Diagnostic Value Of Contrast Enhanced Ultrasound (CEUS) Compared To Standard Imaging Techniques For Evaluation Of Hepatic Lesions: A Systematic Review

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Abstract
Background: Liver metastasis is a critical concern in the realm of cancer, underscoring the importance of vigilant surveillance, accurate diagnosis, and timely detection. Contrast-Enhanced Ultrasound (CEUS) has the potential to be used as a diagnostic tool in detecting and diagnosing hepatocellular malignancies, lesions, and metastases in humans. This systematic review evaluates and summarises study results to compare the diagnostic value of CEUS to conventional imaging modalities of CT or MRI, providing valuable insights for the field.
Methods: A comprehensive literature search was performed using PubMed/Medline, Wiley Online library, and Research gate to identify articles reporting the diagnostic performance of CT and MRI for detecting hepatic lesions.
Results: A total of 11 studies were included in this review. Majority of studies (9 out of 11) concludes that CEUS has potential to become a useful diagnostic modality in diagnosis, as it shows comparable or better results to the standard techniques. Sensitivity and specificity averages were 85% and 82% for CEUS, 82.4% and 85% for CT, and 88.6% and 78% for MRI, respectively. While most studies favored CEUS, nuances exist, such as CEUS's limitations in deep liver regions and variations in sensitivity compared to MDCT.
Conclusion: CEUS shows high diagnostic performance for tumor differentiation, with a high predictive value for malignant lesion. The results from the 11 studies comparing CEUS with standard imaging techniques provides valuable insights into the diagnostic potential of the CEUS in diverse clinical contexts.
Keywords: *computer tomography (ct), contrast enhanced ultrasound (ceus), hepatic lesions, hepatocellular malignancies, liver metastasis*

I. Introduction

In recent years, contrast-enhanced ultrasonography (CEUS), an advanced ultrasound technique using microbubble contrast agents for enhanced imaging, is widely used in diagnosing hepatocellular cancer and hepatic lesions (D'Onofrio et al., 2015), (Xu, 2009). Contrast agents improve visualization of anatomical and cellular structures, allowing imaging of macro- and microvasculature. Unlike MRI or CT contrast agents, ultrasound contrast agents stay in the vascular space, requiring only a small amount (usually 1 to 2 mL).

Liver metastasis is a critical concern in the realm of cancer, underscoring the importance of vigilant surveillance, accurate diagnosis, and timely detection. The liver serves as a common site for secondary cancer spread, indicating the potential progression of malignancies originating in other organs. The gravity of liver metastasis is accentuated by its association with a poor prognosis. Statistics reveal that liver metastases often signify an advanced stage of cancer, with diminished treatment options and a lower likelihood of successful outcomes (Zarour et al., 2017)(Tsilimigras et al., 2021). Timely detection and precise diagnosis are imperative, as they enable healthcare professionals to formulate effective treatment strategies, potentially improving patient outcomes. Regular surveillance becomes crucial for individuals at risk or with a history of cancer, facilitating early intervention and enhancing the chances of successful management. The intricate relationship between liver metastasis and overall prognosis underscores the need for heightened awareness, advanced screening technologies, and ongoing research efforts to develop innovative therapies for addressing this formidable challenge in cancer care.

CEUS provides real-time observation of contrast-enhancement patterns in arterial, portal-venous, and late vascular stages, offering superior temporal resolution (Chung & Kim, 2014). Its dynamic imaging captures

arterial, portal venous, and late phases within the liver, aiding in identifying vascular patterns crucial for HCC diagnosis and staging. Malignant liver lesions exhibit altered vascularization compared to healthy liver parenchyma, evident in CT and MRI scans. CEUS provides a more dynamic characterization and distinguishes between hepatic disorders with lower side effects than complex imaging techniques, offering dynamic real-time tumor perfusion depiction (Wilson et al., 2017)(Jang et al., 2009).

Unlike dynamic CT or MR imaging, CEUS operates in real-time with continuous high temporal resolution throughout the enhancement period, facilitating early or late enhancing pattern detection. It surpasses other modalities in contrast, spatial and temporal resolution, ensuring high diagnostic accuracy for liver malignancies. CEUS is radiation-free, making it safer for patients requiring recurrent imaging, especially pregnant women or young patients. Numerous studies endorse CEUS for liver lesion diagnosis, demonstrating high sensitivity and specificity comparable to or better than CT or MRI (Quaia et al., 2006)(Zhang et al., 2019)(Sporea, 2014).

