

# Hepatocellular Carcinoma

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# EPIDEMIOLOGY

- ▶ the ninth most commonly diagnosed cancer worldwide . Liver cancer is the fourth leading cause of cancer-related death in the world .
- ▶ The majority of HCCs occur in patients with **chronic liver disease** or cirrhosis, Several large prospective studies have noted a mean age at presentation between **50 and 60 years** .

# RISK FACTORS

- ▶ chronic hepatitis C virus (**HCV**) infection.
- ▶ **Hepatitis B** — The association between chronic HBV infection and HCC has been demonstrated in several studies. HCC can develop in patients with chronic HBV, even **in the absence of cirrhosis**. However, 70 to 90 percent of patients with HBV who develop HCC will have cirrhosis .
- ▶ **hereditary hemochromatosis**
- ▶ **cirrhosis** of almost any cause .
- ▶ HCC can also occur in patients **without known risk factors**.

# PROTECTIVE FACTORS

- ▶ Several studies have evaluated the impact of treatment for chronic HBV on the risk of HCC. Systematic reviews of the available data suggest that the relative **risk is reduced by approximately 50 to 60** percent following treatment with interferon or nucleo (t)ide derivatives.
- ▶ There is compelling evidence that successful treatment decreases, **but does not eliminate**, the risk of HCC in patients with chronic hepatitis C
- ▶ Statin use and Dietary factors .

# Pathology

- ▶ The most common primary liver malignant tumor is hepatocellular carcinoma (HCC).
- ▶ The most common malignant tumor is secondary Mets.
- ▶ HCC may form a large solitary circumscribed nodule with or without adjacent smaller satellite nodules.
- ▶ In the presence of cirrhosis, HCC may be **multinodular** within one lobe, or consist of multiple nodules scattered throughout the liver, or may **infiltrate** the liver diffusely without forming circumscribed nodules.
- ▶ The cells of HCC resemble hepatocytes in function, cytologic features, and growth patterns. The degree of differentiation reflects the resemblance of tumor cells to normal hepatocytes.

# Histology

Well-differentiated HCCs are often small (<2 cm) and composed of cells with mild atypia

Moderately-differentiated HCCs are usually larger tumors (>3 cm)

# Pathology

## Fibrolamellar carcinoma

- ▶ Fibrolamellar carcinoma differs clinically, histologically, and molecularly from conventional HCC.
- ▶ It affects **younger individuals**, is often **not** associated with elevated serum alpha-fetoprotein (AFP), and has a **better prognosis** than conventional HCC.
- ▶ Differentiated from the **HCC by immunohistochemical profile** ( as it share many immunohistochemical stain similar to that of HCC )

# STAGING AND PROGNOSTIC SCORING SYSTEMS

- ▶ **four features** that have been recognized as being important determinants of survival:
  - the severity of underlying liver disease
  - the size of the tumor,
  - the extension of the tumor into adjacent structures
  - the presence of metastases.
- ▶ It is typically diagnosed late in the course of these diseases, and the median survival following diagnosis ranges from approximately **6 to 20 months**.

# TNM STAGE

- ▶ T1 has been subdivided into two subcategories: T1a (solitary tumors  $\leq 2$  cm) and T1b (solitary tumors without **vascular invasion**  $> 2$  cm).
- ▶ ● T2 now includes a solitary tumor with vascular invasion  $> 2$  cm, or **multiple tumors, none  $> 5$  cm.**
- ▶ ● The previous T3a category (patients with multiple tumors, any of which are  $> 5$  cm) is now recategorized as T3, while tumors that were previously considered T3b (single or multiple tumors of any size **that involve a major portal vein or hepatic vein**) **are now T4**, as are tumors with **direct invasion** of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum.

# CLIP (Cancer of the Liver Italian Program) scoring system for hepatocellular cancer

Variable	Point Score		
	0	1	2
Child-Pugh Class	A	B	C
Tumor Morphology	Uninodular Extension $\leq 50\%$	Multinodular Extension $\leq 50\%$	Massive or Extension $> 50\%$
AFP (ng/ml)	$\leq 400$	$\geq 400$	
Portal Vein Thrombosis	Absent	Present	

- ▶ used to **predict survival** in patients with hepatocellular carcinoma.
- ▶ The total score is derived by adding each of the subscores. In one study, median survival was 36, 22, 9, 7, and 3 months for patients in CLIP categories 0, 1, 2, 3, and 4 to 6, respectively.

# Child Pugh Score

Parameter	Assign 1 point	Assign 2 points	Assign 3 points
Ascitis	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (second over control) or INR	<4  <1.7	4-6  1.7-2.3	>6  >2.3
Encephalopathy	None	Grade 1-2 (Mild to moderate)	Grade 3-4 (Severe)

# Clinical features and diagnosis of primary hepatocellular carcinoma

- ▶ The diagnosis of **HCC can be difficult** and often requires the use of one or more imaging modalities.
- ▶ Ideally, **tumors should be detected when they are approximately 2 cm in size** so that all treatment options can be offered. However, HCC is frequently diagnosed late in its course because of the absence of pathognomonic symptoms.

