

How to evaluate an Incidental Focal Liver Lesions (FLLs) or Incidentalomas?

Gopal Ramaraju, MD.

Associate Professor, Interim Medical Director, Transplant Hepatology

University of Rochester Medical Center, Rochester, NY

- The wide spread use of imaging techniques for abdominal investigation has led to an increased detection of the so-called “incidental liver lesion” or incidentaloma.
- An incidentaloma is a tumor (-oma) found by coincidence (incidental) without clinical symptoms or suspicion.
- It is a benign growth, which is detected when diagnostic imaging is used for the analysis of unrelated symptoms.
- It is important to recognize that the range of diagnoses encountered will be related to the population under study.
- For example: Patients subjected to imaging studies to investigate benign conditions such as cholecystitis or renal colic are likely to have findings that mirror those of the general population.
- By contrast, the likelihood of encountering malignant hepatic lesions will probably be greater in patients diagnosed with cancer and undergoing extent of disease assessment or in chronic hepatitis patients undergoing screening evaluation.
- Thus, the radiographic finding and the clinical context must always be considered together to formulate an appropriated differential diagnosis.
- It is important to consider the clinical circumstances in which the lesion was identified:
 - Patient's age
 - Gender
 - Use of oral contraceptives
 - History or risk factors for chronic liver disease or cirrhosis
 - History or findings of extra hepatic malignancy
 - Is there a travel history or are there other features suggesting an amebic or pyogenic abscess?

The size of the liver lesion is an important consideration in guiding the evaluation:

Lesions smaller than approximately 1.0 cm are commonly benign incidental findings on imaging studies, and in most cases represent small cysts, hemangiomas, or biliary hamartomas. These are difficult to diagnose and difficult to biopsy percutaneously. Often clinical follow-up is the only recourse for these lesions. Larger lesions can be characterized in most cases.

Clinical and imaging features of various focal liver lesions

Disease	Prevalence	Demographics and clinical features	Imaging findings
Cyst	2-7%, prevalence increases with age	More common in females Origin: developmental or acquired	Fluid content, thin and well defined wall. No further follow up unless complex features
Hemangioma	2-20%	More common among 3-50 yr old females Most common	Well circumscribed, uniform and hyper echoic on ultrasound Initial peripheral nodular enhancement with centripetal fill in
Focal Nodular Hyperplasia (FNH)	3-5%	F:M-8:1, 20-50 yr old Multiple in 20% Second most common tumor of liver	Similar echogenicity to surrounding liver Initial intense homogenous enhancement on imaging, with delayed enhancement of central scar " spoke wheel" pattern of enhancement

Rossai J. Ackerman's surgical pathology, 8th ed. Mosby, 1995;1:898.
 Dickie B, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, et al. Spectrum of hepatic hemangiomas: management and outcome. *J Pediatr Surg* 2009;44:125-33.
 Nguyen BN, Fléjou JF, Terris B, Belghiti J, Degott C. Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. *Am J Surg Pathol* 1999;23:1441-54.

Clinical and imaging features of various focal liver lesions

Disease	Prevalence	Demographics and clinical features	Imaging findings
Focal fatty infiltration or sparing	10-15% (hepatic steatosis)	Seen in excessive alcohol consumption, diabetes, obesity and hyper lipidemia Focal sparing is more common than focal steatosis	Focal sparing appears as hypo echoic against Echogenic back ground "geographic" nature, often adjacent to gallbladder fossa and falciform ligament Diffuse fatty infiltration may mask other focal lesions
Adenomas	0.03-0.04%	Common in women taking OCP's Associated with anabolic steroid use and glycogen storage diseases Surgical resection if pain and hemorrhage	Large, iso or hyper echoic on ultrasound Typically hyper enhancement on arterial phase
Malignancy		May be primary (hepato cellular or cholangio) or secondary Metastasis is 15-20 times more common than primary and usually multiple, but can be solitary	Wide range of appearances and contrast enhancement charectarestics; may need biopsy

Ungermann L, Eliáš P, Zizka J, Ryska P, Klzo L. Focal nodular hyperplasia: spoke-wheel arterial pattern and other signs on dynamic contrast-enhanced ultrasonography. *Eur J Radiol* 2007;63:290-4.
 Hamer O, Aguirre D, Casola G, Lavine JE, Woenckhaus M, Sirlin CB. Fatty liver: imaging patterns and pitfalls. *Radiographics* 2006;26:1637-53.
 Cherqui D, Rahmouni A, Charlotte F, Boulahdour H, Métreau JM, Meignan M, et al. Management of focal nodular hyperplasia and hepatocellular adenoma in young women:a series of 41 patients with clinical, radiological and pathological correlations. *Hepatology* 1995;22:1674-81.

