Comments and illustrations of the WFUMB CEUS liver guidelines: Rare benign focal liver lesion, part II

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Abstract

It is important to be familiar with the typical imaging features of the uncommon or even extremely rare focal liver lesions (FLL). Current guidelines of the World Federation for Ultrasound in Medicine and Biology (WFUMB) is aimed at assessing the usefulness of contrast enhanced ultrasound (CEUS) in the management of various FLL. In this review, we aim to summarize the ultrasound and CEUS characteristics with literature review of some extremely rare benign FLL, which might be helpful for improving diagnostic efficiency clinically.

Keywords: Contrast enhanced ultrasound (CEUS); hepatic adenomatosis; leiomyoma; perivascular epithelioid cell neoplasms (PEComas); solitary fibrous tumor

Introduction

Currently, according to recommendations of contrast-enhanced ultrasound (CEUS) for the evaluation of focal liver lesions (FLL) by the World Federation for Ultrasound in Medicine and Biology (WFUMB) [1-5], CEUS is helpful for improving both detection and characterization of various focal liver lesions (FLL) [6-12].
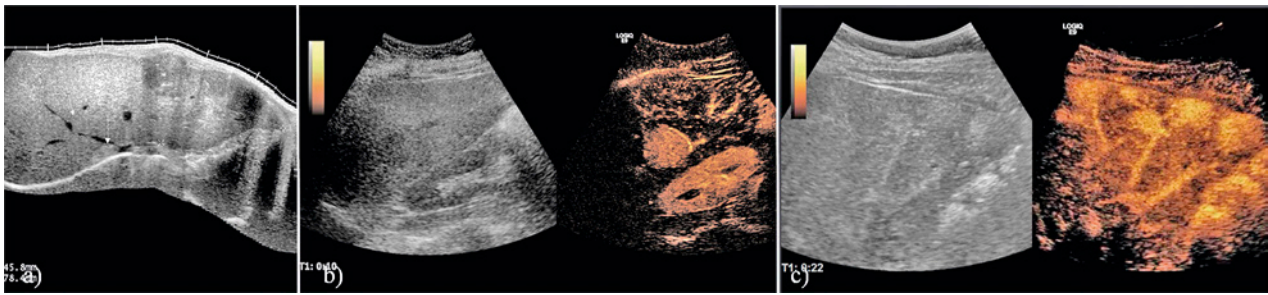
Fig 1. Hepatic adenomatosis. Multiple hepatocellular adenomas in von Gierke´s disease (histological proven) in a 30-year-old female, previously on contraceptives. She had no symptoms, but hepatic steatosis. B-mode image of the liver and kidney using panoramic imaging (a), with hardly any liver tumor visible. CEUS in the early arterial phase shows early enhancement of two liver adenomas as well as the right kidney, long before enhancement of the rest of the liver parenchyma. Note also the feeding artery and the subcapsular artery at the right edge of the tumor, classically observed with high-resolution ultrasound in adenomas of the liver (b). CEUS of another young female patient with hepatic adenomatosis. The arterial phase image shows three feeding arteries and five hyperenhancing tumors in a small section of the liver. This patient also had numerous hyperenhancing lesions in other parts of the liver (c).

Current WFUMB recommendations based on the international literature and the findings of the WFUMB experts are established as answers to common questions. Among all FLL, beside hepatocellular carcinoma (HCC), liver metastasis, and cholangiocarcinoma (ICC), the imaging findings of other relatively rare FLLs are less discussed in the literature. Imaging diagnosis of these rare or extremely rare FLL with atypical imaging characteristics is a real clinical diagnostic challenge [6-20].

Published papers with gold-standard histology cover cholangiocellular adenoma [21], peliosis [22-24], cystadenoma and cystadenocarcinoma [25], hemangioendothelioma [26,27], and hepatocellular carcinoma (HCC) in the non-cirrhotic liver and how to deal with incidental findings in general [8,14,28,29] and we also refer on how to deal with incidental findings in general [30]. There are also several papers and reports on the uncommon and more esoteric hepatic lesions. These include characterization of fibrolamellar hepatocellular carcinoma [16,31], very small HCC (<10 mm) [32], mixed HCC and cholangiocellular carcinoma [33], nodular regenerative hyperplasia [34], sarcoma [35], inflammatory pseudotumour [36], sarcoidosis [37-40], tuberculosis [41,42], hydatid cysts [43-46], alveolar echinococcosis [44], schistosomiasis [47,48], ascariasis [49,50], fasciolosis [51], clonorchis and opisthorchis [52], toxocariasis [53], bacillary angiomatosis [54], amyloidosis with spontaneous hemorrhage [55], and portal venous gas accumulation [20] as well as rare FLLs in pediatric patients [56,57].

