National University Hospital

The Liver Transplant Symposium 2023

Small for Size and its Implications on HCC Recurrence

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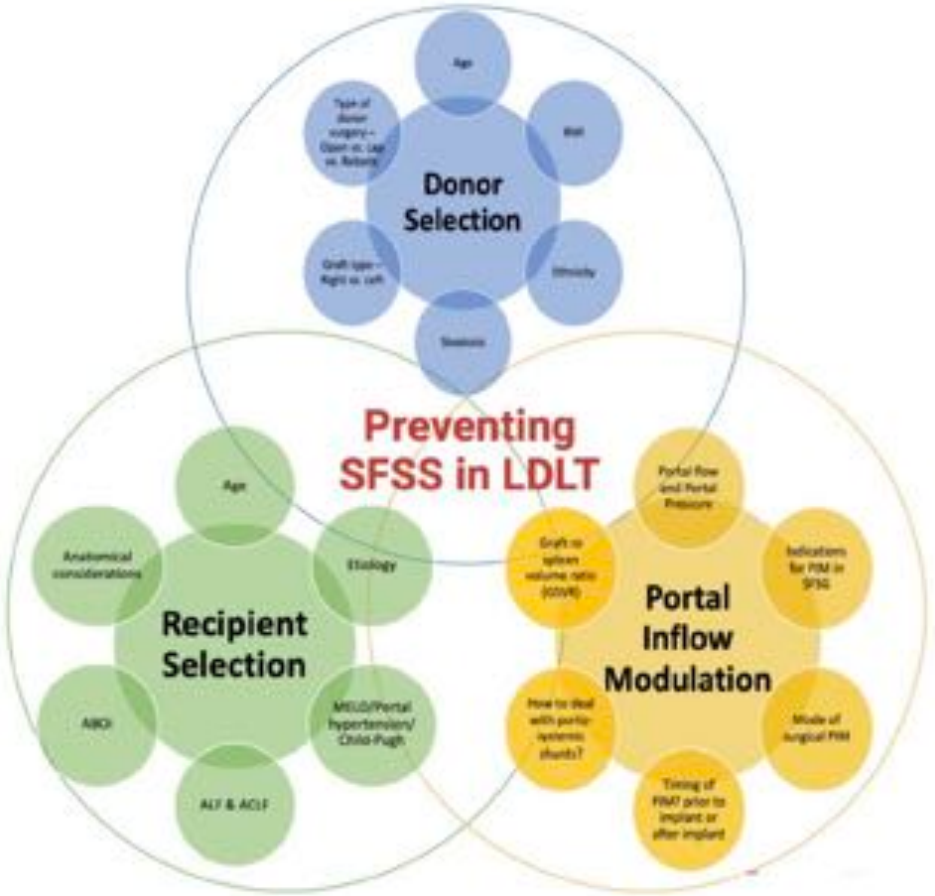
Prediction and Management of Small-for-size Syndrome in Living Donor Liver Transplantation: Methodology of the ILTS-iLDLT-LTSI Consensus Conference

Mohamed Rela, MS, FRCS, DSc,[1] Ashwin Rammohan, FRCS,[1] Prashant Bhangui, MS,[2] and Jean Emond, MD[3]



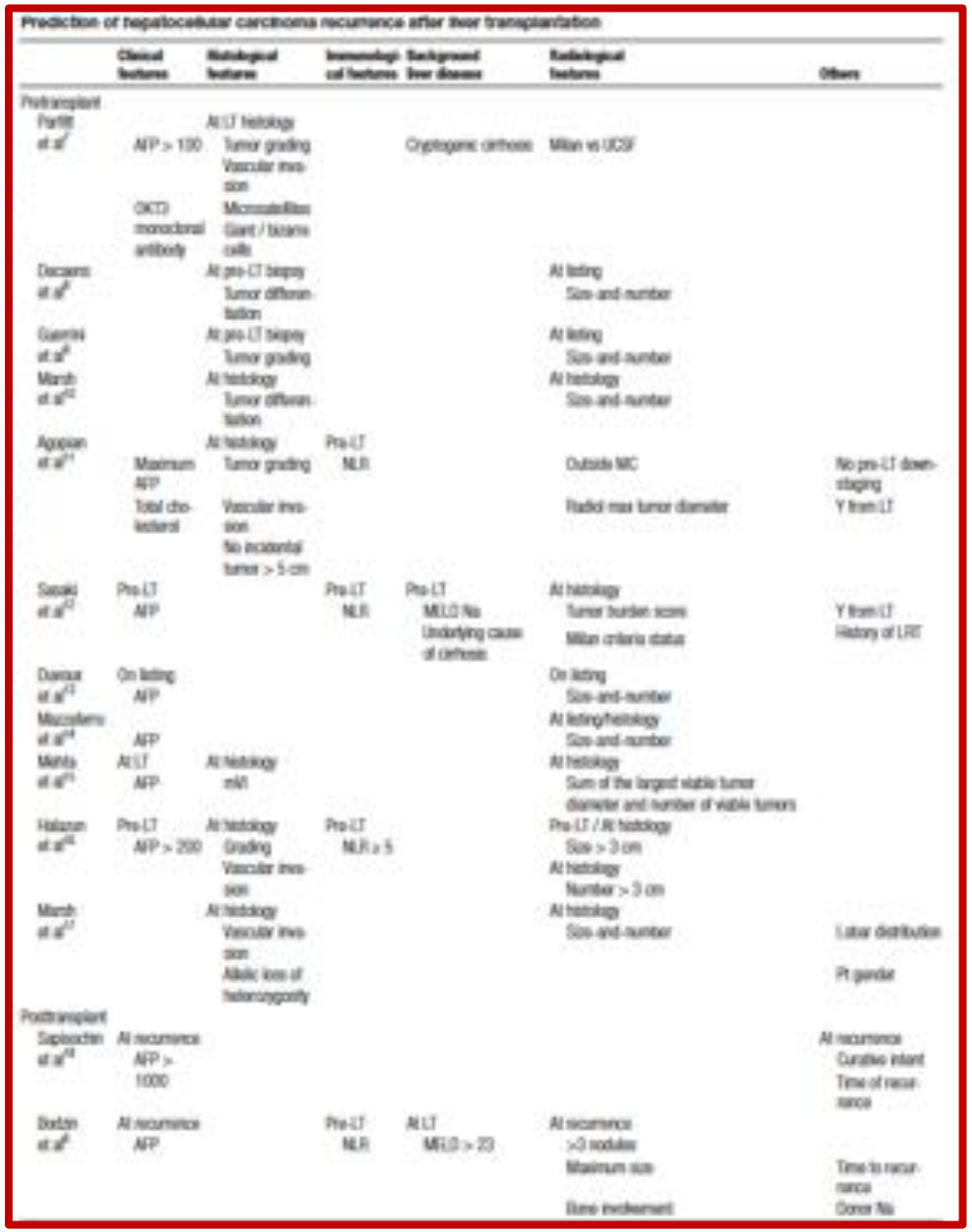
? HCC Recurrence

Transplantation

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]

? Low GRWR/ SFSS / SFSG



Prediction of hepatocellular carcinoma recurrence after liver transplantation

	Clinical features	Histological features	Immunological features	Background liver disease	Radiological features	Others
Pretransplant						
Parfitt et al[7]	AFP > 100	At LT histology Tumor grading Vascular invasion		Cryptogenic cirrhosis	Milan vs UCSF	
	DKD monoclonal antibody	Microsatellites Giant / bizarre cells				
Decaens et al[8]		At pre-LT biopsy Tumor differentiation			At listing Size-and-number	
Guerrini et al[9]		At pre-LT biopsy Tumor grading			At listing Size-and-number	
Marsh et al[10]		At histology Tumor differentiation			At histology Size-and-number	
Agopian et al[11]		At histology	Pre-LT			
	Maximum AFP	Tumor grading	NLR		Outside MC	No pre-LT downstaging
	Total cholesterol	Vascular invasion No incidental tumor > 5 cm			Radiol max tumor diameter	Y from LT
Sasaki et al[12]	Pre-LT AFP		Pre-LT NLR	Pre-LT MELD No Underlying cause of cirrhosis	At histology Tumor burden score Milan criteria status	Y from LT History of LRE
Duvoux et al[13]	On listing AFP				On listing Size-and-number	
Mazzaferro et al[14]	AFP				At listing/histology Size-and-number	
Mehta et al[15]	At LT AFP	At histology mVI			At histology Sum of the largest viable tumor diameter and number of viable tumors	
Halazun et al[16]	Pre-LT AFP > 200	At histology Grading Vascular invasion	Pre-LT NLR ≥ 5		Pre-LT / At histology Size > 3 cm At histology Number > 3 cm	
Marsh et al[17]		At histology Vascular invasion Allelic loss of heterozygosity			At histology Size-and-number	Lobar distribution Pt gender
Posttransplant						
Sapisochin et al[18]	At recurrence AFP > 1000					At recurrence Curative intent Time of recurrence
Bodzin et al[6]	At recurrence AFP		Pre-LT NLR	At LT MELD > 23	At recurrence >3 nodules Maximum size Bone involvement	Time to recurrence Donor Na

Transplantation

Where did this thought come from?

(Possible) Thought No:1

LDLT is in itself a small for size scenario

(as opposed to DDLT) – smaller the graft more the recurrence?

Living Donor Liver Transplantation for Hepatocellular Carcinoma

LAURA KULIK* and MICHAEL ABECASSIS†
*Departments of Medicine, Division of Hepatology, and †Surgery, Division of Transplantation Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

GASTROENTEROLOGY 2004;127:S277–S282

Proposed theories for higher recurrence in LDLT compared to DDLT:

1) Acute phase injury promoted by **partial graft**
   * cell adhesion, invasion, migration, angiogenesis, regeneration promote tumour growth

2) **Modified LT technique** -IVC/ hepatoduodenal ligament sparing

3) **Fast tracking**
   * less pre-LT liver directed therapy
   * insufficient time to assess tumour behaviour and response to alternative therapies
   * absence of natural selection process - transformation of drop out on wait list into post-LT

Is it true that LDLT results in worse outcomes compared to DDLT in matched HCC patients?

