LIVER TRANSPLANTATION FOR HCC

By

Mohamed Soliman, MD


AGENDA
1.
2.
3.
4.
5.

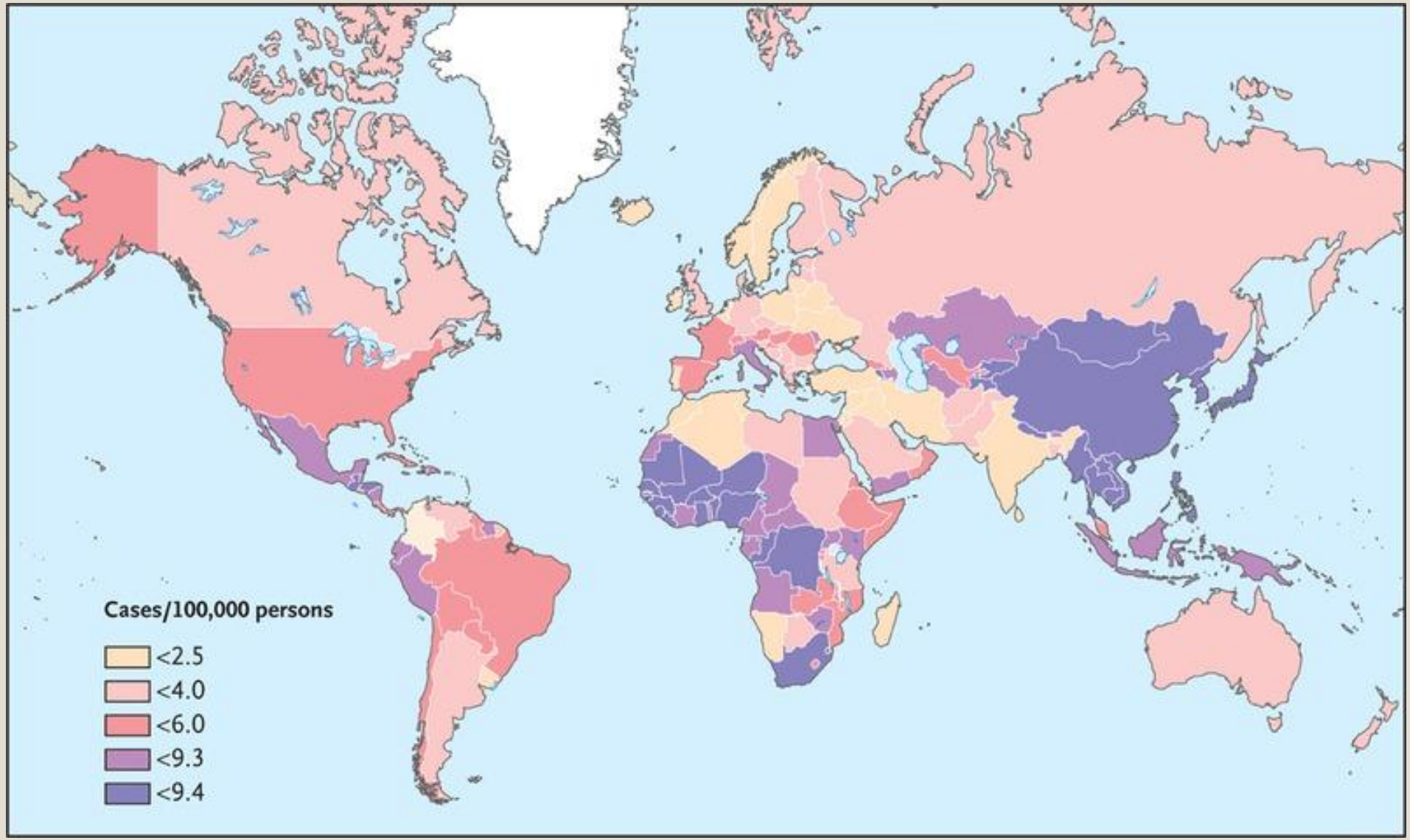
- Introduction
- Patient selection
- Organ allocation
- Bridging and downstaging
- Recurrence

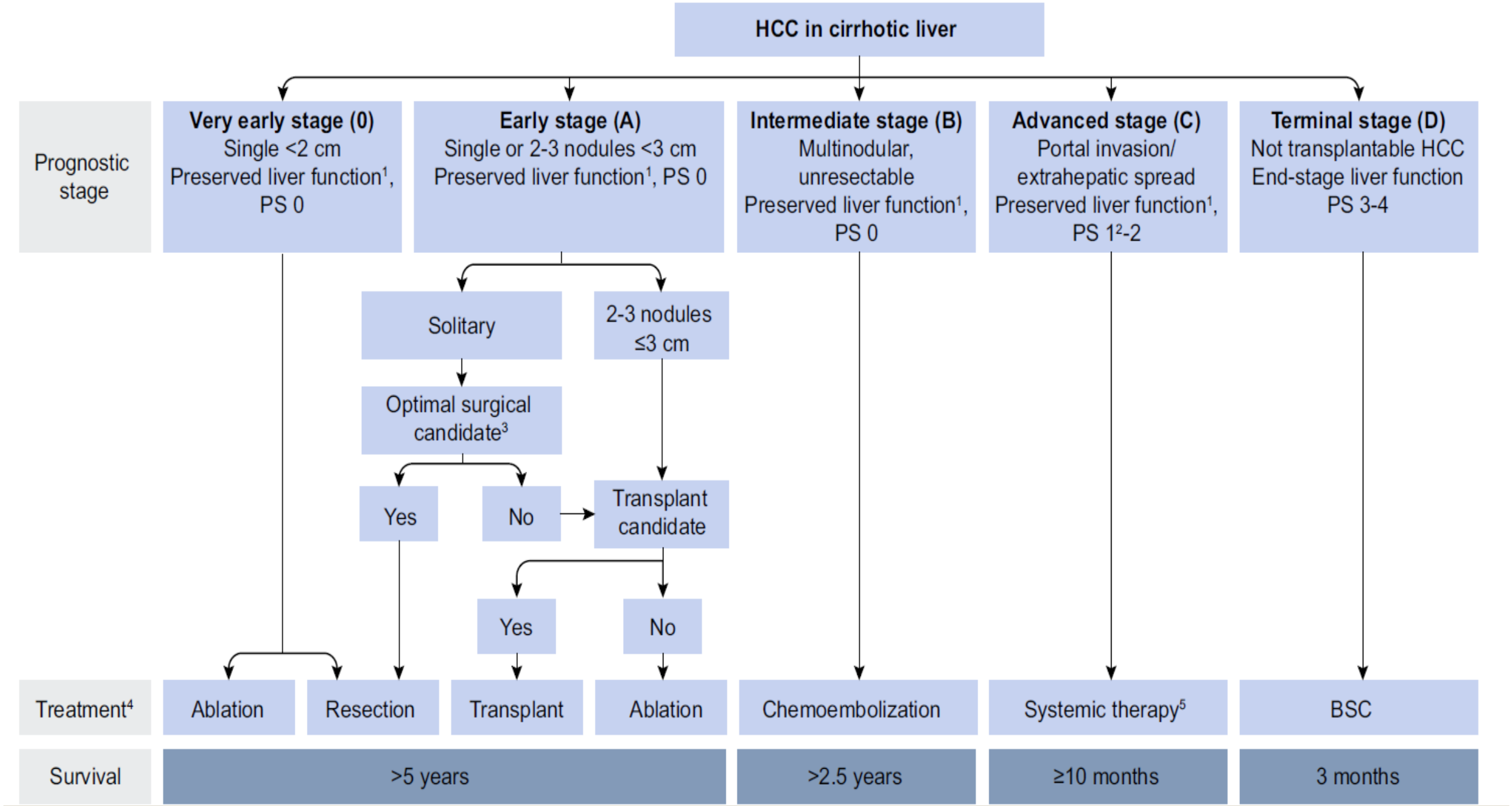
- Primary liver cancer is the 6th most commonly diagnosed cancer and was the 4th cause of cancer death worldwide in 2018, including hepatocellular carcinoma (75%-85%) and intrahepatic cholangiocarcinoma (10%-15%).

Bray et al, Global cancer statistics 2018:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018

- It is more common in men and is currently the 2nd leading cause of cancer death worldwide in men and the 6th in women.

Global Burden of Disease Cancer Collaboration *JAMA Oncol* 2017


Cases/100,000 persons
<2.5
<4.0
<6.0
<9.3
<9.4

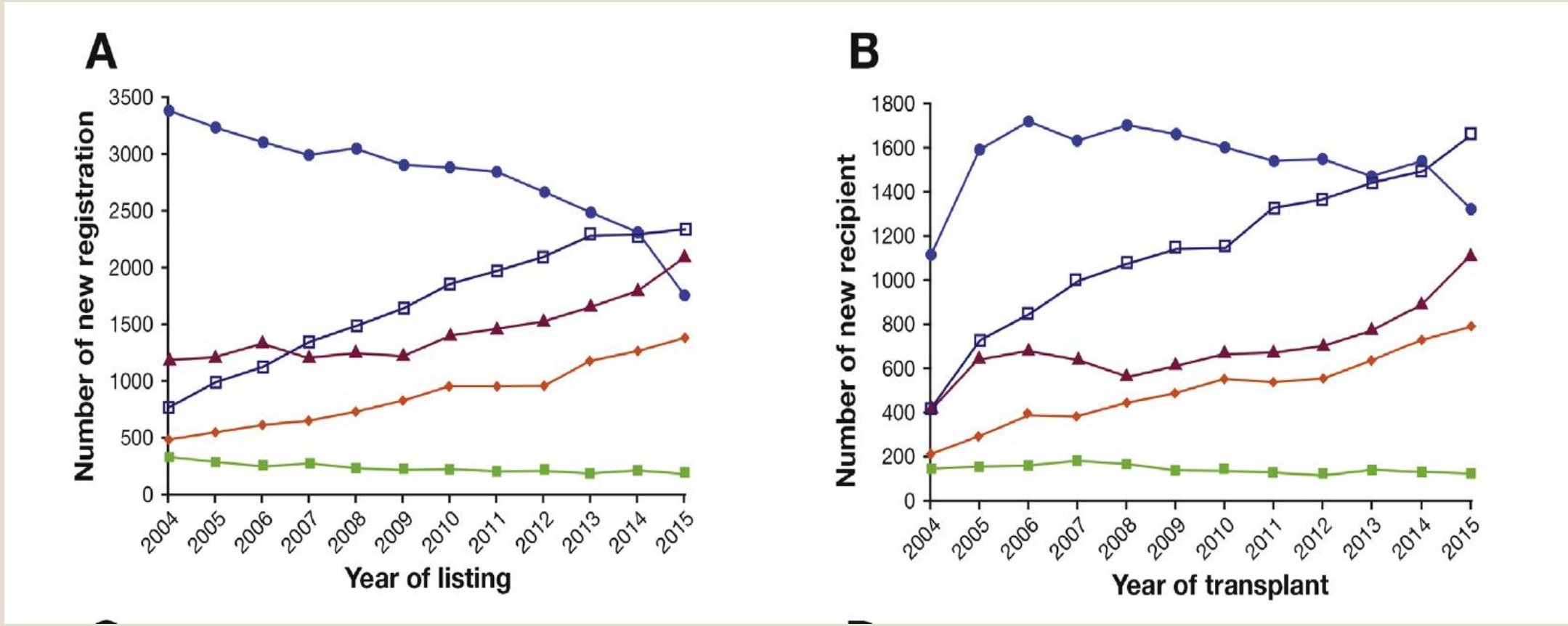

HCC in cirrhotic liver
Prognostic stage
Very early stage (0)
Single <2 cm
Preserved liver function[1], PS 0
Early stage (A)
Single or 2-3 nodules <3 cm
Preserved liver function[1], PS 0
Intermediate stage (B)
Multinodular, unresectable
Preserved liver function[1], PS 0
Advanced stage (C)
Portal invasion/ extrahepatic spread
Preserved liver function[1], PS 1[2]-2
Terminal stage (D)
Not transplantable HCC
End-stage liver function
PS 3-4
Solitary
2-3 nodules ≤3 cm
Optimal surgical candidate[3]
Yes
No
Transplant candidate
Yes
No
Treatment[4]
Ablation
Resection
Transplant
Ablation
Chemoembolization
Systemic therapy[5]
BSC
Survival
>5 years
>2.5 years
≥10 months
3 months

Clinical Gastroenterology and Hepatology 2017;15:767–775

Hepatocellular Carcinoma Is the Most Common Indication for Liver Transplantation and Placement on the Waitlist in the United States

Ju Dong Yang,[*] Joseph J. Larson,[‡] Kymberly D. Watt,[*] Alina M. Allen,[*] Russell H. Wiesner,[*] Gregory J. Gores,[*] Lewis R. Roberts,[*] Julie A. Heimbach,[§] and Michael D. Leise[*]

[*]Division of Gastroenterology and Hepatology; [‡]Division of Biomedical Statistics and Informatics; [§]Division of Transplant Surgery, Mayo Clinic College of Medicine, Rochester, Minnesota


A
Number of new registration
3500
3000
2500
2000
1500
1000
500
0
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Year of listing
B
Number of new recipient
1800
1600
1400
1200
1000
800
600
400
200
0
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Year of transplant
HCV
Alcohol
HCC
HBV
NASH

- According to the Scientific Registry of Transplant Recipients (commonly referred to as the SRTR), in 2019, HCC was the primary diagnosis for 10.6% of waitlist candidates.

Kwong et al , OPTN /SRTR 2019 annual data report: liver. Am J Transplant 2021;21(Suppl 2):208-315

Review

Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference

Neil Mehta, MD,[1] Prashant Bhangui, MBBS, MS,[2] Francis Y. Yao, MD,[1,3] Vincenzo Mazzaferro, MD,[4] Christian Toso, MD, PhD,[5] Nobuhisa Akamatsu, MD, PhD,[6] Francois Durand, MD,[7] Jan Ijzermans, MD, PhD,[8] Wojciech Polak, MD, PhD,[8] Shusen Zheng, MD, PhD,[9] John P. Roberts, MD,[3] Gonzalo Sapisochin, MD, PhD,[10] Taizo Hibi, MD, PhD,[11] Nancy Man Kwan, MD, PhD,[12] Mark Ghobrial, MD, PhD,[13] and Avi Soin, MD[2]

Recommendations

1. Indications for LT in HCC are aimed to cure cancer and improve patient's survival and quality of life (quality of evidence: moderate; strength of recommendation: strong).
2. Selection criteria should consider tumor biology (including AFP), tumor size and number, probability of survival, transplant benefit, organ availability, waitlist composition, and allocation priorities (quality of evidence: low; strength of recommendation: strong).
3. LT is recommended as a first-line option for HCC within Milan criteria, unsuitable for low-morbidity resection and ablation (quality of evidence: moderate; strength of recommendation: strong).

