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INTERVENTIONAL

Percutaneous cryoablation for perivascular hepatocellular carcinoma: Therapeutic efficacy and vascular complications

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Abstract

Objectives To evaluate the therapeutic efficacy of and vascular complications associated with percutaneous cryoablation for the treatment of perivascular HCC.

Methods Between August 2015 and September 2017, 58 consecutive patients (48 men, 10 women; mean age, 61.1 years; age range, 44–84 years) who underwent percutaneous cryoablation were included. All patients had a single perivascular HCC (mean size, 1.3 cm; Barcelona clinic liver cancer-stage 0 or A) that was in contact with hepatic vessels, ≥ 3 mm or larger in axial diameter. Local tumour progression (LTP) was estimated by the Kaplan-Meier method. In addition, several procedure-related vascular complications were evaluated immediately after treatment and during follow-up CT: peritumoral vessel thrombosis; infarction; aggressive intrasegmental recurrence (AIR) (the simultaneous development of ≥ 3 nodular or infiltrative tumours). The follow-up CT was performed in all patients 1 month after the procedure, and every 3 months thereafter.

Results The median follow-up period was 22 months (range, 3–29 months). The technical success rate of cryoablation was 96.6% (56/58). The 1- and 2-year cumulative LTP rates were 3.6% and 14.6%, respectively. Although peritumoral vessel thrombosis occurred in 6.9% of cases (4/58), no cases of hepatic infarction were observed and AIR did not develop during follow-up. Half of the thombi in the peritumoral vessels immediately after cryoablation disappeared on follow-up CT images.

Conclusion Cryoablation could be an effective tool for the treatment of perivascular HCC with a very low risk of vascular complications.

Key Points

- *Cryoablation allowed a high technical success rate for perivascular HCC.*
- *Only 6.9% developed peritumoral vessel thrombosis without major vascular complications like infarction.*
- *Two-year cumulative LTP rate was 14.6%, without aggressive tumour recurrence on follow-up.*

Keywords Liver · Hepatocellular carcinoma · Cryoablation · Treatment outcome

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Abbreviations

BCLC	Barcelona clinic liver cancer-stage
CI	Confidence interval
CT	Computed tomography
HCC	Hepatocellular carcinoma
LTP	Local tumour progression
MR	Magnetic resonance
RF	Radiofrequency
TACE	Transarterial chemoembolisation
US	Ultrasound

Introduction

Radiofrequency (RF) ablation is now accepted as the standard of care for patients with very early-stage hepatocellular carcinoma (HCC) who are not eligible for liver transplantation [1]. Although RF ablation plays a pivotal role due to its therapeutic efficacy in patients with HCC, complete and safe ablation of perivascular tumours remains a challenge [2, 3]. Firstly, failure of local tumour control may occur due to insufficient ablative margins around peritumoral vessels, known as the heat-sink effect, which can decrease the volume of the ablation zone considerably [4]. Secondly, there is a risk of thrombotic complications by thermal injury of peritumoral vessels that can lead to vascular thrombosis as well as hepatic infarction [5]. Furthermore, rapid heating may lead to a sudden increase in internal pressure in the ablated tissue and cause scattering of tumour cells throughout the portal system [6, 7].

Unlike RF ablation using a thermal energy source, cryoablation destroys tumour cells by the application of alternating freezing and thawing. Using ice-ball formation, the technique has several advantages such as more clearly distinguishable ablative margins, decreased pain and absence of gas bubble formation resulting in increased intratumoral pressure during treatment, compared with RF ablation [8]. Thus, we hypothesise that cryoablation could be a useful alternative treatment for perivascular tumours that avoids peritumoral vessel injury or aggressive intrasegmental recurrence [9] through the possibility of transportal tumour spread. Although several long-term studies for cryoablation of HCC have been reported [10, 11], limited data are available on the use of cryoablation for HCC with a new generation of cryoablation devices [12]. In addition, outcomes of cryoablation for perivascular HCC have not yet been assessed.

