Hepatocellular Carcinoma: From early detection to effective therapy

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Historical review

- **Rokitansky (1849):** was the first author to refer to primary liver carcinoma.
- **Noeggerath (1854):** described a congenital hepatic carcinoma.
- **Billroth (1859):** reported the presence of hepatic metastases.
- **In 1881:** Sabourin was the first to term “hepatoma”.
- **Price (1883):** described the development of hepatoma from cirrhosis.
- The first righ-sided lobectomy for hepatic carcinoma was carried out in **1911**.

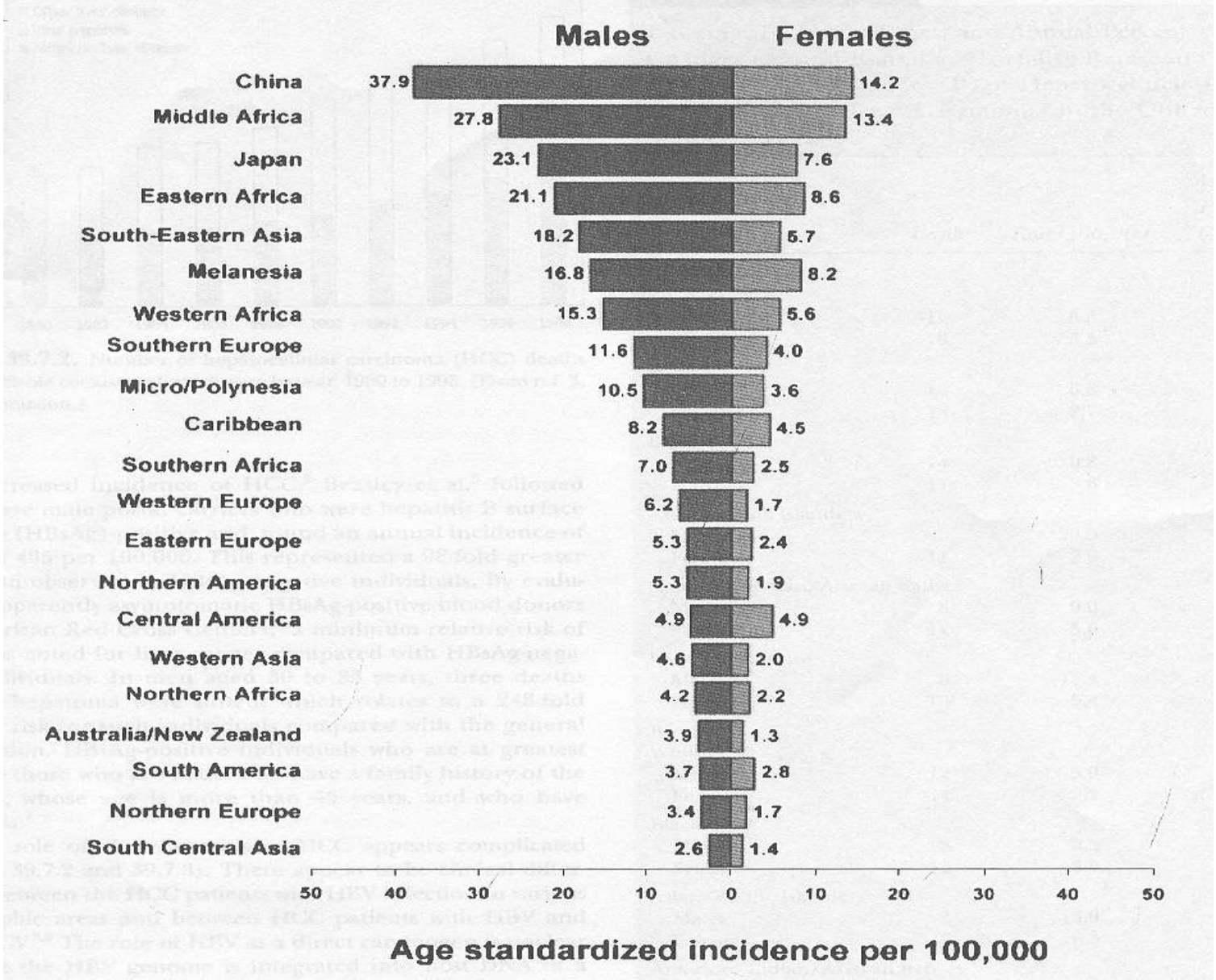
Epidemiology

- HCC is now the fifth common cancer in the world and third cause of cancer related mortality.
- More than half a million cases are diagnosed every year which closely resembles the number of deaths (598.000)/year.
- It is 3 times more common in men than in women, higher levels of testosterone, lower levels of estrogens, higher rates of liver disease are proposed explanation.

- The age at which HCC appears varies according to gender, geographic area and risk factors.
- It has high incidence rates in: Estern Asia and sub-Sahran Africa (>15/100.000) population intermediate rate (5-15/100.000) in Mediterranean basin and southern Europe.
- Very low (<5/100.000) in Northen Europe and America.

- **In Egypt:**
  - HCC proportion had increased in the last years from 4.0% to 7.2% among chronic liver disease patients ***(El-Zayadi et al., 2005)***

- HCC is the 2nd most frequent cancer in males, the 4th in females and constituted 13% of all cancer in Egypt ***(El Attar, 2005).***



Age standardized incidence per 100.000 inhabitants.

Condition associated with HCC

- **Hepatitis viruses**:
  - HBV, HCV
- **Liver disease**
  - Chronic hepatitis
  - Cirrhosis
  - NASH
- **Mycotoxins or phytotoxins**
  - Afltoxin
  - Microcystin
  - Cycasin
  - Ochratoxin
  - Luteoskyrin
  - Safrol
  - maltrozym

- **Nutrition:**
  - Alcohol
  - Ethionine surphus
  - Betel quid chewing
  - Tobacco smoke
  - B6 and choline deficiency.
- **Metabolic diseases:**
  - Alpha1- antitrypsin deficiency
  - Colon polyposis
  - Galactosaemia
  - Glycogenosis type1.
  - Haemochromatosis
  - Neurofibromatosis
  - Porphyria
  - Tyrosinaemia type 1

- **Chemical agents**
  - Alkylating agnets
  - Nitrose compounds
  - Aromatic amines
  - Vinyl chloride
  - Azo-compounds.
- **Inorganic substances**
  - Arsenic, asbestos
  - Lead, manganese
  - Cadmium, chromium
  - Nickel
- **Medications**
  - Androgens, anabolic, contraceptives
  - Methyldopa, methotrexate.
- **Ionizing radiation:**
  - Thorium
  - X-ray

Major risk factor

- **HBV:**
  - 5-15 fold increased risk
  - 70-90% of cases in setting of cirrhosis
  - Treatment does not decrease risk.
  - Early vaccination: associated with a decrease in risk of cancer in children from 0.54 to 0.20 per 100.000 during a 16 year peroid.
- **HCV**
  - 1-3% of HCV cirrhotic patient.
  - Treatment seems to decrease risk

- **Co-infection:**
- **Aflatoxins**: Associated with 4 folds risk of HCC
- **Smoking:** synergistic with HCV and HBV
- **Alcohol:** no direct carcinogenic effect, but synergistic with HBV, HCV.
- **Genetic mechanism:**
  - It is observed that more than 22% of patients suffering from HCC had other organ tumors as well.
  - Patients with obesity and diabetes mellitus, also have a higher risk of HCC.
  - Several hereditary metabolic disease, with or without cirrhosis, may increase risk of HCC.

Clinical features:

- HCC can develop without subjective complaints.
- The complaint may be general, undeceted
- May be explained as a symptoms of cirrhosis or pre-existing chronic liver disease.

- **General**
  - Pain in upper abdomen
  - Weight loss
  - Bloating, flatulance
  - Fatigue, weakness
  - Nausea
  - Disturbed bowel habit
- **Specific:**
  - Fever
  - Arterial mumur
  - Icterus
  - Tender upper abd.
  - Ascites
  - Palpable tumor
  - Latent encephalopathy
  - Perihepatic friction

- **Paraneoplastic findings**
  - Polycythaemia
  - Hypercalciemia
  - Painful gynaecomastia
  - Hyperthyrodism
  - Esteoarthropathy
  - Hypertension
  - Pseudo porphyria
  - Polyneuropathy
  - Watery diarrhea
  - hypoglycemia

Screening for HCC

Aim: to detect early as possible the tumor for better outcome.

- **Abdominal ultrasound:**
  - Better than serologic tests.
  - Sensitivity 65-80%, specificity >90%
- **AFP**
  - Sensitivity not more than 50%.
  - Poor screening test.
  - Should not be used alone.
  - Other serology: des-y-carboxy prothrombin
  - Addose A.
  - α-L-flucosidase

The best screening for early detection

- Combination of:
  - All cirrhotic
  - Interval better not more than 6 months.
  - Abd. US
  - AFP
  - Any alarm sign or poor response to treatment.

Groups recommended to be under screening for HCC
Hepatitis B carriers
Asian men >40 y
Asian women >50y
All cirrhotic hepatitis B carriers
Family history of HCC
Africans >20 y
Patients with high HBV DNA and ongoing hepatic injury remain at risk of HCC.
Non-hepatitis B cirrhosis
Hepatitis C
Alcoholic cirrhosis
Genetic hemochromatosis
Primary biliary cirrhosis
Insufficient data to make recommendations
Cirrhosis due to α_1 –anitrypsin deficiency
Cirrhosis due to nonalcoholic steatohepatitis
Cirrhosis due to autoimmune hepatitis.

HBV, hepatitis B virus.

Prognosis of HCC depend on:

- Patients: related factors: age, sex, race
- Liver related factors: liver cirrhosis, hepatitis, hepatic functinal reserve
- Tumor related factors: pathological features, tumour markers, molecualr markers
- The treatment modality

Unfavorable characteristics:

- T4 tumours
- AFP level > 1.000 ng/ml.
- Total tumour diameters > 8cm.
- Vascular invasion
- Poorly differentiated histologic grade
- Older individuals

Staging of HCC

- Multiple clinical systems for hepatic tumours have been decribed. The most widely used is:
  - Barcetona clinic system (BCLC)
  - Cancer of the liver Italian program (CLIP)
  - American joint commission on cancer staging (AJCC/TNM).
  - The Okuda staging system (1984).

