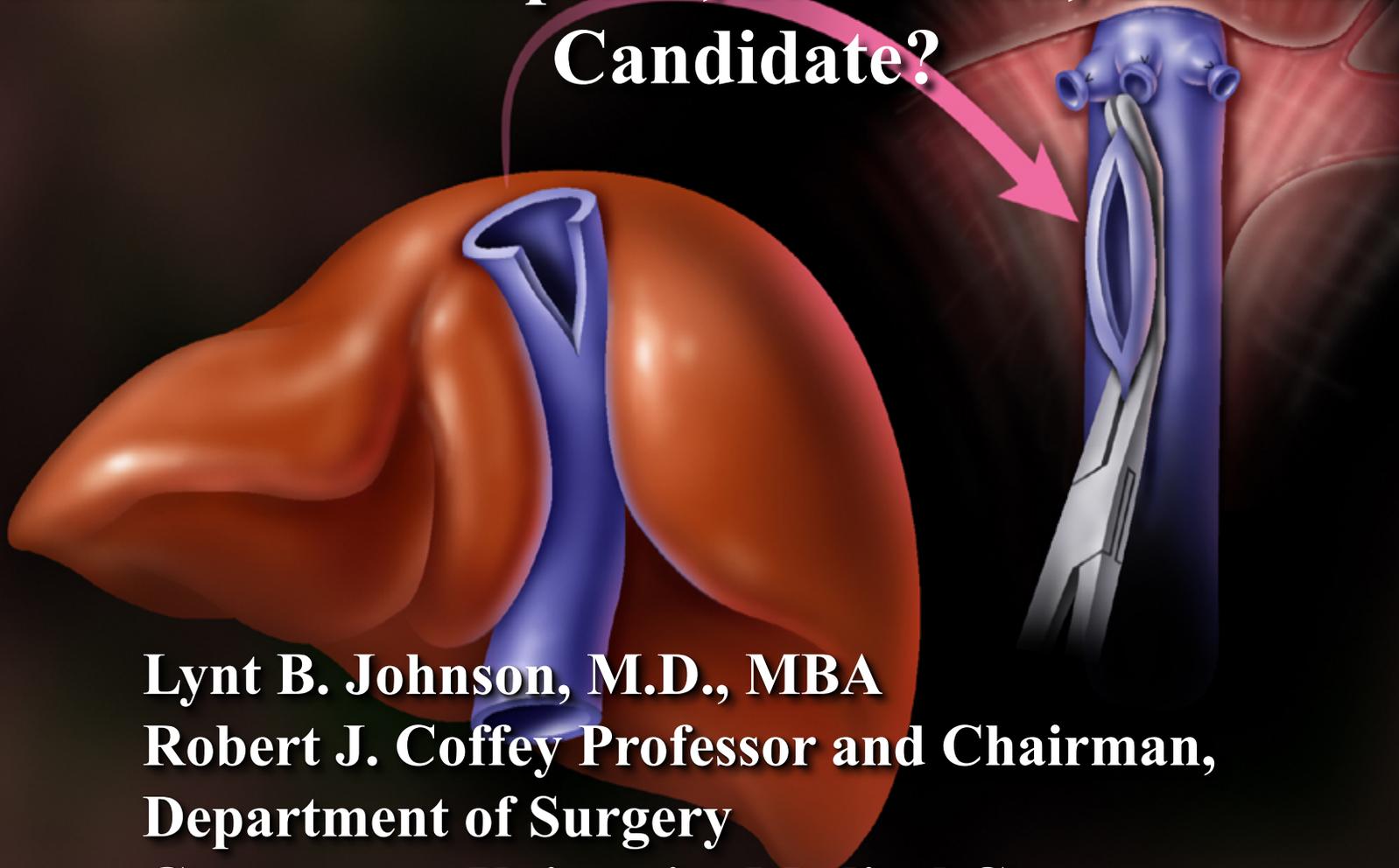


Early Hepatocellular Carcinoma: Is This Patient a Transplant, Resection, or Ablation Candidate?



Lynt B. Johnson, M.D., MBA
Robert J. Coffey Professor and Chairman,
Department of Surgery
Georgetown University Medical Center

Hepatocellular Carcinoma (HCC)

- Most Common Primary Neoplasm of the Liver
- 5th Most Common Cancer and 2nd Most frequent cause of Cancer death Worldwide
- In U.S. Incidence of HCC Increasing 21,000 (2008), est. 27,000 (2020)
- One of Fastest growing Death Rates among Cancers in the U.S.

Epidemiology

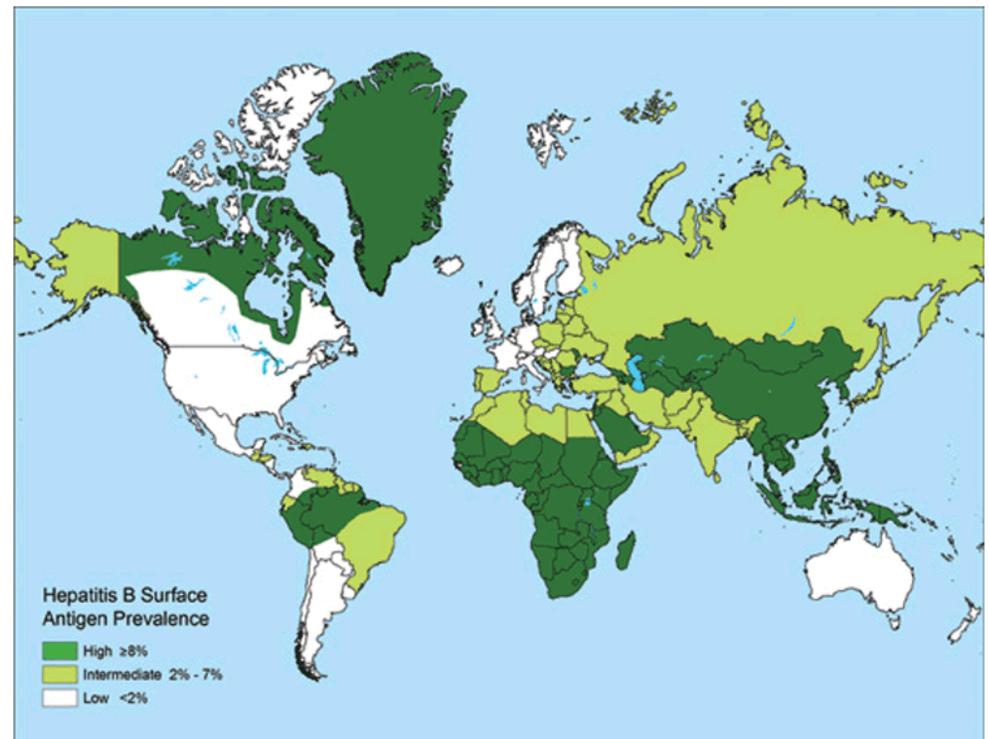
Chronic Liver Disease - #1 Risk Factor



Chronic Hepatitis B (HBV)

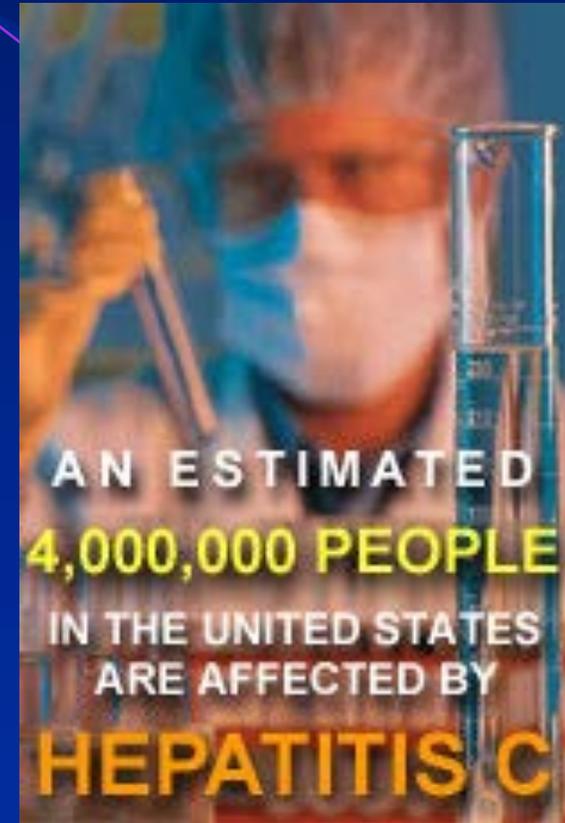
- Vertical Transmission leading Cause
- 5% Worldwide infected with HBV (High Incidence in Asia, Africa)
- Asian Neonatal Vac Program est. Reduction of 70-85% of HBV related HCC
- HBV Carriers , 10-25% Lifetime Risk of HCC
- HBV unique in can develop HCC in absence of Cirrhosis

