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# Comprehensive review of imaging modalities for diagnosis and characterization of focal liver lesions

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**Abstract**
Focal liver lesions (FLLs) include a variety of benign and malignant lesions, hepatocellular cancer (HCC) and metastases are the most common malignant forms of FLLs. FLLs are often discovered incidentally due to the widespread use of imaging modalities. Gray-scale ultrasound (US) is frequently used as the initial screening to detect FLLs. Furthermore, a variety of imaging modalities are used to diagnose FLLs, including contrast-enhanced ultrasound (CEUS), contrast and non-contrast of computed tomography (CT), and magnetic resonance imaging (MRI). Understanding the capabilities of each diagnostic modality is crucial for accurate diagnosis and proper management of FLLs. Therefore, this review provides a comprehensive overview of focal liver lesions (FLLs), including their aetiology, epidemiology, and methods of diagnosis.

**Keywords:** Focal liver lesions, diagnosis methods, CEUS

## 1. Introduction
Focal liver lesions (FLLs) can be described as any lesion presents in the liver with or without functional and structural abnormalities of the hepatobiliary structure, and these lesions can vary in size. FLLs are a common cause for hepatobiliary service consultation and are frequently detected in patients with colorectal cancer or cirrhotic liver [1]. However, incidental FLLs are being discovered more frequently due to the increased and widespread use of imaging modalities during practice for other clinical purposes [1, 2]. The most common malignant liver lesions are hepatocellular cancer (HCC) and metastases [3]. It is crucial to consider not only malignant liver lesions but also benign lesions in the differential diagnosis of FLLs, whether they are cystic or solid. For instance, focal nodular hyperplasia (FNH), hepatic haemangioma, hepatic cysts, and hepatocellular adenoma [4].
To reach a definitive diagnosis, various approaches are used, including: conventional ultrasound (US), contrast enhanced ultrasound (CEUS), contrast enhanced computed tomography (CT) and contrast enhanced magnetic resonance imaging (MRI) [5]. However, due to the lack of guidelines, the majority of organizations resort to using all the obtainable techniques to confirm a diagnosis.
This approach is not only inconvenient and time-consuming but also expensive [5, 6].

## 2. Aetiology and epidemiology of FLLs
The incidence of liver lesions reveals apparent variations across different ethnic groups and geographic areas [7]. Haemangioma is considered the most frequent benign liver lesion, with an incidence ranging from 1-20% among the general population, and a prevalence of approximately 2% of autopsies [8]. Previous studies reported that there is a higher prevalence of haemangioma in women compared to men, with a ratio of 2:1-5:1, and they can occur in individuals all age groups [9, 10].
Furthermore, FNH is the second most frequent benign liver lesion, with an incidence ranging from 1% to 3%, and it is predominantly found in young and middle-aged females, typically occurring between the third to fifth decades of their lives [11]. Primary liver cancer is the sixth most frequent malignancy worldwide and the third most common causes of the death, following lung and stomach malignancy [12]. Hepatocellular cancer (HCC) accounts for 85-90% of primary hepatic cancer and is infrequently detected in the early stages but is typically fatal during the first few months of diagnosis [4]. The main causes of HCC in cirrhotic patients are HBV, HCV, alcoholic liver disease and non-alcoholic steatohepatitis [13].

The highest prevalence rates of HCC (>80%) are in Eastern Asia and sub-Saharan Africa, and prevalence might increase with advancing age with an average onset age of around 70 years old in developed nations [14]. Overall, there is a male predominance in all populations, with male-to-female ratios between 2:1 and 4:1 [4].

It has been stated that metastases are considered the most common malignancy of the liver, occurring about 18-40 times more frequently than primary malignant hepatic cancers [15]. In addition, around 25-50% of patients with a non-haematological malignancy had liver metastases at the time of diagnosis. The most common origins of these metastases were colon, stomach, pancreatic, breast, and lung cancer study [16].

