
Article

Percutaneous Radiofrequency Ablation with or without Chemolipiodolization for Early-stage Hepatocellular Carcinoma: A Propensity Score-matched Analysis

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Simple Summary: Percutaneous radiofrequency ablation (PRFA) is a useful treatment option for early-stage hepatocellular carcinoma. Additionally, chemolipiodolization (CL) is also reported to be useful in preventing recurrence. However, treatment outcomes of PRFA with or without CL for early-stage hepatocellular carcinoma have remained unclear thus far. In this study, we used propensity score-matched analysis to determine prognostic factors for overall survival after PRFA with or without CL. Our results showed that there was no significant difference between the two groups, indicating that PRFA with CL has no prognostic effects than PRFA without CL for early-stage hepatocellular carcinoma.

Abstract: We aimed to compare prognostic factors for overall survival (OS) following percutaneous radiofrequency ablation (PRFA) with or without chemolipiodolization (CL) for early-stage hepatocellular carcinoma (HCC) using propensity score-matched analysis. We enrolled 221 patients with early-stage HCC who received PRFA with (n = 76) or without (n = 145) CL in Saga Central Hospital between April 2004 and December 2020. No significant difference was observed in OS between PRFA with and without CL cohorts (median survival time [MST]: 5.4 vs. 4.5 years; p = 0.0806). To reduce confounding effects, 108 patients were selected using propensity score-matched analysis (n = 54 for each treatment). No significant difference was observed in OS between the cohorts (MST: 3.6 vs. 4.0 years; p = 0.5474). After stratification according to tumor size, no significant difference was observed in OS for patients with tumor size ≥ 20 mm between PRFA with and without CL cohorts (MST: 3.4 vs. 3.5 years; p = 0.8236). PRFA with CL was not a significant prognostic factor in both univariate and multivariate analyses (p = 0.5477 and 0.9600, respectively). Our findings suggest that PRFA with CL does not demonstrate longer prognostic effects than PRFA without CL in early-stage HCC, regardless of tumor size.

Keywords: hepatocellular carcinoma; percutaneous radiofrequency ablation; chemolipiodolization; risk factors; propensity score-matched analysis

1. Introduction

Liver cancer was the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide in 2018, with an estimated 841,000 new cases

and 782,000 deaths [1-4]. Liver cancer includes hepatocellular carcinoma (HCC), which accounts for 75%–85% of all liver cancer cases [1,2]. Early-stage HCC may be curable radically through hepatic resection, radiofrequency ablation (RFA), or liver transplantation [5,6].

Percutaneous RFA (PRFA) is a simple and minimally invasive treatment option for early-stage HCC [7]. Moreover, it is expected that combination therapy with PRFA and transarterial chemoembolization (TACE) can improve survival in patients with early-stage HCC [7]. In a prospective randomized trial, RFA combined with TACE was superior over RFA alone in improving the survival of patients with HCC [8]. Theoretically, it is possible to diminish the cooling effect of blood and consequently expand the area of ablation by performing TACE before PRFA. Recently, there has been accumulating evidence regarding the efficacy of PRFA with TACE for treating early-stage HCC [9-11].

Chemolipiodolization (CL) is performed before embolization in TACE as standard, which is a common practice in the treatment of HCC [12-15]. However, several studies have reported that CL plays a major role and embolization does not improve the survival [16,17], whereas other studies have drawn contrary conclusions [18]. CL is also performed before hepatic resection, and preoperative CL of the entire liver has been reported to be effective in reducing the incidence of postoperative recurrence and prolonging survival in patients with resectable HCC [19]. Thus, the evaluation of CL for HCC remains controversial.

CL for HCC is considered an advantage, in that the effect on the body is smaller than that in TACE because no embolization is performed. However, treatment outcomes of PRFA with or without CL for early-stage HCC remain unclear. Therefore, in this study, we aimed to determine the prognostic effects of PRFA with or without CL and the associated overall survival (OS) duration in early-stage HCC. In view of this, to reduce confounding effects, we performed propensity score-matched analysis.

2. Materials and Methods

2.1. Ethical Approval

The study was approved by the Ethics Committee of Saga Central Hospital (No. 21003) and was conducted according to the guidelines of the 1975 Declaration of Helsinki.

