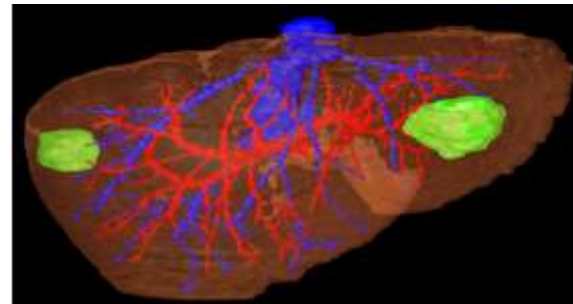


Estimation of Prognosis and Candidacy for Liver Transplantation



Allan M. Concejero, MD

St. Luke's Medical Center-Global City, Taguig

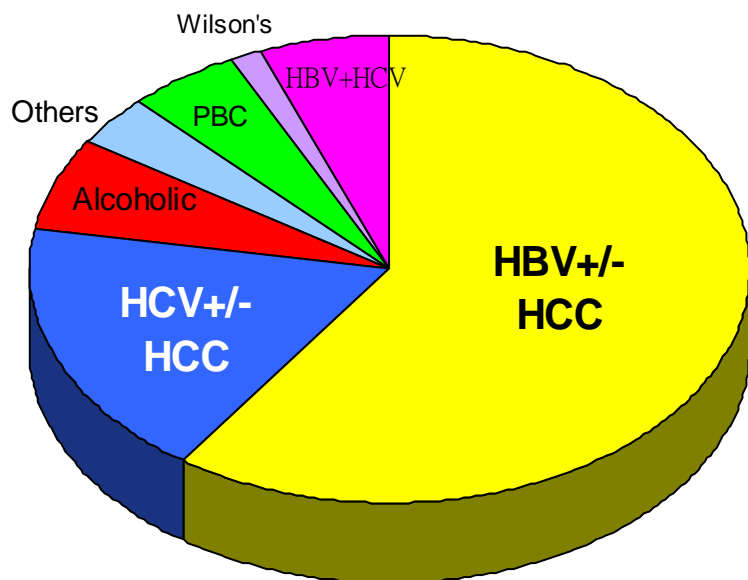
University of the Philippines-Philippine General Hospital

3rd APASL HCC Conference, Cebu, Philippines

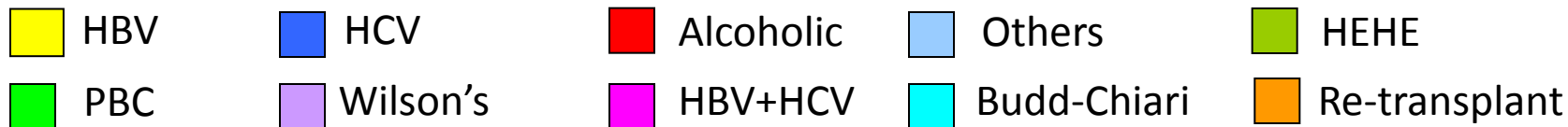
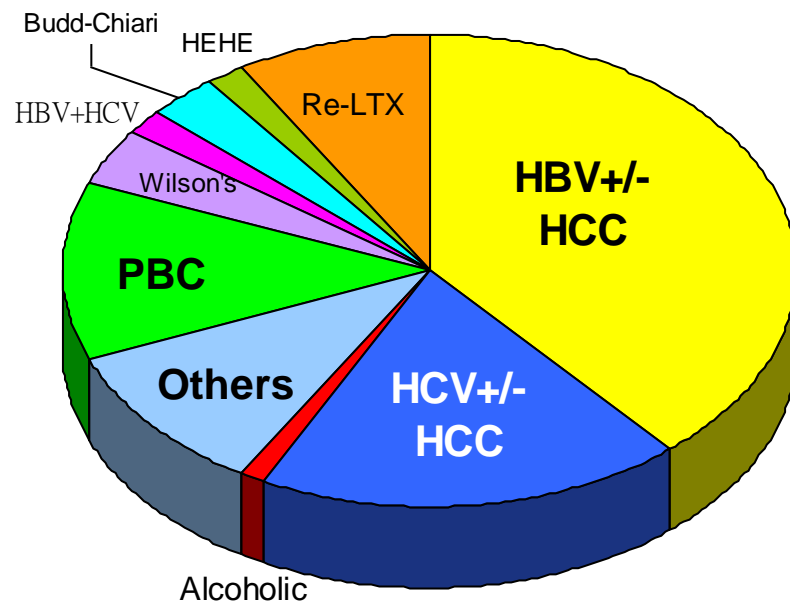
Adult Liver Transplantation

Jan 1999 – May 2009

LDLT 286



DDLT 106





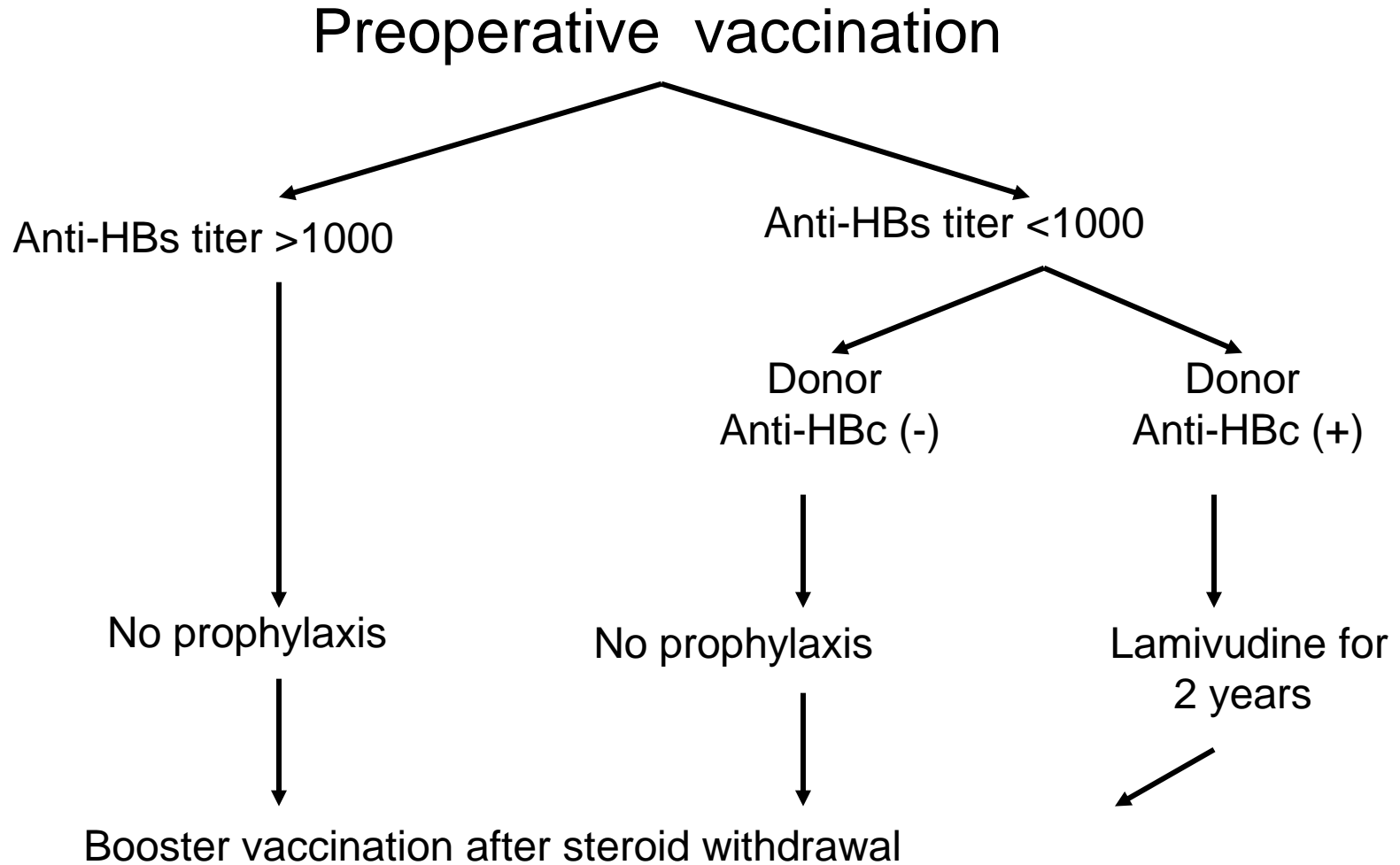
Liver Transplantation for HBV

- Lamivudine 100 mg qd
HBeAg(+)/HBV DNA(+): pretransplant
HBeAg(-) /HBV DNA(-): from POD 1
- Adefovir or Entecavir for mutant
- HBIG 10,000 IU anhepatic phase
2,000 IU qD x 7D
- HBsAb \geq 100 m IU/mL

LDLT for HBV

- Actuarial survival rates
 - 1-year 94%
 - 5-year 91%
- 2 HBV recurrence (2.4%)
- Hospital mortalities 3
- Late mortalities 3
 - HCC lung metastasis
 - Gastric carcinomatosis
 - Veno-occlusive disease

Prophylaxis Against De Novo HBV





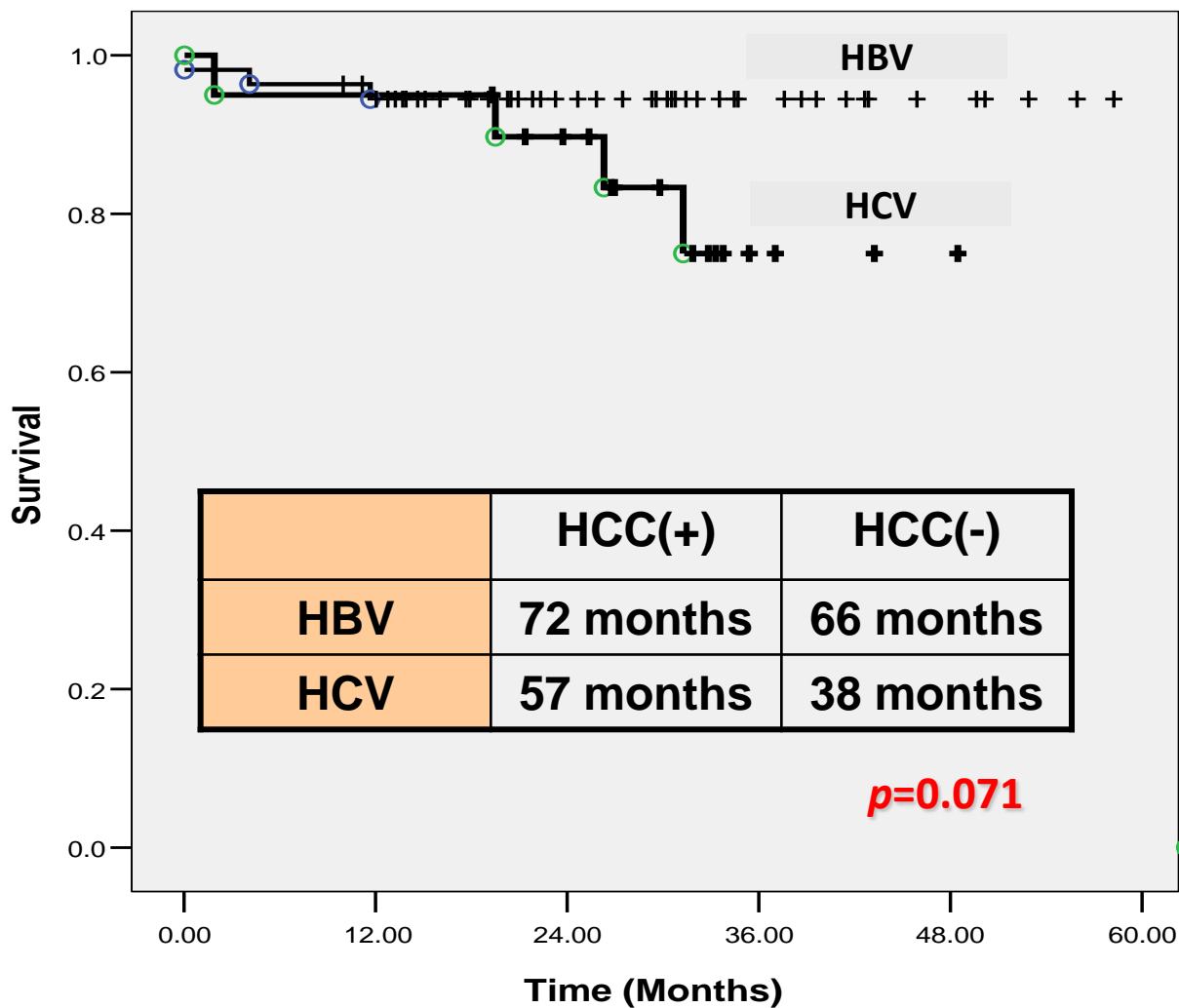
Liver Transplantation for HCV

Treatment Guidelines

- ALT $\geq 2X$; 2 determinations, 3 months apart within 6 months
- Liver biopsy \geq F1 fibrosis score
- Pegylated interferon alpha-2a or alpha-2b + Ribavirin