In a series of papers, particular attention is paid to the US and CEUS features of rare FLL where there are limited reports and images published, in order to create a library of these rare lesions.

Hepatic adenomatosis

Hepatic adenomatosis (HA) is a rare disease defined by the presence of multiple adenomas in the liver. It was first described by Flejou in 1985, and the number of adenomatous lesions needed for diagnosis was arbitrarily set to 10 [58]. In a later paper, the presence of 4 or more lesions was considered sufficient [59]. HA most often occurs in young women aged 20–40 years, and increased prevalence is observed in women with a history of prolonged oral contraceptive (OC) intake. The estimated incidence of HA is 3 per million per year and increases to 30–40 per million among long-term OC users [60]. Patients usually display no symptoms and have normal liver blood analyses, although elevated liver enzymes are sometimes detected, indicating cholestasis [58,61,62]. However, HA is associated with a risk of rupture, hemorrhage, and malignant transformation into HCC [60].

Imaging of hepatic adenomatosis

HA is not associated with any specific subtypes, and its imaging features are similar to those of solitary adenoma [60]. Adenomas are typically well-defined and may have a partial or complete capsule. The differential diagnosis should include multifocal HCC, metastatic disease, and multiple focal nodular hyperplasia (FNH) [60]. HA should also be considered when confronted with multiple hypervascular liver lesions. Standard imaging is most often conducted with computed tomography (CT) and magnetic resonance imaging (MRI) to obtain an optimal overview of all the lesions. However, US and CEUS can also be performed, particularly to study the details of tumor perfusion with respect to the initial direction of enhancement (i.e., centrifugal or centripetal) in the arterial phase.

The clinical symptoms and potential risk of malignant transformation and bleeding in patients with multiple

HA do not much differ from those in patients with a single HA, being driven by the underlying etiology and by the size of the largest nodule, rather than the number of nodules [63]. A higher bleeding risk of patients with HA compared to single and multiple HAs was described in one large United States cohort (2,8 fold increase of risk) [64] (fig 1).

Lipoma

Hepatic lipoma (HL) is a very rare benign neoplasm of mesenchymal origin, consists of mature adipose tissue and has a strong association with fatty involution of the liver parenchyma [65,66]. The first HL case was described in 1970 as an incidental finding during autopsy. In an almost complete review of scientific literatures, fewer than 30 HL have been reported up to 2007. The pathogenesis of HL is unclear, while a statistically significant association between non-alcoholic liver steatosis and lipomas has been reported [67]. Increased levels of insulin in portal blood due to insulin resistance is a potential key factor that results in a greater supply of fatty acids in the liver [68]. HL proved to have no potential of malignant transformation. As most patients are asymptomatic, lipomas appear as incidental findings, and large lipomas can even be discovered during physical examination. Others may present with acute or chronic epigastric pain [69].

Imaging

On US, HL lesions usually appear as well-defined, large, round, and homogeneously hyperechoic masses with posterior acoustic shadowing [70]. They can also have mixed echogenicity due to heterogeneity. Perilesional vascularization can be detected in the color Doppler modality [65,71,72]. On CEUS, HL was reported to be inhomogeneously hyperenhanced in the arterial phase and showed sustained hyperenhancement in the portal venous and late phases [73,74] (fig 2 and 3).

An important differential diagnosis on US is hemangioma. On CT scan, hepatic lipoma lesions present as round, non-infiltrating, lobulated homogeneously
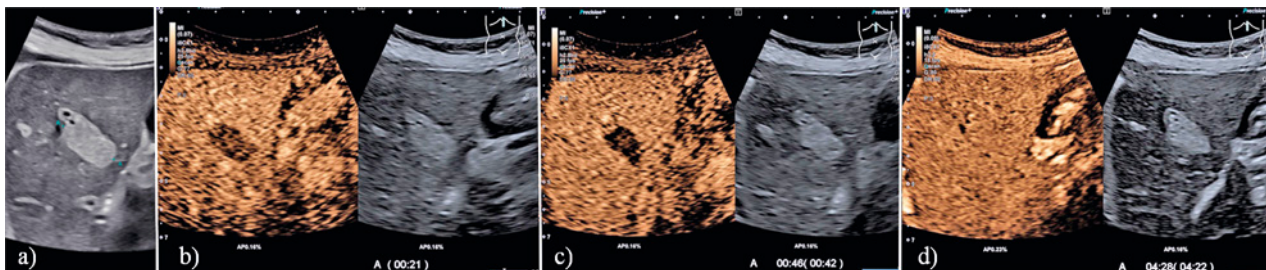