Figure 12.2 Geographic Distribution of Hepatitis B



Hepatitis C

- 4 Million Infected in U.S. (1.9%) - 2.7 Million Chronically Infected
- Chronic Infection Occurs in 70 – 80%
- Highest Incidence in Egypt (18%), vs U.S. (1.8%)
- In U.S. with DAA 30% reduction of DC/HCC (HCV) on Transplant WL



Non Alcoholic Steatohepatitis (NASH)

- NAFLD/NASH most Prevalent Liver Disease in U.S.
- 60% of Pts >50 with Diabetes or Obesity
- NASH –related HCC Liver Transplant increased by 4x from 2002-2012

Background

- In Setting of Advanced Disease Survival is Dismal (< 10% at Five years)
- In Patients with Limited Tumor Burden an Evaluation for Surgical Treatment (Resection, Ablation or Transplant) Should Occur
- HCC has Predilection for Micro and Macrovascular Invasion, Portends Poor Prognosis

Which Are At Risk Populations For Developing HCC?

- A) Chronic Hepatitis C
- B) Cirrhosis due to Hepatitis B
- C) Hepatitis B Carriers with Family History of HCC
- D) Hepatitis B Carriers who are Asian Males > 40 years of Age
- E) A and B only
- F) All of the Above

Groups in which HCC surveillance is recommended

<i>LIVER DISEASE</i>	<i>ANNUAL HCC INCIDENCE</i>
Hepatitis B carriers	
Documented cirrhosis	2.5% -5%
Asian males \geq 40 yrs	0.4%
Asian females \geq 50 yrs	0.2%
Africans > 20 yrs	0.3%
Family history of HCC	0.2%
Hepatitis C	
Cirrhosis	2 – 8 %
Bridging fibrosis	Increased
Other etiologies of cirrhosis	
Alcohol	0.5 – 1%
Hemochromatosis	3 - 4%
NASH	Increased
Other	Unclear

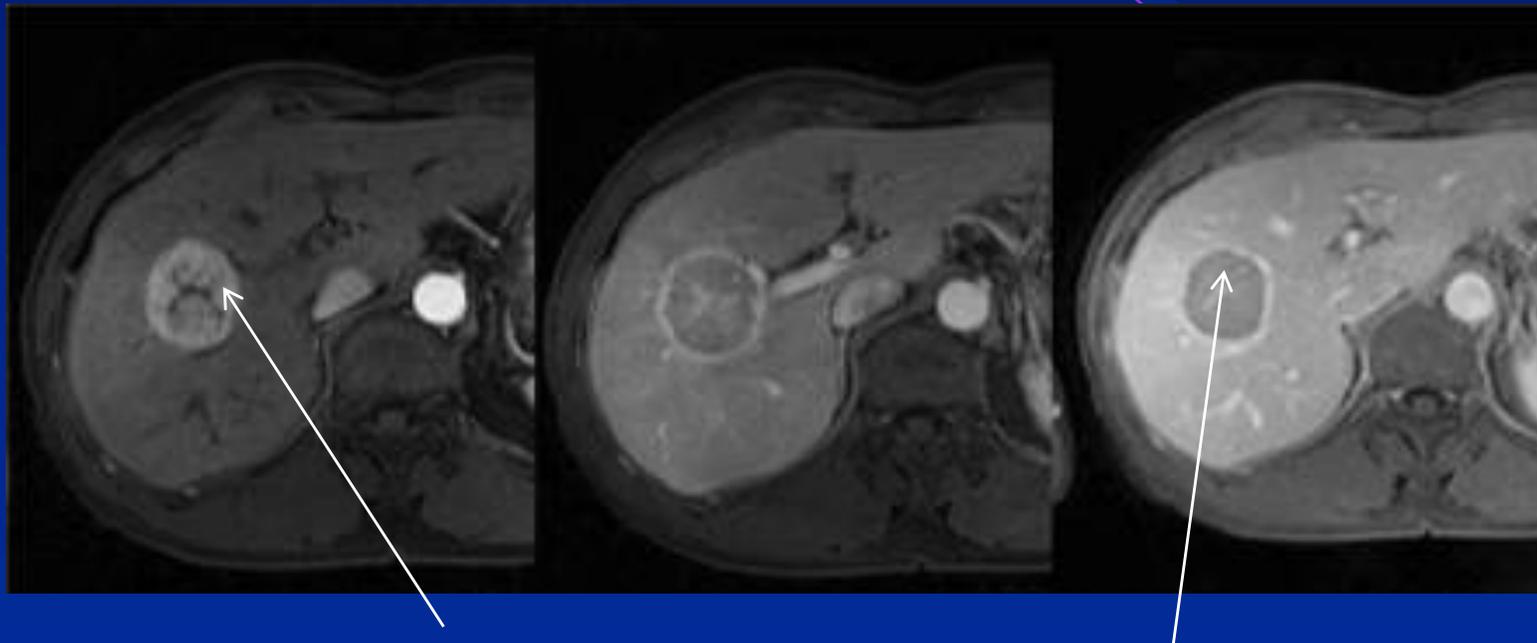
AFP + U/S every 6 – 12 mos.

Options for Treatment of Hepatocellular Carcinoma

- Resection
- Transplantation
- Ablative Techniques
 - Trans Arterial Chemoembolization (TACE)
 - Radiofrequency Ablation (RFA)
 - Trans Arterial Radioembolization - Y^{90} Intraarterial Brachytherapy (TARE)
 - Percutaneous Ethanol Injection
- Chemotherapy (Sorafenib)

Imaging Characteristics of HCC

54 yo AA male with 20 yr h/o HepC Cirrhosis, surveillance U/s showed mass. AFP = 200 , MRI