2.2. Diagnosis

HCC was confirmed histologically or diagnosed using noninvasive criteria according to the European Association for the Study of the Liver [20]. Intrahepatic lesions and vascular invasion were diagnosed using a combination of imaging techniques such as contrast-enhanced computed tomography, magnetic resonance imaging, ultrasonography, and digital subtraction angiography. Additionally, serum alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) levels were measured for up to 1 month before treatment initiation. The presence of intra-abdominal metastases was determined using abdominal computed tomography, magnetic resonance imaging, and ultrasonography, which were performed to evaluate intrahepatic lesions. Liver function was evaluated using the Child–Pugh classification and albumin–bilirubin (ALBI) score [21]. Tumor stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging classification [22,23].

2.3. Patients Receiving PRFA

We treated patients for early-stage HCC with PRFA in Saga Central Hospital between April 2004 and October 2020. Among them, we excluded patients undergoing second or

more PRFA; therefore, we enrolled only consecutive patients who received PRFA at the first treatment.

2.4. Patients Receiving CL

Among the enrolled patients who received PRFA, some patients received CL without embolization the day before PRFA. CL was performed according to the same procedure as that described in previous studies [15,16,19]. After conventional visceral angiography, CL was performed by introducing an angiographic catheter into the feeding artery of HCC using Seldinger's technique. Angiographic survey of abdominal vessels such as the superior mesenteric artery and common hepatic vessels was performed to assess the arterial blood supply to the liver. Epirubicin was mixed water-soluble contrast medium and sterile water for injection. The mixture was thoroughly mixed with lipiodol. The injection was stopped either at the point of near stasis within the feeding artery of HCC or after the entire amount of the agent was administered.

2.5. Treatment Outcome

The treatment outcome was OS, defined as the time from the initiation of PRFA with or without CL to the date of death or the patient's last follow-up, whichever occurred first.

2.6. Statistical Analysis

The following baseline patient characteristics were analyzed using descriptive statistical methods: age, tumor size, albumin level, total bilirubin level, ALBI score, prothrombin time, AFP, and DCP. The data of these variables were calculated using the t-test, and the data of variables such as sex, etiology, Child–Pugh class, and BCLC stage were calculated using the chi-square test. Results are expressed as mean \pm standard deviation (SD) and median (range) or n (%). Survival curves were constructed using the Kaplan–Meier analysis with the log-rank test. A p-value of <0.05 was considered to indicate statistical significance. JMP software (SAS Institute, Inc., Cary, NC, USA), version 15, was used for all statistical analyses.

3. Results

3.1. Patient Characteristics

Overall, 501 patients were treated for early-stage HCC with PRFA, of whom 280 who received second or more PRFA were excluded; therefore, 221 consecutive patients who received PRFA at the first treatment were enrolled.

Table 1 shows the characteristics of the 221 consecutive patients who were diagnosed with early-stage HCC and received either PRFA with (n = 76) or without (n = 145) CL. A higher proportion of patients tested positive for the large tumor size ($p < 0.0001$) in the PRFA with CL cohort, whereas a higher proportion of patients had BCLC stage 0 ($p < 0.0001$) in the PRFA without CL cohort. Age, sex, etiology, Child–Pugh class, albumin level, total bilirubin level, ALBI score, prothrombin time, AFP level, and DCP level were equivalent between the PRFA with and without CL cohorts.

Table 1. Patient characteristics (N = 221).

Variable	CL(+) (n = 76)	CL(-) (n = 145)	p-value
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Age (years)	73.1 ± 10.7 75.4 (32.8–88.6)	73.7 ± 8.3 75.2 (46.0–88.6)	0.6711
Sex (male/female)	52 (68%)/24 (32%)	80 (55%)/65 (45%)	0.0564
Etiology (HBV/HCV/both negative)	4 (5%)/66 (87%)/6 (8%)	8 (5%)/129 (90%)/8 (5%)	0.7881
Child–Pugh class (A/B)	62 (82%)/14 (18%)	120 (83%)/25 (17%)	0.4766
Tumor size (mm)	25.3 ± 9.0 25 (9–48)	18.1 ± 5.6 17 (8–35)	<0.0001
BCLC stage (0/A/B)	20 (26%)/30 (40%)/26 (34%)	85 (59%)/50 (34%)/10 (7%)	<0.0001
Albumin (g/dL)	3.6 ± 0.5 3.7 (2.7–4.7)	3.7 ± 0.5 3.7 (2.5–4.8)	0.4492
Total bilirubin (mg/dL)	1.0 ± 0.4 0.8 (0.3–2.5)	0.9 ± 0.5 0.8 (0.2–3.2)	0.5275
ALBI score	-2.30 ± 0.45 -2.32 (-3.38 to -1.29)	-2.36 ± 0.47 -2.40 (-3.52 to -1.21)	0.3223
Prothrombin time (%)	77.1 ± 12.2 75.2 (44.5–108.7)	78.4 ± 12.7 78.7 (46.9–108.3)	0.4631
AFP (ng/mL)	296 ± 1,009 32 (2–8,400)	118 ± 39 15 (1–5,019)	0.0758
DCP (mAU/mL)	905 ± 5,042 47 (2–42,500)	144 ± 443 25 (8–3,930)	0.0751

