Hepatocellular Carcinoma

Luis S. Marsano, MD
Professor of Medicine
Division of Gastroenterology, Hepatology, & Nutrition
University of Louisville & Louisville VAMC
2010

Magnitude of the Problem

- 95% of world-cases in cirrhotics.
- Incidence in cirrhotics: 2-9% per year.
- 3rd cause of cancer death in the world (500,000 per year).
- In USA, 50% due to HCV.
- In USA, 10,000 new cases/ year; 500 million hospital charges/ year.

Recommended Surveillance Groups

(Risk > 1.5% / year)

- **Hepatitis B**
- All HBV cirrhotics
- Africans > 20 y.o.
- 1st degree w HCC & > 20 y.o.
- Asian males > 40 y.o.
- Asian females > 50 y.o.
- Caucasians w. high HBV-DNA / activity & > 40 y.o.

- **Other Cirrhosis**
- Hepatitis C (F3 ?)
- Alcoholic
- Genetic Hemochromatosis
- Primary Biliary Cirrhosis
- +/- Alpha-1 antitrypsin
- +/- NASH
- +/- Autoimmune hepatitis

Surveillance Test

- **SEROLOGY**
- AFP > 20 ng/mL: sens=60%, PPV=41%
- AFP > 200 ng/mL: sens=22%, PPV=60%
- **AFP should be used only if U/S is not available**
- Des-gamma-carboxy prothrombin (PIVKA II), AFP L3 fraction, Alpha fucosidase, Glypican 3

- **ULTRASOUND**
- Sensitivity: 65-80%
- Specificity > 90%
- False (+) Rate: U/S=2.9%; AFP=5%; AFP+U/S=7.5%
- Classic is hypoechoic; can be isoechoic w halo, hyperechoic, or mixed.
- **Interval**: 6-12 months
- **Positive Result**: nodule > 1 cm

Risk of HCC

- HBV cirrhosis in European: 6% at 5 years.
- HBV cirrhosis in Asian: 2.5% per year.
- HCV cirrhosis: 2 to 8% per year.
- Hemochromatosis cirrhosis: 3 to 4% per year.

Diagnostic Algorithm for HCC in Lesion < 1 cm for Cirrhosis or Chronic HBV

- Low likelihood of HCC
- Repeat **U/S at 3-6 month** intervals
- If remains stable > 24 months: return to U/S at 6 month intervals.
- If lesion grows to 1 cm or larger, follow corresponding protocol.

Evaluation of Liver lesions 1-2 cm Cirrhosis or Chronic HBV

- High likelihood of HCC, but biopsy more difficult to sample (30% false (-)) and read; HCC of this size does not progress rapidly (no additional MELD points). Seeding risk 0.5-2%.
- Forner et al. used contrast ultrasound and MRI to evaluate lesions smaller than 2 cm found on surveillance. The PPV for HCC was 100%, although the NPV was only about 42%. This means that:
  - **if both tests were positive the lesion was always HCC.**
  - **if one or both tests were not conclusive, then the false-negative detection rate of HCC was greater than 50%.**
- The algorithm requires that if one or both test were not conclusive, a biopsy be performed. In this study, up to three biopsies were performed in an attempt to come to the correct diagnosis.
- Contrast enhanced ultrasound is not available in the USA, so these results are not entirely applicable to a North American population.

Evaluation of Liver lesions 1-2 cm Cirrhosis or Chronic HBV

- Leoni S et al. came to very similar conclusions providing external validation of the algorithm.
- Khalili K et al in a study, presented so far only in abstract form, used CT scanning as well as contrast ultrasound and MRI and has also validated the algorithm.
- These analyses showed that using a single contrast enhanced modality had a lower positive predictive value than using two studies, although the positive predictive value was still better than 90%.

Evaluation of Liver lesions 1-2 cm Cirrhosis or Chronic HBV

- Other studies have provided external validation of these algorithms, but have also shown that **typical appearances of arterial hypervascularity and venous washout are so highly specific that only a single study is necessary** if these appearances are present.
  - **The sensitivity of using dual imaging for diagnosis was between 21% and 37% and specificity was 100%.**
- Sangiovanni A, and Khalili K in two different studies have shown that sequential imaging can be used to decrease the need for biopsy.
  - **Using sequential studies rather than requiring two studies to be typical improved the sensitivity to about 74-80%, but the specificity fell to 89-97%.**
  - **However, if atypical lesions were biopsied, the specificity was restored to100%.**

Diagnostic Algorithm for HCC in Lesion > 1 cm for Cirrhosis or Chronic HBV

- Nodules larger than 1 cm found on ultrasound screening of a cirrhotic liver should be investigated further with either 4-phase multidetector CT scan or dynamic contrast enhanced MRI.
- If the appearances are typical of HCC (i.e., hypervascular in the arterial phase with washout in the portal venous or delayed phase), the lesion should be treated as HCC.
- If the findings are not characteristic or the vascular profile is not typical, a second contrast enhanced study with the other imaging modality should be performed, or the lesion should be biopsied (level II).

Evaluation and Follow-up of Bx of Liver Nodule in Cirrhosis

- Biopsies of small lesions should be evaluated by expert pathologists. Tissue that is not clearly HCC should be stained with all the available markers including CD34, CK7, glypican 3, HSP-70, and glutamine synthetase to improve diagnostic accuracy (level III).
- If the biopsy is negative for patients with HCC, the lesion should be followed by imaging at 3-6 monthly intervals until the nodule either disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC a repeat biopsy is recommended (level III).

Diagnostic Algorithm for HCC in Lesion > 2 cm Cirrhosis or Chronic HBV

- Very high likelihood of HCC.
- With **AFP > 200** ng/mL: treat as **HCC** (99.4% confidence)
- False (-) Biopsy in 10%
- Sequential 4-phase multidetector CT scan or dynamic contrast enhanced MRI
- With **non-characteristic pattern** in 4-phase MD**CT & dynamic MRI**: **biopsy**
  - Non diagnostic Bx: repeat 4-hase imaging/Bx in 3 months
  - Diagnostic Bx: treat as HCC

Treatment of HCC

Several slides were modified from CCO Oncology; made by Dr. Luigi Bolondi, Dr. Adrian Di Bisceglie, and Dr. J-F Geschwind

Management of HCC

- Liver transplantation
- Resection
- Tumor ablation
  - Radiofrequency thermal ablation
  - Alcohol injection
  - Chemoembolization
- Targeted molecular therapy
- Chemotherapy
  - Regional/systemic

Potentially curative

Evidence of Benefit in Treatment of HCC

Treatment	Benefit	Evidence
Surgical treatments		
Resection	Increased survival	Case series
▪ **Adjuvant therapies**	Uncertain	Randomized trial, meta-analysis, nonblinded
Liver transplantation	Increased survival	Case series
▪ **Neoadjuvant therapies**	Treatment response	Nonrandomized trials
Locoregional treatment		
Percutaneous treatment	Increased survival	Case series
RFA vs PEI	Better local control	Randomized trial, meta-analysis, nonblinded
Chemoembolization	Increased survival	Randomized trial, meta-analysis, nonblinded
Arterial chemotherapy	Treatment response	Case series
Internal radiation	Treatment response	Case series

Llovet JM, et al. J Natl Cancer Inst. 2008;100:698-711.

