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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Percutaneous cryoablation in early stage hepatocellular carcinoma: analysis of local tumor progression factors

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PURPOSE
We aimed to evaluate the effectiveness and safety of percutaneous cryoablation (PC) for early or very early stage hepatocellular carcinoma (HCC) and assess the risk factors for local tumor progression (LTP) after PC.

METHODS
A total of 45 treatment-naïve patients treated with PC for early or very early stage HCCs were included in this retrospective study. The safety of PC was assessed by evaluating procedure-related complications and comparing hepatic function before and after the procedure. The effectiveness was assessed by evaluating technical success, LTP rates, and disease progression (DP) rates. Prognostic factors associated with LTP after PC were also analyzed.

RESULTS
Technical success and complete response were achieved in all patients (100%) by 1 month after PC. During a mean of 28.1±15.6 months of follow-up, the incidences of LTP and DP were 11.1% and 37.8%, respectively. The LTP-free and DP-free survival rates were 93.3% and 84.4% at 1 year and 88.9% and 62.2% at 2 years, respectively. Hepatic function was normalized within 3 months after PC. There were no major complications and only one minor complication of small hematoma. On univariate and multivariate analysis, minimal ablative margin <5 mm was the only significant risk factor associated with LTP.

CONCLUSION
PC is a safe and effective therapy for patients with early or very early stage HCC. Minimal ablative margin <5 mm was a significant prognostic factor for LTP.

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally, with an increasing incidence in many countries, and the second leading cause of cancer-related mortality worldwide (1, 2). Among the various HCC treatment strategies, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most preferred treatment guideline, because it not only allocates optimal treatment but helps to predict survival outcomes (3, 4). According to the BCLC guidelines, radiofrequency ablation (RFA) is recommended as the first-line treatment for patients with very early (0) or early (A) stage HCC. Prior studies have consistently demonstrated that RFA is comparable to surgical resection in terms of local tumor control rate for these patients (5, 6).

Other thermal ablation techniques have also been developed, and cryoablation in particular has been widely used in various other types of cancers including kidney, prostate, breast, and lung cancers (7). Compared with RFA, cryoablation has several advantages, including larger ablative coverage, more discernible ablative margin, and less intraprocedural pain (8, 9). Furthermore, the advances in cryoablation technology such as thinner cryoprobes with newer argon-helium systems have made it possible to expand its applications to HCC. However, data on the clinical outcomes and safety of cryoablation for HCC are limited, and have been even more sparsely reported in patients with HCC who are indicated for RFA under the BCLC guidelines.

The aim of this study was to evaluate the effectiveness and safety of percutaneous cryoablation (PC) for early or very early stage HCC lesions under the BCLC guidelines and to

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elucidate the factors related with local tumor progression.

Methods

Patients

This retrospective study was approved by our Institutional Review Board (4-2019-0021), and the requirement for informed consent was waived. Between September 2013 and December 2018, 199 patients underwent PC for HCC at our institution. The inclusion criteria for this study were patients with BCLC very early (0) or early (A) stage HCC. Patients who had history of prior treatment for HCC, poor hepatic reserve (Child-Pugh score C), poor general condition (Eastern Cooperative Oncology Group Performance Status ≥2), evidence of extrahepatic metastasis or bleeding tendency (international normalized ratio [INR] of prothrombin time [PT] ≥1.5 and platelet counts ≤50000/μL) were excluded (10). Finally, a total of 45 patients (mean age, 61.0±12.2 years; range, 46–79 years) were included in this study. Some of these patients were reported in a previous work (11).

HCC was diagnosed based on the typical imaging findings of liver dynamic computed tomography (CT) or magnetic resonance imaging (MRI) with elevated levels of serum α-fetoprotein (AFP) and/or prothrombin induced by vitamin K absence-II (PIVKA-II) (n=45) prior to PC. All patients in this study had underlying chronic liver disease or liver cirrhosis associated with hepatitis B (n=25), hepatitis C (n=4), nonviral hepatitis (n=7), or chronic alcoholism (n=9).

