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Original Article

Effect of hepatocellular carcinoma conspicuity on ultrasound on the treatment outcome of percutaneous tumor ablation

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Abstract

Background: Percutaneous tumor ablation is a minimally invasive treatment for early-stage hepatocellular carcinoma (HCC) and relies on real-time ultrasonographic guidance. However, it might not be feasible in some patients due to limitations of grey-scale ultrasound findings.

Objective: To evaluate the effect of ultrasound conspicuity of HCC nodules on the success rate of percutaneous image-guided ablation.

Materials and methods: A single-center retrospective review of patients undergoing percutaneous tumor ablation of treatment-naïve HCC from January 2017 to December 2022 was performed. Three groups of tumors were classified based on the level of ultrasound visualization as complete visibility (399 lesions), partial visibility (219 lesions) and invisibility (88 lesions). Ablation procedure was performed under ultrasound guidance, supplemented with other modalities such as non-contrast CT and fusion ultrasound. Follow-up assessments were conducted at 1, 3, and 24 months post-ablation to compare the technical success rates. Other outcomes including survival analysis and complications were also investigated.

Results: A total of 447 patients with 706 lesions were included. The mean size of lesions in the three groups were 1.84, 1.59, and 1.11 cm, respectively, with statistically significant difference between the groups ($p<0.001$). There was no statistically significant difference in technical success rates at 1 month or primary efficacy at 3 months among the three groups. The technical success rate between the complete visibility, partial visibility, and invisible groups were 95.7%, 95.0%, and 97.7% ($p=0.862$), respectively and primary efficacy rates were 95.2%, 95.0%, 84.1% ($p=0.172$), respectively. The cumulative local tumor progression-free survival at 6, 12, 24 months were 98.0%, 96.9%, and 90.5% for the complete visibility group, 98.9%, 97.9%, and 87.8% for the partial visibility group, and 96.2%, 94.5%, and 87.3% for the invisible group, respectively, with no statistically significant differences ($p = 0.539$). Only one patient experienced a complication that required further treatment.

Conclusion: The usage of other imaging modalities such as non-contrast CT and fusion ultrasound for poorly conspicuous HCC lesions can improve the success rates to levels comparable with those of the conspicuous nodules, while also maintaining similar local tumor control outcomes and avoiding major adverse events.

Keywords: Fusion ultrasound, Hepatocellular carcinoma, Microwave ablation, Radiofrequency ablation, Tumor ablation.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers worldwide and is also one of the leading causes of cancer-related deaths in Thailand [1]. Early detection of HCC is aided by the implementation of screening abdominal ultrasound protocols. A definitive diagnosis of HCC can then be confirmed with cross-sectional imaging such as contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) with hepatocyte-specific contrast agents. A widely adopted staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system, which details optimal treatment strategies for each stage of hepatocellular carcinoma [2]. According to the latest iteration of the BCLC staging, patients in very early to early stage HCC may be treated with surgery or image-guided percutaneous tumor ablation [2].

Image-guided percutaneous tumor ablation is a well-established treatment for very early to early stage HCC where an ablation needle is percutaneously punctured into the liver and directed toward to the target lesion under the guidance of various imaging modalities. The lesion is then destroyed either chemically, via extreme temperatures, or irreversible electroporation. The vast majority of percutaneous tumor ablation procedures are performed under ultrasonographic guidance, which allows real-time visualization of the ablation probe in relation to the target lesion as well as surrounding critical structures in order to achieve technical success and avoid complications.

However, the inherent limitations of ultrasonography also have an effect on the ablation procedure. For one, visualization of hepatic dome lesions is limited on ultrasound due to obscuration by the air artifact from the lung. The patients with cirrhotic livers show heterogeneous liver parenchyma echogenicity on ultrasound which may obscure the conspicuity of some lesions [3]. All of these effects may lead to mistargeting of the tumor nodule on ultrasound, resulting in insufficient coverage of the ablation zone margins or treatment failure altogether [4-6]. Many techniques have been devised to overcome the limitations of using ultrasound-only guidance in percutaneous ablation. Such techniques include

the use of non-contrast-enhanced CT scans to confirm the ablation probe tip in relation to surrounding anatomical landmarks, employing ultrasonography with the aid of fusion software techniques using pre-operative cross sectional imaging (either CT or MRI) [7, 8], or the use of contrast-enhanced ultrasound in which a contrast agent (eg. sulphur hexaflouride microbubbles or perfluorobutane-based US contrast agent), is injected intravenously to allow distinction between hepatic parenchyma and the target lesion [9].

Thus, this study aims to investigate the effect of sonographic conspicuity of HCC lesions on the success rate of image-guided percutaneous tumor ablation, as well as evaluate the short-term recurrent rate and the safety profile.

