Hepatocellular Carcinoma:
Treatment Options Outside of Transplant

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No disclosures

Learning objectives

- Identify treatment options for HCC when transplant is not an option.
- Describe the various bridging techniques for individuals with HCC awaiting liver transplantation.
- Discuss the impact of bridging treatments on the recurrence of HCC and survival after liver transplantation.

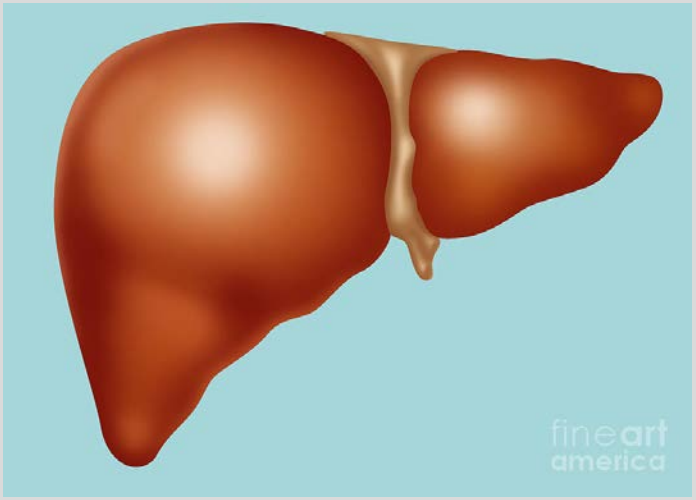
HCC: Treatment Options Outside of Transplant

- Epidemiology of HCC
- Therapeutic decision-making in HCC
- History of liver transplantation for HCC
- Defining transplant criteria for transplant
  - Milan criteria
  - “Beyond Milan”
- Downstaging and bridging therapies for HCC
  - Ablation
  - Arterial-based therapies
  - Radiation therapy
- Outcomes of liver transplantation for HCC

Epidemiology of HCC

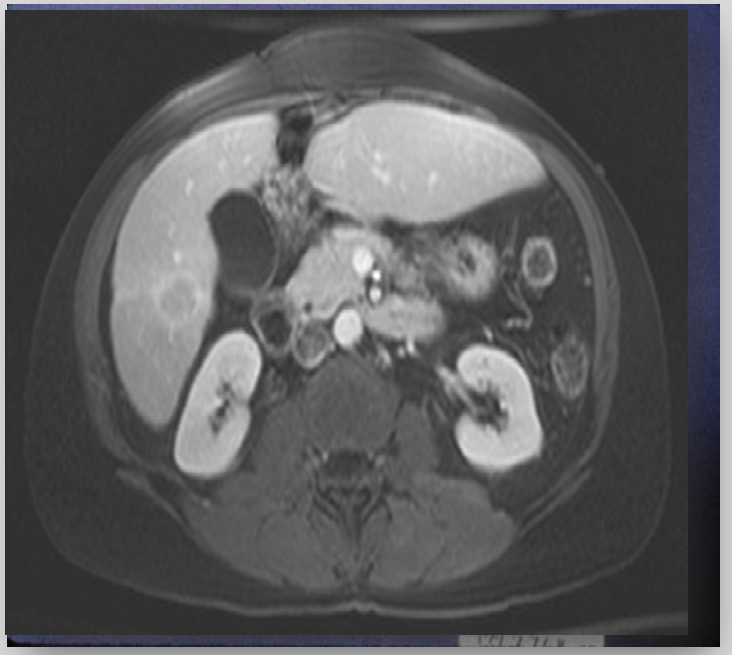
Hepatocellular Carcinoma

- Most common primary hepatic malignancy
- Typically (85%) arises in the setting of cirrhosis or chronic hepatitis



