INTRODUCTION

Percutaneous ablation techniques have been increasingly recognized for their curative success in patients with hepatocellular cancer (HCC). Surgical management in the form of liver...
transplantation or resection remains the best treatment option for these patients. However, only a small percentage of patients is surgical candidates, either due to HCC burden at presentation or due to cirrhosis-related morbidity.[1,2]

Percutaneous ablation has been shown to perform at par with surgery in prolonging survival, especially for lesions smaller than 2 cm, making it a first-line option for early HCC in the Barcelona Clinic Liver Cancer classification.[3,4] For larger tumors, percutaneous ablation has been known to carry a greater risk of residual disease, especially at the outer ablation rim. The recent development of newer high-powered single antenna microwave ablation (MWA) systems with Thermosphere™ technology (which promises quicker, more precise, and predictably spherical ablation zones of larger sizes compared to prior MWA technologies) holds great promise in overcoming this drawback.[5] Although thermal ablation with microwave has been theoretically shown to confer benefits such as overcoming problems of tissue charring and vascular heat sink,[6,7] no definitive evidence supports the superiority of microwave over radiofrequency ablation (RFA).[8,9] Importantly, the abovementioned practical and theoretical advantages are driving greater adoption of MWA over RFA, not only for HCC but also for liver metastases.[10,11] The interventional radiology staff at our institution unanimously switched from RFA to MWA in December 2014.

The availability of data on patient outcomes after ablation with these newer MWA devices (first FDA approved in 2014) is currently limited. Hence, we retrospectively studied our pilot experience with outcomes of the first hundred percutaneous ablations using a high-powered single antenna MWA system with Thermosphere™ technology (Emprint™ system, Covidien, Boulder, CO, USA)[5] in a mixed set of tumors (HCC, cholangiocarcinoma, and metastases) to evaluate its safety and oncologic effectiveness. Although constrained by a small sample size, we also conducted a multivariate analysis for factors that predicated residual disease (or ablative failure).

In addition, recent research has uncovered another critical obstacle against the use of percutaneous ablation – carcinogenic potentiation of the cirrhotic liver with the accelerated appearance of new lesions after ablation of the index lesion.[12,13,14] While this possibility has been reported, only few clinical studies have methodically evaluated and presented its actual incidence. Hence, as a secondary endpoint, we also evaluated the incidence of new liver lesions, close to (same-segment) or distant from (different-segment) the index lesion.

MATERIALS AND METHODS

After institutional review board approval, a prospectively maintained database of patients undergoing MWA for primary and secondary liver malignancies was queried retrospectively from March 2015 to July 2016. The endpoints of our study and parameters studied are indicated in Table 1. Ablations were performed by two interventional radiologists (3 years and 5 years of MWA experience), while the pre- and post-ablation studies were read by fellowship-trained abdominal radiologists. We excluded the first five ablations for each operator from the study, to eliminate any assumed selection bias or effect of the learning curve.[9]

Inclusion criteria

Since our primary endpoint was to evaluative ablative effectiveness based on size, we included all patients who underwent MWA in the study period (differing tumor etiologies, underlying liver disease, lesion sizes, and locations). All patients were referred and discussed at our dedicated liver tumor board for treatment eligibility assessment. We included patients who had prior locoregional interventions only if the target lesion was not located within the same segment as the prior treated lesion. Each tumor was treated as a separate data point and all imaging characteristics and treatment data were collected on a per lesion basis. For HCC, only Liver Imaging Reporting and Data System 4/5

