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Comparison of Radiofrequency Ablation and Transarterial Chemoembolization for Hepatocellular Carcinoma in the Caudate Lobe

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Abstract

Background and Aims Hepatocellular carcinoma (HCC) in the caudate lobe is technically challenging for both radiofrequency ablation (RFA) and transarterial chemoembolization (TACE). However, each of these modalities has its strengths. This retrospective study compares the effectiveness of RFA and TACE in patients with caudate HCC within the Milan criteria.

Methods This study was approved by institutional review board. Between November 2005 and August 2016, we retrospectively reviewed 74 patients with a single HCC $\leq$ 5 cm or up to three HCCs $\leq$ 3 cm without vascular invasion or extrahepatic metastasis who were treated with RFA (n = 43) or TACE (n = 31). The overall survival (OS) and local progression rates were compared after propensity score analysis.

Results The mean follow-up period was 2.8 ± 1.9 years. The 1-, 2-, and 3-year survival rates were 97.1, 94.0, and 80.7% for the RFA group and 89.0, 80.8, and 62.0% for the TACE group, respectively. The clinical variables of the RFA and the TACE groups were well balanced by propensity score adjustment, and the RFA group showed better OS (P = .039) and local progression rates (P = .004) than the TACE group.

Conclusions RFA appears to outperform TACE for patients with caudate HCC within the Milan criteria and should be the favored treatment option when surgical resection is not feasible.

Keywords Chemoembolization · Humans · Liver neoplasms/mortality · Radiofrequency ablation · Survival analysis · Treatment outcome

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Introduction

Hepatocellular carcinoma (HCC) in the caudate lobe is not a common occurrence [1, 2]. Liver transplantation is a feasible treatment option for patients with early HCC in the caudate lobe (defined by the Milan criteria as one lesion $\leq$ 5 cm or 2–3 lesions $\leq$ 3 cm, each without vascular invasion or extrahepatic spread) [3]. However, liver transplantation requires lifelong immunosuppression and there are far fewer liver donors than candidates, making surgical resection a viable curative treatment for cirrhotic patients within Child–Pugh classes A or B. Although surgical resection involves lower risks than liver transplantation and has comparable 5-year survival results [4], the deep location of caudate HCC that is near the porta hepatis and the inferior vena cava (IVC) represents a technical challenge [1, 2, 5, 6]. The complication and recurrence rate after surgical resection of caudate HCC are also higher than those of other lobes [1].

Radiofrequency ablation (RFA) is known to have excellent treatment outcomes for small HCC [7–10], which is equally effective as surgical resection when there is a single HCC and it is ≤ 2 cm [8]. For patients with early caudate HCC, RFA can be a promising alternative treatment when liver transplantation and surgical resection are both not feasible. However, RFA for caudate HCC is considered challenging and risky because the percutaneous puncture route is narrow and surrounded by the IVC, portal vein, and bile ducts [11].

Although transarterial chemoembolization (TACE) is usually reserved for patients with multiple HCCs who fall out with the Milan criteria, there have been several reports on TACE for patients with caudate HCC resulting in variable clinical outcomes [12–15]. Moreover, TACE can serve as an alternative treatment if liver transplantation, surgical resection, and RFA are all unsuitable [16, 17]. To date, it is not clear whether TACE and RFA have a comparable outcome in patients with caudate HCC. In this retrospective study, we compare the overall survival (OS) and local progression rates of TACE and RFA for patients with HCC in the caudate lobe within the Milan criteria.

Materials and Methods

Patients

The institutional review board of our hospital approved this retrospective study, and the informed consent requirement was waived. Patients were included if they had caudate HCC within the Milan criteria (one lesion ≤ 5 cm or 2–3 lesions ≤ 3 cm each without vascular invasion or extra-hepatic spread). Between November 2005 and August 2016, 74 patients within the inclusion criteria were retrospectively reviewed, of which 43 were treated with RFA (Jan 2007–Aug 2016), and the remaining 31 patients underwent TACE (Nov 2005–Aug 2016). All the patients in this study had only one HCC in the caudate lobe.

Patients were excluded if they had a prolonged international normalized ratio (> 1.5), decreased platelet count (< 50,000 cells/μL), or elevated total bilirubin level (> 3 mg/dL). For patients (n = 43) who were treated with RFA, TACE had been attempted in 19 of them (44.2%, 19/43) as an initial treatment, and RFA was subsequently performed because of unselective TACE and expected reduced treatment efficacy (Fig. 1). For patients receiving TACE, RFA was not performed due to unsuitable tumor location (adjacent to the duodenum or hepatic hilum), injury-prone critical structures on the planned puncture route, or personal preference.