Materials and methods

Study Population

This study is a single-center retrospective cohort study, with data obtained via retrospective review of electronic medical records of patients who underwent percutaneous tumor ablation from January 2017 to December 2022, referred to the Siriraj Center of Interventional Radiology (SiCIR) by gastroenterologists or hepatobiliary surgeons in accordance with BCLC guidelines. Patients included in this study were (1) at least 18 years of age (2) diagnosed with primary hepatocellular carcinoma either by tissue pathology or from imaging specifically contrast-enhanced CT scan or MRI with hepatocyte-specific contrast agent, classified as either LI-RADS 4 or 5 according to LI-RADS version 2018 [10] (3) underwent either percutaneous radiofrequency ablation (RFA) or microwave ablation (MWA) (4) had preoperative CT or MRI within 60 days prior to ablation (5) and had follow-up CT or MRI scans within 6 weeks following the ablation session and at least 6 months thereafter. Patients were excluded from the study if they (1) were diagnosed with other hepatic lesions such as liver metastases or (2) had insufficient follow-up imaging. Lesions were excluded from the study if it had undergone prior treatment, such as transarterial chemoembolization (TACE) or represented residual tumor following

prior ablation sessions; only treatment-naïve nodules were included for analysis. Institutional ethics review board approval (No. Si 019/2024) was obtained prior to data collection. Other information such as the patient's gender, age at time of treatment, liver disease etiology, Child Pugh score, prior history of treatment for HCC, modality of diagnosis, lesion size, location, and proximity to liver capsule or other critical structures, was also recorded.

Percutaneous Tumor Ablation

All cases of image-guided tumor ablation were performed under ultrasound guidance by 7 board-certified interventional radiologists. The choice of ablation system was made at the operator's discretion; general rule of thumb at the institution is a predilection towards RFA due to the expandable tines allowing secure placement of the needle while stepping out during each CT scan, but microwave ablation systems would be preferred in cases where the target lesions are in close proximity to vessels and thus prone to the heatsink effect. However, lesion conspicuity or performing intraprocedural NCCT did not necessarily preclude the usage of MWA systems. Patients underwent either sedation or general anesthesia administered by the anesthesiologist. Ablation systems used in this study included RF3000 RFA generator with LeVeen expandable RFA electrodes (Boston Scientific, Massachusetts, USA), Emprint Microwave Ablation System (Medtronic, Minnesota, USA), Saberwave ECO microwave ablation system (ECO Medical Technology, Nanjing, PRC), and MaxBlate microwave ablation generator (Canyon Medical, Nanjing, PRC). The aim of the ablation procedure was to achieve at least a 0.5 cm margin surrounding the target lesion in every case.

Retrospective review of images in the hospital's Picture Archiving and Communication System (PACS) was done to determine the conspicuity of the target lesion and categorized as completely visible, partially visible, or invisible on ultrasound. Lesions were deemed completely visible if all margins of the lesion could be clearly visualized on ultrasound (Figure 1); if any margin was not clearly distinguishable, the lesion would be classified as partially visible (Figure 2). Lesions that were not at all visible on ultrasound were deemed

invisible (Figure 3). Echogenicity of the lesion was also recorded as hypoechoic, hyperechoic, or isoechoic relative to liver parenchyma. If a lesion demonstrated mixed echogenicity, it was recorded as heterogeneous echogenicity. Lesion size was recorded based on the ultrasound image obtained on the day of the ablation procedure if the lesion was visible, otherwise the size was recorded according to the most recent CT or MRI findings prior to ablation. For each ablation procedure, the use of other modalities in conjunction with ultrasonography such as non-contrast CT or fusion ultrasonography was collected. Non-contrast CT was performed to compare the relative position of the ablation needle tip with surrounding anatomical landmarks and correlated with preprocedural cross-sectional imaging (Figure 2F). Fusion ultrasound was performed using Logiq E9 and Logiq E10 ultrasound machines (GE HealthCare Technologies, Illinois, USA) ulitizing volume navigation (V-nav) software with the most recent preprocedural CT or MRI scan was used for fusion (Figure 3D-E). Immediate post-procedural complications were also recorded in accordance with the Society of Interventional Radiology Adverse Events Classification System.