Patient selection
(Selection criteria)

Vol. 334 No. 11 TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AND CIRRHOSIS 693

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.

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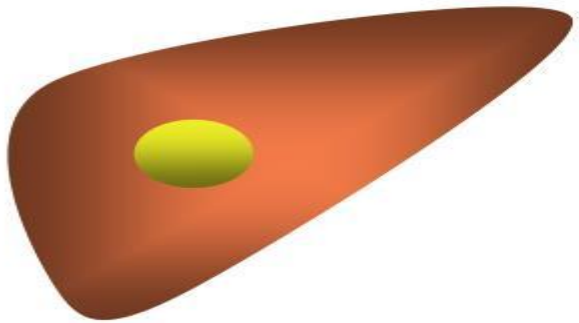
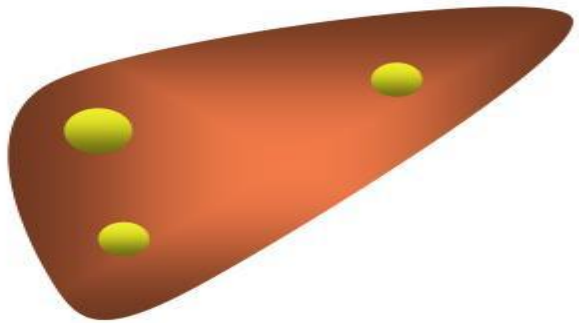
Liver Transplantation for HCC: Milan Criteria

Single tumor, ≤5 cm



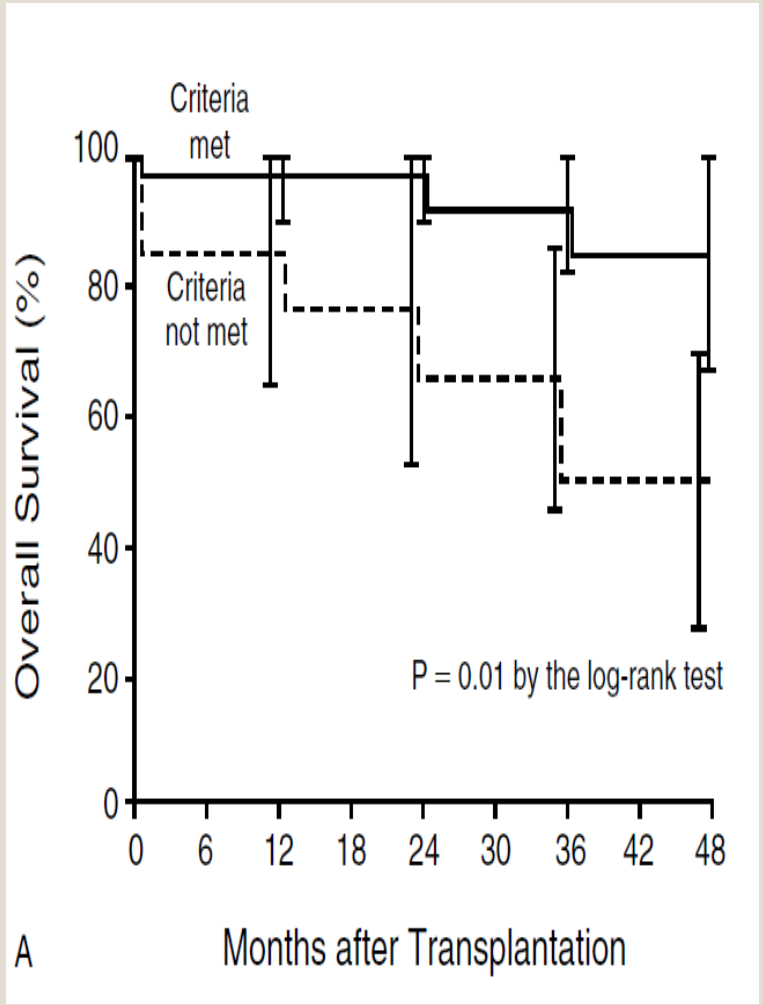
Up to 3 tumors, all ≤3 cm

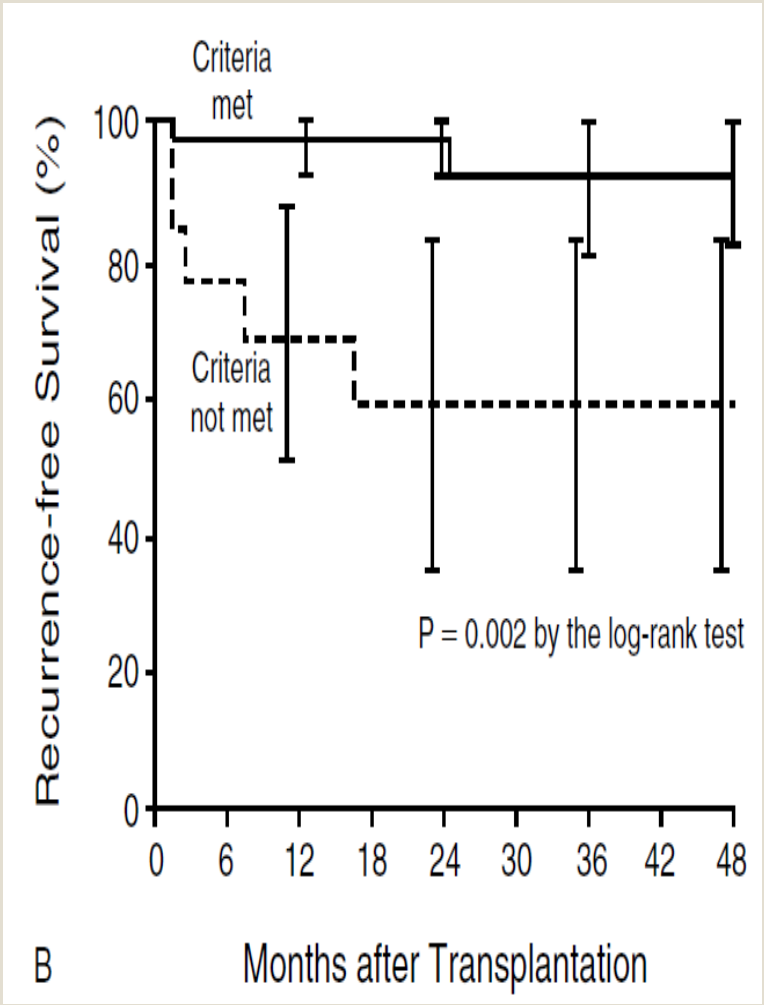


Absence of macroscopic vascular invasion and extra-hepatic spread

- 5-yr survival with transplantation: ~ 70%
- 5-yr recurrent rates: < 15%

Mazzaferro V, et al. N Engl J Med. 1996;334:693-699. Llovet JM. J Gastroenterol Hepatol. 2002;17(suppl 3):S428-S433.


Criteria
met
Criteria
not met
100
80
60
40
20
0
Overall Survival (%)
P = 0.01 by the log-rank test
0
6
12
18
24
30
36
42
48
A
Months after Transplantation


Criteria
met
Criteria
not met
100
80
60
40
20
0
Recurrence-free Survival (%)
P = 0.002 by the log-rank test
0
6
12
18
24
30
36
42
48
B
Months after Transplantation

- However, the MC may seem too restrictive. Several groups have proposed different expansions of these classic criteria, with reasonable life expectancy after LT.

- The rationale behind the expansion is that approximately 25% of the patients classified as Milan in before LT present a Milan-out HCC in the explant histology.

Pavil et al, Expansion of the hepatocellular carcinoma Milan criteria in liver transplantation: Future directions, World J Gastroenterol 2018 August 28; 24(32): 3626-3636

- An important issue to be considered is what the effect of transplanting Milan-out patients on the waiting list for LT will be by balancing the survival benefit for the patients beyond MC against the harm caused by delaying the LT for the other patients on the waiting list.

Volk and Marrero A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. *Am J Transplant* 2008; **8**: 839-846

- The strategy of using LDLT in patients with HCC could be the answer for this.

- First of all, LDLT does not affect the conventional waiting list, therefore an expansion of the MC could be planned in this context without the fear of affecting other patients waiting for an organ could be a good option for such an issue.

Pavil et al, Expansion of the hepatocellular carcinoma Milan criteria in liver transplantation: Future directions, World J Gastroenterol 2018 August 28; 24(32): 3626-3636

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

FRANCIS Y. YAO,[1,5] LINDA FERRELL,[2,5] NATHAN M. BASS,[1,5] JESSICA J. WATSON,[3] PETER BACCHETTI,[3,5] ALAN VENOOK,[1,5] NANCY L. ASCHER,[4,5] AND JOHN P. ROBERTS[4,5]

excellent outcomes of Milan criteria led to explore more expansive criteria

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Expanded Criteria for Liver Transplantation: UCSF Criteria

- Solitary lesion Within ≤ 6.5 cm
- Multiple: ≤ 3 nodules, each ≤ 4.5 cm
- Total tumor diameter ≤ 8 cm

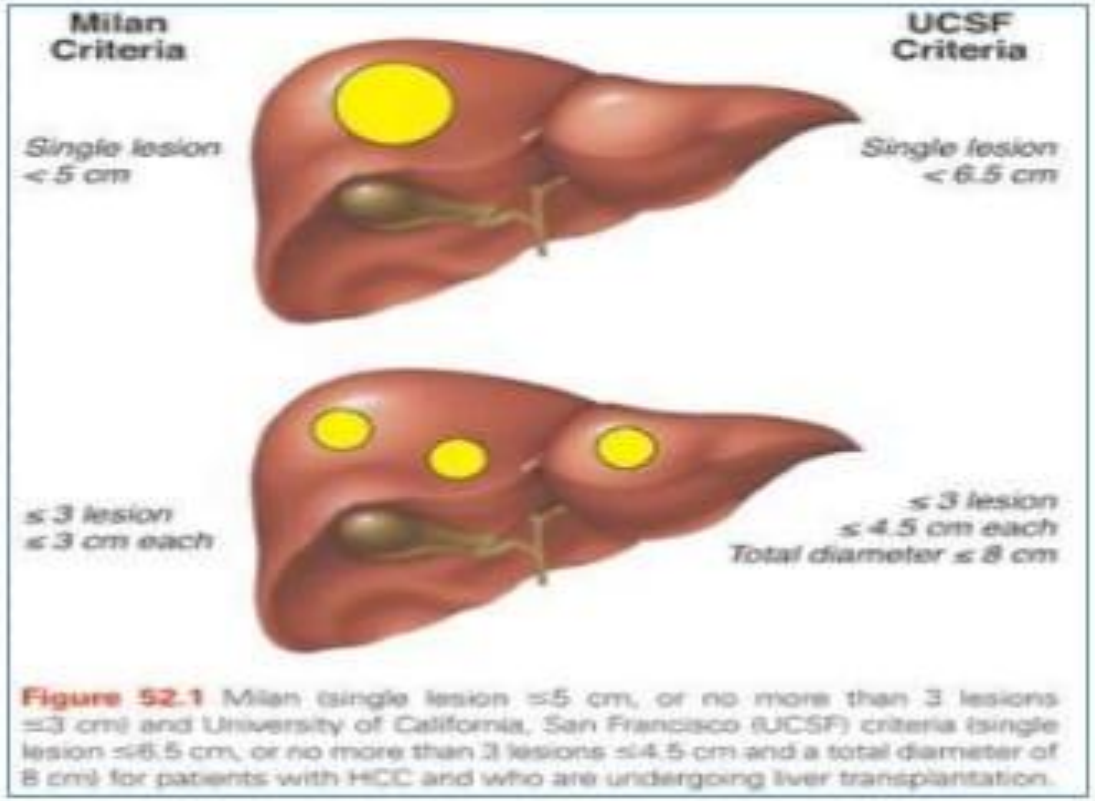
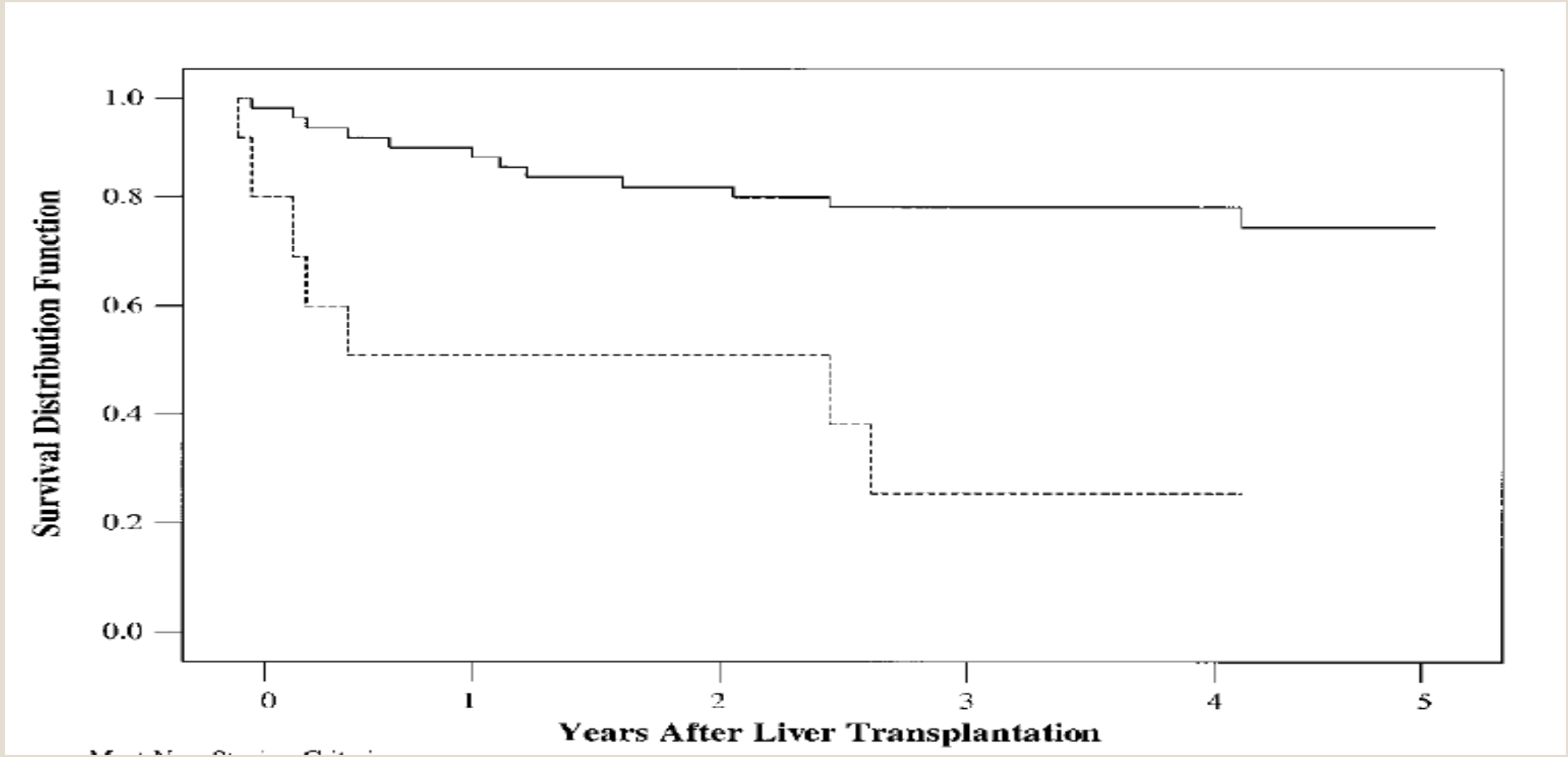


Figure 52.1 Milan (single lesion ≤5 cm, or no more than 3 lesions ≤3 cm) and University of California, San Francisco (UCSF) criteria (single lesion ≤6.5 cm, or no more than 3 lesions ≤4.5 cm and a total diameter of 8 cm) for patients with HCC and who are undergoing liver transplantation.