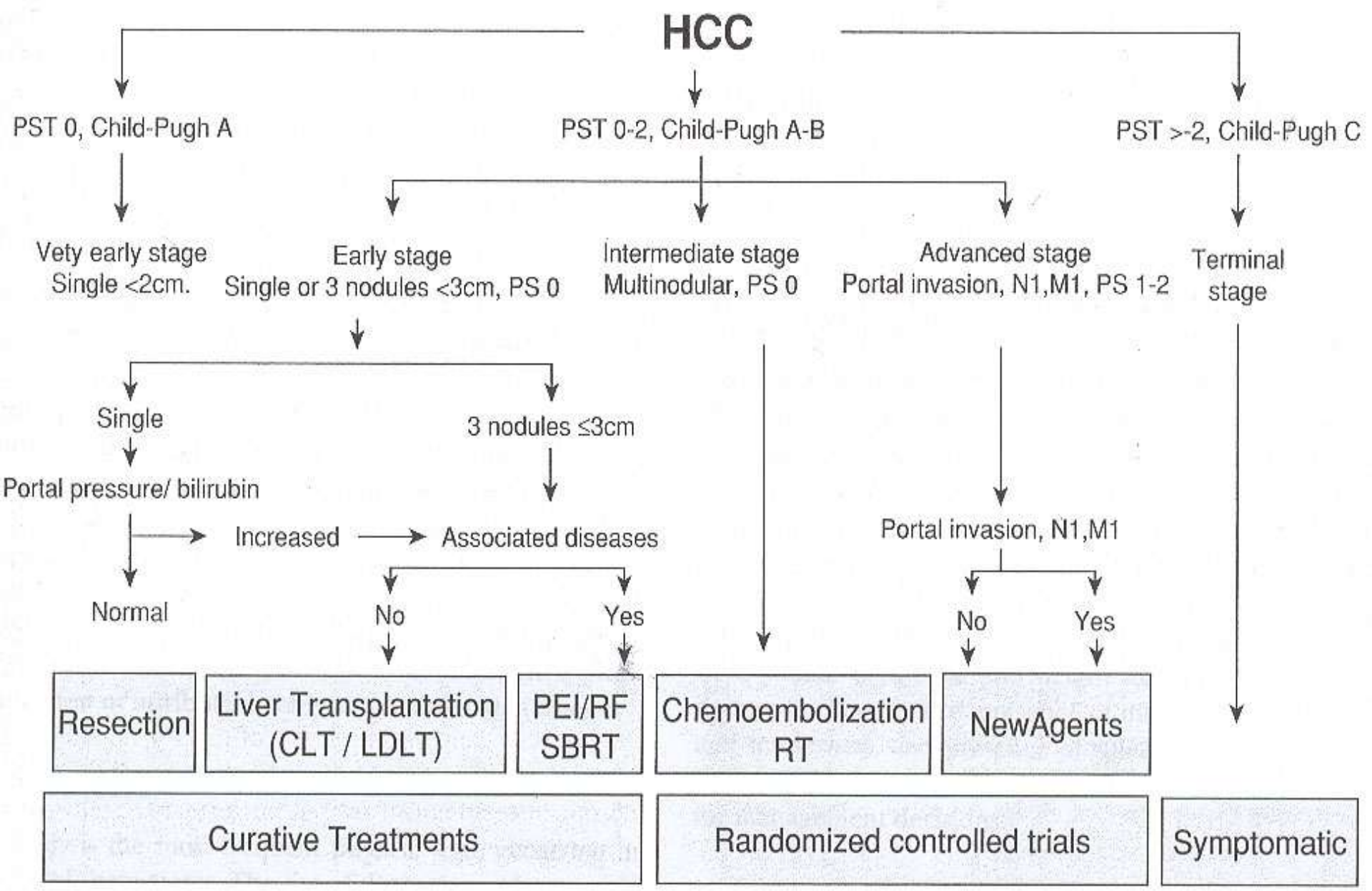
The Okuda staging system

Parameter	Value	points
Tumor size	>50% <50%	1 0
Asites	Present Absent	1 0
Serum albumin	>3 <3	0 1
Serum bilirubin	>3 <3	1 0
Stage 1	0 points	
2	1-2 points	
3	3-4 points	

Cancer of the liver Italian program (CLIP)

Cancer of the liver Italian program (CLIP) staging system			
Variables	Points		
	0	1	2
1. Morphology and hepatic replacement	Single < 50%	Multiple < 50%	>50%
2. child-Pugh Score	A	B	C
3. AFP (ng/ml)	<400	≥ 400	
4. Portal vein thrombosis	No	Yes	
This staging system used classic techniques of analysis of variables. It only included patients with cirrhosis and uses Child-Pugh score rather than its individual components [b]Score = sum of points for four variables			

American Joint Commission on Cancer Staging 3				
Primary tumor (T)				
Primary tumor cannot be assessed				TX
No evidence of primary tumor				T0
Solitary tumor without vascular invasion				T1
Solitary tumor with vascular invasion, or				T2
Multiple tumors no more than 5 cm T3 Multiple tumors more than 5 cm or Tumor involving a major branch of the portal or hepatic vein (s)				
Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum				T4
Regional lymph node (N)				
Regional lymph nodes cannot be assessed				NX
No regional lymph node metastasis				N0
Regional lymph node metastasis				NI
Distant metastasis (M)				
Distant metastasis cannot be assessed				MX
No distant metastasis				M0
Distant metastasis				MI
Stage grouping				
M0	N0	TI		I
M10	N0	T2		II
M0	N0	T3	III	A
M0	N0	T4	III	B
M0	NI	Any T	III	C
Any N	M1	Arty T	IV	
(From ref. 224, with permission.)				


HCC
PST 0, Child-Pugh A
PST 0-2, Child-Pugh A-B
PST >-2, Child-Pugh C
Vety early stage
Single <2cm.
Early stage
Single or 3 nodules <3cm, PS 0
Intermediate stage
Multinodular, PS 0
Advanced stage
Portal invasion, N1,M1, PS 1-2
Terminal stage
Single
3 nodules ≤3cm
Portal pressure/ bilirubin
Increased
Associated diseases
Normal
No
Yes
Portal invasion, N1,M1
No
Yes
Resection
Liver Transplantation (CLT / LDLT)
PEI/RF SBRT
Chemoembolization RT
NewAgents
Curative Treatments
Randomized controlled trials
Symptomatic

Treatment options for hepatocellular carcinoma

Surgery
- partial hepatectomy
- liver transplantation

Local ablative therapies
- cryosurgery
- microwave ablation
- ethanol injection
- acetic acid injection
- Radiofrequency ablation

Regional therapies: hepatic artery transcatheter treatments
- transarterial chemotherapy
- transarterial embolization
- transarterial chemoembolization
- transarterial radiotherapy
- ^{90}Y microspheres
- ^{131}I lipiodol

Conformal external-beam radiation therapy

Systemic therapies
- chemotherapy
- Immunotherapy
- Hormonal therapy + growth control

Supportive care

Currative TTT for Early Stage HCC

- Liver Transplantation / Resection.
- Radiofrequency Ablation (RFA).
- Percutaneous Ethanol or Acetic acid ablation.
- Microwave ablation.

Palliative TTT for Advanced Stage HCC

- **Transart. chemoembolization (TACE).**
- **Radiation therapy.**
- **Systemic chemotherapy.**

1- Surgical resection

The backbone of curative treatment in patients with early HCC.

Favourable criteria for surgical resection

- Single nodules **< 5 cm in size or a maximum of 3 nodules ≤ 3cm in a single liver lobe.**
- In patients with:

1- Mildly impaired liver function (Child A).

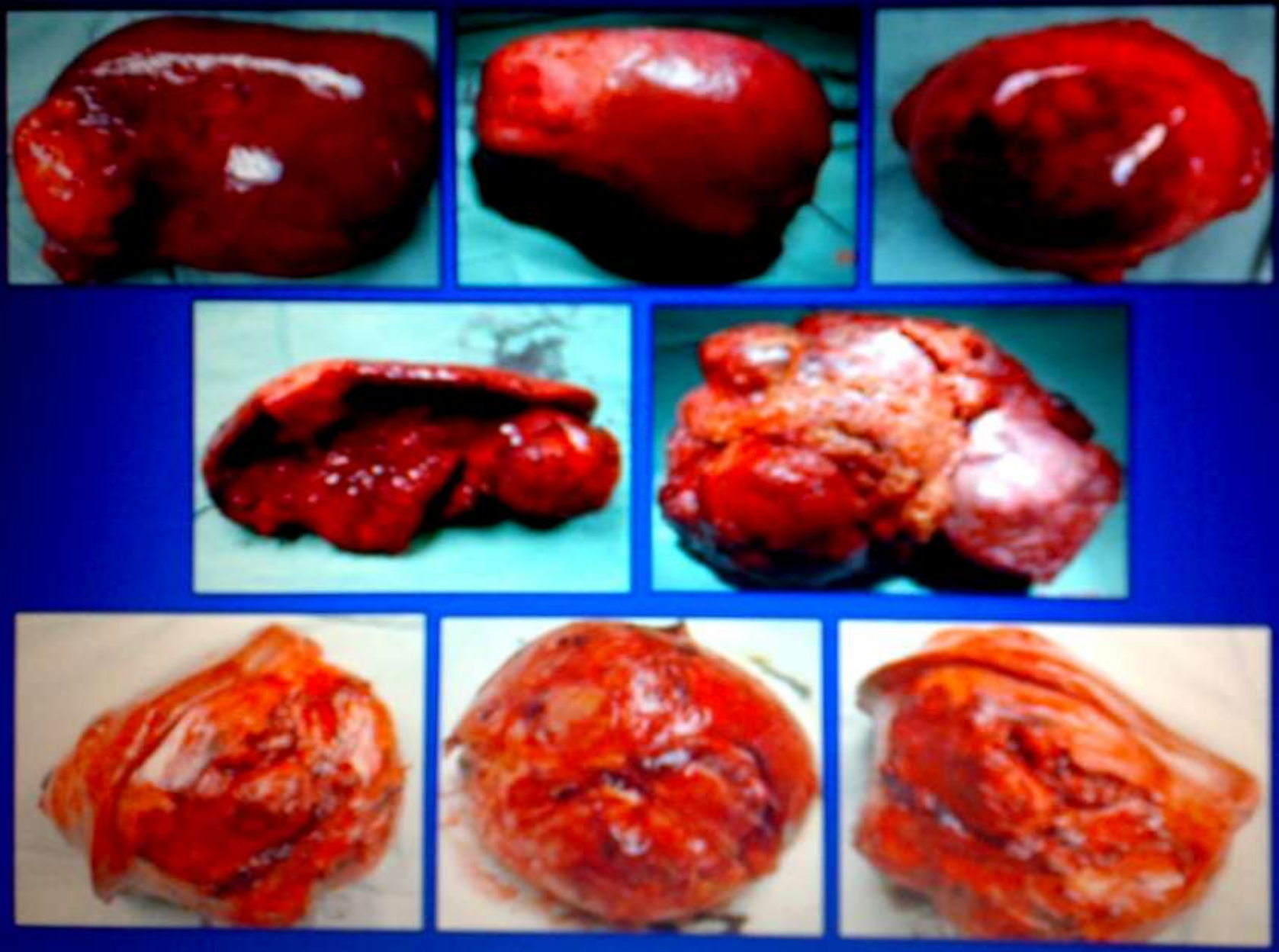
2- Without portal hypertension:

- Hepato-portal-venous pressure gradient <10 mm Hg.
- No esophageal varices.
- Absence of splenomegaly.

3- Platelet counts >100,000/µl and

3- Serum bilirubin in the normal range.

PANORAMA OF DIFFERENT SURGICAL SPECIMEN OF HEPATOMA



Optimal Criteria
Solitary tumor < 5 cm
No vascular invasion
No portal hypertension
Well-preserved hepatic function (Child-Pugh Class A)

Stage 1-2	
5 yr OS	Ranges ≈ 40% - 90%
Long term recurrence free	≈40%

- Resection should be considered the standard therapy for patients with HCC who have adequate liver reserve.

2- Liver Transplantation

Offers better survival rates than resection by offering both decreased tumor recurrence and a treatment of the underlying liver disease.

Indication

Is an alternative therapeutic option:

1- If the liver cancer cannot be cured by local resection due to anatomical reasons.

2- If residual liver function after resection is anticipated to be poor.

3- If there is multi-nodular tumor spread into both liver lobes.

Milano's criteria

- **Solitary nodule with < 5 cm of diameter, or**

≤ 3 nodules with each ≤ 3 cm of diameter.

- **No gross vascular invasion.**
- **No lymph nodes involvement.**

- Milano's criteria patients usually achieve survival rates of 80% and 70% one and five years after liver transplantation.

