

LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

The proposed expanded HCC criteria for
liver transplantation

Intention-to-treat outcome and the pattern
and predictors of dropout from the waiting
list for liver transplantation

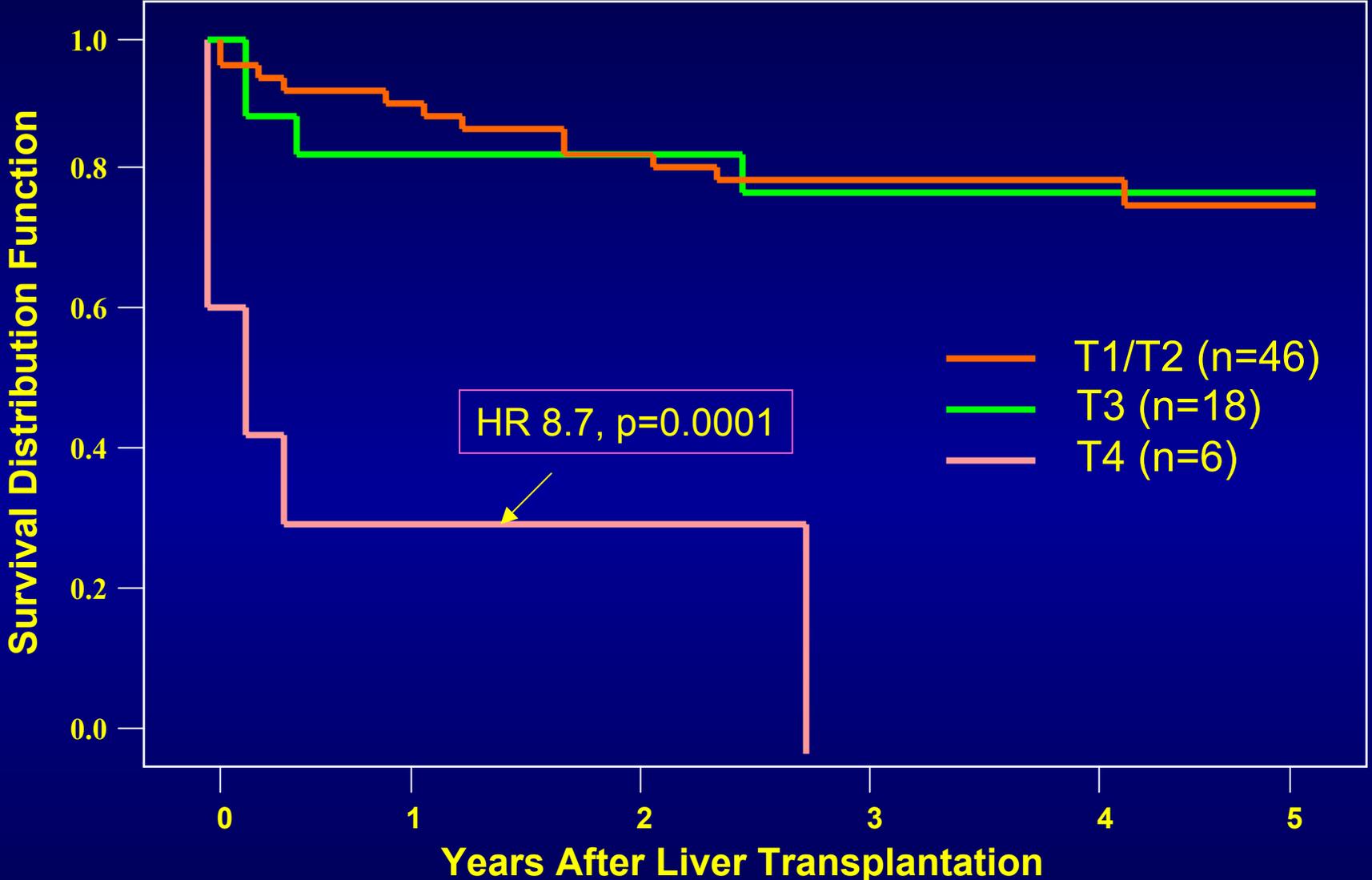
REFINEMENT OF THE HCC CRITERIA FOR LIVER TRANSPLANTATION

- The Milan criteria¹ - solitary tumor ≤ 5 cm or ≤ 3 lesions none > 3 cm - have been incorporated into the UNOS guidelines for liver transplantation (OLT) (T1 and T2).
- We previously reported the UCSF experience ² in 70 consecutive patients with HCC (23 patients with incidental HCC) who underwent OLT between 2/1988 and 2/2000.

¹ Mazzaferro, et.al. *NEJM* 1996;334:693-699

² Yao et.al. *Hepatology* 2001;33:1394-1403

Overall survival according to pathologic tumor staging



Stage	0	1	2	3	4	5
≤ 2:	46	39	28	20	15	12
3:	18	13	12	7	6	4
4:	6	2	1	0	0	0

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PREDICTORS OF MORTALITY: UNIVARIATE ANALYSIS

Predictors	Hazard Ratio (95% CI)	P-value
Pathologic Tumor Stage (versus pT2)		
pT3	1.11 (0.35-3.5)	0.87
pT4	8.65 (2.9-25.9)	<i>.0001*</i>
Vascular invasion	2.11 (0.83-5.4)	0.12
Poorly Differentiated Tumor Grade	3.76 (1.1-12.4)	<i>0.03</i>
Alpha-fetoprotein level > 1000	2.96 (1.0-8.5)	<i>0.04</i>
Total tumor diameter		
> 5 cm	1.70 (0.66-4.4)	0.27
> 8 cm	5.97 (2.1-17.0)	<i>0.0008*</i>
> 10 cm	19.5 (3.9-97.4)	<i>0.0003*</i>
Incidental tumor	1.05 (0.41-2.7)	0.91
No chemoembolization	1.85 (0.74-4.6)	0.18
Age \geq 55 years	2.96 (1.1-8.2)	<i>0.04</i>

