AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

Asian Journal of Medicine and Biomedicine

Diagnostic Accuracy of Conventional Ultrasound (US) Compared to Contrast Enhanced Ultrasound (CEUS) for Diagnosing Liver Tumours : A Systematic Review and Meta-analysis

Davamunisvari Rames*, Ali Azlinawati, Fairuz Mohd Nasir

School of Medical Imaging, Faculty of Health Sciences, Universiti Sultan Zainal Abidin, Gong Badak Campus, 21300, Kuala Nerus, Terengganu

Corresponding author: davamunisvari@gmail.com

Received: 31st July 2023 **Accepted: 30th November 2023** **Published: 24th December 2023**

Abstract

This study is focuses on comparing the diagnostic accuracy of conventional ultrasound (US) and contrast enhanced ultrasound (CEUS) in detecting and characterizing liver tumours, addressing the challenge of distinguishing between benign and malignant tumours. Following Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, a comprehensive search of databases was conducted from inception to March 31, 2023 with specific keywords. The Quality Assessment of Diagnostic Performance Studies (QUADAS-2) was employed to evaluate the reliability of included studies. The study encompassed 11 selected studies involving 1605 patients, published between 2022 till 2004. Comparing conventional US and CEUS, CEUS demonstrated notably high diagnostic accuracy in identifying liver tumours. Pooled estimates for diagnostic accuracy (95% CI) favoured CEUS over conventional US in differentiating benign and malignant tumours. Specifically, CEUS exhibited a sensitivity of 0.89 (95% CI: 0.87-0.90) and specificity of 0.80 (95% CI: 0.78-0.82), surpassing conventional US with a sensitivity of 0.51 (95% CI: 0.49-0.53) and specificity of 0.44 (95% CI: 0.42-0.53). In conclusion, the study emphasizes the significant role of CEUS in clinical practice, particularly in detecting and diagnosing liver tumours. The results advocate for the integration of CEUS into diagnostic protocols to enhance outcomes for patients with liver tumours. The rigorous methodology, adherence to PRISMA guidelines, and application of QUADAS-2 enhance the credibility and applicability of the study's findings in the context of liver tumour diagnosis and treatment.

Keywords

diagnostic accuracy, contrast-enhanced ultrasound, conventional ultrasound, liver tumours, meta-analysis, systematic review.

Introduction

Liver tumours, encompassing both primary and secondary malignancies, represent a significant global health concern [1-3]. Treatment planning and patient management require accurate and timely diagnosis. Due to its non-invasive nature, cost-effectiveness, and real-time imaging capabilities, ultrasonography is

https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb

widely used for liver tumour assessment [4]. In spite of this, conventional ultrasound (US) has inherent limitations, particularly when it comes to identifying benign and malignant liver tumours [5-6].

Recent studies have shown that contrast-enhanced ultrasound (CEUS) can enhance the accuracy of liver tumour detection and characterization [7-8]. CEUS employs the intravenous administration of micro-bubble contrast agents to improve the visualization and evaluation of vascularity within liver tumours. These contrast agents enhance the acoustic signals, enabling better differentiation of liver tumours from the surrounding parenchyma and facilitating the characterization of their vascular patterns [7-9].

Furthermore, accurate differentiation between benign and malignant liver tumours is critical for appropriate treatment planning and patient management. Conventional US has inherent limitations in distinguishing between these two categories of liver tumours, often necessitating further invasive procedures or additional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) [10-11]. It has been demonstrated that CEUS overcomes these limitations by providing a real-time assessment of tumour vascularity, improving the characterization of liver tumours, and reducing the need for invasive procedures [7, 12].

CEUS is increasingly being used as a diagnostic tool for liver tumours, but a comprehensive literature review and meta-analysis is needed to consolidate the existing findings and determine whether CEUS is as accurate when it comes to diagnostic accuracy as conventional US. By reviewing the literature in this way, gaps in evidence and inconsistencies can be identified. In addition, it will be a valuable resource for clinicians, radiologists, and researchers when determining when and how to use CEUS in liver tumour diagnosis and management.

The results of this research have significant implications for clinical practice. If CEUS proves to be more accurate in terms of diagnostic accuracy than conventional US, this could improve the early detection of liver tumours and patient outcomes. Moreover, a comprehensive evaluation of CEUS will contribute to the body of knowledge surrounding liver tumour imaging and guide clinicians in selecting the most appropriate imaging modality based on individual patient characteristics.

In a nutshell, liver tumours present significant challenges in diagnosis and treatment planning. Conventional US has limitations in accurately detecting and characterizing liver tumours, particularly the differentiation of benign and malignant liver tumours. CEUS offers improved diagnostic accuracy by enhancing the visualization of vascularity within liver tumours. In this systematic literature review and meta-analysis, the aim is to evaluate whether conventional US is as accurate as CEUS in identifying benign from malignant tumours. By analysing the available evidence thoroughly, this study aims to enhance understanding of how CEUS may improve liver tumour management and outcomes.

Materials and Methods

Study design

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this systematic literature review and meta-analysis was conducted [13]. As all data are publicly available, approval from the research ethics board was not required.

Literature Search

The Scopus, PubMed, and Cochrane Library were searched extensively for studies evaluating conventional US and CEUS as diagnostic accuracy methods to differentiate benign liver tumours from malignant liver tumours from inception until March 31, 2023. The PICOTS principle was applied to this study search [13]. It consists of a Population, Intervention, Comparator, Outcomes, Time, and Study design. Besides, the following search terms were used with different combinations in different databases as follows: '(contrast-

enhanced ultrasound OR CEUS) AND (conventional ultrasound OR ultrasound) AND (liver tumours OR liver lesions).' Additional search filters, including publication date ranges and language restrictions, were applied to focus the search results. Manual scanning of the reference list of the eligible citations was done to find any relevant studies. The retrieved search results from database searches were exported to a Microsoft Excel document for duplication removal and screening with bibliographic data and abstracts.

