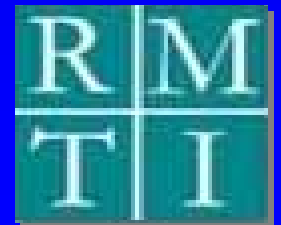


# Deceased- and Living-Donor Liver Transplantation for Hepatocellular Carcinoma

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SIR Research Consensus Panel  
Toronto, Ontario, Canada  
March 30<sup>th</sup>, 2006



# Surgical Treatment of HCC

## *The essential problem*

- > 90% of HCC the result of underlying liver disease
- Physical removal / destruction prior to metastasis only hope for cure
  - no effective medical therapy
- Cirrhosis often precludes resection and is an independent cause of death
- Transplantation seems like the answer
  - eliminates both cirrhosis and cancer

# Transplantation for Known HCC $\leq 5\text{cm}$

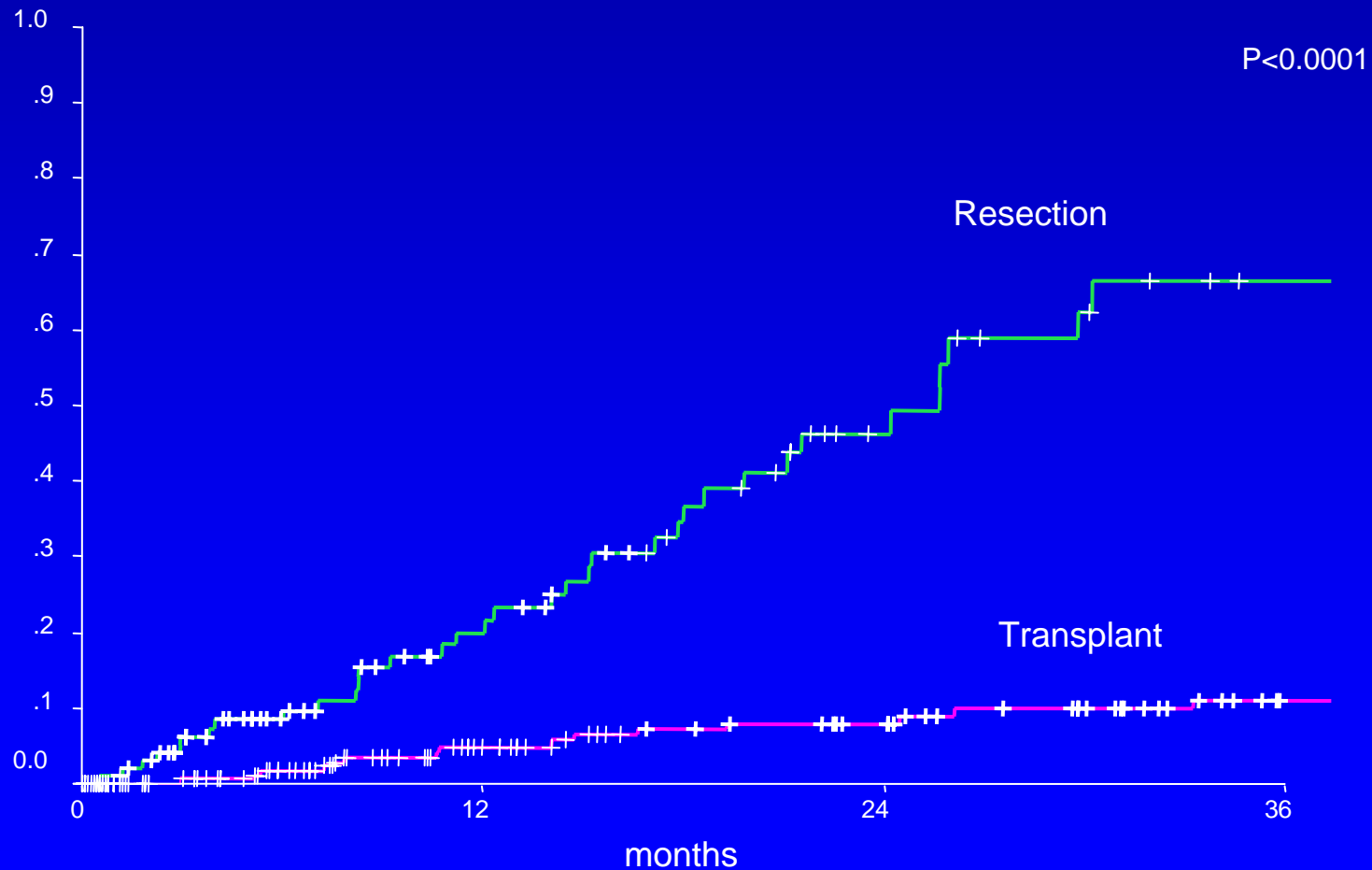
*Mazzaferro et al, NEJM 1996*

- 48 patients with cirrhosis, HCC
- “Milan criteria”
  - if one lesion,  $\leq 5\text{cm}$
  - if two or three lesions, all  $\leq 3\text{cm}$
- No macroscopic vascular invasion
- 75% 4-year patient survival
  - 83% recurrence-free

