

HEPATIC TUMORS AND CYSTS.

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Contents of discussion.

- Brief Case report.
- Classification of liver tumors.
- Brief discussion of common tumors.
- Hepatocellular Carcinoma.

Case Report.

Presenting complaints.

Right upper Abdominal pain- 3-4 months.

HOPI.

- A 57 yr old white male with h/o hepatitis C diagnosed 10 yrs ago complains of vague upper abdominal pain for last 3-4 months.
- Pain is dull, aching in nature and mostly constant. (4/10).
- It is not relieved or aggravated by food, posture and is non- radiating.

Review of systems.

- Nausea +, denies vomiting.
- Decreased appetite.
- Review of other systems – ive.

PMH.

1. Hepatitis C (Genotype 1) non responder to interferon and ribavirin.
- 2 Obesity. (BMI 43)
- 3 HTN.

PSH. s/p cholecystectomy 12 yrs ago.

Medications. Norvasc/lipitor. (not taking them.)

Allergies. NKDA.

Personal H/O IV drugs in past, and ex drinker. Quit 2 yrs ago.

Examination.

- P 88 BP 160/90 Temp 98.4 RR 16
- CNS. Alert oriented x 3, 5/5 all limbs
- CVS. S1+ S2 RRR no rub or murmur.
- Respiratory. A.E equal, normal vesicular bilateral.

- **Abdomen** , mild tenderness right upper quadrant + No rebound or guarding noted. Hepatomegaly. Shifting dullness and fluid thrill –ve. BS +ive.
- **Extremities.** Bilateral trace edema.

Labs.

- WBC 8, HB 9, **PLT 80,000**
- Na 133, K 4.6, BUN/Crt 35/1.0
- INR 1.1 PT 14.9 PTT 36 sec.
- **ALT(SGPT) 99 U/L**
- **AST(SGOT) 108 U/L**
- **ALKALINE PHOSPHATASE 177 H U/L (50 to 136)**
- TOT. BILIRUBIN 0.6 mg/dL (.3 to 1.5)
- LDH 747 H U/L (300 to 650)
- ALBUMIN 2.7 g/dL (3.0 to 4.8)

Ultrasound.

- The liver is enlarged measuring 18 cm in its maximum length.
- A 4.3 x 3.5 cm echogenic mass is located in the right hepatic lobe near the dome.
- Portal venous flow is normal.
- Common hepatic duct is upper limits of normal measuring 6 mm in maximum diameter.

CT scan.

- Hypervascular mass measuring 4.2 cm is seen in the right lobe of the liver highly suspicious for HCC.
- Splenomegaly.
- Recannulization of the umbilical vein as well as some small epigastric varices consistent with portal hypertension.

AFP.

652 ng/ml (0.0 to 15.0)

What to do next?

- 1 Liver Biopsy.
- 2 Make him DNR.
- 3 Supportive care.
- 4 None of the above.

Further workup for metastatic disease was negative.

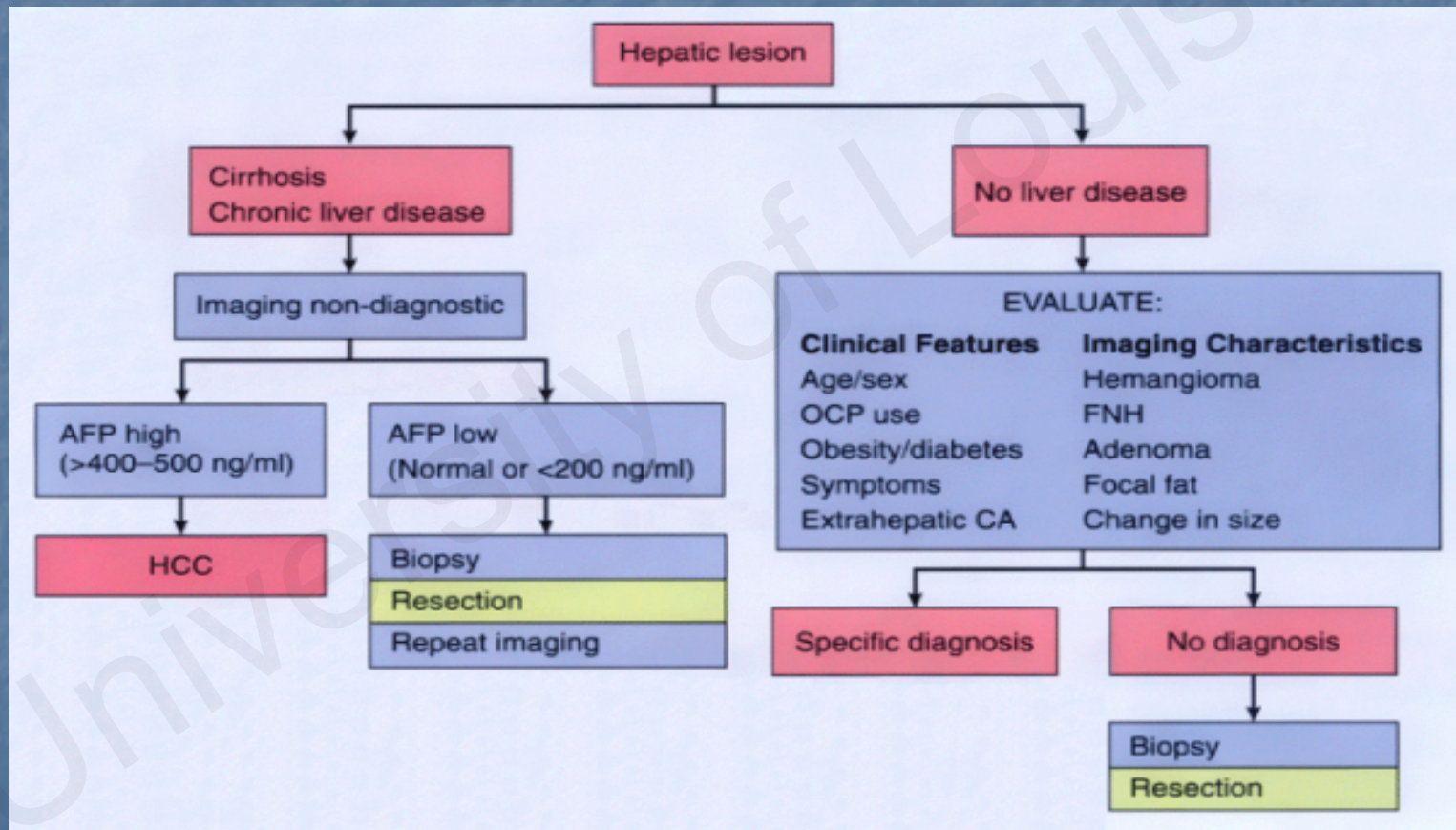
Patient had CT guided liver biopsy which showed HCC.

