Educational Objectives

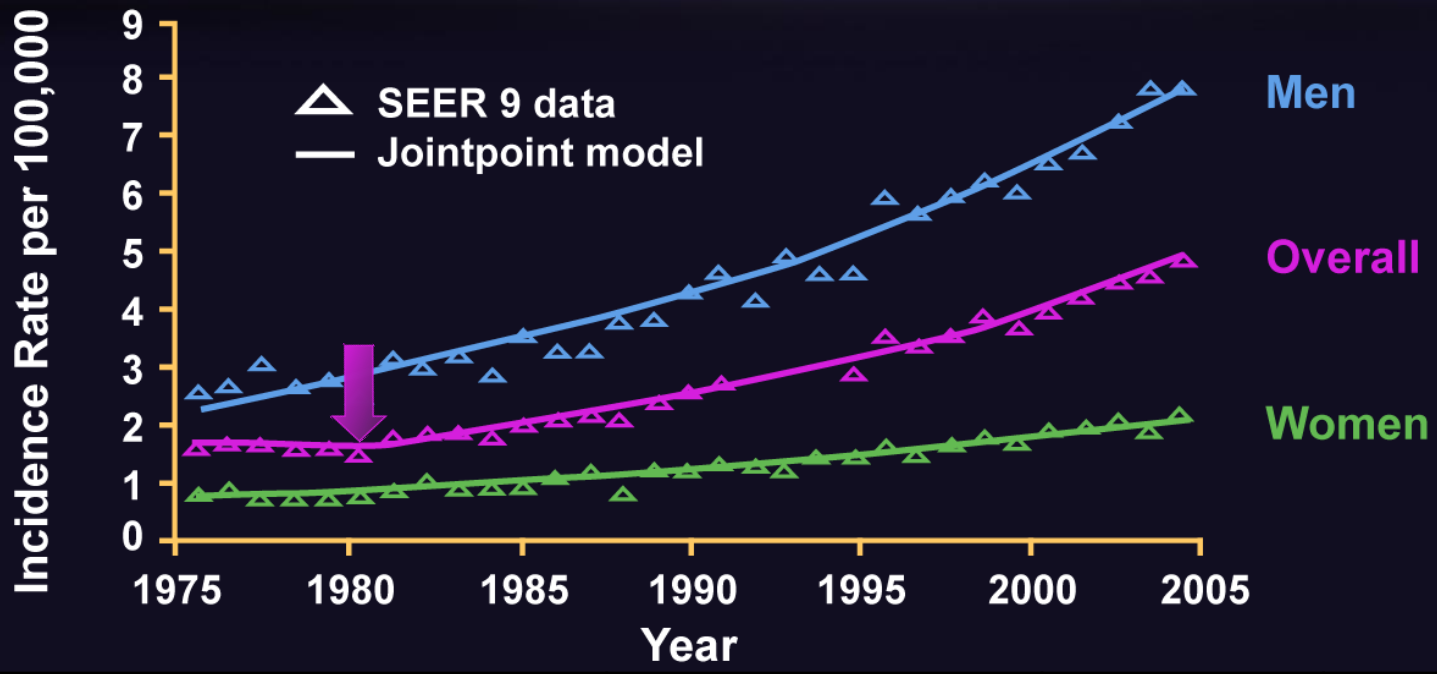
- Discuss the importance of screening and surveillance of HCC and the importance of early disease diagnosis
- Review the currently available treatment algorithms and the role of multiple disciplines in the management of HCC
- Contrast and compare current treatment options for HCC based on individual patient characteristics and stage of disease
- Discuss the most up to date diagnostic criteria for HCC

HCC: Epidemiology

- 6% of all malignancies world wide
- >600,000 cases per year
- 3rd leading cause of cancer related mortality
- US incidence has tripled over the last three decades
- Most rapidly increasing cancer in the US
  - 20,000 new cases expected annually
- 80%-90% of HCC cases occur in cirrhotic livers
- Leading cause of death in cirrhosis

International Agency for Cancer Research. Globocan 2002. McGlynn KA et al. Int J Cancer. 2001;94:290-296; McGlynn KA et al. Cancer Epidemiol Biomarkers Prev. 2006;15:1198-1203; El-Serag HB. Gastroenterology. 2004;127:S27-S34; Altekruse SF et al. J Clin Oncol. 2009;27:1485-1491

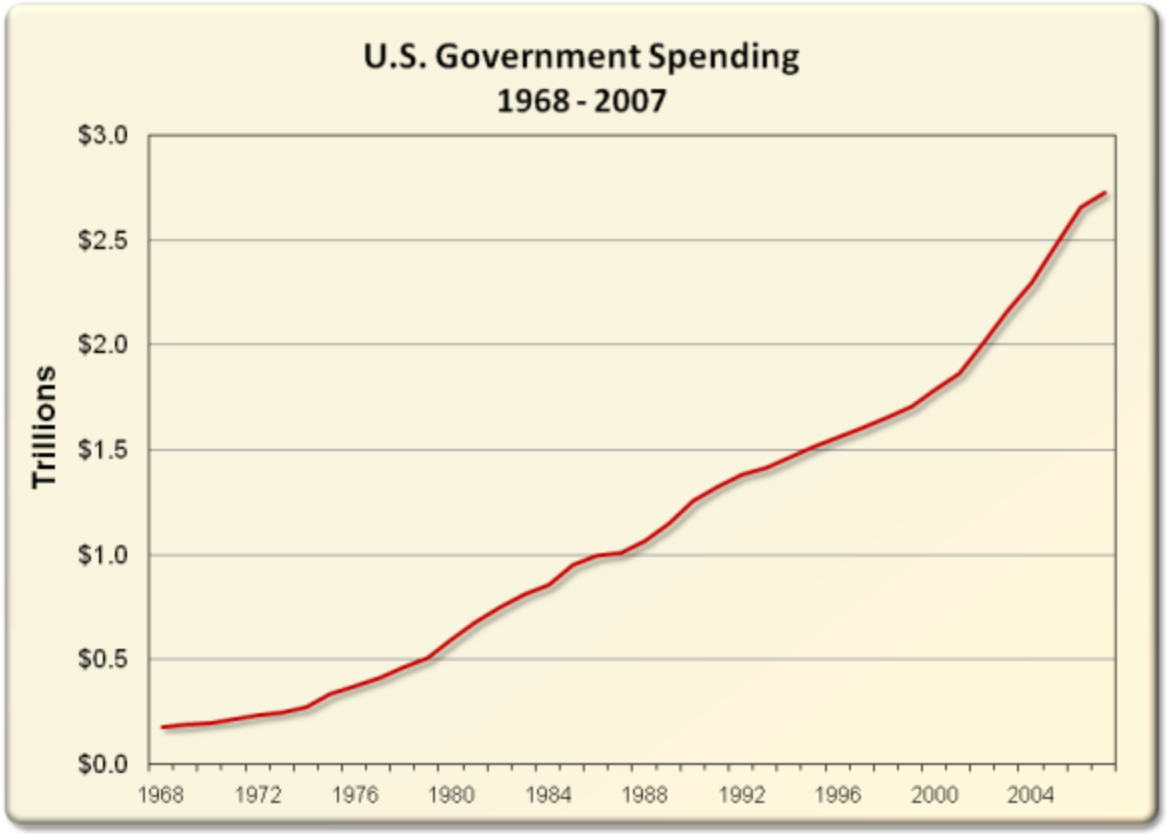
HCC Incidence in US Rising



Joinpoint			Incidence per 100,000		Annual Percent	
Sex	**Segments**	**Years**	**Start**	**End**	**Change (APC)**	**Comments**
Men	1	1975-2005	2.6	7.9	4.1	*P*≤0.05
Overall	2	1975-1980 1975-2005	1.6 1.5	1.5 4.9	-0.04 4.5	Joinpoint at arrow (1980) *P*≤0.05
Women	1	1980-2005	0.8	2.3	3.8	*P*≤0.05

SEER = Surveillance, Epidemiology and End Results

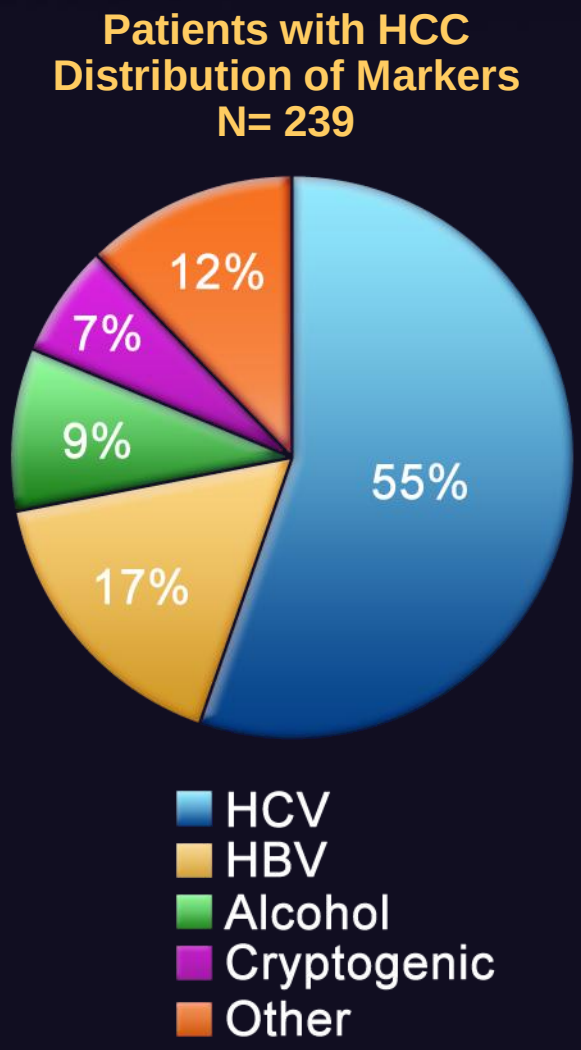
Altekruse SF et al. *J Clin Oncol*. 2009;27:1485-1491



Source: Congressional Budget Office
The Budget and Economic Outlook, January 2008, Table F-1

HCC Risk Factors

- **Major causes of HCC:**
  - Hepatitis B
  - Hepatitis C
  - Alcoholic liver disease
  - Nonalcoholic steatohepatitis
- **Less common causes:**
  - Hereditary hemochromatosis
  - α-1 antitrypsin deficiency
  - Autoimmune hepatitis
  - Some porphyrias
  - Toxic exposures



El-Serag HB, Rudolph kL. *Gastroetnerology* 2007;132:2557-2576.
Snowberger N, et al. Alim Pharm Ther 2007;26:1187.