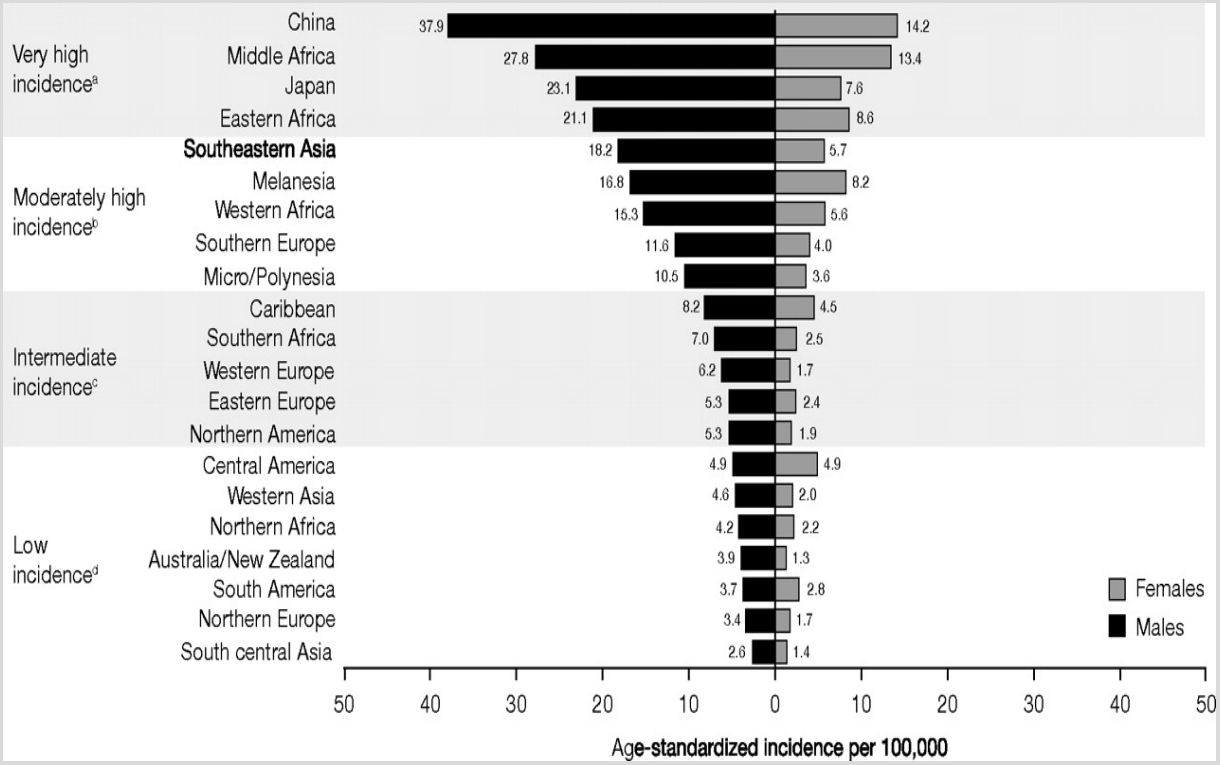
Chronic Hepatitis

Chronic inflammation + fibrosis

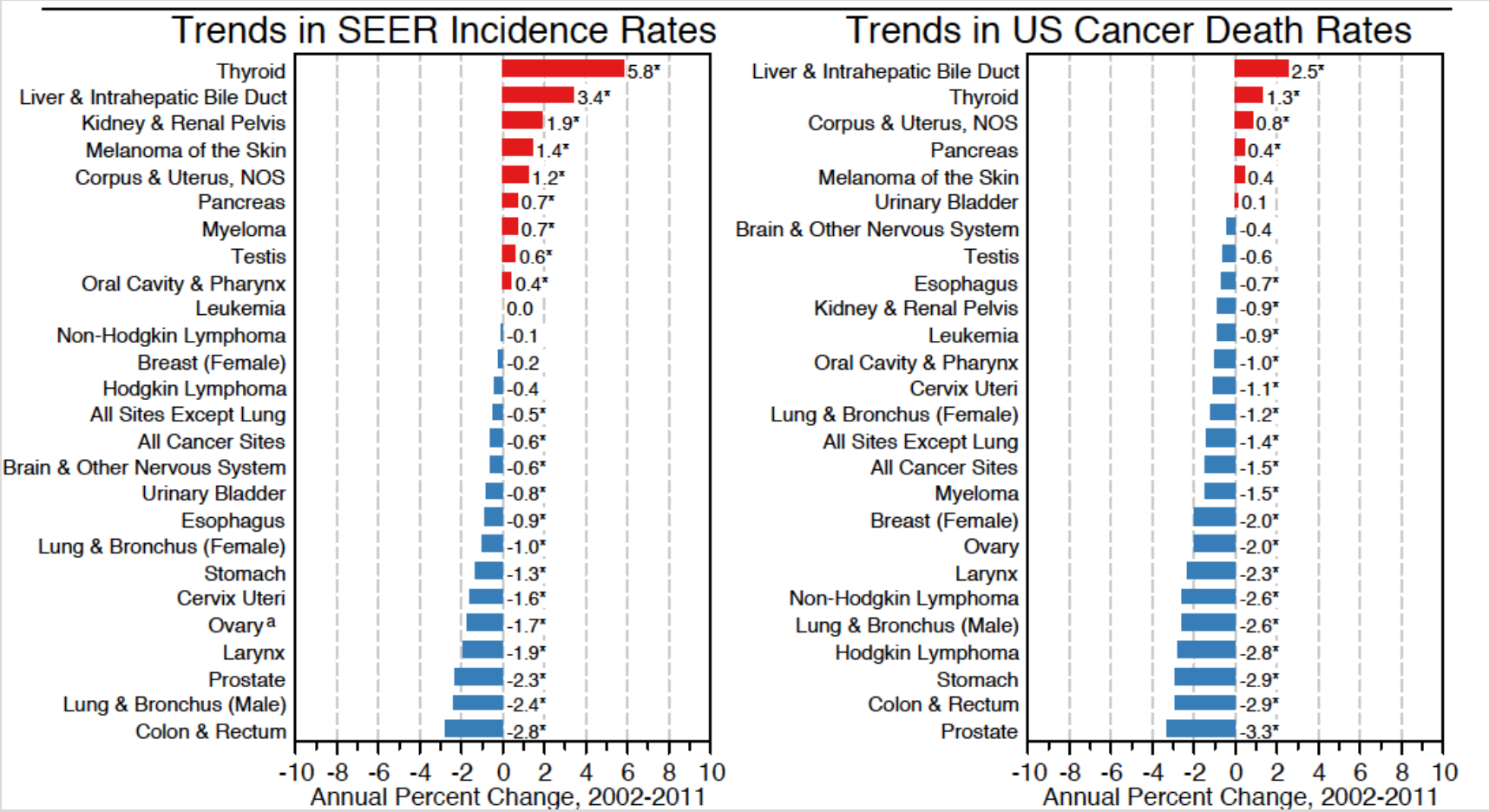


International HCC Epidemic

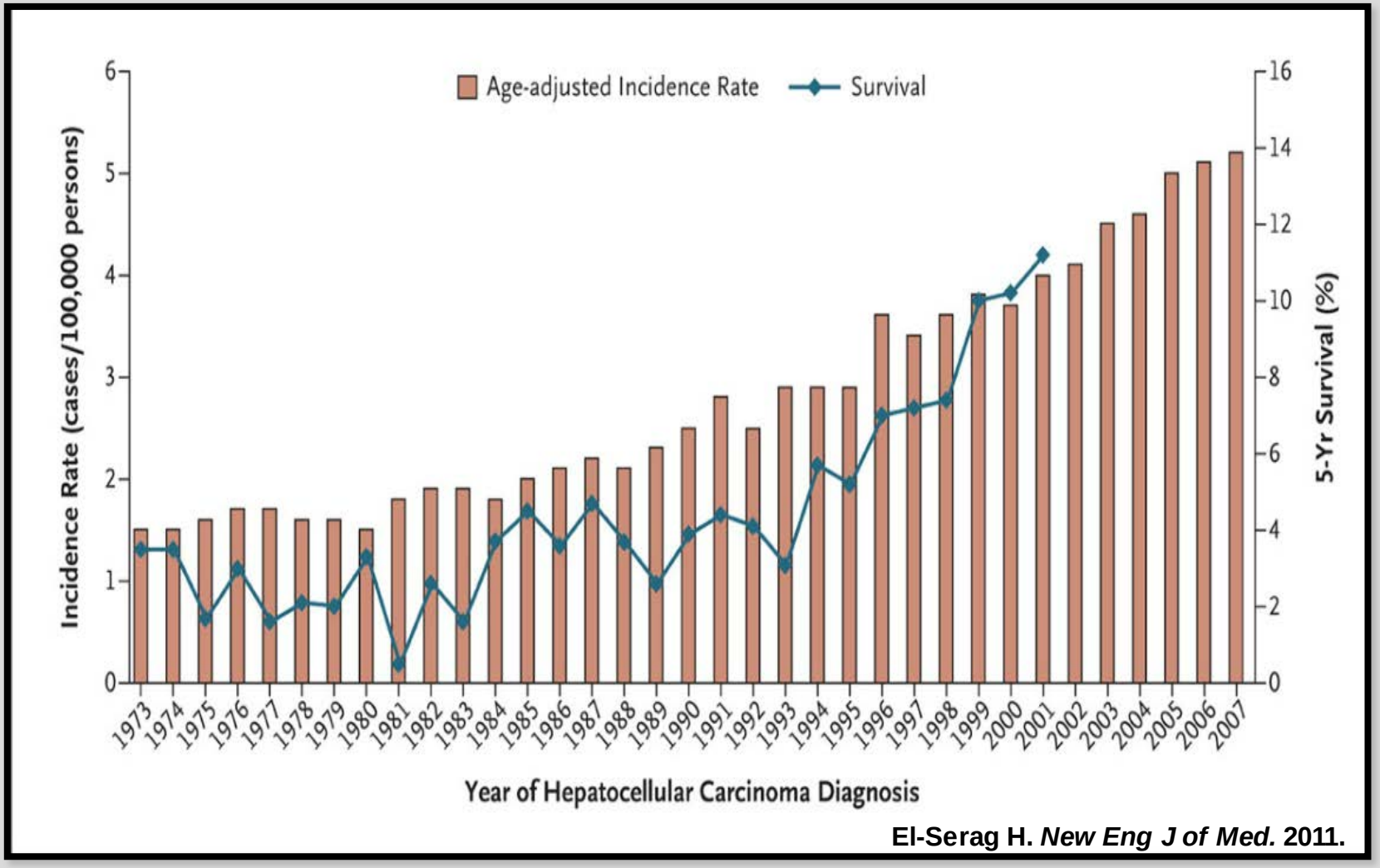
- 3rd most deadly cancer worldwide
- 8th leading cause of cancer death in the US
- Estimated peak incidence in the US will be in 2020?



Increasing Incidence of Liver Cancer (HCC and CCA)



HCC Incidence and 5-yr Survival: 1970s to 2000s



El-Serag H. *New Eng J of Med.* 2011.

Does etiology of liver disease affect HCC risk?

Table 3. Groups for whom HCC surveillance in recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated

Population group	Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)	Incidence of HCC
Surveillance recommended		
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

Bruix and Sherman, *Hepatology.* 2010.

HCV

Table 2. Overall Hepatocellular Carcinoma Incidence Rates in Longitudinal Studies of Patients With Chronic Hepatitis C Infection According to Clinical Setting and Geographic Area

Clinical setting	Geographic area	No. studies	References[a,b]	No. patients	Mean follow-up (y)	HCC incidence[c]	95% Confidence interval
Chronic hepatitis[d]	Europe	1	30	329	4.2	0	—
	Japan	6	31–36	1451	6.2	1.8	1.50–2.05
	Taiwan	1	37[e,f]	553	9.2	0.3	0.16–0.46
Compensated cirrhosis[g]	Europe and United States	13	5, 8, 30, 38–47	1284	4.5	3.7	3.20–4.17
	Japan	7	32, 34, 35, 48–51	626	5.8	7.1	6.19–7.96

HBV

Table 4. Overall Hepatocellular Carcinoma Incidence Rates in Longitudinal Studies of Patients With Chronic Hepatitis B Infection According to Clinical Setting and Geographic Area

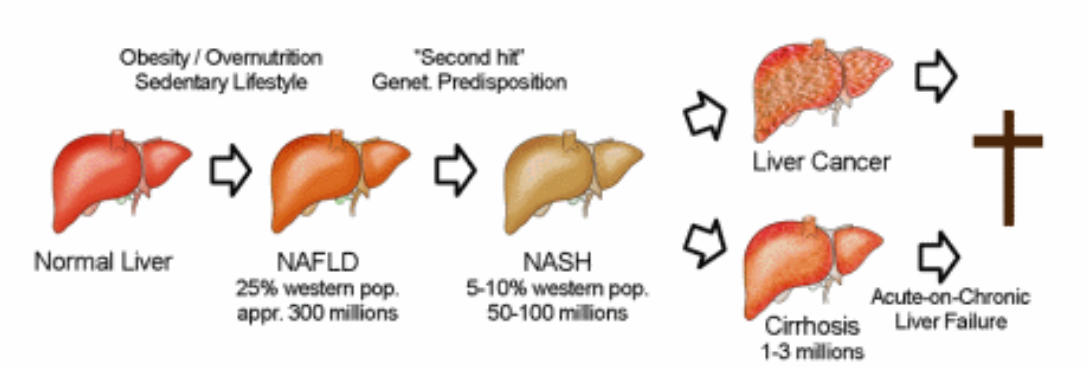
Clinical setting	Geographic area	No. studies	References[a,b]	No. patients	Mean follow-up (y)	HCC incidence[c]	95% Confidence interval
Asymptomatic carrier	North America	2[d]	74, 75	1804	16	0.1	0.07–0.14
	Taiwan and China	4[e]	37, 76–78	18,869	8	0.7	0.61–0.70
	Japan	1[f]	79	513	7.3	0.2	0.08–0.39
Inactive carrier[g]	Europe	3	80–82	410	16	0.02	0–0.04
	Taiwan	1	83	189	8	0.2	0–0.42
Chronic hepatitis[h]	Europe	6	84–89	471	5.9	0.1	0–0.27
	Taiwan	2	90–91	461	4.0	1.0	0.36–1.56
	Japan	2	31, 92	737	5.1	0.8	0.46–1.06
Compensated cirrhosis[i]	Europe	6	8, 38, 40, 41, 85, 89	401	5.8	2.2	1.62–2.80
	Taiwan and Singapore	3	76, 93, 94	278	4.3	3.2	1.94–4.55
	Japan	2	48, 95	306	5.8	4.3	3.40–5.25

Fattovich *et al.*, *Gastroenterology.* 2004.

NAFLD and HCC

- Lower overall HCC incidence of HCC in NAFLD vs. HCV

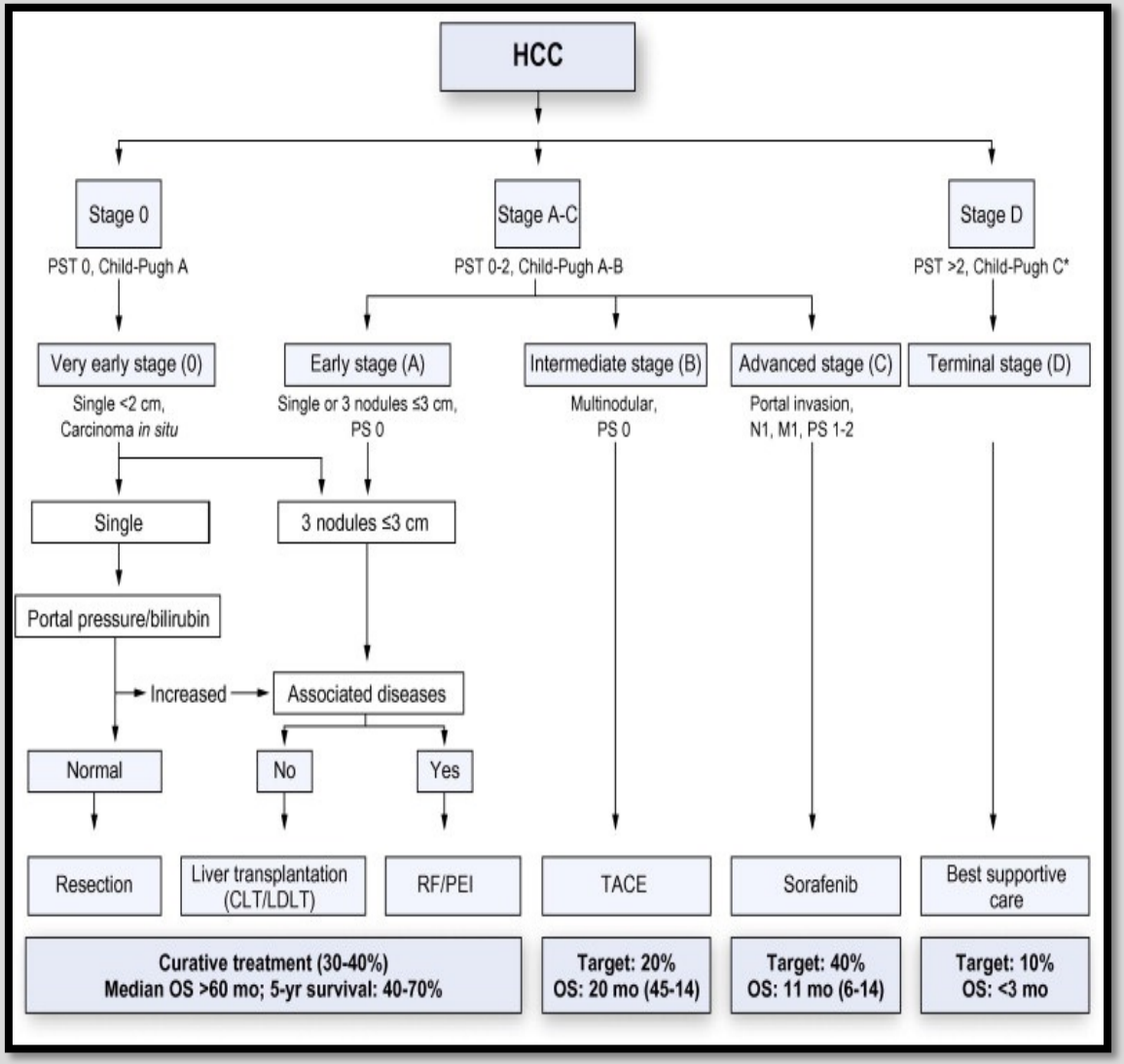
- However, NAFLD-associated HCC appears to have different phenotype
  - Older, higher proportion of females, more comorbid disease (metabolic syndrome)
  - Less severe liver dysfunction
  - Lower AFP production
  - Higher post-resection morbidity and mortality
  - Equivalent 5 year post-resection survival



Michellotti, *Nature Gastroenterol Rev.* 2013.

