Primary Liver Neoplasms

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Outline

Disease Overview

- Background
- Characteristics of Common Malignant liver tumors
- Characteristics of common benign liver lesions
- Basic management

Benign Primary Liver Neoplasms

- Hepatic haemangiomas
- Focal nodular hyperplasia (FNH)
- Hepatocellular adenoma (HCA)
- Patients with multiple lesions

Malignant Primary Liver Neoplasms

- Hepatocellular carcinoma
- Cholangiocarcinoma
- Mucinous cystic neoplasms
- Mesenchymal tumours and Hepatoblastoma

Introduction To Primary Malignant Liver Neoplasms

- Secondary liver tumors are the most frequent malignant liver tumor, 30 to 1 particularly in patients without underlying liver disease
- The majority are HCC, with cholangiocarcinoma comprising most of the remaining cases.
- Primary liver cancer is the sixth most frequently diagnosed cancer worldwide and the fourth leading cause of cancer-related mortality worldwide
- **With a five-year survival of 18 percent, liver cancer is the second most lethal tumor after pancreatic cancer**.

- Primary malignant liver tumors arise from the major constituent cells of the liver
    1. **Hepatocytes** (hepatocellular carcinoma)
    2. **Biliary epithelial cells** (cholangiocarcinoma and biliary cystadenocarcinoma)
    3. **Endothelial cells** (angiosarcoma, epithelioid hemangioendothelioma)
    4. Or combinations of these cells with various mesenchymal cells (eg, hepatoblastoma)
- Many now consider primary liver tumors as a continuum, with typical hepatocellular carcinoma and cholangiocarcinoma at the two ends of the spectrum and a range of tumors in between showing variable degrees of hepatocellular and cholangiocarcinoma differentiation.

Hepatocellular Carcinoma

- More frequently in men, ratio of 3:1
- The differences in sex distribution are thought to be due to variations in hepatitis carrier states, exposure to environmental toxins, and/or potentially protective effects of estrogen mediated through inhibition of interleukin 6.
- HCC increases with age.
    - 53 years in Asia
    - 67 years in the United States
- The median survival following diagnosis approximately 6 to 20 months

Risk Factors for HCC

- **Cirrhosis**
  - Cirrhosis from any etiology
  - **Hepatitis B and C viruses** underlies many of these cases
  - Patients with chronic HBV infection are at risk even in the absence of cirrhosis
  - Up to one-third of patients with cirrhosis will develop HCC during their lifetime, with an annual incidence rate of 1 to 8%
- **Alcohol**
- **Metabolic factors**

  Nonalcoholic fatty liver disease

  Diabetes mellitus

  Obesity

- **Genetic susceptibility**
  - Hereditary hemochromatosis
  - Alpha-1 antitrypsin deficiency
  - Acute intermittent porphyria
- **Environmental toxins**

PROTECTIVE FACTORS

- **Vaccination for hepatitis B virus (HBV)**
- **Treatment for viral hepatitis** Antiviral therapy
- **Medications**.. Statins /Aspirin /Metformin
- **Lifestyle factors**
  - Coffee
  - Diet – consumption of white meat, fish, omega-3 fatty acids, or vegetables
  - Dietary intake of vitamin E
  - Physical activity

Clinical Features

HCC is frequently diagnosed late due the absence of symptoms in early disease and the inadequate surveillance for high-risk patients.

A range of clinical presentations, asymptomatic to presenting with a life-threatening illness such as variceal hemorrhage.

Previously stable patients with cirrhosis may develop features of decompensation (eg, variceal bleeding or ascites) due to the extension of HCC into the hepatic or portal veins.

May develop a paraneoplastic syndrome

Paraneoplastic Syndromes

- **Hypoglycemia**
  - is thought to result from the tumor's high metabolic needs.
  - typically mild
  - Less than 5 percent of tumors secrete insulin-like growth factor-II, which can cause severe, symptomatic hypoglycemia
- **Erythrocytosis**
  - probably due to tumor secretion of erythropoietin
  - most patients are still anaemic at diagnosis because of other effects of the tumor
- **Hypercalcemia**
- **Diarrhea**
- **Cutaneous features**
  - skin changes are rare, none is specific for the diagnosis

Other clinical presentations

- Intraperitoneal bleeding due to tumor rupture
- Obstructive jaundice
- Hemobilia
- Fever developing in association with central tumor necrosis
- Pyogenic liver abscess (very rare)

Extrahepatic metastases

- Approximately 10 to 15 percent of cases
- The most common sites of extrahepatic metastases are lung, intra-abdominal lymph nodes, bone and adrenal gland.

