

## RESEARCH ARTICLE

# Clinical Application of Transcatheter Arterial Chemoembolization Combined with Synchronous C-arm Cone-Beam CT Guided Radiofrequency Ablation in treatment of Large Hepatocellular Carcinoma

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### Abstract

**Objective:** This work aimed to evaluate the safety and clinical efficacy of transcatheter arterial chemoembolization (TACE) combined with c-arm cone-beam CT guided synchronous radiofrequency ablation (RFA) in treatment of large hepatocellular carcinoma (HCC). **Methods:** 21 patients with large HCC were studied from January 2010 to March 2012. TACE combined with synchronous C-arm cone-beam CT guided RFA were performed on a total of 25 lesions. Conventional imaging examination (CEUS, enhanced CT or MRI) and AFP detection were regularly conducted to evaluate the technical success rate of combined treatment, complications, treatment response, time without disease recurrence and survival rate. **Results:** The technical success rate of combined treatment was 100%, without any significant complication. After 1 month, there were 19 cases with complete response and 2 cases with partial response, with an complete response rate of 90.4% (19/21) and a clinical effective rate of 100% (21/21). The complete response rates of single nodular lesions (100%, 17/17) was significantly higher than that of multiple nodular lesions (50%, 2/4) ( $P < 0.05$ ). During 2 to 28 months of follow-up, in 19 cases with complete response, the average time without disease recurrence was  $10.8 \pm 6$  months. The total survival rates of 6, 12 and 18 months in 21 patients were 100%, respectively. **Conclusion:** TACE combined with synchronous C-arm CT guided RFA is safe and effective for treatment of large HCC. The treatment efficacy for single nodular lesion is better than that for multiple nodular lesions.

**Keywords:** Large HCC - chemoembolization - radiofrequency ablation - C-arm cone-beam CT - synchronous

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### Introduction

Hepatocellular carcinoma (HCC) is the sixth major malignant tumor in the world and the third tumor leading to deaths. Only 10-54% of patients with HCC are suitable to surgery (Marín-Hargreaves et al., 2003; Takaki et al., 2009; Forner et al., 2012). Transcatheter arterial chemoembolization (TACE) is one of the main measures for treatment of unresectable HCC. However, the low necrosis rate of local tumor after TACE is an important factor leading to tumor recurrence and metastasis and affecting the long-term postoperative efficacy (Georgiades et al., 2008; Takaki et al., 2009; Miyayama et al., 2010; Forner et al., 2012). In addition, tumor size is also one of important factors affecting TACE efficacy and prognosis. The inactivation ability and efficacy of TACE are significantly reduced for large HCC with diameter more than 5 cm (Yamakado et al., 2002; Fan et al., 2011). Compared with simple TACE, combination of TACE and radiofrequency ablation (RFA) can improve the treatment

efficacy for large HCC and long-term survival rate of patients (Yamakado et al., 2002; Wang et al., 2010; Fan et al., 2011). However, RFA is often performed between 1st to 2nd week after TACE, and ultrasound and CT are the main guidance methods (Veltri et al., 2006; Takaki et al., 2009; Yamakado et al., 2010). Application of TACE combined with C-arm CT guided synchronous RFA to treatment of unresectable large HCC or huge HCC has not been reported. In this paper, a retrospective study on 21 patients with large HCC from January 2010 to March 2012 was conducted, and the safety and preliminary clinical efficacy of combined treatment in treatment of large HCC were evaluated.

### Materials and Methods

#### General data

21 patients (general data were shown in Table 1) in Department of interventional radiology of General Hospital of Chinese People's Liberation Army, China were

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**Table 1. General Data of Patients Before TACE Combined with Synchronous RFA**

Index		Number or value
Age	Range	38-67
	Average	48.3±9.4
Gender	Male	17 (81%)
	Female	4 (19%)
Child-Pugh grade	A	16 (76%)
	B	5 (24%)
Disease cause	Hepatitis B	14 (67%)
	Hepatitis C	5 (23%)
	Combination of hepatitis B and hepatitis C	2 (10%)
AFP	≤ 20 ng/mL	8 (38%)
	> 20 ng/mL	13 (62%)
Lesion site	Subphrenic	9 (43%)
	Non-subphrenic	16 (57%)
Maximum diameter	5-10 cm	16 (57%)
	> 10 cm	9 (43%)
Number of lesions	1	17
	2	4
Previous TACE	1 time	10
	2 times	6
	3 times	3
	4 times	2

studied from January 2010 to March 2012. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Chinese PLA General Hospital. Written informed consent was obtained from all participants.

