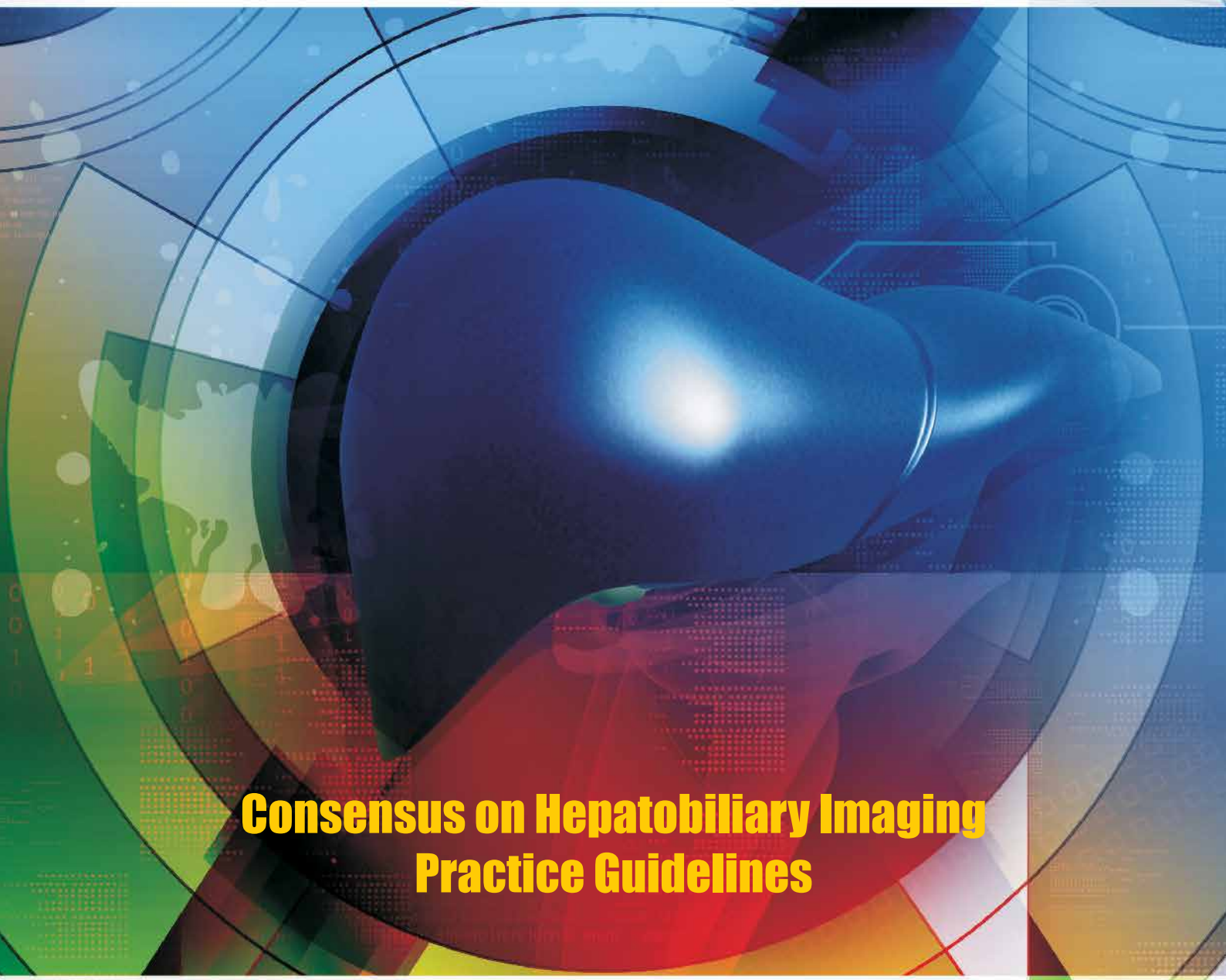
COLLEGE OF RADIOLOGY
Academy of Medicine of Malaysia