Therapeutic Decision-Making in HCC

Barcelona Clinic Liver Cancer (BCLC) Scoring System



Performance status

↓

Child-Pugh score

↓

Tumor burden

↓

Technical factors
Resectability, location

HCC Survival by BCLC Stage

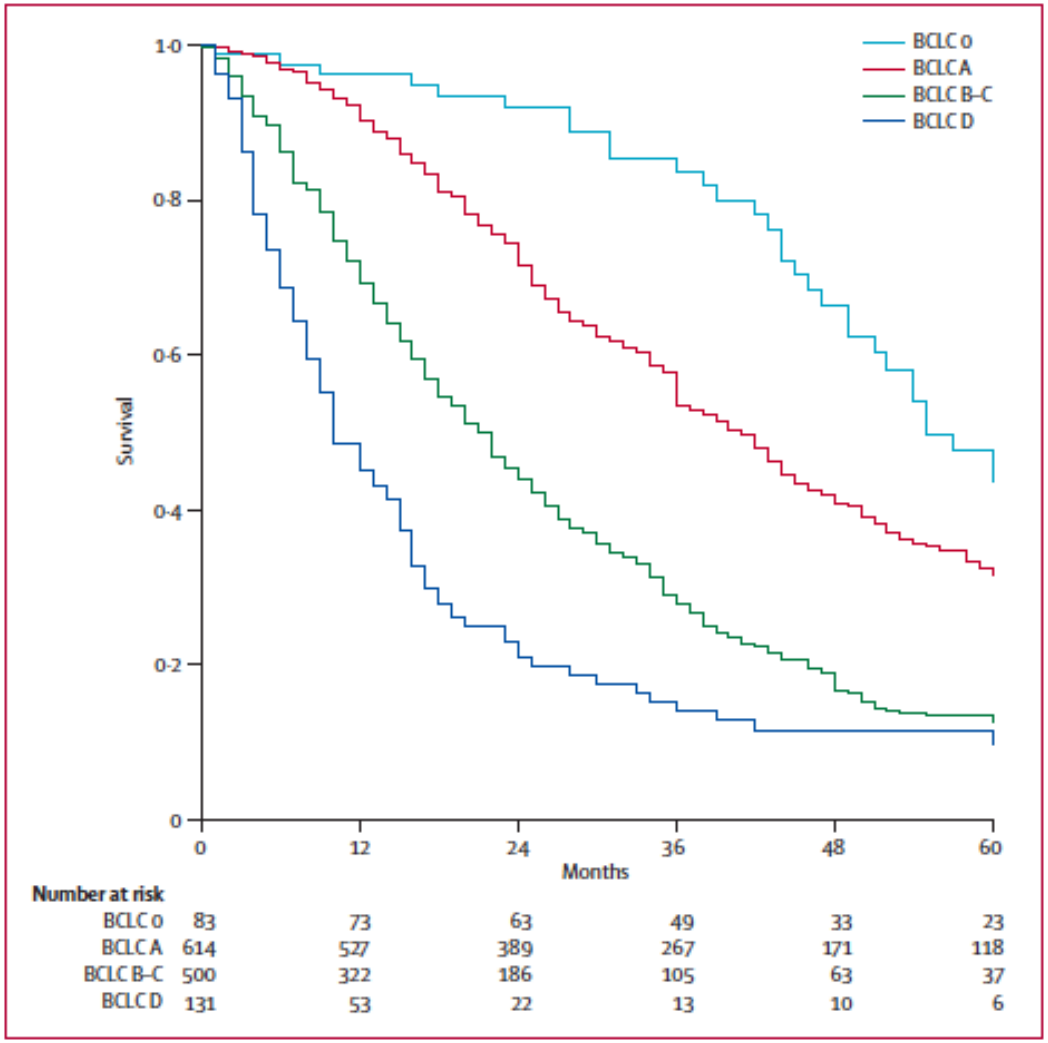


Figure 1: Kaplan-Meier survival curve of the study population according to BCLC stages

Lancet Oncol
2011;12:654-662

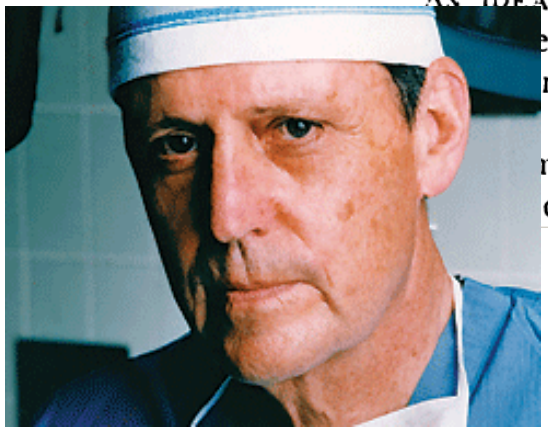
History of Liver Transplantation for HCC

SURGERY
Gynecology & Obstetrics

DECEMBER 1963
VOLUME 117
NUMBER 6

HOMOTRANSPLANTATION OF THE LIVER IN HUMANS

T. E. STARZL, M.D., F.A.C.S., T. L. MARCHIORO, M.D., K. N. VON KAULLA, M.D., G. HERMANN, M.D., R. S. BRITTAIN, M.D., and W. R. WADDELL, M.D., F.A.C.S.,
Denver, Colorado



AN IDEAL TREATMENT for several kinds of ease would be removed of the diseased nd orthotopic replacement with a homograft. Patients with primary na of the liver, congenital atresia of ducts, and terminal cirrhosis would will be described. The first attempt resulted in failure at the operating table. The course of the second 2 patients establishes the feasibility of such an operation in humans, despite the fact that death occurred 22 and 7½ days after transplantation from pul-

Surg Gynecol Obstet. 1963 December ; 117: 659–676.

*“Patient 2 was a 48 year old Negro male with Laennec's cirrhosis and a **primary hepatoma**, proved by operation at another hospital 8 days previous to the transplantation procedure. The tumor and its multiple satellite nodules involved all 4 anatomic segments of the liver and had a localized attachment to the central tendon of the right hemidiaphragm. Except for the diaphragmatic invasion the neoplasm was confined to the liver.”*

*“Patient 3 was a 67 year old white male with progressive jaundice…. Exploratory operation was performed on 3 June 1963, and an **intrahepatic duct cell carcinoma** was found which had obstructed both the right and left main hepatic ducts.”*

Early history of liver transplantation for malignancy

- Earliest experience
  - Starzl, Calne, Pichlmyer, Bismuth, *SGO* 1969
  - HCC with few CCA
  - Longest survival 16 months

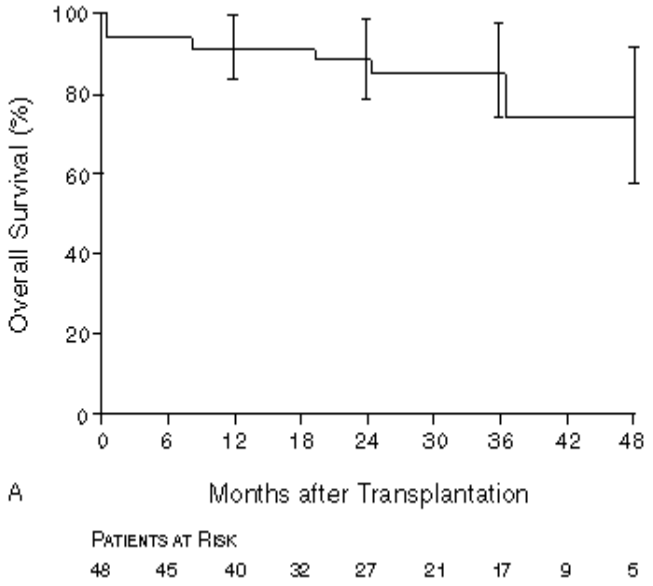
- 1970s-1980s
  - Israel Penn Transplant Cancer Registry, *Surgery 1991*
  - Almost universal recurrence
  - Overall survival in reported series 18-40%

- 1989 – HCC named <u>contraindication</u> to liver transplantation by U.S. Department of Health and Human Services

LIVER TRANSPLANTATION FOR THE TREATMENT OF SMALL HEPATOCELLULAR CARCINOMAS IN PATIENTS WITH CIRRHOSIS

VINCENZO MAZZAFERRO, M.D., ENRICO REGALIA, M.D., ROBERTO DOCI, M.D., SALVATORE ANDREOLA, M.D., ANDREA PULVIRENTI, M.D., FEDERICO BOZZETTI, M.D., FABRIZIO MONTALTO, M.D., MARIO AMMATUNA, M.D., ALBERTO MORABITO, PH.D., AND LEANDRO GENNARI, M.D., PH.D.

- **60 patients** with unresectable HCC single tumor < 5 cm, or multiple tumors with largest <3 cm; 1 death while waiting, 11 untransplanted, **48 transplants**
- Median follow-up 26 months; 3 peri-operative deaths, 8 post-transplant deaths – **only 2 due to recurrence of cancer**



A

Milan criteria:

Solitary tumor, <5 cm

≤ 3 tumors < 3 cm

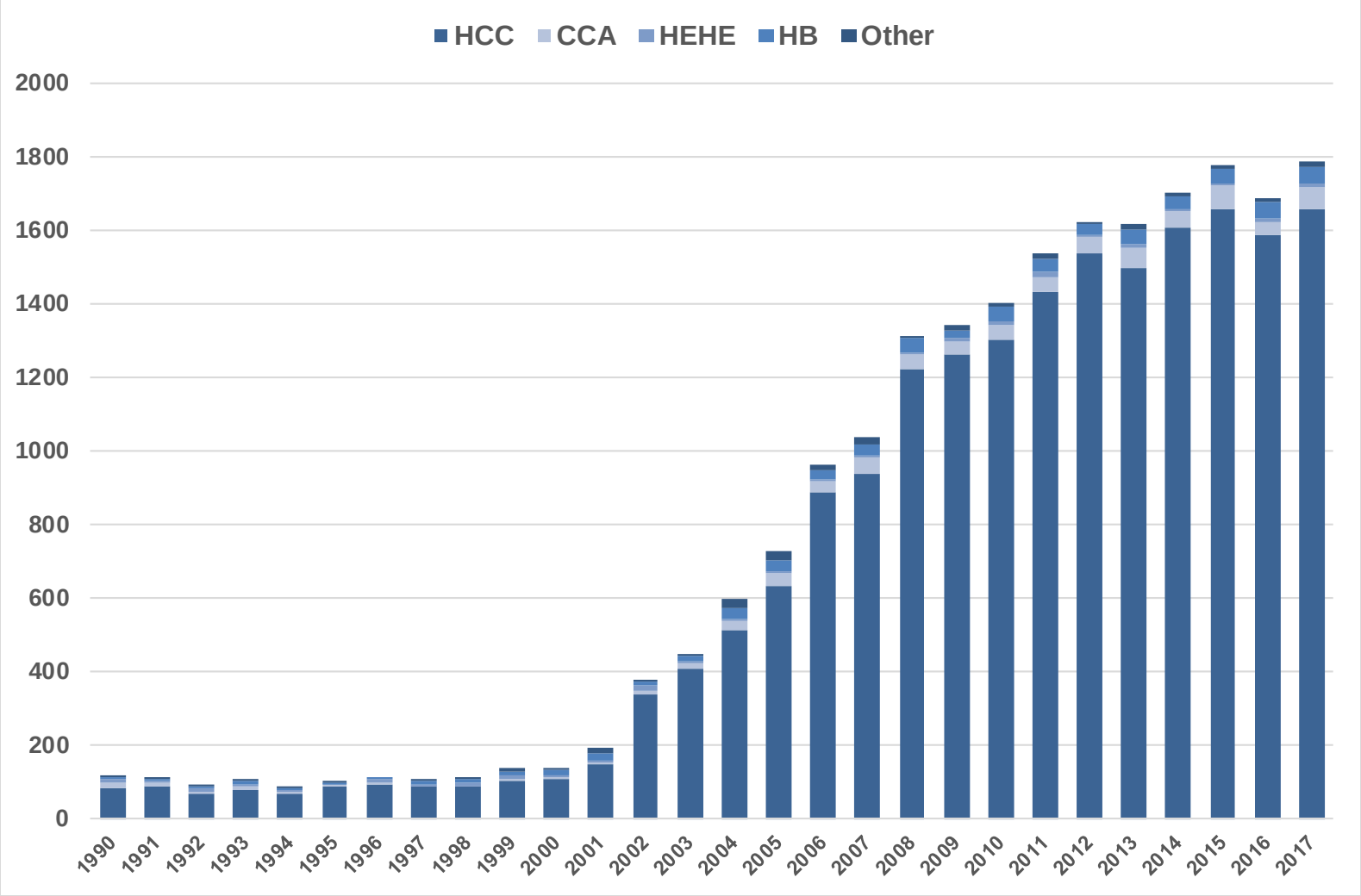
UNOS Criteria (2002):

