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REVIEW

Fusion Imaging and Virtual Navigation to Guide Percutaneous Thermal Ablation of Hepatocellular Carcinoma: A Review of the Literature

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Abstract As medical imaging advancements have improved the detectability of hepatocellular carcinoma (HCC) in early stages, the approach to percutaneous thermal ablation for curative treatment has concomitantly advanced. Although many centers are adopting cross-sectional imaging to guide percutaneous ablation, the majority of procedures are still performed under ultrasound (US) guidance worldwide. Challenges to ultrasound guidance may present due to relatively poor resolution particularly with small or isoechoic lesions, or due to intervening structures such as the bowel or diaphragm that obstruct lesional visualization. Fusion imaging (FI) systems have been employed to address these challenges. By merging or synchronizing the real-time images from US with a previously obtained cross-sectional study, FI mitigates the inherent limitations of each individual imaging modality and expands procedural feasibility and technical outcomes. This manuscript reviews the current literature on the use of FI during percutaneous thermal ablation of HCC.

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Introduction

The technical improvements of percutaneous thermal ablation can have a great impact on the treatment of hepatocellular carcinoma (HCC), which is the sixth most common cancer and the third leading cause of cancer-related death in the world [1]. This curative treatment has become a recognized cornerstone in HCC therapy over the last two decades [2, 3], particularly as advancements in contrast-enhanced CT (CECT) and contrast-enhanced MRI (CEMRI) have facilitated the diagnosis of early stages of HCC when lesions are still small and amenable to minimally invasive therapy [4, 5]. Safe and effective thermal ablation requires appropriate image guidance during the procedure to ensure needle probe placement by visualization of the target lesion, surrounding structures, and needle probe itself. In addition, imaging can also be used to evaluate ablation margins during the procedure to better ensure the desired outcome of local control.

Ultrasound (US) remains the most commonly used image guidance method worldwide to guide percutaneous thermal ablation due to its low cost, availability, high contrast resolution, absence of ionizing radiation, and real-time guidance capabilities in any imaging plane [6, 7]. Despite these advantages, a major challenge to ultrasound guidance during ablation is relatively decreased contrast resolution in comparison with CECT or CEMRI. This limitation is particularly hindering for small lesions under 2 cm, isodense/isoechoic lesions, and lesions located centrally or in the hepatic dome. In addition, poor US visualization can occur due to intrinsic isoechogenicity of the target nodule in relation to the surrounding liver parenchyma, camouflage from macronodular cirrhosis of the surrounding liver parenchyma, and poor acoustic window due to intervening structures such as bowel or lung that are particularly pertinent in the hepatic dome, segment II, or caudate lobe [8].

In cases of poor lesional conspicuity, contrast-enhanced US (CEUS) has been proposed as a means to assist in lesion identification with success rates varying from 42 to 83%– [9–12]. This application is not widely adopted worldwide and requires a certain degree of technical familiarity as the contrast medium rapidly washes out of the liver and an evident washout phase is present in only 20–30% of nodules smaller than 2 cm [10, 13]. The most relevant factors affecting the detection rate with CEUS are tumor size, depth, and lack of an adjacent easily identifiable anatomical landmark.

Many practices have adopted the use of cross-sectional imaging guidance via CT or MRI; however, these imaging modalities also pose their own challenges of cost, equipment availability, limited space for needle probe access due to restrictive bore size, ionizing radiation (CT), metal implant constraints (MRI), need for intravenous contrast agents to visualize isodense or isointense lesions, and suboptimal real-time imaging capabilities [14].

Fusion imaging (FI) has been applied to address the inherent limitations of single-modality image guidance, with a variety of fusion methods that include optical [15], image-based [16], and electromagnetic tracking imaging [17, 18]. Of these options, the latter is the most commonly employed during percutaneous thermal liver ablation procedures. While software products all slightly vary, the overarching theme is to obtain a cross-sectional image of the liver (CECT or CEMRI) and fuse this imaging with the real-time ultrasound via plane and point registration [19–21]. Depending on the software, registration across the different imaging modalities is accomplished via external sensor coils, internal fiducials, or anatomical landmarks such as focal hepatic lesions (i.e., cyst or calcification) and vascular branches [22]. After fusion optimization, the real-time US and cross-sectional images can be displayed on the US monitor in side-by-side or overlaid configuration.

