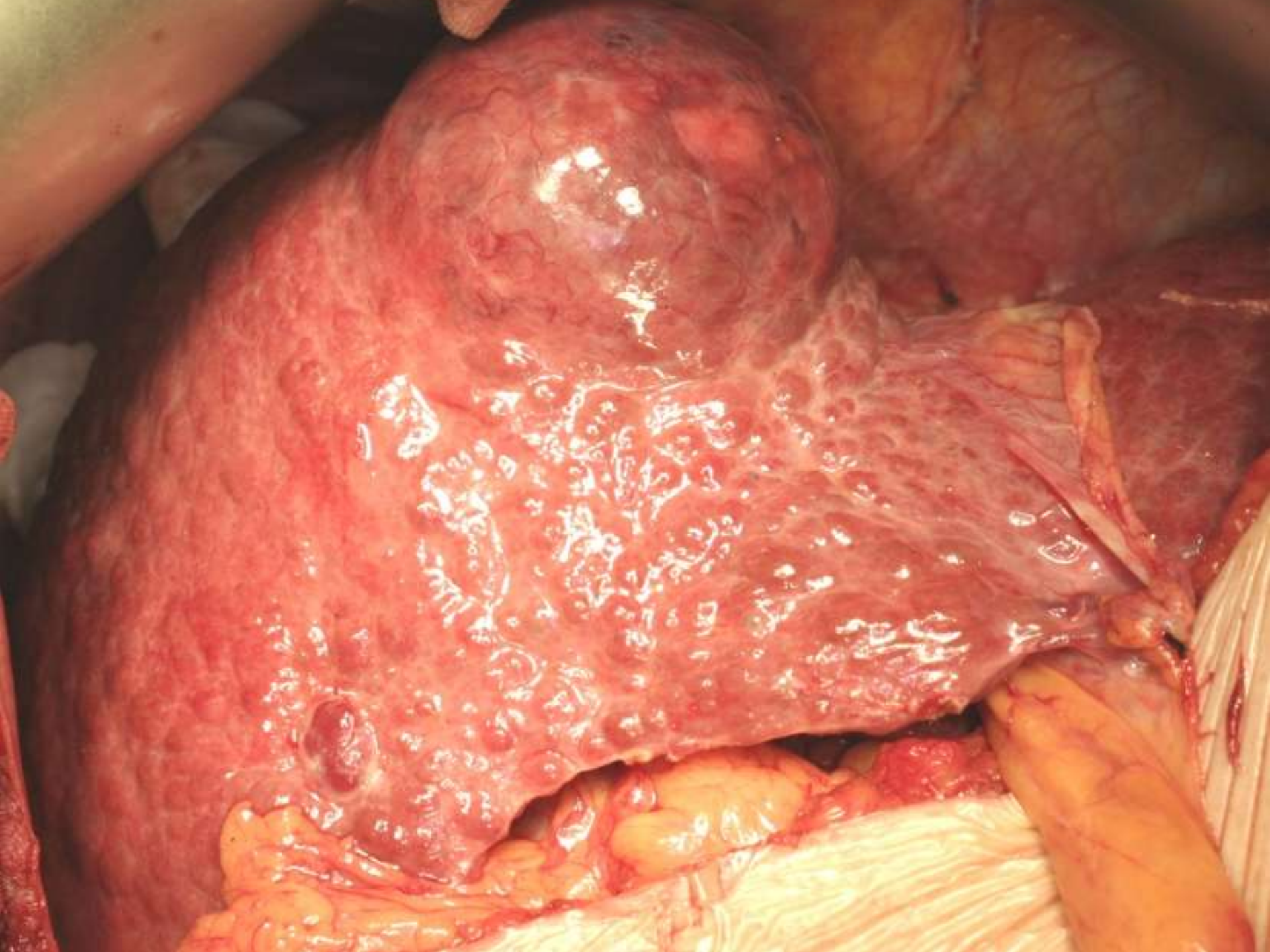
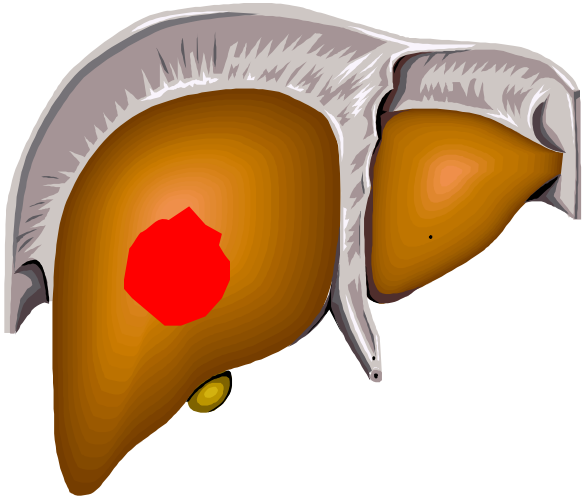
Evolving Concepts and Strategies in Liver Transplantation for Hepatocellular Carcinoma

Chung Mau Lo
Chin Lan-Hong Professor and Head
Department of Surgery
The University of Hong Kong
Queen Mary Hospital
Hong Kong, China

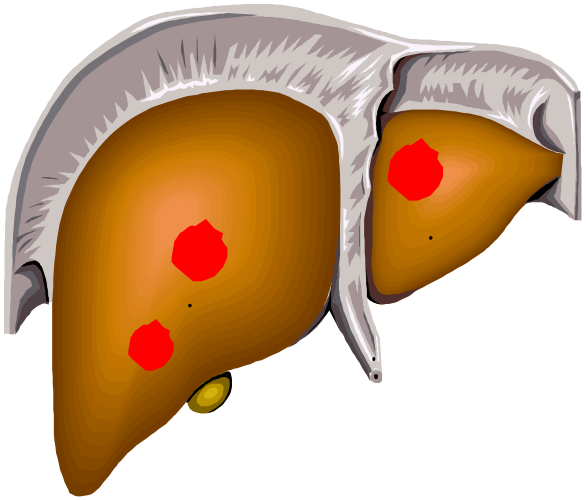


HEPATOCELLULAR CARCINOMA

Liver Transplantation: Milan Criteria



Solitary tumor 5 cm or less



2 to 3 tumors each of 3 cm or less

Tumor number/size as sorrogate marker of biology

Recurrence rate ~ 10%
5-year survival > 70%

Outcome comparable to non-HCC patients

Mazzaferro et al, NEJM 1996

LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Expanded criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

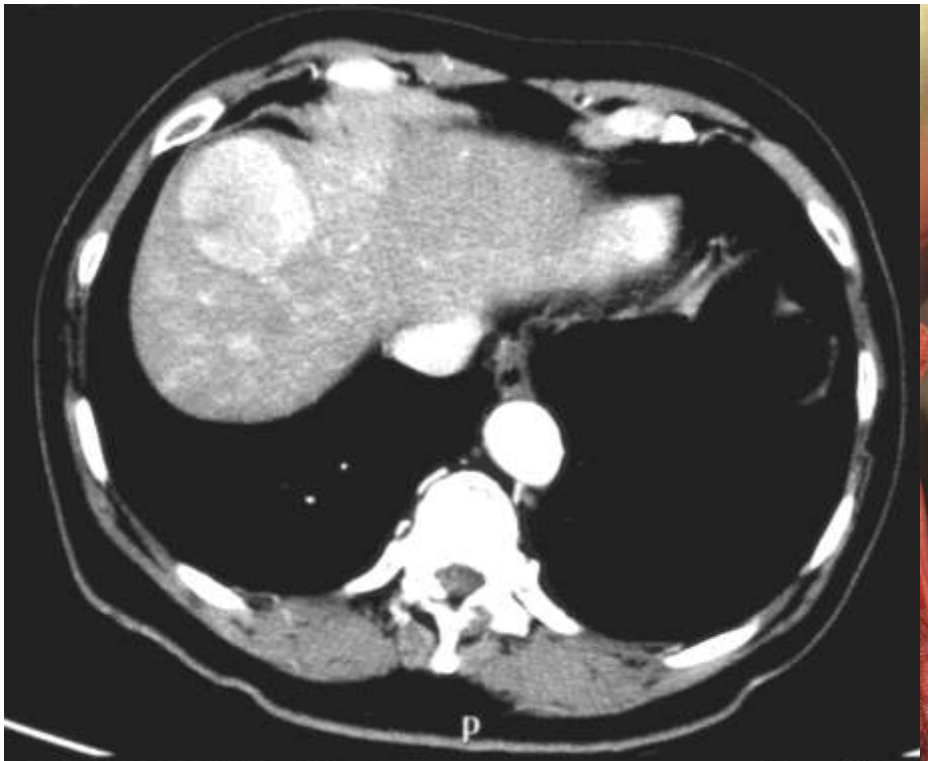
HEPATOCELLULAR CARCINOMA

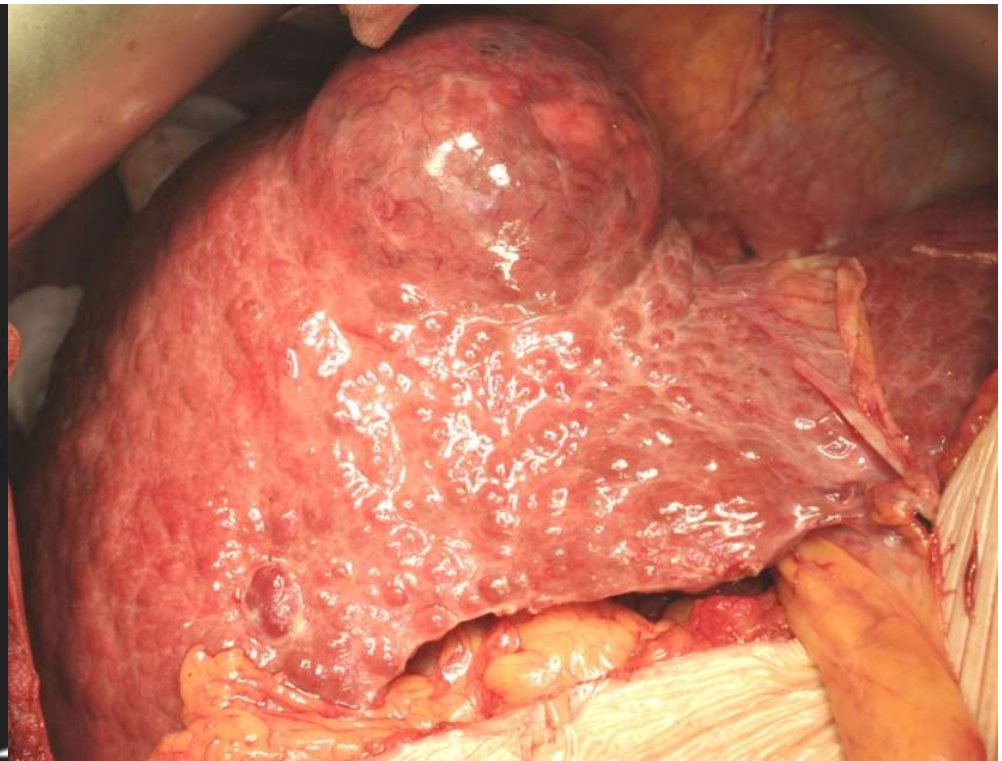
Resection or Transplantation?

compensated cirrhosis with preserved liver function

tumor within Milan criteria

no contraindication for liver transplant





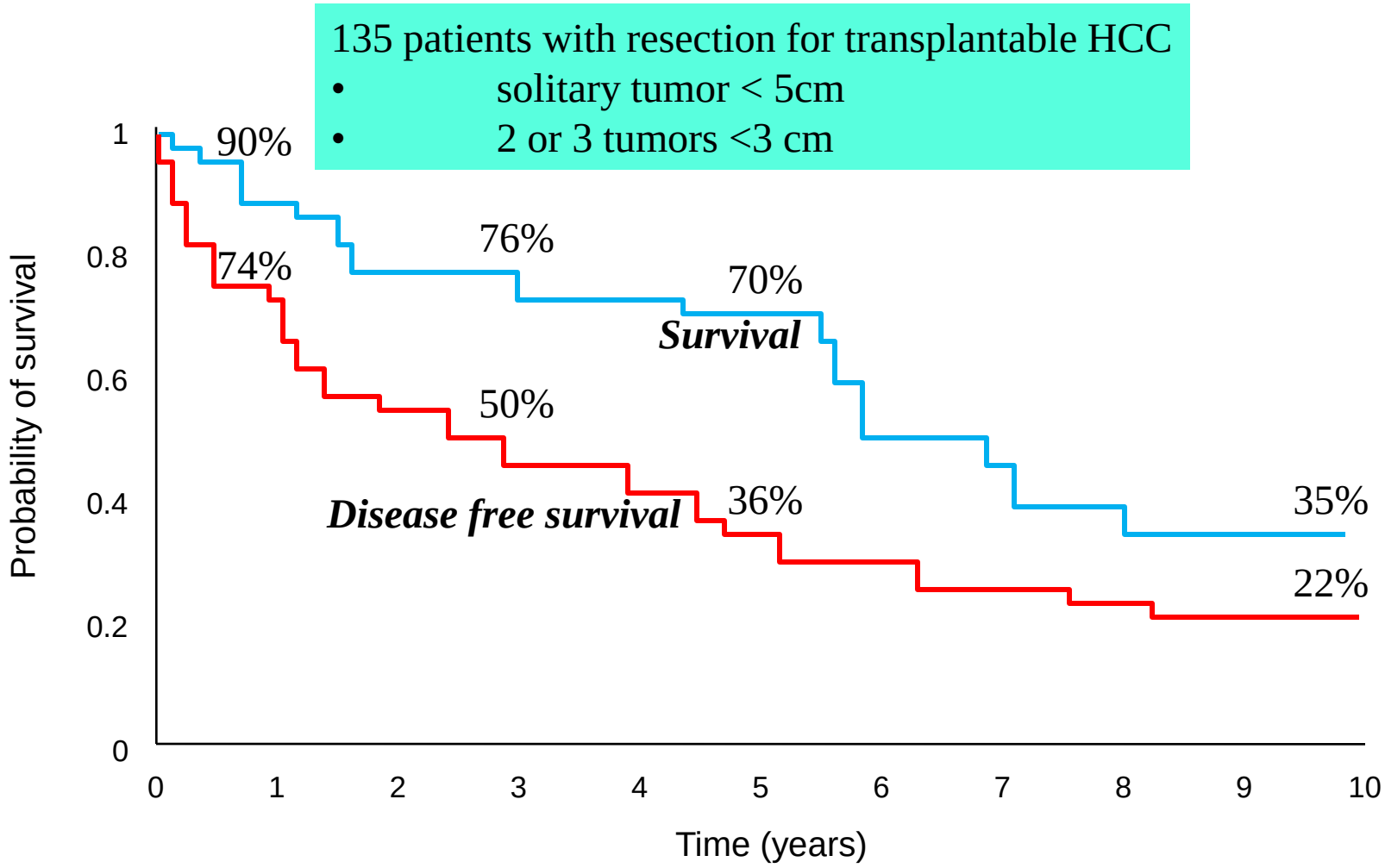
LIVER TRANSPLANTATION FOR HCC

Patient Survival using Milan Criteria

Author	Year	n	1-yr SV %	5-yr SV %
Mazzaferro	1996	48	84	75
Llovet	1998	58	84	74
Bismuth	1999	45	82	74
Jonas	2001	120	90	71
Yao	2001	64	87	75

HEPATOCELLULAR CARCINOMA

Hepatic Resection for Transplantable Tumor



Poon et al, Ann Surg 2002

SALVAGE TRANSPLANTATION

Are recurrences transplantable?

135 patients with resection for transplantable HCC
- solitary tumor < 5cm
- 2 or 3 tumors <3 cm

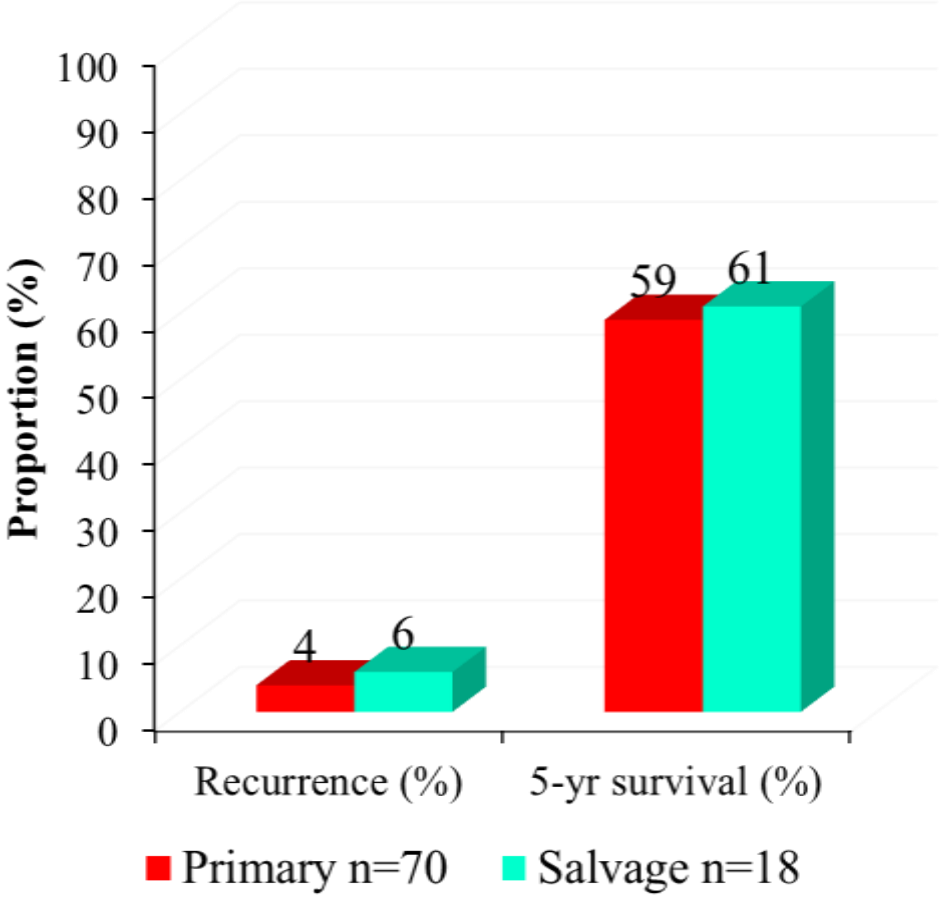
Median time to recurrence 16 months (1 to 84 months)

	no. of patients	
Intrahepatic recurrence alone		
solitary < 5 cm	39	79% transplantable
2-3 nodules < 3 cm	14	
> 4 nodules	6	
extrahepatic recurrence alone	5	
both	3	

