Retrospective Study

Clinical outcome of medium-sized hepatocellular carcinoma treated with microwave ablation

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Abstract

AIM: To evaluate the outcomes of patients with medium-sized hepatocellular carcinoma (HCC) who underwent percutaneous microwave ablation (MWA).

METHODS: We retrospectively reviewed all patients with a single medium-sized HCC who underwent percutaneous MWA from January 2010 to January 2013. Technical success, technical effectiveness and complications were subsequently observed. Survival curves were constructed using the Kaplan-Meier method. The Cox proportional hazards model was fitted to each variable. The relative prognostic significance of the variables for predicting overall survival rate, recurrence-free survival rate and local tumor recurrence(s) was assessed using univariate analysis. All variables with a $P$ value $< 0.20$ were subjected to multivariate analysis.

RESULTS: The study included 182 patients (mean age, 58 years; age range: 22-86 years) with a single HCC (mean size, 3.72 ± 0.54 cm; range: 3.02-5.00 cm). The estimated technical effectiveness rate was 93% in 182 patients. The major complication rate was 2.7% (5/182), including liver abscess in 4 cases, and abdominal bleeding at the puncture site in 1 case. Thirty-day mortality rate was 0.5% (1/182). One patient died due to liver abscess-related sepsis. Cumulative recurrence-free survival and overall survival (OS) rates were 51%, 36%, 27% and 89%, 74%, 60% at 1, 2, and 3 years, respectively. Age ($P = 0.017$) and tumor diameter ($P = 0.029$) were independent factors associated with local tumor recurrence. None of the factors had a statistically significant impact on recurrence-free survival. Serum albumin level ($P = 0.009$) and new lesion(s) ($P = 0.029$) were independently associated with OS.

CONCLUSION: Percutaneous MWA is a relatively safe and effective treatment for patients with medium-sized HCC.
Hepatocellular carcinoma; Medium-sized tumor; Microwave ablation; Outcomes; Cox analysis

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Core tip: This is the first study on the clinical outcome of a large population with medium-sized hepatocellular carcinoma (HCC) treated with microwave ablation (MWA). Our results confirmed that percutaneous MWA is a relatively safe and effective treatment for patients with a single medium-sized HCC.

INTRODUCTION
Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide[1]. Surgical resection and radiofrequency ablation (RFA) are the main treatments for early-stage HCC patients, who are not candidates for liver transplantation[2-4]. If these therapies are contraindicated, other minimally invasive options are used[5-8]. One option is microwave ablation (MWA), which produces a larger ablation zone than RFA, and has similar efficacy to RFA[9,10].

There have been many reports regarding the clinical outcome of small HCC (< 3 cm or < 5 cm) treated with RFA or surgical resection[11-13]. Tumor size is significantly associated with overall survival (OS)[12,14,15]. However, there have been few reports on the clinical outcomes of patients with a single medium-sized (> 3 cm and ≤ 5 cm) HCC treated with percutaneous MWA.

Therefore, the aim of this study was to evaluate the outcomes of patients with a single medium-sized HCC who underwent percutaneous MWA.

MATERIALS AND METHODS

Ethics
This study was approved by the Institutional Review Board of the Eastern Hepatobiliary Surgery Hospital Ethics Committee of the Second Military Medical University, Shanghai, China. Informed consent from patients was waived as this was a retrospective study. However, written informed consent for percutaneous MWA procedures was obtained from patients prior to each treatment.

Study population
Between January 2010 and January 2013, our Minimally Invasive Therapy Center admitted 4998 patients with HCC. The EASL non-invasive diagnostic criteria[12] were used in the diagnosis of cirrhosis and HCC. We reviewed consecutive patients with a single medium-sized HCC without prior therapy who had undergone percutaneous MWA. We recorded tumor maximum diameter in accordance with the measurements of dynamic computer tomography (CT), magnetic resonance imaging (MRI) scans, or ultrasonography (US). Of these measurements, the largest diameter was selected.

