Liver Transplantation

In HCC , Is It Different ?

By :

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Does One Size Fit All .. ??


F I GB USA MEX
ONE SIZE
DOES NOT
FIT ALL
30°C
Von links bügeln/ Iron
repasser sur l'

Does Transplant To HCC patients

Resembles Transplant to Non HCC Patients .. ?

Liver transplantation (LT) is an ideal treatment for hepatocellular carcinoma (HCC) because it not only resects HCCs but it also replaces the underlying damaged liver with normal tissue.

Toshimi Kaido , 2016

What is the best treatment option for HCC ?

CURATIVE

Surgery:

Liver Transplantation

Liver Resection

Ablation:

Percutaneous ethanol injection (PEI)

Radiofrequency (RFA)

Palliative

Transarterial:

Chemoembolization

^{90}Y microspheres

Systemic Therapies:

Sorafenib

Clinical Trials

Why Liver transplantation for patients with HCC is recommended?

- Best Oncologic resection
- Treats Cirrhosis
- Restores normal portal pressure
- Restores normal hepatic function

What is different in :

Pre-transplant Assessment ?

Transplant Operation ?

Post-transplant management ?

Outcome ?

What is different in ：

Pre-transplant Assessment ?

1. Pre-transplant Selection

Need or not ..

??
Survival

Extrahepatic Spread ?

? HCC Recurrence

In Non HCC CLD Patients

Liver transplant indication is justified when :

Child classification > 7

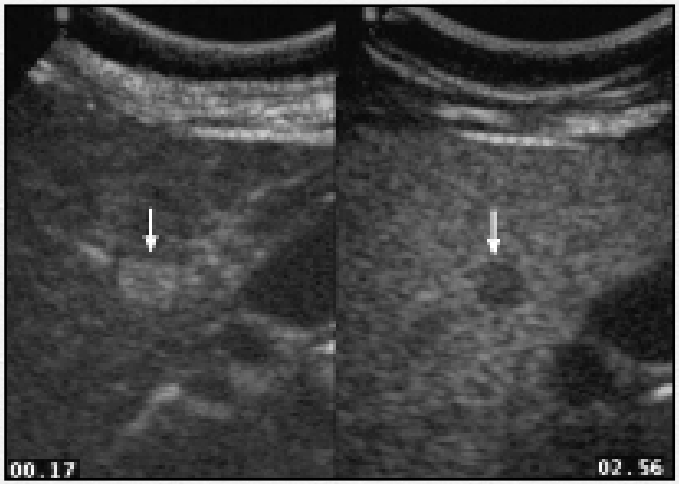
Meld Score ≥ 15

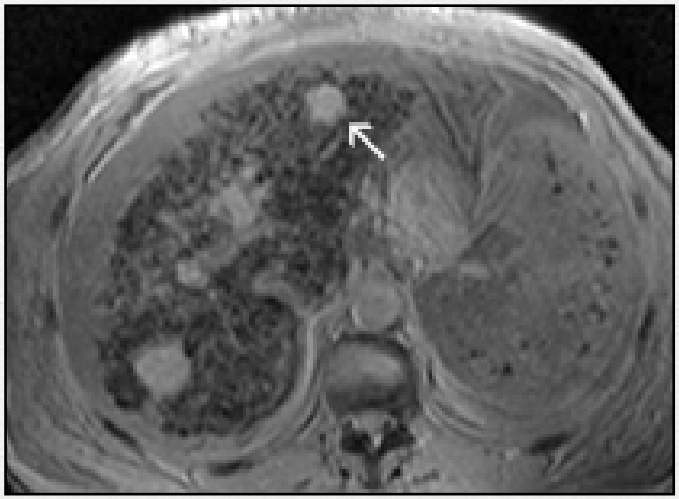
Additional MELD Points

Year	MELD Exception Points
2002	29 exception points for T2 lesions
	24 exception points for T1 lesions
2003	24 exception points for T2 lesions
	20 exception points for T1 lesions
2004	24 exception points for T2 lesions
	No exception points for T1 lesions
2005	22 exception points for T2 lesions
	No exception points for T1 lesions
2015	Natural MELD score at time of listing for T2 lesions
	28 exception points after 6 months
	Maximum of 34 MELD exception points

HCC: Diagnosis & Assessment

- Alpha-Feto Protein
- US & Doppler
- Triphasic CT scan
- Dynamic MRI
- PET CT
- Bone Scan
- CT Brain
- CT Chest
- Ascitic Fluid for malignant cells.
- Diagnostic Laparoscopy
- Liver Biopsy (Pros & Cons)





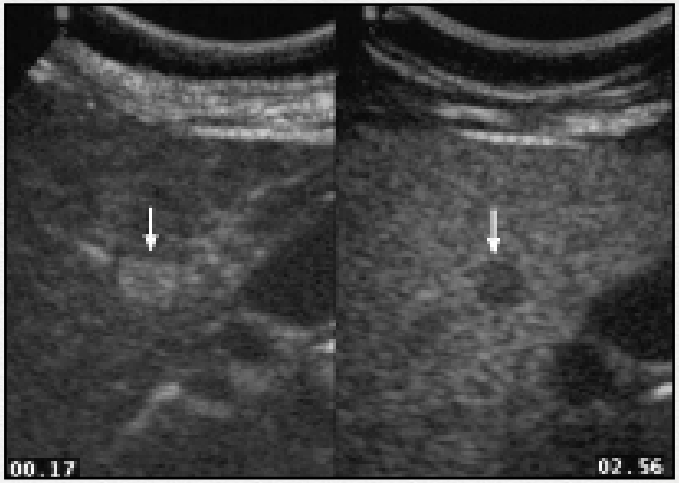
HCC: Diagnosis & Assessment in LTx

If the HFL is

≤ 2cm

Diagnosis of HCC must be confirmed by

2 contrast enhanced imaging modalities.

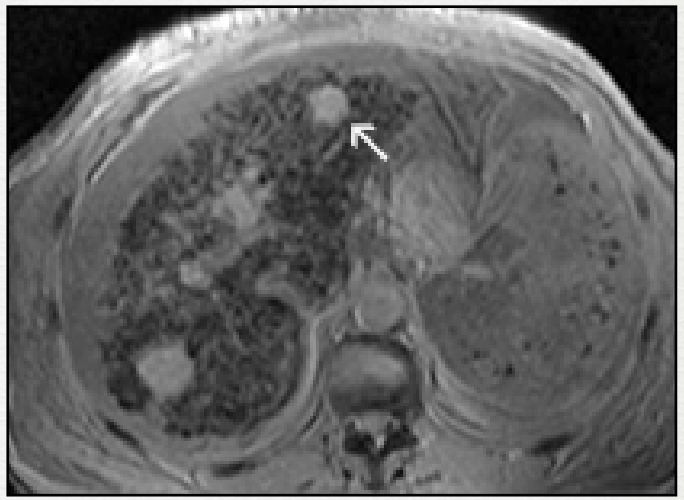


If the HFL is

> 2cm

Diagnosis of HCC must be by

1 contrast enhanced imaging modality.