Abbreviations: CL = chemolipiodolization, HBV = hepatitis B virus, HCV = hepatitis C virus, BCLC = Barcelona Clinic Liver Cancer, ALBI = albumin–bilirubin, AFP = alpha-fetoprotein, DCP = des-gamma-carboxy prothrombin.

Results are expressed as the mean ± standard deviation and the median (range) or n (%).

3.2. Survival Outcomes

Figure 1 shows the results of the Kaplan–Meier analysis of OS assessed with the log-rank test between the PRFA with and without CL cohorts. The median survival time (MST) was 4.5 years in the PRFA with CL cohort (red line; n = 76) and 5.4 years in the PRFA without CL cohort (blue line; n = 145) (p = 0.0806). The OS did not differ significantly between the PRFA with and without CL cohorts.

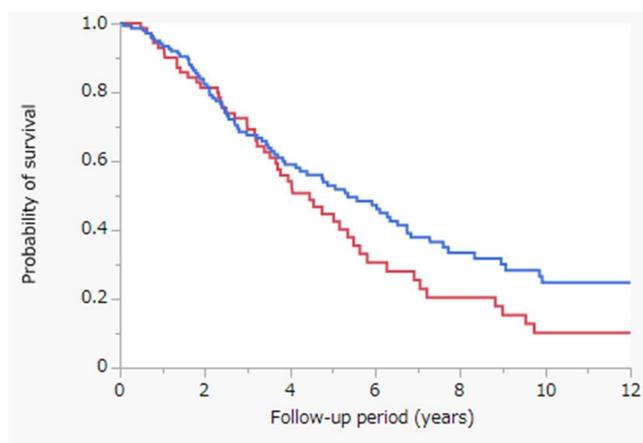


Figure 1. Kaplan–Meier analysis of OS assessed with the log-rank test between the PRFA with and without CL cohorts. Red line: PRFA with CL cohort (n = 76), MST = 4.5 years; blue line: PRFA without CL cohort (n = 145), MST = 5.4 years; p = 0.0806. Abbreviations: OS = overall survival, PRFA = percutaneous radiofrequency ablation, CL = chemolipiodolization, MST = median survival time.

3.3. Propensity Score-Matched Analysis

To reduce confounding effects, we performed propensity score-matched analysis to match patients treated with PRFA with CL (n = 76) with those treated with PRFA without CL (n = 145) [24,25]. The following 12 variables related to the prognosis of early-stage HCC were considered at the start of the follow-up: age, sex, etiology, Child–Pugh class, tumor size, BCLC stage, albumin level, total bilirubin level, ALBI score, prothrombin time, AFP level, and DCP level. The propensity scores (mean \pm SD) of the patients treated with PRFA with or without CL were 0.4036 ± 2.3596 and -2.2509 ± 4.5160 , respectively. We used these propensity scores to conduct one-to-one nearest neighbor matching within a caliper of 0.20, as previous studies have shown this SD percentage of the logit of the propensity score to be generally suitable as a caliper for propensity score-matched analysis [26]. Based on the results of the propensity score-matched analysis, 108 patients were selected (PRFA with CL, n = 54; PRFA without CL, n = 54). After the propensity score-matched analysis, the propensity scores (mean \pm SD) of patients treated with PRFA with or without CL were -0.3854 ± 0.9998 and -0.4535 ± 0.9328 , respectively.

3.4. Patient Characteristics After Propensity Score-Matched Analysis

Table 2 shows the characteristics of 108 patients who were diagnosed with early-stage HCC and underwent PRFA with CL (n = 54) or PRFA without CL (n = 54) assessed using propensity score-matched analysis. No significant differences were observed for any variables between the PRFA with and without CL cohorts using propensity score-matched analysis.

