Percutaneous radiofrequency ablation for hepatocellular carcinoma located in the caudate lobe of the liver

Takeshi Hatanaka[1], Satoru Kakizaki[2], Suzuki Yuhei[1], Suguru Takeuchi[1], Yasushi Shimada[1], Daichi Takizawa[1], Kenji Katakai[3], Ken Sato[2], Masanobu Yamada[2]

(1) Department of Internal Medicine, Isesaki Municipal Hospital, Isesaki, Gunma 372-0817, Japan ; (2) Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Gunma 371-8511, Japan ; (3) Department of Internal Medicine, Katakai Clinic, Isesaki, Gunma 372-0813, Japan.

Abstract

Aim : **This study aimed to evaluate the effectiveness and safety of radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) located in the caudate lobe of the liver.**

Patients and methods : **Between 2012 April and 2014 February, 142 patients with HCC meeting the Milan criteria were enrolled in this study. Of these patients, nine patients had HCC located in the caudate lobe (caudate group). Six of the nine cases were located in the Spiegel lobe, two cases were located in the paracaval portion and one case was located in the caudate process. We evaluated the local recurrence rate and RFA-related complications in the caudate group and non-caudate group.**

Results : **The local recurrence rate in the caudate group was 12.5% at 1 year and 12.5% at 2 years, while the local recurrence rate in the non-caudate group was 14.9% at 1 year and 29.0% at 2 years ; there were no significant differences between the groups. No complications were observed in the caudate group, and minor complications were observed in six patients (4.5%) in the non-caudate group. No major complications or mortalities were observed in either group, and the complication rates were not significantly different between the groups (P = 1).**

Conclusions : **RFA for HCC in the caudate lobe and the non-caudate lobe has equivalent effectiveness and safety. RFA is a promising treatment option for HCC arising in the caudate lobe.** (Acta gastroenterol. belg., **2015**, 78, **267-273**).

Key words : hepatocellular carcinoma, radiofrequency ablation, caudate lobe.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide (1). It is the fifth most common malignant disease in men and the eighth most common malignant disease in women (1). Current options for curative treatment of HCC consist of surgical resection, liver transplantation and radiofrequency ablation (RFA). However, HCC arising in the caudate lobe is considered to be difficult to treat with curative therapy because of its location, between the right and left lobes of the liver, near the hepatic hilus and the inferior vena cava. Surgical resection for HCC in the caudate lobe carries a high surgical risk because it is associated with significantly higher intraoperative blood loss and longer operative time than that in other locations (2,3). Although RFA is a local curative therapy (4,5), RFA for HCC in the caudate lobe is thought to be a contraindication because of the deep tumor location from the body surface, presence of adjacent large vessels, such as the portal vein trunk and inferior vena cava, and difficulty in performing safe puncture of the tumors. Some reports have described the therapeutic outcomes of RFA for HCC in the caudate lobe (6-10), reporting that RFA for HCC in the caudate lobe carries a high local recurrence rate (6,7). Previous authors have also discussed the possibility of the heat sink effect of the inferior vena cava and the restricted puncture approach (7) and concluded that it was necessary to pursue a revised method to reduce local recurrence (7).

In the present study, we evaluated the local recurrence rate and incidence of RFA-related complication for HCC in the caudate lobe compared to that observed in other locations.

Patients and methods

Patient eligibility

Between 2012 April and 2014 February, 142 patients with HCC participated in this study. All patients were treated at Isesaki Municipal Hospital. Of these patients, nine patients had HCC in the caudate lobe. The inclusion criteria were as follows : (a) ineligible for surgical resection/liver transplantation or patient refusal for surgery ; (b) Eastern Cooperative Oncology Group performance status, grade 2 or less ; (c) a single tumor ≦ 5 cm in diameter or three or fewer tumors ≦ 3 cm in diameter ; (d) Child-Pugh class A or B ; (e) no extrahepatic metastasis ; (f) no vascular invasion ; (g) platelet count ≧ 50,000/mm^3 ; (h) prothrombin activity ≧ 50%. The exclusion criteria were as follows : (a) tumors not visualized on ultrasonography ; (b) refractory ascites ; (c) enterobiliary reflux ; (d) total bilirubin level ≧ 3 mg/dl ; (e) other active malignancy that may affect the patient prognosis.