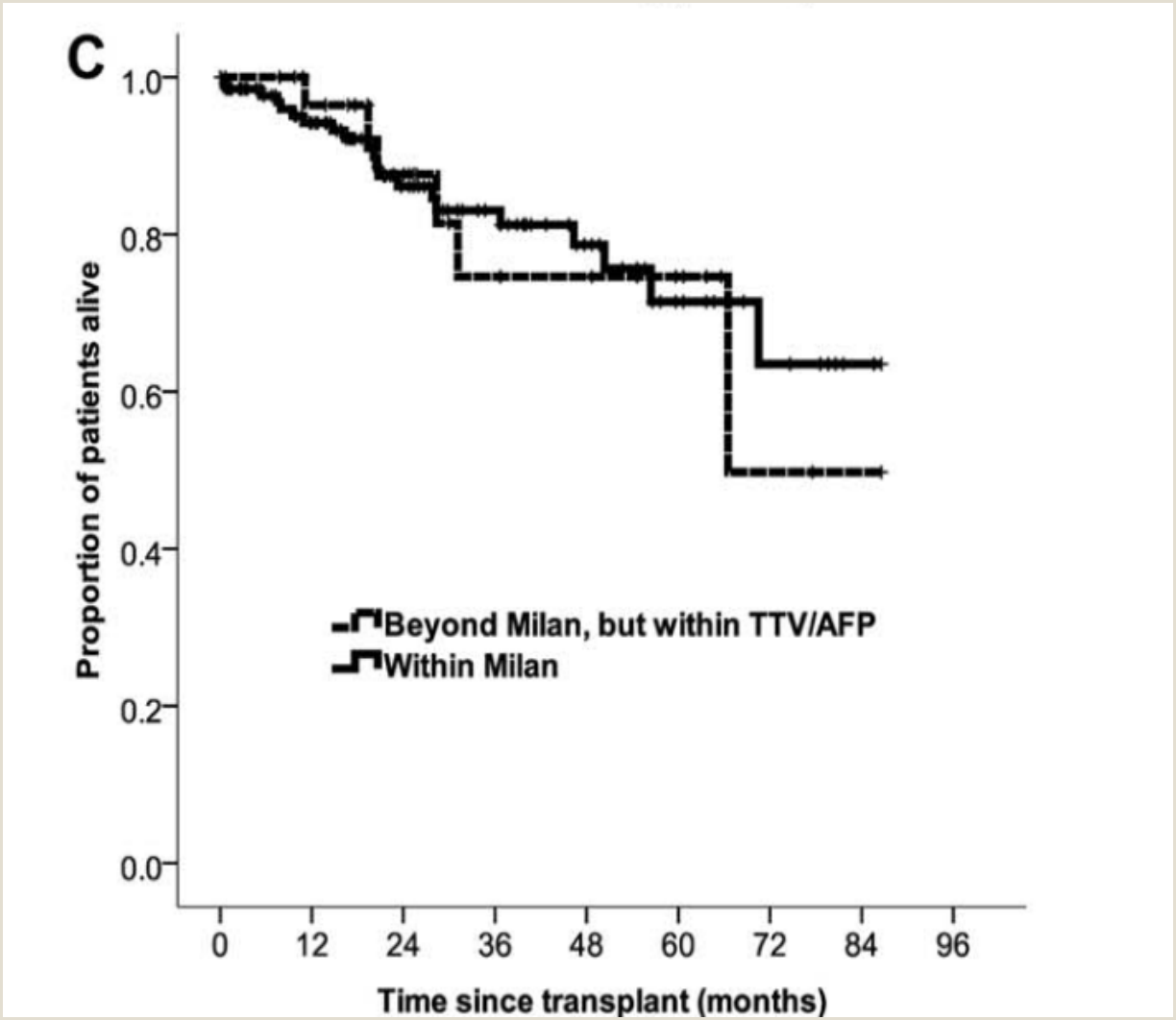

Survival Distribution Function
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
Years After Liver Transplantation

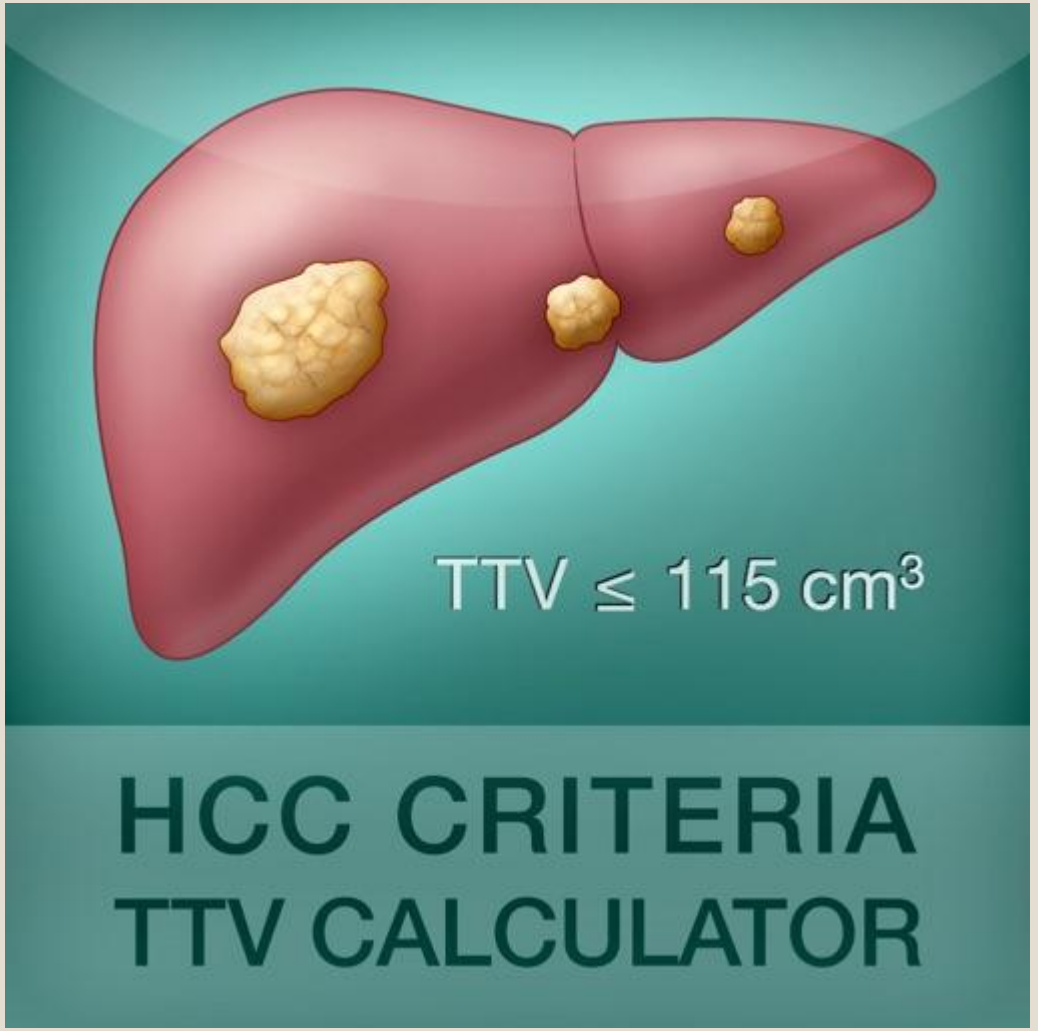
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

HEPATOBILIARY MALIGNANCIES

Total Tumor Volume and Alpha-Fetoprotein for Selection of Transplant Candidates With Hepatocellular Carcinoma: A Prospective Validation

Christian Toso,[1] Glenda Meeberg,[2] Roberto Hernandez-Alejandro,[3] Jean-François Dufour,[4] Paul Marotta,[3] Pietro Majno,[1] and Norman M. Kneteman[2]


C
1.0
0.8
0.6
0.4
0.2
0.0
Proportion of patients alive
Beyond Milan, but within TTV/AFP
Within Milan
0
12
24
36
48
60
72
84
96
Time since transplant (months)


TTV ≤ 115 cm³
HCC CRITERIA
TTV CALCULATOR

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY, VOL. 64, NO. 6, 2016

The Extended Toronto Criteria for Liver Transplantation in Patients With Hepatocellular Carcinoma: A Prospective Validation Study

Gonzalo Sapisochin,[1,2] Nicolas Goldaracena,[1,2] Jerome M. Laurence,[1,2] Martin Dib,[1,2] Andrew Barbas,[1,2] Anand Ghanekar,[1,2] Sean P. Cleary,[1] Les Lilly,[2,3] Mark S. Cattral,[1,2] Max Marquez,[2] Markus Selzner,[1,3] Eberhard Renner,[2,3] Nazia Selzner,[2,3] Ian D. McGilvray,[1,3] Paul D. Greig,[1,3] and David R. Grant[1,3]

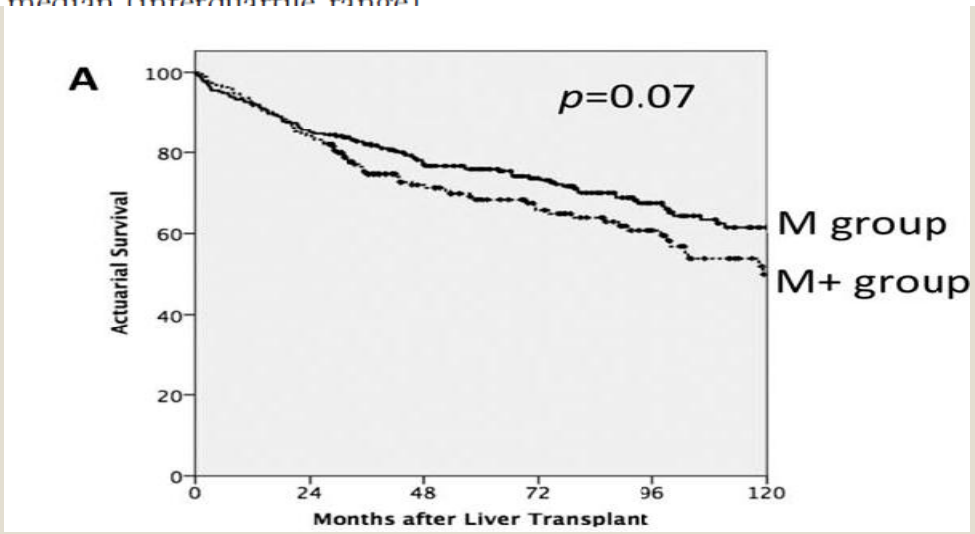
Patients with HCC that exceeded the Milan criteria were included on the if all of the following criteria were met:

1. Tumour confined to the liver
2. No radiologic evidence of venous or biliary tumor thrombus
3. No cancer-related symptoms, like WT loss and patients need to have a good performance status
4. A mandatory percutaneous tumor biopsy of the largest lesion (per protocol) that determined the lesion to be not poorly differentiated as determined

TABLE 2. Explant Pathology Characteristics of Patients in Cohort 2—Validation Cohort

	M Group (n = 124)	M+ Group (n = 86)	*P*
Median number of tumors	2 (1-3)	3.5 (2-7)	<0.001
Median size of the largest tumor (cm)	2.3 (1.3-3.5)	3.9 (2.5-4.7)	<0.001
Tumor differentiation			0.03
Well differentiated	52 (41.9%)	24 (27.9%)	
Moderately differentiated	49 (39.5%)	50 (58.2.%)	
Poorly differentiated	8 (6.5%)	7 (8.1%)	
No viable cells	15 (12.1%)	5 (5.8%)	
Microvascular invasion	35 (28.2%)	32 (37.2%)	0.2
Macrovascular invasion	5 (4%)	2 (2.3%)	0.4
Tumor staging			<0.001
No viable tumor	15 (12.1%)	5 (5.8%)	
Within Milan criteria	71 (57.3%)	13 (15.1%)	
Beyond Milan criteria	38 (30.6%)	68 (79.1%)	

Data are number (percentage) or median (interquartile range)