Table 2. Patient characteristics assessed using propensity score-matched analysis (n = 108).

Variable	CL(+) (n = 54)	CL(-) (n = 54)	p-value
Age (years)	73.2 \pm 11.4	72.8 \pm 7.8	0.8496
	75.7 (32.9–88.6)	74.5 (55.2–88.6)	
Sex (male/female)	36 (67%)/18 (33%)	37 (69%)/17 (31%)	0.8371

Etiology (HBV/HCV/both negative)	3 (6%)/48 (88%)/3 (6%)	3 (6%)/46 (87%)/5 (7%)	0.7624
Child–Pugh class (A/B)	45 (83%)/9 (17%)	42 (78%)/12 (22%)	0.4658
Tumor size (mm)	22.6 ± 7.6 22 (9–37)	21.9 ± 6.2 21 (11–35)	0.5990
BCLC stage (0/A/B)	18 (33%)/24 (50%)/12 (19%)	17 (31%)/27 (50%)/10 (19%)	0.8241
Albumin (g/dL)	3.6 ± 0.5 3.8 (2.5–4.5)	3.59 ± 0.5 3.6 (2.5–4.8)	0.7066
Total bilirubin (mg/dL)	0.9 ± 0.4 0.8 (0.3–2.1)	0.9 ± 0.4 0.9 (0.4–2.2)	0.4172
ALBI score	-2.32 ± 0.43 -2.33 (-3.20 to -1.37)	-2.27 ± 0.47 -2.24 (-3.52 to -1.21)	0.5726
Prothrombin time (%)	77.9 ± 12.8 78.3 (44.5–108.7)	76.6 ± 14.4 74.8 (46.9–106.1)	0.6370
AFP (ng/mL)	154 ± 279 32 (2–1,170)	124 ± 312 22 (4–1,628)	0.5996
DCP (mAU/mL)	286 ± 700 46 (2–3,310)	282 ± 675 34 (8–3,930)	0.9781

Abbreviations: CL = chemolipiodolization, HBV = hepatitis B virus, HCV = hepatitis C virus, BCLC = Barcelona Clinic Liver Cancer, ALBI = albumin–bilirubin, AFP = alpha-fetoprotein, DCP = des-gamma-carboxy prothrombin.

Results are expressed as the mean ± standard deviation and the median (range) or n (%).

3.5. Survival Outcomes After Propensity Score-Matched Analysis

Figure 2 shows the results of the Kaplan–Meier analysis of OS assessed with the log-rank test between the PRFA with and without CL cohorts after propensity score-matched analysis. The MST was 4.0 years in the PRFA with CL cohort (red line; n = 54) and 3.6 years in the PRFA without CL cohort (blue line; n = 54) (p = 0.5474). The OS did not differ significantly between the PRFA with and without CL cohorts after propensity score-matched analysis.

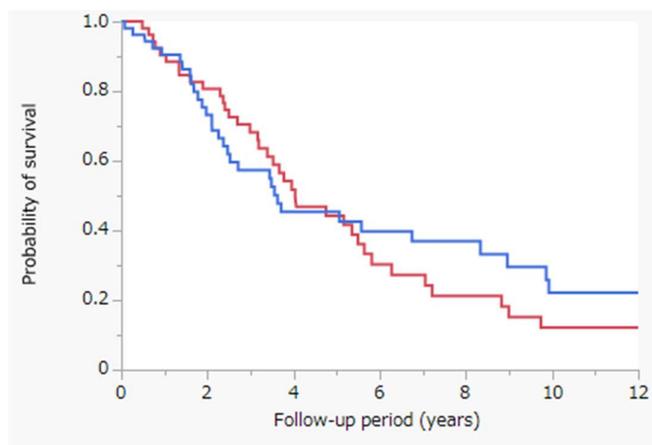


Figure 2. Kaplan–Meier analysis of OS assessed with the log-rank test between the PRFA with and without CL cohorts after propensity score-matched analysis. Red line, PRFA with CL cohort (n = 54), MST = 4.0 years; blue line: PRFA without CL cohort (n = 54), MST = 3.6 years; p = 0.5474. Abbreviations: OS = overall survival, PRFA = percutaneous radiofrequency ablation, CL = chemolipiodolization, MST = median survival time.

