Chapter 2

LI-RADS® Populations: Surveillance, Diagnosis, Staging, Treatment Response

Primary Author

An Tang University of Montreal

Contributing Authors

Victoria Chernyak Montefiore Medical Center
Oussama Hallouch University of Montreal
Aya Kamaya Stanford University
Claude B. Sirlin UC San Diego

Illustrators & figure contributors

Claude B. Sirlin UC San Diego

Editors

Victoria Chernyak Montefiore Medical Center
Claude B. Sirlin UC San Diego

Table of Contents

LI-RADS® Populations:

Surveillance, Diagnosis, Staging, Treatment Response

Introduction

This chapter reviews eight key concepts:

- Screening and surveillance
- Diagnosis
- Staging
- Treatment response
- Target population for screening and surveillance
- Target population for diagnosis
- Target population for staging
- Target population for treatment response

It also briefly reviews the imaging methods recommended for screening and surveillance, diagnosis, staging, and treatment response assessment.

Terminology and Definitions

Screening and surveillance

Surveillance. Surveillance refers to the programmatic and repeated application of tests to detect a disease of interest (i.e., HCC in this case) in a well-defined target population.

- Such a program utilizes standardized tests (e.g. laboratory or imaging) to detect disease before symptoms manifest.
- The goal of early detection is to permit application of effective and possibly curative therapy to prolong or improve quality of life even after adjusting for lead time and length biases.
- To be successful, a surveillance program should incorporate quality control processes and be paired with effective call-back and diagnostic procedures.

Screening. The initial application of a test or tests in a surveillance program is called screening. This aims to detect prevalent disease (i.e., HCC present at time of initial testing) in the target population.

Subsequent application of the same test or tests at a standard, repeated time interval is called surveillance. It aims to detect incident disease (i.e., HCC that develops after initial testing).

Ideally, surveillance tests should be safe, inexpensive, and acceptable to patients, while having high sensitivity and wide availability. Specificity is also important to reduce the frequency of false-positive interpretations, which trigger unnecessary follow-up procedures and may cause physical and/or psychological harms to patients.

Diagnosis

Diagnosis refers to the process by which more definitive tests are applied to establish the presence of disease. Usually, these provide more complete characterization of suspicious abnormalities detected during surveillance or of lesions discovered incidentally on exams done for other purposes.

Ideally, diagnostic tests should have high specificity, so the presence of disease (i.e., HCC) can be confirmed, while assessing the entire liver, so that the intrahepatic burden of disease can be defined.

Imaging plays a critical role in HCC diagnosis: unlike most human cancers, the diagnosis of HCC sometimes can be established, and treatment rendered, based on noninvasive imaging without biopsy confirmation. Even when biopsy is needed, imaging usually is required to guide the biopsy and to inform additional diagnostic and therapeutic decisions.

Terminology and Definitions

Staging

Staging refers to the process of determining the extent to which the cancer has spread.

There are many staging systems for liver cancer. All incorporate data on the number and size of HCC nodules in the liver, the presence of vascular invasion, and the presence of extrahepatic metastases; these data are determined mainly by imaging with biopsy reserved for safely accessible lesions in difficult cases.

Some staging systems such as BCLC also incorporate functional status, because this information helps to determine prognosis and guide treatment selection.

Treatment response assessment

Treatment response assessment refers to the process of determining the tumor burden after a therapy has been applied.

For HCC, this assessment is made mainly on imaging, based on changes in the size and enhancement patterns of treated tumors. Assessment of treatment response is a rapidly evolving field that requires awareness of the applied treatment(s) and their chronology, as well as familiarity with the expected imaging appearances associated with each therapy.

Terminology and Definitions

Target population for screening and surveillance

The **target population for screening and surveillance** refers to the group of individuals in whom screening and surveillance is judged to be cost effective. In general, these are individuals with substantially elevated risk of developing the disease in question (i.e., HCC in this case) and in whom the detection of early asymptomatic disease can prolong or improve the quality of life by enabling timely application of effective treatments. A necessary requirement is that patients' overall health is sufficiently good that they can tolerate and benefit meaningfully from those treatments.

Target population for diagnosis

The **target population for diagnosis** refers to the group of individuals in whom a particular type of diagnostic test (such as multiphase CT or MRI) or a particular diagnostic system (such as LI-RADS) is judged to be accurate.

