Original Article

Classification of hepatocellular carcinoma diameter by statistical technology and prognostic evaluation in patients after the combined use of transarterial chemoembolization and radiofrequency ablation

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ABSTRACT

Objective: This study aimed to classify hepatocellular carcinomas (HCCs) according to their diameter using statistic technology and evaluate the prognosis of the classified groups after the combined use of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA).

Materials and Methods: Electronic medical records of 128 consecutive patients who underwent TACE-RFA as the initial treatment for HCC from January 2010 to April 2018 were retrospectively analyzed. TACE was initially performed with subsequent RFA performed after 3–7 days. The decision tree model was used to classify overall survival (OS), progression-free survival (PFS), local recurrence rate (LRR), and treatment complications in HCC.

Results: The tumors were divided into three groups of sizes ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm. The group of tumors >4.8 cm showed inferior OS, PFS, and LRR than the other two groups ($P < 0.05$) on long-term follow-up but not in the first 6 months ($P > 0.05$). The groups of tumors ≤2.9 cm and 2.9–4.8 cm showed no statistically significant difference in OS, PFS, and LRR ($P > 0.05$).

Conclusions: The cutoff points of 2.9 and 4.8 cm were achieved using the objective decision tree model rather than the artificial division of 3 and 5 cm. The prognosis was not significantly different between the groups of tumors ≤2.9 cm and 2.9–4.8 cm, and the prognosis of the two groups was better than the group of tumors >4.8 cm in the long-term follow-up but not in the first 6 months.

KEY WORDS: Decision tree model, hepatocellular carcinoma, radiofrequency ablation, transarterial chemoembolization, tumor diameter

INTRODUCTION

Liver cancer is the sixth most common tumor, the fourth leading cause of cancer death worldwide, and the second highest cause of death in men.[1] In 2018, 75%–85% of liver cancer cases were hepatocellular carcinoma (HCC).[1] To date, there have been few satisfactory therapeutic outcomes achieved in patients with HCC with medium-sized or large-sized tumors. Surgical resection and transplantation are beneficial for survival, while the ideal candidates for the two treatment methods are limited to 5%–10% due to shortage of donors and the poor hepatic function, such as insufficient liver reserve and severe cirrhosis.[2,3]

Transarterial chemoembolization (TACE) is most commonly used for intermediate-stage HCC

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based on several meta-analyses.[4,5] Cumulative studies have demonstrated that more than half of patients with unresectable HCC achieved extensive tumor necrosis and hence improved survival by TACE.[4,6-10] However, TACE could adequately control large and advanced-stage HCC due to remaining progressing or recurring tumors.[4,11-14] Radiofrequency ablation (RFA) is the first-line technique for ablation and has achieved excellent survival outcomes with HCC <3 cm.[15-22] However, the effectiveness of RFA decreases as the size of tumor increases due to incomplete necrosis by heat loss for high perfusion of peritumoral vessels.[23,24] No consensus has been reached concerning the efficacy of RFA for tumors >3 cm in diameter.

Combined TACE and RFA (TACE–RFA) has been presented as a promising treatment in cumulative studies, as the combination could provide a better outcome than RFA or TACE alone.[3,15,25-30] The synergistic actions of TACE and RFA, such as decreased blood flow caused by TACE, which enhances the ablative effect of RFA, are accepted as the primary theory for better prognosis, which is in accordance with our clinical observation.

Presently, suitable therapies for large liver tumors are limited. Although TACE–RFA is promising, studies comparing the outcomes across varied tumor diameters are rare, particularly for large neoplasms.[31] Therefore, we conducted a retrospective study on patients treated with TACE–RFA for tumors between 0.9 and 15.6 cm. These tumors were grouped statistically according to the tumor diameter, and the safety and treatment efficacy were evaluated.

MATERIALS AND METHODS

Study design and patient selection

This study is in accordance with the ethical standards of our institutional committee on human experimentation and the Declaration of Helsinki. Written informed consent was obtained from all patients prior to treatment.

We reviewed the electronic medical database of 128 consecutive patients who underwent TACE–RFA as an initial treatment for HCC from January 2010 to April 2018 at our hospital. Follow-up data collection was terminated on September 30, 2018. HCC was diagnosed according to the American Association for the Study of Liver Disease practice guidelines.[32] The maximal diameter of the tumors was measured on axial computed tomography (CT) or magnetic resonance imaging (MRI).

