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Comparative study of several microinvasive treatments for large hepatocellular carcinoma

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Abstract. – OBJECTIVE: To study the prognosis of large hepatocellular carcinoma after interventinal radiology and to compare the efficacy of different microinvasive treatments.

PATIENTS AND METHODS: The clinical data of 46 large hepatocellular carcinoma patients confirmed by clinical treatment or pathological examination were retrospectively analyzed. Patients were divided into two groups (TACE+RFA n=23 cases, and Combination group n=23 cases), according to the treatments method. two groups were followed up for 5-48 months. Survival was estimated using the Kaplan-Meier method and the survival curve was compared by log-rank test.

RESULTS: Median follow-up time was 33 months in both groups. The median survival time in Combination group (n=41 months) was significantly longer than TACE+RFA group (n=33 months) (p = 0.052). Median progress-free survival (PFS) is 10 months in Combination group and 8 months in TACE+RFA group. The difference was statistically significant (p = 0.023). The tumor inhibition rate was 82.6% and 52.2%, respectively and the difference was statistically significant (p = 0.028). The overall survival rate at I, 2 and 3 years was 100%, 95.7% and 55.8% respectively in Combination group was higher than TACE+RFA group at 91.3%, 55.8% and 38.3% respectively. The difference was not statistically significant.

CONCLUSIONS: For large hepatocellular carcinoma, combined method was superior to TACE+RFA and comprehensive treatment can improve the local-control rate.

Key Words:
Liver neoplasm, Radiofrequency ablation, Radiography, Interventional.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in China, ranking the third in mortality rate following gastric cancer and lung cancer[1-4]. For the patients with tumor diameter ≥ 3 cm, and which cannot be surgically removed due to the number of lesions, tumor location, and vascular invasion, the comprehensive minimally invasive interventional treatment became the optimal therapy. Currently, the combination of transhepatic arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are the main modality for the patients with unresectable tumors[3-7]. Due to the irregular liver lesions or adjacent to liver capsule, diaphragm, gallbladder or important blood vessels, tumor ablation is still not complete and, then, causes tumor relapse or distant metastasis. Therefore, to further improve the tumor local control rate of HCC with large tumor size becomes the key issue. At present, sequential application of various methods of minimally invasive techniques is promising, but lack randomized controlled clinical trials. In this study, we enrolled 46 patients diagnosed with HCC and the tumor diameter 3-9 cm between August 2009 and September 2011, and compared their clinical outcome.

Patients and Methods

General Information

Iodide [^{131}I] tumor cells' nuclei anti-TNF rcMAb injection combined with radiofrequency ablation, radioactive particles implantation combined with radiofrequency ablation were discussed and approved by the Ethics Committee of the Hospital, and were performed under the surveillance of the Ethics Committee. Informed consents were obtained from all the patients before interventional procedure.

Forty-six patients diagnosed with HCC admitted to our hospital from August 2009 to September 2011 were enrolled in this study. Referring to the diagnostic criteria of HCC[8], eight patients were diagnosed by liver biopsy. The enrollment criteria

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were as follows: (1) if a definite diagnosis of HCC was made by clinical or pathological data; (2) HCC stages are Barcelona Clinic Liver Cancer (BCLC) B and C, when lesion diameter is larger than 3 cm and; (3) those who had not received radio-, chemo-therapy, or molecule targeted therapy within 1 week of the treatment. The excluding criteria were: (1) pregnant or breastfeeding women, or women of childbearing age who were planning for pregnancy, (2) with HCC of BCLC stage A or D, (3) patients allergic to iodine, and/or anti-TNF antibody, (4) those with $< 4.0 \times 10^9$/L white blood cells and $< 80 \times 10^9$/L platelets counts, (5) those who had previously been treated with murine antibody, (6) with acute or chronic infection, (7) with thyroid dysfunction, (8) or with a history or ongoing psychiatric disorders.