Arterial Phase Hypervascularity with Contrast
Washout during Portal Venous Phase

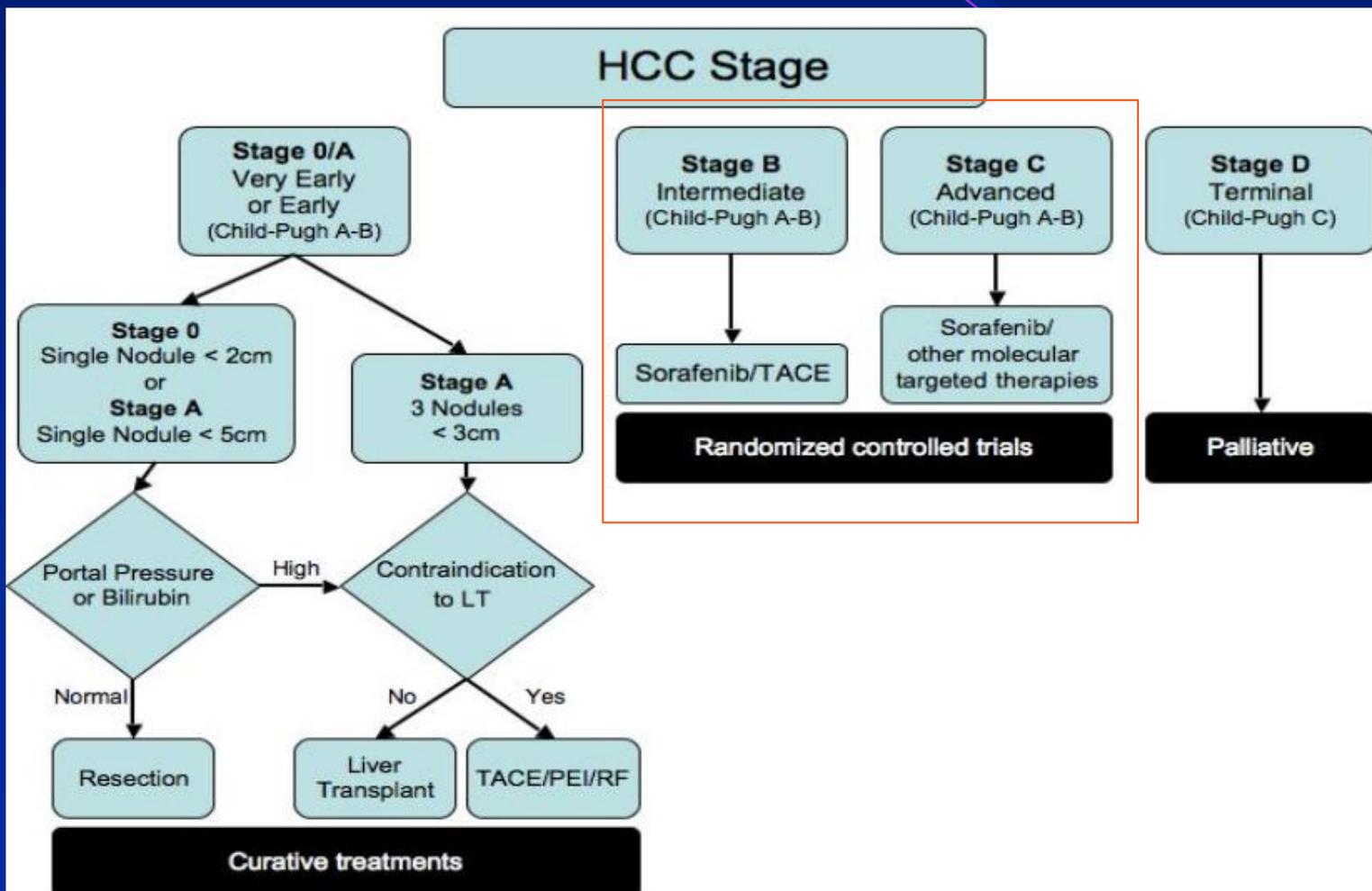
Note: Delayed Pseudocapsule Enhancement

Key Questions for Treatment Algorithm

- Cirrhosis or No Cirrhosis
 - Child's Class, MELD Score
- Tumor Size, Number and Location
- Presence of Portal HTN
- Extent of Resection Required (Liver remnant volume)
- Patient Age and Comorbidities
- Vascular Invasion
- Tumor Biology (AFP, AFP-L3, DCP)

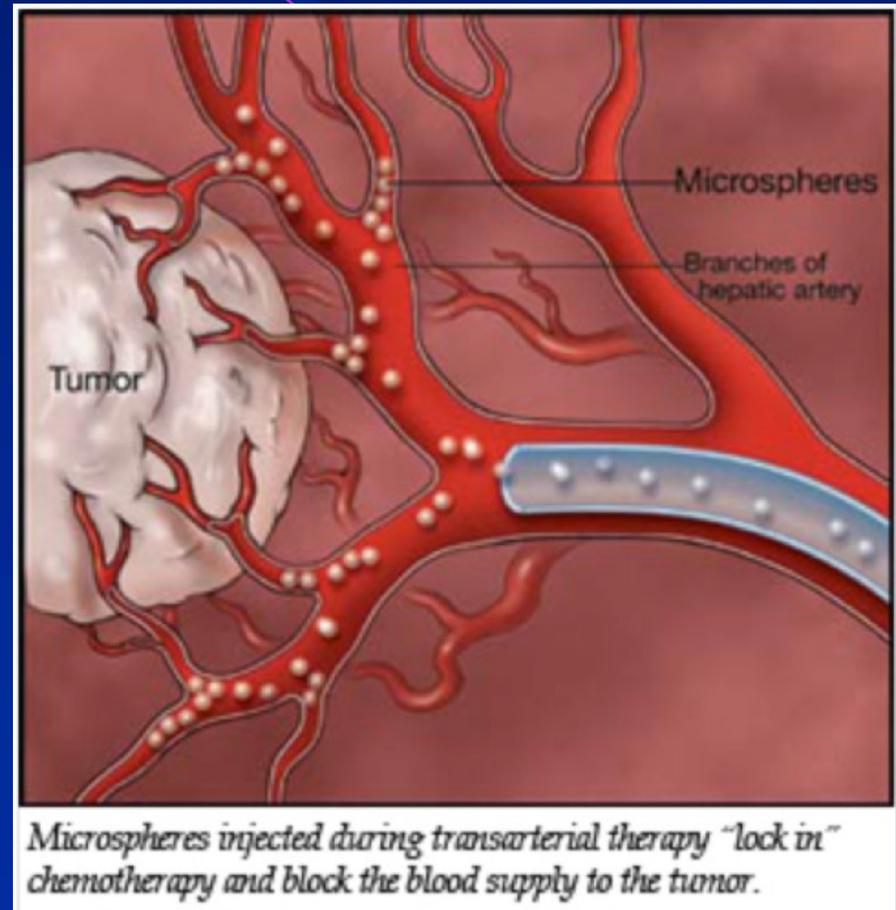
Barcelona Clinic Liver Cancer System

(Staging and Treatment Strategy based on Tumor, underlying Liver Disease and Performance Status)



Transarterial Chemoembolization (TACE)

- Most Commonly used Rx for Advanced Locoregional HCC, often used as Bridge to OLT
- Arterialized Blood Supply to HCC
- Embolization Leads to Tumor Hypoxia and Necrosis
- Prior to Embo., ChemoRx Agent Infused

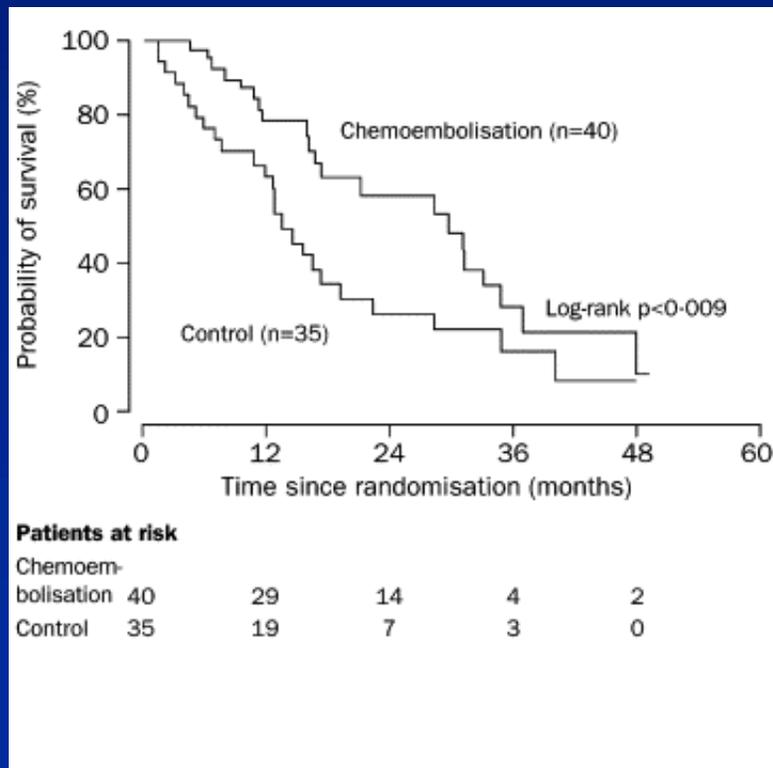


(TACE) Contraindications

- Decompensating Cirrhosis
- Massive Tumor with Replacement of both Lobes
- Portal Vein Occlusion or Hepatofugal Flow

TACE vs. Symptomatic Rx in Pts with Unresectable HCC: RCT

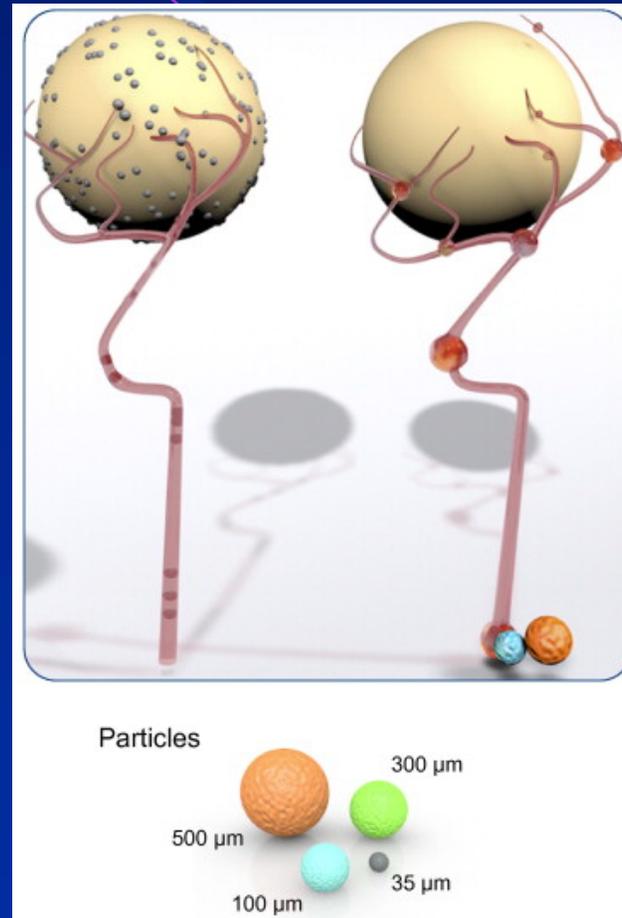
Llovet et al, Lancet 2002



- RCT: Childs A or B, OS (1 endpt)
- 112 Pts
- 1 yr OS 82% vs. 63%
- 2yr OS 63% vs. 27%