Thus, the aim of our study was to evaluate the therapeutic outcomes of and vascular complications associated with percutaneous cryoablation using a state-of-the art system in patients with perivascular HCC.

Materials and methods

Patients

This retrospective study was conducted at a single tertiary academic centre. The study was approved by the institutional review board, and the requirements for informed consent were waived (SMC 2017-07-042). The decision to carry out cryoablation was determined by consensus during our weekly multidisciplinary tumour board meeting for HCC that consisted of hepatologists, surgeons, oncologists, interventional radiologists and radiation oncologists. Since 1999, RF ablation has been the first-line ablative technique for percutaneous treatment of perivascular HCC at our institution. Due to the known risks of aggressive intrasegemental recurrence after RF ablation for periportal HCCs based on a previous study [9], we switched from RF ablation alone to cryoablation or combined treatment of transarterial chemoembolisation (TACE) and RF ablation [13] for treating perivascular HCC. The inclusion criteria were as follows: (1) a small solitary perivascular HCC (≤ 3 cm); (2) Child-Pugh class A or B cirrhosis; (3) absence of macrovascular invasion and extrahepatic metastasis during pre-treatment imaging evaluation; (4) a normal prothrombin time and platelet count ≥ 50,000 cells/ml^3.

Between August 2015 and September 2017, 78 consecutive patients with 86 HCCs were treated with cryoablation at the Samsung Medical Center, Sungkyunkwan University, Seoul, Korea. Of these, 16 patients (20.5%) with non-perivascular HCCs were excluded. A further four patients (2.2%) with multiple HCCs were sequentially excluded to avoid intra-cluster correlation for therapeutic outcome analysis [14]. Finally, 58 patients (48 men, 10 women; mean age, 62.4 years; age range, 44–84 years) with a single perivascular HCC (mean size, 1.3 cm; size range, 0.6–2.0 cm; Barcelona clinic liver cancer-stage [BCLC] 0 or A) were included. The diagnostic criteria for HCC were based on the current clinical guidelines [15]. The patient selection workflow is shown in Fig. 1.

Definition of perivascular HCC

Before cryoablation for HCC, all tumours were classified as perivascular or non-perivascular based on computed tomography (CT) or magnetic resonance imaging (MRI) examination. Axial and coronal reformat images were evaluated using a picture archiving and communication system (Centricity 3.0, GE Healthcare). Based on previous studies [2–4], perivascular HCC was defined as a tumour directly abutting the first- or second-degree branches of a portal or hepatic vein that was 3 mm or greater in axial diameter [11–13]. If the index tumour was in contact with more than two vessels, the largest vessel was selected as the reference vessel.

Cryoablation procedure

All cryoablation procedures were performed by one of five experienced interventional radiologists (K.D.S., T.W.K., M.W.L., H.R. and H.K.L) with more than 3 years of experience in loco-regional treatments for hepatic tumours. The planning US was performed at an outpatient clinic to assess the feasibility of percutaneous cryoablation [16].