Diagnostic Approach

- The goal is to detect the tumors when they are ≤2 cm in size
- The five-year survival rate for patients whose tumors are detected at an early stage and who receive treatment exceeds 70 %

- **Alpha-fetoprotein**

  Other differential diagnosis of an elevated AFP:

  - Patients with acute or chronic viral hepatitis, but without HCC
  - Pregnancy
  - Tumors of gonadal origin
  - Other malignancies, of which gastric cancer is the most common

- **Imaging**
  - Contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI)
  - Diagnosis of HCC can be made radiographically, obviating the need for a biopsy.
  - If the diagnosis remains uncertain, biopsy can be considered if the results are likely to affect the patient's management.
- **Risks of biopsy include**
  - Immediate procedure-related complications
  - Spread of tumor along the needle track
  - The possibility of sampling errors leading to false negative diagnoses

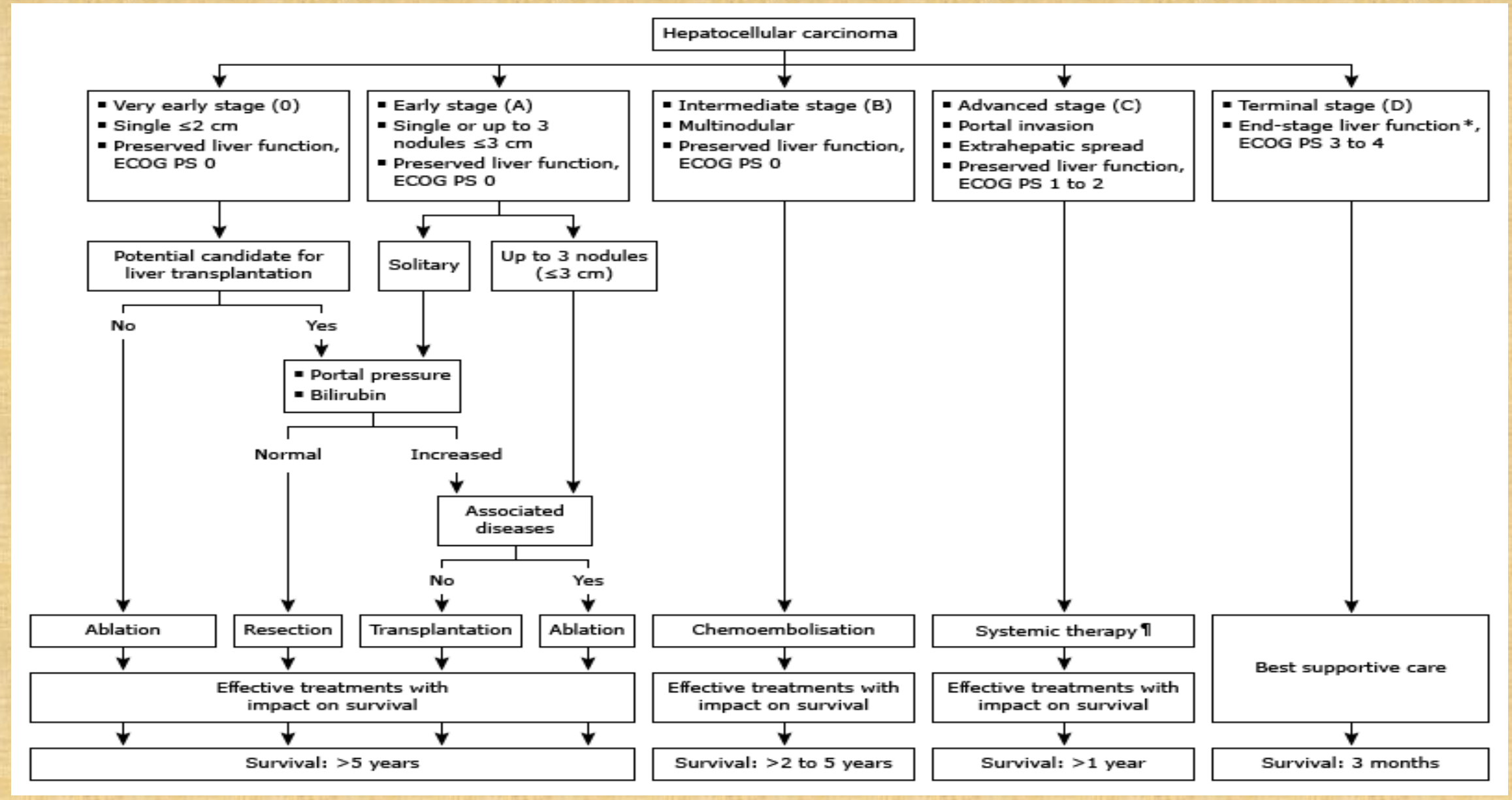
Evaluation After HCC Diagnosis

- Assessment of liver reserve, performance status, co-morbidities, extent of tumor spread, and potential eligibility for liver transplantation.
    - Listing criteria: solitary HCC ≤5 cm or up to three less than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases (**the Milan criteria**).
- Four features that have been recognized as being important determinants of survival:
    - The severity of the underlying liver disease
    - Tumor size
    - Extension of the tumor into adjacent structures
    - The presence or absence of metastases