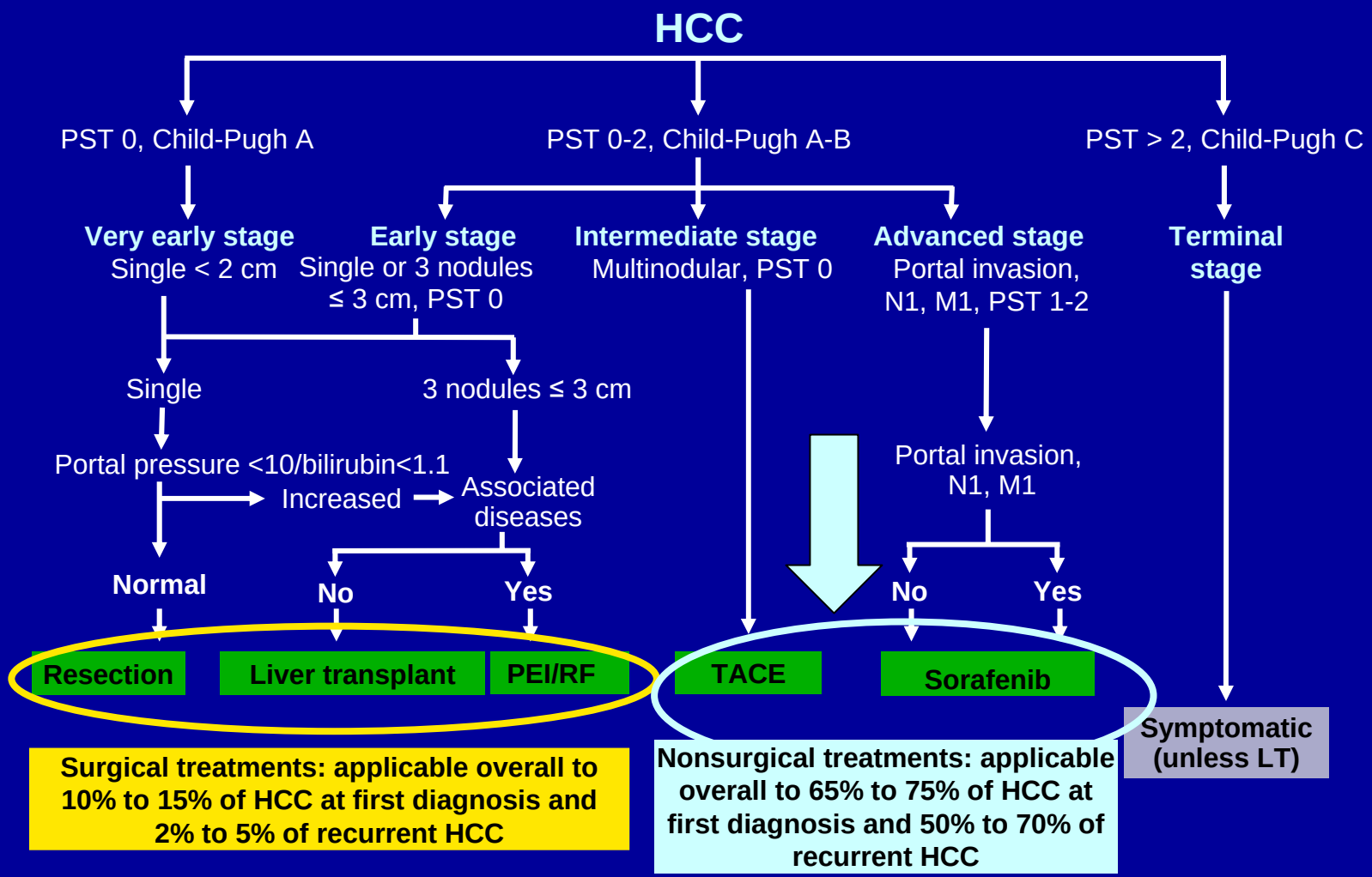
Evidence of Benefit in Treatment of HCC (cont'd)

Treatment	Benefit	Evidence
Systemic therapies		
Sorafenib	Increased survival	Randomized trial, meta-analysis, double blinded
Tamoxifen	No benefit	Randomized trial, meta-analysis, double blinded
Chemotherapy	No benefit	Randomized trial, meta-analysis, nonblinded
IFN	No benefit	Randomized trial, meta-analysis, nonblinded

Llovet JM, et al. J Natl Cancer Inst. 2008;100:698-711.

Staging Strategy and Treatment for Patients With HCC

Barcelona Clinic Liver Cancer - BCLC



Performance Status ECOG/WHO/Zubrod score

- The ECOG score (published by Oken *et al* in 1982), also called the WHO or Zubrod score (after C. Gordon Zubrod)
  - **0 - Asymptomatic** (Fully active, able to carry on all predisease activities without restriction)
  - **1 - Symptomatic but completely ambulatory** (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
  - **2 - Symptomatic, <50% in bed during the day** (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
  - **3 - Symptomatic, >50% in bed, but not bedbound** (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
  - **4 - Bedbound** (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
  - **5 - Death**

Child-Pugh Score

Measure	1 Point Each	2 Points Each	3 Points Each
Bilirubin (mg/dL)	< 2.0	2.0-3.0	> 3.0
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time (sec)	1.0-3.0	4.0-6.0	> 6.0
Ascites	None	Slight	Moderate
Encephalopathy (grade)	None	I-II	III-IV

Grade	Total Points	Surgical Risk
A	5-6	Good
B	7-9	Moderate
C	10-15	Poor

Pugh RN, et al. Br J Surg. 1973;60:646-649.

Very Early Stage

Treatment of HCC
Very Early Stage

- REQUIREMENTS:
  - Performance Status 0 (fully active & asymptomatic)
  - Child-Pugh A
  - Single lesion < 2 cm
- Management:

A) Portal P gradient < 10 mmHg & normal bilirubin =/< 1.1 mg/dL:
- Resection.

B) Elevated Portal P or bili but OLTx candidate:
- OLTx

C) Elevated Portal P or bili and no OLTx candidate:
- RFA or PEI

- Pre-, or Post-Resection adjuvant therapy is not recommended.