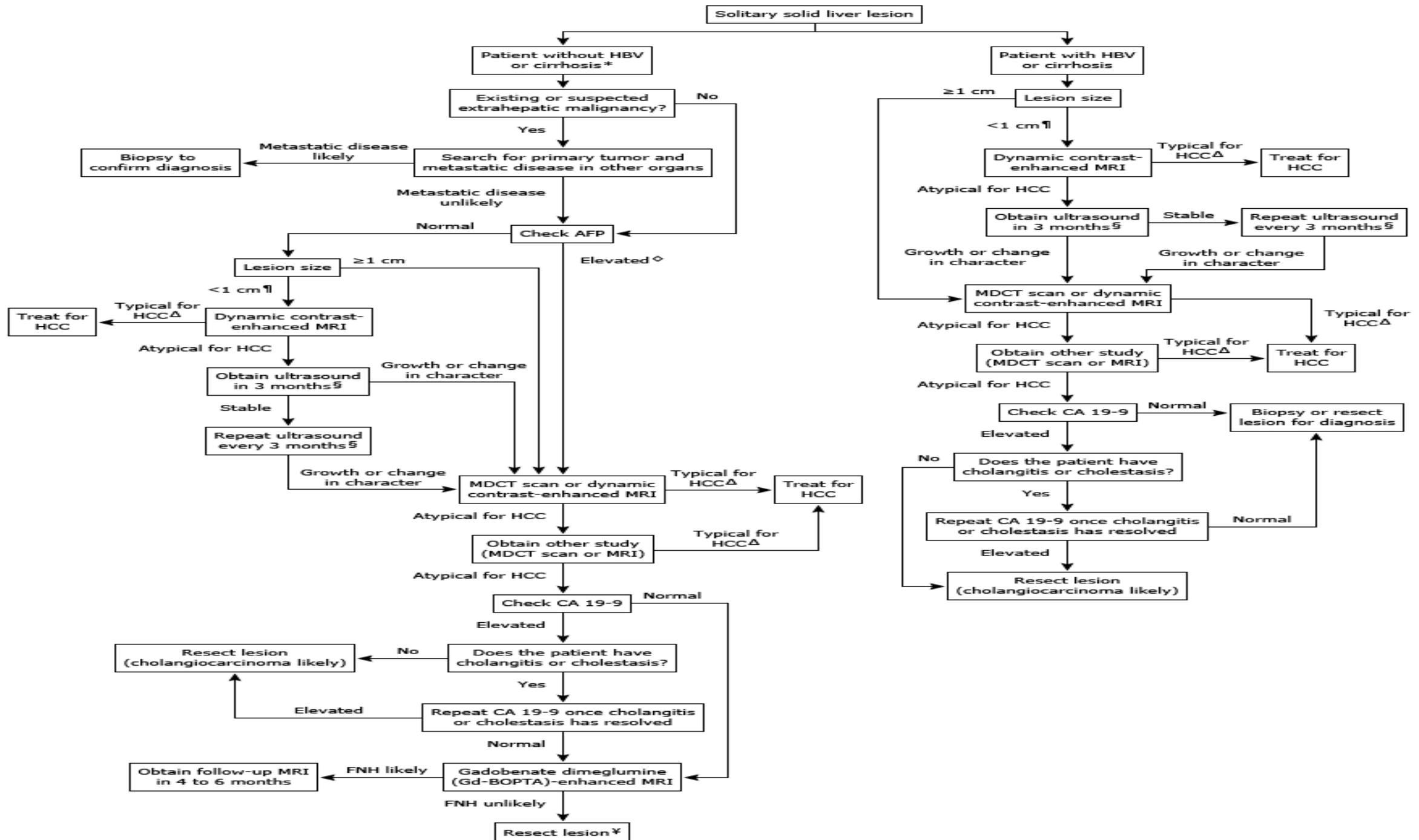
# CLINICAL FEATURES

- ▶ Suspicion for HCC should be heightened in patients with previously compensated cirrhosis who **develop decompensation such as ascites, encephalopathy, jaundice, or variceal bleeding.**
- ▶ **Obstructive jaundice** caused by invasion of the **biliary tree, compression of the intrahepatic duct,** or rarely, as a result of hemobilia.
- ▶ **Diarrhea**
- ▶ **Bone pain** or **dyspnea** due to metastases.
- ▶ Intraperitoneal **bleeding** due to tumor **rupture.**
- ▶ **Fever** may develop in association with central tumor **necrosis.**
- ▶ ● **Paraneoplastic syndromes.**
- ▶ ● **Pyogenic liver abscess (very rare)**

# DIAGNOSIS



**Approach to a solitary focal liver lesion**



# DIAGNOSIS

- ▶ Nodules found on ultrasound surveillance that are **smaller than 1 cm** should be followed with ultrasound at intervals of three to six months. If there has been no growth over a period of up to two years, one can revert to routine surveillance.
- ▶ **Lesions larger than 1 cm** in diameter should be evaluated with dynamic MRI or helical multidetector CT scan using contrast. If the appearance is typical for HCC, no further investigation is required.
- ▶ If the characteristics are not typical for HCC (and do not suggest hemangioma), one of two strategies is acceptable: either a second study (CT or MRI, whichever was not performed) or a biopsy. If a second imaging study does not have imaging features of HCC, the lesion should be biopsied.

# SERUM MARKERS

## Alpha-fetoprotein

- ▶ Alpha-fetoprotein is a glycoprotein that is normally produced during gestation by the fetal liver and yolk sac, the serum concentration of which is often elevated in patients with HCC.
- ▶ Elevated serum AFP occurs in :
  - pregnancy .
  - with tumors of gonadal origin .
  - in a variety of other malignancies, of which gastric cancer is the most common
- ▶ Elevated serum AFP may also be seen in patients with chronic liver disease without HCC such as acute or chronic viral hepatitis .
- ▶ AFP may be slightly higher in patients with cirrhosis due to hepatitis C .
- ▶ In one report, serum AFP decreased significantly in patients with cirrhosis from hepatitis C, treated with peginterferon plus Ribavirin .

# SERUM MARKERS

## Alpha-fetoprotein

- ▶ A rise in serum AFP in a patient with cirrhosis or hepatitis B should raise concern that HCC has developed.
- ▶ It is generally accepted that serum levels greater than 500 mcg/L (normal in most laboratories is between 10 and 20 mcg/L) in a high-risk patient is diagnostic of HCC .
- ▶ However, HCC is often diagnosed at a lower AFP level in patients undergoing screening.
- ▶ AFP cutoff 20 mcg/L (sensitivity 60, specificity 91 percent)

# IMAGING STUDIES

## Ultrasound & Endoscopic ultrasound

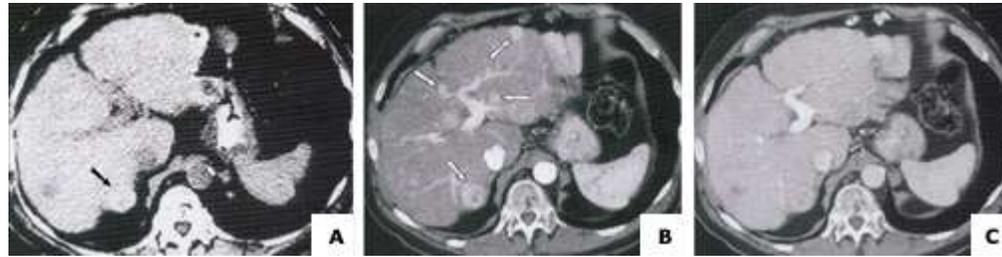
- ▶ Although ultrasound cannot distinguish HCC from other solid tumors in the liver, it is widely available, noninvasive, and commonly used for screening patients for HCC. Ultrasonography has the added benefit of assessing patency of **the hepatic blood supply and the presence of vascular invasion by the tumor.**
- ▶ **Sensitivity is improved when ultrasound is combined with AFP determination**

# IMAGING STUDIES

## Abdominal CT TRI-PHASIC CTSCAN

- ▶ the sensitivity for detecting patients with HCC was 83 percent and specificity was 91 .
- ▶ The ability of CT to detect HCCs has improved with the development of helical CT technology
- ▶ The **late arterial phase** of **enhancement** allows for detection of hyper vascular HCC, Some tumors are iso-attenuating on both arterial and portal phase imaging and may be missed. The addition of **delayed phase imaging RAPID WASH OUT**(triple-phase helical CT) may improve detection of these tumors .

