THE CLINICAL VALUE OF CONTRAST-ENHANCED ULTRASOUND (CEUS) FOR ASSESSING DIAGNOSIS OF VIABLE HEPATOCELLULAR CARCINOMA AFTER TACE IN COMPARISON WITH CONTRAST-ENHANCED MRI AND CT: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction and Objective: TACE is considered an effective treatment and currently represents the standard therapy for intermediate or advanced HCC patients. By using with mRECIST, CECT is an imaging modality to assess the treatment response after TACE; however, there is a weakness that has been observed in detecting residual tumors. The purpose of this study was focused on the assessing diagnosis of CEUS, CECT, and CEMRI which can be used as imaging options for the treatment response evaluation of HCC after TACE.

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Materials and Methods: Online databases were comprehensively and systematically searched. We used the combination of search terms and medical subject heading words (MeSH). Two reviewers independently scanned and extracted all relevant data from the included studies. We extracted the main characteristics of included studies and technical characteristics of each imaging modality, imaging interpretation (blinded or not), and the number of TP, FP, TN and FN. The methodological quality of included studies was assessed by using QUADAS-2 tools. Pooled statistics were calculated with a random-effect or fixed-effect model. Heterogeneity was assessed by the X^2 test and I^2 value. The sources of heterogeneity were explored by meta-regression analysis.

Results: Based on the inclusion criteria, we finally included 19 studies in this meta-analysis. In total, there are 862 patients with 1116 nodules of HCC after treatment. Most of the included studies had a low risk of bias regarding the study design and a low risk of concerns regarding clinical applicability. In terms of pooled sensitivity of CEUS, CECT, and CEMRI, it was 0.94, 0.73, and 0.90, respectively; pooled specificity was 0.90, 0.88, and 0.92, respectively. Pooled +LR of CEUS, CECT, and CEMRI were 7.17, 6.39, and 8.29, respectively; pooled –LR of CEUS, CECT, and CEMRI was 0.08, 0.34 and 0.16, respectively. Pooled DOR of CEUS, CECT, and CEMRI were 101.74, 19.89, and 53.56, respectively. In SROC curves analysis, AUCs of CEUS, CECT, and CEMRI were 0.9635, 0.7969, and 0.9452, respectively. Moreover, Q* indexes of CEUS, CECT, and CEMRI were 0.9097, 0.7332, and 0.8841, respectively. Meta-regression analysis revealed that there is no significant result was identified and these results suggested that country, year of publication, the number of patients, the quality of the included studies, and treatment modality were not the source of heterogeneity; however, there may be confounding biases for the retrospective studies in CECT ($P<0.05$).

Conclusion: This comprehensive meta-analysis revealed that the assessing diagnosis of CEUS is comparable to that of CECT and CEMRI. The assessing diagnosis of CEUS and CEMRI for viable HCC after TACE suggests that both CEUS and CEMRI may play important roles in oncology management and clinical practice.

Keywords: contrast-enhanced ultrasonography; contrast-enhanced computed tomography; contrast-enhanced magnetic resonance imaging; hepatocellular carcinoma; trans-arterial chemoembolization;

KEYPOINTS

- CECT or CEMRI is currently considered as the reference standard to evaluate the treatment response of tumor necrosis after transcatheter arterial chemoembolization (TACE) and the standard recommended time for the imaging follow-up is from 4 to 6 weeks. As the result of lipiodol retention after TACE, various studies have also been reported an overestimated tumor treatment response and a weak correlation with pathologic result; CEUS is low cost and accurate in the evaluation of tumor residual blood flow at 1 to 2 weeks after TACE.
- A comprehensive evaluation of the efficacy of assessing diagnosis of CEUS, CECT and CEMRI of viable hepatocellular carcinoma (HCC) may be a scientific and reasonable choice to provide predictive information of treatment response and decision making during or after transcatheter arterial chemoembolization (TACE) treatment.
- The assessing diagnosis of CEUS is better than that of CEMRI and CECT. The assessing diagnostic performance of CEUS in the assessment of viable hepatocellular carcinoma (HCC) after trans-catheter arterial chemoembolization (TACE) recommends that CEUS may play essential roles in the clinical practice for early assessing diagnosis of viable hepatocellular carcinoma (HCC) after treatment.

ABBREVIATIONS

AUC	**:**	Area under the curve
CECT	**:**	Contrast-enhanced computed tomography
CEUS	**:**	Contrast-enhanced ultrasound

CEMRI	:	Contrast-enhanced magnetic resonance imaging
cTACE	:	Conventional trans-catheter arterial chemoembolization
DOR	:	Diagnostic odds ratio
DTA	:	Diagnostic test accuracy
FN	:	False negative
FP	:	False positive
HCC	:	Hepatocellular carcinoma
+LR	:	Positive likelihood ratio
-LR	:	Negative likelihood ratio
mRECIST	:	Modified Response Evaluation Criteria in Solid Tumors
QUADAS-2	:	Quality Assessment of Diagnostic Accuracy Studies-2
RFA	:	Radiofrequency ablation
SROC	:	Summary receiver operating characteristic curves
TN	:	True negative
TP	:	True positive
TACE	:	Trans-catheter arterial chemoembolization

INTRODUCTION

Liver cancer is the sixth most common cancer and represents the third most common cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death and represents over 90% of all primary liver cancers. Additionally, HCC signifies an important healthcare issue with a strong predominance of males over females

(1-6). Nearly 90% of HCC patients are linked with known underlying risk factors; an important risk factor is liver cirrhosis which is commonly caused by chronic viral hepatitis, metabolic diseases, alcohol liver disease, and non-alcoholic fatty liver disease (7, 8). HCC patients should be considered for possible curative treatment choices such as surgical resection and liver transplantation if they were diagnosed at an early stage of HCC. However, the majority of HCC patients are not eligible for curative treatment (hepatic resection or transplantation) because they reach the intermediate or advanced stage with impaired hepatic function and underlying liver cirrhosis including portal vein hypertension, vein thrombosis, or inversion of the portal vein (9-13). For this circumstance, HCC patients should be considered for nonsurgical treatment choices such as radiofrequency ablation (RFA), microwave ablation therapy, transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection, etc. (14).