Similar to screening and surveillance, the accuracy of diagnostic tests relies on the pre-test probability of disease. Hence, diagnostic algorithms such as LI-RADS should be applied only in high-risk populations. However, to achieve the required high positive predictive value, there is an additional criterion – these individual must have low risk of developing other conditions that may be mistaken for the disease in question by the diagnostic tests or system. This is explained in more detail on *page 2-7*.

Target population for staging

The **target population for staging** refers to the group of individuals in whom a diagnosis of a particular disease is established (HCC in this case) and in whom staging is desired. It is usually a subset of the target population for diagnosis.

Target population for treatment response

The **target population for treatment response** refers to the group of individuals in whom a locoregional treatment was applied a particular type of tumor (i.e., HCC or presumed HCC in the case of LI-RADS). It is usually a subset of the target population for diagnosis and staging.

The LI-RADS treatment response categories apply only to observations treated with locoregional therapies. Radiologists should use their judgment or response criteria such as modified RECIST to assess response after systemic therapy or resection.

The next few pages discuss the following populations in more detail:

- Target population for HCC screening and surveillance
- Target population for HCC diagnosis

Target Population for HCC Screening and Surveillance

Target population for HCC screening and surveillance

- This target population is defined by estimated cost effectiveness: namely, adult patients in whom screening and surveillance is estimated to be cost effective for prolonging or improving the quality of life. Prerequisites are that patients have high risk for developing HCC and sufficiently good overall health to tolerate and benefit meaningfully from treatment if found to have cancer.
- Various major societies have issued guidelines defining this target population.

HCC surveillance recommendation by major societies for adults

						North American societies	
		JSH 2014	APASL 2010	KLCSG-NCC 2015	EASL-EORTC 2012	AASLD 2018	US LI-RADS 2017
HBV cirrhosis	Child-Pugh A or B	+	+	+	+	+	+
HCV cirrhosis		+	+	+	+	+	+
Other causes of cirrhosis		+	—	+	+	+	+
Cirrhosis, Child-Pugh C, not awaiting liver transplant		—	—	—	—	—	—
Cirrhosis, Child-Pugh C, awaiting liver transplant		—	—	—	+	+	+
Non-cirrhotic HBV carriers		+	—	—	+ [a]	+ [b]	+
Chronic HCV with bridging fibrosis but not cirrhosis		+	—	—	+	—	—
Chronic HCV without bridging fibrosis or cirrhosis		+	—	—	—	—	—

"+": Recommended; "—": Not recommended; JSH - Japan Society of Hepatology; APASL - Asian Pacific Association for the Study of the Liver; KLCSG-NCC - Korean Liver Cancer Study Group and the National Cancer Center; EASL-EORTC - European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer; AASLD - American Association for the Study of Liver Diseases

a. EASL-EORTC recommends surveillance in chronic HBV carriers with active hepatitis or family history of HCC
b. AASLD recommends surveillance in chronic HBV carriers if Asian men > 40 yo, Asian women > 50 yo, African or African American, or family history of HCC.

💡 Note: US LI-RADS 2017 has adopted the same target population for surveillance as AASLD

⚠️ Note: no society recommends routine surveillance in children, regardless of risk factors

Target Population for HCC Screening and Surveillance

- In addition to those listed on the prior page, numerous other factors convey HCC risk.
- In general, these additional risk factors do not elevate the risk of HCC sufficiently to justify routine screening and surveillance. Enrollment in a surveillance program is not formally recommended by major societies since the cost effectiveness is thought to be low.
- These additional risk factors are listed below:

Additional risk factors for HCC (routine surveillance usually <u>not</u> recommended)

- HBV carriers: Asian men < 40 yo, Asian women < 50 yo
- HBV carriers: high viral load
- HBV and HCV coinfection
- Non-cirrhotic NASH
- Older age
- Male sex
- Diabetes mellitus
- Obesity
- High AST or ALT
- Low platelet count
- Excess alcohol consumption
- Family history of HCC
- Aflatoxin exposure
- Smoking

In absence of cirrhosis or other risk factors listed on prior page, these additional risk factors do **not** warrant enrollment of patients into a screening and surveillance program

HBV: hepatitis B virus, HCV: hepatitis C virus, NASH: nonalcoholic steatohepatitis, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Target Population for HCC Diagnosis

Target population for HCC diagnosis

- This target population is defined by by a set of inclusion and exclusion criteria, where the patient should have at least one inclusion criterion and none of the exclusion criteria.
- These criteria describe patients in whom the pretest probability of HCC is sufficiently high and the pre-test probability of lesions mimicking HCC is sufficiently low that an observation meeting HCC imaging criteria can be assumed confidently to be HCC.