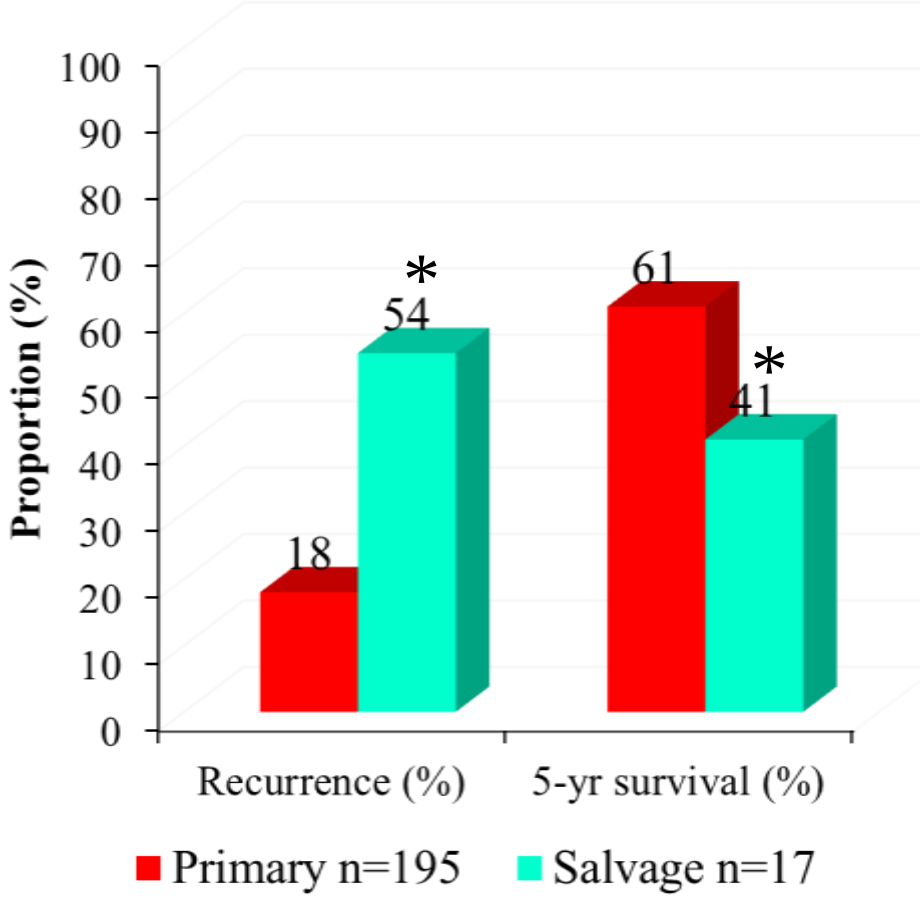
Poon et al, Ann Surg 2002

SALVAGE TRANSPLANTATION

long term outcome



Belghiti et al



Adam et al

* *p<0.05*

Ann Surgery 2003

SALVAGE TRANSPLANTATION

long term outcome

	Proportion with recurrence	Survival rate (%)			*P**	Recurrence rate (%)			*P**
		1 year	3 years	5 years		1 year	3 years	5 years	
Incidental tumour in explant					0·102				0·160
Yes	0 of 8	100	100	100		0	0	0	
No	10 of 52	96	82	64		6	23	23	
Salvage transplantation					0·053				0·002
Yes	5 of 11	100	63	n.a.		18	45	n.a.	
No	5 of 49	96	90	81		2	14	14	
Transarterial chemoembolization while on list					0·301				0·614
Yes	1 of 5	100	100	100		20	20	20	
No	9 of 55	96	84	67		4	20	20	
Graft type					0·187				0·029
Living donor	10 of 43	97	80	58		7	29	29	
Deceased donor	0 of 17	94	94	94		0	0	0	
Graft weight : standard liver weight ratio					0·078				0·009
≤ 0·6	10 of 37	97	78	53		8	32	32	
> 0·6	0 of 23	96	96	96		0	0	0	
Size of largest tumour nodule (cm)					0·642				0·594
≤ 5	9 of 56	96	87	72		6	19	19	
> 5	1 of 4	100	50	n.a.		0	63	n.a.	
No. of tumour nodules					0·152				0·032
≤ 3	7 of 52	98	88	72		2	16	16	
> 3	3 of 8	88	67	67		29	52	52	
Vascular invasion					0·206				0·034
Yes	5 of 18	94	69	69		17	29	29	
No	5 of 42	98	91	74		0	16	16	
Beyond Milan criteria					0·412				0·028
Yes	5 of 16	94	71	71		13	38	38	
No	5 of 44	98	89	71		2	14	14	
Beyond UCSF criteria					0·180				0·047
Yes	3 of 9	89	67	67		25	50	50	
No	7 of 51	98	88	72		2	16	16	

Lo et al, BJS 2007

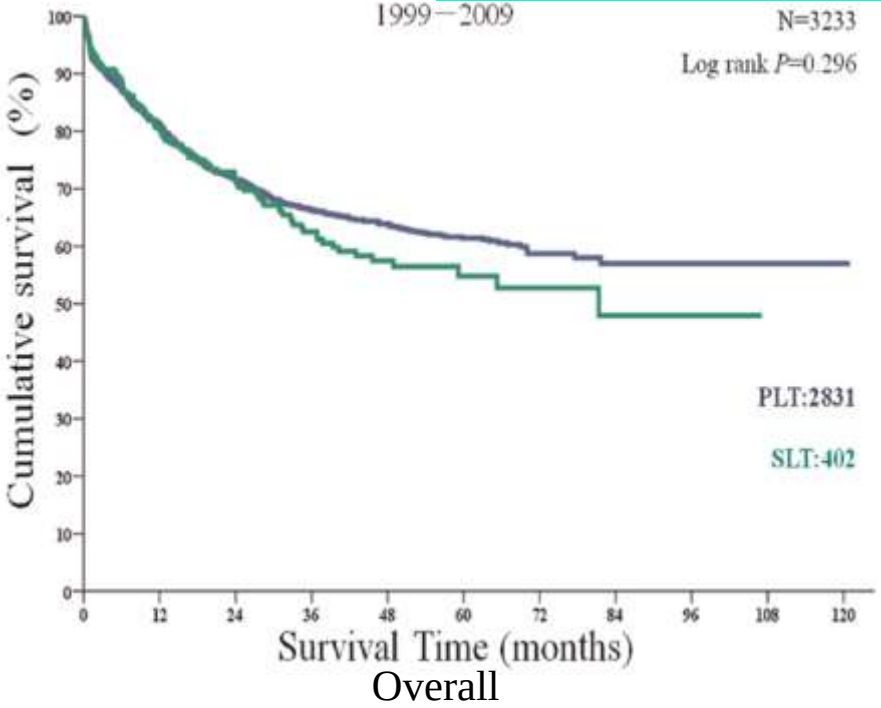
SALVAGE TRANSPLANTATION

long term outcome

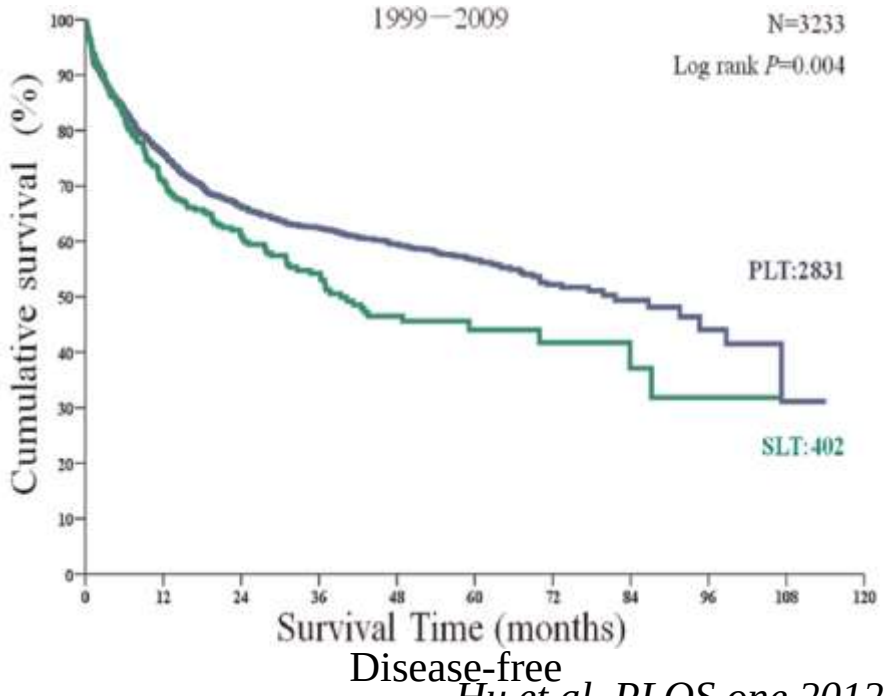
Salvage Liver Transplantation Is a Reasonable Option for Selected Patients Who Have Recurrent Hepatocellular Carcinoma after Liver Resection

Zhenhua Hu[1,2,3], Jie Zhou[1,2,3], Xiaofeng Xu[1,2,3], Zhiwei Li[1,2,3], Lin Zhou[1,2,3], Jian Wu[1,2,3], Min Zhang[1,2,3], Shusen Zheng[1,2,3]*

China Liver Transplant Registry



Overall



Disease-free

Hu et al, PLOS one 2012

HEPATOCELLULAR CARCINOMA

Resection vs Transplantation: Intention-to-treat

Benefit of Initial Resection of Hepatocellular Carcinoma Followed by Transplantation in Case of Recurrence: An Intention-to-Treat Analysis

David Fuks,[1] Safi Dokmak,[1] Valérie Paradis,[3] Momar Diouf,[1] François Durand,[2] and Jacques Belghiti[1]

(HEPATOLOGY 2012;55:132-140)

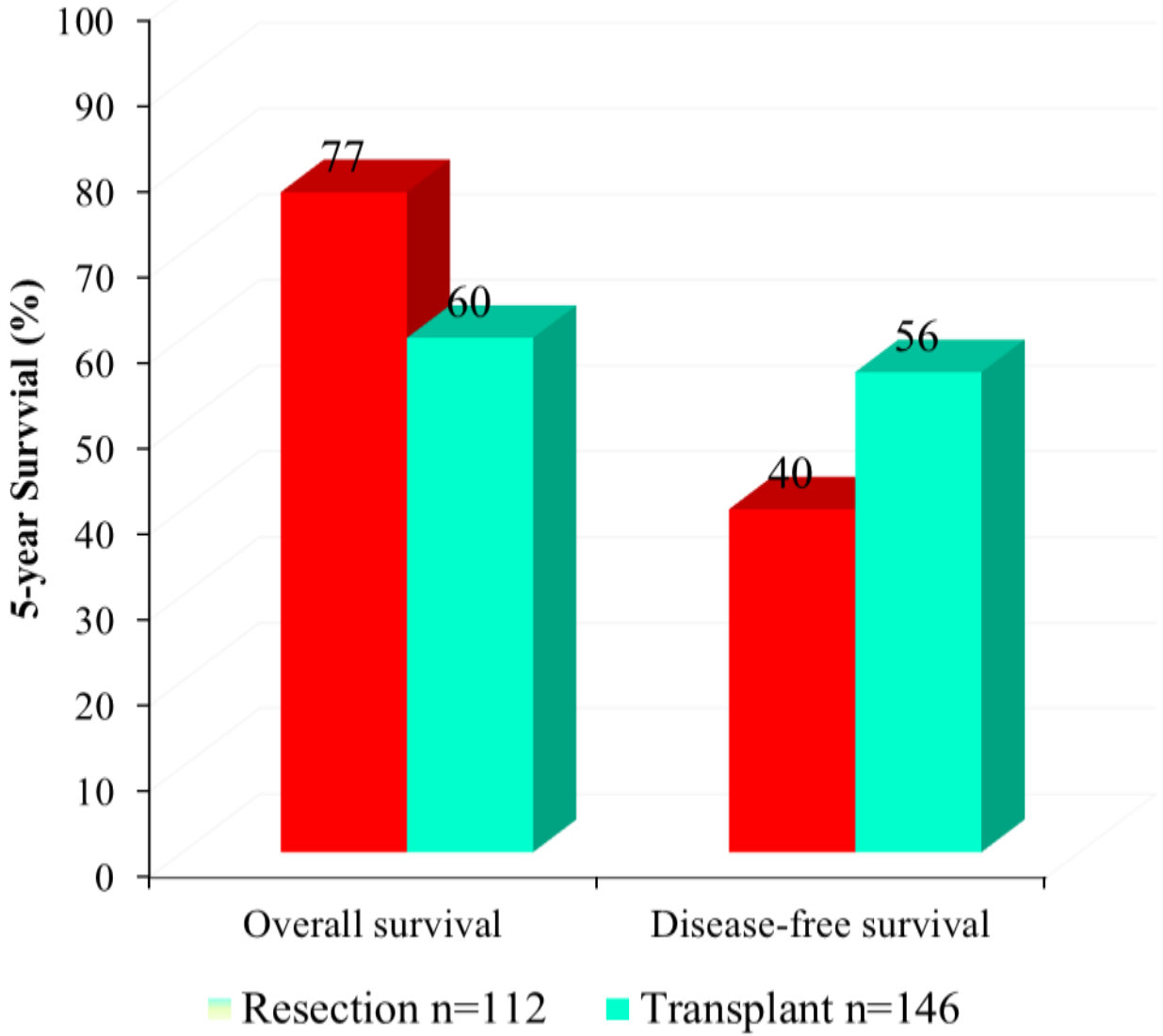
Number of Pejorative Histological Factors*	Number of Patients	No Recurrence (n = 22) n (%)	Recurrence Within MC (n = 60) n (%)	Recurrence Beyond MC (n = 30) n (%)
0	41	10 (24)	31 (76)	0 (0)
1	43	10 (23)	24 (56)	9 (21)
2	14	2 (14)	5 (36)	7 (50)
3	8	0 (0)	0 (0)	8 (100)
4-5	6	0 (0)	0 (0)	6 (100)

Abbreviations: LT, liver transplantation; MC, Milan criteria.

*Factors included: microscopic vascular invasion; presence of satellite nodules; tumor size > 3 cm; poorly differentiated tumor; and cirrhosis.

