Liver Cancer and Liver Transplant

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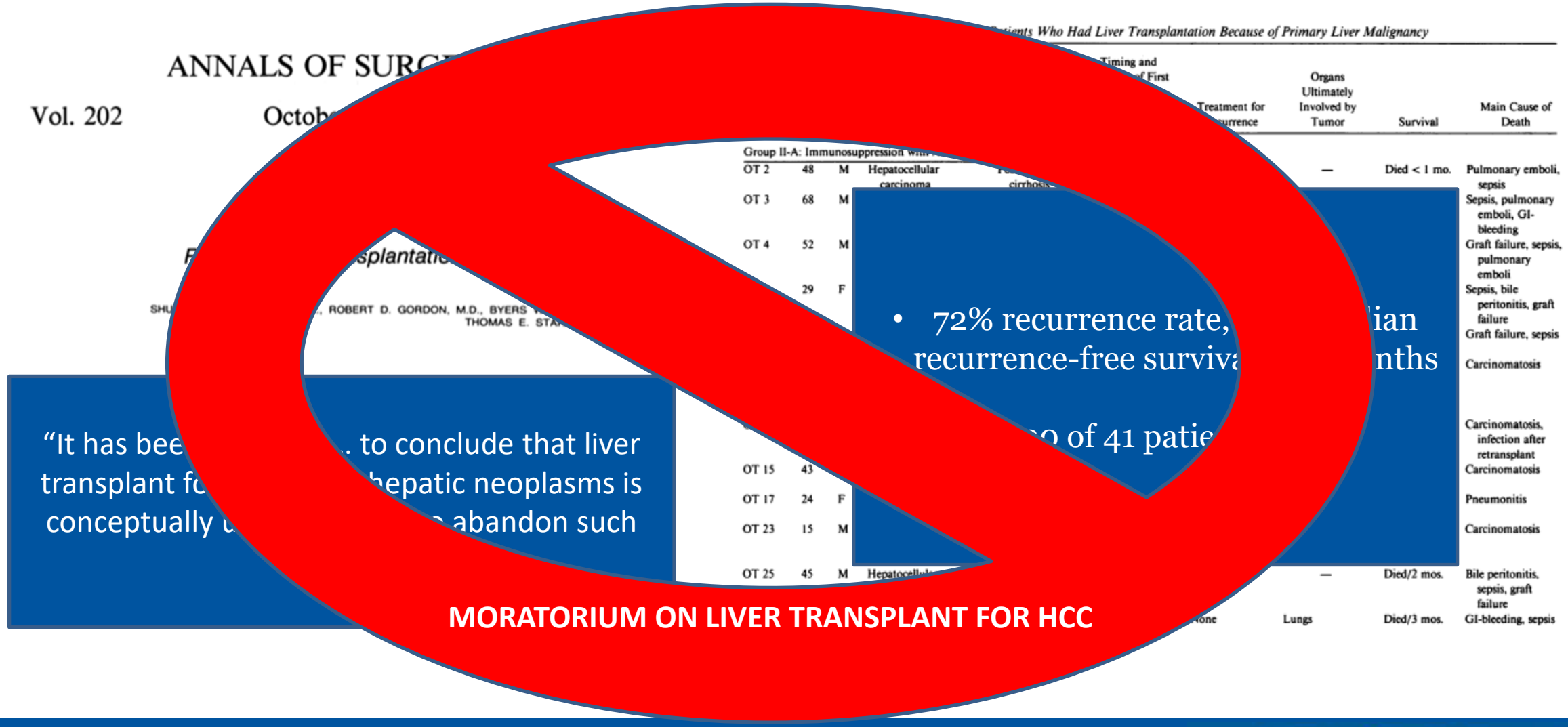
Disclosures

- I have served as a consultant or served on advisory boards for Genentech, AstraZeneca, Bayer, Eisai, Exelixis, Exact Sciences, Glycotest, Universal Diagnostics, GRAIL, Freenome, and FujiFilm Medical Sciences

Patient case

- 54-year-old male with history of hepatitis C cirrhosis, compensated, s/p sustained virological response
- Initially was followed closely with HCC surveillance but then lost to follow-up
- Presented two years later with incidental HCC
  - Two lesions, 4.5 cm and 3 cm, (both LR-5)
- Child Pugh A – Bili 1.2, Alb 3.0, INR 1.1, platelet count 72
- AFP 12 ng/mL
- Actively working, ECOG 0

Initial experiences with liver transplantation for HCC



Iwatsuki et al. Annals of Surgery 1985

Early experience with liver transplantation for HCC

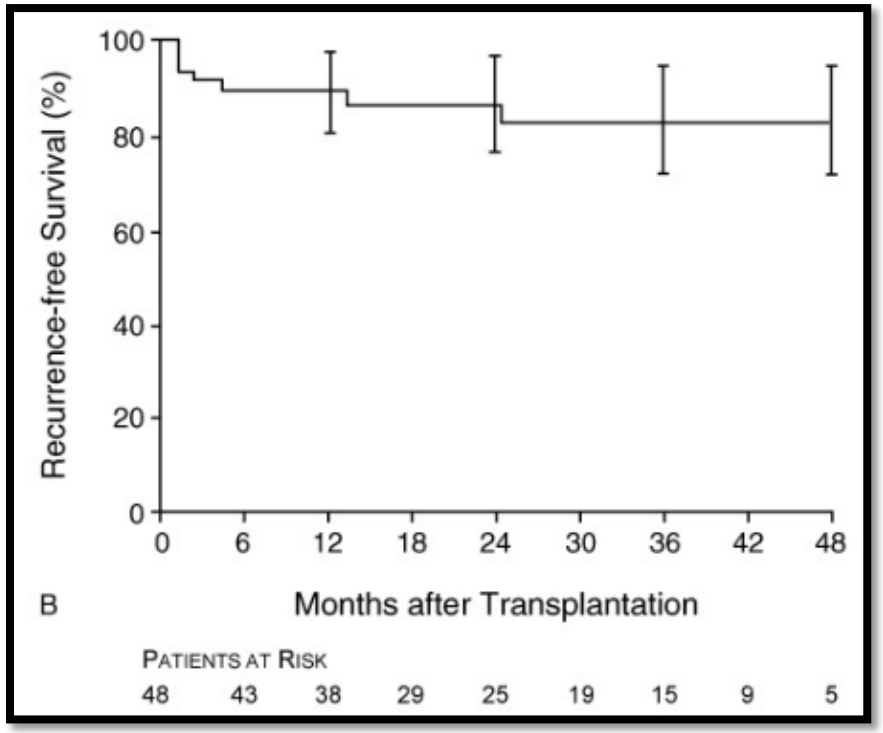
	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Total HCC (n = 105)	85.7% (90)	74.3% (78)	65.7% (69)	49.0% (45)	39.2% (26)	35.6% (16)	35.6% (13)
FL-HCC (n = 10)	90.0% (9)	90.0% (9)	80.0% (8)	70.0% (2)	50.0% (4)	37.5% (3)	37.5% (3)
Non–FL-HCC (n = 95)	85.3% (81)	72.6% (69)	64.2% (61)	46.8% (38)	38.3% (22)	36.5% (13)	36.5% (10)
Cirrhosis (n = 71)	84.5% (60)	71.8% (51)	63.4% (45)	48.6% (28)	42.9% (21)	40.7% (12)	40.7% (10)
Noncirrhosis (n = 34)	88.2% (30)	79.4% (27)	70.6% (24)	50.0% (16)	32.5% (6)	26.0% (4)	26.0% (3)
TNM Stage I (n = 4)	75.0% (3)	75.0% (3)	75.0% (3)	75.0% (3)	75.0% (2)	75.0% (2)	75.0% (2)
TNM Stage II (n = 19)	84.2% (16)	84.2% (16)	79.0% (15)	68.4% (12)	68.4% (12)	68.4% (8)	68.4% (5)
TNM STage III (n = 23)	87.0% (20)	78.3% (18)	78.3% (18)	59.8% (11)	59.8% (8)	52.3% (4)	52.3% (4)
TNM Stage IV-A (n = 59)	86.4% (51)	69.5% (41)	55.9% (33)	36.6% (15)	16.3% (4)	10.9% (2)	10.9% (2)

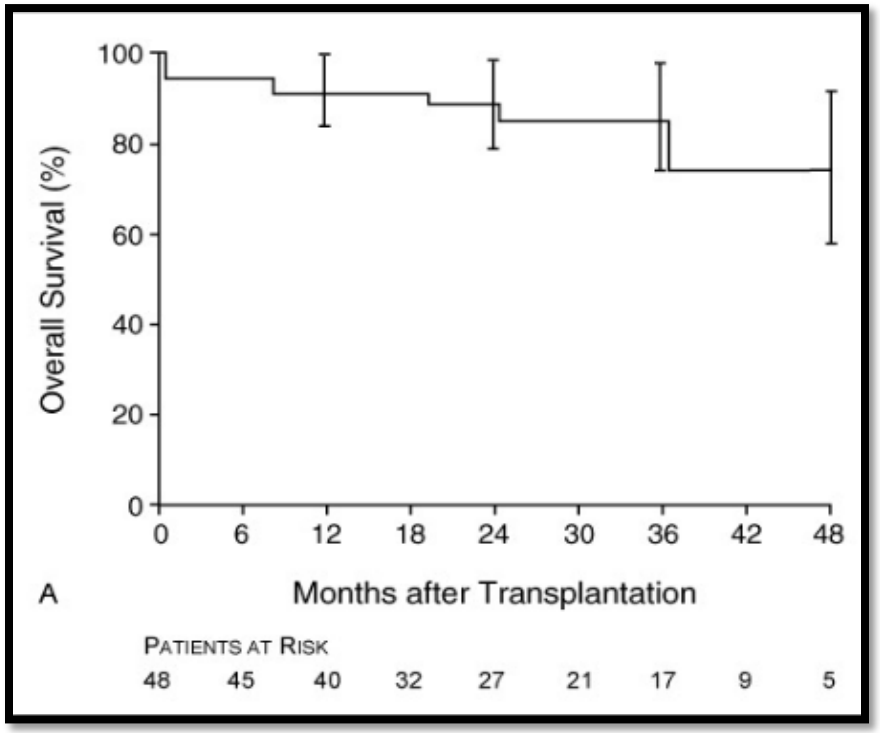
Defining the Milan Criteria for Liver Transplantation