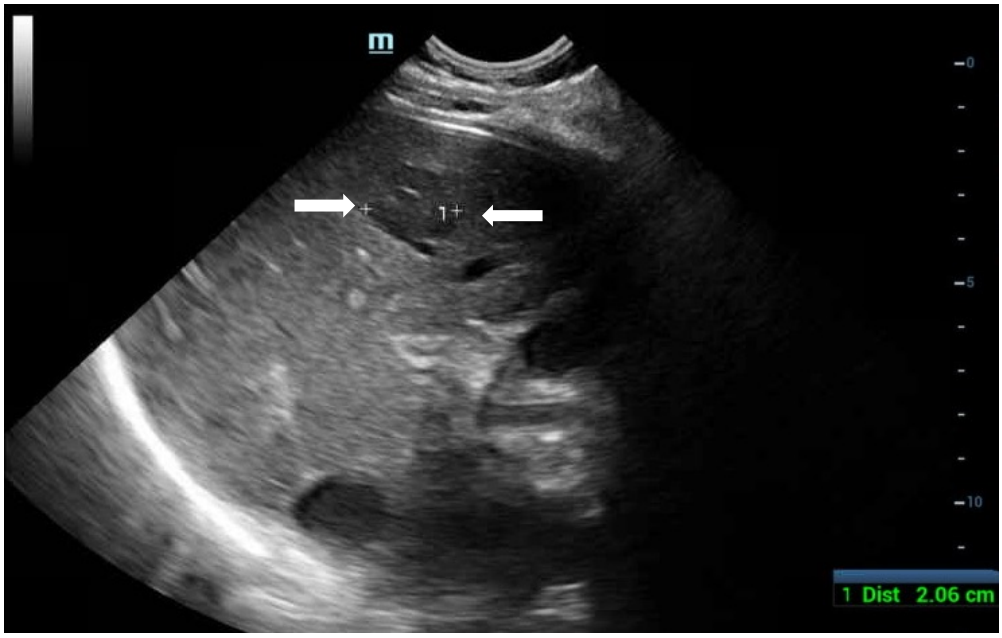

Figure 1. Completely visible nodule on ultrasound
A 67-year-old male with HBV cirrhosis; the lesion appears as a well-defined hypoechoic nodule with all tumor margins clearly visualized (arrows).

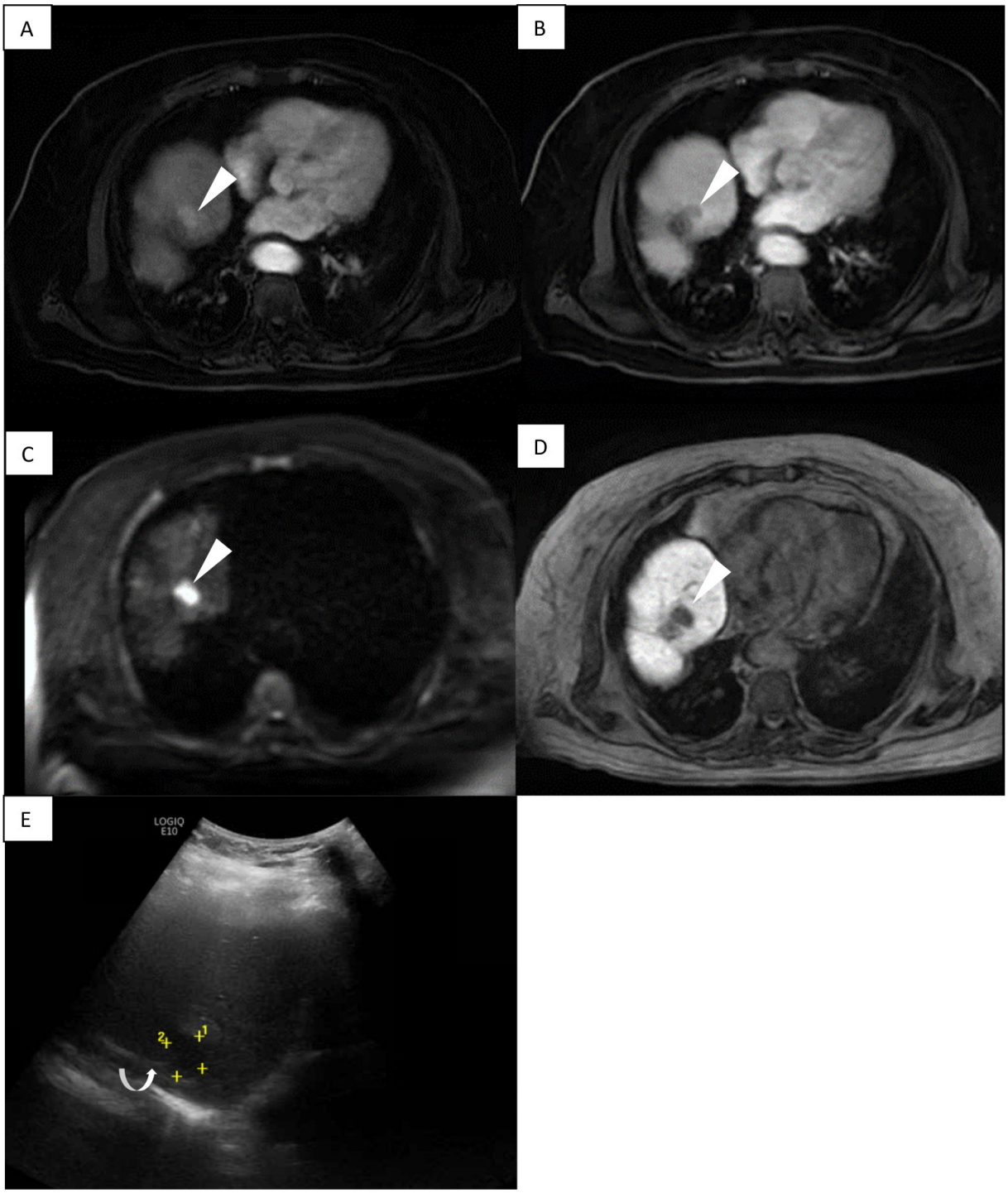
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Figure 2. Partially visible nodule on ultrasound

