SYSTEMATIC REVIEW

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Contrast-Enhanced Ultrasound and Computed Tomography Assessment of Hepatocellular Carcinoma after Transcatheter Arterial Chemo-Embolization: A Systematic Review

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ABSTRACT

Background & Aims: Contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT) are used to assess the response of hepatocellular carcinoma after transarterial chemoembolization. Our aim was to perform a systematic review to compare CEUS and CECT for therapeutic response assessment to transarterial chemoembolization in the treatment of hepatocellular carcinoma.
Method: PubMed, Embase, and the Cochrane Library databases were searched from inception until January 1, 2016. Participants: patients with hepatocellular carcinoma. Intervention: transarterial chemoembolization and CECT vs CEUS.
Results. Sixteen studies were included in the systematic review. The total number of patients was 858 and the mean patient age ranged from 42 to 73 years. The mean tumor size ranged from 1.0 cm to 4.3 cm. The sensitivity and specificity of CEUS ranged from 46% to 100% and 65% to 100%, respectively, and that of CECT ranged from 34% to 87% and 92% to 100%, respectively. The accuracy of CEUS ranged from 72.6% to 100% and that of CECT from 61% to 94%. Marked heterogeneity was present among the studies.
Conclusion: CEUS is comparable with CECT for the therapeutic response assessment after transarterial chemoembolization.

Key words: hepatocellular carcinoma – transarterial chemoembolization – contrast-enhanced ultrasound – contrast enhanced CT.

Abbreviations: CECT: Contrast-enhanced CT; CEUS: Contrast-enhanced Ultrasound; CT: Computed Tomography; HCC: Hepatocellular Carcinoma; MDCT: Multidetector row CT; MRI: Magnetic Resonance Imaging; mRECIST: modified Response Evaluation Criteria in Solid Tumors; NPV: Negative Predictive Value; PPV: Positive Predictive Value; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies; RFA: Radiofrequency Ablation; TACE: Transcatheter Arterial Chemoembolization.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. It is ranked as the fifth most common cancer by the World Health Organization (WHO), and is globally responsible for approximately one-third of cancer-related deaths [1-4]. Epidemiologic studies have shown global variations in the incidence of HCC, with a high incidence in East Asia and sub-Saharan Africa, and a lower but increasing incidence in North America and Europe [5].

Transcatheter arterial chemoembolization (TACE) has become the standard of care for the treatment of uni- and multimodular HCC in patients with preserved liver function, no evidence of vascular invasion or extrahepatic spread, and no cancer-related symptoms [6, 7]. With advances in chemoembolization agents and techniques, the indications of TACE are expanding [6, 7]. Thus, methods to evaluate treatment response to TACE are becoming more important [8].

Imaging modalities used to evaluate tumor response to TACE include computed tomography (CT), ultrasound, and magnetic resonance imaging (MRI) [9]. In the traditional TACE protocols, an iodized oil (e.g., lipiodol) is delivered to the tumor intra-arterially [10-12], and the modified Response

Evaluation Criteria in Solid Tumors (mRECIST) are used to monitor response [13]. Contrast-enhanced CT (CECT) has been the primary method for evaluating tumor response after TACE; however, recent studies have suggested that it is not as accurate as previously thought for evaluating response [14-16], and evaluations generally have to be performed 1 month or more after treatment [9, 17].

In recent years, contrast-enhanced ultrasound (CEUS) has been shown to be useful for the assessment of tumor response after TACE [9, 18]. Advantages of CEUS include reproducibility, high temporal resolution, the absence of radiation, and high safety, making it suitable for patients with renal failure or allergy to iodine [18, 19]. In addition, the technique is less affected by lipiodol retention, the original echogenicity of the lesion, or adjacent parenchyma [9]. However, studies have reported varying results when comparing CEUS with CECT [9, 19-22].

The purpose of the current study was to perform a systematic review of the literature to compare CEUS and CECT for the assessment of therapeutic response to TACE in the treatment of HCC.