*** Statistically significant in multivariate analysis**

MILAN CRITERIA ¹

Solitary lesion ≤ 5 cm

or

≤ 3 lesions none > 3 cm

PROPOSED UCSF CRITERIA ²

Solitary lesion ≤ 6.5 cm

or

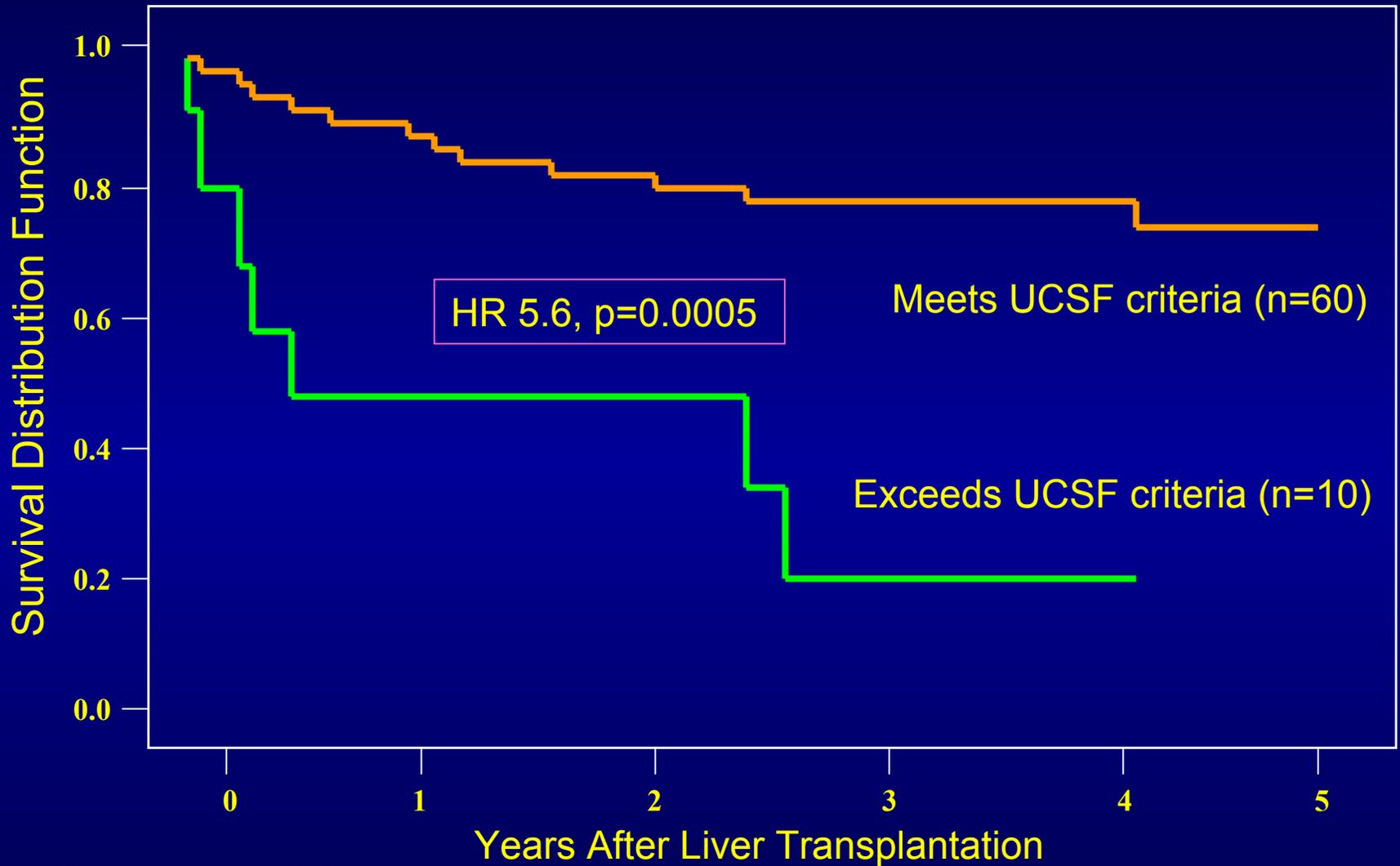
≤ 3 lesions none > 4.5 cm

and total tumor diameter ≤ 8 cm

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

(2) Yao et.al. *Hepatology* 2001;33:1394-1403

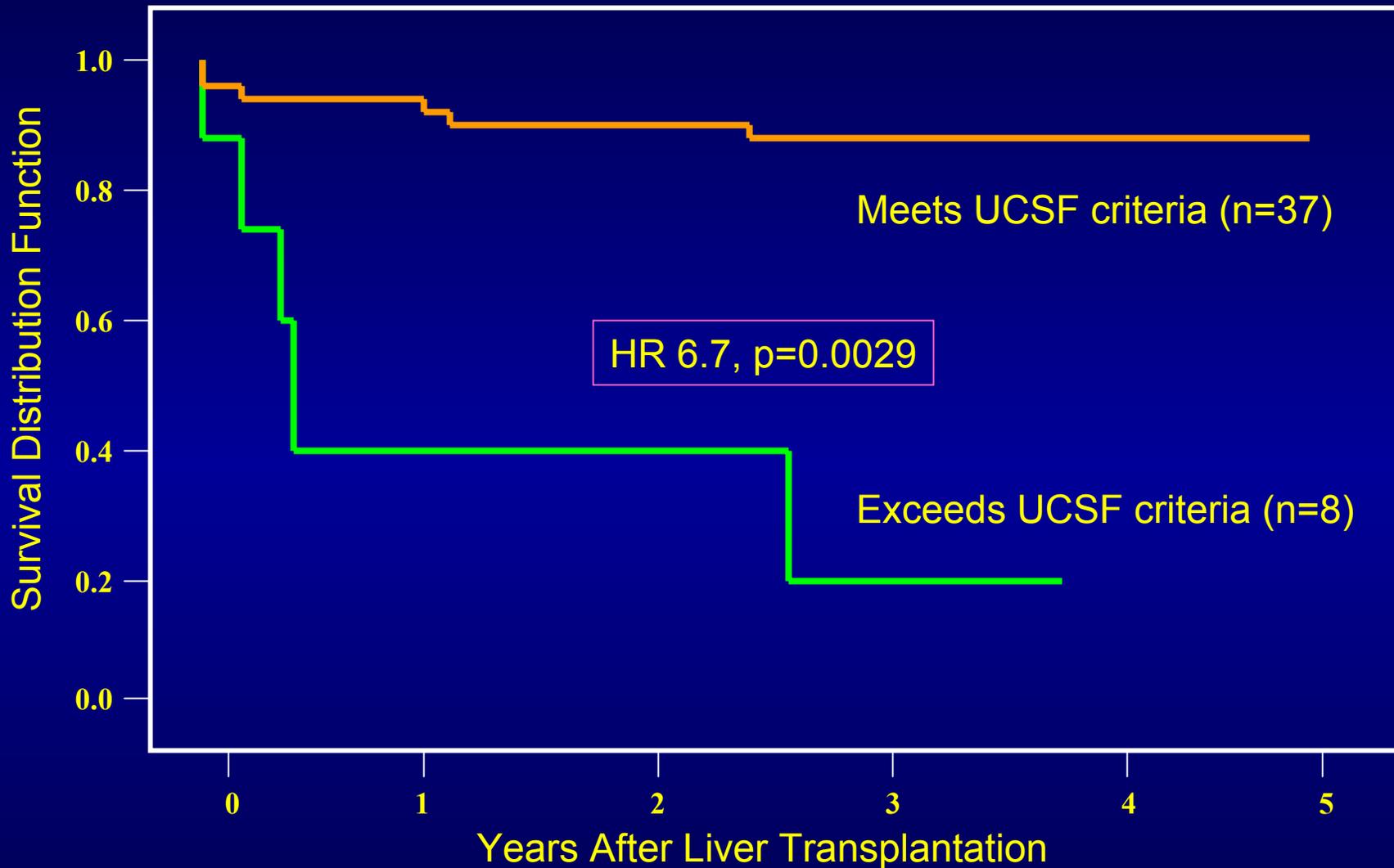
Survival according to pathologic staging based on UCSF criteria



Meet new staging criteria

Yes:	60	49	37	25	20	16
No:	10	5	4	2	1	0

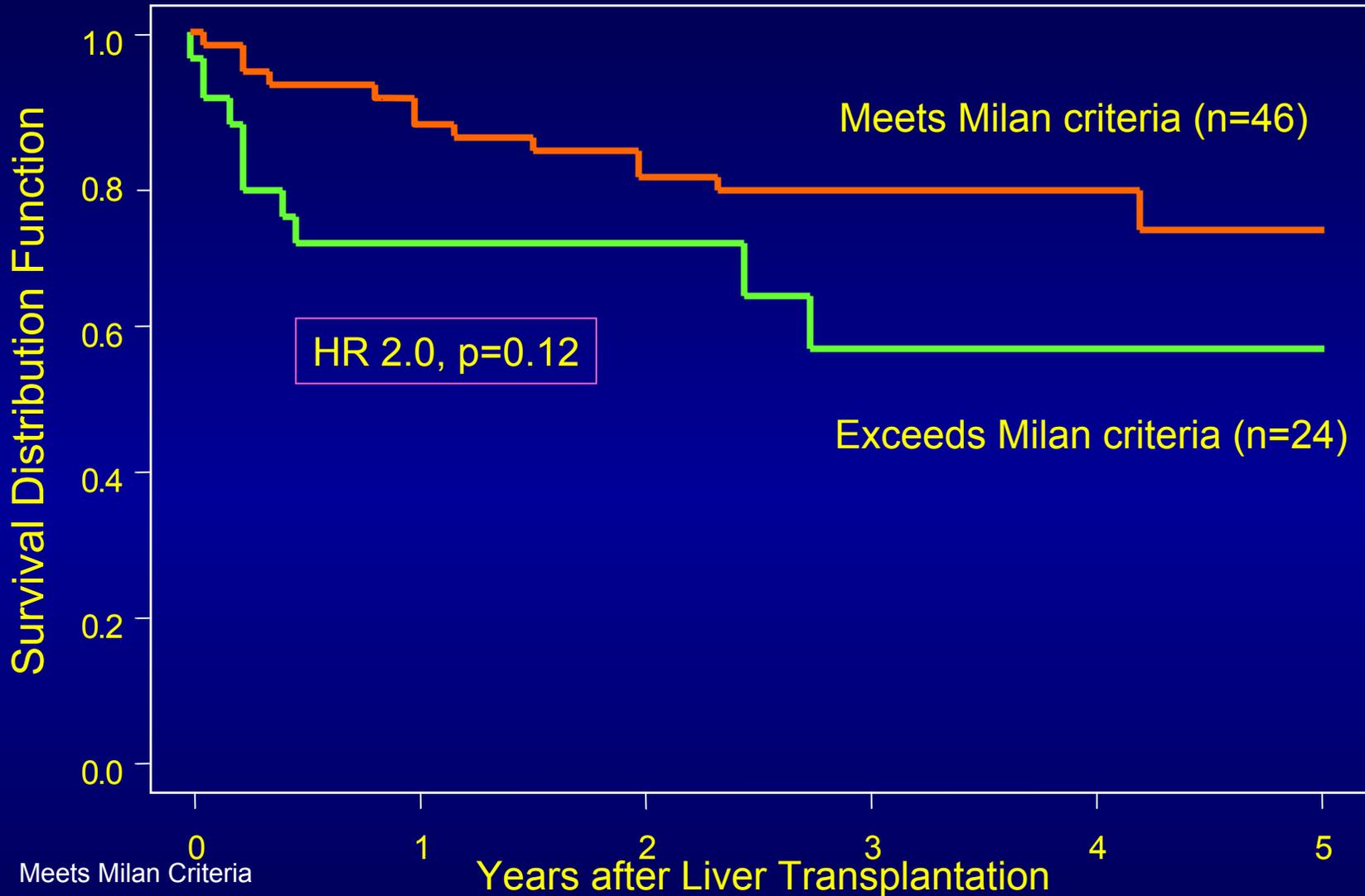
Survival according to pre-operative staging based on UCSF criteria



Meet New Staging Criteria

Yes:	37	34	24	14	13	9
No:	8	3	3	1	0	0

Survival according to pathologic staging based on Milan criteria



	0	1	2	3	4	5
Meets Milan Criteria						
Yes	46	39	28	20	15	12
No	24	15	13	7	6	4

Yao et.al. *Liver Transpl* 2002; 8:765-774

FOLLOW-UP DATA ON EXPANDED HCC CRITERIA FOR LIVER TRANSPLANTATION

- We completed a follow-up analysis in 106 consecutive patients who received OLT for HCC at UCSF from 2/1988 to 2/2002 with at least 6 months of follow-up.
- A prospective study was also initiated in 1/2001 applying the expanded criteria to pre-operative staging based on either CT or MRI of the abdomen.