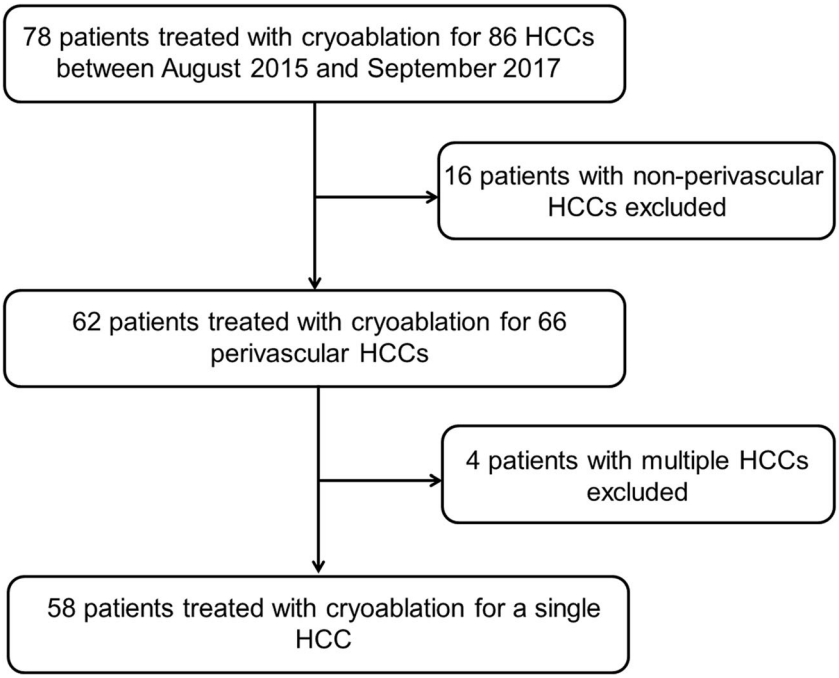

Fig. 1 Flow diagram of patient selection for the study. *HCC* hepatocellular carcinoma

Treatments were performed with the patient under local anaesthesia plus conscious sedation or monitored anaesthesia care on an inpatient basis. We used a commercially available cryoablation system (Visual-ICE® system; Galil Medical). Seventeen-gauge 15-cm cryoprobes (IceSphere 1.5® needle, straight type; Galil Medical) were inserted percutaneously under ultrasound (US) guidance (LOGIQ E9; GE Healthcare or RS80A; Samsung Medison; n = 56) or under dual guidance with US and CT (GE LightSpeed VCT 64; n = 2). For targeting and monitoring the index tumour, the fusion imaging technique (Volume Navigation, GE Healthcare or S-fusion, Samsung Medison) was used when tumours had poor conspicuity on B-mode US. In addition, if the index tumour was not clearly visible even with fusion images, contrast material-enhanced US (Sonazoid®; GE Healthcare) was performed to enhance the lesion conspicuity [17]. When the risk of collateral damage of an adjacent structure was expected during cryoablation or enhancement of the sonic window for a better cryoprobe path was needed, artificial ascites was used [18]. Based on the tumour size and geometry, we used a multiple overlapping ablation technique or multiple cryoprobes. According to the manufacturer's recommended protocol for the device, two cycles including freezing (10 min), thawing (7 min), refreezing (10 min) and rethawing (3 min) were routinely used. Ablative margins of at least 0.5 cm beyond the most outer boundary of the tumour were planned for all lesions, with the exception of perivascular portions. Procedures were finished when the ice-ball induced by cryoablation at US or CT was large enough to cover the entire tumour and surrounding liver. A warm saline-soaked gauze pad was applied for overlying skin protection. In cases where a residual unablated tumour was detected on contrast material-enhanced CT examination immediately after cryoablation, an additional treatment session was attempted on the same day if possible.

Follow-up

The follow-up program consisted of multiphase CT, chest radiography and laboratory tests, including serum α-fetoprotein, 1 month after the procedure and every 3 months thereafter [19]. In cases where a recurrent tumour was identified during follow-up, the optimal second-line treatment was determined by a multidisciplinary tumour board meeting, based on the characteristics of the recurrent tumour, hepatic function and general condition of the patient [20].

Outcome measurement

The primary outcomes of the study were technical success, primary technique efficacy and local tumour progression (LTP). Patients with viable enhancing tumours on contrast-enhanced CT obtained immediately after cryoablation on the day of treatment were considered a technical failure [21] and those with remaining tumour were treated further with other treatments. The primary technique efficacy rate was defined as the percentage of target tumours successfully eradicated on CT at 1 month after initial treatment. LTP was defined as the development of new tumours around the ablation zone, observed on

follow-up images. With regard to vascular complications, aggressive intrasegmental recurrence was defined as the simultaneous development of multiple nodular (at least three) or infiltrative tumour recurrence in the treated segment of the liver during follow-up; this definition was identical to that in a previous study [9]. Peritumoral vessel thrombus and infarction were reviewed by CT. If a thrombus was identified on immediate follow-up CT images, the resolution of the thrombus was evaluated by a further CT scan. Other major complications were defined as events requiring additional treatment or hospitalisation and/or resulting in permanent adverse sequelae or death as a result of procedure-related complications [22].