PC procedure

PC for HCC was performed in the hybrid angiography suite which was equipped with an angio-CT that incorporates a multidetector CT scanner (INFX-8000C combined with Aquilion 128 channel CT scanner, Toshiba Medical Systems Corp.) and angiography system. Thirty minutes before entering the procedural room, all patients were administered 25 mg of pethidine hydrochloride (Pethidine, Myungmoon Pharm) intramuscularly. After using 10–20 mL of 1% lidocaine (Lidocaine, Daihan Pharm) for local anesthesia, the cryoprobes (IceRod i-Thaw 1.5 17 G straight cryoablation probe, Gail Medical) were inserted into the tumor under ultrasonography (US) guidance (LOGIQ E9, General Electric). If the lesion was poorly visualized under US guidance and thus difficult to target, CT and/or fluoroscopy guidance was also utilized. After cryoprobe placement, unenhanced CT was used to determine if the lesion was appropriately targeted. The operators determined the number of cryoprobes, depending on the shape and size of the lesion, and at least two cryoprobes were inserted in a coaxial fashion to overlap the ablation zone. The mean distance between the cryoprobes used was 1.2±0.6 cm (range, 0.7–1.8 cm) and it was close to 1.5 cm, the reported optimum distance between the 17 G cryoprobes (12). The ablation process consisted of a double-thaw cycle of a 10-minute freezing period and 8-minute thawing period in each cycle (13). Between the first and second cycles, unenhanced CT was performed to monitor low-attenuation ice-ball formation in maximum size. The field-of-view was set to cover the liver and adjacent organs with potential risks of procedure-related complications. After completion of PC, three-phase liver dynamic contrast-enhanced CT was performed to evaluate if the ablation zone sufficiently covered the tumor and assess any immediate postprocedure complications.

Main points

- Percutaneous cryoablation is an effective therapy for patients with early or very early stage hepatocellular carcinoma, which is comparable to radiofrequency ablation.
- Based on our study, percutaneous cryoablation could be a safe treatment modality for hepatocellular carcinoma with less pain and no major procedure-related complications.
- A minimal ablative margin <5 mm was a significant prognostic factor for local tumor progression in percutaneous cryoablation.

Definitions and data analysis

Technical success was defined as the tumor being completely within the cryoablation zone, as confirmed on CT immediately after PC. Local tumor progression (LTP) was defined as the appearance of new tumor foci at the ablative margin. Disease progression was defined as the emergence of intrahepatic distant recurrence, extrahepatic metastasis, or LTP (14). The degree of tumor necrosis was determined according to the modified response evaluation criteria in solid tumor (mRECIST) (15). To obtain the minimal ablative margin (MAM), axial, coronal, and sagittal images of the pre- and post-ablation portal phase CT images were reviewed side by side but independently by two radiologists of 4 and 10 years of experience to compare the index tumor and the ablation zone. The distances from the edge of the tumor to the chosen anatomic landmarks (e.g., liver surface, bone, and portal or hepatic vein) at three different sites on each axial, coronal, and sagittal image were measured on both pre- and postablation CT. The corresponding distances were subtracted, and the shortest value was defined as the MAM (Fig. 1). Subcapsular lesion was defined as a lesion located within 1 cm from the liver surface (11).

Complications

Complications related to PC were divided into two categories: major and minor. Major complications were defined as events causing additional hospitalization or permanent adverse effects such as liver failure, severe thrombocytopenia, and cryoshock (multiorgan failure and disseminated intravascular coagulation) (9, 16). All other events were defined as minor complications.

Follow-up after initial cryoablation

For follow-up, patients underwent scheduled triple-phase contrast-enhanced CT 1-month after initial PC and at 2- or 3-month intervals thereafter. Tumor markers (i.e., AFP and/or PIVKA-II) were also assessed at each follow-up. To evaluate changes in hepatic function after PC, biochemical data including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), albumin levels, and the PT-INR were collected 1 day, 1 month, and 3 months after the procedure.

Pain analysis

The visual analog scale (VAS) was used to evaluate pain during the procedure (17). Before the procedure, the VAS was explained to patients. Pain was evaluated before the procedure, after targeting, during cryoablation, and after completion of PC. Patients were also allowed to complain of pain at any time during the procedure. Among these, the most severe VAS value was recorded.

