National University Hospital

The Liver Transplant Symposium 2023

Tumour Thrombosis in HCC – Strategies for Success

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European Inter-University Diploma in HPB Oncology

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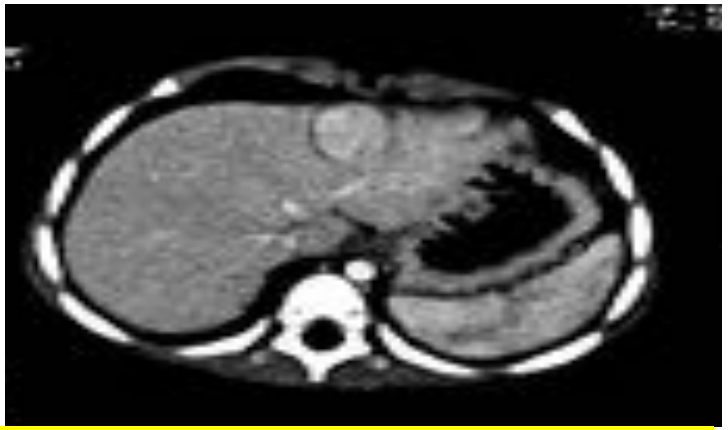
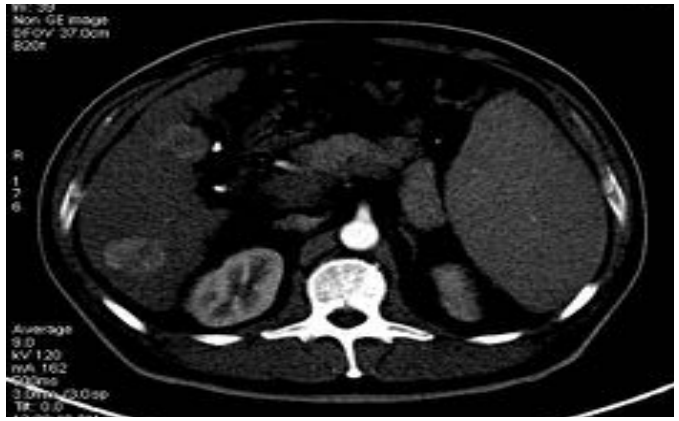
Medanta – The Medicity, Delhi-NCR

Real life..

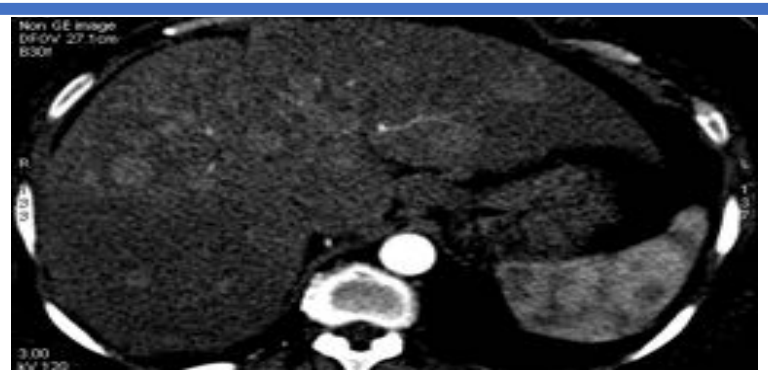
Despite the surveillance programs for high-risk patients, majority of patients present with an advanced HCC at the time of diagnosis – non-resectable, and non-transplantable



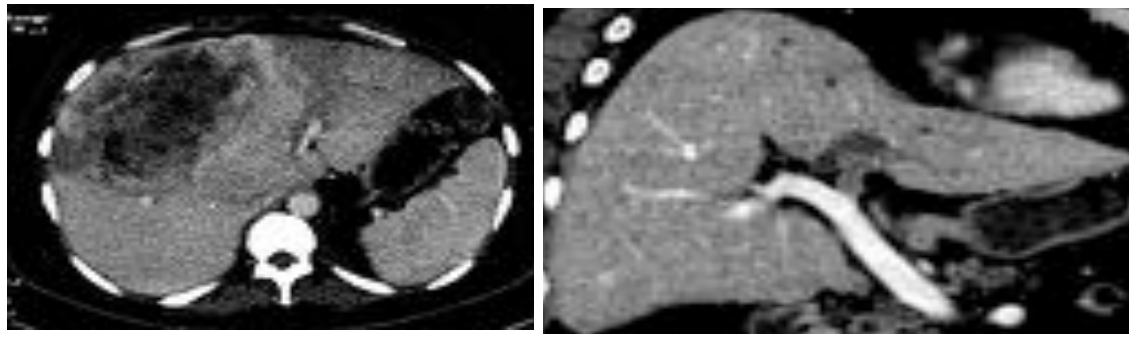
Early HCC, single lesion



< 3 tumours < 3 cm max diameter

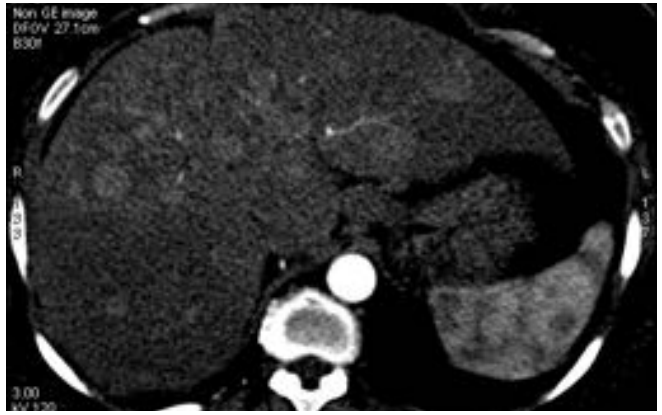


Multifocal HCC

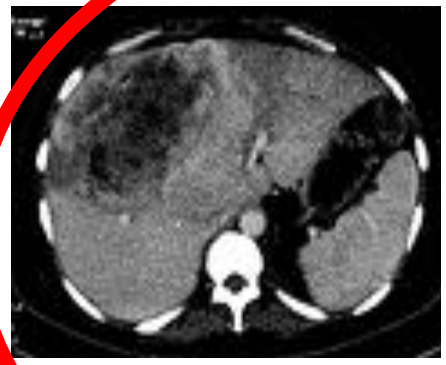


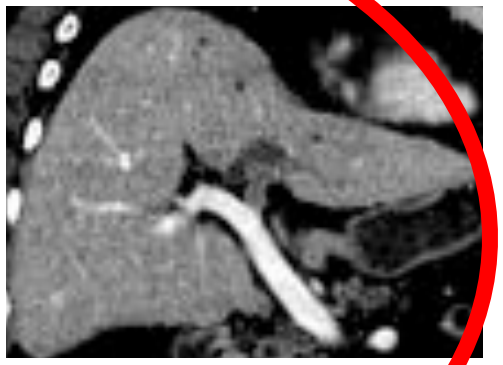
Large HCC with vascular involvement

HCC with PVTT



Multifocal HCC





Large HCC with PVTT


END
OF THE
ROAD

Reason for the “I give up” approach..

➢Assumed to be in the blood = systemic

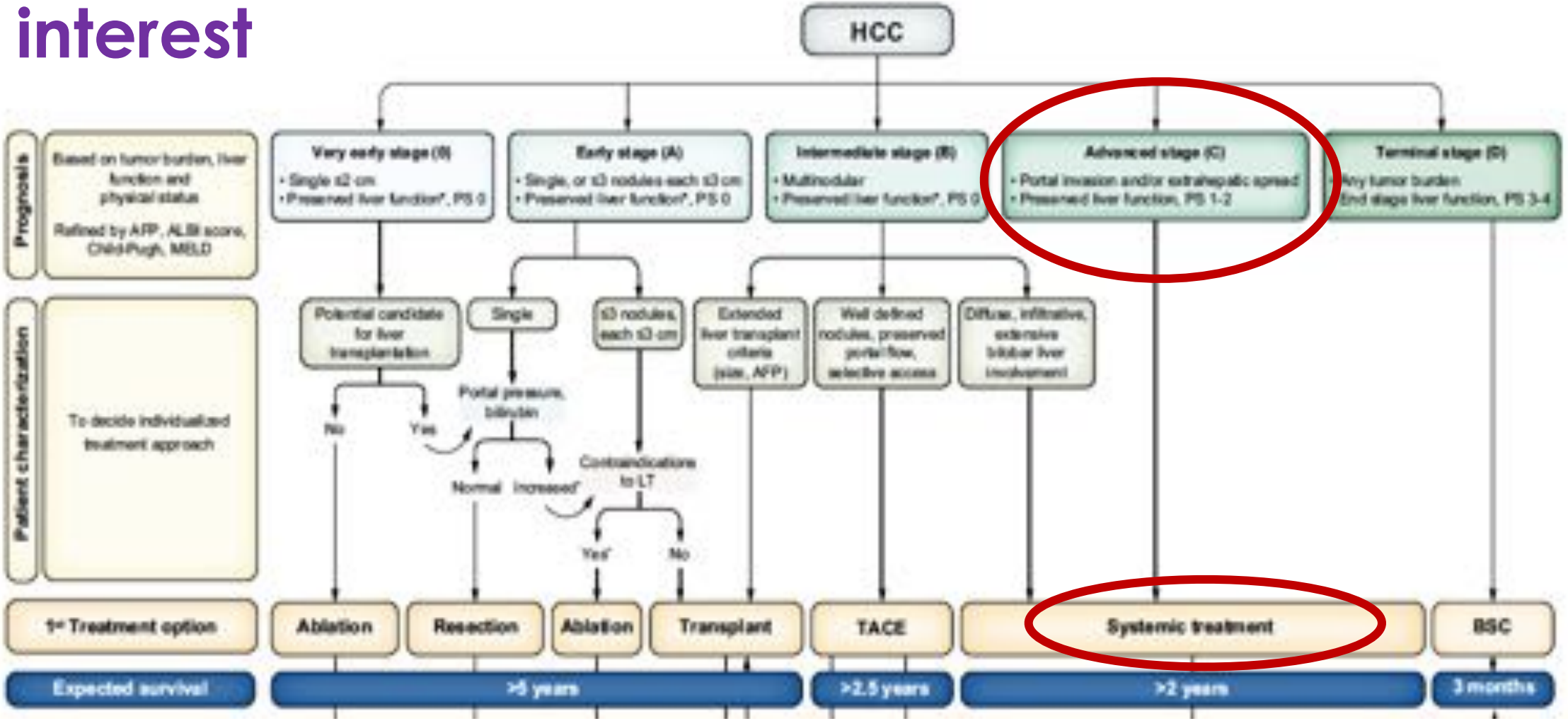
➢Patients with PVTT – untreated / palliative Rx with TKI’s – median overall survival 2 – 11 months; 10% OS at 3 years – immunotherapy results better??

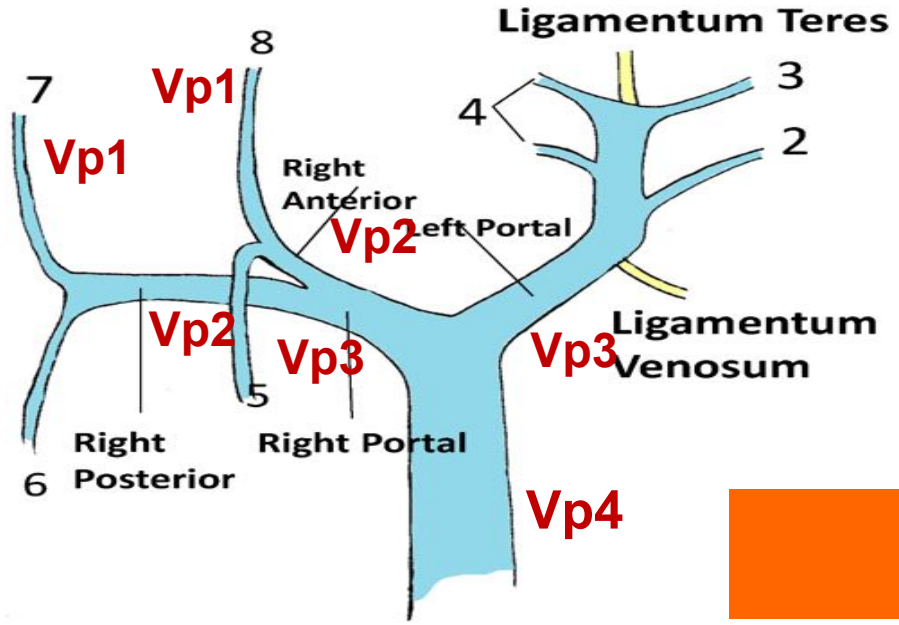
➢AASLD, EASL guidelines – Contraindication for resection, TACE not indicated, absolute contraindication for LT

Siegel RL, et al. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30
Xiang X, et al. Distribution of tumor stage and initial treatment modality in patients with HCC. Clin Transl Oncol 2017

The patient cohort of interest

BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update ☆





Vp0- no thrombus

Vp1- distal to 2nd order branch

Vp2- in 2nd order branch

Vp3- 1st order branch

Vp4- Main trunk or C/L side

Grades of PVTT (VP classification)
Liver cancer study group, Japan

A new classification for hepatocellular carcinoma with portal vein tumor thrombus

J Hepatobiliary Pancreat Sci (2011) 18:74–80

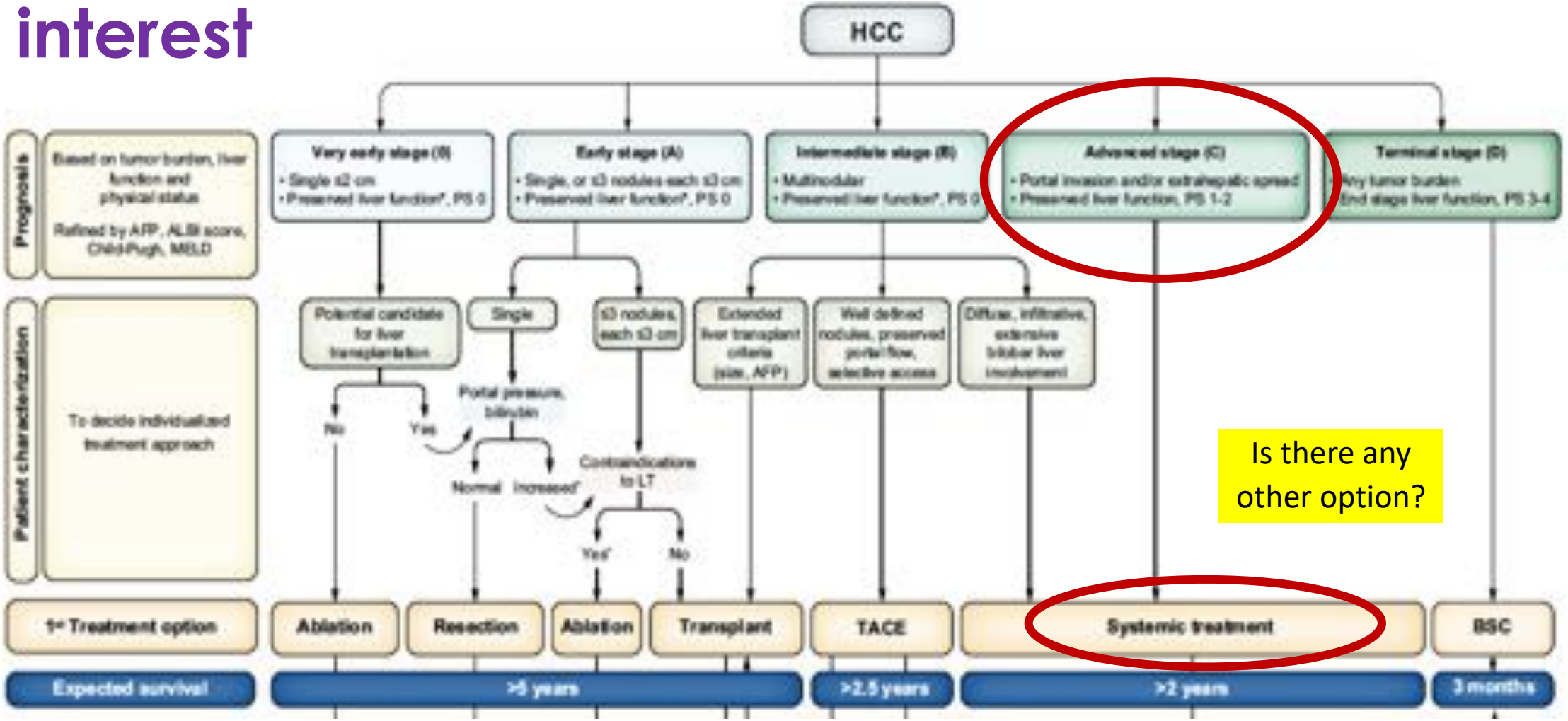
Cheng classification

Table 1 Our classification of PVTT

Types
Type I_0: Tumor thrombus formation found under microscopy
Type I: Tumor thrombi involving segmental branches of portal vein or above
Type II: Tumor thrombi involving right/left portal vein
Type III: Tumor thrombi involving the main portal vein trunk
Type IV: Tumor thrombi involving the superior mesenteric vein

The patient cohort of interest

BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update ☆



Is there any other option?

Should Segmental PVTT (Vp2) Be an Absolute Contraindication for LT in Patients With HCC?

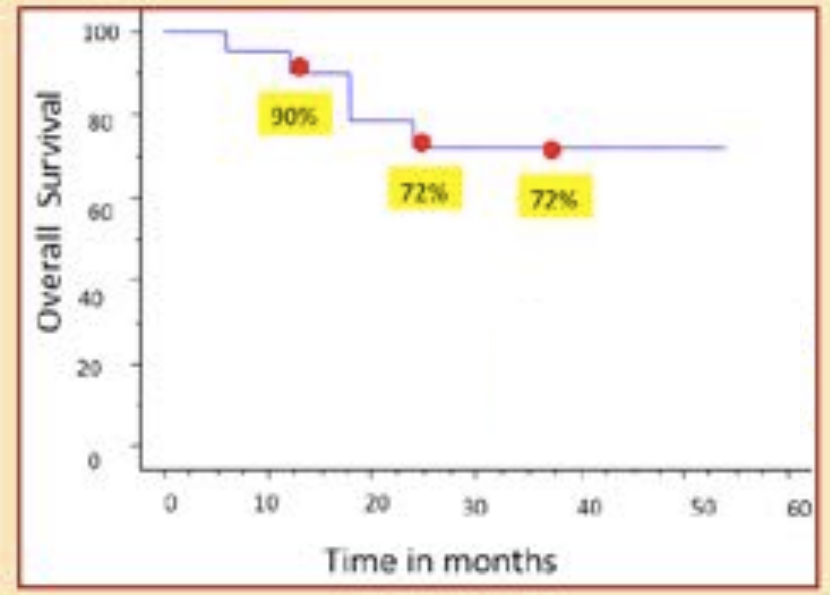
Prashant Bhangui[1], T.Piplani[2], D.Gautam[3], A.Rastogi[1], S.Goja[1], S.Saigal[4], AS Soin[1]

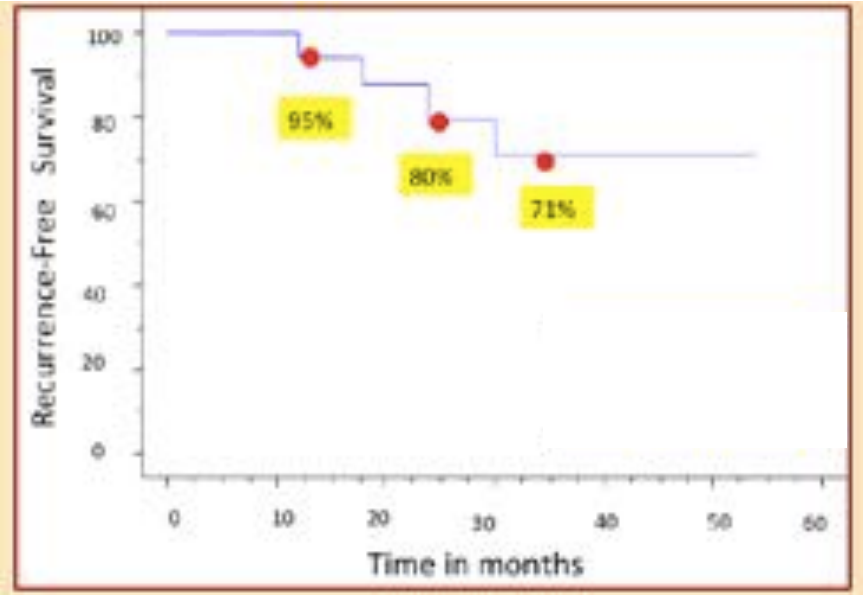
Best Paper Award

2nd World Congress of the International Living Donor Liver Transplant Study Group (ILDLT), Nov 2015, Seoul

Should Segmental PVTT (Vp2) Be an Absolute Contraindication for LT in Patients With HCC?