# Postsurgical HCC Recurrence

*Patients within Milan criteria*

*Mount Sinai data*



# Transplantation for HCC in the U.S.

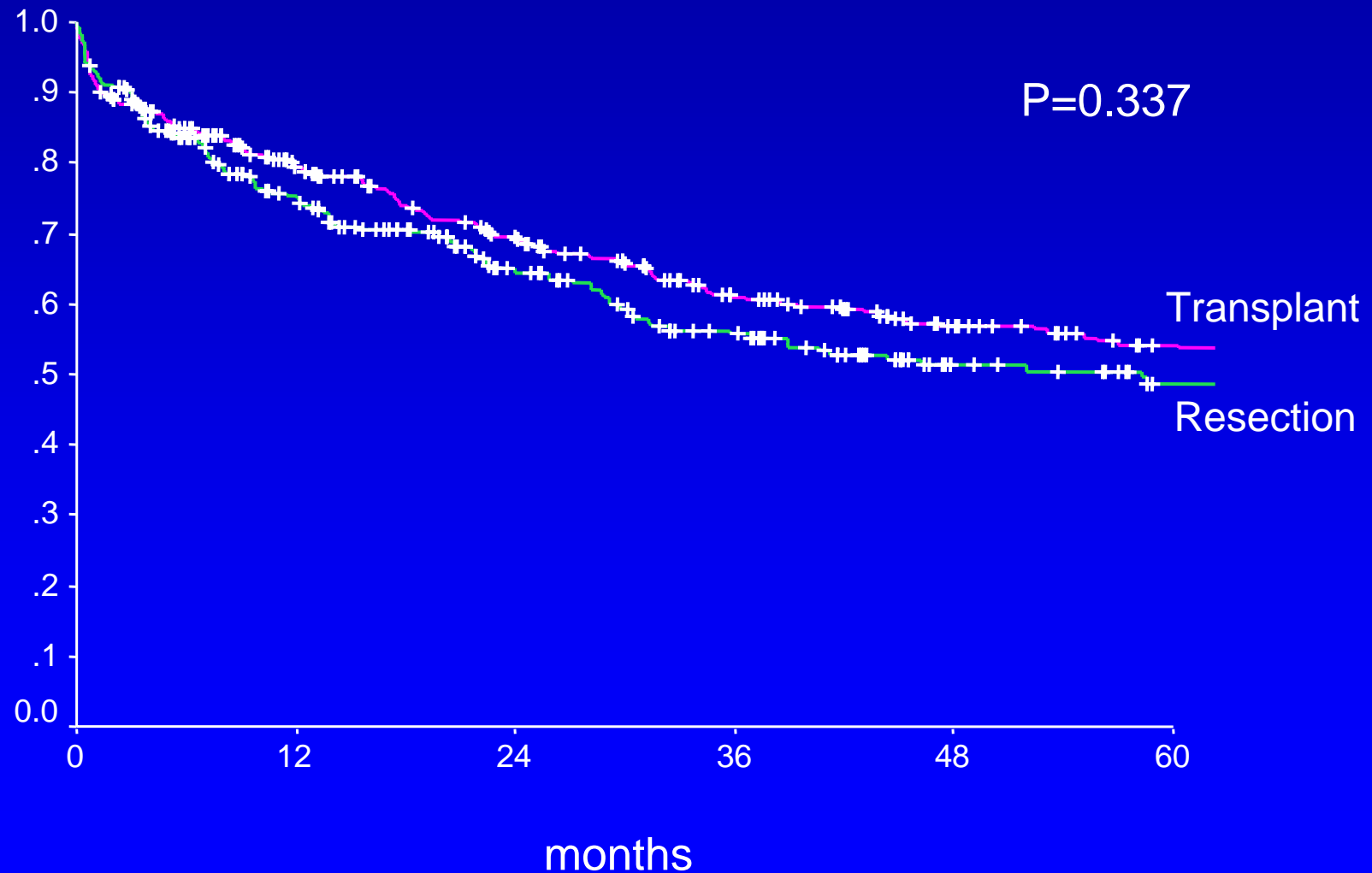
## *Priority for early HCC*

- Excellent results of transplantation for early HCC
- Long waiting time leads to tumor progression
- U.S. allocation scheme priority:
  - unresectable HCC
  - meets Milan criteria
- Other HCC patients eligible, but no priority
  - effectively rules out deceased donor transplantation

