

Ablation Volume Measurement After Percutaneous Cryoablation Using a Two-cryo-probe Technique for Small Hepatocellular Carcinomas

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Abstract

Purpose To calculate the ablation volume of percutaneous cryoablation (PCA) with a two-cryo-probe technique for small hepatocellular carcinomas (HCCs) and to assess risk factors for local tumor recurrence (LTR).

Materials and Methods Between January 2013 and June 2017, 96 patients (mean age, 60.7 years; range, 37–83 years) with 106 small HCCs were retrospectively analyzed. The ablation volume, technical success, LTR rates, and complications were evaluated. Ablation volume was measured after the first freezing and immediately after completing PCA twice via computed tomography imaging. Prognostic factors associated with LTR were analyzed.

Results Technical success was achieved in all patients. The mean final ablation volume was $19.1 \pm 4.8 \text{ cm}^3$, which

was significantly higher than the first freezing ablation volume ($14.7 \pm 4.3 \text{ cm}^3$, $p < 0.001$). During the median follow-up period of 16.7 months (range, 5–52 months), LTR-free survival rates based on Kaplan–Meier analyses at 6 months, 1 year, and 2 years were 87.7%, 84.0%, and 80.2%, respectively. Only one major complication of post-procedural arterial bleeding occurred. A final ablation volume/tumor volume < 10 was a significant risk factor for LTR ($p = 0.044$).

Conclusions A ratio of final ablation volume to tumor volume < 10 was a significant prognostic factor for LTR. Therefore, the measurement and prediction of the final ablation volume are important to reduce LTR.

Keywords Hepatocellular carcinoma · Percutaneous cryoablation · Ablation volume · Local tumor recurrence

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Introduction

Local ablation therapies are considered safe and efficient treatment options for patients with primary or secondary malignancies in the liver [1, 2], kidney [3, 4], and lung [5]. Among ablation therapies, radiofrequency ablation (RFA) is the most widely used modality, showing comparable effectiveness to surgical resection with less invasiveness in local tumor control [2, 3]. Recently, with accumulating studies on the efficacy and safety of percutaneous cryoablation (PCA), it is now considered a feasible alternative treatment option to RFA and is widely used for local tumor control in various organs [1, 4, 6].

In both RFA and PCA for hepatic malignancies, calculating the ablated hepatic volume is important because the proportion of ablated hepatic volume is related to systemic

inflammatory response (SIR) or cryoshock syndrome (multiple organ failure and disseminated intravascular coagulation) [7, 8]. Furthermore, measuring the ablation volume is important to assess whether the ablation zone could adequately cover the tumor and to determine whether additional ablation is necessary. Previous studies of an ex vivo trial reported an approximate ablation volume when using RFA in the liver [9, 10]. However, limited studies have assessed the ablated volume of target lesions in the liver when using PCA.

This study aimed to calculate the ablated volume in PCA with a two-cryo-probe technique for small hepatocellular carcinomas (HCCs) and to assess factors associated with local tumor recurrence (LTR).

Materials and Methods

Patient Selection

This retrospective study was approved by our Institutional Review Board, which waived the requirement for informed consent. From January 2013 to June 2017, 142 consecutive patients underwent PCA for HCCs smaller than 3 cm. Among them, patients without the two-cryo-probe technique and those without computed tomography (CT) images during or immediately after PCA were excluded. HCCs were diagnosed based on the American Association for the Study of Liver Diseases guidelines as follows: typical imaging features in triple-phase contrast-enhanced CT or magnetic resonance image (MRI) with elevated serum α -fetoprotein (AFP) and/or prothrombin induced by vitamin K absence-II (PIVKA-II) levels or ultrasound (US)-guided biopsy [11].

PCA Procedure

PCA was performed under conscious sedation in all patients. Three experienced interventional radiologists performed PCA using an argon–helium-based cryosurgical device. Two cryo-probes (IceRod i-Thaw 1.5 [17G] straight cryoablation probe, Gail Medical, Yokneam, Israel) were inserted into the small HCCs under US guidance after local anesthesia. The PCA process comprised two cycles of freezing and thawing protocol: 10-min freezing and 8-min thawing in the first cycle, followed by 10-min freezing and 5-min thawing in the second cycle [12]. A non-enhanced CT (INFX-8000C combined with Aquilion 128 channel CT scanner, Toshiba Medical Systems Corporation, Otawara, Japan) scan was performed to determine the optimal position of the cryo-probes after insertion and at the end of the first freezing. A contrast-enhanced CT scan was performed to evaluate the ablation

zone and assess complications immediately after completing PCA.