Statistical analysis

All statistical analyses were performed with SPSS 23.0 for Windows (IBM Corp). Data were tabulated as means and standard deviations for continuous variables and absolute numbers and percentages for categorical variables. Serum AST, ALT, TB, albumin levels, PT-INR, and AFP pre- and

postprocedure were compared using the paired sample t-test. Interobserver agreement regarding the CT/MRI features, including measurement of the MAM <5 mm and tumor size <2 cm, in each case was evaluated using kappa (κ) statistics. Kappa values were indicated as follows: less than 0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and greater than 0.81, excellent agreement (18). A univariate Cox proportional hazards model was used to elucidate predictors for LTP. Factors, significantly associated with LTP ($P < 0.1$) in the univariate analysis, were included in the multivariate analysis. Outcomes were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The *P* value of the model for Cox analysis was calculated by using likelihood ratio test. LTP-free survival (LTPFS), progression-free survival (PFS), and overall patient survival rates were calculated by using a Kaplan-Meier curve and compared between groups by using a log-rank test. *P* values < 0.05 were considered statistically significant.

Results

Patients were followed up for a range of 7–68 months (mean, 28.1±15.6 months). The mean tumor size was 1.8±0.5 cm. Among 29 patients with hepatitis B or C, 24 (82.8%) received antiviral medication during follow-up after PC. The patient and tumor characteristics are summarized in Table 1.

The technical success rate was 100%. At 1 month imaging follow-up, complete response (CR) was achieved in all patients (100%). LTP occurred in 5 patients (11.1%), and disease progression, including LTP, occurred in 17 patients (37.8%) during follow-up. In 5 patients with LTP (Fig. 2), additional PC was performed in 2 patients, RFA in 1 patient, and transarterial chemoembolization (TACE) in 2 patients. Three patients who underwent PC or RFA showed no LTP. However, 2 patients who underwent TACE showed second LTP and had to receive repeat TACE. The LTPFS rates at 1 and 2 years were 93.3% (42/45) and 88.9% (40/45), respectively. The PFS rates at 1 year and 2 years were 84.4% (38/45) and 62.2% (28/45), respectively. The median PFS was 35 months (95% CI, 24.583–47.351) (Fig. 3a, 3b) and the mean LTPFS was 24.6±16.1 months. Overall survival rates at 1 year and 2 years were 100% and 95.6% (43/45), respectively. The LTP rates were significantly higher in patients with MAM <5 mm than those with MAM ≥5 mm ($P = 0.018$) on log-rank test (Fig. 3c).