A total of 46 patients meeting the requirements were enrolled (40 male, 6 female), aged 42-75 years (median age: 60.5 years). Forty patients had the history of hepatitis B but 6 patients did not. There were 29 patients with serum alpha-fetoprotein (AFP) < 400 μg/L, and 17 patients with ≥ 400 μg/L, There were 35 cases of A level Child-Pugh and 11 cases of B level Child-Pugh as well as 25 cases of tumor single lesion, and 21 cases of multiple lesions. There were 28 patients with tumors of diameter < 5 cm (the sum of the largest diameter of all tumors) and 18 cases with ≥ 5 cm diameter. The grades of combination group and TACE+RFA group are 84.78 ± 12.01 and 85.22 ± 10.38, pain scores are 4.35 ± 1.49 and 4.04 ± 2.12. No statistical differences were observed between these two groups in all aspects (Table I).

Radiopharmaceuticals

[^{131}I]-chTNT was provided by Shanghai Meien Biotechnology Co. Ltd. Recombinant chimeric antibody, chTNT was produced by genetic engineering using chloramines-T method to mark end product. Specific activity was 370 mBq/mg, radiochemical purity was > 95%, immunocompetence was > 50%, pH 7.0, and antibody passed qualification check without asepsis and heat source. The dosage of 131I -chTNT-1/B (Shanghai Meien Biotechnology Co, Ltd., Shanghai, China) accepted by patients was 0.56 mCi/Kg, total dose was 50 mci, while the dosage in the later period for 7 patients was 60 mCi. The precautions were taken for the treatment of 12 patients and they were taking compound oral potassium iodide solution, 10 drops (3 times/day), 3 days before the treatment, and until 7 days after the treatment to block the thyroid gland and reduce damage to it. In order to avoid allergic reaction, intramuscular injection of dexamethasone (5 mg) and phenergan (25 mg) was given before the treatment.

Radioactive iodine particle, ^{125}I was provided by Tianjin Saide Bio-Pharmaceutical Co. Ltd. The dosage of single particle was 0.8 mCi.

Interventional Procedure

The operation was divided into combination group and TACE+ RFA group according to the interventional procedure method used. TACE+ RFA was adopted in the control group. While in combination group, patients were given [^{131}I]-chTNT injection (n=12) or radioactive particles implantation (n=11) after TACE+ RFA treatment.

Table I. General information of 46 hepatocellular carcinoma patients.

		Combination group	TACE+RFA group	t-value	*p*-value
Age	<60 years	16	11	2.242	0.134
	≥60 years	7	12		
Gender	male	21	19	0.192	0.662
	female	2	4		
Hepatitis background	yes	21	19	0.192	0.662
	no	2	4		
Tumor diameter	<5cm	13	15	0.365	0.546
	≥5cm	10	8		
Tumor number	single	13	12	0.088	0.767
	multiple	10	11		
Child-Pugh classification	A	18	17	0.119	0.73
	B	5	6		
Fetoprotein ng/ml	<400	14	15	0.093	0.76
	≥400	9	8		
KPS grade	standard deviaition	84.78 ± 12.01	85.22 ± 10.38	-0.131	0.896
Pain grade	standard deviaition	4.35 ± 1.49	4.04 ± 2.12	0.562	0.577

Before RFA, all patients were treated with TACE. Radiofrequency ablation was adopted after 1-2 times of TACE according to the imaging results. Patients in the combined group were treated with other treatments on the RFA day or 1-2 weeks after ablation on the basis of patients' preference.

TACE was adopted Seldinger method from femoral artery puncture. At first the arteriography of celiac artery and mesenteric artery was selected to understand the tumor blood supply. It was followed by the use of superselective microcatheter to find the tumor feeding artery. FUDR (floxuridine: 750-1000 mg), Oxaliplatin (100-150 mg) were slowly injected after superselective, then Pirarubicin (20-40 mg) and ultra liquid Iodized Oil 10-20 ml was fully emulsified into a suspension to embolize the feeding arteries under the surveillance of digital subtraction angiography (DSA), and 350-560 microns Gelatin sponge particles (Hang zhou Ailikang Company) were used to those whose blood supply was sufficient for the artery embolization. TACE operation was applied again after the interval of 4-6 weeks.