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

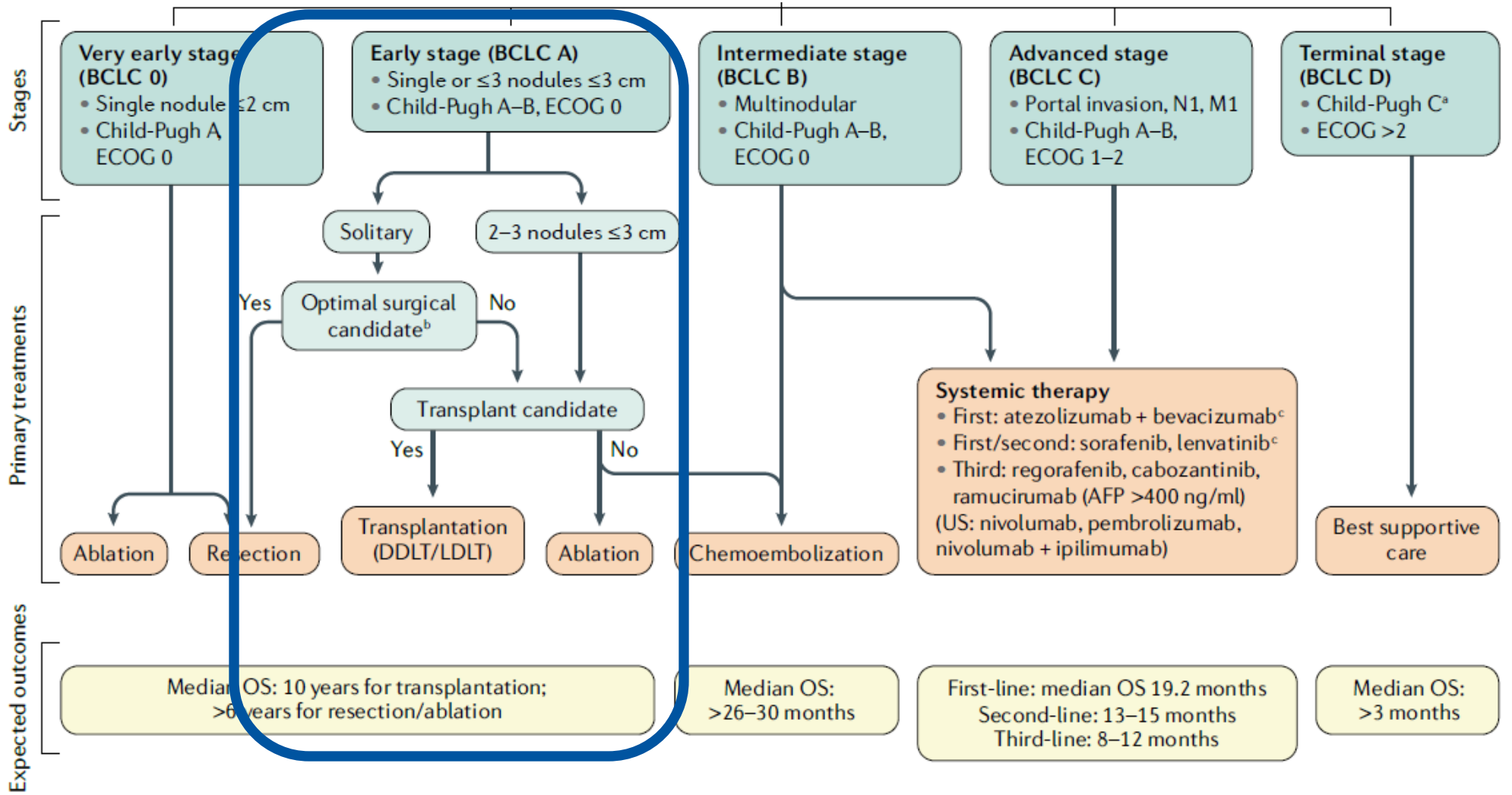
VINCENZO MAZZAFERRO, M.D., ENRICO REGALIA, M.D., ROBERTO DOCI, M.D., SALVATORE ANDREOLA, M.D., ANDREA PULVIRENTI, M.D., FEDERICO BOZZETTI, M.D., FABRIZIO MONTALTO, M.D., MARIO AMMATUNA, M.D., ALBERTO MORABITO, PH.D., AND LEANDRO GENNARI, M.D., PH.D.

- Reported outcomes among 48 patient transplanted using Milan Criteria after median follow-up of 26 months





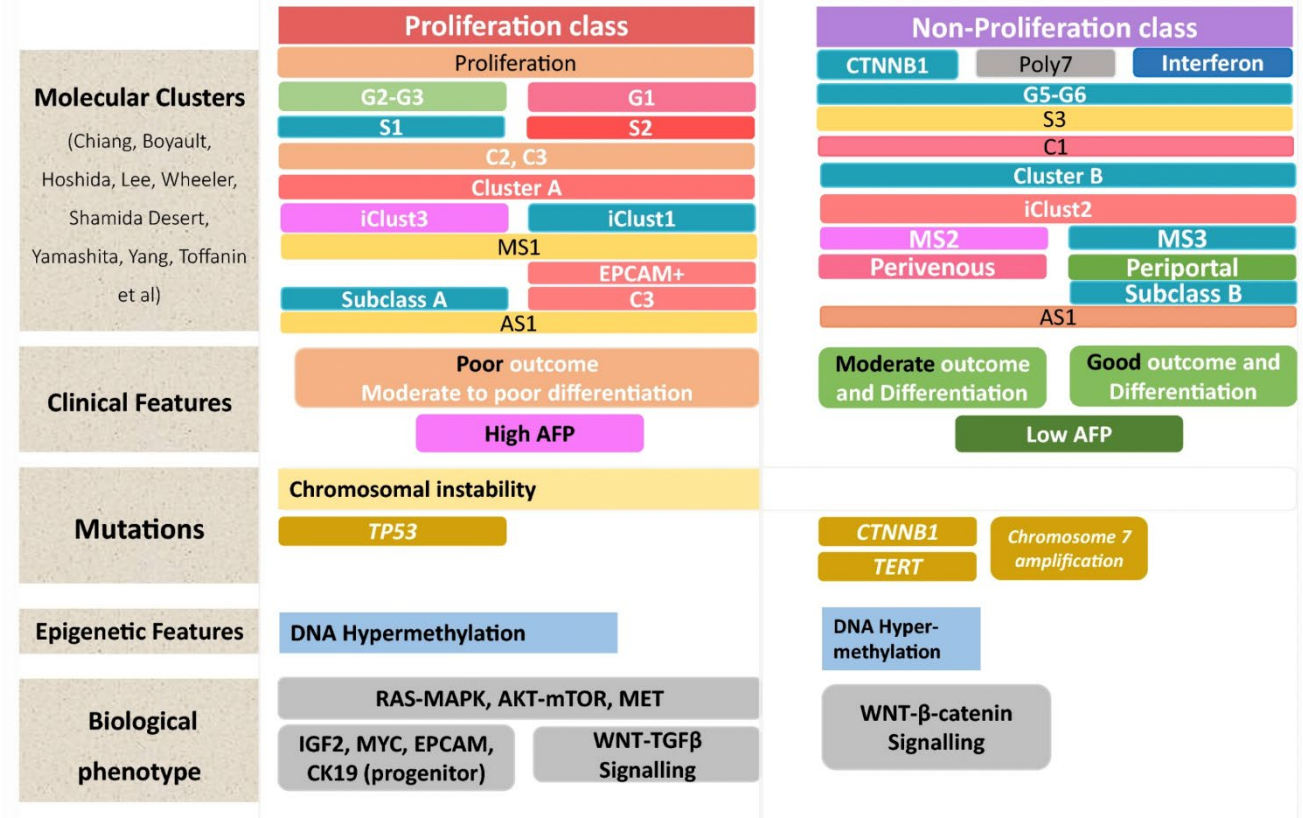
Criteria incorporated into HCC management guidelines



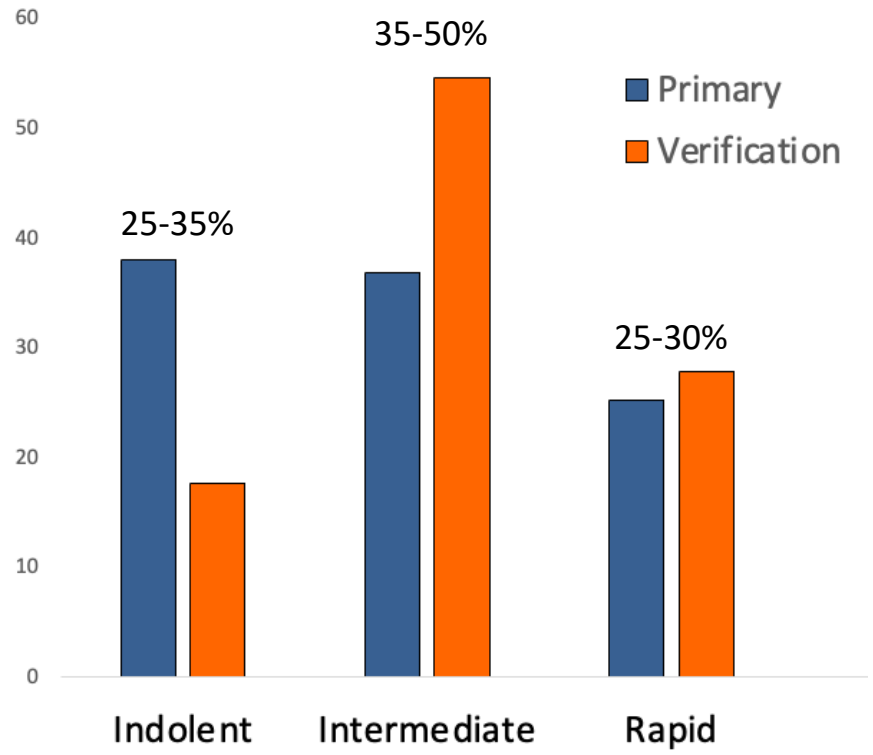
Llovet et al. Nature Reviews Disease Primers 2021

Increasing recognition of tumor heterogeneity

- Molecular subtypes of HCC associated with clinical presentation and prognosis

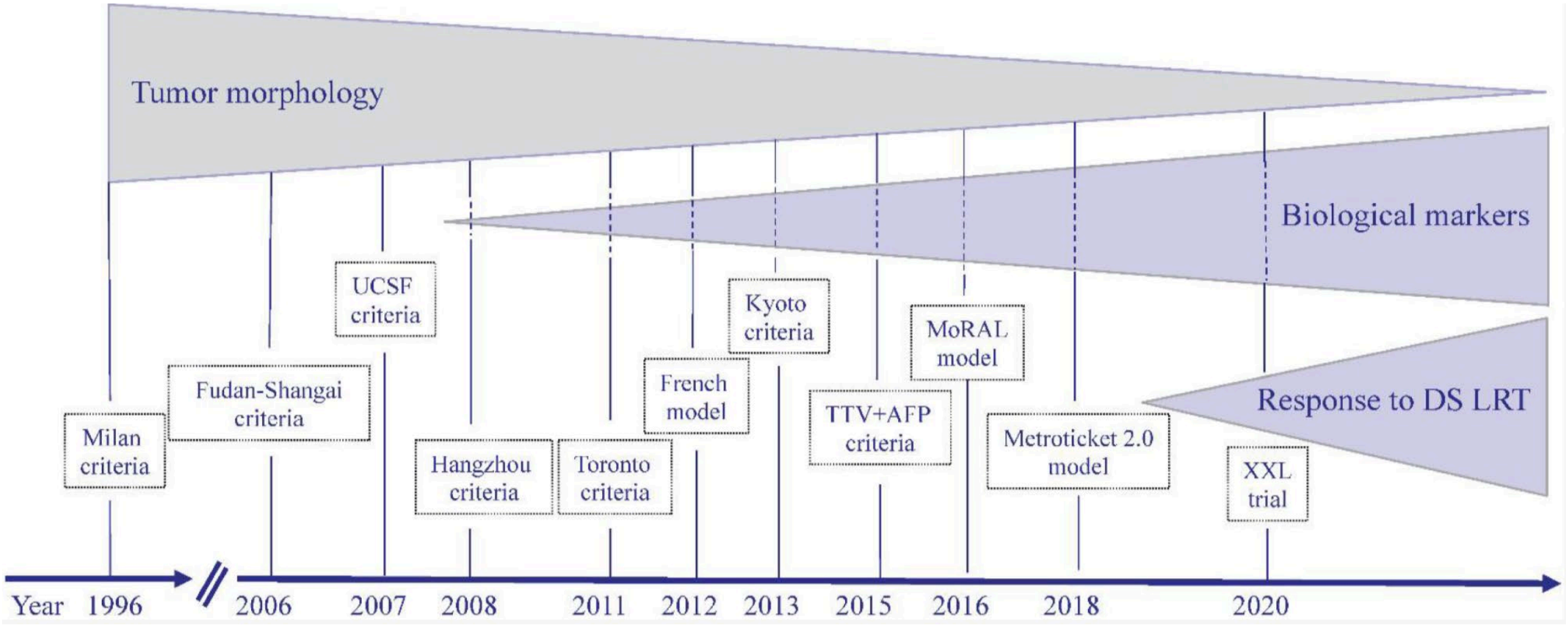


- Retrospective cohort of patients with HCC diagnosed between 2008-2017 at 6 centers
- Results confirmed in meta-analysis

