Hepatocellular Carcinoma

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Epidemiology

- HCC is now the fifth-most common cancer in the world and the third cause of cancer-related mortality
- The age at which HCC appears varies according to sex, geographical area, and risk factor associated with cancer development. In high-risk countries with major HBV prevalence, the mean age at diagnosis is usually below 60 years, in intermediate or low incidence areas, most cases appear beyond 60 years of age.

Epidemiology

- In all areas, males have a higher prevalence than females, the sex ratio usually ranging between 2:1 and 4:1, and, in most areas, the age at diagnosis in females is higher than in males.

Etiology and risk factors

- Approximately 90% of HCCs are associated with a known underlying etiology , most frequently chronic viral hepatitis (B and C), alcohol intake and aflatoxin exposure.
- Worldwide, approximately 54% of cases can be attributed to HBV infection ,while 31% can be attributed to HCV infection , leaving approximately 15% associated with other causes.

Etiology and risk factors

- **Cirrhosis is an important risk factor for HCC**, and may be caused by chronic viral hepatitis, chronic alcohol abuse acquired and inherited metabolic diseases, such as NAFLD, as well as genetic haemochromatosis, or in some cases alpha-1-antitrypsin deficiency. All etiologic forms of cirrhosis may be complicated by tumour formation, but the risk is higher in patients with chronic viral hepatitis. **Overall, one-third of cirrhotic patients will develop HCC during their lifetime.**

Etiology and risk factors

- In general, **features of liver disease severity** (low platelet count of less than 100x109/L, presence of esophageal varices) in addition to **older age** and **male gender** correlate with development of HCC among patients with cirrhosis.
- Recent studies have shown that **liver cancer incidence increases in parallel to portal pressure**, measured directly or linked to the degree of liver stiffness as measured **by transient elastography**.

Etiology and risk factors

- **HbeAg seropositivity, high viral load, and genotype C** are independent predictors of HCC development.
- Recent meta-analyses claimed that the risk of HCC development is **increased in patients with HCV genotype 1b or genotype 3.**
- Epidemiologic and molecular studies have shown a strong correlation between aflatoxin B1 exposure, TP53 mutations (codon 249) and incidence of HCC, specifically in HBV-infected individuals.

Etiology and risk factors

- For patients with **alcoholic liver cirrhosis**, an **increased** risk of developing HCC has been reported
- patients with **haemochromatosis** develop HCC in up to **45%** of cases, almost exclusively in stage III of the disease (cirrhosis). HCC is more frequent in patients affected with **acute hepatic porphyria and porphyria cutanea tarda**, as well as **alpha-1-antitrypsin** deficiency.

Etiology and risk factors

- Growing evidence from retrospective investigations suggests an **increased HCC incidence in patients with NAFLD associated with metabolic syndrome, diabetes, and obesity.** Moreover, metabolic syndrome has an additive risk effect in those patients with chronic viral hepatitis. **Overall, NAFLD is becoming a relevant cause of HCC in developed regions**

Etiology and risk factors

- Epidemiologic evidence of a link between **cigarette smoking** and the occurrence of HCC was traditionally conflicting, but recent evidence supports that **smoking is a significant co-factor.**
- The incidence of HCC is **higher** among patients with **HIV infection** than controls in the general population, and HIV appears to be an additive co-factor, increasing the risk of HCC in patients with chronic viral hepatitis.

Prevention

- **Primary prevention** of HCC can be achieved with **universal vaccination against HBV infection**.
- In **hepatitis C** viral infection, all-cause mortality and the risk of HCC is reduced among patients with HCV who achieve a **sustained virological response (SVR)**

Prevention

- Very recently, a meta-analysis concluded that there is **no evidence that HCC occurrence or recurrence is different between patients receiving DAA or IFN therapy**.
- **Coffee consumption** have shown a consistently **positive effect with regard to lowering HCC incidence**. high levels of coffee consumption were associated not only with reduced HCC incidence, but also with lower chronic liver disease mortality

Surveillance

- Patients at high risk of developing HCC should be entered into surveillance programs .
- **Ultrasound (US) is the method of choice**
- Surveillance should be performed by **experienced personnel** in all high-risk populations using abdominal ultrasound **every six months**