5-Year Cumulative Incidence of HCC in Patients With Cirrhosis*

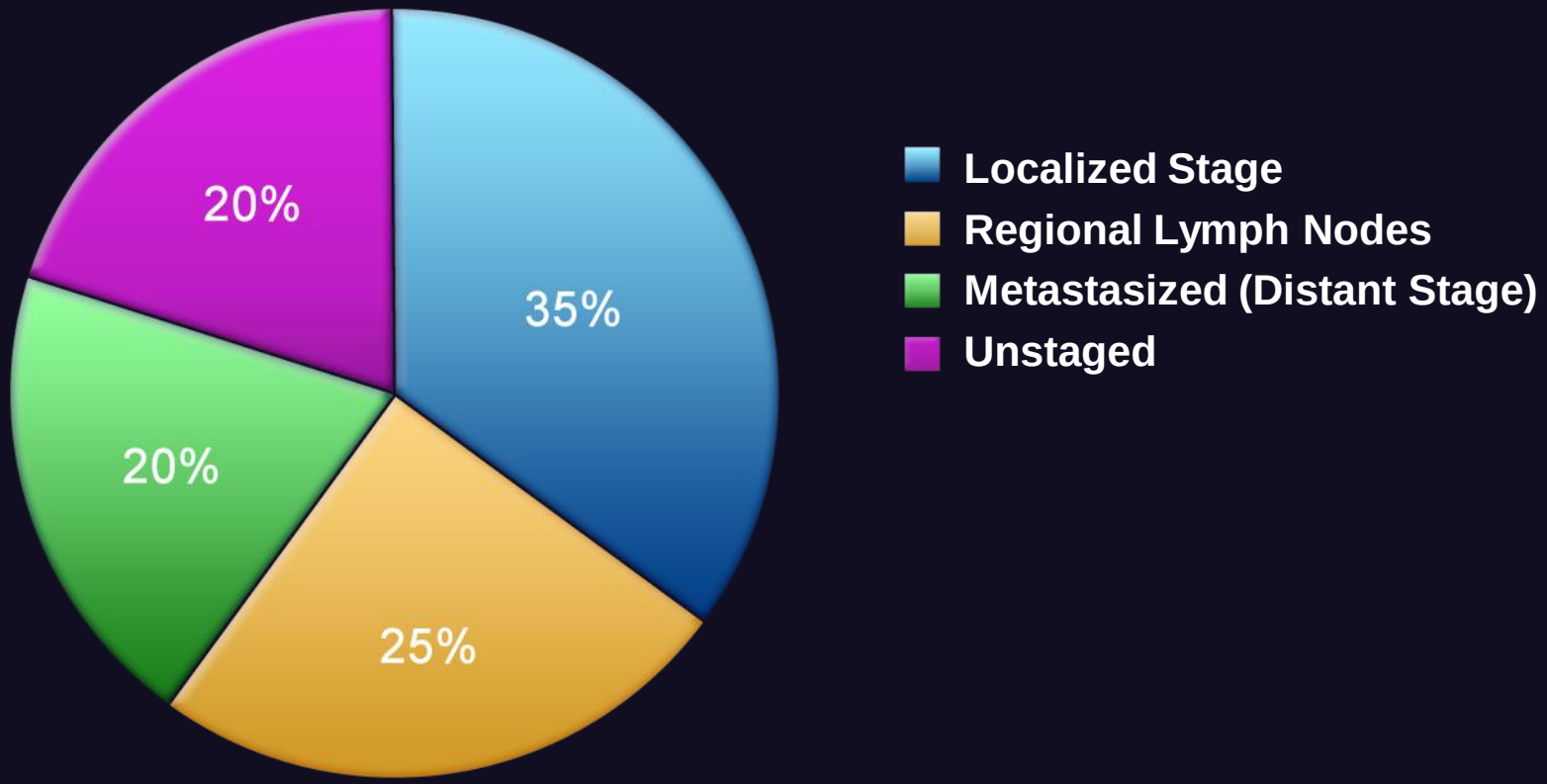
Etiology of Cirrhosis	5-Year Cumulative Incidence of HCC
Hepatitis C virus	
Japan	30%
Europe and US	17%
Hepatitis B virus	
Taiwan and Singapore	15%
Europe	10%
Hereditary hematochromatosis	21%
Alcoholic cirrhosis†	8%
Primary biliary cirrhosis†	4%

* Retrospective analysis of combined data from published studies.

† In the absence of HCV and HBV viral markers.

Fattovich G, et al. *Gastroenterology.* 2004;127:S35-S50.

Primary Liver Cancer
Stage Distribution at Diagnosis



From http://seer.cancer.gov/statfacts/html/livibd.html. Accessed 04/15/10.

Death Rates by Race for Cancer of the Liver and Intrahepatic Bile Duct

Overall age-adjusted death rate: 5.0 per 100,000

Race/Ethnicity	Male (per 100,000)	Female (per 100,000)
All races	7.3	3.1
White	6.7	2.9
Black	10.3	3.9
Asian/Pacific Islander	15.2	6.6
American Indian/Alaska Native	10.6	6.6
Hispanic	11.1	5.1

From http://seer.cancer.gov/statfacts/html/livibd.html. Accessed 04/15/10.

Poor Prognosis for patients with Advanced HCC

- Usually a slow-growing tumor with a long latency[1]
  - Usually diagnosed at advanced stage
- Limited medical therapies[1]
  - Treatments include surgical resection, liver transplantation, local ablation
  - Systemic therapy/chemotherapy
  - Generally refractory to available chemotherapeutic agents
- Poor 5-year survival: 3 to 22% depending on the stage at diagnosis[2]

5-year survival rates by stage of diagnosis, 1996-2001

	All Stages	Local	Regional	Distant
Liver Cancer (%)	10.5	21.9	7.2	3.3

1 Thomas MB, Zhu AX. *J Clin Oncol*. 2005;23:2892-2899.
2. *Cancer Facts and Figures 2007*. American Cancer Society.

AASLD 2010 Guidelines: Groups for Whom HCC Surveillance is Recommended

Population Group	Incidence of HCC
Asian male hepatitis B carriers >age 40	0.4 - 0.6%/yr
Asian female hepatitis B carriers >age 50	0.3 - 0.6%/yr
Hepatitis B carrier with family history of HCC	Incidence higher than without family history
African/North American Blacks with hepatitis B	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	3 - 8%/yr
Hepatitis C cirrhosis	3 – 5%/yr
Stage 4 primary biliary cirrhosis	3 – 5%/yr
Genetic hemachromatosis and cirrhosis	Unknown, but probably >1.5%/yr
Alpha 1-antitrypsin deficiency and cirrhosis	Unknown, but probably >1.5%/yr
Other cirrhosis	Unknown

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 Guidelines: Groups in Whom Risk of HCC is Increased, but Surveillance Benefit Uncertain

Population Group	Incidence of HCC
Hepatitis B carriers < age 40 (males) or < age 50 (females)	<0.2%/yr
Hepatitis C and stage 3 fibrosis	<1.5%/yr
Non-cirrhotic NAFLD	<1.5%/yr

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

Targeted Surveillance for HCC

Non-HBV Cirrhosis

- **Hepatitis C**
- **Alcoholic cirrhosis**
- **Hemochromatosis**
- **Other**
  - Primary biliary cirrhosis
  - α-1 antitrypsin deficiency
  - Autoimmune hepatitis
  - NASH

HBV / Carriers

- **Family history of HCC**
- **All cirrhotic HBV carriers**
- **Africans/NA blacks**
- **Asian males ≥ age 40**
- **Asian females ≥ age 50**

Surveillance tests: Ultrasound at 6 month intervals, AFP is not adequate alone

More frequent interval not needed for pts at higher risk

Modified from Bruix J, Sherman M. *Hepatology* 2005;42:1208-1236.

Targeted Surveillance for HCC

Special population: patients on transplant list

Should continue to have surveillance as these pts receive increased priority for transplantation and failure to test may mean that HCC progresses beyond listing criteria

Modified from Bruix J, Sherman M. *Hepatology* 2005;42:1208-1236.

