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## Original Article

**Percutaneous radiofrequency ablation of tumor feeding artery before target tumor ablation may reduce local tumor progression in hepatocellular carcinoma**

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## ABSTRACT

**Background:** Local tumor progression (LTP) in early-stage hepatocellular carcinoma (HCC) after radiofrequency ablation (RFA) remains high. Tumor feeding artery ablation (FAA) before target tumor ablation was reported to reduce LTP in patients with HCC >3 cm. The aim of our study is to investigate whether FAA before target tumor ablation may reduce LTP in HCC <3 cm.

**Methods:** We retrospectively analysis the outcome of patients with HCC <3 cm undergoing FAA before target tumor ablation (N = 17) compared to direct RFA to target tumor alone (N = 35).

**Results:** FAA significantly reduces LTP (FAA vs. non-FAA: local tumor progression 17.6% vs. 48.6%,  $p = 0.038$ ), but not in intrahepatic recurrence: 29.4% vs. 25.7%,  $p = 0.778$ ; or in overall recurrence rate: 41.2% vs. 62.9%,  $p = 0.14$ ). The cumulative 1-year and 2-year LTP rates in FAA group were 17.6% and 17.6%, while 11.4% and 42.9% in non-FAA group ( $p = 0.073$ ), respectively. The cumulative overall recurrence rates at 1-year and 2-year were 29.4% and 35.3% in FAA group, while 14.3% and 57.1% in non-FAA group ( $p = 0.130$ ), respectively.

**Conclusions:** FAA before target tumor ablation may decrease LTP in HCC <3 cm. Further randomized control study will be helpful for validation.

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### At a glance commentary

#### Scientific background on the subject

Feeding artery thermal ablation before target tumor radiofrequency ablation theoretically can reduce intra-, or peri-tumoral blood flow and subsequently reduce heat-sink effect and create a larger ischemic area around the target tumor, therefore, it would be more effective compared with direct target tumor ablation alone.

#### What this study adds to the field

The current results based on a relatively small sample size still show that feeding artery thermal ablation before radiofrequency ablation of target tumor can reduce local tumor progression in tumors smaller than 3 cm in diameter and in tumors at difficult-to-ablate location.

Hepatocellular carcinoma (HCC) is the most common malignancy worldwide [1]. Curative treatment as surgical resection, radiofrequency ablation (RFA), or liver transplantation are recommended for early-stage HCC [2–4]. RFA has gained attention as the option for unresectable HCC owing to its minimal invasiveness as compared with resection as well as high local tumor control, particularly for HCC smaller than 3 cm [5–10].

Most HCC is a hypervascular tumor with its blood supply majorly from hepatic artery. Many factors including intra-tumoral or peri-tumoral heat-sink effect, insufficient ablative margin or the presence of satellite around the target tumor are associated with incomplete ablation and local

tumor progression (LTP) [5–11]. To overcome these limitations, many novel algorithms have been accepted [5–11] but only one study reported that feeding artery ablation (FAA) before target tumor ablation in HCC >3 cm could reduce LTP [12]. To our knowledge, the effects of FAA for HCC <3 cm or for HCC at difficult-to-ablate location remain unknown. Therefore, the aim of our study is to compare the outcomes between patient with and without FAA before target tumor ablation.

### Patients and methods

#### Patient recruitment

From January 2007 to April 2015, a total of 52 treatment naïve patients with single or two HCC whom underwent RFA in our department were retrospectively recruited. HCC was diagnosed with typical dynamic liver image (contrast-enhanced triphasic CT or MRI) showing characteristic tumor enhancement in the arterial phase with wash out in the portal venous or delay phase [13] in cirrhotic liver or tumor cytology plus dynamic liver image in non-cirrhotic patients [14]. None of these patients had visible vessel invasion or distant metastasis from image study prior to treatment, nor malignancy other than HCC. Baseline laboratory data including liver function,  $\alpha$ -fetoprotein, creatinine, as well as underlying etiology such as HBV or HCV infection, existence of cirrhosis, gender, tumor number and tumor location were analyzed for predictors of recurrence post therapy. The diagnosis of cirrhosis was by histology confirmation or a grading system with coarse parenchyma, torturous vessels, uneven surface under ultrasonography combined with splenomegaly or existence of esophageal/gastric varices [15]. This study was approved by our institutional review board.