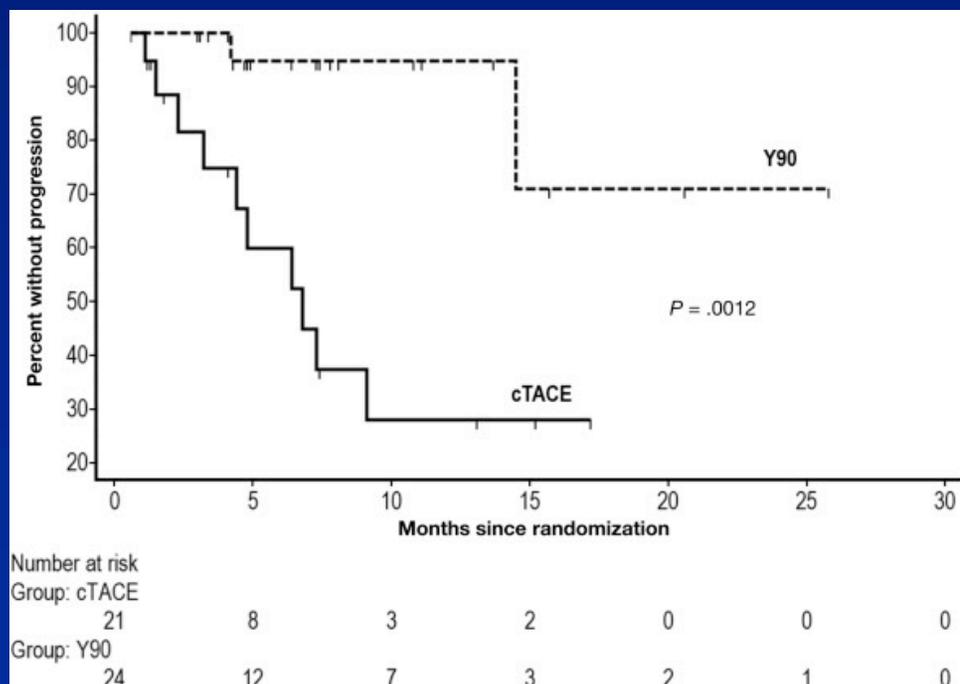
Trans Arterial Y⁹⁰ Radioembolization (TARE)

- Cather Directed Internal Radiation delivered by Y90 Microspheres
- 90% Tumor Necrosis if < 3cm, non –occlusive can be Used in PV Thrombosis
- PreRx Arteriogram to r/o arterioportal shunting to Decrease Unintended Radiation Targets



Y90 TARE Prolongs TTP vs. TACE in Pts with HCC: Premiere Trial

Salem et al, Gastro, 2016

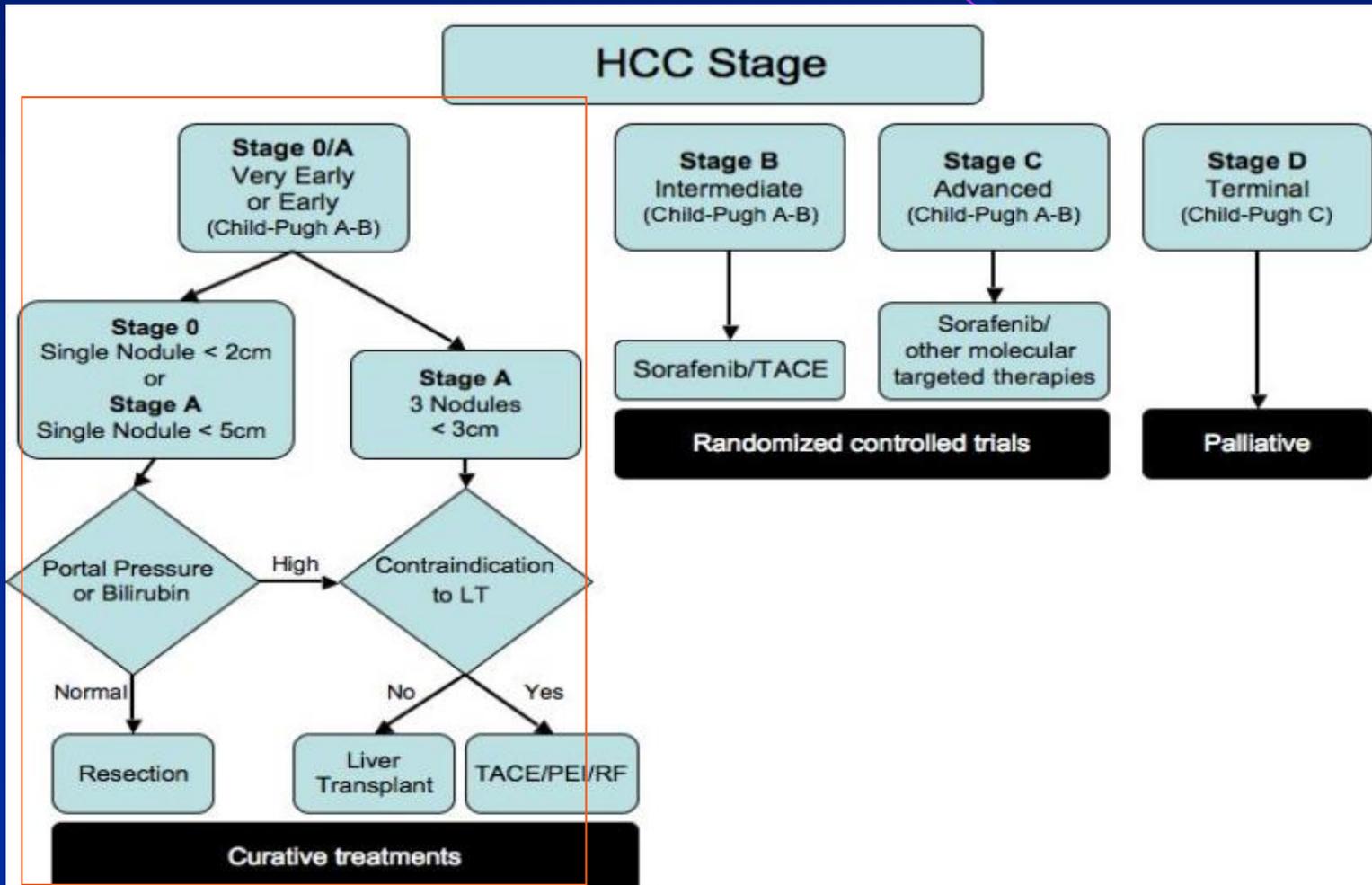


- BCLC stage A or B
- 45 pts RCT ;TARE or TACE
- Primary endpt. ; TTP
- ITT Analysis
- TARE TTP 26 mos. Vs TACE 6 mos ($P < .007$)
- OS censored to OLT ; No sig Diff

Trans Arterial Y⁹⁰ Radioembolization (TARE)

- TARE safe in Patients with PVT
- However, Excessive Radiation may Produce Toxic Side Effects to Liver and Non Target Organs
- Premiere Trial (P2 RCT)- Compares RE vs TACE with Unresectable HCC and Preserved hepatic Function ; TTP Favors TARE , OS similar