Study Screening

This study included and excluded results according to its inclusion and exclusion criteria. Following were the inclusion criteria: (1) population: patient diagnosed with liver tumours, (2) intervention: CEUS, (3) comparator: compared to conventional US, (4) outcomes: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), (5) time: inception to 31st March, 2023 and (6) study design: diagnostic accuracy study. These were the criteria for exclusion: (1) animal or paediatric studies, (2) less than 10 liver tumours studied, (3) patient received only either conventional US or CEUS, (4) case-control study, case series, expert opinions, and conference articles and (5) incomplete accessible data. At each step of the review process, an author reviewed the title, abstract, and full text of each article. As a result of reviewing the debated studies based on the pre-specified PICOTS criteria, all disagreements were resolved after discussion with a senior author.

Data Extraction

The data extraction process was conducted to extract relevant information from the full-text papers of the eligible studies. The following data items were extracted to ensure a comprehensive analysis of the included studies date of data extraction, general information, study characteristics, participant characteristics, intervention, reference standard, and outcome data. The data extraction process followed a predefined data extraction form created specifically for this study by utilizing the guidance provided to develop a self-designed data extraction form [14]. The form was designed to capture the relevant data items consistently and systematically. Any uncertainties or ambiguities encountered during the extraction process were carefully addressed and resolved by referring to the senior author. The extracted data were then organized in a structured manner to facilitate further analysis and synthesis.

Quality Assessment

In each study, the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was used to assess the risk of bias and applicability [15]. A discussion with the senior author resolved any discrepancies. There are four domains in the QUADAS-2: patient selection, reference standard, index test, and flow and timing. The risk of bias is assessed for each domain, and applicability concerns are also considered for the first three domains. The risk of bias was categorized as high, low, or unclear for each domain. Those studies with at least one domain at high risk of bias, or all four domains at unclear risk of bias, were assessed as 'at risk' of bias [15]. The assessment was conducted using Microsoft Excel.

Data Analysis and Synthesis

Statistical analysis was conducted using Microsoft Excel. Estimates of the mean sensitivity and specificity of conventional US and CEUS for differentiation of benign and malignant liver tumours were determined by pooling data using an average weighted 95% confidence interval (95% CI) based on the Wilson interval score [16-17]. Forest plots were created showing the point estimates and 95% CIs of the point estimates [18-19].

Results

Selection of Studies

The search yielded a total of 373 records. After removing duplicates, a total of 370 unique records remained. These records were then screened based on their titles and abstracts to assess their relevance to the research objectives. During this screening process, 211 records were excluded as they did not meet the predetermined inclusion criteria. The remaining 159 full-text articles were retrieved for a more

https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb

detailed assessment of eligibility. Following a thorough evaluation, 148 articles were excluded from the study with reasons. Finally, a total of 11 articles evaluating the diagnostic accuracy for differentiation of benign and malignant liver tumours using conventional US and CEUS [20-30]. A flow chart of the process for the studies included in this study can be found in Figure 1.

Patient and study characteristics

Patient and study characteristics are summarised in Table 1. A total of 2050 liver tumours in 1605 patients were included. The studies took place from 2022 until 2004 and represent works from multiple countries. The number of patients included in the studies varied from 39 to 456, with varying gender distribution across the studies. The mean or median age of the patients ranged from 43.96 to 65.00 years, reflecting a broad age range in the study populations. The mean or median size of the tumours ranged from 19.70 mm to 47.20 mm. The included studies encompassed a mixture of retrospective and prospective designs, with 3 studies classified as retrospective and 9 studies classified as prospective. Regarding image interpretation approaches, 3 studies did not specify their interpretation approach, while 2 studies reported using an unblinded approach. In contrast, 6 studies employed a blinded interpretation approach, where the interpreters were unaware of the clinical and imaging findings. Additionally, different contrast agents were utilized across the studies. Specifically, SonoVue was used in 9 studies, DEFINITY in 1 study, and Levovist in 1 study. The reference standards used for diagnosis also varied among the studies.

Diagnostic accuracy for differentiation of benign and malignant liver tumours

When differentiating between benign and malignant liver tumours, CEUS consistently shows higher specificity and sensitivity values compared to conventional US. In most studies, CEUS also demonstrates higher PPV and NPV than conventional US, indicating that CEUS is more accurate in identifying both malignant and benign liver tumours as shown in Table 2. Overall, CEUS appears to be a more effective diagnostic tool for differentiating liver tumours compared to conventional US.

Quality assessment of included studies

Besides, the quality assessment using the QUADAS-2 tool revealed low risks of bias in patient selection, index test, and reference standard domains for the majority of the included studies. However, some studies had unclear or high risks in certain domains, particularly in the interpretation of the index test and reference standard, as well as the flow and timing of the tests. These findings emphasize the importance of careful consideration of potential biases and applicability concerns when interpreting the results of the included studies. The quality assessment of the included 11 articles is also summarised in Figure 2.

Overall sensitivity and specificity of conventional US and CEUS

The overall sensitivity and specificity with its 95% CIs of conventional US and CEUS for differentiation of benign and malignant liver tumours are summarised in Figure 3. In both sensitivity and specificity, CEUS had a relatively a great diagnostic accuracy of all outcomes (sensitivity: 0.89 [0.87-0.90], specificity: 0.80 [0.78-0.82]) compared to conventional US (sensitivity: 0.51 [0.49-0.53], specificity: 0.44 [0.42-0.53]).

AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

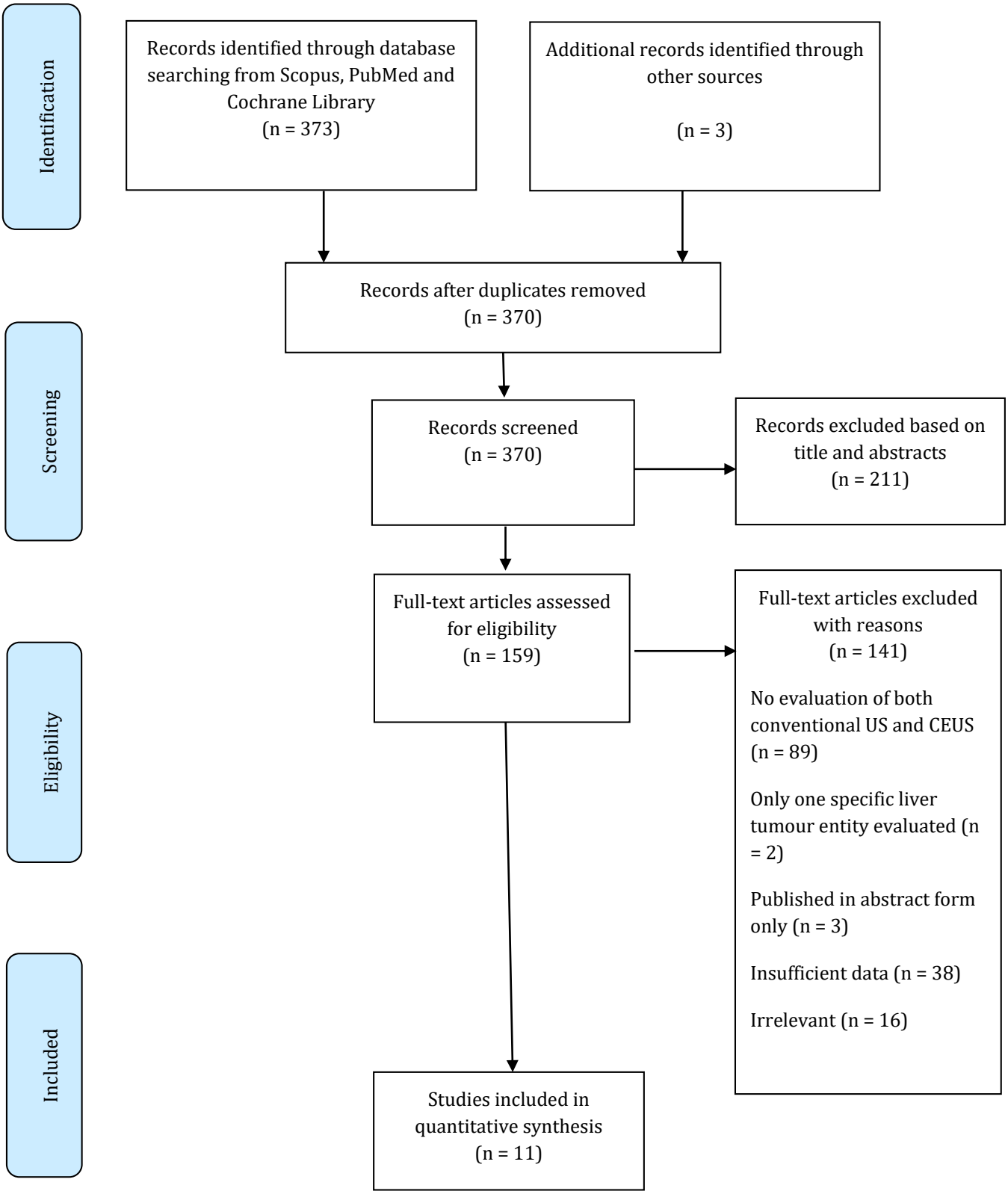


Figure 1: A Prisma chart illustrating the inclusion studies

AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

Table 1: Patient and study characteristics of the included studies

Author	Year	Country	Patient	Patient Characteristics				Study Characteristics			
				Gender		Mean/Median Age (range) (yrs)	Mean/Median size of tumours (range) (mm)	Contrast Agent	Reference Standard	Image Interpretation	Study Type
				Male	Female						
Liu	2022	China	60	36	24	Mean = 49.16 (n/a)	n/a	SonoVue	Pathology	Unclear	Retrospective
Burrowes	2021	Canada	214	93	121	Mean = 57.00 (21 – 96)	n/a	DEFINITY	Pathology or expert consensus	Blinded	Prospective
Moga	2021	Romania	91	47	44	Mean = 62.30 (n/a)	n/a	SonoVue	CECT, CEMRI or biopsy	Blinded	Retrospective
Hu	2019	China	136	75	61	Mean = 43.96 (31 – 83)	Mean = 47.20 (17.1 – 113.2)	SonoVue	CECT, CEMRI, histopathology or diagnostic	Blinded	Retrospective
Zhang	2014	China	156	102	54	Mean = 50.70 (18 – 83)	Mean = 30.00 (60 -121)	SonoVue	CT, MRI, DSA or biopsy/ surgery	Blinded	Prospective
Zuber	2009	Germany	86	55	31	Median = 65 (24 – 88)	Mean = 33.00 (9 – 100)	SonoVue	Histology, CT/NMR or CHI with qontrast	Unclear	Prospective
Trillaud	2009	France	123	54	73	Mean = 54.80 (19 – 93)	n/a	SonoVue	CT, MRI, US, clinical data, biochemical marker or histology	Not blinded	Prospective
Chami	2008	France	116	75	41	Mean = 60.50 (30 – 86)	Mean = 19.70 (3 – 160)	SonoVue	CT, MRI, PET or combination of these techniques	Not blinded	Prospective
D'Onofrio	2008	Italy	128	80	48	Mean = 46.00 (21 – 83)	Mean = 23.70 (50 - 180)	SonoVue	Fine-needle biopsy, CT, MRI, DSA	Unclear	Prospective

AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

Dai	2007	China	456	295	61	Mean = 54.50 (20 – 80)	n/a	SonoVue	Histopathology, CECT or CEMRI	Blind	Prospective
Klein	2004	Germany	39	25	14	Mean = 56.00 (21 – 86)	Mean = 46.00 (10 – 155)	Levovist	Histology	Blind	Prospective

Abbreviations: CECT, contrast enhanced computed tomography; CEMRI, contrast enhanced magnetic resonance imaging; CT, computed tomography; DSA, digital subtraction angiography; mm, millimetre; n/a, not available; MRI, magnetic resonance imaging; PET, positron emission tomography; US, ultrasound; yrs, years

Table 2: Diagnostic accuracy of benign and malignant from inclusion studies

Author	Year	Country	Patient	No. of tumour for analysis	No. of tumours of final diagnosis from reference standard		Malignancy prediction							
							Conventional US (%)				CEUS (%)			
					Benign	Malignant	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV
Liu	2022	China	60	85	30	55	70.90	83.30	n/a	n/a	92.70	93.30	n/a	n/a
Burrowes	2021	Canada	214	214	114	100	82.00	56.00	60.00	78.00	95.00	82.00	82.00	95.00
Moga	2021	Romania	91	91	40	51	15.60	84.60	57.10	43.40	74	45.70	72.50	64.20
Hu	2019	China	136	158	64	94	82.56	68.06	75.53	76.56	92.39	86.36	90.43	89.06
Zhang	2014	China	156	170	58	112	57.10	43.10	65.90	34.30	92.90	89.70	94.60	78.80
Zuber	2009	Germany	86	100	45	55	71.00	56.00	71.00	64.00	93.00	78.00	82.00	76.00
Trillaud	2009	France	123	123	68	55	40.00	36.80	n/a	n/a	98.20	88.20	n/a	n/a
Chami	2008	France	116	306	73	233	58.80	50.70	n/a	n/a	68.70	67.00	n/a	n/a
D'Onofrio	2008	Italy	128	207	101	106	85.80	57.40	67.90	79.40	96.20	97.00	97.10	96.10
Dai	2007	China	456	554	208	346	40.50	14.40	n/a	n/a	88.20	77.90	n/a	n/a
Klein	2004	Germany	39	42	7	29	66.00	26.00	73.00	45.00	83.00	49.00	65.00	82.00

Abbreviations: CEUS, contrast enhanced ultrasound; no, number; NPV, negative predicative value; PPV, positive predicative value; Se, sensitivity; Sp, specificity; US, ultrasound

AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

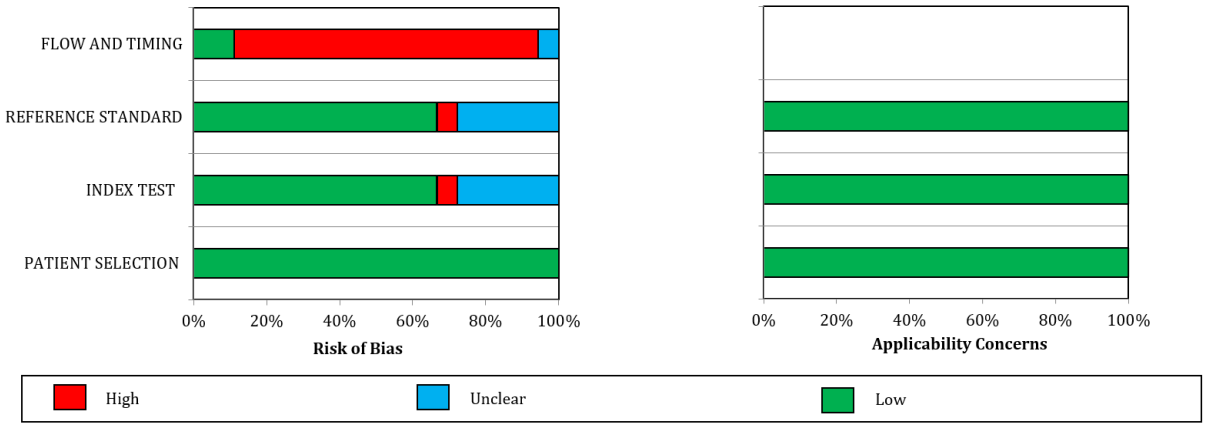


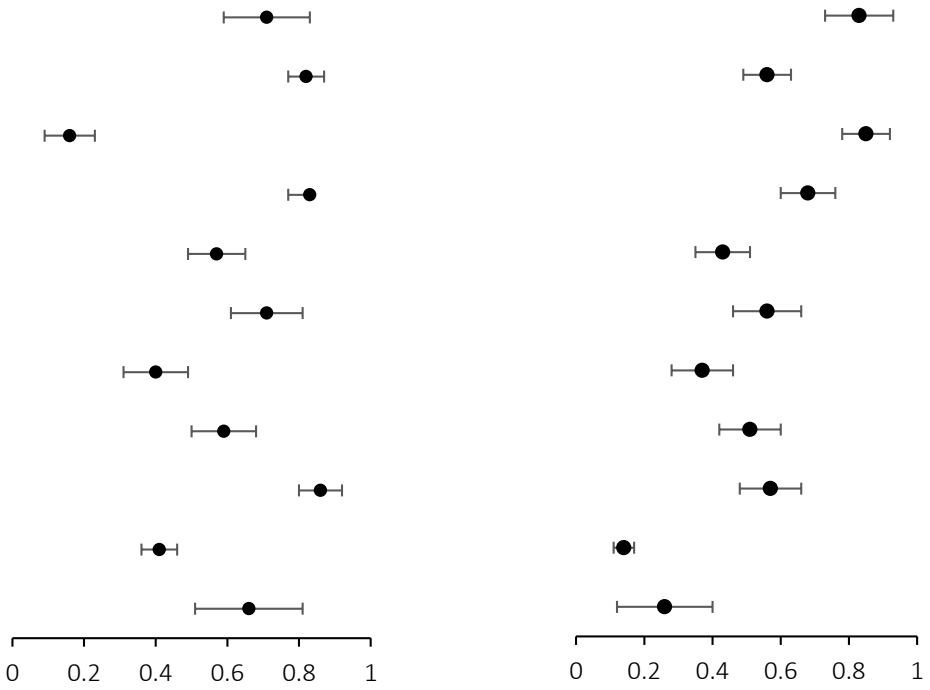
Figure 2: Graph depicting the risk of bias and applicability concerns

Table 3: The overall sensitivity and specificity of conventional US and CEUS for differentiation of benign and malignant liver tumours

Conventional US				
Study	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Liu 2022	0.71 [0.59, 0.83]	0.83 [0.73, 0.93]		
Burrowes 2021	0.82 [0.77, 0.87]	0.56 [0.49, 0.63]		
Moga 2021	0.16 [0.09, 0.23]	0.85 [0.78, 0.92]		
Hu 2019	0.83 [0.77, 0.83]	0.68 [0.60, 0.76]		
Zhang 2014	0.57 [0.49, 0.65]	0.43 [0.35, 0.51]		
Zuber 2009	0.71 [0.61, 0.81]	0.56 [0.46, 0.66]		

AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

Trillaud 2009	0.40 [0.31, 0.49]	0.37 [0.28, 0.46]
Chami 2008	0.59 [0.50, 0.68]	0.51 [0.42, 0.60]
D'Onofrio 2008	0.86 [0.80, 0.92]	0.57 [0.48, 0.66]
Dai 2007	0.41 [0.36, 0.46]	0.14 [0.11, 0.17]
Klein 2004	0.66 [0.51, 0.81]	0.26 [0.12, 0.40]
Pooled estimates	**0.51 [0.49, 0.53]**	**0.44 [0.42, 0.53]**

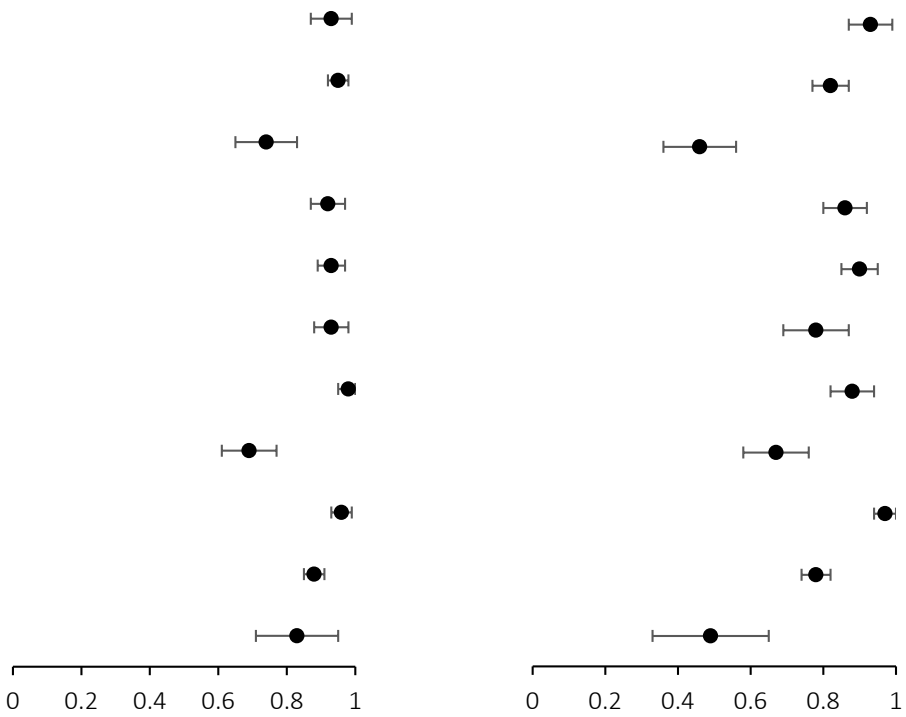


CEUS

Study	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Liu 2022	0.93 [0.87, 0.99]	0.93 [0.87, 0.99]		
Burrowes 2021	0.95 [0.92, 0.98]	0.82 [0.77, 0.87]		

AJMB
eISSN: 2600-8173
https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb
PENERBIT
Universiti Sultan Zainal Abidin