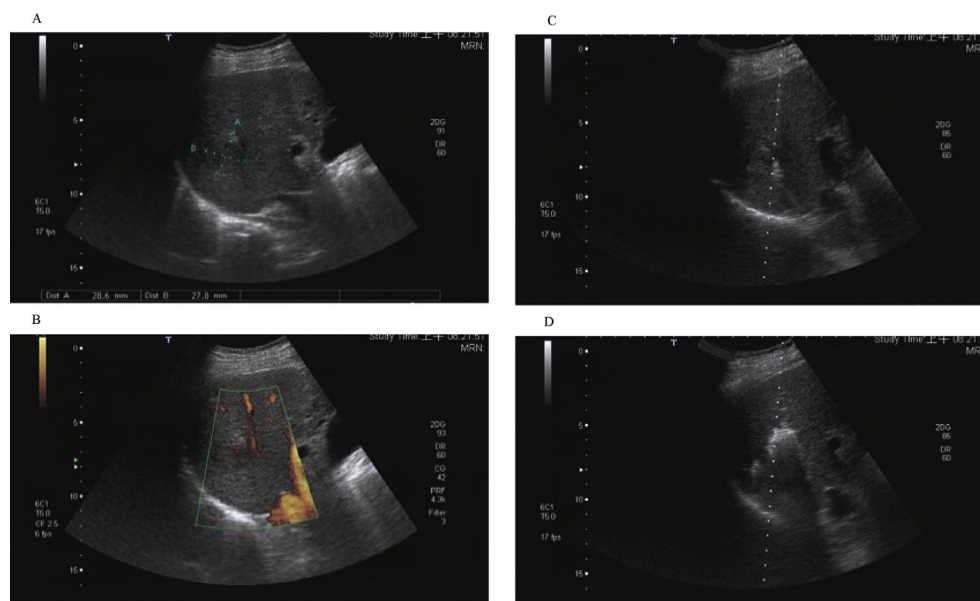


Fig. 1 – The process of feeding artery ablation during radiofrequency ablation treatment in HCC patient. (A: a 2.8 cm mixed echogenic tumor at segment 8; B: to identify the vessel nearby the tumor by color duplex ultrasonography; C and D: the ablated area appeared wedge shape hyperechoic change).