13 patients with Level Vp2 PVTT





~ We didn't use downstaging / neoadjuvant ablative therapies in patients with segmental PVTT

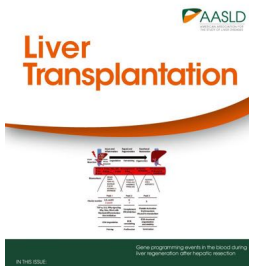
~ Up to Vp2 – ok for LDLT straight away

But segmental PVTT is very different

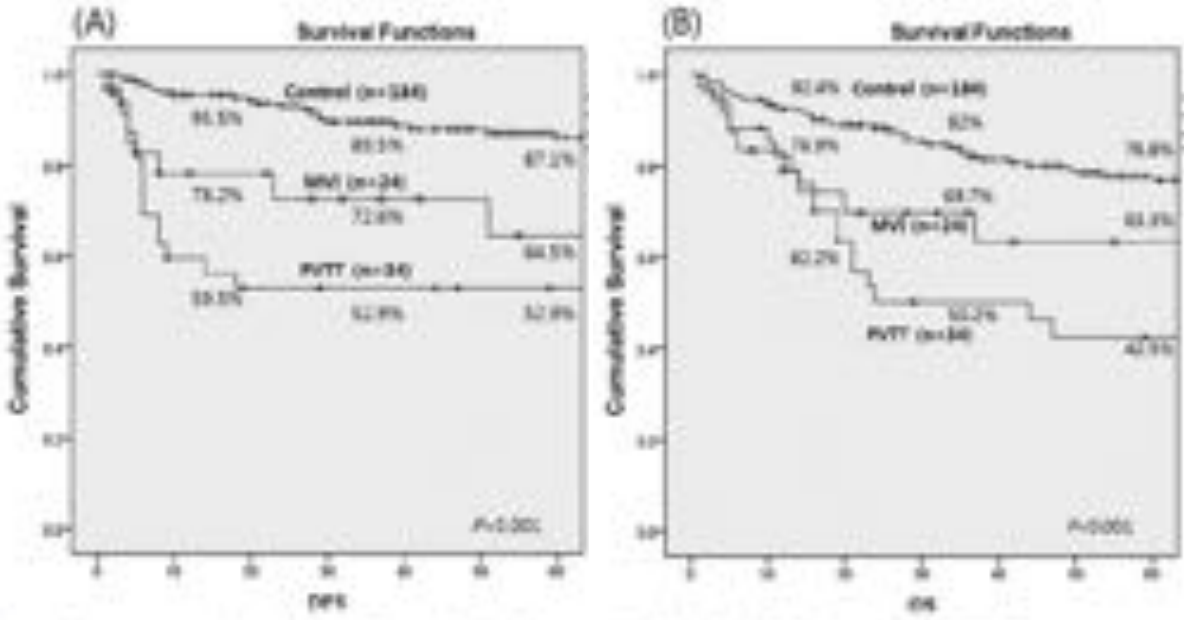
from lobar PVTT

The Clinical Outcomes of Patients with Portal Vein Tumor Thrombi After Living Donor Liver Transplantation

Ho Joong Choi,[1] Dong Goo Kim,[1] Gun Hyung Na,[1] Tae Ho Hong,[1] Si Hyun Bae,[2] Young Kyoung You,[1] Jong Young Choi,[2] and Seung Kew Yoon[2]



2017;23:1023-31



Comparison of the (A) DFS and (B) OS rates in patients with HCC by MVI status and PVTT status.

~ Segmental PVTT with AFP <100 ng/ml –acceptable

~ Vp3 (lobar) should be a contraindication

~ 27 patients with Segmental PVTT – Vp1/Vp2

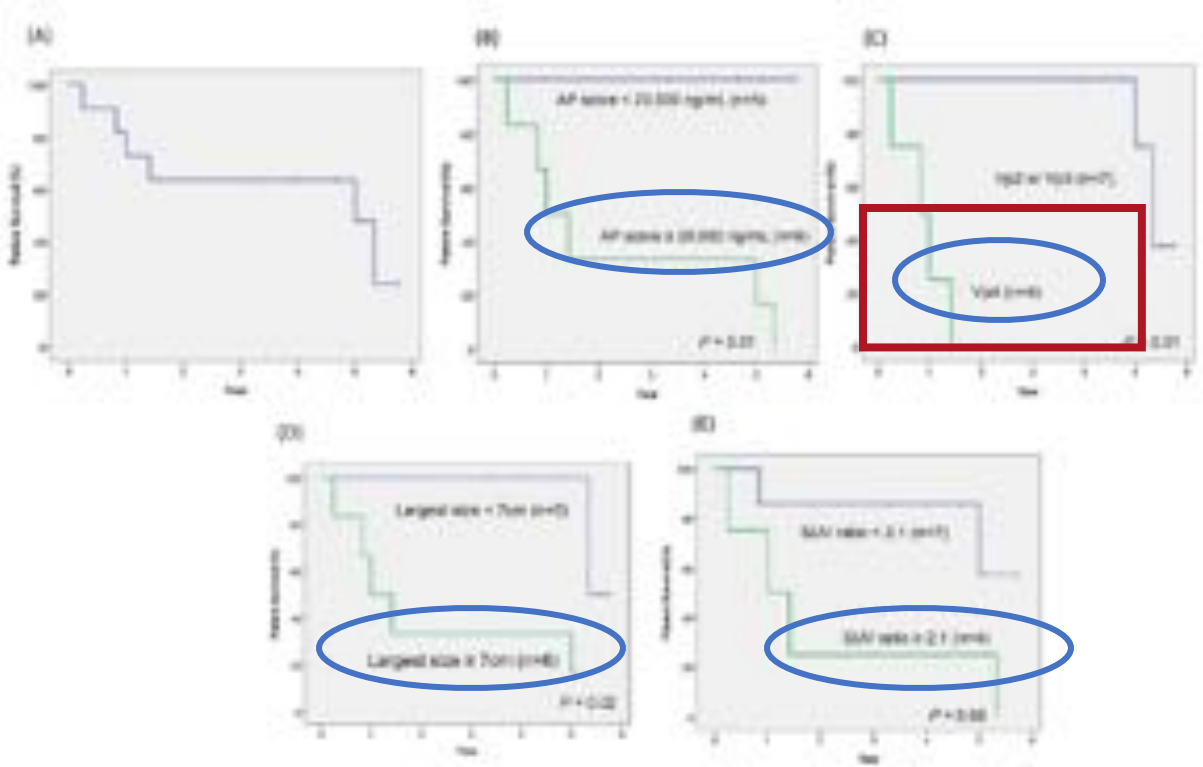
~ No downstaging

~ 5-yr DFS and OS 63.9%, 50.3%

Macrovascular Invasion Is Not an Absolute Contraindication for Living Donor Liver Transplantation

Kwang-Woong Lee,[1] Suk-Won Suh,[1] YoungRok Choi,[1] Jaehong Jeong,[1] Nam-Joon Yi,[1] Hyeyoung Kim,[1] Kyung Chul Yoon,[1] Suk Kyun Hong,[1] Hyo-Sin Kim,[1] Kyung-Bun Lee,[2] and Kyung-Suk Suh[1]

2017;23:19-27



5-yr OS -- 63.6%

~ Retrospective review- 11 pts

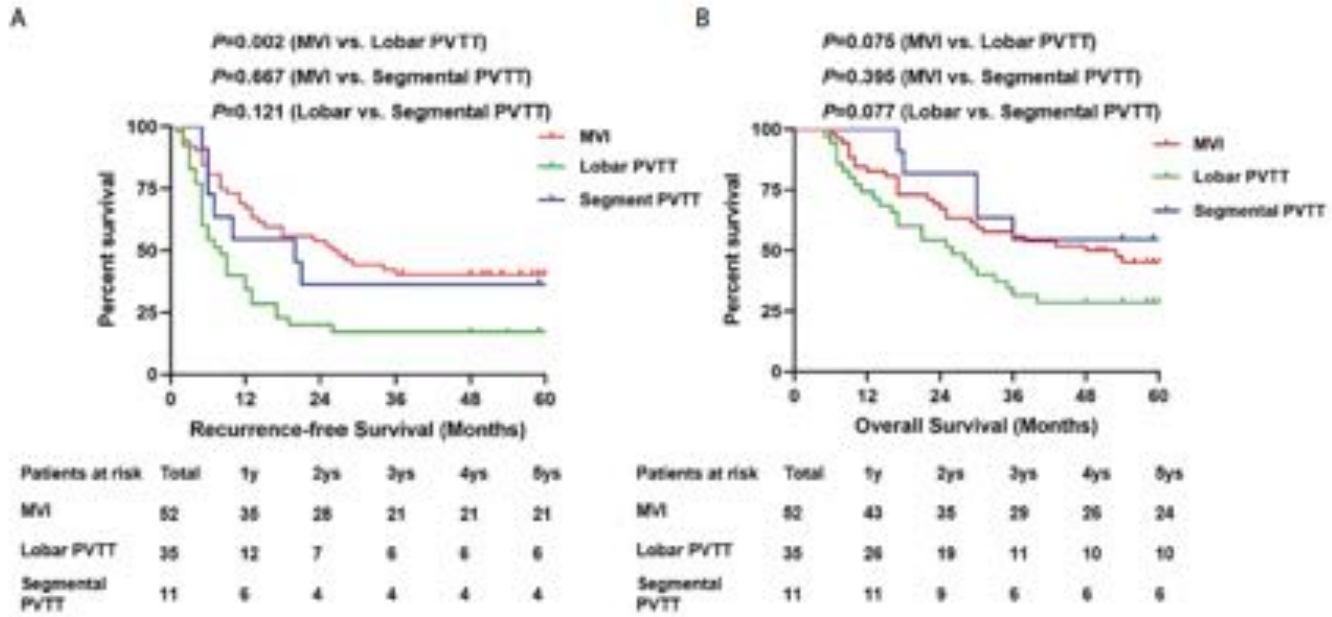
~ No downstaging therapy in most – LDLT upfront

Clinical analysis of deceased donor liver transplantation in the treatment of hepatocellular carcinoma with segmental portal vein tumor thrombus: A long-term real-world study

frontiers | Frontiers in Oncology

Meng Sha[1†], Chen Chen[1†], Chuan Shen[1†], Seogsong Jeong[2,3,4†], Han-yong Sun[1], Ning Xu[1], Hua-lian Hang[1], Jie Cao[1] and Ying Tong[1*]

Conclusions: In summary, lobar PVTT remains a contraindication to DDLT. HCC patients with segmental PVTT and AFP level ≤100 ng/ml may be acceptable candidates for DDLT.



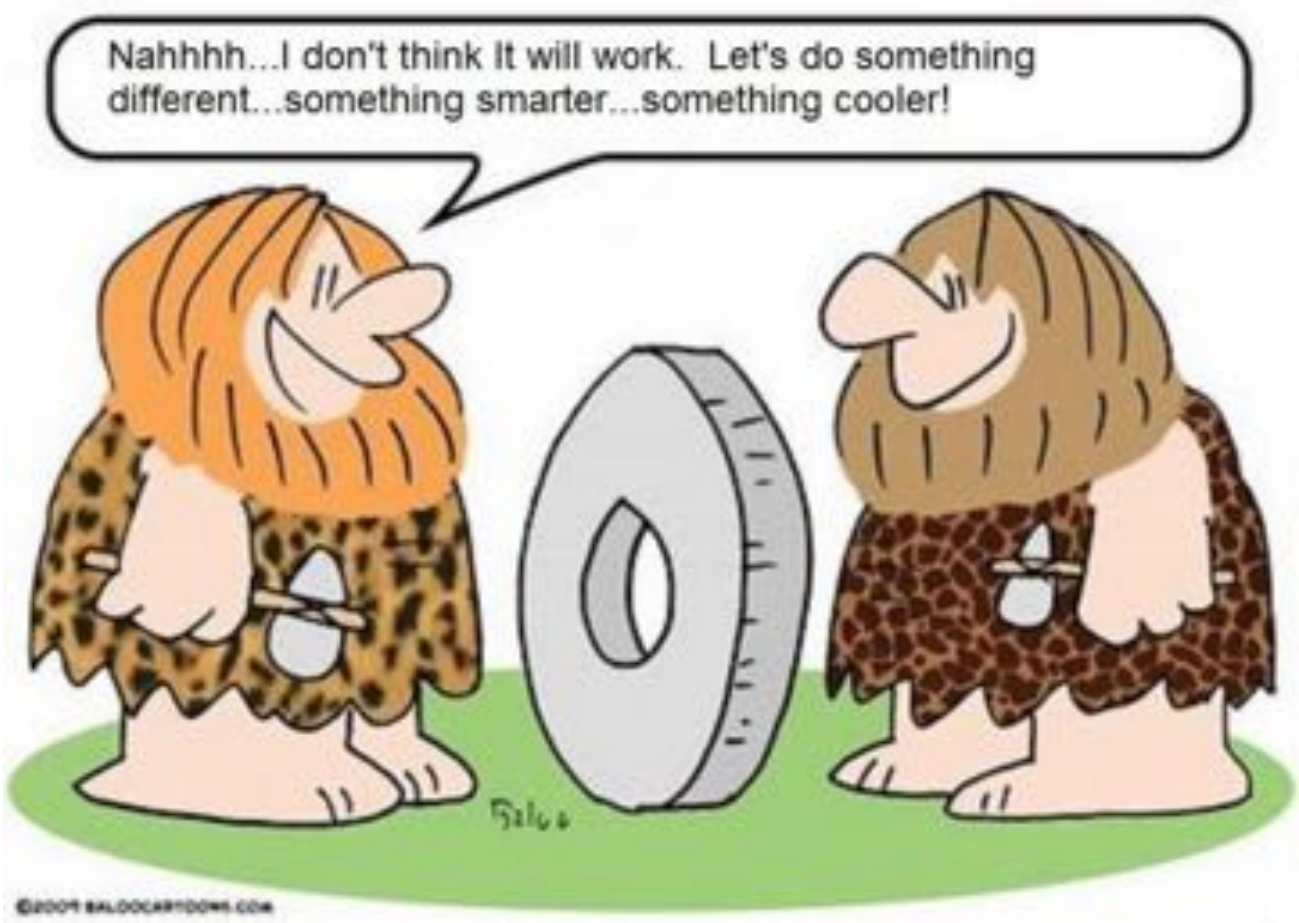
Patients at risk	Total	1y	2ys	3ys	4ys	5ys
MVI	52	35	28	21	21	21
Lobar PVTT	35	12	7	6	6	6
Segmental PVTT	11	6	4	4	4	4

Patients at risk	Total	1y	2ys	3ys	4ys	5ys
MVI	52	43	35	29	26	24
Lobar PVTT	35	26	19	11	10	10
Segmental PVTT	11	11	9	6	6	6

FIGURE 4
Recurrence-free survivals (A) and overall survivals (B) comparison among MVI, lobar and segmental PVTT group.

LT straightaway in presence of PVTT is not great

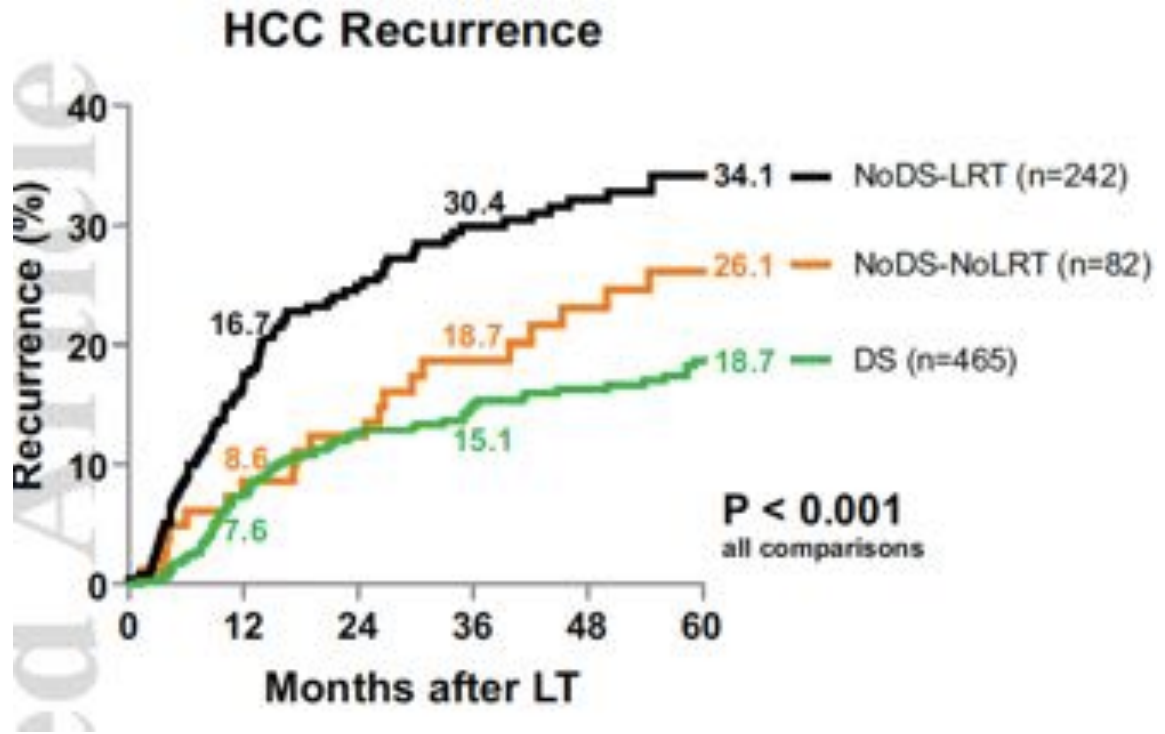
especially in lobar PVTT..



Downstaging with LRT before LT helps yield good outcomes in patients with HCC beyond Milan

Liver Transplantation Outcomes in a U.S. Multicenter Cohort of 789 Patients with Hepatocellular Carcinoma Presenting Beyond Milan Criteria

Ani Kardashian, Sander S. Florman, Brandy Haydel, Richard M. Ruiz ... See all authors



HEPATOLOGY

The gamechangers!!

The significant impact of focused RT in treatment of PVTT -- EBRT/SBRT/TARE

- 41 patients SBRT for PVTT and IVCTT – 31% CR, 39% PR

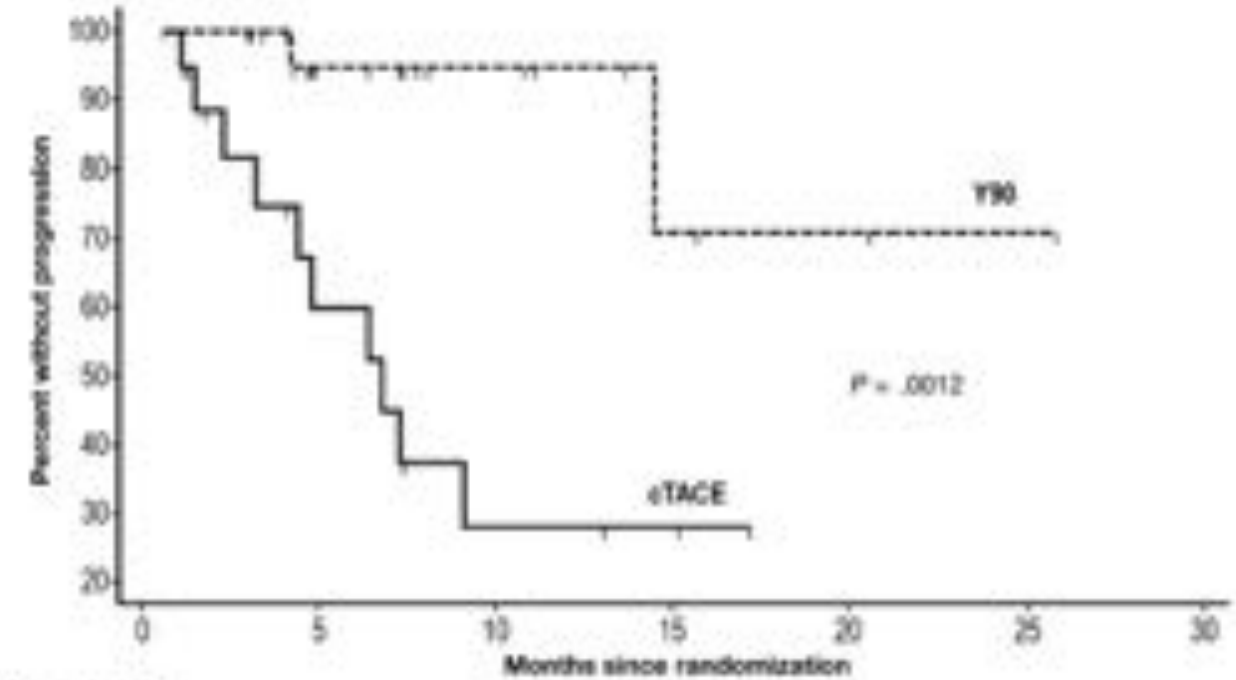
Mian Xi, Plos one 2013

- 120 patients SBRT for PVTT and IVCTT – 33% CR, 49% PR

J Kang, Molecular and Clinical Oncol 2014

Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

Gastroenterology 2016;151:1155–1163



Number at risk						
Group: cTACE						
21	8	3	2	0	0	0
Group: Y90						
24	12	7	3	2	1	0

Figure 1. Time to progression.