HCC was diagnosed according to the guidelines of the American Association for the Study of Liver Disease [18]. At least two dynamic imaging modalities such as triphasic CT scan and MRI were needed for diagnosis. Tissue pathology was acquired in one patient who had an atypical vascular profile on imaging studies and a low α-fetoprotein level (< 200 ng/mL).

RFA Protocol

In this study, all the RFAs for caudate HCCs were performed using CT guidance. For better tumor localization, we routinely used pre-RFA iodized oil targeting (Lipiodol; Andre Guerbet, Aulnay-sous-Bois, France), except for patients with impaired renal function or sufficient tumoral hypodensity in unenhanced CT (n = 3). Informed consent was obtained from all patients before pre-RFA iodized oil targeting and subsequent RFA.

For pre-RFA iodized oil targeting, celiac or common hepatic angiography was performed with a 4- or 5-F angiographic catheter via the right femoral artery. After the feeding arteries of the caudate HCC were identified, we selected the right or left hepatic arteries depending on the origin of the feeding arteries. If difficulty was encountered during catheter advancement, arterial selection was done using a 2.5- or 2.7-F microcatheter (Cantata; Cook Medical, IN, USA, or Progreat; Terumo, Tokyo, Japan). We infused iodized oil until tumor staining was observed in fluoroscopy. Around 2–5 mL of iodized oil was injected according to the HCC size.

For RFA, all patients received moderate intravenous conscious sedation and local infiltration of 2% lidocaine (Xylocaine; AstraZeneca, London, UK) during the procedure. We chose a right intercostal lateral approach (Fig. 2) or anterior epigastric approach (Fig. 3) to treat caudate lobe HCC, as described previously [19]. Percutaneous RFA was performed under CT guidance in all patients using a single RFA electrode with a 200-W generator. We used a 3-cm-long metallic electrode (Big Tip; RF Medical Co., Ltd, Seoul, Korea or Cool-tip; Valleylab, MA, USA) for all types of tumors. In selected cases (n = 2), a 21-gauge Chiba needle was inserted into the tumor margin abutting the IVC and hepatic hilum under CT guidance. Around 1–2 mL of 99% dehydrated ethanol was injected through the Chiba needle during ablation to ensure thermal efficacy of RFA and to avoid bile duct or duodenum injury. A low-dose CT scan with minimalized scan range was obtained after each RFA electrode adjustment. All personnel except the patient were required to step outside the room during

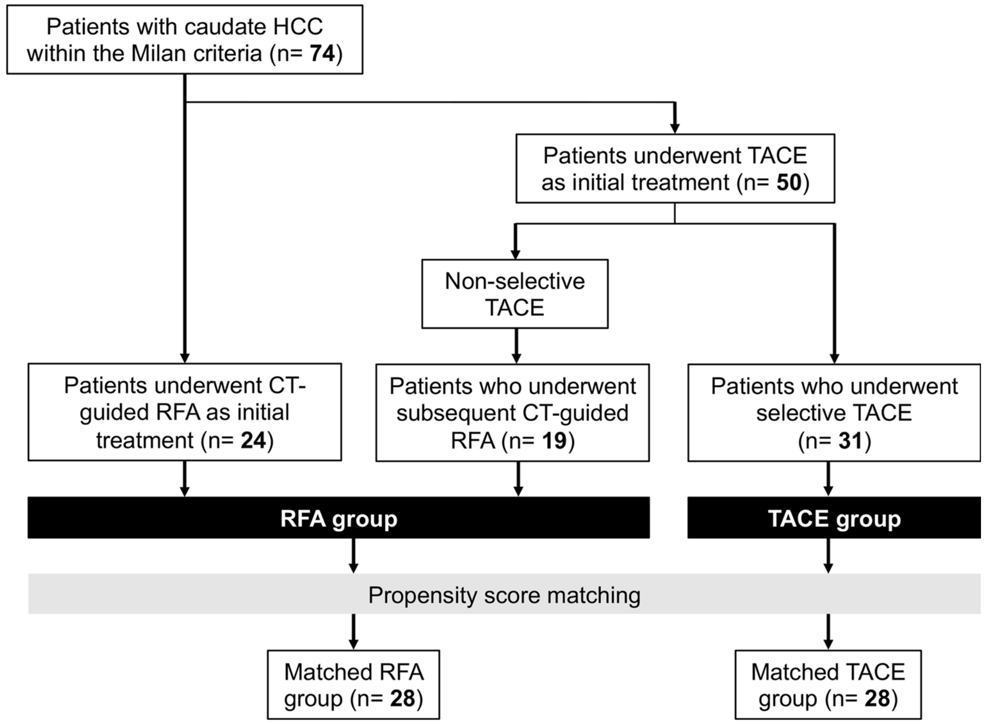

Fig. 1 Flowchart of group assignment

scanning, and the patient was monitored indirectly. We ablated the tract during electrode withdrawal to avoid tumor seeding and tract bleeding after the procedure. Prophylactic antibiotics (Cefazolin, China Chemical & Pharmaceutical, Taipei, Taiwan) were used after the procedure, beginning at the day of RFA for 2 days to prevent infection. The technical success of RFA was defined as complete ablation of the caudate HCC with a surrounding safety margin of 0.5–1.0 cm in the immediate follow-up CT images.