| Table 1: Study design and parameters studied. |
|------------------------------------------------|
| **Primary endpoints – safety and effectiveness** |
| Complete ablation rate at 1 month (defined as no residual disease at 1 month) |
| Procedure-related mortality and major complications (major complications defined as either symptomatic hemoperitoneum or porta-biliary complications) |
| **Secondary endpoints – new lesions, risk factors, and minor complications** |
| Rate of new lesions (defined as resurgence of disease in a different hepatic segment or in the same segment, at least after 3 months of treatment) |
| Risk factors for residual disease |
| Parameters studied: Patient-related factors |
| Age, sex, body mass index >30, comorbidities (insulin-dependent diabetes) |
| Parameters studied: Underlying liver disease |
| Alcohol, non-alcoholic steatohepatitis, hepatitis B, hepatitis C, primary biliary cirrhosis |
| Cirrhosis grading – morphologic (semiquantitative computed tomography/magnetic resonance imaging based), biochemical (Child-Pugh, Model for End-Stage Liver Disease) |
| Parameters studied: Target lesion related factors |
| Size and location including proximity (1 cm) to capsule, diaphragm, heart, gallbladder and inferior vena cava, (5 mm) and vessels >3 mm |
| Multiplicity of tumors |
| Parameters studied: Technique-related factors |
| Cumulative energy applied (energy applied×time of application), total IR suite time |
lesions were targeted with the threshold size being <5 cm and a maximum of 4 nodules per session. For metastatic lesions and cholangiocarcinomas, the same size threshold was used.

**Pre-procedural planning and laboratory data**

All lesions were assessed using liver protocol dynamic contrast-enhanced cross-sectional imaging magnetic resonance imaging or computed tomography (MRI or CT) within 2 weeks before the ablation procedure. While most patients did not have liver elastography or biopsy, a semiquantitative image-based grading of cirrhosis [Figure 1] was carried out in addition to the biochemical scoring of baseline liver disease (Child-Pugh and Model for End-Stage Liver Disease [MELD] scores). The largest anterior-posterior splenic width measurement on axial images was used for "splenic size," and a threshold of 10.5 cm was used to define splenomegaly. Our morphometric grading system was developed by adapting and combining multiple existing criteria previously published in the literature.[17-19] A 1 cm threshold was used to define proximity to larger vessels inferior vena cava or morphologic boundaries (capsule, diaphragm, pericardium, and gallbladder). A 5 mm threshold was used to define a lesion as perivascular (only for vessels >3 mm in diameter).

**MWA technique**

All procedures were performed under general anesthesia and with the use of single-dose prophylactic and post-procedure antibiotics for 5 days. CT guidance was utilized (Somatom Aera, Siemens, Erlangen, Germany). Patient positioning, use of intraprocedural contrast enhancement, and use of hydrodissection were case based. For lesions not visible during the procedure (without contrast), lesion targeting was performed using anatomic landmarks on prior contrast-enhanced imaging. Ultrasound was not used. The Emprint probe is a 13-gauge fiberglass device that comes in 15 cm length which was used for 80% of the lesions while the rest required the use of the longer 20 cm long probe. A pre-coagulation burn with 45 W x 1 min was carried out for subcapsular lesions. An ablation margin of 1 cm was taken into account using ablation curves provided by the manufacturer for 100 W and less frequently, 75 W (choice of power was based on physician preference). The probe was retracted while ablating the tract using 45 W x 20 s every 1 cm until the liver capsule was reached. Here, reduced power and longer durations of ablation were applied to reduce the rate of gas and vapor production, thereby minimizing the likelihood of capsular burst.

**Follow-up imaging**

All patients had cross-sectional imaging (contrast-enhanced CT or MRI) follow-up assessment at 4–6 weeks which were evaluated using modified response evaluation criteria in solid tumors (m-RECIST) criteria. The majority of the patients had up to a year-long imaging follow-up. Patients who did not have a 1-month follow-up or had prior treatment to the same lesion/segment were excluded from the analysis.