METHODS

Literature search strategy and study selection

PubMed, Embase, and the Cochrane Library databases were searched from inception until January 1, 2016 using the search terms: (hepatocellular carcinoma) AND (chemoembolization OR TACE) AND (contrast-enhanced ultrasound OR CEUS OR Doppler sonography) AND (computed tomography OR CECT); [(ultrasound) AND (computed tomography OR CT) AND (transcatheter arterial chemoembolization OR TACE)] AND (hepatocellular carcinoma OR HCC). Inclusion criteria were patients with HCC who had been treated with TACE and diagnostic data of both CEUS and CECT had been reported. Reviews, letters, comments, editorials, case reports, proceedings, and personal communications were excluded, as were single-arm studies (either CEUS or CECT). The studies that did not show specificity and/or sensitivity of both CEUS and CECT were excluded.

Data extraction and quality assessment

Data extracted from eligible studies included the name of the first author and year of publication, type of study, number of patients and nodules, patient age, sex, and Child-Pugh classification, mean tumor size, treatment and imaging modality, time of follow-up after treatment, treatment outcomes, and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of CEUS and CECT.

The quality of the included studies was assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) instrument [23]. Data extraction and quality assessment were carried out independently by the same two investigators, and disagreements were resolved by consensus.

RESULTS

A flow diagram of study selection is shown in Fig. 1. A total of 113 articles were identified in the database searches, and of these 89 non-relevant articles were excluded, including 23 articles that did not have diagnostic data for CECT vs. CEUS. Of the 24 full-text articles assessed for eligibility, 8 were excluded, the reasons for which are shown in Fig. 1. Thus, 16 articles were included in the systematic review [20, 24-38].

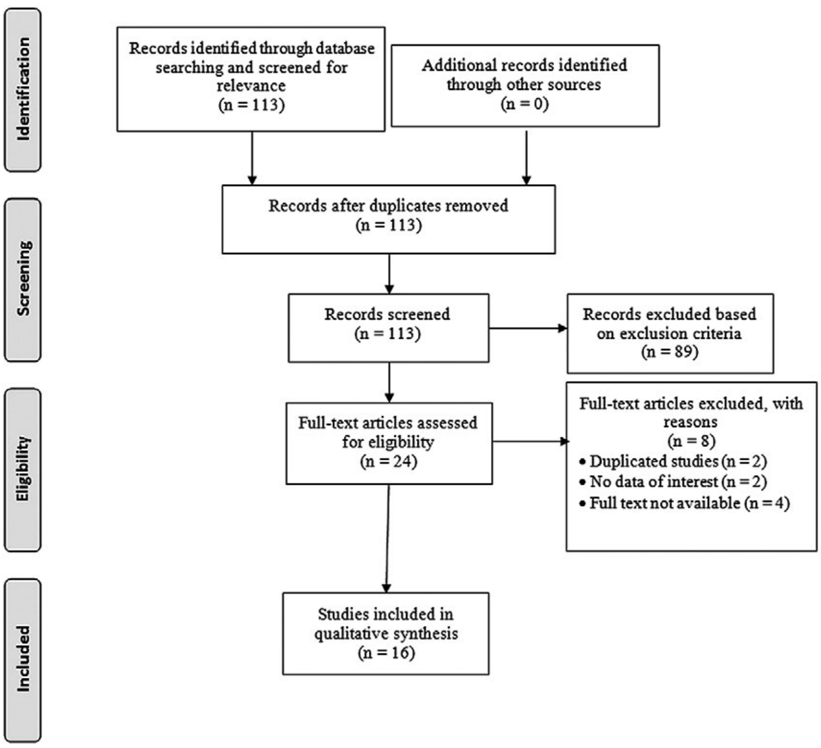

Fig. 1. Flow diagram of study selection.