Treatments Options

- The mainstay therapy is **surgical resection**.
- Other treatment modalities
  - **Liver transplantation**.. the only other potentially curative option.
  - **Locoregional ablation therapies:**
    - Thermal ablation approaches (radiofrequency ablation, microwave ablation, cryoablation)
    - Arterial-based therapies..
      Transarterial chemoembolization (TACE) Transarterial radioembolization (TARE)
  - Radiation therapy and stereotactic radiation therapy
  - Systemic chemotherapy, with cytotoxic agents and molecularly targeted therapies
  - Immunotherapy

Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment algorithm



Fibrolamellar Carcinoma

- Distinctive HCC subtype that differs clinically, histologically, and molecularly from other HCC subtypes
- **FLC differs from HCC in several ways**:
  - affects younger individuals 5 to 35 years of age
  - does not have a male predominance
  - There are no identified risk factors for FLC or cirrhosis
  - Serum AFP levels are normal in 90 percent of cases
  - Better prognosis
- If uncertainty persists following imaging percutaneous biopsy may be necessary

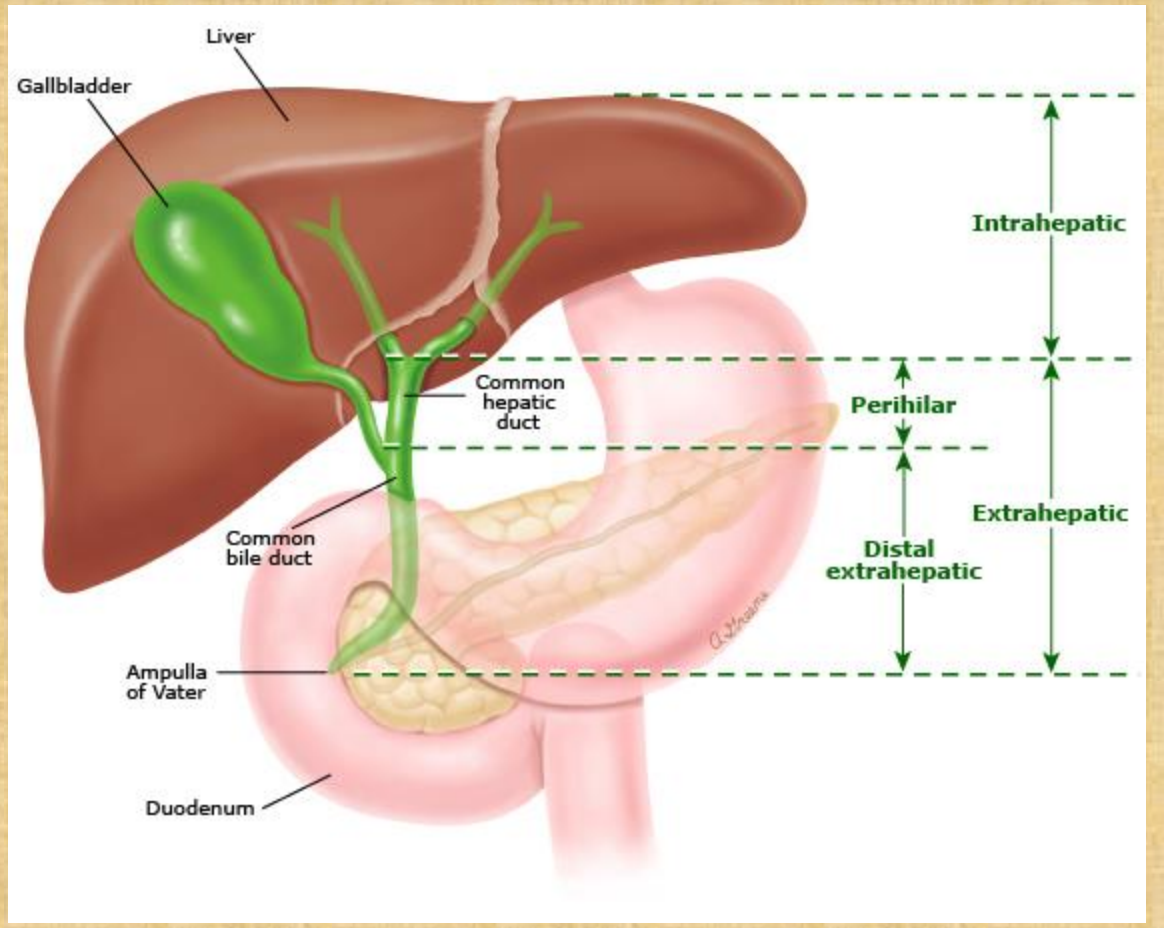
(A) which patients are at high risk for the development of HCC and should be offered surveillance?