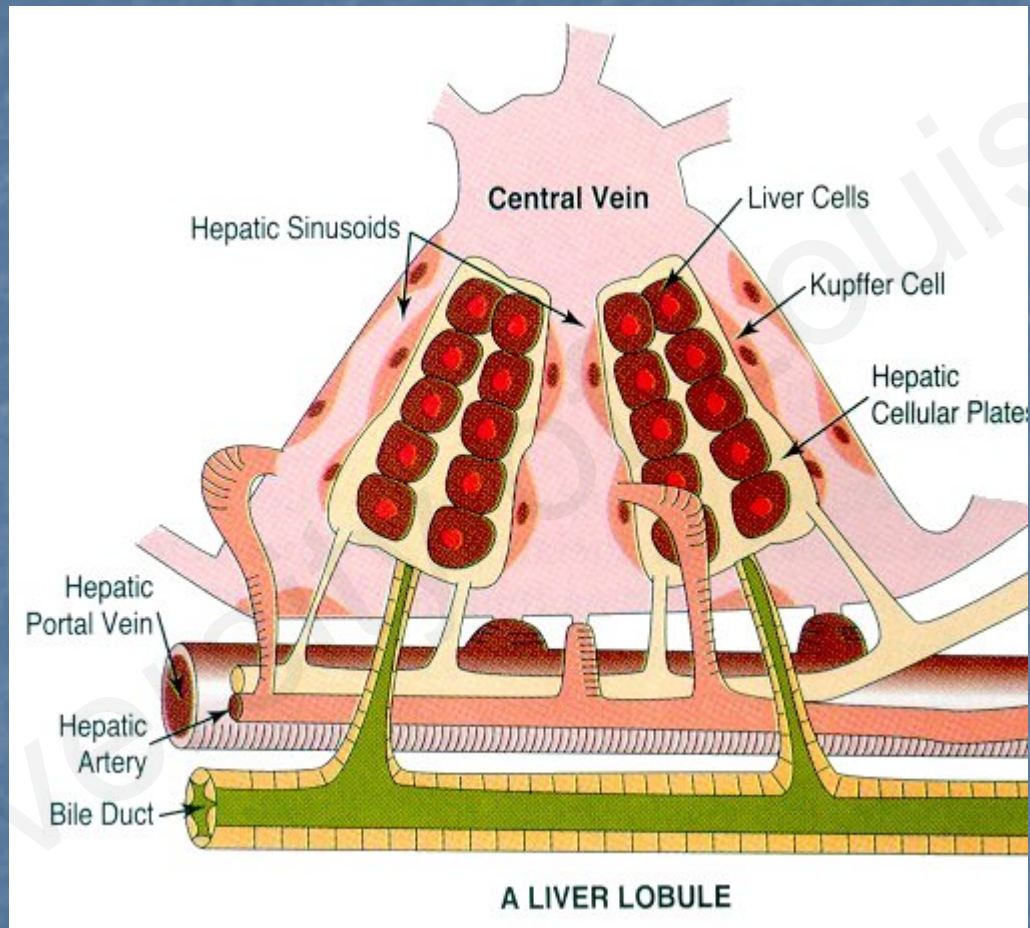
What will be the treatment?

- Resection.
- Transplantation.
- TACE.
- Chemotherapy.

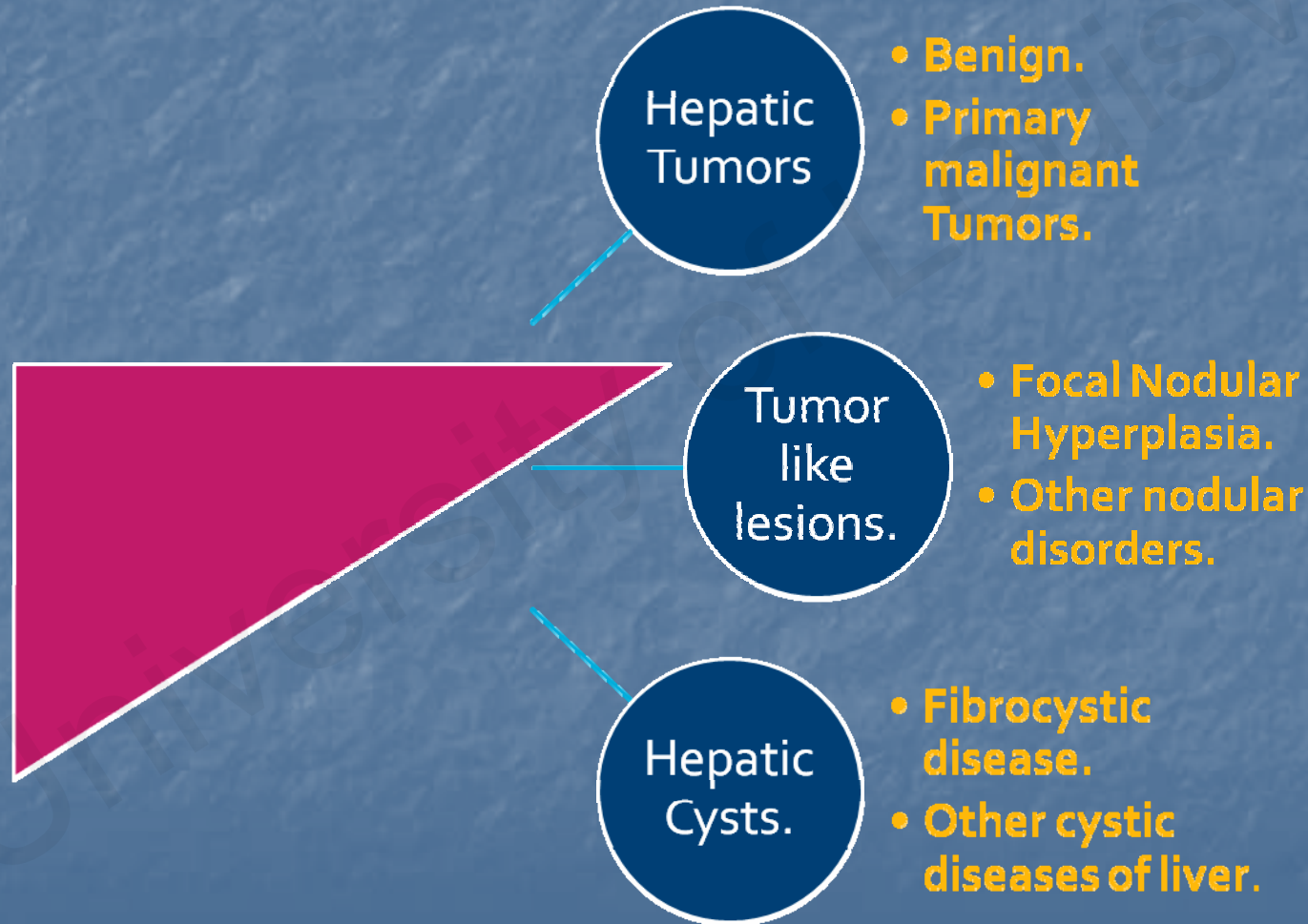
- Because of patient BMI patient was **not considered for surgical intervention.**
- Patient underwent **TACE** without any improvement.
- Patient now being considered for chemotherapy. (Sorafenib)

APPROACH TO SPACE-OCCUPYING LESIONS OF THE LIVER





Classification of Hepatic tumors and cysts.



Benign Liver Tumors.



Hepatocellular
Adenoma

Cavernous
Hemangioma

Hepatocellular Adenoma.

- Seen more commonly in females.
- Has strong association with prolonged use of oral contraceptives.
- Duration of exposure to contraceptive use increases the risk of adenoma formation.
- 5-7 yr exposure increases the risk to 5 times normal and it goes up to 25 times with 9 yrs of exposure.

- Estrogens as well as progestogens play role in adenoma growth.
- Growth of adenomas appears to be hormone dependent (increase in size during pregnancy and regression after cessation of oral contraceptive use).