BASELINE CLINICAL CHARACTERISTICS OF 106 CONSECUTIVE PATIENTS WITH HCC

- Median age (years, range): 54 (36 to 72)
- Sex (M/F): 69/37
- Asian (number/%) 26 (24.5%)
- Etiology of liver disease:
 - HCV 63 (59.4%)
 - HBV 21 (19.8%)
 - Others 22 (20.8%)
- CTP score:
 - 5-6 10 (9.4%)
 - 7-9 36 (34.0%)
 - 10-15 60 (56.6%)

BASELINE HCC CHARACTERISTICS OF 106 CONSECUTIVE PATIENTS WITH HCC

- Pre-transplant HCC stage (n=76)
 - T1 5 (6.6%)
 - T2 47 (61.9%)
 - T3A* 14 (18.4%)
 - T3B 8 (10.5%)
 - T4 2 (2.6%)
- Incidental Tumors 28 (26.4%)
- AFP (Median; range) 16 (0.7-12,700)
- Pre-transplant Treatment
 - TACE only 50 (47.2%)
 - TACE + Ablation 5 (4.7%)
 - Ablation only 5 (4.7%)

* T3A = Stage T3 meeting UCSF criteria

EXPLANT PATHOLOGIC CHARACTERISTICS OF 106 CONSECUTIVE PATIENTS WITH HCC

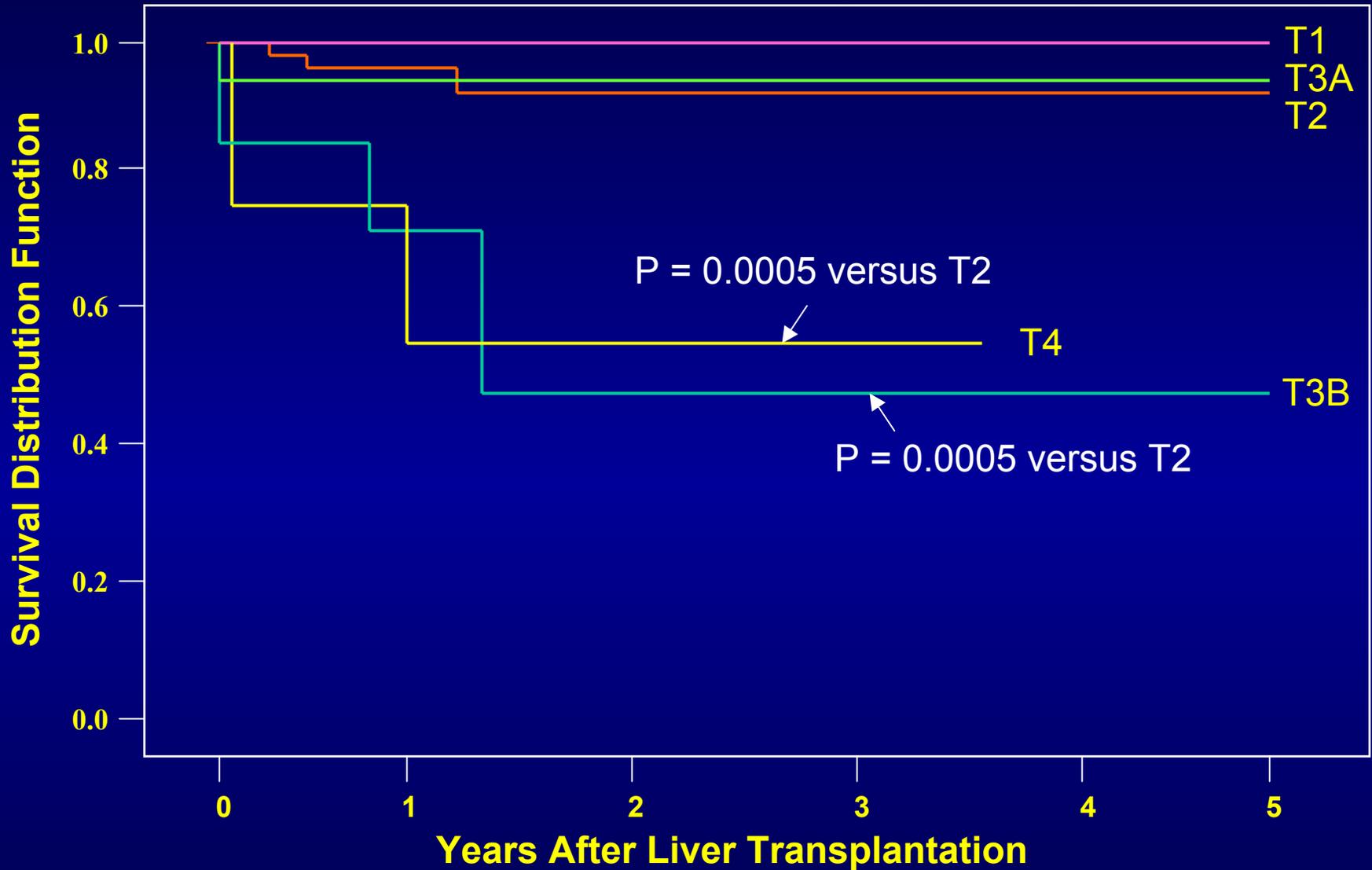
- Pathologic HCC stage in explant (n=106)