**Statistical analysis**

Statistical analysis was carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Chi-square tests and t-tests were utilized to obtain basic descriptive and inferential statistics. For smaller sample sizes and skewed data, nonparametric tests were utilized. Clinically relevant variables with biologically plausible associations as well as variables that were associated with $P < 0.30$ on univariate analysis were introduced into a forward stepwise multivariate Cox proportional hazards model to assess for factors predicting ablative failure, i.e. presence of residual disease.
RESULTS

Demographic parameters (per-patient)

Our inclusion criteria identified 53 patients who underwent 100 MWAs. The median age of these patients was 61 ± 9 years, with the majority being male 39 (71%). Forty-one percent of these patients were obese and 18% had insulin-dependent diabetes mellitus. Patients were followed for a median of 12 months (ranging from 3 months to 2 years). Eleven patients (21%) were lost to follow-up after their first post-procedural visit at 4–6 weeks.

Tumor characteristics and imaging modality (per-lesion)

Out of the 100 lesions ablated, 76 were HCCs and 24 were metastases (colorectal metastasis – 18, neuroendocrine metastasis – 5, cholangiocarcinoma – 3, gastrointestinal stromal tumor – 1, and prostate cancer metastasis – 1). The median lesion size was 16 mm (range: 0.6–4.8 cm). The majority (70%) of the lesions were 1–3 cm in size. Seventeen tumors were sub-centimeter, while 13 tumors exceeded 3 cm. Two-thirds of the tumors (76%) were in the right lobe of the liver and a significant proportion were in the subdiaphragmatic and pericardial regions [Figure 2].

All patients had a pre-procedural liver protocol cross-sectional study (MRI: 77%, CT: 23%). The choice of imaging modality for follow-up was kept the same as that used for pre-procedural imaging.

Underlying liver disease, prior treatment, and multifocality (per-lesion)

Most HCC tumors were from livers with a prior diagnosis of cirrhosis (excluding four tumors that were in the setting of hepatitis B without cirrhosis). Percentage distribution of lesions among different background liver conditions was: Non-alcoholic steatohepatitis (NASH) (33), hepatitis C (29), alcoholic liver disease (22), hepatitis B (4), and primary biliary cirrhosis (1). The majority of the tumors occurred in patients with Child-Pugh A (58%) score, with 41% in Child-Pugh B, and 1% in Child-Pugh C. Median MELD score was 9 ± 3. A median morphological score of 2 ± 0.7 was found using the above described radio-biochemical scoring scale.

One-third of tumors (33%) targeted had some form of prior hepatic treatment (ablation, transarterial chemoembolization [TACE] or radioembolization, or resection) to a different hepatic segment from the index lesion under consideration.

Complications and mortality (per-patient)

There were no 30-day mortality or major complications on 12-month median follow-up. The median progression-free survival was 4.3 months [Figure 3], and the median overall survival was 24.7 months [Figure 4]. A minor complication rate of 9.4% (5/53 patients) was observed. This included two patients requiring chest tubes for pneumothorax after high dome lesions were ablated. These patients remained admitted for observation until the next day. Three patients had partial portal vein thrombosis in the perilesional portal vein on follow-up imaging.

Incidence of complete ablation (no residual disease)

A complete ablation rate of 83% was achieved with only 17 of the 100 lesions showing residual disease (at the margin of the index tumor) using m-RECIST criteria at the first follow-up imaging.

Incidence of new lesions

Nearly half of the patients (25/53; 47%) were found to have new foci of disease: Different-segment (16/25; 64%) and same-segment (9/25; 36%). The majority of new lesions occurred in HCC patients (80% of new lesions).

Figure 2: Distribution of lesion location within the liver and in relation to vessels and anatomic structures (n = 100).
Re-interventions

Thirty-nine percent of the patients (21/53) had re-interventions. The majority (16/53; 31%) had repeat ablation of marginal residual disease or recurrence. One-third (7) of these patients had multiple repeat ablations. Eight percent of these patients were switched to transarterial therapy, either in the form of TACE) or yttrium-90 transarterial radioembolization (TARE).