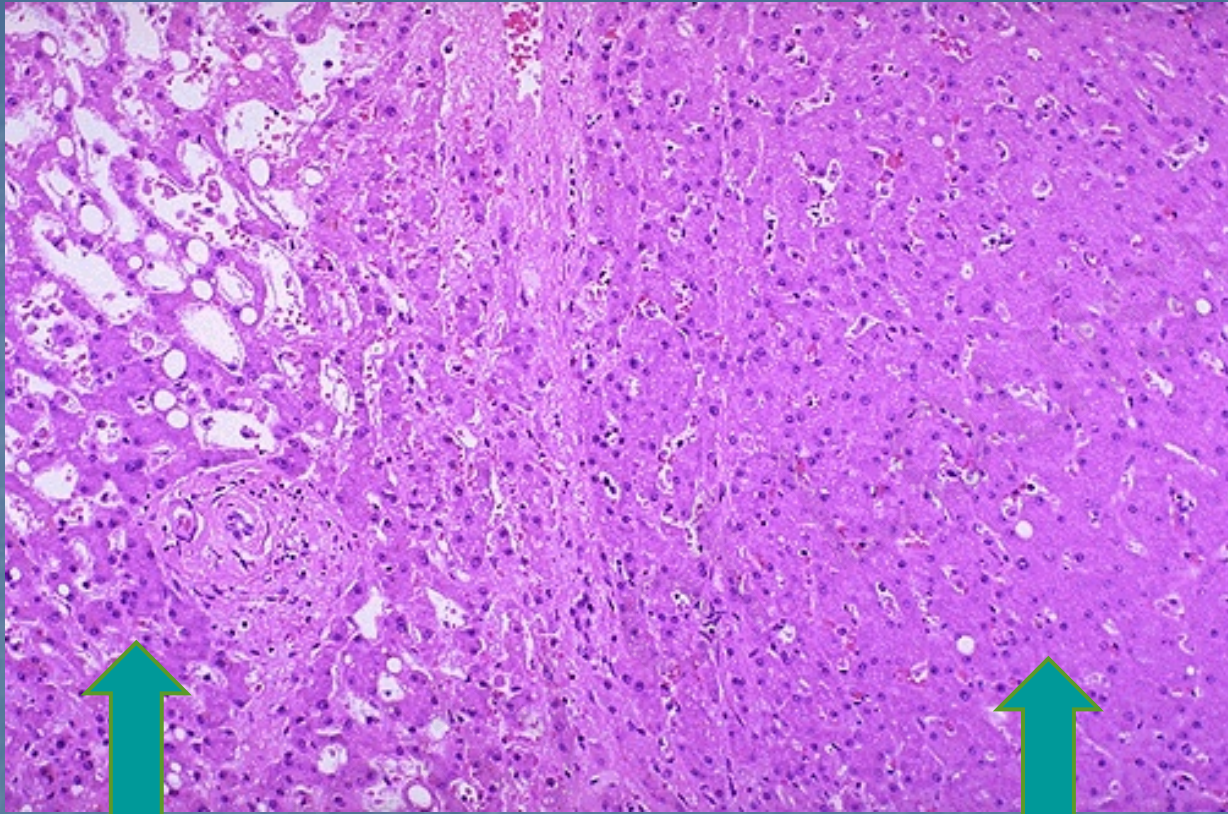
Clinical Features.

- Asymptomatic.
- Pain in the right hypochondrium or epigastrium (bleeding or infarction of adenoma).
- Acute hemoperitoneum.

Diagnosis of Hepatic Adenoma

- 1- **Ultrasonography**
- 2- **CT scan.**
- 3- **Hepatic angiography** . Approximately 50% of hepatocellular adenomas are **avascular**,. The tumor has a clearly defined margin and, often, nearly parallel vessels entering it from the periphery ("**spoke-wheel appearance**")

- 4 - **MRI** may be a useful alternative to hepatic angiography .
- 5 - **Needle biopsy and fine-needle aspiration** are of limited value as adenomas mimic normal liver tissue.



Normal Liver tissue.

Hepatic Adenoma.

The hepatic adenoma is on the right and is composed of cells that closely resemble normal hepatocytes

Treatment.

- Surgical treatment (resection) is recommended because of risk of rupture.
- Avoid taking oral contraceptive
- Pregnancy should be avoided.
- There is a risk of malignant transformation.

Cavernous Hemangioma

- The **most common benign tumor** of the liver and is found in as many as **7%** of autopsies.
- Seen in **all ages**. (30-50 yrs)
- Increase in size with pregnancy or the administration of estrogens

Clinical Features.

- Asymptomatic .
- Larger or multiple lesions produce symptoms like upper abdominal pain , early satiety, nausea, and vomiting.
- If more than 4 cm in diameter are called Giant cavernous hemangiomas.

Diagnosis.

Imaging Studies:

- Ultrasound.
- Computed tomography. (Dynamic contrast-enhanced CT scanning is preferred to routine CT scanning)
- Magnetic resonance imaging
- Nuclear medicine studies.
- Arteriography

Contrast enhanced CT – 4 phases.

1. **Pre contrast.**

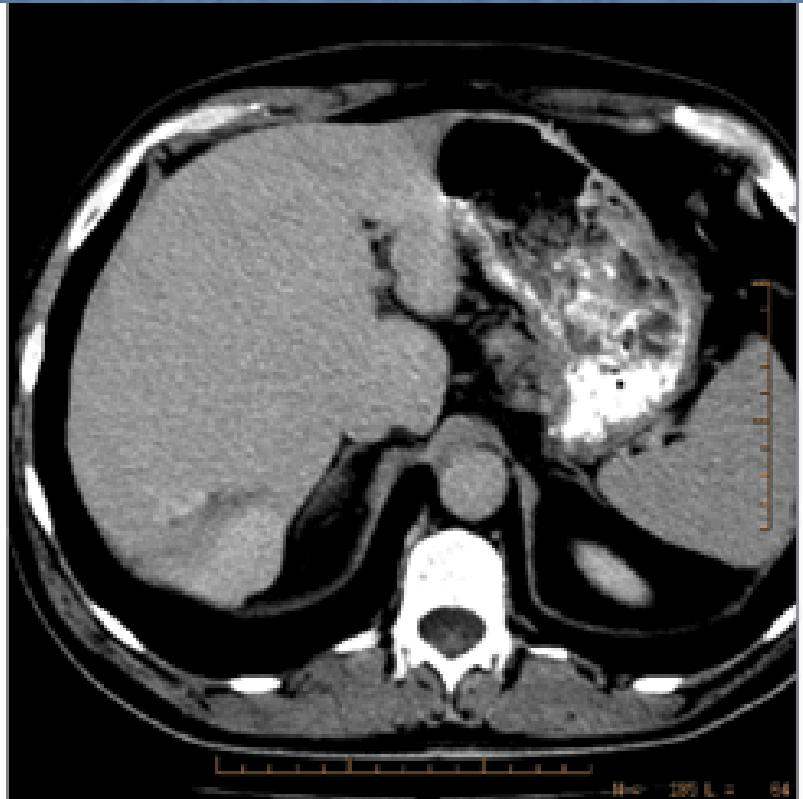
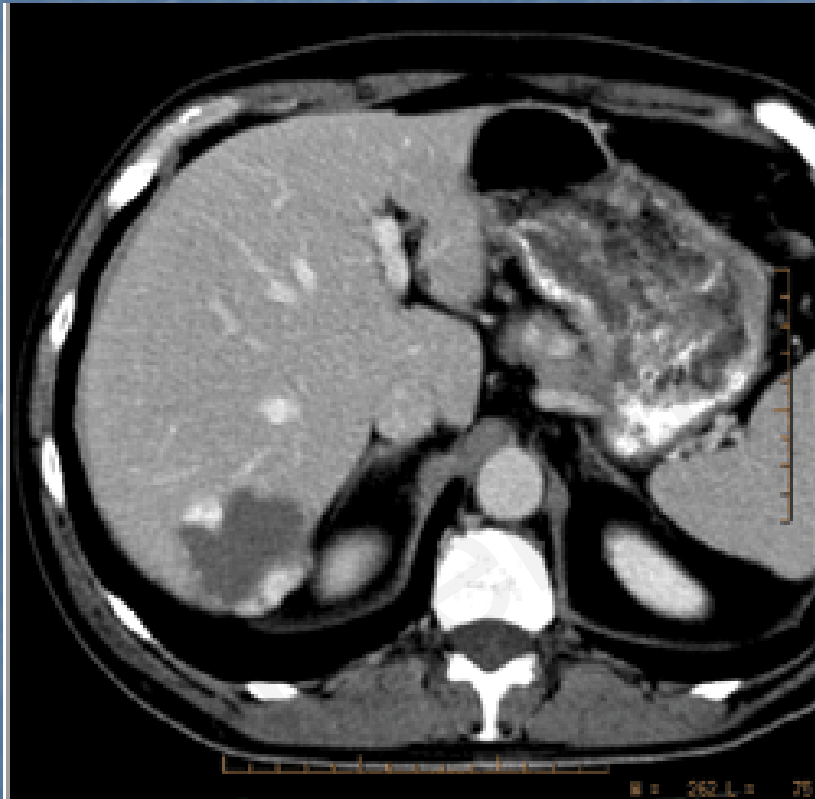
Hemangioma appear hypodense in this phase.