Milan Criteria for OLTx

- No vascular invasion, and
- No extrahepatic disease **(CT Chest (-))**, **and**
  - 1 lesion =/< 5 cm, or
  - 3 lesions =/< 3 cm each

Early Stage

Treatment of HCC
Early Stage

- REQUIREMENTS:
  - Performance status 0 (fully active & asymptomatic) to 2 (Symptomatic, <50% in bed during the day)
  - Child-Pugh A-B
  - 1 to 3 nodules </= 3 cm
- Management:

A) Single nodule < 3 cm, Portal P gradient < 10 mmHg & normal bili =/< 1.1mg/dL:

- Resection

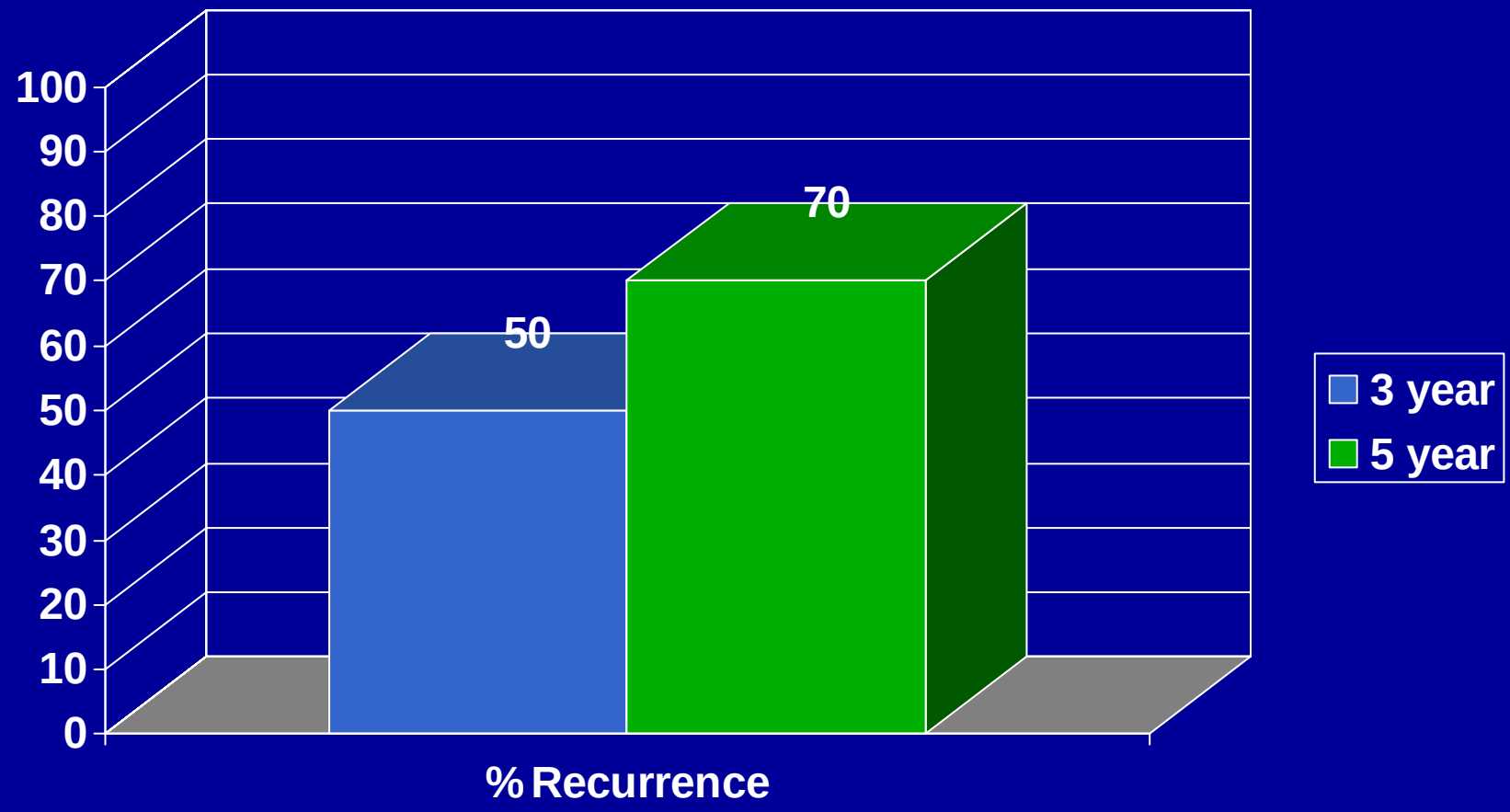
B) Single nodule with high Portal P or bili, or 2-3 nodules </= 3 cm, OLTx candidate:

- OLTx (4 year survival = 85%; 4 y disease free = 92%)

C) As on "B" but **No** OLTx candidate:

- RF if </= 3 cm, or PEI if </= 2 cm (5 year survival 50-60%)

Tumor Recurrence after Resection or Ablation



Approved Curative Treatments for Unresectable HCC: Percutaneous Ablation

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

Bruix J, et al. Hepatology. 2005;42:1208-1236.

Transplant Option
MELD Score in HCC

- **Lesion < 2 cm** = given by cirrhosis score
- **Milan criteria but > 2cm** =
  - 22 points (15% 3-month death-risk);
  - Every 3 months add 10% death risk **(MELD = 25, 28, 29, 31, 33)**
- **Cirrhosis + AFP > 500 without lesion seen** =
  - 8% (MELD= 19-20) 3-month death-risk

Down-Staging Chemo-embolization for Transplantation
UCSF Criteria

- No vascular invasion, and
- No extrahepatic disease (**CT Chest (-)**), and
  - 1 lesion =/< 6.5 cm, or
  - 2-3 lesions,
    - largest =/< 4.5 cm, and
    - total < 8 cm