Definitions and Data Analysis

Various factors including patient characteristics, laboratory findings, and details of the procedure, CT, and/or MRI findings were obtained for analysis. Subcapsular tumors were defined as tumors located within 1 cm of the hepatic edge. Ablation zone was defined as the zone of hypoattenuation (more than 10 Hounsfield Units, [HU]) compared with normal liver parenchyma on precontrast CT or minimal enhancement (less than 20 HU) compared with the adjacent normal enhancing hepatic parenchyma as observed on a contrast-enhanced CT [13]. The first freezing ablation volume refers to the ablation volume at the end of the first freezing. The distance between the two cryo-probes was measured as the distance between the tips of the cryo-probes. The cryo-probe orientation was defined according to the directional nature between them and was classified as parallel, convergent, or divergent (Fig. 1).

Technical success was defined when the ablation zone completely covered the tumor on CT performed immediately after the procedure without acute complications [14]. LTR was defined as the emergence of a viable tumor within or along the peripheral margin of the ablation zone on follow-up CT and/or MRI. Patients were divided into two groups: patients with LTR (group A) or without LTR (group B). Complications requiring additional interventional treatment, transfusion, or hospitalization or long-term morbidities, including liver failure or cryoshock (multiorgan failure and disseminated intravascular coagulation), were considered major complications. All others were considered minor complications [15, 16].

Volume Measurement

The cryoablation volume was measured twice on CT, at the end of the first freezing and immediately after completing PCA. The volume was determined using the formula for calculating sphere volume: $(4/3) \pi \times r^3$; however, due to the elliptical nature of the tumor, the volume was calculated according to the formula $(4/3) \pi \times r_x \times r_y \times r_z$ [7, 10] (Fig. 2). Additionally, to measure the degree of sphericity, the ratio of r_x to r_y (x'/y' quotient) was measured. Hepatic tumor volume was measured similar to ablation volume.

Follow-Up

During the follow-up period, patients underwent contrast-enhanced CT and/or MRI 1 month after PCA and at 2- to 3-month intervals thereafter. Tumor markers including

Fig. 1 Directional nature of the two cryo-probes. **A** 'Parallel' orientation with the probes extending in the same direction. **B** 'Convergent' orientation with the probes getting closer at one point. **C** 'Divergent' orientation with the probes separating at the tips

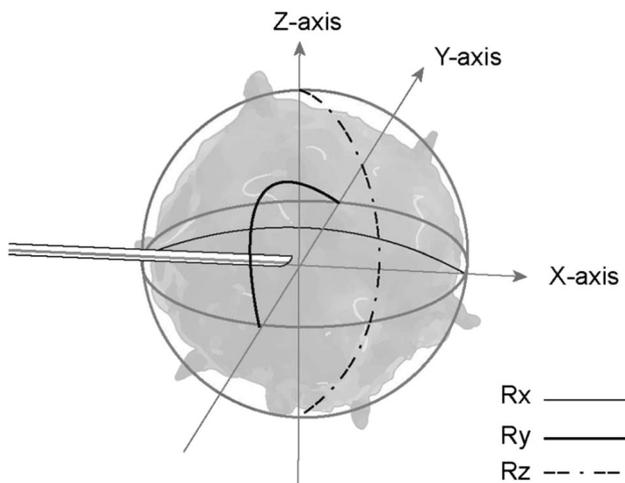
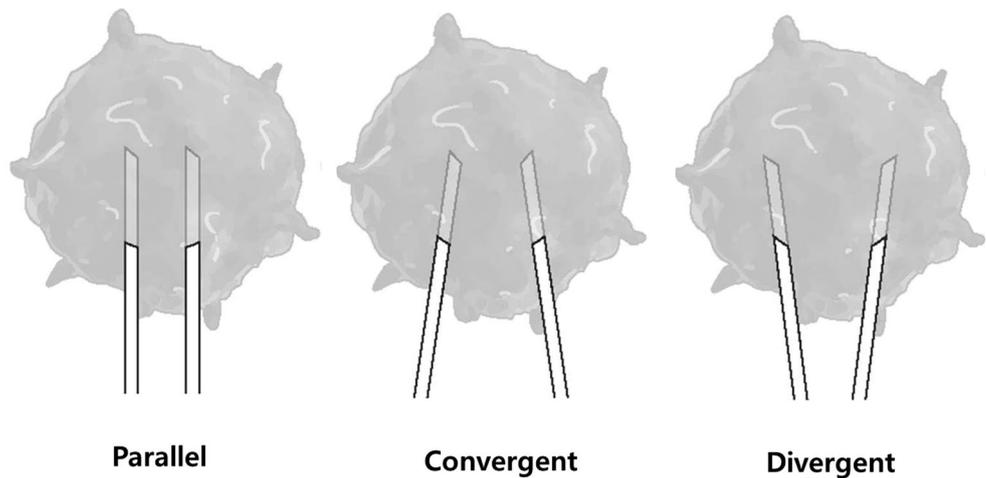