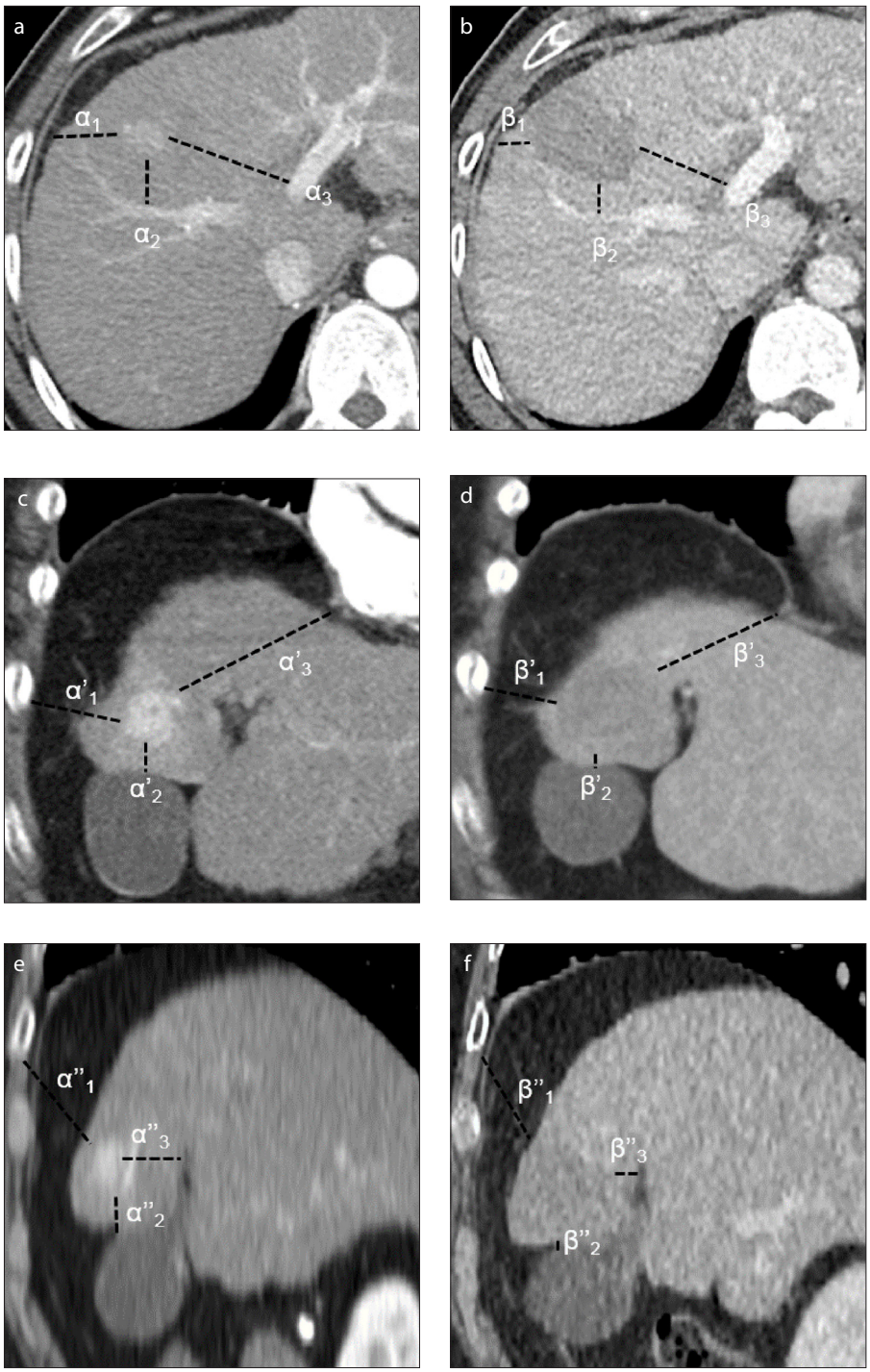

Figure 1. a–f. Minimal ablative margin (MAM) evaluation on each axial **(a, b)**, coronal **(c, d)** and sagittal images **(e, f)** of computed tomography (CT). The shortest distance between pre-ablation CT **(a, c, e)** and post-ablation CT **(b, d, f)** is chosen at each plane and, among them, the shortest value of "αn – βn" is defined as MAM. In this, "α2 – β2" on axial plane is the MAM.

Kappa values (κ) of the tumor size, segmental location, and MAM categorizations were 0.94 ($P < 0.001$), 0.87 ($P = 0.002$), and 0.76 ($P = 0.037$), respectively. As shown in Table 2, independent risk factors associated with LTP were AFP ≥100 ng/mL and a MAM <5 mm on univariate Cox analysis. On multivariate Cox analysis, a MAM <5 mm was identified as the only statistically significant risk factor for LTP ($P = 0.018$).