Hepatic Cysts

May be classified as:

- Developmental
- Infectious
- Traumatic
- Neoplastic

Hepatic cysts:-

- Solitary or multiple
- Adjacent liver tissue is normal and free of fibrosis or inflammation
- 2-7% of the population
- Slightly more prevalent in women
- Ultrasound is the best imaging method for characterizing these purely cystic liver lesions
- Well- defined homogenous cystic component
- Posterior acoustic enhancement
- Absence of a Doppler signal

The demonstration of internal or mural solid components precludes the diagnosis of a simple cyst and justifies further imaging investigations

In these cases, the differential diagnosis should include

1. Cystic malignant tumors, such as the rare cystadenocarcinomas or a cystic metastasis

2. A cystic hydatid lesion

When the criteria for an Ultrasonographic diagnosis of a simple cyst are not fulfilled, a CT or MRI should be performed.

- Treatment: Majority do not require treatment
- Monitor large cysts (≥ 4 cm in diameter) periodically with U/S to assure that they remain stable
- Laparoscopic unroofing curative for simple cysts
- Enucleation for a cyst adenoma
- Formal hepatic resection for cystadenocarcinomas

Hepatic Hemangiomas

- Most common benign neoplasm of the liver, 7% at autopsies.
- Second most common hepatic tumor, exceeded only by the metastases
- Affects all age groups
- Women > men, 1.5-5:1.
- Right lobe of the liver
- Few mm to > 20 cm
- Mesodermal in origin
- Histologically: Blood- filled cavernous vascular spaces of variable size and shape lined by single layer of flat endothelium
- They are usually stable, rarely increase or decrease in size

Characteristic U/S features:

1. Well- defined, homogenous, hyper echoic lesion.
2. Posterior acoustic enhancement.
3. No signal on color Doppler.

In cases where the U/S findings are not diagnostic, or where doubts persist (especially in oncological patients), CT with contrast or MRI is necessary to further evaluate, the findings may show:

1. A lesion hypo dense to the liver before the injection of iodinated contrast media (similar to that of vessels).
2. Patchy globular enhancement in the early phase of contrast media administration (arterial phase) beginning at the periphery of the tumor.
3. Progressive centripetal fill-in.
4. Persistent enhancement on delayed imaging.

Indications of MRI:

- Small sized lesions (< 1 cm.)
- Hyper vascular behavior after contrast (the “flash filling Hemangioma”).
- In case of absent or delayed fill-in pattern.
-

Characteristic features of hemangioma on MRI:

- Homogeneous, well defined lesion with lobulated contour.
- Hypo intensity on T1 weighted images.
- Strong hyper intensity on T2 weighted images.
- Typical filling pattern with dynamic imaging, observed after intravenous administration of gadolinium chelates.

Treatment of hepatic hemangiomas:

- Asymptomatic patients, particularly those with lesions < 1.5 cm but including those ≤ 5 cm, can be reassured and observed.
- Rapid growth of a Hemangioma has been reported, justifying close radiological follow up of patient with lesions >5 cm, particularly those in a sub capsular location.
- In the absence of symptoms, the risk of bleeding is too low to justify prophylactic resection.
- Patients who have pain or symptoms suggestive of extrinsic compression of adjacent structures should be considered for surgical intervention (liver resection, Enucleation, hepatic artery ligation and liver transplantation).
- Non surgical techniques (hepatic artery embolization, radiotherapy and interferon alpha-2a) mainly in children.

Focal Nodular Hyperplasia (FNH):

- A benign tumor like lesion (containing a highly vascularised central scar), predominantly in young females.
- Unlike hepatic adenoma (HA), the association of FNH with oral contraceptives/estrogens has not been clearly established.
- No malignant potential and complications are also exceedingly rare.

