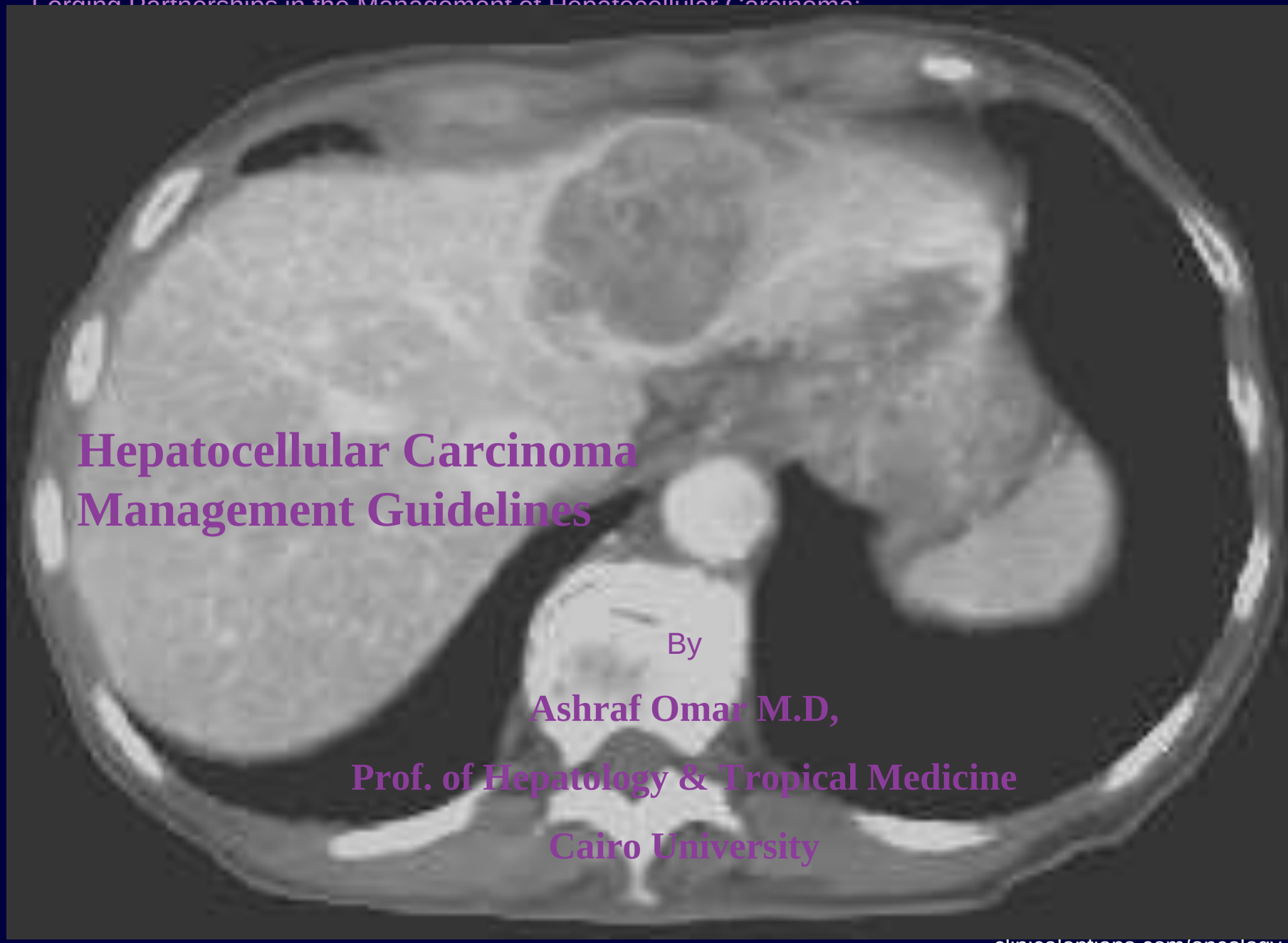


Hepatocellular Carcinoma Management Guidelines

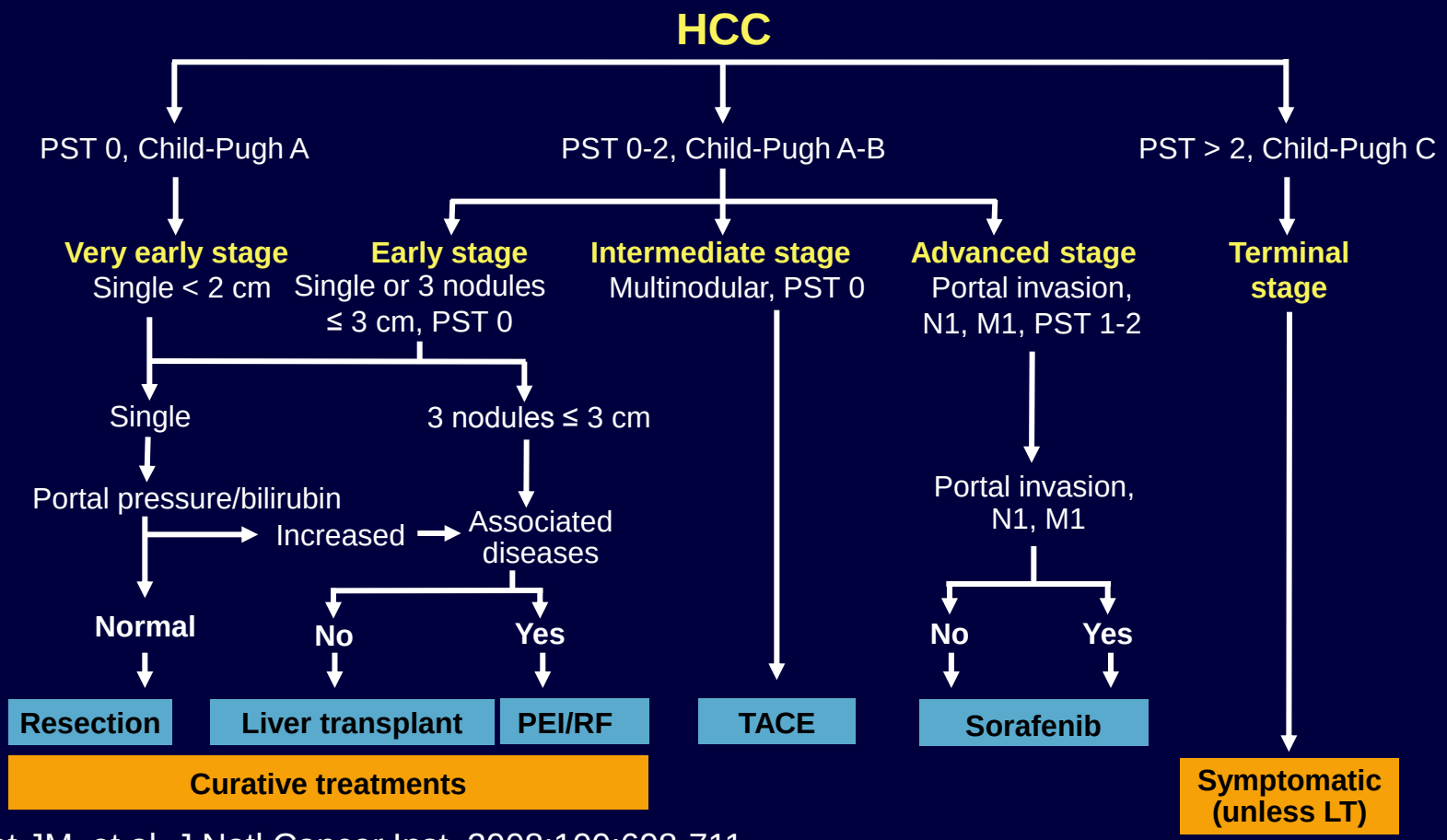
By

Ashraf Omar M.D,

Prof. of Hepatology & Tropical Medicine

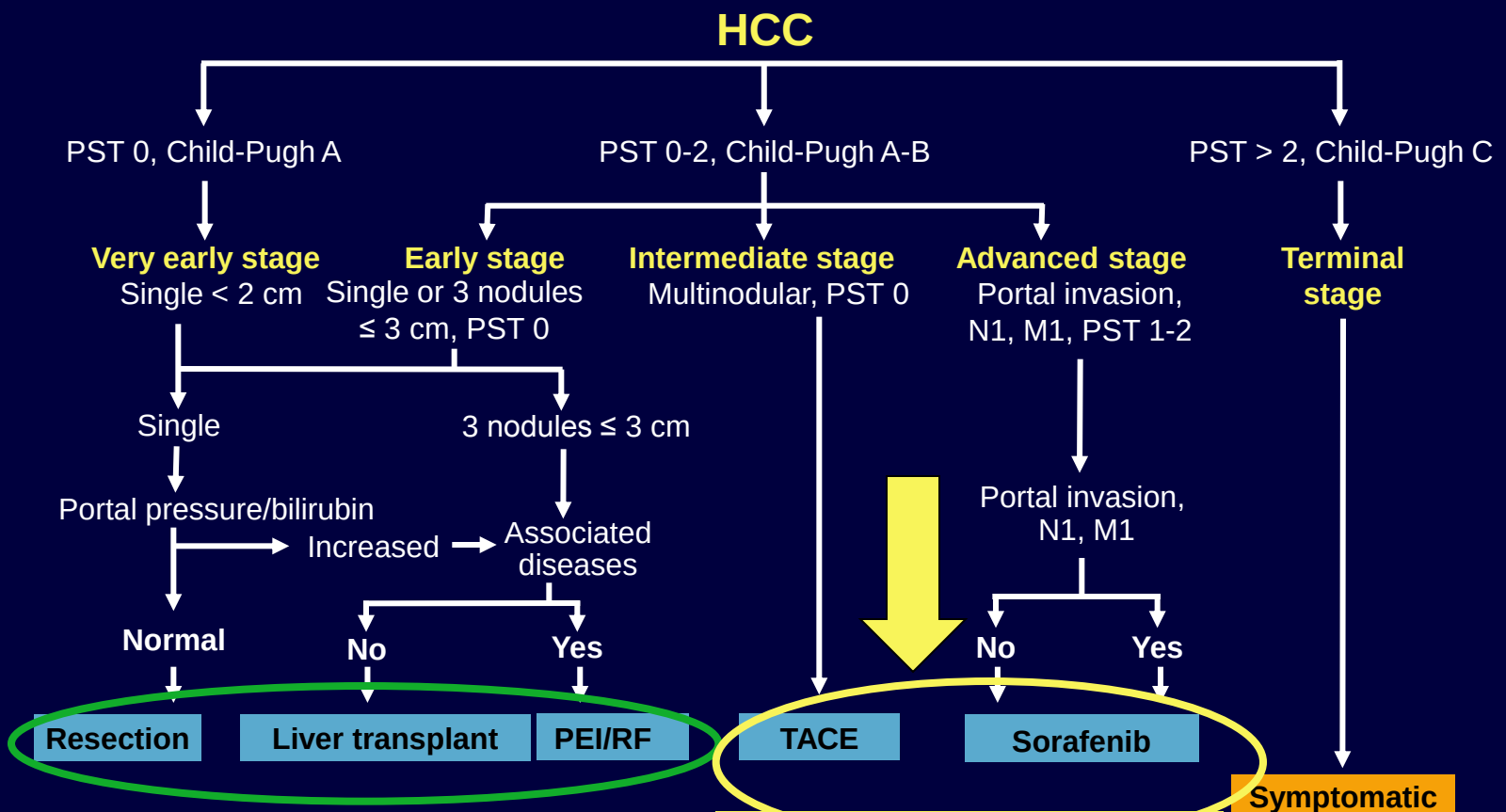
Cairo University

Staging Strategy and Treatment for Patients With HCC



Llovet JM, et al. J Natl Cancer Inst. 2008;100:698-711.
Bruix J, et al. Hepatology. 2005;42:1208-1236.

Staging Strategy and Treatment for Patients With HCC



Approved Curative Treatments for Unresectable HCC: Percutaneous Ablation

- Local ablation: safe and effective therapy for patients who cannot undergo resection or as a bridge to transplantation (level II)
- Alcohol injection and radiofrequency are equally effective for tumors < 2 cm
  - However, necrotic effect of radiofrequency is more predictable in all tumor sizes
  - In addition, efficacy is clearly superior to that of alcohol injection in larger tumors (level I)

Approved & Investigational Noncurative Agents for Unresectable HCC

- AASLD 2005 recommendations
  - Chemoembolization (TACE) (with doxorubicin, cisplatin, or mitomycin) is recommended as first-line, noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (and are not eligible for percutaneous ablation) (level I)
  - Tamoxifen, octreotide, antiandrogens, and hepatic artery ligation/embolization are not recommended (level I); other options such as drug-eluting beads, radiolabelled yttrium glass beads, radiolabelled lipiodol, or immunotherapy cannot be recommended as standard therapy for advanced HCC outside clinical trials

Bruix J, et al. Hepatology. 2005;42:1208-1236.

Treatment of Advanced HCC (BCLC Stage C)

- AASLD 2005 recommendation: no standard therapy; patients should enroll in a randomized clinical trial[1]
- 2008 recommendation: sorafenib has become the standard of care for advanced HCC[2]
  - Prolongs OS by 3 months[3]
  - 1-year survival: 44%[4]

1. Bruix J, et al. Hepatology. 2005;42:1208-1236.
2. Llovet JM, et al. J Hepatol. 2008;48:S20-S37.