Moga 2021	0.74 [0.65, 0.83]	0.46 [0.36, 0.56]
Hu 2019	0.92 [0.87, 0.97]	0.86 [0.80, 0.92]
Zhang 2014	0.93 [0.89, 0.97]	0.90 [0.85, 0.95]
Zuber 2009	0.93 [0.88, 0.98]	0.78 [0.69, 0.87]
Trillaud 2009	0.98 [0.95, 1.00]	0.88 [0.82, 0.94]
Chami 2008	0.69 [0.61, 0.77]	0.67 [0.58, 0.76]
D'Onofrio 2008	0.96 [0.93, 0.99]	0.97 [0.94, 1.00]
Dai 2007	0.88 [0.85, 0.91]	0.78 [0.74, 0.82]
Klein 2004	0.83 [0.71, 0.95]	0.49 [0.33, 0.65]
Pooled estimates	**0.89 [0.87, 0.90]**	**0.80 [0.78, 0.82]**



https://doi.org/10.37231/ajmb.2023.1.S.670
https://journal.unisza.edu.my/ajmb

Discussion

In our knowledge, this is the first systematic literature review and meta-analysis to compare conventional US and CEUS in differentiating benign and malignant liver tumours. The results obtained from multiple studies demonstrated that CEUS outperformed conventional US in terms of sensitivity and specificity. The pooled estimate of CEUS was found to be 0.89 (95% CI 0.87 – 0.90), compared to 0.51 (95% CI 0.49 – 0.53) for conventional US from this study in term of sensitivity. This indicates that CEUS has a higher ability to correctly identify malignant liver tumours, reducing the chances of false-negative results. Due to its capacity to offer a real-time assessment of vascularity and enhancement patterns, which helps in identifying unusual blood flow and differentiating between benign and malignant tumours, CEUS has a higher sensitivity than other imaging techniques. A number of studies lend credence to these findings [20, 23-24, 28].

Parallel to this, conventional US had a lower specificity of 0.44 (95% CI 0.42 – 0.53) while CEUS had a higher pooled estimate specificity of 0.80 (95% CI 0.78 – 0.82) based on the findings of the study. A higher specificity indicates that CEUS is better at correctly classifying benign liver tumours, minimizing false-positive results. CEUS allows for the detailed analysis of hemodynamic and blood flow in tumours, which helps in identifying characteristic enhancement patterns associated with different types of liver tumours. The studies also support the improved specificity of CEUS over conventional US [21-22, 25].

The supporting evidence from the literature further strengthens the superiority of CEUS in differentiating benign and malignant liver tumours. The use of micro-bubble contrast agents in CEUS allows for the evaluation of hemodynamic characteristics and blood flow dynamics in liver tumours. The presence or absence of washout, a key feature in distinguishing benign from malignant tumours, can be effectively observed using CEUS. Additionally, CEUS provides real-time arterial phase imaging, enabling the recognition of specific enhancement patterns associated with different types of tumours allowing for the immediate assessment of vascularity and perfusion within liver tumours. This real-time imaging aids in the precise characterization of liver tumours, such as metastatic tumours, cholangiocarcinomas, and hepatocellular carcinomas. Studies have highlighted the advantageous features of CEUS over conventional US [23, 31-33].

In contrast, the conventional US approach faces limitations in its ability to precisely identify and characterize liver tumours, relying primarily on morphological factors, that may not always be sufficient for accurate differentiation. Prior studies have elucidated that the sensitivity and specificity of conventional US consistently fall short compared to CEUS [34-36]. The findings of this study underscore the enhanced diagnostic accuracy afforded by CEUS in comparison to conventional US. Notably, CEUS exhibit superior sensitivity and specificity, positioning it as a valuable tool for differentiating between benign and malignant liver tumours. Building on previous research, the limitations of conventional US in effectively distinguishing between these tumour types have been identified. Moreover, CEUS's capacity for real-time assessment of vascularity, enhancement patterns, and blood flow dynamics further accentuates its superiority over conventional US [34-36]. This comprehensive evaluation highlights the incremental benefits of CEUS, emphasizing its potential as an indispensable diagnostic modality in liver tumour characterization.

Furthermore, the results obtained from multiple studies support the notion that CEUS has a significant added value in distinguishing between benign and malignant liver tumours when compared to conventional US. The higher sensitivity and specificity of CEUS demonstrate its superiority in accurately identifying and characterizing liver tumours. The unique advantages of CEUS, including its ability to assess hemodynamic and provide real-time imaging of vascularity, make it a valuable tool in clinical practice for improved liver tumour diagnosis. It is necessary to conduct more research and clinical validation in order to fully explore the potential of CEUS for the evaluation of liver tumours and make it an integral part of routine clinical practice.

Additionally, conventional US features were extensively investigated in several studies for their utility in differentiating between malignant and benign lesions. Common features explored included lesion size, shape, margins, echogenicity, and the presence of calcifications. Malignant tumours often exhibited irregular shapes, poorly defined margins, hypoechoic or heterogenous echogenicity, and the presence of microcalcifications, contrasting with the more regular, well-defined, hypoechoic or isoechoic, and often calcification-free characteristics of benign lesions.

There are some limitations on this study that should be considered while analysing the findings. The generalizability and reliability of these findings are impacted by the disparities in sample sizes and study designs, the retrospective character of some studies, inter-observer variability, and the absence of standardised methods for conventional US and CEUS. Standardisation is crucial to ensure consistency and comparability across different studies, enhancing the reliability and reproducibility of the results. In the case of conventional US, standardisation may involve defining specific imaging parameters such as transducer frequency, gain settings, and image acquisition techniques to minimize variability in image quality. For CEUS, standardisation extends to the administration of contrast agents, imaging protocols during the contrast phase, and criteria for lesion characterisation. This includes the timing of contrast injection, duration of imaging, and the specific criteria used to classify enhancement patterns. Lack of standardisation in these aspects can lead to variations in results, making it challenging to draw definitive conclusions or generalise findings across studies. Despite these limitations, this study provides valuable insights into the diagnostic accuracy of conventional US and CEUS in the context of liver tumours, highlighting the need for further research and standardization in this field.