TACE Protocol

Feeding vessels of the caudate HCC were selected similarly to the pre-RFA iodized oil targeting, and microcatheters were routinely used for subsegmental catheterization. TACE was performed with an emulsion of 2–10 mL of iodized oil and 10–40 mg of doxorubicin hydrochloride (Adriblastina; Pfizer, Milano, Italy) according to the tumor size and was infused until arterial flow stasis. Subsequent embolization of the feeding artery was achieved using gelatin sponge particles. The technical success of TACE was defined as successful catheterization and chemoembolization of all caudate feeding arteries with no visible residual tumor stain in post-embolization celiac or common hepatic arteriography.

Follow-Up

After RFA, the patients received α-fetoprotein level checkups and an image study (either ultrasound, dynamic CT, or dynamic MRI) every 3 months. The imaging modalities were used interchangeably depending on the physician's judgment during the follow-up period. Tumor recurrence was diagnosed by the same criteria from the American Association for the Study of Liver Disease guidelines [18]. Local progression was defined as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions according to modified response evaluation criteria in solid tumors [20].

Complications

Complications were graded according to the guidelines of the Cardiovascular and Interventional Radiological Society of Europe [21], which stratify complications into six grades. In short, grade 1 indicates an intra-procedural complication that could be managed within the same session without additional therapy, post-procedural sequelae, or deviation from the normal post-therapeutic course, while grade 6 indicates a procedure-related death.

Statistics

In an attempt to eliminate the potential confounders in patient selection, a matched group of patients for clinical