Down-Staging Chemoembolization: Efficacy Before Transplantation

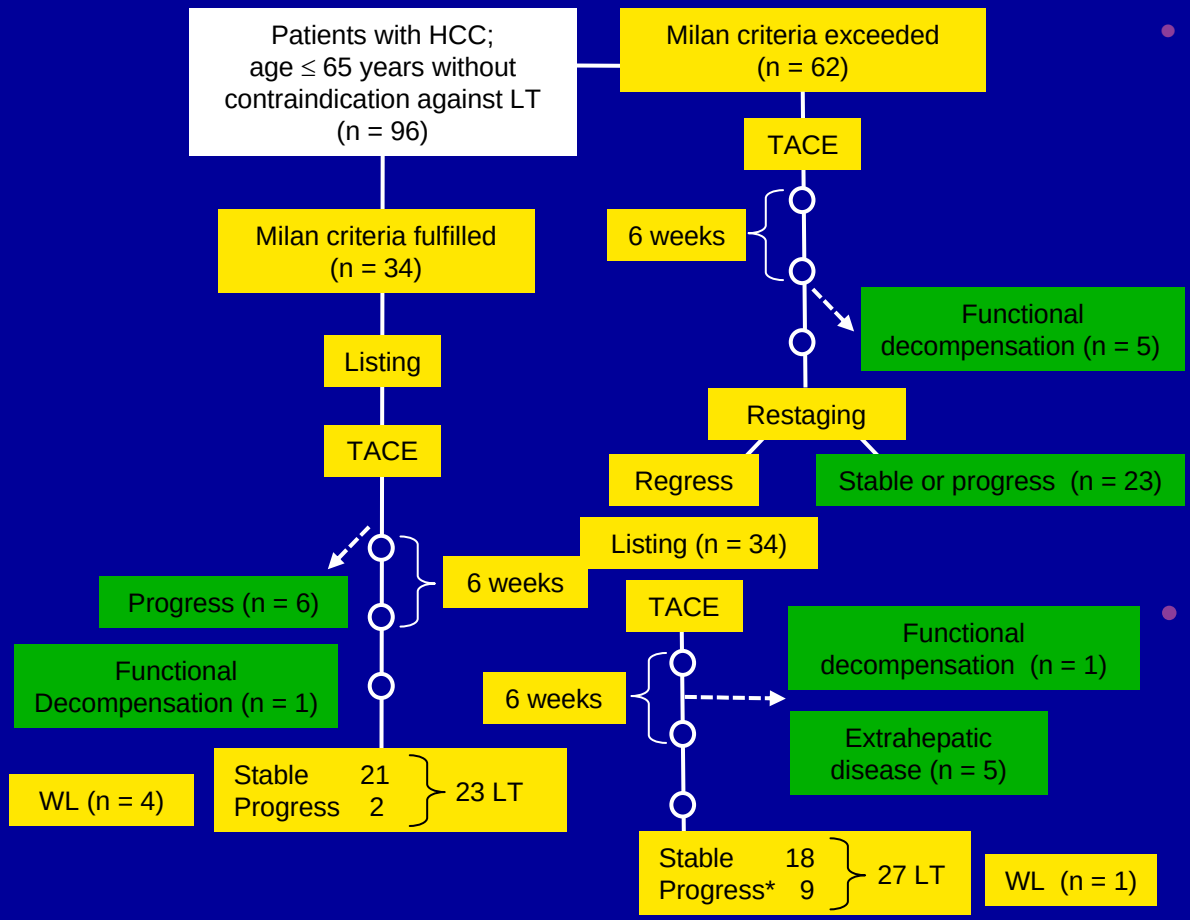
- Major issue: dropout rate (~ 20%)
  - Lower in US since adoption of MELD criteria
- Role of TACE
  - Control tumor and prevent progression
  - Should be considered if waiting time > 6 months
- Complications from TACE: rare (no increased rate of hepatic artery complications)

Richard HM 3rd, et al. Radiology. 2000;214:775-779.
Graziadei IW, et al. Liver Transpl. 2003;9:557-563.
Alba E, et al. Am J Roentgenol. 2008;190:1341-1348.

Definitions of Response to TACE for Down-Staging
Response Evaluation Criteria in Solid Tumors (RECIST)

- Progression: at least 20% increase in the sum of the largest diameter of target lesions or the appearance of new non-target lesions and/or non-measurable lesions.
  - No Transplant.
- Stable: No Progression nor Regression.
  - A) Pre-down-staging: No transplant.
  - B) After down-staging + Listing: Transplant.
- Partial Response (Regression): at least 30% decrease in the sum of the largest diameter of 5 target lesions, taking as reference the baseline sum of the largest diameter.
  - Transplant.
- Progression during Liver Transplant waiting time: any increase in size or number of tumor nodules.
  - No Transplant.
- Functional Decompensation: Child-Pugh C plus any of the following: increase in bili > 2 mg/dL, Encephalopathy, or worsening of ascites.
  - No Transplant.

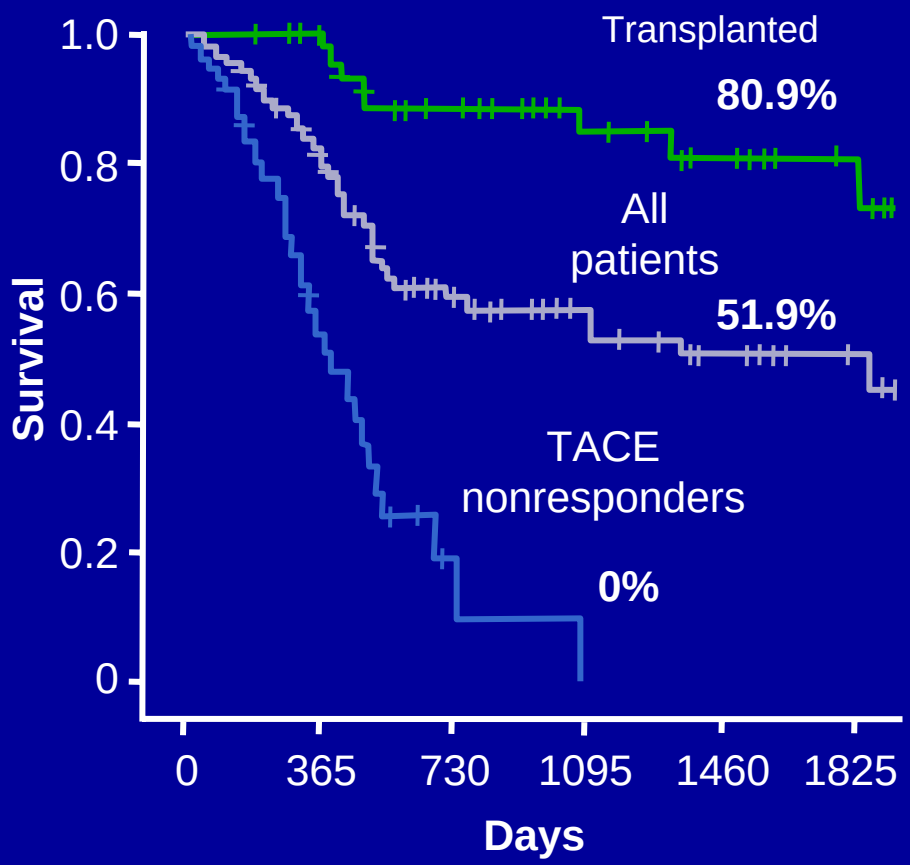
Can TACE Be Used as a Determinant of Tumor Biology?



- 96 consecutive patients treated with TACE
  - 62 exceeded Milan criteria
  - 34 meeting Milan criteria listed immediately
  - TACE q 6 weeks
  - Restaging q 12 weeks
- 50 patients transplanted
  - 27 exceeded Milan criteria

Otto G, et al. Liver Transpl. 2006;12:1260-1267.