The inclusion criteria for ablation were as follows: (1) liver function classed as Child-Pugh class A or B; (2) no evidence of extra-hepatic metastases or vascular invasion; (3) normal pro-thrombin time value ± 4 s; and (4) platelet count ≥ 45000 cells/mm³, otherwise, platelet transfusion was performed. The exclusion criteria for ablation were as follows: (1) the above-mentioned indications were unmet; and (2) the distance from the tumor to important structures, for example, pericardium, gallbladder, bowel loops and hepatic hilum was < 0.5 cm. If the tumor satisfied these criteria, patients with tumors ≤ 2 cm underwent RFA, and those with tumors > 2 cm underwent MWA at our institution.

Percutaneous MWA procedure
Percutaneous MWA procedures were performed under real-time ultrasonic guidance. Local anesthesia was administered without conscious-sedation as breath control of the patient was required for the insertion of two antennas into the tumors. These two antennas were applied based on cost-effectiveness; the delivery power was set at 100 W. Multi-site ablation was performed until the entire tumor with a 0.5-1 cm margin was covered by the ablation zone. Exposure time was normally within 8 min, as the volume [(4.8 ± 0.9) × (4.0 ± 0.9) × (4.0 ± 0.9 cm)] of MWA was always achieved within 8 min when a single antenna was applied[9]. Before March 2011, the FORSEATM MW delivery system, and 14 gauge cooled-shaft antennas with a 1.0 cm active tip (both from Qinghai Electronic Institute, Nanjing, China) were used. After March 2011, the KY-2000 MW delivery system, and 18 gauge cooled-shaft antennas with a 1.1 cm active tip (both from Kang-You Electronic Institute, Nanjing, China) were used.

Definition of terminology
Definition of terminology was based on the standardization by the International Working Group on Image-Guided Tumor Ablation[16]. Technical success was indicated when the tumor was treated according to protocol, and was covered completely by an ablation area on a contrast enhanced (CE)-CT scan within 24 h. Technical effectiveness was defined as ablation of lesions initially showing contrast enhancement during the arterial phase and washout in the venous...
phase not demonstrated by CE-MRI and/or CE-CT scan 1 mo after ablation. Major complications were
defined according to current guidelines[16]. All other
complications were regarded as minor. Intra-hepatic
recurrence included local tumor recurrence(s) and new
lesion(s). Local tumor recurrences were defined as
ablation lesions and areas in contact with the ablation
lesion which showed contrast enhancement during
the arterial phase and washout in the venous phase.
Portal hypertension was diagnosed by the presence
of esophageal varices or splenomegaly with platelet
counts < 100 × 10^9[2].

Follow-up after percutaneous MWA
For early evaluation of therapeutic response or possible
complications, a CE-CT scan was performed within
24 h. Follow-up with CE-MRI and/or CE-CT scan,
liver function tests and alpha-fetoprotein (AFP) were
performed in all patients monthly for the first 2 mo.
Follow-up with liver enzyme and AFP tests, CE-MRI
and/or CE-CT scans were performed every 2 mo up
to two years, and then every 4-6 mo according to the
risk of recurrence.

Treatment strategy after initial percutaneous MWA
When technical success was not achieved at the
immediate follow-up, and intra-hepatic recurrence
was observed during subsequent follow-up, additional
percutaneous MWA was primarily selected. When
percutaneous MWA was not feasible, other therapeutic
modalities were carried out for the tumor according to
the guidelines for the management of HCC[2].

Analysis of therapeutic efficacy and survival
Local therapeutic efficacy in terms of technical success
and effectiveness was assessed on a tumor basis.
Recurrence-free survival and OS were evaluated
on a per patient basis. The OS time was defined as the
interval between the operation time and either
death or end of the study (April 1, 2013). The time of
recurrence-free survival was defined as the time from
the operation to either recurrence including death, or
end of the study (April 1, 2013).