Fig. 2 Cryoablation volume was calculated using the formula $(4/3) \pi \times r_x \times r_y \times r_z$. The x -axis was defined as the axis parallel to the direction in which the cryo-probe was inserted. The y - and z -axes were defined as the axes perpendicular to the x -axis on the axial and coronal planes, respectively. R_x , R_y , and R_z were defined as twice the r_x , r_y , and r_z

AFP and/or PIVKA-II were also measured. Furthermore, laboratory findings including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), albumin levels, and the international normalized ratio (INR) of prothrombin time (PT) were collected 1 day before and 1 day, 1 month, and 3 months after PCA.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., IBM, Armonk, NY, USA). Continuous variables were compared using independent sample t tests, and categorical variables were compared using Pearson's chi-square tests. The LTR-

free survival (LTRFS) rates were analyzed using Kaplan–Meier method. Laboratory findings of pre- and post-procedure and the mean first freezing and final cryoablation volumes were compared using paired t tests. Correlations between cryoablation volume and categorized orientation of the cryo-probes were analyzed using one-way analysis of variance. Correlations concerning the distance between the two cryo-probes and the cryoablation volume were analyzed by Pearson's correlation coefficient. Factors for LTR were evaluated using univariate Cox regression analysis, and the significant factors ($p < 0.1$) were included in the multivariate analysis. A two-sided p value < 0.05 was considered statistically significant. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of the study population and tumors. A total of 96 patients (mean age, 60.7 years; range, 37–83 years) with 106 HCCs were included in this study. The median and mean follow-up periods were 16.7 months (range, 5–52 months) and 20.5 ± 12.0 months, respectively. Of the 106 HCCs, 87 lesions (82.1%) were located in the subcapsular area. The mean diameter and volume of the 106 HCCs were 1.7 ± 0.5 cm and 2.2 ± 1.5 cm³ (range, 0.4–14.1 cm³), respectively. The mean x'/y' ratio was 1.1 ± 0.4 . Before PCA, the mean serum values of AST, ALT, TB, albumin, and PT (INR) were 32.8 IU/L, 26.5 IU/L, 0.7 mg/dL, 3.9 g/dL, and 1.0, respectively.

Table 1 Baseline patient and tumor characteristics

Patient characteristics (<i>n</i> = 96)	<i>N</i> (%)
Age (years)*	60.7 ± 10.4
Sex	
Male	79 (82.3)
Female	17 (17.7)
Follow-up period (months)	
Mean*	20.5 ± 12.0
Median	16.7 (range, 5–52)
Etiology	
HBV	72 (75)
HCV	12 (12.5)
NBNC	8 (8.3)
Alcoholic	4 (4.2)
Child–Pugh class	
A	93 (96.9)
B	3 (3.1)
ECOS PS	
0	61 (63.5)
1	34 (35.4)
2	1 (1.0)
Tumor marker*	
PIVKA-II (mAU/mL)	54.0 ± 118.0
AFP (ng/mL)	78.22 ± 208.3
Tumor number	
Solitary	86 (89.6)
Multiple	10 (10.4)
<i>Tumor characteristics</i> (<i>n</i> = 106)	
Diameter (cm)*	1.7 ± 0.5
Volume (cm ³)*	2.2 ± 1.5
Location	
Subcapsular	87
Non-subcapsular	19

HBV hepatitis B virus, HCV hepatitis C virus, NBNC non-B non-C, ECOG PS Eastern cooperative oncology group performance status, AFP α -fetoprotein, PIVKA-II prothrombin induced by vitamin K absence-II

*Mean ± SD

Technical and Clinical Outcomes

Technical success was achieved in all patients (100%). LTR occurred in 21 of 106 lesions (19.8%) in 17 of 96 patients (17.7%) during the median follow-up period. The LTRFS rates at 6 months, 1, and 2 years were 87.7%, 84.0% and 80.2%, respectively (Fig. 3A). Only one (1.0%) procedure-related major complication occurred. After successful PCA, arterial bleeding from the hepatic capsule was detected on immediate post-procedural CT and hepatic arteriography was performed promptly. However, there

was no bleeding focus on angiography, and the patient recovered after conservative management. Minor complications occurred in five patients (5.2%), including small hematomas (*n* = 4) and minimal pleural effusion (*n* = 1). The patients recovered completely after conservative treatment. The mean serum levels of AST, ALT, and TB increased significantly ($p < 0.001$) and that of albumin decreased significantly ($p = 0.040$) 1 day after PCA. However, these values had normalized 1 month after PCA. There was no significant difference in the mean value of PT (INR) pre- and post-PCA (Fig. 4).