Table 1 Demographic and clinical characteristics of study patients

Variable	Study patients (n = 58)
Age at enrollment (years)	62.4 ± 8.5 (44–84)*
Male patients	48 (82.8)
Underlying chronic liver disease	
Hepatitis B virus	42 (72.4)
Hepatitis C virus	9 (15.5)
Other	7 (12.1)
Liver cirrhosis	53 (91.4)
Child-Pugh Class	
A	51 (87.9)
B	7 (12.1)
α-fetoprotein (ng/ml)	135.4 ± 820.1* (1.3–6301.9)
Platelet count (× 10^9/L)	130 ± 36.6 (55–237)*
Total bilirubin (mg/dl)	0.6 ± 0.3 (0.2–1.9)*
Albumin (g/dl)	4.1 ± 0.4 (2.7–4.7)*
Prothrombin time (INR)	1.1 ± 0.1 (0.9–1.3)*
Tumour size (cm)	1.3 ± 0.4 (0.6–2.0)*
Tumour location (Couinaud segment)	
I	1 (1.7)
II	3 (5.2)
III	5 (8.6)
IV	6 (10.3)
V	16 (27.7)
VI	13 (22.4)
VII	2 (3.4)
VIII	12 (20.7)
Type of peritumoral vessel	
Portal vein	51 (87.9)
Hepatic vein	7 (12.1)
Diameter of peritumoral vessel (cm)	0.5 ± 0.2 (0.3–1.1)*

Note. Unless indicated otherwise, data are the number of patients, with percentages in parentheses

INR international normalised ratio

*Means ± standard deviations with ranges in parentheses

Statistical analysis

Means, standards deviations, ranges, and frequencies were used as descriptive statistics for evaluating the baseline characteristics of the study population. The cumulative LTP rate was estimated by the Kaplan-Meier method. The observational period for recurrence analysis was defined as the interval between initial treatment and death or the date of the last follow-up visit before 20 April 2018. Liver transplantation was considered as censored at the date of transplantation. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

Baseline characteristics

The baseline characteristics of all patients (n = 58) are presented in Table 1. Twenty-four patients (41.3%) underwent cryoablation as first-line treatment, and 34 patients (58.7%) were treated with cryoablation for recurrent HCCs. Most patients had liver cirrhosis (91.4%, 53/58) and the majority of patients had Child-Pugh A status (87.9%, 51/58). The mean size of the index tumour was 1.3 cm (range 0.6–2.0 cm) and most tumours (87.9%, 51/58) were located in the periportal area. Regarding technical profiles for cryoablation, an average of 1.7 cryoprobes (range, 1–3) were used per patient and the mean number of overlapping ablations was 0.7 (range, 0–3). Contrast-enhanced US was performed in six of 58 patients (10.3%) due to poor lesion conspicuity. Artificial ascites was infused in one patient to enhance the sonic window for a better cryoprobe path.

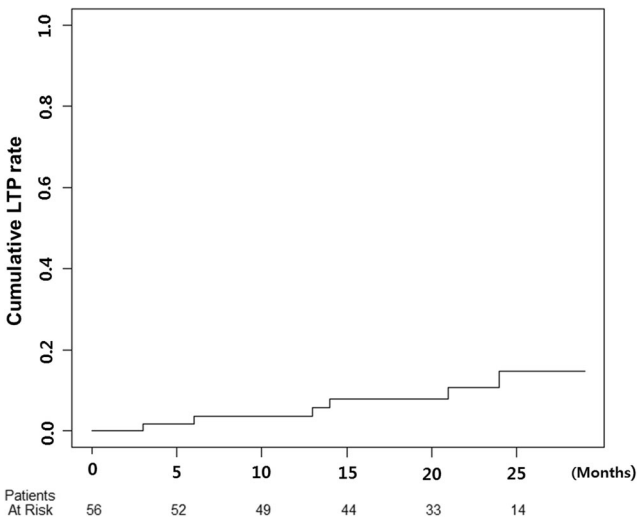

Fig. 2 Cumulative local tumour progression rate in study patients. *LTP* local tumour progression

Therapeutic outcomes

Technical success

Technical success was achieved in 56/58 patients (96.6%). The reasons for technical failure were difficulty placing the cryoprobe due to surrounding vascular structures (n = 1), and mistargeting of the index tumour (n = 1). These patients were treated with TACE or TACE plus RF ablation for the residual unablated HCC due to technical difficulty of the repeated cryoablation and were excluded from the following LTP analysis.