J Hepatobiliary Pancreat Sci (2010) 17:527–532
DOI 10.1007/s00534-009-0162-y

TOPICS

Liver transplantation for hepatocellular carcinoma around the world

Liver transplantation for hepatocellular carcinoma: the Kyoto experience

Yasutsugu Takada · Shinji Uemoto

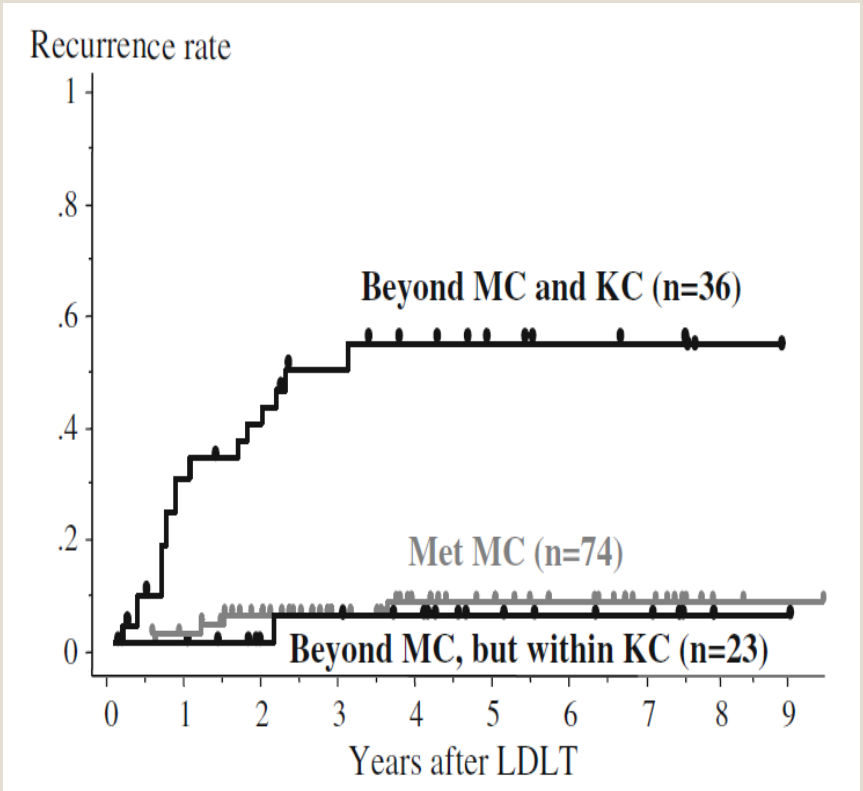


Table 2 Multivariate analysis of preoperative tumor factors and recurrence

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

Pavel MC *et al*. Liver transplantation beyond Milan criteria

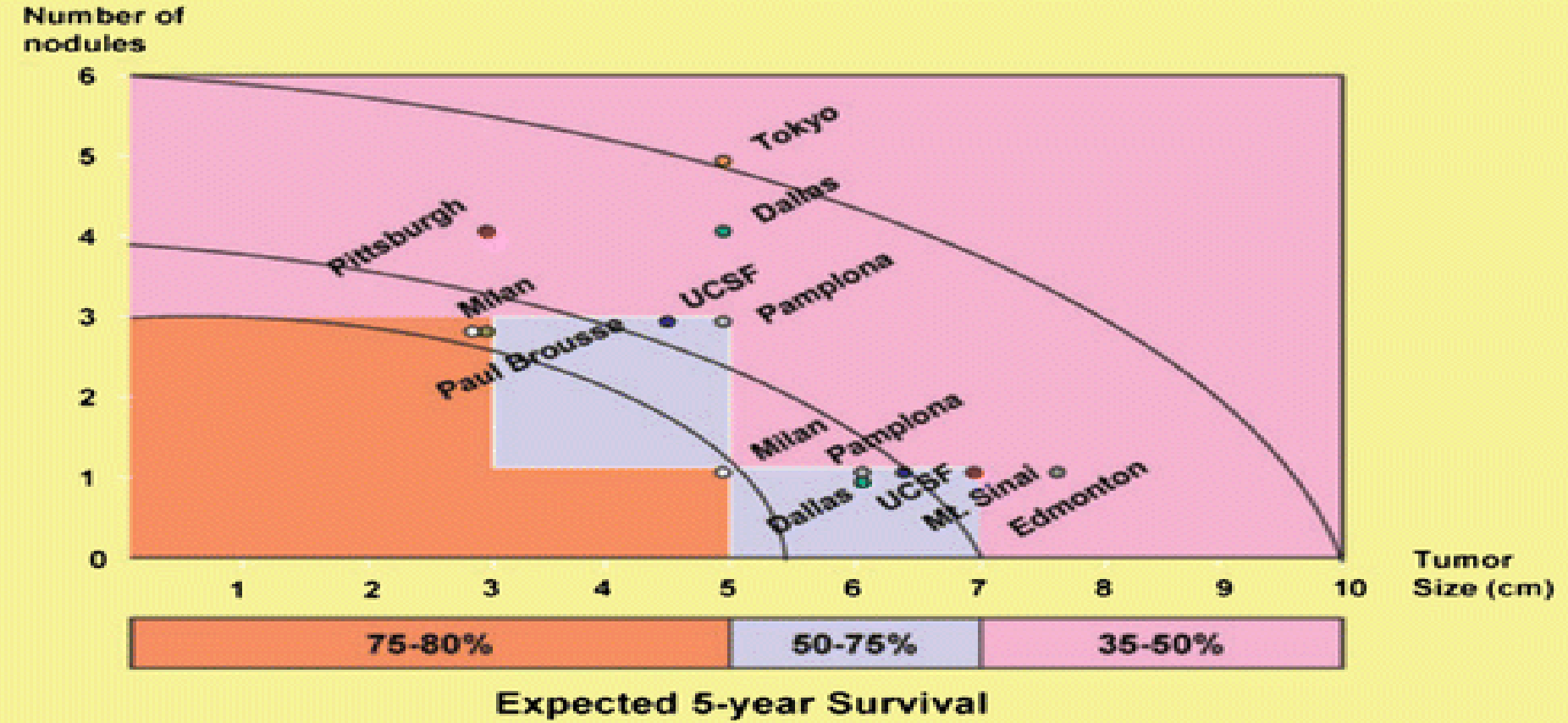
Table 1 Expanded criteria used for liver transplantation

Criteria	Type of donor	Detailed criteria
UCSF[9,27]	Cadaveric	Solitary tumor ⩽ 6.5 cm or ⩽ 3 tumors with the largest ⩽ 4.5 cm
Up-to-seven[10]	Cadaveric/LDLT	Seven: sum of tumor number and size of the largest tumor without microvascular invasion
Clinica Universidad de Navara (CUN)[12]	Cadaveric	1 tumor ⩽ 6 cm or ⩽ 3 tumors with the largest ⩽ 5 cm
Toso[29]	Cadaveric	Total tumor volume ⩽ 115 cm^3 and AFP ⩽ 400 ng/mL
Hangzhou University[13]	Cadaveric	One of the following: Total tumor diameter ⩽ 8 cm Total tumor diameter > 8 cm with histological grade Ⅰ or Ⅱ and AFP ⩽ 400 ng/mL
Onaca (ITR)[32]	Cadaveric	Solitary tumor, ⩽ 6 cm 2-4 tumors, ⩽ 5 cm
Tokyo (5-5 rule)[53]	LDLT	Maximum 5 tumors ⩽ 5 cm
Kyoto[55]	LDLT	⩽ 10 tumors, ⩽ 5 cm, DCP§ ⩽ 400 mAU/mL
Kyushu University[57]	LDLT	Any number of tumors with diameter ⩽ 5 cm or DCP§ ⩽ 300 mAU/mL
Asan[58]	LDLT	⩽ 6 tumors, diameter ⩽ 5 cm
Samsung[59]	LDLT/cadaveric	⩽ 7 tumors, diameter ⩽ 6 cm, AFP ⩽ 1000 ng/mL
BCLC[14]	LDLT	1 tumor, ⩽ 7 cm 3 tumors, ⩽ 5 cm 5 tumors, ⩽ 3 cm Maintained response within Milan criteria during 6 mo after downstaging

Table 2 Results after liver transplantation with expanded criteria

Ref.	Type	Patients, *n* (type)	Criteria (findings)	Survival, time (%)	Recurrence, time (%)	Factors for survival	Factors for recurrence
Yao *et al*[9], 2001	R	14 (MO)	UCSF (Histol)	5 yr (84.6)	-	pT4, total tumor diameter	-
Yao *et al*[27], 2007	P	38 (MO)	UCSF (Radiol)		5 yr DFS (93.6)		UCSF Vascular invasion AFP > 1000 ng/mL
Onaca *et al*[32], 2007	R	129 (MO)	Onaca		5 yr DFS (63.9)		Tumor > 6 cm AFP > 200 ng/mL Tumors > 4
Herrero *et al*[28], 2008	P	26 (MO)	CUN (Radiol)	5 yr (73) 5 yr I-to-T (68)			Vascular invasion
Zheng *et al*[13], 2008	R	99 (MI and MO), 26 (MO)	Hangzhou (Histol)	5 yr (70.7)	5 yr DFS (62.4)	Macrovascular invasion Tumor size > 8 cm AFP > 400 ng/mL Histological grading (Ⅲ)	Macrovascular invasion Tumor size > 8 cm AFP > 400 ng/mL Histological grading (Ⅲ)
Mazzaferro *et al*[10], 2009	R	283 (MI and MO)	Up-to-seven (Histol)	5 yr (71.2)	-	Microvascular invasion Tumor grade	-
Toso *et al*[29], 2015	P	38 (MO)	Toso (Radiol)	4 yr (74.6) 4 yr I-to-T (53.8)	4 yr DFS (68)	-	-
Togashi *et al*[54], 2016	R	14 (MO)	Tokyo	-	5 yr (8)	-	Tokyo criteria AFP ⩾ 400 ng/mL DCP ⩾ 200 mAU/mL
Kaido *et al*[56], 2013	R	42 (MO)	Kyoto	5 yr (80)	5 yr (7)		Kyoto criteria Pretreatment of the HCC
Shirabe *et al*[57], 2011	R	48 (MI and MO)	Kyushu (Histol)		5 yr DFS (80)		Kyushu criteria
Lee *et al*[58], 2008	R	174 (MI and MO)	Asan (Histol)	5 yr (81.6)	5 yr (15)	Largest tumor > 5 cm Number > 6 Gross vascular invasion	Largest tumor > 5 cm Number > 6 Gross vascular invasion
Kim *et al*[59], 2014	R	180 (in the whole study, including Samsung-out)	Samsung (Histol)		5 yr DFS -89.6		Tumors ⩽ 7 Diameter ⩽ 6 cm AFP ⩽ 1000 ng/mL
Llovet *et al*[14], 2018	P	22	BCLC (Radiol)	5 yr (80.2)	5 yr (23.8)	MI after locoregional therapies	

HCC "Metro Ticket" - The further the distance, the higher the price



Small HCC(resection versus transplantation)

There are no randomized control trials evaluating resection versus LT, leading to the ongoing debate of which is most appropriate for patients within Milan criteria and adequate liver function.

Resection confers up to 10-fold higher odds of recurrence compared to LT.

Menahem et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: an attempt to perform an ideal meta-analysis. *Liver Transplant.* 2017;23:836–844

Review

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Recommendations

1. HCC patients with compensated liver disease and minimal tumor burden have a low risk of waitlist dropout and do not derive the same immediate benefit from LT as other waitlist candidates (quality of evidence: moderate; strength of recommendation: strong).
2. Particularly in areas of organ shortages, due to competition with patients with higher transplant benefit, deceased donor LT is recommended only as second line treatment in resectable patients with single <3 cm HCC in case of tumor recurrence or liver failure after resection or ablation (quality of evidence: moderate; strength of recommendation: conditional).
3. Patients with well-compensated disease and single <3 cm HCC with complete response to LRT have reduced the urgency for LT (quality of evidence: moderate; strength of recommendation: strong).

ANNALS OF TRANSPLANTATION

META-ANALYSIS

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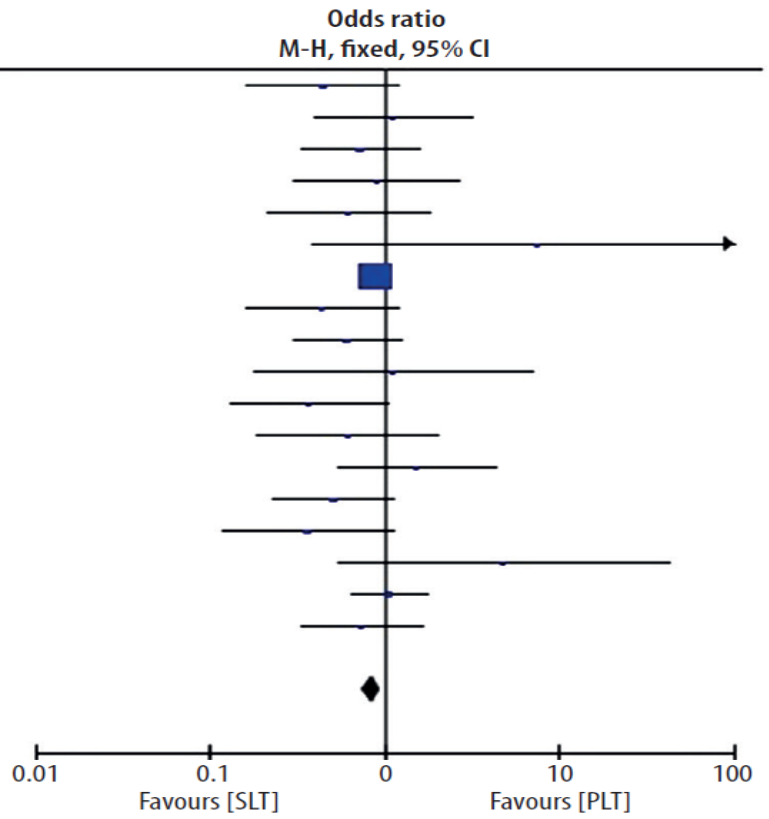
Salvage Liver Transplant versus Primary Liver Transplant for Patients with Hepatocellular Carcinoma

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	7	17	119	195	1.9%	0.45 [0.16, 1.22]
Belghiti 2003	10	18	37	70	1.2%	1.11 [0.39, 3.16]
Bhangui 2016	10	31	135	340	2.6%	0.72 [0.33, 1.58]
Cherqui 2009	13	18	101	136	1.1%	0.90 [0.30, 2.71]
Del Gaudio 2008	10	16	107	147	1.4%	0.62 [0.21, 1.83]
Faciutto 2008	5	5	19	32	0.1%	7.62 [0.39, 149.49]
Hu 2012	407	888	2971	6087	70.7%	0.89 [0.77, 1.02]
Hwang 2007	9	17	144	200	1.8%	0.44 [0.16, 1.19]
Liu 2012	24	39	130	180	3.1%	0.62 [0.30, 1.27]
Margarit 2005	2	6	11	36	0.4%	1.14 [0.18, 7.15]
Moon 2012	10	17	134	169	1.7%	0.37 [0.13, 1.05]
Sapisochin 2010	9	17	22	34	1.2%	0.61 [0.19, 2.00]
Scatton 2008	13	20	40	73	1.0%	1.53 [0.55, 4.28]
Shan 2017	12	28	125	211	2.9%	0.52 [0.23, 1.15]
Vasavada 2015	12	18	77	91	1.5%	0.36 [0.12, 1.13]
Vennarecci 2007	8	9	23	37	0.2%	4.87 [0.55, 43.18]
Wang 2006	35	76	131	295	5.0%	1.07 [0.64, 1.77]
Wu 2012	25	36	111	147	2.3%	0.74 [0.33, 1.64]
Total (95% CI)		**1276**		**8480**	**100.0%**	**0.85 [0.76, 0.96]**
Total events	621		4437			

Heterogeneity: $Chi^2=18.33$, df=17 (P=0.37); $I^2=7\%$
Test for overall effect: Z=2.61 (P=0.009)



Recommendations

1. Patients with single <3 cm HCC who undergo resection but have tumor recurrence are highly likely to be eligible for SLT (quality of evidence: moderate; strength of recommendation: strong).
2. SLT and primary LT appear to have equivalent outcomes from the time of LT (quality of evidence: moderate; strength of recommendation: strong).