Consensus on Hepatobiliary Imaging Practice Guidelines

Practice Guidelines on Hepatobiliary Imaging:

A Malaysian Perspective

College of Radiology, Consensus Document

Executive Summary

- This is a consensus document from the College of Radiology regarding the Malaysian perspectives 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 Malaysia. A panel of doctors related to the field of HCC and liver secondaries reviewed the hepatobiliary imaging guidelines of different regions and the merits and demerits of various tests involved. They then discussed and debated to come to the following consensus:
  - 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 or mass detected on US scan can be decided based on the nodule/mass size (<1 cm or > 1 cm).
  - If multiple nodules <1 cm are detected, a contrast-enhanced computed tomography (CT) scan or contrast-enhanced magnetic resonance imaging (MRI) is recommended to confirm the diagnosis of HCC.
  - Contrast-enhanced MRI is recommended to diagnose liver secondaries.
  - Use of MRI can help minimize the need for liver biopsy in patients with HCC.
  - For posttherapy monitoring, cross-sectional imaging (CT or MR) and a close-range scanning at least every 3 months are recommended.

Introduction

Globally, hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths.[1] Although it is the sixth most prevalent cancer, it takes third place when it comes to cancer-related deaths owing to its poor prognosis.

The poor prognosis associated with this cancer further necessitates the need for its early diagnosis and management. One of the notable epidemiological findings of HCC is its association with viral infections and excessive alcohol intake. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections account for 80–90% of all HCC cases worldwide. Other factors associated with the increased risk of HCC include male sex, older age, smoking, genetic factors, chemical factors, environmental factors, diabetes, and obesity. Subjecting the at-risk population to an effective surveillance and diagnostic protocol can help in the early diagnosis and management of HCC.

Liver cancer varies worldwide in its incidence, with moderately high or very high incidence of 11–20 or >20 cases per 100,000 male inhabitants in China, Southeast Asia, and sub-Saharan Western and Eastern Africa to low

or intermediate levels of <5 or 5–10 per 100,000 in most of the developed areas of the world, including North America and most of Europe. However, the notable exceptions are Southern Europe and Japan, with higher incidence rates of 11.6 per 100,000 and 23.1 per 100,000, respectively.[2,3] The hepatobiliary surveillance and diagnostic guidelines have evolved worldwide based on local epidemiology, diagnostic facilities, and healthcare priorities. The European Association for the Study of the Liver (EASL) issued hepatobiliary imaging guidelines for HCC in 2001, which were later updated in association with the European Organization for Research and Treatment of Cancer (EORTC) in 2011. The American, Asian, Korean, and Japanese guidelines followed over the course of time.[5,6,7,8,9,10]

Need for a Malaysian Consensus Document on HepatobiliaryImaging

As of now, there are no Malaysian guidelines or consensus documents for hepatobiliary imaging in HCC and liver secondaries. The need for standard guidelines is imperative as the incidence of HCC in Malaysia is high, in comparison with the global levels. Furthermore, many cases of HCC may not be diagnosed because of lack of ultrasound (US), computed tomography (CT) scan, or liver biopsy facilities in some medical centers.[4] This consensus document aims to fill this lacuna with recommendations to standardize the surveillance and diagnosis of HCC and liver secondaries in Malaysia.

Review of Salient Features of Other Regional Hepatobiliary Imaging Guidelines

European Association for the Study of the Liver (EASL)

The EASL was the first professional body to issue guidelines for hepatobiliary imaging in HCC in 2001. The updated 2011 clinical practice guidelines for HCC surveillance are described here:[5]

