Liver-specific MRI contrast agent in the diagnosis and management of hepatocellular carcinoma (2020): Consensus document by College of Radiology, Malaysia

Executive summary

- This is a consensus document from a multidisciplinary panel of general and interventional radiologists, hepatologists and hepatic surgeons regarding guidance for hepatobiliary imaging in hepatocellular carcinoma (HCC) and liver secondaries.
- The objective of this consensus document is to serve as a reference document for hepatobiliary imaging in HCC patients in Malaysia. The multidisciplinary panel of doctors reviewed the hepatobiliary imaging guidelines of different regions around the world and discussed the pros and cons of the various strategies involved. After discussion and deliberation, the following consensus was arrived at:
  - Abdominal ultrasound (US) scan along with serum alpha fetoprotein (AFP) level estimation should be the methodology for HCC surveillance.
  - If a nodule is detected on abdominal US scan, the patient should be subjected to further confirmatory diagnostic tests.
  - Further diagnostic tests for a single nodule of mass detected on US scan can be decided based on the size of the nodule/ mass (<1cm or >1cm).
  - If multiple nodules <1 cm are detected, gadolinium ethoxy-benzyl diethylenetriamine pentaacetic acid-enhanced MRI (EOB-MRI) is highly recommended to confirm the diagnosis of HCC and metastasis.
  - EOB-MRI is recommended to diagnose liver secondaries.
  - Use of MRI can help minimize the need for liver biopsy in patients with HCC.
  - For post-therapy monitoring, cross-sectional imaging (CT or MRI) and a close-range scanning at least every 3 months is recommended.

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of death and accounts for 90% of primary liver cancers globally.(1) As per data from the National Cancer Registry in 2007, liver cancer was the tenth most common cancer in Malaysia and the sixth most common cancer in Malaysian men. The incidence was highest in patients in the seventh decade of life. (2) The annual mortality rate of liver cancer in Malaysia has been showing an upward trends since the last few decades and was 6.1% in 2013.(1)

The high prevalence of HCC in Malaysia is partly attributed to the high incidence of hepatitis B and hepatitis C in the country.(1) Hepatitis B and C virus infections are responsible for 80-90% cases of HCC worldwide. Other risk factors include male sex, elderly, smoking, genetic factors, chemical and environmental factors, diabetes and obesity.(3) Early diagnosis and treatment of the disease can improve the survival by up to 50%.(1)

Hepatobiliary surveillance and diagnostic guidelines have been evolving across various regions and are framed to complement the local epidemiology, diagnostic facilities and healthcare priorities.The European, American, Asian, Korean, Chinese and Japanese guidelines on HCC have been updated in recent times keeping in line with the local demands and changing technologies.(3)

Comparison of International Guidelines

In Malaysia, majority (62%) patients with HCC are diagnosed in advanced (stage 4) stage of disease due to lack of screening programs. Further, limited imaging and liver biopsy facilities also contribute to delayed diagnosis. While computed tomography (CT) and magnetic resonance imaging (MRI) scans are not easily available, most patients refuse liver biopsy as it is an invasive procedure.(2) A study in Malaysian patients with HCC showed that more than 50% patients were positive for Hepatitis B.(2)

European Association for the Study of Liver guidelines (2018)

The European Association for the Study of Liver (EASL) guidelines were updated in 2018 over the previous EASL-EORTC guidelines. The key recommendations for diagnosis and management were(4):

- Implementation of screening programs to identify at-risk populations.
- Surveillance of patients at high risk with abdominal US scan every 6 months.
- Biomarkers such as alpha-fetoprotein (AFP), AFP-L3 isoform and des-gamma-carboxy-prothrombin (DCP) are not optimal or cost-effective for surveillance in early HCC.
- Diagnostic algorithm and recall policy in high risk/cirrhotic patients is as follows:
  - In case of cirrhotic patients with nodule(s) ≥1cm, multiphasic CT or dynamic CE-MRI should be used for the diagnosis based on identification of the classical hallmarks of the disease and/or liver biopsy.
  - In high-risk patients, nodules <1cm in diameter detected by US scan should be followed up at least every four monthly in the first year and six monthly thereafter.
  - CT or MRI should be the first line investigation due to their higher sensitivity.
  - Fluorodeoxyglucose positron-emission tomography (FDG PET) scan is not recommended for early screening of HCC due to the high rate of false-negative results.
  - Liver biopsies can be used for diagnosis in patients with inconclusive imaging findings.
- Multiphasic contrast-enhanced CT or MRI are recommended for assessment of response after therapeutic interventions.
- Barcelona Clinic Liver Cancer (BCLC) classification should be used for the staging of disease.