## 3. Diagnosis of FLLs

The diagnostic components for assessing FLL are history taking, physical examination, radiological investigations, and histopathology [4]. Specific aspects to consider during history taking, such as alcohol consumption, hepatitis, and the usage of oral contraceptive tablets as risk factors for liver cirrhosis. Additionally, obesity, diabetes and metabolic syndromes are factors known to play a major role in increasing HCC [1]. It is also crucial to elicit a family history of cancer, as well as inquire about any previous malignancies, which could indicate the possibility of metastatic lesions 1. In a physical examination of the patient, healthcare professionals should look for signs such as jaundice, palpable abdominal masses, cachexia, and palpable lymphadenopathy [4].

A radiological examination is a vital aspect in the assessment of the hepatic lesion and there are several imaging approaches available to detect and differentiate FLLs [14, 17]. Conventional Ultrasound (US) is the initial investigation that is utilized for the detection of the FLLs. However, it has limitations in accurately differentiating between different types of liver lesions [18]. As reported by Lorusso *et al*. [19] the overall accuracy of US techniques in characterising liver lesions is roughly 50%. Color Doppler ultrasound can provide additional information for characterizing the FLLs, but its effectiveness is limited by motion artifacts caused by breathing and cardiac activities, and it can only examine the macro circulation, unable to visualize small vessel size [20]. This limitation condition has improved with the initiation of the CEUS into clinical practice.

The CEUS technique is a relatively procedure that allows for the examination of dynamic enhancement patterns of FLLs in real-time, and providing a better characterization of FLLs compared to non-enhanced US [21]. Cosgrove [22] demonstrated that CEUS is considered a reliable technique for differentiating between benign and malignant FLLs, with a sensitivity and specificity from 85% to 90% and 80% to 99%, respectively. During the last 20 years, contrast-enhanced CT and contrast-enhanced MRI have been commonly used as non-invasive techniques for the differentiating FLLs. The diagnosis is established based on vascular information obtained from both phases of arterial and portal venous contrast enhancement [23]. Contrast enhanced MRI has been revealed to have greater diagnostic accuracy for the detection and characterization of FLLs compared to spiral CT [24]. However, in cases where lesion characterization remains uncertain after CT-scan, or MRI, FLLs biopsy or long-term follow-up is frequently recommended [25]. Indeed, two previous studies of accuracy diagnostics have shown that CEUS is as accurate as contrast enhanced CT and MRI in the evaluation of FLLs [26, 27]. Therefore, CEUS in liver imaging is progressively becoming the radiologic method of choice for diagnosing patients with FLLs.

### 3.1 Conventional ultrasound

Conventional ultrasound (US) is commonly used as the initial imaging modality for evaluating FLLs due to its non-invasive, safe, affordability, and accessibility [1, 28, 29]. Reddy and Reddy [30] explained that gray scale US provides valuable information about liver anatomy and hepatic lesions through its excellent spatial and contrast resolution, without the need for contrast-specific agents. However, despite these advantages, the accuracy of US in differentiating FLLs is poor, mainly due to the similarity of echo patterns and vascular architectures [25]. A wide range of FLLs can be detected and diagnosed using US, particularly liver cysts, for which it is the most specific test [31]. Liver cysts are investigated as echo-free round spaces with smooth thin walls. They can be distinguished from the liver tissue by a brighter band distally, produced by decreased attenuation of the ultrasound waves through their fluid compared to the liver texture [1]. Haemangiomas are typically show as homogeneously solid echogenic masses, with possible increased enhancement of the mass in a patient without the risk of HCC or metastases [32]. On a Color Doppler ultrasound, they are hypovascular and rarely show weak venous signals [33]. In fact, FNH covers normal liver elements in an irregular arrangement and some of FNHs have a central vascularized scar which appears as an echo-poor streak on Color Doppler US that characteristically radiates outward in a spoke-wheel way demonstrated after contrast enhancement [34]. The presence of a hypoechoic rim around an isoechoic or echogenic liver mass suggests possible malignancy, and lesions with this characteristic would require confirmatory diagnostic imaging through either CT or MR scans [35]. However, the HCC can manifest as masses with variable echogenicity and predominantly exhibit a heterogeneous texture. Their characteristic hyper vascularity can be illustrated with Color Doppler [1]. Despite this, HCCs are typically multicentric and considerably invasive; therefore, they may not have extremely defined borders, combined with the fact that they commonly occur in cirrhotic irregular liver texture, making them difficult to discover [36]. Multiple hypoechoic liver masses most frequently indicate metastases [25]. The variability of manifestations of metastases on ultrasound remains unexplained. However, there are trends, such as echogenic metastases typically originating from gastro-intestinal or genitourinary tract sources, while poorly echoic lesions are typical in breast and bronchus carcinoma [37].