Living Donor Liver Transplantation for Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis after Concurrent Chemoradiation Therapy

Dai Hoon Han[1,2], Dong Jin Joo[1,2,3], Myoung Soo Kim[1,3], Gi Hong Choi[1,2,3], Jin Sub Choi[1,2,3], Young Nyun Park[2,4], Jinsil Seong[2,5], Kwang-Hyub Han[2,6], and Soon Il Kim[1,3]

[1]Department of Surgery, [2]Liver Cancer Special Clinic, [3]Research Institute for Transplantation, Departments of [4]Pathology, [5]Radiological Oncology, and [6]Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.

Yonsei Medical Journal
YMJ

- 8 patients with PVTT
- **CCRT** 45 Gy over 5 weeks → followed by HAIC (5-FU + Cisplatin for 3-12 months) → successful DS → LDLT
- 87.5% 1 year DFS vs. < 10% with standard therapy
- 3 recurrences
- Median survival 33 months

Liver Transplantation After Transarterial Chemoembolization and Radiotherapy for Hepatocellular Carcinoma with Vascular Invasion

J Gastrointest Surg (2017) 21:275–283
DOI 10.1007/s11605-016-3302-0

Yuri Jeong[1] · Min-Ho Shin[2] · Sang Min Yoon[1] · Gi-Won Song[2] · Ki-Hun Kim[2] · Chul-Soo Ahn[2] · Deok-Bog Moon[2] · Shin Hwang[2] · Jin-hong Park[1] · Jong Hoon Kim[1] · Sung-Gyu Lee[2]

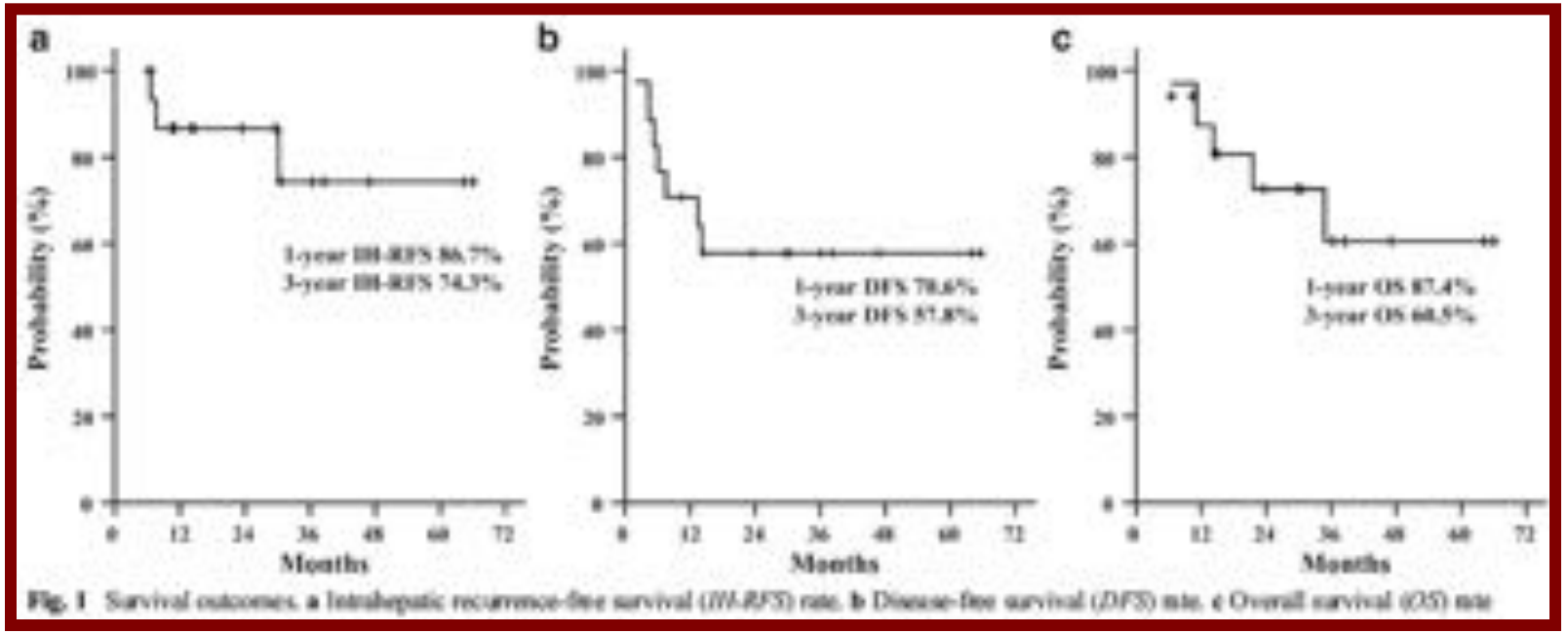


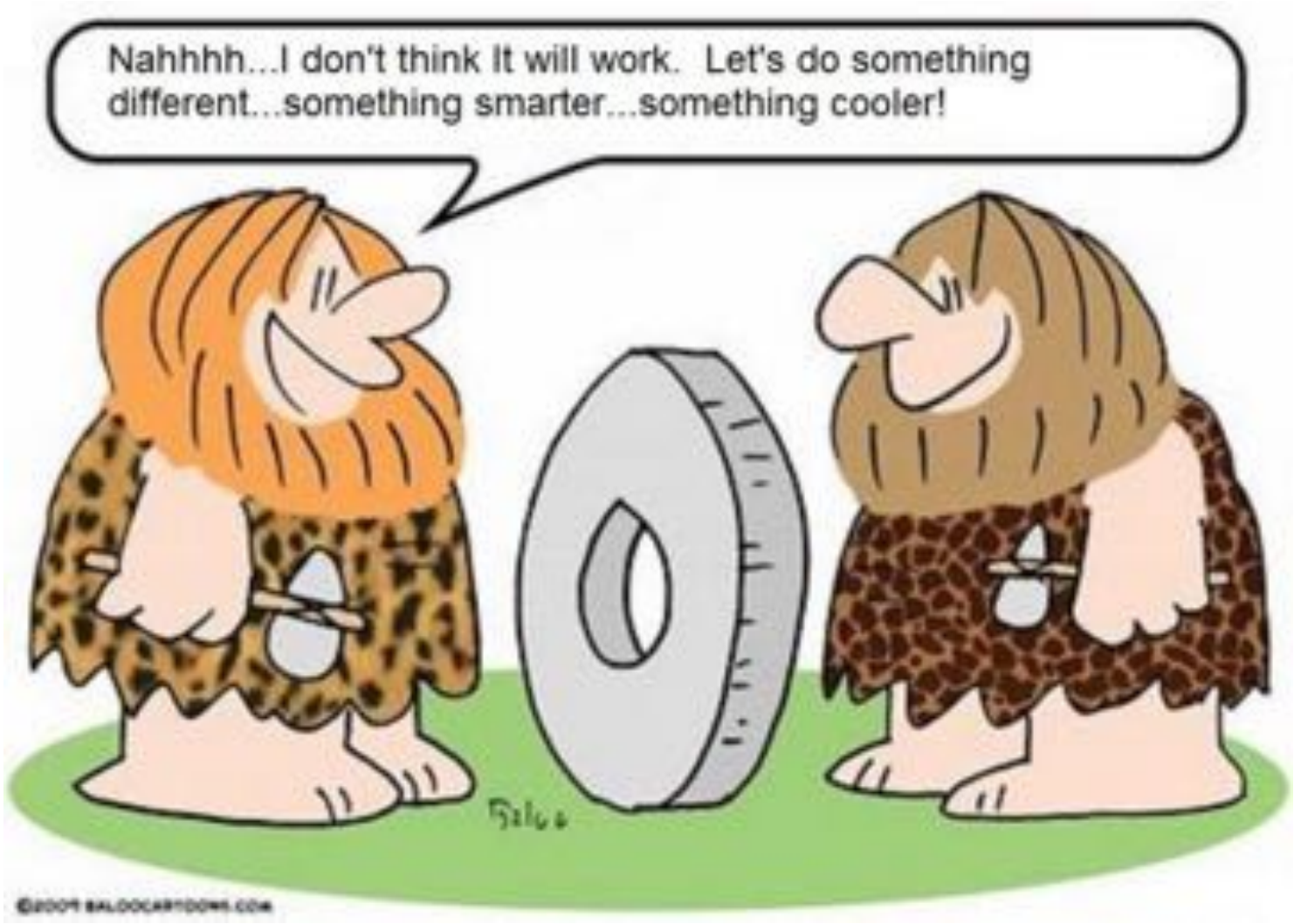
Fig. 1 Survival outcomes. a Intrahepatic recurrence-free survival (*IHRFS*) rate. b Disease-free survival (*DFS*) rate. c Overall survival (*OS*) rate

17 HCC patients with major vascular invasion

LDLT after combined TACE and radiotherapy

3-year OS and DFS 60.5% and 57.8%, respectively

Could downstaging with RT or TACE help improve outcomes in patients with lobar or main PV tumour thrombosis?

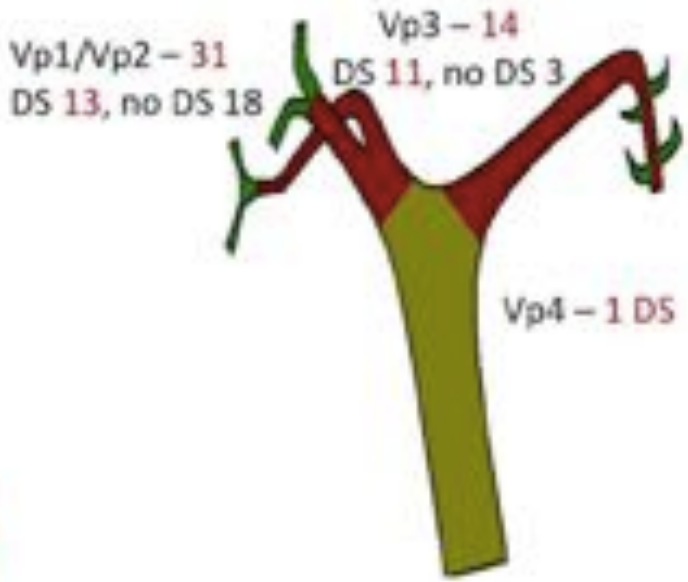


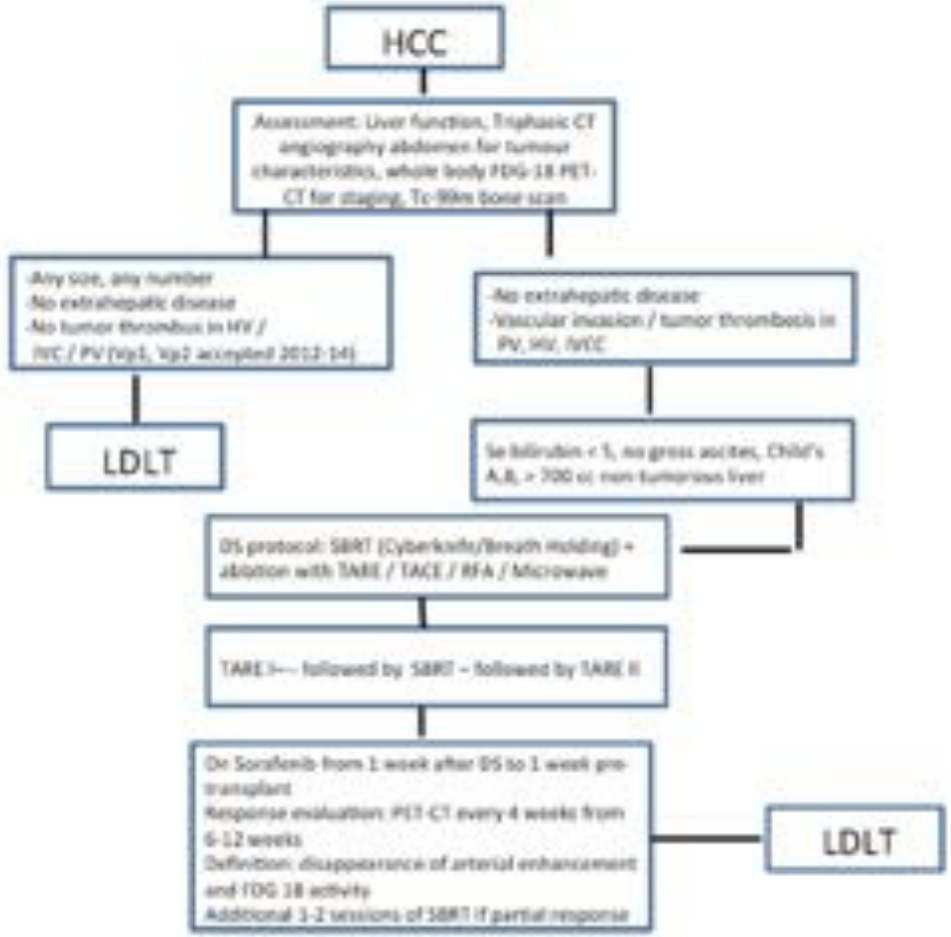
Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

Arvinder S. Soin, MS, FRCS,[1] Prashant Bhangui, MS,[1] Tejinder Kataria, MD,[2] Sanjay S. Baijal, MD,[3] Tarun Piplani, MD,[3] Dheeraj Gautam, MD,[4] Narendra S. Choudhary, DM,[1] Srinivasan Thiagarajan, MS,[1] Amit Rastogi, MS,[1] Neeraj Saraf, MD,[1] and Sanjiv Saigal, DM[1]

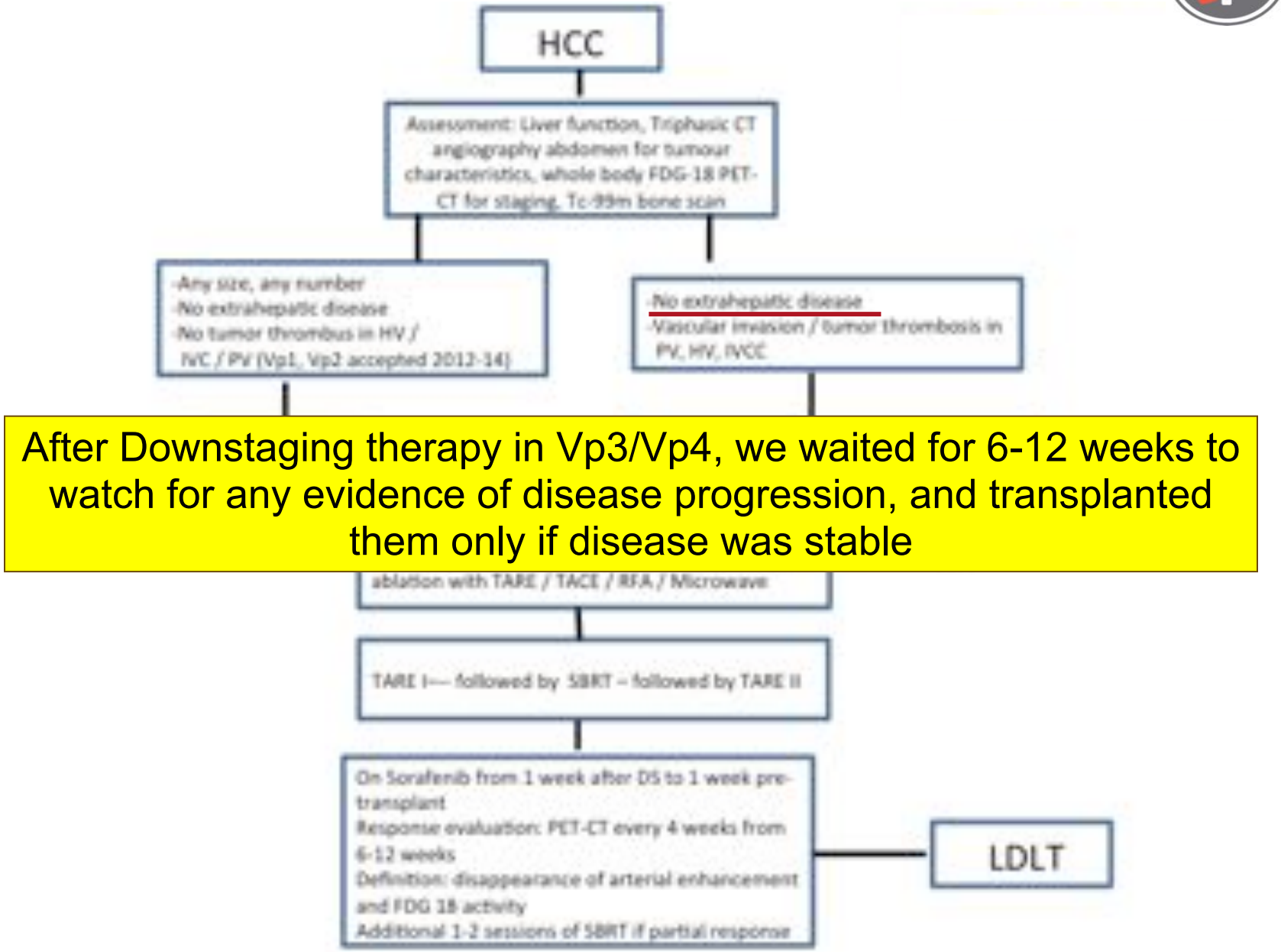
A

B





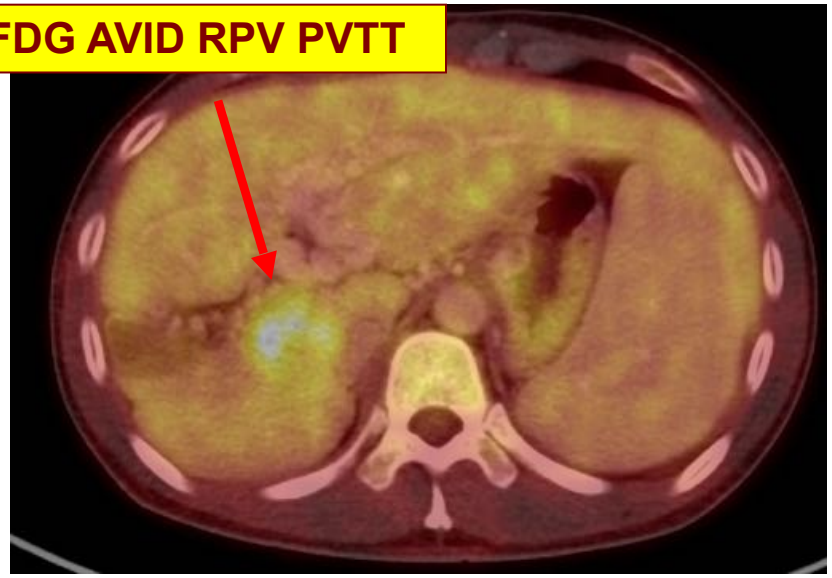
Protocol


HCC
Assessment: Liver function, Triphasic CT angiography abdomen for tumour characteristics, whole body FDG-18 PET-CT for staging, Tc-99m bone scan
-Any size, any number
-No extrahepatic disease
-No tumor thrombus in HV / IVC / PV (Vp1, Vp2 accepted 2012-14)
-No extrahepatic disease
-Vascular invasion / tumor thrombosis in PV, HV, IVCC
After Downstaging therapy in Vp3/Vp4, we waited for 6-12 weeks to watch for any evidence of disease progression, and transplanted them only if disease was stable
ablation with TARE / TACE / RFA / Microwave
TARE I— followed by SBRT – followed by TARE II
On Sorafenib from 1 week after DS to 1 week pre-transplant
Response evaluation: PET-CT every 4 weeks from 6-12 weeks
Definition: disappearance of arterial enhancement and FDG 18 activity
Additional 1-2 sessions of SBRT if partial response
LDLT