Taiwan National Health Insurance Policy

LDLT for HBV vs. HCV





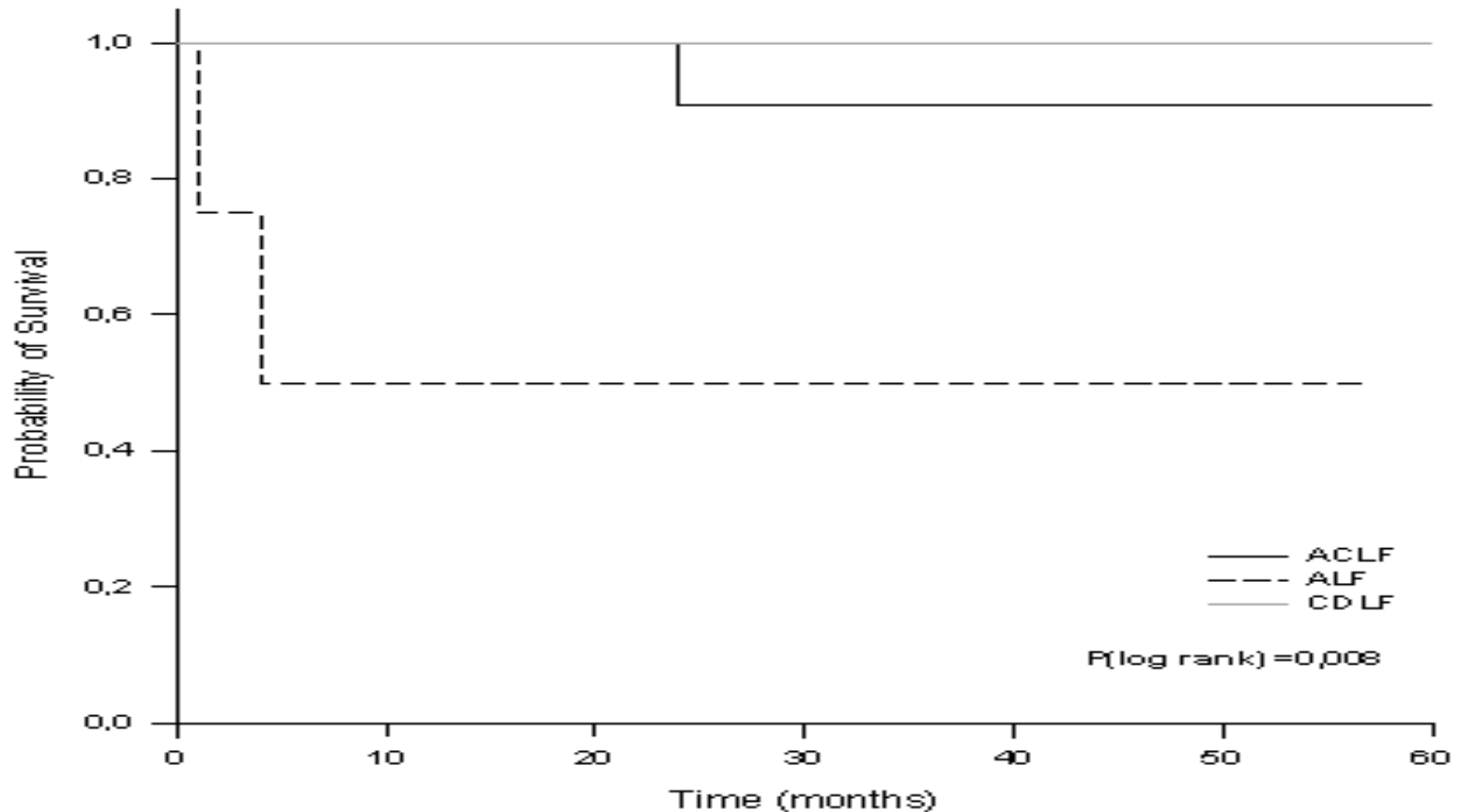
ALF vs. Acute-on-Chronic vs. DELF

Univariate analysis between subtypes of liver failure versus postoperative outcome after transplantation

Variable	ALF (n=4)	ACLF (n=22)	CDLF (n=3)	Total (n=29)	P value
Postoperative mortality	50%	0%	0%	6.9%	0.001*
Short term morbidity	100%	77.27%	66.67%	77.8%	0.674
GWSLV recipient % (SD)	75.650 (13.543)	67.750 (21.534)	60.733 (21.786)	68.114 (20.381)	0.639
Median postoperative ICU days (25-75% CI)	26 (23-69.5)	21.5 (19-31)	32 (31.250- 34.250)	24 (20-32)	0.154
Median extubation day (25-75% CI)	7 (3-18.5)	2 (1-8)	2 (2-9.5)	2 (2-10.25)	0.285
Mean hospital stay in days (25-75% CI)	65.75 (+/- 35.208)	56.636 (+/- 18.854)	56 (+/-11.79)	57.828 (+/- 20.489)	0.721

CI, Confidence interval; *p<0.05 is considered significant

ALF vs. Acute-on-Chronic vs. DELF



Kaplan-Meier survival curves showing patient survival in the 3 subtypes of liver failure

HCC in Asia

Asia accounts for 78% of 600,000 reported globally/ year

- Aflatoxin, algal hepatotoxins in contaminated water
betel nut chewing, alcohol
- Chronic hepatitis infection
 - Chronic HBV:** 1-5% Japan, Singapore, Thailand
6-10% Northern China, Indonesia
>10% Taiwan, Korea, Philippines
 - Chronic HCV:** Japan and Taiwan
- HCC disease-control measures involving surgical, locoregional, systemic strategies remain highly relevant

Child-Turcotte-Pugh Classification

Definition of the Child-Turcotte-Pugh Stage Classification

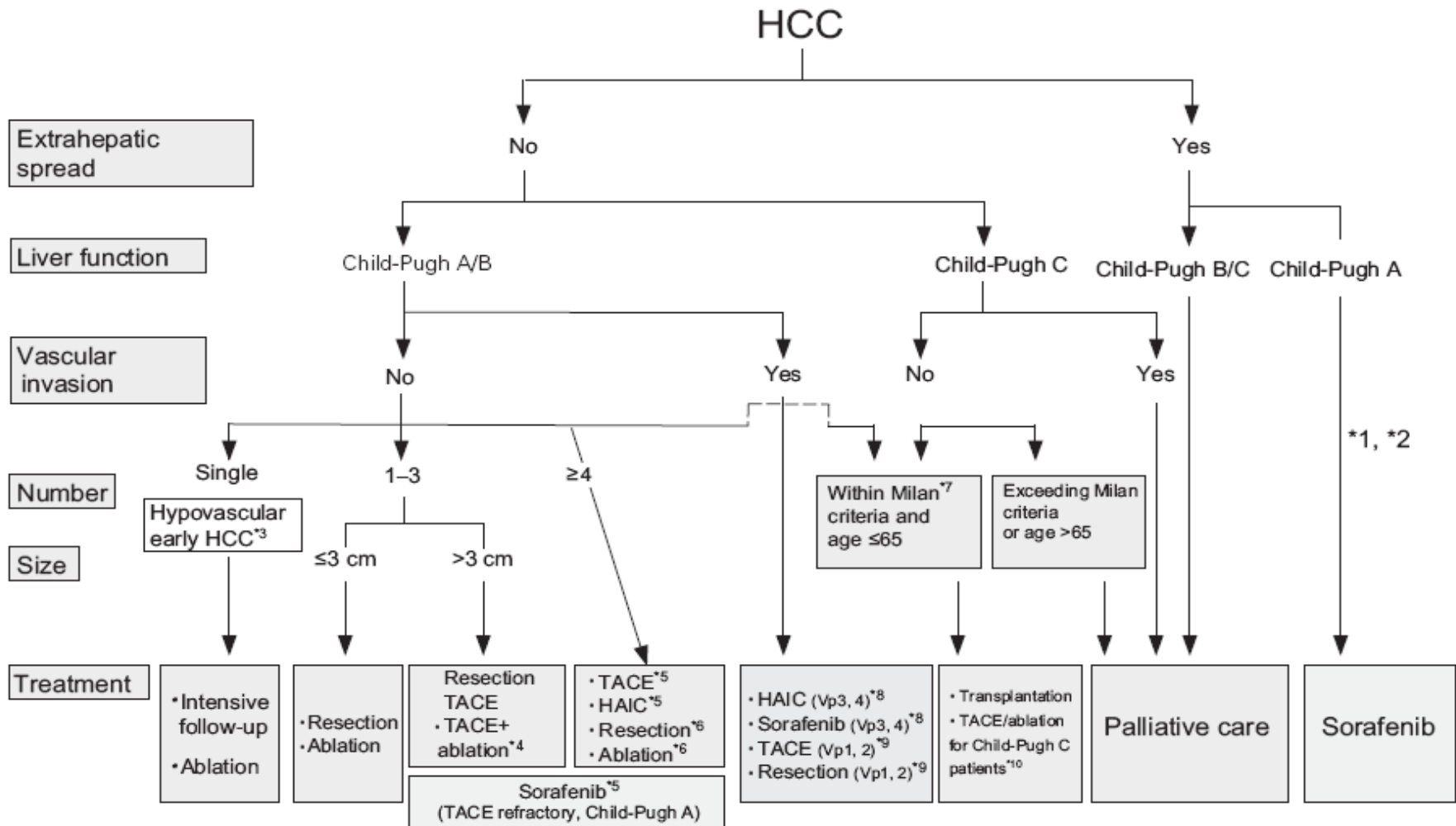
	1	2	3
Encephalopathy	none	mild	coma
Ascites	none	responsive	unresponsive
Serum bilirubin, mg/dl	<2.0	2.0–3.0	>3.0
Serum albumin, g/dl	>3.5	2.8–3.5	<2.8
Prothrombin activity, %	>70	40–70	<40

Class A: score 5-6

Class B: score 7-9

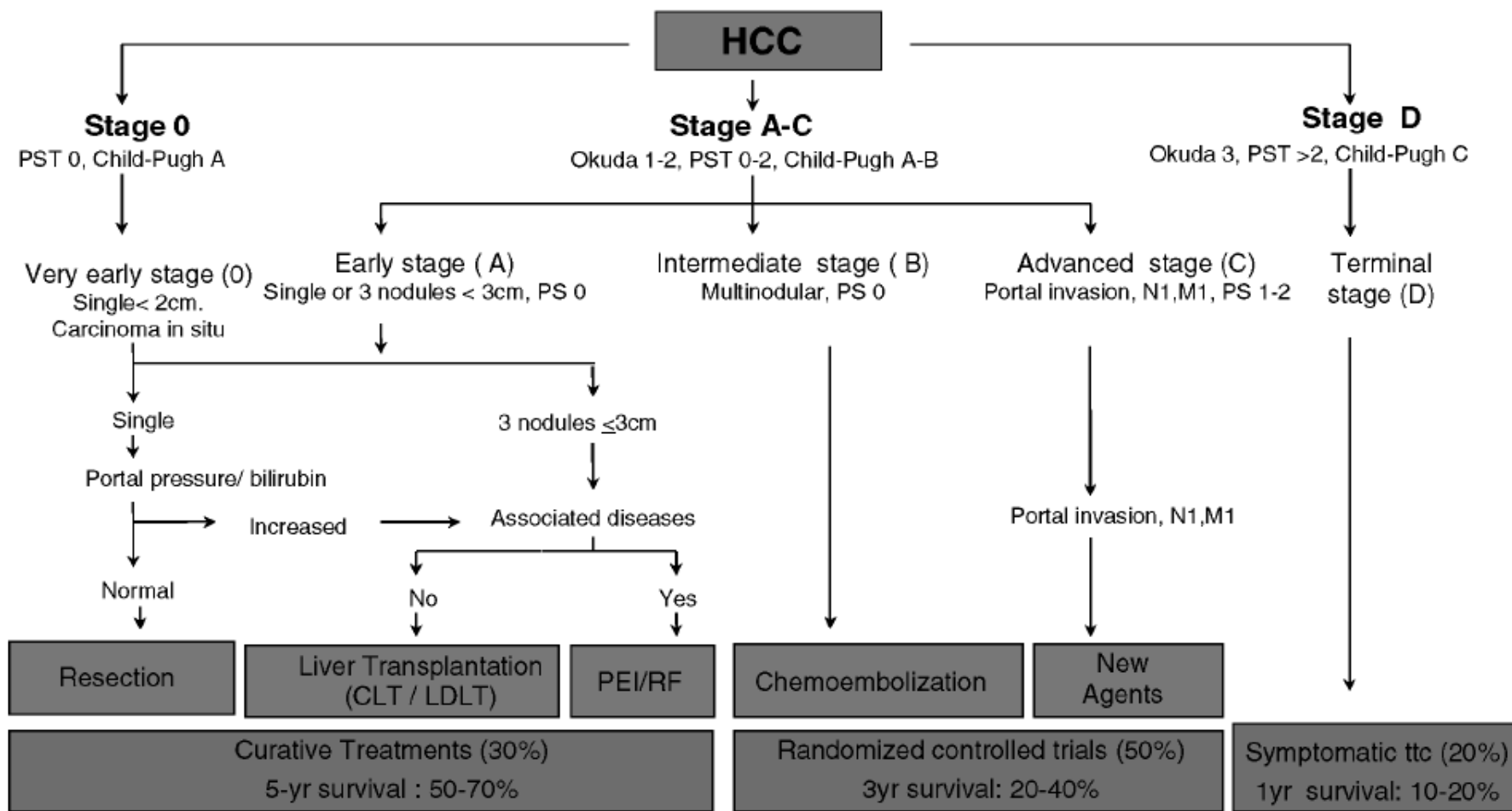
Class C: score 10-15

Japan Society of Hepatology Consensus



BCLC Staging and Classification

BCLC Staging and treatment schedule



Prognostic Variables in the Staging Systems

Classification	Variables		
	Tumor stage	Liver function	Health status
Okuda stage [7]	50% liver involvement	Bilirubin Albumin Ascites	–
French [26]	Portal invasion AFP	Bilirubin Alkaline phosphatase	Karnofsky
CLIP [27]	Portal invasion </> 50% liver involvement AFP	Child-Pugh	–
BCLC [4,11]	Portal invasion Metastases Morphology Okuda	Child-Pugh Portal hypertension Bilirubin.	PST
CUPI [28]	TNM AFP	Ascites Bilirubin Alkaline phosphatase	Symptoms
TNM [29]	Morphology Vascular invasion Metastases	Fibrosis	–
JIS score [30]	TNM	Child-Pugh	–
ER [31]	Estrogen receptor	–	–

HCC in Patients with Cirrhosis

For patients with resectable HCC

- Conventional treatment is partial hepatectomy
- Major hepatic resection can be performed safely
- Key is preservation of liver function after resection
- Treatment modalities to increase remnant liver volume
- Multi-modality treatments to make the tumor operable

HCC in Patients with Cirrhosis

For patients with non-resectable HCC

- Best treatment seems to be in combination strategies (TAE, RFA, PEI) with or without systemic chemotherapy
- Drug eluting bead and Y-90 alone with or without chemotherapy has the potential to downstage unresectable HCC to become resectable
- Liver transplantation for select patients

HCC in Patients with Cirrhosis

Liver Transplantation: Rationale

- Most HCC multifocal
- Best oncologic resection
- Treat underlying cirrhosis and restore normal liver function

Liver Transplantation for HCC

Potential Advantages

- Eliminates the tumor
- Cures the underlying disease
- Lower recurrence rate
- Good survival in selected cases