Predictors of ablative failure

Factors that were included in the stepwise regression were: Age, body mass index >30, presence of cirrhosis, cirrhosis grade, etiology of cirrhosis, tumor etiology, hepatic lobar location, lesion size, prior TACE, proximity to major vessels, lesion multiplicity, and subcapsular location.

The following factors were significant predictors of ablative failure: Higher degree of morphologic cirrhosis based on our gradation ($P < 0.01$), NASH cirrhosis ($P = 0.01$), and subcapsular location of the lesion ($P = 0.03$).

No significant differences were found based on other lesional (lesion type, size, or multiplicity) and perilesional factors (proximity to vessels or anatomical structures).

Subgroup analysis for HCC patients with lesion sizes >1 cm

Lesions <1 cm are difficult to visualize and prone to mistargeting. To overcome this problem and to neutralize the effect of lesion type, we analyzed the subgroup of HCC lesions >1 cm in size. Sixty-four lesions from 35 patients (median age 62 years; 74% of males) had HCC lesions that were >1 cm in size. Median lesion size was 19.6 mm and 72% (46/64) were in the right lobe. A complete ablation rate of 86% (55/64) was observed in HCC patients. Forty-eight percent (17/35) of these patients had recurrent lesions and the majority 76% (13/17) of these were in a different hepatic segment. Mean time-to-recurrence for the same segment new lesions was 1.6 months while that for different segment new lesions was 2.9 months. A multiple regression analysis was carried out in this subgroup with similar thresholds for variable inclusion. As a large majority of these patients had cirrhosis, cirrhosis gradation did not hold significance. Only the presence of NASH ($P = 0.03$) remained statistically significant.

DISCUSSION

High-powered (2.4 GHz) MWA devices were FDA approved in 2010. The first single probe device was approved in 2014.[5,20] This small sample study demonstrates the safety and effectiveness of ablation using high-powered MWA systems with Thermosphere™ technology for liver lesions of various etiologies and sizes with a low risk of residual disease and complication rate.

At the time of the submission of this study, we are aware of one prior published study and one abstract reporting on the outcomes of percutaneous microwave liver ablation using the high-powered MWA system with Thermosphere™ technology. Imajo et al. (Japan)[20] evaluated outcomes after ablation of 21 solitary liver metastatic lesions >3 cm in size. Their rate of residual disease was 5% with no intrahepatic recurrence, but with a limited 3-month follow-up.

Pua et al. (Singapore; $n = 119$)[21] observed excellent overall outcomes (99% technical success; 6% residual rate; and 3% recurrence rate), but their study population included
mostly solitary liver lesions and they had a higher minor complication rate with greater number of pneumothoraces and subcapsular hematomas. Their study could not be thoroughly compared with, as only an abstract was available.

Limited data are available comparing the newer 2.4 GHz and older 915 MHz MWA systems. Although theoretically, the longer wavelengths of the 915 MHz system may have better tissue penetration, the 2.4 GHz system has multiple practical advantages, reaching higher intratumoral temperatures in shorter times and more predictable time-dependent spherical ablation zones.

We found the degree of cirrhosis ($P < 0.01$), presence of NASH ($P = 0.01$), and subcapsular location of lesions ($P = 0.03$) to be significant predictors of residual disease after MWA. However, the degree of cirrhosis and subcapsular location was no longer significantly predictive of ablation failure when the subset of only HCC lesions was re-analyzed. These results should however be interpreted with caution, given relatively small number of target events and limitations of stepwise covariate modeling designed to avoid overfitting.