Bundesaerzetkammer , German Medical Association, 2008

HCC: Diagnosis & Assessment

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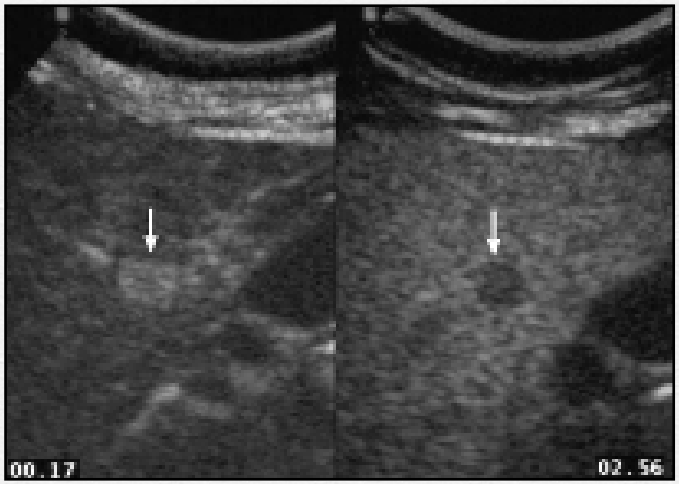
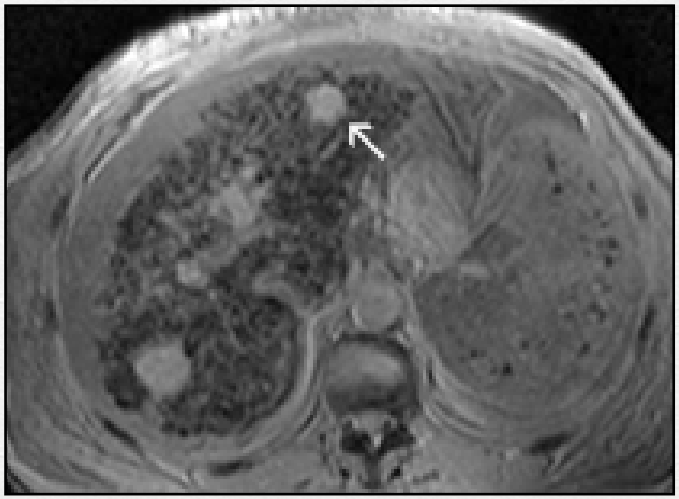
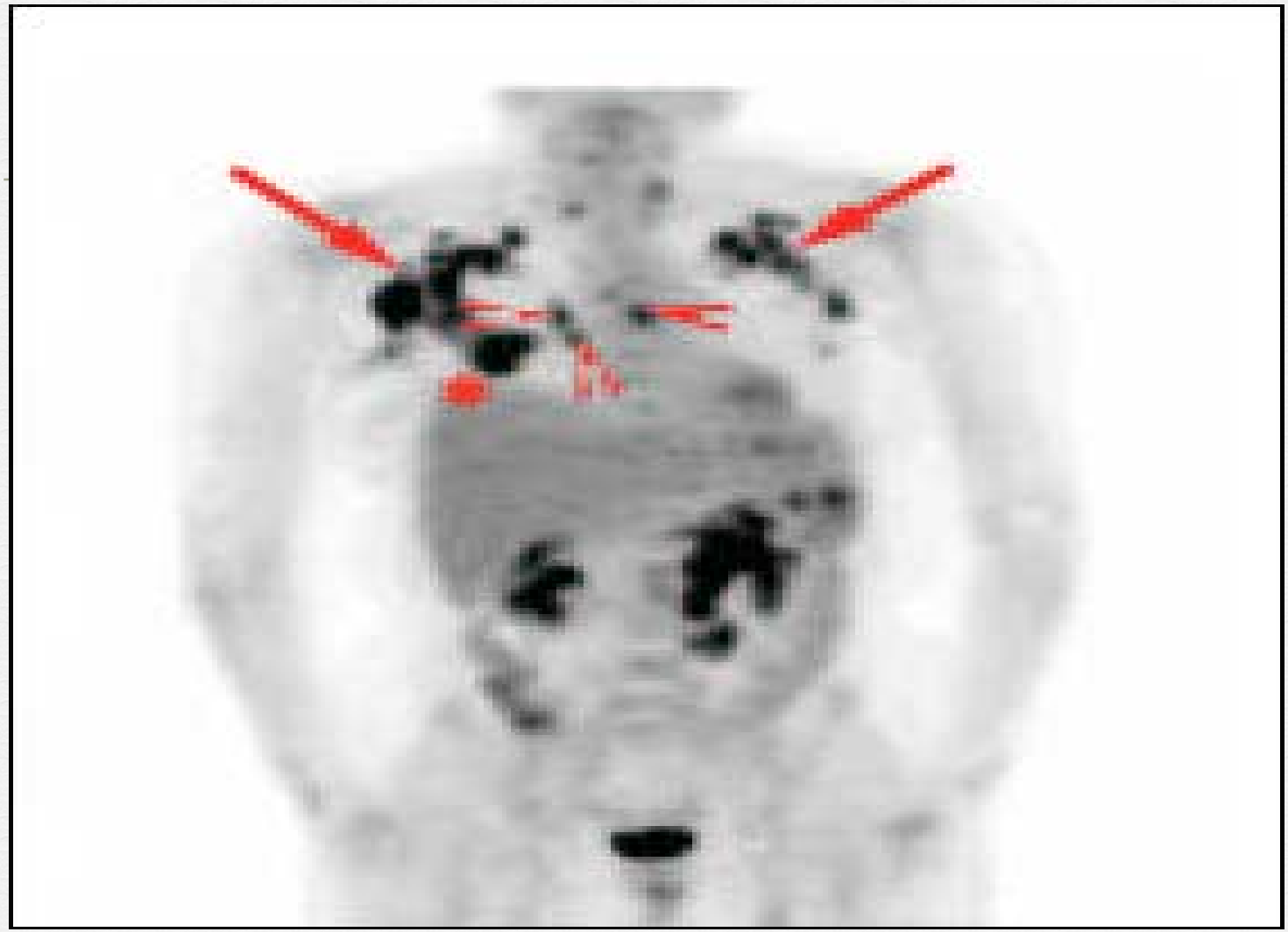