The diagnosis of HCC was established based on findings of nodular enhancement in the arterial phase and wash out in the delayed phase on dynamic computed tomography (CT) and/or dynamic magnetic resonance imaging (MRI) according to the AASLD guidelines (11).

Correspondence to : Correspondence to : Satoru Kakizaki, M.D., Ph.D., Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan. E-mail : kakizaki@ gunma-u.ac.jp

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When the nodules were not typical on CT or MRI imaging, we performed a liver biopsy and diagnosed it based on the results of a histological examination.

All RFA procedures were performed percutaneously using ultrasonographic guidance. We performed RFA alone or in combination with transarterial chemoembolization (TACE). In principle, HCC lesions were treated with RFA combined with TACE when measuring 2 cm larger or exhibiting contact with major vessels in the caudate group. Informed consent was obtained from all patients.

RFA procedure

We performed RFA with the patient in the supine or head up position in all cases. We continuously monitored the heart rate, blood pressure and saturation of oxygen during treatment. One gram of cefazolin sodium was intravenously administered before the RFA procedure to prevent infectious disease. A local anesthetic (1% lidocaine) was injected from the site of insertion in the skin and liver surface along the planned puncture line. We incised the skin with a small lancet and inserted the 17-G cool tip needle with a 2- or 3-cm exposed tip (Covidien, Mansfield, MA, USA) into the tumor area with ultrasound guidance. During treatment, all patients were treated with conscious sedation via the intravenous injection of 15 mg of pentazocine hydrochloride. When the patients complained of intolerable pain, we intravenously administered an additional 15 mg of pentazocine hydrochloride. The ablation time ranged from 3-12 min per procedure. When the roll off temperatures were under 60°C after ablation, then we increased the ablation time until we obtained a roll off temperature above 60°C. After ablation, we withdrew the needle and evaluated the degree of tract needle bleeding using Color Doppler imaging. When we detected continuous tract needle bleeding, we ablated the bleeding point at the surface of the liver. This process was repeated until the entire tumor was adequately ablated.

Approaches for RFA

We identified two approaches to insert the ablation needle into the HCC in the caudate lobe. The first is the epigastric approach (EA), in which the ablation needle is transfixed from the lateral segment to the targeted HCC via the lesser omentum. In this approach, we evaluated the vessels between the lateral segment and caudate lobe using color Doppler imaging and CT or MRI and carefully placed the ablation needle forward to the target the HCC lesion because it exits the liver once and may potentially penetrate any major vessel in the trans-omental tract. The second method is the right costal approach (RCA), in which the ablation needle is transfixed from the right lobe of the liver to the targeted HCC lesion. We mainly used the epigastric approach. When the HCC was located in the paracaval portion or caudate process and we could not find the puncture route via the epigastric approach, we used the right costal approach.

Assessment of ablation and follow-up schedule

One to three days after RFA, dynamic CT with a 3-5 mm section thickness was performed to evaluate the RFA procedure. When the ablated area was large enough to cover the pretreatment HCC area on arterial and portal venous phase images, we defined such case as complete ablation. When complete ablation was not obtained, the RFA procedure was repeated until complete ablation was achieved.

In order to detect HCC recurrence earlier, we performed dynamic CT or dynamic MRI every 3-4 months. The serum alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) levels were measured every 1-3 months. Local tumor recurrence was defined as the appearance of enhancement in the arterial phase around the ablation area.

Statistical analysis

The statistical analyses were performed with the EZR graphical interface (12). Student's *t*-test was used to compare continuous data following a normal distribution, and Welch's t test was used to compare data without a normal distribution. Fisher's exact test was employed to compare categorical data. The local tumor recurrence rate was calculated according to the Kaplan Meier method. A P value of < 0.05 was considered to be statistically significant.