The association between the degree of cirrhosis and presence of NASH and high residual disease could be related to different tissue characteristics having differing susceptibility to ablation and tissue contraction.$^{[22,23]}$ This is supported by prior studies showing substantial differences in cavity sizes in patients with different degrees of cirrhosis or fatty infiltration.$^{[21]}$ Conventionally, subcapsular tumors were less commonly treated with thermal ablation due to technical difficulties with probe placement, fear of intraperitoneal tumor spill or hemorrhage and ready accessibility for surface wedge resection. A considerable proportion of tumors (61%) in this study were subcapsular in location. Multiple other studies were done with RFA support a higher risk of recurrence with subcapsular lesions.$^{[34,35]}$

Interestingly, lesion factors such as tumor type and size as well as proximity to vessels or anatomical structures did not significantly influence ablative success in our study. This is supported by other prior studies with lower power or multi-antenna MWA systems.$^{[16,26]}$ This echoes the findings of multiple studies showing greater reliability of MWA systems due to a reduced heat sink effect.$^{[6,27,28]}$ However, contrary to our study, Zhang et al. ($n = 60$)$^{[29]}$ showed poorer outcomes with greater residual disease in lesions in proximity to “risk areas” (large bile ducts, blood vessels, etc.) using a multi-antenna 2.4 GHz MWA system.

Our recurrence rate of new disease foci within the first few months is a concerning finding. However, we believe this is most likely due to the relatively aggressive disease profile of our cases (with two-thirds of the patients having multifocal disease) and the inherent field-carcinogenesis attributable to underlying cirrhosis. However, it would be irrational to dismiss the alternative possibility of iatrogenic carcinogenic potentiation after thermal ablation. Similar phenomenon of accelerated recurrence has also been cited in the RFA and surgical literature and has been suggested to be linked to treatment-related release of inflammatory cytokines.$^{[14,30-34]}$ Although we predominantly used the superior contrast resolution of liver protocol MRI for both pre- and post-procedural imaging, these lesions may still represent micrometastatic disease that may have been too small to detect on pre-procedural imaging. A review of literature on rates of intrahepatic recurrence of HCC at intermediate-term follow-up revealed significant variation among reports, either post-ablation ($5-42\%$)$^{[6,12,13,16,35,36]}$ or post-resection ($30-50\%$)$^{[37]}$. A recent large sample study by Jung et al. ($n = 628$ recurrences) is an example of well-orchestrated research into characterizing and predicting HCC recurrence after curative resection. A recurrence rate of $27\%$ was seen with solitary HCCs that were pathologically confirmed. Our recurrence rate was nearly twice this, but this can be reasonably explained by our very high rates of perivascular location ($50\%$) and pre-treatment multifocal disease ($75\%$). Larger prospective studies are needed to reliably decipher any association between thermal ablation and increased rates of $de$ $novo$ tumor recurrence. This finding highlights the need for careful patient selection and vigilant post-procedural follow-up at this time until such an association is confirmed. Furthermore, it highlights a possible future role for concomitant systemic therapies such as immunotherapy, which is currently being investigated in multiple clinical trials.$^{[38]}$

Our study has several limitations. It is a retrospective, single-center analysis. We had liberal inclusion criteria with a heterogeneous group of patients and diseases. Considering pre-procedural parameters, we used data on cirrhosis from patient charts as well as qualitatively scored cirrhosis with a non-validated morphologic score. Pre-procedural and post-procedural alpha-fetoprotein measurements were not recorded since we included both primary and secondary liver malignancies. For most patients, liver elastography data or biopsy data were not available.

**CONCLUSION**

Single probe high-power MWA was found to be safe and effective in this pilot cohort. The higher degree of underlying cirrhosis and NASH etiology as well as subcapsular location of lesions was predictors of ablative failure at short-term follow-up. A significant rate of new lesions was observed after the ablation of HCC tumors which may or may not be linked to MWA itself. Although a causal relationship cannot be deduced from our study, this finding warrants close follow-up of these patients and need for further investigation into the possibility of iatrogenic tumor potentiation after thermal...
ablation and into whether concomitant systemic therapies such as immunotherapy may play a future role.

**Declaration of patient consent**

Patient's consent not required as patients identity is not disclosed or compromised.

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**Conflicts of interest**

There are no conflicts of interest.

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