Patients were included in if they met the following eligibility criteria: (1) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (2) Child–Pugh liver disease class A or B; (3) ≤3 tumors; and (4) HCC stage A or B according to the Barcelona Clinic Liver Cancer (BCLC) system. The exclusion criteria were as follows: (1) any previous treatment for HCC; (2) other treatments, such as liver resection or transplantation, or iodine 125 seed implantation besides TACE or RFA during this study; (3) renal or cardiac failure, severe infection, or hemorrhagic risk (platelet count $<30 \times 10^9$/L or prothrombin activity <40%) that could not be corrected; and (4) other malignancies besides HCC [Figure 1].

Transarterial chemoembolization procedure

TACE was performed by senior hepatologists with at least 5 years of experience in interventional techniques. The procedure was commenced by introducing a 5-Fr catheter (Terumo,Tokyo, Japan) via the femoral artery punctured using the Seldinger technique. Superior mesenteric, celiac angiography, and indirect portovenography were performed to localize the tumors and assess the portal blood flow. Using a coaxial catheter technique, a 2.6-Fr microcatheter (Terumo, Japan) was superselectively advanced to the tumor feeding arteries. A chemotherapeutic agent was administered as slowly as possible by injecting a mixture of 20–60 mg doxorubicin and 2–12.5 mL lipiodol (Lipiodol Ultra-Fluid; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) into the feeder vessels. Polyvinyl alcohol particles of 300 μm diameter (gelatin sponge particles; Cook, IN, USA) mixed with contrast material were slowly injected into the target arteries until arterial flow was static or stasis was approximated. After embolization, hepatic angiography was repeated to assess the extent of vascular occlusion. If the feeding artery was not completely embolized, gelatin sponge particle embolism was repeated.

Radiofrequency ablation procedure

Three to seven days after TACE, RFA was performed percutaneously under ultrasound or CT guidance by senior hepatologists with at least 5 years of experience in interventional techniques. Local or general anesthesia was administered according to the patient's condition before introduction of the RFA system (RITA Medical Systems Inc., Mountain View, California, USA). For tumors <3 cm in diameter, a single electrode was inserted into the center of the tumor; the multilined expandable electrode (StarBurst® XL, RITA Medical Systems Inc., Mountain View, USA) was applied

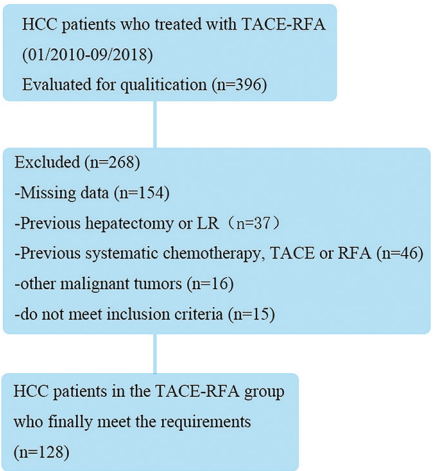

Figure 1: Flow diagram showing the exclusion criteria in patients with hepatocellular carcinoma. LR = Liver resection, LT = Liver transplantation, RFA = Radiofrequency ablation, TACE = Transarterial chemoembolization

in tumors >3 cm, and multiple overlapping zones of ablation were executed to cover the target lesion as described by Chen *et al*.[33] In each case, needle track ablation was performed before withdrawal. Early efficacy was assessed by intraoperative ultrasound or CT. Additional RFA was performed until complete ablation of the tumor or as much ablation as possible was achieved; otherwise, another TACE procedure was performed after a short interval. All procedures were performed according to the manufacturer's recommended protocol.

Assessment and follow-up

Four weeks after TACE-RFA, all patients were required to undergo follow-up laboratory tests and imaging. Laboratory tests included prothrombin time and α-fetoprotein, whereas imaging examinations included dynamic contrast-enhanced CT or MRI. If complete tumor ablation was achieved, follow-up abdominal contrast-enhanced CT or MRI and laboratory tests were conducted every 3 months. Otherwise, repeated TACE or RFA was performed according to patient's preferences and experienced physicians' clinical decision.

Tumor response during the follow-up period was evaluated using the modified Response Evaluation Criteria in Solid Tumors, and complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were defined accordingly.[34] Local recurrence was classified as appearance of a viable intrahepatic tumor at the periphery of the original ablated lesion.