Results

We divided the 142 consecutive patients with HCC into two groups according to the tumor location, the caudate group (n = 9) and non-caudate group (n = 133). The characteristics of the caudate and non-caudate groups are summarized in Table 1 and Table 2. In the caudate group, six HCCs were located in the Spiegel lobe, two were located in the paracaval portion and one was located in the caudate process according to the Kumon classification (13). In the caudate group, five patients were male and four patients were female. In the non-caudate group, 73 patients were male and 61 were female. The mean age of the patients was 69.0 ± 9.4 years (caudate group), 71.5 ± 7.5 years (non-caudate group), respectively. The etiology of HCC was HBV/HCV/other in 1/5/3 patients (caudate group) and 5/111/18 patients (non-caudate group), respectively. The Child-Pugh class was A/B in 8/1 patients (caudate group) and 105/29 patients (non-caudate group), respectively. All characteristic parameters in the caudate group and non-caudate group showed no significant differences between the groups, except for the serum level of total bilirubin.

Local recurrence rate

Local recurrence was observed in two nodules in the caudate lobe at 4.8 and 27.1 months after RFA treatment. In the non-caudate group, local recurrence was observed

Table 1. — **Characteristic of the nine patients with HCC in the caudate lobe of the liver**

Case	Age/sex	Diameter (cm)	Location	Vascular contact	Combination With TACE	Puncture approach	Number of session	Length of needle	Follow up (month)
1	64/M	2.1	Spiegel	None	No	EA	1	2 cm	29.3
2	68/M	2.9	Paracaval	PVT	Yes	EA	1	2 cm	27.2
3	64/F	2.2	Spiegel	IVC	Yes	EA	1	2 cm	26.7
4	73/F	4.5	Caudate process	IVC, PVT	Yes	RCA	1	3 cm	25.8
5	68/M	3.9	Spiegel	IVC, PVT	Yes	EA	2	2 cm	20.2
6	53/M	1.8	Paracaval	IVC	Yes	EA	2	2 cm	13.3
7	80/F	0.7	Spiegel	IVC	No	EA	1	2 cm	4.8
8	66/M	1.8	Spiegel	PVT	No	EA	2	2 cm	2.1
9	85/F	3.0	Spiegel	None	Yes	EA	1	3 cm	13.5

TACE, trans arterial chemoembolization ; PVT, portal vein trunk ; IVC, inferior vena cava ; EA epigastric approach, RCA ; right costal approach.

Table 2. — **Characteristics of the patients and tumors in the caudate group and non-caudate group**

Case (n)	Caudate group (N = 9)	Non-caudate group (N = 134)	*P*-value
Age (mean ± SD, years)	69.0 ± 9.4	71.5 ± 7.5	0.336*1
Sex (Male / Female)	5 / 4	73 / 61	1.0*2
ECOG PS 0 / 1 / 2	6 / 2 / 1	67 / 63 / 4	0.493*3
Etiology (HBV / HCV / others)	1 / 5 /3	5 / 111 / 18	0.382*3
Child-Pugh classification A / B	8 / 1	105 / 29	1.0*2
Total bilirubin, median (range) (mg/dl)	0.67 (0.50-0.86)	0.69 (0.29-2.02)	< 0.001*4
AST (mean ± SD, IU/l)	40.5 ± 24.6	51.5 ± 22.2	0.255*1
ALT (mean ± SD, IU/l)	37.4 ± 32.5	42.5 ± 27.4	0.613*1
Albumin (mean ± SD, g/dl)	3.67 ± 0.43	3.59 ± 0.47	0.603*1
Platelet (mean ± SD, /mm^3)	12.9 ± 5.7	9.9 ± 4.5	0.07*1
PT, median (range) (%)	87 (73-92)	85 (52-133)	0.273*4
Tumor size, median (range) (cm)	2.2 (0.7-4.5)	1.8 (0.7-4.7)	0.135*4
Number of tumor (mean ± SD)	1.44 ± 0.72	1.26 ± 0.52	0.32*1
Follow up period (mean ± SD , month)	16.6 ± 7.1	14.7 ± 7.0	0.051*1
Combined TACE (yes / no)	6 / 3	84 / 50	1.0*2
Number of RFA session 1 / 2 / 3	5 / 3 / 0	134 / 22 / 1	0.148*2
AFP, median (range) (ng/ml)	15 (2-2373)	16 (7-2878)	0.414*4
DCP, median (range) (mAU/ml)	23 (3-3097)	19 (15-550)	0.765*4