American Association for the Study of Liver Diseases guidelines (2018)

The American Association for the Study of Liver Diseases (AASLD) recommends the following strategies for the diagnosis of HCC(5):

- US scan with or without AFP is recommended for surveillance of HCC in cirrhotic patients.
- Recall procedures for diagnosis of HCC should be triggered if:
  - Lesion size is >1 cm on US scan
  - AFP >20ng/mL
- Diagnosis of HCC should be done on basis of multiphase CT or multiphase MRI if the following diagnostic criteria are present:
  - size ≥1 cm, arterial phase hyper enhancement, and, depending on exact size, a combination of washout, threshold growth, and capsule appearance.
  - In case of inconclusive imaging findings, liver biopsy should be considered for diagnosis.
- BCLC classification should be used for the staging of disease.
- Surveillance should be performed with CE-CT or CE-MRI every 3-6 months following therapeutic interventions.

Asia-Pacific Association for the Study of the Liver guidelines (2017)

The Asia-Pacific Association for the Study of the Liver (APASL) guidelines are more suited to the healthcare settings in Asia-Pacific region.(6)

- US scan should be used as a screening tool and not for diagnosis of HCC.
- Typical HCC is diagnosed on imaging if a characteristic vascular pattern is seen on dynamic CT, dynamic MRI or contrast-enhanced US (CEUS) scan.
  - Dynamic CT, dynamic MRI or gadolinium ethoxy-benzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)- enhanced MRI (also called EOB-MRI) is recommended as the first line tool for the diagnosis of HCC when a screening test result is abnormal.
  - Characteristics of HCC during dynamic CT scan or dynamic MRI include arterial enhancement, followed by wash-out of the tumour during the portal venous and/or delayed phases.
  - HCC is diagnosed if the above imaging criteria are present in high-risk patients i.e. patients with chronic hepatitis B, chronic hepatitis C or cirrhosis.
  - Nodular lesions with atypical imaging pattern have to be further examined.
  - The combined interpretation of dynamic and hepatobiliary phase of EOB-MRI with diffusion-weighted imaging (DWI) improves the accuracy of MRI in diagnosing HCC.EOB-MRI can detect early HCC including high grade dysplastic nodules (HGDN).
  - AFP is not recommended as confirmatory test in small HCC.

- Surveillance:
  - Should be undertaken in patients with cirrhosis and chronic hepatitis B.
  - AFP can be used in combination with US scan for surveillance programs when the cut-off level for diagnosis is set at 200 ng/mL.
  - Combination of US and AFP 6 monthly should be used for surveillance.

Japan Society of Hepatology guidelines (2019)

Japanese guidelines for HCC were updated in 2019 with the following recommendations:(7)

- Patients with cirrhosis, chronic hepatitis B or chronic hepatitis C are considered as high-risk patients while those with cirrhosis type B and C are considered extremely high-risk group.
- US scan should be used as a screening tool concomitantly with AFP, DCP and AFP-L3.
  - Screening is recommended every 6 months in high-risk patients and every 3-4 months in the extremely high-risk patients.
- Dynamic CT /MRI is used for the differential diagnosis or to confirm the diagnosis of HCC. Typical findings on CE imaging include: intense arterial enhancement followed by washout of agent in the various delayed phases.
- In tumours> 1.5 cm in diameter with negative arterial enhancement or in tumours >1 cm with positive arterial enhancement and negative delayed washout– it is recommended to use liver biopsy, EOB-MRI, CEUS, superparamagnetic iron oxide-enhanced MRI, CT during arterial portography or CT during hepatic arteriography for confirming the diagnosis.
- Surveillance:
  - Smaller lesions can be followed up with US scans every 3 months.
  - Lesions not visualised on US scan may be followed up with dynamic CT/MRI.

Korean Liver Cancer Study Group (KLCSG)- National Cancer Centre (NCC) guidelines (2019)

The Korean Liver Cancer Study Group (KLCSG)- National Cancer Centre (NCC) Korea were last revised in 2019. (8)

- Surveillance should be conducted for high-risk populations i.e. patients with chronic hepatitis B, chronic hepatitis C and cirrhosis:
    - Use US scanning in combination with serum AFP every 6 months.
    - If liver US scan is inconclusive, liver dynamic CT or dynamic CE-MRI may be performed.
- Definitive diagnosis of HCC is based on characteristic findings on multiphase MR/CT with extracellular contrast agents or hepatobiliary contrast agents.
    - Characteristic features for diagnosis include arterial phase hyperenhancement with washout in the venous, delayed or hepatobiliary phases on CT/MRI in lesions which do not show either marked T2-hyperintensity or targetoid appearance on diffusion-weighted images or contrast-enhanced sequences.
    - Characteristic features on CEUS are arterial phase hyperenhancement followed by late (>60 secs) washout of mild degree.
- Biopsy is indicated if diagnosis is inconclusive following imaging studies.