Liver Transplantation for HCC

Potential Disadvantages

- High economic cost
- Recurrence of viral diseases
- Limited donor resources



Liver Transplantation for HCC

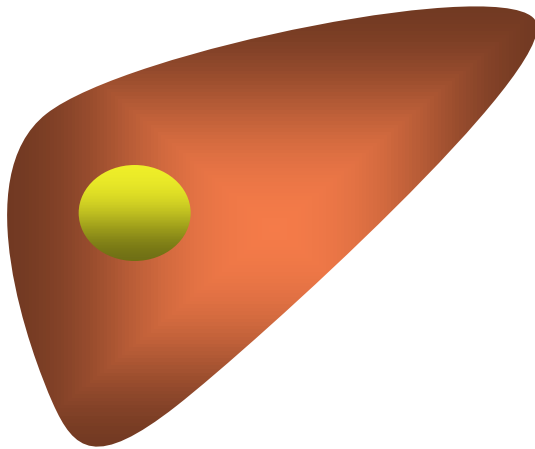
Indications

- Worsening cirrhosis with poor functional reserve
- Complications : EVB, SBP, encephalopathy
- Limited tumor without vascular invasion
- Age < 65 years ?
- No contraindication to major surgery

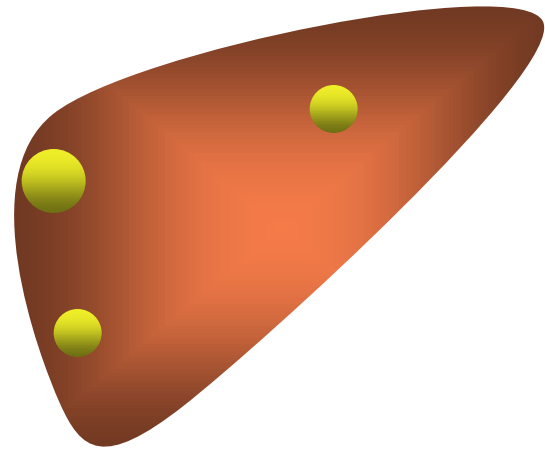
LT for HCC with Cirrhosis

Milan Criteria (Stage I+II)

Single, not > 5cm



Up to 3, none > 3cm



+

Absence of Macroscopic Vascular Invasion
Absence of Extrahepatic Spread

Criteria for Transplantation

Hepatocellular Carcinoma

Milan criteria

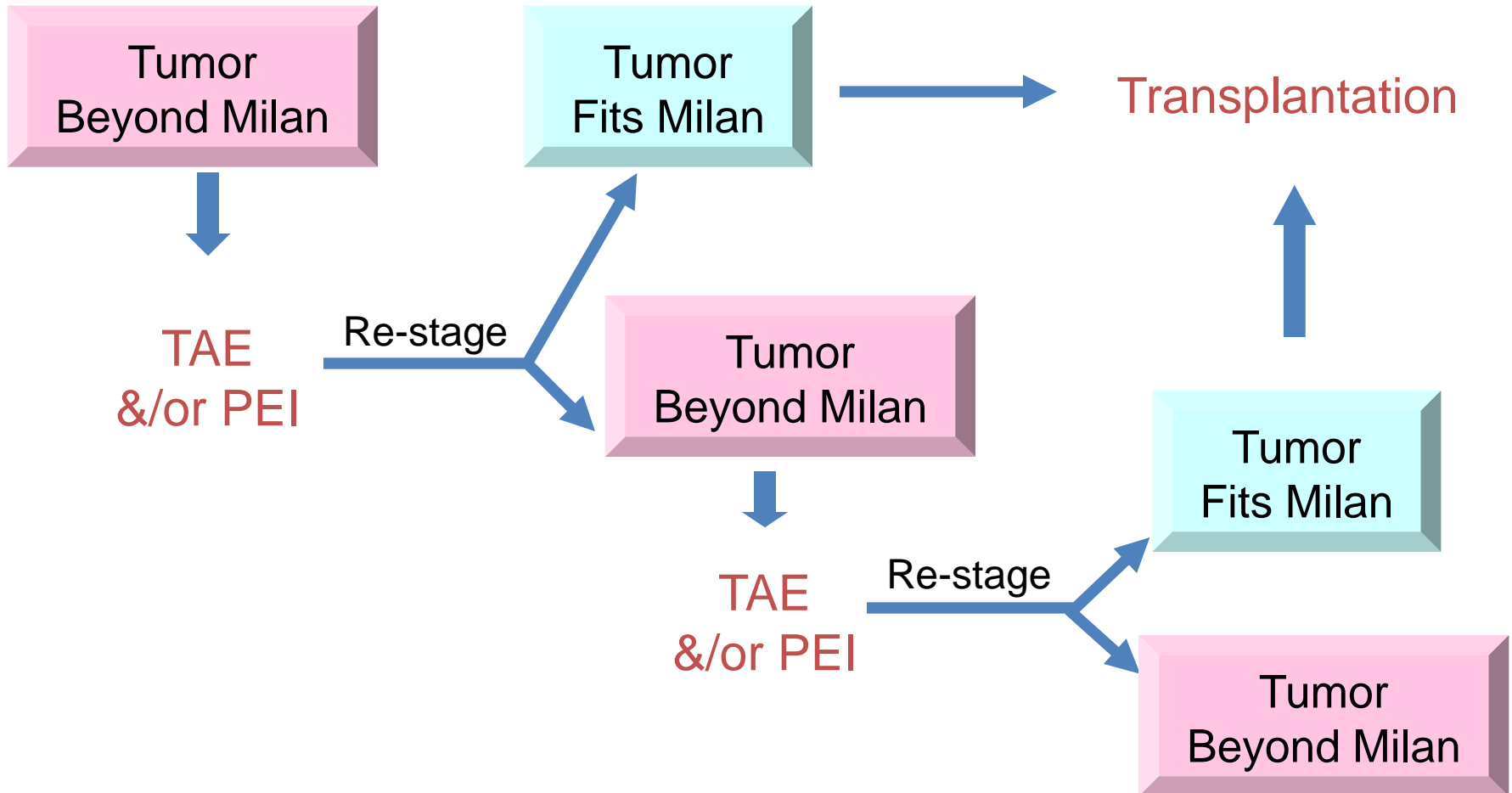
- Solitary ≤ 5 cm
- ≤ 3 tumors
none > 3 cm

UCSF criteria

- Solitary ≤ 6.5 cm
- ≤ 3 tumors
none > 4.5 cm
- Total diameter ≤ 8 cm

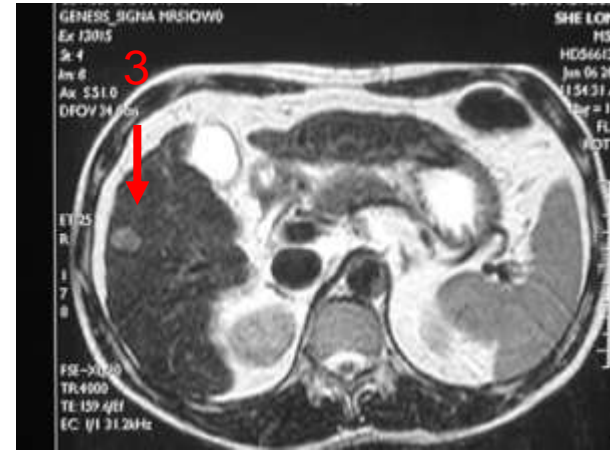
- Important factor for tumor recurrence:
vascular invasion
- Anticipated by tumor size and number
- Tumor biology & differentiation characteristics

Pre-Transplant Down-Staging

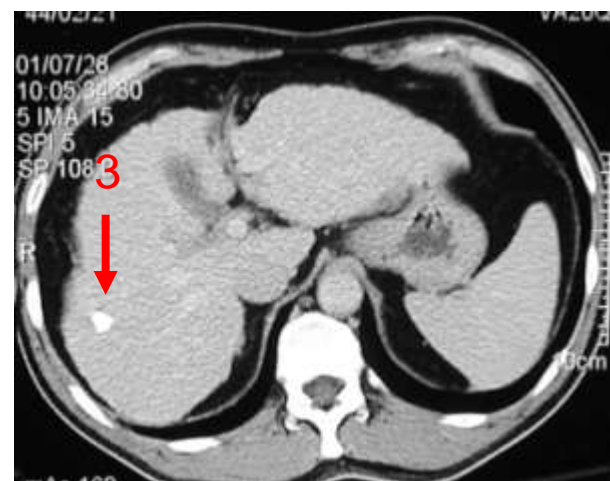
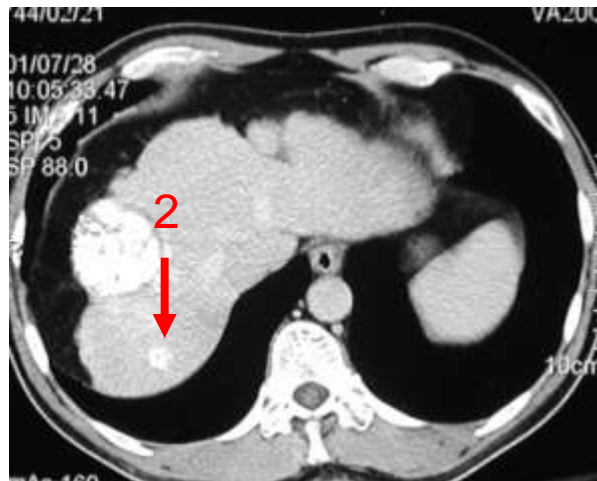
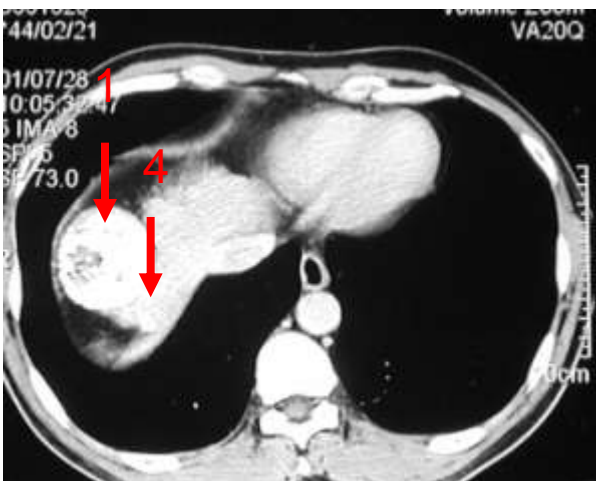


Pre-Transplant Down-Staging

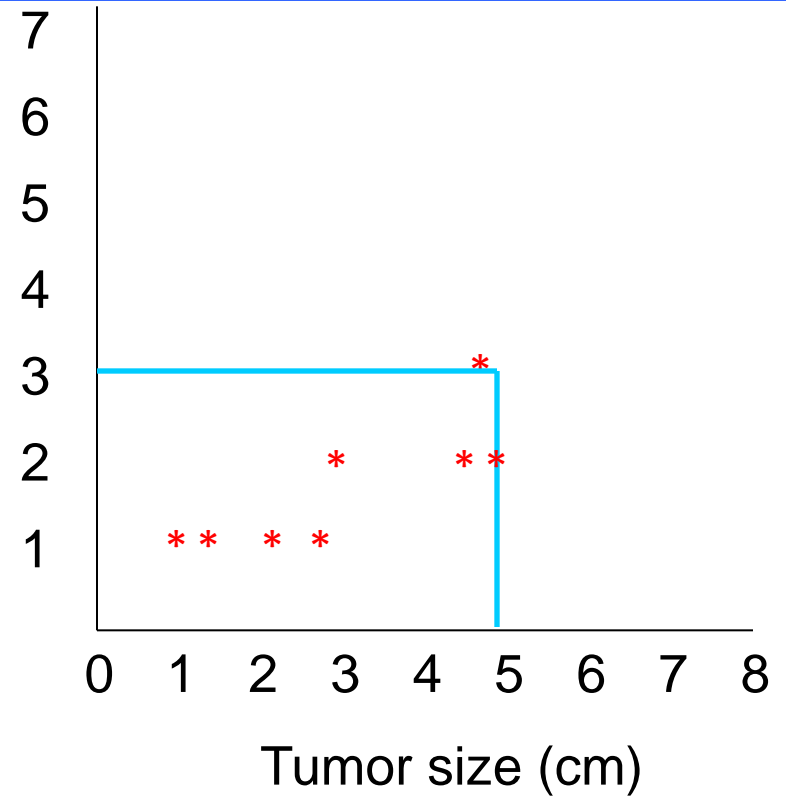
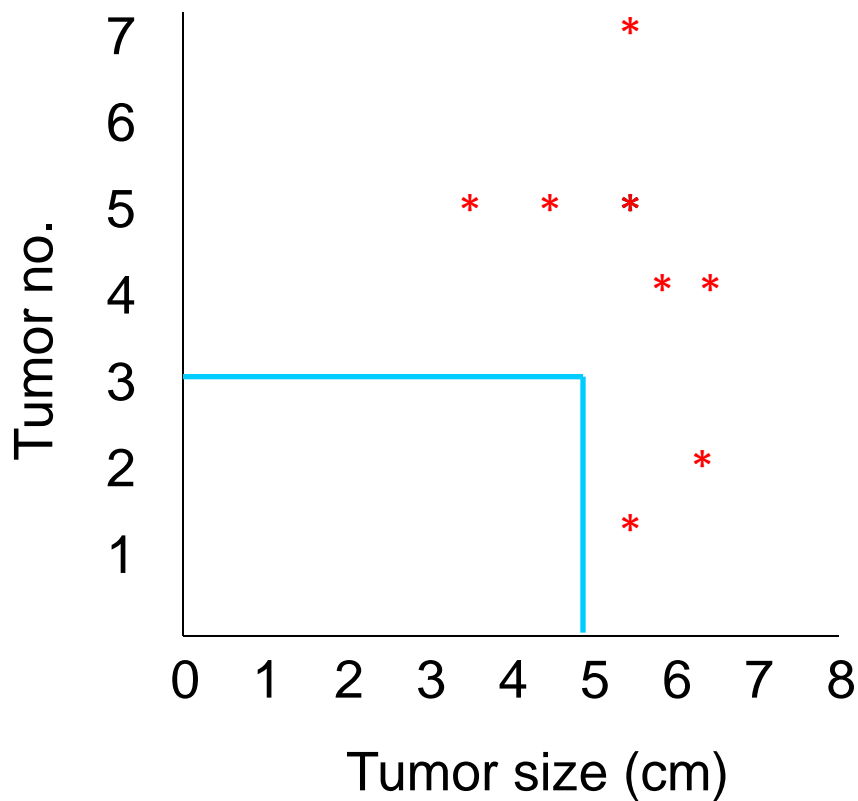
Pre-TAE