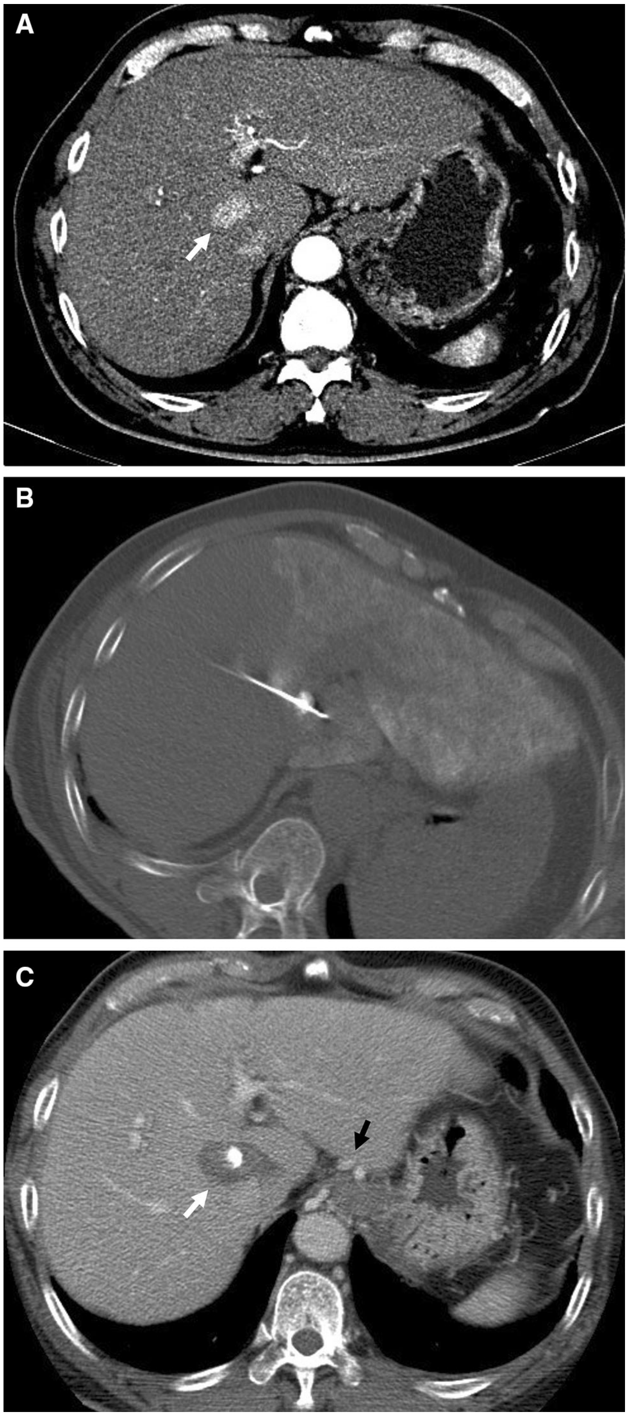

Fig. 2 A 67-year-old male with HCV-related liver cirrhosis and HCC. **A** Axial arterial phase CT of the abdomen showed a 2.4-cm avid enhancing lesion (white arrow) in the caudate process of segment I with delayed phase washout (not shown), which was characteristic of HCC. **B** CT-guided RFA from a right intercostal lateral approach was performed after iodized oil targeting. **C** CT of the abdomen at 3-month follow-up shows complete ablation of the caudate HCC (white arrow). Note the gastroesophageal varices (black arrow). The patient died 2 years later due to variceal bleeding

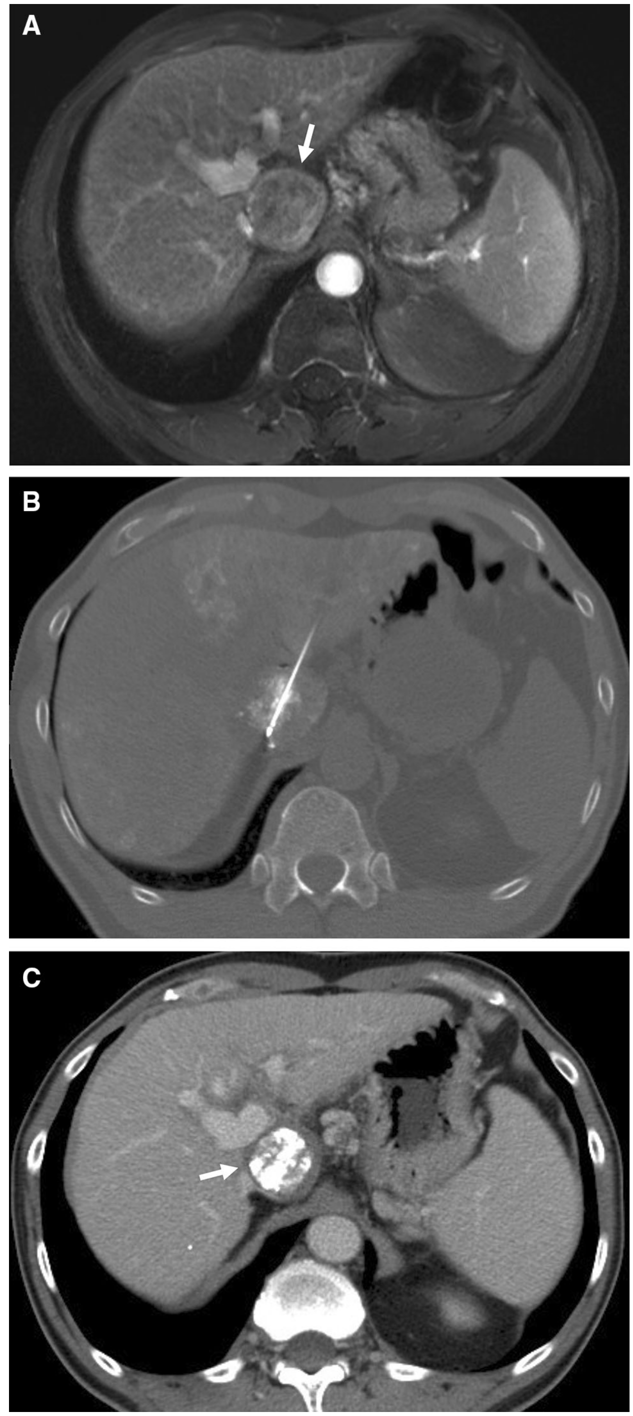

Fig. 3 A 58-year-old male with HBV-related liver cirrhosis and abnormal screening ultrasound. **A** T1-weighted arterial phase MRI of the abdomen demonstrated a 3.3-cm HCC (white arrow) in the Spiegel lobe of segment I with delayed washout (not shown). **B** CT-guided RFA was performed via anterior epigastric approach. **C** CT of the abdomen after 6 months revealed complete ablation of the caudate HCC (white arrow), and this patient has remained free of recurrence for 6 years

outcome comparison was generated using propensity score analysis. We used the software R (version 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) and the R package MatchIt for the matching process, and 1:1 matching with the nearest neighbor method was used to select patients from both groups (RFA and TACE) for the subsequent analysis [22]. Clinical variables with $P < .25$ between the RFA and the TACE groups were included for propensity score generation, including HBV carrier status, alcoholism, serum albumin level, total bilirubin level, serum aspartate transaminase level, prothrombin time, presence of ascites, and tumor location. Statistical analyses other than the propensity score analysis were performed using MedCalc statistical software (MedCalc version 15.4.0.0, Frank Schoonjans, Mariakerke, Belgium). The difference between categorical variables was compared using a X^2 test, and the difference between independent continuous variables was compared using an independent *t* test. The survival analysis was calculated using the Kaplan–Meier method and compared using the log-rank test. The results were considered statistically significant with $P < .05$.