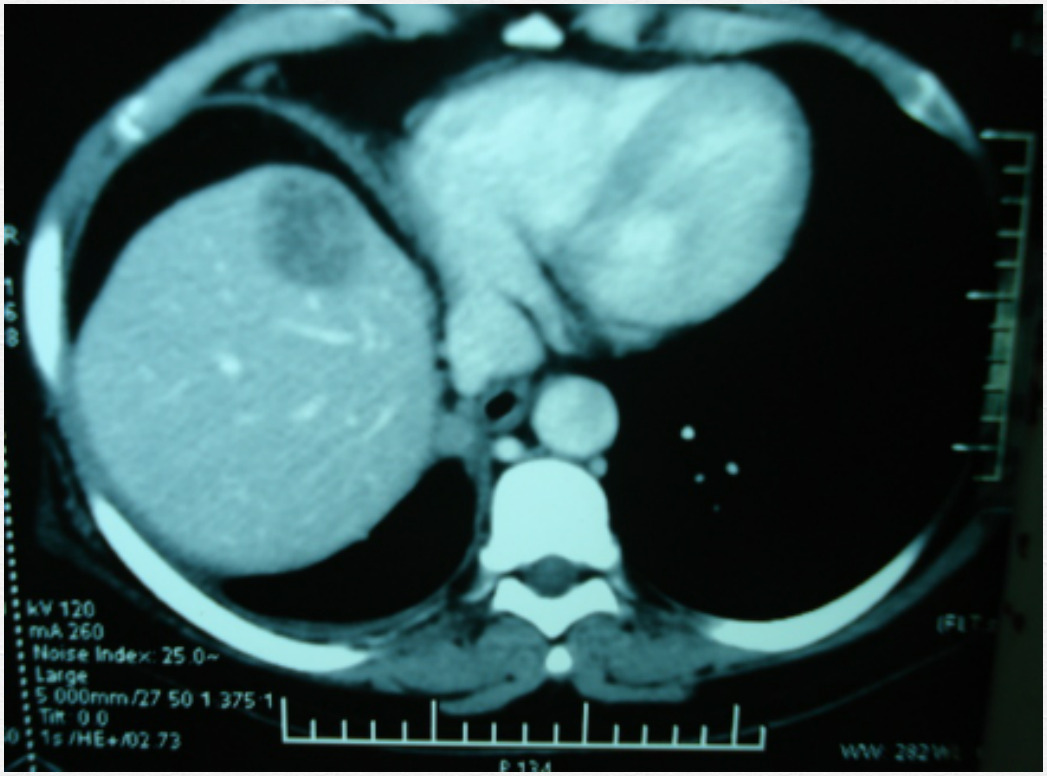


Extra-hepatic spread



PET scan showing abnormal Lymph Nodes

HCC Selection Criteria



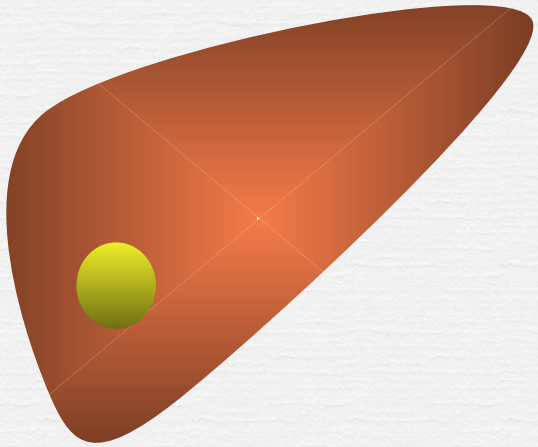
Milan's Criteria

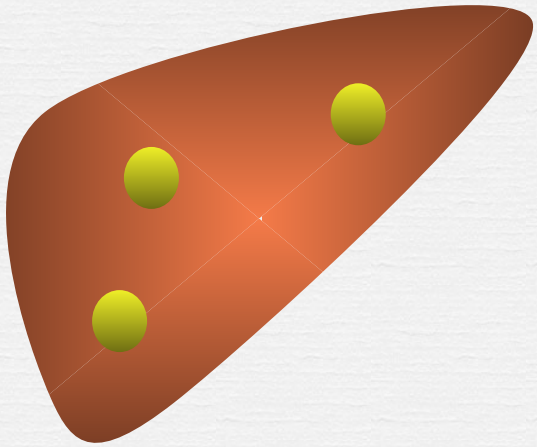
EASL Clinical Peactice Guidelines

LT for HCC patients meeting Milan criteria has an excellent outcome . An expansion of these criteria is acceptable if the recurrence-free survival is comparable . All new models should be compared to the Milan Model.

EASL Clinical Practice Guidelines

Milan's Criteria





Single tumor ≤ 5 cm

or

≤ 3 lesions, each lesion ≤ 3 cm

\+ No Macro-Vascular Invasion and No Extra-hepatic Spread

Mazzaferro et al, 1994

Selection Policy

Milan Criteria

Single tumor ≤5 cm in diameter

3 or fewer lesions, each one ≤3 cm in diameter.

No extra-hepatic or nodal disease and no evidence of vascular invasion.

▪**(93% 1-year survival and 85% 4-year survival)**

UCSF Criteria

Single tumor ≤6.5 cm in diameter

3 or fewer lesions, each one ≤4.5 cm in diameter, all diameters ≤ 8 cm .

▪No extra-hepatic or nodal disease and no evidence of vascular invasion.

▪**(93% 1-year survival and 85% 4-year survival)**

Liver Transplantation for HCC

Expanding the Milan Criteria

UCSF Criteria: (single lesion < 6.5 cm; ≤ 3 in number, < 4.5 cm; combined diameter < 8cm)

	Survival	
Milan Criteria	94%	88%
UCSF Criteria	90%	90%

Yao et al. Hepatology 2005, 197A

5-5 rule

Sugawara et al. reported that 72 HCC patients within their 5–5 rule (up to five nodules with a maximum diameter of 5 cm) achieved a 3-year recurrence- free survival rate of 94% after LDLT.

Sugawara Y, 2007

Up-to-7 Criteria

Mazzaferro et al. proposed more liberal criteria than the Milan criteria: the “up-to-7 criteria” (HCC with seven as the sum of the size of the largest tumor in cm and the number of tumors).

Mazzaferro V, 2009

Total Volume Criteria

Toso et al. **proposed new selection criteria by combining total tumor volume ≤115 cm3 and α-fetoprotein (AFP) ≤ 400 ng/ml.**

Toso C , 2009 , Takada Y , 2009

Kyoto Criteria

Tumor number and

tumor size based on the

findings of pretransplant

imaging and tumor

markers; tumor number

≤10, maximal diameter of each tumor ≤5 cm; and serum des-gamma-carboxy prothrombin (DCP)levels ≤

400 mAU/ml (5-year overall survival rate and the recurrence rate were 82%

and 7%, respectively).

Takada et al , 2007
Kaido et al. , 2013

Metro-ticket Model

To have a **70 %** chance Of HCC specific **survival 5 years** after LTx :

If AFP < 200 → Sum of No. and Size should not exceed 7cm

If AFP = 200-400 → Sum of No. and Size should not exceed 5 cm

If AFP = 400-1000 → Sum of No. and Size should not exceed 4 cm

Mazzafero V ,et al. Gastroenterology . 2018

The Target

The Kyoto group set :