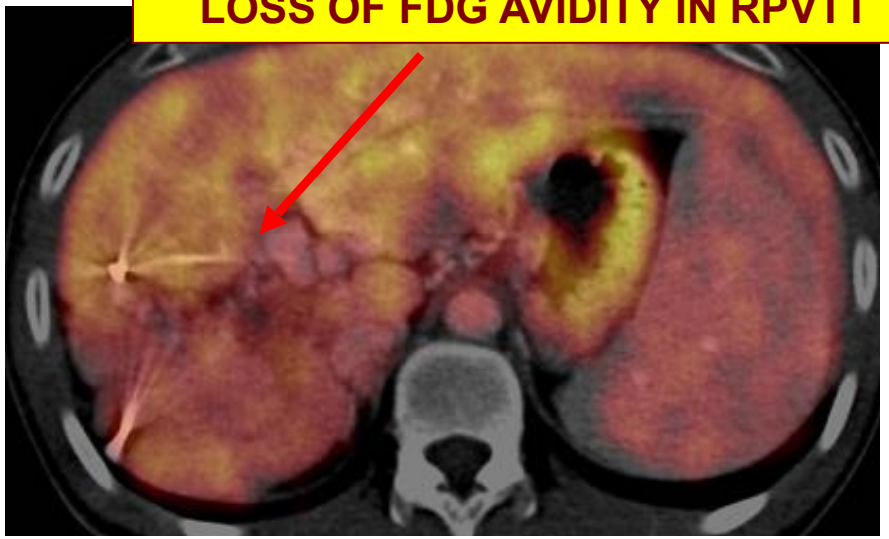
PRE SBRT

POST SBRT

FDG AVID RPV PVTT

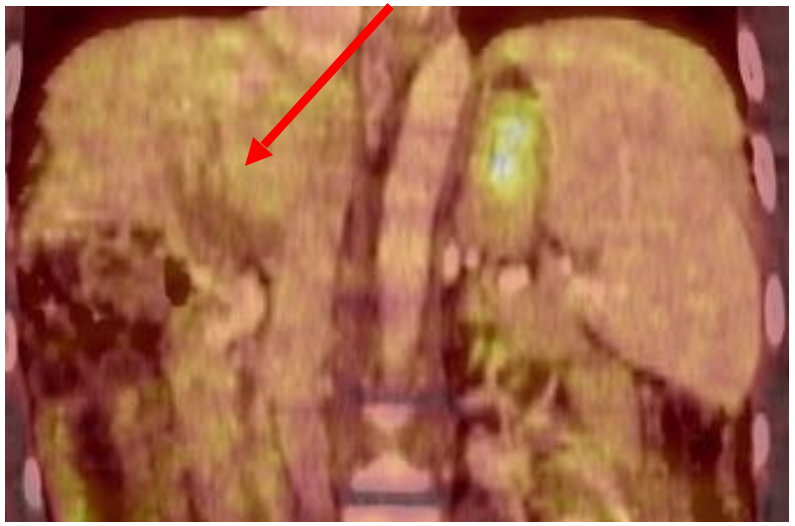


LOSS OF FDG AVIDITY IN RPVTT

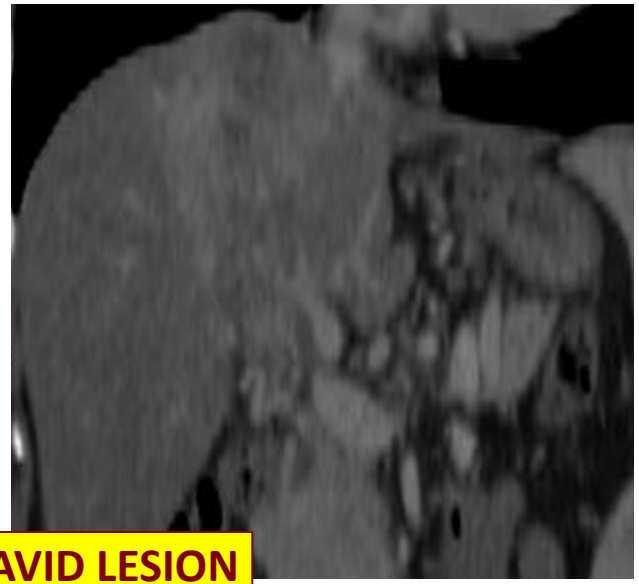


FDG AVID HCC and PVTT

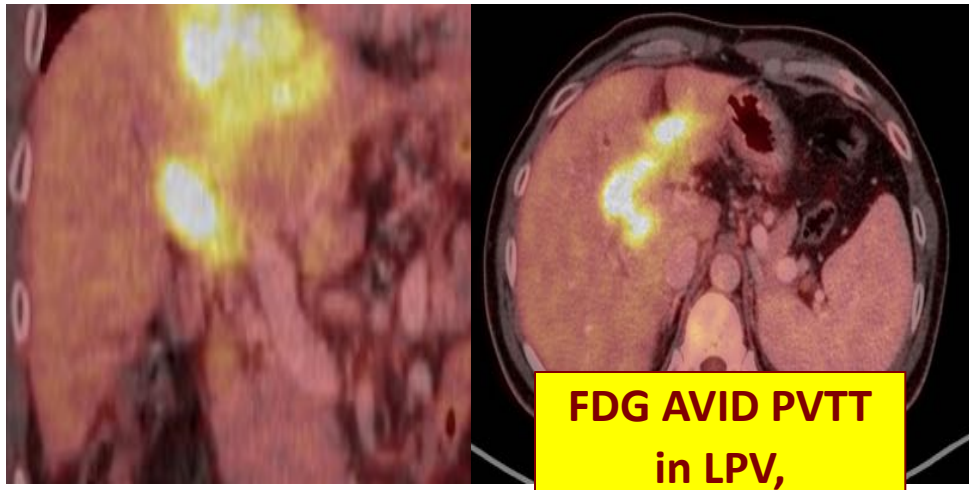
LOSS OF FDG AVIDITY



PRE TARE/SBRT

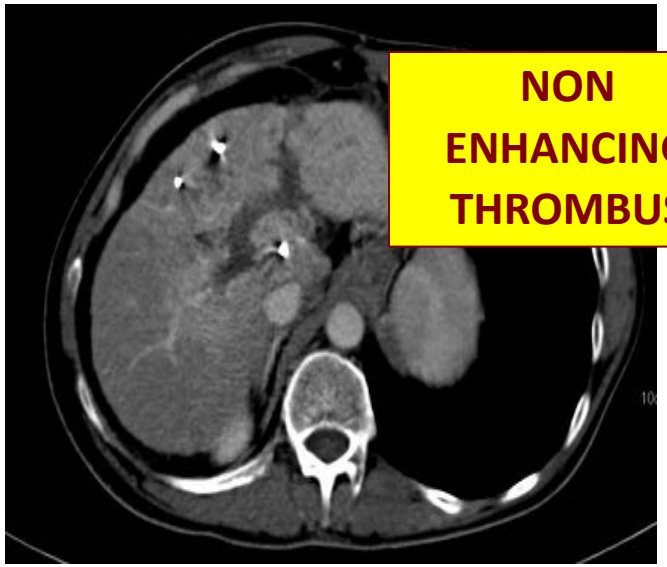


FDG AVID LESION

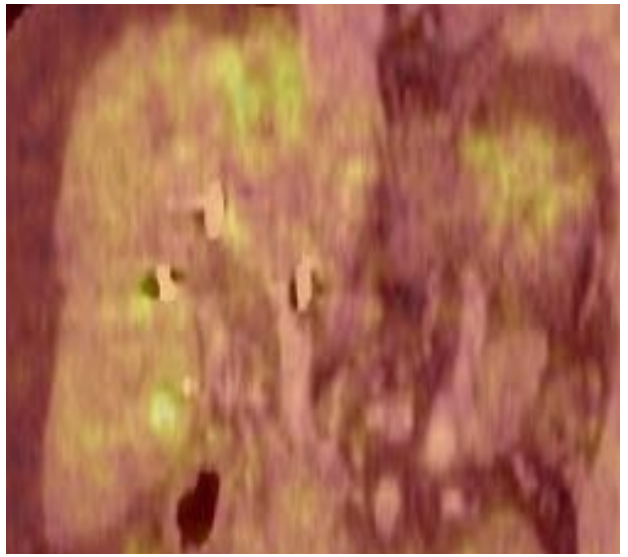


FDG AVID PVTT
in LPV,
MPV, RAPV

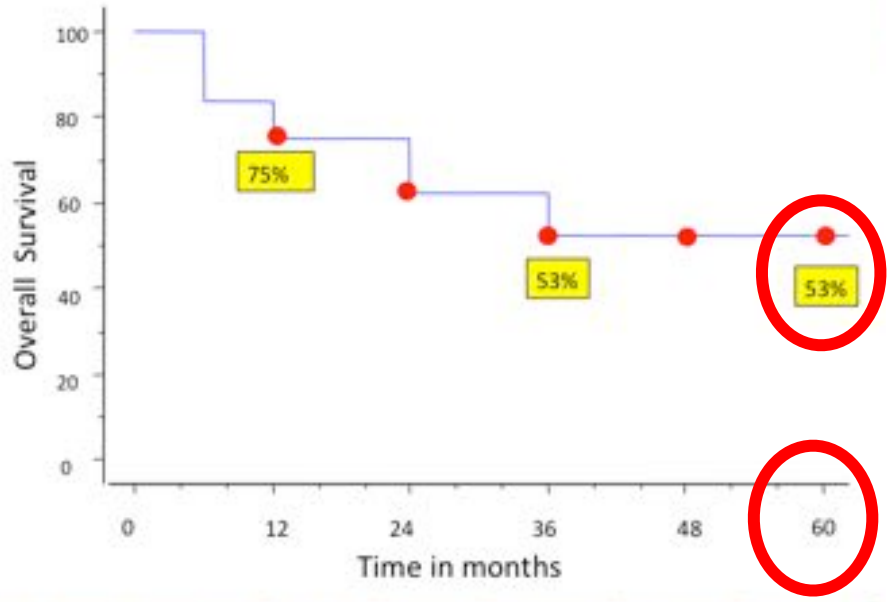
POST TARE/SBRT



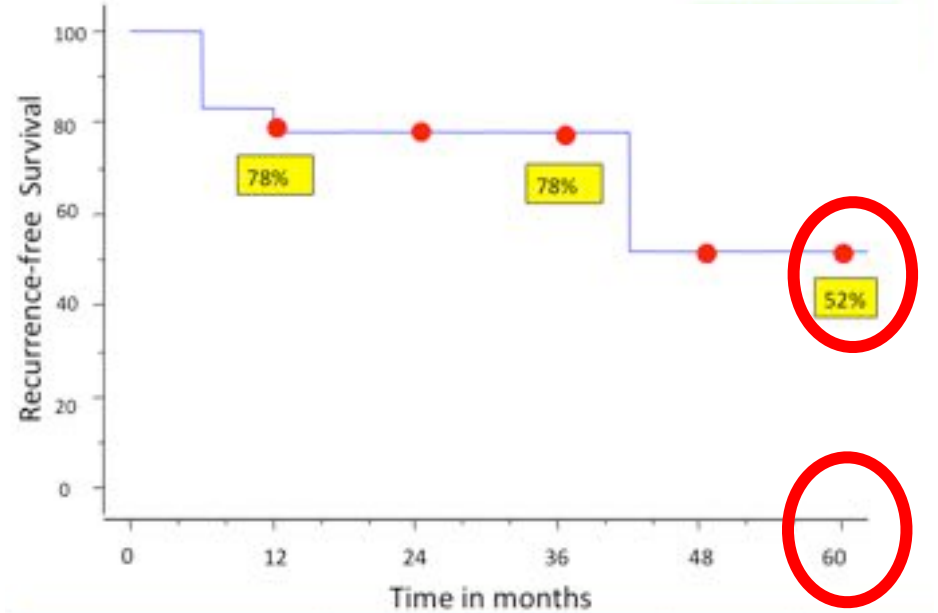
NON
ENHANCING
THROMBUS



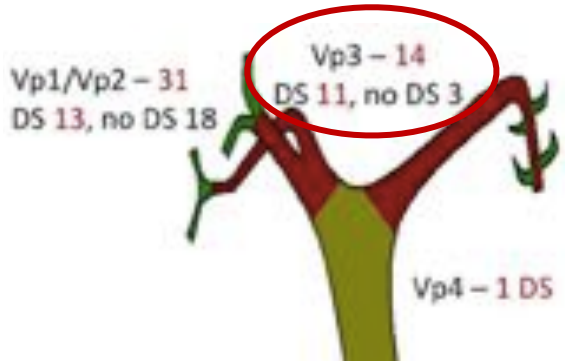
Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging



No. of patients exposed	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
All Downstaged patients (25)	15	8	4	2	2

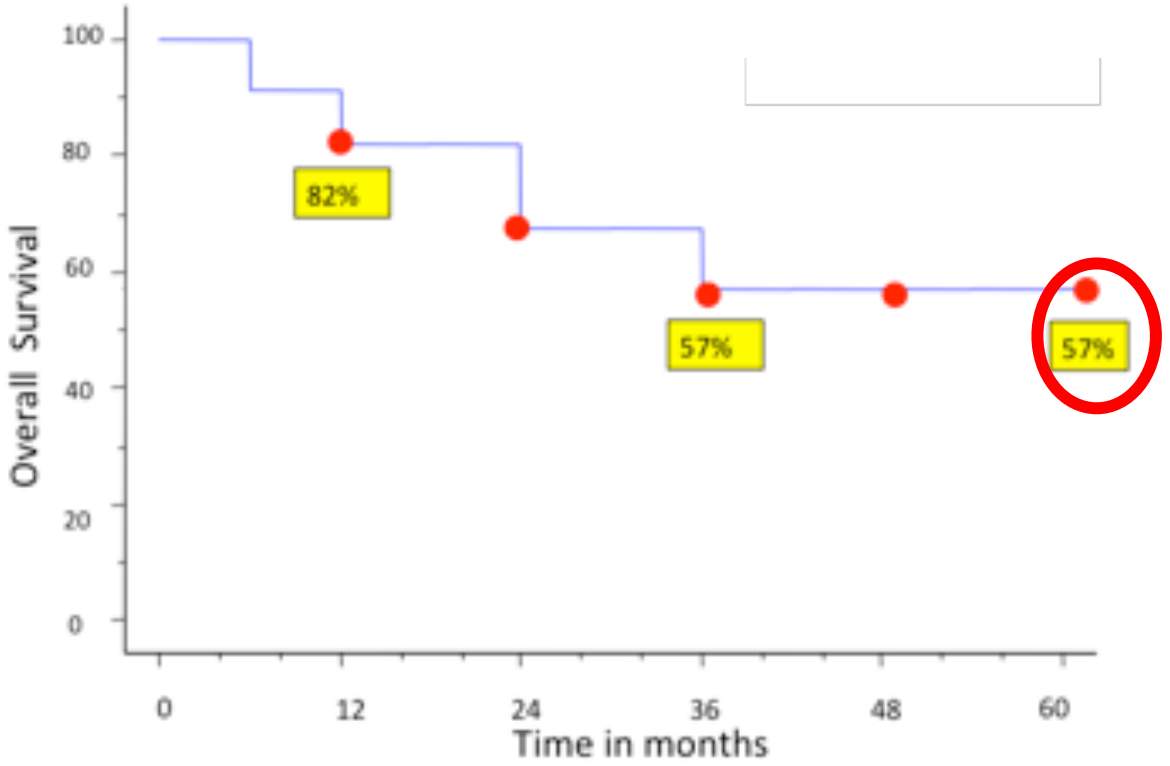


No. of patients exposed	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
All Downstaged patients (25)	13	7	4	2	1



Survival in 25 HCC PVTT patients following LDLT Post downstaging

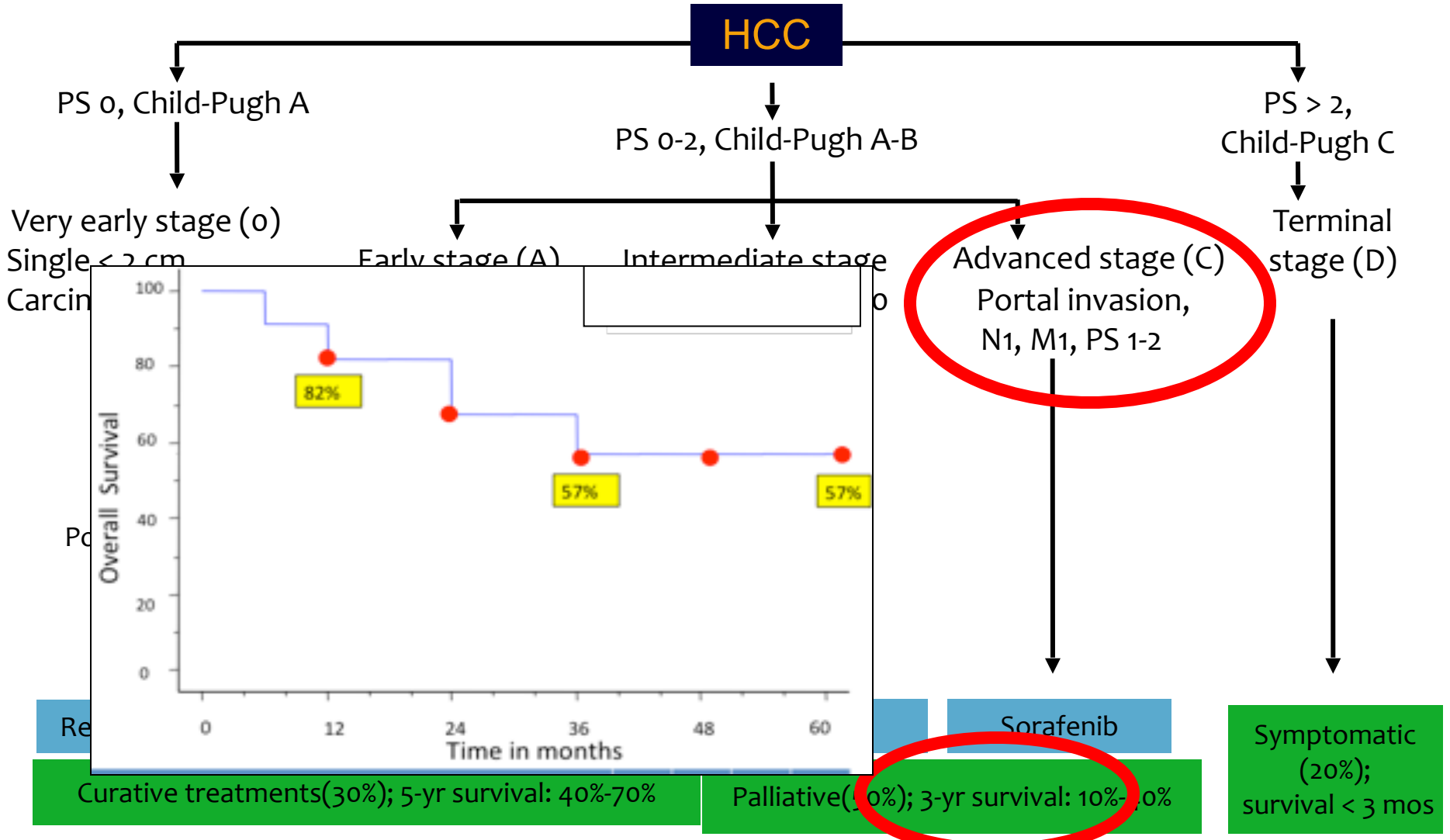
Survival in 23 HCC PVTT patients following LDLT Postdownstaging (excl. periop deaths)



No. of patients exposed	1 yr	2 yrs	3 yrs	5 yrs
Downstaged patients excluding perioperative deaths (23)	15	8	4	2

Soin AS, Bhangui P. et al. Transplantation 2020

BCLC Staging and Treatment Strategy



Llovet JM, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. Journal of the National Cancer Institute. 2008;100(10):698-711

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ELITA ESOT
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Updated data -- DS+LDLT in HCC-PVTT (36)

Medanta Liver Transplants
(2004-2020)
N=3286

Total number of HCC patients who underwent LT
n= 462

No PVTT
N=405

HCC with PVTT who underwent right lobe LDLT
N= 57

Down staged using TARE/TACE
+/- SBRT
(Vp2, Vp3, Vp4)
N= 36

vP1	vP2	vP3	vP4
4	16	13	3

Downstaging details

Downstaging modality	No.
SBRT	33
TARE	15
TACE	13
RFA	6

Time from downstaging to LDLT (mean)	**2.86 (1-11) m**

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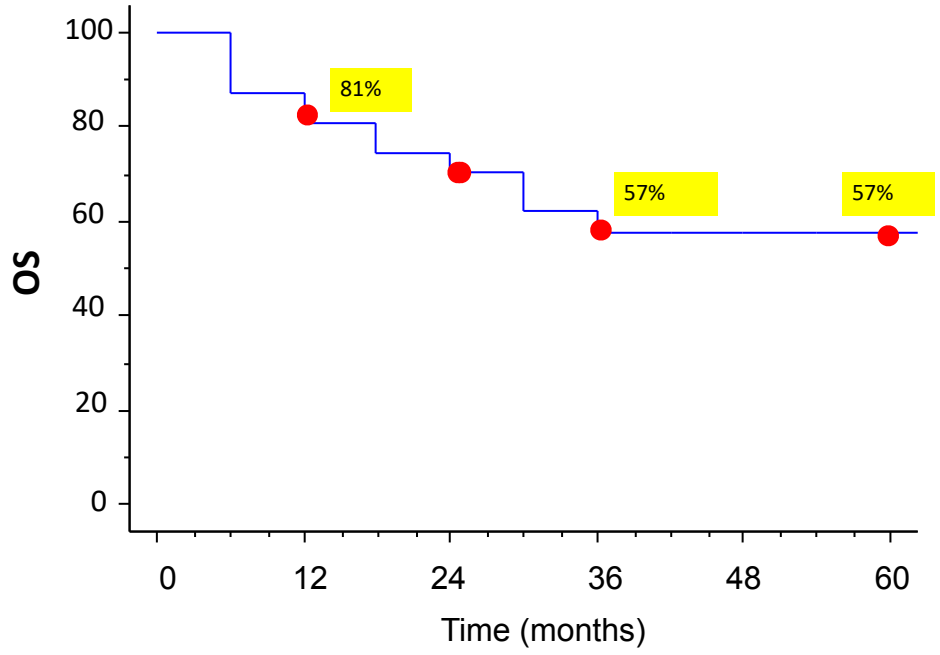
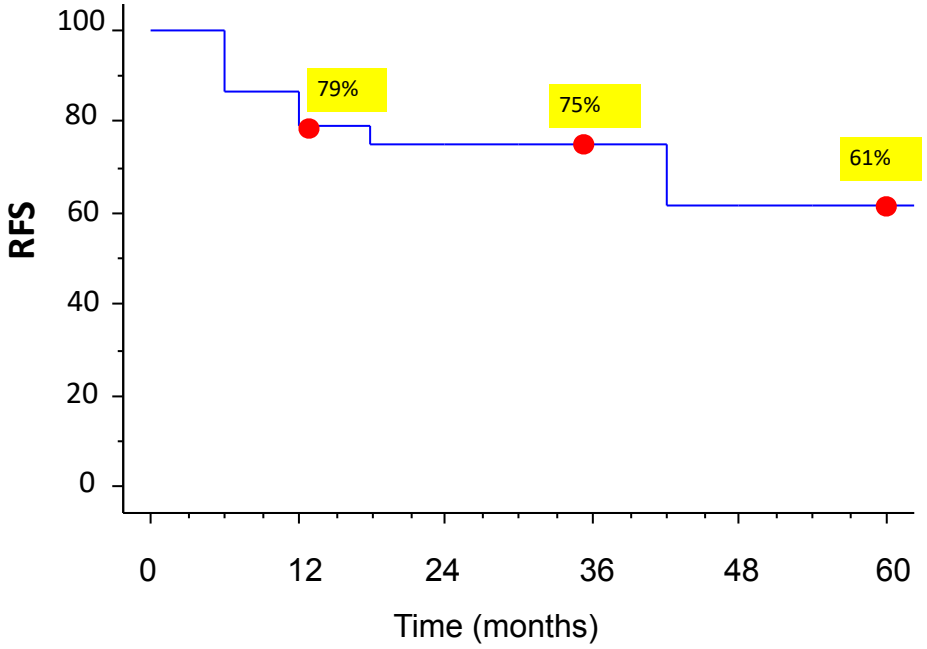
ELITA ESOT
Licage