Based on this systematic review and meta-analysis of the diagnostic accuracy of conventional US compared to CEUS in liver tumour evaluation, this study recommends conducting larger prospective studies, establishing consensus guidelines, exploring the potential of machine learning algorithms, and addressing the limitations identified. These recommendations will contribute to advancing the field and improving the clinical utility of CEUS in the diagnosis and management of liver tumours.

Conclusion

This study provides compelling evidence supporting the high diagnostic accuracy of CEUS compared to conventional US in the diagnosing of liver tumours. The potential of CEUS in differentiating benign and malignant liver tumours underscores its significance in clinical practice. While acknowledging the limitations of this study, the findings emphasize the value of CEUS as a valuable tool in the diagnosis and management of liver tumours.

Abbreviations

95% CI, 95% confidence interval; CEUS, contrast enhanced ultrasound; CT, computed tomography; mm, millimetre; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; QUADAS-2, Quality Assessment of Diagnostic Performance Studies-2; US, ultrasound

Funding

This study was not supported by any specific funding.

Acknowledgements

Dr Azlinawati Ali, PhD and Dr Fairuz Mohd Nasir, PhD are thanked for their significant and persistent support, which led to the creation of this manuscript.

Conflict of Interest Disclosure

There is none to declare.

References

1. Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D. Hepatocellular carcinoma (HCC): Epidemiology, etiology and molecular classification. In: *Advances in Cancer Research*. Elsevier BV; 2021:1-61. doi:10.1016/bs.acr.2020.10.001
2. Oh JH, Jun DW. The latest global burden of liver cancer: A past and present threat. *Clinical and Molecular Hepatology*. 2023;29(2):355-357. doi:10.3350/cmh.2023.0070
3. Schöler D, Castoldi M, Jördens MS, et al. Enlarged extracellular vesicles are a negative prognostic factor in patients undergoing TACE for primary or secondary liver cancer–a case series. *PLOS ONE*. 2021;16(8):e0255983. doi:10.1371/journal.pone.0255983
4. Hydes TJ, Cuthbertson DJ, Palmer DH, et al. Ultrasonography in surveillance for hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. *Hepatoma Research*. 2023;9:12. doi:10.20517/2394-5079.2022.97
5. Hu J, Zhou Z, Ran H, Yuan XC, Zeng X, Zhang Z. Diagnosis of liver tumors by multimodal ultrasound imaging. *Medicine*. 2020;99(32):e21652. doi:10.1097/md.0000000000021652
6. Shah SS, Shukla A, Paunipagar BK. Radiological Features of Hepatocellular Carcinoma. *Journal of Clinical and Experimental Hepatology*. 2014;4:S63-S66. doi:10.1016/j.jceh.2014.06.009
7. Faccia M, Garcovich M, Ainora ME, et al. Contrast-Enhanced Ultrasound for Monitoring Treatment Response in Different Stages of Hepatocellular Carcinoma. *Cancers*. 2022;14(3):481. doi:10.3390/cancers14030481
8. Hsiao CY, Chen PS, Huang KW. A Prospective Assessment of the Diagnostic Value of Contrast-Enhanced Ultrasound, Dynamic Computed Tomography and Magnetic Resonance Imaging for Patients with Small Liver Tumors. *Journal of Clinical Medicine*. 2019;8(9):1353. doi:10.3390/jcm8091353
9. Chammas MC, Bordini A. Contrast-enhanced ultrasonography for the evaluation of malignant focal liver lesions. *Ultrasonography*. 2021;41(1):4-24. doi:10.14366/usg.21001
10. Dietrich CF, Sharma M, Gibson RA, Schreiber-Dietrich D, Jenssen C. Fortuitously discovered liver lesions. *World Journal of Gastroenterology*. 2013;19(21):3173. doi:10.3748/wjg.v19.i21.3173
11. Rantala ES, Peltola E, Helminen H, Hernberg M, Kivelä T. Hepatic Ultrasonography Compared With Computed Tomography and Magnetic Resonance Imaging at Diagnosis of Metastatic Uveal Melanoma. *American Journal of Ophthalmology*. 2020;216:156-164. doi:10.1016/j.ajo.2020.03.049
12. Fang C, Anupindi SA, Back SJ, et al. Contrast-enhanced ultrasound of benign and malignant liver lesions in children. *Pediatric Radiology*. 2021;51(12):2181-2197. doi:10.1007/s00247-021-04976-2
13. Kim KW, Lee J, Choi SH, Huh J, Park SH. Systematic Review and Meta-Analysis of Studies Evaluating Diagnostic Test Accuracy: A Practical Review for Clinical Researchers-Part I. General Guidance and Tips. *Korean Journal of Radiology*. 2015;16(6):1175. doi:10.3348/kjr.2015.16.6.1175
14. Petticrew, M. and Roberts, H. (2012) Systematic reviews in the Social Sciences: A practical guide. Malden (Mass.): Blackwell Publishing.
15. Whiting PF. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Annals of Internal Medicine*. 2011;155(8):529. doi:10.7326/0003-4819-155-8-201110180-00009
16. Liu Y, Tsalik EL, Jiang Y, et al. Average Weighted Accuracy: Pragmatic Analysis for a Rapid Diagnostics in Categorizing Acute Lung Infections (RADICAL) Study. *Clinical Infectious Diseases*. 2019;70(12):2736-2742. doi:10.1093/cid/ciz437
17. Erdoğan S, Gülhan O. Alternative Confidence Interval Methods Used in the Diagnostic Accuracy Studies. *Computational and Mathematical Methods in Medicine*. 2016;2016:1-7. doi:10.1155/2016/7141050
18. Hernaez R, Lazo M, Bonekamp S, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis. *Hepatology*. 2011;54(3):1082-1090. doi:10.1002/hep.24452
19. Li X, Song J, Sun ZJ, Yang Y, Deng S, Wang H. Conventional Ultrasound and Contrast-Enhanced Ultrasound in the Diagnosis of Splenic Diseases. *Journal of Ultrasound in Medicine*. 2020;39(9):1687-1694. doi:10.1002/jum.15291