Fig 2. Lipoma in the left liver lobe as an incidental finding in a 57-year-old woman: The liver enzymes were normal, B-mode and 2D-elastography did not indicate cirrhosis. The benign character was proven by clinical course and MRI which confirmed a lipoma. Ultrasound-guided biopsy for definite diagnosis was rejected by the patient. B-mode displays a hyperechoic homogenous lesion with a clear border (a). After injection of 1,2 ml Sonovue in the arterial and portal phase, showed hypoenhancement compared to the surrounding liver parenchyma (b, c). In the very late phase (> 4 minutes) the lesion develops nearly isoechoic (d).
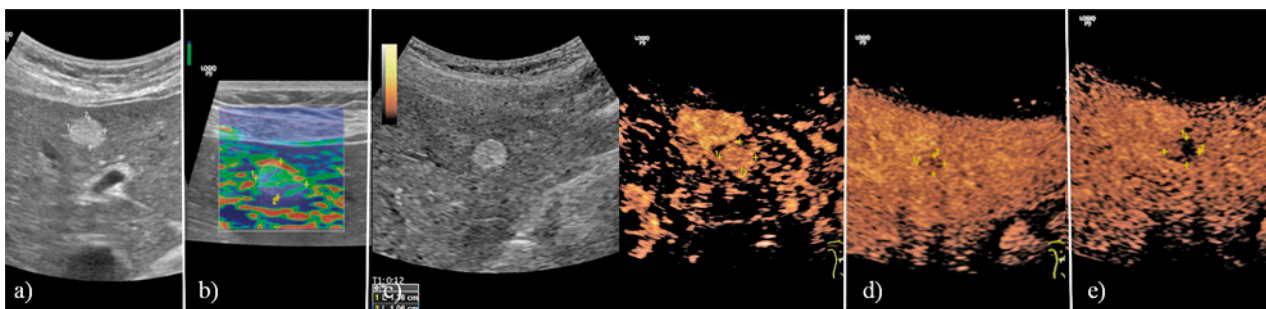

Fig 3. Lipoma of the liver (proven benign by an indolent clinical course). 51 y/o asymptomatic female presenting in 05/2021 with an incidentally detected focal liver lesion during follow-up of malignant melanoma in 2013. The focal liver lesion was first detected in 03/2020 by computed tomography. MRI 06/2020 and CT 04/2021 revealed stable size. Both CT- and MRI-findings were suspicious of hepatic lipoma. B-mode ultrasound 05/2021 showed a homogeneous hyperechoic lesion in liver segment IV (a) with a diameter of 12 x 11 x 14 mm. On ultrasound elastography, the lesion appeared to be soft (b). Contrast enhanced ultrasound in 11/2021 revealed homogeneous hyperenhancement during the arterial phase (c) with slight wash-out during the portal venous (d) and late phases (e). Ultrasound-guided biopsy for definite diagnosis was rejected by the patient. During follow-up with ultrasound 05/2022, the focal liver lesion remained stable, and the patient was still asymptomatic. It is important to comment that lipoma typically do not show arterial phase hyperenhancement.

hypoattenuating masses with fat attenuation. No increased attenuation can be observed after administration of the contrast medium in the early and delayed phases [65,71,72]. It may be difficult to differentiate hepatic lipomas from hepatic angiomyolipomas, especially when there is a density increase in post-contrast images over 30 HU. Attenuation values must be less than 20 HU to identify a lipoma.

On MRI scans, there may be multiple hepatic lipomas, where these lesions are hyperintense on both T1- and T2- weighted images with no signal drop-out in out-of-phase sequences and is hypo-intense on T2-weighted fat saturated images [75]. There is no significant contrast enhancement following the administration of the contrast medium [71,72]. MRI is the most predictive imaging method. Owing to the absent risk of malignancy, hepatic lipoma has a good prognosis [72], and most cases do not require resection [72].