Solitary tumor, 2-5 cm

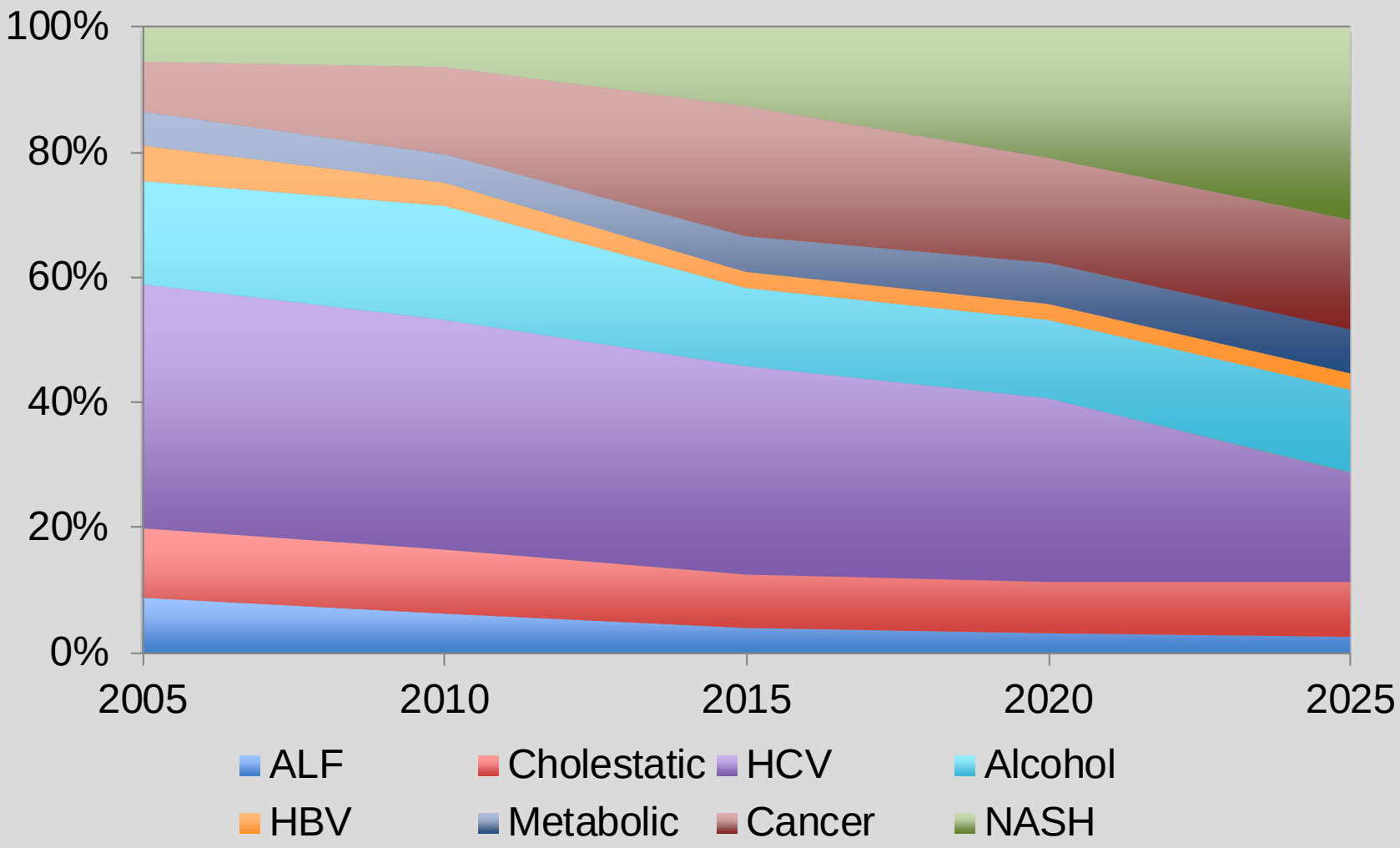
≤ 3 tumors < 3 cm

Mazzaferro V et al; *New Engl J Med* 1996;334:693-699

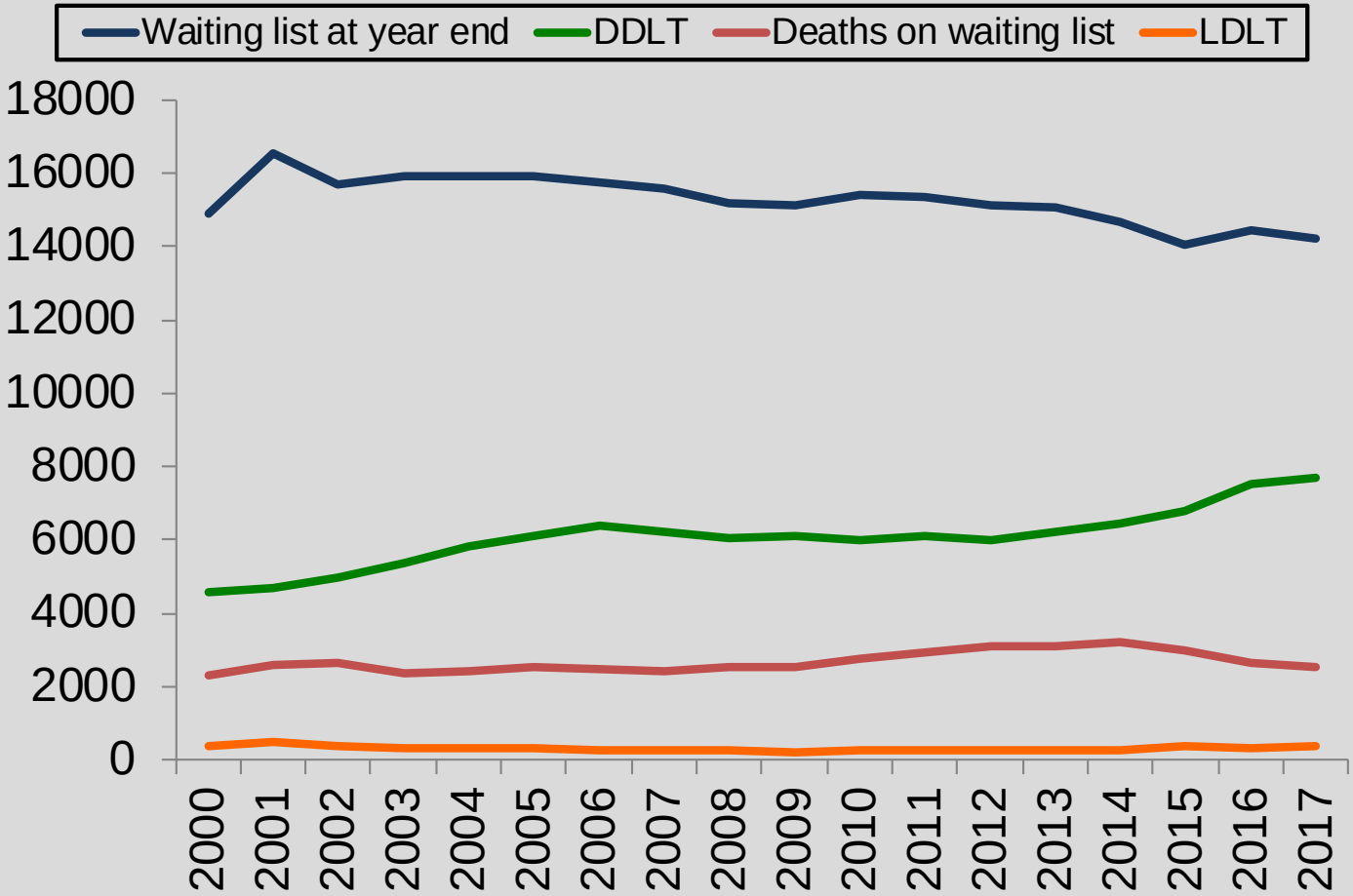
Liver Transplantation for Cancer, USA 1995-2006



Indications for liver transplantation, 2005-2025



Supply and demand in liver transplantation, 2000-2017



Acceptable outcomes for HCC in the MELD era

Mazzaferro et al, *Liver Transpl* 2011;17:S44-S57

- Meta-analysis of 25 adequate studies aimed at validating Milan criteria (vs. attempts to expand Milan)
- Milan criteria consistently predicts "**acceptable**" liver transplant outcomes – **5 year survival of 70%; recurrence rate < 10%**
- Transplants outside of Milan criteria consistently associated with inferior survival
  - Higher grade tumors
  - Higher rates of VI

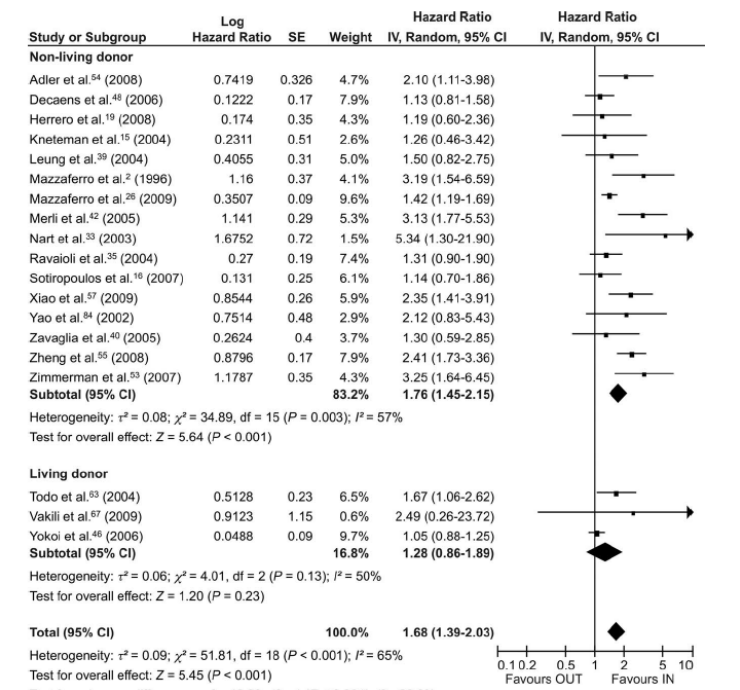
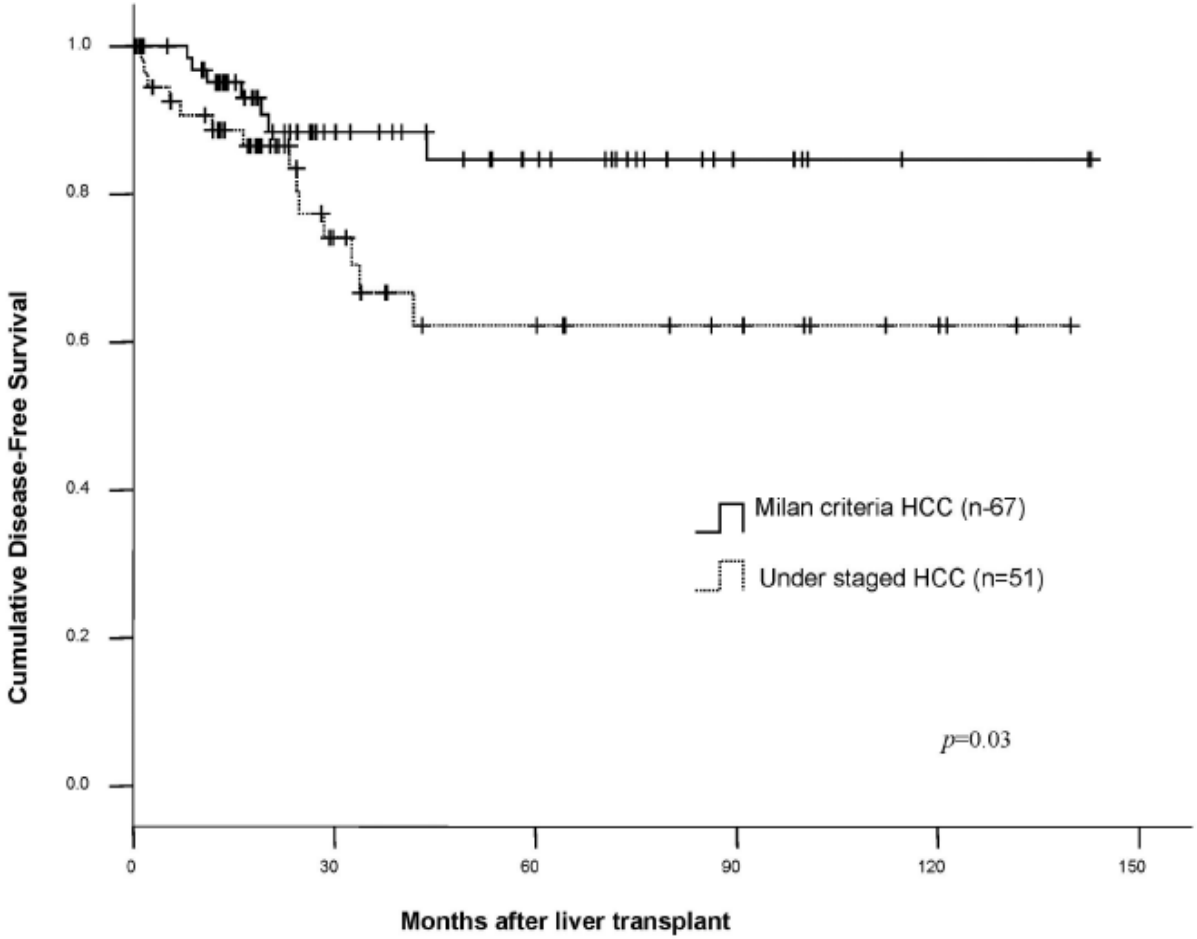


Figure 2. Meta-analysis of the 19 studies comparing the overall survival of patients with HCC meeting the MC and patients with HCC exceeding the MC at the time of the explant pathology examination. The studies are stratified by the graft type (deceased or living donor).