HEPATOCELLULAR CARCINOMA

Resection vs Transplantation: Intention-to-treat

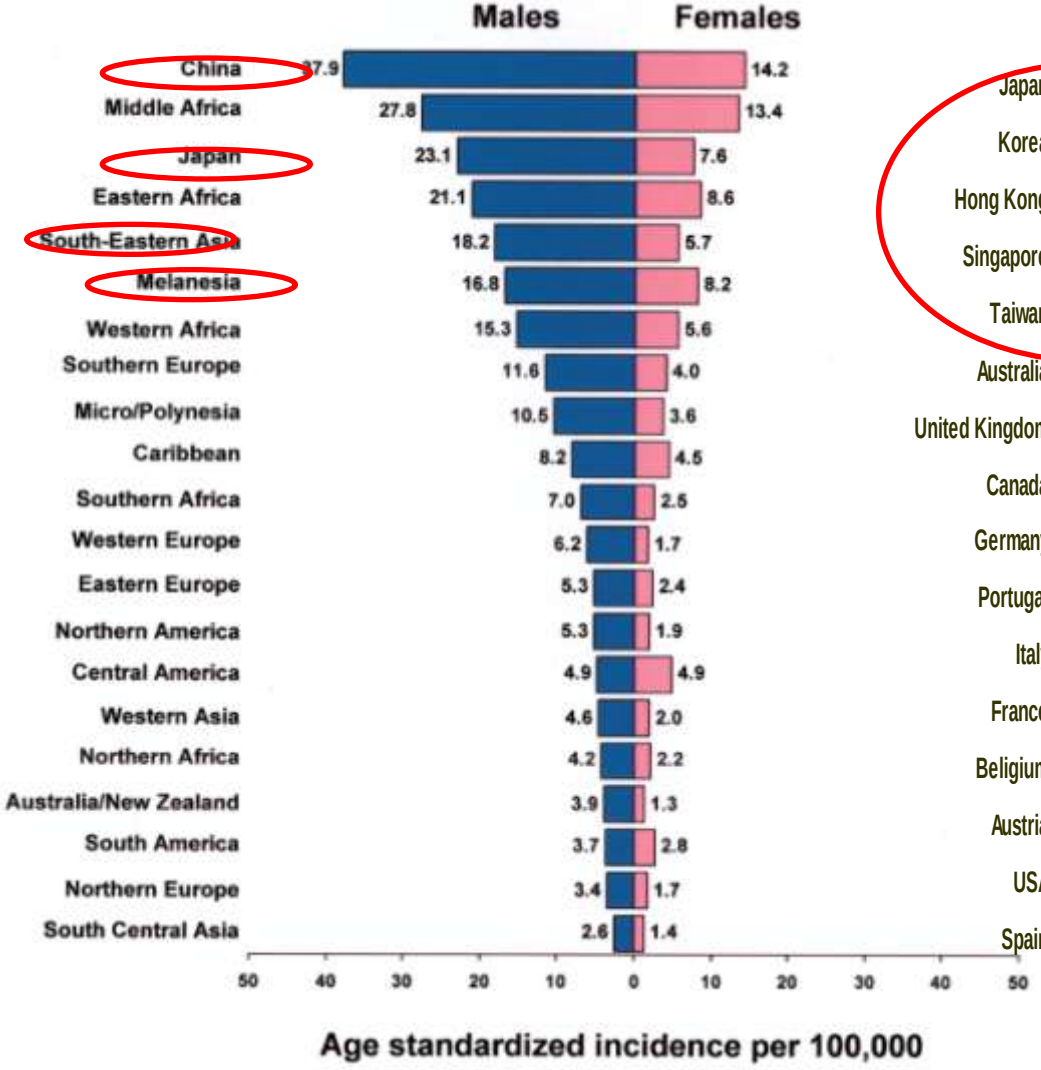


Fuks et al, Hepatology 2012

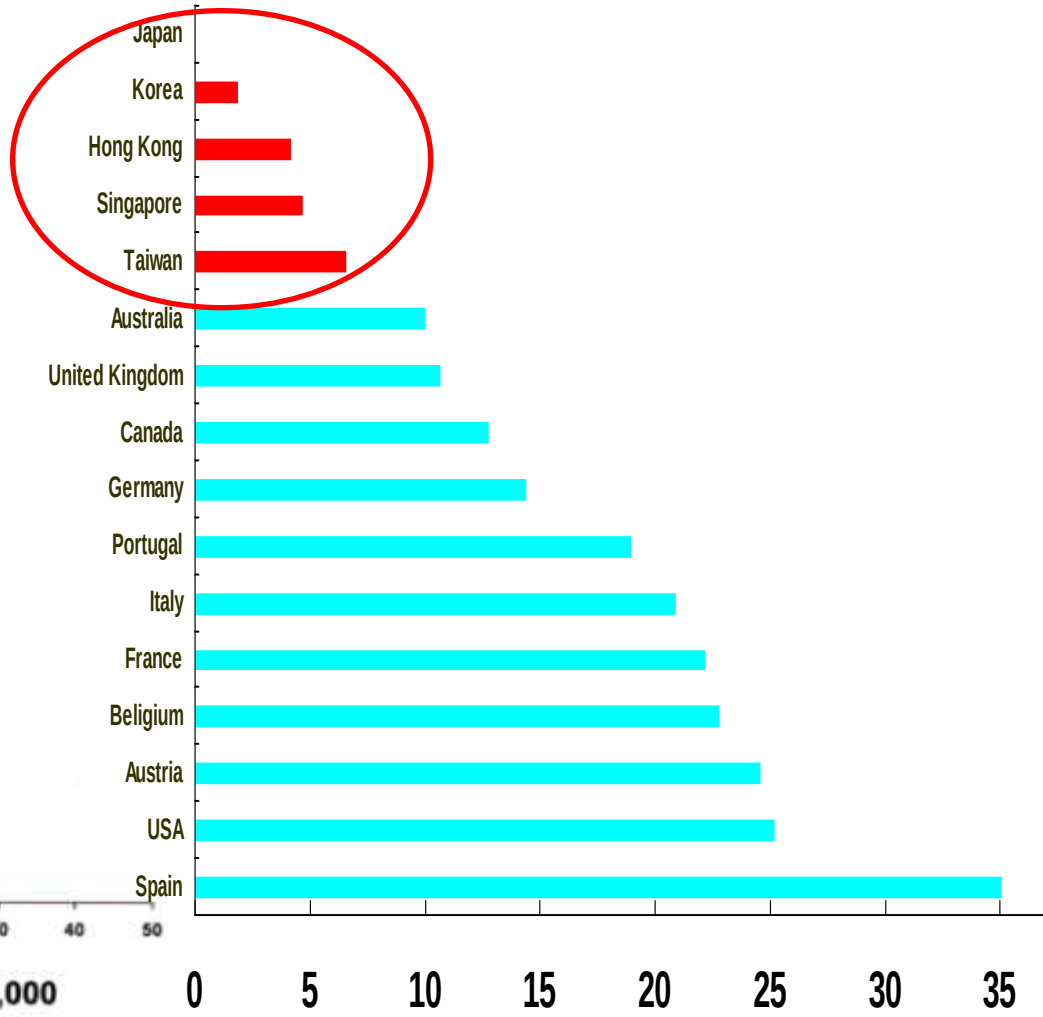
HEPATOCELLULAR CARCINOMA

Incidence of HCC and Organ donation rate

Incidence of HCC



Organ donation rate



Parkin et al, CA Cancer J Clin 2005

HEPATOCELLULAR CARCINOMA

Primary Transplant for Resectable Tumor: Con

- Deceased donor graft:
  - waiting time and drop outs
  - burden on the waiting list
- Living donor graft: risks of donor
- Need for immunosuppressant with adverse effects
- Higher costs
- Possibility of salvage transplant for recurrence after liver resection

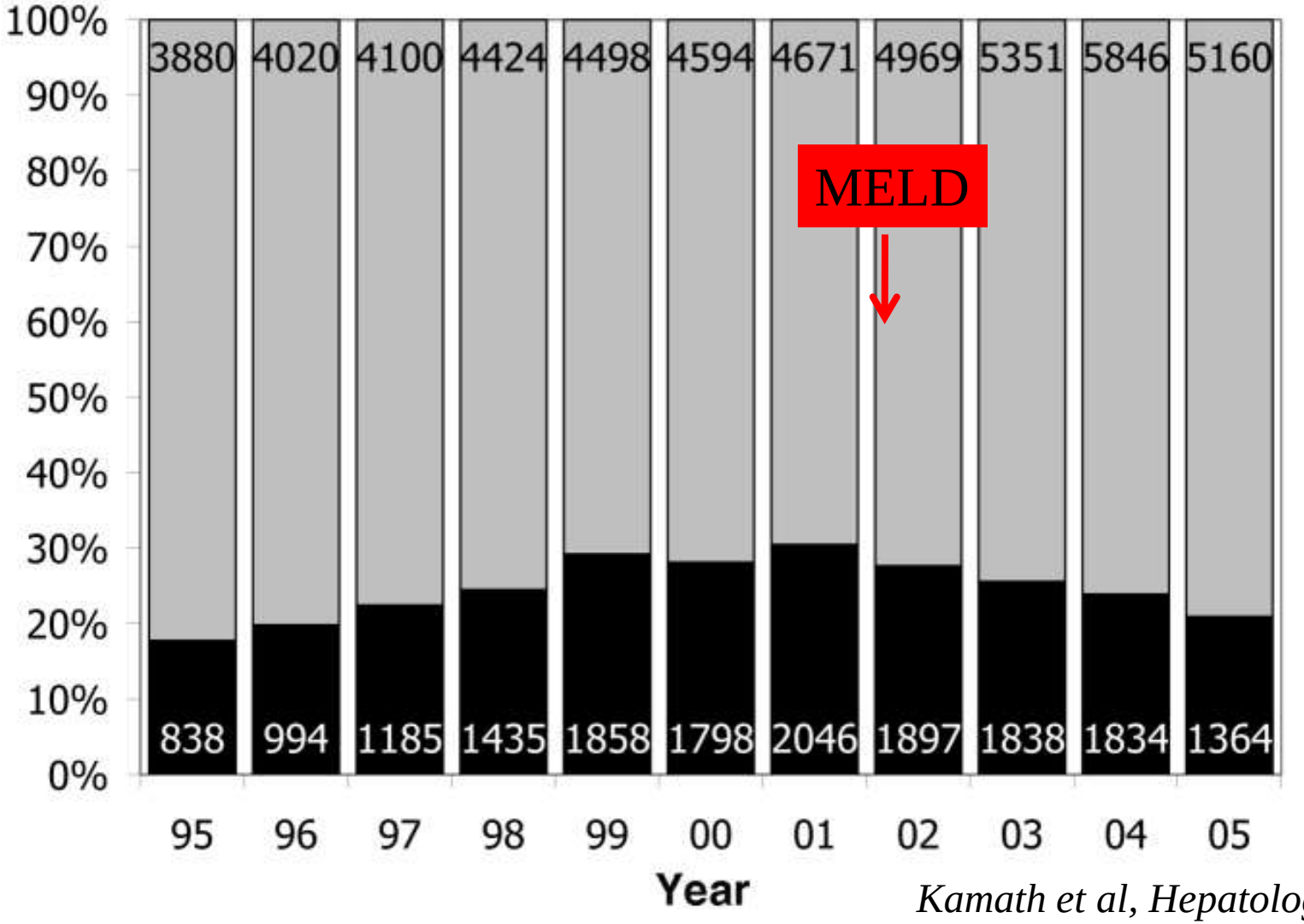
LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Expanded criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

MELD/PELD score

Deaths on Waiting List in US



Kamath et al, Hepatology 2007

HCC - Evolution of MELD Prioritization

	Original Feb 2002	April 2003	Jan 2004	Jan 2005
Stage I 1 tumor < 2cm	15% Risk =MELD 24	8% Risk =MELD 20	0 Risk =MELD calculated	**0 Risk =MELD calculated**
Stage II 1 tumor ≥ 2CM but < 5 cm or 2-3 tumors largest < 3 CM	30% Risk =MELD 29	15%Risk =MELD 24	15% Risk =MELD 24	**15% Risk =MELD 22**

Centers recertify every 3 months. Patients continuing to meet stage II definition by either CT or MRI receive additional 10% mortality risk points (~3 MELD points)

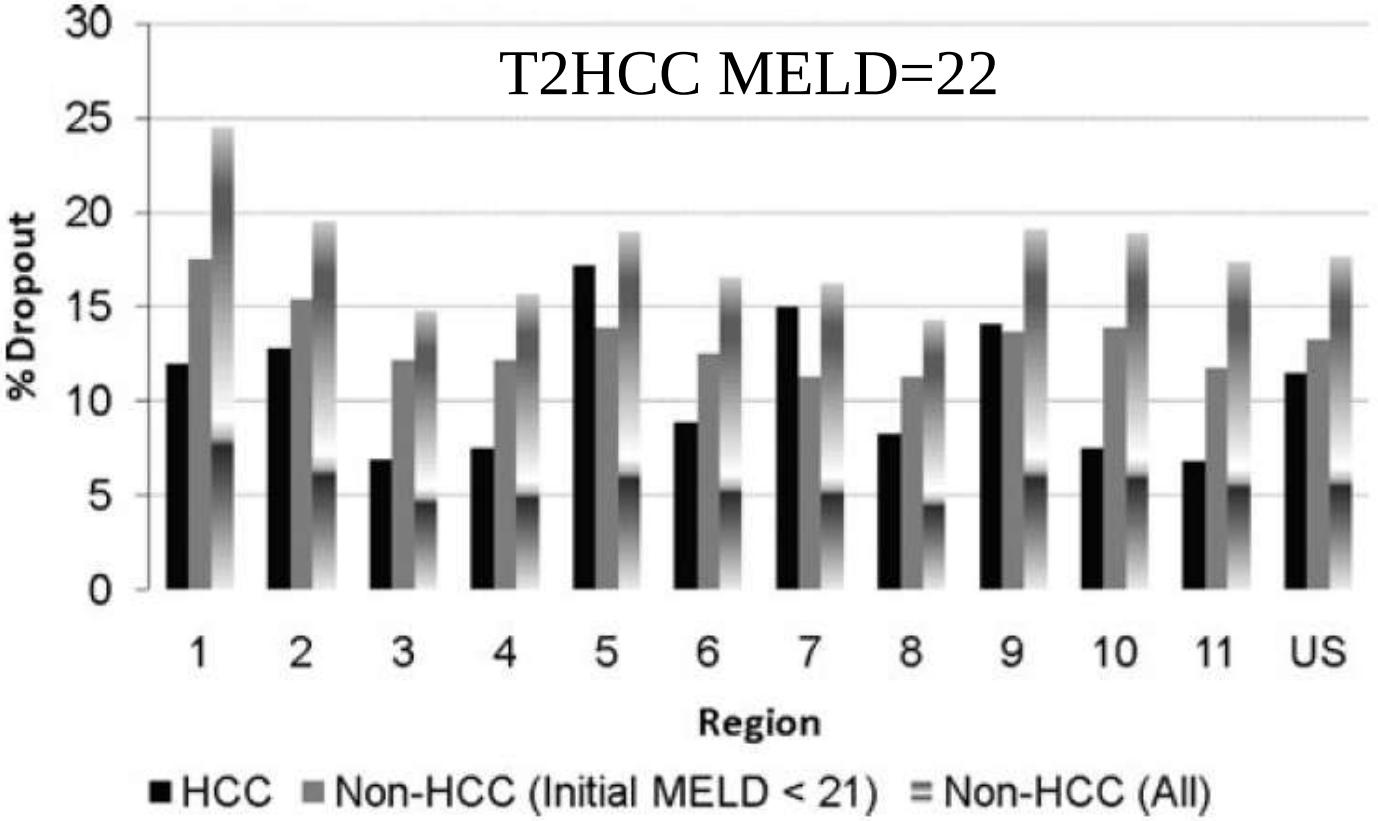
Cleveland Clinic

Courtesy of J Fung

HEPATOCELLULAR CARCINOMA

Organ Allocation/Priority System

Hepatocellular Carcinoma Patients Are Advantaged in the Current Liver Transplant Allocation System



Washburn et al AJT 2010

LIVER GRAFT ALLOCATION

Implementation of MELD in Hong Kong

July 8, 2003:

MELD for liver graft allocation

- Automatic points for FAP/familial hyperoxaluria (2 points every 3 months)
- No automatic points for HCC

October 1, 2009:

Automatic points for T2 HCC-

- upgrade to at least 18 points after on list for 6 months
- additional 2 points every 3 months

LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

HEPATOCELLULAR CARCINOMA

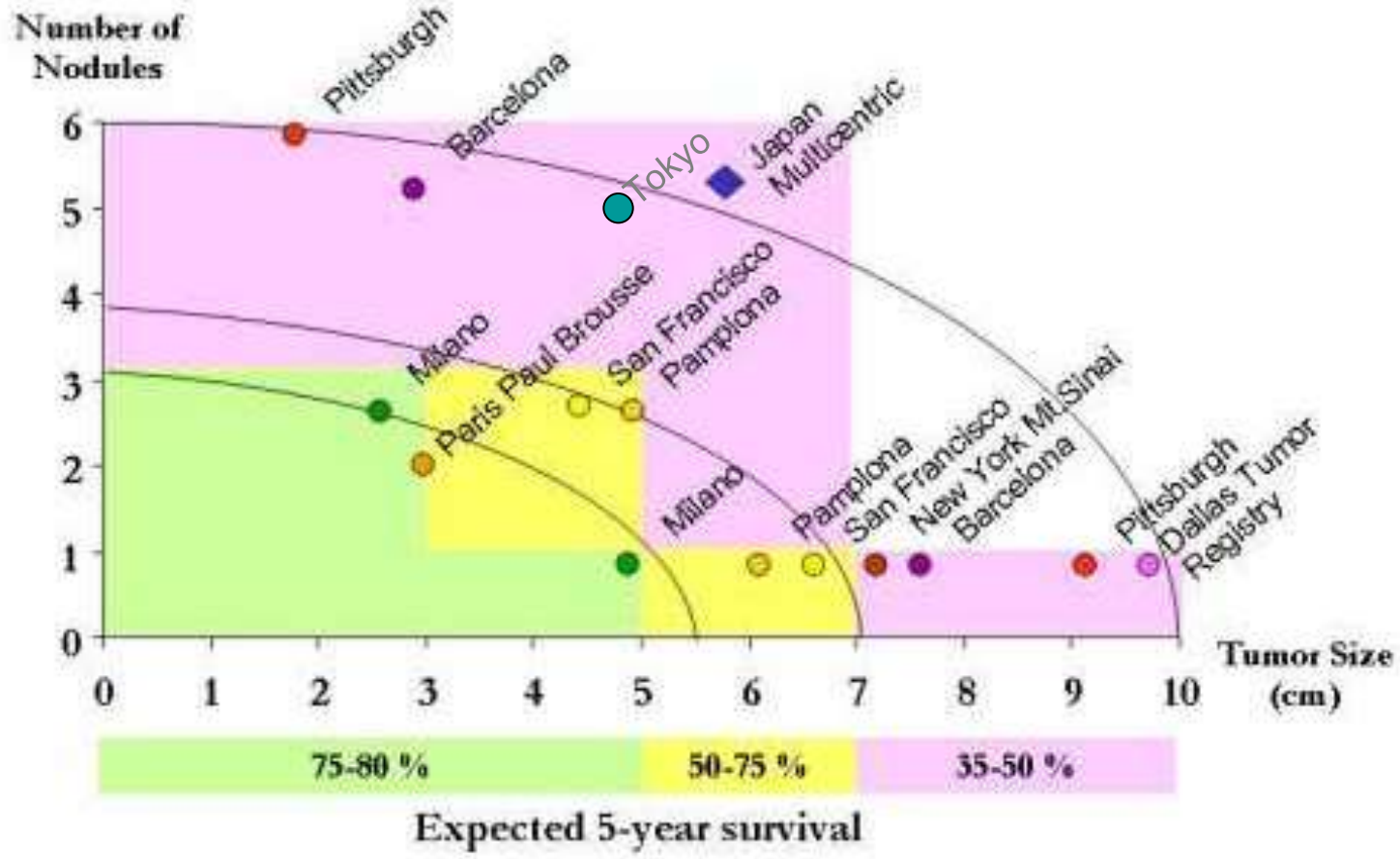
Liver Transplantation: Extended Criteria

Author, year	**Proposed criteria**
Yao, UCSF, 2001	1 nodule < 6.5 cm or
	≤3 nodules, ≤4.5 cm, total < 8 cm
Sugawara, Tokyo 2007	≤5 nodules, ≤5 cm
Takada, Kyoto 2007	≤10 nodules, ≤5 cm
Soejima, Fukuoka 2007	Any number, ≤5 cm
Herrero, Navarra 2007	1 nodule < 6 cm or
	≤3 nodules, ≤ 5 cm
Kwon, Seoul 2007	Any number, ≤5 cm, AFP ≤ 400 ng/ml
Zheng, Hangzhou 2008	total < 8 cm or
	total > 8 cm, Grade I/II and AFP < 400 ng/ml
Mazzaferro, Milan 2009	Up to 7, no microvascular invasion

HEPATOCELLULAR CARCINOMA

Liver Transplantation "Metro Ticket"

The further the distance, the higher the price



LIVER TRANSPLANTATION

Organ Shortage

Demand > Supply: A zero-sum game

Extending criteria = Increasing demand

Organ shortage:

