Solitary huge hepatocellular carcinomas 10 cm or larger may be completely ablated by repeated radiofrequency ablation combined with chemoembolization: Initial experience with 9 patients

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Abstract. The treatment of solitary huge hepatocellular carcinoma (SHHCC) larger than 10 cm remains a challenge. The aim of the present study was to assess the therapeutic effects of repeated radiofrequency ablation (RFA) combined with chemoembolization on SHHCC. This was a retrospective study based on data obtained from a prospectively collected database that included 9 SHHCC patients who underwent repeated RFA combined with chemoembolization between July 2008 and June 2011. A new management strategy for SHHCC was described. The mean tumor size of the patients was 11.5±1.0 cm. No technical failure occurred, no patient succumbed to the disease during this treatment and the median survival of all 9 patients was 34 months. Treatment of the 9 tumors required a mean of 8.2±1.5 sessions. The mean of RF applications per session was 5.3±0.9 and the mean time of one session was 165±30 min, including a mean time of RF application of 113±19 min. The SHHCCs were found to be completely ablated. The mean number of RFA for primary complete ablation was 7.0±0.9 sessions, and the mean time for primary complete ablation was 5.3±1.1 months. The overall survival rate was 100%. There were 4 actual 2-year survivors. Our data reveal that tactically and strategically performed RFA should be recommended to SHHCC patients who are not suitable or do not agree to surgery, with satisfactory efficacy and safety.

Introduction

Hepatocellular carcinoma (HCC) remains one of the most common solid cancers worldwide (1). Small HCC has a relatively good prognosis; however, the majority of HCC tumors worldwide, and particularly in Asia, are medium- or large-sized. In China, many patients suffer from HCC ≥10 cm, owing to a lack of screening and awareness programs for early detection.

Generally, most HCCs ≥10 cm are of late stage, with intra- or extra-hepatic metastases and gross venous invasion. However, some of the HCCs of this size are of a specific subtype of HCC, with little or less invasive and metastatic risk, that grow expansively within an intact capsule or pseudocapsule (2). The HCC of this type is localized in tumor extent, although it is large in size and can be recognized as solitary huge HCC (SHHCC), for which complete eradication, and a high survival rate, is possible.

At present, the treatment of SHHCC remains a challenge. Hepatic resection appears to be the most widely accepted treatment for SHHCC, but the resection of such large-sized tumors is technically difficult and usually requires major hepatic resection, which is associated with a higher risk of operative mortality (3). Liver transplantation offers better chances of survival and an improved quality of life, however, patients with SHHCC are not suitable candidates for it. In patients with inoperable SHHCC, transarterial chemoembolization (TACE) is considered an alternative, but the response rates are generally poor and the 5-year survival rate is less than 20% (4). Sorafenib may improve survival in SHHCC, however, Sorafenib appears to function more as a disease stabilizer than as a cure (5).

Radiofrequency ablation (RFA) has become one of the most promising loco-regional therapies for the treatment of HCC. Traditionally, it has been restricted to the treatment of lesions ≤5 cm in size. However, there has been a rising trend in the use of repeated RFA for large HCC in many centers, with promising results (6-8). With the development of highly efficient RFA equipment and the experience that ensues from their use, RFA is likely to gain efficacy and play a pivotal role in the therapeutic management of SHHCC. The purpose of this study was to assess the feasibility, safety and efficacy of RFA therapy for the treatment of SHHCC; herein, we provide a discussion on the initial findings of this study.

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Patients and methods

Patients. Between July 2008 and June 2011, 9 patients with SHHCC underwent a combined treatment strategy with TACE and repeated RFA at the Hepatobiliary Surgery Department of Beijing Chaoyang Hospital, China. Approval from our institutional review board and written informed consent from all participants were obtained prior to treatment. Data were recorded in a computerized database by a single research assistant. We performed a retrospective study on these patients according to the following selection criteria: i) the patients were not amenable to or did not agree to surgery; ii) there were no prohibitive co-morbid medical conditions; iii) they had a favorable Child-Pugh Class (grade A plus selected grade B); iv) the tumor size was ≥10 cm; v) the tumor did not protrude from the liver surface; and vi) the tumor was solitary within an intact capsule or pseudocapsule with no gross venous invasion, obvious satellite lesion or extrahepatic metastasis on pre-treatment images.