Radiofrequency ablation group adopted RITA 1500 X radiofrequency generator (RITA Medical Systems, Angio Dynamics Inc., Queensbury, NY, USA) in 3-7 days after TACE. Before local anesthesia, CT scanning was performed to determine the punctuation site, angle, and direction. Ablation needle was then introduced after local anesthesia. For most of the patients, an ablation needle with the ablation zone of 5 cm was used, while ablation needle with the ablation zone of 7 cm was used only for patients with lesion size > 6 cm. MRI checks are done in 0.5-1 month after RFA, and ablation was given again so as to achieve complete ablation of survived lesions.

[^{131}I]-chTNT (Shanghai Meien Biotechnology Co. Ltd.) injection (total dosage, 50-60 mCi) was given for more than 10 min through the side hole of the ablation needle after the completion of ablation.

Radioactive particles implantation was performed 1-2 weeks after ablation, and the treatment time was arranged according to the patients' physical condition and test results. ^{125}I radionics implantation was used on those who were not satisfied with RFA or mass region of approaching vessels, gallbladder, diaphragmatic dome and liver marginal region. Abdominal CT scan were arranged before treatment and the tumor contours outlined. The number of the particles implanted and the activity through radioactive particles implantation plan (three dimensional treatment planning system, TPS) as well as the position of the needle path, and the angle under the CT guide were determined. ^{125}I was implanted according to TPS plan system, and the distance between single particles was within 0.8-1.5 cm.

Observation Target

Symptomatic treatment was done for normal liver protection after interventional procedure. Function of thyroid, liver, renal, blood, and urine were checked 1 week and 1 month post procedure. For patients injected with [^{131}I]-chTNT, a SPECT body scan was taken after 3-5 days, and 1-2 months of procedure to observe the distribution of [^{131}I]-chTNT. One month after operation, enhanced liver CT or MRI was performed to review the treatment effect. The evaluation criteria of imaging mass as "viable tumor" was the evaluated object as proposed by AASLD, which is modified RECIST criteria (mRECIST)[9].

Imaging was carried out every 2-3 months to detect tumor recurrence, until the lesion was developed or if the patient had died. The end point observation of survival period without progress is the enlarged scope of new lesions or portal vein thrombosis, which appeared after this treatment. If the patients had new lesions, they were treated with TACE or again with radiofrequency ablation therapy.

Statistical Analysis

SPSS16.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data for comparison of clinical indicators between the two groups. For related indicators, before and after the treatment, the paired *t* test or the rank sum test was used. Overall survival was analyzed by Kaplan-Meier method. *p* value of < 0.05 was considered significant.

Results

Postoperative Complications: Twelve patients of the two groups felt severe pain due to the lesions that were adjacent to envelop. Three of them received intravenous infusion of Fentanyl as they could not bear the pain while others completed the radiofrequency ablation after the proper reduction of RF temperature. Six patients were presented with right shoulder reflex pain. Three patients appeared to have hemoperitoneum after RFA. Whereas, one case appeared to have Glisson's capsule hematocele, and the

Table II. Comparison of treatment on tumor remission between two groups.

Group	n	CR	PR	SD	PD	RR%
Combination group	23	3	16	4	0	82.6
TACE+RFA group	23	2	10	9	2	52.2

Note: $p = 0.028$, Partial response (PR) = Remission rate (RR), together complete response (CR) + partial response (PR). Stable disease (SD); progression disease (PD)

diameter was 3 cm, the vital signs were stable. A large number of liquid pneumothorax appeared in the right pleural of one patient after RFA. This patient had difficulty breathing after RFA, but got better after catheter drainage. Two patients appeared to have aseptic necrosis of the tumor after TACE+ RFA, as local pumping fluid could not culture the bacteria. Two patients had nausea and vomiting after local radioactive particles, but were not given any special treatment. Most of the patients seemed to have fever and pain after intervertional radiology but for a short time. All patients felt better after 15 days of RFA (Table II).