(B) what investigations are required to make a definite diagnosis?

(C) which treatment modality is most appropriate in a given clinical context?

Intrahepatic Cholangiocarcinoma

- The term cholangiocarcinoma refers to cancer arising anywhere in the biliary tree (intrahepatic CC) and (extrahepatic CC), excluding the gallbladder & ampulla of Vater.
- The majority are adenocarcinomas
- Intrahepatic CCs account for fewer than 20%
- A distinction is made between intrahepatic and extrahepatic CC not only because of differences in anatomic location, but also because they have distinct risk factors, clinical presentation, therapy, and epidemiology



Risk Factors

- The incidence increases with age, between 50 and 70.
- Specific risk factor cannot be identified for the majority.
  - **Primary sclerosing cholangitis**
    - Inflammatory disorder leads to fibrosis and stricturing of the intrahepatic and/or extrahepatic bile ducts.
    - Strongly associated with inflammatory bowel disease, ulcerative colitis
    - Develop at a significantly younger age (between the ages of 30 and 50)
  - **Choledochal cysts** (fibropolycystic liver disease)
  - **Hepatobiliary flukes.**
  - **Chronic intrahepatic stone disease**
  - Chronic liver disease (cirrhosis and viral infection)
  - Genetic disorders; lynch syndrome (hereditary nonpolyposis colorectal cancer) and multiple biliary papillomatosis

Clinical Manifestations And Diagnosis

- less likely to be jaundiced. Instead, they usually have a history of dull right upper quadrant pain, weight loss, and an elevated alkaline phosphatase.
- Some patients are asymptomatic, with the lesions detected incidentally

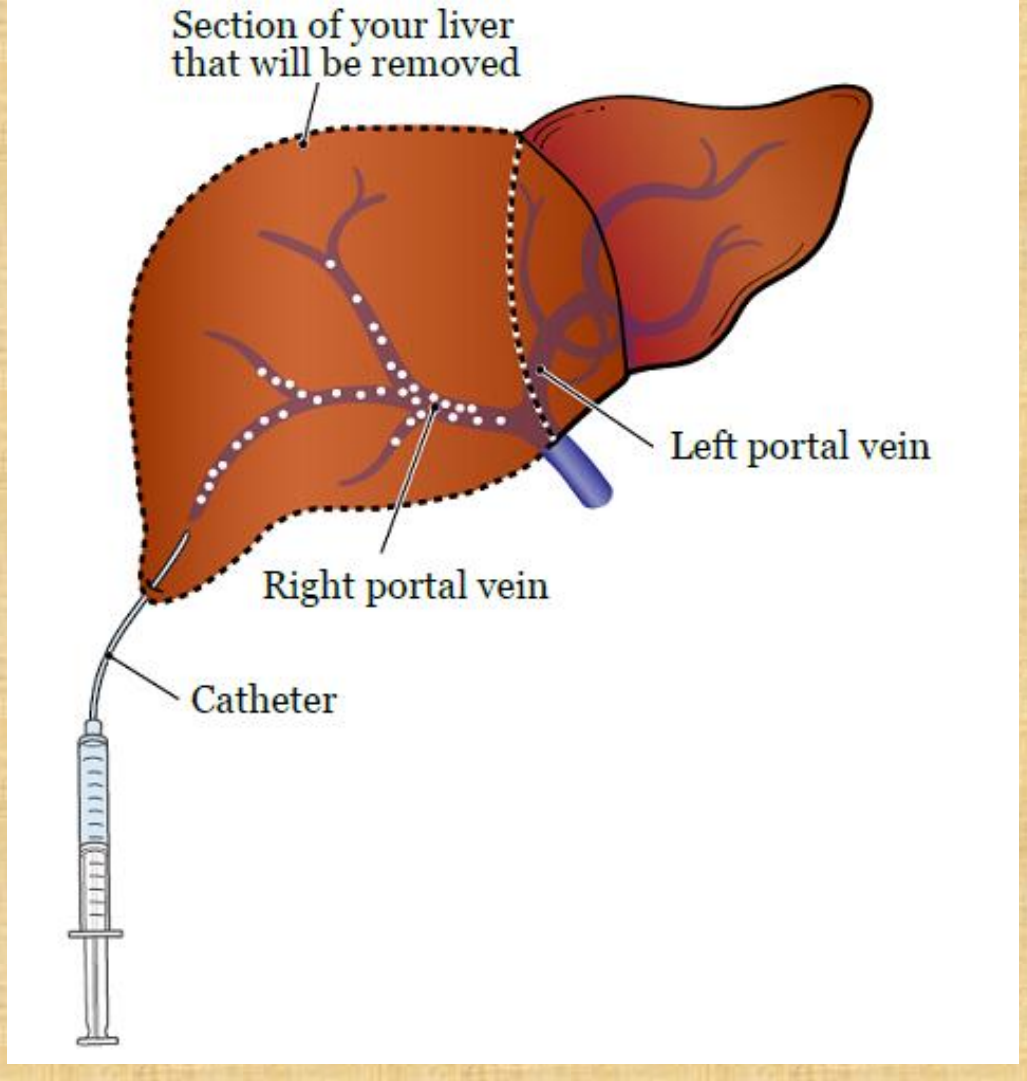
- Tumor markers (carbohydrate antigen 19-9 [**CA 19-9**], carcinoembryonic antigen [CEA], and alpha-fetoprotein [AFP]).
- Cross-sectional imaging (MDCT scan or MRI)
- Even after extensive diagnostic workup, surgical exploration may be required.

