PSC PARTNERS SEEKING A CURE

TEN YEAR ANNIVERSARY

Indications for Liver Transplantation

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DONATE LIFE

Objectives

- Review the history of liver allocation in the US
- Understand the MELD score and its use in allocating organs
- Understand complications of liver disease that warrant liver transplant evaluation
- Understand the protocol for transplanting patients with cholangiocarcinoma

Magnitude of the Problem

- 15,736 on liver transplant waiting list (4/20/14)

- 6,455 liver transplants performed in 2013
  - 6,203 deceased donor transplants
  - 252 living donor liver transplants

- The number in need of transplantation far exceeds the availability of organs

History of Liver Allocation in US

Child-Turcotte-Pugh (CTP) Scoring System

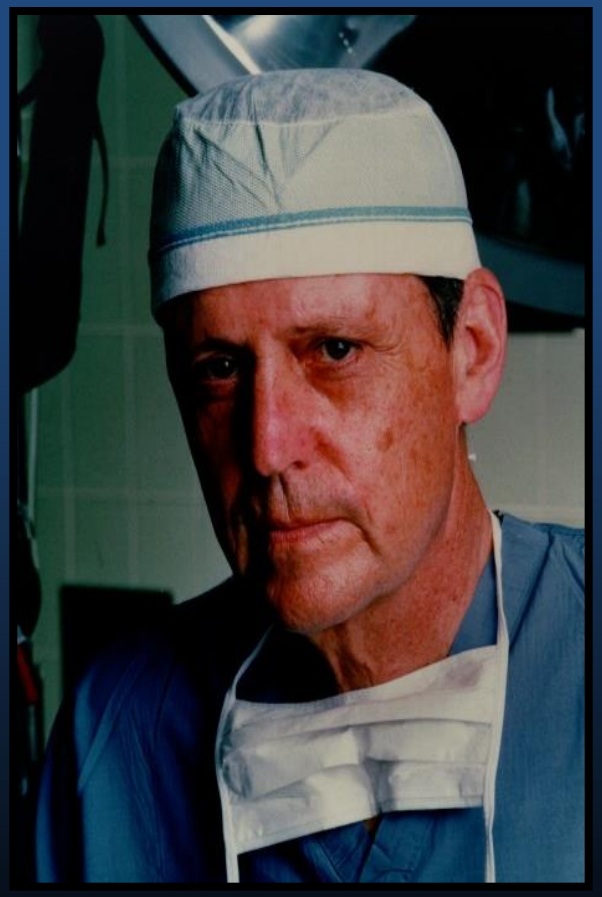
- 1964 – Child-Turcotte system developed
  - Risk of undergoing shunt surgery for variceal bleeding
  - Composed of 5 parameters:
    - Albumin
    - Bilirubin
    - Ascites
    - Encephalopathy
    - Nutritional state
- 1972 – Pugh modified system
  - INR substituted for nutritional state

CTP Scoring System

Clinical or Biochemical Measurement	Points 1	2	3
Hepatic Encephalopathy	None	I-II	III-IV
Ascites	Absent	Mild	Moderate
Total bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Grade A = 5-6 **Grade B = 7-9** **Grade C = 10-15**

Thomas E. Starzl, MD, PhD



- 1926 - born LeMars, Iowa, son of a newspaper editor
- 1952 - graduated Northwestern Univ. Medical School with masters in anatomy and PhD in neurophysiology
- Surgical training at Johns Hopkins, Univ. of Miami, and VA Research Hospital in Chicago
- 1962 - joined the Univ. of Colorado as Associate Professor in surgery
- 1963 - performed world's first liver transplant in human
- 1967 -performed the first *successful* liver transplant

History of Liver Allocation in the US

- 1968 – Southeast Organ Procurement Foundation
  - Organization for transplant professionals
- 1977– SEOPF implements computerized network for organ matching
  - Dubbed the “United Network for Organ Sharing”
- 1982 – SEOPT establishes Kidney Center
  - Round-the-clock assistance in placing donated organs

History of Liver Allocation in the US

- 1983 – NIH consensus conference
  - Affirmed LT no longer experimental
  - Deemed therapeutic modality to manage ESLD
- 1984 – UNOS separates from SEOPF, incorporates as a non-profit organization
- 1986 – UNOS receives federal contract to operate the Organ Procurement and Transplantation Network

History of Liver Allocation in the US

- 1987 – Demand for organs quickly surpassed supply
  - Policy of “sickest first”
  - Limited number of statuses
    - Waiting time became tiebreaker

UNOS Listing Statuses in 1987

Status	
1	Fulminant liver failure Primary graft failure (<7d) Hepatic artery thrombosis (<7d) Acute Wilson's disease
2A	In ICU with CTP >10: (1) Active GIB (2) Stage 3 or 4 coma (3) Hepatorenal syndrome (4) Refractory ascites
2B	CTP score 7-10 hospitalized with: (1) GIB (2) Hepatorenal syndrome (3) SBP or refractory ascites (4) HCC
3	Continuous medical care at home

History of Liver Allocation in the US

- 1997 – "Minimal listing criteria" developed
  - CTP score ≥ 7
  - Exceptions:
    - History of variceal hemorrhage
    - History of SBP
    - HCC w/o LN, vascular invasion, and spread to other organs
- System helped standardize indication for LT
  - Failed to stratify urgency status of patients on wait list

History of Liver Allocation in the US

- 1998 – UNOS system redefined urgency
  - CTP score and estimated short term survival rather than hospital admission
  - CTP score calculated on regular basis