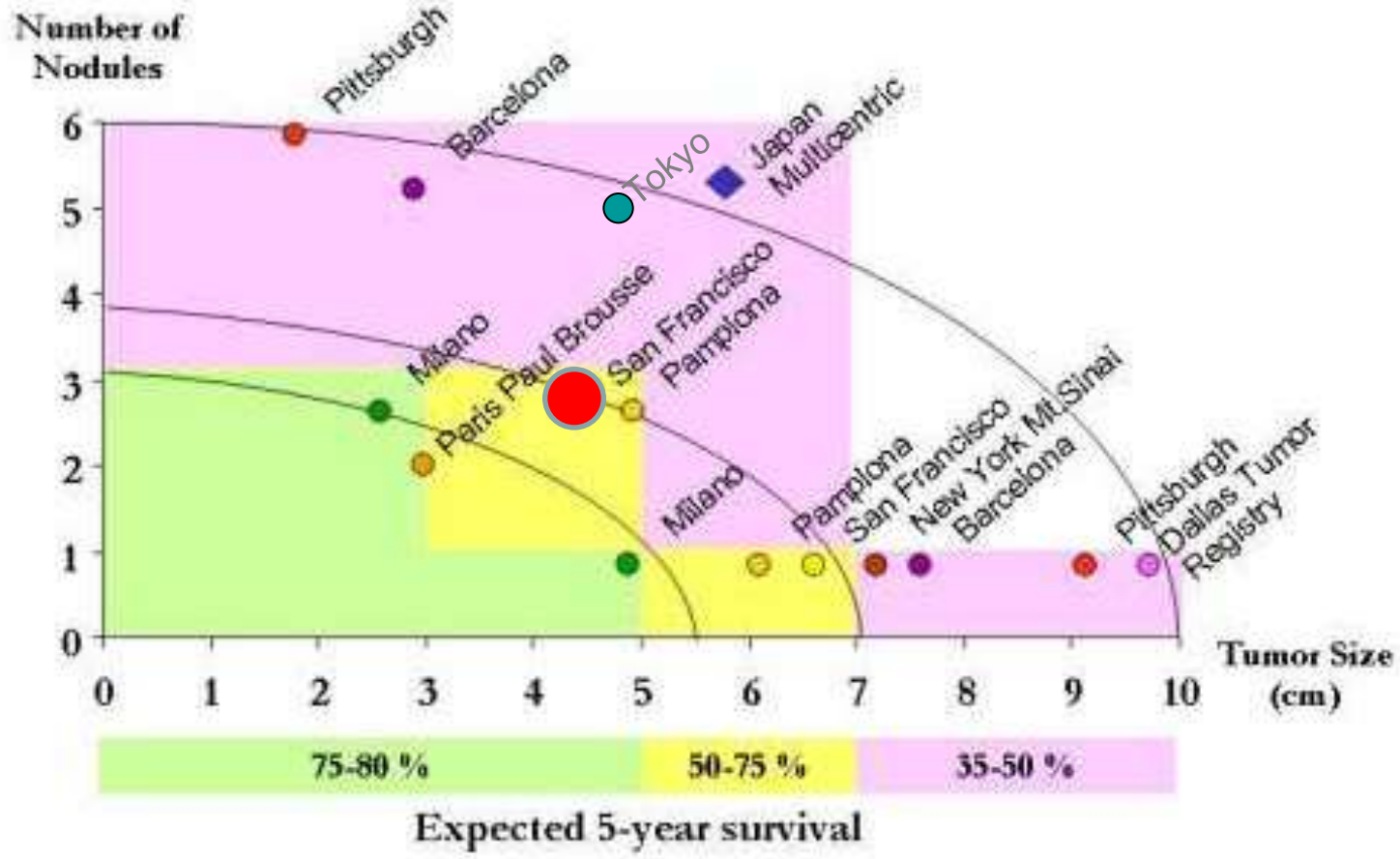
- Mortality on waiting list: when one extended criteria patient receives a graft, another patient on list will die
- Waiting time: increased for all other patients on list

Extending criteria aggravates organ shortage

HEPATOCELLULAR CARCINOMA

Liver Transplantation "Metro Ticket"

The further the distance, the higher the price



HEPATOCELLULAR CARCINOMA

UCSF criteria: How many more?

10 %?

Author, year	**Milan+**	**Milan-UCSF+**
Yao, UCSF 2007	130	38 (29%)
Duffy, UCLA 2007	173	185 (107%)

HEPATOCELLULAR CARCINOMA

Minimum 5-yr survival justifying OLT in USA

A Novel Model Measuring the Harm of Transplanting Hepatocellular Carcinoma Exceeding Milan Criteria

- Decision analysis using Markov model
- UCSF criteria
- Survival benefit for Milan-UCSF+ HCC patients
- Harms to other patients on list:
  - 44% increase in risk of death
  - Utility loss of 3 quality-adjusted years of life pre/post OLT

–Harm < benefit if 5-yr survival > 61%

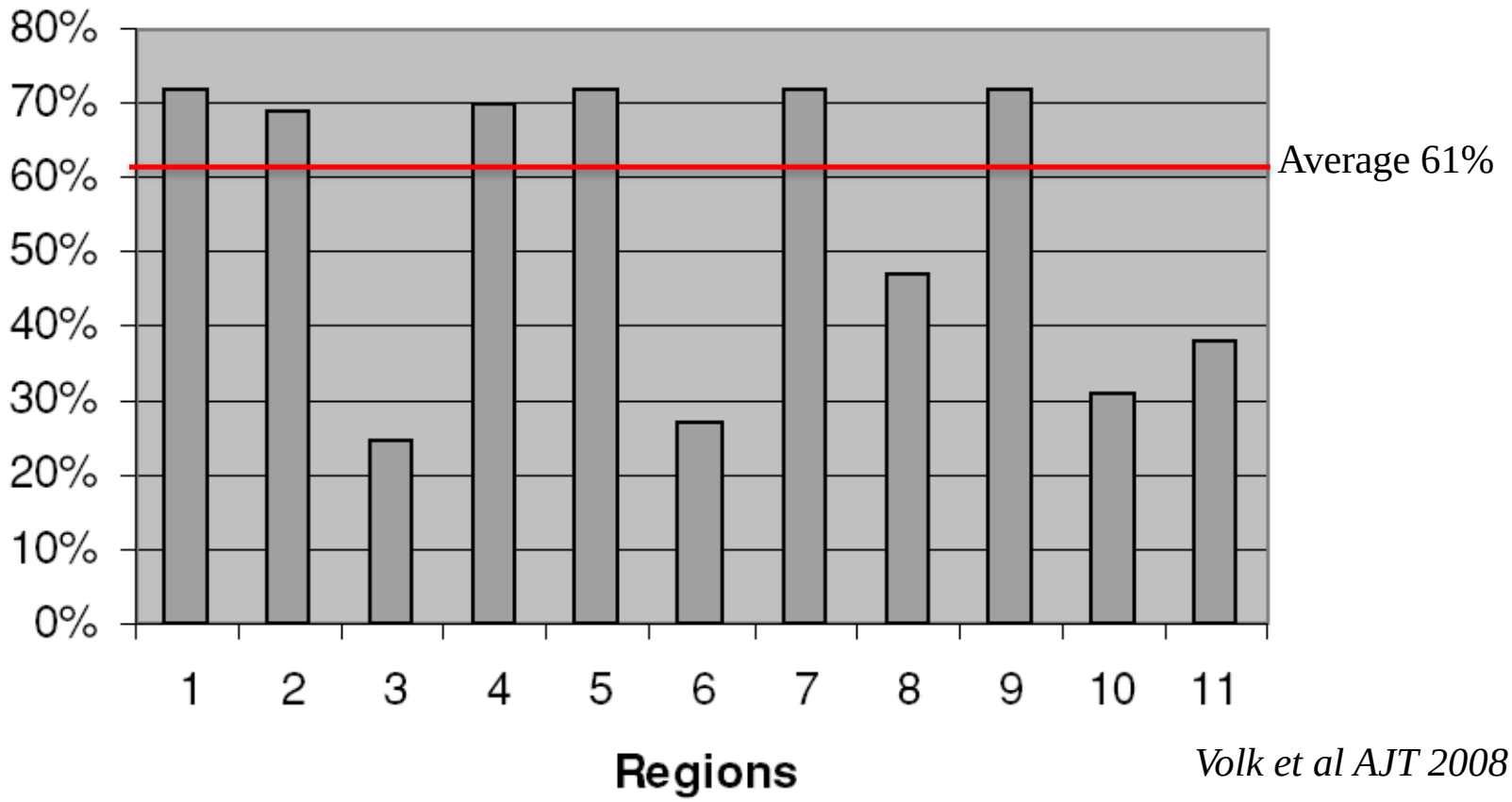
Maintaining a zero-sum game

Volk et al AJT 2008

HEPATOCELLULAR CARCINOMA

Minimum 5-yr survival justifying OLT in USA

Wide variation in zero-sum survival threshold



Volk et al AJT 2008

LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

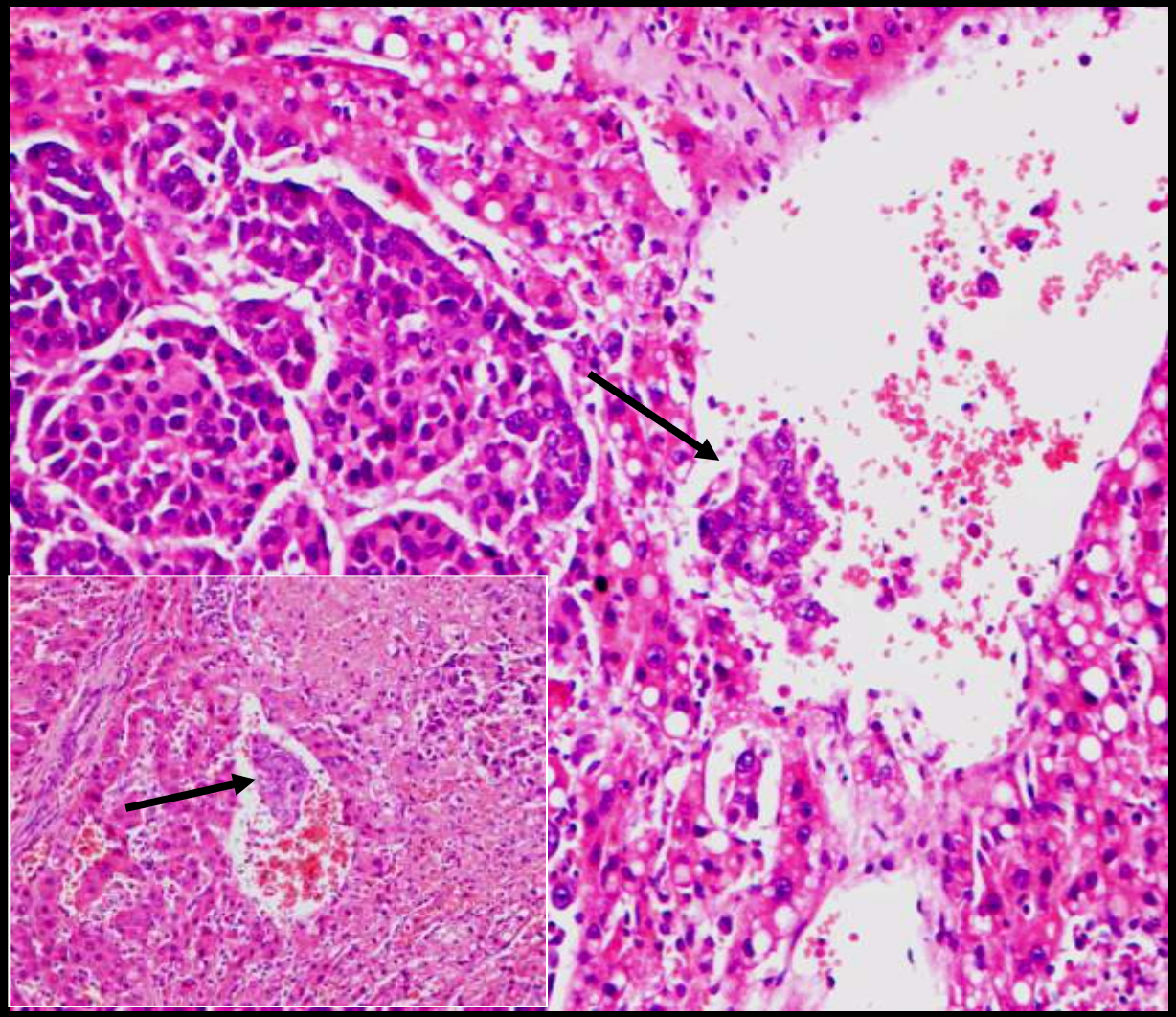
LIVER TRANSPLANTATION FOR HCC

Tumor Number/Size: Problems

1. Errors in preoperative imaging
   - understaging 20-30%
   - overstaging 10 -20%
2. Inter-observer variation in interpretation
3. Difficult to repeat immediately before transplantation
4. Surrogate marker for tumor biology only
   - low volume but high-risk tumor
   - high volume but low-risk

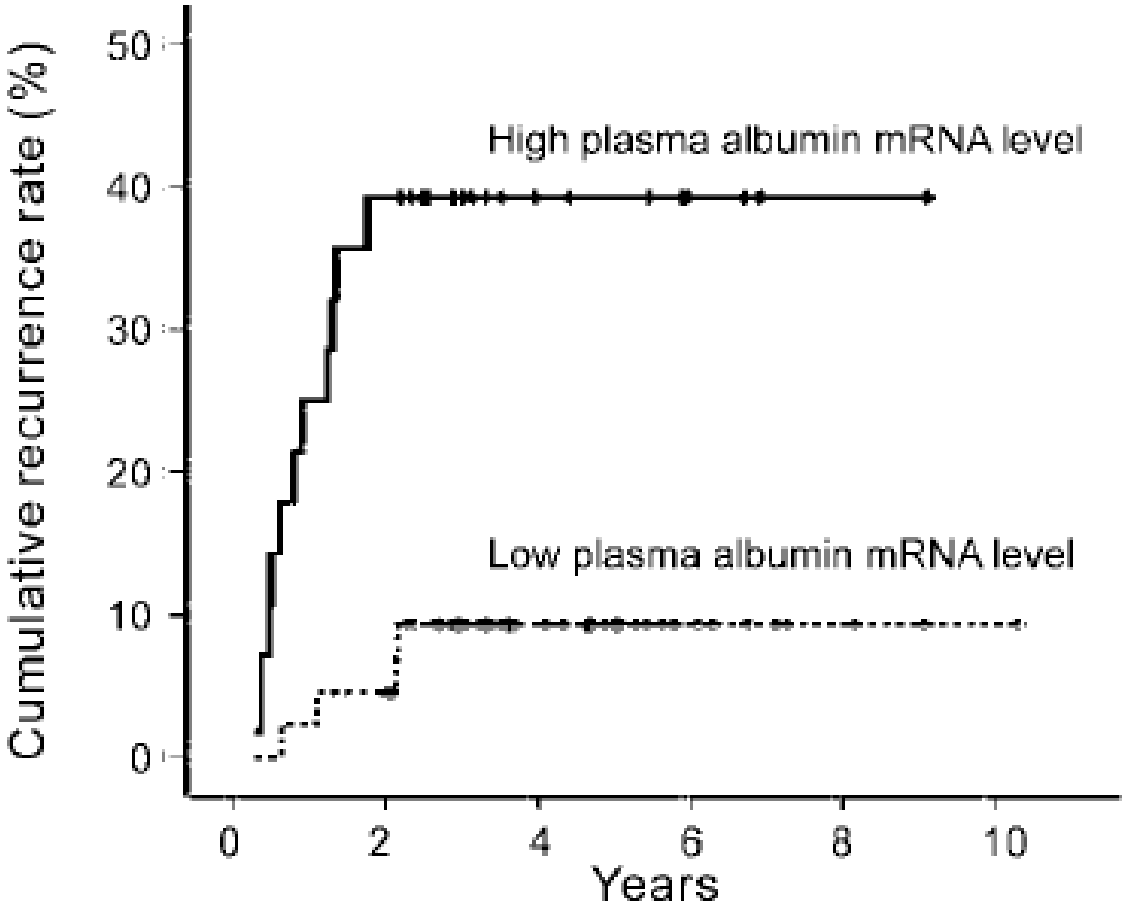
HEPATOCELLULAR CARCINOMA

Poor Prognostic Factor: Vascular Invasion



LIVER TRANSPLANTATION FOR HCC

Biomarkers: Plasma Albumin mRNA



No. at risk						
High plasma alb mRNA	28	17	8	3	1	0
Low plasma alb mRNA	44	42	22	8	3	1

Cheung et al, Transplantation 2008

BIOMARKERS FOR HCC

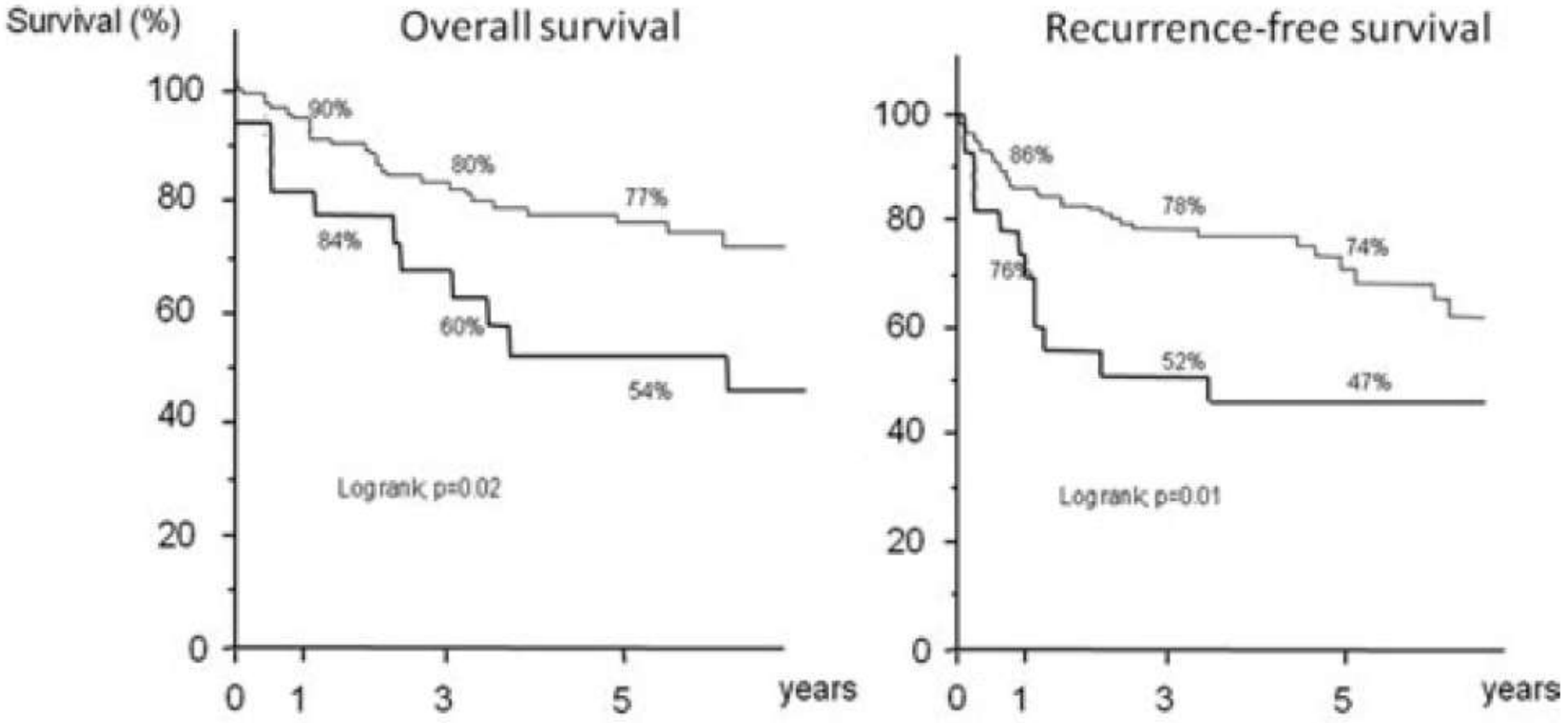
Liver Transplantation: prognostic role of AFP