**Table 1 – Baseline characteristics of study population.**

Variables	N = 52	FAA (N = 17)	Non-FAA (N = 35)	p value
Age (y) <sup>a</sup>	68.56 ± 9.53	66.7 ± 11.04	69.46 ± 8.74	0.376
Male (No/%) <sup>b</sup>	29 (55.8%)	10 (58.8%)	19 (54.3%)	0.757
Liver cirrhosis <sup>b</sup>	46 (88.5%)	17 (100%)	29 (82.9%)	0.161
Underlying liver disease: HBV/HCV <sup>b</sup>	16 (30.8%)/29 (55.8%)	5 (29.4%)/9(52.9%)	11 (31.4%)/20 (57.1%)	0.757
ALT (IU/L)	39.5 (12–245)	38 (15–245)	40 (12–237)	0.838
Total bilirubin (mg/dL)	0.8 (0.2–6.7)	1.1 (0.4–6.7)	0.7 (0.2–4.2)	0.17
Albumin (g/dL) <sup>a</sup>	3.76 (2.45–4.7)	3.5 (2.73–4.5)	4 (2.45–4.7)	0.032
Prothrombin time (INR)	1.2 (1.0–1.6)	1.3 (1–1.6)	1.1 (1–1.5)	0.009
AFP (ng/ml)	10.45 (1.8–5270)	14.2 (4.3–204.7)	8 (1.8–5270.3)	0.223
Creatinine (mg/dL)	0.83 (0.36–7.13)	0.69 (0.36–1.63)	0.9 (0.48–7.13)	0.019
Tumor number	1 (1–2)	1 (1–2)	1 (1–2)	0.598
Tumor size (cm)	2.02 (1.1–3)	2.01 (1.21–2.86)	2.03 (1.1–3)	0.845
Location (Lt lobe/Rt lobe)	12 (23%)/40 (76.9%)	12 (70.6%)/5 (29.4%)	28 (80%)/7(20%)	0.45
Difficult-to-ablate location <sup>b</sup>				
Sub-capsule <sup>b</sup>	14 (26.9%)	7 (41.2%)	7 (50%)	0.623
Near vessel <sup>b</sup>	18 (34.6%)	8 (47.1%)	10 (30.3%)	0.242
Follow-up (days)	706 (203–1528)	901 (216–1045)	684 (203–1528)	0.407
Overall recurrence <sup>b</sup>	29 (55.8%)	7 (41.2%)	22 (62.9%)	0.14
Local tumor progression <sup>b</sup>	20 (38.5%)	3 (17.6%)	17 (48.6%)	0.038
Intrahepatic/distant <sup>b</sup>	14 (26.9%)/2 (3.8%)	5 (29.4%)/0 (0%)	9 (25.7%)/2 (5.7%)	0.778/1.0
Mortality <sup>b</sup>	9 (17.3%)	4 (23.5%)	5 (14.3%)	0.451

Abbreviations: HBV: hepatitis B virus; HCV: hepatitis C virus; ALT: alanine aminotransferase; AFP: a-fetoprotein; FAA: feeding artery ablation.

<sup>a</sup> Mean ± SD.

<sup>b</sup> Data are expressed as numbers (%).

### Ablation method

The patients were treated by two expertise operators who each had at least 10 year' experience in RFA. Ultrasound-guided percutaneous RFA was carried out using a single 17-gauge, 20 cm long internally cooled electrode with a 3 cm uninsulated dispersive electrode (Valleylab Inc, Boulder, CO). The major feeding artery was identified by color power flow imaging (Aplio™ SSA-700A; Toshiba, Tokyo, Japan) and the RF electrode was inserted into the area where the artery entered the tumor. This area was ablated with single placement of electrode for achieving estimated ablation area of 2 × 3 cm<sup>2</sup> by using the electrode of 3-cm thermal diameter. After FAA, further ablation of the target tumor was performed subsequently, and the sufficient ablation margin with 0.5–1 cm beyond the tumor margin was attempted if possible. After ablation procedure, the electrode was withdrawn slowly with the tip temperature maintained at least over 70 °C and a linear ablation line during electrode withdrawal was achieved for the prevention of tumor tract seeding [Fig. 1]. The feeding artery of tumor was also visualized on artery phase of dynamic CT. Those without FAA was performed as electrode positioned into the tumor first following an overlapping ablation to achieve and adequate coagulation volume covering the entire tumor.

### Follow-up protocol

All patients had follow-up for exceeding 6 months after therapy with at least one dynamic imaging study (CT or MRI) at month 1, month 3 and 6 within the first 6 months after RFA and thereafter every 6 months with the first 2 years after RFA for assessment of complete ablation and early diagnosis of HCC

recurrence. An abdominal echo was routinely performed the day after RFA treatment and every 3 months after RFA within first 2 years after RFA. Local tumor progression (LTP) was defined as visible viable HCC besides the ablated region, intrahepatic recurrence as viable HCC other than the ablated region, and distant metastasis as HCC recurred in extrahepatic organ. There were 6 patients with coexisted LTP and later intrahepatic recurrence or distant metastasis during image follow-up. These 6 patients were regarded as LTP group rather than intrahepatic recurrence or distant metastasis group due to time events when doing analysis of recurrence site.