ECOG PS, Eastern Cooperative Group Performance Status ; HBV, hepatitis B virus ; HCV, hepatitis C virus ; AST, aspartate aminotransferase ; ALT, alanine aminotransferase ; TACE, transarterial chemoembolization ; AFP, α-fetoprotein ; DCP, des-γ-carboxy prothrombin .
*1 Student's *t*-test, *2 Fisher's exact test, *3 Mann-Whitney U test, *4 Welch's *t*-test.

in 35 cases. The cumulative local recurrence rate in the caudate group was 12.5% and 12.5% at 1 and 2 years, respectively (Fig. 1), while that in the non-caudate group was 14.9% and 29% at 1 and 2 years, respectively. There were no significant differences in the local recurrence rates between the caudate group and the non-caudate group ($P = 0.875$).

Representative cases

Epigastric approach

Figure 2 shows a representative case of the epigastric approach (Case 9). Dynamic computed tomography (CT) revealed HCC of 3.0 cm in diameter in the Spiegel lobe. Trans-arterial chemoembolization (TACE) was performed before RFA. Percutaneous RFA was then performed five days after chemoembolization. We used the epigastric approach because there were no major vessels in the puncture route.

Right intercostal approach

Figure 3 shows a representative case of the right intercostal approach (Case 4). Dynamic magnetic resonance imaging (MRI) revealed HCC of 4.5 cm in diameter in the caudate process of the caudate lobe. The HCC lesion was adjacent to the portal vein trunk and inferior vena

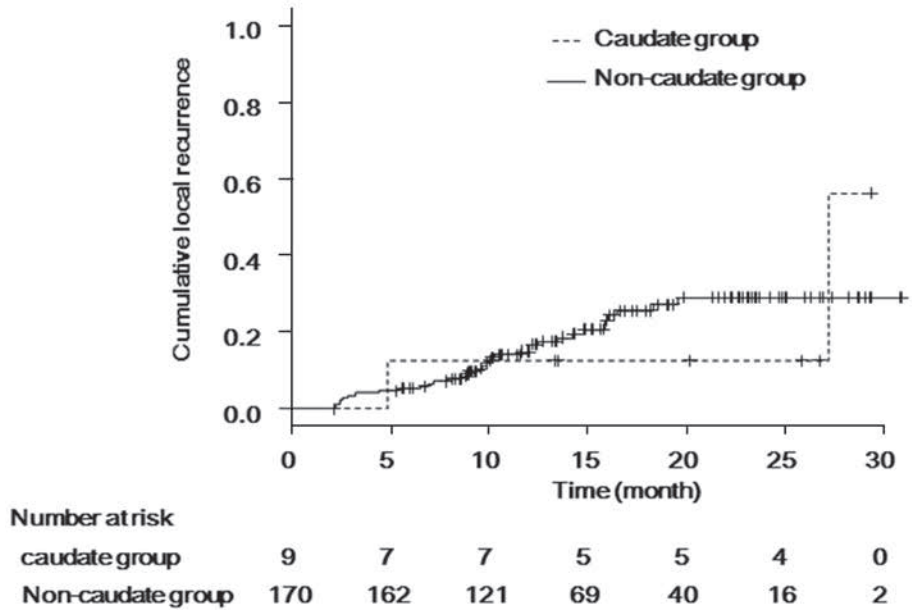

Fig. 1. — Cumulative local recurrence rates. There were no significant differences in the local recurrence rates between the caudate group and the non-caudate group ($P = 0.875$).