From a total of 46 patients with hepatocellular cancer, 11 cases were with multiple lesions in the TACE + RFA group and others had single lesion. The diameter of lesions in all patients was 3.0-8.9 cm. There was lesser lipiodol deposition in multiple lesions and complete ablation after 1-2 times. For 6-9 cm lesions, 7 cm diameter ablation needle was adopted. Six patients accepted RFA two times. Among 10 cases of multiple lesions in the combination group, the diameter of a single lesion was 2.6-7.7 cm. Two cases accepted RFA twice and 3 cases accepted radionics implantation twice (Figure 1).

Survival analysis: The last follow-up was on October 30th 2013. The median follow-up time was 33 months. The median survival time was 41 months in the combination group, and 33 months in the TACE + RFA group (Figure 2). The overall median survival time of combination group was longer than the TACE + RFA group ($p = 0.052$). The median PFS time was 8 months in the TACE + RFA group, and the median survival period was 10 months in the combination treatment group. Difference in PFS time was statistically significant between these two groups ($p = 0.023$, Figure 3). Tumor remission rate in combination group was 82.6%, and 52.2% in RF group which is statistically significant ($p = 0.028$, Table III). The survival rate in the first, second and third year in these two groups was 100%, 95.7%, 55.8% and 91.3%, 75.2%, 38.3% respectively showing no statisti-

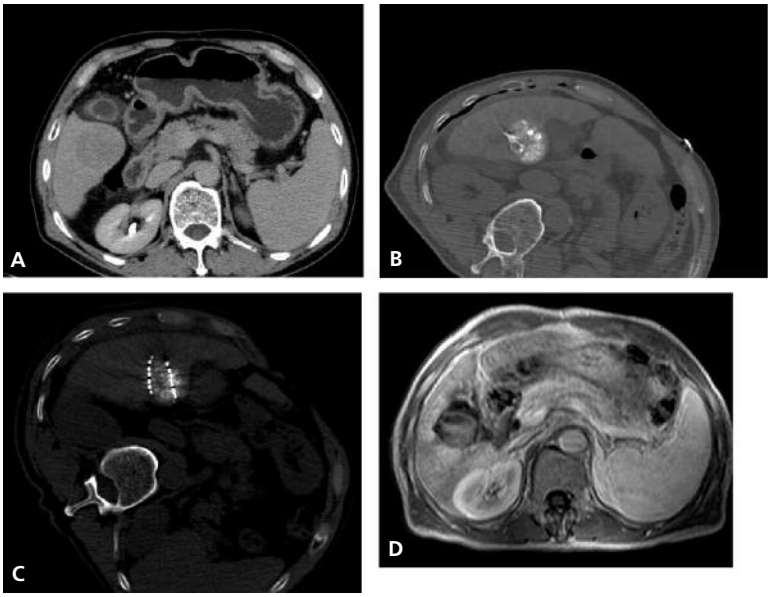

Figure 1. ***(A-D) A,*** 2011.1. CT right liver low-density mass. ***B,*** 2011.2. RF ablation was given 1 month after TACE treatment. ***C,*** 2011.3. Due to mass being close to envelop, ablation is not complete, radionics implantation. ***D,*** 2013.09 liver MRI review, complete lesions necrosis

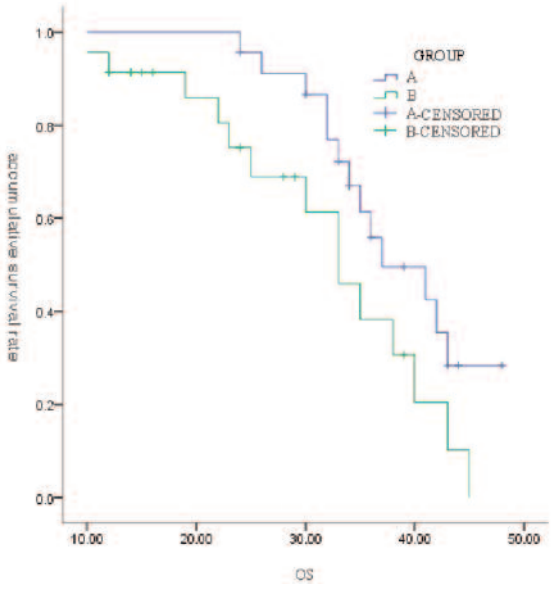

Figure 2. Kafllan-Meier overall survival curves of the patients in 2 groups. ***A,*** Combination group; ***B,*** TACE + RFA group.