Post-TAE



Pre-Transplant Down-Staging

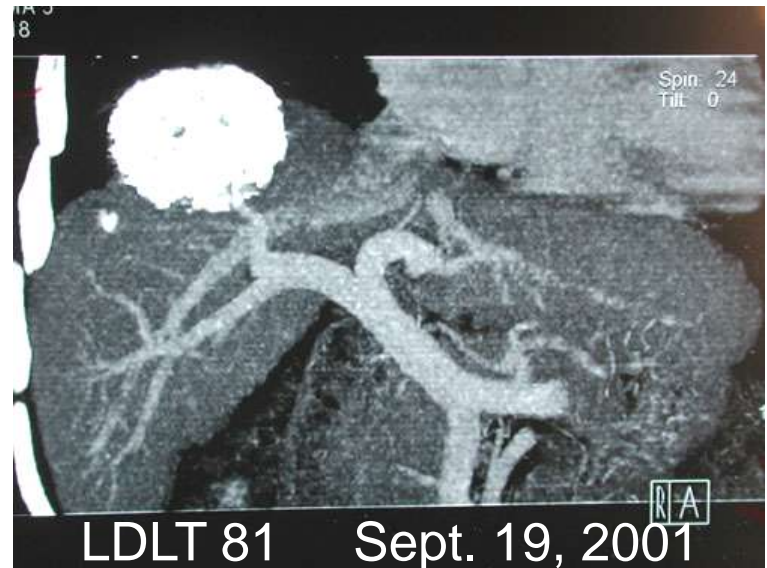
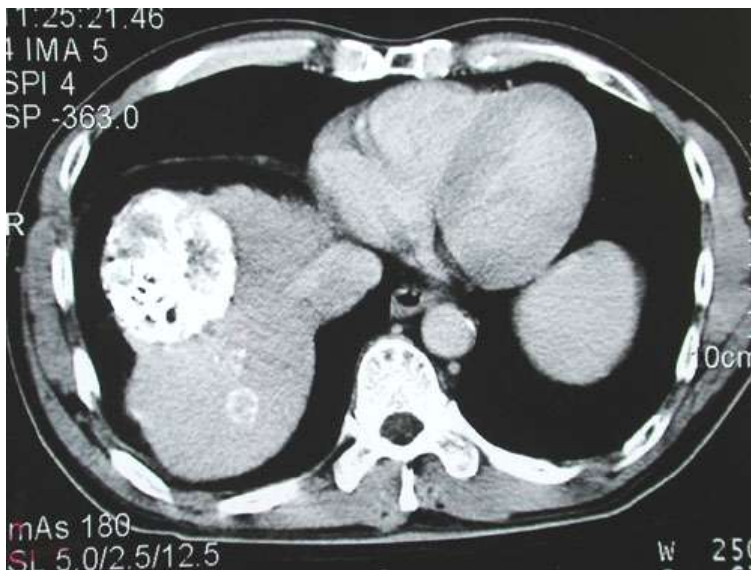


N=8, Beyond Milan criteria ➔ N=8, Within Milan criteria
TAE
& / or PEI

Initially Beyond Milan Criteria



- biggest 5.5 cm
- diaphragmatic invasion
- 80% necrosis
- 2 satellite nodules (1.5 cm)
- microscopic PVT (+)



LDLT 81

Sept. 19, 2001

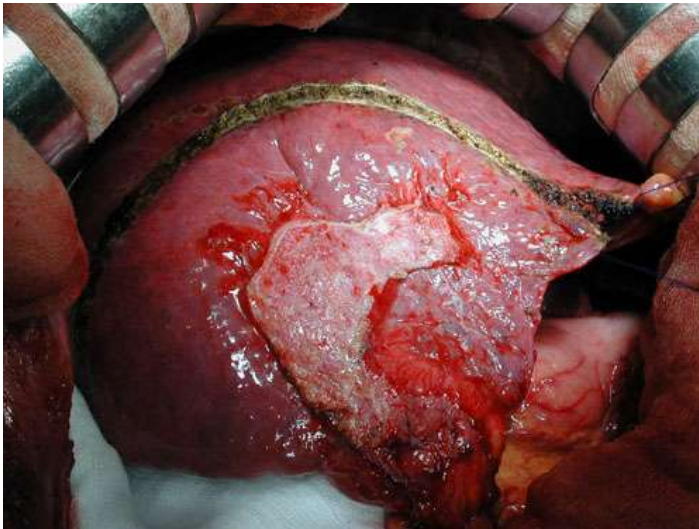
Liver Transplantation for HCC

- Sequential Liver Transplantation “salvage transplantation”
- High pathological risk of recurrence after surgical resection : an indication for salvage transplantation

Sequential LDLT

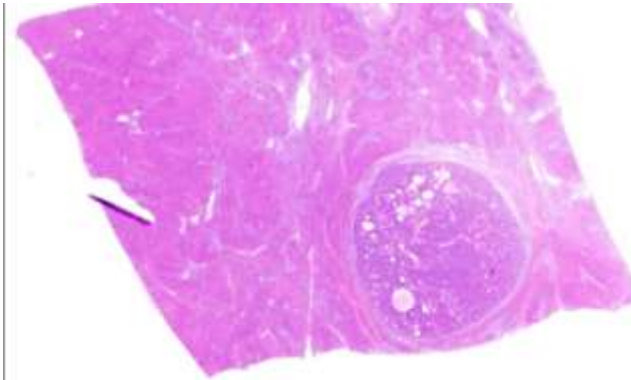


**Resection
July 12, 2001**

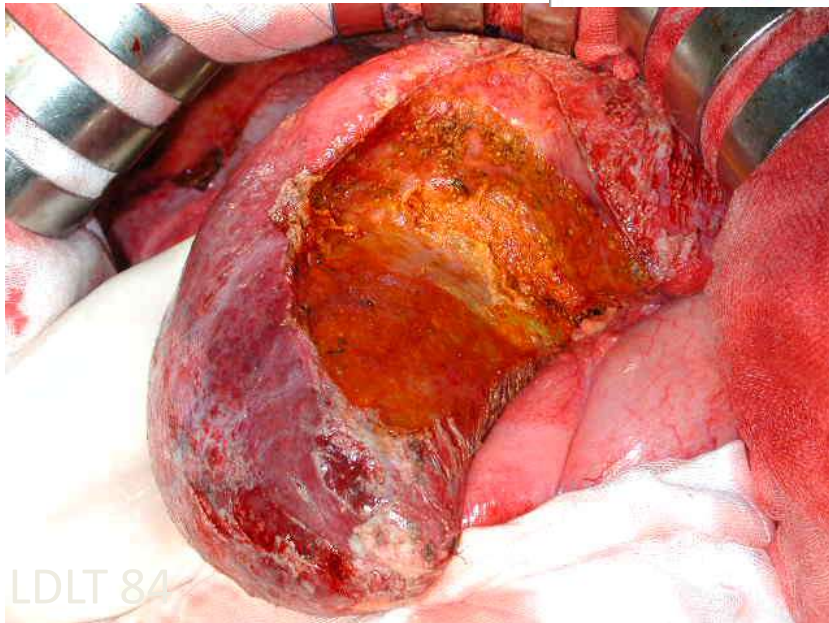


Sequential LDLT

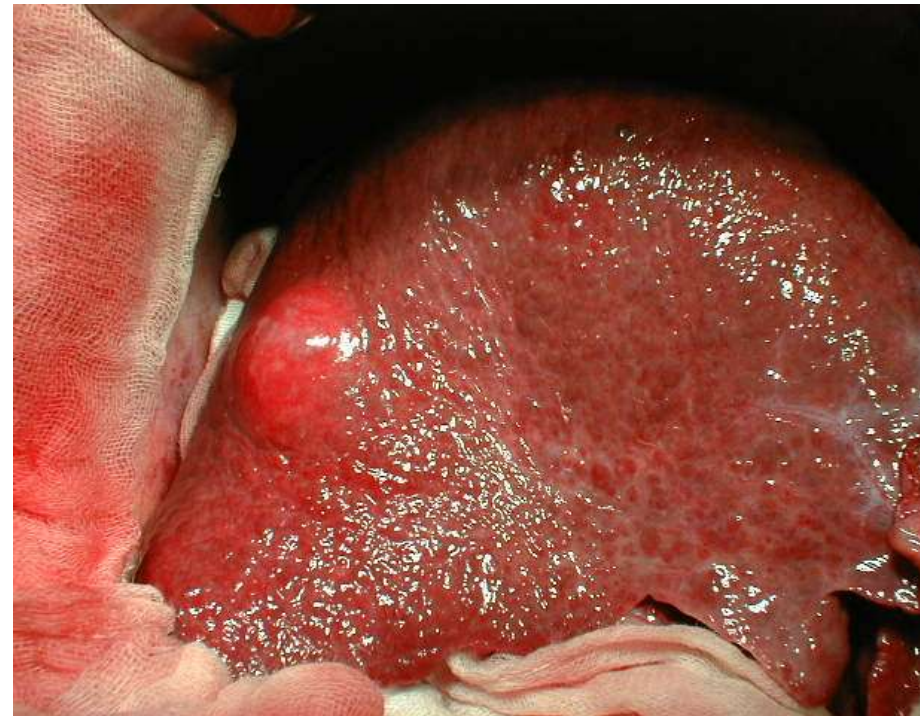
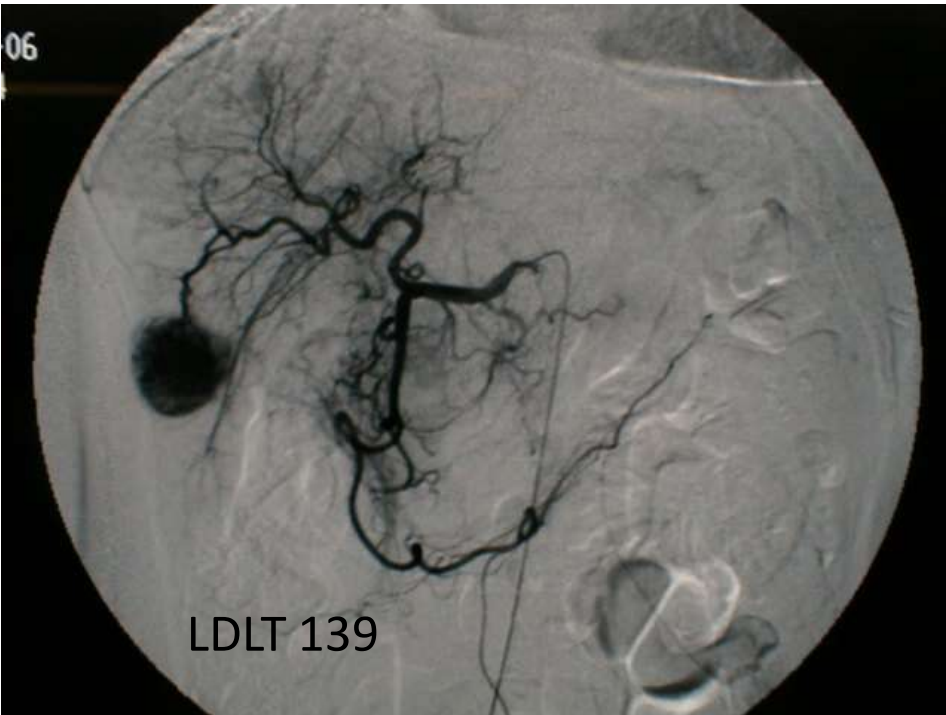
LDLT Oct. 23, 2001



6 mm HCC

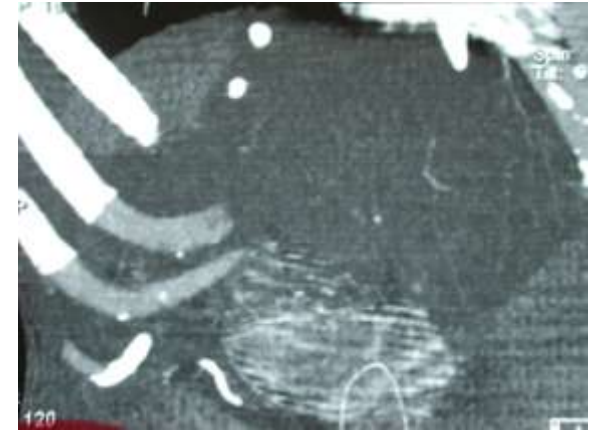
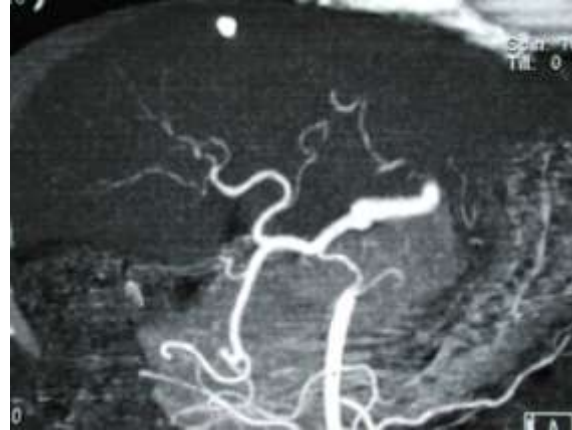