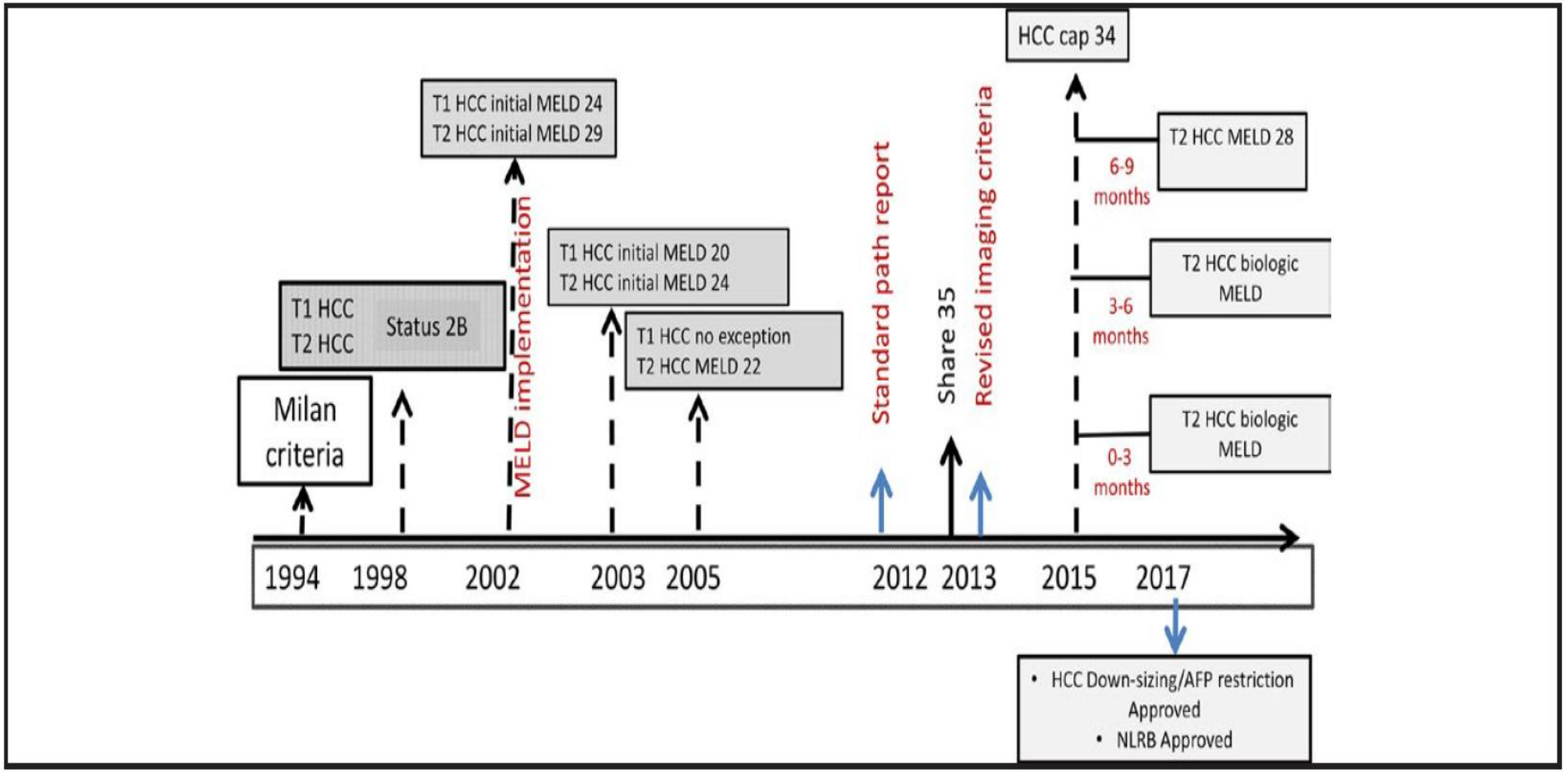
Organ Procurement

.

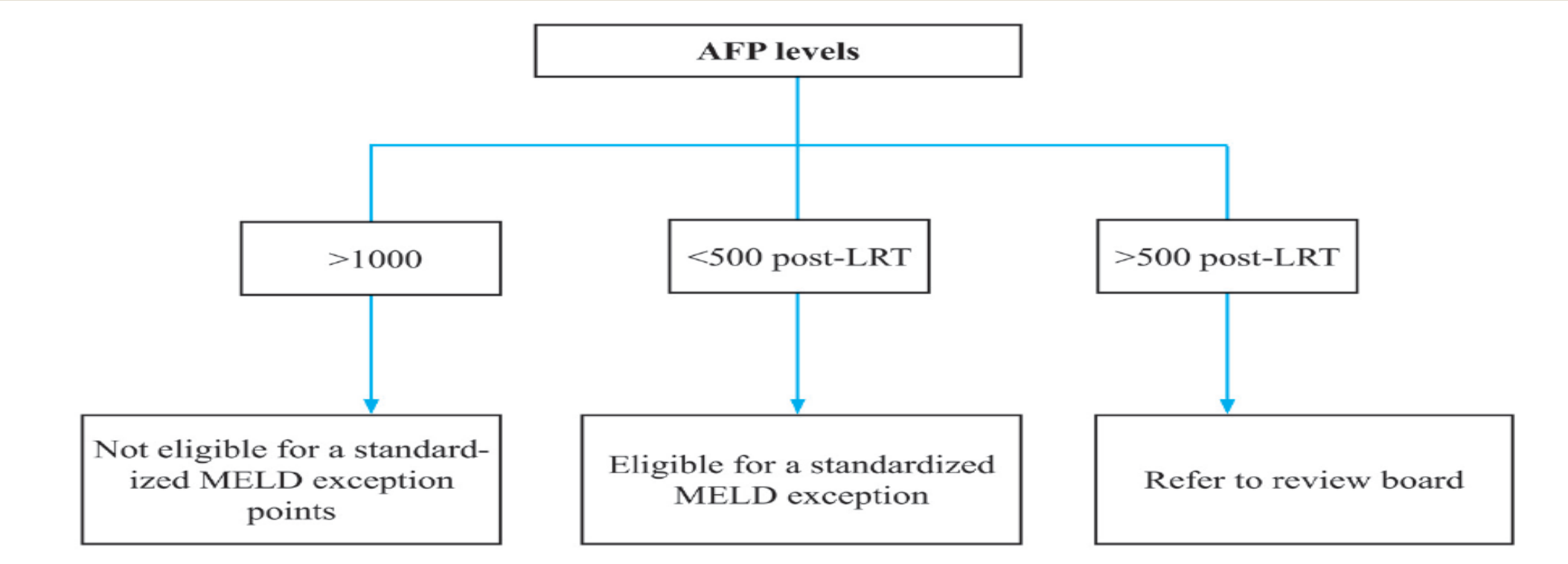
Before the MELD era strict criteria for LT were used as MC ,However despite these advancements, patients with HCC remained on the waiting list longer than candidates without HCC, resulting in less than 5% LT for HCC in the USA from 1997–2002.

Ioannou et al Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology 2008;134(5):1342–1351.

- Therefore, in order to promote equal allocation of donor organs between HCC and non-HCC patients on the waiting list, MELD exception points are given to HCC candidates.



AASLD guidelines, 2018

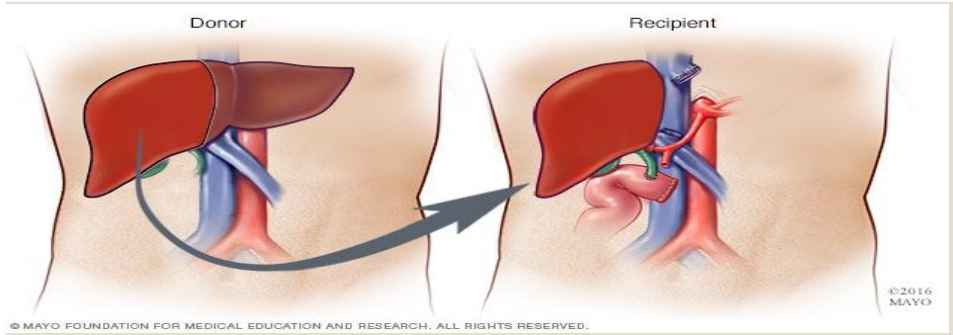

AFP levels
>1000
<500 post-LRT
>500 post-LRT
Not eligible for a standard-ized MELD exception points
Eligible for a standardized MELD exception
Refer to review board

- Initially, This resulted in a rise from 5% to 26% LT for HCC from 2002–2007.

Ioannou et al Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. Gastroenterology 2008;134(5):1342–1351

- Despite the changes made in 2005, patients with HCC still had a lower waitlist dropout and a higher transplant rate and slightly inferior long-term outcomes than non-HCC patients, and thus, in 2015, a system of delaying the MELD score assignment for 6 months was implemented.

Washburn et al, Hepatocellular carcinoma patients are advantaged inthe current liver transplant allocation system. Am JTransplant 2010;10:1643-1648



LDLT

- Unfortunately, many HCC patients listed for deceased donor liver transplantation (DDLT) died in the waiting period due to the shortage of deceased donors.
- LDLT became a reliable alternative to DDLT by decreasing threats of dropping out from the waiting list.

Axelrod et al. (2008 Jan 9) Rates of solid organ wait-listing, transplantation, and survival among residents of rural and urban areas. J Am Med Assoc 299:202–207

- In clinical practice, whether there is a higher recurrence rate after LDLT remains controversial.

- First, for HCC patients who underwent LDLT, the wait time was relatively short and not enough to comprehensively assess the biological features of the tumour, so the aggressive behaviour of tumour might not be identified.

Fonseca et al. (7 May 2016) Living donor versus deceased donor liver transplantation for hepatocellular carcinoma. Abstracts of the ILTS 22nd Annual International Congress Annual International Congress. Transplantation 100

- Second, all available grafts were split livers for LDLT, in the process of rapid regeneration of a partial graft after LT, the released growth factors and cytokines might promote tumor progression and recurrence.

Di Sandro et al. (2009) Living donor liver transplantation for hepatocellular carcinoma: long-term results compared with deceased donor liver transplantation. Transplant Proc 41:1283.

- Third, the surgical technique of LDLT does not comply with the principles of oncologic surgery. During LDLT, the native inferior vena cava, the longer bile duct, hepatic artery and portal vein would be preserved to match the volume-limited split liver, leading to possible tumor remnants.

Shi et al.(2011) Growth of hepatocellular carcinoma in the regenerating liver. Liver Transplant 17:866–874.

- Fourth, a higher percentage of recipients beyond the Milan criteria in patients undergoing LDLT can reasonably explain the higher recurrence rate.

Zhu et al. Living or deceased organ donors in liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. HPB 2019, 21, 133–147

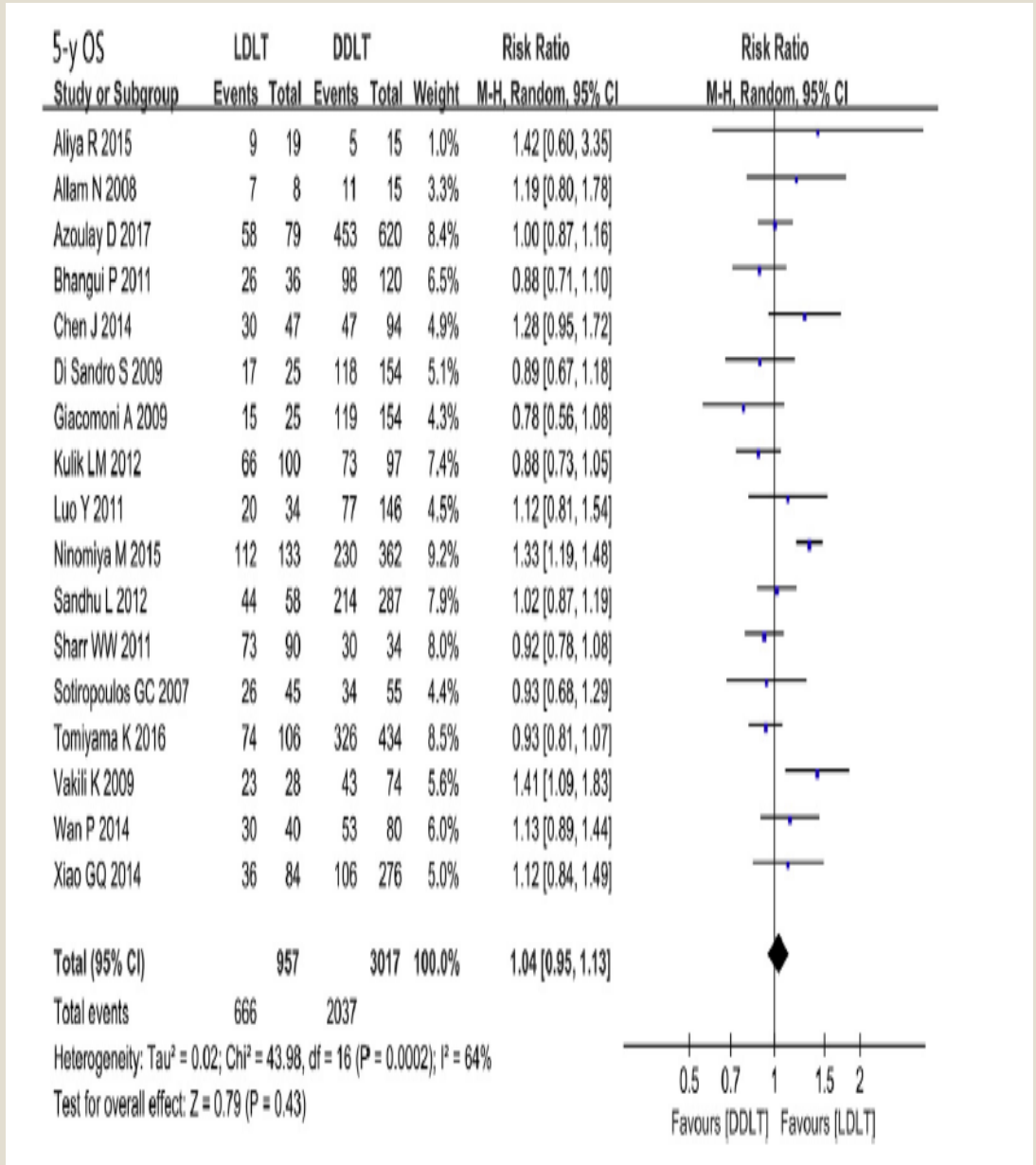
https://doi.org/10.1016/j.hpb.2018.11.004 HPB