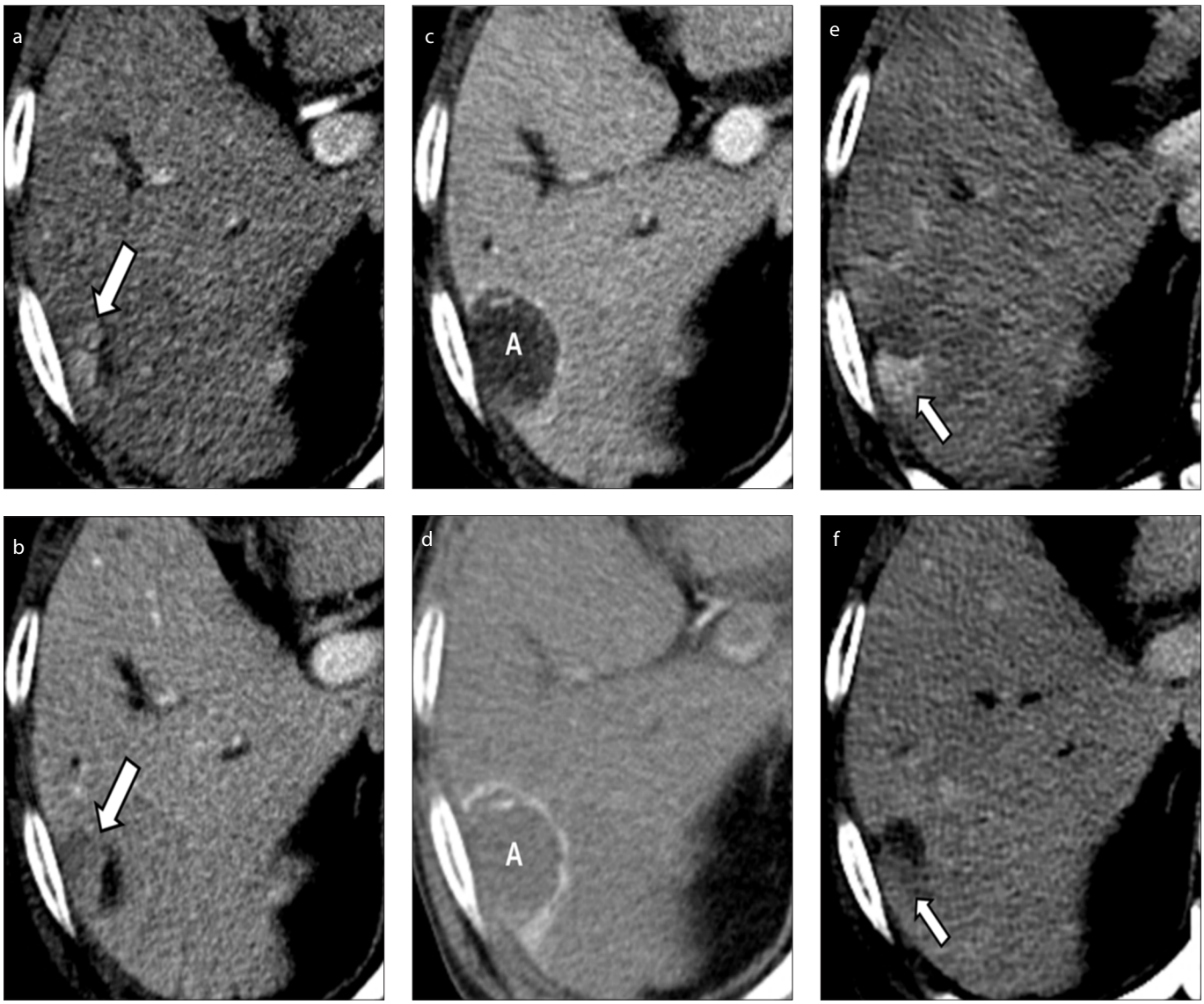

Figure 2. a–f. A 75-year-old man with hepatocellular carcinoma (HCC) treated with percutaneous cryoablation (PC). Liver dynamic computed tomography (CT) images **(a, b)** demonstrated an enhancing mass with washout on portal phase in segment 6 measuring 2 cm *(arrow)*, suggesting HCC. Follow-up CT images **(c, d)** obtained at 1 month after PC. The tumor was completely replaced by ablation zone **(a)**, but its MAM was 3 mm, measured on axial plane. Follow-up CT images **(e, f)** obtained at 1 year after PC showed local tumor recurrence.