2. **Arterial phase.** (30 seconds after contrast given. Contrast is entering liver via hepatic artery). Enhancement of the peripheral portions of the lesion. (**ring enhancement**) The center of the lesion remains hypodense.

3. **Portal phase.** (60 seconds later. Contrast returning to liver by mesenteric and portal veins.) Contrast enhancement progresses centripetally.

4. **Delayed images** . (several minutes later) The center of lesion appear hyperdense.

Dynamic CT. (a) The **hypodense lesion on the right liver lobe** shows peripheral enhancement at the early phase of this study with (b) subsequent hyperdensity (retention) in the late phase



MRI.

- Has a sensitivity and specificity of greater than 90% and is the **imaging modality of choice**.
- T1 - **weighted images**- Hypointense.
- T2 - **weighted images**- Hyperintense.
(**Light bulb sign**)

Ultrasound

Well-defined **hyperechoic masses** (though few can appear relatively hypoechoic when imaged within a fatty liver).

Accuracy of Imaging Studies

Imaging Tools	Sensitivity (%)
□ US	46
■ Combined B-mode and color Doppler US	69
■ Contrast-enhanced CT scan	66
■ T2-weighted MRI	96
■ Gadolinium-enhanced MRI combined with dynamic CT scan	100

Radiological follow-up for Hemangioma.?

- It remains **uncertain** if follow-up radiologic studies are warranted to reassess the size of the hemangioma.
- Some recommend to have US at **6 months and at 12 months after the initial diagnosis**. If there is no change in hemangioma size long-term follow-up radiologic studies are probably not necessary.

Treatment of Hemangiomas.

- No treatment if no symptoms.
- The management of a large (ie, >10 cm) hepatic hemangioma is controversial.
- Large symptomatic hemangiomas should undergo treatment .

TUMOR-LIKE HEPATIC LESIONS

- Focal Nodular Hyperplasia .
- Nodular regenerative hyperplasia .

FOCAL NODULAR HYPERPLASIA

- More common in **women** than in men.
- Seen in **all ages** (30-40 yrs)
- The **cause** of focal nodular hyperplasia is unknown. ? role for oral contraceptive .

Clinical Features.

- Asymptomatic
- Pain (bleeding into or necrosis of the lesion)

Diagnosis.

- Ultrasonography and CT is not specific for FNH.
- Doppler ultrasonography with intra-arterial infusion of CO₂ microbubbles is characteristic.
- Selective hepatic arteriography. (vascular lesions).

Pathology.

- Show central scar and radiating fibrous septa that divide the lesion into lobules.
- Microscopically, focal nodular hyperplasia closely resembles inactive cirrhosis.

Treatment

- **No treatment if not symptomatic.**
- Periodic ultrasonography should be performed and a lesion seen to increase substantially in size should be resected.
- **Large symptomatic or complicated lesions** should be resected. (or enucleated).
- **Discontinuation of contraceptive steroids** may result in regression of the lesion.

HEPATIC CYSTS

1- FIBROCYSTIC DISEASES OF THE LIVER

- a. Polycystic liver disease.
- b. Caroli's disease (type V choledochal cyst)

2- Hydatid cyst.

3- solitary congenital cysts

Polycystic Liver Disease

A. Childhood variety.

- Autosomal recessive disorder.
- Rapidly fatal as a consequence of the associated (autosomal recessive) polycystic kidney disease (ARPKD).
- **PKHD1** is the responsible gene and is identified at chromosomal locus **6p21-cen**.

Adulthood variety.

- Multiple cysts of the liver are diagnosed in adulthood. They present either in association with autosomal dominant polycystic kidney disease (ADPKD) or as isolated polycystic liver disease.
- Gene affected in **ADPKD1** is located on the short arm of chromosome **16** at locus q13-q23 and expresses a protein, polycystin-1
- The gene responsible for **ADPKD2** is located on chromosome 4 and expresses polycystin-2.

Clinical features.

- **Asymptomatic.**
- Discomfort or pain, postprandial fullness, upper abdominal mass
- Liver biochemical test results generally are not abnormal, a **serum alkaline phosphatase and GGT levels** may be increased

Treatment of Polycystic Liver disease.

Usually **no treatment** required

- Fenestration (unroofing)
- Injection of sclerosing agents (alcohol or doxycycline).
- Octreotide trial.

Octreotide inhibits hepatic cystogenesis in a rodent model of polycystic liver disease by reducing cholangiocyte adenosine 3',5'-cyclic monophosphate.

In polycystic liver diseases (PCLDs), increased cholangiocyte proliferation and fluid secretion are key features cAMP is an important regulator of these processes.

(Gastroenterology. 2007 Mar;132(3):1104-16)

RESULTS.

- Octreotide lowered cAMP content in cholangiocytes and serum by 32%-39% and inhibited hepatic disease progression.
- It lead to 22%-60% reductions in liver weight, cyst volume, hepatic fibrosis, and mitotic indices. Similar effects were observed in kidneys of PCK rats.

CONCLUSIONS:

This preclinical study provides a strong rationale for assessing the potential value of octreotide in the treatment of PCLDs.

(Gastroenterology. 2007 Mar;132(3):1104-16)

Hepatocellular Carcinoma (HCC)

- The commonest primary malignant tumor of the liver.
- Seen more commonly in Men > females.
- Fifth most common cancer in men and the eighth most common in women
- The incidence increases progressively with advancing age

Clinical Features.

- Asymptomatic.

Symptom

Frequency(%)

- Abdominal pain 59-95
- Weight loss 34-71
- Weakness 22-53
- Abdominal swelling 28-43
- Nonspecific gastrointestinal symptoms 25-28
- Jaundice 25-26

Physical findings

Sign	Frequency (%)
■ Hepatomegaly	54-98
■ Hepatic bruit	6-25
■ Ascites	35-61
■ Splenomegaly	27-42
■ Jaundice	4-35
■ Wasting	25-41
■ Fever	11-54

Paraneoplastic Syndromes Associated with HCC.

- Hypoglycemia
- Polycythemia (erythrocytosis)
- Hypercalcemia
- Osteoporosis
- Hypertrophic osteoarthropathy
- Thyrotoxicosis
- Polymyositis
- Neuropathy

Hypoglycemia with Hepatic tumors

A. Type A hypoglycemia.

Mild form of hypoglycemia because of inability of diseased liver to satisfy the demands of glucose by both a large rapid growing tumor and the other tissues of the body.