Survival





Mean follow up = 34 months after DS, and 28 months post LDLT

12 long-term survivors (> 3 years; 5 over 5 years)

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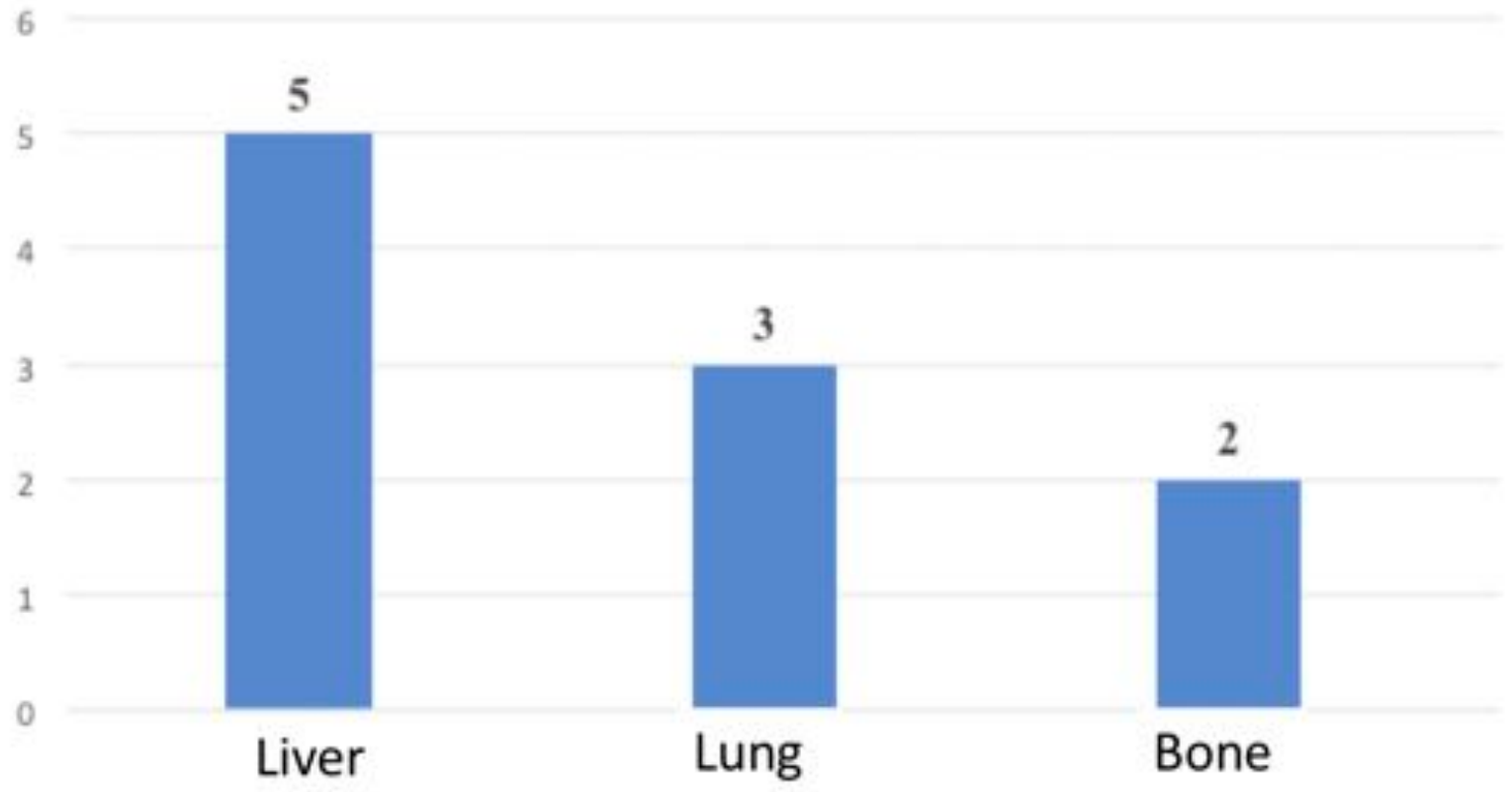
Recurrence (n = 6)



Median time to recurrence:
5 months (1-39 months)

Living donor liver transplantation for advanced hepatocellular carcinoma including macrovascular invasion

Abu Bakar Hafeez Bhatti[1,2] · Wajih Naqvi[1] · Nusrat Yar Khan[1] · Haseeb Haider Zia[1] · Faisal Saud Dar[1] · Zahid Amin Khan[3] · Atif Rana[3]

LDLT in Vp1-Vp3

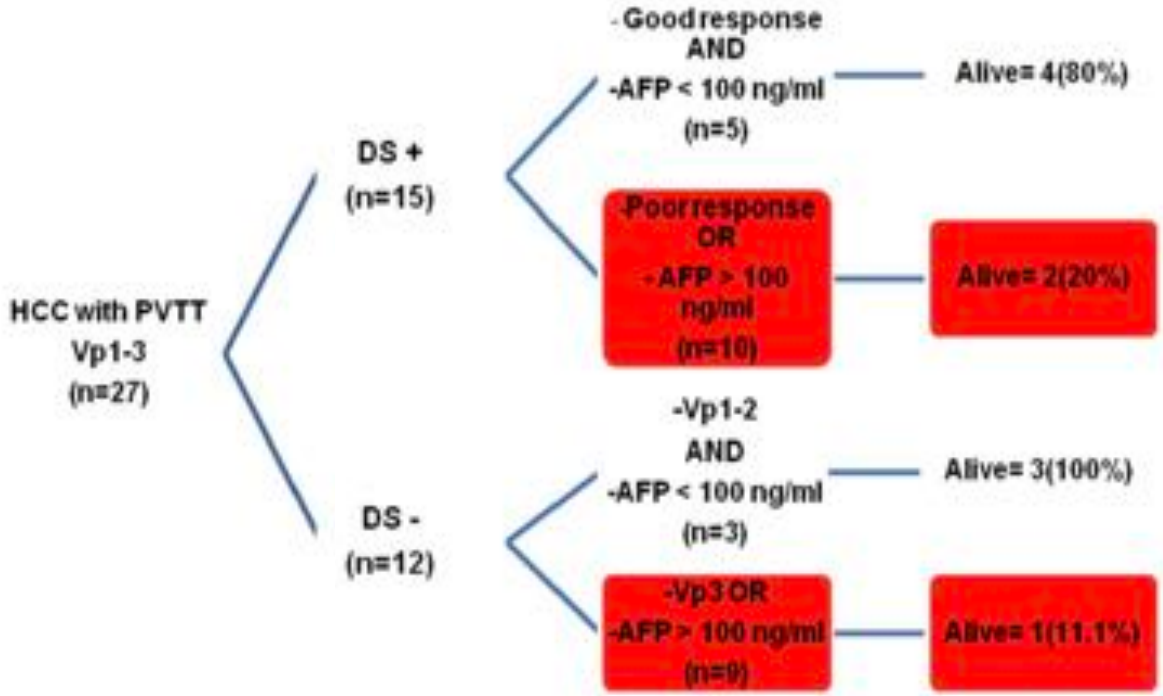
All patients -- DS with response evaluation and an observation period (4–6 months)

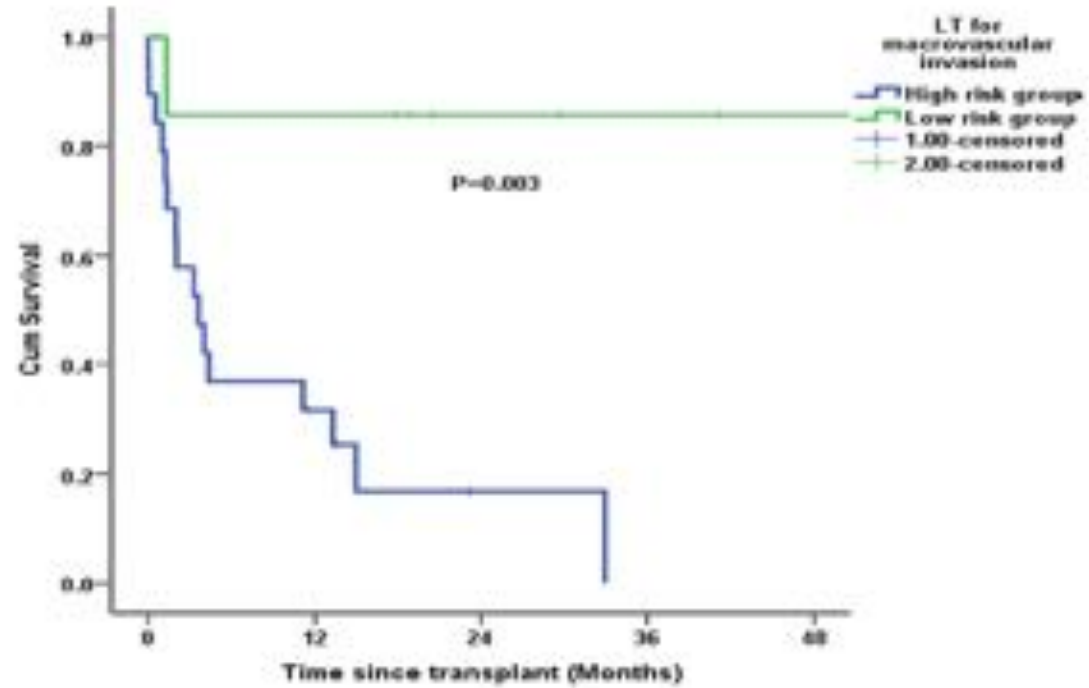
LDLT in only those with stable disease (no interval progression to EHD and substantial rise in AFP)

In patients with decompensated liver disease precluding DS, LDLT was offered selectively

low vs. high-risk group (poor response to DS or AFP > 100 ng/ml)

Journal of Cancer Research and Clinical Oncology (2022) 148:245–253


HCC with PVTT
Vp1-3
(n=27)
DS +
(n=15)
DS -
(n=12)
-Good response
AND
-AFP < 100 ng/ml
(n=5)
Alive= 4(80%)
-Poor response
OR
- AFP > 100 ng/ml
(n=10)
Alive= 2(20%)
-Vp1-2
AND
-AFP < 100 ng/ml
(n=3)
Alive= 3(100%)
-Vp3 OR
-AFP > 100 ng/ml
(n=9)
Alive= 1(11.1%)


LT for macrovascular invasion
High risk group
Low risk group
1.00-censored
2.00-censored
P=0.003
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
Time since transplant (Months)

Liver transplantation for hepatocellular carcinoma after successful treatment of macrovascular invasion – a multi-center retrospective cohort study

Transplant International

Michela Assalino[1], Sylvain Terraz[2], Michal Grat[3], Quirino Lai[4], Neeta Vachharajani[5], Enrico Gringeri[6], Marco Angelo Bongini[7], Laura Kulik[8], Parissa Tabrizian[9], Vatche Agopian[10], Neil Mehta[11], Raffaele Brustia[12], Giulio Cesare Vitali[1], Axel Andres[1,13], Thierry Berney[1,13], Vincenzo Mazzaferro[7], Philippe Compagnon[1,13], Pietro Majno[14], Umberto Cillo[6], William Chapman[5], Krzysztof Zieniewicz[3], Olivier Scatton[12] & Christian Toso[1,13]

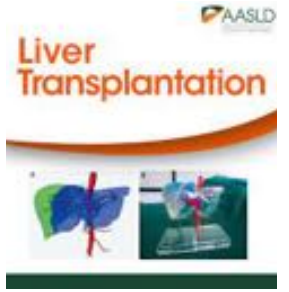
SUMMARY

Macrovascular invasion is considered a contraindication to liver transplantation for hepatocellular carcinoma (HCC) due to a high risk of recurrence. The aim of the present multicenter study was to explore the outcome of HCC patients transplanted after a complete radiological regression of the vascular invasion by locoregional therapies and define subgroups with better outcomes. Medical records of 45 patients were retrospectively reviewed, and imaging was centrally assessed by an expert liver radiologist. In the 30 patients with validated diagnosis of macrovascular invasion, overall survival was 60% at 5 years. Pretransplant alpha-fetoprotein (AFP) value was significantly different between patients with and without recurrence ($P = 0.019$), and the optimal AFP cutoff was 10ng/ml (area under curve = 0.78). Recurrence rate was 11% in patients with pretransplant AFP < 10ng/ml. The number of viable nodules ($P = 0.008$), the presence of residual HCC ($P = 0.036$), and satellite nodules ($P = 0.001$) on the explant were also significantly different between patients with and without recurrence. Selected HCC patients with radiological signs of vascular invasion could be considered for transplantation, provided that they previously underwent successful treatment of the macrovascular invasion resulting in a pretransplant AFP < 10 ng/ml. Their expected risk of post-transplant HCC recurrence is 11%, and further prospective validation is needed.

	Total $n = 30$	Nonrecurrent $n = 22$	Recurrent $n = 8$
Radiological and laboratory data at MVI diagnosis			
Type of MVI, *n* (%)			
Vp1	7 (23)	5 (23)	2 (25)
Vp2	12 (40)	8 (36)	4 (50)
Vp3	5 (17)	5 (23)	0
Vv1	1 (3)	0	1 (12.5)
Vv2	3 (10)	2 (9)	1 (12.5)
Vv3	2 (7)	2 (9)	0

Deceased Donor Liver Transplantation After Radioembolization for Hepatocellular Carcinoma and Portal Vein Tumoral Thrombosis: A Pilot Study

Matteo Serenari,[1,*] Alberta Cappelli,[2,*] Alessandro Cucchetti,[3] Cristina Mosconi,[1] Lidia Strigari,[4] Fabio Monari,[5] Matteo Ravaioli,[1,3] Elisa Lodi Rizzini,[5] Stefano Fanti,[6,7] Rita Golfieri,[2,**] and Matteo Cescon[1,3,**]



Aim: Yttrium-90 TARE in downstaging HCC patients with PVTT to meet criteria for DDLT.

"Superdownstaging" protocol

Listed for LT after complete radiographic response defined by disappearance of PVTT enhancement for at least 6 months after Y-90, along with downstaging of HCC to within Milan criteria and alpha-fetoprotein (AFP) less than 100 ng/mL.

PVTT main trunk and/or in the contralateral portal vein branch were excluded

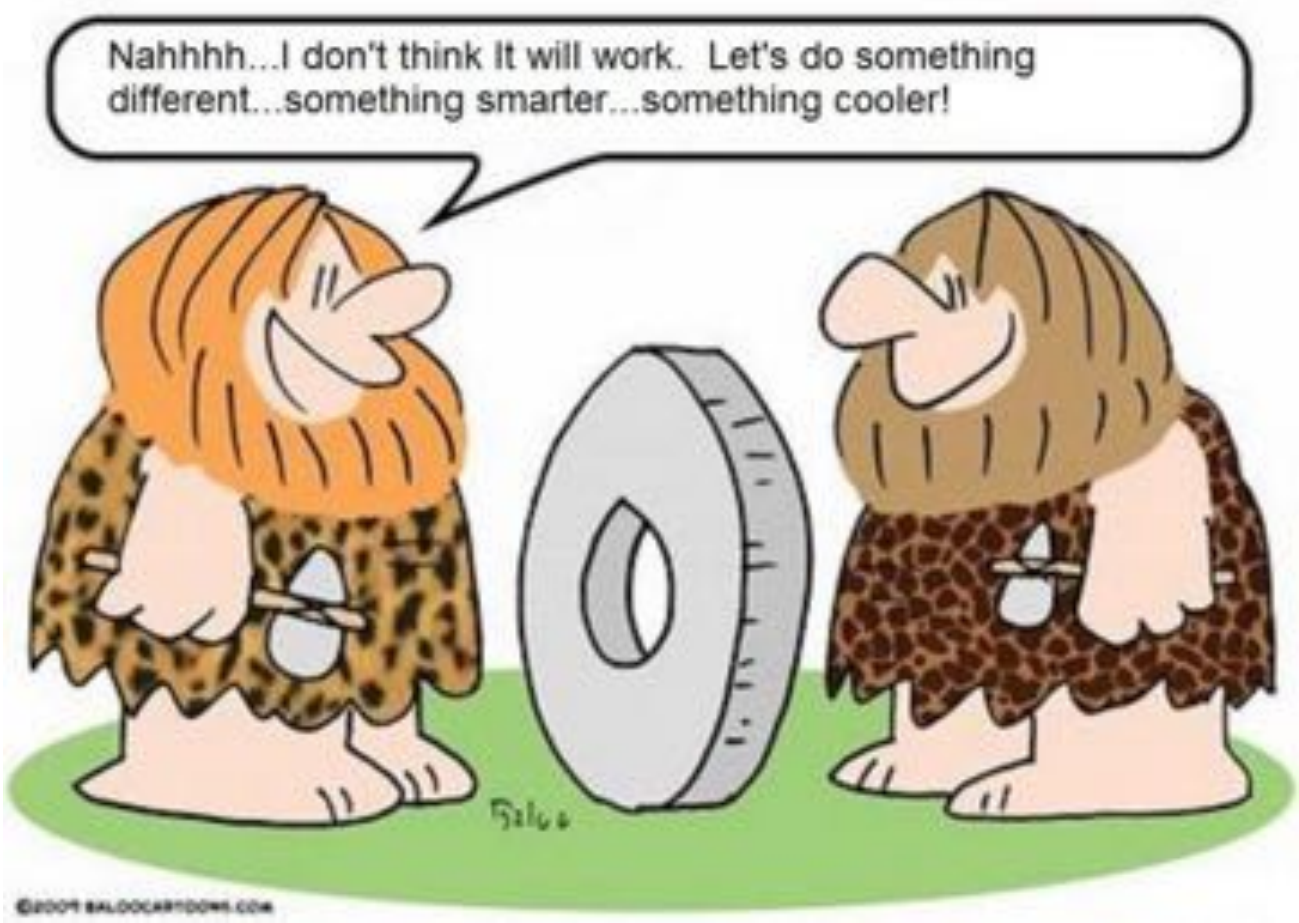
TARE was effective in DS and receiving DDLT in 5/17 patients (29.4%)

5-year OS was significantly higher in patients who underwent DDLT compared with those who were not transplanted (60.0% versus 0.0%, P = 0.03)

Three out of 5 patients developed recurrence within 1 year after LT

Showed a clear survival gain in those patients who were able to receive DDLT after TARE but careful selection is required

LT post DS does work in some patients with HCC and lobar PVTT



Caveats

- Conversion rate to “transplantability” in HCC patients with PVTT using downstaging therapy is around 50%-60% -- **need to treat and see**
- Liver function does determine feasibility of DS therapies – **he is CTP A with good amount of non tumoral liver volume**
- An adequate waiting period after successful downstaging is important especially in patients with lobar (Vp3,Vp4) PVTT – **absolutely essential**
- How effectively you deliver the DS therapy matters – **needs to be done by an expert IR and radiation oncologist**

Use of immune check point inhibitors to bridge / DS HCC

Reference	# of Patients	Drug(S) Used	Lines of Treatment Prior to ICI	Washout Period (Days)	Successful LT at 12 Months?	Rejection?	Tumor Regression/ Tumor Necrosis on Explant?
Qiao [62]	7	pembrolizumab or camrelizumab in combination with lenvatinib	unknown	40 (average)	In 7/7	Yes—in 1/7 (reversed with altered IS)	unknown
Tabrizian [69]	9	nivolumab	0–7	1–253	In 9/9	Yes—in 1/9 (reversed with altered IS)	In 3/9 patients
Schwacha-Eipper [70]	1	nivolumab	unknown	105	yes	No	unknown
Abdelrahim [71]	1	atezolizumab and bevacizumab	unknown	60	yes	No	unknown
Lizaola-Mayo [72]	1	nivolumab	1 (TARE)	unknown	yes	No	unknown
Nordness [66]	1	nivolumab	4 (laparoscopic resection, sorafenib, TARE, TACE)	8	no	Yes—fatal hepatic necrosis, death on POD 10	yes
Schnickel [73]	5	nivolumab	unknown	10–183	In 4/5	Yes—in 1/5 (successful retransplant for massive hepatic necrosis)	unknown
Sogbe [76]	1	durvalumab	unknown	>90	yes	No	unknown
Chen [65]	1	toripalimab	3	93	no	Yes—fatal hepatic necrosis, death on POD 3	unknown
Aby & Lake [75]	1	nivolumab	4 (TARE, TACE, MWA, sorafenib)	16	yes	Yes—treated successfully	yes

Table 1. Summary of ICI use pre-LT.