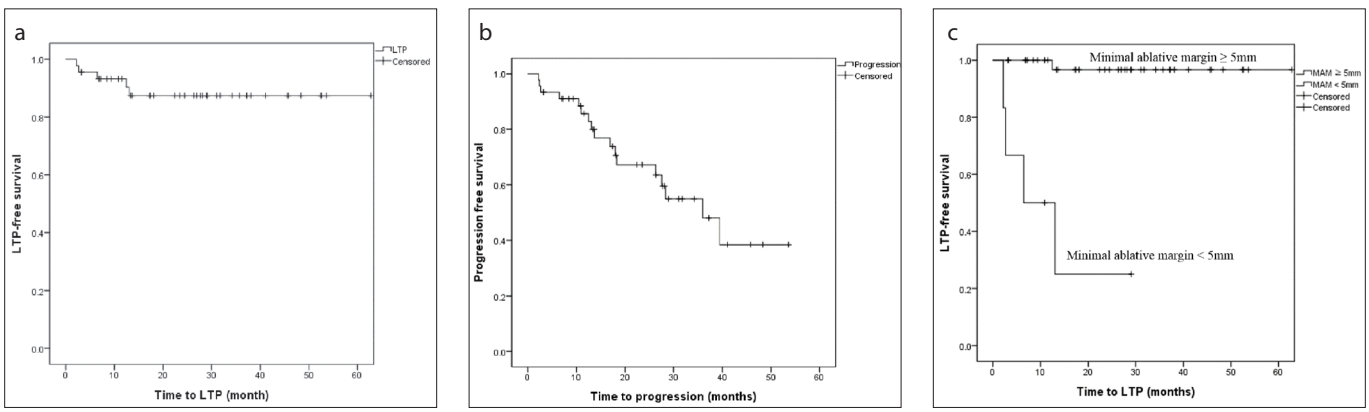

Figure 3. a–c. Kaplan-Meier curves of **(a)** local tumor progression (LTP)-free survival and **(b)** progression-free survival in patients who underwent percutaneous cryoablation for hepatocellular carcinoma. Log-rank test **(c)** shows significantly higher LTP rates in patients with a MAM <5 mm ($P = 0.018$).

Table 1. Characteristics of patients and lesions

Characteristics	Value
Age (years), mean±SD	61.0±12.2
<65 years	25 (55.6)
≥65 years	20 (44.4)
Sex (M:F), n	33:12
Etiology	
HBV	25 (55.6)
HCV	4 (8.9)
NBNC	7 (15.5)
Alcoholic	9 (20.0)
Child-Pugh class	
A	41 (91.1)
B	4 (8.9)
ECOG PS	
0	36 (80.0)
1	9 (20.0)
Tumor number	
Solitary nodule	43 (95.6)
Two or three nodules	2 (4.4)
Tumor size (cm), mean±SD	1.8±0.5
<2 cm	28 (58.3)
≥2 cm	20 (41.7)
Minimal ablative margin (mm), mean±SD	6.3±1.8
<5 mm	6 (12.5)
≥5 mm	42 (87.5)
AFP (ng/mL), mean±SD	85.7±193.6
<100	34 (75.6)
≥100	11 (24.4)
Antiviral therapy during follow-up	
Yes	24 (82.8)
No	5 (17.2)

Unless stated otherwise, values are presented as n (%).
M, male; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B non-C; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AFP, α-fetoprotein.

The mean AFP levels were 85.7±193.6 ng/mL before PC, which significantly decreased to 30.2 ng/mL (P = 0.023) and 28.0 ng/mL (P = 0.040) 1 and 3 months after PC, respectively. The mean values of serum AST, ALT, TB, albumin, and PT-INR were 35.8 IU/L, 27.7 IU/L, 0.9 mg/dL, 3.9 g/dL, and 1.1, respectively, before PC. One day after PC, the mean serum AST and ALT levels were significantly elevated to 241.4 IU/L (P < 0.001) and 205.5 IU/L (P < 0.001), respectively. The mean TB levels were also significantly elevated to 1.1 mg/dL (P = 0.001), but this was still within the normal limits. The mean serum albumin level was significantly decreased to 3.5 g/dL (P < 0.001). One month after PC, serum AST, TB, and albumin levels had normalized to 35.0 IU/L (P = 0.565), 0.8 mg/dL (P = 0.700), and 4.0 g/dL (P = 0.238), respectively. The mean ALT level was significantly decreased to 21.0 IU/L (P = 0.04) at 1 month, but normalized to 28.3 IU/L (P = 0.881) at 3 months, showing no significant differences compared with preprocedural levels. The mean value of PT-INR showed no significant differences before and after PC (Fig. 4).

There were no major procedure-related complications. A small hematoma around the abdominal wall where the cryoprobes were placed was noted in one patient immediately after PC, which was managed by conservative treatment. Two patients died during the follow-up period, but neither death was related to the procedure or HCC. The reasons for mortality included sepsis due to infective spondylitis and aspiration pneumonia, respectively. During the procedure, pain was tolerable in all patients, with VAS ranging from 0 to 5 (mean, 2.6±1.5). Ten patients required additional pain control: fentanyl (mean dosage,