Among these treatment decisions, TACE is considered an effective treatment and currently represents the standard therapy for intermediate or advanced HCC patients (15-17). In the conventional TACE (cTACE) procedure, several anticancer agents, iodized oil (lipiodol), and gelatin sponge particles were used for delivering into feeding arteries of the liver tumors. TACE with an emulsion of iodized oil has been widely performed for the treatment of intermediate or advanced HCC and is recommended as the standard treatment choice for patients with large or multifocal tumors. In recent years, drug-eluting beads (DEB) have been used as embolic agents. After repeated TACE procedures, permanent occlusion of the hepatic artery has been reported (18-20). The successful TACE is the changes of tumor necrosis occurring as early as 1 to 2 months after treatment while the changes of tumor shrinkage always take longer to arise. Viable HCC is defined as the persistence of hyper arterial enhancement after treatment. In recent years, the modified Response Evaluation Criteria in Solid Tumors (mRECIST) are widely applied for evaluating the response of HCC to loco-regional therapies. Complete Response (CR) is disappearance of any intra-tumoral arterial enhancement in all target lesions. Partial Response (PR) is the decrease at least a 30% in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference in the baseline sum of the diameters of target lesions, while Progressive Disease (PD) is the increase in 20% in the sum of diameters of viable

(enhancing) target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started. Stable Disease (SD) is neither partial response nor progressive disease. mRECIST is reproducible and reliable in differentiating response and non-response post-embolization treatment; some clinical studies have also shown that mRECIST is superior to other criteria, especially for patients treated with loco-regional therapies. As we have known, the estimation of viable HCC following TACE can be done by using mRECIST criteria on contrast-enhanced computed tomography (CECT), contrast-enhanced ultrasound (CEUS) , or magnetic resonance imaging (MRI) (14, 21). By using with mRECIST, CECT is an imaging modality to assess the treatment response after TACE; however, there is a weakness that has been observed in detecting residual tumor. In the TACE procedure, the high intensity of lipiodol increases the difficulty of differentiating the arterial hyper-vascularization in the viable tumor from lipiodol deposition in CECT. The complete response (CR) assessed by CECT doesn't reflect the complete necrosis of the tumor pathologically.

As the result of lipiodol retention after TACE, various studies have also been reported an overestimated tumor treatment response and a weak correlation with pathologic results (22, 23). The size of the ultrasound contrast agent is smaller than that of red blood cells; CEUS with the second-generation contrast agent can be used to detect the viable cells and the patency of blood vessels (24, 25). CEUS is recognized as an important imaging modality to detect small newly hepatic nodules during surveillance and to guide or assess the HCC nodules after loco-regional treatment option (26, 27). In recent years, CEUS has been applied to early assess the therapeutic response to TACE. By comparison with CECT, CEUS is not affected by the original echogenicity of the lesion and less affected by lipiodol retention (28-30). Furthermore, CEMRI, high-quality imaging of the entire liver parenchyma and high intrinsic soft-tissue contrast, is superior to CECT as shown high sensitivity on T2WI and not affected by the presence of Lipiodol that makes CEMRI as a reference standard imaging modality for HCC treatment evaluation after TACE; however, enhanced areas in the embolization site on CEMRI apparently represent viable tumors with high sensitivity but low specificity (31, 32). The treatment response of HCC patients after TACE is routinely assessed with different imaging

modalities to determine additional therapies and an accurate imaging modality is importantly required for the diagnostic assessment. However, at present, no study directly compared these three imaging modalities together on which the best and accurate imaging modality should be selected to early assess the treatment response of HCC after TACE. Additionally, meta-analysis is a statistical method that allows the results of individual studies to be pooled and to be systematically evaluated. Therefore, the purpose of this study was focused on the assessing diagnosis of CEUS, CECT, and CEMRI which can be used as imaging options for the treatment response evaluation of HCC after TACE.

MATERIALS AND METHODS

Literature Search

Online databases were comprehensively and systematically searched to identify the relevant original studies about the assessing diagnosis of viable hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE) by using different imaging modalities including contrast-enhanced ultrasound (CEUS), contrast-enhanced computed tomography (CECT) and/ or contrast-enhanced magnetic resonance (CEMRI). We used the combination of search terms and medical subject heading words (MeSH) as follows: (A) hepatocellular carcinoma or hepatic carcinoma or hepatoma or liver cancer or liver cell carcinoma or HCC. (B) Transarterial chemoembolization or Trans hepatic arterial chemotherapy and embolization or transcatheter chemoembolization or TACE. (C) contrast-enhanced ultrasound or contrast-enhanced ultrasonography or ultrasound contrast imaging or contrast-enhanced US or CEUS. (D) contrast-enhanced computed tomography or computerized tomography or tomodensitometry or contrast-enhanced CT or CECT. (E) contrast-enhanced magnetic resonance or magnetic resonance or MR tomography or MR or MRI. The reference lists of all relevant articles and reviews were searched for additional records.

Study Selection

Two reviewers independently scanned all relevant studies to determine their eligibility for inclusion. In the event of disagreement, rechecking of the original article followed by

discussion between the two reviewers was used to reach a consensus. The following inclusion criteria were applied: (A) CEUS with the second generation of contrast agent and/or CECT and/or CEMRI were used to detect viable HCCs after TACE. (B) Pathology and/or digital subtraction angiography and/or imaging follow-up results severed as the reference standard. (C) The number of patients is more than 10 patients. (D) Original studies provided sufficient data to construct the 2x2 table including true positive (TP), false positive (FP), false negative (FN), and true negative (TN). (E) When the studies were published more than one time, the latest published paper and sufficient data of these studies were selected. Reviews, case reports, animal studies, editorial comments, conference abstract without detailed information or data, and non-English articles were excluded from consideration.

