ORIGINAL ARTICLE

# Feeding artery ablation before radiofrequency ablation for hepatocellular carcinoma may reduce critical recurrence

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## Abstract

**Background and Aim:** Percutaneous radiofrequency ablation (RFA) is a minimally invasive and curative local treatment for hepatocellular carcinoma (HCC). However, serious concerns remain regarding critical recurrences such as metastasis, dissemination, and/or seeding due to RFA. In August 2006, we introduced selective feeding artery ablation before tumor ablation to reduce the risk of critical recurrence by blocking tumor blood flow. The aim of the present study was to clarify whether feeding artery ablation before tumor ablation can reduce the risk of critical recurrence after RFA.

**Methods:** This study retrospectively analyzed 279 patients with primary, solitary, and hypervascular HCC $\leq 5$ cm in diameter who were treated with RFA alone between April 2001 and August 2013. Critical recurrence was defined as intra- or extrahepatic metastasis, dissemination, or seeding that was difficult to treat radically.

**Results:** Of the 279 HCC patients, 157 patients were treated with conventional RFA alone, and 122 patients underwent RFA with prior feeding artery ablation. Although no significant differences were seen in the rates of local tumor progression-free survival, overall recurrence-free survival, or overall survival between a conventional RFA group and a prior feeding artery ablation group, significant differences were seen in rates of critical recurrence-free survival and cancer-specific survival (5-year, 69 *vs* 81%, $P = 0.01$ and 76 *vs* 88%, $P = 0.03$, respectively). On multivariate analysis, prior feeding artery ablation, tumor diameter, and alpha-fetoprotein were independent factors related to critical recurrence.

**Conclusions:** Feeding artery ablation before tumor ablation may reduce the risk of critical recurrence.

## Introduction

Radiofrequency ablation (RFA) is a minimally invasive, repeatable, and curative local treatment that has already been recommended for early-stage hepatocellular carcinoma (HCC) that is unsuitable for surgical resection.[1,2] However, serious concerns remain regarding critical recurrences such as metastasis, dissemination, and/or seeding caused by RFA[3–6] as such recurrences are difficult to treat radically and almost certainly to lead to primary cancer death.[7,8] Excessive elevation of intratumor pressure by RFA has been considered an underlying mechanism of critical recurrence after RFA for HCC. Tanaka et al. indicated that arterial hypervascular tumors already have an elevated intratumor pressure compared with surrounding liver tissue.[9] Kotoh et al. reported that intratumor pressure is elevated during RFA.[10] Therefore, a further elevation of intratumor pressure during RFA causes expulsive tumor cell dissemination and may increase the risk of uncontrollable critical recurrence, such as metastases or

dissemination. If tumor blood flow could be blocked before tumor ablation, the risk of critical recurrence may be reduced to avoid excessive elevation of intratumor pressure. In August 2006, we introduced selective ablation of the feeding artery before tumor ablation to reduce the risk of critical recurrence as this technique is able to block tumor blood flow. The aim of the present study was to clarify whether feeding artery ablation before tumor ablation can reduce the risk of critical recurrence after RFA for hypervascular HCC.

## Methods

***Patients.*** This was a retrospective cohort study. Between April 2001 and December 2015, 476 consecutive primary HCC patients were curatively treated with percutaneous RFA in Wakayama Medical University Hospital. HCC was diagnosed on the basis of the typical hallmarks of HCC on contrast imaging modalities (hypervascular in the arterial phase with washout in
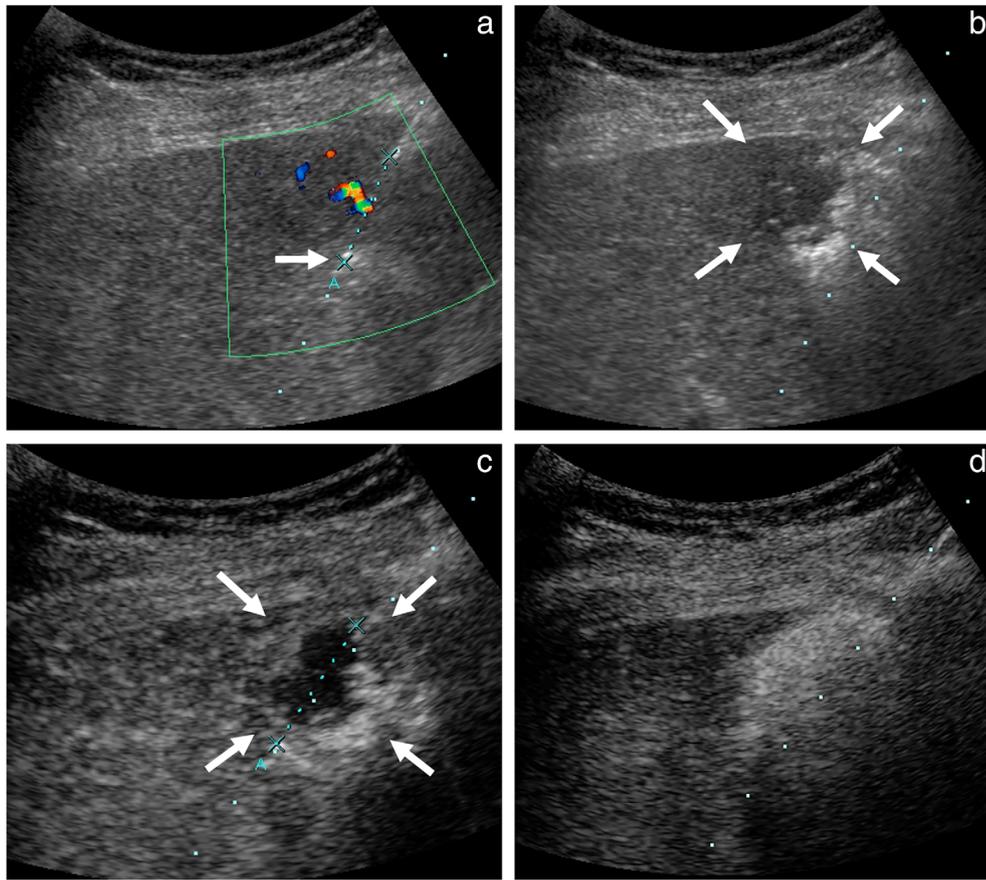
**Figure 1** (a) The feeding artery of an S6, 15-mm hepatocellular carcinoma is identified using color Doppler imaging, and an electrode (electrode tip, arrow) is inserted near the feeding artery close to the tumor. (b) Arrows show the tumor after feeding artery ablation. (c) Disappearance of tumor blood flow is immediately confirmed using contrast-enhanced ultrasonography (arrows), and an electrode is inserted into the tumor. (d) the entire tumor has been completely ablated.