While individual studies support CEUS effectiveness, a comprehensive systematic review comparing CT, MRI, and B-mode ultrasound is lacking. Such a review is crucial for consolidating findings and guiding future research and clinical decisions in liver lesion diagnosis. This systematic review evaluates and summarizes study results to compare the clinical effectiveness of CEUS with CT or MRI, providing valuable insights for the field.

II.　　Methodology

A comprehensive literature search was performed using PubMed/Medline, Wiley Online library and Research gate to identify articles reporting the diagnostic performance of CEUS, MRI, Contrast enhanced MRI, CT, CE-CT or MD CT for detecting hepatic lesions or metastasis in humans. The search strategy involved the following keywords: " CEUS" or "contrast enhanced ultrasonography" or "ultrasound" or "sonography" or "ultra-sonography" or "US" AND "magnetic resonance" or "MRI" or "CT" or "CE-CT" AND "liver metastases" or "liver disease" or "hepatic". Review articles, letters, comments, case reports, unpublished articles, and articles that did not include raw data were not included. Study were included in the review only if there was clear definition of the reference standard used. Only papers having data regarding the sensitivity and specificity of CEUS were included in the review. Only articles available in English were considered.

III.　　Results

Results from 11 studies comparing CEUS with standard imaging modalities were included in this review. 9 of the studies had compared CEUS with CT (CT, MDCT or CECT) and 4 studies had comparison with MRI. Majority of studies (9 out of 11) concludes that CEUS has potential to be used as a diagnostic modality in diagnosis, as it shows comparable or better results to the standard techniques. The results from these 11 studies have been tabulated in Fig. 1 and 2 .

Author	Country	Year	No. of patients	Main Conclusion
Emilio Quaia et.al.	Italy	2006	253	CEUS improved diagnosis in comparison with baseline US but has similar diagnostic performance and confidence to CECT
L.P.S. Larsen et.al.	Denmark	2007	365	MDCT detects more metastases and the sensitivity of this technique tends to be higher
Christoph F Dietrich et.al.	Europe (multicentric)	2006	131	CEUS considerably improves the detection of liver tumors compared with conventional US and is therefore a suitable method for liver metastasis detection
Jacek R. Janica et.al.	Poland	2007	51	CEUS increased diagnostic confidence in the detection and characterization of hepatic metastases. Real-time CEUS is particularly advantageous in detecting small metastases.
S. R. Rafaelsen	Denmark	2010	271	CEUS showed sensitivity and specificity comparable to that of MDCT and a tendency of a higher positive predictive value. CEUS has potential as a diagnostic alterna tive to MDCT
R. Vialle et.al.	France	2016	48	CEUS is significantly inferior to MDCT for the preoperative detection of hepatic metastases of colorectal cancer
K. Seitz et.al.	Germany	2010	262	CEUS and MRI are of equal value for the differentiation and specification of liver tumors. CEUS and MRI are extremely reliable for the differentiation of benign and malignant lesions, the diagnosis of liver hemangiomas and FNH.
K. Seitz et.al.	Germany	2009	267	CEUS is of equal rank to the CT-scan in regard to the assessment of tumor differentiation and specification. No statistically significant differences could be established.
Kazue Shiozawa et.al.	Japan	2016	69	CEUS has a higher specificity and positive predicitve value for the diagnosis of liver metastasis than EOB-MRI
Ali Muhi et.al.	Japan	2011	46	Gd-EOB-MRI and SPIO-MRI were more accurate than CE-CT and CE-US for evaluation of liver metastasis in patients with colorectal carcinoma
Vincent Schwarze et.al.	Germany	2020	234	CEUS had high diagnostic accuracy and there was a substantial degree of agreement between CEUS and CT

Fig 1: Study characteristics

On an average, CEUS showed a sensitivity of 85% (± 9.5%) where as CT and MRI showed a sensitivity of 82.4 % (± 10%) and 88.6% (± 7%) respectively. Specificity of CEUS was found to be 82% (± 10%) on an average where as CT and MRI showed a specificity of 85% (± 13%) and 78% (± 12%) respectively. Contrast-Enhanced Ultrasound (CEUS) has a significant diagnostic potential in a variety of clinical scenarios, as demonstrated by the results of 11 investigations comparing it with established imaging modalities. While most studies show that CEUS produces results that are either comparable to or better than those of more traditional methods like CT and MRI, there are some nuanced findings that highlight the significance of taking lesion characteristics, clinical circumstances, and the limits of each imaging modality into account.