The consents were obtained from all patients. According to HCC diagnostic standard from National Liver Cancer Research Association, all patients were diagnosed with primary HCC by B ultrasound, CT, MRI and AFP detection or pathological examination, and they accepted treatment by combination of TACE and synchronous C-arm guided RFA.

Inclusion criteria for treatment with combined therapy technology were as follows: (1) less than 3 intrahepatic lesions by B ultrasound, CT, MRI and angiography, with maximum tumor diameter of 5 cm, no surgical indication or refusing surgery; (2) grade A or B liver function (Child-Pugh grading). The exclusion criteria were as follows: (1) cancer embolus in main portal vein or left or right branch, arteriovenous fistula, biliary invasion, extrahepatic metastasis; (2) severe coagulation disorders (prothrombin activity < 40%, blood platelet < 30×10<sup>9</sup>/L). The distances from lesion for RFA to gall bladder, intestinal canal, bile duct, important great vessel were not less than 1 cm, respectively. Before combined treatment, routine examination, laboratory tests (routine blood, liver and renal function, electrolyte, blood coagulation, serum, and tumor marker) and related examinations (liver CT, B ultrasound or MRI, lung CT scanning, skull CT scanning, bone CT scanning) were conducted on all patients. The maximum diameter of lesion in CT or MRI was used as the diameter of tumor.

#### TACE

All interventional procedure were performed by interventional radiologist with 8-10 years of experience INNOVA4100 IQ (GE Corp. USA) were used for TACE

procedure. After access to right femoral artery with standard seldinger technique, the angiography of celiac artery and superior mesenteric artery with 4F-RH catheter (Terumo Medical Corp., Tokyo, Japan) was conducted, respectively as well as selective hepatic arteriography when necessary. Superselective catheterization with 3F Progreat® microcatheter (Terumo Medical Corp., Tokyo, Japan) into tumor feeding artery was conducted. Intraprocedure drugs were as follows: epirubicin (30-50 mg, EPI Pfizer Inc., New York, USA), cisplatin (40-60 mg, Qiru Pharmaceutical Co. Ltd., Shangdong, China) or oxaliplatin (100-150 mg, Hengrui Medicine Co., Ltd., Jiangsu, China), mitomycin (10-14 mg, MMC Hisun Pharmaceutical Co., Ltd., Zhejiang, China), 5-FU (500-750 mg, Xudong Haipu Pharmaceutical Co., Ltd., Shanghai, China), calcium folinate and HCPT (200-300 mg, 10-14 mg, respectively, Hanfan Pharmaceutical Co., Ltd., Guizhou, China). 3-4 kinds of above drugs were used for chemoembolization. Powder drugs were mixed with iodized oil (Guerbet Inc., Villepinte, France). Liquid drugs were directly infused to the target vessels. When small portal vein branched were visualized or the blood flow was significantly reduced after embolization with iodized oil emulsion, gelatin sponge particles were used for embolization. For larger lesions with abnormally abundant blood vessel, PVA particles (500-700 μm, COOK Inc., USA) were used for combined embolization. The embolization was also conducted on collateral arteries supplying to target lesions.

#### C-arm cone-beam guided CT synchronous RF ablation Establishment of 3D-CT image

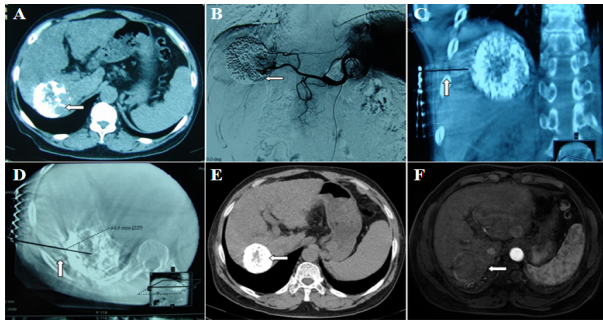
After TACE, C-arm cone-beam CT guided percutaneous transhepatic RFA was immediately performed under general anesthesia using INNOVA4100 IQ angiography machine with 3D-CT navigation function. A square metal grid (6×6, 1cm) was parallelly placed posteroinferior to right 8-10 costal margin or ensisternum, for 3D-CT scanning and image reconstruction of target lesions (Figure 1 A-D). The puncture point on body surface and route to target lesion were determined avoiding ribs and important organs (intestine canal, gall bladder, lung). Under bull's-eye view, the puncture angle and probe insertion depth were determined. Finally, the automatically adjusting system of angiography machine was initiated to adjust the puncture angle.