Statistical analysis
Survival and recurrence curves were calculated using
the Kaplan-Meier method. Prognostic factors for
recurrence-free survival, local tumor recurrence(s),
and OS were assessed using univariate analysis.
Potential prognostic factors for recurrence-free survival
and local tumor recurrence(s) included all the factors
shown in Table 1. In addition to the factors in Table
1, potential prognostic factors of OS included local
tumor recurrence(s) and new lesion(s). A univariate
Cox proportional hazards model was fitted to each
variable, and all variables with a P value < 0.20 were
subjected to multivariate analysis to assess their value
as independent predictors of recurrence-free survival
and OS.

A P value < 0.05 was considered statistically
significant. Data analyses were performed using the
commercially available software, IBM SPSS 20.0
(Chicago, IL, United States).

RESULTS

Patients
One hundred and eighty-two consecutive patients
(male:female = 155:27, mean age, 58 years, range:
22-86 years) with a single medium-sized HCC (mean
size, 3.72 ± 0.54 cm; range: 3.02-5.00 cm) were
initially diagnosed and enrolled in this study. Eighty-
seven patients were diagnosed with cirrhosis. The
Child-Pugh scores in 12 patients with Child-Pugh
classification B were ≤8. None of the patients had
ascites. Maximum tumor diameters were recorded
according to CT/MRI scans in 94 patients, and US
scans in 88 patients. The clinical characteristics of the

| Table 1 Baseline characteristics of the study population (n = 182) |
|-----------------|-----------------|
| Clinical features | Number of patients |
| HCC size range 3.02-5.0 cm | mean size 3.72 ± 0.54 cm |
| Sex | |
| Males | 155 |
| Females | 27 |
| Age (yr) | |
| < 60 | 105 |
| > 60 | 77 |
| Child-Pugh classification | |
| A | 170 |
| B | 12 |
| ALB (g/L) | |
| < 35 | 37 |
| > 35 | 145 |
| ALT (U/L) | |
| < 41 | 107 |
| > 41 | 75 |
| Portal hypertension | |
| Yes | 82 |
| No | 100 |
| Total bilirubin (µmol/L) | |
| < 18.8 | 115 |
| 18.8-34.2 | 50 |
| > 34.2 | 17 |
| AFP (µg/L) | |
| < 20 | 98 |
| 20-400 | 52 |
| > 400 | 32 |
| Etiology of HCC | |
| HBV | 140 |
| HCV | 3 |
| HBV + HCV | 3 |
| Other reason(s) | 36 |
| PLT (× 10^9/L) | |
| < 45 | 14 |
| 45-100 | 66 |
| > 100 | 102 |

PLT: Platelet; ALB: Albumin; ALT: Alanine aminotransferase; AFP:
Alpha-fetoprotein; HBV: Hepatic B virus; HCV: Hepatic C virus; HCC:
Hepatocellular carcinoma.
bleeding, and 2 patients died due to liver failure. Local tumor recurrence(s), new lesion(s) or both occurred in 29, 52 and 2 patients, respectively. The local tumor recurrence rate was 20.3% (31/153). Twenty-nine patients developed local tumor recurrence(s), and 2 patients developed both new tumors and recurrences managed with MWA, hepatic resection, TACE (transcatheter arterial chemoembolization), percutaneous ethanol injection, or radiation therapy. A summary of patient management is shown in Figure 2.

Cumulative local tumor recurrence rates were estimated to be 23%, 25%, and 25%, and intra-hepatic recurrence rates were estimated to be 48%, 61%, and 73% at 1, 2, and 3 years in 182 patients, respectively (Figure 3). In univariate and multivariate analysis, age ($P = 0.010$ and $P = 0.017$) and tumor diameter ($P = 0.016$ and $P = 0.029$) were independent factors significantly associated with local tumor recurrence(s). Of the 83 patients who suffered a first intra-hepatic recurrence, 33 (38.4%, 33/83) experienced a second recurrence. Forty-five patients (54.2%, 45/83) underwent a second MWA, and 13 patients (39.4%, 13/33) underwent a third MWA.

