacrifice of large amounts of parenchyma. A considerable proportion of tumors (16%) in this study were subcapsular in position. There may be an advantage for ablation over multiple wedge resections in patients with gross steatosis or sinusoidal obstruction due to chemotherapy to reduce morbidity from bleeding or bile leak. The reduced heat sink effect with MWA compared to RFA has been widely cited as a theoretical advantage of MWA. However, data to support this are largely extrapolated from experimental studies. In porcine livers, ablation

zones next to major vessels were minimally affected by the vessels.^{1, 2} Previous clinical studies that looked at local recurrence after MWA have not specifically examined the effect of proximity of vessels. The present study suggest that proximity to a vessel has an adverse effect on recurrence. Despite the theoretical advantages of MWA over RFA, the efficacy of MWA for larger tumors and perivascular tumors still appears to be limited. However the speed of microwave ablation is a major advantage. Further studies are needed to establish the relative oncological efficacy of MWA vs RFA.

An unexpected finding on univariable analysis was an inverse relationship between number of tumors treated and local recurrence. Literature on RFA suggests that a larger number of tumors is associated with increased local recurrence.²⁸ However, it is possible that patients with larger number of tumors were selected for MWA only if they had favorable features otherwise, contributing to the apparent lower recurrence rates for these patients.

The main weakness of this study is the retrospective nature. The multivariable analysis was limited by the relatively small number of events, and only 3 covariates were able to be entered into the model to avoid overfitting. An alternative method to control for confounders would be through matching but at the expense of reducing the power to detect a difference. The ablation system was entered into the model because one of the objectives of this study was to compare local recurrence rates between the two systems. The size of tumors and proximity to vessels were chosen because of their biological plausibility and their lower p-values in the univariable analysis. Therefore there are likely further confounding factors which are unaccounted for due to the statistical limitations of the multivariable model.

A problem common to studies investigating local recurrence after ablation of small (<1cm) tumors is the diagnostic uncertainty. Therefore without histological confirmation, there is potential for diagnostic error and a spuriously low local recurrence rate. However, high quality pre-operative imaging and the use of intra-operative ultrasound by experienced high-volume surgeons would have likely minimized the error rate. As MWA is still a relatively new technology, the length of follow-up was limited, with 33% of patients and 15.4% of tumors at risk at 2 years. The low number of true long-term survivors does limit the conclusions that could be drawn from these data with regards to survival. However, the median time to local recurrence was 7 months, with only 3 tumors recurring after 18 months, therefore the local recurrence rate estimated by Kaplan Meier method probably approximates the true rate. Strengths of this study include a comprehensive prospective data collecting system that resulted in good quality data, and the fact that this is a large series of operative microwave ablation for liver malignancy, at a high-volume academic center experienced in ablation.

Finally, it should be noted that although MWA appeared to achieve good local control for small tumors, a substantial number of patients developed intrahepatic recurrences away from the ablation site, or systemic recurrence. Therefore the favorable longterm survival must be interpreted in the context of effective systemic and regional therapy. However, it is likely that MWA contributed to such outcomes by allowing complete local treatment which may not have been possible through resection alone.

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Fig. 1. Local recurrence after ablation of tumors <1cm, 1-3cm, and >3cm in size. $p < 0.001$ (log rank test)

Fig. 2.

Local recurrence after ablation for colorectal metastases, hepatocellular carcinoma, non-colorectal metastases, and biliary carcinoma. $p < 0.001$ (log rank test)

Fig. 3.
Overall survival after microwave ablation for colorectal metastases (CRLM) and other pathology. $p=0.360$ (log rank test)

Table 1

Patient Characteristics

	No. of patients (n =176)
Number of Tumors Ablated	416
Age, median (range)	57 (28–81)
Sex Ratio (M:F)	94 : 82
No. of tumors ablated per patient, median (range)	2 (1–11)
Ablation with Resection	140 (80%)
Wedge resection	45
Resection, <3 segments	56
Resection, 3 segments	39
Extrahepatic Disease Resection	58 (33%)
Colorectal	41
Ovary	4
Lung	2
Chest/Abdominal Wall	2
Duodenum	1
Stomach	1
Pancreas	1
Adrenal	1
Diaphragm	1
Colorectal and Ovary	4
Chemotherapy	
No Chemotherapy	21 (11.9%)
Systemic Chemotherapy	155 (88.1%)
Pump FUDR Chemotherapy	85 (48.3%)

Table 2**Tumor Characteristics**

	No. of tumors (n = 416)
Diagnosis	
Colorectal Metastases	337 (81.0%)
Hepatocellular Carcinoma	35 (8.4%)
Primary Biliary Cancer	7 (1.7%)
Non-Colorectal Metastases	37 (8.9%)
Tumor Size, median (range)	1cm (0.2–6cm)
<1cm	103 (24.8%)
1.0–3.0cm	301 (72.4%)
>3cm	12 (2.9%)
Proximity to Vessel	
Yes	74 (17.8%)
No	342 (82.2%)
Subcapsular	
Yes	68 (16.3%)
No	348 (83.7%)
System Used	
915MHz	226 (54.3%)
2.4GHz	190 (45.7%)

Table 3

Univariable analysis of factors associated with local recurrence

	Hazard Ratio**	p-value
System (2.4GHz vs 915MHz)	3.79 (1.74, 8.26)	0.001
Tumor size (continuous)*	2.05 (1.65, 2.54)	<0.001
Concomitant Resection (Y vs N)	0.37 (0.18, 0.77)	0.007
Systemic Chemotherapy (Y vs N)	0.77 (0.28, 2.18)	0.63
Hepatic Artery Pump Chemotherapy (Y vs N)	0.49 (0.24, 0.99)	0.049
Histology (non-CRLM/biliary vs CRLM/HCC)	2.47 (1.06, 5.77)	0.036
No. of tumors (>3 vs 3)	0.30 (0.10, 0.89)	0.03
Subcapsular Position (Y vs N)	2.71 (1.30, 5.65)	0.008
Proximity to Vessel (Y vs N)	3.71 (1.76, 7.82)	0.001

* HR per 1cm increase in tumor size.

** Values in parentheses are 95% confidence intervals.

Table 4

Multivariable analysis of factors associated with local recurrence

	Hazard Ratio**	p-value
System (2.4GHz vs 915MHz)	2.32 (0.96, 5.56)	0.061
Tumor size (continuous)	1.68 (1.26, 2.23)	<0.001
Proximity to Vessel (Y vs N)	2.46 (1.02, 5.91)	0.045

* HR per 1cm increase in tumor size.

** Values in parentheses are 95% confidence intervals.