

Liver Transplantation for HCC Beyond the Milan Criteria

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LONG TERM RESULTS OF LIVER TRANSPLANTATION
AND MULTIMODAL ADJUVANT THERAPY FOR THE
TREATMENT OF HEPATOCELLULAR CARCINOMA
LARGER THAN 5CM

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Background: HCC

- most common solid organ tumor worldwide
- one million deaths annually
- incidence rising in US
 - 2.4 per 100,000
- good survival with transplant for tumors < 5cm
 - 75% at 4 years
- poor survival with transplant for tumors \geq 5cm
 - 18-30% at 5 years

Previous Studies

study	year	(n)	(n) with HCC≥5cm	median f/u	survival
Stone <i>et al</i> -Baylor chemo	1993	20	17	26.5 mo	54%-3yr
Carr <i>et al</i> -Pittsburgh TACE, chemo	1993	11	n/a	16 mo	91%-1yr
Cherqui <i>et al</i> -France TACE,rads,chemo	1994	9	4	25 mo	64%-3yr
Olthoff et al-UCLA chemo	1995	25	15	33 mo	46%-3yr

Candidate Entry Criteria

- unresectable HCC $\geq 5\text{cm}$
- free of extrahepatic disease
 - CT chest, abdomen & pelvis
 - bone scan
- patent major hepatic & main portal veins
- multicentric tumors not excluded
- largest tumor in less involved lobe $<5\text{cm}$
- tumor involving $<75\%$ parenchyma

Entry Criteria

- no significant ascites or encephalopathy
- INR < 1.5
- creatinine < 2mg/dl
- bilirubin < 2mg/dl
 - unless suffering from cholestatic liver disease
- normal MUGA
- no prior chemotherapy or radiation

Pretransplant Management

- subselective arterial chemoembolization
 - mitomycin-C, doxorubicin, cisplatin
 - collagen or polyvinyl alcohol
- CT scan & AFP level every 3 months
 - response - AFP decrease $>50\%$
 - TACE repeated as needed
- excluded when entry criteria no longer met

Intra- Operative Protocol

- backup recipient in hospital
- exploratory laparotomy for extrahepatic disease
- standard hepatectomy and transplant
- doxorubicin 10mg/m² while anhepatic

Post-transplant Protocol

- chemotherapy beginning 6th postop week
 - doxorubicin 50mg/m²
 - G-CSF 5μg/kg for 14 days
 - repeated as tolerated every 3 weeks x 6 cycles
- immunosuppression
 - corticosteroids with cyclosporine or tacrolimus
 - pulse steroids ± OKT3 for rejection
 - no azathioprine

Follow-up

- CT scan chest and abdomen/pelvis
 - every 3 months - 1st year
 - every 6 months thereafter
- AFP
 - every 6 weeks - 1st year
 - every 3 months thereafter

Results

- October 1991 - January 1999
- 80 patients enrolled
 - 43 transplanted
 - 37 eventually excluded
 - tumor progression - 2
 - distant metastasis - 6
 - main portal vein tumor - 9
 - GI bleeding - 4
 - liver failure - 5
 - other malignancies - 2
 - lymph node metastasis - 6
 - patient preference - 3
- median time on waiting list
 - transplanted - 142±168 days
 - excluded - 207±306 days

Demographics

	excluded (n=37)	transplanted (n=43)	p
age (yr)	58.7±8.7	56.3±11.1	ns
male:female	30:7	31:12	ns
Child-Pugh score	6.71±2.2	5.91±2.2	ns
peak AFP	284±11007	215±9393	ns

Tumor Characteristics

	excluded (n=37)	transplanted (n=43)	p
CT size largest tumor	8.2±4.3	6.3±2.3	0.023
multiple lesions (n)	23	24	ns
bilateral tumors	22	33	ns
AFP response to TACE	17	14	ns

Underlying Liver Disease

	Excluded (n=37)	Transplanted (n=43)	p
hepatitis C	25	21	ns
hepatitis B	2	10	0.033
alcohol	3	6	ns
other	5	4	ns
none	2	2	ns

Complications

- TACE
 - 2/80 (2.5%) mortality from liver failure
- perioperative mortality
 - 2/43 (4.7%)
- chemotherapy
 - mean 4.8 ± 1.79 cycles
 - 4/43 (9.3%) did not receive any postop chemo
 - 2 perioperative mortalities
 - 1 patient refusal
 - 1 poor postop cardiac function