Barcelona Clinic Liver Cancer Staging and Treatment Strategy

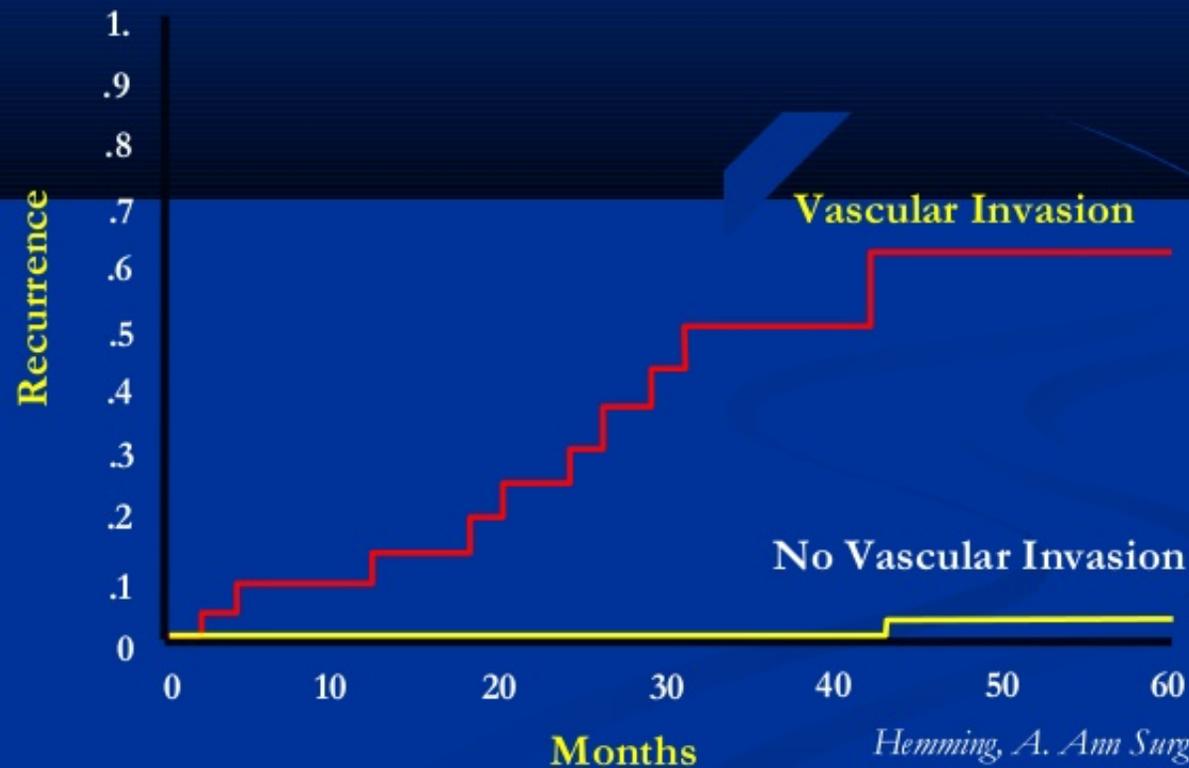


Liver Transplantation (LT)

- LT Most Durable outcome with Lowest Recurrence
- Organ Availability Remains a Challenge
- Transplant Benefit Pressure For Early Stage HCC with Child's A vs. non Malignant Persists

Size and Number are Surrogates for Vascular Invasion

HCC Recurrence after OLT



Henning, A. Ann Surg 2001

Liver Transplantation

Milan¹

- 1 nodule 2.0-5.0cm; 2-3 nodules all ≤ 3.0 cm
- No gross intrahepatic portal or hepatic vein involvement on imaging
- No lymph node or distant metastasis or extrahepatic portal or hepatic vein involvement

UCSF²

- 1 nodule ≤ 6.5 cm
- Up to 3 tumors, none ≥ 4.5 cm and sum of diameter ≤ 8 cm

Authors	N	Selection Criteria	Recurrence	Survival
Bismuth (1993) ³	60	Single <3 cm; 3 nodules <3 cm	11%	83% at 3 yrs
Mazzaferro (1996) ³	48	Single <5cm; 3 nodules <3 cm	8%	74% at 4 yrs
Llovet (1998) ³	79	Single <5 cm, multinodular	4%	74% at 5 yrs
Jonas (2001) ³	120	Single <5cm; 3 nodules<3 cm	17%	71% at 5 yrs
Yao (2007) ²	168	Single ≤ 6.5 cm, or 2-3 ≤ 4.5 cm, total tumor diameter ≤ 8 cm	9.1%*	82% at 5 yrs

*This represents 100 minus 5-year recurrence-free probability of 90.9%.

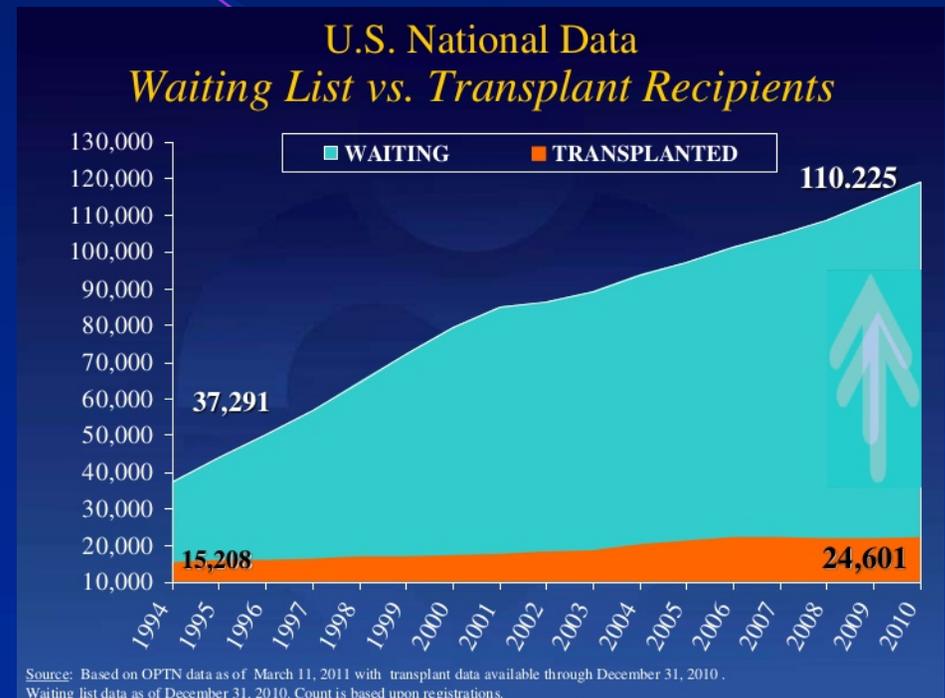
¹ Mazzaferro V., et al. *N Engl J Med.* 1996; 334:693-699

² Yao, et al. *Am J Transplant.* 2007; 7:2587-2596

³ Said A., Wells J. *Minerva Medica.* 2009; 100:51-68

Liver Transplantation Disadvantages

- HCC Avg. Waiting Time , 6 to 12 mos.
- Tumor Progression on Waiting List (Intent to Treat)
- Lifelong Immunosuppression



MELD Score - Allocation Priority

MELD SCORE

MODEL FOR END-STAGE LIVER DISEASE

Survival probability of a patient with end-stage liver disease is estimated based on the following variables.

- Serum bilirubin
- Serum Creatinine
- International Normalized ratio
- (etiology)

UTILITY:

1. To predict death within three months of TIPS
2. For prioritizing allocation of liver transplants instead of the older Child-Pugh Score

INSTITUTE OF GASTROENTEROLOGY AND LIVER SURGERY



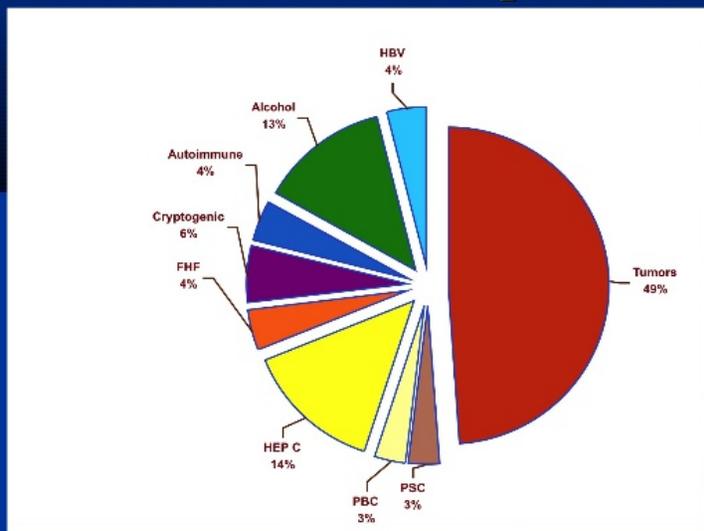
United Network for Organ Sharing
OPO Donation Service Areas