Results

Patients

There were 74 patients enrolled in this study (RFA group, 43; TACE group, 31). The baseline clinical characteristics of the RFA and TACE groups are shown in Table 1. The majority of patients (*n* = 56, 75.7%) included in this study were not treatment-naïve and had received curative treatment such as hepatectomy or RFA for non-caudate tumors in the past. The number of treatment-naïve patients was similar between RFA (*n* = 10, 23.3%) and TACE (*n* = 8, 25.8%) groups (*P* = .801). Patients in the TACE group had significantly higher total bilirubin levels (0.91 ± 0.41 vs. 1.22 ± 0.66 mg/dL, *P* = .024), while the other clinical variables remained insignificant between both groups. After propensity score analysis, 28 patients from each group were matched, and the clinical variables were well balanced between the two groups (Table 2).

CT-guided RFA for caudate HCC was technically successful in 42 (97.7%) patients. One (2.3%) patient had failed RFA in retrospective review because of inadequate ablation of the superior margin of the caudate HCC. Technically successful TACE with selective chemoembolization via all the caudate arteries was achieved in 31 (62%) of the 50 patients with initial TACE attempts. Unselective TACE was performed in 19 (38%) patients due

Table 1 Baseline demographics data of the RFA and the TACE groups

Clinical variables	RFA group (*n* = 43)	TACE group (*n* = 31)	*P* value
Age (years)	64.5 ± 12.8	64.8 ± 12.4	.917
Gender (male/female)	30/13	19/12	.467
HBV carrier, *n* (%)	26 (60.5)	13 (41.9)	.158†
HCV carrier, *n* (%)	18 (41.9)	13 (41.9)	1
Alcoholism, *n* (%)	2 (4.7)	4 (12.9)	.23†
Child–Pugh class (A/B)	41/2	28/3	.644
Albumin (g/dL)	4.23 ± 0.47	4.02 ± 0.60	.103†
Bilirubin (mg/dL)	0.91 ± 0.41	1.22 ± 0.66	.024*†
AST (U/L)	57.79 ± 56.42	70.94 ± 42.84	.245†
ALT (U/L)	53.65 ± 48.38	62.71 ± 43.74	.335
α-Fetoprotein (ng/mL)	178.45 ± 479.66	198.97 ± 418.18	.849
PT (s)	11.05 ± 0.90	11.44 ± 1.09	.098†
Ascites, *n* (%)	1 (2.3)	4 (12.9)	.154†
Tumor size (cm)	2.03 ± 0.88	2.16 ± 1.15	.57
Tumor number (1/2–3)	28/15	20/11	1
Tumor location (S/P/C)	23/9/11	19/10/2	.089†
Treatment-naïve patients	10	8	.801

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *C* caudate process, H*BV* hepatitis B virus, *HCV* hepatitis C virus, *P* paracaval portion, *PT* prothrombin time, *S* Spiegel lobe

*Reached statistical significance

†Clinical variables with *P* value < 0.25 between the RFA and the TACE groups were included for the propensity score analysis

Table 2 Demographics data of the RFA and the TACE groups after propensity score analysis

Clinical variables	RFA group (*n* = 28)	TACE group (*n* = 28)	*P* value
Age (years)	65.6 ± 13.0	65.3 ± 13.0	.927
Gender (male/female)	20/8	16/12	.403
HBV carrier, *n* (%)	14 (50)	13 (41.9)	1
HCV carrier, *n* (%)	15 (53.6)	12 (42.9)	.593
Alcoholism, *n* (%)	2 (7.1)	2 (7.1)	1
Child–Pugh class (A/B)	26/2	27/1	.618
Albumin (g/dL)	4.16 ± 0.52	4.08 ± 0.61	.597
Bilirubin (mg/dL)	1.02 ± 0.44	1.16 ± 0.60	.323
AST (U/L)	72.29 ± 64.64	68.71 ± 42.93	.809
ALT (U/L)	66.18 ± 54.74	63.04 ± 45.06	.815
α-Fetoprotein (ng/mL)	262.38 ± 595.50	210.68 ± 437.49	.713
PT (s)	11.20 ± 1.01	11.36 ± 1.11	.573
Ascites, *n* (%)	1 (3.6)	1 (3.6)	1
Tumor size (cm)	2.06 ± 0.84	2.21 ± 1.20	.59
Tumor number (1/2–3)	17/11	19/9	.781
Tumor location (S/P/C)	15/9/4	17/9/2	.792
Treatment-naïve patients	6	7	.752

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *C* caudate process, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *P* paracaval portion, *PT* prothrombin time, *S* Spiegel lobe

to unsuccessful catheterizations of the caudate artery, despite the use of microcatheters. These patients subsequently received curative RFA (Fig. 1).