Cryoablation Volume and Associated Factors

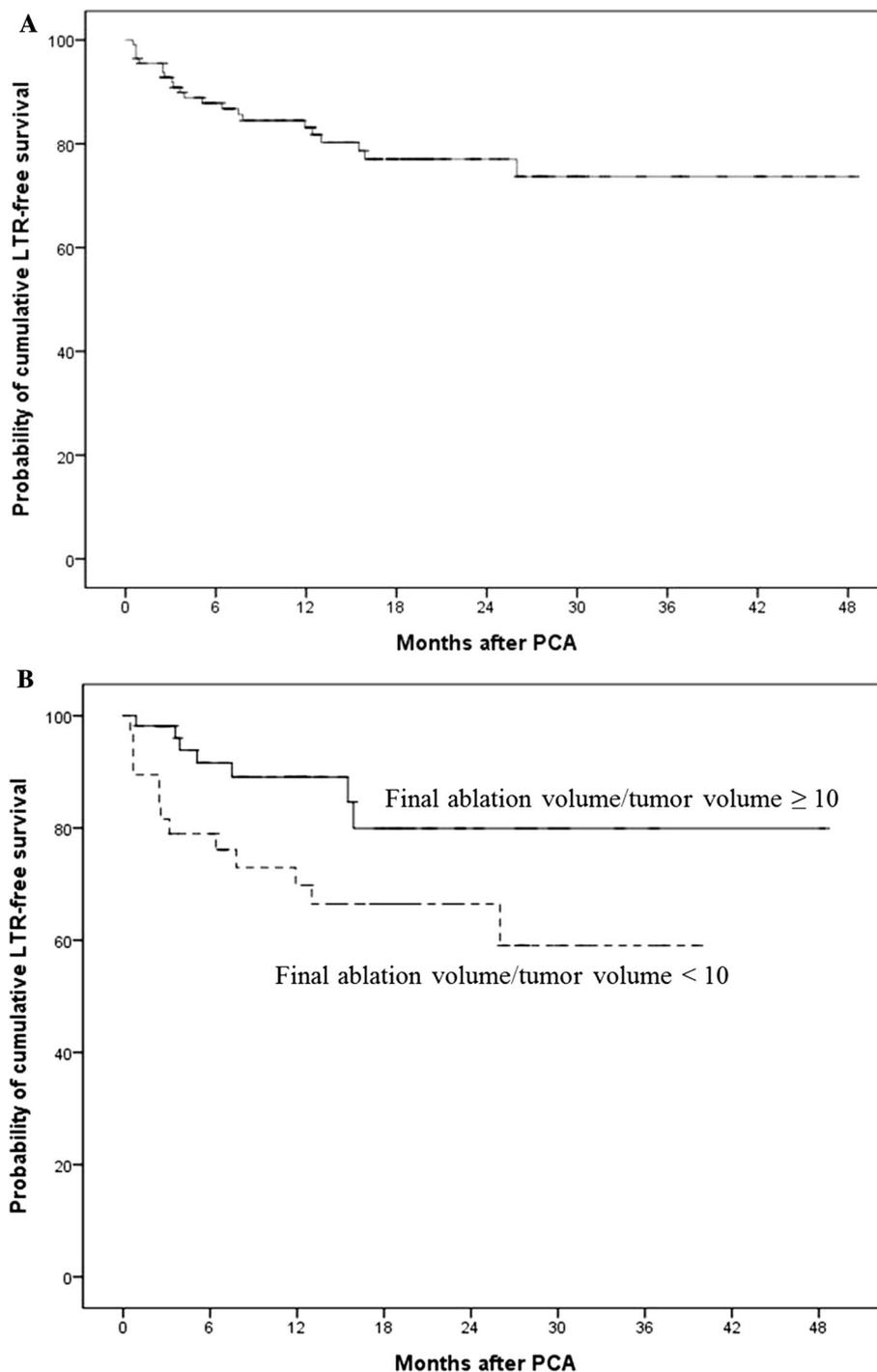
Table 2 shows the details of the procedure. The mean first freezing ablation volume was 14.7 ± 4.3 cm³, which increased significantly to 19.1 ± 4.8 cm³ at the end of PCA ($p < 0.001$). The mean r_x/r_y ratio of the first freezing and final ablation zones was 1.3 ± 0.4 and 1.2 ± 0.5 , respectively. The mean distance between the cryo-probes was 1.3 ± 0.6 cm. The correlation between the distance and final ablation volume was not significant ($p = 0.640$). The final ablation volumes according to cryo-probe orientation were as follows: parallel (18.3 ± 5.4 cm³, *n* = 39), convergent (16.6 ± 5.4 cm³, *n* = 23), and divergent (21.2 ± 5.5 cm³, *n* = 44). The final ablation volume of the divergent group was significantly larger than that of the convergent group ($p = 0.001$).

