Transcatheter arterial chemoembolization combined with simultaneous cone beam computed tomography-guided multipolar microwave ablation for massive hepatocellular carcinoma (>10 cm): Safety and primary clinical results

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\textbf{ABSTRACT}

\textbf{Purpose:} To explore the safety and clinical efficacy of transcatheter arterial chemoembolization (TACE) combined with simultaneous cone beam computed tomography (CBCT)-guided multipolar microwave ablation (MWA) in the treatment of massive hepatocellular carcinoma (HCC).

\textbf{Materials and methods:} Records of nine patients who underwent TACE combined with simultaneous CBCT-guided multipolar MWA for massive HCC, between January and June 2015, were retrospectively reviewed. Technical success rate, blood levels of liver function indicators, complications, and tumor response one month after treatment were investigated.

\textbf{Results:} The technical success rate of TACE combined with simultaneous MWA was 100%. The mean procedure time was 195.0 min (range, 125–350 min), the mean hospital stay after the treatment was 4.0 ± 1.0 days (range, 3–7 days), and no serious complications occurred. Minor complications were experienced by some patients but were relieved after conservative treatment. One month after treatment, enhanced CT revealed a complete response rate of 66.7% (6/9), a partial response rate of 22.2% (2/9), and a stable disease rate of 11.1% (1/9). Mild and reversible injury of liver function occurred in these patients.

\textbf{Conclusion:} TACE combined with simultaneous CBCT-guided MWA for massive HCC was feasible and safe, and yielded a high response rate.

\section*{Introduction}

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-associated death globally.\textsuperscript{1} Although surgical resection can provide long-term survival for patients with HCC, only 10%–30% of these patients are considered to be suitable candidates for resection due to tumor burden or liver function.\textsuperscript{2} An important factor influencing HCC treatment decisions is tumor size. Patients with tumors ≥5 cm are considered to be unsuitable for liver transplantation or thermal ablation due to limited effectiveness.\textsuperscript{3} Transarterial chemoembolization (TACE) is also considered to be ineffective for massive HCC (>10 cm), in which blood supply usually originates from several sites and makes super-selective embolization even more difficult.\textsuperscript{4} (see Fig. 1)

Many studies have demonstrated that TACE combined with radiofrequency ablation or microwave ablation (MWA) can yield better...
efficacy compared to any single treatment for large or massive HCC.\(^5\)–\(^7\) However, in these studies, combination treatment was usually not performed simultaneously, and often at intervals of up to 2–4 weeks.\(^5\)–\(^7\)

Advanced technologies, such as flat-panel detector digital subtraction angiography (DSA) with cone beam computed tomography (CBCT) were developed for interventional purposes. This technology integrates a cone-beam X-ray tube and a flat panel detector on the same C-arm gantry. In this configuration, both real-time fluoroscopy and CT-like imaging are available in one procedure. Therefore, researchers can combine TACE with radiofrequency ablation or MWA in treating HCC using this instrument and achieve more satisfactory outcomes.\(^8\)

Although this simultaneous combination is mostly used in HCCs ≤ 7 cm in size,\(^5\)–\(^7\) few—if any—studies have examined the effect of simultaneously combining TACE with multipolar ablation for massive HCCs (≥ 0 cm). Accordingly, this study aimed to explore the safety and effectiveness of combined therapy for treating massive HCCs > 10 cm in size.

Materials and methods

Patients

This retrospective study was approved by the institutional ethics committee, and informed written consent was obtained from all patients. Between June and October 2015, nine patients (8 male, 1 female; mean age, 56 years [range, 41–76 years]) (Table 1) with a total of 10 HCCs (mean diameter, 154 mm [range, 115–187 mm]) underwent 10 TACE procedures with simultaneous multipolar ablation (Allura Xper FD20, Philips Healthcare, The Netherlands) in the angiography suite.

Inclusion criteria were as follows: patients with diagnosis of HCC by biopsy or according to the American Association for the Study of Liver Diseases (AASLD) criteria;\(^3\) tumor diameter ≥ 10 cm, or multiple HCCs (≤3 lesions); unsuitable for ablation alone due to large tumor size, or unsuitable for TACE alone determined by the consulting physicians; and Child-Pugh class A or B.

Patients with HCC with extra hepatic metastases; cholangiocarcinomas; tumor thrombosis located in the portal vein III/IV branch (Vp classification), hepatic vein trunk, or inferior vena cava; high risk for thermal injury to the adjacent vessel or organs (tumor distance from gallbladder, intestine, and major blood vessel ≤ 1 cm); or severe coagulation dysfunction, such as prothrombin activity ≤ 40% or a platelet count ≤ 50 × 10^9/L, were excluded.

TACE procedure

All TACE and MWA procedures were performed by the same medical team. First, using a therapeutic angiography unit equipped with a digital flat-panel detector system (Allura Xper FD20, Philips Healthcare, Netherlands), TACE was performed according to the following protocol.