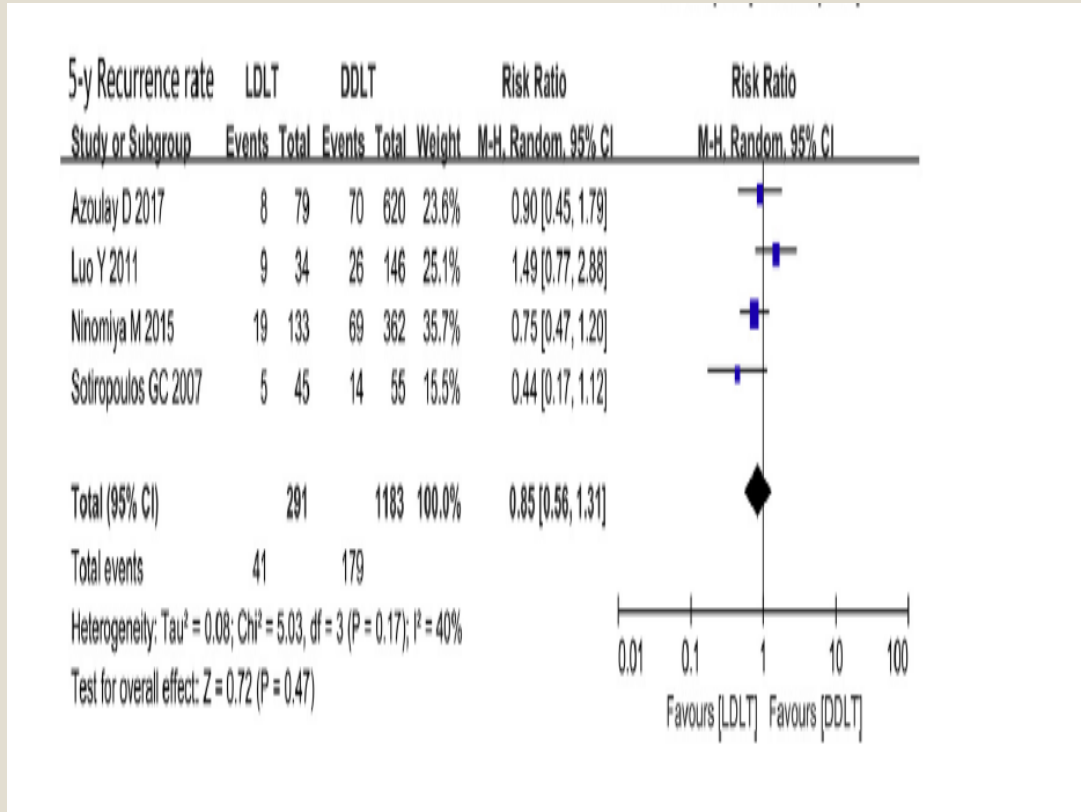
REVIEW ARTICLE

Living or deceased organ donors in liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis

Bo Zhu[1,2], Jinju Wang[1,2], Hui Li[1,2], Xing Chen[1,2] & Yong Zeng[1,2]

[1]Department of Liver Surgery & Liver Transplantation Center, and [2]Laboratory of Liver Surgery, West China Hospital, Sichuan University, Chengdu, 610041, China


5-y OS
LDLT
DDLT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Aliya R 2015 9 19 5 15 1.0% 1.42 [0.60, 3.35]
Allam N 2008 7 8 11 15 3.3% 1.19 [0.80, 1.78]
Azoulay D 2017 58 79 453 620 8.4% 1.00 [0.87, 1.16]
Bhangui P 2011 26 36 98 120 6.5% 0.88 [0.71, 1.10]
Chen J 2014 30 47 47 94 4.9% 1.28 [0.95, 1.72]
Di Sandro S 2009 17 25 118 154 5.1% 0.89 [0.67, 1.18]
Giacomoni A 2009 15 25 119 154 4.3% 0.78 [0.56, 1.08]
Kulik LM 2012 66 100 73 97 7.4% 0.88 [0.73, 1.05]
Luo Y 2011 20 34 77 146 4.5% 1.12 [0.81, 1.54]
Ninomiya M 2015 112 133 230 362 9.2% 1.33 [1.19, 1.48]
Sandhu L 2012 44 58 214 287 7.9% 1.02 [0.87, 1.19]
Sharr WW 2011 73 90 30 34 8.0% 0.92 [0.78, 1.08]
Sotiropoulos GC 2007 26 45 34 55 4.4% 0.93 [0.68, 1.29]
Tomiyama K 2016 74 106 326 434 8.5% 0.93 [0.81, 1.07]
Vakili K 2009 23 28 43 74 5.6% 1.41 [1.09, 1.83]
Wan P 2014 30 40 53 80 6.0% 1.13 [0.89, 1.44]
Xiao GQ 2014 36 84 106 276 5.0% 1.12 [0.84, 1.49]
Total (95% CI) 957 3017 100.0% 1.04 [0.95, 1.13]
Total events 666 2037
Heterogeneity: Tau² = 0.02; Chi² = 43.98, df = 16 (P = 0.0002); I² = 64%
Test for overall effect: Z = 0.79 (P = 0.43)
0.5 0.7 1 1.5 2
Favours [DDLT] Favours [LDLT]


5-y Recurrence rate
LDLT
DDLT
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Azoulay D 2017 8 79 70 620 23.6% 0.90 [0.45, 1.79]
Luo Y 2011 9 34 26 146 25.1% 1.49 [0.77, 2.88]
Ninomiya M 2015 19 133 69 362 35.7% 0.75 [0.47, 1.20]
Sotiropoulos GC 2007 5 45 14 55 15.5% 0.44 [0.17, 1.12]
Total (95% CI) 291 1183 100.0% 0.85 [0.56, 1.31]
Total events 41 179
Heterogeneity: Tau² = 0.08; Chi² = 5.03, df = 3 (P = 0.17); I² = 40%
Test for overall effect: Z = 0.72 (P = 0.47)
0.01 0.1 1 10 100
Favours [LDLT] Favours [DDLT]

Hindawi
BioMed Research International
Volume 2020, Article ID 1320830, 19 pages
https://doi.org/10.1155/2020/1320830

Review Article

Increased Surgical Complications but Improved Overall Survival with Adult Living Donor Compared to Deceased Donor Liver Transplantation: A Systematic Review and Meta-Analysis

Wei Tang, Jian-Guo Qiu, Yang Cai, Luo Cheng, and Cheng-You Du

Department of Hepatobiliary Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Bridging and Downstaging

- While on the waiting list, candidates are prone to tumor growth, resulting in going beyond the transplant criteria and an eventual 12 month dropout probability of 25%.

- When defining neoadjuvant treatments, ‘‘bridging’’ describes treatment of accepted transplant candidates within Milan criteria while on the waiting list.

Yao *et al*. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. Liver Transpl 2002;8(10):873–883.

- European guidelines recommend LRT to reduce the risk of pre-LT drop-out in regions of anticipated wait times longer than 6 months.

- With the changes in UNOS model for end-stage liver disease score exception criteria now mandating a 6-month delay before exception points can be obtained, LRT has become standard of care in patients with HCC awaiting liver transplant.

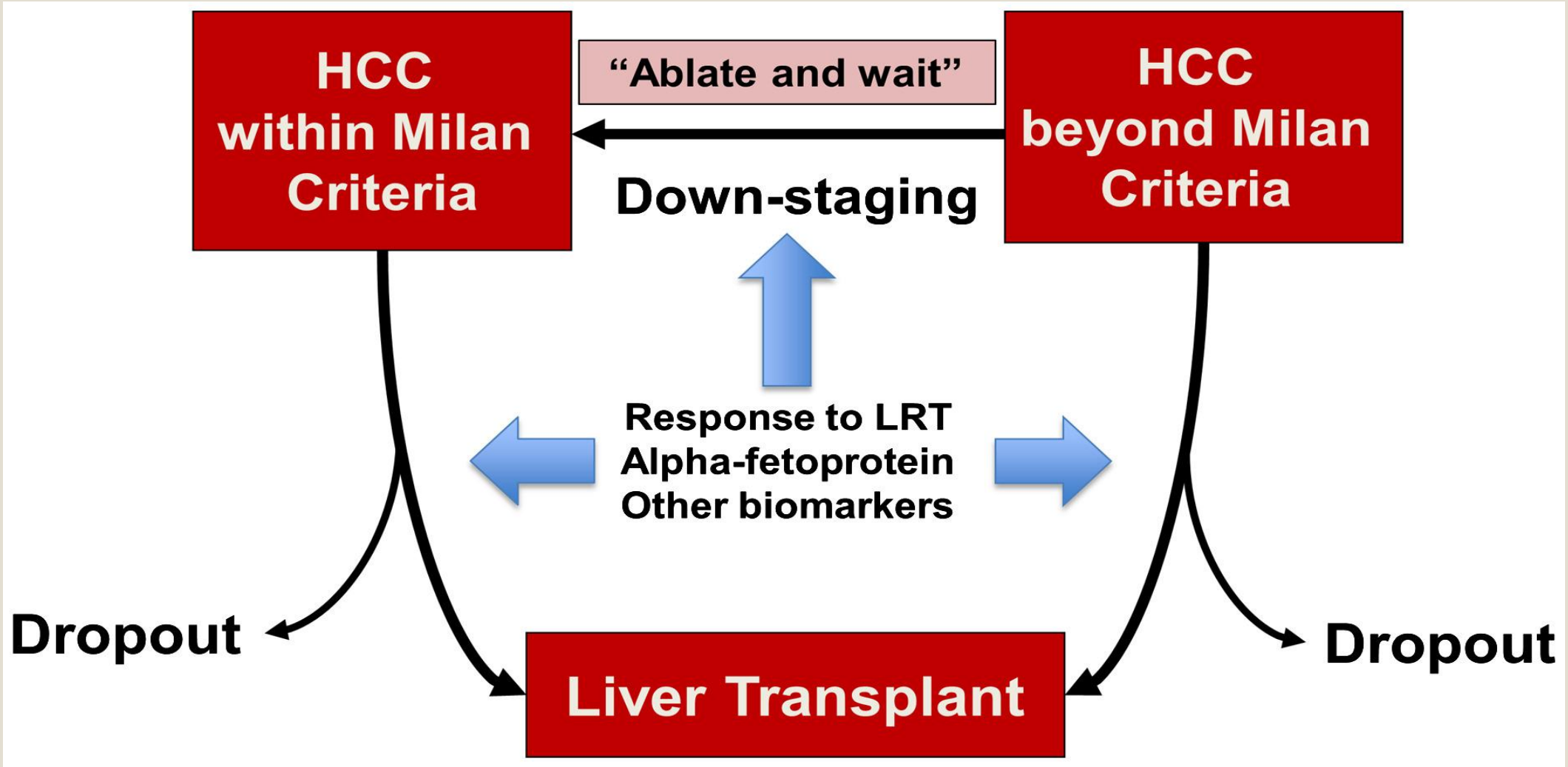
Frankul et al. Hepatocellular Carcinoma: Downstaging to Liver Transplantation as Curative Therapy. Journal of Clinical and Translational Hepatology 2021 vol. 9(2) | 220–226

- ‘‘Downstaging” describes treatment used to bring patients whose tumour burden is outside accepted criteria for transplantation to within acceptable criteria.

- Acceptable criteria are defined as those criteria achieving an expected survival after LT equal to patients who meet transplant criteria without downstaging.

EASL HCC guidelines, 2018

Schlesinger et al. Diabetes mellitus, insulin treatment, diabetes duration, and risk of biliary tract cancer and hepatocellular carcinoma in a European cohort. Ann Oncol 2013;24:2449–2455

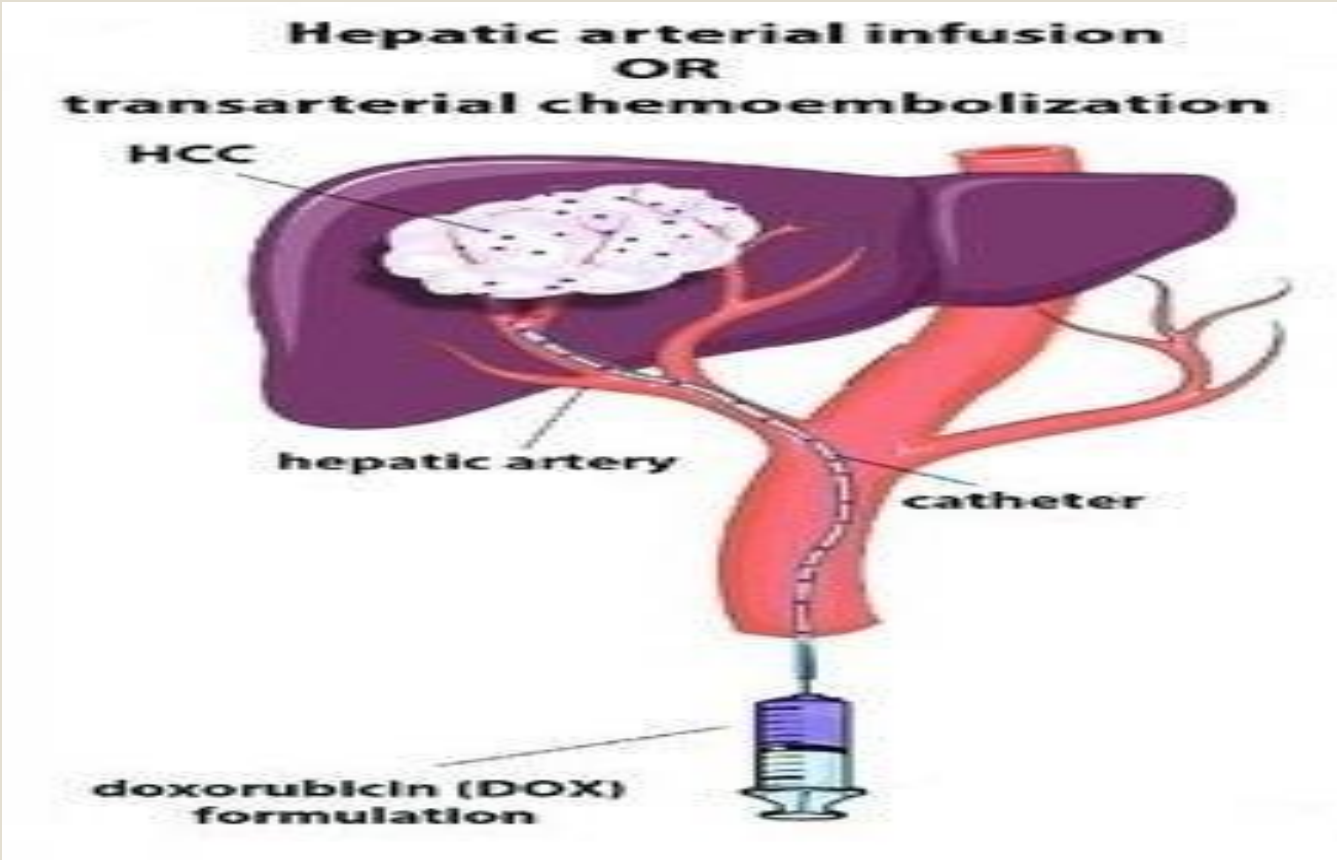

HCC within Milan Criteria
"Ablate and wait"
HCC beyond Milan Criteria
Down-staging
Response to LRT
Alpha-fetoprotein
Other biomarkers
Dropout
Liver Transplant
Dropout