Primary technique efficacy rate and local tumour progression

All patients underwent at least one follow-up CT examination. The median follow-up period was 22 months (range, 3–29 months). Primary technique efficacy rate was 100% (56/56) at the 1-month follow-up CT examination. Two patients underwent liver transplantation during follow-up. As of

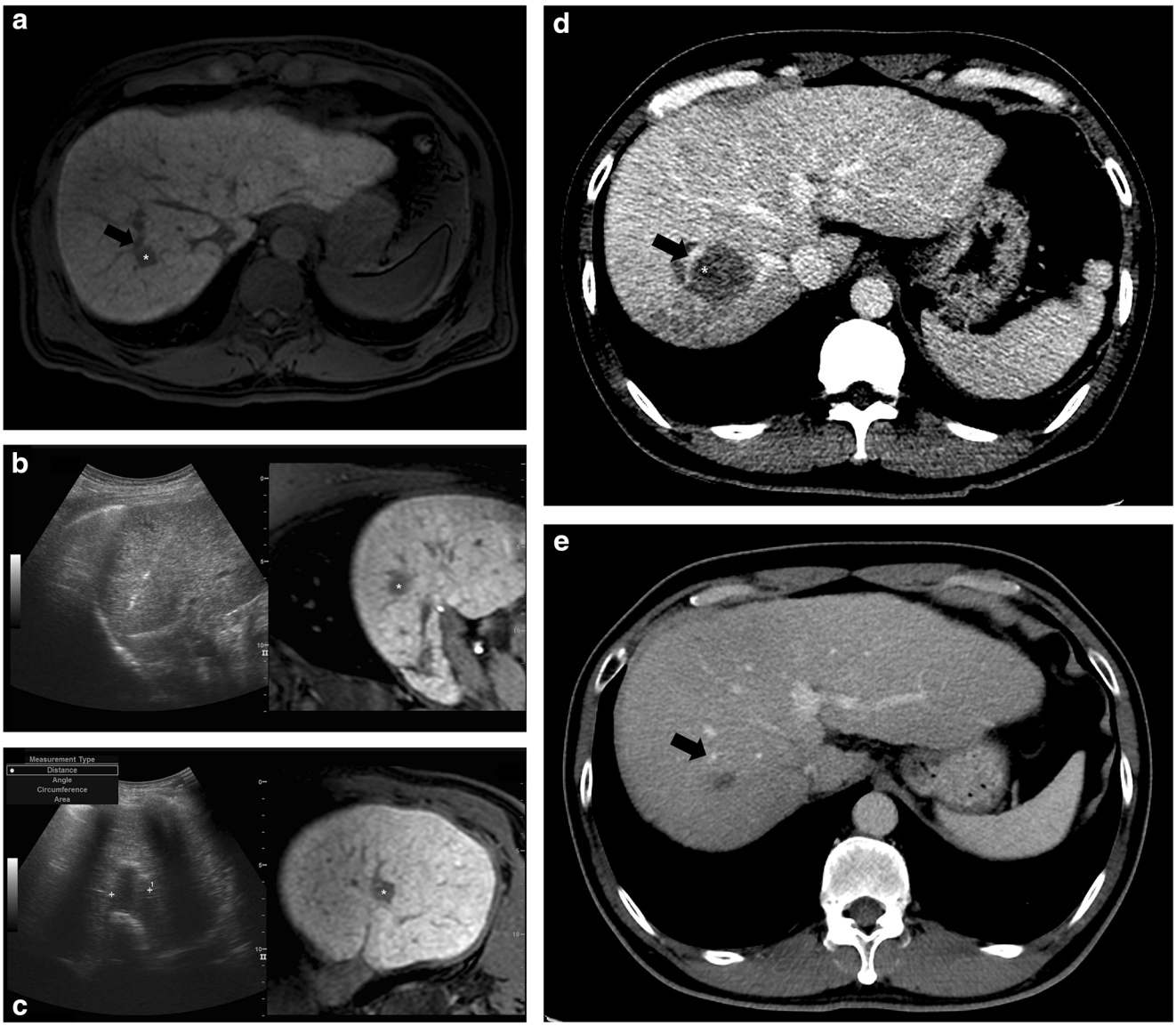

Fig. 3 Images from a 54-year-old-man who underwent cryoablation for perivascular HCC. (**a**) Axial MR image obtained during the hepatobiliary phase shows a 1.1-cm HCC (asterisk) in segment VII before cryoablation. The index tumour was adjacent to the portal vein (black arrow). (**b**) US imaging shows that the echogenic cryoprobe is located in the centre of the index tumour (asterisk). Two cryoprobes were inserted in parallel to evade the adjacent portal vein. (**c**) The anechoic area indicates the ice ball according to the freezing of the two cryoprobes. (**d**) Axial CT image obtained during the portal phase immediately after cryoablation shows an ablation zone over the index tumour (asterisk) with an intact peritumoral portal vein (black arrow). (**e**) Follow-up axial CT image shows the intact peritumoral portal vein (black arrow) adjacent to the previous ablation zone 2 years after cryoablation without evidence of local recurrence