Target populations

- **Cirrhotic patients**:

  Child-Pugh stage **A and B**

  Child-Pugh stage **C awaiting liver transplantation**

Non-cirrhotic:

HBV patients at intermediate or high risk of HCC

F3 patients, regardless of etiology may be considered for surveillance based on an individual risk assessment

Target populations

- It is estimated that half of the cases of NASH-induced HCC arise in non-cirrhotic patients.
- Some factors are associated with a higher risk of severe/ fibrosis cirrhosis and HCC occurrence, such as **the presence of diabetes mellitus, older age and concurrent alcohol intake.**
- Patients with metabolic syndrome or NASH identified to be affected by severe fibrosis or cirrhosis either by histology or elastography should undergo surveillance

Treated viral chronic hepatitis

- Surveillance should be offered to treated patients with **chronic hepatitis B** who remain at risk of HCC development because of **baseline factors**, or **those with hepatitis C** virus (HCV)-induced **advanced fibrosis or cirrhosis, even after achieving SVR.**

Surveillance tests

- The imaging test most widely used for surveillance is US, which has an acceptable diagnostic accuracy when used as a surveillance test
- US surveillance detect the majority of HCC tumours before they presented clinically, However**, US is less effective for detecting early-stage HCC**

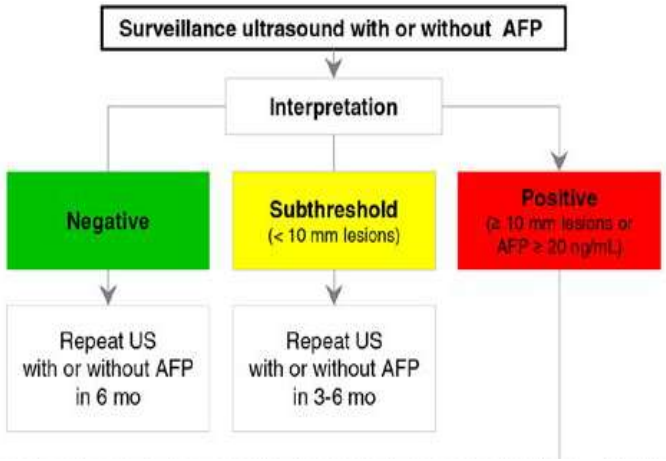
Surveillance tests

- Serological tests that have been investigated or are under investigation for early diagnosis of HCC include alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) -also known as prothrombin induced by vitamin K absence II (PIVKA II)- the ratio of glycosylated AFP (L3 fraction) to total AFP, alpha-fucosidase, and glypican.

Surveillance tests

- In conclusion, **US can be seen as the most appropriate test to perform surveillance.** The **combination with AFP is not recommended in patients with active liver inflammation,** as the 6–8% gain in the detection rate does not counterbalance the increase in false-positive results, ultimately leading to an approximately 80% increase in the cost of each small HCC diagnosed.

Diagnosis



Diagnosis

- Diagnosis of HCC **in cirrhotic** patients should be based on **non-invasive** criteria and/or pathology
- In **non-cirrhotic** patients, diagnosis of HCC should be **confirmed by pathology**
- Non-invasive criteria can only be applied to cirrhotic patients for nodule(s) ≥1 cm, in light of the high pre-test probability and are based on imaging techniques obtained by multiphasic CT, dynamic contrast-enhanced MRI or Contrast-enhanced ultrasound (CEUS)

- A lesion of >1 cm on US should trigger recall procedures for the diagnosis of HCC.
- If using AFP with US, then an AFP >20 ng/mL should trigger recall procedures for diagnosis of HCC.
- The AA SLD suggests **against routine biopsy of every indeterminate nodule.**

Diagnosis

- Imaging plays a critical role in HCC diagnosis.
- Unlike most solid cancers, the diagnosis of HCC can be established, and treatment rendered, based on noninvasive imaging without biopsy confirmation.
- AFP and other serum biomarkers generally have a minor role in the diagnosis of HCC.
- FDG PET-scan is not recommended for **early diagnosis** of HCC because of the high rate of false negative