3.6. Survival Outcomes in Patients with a Tumor Size of ≥ 20 mm After Propensity Score-Matched Analysis

Figure 3 shows the results of the Kaplan–Meier analysis of OS assessed with the log-rank test between the PRFA with and without CL cohorts in patients with a tumor size of ≥ 20 mm using propensity score-matched analysis. For patients with a tumor size of ≥ 20 mm, the MST was 3.5 years in the PRFA with CL cohort (red line; n = 26) and 3.4 years in the PRFA without CL cohort (blue line; n = 24) (p = 0.8236). The OS did not differ significantly between the PRFA with and without CL cohorts in patients with a tumor size of ≥ 20 mm after propensity score-matched analysis.

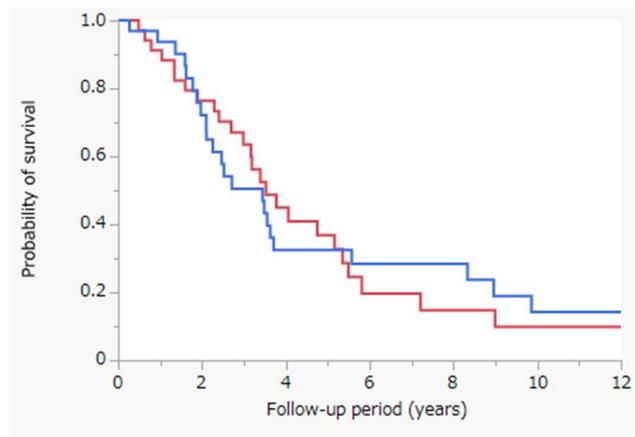


Figure 3. Kaplan–Meier analysis of OS assessed with the log-rank test between the PRFA with and without CL cohorts in patients with a tumor size of ≥ 20 mm after propensity score-matched analysis. Red line: PRFA with CL cohort in patients with a tumor size of ≥ 20 mm (n = 26), MST = 3.5 years; blue line: PRFA without CL cohort in patients with a tumor size of ≥ 20 mm (n = 24), MST = 3.4 years; p = 0.8236. Abbreviations: OS = overall survival, PRFA = percutaneous radiofrequency ablation, CL = chemolipiodolization, MST = median survival time.

3.7. Univariate and Multivariate Analyses of OS After Propensity Score-Matched Analysis

Table 3 shows the results of univariate and multivariate analyses of OS obtained using propensity score-matched analysis (n = 108). Univariate analyses of OS revealed four variables as significant prognostic factors: Child–Pugh class (p = 0.0012), ALBI score (p <

0.0001), AFP level ($p = 0.0032$), and DCP level ($p = 0.0119$). Multivariate analyses of OS identified two variables as independent significant prognostic factors: Child–Pugh class ($p = 0.0245$) and DCP level ($p = 0.0442$). PRFA with CL was not a significant prognostic factor in both univariate and multivariate analyses in propensity score-matched analysis.

Table 3. Results of univariate and multivariate analyses of OS calculated using propensity score-matched analysis (n = 108).

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (≥ 75.2 years)	1.237 (0.771–1.993)	0.3767	1.043 (0.614–1.785)	0.8752
Sex (male)	1.249 (0.758–2.057)	0.3757	1.581 (0.906–2.759)	0.0995
Etiology (HCV)	1.946 (0.980–4.447)	0.0574	1.512 (0.697–3.655)	0.3063
Child–Pugh class (B)	3.126 (1.616–5.720)	0.0012	2.283 (1.117–4.507)	0.0245
Tumor size (≥ 22 mm)	1.541 (0.963–2.494)	0.0712	1.338 (0.690–2.804)	0.4001
BCLC stage (A or B)	1.477 (0.888–2.566)	0.1356	0.928 (0.411–1.994)	0.8525
ALBI score (≥ -2.31)	3.097 (1.750–5.488)	< 0.0001	1.370 (0.749–2.496)	0.3036
AFP (≥ 27.6 ng/mL)	2.059 (1.274–3.361)	0.0032	1.669 (0.971–2.907)	0.0638
DCP (≥ 43 mAU/mL)	1.862 (1.146–3.062)	0.0119	1.705 (1.013–2.903)	0.0442
Treatment (PRFA with CL)	1.155 (0.721–1.851)	0.5477	1.012 (0.615–1.667)	0.9600

Abbreviations: OS = overall survival, HR = hazard ratio, CI = confidence interval, HCV = hepatitis C virus, BCLC = Barcelona Clinic Liver Cancer, ALBI = albumin–bilirubin, AFP = alpha-fetoprotein, DCP = des-gamma-carboxy prothrombin, CL = chemolipiodolization, PRFA = percutaneous radiofrequency ablation.