3. Llovet J, et al. ASCO 2007. Abstract LBA 1.
4. Llovet J, et al. N Engl J Med. 2008;359:378-390.

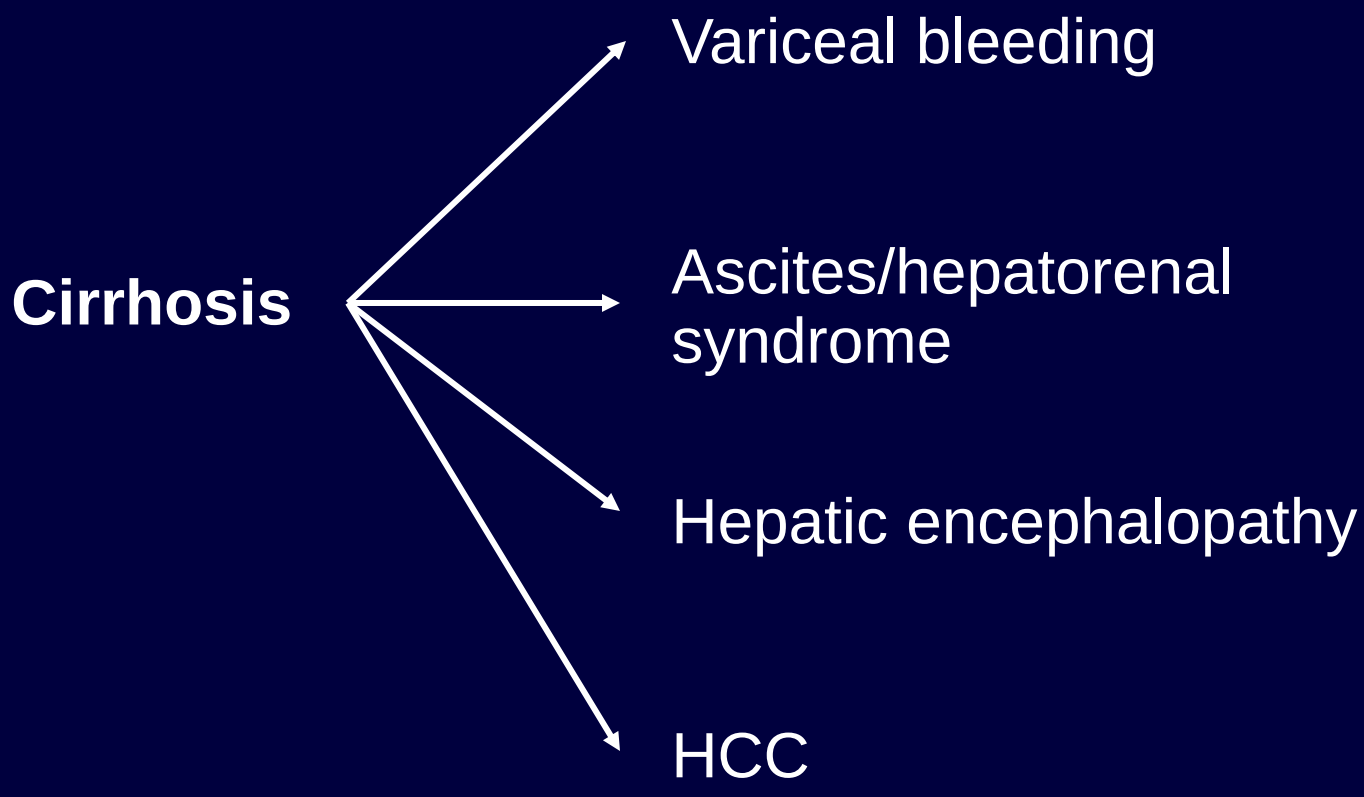
Intermediate/Advanced HCC: Future Directions

- 499 trials registered at clinicaltrials.gov for HCC as of August 21, 2008, including
  - Improving efficacy of RF and TACE (drug-eluting beads)
  - Exploring alternative treatments for intermediate HCC (yttrium-90)
  - Molecularly targeted agents in combination regimens (advanced HCC)
  - Molecularly targeted agents in combination with current modalities (early/intermediate HCC)
  - Improving tumor targeting of chemotherapeutic agents
  - New molecular targets and new molecularly targeted agents

Treatment of Liver Disease

- Hepatitis C: IFN + RBV
- Hepatitis B: IFN, lamivudine, adefovir, entecavir
- Alcohol: Abstinence
- Primary biliary cirrhosis: Ursodeoxycholic acid
- Hemochromatosis: Phlebotomy
- Alpha-1 ATD: None
- Nonalcoholic fatty liver: Diet and exercise
- Wilson’s disease: Zinc, trientene
- Sclerosing cholangitis: Ursodeoxycholic acid, biliary stents
- Autoimmune hepatitis: Immunosuppression

Complications of Cirrhosis



Management of HCC

- Liver transplantation
- Resection
- Tumor ablation
  - Radiofrequency thermal ablation
  - Alcohol injection
  - Chemoembolization
- Targeted molecular therapy
- Chemotherapy
  - Regional/systemic

Potentially curative

Evidence of Benefit in Treatment of HCC

Treatment	Benefit	Evidence
Surgical treatments		
Resection	Increased survival	Case series
▪ Adjuvant therapies	Uncertain	Randomized trial, meta-analysis, nonblinded
Liver transplantation	Increased survival	Case series
▪ Neoadjuvant therapies	Treatment response	Nonrandomized trials
Locoregional treatment		
Percutaneous treatment	Increased survival	Case series
RFA vs PEI	Better local control	Randomized trial, meta-analysis, nonblinded
Chemoembolization	Increased survival	Randomized trial, meta-analysis, nonblinded
Arterial chemotherapy	Treatment response	Case series
Internal radiation	Treatment response	Case series