#### Puncture and positioning under fluoroscopy

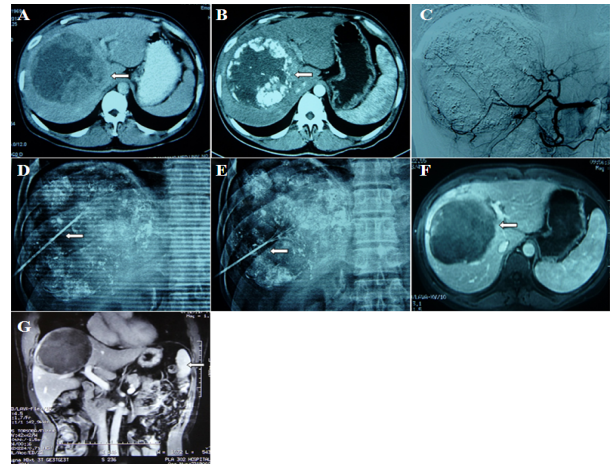
The puncture of target lesion with RFA probe was conducted under bull's-eye view. The activity performance of target lesion appeared after the RFA probe touched target lesion. When the RFA needle reached the proper position, the multi-polar radiofrequency was opened, and angiography machine tube was rotated to left and right by 70 to 90 degrees to confirm RFA probe was in target lesion (Figure 2 A-E).

#### RFA parameters

RFA parameters were determined according to tumor location, size and shape. As all cases in this study were with large HCC, multi-polar RFA needle (RITA Medical



**Figure 1. Male, 60 Years Old, Primary HCC.** After first interventional therapy, CT reexamination showed intrahepatic residual lesion. So TACE combined with synchronous DSA-CT guided RFA was conducted. A, liver CT plain scanning after first interventional therapy: partial intrahepatic iodized oil deposition (←). B, angiography before RFA: intrahepatic iodized oil deposition, schistose staining in and around tumor (←). C/D, sagittal and cross-sectional reconstruction by INNOVA4100 IQ angiography machine with DSA-CT function for establishing puncture route and angle (↑). E/F, liver CT plain scanning at the 23rd month after combined treatment: good intrahepatic iodized oil deposition, no arterial blood supply (←).



**Figure 2. Male, 42 Years Old, Poorly Differentiated HCC (AFP, 345 ug/mL).** After first interventional therapy, CT reexamination showed intrahepatic residual lesion. So TACE combined with RFA was conducted. A, liver CT plain scanning before first interventional therapy: huge occupying lesion with hypervascularity in right liver lobe (←). B, liver CT plain scanning after interventional therapy: intrahepatic iodized oil deposition around tumor, enhanced residual lesion (←). C, TACE before RFA: residual tumor staining in and around lesion. D/E, RFA (two multi-polar needles, maximum ablation diameter of 5 cm) after TACE for lesion involving diaphragmatic dome, with puncture avoiding lung tissue (←). F/G, reexamination at the 15th month after combined treatment: good control of lesion, no recurrence (←).

Systems Inc., Fremont, USA) was used. The parameters were as follows: maximum ablation diameter, 5 cm; length, 15-25 cm; power, 150-200 w; ablation time, 6 min for 3 cm ablation diameter, 8 min for 4 cm diameter, 15 min for 5 cm diameter; ablation temperature, 105 oC. Two times of RFA were conducted for conventional lesions, with three times of RFA when necessary. After ablation, the solidification was conducted to avoid bleeding and tumor implantation and metastasis in probe tract.

#### Postprocedure treatment and follow-up

Postprocedure ECG monitoring was performed for 24 h, with continued local pressurization and use of analgesia pump for 3 days. At the same time, anti-infection, hydration, hepatoprotection, nutritional supporting and purgation were conducted. The routine blood, liver and renal function and electrolyte were reexamined between the 3rd and 7th postprocedure day. After 1 month, CT, B ultrasound or enhanced MRI examination, and blood, liver and renal function, tumor marker (AFP, CA199, CEA) detection were performed. For patients with good control of tumor, the reexamination was conducted once for every 2 to 3 months. All image data were read by radiologists with 8 years of experience.