Treatment

- Surgery provides the only possibility for cure, only a minority!

- **Preoperative portal vein embolization**

  - To induce lobar hypertrophy in patients who are predicted to have an inadequate future liver remnant
  - May permit a margin-negative resection



Mesenchymal And Endothelial Liver Tumors

HEPATOBLASTOMA

- Most common primary hepatic malignancy in early childhood
- The majority occur in the first two years of life, rarely older than five
- The incidence in boys is twice that in girls
- commonly occur as a single mass, more often in the right lobe of the liver
- Because of rapid growth, death can occur from rupture and hemorrhage
- Serum alpha-fetoprotein (AFP) levels are markedly elevated
- Chemotherapy followed by Surgical resection
- Liver Transplantation if resection is not applicable

EPITHELIOID HEMANGIOENDOTHELIOMA

- Low-grade malignant vascular neoplasm that affects middle-aged women patients.
- may result in Budd-Chiari syndrome
- **Despite being a low-grade tumor, high rate of regional and distant metastases**

ANGIOSARCOMA

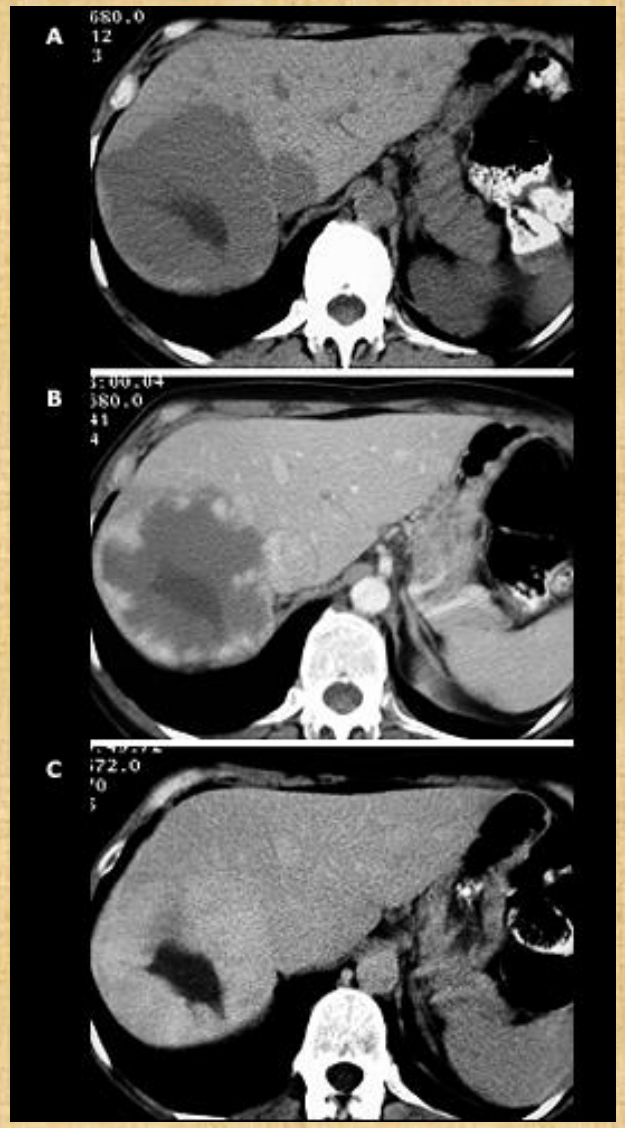
- high-grade malignant vascular neoplasm
- it is the most common sarcoma arising in the liver
- It occurs in older patients (>60 years old) and is more common in men
- Patients typically present with abdominal pain, fatigue, jaundice, ascites, and weight loss.
- Budd-Chiari syndrome is rare
- Hepatomegaly with or without splenomegaly and thrombocytopenia are common findings.
- Liver failure and intraabdominal bleeding due to liver rupture are common causes of death.