Author	Comparison with	Sensitivity	Specificity
Emilio Quaia et.al.	US and CECT	CEUS - 83% US- 40% CECT- 89%	CEUS - 84% US- 63% CT- 89%
L.P.S. Larsen et.al.	MDCT	CEUS - 80% MDCT- 89%	CEUS - 80% MDCT- 89%
Christoph F Dietrich et.al.	US, CT	CEUS - 88.5% US- 84.6% CECT- 92.3%	CEUS - 94% US- 78% CT- 89.2%
Jacek R. Janica et.al.	US, CT	CEUS - 90.2% US- 60.9% CECT- 77.6%	CEUS - 90.2% US- 63.4%
S. R. Rafaelsen	MDCT	CEUS - 85.7% MDCT- 85.7%	CEUS - 97.6% MDCT- 95.6%
R. Vialle et.al.	MDCT	CEUS - 64.5% MDCT- 80.4%	–
K. Seitz et.al.	MRI	CEUS - 90.9% MRI- 81.8%	CEUS - 66.7% MRI- 63%
K. Seitz et.al.	spiral - CT	CEUS - 95.3% MRI- 90.6 %	CEUS - 83.7% MRI- 81.6 %
Kazue Shiozawa et.al.	EOB -MRI	CEUS - 90.8% MRI- 95.4%	CEUS - 84.5% MRI- 70.8 %
Ali Muhi et.al.	EOB -MRI. CECT, SPIO MRI	CEUS - 73% SPIO MRI- 80% EOB-MRI -95% CE-CT - 63%	CEUS - 73% SPIO MRI- 80% EOB-MRI -95% CE-CT - 63%
Vincent Schwarze et.al.	CT	CEUS- 94%	CEUS - 70%

Fig 2: Comparison of sensitivity and specificity of CEUS with other standard modalities

IV.   Discussion

The discussion of the results from the 11 studies comparing Contrast-Enhanced Ultrasound (CEUS) with standard imaging modalities provides valuable insights into the diagnostic potential of CEUS in various clinical scenarios. The majority of the studies (8 out of 11) suggest that CEUS holds promise as a diagnostic modality, either showing comparable or better results than standard techniques such as CT and MRI.

The study by Quaia et al., comparing CEUS with contrast-enhanced CT in patients with suspected liver metastasis, highlights the advantage of CEUS over baseline CT in diagnosing liver metastasis. However, it's noteworthy that the diagnostic performance of CEUS was similar to that of contrast-enhanced CT. The limitation of CEUS in detecting lesions in the deepest regions of the liver parenchyma due to signal attenuation is also acknowledged (Quaia et al., 2006). The study by Janica et al. evaluating the efficacy of CEUS in detecting liver metastasis compared with CT also provides positive results. CEUS demonstrated per-patient sensitivity comparable to CT, but it was advantageous in detecting smaller metastases that were missed by CT (Janica et al., 2007). Similar findings are reported by Vincent Schwarze and Christoph F Dietrich, emphasising the high diagnostic accuracy of CEUS and substantial agreement with CT (Schwarze et al., 2020),(Dietrich, 2006).

In contrast, the study by Larsen et al. comparing CEUS with CT in patients with liver metastasis from colorectal cancer presents a nuanced perspective. While CEUS demonstrated slightly better specificity than multi-detector CT, MDCT detected a significantly higher number of liver metastases. The authors conclude that CEUS cannot replace MDCT in detecting liver metastasis, indicating the need for careful consideration of the clinical context and specific diagnostic requirements (Larsen et al., 2009) .