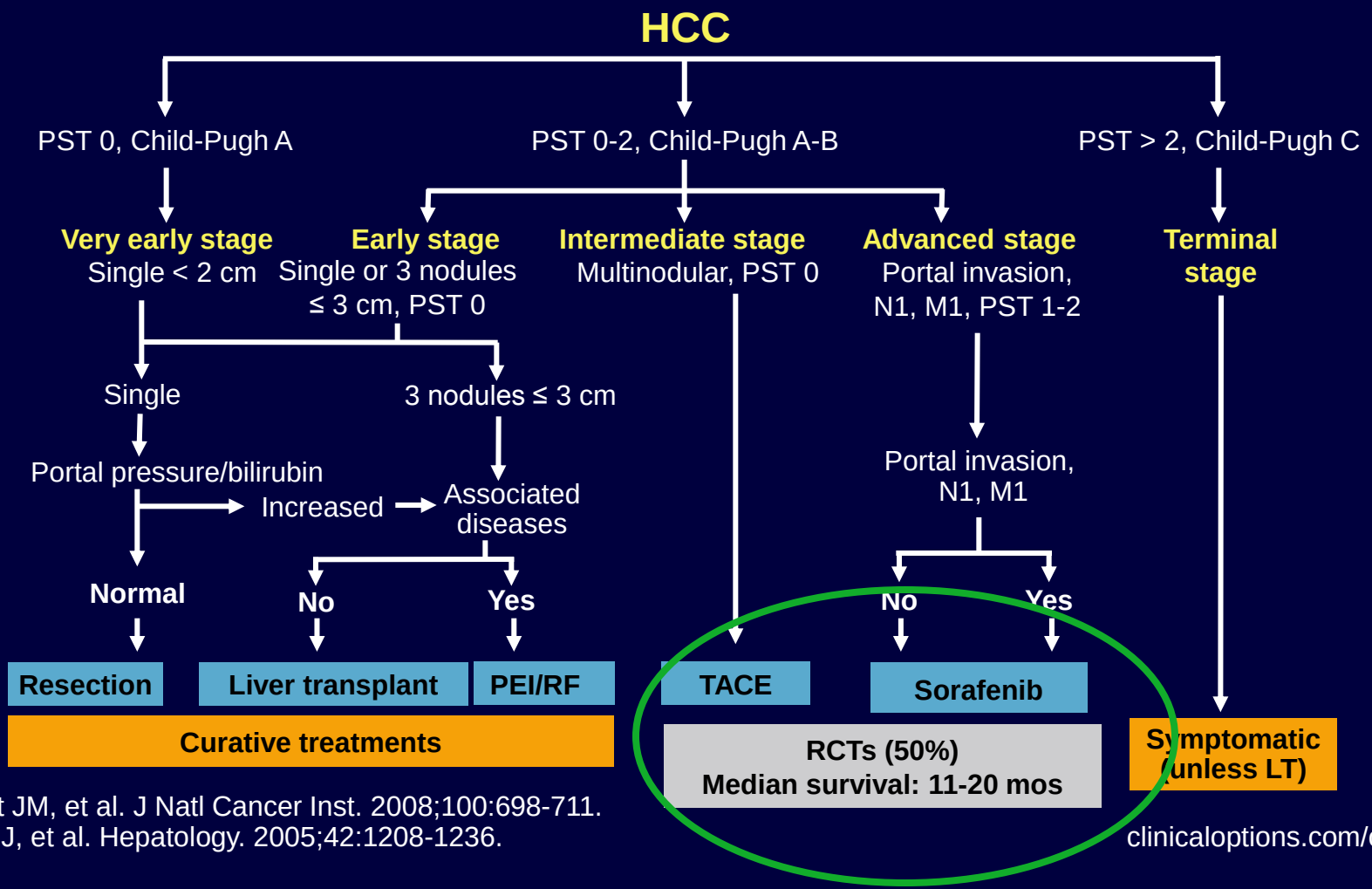
Llovet JM, et al. J Natl Cancer Inst. 2008;100:698-711.

Evidence of Benefit in Treatment of HCC (cont'd)

Treatment	Benefit	Evidence
Systemic therapies		
Sorafenib	Increased survival	Randomized trial, meta-analysis, double blinded
Tamoxifen	No benefit	Randomized trial, meta-analysis, double blinded
Chemotherapy	No benefit	Randomized trial, meta-analysis, nonblinded
IFN	No benefit	Randomized trial, meta-analysis, nonblinded

Llovet JM, et al. J Natl Cancer Inst. 2008;100:698-711.

Staging Strategy and Treatment for Patients With HCC



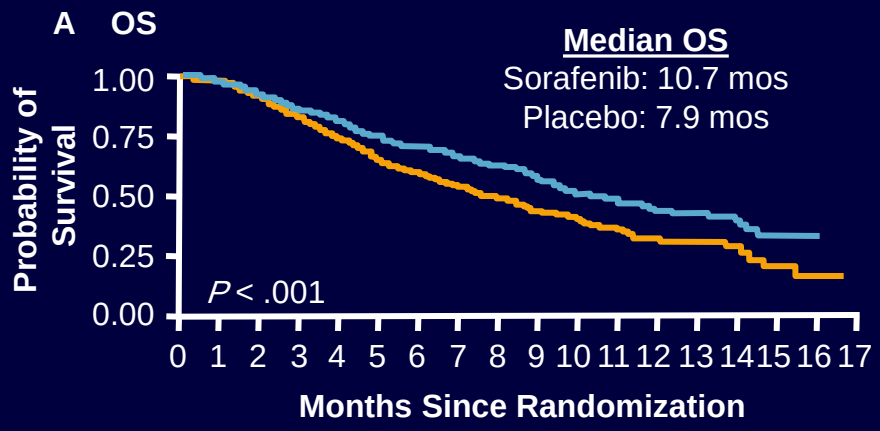
Llovet JM, et al. J Natl Cancer Inst. 2008;100:698-711.
Bruix J, et al. Hepatology. 2005;42:1208-1236.

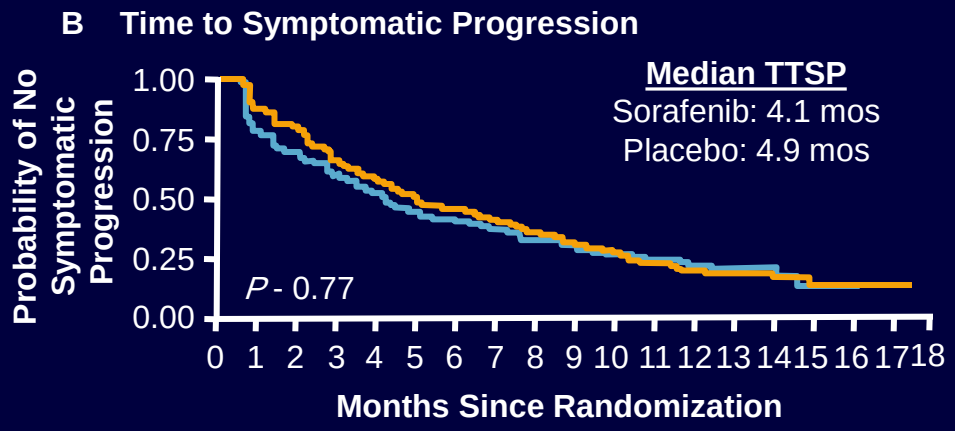
Sorafenib in Advanced HCC: The SHARP Trial

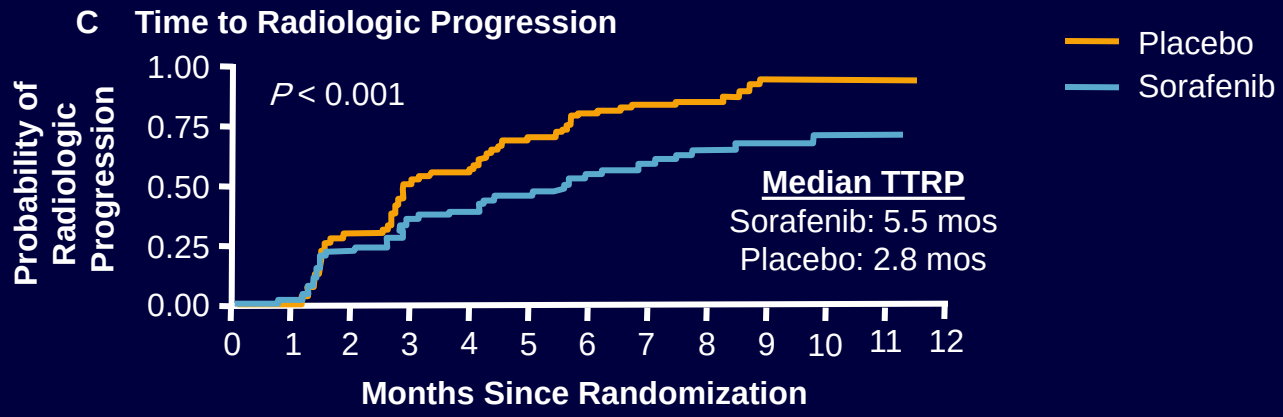
- Entry criteria
  - Advanced HCC
    - Not eligible for or failed surgical or locoregional therapies
  - Child-Pugh class A disease
  - At least 1 untreated target lesion
  - Exclusions
    - Previous chemotherapy
    - Previous molecularly targeted therapy

Llovet JM, et al. N Engl J Med. 2008;359:378-390.

The SHARP Trial: OS and Time to Progression







Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.