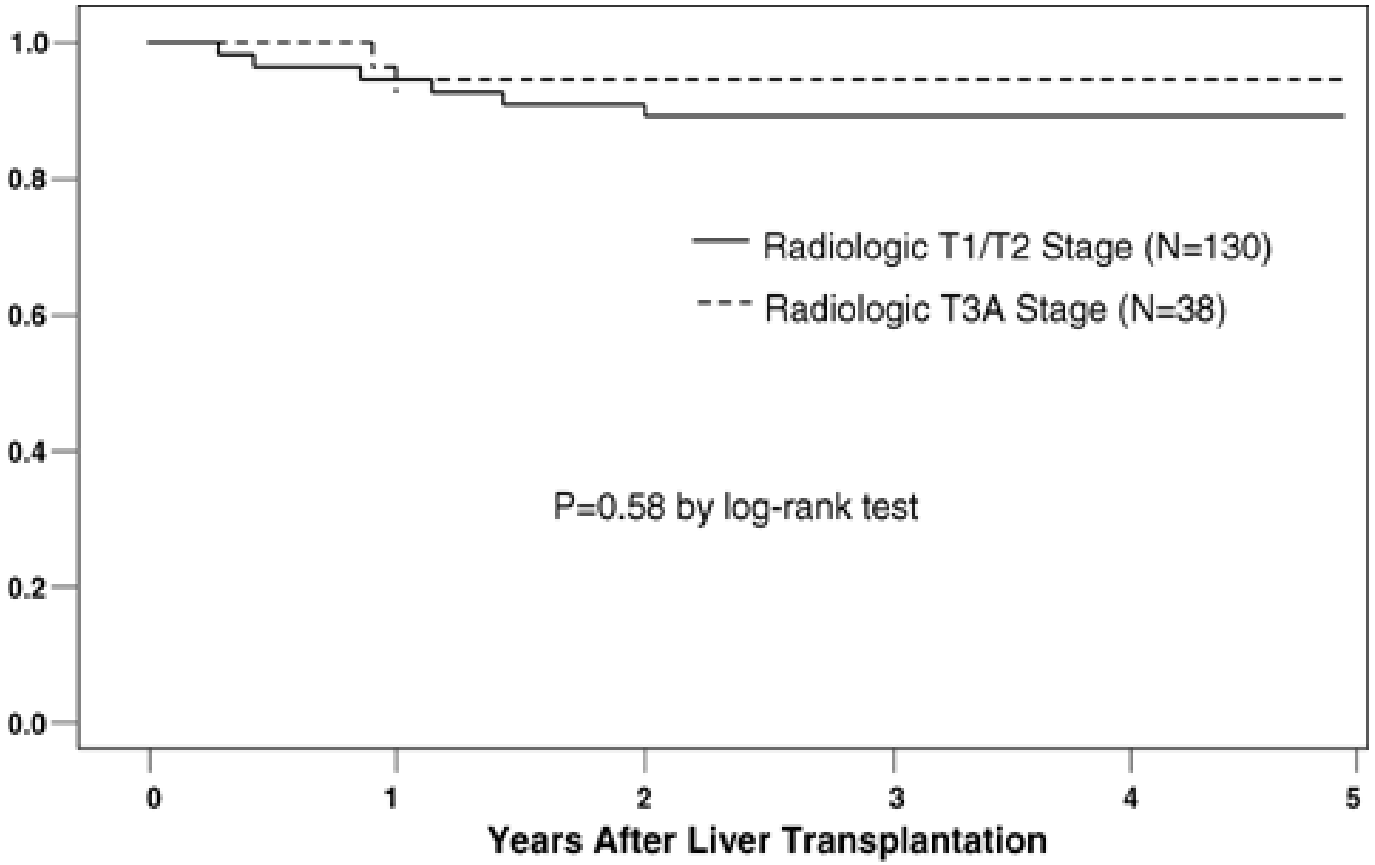


Rich et al. Hepatology 2018; Raja et al. J Cancer Research and Clinical Oncology 2021

Evolving criteria for patient selection over time



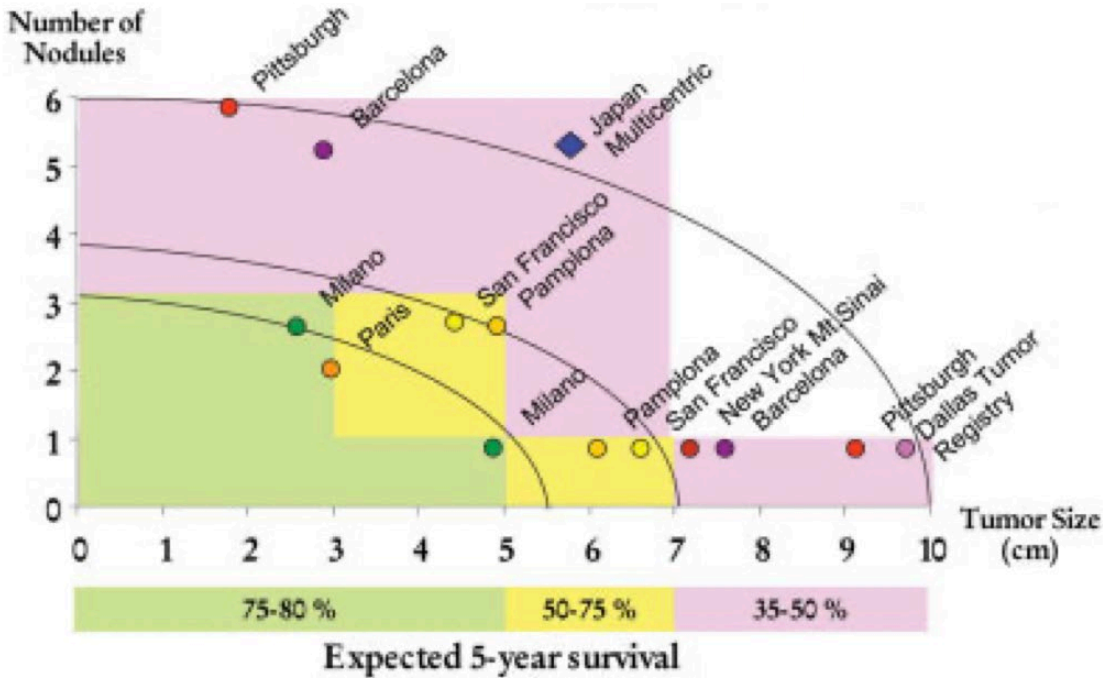
Good post-transplant outcomes possible with expanded criteria

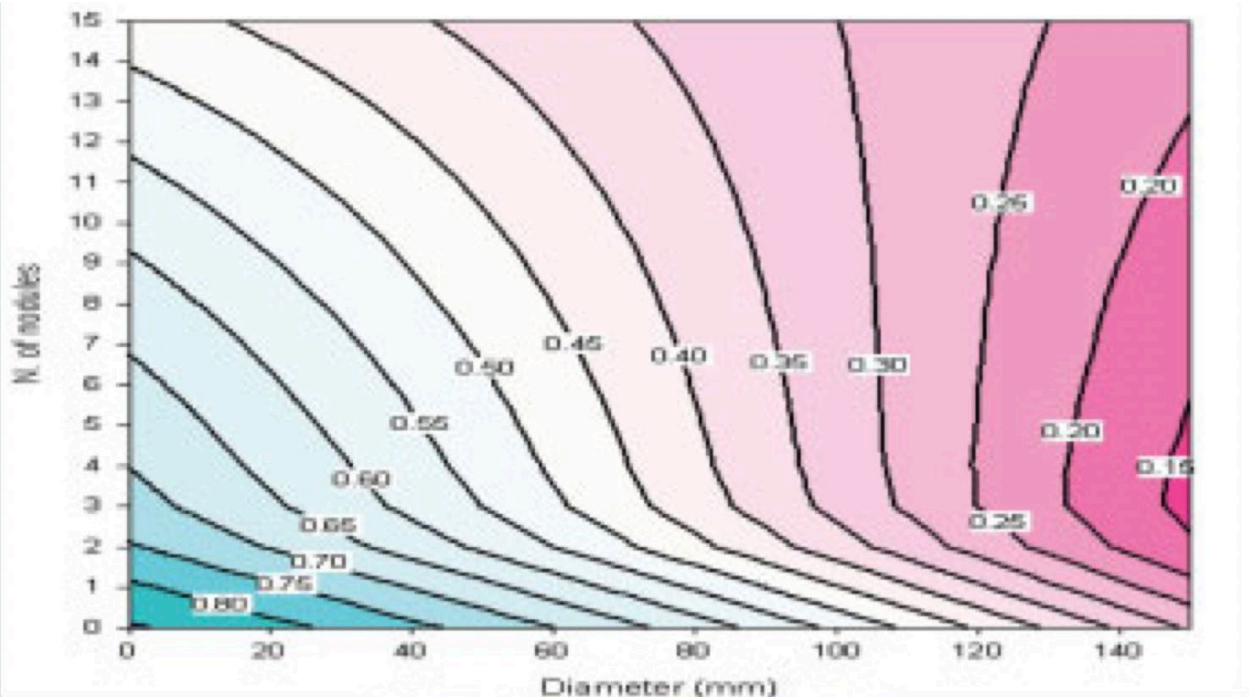


- Prospective validation of UCSF Criteria
  - One tumor ≤ 6.5 cm or 2-3 tumors, each ≤ 4.5 cm and TTV ≤ 8 cm
- Cohort of 168 patients, including 38 with T3A tumors
- 1- and 5-year recurrence free survivals for T1/T2 vs. T3A were 95.7% vs. 96.9% and 90.1% vs. 93.6%, respectively

Yao et al. Am J Transplant 2007; Xu et al, Gut 2016

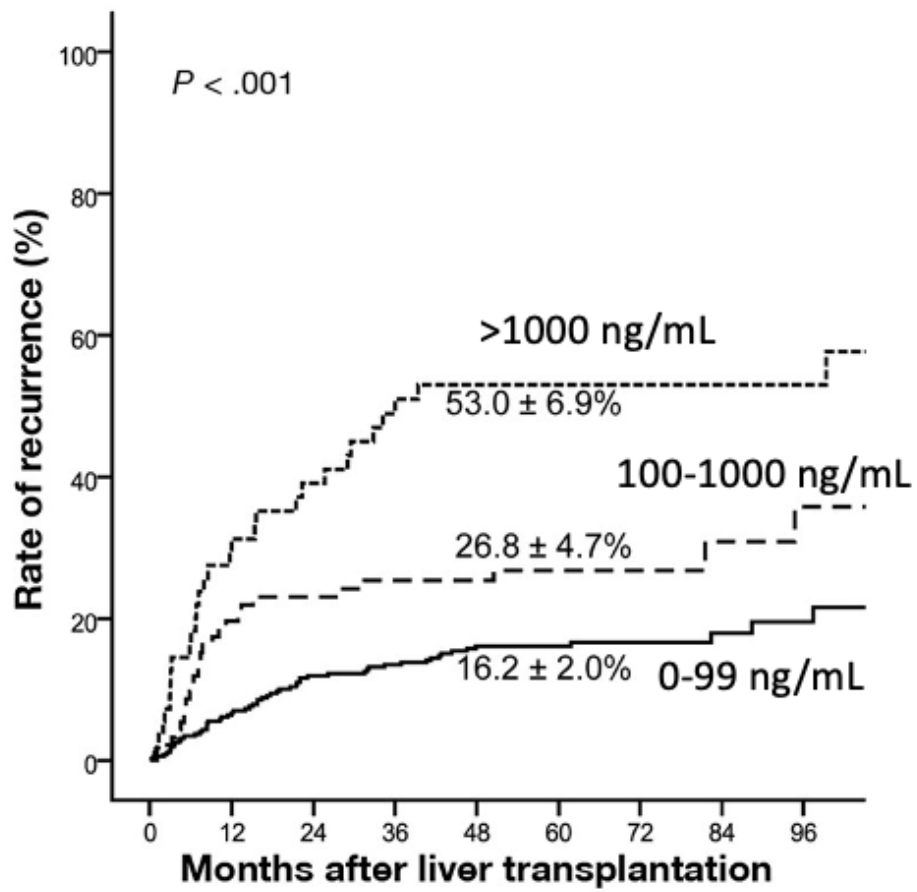
Original MetroTicket showing interaction of tumor number and size