# Patient Survival: Resection vs. Transplant

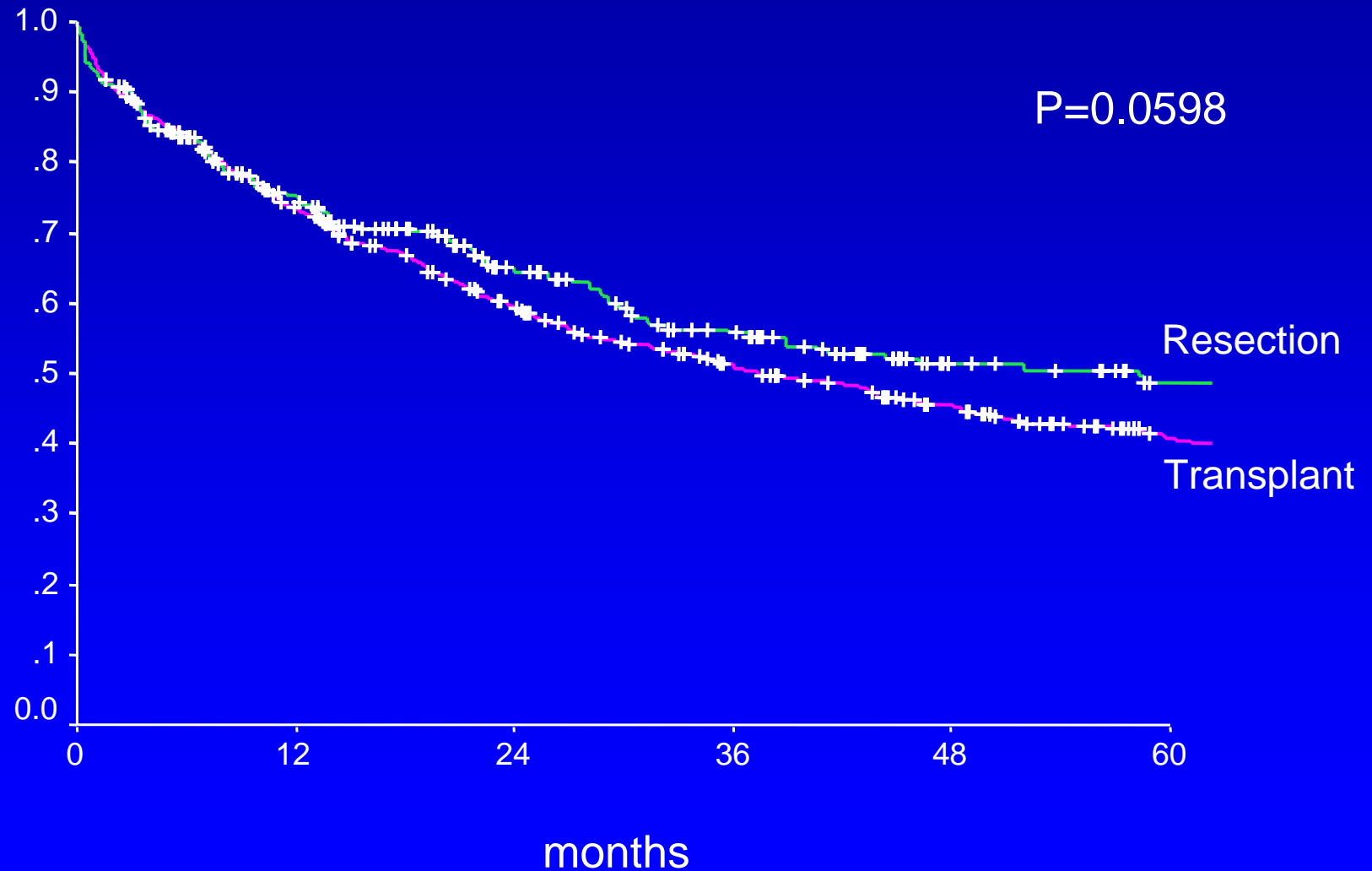
*Patients effectively transplanted*

*Mount Sinai data*



# Patient Survival: Resection vs. Transplant

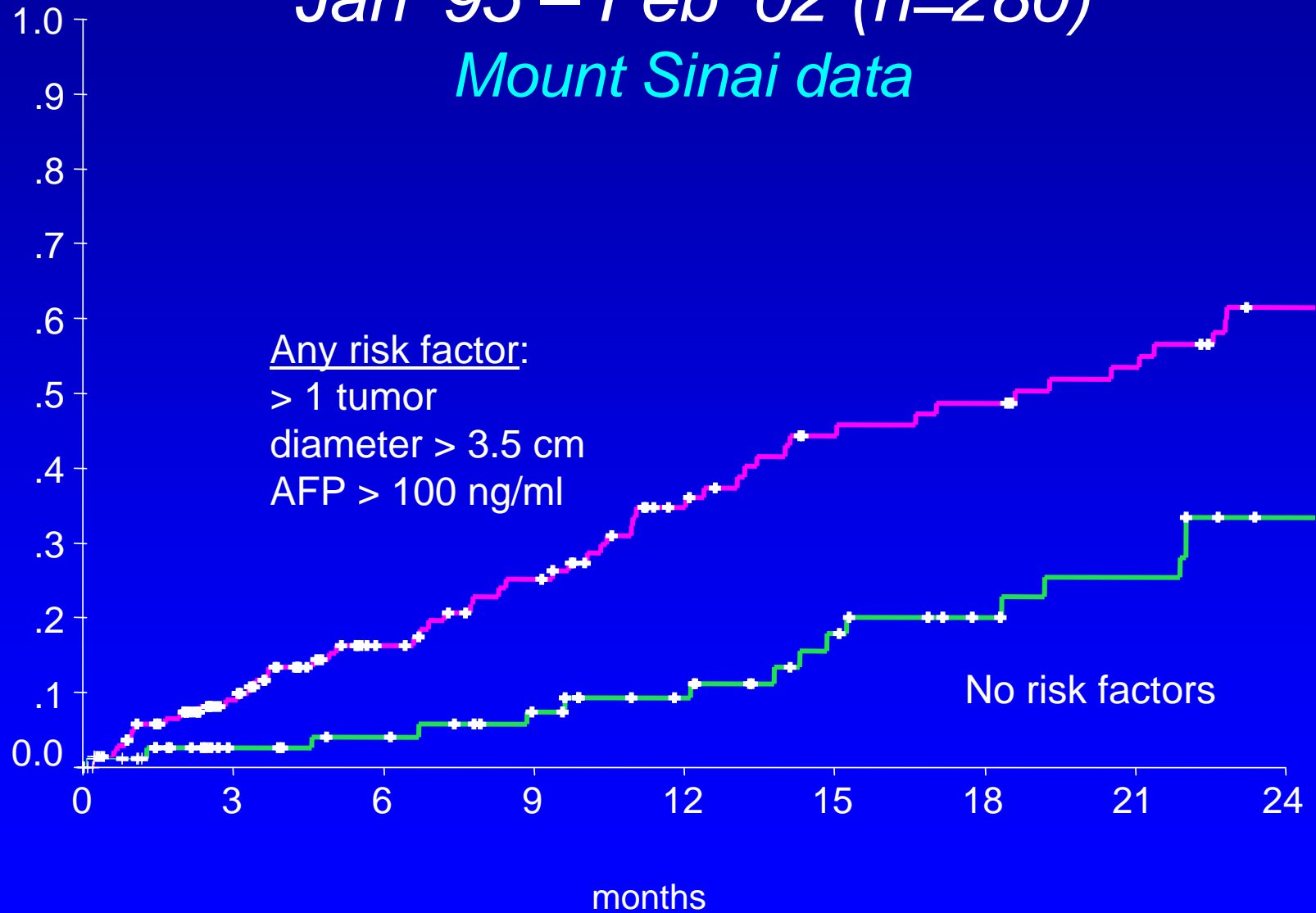
*Intention-to-treat analysis*  
*Mount Sinai data*