LI-RADS Inclusion and exclusion criteria

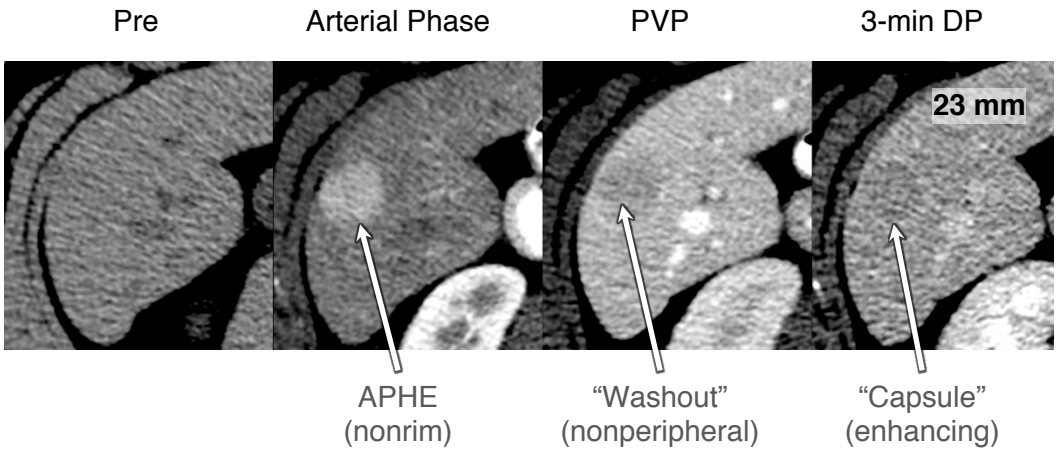
Inclusion criteria	Rationale
Cirrhosis	• Patients with cirrhosis have substantially elevated risk of developing HCC. • 70-90% of patients with HCC have underlying cirrhosis. • HCC is by far the most common cancer in cirrhosis. • Imaging can provide near-100% PPV for HCC in patients with cirrhosis.
Chronic HBV carriers	• Chronic HBV carriers have elevated risk of developing HCC even in the absence of cirrhosis, mainly because HBV has direct oncogenic effects. • 20-50% of chronic HBV carriers with HCC have no cirrhosis. • HCC is the most common cancer in chronic HBV carriers.
Current or prior HCC	• Patients with current or prior HCC are included in the high risk population, although scientific evidence for this is lacking. • This assumption is concordant with clinical practice, where a new lesion that meets imaging criteria for HCC is treated as HCC without confirmatory biopsy in patients with current or prior HCC.

Exclusion criteria	Rationale
Cirrhosis due to congenital hepatic fibrosis or vascular disorders	• Patients with cirrhosis from congenital hepatic fibrosis or from vascular disorders frequently have arterialized nonmalignant hepatocellular nodules that may resemble HCC. • The high prevalence of nonmalignant lesions whose imaging appearance resembles HCC lowers the PPV of imaging for HCC diagnosis.
Age < 18 years	• Performance of LI-RADS has not been validated in pediatric populations.

Target Population for HCC Diagnosis

LI-RADS diagnostic criteria apply **ONLY** in patients with or at high risk for developing HCC. The criteria do NOT apply in general population.

Example: CT



If patient is high risk for HCC

If patient is NOT high risk for HCC

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count major features:	None	LR-3	LR-3	LR-3	LR-3	LR-4
• "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	One	LR-3	LR-4	LR-4	LR-4	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count major features:	None	LR-3	LR-3	LR-3	LR-3	LR-4
• "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	One	LR-3	LR-4	LR-4	LR-4	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-5

Provide the most reasonable differential diagnosis <u>without</u> using LI-RADS

CT above was performed in 53-year-old woman with NO risk factors for HCC. LI-RADS was NOT applied. Further workup eventually established a diagnosis of focal nodular hyperplasia. Had LI-RADS been applied, patient would have been diagnosed incorrectly with HCC, with potential for serious psychological, physical, and financial harms.