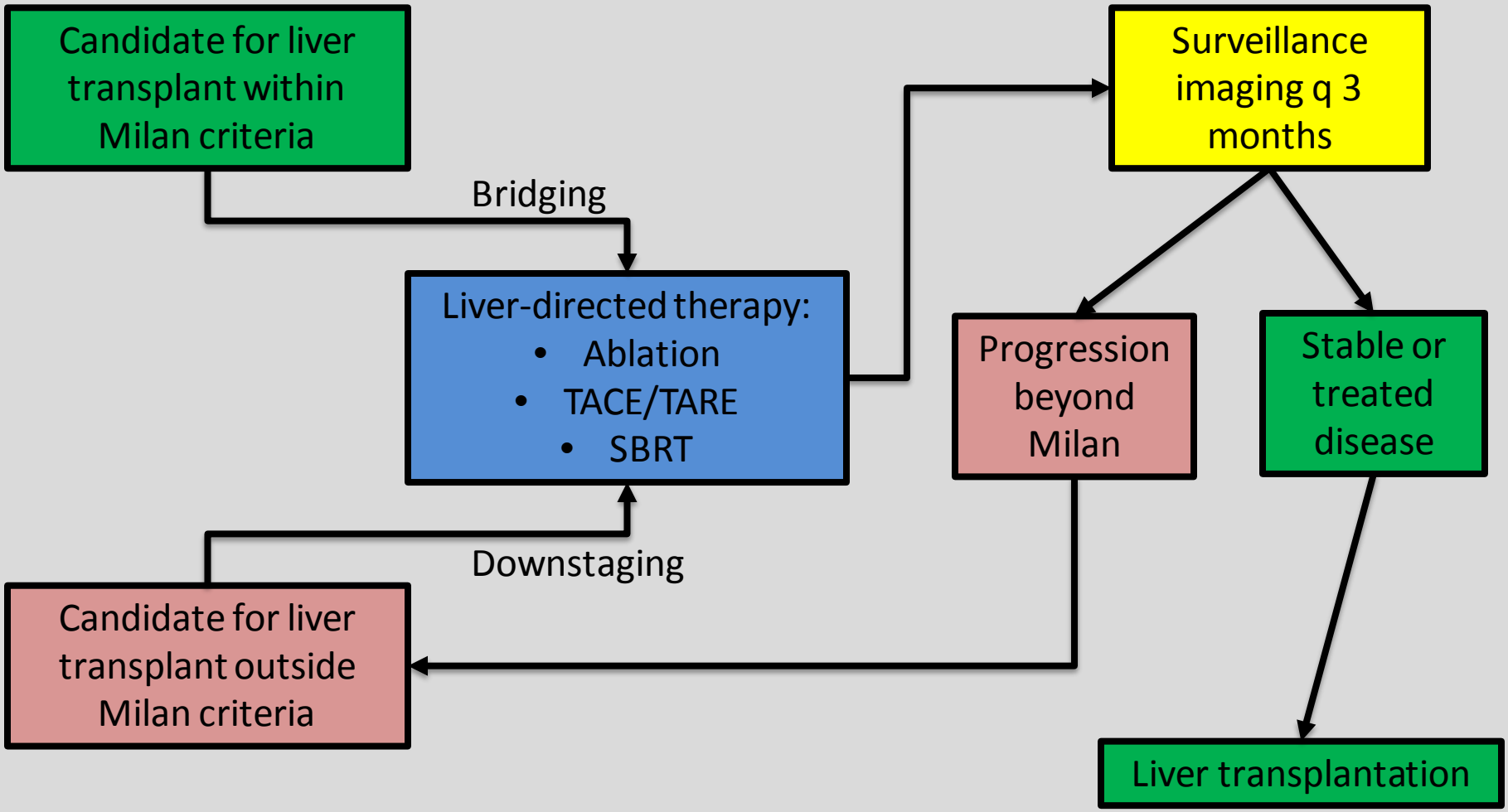
Challenges in OLT for HCC: Understaging



Shah et al, *Transplantation* 2006;81:1633-1639.

Downstaging and Bridging Therapies for HCC

Bridging or Downstaging?



Management of HCC patients waiting for transplant

- "Bridging" therapies of controversial benefit, but appear to benefit patients within Milan criteria expected to wait $\geq$ 6 months
  - Majno et al, *Liver Transpl* 2011;17:S98-S108.
- No definitive studies on preferred modality of bridging therapy – TACE vs. RFA vs. Y^{90} radioembolization vs. …
- Progression beyond Milan on serial imaging (q 3 months) should be a contraindication to transplant

Downstaging HCC to Milan

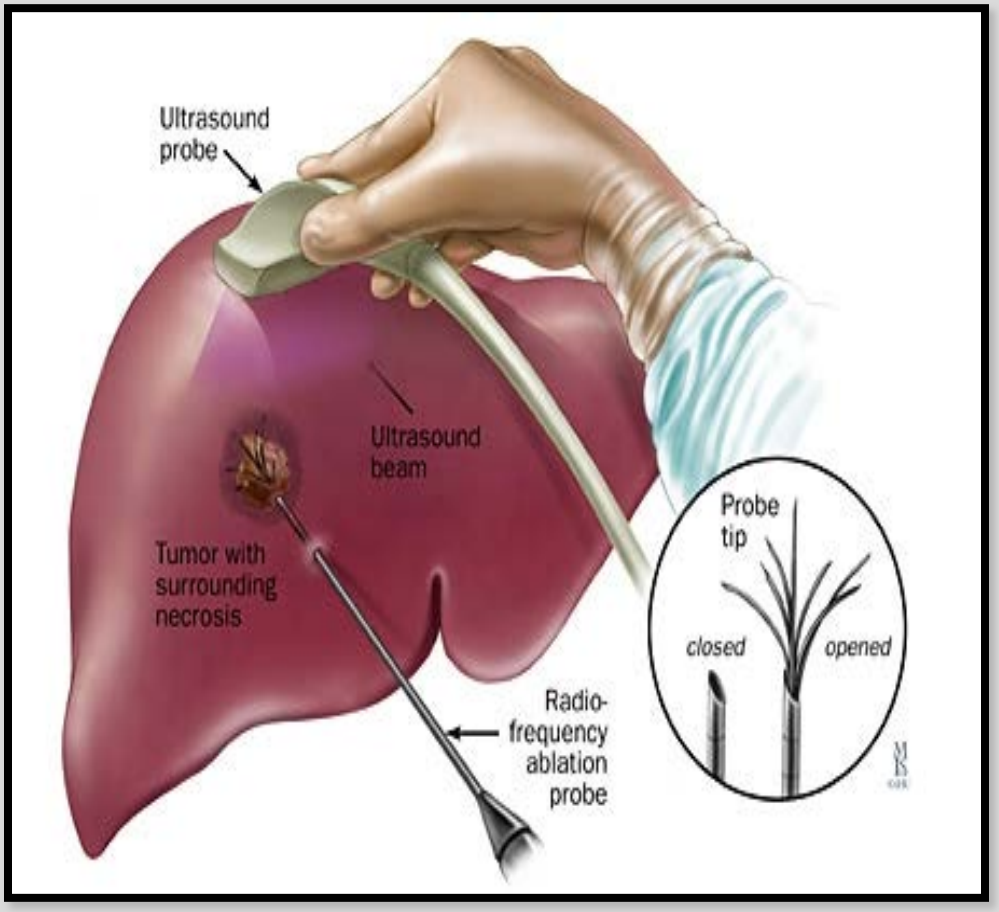
- **Extrahepatic disease and vascular invasion remain contraindications**
- **Should there be "maximum entry criteria"?**
  - Single lesion 8 cm
  - 2 or 3 lesions each 5cm with the sum of the maximal tumor diameters of all lesions 8 cm
  - Only single center data
- **Should downstaging technique be standardized?**
- **How do you measure response?**
  - RECIST criteria
  - Only viable tumor(s) considered; tumor diameter measurements should not include the area of necrosis from tumor-directed therapy
  - If there is more than one area of residual tumor enhancement, then the diameter of the entire lesion should be counted toward the overall tumor burden

***Liver Transpl* 2010; 16:249-251**

***Hepatology* 2016; 63:1014-1025**

Ablative therapies for HCC

- **Percutaneous ethanol ablation**
- **Radiofrequency ablation**
- **Microwave ablation**



Radiofrequency ablation

- High frequency alternating current from probe placed into tumor.
- Ionic agitation leads to heating and necrosis.
- May have limited efficacy near large blood vessels (“heat sink”).
- Slow…

RFA and PEI for HCC

TABLE 4. Characterstics of Randomized Controlled Trials Comparing Radiofrequency Ablation to Percutaneous Ethanol Injection for the Treatment of Hepatocellular Carcinoma

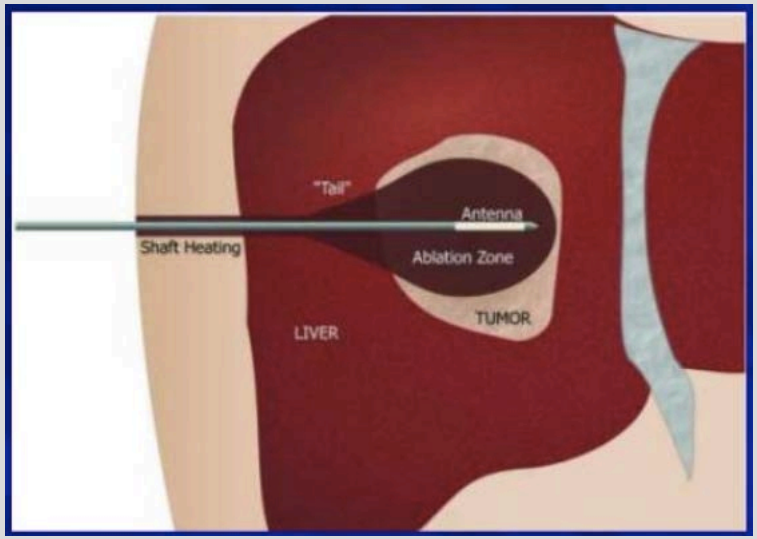
		Sample Size			CTP Class A/B		Complete Necrosis Rate (%)		
First Author	Year	RFA	PEI	Tumors	RFA	PEI	RFA	PEI	3-year OS Rate
Lencioni[155]	2003	52	50	Milan criteria	45/7	35/15	91	82	RFA: 98% PEI: 88%
Lin[156]	2004	52	52	1–3 lesions ≤4 cm	41/11	39/12	96	88	RFA: 74% PEI: 48%
Lin[157]	2005	62	62	1–3 lesions ≤3 cm	46/16	47/15	96	88	RFA: 74% PEI: 51%
Shiina[158]	2005	118	114	Milan criteria	85/33	85/29	100	100	RFA: 81% PEI: 67%
Brunello[159]	2008	70	69	1–3 lesions ≤3 cm	56/44	56/44	95	65	RFA: 63% PEI: 59%