A 70-year-old male with NASH cirrhosis post-RFA since 2019; Routine follow-up MRI in 2022 showed a new HCC nodule at segment VIII (arrowhead) demonstrating arterial enhancement (A) with portovenous washout (B), restricted diffusion (C), and hepatobiliary defect (D). Ultrasound visualization of the entire lesion due to the high location (E), and parts of the supero-posterior border are partially obscured by air artifact from the lungs (curve arrow).

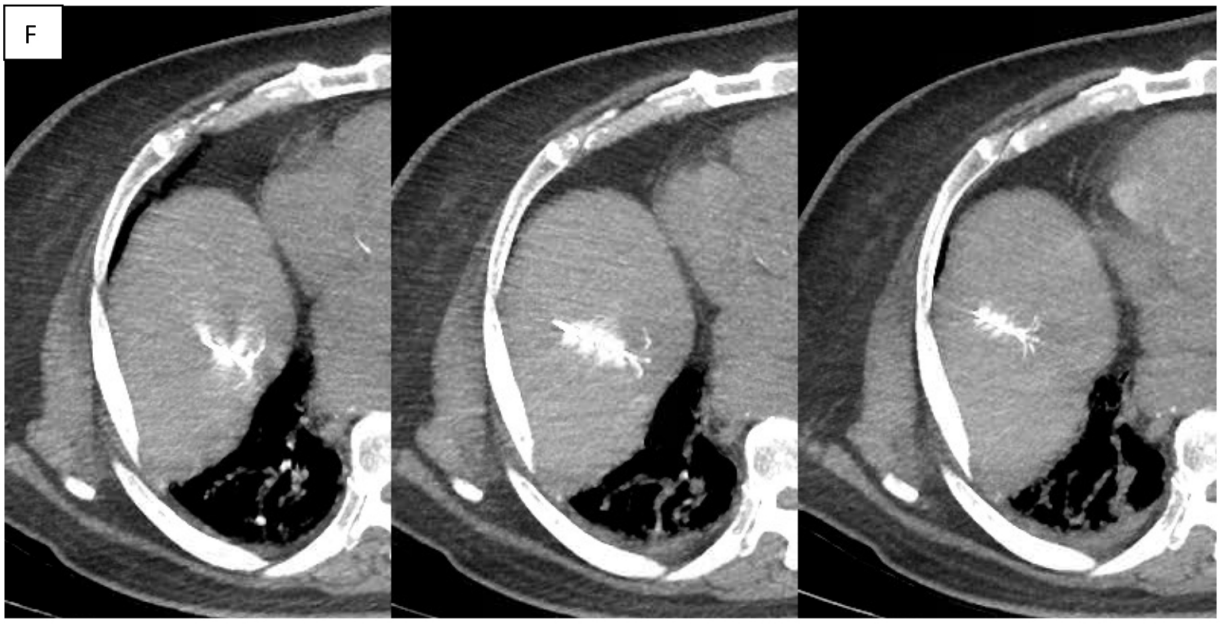

Figure 2. (cont.)

Usage of non-contrast CT in conjunction with greyscale ultrasound to confirm the tip of the ablation needle covers the target lesion and intended margins (F). The location of the needle tip is compared to the surrounding structures such as contours of the liver capsule, which is then correlated with preoperative cross-sectional imaging to improve precision and accuracy.