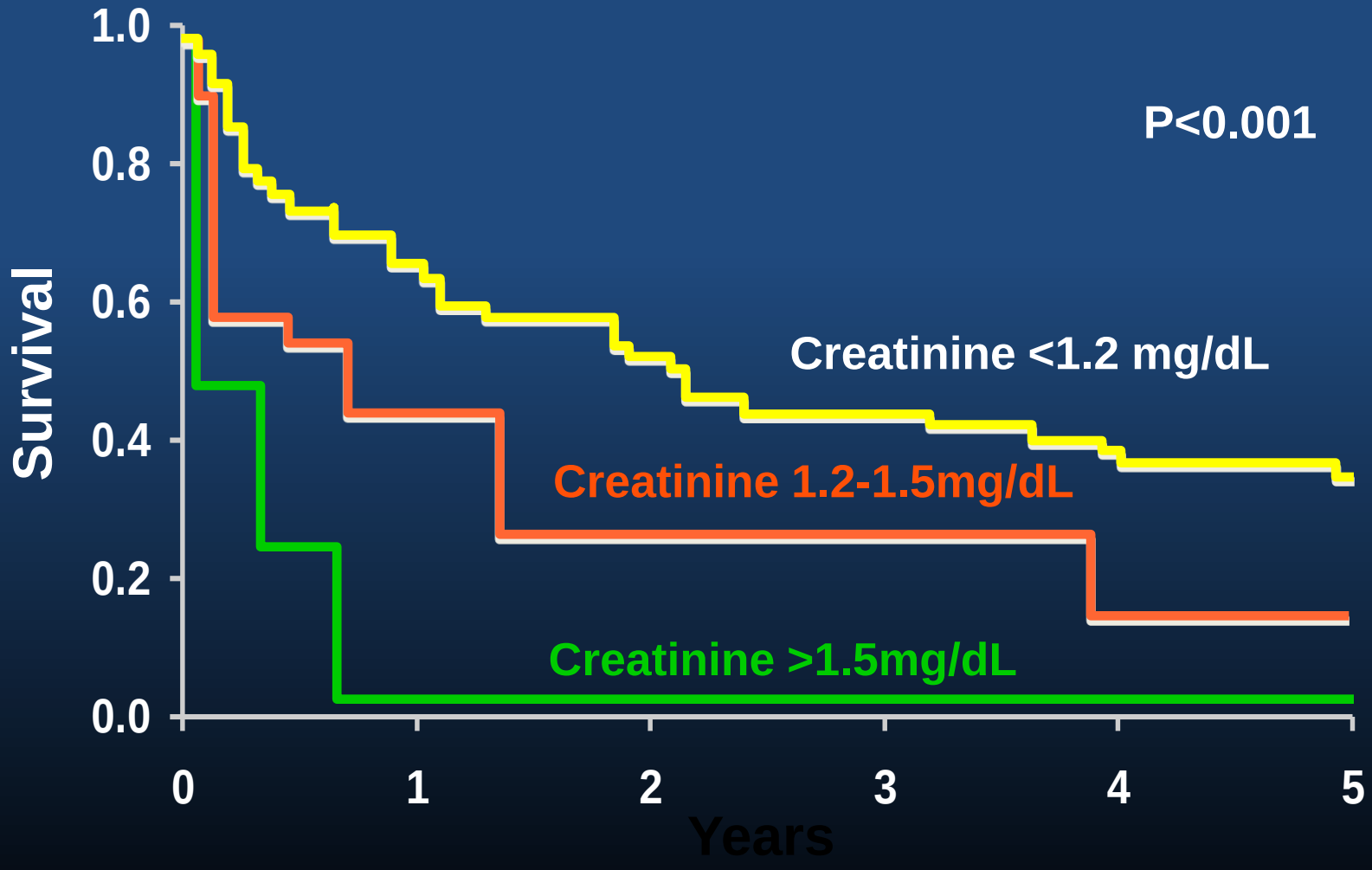
UNOS Listing Statuses in 1998

Status	
2A	CTP score ≥10, ICU care and estimated <7 days to live
2B	CTP score ≥ 10 CTP score ≥7 associated w/ refractory portal hypertensive complications or HCC without metastatic disease
3	CTP ≥7 minimal listing

Problems with CTP Allocation Scheme

- Limited number of categories
  - Fails to prioritize large number of patients
- Limited discriminating ability
- Waiting time became main determinant
  - Waiting time does not reflect medical need (i.e., HCC)
- Uses subjective parameters
  - Gaming the system
- Never validated for waiting list
- Creatinine not included

Survival in Cirrhosis Based on Level of Renal Dysfunction



Blackwell: Science, Oxford, UK

Final Rule Mandate

Organ Procurement and Allocation Defined

- 1998 –Final Rule issued by DHHS under National Organ Transplant Act mandating:
  1. Organs should be allocated in the order of medical urgency
  2. Role of waiting lists should be minimized
  3. Efforts should be made to avoid futile transplantation and ensure efficient use of scarce organs

Federal Register 1998;63:16296-338.

Development of the MELD Score

Model for End-Stage Liver Disease (MELD) Score

- Developed initially to predict 3-month survival in patients undergoing TIPS

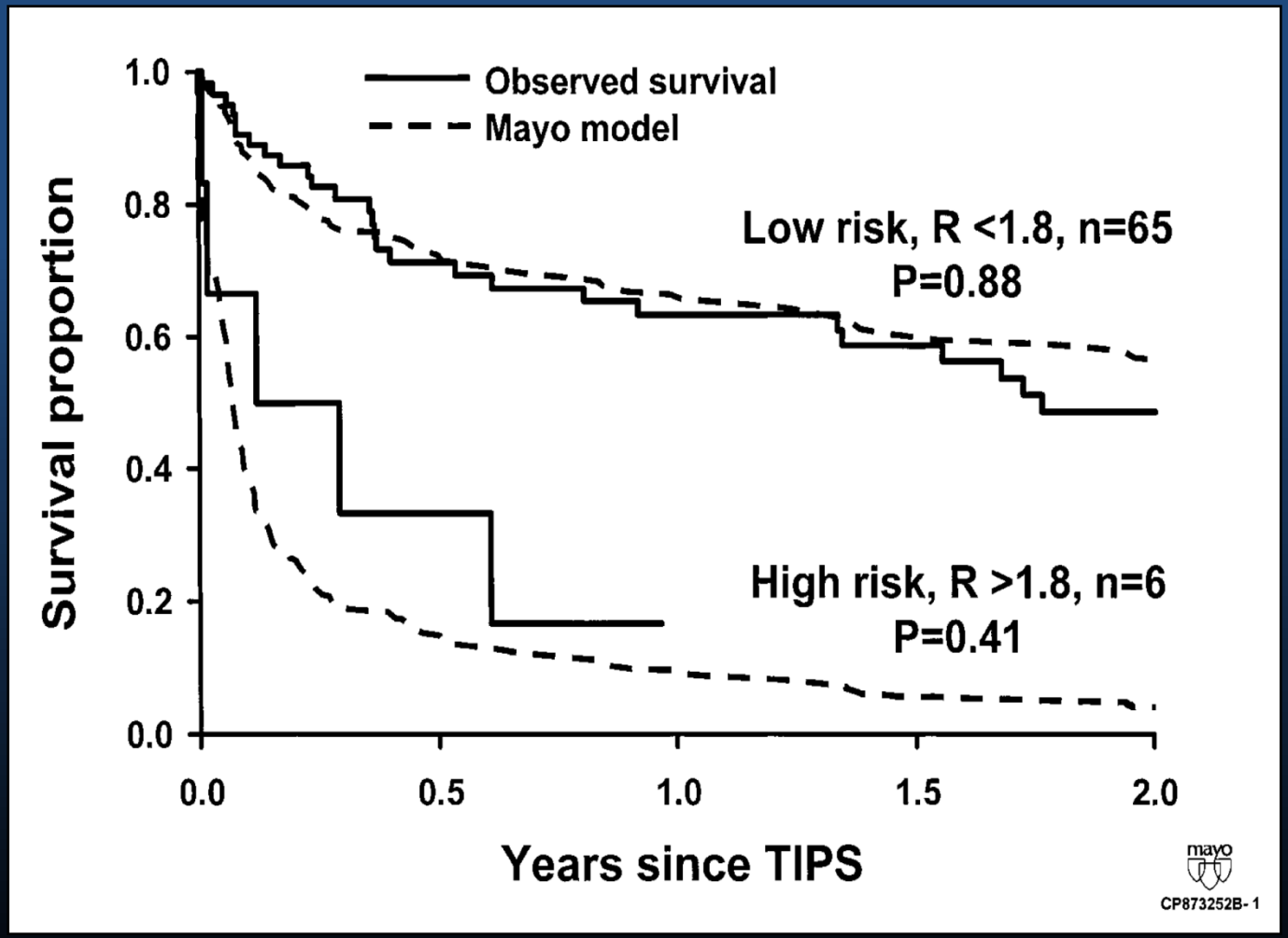
TABLE 4. Survival Model for Patients Undergoing Elective TIPS (n = 231, death = 110)

Variable	Regression Coefficient	Regression Coefficient Standard Effort	*P*
Serum creatinine ($\log_e$ value)	0.957	0.142	<.01
Serum bilirubin ($\log_e$ value)	0.378	0.117	<.01
INR ($\log_e$ value)	1.120	0.331	<.01
Cause of cirrhosis*	0.643	0.211	<.01

*For cause of cirrhosis, use 0 for alcohol-related liver disease or for cholestatic liver disease; 1 for all other causes.

Malinchoc et al. Hepatology 2000;31:864-71.