Statistical analysis

All data analyses were performed using R language version 3.3.3 (https://cran.r-project.org/src/base/R-3/), and $P < 0.05$ indicated a significant difference. Pearson's Chi-square test and Student's *t*-test were used to compare categorical and continuous variables, respectively. Decision tree models were established according to the arithmetic expression:

$$G(x) = \sum_{c}^{C} \text{if}\left(b(x) == c\right) \times G_{c}(x)$$

which splits the nodes on variables and then selects the split that results in most homogeneous subnodes till the terminal nodes, to yield the optimal cutoff points. Overall survival (OS), progression-free survival (PFS), cumulative survival, and local recurrence rates (LRRs) were analyzed using the Kaplan–Meier method. Survival curves were compared by log-rank test. Univariate and multivariate analyses were performed using the Cox regression model, and the variables were attained by Akaike information criterion to evaluate the related factors of OS, PFS, and LRR.

RESULTS

Baseline demographic and tumor groups

Table 1 shows the baseline characteristics of a total of 128 patients, including 109 (85.2%) men and 19 (14.8%) women. The median age of patients was 55.3 years, and the median follow-up period was 38.1 months, ranging from 5.7 to 110.5 months.

Table 1: Pretreatment characteristics of the 128 patients

Characteristics	*n*
Sex	
Male	109 (85.2)
Female	19 (14.8)
Age (years)	55.3±10.4
Albumin (mg/dL)	38.0±5.9
Total bilirubin (μmol/L)	24.0±54.4
AFP (ng/mL)	
≤mL)	95 (74.3)
>400	33 (25.7)
Child–Pugh Class	
A	111 (86.5)
B	17 (13.5)
ECOG score	
0	115 (89.8)
1	13 (10.2)
BCLC stage	
A	88 (68.8)
B	40 (31.2)
Hepatitis type	
HBV	114 (89.1)
HCV	10 (7.8)
Others	4 (3.1)
Antihepatitis treatment	128 (100)
Tumor diameter (cm)	
<2.9	50 (39.1)
2.9-4.8	40 (31.2)
>4.8	38 (29.7)
Number of tumors	
1	102 (79.7)
2	23 (18.0)
3	3 (2.3)

BCLC=Barcelona Clinic of Liver Cancer, ECOG=Eastern Cooperative Oncology Group, AFP=Alpha fetoprotein, HBV=Hepatitis B virus, HCV=Hepatitis C virus

According to the maximizing differences of OS between groups separated by optimal cutoff point in statistics considering the tumor size, the decision tree model was established. The tumors were classified by results of the decision tree model into groups of ≤4.8 cm and >4.8 cm (node 2 vs. node 5, $P = 0.004$) in the first step; then, node 2 was further classified into the ≤2.9 cm and >2.9 cm groups (node 3 vs. node 4, $P = 0.123$) [Figure 2]. A significant difference was noted between groups of tumors ≤4.8 cm and >4.8 cm, while the difference between groups of tumors ≤2.9 cm and >2.9 cm was not significant. The number of patients in the graded groups was 50 (39.1%), 40 (31.2%), and 38 (29.7%).

Local response

During the follow-up period, CR was achieved in 36 of 50 (72%), 20 of 40 (50%), and 8 of 38 (21.2%) patients; PR was attained in 9 of 50 (18%), 14 of 40 (35%), and 20 of 38 (52.6%) patients; SD in 1 of 50 (2%), 4 of 40 (10%), and 6 of 38 (15.8%) patients; and PD in 4 of 50 (8%), 2 of 40 (5%), and 4 of 38 (10.5%) patients in the ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm groups, respectively.

Overall survival

The median observational period was 38 months (range, 5.7–110.5) for all patients. The median survival time was 30 months for the >4.8 cm group and 59 months for the