The clinical and follow-up data of the 9 patients are shown in the Table I. There were 8 males and 1 female, and the mean age was 57 years of age. All 9 patients were positive for hepatitis B surface antigen and 7 of them had cirrhotic livers. The median follow-up for the 9 patients was 23 months. The mean tumor size in the entire cohort was 11.5±1.0 cm (range 10.2-13.5). The tumors were located mainly in the right liver lobe, with 6 tumors involving the left liver lobe.

Assessment of clinical and pathological diagnostic criteria. The clinical diagnosis of HCC in this study was based on the diagnostic criteria of typical HCC presentations on at least two of the medical imaging examinations [ultrasonography and/or CT and/or magnetic resonance imaging (MRI)] (9). Liver puncture biopsy was performed with a 17 gauge needle (Super-Core Biopsy Instrument; Medical Device Technologies, Gainesville, FL, USA) to obtain tumor tissues for pathological examination. All 9 patients were diagnosed with HCC. Seven of them were well-differentiated and the remaining 2 patients were well- to moderately differentiated.

Pre-treatment studies. The pre-treatment assessment of each patient included a complete history screening, physical examination, complete blood count, prothrombin time, α-fetoprotein, renal and liver function tests, electrocardiogram, chest X-ray, abdominal US and either spiral CT or MRI of the abdomen. Extra-hepatic metastasis (detected by brain, chest and pelvic cavity CT scan or total-body bone scintigraphy) was excluded from the study.

Management strategy for complete ablation. The staff team consisted of assigned hepatobiliary surgeons, anesthesiologists and radiologists. Percutaneous RFA (PRFA) was the preferred approach for HCC of this size. When tumor involved the hepatic dome, PRFA was safely and effectively performed with left single lung ventilation (10). PRFA was performed in CT suite and guided with a Synergy Plus CT scanner (GE Yokogawa Medical Systems Ltd., Tokyo, Japan). Patients were positioned supine on the CT table and intubated under intravenous anesthesia for respiratory control. Patients with HCC of non-specific site were under single-lumen endotracheal intubation (Mallinckrodt Medical, Athlone, Ireland), while patients with HCC involving the hepatic dome were under double-lumen endotracheal intubation (Mallinckrodt Medical) to allow for left single lung ventilation during the

Table I. Radiofrequency ablation (RFA) for solitary huge hepatocellular carcinoma ≥10 cm in diameter in 9 patients.

Patient	Age/gender	Greatest diameter of tumor (mm)	Tumor location	Child-Pugh class	α-fetoprotein	No. of RFA sessions	TACE (no.)	Complete ablation of tumor	Cell differentiation	LTP	DTP	Status/ follow-up (month)
1	50/M	135	V, VI, VII, VIII	B	Positive	11	1	Yes	Well	Yes	No	Alive/35
2	69/F	120	V, VI, VII, VIII	B	Positive	9	1	Yes	Well	Yes	No	Alive/31
3	55/M	118	V, VI, VII, VIII	A	Positive	8	1	Yes	Well to moderate	Yes	Yes	Alive/29
4	57/M	120	V, VI, VII, VIII	B	Positive	9	1	Yes	Well	Yes	No	Alive/25
5	52/M	115	V, VI, VII, VIII	B	Positive	9	1	Yes	Well	Yes	No	Alive/23
6	65/M	108	VII, VIII	B	Positive	6	1	Yes	Well	Yes	No	Alive/6
7	57/M	105	V, VI, VII, VIII	A	Positive	8	1	Yes	Well	No	No	Alive/11
8	48/M	110	V, VI, VII, VIII	A	Positive	6	2	Yes	Well	No	No	Alive/8
9	58/M	102	VII, VIII	A	Positive	8	1	Yes	Well to moderate	Yes	No	Alive/18

TACE, transarterial chemoembolization; LTP, local tumor progression; DTP, distant tumor progression.