System of Prioritization Pts. 6 – 40, Region Mandatory
Share <15 or >35

Utility vs. Equity

Indications for Transplantation



NYUC Trans 2007

32

- Many Pts with HCC have Low MELD and thus Lack Priority for OLT
- 2002, MELD Elevator instituted, for eligible HCC (22) pts and additional 3 pts every 3 mos eligible on the list
- HCC pts dominated OLT with < wait list mortality and drop out, vs. sicker Non HCC pts

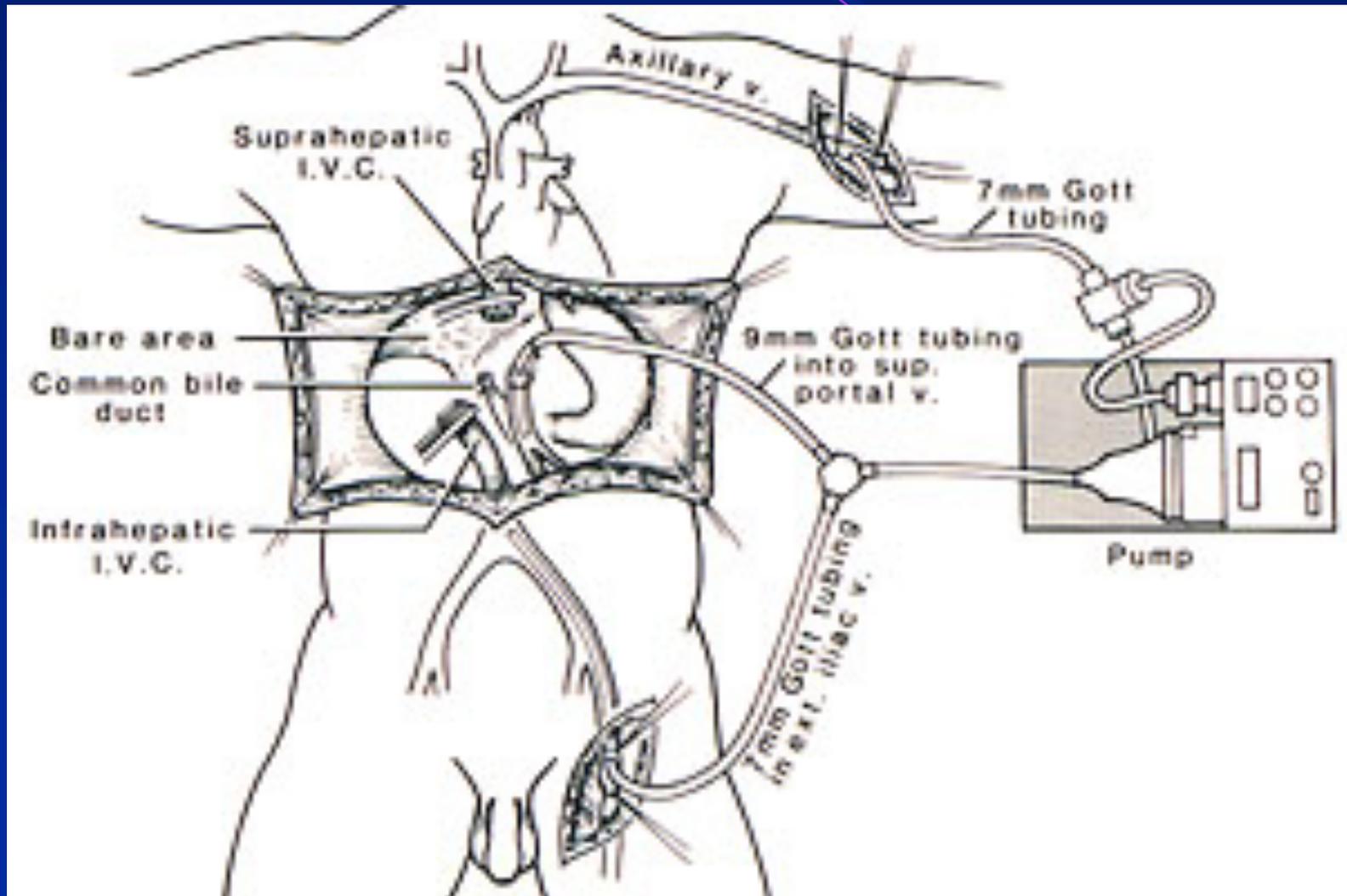
Liver Transplantation Prioritization

- 2015, HCC Delay Policy
- 6 mo delay after listing before assigning exceptional MELD pts (28), then MELD elevator
- Idea, Decrease HCC OLT rates in regions where Transplants occur < 28 points and Identify pts with Aggressive Tumor Biology
- MELD cap at 34 pts so would not Default to Mandatory Regional Share 35

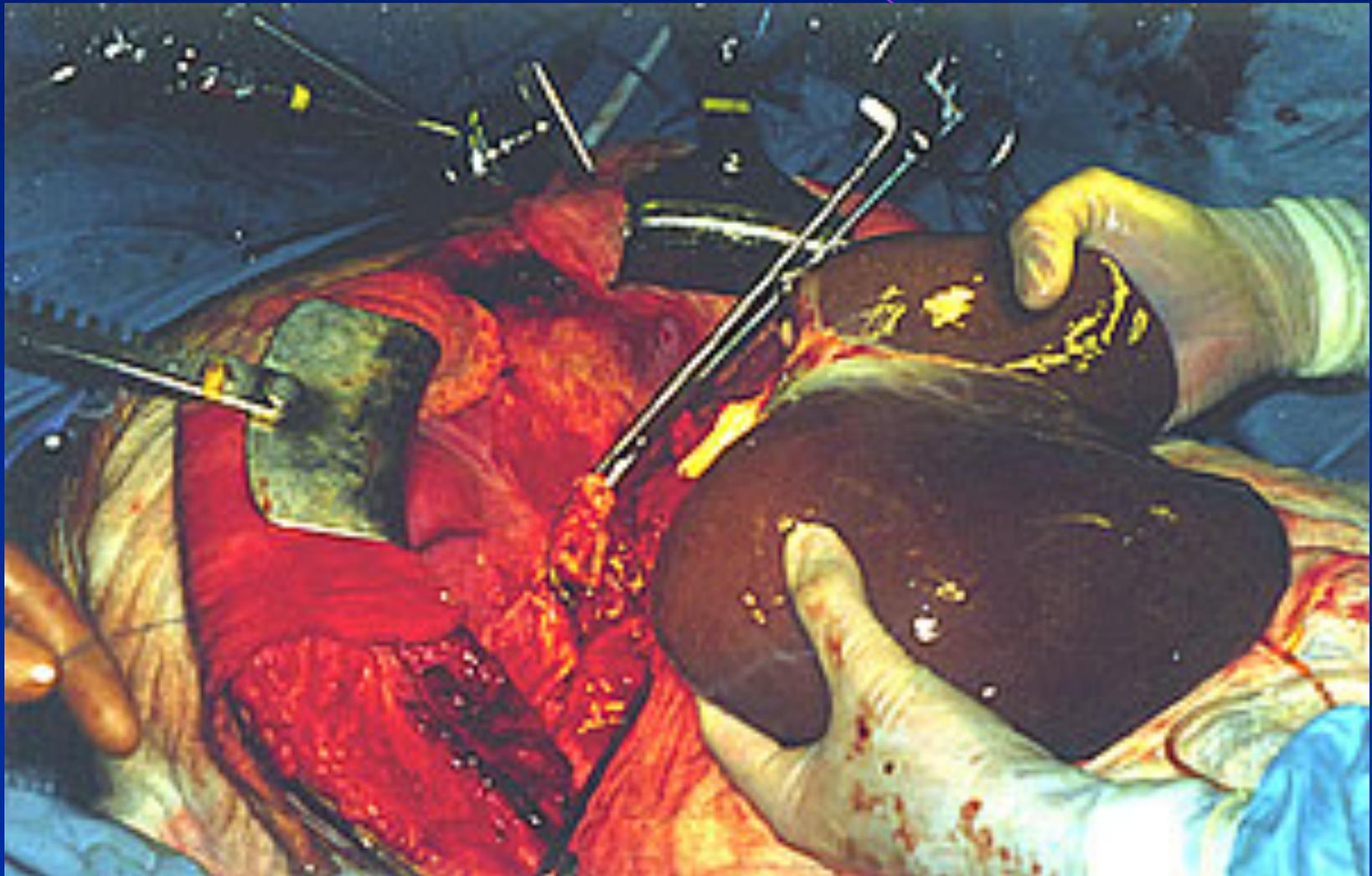
Liver Transplantation Prioritization Issues