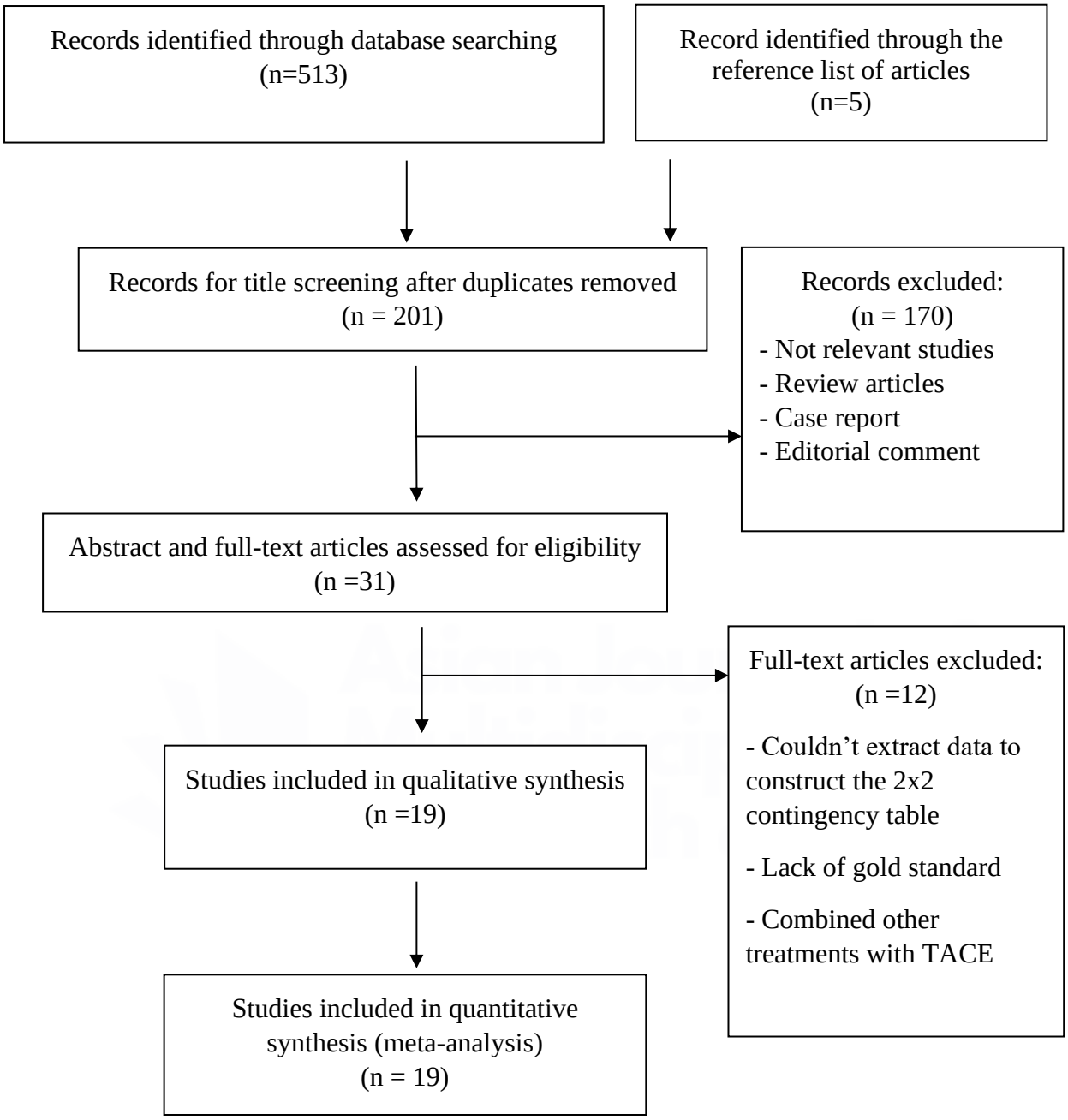

Figure1: PRISMA flow chart for systematic search and study selection

Data Extraction

Two reviews independently extracted all relevant data from the included studies and disagreements were resolved by consensus. The following basic information was extracted from each study: name of the first author, year of publication, country of study, study design, number of patients, patient age (mean), patient sex (male/female), number of HCC nodules, mean tumor diameter (cm), imaging modalities (index test), reference standard, TACE emulsion and timing/ interval of test after Treatment.

Then, we extracted the technical characteristic of each imaging modality, imaging interpretation (blinded or not), and the number of TP, FP, TN and FN.

Quality Assessment

The methodological quality of included studies was assessed using QUADAS-2 tools (Quality Assessment of Diagnostic Accuracy Studies-2). Two reviewers independently performed the quality assessment of the included studies. The quality of original diagnostic studies was evaluated by estimating the risk of bias in four important domains (patient selection, index test, reference standard, and flow and timing) and the applicability concerns in three important domains (patient selection, index test, and reference standard) of the included studies. Each domain was scored as high, low, or unclear. In the event of disagreement, rechecking of the original article followed by a discussion between the two reviewers was used to reach a consensus.

Data Synthesis and Statistical Analysis

Threshold effect was estimated using Spearman correlation analysis; $P<0.05$ was considered statistically significant and meta-analysis of the data using a random effect model was performed when there is significant heterogeneity ($I2>50\%$ and/or $P<0.05$); otherwise, a fixed-effect model was used (33, 34). A random-effect model was used to obtain pooled sensitivity, pooled specificity, pooled positive likelihood ratio, pooled negative likelihood ratio, and pooled diagnostic odds ratio (DOR) with 95% CI of each imaging modality. Summary receiver operating characteristic (SROC) curves, area under the curve (AUC), and Q* index (the points

on the SROC curve where sensitivity and specificity are equal) were also calculated. Cochran's Q-coefficient and I2 values were calculated to assess heterogeneity. Cochran's Q is a form of the X2-test which provides information about the applicability of pooling the data, while I2 value provides a quantitative measure of the amount of heterogeneity which can be interpreted as low (I2=25%), moderate (I2=50%), and high heterogeneity (I2=75%) (35). Heterogeneity resource was assessed using meta-regression analysis. This meta-analysis was performed using Meta-Disc 1.4 software for meta-analysis of diagnostic test accuracy (DTA) (33, 36). The Cochrane meta-analysis guidelines recommend the use of Egger's test for publication bias for analyses when there are more than 10 studies. Therefore, publication bias was not assessed because of the small number of studies in pooling of each imaging modality in our meta-analysis.

RESULTS

Study selection and characteristics of included studies

Based on the inclusion and exclusion criteria, we finally included 19 studies in this meta-analysis. (37-55) English papers (published from 2000 to 2020) are 1 study done in China, 4 in the USA, 4 in Japan, 3 in Korea, 2 in Greece, 1 in Switzerland, 1 in Italy, 1 in Canada, 1 in Egypt , and 1 in India. The main characteristics of the included studies are shown in table1. In total, there are 862 patients with 1116 nodules of HCC after treatment; 16 studies of conventional TACE, 2 studies of DEB-TACE, and 1 study of DEB-TACE+ Iodized oil. The contrast dose of the second generation of CA used in CEUS ranged from 0.2 to 2.4 ml, the probe frequency of CEUS varied from 1 to 6 MHz, and time interval after TACE varied from 1 day to 3 months. The range in slice thickness of CECT was 2 to 8 mm, and the time interval after TACE varied from 1 day to 3 months. For CEMRI, the strength field is 1.5 or 3T, and the time interval after TACE varied from 2 days to 6 months. TP, FP, FN, TN, and other features of each imaging modality were shown in tables 2, 3, and 4.