Table I. Patients characteristics of the included studies

1st author (year) [Ref]	Study design	Number of patients	Age (years)*	Males, N (%)	Child-Pugh classification	Mean tumor size
Kaufmann (2016) [30]	Retrospective	20	66 (51–81)	18 (90%)	16 class A and 4 class B	3.8 cm (range, 1.1–7.1 cm)
Palmieri (2015) [31]	Retrospective	124	72 (46–97)	96 (77.4%)	Child-Pugh A or B	34 nodules < 20 mm and 114 nodules > 20 mm.
Wobser (2014) [24]	Prospective	40	63.8 ± 9.2	26 (65%)	Child A 23 Child B 17	3.9 ± 1.9 cm
Laroia (2013) [28]	Retrospective	50	(25–75)	40 (80%)	n/a	n/a
Takizawa (2013) [29]	Prospective	32 (59 HCC)	70 ± 7 (51–83)	24 (75%)	Child-Pugh, all included	29 ± 12 mm (10–73 mm)
Shiozawa (2010) [25]	Retrospective	71 (87 HCC)	70 ± 8	51 (72%)	n/a	20 ± 10 mm (8–65 mm)
Salvaggio (2009) [20]	Prospective	139 (148 HCC)	59 ± 8.4	n/a	n/a	n/a
Xia (2008) [34]	Prospective	43 HCC	73.3 (60–85)	24 (55.8%)	Child-Pugh A or B liver cirrhosis only	2.9 ± 1.8 cm
Zhou (2007) [26]	Retrospective	56 (64 HCC)	42±13.8	40 (71%)	n/a	3.4 ± 1.6 cm
Kono (2007) [33]	Prospective	33	n/a	21 (64%)	n/a	1–10 cm
Kim (2006) [27]	Prospective	29	58 (36–74)	19 (65.5%)	n/a	2.5 cm (0.6-12.0cm)
Shima (2005) [35]	Prospective	51 (63 HCC)	70 (32–87)	34 (66.7%)	n/a	2.8 cm (1-9cm)
Minami (2003) [32]	Prospective	40 (44 HCC)	67.7 (52–87)	29 (72.5%)	Child-Pugh A or B	3.9 ± 2.0
Morimoto (2003) [36]	Prospective	29 (29 HCC)	69.9 (58–79)	17 (59%)	n/a	n/a
Kubota (2001) [37]	Retrospective	54 (84 HCC)	68.97 (50–84)	45 (83.3%)	n/a	2.2 ± 1.4 cm
Cioni (2000) [38]	Prospective	47 (68 HCC)	65.7 ± 5.6	35 (74%)	Child-Pugh A 43 (91.5%); B 4(8.5%)	4.3 ± 1.7 cm

*Age was presented as mean ± standard deviation; mean (range: min to max); or mean ± standard deviation (range: min to max). HCC; hepatocellular carcinoma; n/a, not available.

The characteristics of the included studies are summarized in Table I and II. The total number of patients in the eight studies was 858, the mean patient age ranged from 42 to 73 years, and the majority of patients were male (range, 59% to 90%). The mean tumor size ranged from 1.0 cm to 4.3 cm. TACE and radiofrequency ablation (RFA) were the most common treatments, but other treatments included microwave ablation, percutaneous ethanol injection, and percutaneous microwave coagulation therapy. The types of CT used for evaluation included helical CT, dynamic CT, and multidetector row CT (MDCT), and the time between treatment and CEUS or CECT evaluation varied considerably between the studies (Table II).

A summary of the diagnostic data and treatment outcomes reported in the 16 studies is presented in Tables III and IV. The majority of the studies used biopsy or angiography as the reference standard for evaluating the accuracy of CEUS and CECT. Generally, the two techniques compared favorably with the reported sensitivity and specificity of CEUS ranging from 46% to 100% and 65% to 100%, respectively, and that of CECT ranging from 34% to 87% and 92% to 100%, respectively. Five studies reported data with respect to PPV and NPV [20, 24, 31, 33, 37]. The referenced standards were different among the studies. Palmieri et al. [31] used helical CT, Kono et al. [33] used CECT, Kubota et al. [37] used Lipiodol-CT, and both Wobser et al. [24] and Salvaggio et al. [20] used MDCT. Seven studies reported accuracy data [20, 26, 29, 33, 35, 37, 38], and the accuracy of CEUS ranged from 72.6% to 100% and that of CECT from 61% to 94%.

Quality assessment results of the included studies are summarized in Fig. 2. Overall, the quality of the included studies was high.

DISCUSSION

The results of this systematic review of 16 studies suggest that both CEUS and CECT are useful for assessment of response to TACE for HCC, but they might differ in sensitivity, specificity, and accuracy. The assessment of response to TACE is critically important so that the best possible outcomes can be achieved. CECT has been the primary method of evaluating tumor response after TACE, and lipiodol accumulation in the tumor is regarded as representing necrotic tissue, with a greater amount of accumulation indicating a larger area of necrosis [9]. On the other hand, washout of lipiodol or a focal defect in the mass indicates the presence of the viable tumor and that further treatment is necessary. Because accumulation of lipiodol can mask the enhancement of the residual viable tumor, it is necessary to wait until lipiodol washes out of the areas of viable tumor before CT assessment can be performed, typically at least 4-6 weeks after TACE [9, 16].