Leiomyoma

Primary hepatic leiomyoma is a rare benign mesenchymal tumor that is secondary to benign smooth muscle proliferation [76]. Its complex pathogenesis remains largely unknown. Several cases have been reported in which primary liver leiomyoma occurred in immunosuppressed patients [77,78]. The mean age of patients with leiomyoma is 43 years, and the prevalence is slightly more common in females. In this study, the average size of the tumors was 8.7 cm, and 34% of the cases were incidental findings with a mean follow-up time of 33 months without any symptoms reported in most patients. Cases of leiomyomas originating from vascular smooth muscle have been described, including from the hepatic veins [79]. The prognosis of this condition is encouraging, and no adverse events have been observed during the follow-up to the reported cases [76]. Surgical resection is recommended in primary hepatic leiomyoma not only for diagnostic but also for curative purposes [76].

Imaging
On US images, primary leiomyoma of the liver appears as hypoechoic solid lesions with varying degrees of heterogeneity [80-83]. Previously, it was reported as a heterogeneous mass the inferior vena cava (IVC) and the right kidney medially across the midline [84]. Primary hepatic leiomyomas present on CT scans as heterogeneously hypodense lesions with strong hyperenhancement in the arterial phase and sustained homogeneous enhancement in the hepatic venous and equilibrium phases [76,85]. Furthermore, peripheral rim enhancement has also been reported [86]. Various studies report that primary hepatic leiomyoma lesions display hypointense or isointense masses T1-weighted sequences and hyperintense masses T2-weighted sequences [80,85]. However, hypointense lesions have also been reported T2-weighted sequences [85,86]. After injection of contrast medium, the lesions exhibit intense enhancement during the arterial phase, persistent and homogeneous enhancement during the hepatic venous and equilibrium phases [85]. However, on liver-specific contrast-enhanced MRI, the absence of contrast retention may lead to the misdiagnosis of primary liver leiomyoma [85,86]. Since the imaging features of the tumor do not allow for a tissue-specific diagnosis, histological results of the tissue specimen and immunohistochemical stains are important for diagnosis. In addition, a metastatic workup to exclude occult leiomyoma elsewhere should be undertaken. Up till now, CEUS findings have not been reported in the literature. The differential diagnosis of primary liver leiomyoma should be considered in the management of liver tumors.

Perivascular epithelioid cell neoplasms (PEComas)

Perivascular epithelioid cell tumors (PEComa) are rare mesenchymal liver tumors [87]. Histopathologically, polygonal epithelioid and spindle-shaped mesenchymal cells are present. Immunohistochemically, the tumor shows dual expression of melanocytic (HMB 45 and/or Melan-A) and smooth muscle markers (actin and/or desmin) [87,88]. In 1944 Aitz et al first described the characteristic of perivascular epithelioid cells [87]. The term "PEComa" was first introduced by Bonetti in 1992 and was defined in the World Health Classification of Tumors in 2002 [87, 89]. According to the WHO classification (2013) for soft tissue tumors, PEComa include epithelioid angiomyolipoma, clear cell tumor, clear-cell myomelanocytic tumors of the falciform ligament/ligamentum teres, clear-cell "sugar" tumors, lymphangioleiomyoma/lymphangiomyomatosis of the lung, and other PEComa of uncertain differentiation, so-called "PEComa-NOS" (perivascular epithelioid cell tumor not otherwise specified) [87,90]. They are mostly considered benign, but on occasions can develop malignant characteristics with metastases.