T1	17 (16.0%)
T2	54 (50.9%)
T3A	18 (17.0%)
T3B	7 (6.6%)
T4	10 (9.4%)
- Histologic grade (n= 105)

1	39 (37.1%)
2	52 (49.5%)
3	14 (13.3%)
- Vascular invasion (n=106)

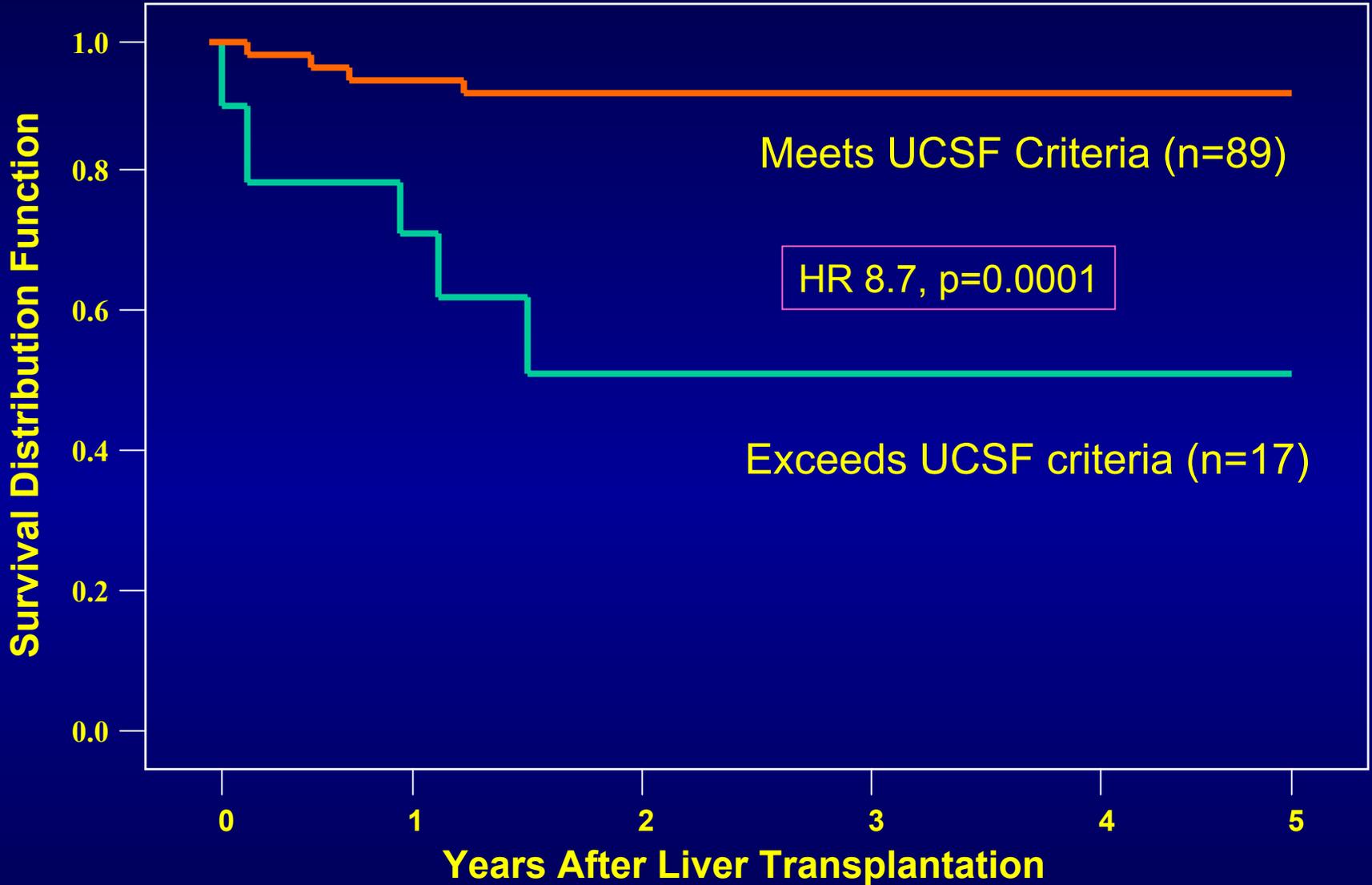
Yes	24 (22.6%)
No	82 (77.4%)

Recurrence-free survival according to pathologic HCC stage



T3A = Stage T3 meeting UCSF criteria (n=18)

Recurrence-free survival according to proposed UCSF criteria



—	89	74	58	46	39	32
—	17	9	5	4	3	3

CORRELATION BETWEEN PRE-TRANSPLANT AND PATHOLOGIC HCC STAGING

- Pre-operative Tumor Staging (n=76)

Accurate	52 (68.4%)
Underestimate	16 (21.1%)
T2 → T3A	7
T2 → T3B/T4	6
T3A → T3B/T4	2
T3B → T4	1
	9 (11.8%)
Overestimate	8 (10.5%)
T3A → T2	5
T3B → T2	3

CONCLUSIONS

- The criteria for OLT based on tumor size and number may be modestly expanded (the UCSF criteria) and still preserve excellent recurrence-free survival after OLT.
- Tumor stage underestimation occurred in about 20% of patients, 10% associated with advanced tumor stage (T3B or T4).
- A prospective study applying the proposed criteria based on pre-operative imaging studies is in progress.

THE PATTERN AND RATE OF DROPOUT FROM THE WAITING LIST FOR LIVER TRANSPLANTATION AMONG PATIENTS WITH HEPATOCELLULAR CARCINOMA: IMPLICATIONS FOR THE CURRENT ORGAN ALLOCATION POLICY

FRANCIS Y. YAO, NATHAN M. BASS, BEV NIKOLAI, RAPHAEL MERRIMAN, TIMOTHY J. DAVERN, ROBERT KERLAN, NANCY L. ASCHER, JOHN P. ROBERTS.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

BACKGROUND

- The success of liver transplantation (OLT) for hepatocellular carcinoma (HCC) is limited by the prolonged waiting time and risk for tumor growth leading to dropout from the waiting list for OLT.^{1,2}
- We recently reported the preliminary data on intention-to-treat outcome of OLT for 46 patients with HCC and observed a dropout rate of about 25% per year under the previous system for organ allocation.²

¹ Llovet et.al. *Hepatology* 1999;30:1434-1440

² Yao, et.al. *Liver Transplantation* 2002;8:873-883

STUDY OBJECTIVES

- In the present study, we present longer follow-up data on a larger cohort of 70 consecutive patients with HCC to evaluate:
 - 1) The pattern and predictors of dropout from the waiting list for OLT.
 - 2) The potential implications for the current HCC - adjusted MELD organ allocation scheme for OLT.