Author, year	**No. of patients**	**cut-off level of AFP**
Figueras, 2001	307	AFP < 300 ng/mL
Ravaioli, 2004	70	AFP </= 300 ng/mL
Shetty, 2004	109	AFP </= 300 ng/mL
Leung, 2004	144	AFP </= 100 ng/mL
Todo, 2004	316	AFP </= 20 ng/mL
Yang, 2007	63	AFP </= 200 ng/mL
Zheng, 2008	195	AFP </= 400 ng/mL
Ravaioli, 2008	177	AFP <300 ng/mL
Toso, 2009	6478	AFP </= 400 ng/mL

LIVER TRANSPLANTATION FOR HCC

Progression of AFP as Prognostic Factor

Retrospective study of 153 patients
AFP progression: > 15 ngmL per month



Vibert et al, AJT 2010

LIVER TRANSPLANTATION FOR HCC

Revised Scoring System

	No. of points			
Factors	**1**	**2**	**3**	**4**
Tumor size (cm)	≤3	>3, ≤ 5	>5, ≤6.5	>6.5
Tumor no. (nodules)	1	2, 3	4, 5	≥6
AFP (ng/mL)	≤20	>20, ≤ 200	>200, ≤1000	>1000

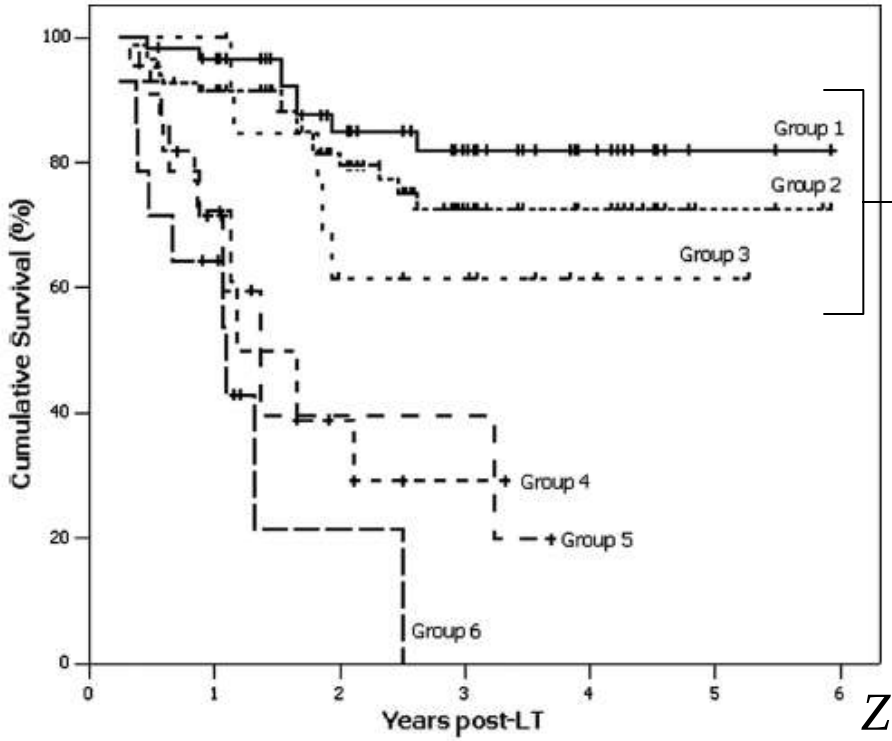
3 – 6 points: transplantable
7 – 12 points: not transplantable

Yang et al, Surgery 2007

LIVER TRANSPLANTATION FOR HCC

Hangzhou Criteria

Groups	N	Tumor size less than or equal to 8 cm	Preoperative AFP level (≤400 ng/mL)	Histopathologic grades I or II	Fulfilling Hangzhou criteria
1	59	Yes	Yes	Yes	Yes
2	84	Yes	Yes/no	Yes/no	Yes
3	15	No	Yes	Yes	Yes
4	22	No	No	Yes	No
5	14	No	Yes	No	No
6	14	No	No	No	No



Hangzhou criteria ($p<0.001$)

Zheng et al, Transplantation 2008

LIVER TRANSPLANTATION FOR HCC

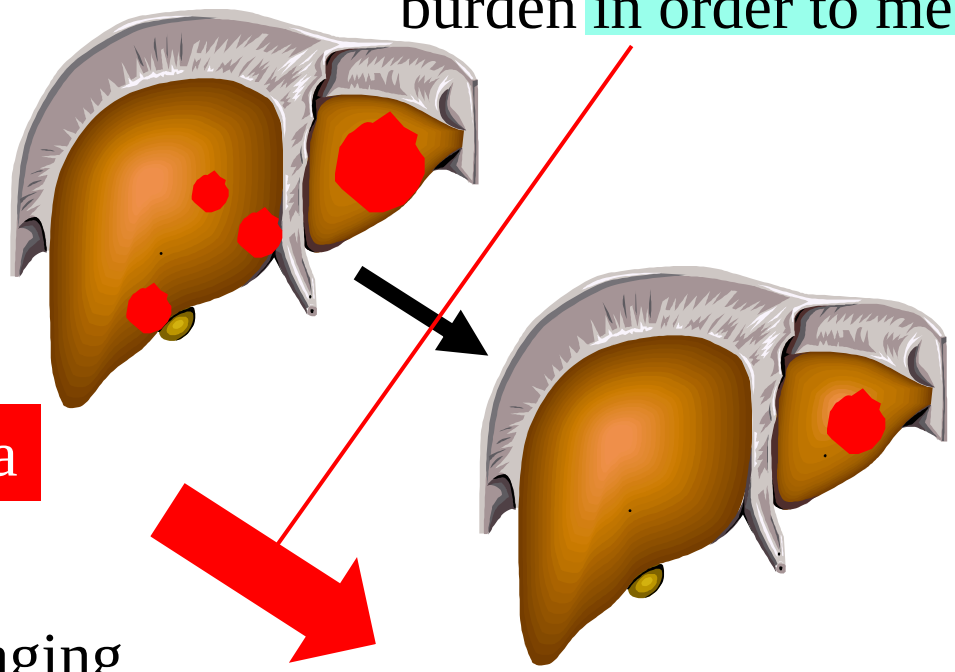
Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

DOWNSTAGING

Definition- Liver Transplantation

Neo-adjuvant therapy to reduce tumor burden in order to meet criteria for OLT



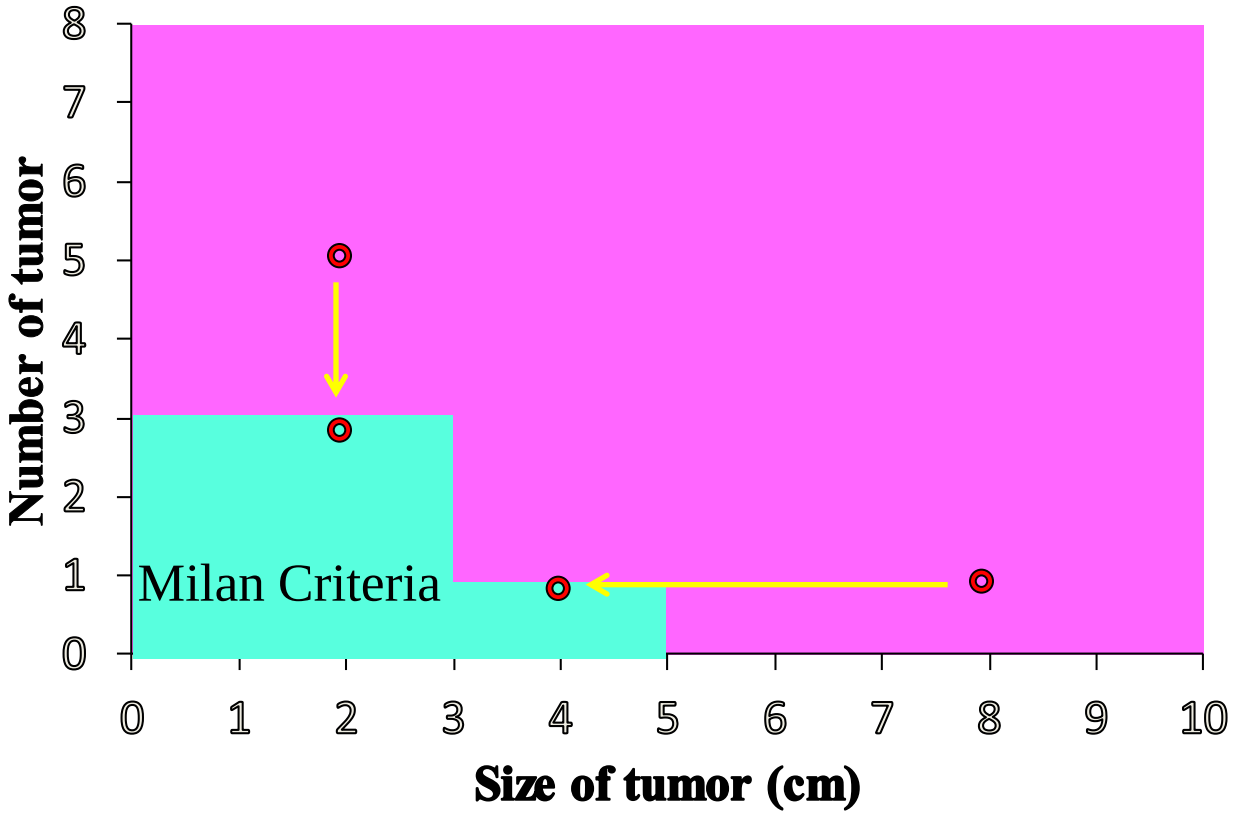
Beyond criteria

Downstaging

Within criteria

DOWNSTAGING

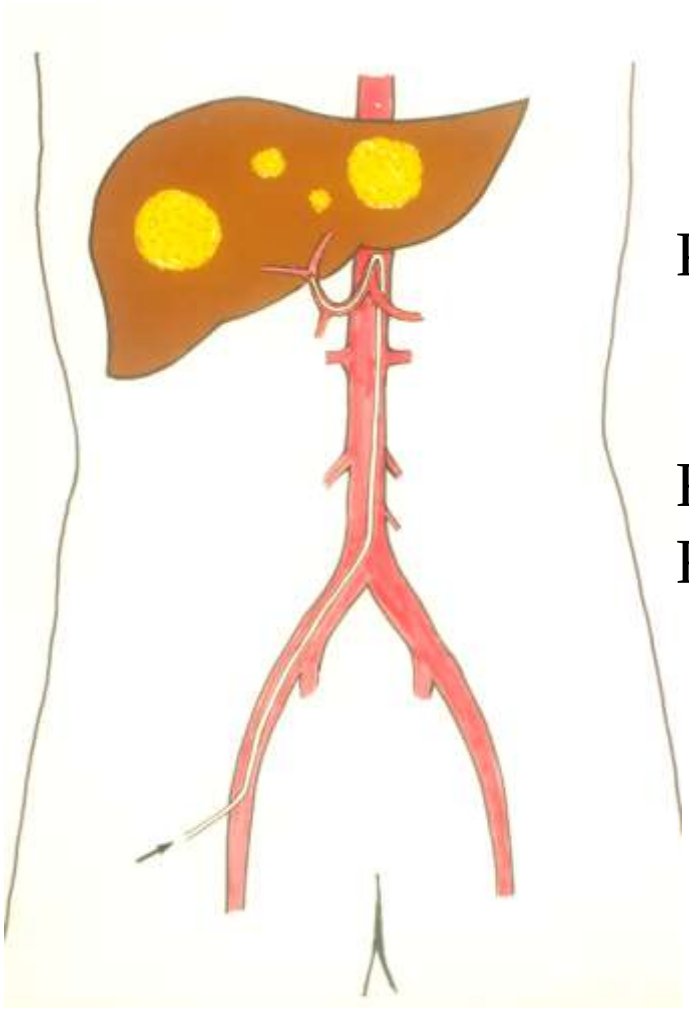
Definition and Objective



To achieve a 5-yr survival comparable to Milan criteria

DOWNSTAGING

Transarterial Chemoembolization



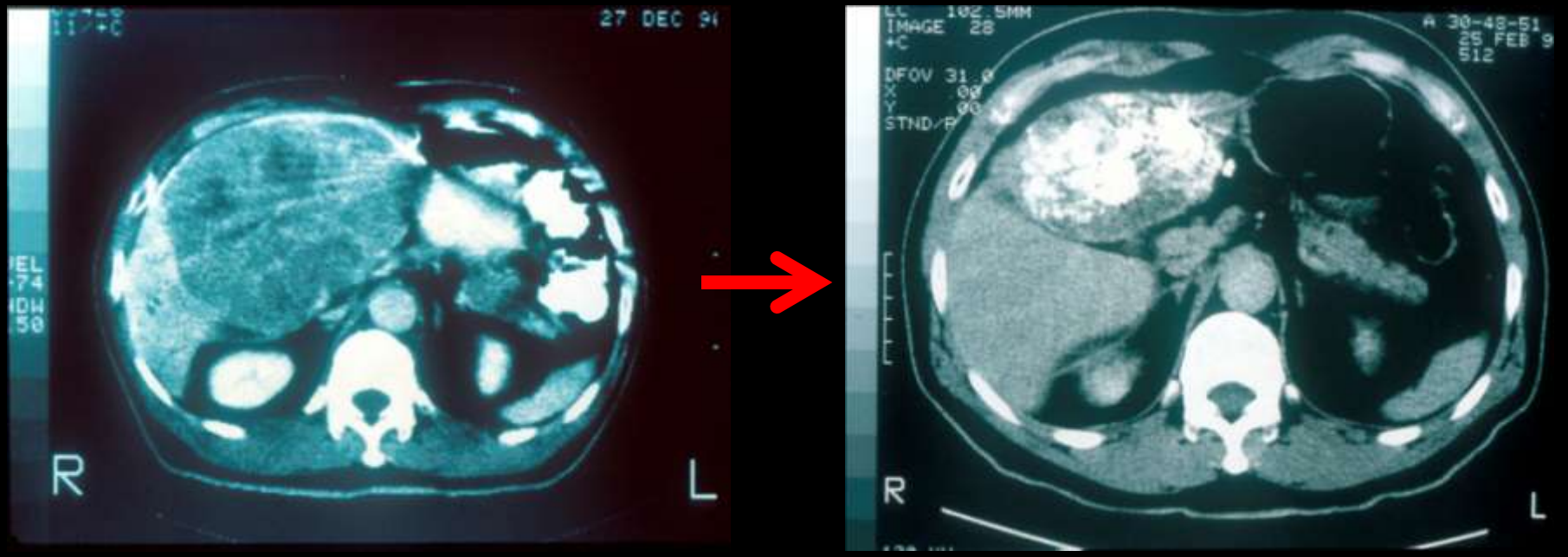
Proven efficacy for unresectable HCC:

50 to 70% response rate

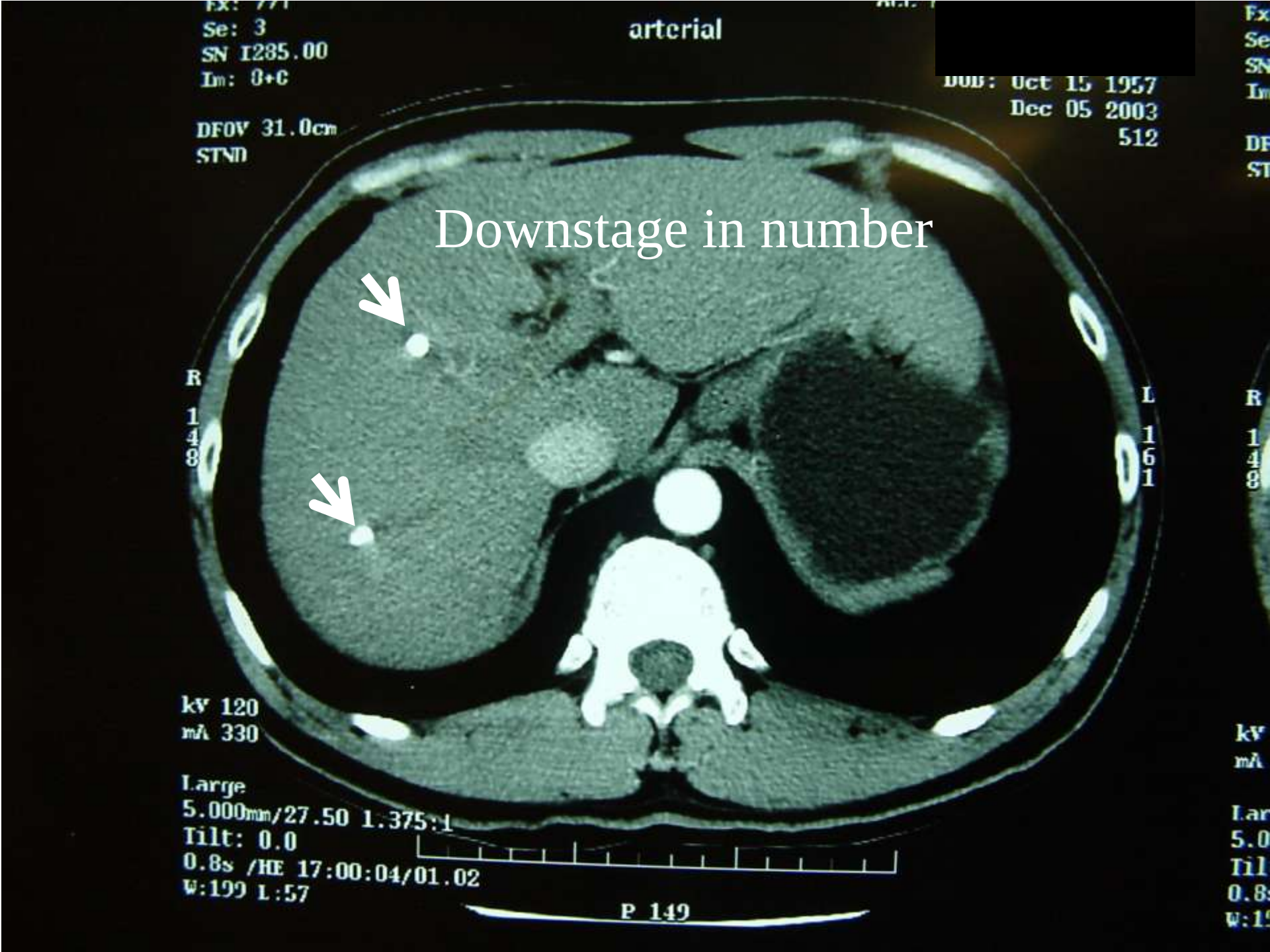
improves survival

Reduce tumor size and number

Response as indicator of tumor biology

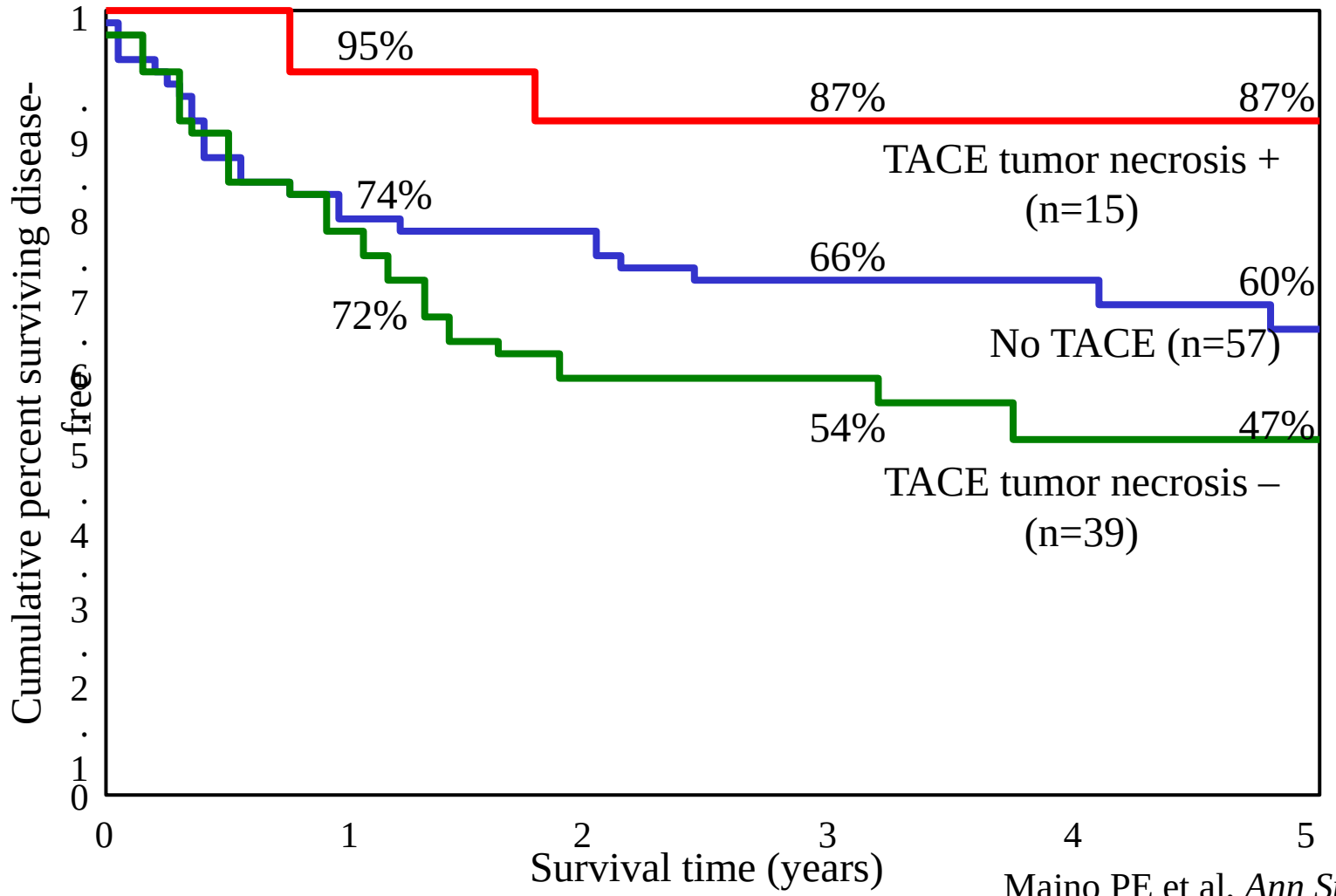


Downstage in size


Se: 3
SN I285.00
Im: 8+C
arterial
DFOV 31.0cm
STND
Dec 05 2003
512
Downstage in number
R
148
L
161
kV 120
mA 330
Large
5.000mm/27.50 1.375:1
Tilt: 0.0
0.8s /HE 17:00:04/01.02
W:199 L:57
P 149

DOWNSTAGING

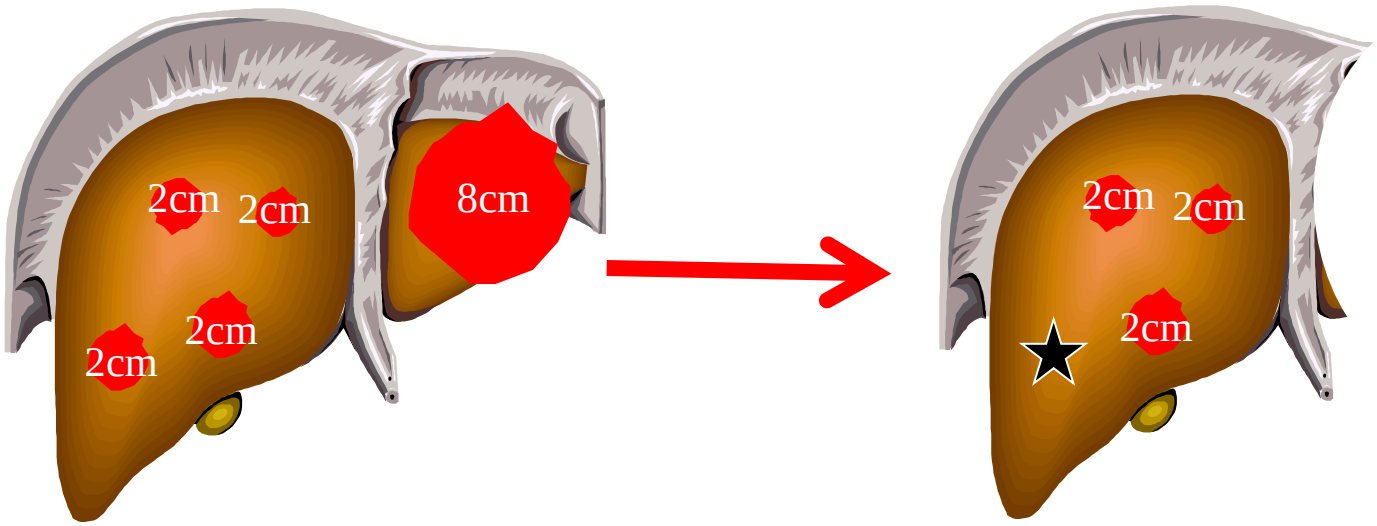
Tumor Necrosis after TACE and Survival



Majno PE et al, *Ann Surg*, 1997

DOWNSTAGING

Local Ablation or Resection



Is this successful downstaging?
Should the patient be eligible for transplantation?

DOWNSTAGING

Response to TACE

Author/year	**Eligibility criteria**	**Response rate**	**No. of OLT after downstaging**	**Outcome**
Majno/1997	Any number > 3 cm	WHO 54%	19	71% at 5 yr
Graziadei/2003	>Milan no upper limit	WHO 67%	10	41% at 4 yr
Otto/2006	Milan no upper limit	RECIST 44%	27	75% at 5 yr
Millonig/2006	>Milan < UCSF	RECIST 85%	28	65% at 5 yr
Chapman/2008	Milan no upper limit	RECIST 22%	17	94% at 5 yr

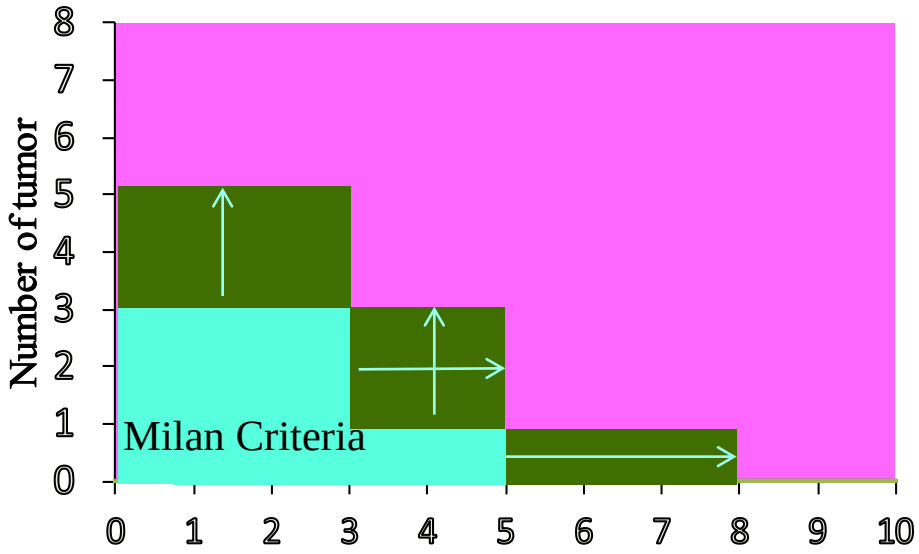
DOWNSTAGING

Milan criteria as end-point

Author/year	Eligibility criteria	Treatment	Success rate	No. of OLT after downstaging	Outcome
Yao/2008	One </= 8 cm 2-3 </= 5cm 4-5 </= 3 cm Total </=8 cm	TACE, RFA, PEI, resection	71%	35	92% at 4 yr
Ravaioli/2008	One </=6cm 2 </=5cm 3-5 </=4 cm Total </=12 cm	TACE, RFA, PEI, resection	69%	32	71% at 3 yr
Lewandowski/ 2009	no upper limit for up to 3 lesions	Radioembolization	58%	9	89% at 1 yr
De Luna/2009	no upper limit	TACE	63%	15	79% at 3 yr
Barakat/2010	no upper limit	TACE, RFA, radioembolization	56%	14	75% at 2 yr

DOWNSTAGING

UCSF Protocol



Total tumor diameter up to 8 cm

Min observation period of 3 months

Downstaging treatment:

- TACE
- RFA
- Resection

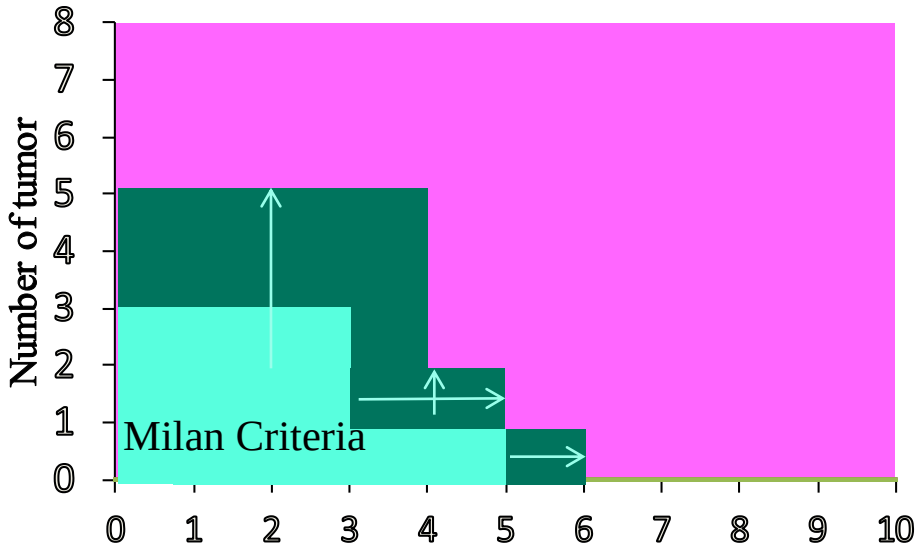
Predictive factor for treatment failure: AFP > 1000 ng/mL

No. of patients	61
Procedure related deaths	2 ((3.3%)
Successful down-staging	43 (70.5%)
Liver transplant	35
4-yr post-transplant survival	92.1%

Yao et al, Hepatology 2008

DOWNSTAGING

Bologna Protocol



Total tumor diameter up to 12 cm

Min observation period of 3 months

AFP < 400 ng/mL

Downstaging treatment:

- TACE
- RFA
- PEI
- Resection

Prognostic factor: AFP > 30 ng/mL

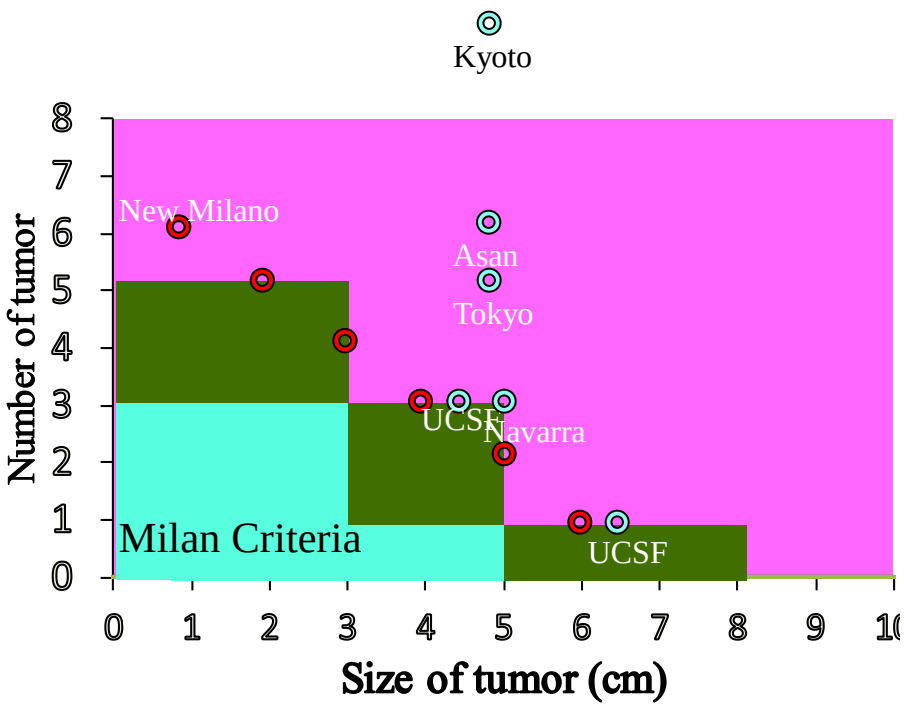
No. of patients	48
Successful down-staging	43 (90%)
Liver transplant	32 (67%)
3-yr post-transplant DFS	71% (18% HCC recurrence)

Ravaioli et al, AJT 2008

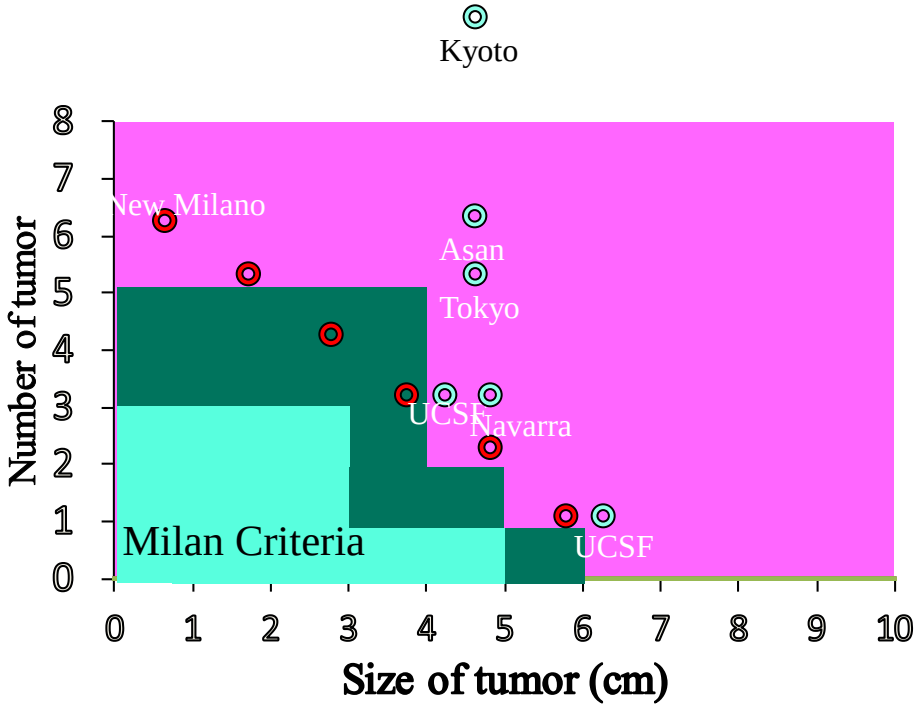
LIVER TRANSPLANTATION FOR HCC

Extended Criteria

Is downstaging necessary?