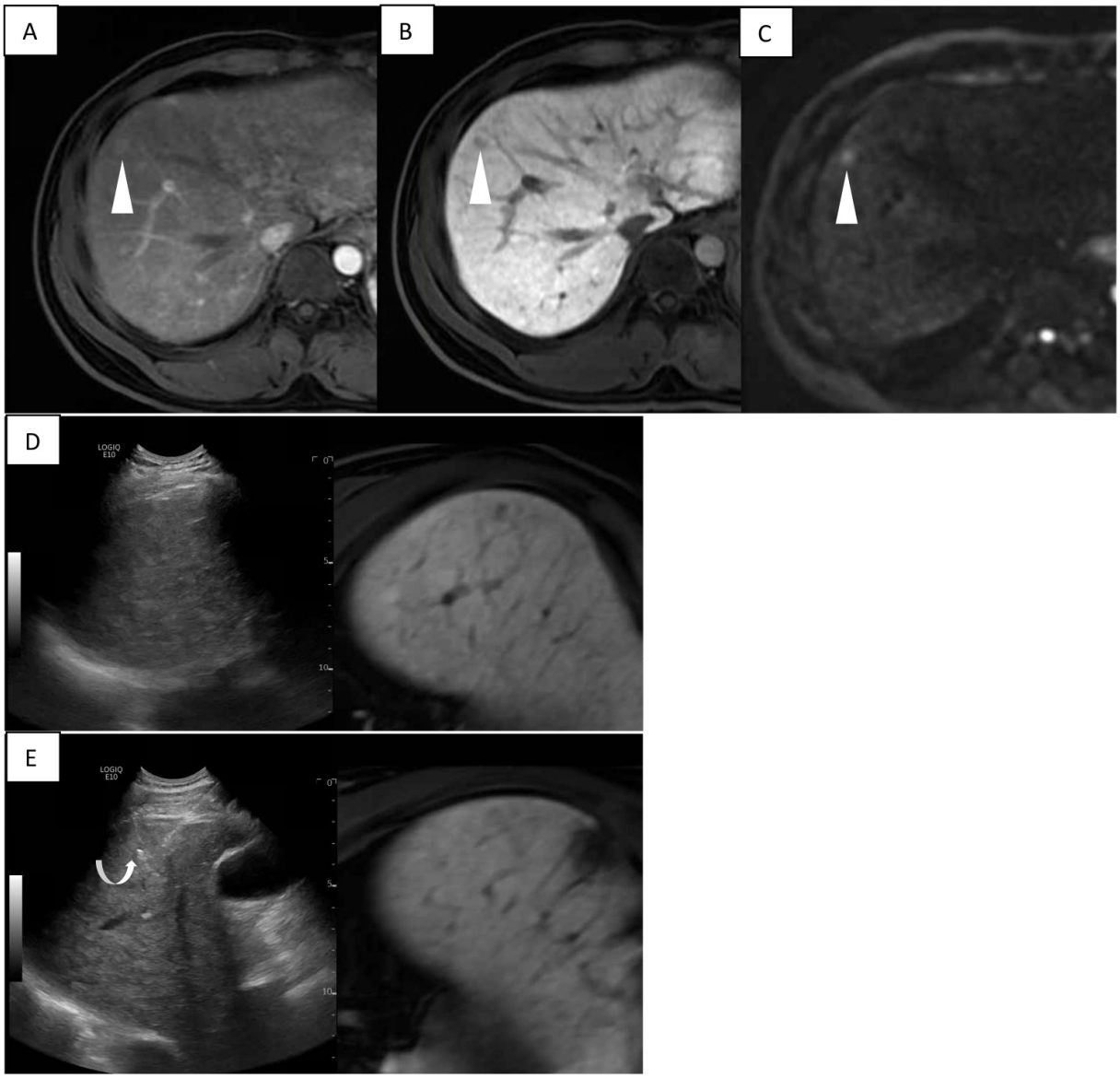

Figure 3. Nodule invisible on ultrasound

A 39-year-old male with HBV cirrhosis; MRI showed a tiny faint arterial enhancing lesion (A) at segment IV/VIII (arrowhead) with hepatobiliary defect (B), and restricted diffusion (C), likely HCC. Greyscale ultrasound was unable to discern the lesion due to heterogeneous background liver parenchyma (D). Fusion US was used to assist ablation in this case (E) (Curve arrow point to the needle tip).

Follow Up

Technical success was defined as complete coverage of the target lesion by the ablation zone on cross-sectional imaging performed within 4 to 6 weeks after ablation. The standard follow-up protocol of HCC patients at our institution is typically four weeks or 30 days post ablation. However, due to the high patient volume across all departments, the center services often could not feasibly schedule for the follow-up imaging within the desired 30 days. Thus, the follow-up imaging interval from the time of ablation to the initial imaging was extended to 60 days to take into an account this real-world logistical constraint in this study. All subsequent follow-up imaging was reviewed at 3 months post-ablation and at least 6 months up to 2 years post ablation to determine primary efficacy and monitor for local tumor progression at the ablation site, respectively. Primary efficacy was defined as the absence of residual viable tumor at 3-month post-ablation, and local tumor progression was defined as evidence of viable tumor despite achieving primary efficacy. The date at which local tumor progression was detected and time interval in days from the ablation procedure to date of local progression were also recorded.

Statistical Analysis

Descriptive variables such as age and tumor size were expressed as means with standard deviations, and categorical variables as percentages. Comparisons of characteristics between study groups were performed using the Chi-square test or Kruskal-Wallis test. Kaplan-Meier survival analysis was performed for each of the three study groups, and the log-rank test was used to compare survival outcomes between groups. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 13.1 (StataCorp LLC).