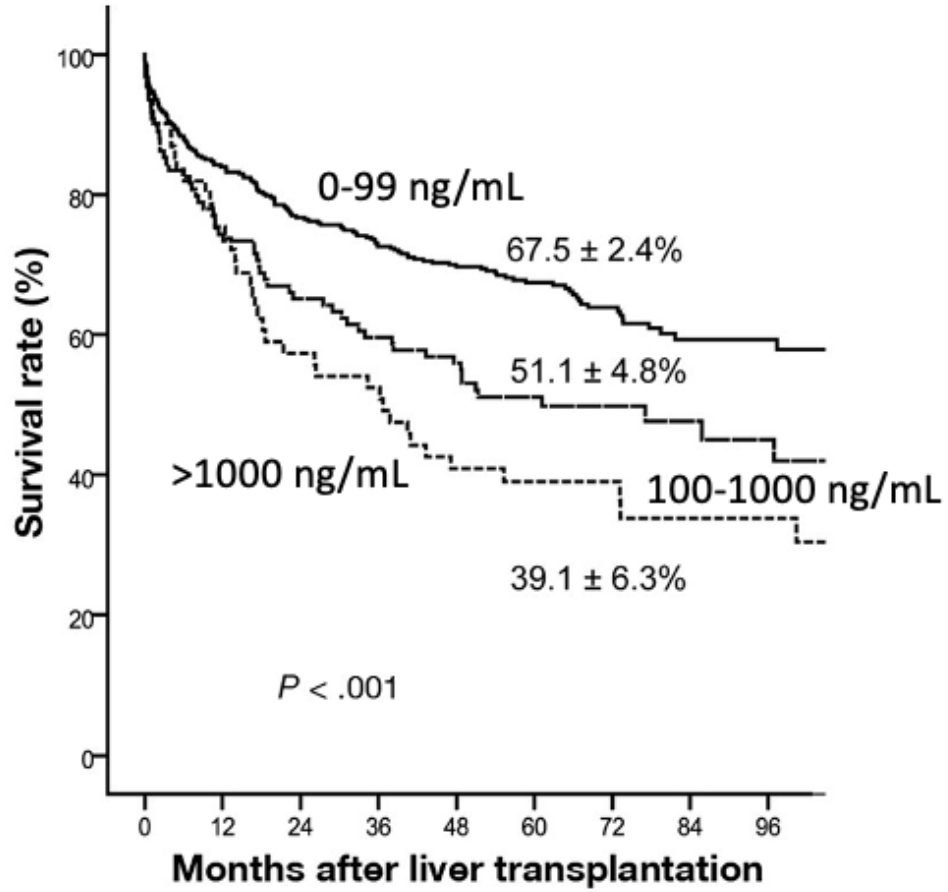




The longer the trip, the higher the price

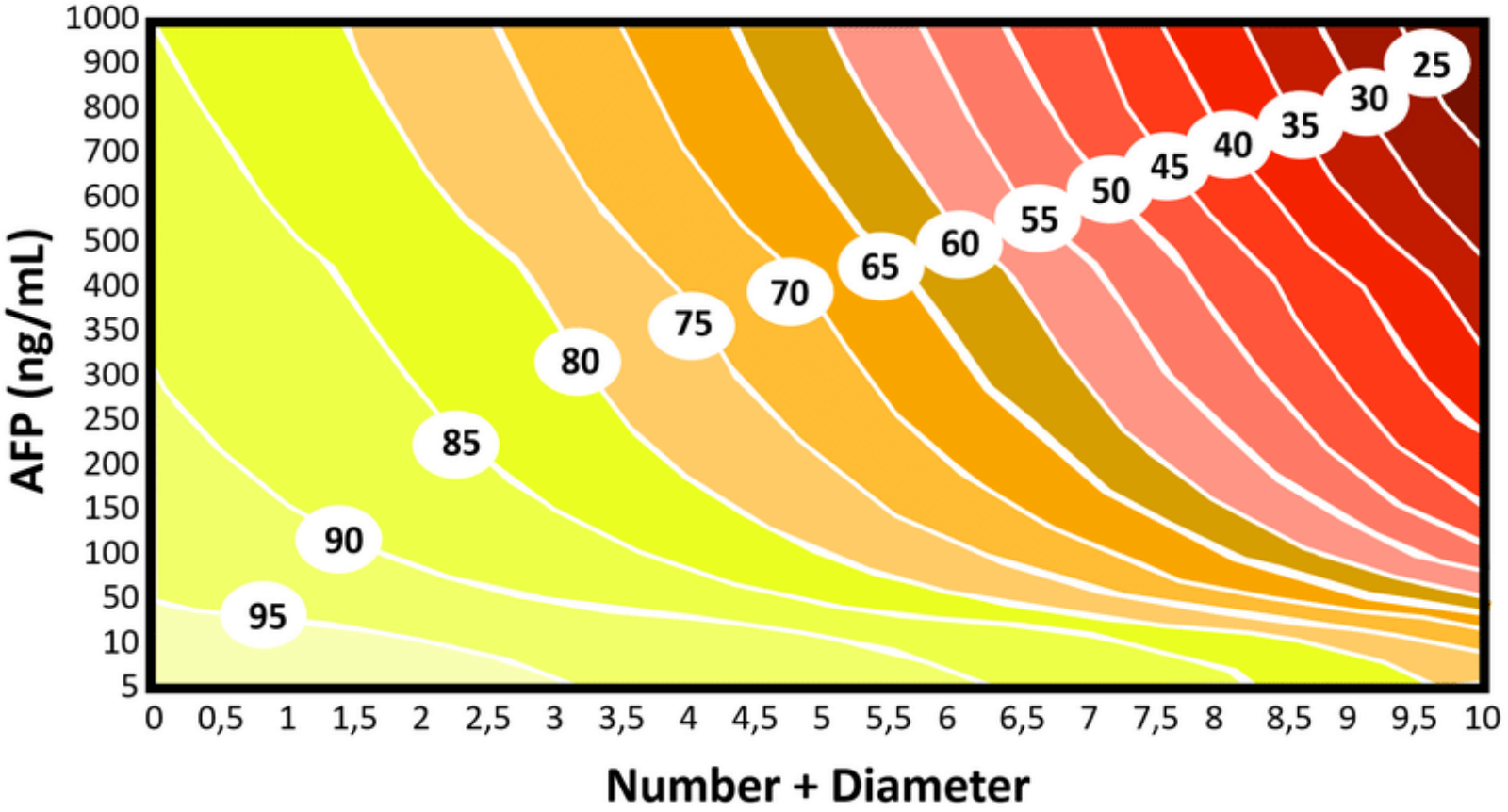
AFP levels are independently associated with post-OLT survival





- Cohort of 597 patients with HCC transplanted between 1998-2001 at 16 centers in France
- AFP associated with post-OLT recurrence and survival

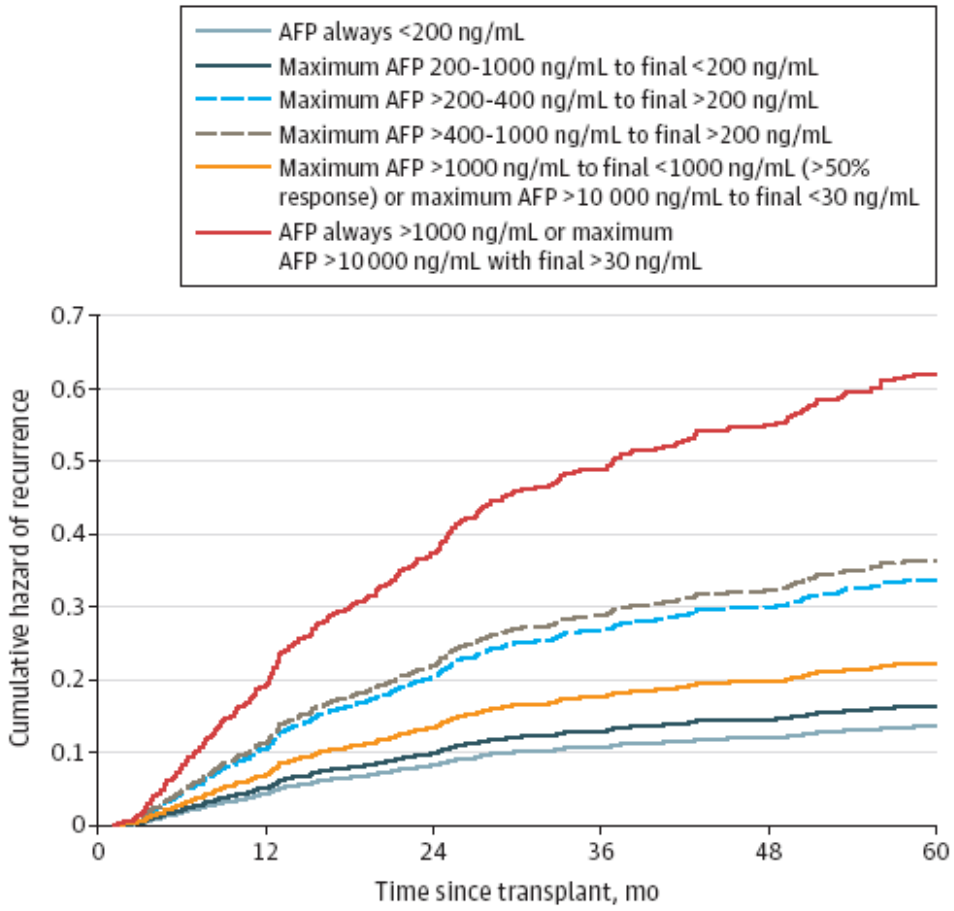
MetroTicket 2.0 includes AFP levels to predict HCC-related survival