# Triple phase CT scanning of hepatocellular carcinoma

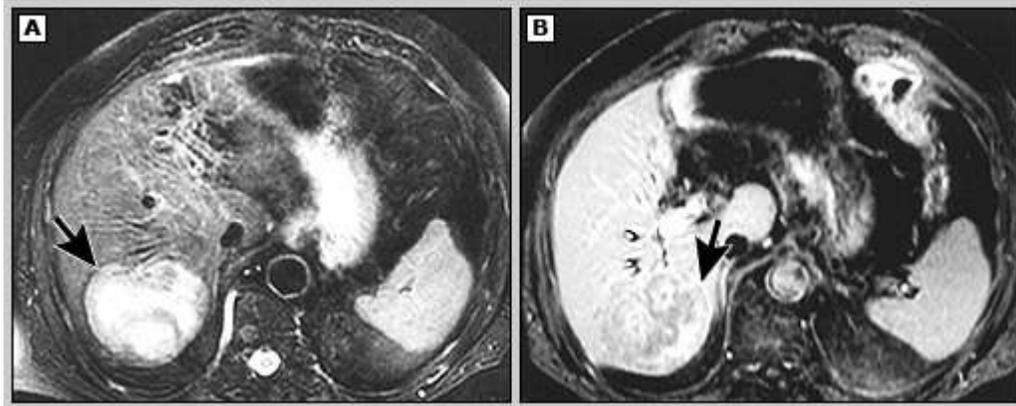


# IMAGING STUDIES

## Magnetic resonance imaging

- ▶ MRI has the advantage of achieving high-resolution images of the liver without the use of nephrotoxic contrast agents or ionizing radiation.
- ▶ MRI has a similar sensitivity for the diagnosis of HCC as helical CT .
- ▶ On MRI, HCC appears as a high-intensity pattern on T2-weighted images, and a low-intensity pattern on T1-weighted images .
- ▶ A meta-analysis estimated that the per-patient sensitivity was 86 percent and specificity was 89 percent compared with histopathologic findings . The sensitivity may be higher when used in conjunction with ultrasound .
- ▶ Helical CT scanning remains the favored technique by most radiologists because of the high cost of MRI, and the long duration required to obtain standard MRI images

T1-weighted MRI enhances the signal of the fatty tissue and suppresses the signal of the water. T2-weighted MRI enhances the signal of the water



# Biopsy

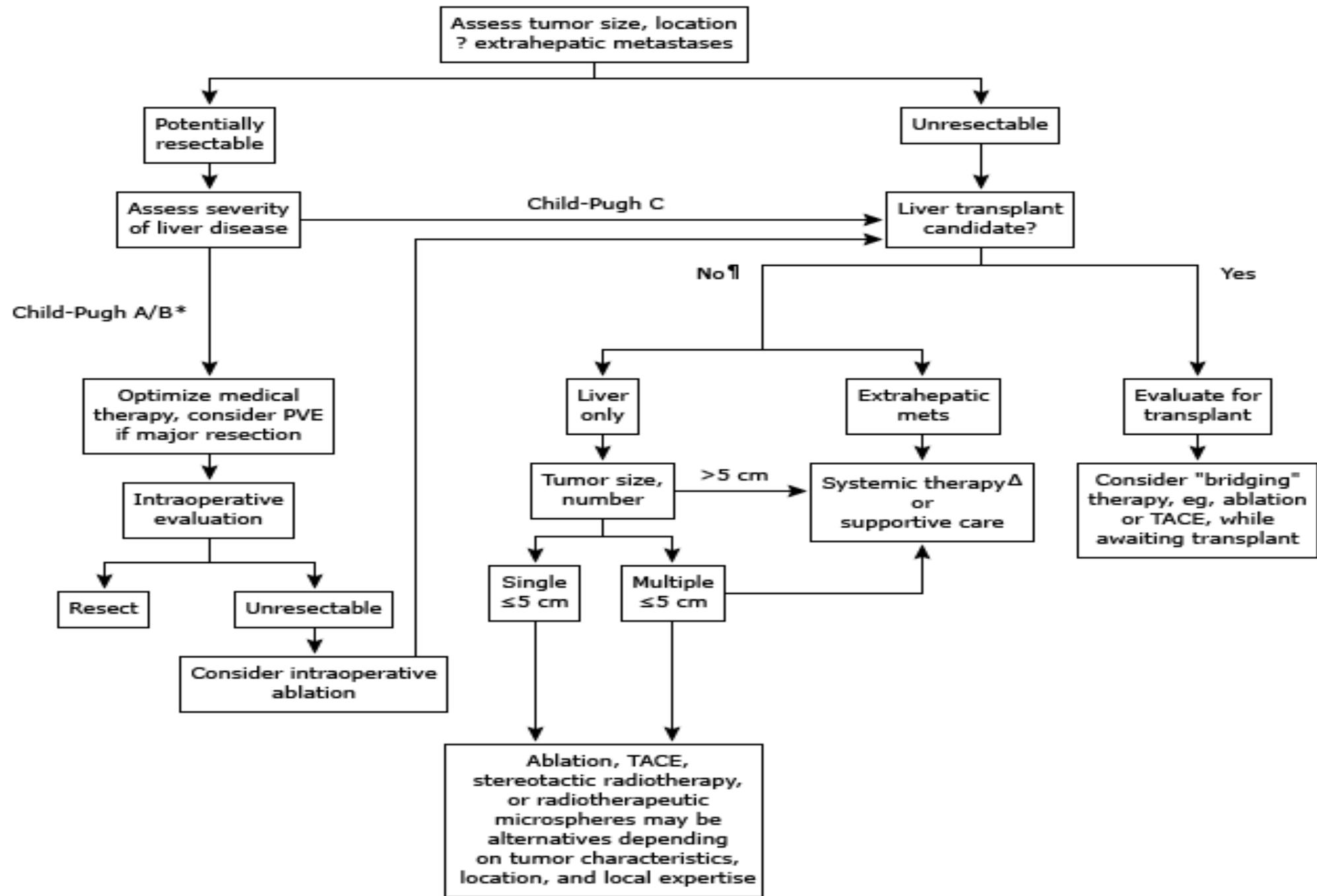
- ▶ ultrasound or computed tomography (CT) guidance can be helpful in patients with a focal liver lesion in whom the **diagnosis is uncertain when the results would influence management.**
- ▶ Directed core biopsies are more useful than fine-needle biopsy.
- ▶ For noncirrhotic patients, **the diagnosis of HCC should be considered for any hepatic mass that is not clearly a hemangioma or focal nodular hyperplasia,** especially if it is hypervascular. In the absence of specific clues to the diagnosis, **biopsy may be appropriate**

# Overview of treatment approaches for hepatocellular carcinoma

- ▶ Although **the mainstay of therapy is surgical resection**, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction.
- ▶ Several other treatment modalities are available, including:
  - Liver transplantation
  - Radiofrequency ablation (RFA) and microwave ablation
  - Percutaneous ethanol ablation
  - Transarterial chemoembolization (TACE)
  - Radioembolization
  - Cryoablation
  - Radiation therapy and stereotactic radiotherapy
  - Systemic chemotherapy, with cytotoxic agents and molecularly targeted therapies
  - Immunotherapy

# **Treatment algorithm for hepatocellular carcinoma**





# surgical resection

- ▶ **Potentially curative** partial hepatectomy is the optimal treatment for hepatocellular carcinoma (HCC) in patients with adequate liver functional reserve.
- ▶ The ideal patient for resection has a solitary HCC confined to the liver that shows no radiographic evidence of invasion of the hepatic vasculature, no evidence of portal hypertension, and well-preserved hepatic function.