Fusion imaging has been advanced as a means to facilitate percutaneous thermal ablation of HCC lesions that are not well visualized by ultrasound. Contrast-enhanced cross-sectional imaging provides a superior contrast resolution, and fusion of this imaging with US retains all the intra-procedural advantages of ultrasound guidance during needle probe placement and evaluation of ablation margins [17]. This manuscript reviews the current literature on the use of fusion imaging during the percutaneous thermal ablation of HCC for the purposes of ablation planning, procedural execution, and immediate assessment of ablation margins.

Literature Search

A systematic review was conducted with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23]. Two authors (M.C. and D.B.) independently performed a literature search using MEDLINE and Cochrane Library Central Registry to identify articles relevant to FI applications in HCC ablation. Search terms used were "hepatocellular carcinoma," "HCC," "fusion imaging," "radiofrequency," "ablation," "thermal ablation," and "RF ablation." Abstracts were screened for relevance, and full-text articles were obtained. These were independently analyzed and assessed for eligibility by both reviewers. The reference lists of these articles were thoroughly screened to identify additional relevant papers.

Only English language articles that employed fusion technology with electromagnetic tracking were included in the literature review. Individual case reports were excluded, as well as ex vivo only, phantom, or animal studies. There were no publishing date limitations. In the event of multiple publications from the same center, care was exercised to mitigate overlapping patient populations (Fig. 1).

Tumor Ablation Planning

Liver evaluation with a pre-treatment ultrasound has been reported as a routine practice in several centers with expertise in HCC tumor ablation, especially in Europe and Asia [6, 24, 25]. Definitive US visualization of the target lesion has been suggested as a necessary precondition for effective ablative treatment [26]. Approximately 21.5–30.8% of the HCC nodules are not definitively identifiable on US evaluation, which would preclude ablation by US guidance [8, 24, 25, 27].

The application of fusion imaging has been described to improve visibility of target HCC lesions in several retrospective single-institution case series (Table 1). After the introduction of fusion imaging into their clinical practice, Makino et al. [28] reported an increased number of poorly visible nodules ablated (1.7–15.4%) with no decrease in successful ablation outcomes as measured by complete

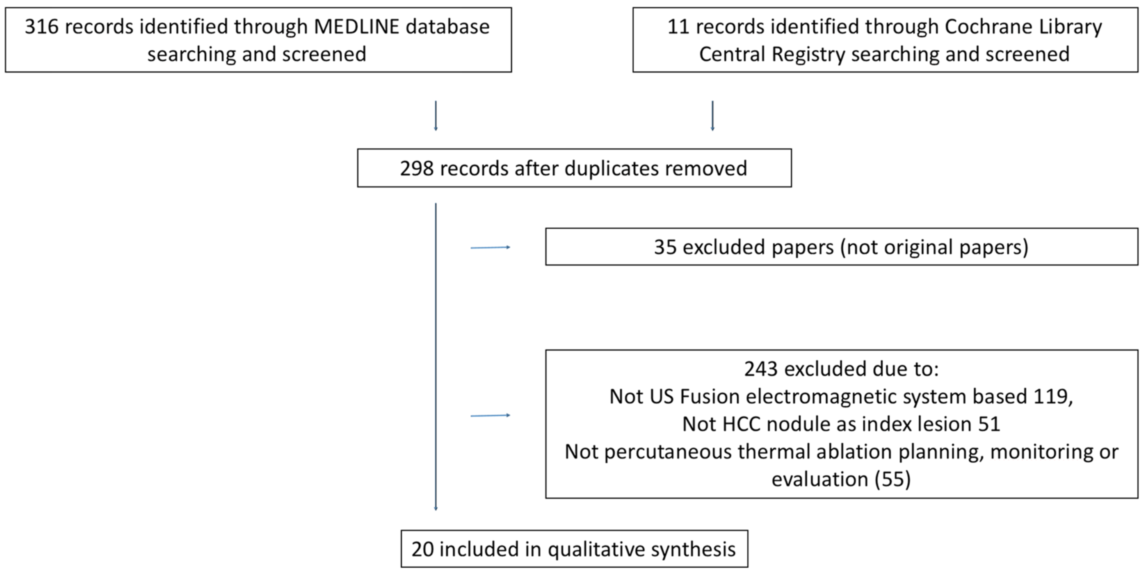

Fig. 1 Flow diagram of the analysis of the literature

local control. Lee et al. [29] reported an increased conspicuity of poorly visible HCC lesions from 78.8 to 90.5% after the application of fusion imaging with either CECT or CEMRI. Of 20 lesions that were completely undetectable by conventional US, fusion imaging allowed lesion detection in 45% (9 lesions).