Neoadjuvant programmed cell death 1 inhibitor before liver transplantation for HCC is not associated with increased graft loss

Tielong Wang[1,2,3] | Zhitao Chen[1,2,3] | Yao Liu[1,2,3] | Yu Jia[1,2,3] | Weiqiang Ju[1,2,3] | Maogen Chen[1,2,3] | Qiang Zhao[1,2,3] | Dongping Wang[1,2,3] | Zhiyong Guo[1,2,3] | Yunhua Tang[1,2,3] | Xiaoshun He[1,2,3]

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

TABLE 1 Summary of characteristics in patients who received PD1 inhibitor before liver transplant

No	Age (y)	Sex	ULD	AFP pre-LT (μg/L)	Max tumor diameter (cm)	Macrovascular invasion	LRT pre-LT	Targeted therapy	Radiologic response	Pathologic response	Pathologic type and grade	Pathology staging	AR post-LT	Tumor recurrence post-LT
7	51	Male	HBV	57.9	9.1	Yes (PV)	Yes	Lenvatinib	PR	MPR	HCC/II	IIIA	No	No
8	52	Male	HBV	3.9	4.1	No	Yes	Lenvatinib	CR	MPR	HCC/II	II	Yes (POD15)	No
9	43	Male	HBV	96.8	2.0	No	Yes	Lenvatinib	PR	CPR	HCC/NA	IIIB	Yes (POD7)	No
10	66	Male	ALD	28.1	1.5	Yes (PV)	Yes	Lenvatinib	SD	MPR	HCC/III	II	Yes (POD4)	Yes (POD245)
11	38	Male	HBV	56.9	4.4	No	Yes	Lenvatinib	PR	MPR	HCC/III	II	Yes (POD4)	No
12	55	Male	HBV	2.9	9.7	No	Yes	Lenvatinib	PR	CPR	HCC/NA	IIIA	No	No
13	41	Male	HBV	165.0	6.1	Yes (PV)	Yes	Lenvatinib	CR	MPR	HCC/III	IB	Yes (POD9)	No

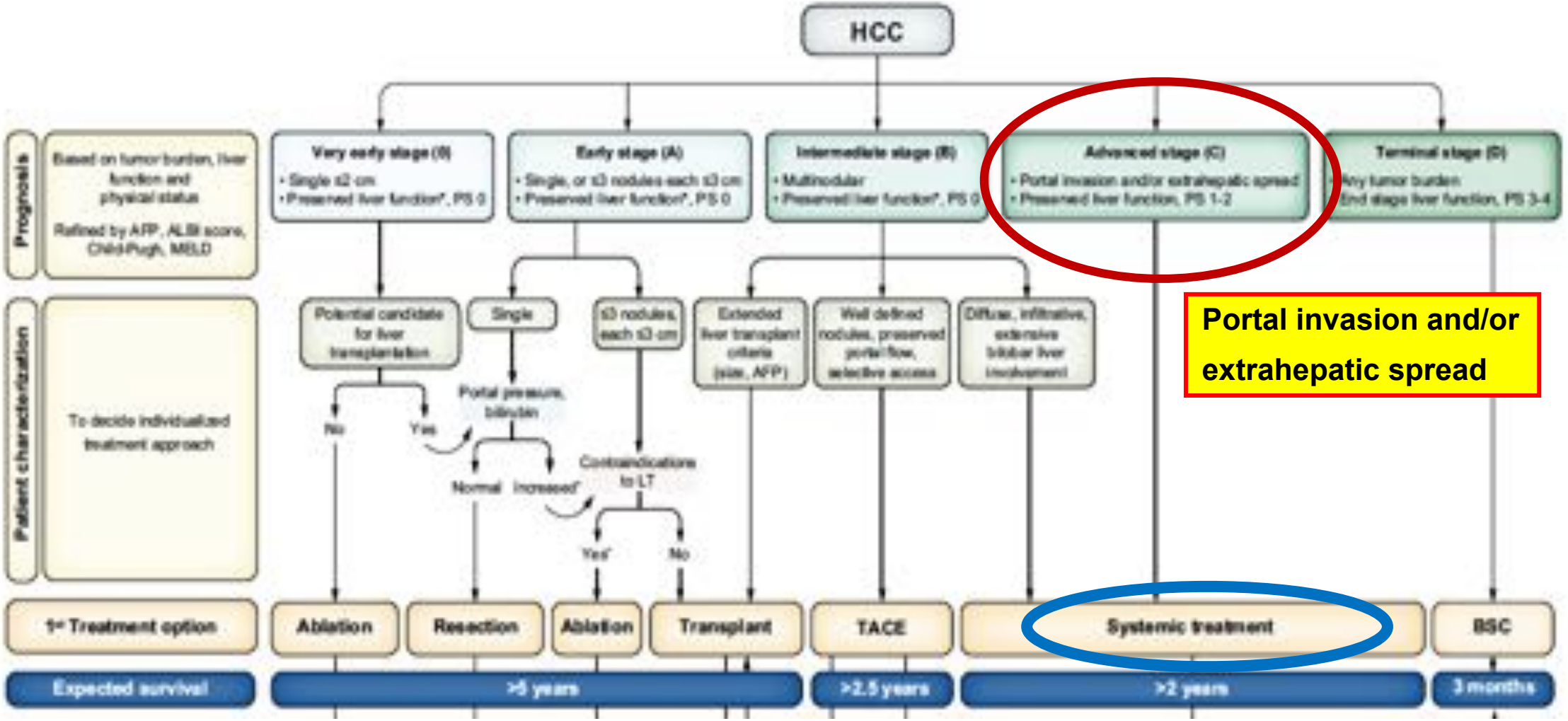
My submissions….

3 concepts and a 3 “mantras” for success

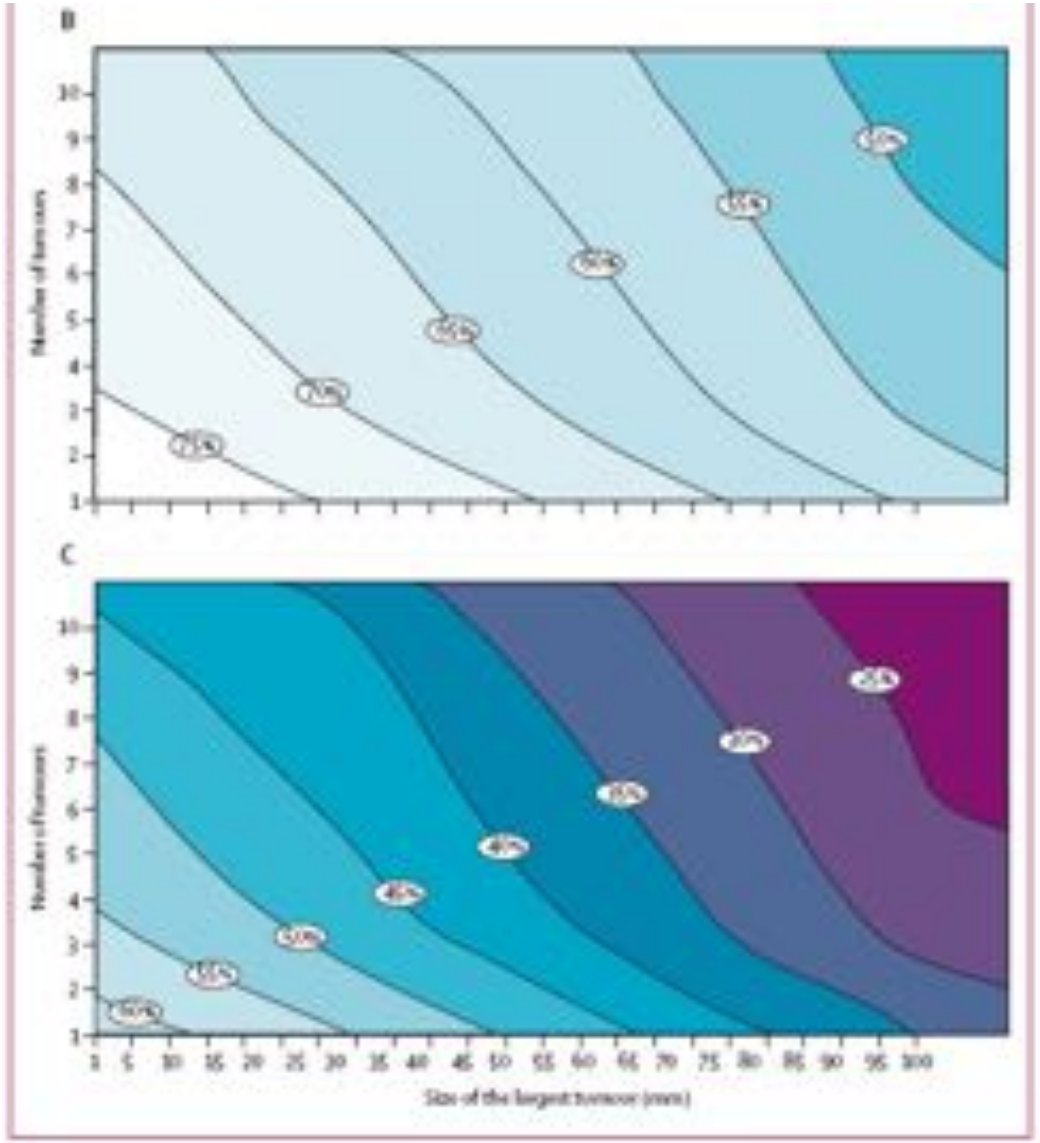
A Few Concepts

1

BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update ☆



Is vascular invasion (portal) = systemic disease



Patients with vascular invasion may survive long

- **55%** at 5 yrs with 10 cm HCC; no vasc invasion
- **45%** at 5 yrs for 6 cm with micro- (+/- macro) vasc invasion

Mazaferro et al, Lancet Oncol 2009

…. if it was to be a systemic disease, this wouldn't have been the case

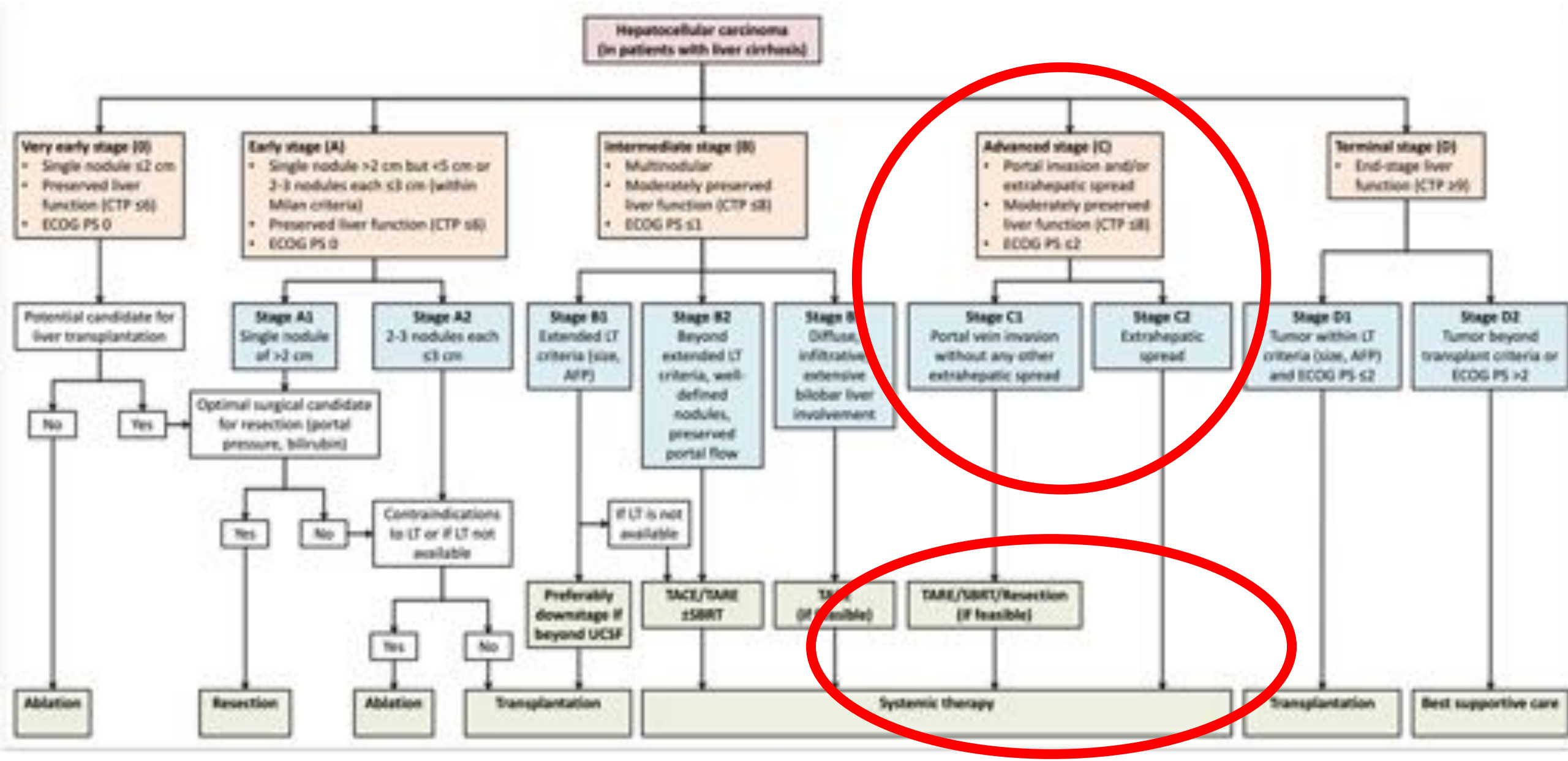
Journal of Clinical and Experimental Hepatology

DISCUSSION | ARTICLES IN PRESS

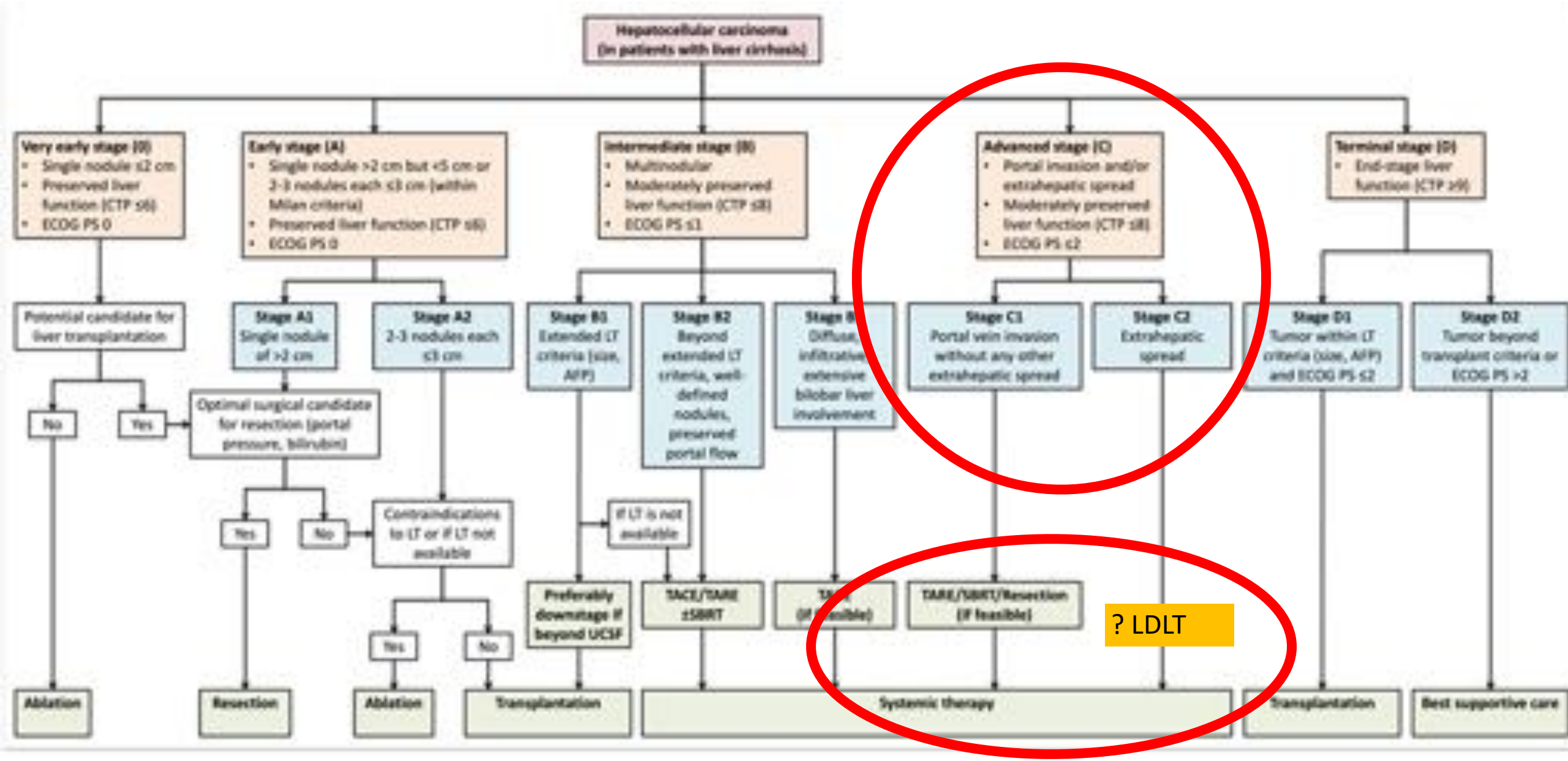
2023 Update of Indian National Association for Study of the Liver Consensus on Management of Intermediate and Advanced Hepatocellular Carcinoma: The Puri III Recommendations

Ashish Kumar • Subrat K. Acharya • Shivaram P. Singh • Ajay Duseja • Kaushal Madan • Akash Shukla • Anil Arora • Anil C. Anand • Ankur Bahl • Arvinder S. Soin • Bhawna Sirohi • Debnarayan Dutta • Dinesh Jothimani • Dipanjan Panda • Gagan Saini • Joy Varghese • Karan Kumar • Madhumita Premkumar • Manas Kumar Panigrahi • Manav Wadhawan • Manoj K. Sahu • Mohamed Rela • Naveen Kalra • Padaki N. Rao • Pankaj Puri • Prashant Bhangui • Premashis Kar •

The Puri III Recommendations -- INASL



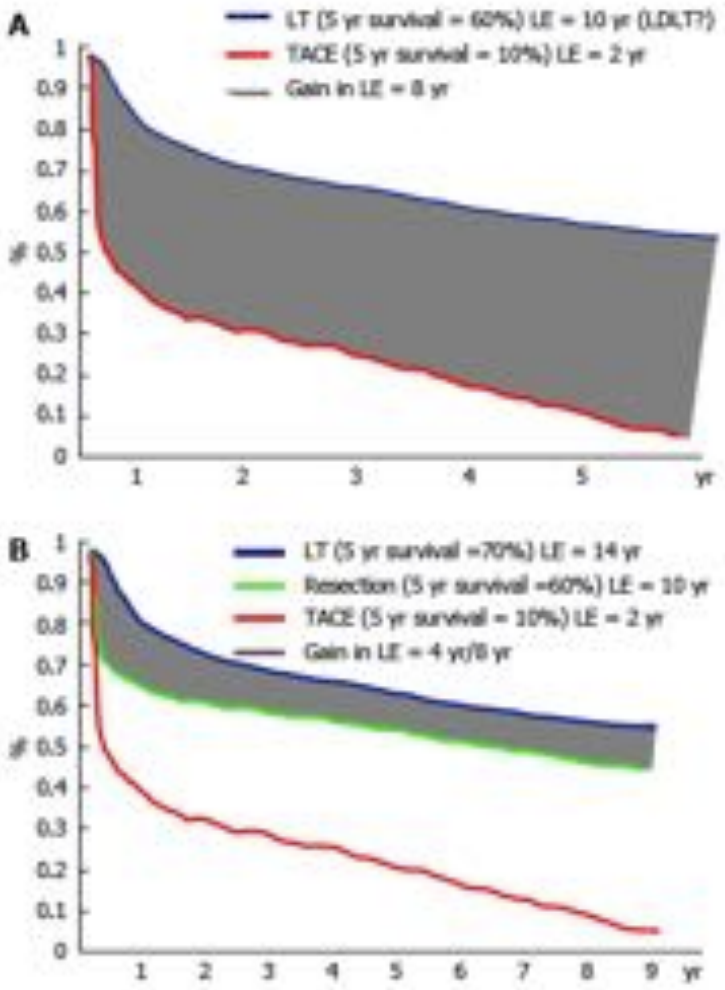
The Puri III Recommendations -- INASL



A Few Concepts

2

Transplant benefit = gain offered by LT in comparison with the best alternative therapy (survival after LT minus survival with best alternative therapy)