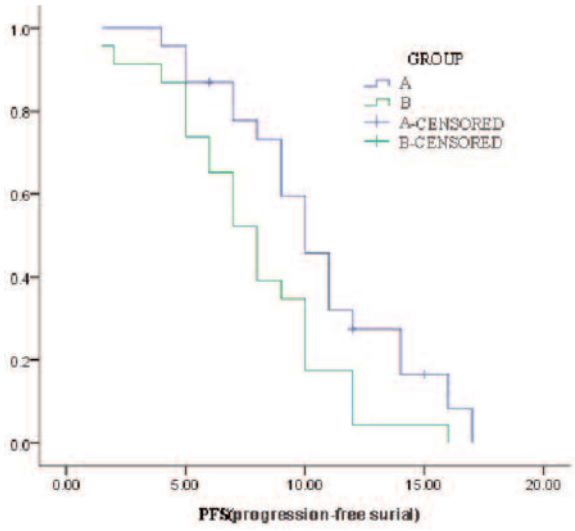

Figure 3. Kafllan-Meier progression-free survival curves of the patients in 2 groups, ***A,*** Combination group; ***B,*** TACE + RFA group.

cal significance. No recurrence was seen in five patients during the follow up time whereas other patients were able to accept the treatment again according to the previous process after the emergence of new lesions.

Security Analysis of [^{131}I]-chTNT Treatment: This study observed the changes in blood indicator, liver function, thyroid function in 12 cases after [^{131}I]-chTNT treatment for 7 days. No significant decrease was seen in erythrocytes and platelets before and after the operation, but the leukocyte index was slightly higher but not statistically significant, ALT, AST increased significantly but TBIL increased only slightly after the procedure. Compared to the preoperative, the difference between ALT and AST showed statistical significance, but the difference in TBIL was not statistically significant (Table IV). After the antiviral treatment to protect liver, ALT, AST, and TBIL were back to the preoperative levels 30 days post procedure.

After 1 week of treatment, the thyroid function (T3, T4, TSH, FT3, FT4) in this group of patients showed no significant change compared to the preoperative levels (Table V), thus, showing that the thyroid function is well protected during this treatment. In one patient thyroid dysfunction did not appear after operation even when the treatment was withdrawn for two days without doctors' advice.

[^{131}I]-chTNT patients were examined by ECT after 3 or 5 days and 1 month of injection. Significant concentrations of [^{131}I]-chTNT was observed in liver tumors, which showed that the radiation was still concentrated in the tumor area (Figure 4).

Table III. Changes in KPS grades of two groups before and after the treatment

Group	KPS grades		NRS pain score	
	Pre-operation	Post-operation	Pre-operation	Post-operation
Combination group (n=23)	84.78 ± 12.01	95.22 ± 5.93*§	4.35 ± 1.49	1.13 ± 0.86
TACE+RFA group (n=23)	85.22 ± 10.38	89.57 ± 8.77	4.04 ± 2.12	1.87 ± 1.25
t-value	-0.131	2.558	0.562	-2.323
p-value	0.896	0.014	0.577	0.025

Comparison between the two groups $^{*}t$ test of independent sample, comparison within the groups $^{\S}t$ test of paired sample, $p < 0.05$

Table IV. Effect on blood, and liver function before and after the treatment.

