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Original Article

Clinical efficacy and safety of percutaneous microwave ablation in treatment of hepatocellular carcinoma

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Abstract: Objective: To evaluate the clinical efficacy and safety of microwave ablation (MWA) in the resection of hepatocellular carcinoma. Methods: Clinical data of 168 patients with hepatocellular carcinoma (HCC) adjacent to the gallbladder (less than 1.0 cm) undergoing ultrasonography-guided percutaneous MW ablation were retrospectively analyzed. Among them, 162 patients underwent MW ablation combined with percutaneous ethanol injection (PEI). One or two microwave cooled-shaft microwave antenna were inserted and placed at designated places in the tumor. One or two 21G PTC needles were placed into the tumor abut to gallbladder. 0.5-8 mL of absolute ethanol was injected into the tumor at the same time as microwave emission. A thermocouple was placed in 163 patients to monitor the temperature during ablation to avoid thermal injury. The safety and therapeutic efficacy of the procedures were assessed with clinical and imaging follow-up examinations. Follow-up by using the contrast-enhanced US from one to two days after therapy and contrast material-enhanced computed tomography (CT) or magnetic resonance (MR) imaging at 1 and 3 months after MW ablation and then at 3-6 months intervals. Results: No more than two sessions were performed to complete the treatment in all patients, (one session for 150 patients, two sessions for 18). The primary technique effectiveness rate was 96.5% based on one-month follow-up CT or MRI imaging (170 sessions 6). PEI or other therapies were performed to incompletely treated patients. In a median follow up of 30.1 months (range 4 to 68 months), no major complications occurred. There were no treatment-related deaths and no major complications such as cholecystitis or gallbladder perforation in the patients. Thirty-one patients (18.5%) died of progression of primary disease not directly attributable to MW ablation. Local tumor progression was noted in 5 patients (3%) completely ablated tumors during the follow-up period. More therapies were performed to local progressed tumors. Conclusion: Ultrasound-guided percutaneous microwave ablation combining with percutaneous ethanol injection and thermal monitoring is a safe and effective treatment of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma, microwave ablation, ethanol injection, gallbladder, thermal monitoring

Introduction

Ultrasound-guided percutaneous thermal ablation as a minimally invasive technique has been widely used for the treatment of primary and metastatic liver cancer in the past decade. Hepatocellular carcinoma (HCC), as the mainly primary liver tumor in malignant liver tumors, is currently the fifth most common malignant neoplasm in the world, causing more than 500,000 deaths every year [1, 2]. HCC is prevalent in Asia and Africa and its incidence has increased in European and American populations in recently years [3, 4].

Surgical resection was accepted as the first choice treatment of liver tumors [5, 6]. However, curative surgical resection is not suitable for the majority of patients with liver tumors, due to cirrhosis, impaired liver function, or multiplicity of lesions [5, 7]. Shortage of donor organs is also limited the orthotropic liver transplantation which is the chance for therapeutic success. Thermal ablation methods such as microwave (MW) and radiofrequency (RF) have become another choice to the therapy of liver tumors with good efficacy and low complication rates [8-14]. Collateral thermal damage of adjacent extrahepatic organs can occur when thermal ablation treats the subcapsular tumors. The gallbladder is at risk for potential thermal damage which would lead to perforation or acute cholecystitis during or after thermal ablation [15, 16].

Percutaneous ethanol injection (PEI) therapy, once accepted as an effective and invasive treatment for small HCC [17, 18], is now almost substituted for thermal ablation with use of different energy sources, such as radiofrequency, microwave [15, 16, 18-21]. MW ablation therapy combined with PEI could coagulate significantly larger volumes of tumor and improve the rate of complete necrosis [22]. The objective of this study was to evaluate the safety and efficacy of ultrasound-guided (US-guided) percutaneous MW ablation combined with PEI in the treatment of liver tumors adjacent to gallbladder.