# surgical resection

- ▶ The best outcomes are reported in carefully selected patients who have solitary lesions without intrahepatic metastasis or vascular invasion (gross or microscopic invasion of branches of the portal or hepatic veins), tumor diameter  $\leq 5$  cm, and a negative surgical margin of  $>1$  cm; five-year survival rates are as high as 78 percent (i.e. **the presence and degree of vascular invasion, tumor number and size, and surgical margin status**)
- ▶ Role of preoperative portal vein embolization (PVE) to produce hypertrophy in the future liver remnant.

# surgical resection

- ▶ Given the high rates of local recurrence after hepatic resection, several types of locoregional neoadjuvant therapy have been evaluated, including:
  - transarterial chemoembolization [TACE]
  - hepatic arterial infusion of radiolabeled lipiodol
  - regional irradiation with or without chemotherapy or TACE.

Given the **lack of survival benefit** in most studies it is suggested **not to give neoadjuvant therapy prior to hepatic resection.**

# Adjuvant antiviral therapy

- ▶ **Adjuvant antiviral therapy improves outcomes after potentially curative treatment of hepatitis B virus (HBV) related HCC.** For patients with HBV related HCC and active HBV related liver disease, it is recommended to use nucleos(t)ide analogs . The benefits of nucleos(t)ide analogs on oncologic outcomes in resected patients who do not have active hepatitis and/or a high viral load remain uncertain and require confirmation in large controlled trials .
- ▶ **The chemopreventive benefits of antiviral therapy after potentially curative resection of hepatitis C virus (HCV) related HCC are debated.** Although data suggested decreased recurrence and improved survival with interferon (IFN)-based HCV therapy, the same may not be true for the newer direct-acting antiviral (DAA) agents used for HCV therapy.

# Adjuvant Therapy

- ▶ a conclusive role for adjuvant systemic or intraarterial anticancer treatment has not yet been established, **and IT IS suggested not pursuing adjuvant therapy after complete resection of HCC.**

# posttreatment surveillance

- ▶ Imaging every three to six months for two to three years, then every 6 to 12 months .
- ▶ Assay of serum alpha-fetoprotein (AFP), if initially elevated, every three months for two to three years, then every 6 to 12 months.
- ▶

# Liver transplantation

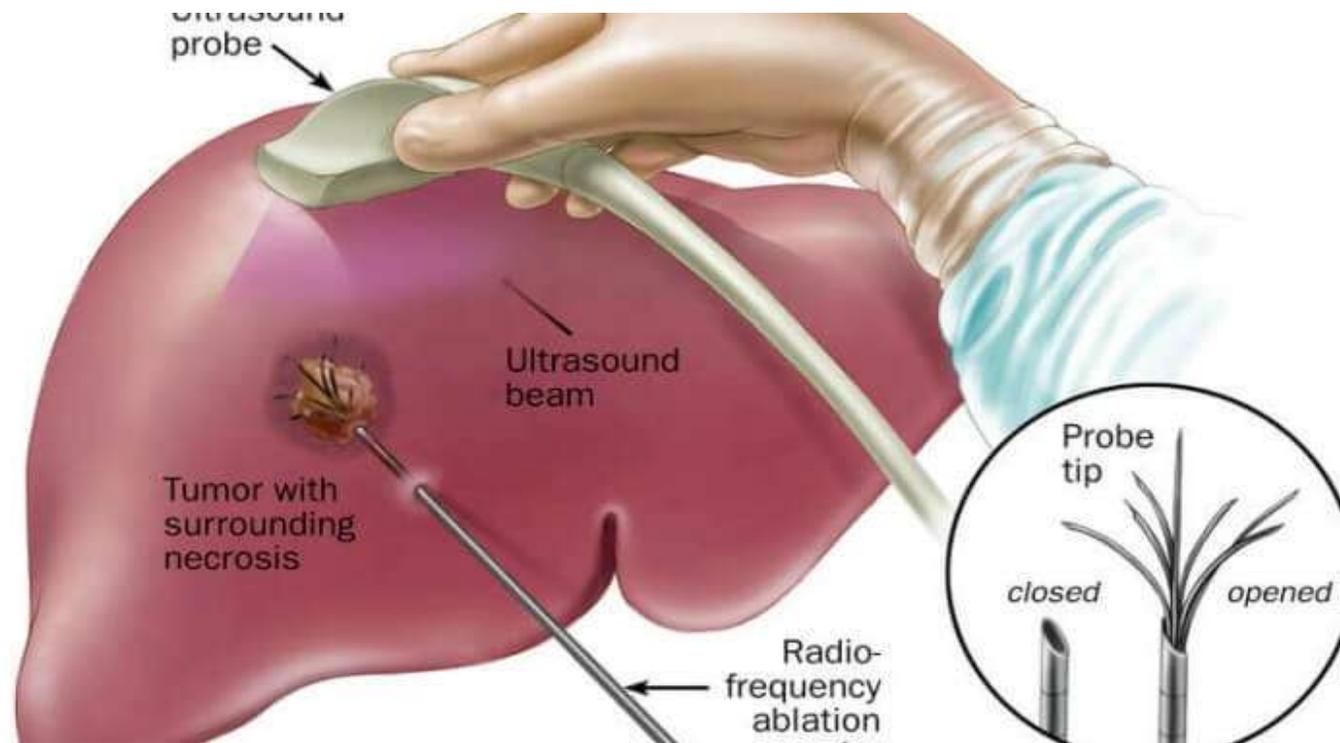
- ▶ Virtually all patients who are considered for liver transplantation are unresectable **because of the degree of underlying liver dysfunction rather than tumor extent.**
- ▶ liver transplantation can be described as appropriate for patients with earlier stage HCC and advanced liver disease.
- ▶ Orthotopic liver transplantation (OLT) is a suitable option for patients with liver disease (usually cirrhosis) who would not tolerate liver resection and **who have a solitary HCC  $\leq 5$  cm in diameter or up to three separate lesions none of which is larger than 3 cm ( Milan criteria),** no evidence of gross vascular invasion, and no regional nodal or distant metastases.