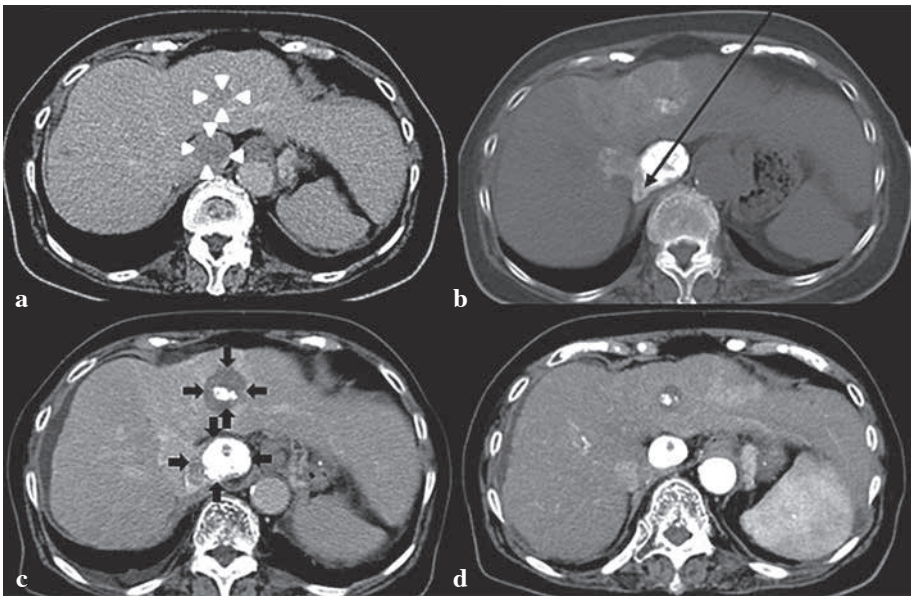

Fig. 2. — Case 9 (a) Dynamic computed tomography (CT) showed two hepatocellular carcinoma (HCC) lesions 3.0 cm in diameter in the Spiegel lobe and 1.2 cm in diameter in segment 3. An assay for hepatitis C antibodies was positive. (b) Transarterial chemoembolization was performed. (c) Percutaneous radiofrequency was performed five days after chemoembolization. We used the epigastric approach because there were no major vessels in the puncture route. Dynamic CT was performed three days after RFA. The tumor was surrounded by hypo-attenuating non-enhancing areas. (d) No local recurrence has been observed for 13.5 months after RFA.
(△) viable tumor. (→) puncture route. (⬆) coaguoblated area.

cava. We were unable to find the puncture route via the epigastric approach, because the lateral segment showed atrophy. Therefore, we used the right intercostal approach after TACE. No local recurrence has been observed for 25.8 months after RFA.

Complications

There were no major complications or mortalities related to the RFA procedure in either group. No minor complications were observed in the caudate group. In the