Materials and methods

Baseline data

From January 2012 to December 2015, 168 patients with HCC underwent percutaneous microwave ablation (MWA) with curative intention at Qingdao No. 6 People's Hospital. We reviewed our institutional database for MW ablation cases and identified 168 patients who had 170 HCC. Two HCCs that occurred at different times of the study period in two patients were ablated in two different sessions. The patient population included 126 men and 42 women (age range, 30-86 years; mean age, 59.5 years). Nine patients had gallstones in the gallbladder, 6 patients had gallbladder wall edema related to cirrhosis as detected on CT or MRI scans obtained before MW ablation. These patients did not have Murphy's sign; two patients had low-grade discontinuous right upper quadrant pain. The criteria for MW ablation for an HCC at our hospital was the following: 1, tumor accessible via a percutaneous approach; 2, single nodular HCC lesions of 5 cm or smaller; 3, three or fewer multiple nodular hepatic lesions with a maximum dimension of 3 cm or less in each nodule; 4, absence of portal vein thrombosis or extra-hepatic metastases; 5, prothrombin time of less than 25 seconds, prothrombin activity higher than 40%, and platelet count higher than 30 cells × 10^9/L. Patients had Child-Pugh classification A or B liver cirrhosis. Institutional Review Board approval and patient written informed consent were obtained routinely prior to performing MW ablation therapy.

Diagnostic criteria

The diagnosis of HCCs was based on the results of a percutaneous biopsy by using an 18-gauge needle in 43 patients for tumors (6 of them were well-differentiation, 18 were moderately differentiated, 1 was poorly differentiated HCC and 8 of them were HCC), and the characteristic enhancement pattern was depicted on contrast-enhanced multiphase helical CT, MRI or CEUS. Among primary liver cancer patients there are 107 patients with relevated serum tumor markers (α-fetoprotein level > 200 ng/mL [> 200 μg/L], from 216 to 10236 ng/mL). Among these patients, 127 patients had hepatitis B infection, 14 patients had hepatitis C infection, and 4 patients had both hepatitis B and hepatitis C infection. Among these patients, the severity of liver dysfunction was classified by Child-push classification as Child class A in 94 patients, Child class B in 74 patients and Child class C in two patients. These two cases of Child class C were treated and liver dysfunction was subsequently classified into Child class B. Twenty patients had a history of previous treatment with trans-catheter arterial chemoembolization (TACE) (n=19), RF ablation (n=4). Seventeen patients had a history of undergoing an operation on liver.

Microwave ablation

The commercially available MW ablation system (KY2000, Kangyou Medical, China) consists of a microwave generator, a flexible coaxial cable and a 20-cm long, 15-gauge cooled-shaft antenna. The generator is capable of producing 1-100 W of power at 2450 MHz, which can drive up to two antennae simultaneously. The antenna has a shaft coated with Teflon to prevent adhesion. The antenna was designed to minimize power feedback and provide optimal energy deposition into the tissue. Inside the antenna shaft, there are dual channels through which distilled water is circulated by a peristaltic pump, continuously cooling the shaft to prevent shaft overheating. The microwave machine is also equipped with a thermal monitoring system which can measure temperature in real time during ablation.

Surgical procedures

All treatments were performed at our institution under US (Sequoia 512 unit, Siemens Medical Solutions, Erlangen, Germany) guidance and under intravenous anesthesia in the operating room. Before treatment, a detailed protocol was worked out for each patient, which included the placement of the antennae, power output setting, emission time, and appropriate approach. In general, If the tumors are less than 2 cm in diameter, a single antenna was used; If tumors are 2 cm or larger, multiple antennae were required. After local anesthesia with 1% lidocaine, the microwave antenna was percutaneously inserted and placed at the designated places of the tumor under US guidance. The tip of antenna was at least 3 mm away from the gallbladder (perpendicular approach) and the body of antenna was at least 5 mm away from the gallbladder (parallel approach) according to antenna's thermal field effect. One or two 21-gauge ethanol needles were inserted and placed at the tumor periphery close to the gallbladder. A 20-gauge thermocouple was inserted proximal to the gallbladder allowing real-time temperature monitoring during MW ablation and prevention of thermal-mediated gallbladder injury. All insertions were performed by experienced radiologists who had more than ten years in MW ablation. After all insertions, intravenous anesthesia was administered by a combination of propofol and ketamine via a peripheral vein. During the procedure, vital signs were monitored continually. Power was applied from 40 watts and was increased to the maximum level 50-60 watts if the patient could tolerate the procedure with stable vital signs. The threshold of coagulation necrosis for thermal ablation is 60°C or 54°C for 3 min. To avoid thermal injury to gallbladder during ablation for the tumors, the temperature proximal to gallbladder was monitored by one or two 21-G thermal monitoring needles throughout the ablation procedure. If the temperature measured by the thermocouple reached 56°C, MW emission was stopped immediately and was restarted when the temperature became lower than 45°C. The total time of ablation add up to 300 seconds and this continued until the entire tumor was completely covered by the hyper-echoic micro-bubbles on grey-scale US. If the tumors are larger than 30 mm, antennae were first inserted into the deeper region of lesions. If the hyper-echoic region covered the deeper region of lesion on US after a series of microwave emission, antennae were withdrawn 5-10 mm and microwave emission was restarted and stopped until the hyper-echoic region covered the lesion along the axis of antennae, and/or antennae were re-inserted to the non-ablation tumor zone for another ablation. The treatment session was ended if the hyper-echoic region on gray-scale US covered the entire target region.