Guidelines for primary liver cancer in China (2017)

The guidelines for diagnosis and management of HCC in China were updated in 2017.(9)

- High risk populations include patients with Hepatitis B and/or Hepatitis C, non-alcoholic fatty hepatitis, liver cirrhosis, family history of liver cancer, long-term alcohol abuse and consumption of aflatoxin contaminated foods.
- Screening is done with US scan and AFP every six monthly in the high-risk patients.
- Diagnosis in nodules ≤2 cm:
    - Based on classical imaging signs seen on at least two imaging modalities (MRI/ CT/CEUS/EOB-MRI).
- Diagnosis in nodules >2 cm and/or positive AFP
    - Based on classical imaging signs seen on at least one imaging modality (MRI/ CT/CEUS/EOB-MRI).
- Liver biopsy can be performed for cases which are inconclusive on imaging tests.
- Surveillance of high-risk patients should be performed every 2-3 months.

Overview of available diagnostic modalities

Serum alpha-fetoprotein

While serum AFP is considered to be an important tumour biomarker, its utility to confirm the diagnosis of HCC is limited as elevated levels are also seen in patients with intrahepatic cholangiocarcinoma, metastasis from the colon, testicular cancers and during flare up of chronic viral hepatitis.(10) It is not suitable for screening of HCC by itself due to a low positive predictive value (25%) in high-risk patients. However, it can be used as a screening tool in combination with US scanning.(3)

Serum AFP has the advantage of being inexpensive, safe and easily available. However, it cannot be used for the non-invasive diagnosis of HCC.(3)

Liver biopsy

Liver biopsy has a sensitivity of 70-90% in diagnosing HCC. However, this is dependent on the location and size of the lesion and expertise to perform the investigation. The pathological hallmark of HCC is stromal invasion which can be absent or difficult to identify on biopsy. Thus, a negative result does not rule out HCC. In addition, it is associated with a 2.7% seeding risk with 17 months being reported as the time between liver biopsy and tumour seeding.(3)

Ultrasonography

Ultrasonography can detect 85-95% lesions measuring 3-5 cm in diameter and has a sensitivity of 60-80% in detecting lesions <1 cm. It has the advantage of being inexpensive, non-invasive, safe and having good patient acceptability. However, smaller lesions are difficult to identify and reliability of results is operator-dependant. The sensitivity of US is further reduced in the presence of cirrhosis.(3)

Contrast-enhanced ultrasonography (CEUS)

Contrast-enhanced US has a sensitivity of 87%, specificity of 100% and accuracy of 93% in diagnosing HCC. It has a similar diagnostic accuracy as multidetector row CT (MDCT) or dynamic MRI and has been accepted by the APASL as an imaging modality to detect lesions <2 cm. However, it is not regarded as specific enough to diagnose HCC by the AASLD guidelines. The short duration of the arterial phase prevents detailed evaluation of the liver parenchyma; hence a CT or MRI is still required for intrahepatic staging of the disease. Though CEUS is a safe investigation, its availability is limited.(3)

Computed tomography (CT) scan

The sensitivity is significantly higher with the use of multidetector computed tomography (MDCT) compared with single-detector row CT (SDCT) (65–79% *vs*. 37–54%) to detect HCC. The multiphasic spiral CT has a sensitivity of 61–87.7% and a specificity of 91% for HCC diagnosis. Further, CT scans have the advantage of not being dependant on patient cooperation and allowing faster single-breath-hold total liver imaging, requiring an average of <10 sec. However, its use is limited by the cost, availability and exposure to radiations. Further, it only assesses the vascular pattern of a mass and not the tissue characteristics, unlike MRI.(3)

Magnetic Resonance Imaging

The dynamic MRI has a sensitivity of 91–100% for lesions >2 cm and 35–71% for lesions <2 cm. However, its use is limited by high cost and technical demands and longer overall examination time of 30-45 mins. Further, it is contraindicated in patients with metallic implants, claustrophobia, or pacemakers. Patient cooperation is required for an average time of 15–20 sec for single-breath-hold liver imaging. Artefacts may be produced in patients with ascites. (3)

Gd-EOB-DTPA–enhanced MRI (EOB-MRI)