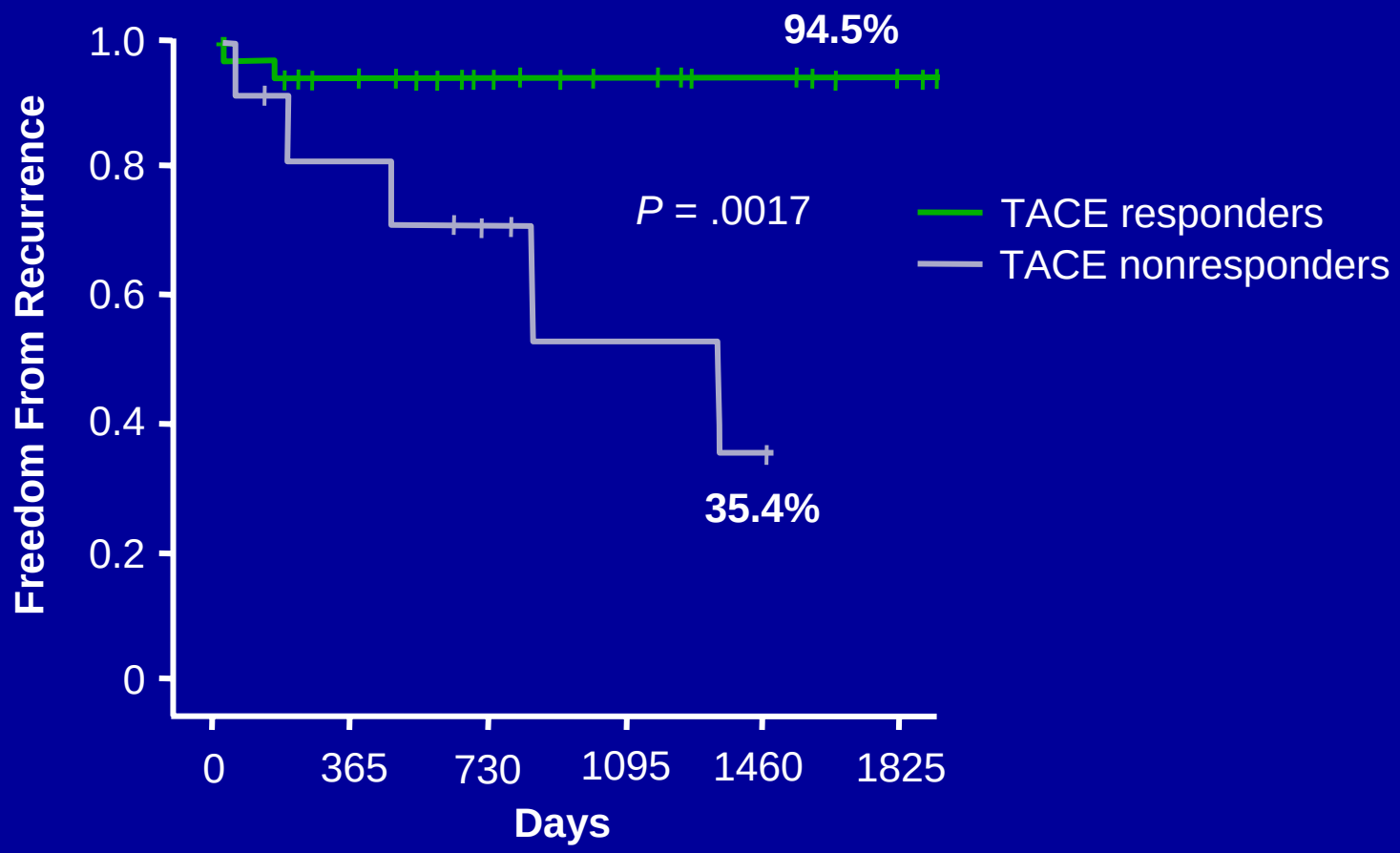
Response to TACE as a Biological Selection Criterion for LT in HCC



- Overall 5-year survival: 51.9%
  - Highly significant difference in 5-year survival between downstaged (transplanted) patients and patients not responding to TACE ($P < .0001$)
- Survival calculated from the beginning of TACE treatment

Otto G, et al. Liver Transpl. 2006;12:1260-1267.

Response to TACE as a Biological Selection Criterion for LT in HCC



Otto G, et al. Liver Transpl. 2006;12:1260-1267.

Chemoembolization: Ineligibility Criteria

- Absolute contraindications
  - Child-Pugh class C disease
  - Poor performance status (ECOG PS > 2)
- Relative contraindication
  - Extrahepatic disease (benefit unclear)
- Former contraindication
  - PVT
    - Minimize embolization and be more selective

Safety & Efficacy of TACE in Patients With Unresectable HCC & PVT

- 32 patients with HCC and PVT
- Median Overall Survival: 10 months
- Child-Pugh score: best prognostic factor (ie, most strongly related to survival)
- 30-day mortality: 0%
- No evidence of TACE-related hepatic infarction or acute liver failure

Georgiades CS, et al. J Vasc Interv Radiol. 2005;16:1653-1659.

Intermediate Stage

Staging of HCC
Intermediate Stage

- REQUIREMENTS:
  - Performance status 0 (fully active & asymptomatic) to 2 (Symptomatic, <50% in bed during the day)
  - Child-Pugh A-B
  - More than 3 nodules, or > 3 cm
- Management:

A) Chemoembolization (TACE)

B) Randomized controlled trials

Approved & Investigational Noncurative Agents for Unresectable HCC

- AASLD 2005 recommendations
  - Chemoembolization (TACE) (with doxorubicin, cisplatin, or mitomycin) is recommended as first-line, noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (and are not eligible for percutaneous ablation) (level I)
  - Tamoxifen, octreotide, antiandrogens, and hepatic artery ligation/embolization are not recommended (level I);
  - Clinical trials only: drug-eluting beads, radiolabelled yttrium glass beads, radiolabelled lipiodol, or immunotherapy for advanced HCC.

Bruix J, et al. Hepatology. 2005;42:1208-1236.

Chemoembolization: Randomized Trials (Nearly Identical Techniques)

Lo et al[1]: N = 80 with newly diagnosed unresectable HCC, 80% HBV positive, 7-cm tumors (60% multifocal)

Technique	Survival, %		
	Year 1	Year 2	Year 3
TACE	57	31	26
Supportive care	32	11	3

Llovet et al[2]: N = 112 with unresectable HCC, 80% to 90% HCV positive, 5-cm tumors (~ 70% multifocal)

Technique	Survival, %	
	Year 1	Year 2
TACE	82	63
Supportive care	63	27

1. Lo CM, et al. Hepatology. 2002;35:1164-1171.
2. Llovet JM, et al. Lancet. 2002;359:1734-1739.

Chemoembolization: Predictors of Survival

- Lo et al[1]
  - Absence of presenting symptoms (ECOG PS < 2)
  - Absence of portal vein obstruction
  - Tumor size (≤ 5 cm vs > 5 cm)
  - Okuda stage (I vs II)
- Llovet et al[2]
  - Absence of constitutional syndrome (ECOG PS < 2)
  - Low serum bilirubin
  - Treatment response (modified WHO criteria, > 6 months)

1. Lo CM, et al. Hepatology. 2002;35:1164-1171.
2. Llovet JM, et al. Lancet. 2002;359:1734-1739.

Largest Prospective Study of TACE for Unresectable HCC to Date

- N = 8510 patients
- Primary endpoint: Overall Survival (OS)
- Multivariate analysis conducted of factors affecting survival
- Overall Survival
  - Year 1: 82%; Year 3: 47%; Year 5: 26%; Year 7: 16%
  - Overall Survival better with lesser degree of liver damage
- Factors affecting survival
  - Child-Pugh stage
  - TNM stage (OS better with stage I, increasingly worse progressing toward stage IV)
  - Alpha-fetoprotein level

Takayasu K, et al. Gastroenterology. 2006;131:461-469.