the portal venous or delayed phases),[11] such as contrast-enhanced computed tomography (CT), dynamic magnetic resonance imaging (MRI), and/or contrast-enhanced ultrasonography (CEUS). Eligibility criteria for RFA were as follows: (i) no vascular invasion on diagnostic imaging; (ii) no refractory ascites; (iii) platelet count $\geq 5 \times 10^4/mm^3$; (iv) prothrombin time $\geq 50\%$; (v) total bilirubin level < 3 mg/dL; and (vi) no extrahepatic metastases. Of the 476 patients with primary HCC, 71 patients treated using a combination of RFA and transcatheter arterial embolization (TACE) and six patients treated using a combination of RFA and percutaneous ethanol injection therapy were excluded from the present study because these lesions were almost all located adjacent to a large Glisson's sheath. Furthermore, another 78 patients with multiple HCCs or maximum tumor diameter > 5 cm, 3 patients lost to follow-up after RFA, 1 patient treated by liver transplantation after RFA, and 1 patient with advanced cancer of another organ were excluded. Finally, 279 patients with solitary HCC $\leq 5$ cm in diameter were divided into groups receiving either conventional RFA (n = 157) or RFA after feeding artery ablation (n = 122). This retrospective study was approved by the ethics committee at our institution and conformed to the Declaration of Helsinki. The need for patients to provide written informed consent was waived due to the retrospective nature of the investigation.

***Conventional RFA technique.*** Percutaneous RFA using the Cool-tip RF system (Medtronic, Minneapolis, MN, USA) was performed under ultrasonographic guidance in all patients. Artificial pleural effusion or artificial ascites was produced using saline as needed. The impedance control mode was used with a 17-gauge, cooled-tip electrode with a 2- or 3-cm exposed tip. After an electrode was inserted into the tumor, ablation was started at 40 W for the 2-cm exposed tip or 60 W for the 3-cm exposed tip. Electric power was increased at a rate of 10 W/min. When a rapid increase in impedance occurred, output was stopped automatically, and ablation was restarted after a short time at an output 10 W lower. Duration of a single ablation was 6 min for the 2-cm electrode and 12 min for the 3-cm electrode. Temperature of the needle tip was measured after radiofrequency (RF) exposure, with additional ablation performed if the temperature was below 65°C. The electrode track was not ablated in any patient to prevent seeding and hemorrhage.

**Table 1** Comparison of baseline characteristics between conventional RFA and prior feeding artery ablation groups

|  | Overall ($n$ = 279) | Conventional RFA group ($n$ = 157) | Prior feeding artery ablation group ($n$ = 122) | $P$ value |
| --- | --- | --- | --- | --- |
| Age (year) | 70 (30–88) | 68 (42–87) | 71 (30–88) | 0.03 |
| Gender (male/female) | 156/123 | 90/67 | 66/56 | 0.63 |
| Tumor diameter (mm) | 20 (10.0–50.0) | 20.0 (10.0–50.0) | 20.0 (10.0–50.0) | 0.46 |
| Child-Pugh class (A/B/C) | 185/90/4 | 101/53/3 | 84/37/1 | 0.45 |
| Etiology (HBV/HCV/non-virus) | 26/210/43 | 16/122/19 | 10/88/24 | 0.22 |
| AFP (ng/mL) | 16.1 (0.6–7836.9) | 18.6 (1.3–7836.9) | 14.1 (0.6–5934.3) | 0.08 |
| AFP-L3 (%) | 0.0 (0.0–84.7) | 0.0 (0.0–84.7) | 0.0 (0.0–84.7) | 0.96 |
| DCP (mAU/mL) | 41 (8.0–33 655.0) | 32 (9.0–33 655.0) | 50.0 (8.0–23 608.0) | 0.155 |

Values are expressed as median and range.
AFP, alpha-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; RFA, radiofrequency ablation.