Diagnosis

- In at-risk patients with abnormal surveillance test results or a clinical suspicion of HCC, **multiphase CT or MRI is recommended for initial diagnostic testing.** The **typical hallmark** is the combination of **hypervascularity in late arterial phase** (defined as arterial phase hyperenhancement [APHE] and **washout on portal venous and/or delayed phases,** which reflects the vascular derangement occurring during hepatocarcinogenesis

- Stringent criteria on multiphase imaging should be applied to enable noninvasive diagnosis of HCC in high-risk patients. For multiphase CT and MRI, key imaging features include size ≥1 cm, arterial phase hyperenhancement, and, depending on exact size, a combination of washout, threshold growth, and capsule appearance. If these criteria are not present but HCC or other malignancy is considered probable, then a liver biopsy should be considered for diagnosis.

- Diagnosis of HCC cannot be made by imaging in patients without cirrhosis, even if enhancement and washout are present, and biopsy is required in these cases.

Liver Imaging Reporting and Data System

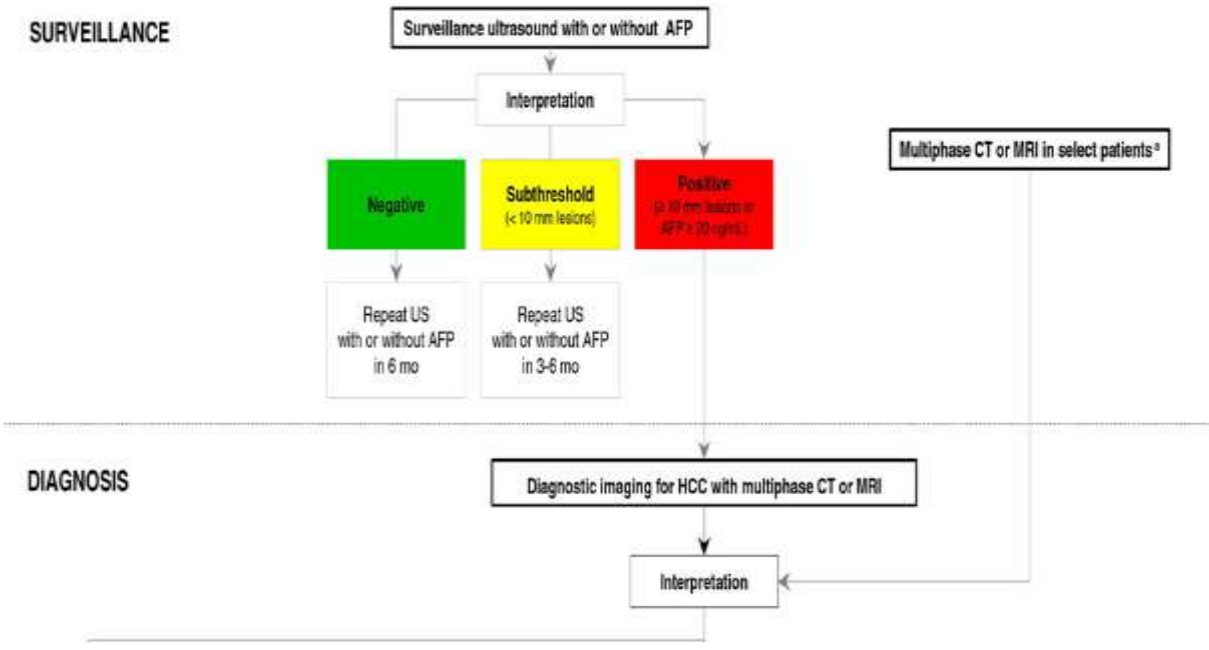
- LI-RADS 1 and LI-RADS 2 indicate definitely and probably benign, respectively.
- Definitely benign observations include cysts and typical hemangiomas. Probably, benign observations include atypical hemangiomas and focal parenchymal abnormalities likely attributable to underlying cirrhosis.