Salvage Transplantation



Resection June 11, 2002

Salvage Transplantation

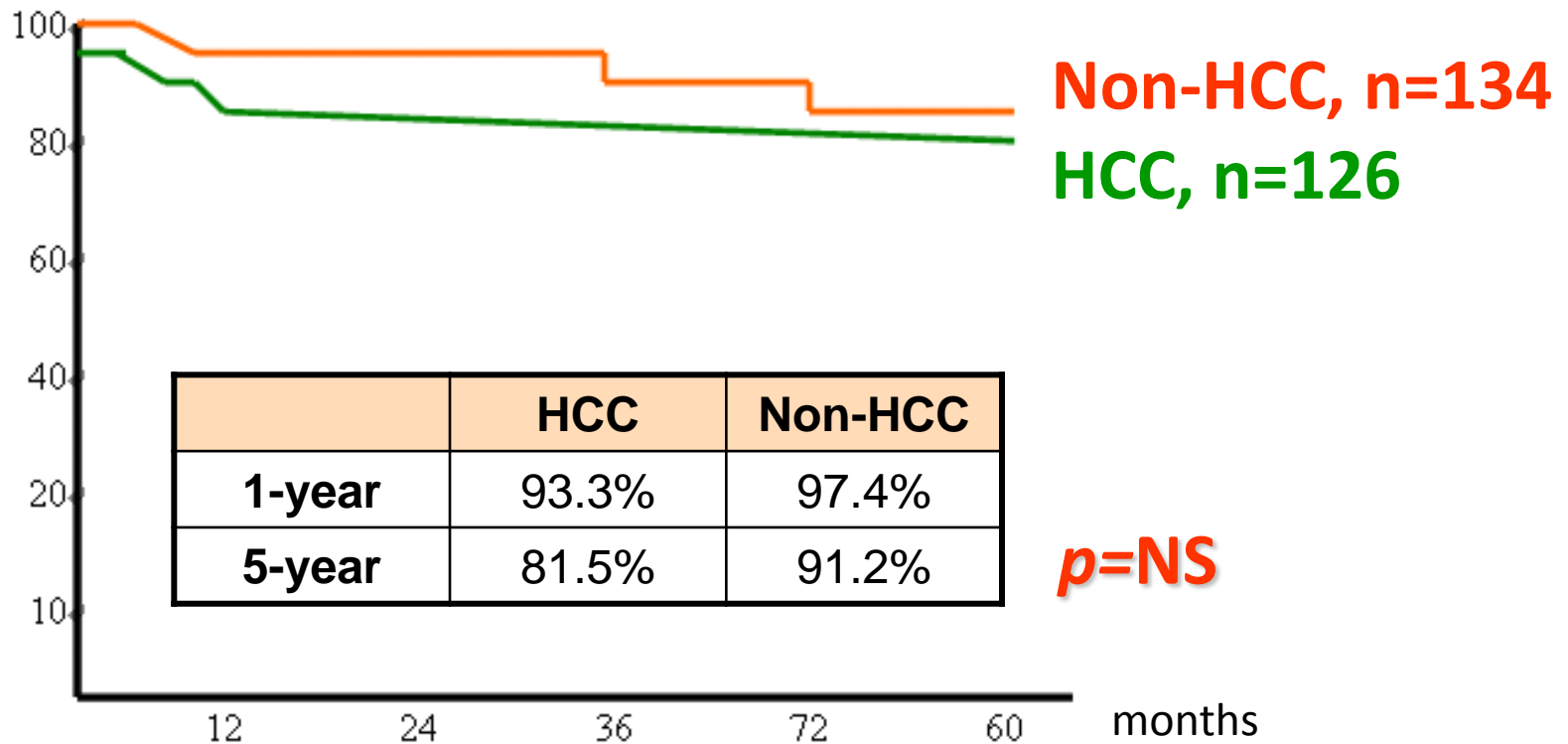


LDLT 139

LDLT
June 18, 2003

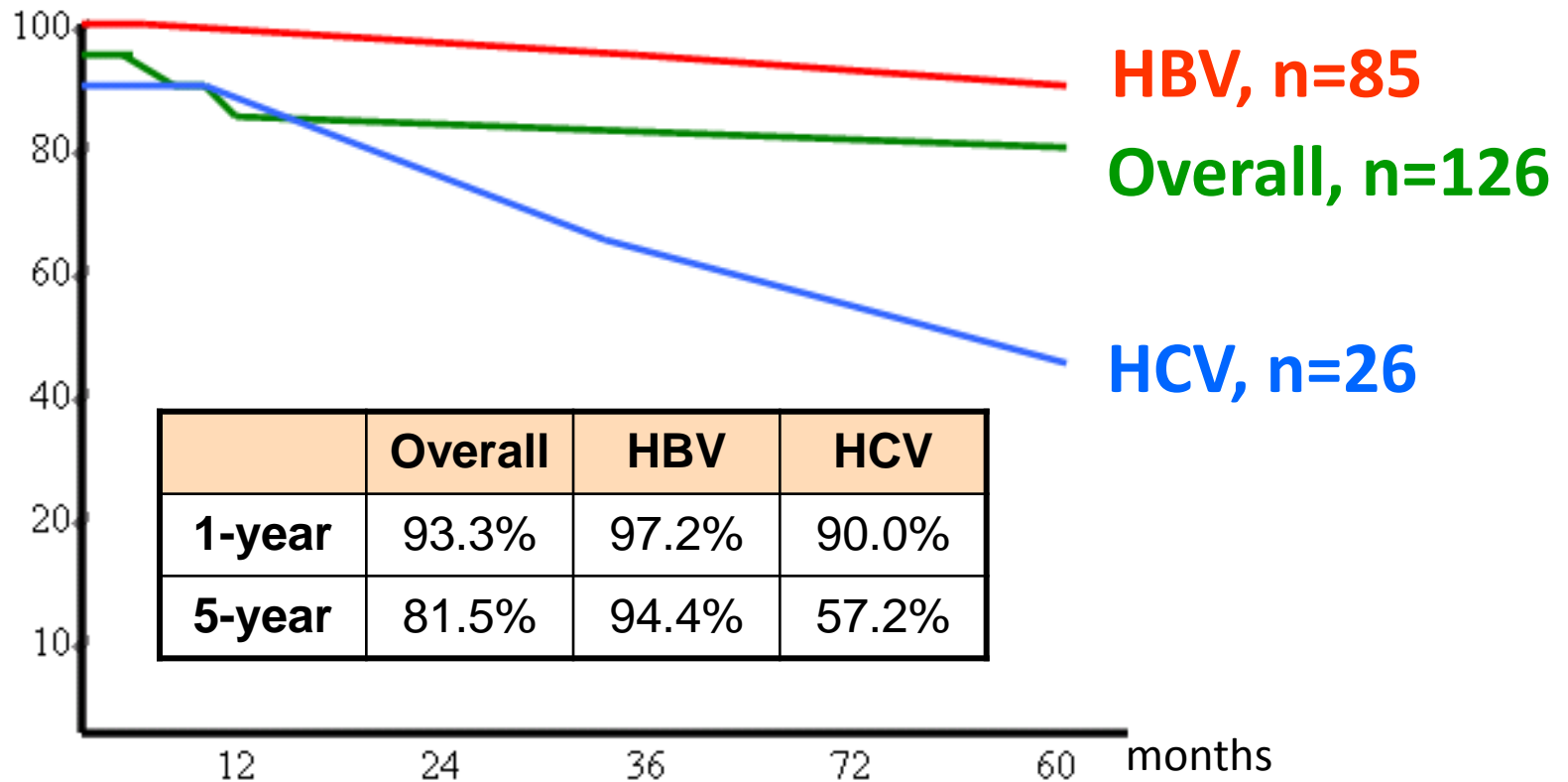
LDLT for HCC

HCC vs. non-HCC



LDLT for HCC

Overall vs. Hepatitis





LDLT for HCC

Non-estimated Survival Rates :

- 1 year : 98%
- 3 year : 96%
- 5 year : 90%

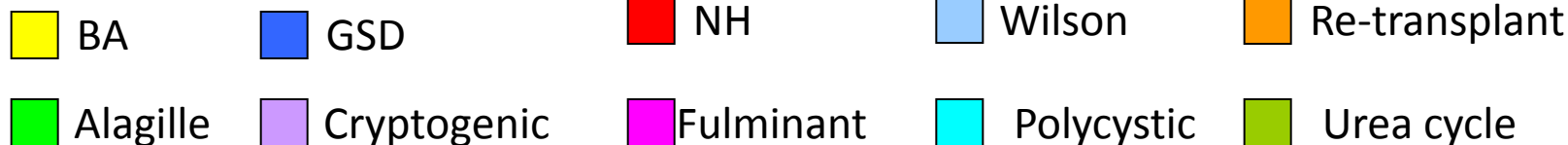
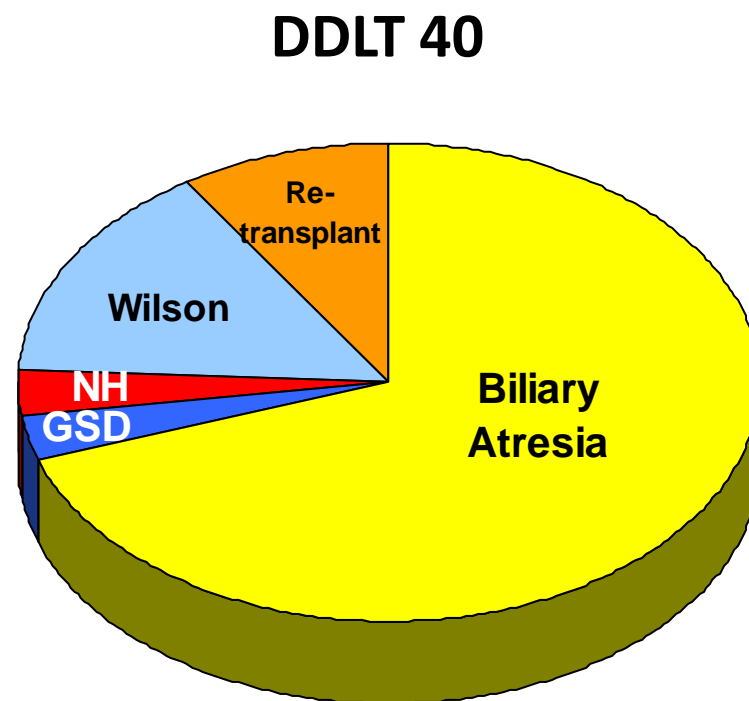
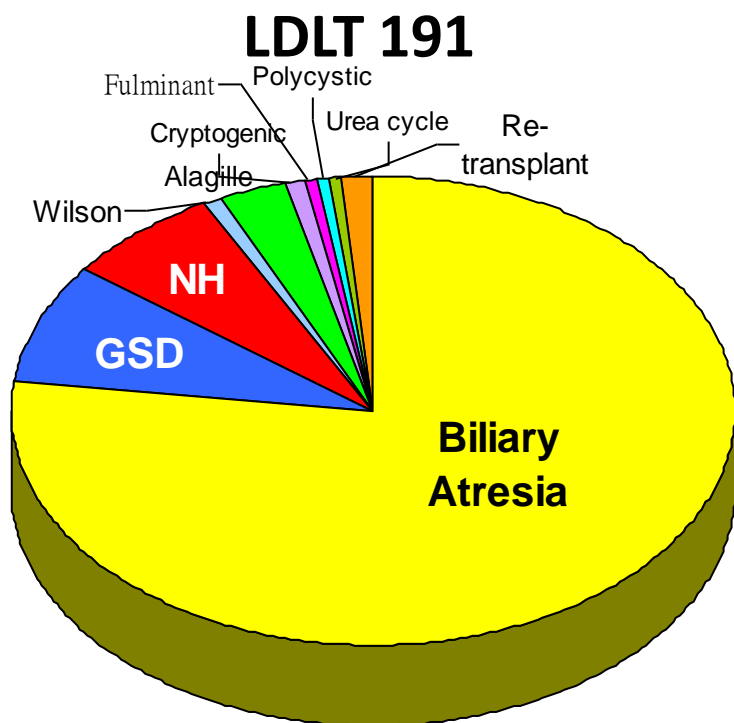
Liver Transplantation for HCC

Summary

- More patients are selected for transplantation based on expanded clinical criteria
- Refinement of selection and extension of criteria in number of tumor and use of tumor markers produces acceptable results and benefits
- Eradication of circulating cancer cells may be the focus of future research
- LDLT for early HCC due to graft shortage seems logical

Pediatric Liver Transplantation

1984.3 – 2010.3



LDLT for Biliary Atresia

June 1994 – September 2005



Pre-Tx



6 m Post Tx

- 237 LDLT
- 124 pediatric LDLT
- 100 LDLT for BA
- mean follow-up:
85 months
(range: 13-148)

LDLT for Biliary Atresia

Real-Time Survival Rates

- 6 – month 99%
- 1 – year 98%
- 5 – year 98%



First Successful Liver Transplant in Asia

March 22, 1984



Liver Transplantation for Wilson's Disease
Report of the first successful liver transplant in Taiwan
Chen CL, et al. Jpn J Transplant 1987; 22: 178

Longest Surviving Liver Transplant in Asia

November 3, 1985



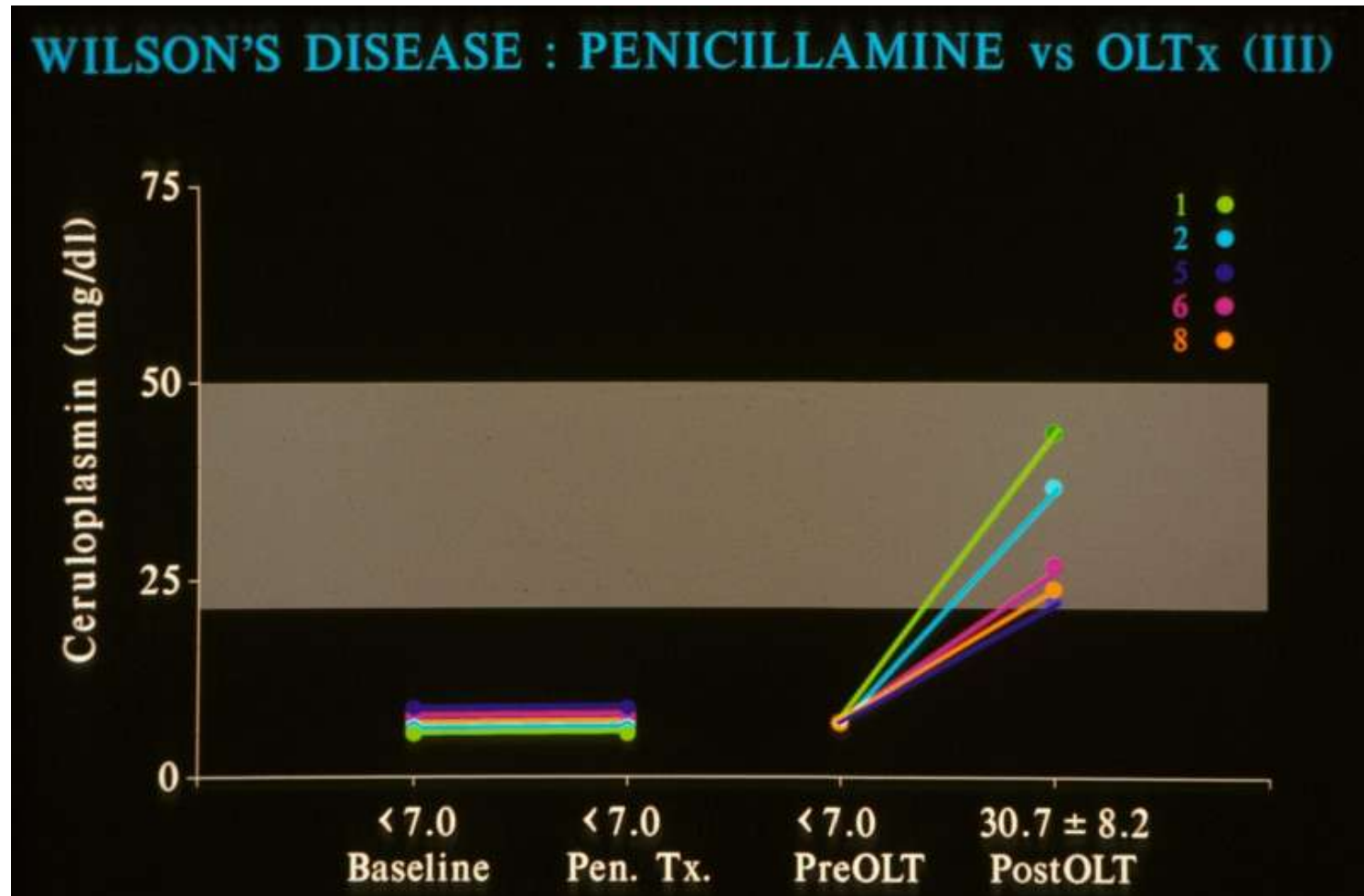
Chen CL, et al. Asian J Surgery 1989; 12:31