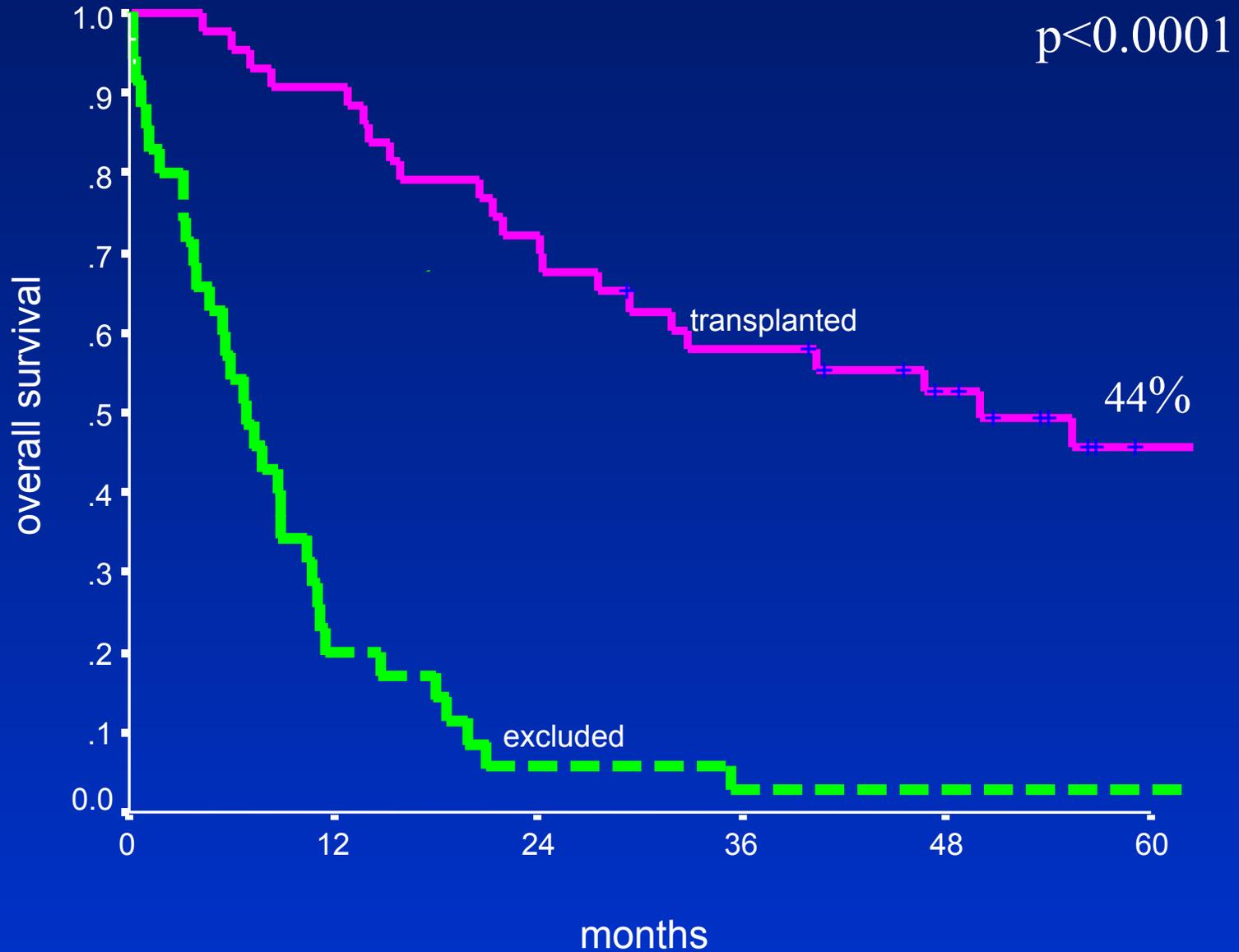
Complications

- Chemotherapy discontinued early
 - 3 (7%) thrombocytopenia
 - 2 (5%) hepatotoxicity
 - 4 (9%) progressive recurrent tumor
 - 2 (5%) refusal to continue

