Hepatocellular Carcinoma (HCC)

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EPIDEMIOLOGY

- The ninth most diagnosed cancer worldwide .
- 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: mean age at presentation is between 50 and 60 years .

RISK FACTORS

- chronic hepatitis C virus (HCV) infection
- Hepatitis B
- hereditary hemochromatosis
- cirrhosis
- Idiopathic

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 nucleotide 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 metastasis**.
- 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.

Pathology

- 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**:

1. The **severity** of underlying liver disease
2. the tumor **size**
3. The tumor **extension** of into adjacent structures
4. The presence of **metastases**.

STAGING AND PROGNOSTIC SCORING SYSTEMS

- 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 STAGING

- T1 has been subdivided into two subcategories: T1a (solitary tumors ≤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.

TNM STAGING

- 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 ≤ 50%	Uninodular extension ≤ 50%	Massive or extension >50%
AFP (ng/ml)	≤ 400	≥ 400	
Portal Vein Thrombosis	Absent	Present	

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Used to predict survival in patients with hepatocellular carcinoma.
The total score is derived by adding each of the sub scores.

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
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

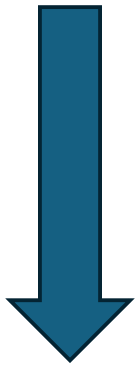
- Suspicion for HCC should be heightened in patients with previously compensated cirrhosis who develop decompensation such as ascites, encephalopathy, jaundice, or variceal bleeding.
- Obstructive jaundice caused by invasion of the biliary tree, compression of the intrahepatic duct, or rarely, because of haemobilia.
- Diarrhea
- Bone pain or dyspnea due to metastases.