Type B hypoglycemia.

- Seen less commonly.
- More severe hypoglycemia.
- Presence of pro-IGF II in serum. Big IGFII increase glucose uptake and decrease gluconeogenesis. Also suppresses growth hormone and glucagon secretion leading to hypoglycemia.

Risk Factors for Hepatocellular Carcinoma

Major Risk Factors

- Chronic hepatitis B virus infection
- Chronic hepatitis C virus infection
- Cirrhosis
- Dietary exposure to aflatoxin B₁

Minor Risk Factors

- Oral contraceptive steroids
- Cigarette smoking
- Dietary iron overload in persons of black African ancestry
- Hereditary hemochromatosis
- Wilson disease
- α_1 -Antitrypsin deficiency
- Type 1 hereditary tyrosinemia
- Type 1 and type 2 glycogen storage disease
- Hypercitrullinemia
- Ataxia-telangiectasia

Diagnosis of HCC

- Radiology (USG/CT/MRI)
- Biopsy
- AFP serology.
- The sequence of tests used to diagnose HCC depends on the size of the lesion.

TUMOR MARKERS.

Marker	Sensitivity (%)	Specificity (%)	Comments
Alpha-fetoprotein	50-90%	90	Relatively quick and easy to measure; most extensively studied
Des-ã-carboxyprothrombin	58-91	84	Quick and easy to measure. Much more expensive than a-fetoprotein
á-L-Fucosidase	75	70-90	Quick and easy to measure; relatively inexpensive

Ultrasonography

- Safe, easily available, and cost effective.
- Approximately two thirds of HCC are **hyperechoic**, whereas the remainder are partly hyperechoic and partly hypoechoic

- Computed Tomography
- Magnetic Resonance Imaging
- Hepatic Angiography

Treatment.

Treatment of hepatocellular carcinoma depends on

- the extent of the disease
- presence or absence of cirrhosis,
- degree of hepatic dysfunction.

Different Treatment Options.

- 1 Surgery. (Resection/Transplantation.)
- 2 Transarterial Embolization and Chemoembolization (TACE)
- 3 RFA (radiofrequency ablation)/ Percutaneous Ablation
- 4 Chemotherapy

EARLY STAGE DISEASE

Includes patients with

- 1 Child–Pugh A and B (preserved liver function)
- 2 Solitary HCC or up to 3 nodules 3 cm in size.
3. No evidence of metastatic disease.

Early stage disease patients can be effectively treated by:

- Resection.
- Liver transplantation.
- Percutaneous ablation.

5-year survival figures ranging from 50% to 75%.

Surgical Resection.

Selection of candidates for resection has been based on

1. **Child -Pugh classification** (inconsistent predictive value)
2. **Evidence of Portal Hypertension.**
 - A . Ascites, splenomegaly, varices, thrombocytopenia ($<100,000$)
 - B Hepatic vein catheterization. (not needed if above present.

Predictor of excellent outcome after surgery.

- Absence of portal hypertension (hepatic venous pressure gradient less than 10 mm Hg) and normal bilirubin.
- These patient may achieve a 5-year survival of more than 70%

Recurrence rate after resection.

- Tumor recurrence rate exceeds 70% at 5 years.
- The most powerful predictors of recurrence are the presence of microvascular invasion and/or additional tumor sites besides the primary lesion.

Liver Transplantation.

- Liver transplantation is an effective option for patients with HCC corresponding to the Milano criteria:
- Solitary tumor <5 cm or up to three nodules <3 cm.
- Living donor transplantation can be offered for HCC if the waiting time is long enough .

- Surgical removal of liver tumors offers the best chance for a cure.
- Surgical removal is not possible for more than 75% with primary and 90% with secondary (metastases) liver cancer

Other Options for non surgical candidates.

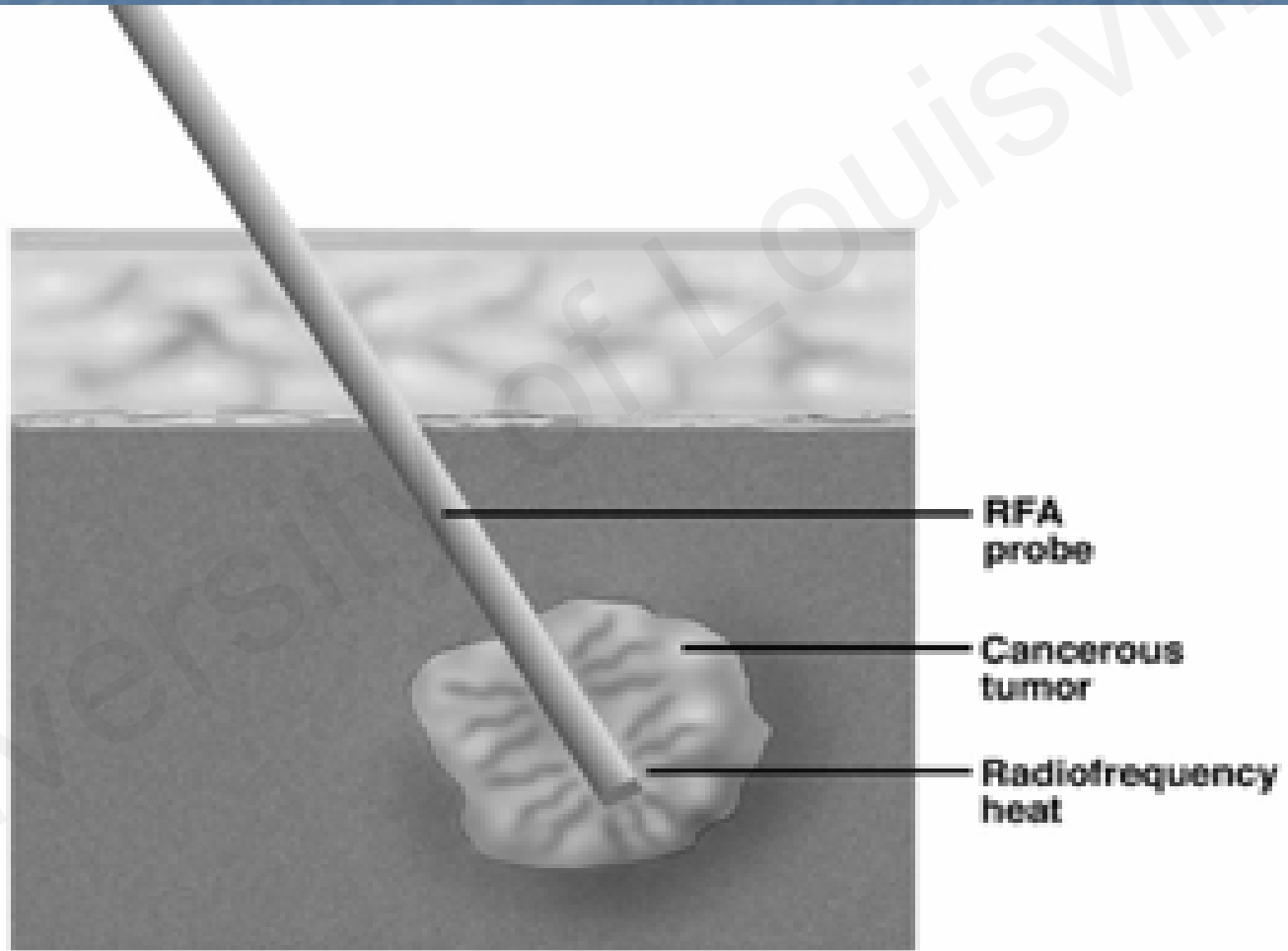
Percutaneous Ablation

- This is the best treatment option for patients with **early stage HCC** who are not suitable for resection or transplantation.
- Percutaneous ablation is usually performed under ultrasound guidance.
- **Ethanol injection** is the best known and best studied approach.