CTP indicates Child-Turcotte-Pugh; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

Rahbari *Ann Surg*. 2011

Microwave ablation

- Higher frequency radiofrequency energy
- Creates electromagnetic field with greater heating
- Energy does not respect boundaries (vessels), so no “heat sink”
- Able to address larger lesions (up to 4 cm)
- Faster application

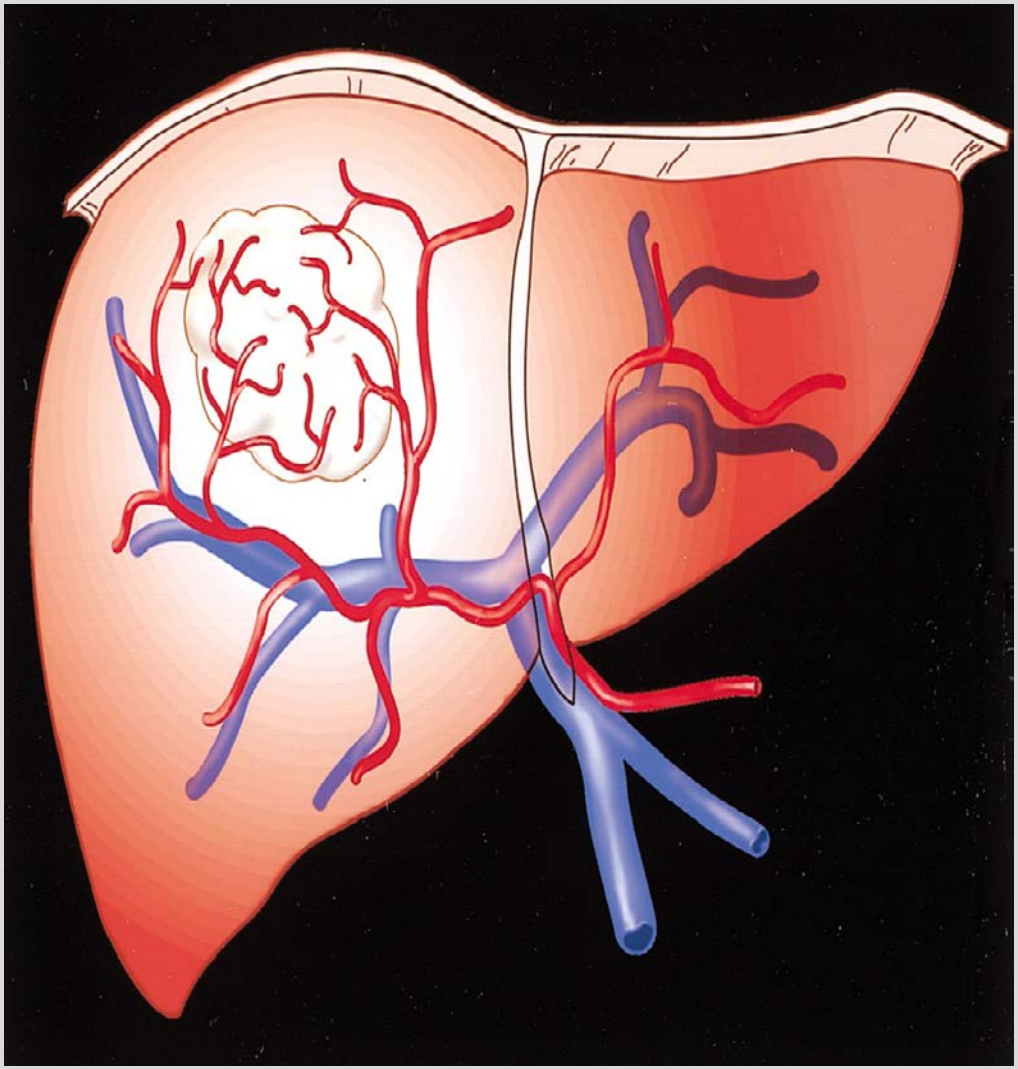


RFA vs MWA?

- Limited data for comparison
- *Lancet Gastro & Hepatol* 2018;3(5):317-325.
  - Phase 2 randomized clinical trial; N=152
  - Primary outcome 2 year recurrence, tumors≤4 cm
  - RFA 12% vs MWA 6%, RR 1.62, P=0.27
  - Slightly better outcomes at 3-4 cm with MWA

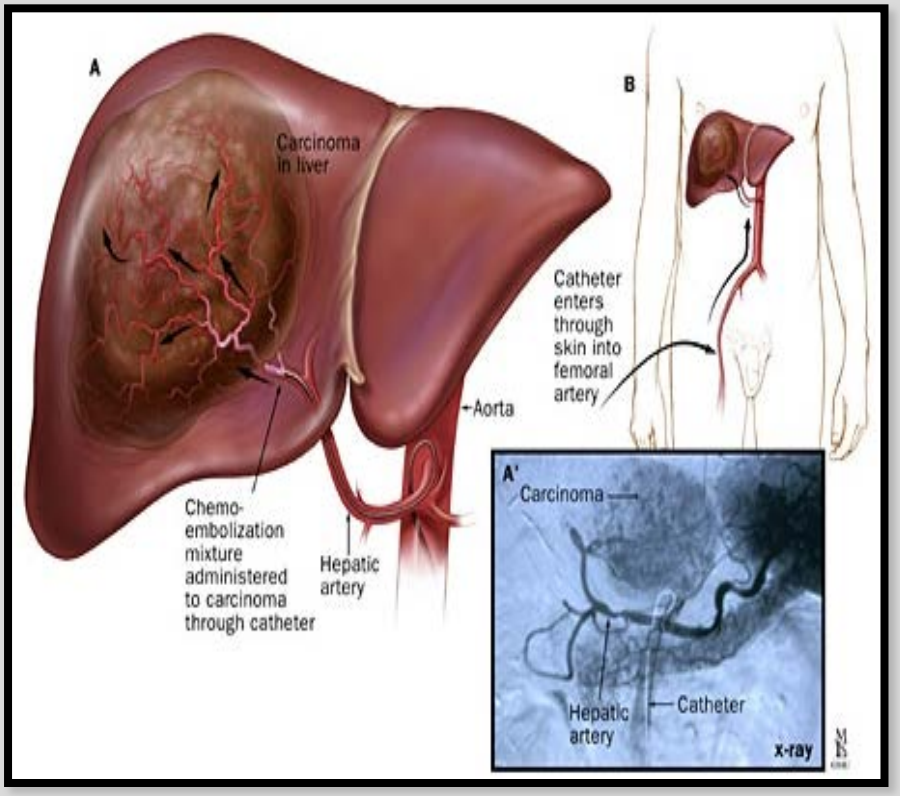
- Advantages of speed and slightly more versatility with larger tumors favors MWA

Hepatic artery based therapies for HCC



Transarterial chemoembolization (TACE)

- Most well-established therapy for multifocal and/or locally advanced HCC
- Demonstrated survival benefit (~11 months) in locally advanced HCC (non-transplant).
- Multiple studies reporting use prior to liver transplantation:
  - Average of 2 sessions required
  - Rare decompensation in Childs A and B patients
  - No change in post-transplant survival
  - Downstaging effective in ~60% of patients



TACE in selection of HCC patients for transplant

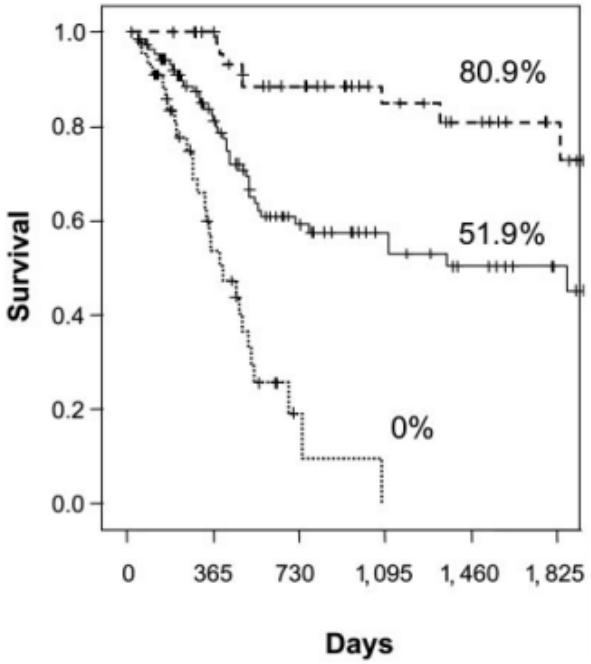


Figure 2. Survival of 96 patients enrolled in the TACE protocol. The difference in 5-year survival between downstaged (transplanted) patients and patients not responding to TACE is highly significant ($P < 0.0001$). (Survival is calculated from the beginning of TACE treatment.) Solid line denotes all patients included in the analysis. Dotted line denotes patients not responding to TACE. Dashed line denotes transplanted patients. Cross denotes censored.

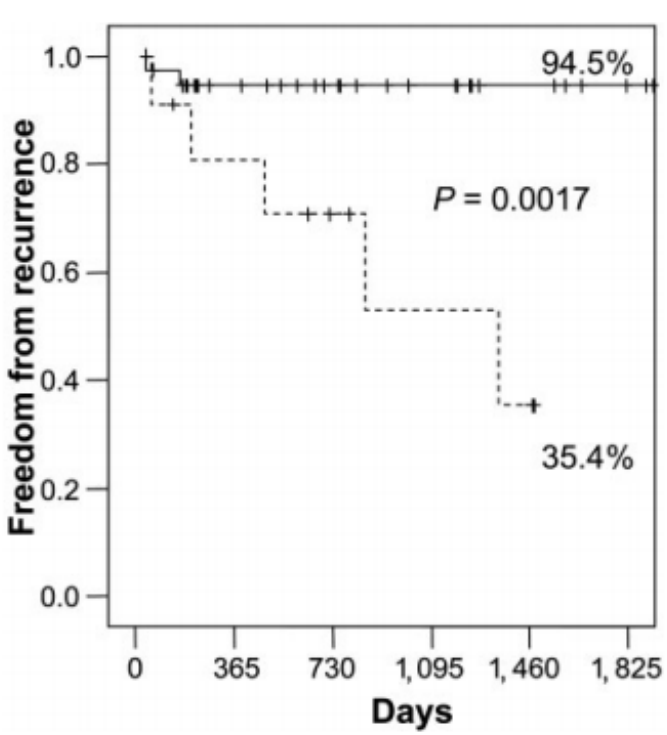


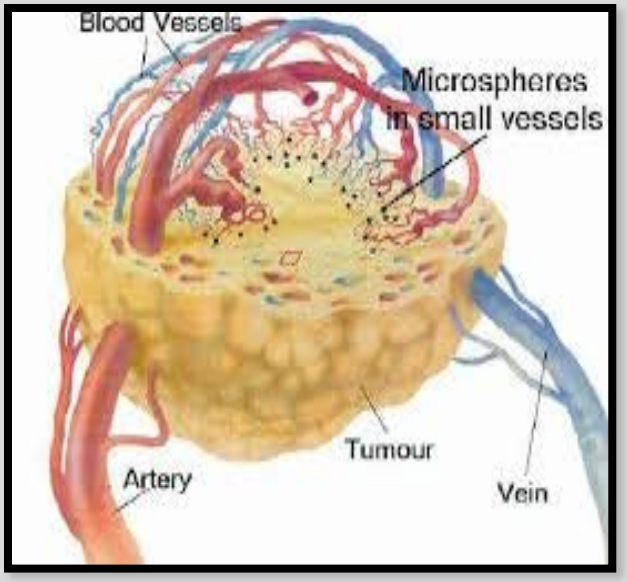
Figure 4. Posttransplant freedom from recurrence. TACE without progression (denoted by solid line) during waiting time vs. TACE with progression (denoted by dashed line) during waiting time. Cross denotes censored.