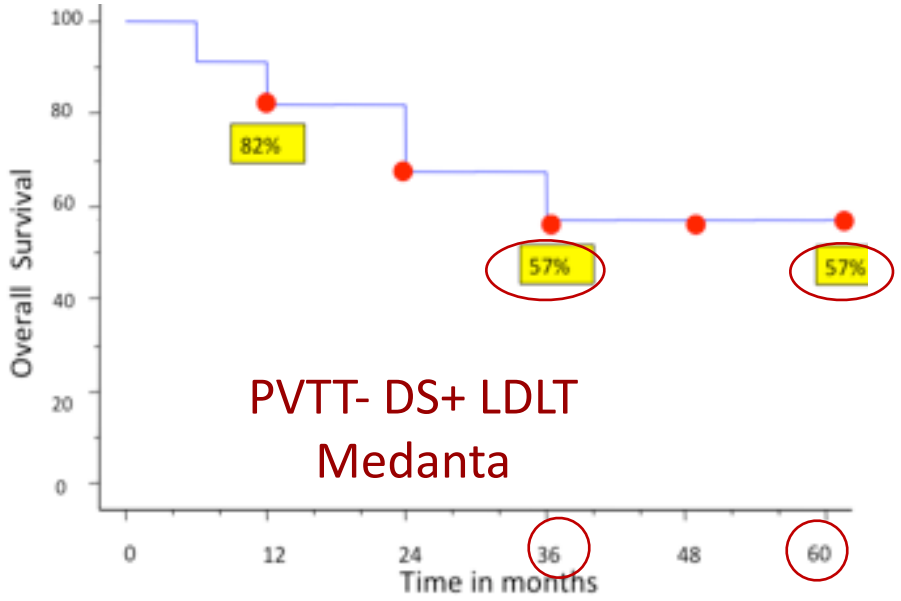


40/M, Childs B, HBV
2 HCC nodules, largest 6 cm
Outside Milan/UCSF

65/M, Child A, HCV
1 HCC nodule, 4 cm
Within Milan/UCSF

Vitale A, Volk M, Cillo U. Transplant benefit for patients with HCC World J Gastroenterol 2013

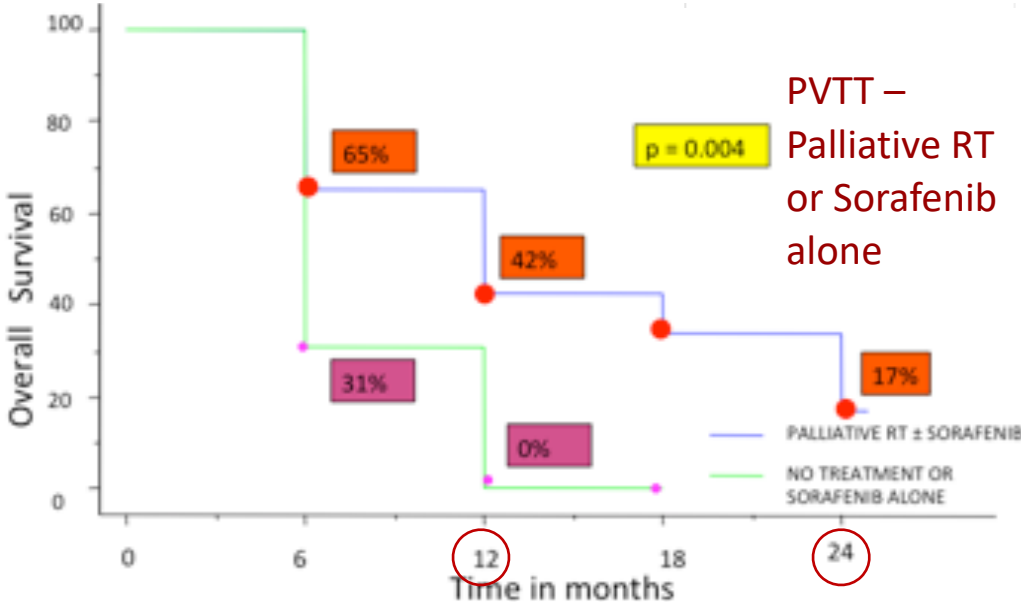
“Transplant benefit” concept..



PVTT- DS+ LDLT
Medanta

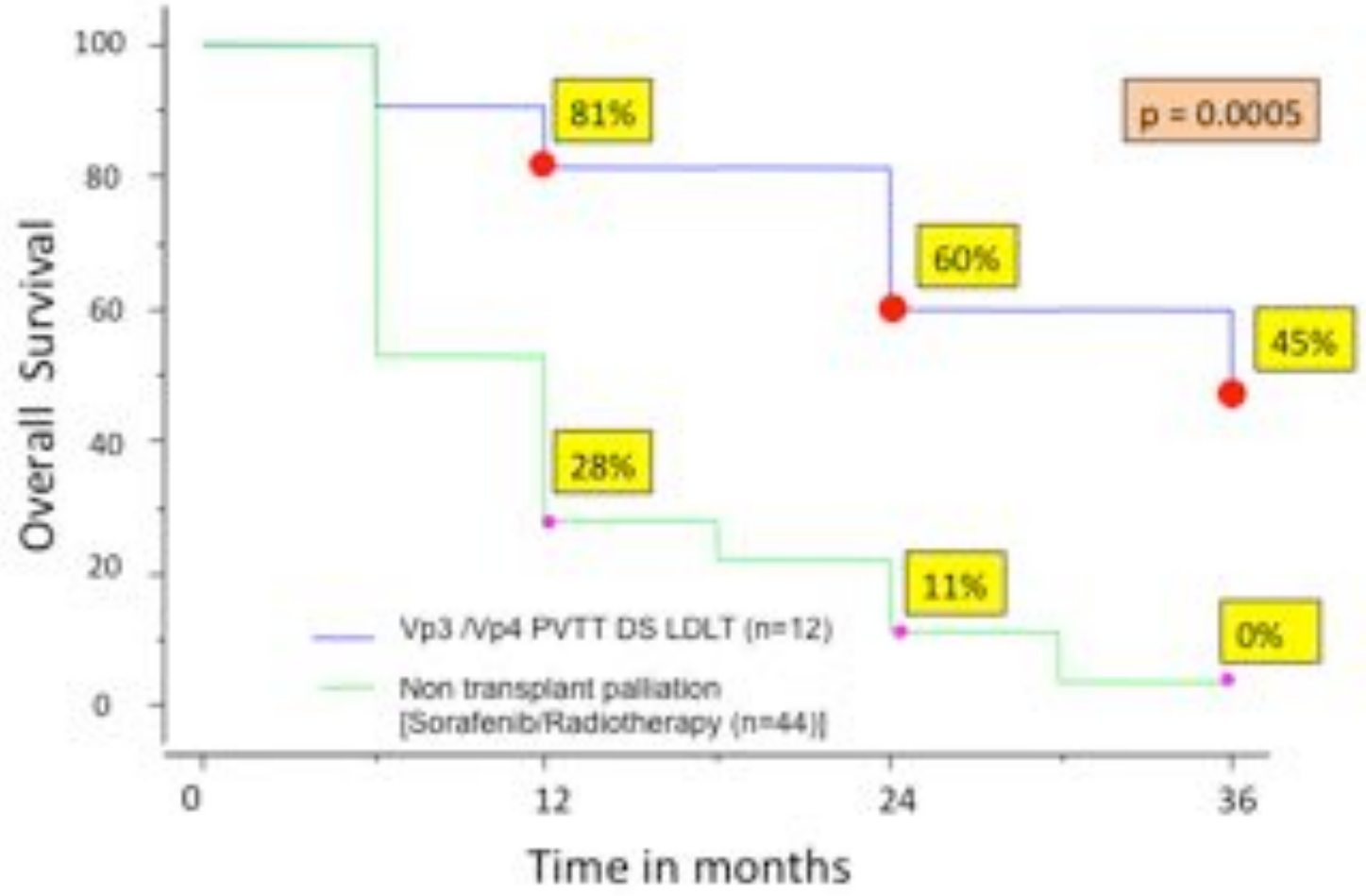
TB at 36 months

25.1 – 1.8 = 23 m

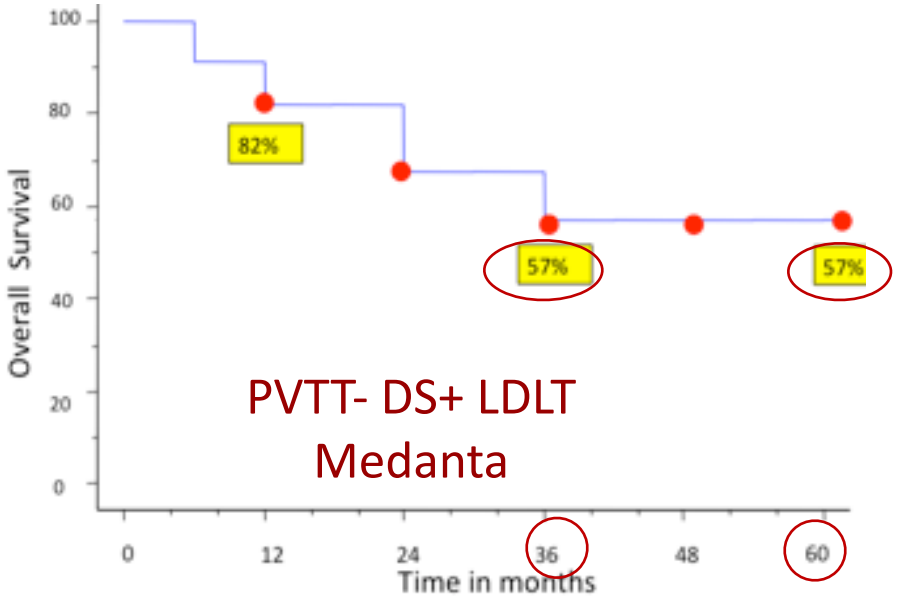


PVTT – Palliative RT or Sorafenib alone

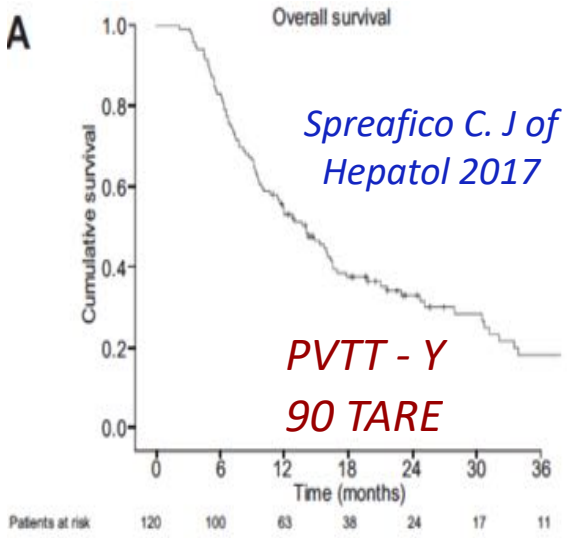
Vp3/Vp4 PVTT DS and LDLT vs. Palliative (TKI's/ RT)



“Transplant benefit” concept..

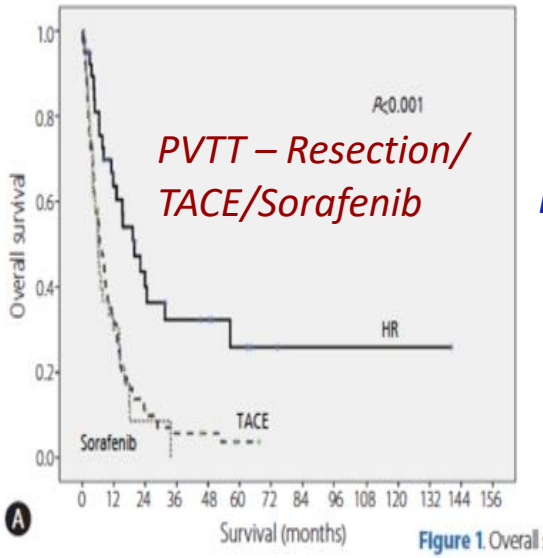


PVTT- DS+ LDLT
Medanta



Spreafico C. J of Hepatol 2017

PVTT - Y 90 TARE



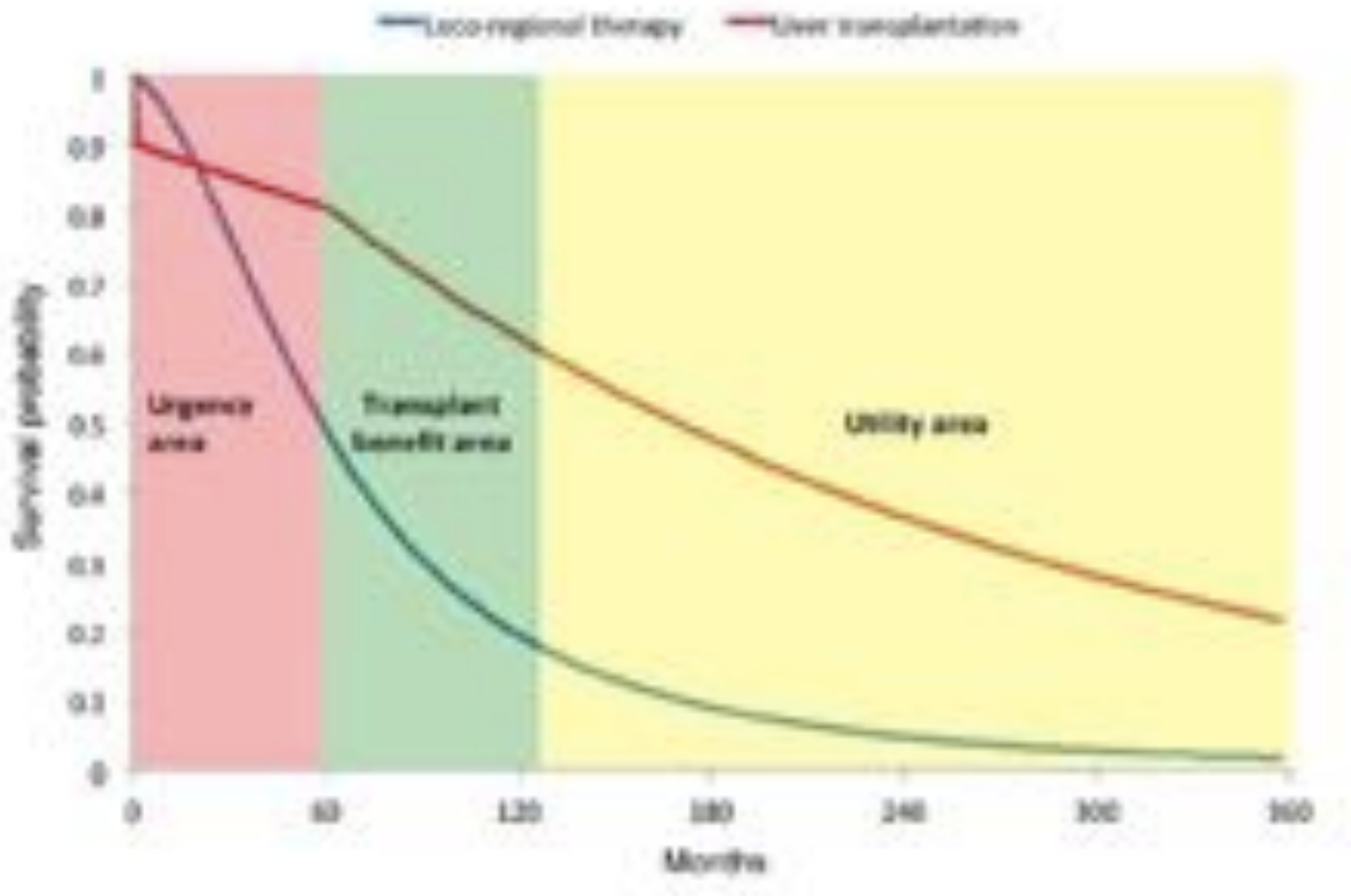
PVTT – Resection/ TACE/Sorafenib

Lee JM, Clin Molec Hepatol 2016

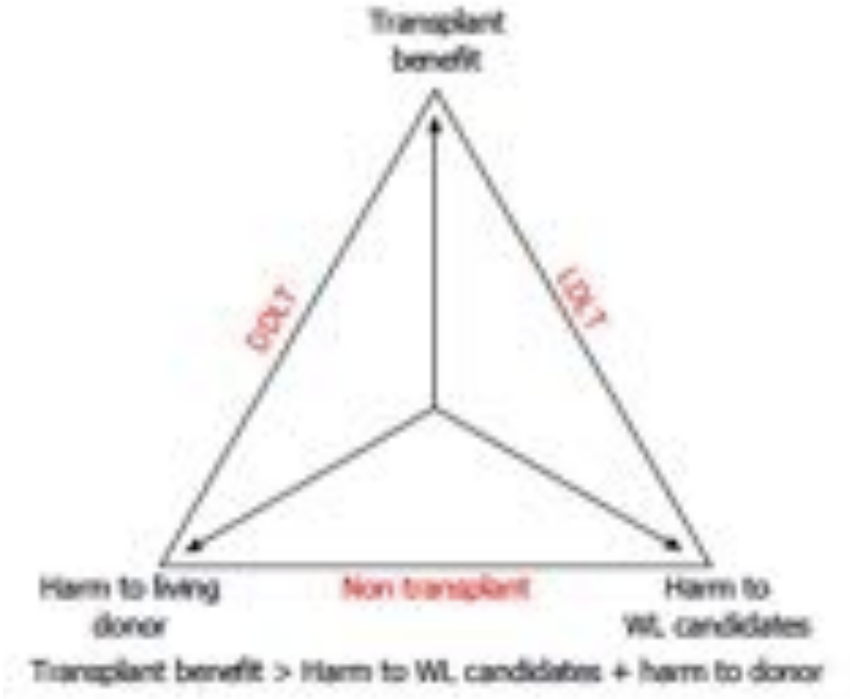
Figure 1. Overall

Should we transplant everyone citing transplant benefit?

DDLT- Should adhere to the urgency, utility, transplant benefit principle !!



Triangular equipoise: transplant benefit, live donor harm, harm to W/L candidates



Be Careful when you think of expanding criteria in LDLT !!

LT indicated when transplant benefit exceeds harm

Few Concepts

3

How far is too far?

NEVER FOR LT

- Presence of extrahepatic disease
- Upfront LT in patients with macrovascular invasion
- Failure of downstaging in patients with macrovascular invasion
- Expansion of criteria doesn’t conform to the triple equipoise concept

How far is too far?

RELATIVE CONTRAINDICATIONS

- Vp4 PVTT and patients with PVTT and HVTT

- Very high levels of AFP, PIVKA II to start with, or increasing levels in the waiting period

A Few "Mantras" for Success

1

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]

ILTS Consensus Guidelines – some points to consider

- Consensus on expanded criteria for LT in HCC has not been reached but **composite criteria that consider surrogates of tumor biology and response to neoadjuvant treatments, are likely to replace conventional morphological criteria for defining transplant feasibility** (quality of evidence: moderate; strength of recommendation: strong)

- Selection criteria for patients with HCC **may be different in LDLT than DDLT** in selected cases (quality of evidence: moderate; strength of recommendation: strong).

- **Minimum acceptable recipient overall survival should be 60% at 5 years after LDLT** (quality of evidence: moderate; strength of recommendation: strong).