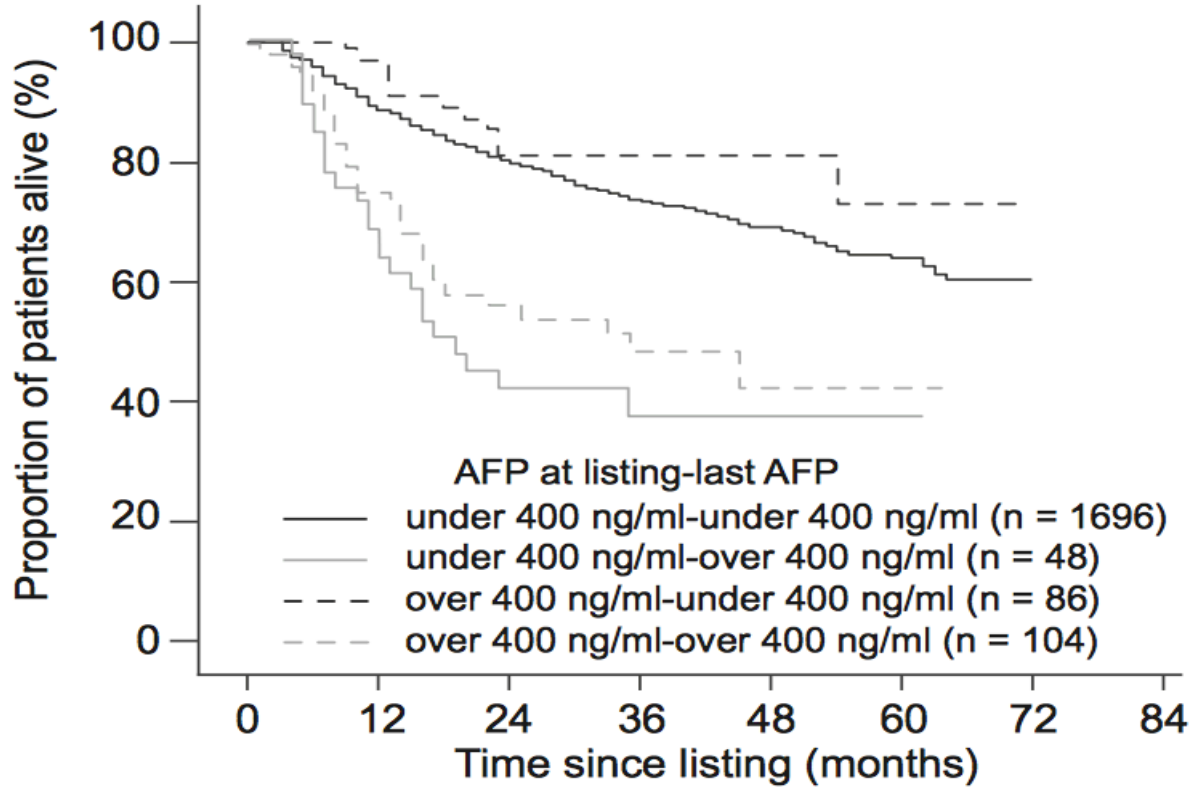


The longer the trip, the higher the price

Mazzaferro et al, Lancet Oncol 2009

Longitudinal changes in AFP associated with prognosis

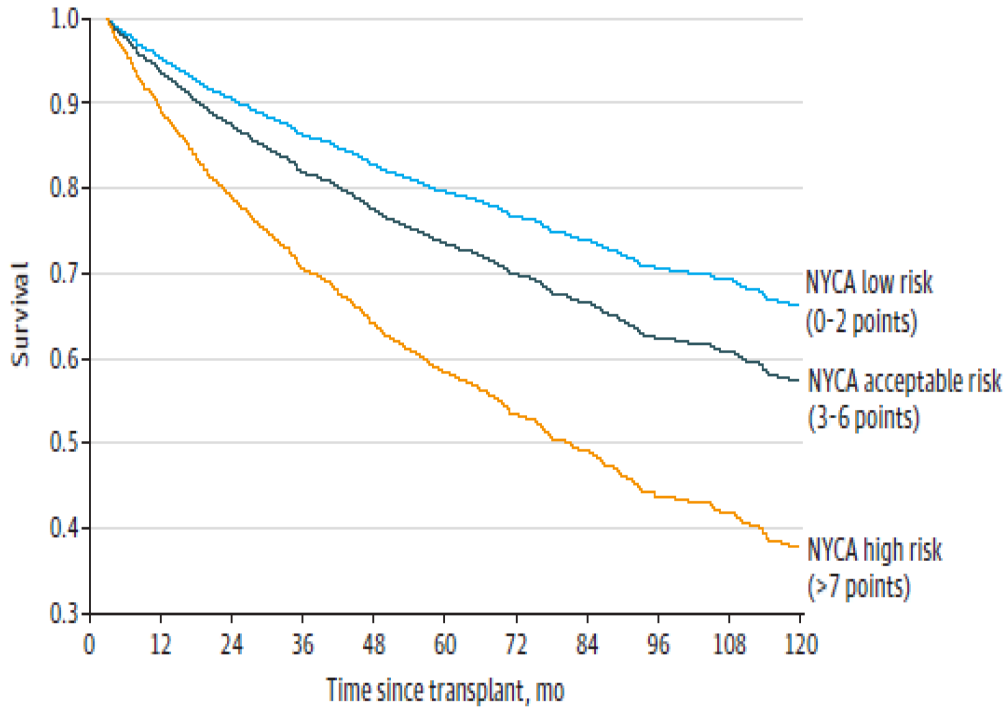




NYCA Criteria incorporates longitudinal change in AFP

- Prospective database of 2236 patients undergoing transplant 2001 – 2013 at 8 centers
  - 545 beyond Milan
- NYCA score generated with points per factor
- NYCA risk category (low, acceptable, high) associated with recurrence-free survival

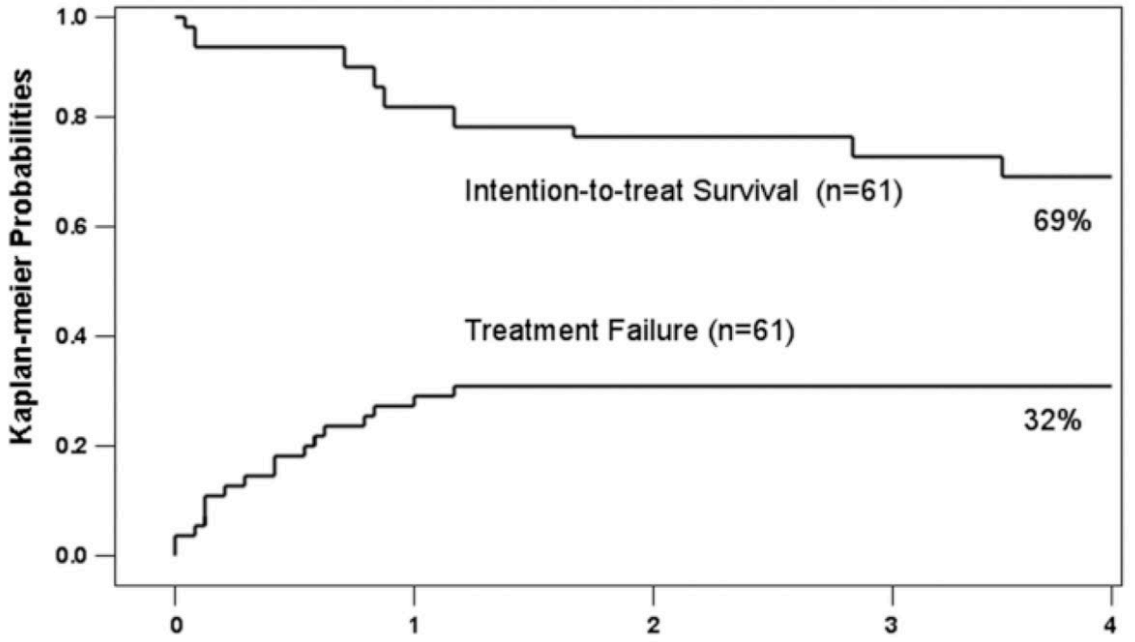
Factors affecting 5-y RFS	NYCA score
Maximum tumor size at diagnosis, cm	
0-3 (Reference)	0
>3-6	2
>6	4
Maximum tumor No. at diagnosis	
1 (Reference)	0
2-3	2
≥4	4
AFP response (maximum to final AFP level)	
AFP always <200 ng/mL	0
Responders	
Maximum >200-1000 to final <200 ng/mL	2
Maximum >1000 to final <1000 ng/mL (must be >50% decrease)	2
Nonresponders	
Maximum >200-400 to final >200 ng/mL	3
Maximum >400-1000 to final >200 ng/mL	4
Maximum >1000 to final >1000 ng/mL	6
Recurrence risk, NYCA score	
Low	0-2
Acceptable	3-6
High	≥7s



Downstaging (treatment response) can help select ideal patients

- Downstaging can provide potential curative option to patients beyond Milan, who do not traditionally have a curative treatment option
  - Differs from bridging therapy used in patients with T2 HCC
- Theoretically selecting patients with favorable tumor biology and lower risk of post-transplant recurrence

- Prospective cohort of 61 patients with HCC beyond T2 between 2002 – 2007
- Minimum observation period of 3 months
- DS success in 70.5% and 57% underwent OLT
- 4-year post-OLT survival: 92%

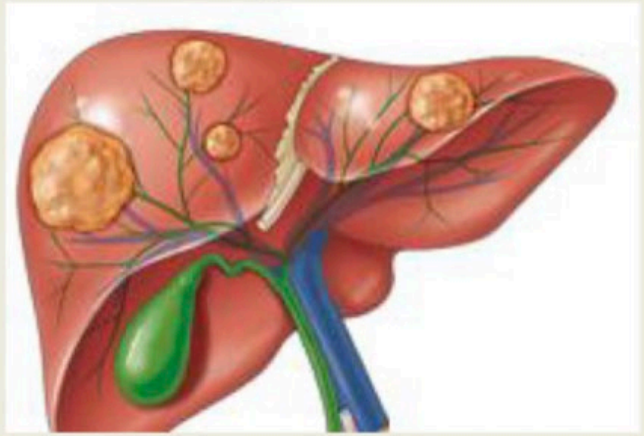


Yao et al. Hepatology 2008

MERITS-LT Consortium Experience using UNOS-DS Criteria

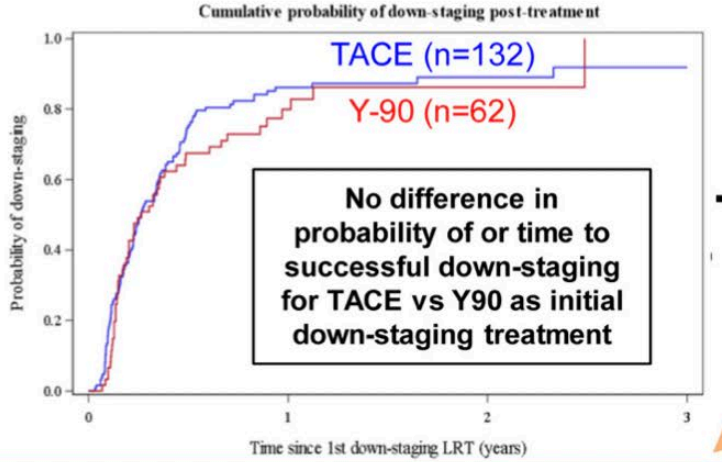
Multicenter study of 194 patients undergoing downstaging between 2016-2019

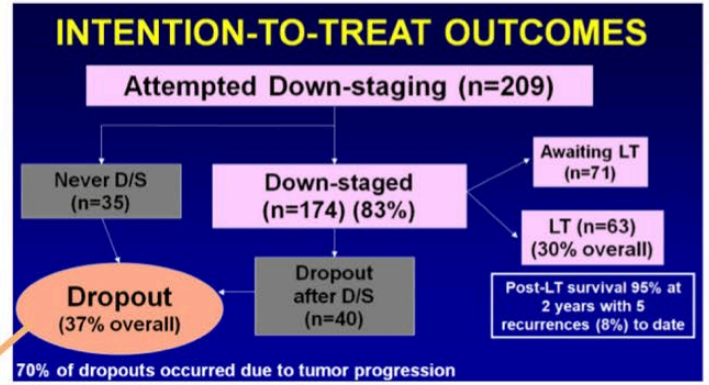
HCC meeting UNOS-DS criteria*



UNOS-DS inclusion criteria*

1 lesion > 5 cm and ≤ 8 cm
2 or 3 lesions ≤ 5 cm w/ total diameter ≤ 8 cm
4 or 5 lesions ≤ 3 cm w/ total diameter ≤ 8 cm
No vascular invasion or extrahepatic spread





Protocol Dropout

- No difference in dropout probability for TACE vs Y90 as 1st down-staging treatment
- Pre-tx AFP-L3 ≥10% (competing risks HR 3.7, p=0.02) only variable associated w/ dropout