Recent years have seen an increase in the utilisation of EOB-MRI for the diagnosis of HCC. It has the advantages of enabling dynamic and hepatocyte-specific imaging of the liver.The contrast is excreted through liver and kidneys which helps to improve the safety profile.(11) The APASL, JSH and Chinese guidelines recommend the use of EOB-MRI for diagnosis of HCC.(12) Clinical studies have established that EOB-MRI has a key role in the diagnosis and management of HCC. Staging is more accurate with EOB-MRI compared with CT.(13) It also helps in earlier detection of HCC compared with US and has a significantly lower false positive rate.(14) The accuracy of EOB-MRI in diagnosing and characterising malignancies is higher compared with dynamic CT.(15)(16) Further,the safety of EOB-MRI and lack of clinically significant gadolinium presence in the brain when used as per current clinical practice has been proven in clinical studies.(17)

However the cost and technical demands limit the availability of this investigation.(3)

Proposed Malaysian guidelines

As emphasized by the EASL guidelines, the recommendations of guidelines need to be adapted to the local healthcare settings and cost-benefit strategies.(4) After reviewing the current practice guidelines used internationally and regionally, the panel proposed the following guidelines for use in Malaysia:

HCC Surveillance

- Abdominal US scans along with AFP estimation should be used for surveillance of HCC.
    - AFP should be used as a surrogate marker or sequential increase in AFP levels from baseline should be monitored.
    - Abdominal US scans should be done every 3-4 months in all cirrhotic patients regardless of aetiology of cirrhosis. Cirrhosis should preferably be diagnosed by imaging or by liver elastography.
    - Abdominal US scan should be performed every 6 months for patients with non cirrhotic hepatitis B (men aged >40 years; women aged >50 years), with a family history of cirrhosis or HCC.
    - US scans should be performed by trained personnel, using good, intermediate to high-end equipment. The equipment should be well maintained and serviced on a regular basis.
    - Any nodule detected on abdominal US scan should be evaluated with further diagnostic tests to confirm the diagnosis of HCC.

HCC Diagnosis

- An algorithm for the diagnosis of HCC based on the nodule/mass size (<1 cm or >1 cm) detected on US scan is presented in Fig. 1.
    - In cases of both single and multiple nodules, MRI should be preferred over CT as it has a better resolution. However, one should also consider the availability, practicability, patient load, affordability, and the imaging expertise of each centre.
    - In case of clinical suspicion of HCC with no nodules detected on US scan, cross-sectional imaging can be used for detection and monitoring of HCC.
    - In case of dysplastic nodules detected by EOB-MRI, follow-up surveillance should be done by EOB-MRI only.