The role of CEUS is still controversial in the diagnosis of HCC. The updated European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines do not specifically recommend any role of CEUS in the treatment or follow-up of HCC [31]. The ability to detect a suspicious nodule for small HCC is highly dependent on the expertise of the radiologist. A

Table II. Summary of the treatments among the selected studies

1st author (year) [Ref]	Comparison groups	Contrast agents used in CT and US	Other treatment
Kaufmann (2016) [30]	CEUS	SonoVue	TACE
	VPCT	Ultravist 370	
Palmieri (2015) [31]	CEUS	SonoVue	Open surgical resection, TACE, locoregional treatment and combination of TACE or locoregional ablation with sorafenib.
	Helical CT	Iomeron	
Wobser (2014) [24]	MDCT	Bolus triggering technique (Solutrast®).	Superselective TACE: doxorubicin emulsified in lipiodol followed by gelfoam.
	CEUS	SonoVue	
Laroia (2013) [28]	CEUS	SonoVue	TACE/ RFA
	Dynamic CT/ MRI	Iomeron / gadobenate dimeglumine	
Takizawa (2013) [29]	CEUS	Sonazoid	TACE
	CECT	Iodine	
Shiozawa (2010) [25]	CEUS	Sonazoid	RFA (n = 55), TACE (n = 22), and RFA combined with TACE (n = 10)
	Dynamic CT	Iopamiron	
Salvaggio (2009) [20]	CEUS	SonoVue	110 RFA; 38 TACE
	MDCT	Iopromide (Ultravist 370)	
Xia (2008) [34]	CEUS	Sonazoid	TACE
	MDCT	Iomeprol	
Zhou (2007) [26]	CEUS	SonoVue	TACE
	CECT	Omnipaque	
Kono (2007) [33]	CEUS	Optison or Imagent	TACE
	CECT	Ioversol	
Kim (2006) [27]	CEUS	Levovist (galactose-palmitic acid mixture contrast medium)	TACE
	Helical CT	Iopamidol	
Shima (2005) [35]	PD sonography	Levovist (galactose-palmitic acid mixture contrast medium)	TACE
	CT	No enhancement	
	Dynamic MRI	Gadopentetate dimeglumine	
Minami (2003) [32]	Code phase inversion harmony sonography	Levovist (galactose-palmitic acid mixture contrast medium)	17 TACE; 23 received additional radiofrequency ablation or percutaneous ethanol injection.
	dynamic CT	Ioversol	
	Dynamic MRI	Gadolinium chelate	
Morimoto (2003) [36]	CE gray-scale sonography	Levovist (galactose-palmitic acid mixture contrast medium)	29 patients with TACE
	CECT	Iopamidol	
Kubota (2001) [37]	PD sonography	n/a	TACE
	Lipiodol-CT	2 mL/kg iopamidol 300 3 mL/s through	
Cioni (2000) [38]	CEUS	Levovist (galactose-palmitic acid mixture contrast medium)	TACE
	CT / MRI	MRI: Gadolinium chelate.	
	Dynamic MRI	Gadopentetate dimeglumine	

CECT: contrast-enhanced computer tomography; CEUS: contrast-enhanced ultrasound; MDCT: multiple detector computed tomography; MRI: magnetic resonance imaging; n/a: not available; PD: power Doppler; TACE: transcatheter arterial chemoembolization.

previous study suggested that CEUS can be incorporated in the diagnostic algorithm of small nodules (≤ 20 mm) in cirrhotic patients because CEUS is simpler, cheaper, and faster than CT, and monitoring of post TACE by CEUS is a cost effective and radiation free method [28]. However, CEUS cannot replace CT in the follow-up of treated nodules because it cannot always clearly depict the border between the tumor and the surrounding liver parenchyma and the possible onset of new nodules (relapse) [31].