What's the difference between screening and surveillance?

Screening:

Diagnostic testing in patients at risk for HCC, but in whom there is no *a priori* reason to suspect that HCC is present.

Surveillance:

The repeated application of screening tests.

Bruix J, Sherman M. Hepatology 2005;421208-1236.

AASLD 2010 Guidelines: HCC Surveillance Recommendations

- Patients at high risk for developing HCC should be entered into surveillance programs
- Surveillance for HCC should be performed using ultrasonography
- Patients should be screened at 6 month intervals
- The surveillance interval does not need to be shortened for patients at higher risk of HCC

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

HCC Surveillance by CT Scan

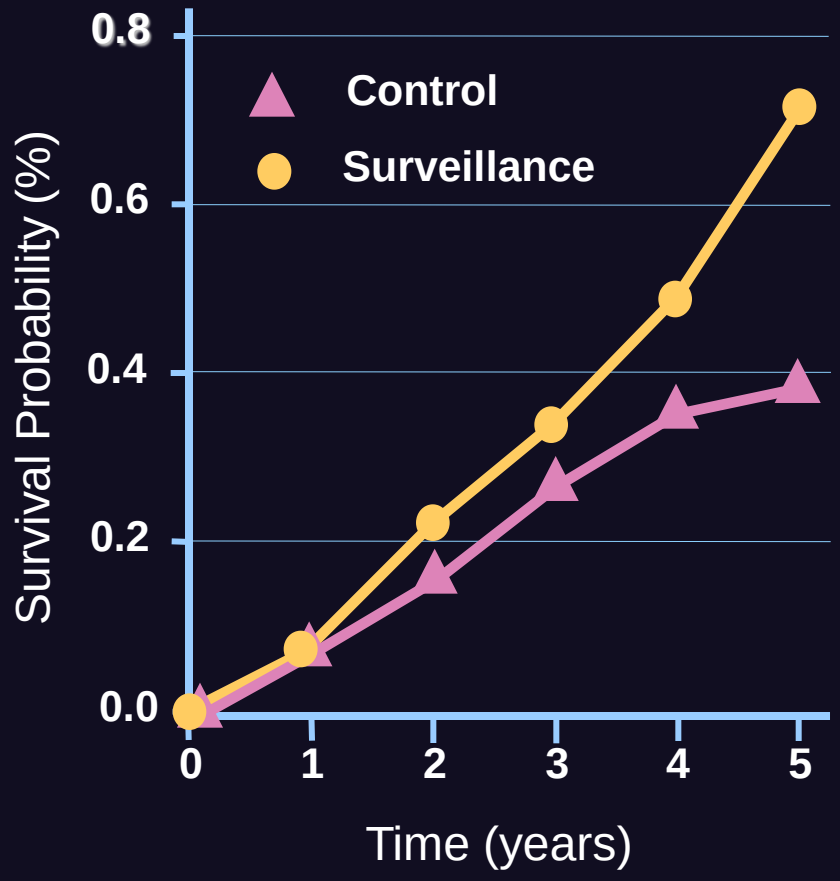
- No evidence to support the use of CT scanning for routine HCC surveillance
  - PPV and NPV unknown
  - Accurate use of CT requires 4-phase contrast CT
    - Radiation exposure is significant
  - In the absence of contrast CT, false-positive rate very high
    - Cannot distinguish small HCC from dysplastic nodules or arterialized cirrhotic nodules
    - Flow abnormalities create diagnostic difficulty

HCC Surveillance Tests: Performance Characteristics

Test	Source	Sensitivity	Specificity
AFP >20	Lin	21-80%	60-98%
DGCP >60	Ishii	41%	91%
AFP >10 + DGCP >80	Ishii	66%	85%
Ultrasound	Bruix & Sherman	65-80%	90%
US + AFP	Lin	55-95%	70-90%
CT (contrast enhanced)	Collier & Sherman	68% (>3 cm)	81% (>3 cm)
MRI	Collier & Sherman	81% (<2 cm) 64% (<1 cm)	
Helical CT	Collier & Sherman	87% (<1 cm)	

Surveillance for HCC Improves Mortality: A Randomized Controlled Trial

Survival rate higher in surveillance vs control group (*P*<.01)



Zhang BH, et al. *J Cancer Res Clin Oncol* 2004

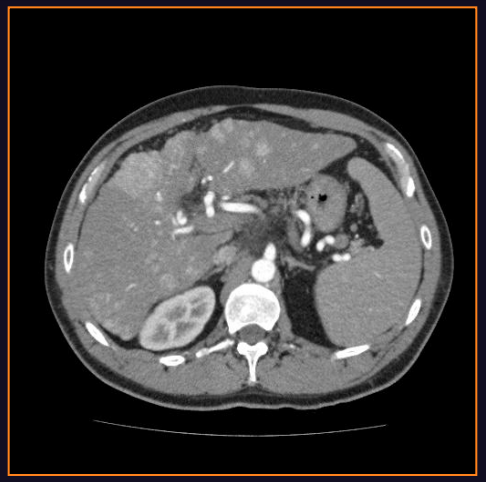
Effect of Surveillance on Outcomes

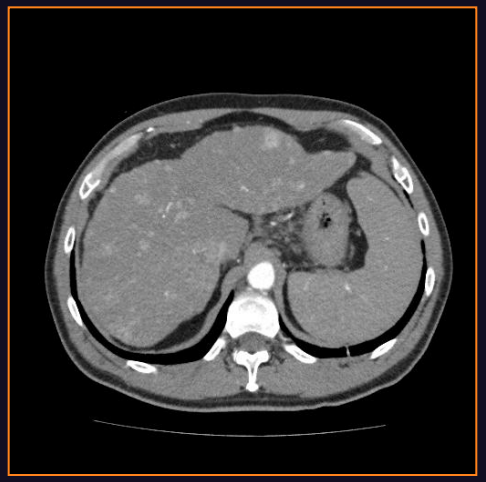
- Retrospective analysis of patients with cirrhosis and HCC (N = 269)
  - Standard-of-care surveillance (n = 172)
    - Ultrasound or other abdominal imaging ≥ 1 time/year
  - Substandard surveillance (n = 48)
    - Lack of abdominal imaging within 1 year of cancer diagnosis
  - Absence of surveillance (n = 59)

Outcomes, %	Standard-of-Care Surveillance (n = 172)	Substandard Surveillance (n = 48)	Absence of Surveillance (n = 59)	*P* Value
HCC diagnosis at stages 1/2	69	35	18	< .001
Liver transplantation	32	13	7	< .05
Mean 3-year survival from cancer diagnosis	40	27	13	< .005

Stravitz RT, et al. Am J Med. 2008;121:119-126.

Case #1:





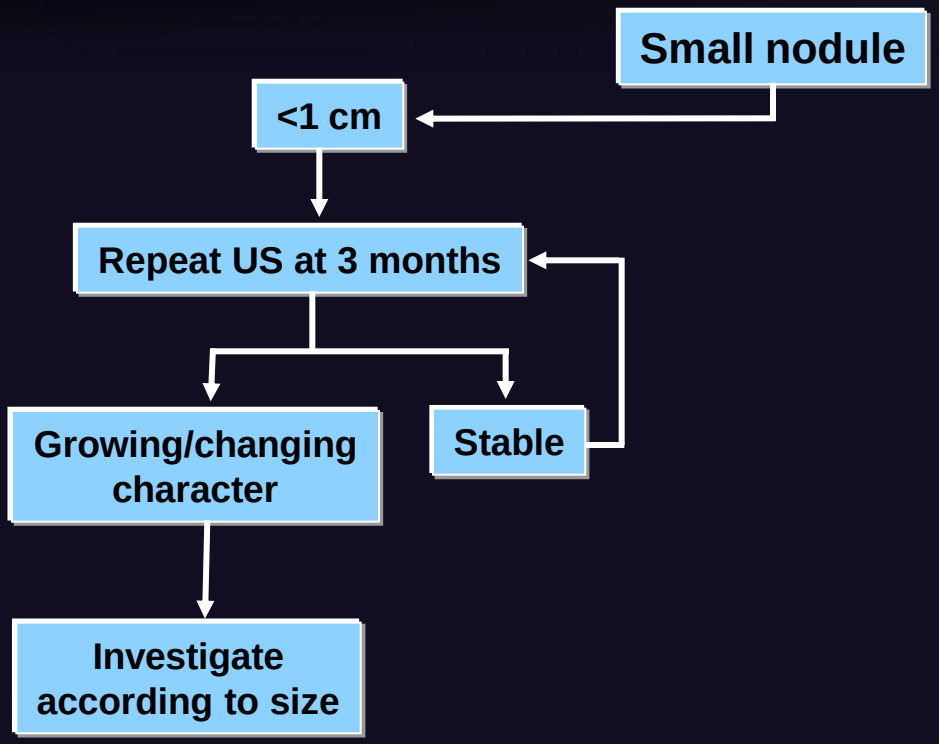
- Patient evaluated by the Multi Disciplinary Team
- CT scan
  - Innumerable bilobar arterial enhancing lesions consistent with diffuse HCC
  - Invasion of the posterior branch of the right portal vein
  - Findings of cirrhosis without ascites
- Extensive bilobar disease with macroscopic vascular invasion (BCLC stage C)
- Further testing initiated
  - EGD small/grade 1 esophageal varices
- Treatment Options?