Intention-to-Treat Analysis of Liver Transplantation for Hepatocellular Carcinoma: Living Versus Deceased Donor Transplantation

Prashant Bhangui,[1] Eric Vibert,[1,2,4] Pietro Majno,[5] Chady Salloum,[1] Paola Andreani,[1] Joao Zocrato,[1] Philippe Ichai,[1,4] Faouzi Saliba,[2,4] Rene Adam,[1,2,4] Denis Castaing,[1,2,4] and Daniel Azoulay[1,2,3]

HEPATOLOGY 2011;53:1570-1579

- ITT analysis to compare tumor recurrence (primary endpoint) following LDLT vs. DDLT for HCC within Milan
- 36 LDLT vs. 147 DDLT
- 27 (18.4%) dropped out, all from DDLT waiting list, mainly due to tumor progression (70%)

Intention-to-Treat Analysis of Liver Transplantation for Hepatocellular Carcinoma: Living Versus Deceased Donor Transplantation

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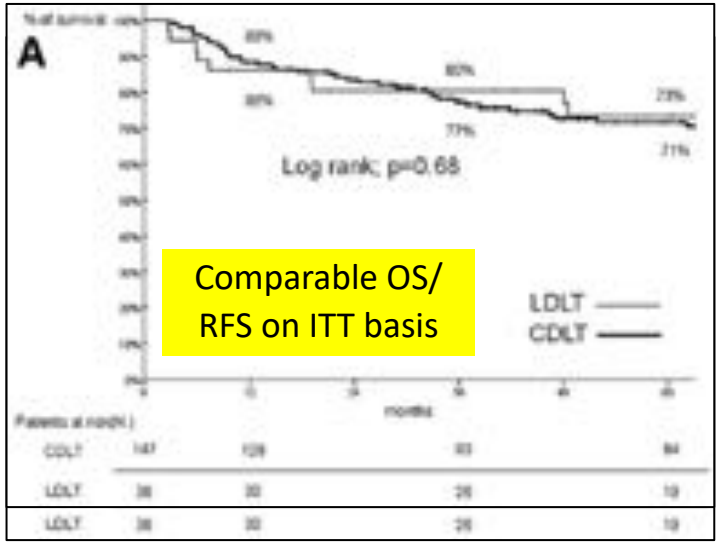


Comparable OS/ RFS on ITT basis

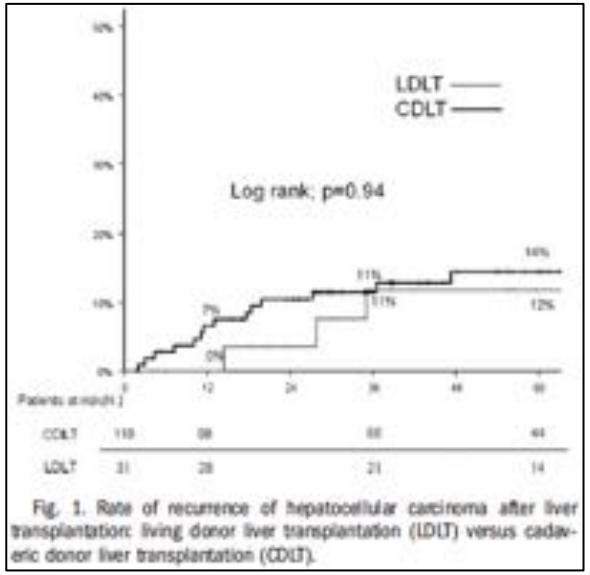


Fig. 1. Rate of recurrence of hepatocellular carcinoma after liver transplantation: living donor liver transplantation (LDLT) versus cadaveric donor liver transplantation (CDLT).

LDLT higher recurrence within criteria – NO

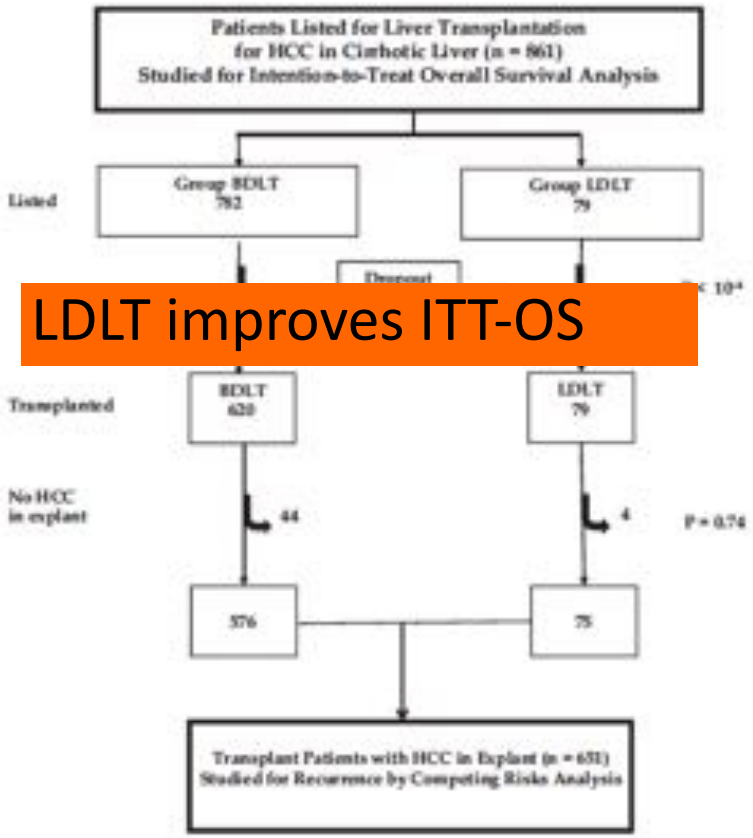
- ~ Recurrence rate LDLT vs. CDLT -- 12.9% vs. 12.7%, p= 0.78
- ~ Trend towards longer time to recurrence in LDLT (38±27 months vs. 16±13 months; p=0.06)

Follow Up Multicenter Study

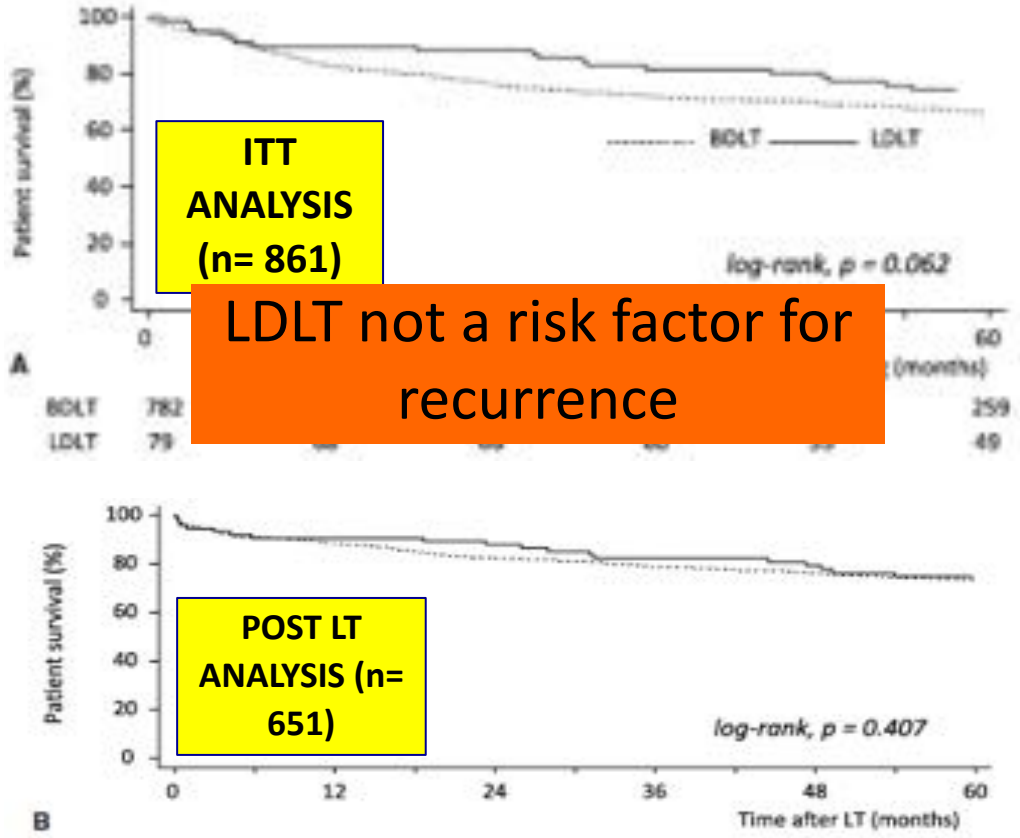
Living or Brain-dead Donor Liver Transplantation for Hepatocellular Carcinoma

A Multicenter, Western, Intent-to-treat Cohort Study

Daniel Azoulay, MD, PhD, Etienne Audureau, MD, PhD,† Prashant Bhangui, MD,‡ Jacques Belghiti, MD, PhD,§ Olivier Boillot, MD, PhD,¶ Paola Andreani, MD, PhD,‡ Denis Castaing, MD, PhD,‡ Daniel Cherqui, MD, PhD,‡ Sabine Irtan, MD,§ Yvon Calmus, MD, PhD,|| Olivier Chazouillères, MD, PhD,|| Olivier Soubrane, MD, PhD,|| Alain Luciani, MD, PhD,** and Cyrille Feray, MD, PhD††*



LDLT improves ITT-OS



ITT ANALYSIS (n= 861)