UCSF downstaing protocol



Bologna downstaging protocol

DOWNSTAGING

Modulation or Selection

- Modulation: change tumor biology
  - A 8 cm tumor will have better tumor biology after being down-staged to 4 cm

- Selection: select tumor biology
  - A 8 cm tumor that can be down-staged to 4 cm has better tumor biology

LIVER TRANSPLANTATION FOR HCC

Evolving Concepts and Strategies

- Primary vs salvage transplant
- Prioritization of organ allocation
- Extended criteria
- Biomarkers
- Downstaging
- Living donor liver transplantation

HEPATOCELLULAR CARCINOMA

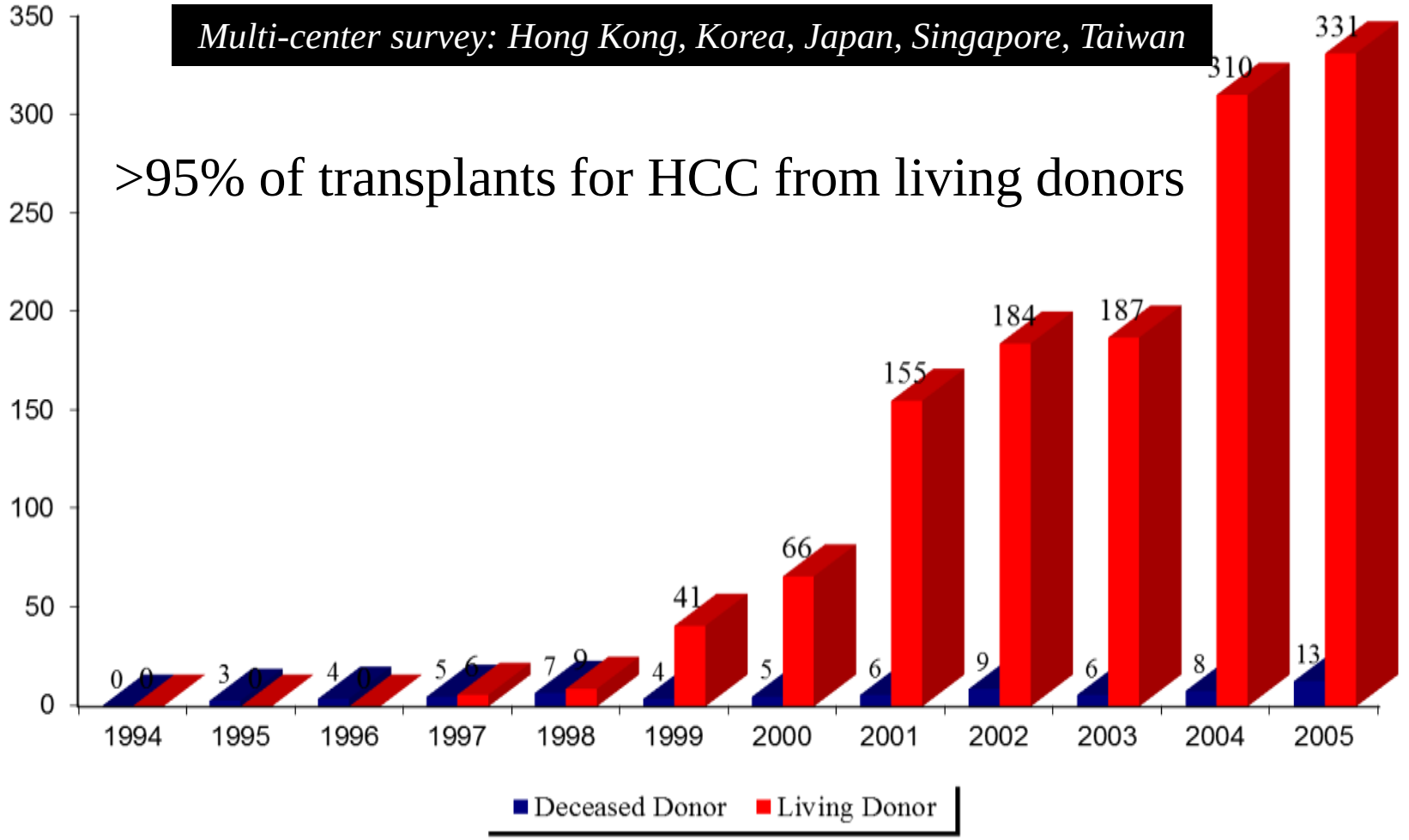
Liver Transplantation: Deceased Vs Living Donor

	Deceased donor	**Living donor**
Availability		
Source	Limited	Unlimited
C		sis
		terion
Allocation	Objective criteria	Dedicated gift
Waiting time	Long	Short
Timing	Unpredictable	Planned

LDLT: a non-zero-sum game

LIVER TRANSPLANTATION FOR HCC

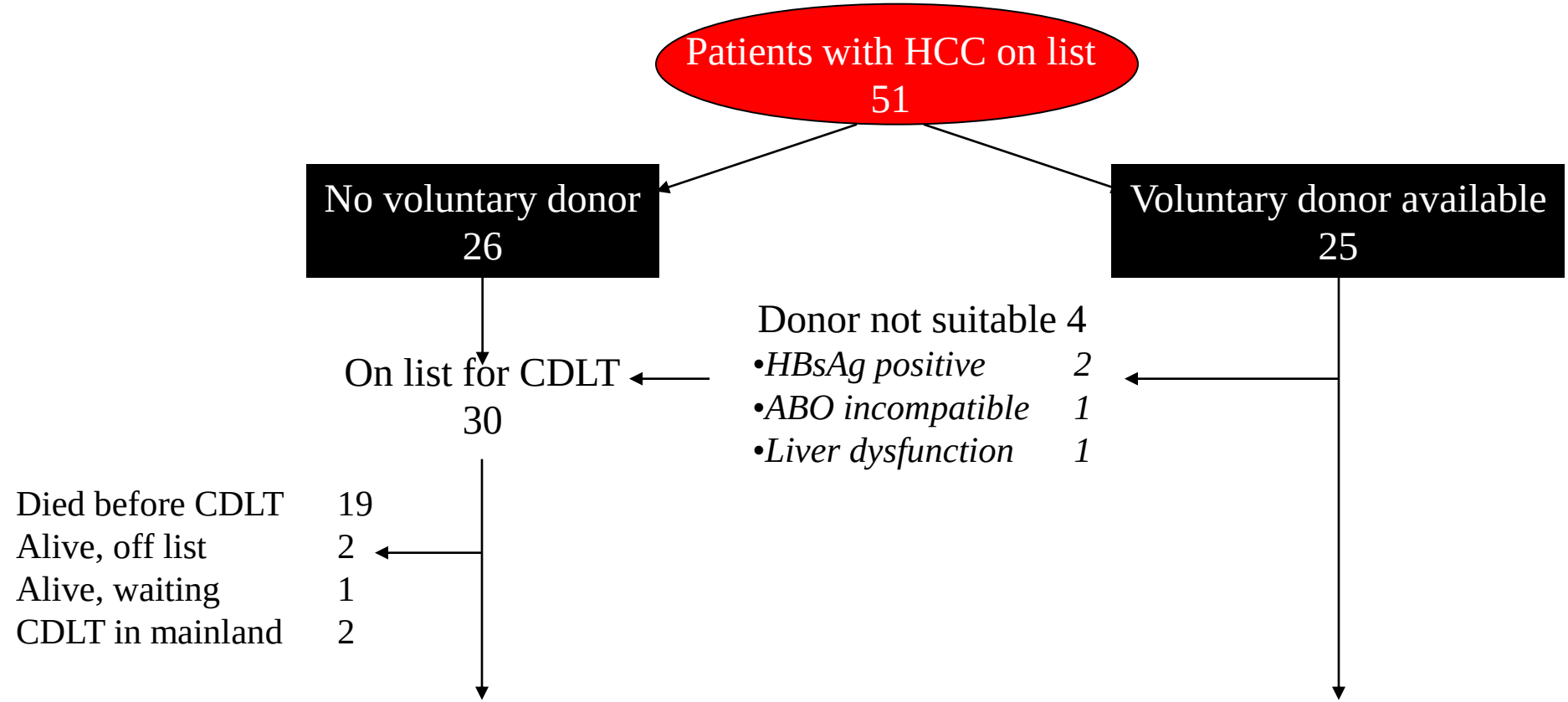
Number of Operations



De Villa and Lo, The Oncologist 2007

LIVER TRANSPLANTATION

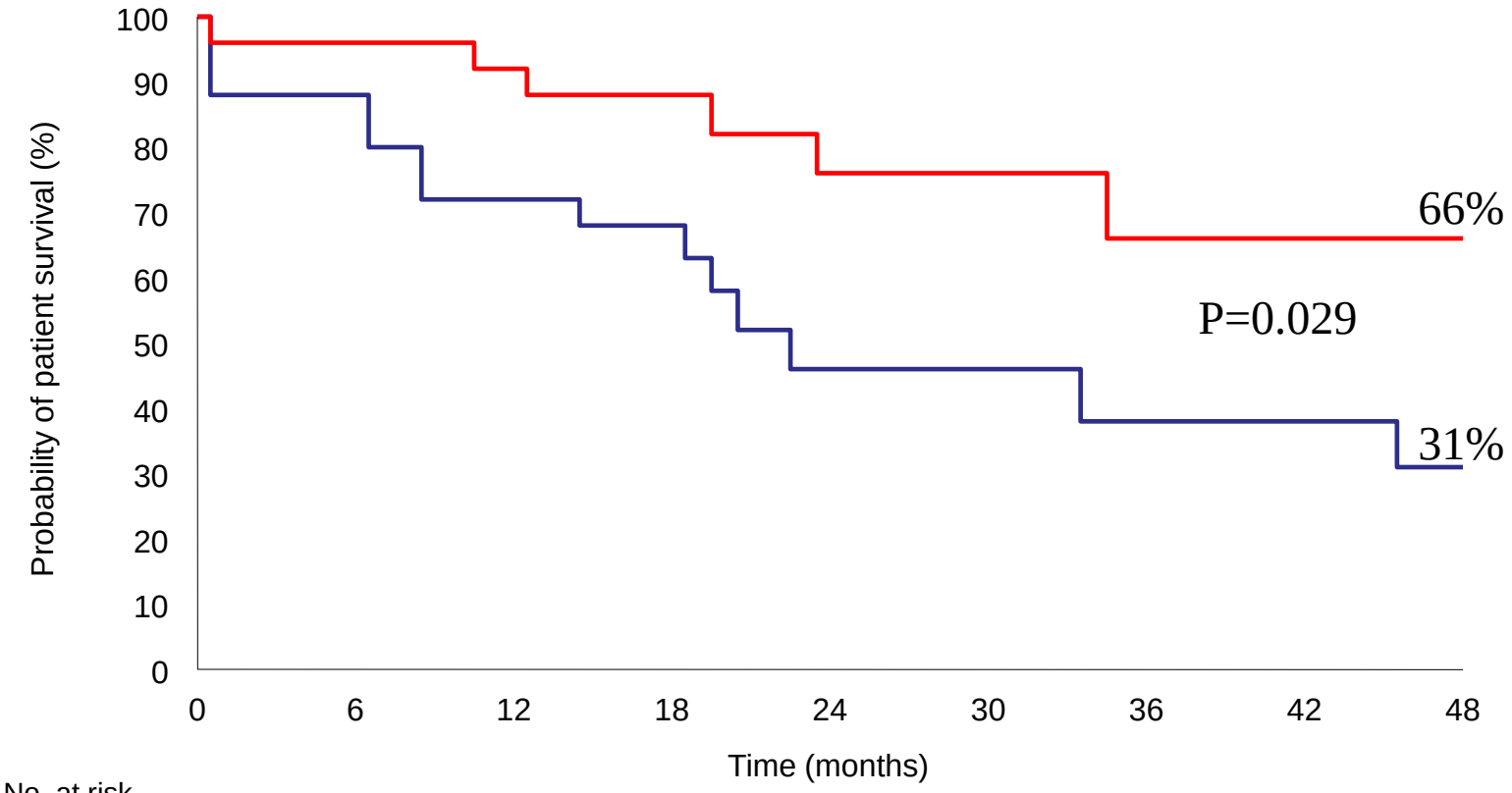
Hepatocellular Carcinoma



Lo et al, Liver Transplantation 2004

HEPATOCELLULAR CARCINOMA

Intention-to-treat Patient Survival



Lo et al, Liver Transplantation 2004

LIVING DONOR LIVER TRANSPLANTATION

Donor Deaths

Location		Number	Total
Asia	Japan	1 + (2)	5 + (2)
	Hong Kong	1	
	Singapore	1	
	India	1+1 vegetative state	
Europe	Germany	2 + (1)	4 + (1)
	France	1	
	Unknown	1	
N. America	USA	3 + (3)	3 + (3)
S. America	Brazil	1	1
Africa	Egypt	1	1
Total			14 (6)

Donor mortality 5/7573 (0.07%)

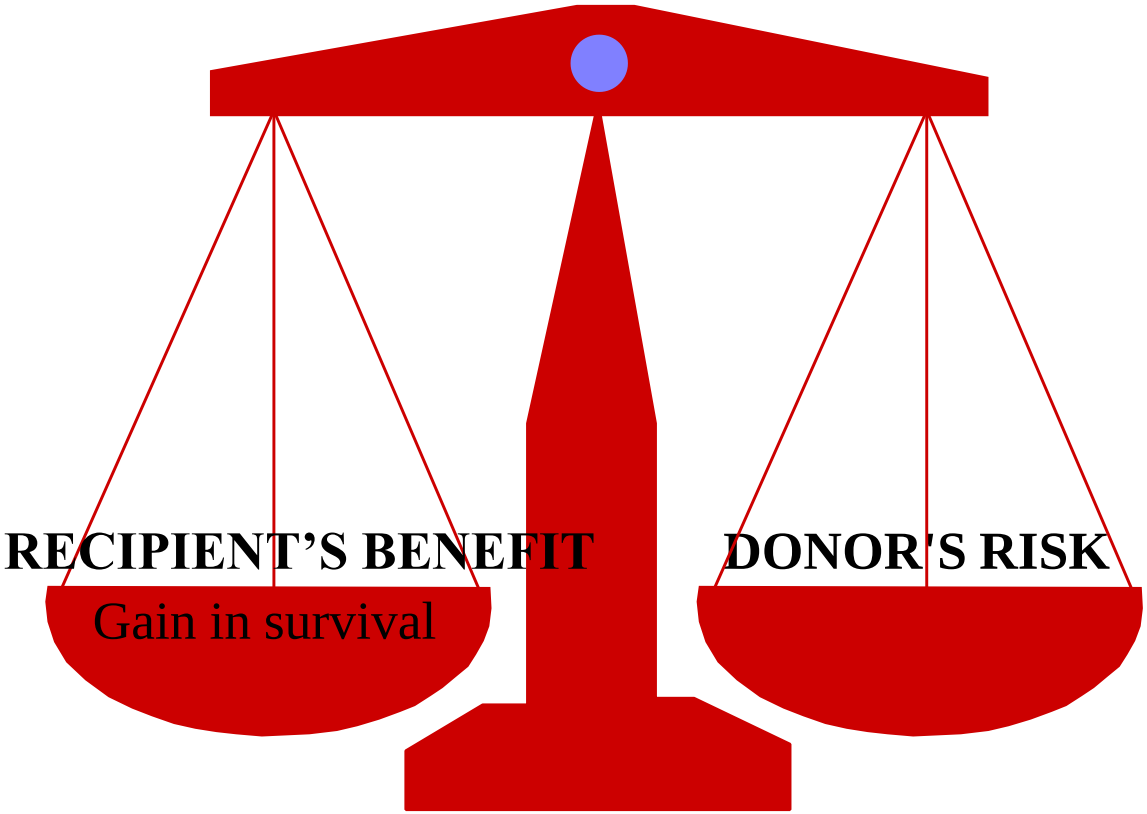
Donor mortality 7/4598 (0.15%)

( ) Late deaths possibly/unlikely related to surgery

Trotter, Adam and Lo Liver Transplantation 2006

LIVING DONOR LIVER TRANSPLANTATION

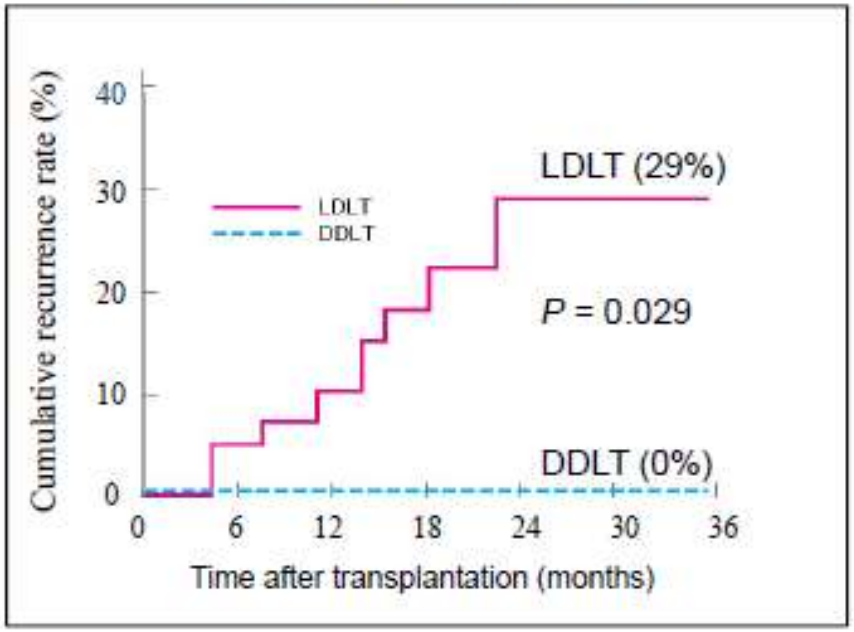
Benefits and Risks



LIVER TRANSPLANTATION FOR HCC

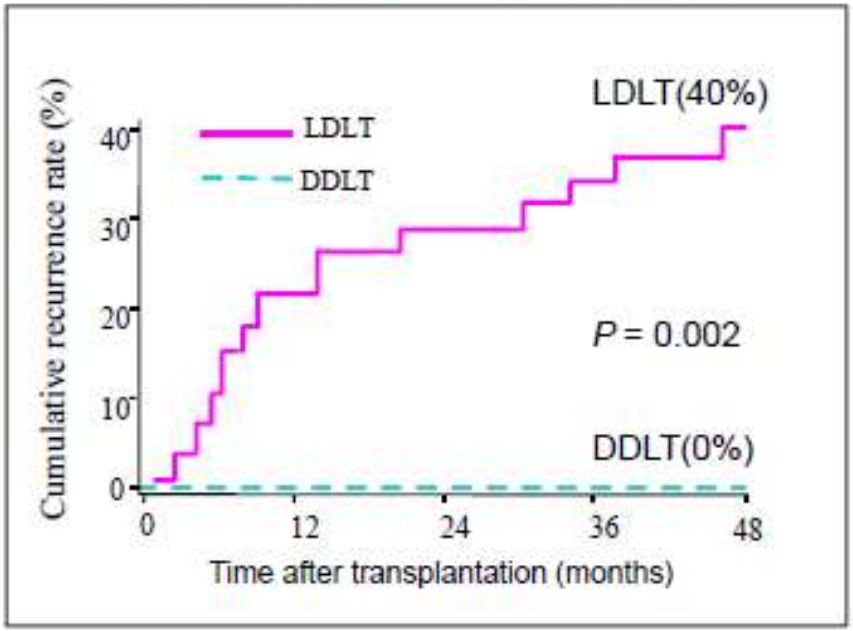
Recurrence Rate: Deceased Donor vs Living Donor

Queen Mary Hospital (HK)



Lo et al, BJS 2007

9 transplantation centers (US)



Fisher et al, AJT 2007

LDLT: Living donor liver transplantation DDLT: Deceased donor liver transplantation