Quality of included studies

The quality assessment results revealed that the overall quality of the included studies was high, but some individual studies had a medium quality. Most of them had a low risk of bias regarding study design and a low risk of concerns regarding clinical applicability. The quality assessment was evaluated according to QUADAS-2 items and the assessment results were re shown in table 5.

Table1: Main characteristics of included studies

No	First author and year	Country	Study design	No of patients	Gender (M/F)	Mean Age (year)	No of Nodules	Mean tumor diameter (mm)	Imaging modalities	TACE
1	Yukinobu Watanabe et al (2020)	Japan	Retro	70	43/27	72	89	18.1	CEUS	cTACE
2	Hippocrates Moschouris et al (2014)	Greece	Retro	47	37/10	67.5	80	73	CEUS	DEB-TACE
3	S.B. Paul et al (2017)	India	Pro	50	41/9	53	70	50	CEUS, CECT	cTACE
4	Youn Zoo Cho et al (2015)	Korea	Pro	12	10/2	63.9	12	32	CEUS, CECT	cTACE

5	Ming Liu et al (2015)	China	Pro	130	122/8	53	130	44	CEUS, CECT	cTACE
6	Kenichi Takizawa et al (2013)	Japan	Pro	32	24/8	70	59	29	CEUS, CECT	cTACE
7	Giuseppe Salvaggio et al (2010)	Italy	Pro	29	NR	59	38	NR	CEUS,CECT	cTACE
8	Hippocrates Moschouris et al (2020)	Greece	Pro	30	26/4	68	55	52	CECT	DEB-TACE
9	Hyun Jin Kim et al (2006)	Canada	Pro	29	19/10	58	32	25	CECT	cTACE
10	K. Kubota et al (2001)	Japan	Pro	54	45/9	68.97	84	22	CECT,CEMRI	cTACE

11	Stephen J. Hunt et al (2009)	USA	Retro	31	28/3	60	31	NR	CECT,CEMRI	cTACE
12	Bobby Kalb et al (2010)	USA	Pro	21	17/4	61	23	34	CEMRI	DEB-TACE+ Iodized oil
13	Sooah Kim et al (2010)	USA	Retro	34	25/9	58	57	24	CEMRI	cTACE
14	Jeong-Sik Yu et al (2009)	Korea	Retro	32	25/7	58	36	NR	CEMRI	cTACE
15	Jae Hyun Yim et al (2019)	Korea	Retro	135	108/27	NR	136	NR	CEMRI	cTACE
16	Jordi Rimola et al (2019)	USA	Retro	49	34/15	57	75	NR	CEMRI	cTACE

17	Ahmed Ebraheem Ebeed et al (2017)	Egypt	Retro	30	24/6	58.76	40	41	CEMRI	cTACE
18	Satoshi Goshima et al (2008)	Japan	Retro	25	18/7	60.2	39	16	CEMRI	cTACE
19	Nicolae Bolog et al (2008)	Switzerland	Retro	22	16/6	57.8	30	31	CEMRI	cTACE

CEUS= contrast-enhanced ultrasound, CECT= contrast-enhanced computed tomography, CEMRI= contrast-enhanced magnetic resonance imaging, cTACE= conventional trans-arterial chemoembolization, DEB-TACE= drug-eluting bead trans-arterial chemoembolization, Pro= prospective, Retro= retrospective, NR= not reported, USA= United States of America

Table2: Technical characteristics of CEUS with TP, FP, FN, and TN

First author and year	Probe frequency	Mechanical Index	Contrast agent and dose	Time interval after TACE	Reference standard	Imaging interpretation	TP	FP	FN	TN
Yukinobu Watanabe et al (2020)	1 to 6 MHz	0.20 to 0.40	Sonazoid 0.5 ml	1 to 2 days	CECT at 4 weeks	Blind	22	5	10	52
Hippocrates Moschouris et al (2014)	1 to 5 MHz	0.08 to 0.12	Sonovue 2.4 ml	1 month	CECT or CEMRI	Blind	67	1	1	11
S.B. Paul et al (2016)	NR	NR	Sonovue, 2.4 ml	1.7 month	CEMRI	Blind	34	0	2	21
Youn Zoo Cho et al (2017)	4 MHz	0.09	Sonovue, 2.4 ml	1 month	CEMRI at 1month or 3months	Blind	4	4	0	4

Ming Liu et al (2015)	1 to 6 MHz	NR	Sonovue, 2.4 ml	0.5 to 3 months	Histopathology or DSA	Blind	117	0	5	8
Kenichi Takizawa et al (2013)	3.5 MHz	0.7 to 1	Sonazoid, 0.2 ml	1 day	DSA and CECT at 2 to 6 months	Blind	45	2	2	10
Giuseppe Salvaggio et al (2010)	2 to 5 MHz	< 0.09	Sonovue, 2.4 ml	1 month	DSA	Blind	23	15	0	0

CEUS= contrast-enhanced ultrasound, CECT= contrast-enhanced computed tomography, CEMRI= contrast-enhanced magnetic resonance imaging, DSA= digital subtraction angiography, NR= not reported

Table3: **Technical characteristics of CECT with TP, FP, FN, and TN**

First author and year	Slice thickness	Contrast agent	Dose of contrast Agent	Time interval after TACE	Reference standard	Imaging Interpretation	TP	FP	FN	TN
S.B. Paul et al (2017)	5 mm	Iodinated	80 ml	1 month	CEMRI at 1month or 3 months	Blind	18	0	18	21
Youn Zoo Cho et al (2015)	2 to 2.5 mm	Iodinated	370 mg/dl	1 month	CEMRI at 1month or 3 months	Blind	3	0	1	8
Ming Liu et al (2015)	NR	Iodinated	1.5 ml/kg	0.5 to 3 months	Histopathology or DSA	Blind	93	0	29	8
Kenichi Takizawa et al (2013)	5 mm	Iodinated	100 ml	1 month	DSA and CECT at 2 to 6 months	Blind	37	0	10	12

Giuseppe Salvaggio et al (2010)	6.5 mm	Iodinated	120 to 140 ml	1 month	DSA	Blind	20	0	3	15
Hippocrates Moschouris et al (2020)	1.25 to 5 mm	Iodinated	1.5 ml/kg	1 to 3 days	CEMRI at 1month	Blind	37	1	9	8
Hyun Jin Kim et al (2006)	3 to 8 mm	Iodinated	150 ml	NR	DSA	Blind	9	1	5	17
K. Kubota et al (2001)	10 mm	Iodinated	2ml/kg	1 week	Imaging follow-up within 1 year , Histopathology or DSA	Blind	38	11	12	23
Stephen J. Hunt et al (2009)	5 mm	Iodinated	100 to 120 ml	2 days	Histopathology	Blind	5	3	9	4