According to method from European Association for the Study of the Liver (EASL) (Bruix et al., 2001), the evaluation criteria of combined treatment for local tumor were as follows: (1) Complete response (CR). There was no enhanced lesion manifestation within and around tumor. (2) Partial response (PR). The range of measurable lesion enhancement region was reduced by more than 50%. (3) Progressive disease (PD). New lesions appeared or the range of measurable lesion enhancement region was increased by more than 25%. (4) Stable Disease (SD). The efficacy was between PR and SD. During follow-up, the inactivation rate of local tumor, inactivation duration, local tumor necrosis characteristics and survival status of patients were evaluated.

The treatment modality (single RFA, single TACE

or combination of RFA and TACE) were determined according to characteristics of emerging or residual lesions. The definition to main complications is bleeding or injury in intestinal canal, bile duct and gall bladder. The minor complication definition is postprocedure liver and kidney function change and pain.

#### Statistical analysis

Quantitative data were statistically analyzed using CHISS2004 statistical software. t-test was used to compare the preprocedure and preprocedure liver function (Child-Pugh grading), and chi-square test was performed to analyze the treatment efficacy for target tumor.

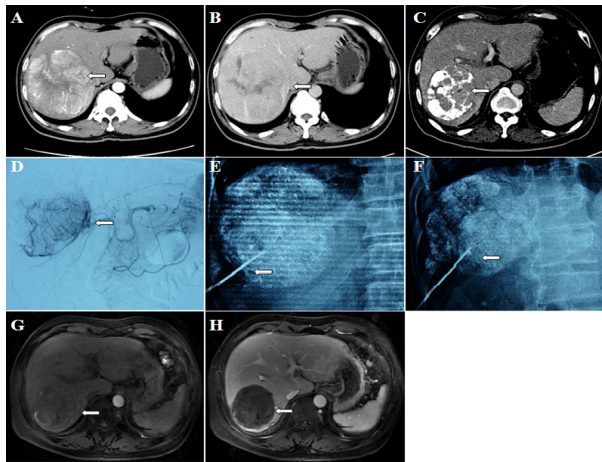
## Results

#### Technical success and clinical efficacy

All patients could tolerate the combined treatment. In TACE procedure, 25 previously confirmed lesions were successfully marked by iodized oil deposition. All RFA needles successfully entered the target lesions for each puncture. There were totally 60 times of puncture, with 2-3 times of puncture. The technical success rate of combined treatment was 100%. For 9 cases with subphrenic lesions, RFA was performed by puncture avoiding normal lung tissue under fluoroscopy. Conventional imaging examination (CEUS, enhanced CT or MRI) and AFP detection were performed at 1st postoperative month for evaluation of clinical efficacy. Results showed that coagulation necrosis was the main feature of local lesion necrosis. In 13 patients with preprocedure increased AFP level, the preprocedure AFP level was significantly

**Table 2. Inactivation Abilities of Combined Treatment on Different Types of Lesion (n)**

Lesion type	CR	PR	Total
Single nodular lesion	17	0	17
Multiple nodular lesions	2	2	4
Total	19	2	21



**Figure 3. Male, 53 Years Old, Large HCC with Huge Occupying Lesion in Right Liver Lobe, Recurrence after Three Times of TACE.** TACE combined with DSA-CT guided RFA was conducted. A/B, huge occupying lesion with hypervascularity in right liver lobe (←). C/D, new lesions around iodized oil after three times of TACE (←). E/F, the lesion was successfully marked. The multi-polar needle was rotated to left and right by 70 degrees to determine whether it was in lesion (←). G/H, MRI reexamination at the 13th month after combined treatment: good control of lesion, no recurrence (←).

decreased. As shown in Table 2 and Figure 1, 2, 3, in 21 patients, there were 19 cases with CR and 2 cases with PR, with complete response rate of 90.4% (19/21) and clinical effective rate of 100%. The complete response rate of single nodular lesion (100%, 17/17) was significantly higher than that of multiple nodular lesions (50%, 2/4) ( $P < 0.05$ ). During 2 to 28 months of follow-up, in 19 cases with CR, the average time without disease recurrence was  $10.8 \pm 6$  months. The overall survival rate of 6, 12 and 18 months in 21 patients were 100%, respectively.