Recurrence-free survival and OS

Except for the 5 patients (4 + 1) mentioned above who died without recurrence, 26 patients developed recurrence and died due to HCC progression during follow-up. Cumulative recurrence-free survival rates were estimated to be 51%, 36%, and 27% at 1, 2, and 3 years, respectively (Figure 4). In univariate and multivariate analysis, recurrence-free survival rates were not affected by the variables shown in Table 2. Cumulative OS rates were estimated to be 89%, 74% and 60% at 1, 2, and 3 years, respectively (Figure 4). In univariate analysis, portal hypertension ($P = 0.004$), serum albumin ($P = 0.000$), total bilirubin ($P = 0.003$), AFP ($P = 0.049$), platelet count ($P = 0.003$), and new lesion(s) ($P = 0.001$) all had a statistically significant impact on OS. In multivariate analysis, serum albumin ($P = 0.009$), and new lesion(s) ($P = 0.029$) were significantly associated with OS (Table 3).

Serum albumin level and new lesion(s) were independently associated with OS. When albumin was stratified as $> or \leq 35$ g/L, cumulative OS rates were estimated to be 95.5%, 81.4%, 75.0% and 59.5%, 45.4%, 36.4% at 1, 2, and 3 years, respectively. When the presence of new lesions was stratified according to “no” or “yes”, cumulative OS rates were estimated to be 94%, 84.8%, 84.8% and 80.7%, 69%, 38.4% at 1, 2, and 3 years, respectively.

Complications

Complications were experienced by 15 patients (8.2%, 15/182) during follow-up. Major complications were identified in 5 cases (2.7%, 5/182) including liver abscess in 4 cases, and abdominal bleeding at the...
Figure 2  Intra-hepatic recurrences and management. Local tumor recurrence(s) and intra-hepatic recurrence(s) occurred in 31 patients, which were managed with various therapeutic modalities. PMWA: Percutaneous microwave ablation; TACE: Transcatheter arterial chemoembolization; PEI: Percutaneous ethanol injection.

| Outcome | Count |
|---------|-------|
| No recurrence | 66 |
| Local tumor recurrence(s) | 29 |
| New lesion(s) | 52 |
| Local tumor recurrence(s) and new lesion(s) | 2 |
| Mortality | 4 |
| Lost to follow-up | 28 |
| Mortality within 30 d | 1 |

Figure 3  Local tumor recurrence(s) and intra-hepatic recurrence curves for 182 patients with medium-sized hepatocellular carcinoma who underwent microwave ablation.

Figure 4  Recurrence-free survival and overall survival curves for 182 patients with medium-sized hepatocellular carcinoma who underwent microwave ablation.
puncture site in 1 case. Liver abscess occurred within the ablation zone of coagulation necrosis in 3 patients, and was due to bile duct injury in 1 patient. One patient died of liver abscess-related septicemia. The 30-day mortality rate was 0.5% (1/182). The other complications observed were minor. All patients with complications received supportive care with antibiotics and hemostatics. With the exception of one patient who died, all patients recovered after treatment.

**DISCUSSION**

When liver transplantation is not possible, surgical resection is recommended for early-stage HCC[2,3]. Some authors consider RFA as the treatment of choice for very early stage HCC, even when surgical resection is possible[4]. However, surgical resection is considered the main treatment for medium-sized HCC[17]. When surgical resection is not appropriate treatment for medium-sized HCC, the combination of RFA and TACE has been recommended by some authors for the following reasons[17-22]: (1) the complete necrosis rate of medium-sized HCCs in patients who underwent RFA decreased; (2) TACE enhanced the efficacy of RFA; and (3) the effectiveness of the combination therapy was similar to that of hepatectomy.