Fig 1: Algorithm for the diagnosis of HCC based on nodule/mass detected on US scan
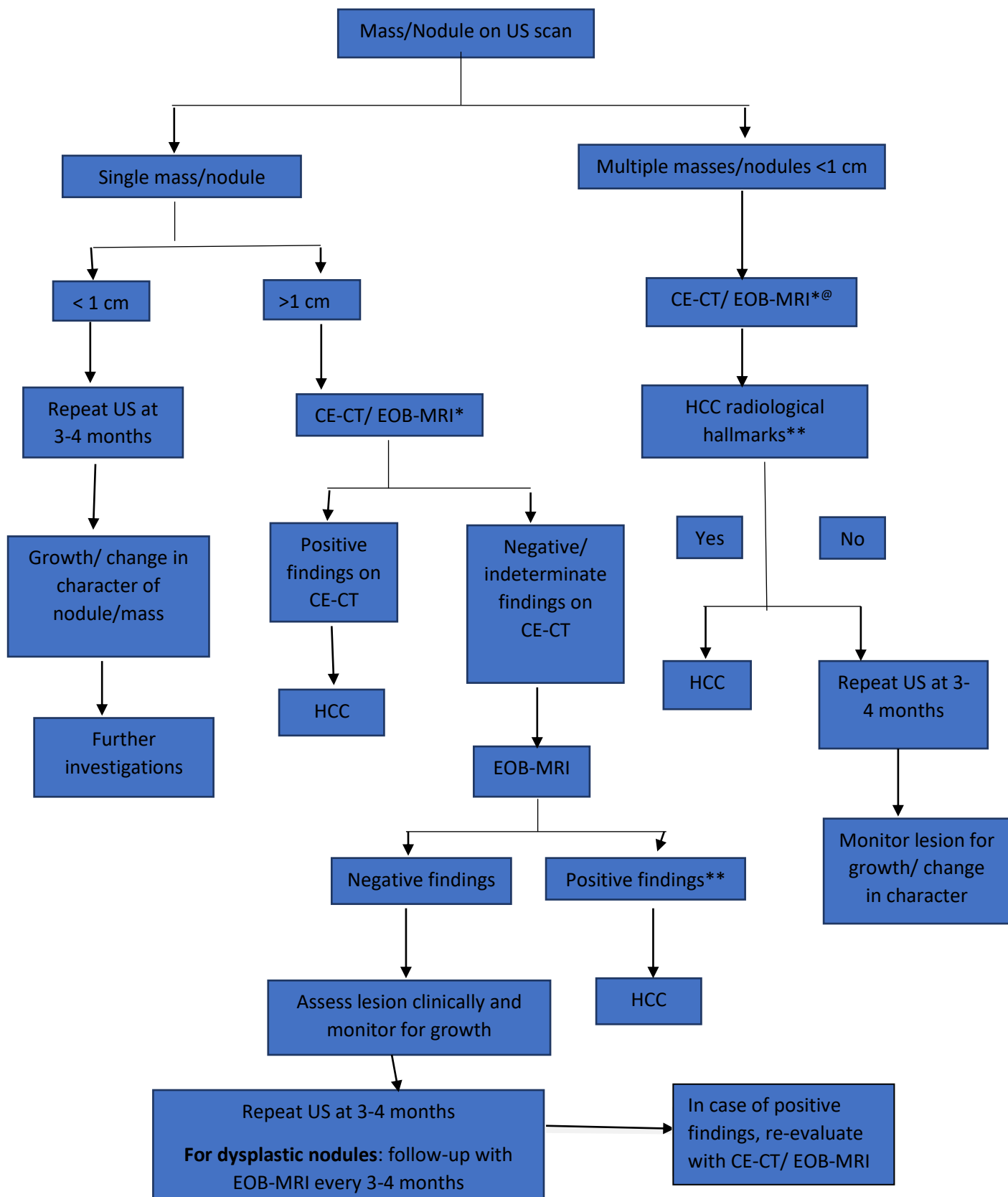
CE CT: Contrast-enhanced computed tomography scan; EOB-MRI: gadoxetic acid-enhanced magnetic resonance imaging; HCC: Hepatocellular carcinoma; US: ultrasound; *: Only one imaging technique is recommended in centres with high-end radiological equipment; **: HCC radiological hallmarks (arterial hypervascularity and venous/late phase washout); @: if dysplastic nodules are detected on cross sectional imaging CT/MR, they should be followed up with EOB-MRI surveillance every 3-4 months.

Post-therapy Monitoring

- Following resection/ablation/trans arterial treatment, cross-sectional imaging (CT or MR) and a close-range scanning at least every three months for the first year is recommended.
- EOB-MRI is recommended for post-therapy monitoring.

Liver Secondaries Imaging

- EOB-MRI is recommended to diagnose liver secondaries (see Fig. 2). Magnetic resonance imaging is superior to CT in detecting liver secondaries.
- The use of liver biopsy can be minimized by using MRI. A clinical assessment is recommended before obtaining a biopsy.

Figure 2: Algorithm for liver secondaries imaging

Metastatic lesions present with peripheral rim enhancement and lack of central enhancement in the dynamic phase of EOB-MRI when central tumour necrosis is present. During the hepatobiliary phase, lesions appear hypointense and may also show rim enhancement and a "target sign".(18)
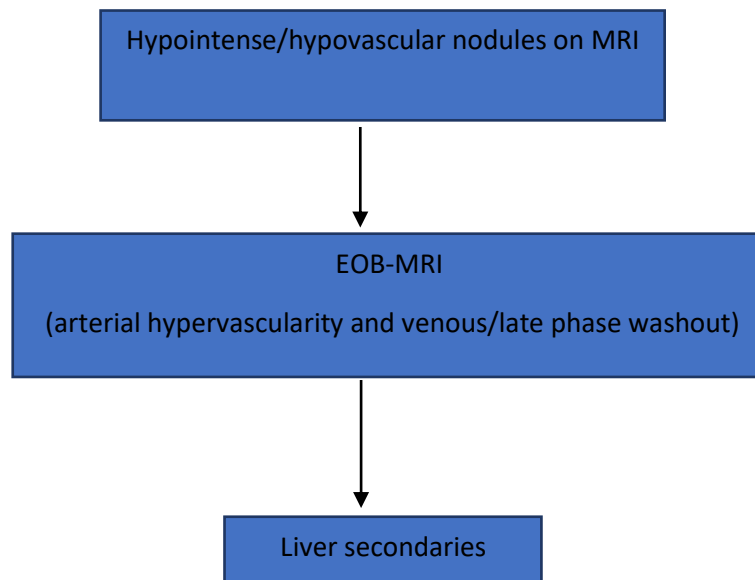
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