CECT= contrast-enhanced computed tomography, CEMRI= contrast-enhanced magnetic resonance imaging, DSA= digital subtraction angiography, NR= not reported

Table 4: **Technical characteristics of CEMRI with TP, FP, FN, and TN**

First author and year	Strength field	Contrast agent	Contrast dose	Time interval after TACE	Reference standard	Imaging interpretation	TP	FP	FN	TN
K. Kubota et al (2001)	NR	Gd-DTPA	0.1 mmol/kg	1 week	Imaging follow-up within 1 year , Histopathology or DSA	Blind	48	0	0	22
Stephen J. Hunt et al (2009)	1.5T	Gd-DTPA	30ml	2 days	Histopathology	Blind	3	1	4	3
Bobby Kalb et al (2010)	1.5T	Gd-DTPA	0.05	1 month	Histopathology	Blind	6	0	1	16

			mmol/kg							
Sooah Kim et al (2010)	1.5T	Gd-DTPA	20 ml	4.5 months	Histopathology	Blind	25	6	7	76
Jeong-Sik Yu et al (2009)	1.5T	Gd-DTPA	NR	1 to 6 months	Imaging follow-up at 6 months	NR	24	5	2	5
Jae Hyun Yim et al (2019)	3T	Gd- DTPA	0.025 mmol/kg	1 month	Histopathology or Imaging follow-up	Blind	111	1	10	14
Jordi Rimola et al (2019)	1.5T	Gd- DTPA	0.1 mmol/kg	1 to 3 months	Histopathology	Blind	8	1	2	8
Ahmed Ebraheem Ebeed et al (2017)	1.5T	Gd-DTPA	0.1 mmol/kg	1 month	Imaging follow-up at 3 months	NR	16	1	1	22
Satoshi Goshima et al (2008)	1.5T	Gd-DTPA	1ml	2 to 6 months	Imaging follow-up within 6 to 9 months	Blind	12	2	2	23

Nicolae Bolog et al (2008)	1.5T	Gd-EOB-DTPA and Gd-DTPA (double contrast)	1.4 ml and 0.2 ml/kg	1 month	Histopathology and DSA	Blind	24	0	2	4

Gd-DTPA= gadolinium-diethylenetriamine-pentaacetic acide, Gd-EOB-DTPA= gadolinium- ethoxybenzyl-diethylenetriamine -pentaacetic acide, DSA= digital substract angiography, NR= not reported

Table 5: The quality assessment of the included studies (QUADAS-2)

			Risk of Bias				Applicability Concerns		
No	**Study**	**Year**	**Patient Selection**	**Index Test**	**Reference Standard**	**Flow and Timing**	**Patient Selection**	**Index Test**	**Reference Standard**
1	Yukinobu Watanabe et al	2020	Low	Low	Low	Low	Low	Low	Low
2	Hippocrates Moschouris et al	2014	Low	Low	Low	Low	Low	Low	Low
3	S.B. Paul et al	2017	Low	Low	Low	Low	Low	Low	Low

4	Youn Zoo Cho et al	2015	Low	Low	Low	Low	Low	Low	Low
5	Ming Liu et al	2015	Low	Low	Low	Unclear	Low	Low	Low
6	Kenichi Takizawa et al	2013	Low	Low	Low	Unclear	Low	Low	Low
7	Giuseppe Salvaggio et al	2010	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
8	Hippocrates Moschouris et al	2020	Low	Low	Low	Low	Low	Low	Low
9	Hyun Jin Kim et al	2006	Low	Low	Low	Low	Low	Low	Low
10	K. Kubota et al	2001	Low	Low	Low	Unclear	Low	Low	Low
11	Stephen J. Hunt et al	2009	Low	Low	Low	Low	Low	Low	Low
12	Bobby Kalb et al	2010	Low	Low	Low	Unclear	Low	Low	Low
13	Sooah Kim et al	2010	Low	Unclear	Low	Low	Low	Unclear	Low
14	Jeong-Sik Yu et al	2009	Low	Unclear	Low	Low	Low	Unclear	Low
15	Jae Hyun Yim et al	2019	Unclear	Low	Low	Unclear	Unclear	Low	Low
16	Jordi Rimola et al	2019	Unclear	Low	Low	Low	Unclear	Low	Low

17	Ahmed Ebraheem Ebeed et al	2017	Low	Unclear	Low	Low	Low	Unclear	Low
18	Satoshi Goshima et al	2008	Low	Low	Low	Low	Low	Low	Low
19	Nicolae Bolog et al	2008	Low	Low	Low	Unclear	Low	Low	Low

Pooled Statistics for the Assessing Diagnostic Value of CEUS, CECT, and CEMRI

By using the Spearman correlation coefficients, the analysis of the threshold effect shows that there is no threshold effect of CEUS (Coefficient= -0.20, P>0.05), CECT (coefficient=-0.237, P>0.05), and CEMRI (coefficient=-0.418, P>0.05). The sensitivity, specificity, +LR, -LR, and DOR were pooled by the random-effects model because of significant heterogeneity (I2>50% and/or P<0.05) except DOR of CEMRI which was pooled by fixed-effect model due to not significant heterogeneity (I2<50% and/or P>0.05). In terms of pooled sensitivity of CEUS, CECT, and CEMRI, it was 0.94, 0.73, and 0.90, respectively; pooled specificity was 0.90, 0.88, and 0.92, respectively. Pooled +LR of CEUS, CECT and CEMRI was 7.17, 6.39, and 8.29, respectively; pooled –LR of CEUS, CECT and CEMRI was 0.08, 0.34 and 0.16, respectively. Pooled DOR of CEUS, CECT, and CEMRI were 101.74, 19.89, and 53.56, respectively. On the basis of a random effect model or fixed-effect model, the pooled sensitivity, pooled specificity, and pooled DOR of these three imaging modalities were shown in table6. The SROC analysis was calculated to compare these three imaging modalities and SROC curves were shown in figure 2 to 4. In these SROC curves, AUCs of CEUS, CECT, and CEMRI were 0.9635, 0.7969, and 0.9452, respectively. Moreover, Q* indexes of CEUS, CECT, and CEMRI were 0.9097, 0.7332, and 0.8841, respectively.