Predictors of LTR

Table 3 demonstrates tumor characteristics and procedure details according to LTR. The mean tumor diameter and volume were significantly higher in patients with LTR (group A) than in those without LTR (group B) (tumor diameter, $p = 0.007$; tumor volume, $p = 0.009$). Although the mean final ablation volume did not differ significantly between the two groups ($p = 0.733$), the ratio of final ablation volume to tumor volume was significantly lower in group A than in group B ($p = 0.007$).

Table 4 shows factors affecting LTR. Univariate analysis showed that subcapsular location (HR 3.984, $p = 0.032$), first freezing ablation volume < 15 cm³ (HR 2.817, $p = 0.099$), and a ratio of final ablation volume to tumor volume < 10 (HR 5.882, $p = 0.016$) were related to LTR. Multivariate analysis showed that a ratio of final ablation volume to tumor volume < 10 (HR 4.227, $p = 0.044$) was the only factor associated with LTR (Figs. 3B, 5).

Fig. 3 Kaplan–Meier curves showing local tumor recurrence (LTR)-free survival rates. **A** The LTR-free survival rates at 6 months, 1 year, and 2 years were 87.7%, 84.0%, and 80.2%, respectively. **B** There was a significant difference in the LTR-free survival rate ($p = 0.044$) in the factor of final ablation volume/tumor volume < 10



Discussion

Cryoablation is a therapeutic approach emerging as an alternative to RFA offering technological advances including thinner cryo-probes [17]. The cryoablation device generates an ice-crystal, which is lethal to the target tissues around tips of cryo-probe by using high-pressure argon and helium gas based on the Joule–Thompson

principle [18]. The treatment outcomes of PCA have comparable efficacy and improved safety compared to RFA in patients with hepatic malignancies [19–21].

However, the smaller ablation zone of PCA is a disadvantage, as compared to RFA [22]. In a previous phantom study, two or more cryo-probes resulted in a 35–70% increase in lethal ice-crystal diameters, compared to a single cryo-probe. Moreover, clinically, several cryo-