- Abdominal US should be used as the surveillance method in at-risk population and should be performed[5]
  - Every 6 months in all at-risk patients having:
    - Cirrhosis
    - Cirrhosis, awaiting liver transplantation
    - Noncirrhotic HBV and HCV infection
  - Every 3–4 months in the following cases:[5]
    - Patients in whom a nodule of <1 cm has been detected
    - In the follow-up strategy after resection or loco-regional therapies
- Accurate tumor biomarkers need to be developed for early detection. Data available with tested biomarkers [i.e., alpha fetoprotein (AFP), its glycosylated fraction (AFP-L3), and des-gamma-carboxy prothrombin (DCP)] show that these tests are suboptimal for routine clinical practice.[5]

The EASL-EORTC diagnostic algorithm and recall policy are as follows:[5]

- Here, the investigational algorithm is driven by tumor size:
  - Tumor <1 cm is monitored by abdominal US every 4 months during first year and every 6 months thereafter.
  - If the tumor is >1 cm, imaging techniques by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI are used. While one or two imaging techniques are required for nodules of 1–2 cm, one technique is recommended for nodules greater than 2 cm in diameter.

- Biopsies are employed if the lesions do not show characteristic arterial hypervascularity and venous/late phase washout on imaging studies. The biopsy specimens need to be reviewed by expert hepatopathologists.
- If all these investigations reveal inconclusive results, these patients enter the surveillance protocol with periodic US monitoring.

American Association for Study of Liver Diseases (AASLD) 2010 and Asian Pacific Association for the Study of the Liver (APASL) 2008 and 2012 Consensus Guidelines

Some of the salient features of the AASLD and APASL Consensus Guidelines are as follows:[7,8]

- The AASLD and APASL recommend the use of AFP estimation and gray-scale US of the liver for active surveillance of HCC in at-risk population.
- Currently, CT and magnetic resonance imaging (MRI) are not recommended for screening. Although they have higher sensitivity and specificity for detection of HCC, they have not been validated for this use.
- Both organizations agree that the presence of arterial hypervascularity and washout has a high specificity for a diagnosis of HCC. For nodules <1 cm that are round, oval, and intraparenchymal or for nodules in a dominant mass, the lesion should be followed up with imaging once every 3 months. Imaging can be performed once in 6 months in the presence of hypervascular nodules that are <5 mm, subcapsular, wedge shaped, or ill defined.
- The diagnostic algorithm, however, differs between AASLD and APASL, if there are no classical CT findings.[7]
  - The AASLD recommends to consider lesions >2 cm as HCC and manage them accordingly as they have a clear risk for HCC. It is recommended that to confirm the presence of HCC without biopsy, in case of nodules of 1–2 cm, the presence of classical features should be sought in 2 imaging modalities: CT and MRI.
  - If there are no classical CT findings, the APASL recommends liver cell-specific imaging modalities based on vascularity of the lesions. HCC is diagnosed in hypervascular lesions if there are unenhanced areas on contrast enhanced (CE) US and T2 -hyperintense lesions on SPIO-enhanced MRI. The hypovascular lesions are subjected to CE US and Kupffer-specific imaging. If there is enhancement in hepatic arterial phase in the former and/or lack of uptake in the latter, HCC is diagnosed. However, the limitation of this mode of diagnosis of HCC based on vascularity of the lesions is the possible presence of confounding factors. Other hypervascular malignancies such as neuroendocrine carcinoma metastasis confounds hypervascular lesions, while adenocarcinoma metastasis confounds Kupffer-specific imaging of hypovascular lesions.
  - Both organizations recommend biopsy as the diagnostic step if both CT and MRI scans are inconclusive.[7]

Japan Society of Hepatology

The Japan Society of Hepatology (JSH) is the first body to recommend dynamic CT or dynamic MRI/ethoxybenzyl MRI (EOB-MRI) in populations at very high risk of HCC. Some salient features of the JSH Clinical Practice Guidelines 2010 are as follows:[10]

- Patients at risk for HCC are categorized into super-high-risk and high-risk populations. Super-high-risk population includes those with HBV- or HCV-related liver cirrhosis. High-risk population includes those with chronic hepatitis B or C or liver cirrhosis (causes other than HBV or HCV).[10]
- The surveillance protocol for super-high-risk-population includes an US scan examination and evaluation of either AFP, a protein induced by vitamin K absence or antagonist-II (PIVKA-II), or AFP lectin fraction (AFP-L3)

performed every 3–4 months, and a dynamic CT or dynamic MRI or ethoxybenzyl MRI (EOB-MRI) performed every 6–12 months.[10]

- Patients at high risk should be subjected to US examination and AFP/PIVKA-II/AFP-L3 measurements every 6 months.[10]

Overview of Available Diagnostic Modalities

The techniques used for surveillance, diagnosis and monitoring of HCC and liver secondaries are discussed below.