Benign Liver Tumors

Hepatic Hemangioma (Cavernous Hemangioma)

- The most common benign liver tumor
  - Prevalence on imaging/ autopsy series: ~5%-20%

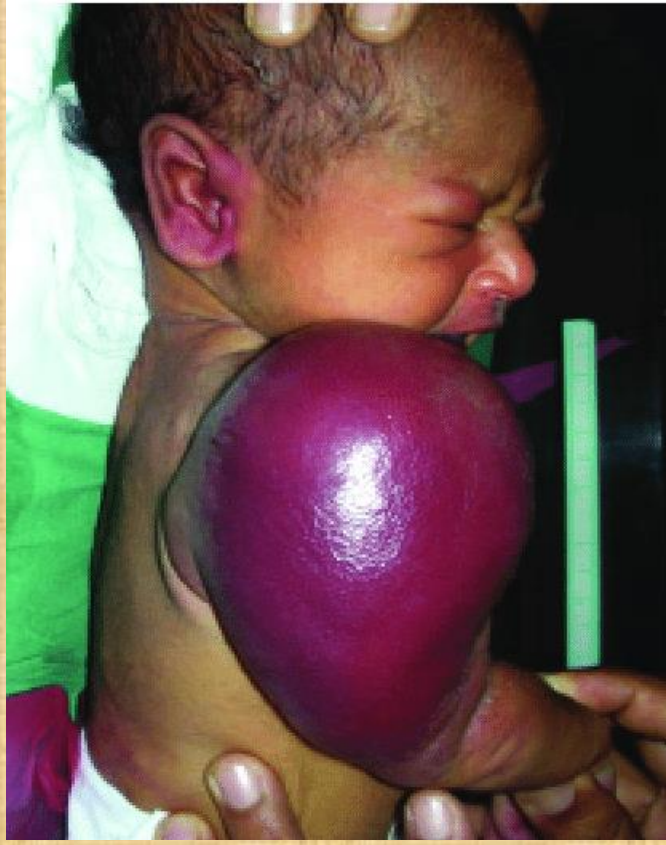
    Most common in women aged 30–50 years
- Thought to be vascular malformations or hamartomas of congenital origin that enlarge by ectasia rather than by hyperplasia/ hypertrophy
- Rarely of clinical significance
- Often solitary but multiple lesions may be present
- ≥10 cm are referred to as giant hemangiomas