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Results

The study population included a total of 447 unique patients and 706 lesions. Patient demographic data are depicted in Table 1. The average age of patients undergoing percutaneous tumor ablation was 66.3 years with the majority (65.9%) being males, and the most common etiology of liver disease was hepatitis B. Most of the patients were also classified as Child Pugh score A during the time of treatment.

Table 1. *Baseline characteristics of study population.*

Patient Demographics	
Total n = 447	
Age at treatment (years) mean (±SD)	66.3 (11.3)
Sex n (%)	
Male	295 (65.9%)
Female	152 (33.1%)
Viral Hepatitis n (%)	
None	123 (27.5%)
Hepatitis B	207 (46.3%)
Hepatitis C	114 (25.5%)
Both Hepatitis B and C	3 (0.7%)
Child Pugh Score n (%)	
A	402 (89.9%)
B	43 (9.7%)
C	2 (0.4%)

Of the 706 lesions, 399 were classified in the complete US visibility group, 219 in the partial visibility group, and 88 in the US-invisible group (Table 2). The mean size of lesions in the complete visibility, partial visibility, and invisible groups were 1.84, 1.59, and 1.11 cm, respectively, with a statistically significant difference between the groups ($p<0.001$). The majority of lesions in the complete visibility and partial visibility groups displayed hypoechogenicity on ultrasound (56.9% and 60.3%, respectively). Regarding the ablation procedure, the majority of all groups underwent ablation using a combination of ultrasonography and non-contrast CT, followed by ultrasonography alone, usage of US with both fusion and NCCT, and finally fusion ultrasonography only. There were no statistically significant differences in the frequency of each modality combination used in each group.

Table 2. *Characteristics of lesions.*

Age (year) (mean ± SD)				
Total n = 706				
	Complete visibility N = 399	Partially visible N = 219	US invisible N = 88	*p* value
Size (cm) mean (±SD)	1.84 (±0.83)	1.59 (±0.68)	1.11(±0.51)	<0.001
Echogenicity n (%)				
Hypoechoic	227 (56.9%)	132 (60.3%)	-	
Heterogenous	49 (12.3%)	55 (25.1%)	-	
Hyperechoic	111 (27.8%)	26 (11.9%)	-	
Isoechoic	12 (3.0%)	6 (2.7%)	-	
Guidance techniques n (%)				
US alone	156 (39.1%)	25 (11.4%)	0 (0%)	0.079
US + NCCT	184 (46.1%)	139 (63.5%)	57 (64.8%)	0.319
US + Fusion	16 (4.0%)	9 (4.1%)	0 (0%)	0.165
US + NCCT + Fusion	43 (10.8%)	46 (21.0%)	31 (35.2%)	0.132

US = Ultrasound, NCCT = Non-contrast computed tomography

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There were no statistically significant differences in technical success and primary efficacy among the three US visibility groups in this study (Table 3). All three groups demonstrated primary efficacy rates above 95% (p = 0.862), and primary efficacy evaluated at 3 months post-ablation of the US invisible group was slightly lower than the two other groups, 84.1% versus 95.2% and 95% for the complete visibility and partial visibility groups, respectively (p = 0.172). Similar complication rates were also observed across the three groups (p = 0.218) with most groups experiencing minor class B complications such as subcapsular hematoma which spontaneously resolved in all cases. One patient in the invisible group developed post-ablation liver abscess requiring percutaneous catheter drainage insertion for 22 days before resolution.

Table 3. *Ablation outcomes.*

Ablation Outcomes				
	US visible N = 399	Partially visible N = 219	US invisible N = 88	*p* value
Technical Success n (%)				
	382 (95.7%)	208 (95.0%)	86 (97.7%)	0.862
Primary Efficacy n (%)				
	380 (95.2%)	208 (95.0%)	77 (87.5%)	0.172
Complications n (%)				
	15 (3.8%)	5 (2.3%)	4 (4.5%)	0.218
Class B	15	5	3	
Class C	0	0	1	

The cumulative local tumor progression-free survival at 6, 12, 24 months were 98.0%, 96.9%, and 90.5% for the complete visibility group, 98.9%, 97.9%, and 87.8% for the partial visibility group, and 96.2%, 94.5%, and 87.3% for the invisible group, respectively. There were no statistically significant differences in the cumulative survival rates among the three groups (p = 0.539) (Figure 4).