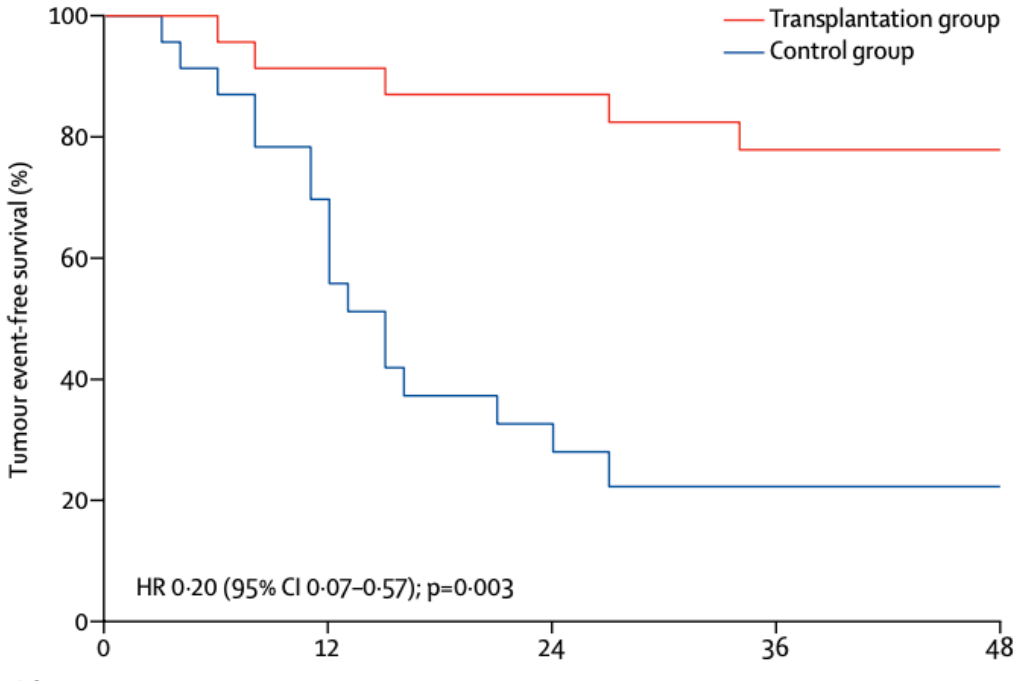
Overall intention-to-treat survival

92% at 1 year and 72% at 3 years from 1st down-staging treatment

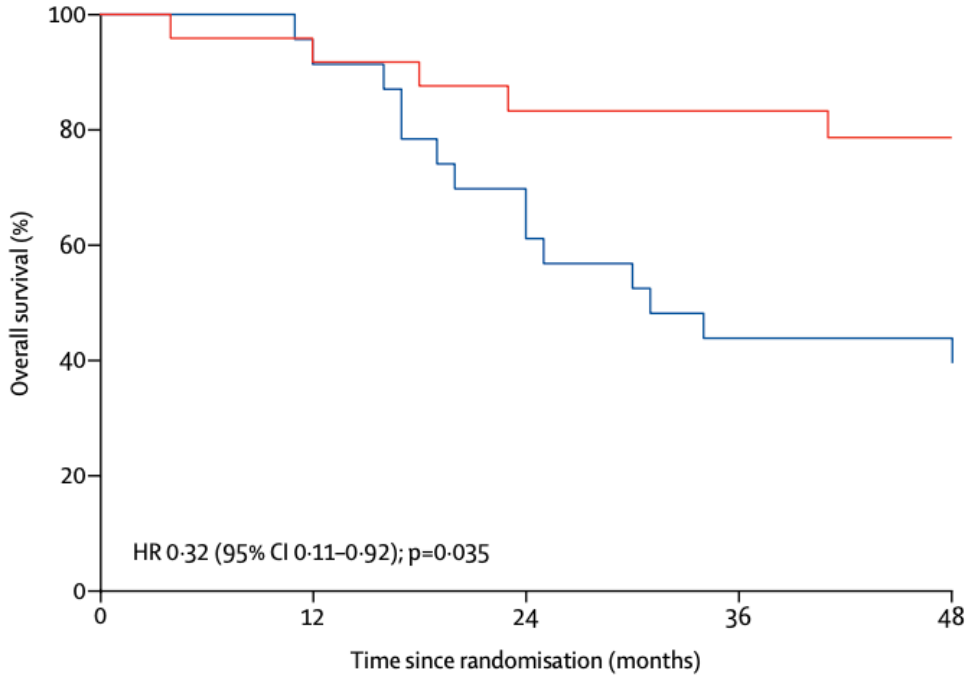
Benefits of downstaging: The XXL Trial

Open-label, multicenter phase 2/3 RCT among patients with liver-localized HCC beyond Milan Criteria
Patients with response after downstaging therapies were randomized to liver transplant or non-transplant therapy
After 29 patients failed downstaging, 45 patients randomized to transplant vs. non-transplant therapy

5-year HCC-free survival: 76.8% vs. 18.3%

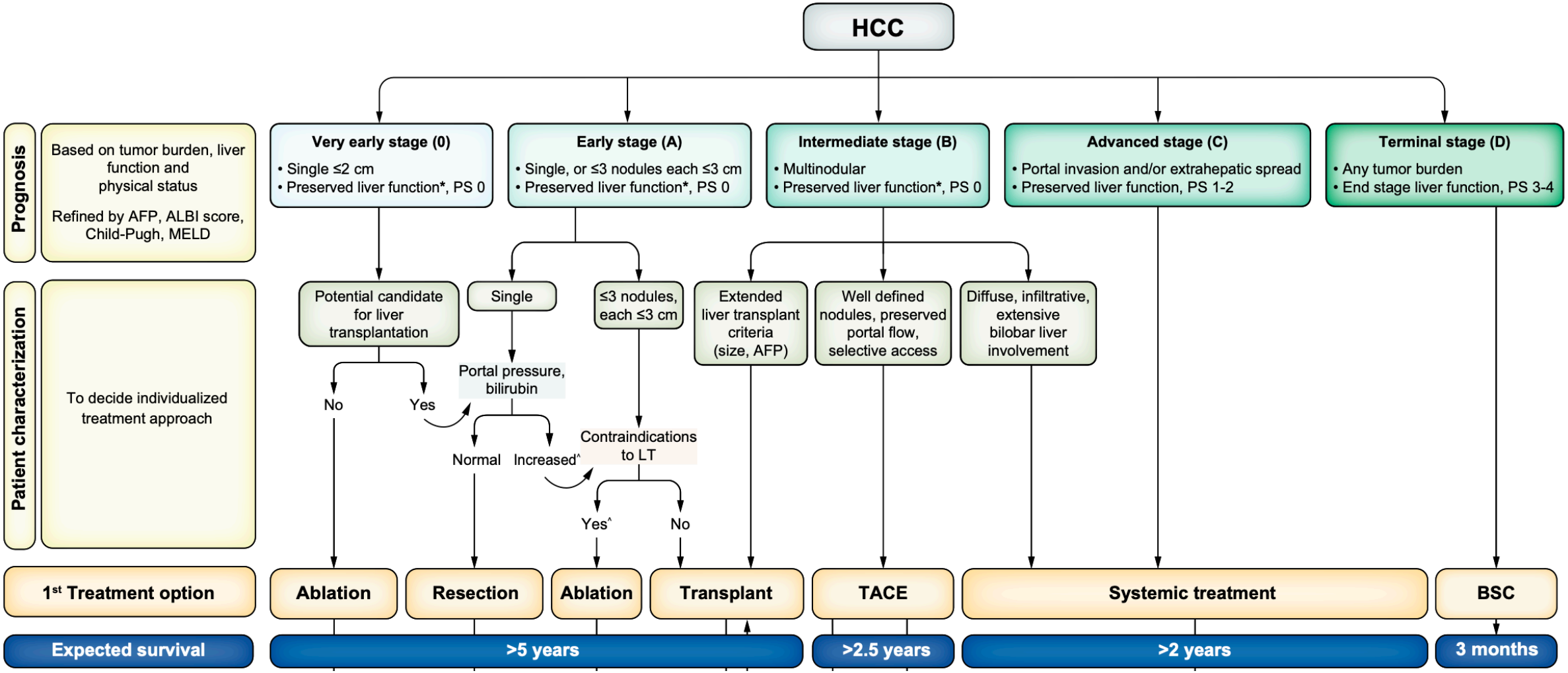


5-year overall survival: 77.5% vs. 31.2%



Mazzaferro et al. Lancet Oncology 2020

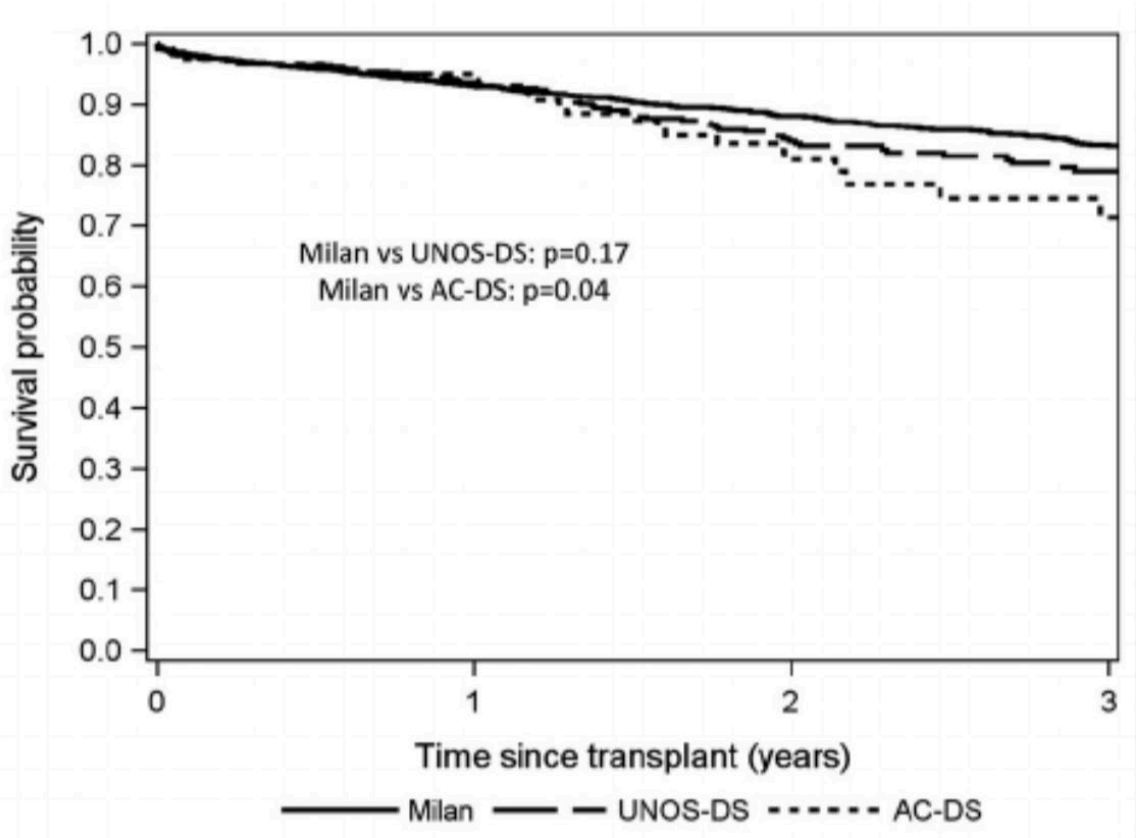
Expanded criteria now recognized in BCLC 2022 Update