Sources of heterogeneity

Meta-regression analysis was used to assess the source of heterogeneity. The sources of heterogeneity were considered with some factors including country, year of publication, the number of patients, the quality of the study, and treatment modality. No significant result was identified and these results suggested that country, year of publication, the number of patients, the quality of the study, and treatment modality were not the source of heterogeneity; however, there may be confounding biases for the retrospective studies in CECT (P<0.05) (Table7).

Table6: The pooled statistics for diagnostic accuracy test of CEUS, CECT and CEMRI

Imaging modality	Parameter	Pooled diagnostic value	95% CI	Model	I2 (%)	P value
CEUS	Sensitivity	0.94	0.90- 0.96	Random	79.4	<0.05
	Specificity	0.90	0.83- 0.95	Random	66.5	<0.05
	+LR	7.17	2.32- 22.14	Random	75.5	<0.05
	-LR	0.08	0.03- 0.23	Random	80.8	<0.05
	DOR	101.74	24.43- 423.63	Random	53.5	>0.05
CECT	Sensitivity	0.73	0.68- 0.78	Random	65.6	<0.05
	Specificity	0.88	0.81- 0.93	Random	74.3	<0.05
	+LR	6.39	2.29- 17.83	Random	68	<0.05
	-LR	0.34	0.24- 0.48	Random	68	<0.05
	DOR	19.89	6.17- 64.17	Random	58.2	<0.05
CEMRI	Sensitivity	0.90	0.86- 0.93	Random	65.2	<0.05
	Specificity	0.92	0.87- 0.95	Random	57.1	<0.05
	+LR	8.29	3.46- 19.87	Random	69.8	<0.05
	-LR	0.16		Random	62.8	<0.05

DOR	53.56	0.09- 0.29 27.51- 104.30	Fixed	42.8	>0.05	

CEUS= contrast-enhanced ultrasound, CECT= contrast-enhanced computed tomography, CEMRI= contrast-enhanced magnetic resonance imaging, +LR=positive likelihood ratio, -LR= negative likelihood ratio, DOR= diagnostic odd ratio

Table7: Results of meta-regression analysis

Imaging modality	**Variable**	**Country (ASIA vs non-ASIA)**	**Year of publication (After 2015 vs Before 2015)**	**Study design (Retrospective vs Prospective)**	**Number 0f patients (>100 vs <100)**	**Quality of study (Good vs Medium)**	**Treatment modality (cTACE vs DEB-TACE)**
CEUS	Coefficient SE P value RDOR	-2.56 2.46 0.37 0.08	-0.93 2.25 0.45 0.15	0.28 1.96 0.89 1.33	1.42 2.42 0.60 4.14	-0.82 1.95 0.70 0.44	-2.56 2.46 0.37 0.08

CECT	Coefficient	0.56	0.66	3.28	0.87	-1.78	-1.19
	SE	1.15	1.28	1.01	2.03	1.08	1.78
	P value	0.64	0.62	0.02	0.68	0.15	0.53
	RDOR	1.75	1.93	26.58	2.39	0.17	0.30
CEMRI	Coefficient	1.12	0.99	2.73	1.09	-0.80	-0.09
	SE	1.44	1.14	1.58	1.71	1.36	2.43
	P value	0.46	0.41	0.13	0.55	0.23	0.67
	RDOR	3.06	2.71	15.32	2.96	0.16	0.34

CEUS= contrast-enhanced ultrasound, CECT= contrast-enhanced computed tomography, CEMRI= contrast-enhanced magnetic resonance imaging, cTACE= conventional trans-arterial chemoembolization, DEB-TACE= drug-eluting bead trans-arterial chemoembolization, SE= standard error