Serum AFP Level Estimation

According to the AASLD guidelines, the cutoff level of AFP to diagnose HCC has been lowered from the earlier recommended level of 400 ng/mL to 200 ng/mL by the 2000 EASL conference. At a cutoff level of 200 ng/mL, serum AFP has been reported to be associated with several advantages. A cutoff level of 200 ng/mL has been reported to be superior to the cutoff level of 400 ng/mL with a sensitivity of 22.4% vs. 17.1% and a specificity of 66–97% vs. 60–96%. At a cutoff level of 200 ng/mL, AFP has been reported to have a sensitivity, specificity and positive predictive value of nearly 99%.[9] Alpha-fetoprotein when combined with US screening is associated with increased rates of HCC detection. Despite these advantages, AFP is associated with certain disadvantages. On its own, AFP is not sufficient to screen for HCC, because it is associated with a low positive predictive value of approximately 25%, especially in patients at high risk for HCC. The sensitivity of AFP is reduced when a higher threshold is applied to improve specificity.[7]

Serum AFP test is relatively safe and inexpensive. It is available in most laboratories. High-end expertise or complex instruments are not required to perform this test.[11] However, the use of AFP estimation for the diagnosis of HCC is associated with inherent false-positive results in patients with cirrhosis and with false-negative results.[7]

Liver Biopsy

The location and size of the lesion, and the expertise to do the test, affect the sensitivity of liver biopsy results. For all tumor sizes, liver biopsy has sensitivity in the range of 70–90%. However, liver biopsy is associated with certain disadvantages. Stromal invasion, the pathological hallmark of HCC, can be absent or difficult to identify in biopsy specimens. Hence, a negative biopsy does not rule out malignancy. A 2.7% risk of tumor seeding, with a median time interval of 17 months between biopsy and tumor seeding has been reported following liver biopsy.[5]

Technical expertise is needed to perform the procedure and a pathologist is required to interpret the results of liver biopsy. In addition, it is associated with a risk of bleeding, and an overall reported mortality of 0.06%.[12]

Ultrasound Screening

This diagnostic modality is superior to AFP assay in detecting HCC.[7] It can detect 85–95% of lesions measuring 3–5 cm in diameter. The sensitivity of US to detect HCC lesions of 1 cm is 60–80%. The procedure is noninvasive and is not associated with any risks; hence, it is well accepted by patients. The disadvantages of US are that it is less reliable to identify smaller lesions and that the expertise of the operator influences the results.[13] Furthermore, in the presence of cirrhosis, the sensitivity of US is reduced to 60%.[14]

Ultrasound screening is a very safe and relatively inexpensive procedure.[11] Hence, a relatively less complicated set up is required to perform this test.

Contrast-Enhanced US Screening

According to the APASL guidelines, Contrast-Enhanced US Screening (CEUS) on its own is an accepted imaging modality to diagnose HCC and has been validated even for lesions <2 cm. It has been reported that CEUS has a sensitivity of 87%, specificity of 100%, and accuracy of 93% to diagnose HCC.[7] The diagnostic performance of CEUS is similar to that of multidetector row CT (MDCT) or dynamic MRI.[9] When compared with iodinated