LDLT not a risk factor for recurrence

POST LT ANALYSIS (n= 651)

Metaanalysis: LDLT vs. DDLT for HCC

Can living donor liver transplantation provide similar outcomes to deceased-donor liver transplantation for hepatocellular carcinoma? A systematic review and meta-analysis Hepatology International (2023)

Conclusion The cancer bi… …it of recurrence and survival after LT. However, LDLT pro… …ally in regions that suffer from low deceased organ availabil…

LDLT is not associated with higher recurrence rates compared to DDLT

Long-Term Outcomes of Living Do… Donor Liver Transplan… Carcinoma …

Haris Muhammad,[1] Mer…
Duha Zaffar,[1] Su…

… (2022) 3: 279-284

Conclusions: **Survival was similar in between the living donor versus deceased donor recipients with hepatocellular carcinoma. With changes in Model for**

Long-Term Survival … Between Living Donor and Deceased Donor L…ver Transplant for Hepatocellular Carcinoma: Intention-to-Treat and Propensity Score Matching Analyses

Tiffany C. L. Wong, MBChB, FRCS (Edin)[1,2,3], Kelvin K. C. Ng, MBBS, MS, PhD, FRCS (Edin)[3], James Y. Y. Fung, MBChB, MD, FRACP[4,5], Albert A. C. Chan, MBBS, FRCS (Edin)[1,2,3], Tan-To Cheung, MBBS, MS, FRCS (Edin)[1,2,3], Kenneth S. H. Chok, MBBS, MS, FRCS (Edin)[1,2,3], Jeff W. C. Dai, MBBS, FRCS (Edin)[1,2], and Chung-Mau Lo, MBBS, MS, FRCS (Edin), FRACS[1,2,3]

Ann Surg Oncol
https://doi.org/10.1245/s10434-019-07206-0

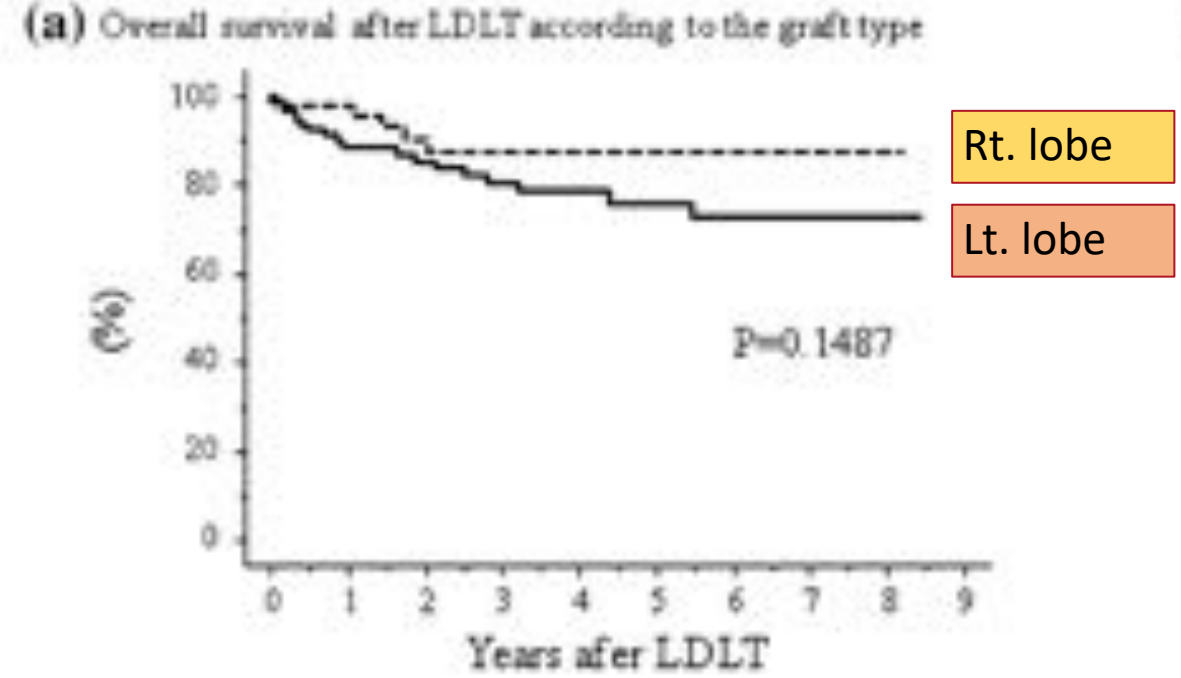
Conclusion. Survival benefit of LDLT was observed for HCC patients with ITT analysis. Despite a more advanced tumor stage, overall and recurrence-free survival rates were comparable between LDLT and DDLT using PSM analysis.

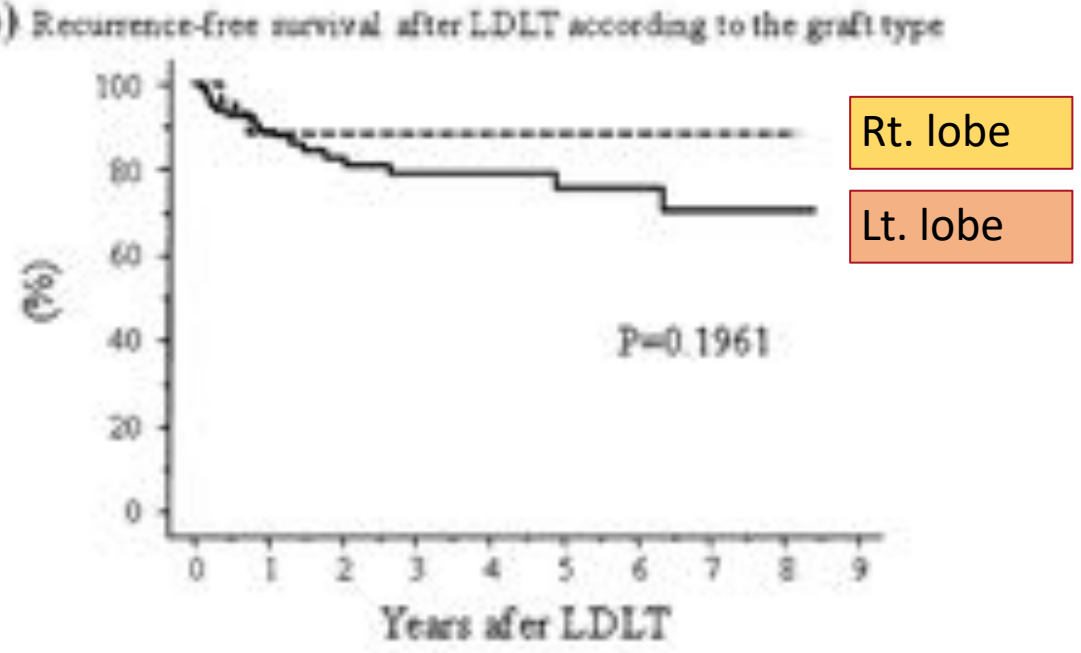
(Possible) Thought No:2

Left lobe adult LDLT (smaller graft) vs. right lobe LDLT in HCC – is the risk of recurrence higher?

The long-term outcomes of patients with hepatocellular carcinoma after living donor liver transplantation: a comparison of right and left lobe grafts

Akinobu Taketomi · Ken Shirabe · Takeo Toshima · Kazutoyo Morita · Naotaka Hashimoto · Hiroto Kayashima · Tohru Ikegami · Tomoharu Yoshizumi · Yuji Soejima · Yoshihko Maehara





Surg Today (2012) 42:559–564

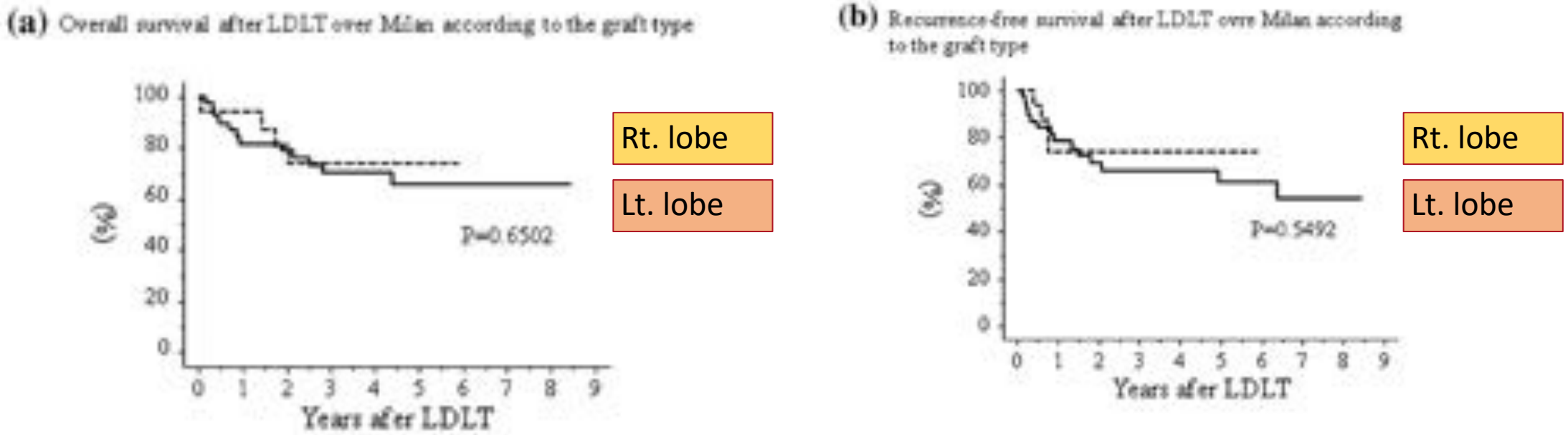


Fig. 2 The overall (**a**) or recurrence-free (**b**) survival after LDLT for 39 patients who were classified beyond the Milan criteria treated with LL grafts (*continuous line*) and 17 patients beyond the Milan criteria treated with RL grafts (*dotted line*)

(Possible) Thought No:3

The Systematic Review that proposed this….