Follow-up

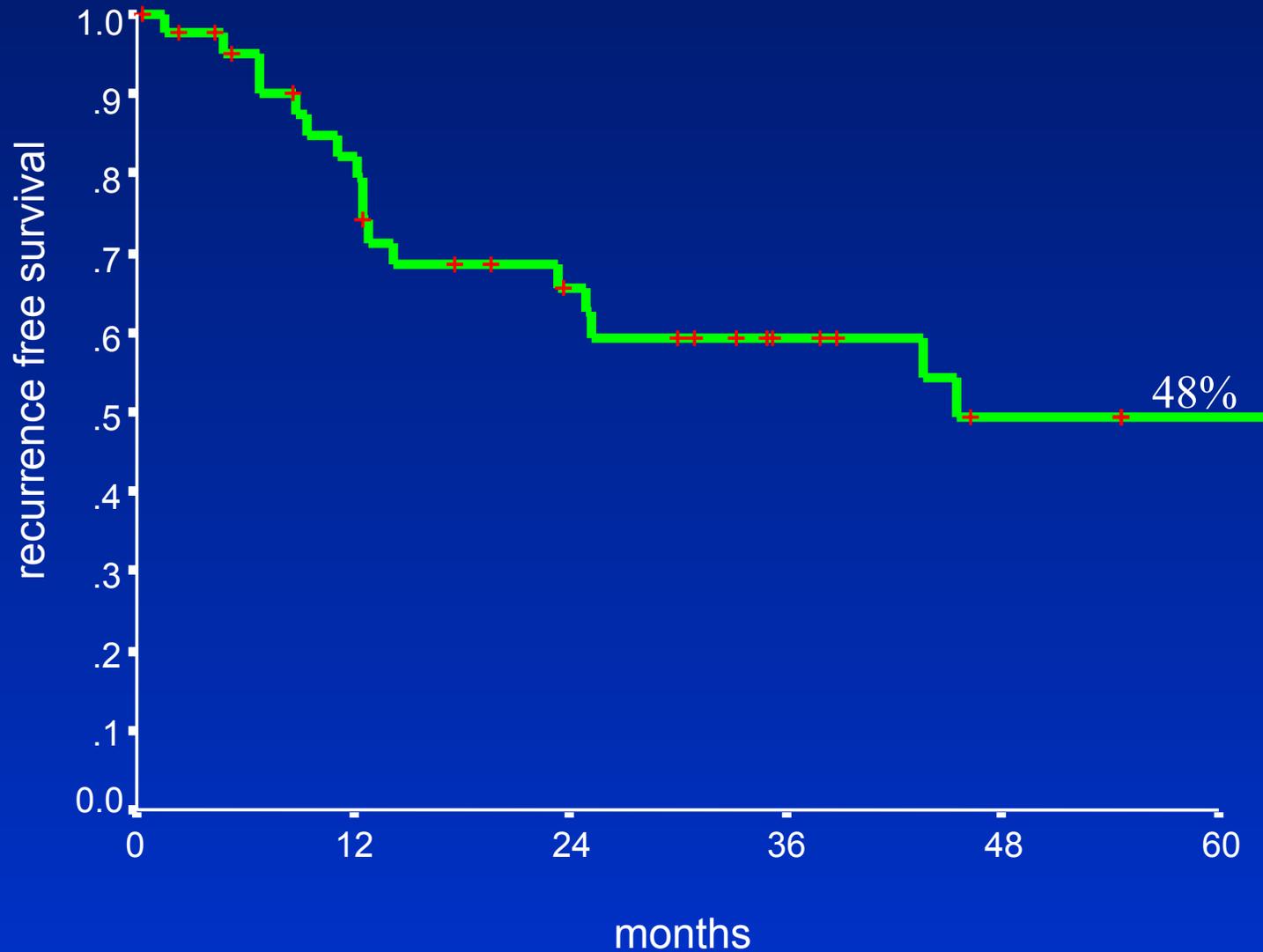
- median follow-up 55.1 ± 24.9 mo.
 - 19/43 (44%) alive
 - 17/43 (40%) free of disease
- recurrence in 17/43 (40%)
 - median time to recurrence 12.5 ± 12.6 mo.
 - intrahepatic only 2
 - extrahepatic only 9
 - both 5
 - rise in AFP 1