Bridging and Down staging Modalities

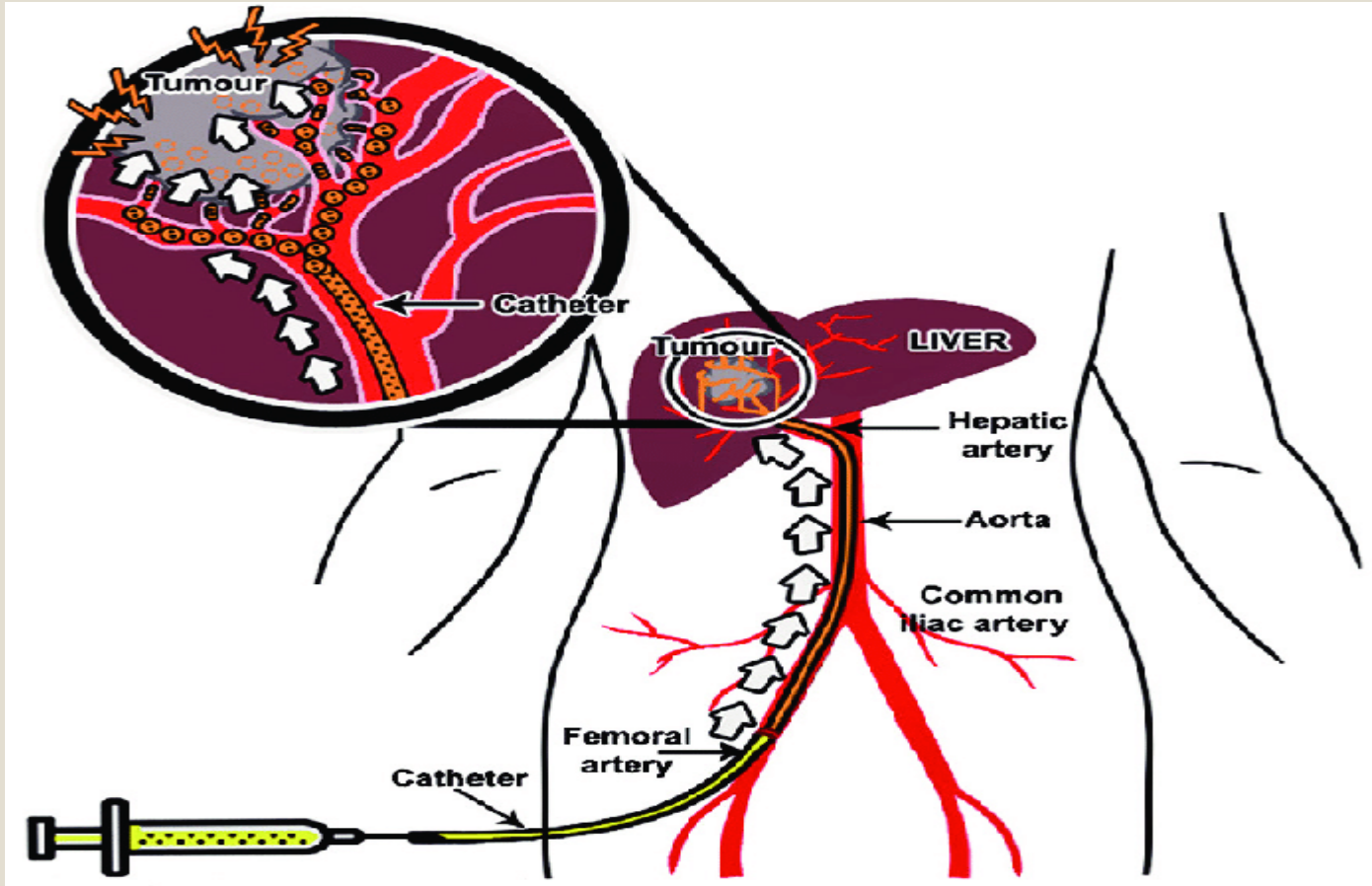
Radiofrequency Ablation

- thin probe (18 gauge) is inserted into middle of a tumor
- needle electrodes are deployed to adjustable distances.
- A.C current (400 to 500 kHz) is delivered through electrodes -agitation of particles of surrounding tissues,
- Generate frictional heat lead to sphere of necrosis.
- Size of the sphere depends on length of deployment of electrodes.
- Currently, the maximum size of probe arrays allows for 7-cm zone of necrosis, adequate for a 5-cm tumor..

Nonsurgical treatment of a single liver metastasis with microwave ablation in a 64-year-old man with colon cancer


Hepatic arterial infusion
OR
transarterial chemoembolization
HCC
hepatic artery
catheter
doxorubicin (DOX)
formulation


DCBead
500-700µm
DCBead
300-500µm
DCBead
100-300µm
DCBead
embolic Drug-Eluting Bead
70-150µm


Tumour
Catheter
Tumour
LIVER
Hepatic artery
Aorta
Common iliac artery
Femoral artery
Catheter


SIR-Spheres
microspheres
SIR-Y001
SIRTeX

- There are obviously safety concerns related to down staging, including hepatic decompensation following LRT.
- It has been proposed that only patients with adequate hepatic function (Child's A/B, bilirubin ≤3mg/dl)should undergo downstaging.

Yao et al. Reassessing the boundaries of liver transplantation for hepatocellular carcinoma: where do we stand with tumor down-staging? *Hepatology.* 2016;63:1014–1025.

- TACE is the most frequently used palliative treatment technique in downstaging protocols, particularly for multifocal HCC.

Cescon et al. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplant ability and recurrence rate. J Hepatol 2013;58(3):609–618

Trans arterial radioembolization with Yttrium-90 (Y-90) beads is a safe alternative downstaging therapy . Per available data there is no statistically significant difference between success rates of TACE and radioembolization for downstaging.

Parikh et al . Downs taging hepatocellular carcinoma: A systematic review and pooled analysis. Liver Transpl 2015;21(9):1142–1152

Salem, *et al*. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140(2):497–507.e2.

Response to LRT

TABLE 4. mRECIST CLASSIFICATION OF TUMOR RESPONSE	
Response	**Description**
Complete response	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	An increase of at least 20% of the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Downstaging of Hepatocellular Cancer Before Liver Transplant: Long-Term Outcome Compared to Tumors Within Milan Criteria

Francis Y. Yao,[1,2] Neil Mehta,[1] Jennifer Flemming,[1] Jennifer Dodge,[2] Bilal Hameed,[1] Oren Fix,[1] Ryutaro Hirose,[2] Nicholas Fidelman,[3] Robert K. Kerlan, Jr.,[3] and John P. Roberts[2]

Table 1. UCSF Downstaging Protocol

Inclusion criteria

HCC exceeding UNOS T2 criteria, but meeting one of the following criteria:

1. Single lesion $\leq$8 cm
2. 2 or 3 lesions each $\leq$5 cm with the sum of the maximal tumor diameters $\leq$8 cm
3. 4 or 5 lesions each $\leq$3 cm with the sum of the maximal tumor diameters $\leq$8 cm

Absence of vascular invasion based on cross-sectional imaging

Criteria for successful downstaging

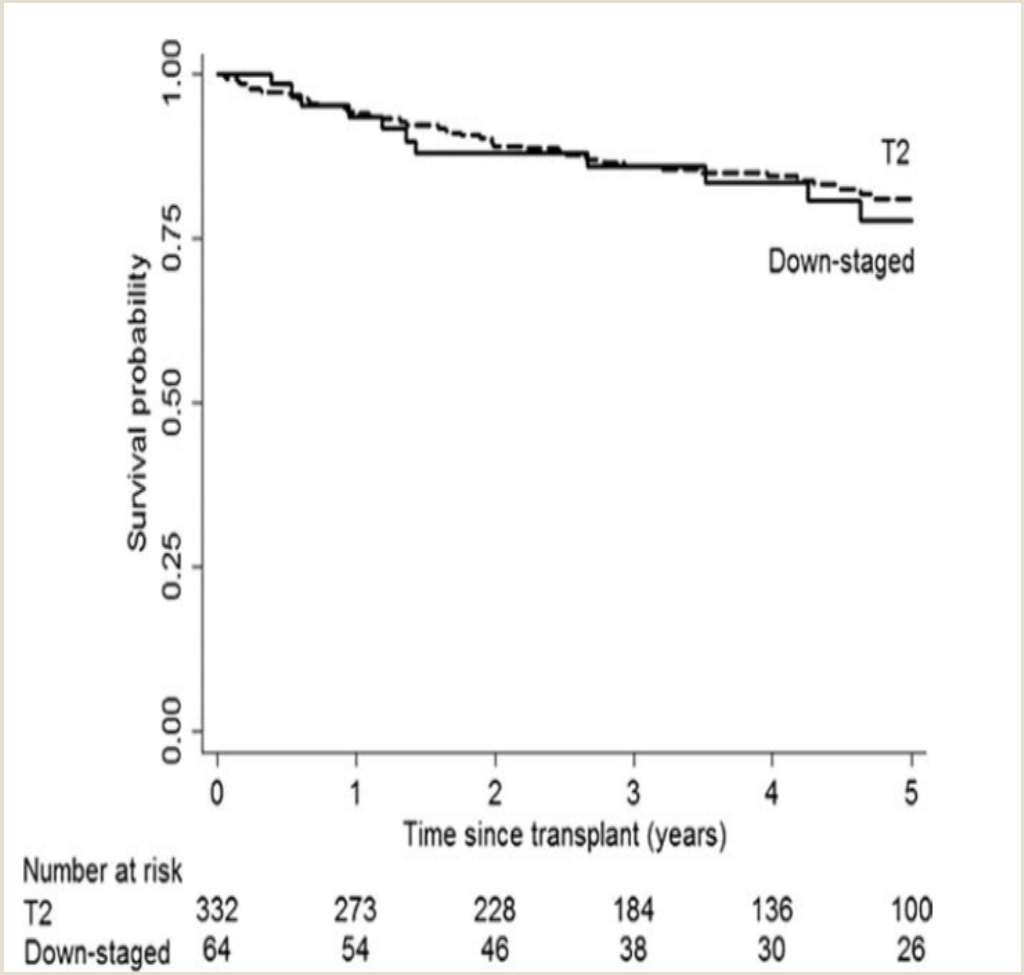
1. Residual tumor(s) within UNOS T2 criteria for deceased donor LT and to within UCSF criteria for live donor LT*
2. In patients with 4 or 5 tumors, successful downstaging requires obliteration (complete necrosis) of at least 1-2 tumor(s) so that there will be no more than 3 lesions with viable tumor each $\leq$3 cm to meet UNOS T2 criteria.

Criteria for downstaging failure and exclusion from LT

1. Progression of tumor(s) to beyond inclusion criteria for downstaging based on tumor size and number
2. Invasion of a major hepatic vessel based on cross-sectional imaging or Doppler ultrasonography of the abdomen
3. Lymph node involvement by tumor or extrahepatic spread of tumor

Additional guidelines

1. A minimal observation period of 3 months between downstaging and LT is required.
2. A patient with acute hepatic decompensation after downstaging treatment is not eligible for LT unless criteria for successful downstaging and minimal observation period are met.



Multivariate Analysis

Predictor Variables	HR (95% CI)	*P* Value
Child's class cirrhosis		
B (vs. A)	2.19 (1.04-4.64)	**0.04**
C (vs. A)	1.66 (0.61-4.51)	0.31
AFP ≥1,000 ng/mL	2.42 (1.16-5.05)	**0.02**

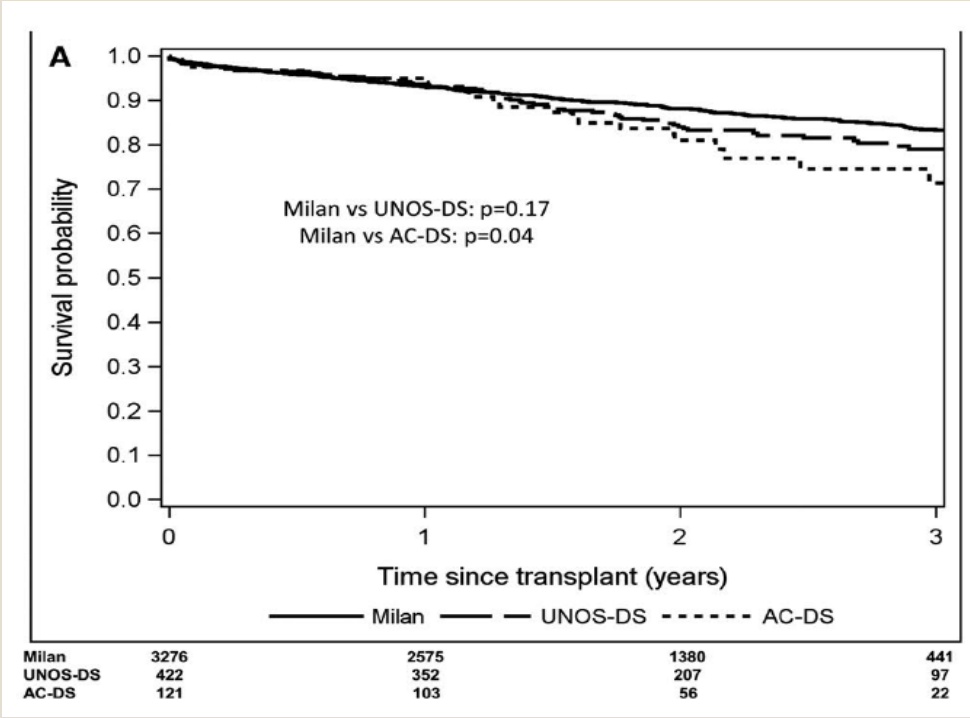
HEPATOLOGY

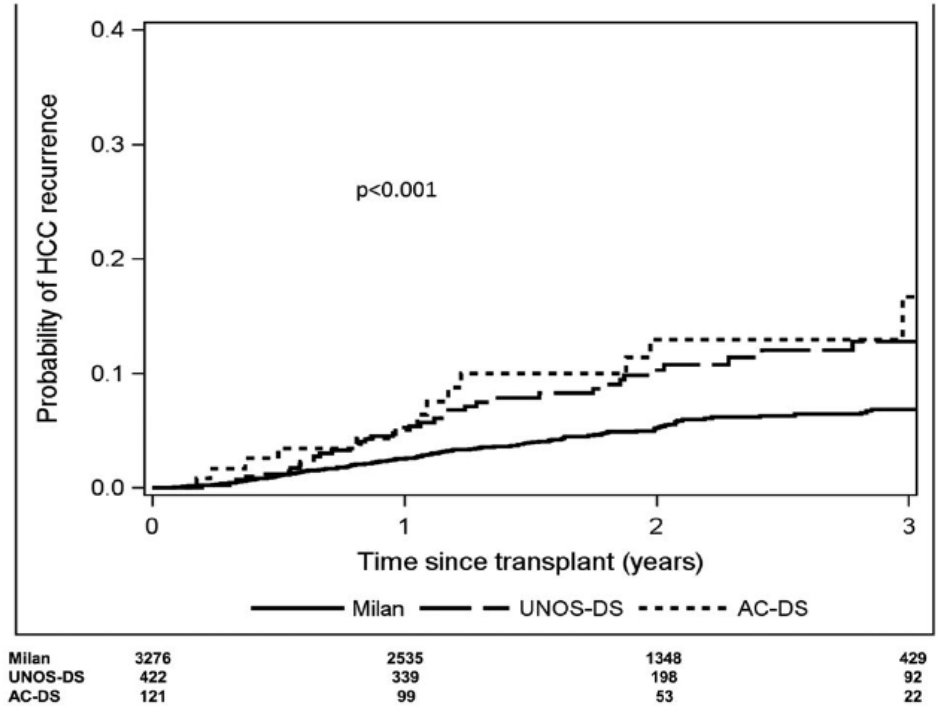
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