Survival

During a mean follow-up period of 2.8 ± 1.9 years, five patients undergoing CT-guided RFA (11.6%) and 12 patients undergoing TACE (38.7%) died. The 1-, 2-, and 3-year survival rates were 97.1, 94.0, and 80.7% for the RFA group and 89.0, 80.8, and 62.0% for the TACE group, respectively. A comparison of the OS of the RFA and the TACE groups is presented in Fig. 4. The RFA group had better OS compared to the TACE group ($P = .016$), which remained significant after the propensity score analysis ($P = .039$).

Treatment Response

The 1-, 2-, and 3-year local progression rates were all 2.4% for the RFA group and 18.6, 32.9, and 38.5% for the TACE group, respectively. Regarding the local progression rate (Fig. 5), the RFA group outperformed the TACE group before ($P = .001$) and after ($P = .004$) the propensity score analysis. In the subgroup analysis of the RFA group, patients with ($n = 19$) and without ($n = 24$) prior TACE attempts had similar local progression rates ($P = .282$).

Complications

No complications were associated with pre-RFA iodized oil targeting or TACE. Grade 1 complications were found in 3 (6.9%, 3/43) patients who had mild pneumothorax after RFA, and 2 of them were related to the transpulmonary right intercostal lateral approach. No chest tube insertion was required in these patients with pneumothorax. Grade 3 complications were found in 3 patients in the RFA group, including liver abscess ($n = 1$), acute cholecystitis ($n = 1$), and hepatic artery pseudoaneurysm ($n = 1$). There was no case of RFA-related mortality.

Discussion

The curative treatment for patients with inoperable caudate HCC within the Milan criteria includes liver transplantation and percutaneous ablative therapies. However, the shortage of liver donors limits the utilization of liver transplantation [23]. Due to the deep and difficult location of caudate HCC for percutaneous ablative therapies, a substantial proportion of patients with caudate HCC underwent TACE as an initial treatment. In this well-balanced comparative study, we investigated the survival benefits of TACE in comparison with those of RFA for treating HCC in the caudate lobe with propensity score analysis. Our results demonstrated that RFA induced superior treatment response rates compared to TACE in patients with caudate HCCs within the Milan criteria,