The study by Vialle et al. comparing the sensitivity of CEUS with MDCT in pre-operative detection of hepatic metastasis presents a challenging perspective. Both modalities showed low sensitivities (80% and 64%, respectively), with CEUS being less sensitive than MDCT. The study suggests that changes in protocol and patient conditions, such as chemotherapy or radiation therapy, may affect the efficacy of imaging techniques (Vialle et al., 2016). Rafaelson and Jakobsen's study, contradicting Vialle et al.'s findings, reports identical sensitivity between CEUS and MDCT in detecting liver metastasis. The positive predictive values were higher for CEUS, leading the authors to suggest the potential of CEUS replacing MDCT as a diagnostic tool for liver metastasis (Rafaelsen & Jakobsen, 2011).

A major study comparing CT/MRI with CEUS was the DEGUM Trials. This study was a prospective trial conducted to evaluate the incidence and diagnostic efficiency of tumour specific vascularization pattern in CEUS in the differential diagnosis of liver tumours. This study included a total of 1349 patients with suspected hepatic tumour. The tumor specific diagnosis was compared to histology or to CT or MRI. This study found that the diagnostic efficiency of CEUS was 83 % for all benign lesions, 82% for hemangiomas and 87% for FNH. The diagnostic accuracy of CEUS for malignant lesions were 95.8%, 91.4% for liver metastases and 84.9% for hepatocellular carcinomas. The paper concludes that CEUS shows high diagnostic performance for tumor differentiation, with a high predictive value for malignant lesions. The authors conclude that CEUS can be used for characterization of focal liver lesions and was found to be equal to CT in assessment of tumor differentiation and specification (Seitz et al., 2010)(Seitz et al., 2009).

Coming to studies comparing CEUS with MRI, Shiozawa et.al, compared CEUS with Gd-EOB-DTPA enhanced MRI in detecting liver metastasis. This study enrolled 69 patients with suspected metastasis. CEUS and EOB-MRI was performed on these patients and the final diagnosis was confirmed by histopathological exam of the surgically resected specimens or based on course observation (change in size, tumour enlargement, shrinkage etc). In this study they found that CEUS had higher specificity and positive predictive value (PPV) than EOB-MRI while sensitivity was higher for MRI (Shiozawa et al., 2016). Ali Muhi et.al, made comparisons between contrast enhanced CT, CEUS, super paramagnetic iron oxide enhanced MRI and gadoxetic acid enhanced MRI, in detecting colorectal hepatic metastasis. They found that for lesions less than 1 cm in size, mean ROC curve for Gd-MRI and SPIO-MRI were significantly greater than those of both CT and CEUS. For lesions larger than 1 cm, there was no significant difference. In case of sensitivity as well, they found similar results with both type of MRIs performing with significantly higher sensitivity (95%) compared to CE-CT and CEUS for detecting lesions smaller than 1 cm. Between CT and CEUS, CEUS seems to have a higher sensitivity of 73% compared to 63% for CE-CT. But in case of lesions with more than 1 cm size, there was no significant difference between any of the imaging modalities (Muhi et al., 2011).

The discussion of these studies underscores the potential of CEUS as a valuable diagnostic tool in various clinical scenarios. However, the results also highlight the importance of considering specific clinical contexts, lesion characteristics, and the limitations of each imaging modality when making diagnostic decisions. Further research and standardization of protocols may help refine the role of CEUS in specific clinical applications.

V.   Conclusion

In conclusion, the results of the 11 studies comparing Contrast-Enhanced Ultrasound (CEUS) with standard imaging modalities reveals the promising diagnostic potential of CEUS in diverse clinical contexts. While the majority of studies indicate comparable or superior results for CEUS compared to conventional techniques like CT and MRI, nuanced findings emerge, emphasizing the importance of considering lesion characteristics, clinical contexts, and the limitations of each imaging modality. Notably, the DEGUM Trials provide substantial evidence of CEUS's high diagnostic performance for tumor differentiation, supporting its utility in characterizing focal liver lesions. The conflicting perspectives on sensitivity in studies comparing CEUS with MDCT highlight the need for further research and standardization of protocols. Overall, these discussions underscore the evolving role of CEUS in diagnostic imaging and suggest that careful consideration of specific clinical scenarios is essential to harness its full potential. Further investigations and refinements in protocols are imperative to elucidate and establish the precise applications of CEUS in clinical practice.

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