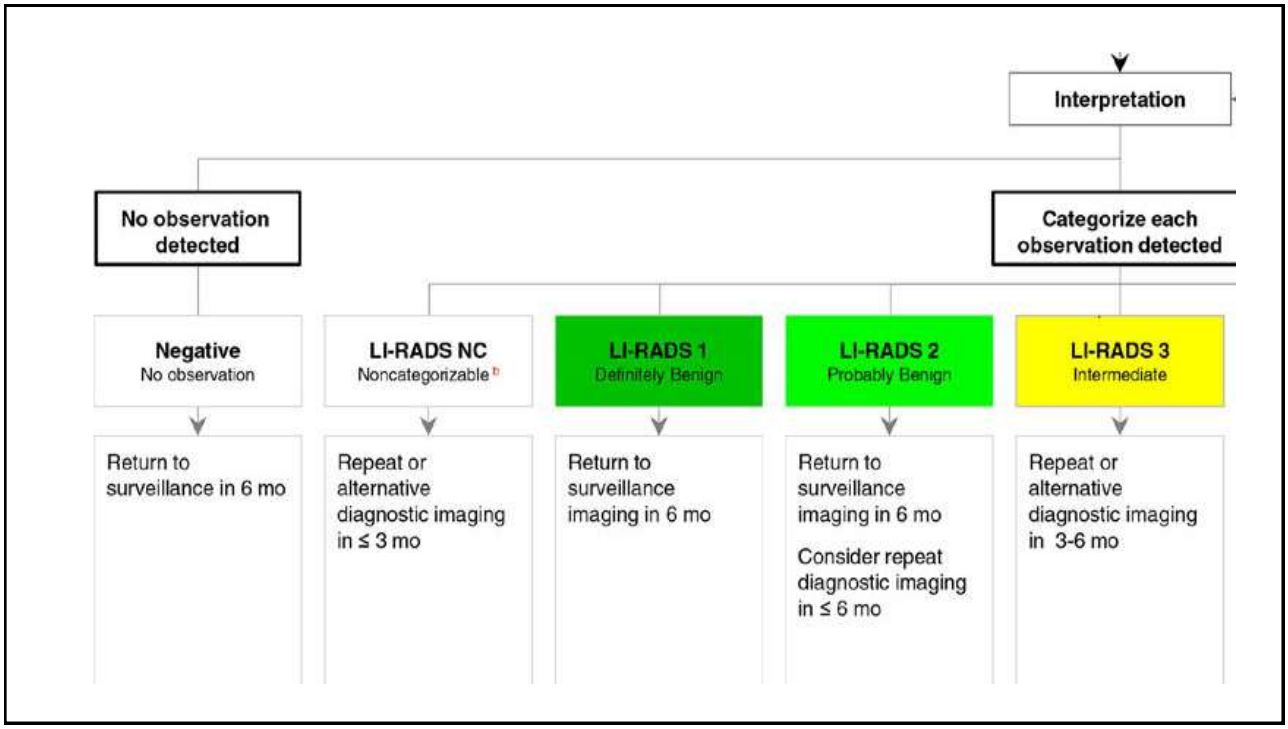
Diagnosis

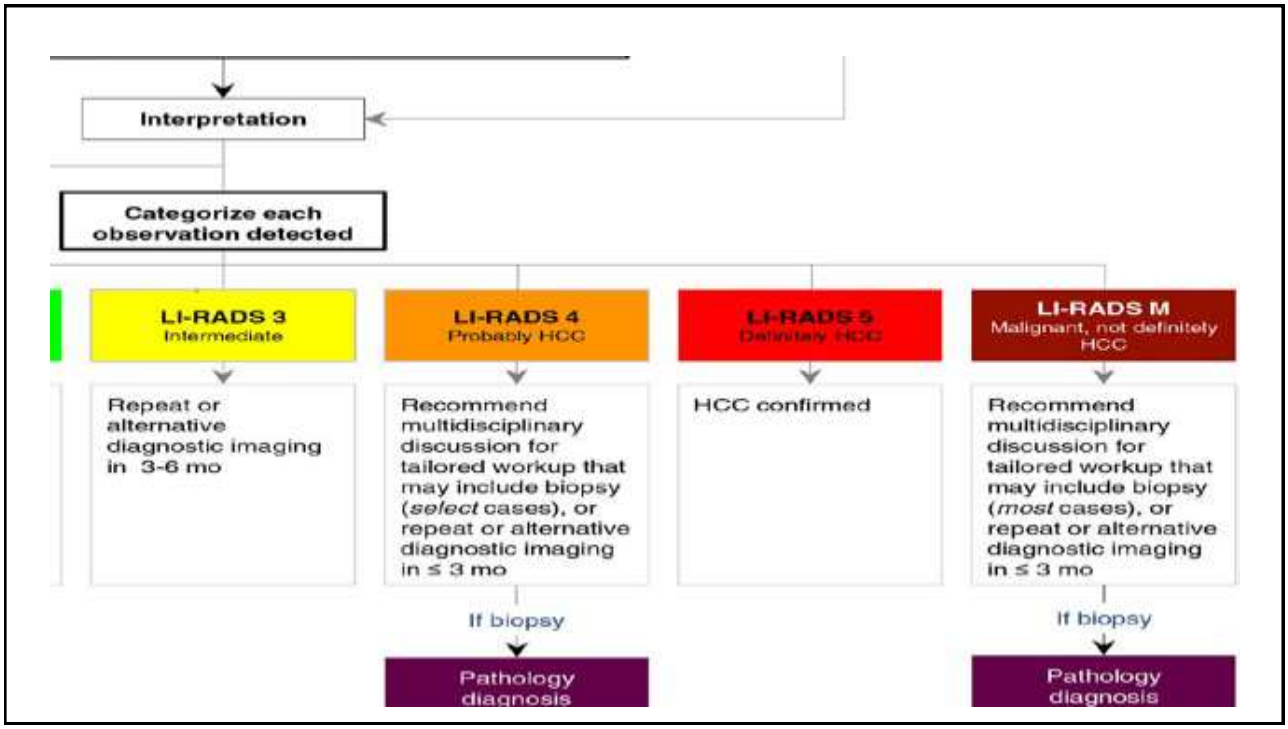
- LI-RADS 3 indicates a low probability of HCC
- LI-RADS 4 indicates probable HCC. An example is **a ≥2-cm encapsulated lesion with arterial phase hyperenhancement, but without "washout."** Another example is **a ≥2-cm lesion that enhances to the same degree as liver in the arterial phase, but enhances less (i.e., is hypoenhanced) in the postarterial phases**