Yttrium-90 Radiotherapy for HCC Patients With and Without PVT

- **Phase II study: N = 108 (37 with PVT, 71 without PVT)**
- **Stratified by toxicity: Child-Pugh score (in cirrhotics), dose, location of PVT**
- **Median dose: 134 Gy**
- **Partial response rate: 42% (WHO), 70% (EASL)**
- **Adverse event rate highest in patients with main PVT and cirrhosis**
- **Median survival:**
  - **Main PVT: 260 days**
  - **Branch PVT: 370 days**
  - **No PVT: 460 days**

Kulik LM, et al. Hepatology. 2008;47:5-7.

Intermediate/Advanced HCC: Future Directions

- 499 trials registered at clinicaltrials.gov for HCC as of August 21, 2008, including
  - Improving efficacy of RF and TACE (drug-eluting beads)
  - Exploring alternative treatments for intermediate HCC (yttrium-90)
  - Molecularly targeted agents in combination regimens (advanced HCC)
  - Molecularly targeted agents in combination with current modalities (early/intermediate HCC)
  - Improving tumor targeting of chemotherapeutic agents
  - New molecular targets and new molecularly targeted agents

Advanced Stage

Staging of HCC
Advanced Stage

- REQUIREMENTS:
  - Child-Pugh A or B
  - Portal invasion, or N1M1
  - Performance Status 1 or 2:
    - 1. Symptomatic but completely ambulatory
    - 2. Symptomatic, <50% in bed during the day
- Management:
  - Sorafenib

Treatment of Advanced HCC (BCLC Stage C)

- AASLD 2005 recommendation: no standard therapy; patients should enroll in a randomized clinical trial[1]
- 2008 recommendation: sorafenib has become the standard of care for advanced HCC[2]
  - Prolongs OS by 3 months[3]
  - 1-year survival: 44%[4]

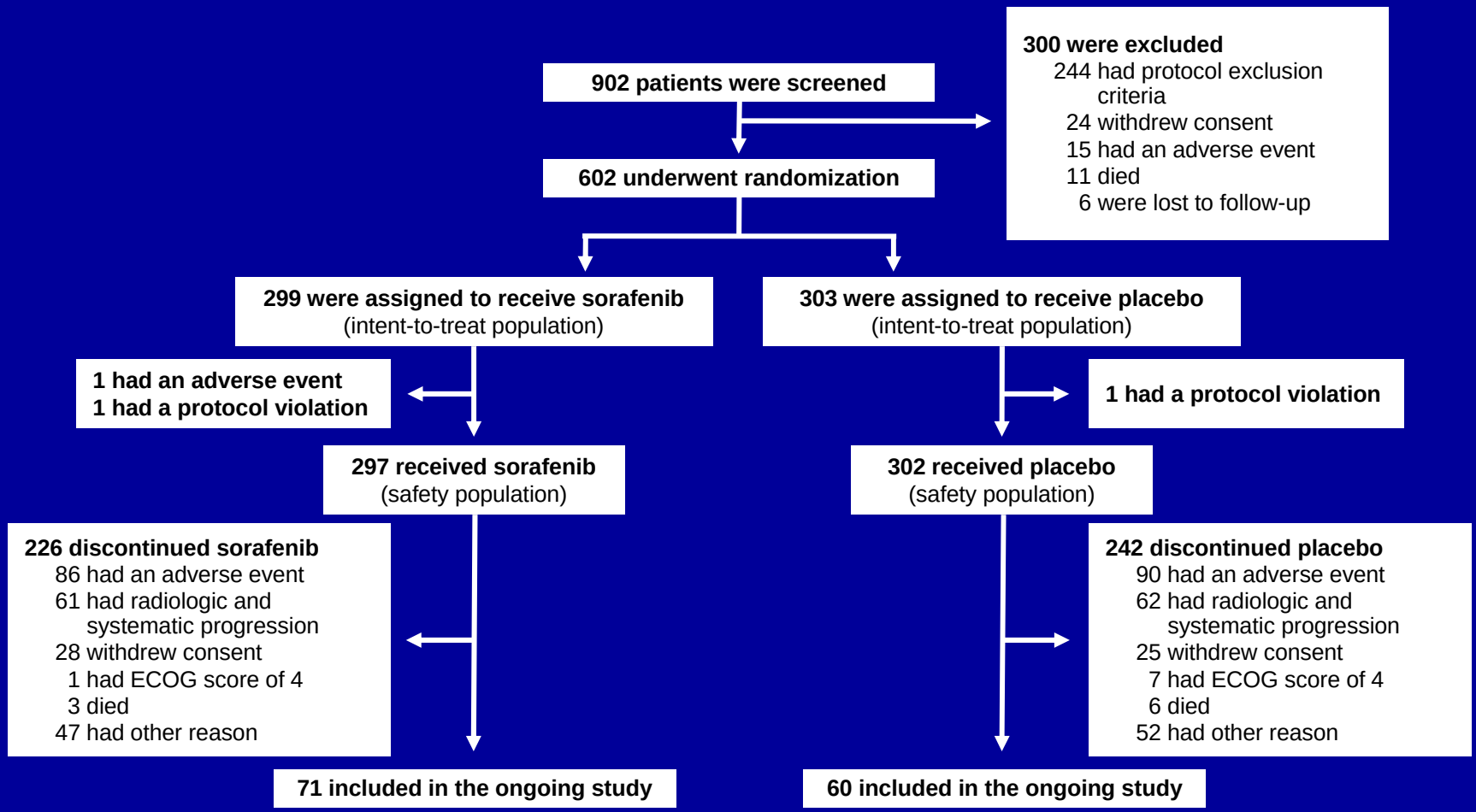
1. Bruix J, et al. Hepatology. 2005;42:1208-1236.
2. Llovet JM, et al. J Hepatol. 2008;48:S20-S37.
3. Llovet J, et al. ASCO 2007. Abstract LBA 1.
4. Llovet J, et al. N Engl J Med. 2008;359:378-390.