Review

Association between Hepatocellular Carcinoma Recurrence and Graft Size in Living Donor Liver Transplantation: A Systematic Review

Alessandro Parente [1,2], Hwui-Dong Cho [2], Ki-Hun Kim [2] and Andrea Schlegel [3,4,*]

International Journal of *Molecular Sciences*

~ search of the MEDLINE and EMBASE databases till Dec 2022

~ studies comparing different GRWRs in the prognosis of HCC recipients in LDLT

~ **3 studies** – 782 patients -- (168 GRWR < 0.8 vs. 614 GRWR ≥0.8%)

~ pooled overall survival was 85% and 77% at one year and 90% and 83% at three years for GRWR ≥0.8 and GRWR <0.8, respectively

~ In patients within Milan criteria, low GRWR was not associated with worse oncological outcomes --

in patients with HCC outside the Milan criteria with a GRWR < 0.8% had lower survival and higher tumor recurrence rates.

~ Novel perfusion technologies and pharmacological interventions may contribute to improving outcomes

The three studies on which this review was based

35. Hwang, S.; Lee, S.G.; Ahn, C.S.; Kim, K.H.; Moon, D.B.; Ha, T.Y.; Park, K.M.; Song, G.W.; Jung, D.H.; Kim, B.S.; et al. Small-sized liver graft does not increase the risk of hepatocellular carcinoma recurrence after living donor liver transplantation. *Transplant. Proc.* **2007**, *39*, 1526–1529. [CrossRef]
36. Hu, Z.; Zhong, X.; Zhou, J.; Xiang, J.; Li, Z.; Zhang, M.; Wu, J.; Jiang, W.; Zheng, S. Smaller grafts do not imply early recurrence in recipients transplanted for hepatocellular carcinoma: A Chinese ex- perience. *Sci. Rep.* **2016**, *26*, 26487. [CrossRef]
37. Lee, E.C.; Kim, S.H.; Shim, J.R.; Park, S.J. Small-for-size grafts increase recurrence of hepatocellular carcinoma in liver transplantation beyond milan criteria. *Liver Transpl.* **2018**, *24*, 35–43. [CrossRef]

Table 3. Graft and tumor characteristics

Study (First Author [Ref])	Previous Treatment *		Vascular Invasion		Tumor Size (cm)		No. of Nodules		T Stage		Preop. AFP		Graft Type		Graft Weight (g)		Operation Time *		Blood Loss (mL)	
	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%	GBWR ≥ 0.8%	GBWR < 0.8%
Hwang et al. [19]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Right Lobe: 65 (IB679) Left lobe: 35 (IB1234) Dual: 29	Right Lobe: 7 (IB679) Left lobe: 20 (IB1234) Dual: 3	NA	NA	NA	NA	NA	NA
Hu et al. [16]	108 (40%)	16 (28%)	366 (77%)	44 (78.5%)	5.5 (2.4-5.5)	4 (2.6-5)	1 (1–3)	1 (1–2.5)	NA	NA	507.7 (9.2-5000)	235.6 (9.7-1250)	Right Lobe: 225 (IB679) Left lobe: 4 (IB1234) Dual: 5	Right Lobe: 52 (IB679) Left lobe: 3 (IB1234) Dual: 0	680 (635-745)	555 (500-607.5)	10.3 (8–12.5)	10.8 (9.5-12.85)	1800 (1000-3000)	2000 (1000-3000)
Lee et al. [17]	NA	NA	306 (82.2%)	41 (80%)	2.2 (1.5-3.5)	2.3 (1.6-3.5)	1 (1–3)	1 (1–1)	I—62 (25.2) II—141 (57.3) III—39 (15.9) IV—4 (1.6)	I—25 (16.5) II—80 (63.0) III—19 (16.5) IV—2 (2.4)	53 (8.1-737.8)	9.6 (3.7-350.4)	Right Lobe: 246 (IB679)	Right Lobe: 82 (IB679)	NA	NA	446.8 ± 125.2	487.8 ± 108.5	1550 (800-3500)	1500 (800-3000)

Around 40% of the parameters -- NA

2.5.1. Overall Survival

One study [37] reported the 1-, 3- and 5-year overall survival (OS) rates, which were 87.8%, 80.3% and 78.7%, respectively, for patients with GRWR < 0.8%, and 93.5%, 87.1% and 84.1%, respectively, for patients with GRWR ≥ 0.8%. The other survival rates were extrapolated and are merged in Figure 2.

2.5.2. Disease-Free Survival

One study reported [37] the 1-, 3- and 5-year disease-free survival rates which were 75.9%, 73.3% and 71.7%, respectively, for patients with GRWR < 0.8%, and 86.4%, 80.8% and 77.9%, respectively, for patients with GRWR ≥ 0.8%. The other survival rates were extrapolated and are merged in Figure 2.

The moot point of the systematic review

The GRWR < 0.8% appears to be associated with lower survival rates in HCC recipients, particularly for candidates with tumors outside established HCC criteria.

Based on mainly one study by Lee EC, 428 patients

Review

Association between Hepatocellular Carcinoma Recurrence and Graft Size in Living Donor Liver Transplantation: A Systematic Review

Additional risk factors may contribute to the observed SFSS, including the transplanted liver graft volume and the cytokine release triggered by both liver transection during donation surgery and after reperfusion [17]. The mechanistic link between an advanced hepatic ischemia-reperfusion injury (IRI) and liver tumor regrowth and metastasis was previously demonstrated in 2007 by Man et al., who described higher HCC recurrence rates and more lung metastases when a small liver remnant was evident [17,18].

Greater hepatic IR injury leads to liver tumour regrowth and metastases – Man et al.

Ischemia-Reperfusion of Small Liver Remnant Promotes Liver Tumor Growth and Metastases—Activation of Cell Invasion and Migration Pathways

Kwan Man, Kevin T. Ng, Chung Mau Lo, Joanna W. Ho, Bai Shun Sun, Chris K. Sun, Terence K. Lee, Ronnie T. P. Poon, and Sheung Tat Fan
Department of Surgery, The University of Hong Kong, Pokfulam, Hong Kong, China

~ SFS graft from living donor – more severe acute phase injury → increased tumour recurrence

~ **Reasons**

increase in VEGF expression → angiogenesis → favors tumor growth and metastasis

Significant activation of cell signalling pathways in SFS grafts → leading to tumor invasion and migration → promoting tumor growth and metastasis after transplantation

mobilizes the circulating progenitor, immune cells → tumor recurrence and metastasis.

Probable main culprit - hepatic ischemia-reperfusion (I/R) injury of a small liver remnant

LIVER TRANSPLANTATION 13:1669-1677, 2007

Ischemia-Reperfusion of Small Liver Remnant Promotes Liver Tumor Growth and Metastases—Activation of Cell Invasion and Migration Pathways

TABLE 1. Groups of Animals

Group	Surgical procedure before cell injection
1 (n = 12)	None
2 (n = 12)	Major hepatectomy (left and caudate lobes)
3 (n = 12)	60 minutes'/60 minutes' I/R injury for right and median lobes
4 (n = 12)	(1) 60 minutes' ischemia injury for right and median lobes (2) Major hepatectomy (left and caudate lobes) (3) 60 minutes' reperfusion for right and median lobes

Abbreviation: I/R, ischemia-reperfusion.

4 groups of rats for study and comparison -- 6 rats in each group

Significant tumor growth and intrahepatic metastasis and lung metastasis in rats undergoing I/R and major hepatectomy compared with the control group

Upregulation of mRNA levels for Cdc42, ROCK (Rho kinase), VEGF, as well as activation of hepatic stellate cells.

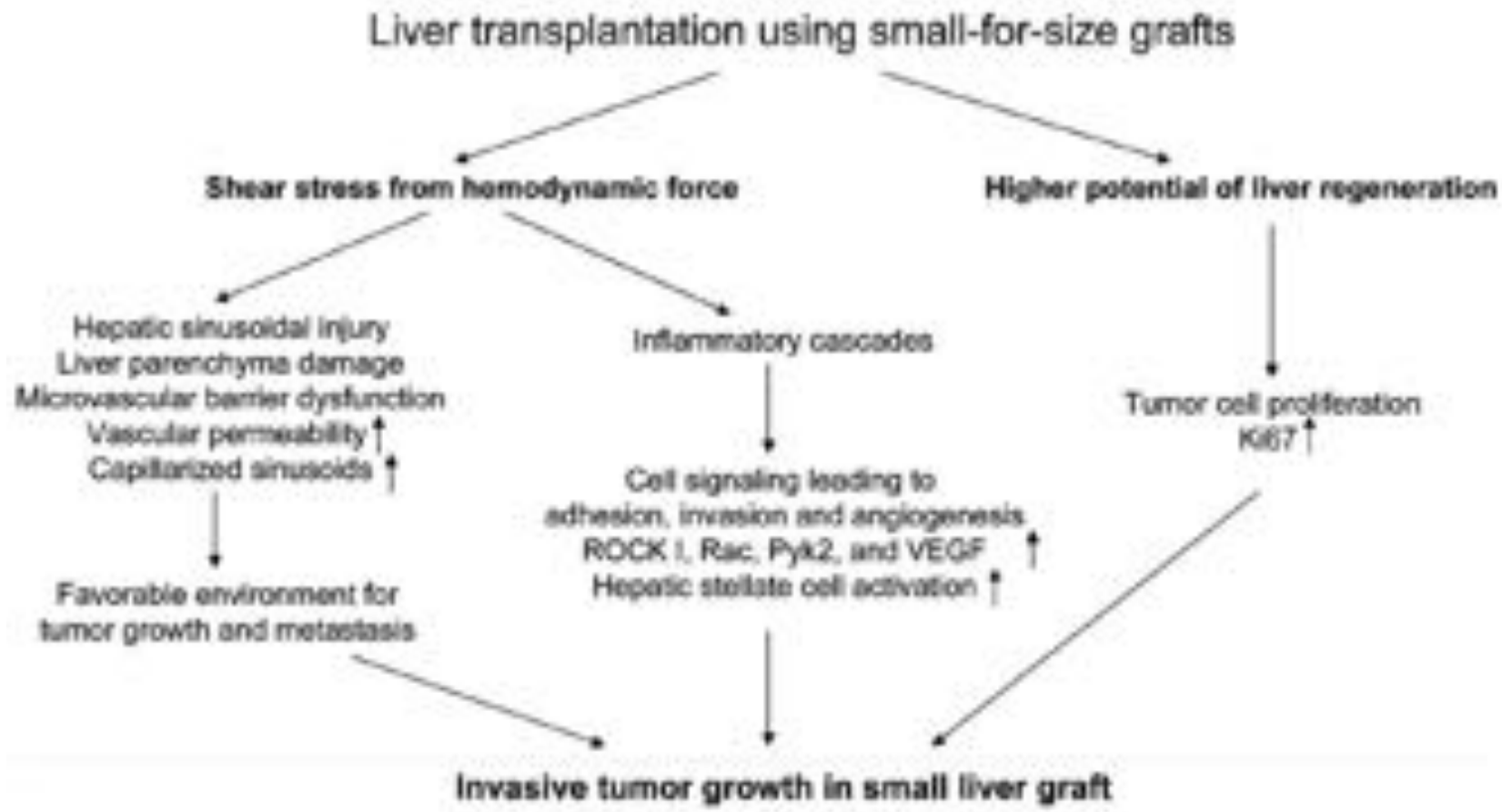
The Significance of Acute Phase Small-for-Size Graft Injury on Tumor Growth and Invasiveness After Liver Transplantation