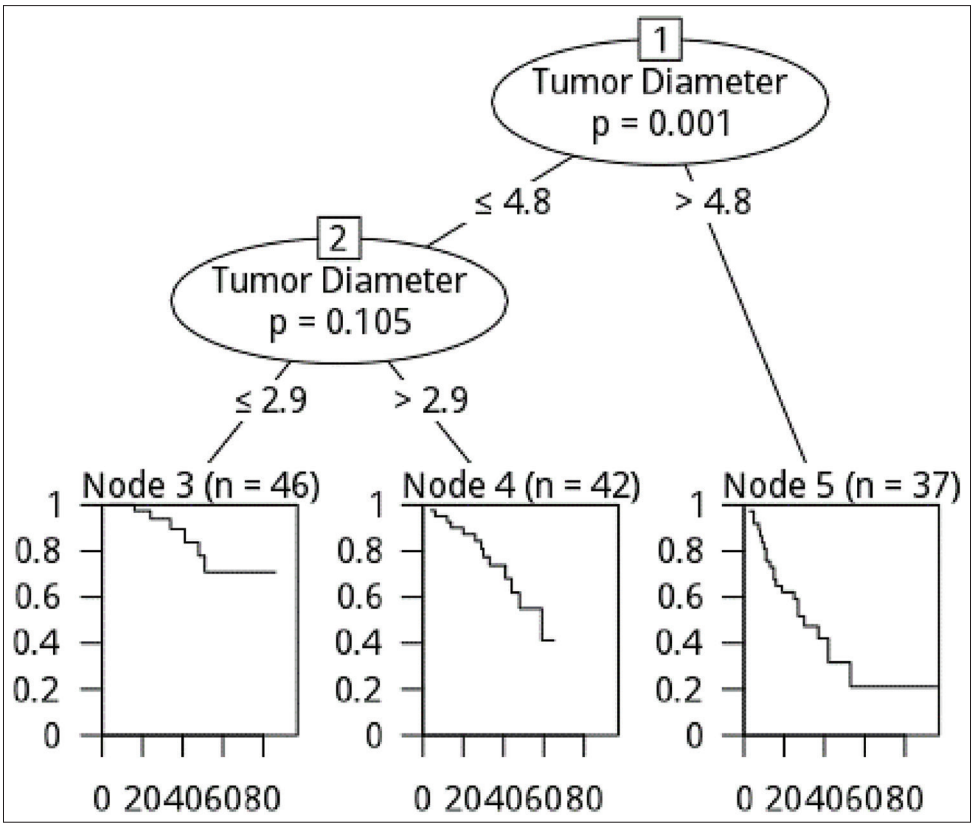

Figure 2: The tumors were classified based on the results of the decision tree model. The difference between the >4.8 cm and ≤4.8 cm groups was statistically significant (P = 0.001), whereas the difference between the ≤2.9 cm and 2.9–4.8 cm groups was not statistically significant (P = 0.105)

2.9–4.8 cm group. However, because the number of patients who died was too low, the median survival time of the ≤2.9 cm group and the 95% confidence interval of all the three groups were not suitable for statistical analyses.

Regarding OS [Figure 3], there was a statistically significant difference between the ≤4.8 cm and >4.8 cm groups (P = 0.004), while the difference between the ≤2.9 cm and 2.9–4.8 cm groups was not statistically significant (P = 0.105). The 1-, 3-, and 5-year cumulative OS rates were 98%, 92%, and 86%, respectively, in the ≤2.9 cm group; 95%, 77.5%, and 67.5%, respectively, in the 2.9–4.8 cm group; and 76.3%, 55.3%, and 44.7%, respectively, in the >4.8 cm group. During the follow-up, no significant difference in cumulative OS rate between the ≤2.9 cm and 2.9–4.8 cm groups has been shown, but there was a significant difference between the ≤2.9 cm and >4.8 cm groups after 12 months, and the difference between the 2.9–4.8 cm and >4.8 cm groups was significant after 18 months.

Univariable analysis revealed that total bilirubin level, BCLC B stage, and tumor diameter >4.8 cm were significantly associated with poor OS (P < 0.05) [Table 2], and the Cox regression model identified tumor diameter >4.8 cm (hazard ratio [HR] = 5.547; P = 0.001) to be a significant prognostic factor of OS [Table 3].

Progression-free survival

Similar to OS, PFS was analyzed based on the maximal differences between groups, which were classified according to the established decision tree model [Figure 4].

The median PFS time was 14 and 45 months in the >4.8 cm and 2.9–4.8 cm groups, respectively. The median PFS time was unattainable in either the <2.9 cm group or the few patients who died.