Target Outcomes

as

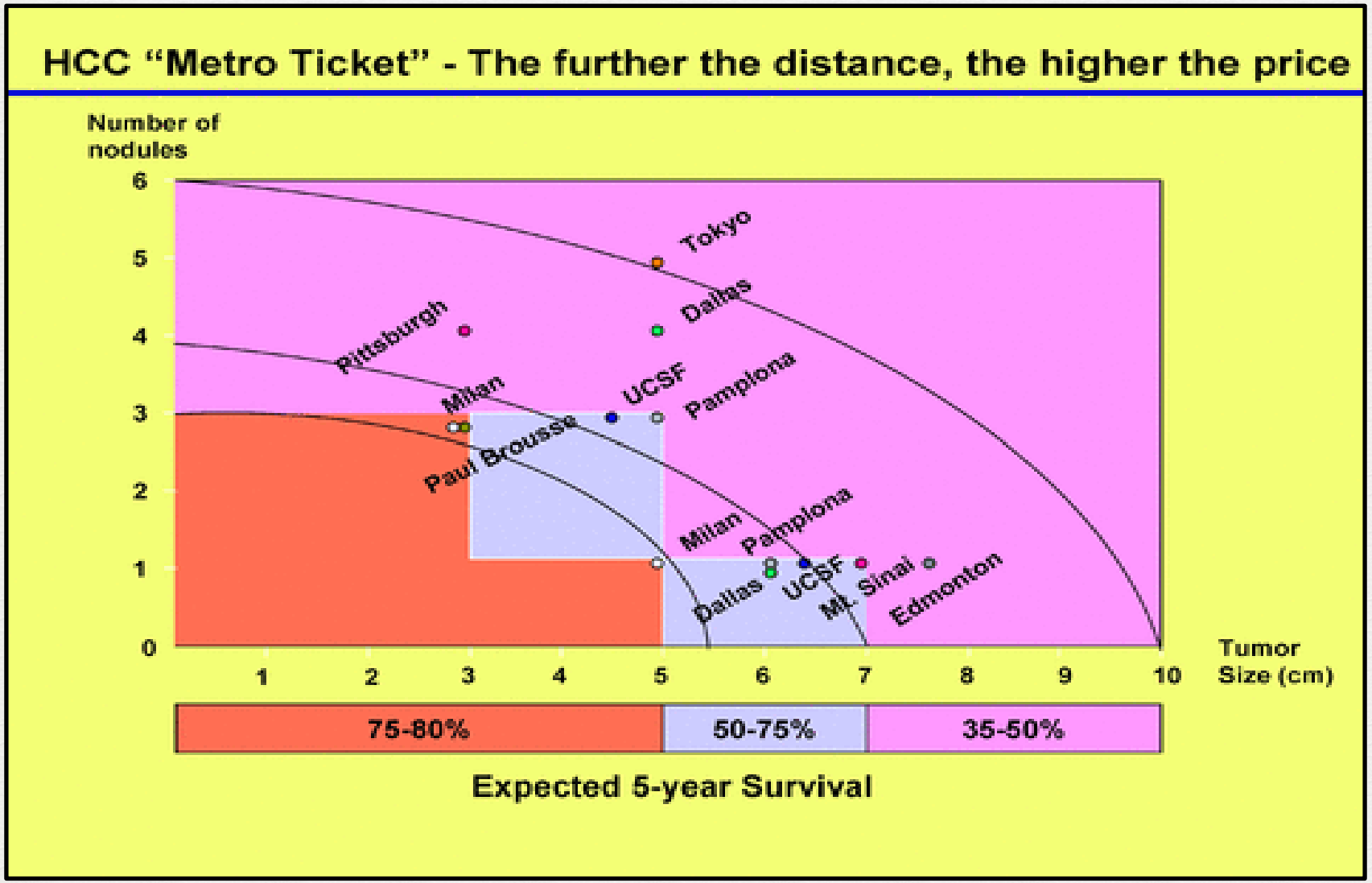
5-year survival rate ≥ 80% and

5-year recurrence rate ≤ 10%.

Toshimi K. ,2016

Beyond Milan Criteria – HCC “Metro Ticket”

Beyond Milan Criteria – HCC "Metro Ticket"



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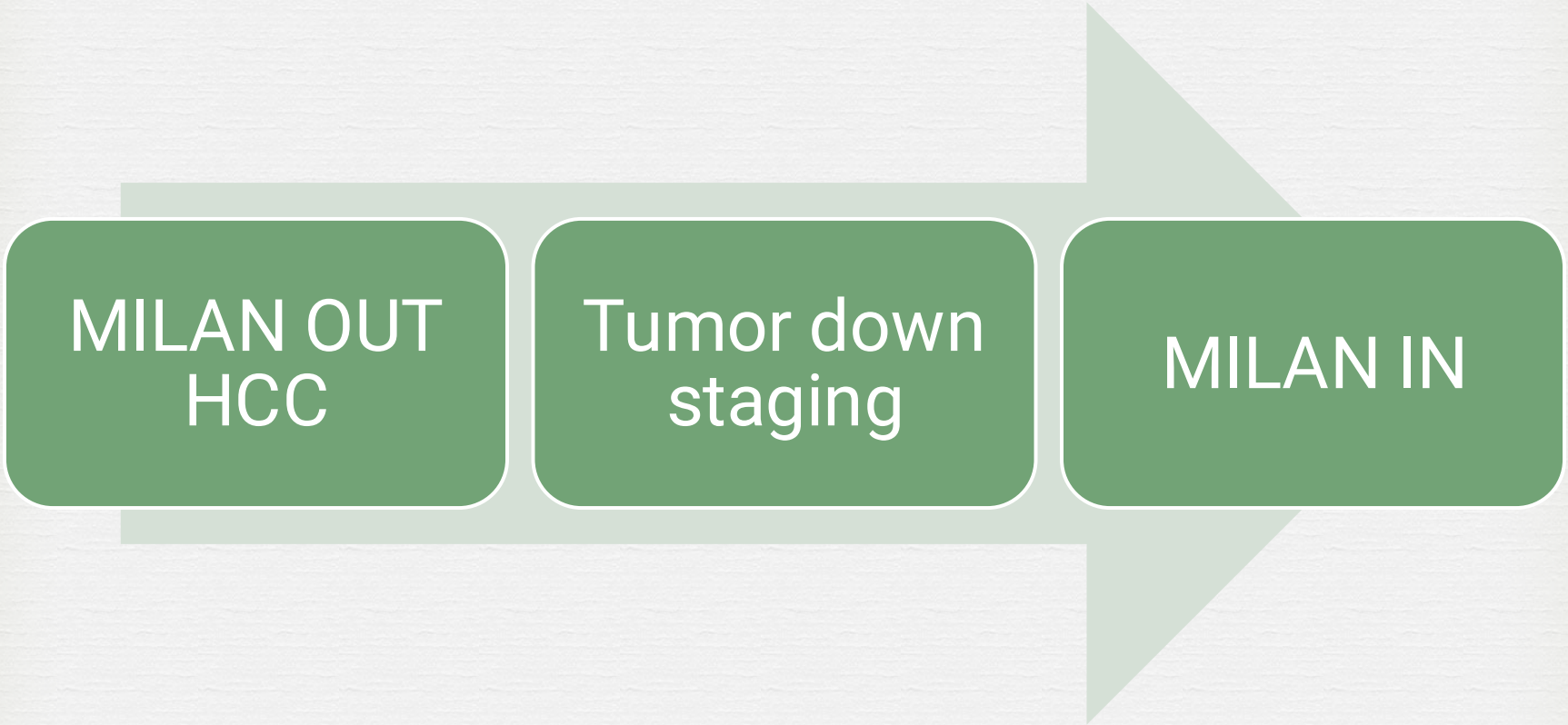
EASL Clinical Practice Guidelines , 2016

Down-staging …

Down-staging



Downstaging

AASLD 2018 : Down-staging of T3 (beyond Milan)

patients compared with no therapy (in T2 patients)

before liver transplantation was associated with similar

overall and recurrence-free survival.

Down-Staging of HCC prior to LTx

A Prospective Study on Downstaging of Hepatocellular Carcinoma prior to Liver Transplantation

Laparoscopic/open RFA only*
Laparoscopic RFA + TACE†
TACE only
TACE + percutaneous ablation
TACE + PEI
TACE + percutaneous RFA
Resection‡

In conclusion, our encouraging initial results support tumor downstaging as a potentially viable treatment option among carefully selected patients with HCC beyond conventional criteria for OLT.[redacted]

Yao et al *Liver Transplantation, Vol 11, No 12 (December), 2005: pp 1505-1514*

Importance of Interventional Oncology in Bridging/Downstaging of Patients with Hepatocellular Carcinoma to Liver Transplantation

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University of Wisconsin
School of Medicine and Public Health

Background Information

- ***Interventional oncology (IO)*** treatments are vital in the management of patients with hepatocellular carcinoma (HCC), including in bridging/ downstaging patients to liver transplantation.
- According to the updated ***American Association for the Study of Liver Disease*** (AASLD) guidelines, HCC patients ***beyond Milan criteria should be considered for transplantation after successful downstaging*** to Milan criteria.
- ***AASLD*** also suggests ***bridging therapy*** for patients listed for liver transplantation ***within Milan criteria*** to ***decrease progression*** of HCC and ***dropout*** from the waiting list.

Purpose: This study aims to characterize the ***role of IO therapies*** in ***bridging/ downstaging*** of HCC patients to liver transplantation in a single center setting based on the decisions of multidisciplinary tumor board on treatment allocations.

Materials and Methods

- This IRB approved study was compliant with HIPAA guidelines.
- A total of ***516 patients*** who were discussed by the primary ***liver tumor board*** of our institution from ***2012 to 2017*** were reviewed retrospectively.
- Among them, ***288 patients (56%)*** with a definitive ***diagnosis of HCC*** were identified.
- Patient ***demographics***, ***tumor characteristics***, and ***liver function*** at the time of the initial tumor board were recorded to calculate Barcelona Clinic Liver Cancer (BCLC) stage.
- After reviewing patients' medical records, the ***patients with prior treatments or inadequate medical information*** were ***excluded***, resulting in ***176 patients*** with HCC that were included in the study.
- Descriptive statistics were used for analysis.