The optimal fusion combination is unclear from the available literature. While a diagnostic CECT is commonly performed to detect HCC in cirrhotic liver [30, 31], CEMRI has been championed as a more specific cross-sectional modality for small atypical HCC lesions that measure less than 2 cm [32], particularly in the hepatobiliary phase with Gd-EOB-DTPA [9]. Moreover, CEMRI in the hepatobiliary phase provides better visualization of internal landmarks such as bile ducts and vasculature, which can assist during fusion imaging.

Two studies suggest that the best detection of inconspicuous HCC nodules might be through the fusion of cross-sectional imaging with CEUS, although study methods are inhomogeneous in these small retrospective case cohorts. Bo et al. [26] evaluated 70 lesions with US alone, fusion of CECT or CEMRI with US, and fusion of CECT or CEMRI with CEUS to demonstrate a higher lesional identification with fusion of cross-sectional imaging and CEUS (35.7%, 70%, and 95.7%, respectively). Dong et al. [11] evaluated 49 HCC lesions initially found to be inconspicuous on conventional US to report an increased detection rate of 42.9% (21/49) with CEUS and 95.9% (47/49) with the fusion of CEUS and CEMRI.

Tumor Ablation Procedure

Fusion imaging techniques are playing an increasingly important role during the procedure itself. Fusion imaging may be used during the ablation procedure to guide the needle to the target lesion. Even when nodules remain completely invisible despite the use of CEUS and correlation with fused cross-sectional imaging, the fused image can be used to guide ablation probes based on peritumoral anatomical landmarks and virtual needle trajectors [22, 33]. Lastly, fusion imaging can allow superposition of the lesion on cross-sectional imaging with the ablation-related gas formation seen on US to confirm ablation coverage.

Several [5, 34–37] retrospective and two prospective studies [20, 38] have compared ablation techniques by guided by US alone versus fusion imaging (Table 2). In the retrospective studies, the technical success rate of fusion-guided procedures ranged from 89.2 to 100% in a total of 1591 ablation procedures, which is similar to the ablation technical success rates in procedures on nodules readily identifiable by conventional US [6]. Furthermore, according to the data presented by Minami et al. there was no significant difference in the mean number of ablation procedures required to obtain a complete local control by CEUS, CEUS–CECT/CEMRI, or US–CECT/CEMRI (1.1 ablation session per nodule) [35]. A prospective study by Ahn et al. [38] found similar conclusions, with complete local control obtained in 97.1% (236/243) of the treated nodules treated under fusion imaging guidance. The cumulative incidence of local tumor progression for this published prospective study was 1.1%, 3.2%, and 4.7% (6, 12, and 24 months, respectively), which are in line with or even superior to the results obtained by ablation procedures

Table 1 Published studies on ablation planning with FI

References	Ewertsen et al. [50]	Kunishi et al. [9]	Lee et al. [29]	Min et al. [36]	Makino et al. [51]	Dong et al. [11]	Song et al. [34]*
Type of study	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Prospective	Retrospective
N patients/lesions	40/40	50/87	137/137	30/30	164/243	41/49	186/210
Lesion size (mm)	15	17 ± 5	17 ± 6	12 ± 3	15	25.2 ± 5.3	7.8 ± 1
Age (years)	NA	71 ± 6.5	59.1 ± 10.1	52.8 ± 8	NA	52.5 ± 3.2	61
HCC only (H)/other (O)	O	H	H	H	H	H	H
Previous treatment of HCC	No	No	No	No	No	Yes 59.1%	No
Previous treatment on the liver	NA	Yes	Yes	Yes	No	No	Yes
Conspicuity classification	No	No	Yes (4 grades)	Yes (4 grades)	No	No	No
Technical feasibility classification	No	No	No	Yes	No	No	No
Segment description	Yes	NA	NA	NA	NA	Yes	Yes**
CEUS	Yes	Yes	No	Yes	Yes	Yes	Yes
Average fusion time (minutes)	10	NA	NA	NA	NA	9.2 ± 2.1	NA
Conventional US detection rate	35%	76%	78.8%	0%	84.6%	No	No
CEUS-only detection rate	56%	83%	NA	NA	NA	42.9%	NA
US–CEMRI/CECT detection rate	57.5%	98%	90.5%	40%	89%	NA	65.7%
CEUS–CEMRI/CECT detection rate	67.5%	NA	NA	83.3%	96%	95.9%	68.6%
Time from previously acquired CT acquired CT/RM (days)	20 (13–27)	NA	9.6 (0–45)	16.8 (5–29)	NA	NA	NA