After local anesthesia was established, a 5Fr vascular sheath was inserted into the right femoral artery using the Seldinger technique. Arterial photography was performed to diagnose patency of the portal vein. Lipiodol (10 ml) were injected and a gelatin sponge was placed at the right hepatic lobe. Subsequently, four cycles of three-antenna microwave ablation under cone beam computed tomography guidance was performed in one session (C1 & C2). The ablation procedure lasted for 2 h, with ablation energy deposition lasting for 40 min. One month later, follow-up magnetic resonance imaging revealed total coagulation necrosis of the huge tumor, without injury to adjacent tissues (D). Follow-up arterial angiography revealed no clear tumor staining from the diaphragmatic artery (E1), superior mesenteric artery (E2), or hepatic artery (E3).

MWA procedure

MWA was performed immediately after TACE using the same therapeutic angiography unit. First, an unenhanced CBCT scan was performed during a breath hold. The tumor was clearly identified due to lipiodol deposition during TACE. The acquired images were transferred to a workstation on which navigation software (X-Per Guide, Philips Healthcare, Netherlands) was used to plan needle trajectory in three-

Table 1

| Age (years), mean ± SD | 56 ± 15 |
|-----------------------|--------|
| Sex                   |        |
| Male                  | 8      |
| Female                | 1      |
| Tumor diameter (mm), mean ± SD | 154 ± 28 |
| Tumor with portal branch invasion |        |
| Subsegmental branch | 1      |
| No                    | 8      |
| AFP level (ng/L)      |        |
| ≥400                  | 8      |
| <400                  | 1      |
| Child-Pugh class      |        |
| A                     | 7      |
| B                     | 2      |

Data presented as n unless otherwise indicated. AFP, alpha fetoprotein.
dimensional (3D) images. All ablations relied on multiple overlapping MWA technology in which 2–4 microwave antennas were parallel and equidistant around the center of the tumor. The interval distance from each needle was 4 cm. The number of microwave antennas depended on the size and the shape of the tumor. C-arm angulation was automatically calculated so that two different views of the electrode path were available—the first determined the entrypoint, and the second the progression of the needle. Under the entrypoint view, the skin entry point was located and marked using fluoroscopy. The C-arm was then positioned in the progress view. The needle was placed in the planned trajectory, while fluoroscopy was used to verify angulation of the needle. CBCT scans were performed to confirm puncture progression. Once the antennas were placed in the proper location along the planned trajectory, all MWA antennas were activated simultaneously. The power of MWA was set at 60 W, and each ablation procedure lasted 15 min. The position of the antennas was drawn back to a shallower portion of the tumor for additional ablation, if necessary, to induce complete tumor necrosis. 4 to 10 ablation positions were applied.

Patient radiation parameters, such as air kerma (AK) and dose area product (DAP), were collected manually after each DSA acquisition and CBCT scan during the procedure. AK is an estimate of the air kerma at the approximate entry point of the patient's skin and, is therefore, the best approximation of the patient's skin dose. DAP is a measure of the total X-ray energy output of the X-ray tube and, as such, is a good approximation of the total X-ray energy absorbed by the patient.

Follow up

Patients were strictly observed during the first 2 or 3 days after the procedure and during hospitalization. One month after combination treatment, an enhanced CT/MR scan was performed to evaluate treatment response, and therapeutic efficacy was assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Routine blood tests, including serum liver function tests and a-fetoprotein (AFP), were performed one month after treatment. A major complication was defined as any event that resulted in additional hospitalization or treatment; any other complication(s) were classified as minor. Contrast-enhanced spiral CT was used to assess treatment response.

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (SD) and compared using the Student's t-test; P < 0.05 was considered to be statistically significant. SPSS version 25.0 (IBM Corporation Armonk, NY, USA) was used for data analyses.

Results

Combined TACE/multipolar MWA therapy was well-tolerated in all patients, with a technical success rate of 100% (9/9). Total procedural AK was 678.5 mGy (range, 328–6425 mGy), in which the AK for TACE was 445.5 mGy (range, 108–5325 mGy) and 233.5 mGy for CBCT (range, 113–875 mGy). Total procedural DAP was 279.9 Gy cm² (range, 158.7–699.8 Gy cm²), in which DAP for TACE was 185.3 Gy cm² (range, 88.4–459.2 Gy cm²) and 94.5 Gy cm² for CBCT (range, 47.3–289.1 Gy cm²). The mean Xper CT scan duration was 4.5 ± 2.0 min. The mean procedure time was 195.0 min (range, 125–350 min). The mean hospital stay after treatment was 4.0 ± 1.0 days (range, 3–7 days).

One month after combination treatment, according to the mRECIST criteria, the complete tumor response rate was 66.7% (6/9), the partial response (PR) rate was 22.2% (2/9), and the stable disease rate was 11.1% (1/9). No peritoneal dialysis was required in any patients. Table 2 lists the main blood indicators of liver function before and one month after treatment. There were no significant differences between the two groups. Combination treatment led only to a mild and recoverable damage in liver function.