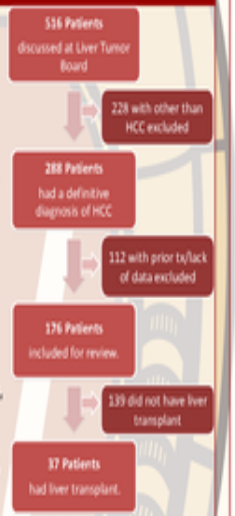


Figure 1: A schematic representation of patient selection.

Results

Figure 2: Treatment paradigm suggested by Sangro et al (adapted).

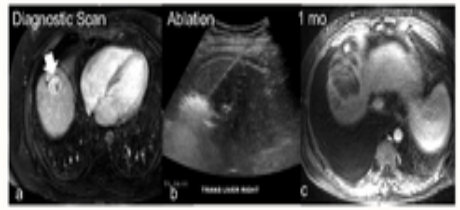


Figure 4a-c: 63 yo M with HCV cirrhosis (Child-Pugh B), a 3.8 cm HCC in segment 8 (arrow) and 1.0 cm HCC in segment 6 (not shown). He had BCLC stage B (intermediate) disease and underwent ultrasound-guided microwave ablation of both tumors. Fig. 4b shows the ultrasound image during the ablation. Fig. 4c shows the ablation zone on MRI at 1 month. Approximately 10 months after his ablation procedure, patient underwent liver transplantation due to his declining liver function.

- Of 176 patients with a definitive diagnosis of HCC, ***37 patients*** were found to ***undergo liver transplantation***.
- Of 37 patients, ***2*** were ***BCLC stage 0***, ***24*** were ***stage A***, ***2*** were ***stage B***, ***7*** were ***stage C***, and ***2*** were ***stage D***.

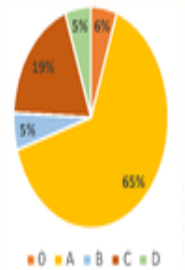


Figure 3: Percent distribution of BCLC stages of 37 liver transplant patients.

- Of all transplantations, ***only two*** were ***first-line treatments*** with no other prior therapies, while ***35 patients*** were treated with at least one type of ***IO therapy as a bridge or downstaging to their transplantation***.
- Of the 35 patients, ***26*** underwent ***one treatment*** prior to transplant while ***9*** patients had ***more than one*** treatment.
- For bridging/downstaging of 35 patients, a total of ***45 procedures*** were performed with a **median of one** (range, 1-5) procedure per person.
- ***Among 45*** procedures, ***ablative therapies*** were the ***most common*** (32/45, 71.1%) followed by ***TACE*** (8/45, 17.8%), ***radioembolization*** (4/45, 8.9%), and ***resection*** (1/45, 2.2%).

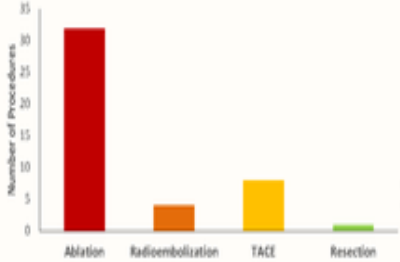


Figure 5: Distribution of 45 procedures.

- ***Median time to liver transplantation*** was ***11.3 months*** (0.6-28.4 mo).

Conclusion

- The **majority** of patients with **HCC** who underwent **liver transplantation** at our institution were **bridged or downstaged** with **IO therapies** including:
  - ***ablation***,
  - ***chemoembolization*** and
  - ***radioembolization***.
- **IO therapies** are vital in **increasing** the number of patients that can receive a transplant or to **maintain** their transplant candidacy.

References

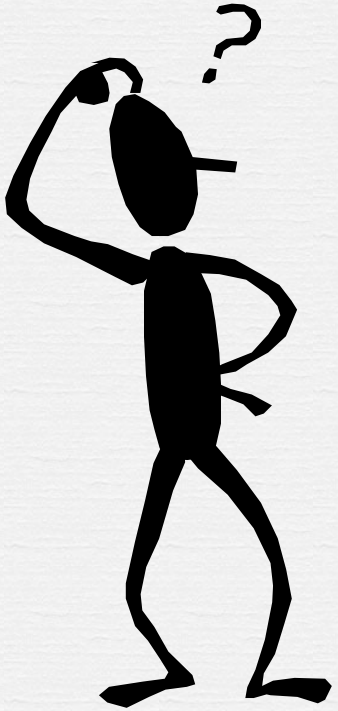
Bruix, J., M. Sherman and D. American Association for the Study of Liver (2011). "Management of hepatocellular carcinoma: an update." Hepatology **53**(3): 1020-1022.

Forner A, Llovet JM and Bruix J. (2012). "Hepatocellular carcinoma." Lancet **379**(9822): 1245-1255.

Heimbach JK, Kulik LM, Finn RS et al. (2017) "AASLD guidelines for the treatment of hepatocellular carcinoma." Hepatology 67(1):358-380.

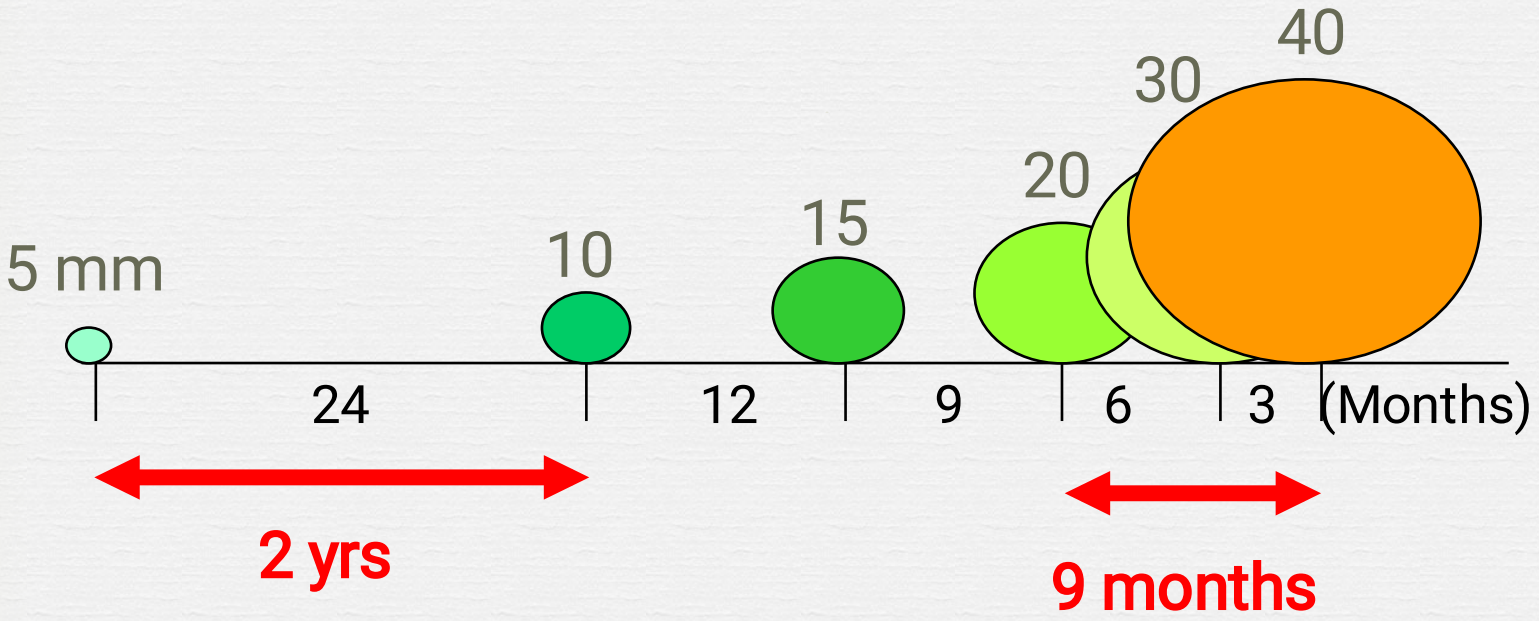
Sangro B, Salem R, Kennedy A, Coldwell D, Wasan H.(2011) Radioembolization for Hepatocellular Carcinoma: Review of Evidence and Treatment Recommendations. Am J Clin Oncol. 34(4):422-31

Who needs down-staging ?