### Statistic analysis

Continuous data with normally distribution were expressed as the mean ± SD and were compared between groups using independent student t test/analysis of variance (ANOVA) while non-normally distribution as median (range) and were compared by Mann–Whitney U test between two groups. Whether the variables being normally distribution was tested by Shapiro–Wilk test which p value less than 0.05 regarded as non-normally distributed, vise versa. Categorical variables were compared using the  $\chi^2$  test or Fisher's exact test. Local tumor progression and overall recurrence were calculated by Kaplan–Meier method and compared between groups using the log-rank test. Cox regression analysis with forward logistic regression was used to model independent predictors of LTP and overall recurrence. Uni-variate and multi-variate analysis used for evaluating the predictors of overall recurrence and local recurrence after radiofrequency ablation. All analysis was carried out using the SPSS v. 20 statistical packages (SPSS Inc., Chicago, IL),  $p < 0.05$  was considered statistically significant.

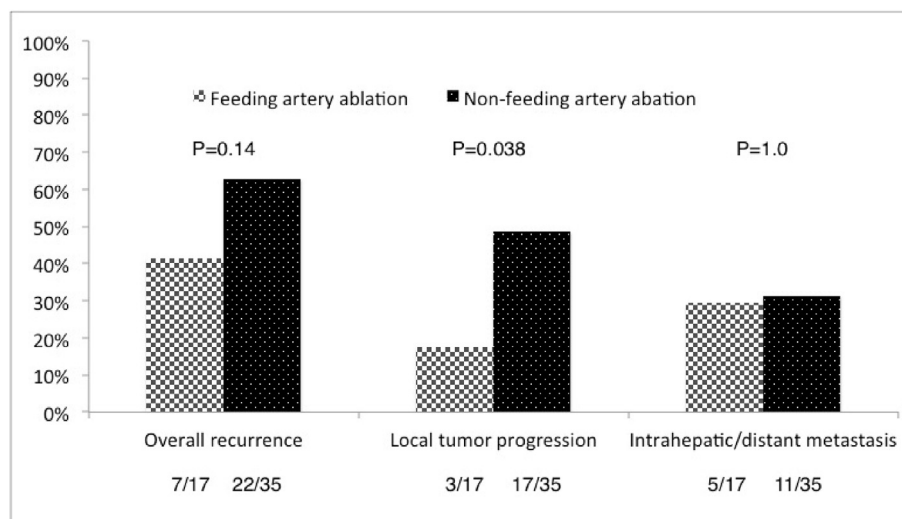


Fig. 2 – Feeding artery ablation method appears lower overall recurrence especially in local tumor progression rate.

## Results

### Baseline characteristics

The average age of 52 treatment naïve HCC patients was 68.56 year-old. More than half of the patients are male (55.8%) and most of them were cirrhotic (88.5%). Underlying etiology of HCC composed mainly viral hepatitis (HBV: 30.8%, HCV: 55.8%). The HCCs located more in right lobe (76.9%) with 26.9% subcapsular location and 34.6% located within 0.5–1 cm distance to hepatic vein or portal vein. The baseline characteristics between FAA and non-FAA were comparable except albumin level appeared lower, longer INR, and lower creatinine level in the FAA group [Table 1].

### HCC recurrence rate between FAA and non-FAA

Among the 52 patients, overall recurrence rate was 55.8% which LTP composed 69.0% of these recurrent patients. The overall recurrence rate is higher in the non-FAA group but it did not achieve significant difference (62.9% vs. 41.2%,  $p = 0.14$ ) [Fig. 2]. But the LTP rate was higher in the non-FAA group (48.6% vs. 17.6%,  $p = 0.038$ ). However, both cumulative overall recurrence and local tumor progression rates did not reach statistical significance by the log-rank test (non-FAA vs. FAA:  $p = 0.582$  and  $p = 0.101$ , respectively) [Fig. 3]. The cumulative 1-year and 2-year LTP rates in FAA group were 17.6% and 17.6%, while 11.4% and 42.9% in non-FAA group ( $p = 0.073$ ), respectively. The cumulative overall recurrence rates at 1-year and 2-year were 29.4% and 35.3% in FAA group, while 14.3% and 57.1% in non-FAA group ( $p = 0.130$ ), respectively [Table 2].