What is the best treatment option for this patient?

1. Liver Transplant
2. Transarterial Chemoembolization or Radioembolization (TACE, TARE)
3. Liver Resection
4. Systemic Therapy (Sorafenib)
5. Ablative Therapy (RFA, PEI)

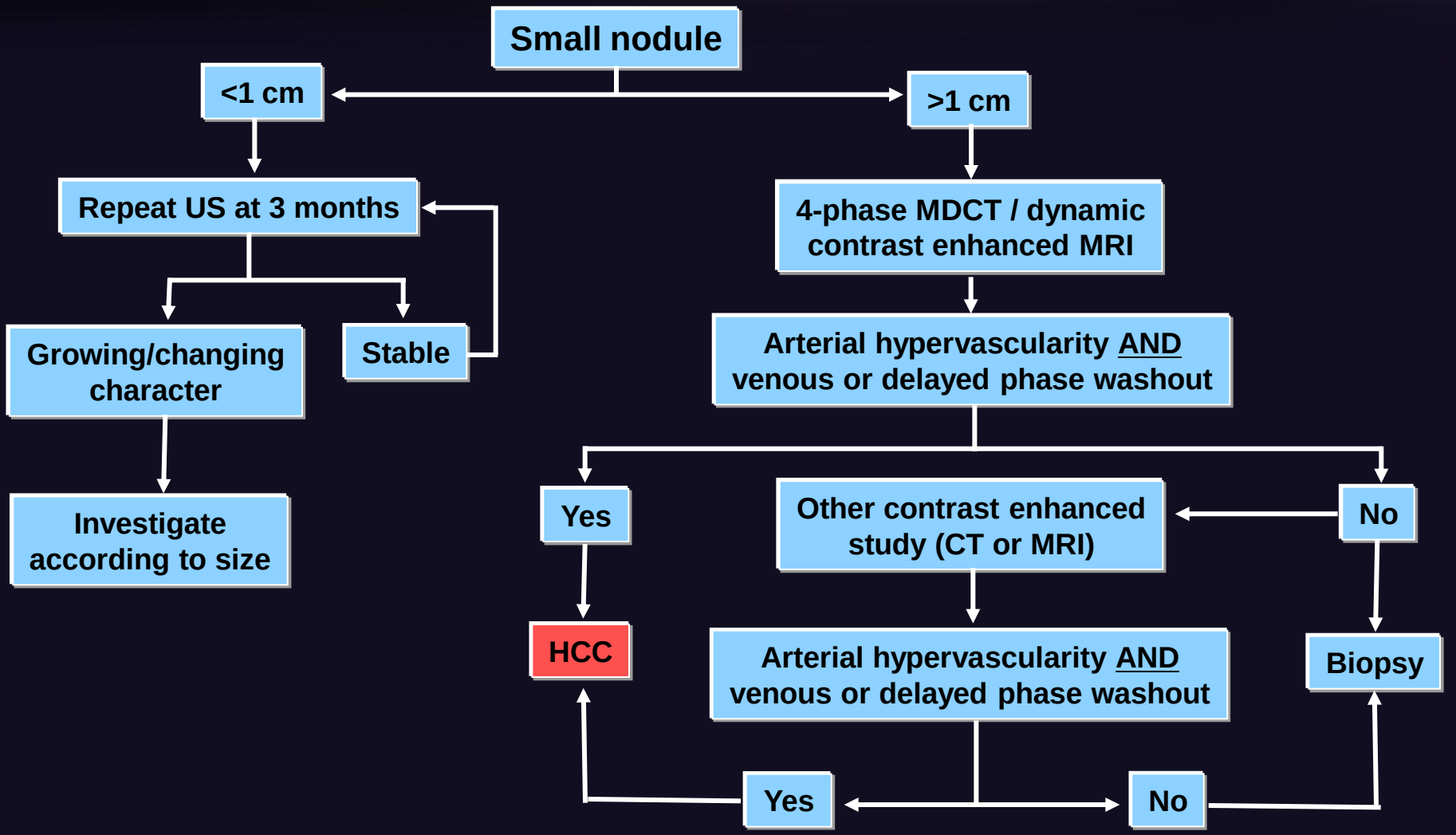
HCC Diagnostic Criteria

AASLD 2010 Guidelines: Algorithm for Investigation of Small Nodules Found on Screening in Patients at Risk for HCC



Adapted from Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 Guidelines: Algorithm for Investigation of Small Nodules Found on Screening in Patients at Risk for HCC

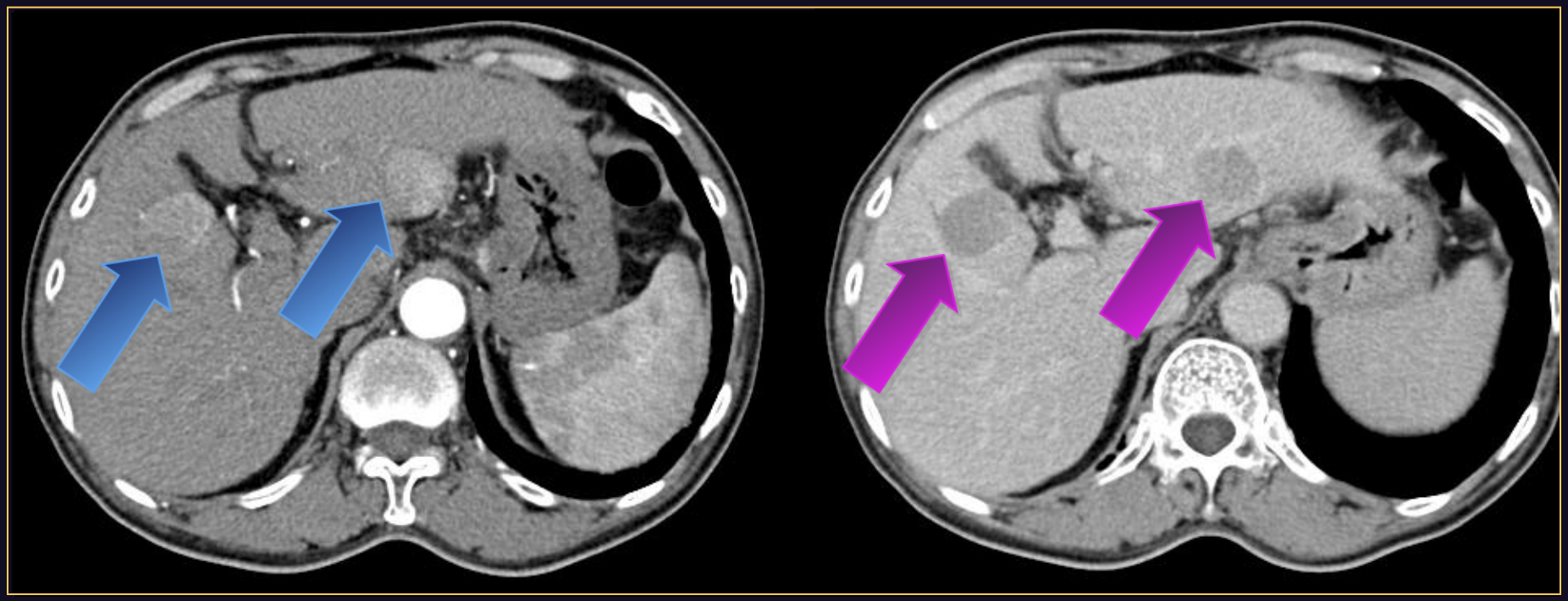


Adapted from Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

CT SCAN of Multifocal HCC

Arterial phase
(Enhancement)

Venous phase
(Washout)