contrast agents used for CT and gadolinium chelates used for MRI, the contrast agents used in US screening are not cleared by the kidneys. Thus, CEUS is a safe diagnostic modality in patients with compromised renal function, and there is no need to perform renal function tests before the administration of contrast agent.[15] However, this modality is associated with several disadvantages. It is not regarded as specific enough for diagnosing HCC and has therefore been excluded from the revised AASLD guidelines.[7] Benign lesions such as hemangiomas that do not contain Kupffer cells appear to be hypoechoeic on Kupffer-specific phases of CEUS imaging. Hence, the Kupffer phase imaging is nonspecific by itself. The short duration of arterial phase precludes a comprehensive evaluation of the entire liver parenchyma. Therefore, a CT or MRI is still mandatory for proper intrahepatic staging of the disease.[15]

The contrast agents used in this modality have been reported to be very safe with a low incidence of side-effects.[15] The use of contrast agents containing perfluorobutane microbubbles (e.g., Sonazoid) is currently limited because it is not available outside Japan.[7]

Computed Tomography Scan

This diagnostic modality is associated with several advantages. It facilitates faster single-breath-hold total liver imaging, requiring an average of <10 sec. The use of MDCT when compared with single-detector row CT (SDCT) is associated with increased sensitivity (65–79% vs. 37–54%) to detect HCC. The multiphasic spiral CT is associated with a sensitivity of 61–87.7% and a specificity of 91% for HCC diagnosis.[9] In addition, the technique is less dependent on patient cooperation.[16] The disadvantages of CT are that the equipment and the image acquisition conditions influence the frequency of obtaining typical findings;[10] and a high radiation dose associated with CT prevents short interval follow-up. Moreover, a CT scan, when compared with an MRI, can assess only the vascular pattern of a mass and not the tissue characteristics.[17]

Patients undergoing CT scan are exposed to X-ray radiations and the associated complications.[16]

Magnetic Resonance Imaging

This modality when directly compared with the 64-row CT has been shown to be significantly more sensitive in detecting tumor nodules.[7] The sensitivity of a dynamic MRI has been reported to be 91–100% for tumors >2 cm and 35–71% for tumors <2 cm.[9] Despite these advantages, MRI is also associated with certain disadvantages. The relatively high cost and technical demand of MRI may limit its selection over CT.[7] This modality requires a longer overall examination time of 30–45 min and is contraindicated in patients with certain metallic implants, claustrophobia, or pacemakers. Better patient cooperation is required for an average time of 15–20 sec for single-breath-hold liver imaging. This procedure is associated with a small risk of nephrogenic systemic fibrosis in patients with renal insufficiency. Artifacts may be produced in patients with ascites.[16]

The MRI is a safe diagnostic procedure and patients are not exposed to radiation as in CT scanning. The procedure is expensive and requires complex technical instrumentation and expertise.[16]

Contrast-Enhanced MRI

The diagnosis of HCC can be improved with the use of hepatocyte-specific MRI agents gadoxetic acid (Gd-EOB-DTPA: Primovist, Bayer) and gadopentetate dimeglumine (Gd-BOPTA: Multihance, Bracco). The diagnostic performance of MRI using these agents is similar to or better than SPIO and comparable to double contrast MRI. Primovist-enhanced MRI is superior to CT (reported accuracy: 0.88 vs. 0.74).

Primovist has been reported to be more sensitive than Multihance in detecting HCC (sensitivity: 86% vs. 64%) and this could perhaps be attributed to the reduced uptake of Multihance, which is 5% *vs.* 50% of Primovist. Diffusion-weighted MRI improves the detection of HCCs, especially in lesions <2 cm (sensitivity: 84–98% vs. 76–85% for multiphasic MRI alone).[7] In hepatocyte-selective phases of Primovist-based MRI, the enhancement of focal lesions is hepatocellular selective and can enable distinction of primary and secondary liver tumors.[18]

The disadvantage of CE MRI is that assessment of lesions <1 cm is poor as the sensitivity of Primovist-enhanced MRI combined with diffusion-weighted MRI is only 29–43%. Hence, further experience is required with this hepatocyte-specific MRI agent.[7]