### Predictors for recurrence post HCC ablation

We used multi-variate analysis to evaluate the predictor factors of overall tumor recurrence and local tumor progression. The results showed that higher creatinine level (adjusted HR:

11.83, 95% CI: 1.522–91.963,  $p = 0.018$ ) was associated with overall tumor recurrence, while feeding artery ablation of liver tumor was associated with lower local tumor progression (adjusted HR: 0.235, 95% CI: 0.056–0.994,  $p = 0.049$ ) [Table 3].

### Clinical outcome and major complications or adverse events

Nine of the fifty-two patients expired (17.3%). Three patients died of deterioration of liver function at least 6 months after treatment, two patients died of tumor progression more than 1-year post treatment and the others died of sepsis. None occur within 3 months post therapy.

There were no major complications, especially bile duct injury, in the entire patients. Most patients may complain of mild pain over RFA site or upper abdomen area but subsided after supportive treatments or some oral analgesics.

## Discussion

The LTP after RFA remains high [7–18]. The current study using RFA with FAA showed a satisfactory LTP rate (12.3% at 1-year) and the estimated overall 1-, 2-year recurrence rates as 17.5%, 47.4% respectively. Though the LTP in our study was higher than other studies (17.6% vs 4.8–8.1% at 1-year follow-up) [16–18], it was comparable to 17.3% of 6-month LTP by using FAA [12]. Moreover, our study subjects have some risks of recurrence or incomplete ablation as shown that 53.84% of tumors larger than 2 cm and more than sixty percent of tumors located in subcapsular area or near vessels. Tumor with these risk factors tends to have higher local or overall recurrence [19–21]. Our results still showed that FAA for tumors near vessel or in difficult-to-ablate location can achieve comparable effects as compared with those in location other than vessel or difficult-to-ablate.

The LTP was also associated with an insufficient ablative margin around hepatic vessels and modified ablation strategies should be considered to improve ablation [20],