LIVER TRANSPLANTATION FOR HCC

Recurrence Rate: Deceased Donor vs Living Donor

	DDLT	**LDLT**
Selection		
Salvage transplant	Uncommon	Common
Waiting time	Long	Short
Tumor behavior	Slow growing	No selection
Bridging treatment	Responsive	No selection
Graft size	Appropriate-for-size	Small-for-size
Angiogenesis	Less	More
Regeneration	Less	More

HEPATOCELLULAR CARCINOMA

Living Donor Liver Transplantation

LIVING DONOR LIVER TRANSPLANTATION

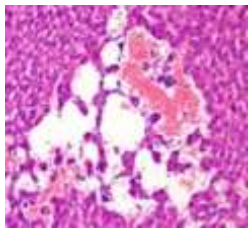
Right vs Left Lobe

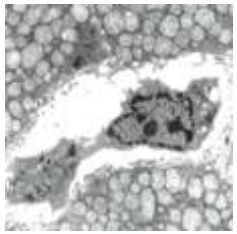
	Right lobe (n=330)	Left lobe (n=22)	P-value
Donor/Recipient sex match			
M to F	34	12	0.000
F to M	167	0	
M to M or F to F	129	10	
Recipient BW (Kg)	66(42.5-116)	57.5(39.5-79)	0.005
Donor BW (Kg)	56.5(37-108.5)	73.5(51-109.2)	0.000
GW (g)	600(320-1140)	410(310-623)	0.000
GW to Recipient BW (%)	0.91(0.49-1.95)	0.73(0.49-1.28)	0.000
GW to Recipient SLV (%)	49.3(28.4-89.4)	36.5(27.3-54.9)	0.000
GW to Recipient SLV			
<40%	60	15	0.000
40% to 60%	217	7	
>60%	53	0	

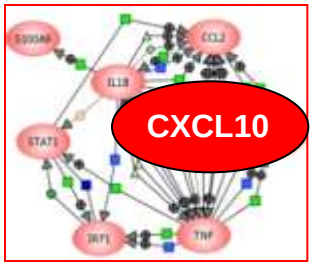
GRAFT INJURY AND TUMOR RECURRENCE

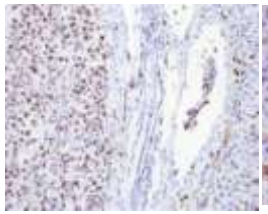
Animal Studies

Liver transplantation using small-for-size liver graft in a rat model

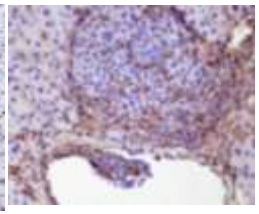




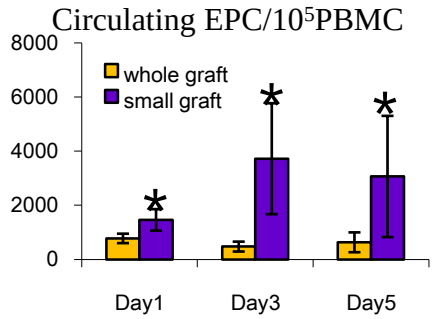




Ki67



SMA



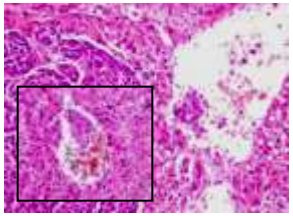
Hepatic sinusoidal disruption

Inflammatory cascades
Cell adhesion, migration and invasion

Tumor cell proliferation
Angiogenesis

Mobilization of circulating EPCs

Invasive tumor growth and recurrence

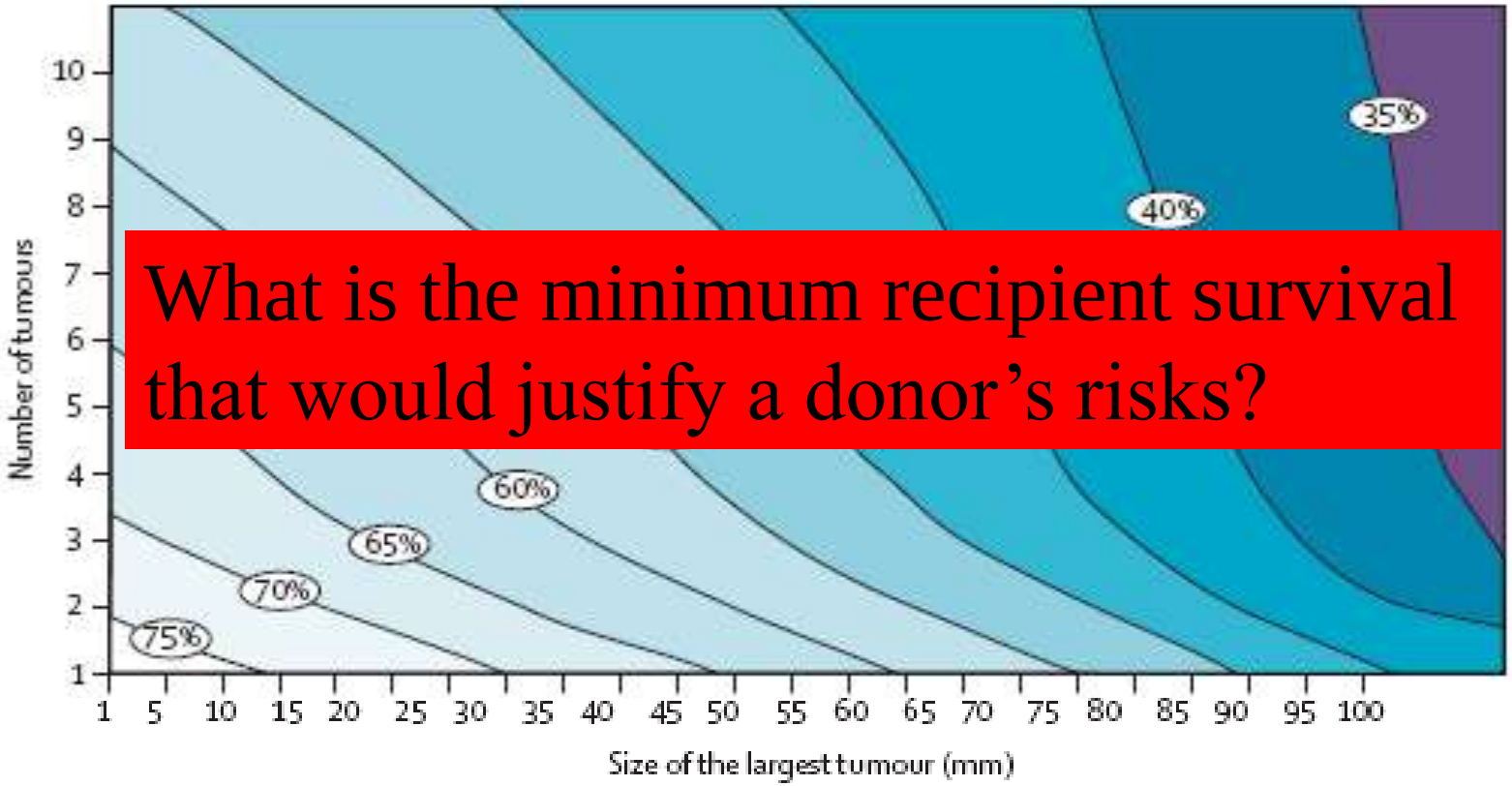


Man et al. Annals of Surgery 2008
Man et al, Annals of Surgery 2010

HEPATOCELLULAR CARCINOMA

Liver Transplantation "Metro Ticket"

The further the distance, the higher the price



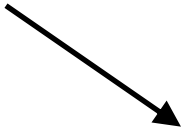
What is the minimum recipient survival that would justify a donor's risks?

Mazzaferro et al, Lancet Oncology 2009

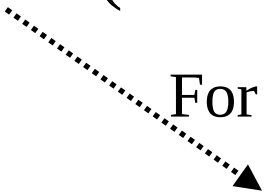
HEPATOCELLULAR CARCINOMA

Selection criteria forLDLT: QMH Approach

Milan criteria (1996)



UCSF criteria (2001)



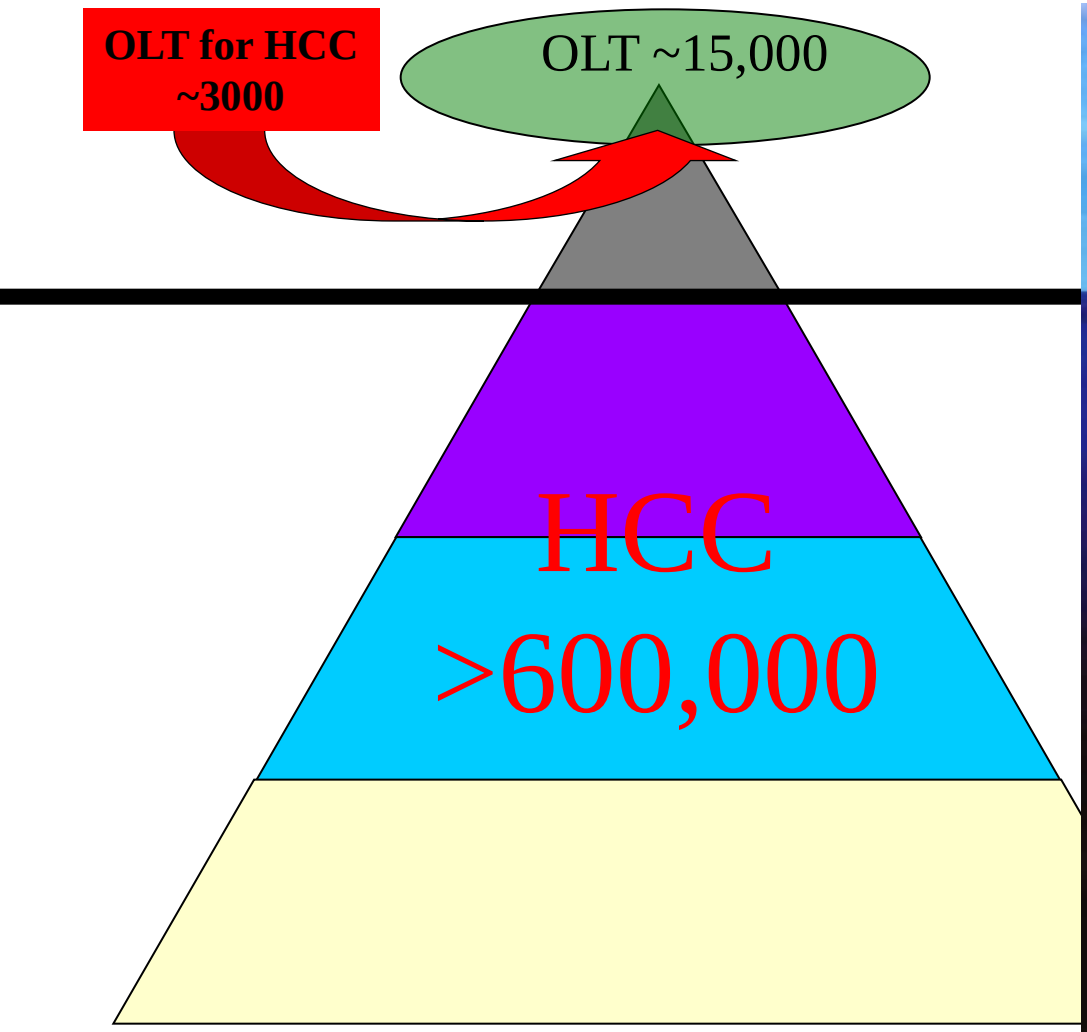
For LDLT

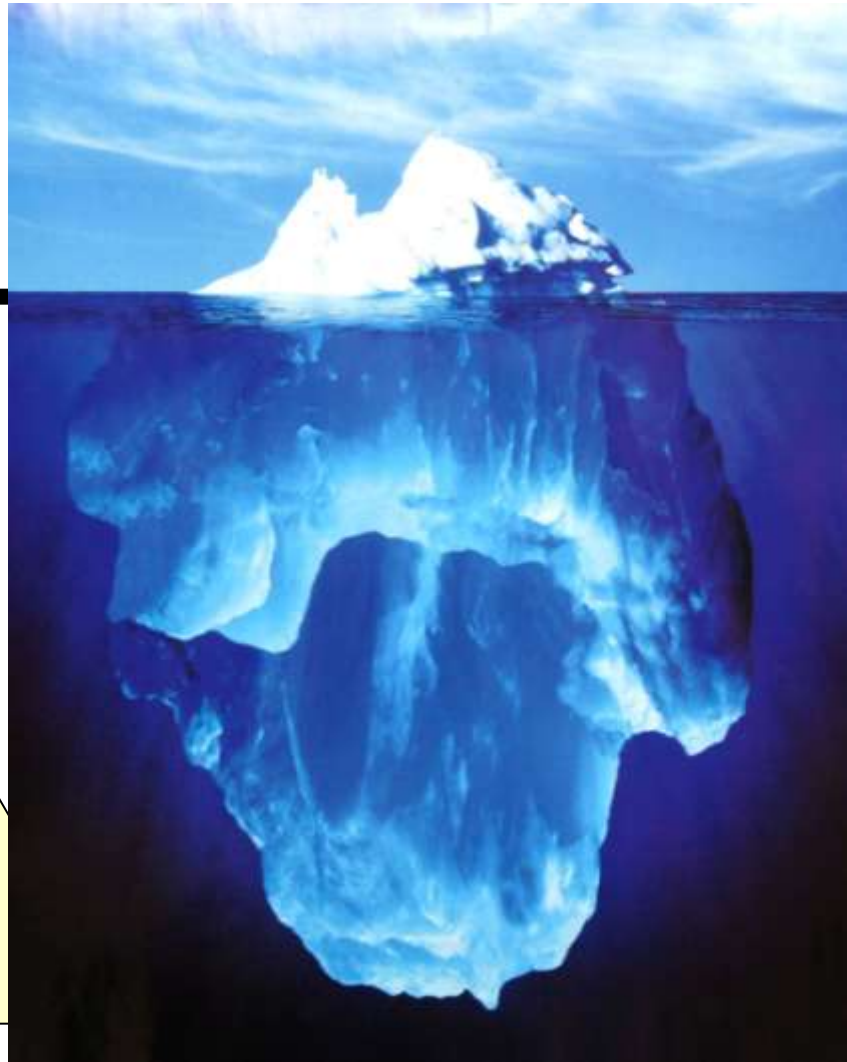
Survival estimation

>50% survival at 5 years

HEPATOCELLULAR CARCINOMA

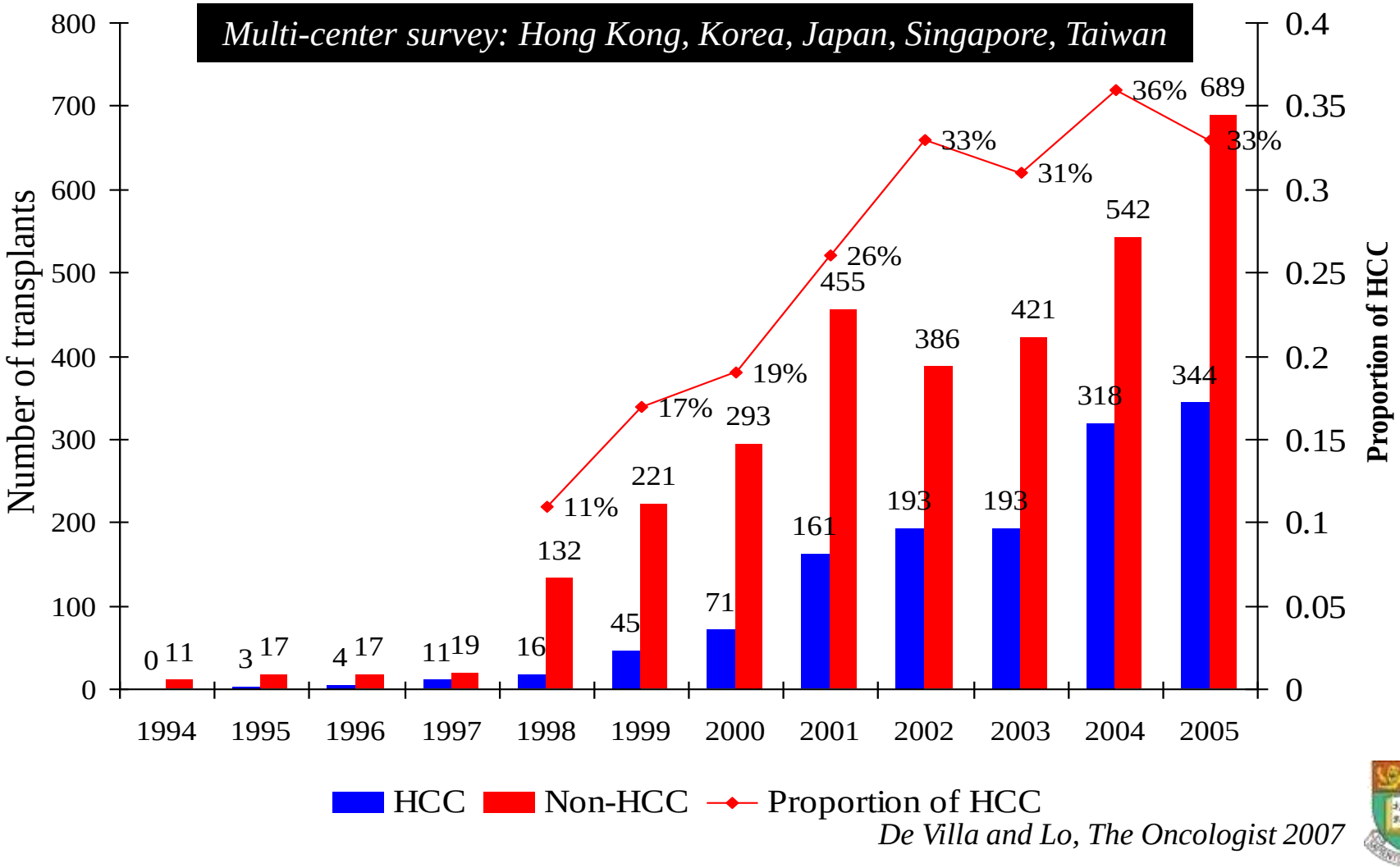
Liver Transplantation





LIVER TRANSPLANTATION

Disease Indications



De Villa and Lo, The Oncologist 2007

LIVER TRANSPLANTATION

HCC as Disease Indication

- Europe 10%
- USA 10% (pre-MELD)
  20% (post-MELD)
- Asia 30-40%
- Mainland China 50%