#### Postprocedure complications

There was no major complication of TACE or RFA in 21 patients. In 19 patients, after treated with continuous infusion of fentanyl mixture by analgesic pump, the pain was completely relieved. For other 2 cases, on base of using analgesic pump, morphine was intravenously injected within 24 h. From the 4th postprocedure day, all patients were treated by oral administration of central analgesics drugs (e.g. oxycodone hydrochloride), and could tolerate the pain. There were 8 cases with different degrees of constipation, 10 cases with different degrees of fever ( $37.3 - 38.5^\circ\text{C}$ ), 5 cases with nausea or vomiting. After treatments, all these complications were alleviated. On the 3rd postprocedure day, ALT ( $203.2 \pm 65.4$  U/L) and AST ( $228.1 \pm 10.4$  U/L) in all patients transiently increased, compared with postprocedure ALT ( $28.7 \pm 10.8$  U/L), AST ( $30.7 \pm 9.8$  U/L) level ( $P = 0.00$ ). On the 7th postoperative day, ALT and AST level were decreased to

$30.8 \pm 13.5$  U/L,  $33.8 \pm 14.5$  U/L, respectively, which were not significantly different with postprocedure levels ( $P = 0.32$ ). There was no significant difference of bilirubin and albumin between before and after treatment.

#### Discussion

Tumor diameter and size and inactivation ability are important factors affecting the short- and medium-term recurrence of local lesion and long-term survival rate for patients (Yamakado et al., 2002; Marín-Hargreaves et al., 2003; Takaki et al., 2007; Georgiades et al., 2008; Takaki et al., 2009; Miyayama et al., 2010; Wang et al., 2010; Fan et al., 2011; Forner et al., 2012). At present, surgical treatment is the preferred means for large and huge HCC. However, this method has deficiencies such as great operation difficulty massive bleeding, postoperative complications and high recurrence rate (Zangos et al., 2007; Shimada et al., 2008). Other commonly used non-surgical methods including TACE and RFA are applied in treatment of large HCC. However, with increase of tumor diameter, either single TACE or RFA has certain limit for complete inactivation of local large lesion (Zangos et al., 2007; Takaki et al., 2009; Miyayama et al., 2010). In this study, 21 patients have been treated with TACE for 1 to 4 times before combined treatment, but the reexamination still finds the tumor residual or surrounding neonatal tumor. This indicates that, single technique is difficult to completely inactivate large HCC, with high postoperative recurrence rate.

TACE combined with RFA has been proved as one of the main measures for improving inactivation rate of local tumor, reducing the short- and long-term recurrence rate and prolonging patients' survival time (Yamakado et al., 2002; Zangos et al., 2007; Georgiades et al., 2008; Kang et al., 2009; Takaki et al., 2009; Miyayama et al., 2010; Wang et al., 2010; Yamakado et al., 2010; Fan et al., 2011). However, the interval between TACE and RFA is more than 1 week, with the longest 2 weeks. Due to long interval, the recanalization, collateral formation, and clearance of iodine oil chemotherapy agent may appear after TACE. So this is not a strict real-time synchronous combination treatment, and the synergism between TACE and RFA has not been fully exerted.

Immediately synchronous RFA after TACE can enhance the synergism between them, and improve the inactivation ability for local tumor less than 5 cm (Gadaleta et al., 2009; Kang et al., 2009). The mechanism may be as follows: (1) Enhancement of synergism between TACE and RFA. Incomplete inactivation of local lesion around tumor is the important factor leading to tumor recurrence in single TACE and RFA. Synchronous RFA after TACE can form a dense inclusion for lesion with iodized oil, especially for peripheral lesions. So the inactivation effect of on surrounding tumor tissue can be exerted for reducing the residual and recurrence of peripheral lesions (Shiraishi et al., 2008; Takaki et al., 2009). (2) Improvement of synergism between chemotherapy drugs and RFA. In TACE, iodized oil is used as the therapeutic drug carrier, and its drug carrying function is uncontrollable and instable, with no sustained

slowly-releasing ability with high concentration. If it is not combined with other embolic agents such as sponge, the chemotherapy drug in iodized oil will soon be cleared with time prolonging. Immediately synchronous RFA after TACE can exert the maximum tumor-killing effect with the highest concentration of chemotherapy drugs such as doxorubicin in and around lesion (Head et al., 2010; Renumathy et al., 2010). (3) TACE can accurately locate and mark the new and residual lesion and lesion which ordinary CT and B ultrasound cannot display by iodized oil deposition, leading to more definite targets for RFA. For complex lesions with multiple times of TACE (previous necrotic lesion, new lesion or residual lesion), the marking role of iodized oil deposition is more obvious (Lee et al., 2009; Lee et al., 2011).