No major complications, such as procedure-related death, were observed, nor did any situation require prolonged hospitalization or extra treatment, or involve infection or liver failure. After therapy, 3 (33.3%) patients experienced postoperative pain (relieved by oral analgesic treatment), 5 (55.6%) experienced postoperative fever (maximum 38 °C), 2 (22.2%) exhibited right pleural effusion (without additional treatment), and 1 (23%) exhibited asymptomatic intrahepatic bile duct dilation.

Discussion

In this study, we simultaneously combined TACE with multiple antenna MWA to treat massive HCC and achieved a total response rate of 100%. Embolization of hepatic arterial flow around the tumor using TACE can reduce the heat sink effect. In addition, this technique shortened the time interval between the two treatments, thus avoiding the clearance of lipiodol and chemotherapeutics and the formation of new collateral vessels and vascular recanalization after embolization in the interval. Lipiodol deposition by TACE could also improve conduction of heat, and thermal ablation after TACE may maximize the heat conduction effect caused by the ablation method. Moreover, as a local therapy, TACE can assist in the detection of satellite tumors surrounding the zone of ablation-induced necrosis missed by imaging examination. Large tumor ablation requires simultaneous multi-applicator ablations to cover the entire tumor, meanwhile minimizing damage to healthy tissues. The needle tracks should avoid vulnerable anatomical structures. CBCT guidance is a new, emerging technique integrating real-time fluoroscopy and CT-like imaging in one device. This technology is safe, with no puncture-related complications occurring in our previous clinical practice. Images are acquired using a C-arm angiography system that rotates around the patient and enables quality similar to CT scanning. A C-arm system equipped with a large flat panel detector can acquire high-resolution images and has a large field of view. Soft-tissue scanning performed using a C-arm angiography system provides higher spatial resolution than that obtained by CT. Targets and needle pathways are planned on the basis of CT-like volumetric information, and the planning information can be displayed on a fluoroscopy screen. In addition, iodized oil deposition in the lesions after TACE is helpful to judge the extent of tumors. Using the fluoroscopic view, a real-time image for needle insertion into targeted hepatic lesions can be obtained. Recent advances in overlay technology have enabled the superimposition of fluoroscope and three-dimensional images obtained using a CBCT system with an integrated tracking and navigation system, enabling real-time, three-dimensional guidance during needle placement.

Radiation exposure to patients and physicians, however, remains a serious concern with TACE- or CBCT-guided ablations. Because the abdomen is often the thickest part of the body and exhibits a breathing motion, greater X-ray exposure is expected. However, although published data regarding patient radiation exposure in TACE or CBCT-guided ablations are limited, our results suggest that the majority of radiation exposure occurs during the TACE procedure. The RAD-IR study,

| Table 2: Liver function characteristics before and one month after treatment. |
|-----------------|-----------------|--------|
|                  | Before treatment | One month after treatment | P     |
| AST, U/L         | 65 ± 12         | 56 ± 14 | > 0.05 |
| ALT, U/L         | 53 ± 21         | 48 ± 17 | > 0.05 |
| TBIL, μmol/L     | 11 ± 3          | 12 ± 5  | > 0.05 |
| PLT, 10⁹/L       | 112 ± 21        | 132 ± 12| > 0.05 |
| Prothrombin activity, % | 60 ± 15    | 62 ± 16 | > 0.05 |
| ALB, g/L         | 36 ± 4          | 37 ± 6  | > 0.05 |

Data presented as mean ± standard deviation unless otherwise indicated. AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; ALB, albumin; TBIL, total bilirubin.
including 126 TACE cases, reported mean AK value of 1.4 Gy and DAP of 282 Gy cm².12 Furthermore, substantial radiation reduction in TACE has been reported using a novel low-dose, X-ray imaging technology.13 Using this technology, an AK value of 48.6% and a 50.3% DAP dose reduction in TACE procedure was achieved, and image quality was not impaired. This is beneficial to patients who undergo radiological interventions, particularly when undergoing repetitive treatments.

Based on our findings, simultaneous TACE with multipolar MWA appeared to be safe and reliable for the treatment of massive HCCs. No serious complications were observed, and only mild and recoverable injury to liver function occurred in these patients. In our opinion, this simultaneous combination treatment can create a large area of coagulation necrosis with thermal damage, and inflammatory reactive substances are not released in large quantities. Moreover, the inflammatory reaction is mild and recoverable.

Our study, however, had several limitations, the first of which was its retrospective, single-center design and the absence of comparative control groups. As such, a comparison of the effectiveness and safety between TACE combined MWA, TACE alone, and multi-antenna MWA alone procedures should be performed. Second, the sample size in the present study was small. Third, whether the chemotherapeutic drugs in TACE could influence the efficacy of the combination treatment remains unclear. Further studies comparing TACE and TAE in the combination treatment may provide clarification.

Conclusion

TACE combined with simultaneous CBCT-guided multi-antenna MWA is a safe and feasible treatment strategy for massive HCCs (>10 cm). Results of the present study demonstrated that this combination treatment achieved a high response rate for massive HCC. Parallel controlled studies with a larger sample size and longer follow-up periods may confirm the utility of this combined therapy in the clinic.

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Conflict of interest declaration

The authors report no conflicts of interest in this research.

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