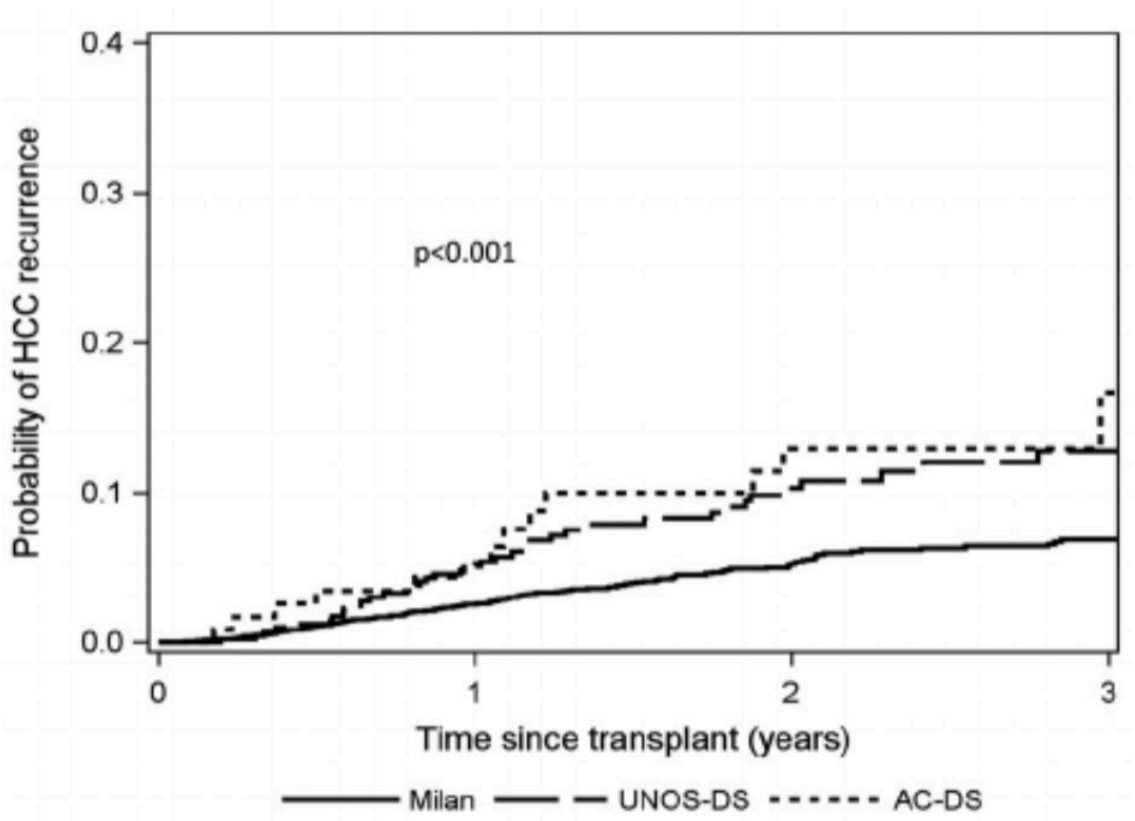


Reig et al *J Hepatology* 2022

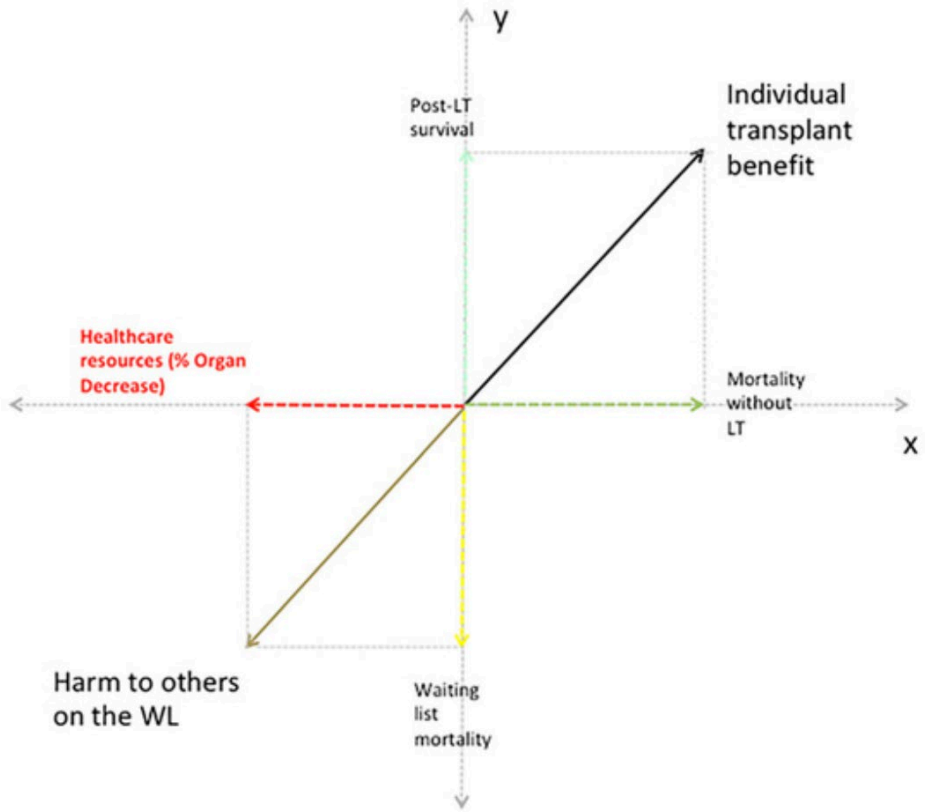
Patients within UNOS-DS achieve better survival than AC-DS

Multicenter study of patients undergoing LT from 2012-2015 comparing downstaged patients (n=422) vs. within Milan (n=3276) vs. beyond Milan (n=121)

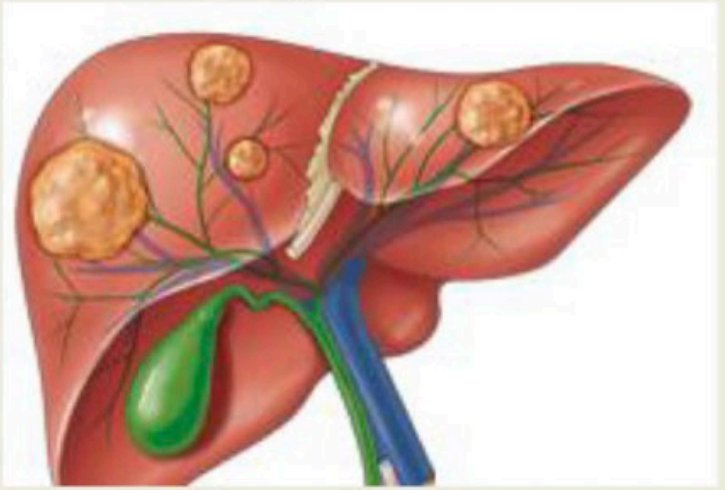




Ethical framework of net benefit demands good organ stewardship



HCC meeting UNOS-DS criteria*



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No vascular invasion or extrahepatic spread

Living donor LT offers a pathway to patients beyond UNOS-DS

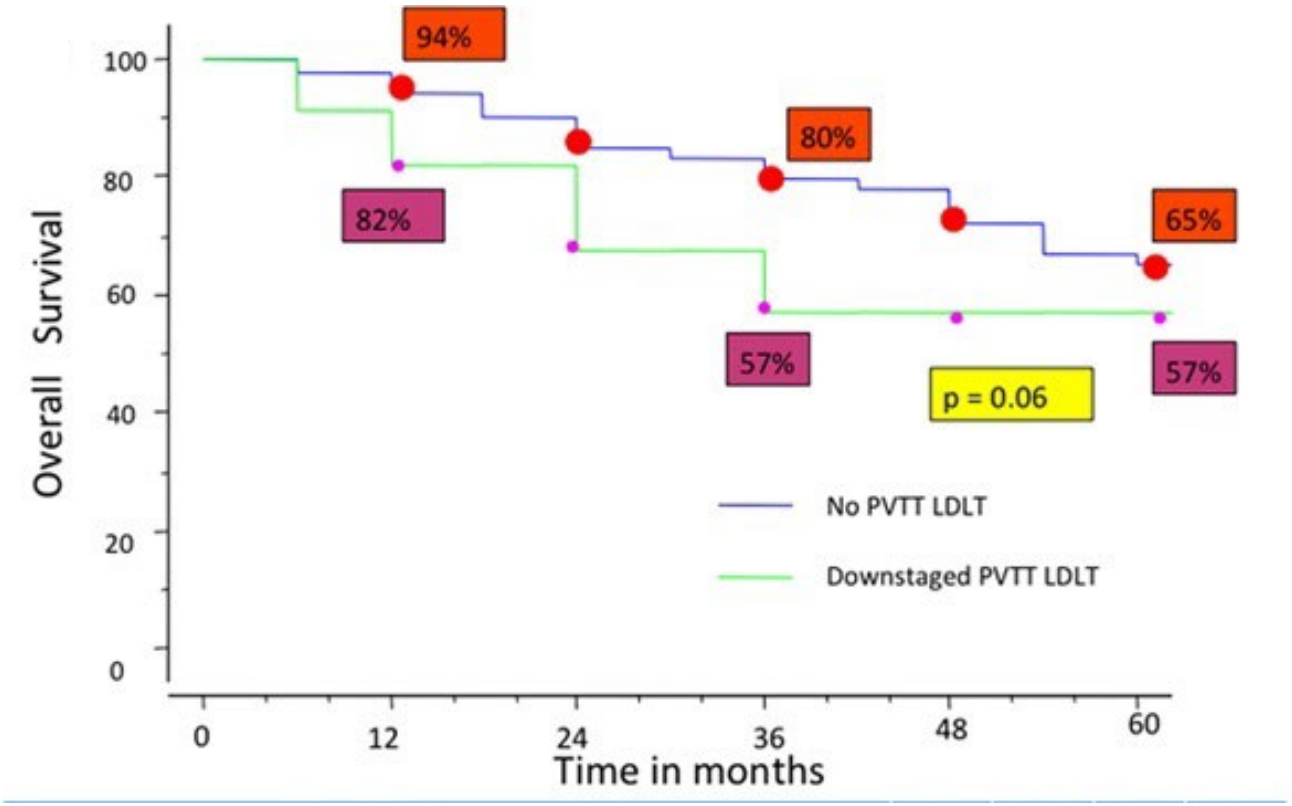
Immune checkpoint inhibitors induce objective responses in one-third of patients so revisiting role of transplant in select patients

Outcome	RECIST 1.1		mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR,% (95% CI)	**30 (32-35)**	**11 (7-17)**	**35 (30-41)**	**14 (9-20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Median DoR, mos (95% CI)	**18.1 (14.6-NE)**	**14.9 (4.9-17.0)**	**16.3 (13.1-21.4)**	**12.6 (6.1-17.7)**

Finn et al *NEJM* 2020

Living donor liver transplant may offer pathway for selected patients beyond UNOS-DS

- Study comparing survival post LDLT among 23 patients with PVTT who underwent downstaging and LDLT vs. 382 patients without PVTT
- 5-year OS were 65% vs. 57% (p=0.06)
- 5-year recurrence-free survival were 66% vs. 51% (p=0.33)
- When including an additional 20 patients with PVTT who underwent LDLT, 5-year survival was worse (65% vs. 50%, p=0.006)

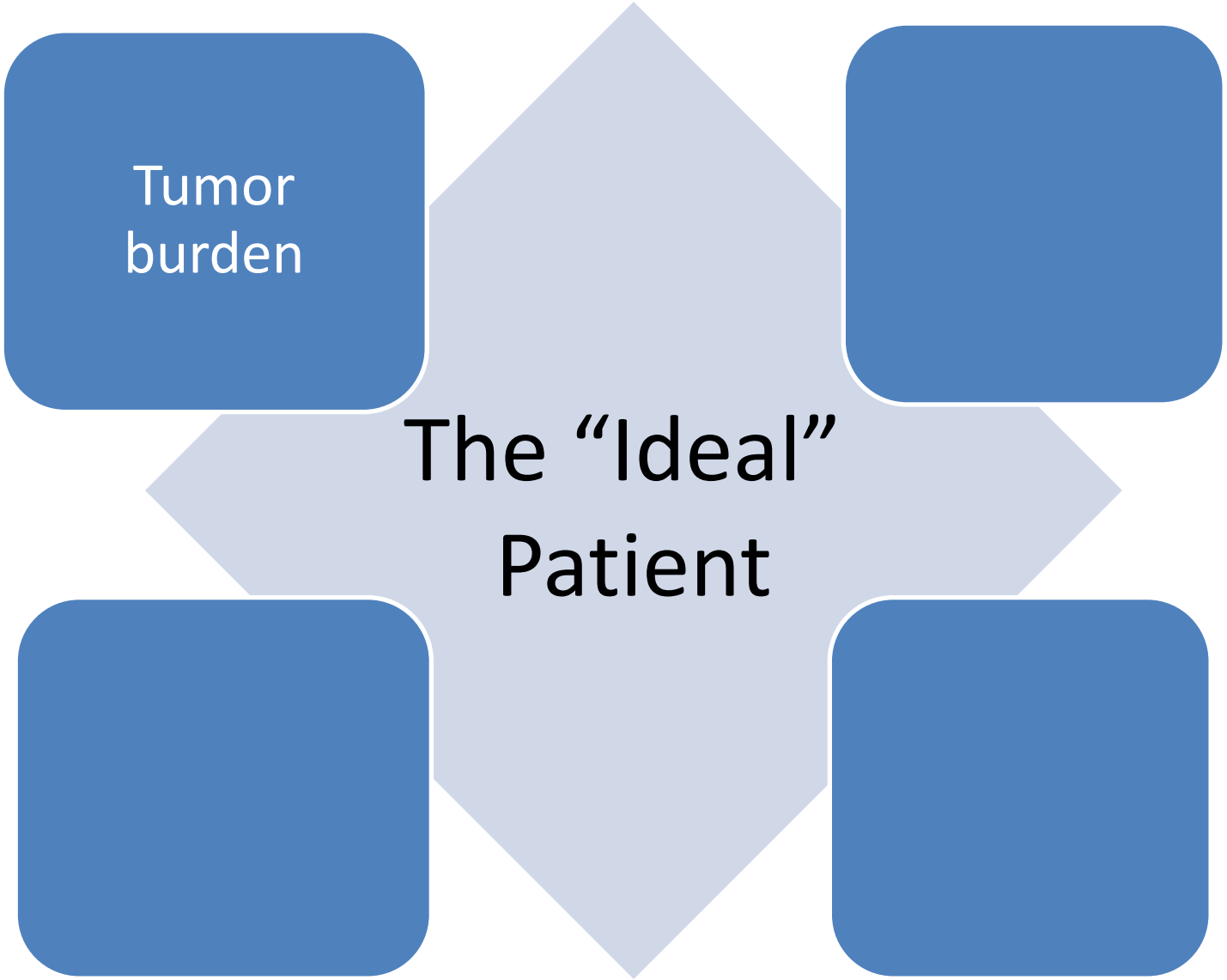


Recent data suggesting possible safety of immunotherapy prior to liver transplant