Complex technical instrumentation and expertise are required for MRI scanning and the technique is expensive.[7,11] Hence, the relatively high cost and technical demand may limit the selection of this procedure over a CT scan.[7]

Proposed Malaysian Consensus Guidelines

After reviewing the hepatobiliary imaging guidelines of other regions and the merits and demerits of the different diagnostic tests, the panel has put forth the following guidelines as most suitable for the Malaysian context:

HCC Surveillance

- Abdominal US along with AFP estimation should be the method used for surveillance of HCC.
- Although an AFP value of 200 ng/mL has the highest specificity, its sensitivity in detecting HCC is poor as some HCC lesions do not have elevated AFP levels. In this background, it is recommended that AFP be used as a surrogate marker or a continued increase of AFP from baseline values be monitored.
- Use of abdominal US scan for HCC surveillance:
  - An abdominal ultrasound should be scheduled every 3–4 months for all cirrhotic patients regardless of etiology (for e.g. hepatitis B, hepatitis C, nonalcoholic steatohepatitis, hematochromatosis, etc). Cirrhosis should preferably be diagnosed by imaging or by liver elastography.
  - An abdominal US scan should be scheduled every 6 months for patients with noncirrhotic hepatitis B (men aged >40 years; women aged >50 years), with a family history of cirrhosis or HCC.
  - Ultrasound scanning 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.
  - If a nodule is detected on abdominal US scan, further confirmatory diagnostic tests should be performed.