### 3.2 Contrast-enhanced ultrasound

Contrast-enhanced ultrasound (CEUS) has been accepted as a highly accurate investigation in the detection and differentiation of FLLs by utilizing a microbubble contrast agent of the second generation, which allows for the enhancement pattern of liver lesions and assessment of vascularity [38]. In addition, Hohmann group stated that the CEUS has changed the practice of performing US examinations as it is a feasible, cost-effective and safe option that improves the ability to attain a diagnosis, and

increases the probability to differentiate various FLLs compared with conventional US. It can frequently preclude the requirement for further cross-sectional imaging when examining FLLs [19]. The guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) recommends the use of CEUS in several situations. These include the detection of incidental FLLs that cannot characterised on conventional US, in suspected lesions in the context of liver cirrhosis or chronic hepatitis, and cases where the diagnosis is uncertain following CT or MRI examinations [36]. A study by Albrecht *et al*. [39] found that for diagnosing FLLs, CEUS was more sensitive and specific at about 95.5% and 70.5% respectively than contrast enhanced CT (72.2% and 37.5%) or contrast enhanced MRI (81.8% and 42.9%).

The characterizations of FLLs using CEUS are established based on the evaluation of morphological manifestations, including the vascularity and enhancement patterns of the liver lesions [33]. CEUS provides a reliable diagnosis for both benign and malignant liver lesions by assessing their enhancement in the arterial, portal venous and late vascular phases compared to the adjacent hepatic parenchyma [31]. This is demonstrated by the high spatial and high contrast resolution of CEUS through sensitivity to harmonic frequencies generated by the contrast agents, and its high temporal resolution allows for real-time evaluation of contrast enhancement [40]. According to Sugimoto *et al*. [41], malignant lesions typically exhibit a low signal intensity echos in the late phase, despite being hypo or hyper enhancing lesions. On the other hand, benign lesions commonly present a constant enhancement with iso or hyper-enhancing manifestations compared to the adjacent liver parenchyma [34].

According to Claudon *et al*. [40], the majority of benign lesions has a particular contrast enhancement, which is equivalent to that on CT-scan and MRI and allows characterization in the majority of cases. In the case of liver haemangiomas, a typical peripheral nodular enhancement is observed in the portal venous and late vascular phase [9]. Moriyasu and Itoh [42] mentioned that small hemangiomas may show total filling within seconds, while larger hemangiomas may require several minutes. Regarding FNHs, Bartolotta *et al*. [9] explained that these lesions can appear with a typical central spoke wheel enhancement pattern during the hepatic arterial phase, along with centrifugal filling. Alternatively, FNHs can exhibit homogeneous enhancement. Subsequently, these lesions show the same degree of enhancement in the subsequent phases due to the tissue- like liver composition within the lesion. Bartolotta *et al*. [43] stated that the late-phase imaging is helpful in identifying FNHs, as they appear as hyperechoic or isoechoic lesions, frequently with a central scar.

Metastatic lesions exhibit typical features in all phases of contrast-enhanced ultrasound. In the hepatic arterial phase, the manifestation is varying: hypervascular metastases show as hyper-reflective with brightly enhancement and homogenous lesions, whereas hypovascular deposits present as hypo-reflective lesions with or without rim enhancement [32]. However, metastases in the portal venous, delayed vascular and the liver-specific late phase appear as defects due to the lack of normal parenchymal liver [9]. The combination of delayed vascular and late-phase imaging significantly improves the contrast between normal liver enhancement and the non-enhancing metastases; therefore, improving the detection, particularly of lesions that are isoechoic on the grey scale US or small lesions [42].