# HCC Waiting List Drop-out

Jan '95 – Feb '02 (n=280)

Mount Sinai data



# Transplantation for HCC $\geq 5\text{cm}$

## *Mount Sinai multimodality protocol*

- No extrahepatic disease, main PV patent,  $< 75\%$  liver replacement
- Pretransplant chemoembolization
- Intra- and post-op doxorubicin
- 80 patients enrolled between 10/91 - 1/99
  - 43 transplanted
  - 37 eventually excluded
- Median waiting time:  $142 \pm 168$  days

# Transplantation for HCC $\geq 5\text{cm}$

## *Overall survival*

Median follow-up  $55.1 \pm 24.9$  mo.



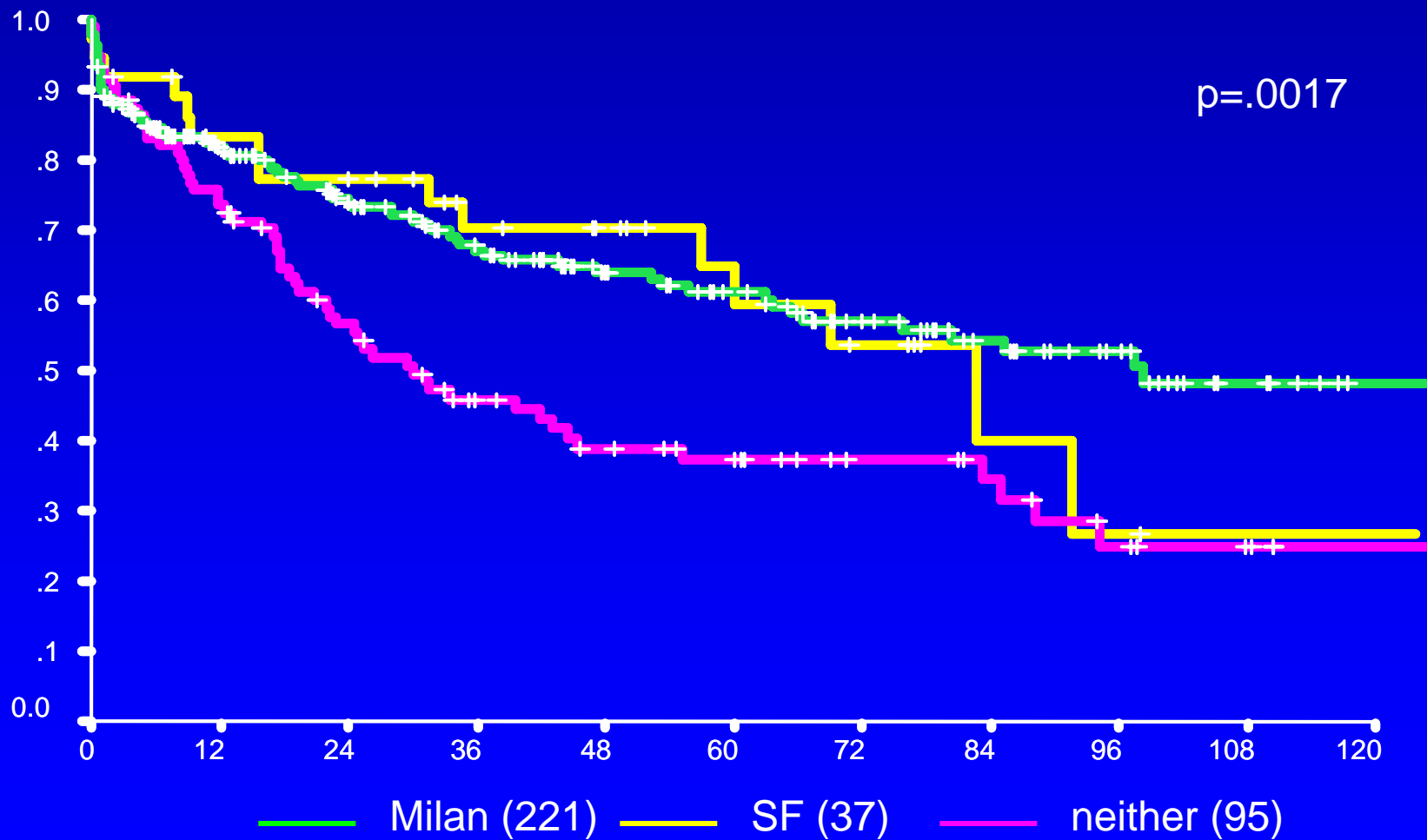
# Transplantation for HCC

## *Expanded criteria: UCSF*

- Solitary tumor  $\leq 6.5$  cm
- $\leq 3$  tumors; largest lesion  $\leq 4.5$  cm and total tumor diameter  $\leq 8$  cm
- No gross vascular invasion
- Based on pathology correlation in 70 patients
  - 60 met criteria, 10 did not