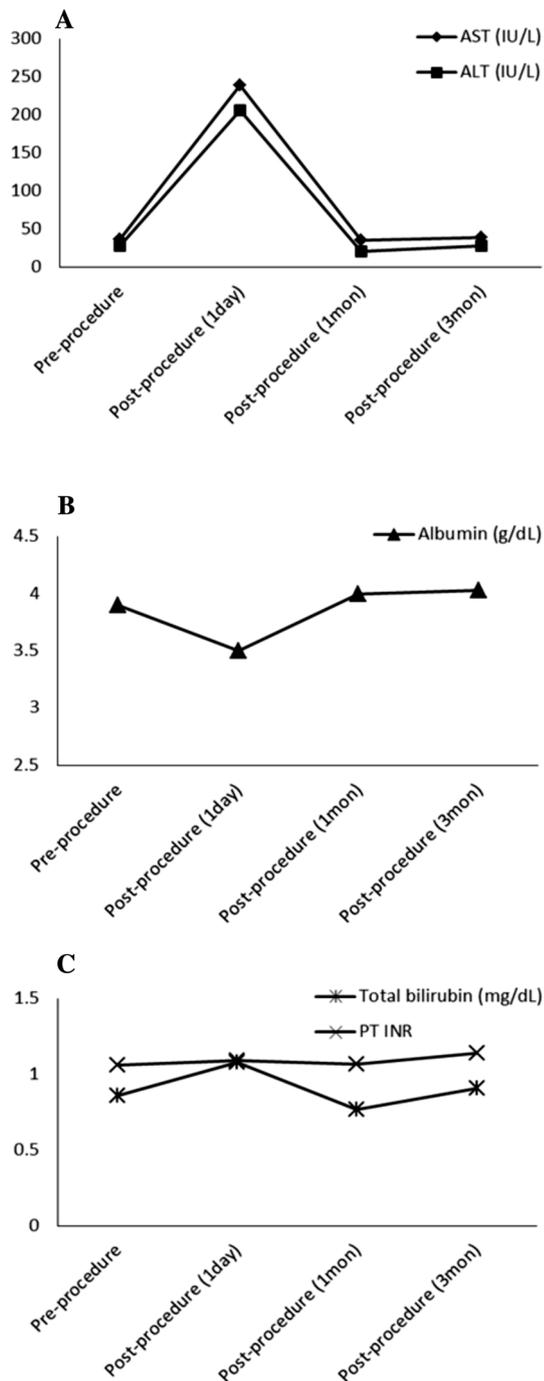


Fig. 4 Mean values of biochemical data collected 1 day before and 1 day, 1 month, and 3 months after PCA. **A** Mean levels of serum aspartate aminotransferase and alanine aminotransferase, **B** albumin and **C** total bilirubin and the international normalized ratio of prothrombin time

probes are usually required to treat most tumors due to the smaller ablation zone of a single cryo-probe. Accordingly, we assumed that a single cryo-probe would not reach cell-killing temperatures in an in vivo environment; thus, we used at least two cryo-probes for local control of most

Table 2 Details of the procedures for tumors

Procedural details	N (%)
Distance between cryo-probes (cm)*	1.3 ± 0.6
Orientation of cryo-probes (n)	
Parallel	39 (36.8)
Convergent	23 (21.7)
Divergent	44 (41.5)
First freezing ablation volume (cm ³)*	14.7 ± 4.3
Final ablation volume (cm ³)*	19.1 ± 4.8
Final ablation volume/tumor volume*	13.4 ± 9.1

*Mean ± SD

hepatic tumors [22, 23]. In the present study, 96 patients underwent PCA using two cryo-probes for local control of small HCCs. The technical success rate was 100%, and LTR was observed in 21 of 106 lesions (19.8%) in 17 of 96 patients (17.7%) during the median follow-up of 16.7 months. These results are comparable to those of previous studies on ablation therapies including RFA and PCA, which reported LTR rates of 9.7–24.0% and 3.1–33.3% at 1 and 2 years after procedures, respectively [21, 24–28].

The measurement and prediction of final ablation volume are important because it is related to not only SIR or cryoshock syndrome but is also used to determine the treatment plan [7, 8]. In the present study, the mean final ablation volume increased significantly by approximately 29.9% compared to the mean first freezing ablation volume (19.1 ± 4.8 vs. 14.7 ± 4.3, $p < 0.001$). Consequently, the final volume can be predicted at the end of the first freezing cycle to guide treatment plans, including adding cryo-probes or performing additional cycle to ensure sufficient ablation volume to cover the tumor before completing the procedure. Therefore, it is worthwhile to confirm the ablation volume by performing CT both at the end of the first freezing and immediately after PCA, as in this study.

Regarding the orientation of cryo-probes, the final ablation volume was significantly different between the two groups (convergent group: 16.6 ± 5.4 cm³ vs. divergent group: 21.2 ± 5.5 cm³, $p = 0.001$). A possible explanation could be the difference in the distance between the cryo-probes (convergent: 10.0 ± 0.9 mm vs. divergent: 15.3 ± 1.2 mm, $p = 0.001$). When using multiple cryo-probes, an appropriate distance between the cryo-probes is required for a sufficient ablation zone with the best therapeutic efficacy. The reported optimum distance between 17G cryo-probes to achieve a synergistic effect with maximum efficiency was 1.5 cm [29]. In the present study, a ratio of final ablation volume to tumor volume showed statistical correlation with LTR. Therefore, ensuring a

Table 3 Tumor characteristics and procedure details according to local tumor recurrence

	Group A (<i>n</i> = 17)	Group B (<i>n</i> = 79)	<i>P</i> value
Tumor number (<i>n</i>)			0.051
Solitary	13	73	
Multiple	4	6	
Tumor diameter (cm)*	2.1 ± 0.6	1.7 ± 0.4	0.007
Tumor volume (cm ³)*	3.2 ± 2.1	1.8 ± 1.2	0.009
Tumor location (<i>n</i>)			0.079
Subcapsular	20	67	
Non-subcapsular	1	18	
Distance between cryo-probes (cm)*	1.2 ± 0.5	1.3 ± 0.6	0.424
Orientation of cryo-probes (<i>n</i>)*			0.588
Parallel	6	33	
Convergent	6	17	
Divergent	9	35	
First freezing ablation volume (cm ³)*	14.5 ± 4.9	15.1 ± 4.1	0.704
Final ablation volume (cm ³)*	18.9 ± 5.4	19.1 ± 4.8	0.733
Final ablation volume/tumor volume*	9.1 ± 6.7	16.0 ± 10.9	0.007