HCC exhibits complex appearances that cannot always be diagnosis through contrast investigation alone [31]. Typically, HCCs appear hypervascular during the arterial phase while defects in the enhancement are observed in both the portal venous and late vascular phase imaging 9. However, HCC may also show iso-enhancing in the venous and late phase in approximately 40% of cases compared to the adjacent liver parenchyma [32, 44].

### 3.3 Computed tomographic scan (CT)

#### 3.3.1 Non-Contrast-Enhanced CT

The majority of benign and malignant liver lesions have been detected non-invasively using CT scans since 2006, and the diagnosis is typically confirmed through contrast enhancement in the arterial and portal venous phases [36]. Non-enhanced CT scans have limited capabilities in differentiating liver lesions [33]. In cases of isoattenuating lesions, it suggests a hepatocellular source, and the findings of fat, acute haemorrhage or calcification within a lesion help to the restriction of the differential diagnosis [25].

#### 3.3.2 Contrast enhanced CT

Contrast enhanced CT (CECT) is a commonly used modality for characterising FLLs and this due to the various vascular patterns of FLLs, their diagnosis by contrast-enhanced CT scan primarily relies on the ability of this modality to delineate the enhancement pattern following the intravenous injection of a contrast agent [45]. Hafeez *et al* [46] stated that triphasic images are an excellent technique of choice, which significantly improves in the characterization of FLLs compared to single-phase examinations. Notably, triphasic spiral CT allows imaging of the entire liver in the arterial, portal and equilibrium phases [47]. Hammerstingl *et al*. [37] reported that the portal phase is the most sensitive phase for detecting of the lesion, while the arterial and equilibrium phases can provide additional information on the vascularity of the lesion in order to identify the nature of lesion.

The introduction of spiral CT has significantly improved the speed of scanning, allowing for the establishment of multiphasic contrast-enhanced CT studies in the entire liver, which has proven to be an important technique for identifying and differentiating FLLs [46]. In addition to that multiphasic contrast-enhanced CT has many improvements in imaging the liver throughout different phases of enhancement, in which localizing the lesions based on the lobes and segments, distinguishing between benign from malignant lesions, discriminating cystic from solid lesions, identifying the number and size of the lesions, and differentiating the lesions into different types by morphology and contrast enhancement patterns of the lesions [48].

According to Hammerstingl *et al*. [37], the discrimination between benign and malignant lesions relies on the uptake of the amount of contrast agent at different phases of the examination. Evaluation of the enhancement of the lesion is performed in different phases, and the lesions are tabularized according to iso-dense to liver parenchyma, hypo, hyper and mixed enhancement [49]. Benign lesions such as hepatic cysts show hypodense with no enhancement in the arterial, portal and equilibrium phases [45]. Hepatic

haemangioma, on the other hand, exhibit peripheral enhancement in the arterial phase with subsequent centripetal filling in the portal and equilibrium phases [48]. FNH typically demonstrates a pattern of hyper and mixed enhancement in all phases (Arterial, portal and equilibrium) as described by LeGout *et al*. [11].

Metastatic lesions, which can be either hypervascular or hypovascular, show different enhancement patterns. Hypervascular Metastasis of lesions exhibit hyper enhancement in the hepatic arterial phase and mixed enhancement in portal and equilibrium phases, and however metastasis of hypovascular lesions shows hypo enhancement in the hepatic arterial phase with maximum enhancement in the portal phase [50]. On the other hand, HCC shows hyper enhancement in the hepatic arterial phase with mixed enhancement in both the portal and equilibrium phases [44].

### 3.4 Magnetic Resonance Imaging (MRI) in FLL diagnosis

#### 3.4.1 Non-Contrast-Enhanced MRI

T1 and T2 weighted sequences of non-contrast-enhanced MRI are significant in the differentiating FLLs in non-cirrhotic and cirrhotic liver [51]. High signal intensity on T1-weighted sequence, can be produced by fat, bleeding and deposition of glycogen and copper, and also can be observed in HCC [51]. The majority of benign lesions appear bright on T2-weighted sequence, while malignant lesions are slightly hyperintense [52]. In the opposed-phase T1 imaging technique, abnormal accumulation of fat in the liver appears as a hypointense pattern, and this technique is considered more precise than conventional US and the CT scan for detecting steatosis and the fatty infiltration of the liver [53].