Strategies for Managing AEs

- Hand-foot syndrome
  - Creams and lotions
  - Avoid tight footwear
  - May require dose reduction
- Diarrhea
  - Antidiarrheal agents if severe
- Fatigue
  - Consider modafinil or methylphenidate if severe
- Hypertension
  - Start or adjust antihypertensives

Intra-arterial Locoregional Therapy

- Established
  - TACE
  - Radioembolization: yttrium-90 radioactive microspheres
- Undergoing clinical trials
  - Drug-eluting beads

Chemoembolization: Randomized Trials (Nearly Identical Techniques)

Lo et al[1]: N = 80 with newly diagnosed unresectable HCC, 80% HBV positive, 7-cm tumors (60% multifocal)

Technique	Survival, %		
	Year 1	Year 2	Year 3
TACE	57	31	26
Supportive care	32	11	3

Llovet et al[2]: N = 112 with unresectable HCC, 80% to 90% HCV positive, 5-cm tumors (~ 70% multifocal)

Technique	Survival, %	
	Year 1	Year 2
TACE	82	63
Supportive care	63	27

1. Lo CM, et al. Hepatology. 2002;35:1164-1171.
2. Llovet JM, et al. Lancet. 2002;359:1734-1739.

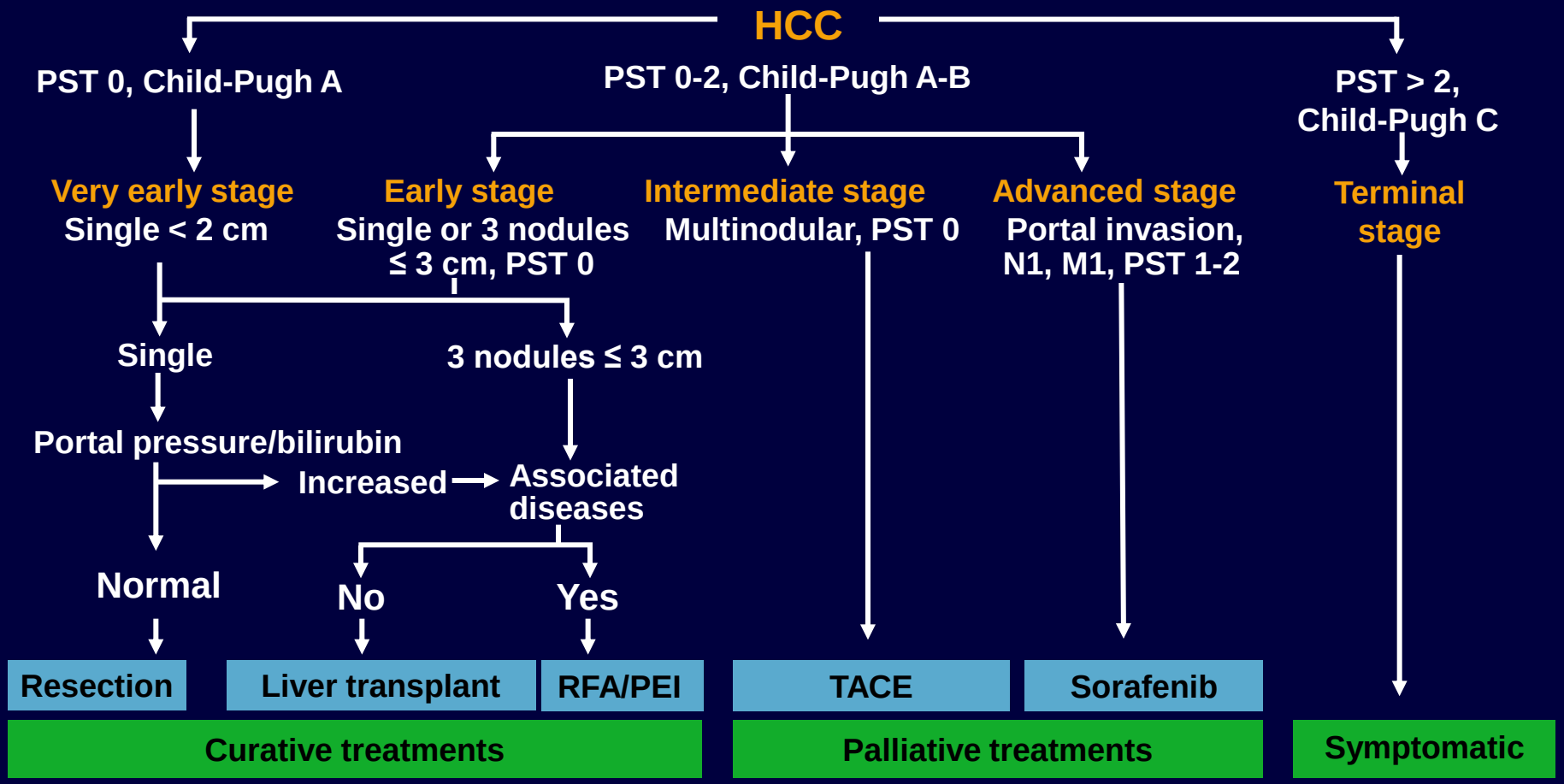
Chemoembolization: Ineligibility Criteria

- Absolute contraindications
  - Child-Pugh class C disease
  - Poor performance status (ECOG PS > 2)
- Relative contraindication
  - Extrahepatic disease (benefit unclear)
- Former contraindication
  - PVT
    - Minimize embolization and be more selective

Conclusions

- TACE accepted as treatment of choice for unresectable (nonablatable?) HCC
- Prolonged survival established through randomized trials and prospective studies
- Best vs good performance status, Child-Pugh class A-B
- Role for yttrium-90 microspheres
- Growing role for doxorubicin-loaded beads, pending outcome of clinical trials

AASLD Guidelines: Staging Strategy and Treatment for Patients With HCC



Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects.Semin Liver Dis. 2010;30(1):61-74 (reprinted by permission).

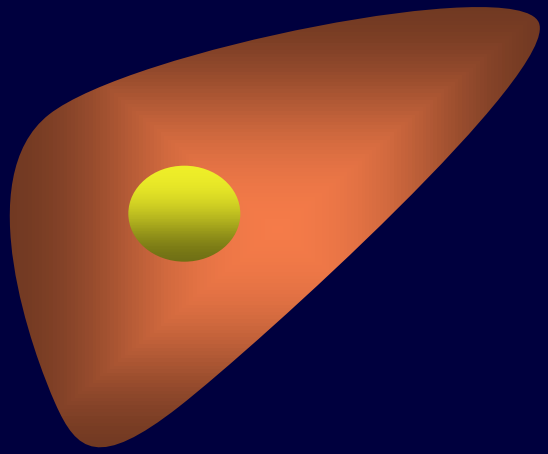
- WHY LT for HCC?

- LT is attractive because both the tumour as well as cirrhosis presents in 50-90% which is the fertile soil for the development of new lesions are removed by this procedure

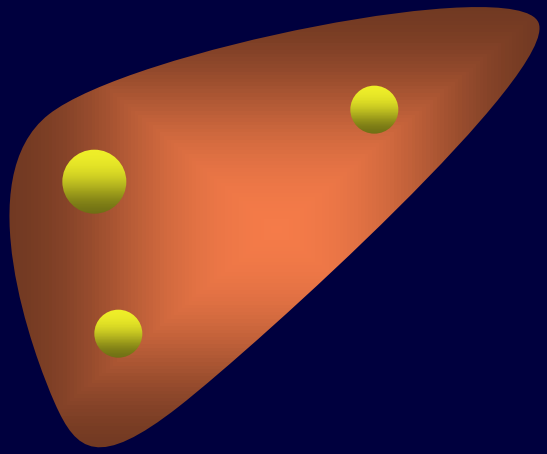
- What should be a suitable criteria for liver transplantation for HCC?

Liver Transplantation for HCC: Milan Criteria (Stage 1 and 2)

Single tumor, not > 5 cm



Up to 3 tumors, none > 3 cm



+

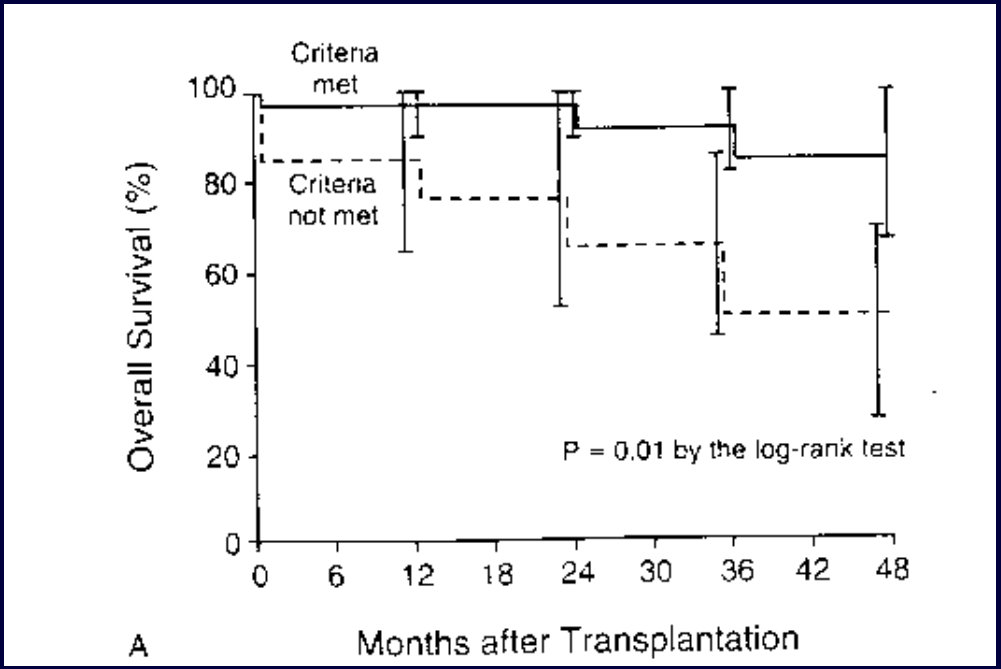
Absence of macroscopic vascular invasion, absence of extrahepatic spread

Mazzaferro V, et al. N Engl J Med. 1996;334:693-699.

Current indications

Mazzafero et al. N Engl J Med 1996

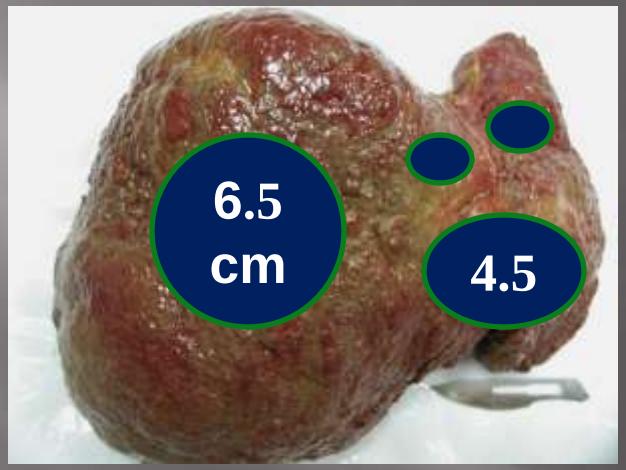
- Single tumour < 5 cm
  ou ≤ 3 nodules < 3 cm
- No portal thrombosis
- Overall survival
  1-year : 90 %
  4-year : 75 %
- Recurrence : 8 %



Survival according the Milan's Criteria on the explanted liver

- Can we expand the Milan criteria for hepatocellular carcinoma in liver transplantation?