Table III. Outcomes after treatment

1st author (year) [Ref]	Comparison groups	Time of study	Positive tumor enhancement	Residual viability	Residual tumor vascularization	Compete response rate	Successful treatment
Kaufmann (2016) [30]	CEUS	1 day pre and 1 day after TACE	n/a	n/a	NS	10/20 (50%)	n/a
	VPCT	n/a	n/a	n/a	NS	9/20 (45%)	n/a
Palmieri (2015) [31]	CEUS	Before and 1 month after treatment	n/a	< 20 mm 8/19 (42%); > 20 mm 39/88 (44%)	n/a	n/a	n/a
	Helical CT	n/a	n/a	< 20 mm 11/19 (57%); > 20 mm 51 (58%)	n/a	n/a	n/a
Wobser (2014) [24]	MDCT	6-8 weeks after TACE	30/40 (75%)	30/40 (75%)	n/a	10/40 (25%)	n/a
	CEUS	24 hours after TACE	24/40 (60%)	24/40 (60%)	n/a	16/40 (40%)	n/a
Laroia (2013) [28]	CEUS	Over 24 months of study	n/a	n/a	n/a	n/a	n/a
	Dynamic CT/ MRI		n/a	n/a	n/a	n/a	n/a
Takizawa (2013) [29]	CEUS	One day after study	n/a	n/a	47/59 (79.7%)	n/a	12 (20.3%)
	CECT	One month after study	n/a	n/a	37/59 (62.7%)	n/a	22 (37.3%)
Shiozawa (2010) [25]	CEUS	3.1± 2.5 days	n/a	n/a	n/a	n/a	n/a
	Dynamic CT		n/a	n/a	n/a	n/a	n/a
Salvaggio (2009) [20]	CEUS	1 month after treatment	n/a	20/23 (87%)	n/a	107/148 (72.3%)	n/a
	MDCT	n/a	n/a	n/a	n/a	n/a	n/a
Xia (2008) [34]	CEUS	1 week after treatment	25/43 (58.1%)	n/a	n/a	n/a	n/a
	MDCT	n/a	17/43 (39.5%)	n/a	n/a	n/a	n/a
Zhou (2007) [26]	CEUS	1 week after treatment	18/64 (28%) partial enhancement	28%	n/a	n/a	n/a
	Contrast enhanced helical CT		16/64 (25%) partial enhancement	25%	n/a	n/a	n/a
Kono (2007) [33]	CEUS	2 weeks after TACE	n/a	(17/23)74%	n/a	n/a	6/23 (26%)
	CECT	One month after	n/a	n/a	n/a	n/a	8/33(24%) 4 confirmed by histology, other by CT/ MRI 6 months later
Kim (2006) [27]	CEUS	Mean 1.2 days after treatment (1-7 days)	19 HCCs (61%)	61%	n/a	n/a	n/a
	Helical CT		12 HCCs (39%)	39%	n/a	n/a	n/a
Shima (2005) [35]	PD sonography	1 week after TACE	n/a	24 (38%) incomplete response	n/a	39 (62%)	39 (62%)
	CE-power Doppler sonography	n/a	n/a	n/a	n/a	n/a	n/a
	CT	n/a	n/a	n/a	n/a	n/a	n/a
	Dynamic MRI	n/a	n/a	n/a	n/a	n/a	n/a
Minami (2003) [32]	Code phase inversion harmony sonography	4-8 days (median, 6 days) after TACE	38/44 (86%)	n/a	n/a	n/a	n/a

Table III (continued)

	Dynamic CT	4–9 days (median, 7 days) after TACE	19/44 (43%)	n/a	n/a	n/a	n/a
	Dynamic MRI	4–10 days (median, 5 days) after TACE	10/20 (50%)	n/a	n/a	n/a	n/a
Morimoto (2003) [36]	CE gray-scale sonography	Before and 7 days after treatment	16/29 (55%)	n/a	n/a	13/29 (45%)	n/a
	CECT	n/a	n/a	n/a	n/a	n/a	n/a
Kubota (2001) [37]	PD sonography	5-7 days after TACE	n/a	n/a	n/a	n/a	n/a
	Lipiodol-CT	n/a	n/a	n/a	n/a	n/a	n/a
Cioni (2000) [38]	CEUS	Pre treatment/ 3-4 weeks after treatment	65/68(95%)	3/68 (4%)	n/a	n/a	n/a
	CT/ MRI	Post treatment	n/a	n/a	43/65 (66%)	22/65 (34%)	n/a
	Dynamic MRI	n/a	n/a	n/a	n/a	n/a	n/a

CECT: contrast-enhanced computer tomography; CEUS: contrast-enhanced ultrasound; MDCT: multiple detector computed tomography; MRI: magnetic resonance imaging; n/a: not available; NS: non-significant; PD: power Doppler; TACE: transcatheter arterial chemoembolization.