According to clinical, radiologic, and morphologic diagnostic features, PEComa of the liver may appear different from angiomyolipoma of the liver [87,90,91]. In contrast to a "classic angiomyolipoma," a PEComa does not have adipocytes or abnormal vessels [87,88]. Furthermore, PEComa of the liver is very rare. Only 25 cases of hepatic PEComa were described worldwide between 1999 and 2014 [87].
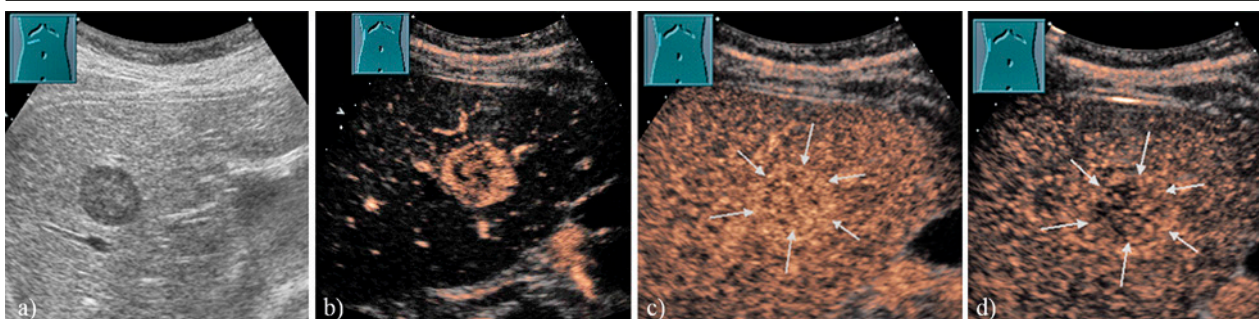
Fig 4. PEComa. A 49-year-old female patient with a hypoechoic hepatic mass as an incidental finding (a). On contrast-enhanced ultrasound, the lesion showed homogeneous marked hyperenhancement after 20 s (b). The lesion is still mildly hyperenhanced (arrows) after 4 min (c) and shows mild hypoenhancement (arrows) after 6 min (d). An ultrasound-guided biopsy was performed, and the diagnosis of PEComa was confirmed histologically.

Imaging

No standardized specific imaging morphological characteristics exist at this time [87]. On the basis of casuistic data, the mostly hypoechoic tumor shows early arterial adenoma-like hyperenhancement with an inhomogeneous slight parenchymal washout [87]. The diagnosis is always made histologically. Although the tumor is often classified as benign, aggressive courses with the occurrence of metastases have also been described [87,92]. Folpe et al [87,93] established a classification to assess malignancy. Based on this classification, tumors with a size of >5 cm, a vascular infiltration and proliferation index of >1/50 HPF (high power fields), and tumor necrosis have a higher risk of malignancy and should be resected [87,92] (fig 4).

Solitary fibrous tumor

Solitary fibrous tumors of the liver (SFTLs) are uncommon neoplasms of mesenchymal origin histologically characterized by spindle cells and collagen. They are most frequently found in the pleura [94] and secondarily in other serous cavities such as the pericardium and the peritoneum [95], as well as non-serous cavities, soft tissues, and solid organs [96,97]. The vast majority of SFTs are benign neoplasms, with a higher frequency of malignity in the pleura [98]. In 1959, solitary fibrous tumors of the liver (SFTLs) were first reported [99] in a case series that encompassed three different tumors; one was a SFTL with hypoglycemia as a manifesting symptom. SFTLs are extremely rare, and fewer than 100 cases have been reported in the literature. Prognosis is uncertain due to their erratic behavior: although the vast majority of the reported cases are benign neoplasms [100], malignant progression was reported, occurring with the loss of CD34 positivity [101]. Primary malignant SFTLs have been described in rare cases [102] and can recur even 10 years after surgery.

England's criteria [103] are used to identify malignant SFTLs based on pathology; these include mass diameter, mitotic rate, metastasis, and nuclear pleomorphism [104]. A certain diagnosis is possible only with a histopathological analysis on the resected lesion; the role of fine-needle biopsy is debated [105]. Therefore, pathology plays a pivotal role in diagnosing SFTLs. The macroscopical appearance is of a solid mass, firmly elastic at the edge with a smooth, thick white-yellow capsule [104]; in the context of the lesion necrosis, hemorrhage as well as areas of cystic necrosis and myxoid degeneration [106] can be observed. Initially, STFLs were described as hemangiopericytomas (HPCs), soft tissue neoplasms with a characteristically branched vascular pattern, a feature later understood to be non-specific and shared among many neoplasms [107]. These lesions do not have a microscopical unequivocal appearance, ranging from more to less fibrous tumors.