*Both planning and intra-procedural FI were evaluated

**Left segments/right segments/caudate lobe

guided by conventional ultrasound guidance only [6, 39]. Furthermore, in the Ahn et al.'s prospective study [38], the fusion imaging technique improved the operator's self-reported subjective technical feasibility from grade 1 (not feasible) to a grade of 2 or 3 (equivocally feasible or fairly feasible, respectively). Interestingly, operator judgement on feasibility grade was found as a significant predictive factor for the development of local tumor progression.

The above-cited studies are inhomogeneous in reported use of anesthesia to assist in control of patient breathing to improve fusion registration.

Only one retrospective study is published specifically on incidence of fusion errors affecting mistargeting of HCC ablation, with an error of $< 2\%$ (7/551 ablation procedures) [40]. The cause of ablation probe misplacement was attributed to persistent inconspicuity due to small lesion size within a background of macronodular cirrhosis with surrounding pseudolesions and needle probe trajectory limitations due to patient positioning. As pre-procedure CECT and CEMRI are generally acquired in supine position, any deviation from this positioning during the procedure to facilitate needle trajectory can cause fusion misregistration. The availability of CT in the operatory room might allow for acquisition of CECT images with the patient already under general anesthesia and in the desired position, so as to increase the correspondence between CECT and US images [7, 41].

Post-procedure Evaluation

Fusion imaging has also been suggested as a method to allow assessment of ablation margins intra-procedurally and during postoperative follow-up (see Table 3). Although fusion imaging improves the conspicuity of HCC lesions, the outcomes of ablations performed under fusion imaging guidance are limited by the same factors that affect ablation performed under conventional US guidance: large tumor size, infiltrating tumor morphology, insufficient ablative margins, blood vessels close to the tumor, subcapsular tumor location, poor histologic grade, and history of previous treatments [7, 38, 40].

In the setting of these challenging factors, intra-procedural assessment of ablation margins may obviate the necessity for a second procedure [42]. Li et al. [21] reported improved complete ablation rate using fusion imaging with CECT/CEMRI and CEUS in 12/55 (21.8%) lesions that were found to have inadequate ablation margins after first ablation impact based on intra-procedural review of fusion imaging and were successfully treated by immediate application of a second overlapping impact.

Table 2 Published studies on HCC ablation with FI guidance

References	Lee et al. [20]	Lee et al. [33]	Song et al. [46]	Minami et al. [35]	Min et al. [47]	Xu et al. [37]	Park et al. [48]	Mauri et al. [6]	Makino et al. [49]	Ahn et al. [38]
Type of study	P	R*	R	R***	R	R	R****	R	R	P
N patients\lesions	30\30	37\51	96\120	352\556	50\57	92\136	46\46	175\295	68\85	216\243
Age (years)	58.8 ± 8.8	55.8	59.9 ± 9.4	65.8 ± 27.6	62 ± 10.5	51.9 (28–74)	62.2 (33–87)	66 ± 12.3	76 (52–89)	65 (30 – 85)
HCC only (H)/other (O)	H	O	H	H	H	O	H	O	H	H
Lesion size (mm)	10 ± 3	17.2 ± 8.6	10 ± 4	15 ± 9	15 ± 6	25 (10–68)	30 ± 5	13 ± 6	11.9 (4.4–37)	15 (3–50)
Previous treatment of the nodule	No	No	No	No	Yes	Yes (27.2%)	Yes (60.8%)	NA	NA	No
Previous treatment on the liver	Yes	No	Yes	No	Yes	Yes	Yes	NA	NA	Yes
Number of procedure per nodule	NA	1	NA	1.1 ± 0.3	NA	1.2 ± 0.5	1	NA	80/4/1 (1, 2, 3 procedures)	237: 1 procedure 6: 2 procedures
US conspicuity of the lesion (%)	78.8	58.9	No**	Yes	NA	28.7	NA	0	NA	68.7
Conspicuity classification	No	No	No	No	Yes	No	No	No	No	Yes
CEUS	No	No	No	Yes	No	No	No	Yes	Yes	No
US–CEMRI/CECT detection rate (%)	90	NA	36.5	NA	92	100	NA	95.6	NA	81
Ablation margin evaluation	NA	Yes	NA	NA	NA	NA	NA	NA	Yes	NA
C.A. (%)	100	84.3	100	92.2/91.1/89.2***	100	92.6	100	90.2	94.9	97.1
L.T.P. (%)	0	11.8	NA	4.9/7.2/5.9***	14.3	11.9	8.7	NA	8.9 margins < 5 mm, 0 > 5 mm	7.2
F.U. (months)	8.1	12	NA	43.2 ± 5.9	6.2	28.1 ± 5.7	18.2	3–4	17	19.2