***Feeding artery ablation technique.*** We introduced selective ablation of the feeding artery before tumor ablation in August 2006. This technique was subsequently applied where possible. Feeding arteries of the tumor were identified on color Doppler ultrasonography or CEUS using perflubutane microbubbles (Sonazoid; Daiichi-Sankyo, Tokyo, Japan). CEUS was performed in the tissue harmonic imaging mode with the mechanical index set at 0.6. The Sonazoid dosage was 0.7 mL/body/time. When the feeding artery was invisible under CEUS, conventional RFA was performed. When the feeding artery was judged as possible for selective ablation without a high risk of large bile duct injury, an electrode was inserted near the feeding artery beside the tumor under color Doppler or CEUS guidance and was ablated using the same technique as for conventional RFA. After feeding artery ablation, disappearance of tumor blood flow was immediately confirmed using CEUS in the contrast harmonic imaging mode. When obvious residual tumor blood flow was detected, feeding artery ablation was repeated until residual tumor blood flow disappeared. When several feeding arteries were detected, all were ablated until tumor blood flow disappeared. After the disappearance of tumor blood flow was confirmed on CEUS, an electrode was inserted inside the tumor, and ablation was performed under the same settings as conventional RFA (Fig. 1).

***Evaluation of treatment efficacy and follow-up.***
Treatment efficacy was evaluated on contrast-enhanced CT or MRI 1–3 days after the RFA procedure. Complete tumor ablation was defined as no enhancement in the entire lesion with a safety margin of ≥5 mm on imaging. When the safety margin was considered insufficient, additional ablation was performed 1 week after RFA until complete tumor ablation was confirmed. In principle, all patients were followed up by contrast-enhanced CT or MRI, and tumor markers such as alpha-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive AFP (AFP-L3), and des-gamma-carboxy prothrombin (DCP) every 3 months.

***Evaluation of outcome after RFA.*** Local tumor progression, overall recurrence, and overall survival were set as standard primary end-points. Local tumor progression was defined as tumor growth inside or adjacent to the post-RFA lesion. Secondary end-points were critical recurrence, which is difficult to treat radically, and cancer-specific survival. Critical

recurrence was defined as >3 intrahepatic recurrences, recurrence with vascular invasion, seeding, dissemination, and/or extrahepatic metastasis.[12] The reason for including >3 intrahepatic recurrences in the criteria for critical recurrence was that this situation represents an advanced stage outside the indications for RFA. Seeding was defined as present when, during the course of follow-up after RFA, new lesions were identified in the thoracic wall, abdominal wall, diaphragm, or peritoneal cavity on imaging. Dissemination was defined as diffuse local tumor progression around the treated lesion with RFA.[5] Factors related to critical recurrence and cancer-specific survival were also analyzed.

***Evaluation of safety.*** To evaluate the safety of the feeding artery ablation method, the frequency of ablation-related complications was compared between conventional RFA and prior feeding artery groups. Major complications were defined as an increase in the level of care, a need for hospital admission, or a requirement for treatment of a complication.[13]

***Statistical analysis.*** Values are expressed as median and range. The Mann–Whitney $U$ test was used to analyze continuous variables that did not show normal distributions. When continuous variables were normally distributed, Student's *t*-test was used. Fisher's exact test or the $\chi^2$ test was used to analyze categorical variables. Cumulative recurrence-free survival, local tumor progression-free survival, critical recurrence-free survival, and cancer-specific survival rates were computed using the Kaplan–Meier method and compared using log-rank testing. Uni- and multivariate analyses for factors related to critical recurrence and cancer-specific survival were performed using Cox proportional hazards regression models. The criterion for selecting factors for multivariate analysis was a result of $P < 0.05$ from univariate analysis. Results are expressed as hazard ratios with 95% confidence intervals, and values of $P < 0.05$ were considered significant for all analyses using SPSS version 22.0 software (SPSS, Chicago, IL, USA).

# Results

***Patients characteristics.*** As all patients were judged as having achieved complete ablation on imaging, the technical success rate was 100% in both groups. Median follow-up periods

for the conventional RFA and prior feeding artery ablation groups were 1710 days (range, 113–5564 days) and 1507 days (range, 158–3639 days), respectively. Patient characteristics and comparison of baseline characteristics between conventional RFA and prior feeding artery ablation groups are summarized in

Table 1. While age differed significantly between groups ($P = 0.03$), no significant differences were seen in other baseline factors such as gender, tumor diameter, Child-Pugh class, etiology, AFP, AFP-L3, or DCP levels.