Target Populations Compared:

Screening/Surveillance vs. Diagnosis

The screening/surveillance target population and the diagnostic target population may differ

In some patients, LI-RADS is applicable for diagnosis but screening and surveillance are not appropriate (e.g. patients with cirrhosis and short life expectancy due to non-hepatic disease).

In some patients, screening and surveillance may be performed but the LI-RADS diagnostic algorithm should not be applied (e.g., patients with endstage liver disease due to vascular disorders).

Recommended Imaging Methods

HCC Screening and Surveillance

Recommended imaging methods for HCC screening and surveillance

The recommended initial imaging method for HCC screening and surveillance is ultrasound.

- Rationale:
  - Ultrasound is safe, well tolerated, and widely available.
  - Ultrasound has been validated for HCC screening and surveillance in prospective studies.
  - Ultrasound is advocated for this purpose by all major societies.

The use of AFP in addition to imaging is optional. See *AASLD guidelines*

What about CT or MRI for HCC screening and surveillance?

LI-RADS recognizes that many imaging centers perform contrast-enhanced CT or MRI rather than or in addition to ultrasound for HCC screening and surveillance, due to sonographic limitations in obese patients and in those with severe parenchymal heterogeneity due to cirrhosis.

LI-RADS recommends neither for nor against the use of contrast-enhanced CT and MRI for screening and surveillance, deferring the choice of modality to radiologists, referrers, institutions, and patients.

What about abbreviated MRI for HCC screening and surveillance?

LI-RADS recognizes that some imaging centers perform abbreviated or focused MRI rather than or in addition to ultrasound for HCC screening and surveillance. These abbreviated or focused MRI protocols are shortened versions of complete MRI protocols, typically consisting of only a few sequences, and require about 10 minutes of scan time. Some of these protocols utilize extracellular agents and others utilize hepatobiliary agents. See *Chapter 12* for discussion of extracellular and hepatobiliary agents.

There is insufficient data for LI-RADS to recommend for or against abbreviated MRI using either type of contrast agent for HCC screening and surveillance.

Recommended Imaging Methods

HCC Diagnosis

Recommended imaging methods for HCC diagnosis

The recommended imaging methods for HCC diagnosis are CEUS, multiphase CT, multiphase MRI with ECA, and multiphase MRI with HBA.

- Rationale:
  - Performed properly and interpreted stringently, each of these methods can establish the diagnosis of HCC noninvasively.

Although published studies suggest that MRI may have slightly higher sensitivity with similar specificity compared to CEUS or multiphase CT, LI-RADS recognizes that many factors beyond reported diagnostic accuracy inform the selection of optimal imaging methods in individual patients.

These factors overlap and include:

- Patient factors: preferences, concerns, and convenience, breathhold capability, claustrophobia, liver function, renal function, body habitus, presence of co-morbidities such as allergies, ascites or renal failure that may affect image quality or exam safety
- Institutional factors: available technology and expertise, appointment scheduling and backlog
- Lesion factors: number, size, LI-RADS category, and imaging features of observations on prior exams if any
- Financial: exam charge, insurance authorization and reimbursement

For these reasons, LI-RADS recommends neither for nor against any particular imaging method. Instead, it recommends that the choice of method be tailored to the individual patient.

Multidisciplinary discussion is often helpful for guiding the optimal approach.

Recommended Imaging Methods

HCC Staging

Recommended imaging methods for HCC staging

The recommended imaging methods for staging hepatic tumor burden are multiphase CT, multiphase MRI with ECA, and multiphase MRI with HBA.

- Rationale:
  - Each of these methods can visualized the entire liver and assess the hepatic tumor burden.
  - CEUS is not recommended for routine staging because this method does not reliably assess the entire liver.

The recommended imaging methods for staging extrahepatic tumor burden are:

- Chest CT for detecting or excluding metastases in the thorax
- Whole-body bone scan for detecting or excluding skeletal metastases
- Optional: pelvic CT or MRI for detecting or excluding metastases in the pelvis

HCC staging decisions should be made by a multidisciplinary team.