Sorafenib in Advanced HCC: The SHARP Trial

- Entry criteria
  - Advanced HCC
    - Not eligible for or failed surgical or locoregional therapies
  - Child-Pugh class A disease
  - At least 1 untreated target lesion
  - Exclusions
    - Previous chemotherapy
    - Previous molecularly targeted therapy

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

Sorafenib in Advanced HCC: The SHARP Trial



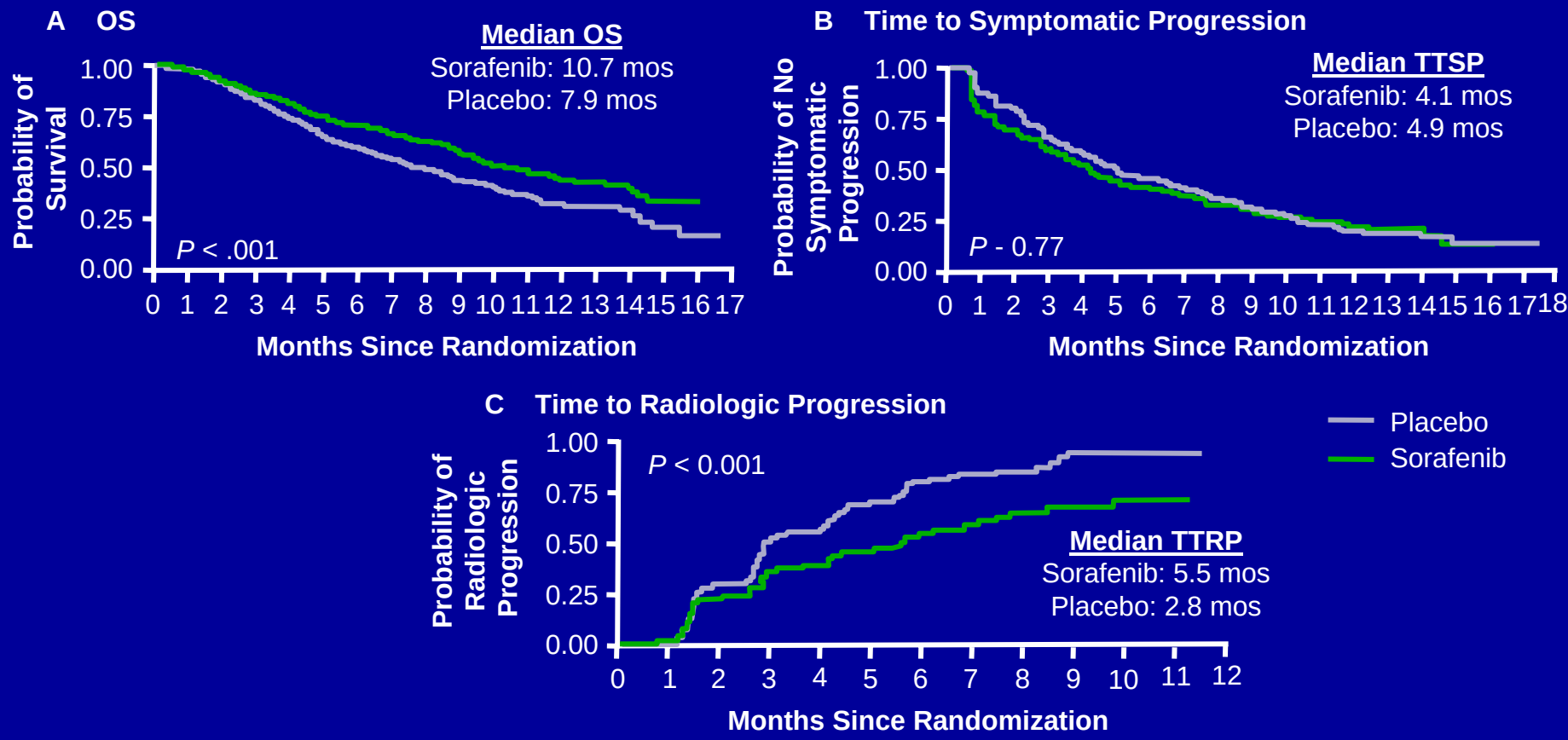
Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.

SHARP Trial: Baseline Characteristics

Characteristic	Sorafenib (n = 299)	Placebo (n = 303)
Median age, yrs	64.9	66.3
Male, %	87	87
BCLC stage, %		
• B (intermediate)	18	17
• C (advanced)	82	83
Vascular invasion, %	70	70

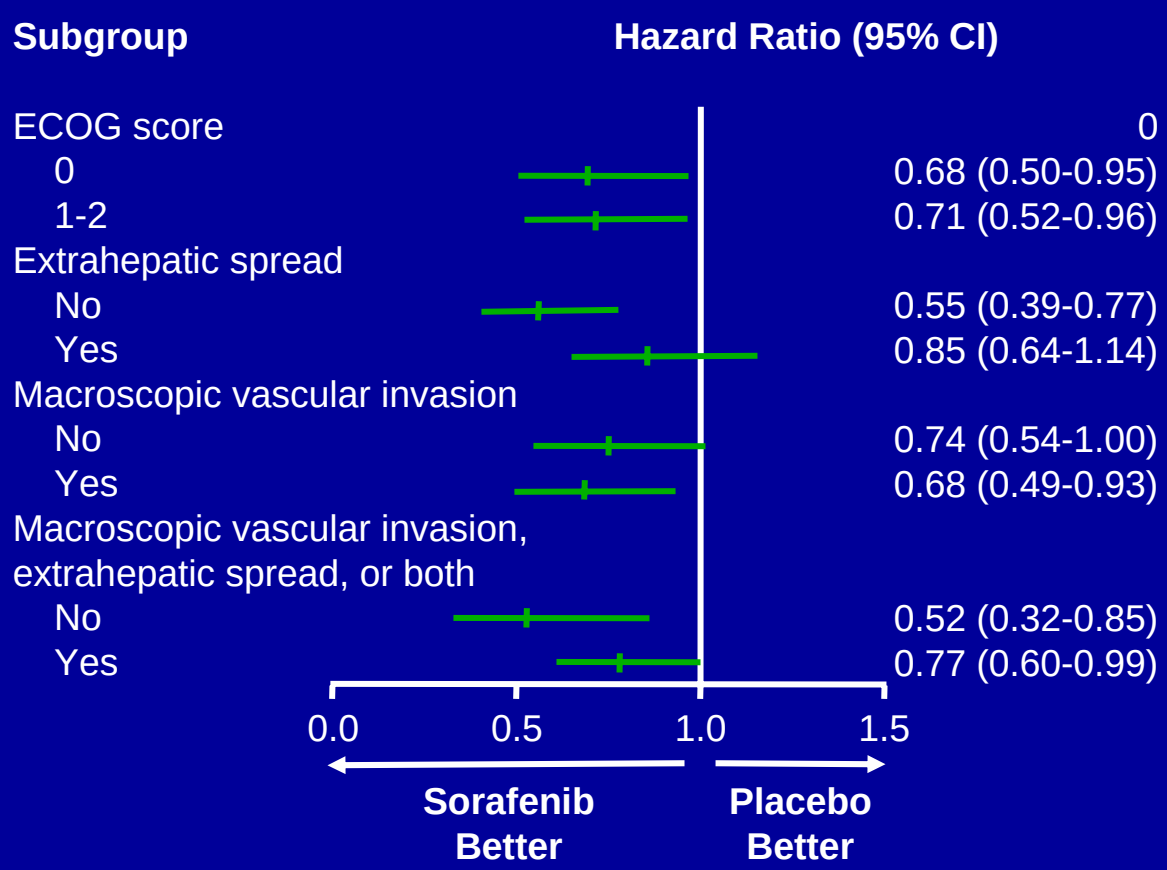
Llovet JM, et al. N Engl J Med. 2008;359:378-390.