April 2018, LTP occurred in 6/56 patients (10.7%). Five of these patients with LTP (83.3%) had a recurrent tumour along the peritumoral vessel. Among them, three patients underwent TACE for tumour control; among the remaining three patients, one each underwent TACE with radiation therapy, surgical resection and RF ablation. The cumulative LTP rates at 1 and 2 years were 3.6% (95% confidence interval [CI]: 1.1–11.8) and 14.6% (95% CI: 6.7–32.7), respectively (Fig. 2).

Complications

There were no treatment-related or in-hospital deaths. Although thrombus developed in the peritumoral vessels immediately after cryoablation in four patients (6.9%), half of them disappeared and recanalisation of peritumoral vessels was observed on follow-up CT images without anticoagulation treatment. Cryoshock or bleeding requiring transfusion or embolisation did not occur as early major complications. Regarding late major complications, abscess, biloma, infarction, tumour seeding and aggressive intrasegmental recurrence were not observed during follow-up (Figs. 3 and 4).

Discussion

Our results showed that cryoablation was effective and safe in patients with small perivascular HCCs. In particular, persistent thrombotic occlusion of peritumoral vessels was less than 5% and major complications related to the procedure did not occur.

When perivascular tumours are treated with RF ablation, the blood flow drags thermal energy away from the targeted