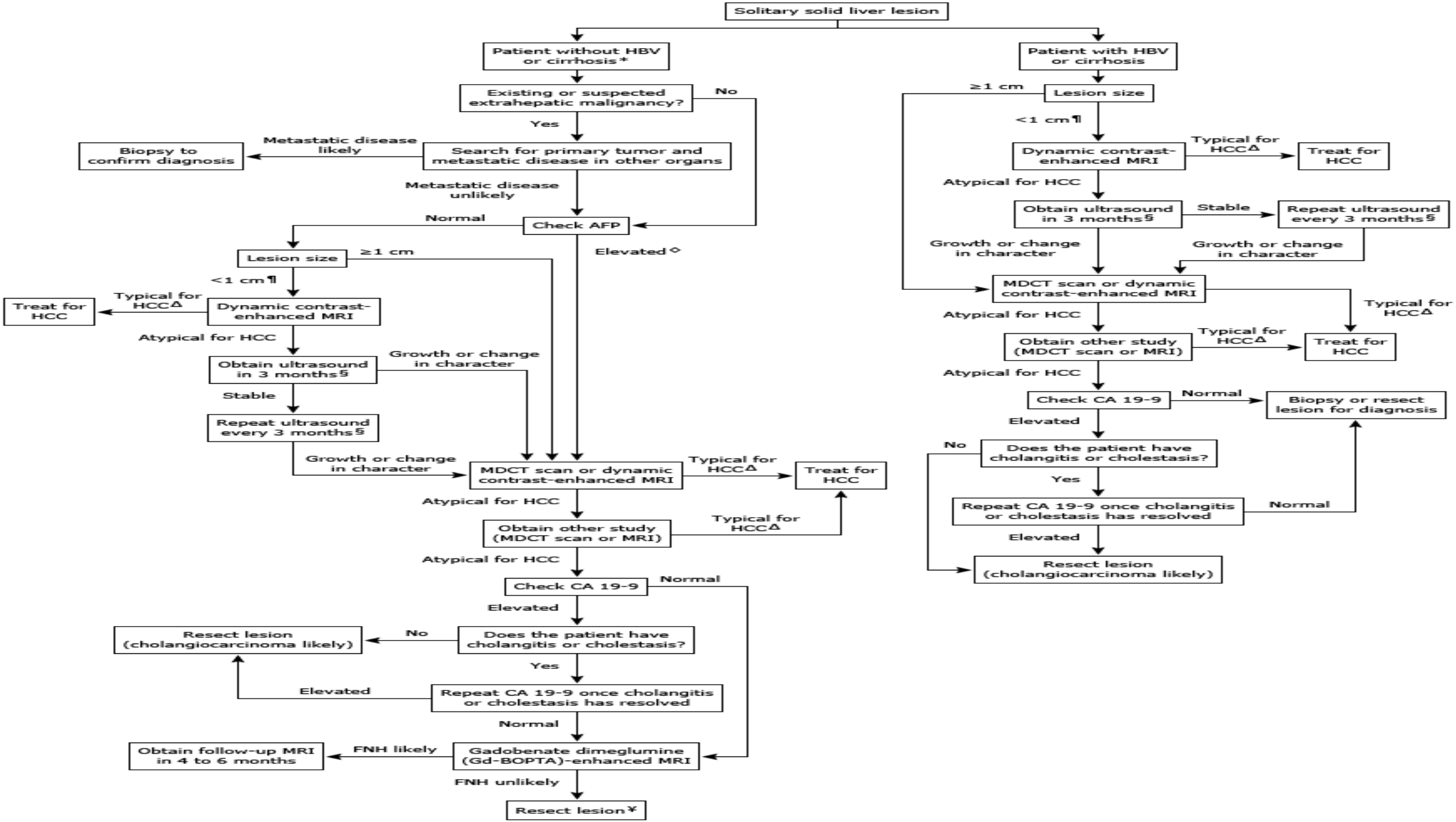
Clinical Features

- 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




Solitary solid liver lesion
Patient without HBV or cirrhosis*
Patient with HBV or cirrhosis
Existing or suspected extrahepatic malignancy?
No
Yes
Metastatic disease likely
Biopsy to confirm diagnosis
Search for primary tumor and metastatic disease in other organs
Metastatic disease unlikely
Normal
Check AFP
Elevated◇
Lesion size
≥1 cm
<1 cm¶
Typical for HCCΔ
Treat for HCC
Dynamic contrast-enhanced MRI
Atypical for HCC
Obtain ultrasound in 3 months§
Growth or change in character
Stable
Repeat ultrasound every 3 months§
Growth or change in character
MDCT scan or dynamic contrast-enhanced MRI
Typical for HCCΔ
Treat for HCC
Atypical for HCC
Obtain other study (MDCT scan or MRI)
Typical for HCCΔ
Atypical for HCC
Check CA 19-9
Normal
Elevated
No
Does the patient have cholangitis or cholestasis?
Yes
Repeat CA 19-9 once cholangitis or cholestasis has resolved
Elevated
Normal
Resect lesion (cholangiocarcinoma likely)
Lesion size
≥1 cm
<1 cm¶
Dynamic contrast-enhanced MRI
Typical for HCCΔ
Treat for HCC
Atypical for HCC
Obtain ultrasound in 3 months§
Stable
Repeat ultrasound every 3 months§
Growth or change in character
Growth or change in character
MDCT scan or dynamic contrast-enhanced MRI
Typical for HCCΔ
Atypical for HCC
Obtain other study (MDCT scan or MRI)
Typical for HCCΔ
Treat for HCC
Atypical for HCC
Check CA 19-9
Normal
Biopsy or resect lesion for diagnosis
Elevated
No
Does the patient have cholangitis or cholestasis?
Yes
Repeat CA 19-9 once cholangitis or cholestasis has resolved
Normal
Elevated
Resect lesion (cholangiocarcinoma likely)
Check CA 19-9
Normal
Elevated
Resect lesion (cholangiocarcinoma likely)
No
Does the patient have cholangitis or cholestasis?
Yes
Elevated
Repeat CA 19-9 once cholangitis or cholestasis has resolved
Normal
Obtain follow-up MRI in 4 to 6 months
FNH likely
Gadobenate dimeglumine (Gd-BOPTA)-enhanced MRI
FNH unlikely
Resect 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.

Diagnosis

- 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.

Diagnosis

- 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

Serum Markers
Alpha-fetoprotein

- 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** .