- Therefore, adequate diagnosis by non invasive imaging techniques avoids unjustified surgical resection.
- However, FNH shares some imaging features with other primary liver tumors including some of malignant origin (e.g. adenoma, hepatocellular carcinoma (HCC)), and thus a diagnosis of FNH must be unequivocal.
- An accurate diagnosis of FNH can be made from an ultrasound study showing:

Imaging characteristics:

On Ultrasound:

- A homogenous, solid lesion of variable echogenicity.
 - Absence of a peripheral hypo echoic rim (capsule).
 - Hyper echoic or hypo echoic central scar, displaying arterial vessels within the central scar on color coded Doppler.
- In doubt get a dynamic CT or MRI.

The pathognomonic macroscopic feature is the presence of a central stellate scar with radiating fibrous septa, thereby dividing the lesion into numerous nodules of normal hepatocytes that are abnormally arranged.

CT features of FNH:

On unenhanced CT, focal nodular hyperplasia is classically seen as a solitary, homogeneous, and slightly hypo attenuating or isoattenuating area compared with normal liver. In approximately 20% of patients, a central hypo attenuating scar may be seen. Related to the hypervascularity of the tumor, during the arterial phase of hepatic enhancement, focal nodular hyperplasia shows an immediate and intense enhancement (96%), with the exception of the central scar, which has delayed enhancement caused by the presence of abundant myxomatous stroma. CT performed during peak portal venous enhancement shows decreased enhancement of the lesion relative to the normal enhancing hepatic parenchyma, resulting in the lesion being isoattenuating to the liver, with gradual diffusion of the contrast material into the myxomatous stroma of the central scar. Because delayed washout of contrast material from this myxomatous tissue relative to surrounding liver is also found, the central scar may appear hyper attenuating on delayed CT.

MRI features of FNH:

Typical MR features of focal nodular hyperplasia are iso- or hypointensity on T1-weighted images (94-100%); slight hyper- or isointensity on T2-weighted images (94-100%); homogeneity (96%); and the presence of a central scar that appears hyper intense on T2-weighted images (84%) because of its vascular channels, bile ductules, and increased edema in the myxomatous tissue. After administration of gadolinium chelates, the enhancement profile is identical to that seen on contrast-enhanced CT: dramatic enhancement in the arterial phase, followed by isointensity of the lesion during the portal venous phase. On delayed phase imaging, the central scar shows high signal intensity because of the accumulation of contrast material.

- If any of the features of FNH are lacking from CT or MRI images, a confident diagnosis is precluded and patients must undergo a more invasive diagnostic procedure, preferably a surgical biopsy.
- Image guided percutaneous biopsies can be inconclusive since they may not represent the overall histology of the tumor
- Surgical removal remains the treatment of choice in the case of an atypical diagnosis of FNH

Treatment of FNH:

- The natural history of FNH is one of stability and lack of complications
- Surgery for:
 - Rare, very symptomatic FNH
 - Highly suspicious lesion, which has eluded diagnosis by all other modalities

Hepatic Adenoma:

- Benign tumor of hepatocellular origin.
- Exceedingly rare compared with the previously described lesions.
- Most commonly seen in premenopausal women older than 30.
- Generally related to long term use of contraceptive pills or the use of sex steroids.
- Has a high propensity to bleed, rupture and may undergo malignant transformation. Therefore, it should generally be resected.
- Can be difficult to distinguish from an extremely well differentiated hepatocellular carcinoma.

Epidemiology:

- 3rd and 4th decade.
- Female predominance- 2-6:1.
- Associated with use of oral contraceptive use.
 - Relative Risk (RR) of 2.5 after 3-5 yrs of use.
 - RR 25-40 after 9 yrs of use.
- Familial in maturity onset diabetes and glycogen storage diseases, acromegaly, androgen usage.
- Multiple in 20%, greater than 10 is adenomatosis.
- 4.2% malignancy
- Pathology:
 - 4 subtypes: HNF1 α inactivation, β -catenin activation, inflammatory, unclassified
 - β -catenin associated with increased malignancy
 - β -catenin implicated in malignancy - only 20-30% malignant show β -catenin mutations
- GSD Type I, steroid use, male gender – high risk
- Inflammatory- > 50%
- T2 bright
- + risk of HCC with β -catenin mutation (10%)
- Hepatocyte nuclear factor 1 α -inactivated, 35-40%

- Diffuse fat
- Very low risk of HCC
- β -catenin-activated, 10%-15%, common in men
- Absent fat, 45% risk HCC
- Unclassified-non-mutated 5-10%
- No fat, no inflammation, no increased risk of HCC
- Ultrasonography: Nonspecific.
- Often large and in the right lobe of the liver.
- Usually hyper echoic in relation to the surrounding liver parenchyma.
- Given the tendency for these lesions to bleed, there is often a central hypo echoic region, which corresponds to hemorrhage.
- Contrast enhanced ultrasound may improve accuracy compared with standard ultrasound.