# Radiofrequency ablation

- ▶ RFA involves the local application of radiofrequency thermal energy to the lesion, in which a high frequency alternating current moves from the tip of an electrode into the tissue surrounding that electrode.
- ▶ As the ions within the tissue attempt to follow the change in the direction of the alternating current, their movement results in frictional heating of the tissue. As the temperature within the tissue becomes elevated beyond 60°C resulting in a region of necrosis surrounding the electrode

# Radiofrequency ablation

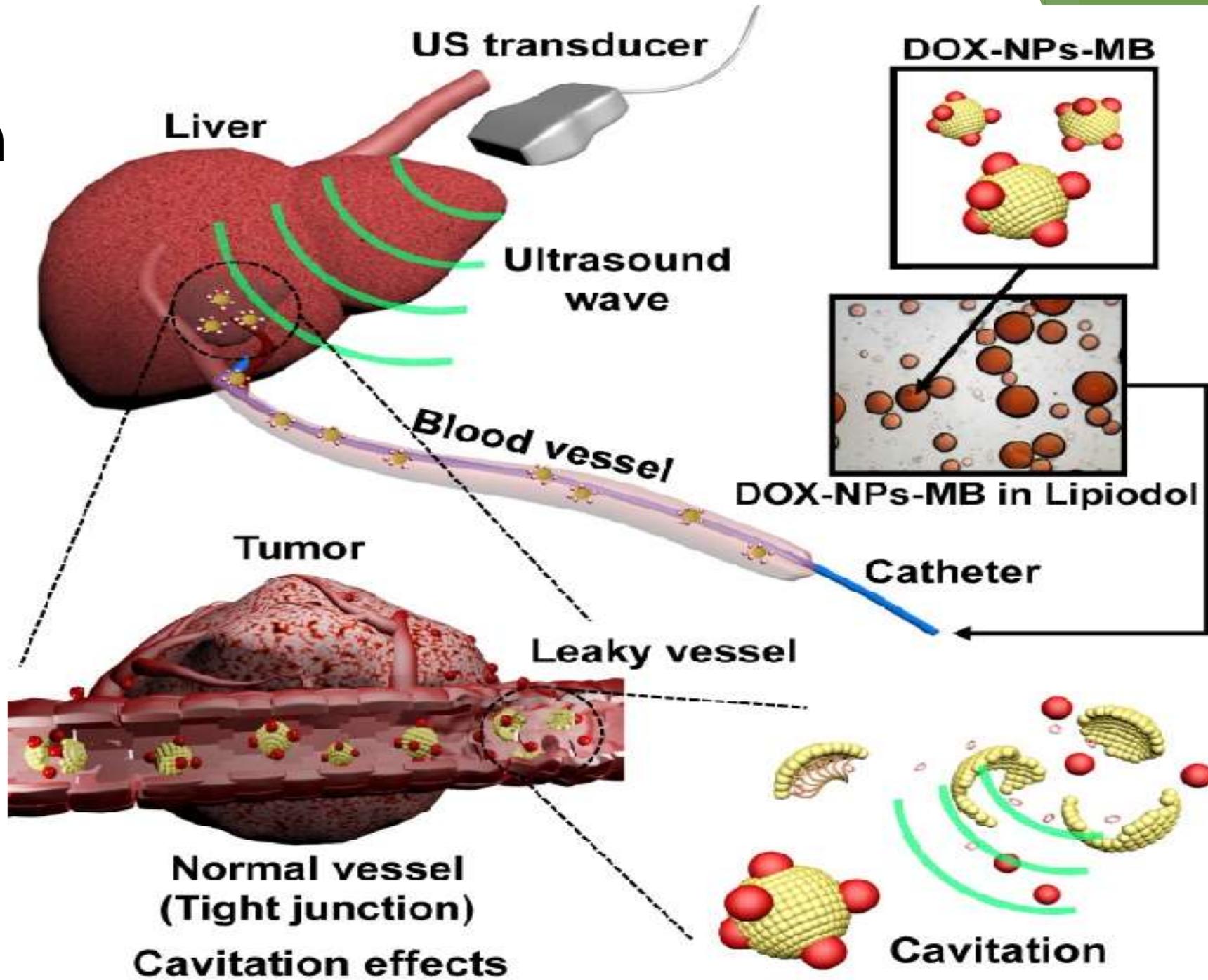
the best outcomes are in patients with **a single tumor <4 cm** in diameter. For cirrhotic patients, some clinicians restrict RFA to those with Child-Pugh class A or B severity only



# Trans arterial chemoembolization TACE

- ▶ Administration of cytotoxic chemotherapy directly to the tumor.
- ▶ Lipiodol is an oily contrast agent that promotes intratumoral retention of chemotherapy drugs.
- ▶ A more recent method of chemoembolization involves the use of drug-eluting polyvinyl alcohol microspheres ("beads"), which seem to cause less toxicity with similar efficacy.
- ▶ Simultaneous or sequential occlusion of the hepatic artery until stagnation of blood flow to the tumor occurs may result in greater anti-tumor efficacy than chemotherapy alone.

**Tran**



# Trans arterial chemoembolization TACE

- ▶ TACE is used most often for the **treatment of large unresectable HCC.**
- ▶ It is suggested to use RFA plus TACE as a recommendation for intermediate-sized HCC (ie, 3 to 5 cm).

# Percutaneous ethanol or acetic acid ablation

- ▶ considered for patients with small HCCs who are not candidates for resection due to their poor functional hepatic reserve.
- ▶ was the most widely accepted, minimally invasive method for treating such patients. it is low cost, requires a minimal amount of equipment.

# Systemic therapy

- ▶ **Molecularly targeted therapy: Sorafenib** statistically significant survival benefit fo (a multitargeted tyrosine kinase inhibitor) over supportive care alone in patients with advanced HCC.
- ▶ **Immunotherapy :** **Nivolumab** is a fully human monoclonal antibody that targets the programmed cell death 1 receptor (PD-1)
- ▶ **Cytotoxic chemotherapy** — Chemotherapy has not been used routinely against HCC .
- ▶ Radiotherapy: HCC radiosensitive but not applicable at the liver .

# Surgical Jaundice

The slide features a white background with a decorative graphic on the right side. This graphic consists of several overlapping, semi-transparent green triangles and polygons in various shades of green, ranging from light lime to dark forest green. The shapes are arranged in a way that they appear to be layered, creating a modern, abstract design.