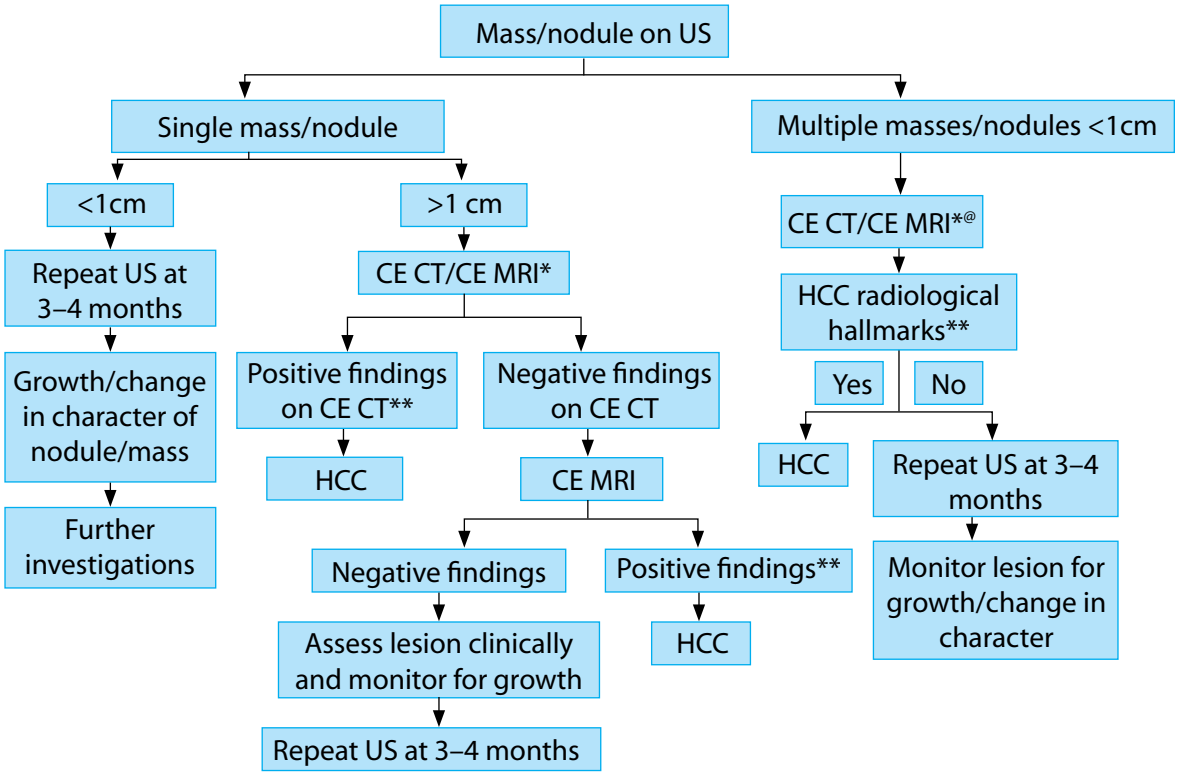
HCC Dagnosis

- An algorithm for the diagnosis of HCC based on the nodule/mass size (<1 cm or >1 cm) detected on US is presented in Fig. 1.
- For diagnosing HCC, in cases of both single and multiple nodules, MRI should be preferred over CT as it has better resolution. However, one should consider the availability, practicability, patient load, affordability, and the imaging expertise of each center.
- If hybrid PET-CT is available, it can be used for the diagnosis of HCC.
- In cases of a clinical suspicion of HCC, if nodules are not seen with the US scan, cross-sectional imaging can be used for detection and monitoring of HCC.

Post-therapy Monitoring

- Following resection/ablation/transarterial treatment, cross-sectional imaging (CT or MR) and a close-range scanning at least every three months is recommended.

Fig. 1: Algorithm for the diagnosis of HCC based on the nodule/mass detected on ultrasound.

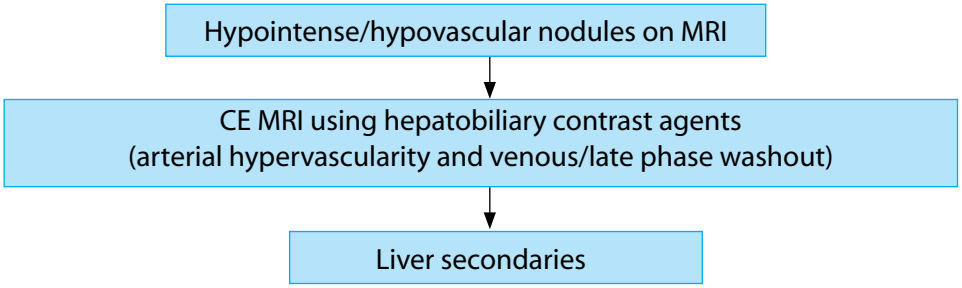


CE CT: Contrast-enhanced computed tomography scan; CE MRI: Contrast-enhanced magnetic resonance imaging; HCC: Hepatocellular carcinoma; US: Ultrasound; *: Only one imaging technique is recommended in centers with high-end radiological equipment; **: HCC radiological hallmarks (arterial hypervascularity and venous/late phase washout); @: if dysplastic nodules are detected on cross sectional imaging CT/MR, US surveillance should be conducted every 3-4 months.

Liver Secondaries Imaging

- Contrast-enhanced 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 using MRI. A clinical assessment is recommended before obtaining a biopsy.
- Hybrid PET scan may soon emerge as the future modality to diagnose liver secondaries and extrahepatic manifestations.

Fig. 2: Algorithm for liver secondaries imaging.