### Comparisons of local tumor progression, overall recurrence, and overall survival between conventional RFA and prior feeding artery ablation groups.

Comparisons of cumulative local tumor progression-free survival, overall recurrence-free survival, and overall survival curves between conventional RFA and prior feeding artery ablation groups are shown in Figure 2. No significant difference in local tumor progression-free survival was seen between groups ($P = 0.55$). Five-year local tumor progression-free survival rates for conventional RFA and prior feeding artery ablation groups were 84 and 80%, respectively. Comparing local tumor progression-free survival rates between conventional RFA and prior feeding artery ablation groups according to tumor size categories, tumors of diameter ≤2 cm, >2 cm but ≤3 cm, and >3 cm showed no significant differences (5-year 93 *vs* 86%, $P = 0.45$; 77 *vs* 57%, $P = 0.10$; and 59 *vs* 84%, $P = 0.25$, respectively). No significant difference in overall recurrence was seen between groups ($P = 0.23$). Five-year overall recurrence-free survival rates for conventional RFA and prior feeding artery ablation groups were 27 and 25%, respectively. Similarly, no significant difference in overall survival was seen between the two groups ($P = 0.18$). Five-year overall survival rates for conventional RFA and prior feeding artery ablation groups were 57 and 63%, respectively.

### Comparisons of critical recurrence and cancer-specific survivals between conventional RFA and prior feeding artery ablation groups.

Comparisons of cumulative critical recurrence-free and cancer-specific survival curves between conventional RFA and prior feeding artery ablation groups are shown in Figure 3. A significant difference in critical recurrence-free survival rates was seen between groups ($P = 0.01$). Five-year critical recurrence-free survival rates for conventional RFA and prior feeding artery ablation groups were 69 and 81%, respectively.
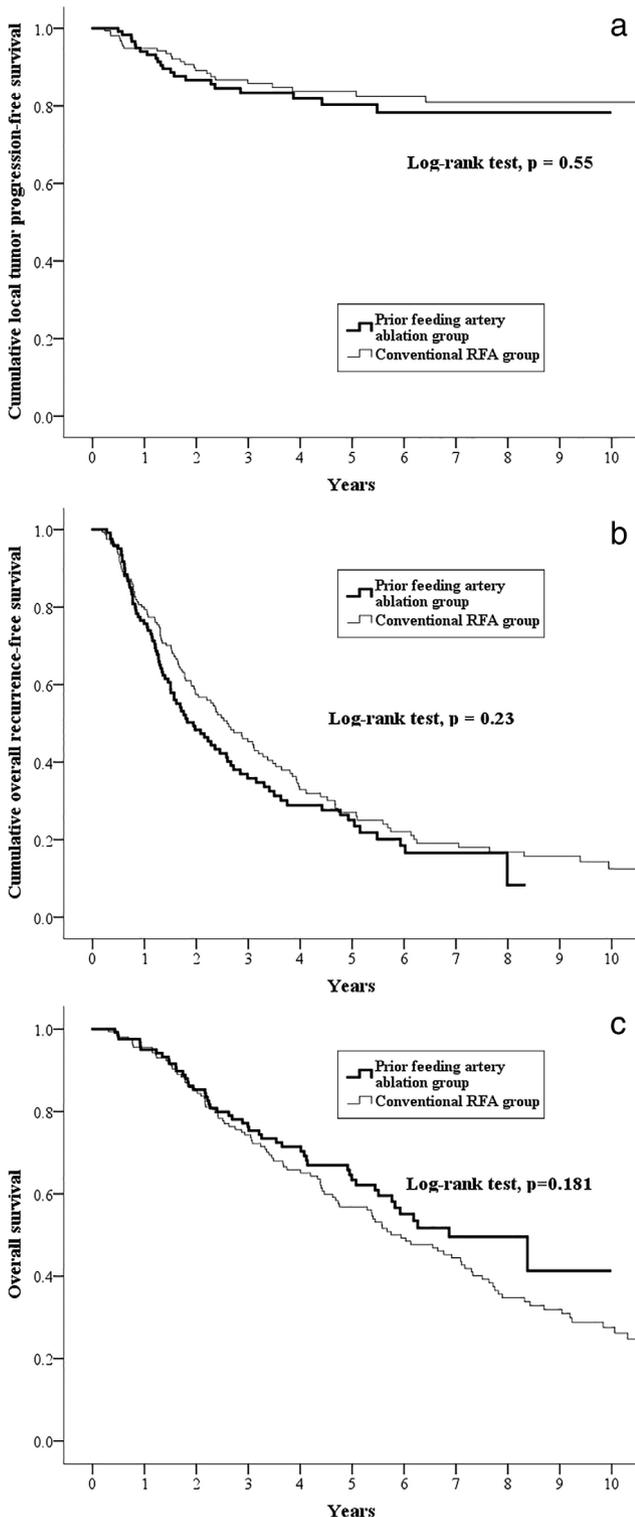