Mazzaferro V. et al. NEJM 1996

Beyond Milano's criteria

- **1112 exceeding Milano's criteria:**

  -Median size of largest nodule: 4cm

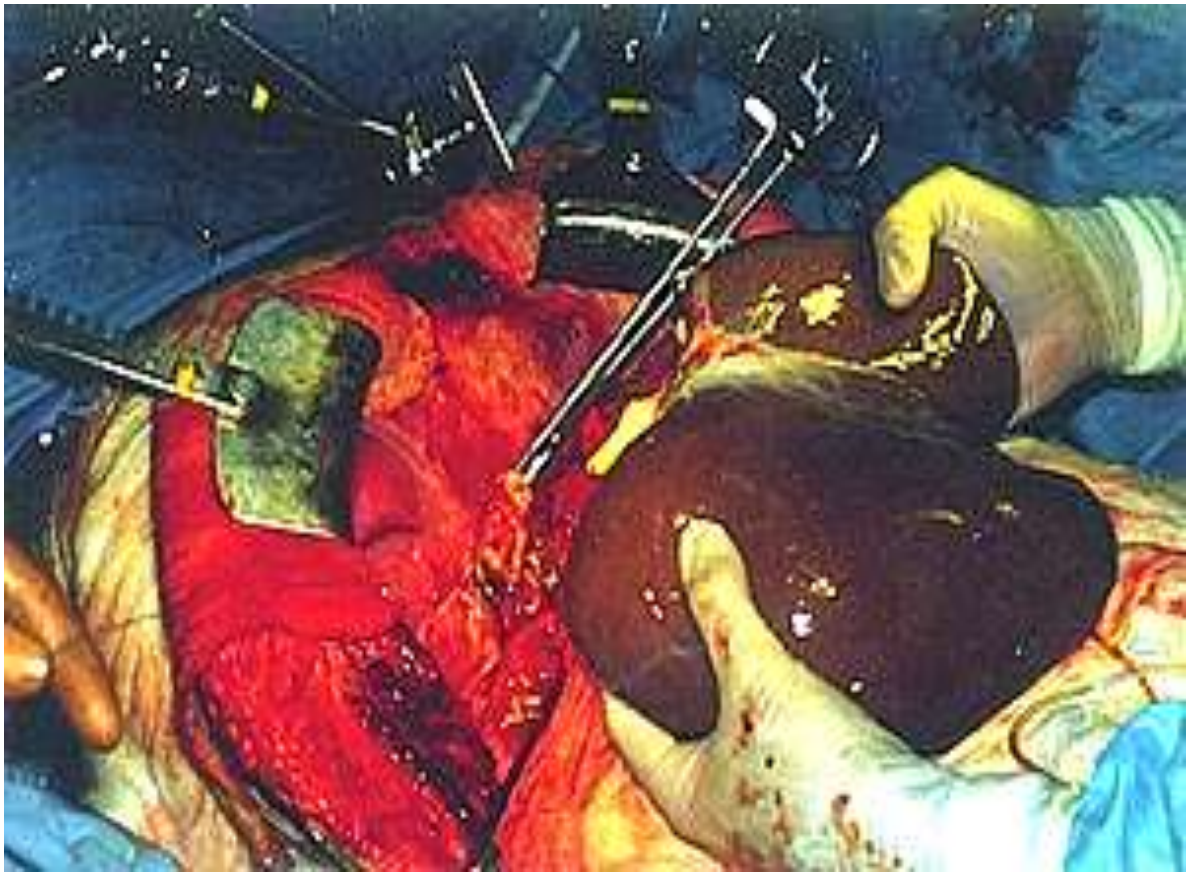
  -Median numbers of nodules: 4

  -41% of microvascular invasion (worst prognostic factor).

- 5-years overall survival 53% vs 73% in patient meet Milano's criteria.

Mazzaferro V. et al. Lancet 2009

Liver Transplant

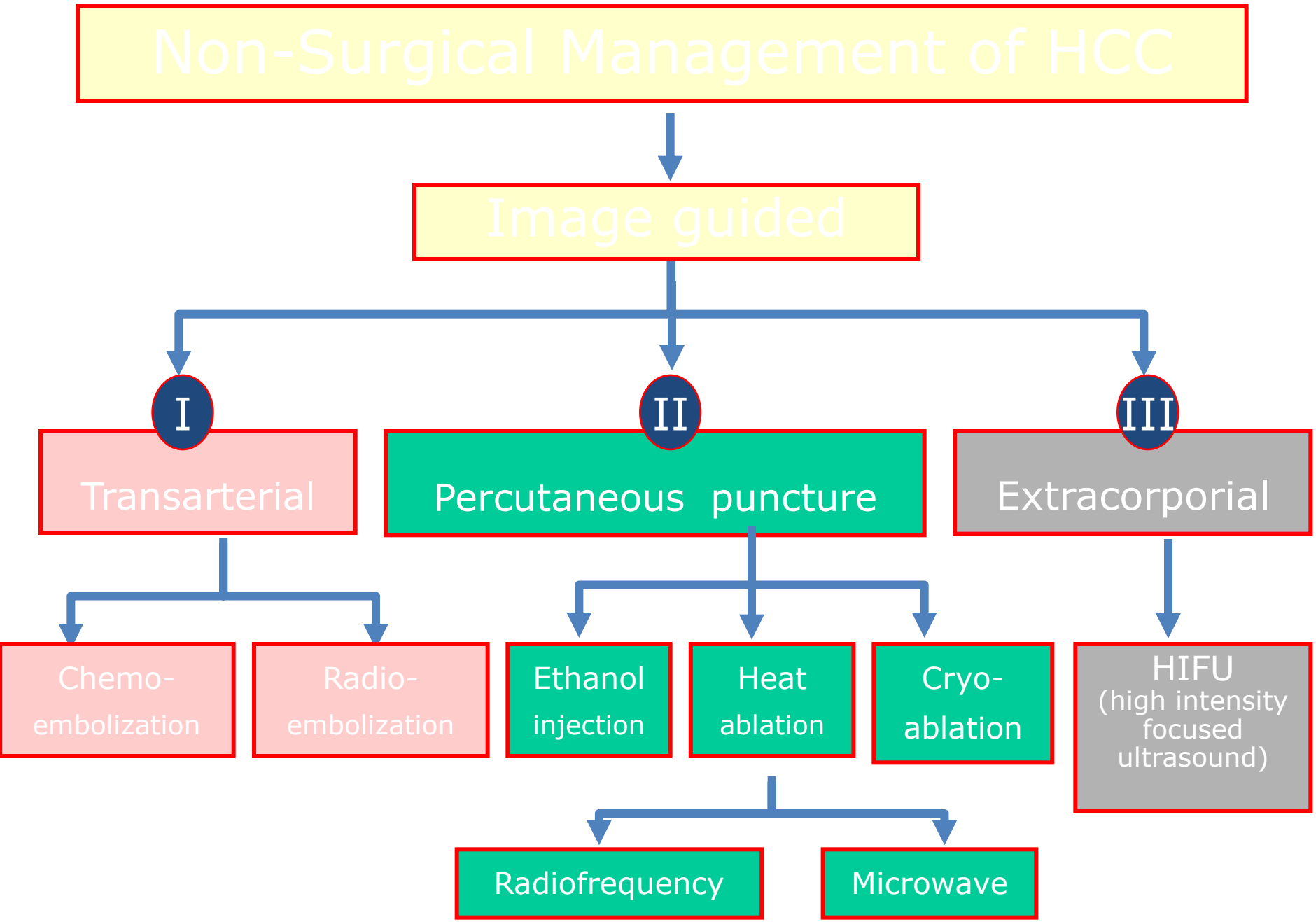


Anastomosis between celiac tripode of the graft and accessory left hepatic artery of the receiver.

Optimal Criteria
Solitary tumor < 5 cm
Up to three nodules ≤3 cm
No vascular invasion
No regional nodal or distant metasteses

Stage 1-2	
3 yr OS	≈ 75%

- Transplantation is frequently the only surgical option due to liver dysfunction.
- Very good outcomes.
- Long wait times, unpredictabile course.


Non-Surgical Management of HCC
Image guided
I
II
III
Transarterial
Percutaneous puncture
Extracorporial
Chemo-embolization
Radio-embolization
Ethanol injection
Heat ablation
Cryo-ablation
HIFU (high intensity focused ultrasound)
Radiofrequency
Microwave

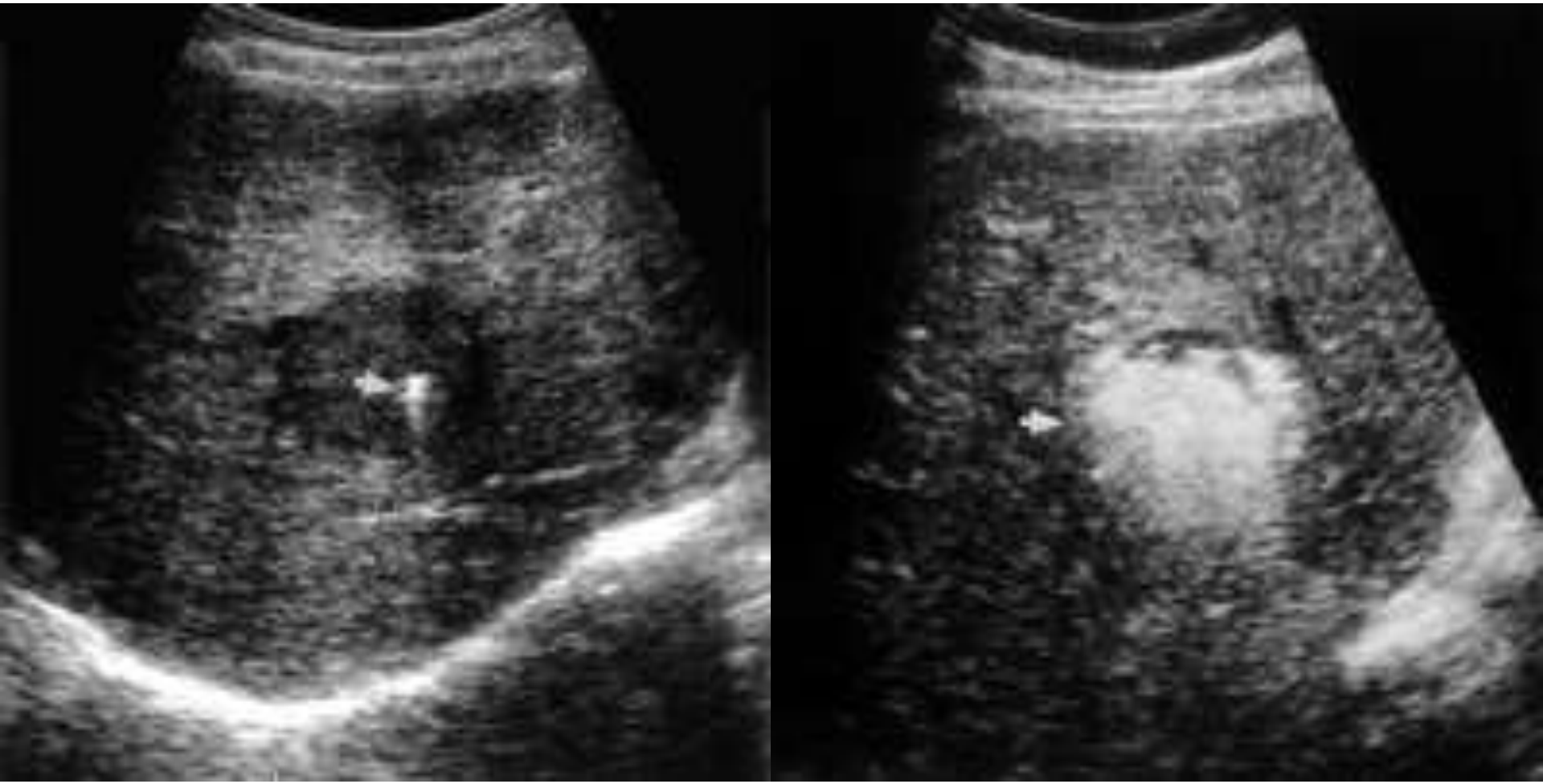
Percutaneous Ethanol injection

- Absolute ethanol.
- Usually special needle.
- Usually multiple sessions (4-8 sessions).