Author, Reference Number, Country, Year	Number of patients	Transplant Type	Downstaging (DS) modality before LT	Classification of PVTT (n)	OS rate (1-,3-,5-year)	DFS/RFS rate (1-,3-,5-year)	Prognostic Factors
Lee *et al.*, [32], Korea (2017)	11	LDLT	DS YES – TACE NO	Vp3 (3); Vp4 (1) Vp2 (3); Vp3 (1); Vp4 (3)	72.7%, 63.6%, 63.6%	63.9%, 45.5%, 45.5%	Univariate analysis OS – [illegible] invasion (Vp4), pre-LT AP score ≥20,000, largest tumor ≥7 cm RFS – [illegible] invasion (Vp4), pre-LT AP score, ≥2.1 SUV ratio on PET scan, largest tumor ≥7 cm
Choi *et al.*, [33], Korea (2017)	34	LDLT	NA	Type I Cheng (27) Type II Cheng(7)	85%, 60.3%, 50.3% 71.4%,14.3%,14.3%	68.2%, 63.9%,63.9% 28.6%, 14.3%,14.3%	Lobar PVTT, AFP > 100 ng/ml
Jeong *et al.*, [41], Korea (2017)	17	LDLT	TACE (Lipiodol/Cisplatin) + 3D-CRT	Vp2 (7); Vp3 (7); Vp4 (1); Hepatic vein (2)	87.45%, 60.5%, NA	RFS 70.6%, 57.8%, NA	Beyond Milan Criteria at transplant
Han DH *et al.*, [42], Korea (2016)	8 (3 post HR)	LDLT	CCRT followed by HAIC	-	1-yr OS – 87.5% Median survival 33 months	1-year disease-free survival rate was 87.5%	-
Soin *et al.*, [43], India (2020)	46	LDLT	DS YES (25) – SBRT + TACE / TARE NO (21)	Vp1 (1); Vp2 (12); Vp3 (11); Vp4 (1) Vp1 (5); Vp2 (13); Vp3 (3); Vp4 (0)	75%, 53%, 53% Excluding 2 post op deaths 5-yr OS 57% 80%, 59%, 48%	78%, 78%, 52% Excluding 2 post op deaths 5-yr RFS 51% 63%, 48%, 40%	RFS - Initial [illegible] ng/mL and AFP fall <2000 ng/mL OS – Tumour grade III/IV (in DS patients)
Bhatti, *et al.*, [44], Pakistan (2022)	27	LDLT	DS YES – 15 DS NO - 12	Vp1 / Vp2: 16 Vp3: 11	Estimated 5-yr OS – 85% in low-risk group; 0% in high risk	18.5% recurrence rate	Poor response to DS, AFP > 100 before LT differential risk groups (low vs. high)
Serenari et al. [46], Italy (2021)	5	DDLT	DS YES – 5	First order only	5-yr ITT OS – 60%	60% within 1 year	(low vs. high) 3/5 patients had tumor recurrence within 1 year of LT, 2 of them achieved long-term survival after [illegible] metastases
Assalino *et al.*, [49], Switzerland (2020)	30	DDLT (29) / LDLT (1)	TACE/SIRT/AR	Vp1 (7); Vp2 (12), Vp3 (5), Hepatic vein (6)	76.7%, 66.2%, 59.6%	63.3%, 56.3%, 56.3%	AFP > 10 ng/ml, number of viable nodules, the presence of residual HCC and satellite nodules (in the [illegible]
Yang *et al.*, [50], China (2020)	75	DDLT	NA	Vp2-3 (47) Vp4 (28) Low risk Vp2-3	74.1%, 65.4%, NA 64.3%, 30.6%, NA 95.2% (3-years)	44.4%,40.0%, NA 28.6%,21.4%, NA 67.6% (3-years)	[illegible]=8 cm, AFP>100 ng/ml, SUV max- tumor >5 (in Vp2/Vp3)
Levi Sandri et al., [51], Italy (2017)	4	DDLT	DS – Y-90 TARE	Vp1 (3); Vp3 (1)	-	Median DFS of 39.1 months (range, 6-76)	-
Yu et al., [52], China, (2022)	176	DDLT		Type I Cheng - 83 Type II Cheng - 93	Type I - median OS 21.8 months Type II - 21.4 months	Type I - median RFS 14.6 months Type II – 12.7 months	Type I/II PVTT patients with AFP ≤100 ng/mL similar OS. Type II PVTT to be independent risk factor for RFS
Sha et al., [53], China (2022)	46	DDLT		Segmental PVTT (11) Lobar PVTT (35)	Segmental PVTT 5-year OS 54.5%Lobar PVTT 5-year OS 17.1%	Segmental PVTT 5-year RFS 36.4% Lobar PVTT 5-year RFS 28.6%	Lobar PVTT - [illegible] DDLT. Segmental PVTT, AFP level ≤100 ng/ml may be [illegible] for DDLT

Bhangui P Liver transplantation and resection in patients with hepatocellular cancer and portal vein tumour thrombosis: feasible and effective***?*** ***In Press.. HPD Int***

Experience With LDLT in Patients With Hepatocellular Carcinoma and Portal Vein Tumor Thrombosis Postdownstaging

Factors	HCC PVTT undergoing LDLT			
	All 43 PVTT LDLT			
	Overall Survival			Survival
Pre-LT AFP				-
			0.028	-
		-	-	0.04
<2000 ng/ml	-	-	-	0.024

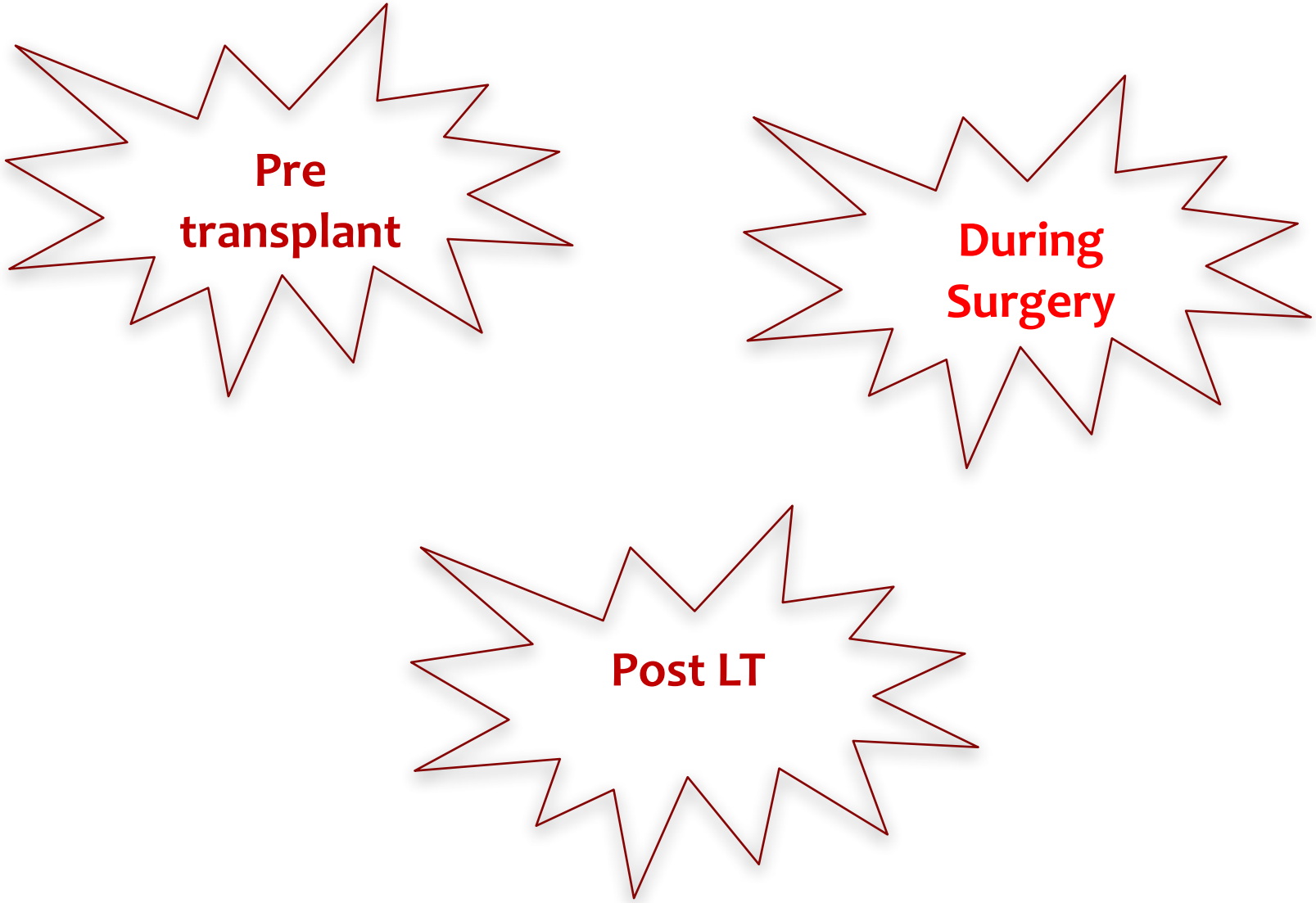
Tumour Biology is the King!!
AFP, PIVKA-II, PET, success of DS, waiting period are surrogates

Multivariate Analysis – Prognostic Factors

A Few "Mantras" for Success

2

Prevent recurrence – The Achilles Heel..



A Thorough Pre Transplant Work Up To Rule Out EHD

- MDCT angiography abdomen
- Whole body FDG-18 PET scan
- Whole body bone scan
- AFP (now also PIVKA-II)
- **EUS FNAC of suspicious LN's**

Rule out metastatic disease

Indian J Gastroenterol
DOI 10.1007/s12664-016-0718-0

ORIGINAL ARTICLE

Impact of endoscopic ultrasound-guided fine-needle aspiration in prospective liver transplant recipients with hepatocellular carcinoma and lymphadenopathy

Narendra S. Choudhary[1] · Rajesh Puri[2] · Sanjiv Saigal[1] · Prashant Bhangui[1] · Neeraj Saraf[1] · Vinit Shah[2] · Mukesh Nasa[2] · Haimanti Sarin[3] · Mridula Guleria[2] · Randhir Sud[3] · Arvinder S. Soin[1]

Thus, EUS-guided FNA precluded transplantation in 30% of patients with lymphadenopathy, and 4 (8%) patients received anti-tubercular therapy before liver transplantation.

Conclusion In patients with HCC and lymphadenopathy, EUS-guided FNA detected metastatic disease and precluded liver transplantation in approximately one third of patients.

During LT

1) Recipient first approach

2) Minimal handling of tumour and liver

3) Extension graft from confluence for PV in recipient in Vp3/Vp4

Original Article/Transplantation

The "No-touch" technique improves the survival of patients with advanced hepatocellular carcinomas treated by liver transplantation: A single-center prospective randomized controlled trial

Xin Lin [a, b, c, 1], Min Xiao [a, c, 1], Yang-Jun Gu [a, c], Heng-Kai Zhu [a, c], Meng-Xia Li [b], Li Zhuang [a], Shu-Sen Zheng [a, b, c], Qi-Yong Li [a, c]

No touch isolation technique for the prevention of postoperative recurrence of hepatocellular carcinoma after liver transplantation-combined with trans-arterial radioembolization

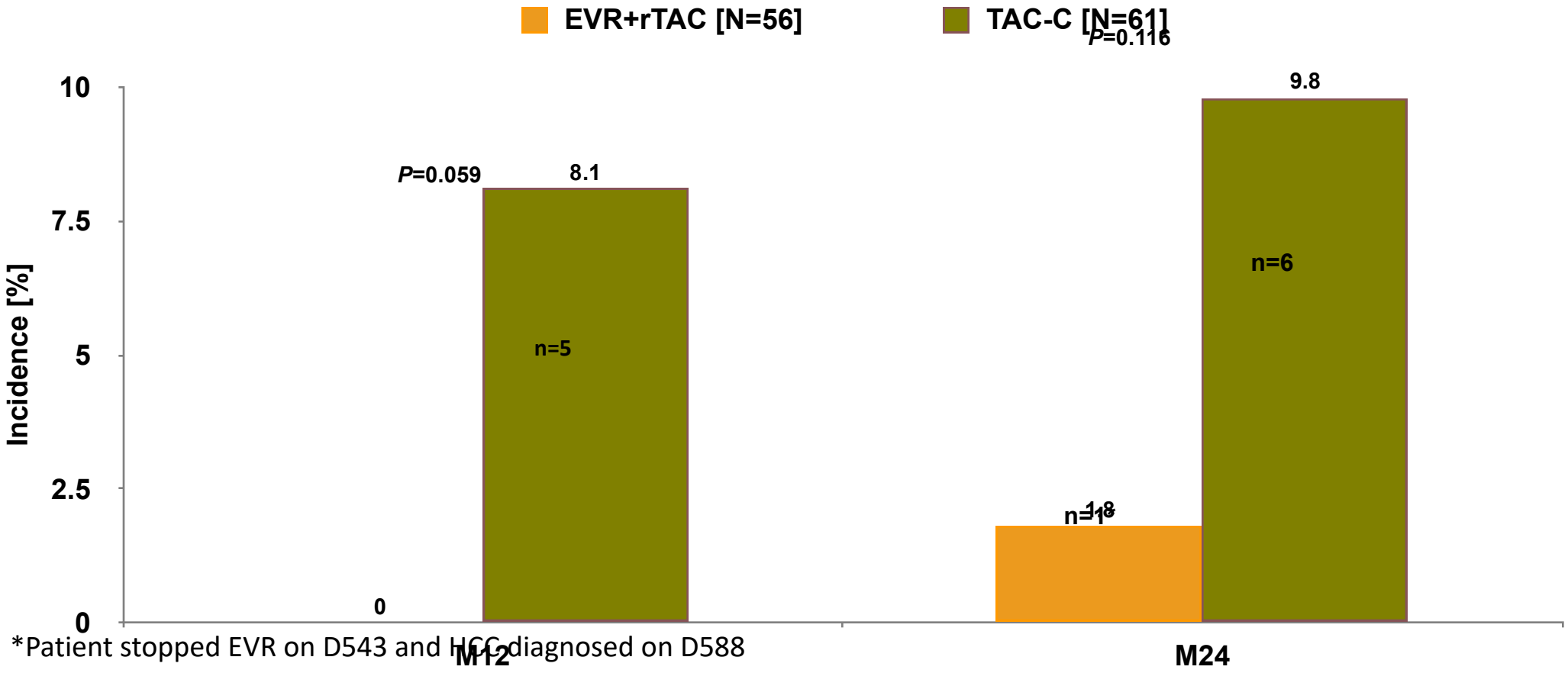
Jeong-Moo Lee [a], Kwang-Woong Lee [a,*], Hyo-Cheol Kim [b], Nam-Joon Yi [a], Kyung-Suk Suh [a]

Post LT IS

Cumulative HCC Recurrence Month 24

Low HCC recurrence in EVR group

Safety set: 24M analysis



- *Patient stopped EVR on D543 and HCC diagnosed on D588

EVR, everolimus; HCC, hepatocellular carcinoma; M, month; TAC-C, tacrolimus control;

Hepatology 2018 ASSLD Abstracts

Stringent follow up especially in beyond criteria tumours

POST LT FOLLOW UP

Medanta Protocol

- **CT scan**
  ~ 6 monthly x 2 yrs,
  then yearly
- **USG**
  ~ 3 monthly X 2 yrs
  then 6 monthly
- **AFP**
  ~ 3 monthly X 2 yrs
  then 6 monthly

Post liver transplant recurrence in patients with hepatocellular carcinoma: not necessarily the end of the road!

Prashant Bhangui, Sanjay Yadav, AS Soin

435 HCC patients undergoing LDLT – 51% had HCC beyond Milan and 43% beyond UCSF criteria

Median follow-up more than 4 years

100 patients (23%) overall developed HCC recurrence

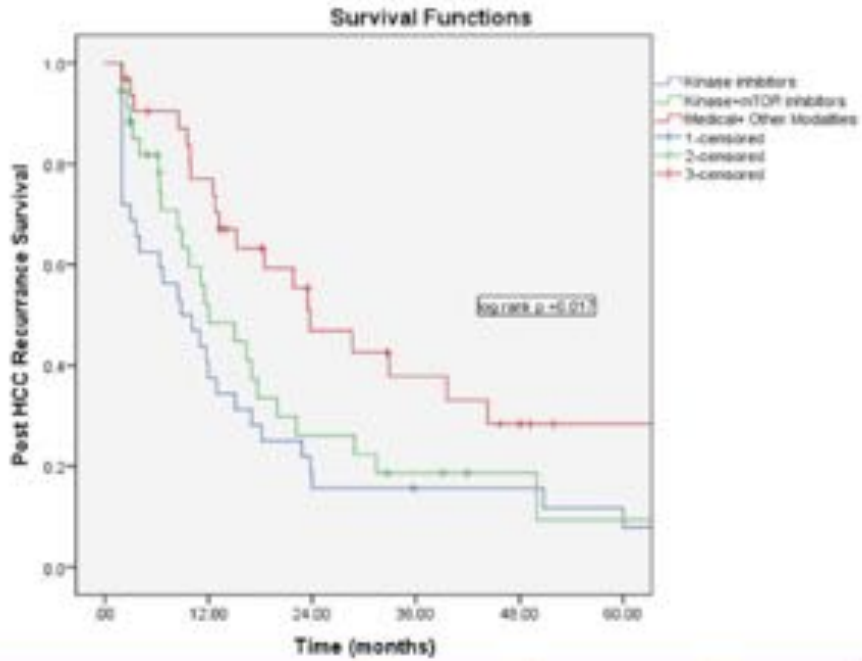
One- and 3-yr OS after recurrence were 57%, and 24% respectively, with a maximum post recurrence survival of 7.5 years.

Bhangui *et al*. *Hepatoma Res* 2020;6:71
DOI: 10.20517/2394-5079.2020.67

Post liver transplant recurrence in patients with hepatocellular carcinoma: not necessarily the end of the road!

Hepatoma Research

Prashant Bhangui, Sanjay Yadav, AS Soin



Overall Survival	1 year	2 years	3 years	5 years
Tyrosine kinase inhibitors alone	38%	19%	15%	12%
Tyrosine kinase and mTOR inhibitors	56%	28%	19%	10%
Medical plus other treatment modalities	77%	48%	39%	28%

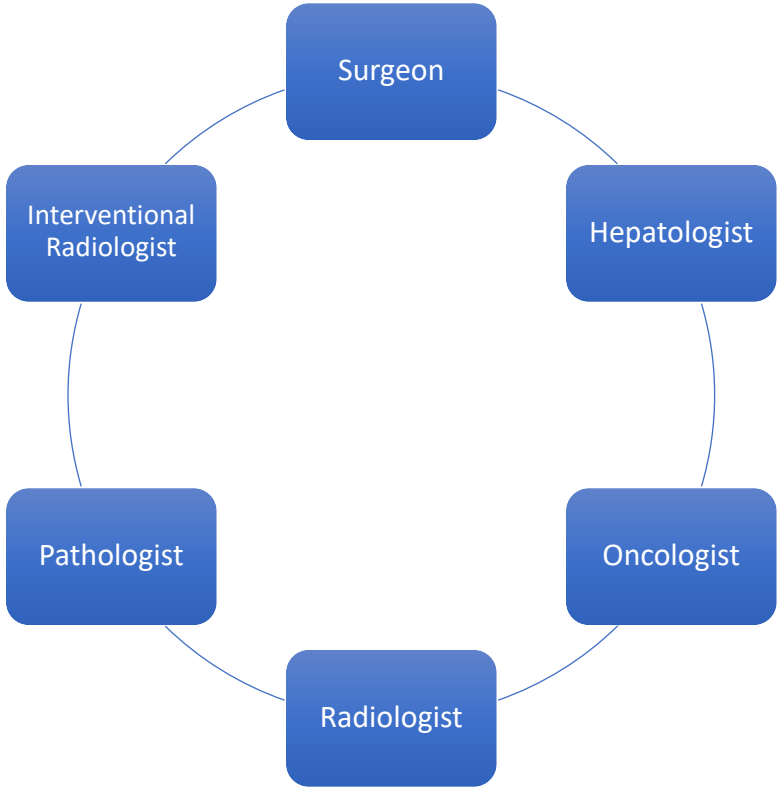
Bhangui *et al. Hepatoma Res* 2020;6:71
DOI: 10.20517/2394-5079.2020.67

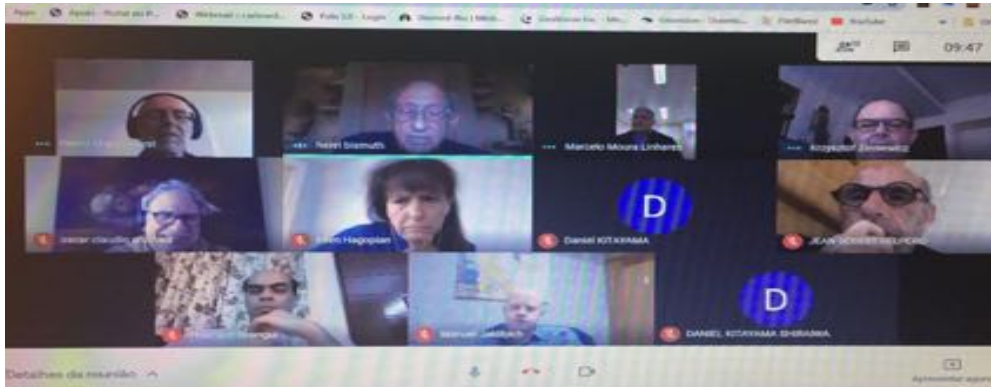
A Few "Mantras" for Success

3

TRANSPLANT ONCOLOGY

Multidisciplinary Tumor/Transplant Board





Decide what's best for each individual

Review > Curr Opin Organ Transplant. 2022 Aug 1;27(4):312-319.
doi: 10.1097/MOT.0000000000000997.

Liver transplantation and portal vein tumour thrombus: futile enterprise?

Prashant Bhangui [1]

Affiliations + expand

PMID: 36354257 DOI: 10.1097/MOT.0000000000000997

Review > J Hepatol. 2023 Jun;78(6):1124-1129. doi: 10.1016/j.jhep.2023.03.032.

Are patients with hepatocellular carcinoma and portal vein tumour thrombosis candidates for liver transplantation?

Arvinder Soin [1], Mickaël Lesurtel [2], Prashant Bhangui [1], Lorenzo Cocchi [2], Mohamed Bouattour [3], Pierre-Alain Clavien [4]

Affiliations + expand

PMID: 37208099 DOI: 10.1016/j.jhep.2023.03.032

May not be …

.. in all patients with HCC and PVTT…

Maybe the best hope is a new liver!!