UCSF Criteria



Total ≤ 8 cm

* **Explant pathology: *Criticised***

* **Clinical applicability**

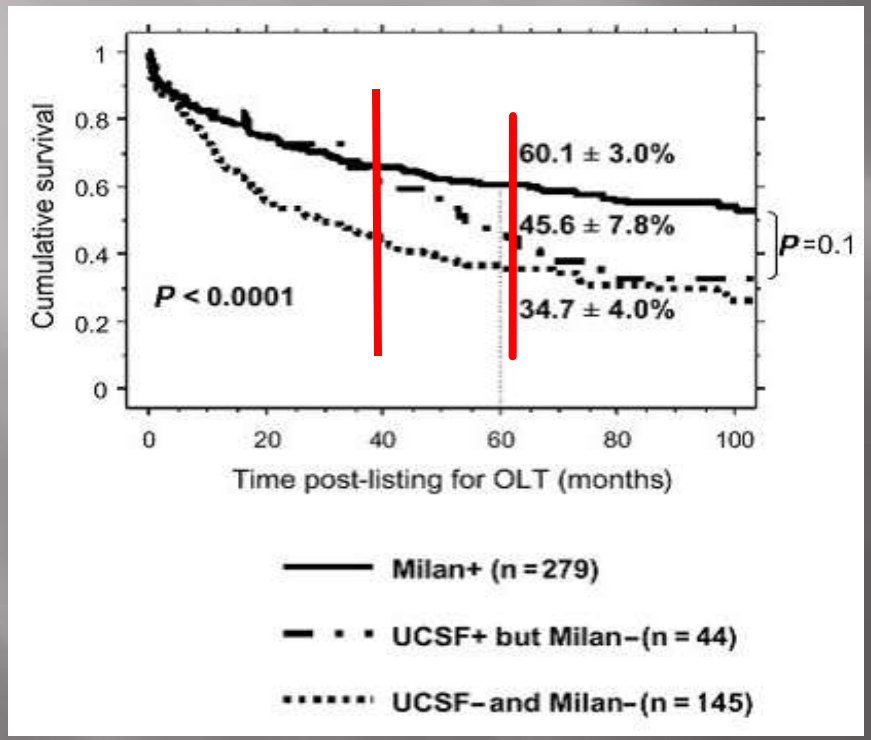
UCSF Criteria

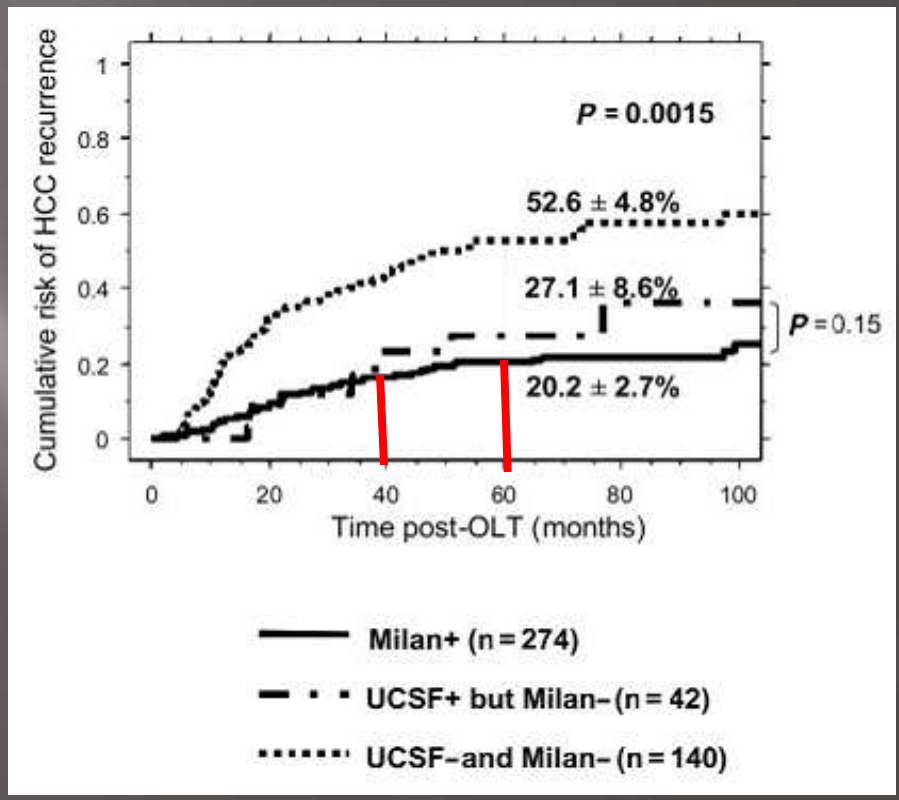
Results:

- **Tumors within UCSF criteria**
  - **1 yr survival 90%**
  - **5 yr survival 75%**

- **Tumors outside UCSF criteria**
  - **1 yr survival 50%**
  - **5 yr survival < 30%**

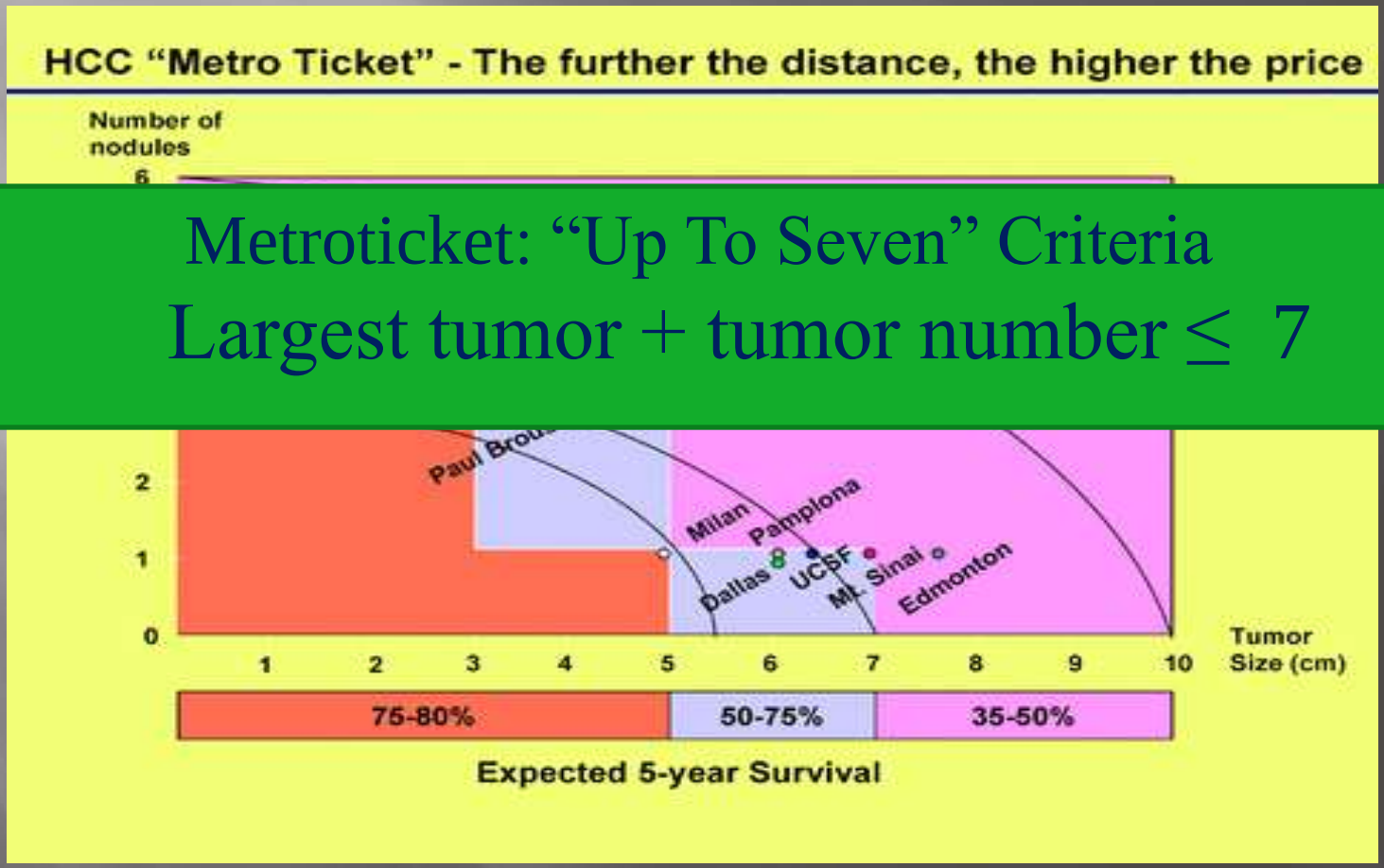
Milan & UCSF Criteria
Radiologic Staging





Decaens et.al. Liver Transpl, 2006

Beyond Milan Criteria–HCC "Metro Ticket"