Overall Survival



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Recurrence-free Survival

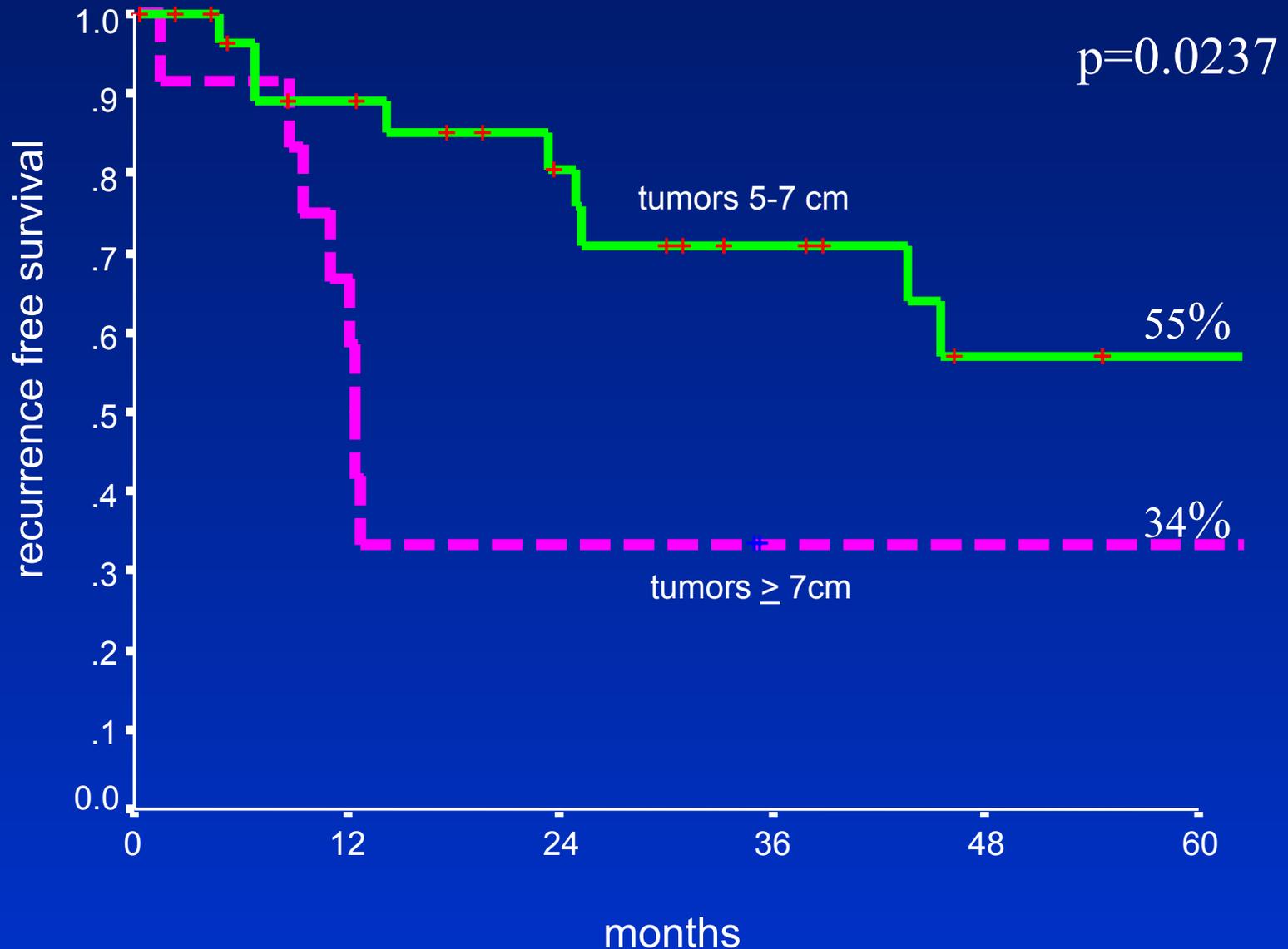


Recurrence: tumor size