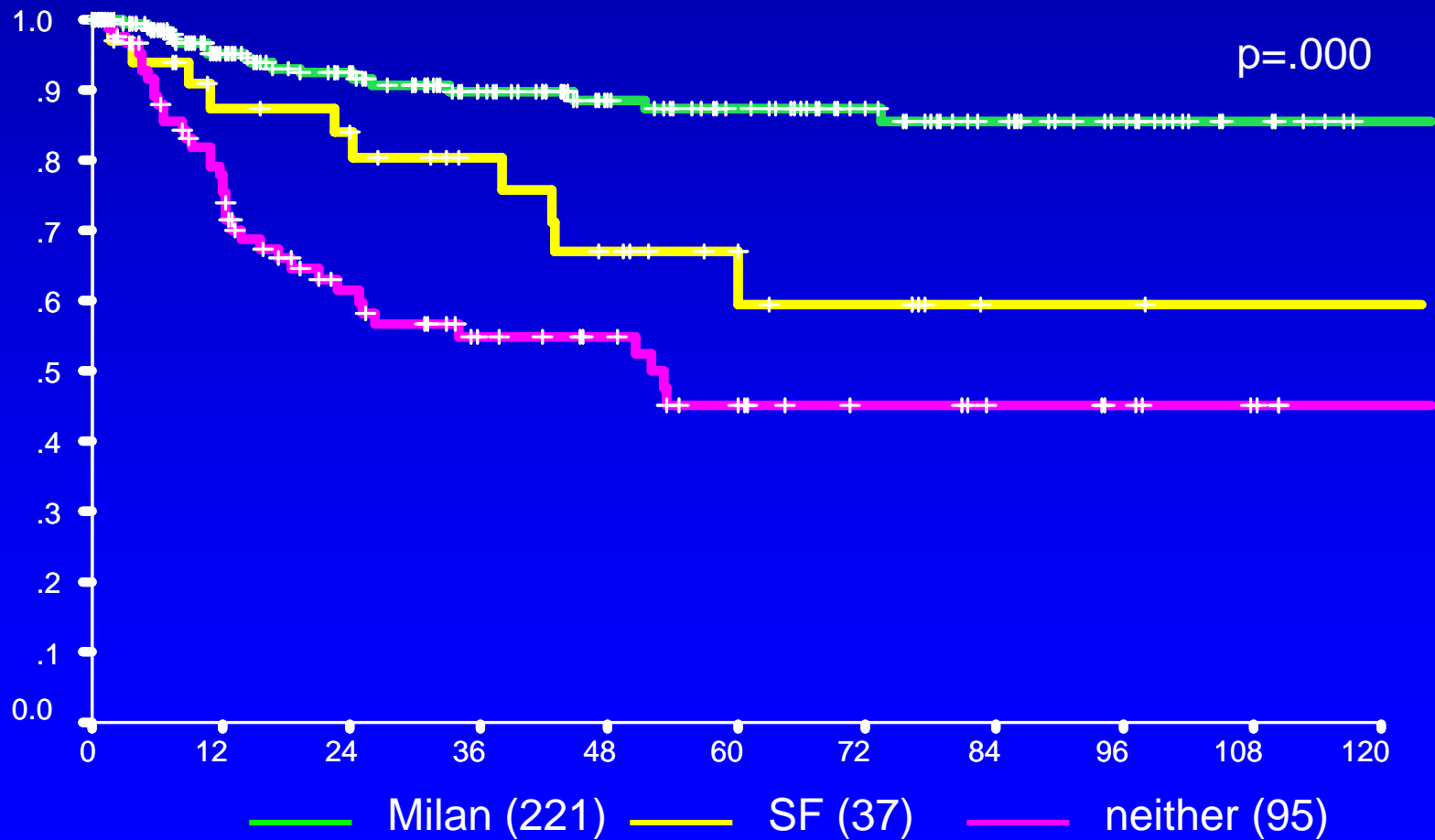
# OLT for HCC: Overall Survival

## *Milan vs. SF vs. neither*



# OLT for HCC: Freedom from Recurrence

## *Milan vs. SF vs. neither*



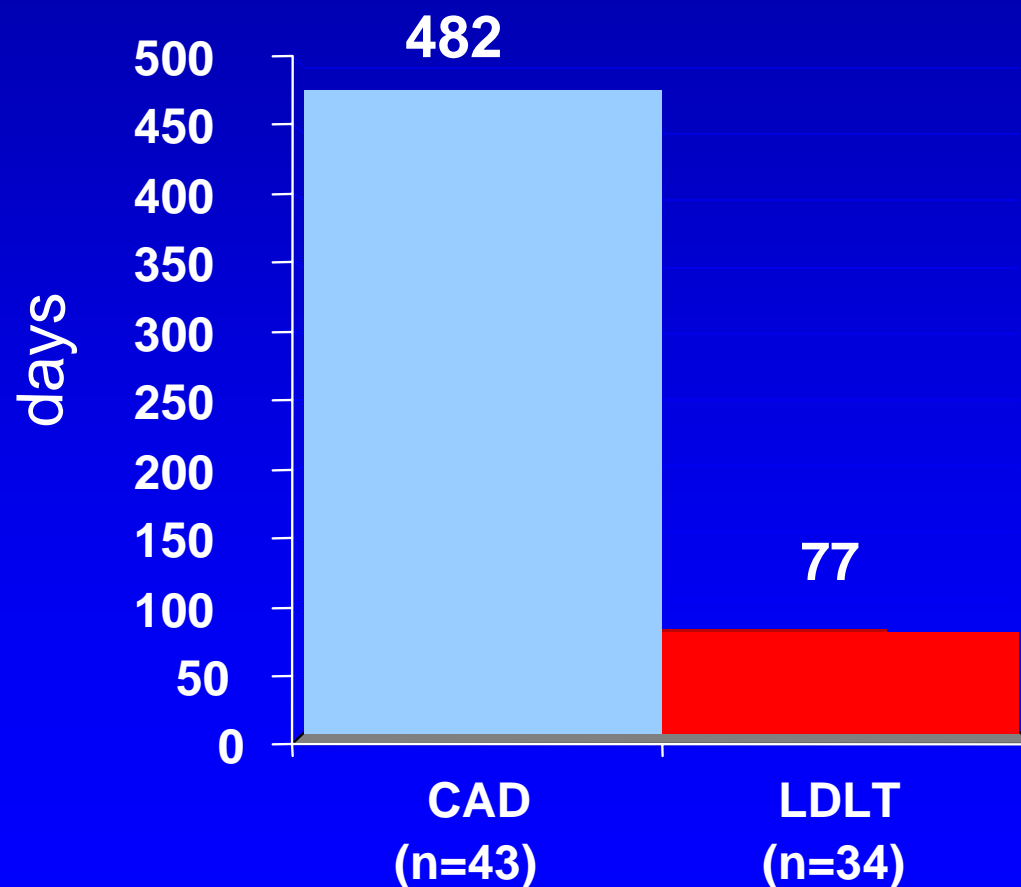
# Indications vs. Selection Criteria

*What changes with LDLT?*

- Indications don't change
  - Whether transplant is the best treatment for a patient does not depend on donor source
- Selection criteria may change
  - Stringency of deceased donor criteria depends on degree of scarcity
    - Fewer organs  $\Rightarrow$  higher priority needed to get one
  - Living donor organs, while precious, are not scarce

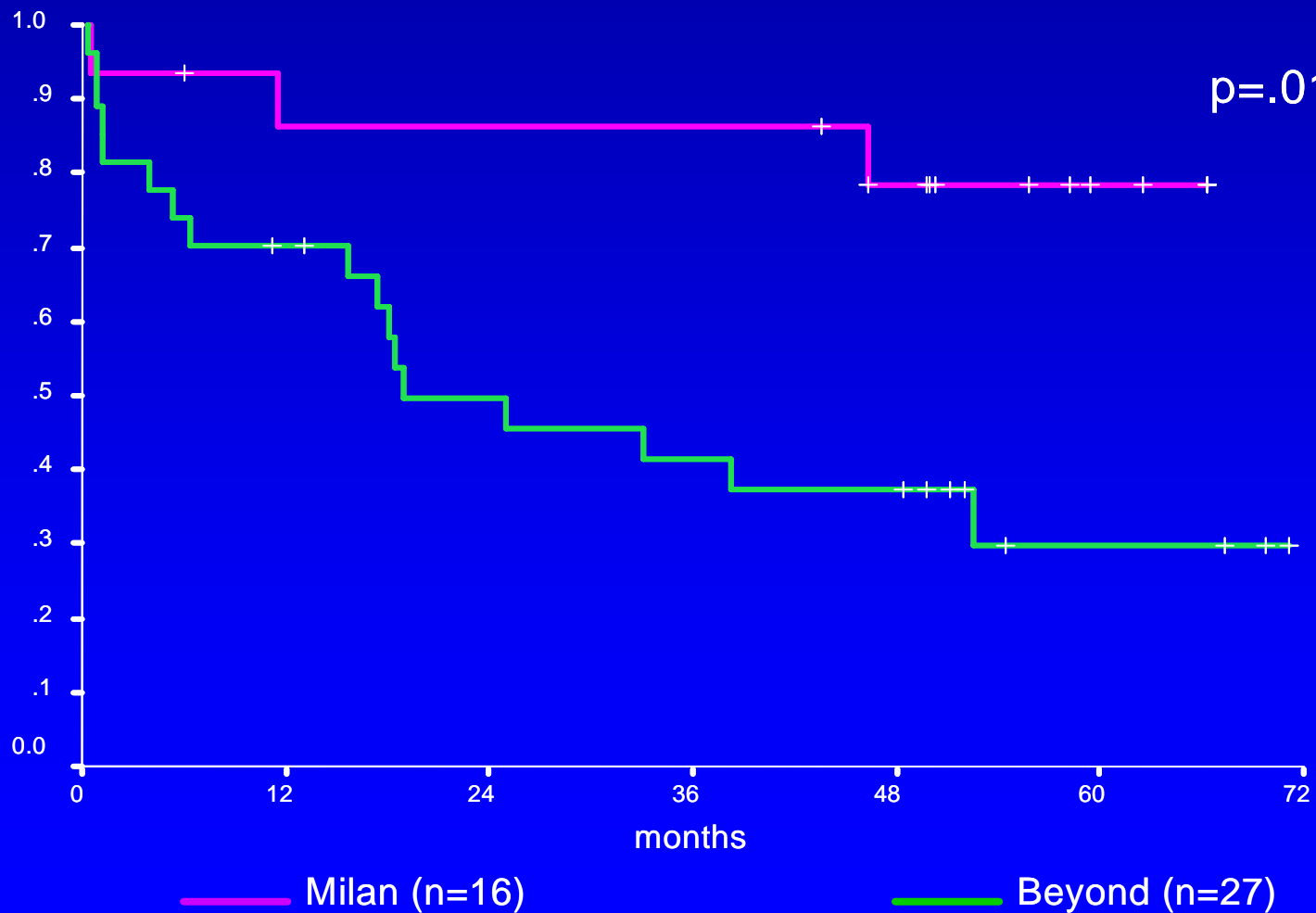
# Mean Waiting Time: Known HCC

*Deceased donor vs LDLT: 8/98 - 1/02*



# LDLT for HCC: Patient Survival

*n=43; mean follow-up 49 months*



# Microsatellite Allelic Imbalance

## *Prognostic and diagnostic application in HCC*

- Hypothesis: that a profile of copy number change at selected chromosomal loci throughout the genome reflects stage of cancer progression and is, therefore, a potential prognostic indicator.
- “Microdissection-based allelotyping discriminates de-novo tumor from intrahepatic spread in hepatocellular carcinoma.” Finkelstein et al, *Hepatology* 2003
- “Genotyping of hepatocellular carcinoma in liver transplant recipients adds predictive power for determining recurrence-free survival.” Marsh et al, *Liver Transplantation* 2003