Indications

- Small lesions < 5 cm in diameters and at risk for RFA i.e. adjacent to main biliary or to intestinal loops.
- In combination with other locoregional methods e.g. chemo-embolization or RFA to improve the results.

Ultrasound Guided Percutaneous Ethanol Injection



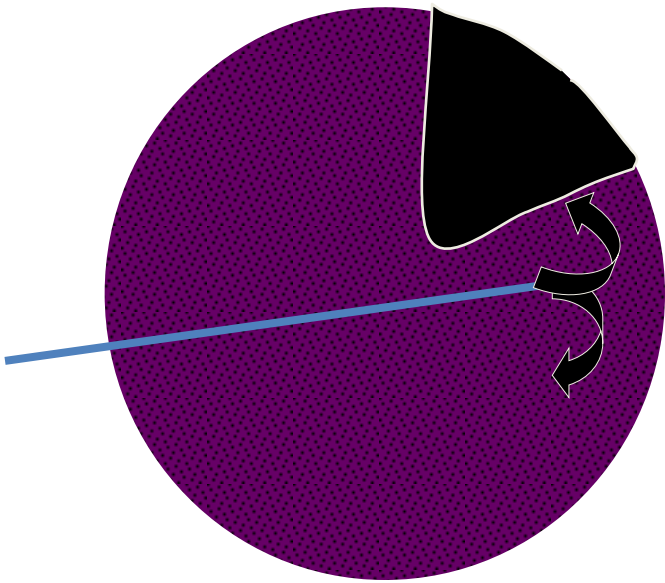
Pre-injection
Needle within tumor

Post-injection
Increased tumor echogenicity

PEI

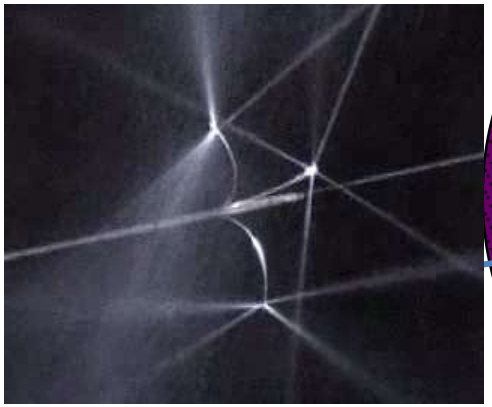
has 1 main problem:

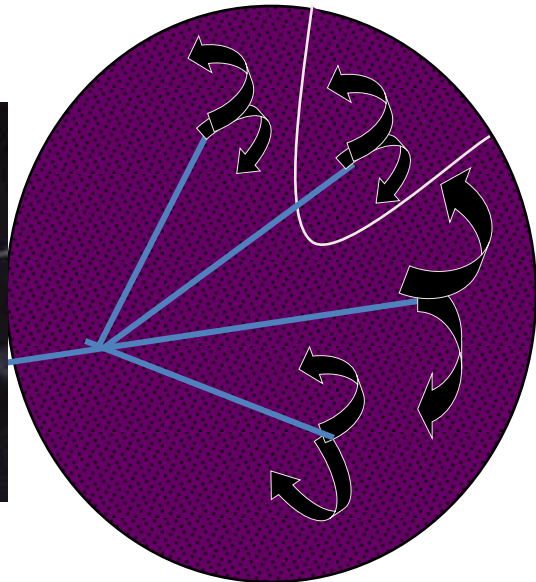
Non-uniform distribution of ethanol due to intra-tumoral septae



New needle

To solve the problem of non-uniform distribution of ethanol inside the tumor and to overcome the septations.



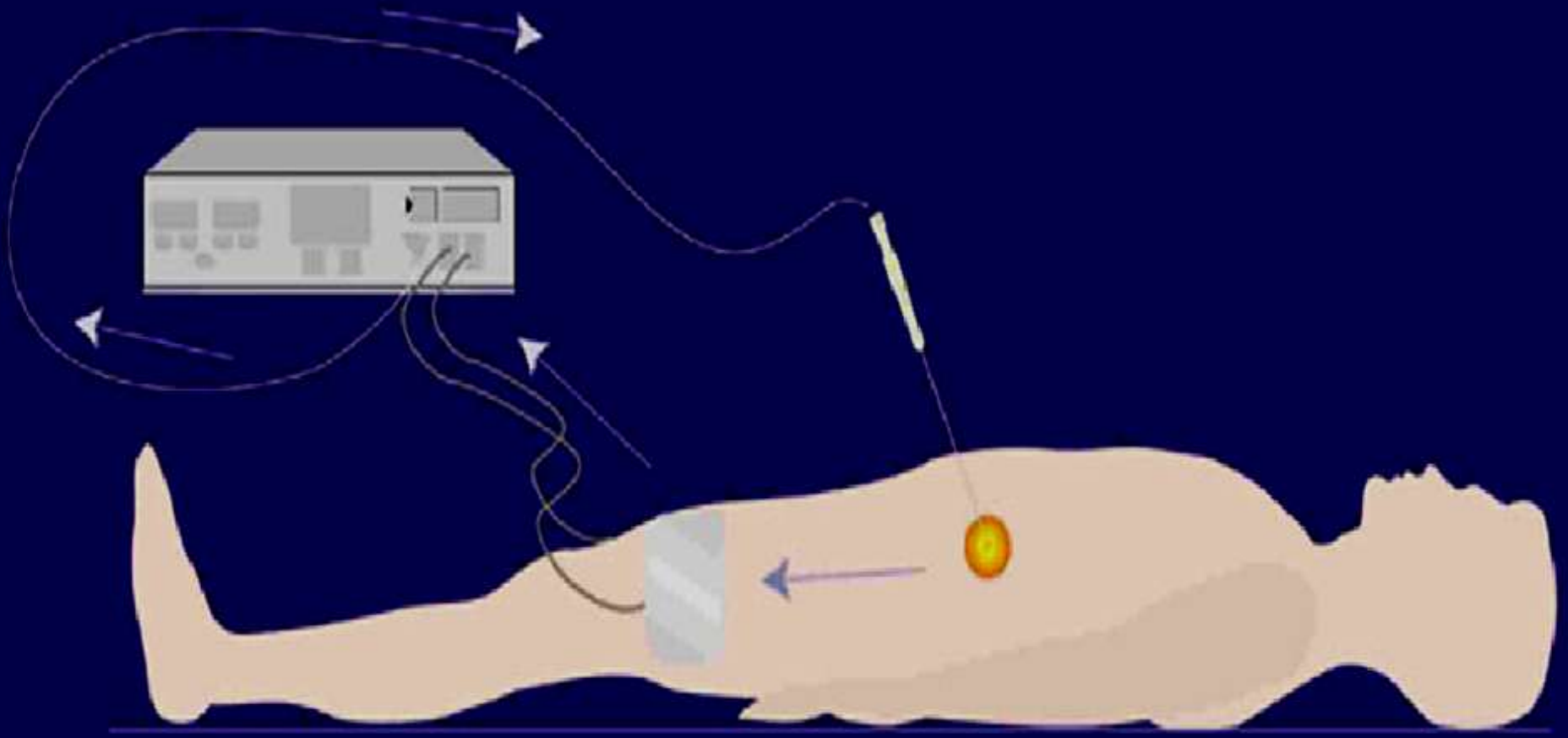


Optimal Criteria
-Early stage HCC
-Not resectable
-Solitary tumors <3cm

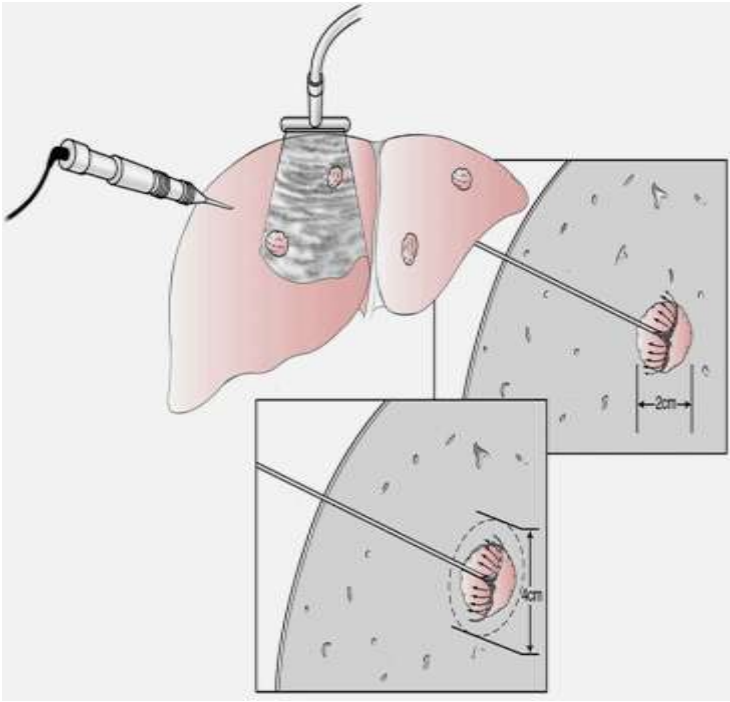
Child-Pugh Class A, <5cm	
Complete Ablation	70-75%
5 yr OS	47%

- Injection of ethanol or acetic acid → cellular dehydration → tumor necrosis and fibrosis.
- Replaced in popularity by RFA.

Radiofrequency



- Radiofrequency ablation:
- Thermal necrosis to tumors by electromagnetic energy through needle electrodes.
- RFA versus resection for patients with single small lesions show comparable 1- and 3-year overall survival results, higher 1- and 3-year local recurrence rates.
- May be considered as a bridge to transplantation.



Patient Selection

I.Tumor Size:

- **The ideal tumor is less than** 3.5 cm but up to 5cm included.
- **Tumors between** 3.5-7cm **in diameters are performed with special technique.**
- **Best outcomes are achieved in patients with** Child A **liver cirrhosis and tumors** <2 cm **in size.**