Kwan Man, PhD, Chung Mau Lo, MS,* Jiang Wei Xiao, PhD,*† Kevin T. Ng, MPhil,* Bai Shun Sun, PhD,* Irene O. Ng, MD,‡ Qiao Cheng, MS,* Chris K. Sun, MPhil,* and Sheung Tat Fan, MD**

Buffalo rat hepatoma cell line (McA-RH7777, 2 105/200 L) was injected via the portal vein after reperfusion to mimic the clinical scenario of circulating tumor cells homing to the graft after liver transplantation in a recipient.

Annals of Surgery • Volume 247, Number 6, June 2008

The Significance of Acute Phase Small-for-Size Graft Injury on Tumor Growth and Invasiveness After Liver Transplantation



A few contentions..

~ This will hold true for marginal DDLT grafts as well (fatty grafts, long cold ischemia, DCD) – increased IR injury – increased chance of HCC recurrence → ***has been shown in some studies – but LD grafts are good quality, well selected grafts***

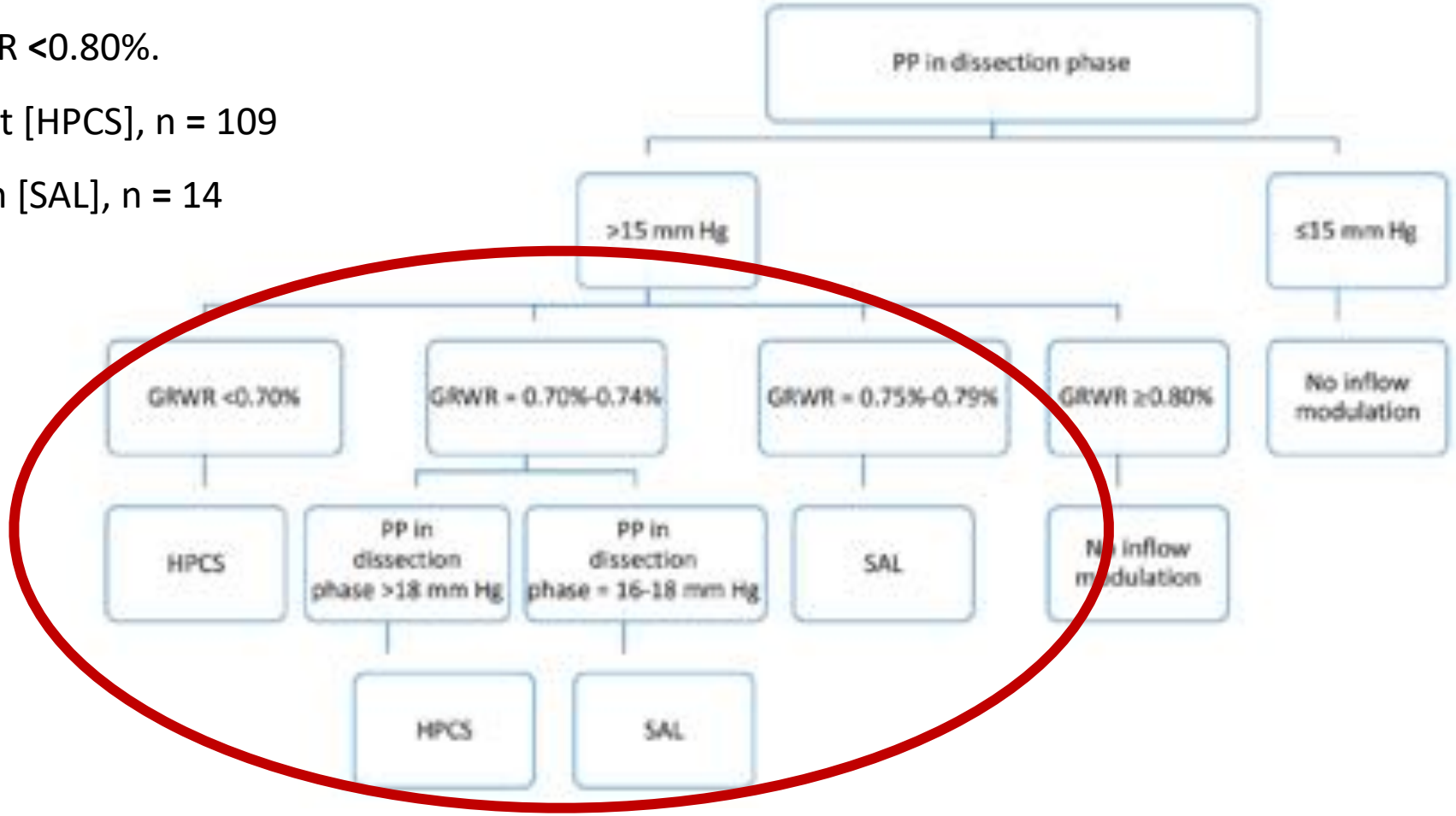
~ All LDLT grafts are essentially small for size – so higher recurrence → ***but this is not true***

~ **Main culprit** – IR injury – main cause for IR injury in SFSGs – portal hyperperfusion – ***so don't expose the small LD grafts to higher portal flow*** – ***you should be fine***!!

Is Portal Inflow Modulation Always Necessary for Successful Utilization of Small Volume Living Donor Liver Grafts?

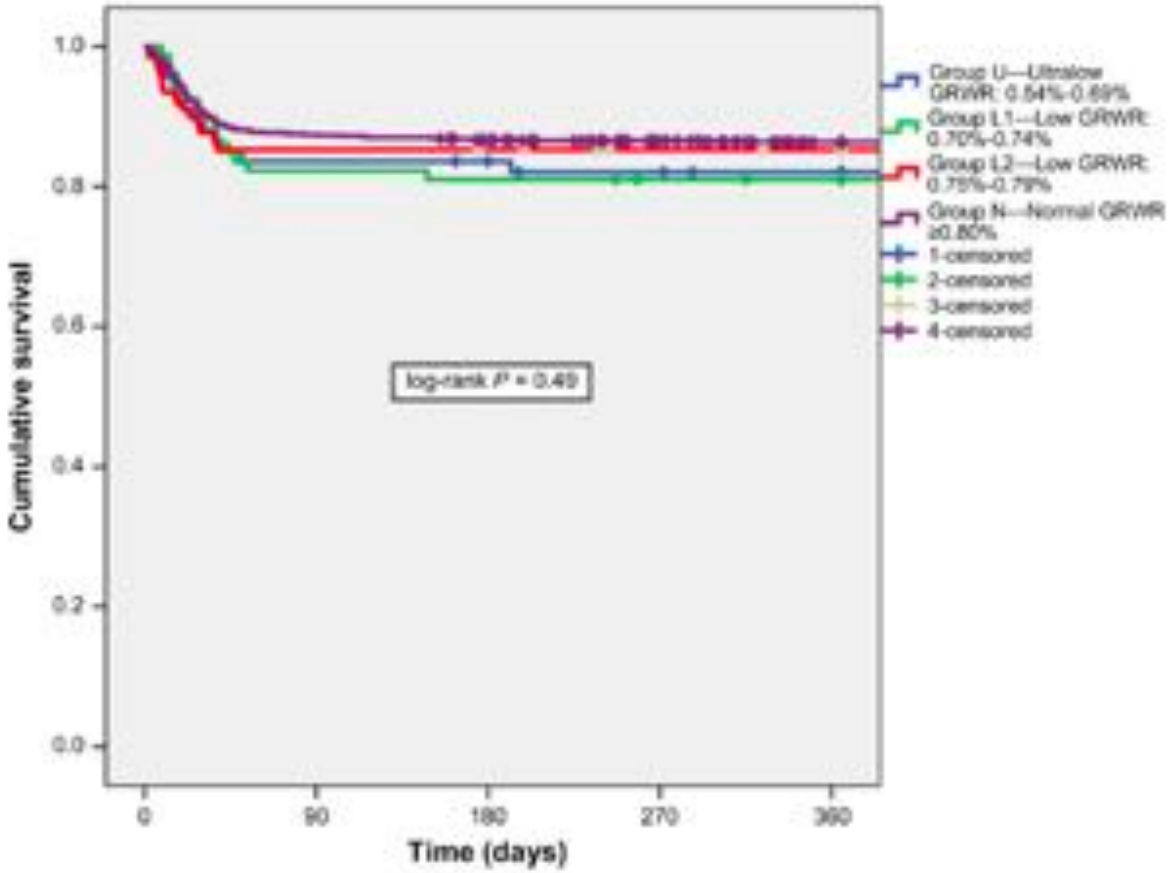
N=287 (21.7%) had GRWR <0.80%.