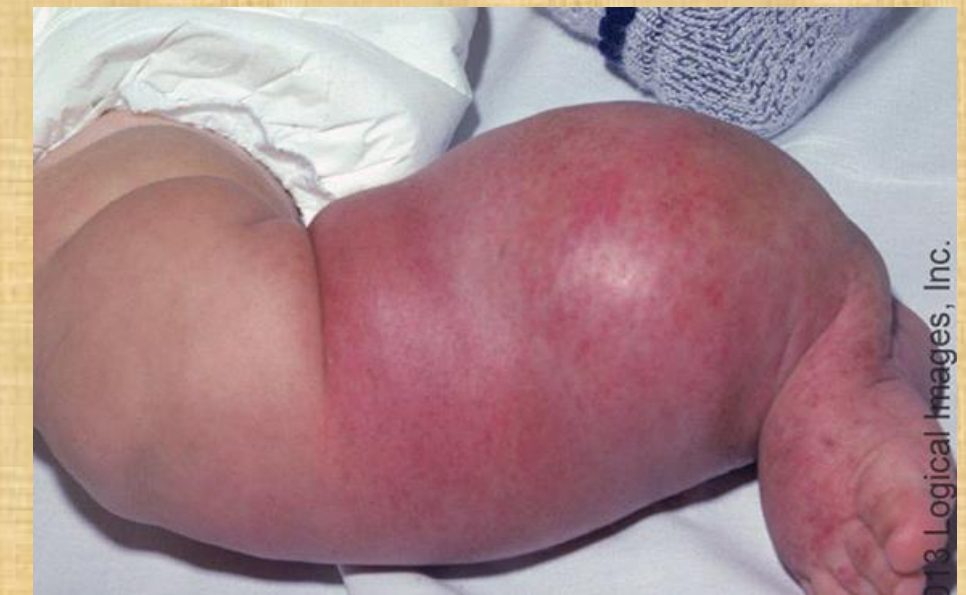


- Most patients are asymptomatic and have an excellent prognosis
- Rarely, acute abdominal pain can result from lesion thrombosis or bleeding
- Other rare presentation; Hemobilia following hemangioma rupture into the biliary tree
- Symptoms are generally associated with larger hemangiomas (ie, >10 cm)
- A bruit is rarely heard over the hemangioma
- Due to its benign course, imaging follow-up is not required for typical haemangioma
- Pregnancy and OCPs are not contraindicated
- Surgical resection maybe appropriate in growing lesions or lesions that are symptomatic by compression

Kasabach-Merritt Phenomenon

- (KMP) is a life-threatening complication occurring mainly in kaposiform hemangioendothelioma
- Characterized by profound thrombocytopenia and consumption coagulopathy. leading to intralesional bleeding and tumor enlargement.
- However, it is now clear that KMP is not a complication of infantile or congenital hemangiomas





Focal Nodular Hyperplasia (FNH)

- The second most commonly encountered benign liver lesion
- Composed of a proliferation of hyperplastic hepatocytes surrounding a central stellate scar
  - Up to 90% of patients are female

- Clinical characteristics
  - Most are solitary and <5 cm; multiple FNH in 20–30% of cases
  - Most patients are asymptomatic and complications are extremely rare
  - Kupffer cells are typically present, a feature that distinguishes FNH from hepatocellular adenoma.
  - Symptoms such as abdominal pain are uncommon, but some patients with persistent pain attributed to FNH may require procedural intervention

Management of FNH

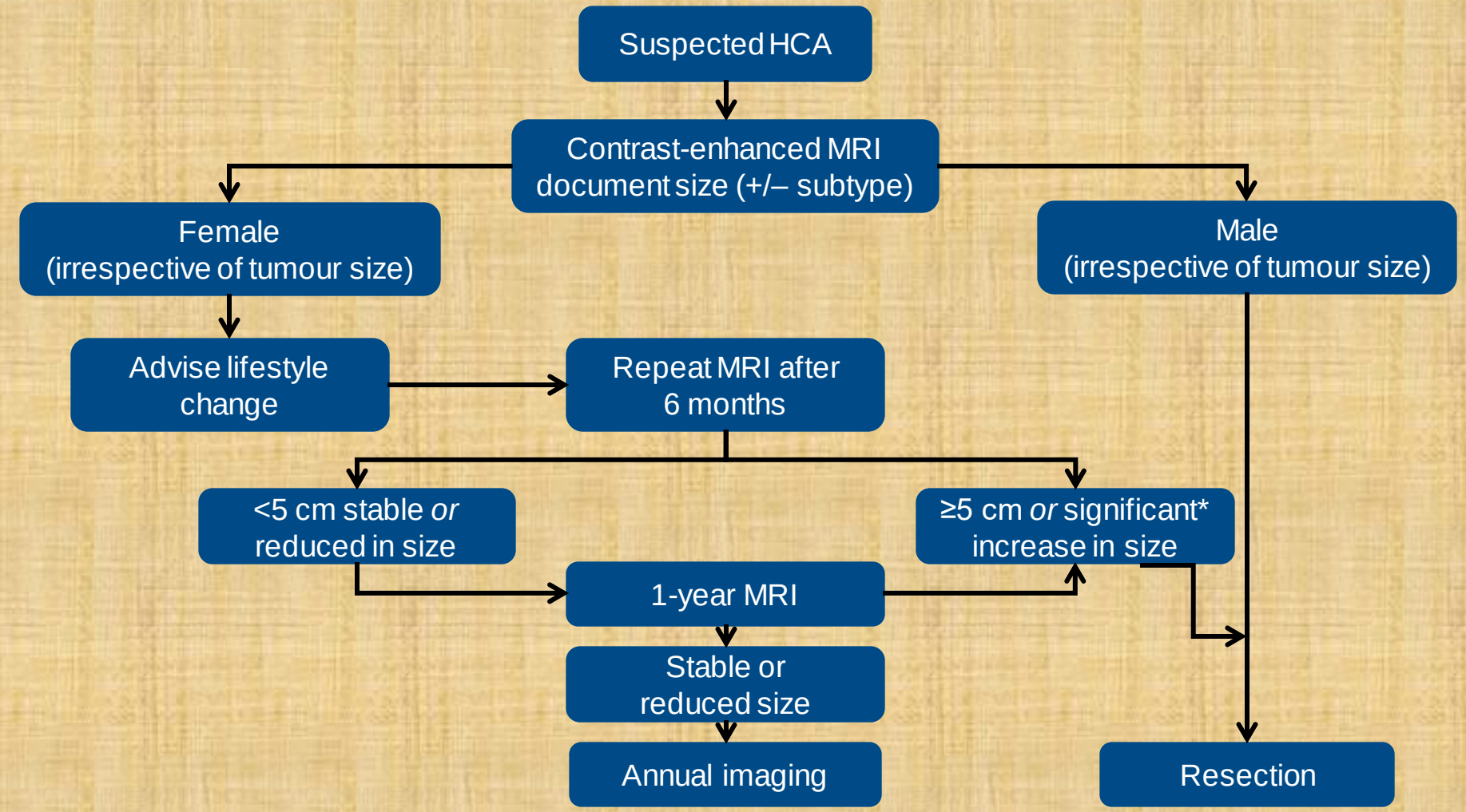
- No routine surveillance imaging for asymptomatic patients with FNH because of the low risk of lesion growth or complications.
- No indication for discontinuing OCPs
- Follow-up during pregnancy is not necessary
- For symptomatic lesions, Surgical resection may be performed, although less invasive approaches (transarterial embolization, radiofrequency ablation) have also been used