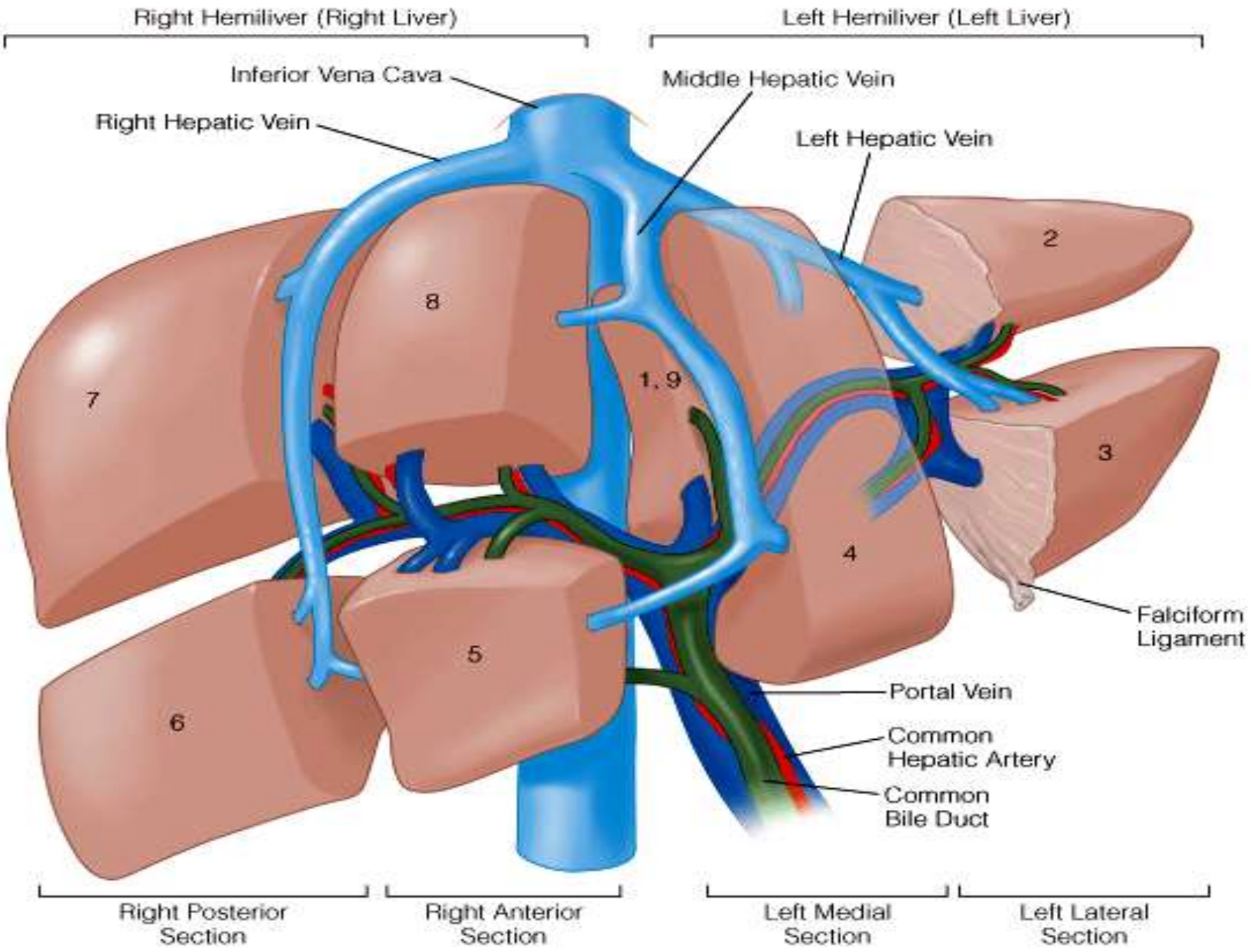
II.Number of the tumors: **the less the number the better the results.**

III.Patients condition: **Child C patients → contraindication. Bleeding profile should be acceptable.**

IV.Vascular invasion and distant metastases: **are contraindication**

V.Location of the tumor:

- Tumors near the hilum **are contraindicated for fear of main duct injury.**
- Subcapsular tumors **in close contact with intestinal loops are performed either intra-operative or after introduction of artificial ascites.**
- Tumors close to large blood vessels **are performed with temporary balloon occlusion of these vessels to prevent cooling effect of the blood flow or with local ethanol injection in the part adjacent to the vessel.**


Right Hemiliver (Right Liver)
Left Hemiliver (Left Liver)
Inferior Vena Cava
Middle Hepatic Vein
Right Hepatic Vein
Left Hepatic Vein
2
8
7
1, 9
3
4
Falciform Ligament
5
6
Portal Vein
Common Hepatic Artery
Common Bile Duct
Right Posterior Section
Right Anterior Section
Left Medial Section
Left Lateral Section
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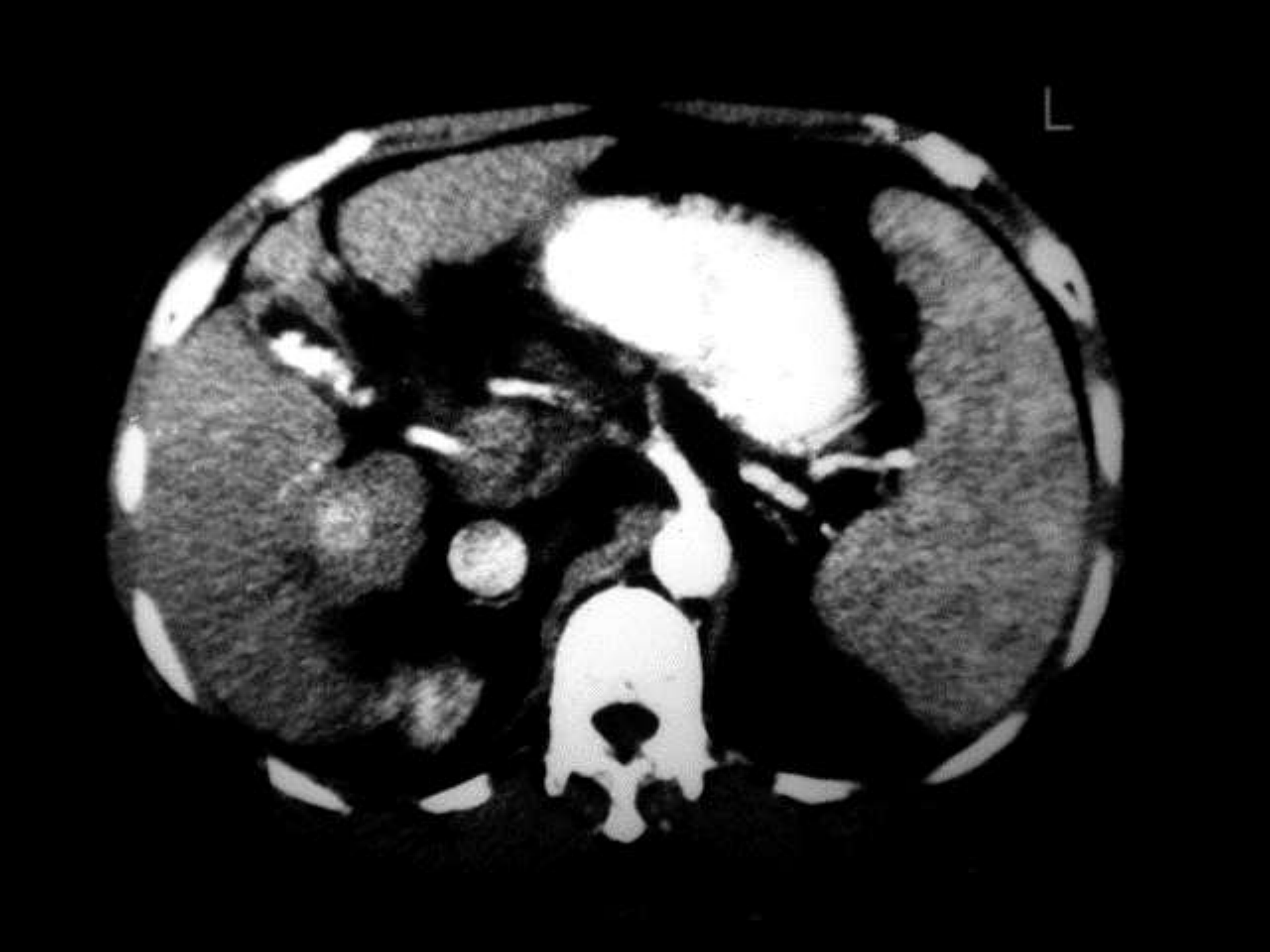
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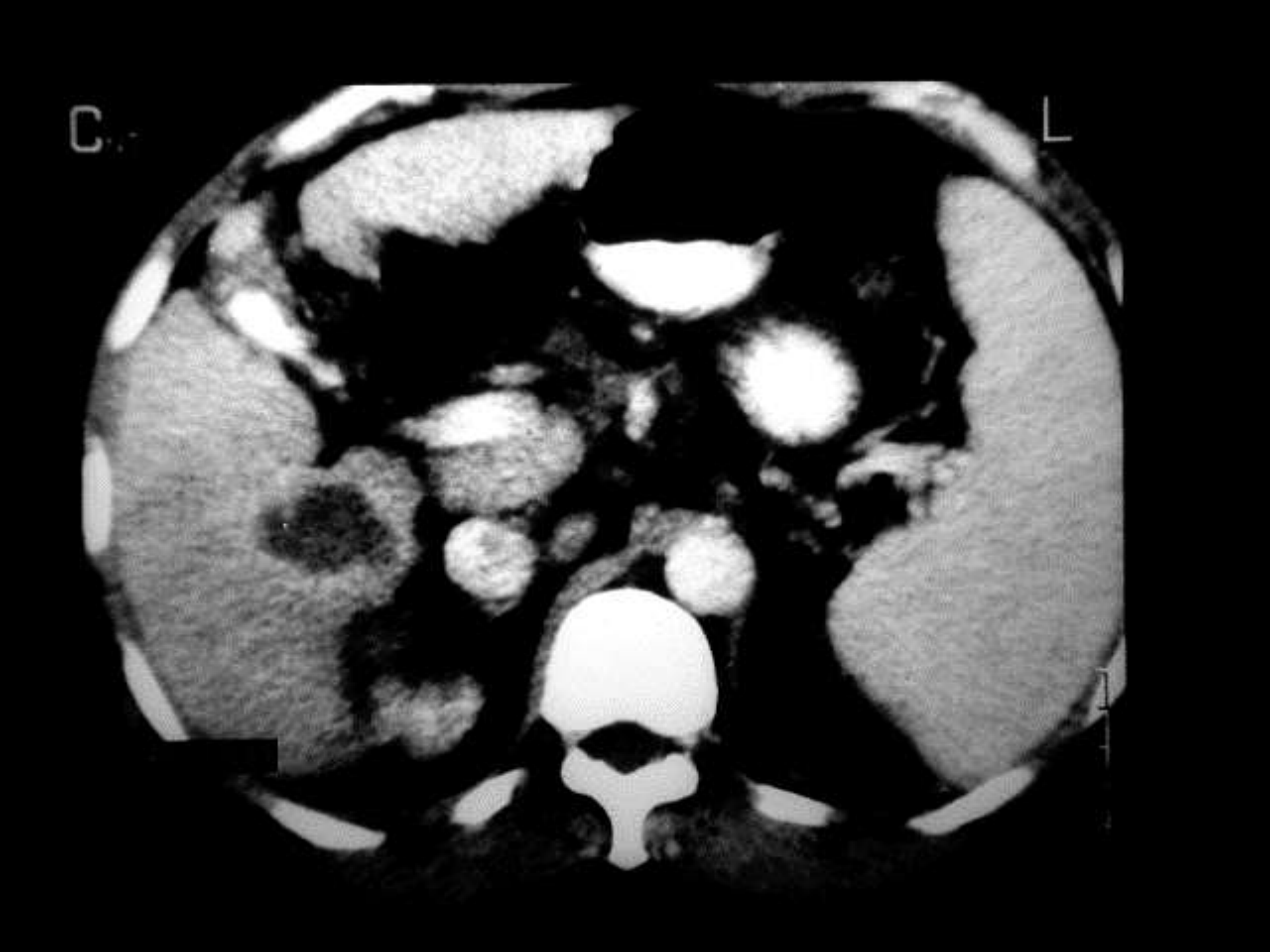