- Assign same MELD for HCC, regardless of Natural MELD
- Natural MELD, Tumor Burden, AFP, and Transplant related survival benefit may be better Means to predict wait list dropout
- MELD elevator, length of time on list only determinant for Increase in Points (although eliminated for olt priority in non HCC pts)

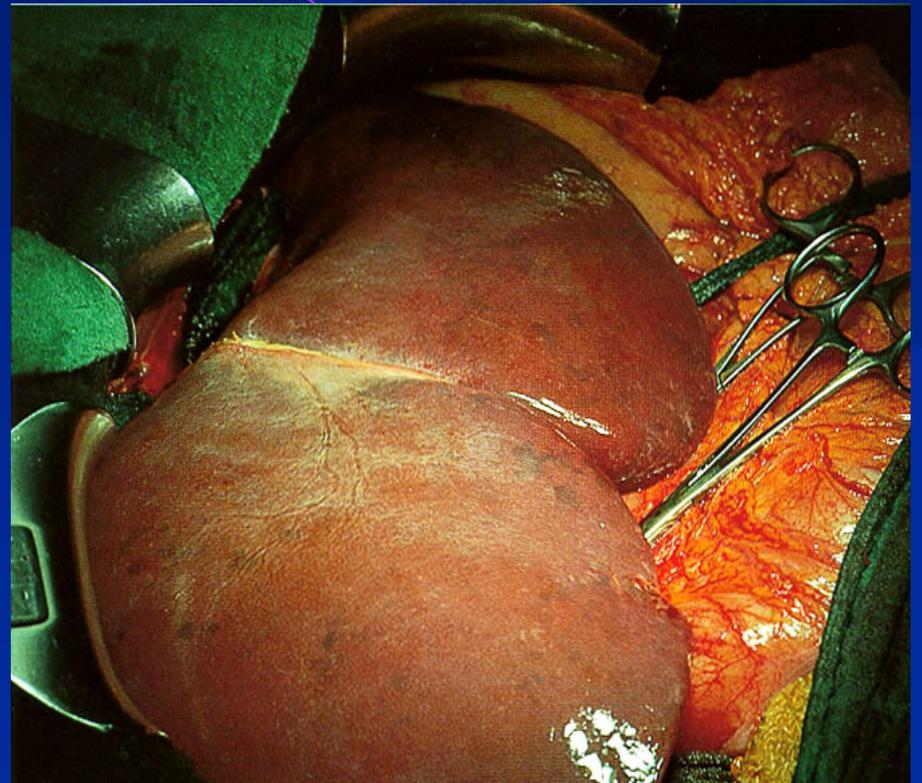
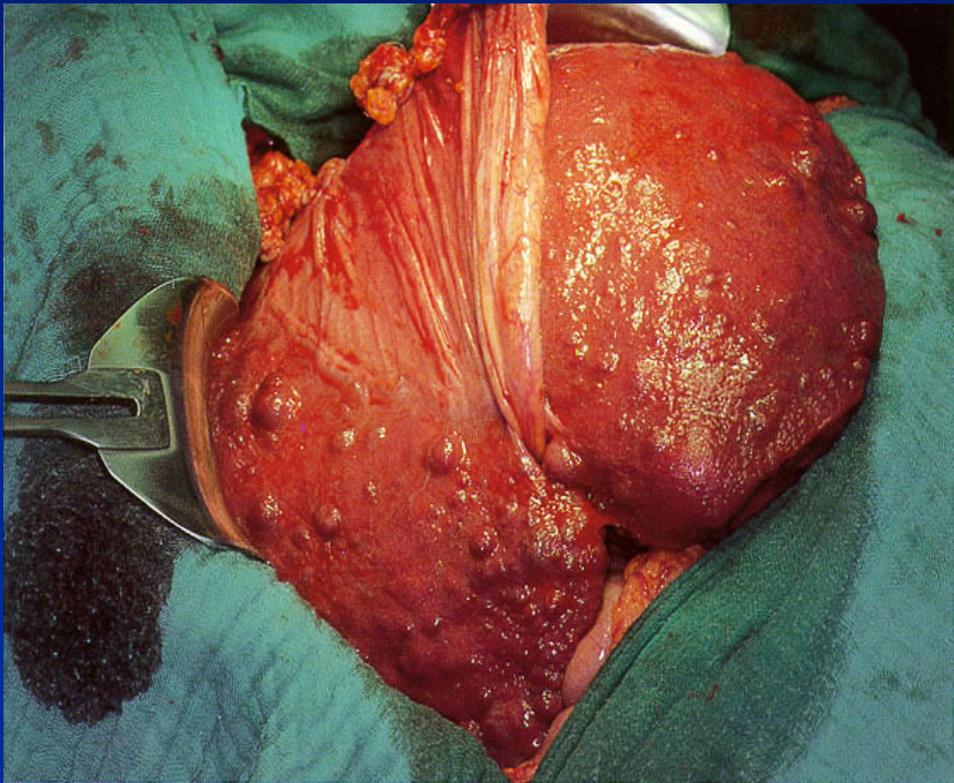
Venovenous Bypass



Implantation of the Liver

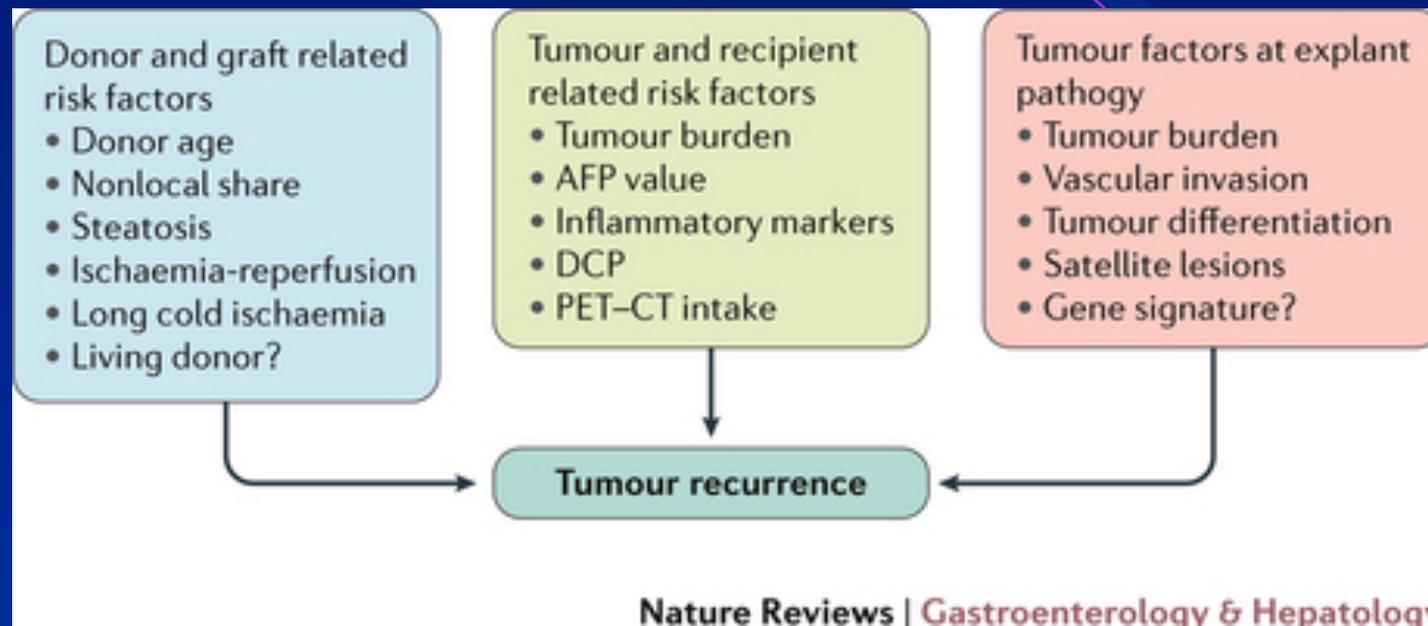


Implantation of the Graft



Before and After

Risk Of HCC Recurrence



Most Common Long-Term Complications of Immunosuppression

- Nephrotoxicity (including hyperkalemia and gout)
- Neurotoxicity (e.g. tremors)
- Obesity
- Hypertension
- Diabetes
- Hyperlipidemia
- Tumors related to immunosuppression
- Bone disease
- Cosmetic changes (e.g. hirsutism, gingival hyperplasia)
- Late rejection (chronic > acute)
- Infection susceptibility