Serum Markers
Alpha-fetoprotein

- However, HCC is often diagnosed at a lower AFP level in patients undergoing screening.
- AFP cutoff **20 mcg/L** (sensitivity 60, specificity 91 percent)

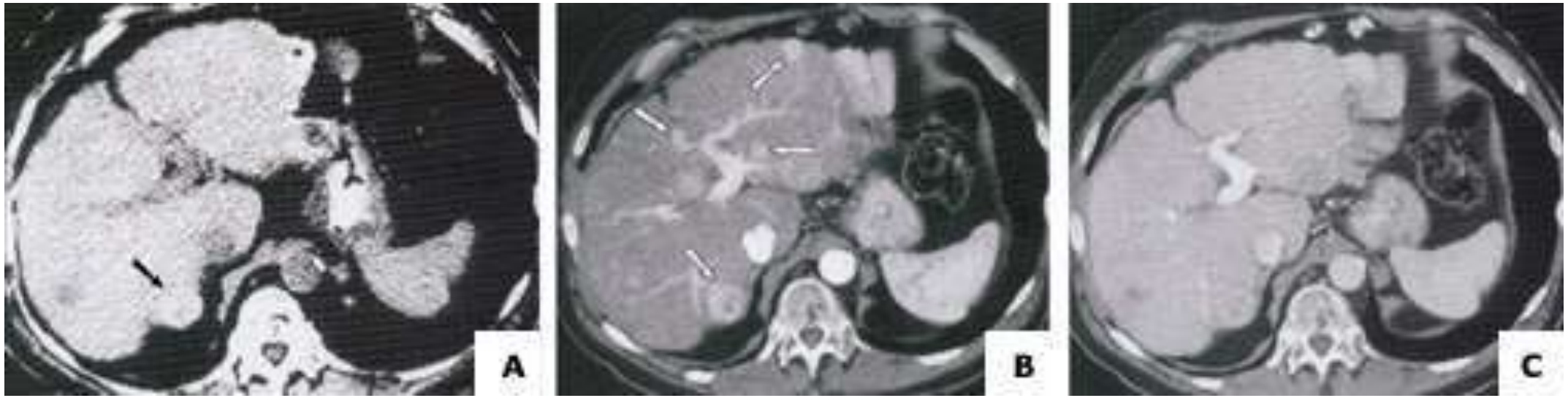
Imaging Studies
Ultrasound and Endoscopic ultrasound