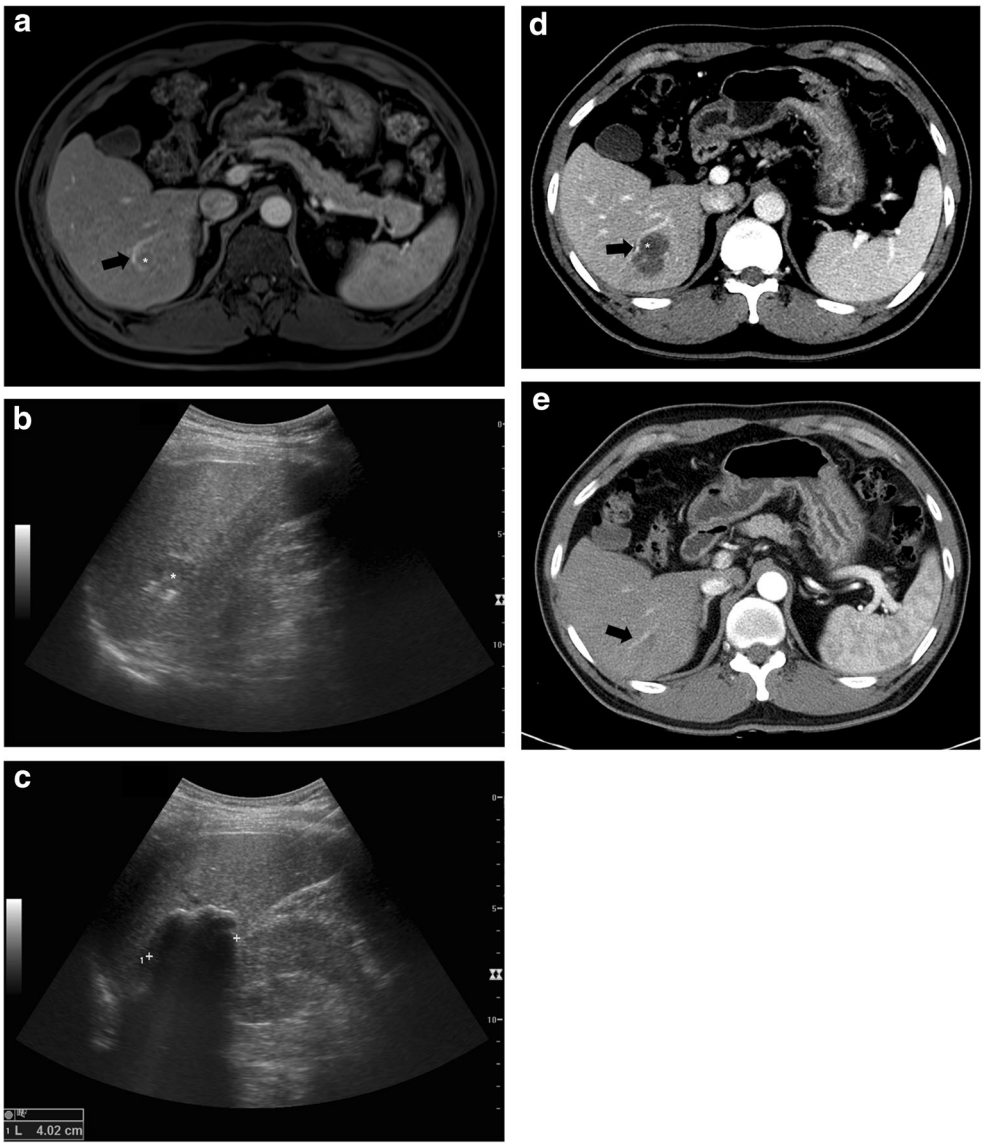

Fig. 4 Images from a 56-year-old-man who underwent cryoablation for perivascular HCC. (**a**) Axial MR image obtained during the portal phase shows a 1.3-cm HCC (asterisk) in segment VI before cryoablation. The index tumour with an enhancing capsule is in contact with the portal vein (black arrow). (**b**) US imaging shows that two echogenic cryoprobes are inserted into the index tumour (asterisk). (**c**) The anechoic ice ball adequately covers the index tumour following completion of cryoablation. (**d**) Axial CT image obtained during the portal phase immediately after cryoablation shows an ablation zone over the index tumour (asterisk) with the intact peritumoral portal vein (black arrow). (**e**) Three months after cryoablation, axial CT imaging shows the intact peritumoral portal vein (black arrow) around the previous involuted ablation zone. There was no LTP on follow-up CT 23 months after the initial cryoablation