Regarding PFS [Figure 5], there was a statistically significant difference between the ≤4.8 cm and >4.8 cm groups (P = 0.004), while the difference between the ≤2.9 cm and 2.9–4.8 cm groups was not statistically significant (P = 0.123). The 1-, 3-, and 5-year PFSs for the three groups were 84%, 56%, and 52%; 72.5%, 50%, and 42.5%; and 52.6%, 29%, and 23.7%, respectively. There was no significant difference between the ≤2.9 cm and 2.9–4.8 cm groups until the final follow-up, whereas differences were significant between the ≤2.9 cm and >4.8 cm groups after 12 months and between the 2.9–4.8 cm and >4.8 cm groups after 42 months.

The Cox regression model indicated a tumor diameter >4.8 cm and α-fetoprotein level >400 ng/mL to be significant predictors of PFS (HR = 5.10, P = 0.002, and HR = 2.22, P = 0.037, respectively) [Table 4].

Cumulative local recurrence rate

The 1-, 3-, and 5-year cumulative LRRs were 6%, 14%, and 14%; 15%, 27.5%, and 27.5%; and 44.7%, 57.9%, and 60.5% in the ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm groups, respectively. There was no significant difference between the ≤2.9 cm and 2.9–4.8 cm groups until the final follow-up, whereas a significant difference was shown in the first 6 months between the ≤2.9 cm and >4.8 cm groups. A statistically significant difference between the 2.9–4.8 cm and >4.8 cm groups was noted after 12 months [Figure 6].

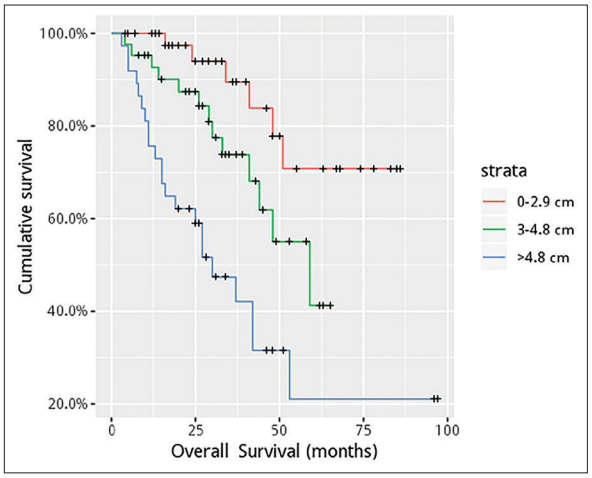

Figure 3: The overall survival curve of the three groups was drawn using the Kaplan–Meier method. The median survival time was NA, 59 months, and 30 months in the ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm groups, respectively (NA due to the number of patients who died being too low to analyze)

Univariable analysis identified tumor diameter >4.8 cm, α-fetoprotein level >400 ng/mL, and ECOG score of 1 point as unfavorable factors leading to recurrence ($P < 0.05$) [Table 5]. However, age, albumin level, and Child–Pugh B grade were

Table 2: Univariate analyses of factors that influenced overall survival

Factors	HR	*P*
Sex	0.7049	0.4643
Age (years)	1.027	0.07397
Diameter 2.9-4.8 cm	2.376	0.06524
Diameter >4.8 cm	5.613	8.386e-05
Albumin (<28 mg/dL)	0.9678	0.2341
ALT level (>80 IU/L)	0.874	0.651
Platelet count (<105/μL)	1.583	0.114
Total bilirubin (>51.3 μmol/L)	1.007	0.0007927
AFP >400 ng/mL	1.934	0.06324
Child–Pugh B	1.974	0.07317
ECOG 1	2.462	0.06988
BCLC stage B	3.169	0.00025
Number of tumors	0.6169	0.2107
Hepatitis B	0.5043	0.1267

OS=Overall survival, HR=Hazard ratio, ALT=Alanine aminotransferase, BCLC=Barcelona Clinic of Liver Cancer, ECOG=Eastern Cooperative Oncology Group, AFP=Alpha fetoprotein