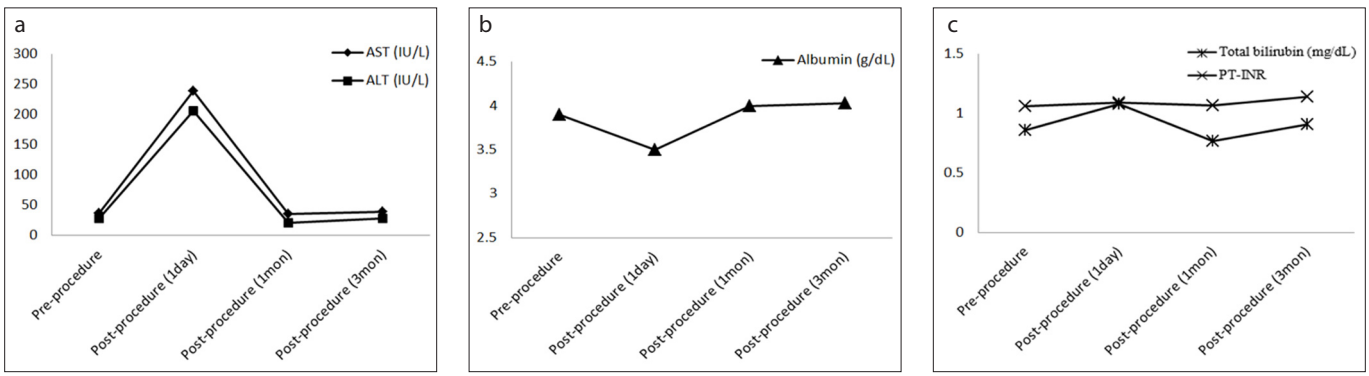

Figure 4. a–c. The mean values of collected biochemical data from the patients at 1 day before, and 1 day, 1 month, and 3 months after percutaneous cryoablation: **(a)**, mean values of aspartate aminotransferase and alanine aminotransferase; **(b)**, albumin; and **(c)**, total bilirubin levels and prothrombin time international normalized ratio (PT-INR).

Table 2. Univariate and multivariate Cox analyses for predictors of LTP

	Univariate analysis			Multivariate analysis*		
Variables	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
AFP ≥100 ng/mL	17.305	3.445–33.988	0.004	13.783	2.425–53.339	0.078
Subcapsular location	1.237	0.778–3.261	0.832			
Tumor multiplicity	1.889	1.185–15.364	0.525			
Size ≥2 cm	2.108	0.263–17.062	0.456			
MAM <5 mm	24.391	2.043–79.317	0.001	23.877	1.808–274.210	0.018

LTP, local tumor progression; HR, hazard ratio; CI, confidence interval; OR, odds ratio; AFP, α-fetoprotein, MAM, minimal ablative margin.
*The *P* value of the model for Cox analysis (likelihood ratio test *P* value) < 0.001.

39.3±13.3 μg) in 7 patients and pethidine (mean dosage, 16.6±6.7 mg) in 3 patients.

Discussion

Cryoablation is thought to have tumoricidal effects by extra- and intracellular ice formation, hypoxia induced by small vessel occlusion, cell dehydration and rupture, and promoting an immunologic response that suppresses tumor growth (19). With efficacy and safety profiles comparable to those of RFA, cryoablation may serve as a reliable alternative to RFA in the management of early stage HCC (8). However, little data regarding the use of PC for early stage HCC exist.

Many studies regarding the risk factors of LTP after RFA for HCC have been published, but there exist only a few such studies on PC for HCC (9, 20–22). Rong et al. (9) reported that multiple lesions, tumor size >3 cm, and repeated ablation of the same lesions were independent risk factors associated with LTP after PC. However, MAM, known to be one of the most important risk factors associated with LTP after RFA, has not been evaluated in prior studies. In our study, the multivariate analysis demonstrated that a MAM <5 mm (P = 0.018) was the only significant risk factor for LTP after PC. This suggests that establishment of an at least 5 mm ablative margin is effective in suppressing LTP after PC of HCC, which is consistent with the findings from the previous studies of RFA (23, 24). Furthermore, contrary to PC, there were studies evaluating the effectiveness and safety of RFA for subcapsular HCC with conflicting outcomes (25–27). Due to incomplete ablation and risk of thermal damage when performing ablation therapy, subcapsular location could be a risk factor for local tumor recurrence. However, in our study, subcapsular location was not associated with local tumor recurrence after PC (P = 0.832), in line with the recent studies on RFA. In a study by Lee et al. (28), to measure the maximal ablation capacity and minimize complications, the investigators performed PC with a single cryoprobe for solitary HCC lesions <3 cm in size. The CR rate in their study was significantly higher in patients with lesions ≤2 cm than in those with lesions with a diameter of 2–3 cm (100% vs. 65%). In a large retrospective study, a single cryoprobe was used for lesions ≤2 cm, two cryoprobes for lesions >2 cm but ≤3.5 cm, and three cryoprobes for lesions >3.5 cm, and their CR rate was 97.2% (9). In the present study, two or more cryoprobes were utilized in all patients, and the CR rate was 100%. This suggests that the ablation zone induced by a single cryoprobe may not be sufficient in covering lesions measuring up to 3 cm in size. In addition, *in vivo* experiment is warranted to test the actual ablation coverage of a cryoprobe in relation to the varying degrees of underlying liver disease.