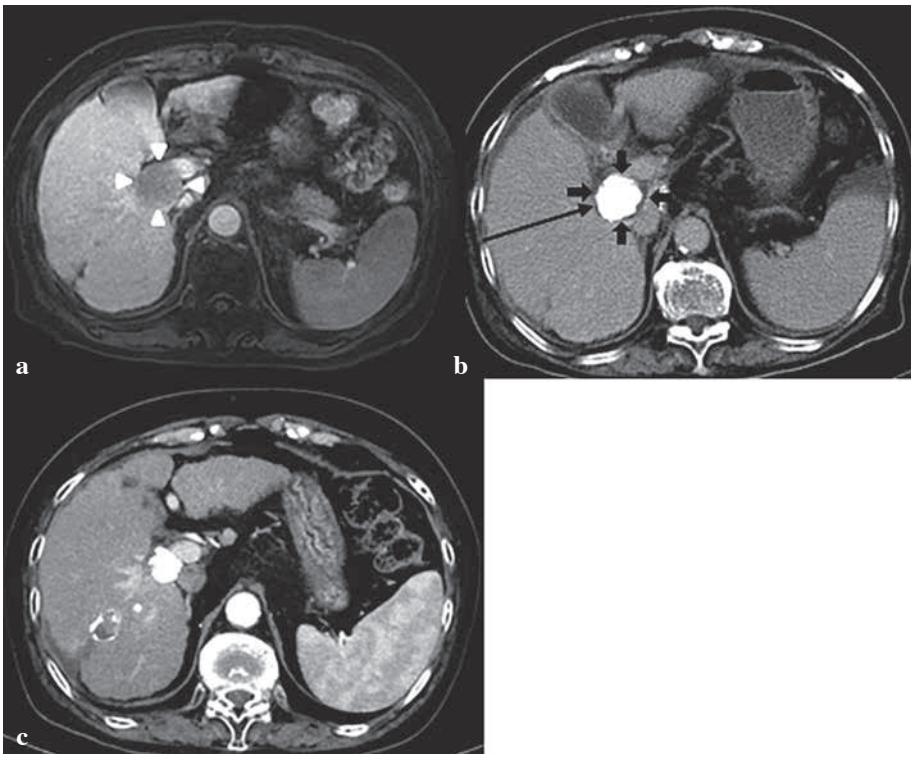

Fig. 3. — Case 4. (a) Dynamic magnetic resonance imaging (MRI) revealed hepatocellular carcinoma (HCC) 4.5 cm in diameter in the caudate process of the caudate lobe. The HCC lesion was adjacent to the portal vein trunk and inferior vena cava. (b) We performed transarterial chemoembolization (TACE) plus radiofrequency ablation (RFA). We were unable to detect the puncture route via the epigastric approach, because the lateral segment showed atrophy. Therefore, we used the right intercostal approach. The tumor was surrounded by hypoattenuating, non-enhancing areas on dynamic computed tomography (CT). (c) No local recurrence has been observed for 25.8 months after RFA.
(△) viable tumor ; (→) puncture route ; (⬆) ablated area.

non-caudate group, there were minor complications in six patients (4.5%), including sub-segmental hepatic infarction in five patients (3.75%) and biloma in one patient (0.76%). All complications were improved with conservative therapy and did not require additional therapy or longer hospitalization. The incidence of RFA-related complications in the groups was not significantly different ($P = 1$).

Discussion

This study suggests that percutaneous RFA for HCC in the caudate lobe of the liver is an effective and safe treatment. In the present study, the local recurrence rate of RFA for HCC in the caudate lobe of the liver was not significantly higher than that in the non-caudate lobe. The caudate lobe is located in the central liver around large vessels deep from the hepatic surface. Therefore, for HCC in the caudate lobe, it is thought to be difficult and dangerous to puncture the nodule from the skin using RFA. However, this study showed no complications or mortalities in the caudate group.

Hepatic resection is a curative therapy, although hepatic resection for HCC arising in the caudate lobe is associated with significantly higher intraoperative blood loss and a longer operative time than that arising in non-caudate regions (2,3). As a result, hepatic resection for HCC in the caudate lobe is a high-risk procedure. In the present study, local recurrence in the caudate group was observed in two nodules in the caudate lobe at 4.8 and 27.1 months after RFA treatment, respectively. The cumulative local recurrence rate in the caudate group was 12.5% and 12.5% at 1 and 2 years, respectively. Kariyama *et al*. (6), Nishigaki *et al*. (7) and Fujimori *et al*. (8) reported local recurrence rates of 12% at 2 years, 22.3% at 4 years and 13.5% at 3 years, respectively, which is similar to our data (See Table 3). Nishigaki *et al*. (7) reported that the local recurrence rate of RFA alone for HCC in the caudate group is significantly higher than that in the non-caudate group. They reported that the location in the caudate lobe of the liver is an independent risk factor for local recurrence according to a multivariate analysis (7). However, there were no significant differences in the local recurrence rates between the caudate group and non-caudate groups in this study. A possible explanation for this discrepancy may the differences in both patient and tumor characteristics. Comparing the patients and tumor characteristics between our and their study, the

Table 3. — **Previous reports concerning RFA for HCC in the caudate lobe of the liver**