Validation of Model With An Independent Group from Netherlands (n=71)



Malinchoc et al. Hepatology 2000;31:864-71

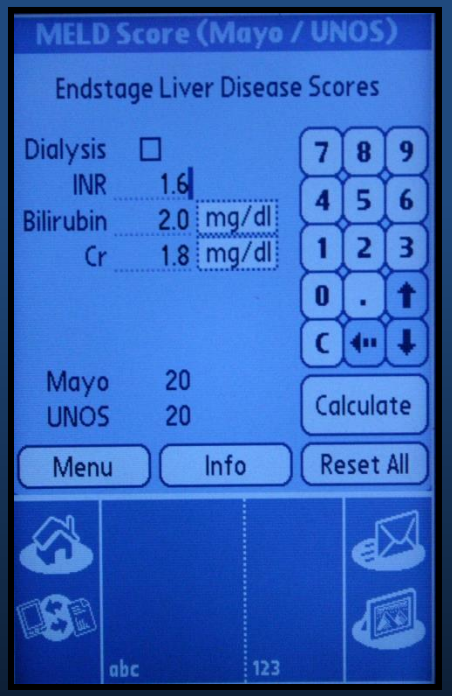
The Current MELD Score Calculation

MELD Score =

$0.378 * \log_e(\text{bilirubin [mg.dL]}) +$

$1.120 * \log_e(\text{INR}) +$

$0.957 * \log_e(\text{creatinine [mg/dL]}) + 0.643$



UNOS MELD score:

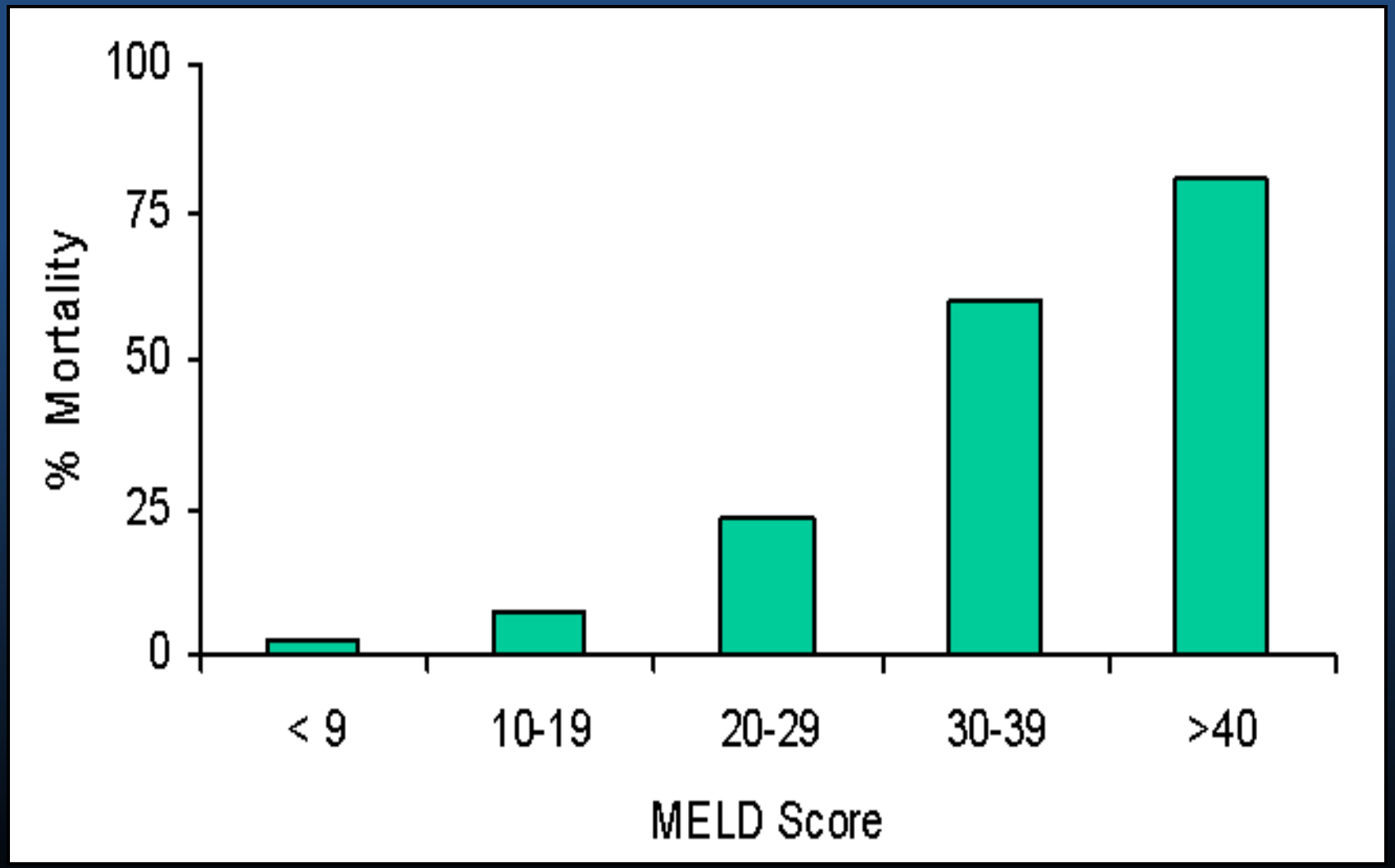
- Minimum values set at 1.0
- Maximum creatinine is 4.0 mg/dL
- For patients on dialysis ≥2 times in prior week, creatinine level is automatically 4.0 mg/dL

MELD and Allocation of Donor Livers

- Study of MELD and 3-month waiting list mortality
  - Prospective study on 3,437 patients
  - November 1999 to December 2001
- Demonstrated ability of MELD to accurately predict 3-month mortality in patients with ESLD

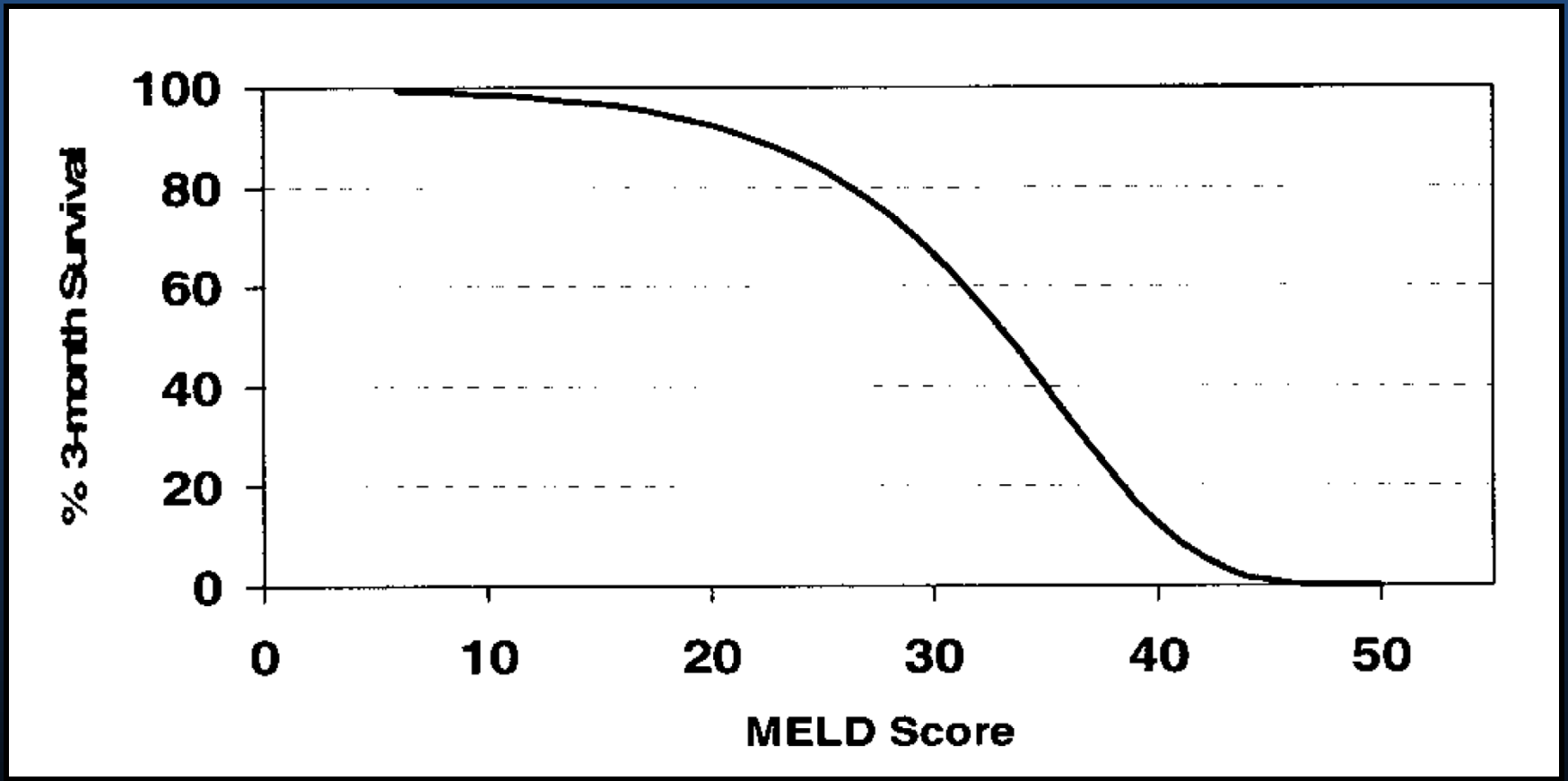
Wiesner et al. Gastroenterology 2003;124;9:91-6.