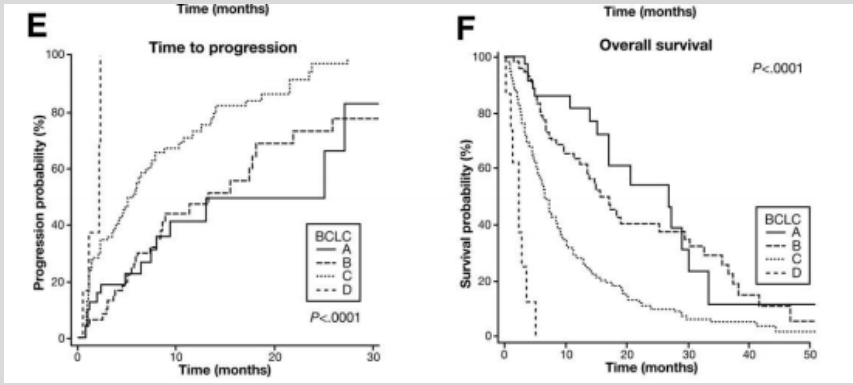
Otto et al, *Liver Transpl* 2006;12:1260-1267

Transarterial radioembolization (TARE)

- Transarterial injection of Y^{90} coated microspheres
- Demonstrated survival benefit in Childs A/B patients with HCC (non-transplant).
- Demonstrated survival benefit in Childs A patients with PVT
- Rare severe toxicities

Salem et al, *Gastro* 2010;138:52-64.





TARE prior to liver transplantation

- Well-tolerated with minimal toxicity/dropout
- Appears to be more effective in treatment of more advanced HCC (larger tumors > 5 cm, multifocal tumors)
- Response to TARE predicts low recurrence risk post-transplant

Lewandowski et al, *American Journal of Transplantation* 2009; 9: 1920–1928

Table 2: Treatment characteristics

Characteristic N (%)		TACE N = 43	Y90 N = 43	p-Value
Mean number of treatments (range)		2.0 (1–5)	1.8 (1–6)	–
Median number of treatments (95% CI)		2 (1–2)	1 (1–2)	0.21
Treatment type	Lobar	19 (44)	23 (53)	0.52
	Selective	24 (56)	20 (46)	
Median activity delivered to treatment site (range) (GBq)		–	1.61 (0.54–2.97)	–
Median dose administered to treatment site (range) (Gy)		–	110.2 (53–284)	–
Mean number of days hospitalized (range)		3 (1–11)	0 (-, -)	–
Median number of days hospitalized (95% CI)		2 (1–2)	0 (-, -)	<0.001

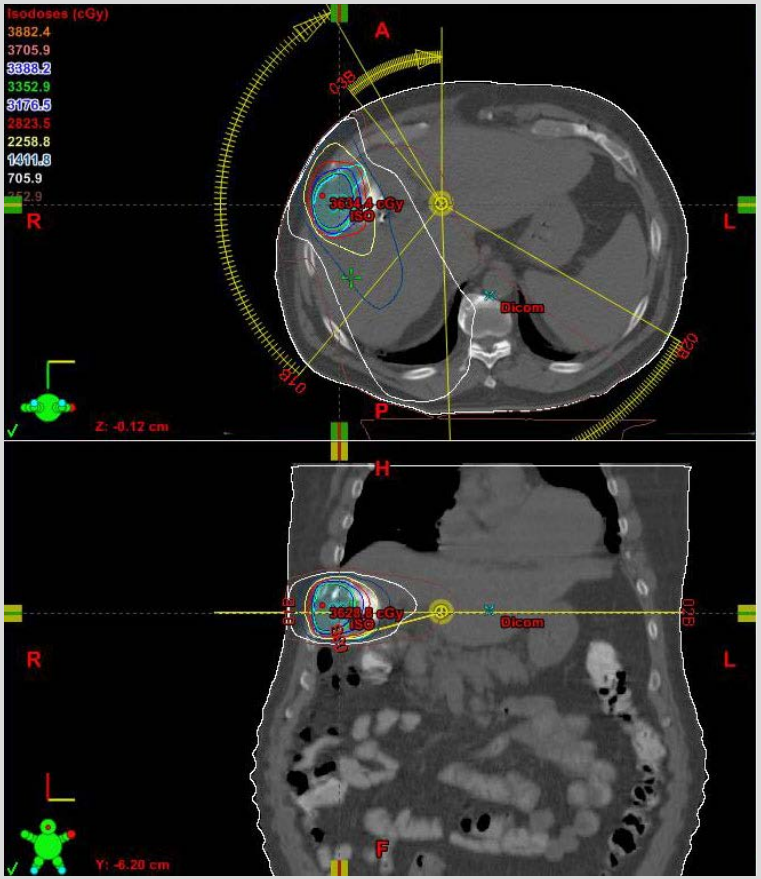
Table 3: Imaging findings (response)

Characteristic		TACE N = 35	Y90 N = 43	p-Value
WHO	CR	0 (0)	0 (0)	0.12
	PR	13 (37)	26 (61)	
	SD	17 (49)	16 (37)	
	PD	5 (14)	1 (2)	
Median time to WHO PR (95% CI) (months)		10.9 (7.3, -)	4.2 (3.3–6.9)	0.025
EASL	CR	6 (17)	20 (47)	0.13
	PR	19 (54)	17 (39)	
	SD	9 (26)	6 (14)	
	PD	1 (3)	0 (0)	
Median time to EASL PR (95% CI) (months)		1.9 (1.4–3.3)	1.3 (1.1–2.4)	0.04
Median time to EASL CR (95% CI) (months)		- (-, -)	6.1 (4.2, -)	0.017
UNOS downstaged T3→T2		11 (31)	25 (58)	0.023
Median time to UNOS downstaging (95% CI) (months)		- (4.3, -)	3.1 (1.8–8.7)	0.027

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Stereotactic Body Radiotherapy (SBRT)

- High dose focused radiation given over 3-5 sessions
- May be dose adjusted to minimize liver-specific toxicity
- Effective alternative for local control for tumors that cannot be ablated (location etc.)
- Limited reports of successful bridging to liver transplantation



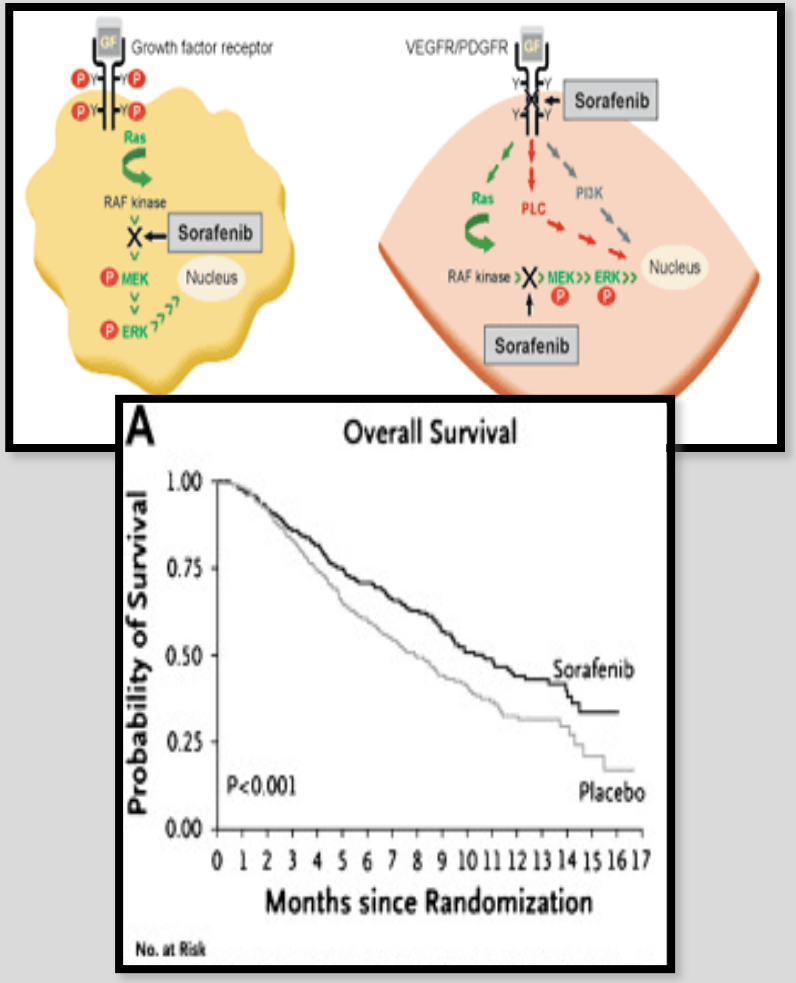
Neoadjuvant chemotherapy for HCC

Sorafenib – tyrosine kinase inhibitor

SHARP trial showed improved survival for patients with advanced HCC; Bruix et al, *New Eng J Med* 2008;358:378-390

No evidence of improved survival in patients who receive sorafenib after liver transplantation for HCC.

No definitive studies of using sorafenib PRIOR to transplant for downstaging or bridging therapy.



Outcomes of liver transplantation for HCC

Acceptable outcomes for HCC in the MELD era

Mazzaferro et al, *Liver Transpl* 2011;17:S44-S57

- Meta-analysis of 25 adequate studies aimed at validating Milan criteria (vs. attempts to expand Milan)
- Milan criteria consistently predicts “acceptable” liver transplant outcomes – 5 year survival of 70%; recurrence rate < 10%
- Transplants outside of Milan criteria consistently associated with inferior survival
  - Higher grade tumors
  - Higher rates of VI

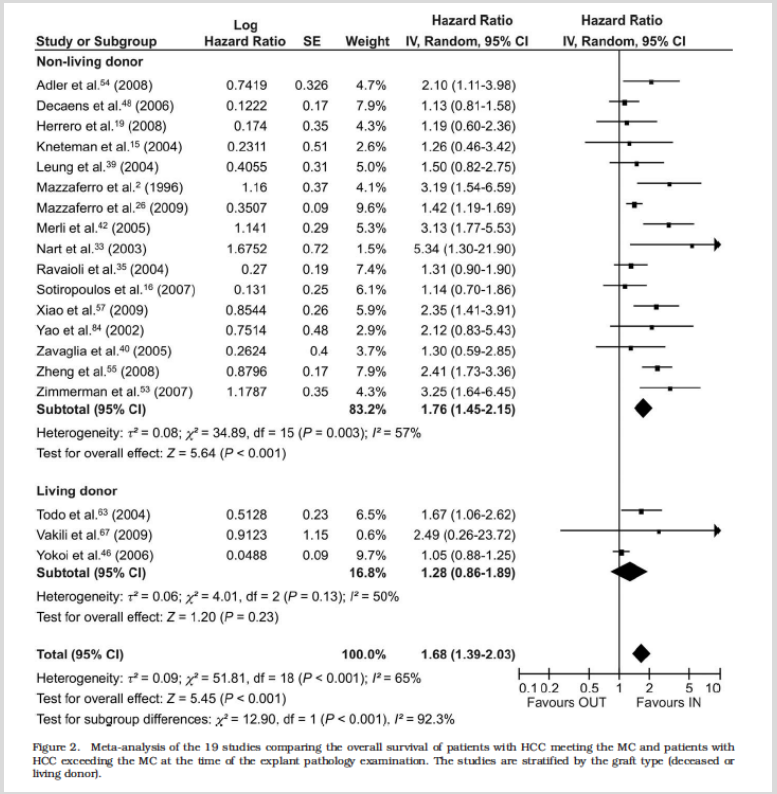


Figure 2. Meta-analysis of the 19 studies comparing the overall survival of patients with HCC meeting the MC and patients with HCC exceeding the MC at the time of the explant pathology examination. The studies are stratified by the graft type (deceased or living donor).