Radiofrequency Ablation (RFA) of tumors

- Using radiofrequency (RF) energy to cook and kill cancerous tissue.
- Alternative to surgical resection.

Radiofrequency ablation.



Transarterial Chemoembolization for liver cancer. (TACE)

Delivers a high dose of chemotherapy directly to the tumor while depriving the tumor of its blood supply by blocking (embolizing) the arteries feeding the tumor.

Indication.

TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread. (child Pugh A and B)

TACE.

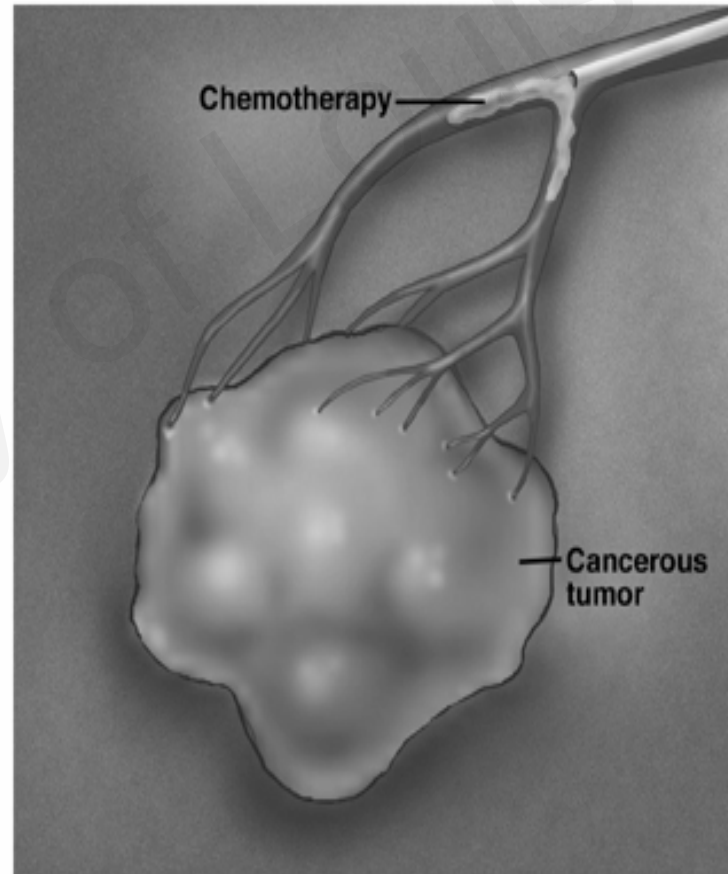
- Includes delivery of a combination of embolic agent and chemotherapeutic agent.

(Ethiodol Poppyseed Oil accumulates preferentially in HCC + Adriamycin or cisplatin)

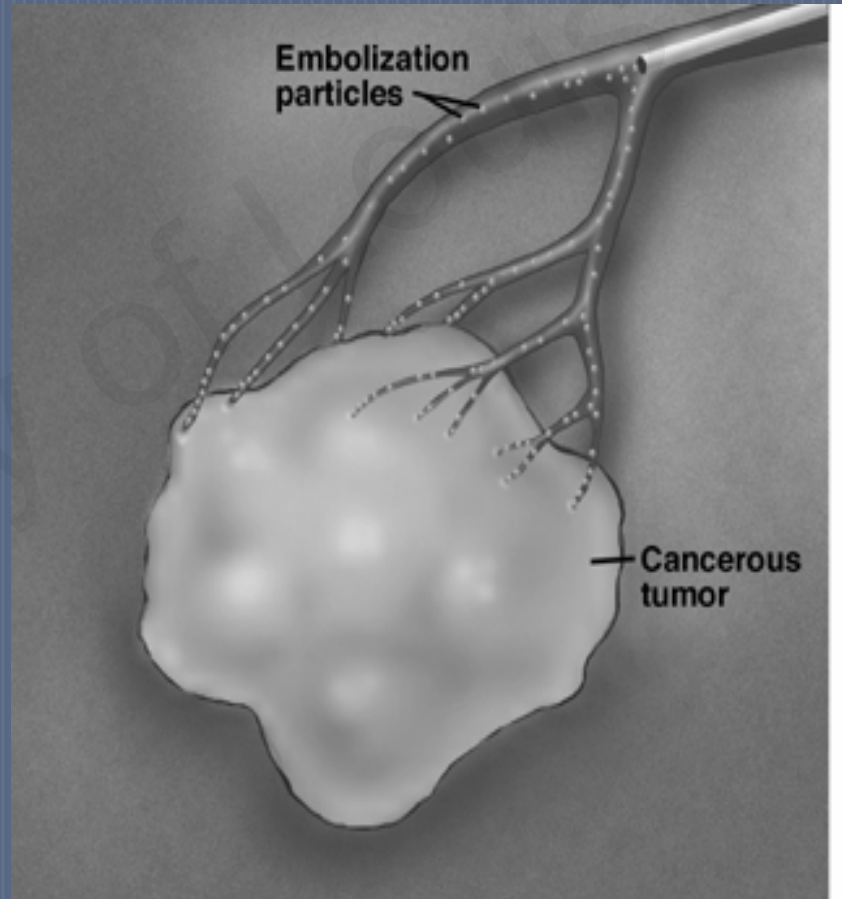
Complications of TACE.

- **Hepatic injury (30.8%)** - Abnormal liver function tests, acute hepatic failure, and hepatic infarction
- **Severe postembolization syndrome (15.1%)** right upper quadrant pain, nausea, vomiting, fevers ($> 38^{\circ}\text{C}$), leukocytosis, adynamic ileus, and elevation of liver function test
- Gallbladder infarction (14%)
- Nontarget embolization (4.6%)
- Gastrointestinal bleeding (2.8%)
- Septicemia (2.6%)
- Pulmonary embolism (1.7%)
- Splenic infarction (1.1%)

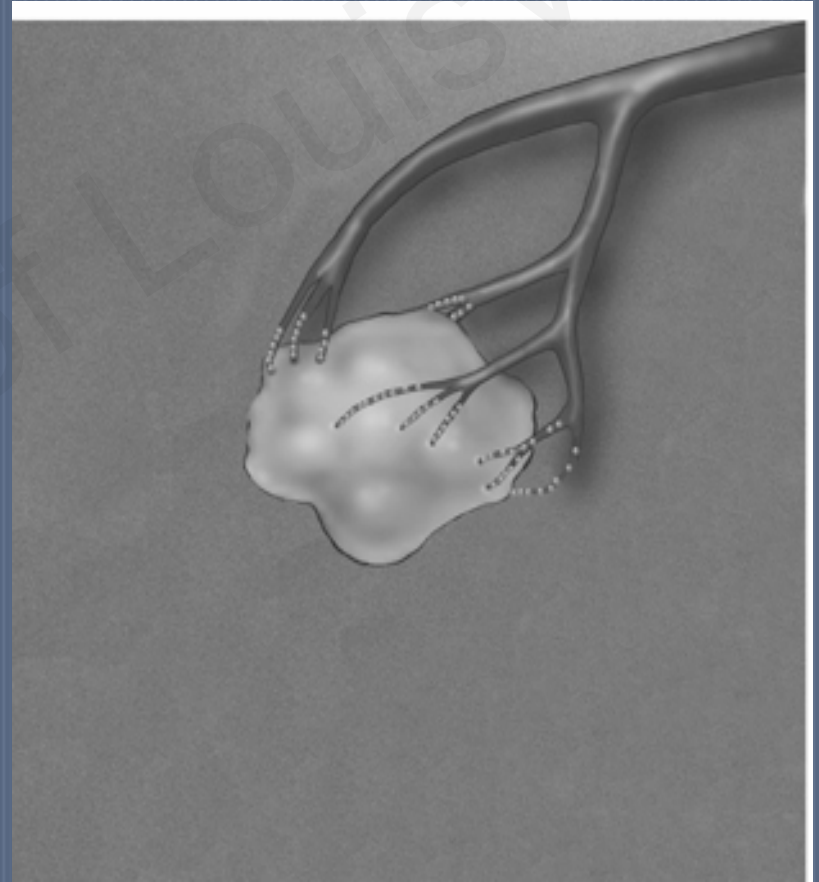
Using imaging, a catheter is fed through the femoral artery to the blood vessels feeding the tumor



- Small embolic particles are injected to block the blood vessel



- The drugs and lack of blood supply cause the tumor to shrink
- (*Information provided by the Society of Interventional Radiology, 2004*)



Chemotherapy .