3-Month Mortality Based on Listing MELD in Patients on the Waiting List



Wiesner et al. Gastroenterology 2003;124;9:91-6.

Estimated 3-Month Survival Based on Listing MELD in Patients on the Waiting List



Wiesner et al. Gastroenterology 2003;124;9:91-6.

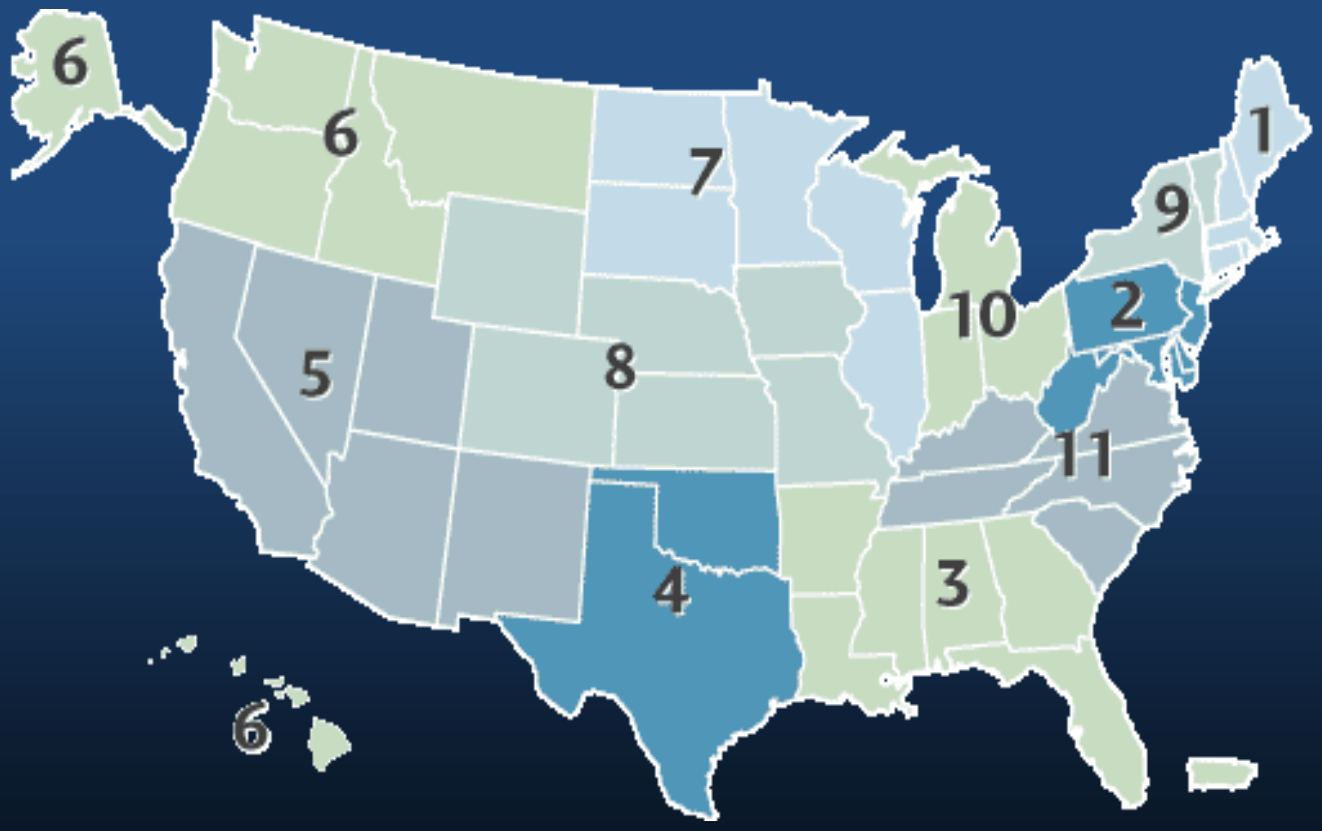
Comparison of MELD and CTP Allocation Schemes

	MELD Allocation Scheme	CTP Allocation Scheme
Development & rational	TIPS outcome	Surgical shunt outcome
Assessment	Prospective	Empiric
Parameters	Objective	Partially subjective
Variability	Minimal	Center interpretation
Spectrum	Continuous	Ceiling effect, categorical
Validation	Yes	No
Allocation emphasis	Disease severity	Waiting time

February 27, 2002

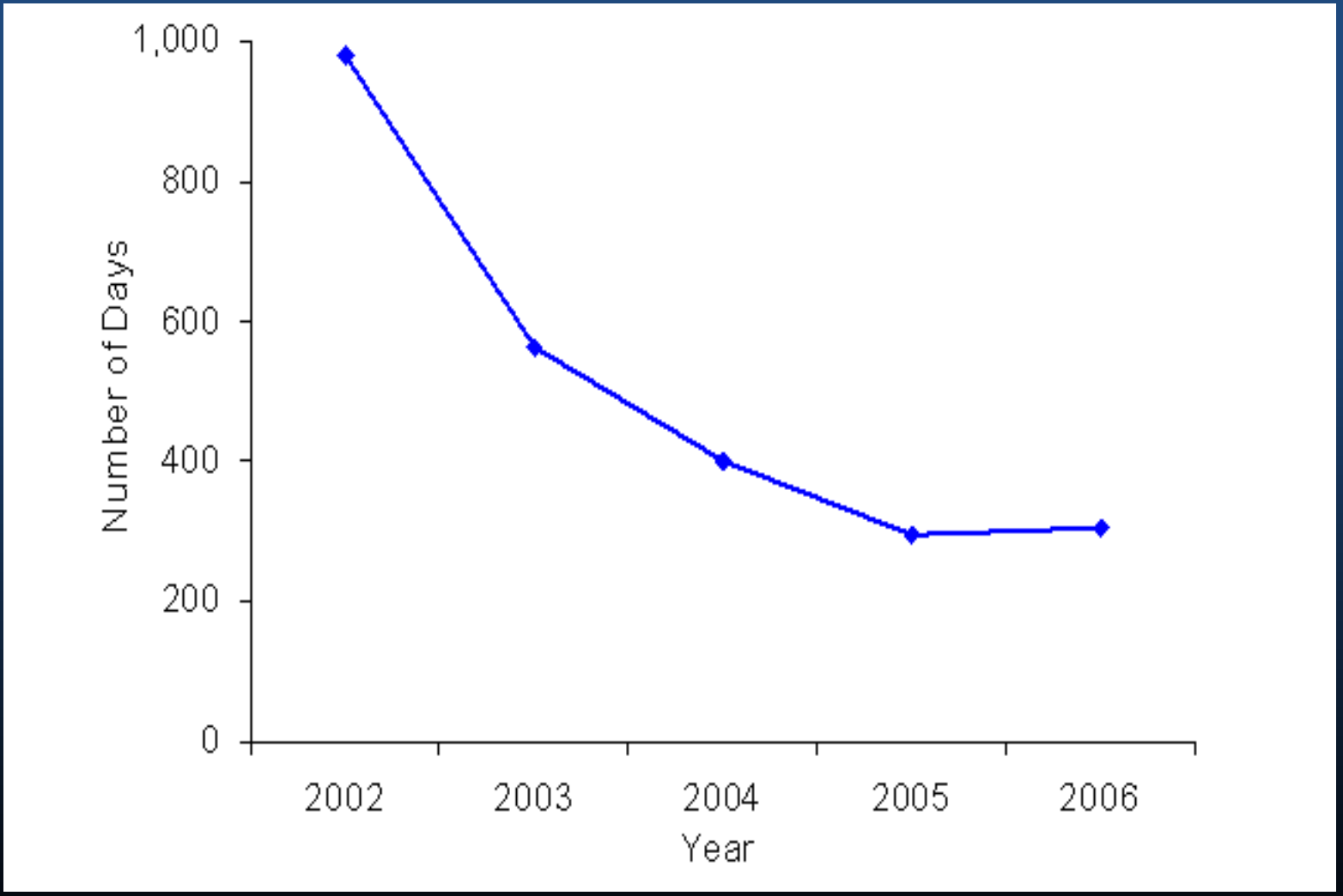
MELD liver allocation policy was implemented