The CR rate of 100% in our study is not thought to be solely dependent on the use of multiple cryoprobes. It is assumed that the built-in CT scanner in the hybrid angio-CT unit helped to target the lesion accurately, and immediate post-ablation multi-phase contrast-enhanced CT allowed evaluation of the ablation zone and post-procedural complications. If the tumor is not sufficiently replaced by the ablation zone, additional ablation can be performed, and if there are signs of bleeding along the ablation tract, emergency angiography can be immediately performed. Therefore, the angio-CT unit can serve as an adjunctive tool that makes PC safer and more effective.

Massive bleeding associated with parenchymal dehiscence along the cryoprobe trajectory and cryoshock syndrome are the two most devastating complications of cryoablation (29, 30). In our study, only one (2.2%) minor complication occurred. The use of thinner (17 G) cryoprobes may explain the lack of parenchymal dehiscence and massive bleeding. Cryoshock is known to develop in up to 1% of liver ablations, and may be attributed to necrotic debris flowing directly into the bloodstream during the procedure (31, 32). As freezing 30% to 35% of the liver volume is associated with cryoshock syndrome (33), PC for large lesions carries a higher risk for this severe systemic adverse event. Therefore, small and early lesions, e.g., BCLC 0 or A category, seem to be better candidates for PC.

As severe pain is not uncommon in RFA even with conscious sedation, general anesthesia is sometimes or routinely required. In a study by Lee et al. (34), the mean procedural VAS score was 5.53 in patients undergoing RFA. Cryoablation is reported to be less painful in the treatment of nonliver tumors, and hence a lower dose of sedatives and narcotic analgesics needs to be administered (35, 36). In our patients who underwent PC without sedation, the mean VAS score was 2.6±1.5 (range, 0–5), and additional pain medication was required in 10 patients (22.2%). This obviates the need for conscious sedation or general anesthesia, and thus PC can be more safely performed than other percutaneous ablative treatment in HCC patients.

In recent years, microwave ablation (MWA), one of the thermal ablative therapies, has also been used to treat HCC, showing clinical outcomes comparable to RFA. However, there have been procedure-related complications on thermal ablative therapies, with major complication rates 4.1% for RFA and 4.6% for MWA, respectively, and the overall incidence of gastrointestinal track perforation was reported in about 0.1%–0.3% (37). Furthermore, microwave

could cause severe pain during the procedure, which possibly interferes with complete ablation. In contrast, PC causes less pain and thus patients are usually stable during the procedure (16). Compared with MWA, PC may be more expensive in some regions, but it has advantages in terms of less procedure-related major complications and less pain. However, long-term oncologic outcomes should be evaluated and compared in a future study.

There were some limitations in our study. First, it was a retrospective study, and selection bias could affect the results. Second, the MAM was determined by measuring distances between two landmarks manually on each axial, coronal, and sagittal image on both pre- and postablation CT. Though the κ value for the MAM <5 mm was good (0.76), it could be inaccurate because the distances were measured by free-hand drawing. Third, our population was relatively small, and the follow-up intervals were relatively short. Long-term outcomes should be further investigated. However, the short-term outcomes we describe are in line with previous reports, as mentioned above. Finally, we did not have a control group.

In conclusion, PC is a safe and effective ablative treatment modality for early or very early stage HCC. Moreover, a MAM <5 mm was a significant prognostic factor for LTP.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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