- Alkylating agents, antitumor antibiotics, antimetabolites, plant alkaloids, platinum derivatives, and procarbazine.
- **Response rates** have been less than 20%.

Surveillance for HCC

(HEPATOLOGY, Vol. 42, No. 5, 2005)

Who needs surveillance ?

Hepatitis B carriers

- Asian males 40 years
- Asian females 50 years
- All cirrhotic hepatitis B carriers
- Family history of HCC
- Africans over age 20

Non-hepatitis B cirrhosis

- Hepatitis C
- Alcoholic cirrhosis
- Genetic hemochromatosis
- Primary biliary cirrhosis

Non Hepatitis B cirrhosis.

Following groups have an increased risk of HCC **no recommendations** for or against surveillance can be made because a lack of data

- Alpha1-antitrypsin deficiency.
- Non-alcoholic steatohepatitis.
- Autoimmune hepatitis.

Surveillance Tests.

- AFP

OR

- Ultrasound.

AFP (Alfa- feto protein)

- Has a role in the **diagnosis of HCC**.
- Cirrhotic patients with a mass in the liver an AFP **greater than 200 ng/mL** has a very high positive predictive value for HCC.
- Persistently elevated AFP has been clearly shown to be a **risk factor for HCC**.
- AFP can be used to help define patients at risk but appears to have **limited utility as a screening test**.

Combined use of AFP and ultrasonography increases detection rates, but also increases costs and false-positive rates.

Test.	False Positive rates.
AFP	5.0%
Ultrasound	2.9%
AFP + Ultrasound	7.5%

- Ultrasound alone cost about \$2000 per tumor found.
- where as the combination cost (AFP + ultrasound) about \$3000 per tumor found.

CT scan

Not recommended for routine screening

- Risk of radiation exposure.
- High false-positive rate.

Surveillance Interval

- Most experts use a **6-month interval**, but there are no firm data to suggest that 6 months is better than 12 months.
- The surveillance interval is determined by the **tumor growth rates** and not by the degree of risk.

Recommendations

(HEPATOLOGY, Vol. 42, No. 5, 2005)

1. Surveillance for HCC should be performed using **ultrasonography** .
2. **AFP alone should not be used** for screening unless ultrasound is not available.
3. Patients should be screened **at 6 to 12 month intervals** .
- 4 The surveillance interval does not need to be shortened for patients at higher risk of HCC.