#### 3.4.2 Contrast-Enhanced MRI

Contrast enhanced• MRI (CE-MRI) is considered the best method for the assessing FLLs, primary and metastatic malignancy [51]. According to Haimerl *et al*. [54], CE-MRI is the preferred technique of choice in a clinical setting due to its lack of ionizing radiation and its usability in patients with renal impairment. Additionally, it provides high contrast resolution through various sequences and types of contrast agents. The most frequently of the used contrast agent is gadolinium•chelates, which have an extra•cellular liver distribution, and aid in differentiating FLLs and acquiring angiography [55].

However, Haimerl *et al*. [54] claimed that MRI with an extracellular contrast agent, such as liver- specific contrast medium or gadopentetate dimeglumine has demonstrated greater specificity and sensitivity in detecting and differentiating lesion compared to spiral CT. 55 stated that the liver- specific contrast media have been developed to provide functional information and enhance morphological evaluation. Then, the clinical application of liver-specific contrast agents has undergone a remarkable increase, and these agents can be divided into two categories based on their uptake mechanism. The first category includes agents like gadobenate dimeglumine (Gd- BOPTA, MultiHance, Bracco, Milan, Italy), which are taken up by hepatocytes. The second category comprises agents such as gadoxetate disodium (Gd-EOB-DTPA, Primovist, Bayer Healthcare Pharmaceuticals; Berlin, Germany), which are specifically taken up by Kupffer cells [56]. Both contrast agents allow for the evaluation of vascular structures in addition to multiphase contrast medium alterations within FLLs [55]. These contrast agents primarily distribute in to the vascular and interstitial parts, similar to extracellular contrast medium, allowing imaging of the arterial and portal venous phases [51].

Reimer *et al*. [56] revealed that Gd-EOB-DTPA enhanced MRI is more precise in discriminate benign from malignant lesions and provides a more definite diagnose for FNH and focal infiltration of eosinophilic condition. Both Contrast-enhanced CT and MRI scans exhibit comparable high diagnostic performance for hemangioma and HCC [54]. The pattern of tumour vascularity in gadolinium chelate-enhanced MRI as described Nasu *et al*. [57], is utilized for the detection of liver metastases. Hyper-vascular hepatic metastases often exhibit peak enhancement in the arterial phase images, while hypo-vascular hepatic metastases are commonly hypo-vascular, and they are obvious in the portal phase as hypo-intense compared to normal liver parenchyma [57].

In terms of enhancement patterns, HCCs typically show hyperintensity in arterial phase of T1- weighted sequences, and appear somewhat hypointense in the portal and delayed phases. However, contrast enhancement of hemangioma is characterized by peripheral enhancement in the early arterial phase is nodular, followed by gradual centripetal filling in the portal venous and delayed phases [5]. The classic enhancement appearance of FNH includes an intensely enhancing lesion in the arterial phase with a centrally located fibrous scar. On T2-weighted sequences, FNH appears hyperintense, and delayed enhancement is observed in less than 50% of the lesions [11].

## 4. Conclusion

In conclusion, for appropriate patient management and prognosis, the diagnosis and characterization of focal liver lesions (FLLs) are essential. Throughout this review a variety of imaging modalities, including US, CEUS, Contrast-enhanced CT, and MR are vital. Although various factors influence the choice of imaging modalities including patient state, availability, and lesion characteristics, Conventional US remains the first line of investigation due to its accessibility, lack of invasiveness, and safety, despite its poor accuracy in differentiating FLLs. Contrast-enhanced techniques like CEUS offer real-time dynamic enhancement patterns that improve differentiation accuracy, have become valuable tool compared to non-enhanced US. Indeed, CT and MRI, especially with contrast-enhanced provide better potential characterization. Multiphasic CT scans help differentiate benign from malignant lesions by providing a comprehensive evaluation of the arterial and portal venous phases. Similarly, gadolinium-based contrast agents used in contrast-enhanced MRI provide excellent sensitivity and specificity for lesion detection as well as high resolution images without ionizing radiation.

## 5. Conflict of Interest

Not available

## 6. Financial Support

Not available

## 7. References

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