C
L

Radio-frequency

has **1 main problem**

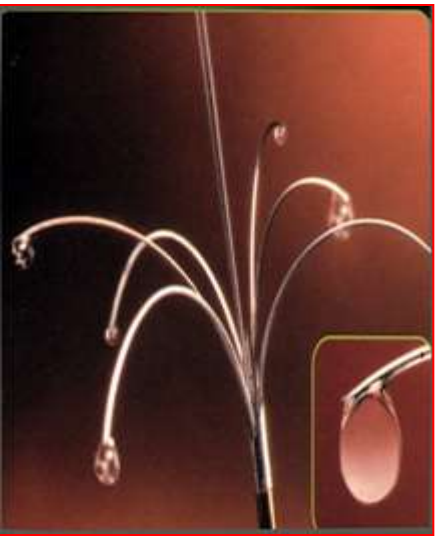
Only small tumor less than 5 cm

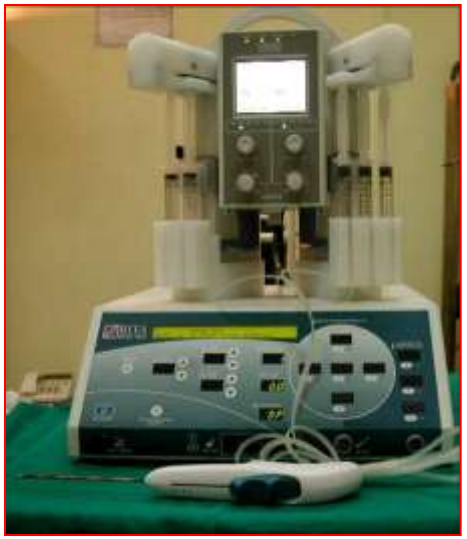
2 New Machines

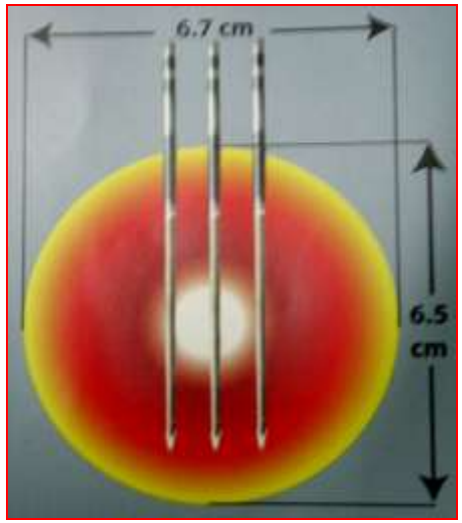
To ↑ the ablation size > 5 cm

1

2

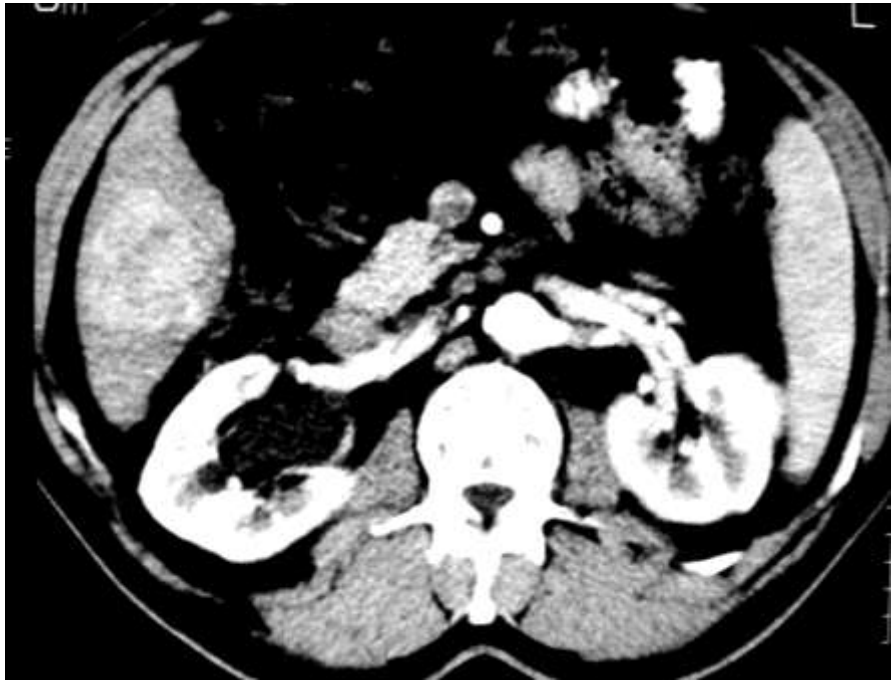




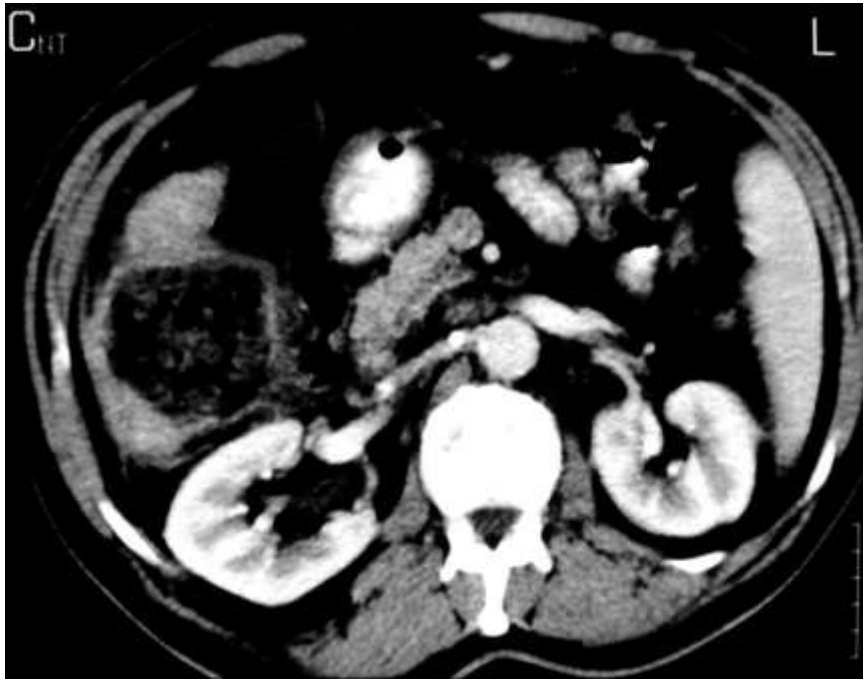


3- Combined therapy

5 – 7 cm lesion with saline infusion



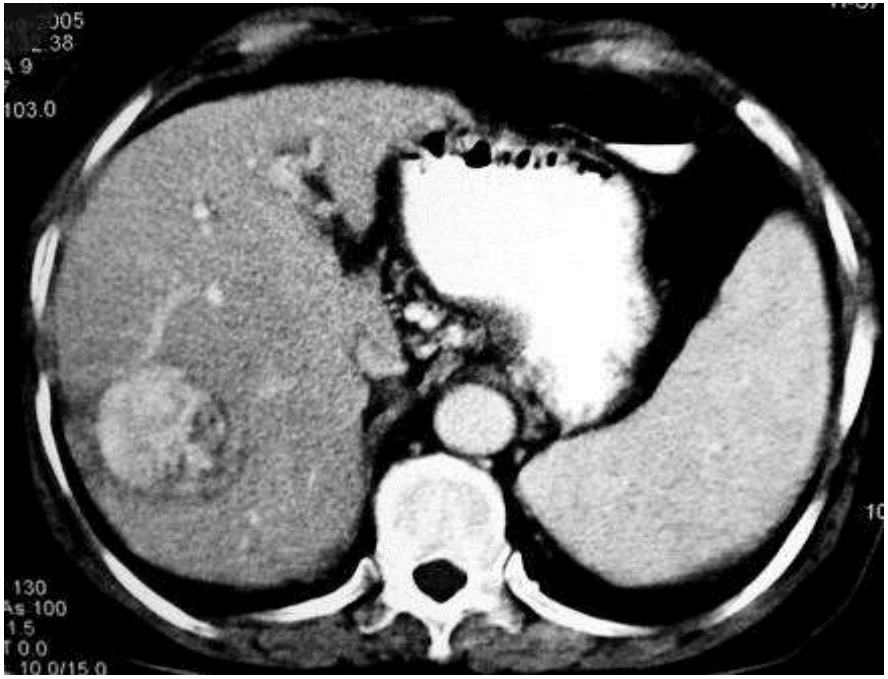
6 cm tumor
before RF ablation



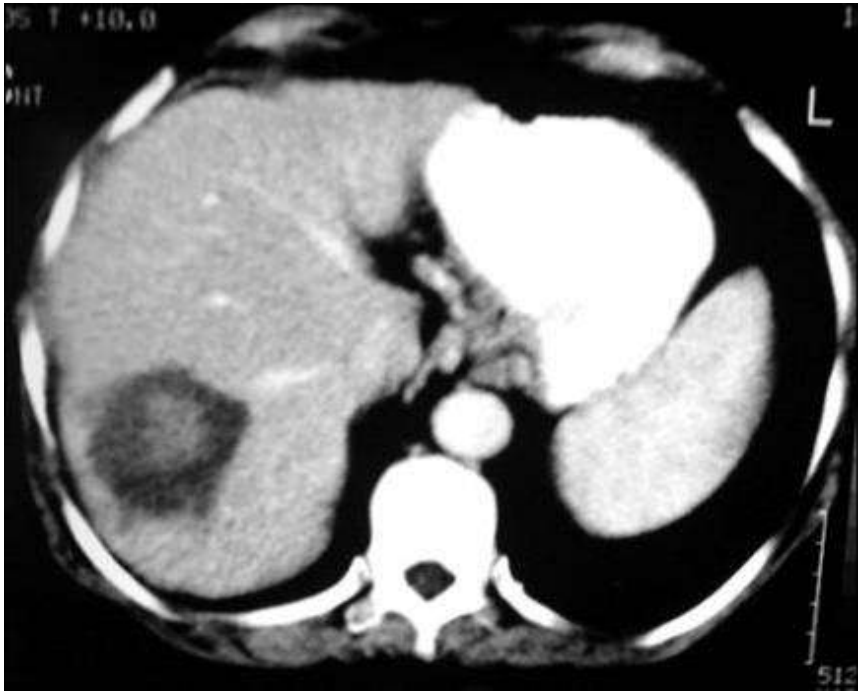
After RF ablation
with saline infusion

Lesions 5 – 7 cm

Three RF electrodes in the same time



Before RF ablation



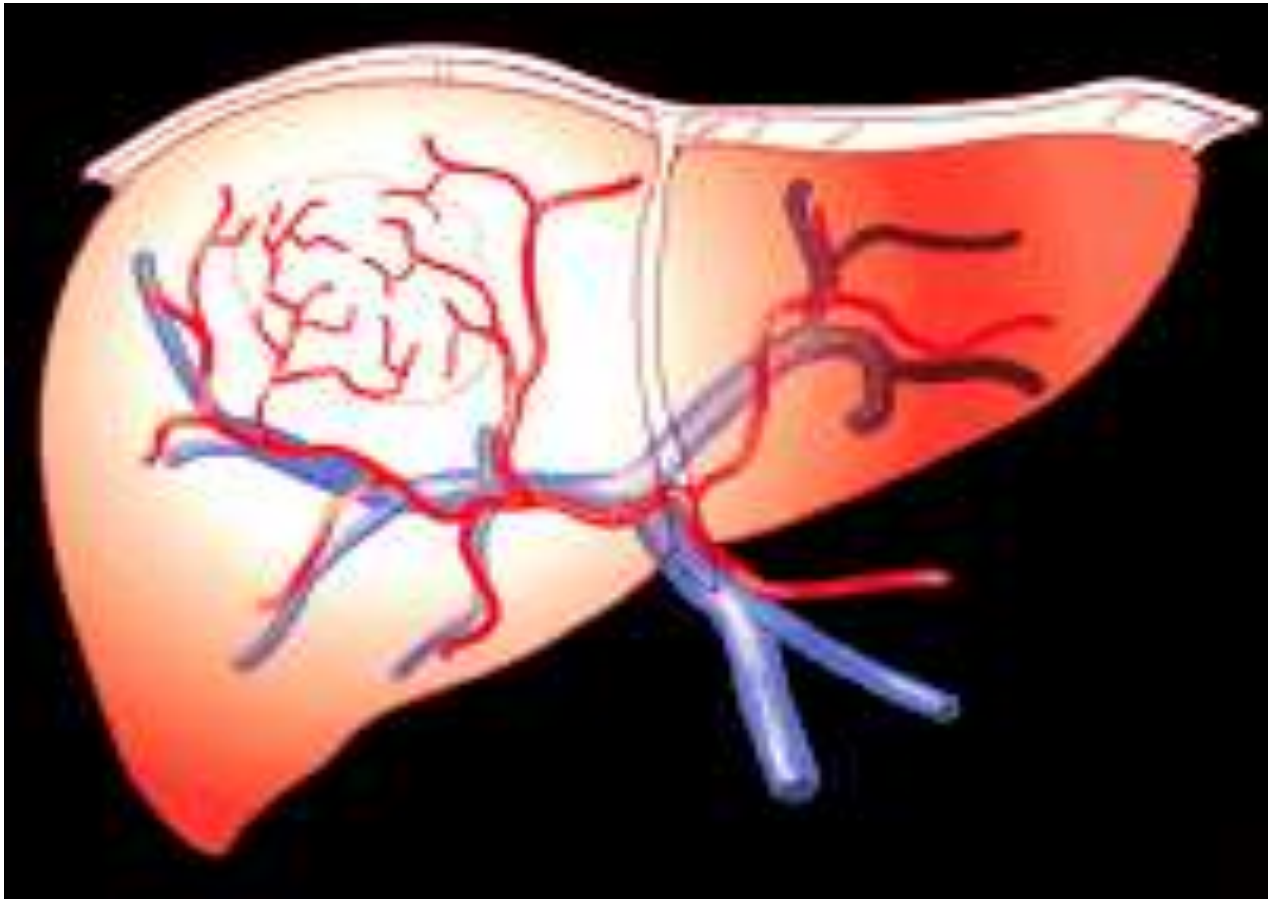
After RF ablation

Optimal Criteria
Child-Pugh Class A/B
Solitary tumors <5cm

Child-Pugh Class A/B	
3 yr OS	78-87%

- Less side effects than PEI with better outcomes.
- Similar results to surgery in potentially resectable patients.

Chemo-embolization



Tumor blood supply 95% **from hepatic artery.**