- 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

Abdominal CT Tri-Phasic CT-Scan

- 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



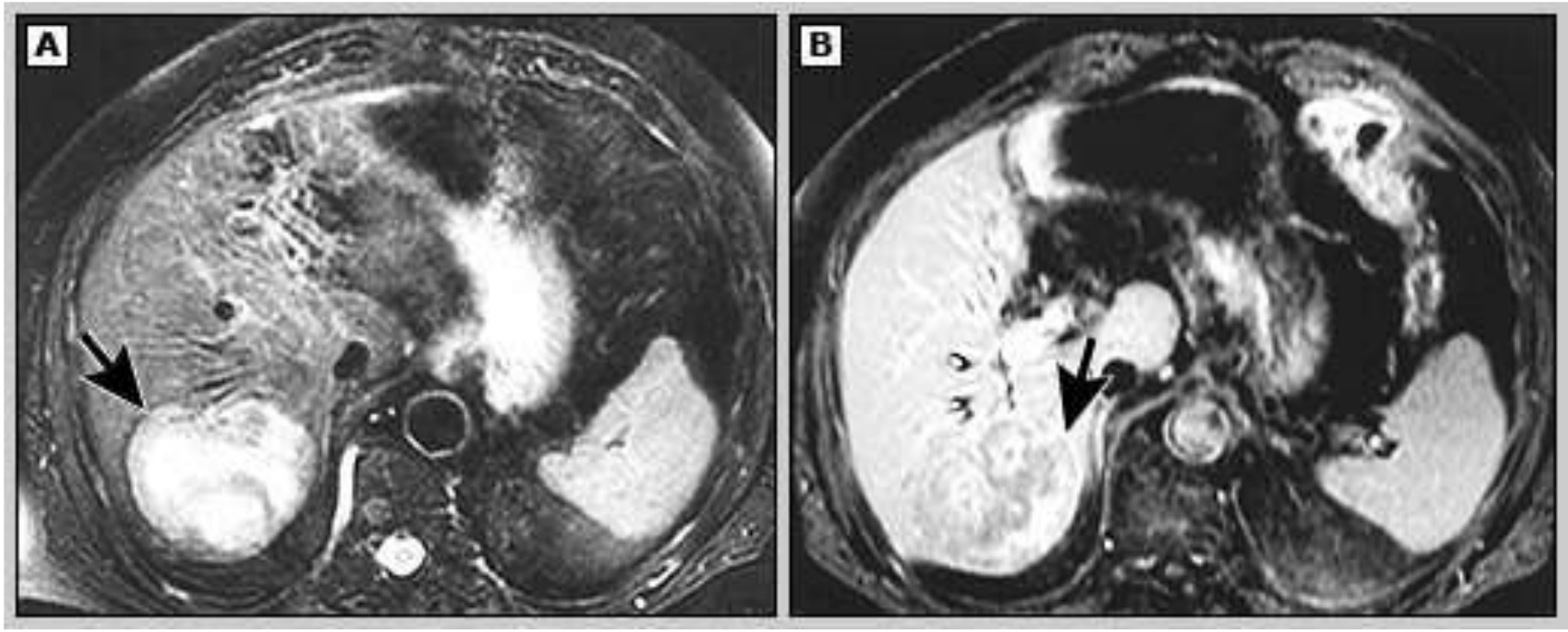
Magnetic Resonance Imaging

- 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 .

Magnetic Resonance Imaging

- 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.

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 hyper vascular.
- In the absence of specific clues to the diagnosis, biopsy may be appropriate

Treatment Approaches for Hepatocellular Carcinoma

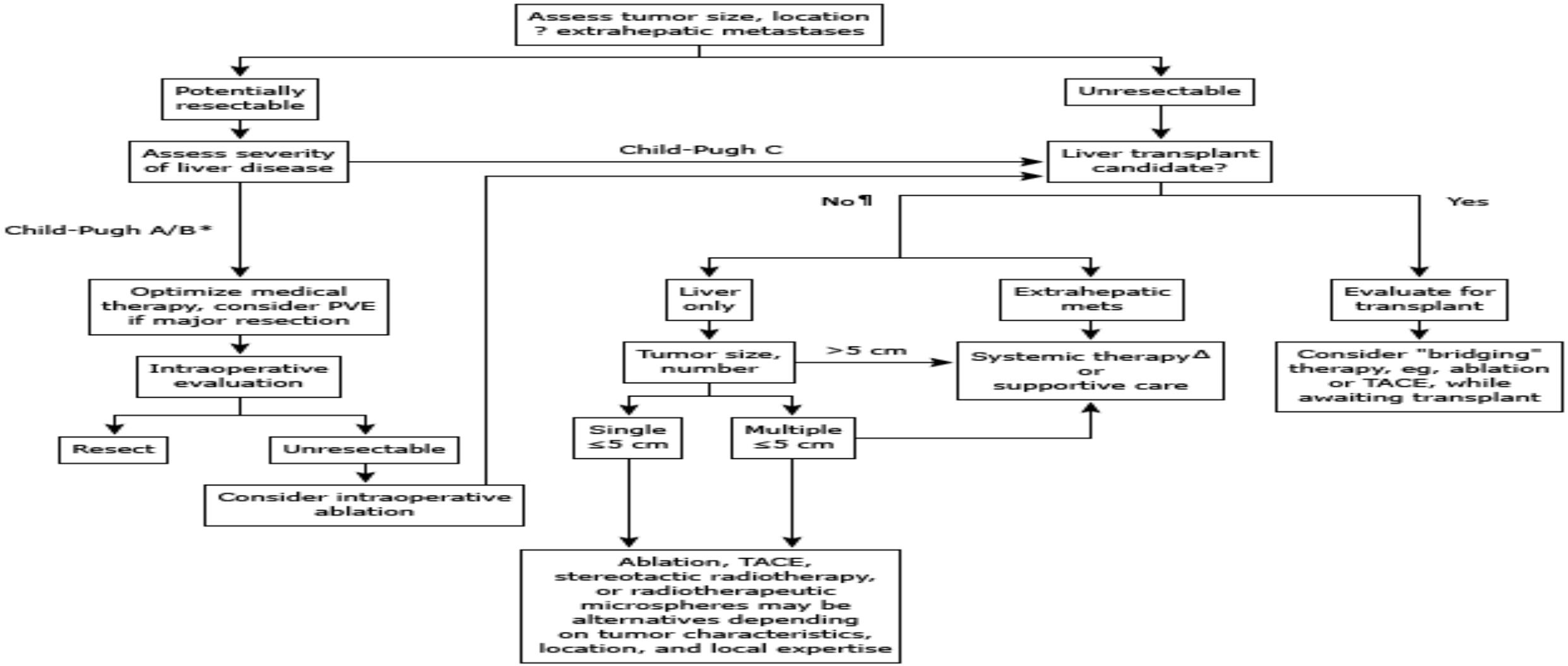
- Although the mainstay of therapy is **surgical resection**, the majority of patients are not eligible because of tumor extent or underlying liver dysfunction.