- Hemiportocaval shunt [HPCS], n = 109
- Splenic artery ligation [SAL], n = 14



Aim of obtaining a postreperfusion PP of <16 mm Hg

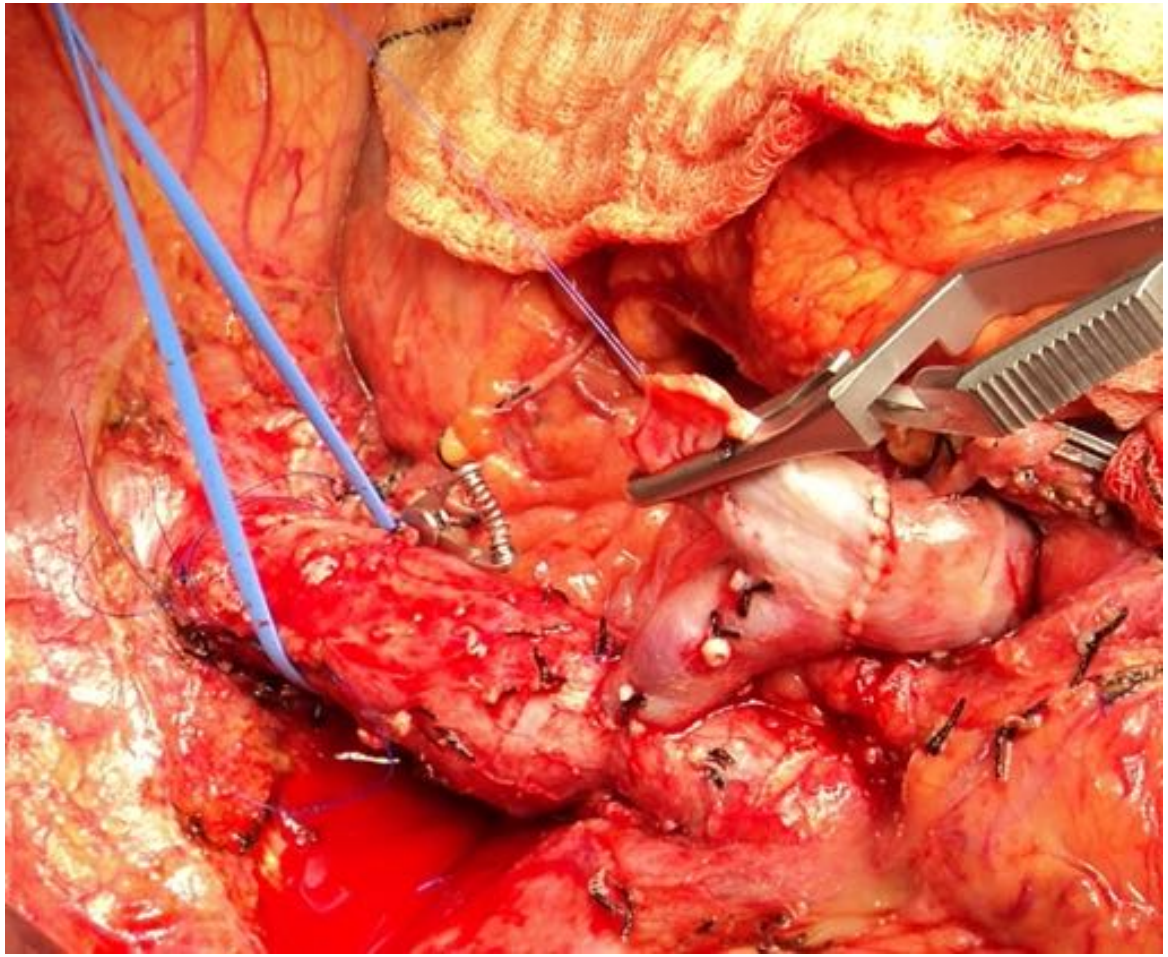
Soin AS, Bhangui P et al. Liver Transplantation, 2019



- Small-for-size syndrome developed in 2.8% patients.
- Three patients needed shunt closure at 1 and 4 weeks and 60 months
- Survival of GRWR < 0.8% comparable

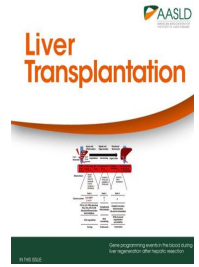
HPCS is performed before reperfusing the living donor graft – with the aim of reducing initial portal hyperperfusion injury

Portal inflow modulation



Hemi porto-caval shunt made in anhepatic phase using recipient PV graft

Low GRWR is associated with higher recurrence? – Our results….



Incorporating Tumor Biology to Predict Hepatocellular Carcinoma Recurrence in Patients Undergoing Living Donor Liver Transplantation Using Expanded Selection Criteria

Prashant Bhangui ,[1] Sanjiv Saigal,[1] Dheeraj Gautam,[2] Tarun Piplani,[3] Narendra Choudhary ,[1] Rohan Chaudhary,[1] Sanjay Yadav ,[1] S. Thiagarajan,[1] Amit Rastogi,[1] Neeraj Saraf,[1] Samiran Nundy,[4] and A.S. Soin[1]

Liver Transplantation 27 209–221 2021 AASLD.

OUR CURRENT SELECTION FOR UPFRONT LDLT IN HCC PATIENTS AT MEDANTA

- No extrahepatic disease

- No major vascular invasion by tumour on pre-op imaging (portal vein, hepatic veins, IVC)

- No medical contraindication to LT

irrespective of tumour size and number

Total till date
4085

LIVER TRANSPLANTS AT OUR CENTER
(Jan 2006 – Dec 2017)
n= 2348

TOTAL NUMBER OF HCC-CIRR PATIENTS
on pre-op imaging who underwent LT
n= 469

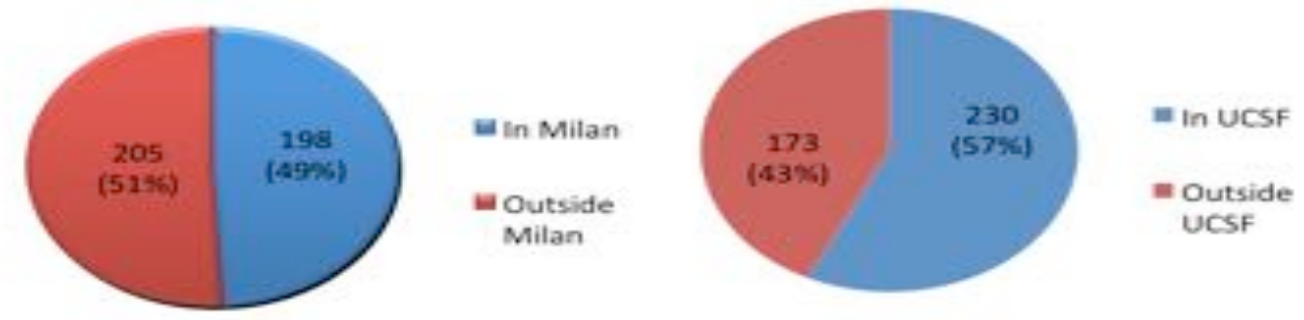
DDLT
n = 6

NO HCC ON EXPLANT (PATHOLOGY)
n = 12

HCC with PVTT
n = 46

HCC-CIRR PATIENTS UNDERGOING LDLT
n= 405 (17.2%)