Technetium-99m (^{99m}Tc) sulfur colloid scanning:

- Most adenomas do not take up the sulfur colloid; thus the scintigram shows a 'cold' spot in the liver.
- Focal nodular hyperplasia, on the other hand, shows equal or greater uptake of the radio labeled agent compared to surrounding liver.
- Thus, sulfur colloid scanning is generally not useful for establishing the diagnosis of an adenoma, but may be helpful when the clinical setting and results of other radiologic testing point to a diagnosis of FNH.
- In many centers, nuclear imaging has been largely replaced by Gd-BOPTA (gadobenate dimeglumine) -enhanced MRI or dynamic multi-phase CT angiography.
- The natural history and prognosis of hepatic adenomas is not well established. As a result, decisions regarding management of these tumors depend upon symptoms, size, number, location, and certainty of the diagnosis.
- Recommended resection of all symptomatic hepatic adenomas and those > 5cm and before pregnancy.
- Adenomas that do not resolve or enlarge after discontinuation of steroid medication should also be considered for surgical resection after discussion with the patient.

Malignant Tumors of Liver:

- More common than benign lesions and are associated with a poor outcome.
- Thus, it is important to establish a correct diagnosis, especially when the potential for therapy exists.
- In Western countries, metastatic liver tumors are the most common malignant hepatic neoplasm.
- The presence of an extra hepatic malignancy should be sought in patients with characteristic liver lesions on imaging studies.
- A thorough physical examination and history should be performed to identify clues to the primary malignancy.

- In patient know to have extra hepatic malignancy, it is usually necessary to clarify if a hepatic lesion might be metastatic in origin, because then it typically requires a biopsy.
- Ultrasound or CT guided liver biopsy or fine needle aspiration is often useful to confirm the diagnosis.
- However, histologic confirmation is not always essential if reasonable certainty can be achieved with imaging studies or in settings in which there would be little benefit to the patient to establish a firm diagnosis.
- Ultrasound findings in metastatic liver tumors are variable.
- Metastases from adenocarcinoma are multiple and hypo echoic in comparison to the surrounding liver parenchyma.
- Transabdominal Ultrasound is inferior in sensitivity for liver metastases compared to either CT or MRI.
- Intraoperative ultrasound is the most sensitive imaging technique for diagnosing liver metastases and can be helpful in delineating the extent of disease and vascular landmarks during hepatic resection.

Triphasic CT:

- Metastatic liver lesions from the colon, stomach, and pancreas usually show lower attenuation (i.e., are darker) in contrast to the brighter surrounding liver parenchyma.
- Hyper vascular metastases, such as those from neuroendocrine tumors, renal cell carcinoma, breast carcinoma, melanoma, and thyroid carcinoma, appear as rapidly enhancing lesions visible on the arterial phase of enhancement.
- MRI is useful for delineating vascular involvement and identifying additional intraabdominal lesions.
- Specialized contrast agents, such as super paramagnetic iron oxide agents, improve the sensitivity of MRI for metastases.
- However, intraoperative ultrasound is still more sensitive for the detection of liver metastases.
- Resectable colo rectal cancer metastases are defined simply as tumors that can be resected completely, leaving an adequate liver remnant.
-
- Most surgeons would require that there be no radiographic evidence of involvement of the hepatic artery, major bile ducts, main portal vein, or celiac/Para aortic lymph nodes and adequate predicted functional hepatic reserve post resection.

Hepato Cellular Carcinoma (HCC):

- History of risk factors for chronic liver disease, viral hepatitis, metabolic liver diseases such as Hereditary Hemochromatosis, non alcoholic steato hepatitis and alcohol abuse.