# Choledocholithiasis

## EPIDEMIOLOGY & Risk factor

- ▶ **Age** — Age is a major risk factor for the gallstones. Gallstones are exceedingly rare in children except in the presence of hemolytic states; in addition, less than 5 percent of all cholecystectomies are performed in children. Age 40 appears to represent the cutoff between relatively low and high rates of cholecystectomies.
- ▶ **Sex** — As noted above, a higher prevalence of gallstones has been observed in women in all age groups . The difference between women and men is particularly striking in young adults. One study found a female-to-male ratio of 2.9 between the ages of 30 to 39 years; the ratio narrowed to 1.6 between the ages of 40 to 49 years and 1.2 between the ages of 50 to 59 years . The higher rates in young women is almost certainly a result of pregnancy and sex steroids.
- ▶ **Pregnancy** — Pregnancy is a major risk factor for the development of cholesterol gallstones. The risk is related to both the frequency and number of pregnancies. In one report, for example, the prevalence of gallstones increased from 1.3 percent in nulliparous females to 12.2 percent in multiparous females. Another study recruited 272 women in the first trimester of pregnancy . The incidence of new biliary sludge and gallstones was 31 and 2 percent, respectively.

# Cholelithiasis

## **EPIDEMIOLOGY & Risk factor**

- ▶ **Oral contraceptives and estrogen replacement therapy**
- ▶ **Family history and genetics**
- ▶ **Obesity**
- ▶ **Rapid weight loss**
- ▶ **Diabetes mellitus**
- ▶ **Serum lipids**
- ▶ **Cirrhosis**
- ▶ **drugs ( ceftriaxone )**
- ▶ **Crohn disease**
- ▶ **Hemolysis**
- ▶ **RECURENT BILIARY INFECTION .**
- ▶ **large bile ducts and periampullary diverticular are at elevated risk for the formation of primary bile duct stones**

# Cholelithiasis

## **PROTECTIVE FACTORS**

- ▶ **Statins**
- ▶ **Ascorbic acid**
- ▶ **Coffee**
- ▶ **Vegetables**
- ▶ **Poly- and monounsaturated fats.**

# CLINICAL MANIFESTATIONS

- ▶ Most patients with choledocholithiasis are **symptomatic**, although occasional patients are asymptomatic.
- ▶ The most common cause of **painless obstructive Jaundice is CBD stones.**

# Physical examination

- ▶ On physical examination, patients with choledocholithiasis often have right upper quadrant or epigastric tenderness. Patients may also appear jaundiced.
- ▶ **Courvoisier's sign** (a palpable gallbladder on physical examination) may be seen when gallbladder dilation develops because of an obstruction of the common bile duct.
- ▶ **Courvoisier's Law** .

# Laboratory tests

- ▶ Serum ALT and AST concentrations are typically elevated early in the course of biliary obstruction.
- ▶ Later, liver tests are typically elevated in a cholestatic pattern, with increases in serum bilirubin, alkaline phosphatase, and GGT exceeding the elevations in serum ALT and AST.
- ▶ An elevation in serum bilirubin had a sensitivity of 69 percent and a specificity of 88 percent for diagnosing a common bile duct stone. For elevations in serum alkaline phosphatase, the values were 57 and 86 percent, respectively.
- ▶ normal liver tests play a greater role in excluding choledocholithiasis than elevated liver tests play in diagnosing stones.

# Complicated choledocholithiasis

- ▶ The two major complications associated with choledocholithiasis are **pancreatitis** and **acute cholangitis**.
- ▶ Patients with acute cholangitis often present with **Charcot's triad** (fever, right upper quadrant pain, and jaundice) and leukocytosis. In severe cases, bacteremia and sepsis may lead to hypotension and altered mental status (**Reynolds' pentad**)
- ▶ Long-standing biliary obstruction from various causes, including common bile duct stones, may result in liver disease that may progress to cirrhosis, a phenomenon referred to as **secondary biliary cirrhosis**.

# DIAGNOSIS

- ▶ We use the results of laboratory tests and transabdominal ultrasound to stratify a patient as high risk, intermediate risk, or low risk for having choledocholithiasis.
- ▶ Subsequent management varies depending on the patient's level of risk whether low , Intermediate and high .

# Diagnosis

## Risk assessment

### the American Society for Gastrointestinal Endoscopy (ASGE)

▶ **Very strong" predictors**

- The presence of a common bile duct stone on transabdominal ultrasound
- Clinical acute cholangitis
- A serum bilirubin greater than 4 mg/dL .

▶ **"Strong" predictors**

- A dilated common bile duct on ultrasound (more than 6 mm in a patient with a gallbladder in situ)
- A serum bilirubin of 1.8 to 4 mg/dL

▶ **Moderate" predictors**

- Abnormal liver biochemical test other than bilirubin
- Age older than 55 years
- Clinical gallstone pancreatitis

# Diagnosis

## Risk assessment

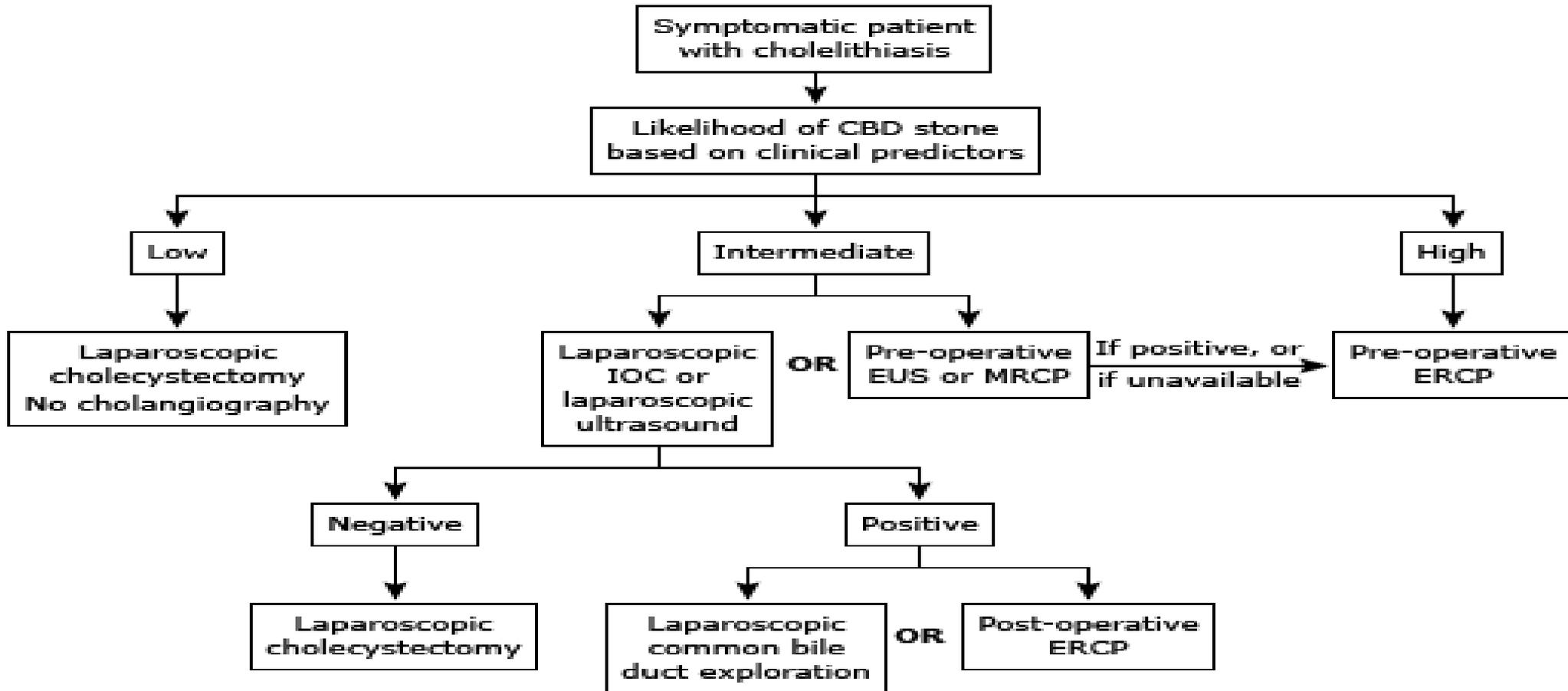
### the American Society for Gastrointestinal Endoscopy (ASGE)