## Patient Characteristics (n=70)

- Transplanted prior to 1998
  - Recurrence: 24
  - 5yr recurrence-free survival: 46
- Underlying disease
  - Hepatitis C 37
  - Ethanol 9
  - Cryptogenic/NASH 9
  - Hepatitis B 8
  - Other 7
- ***Milan Criteria***
  - ***Within criteria:*** 35
  - ***Beyond criteria:*** 35

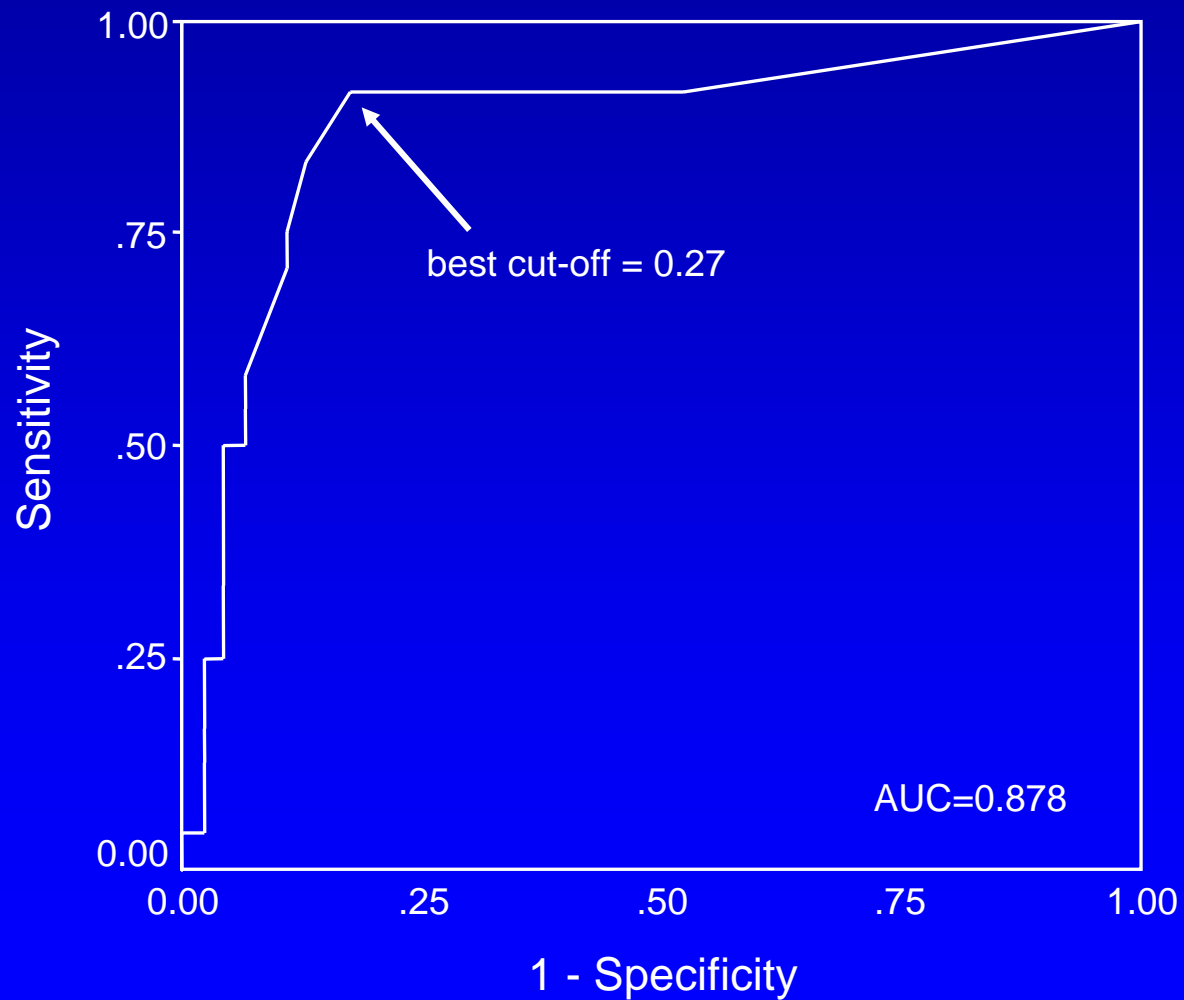
# Allelic Imbalance in HCC

*Chromosomal loci, associated genes and microsatellites*

| Locus | Gene   | Type       | Microsatellite | GenBank | % N.I.† | % AI  | p value |
|-------|--------|------------|----------------|---------|---------|-------|---------|
| 1p34  | L-MYC  | oncogene   | MYCL 5NT *     | M19720  | 24.3%   | 34.0% | <0.0001 |
| 1p36  | P73    | suppressor | D1S407 *       | L18040  | 28.6%   | 36.0% | 0.0016  |
| 3p26  | OGG1   | suppressor | D3S1539 *      | L16393  | 21.4%   | 29.1% | 0.0026  |
|       |        |            | D3S2303        | L17972  | 28.6%   | 34.0% | 0.0085  |
| 5q21  | APC    | suppressor | D5S592         | L16423  | 24.3%   | 34.0% | 0.57    |
|       |        |            | D5S615 *       | L18737  | 24.3%   | 24.5% | 0.09    |
|       |        |            | MCC E10        | M62397  | 37.1%   | 11.4% | 0.2     |
| 7q31  | MET    | oncogene   | D7S1530        | L30387  | 22.9%   | 22.2% | 0.46    |
| 8q24  | C-MYC  | oncogene   | D8S373         | L16320  | 25.7%   | 23.1% | 0.024   |
| 9p21  | CDKN2A | suppressor | D9S251 *       | L18726  | 25.7%   | 17.3% | 0.29    |
|       |        |            | D9S254         | L18040  | 17.1%   | 31.0% | 0.12    |
| 10q23 | PTEN   | suppressor | D10S520        | L16357  | 28.6%   | 20.0% | 0.06    |
|       |        |            | D10S1173       | L30341  | 25.7%   | 30.8% | 0.14    |
| 17p13 | P53    | suppressor | D17S974 *      | G07961  | 22.9%   | 20.4% | 0.0006  |
|       |        |            | D17S1289 *     | G09615  | 17.1%   | 10.3% | 0.0031  |
|       |        |            | TP53 L1 *      | M13121  | 38.6%   | 11.6% | 0.98    |
| 17q25 | DMC1   | suppressor | D17S1163       | L30445  | 18.6%   | 14.0% | 0.0022  |
| 18q21 | DCC    | suppressor | D18S814 *      | L17776  | 34.3%   | 47.8% | 0.0022  |