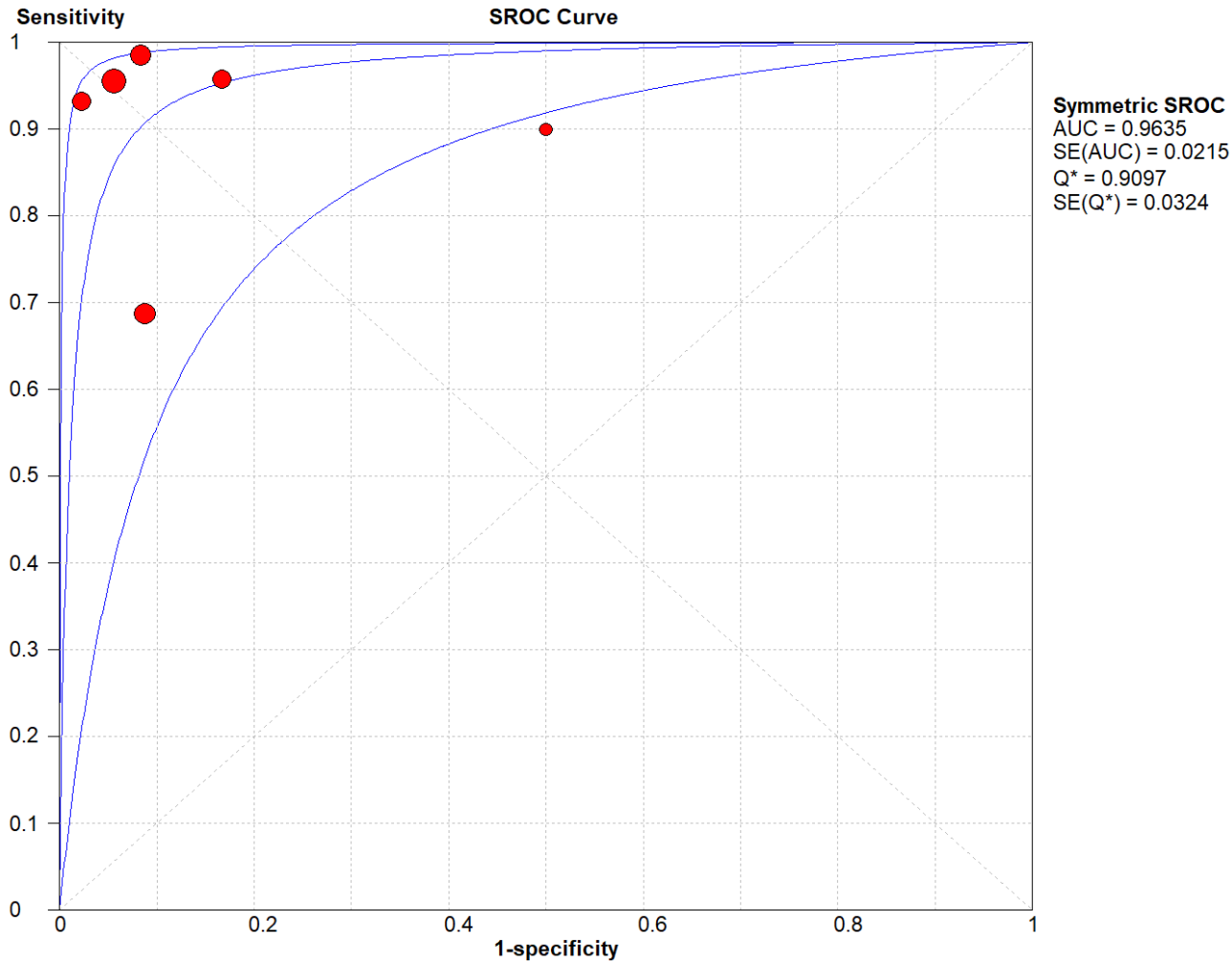

Figure2: The SROC curve of CEUS

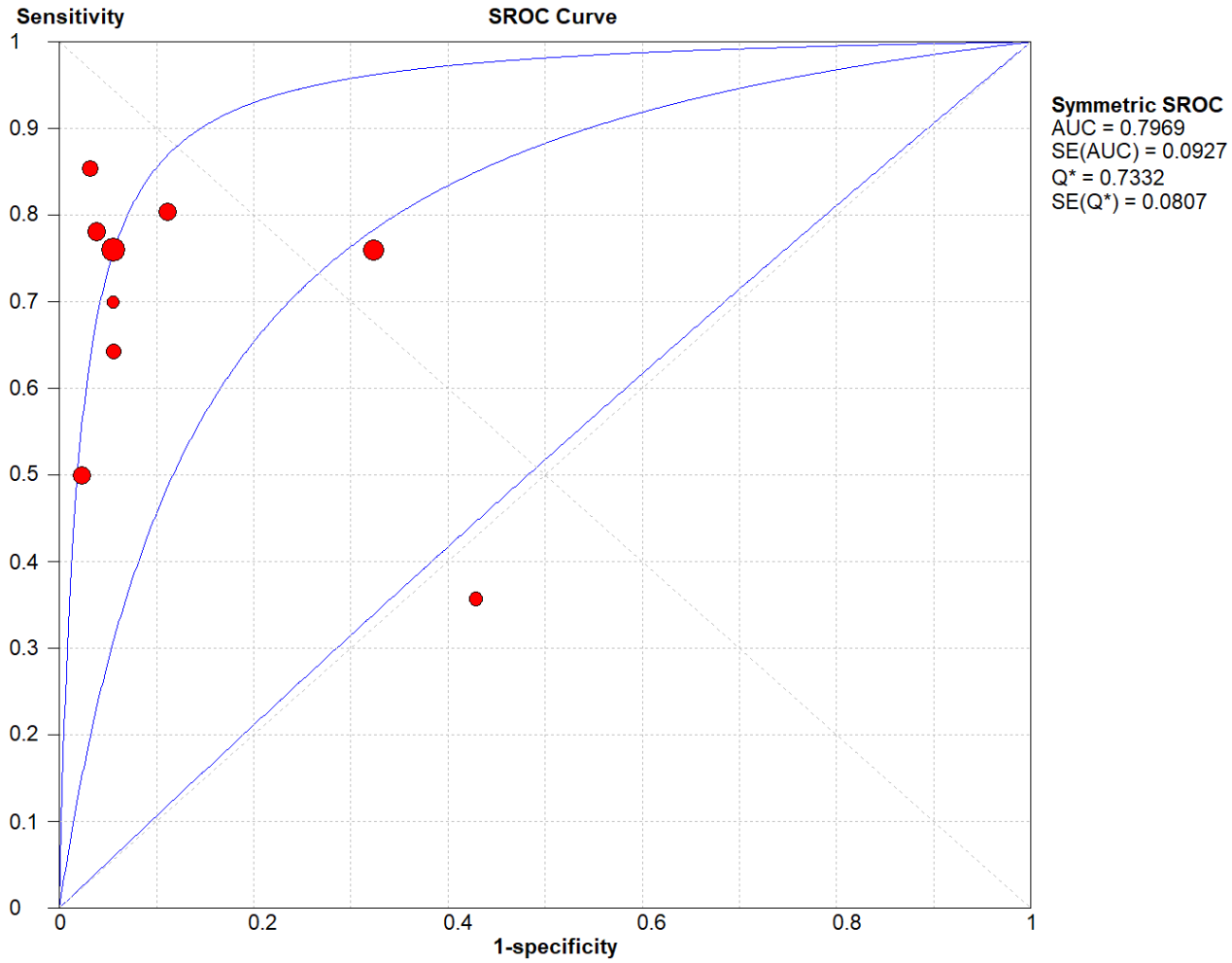

Figure3: The SROC curve of CECT

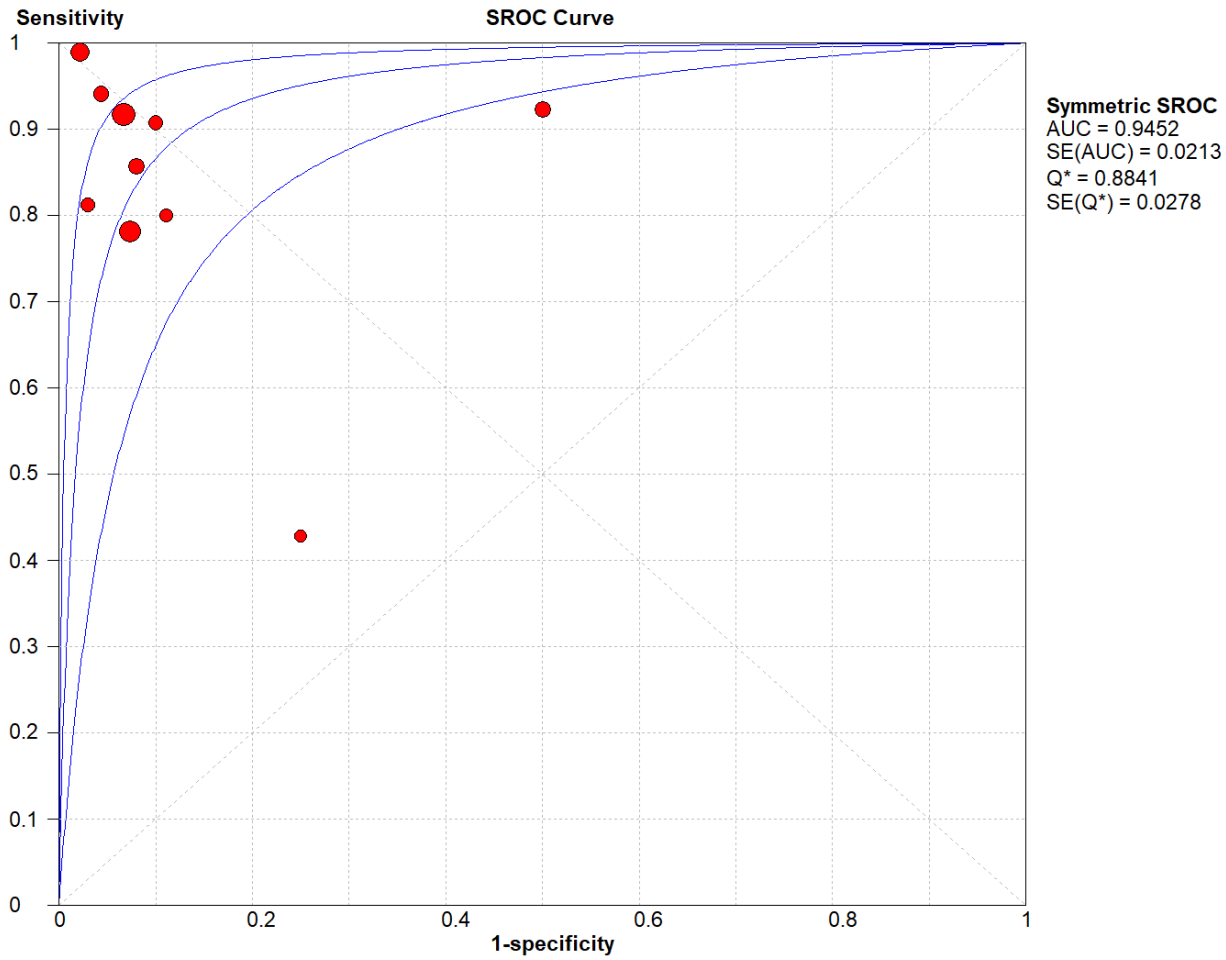

Figure4: The SROC curve of CEMRI

DISCUSSION

TACE is considered the best option for the intermediate stage of HCC and an accurate assessment of tumor response is essential for clinical management and clinical outcomes. The disappearance of tumor arterial hyperenhancement on assessing imaging after treatment defines tumor necrosis and the efficacy of treatment associated with improved survival rate in HCC patients. Additionally, Successful TACE is defined by the complete occlusion of tumor feeding arterials; however, the residual blood flow of tumor was reported with up to 75%; repeat TACE or alternative treatment are required to achieve complete occlusion of feeding

arterials of tumors and to improve the survival rate of patients after treatment (56-58). At present, CECT or CEMRI is considered as the reference standard imaging option to evaluate the treatment response of tumor necrosis after TACE and the standard recommended time for the imaging follow-up is from 4 to 6 weeks. Apart from CECT and CEMRI, CEUS is low cost and accurate in the evaluation of tumor residual blood flow at 1 to 2 weeks after TACE (59, 60).

Furthermore, the study by Ipek Oezdemir et al (2020) showed that TACE is a method to restrict the tumor feeding vessels and its characteristic of vascular morphology may provide predictive information of treatment response and decision making during TACE treatment. The prediction of HCC response to TACE using vascular morphologic features in CEUS assessment reveals the results that sensitivity, specificity, and accuracy were 89%, 82% , and 86% respectively (61). This is the first comprehensive meta-analysis evaluating the diagnostic ability of CEUS, CECT, and CEMRI of viable HCC after TACE. The objective of this study was to make a comprehensive evaluation of the efficacy of assessing diagnostic imaging modalities which may be a scientific and reasonable choice based on evidence-based medicine. According to the results from the analysis of included studies, CEUS, CECT, or CEMRI were simultaneously used with the reference standard for the assessing diagnosis of HCC in each patient after TACE.

Because the results of the individual study were unstable and can be affected by many confounding factors so that we extracted data of individual study and the diagnostic accuracy statistics were pooled. The pooled results achieved by meta-analysis enlarged the sample sizes and enhanced the statistical power, providing accurate and reliable evidence for a better conclusion in diagnostic accuracy study of the routine medical practice of medical imaging.