Fig. 2. Quality assessment of the included studies

Table IV. Diagnostic results for different techniques

1st author (year) [Ref]	Comparison groups	Sensitivity	Specificity	Accuracy	PPV	NPV	TPV
Kaufmann (2016) [30]	CEUS	n/a	n/a	n/a	n/a	n/a	n/a
	VPCT	n/a	n/a	n/a	n/a	n/a	n/a
Palmieri (2015) [31]	CEUS	73% for small nodules					
76% for larger nodules	100%	n/a	100%	73% for small nodules			
76% for larger nodules	n/a						
	Helical CT	n/a	n/a	n/a	n/a	n/a	n/a
Wobser (2014) [24]	CEUS	100%	80%	n/a	100%	63%	n/a
	MDCT	Reference	Reference	n/a	Reference	Reference	n/a
Laroia (2013) [28]	CEUS	n/a	n/a	n/a	n/a	n/a	15 HCC / post TACE 3
	Dynamic CT/ MRI	n/a	n/a	n/a	n/a	n/a	17 HCC / post TACE 3
Takizawa (2013) [29]	CEUS	95.70%	83.30%	93.2%,	n/a	n/a	n/a
	CECT	78.70%	100%	83.10%	n/a	n/a	n/a
Shiozawa (2010) [25]	CEUS	81.50%	96%	n/a	n/a	n/a	n/a
	Dynamic CT	n/a	92%	n/a	n/a	n/a	n/a
Salvaggio (2009) [20]	CEUS (ref. angiography)	83.30%	100%	100% (38/38)	100%	96.80%	n/a
	MDCT (ref. angiography)	86.9%	100%	92.1% (35/38)	100%	83.30%	n/a
Xia (2008) [34]	CEUS	n/a	n/a	n/a	n/a	n/a	n/a
	MDCT	n/a	n/a	n/a	n/a	n/a	n/a
Zhou (2007) [26]	CEUS	94.40%	97.80%	96.90%	n/a	n/a	n/a
	Contrast enhanced helical CT	83.30%	97.80%	93.80%	n/a	n/a	n/a
Kono (2007) [33]	CEUS	100%	83.30%	95.70%	94.40%	100%	n/a
	CECT	n/a	n/a	n/a	n/a	n/a	n/a
Kim (2006) [27]	CEUS	93%	65%	n/a	n/a	n/a	n/a
	helical CT	64%	100%	n/a	n/a	n/a	n/a
Shima (2005) [35]	PD sonography	11/24(46%)	100%	50/63 (79%)	n/a	n/a	n/a
	CE-PD Sonography	21/24(88%)	100%	60/63 (95%)	n/a	n/a	n/a
	CT	10/24 (42%)	100%	49/63 (78%)	n/a	n/a	n/a
	dynamic MRI	19/24 (79%)	100%	58/63 (92%)	n/a	n/a	n/a
Minami (2003) [32]	Code phase inversion harmony sonography	n/a	n/a	n/a	n/a	n/a	n/a
	Dynamic CT	n/a	n/a	n/a	n/a	n/a	n/a
	Dynamic MRI	n/a	n/a	n/a	n/a	n/a	n/a
Morimoto (2003) [36]	CE gray-scale sonography	100%	81%	n/a	n/a	n/a	n/a
	CECT	n/a	n/a	n/a	n/a	n/a	n/a
Kubota (2001) [37]	PD sonography	76%	67.60%	72.6%	77.60%	65.70%	n/a
	Lipiodol-CT	34%	100%	60.7%	100%	50.70%	n/a
Cioni (2000) [38]	CEUS	88%	100%	92%	n/a	n/a	n/a
	CT / MRI	n/a	n/a	n/a	n/a	n/a	n/a
	Dynamic MRI	100%	100%	100%	100%	100%	n/a

CECT: contrast-enhanced computer tomography; CEUS: contrast-enhanced ultrasound; MDCT: multiple detector computed tomography; MRI: magnetic resonance imaging; n/a: not available; NPV: negative predictive value; PPV: positive predictive value; PD: power Doppler; TACE: transcatheter arterial chemoembolization; TPV: true positive predictive value.