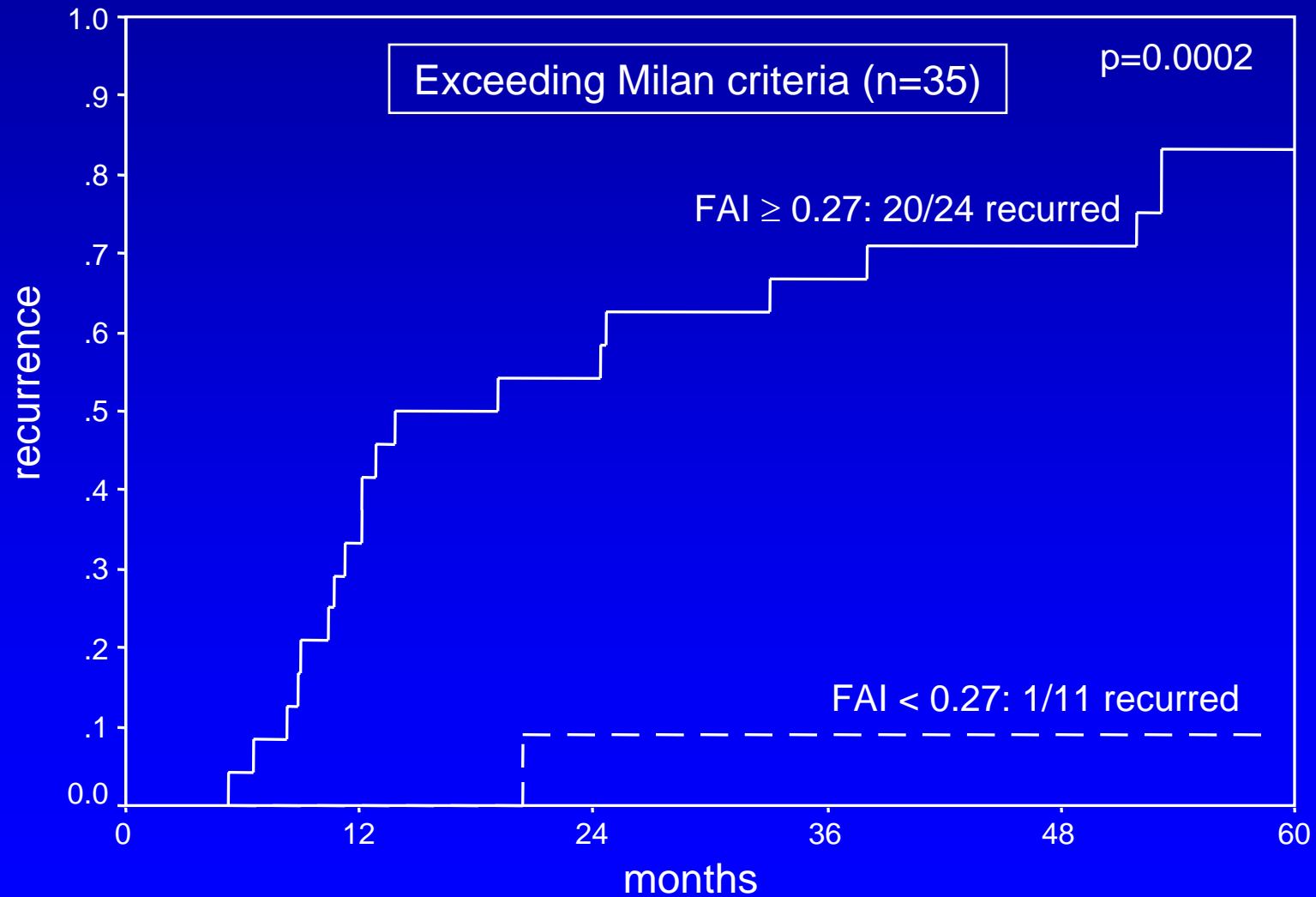
# Allelic Imbalance in HCC

*ROC curve: FAI*



# Allelic Imbalance in HCC

Recurrence-free survival:  $FAI \geq .27$  vs.  $< .27$



# Summary

- Patients with unresectable HCC within Milan should be listed for LT
  - significant drop-out rate remains despite priority
- Many patients with HCC beyond Milan can be cured
  - need to incorporate molecular criteria
- HCC is a prime indication for LDLT
  - less drop-out
  - no need for pretreatment
  - not bound by Milan criteria

# Research Questions

- Waiting list treatment
  - Which modality?
  - Does it help?
- Downstaging
  - A valid concept?
  - How much, how long?
- Tumor sampling for molecular studies
- Is nonsurgical therapy definitive?