**Mass on surveillance
Ultrasound in cirrhotic liver.**

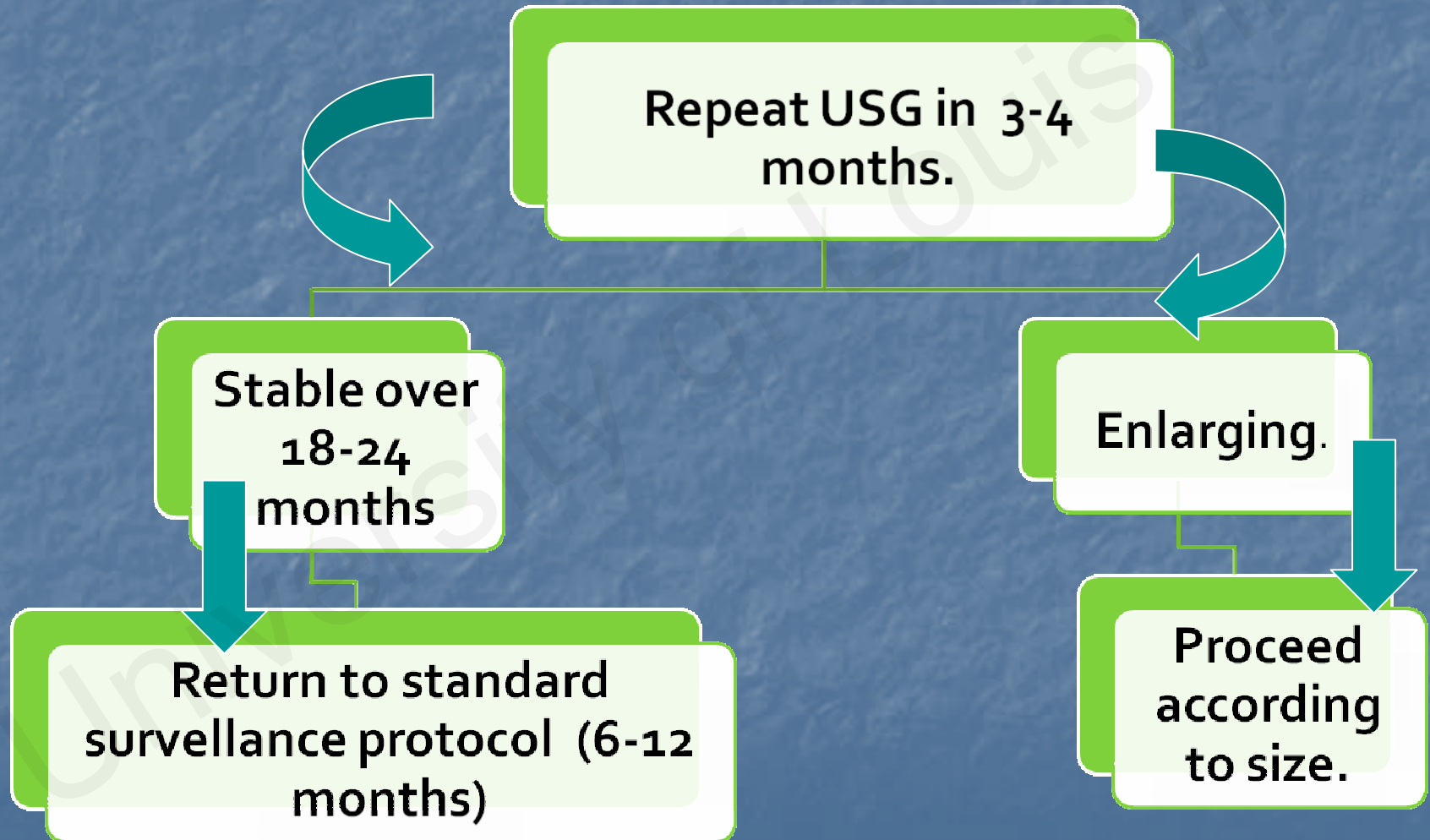
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**1-2
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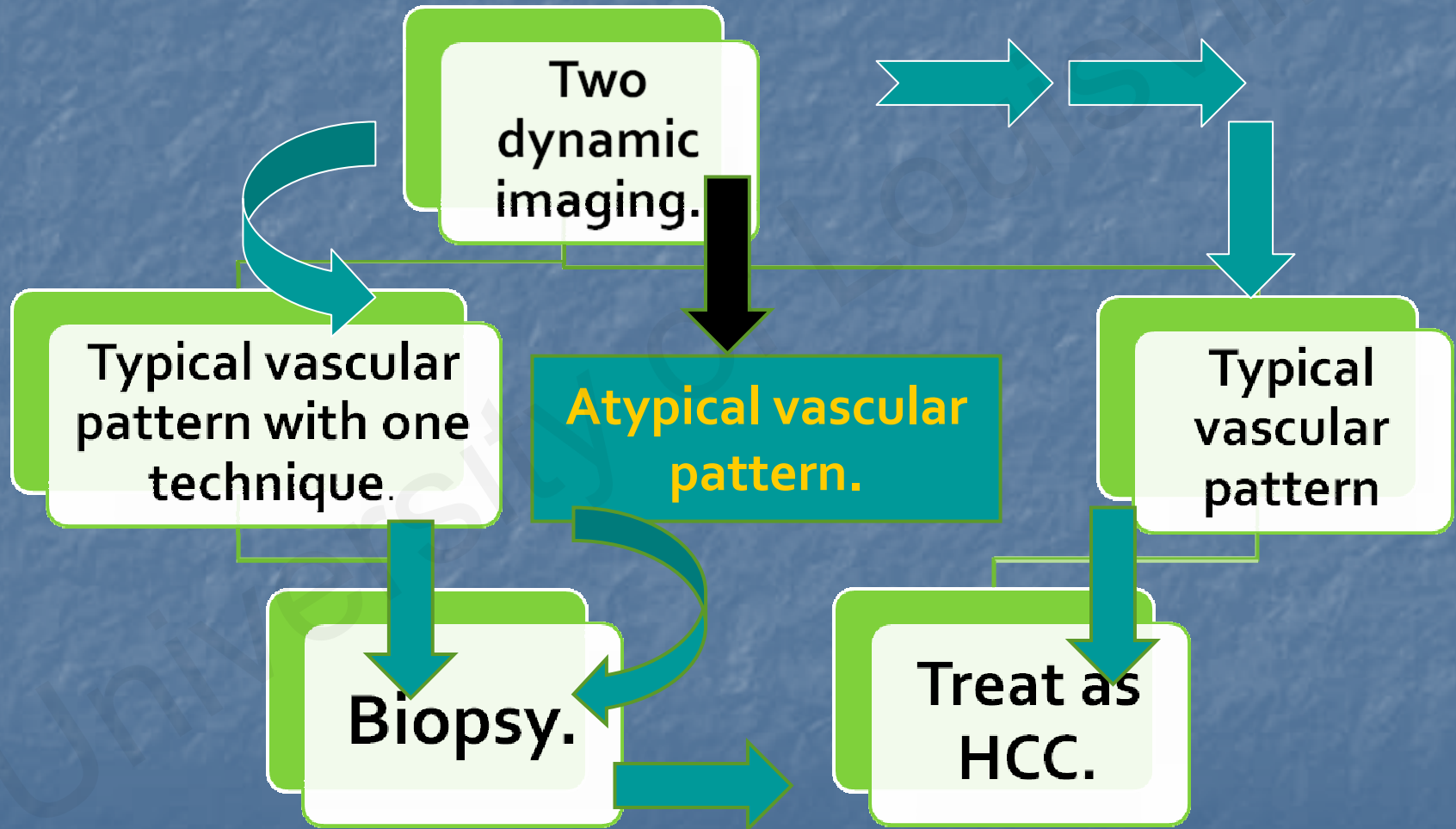
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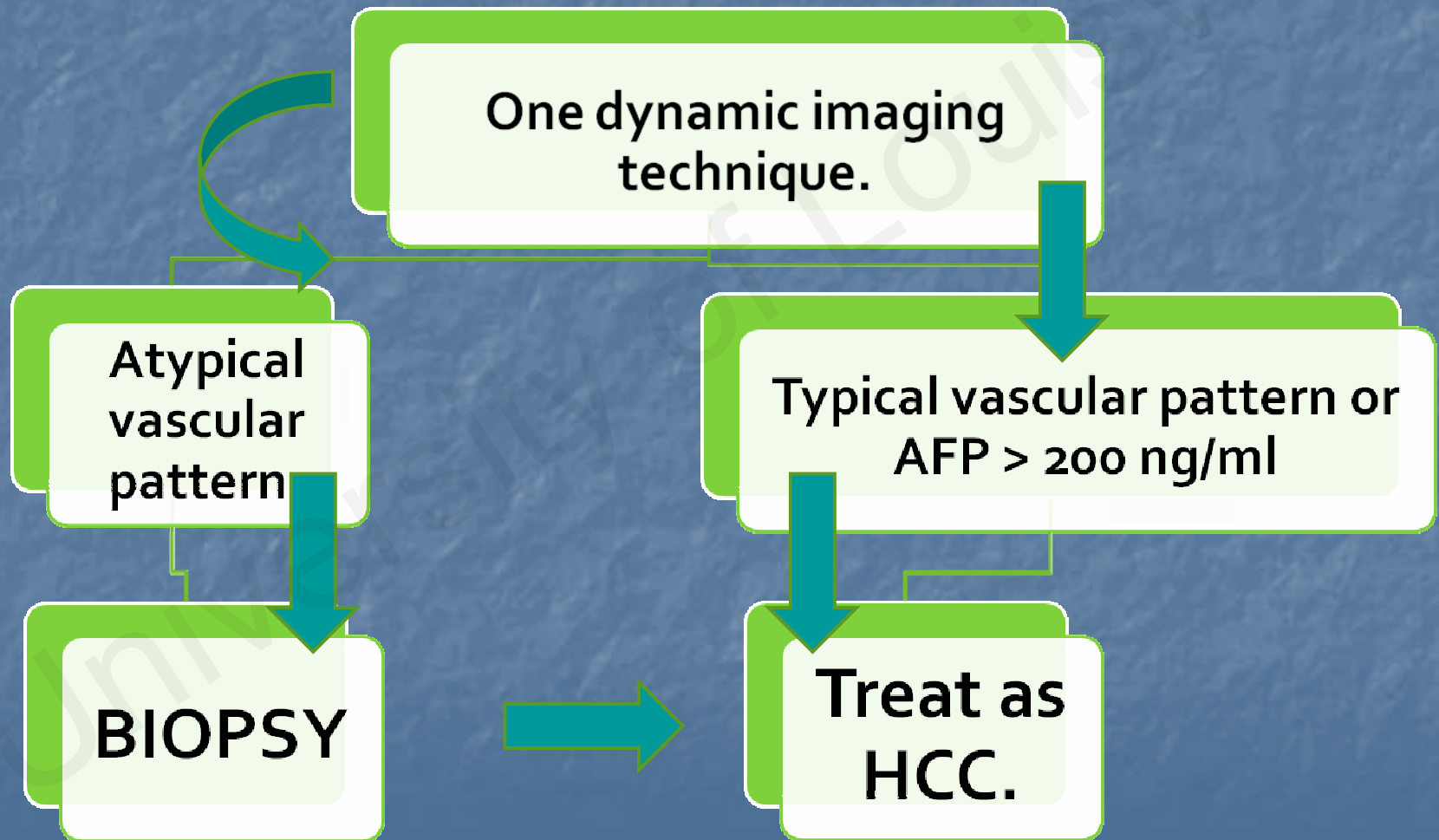
Lesions less than 1 cm.



Lesions 1-2 cm



Lesions greater than 2 cm.



Hepatocellular Cancer