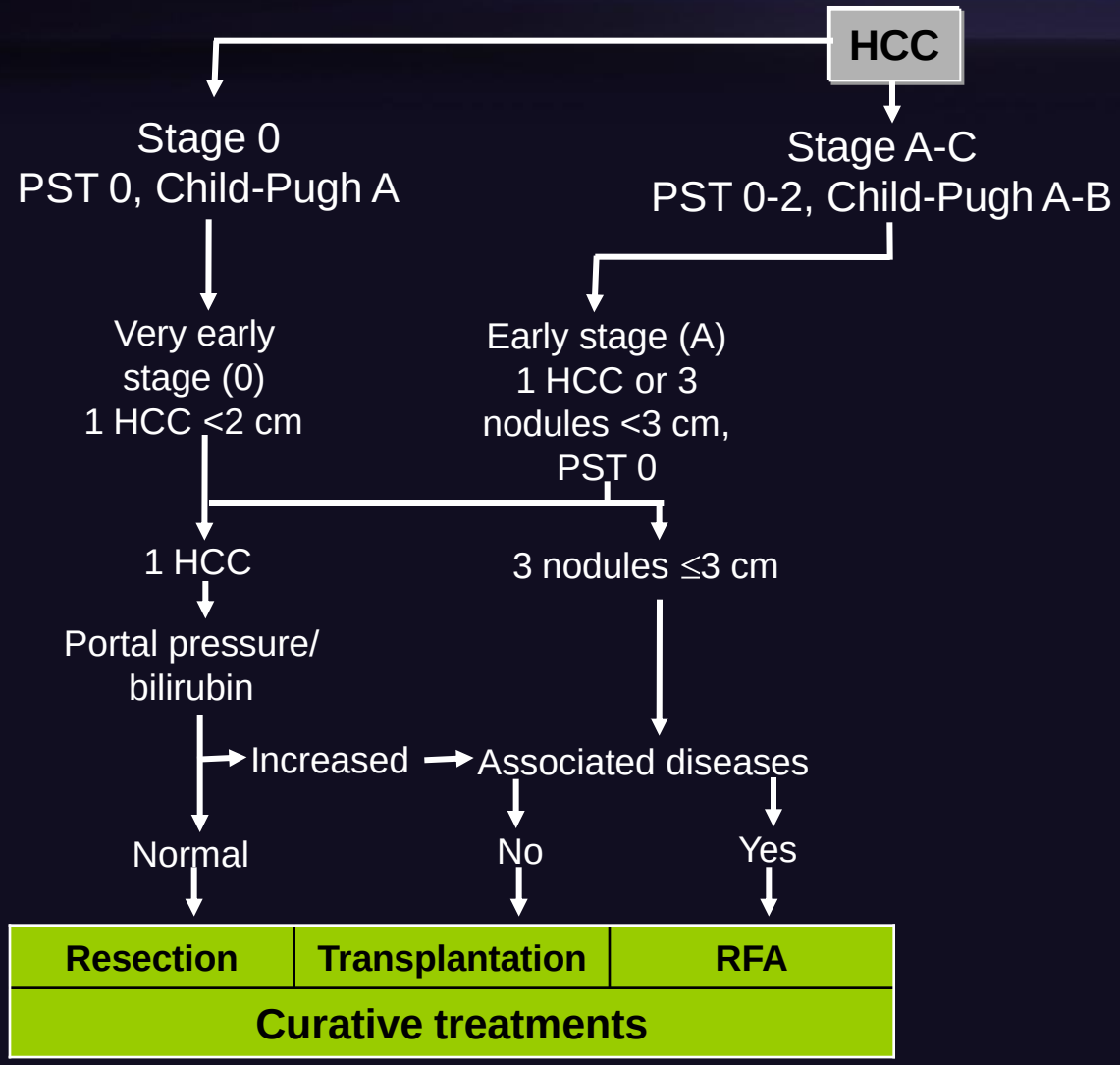
Cabrera R, Nelson DR. *Aliment Pharmacol Ther*. 2010 Feb 15;31(4):461-76.

AASLD 2010 HCC Guidelines: The BCLC Staging System and Treatment Allocation

- To best assess the prognosis of HCC patients it is recommended that the staging system take into account:
  - Tumor stage
  - Liver function
  - Physical status
- The impact of treatment should be considered when estimating life expectancy
- Currently, the BCLC (Barcelona Clinic Liver Cancer) system is the only staging system that accomplishes these aims

Adapted from Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: The BCLC Staging System and Treatment Allocation



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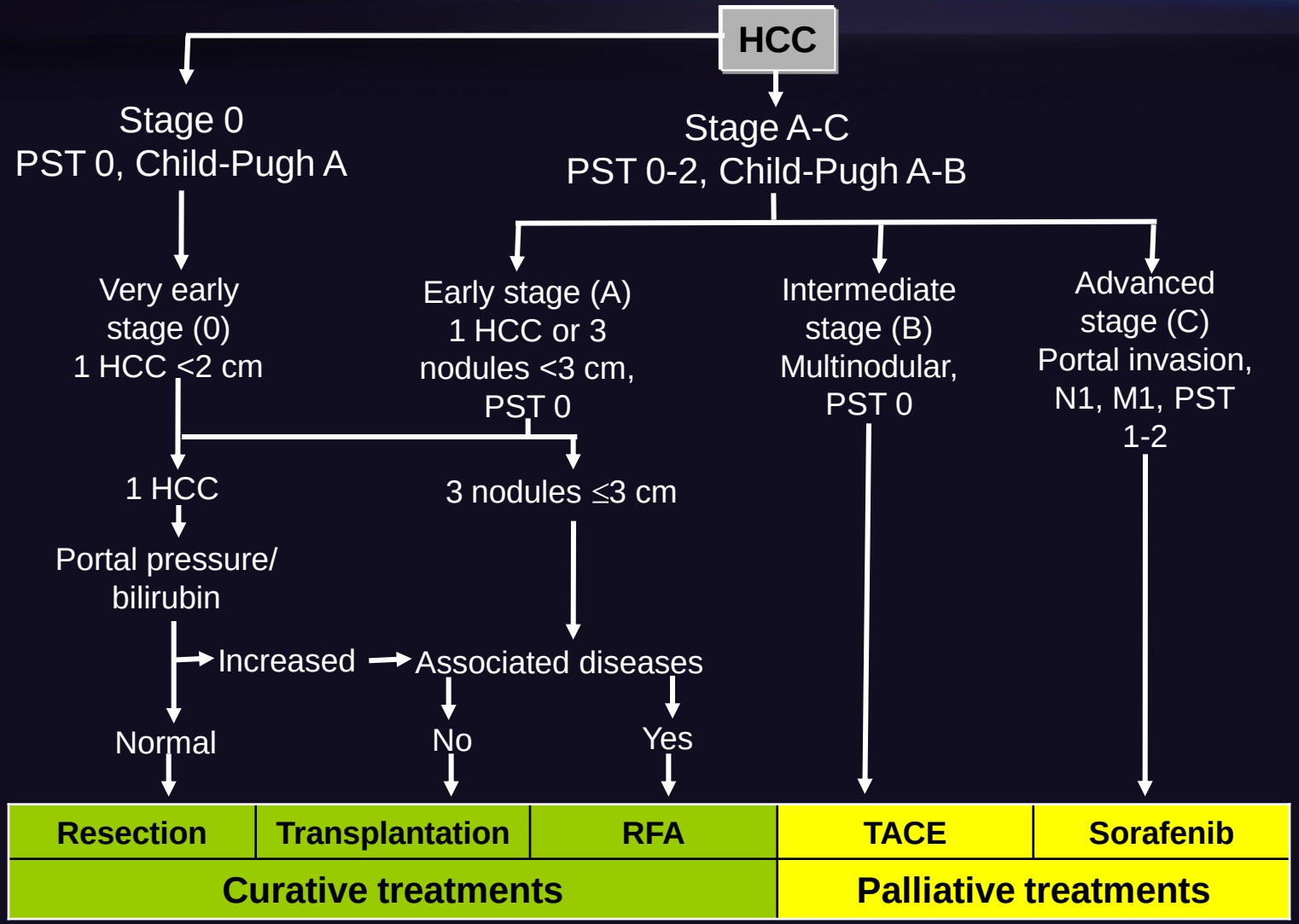

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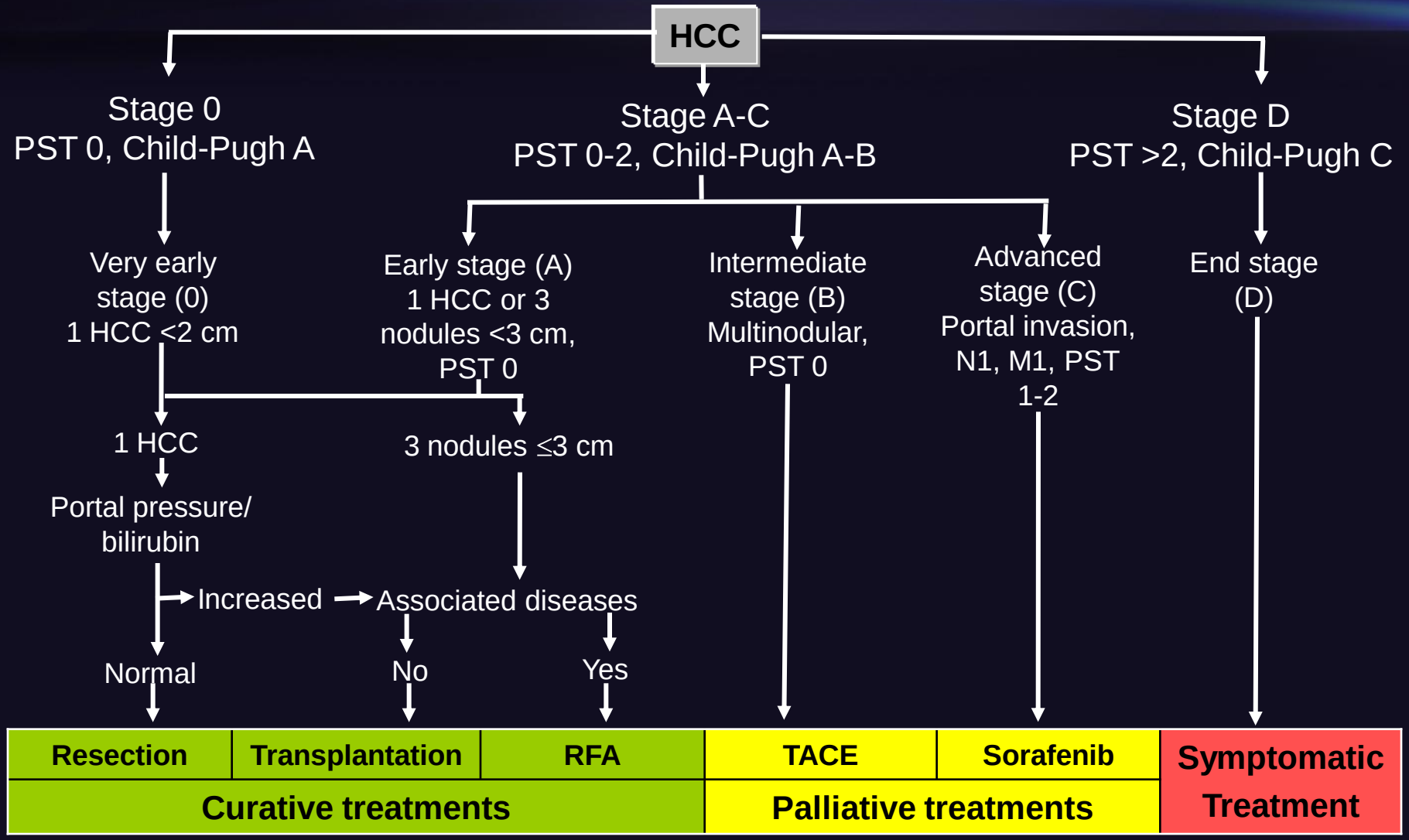