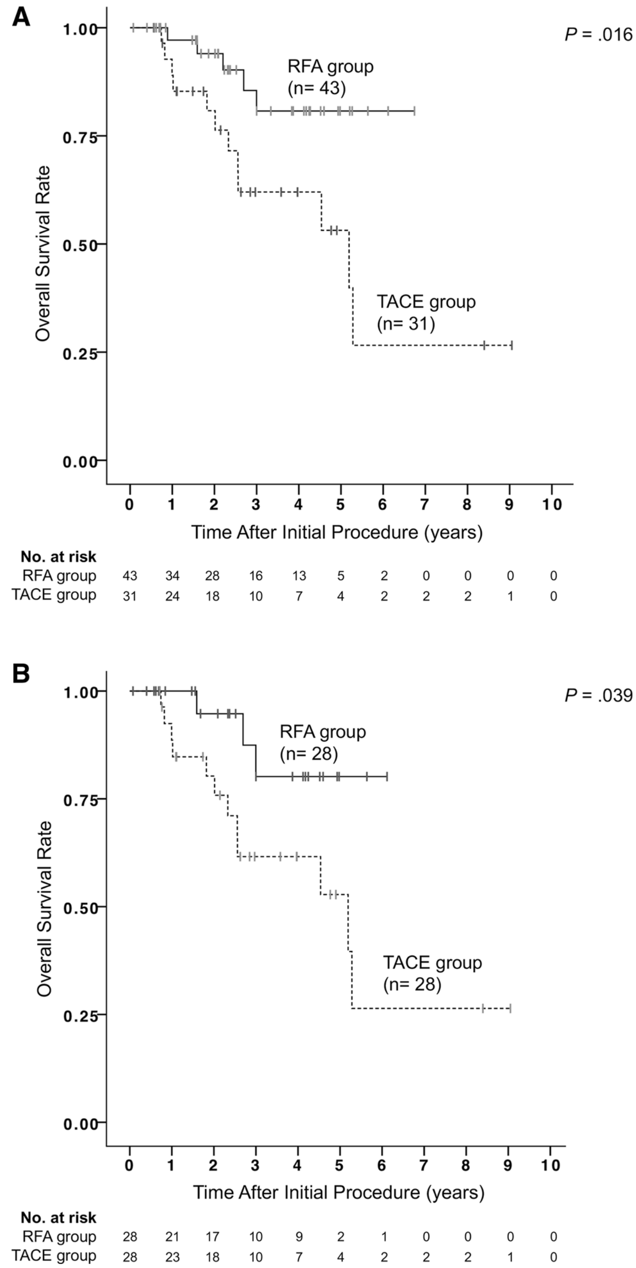

Fig. 4 Comparison of the overall survival (OS) of patients with HCC in the caudate lobe according to RFA and TACE. Significantly better OS was found in the RFA group before (**A**) and after (**B**) propensity score analysis

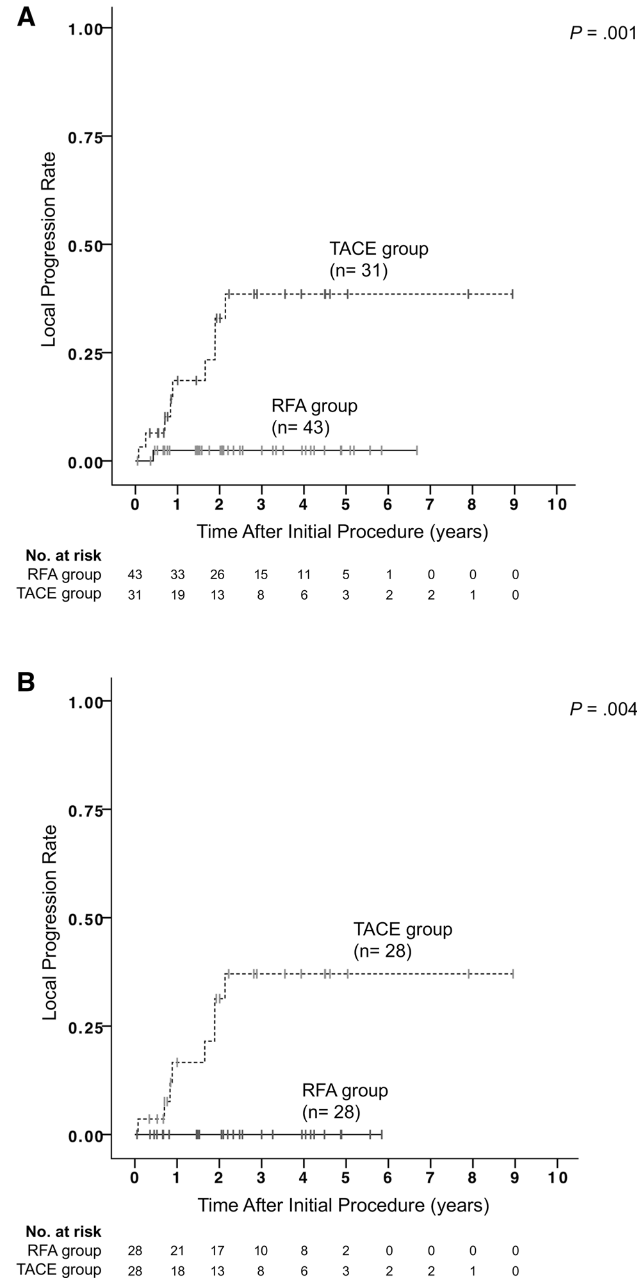

Fig. 5 Comparison of the local progression rate of patients with HCC in the caudate lobe according to RFA and TACE. Significantly lower local progression rates were found in the RFA group before (**A**) and after (**B**) propensity score analysis

which has not been reported previously. The promising results of RFA may affect future clinical decisions for patients with caudate HCC, especially for those who are unsuitable or unwilling to receive liver transplantation and surgical resection.

Due to its deep location between the IVC and hepatic hilum, the caudate lobe has been known as a difficult location for RFA in the past. Several recent reports have described image-guided RFA for HCC in the caudate lobe [11, 19, 24, 25]. Most studies have used ultrasound for guidance, and RFA appears to have good treatment efficacy with a local recurrence rate of 12–29.4%. However, the long distance between the body surface and the caudate lobe makes RFA probe localization and adjustment challenging, especially under ultrasound guidance. Moreover, there are shadowing artifacts in ultrasound from tiny bubbles during the ablative process, which may lead to inaccurate estimation of the ablative margin. In contrast to ultrasound, which is highly dependent on the operator, CT allows accurate estimation of the puncture route and ablative zone, thus avoiding inadvertent injury to the major vascular structures surrounding the caudate lobe. Furthermore, the transpulmonary approach is made possible under CT guidance, and visualization of the tumor margin is unaffected by the gas production during an ablation session.