The distinction between imaging contexts may be blurred.

Screening/surveillance vs. diagnosis

- Some imaging centers perform multiphase contrast-enhanced CT or MRI for screening and surveillance, particularly in patients with technically limited ultrasound, large body habitus, or cirrhotic liver with innumerable nodules preventing identification of distinctive nodules. In such instances, the same modality is the screening/surveillance test as well as the diagnostic test.

- Some patients with cirrhosis may not be in active surveillance programs, either because their cirrhosis is clinically silent and therefore unknown, or because they are noncompliant with surveillance recommendations. Such patients may have abnormalities detected incidentally on imaging done for other reasons, rather than on a screening ultrasound.

- In patients with an abnormality detected at surveillance ultrasound, CT or MRI may identify additional abnormalities that were not visible on ultrasound but need characterization.

Diagnosis vs. staging

- Multiphase CT or MRI are used for diagnosis of HCC and for staging the hepatic tumor burden. Thus, the same modality is used to establish the diagnosis of HCC and its intrahepatic extent.

- LI-RADS provides the same imaging criteria for all observations, including the index lesion(s) detected at screening or surveillance as well as any additional lesions encountered during diagnostic workup or follow up.

Recommended Imaging Methods

Terminology

LI-RADS adopts the terminology used by clinical practice guidelines

- LI-RADS refers to unenhanced US as a “screening or surveillance” test and refers to CEUS, multiphase CT, and multiphase MRI as “diagnostic” tests to maintain concordance with clinical practice guidelines.
- Use of the terms “screening or surveillance” vs. “diagnostic” in this context are intended to clarify the setting in which these imaging modalities are used and are not intended to imply differing levels of quality or value between these modalities.

Summary of LI-RADS® Target Populations

		US	CEUS	CT/MRI	CT/MRI
		Screening & surveillance	Diagnosis	Diagnosis & staging	Treatment response
Apply in patients undergoing US for HCC screening & surveillance [a]			**Comment:** LI-RADS recognizes that US may be suboptimal for HCC screening and surveillance due to severe parenchymal heterogeneity and/or obesity. Some centers may elect to perform CT or MRI instead of US for screening and surveillance in select patients. LI-RADS recommends neither for nor against the use of these modalities for this purpose.		
Cirrhosis of any etiology, adult	Child-Pugh A or B	✓			
	Child-Pugh C awaiting liver transplantation	✓			
Noncirrhotic HBV	Asian male > 40 yo	✓			
	Asian female > 50 yo	✓			
	African or North American black	✓			
	Family history of HCC	✓			
Apply in patients at high risk for HCC:		Not applicable			
Cirrhosis	Including liver transplant candidates and recipients		✓	✓	✓
Chronic HBV			✓	✓	✓
Current or prior HCC			✓	✓	✓
Do not apply in patients					
Without the above risk factors			✗	✗	✗
< 18 years old			✗	✗	✗
With vascular disorders [b] or cirrhosis due to congenital hepatic fibrosis			✗	✗	✗

a. Listed above are the groups recommended by 2018 AASLD guidance for screening and surveillance. Other regional clinical practice guidelines may expand the groups to potentially include:
   - Adults with cirrhosis of any cause, regardless of Child-Pugh score
   - Some adults with chronic HBV infection even in the absence of cirrhosis
   - Some adults with chronic HCV infection even in the absence of cirrhosis

   See your regional HCC clinical practice guidelines for details.

b. Vascular disorders of the liver include
   - Chronic vascular outflow obstructions (cardiac congestion, pulmonary hypertension, Budd-Chiari)
   - Chronic sinusoidal obstructions (diffuse nodular regenerative hyperplasia)
   - Chronic inflow obstructions (occlusion or absence of portal vein)
   - Hereditary hemorrhagic telangiectasia

   Note: some vascular disorders can cause cirrhosis and others can mimic cirrhosis. See *Chapter 4.*