Adapted from Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: Surgical Resection

- Surgical resection can be offered to patients who have a single lesion if:
  - They are non-cirrhotic, or
  - Have cirrhosis but still have well preserved liver function, normal bilirubin and hepatic vein pressure gradient >10 mmHg
- Pre or post-resection adjuvant therapy is not recommended

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: Liver Transplantation

- Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria: Solitary tumor = 5 cm or up to three nodules = 3 cm
  - Living donor transplantation can be offered if the waiting time is expected to be so long that there is a high risk of tumor progression leading to exclusion from the waiting list

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: Liver Transplantation (cont)

- No recommendation can be made re expanding the listing criteria beyond the standard Milan criteria
- Preoperative therapy can be considered if the waiting list exceeds 6 months

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: Percutaneous Ablation

- Local ablation is safe and effective therapy for patients who cannot undergo resection, or as a bridge to transplantation
- Alcohol injection and radiofrequency are equally effective for tumors <2 cm, but:
  - The necrotic effect of radiofrequency ablation is more predictable in all tumor sizes, and
  - The efficacy of radiofrequency ablation is clearly superior to that of alcohol injection in larger tumors

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: Transarterial Embolization and Chemoembolization

- 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
- Sorafenib is recommended as first line option in patients who cannot benefit from resection, transplantation, ablation or transarterial chemoembolization, and still have preserved liver function
- Tamoxifen, anti-androgens, octreotide or hepatic artery ligation/embolization are *not* recommended

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

AASLD 2010 HCC Guidelines: Transarterial Embolization and Chemoembolization (cont)

- Radioembolization with Yttrium90-labeled glass beads has been shown to induce extensive tumor necrosis with acceptable safety profile, but:
  - There are no no studies demonstrating an impact on survival
  - Its value in the clinical setting has not been established and cannot be recommended as standard therapy for advanced HCC outside clinical trials
- Systemic or selective intra-arterial chemotherapy is not recommended and should *not* be used as standard of care

Bruix J, Sherman M. Hepatology July, 2010. Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed 08/03/10.

Treatment Options for HCC

Surgery:

- Transplantation
- Resection

Ablation:

- Ethanol ablation
- Radiofrequency (RFA)
- Cryotherapy ablation
- IRE
- High frequency ultrasound
- Microwave

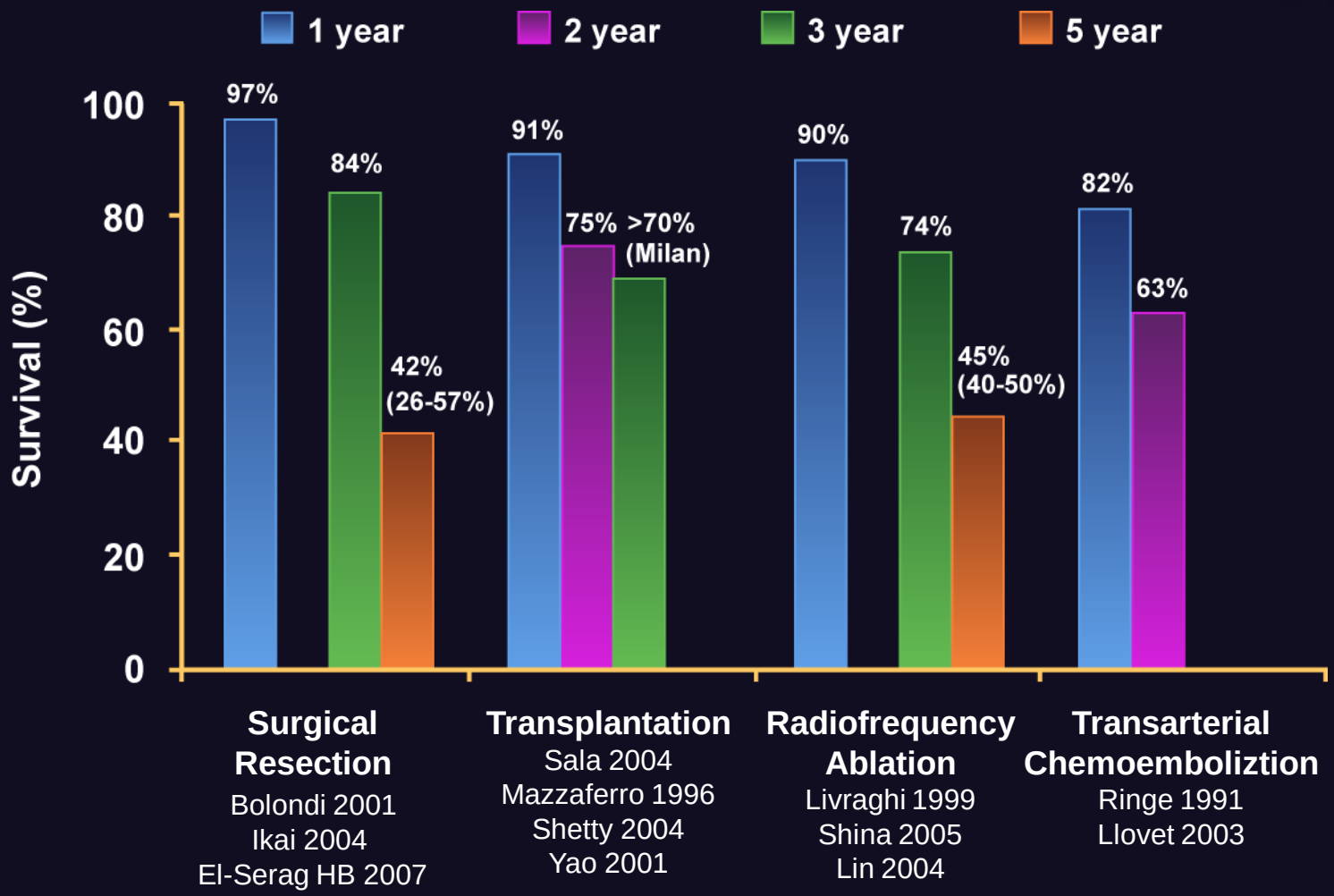
Transarterial:

- Bland
- TACE
- Drug elutuing beads
- ^{90}Y microspheres

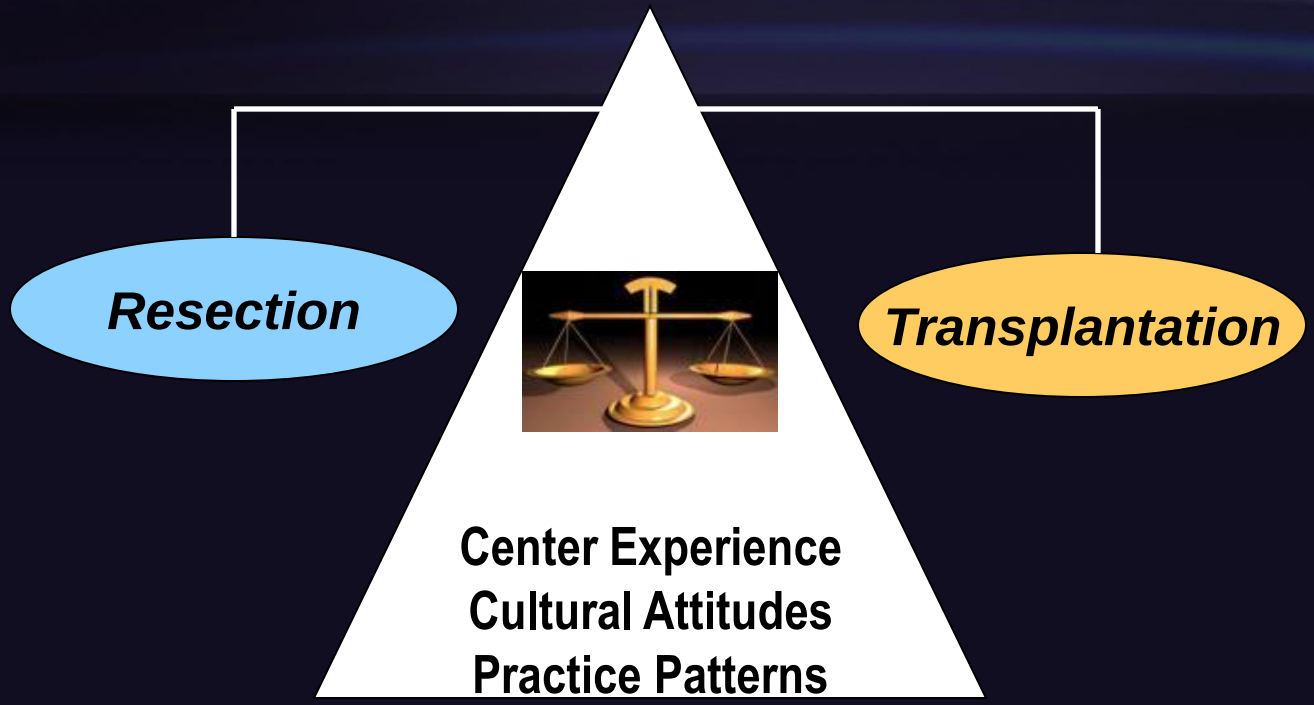
Systemic Therapies:

- Sorafenib
- Clinical Trials

HCC Treatments and Overall Survival



Resection vs Transplantation



Pro	Con
• No waiting time • 5-yr OS: 50%-70% (selected pts; CP A with single nodule) • Provides histologic information	• High recurrence rates; 50%-70% at 5 yrs • Limited appropriate candidates

Pro	Con
• Removes cirrhotic liver and treats HCC • 5-yr OS > 70% (within Milan)	• Shortage of organs • Dropout/progression • Potential recurrence of disease (ie, HCV)

Radiofrequency Ablation (RFA)

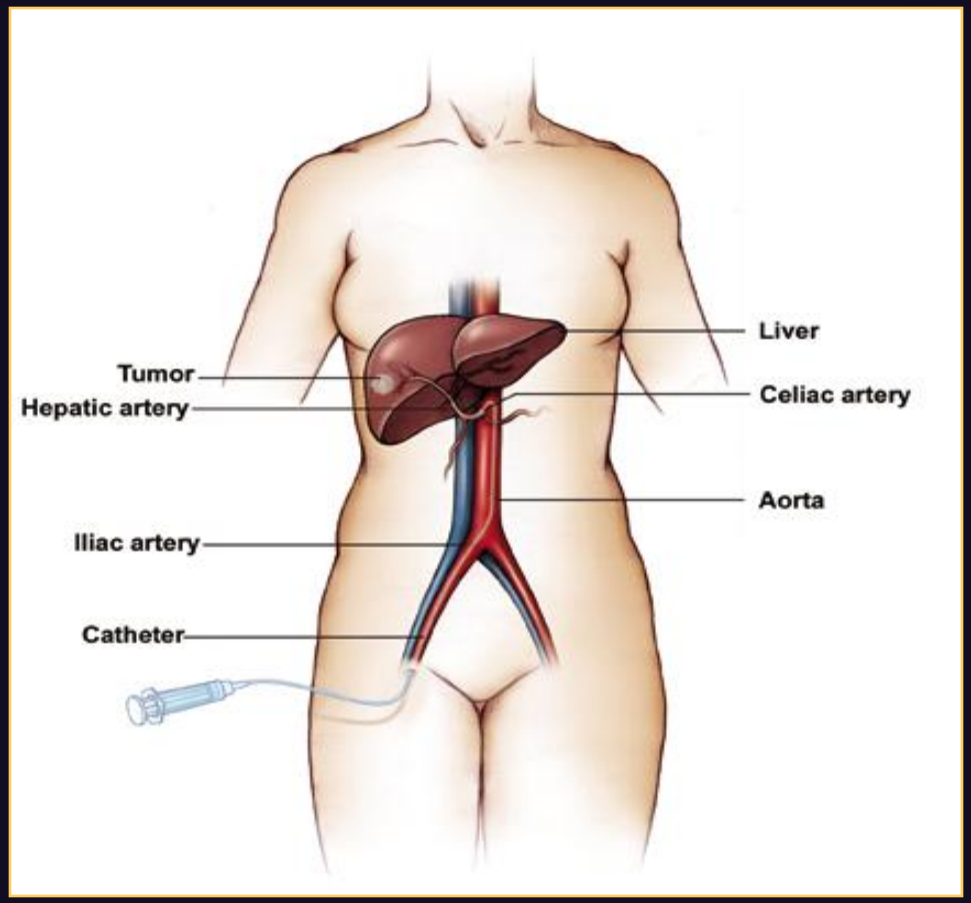
- RFA = Surgery for HCC </= 3 cm
- 5 year survival 43 – 64%
- RFA efficacy limited by size of the tumor and proximity to vessels (>/= 3mm)

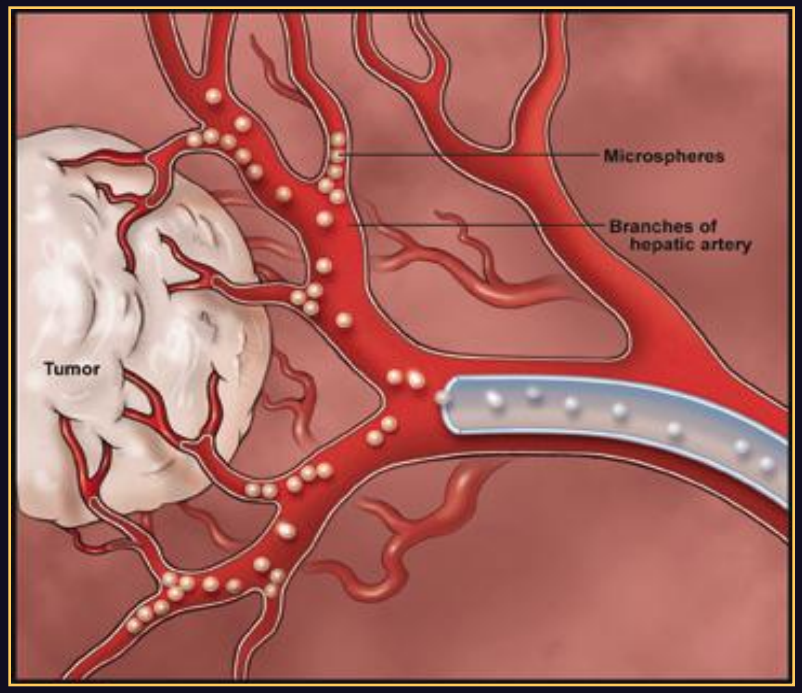
Livraghi et al, *Radiology* 2000 214:761-768

Transarterial Definitions

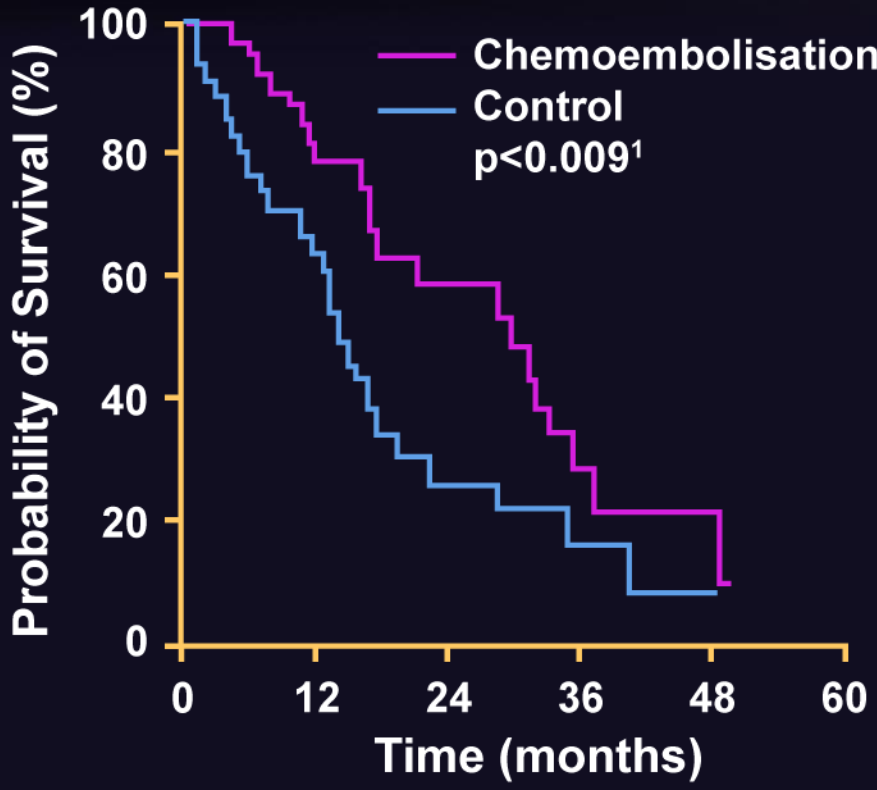
- TAE – transhepatic arterial embolizaton
  - Bland embolization, no chemo agent
- TACE – transhepatic arterial chemoembolization
  - One or more chemo agents plus lipiodol plus embolic
- Drug eluting beads –
  - PVA hydrogel spheres with ionically attached chemo agent
- TARE – transarterial radioembolization
  - ^{90} Yt microspheres