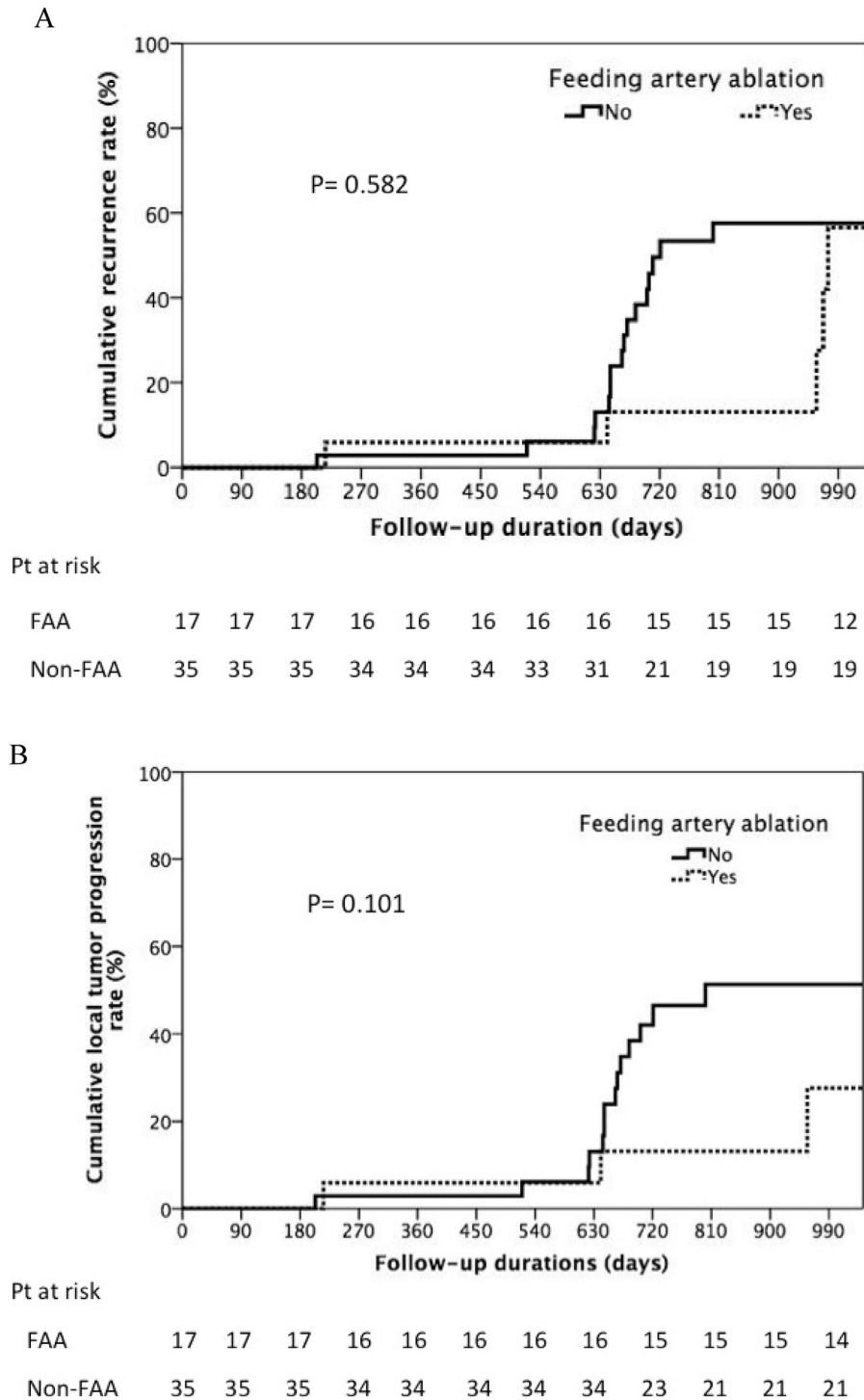


Fig. 3 – (A) The cumulative overall recurrence rate post RFA with and without FAA; (B) The cumulative local tumor progression rate post RFA with and without FAA.

mimicking the concept application of transarterial chemo-embolization (TACE) by applying embolic material to cause ischemic effects [22]. In our study, the LTP rate by 2-year post RFA treatment in FAA and non-FAA group was 17.6% vs. 42.9% ( $p = 0.073$ ) respectively and in further follow-up in our study had showed significant lower LTP in FAA group (17.6% vs. 48.6%,  $p = 0.038$ ). This result might be due to ischemic effects of target tumor after FAA. However, no significant

difference in tumor recurrence was found between tumor with and without near vessel in our study. This is probably due to mature experiences of RFA by operators in this study but some bias might be present such as small sample size. Our study also showed that higher creatinine level was associated with overall tumor recurrence, while feeding artery ablation of liver tumor was associated with lower local tumor progression [Table 3].