Indications of Chemoembolization

-HCC unsuitable for neither surgery nor other minimally invasive therapy (RFA or PEI).

-In combination with other minimally invasive techniques (RFA and/or PEI) to obtain optimum results.

-Preoperative to reduce the tumor size to discover other non-visualized tumors which may be not seen by US, CT or MRI.

-Pre-liver transplantation for patients on waiting lists.

Contraindications

1-Poor liver functions:

- -Serum bilirubin > 3 mg/dL
- -SGOT > 100 IU/L
- -Serum Albumin < 3
- -LDH > 425 IU/L

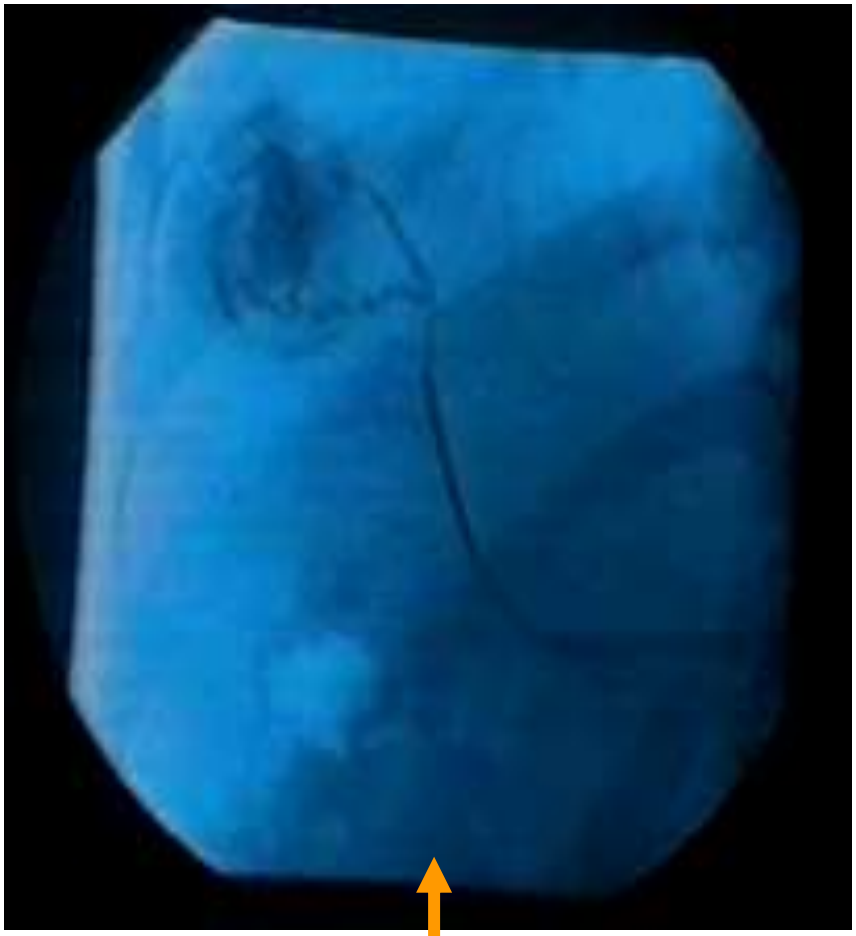
2-Significant portal vein or hepatic vein invasion.

3-Ascites, recent variceal bleed, or significant thrombocytopenia.

4-Poor cardiac or renal function (creatinine >2.0).

Technique

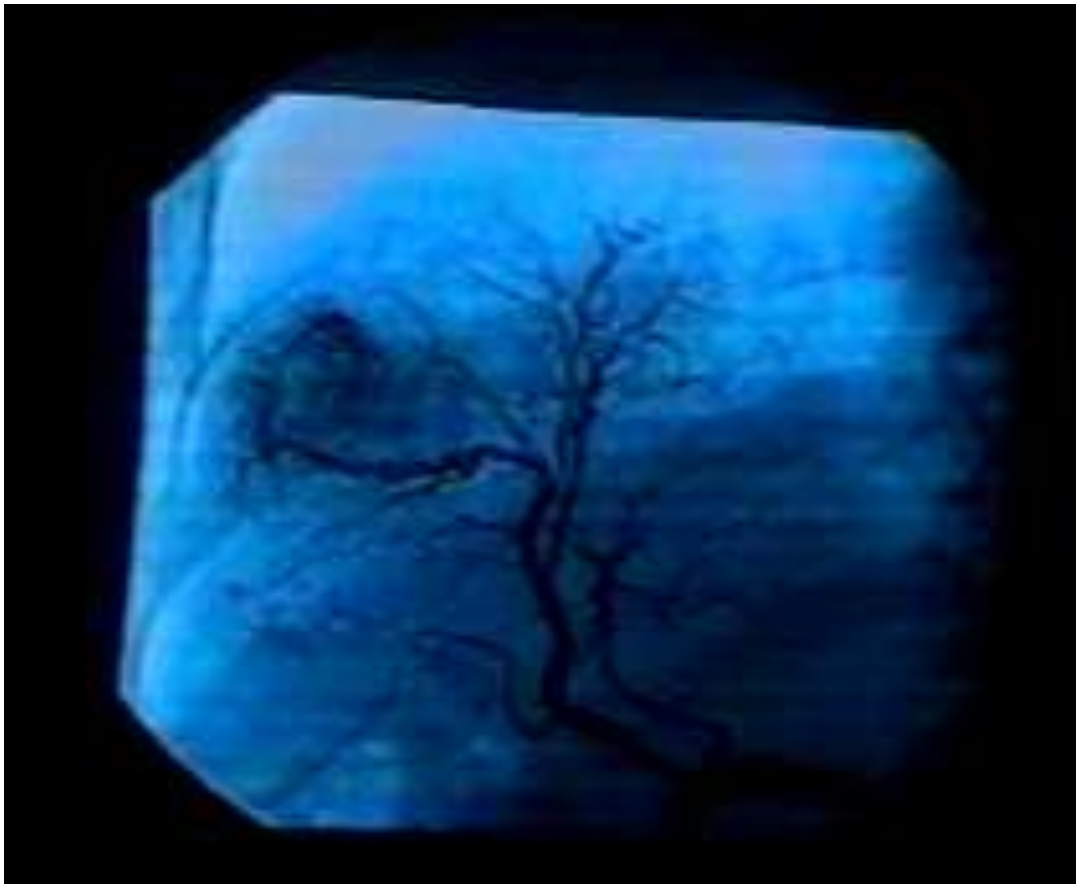
Lipidol cytotoxic drug mixture



During injection

Very small pieces of gel foam

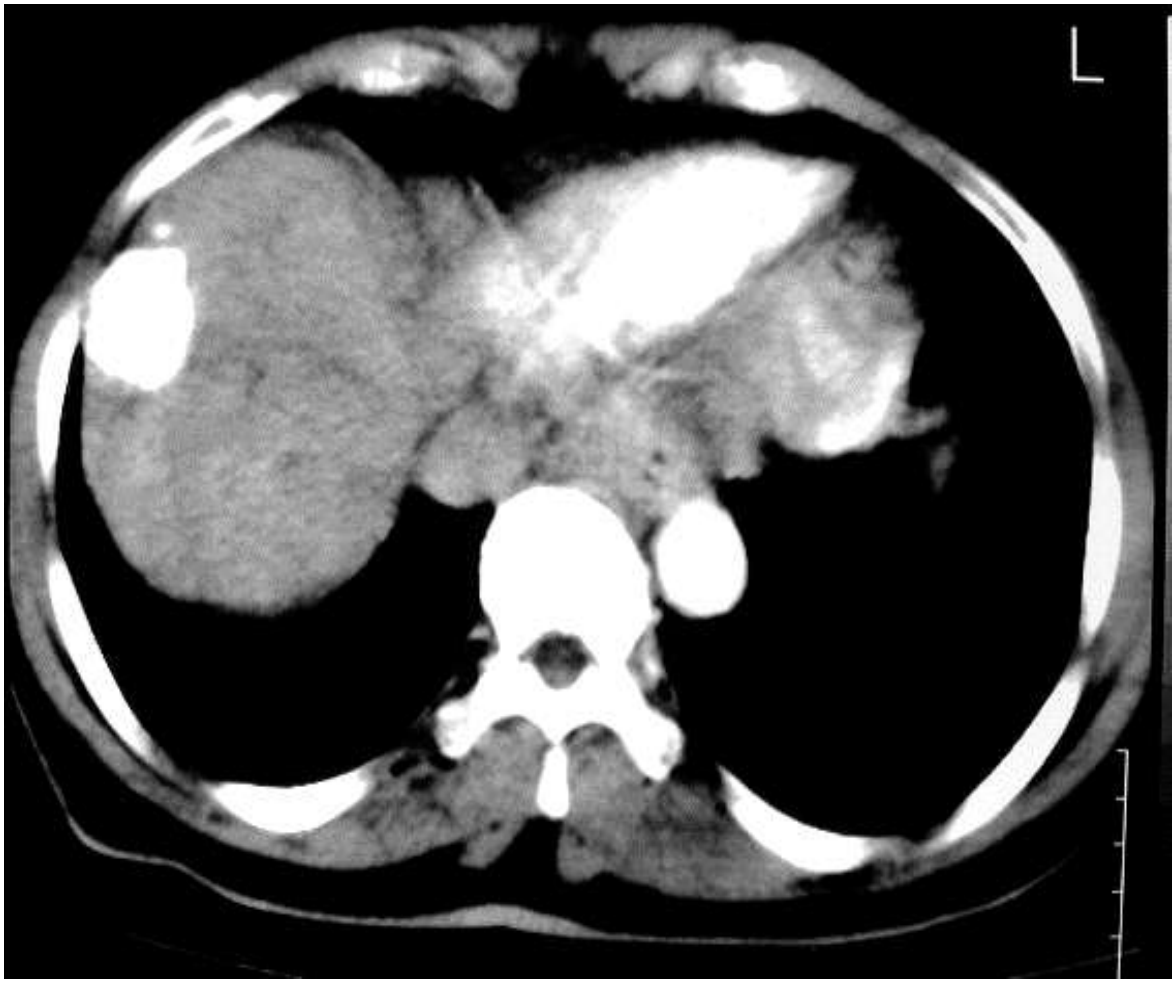
Technique



Mix the cytotoxic drug with Lipiodol and inject it in feeding artery.