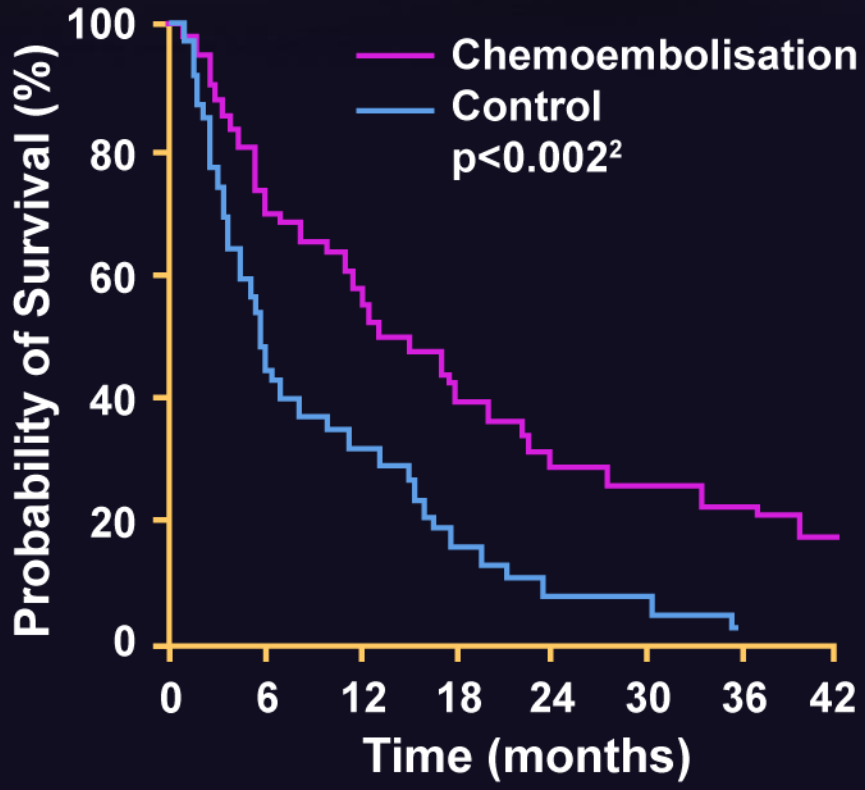
Transarterial Chemoembolization TACE





TACE: Long-term survival outcomes





- 3-year overall survival rates: 26-29%
- Sustained objective response (≥3–6 months): 35–42%
- No differences in intent-to-treat survival between non-responders and controls
- No evidence of survival benefit in patients with vascular invasion

1. Llovet JM, et al. Lancet 2002;359:1734–9.
2. Lo CM, et al Hepatology 2002;35:1164–71.

Transarterial Yttrium Microspheres TARE

- FDA approved in 1999 including PVT
- Beta radiation; half-life 64 hours
- Well tolerated; outpatient procedure
- Less postemobilization syndrome
- Size: 25 microns
- Mean penetration: 2.5 mm
- No special patient precautions needed due to radiation
- Preparation time required
  - Need a 2-step procedure; first step is to calculate shunt fraction
  - Confirm perfusion limited to liver

Long-term Outcomes of Radioembolization Using Yttrium-90 Microspheres

Single institution cohort study

- Endpoints: Response rate,* TTP,* survival, toxicity

- 273/291 (94%) of patients had follow-up imaging
- 58% Downstaged T3→ T2, 32 transplanted
- Response rate 42% (WHO) and 57% (EASL)
- No GI ulcers

	TTP	Overall Survival
Stage B	13.3 months	17.2 months Child A = 17.3 months Child B = 13.5 months
Stage C	6 months	7.3 months Child A = 13.8 months Child B = 6.4 months

•Assessed using WHO and EASL criteria.

Salem R et al. *Gastroenterology*. 2010;138(1):52-64.

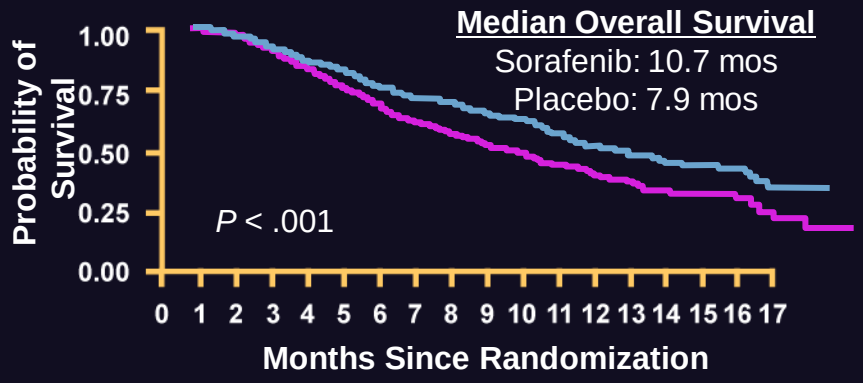
Sorafenib

- Small molecule, orally administered
- Inhibits tumor-cell proliferation and tumor angiogenesis
- Increases the rate of apoptosis in a wide range of tumor models
  - Inhibits molecular components of the Raf-MEK-ERK signaling pathway, therby inhibiting tumor growth
  - Inhibits the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor β (PDGFR- β), thereby inhibiting neoangiogenesis

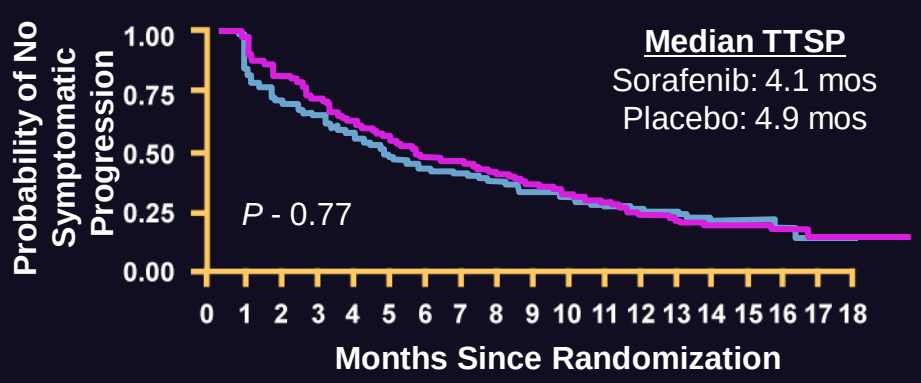
Llovet JM et al. *N Engl J Med* 2008:359:378-390.

Survival and Time to Progression

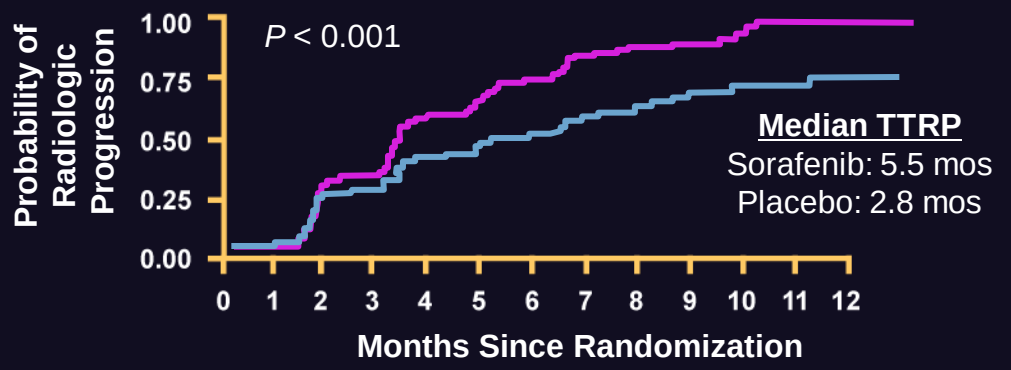
Time to Survival



Time to Symptomatic Progression



Time to Radiologic Progression



Llovet JM, et al. *N Engl J Med*. 2008;359:378-390.

Most Common Adverse Events and Management Strategy

- Hand-foot skin reaction (HFSR)

Grades	Definition	Intervention
1	Paresthesias, erythema	Maintain and monitor for change. Use urea containing topical creams
2	Painful erythema, interferes ADLs	Reduce dose to 400 mg q.d.s. x 7-28 days. If resolves, then increase. If no resolution, then stop
3	Desquamation, ulcers, blistering	Interrupt treatment for 7 days and until improvement to grades 0-1. Then resume decrease by 1 dose level

  - Management of dermatological reactions should begin early in the course of therapy to decrease symptom severity and should include topical therapies
- Diarrhea
  - Take anti-diarrheal medications as recommended
- Fatigue
  - Exclude secondary causes
- Dose modifications and treatment interruptions as well as close monitoring are the keys to successful management of adverse reactions.

Cabrera R, Nelson DR. *Aliment Pharmacol Ther*. 2010 Feb 15;31(4):461-76.

Where do we go from here?

- Empower multidisciplinary teams
  - Hepatology, Surgery, Diagnostic and Interventional Radiology, Oncology, Pathology
- Improve provider and patient education regarding risk factors
- More effective surveillance should increase number of patients diagnosed early
- Utilization of a validated staging system
- Optimize screened patients for curative therapy

El-Serag HB, et al. *Gastroenterol* 2008;134:1752-1763