PATIENTS AND METHODS

- Between January 1998 and February 2002, 70 consecutive patients either with a known diagnosis of HCC at the time of listing for OLT (38 patients) or with the discovery of HCC subsequent to OLT listing for liver failure (32 patients) were prospectively evaluated under the previous system of organ allocation for HCC (status 2B).
- At presentation, all except one patient had HCC stage meeting the Milan criteria (single lesion $\leq 5\text{cm}$ or ≤ 3 lesions none $> 3\text{cm}$).

PATIENTS AND METHODS

- All patients were evaluated with abdominal computed tomography or magnetic resonance imaging every 3 months.
- Patients were excluded for OLT if HCC exceeded following criteria: A single lesion $\leq 5\text{cm}$ or ≤ 3 lesions not $> 5\text{cm}$. The criteria were modified after January 2001 as: A single lesion $\leq 6.5\text{cm}$ or ≤ 3 lesions none $> 4.5\text{cm}$ with total tumor diameter $\leq 8\text{cm}$.
- Follow-up was censored on February 27, 2002, when the MELD scheme for organ allocation was implemented by UNOS.

BASELINE CHARACTERISTICS

- Median age (years, range): 54.2 (19 to 65)
- Sex (M/F): 49/21
- Asian (number/%) 25 (35.7%)
- ABO Blood Group:
 - 25 (35.7%)
 - A 23 (32.9%)
 - B 17 (24.3%)
 - AB 5 (7.1%)
- Waiting time before HCC
 - 38 (54.3%)
 - ≤ 1 year 11 (15.7%)
 - > 1 year and ≤ 2 years 12 (17.1%)
 - > 2 years 9 (12.9%)

BASELINE CHARACTERISTICS

- Child's Class (CTP score): Number (%)
 - A (5-6) 21(30%)
 - B (7-9) 27(38.6%)
 - C (10-15) 22(31.4%)
- Etiology of Liver Disease:
 - HCV 45(64.3%)
 - HBV 18(25.7%)
 - Others 7(10%)
- HCC Number
 - 1 56 (80%)
 - 2 8 (11.4%)
 - 3 6 (8.6%)
- Median Alpha-fetoprotein 28.6 (range 0.7-3344)

TREATMENT OF HCC WHILE ON WAITING LIST FOR OLT

Types of treatment	Number of Patients (Treatments)
Percutaneous Alcohol ablation (PEI)	7 (22)
Radiofrequency Ablation (RFA)	11 (11)
Percutaneous	6
Open	2
Laparoscopic	3
Other Ablations	3 (3)
Microwave	1
Open Cryoablation	2

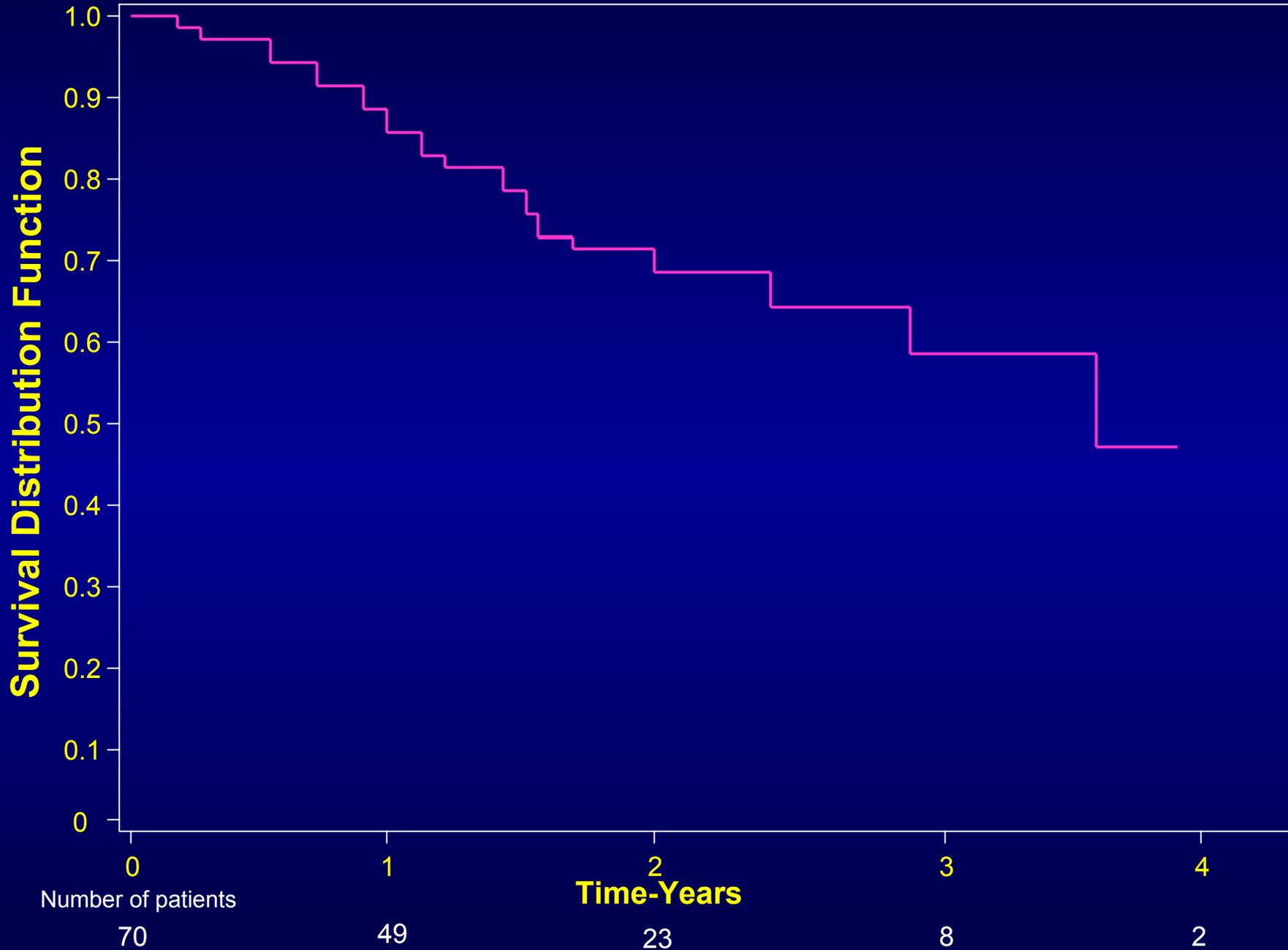
TREATMENT OF HCC WHILE ON WAITING LIST FOR OLT