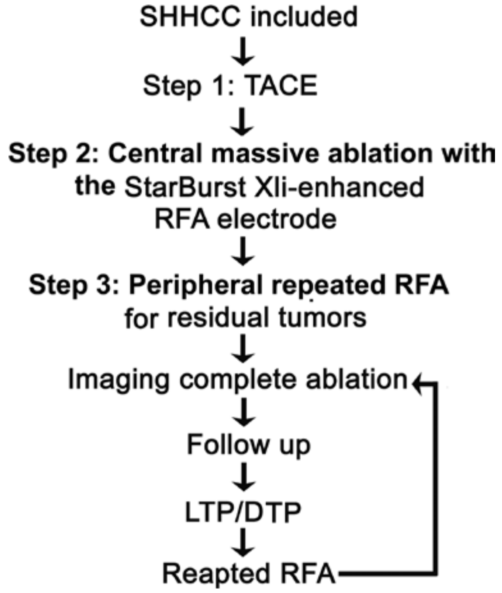

Figure 1. Schematic diagram of management strategies for SHHCC. TACE, transarterial chemoembolization; LTP, local tumor progression; DTP, distant tumor progression.

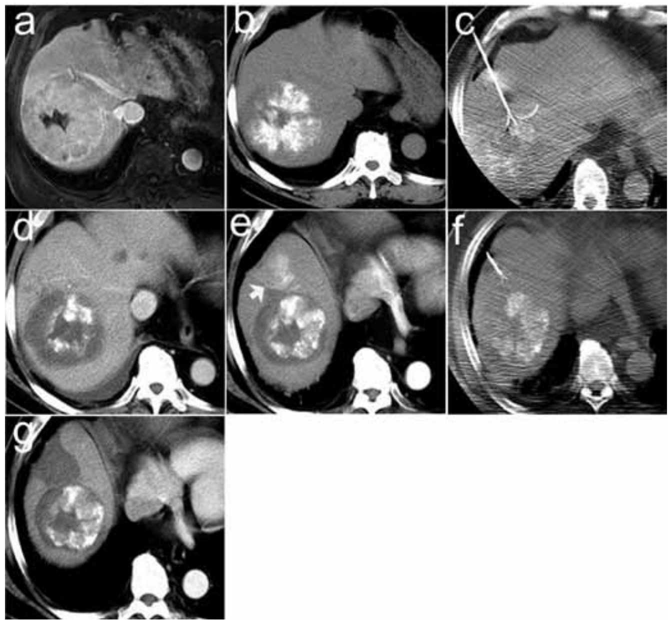

Figure 2. A selected case from this study. (a) MRI scan of the tumor prior to treatment; (b) CT scan of the tumor following TACE; (c) CT scan from the procedure of repeated RFA (central massive destruction with the StarBurst Xli-enhanced RFA electrode); (d) CT scan of the first complete ablation; (e) local tumor progression following initial complete ablation (white arrow); (f) peripheral ablation with StarBurst XL RFA electrode; (g) CT scan of the tumor at the end of this study (complete ablation was achieved).

procedure. Datex-Ohmeda Aestiva/5 ventilator (Datex-Ohmeda; GE Healthcare, Buckinghamshire, UK) was used to assist respiration. The optimal site of puncture and angle of insertion was calculated with CT. Insertion of the probe was carried out at end expiratory state (for patients under single-lumen endotracheal intubation).

The management strategy for complete ablation of SHHCC is schematically shown in Fig. 1.

Step 1: TACE pre-treatment. TACE was mainly used to decrease the tumor vascularity 3-4 weeks prior to RFA. TACE was performed through the femoral artery using the technique of Seldinger under local anesthesia (11) by injecting 10-15 ml of an emulsion of iodized oil (Lipiodol; Aulnay-Sous-Bois, France) and 20-40 mg of epirubicin hydrochloride (Zhejiang Haizheng, China) into the feeding arteries. The selected doses of iodized oil and anticancer drugs were based on the liver function and tumor size of each individual patient. Injection was discontinued upon full accumulation of iodized oil in the tumor vessels. No gelatin sponge was used after TACE in the present study. The feeding artery was embolized with an embolic coil when another TACE was not planned. TACE was performed by the same experienced interventional radiologist (K. Gao) and repeated as required.