Treatment Approaches for Hepatocellular Carcinoma

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 ≤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 .

Adjuvant Antiviral Therapy

- The chemo preventive 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.

Liver Transplantation

- 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 ≤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)

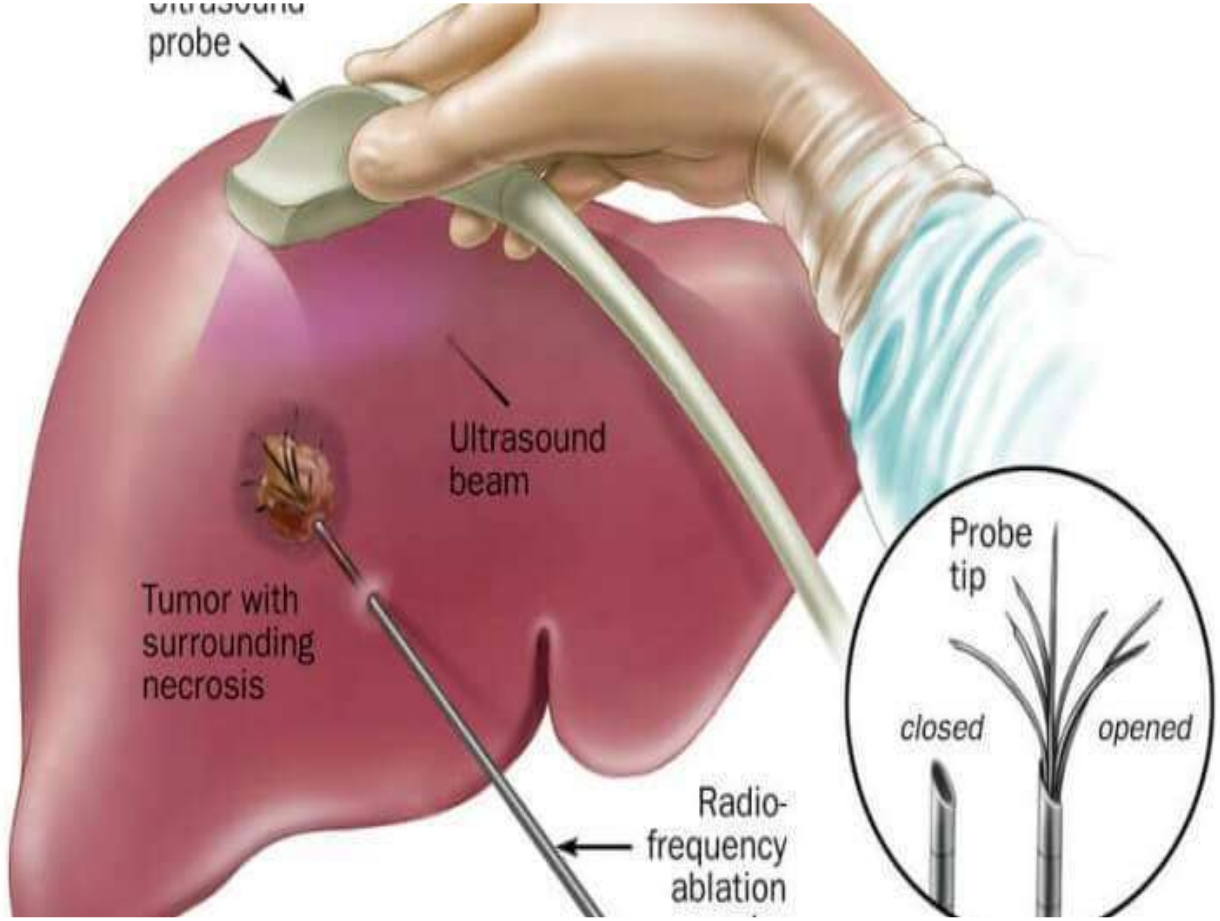
- RFA involves the local application of radiofrequency thermal energy to the lesion, in which a high frequency alternating current moves from the tip of an electrode into the tissue surrounding that electrode.

Radiofrequency Ablation (RFA)

- 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 60ºC resulting in a region of necrosis surrounding the electrode

Radiofrequency Ablation (RFA)

- 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.