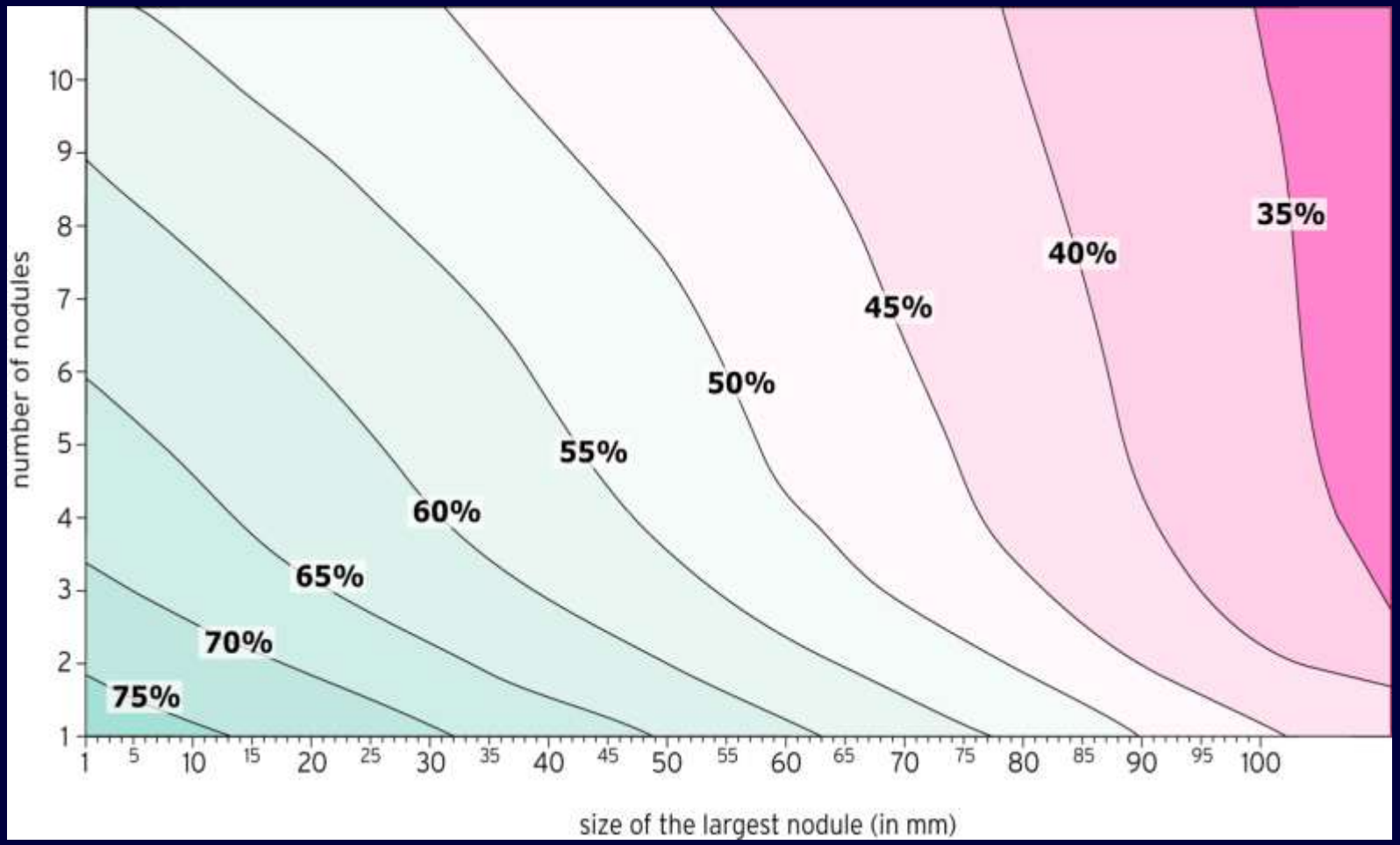


Metroticket: "Up To Seven" Criteria

Largest tumor + tumor number ≤ 7

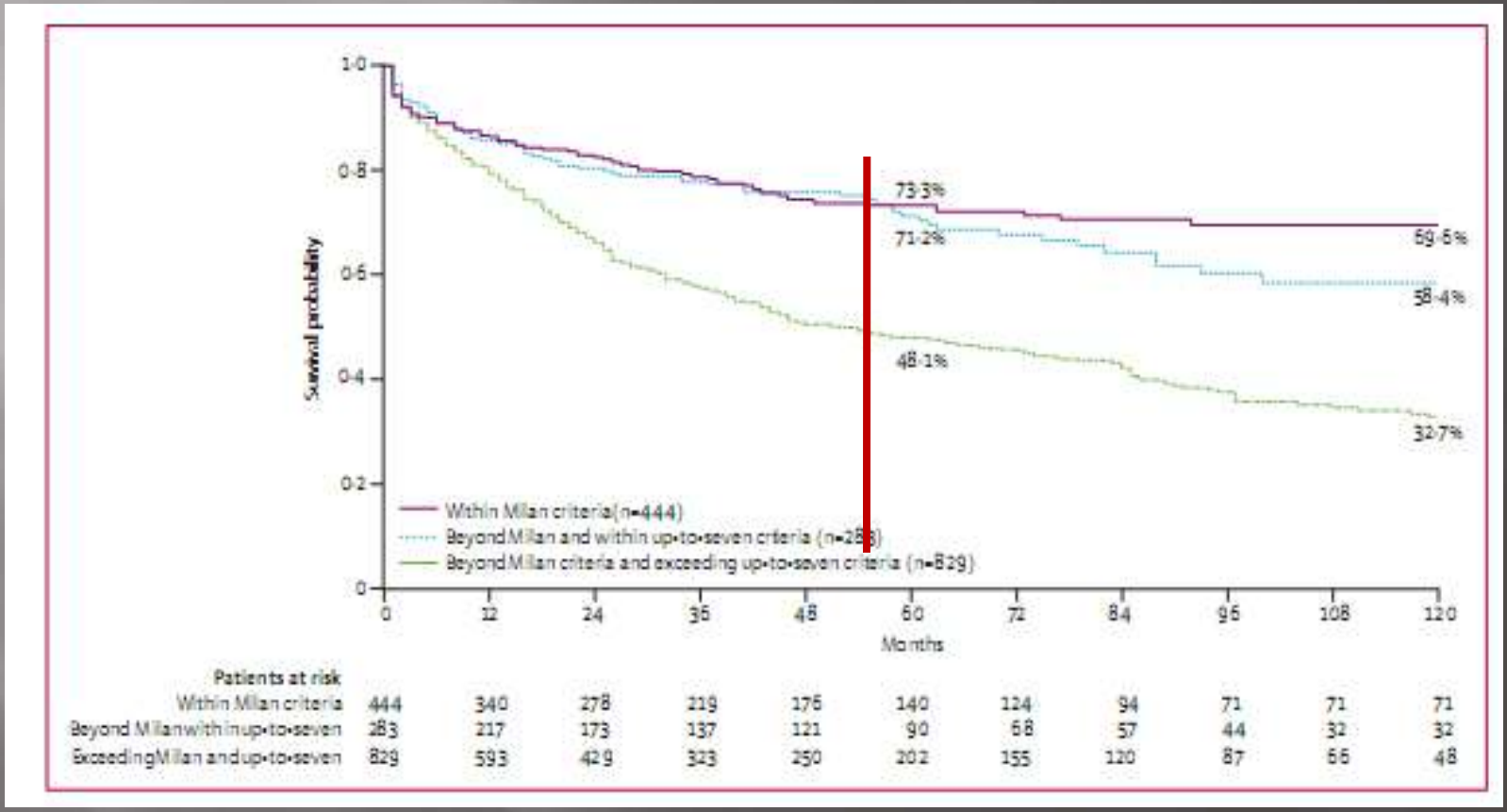
Mazzafero, et. al. Lancet Oncol, 2009

Liver transplantation for HCC

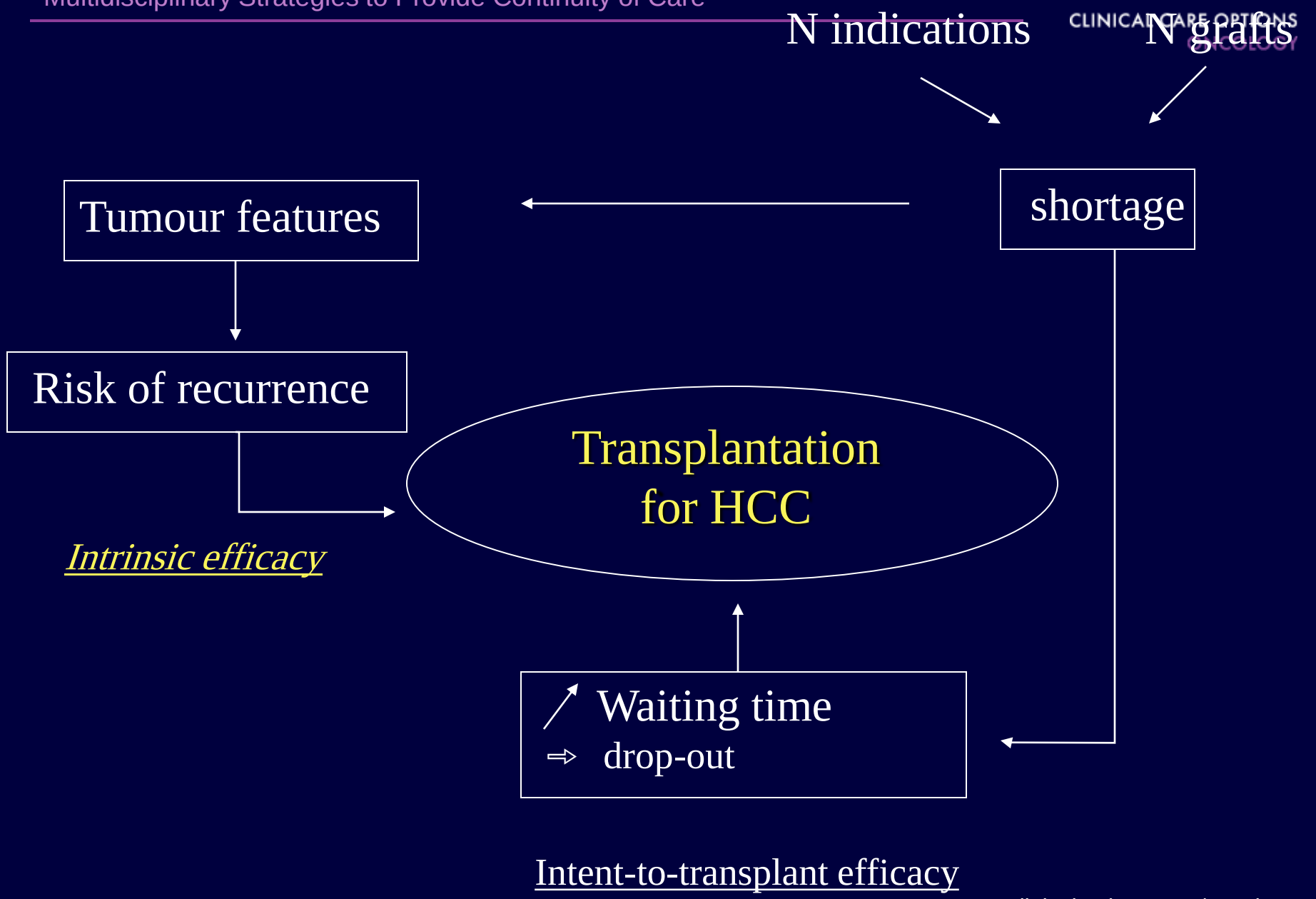


Mazzaferro V, et al. Lancet Oncol. 2009;10:35-43.