Types of treatment	Number of Patients (Treatments)
Chemoembolization (TACE)	11 (12)
Limited Hepatic resection	5
≥ 2 types of treatments	6
TACE + PEI	3
TACE + RFA	1
TACE + RFA + PEI	1
Resection + TACE + RFA	1
No specific HCC treatment	41

INTENTION-TO-TREAT OUTCOME

- Median follow-up: 1.5 years (0.22-4.1 years)
- Number of deaths: 17 (10 after dropout, 2 from liver failure without OLT, 5 after OLT).
- Thirty-eight of 70 patients (54.3%) underwent OLT, including 9 with living-donor liver transplantation and 3 with “domino” or sequential OLT from patients with familial amyloidosis.
- Three had HCC recurrence after OLT and 1 of these 3 patients had died.

KAPLAN-MEIER INTENTION-TO-TREAT SURVIVAL



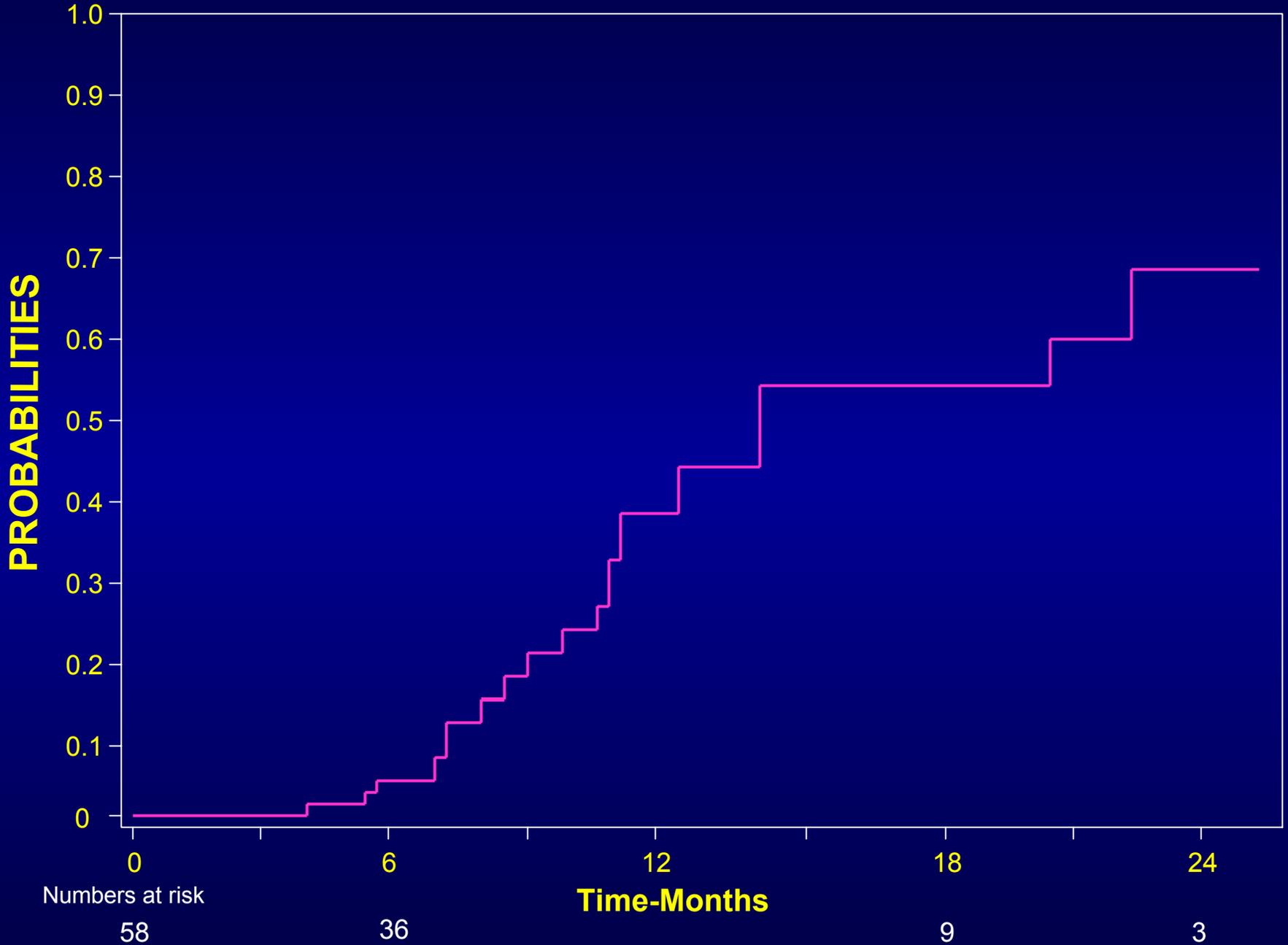
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DROPOUT FROM THE WAITING LIST

- Number of dropouts: 18 (22.6%).
- Median waiting time was 10.6 months and 6.1 months, respectively for those with and without dropout ($p=0.036$).
- Monthly dropout rates (OLT and death before dropout counted as censor points):