Step 2: Central massive tumor ablation with the StarBurst Xli-enhanced RFA electrode. A StarBurst Xli-enhanced RFA electrode and a 250 W (maximal output power) RFA generator (Radiofrequency Interstitial Thermal Ablation Medical System, USA), which could create a maximal ablation zone of 7 cm in one application, were used in this study. When the electrode needle was inserted into the tumor and positioned satisfactorily, the generator was activated to achieve radiofrequency energy and maintain an average temperature of 105˚C. The electrode needles were pushed forward and unfolded gradually to 3, 4, 5, 6 and/or 7 cm until they reached the borders of the SHHCC, delivering RF energy for ~5 min for every intermediate step, until the output power dropped to <30 W in the final step of the procedure. In the RFA procedure, over-lapping ablations were performed, ranging from 4 to 7 per tumor (mean 5.3). Electrode track ablation technique was also performed to minimize post-procedural bleeding and tumor seeding.

Step 3: Peripheral residual tumor ablation with StarBurst XL RFA electrode. Following the massive ablation of the central tumor, there was usually residual tumor left in the peripheral area of the tumor (Fig. 2). For these lesions, repeated RFA was used to achieve imaging complete ablation with a RITA 1500 RFA system and a 15-gauge multitined electrode (Starburst XL; RITA Medical Systems, Manchester, GA, USA), which enabled the ablation of a 5-cm region by one application. The final number of repeated PRFA and the interval between two PRFAs was mainly determined by the post-treatment assessment.

Image analysis and post-treatment assessment. The interpretation of radiological studies was based on the consensus of two abdominal radiologists with 11 and 14 years of experience in abdominal radiology, respectively. The radiologists were aware of the clinical history of the patients. They compared the morphology and enhancement pattern of the treated lesions to the morphology and enhancement pattern of the lesions prior to treatment. Images were read on a PACS work-station (Centricity RA1000; GE Healthcare). The following tumor characteristics were analyzed directly from CT scans (n=8) or MRI (n=1): tumor size, tumor location and presence of blood vessels (first to third branches of the portal vein or first and second branches of the hepatic veins) within 5 mm from the border of the HCC. Tumor response to RFA was assessed by CT scan (n=8) or MRI (n=1) 2 weeks or 1 month after ablation, based on the patient's condition.

Ablation was considered to be complete when no enhancement was observed within the treated lesion. Any nodular or irregular enhancement during the arterial phase (corresponding to the target lesion) on post-ablation CT scan or MRI indicated incomplete tumor ablation. Local tumor progression (LTP) was defined as the appearance of nodular or irregular enhancement adjacent to the ablation zone, and distant intrahepatic tumor progression (DITP) was defined as the emergence of one or several tumor(s) not adjacent to the site of the initial ablation zone (12). If LTP or DITP were detected, patients were referred for additional session(s) of PRFA considering they still met the inclusion criteria. The number of applications and sessions, the amount of energy delivered per treatment, and the duration of the sessions and applications were recorded. The diagnosis and treatment procedures were repeated until no LTP or DITP were detected (Fig. 1). Clinical evaluation, including an α-fetoprotein assay, was performed every month for the first year and subsequently every 2 or 3 months.

Morbidity prior to RFA was broadly categorized into minor and major complications. Minor complications were defined as complications that could be treated conservatively or resolved with oral or intravenous medications without further intervention. Major complications required intensive care unit (ICU) stay, treatment by an interventional radiologist, surgical procedure, or resulted in mortality.

Statistical analysis. Data analyses in calculating the mean and median value of measurement were performed with SPSS 15.0.

Results

Technical success. No technical failure occurred. Treatment of the 9 tumors required a mean of 8.2±1.5 sessions. The mean of RF applications per session was 5.3±0.9 (range 4-7). The mean time of one session was 165±30 min (range 125-210), including a mean time of RF application of 113±19 min.

Primary effectiveness. All 9 tumors of SHHCC were completely ablated. Thus, the primary effectiveness of the management strategy for SHHCC was 100% (9 of 9). The mean number of RFA for primary complete ablation was 7.0±0.9 sessions and the mean time from the first RFA to complete ablation was 5.3±1.1 months.

Tumor progression and survival

Local tumor progression. Seven (77.8%) of the 9 patients developed LTP after initial complete ablation at CT in the follow-up period. One of the 7 patients developed LTP twice, at 2 and 7 months and the other six developed LTP once: 2 months after initial complete ablation in 3 cases, 4 months after initial complete ablation in 2 cases, and 5 months after initial complete ablation in 1 case. All of these instances of LTP were successfully treated with PRFA (Table I and Fig. 2).