In this meta-analysis, we included 19 previously published studies associated with imaging modalities including CEUS, CECT, or CEMRI to assess the viable HCC after TACE. The sample size ranged from 12 to 130 which were relatively small for diagnostic accuracy study (DAS).

The sensitivity, specificity, +LR, -LR, and DOR were pooled by the random-effect model because of significant heterogeneity (I2>50% and/or P<0.05) except DOR of CEMRI which

were pooled by fixed effect model due to not significant heterogeneity (I2<50% and/or P>0.05). The area under the ROC curve (AUC) is a reflection of how good the test is at distinguishing patients with or without the target disorder. AUCs of CEUS, CECT, and CEMRI were 0.9635, 0.7969, and 0.9452, respectively; CEUS is better than CECT and CEMRI in assessing diagnosis of viable HCC after TACE. Additionally, the DOR is considered as an indicator of ranking for comparative diagnostic tests (62). According to our results, the DOR of CEUS, CECT, and CEMRI were 101.74, 19.89, and 53.56, respectively. CEUS achieved the highest DOR; therefore, these results indicated that CEUS is better than CEMRI and CECT for assessing diagnosis of viable HCC after TACE. To minimize the risk of bias in the study selection and data extraction, reviewers independently selected clinical studies based on the inclusion criteria and the quality assessment was evaluated by using the standardized form of QUADAS-2 which is an evidence-based quality assessment tool developed for the use in systematic reviews and meta-analysis of studies of diagnostic test accuracy (DTA). However, this meta-analysis has 2 limitations. First, the number of included studies is relatively small and the sources of heterogeneity for the analysis were limited. We acknowledge the limitations of our study because it was a meta-analysis and the validity of our results is dependent on the validity of the included studies. Second, only studies published in English were systematically searched in the database and included in this meta-analysis. Hence, further relevant and multi-center studies or trials for assessment of CEUS in comparison with CECT or CEMRI are necessary needed.

CONCLUSION

In conclusion, this comprehensive meta-analysis revealed that CEUS is comparable to CEMRI and CECT for the assessing diagnosis of viable HCC. The diagnostic value of CEUS and CEMRI in the assessment of viable HCC after TACE suggests that both CEUS and CEMRI may play important roles in oncology management and clinical practice.

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