0%	0 - 3 months
2.3%	3 - 6 months
4.0%	6 - 9 months
7.2%	9 - 12 months
9.2%	12 - 15 months

CUMULATIVE PROBABILITIES OF DROPOUT



PREDICTORS OF DROPOUT

HCC CHARACTERISTICS

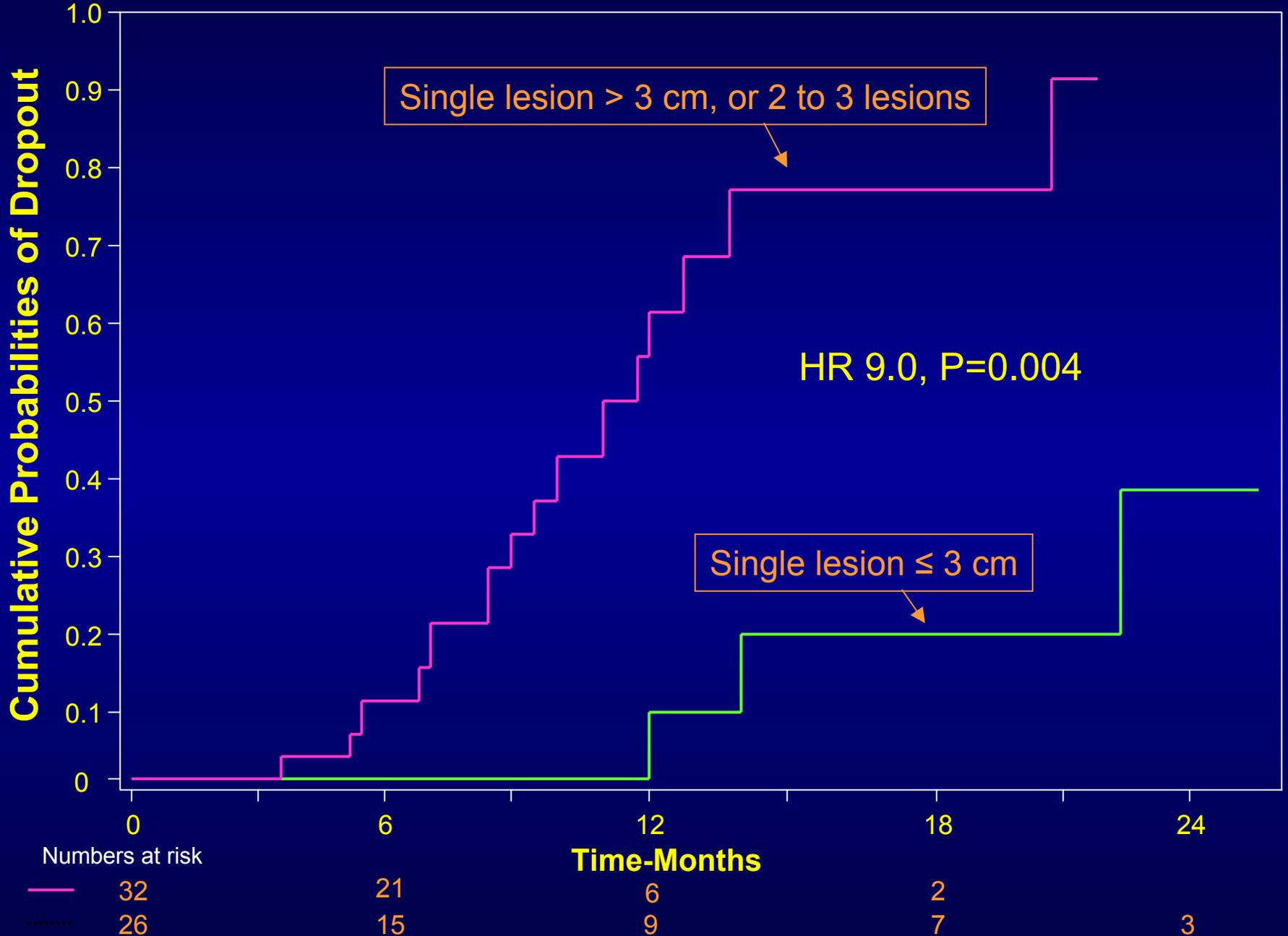
Predictors (Univariate analysis)	Hazard Ratio (95% CI)	P-value
Size of HCC > 3cm & ≤ 5cm (versus ≤ 3cm)	5.52 (1.45-21.1)	0.012
Number of Lesions (versus 1 lesion)		
2	3.17 (0.88-11.4)	0.077
3	4.87 (1.52-15.6)	0.0078
Resection	2.57 (0.84-7.90)	0.10
Ablation / TACE	1.42 (0.56-3.58)	0.46
AFP > 500	1.27 (0.37-4.41)	0.70

PREDICTORS OF DROPOUT

OTHER VARIABLES (PARTIAL LIST)

Variables (Univariate analysis)	Hazard Ratio (95% CI)	P-value
Age	1.3 (0.68-2.3)	0.47
CTP Score	0.92 (0.78-1.08)	0.30
ABO Blood Type (versus O blood type)		
A	0.92 (0.34-2.49)	0.86
B	0.29 (0.06-1.36)	0.12
Waiting time before HCC (versus 0 waiting time)		
≤ 1 year	0.81 (0.23-2.89)	0.75
>1 & ≤ 2 years	0.27 (0.03-2.06)	0.21
> 2 years	0.54 (0.12-2.41)	0.41

DROPOUT ACCORDING TO HCC CHARACTERISTICS



CONCLUSIONS

- The high dropout rate and its adverse impact on intention-to-treat survival in patients with HCC awaiting for OLT justify giving these patients a high priority for organ allocation.
- Further refinements in the current HCC-adjusted MELD scheme may be appropriate, restricting priority to those at high risk for dropout (2 or 3 tumor nodules or a solitary lesion at least 3cm).

CONCLUSIONS

- Based upon the observed exponential pattern of dropout and the relatively low rate of dropout in the first 6 months, considerations should also be made for assigning these patients a lower initial MELD score with a greater MELD score increment with time on the waiting list.