In this study, after treated with TACE combined with synchronous RFA, good preliminary efficacy is obtained in 21 patients with large HCC. Compared with single TACE, the inactivation rate in combined treatment is increased, with significantly prolonged time without disease recurrence (Miyayama et al., 2010). The local treatment response of TACE combined with synchronous RFA is similar with asynchronous (traditional) combined treatment, but the total survival rate of recent 12 months in the former is significantly prolonged, indicating the potential value of synchronous combined treatment (Kim et al., 2006). In addition, the inactivation rate for single nodular lesion by combined treatment is higher than that for multiple nodular lesions. This may be related with tumor biological characteristics. Single nodular lesion is more sensitive to combined treatment compared with multiple nodular lesions (Zangos et al., 2007; Shimada et al., 2008).

At present, RFA on liver tumor is often conducted mainly under ultrasound guidance, which has advantage of convenient operation, low cost, real-time display of multidimensional dynamic image, with no radioactivity. However, B ultrasound guidance still has some deficiencies. For larger lesions with multiple overlapping ablations, the high-strength echo micro bubbles generated by previous lesion ablation often affect the positioning accuracy of next ablation needle. For specific lesion sites such as diaphragmatic dome and left lateral lobe, ultrasound guided RFA is often difficult to be performed. In addition, the depositions of iodized oil and chemotherapy drugs after TACE can also affect the boundary between tumor tissue and surrounding normal liver tissue, which changes the ultrasound visibility and affects the localization of target lesion. CT guided RFA is also used for combined treatment of liver tumors after TACE. However, the high dose radiation of real-time CT (60 times of traditional angiography machine) has important influences on health of patients and operators, especially in repeated ablation. In addition, the target lesion location time by CT is longer than B ultrasound and traditional angiography. For diaphragmatic dome lesions which require avoiding thoracic approach, CT guided RFA is often difficult and trivial, with risk of pneumothorax by direct transthoracic approach, in which 18 to 40% of patients require surgical drainage.

Compared with traditional CT and B ultrasound

guidance, real-time c-arm cone beam CT guided RFA has advantages as follows: (1) The parameters such as needle path and angle are established by CT image reconstruction in angiography machine, avoiding important organs such as lung, intestine and gall bladder. (2) RFA can be performed on special sites such as diaphragmatic dome and left lobe. In this study, for 9 patients with subphrenic lesions, RFA is successfully conducted by one puncture, avoiding occurrence of serious complications such as pleural effusion, hemothorax, and pneumothorax. (3) Compared with CT guidance or CT fluoroscopy alone, c-arm cone beam CT guidance can obtain higher positioning accuracy, and reduce the damage of ray on body, without interference after iodized oil embolization compared with B ultrasound. And DSA and c-arm cone beam CT guidance can make synchronous combined therap possible in one catheter room.

In TACE combined with synchronous RFA, the incidence of all kinds of complication is 4-6%, with less serious complication (Gadaleta et al., 2009; Kang et al., 2009; Takaki et al., 2009; Lee et al., 2011). Kang et al. (2009) find that, after treatment by TACE combined with synchronous RFA, there are 2 cases with severe liver function damage and 1 case with hepatic artery rupture and hemorrhage. In this study, there is no serious postoperative complication, with only different degrees of embolization syndromes such as pain and fever, constipation, and transient liver dysfunction, which may be related to absorption of necrotic tumor, persistent use of analgesic drugs, and combined treatment, respectively. All complications are relieved after proper treatment. As synchronous TACE and RFA may increase the pain in patients, RFA is conducted under conventional general anesthesia and tracheal intubation after TACE, and postoperative analgesia pump is used for 3 days. For cases with tumor necrosis, coagulation necrosis is the main feature of lesion after combined treatment, with no appearance of liquefaction necrosis due to single TACE or RFA, thus avoiding occurrence of secondary local liver abscess (Kim et al., 2006).

This study is a retrospective research with small sample size, which may have a certain influence on experimental results. In addition, due to short-term follow-up, the long-term efficacy should be further evaluated by collecting more cases and conducting comparative study. In summary, TACE combined with synchronous C-arm cone beam CT guided RFA is safe and effective for treatment of large HCC. The treatment efficacy for single nodular lesion is better than that for multiple nodular lesions.

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