**Figure 2** (a) Comparison of cumulative local tumor progression-free survival curves between conventional radiofrequency ablation (RFA) and prior feeding artery ablation groups. No significant difference is evident between groups ($P = 0.55$). Five-year local tumor progression-free survival rates for conventional RFA and prior feeding artery ablation groups are 84 and 80%, respectively. (b) Comparison of cumulative overall recurrence-free survival curves between conventional RFA and prior feeding artery ablation groups. No significant difference is seen between groups ($P = 0.23$). Five-year overall recurrence-free survival rates for conventional RFA and prior feeding artery ablation groups are 27 and 25%, respectively. (c) Comparison of cumulative overall survival curves between conventional RFA and prior feeding artery ablation groups. No significant difference is seen between groups ($P = 0.18$). Five-year overall survival rates for conventional RFA and prior feeding artery ablation groups are 57 and 63%, respectively.
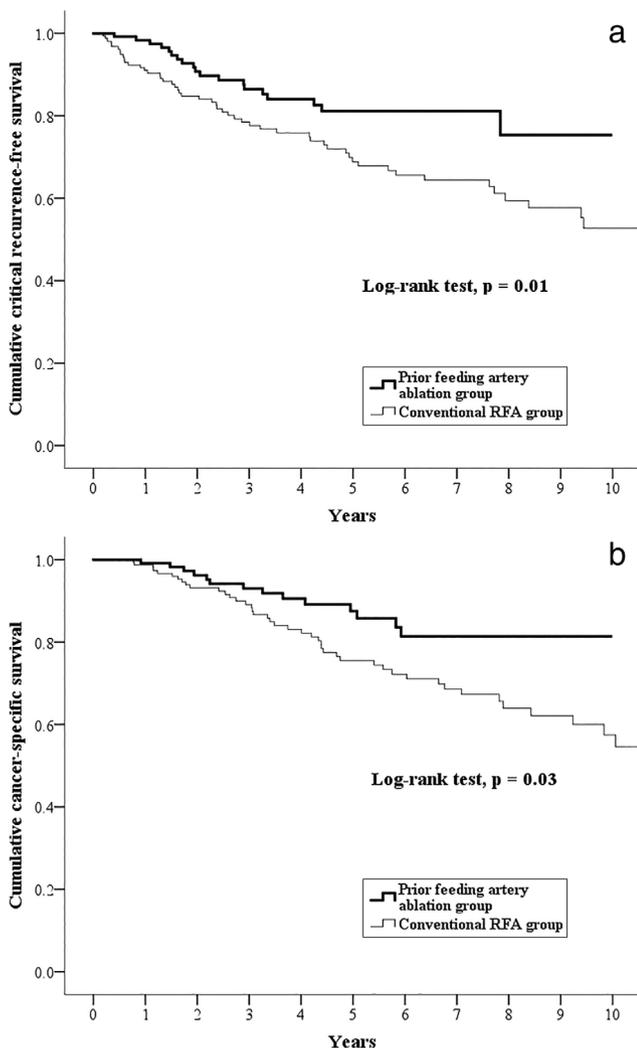
**Figure 3** (a) Comparison of cumulative critical recurrence-free survival curves between conventional radiofrequency ablation (RFA) and prior feeding artery ablation groups. A significant difference in recurrence is seen between groups ($P = 0.01$). Five-year critical recurrence-free survival rates for conventional RFA and prior feeding artery ablation groups are 69 and 81%, respectively. (b) Comparison of cumulative cancer-specific survival curves between conventional RFA and prior feeding artery ablation groups. A significant difference is again seen between groups ($P = 0.03$). Five-year cancer-specific survival rates for conventional RFA and prior feeding artery ablation groups are 76 and 88%, respectively.

A significant recurrence was also seen in cancer-specific survival between groups ($P = 0.03$). Five-year cancer-specific survival rates for conventional RFA and prior feeding artery ablation groups were 76 and 88%, respectively.

***Factors related to critical recurrence and cancer-specific survival.*** Results of uni- and multivariate analyses for factors related to critical recurrence are shown in Table 2. On univariate analyses, significant differences were apparent in prior feeding artery ablation, tumor diameter, and AFP level.

Multivariate analysis revealed all of these factors as independently associated with critical recurrence.

Results of uni- and multivariate analyses for factors related to cancer-specific survival are shown in Table 3. Univariate analyses revealed prior feeding artery ablation, tumor diameter, and AFP level as significant factors. Of these factors, tumor diameter and AFP level were independent factors on multivariate analysis.

***Comparison of ablation-related complication between conventional RFA and prior feeding artery ablation groups.*** A total of 18 complications were encountered. No patient deaths occurred within 30 days of RFA. A comparison of ablation-related complications between conventional RFA and prior feeding artery ablation groups is shown in Table 4. No significant differences in incidences of major or minor complication were seen between groups.