20. Liu L, Liu GL, Yi L, Yan HQ, Feng B. An ultrasonography-based contrast-enhanced for distinguishing between benign and malignant hepatocellular carcinoma. *Materials Express*. 2022;12(8):1135-1139. doi:10.1166/mex.2022.2254
21. Burrowes DP, Medellin A, Harris A, Milot L, Lethebe BC, Wilson SR. Characterization of Focal Liver Masses: A Multicenter Comparison of Contrast-Enhanced Ultrasound, Computed Tomography, and Magnetic Resonance Imaging. *Journal of Ultrasound in Medicine*. 2021;40(12):2581-2593. doi:10.1002/jum.15644
22. Moga T, David C, Popescu A, et al. Multiparametric Ultrasound Approach Using a Tree-Based Decision Classifier for Inconclusive Focal Liver Lesions Evaluated by Contrast Enhanced Ultrasound. *Journal of Personalized Medicine*. 2021;11(12):1388. doi:10.3390/jpm11121388
23. Hu J, Zhou Z, Ran H, Yuan XC, Zeng X, Zhang Z. Diagnosis of liver tumors by multimodal ultrasound imaging. *Medicine*. 2020;99(32):e21652. doi:10.1097/md.0000000000021652
24. Zhang P, Zhou P, Tian S, Qian Y, Li J, Li R. Diagnostic Performance of Contrast-Enhanced Sonography and Acoustic Radiation Force Impulse Imaging in Solid Liver Lesions. *Journal of Ultrasound in Medicine*. 2014;33(2):205-214. doi:10.7863/ultra.33.2.205
25. Zuber-Jerger I, Schacherer D, Woenckhaus M, Jung EM, Schölmerich J, Klebl F. Contrast-enhanced ultrasound in diagnosing liver malignancy. *Clinical Hemorheology and Microcirculation*. January 2009. doi:10.3233/ch-2009-1225
26. Trillaud H, Bruel JM, Valette PJ, et al. Characterization of focal liver lesions with SonoVue®-enhanced sonography: International multicenter-study in comparison to CT and MRI. *World Journal of Gastroenterology*. 2009;15(30):3748. doi:10.3748/wjg.15.3748
27. Chami L, Lassau N, Malka D, et al. Benefits of Contrast-Enhanced Sonography for the Detection of Liver Lesions: Comparison with Histologic Findings. *American Journal of Roentgenology*. 2008;190(3):683-690. doi:10.2214/ajr.07.2295
28. D'Onofrio M, Faccioli N, Zamboni G, et al. Focal liver lesions in cirrhosis: value of contrast-enhanced ultrasonography compared with Doppler ultrasound and α-fetoprotein levels. *Radiologia Medica*. 2008;113(7):978-991. doi:10.1007/s11547-008-0316-z
29. Dai Y, Chen MH, Yin S, et al. Focal Liver Lesions. *Investigative Radiology*. 2007;42(8):596-603. doi:10.1097/rli.0b013e318050ab29
30. Klein D, Jenett M, Gassel HJ, Sandstede J, Hahn D. Quantitative dynamic contrast-enhanced sonography of hepatic tumors. *European Radiology*. 2004;14(6):1082-1091. doi:10.1007/s00330-004-2299-z
31. Cantisani V, Wilson SR. CEUS: Where are we in 2015? *European Journal of Radiology*. 2015;84(9):1621-1622. doi:10.1016/j.ejrad.2015.05.028
32. Bhayana D, Kim TY, Jang HJ, Burns PC, Wilson SR. Hypervascular Liver Masses on Contrast-Enhanced Ultrasound: The Importance of Washout. *American Journal of Roentgenology*. 2010;194(4):977-983. doi:10.2214/ajr.09.3375
33. Quaia E, Calliada F, Bertolotto M, et al. Characterization of Focal Liver Lesions with Contrast-specific US Modes and a Sulfur Hexafluoride–filled Microbubble Contrast Agent: Diagnostic Performance and Confidence. *Radiology*. 2004;232(2):420-430. doi:10.1148/radiol.2322031401
34. Zhang J, Yu Y, Li Y, Wei L. Diagnostic value of contrast-enhanced ultrasound in hepatocellular carcinoma: a meta-analysis with evidence from 1998 to 2016. *Oncotarget*. 2017;8(43):75418-75426. doi:10.18632/oncotarget.20049
35. Harvey CM, Albrecht T. Ultrasound of focal liver lesions. *European Radiology*. 2001;11(9):1578-1593. doi:10.1007/s003300101002
36. Rettenbacher T. Focal liver lesions: Role of contrast-enhanced ultrasound. *European Journal of Radiology*. 2007;64(2):173-182. doi:10.1016/j.ejrad.2007.07.026