Milan vs “Up to 7”



Mazzafero, et. al. Lancet Oncol, 2009


N indications
N grafts
shortage
Tumour features
Risk of recurrence
Transplantation for HCC
Intrinsic efficacy
Waiting time
drop-out
Intent-to-transplant efficacy

Definitions

- Neoadjuvant treatment.
- Bridging
- Downstaging

- Downstaging

lowering the stage to allow for transplannation for patients who when firsty seen don’t qualify fro LTx

- Bridging

Strategy to allow patient to wait for a longer time without progression

TACE RFA

- Neoadjuvant treatment.

Treatment before a procedure to improve outcome

- TACE

-RFA

Excellent outcome following down-staging of HCC prior to liver transplantation: an intention-to-treat analysis

Criteria for downstaging

- 1 lesion > 5 cm and up to 8 cm
- 2–3 lesions with 1 or more lesions > 3 cm and not > 5 cm, with total tumor diameter up to 8 cm
- 4–5 lesions with none > 3 cm, with total tumor diameter up to 8 cm

Yao FY, et al. Hepatology. 2008;48:819-27.

Excellent outcome following down-staging of HCC prior to liver transplantation: an intention-to-treat analysis

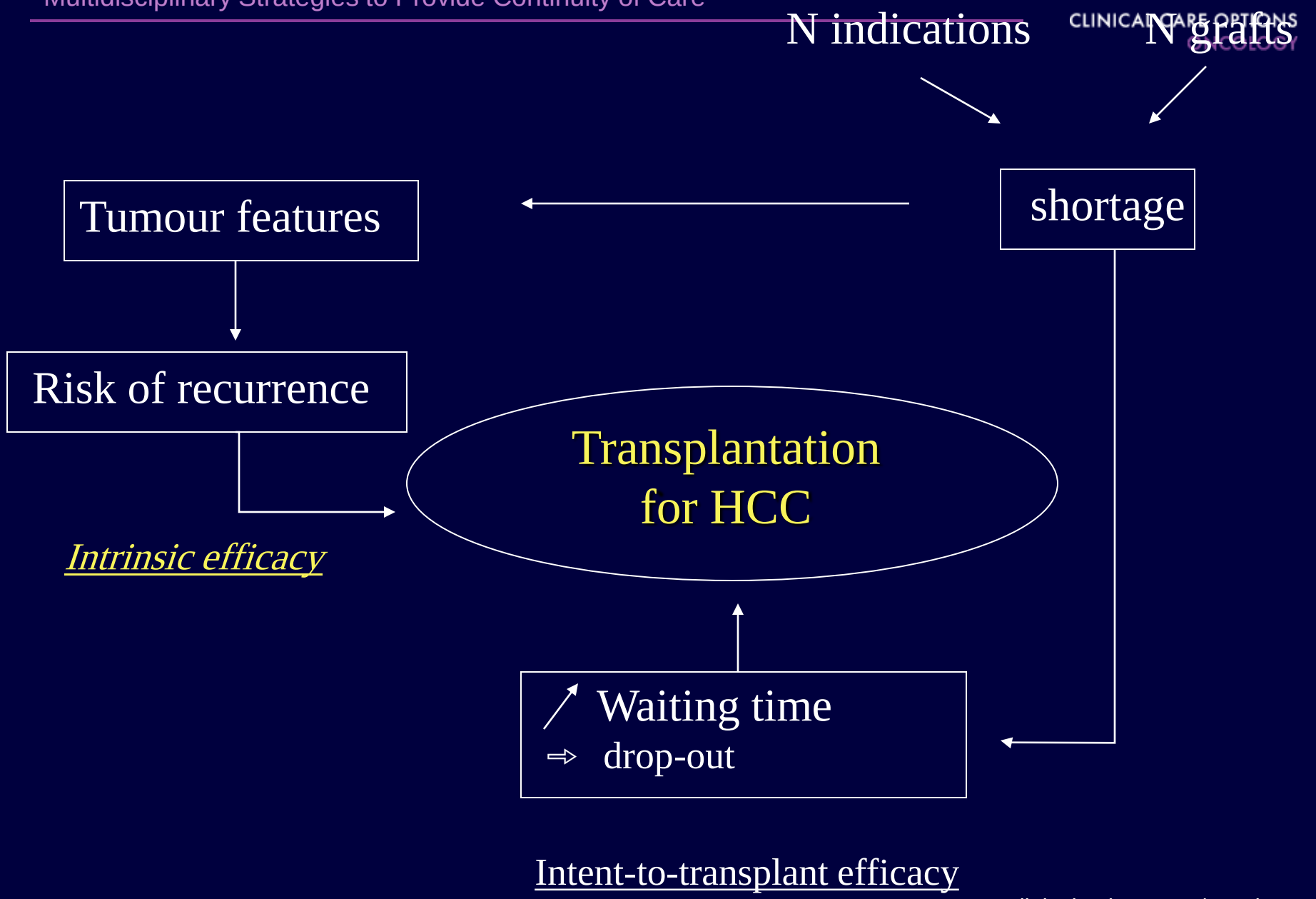
Table 4. Down-Staging Treatments Received by the 61 Patients

Treatment	No. of Patients (No. of Treatments)
Laparoscopic/open RFA only*	11 (11)
TACE only	15 (34)
TACE + percutaneous ablation	15 (54)
TACE + percutaneous ethanol ablation	6 (27)
TACE + percutaneous RFA	9 (27)
Laparoscopic RFA + TACE	14 (34)
Resection†	6 (6)

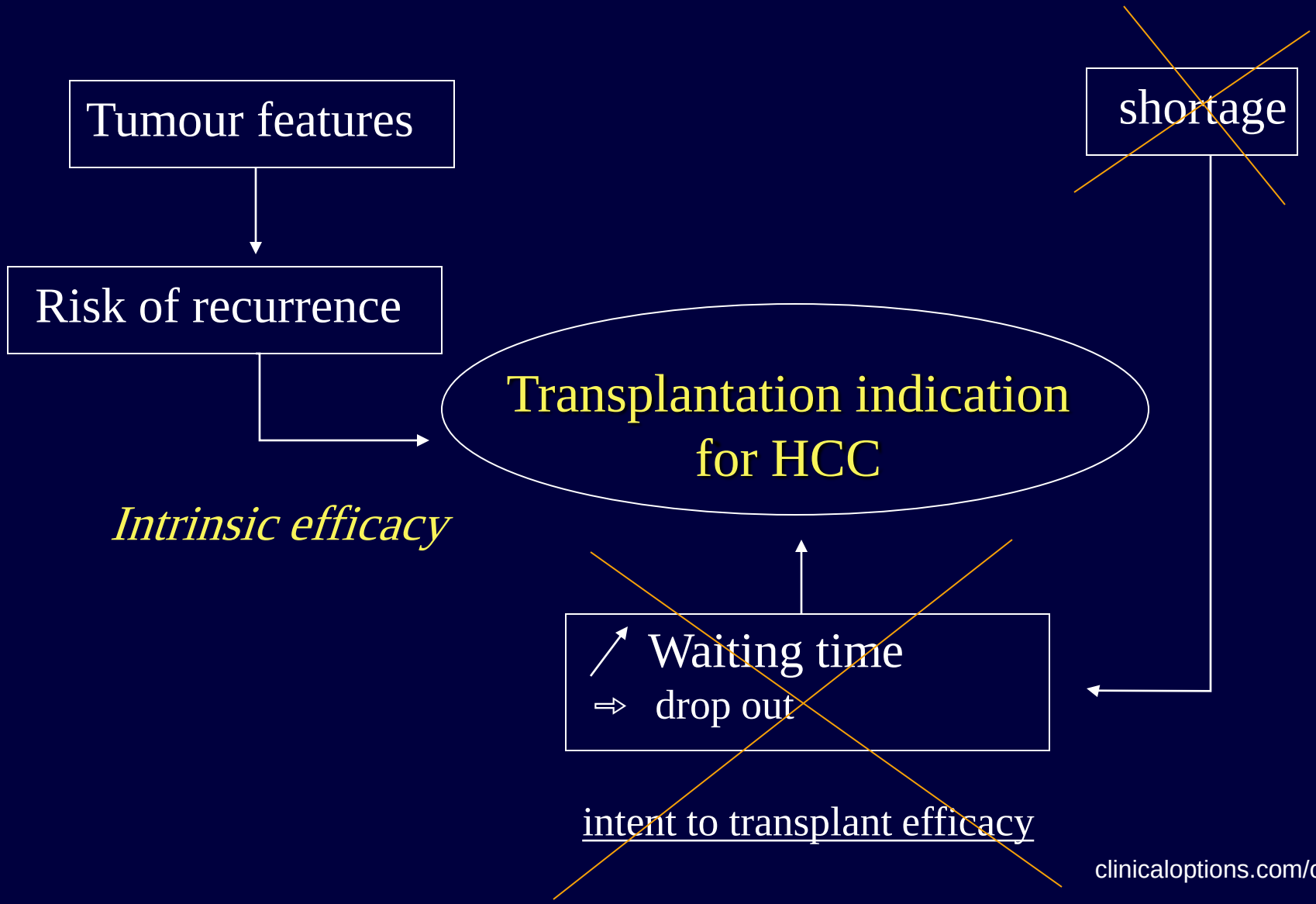
*Two received open RFA, nine received laparoscopic RFA.