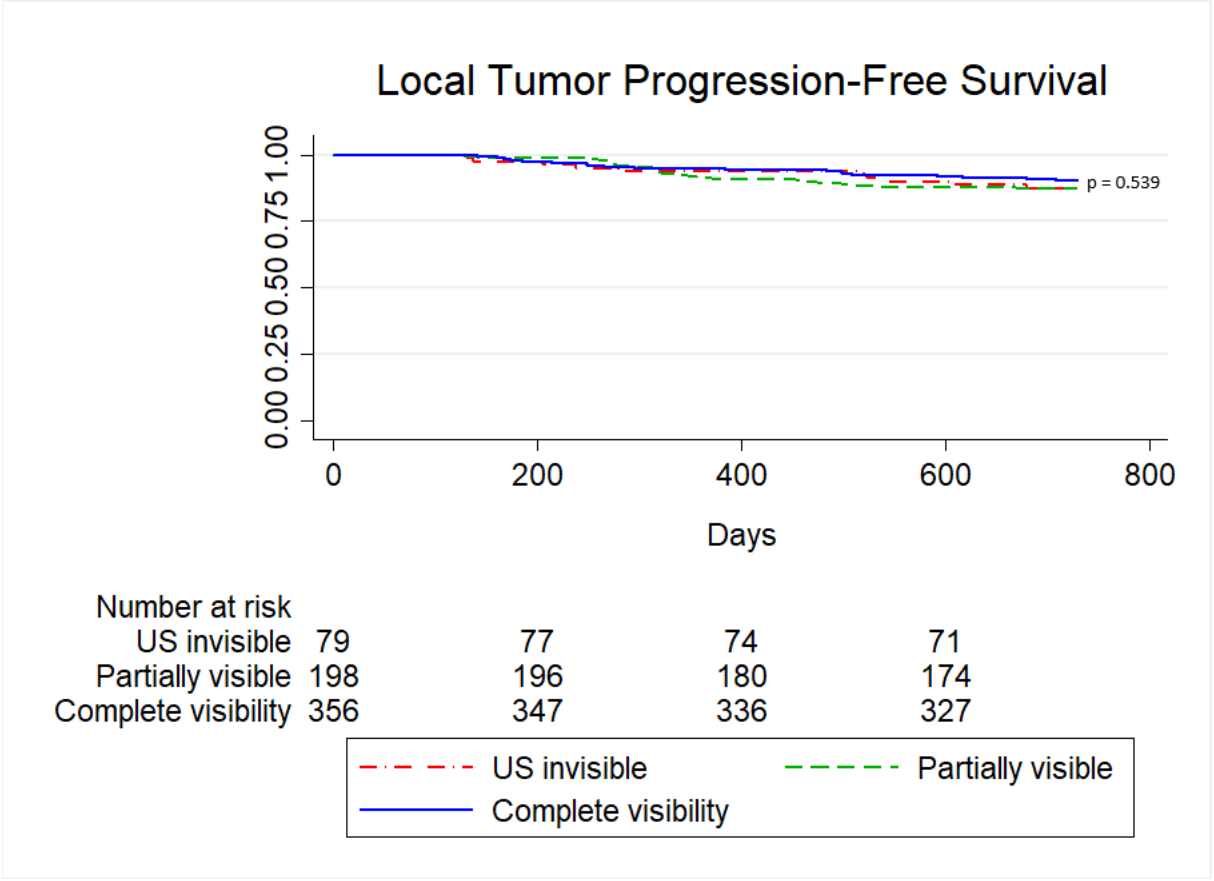

Figure 4. *Kaplan-Meier survival curve of local tumor progression-free survival.*

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Discussion

Percutaneous image-guided tumor ablation is a minimally invasive and widely accepted treatment option for early-stage hepatocellular carcinoma which relies on real-time ultrasonographic guidance to achieve adequate tumor ablation margins. However, the limitations of ultrasound and poor conspicuity of some HCC nodules may limit feasibility of ultrasound-guided interventions by up to 33% [4], and may cause treatment failure altogether due to mistargeting [5]. Therefore, visualization of the target lesion during placement of the ablation probe is key in performing successful ablation. Several methods have been developed to overcome the limitations of sole ultrasound guidance in order to improve the success rate of tumor ablation.

One reported technique in overcoming the problem of inconspicuous nodules is the utilization of contrast-enhanced ultrasound, where a contrast agent is injected intravenously to allow distinction between hepatic parenchyma and the target lesion [9]. Numerous studies on the usage of contrast-enhanced ultrasound (CEUS) in improving ablation success rates of inconspicuous HCC nodules have been reported in literature. Dohmen T, et al reported the efficacy of CEUS in RFA for HCC comparing outcomes between patients treated with and without CEUS. The group using CEUS showed significantly better radicality, and the non-local recurrence rate was significantly higher compared to the group without CEUS [11]. Rajesh S, et al [12] reviewed 14 patients using CEUS guided RFA of HCC and found that complete tumor ablation was achieved in all 19 lesions (in 14 patients) with no evidence of residual or recurrent tumor in the ablated areas after a mean follow-up of 16 months. Unfortunately, the contrast-enhanced ultrasound is not currently available for domestic use but may become accessible in the near future, leading to workarounds such as relying on non-contrast CT guidance or fusion ultrasonography. Fusion ultrasonography operates on the principle of a magnetic field to track the position of the ultrasound probe in 3D space in order to correlate spatial information with prior cross-sectional imaging. In theory, this allows synchronization between real-time ultrasound and cross-sectional imaging modalities such as contrast-enhanced CT or MRI [13]. However, fusion ultrasound

carries potential for errors due to the fusion of static cross-sectional images with real-time ultrasound where there is respiratory motion or other subtle changes in anatomy.