Gengler et al proposed a classification system that account for this difference; they further identified a cellular and a fibrous type of solitary fibrous tumor [107]. Cells with a spindle-like appearance and ovoid, banded, or fusiform nuclei are interspersed in a "pattern-less" pattern in a hyaline-radiated area [104, 108]. Other notable features include a myxoid stroma and branching vessels with thick walls, leading to its previous classification as an HPC [104,107]. Known malignancy predictors are nuclear atypia, areas of necrosis, and a high rate of mitotic figures [109]. Immunohistochemistry is a tool of utmost importance in correctly diagnosing an SFTL, and stains are positive for the following proteins: CD34, expressed in endothelial and mesenchymal cells [108]; CD99; BCL-2; and vimentin [110]. They are negative for epithelial membrane antigen (EMA), smooth muscle actin (SMA), CD117, S-100, IgG4, cytokeratin AE1/AE3, and desmin [107,110]. Clinical features are nonspecific: this neoplasm is usually detected incidentally while investigating other conditions. Mass effect-relat-
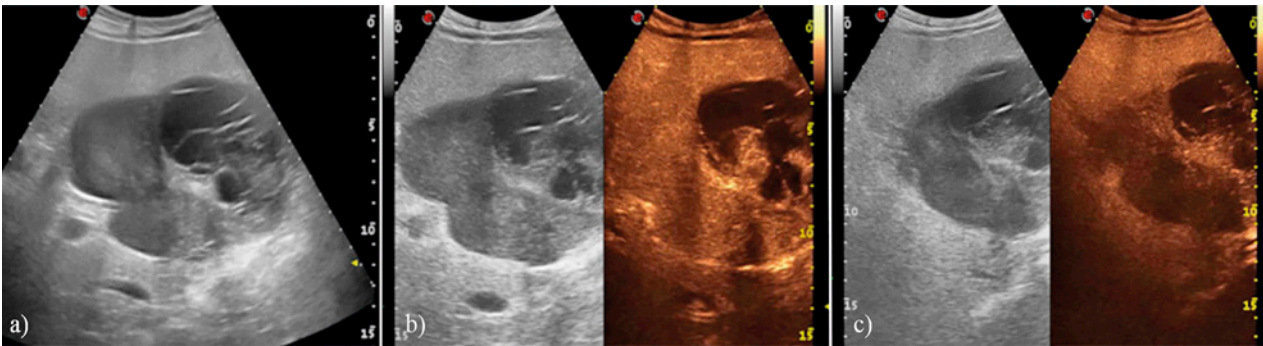
Fig 5. Solitary fibrous tumor (histological proven). 69 y/o male with a hepatic lesion in segment 3, discovered while undergoing surveillance for an IPMN. B-mode ultrasound showed a large heterogeneous lesion with a mixed pattern both hypo- and anechoic, compatible with a solid and fluid component (a). Upon injection of contrast (2.4 ml, Sonovue©) the solid portion appeared isoechoic in the arterial phase, with a well visible vascular pattern, with protrusion into the fluid segments. (b) Washout started at 50 seconds and increased in intensity (c – 90 seconds).

ed symptoms such as epigastric fullness are common, although the mass may remain largely asymptomatic [111]. Hypoglycemia may occur due to the ectopic production of insulin-like growth factor 2 (IGF-2) by the tumor. High circulating serum levels was demonstrated in such cases [112].

Imaging

Imaging is paramount for diagnosing this neoplasm. Contrast-enhanced CT detects SFTL as a hypodense and hypervascularized mass that has a thick capsule with strong hyperenhancement in both the arterial and portal phases, becoming even more hyperenhanced in the late venous phase [108,111]. The MRI appearance of this neoplasm is iso-hypo-intense in T1-w and T2-w sequences with respect to the normal parenchyma, given the high fiber content of the lesion [110]. Following contrast administration, a heterogeneous enhancement is observed in the arterial, portal, and late phases [95,100,110], while the contrast biliary excretion phase demonstrates hypo-intensity [113]. In PET/CT scans, mass uptake is heterogeneous [113], the higher the uptake, the more likely the mass displays malignant behavior [110,113]. US reports a solid and well-defined heterogenous mass, while CEUS reveals heterogeneously isoenhanced lesions in the arterial phase that progressively become hypoenhanced during the venous and late phases. The lesion often presents as a solitary large heterogeneous lesion, with marked peripheric enhancement mimicking sclerosing hemangioma, cholangiocarcinoma and fibrolamellar hepatocellular carcinoma [66].

Surgical resection is the main option currently available for malignant tumors [100], and it has proven to be curative in most cases [114]. Other options reported in literature include transarterial chemoembolisation (TACE) [115] and chemotherapy [116], although neither has strong evidence to support its use (fig 5).

Conclusion

Owing to its unique advantages of a non-invasive technique without ionizing radiation and real time scanning capability, CEUS has become an established complementary imaging modality which can be very helpful for non-invasive assessment of rare liver tumors, particularly when CT/MRI results are inconclusive. "Washout" as a sign of malignancy using CEUS is regarded a marker of cases which need biopsy. Also, if imaging findings are not typical or diagnostic, biopsy is required.

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