No.	Age	Gender	ULD	Max tumor diameter (cm)	Max pre-LT AFP	No. of LRT	Salvage/type transplantation	Pathology Milan in/ out	Cycles	Nivolumab (days pre-LT)	PRBC (U)	Duration of follow-up post LT (months)	Complication	Rejection	Recurrence
1	69	M	None	10	3	2	Yes/LDLT	Milan out within UCSF	21	18	0	23	None	None	None
2	56	F	HCV	5.4	4.4	2	No/DDLT	Milan out within UCSF	8	22	14	22	None	None	None
3	58	M	HBV	21	9.4	6	Yes/DDLT	Milan in	32	1	30	22	None	None	None
4	63	M	HCV, HIV	4.4	507	7	No/DDLT	Milan in	4	2	15	21	None	None	None
5	30	M	HBV	3.2	1493	2	Yes/DDLT	Milan in	25	22	0	16	None	Mild (low tacrolimus level)	None
6	63	M	HBV, HIV	2	158	0	No/DDLT	Milan in	4	13	1	14	Bile leak	None	None
7	66	M	HBV	2.5	479	2	Yes/DDLT	Milan in	9	253	7	14	None	None	None
8	55	F	HBV	2.8	820	3	No/DDLT	Milan in	12	7	0	8	None	None	None
9	53	F	NASH	8.7	124	1	Yes/DDLT	Milan out within UCSF	2	30	17	8	None	None	None

Tabrizian et al. Am J Transplant 2021

Patient selection is driven by multiple surrogates of tumor biology



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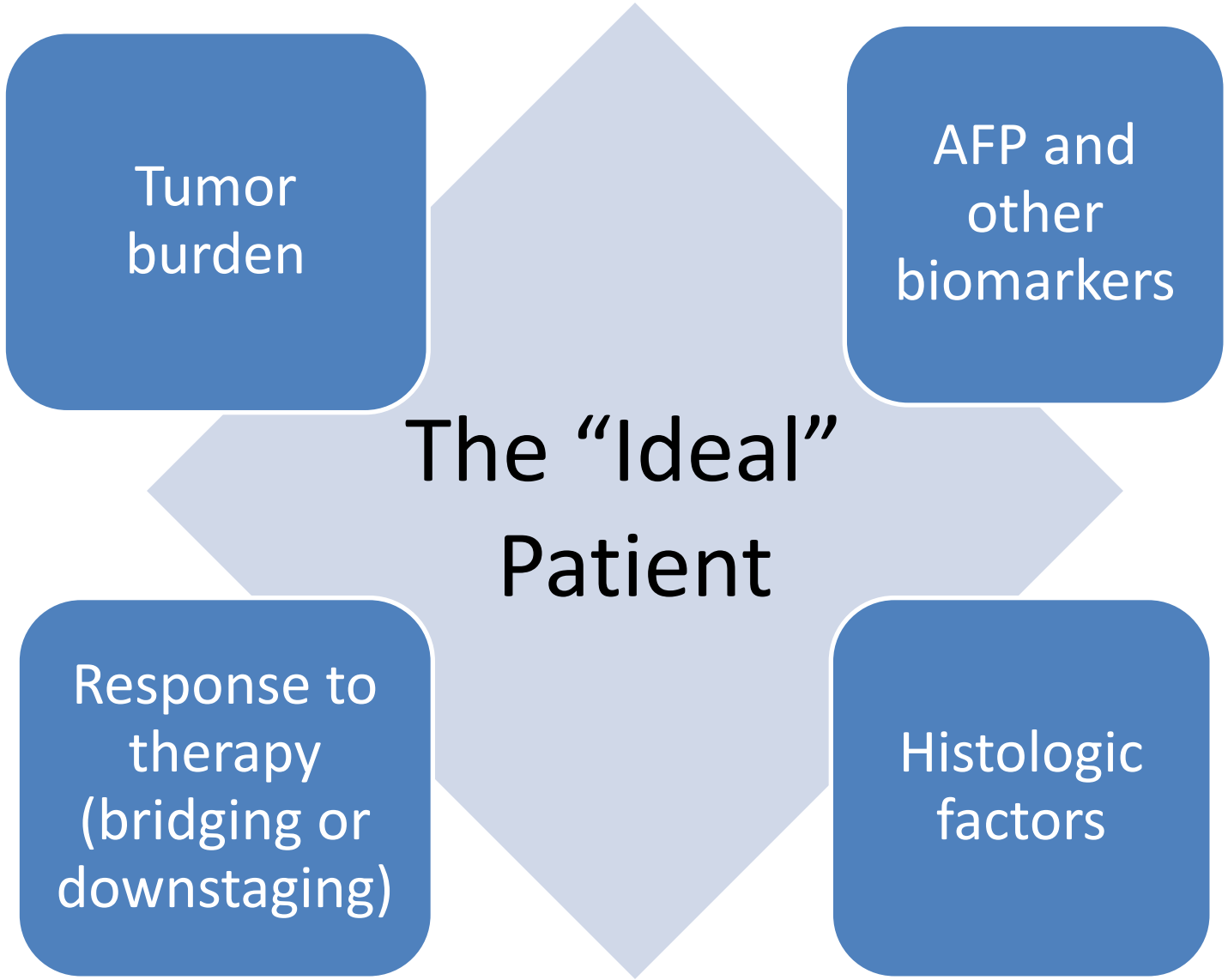
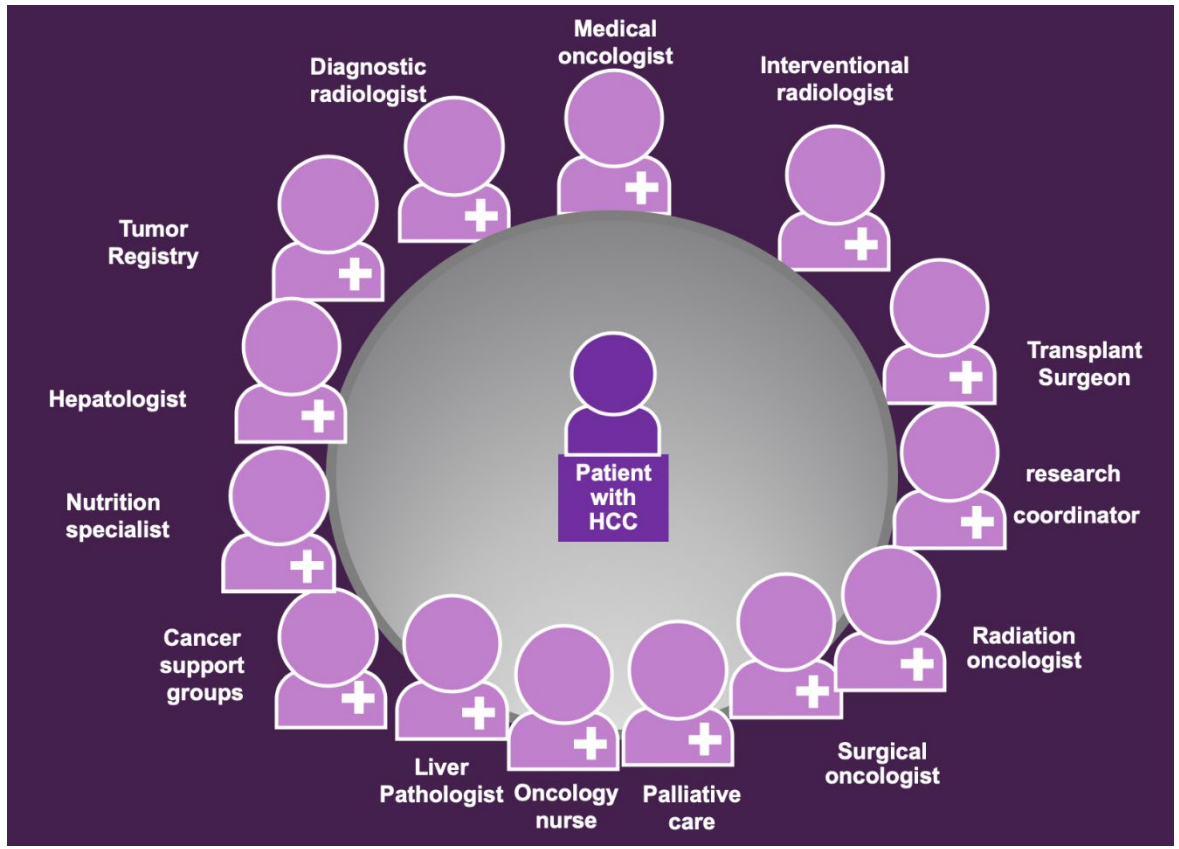


Decisions should be made in multidisciplinary setting



Study	Description	Outcomes
Serper 2017 (n=3988)	Multi-specialty evaluation or tumor board	Increase HCC treatment receipt and improve survival
Yopp 2014 (n=355)	Single day MDT clinic and conference	Improve early detection, curative treatment, time to treatment, and survival
Zhang 2013 (n=343)	Single day MDT clinic	Changed imaging/pathology interpretation and therapy plan
Chang 2008 (n=183)	Fluid referrals and joint conference	Improve early detection, curative treatment, and survival

Serper et al. Gastro 2017; Yopp et al *Ann Surg Onc*. 2014; Chang et al *HPB* 2008; Zhang et al *Curr Oncol* 2013

Patient case

- 54-year-old male with history of hepatitis C cirrhosis, compensated, s/p sustained virological response
- Initially was followed closely with HCC surveillance but then lost to follow-up
- Presented two years later with incidental HCC
  - Two lesions, 4.5 cm and 3 cm, (both LR-5)
- Child Pugh A – Bili 1.2, Alb 3.0, INR 1.1, platelet count 72
- AFP 12 ng/mL
- Actively working, ECOG 0

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- Child Pugh A – Bili 1.2, Alb 3.0, INR 1.1, platelet count 72
- AFP 12 ng/mL → Low AFP
- Actively working, ECOG 0
- Treated with TACE and partial response (One lesion, 2 cm viable disease)

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- AFP 12 ng/mL → Low AFP
- Actively working, ECOG 0
- Treated with TACE and partial response (One lesion, 2 cm viable disease)
- Listed and underwent liver transplantation, doing well with no recurrence

Summary

- There have been notable changes in the role of liver transplantation for HCC
- Increasing recognition that ideal patient selection extends beyond tumor number and size
- Important to assess tumor biomarkers (e.g., AFP), response to locoregional therapy, +/- histology
- Doing so allows us to extend benefits of liver transplantation to a greater number of patients