	≤ 7 cm (n)	> 7 cm (n)
recurrence	9	8
no recurrence	22	4

p= 0.024

Recurrence-free survival

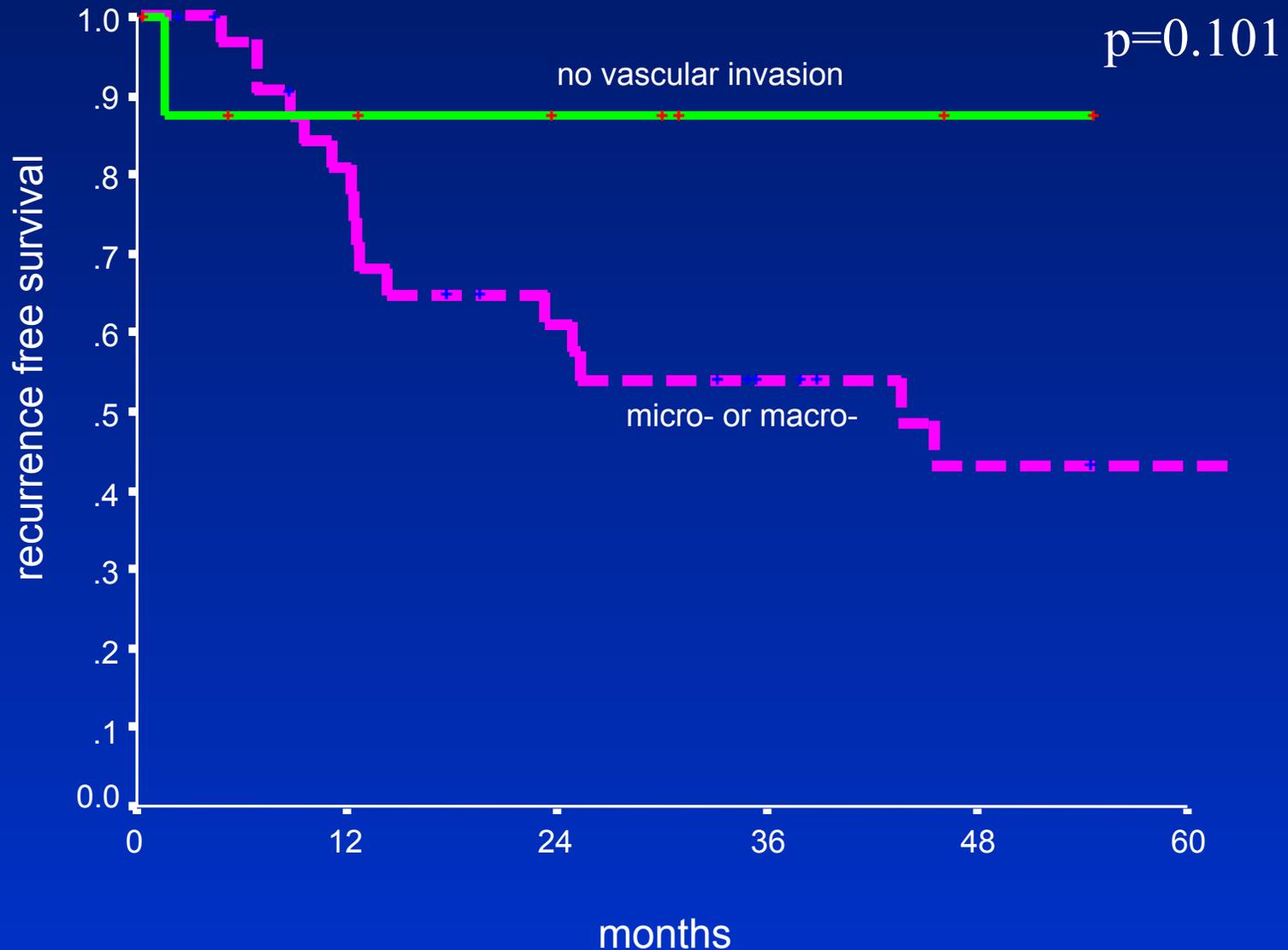