Follow-up

Contrast-enhanced sonography was performed one or two days after ablation to assess the completeness of the ablation and to detect the presence of immediate complications. If residual tumor was detected, a further session was performed to completely ablation. The follow-up period was calculated starting from the beginning of microwave ablation for all patients. All patients received contrast-enhanced CT or MRI examination one month after MW ablation and then at 3-6 months intervals. If the patients were not suitable for contrast agent of CT or MRI, a Contrast-enhanced Ultrasonography was performed. Therapeutic effectiveness was based on the result of contrast-enhanced imaging and serum tumor marker levels. A residual tumor which is incompletely ablated was defined as the presence of any remaining enhancing foci in the ablation zone as depicted on either contrast-enhanced sonography or other early follow-up contrast-enhanced imaging. Complications were identified by using clinical symptoms and imaging techniques. The complications include perforation, acute cholecystitis, bile duct stricture, biloma and skin burn. Side effects such as fever, pleural effusion and pain were also documented.

Statistical analysis

All statistical analyses were performed by using a software package (SPSS 19.0 for Windows; SPSS, Chicago, Ill). A difference with $P < 0.05$ was considered to be significant.

Results

All patients were successfully treated. There were no treatment-related deaths and no major complications such as cholecystitis or gallbladder perforation in the patients. There are 168 patients with HCCs. The maximum diameter of the tumors ranged (2.87±1.4) cm × (2.42±1.32) cm. The distance between the edge of the tumor and the gallbladder was measured as the shortest distance on an axial image or on an axial image on CT or MRI images reconstructed at 5-mm intervals (part at 1.5-mm intervals) and on US. 87 tumors were located < 0.5 cm from the gallbladder and 83 tumors

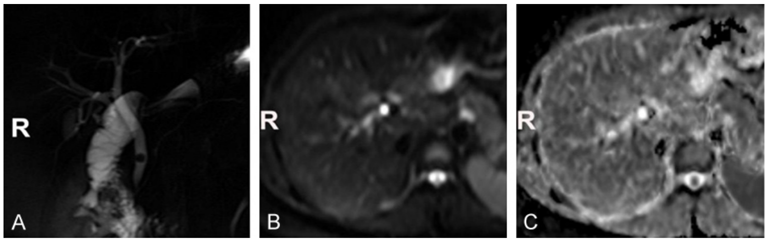

Figure 1. A 59-year-old female patient who had abdominal pain because of CBD stones. TBIL=108.8 μmol/L, DBIL=89.3 μmol/L, IBIL=19.5 μmol/L, ALT=330 U/L, AST=330 U/L, γ-GGT=127 U/L, ALP=128 U/L. A. MRCP shows that there was a stone in the lower segment of the common duct and bile duct in the liver didn't dilate significantly. B. DWI (b=800 s/mm^2) did not show significant hyper intensity by naked eyes; C. Apparent diffusion coefficient map show that signal intensity of liver parenchyma seems reduced diffusely. After ADC measurements, mean ADC values of eight segments: ADC_{mean}=1189 mm^2/s (Normal ADC > 1249 mm^2).

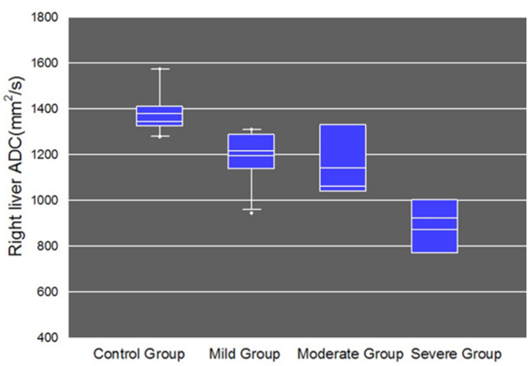

Figure 2. Box plots of the average liver ADC, control, mild, moderate and severe groups were statistically different, with the exception of the mild group vs. the moderate group.

were located 0.6-1.0 cm from the gallbladder, as illustrated in **Figure 1**. 49 tumors were located in liver segment IV, 71 tumors were located in liver segment V, 21 was located in liver segment VIII, 7 was located in other liver segment, 12 was between in liver two segments.