→ Embolise the feeding arteries → severe infarction and ischemia aggrevating the effect of Lipiodol cytotoxic drug mixture.

Follow up



After 1 month

- High lipidol concentration in CT
- ↓AFP

Indications
-Large unresectable HCC
-Prior to resection or RFA
-Palliative purposes

- Intraarterial embolization with lipoidol and chemotherapy (doxorubicin or cisplatin).
- Standard palliative treatment for patients with unresectable HCC.

Additional Treatment Considerations

- Microwave Coagulation Therapy
- Interstitial Laser Hyperthermic Ablation
- Radiotherapy
- Adjuvant and Neoadjuvant Treatment
- Antiangiogenic agents
- Oncolytic viral agents
- Chemosensitizing agents.

- **Microwave ablation:**

- It is a technique that destroys tumors by heating cells, resulting in localized areas of necrosis and tissue destruction. It appears promising and generally well tolerated, even in patients with limited hepatic reserve as it is effective in sparing uninvolved liver tissues *(Lu et al., 2005).*

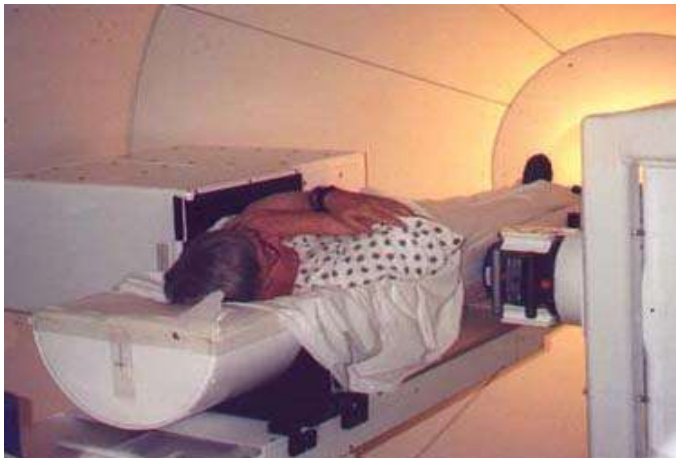
Cryoablation:

- Intraoperative cryoprobe tumor insertion with alternating freeze/thaw cycles.
- Largely replaced by RFA.
- High complication rates.

Radiotherapy:

Recently, it had been shifted from palliative purposes to cure-oriented therapies, including three-dimensional conformal RT, stereotactic RT, proton therapy and Thera-Sphere radiation.

Indications
-Large unresectable HCC
-Symptomatic portal vein thrombosis
-Symptomatic jaundice
-Part of combined modality treatment



Gene therapy:

It is considered as a potential adjuvant to other therapies. Interventional therapies such as TACE and PEI provides new possibilities for the delivery of gene therapy vectors into hepatic tumours, subsequently, increasing the effectiveness and minimizing the potential side effects *(Alcoceba et al., 2006).*

Systemic therapies:

1- Chemotherapy :-

No single or combination chemotherapy regimen had been found to be particularly effective in HCC.

2-Hormonal treatment :-

Antiandrogen therapies and long acting octreotide were not effective in prolonging survival in patients with advanced HCC.

3-Interferon:-

Clinical trials in patients with HCC failed to demonstrate anti-tumor response to interferon.

4-Vitamin K:-

Treatment with high dose vitamin K does not affect survival in patients with advanced HCC.

Sorafinib

To solve the problems of new angiogenesis

(Sorafinib)

Block VEGF receptor

Inhibit new angiogenesis

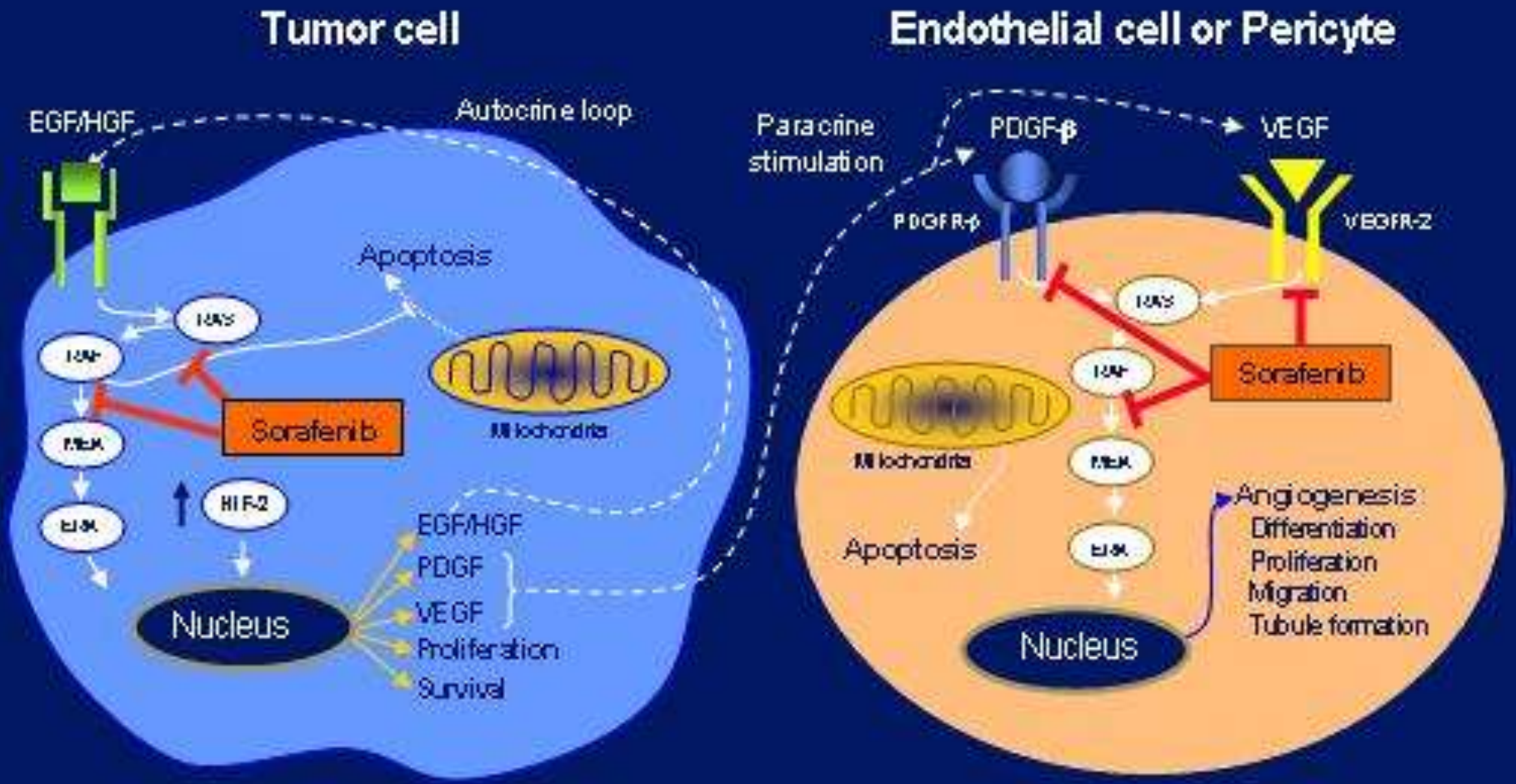
Multi-Kinase inhibitor

↓ Cell proliferation

↑apoptosis

- Systemic therapy is appropriate for patients with advanced unresectable HCC who are unsuitable for locoregional therapy.

Sorafenib Targets Both Tumor-Cell Proliferation and Angiogenesis



Wilhelm S et al. *Cancer Res.* 2004;64:7099-7109.

EGYPTIAN GUIDELINES
FOR HCC MANAGEMENT

1-Early stage disease:

*Includes patients with preseved liver function (Child-Pugh A,B) with solitary HCC or up to 3 nodules ≤3cm in size.

*These patients can be effectively treated by resection, liver transplantation or percutaneous ablation with posiibility long term cure and 5 year survival figures ranging from 50%-75%.

2-Intermediate stage disease:

*Consists of Child-Pugh class A/B patients with large/multifocal HCC who do not have cancer related symptoms and do not have macrovascular invasion or extrahepatic spread.

*These are the optimal candidate for transarterial chemoembolization.

3-Advanced stage disease:

*Includes patients who present with cancer symptoms and/or with vascular invasion or extrahepatic spread.

*They have shorter life expectancy (50% survival at one year) and are candidates to enter therapeutic trials with the new agents.

4-End stage HCC:

Includes patients with extensive tumor involvement leading to severe deterioration of their physical capacity (performance status > 2 and/or major impairment of liver function (Child-Pugh class C).

Egyptian performance status:

Status	Definition
0	Normal activity
1	Symptoms but ampulatory
2	In bed < 50% of time
3	In bed > 50% of time
4	Bed ridden 100%

The different modalities of TTT of HCC:

Locoregional:

*Percutaneous ethanol injection (PEI).

*Radiofrequency ablation (RFA).

*Transarterial chemoembolization.

Surgical:

*Resection

*Liver transplantation

Palliative:

*Sorafinib

Systemic or elective chemotherapy: Is not recommended and should not be considered as standard of care.

Surgical Treatment:

Non cirrhotics:

Resection in a single lesion.

In cirrhotics:

Liver transplatation for those fulfilling Milan criteria.

N.B. Preoperative therapy is considered if the waiting list exceeds 6 months.

Resection can be an alternative option for single lesion in those of stage A1 (normal bilirubin and no PH) with preserved liver function.

N.B. Pre or post-resection adjuvant therapy is not recommended.

Locoregional tratment:

If the size of the lesion

***≤ 3cm ----- PEI= RFA**

***3-5 cm ----- RFA**

Except difficult sites---PEI

---Surgical approach

***5-7 cm (stage B) TACE followed by RFA/PEI**

***> 7cm (stage B) TACE (repeated) ± RFA/PEI**

In cirrhotics:

*Stage A (Child A and B):

Single tumoor ---A1 LTx, resection- RFA/PEI

---A2 LTx – RFA/PEI

---A3 LTx- RFA/PEI

Multiple (all ≤ 3cm) ---A4 LTx- RFA/PEI

*Stage B (Child A and B):

--- If < 10cm TACE ± RFA/PEI

--- If > 10cm in Child A--- resection

Large size --- Sorafinib (if possible as supportive TTT)

*Stage C (Child A and B):

--- Vascular invasion --- Sorafinib.

--- Extrahepatic spread --- Conservative

*Stage D (Child C):

--- Within Milan criteria --- LTx.

--- Outside Milan criteria --- Conservative treatment

Post-treatment follow up:

Laboratory investigations:

*Liver function tests (AST, ALT, Total and direct bilirubin, albumin, PT/INR).

*Kidney function tests (creatinine, urea, Na, K).

*AFP

Radiology:

*Triphasic CT (Multislice if possible)

Frequency of follow up:

1. One month after end of therapy
2. During 1st year F/U -- repeat every 3 month
3. During 2nd year F/U -- repeat CT every 6 month
   -- repeat LAB invest / 3 mo
4. After 2 ys -- repeat CT one/year
   -- repeat LAB investigations every 3 mo

AS LONG AS NO NEW LESIONS DEVELOPE.

Thank You