Trans Arterial Chemoembolization (TACE)

- 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.

Trans Arterial Chemoembolization (TACE)

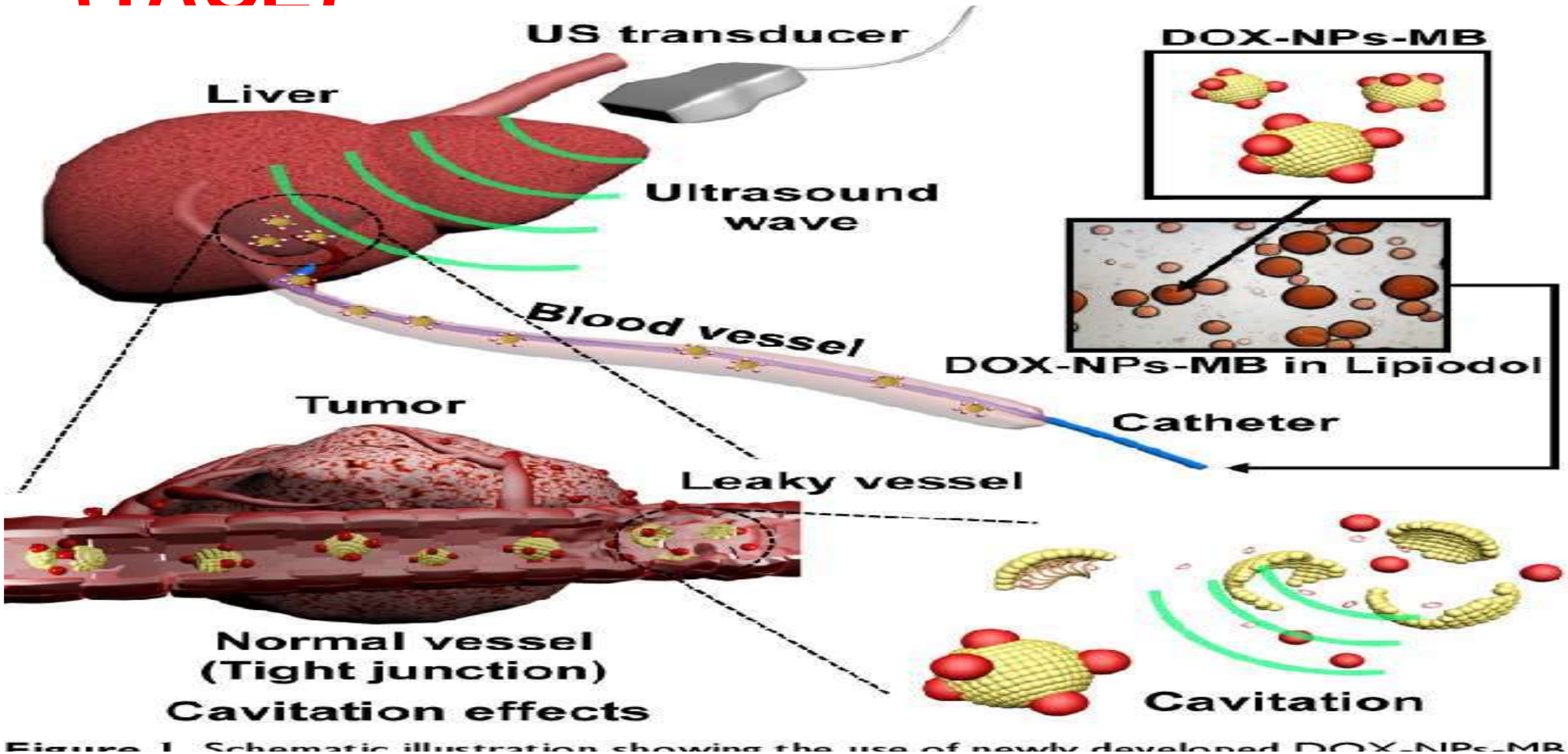


Figure 1. Schematic illustration showing the use of newly developed DOX-NPs-MB

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 (i.e., 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.
- It 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 for (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)

Systemic Therapy

- Cytotoxic chemotherapy — Chemotherapy has not been used routinely against HCC .
- Radiotherapy: HCC radiosensitive but not applicable at the liver .

Have A Nice Day