Management While on the Waiting List

Tumor Doubling Time (TDT)



(From J Fung with permission)

AASLD 2018

Management While on the Waiting List

Down staging is indicated in :

* Patients within Milan Criteria

(to decrease disease progression)

* Patients Beyond Milan Criteria

(to reach Milan criteria)

Not recommend one form down staging procedure over another .

Down-staging

Ablative Therapies

- Percutaneous ethanol injection (PEI)
- Radiofrequency ablation (RFA)
- Microwave ablation (MWA)
- Cryoablation

Intra-arterial Therapies

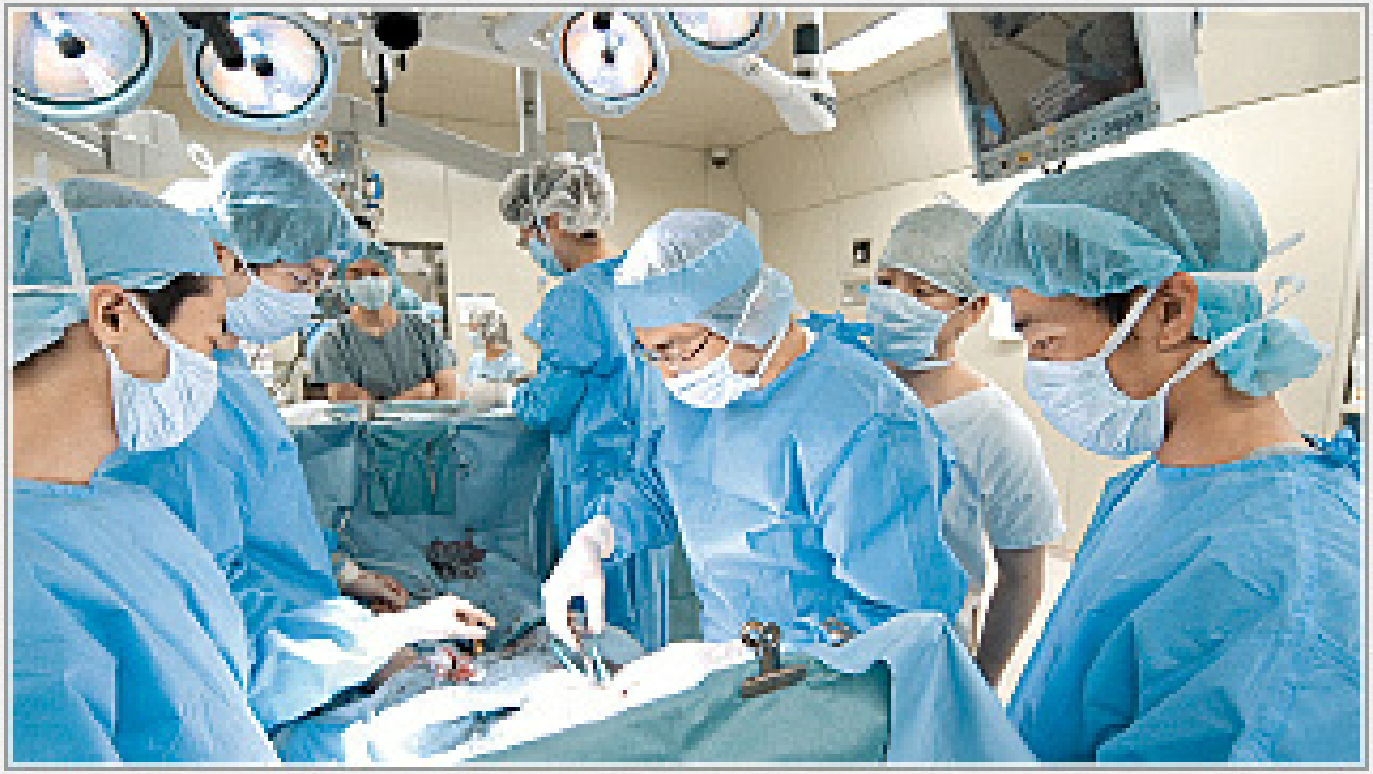
- Transarterial Chemoembolization
  - Conventional
  - Drug-Eluting Beads (DEB)
- Radioembolization

What is different in :

Pre-transplant Assessment ?

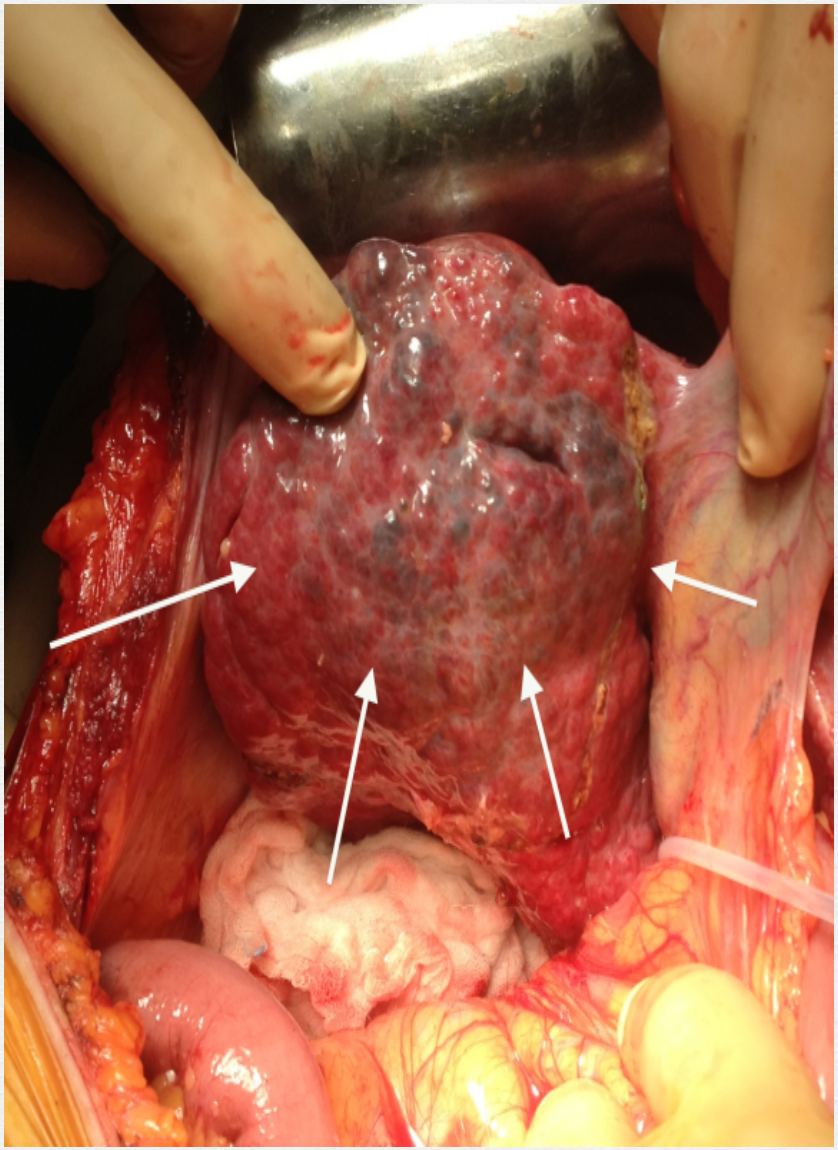
Transplant Operation ?