Hepatic Adenoma

- Epidemiology
  - ~10x less common than FNH
  - Most common in women (10:1 female to male), especially aged 35–40 years
- Potential role of sex hormones
  - 30–40-fold increase in incidence with long-term OCP use
  - Incidence among males is associated with androgenic steroids
- Patients with glycogen storage disease or metabolic syndrome are at higher risk for developing HCA
- The spectrum of clinical presentation ranges from asymptomatic individuals with incidental finding to patients with acute, life-threatening hemorrhage resulting from lesion hemorrhage, rupture, and intraabdominal bleeding.
- **Significant risk of malignant transformation, risk factors include male sex, lesion size >5 cm, and beta-catenin activation subtype**

HCAs need to be followed more closely than other benign tumours

Management of HCA



Multiple Hepatocellular Adenomas

- The presence of more than ten HCAs is referred to as multiple HCAs (liver adenomatosis)
- Risk of bleeding and malignant transformation:
  - Does not differ in patients with multiple HCAs versus a single HCA
  - Driven by the size of the largest nodule
- Hepatic resection may be considered in unilobular disease
- For widespread HCA, resection of the largest adenomas may be an option

Characteristics Of Common Benign Liver Lesions

	Haemangioma	FNH	HCA
Estimated prevalence	Common ~5%*	Less common 0.03%	Rare ≤0.004%
Age	30–50 years	20–40 years	All ages
Gender	F > M	F >> M	F >>> M
CT	Centripetal enhancement	Central scar	Varied
Relation with OCP	No	slightly	Yes
Rupture/ risk of bleeding	Rare	No	Yes
Malignant transformation	**No**	**No**	**Yes**

Basic Management Of A 'Liver Nodule'

Examination and baseline investigations

- Associated symptoms:
  - Abdominal pain
  - Weight loss
  - Hepatomegaly
  - Abnormal liver function tests
- Medical history
  - Conditions associated with liver lesions (e.g. cancer, anorexia)
  - History of foreign travel or dysentery
  - Medication history, particularly OCPs
- Exclude primary tumour distant to liver
- Risk factors
  - History of/current viral hepatitis/cirrhosis
  - History of transfusion, tattoos, IV drug abuse
  - Family history of liver disease/tumours
  - Alcohol excess, smoking
  - Features of metabolic syndrome (obesity, T2DM, HTN, CV disease)
  - Drug history (methotrexate, tamoxifen, androgens)

Following examination and baseline investigations

Contrast-enhanced imaging (CEUS, CT, MRI) for tumour characterization

- Imaging and baseline investigations should be sufficient to diagnose benign liver tumours
- In cases of significant doubt, a biopsy or resection may be appropriate

THANK YOU