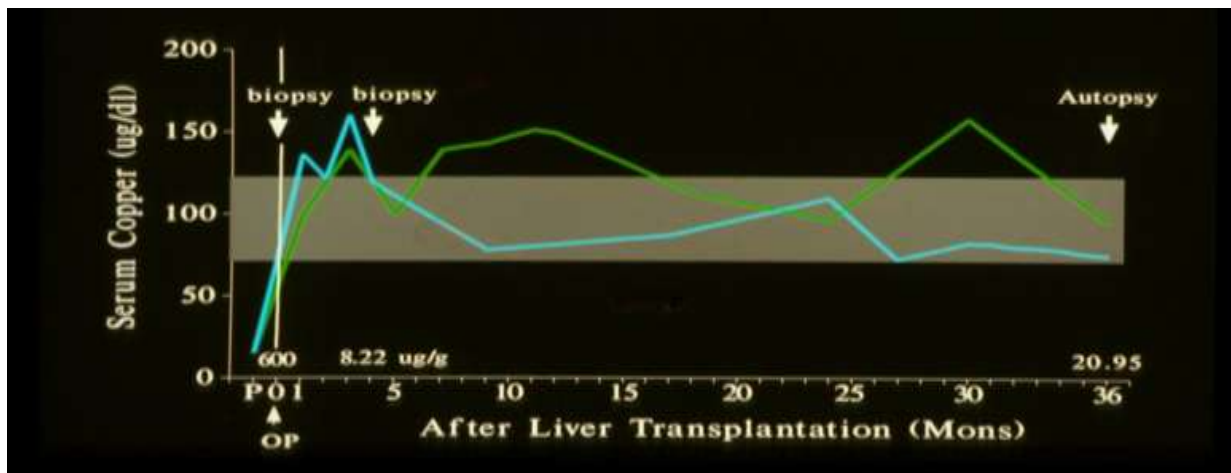
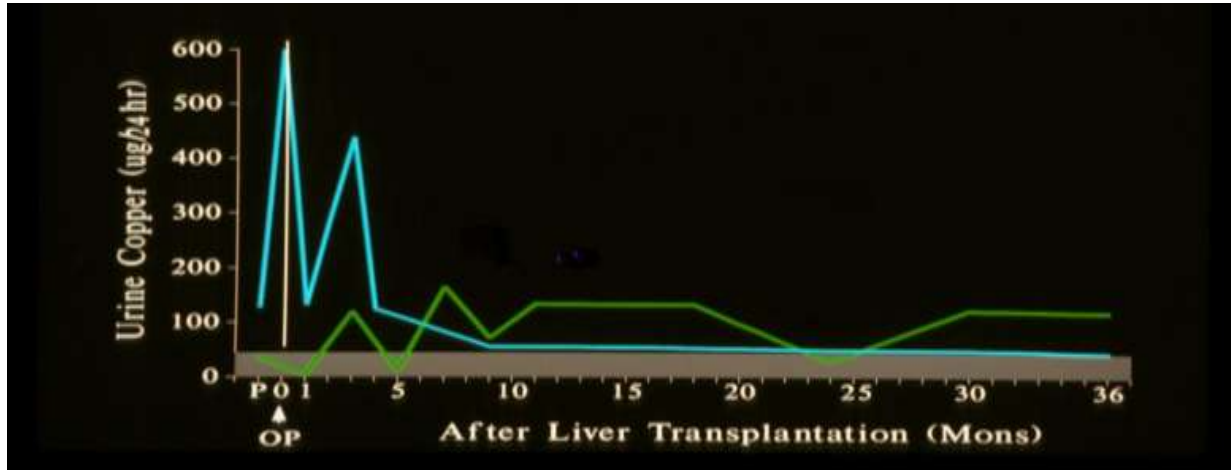
Liver Transplant for Wilson's Disease

- Life-saving procedure for end-stage Wilsonian cirrhosis
- Normalization of biochemical defects of copper metabolism
- Reversion of neurological impairments
- Disappearance of Kayser-Fleischer rings
- Abatement of secondary amenorrhea

Liver Transplant for Wilson's Disease



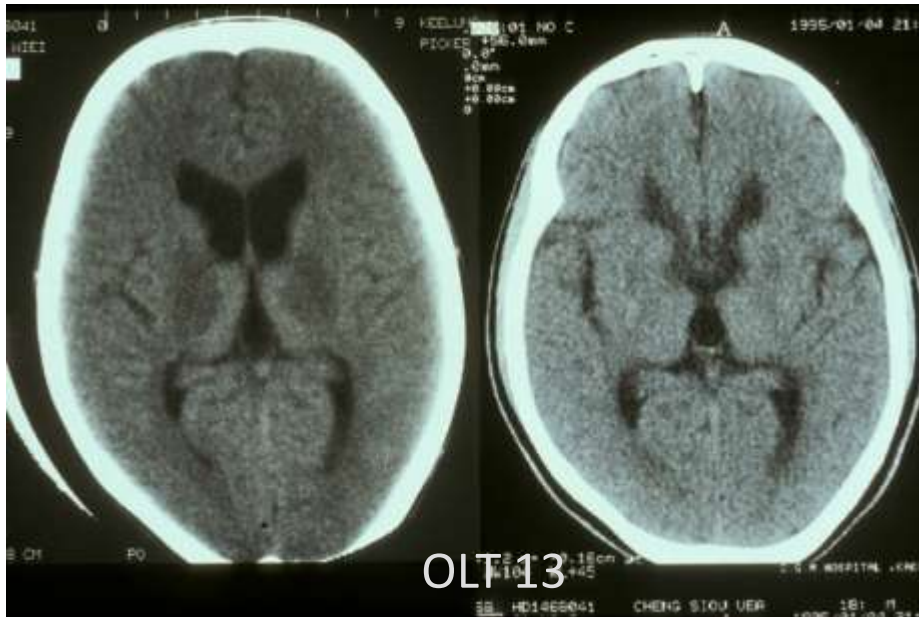
Liver Transplant for Wilson's Disease





Liver Transplant for Wilson's Disease

Neurological Improvement



23 MAR 肝 硬 化 症 併 腦 水 腫
 陳 孝 偉 啟
 1993年3月23日 正

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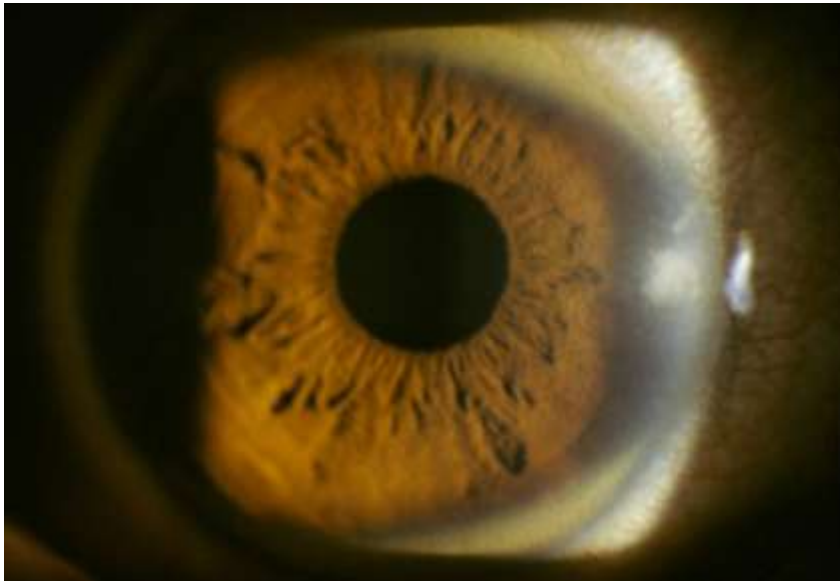
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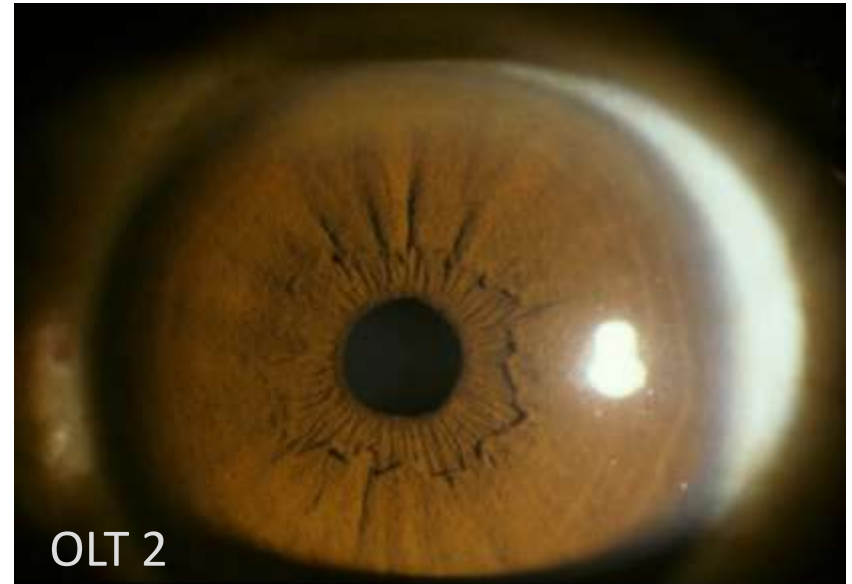
30 JUL 謝 謝 醫 生、言 護 士 小 姐 的 細 心 照 料 陳 孝 偉
 82.7.10.

09 AUG 肝 硬 化 症 (1.7X)

Kayser-Fleischer rings



Pre-transplant



Post-transplant



Liver Transplant for Wilson's Disease

- Mean follow-up : 114.1 months
range : 36-192
- 6 of 7 Wilson's disease adolescents are surviving after transplant to date
- The only mortality died of traffic accident 3 years post transplant



LDLT for Glycogen Storage Disorders

March 1984 – December 2006

- 13 GSD / 400 LTx = 3%
13 GSD / 174 Ped LTx = 7.5%
- GSD type I 10
GSD type II 3
- Mean age at presentation : 6.98 years
- All presented with metabolic abnormalities
- All unresponsive to medical treatment
- Mean post transplant follow-up : 47.40 months



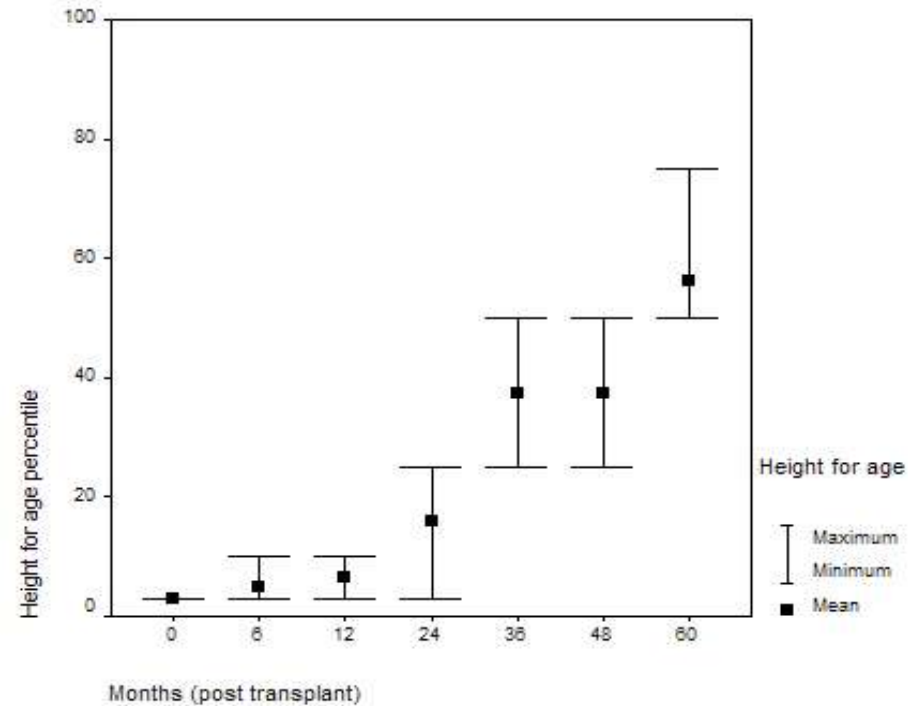
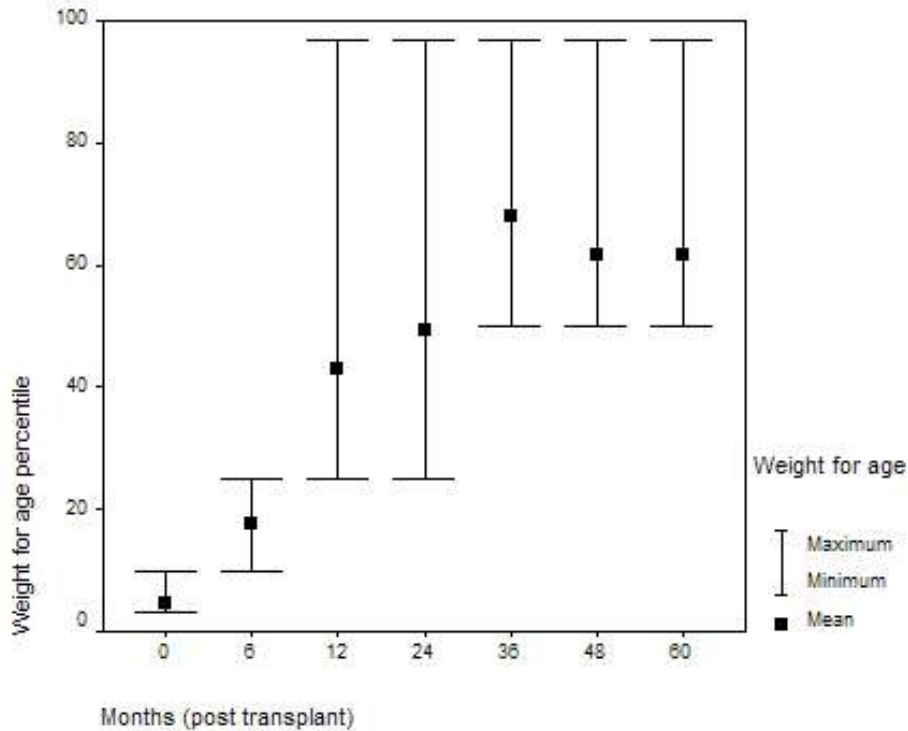
LDLT for Glycogen Storage Disorders