## Discussion

This is the first study to evaluate whether ablation of the tumor-feeding artery before tumor ablation in RFA for hypervascular HCC could reduce the risk of critical recurrence after RFA. The present study demonstrated that the prior feeding artery ablation method could reduce the critical recurrence risk compared to conventional RFA, presumably by decreasing intratumoral pressure after blocking tumor blood flow.

Previous studies have already reported that feeding artery ablation before tumor ablation reduces recurrence rates. A 2009 randomized controlled trial by Hou *et al.* found that HCC recurrence rates at 6 months after RFA were 17.33% in a feeding artery ablation group and 31.33% in a conventional RFA group ($P = 0.04$).[14] In 2018, the same group consecutively demonstrated that, although no significant difference between the prior feeding ablation artery group and the conventional RFA group was seen in intrahepatic distant recurrence rate (40.4 *vs* 42.6%, respectively; $P = 0.834$), the local tumor progression rate tended to be lower with prior feeding artery ablation (8.5 *vs* 21.3%, respectively; $P = 0.082$).[15] Cheng *et al.* also indicated in a retrospective study that the local tumor progression rate was significantly reduced in a prior feeding ablation group compared to a conventional RFA group (17.6 *vs* 48.6%, respectively; $P = 0.038$), although neither intrahepatic recurrence rate (29.4 *vs* 25.7%, respectively; $P = 0.778$) nor overall recurrence rate (41.2 *vs* 62.9%, respectively; $P = 0.14$) differed significantly.[16] The probable benefit of prior feeding artery ablation is to avoid tumor blood flow-induced heat sink effects, which might cause insufficient ablation margins or local residual tumor. After tumor blood flow was blocked by feeding artery ablation, thus reducing heat sink effects via tumor blood flow, the results resemble treatment with TACE before RFA. RFA combined with TACE has already been reported to achieve a larger ablation zone than RFA alone.[17] Prior feeding artery ablation would thus be effective to avoid incomplete tumor ablation due to heat sink effects. In the present study, however, no significant differences in local tumor progression, overall recurrence, or overall survival were identified between prior feeding artery ablation and conventional RFA groups. Furthermore, although local tumor progression-free survival between groups was compared according to tumor size categories, no significant differences were seen in any tumor size

**Table 2** Uni- and multivariate analyses of factors related to critical recurrence

| Variable | Univariate *P* value | HR (95% CI) | Multivariate *P* value | HR (95% CI) |
|---|---|---|---|---|
| Prior feeding artery method | 0.02 | 0.52 (0.31–0.89) | 0.02 | 0.52 (0.31–0.89) |
| Age (y) | 0.11 | 0.98 (0.96–1.00) | | |
| Gender (male) | 0.79 | 0.94 (0.59–1.49) | | |
| Tumor size (mm) | <0.01 | 1.08 (1.05–1.10) | <0.01 | 1.08 (1.05–1.10) |
| Child-Pugh class B, C | 0.42 | 1.23 (0.75–2.03) | | |
| Viral hepatitis | 0.85 | 1.06 (0.56–2.02) | | |
| AFP (ng/mL) | <0.01 | 1.00 (1.00–1.00) | 0.03 | 1.00 (1.00–1.00) |
| AFP-L3 (%) | 0.07 | 1.01 (1.00–1.02) | | |
| DCP (mAU/mL) | 0.08 | 1.00 (1.00–1.00) | | |

AFP, alpha-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive alpha-fetoprotein; CI, confidence interval; DCP, des-gamma-carboxy prothrombin; HR, hazard ratio.

**Table 3** Uni- and multivariate analyses of factors related to cancer-specific death

| Variable | Univariate *P* value | HR (95% CI) | Multivariate *P* value | HR (95% CI) |
|---|---|---|---|---|
| Prior feeding artery method | 0.03 | 0.51 (0.28–0.94) | 0.09 | 0.59 (0.32–1.09) |
| Age (year) | 0.20 | 0.98 (0.96–1.01) | | |
| Gender (male) | 0.36 | 1.27 (0.76–2.12) | | |
| Tumor size (mm) | <0.01 | 1.06 (1.04–1.09) | <0.01 | 1.06 (1.03–1.08) |
| Child-Pugh class B, C | 0.22 | 1.41 (0.81–2.45) | | |
| Viral hepatitis | 0.69 | 0.85 (0.39–1.88) | | |
| AFP (ng/mL) | <0.01 | 1.00 (1.00–1.00) | <0.01 | 1.00 (1.00–1.00) |
| AFP-L3 (%) | 0.72 | 1.01 (0.10–1.02) | | |
| DCP (mAU/mL) | 0.05 | 1.00 (1.00–1.00) | | |

AFP, alpha-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive alpha-fetoprotein; CI, confidence interval; DCP, des-gamma-carboxy prothrombin; HR, hazard ratio.