Liver Transplantation for Hepatocellular Carcinoma: Expansion of the Tumor Size Limits Does Not Adversely Impact Survival

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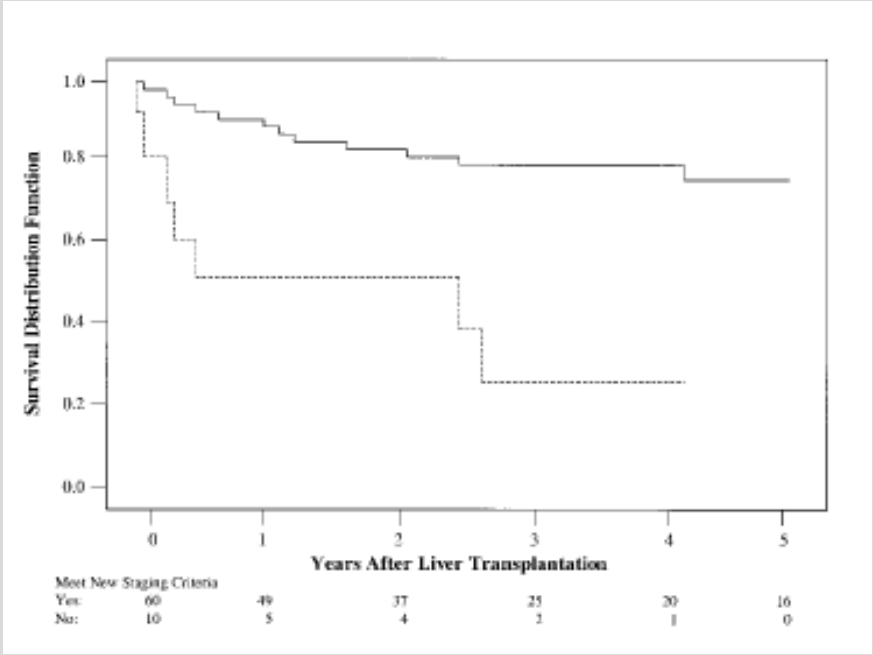
UCSF Criteria

- Solitary tumor ≤ 6.5 cm
- OR
- ≤ 3 tumors
- Largest ≤ 5 cm
- Total tumor diameter ≤ 8 cm
- No vascular invasion
- AFP < 500 if initially > 500



Hepatology 2001;33:1394-1403

Transplant outcomes by selection criteria

Table 1 | **Liver transplantation criteria for patients with hepatocellular carcinoma**

Transplantation criteria	Intention-to-treat survival	Disease-free survival	Post-transplantation survival	Comments
Milan criteria[51] • Single tumour ≤5 cm or 3 tumours all ≤3 cm	N/A	92% 4 years	85% 4 years	Based only on size and number
UCSF criteria[39] • Single tumour ≤6.5 cm or 3 tumours all ≤4.5 cm with TTD ≤8 cm	N/A	90.9% 5 years	80.9% 5 years	Based only on size and number
Up-to-7 criteria[49] • The sum of the maximum tumour diameter and number <7	N/A	• Beyond Milan but within Up-to-7 • 64.1% 5 years	• Beyond Milan but within Up-to-7 • 71.2% 5 years	Based only on size and number
Total Tumour Volume (TTV)[47] • Total tumour volume ≤115 cm^3 • AFP ≤400 ng/mL	• Beyond Milan but within TTV/AFP • 53.8% 4 years	• Beyond Milan but within TTV/AFP • 68% 4 years	• Beyond Milan but within TTV/AFP • 74.6% 4 years	Size and number and biological marker (AFP)
Extended Toronto Criteria (ETC)[43] • No limit in size and number • No vascular invasion • No extrahepatic disease • No cancer-related symptoms • Biopsy of largest tumour not poorly differentiated	• Beyond Milan but within ETC • 55% 5 years	• Beyond Milan but within ETC • 30% 5 years • (Cumulative risk of recurrence)	• Beyond Milan but within ETC • 68% 5 years	No size and number limit but biological behaviour (cancer-related symptoms and tumour differentiation)
Kyoto Criteria[55] • Number ≤10 tumours • Size ≤5 cm • DCP ≤400 mAU/mL	N/A	• Beyond Milan but within Kyoto • 30% 5 years • (Cumulative risk of recurrence)	• Beyond Milan but within Kyoto • 65% 5 years	Size and number and biological marker

AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; TTD, total tumour diameter; UCSF, University of California San Francisco.

Sapisochin et al., *Nature Reviews Gastro Hepat* 2017;14:205-217

Challenges in OLT for HCC: Understaging

Shah et al, *Transplantation* 2006;81:1633-1639.

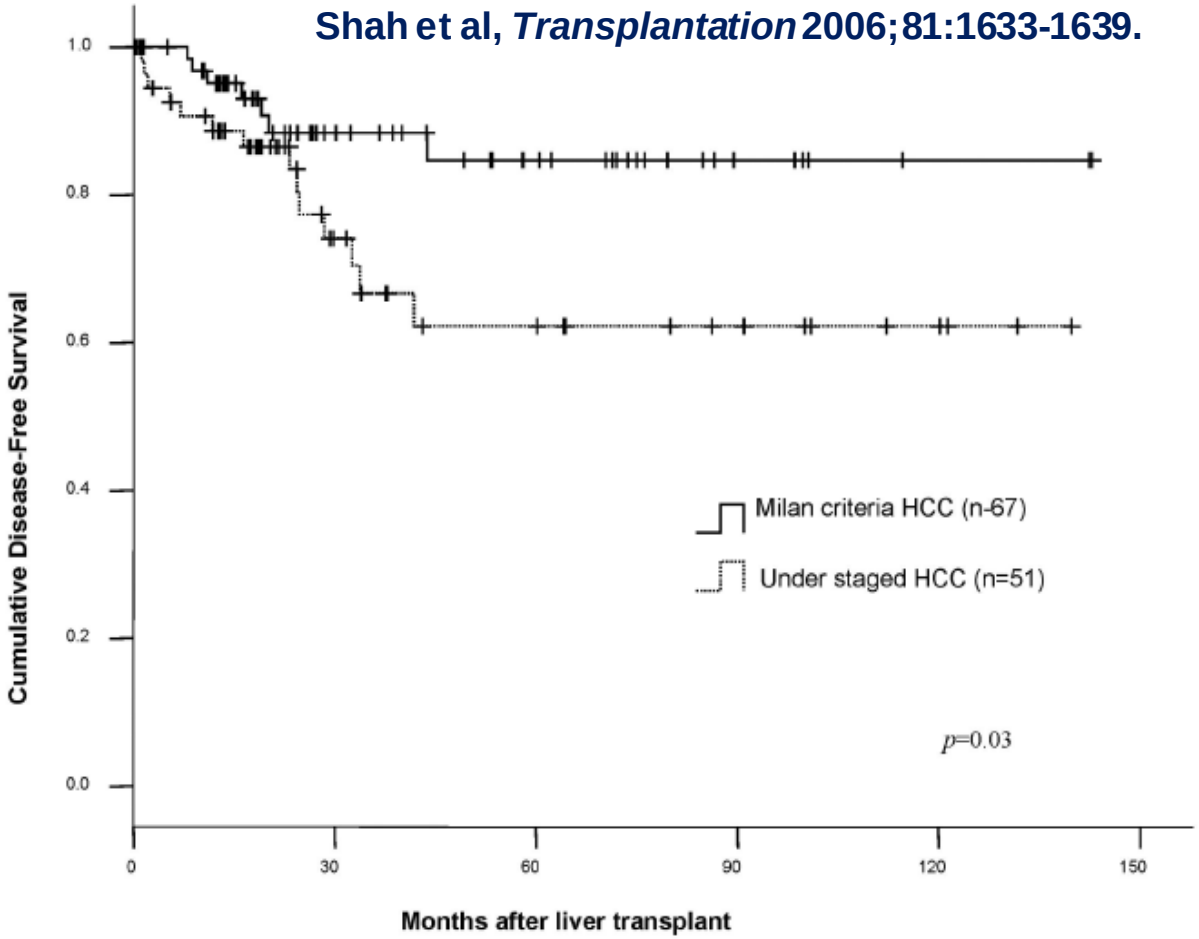


FIGURE 2. Recurrence-free survival comparing patients who were within Milan criteria and appropriately staged (n=67) or understaged (n=51) after LT for HCC.

LT for HCC: Impact of Underlying Liver Disease

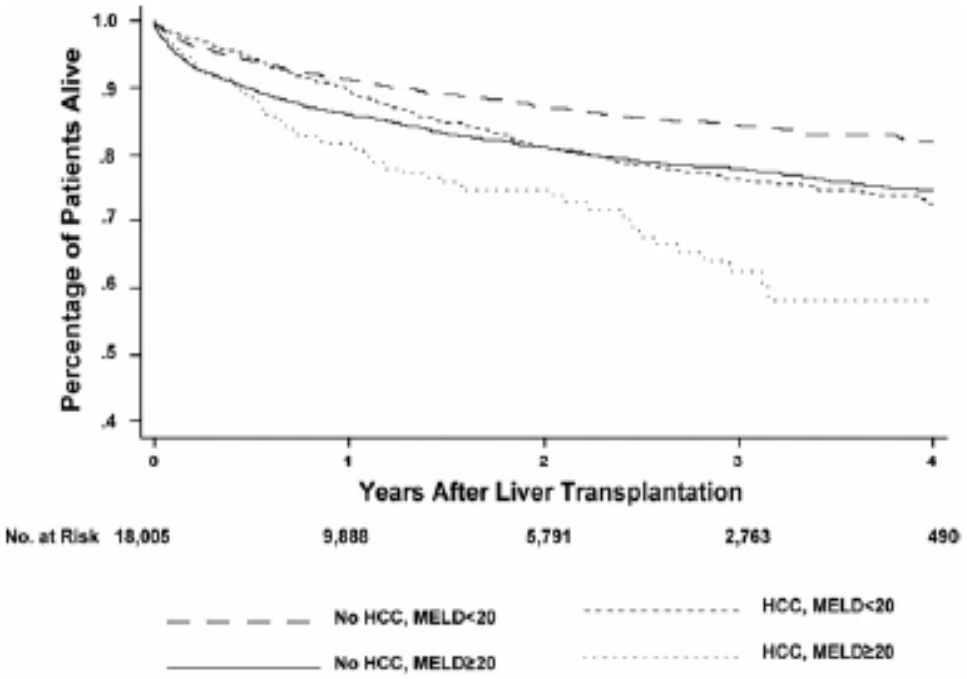


Figure 2. Kaplan–Meier curves of survival after liver transplantation in 2002–2007, presented according to presence of HCC* and MELD level. *Limited to patients with tumors ≥2 cm who obtained an "HCC-MELD-exception" from the MELD-based allocation system.

Ioannou et al, *Gastroenterology* 2008;134:1342-1351.

Living Donor LT for HCC

- Outcomes of LDLT for non-HCC diagnoses are equivalent to slightly better than DDLT
- LDLT for HCC associated with slightly higher recurrence rate in published studies:
  - differences in pre-transplant therapies (such as decreased use of liver-directed therapy)
  - differences in patient selection (potential tendency to consider patients beyond Milan criteria for LDLT)
  - expedited transplant via LDLT such that a period of observation of tumor behavior does not occur
- Utilization of 3-6 month observation period prior to LDLT may decrease risk of early recurrence

Olthoff KM et al. *Liver Transpl* 2011;17(7):789-797.
Fisher RA et al. *Am J Transplant* 2007;7(6):1601-1608.
Kulik LM et al. *Am J Transplant*. 2012;12(11):2997-3007.

HCC: Treatment Options Outside of Transplant

- Transplantation of patients with HCC beyond Milan or UCSF criteria may be associated with increased recurrence and decreased survival.
- Bridging therapies appear to be effective in controlling HCC in patients with waiting time $\geq$ 6 months.
- Bridging and downstaging therapies should be catered to patient and tumor factors
  - MWA, TACE/TARE, SBRT
- Outcomes post-transplant should target recurrence rate of < 10% and 5 year survival 75%

Thank you

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