References

1. Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. *Hepatic Med Evid Res*. 2012;(4):19–37.
2. Parkin DM, Bray F, Ferlay J, *et al*. Global cancer statistics, 2002. *J Clin Cancer*. 2005;55:74 –108.
3. Venook AP, Papandreou C, Furuse J. *et al*. The Incidence and Epidemiology of hepatocellular carcinoma: A global and regional perspective. *The Oncologist*. 2010;15(suppl 4):5–13.
4. Norsa'adah B, Nurhazalini-Zayani CGC. Epidemiology and survival of hepatocellular carcinoma in North-east Peninsular Malaysia. *Asian Pac J Cancer Prev*. 2013;14 (11): 6955–6959.
5. European Association For The Study Of The Liver1; European Organisation For Research And Treatment Of Cancer. EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908–943.
6. Bruix J, Sherman M; American Association for the study of liver diseases. Management of hepatocellular carcinoma: An update. *Hepatology*. 2011;53(3):1020–1022.
7. Tan CH, Low SC, Thng CH. APASL and AASLD consensus guidelines on imaging diagnosis of hepatocellular carcinoma: A review. *Int J Hepatol*. 2011;2011:519783.
8. Liaw YF, Kao JH, Piratvisuth T, *et al*. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int (2012) 6:531–561.
9. Song do S, Bae SH. Changes of guidelines diagnosing hepatocellular carcinoma during the last ten-year period. *Clin Mol Hepatol*. 2012;(18):258–267.
10. Kudo M, Izumi N, Kokudo N, *et al*. Management of hepatocellular carcinoma in japan: consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version. *Dig Dis*. 2011;(29):339–364.
11. Coon JT, Rogers G, Hewson P, *et al*. Surveillance of cirrhosis for hepatocellular carcinoma: A cost–utility analysis. *Br J Cancer*. 2008;98:1166–1175.
12. Schölmerich J, Schacherer D. Diagnostic biopsy for hepatocellular carcinoma in cirrhosis: Useful, necessary, dangerous, or academic sport? *Gut*. 2004;53(9):1224–1226.
13. Ryder SD; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut*. 2003;52(Suppl 3):iii1–8.
14. Singal A, Volk ML, Waljee A, *et al*. Meta-analysis: Surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther*. 2009;30(1):37–47.
15. Lencioni R, Piscaglia F, Bolondi L. Contrast-enhanced ultrasound in the diagnosis of hepatocellular carcinoma. *J Hepatol*. 2008;48(5):848–857.
16. Russo MW, Wald C. Radiological diagnosis of hepatocellular carcinoma. *Clin Liver Dis*. 2012;1(6):190–193.
17. Brown L. Role of imaging in hepatocellular carcinoma. *Thai J Gastroenterol*. 2014;15(1):56–60.
18. Huppertz A, Haraida S, Kraus A. Enhancement of focal liver lesions at gadoxetic acid– enhanced MR Imaging: Correlation with histopathologic findings and spiral CT—initial observations. *Radiology*. 2005; 234:468–478.

Contributors

Dr. Nur Yazmin Yaacob
Consultant Radiologist & Interventional Radiologist,
Hospital Universiti, Kebangsaan, Malaysia

Dr. Umarani Ann Ranjini
Consultant Radiologist (Body Imaging),
Hospital Selayang

Dr. Haniza Bt Omar
Consultant Physician (Hepatology),
Hospital Selayang

Dr. Shanthi Palaniappan
Consultant Physician (Gastroenterology),
Hospital Universiti, Kebangsaan, Malaysia

Dr. Azah Bt Alias
Consultant Radiologist (Body Imaging),
Hospital Selayang

Dr. Shahrina Man Harun
Consultant Radiologist & Interventional Radiologist,
Pantai Hospital Kuala Lumpur

Mr. Krishnan Raman
Consultant Surgeon (Hepatobilliary),
Hospital Selayang

Dr. Mohd Rizal Roslan
Consultant Radiologist & Interventional
Radiologist, Hospital Selayang

Professor Rosmawati Mohamed
Consultant Hepatologist
University Malaya Medical Centre

Professor Hamizah Razlan
Consultant Gastroenterologist and
hepatologist, UKM medical Centre.

Professor Abdul Jalil Nordin
Consultant Radiology (Nuclear Medicine)
University Putera Malaysia

Other Contributors

Dr. Murbita Sari Binti Baharuddin
Consultant Radiologist
Hospital Selayang

Dr. Amir Fuad Hussain
Consultant Radiologist
DEMC Specialist Hospital

Dr. Alex Tang
Consultant Radiologist
Sime Darby Medical centre


Developed & Designed by BioQuest Solutions www.bioquestglobal.com