Donor Matching System



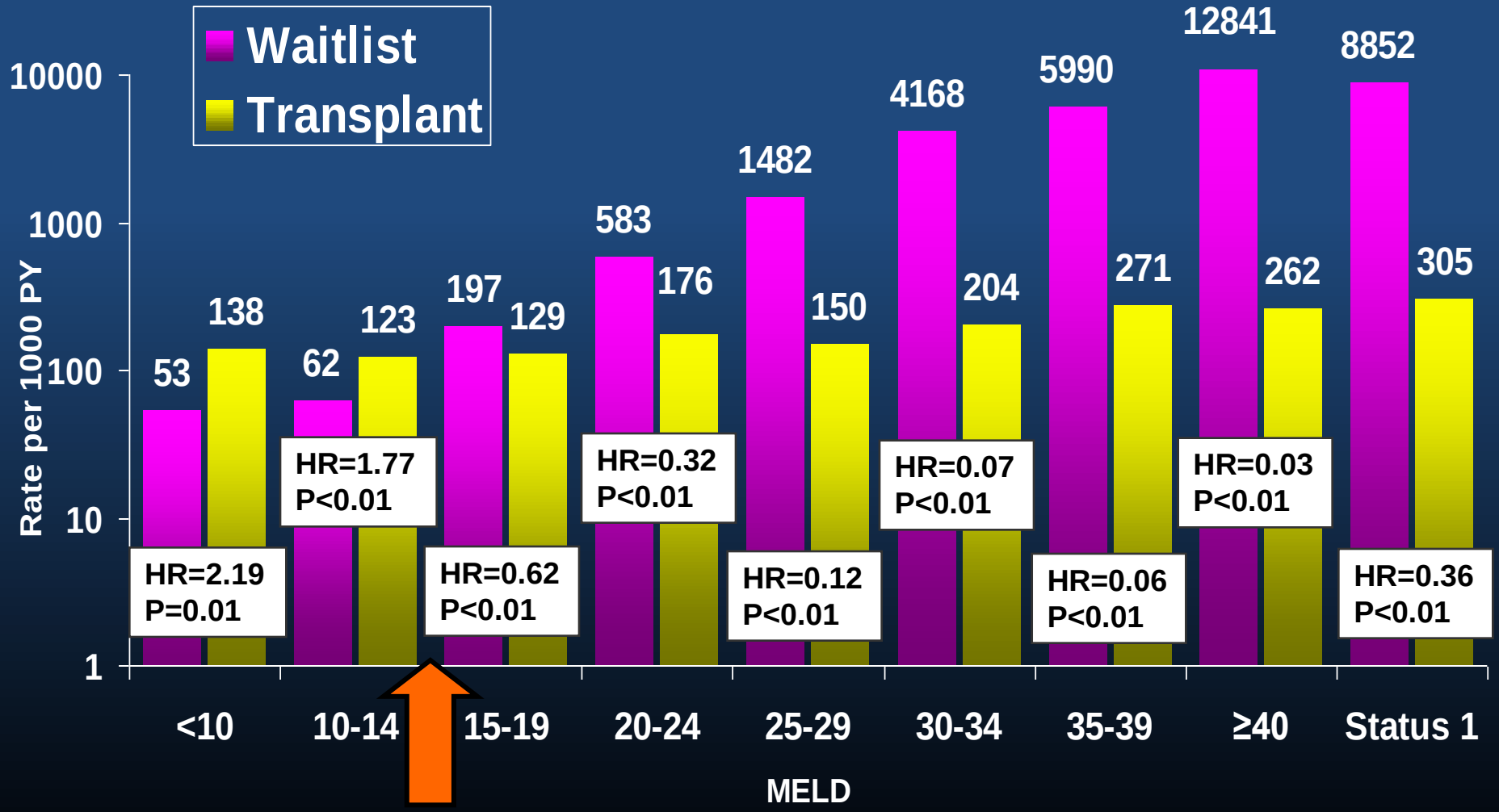
~59 organ procurement areas ranging from 1-12 million

Median Time to Transplant for New Liver Waiting List Registrations, 2002-2006



Source: 2007 OPTN/SRTR Annual Report, Table 1.5

Mortality Rates on Waitlist and with Transplant by MELD Score



Freeman. Liver Transpl 2003;9:S54-S59.

Liver Transplantation in the MELD Era

Summary

- Excellent predictor of pretransplant survival
- Decreased registrations (MELD <10)
- Decreased death rate on waiting list
- Sicker patients are being transplanted
- Post transplant survival unchanged
- Resource utilization correlates with MELD
- Better defining survival benefit - optimal timing
- Evidence-based decision-making

Indications for Liver Transplantation

- Non-cholestatic liver disorders
  - Chronic hepatitis B
  - Chronic hepatitis C
  - Alcoholic liver disease
  - Autoimmune hepatitis
- Cholestatic liver disorders
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Biliary atresia
  - Cystic fibrosis
- Primary malignancies
  - Hepatocellular carcinoma
  - Hepatoblastoma
  - Fibrolamellar hepatocellular carcinoma
  - Hemangioendothelioma
  - Cholangiocarcinoma
- Metabolic disorders causing cirrhosis
  - Alpha-1 antitrypsin deficiency
  - Wilson disease
  - Non-alcoholic steatohepatitis
  - Hemochromatosis
  - Glycogen storage disease
- Metabolic disorders causing severe extrahepatic morbidity
  - Amyloidosis
  - Hyperoxaluria
  - Urea cycle disorders
- Fulminant hepatic failure
- Miscellaneous
  - Budd-Chiari syndrome
  - Metastatic neuroendocrine tumors
  - Polycystic disease

Determining the Need for LT

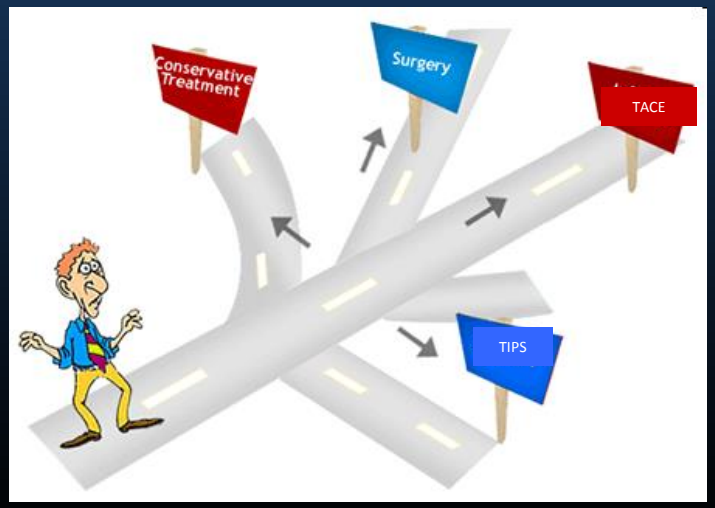
- Alternatives to transplantation
- Natural history of underlying liver disease
  - Survival after LT vs. risk of death without LT
- Prognostic criteria
  - MELD score >15
- Complications of liver disease
  - Ascites
    - Spontaneous bacterial peritontitis
    - Hepatorenal syndrome
  - Variceal bleeding
  - Hepatoma
  - Hepatic encephalopathy
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- Quality of life issues – pruritis, malnutrition