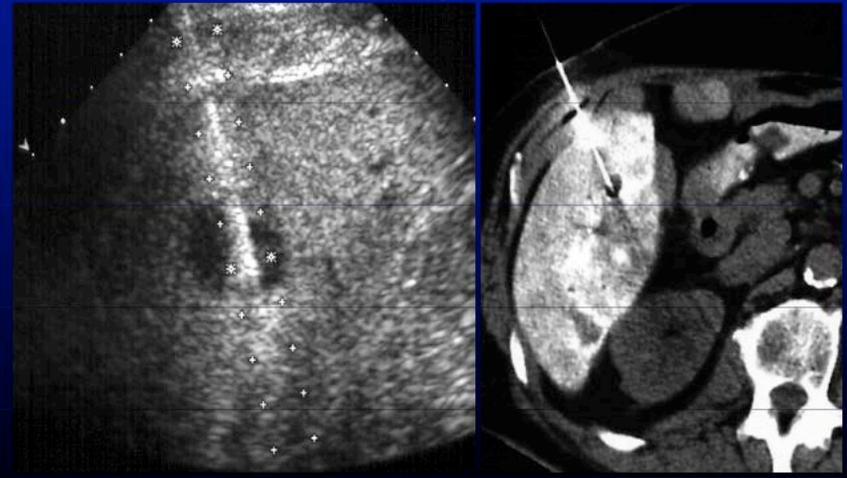
Radiofrequency Ablation

- At temperatures $> 50^{\circ}\text{C}$ > 3 minutes:
 - Intracellular protein denaturation
 - Melting lipid bilayers \Rightarrow cell death
- Gradual alternative current heating to 80-110 $^{\circ}\text{C}$
- Complete Necrosis Difficult for Tumors $> 3\text{cm}$
- Difficult to Reach Certain Segments esp. Percutaneous

RFA Technique



RF ablation: Technique



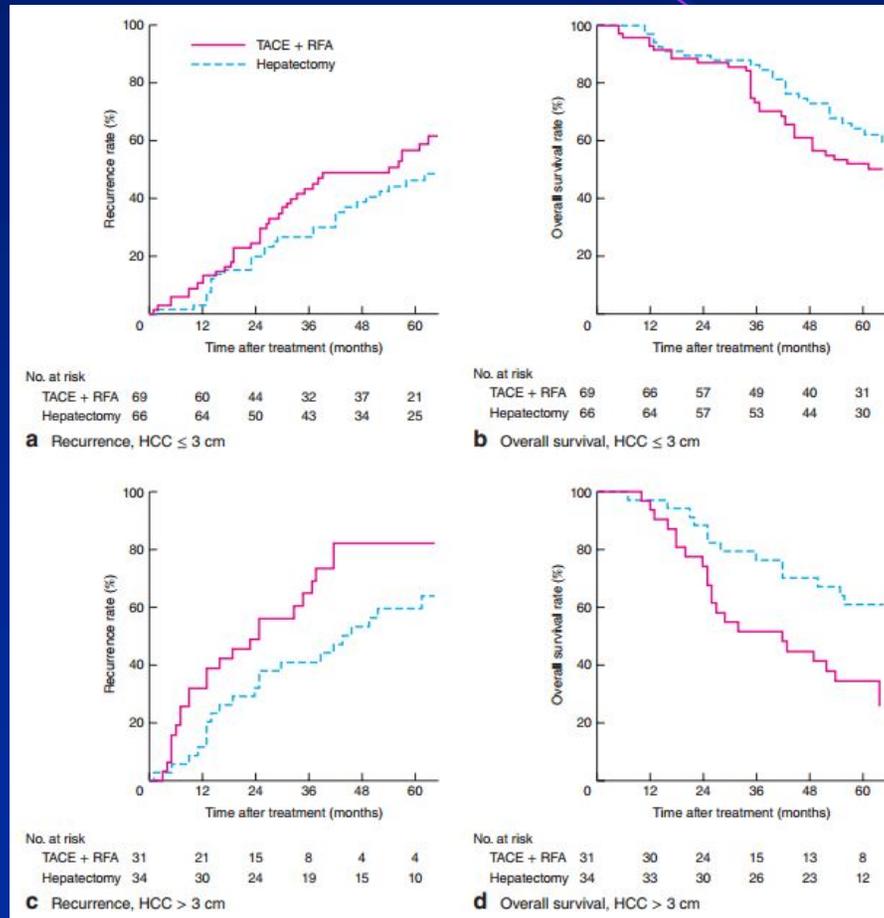
RCT of TACE+RFA vs. Resection for HCC within Milan Criteria

LIU et al, BJS, 2016

- RCT ; 1:1 200 pts
- Primary Endpt: OS, Secondary Endpt: DFS
- 1yr OS 97% vs 94%, 3yr 83.7% vs 67.2, 5 yr 61.9% vs 45.7% favoring Resection (P=.007)
- 1yr DFS 94% vs 83% 3yr 68.2 vs 44.9%, 5 yr 48.4 vs 35.5% favoring Resection (P=.026)

RCT of TACE+RFA vs. Resection for HCC within Milan Criteria

LIU et al, BJS, 2016



Greater Superiority >3cm of SR in OS and DFS

RCT of TACE+RFA vs. Resection for HCC within Milan Criteria

LIU et al, BJS, 2016

- Pts with HCC within Milan Criteria ,
Resection Provides better OS and DFS than
Sequential Rx with RFA and TACE
- Incidence of Complication (23 vs 11%)
Higher in resection Gp

Liver Resection Disadvantages

- Only 20% of Patients Eligible due to Multicentricity
- In Asia 40% of HCC in Non- Cirrhotics, only 5% in U.S.
- HCC Recurrence in Liver Remnant (10% /year cumulative), est. 50% @ 5 yrs
- Limited to Patients with Early HCC and Early Cirrhosis

Surgical Resection¹

- Surgical resection is best suited for HCC patients with a single HCC nodule, Child-Pugh A w/o portal hypertension (HVPG <10 mg Hg)
- Five year OS in selected pts 60-70%

	N	Tumor Criteria	Survival	Recurrence
Bruix	29	Single HCC nodule	70% at 5 years	38% had recurrence
Llovet	77	Child A, Single nodule <5 cm	85% at 1 year 51% at 5 years	34% died from tumor recurrence
Ishizawa	432	Child A, Single HCC	68% at 5 years	60% 5 year recurrence
		Child A, Multiple HCC	58% at 5 years	75% 5 year recurrence
		Child B, Single HCC	45% at 5 years	73% 5 year recurrence
		Child B, Multiple HCC	19% at 5 years	100% 5 year recurrence
Ng	784	Small HCC (<5 cm)	88% at 1 year, 58% at 5 years	77 month median DFS, 34% recurrence
		Large or multinodular HCC	74% at 1 year, 39% at 5 years	16 month median DFS, 52% recurrence
Pawlik	300	Larch HCC (>10 cm)	5 year survival 27%	Not stated

1. Said A and Wells J. *Minerva Medica*. 2009; 100:51-68.

Conclusions

- Transplantation Provides Most Durable Outcomes for Early HCC, but ITT Analysis ?No Survival Advantage and Organ Availability Remains Difficult
- Selected pts with Very Early or Early Stage Tumor with Normal Synthetic Function Candidates for Resection or Ablative Therapies
- Overall Survival/DFS with Current Data suggests advantage for Surgical Resection vs. Ablative Therapies
- HCC Commonly Presents with Advanced Tumor in Chronic Liver Disease, TACE or Radioembolization may Provide Benefit in this Setting

Future Considerations

- Cost Effective Life Year Analysis
- Adjuvant and Combined Therapy Trials
(Kinase Inhib, I/O Drugs)
- Impact of Effective Antiviral Treatment on
Recurrent HCC in Hep C, B