- ▶ **High risk**
  - At least one very strong predictor **and/or**
  - Both strong predictors
- ▶ **Intermediate risk**
  - One strong predictor **and/or**
  - At least one moderate predictor
- ▶ **Low risk**
  - No predictors

# Diagnosis

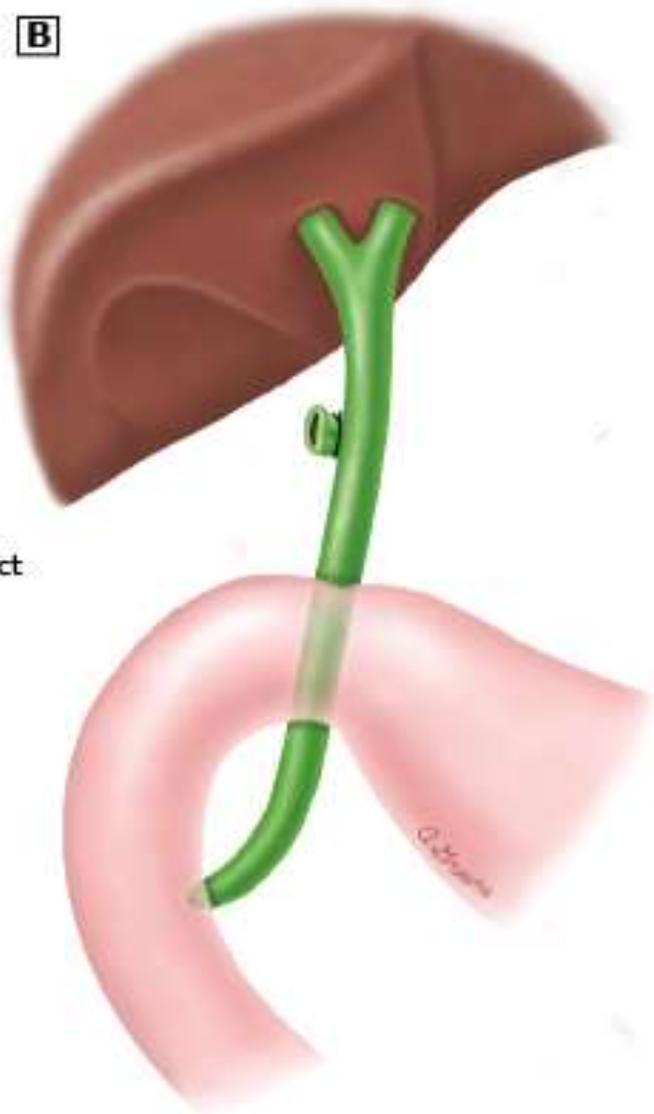
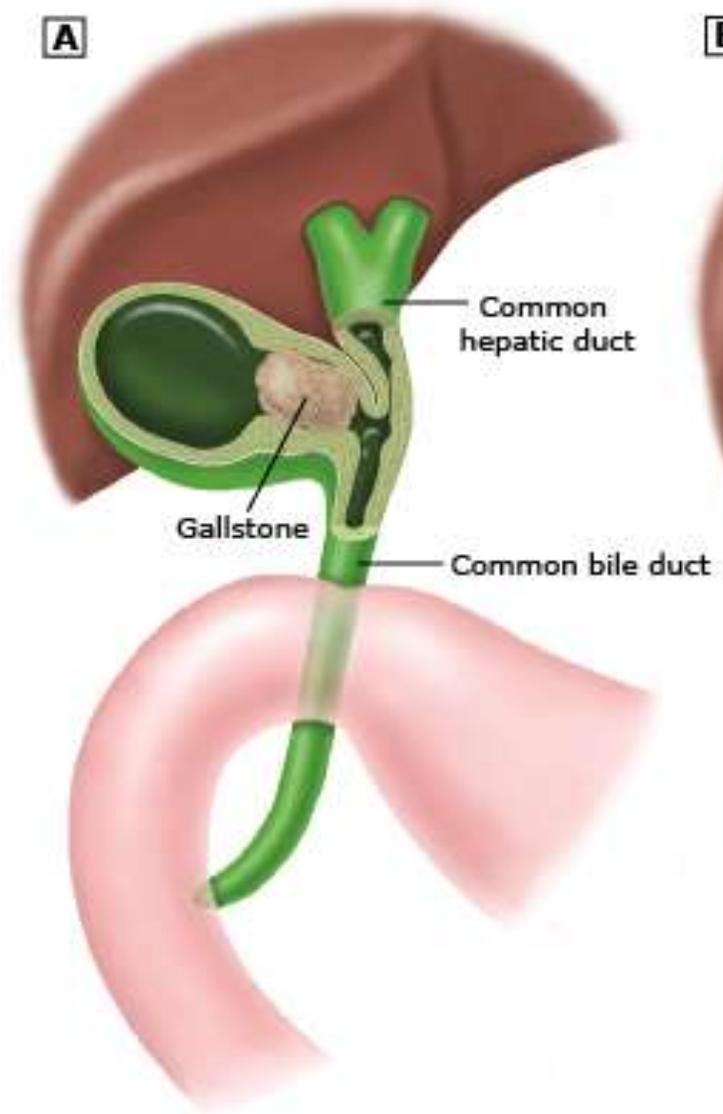
- ▶ MRCP is preferred for many patients because it is noninvasive. However, the sensitivity of MRCP may be lower for small stones (<6 mm[]), and biliary sludge can be detected by EUS, but generally not by MRCP. As a result, **EUS should be considered in patients in whom the suspicion for choledocholithiasis remains moderate to high despite a negative MRCP.**