For tumors in the caudate process and paracaval portion, our first choice is the right intercostal lateral approach through the right hepatic lobe, which is far from major hepatic vessels or bile ducts. The long distance between the right hepatic surface and the caudate lobe allows multiple manipulations of the electrode under CT guidance before reaching the desired position, making electrode placement relatively safe. Anterior epigastric approach is usually chosen for tumors in Spiegel lobe. Particular care should be taken for trespassing into the left hepatic artery or accessory left hepatic artery on the electrode route.

We did not use an artificial ascites technique in this study since the relationship between the tumor and nearby structure can be depicted in detail using CT. For tumors located near the IVC and hepatic hilum, such as those in the paracaval portion, the heat-sink effect is a concern that may compromise the thermal efficacy of RFA. In selected cases near vital structures, ethanol injection into the tumor margins is advocated to enhance the thermal efficacy of RFA and avoid thermal injury to the bile ducts or duodenum.

Major complications were observed in three patients in the RFA group. Hemoglobin levels dropped after the procedure in one patient, and a tiny pseudoaneurysm from the left hepatic artery crossing the puncture tract was found and successfully embolized. Another patient developed diffuse pain in the right upper quadrant of abdomen after the procedure. An abdominal CT scan showed hemorrhagic cholecystitis, which was treated with percutaneous transhepatic cholecystostomy. The third patient developed a post-procedural fever due to abscess formation at the ablation site, which was treated by percutaneous drainage.

The use of iodized oil targeting before CT-guided RFA remains controversial. However, increased visualization of the tumor margin and detection of microsatellite nodules are obvious advantages [26]. Additionally, the infusion of iodized oil may induce HCC necrosis via arterial embolization [27]. In this study, there were no complications that were directly attributable to pre-RFA iodized oil targeting, such as post-embolization syndrome, arterial dissection, or inguinal hematoma.

TACE for caudate HCC is known to be more difficult than for other intrahepatic locations of HCC. Around 20% of caudate HCC cases had multiple arterial supplies, of which the tiny caudate arteries can originate from left, right, or both hepatic arteries [15, 28]. A previous report showed that subsegmental embolization of the HCC is crucial for avoiding local recurrence [15]. Our technical success rate was 62% (31/50) for TACE with subsegmental catheterization of the caudate arteries and selective chemoembolization. This is slightly less than in previous reports (68–85%) and might be due to the larger size of the microcatheter (2.5 or 2.7 F) used in this study [14, 15]. Our survival rate after TACE was 62.0% at 3 years, which was also slightly lower than in the literature (3-year survival rate: 65–85%) [14, 15].

Some limitations of our study need to be highlighted. First, TACE was used as an initial treatment in 44.2% (19/43) of patients in the RFA group, which may have induced bias because combined TACE–RFA is known to improve survival [29]. However, all of the cases of initial TACE in the RFA group (n = 19) had unsuccessful cannulation of the tumor-feeding caudate artery, and non-selective TACE of caudate HCC was reported to have poor treatment efficacy for patients (3-year survival: 33%; 6-month progression rate: 50%) [15]. In this study, RFA was performed as an alternative treatment after unselective TACE for caudate HCC, and further subgroup analysis showed that patients receiving RFA with or without a prior TACE attempt had similar local progression rates. Second, all the RFA and TACE procedures were performed in a single center, so the study results may not be generalizable to other centers with different intervention protocols. Furthermore, the imaging modalities during follow-up were used interchangeably. It might affect the timing and detection of treatment responses in our study. Third, all of the RFA procedures involved CT guidance with or without pre-RFA iodized oil targeting, and the results may not extend to ultrasound-guided RFA due to the difference in guiding modality. Finally, most of the patients in our study had received prior curative treatment for their non-caudate tumors. The different prior treatments potentially affected and biased the overall survival, but the effect should be mild since these treatments were performed remotely and were considered unrelated to the current disease.

In conclusion, our study suggested that RFA is superior to TACE for caudate HCC within the Milan criteria regarding treatment response. Despite RFA involving more procedure-related complications, the clear survival benefits of RFA suggest that TACE should be reserved as only a salvage treatment for caudate HCC when liver transplantation, surgical resection, and echo-guided or CT-guided RFA are not suitable.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This retrospective study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our institution.

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