†One of these patients underwent resection despite a high preoperative CTP score of 11. This patient had a 5.3-cm lesion very close to the liver surface at risk for rupture. The other five patients had a CTP score of ≤7 before resection.

Yao FY, et al. Hepatology. 2008;48:819-27.


N indications
N grafts
shortage
Tumour features
Risk of recurrence
Transplantation for HCC
Intrinsic efficacy
Waiting time
drop-out
Intent-to-transplant efficacy

Living donor transplantation and HCC



Is LDLT for HCC as efficacious as DDLT ?

Is LDLT for HCC as efficacious as DDLT ?

PRO

Thuluvath PJ, Yoo HY. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. Liver Transpl 2004;10:1263-8.

Lo CM, Fan ST, Liu CL, et al. The role and limitation of living donor liver transplantation for hepatocellular carcinoma. Liver Transpl 2004;10:440-7.

CON

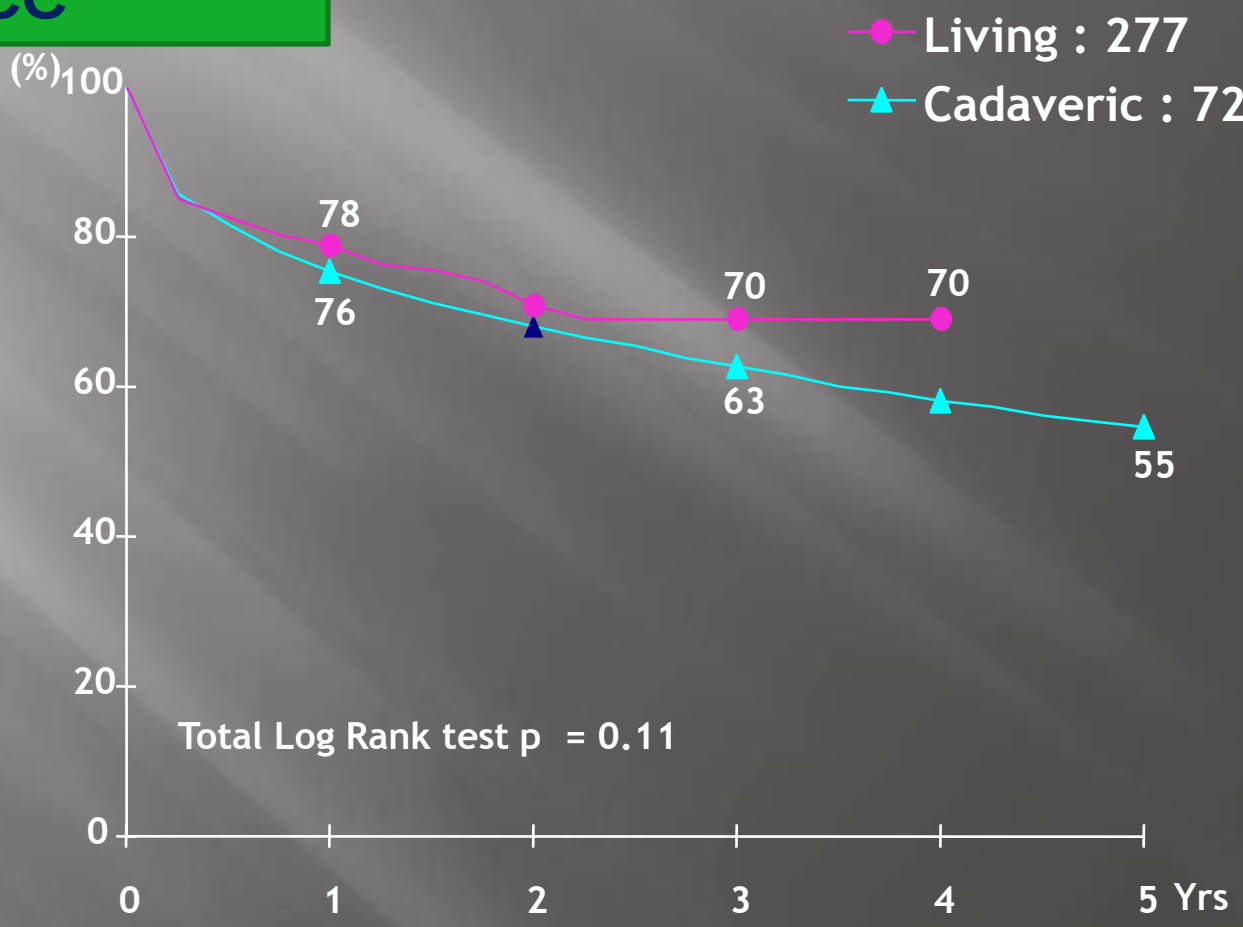
Fisher RA, Kulik LM, Freise CE, et al. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant 2007;7:1601-8.

Lo CM, Fan ST, Liu CL, et al. Living donor versus deceased donor liver transplantation for early irresectable hepatocellular carcinoma. Br J Surg 2007; 94:78-86.

Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology 2004;127(5 Suppl 1):S277-82.

Is LDLT for HCC as efficacious as DDLT ?

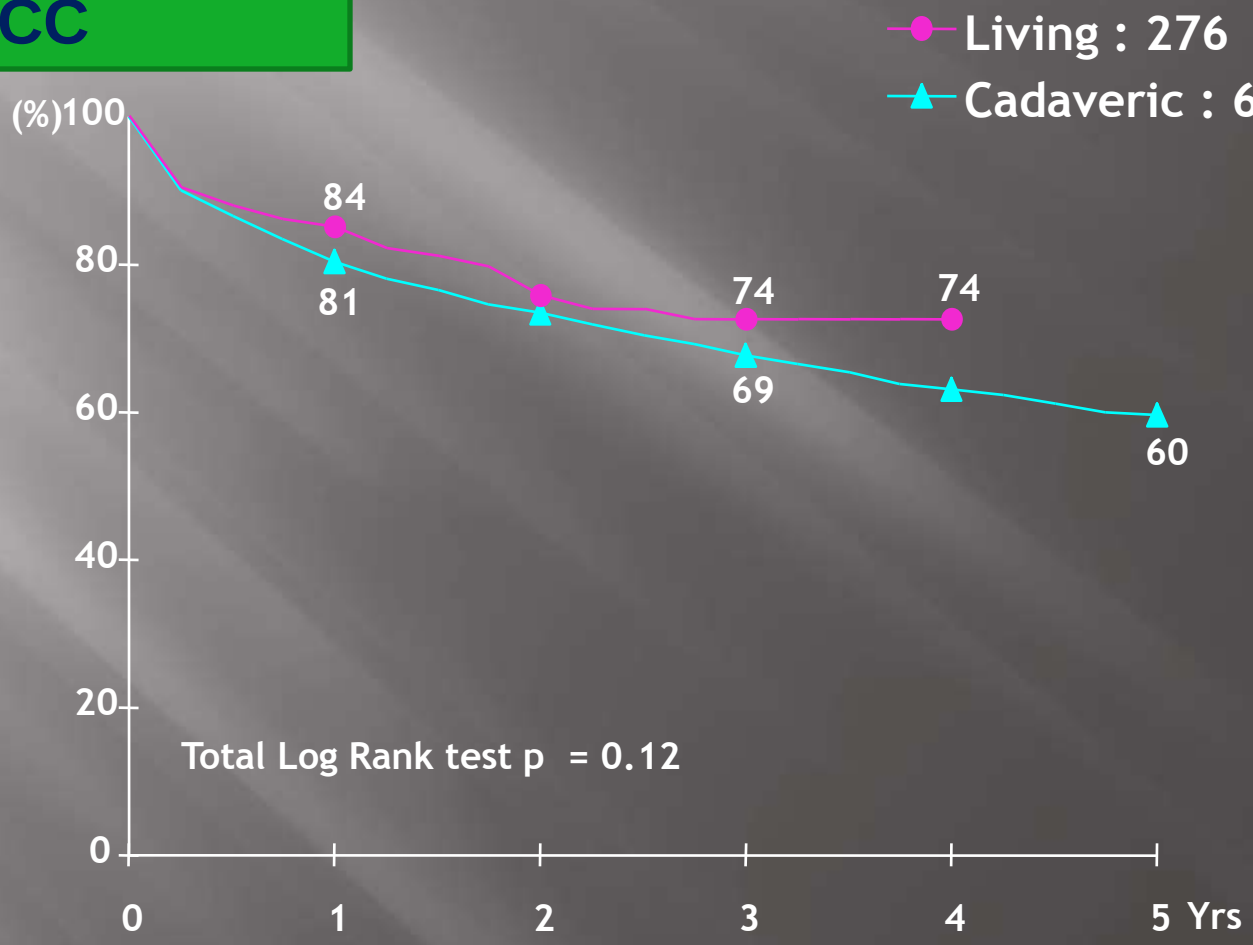
Graftsurvival in HCC



ELTR

Is LDLT for HCC as efficacious as DDLT ?

Patients survival in HCC



ELTR

Predictors of Recurrence after LT

1.L.N involvement

2.gross vascular invasion (angio / CT)

3.microscopic invasion (in the specimen)

4.> 5cm

5.multiple lesions

6.infiltrating rather than circumscribed lesion

7. More than one lobe

8.pTNM staging

How to Minimize Risk of Recurrence ?

- **HCC biology**
- **Refinement of immunosuppression: “ mTOR” ?**
- **Radiologic identification of VI**
- **Prospective multicenter RCT: is the key.**

Conclusion

- HCC patients exceeding Milan criteria can still be cured ; nodules 5-7cm and with no gross vascular invasion >> good survival & higher recurrence rate.
- HCC is a prime indication for LDLT ...>.lower dropout ,extending the acceptance of HCC for LT without waiting for cadaveric LT.
- However is no consensus on the use of LDLT for HCC due to lack of adequate data

Thank You