The SHARP Trial: Overall Survival (OS) and Time to Progression



Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.

The SHARP Trial: OS and Baseline Prognostic Factors



Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.

The SHARP Trial: Drug-Related AEs

AEs, %	Sorafenib (N = 297)			Placebo (N = 302)			*P* Value	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3 or 4
Overall incidence	80			52				
Constitutional symptoms								
Fatigue	22	3	1	16	3	< 1	.07	1.00
Weight Loss	9	2	0	1	0	0	< .001	.03
Dermatologic events								
Alopecia	14	0	0	2	0	0	< .001	NA
Dry skin	8	0	0	4	0	0	.04	NA
Hand-foot skin reaction	21	8	0	3	< 1	0	< .001	< .001
Pruritus	8	0	0	7	< 1	0	.65	1.00
Rash or desquamation	16	1	0	11	0	0	.12	.12
Other	5	1	0	1	0	0	< .001	.12

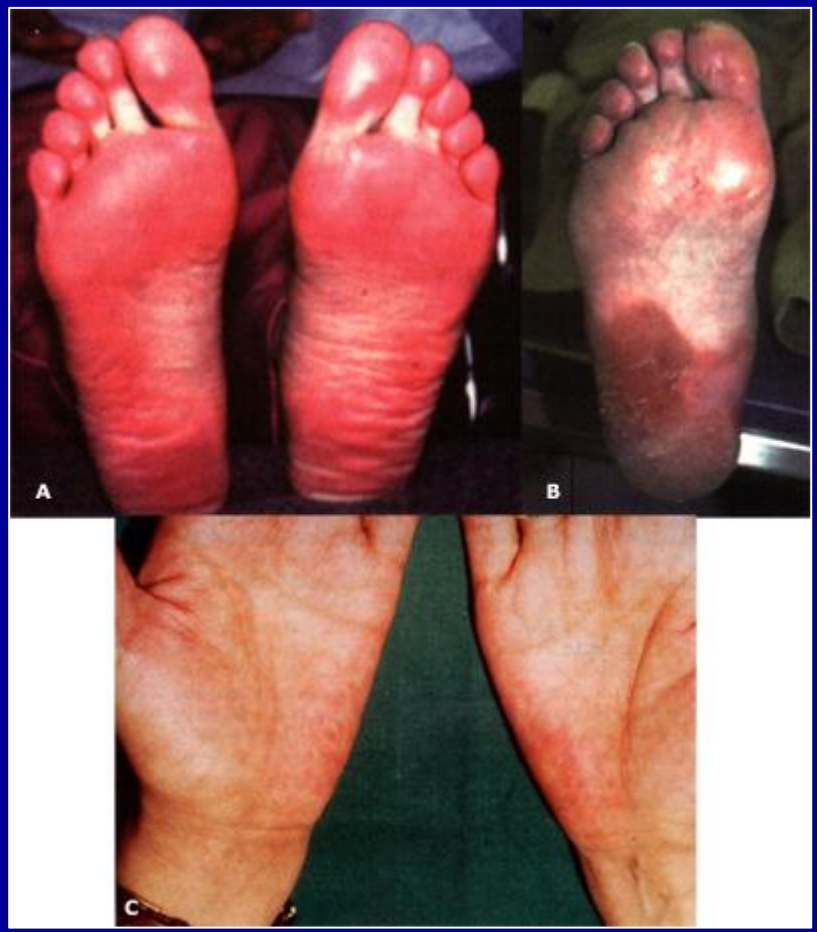
Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.

The SHARP Trial: Drug-Related AEs (Cont'd)

AEs, %	Sorafenib (N = 297)			Placebo (N = 302)			*P* Value	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3 or 4
Gastrointestinal events								
Anorexia	14	< 1	0	3	1	0	< .001	1.0
Diarrhea	39	8	0	11	2	0	< .001	< .001
Nausea	11	< 1	0	8	1	0	.16	.62
Vomiting	5	1	0	3	1	0	.14	.68
Voice changes	6	0	0	1	0	0	< .001	NA
Hypertension	5	2	0	2	1	0	.05	.28
Liver dysfunction	< 1	< 1	0	0	0	0	.50	.50
Abdominal pain not otherwise specified	8	2	0	3	1	0	.007	.17
Bleeding	7	1	0	4	1	< 1	.07	1.00

Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.

Hand-Foot Syndrome



Scheithauer W, et al. Oncology (Williston Park) 2004; 18:1161.

Grading of Hand-Foot Syndrome

Grade	Symptom
1	Minimal skin changes or dermatitis (eg, erythema) without pain
2	Skin changes (eg, peeling, blisters, bleeding, edema) or pain, not interfering with function
3	Skin changes with pain, interfering with function

Common Terminology Criteria for Adverse Events, Version 3.0. Available at: http://ctep.cancer.gov. Accessed October 13, 2008.

Strategies for Managing AEs

- Hand-foot syndrome
  - **Creams and lotions**
  - **Avoid tight footwear**
  - **May require dose reduction**
- Diarrhea
  - **Antidiarrheal agents if severe**
- Fatigue
  - **Consider modafinil or methylphenidate if severe**
- Hypertension
  - **Start or adjust antihypertensives**

Sorafenib: Ongoing Studies in HCC

Europe

- 10 studies approved
  - 4 TACE + sorafenib (1 phase I, 1 phase II, 2 phase III)
  - Sorafenib + tegafur
  - Sorafenib + erlotinib
  - Sorafenib + temsirolimus
  - Sorafenib dose escalation
  - Sorafenib + gemcitabine/oxaliplatin
  - Biomarkers

Asia-Pacific

- 4 studies approved
  - Sorafenib + tegafur
  - Sorafenib + capecitabine/oxaliplatin
  - Sorafenib + bevacizumab
  - Sorafenib + gemcitabine

United States

- 4 studies (nonactivated)
  - 2 TACE + sorafenib
  - Sorafenib + erlotinib
  - Sorafenib + lapatinib

Terminal Stage

Staging of HCC
Terminal Stage

- REQUIREMENTS:
  - Child-Pugh C
  - Performance Status
    - PS-3 (confined to bed or chair > 50% of waking hours; limited self care capability), or
    - PS-4 (bedbound, completely disabled, cannot carry on any self-care. Totally confined to bed or chair) due to tumor involvement.
- Management:
  - Symptomatic, or Liver Transplant.
  - Median survival < 3 months.