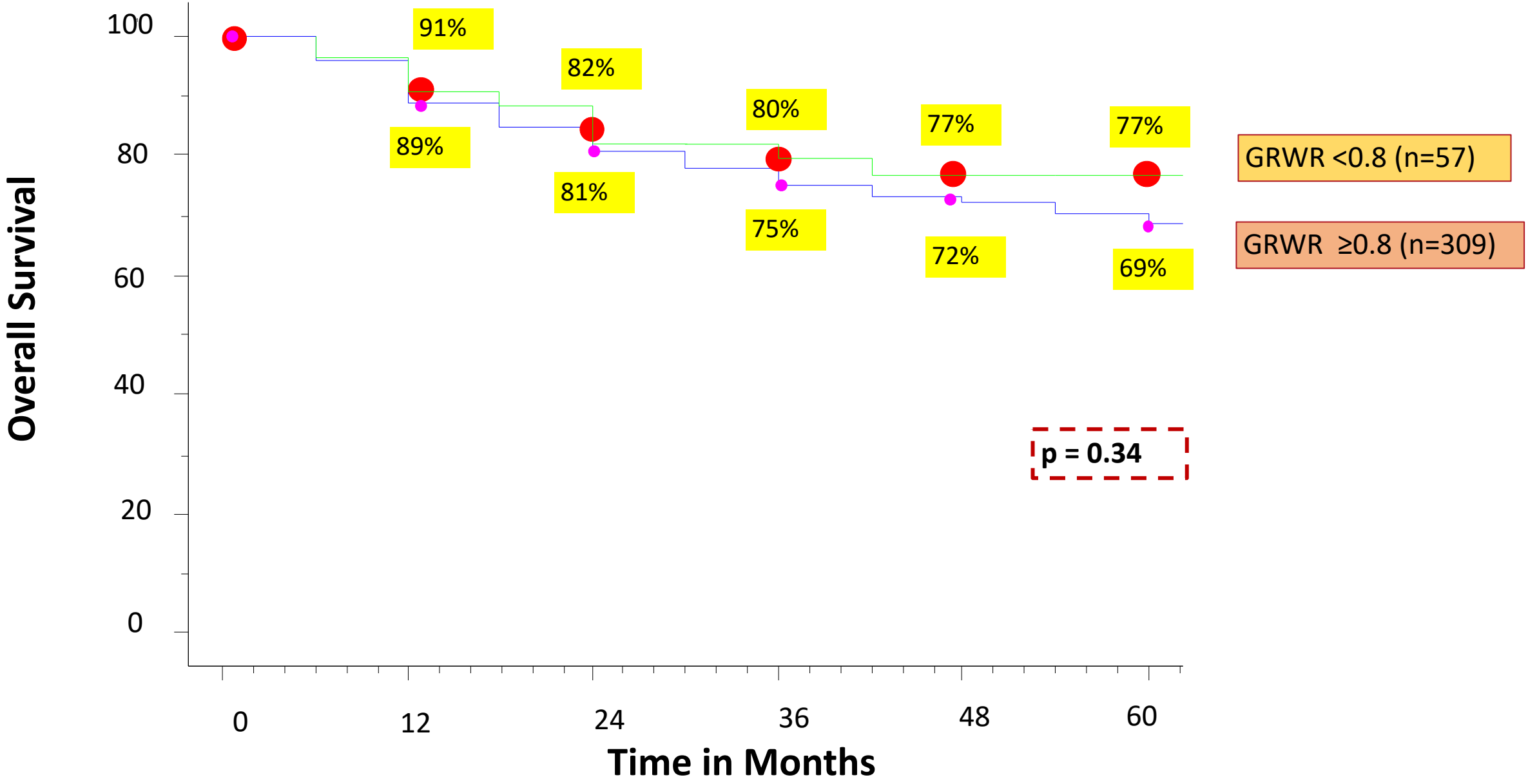
Total till date
587



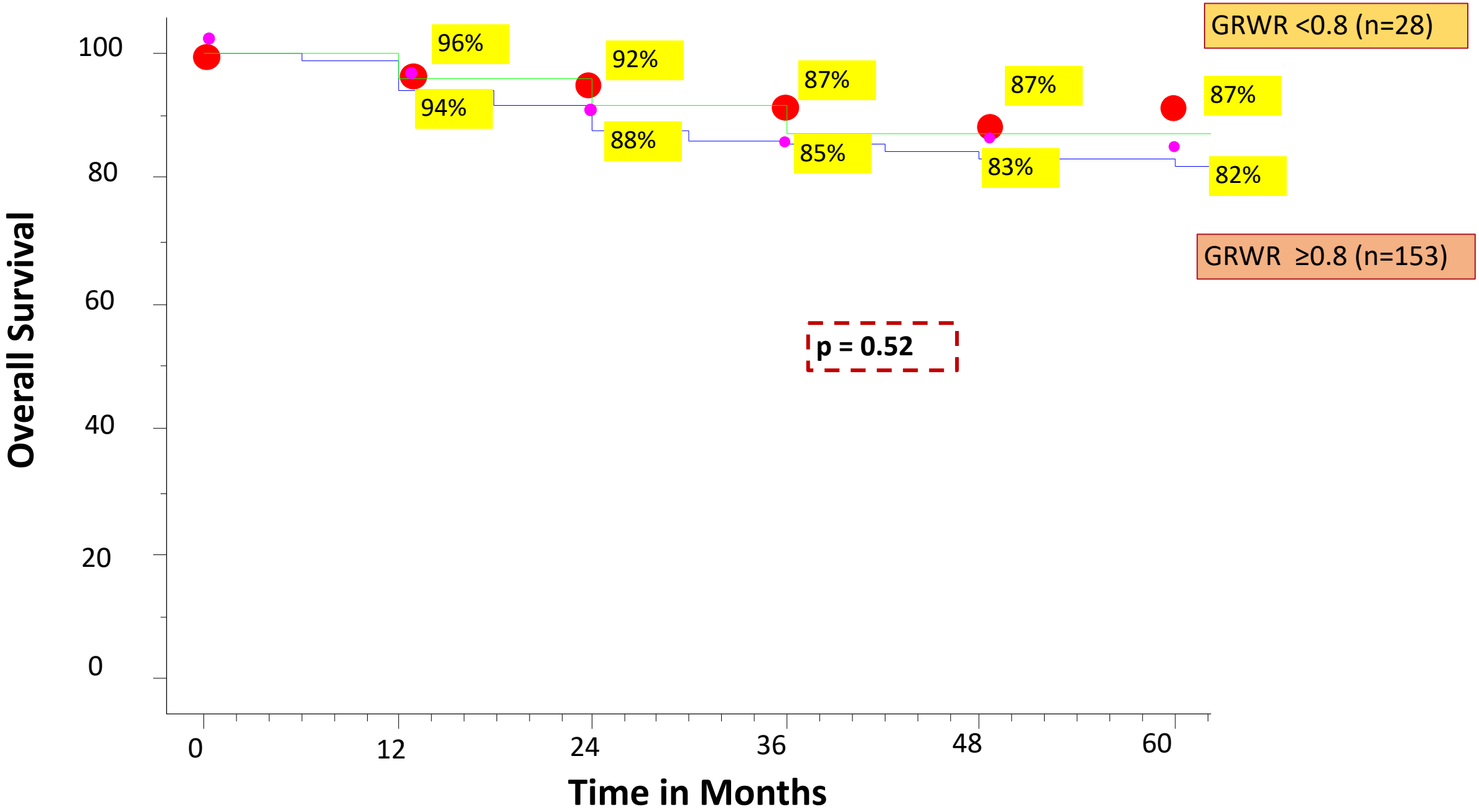
Prognostic Factors for Recurrence

HCC-CIRR PATIENTS UNDERGOING LDLT	RECURRENCE-FREE SURVIVAL							
	UNIVARIATE				MULTIVARIATE			
			95% Confidence Interval				95% Confidence Interval	
	Sig	HR	Lower	Upper	Sig	HR	Lower	Upper
Age	0.185	0.98	.952	1.010				
Gender	0.151	1.79	.809	3.959				
Etiology HBV vs. Non HBV	0.478	1.24	.684	2.250				
MELD (Model for End Stage Liver Disease)	0.224	0.97	.913	1.022				
Pre-LT AFP ≤ 100 vs. >100 ng/ml	< 0.0001	2.67	1.540	4.633	0.005	2.190	1.269	3.780
Milan In/Out	0.001	2.60	1.451	4.671				
UCSF In/Out	< 0.0001	2.76	1.592	4.769	0.001	2.640	1.519	4.590
Tumour FDG-18 PET avidity	< 0.0001	3.09	1.698	5.627	0.004	2.442	1.327	4.494
NLR (neutrophil lymphocyte ratio)	0.498	0.96	.863	1.074				
PLR (platelet lymphocyte ratio)	0.379	1.00						
GRWR ≤ 0.8 vs. >0.8	0.427	2.76	.623	3.059				
Explant maximum tumour size	0.016	1.08						
Sum tumour number plus maximum diameter	0.058	1.07	0.998	1.143				
Tumour microvascular invasion (MVI)	0.001	2.76	1.504	5.050				
Tumour macrovascular invasion	0.147	0.04	.001	3.086				
Tumour capsular invasion	0.612	0.78	.296	2.049				
Tumour Grade (Edmonson) III/IV vs. I/II	0.373	1.91	.460	7.959				