2. Transplant Operation ?

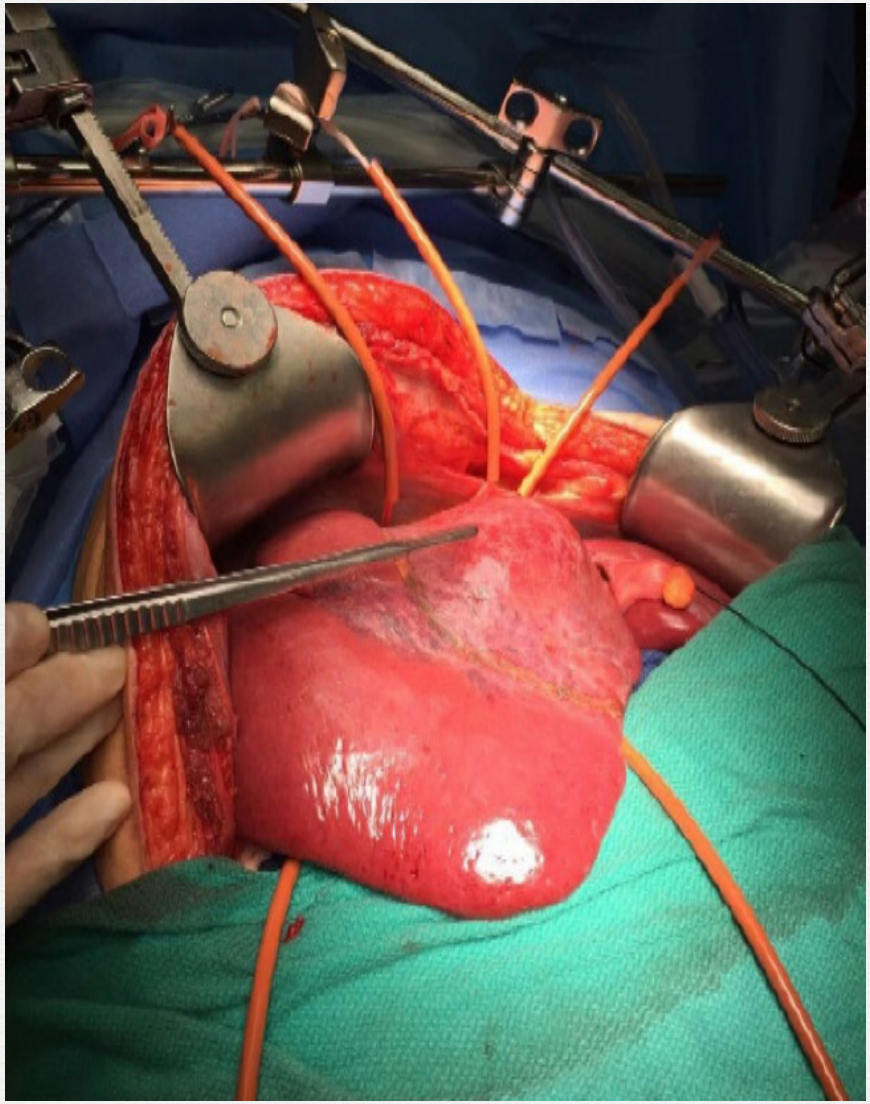


2. Transplant Operation ?

- Recipient Exploration First
- Non touch technique
- Hilum first
- Ligation of all Short HVs