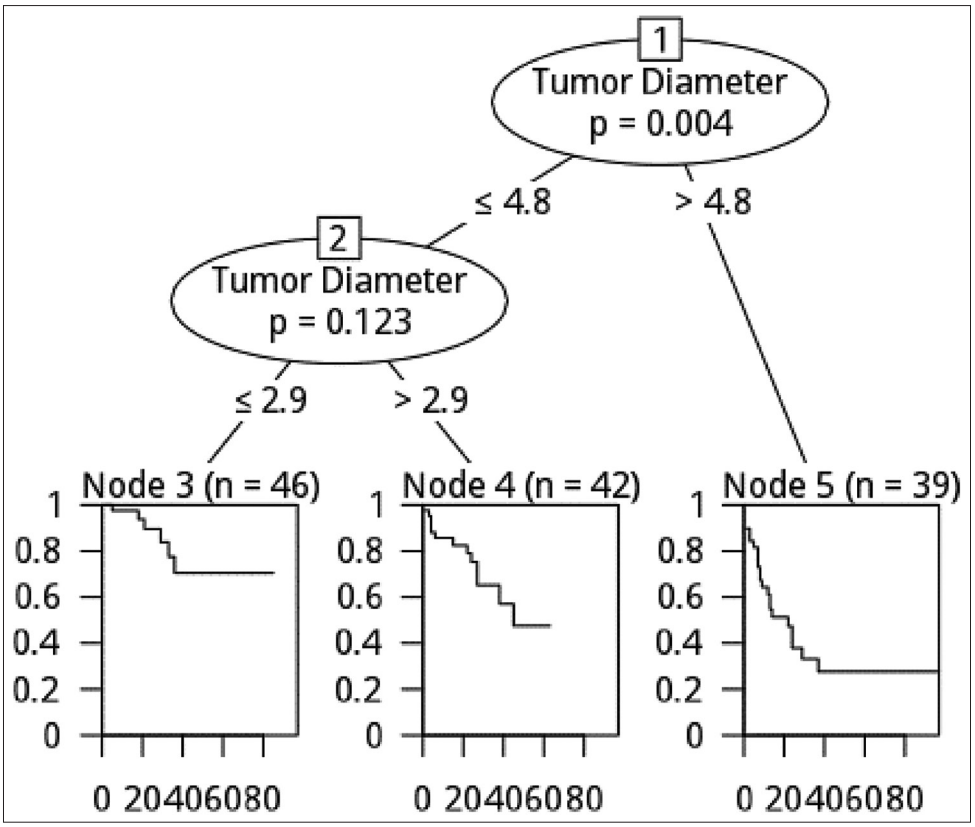

Figure 4: The recurrence-free survival curve of the three groups was drawn using Kaplan–Meier method. The median survival time was NA, 14 months, and 45 months in the ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm, respectively (NA due to the number of patients who died being too low for analysis)

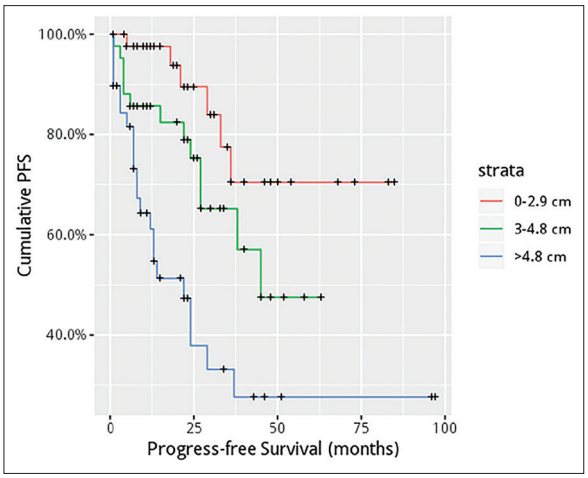

Figure 5: The tumors were classified based on the results of the decision tree model. The difference between the >4.8 cm and ≤4.8 cm groups was statistically significant ($P = 0.001$), whereas the difference between the ≤2.9 cm and 2.9–4.8 cm groups was not statistically significant ($P = 0.105$)

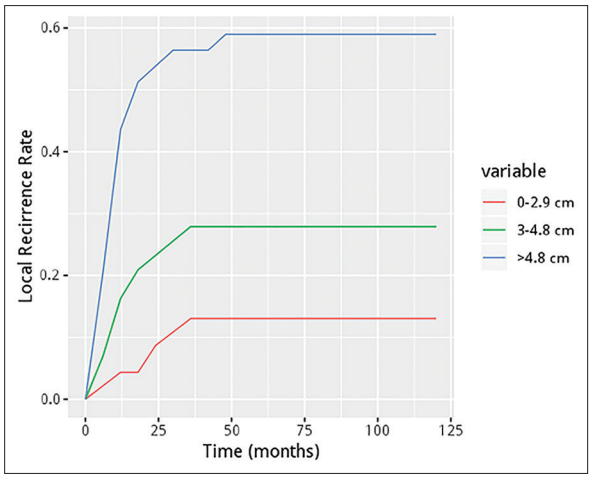

Figure 6: The curve of the local cumulative recurrence rates of the three groups was drawn. The overall local recurrence rate in the ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm groups was 14%, 27.5%, and 60.5%, respectively