*Mean ± SD

Table 4 Univariate and multivariate Cox regression analysis of the risk factors for local tumor recurrence

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	Adjusted HR	95% CI	<i>P</i> value
Tumor multiplicity	1.352	0.105–17.407	0.817			
Subcapsular location	3.984	1.122–14.085	0.032	2.695	0.787–16.259	0.066
Distance between cryo-probes < 1 cm	2.320	0.861–8.772	0.213			
Convergent orientation of cryo-probe	1.066	0.254–4.484	0.930			
Tumor volume > 2 cm ³	1.513	0.193–11.904	0.694			
Diameter of tumor > 2 cm	2.733	0.418–16.878	0.335			
First freezing ablation volume < 15 cm ³	2.817	0.687–11.494	0.099	1.842	0.613–12.525	0.226
Final ablation volume < 20 cm ³	2.160	0.463–10.083	0.327			
Final ablation volume/tumor volume < 10	5.882	1.385–25.000	0.016	4.227	1.130–30.109	0.044

HR hazard ratio, CI confidence interval

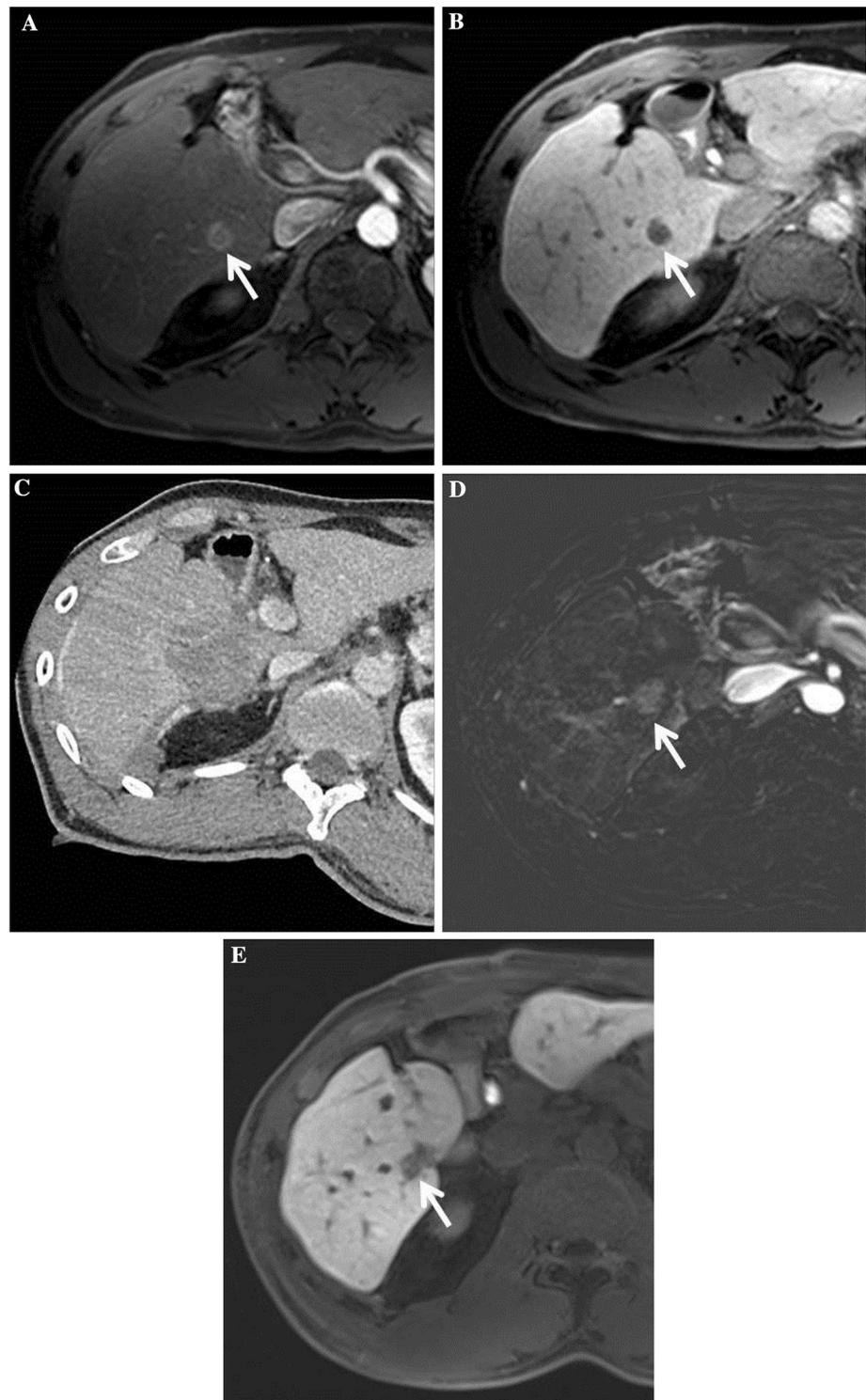
sufficient ablation volume through appropriate distance and orientation of the cryo-probes is essential.