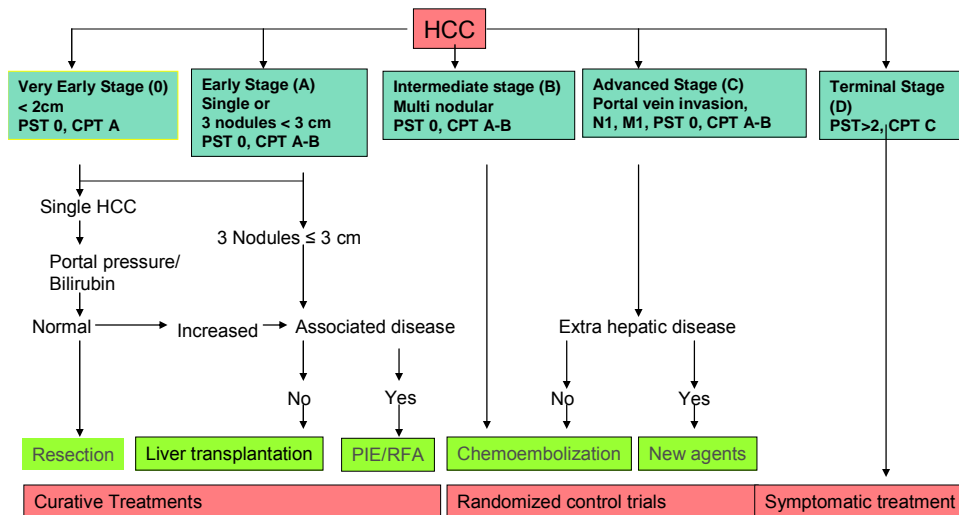
- Physical examination: Peripheral stigmata of cirrhosis or decompensated liver disease, which should raise suspicion for HCC.
- The diagnosis can be difficult, and often requires the use of serum markers, one or more imaging modalities, and histologic confirmation.
- It can be challenging to distinguish HCC from regenerative or even dysplastic nodules in patients with cirrhosis.
- MRI is currently the modality of choice in such settings since distinctions can sometimes be made based upon the enhancement pattern and the presence of iron in regenerative nodules.
- Serum AFP is normal in the majority of patients with fibro lamellar HCC and in up to 40% of HCC of patients.
- Biopsy is often not required for diagnosis.
- A central scar (typical of focal nodular hyperplasia) can also be seen in patients with fibro lamellar HCC.

Non invasive criteria to diagnose HCC.

- New lesion > 2 cm in a cirrhotic liver
 - Arterial enhancement and venous wash out on 1 CT or MRI (or contrast ultrasound or angiogram)
 - Arterial enhancement on 2 imaging modalities, CT or MRI or contrast ultrasound or arteriogram
- New lesion 1-2 cm in cirrhotic liver
 - Arterial enhancement and venous wash out on 2 imaging modalities, CT or MRI or contrast US or arteriogram
 - Arterial enhancement alone or AFT > 200-400 ng/ml

HCC Management

Barcelona Clinic Liver Cancer Staging and Treatment Strategies



PIE: Percutaneous Ethanol Injection, RFA: Radio Frequency Ablation, PST: Performance Status Testing, CPT: Child Pugh Turcot

Llovet JM, et al, Lancet 2003; 362: 1907-17

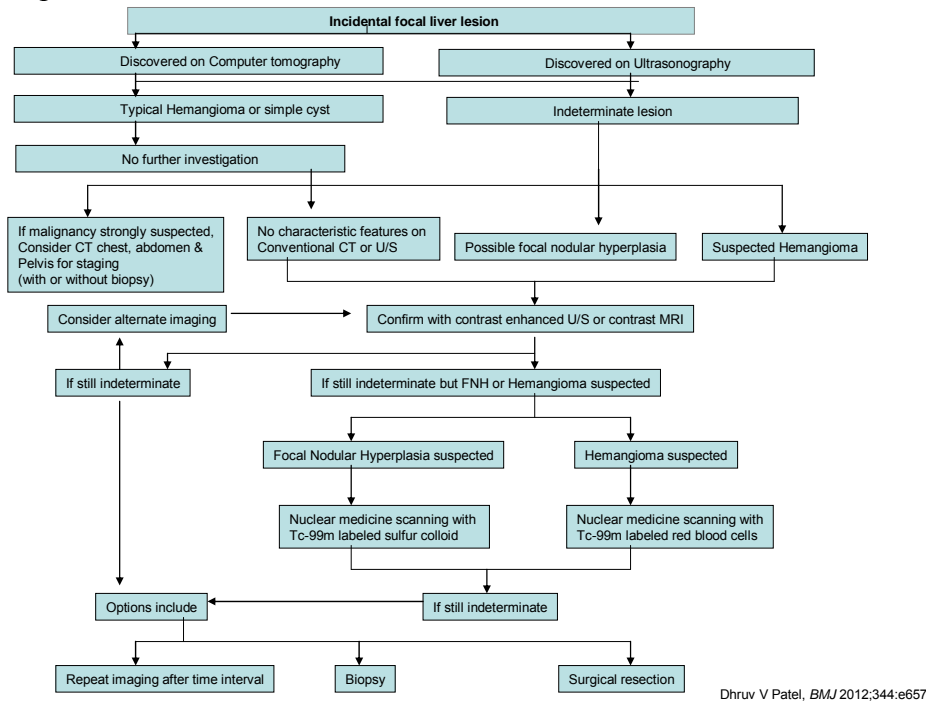
The “sub centimeter lesion” in Liver:

- With increased resolution of CT and MRI has come an increased detection of small nodules: 17% of patients with or without known previous malignancies may display small liver nodules ≤ 10 mm in diameter which are difficult or even impossible to characterize adequately.
- The majority of these small lesions are benign, such as tiny liver cysts or hamartomas, but they can also be malignant.
- High resolution, state of the art Ultrasonographic techniques can be diagnostic for sub centimeter cystic nodules.
- Small nodules are generally invisible on most ultrasound examinations.
- It is advisable to obtain a new control examination after about 3-4 months.
- Any intervening growth may justify the use of another diagnostic procedure, such as an image guided per cutaneous biopsy.

Conclusions:

- Current imaging techniques can accurately characterize incidental liver lesions in a non invasive fashion.
- Ultrasound is used as a primary screening modality, but in several instances, CT or MRI act as the “problem-solving” technique.
- MRI is superior to CT for focal liver lesion characterization as a result of its high intrinsic contrast resolution and potential use of different types of contrast agents, both specific and non specific.

- Sub centimeter nodules continue to be a diagnostic dilemma demanding a close imaging examination, which depends largely on the clinical situation of the patient.



References:

- Investigating focal liver lesions: *BMJ* 2012; 344:e657 doi: 10.1136/bmj.e657 (Published 8 February 2012).
- Characteristics of common solid liver lesions and recommendations for diagnostic workup: *World J Gastroenterol* 2009 July 14; 15(26): 3217-3227.
- Hepato biliary cancer: Schwartz's Principles of Surgery.
- Little JM, Richardson A, Tait A. Hepatic dystychoma: a five-year experience. *HPB Surg* 1991; 4:291-7.
- Imaging of liver cancer: *World J Gastroenterol* 2009 March 21; 15(11): 1289-1300.
- Up-To-Date: 2012
- CT and MR Imaging Findings in Focal Nodular Hyperplasia of the Liver: Radiologic-Pathologic Correlation. *AJR*:175, September 2000
- Rossai J. Ackerman's surgical pathology. 8th ed. Mosby, 1995; 1:898.
- Dickie B, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, et al. Spectrum of hepatic hemangiomas: management and outcome. *J Pediatr Surg* 2009; 44:125-33.
- Nguyen BN, Fléjou JF, Terris B, Belghiti J, Degott C. Focal nodular hyperplasia of the liver: a comprehensive pathologic study of 305 lesions and recognition of new histologic forms. *Am J Surg Pathol* 1999; 23:1441-54.
- Ungermann L, Eliáš P, Zizka J, Ryska P, Klzo L. Focal nodular hyperplasia: spoke-wheel arterial pattern and other signs on dynamic contrast-enhanced ultrasonography. *Eur J Radiol* 2007;63:290-4.

- Hamer O, Aguirre D, Casola G, Lavine JE, Woenckhaus M, Sirlin CB. Fatty liver: imaging patterns and pitfalls. *Radiographics* 2006; 26:1637-53.
- Cherqui D, Rahmouni A, Charlotte F, Boulahdour H, Métreau JM, Meignan M, et al. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological and pathological correlations. *Hepatology* 1995; 22:1674-81.
- Bruix and Sherman, 2005: AASLD practice guidelines on Hepato Cellular Carcinoma.