LI-RADS® Target Populations – Caveats

	CEUS	CT/MRI	CT/MRI
	Diagnosis	Diagnosis & staging	Treatment response
Apply to observations		Not applicable	Not applicable
Visible at precontrast ultrasound	✓		
Do not apply to observations			
Invisible at precontrast ultrasound	✗		
Apply for CEUS performed with			
Pure blood-pool agents [a]	✓		
Do not apply for CEUS performed with			
Combined blood-pool and Kupffer-cell agents [b]	✗		
Apply for multiphase exams	Not applicable		
CT or MRI with extracellular agents		✓	✓
MRI with hepatobiliary agents		✓	✓
Do not assign LI-RADS diagnostic categories to path-proven:			
Malignancies	✗	✗	–
Benign lesions of non-hepatocellular origin such as hemangiomas	✗	✗	–
Assign LI-RADS treatment response categories after:		Not applicable	
Locoregional treatment	Pending		✓
Do not assign LI-RADS treatment response categories after:			
Systemic treatment or surgical resection	✗		✗

a. Blood-pool agents include Lumason® (in USA)/SonoVue® (outside USA) and Definity® (in USA, Canada)/ Luminity® (outside USA, Canada)
b. Currently, the only combined blood-pool and Kupffer-cell agent is Sonazoid®

References

Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004;127(5 Suppl 1):S5-S16.

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2.

Do AL, Wong CR, Nguyen LH, Nguyen VG, Trinh H, Nguyen MH. Hepatocellular carcinoma incidence in noncirrhotic patients with chronic hepatitis B and patients with cirrhosis of all etiologies. Journal of clinical gastroenterology. 2014;48(7):644-9.

Donato MF, Arosio E, Del Ninno E, Ronchi G, Lampertico P, Morabito A, et al. High rates of hepatocellular carcinoma in cirrhotic patients with high liver cell proliferative activity. Hepatology. 2001;34(3):523-8.

El-Serag HB. Hepatocellular carcinoma. The New England journal of medicine. 2011;365(12):1118-27.

European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012 Apr;56(4):908-43.

Flor N, Zuin M, Brovelli F, Maggioni M, Tentori A, Sardanelli F, et al. Regenerative nodules in patients with chronic Budd-Chiari syndrome: a longitudinal study using multiphase contrast-enhanced multidetector CT. Eur J Radiol. 2010;73(3):588-93.

Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018 Jan;67(1):358-380.

Kitao A, Zen Y, Matsui O, Gabata T, Nakanuma Y. Hepatocarcinogenesis: multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography--radiologic-pathologic correlation. Radiology. 2009;252(2):605-14.

Korean Liver Cancer Study Group (KLCSG); National Cancer Center, Korea (NCC). 2014 Korean Liver Cancer Study Group-National Cancer Center Korea practice guideline for the management of hepatocellular carcinoma. Korean J Radiol. 2015 May-Jun;16(3):465-522.

Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M; HCC Expert Panel of Japan Society of Hepatology. 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(3):339-64.

References

Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, Miyayama S, Tsuchiya K, Ueshima K, Hiraoka A, Ikeda M, Ogasawara S, Yamashita T, Minami T, Yamakado K; Liver Cancer Study Group of Japan. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer. 2014 Oct;3(3-4):458-68.

Liaw YF, Tai DI, Chu CM, Lin DY, Sheen IS, Chen TJ, et al. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study. Gastroenterology. 1986;90(2):263-7.

Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018. Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723-750.

Michielsen P, Ho E. Viral hepatitis B and hepatocellular carcinoma. Acta Gastroenterol Belg. 2011;74(1):4-8.

Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shiina S, Cheng AL, Jia JD, Obi S, Han KH, Jafri W, Chow P, Lim SG, Chawla YK, Budihusodo U, Gani RA, Lesmana CR, Putranto TA, Liaw YF, Sarin SK. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010 Mar 18;4(2):439-74.

Reshamwala PA, Kleiner DE, Heller T. Nodular regenerative hyperplasia: not all nodules are created equal. Hepatology. 2006;44(1):7-14.

Simonetti RG, Camma C, Fiorello F, Politi F, D'Amico G, Pagliaro L. Hepatocellular carcinoma. A worldwide problem and the major risk factors. Digestive diseases and sciences. 1991;36(7):962-72.

Vilgrain V, Lewin M, Vons C, Denys A, Valla D, Flejou JF, et al. Hepatic nodules in Budd-Chiari syndrome: imaging features. Radiology. 1999;210(2):443-50.

Zhou XD, Tang ZY, Yang BH, Lin ZY, Ma ZC, Ye SL, et al. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. Cancer. 2001;91(8):1479-86.