Biochemical Parameters Pre and Post Transplantation

Parameters	Pre-Tx	Post-Tx 3m	P value
Lactate	34.24	6.34	0.002
AST	272.73	34	0.036
ALT	209.18	25.09	0.014
Triglyceride	473.36	158.09	0.008
Cholesterol	258.62	143.5	0.004
Creatinine	0.463	0.609	0.001

Iyer S, Chen CL, et al. Liver Transplant 2007; 13 : 848

Catch-up **weight-for-age** and **height-for-age** in children with pre-transplant growth retardation after LDLT





Pediatric LDLT

Better long-term survival due to

- Careful preoperative planning
- Better anesthesia management
- Meticulous surgical techniques
- Prompt detection and treatment of complications
- Improved use of immunosuppression

A dramatic seascape at sunset or sunrise. The sky is filled with dark, heavy clouds, but a bright light source is breaking through, creating several distinct sunbeams (crepuscular rays) that illuminate the scene. The sea below is dark and choppy, with small waves visible. The overall mood is serene and powerful.

Thank You For Your Kind Attention

Liver Transplant for HCC

Authors	Year	Actuarial Survival		Journal
		1 year	5 year	
Mazzafero	1996	90%	75%	NEJM
Bechstein	1998	88%	71%	Transplant Int
Llovet	1999	84%	74%	Hepatology
Iwatsuki	2000	73%	49%	J Am Coll Surg
Yao	2001	91%	72%	Hepatology
Margarit	2002	81%	58%	World J Surg
Perez- Saborido	2003	79.3%	50.3%	Transplant proc
Leung	2004	80.3%	46.7%	Liver transplantation
Zavaglia	2005	84%	72%	Am J Gastroenterol
Grasso	2006	79%	53%	Transplantation
Sugawara	2007	91%	75%	Dig Dis
Chen CL	2008	98%	90%	Transplantation

HBcAb(+) Donor

- Before Dec. 31, 1997
No Prophylaxis
- After Jan. 1, 1998
Pre Tx vaccination
Post Tx lamivudine, if anti-HBs < 1000

	HBcAb(+) donor	de novo HBV
No Prophylaxis	8	3 (37.5%)
PreTx vaccination ± Post Tx 3TC	94	1 (1.1%)

HBcAb(+) Donor

HBs Ab	de novo hepatitis B	
	Yes	No
> 1000 IU/L	0	47
< 1000 IU/L	2 (15.4%)	11

Fisher's exact test < 0.05

Lin CC, Chen CL, et al. Am J Transplant 2007; 7:195-200



Strategies on Patient Follow-up

- Low immunosuppression as long as the liver functions are within acceptable limits
- Avoid intravenous bolus steroids, OKT3, whenever possible, in rejection cases

Concejero A, Chen CL et al. Transplantation 2007 (in press)



Liver Transplantation for HCC

Future Directions

- Better understanding of tumor biology
- Specific molecular targets
- Control / cure Hepatitis C

Asian Experience

Queen Mary Hospital, University of Hong Kong

TABLE 6. Comparison of Era II Right Liver Living Donor Liver Transplantation and Deceased Donor Liver Transplantation Recipient Survivals

	1 Yr	3 Yr	5 Yr
All			
RLDLT (n = 184)	97.3%	88.7%	85.1%
DDLT (n = 91)	93.4%	91.1%	88.1%
			<i>P</i> = 0.784
All except HCC			
RLDLT (n = 128)	96.1%	93.4%	93.4%
DDLT (n = 76)	93.4%	91.9%	88.2%
			<i>P</i> = 0.493
HCC patients			
RLDLT (n = 56)	100%	77.5%	65.5%
DDLT (n = 15)	93.3%	86.7%	86.7%
			<i>P</i> = 0.507
HCC within Milan criteria			
RLDLT (n = 34)	100%	84.1%	72.0%
DDLT (n = 10)	100%	100%	100%
			<i>P</i> = 0.091

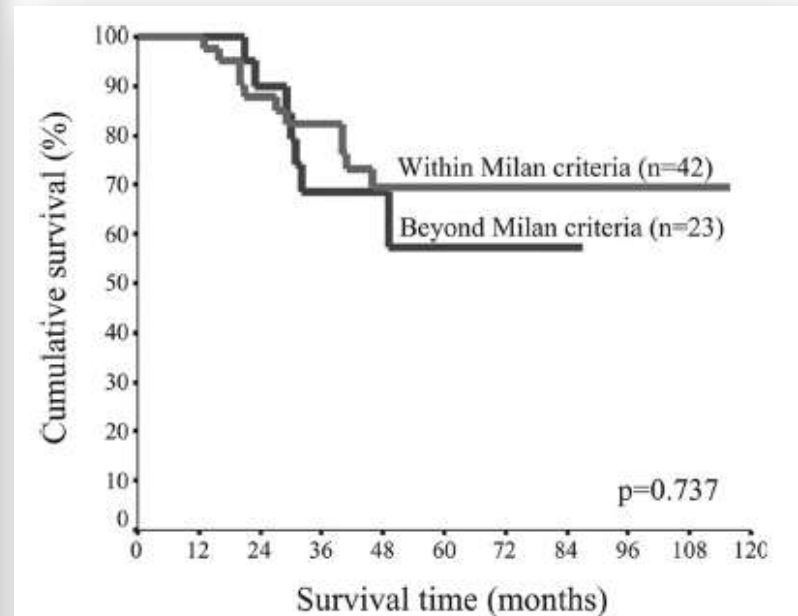
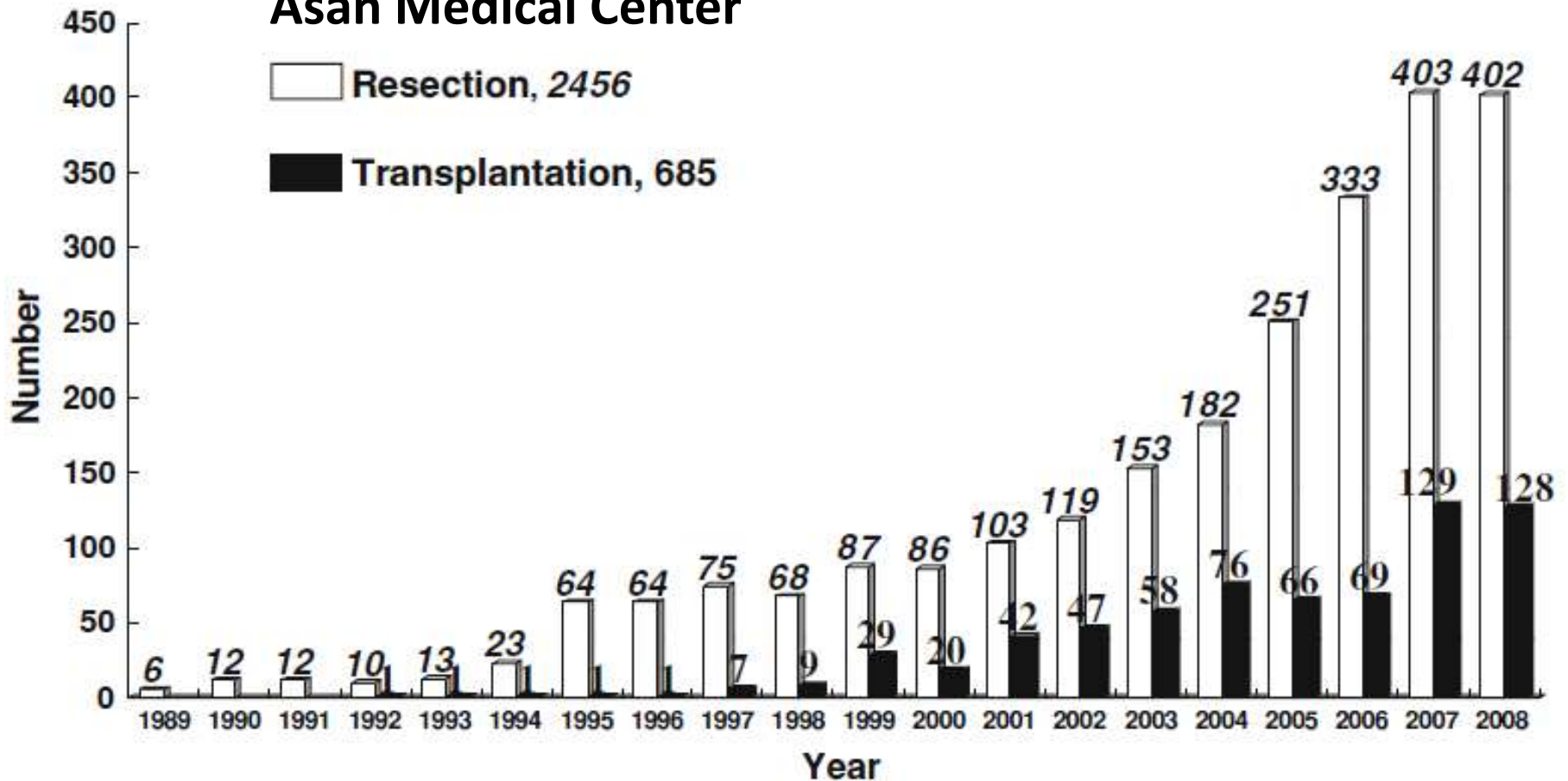


FIGURE 3. Hepatocellular carcinoma right liver living donor liver transplantation recipient survivals: within versus beyond the Milan criteria.

Asian Experience

Korean Experience

Asan Medical Center



Asian Experience

Asan Medical Center Criteria (Korea)

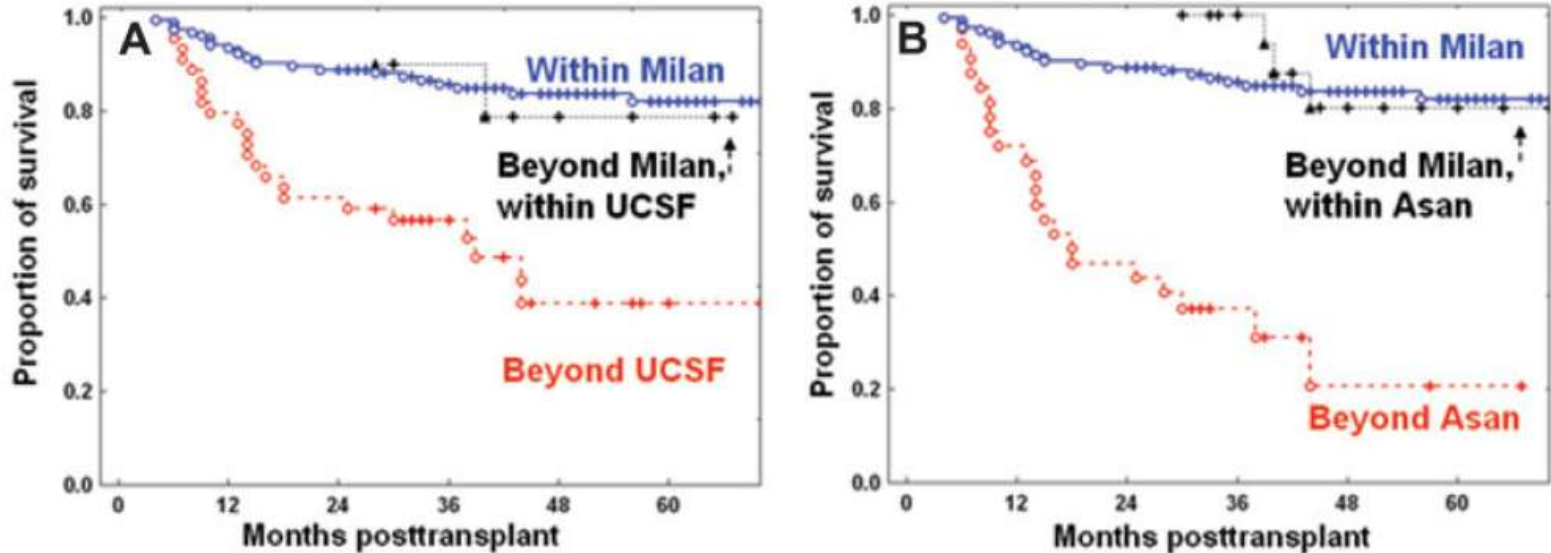


TABLE 3. Multivariate Analysis of Significant Risk Factors for Hepatocellular Carcinoma Recurrence and Patient Survival in 206 Surviving Patients