**Table 4** Comparison of ablation-related complications between conventional radiofrequency ablation (RFA) and prior feeding artery ablation groups

| | Conventional RFA group (*n* = 157) | Prior feeding artery ablation group (*n* = 122) | *P* value |
|---|---|---|---|
| Major complications | 6 | 4 | 1.00 |
| Hemoperitoneum | 0 | 1 | 0.44 |
| Liver abscess | 1 | 3 | 0.32 |
| Portal vein thrombosis | 1 | 0 | 1.00 |
| Seeding | 4 | 0 | 0.13 |
| Minor complications | 3 | 5 | 0.30 |
| Hemoperitoneum | 1 | 3 | 0.32 |
| Biliary ductal stricture | 2 | 1 | 1.00 |
| Biloma | 0 | 1 | 0.44 |

categories. The lack of significant difference in local tumor progression may be attributable to our strict methods of evaluating treatment efficacy. In our hospital, additional ablation was performed until complete ablation with sufficient margins was confirmed, meaning that local tumor progression would depend on the ablation margin regardless of the actual method of ablation. The lack of significant differences in overall recurrence or survival may be attributable to multicentric recurrence and other causes of death except for liver cancer. Prior feeding artery ablation methods would probably have had no inhibitory effects on multicentric recurrence or other causes of death.

Regarding factors contributing to critical recurrence, tumor diameter, AFP level, and prior feeding artery ablation were identified as independent factors in the present study. Both tumor diameter and AFP level are well-known risk factors for recurrence following RFA for HCC.[18,19] Growing HCC shows a strong tendency to invade outside the fibrous capsule, and HCC growth into a portal or hepatic vein causing metastasis is seen with high frequency.[20] On the other hand, AFP and DCP are significantly associated with histological differentiation, closely related to the presence of microvascular portal invasion.[21] A large proportion of poorly differentiated HCCs shows microvascular portal invasion and intrahepatic metastasis.[22] HCC with high tumor marker levels would thus obviously carry a high risk of critical recurrence even when small because occult metastases would exist before RFA. The reduction in risk of critical recurrence by the prior feeding artery ablation method may be due to decreased metastasis or dissemination due to RFA by avoiding excessive intratumor pressure by blocking tumor blood flow before tumor ablation. Based on the above, this method should

be applied to poorly differentiated HCC with microvascular invasion regardless of tumor diameter, such as HCC with high levels of tumor markers or irregular tumor margins.[23] To validate our results, whether this method can reduce the risk of critical recurrence after RFA for HCC with high-grade malignancy should be investigated.

Regarding the prognosis after RFA, both tumor size and AFP are predictors of worse prognosis after RFA.[1,2] In the present study, although tumor size and AFP were also independently related to cancer-specific survival, prior feeding artery ablation was not independently related to cancer-specific survival, whereas prior feeding artery ablation was a factor significantly related to cancer-specific survival on univariate analysis. This might be attributable to differences in the observation period and treatment for critical recurrence between the two groups.

Regarding the safety of prior feeding artery ablation, complication rates were comparable between groups in the present study. Previous studies have also demonstrated feeding artery ablation as a feasible ablation method.[14–16] However, treatment of HCC adjacent to a large Glisson's sheath by either prior feeding artery ablation or conventional RFA is difficult because of the risk of bile duct injury or incomplete ablation due to heat sink effects. As HCC adjacent to a large Glisson's sheath was mainly treated by TACE and RFA in our hospital, patients with such HCCs were not included in the present study. Other methods to decrease intratumor pressure, temporary hepatic vein, or portal branch occlusion with a balloon catheter during RFA have been reported.[24,25] However, the present method of prior feeding artery ablation would be easier and more reliable than those methods. This is because we could repeatedly perform feeding artery ablations until tumor blood flow disappeared on CEUS.

Certain limitations must be considered when interpreting the results of the present study. First, this was a single-center, retrospective observational study and thus entailed some degree of bias. As the feeding artery ablation method was introduced after conventional RFA, the conventional RFA group represents a historical control group, not matched case–controls. A significant difference in age was seen between groups. In addition, selection bias might exist according to the ablation method. This is because the assignment of patients to RFA alone or RFA with prior feeding artery ablation is unclear, and selection of feeding artery ablation is not possible in all HCC cases treated by RFA. Second, the number of patients in the present study was too small to reach definitive conclusions from our results. A larger-scale randomized study is needed to validate our results. Third, whether prior feeding artery ablation can decrease the risk of cancer-specific death remains unclear from our results because this ablation method was not an independent factor related to cancer-specific survival but was one of the independent factors related to critical recurrence leading to cancer-specific death.

In conclusion, prior feeding artery ablation before RFA for hypervascular HCC may reduce the risk of critical recurrence after RFA. We suggest that feeding artery ablation to block tumor blood flow before tumor ablation should be performed where possible to improve the quality of treatment.

## References

1 European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J. Hepatol.* 2018; **69**: 182–236.

2 Heimbach JK, Kulik LM, Finn RS *et al.* AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018; **67**: 358–80.

3 Nicoli N, Casaril A, Abu Hilal M *et al.* A case of rapid intrahepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation. *Am. J. Surg.* 2004; **188**: 165–7.