C.A. complete ablation, *L.T.P.* local tumor progression, *L.T.P.F.S.* local tumor progression-free survival, *F.U.* follow-up

*Three groups according to: (1) 5-mm margin goal, (2) inconspicuity at B mode US, (3) multiple surrounding nodules. Of note, the study included ex vivo analysis of the target

**All lesions were declared undetectable at conventional US

***Three groups (CEUS, US–CT/MR, and CEUS–CT/MR)

**** FI with CT/MRI, then 3D US

Table 3 Published studies on FI evaluation after ablation and during follow-up

References	Numata et al. [52]	Bo et al. [42]	Xu et al. [53]
Type of study	P	R	P
N patients/lesions	67/80	34/47	115/157
Age	73 (51–84)	58.1 ± 8.9	54 ± 11
HCC only (H)/other (O)	H	O	O
Previous treatment of the nodule	NA	Yes 4 TACE	NA
Previous treatment of the liver	NA	Yes	NA
Conspicuity classification	No	NA	NA
Subcapsular/central	NA	NA	NA
CEUS	Yes	Yes	Yes
Fusion imaging modality	CEUS–CECT	CEUS–CECT/CEMRI	CT/MRI–CEUS, US–CEUS
Time from ablation	1 day and 1 month	1–3 days	End of the procedure
Average fusion time	NA	NA	5.7 ± 2.7 (FI CEUS) 3.7 ± 1.7 (FI US)
Conventional US detection rate (%)	NA	NA	73.3
CEUS detection rate (%)	NA	44.7	NA
US–CEMRI/CECT detection rate (%)	NA	76.6	81.3
CEUS–CEMRI/CECT detection rate (%)	NA	100	93.8
Safety margin (> 5 mm)	NA	91.5	NA
C.A. (%)	92.5	95.7	99.3
L.T.P. (%)	4	4.4	NA
F.U. (months)	16	2–34	NA

According to the role of CEUS as a positive factor in the delineation of the avascular ablated area [12], one study reported an improved evaluation of ablation margins by the fusion of 3D US/CEUS acquired immediately before the ablation with real-time CEUS performed 10–15 min after the end of the procedure [43]. Of note, no specific study was found to evaluate the use of fusion imaging to evaluate the post-ablation zone on follow-up visits.

Recommendations Based on the Literature

- Fusion imaging with cross-sectional contrast-enhanced CT or MRI improves the detectability of poorly visible HCC lesions compared to conventional US (low-level evidence).
- Fusion of CECT or CEMRI with real-time CEUS improved detectability of poorly visible HCC lesions compared to CEUS alone, or fusion of conventional US with CECT or CEMRI (low-level evidence).
- Fusion imaging with CECT or CEMRI increases the number of HCC lesions that are judged treatable with percutaneous thermal ablation, with greater operator confidence, and technical success rates comparable to ablation performed for readily conspicuous lesions under conventional US guidance alone (low-level evidence).
- Fusion imaging can provide intra-procedural evaluation after ablation to assess ablation margins and guide decision making for additional overlapping ablation (low-level evidence).

Limitations and Future Perspective

Despite the prevalent use in clinical practice at many institutions, there is a paucity of prospective literature on fusion image guidance for the percutaneous thermal ablation of HCC. The majority of the small patient cohorts are retrospective in nature. No RCTs were found in the literature on this topic. Relevantly, there is a lack of homogeneity regarding subjectivity classification of lesion conspicuity and pre-treatment feasibility score, which makes comparison of results challenging. As a future goal for IR community, to standardize the reporting criteria of the FI guidance will be a precondition for further studies and subsequently for a better comprehension of the published literature results.