Recurrence: vascular invasion

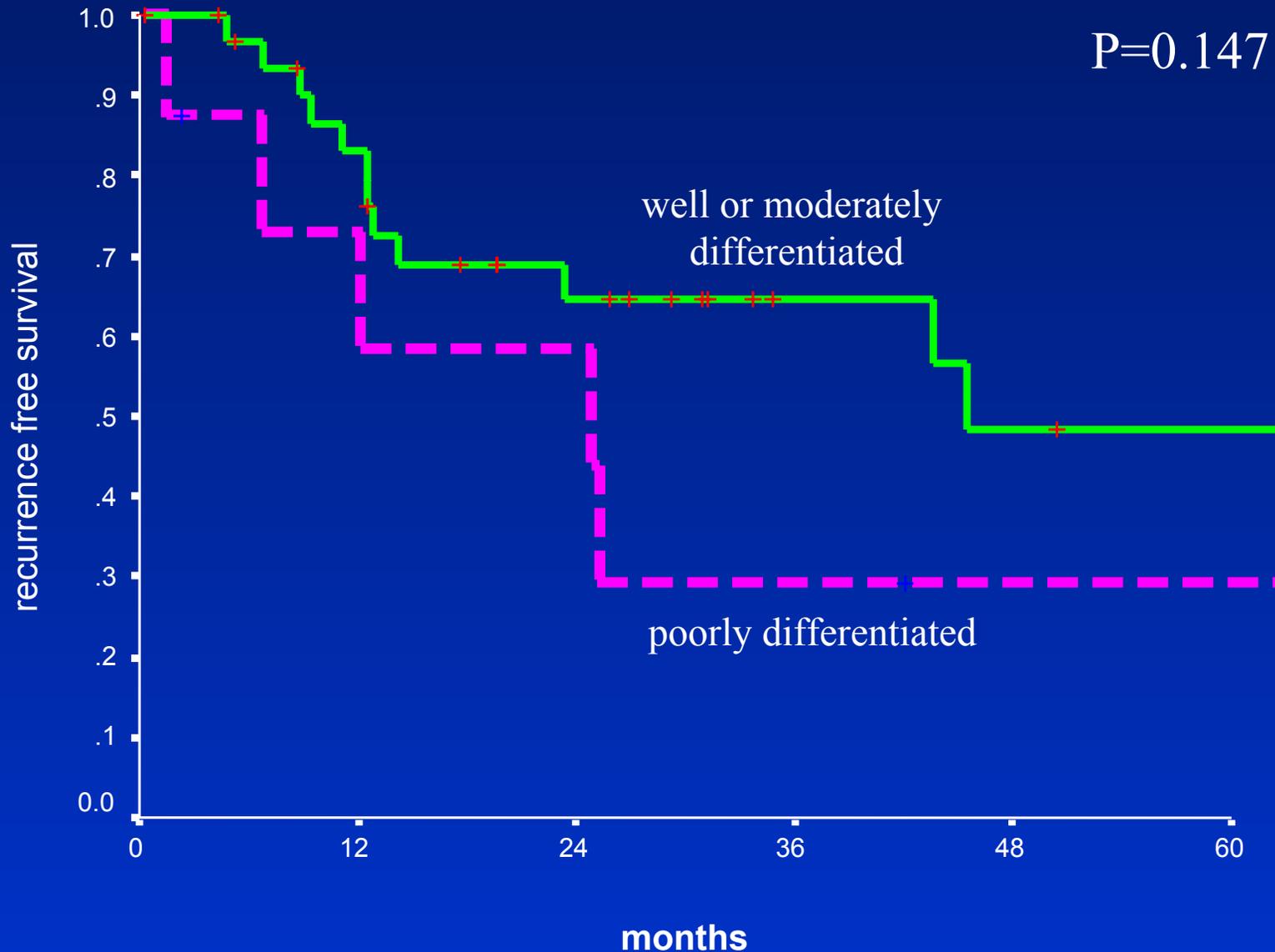
	micro or macro vascular invasion (n)	no vascular invasion (n)
recurrence	16	1
no recurrence	18	8