Several studies have identified risk factors for LTR after PCA for HCC, including minimal ablation margin (at least 5 mm), multiple lesions, tumor size larger than 3 cm, and repeated ablation of the same lesions [24, 30]. However, the association between ablation volume and LTR has not been evaluated. In the present study, final cryoablation volume itself was not significantly associated with LTR but a ratio of final ablation volume to tumor volume smaller than 10 was a significant risk factor for LTR. This suggests the importance of ensuring a sufficient cryoablation volume in consideration of hepatic tumor volume to suppress LTR after PCA.

Minimal ablation margin is one of the most important risk factors for LTR after RFA [30]. In this study, two patients had LTR despite a ratio of final ablation volume to tumor volume above 10. A retrospective analysis revealed that sufficient volume was ablated but that the minimal ablation margin was less than 5 mm, meaning that the cryo-probes were located away from the center of the tumor. Therefore, evaluating the position of the cryo-probes by CT at the end of first freezing is necessary to ensure sufficient minimal ablation margins and volumes.

In terms of tumor location, previous studies of RFA for subcapsular HCC treatment reported overall higher LTR rates of 16–21% [30–32]. Furthermore, despite controversial findings, more major complications, including tumor

Fig. 5 A 37-year-old man underwent percutaneous cryoablation (PCA) for hepatocellular carcinoma (HCC). **A, B** The liver dynamic magnetic resonance image (MRI) shows an HCC with a tumor volume of 3.49 cm^3 in S6. **C** Immediate post-PCA computed tomography shows an ice-ball formation with a cryoablation volume of 25.94 cm^3 . The final ablation volume/tumor volume was 7.4. **D, E** The liver dynamic MRI performed 5 months after PCA shows arterial enhancement with wash-out adjacent to the treated lesion (arrows) in liver S6, suggesting local tumor recurrence. The patient underwent additional radiofrequency ablation and was followed up without evidence of tumor recurrence until now



seeding along the probe tract or thermal injury to adjacent organs, were reported on subcapsular lesions than on non-subcapsular lesions after RFA [33, 34]. In contrast, PCA has been reported to be safe for subcapsular lesions, with a comparable efficacy to RFA [1]. In the present study, despite the large number of tumors in the subcapsular

location (87 of 106 tumors, 82.1%), there were no complications associated with adjacent organ injury, and the LTR was comparable to that of previous studies (17.7%). These results reaffirm that PCA is safe for subcapsular lesions.

The current study has several limitations. First, this study had a retrospective design. Second, the difference in ablation volume according to the degree of liver cirrhosis was not analyzed. Liver cirrhosis affects the ablation volume in thermal therapies [10]. Therefore, future studies are necessary to compare ablation volume based on the degree of liver cirrhosis. Third, patients with more than three cryoprobes were excluded. Further studies on the differences in ablation volume according to the number of cryoprobes are needed.

In conclusion, the ratio of final ablation volume to tumor volume (less than 10) was a significant prognostic factor for LTR. Therefore, the final ablation volume should be confirmed by performing CT immediately after PCA. Furthermore, ablation volume measurement at the end of the first freezing may be helpful to guide treatment plans, because final ablation volume is predictable based on the first freezing ablation volume. Additionally, the evaluation of the cryoprobes' position at the first end of freezing is necessary to obtain sufficient tumor coverage.

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Compliance with Ethical Standards

Conflict of interest The authors do not have any conflict of interests to report.

Informed Consent This retrospective study was approved by our Institutional Review Board, and the need for informed consent was waived.

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