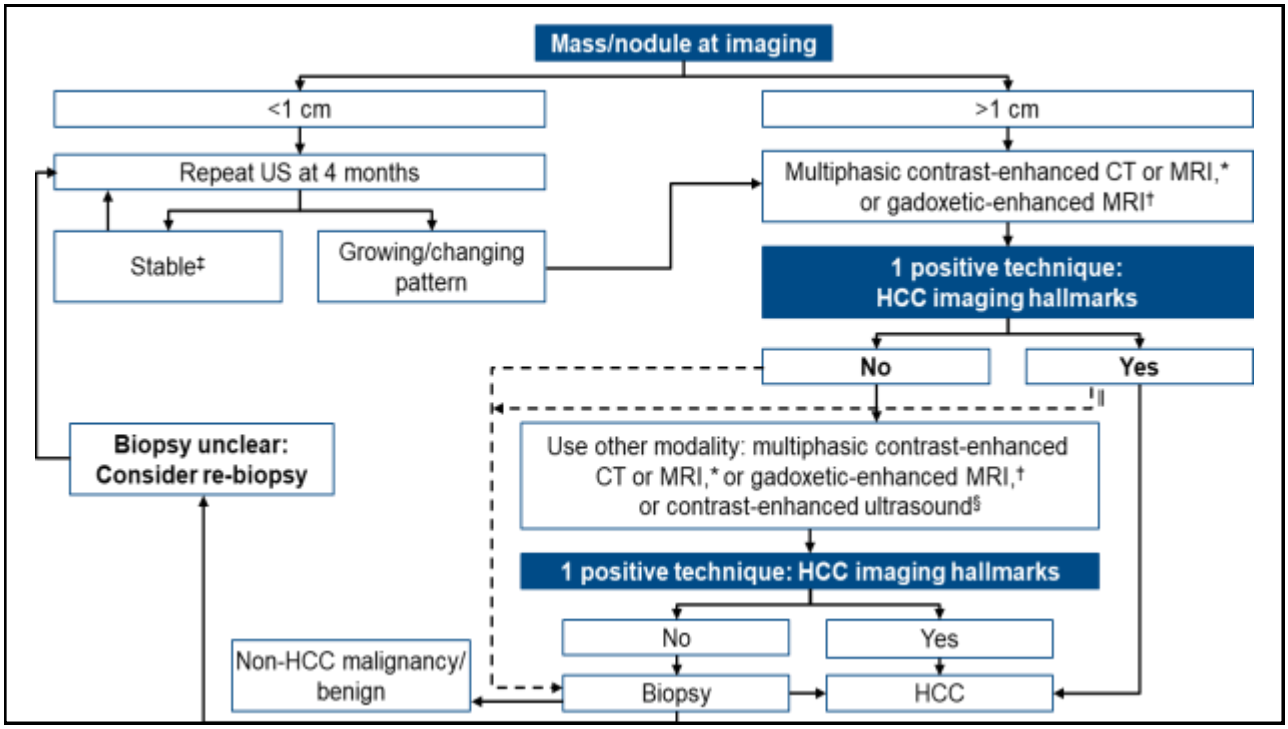
Diagnosis

- LI-RADS 5 indicates **definite HCC**
- **LI-RADS M** is assigned to observations with features highly suggestive or even diagnostic of malignancy, but not specific for HCC. Examples of such features include rim arterial phase hyperenhancement, peripheral washout appearance, delayed central enhancement, targetoid diffusion restriction, and—if a hepatobiliary agent is given—targetoid appearance in the hepatobiliary phase. These features are characteristic of **intrahepatic CCA** (ICC), but can be observed **atypically in HCC**.

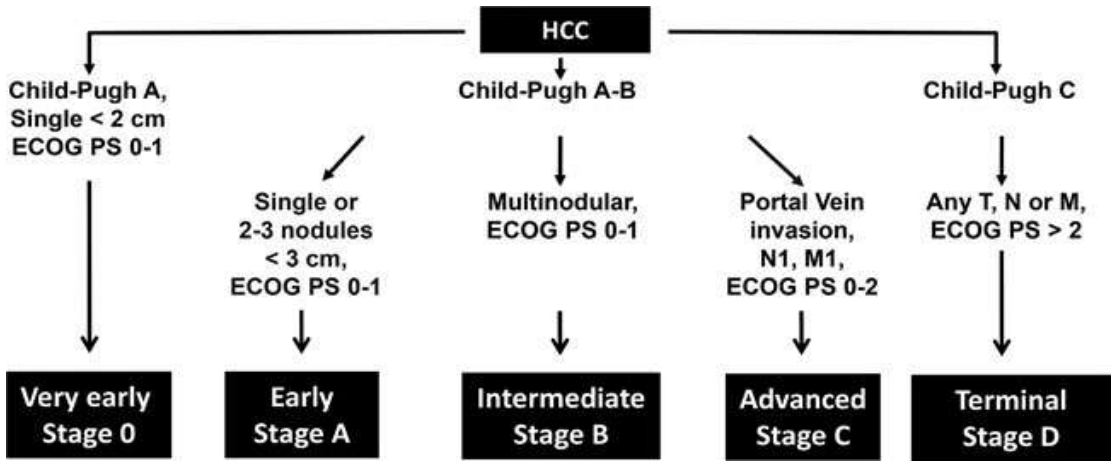


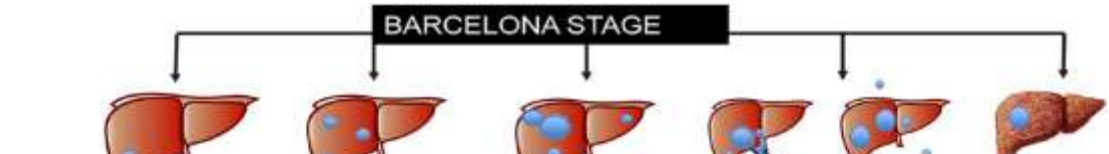

Interpretation
No observation detected
Categorize each observation detected
Negative
No observation
LI-RADS NC
Noncategorizable b
LI-RADS 1
Definitely Benign
LI-RADS 2
Probably Benign
LI-RADS 3
Intermediate
Return to surveillance in 6 mo
Repeat or alternative diagnostic imaging in ≤ 3 mo
Return to surveillance imaging in 6 mo
Return to surveillance imaging in 6 mo
Consider repeat diagnostic imaging in ≤ 6 mo
Repeat or alternative diagnostic imaging in 3-6 mo