Although ex vivo experimental studies suggest a registration error between real-time US and CECT images is

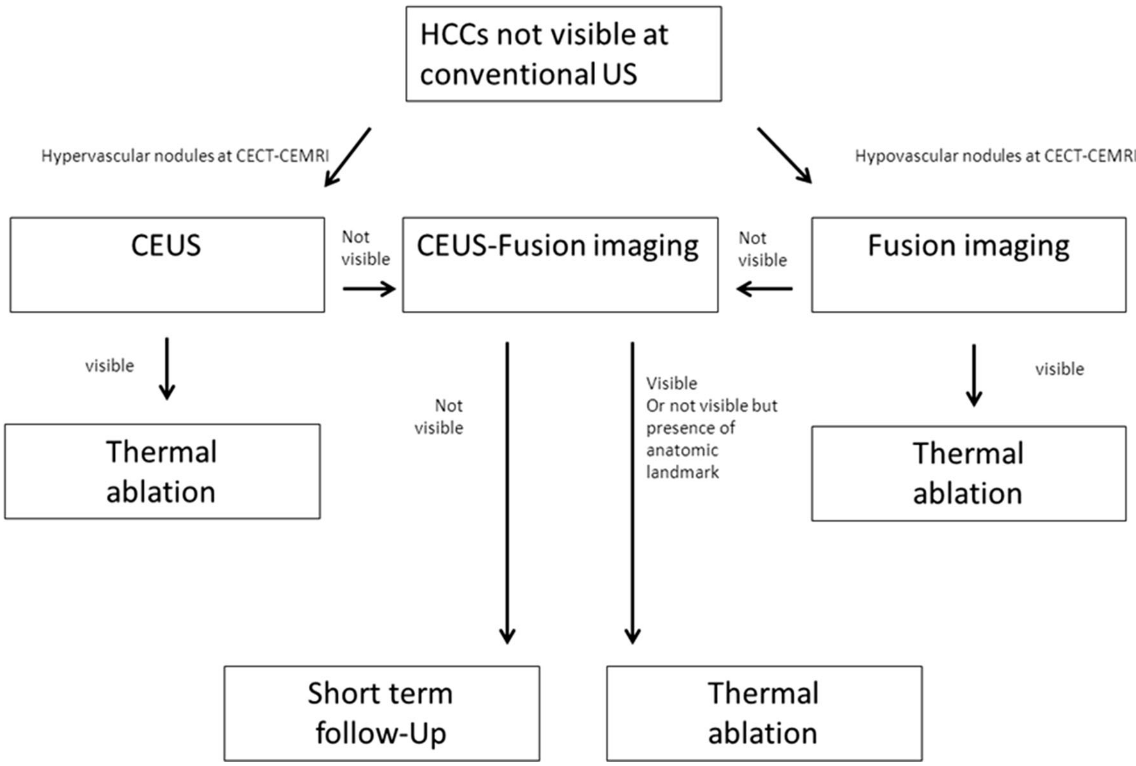

Fig. 2 Proposal of an operative flow diagram of ablation planning (including CEUS and fusion imaging)

within 3 mm [33], clinical practices likely vary greatly based upon the fusion device employed and procedural specificity. Indeed, fusion misregistry may be related to operator error, but also software potential to cope with breathing motion artifact. Manufacturers are improving devices with breathing synchronization [44] and automatic recognition and registration according to hepatic vasculature [45].

Lastly, selected studies only evaluated fusion imaging with US guidance only, whereas no comparison was made between outcomes of ablation performed under fusion image and CECT or CEMRI alone.

A Personal View on the Data

The current literature supports the use of fusion imaging with CECT or CEMRI and US to expand treatment feasibility, increase operator confidence in technique, and improve treatment outcomes for the percutaneous thermal ablation of HCC lesions based on low-level evidence. The use of fusion imaging may be considered as the most appropriate for small hypovascular HCC lesions at CECT–CEMRI that are not easily detected with US, whether due to lesion isoechogenicity to surrounding liver parenchyma, small size, or location obscured by ribs, lung, diaphragm, or bowel. CEUS alone can be proposed as a second-level guidance in case of hypervascular HCC lesions at CECT–CEMRI that are not easily visualized with ultrasound. In case of HCC nodules, still not visible after the two above-mentioned guidance methods, a combined approach (CEUS–CECT/CEMRI fusion imaging) should be always performed, due to the reported increased detection rate. The proposed flowchart in Fig. 2 can clarify in this regard.

Although recent reports confirm technological improvements, some limitations persist with fusion registration in the setting of respiratory motion that can be mitigated with controlled respiration techniques via intubation or conscious breath holds.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights This study was not supported by any funding and does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent For this type of study, formal consent is not required.

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