Table 3: Multivariate analyses of factors that influenced overall survival

Factors	HR	*P*
Sex	1.013	0.9828
Age (years)	1.027	0.09708
Diameter 2.9-4.8 cm	2.216	0.1298
Diameter>4.8 cm	5.547	0.0007906
Albumin (<28 mg/dL)	0.9584	0.2454
Total bilirubin (>51.3 μmol/L)	1.008	0.6261
AFP>400 ng/mL	2.047	0.05966
Hepatitis B	0.5725	0.2951

HR=Hazard ratio, AFP=Alpha fetoprotein

Table 4: Multivariate analyses of factors that influenced progression-free survival

Factors	HR	*P*
Sex	1.216	0.7488
Age (years)	1.028	0.09106
Diameter 2.9-4.8 cm	2.046	0.172
Diameter>4.8 cm	5.102	0.001656
Albumin (<28 mg/dL)	0.9489	0.1528
Total bilirubin (>51.3 μmol/L)	1.003	0.8067
AFP>400 ng/mL	2.223	0.03772
Hepatitis B	0.562	0.2861

HR=Hazard ratio, AFP=Alpha fetoprotein

shown to be predictors in the multivariable analysis (HR = 0.96, $P = 0.008$; HR = 0.93, $P = 0.029$; and HR = 0.26, $P = 0.038$, respectively) [Table 6].

Complications

There was one patient with a deep-seated, middle-sized liver tumor who had needle track bleeding, and one patient sustained intrahepatic bile duct injury, possibly due to the large size of the tumor. However, these two patients recovered by conservative management and symptomatic treatment, respectively. Common complications were fever, hepatic regional pain, and vomiting. There was no treatment-related death.

DISCUSSION

The liver cancer staging system graded HCC diameter as 3 and 5 cm by artificial division mainly depending on HCC pathobiological characteristics.[35] The tumors in this retrospective study were entirely classified into three groups based on sizes ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm by an objective statistical method known as decision tree model from a reverse direction according to the most benefit patients could obtain. Then, univariable and multivariable analyses were conducted, and the safety and efficacy of the combined therapeutic strategy between the groups were assessed. To the best of our knowledge, we are the first to conduct such a therapeutic method in the field of interventional oncology. A remarkable finding is that the optimal cutoff points of 2.9 and 4.8 cm attained from the statistical analysis are similar to the existing values of 3 and 5 cm in the current clinical practice. This further proved by statistics the rationale of clinical application of 3 and 5 cm as cutoff points of tumor diameter.

As demonstrated by the study, the two ≤4.8 cm groups showed better OS and PFS than the >4.8 cm group, whereas there was no difference between the ≤2.9 and 2.9–4.8 cm groups. The Cox regression model indicated that a tumor diameter >4.8 cm was associated with poor OS and PFS.

Although the 1-, 3-, and 5-year OS and PFS in the >4.8 cm group were similar to or even better than those in other studies that included large tumors,[25,36-38] the effect was still inferior to those of the smaller diameter groups. Particularly, our study included tumors up to 15 cm in size. Despite the combination strategy implemented, it was still not possible to completely ablate all malignant cells in larger tumors compared to smaller tumors, which was identified by the Cox regression model to some extent. However, the cumulative OS of the >4.8 cm group was not inferior to those of the ≤2.9 cm and 2.9–4.8 cm

Table 5: Univariate analyses of factors that influenced local recurrence rate

Factors	HR	*P*
Sex	0.9511	0.87
Age (years)	0.9816	0.09725
Diameter 2.9-4.8 cm	1.196	0.5444
Diameter>4.8 cm	2	0.01528
Albumin (<28 mg/dL)	0.9923	0.7072
ALT level (>80 IU/L)	0.795	0.603
Platelet count (<105/μL)	1.658	0.125
AFP>400 ng/mL	1.885	0.03372
Child–Pugh B	0.9051	0.7457
ECOG 1	1.993	0.04259
BCLC stage B	1.583	0.05567
Number of tumors	1.068	0.7923
Hepatitis B	1.337	0.444