	Pre-operation	Post-operation	Z-value	*p*-value
WBC	4.3 (2.8,5.9)	6 (3.7,7.9)	-2.752	0.006
RBC	3.6 (2.58,3.89)	3.36 (2.43,3.91)	-1.181	0.238
PLT	86 (43,133)	121 (44.5,194)	-1.068	0.285
ALT	31 (20,92)	100 (60,111.5)	-1.604	0.109
AST	41 (27,46)	60 (50.5,102)	-2.268	0.023
TBil	19 (13.15 30.35)	21.9 (19.9,40.5)	-1.334	0.182
DBil	9.6 (4.55,17.85)	9 (6.3,22.2)	-1.02	0.308
TBA	31.7 (6.45,73.9)	20.6 (8.6,58.1)	-0.471	0.638

Table V. Thyroid function of the patients in the combination group.

	T3	T4	TSH	FT3	FT4
Pre-operation	0.852 ± 0.213	7.253 ± 1.407	1.063 (0.794,1.961)	2.289 ± 0.358	1.260 ± 0.268
Post-operation	0.863 ± 0.187	7.473 ± 2.424	1.379 (1.172,1.689)	2.158 ± 0.645	1.147 ± 0.345
t-value	-0.139	-0.305	(Z-value)-0.784	0.638	1.115
p-value	0.892	0.766	0.433	0.536	0.288

Discussion

For tumor of more than 3.0 cm in size or multi-center HCC, surgical resection rate is low. The treatment mainly relies on interventional comprehensive therapy. The one of the most important means of interventional comprehensive treatment is TACE. TACE is the best choice of palliative treatment for inoperable liver cancer patients[1,11-13]. But TACE alone cannot completely treat larger tumor lesions, with residual tumor and higher relapse rate. Especially cirrhosis is increased, liver function is damaged, VEGF is increased, and it is easy to be transferred many times after intervention. Many local minimally invasive treatments have been recently developed, including RFA, percutaneous intratumoral ethanol, intratumoral frozen ablation, radioactive particles implantation, etc. Various methods inactivate tumor area, which is limited to a certain range and reach therapeutic purpose via different mechanisms. Absolute alcohol is the cheapest treat-

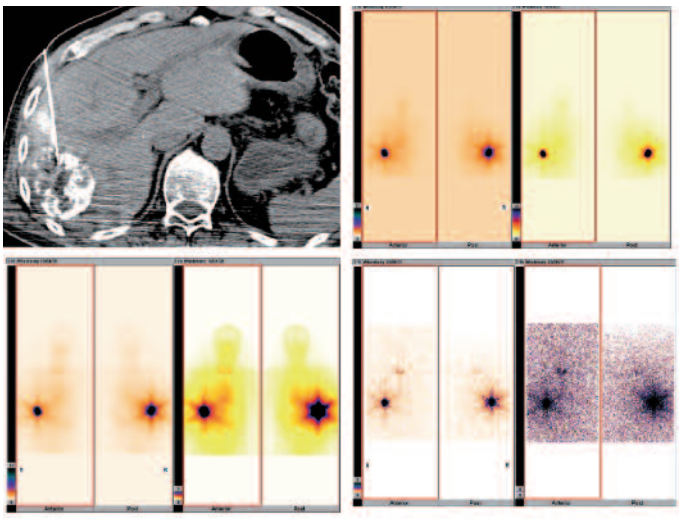

Figure 4. A, patient with liver cancer, two times radiofrequency ablation + [131I]-chTNT injection after TACE operation, 1 day (Figure b), 3 days (Figure c), 57 days (Figure d) after operation. Liver ECT shows that there are still drug concentrations in the lesions, and the concentration was the highest on the third day.

ment. It was used to apply to small HCC. Ming et al[14] found that only 12% of patients appeared to show partial progress in a short term, but for the 3.1-5.0 cm of tumors, 56% of patients showed progress, but obvious deficiencies for the treatment of large HCC. RFA is the main local ablation mean to cure HCC. It has formed a consensus for small HCC This group adopts RFA ablation for HCC with more than 3.0 cm lesion and remission rate is only 52.2%. The median PFS time is 8 month because of the single- point radiofrequency ablation is difficult to achieve complete ablation, especially for tumor diameter over 5.0 cm as reported earlier[15-17]. Many specialists have attempted to change the ablation technique, such as the multi-pin multi-point plan of polyhedral geometric model, multi-needle combination bipolar RFA ablation, etc.[15,16]. Although partial results were achieved, but overall results are still not satisfactory.