One session of MW ablation or combined with PEI was performed on the tumor adjacent to gallbladder in all patients. Two session of MW ablation or combined with PEI was performed in 18 patients with residuals. If there is still a residual which is depicted on contrast-enhanced sonography or CT, MR especially abut to gallbladder, PEI or other therapies were performed to incompletely treated patients (6 patients for PEI, and more therapy including 1 for TACE, 1 for liver transplantation, and 2 for liver resection). 0.5-6.8 mL ethanol (mean 2.4 mL, up to two needles per session and up to 4 mL per needle) was injected into the tumors in 162 patients. 1-8 mL absolute ethanol (mean 3.8 mL, up to two needles per session and up to 4 mL per needle) was injected into the residual in second session in 18 patients. Complete ablation was achieved in 96.5% (164/170). All patients were followed up regularly according to the protocol. During a median follow up of 30.1 months (range 4 to 68 months), no major complications occurred. 31 patients (18.5%, 31/168) died of progression of primary disease not directly attributable to MW ablation (**Figures 2** and **3**).

Local tumor progression was noted in 5 patients (3%, 5/164) completely ablated tumors during the follow-up period. More therapies were performed to local progressed tumors (3 patients for PEI, and 1 for TACE and 1 for liver resection).

The 1-, 3- and 5-year cumulative survival rates in primary liver cancer were 91.7%, 71.5% and 56.1%, respectively. There were no treatment-related deaths and no major complications such as cholecystitis or gallbladder perforation in the patients. After treatment, 24 patients experienced grade 1-3 pain at the puncture site according to the standardization of terms and reporting criteria for image-guided tumor ablation [23]. Severe abdominal pain that required the administration of analgesics was noted in 10 patients (6%). 32 patients (19%) had a fever of 37.5-39.8°C which persisted for 1-5 days. All patients were ordered antibiotics in the operation day. Nausea occurred in 76 patients (45.2%). Right side pleural effusion occurred in 7 (4.2%) patient as seen on sonography without therapy and disappeared on one-month follow-up US examination. The ablation zone was well defined on contrast-enhanced CT/MRI and contrast enhanced US and shrank gradually after ablation.

Discussion

In the past two decades, local thermal ablation has been widely performed in the therapy of liver tumors as a minimally invasive and effec-

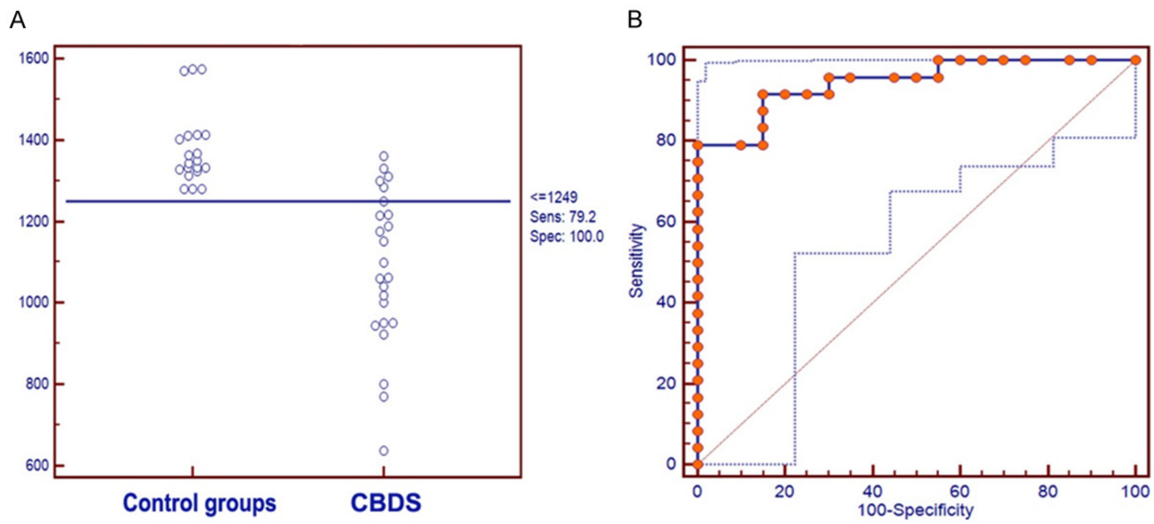

Figure 3. A. When the threshold was 1249 mm²/s, B. The maximum diagnostic value was obtained, AUC=0.945, sensitivity =79.1%, specificity =100%.