tissue, resulting in reduced coagulation volume, the so-called 'heat-sink effect' [4]. Similarly, the same phenomenon may also occur during cryoablation. The convective influx of circulating warm blood into tumour with an ice-ball would theoretically make the ablation of perivascular tumour tissue insufficient. As there is a lack of direct comparisons between RF ablation and cryoablation for perivascular HCC, we compared our results to those from our previous study [3] in which 241 patients underwent RF ablation for perivascular HCC with long-term follow-up. Their cumulative LTP rates were similar to ours (17% at 2 years vs. 14.6% at 2 years). However, there may be different clinical and tumour characteristics between the studies. Recently, there has been increasing interest in microwave ablation over RF ablation due to potential physical advantages such as higher intratumoral temperatures and less dependence on the electrical conductivities of tissue. These unique characteristics of microwave ablation may render it less affected by the 'heat-sink effect' [23]. Huang et al reported that the long-term local tumour control of microwave ablation for perivascular HCC was similar to that for non-perivascular HCC [24]. However, more prospective comparative studies are needed to assess whether the physical differences between RF ablation, cryoablation and microwave ablation translate into better clinical outcomes in patients with perivascular HCC.

A previous study investigating hepatic infarction after RF ablation reported a low incidence of 1.8% [25]. However, this can be increased in patients with perivascular HCC by up to 5% due to the frequent development of thrombosis in peritumoral vessels by thermal injury [3]. In clinical practice, loco-regional treatment is preferred when the patient has recurrent tumours after curative surgical resection because more limited hepatic function reserve is expected [26]. In these patients in particular, hepatic infarction by RF ablation may cause acute hepatic failure and subsequent mortality. A recent study showed that thermal injury-induced hepatic parenchymal hypoperfusion during RF ablation for HCC can also aggravate intrahepatic tumour recurrence by promoting hepatic proliferation as well as tumour cell growth [27]. In our study, persistent thrombosis of peritumoral vessels was 3.4% (2/58) and no case of hepatic infarction was observed during immediate or follow-up CT examinations.

Although the exact mechanism of aggressive tumour recurrence after RF ablation remains unclear [28], one possible hypothesis is that rapid heating of a HCC may lead to a sudden increase in internal pressure and cause tumour spread through the portal system. In line with this assumption, a recent study showed that periportal location of HCC was a significant factor for this type of tumour recurrence [9]. To prevent this serious complication, longer ablation times at lower power [29] and combined RF ablation treatments with TACE [13] have been used. However, RF ablation is inherently associated with tissue boiling during heat conduction and combined ablation with TACE can theoretically increase the occurrence of hepatic infarction [30]. Based on the absence of aggressive intrasegmental recurrence in our cohort, which mainly consisted of periportal tumours, the use of cryoablation may prevent transportal tumour spread by not employing tissue boiling.

Our study has several limitations. Firstly, we used a retrospective approach. Therefore, inherent selection bias was unavoidable. Secondly, our study patients did not undergo long-term follow-up for evaluation of late major complications including tumour seeding. However, judging by the known early peak of LTP in patients treated with RF ablation for HCC [31, 32], there would not be significant differences in LTP and early major complications if a longer follow-up period was included. Thirdly, the mean tumour size in our cohort was relatively small. This is because most HCCs were detected early due to periodic surveillance after initial treatment for HCC. Thus, our results might not be consistently reproducible in other settings with larger tumours (> 2 cm). Despite these limitations, our results indicate that residual liver function and tumour location need to be considered in the selection of RF ablation or cryoablation for HCC. Although cryoablation has not been included as a standard of care for HCC according to the recent BCLC guidelines [1], cryoablation may be a reasonable alternative for patients with limited liver function to avoid vascular complications. Regarding technical advances in cryoablation, a new generation of cryoablation systems with thin cryoprobes that use argon-helium has been introduced, which may lead to a low risk of bleeding and cryoshock related to the procedure [12]. In addition, recent randomised controlled trial showed that cryoablation was equally safe and effective compared with RF ablation for HCC treatment [33]. However, more comparative studies are needed to validate the effectiveness of cryoablation.

In conclusion, cryoablation could provide acceptable local tumour control without vascular complications for patients with perivascular HCC. In particular, it may become the effective local ablation modality in patients with limited hepatic reserve due to the very low risk of procedure-related vascular complications including hepatic infarction.

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Compliance with ethical standards

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Conflict of interest The authors of this paper declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Observational
- Performed at one institution

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