p=0.036

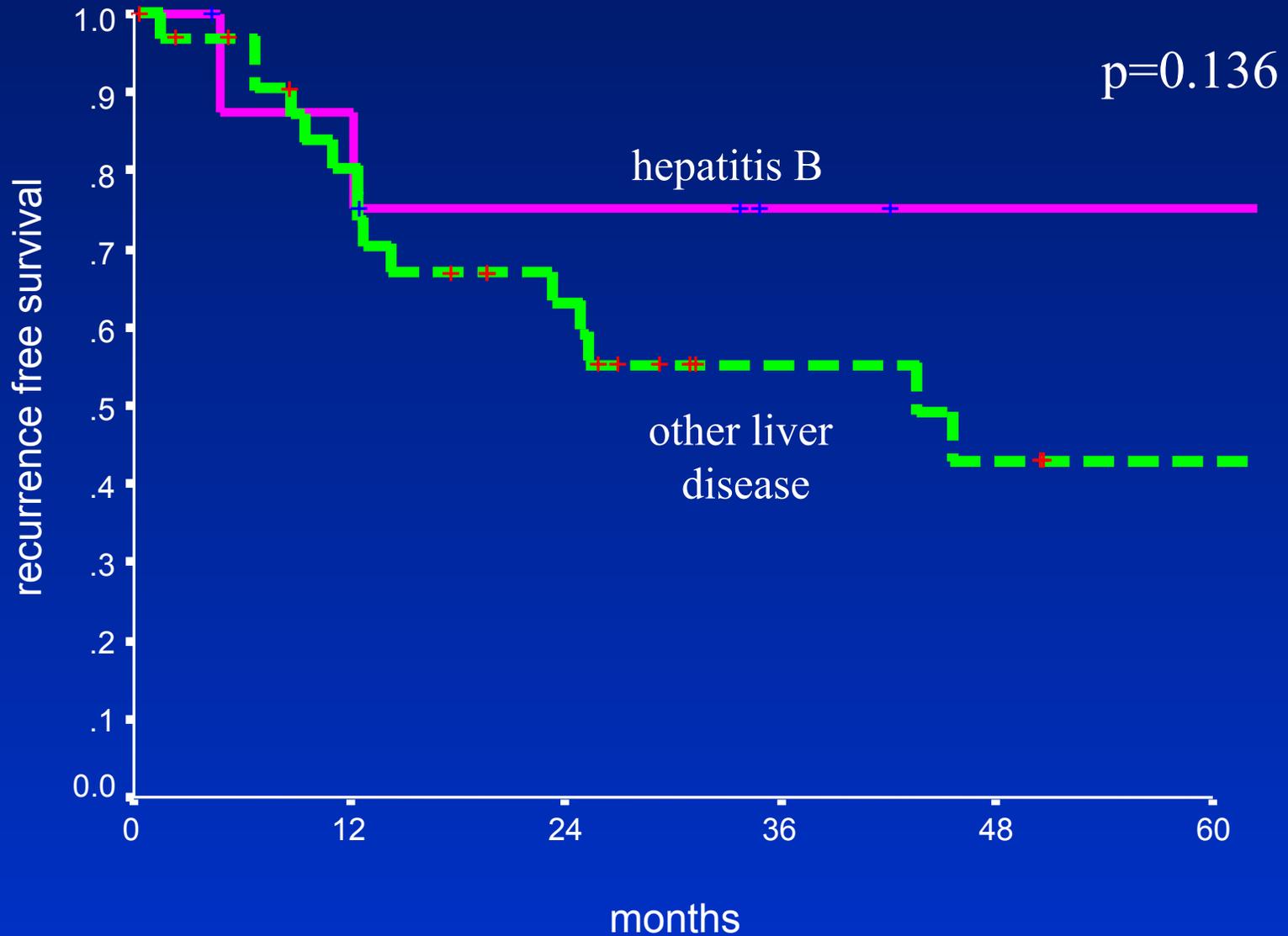
Recurrence-free Survival



Recurrence-free survival



Recurrence-free survival



Conclusions

- liver transplantation for HCC ≥ 5 cm
 - 5 year overall survival 44%
 - 5 year recurrence-free survival 48%
- predictors of recurrence
 - tumor size > 7 cm
 - presence of vascular invasion
- possible predictors of recurrence
 - poorly differentiated tumors
 - underlying liver disease other than hepatitis B

Role of adjuvant therapies

- results better than historic series, but...
 - not a randomized study
 - careful scrutiny of cases
 - ? natural selection due to waiting time
- chemoembolization may be useful in delaying tumor progression while waiting
- systemic chemotherapy of questionable value

Conclusions

- decreased survival compared to HCC < 5cm
 - overall survival 44% vs 75%
 - recurrence-free survival 48% vs 83%
- UNOS: HCC \geq 5cm eligible, but no priority
 - in effect rules out cadaveric transplantation
- Results justify transplantation of selected patients with HCC beyond Milan criteria