tive treatment measurement. However, tumors near special area such as the hepatic hilum, large vessels, gastrointestinal tract, gallbladder and diaphragm are considered to be difficult to treat completely under imaging guiding [18, 21, 24-26]. Thermal ablation for these tumors may result in incomplete necrosis or collateral damage to adjacent organs. Therefore, special precautions and strategies are needed to treat tumors in these dangerous locations.

Local RF ablation of liver tumors adjacent to gallbladder was a feasible and safe procedure, which is first reported by Chopra et al. [24]. More investigators of RF ablation of the feasibility and safety of liver tumors adjacent to gallbladder drew the same opinion [25-27]. Liang et al. argued that ultrasound-guided percutaneous cooled-tip MWA is effective and safe in treating patients with primary liver cancer with favorable local tumor control and long-term outcomes in a large-scale study [28].

In this clinical trial, percutaneous microwave ablation therapy to hepatocellular carcinoma with neither procedure-related death nor major complications, some minor complications in our study are like some RF ablation investigations. MW ablation of liver tumors adjacent to gallbladder was also a feasible and safe tactic as RF ablation strategy, for both of them are belong to thermal ablation. Ablation of tumors adjacent to the gallbladder is always accompanied by the risk of gallbladder perforation or acute cholecystitis. The main reason of thermal damage is temperature over the threshold of coagulation. Temperature can be used as a reliable indicator to reflect the pathologic changes of microwave ablation in liver cancers. In our study, a real-time peri-tumoral temperature monitoring was used as an indicator for avoiding thermal injury. Temperature monitoring is divided into two ways in our study: protective thermometry and therapeutic thermometry methods. In protective thermometry way, thermometric probe is put proximate to gallbladder to avoid thermal damage of adjacent organ which the temperature of marginal tissue of gallbladder lower than 56°C, while In therapeutic thermometry, thermometric probe is inserted into the marginal tissue of tumor to monitor the threshold temperature over than 60°C to guarantee the tumor coagulation. Our results-0% immediate and periprocedural complications-show that our procedure is safe in the therapy of tumors adjacent to gallbladder.

To avoid thermal damage to gallbladder, one study suggests that an aseptic solution was injected into the gallbladder fossa [21]; laparoscopic-assisted microwave ablation therapy was done after Laparoscopic cholecystectomy (LC) in another report [29]. Jiang Kai *et al.* reported five cases of HCC adjacent to different location of gallbladder were performed by Laparoscopy-assisted radiofrequency ablation without isolation or resection of gallbladder [30]. Elena Levit *et al.* reported that 6 patients underwent RFA combined with percutaneous bile aspiration from the gallbladder and four patients with additional hydrodissection to avoid gallbladder damage the gallbladder [31]. The combination of RF or MW ablation with PEI in the management of HCC in high-risk locations was more effective than RF ablation alone in some reports [22, 32].

In our study, PMW ablation combined with PEI was performed. Ethanol was injected slowly to ablate the tissue abut to gallbladder, at the same time microwave gave out to ablation, and would enlarge the coagulation zone by the diffusion of hot ethanol. If contrast enhanced US one or two days after treatment showed residual, a repeated PEI with or without MW ablation was performed until complete necrosis of the entire tumor was confirmed. If contrast enhanced imaging shows residual or neoplasm recurrence in other areas in the follow-up, another therapy was performed with MW ablation, PEI or TACE.

This study has some limitations. First, these data were obtained in two centers with extensive experience in microwave ablation for liver tumors. A multi-center study is required. Second, we used imaging and clinical symptoms as indicators of thermal injury of the gallbladder. Taken together, ultrasound-guided percutaneous microwave ablation combined with ethanol injection under a real-time temperature monitoring is a safe and effective treatment option to Hepatocellular carcinoma adjacent to the gallbladder.

Disclosure of conflict of interest

None.

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