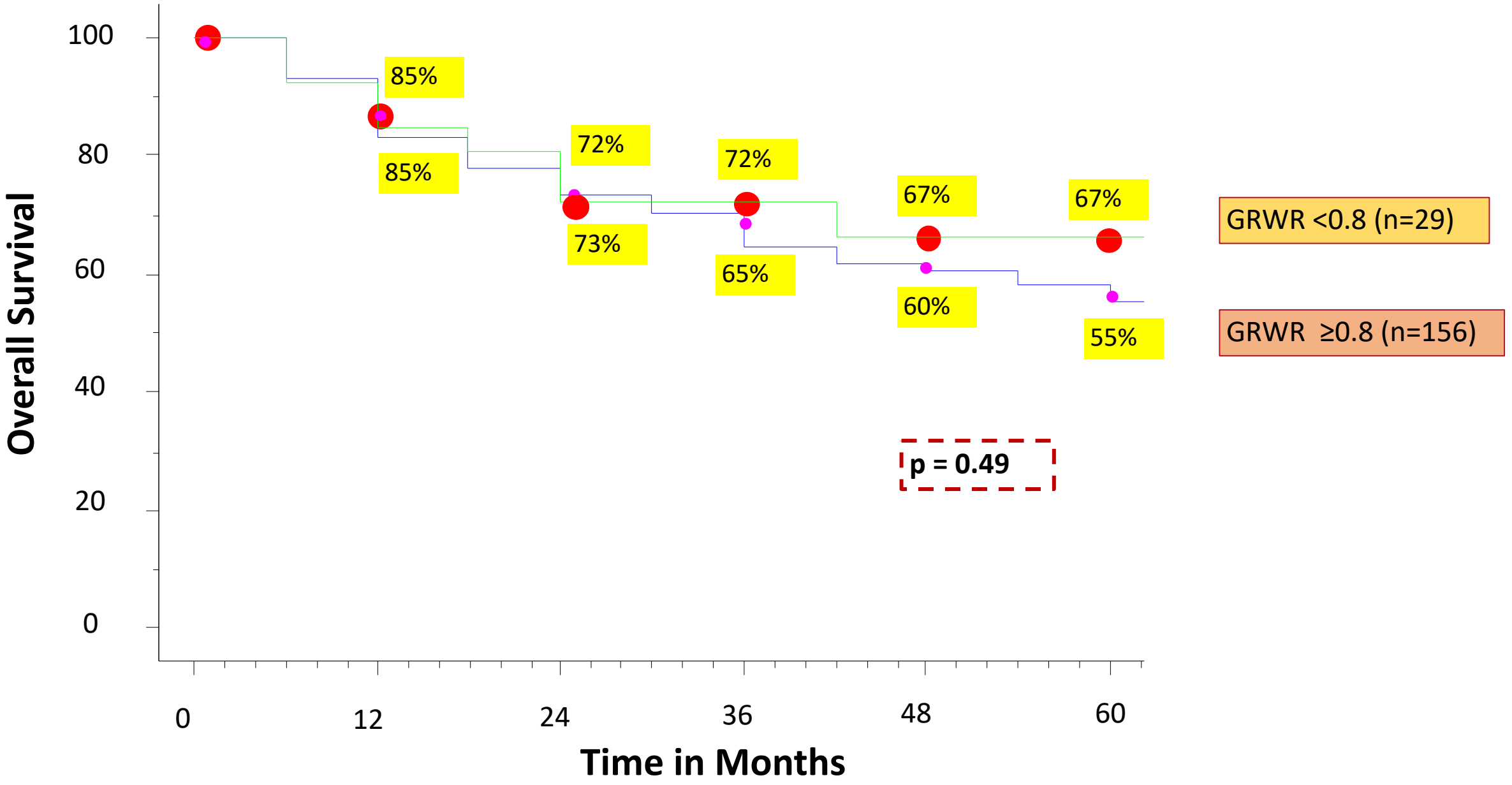
All HCC Patients



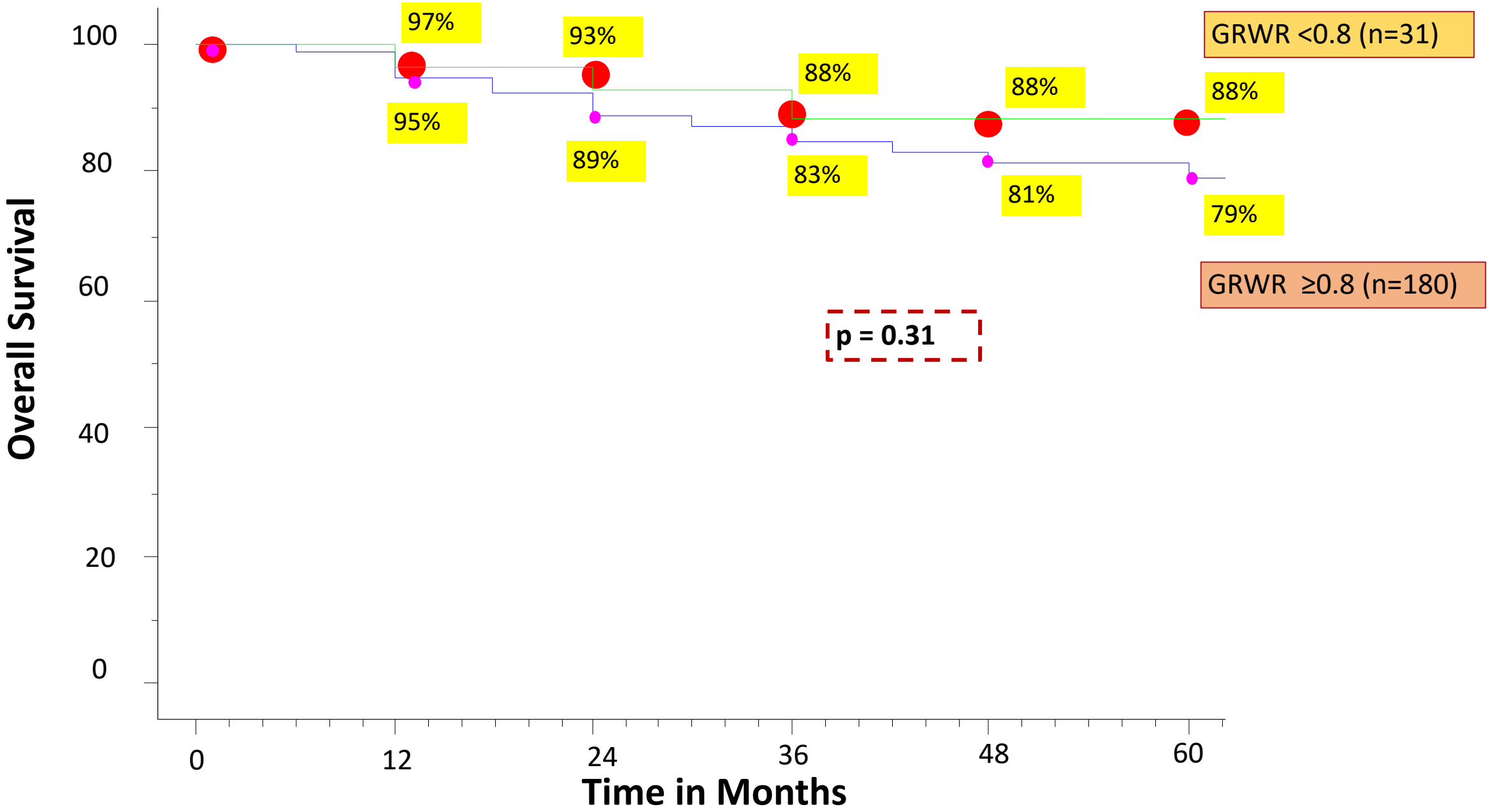
Patients with HCC within Milan criteria



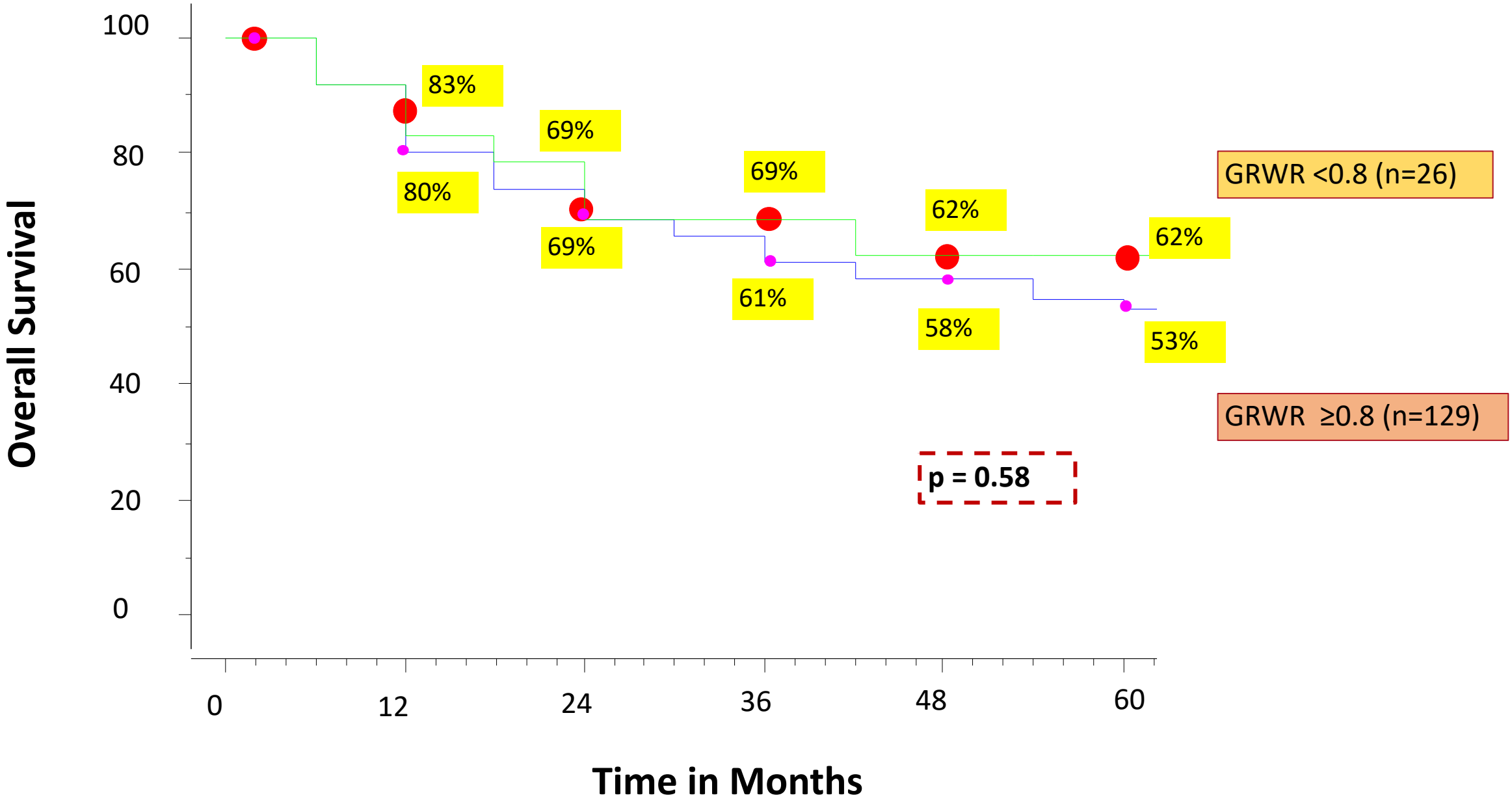
Patients with HCC beyond Milan criteria



Patients with HCC within UCSF criteria



Patients with HCC beyond UCSF criteria



Take home…

- No concrete evidence to say that low GRWR is associated with HCC recurrence post LT
- HCC recurrence depends more on tumour biology and not merely on a small for size liver
- Whether greater hepatic IR injury leads to early recurrence? – avoid it if possible – PIM plays a role