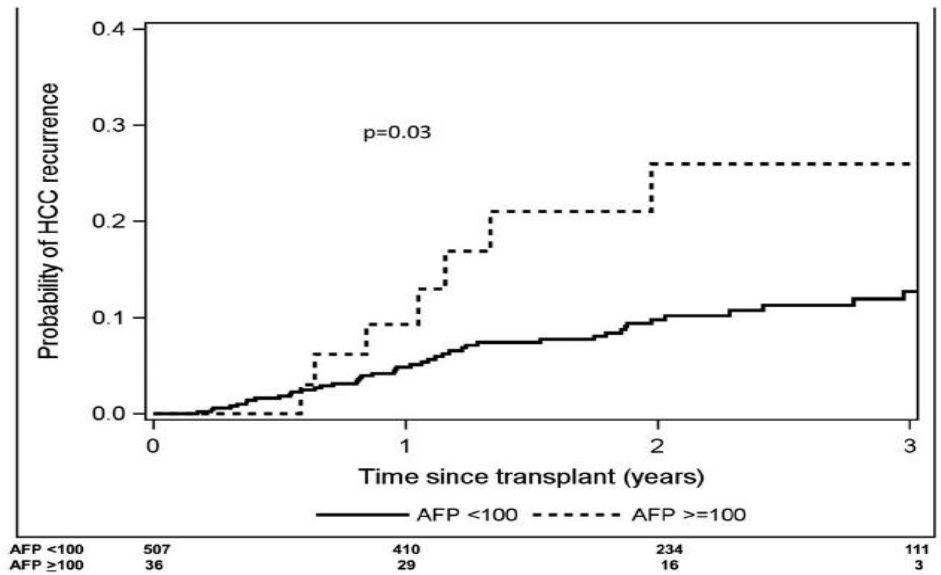
HEPATOLOGY, VOL. 0, NO. 0, 2019

National Experience on Down-Staging of Hepatocellular Carcinoma Before Liver Transplant: Influence of Tumor Burden, Alpha-Fetoprotein, and Wait Time

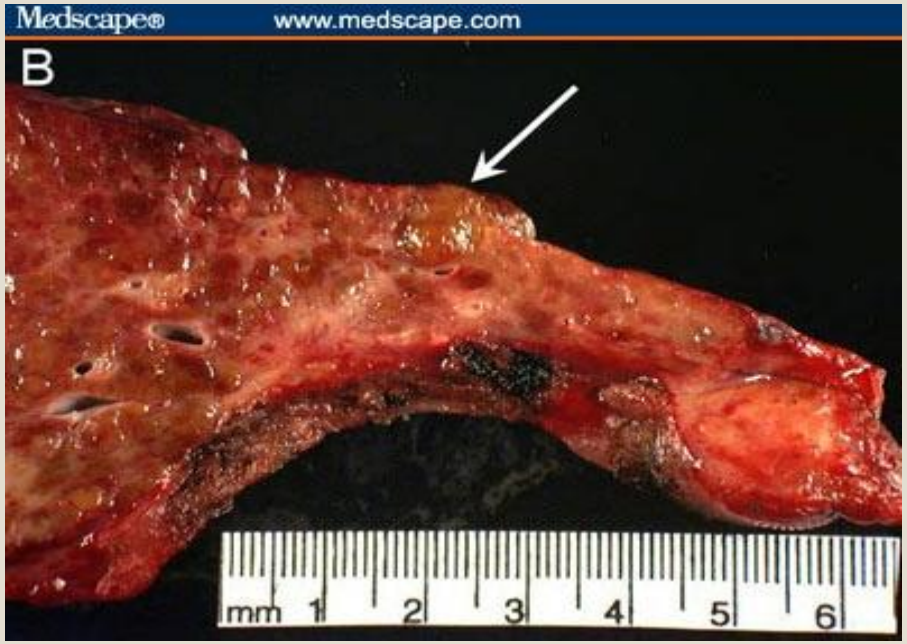
Neil Mehta [1], Jennifer L. Dodge,[2] Joshua D. Grab,[2] and Francis Y. Yao[1,2]


A
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Milan vs UNOS-DS: p=0.17
Milan vs AC-DS: p=0.04
0
1
2
3
Time since transplant (years)
Milan
UNOS-DS
AC-DS
Milan 3276 2575 1380 441
UNOS-DS 422 352 207 97
AC-DS 121 103 56 22


Probability of HCC recurrence
0.4
0.3
0.2
0.1
0.0
p<0.001
0
1
2
3
Time since transplant (years)
Milan
UNOS-DS
AC-DS
Milan 3276 2535 1348 429
UNOS-DS 422 339 198 92
AC-DS 121 99 53 22


Probability of HCC recurrence
0.4
0.3
0.2
0.1
0.0
p=0.03
0
1
2
3
Time since transplant (years)
AFP <100
AFP >=100
AFP <100 507 410 234 111
AFP ≥100 36 29 16 3

Recurrence



Despite using morphologic criteria, such as the Milan criteria (MC) ,to select HCC patients for LT, tumor recurrence (TR) still occurs in 15% to 20% of cases, being associated with an unfavorable prognosis.

Mazzaferro et al.Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699

de'Angelis et al. Managements of recurrent hepatocellular carcinoma afterliver transplantation: A systematic review. *World J Gastroenterol* 2015; 21: 11185-11198

Table 1 Factors possibly associated with the recurrence of hepatocellular carcinoma after liver transplantation

Related to the tumor	Related to the patient	Related to the treatment
Tumor staging	Obesity	**Pretransplantation:**
Vascular invasion	Viral etiology	Percutaneous tumor biopsy
Differentiation's grade	HCV treatment	Waiting time
	NAFLD	Bridging therapy
		Peri-transplantation:
Alpha-fetoprotein		Donor's age
Neutrophil-lymphocyte ratio		Ischemia time
		Surgical technique
		Posttransplantation:
Enhanced uptake in PET scan		Immunosuppression
MRI findings with gadoxetic acid		Adjuvant sorafenib
Response to LRT		

Filgueria . Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation. World *J Hepatol* 2019 March 27;11(3): 261-272

A meta-analysis showed that the risk of TR was proportional to the diameter of the larger nodule, with no association with the number of nodules, probably because multiple nodules, however small, did not present higher frequency of vascular invasion.

Germani et al . Which matters most: number of tumors, size of the largest tumor, or total tumor volume? *Liver Transpl* 2011; **17** Suppl 2: S58-S66

Microvascular invasion(mIV)tends to be associated with tumor staging, being observed in 16.6% of the tumors within the MC, and in 50.2% of those beyond the Up-to-seven criteria group.

The mIV is a determining factor in the risk of TR and survival, doubling the risk of death.

Mazzaferro et al. Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; 10: 35-43

- Some tumors induce an inflammatory response that induces the release of cytokines and inflammatory mediators, increasing the risk of metastasis by inhibition of apoptosis, promotion of angiogenesis, and DNA damage.

Filgueria . Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation. World *J Hepatol* 2019 March 27;11(3): 261-272

- Halazun et al 2009 found NLR(neutrophil-lymphocyte ratio)≥5 in 9% of the individuals transplanted for HCC, who presented a 5-year RFS of only 25%.

- FDG uptake by the tumor has been used as a marker of HCC aggressiveness, based on the association with mIV and poor tumoral differentiation, greater risk of dropout, greater risk of TR, and lower RFS and overall 5-year survival .

Kornberg et al. Patients withnon-[18 F]fludeoxyglucose-avid advanced hepatocellular carcinoma on clinical staging may achieve long term recurrence-free survival after liver transplantation. *Liver Transpl* 2012; **18**: 53-61

- In one sample, 25% of patients with HCC who underwent LT were obese and had twice the risk of death, a higher frequency of mIV, and tendency for a higher rate of TR, suggesting that the increased expression of vascular endothelial growth factor(VEGF) induced by adipose tissue may stimulate tumor angiogenesis.

Siegel et al.Diabetes, body mass index, and outcomes in hepatocellular carcinoma patients undergoing liver transplantation. *Transplantation* 2012**;** 94: 539-543

- One study analyzed the UNOS database and observed that the cases with HCC secondary to NAFLD presented a 32% lower rate of high-risk characteristics for TR.

Lewin SM, Mehta N, Kelley RK, Roberts JP, Yao FY, Brandman D. Liver transplantation recipients with nonalcoholic steatohepatitis have lower risk hepatocellular carcinoma. *Liver Transpl* 2017; **23**: 1015-1022

- The risk of 5-year TR was greater in patients transplanted before 6 months or after 18 months of diagnosis of HCC.

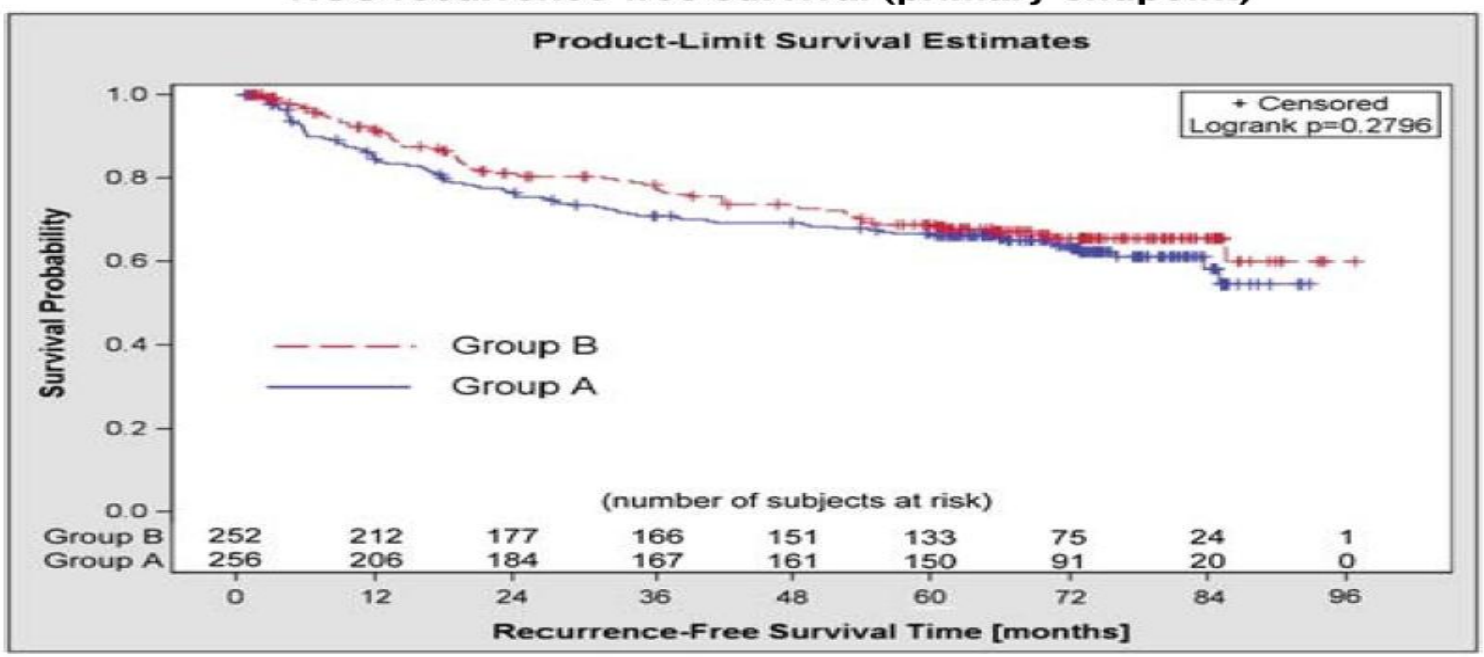
Mehta et al. Wait Time of Less Than 6 and Greater Than 18 Months Predicts Hepatocellular Carcinoma Recurrence After Liver Transplantation: Proposing a Wait Time "Sweet Spot". *Transplantation* 2017; **101**: 2071-2078

Original Clinical Science—Liver

OPEN

Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial

HCC recurrence-free survival (primary endpoint)



MONITORING OF THE PATIENT AFTER LT FOR HCC

- There is no consensus on the protocol for monitoring TR after LT, without definition on the modality of exams to be performed and frequency or duration of follow up.

- Approximately 75% of the TR occur during the first 2 years after the LT, and only 10% of them are detected after the fourth year.

Most authors monitored the patients with (CT) and AFP levels with 3- to 6-mo intervals in the first 2 or 3 years, increasing the interval between exams from that date.

Bodzin et al. Predicting Mortality in Patients Developing Recurrent Hepatocellular Carcinoma After Liver Transplantation: Impact of Treatment Modality and Recurrence Characteristics. *Ann Surg* 2017; **266**: 118-125

Table 2 RETREAT score to estimate the risk of tumor recurrence after liver transplantation in patients with tumors within the Milan criteria and proposed protocol for tumor recurrence screening[74]

Risk factor	Score
Alpha-fetoprotein level before LT	
0–20 ng/mL	0
21–99 ng/mL	1
0–999 ng/mL	2
> 1000 ng/mL	3
Microvascular invasion	2
Sum of the diameter of the largest viable tumor and the number of viable nodules	
0	0
1.1–4.9	1
5.0–9.9	2
≥ 10	3
RETREAT Score	**Screening Protocol**
0 points	Screening not needed
1-3 points	Screening every 6/6 mo for 2 yr
4 points	Screening every 6/6 mo for 5 yr
≥5 points	Screening every 3-4 mo for 2 yr Exams every 6 mo between the 2nd and 5th year

Mehta et al. Validation of a Risk Estimation of Tumor Recurrence After Transplant (RETREAT) Score for Hepatocellular Carcinoma Recurrence After Liver Transplant. *JAMA Oncol* 2017; **3**: 493-500


CONCLUSIONS

- HCC nowadays is the most common indication for liver transplantation
- MC is the standard criteria used for liver transplantation
- Extended criteria and LDLT are important alternatives to compensate for organ shortage

- Successful downstaging to within accepted criteria for liver transplantation is an important achievement with comparable overall survival and disease free survival

- Risk factors for recurrence should be addressed well to prevent HCC recurrence after liver transplantation


THANK
YOU