Live Donor Liver Transplantation

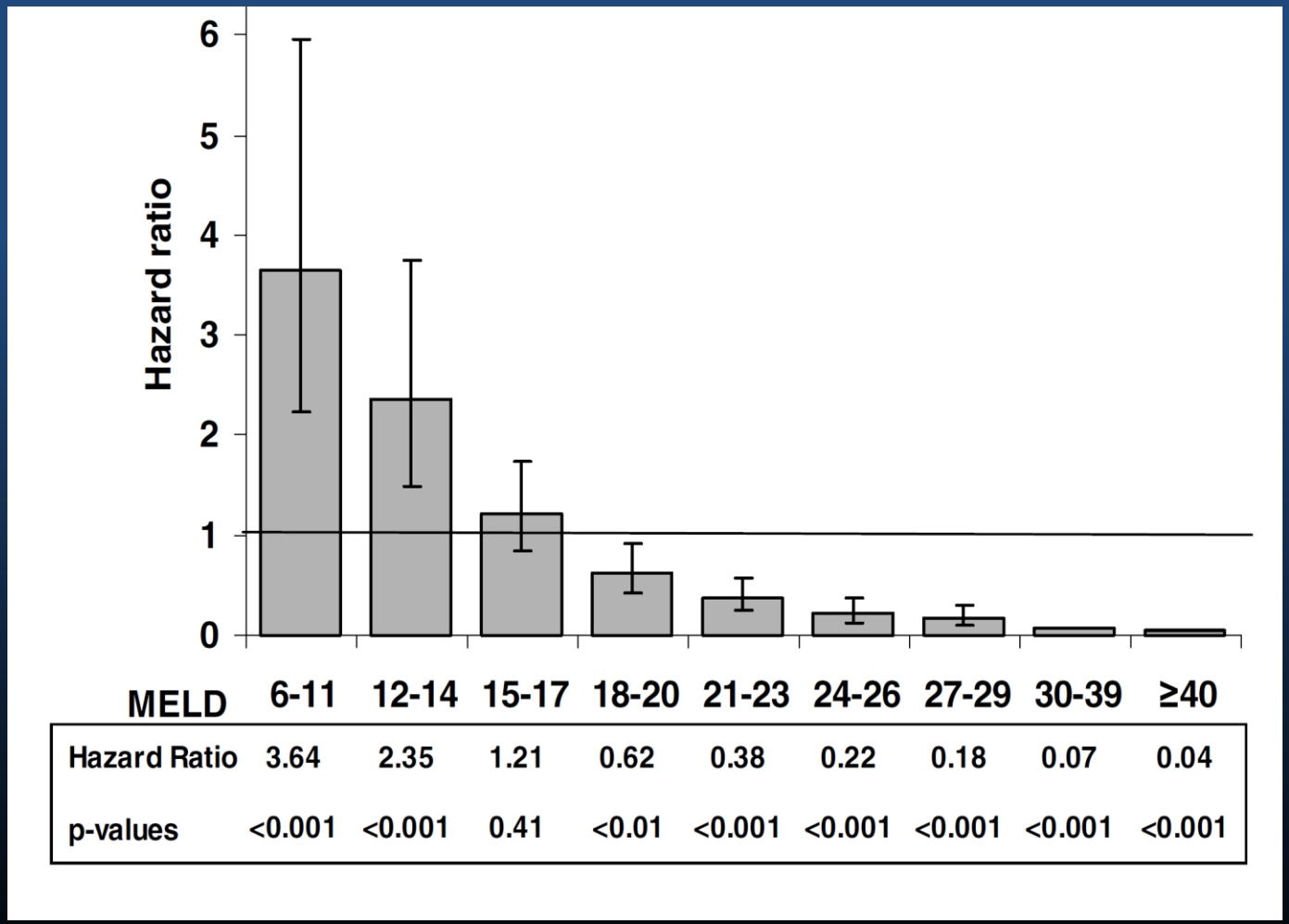
- Recipient must be candidate and listed
- Indication and MELD taken into consideration
  - MELD >15 or “sicker than the MELD score”
  - HCC within or outside Milan criteria
  - Cholangiocarcinoma
- Donor
  - Compatible blood type
  - Young, thin, relatively same size as recipient
  - Biliary and vascular anatomy is major determinate
  - Risk of right lobe resection (death 1 in 200)

Alternatives to Transplantation

- Autoimmune hepatitis → immunosuppression
- Wilson disease (copper) → chelation therapy
- Hemochromatosis (iron) → phlebotomy
- Decompensated chronic HBV → antiviral therapy
- Hepatcellular carcinoma → liver resection



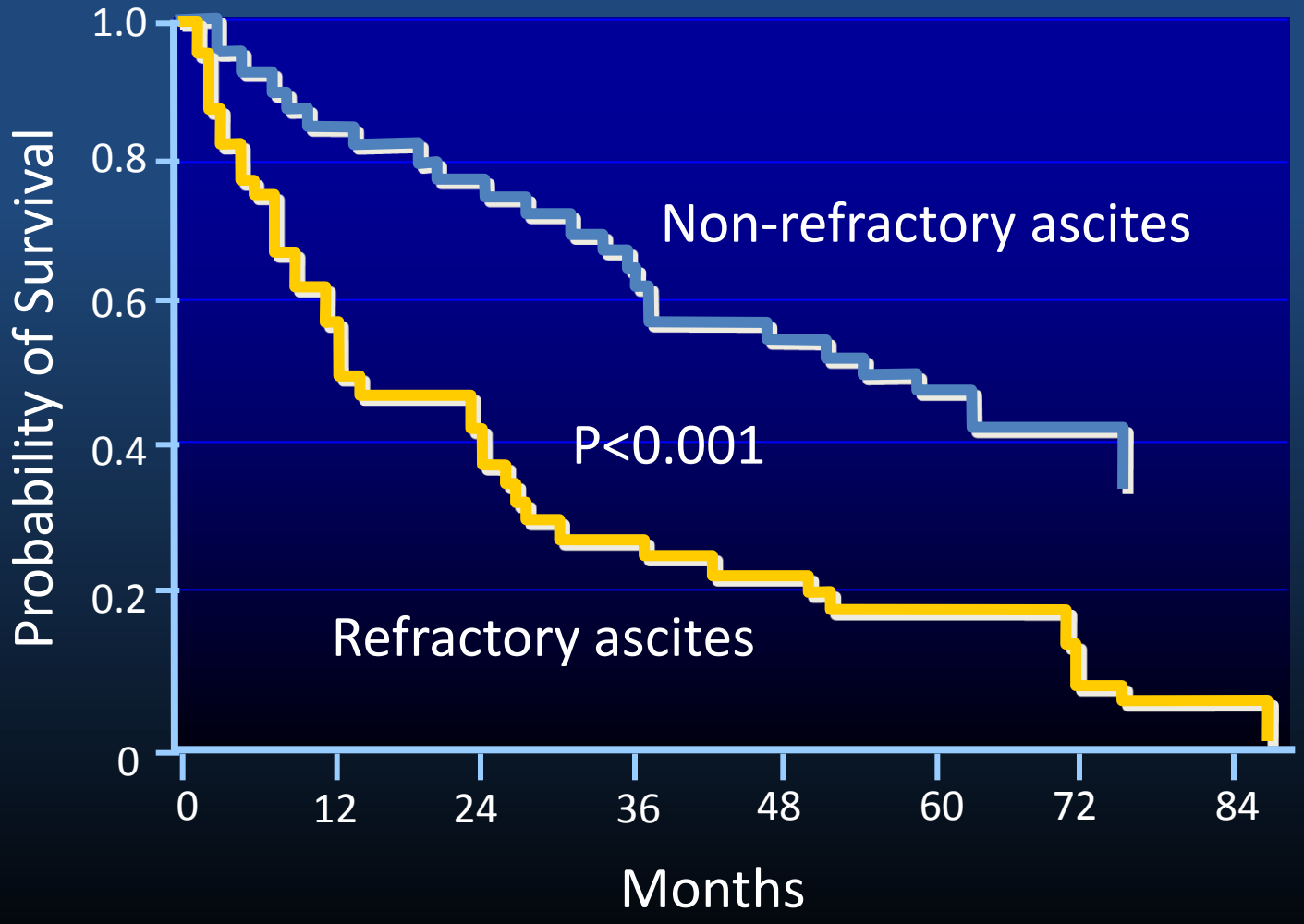
Comparison of Mortality Risk For LT Recipients vs. Candidates on Waiting List