CEUS can be considered to replace CT in certain clinical conditions. It is difficult to assess the effectiveness of chemoembolization with dynamic CT immediately after TACE, as both necrotic and viable areas exhibit high attenuation on

CT owing to the deposited iodized oil [34]. In addition, it seems more appropriate to use CEUS for those patients who have undergone multiple CT/MRI scans earlier [28], and for the evaluation of the presence or absence of local recurrence [25]. CEUS is typically performed with a microbubble contrast agent, which provides high accuracy for depicting residual flow in tumors after TACE [9, 19]. For the assessment of TACE effectiveness in the days shortly after treatment, CEUS can be performed immediately after TACE before washout of iodized oil [27]. Wobser et al. [24] evaluated 40 patients with HCC 24 hours after TACE with CEUS and image fusion with CT, and at 6-8 weeks with CECT. In 24 patients post-interventional image fusion with CEUS revealed residual tumor vascularity that was confirmed by CECT at 6-8 weeks. Takizawa et al. [29] found that CEUS using Sonazoid performed 1 day after TACE was more sensitive than contrast-enhanced CT performed 1 month after TACE for detecting residual viable HCC tissue. Shiozawa et al. [25] compared the results of two observers in interpreting CEUS and CECT for the diagnosis of local recurrence of HCC after TACE or TACE/RFA and reported that CEUS using Sonazoid was less affected by observer experience and was more accurate than CT for the diagnosis of recurrence.

The 16 studies examined in the current analysis were markedly heterogeneous, and the definitions of treatment response were different among the studies. For example, Wobser et al. [24] used vascularized tumor volume, and Salvaggio et al. [20] used positive enhancement as an indicator of viable tumor in treated nodules. Other studies used residual HCC or depicting flow as outcomes measures. The reference standard was also different among studies. For example, Kim et al. [27] and Kono et al. [33] used conventional angiography as the reference standard, Takizawa et al. [29] used contrast-enhanced CT performed 2–6 months after TACE as the reference standard, and Kubota et al. [37] used dynamic MRI as the reference standard. Several studies found that the sensitivity of CEUS was higher than that of CECT, while the specificity of CECT was higher than that of CEUS [26, 27, 29, 37]. For example, Kim et al. [27] reported the sensitivity of CEUS and CECT were 93% vs. 64%, respectively, but the specificity of CEUS and CECT were 65% vs. 100%, respectively, when conventional angiography was used as the reference standard. In a study by Takizawa et al. [29], the sensitivity of CEUS and CECT were 95.7% vs. 78.7%, respectively, but the specificity of CEUS and CECT were 83.3% vs. 100%, respectively. The relatively low specificity for CEUS might result from several limitations of CEUS. False positive results may be due to the artifactual signals within the tumor associated with microbubbles, and false negative results may occur when the HCC lesion is undetectable by CEUS due to obscure margins or a distance more than 12 cm from the skin surface [29].

There are a number of limitations of the current analysis that should be considered. Most important is the marked eterogeneity among the studies. The CT techniques, reference standard, diagnostic data reported, and the criteria for monitoring response all varied among the studies. Furthermore, the contrast agents and time of evaluation after TACE also varied among the studies. These variations make comparisons of the different studies difficult, and made performing a meta-analysis impossible.

CONCLUSIONS

CEUS is a useful tool for therapeutic response assessment after TACE, and may provide comparable sensitivity and other benefits to CECT. More rigorous and well-designed studies are required for further investigation.

Conflicts of interest: The authors declare that there is no conflict of interest. **Source(s) of suppor**t: None

STUDY HIGHLIGHTS

What is current knowledge?

- Hepatocellular carcinoma (HCC) is one of the most common malignant diseases worldwide, and is globally responsible for approximately one-third of cancer-related deaths.
- Transcatheter arterial chemoembolization (TACE) has been recognized as a standard treatment option for patients with advanced HCC.
- Contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT) are used to assess response of hepatocellular carcinoma after TACE.

What is new here?

- The sensitivity and specificity of CEUS ranged from 46% to 100% and 65% to 100%, and that of CECT ranged from 34% to 87% and 92% to 100%, respectively.
- The accuracy of CEUS ranged from 72.6% to 100%, and that of CECT ranged from 61% to 94%.
- The diagnostic performance of CEUS is comparable to CECT for assessing residual tumours after TACE.

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