For tumors more than 3.0-5.0 cm, faced with so many minimally invasive treatments, how to achieve sequential, effective application and standardized, individualized unification of treatment program so as to get a better prognosis is still the main issue of clinical studies. As one of the key means of non- surgical removal of HCC, TACE has obvious shortcomings. Many research article shave adopted combination therapy and achieved better results[18-21]. But for larger lesions or mass with irregular border, or near the liver envelop, vascular, diaphragmatic dome or other hazardous areas, radiofrequency ablation is not complete and is, therefore, difficult to improve the prognosis of these patients. This study explored a new sequential therapy mode. Taking into account the small ablation range of absolute alcohol,we combined radiotherapy with TACE+RFA. in the early stage, we used radiation immune therapy, [^{131}I]-chTNT injections. [^{131}I]-chTNT injection can get specifically concentrated into necrotic tissue. After TACE and RFA significantly increased tumor necrosis, eventually leading to the effect of "gangrene-like" of the whole tumor, which greatly improved targetingchTNT-1/B to tumor tissue[22]. The purpose of the expansion of the lesion ablation, especially of hazardous area is to play a remedial role on inadequate ablation. According to our ECT follow-up results, medicinal effect on the tumor lasts longer after local injection. Smaller dose seems to have less effect after injection in this group. it still needs further studies to find out the relation between tumor size and the dose of drug. Later we adopted radioactive seeds implantation due to patients' affordability and protection. The intensity of ^{125}I particles used is weak, in order to avoid damaging liver caused by high-dose of radiation, it works on proliferative tumor cells sensitive to radiation (G2→M phase) to destroy the reproductive capacity of tumor[23]. Blood supply to tumor disappeared after TACE and RFA. ^{125}I particles play a role in killing new vessels in peripheral part, which effectively improved the local control rate and survival rate.

Previously, we showed that [^{131}I]-chTNT was safe to apply for HCC. Our data showed that the number of white blood cells was slightly increased 7days after the injection of [^{131}I]-chTNT. It may be related to the injection of immune drug after tumor necrosis. In the follow-up period, white blood cells did not show any abnormal change. ALT and AST were significantly increased compared to the preoperative, which could be related to RFA and drug injury, but can return to normal after the treatment of liver. It is important that the drug is accumulated in the tumor after injection, which is important to kill the effect of disease and confirmed by ECT follow-up after operation. The only deficiency is that it demands high protection after injection, and the drug costs are high, so it is challenging to provide this treatment.

Studies have shown that the time of PFS combination therapy is 10 months, and tumor remission rate is significantly improved, and reached to 82.6% in three of 16 CR and PR cases during the long term follow-up period, which is significantly higher than the rate of 52.2% in TACE + RFA group. These indicators have a statistical significance, and reflect that the combination of different treatments have advantage in local tumor control. In terms of median survival time, although combination group has no statistical significance, it was extended to 8 months compared to TACE+RFA group. As for the control study between [^{131}I]-chTNT and radionics implantation, we could not take further control due to fewer samples. We think radioactive seeds treatment is more valuable from the cost of operation, security management after operation, and convenience to implement. We did not make in-depth study about the best time of sequential therapy by using a variety of minimally invasive techniques.

We would like to underline that a small number of patients were enrolled. Also the follow-up indicator about the evaluation of efficacy is not

comprehensive which may cause analysis deviation. Followed by retrospective data analysis, although two groups' analysis is unbiased, it causes a certain imbalance to the final results. Thus, it still needs to be carried out in a large sample size and a strict designed multi-center randomized control study.

Conclusions

For tumor diameter not less than 3.0 cm, we should adopt to microinvasive sequential treatments. It has advantages in tumor progression-free survival, tumor remission rate, and fewer side effects. It is one of the best choices for the treatment of large HCC, but it still needs further research on sequential treatment time of several microinvasive treatments.

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Conflict of Interest disclosure

Authors declare no conflict of interest and make no disclosures.

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