MELD	6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-39	≥40
Hazard Ratio	3.64	2.35	1.21	0.62	0.38	0.22	0.18	0.07	0.04
p-values	<0.001	<0.001	0.41	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

Am J Transplant 2005;5:307-313.

Worse Survival in Patients with Refractory Ascites



Am J Gastroenterol 1993;88:514.

Liver Transplantation for PSC

- Treatment of choice for advanced disease
- Excellent survival – 85% at 5 years

Mayo Risk Score

- Predicts mortality in PSC patients
  - Age
  - Total bilirubin
  - AST
  - Variceal bleeding
  - Albumin

MELD Score

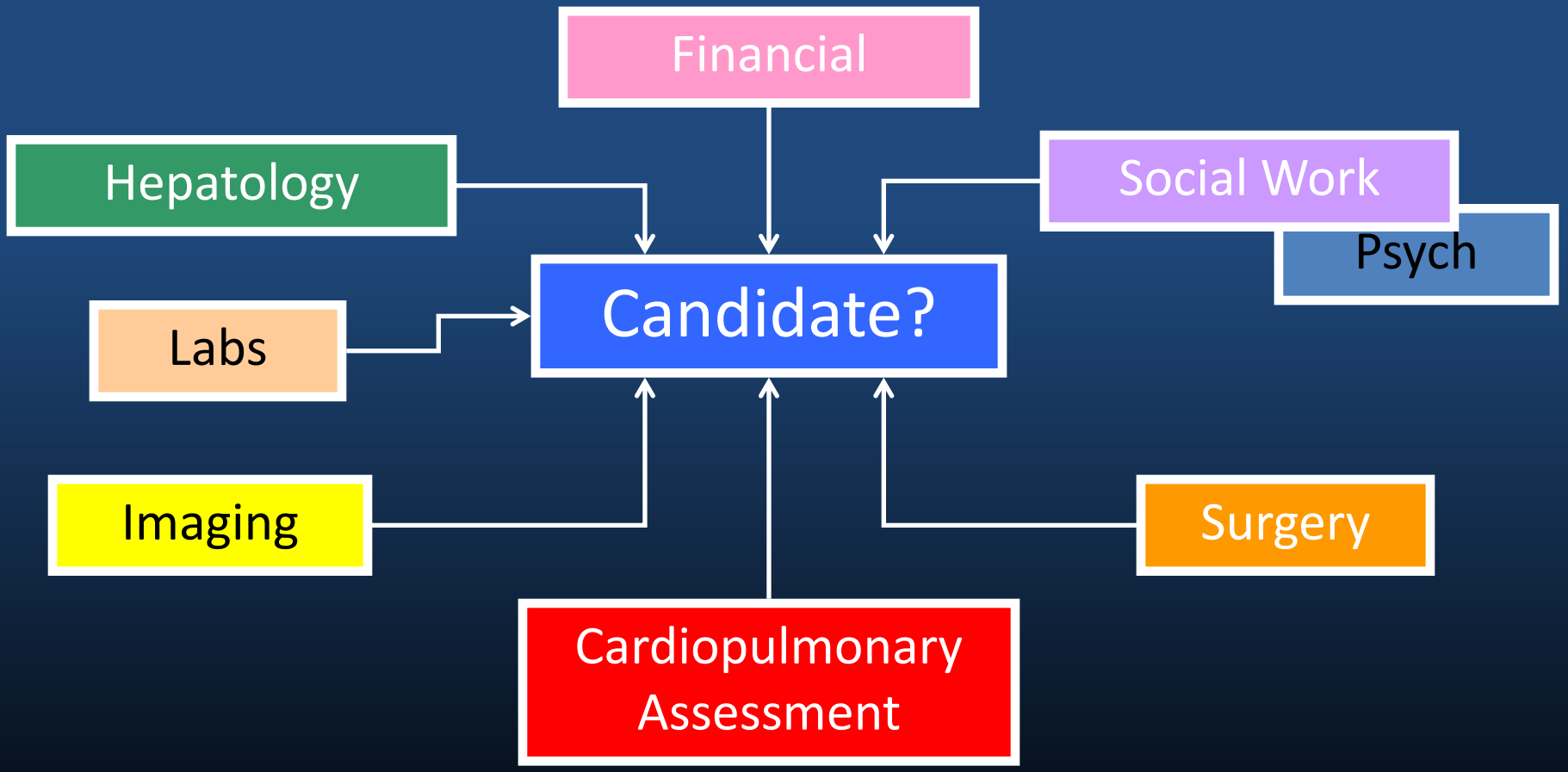
- Predicts mortality in pts with ESLD
- Used to rank pts on LT list
  - Total bilirubin
  - INR
  - Creatinine

Role for living donor liver transplantation?

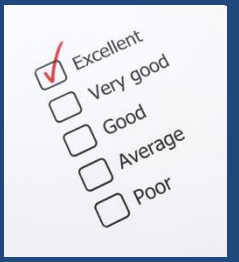
Liver Transplant Evaluation: Determining Potential Success of LT

- Can patient survive the operation and immediate post-op period?
- Can patient comply with complex management post-LT?
- Existence of comorbid conditions so severe to compromise graft or patient survival?