Distant tumor progression. One of the 9 patients experienced distant tumor progression (DTP) within the follow-up period. Tumor metastasis to the right adrenal was found 15 months and DITP of the left hepatic lobe was found 21 months following initial complete ablation.

Survival. The patients were alive at the end of this study. The median survival of the SHHCC patients was 34 months. The overall survival rate was 100% (9 of 9). There were 4 actual 2-year survivors (Table I).

Complications

Major complications. One patient suffered from massive peritoneal hemorrhage immediately after her second RFA treatment. The patient recovered the following day with conservative therapy, including blood transfusion.

Minor complications. The patients experienced post-ablation syndrome, including fevers from 38 to 39˚C and general malaise that persisted for up to 1-2 weeks. No hepatic decompensation occurred. Within 72 h following the ablation, 2 (22%) of the 9 patients required a morphine injection to relieve post-procedural pain. The mean hospital stay per session was 10.0±2.6 days (range 7-14).

Discussion

Due to their numerous advantages that include definitive therapeutic effects, minimal invasiveness, repeatability, safety and a shorter period of hospitalization, various local ablative therapies, including RFA, are currently accepted as an alternative treatment option for HCC (13). Studies comparing the efficacy of surgery and local ablative therapies in small and medium-sized HCCs have clearly demonstrated that a well-performed local ablation yields similar survival rates and less morbidity compared to surgery (14-16). Therefore, it is generally recognized that RFA can be used as the first-line treatment for HCC ≤5 cm.

The emergence of new RFA electrodes, new equipment and the increase in clinical experience have led doctors to use RFA for the treatment of large HCC in selected cases, with promising preliminary results (12,17-19). SHHCC can be completely ablated using a well-designed strategy featured by repeated RFA. However, to the best of our knowledge, there the efficacy of RFA for SHHCC has yet to be reported.

The results of the treatment strategy used in the present study strongly support the possibility of complete ablation of SHHCC. This treatment strategy has two distinct characteristics: the combination of TACE and repeated RFA and the combination of high- and low-power RFA electrodes. Several studies (20-23) have demonstrated that pre-treatment of TACE/TAE prior to RFA may provide better local tumor control than RFA alone for the treatment of patients with medium-sized HCC (3.1-5 cm), presumably by either downsizing the tumor or decreasing the tumor vascularity. Compared to the conventional electrodes, the StarBurst Xli-enhanced RFA electrode used in the present study has a higher power output and longer times covering a wider scope; it can create an ablation zone of up to 7 cm in one application and is thus capable of greater ablation of SHHCC. Nevertheless, the StarBurst Xli-enhanced RFA electrode has its limitations, mainly, that it is not suitable for ablation of the peripheral area of SHHCC. The conventional 'small' electrode was selected in the present study to clear the residual tumor in the peripheral area following the central massive ablation. It is highly encouraging that 9 out of 9 (100%) of the SHHCC cases were completely ablated in our study using this strategy. It is, therefore, reasonable to expect that with the development of new RFA devices as well as with the accumulation of more experience, treatment of patients suffering from SHHCC is likely to progressively become even simpler.

Repetition is clearly the major advantage of RFA, particularly PRFA treatment, which has been proven to be effective for treating HCC nodules of various sizes (24). Nevertheless, there are at least two underlying theoretical issues related to repeated use of RFA that require further evaluation. The first issue is the risk of rapid progression of the residual tumor, due to the low target temperature, as we have experimentally demonstrated before (25). In this study, we observed that repeated RFA did not increase the possibility of intrahepatic or extrahepatic metastasis and the risk of rapid progression. We postulate that the main reason is the relatively benign biological behavior of the SHHCC. The second issue is whether the repetition of RFA further enhances the antitumor immunity on the basis of the first RFA-induced elevation of antitumor immunity (26-28). Further experimental study is required to clarify this.

Despite the limited sample of patients used, our results have essentially shown the potential of RFA therapy for patients with SHHCC, who are not responsive to or do not agree with surgery. Tactically and strategically performed RFA should be recommended to these patients as the first option, with satisfactory efficacy and safety.

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