HR=Hazard ratio, ALT=Alanine aminotransferase, BCLC=Barcelona Clinic of Liver Cancer, ECOG=Eastern Cooperative Oncology Group, AFP=Alpha fetoprotein

Table 6: Multivariate analyses of factors that influenced local recurrence rate

Factors	HR	*P*
Sex	0.6059	0.3269
Age (years)	0.9565	0.008051
Diameter 2.9–4.8 cm	0.7667	0.4758
Diameter>4.8 cm	1.403	0.342
Albumin (<28 mg/dL)	0.9342	0.02931
Total bilirubin (>51.3 μmol/L)	1.014	0.5888
AFP>400 ng/mL	1.439	0.299
Child–Pugh B	0.2592	0.03828
ECOG 1	2.294	0.08471
Hepatitis B	0.7153	0.5222

ECOG=Eastern Cooperative Oncology Group, AFP=Alpha fetoprotein, HR=Hazard ratio

groups until 12 and 18 months, respectively, which indicates a comparable benefit from TACE–RFA during this period. Similar results were also achieved in PFS between these groups, where the PFS in the 2.9–4.8 cm group was not better than that in the >4.8 cm group in 36 months of follow-up.

The two smaller diameter groups both achieved satisfactory outcomes, and there was no strong evidence for advantage in the ≤2.9 cm group compared to that in the 2.9–4.8 cm group in OS, PFS, or cumulative LRR. However, the ≤2.9 cm group still achieved better overall prognosis than the 2.9–4.8 cm group.

It has been suggested that the future expansion of HCC therapy criteria should maintain a 5-year OS of ≥50%.[39] The OS in this study was 67.5% in the 2.9–4.8 cm group and 44.7% in the >4.8 cm group, which approximates the abovementioned criteria. While the methods of treating HCC >3 cm in size remain controversial, expanding TACE–RFA to the scope of tumor range from 3 to 5 cm could offer patients more benefits. This method may also add potential advantages to liver tumors >5 cm.[15,25,37,38]

As the recurrence rate and risk factors for recurrence after TACE–RFA are not well established,[31] this study also filled this information gap. Satisfactory results were achieved in the LRR. The overall LRRs in the ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm groups were 14%, 27.5%, and 60.5%, respectively. However, compared with smaller tumors, the >4.8 cm group had rapid progression as shown in Figure 6, although no significant difference was noted between the 2.9–4.8 cm and >4.8 cm groups during the 6-month follow-up. Despite some preclinical studies claiming that incomplete ablation may promote liver cancer progression, this relationship remains controversial in clinical practice.[40-42] Our results in the Cox regression model are consistent with it to some extent.

TACE–RFA has several advantages. First, the heat-sink effect that leads to the irregular burn shape by RFA, especially in medium or large tumors, could be prevented by arterial embolization during the TACE procedure. Accordingly, TACE expands the short axis of the ablated area and produces a more spherical ablated region, thereby further assisting RFA in covering the whole tumor and improving the prognosis.[43] Second, TACE is effective in treating undetected microlesions adjacent to the primary tumor, where RFA is unable to reach, particularly beside the large lumps. Third, intratumoral septae and fibrosis seemed to block the heat diffusing within the tumor, whereas TACE destroys the intratumoral septae, hence enhancing the effect of RFA.[44] Lastly, we presumed that the lipiodol within the tumor infused by TACE may increase the heat conduction of ablation, thus synergizing the effect of RFA and TACE.

There were several limitations in our study. First, it was a retrospective study. Second, the conclusion was drawn based on a small sample size at a single center. Finally, several giant HCCs with diameters up to 15 cm were included, while there was no visible metastasis in each case before TACE–RFA. This may result in a biased conclusion. Large-scale randomized controlled trials are needed.

CONCLUSIONS

BCLC A/B stage tumors were classified into three groups based on sizes ≤2.9 cm, 2.9–4.8 cm, and >4.8 cm by the decision tree model according to the most benefit patients could gain from TACE–RFA. The prognosis of the two smaller groups was better than that of the >4.8 cm group, but the latter was not inferior to the two smaller groups at least during the first 6 months of follow-up. Although the overall outcome of the <2.9 cm group was better than that of the 2.9–4.8 cm group, there was no significant difference between the two groups.

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Conflicts of interest

There are no conflicts of interest.

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