Liver Transplant Evaluation



Recipient Evaluation

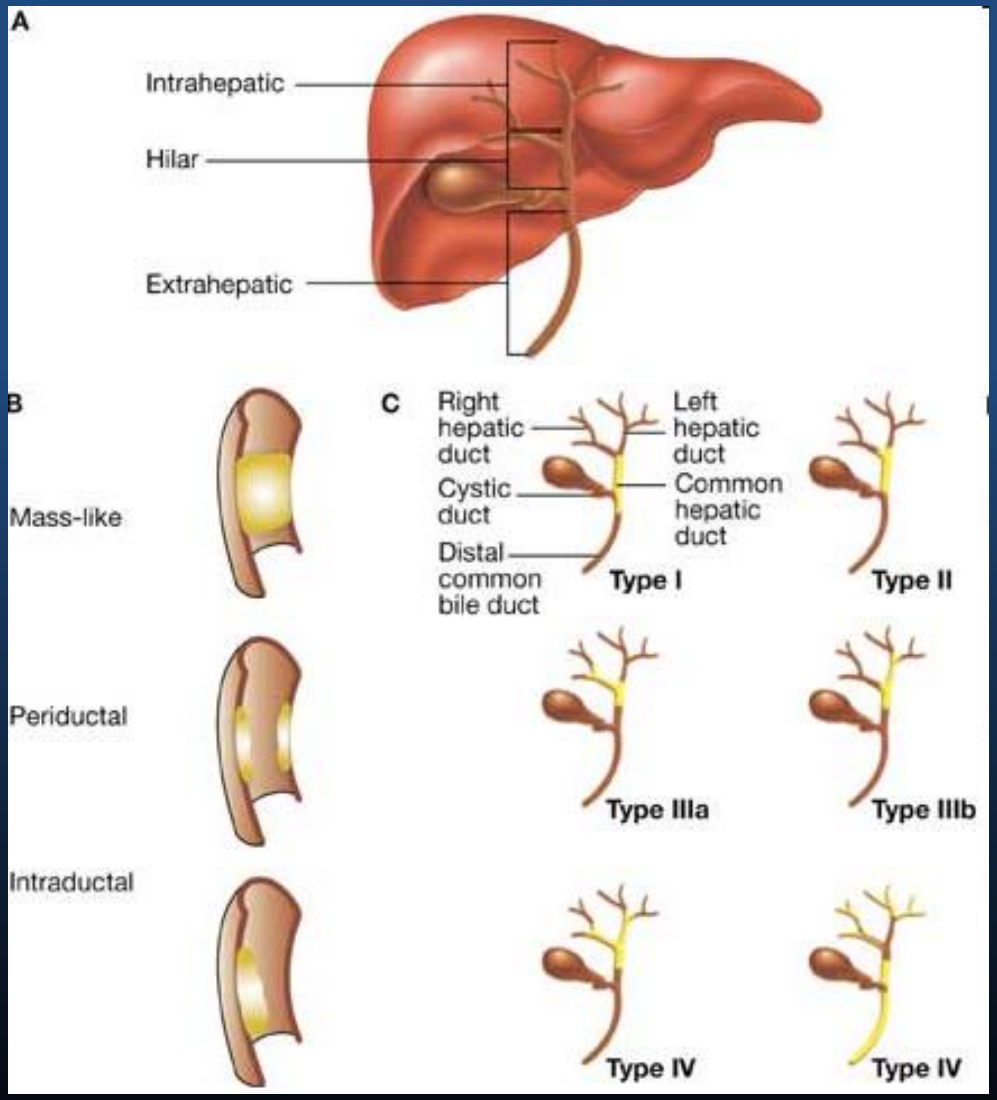


- Hepatology Evaluation
  - History
  - Complications of liver disease
  - Medications
  - Allergies
  - Physical examination
  - Patient education
- Cardiopulmonary assessment
  - EKG
  - Contrast enhanced Echo
  - Dobutamine stress echo
  - Pulmonary function tests
  - CXR
- Age appropriate screening
  - Colonoscopy
  - Mammography
  - PAP smear
- Laboratory studies
  - Etiology and severity of liver disease
  - Creatinine clearance
  - Comorbid conditions (diabetes, iron overload)
  - Previous infections (HBV, HCV, EBV, CMV, HIV, RPR)
- Abdominal imaging
  - Portal vein patency
  - Hepatocellular carcinoma
- Financial Counseling
- Psychosocial assessment
  - Psychiatric evaluation
  - Social work evaluation
  - Patient education
  - Drug/alcohol rehab
- Surgical assessment

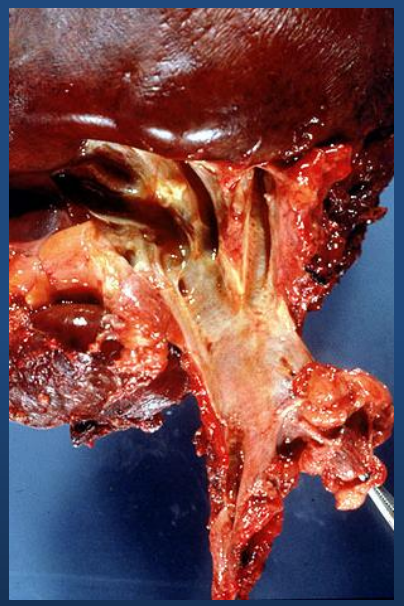
Transplant Labs

- α-1-antitrypsin level
- α-1-antitrypsin phenotype
- α-fetoprotein
- ABO blood type x 2
- Anti-nuclear antibody
- Anti-smooth muscle antibody
- Anti-mitochondrial antibody
- Cerulplasmin
- CMV IgG
- Complete blood count
- Comprehensive metabolic panel
- EBV IgM, IgG
- Ferritin
- Hemoglobin A1C
- Hepatitis A antibody total
- Hepatitis B core antibody
- Hepatitis B surface antibody
- Hepatitis B surface antigen
- Hepatitis B DNA
- Hepatitis C antibody
- Hepatitis C PCR
  - Hepatitis C genotype
- HIV antibody 1&2
- HSV Type specific antibody
- INR
- Iron
- Iron binding capacity
- PTT
- RPR
- TSH
- Transplant abused substances
- Urinalysis

Cholangiocarcinoma



Risk of Cholangiocarcinoma in PSC



- 10-15% lifetime risk
- Increased risk with ulcerative colitis
- Often heralded by clinical deterioration
  - Jaundice
  - Weight loss
  - Abdominal discomfort
- Diagnosis is extremely difficult
  - 10% pts undergoing LT for PSC have incidental CCA
- Prognosis is poor; liver transplantation offers only cure in patients with PSC

Burak KW et al. *AJG* 2004.
Chalasani et al. Hepatology 2000.

Cholangiocarcinoma:
Criteria for MELD Exception for LT

- Malignant stricture on cholangiography with:
  - Biopsy or cytology demonstration malignancy
  - CA-19-9 >100 U/ml
  - Aneuploidy
- Mass lesion on cross-sectional imaging <3cm
- Unresectable on basis of technical considerations or underlying liver disease (e.g., PSC)
- Exclusion of intra- and extrahepatic metastases every three months
- Operative staging after completion of neoadjuvant therapy and before LT
- MELD exception of 10% mortality at 3-months with score increased 10% mortality equivalents every 3-months

Liver Transplantation 2006;12:S85–S92

Recurrent PSC after Liver Transplantation

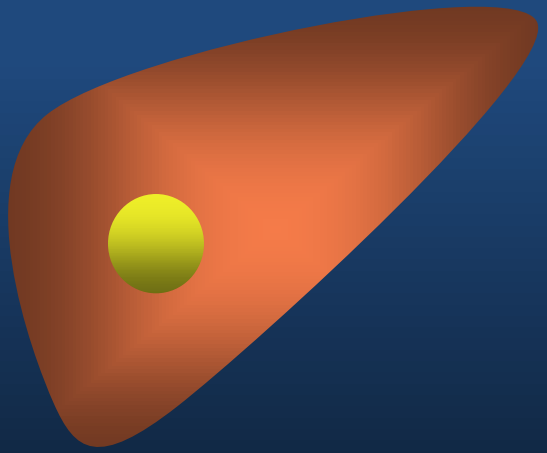
- Recurrent PSC 14-20%
  - 1/3rd may need retransplantation
- Diagnosis based on liver biospy and cholangiogram
  - Exclude: ABO incompatibility, HAT, anastamotic stricture
- UCH Experience 1988-2006
  - 130/1102 (11.7%) for PSC
  - 22 (16.9%) with recurrence
  - 7 (31.8%) retransplanted

Gastroenterol Clin North Am 2008

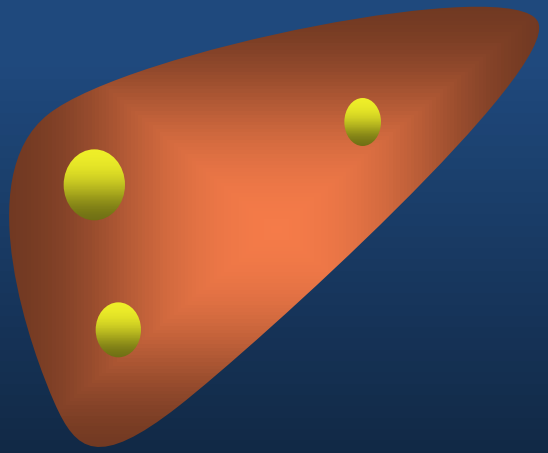
END

Liver Transplantation for HCC:
Milan Criteria

1 lesion ≤ 5 cm



2 or 3, all <3 cm



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Absence of Macroscopic Vascular Invasion
Absence of Extra-hepatic Spread

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