Risk Factor	Hepatocellular Carcinoma Recurrence			Patient Survival		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Largest tumor diameter > 5 cm	6.08	2.72-13.59	<0.001	4.63	2.11-10.19	<0.001
Tumor number > 6	6.65	3.02-14.63	<0.001	6.22	2.96-13.08	<0.001
Gross vascular invasion present	2.53	1.39-6.28	0.042	2.63	1.07-6.48	0.035

Asian Experience

Tokyo University Criteria

Table 1. Recurrence-free rates (%) according to the classifications

Criteria	1 year	3 years
The Milan criteria		
Within (n = 68)	97	94
Exceeding (n = 10)	70	70
Tokyo 5-5 rule		
Within (n = 72)	97	94
Exceeding (n = 6)	50	50

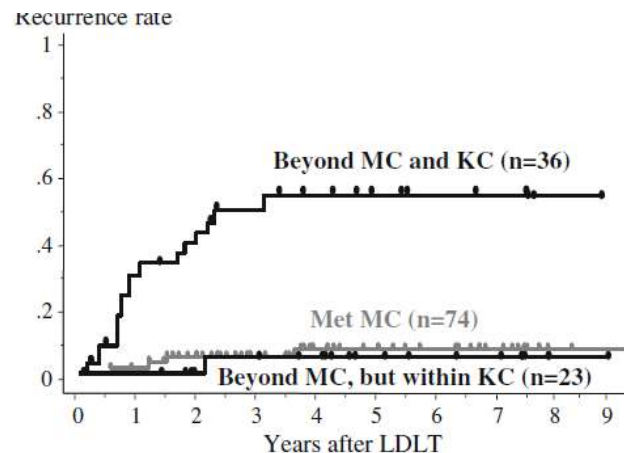
Asian Experience

Kyoto University Criteria

Table 2 Multivariate analysis of preoperative tumor factors and recurrence

Variables	Risk ratio	95% Confidence interval	<i>P</i>
Tumor number ≥ 11 nodules	3.048	1.129–8.196	0.0277
Tumor diameter >5 cm	8.333	2.109–32.258	0.0024
Beyond MC	1.423	0.183–2.695	0.6073
AFP >400 ng/ml	1.429	0.192–2.545	0.5880
PIVKA-II >400 mAU/ml	5.618	2.123–14.925	0.0005

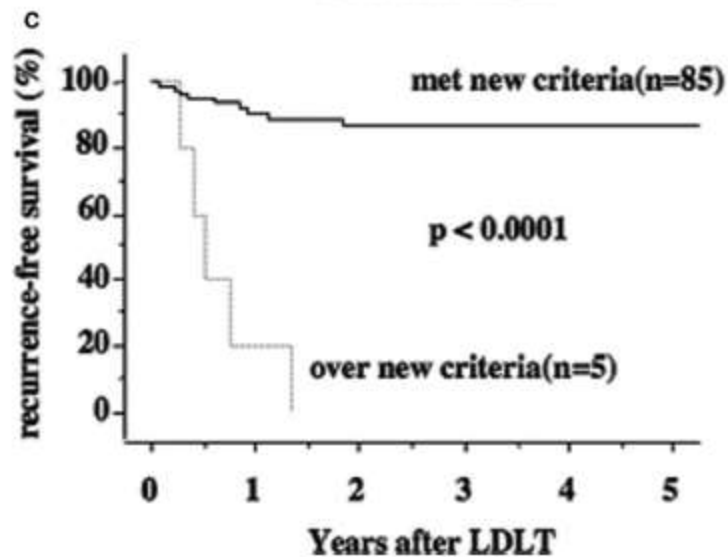
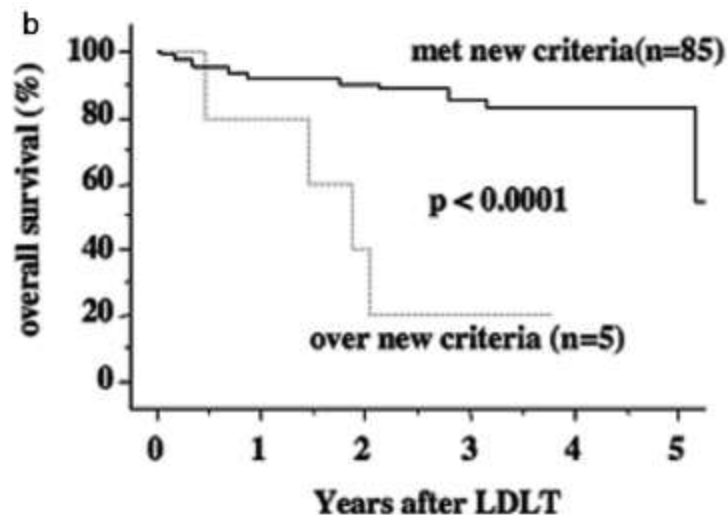
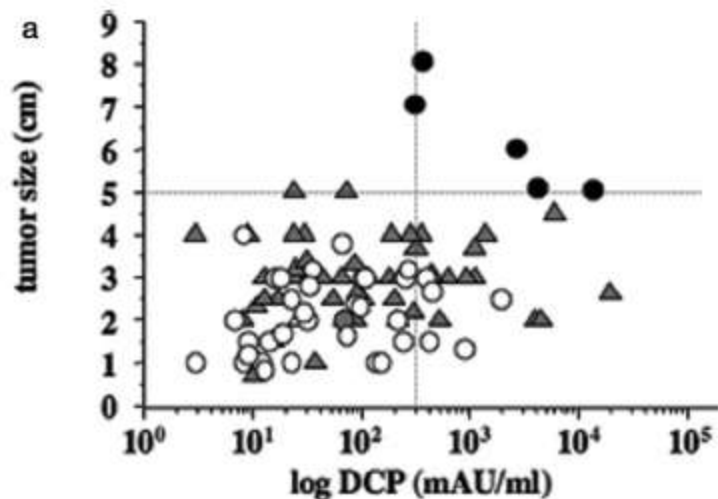
Multivariate analysis was performed using Cox's proportional hazard model



Asian Experience

Kyushu Criteria

- Size: 5 cm
- No.: Any
- PIVKA II: <300 mAU/ml



Asian Experience

Hangzhou Criteria

- Total tumor diameter
 - Less than or equal to 8 cm
 - No macrovascular invasion

OR

- Total tumor diameter
 - More than 8 cm
 - Histopathology grade I or II
 - AFP less than or equal 400 ng/ml
 - No macrovascular invasion

5-year Survival Rate

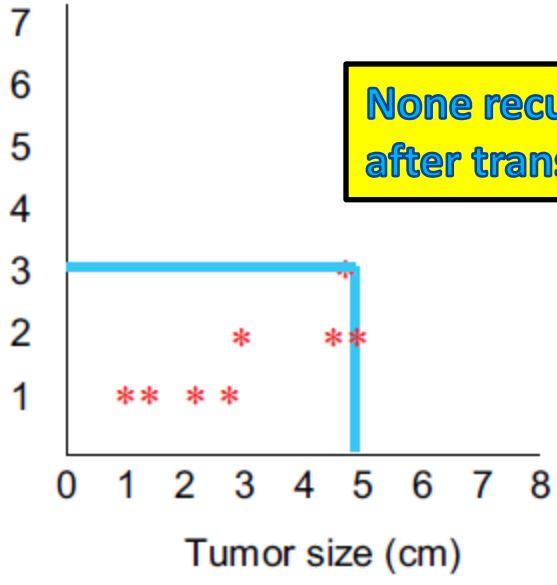
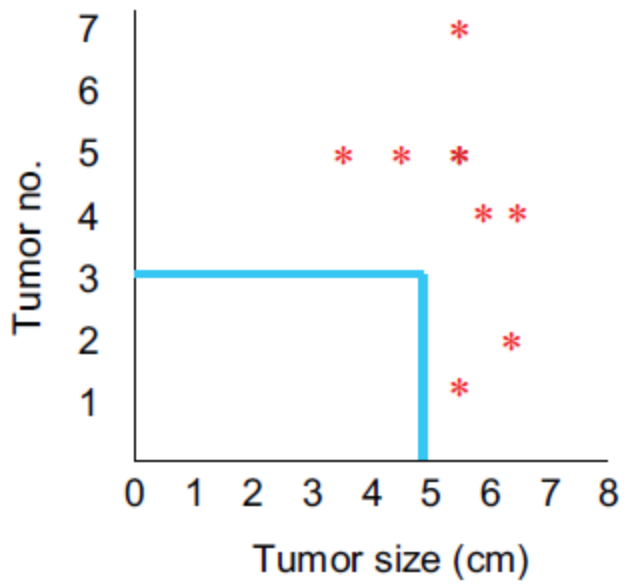
Milan criteria 78.3%

Hangzhou criteria 72.3%

Living Donor Liver Transplantation for Hepatocellular Carcinoma: A Single-Center Experience in Taiwan

Allan Concejero,^{1,2} Chao-Long Chen,^{1,2,6} Chih-Chi Wang,^{1,2} Shih-Ho Wang,^{1,2} Chih-Che Lin,^{1,2} Yueh-Wei Liu,^{1,2} Chin-Hsiang Yang,^{1,2} Chee-Chien Yong,^{1,2} Tsan-Shiun Lin,^{1,2} Bruno Jawan,^{1,3} Tung-Liang Huang,^{1,4} Yu-Fan Cheng,^{1,4} and Hock-Liew Eng^{1,5}

1, 3, & 5-year survivals of 98%, 96%, & 90%, respectively



None recurred after transplantation

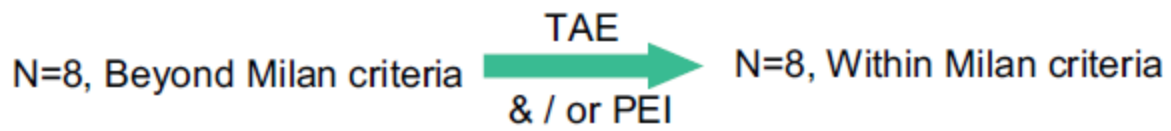


TABLE 4. Histopathologic profile of patients with microvascular tumor invasion, patient management, and outcome (n=9)

LDLT no.	Satellite nodule	Degree of necrosis	Presence of capsule	No. of tumors	Tumor size	Histologic grade	Doxorubicin	Recurrence	Alive	Hepatitis
77	—	>60%	+	2	<3 cm	Mod Diff	+	—	+	B
81	+	>60%	—	1	>3 cm	Mod Diff	+	—	+	B
92	—	>60%	+	1	<3 cm	Mod Diff	—	+	—	B
119	—	10–60%	—	2	>3 cm	Mod Diff	+	—	+	C
172	+	10–60%	+	1	<3 cm	Mod Diff	+	—	+	C
180 ^a	—	<10%	+	2	<3 cm	Mod Diff	—	—	—	C
188	—	>60%	+	2	<3 cm	Mod Diff	—	—	+	B
191	—	<10%	+	2	<3 cm	Mod Diff	+	—	+	B
193	+	<10%	+	>5	>3 cm	Mod Diff	+	—	+	B+C

Mean follow-up was 32.5 months (range, 13–52 months), excluding LDLT 180.

^a Early death (2 months).

TABLE 5. Interval to recurrence, interval to transplantation, and histopathologic profile of patients who underwent liver resection prior to transplantation (N=7)

LDLT no.	Interval to recurrence (months)	Interval to transplantation (months)	Months post-LT	Recurrence	No. of tumors	Tumor Size	Histologic grade	Microvascular invasion	Hepatitis
74	—	7	53	—	2	>3 cm	Well-Diff	—	B
84	3	3	50	—	1	<3 cm	Well-Diff	—	B
85	—	10	50	—	3	<3 cm	Well-Diff	—	B
88	18	24	48	—	1	<3 cm	Mod-Diff	—	B
93	12	14	47	—	1	<3 cm	Mod-Diff	—	B
139	7	12	29	—	2	<3 cm	Poor-Diff	—	B
184	79	84	16	—	1	<3 cm	Well-Diff	—	C









LDLT nos. 74 and 85 showed no radiological evidence of recurrence prior to transplant. LDLT no. 84 showed microvascular invasion in tumor specimen at initial resection.

Degree of Liver Damage by LCSGJ

Clinical and laboratory findings	Grade ¹		
	A	B	C
Ascites	none	controllable	uncontrollable
Serum bilirubin, mg/dl	<2.0	2.0–3.0	>3.0
Serum albumin, g/dl	>3.5	3.0–3.5	<3.5
ICGR ₁₅ , %	<15	15–40	>40
Prothrombin activity, %	>80	50–80	<50

¹ Degree of liver damage is designated as class A, B, or C, based on the highest grade containing at least two findings.

TNM Based on LCSGJ

Criteria	T1	T2	T3	T4
(1) Number of tumors: solitary	(2) All three criteria are fulfilled	(3) Two of the three criteria are fulfilled	(4) One of the three criteria is fulfilled	(5) None of the three criteria are fulfilled
(2) Tumor diameter: no more than 2 cm				
(3) No vascular or bile duct invasion: Vp0, Vv0, B0				
				

Portal micro-invasion and intra-hepatic metastasis occurs in 27% and 10% of tumors with a tumor size of ≥ 2 cm, respectively, a TNM staging classification setting the cut-off size to 2 cm is necessary

CTP and LCSGJ-JIS

Definition of the TNM stages by the LCSGJ

T ₁	fulfilling 3 factors
T ₂	fulfilling 2 factors
T ₃	fulfilling 1 factor
T ₄	fulfilling 0 factors
Stage I	T ₁ N ₀ M ₀
Stage II	T ₂ N ₀ M ₀
Stage III	T ₃ N ₀ M ₀
Stage IV-A	T ₄ N ₀ M ₀ or any TN ₁ M ₀
Stage IV-B	any TN ₀₋₁ M ₁

T factor: I = Single; II = <2 cm; III = no vascular involvement.

Definition of the JIS score

Variable	Score			
	0	1	2	3
Child-Pugh stage	A	B	C	
TNM stage by LCSGJ	I	II	III	IV

Cancer of the Liver Italian Program

Component	CLIP score ^t		
	0	1	2
Child-Pugh classification	A	B	C
Tumor morphology	Uninodular and extension \leq 50%	Multinodular and extension \leq 50%	Massive or extension $>$ 50%
AFP (ng/mL)	$<$ 400	\geq 400	
Tumor thrombus in the portal vein	No	Yes	