Because the majority of MWAs is not or is only minimally affected by the heat sink effect[23], the ablation zone of MWA is larger than that of RFA[9], and patients treated with combination RFA and TACE suffer more than patients treated with MWA. Medium-sized HCCs have been treated with percutaneous MWA when liver transplantation and surgical resection were contraindicated and/or patients preferred minimally invasive therapy.

In the current study, the technical success and effectiveness rates were similar to those seen with combination RFA and TACE[18,19]. Our experience...
indicated that, in addition to the above-mentioned reasons for this success, three additional reasons were: (1) a higher delivery power was set for a large ablation area; (2) MWA operators had significant clinical experience; and (3) patients who underwent ablation were selected.

In a previous study, the 3-year recurrence rate exceeded 50% after hepatic resection. In the present study, a similar result (71%) was obtained. MWA and hepatic resection of HCC are not necessarily associated with recurrences. Tumor pathology and angiogenesis may be the main factors in recurrence.

In a previous study, the OS rate of patients with medium-sized HCC and small HCC (<5 cm) ranged from 66.67%-95.45% and 69.57%-92.17%, respectively. Tumor size was found to be significantly associated with OS. Although the OS rate in patients with a solitary medium-sized HCC who underwent MWA was 60%, this result was inferior to that in a previous study. When patients preferred MWA, or were not candidates for surgery or liver transplantation, MWA was an alternative therapy.

Frequently reported prognostic factors of HCC included tumor size, Child-Pugh classification, and recurrence in multivariate analysis in some studies. However, in the current study, serum albumin level and the appearance of new lesion(s) were prognostic factors. The reason for the difference between previous studies and the present study may be related to the following: (1) tumor size ranged from 3 cm to 5 cm and may have been at the same stage; and (2) Child-Pugh classification and recurrence were ambiguous factors. In addition, platelet count was a prognostic factor in univariate analysis. This result is consistent with that of a previous study in patients with small HCCs (<2 cm) who underwent resection, where a platelet count of ≤150 x 10^9 was found to be an independent prognostic factor regarding OS. The reason for this phenomenon is unknown.

The major complication rate (2.7%) was similar for RFA with or without TACE for medium-sized HCCs (0%-3%) and ablation for large HCCs (5-10 cm) (2.6%-3.29%). Therefore, the treatment schedule for patients with a single medium-sized HCC who underwent percutaneous MWA was relatively safe.

Our study had several limitations. Firstly, these data were obtained from a single center. A multicenter study with a larger number of patients and a longer observation period would be helpful. Secondly, not all HCC cases were confirmed by histopathology. Only clinical criteria were used. Thirdly, this study was not a prospective trial and lacked a control group. Large randomized controlled studies are needed to confirm these results.

In conclusion, when liver transplantation and surgical resection are contraindicated and/or patients prefer minimally invasive therapy, percutaneous MWA is a relatively safe and efficacious treatment for patients with a single medium-sized HCC.

### COMMENTS

#### Background

There have been few reports on the clinical outcomes of patients with a single medium-sized hepatocellular carcinoma (HCC) who have undergone percutaneous microwave ablation (MWA), although there have been many reports regarding the outcomes of patients with small HCC (<3 cm or ≤5 cm) treated with radiofrequency ablation (RFA) or surgical resection.

#### Research frontiers

This is the first study on patients with a medium-sized HCC who underwent MWA.

#### Innovations and breakthroughs

When liver transplantation and surgical resection are contraindicated and/or patients prefer minimally invasive therapy, percutaneous MWA is a relatively safe and efficacious treatment for patients with medium-sized HCC.

#### Applications

This study involved 182 patients with medium-sized HCC treated with MWA. The major limitation in the study was the absence of a control group.

#### Peer-review

This research is very useful because it is still controversial whether locoregional methods such as MWA or RFA are beneficial for patients with medium-sized HCC (>3 cm).

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