This study aimed to investigate the effect of visibility of HCC nodules on the success rate of percutaneous tumor ablation, as well as the effect on the local recurrence rate and the complication rate. A total of 706 lesions were classified into three groups based on the level of visibility on ultrasound, with a statistically significant difference in size among the three groups. This could be due to the fact that the size of the nodule in the invisible group was recorded based on pre-procedural CT or MRI scan, as opposed to those complete and partial visible lesions seen on ultrasound on the day of the procedure, which could have allowed the tumor to progress in size from preprocedural imaging. Another explanation could be due to poorly visible tumor margins obfuscating the actual size of the tumor, leading to inaccurate measurement of its size. On the other hand, the small size of lesions in the invisible group may explain the difficulty in detecting the lesion on ultrasound.

There was no statistically significant difference in the success rate of ablation among the complete visibility, partial visibility, and invisible groups, with all three achieving comparable technical success rates ($p = 0.862$) which could be explained by the use of aforementioned techniques including NCCT and fusion ultrasonography to assist in precise targeting of tumors irrespective of its appearance on ultrasound. The technical success rate in this study was relatively comparable to previously reported numbers. Several studies by Minami, et al utilizing fusion US assistance in RFA of inconspicuous HCC reported technical success rates of 90% to 92% [14, 15].

As for the primary efficacy at 3 months post-ablation, there was a slightly lower tendency in the ultrasound invisible group compared to the two other groups but was not sufficient to be statistically significant ($p = 0.172$). A possible explanation for this finding could be due to the target lesion having increased in size from the time of preprocedural reference imaging to the time of procedure as mentioned

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previously, leading to underestimation of the tumor size and thus ablation margins leading to ultimately a slightly lower albeit statistically insignificant primary efficacy rate. Further statistical analyses may reveal significant factors contributing to the high success rate.

The local recurrence rate of the ultrasound invisible group in this study was 12.7% which is relatively high compared to previously reported numbers by Hirooka, et al [16] and Nakai, et al [17] who reported no local recurrence, albeit with smaller study populations and shorter follow-up periods than this study. However, a study by Huang, et al [8] had reported about ablation of conspicuous and inconspicuous HCC and found that the cumulative local recurrence rate after 12 months was 10% and 13% after 24 months for conspicuous HCC and 4% equally after 12 and 24 months for inconspicuous HCC. The cumulative local recurrence at 6, 12, and 24 months of the US invisible group of our study were 5 to 12% which was slightly higher than those of the complete visible and partial visible group which might be due to the underestimation of the tumor size and the ill-defined boundary. Thus, in the very poorly conspicuous cases, both fusion US and NCCT may be helpful for the imaging guidance during the ablation procedure as well as the shorter time to follow up imaging, for example, 30 days instead of 60 days.

The complication rates were also not significant between the groups, and any complications that did occur were mostly minor self-limiting complications except for a case in the US invisible lesion that developed a liver abscess following RFA where the target lesion was at hepatic segment 2 and not well visualized on ultrasound. The patient received a percutaneous drainage catheter insertion of liver abscess which was retained for two weeks after and was able to be removed successfully. Subsequent follow-up MRI revealed no adjacent bile duct injury or injury of surrounding organs, decreasing the likelihood of cause of abscess to be related to ultrasound visibility.

There are several limitations present in this study, with the most obvious being the retrospective review nature of the study which could have introduced confounding effects into interpretation of the visibility of the target lesion. Data collection on

the visibility of the lesion based on the assumption that a pre-ablation ultrasound image of the target lesion would be captured and stored in PACS based on the standard protocol of our institution. And any procedure missing an image of the target lesion prior to ablation was deemed as invisible.

Conclusion

Poor conspicuity of HCC lesions on ultrasound is a challenge for successful percutaneous image-guided ablation. The usage of ultrasound in conjunction with other modalities such as non-contrast CT scan and fusion ultrasound improves the success rate of percutaneous ablation to similar levels as conventional ablation of conspicuous nodules, while also showing comparative local tumor control without major adverse events. Future studies may adopt a prospective design approach with more robust or thorough collection on sonographic appearance of the target lesion.

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Conflicts of Interest - No potential conflicts of interest to disclose.

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