4 Masuda T, Beppu T, Ishiko T *et al.* Intrahepatic dissemination of hepatocellular carcinoma after local ablation therapy. *J. Hepatobiliary Pancreat. Surg.* 2008; **15**: 589–95.

5 Mori Y, Tamai H, Shingaki N *et al.* Diffuse intrahepatic recurrence after percutaneous radiofrequency ablation for solitary and small hepatocellular carcinoma. *Hepatol. Int.* 2009; **3**: 509–15.

6 Shirai K, Tamai H, Shingaki N *et al.* Clinical features and risk factors of extrahepatic seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. *Hepatol. Res.* 2011; **41**: 738–45.

7 Yang Y, Nagano H, Ota H *et al.* Patterns and clinicopathologic features of extrahepatic recurrence of hepatocellular carcinoma after curative resection. *Surgery.* 2007; **141**: 196–202.

8 Kawano Y, Sasaki A, Kai S *et al.* Prognosis of patients with intrahepatic recurrence after hepatic resection for hepatocellular carcinoma: a retrospective study. *Eur. J. Surg. Oncol.* 2009; **35**: 174–9.

9 Tanaka T, Yamanaka N, Oriyama T, Furukawa K, Okamoto E. Factors regulating tumor pressure in hepatocellular carcinoma and implications for tumor spread. *Hepatology.* 1997; **26**: 283–7.

10 Kotoh K, Nakamuta M, Morizono S *et al.* A multi-step, incremental expansion method for radio frequency ablation: optimization of the procedure to prevent increases in intra-tumor pressure and to reduce the ablation time. *Liver Int.* 2005; **25**: 542–7.

11 EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J. Hepatol.* 2012; **56**: 908–43.

12 Shimizu R, Tamai H, Mori Y *et al.* The arterial tumor enhancement pattern on contrast-enhanced computed tomography is associated with primary cancer death after radiofrequency ablation for small hepatocellular carcinoma. *Hepatol. Int.* 2016; **10**: 328–39.

13 Ahmed M, Solbiati L, Brace CL *et al.* Image-guided tumor ablation: standardization of terminology and reporting criteria – a 10-year update. *J. Vasc. Interv. Radiol.* 2014; **25**: 1691–1705.e4.

14 Hou YB, Chen MH, Yan K, Wu JY, Yang W. Adjuvant percutaneous radiofrequency ablation of feeding artery of hepatocellular carcinoma before treatment. *World J. Gastroenterol.* 2009; **15**: 2638–43.

15 Zhang ZY, Lee JC, Yang W *et al.* Percutaneous ablation of the tumor feeding artery for hypervascular hepatocellular carcinoma before tumor ablation. *Int. J. Hyperthermia.* 2018; **35**: 133–9.

16 Cheng YT, Jeng WJ, Lin CC *et al.* Percutaneous radiofrequency ablation of tumor feeding artery before target tumor ablation may reduce local tumor progression in hepatocellular carcinoma. *Biom. J.* 2016; **39**: 400–6.

17 Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. *Cancer.* 2010; **116**: 5452–60.

18 Izumi N, Asahina Y, Noguchi O *et al.* Risk factors for distant recurrence of hepatocellular carcinoma in the liver after complete coagulation by microwave or radiofrequency ablation. *Cancer.* 2001; **91**: 949–56.

19 Kim YS, Rhim H, Cho OK, Koh BH, Kim Y. Intrahepatic recurrence after percutaneous radiofrequency ablation of hepatocellular

carcinoma: analysis of the pattern and risk factors. *Eur. J. Radiol.* 2006; **59**: 432–41.

20 Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y. Growth and spread of hepatocellular carcinoma. A review of 240 consecutive autopsy cases. *Cancer.* 1990; **66**: 2174–9.

21 Zhang X, Li J, Shen F, Lau WY. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* 2018; **33**: 347–54.

22 Fukuda S, Itamoto T, Nakahara H *et al.* Clinicopathologic features and prognostic factors of resected solitary small-sized hepatocellular carcinoma. *Hepatogastroenterology.* 2005; **52**: 1163–7.

23 Tamai H. The prediction of microvascular invasion of hepatocellular carcinoma using multiple imaging modalities. *Hepatoma Res.* 2018; **4**: 75.

24 de Baere T, Bessoud B, Dromain C *et al.* Percutaneous radiofrequency ablation of hepatic tumors during temporary venous occlusion. *AJR Am. J. Roentgenol.* 2002; **178**: 53–9.

25 Yamasaki T, Kurokawa F, Shirahashi H, Kusano N, Hironaka K, Okita K. Percutaneous radiofrequency ablation therapy for patients with hepatocellular carcinoma during occlusion of hepatic blood flow. Comparison with standard percutaneous radiofrequency ablation therapy. *Cancer.* 2002; **95**: 2353–60.