Author	Kariyama K. (6)	Nishigaki Y. (7)	Seror O. (9)	Fujimori M. (10)	This study
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Cancer	HCC	HCC	HCC and colon metastases	HCC	HCC
Number of cases	50	20	10	20	9
RFA indication	milan criteria	Solitary	NA	Solitary ≦ 5 cm	milan criteria
tumor size	1.5 cm (median)	1.7 ± 0.5 cm (mean ± SD)	4.1 cm (median)	≦ 3 cm 14 case 3.1-5.0 cm 6 case	2.2 cm (median)
Treatment	RFA alone or TACE plus RFA	RFA alone	RFA alone	TACE plus RFA	RFA alone or TACE plus RFA
Type of guidance	US	US	US and CT	CT	US
Follow up period (mean)	18 month	NA	11.4 month	NA	16.6 month
Local recurrence rate	12% at 2 years	22.3% at 4 years	3/10 nodule	13.5% at 3 years	12.5% at 2 years
Complication	No major complication	No major and minor complication	Major in 1 case and minor in 1 case	Major in 2 cases and minor in 3 cases	No major and minor complication

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; NA, not available; TACE, transarterial chemoembolization; US, ultrasonography; CT, computed tomography.

median size of HCC treated in our study was 2.2 cm and the mean size of HCC in their study was 1.7 cm ± 0.5 cm in the caudate group (See Table 3). In the control group, we evaluated single tumors of ≦ 5 cm in diameter or three or fewer tumors of ≦ 3 cm in diameter in the non-caudate group. On the other hand, they evaluated solitary tumors of less than 3 cm in diameter in the non-caudate group. Several authors have reported that the tumor size is an independent risk factor for local recurrence (14,15). Therefore, the differences in the tumor size may have affected the results of our and their studies.

With respect to reducing the local recurrence rate of RFA, the effectiveness of preceding TACE prior to RFA is controversial. Shibata *et al*. (16) reported that combined RFA plus TACE and RFA alone have equivalent effectiveness for the treatment of small (≦ 3 cm) HCCs. However, in patients with intermediate-sized lesions (diameter, 3.1-5 cm), RFA plus TACE is more effective than RFA alone for extending the ablated area in fewer treatment sessions and needle insertions and decreasing the rate of local tumor progression (17). Peng *et al*. (18) reported that the efficacy of sequential TACE-RFA is better than that of RFA alone for HCC measuring 5 cm in diameter or smaller. They also reported that, in their subgroup analyses, the recurrence-free survival and overall survival rates were better in the sequential TACE-RFA group than in the RFA alone group with tumors measuring 3.1-5.0 cm in diameter. Therefore, preceding TACE before RFA was found to be a better treatment than RFA alone when performing RFA for HCC measuring 3.1-5.0 cm in diameter. Although it is not easy to detect the feeding artery on angiograms and TACE is performed for HCC arising in the caudate lobe (19), preceding TACE before RFA for HCC arising in the caudate lobe is also a better treatment with less complications for reducing the number of punctures. In the present study, all three patients with HCC measuring 3 cm larger in the caudate group were treated with RFA combined with TACE, and no local recurrence was observed.

No complications were observed in the caudate group, and major complications requiring additional therapy or longer hospitalization were absent in both groups. Minor complications were observed in six patients (4.5%) in the non-caudate group and improved with conservative therapy. There were no statistical differences between the groups. In past studies, major complications were observed in 0-10% of cases, and all types of complications were observed in 0%-25% of cases (See Table 3). The low complication rates noted in our study were achieved by careful advancing the ablation needle and avoiding the vital strictures and vessels. A careful examination of the puncture needle line in epigastric approach (EA) and right costal approach (RCA) before RFA is important for avoiding serious complications.

A limitation of this study is the retrospective design with a small number of patients and the short follow-up period. In conclusion, our findings suggest that RFA for HCC in the caudate lobe and the non-caudate lobe has equivalent effectiveness and safety and that RFA is a promising treatment option for HCC arising in the caudate lobe. When encountering HCC lesions measuring 3 cm in diameter or larger in the caudate lobe, RFA combined with TACE may be a better treatment for reducing the local recurrence rates.

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