All cutoff values were set for the median.

4. Discussion

In this study, we observed that the OS did not differ significantly between the PRFA with and without CL cohorts among the enrolled patients (Figure 1). However, in the PRFA without CL cohort, tumor factors, especially tumor size, were significantly better (Table 1). To reduce confounding effects, we performed propensity score-matched analysis to match patients treated with PRFA with and without CL (Table 2). Again, the OS did not differ significantly between the PRFA with and without CL cohorts after propensity score-matched analysis (Figure 2). Similarly, the OS did not differ significantly between the PRFA with and without CL cohorts in patients with a tumor size of ≥ 20 mm after propensity score-matched analysis (Figure 3). Furthermore, our results suggest that PRFA with CL does not demonstrate longer prognostic effects than PRFA without CL in early-stage HCC, regardless of the tumor size. Additionally, in both univariate and

multivariate analyses, PRFA with CL was not a significant prognostic factor after propensity score-matched analysis (Table 3).

There are several treatment strategies for early-stage HCC, such as PRFA and surgical resection. PRFA is an effective therapy for early-stage HCC wherein the tumor size is <3 cm in diameter and the number of tumors is <3 [7]. On the contrary, CL is an effective treatment option for unresectable HCC [27]. PRFA with TACE is reported as an effective treatment option for HCC [28]. PRFA combined with TACE was superior over PRFA alone in improving the survival of patients with HCC of <7 cm [8]. Percutaneous microwave coagulation therapy with TACE can also be used to effectively treat an HCC measuring >2 cm but <3 cm [29]. A meta-analysis indicated that PRFA combined with TACE can demonstrate higher tumor response rates and improvement in survival [30]. On the contrary, in a propensity score-matched study, embolization in TACE combined with PRFA could not improve the survival of patients with HCC within the Milan criteria [15]. However, only few studies have reported improved OS by PRFA with CL. Our study identified no significant value of adding CL to PRFA.

The reason why there was no significant difference in the OS of patients who underwent PRFA with CL is the induction of the cooling effect, although a previous study showed prolongation of survival in patients undergoing PRFA with TACE [8]. Obstruction of the hepatic artery is effective in reducing the cooling effect because the hepatic artery provides the main blood supply to HCC; therefore, PRFA is sufficient to expand the area of necrosis after hepatic artery obstruction [31]. Because CL is a procedure that does not use embolic substances, it is not good at reducing the cooling effect of the hepatic blood flow on PRFA, attributing to the diminishing of the cauterization effect. The removal of embolization in the combination therapy with TACE and RFA is not important for improving the survival rate of patients with HCC [15]. In our study, there was no significant difference between PRFA with CL and PRFA without CL; therefore, this may suggest the importance of embolization with PRFA.

In summary, PRFA in combination with CL could not improve OS in patients with early-stage HCC. The reason is that CL does not involve the use of embolic substances, which does not reduce the cooling effect. In addition, CL increases the risk of complications such as bleeding and infections, including biloma and skin abscess, and may increase medical expenses.

The present study had some limitations. First, our study had a single-center retrospective design with a relatively small sample size (n=221) for patients with early-stage HCC. Second, the treatment (PRFA with or without CL) was selected at the discretion of the chief physician, and patients were not randomized to the treatment. This resulted in a selection bias for patients with early-stage HCC. Third, therapeutic effects and adverse events in all cases could not be evaluated. Fourth, no further investigations were conducted after secondary treatment. Therefore, to overcome these limitations, a multicenter prospective study with a larger patient population should be conducted in the future.

5. Conclusions

The present study showed that PRFA with CL does not demonstrate longer prognostic effects than PRFA without CL for early-stage HCC. Our results suggest that PRFA with CL should not be employed for patients with early-stage HCC, regardless of the tumor size.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Saga Central Hospital (protocol code 21003 approved on 21 June 2021).

Informed Consent Statement: Informed consent was obtained from all patients regarding treatment. However, the consent regarding the study was waived because of the retrospective study design.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, M.Nakano, on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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