# management of choledocholithiasis

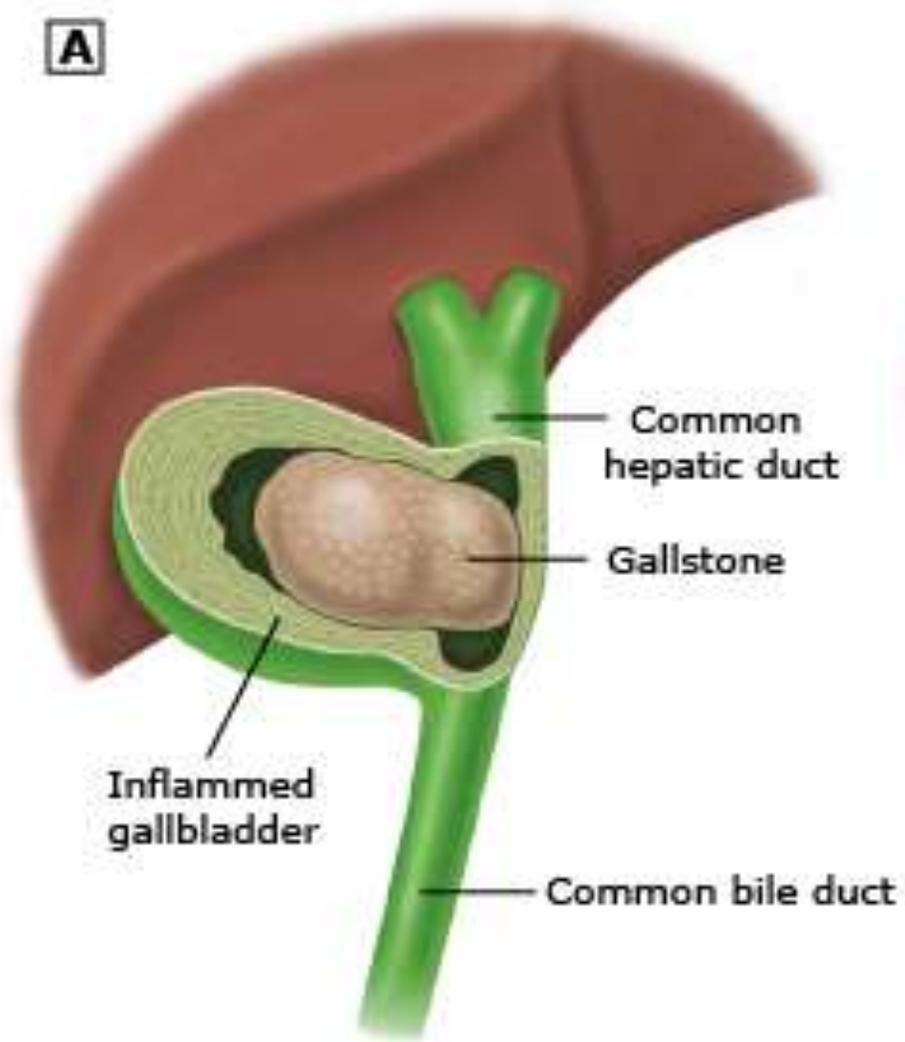


# Mirizzi syndrome

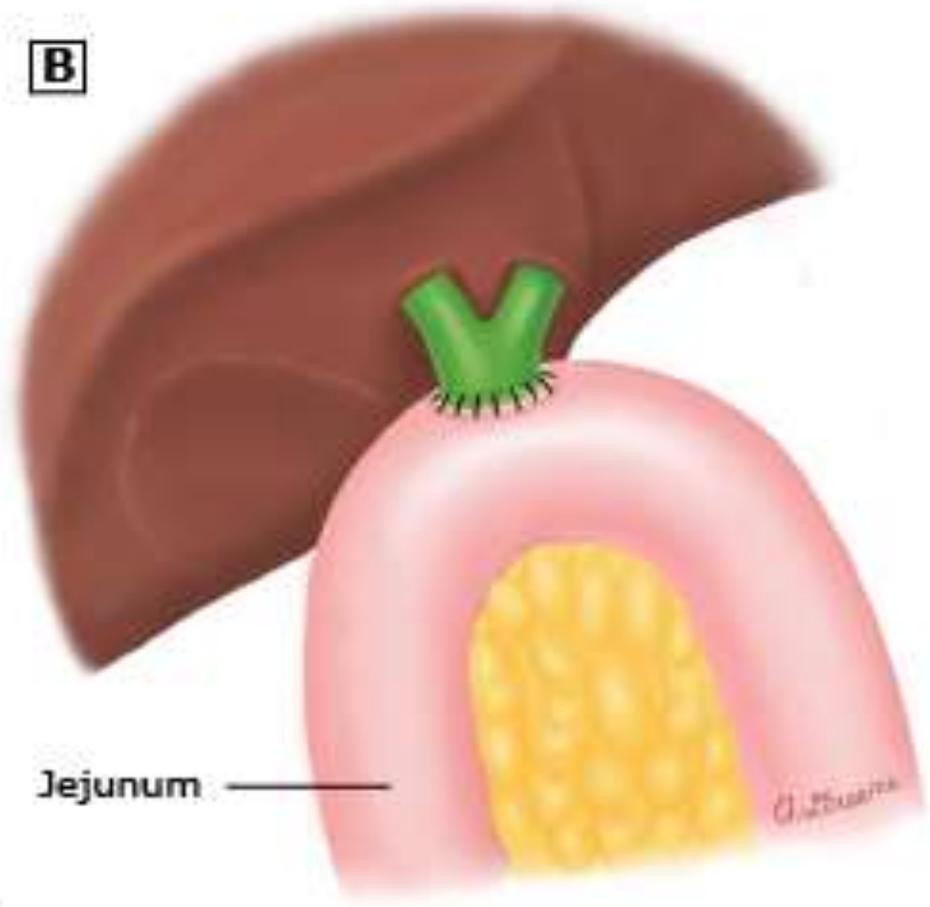
- ▶ defined as common hepatic duct obstruction caused by an extrinsic compression from an impacted stone in the cystic duct or Hartmann's pouch of the gallbladder.
- ▶ Mirizzi syndrome has been associated with gallbladder cancer . It has been hypothesized that recurrent inflammation and biliary stasis may predispose to both conditions.



**A**



**B**



# Mirizzi syndrome

## **CLASSIFICATION**

- ▶ Mirizzi syndrome has been classified based on the presence and extent of a cholecystobiliary fistula