**Table 2 – Comparison of factors between recurrence and non-recurrence.**

Variables	No recurrence (N = 23)	Recurrence (N = 29)	p value
Age (y) <sup>a</sup>	66.94 ± 10.64	69.84 ± 8.53	0.294
Male <sup>b</sup>	12 (52.2%)	17 (58.6%)	0.642
Liver cirrhosis <sup>b</sup>	22 (95.7%)	24 (82.8%)	0.21
Child Pugh score			
A <sup>b</sup>	15 (65.2%)	20 (69%)	0.309
B <sup>b</sup>	7 (30.4%)	4 (13.8%)	
C <sup>b</sup>	0 (0%)	1 (3.4%)	
Underlying liver disease: HBV/HCV <sup>b</sup>	9 (39.1%)/12 (52.2%)	7 (24.1%)/17 (58.6%)	0.224
Baseline ALT (U/L)	40 (15–237)	39 (12–245)	0.333
Baseline total bilirubin (mg/dL)	0.8 (0.2–4.2)	0.7 (0.4–6.7)	0.985
Baseline albumin (g/dL)	3.85 (2.45–4.7)	3.67 (2.73–4.46)	0.407
Prothrombin time (INR)	1.1 (1.0–1.5)	1.2 (1.0–1.6)	0.188
Baseline AFP (ng/ml)	12 (1.8–5270)	8.3 (2.8–277.2)	0.381
Baseline creatinine (mg/dL)	1 (0.46–7.13)	0.69 (0.36–1.63)	0.002
Size of tumor (cm)	2.1 (1.21–3)	1.9 (1.1–2.86)	0.112
Location (Lt/Rt lobe)	8 (34.8%)/15 (65.2%)	4 (13.8%)/25 (86.2%)	0.102
Vascular ablation <sup>b</sup>	10 (43.5%)	7 (24.1%)	0.14
Difficult-to-ablate location <sup>b</sup>			
Sub-capsular	7 (46.7%)	7 (43.8%)	0.87
Near vessel	9 (39.1%)	9 (33.3%)	0.67
Follow-up (days)	704 (203–1528)	708 (214–1008)	0.124
Mortality	2 (8.7%)	7 (24.1)	0.268

<sup>a</sup> Mean ± SD.  
<sup>b</sup> Data are expressed as numbers (%).

Survival rates after RFA with and without feeding artery ablation were 94.12% vs. 97.14%, and 76.47% vs. 91.43% by 1-year and 3-year post ablation respectively ( $p = 0.198$ ), similar to other studies report in HCC patients within the Milan criteria receiving RFA treatment (87.0–99.0% at 1-year, 60.0–87.4% at 3-year, and 42.3–74.8% at 5-year) [16–19,23], supporting FAA is an equivalently safe ablation way in HCC RFA treatment. Besides, none of the cause of death is directly caused by the procedure itself in 9 mortality patients.

There were several limitations in our studies. First, the following time of our study was not long enough (median [range]: 706 [203–1528] days). The long-term outcome between the FAA and non-FAA group could not be well demonstrated in our study. Another limitation was that we found the feeding vessel of HCC via color Doppler

ultrasonography. Peri-tumor vessel could be detected under echo window and we supposed it was feeding vessel of HCC, however, the definite feeding artery of HCC just absolutely localized by transarterial angiography. Moreover, this is a small scale study in a retrospective design. There should be a lot of bias and limitation, such as criteria of patients selected for FAA, criteria of patients selected as control, standard procedure of FAA, and et al. However, the current study provided a new insight of ablation technique rather than a solid conclusion. In addition, the finding of our study needs further validation by larger cohort or randomized study.

In conclusion, RFA plus FAA tends to improve the local tumor progression rate compared to non-FAA group. Further studies are warranted to clarify the benefit of RFA with feeding artery ablation in controlling local tumor progression.

**Table 3 – Logistic regression analyses for factors associated with tumor recurrence and local recurrence after radiofrequency ablation.**

Variables	Crude OR	95% CI	p value	Adjusted OR	95% CI	p value
<b>Overall recurrence</b>						
Baseline INR	0.117	0.003–4.616	0.252			
Baseline Cr	12.876	1.75–94.736	0.012	11.831	1.522–91.963	0.018
Tumor size	2.323	0.725–7.439	0.156			
Location (Rt lobe)	3.333	0.855–12.991	0.083	2.457	0.587–10.293	0.219
Vascular ablation	0.414	0.127–1.352	0.144			
<b>Local recurrence</b>						
Baseline AFP	1.001	1–1.002	0.179			
Tumor size	1.469	0.474–4.552	0.506			
Location (Rt lobe)	4.091	0.793–21.111	0.092	3.899	0.72–21.121	0.114
Sub-capsule	0.96	0.202–4.567	0.959			
Near vessel	0.562	0.161–1.961	0.366			
Vascular ablation	0.227	0.055–0.931	0.04	0.235	0.056–0.994	0.049

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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