Interpretation
Categorize each observation detected
LI-RADS 3
Intermediate
LI-RADS 4
Probably HCC
LI-RADS 5
Definitely HCC
LI-RADS M
Malignant, not definitely HCC
Repeat or alternative diagnostic imaging in 3-6 mo
Recommend multidisciplinary discussion for tailored workup that may include biopsy (select cases), or repeat or alternative diagnostic imaging in ≤ 3 mo
HCC confirmed
Recommend multidisciplinary discussion for tailored workup that may include biopsy (most cases), or repeat or alternative diagnostic imaging in ≤ 3 mo
If biopsy
Pathology diagnosis
If biopsy
Pathology diagnosis



BCLC HCC staging system





Level of Evidence					
1	Resection		TACE	Sorafenib (1L) Lenvatinib (1L) Regorafenib (2L) Cabozantinib (2L)	
2	RFA MWA	Resection OLT RFA MWA TARE TACE SBRT	TARE Downsize OLT	Nivolumab (2L)	OLT BSC
3				TARE	

- Resection is the treatment of choice for localized HCC occurring in the absence of cirrhosis, or resectable HCC occurring in the setting of cirrhosis with intact liver function and absence of CSPH.
- Transplantation is the treatment of choice for patients with early-stage HCC occurring in the setting of CSPH and/or decompensated cirrhosis, though access is limited by the extreme organ shortage.
- Surveillance for HCC recurrence in posttransplant patients should include abdominal and chest CT scan for better evaluation of the soft tissue, though optimal timing and duration, as

- The preferred therapy for localized HCC is surgical resection, but the majority of patients are not eligible because of tumor extent or underlying liver dysfunction.

- For patients who are not surgically resectable, **liver transplantation** is the only other potentially curative option.. At least in the United States, listing for a liver transplant requires a **solitary HCC ≤5 cm in diameter or up to three separate lesions, none of which is larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases**

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For patients with liver-isolated disease who are not eligible for resection or liver transplantation, treatment options include local nonsurgical methods of liver-directed tumor thermal ablation (RFA, microwave ablation, or cryoablation , TACE, and transarterial radioembolization), external beam radiation therapy, and finally, systemic therapy. The selection of treatment is determined by the severity of underlying liver disease, the size and distribution of the intrahepatic tumors, the vascular supply, and the patient's overall performance status

- The best results with RFA and microwave ablation are in patients with one or two tumors <4 cm in diameter. For cirrhotic patients, some clinicians restrict RFA and microwave ablation to those with Child-Turcotte-Pugh class A or B severity only .

- TACE is used most often for the treatment of large unresectable HCCs that are not amenable to other treatments, such as resection or RFA; the best candidates are patients with unresectable HCC without vascular invasion or extrahepatic spread, and with preserved liver function .
- In addition, the use of TACE as "bridging therapy" prior to liver transplantation for HCC is common. Some centers use TACE in conjunction with portal vein embolization prior to resection, particularly for large right-sided tumors

- One clinical scenario in which radioembolization may be preferred over TACE is in the setting of an HCC complicated by malignant branch or lobar portal vein thrombus.

- Systemic therapy is also appropriate for patients with **advanced unresectable HCC who are unsuitable for resection, transplantation, or locoregional liver-directed therapy and who retain an adequate performance status and liver function (ie, Child-Turcotte-Pugh A or B cirrhosis**
- Supportive care alone is appropriate for patients with **Child-Turcotte-Pugh C cirrhosis** and for those with a poor functional status or extensive comorbidity