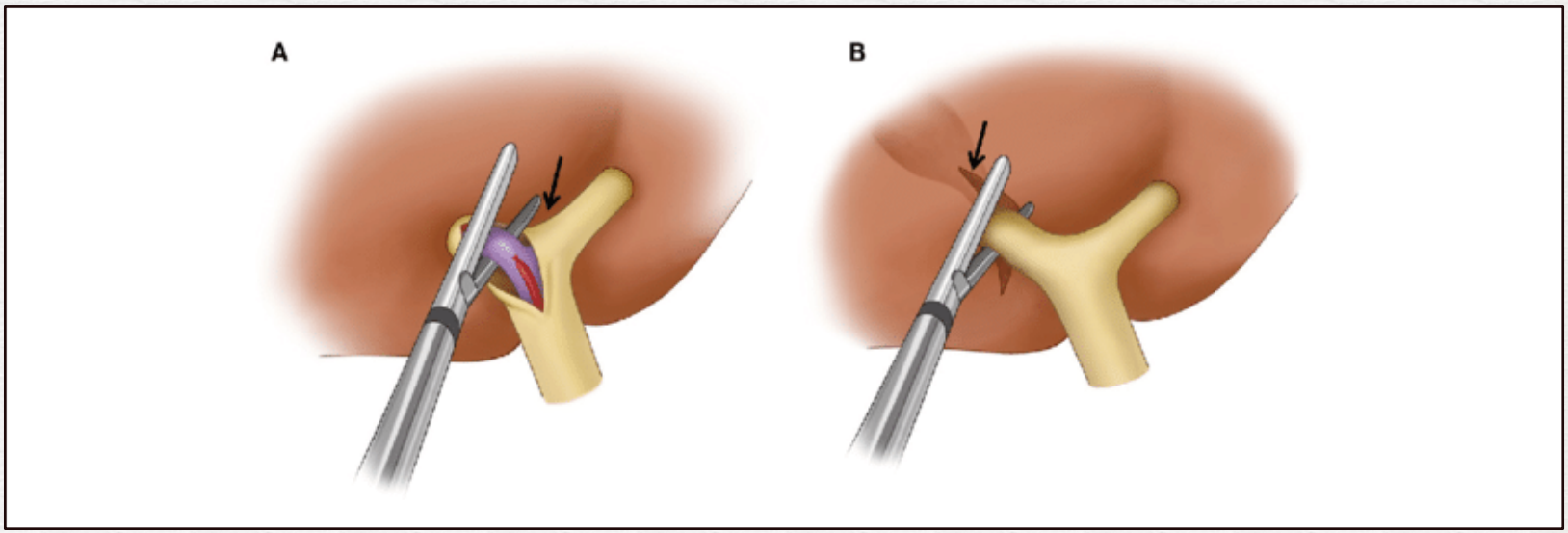


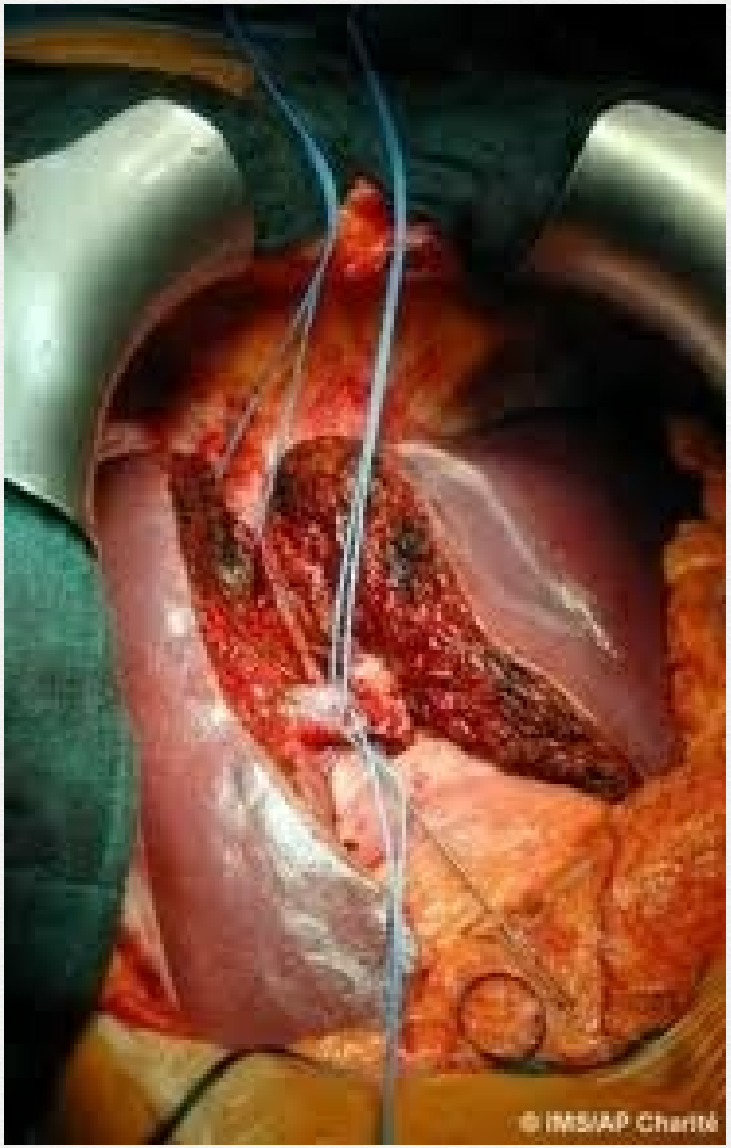
1. Recipient Expolration First



2. Non Touch Techniques

3. Hilum Dissection First





4. Ligation of Venous Outflow to IVC

What is different in :

Pre-transplant Assessment ?

Transplant Operation ?

Post-transplant management ?

3. Post Transplant Management

Recurrence detection

How to avoid recurrence

Immuno-suppression

Treat HCV or not ..??

3. Post Transplant Management

* Follow up (by CT every 6 months)

* Immunosuppression Protocol

* HCV treatment

Immunosuppression Protocol

Post-transplant Immunosupression Protocol

Adjustment of immunosuppression in these patients

is necessary to minimize the tumor promoting effect .

Manhal I et al , 2018

1) Calcineurine Inhibitors

Adjustment of immunosuppression could include minimizing CNI doses while adding MMF or mTOR inhibitors to maintain sufficient immunosuppression or entirely replacing CNI with mTOR inhibitors

Manhal I et al , 2018

2) Antimetabolites

In fact, patients treated with MMF experienced a longer malignancy free survival compared with those not on MMF (p=0.02). Whether the beneficial effects of MMF is the drug itself or simply the effect of lower CNI dosing.

Robson R et al, Am J Transplant. 2005

3) Mammalian Target Of Rapamycin (mTOR) inhibitors

The risk for malignancy remained reduced under mTOR inhibitors (alone or combined with CNI, RR 0.43, p=0.004).

Ying T et al , Am J Transplant. 2018

HCV treatment in transplant recipient with HCV/ HCC

HCV treatment in transplant recipient with HCV/ HCC

Treat or not ..?

Timing Before or After.. ??

Dilemma of DAAs and HCC.. ??

* The ongoing debate around DAA therapy and HCC has generated much discussion.

* LT for HCC remains a curative option and HCC-LT outcomes should not be compromised by a delay in initiation of DAA therapy.

Friedrich Foerster et al. , Journal of Hepatology 2018

HCV treatment in transplant recipient with HCV/ HCC

EASL 2018 Recommendations

EASL 2018 Recommendations

Patients with HCC should be treated before or after liver transplantation according to the general recommendations in patients without HCC

EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol (2018)

What is different in :

Pre-transplant Assessment ?

Transplant Operation ?

Post-transplant management ?

Outcome ?

Outcome . ?

LTx for HCC **Vs** LTx for Non HCC

Survival compared to Non HCC transplantation

Overall survival in carefully selected HCC is similar to or only slightly worse than nonmalignant causes.

- United Network for Organ Sharing (UNOS) :

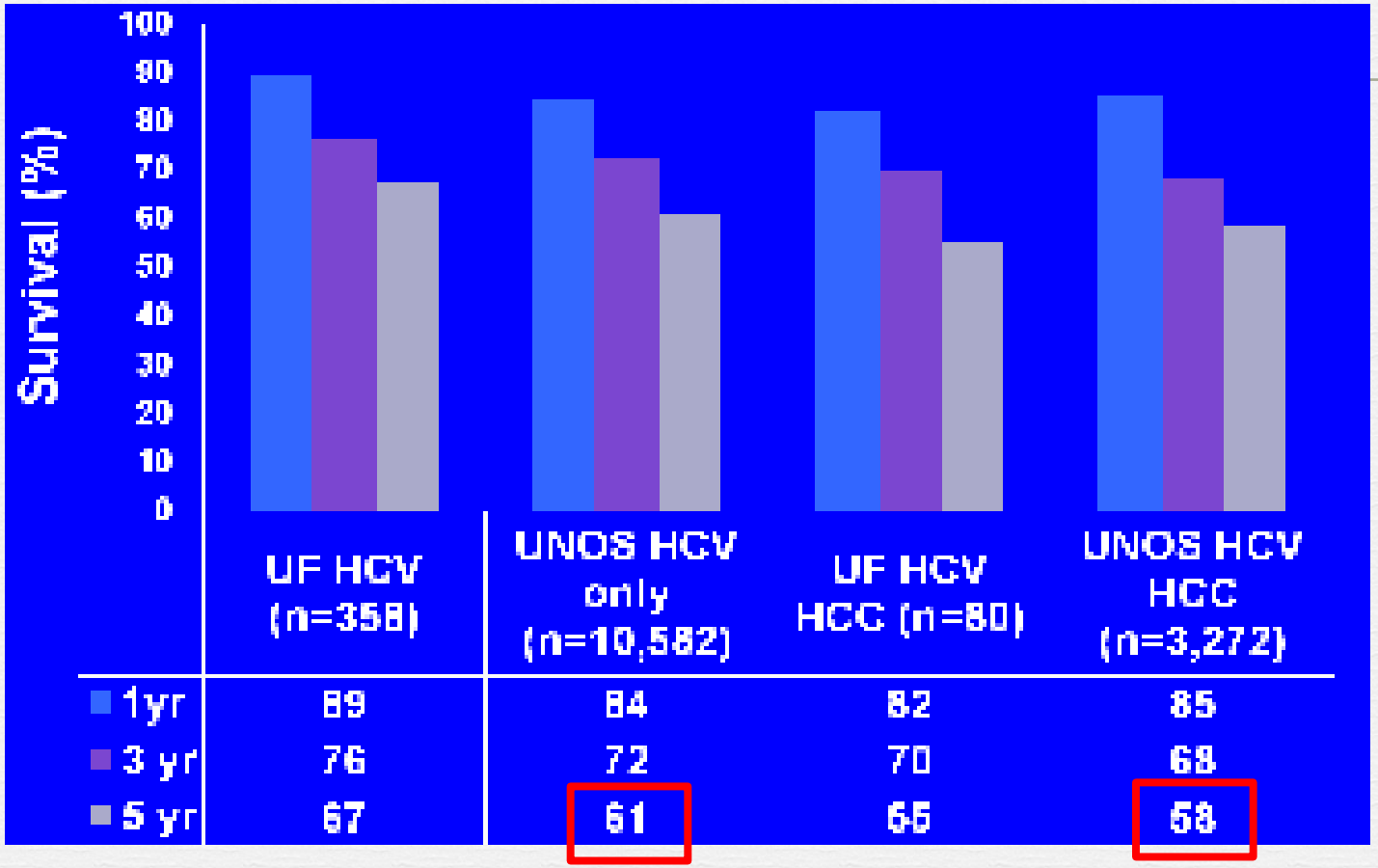
  34,324 liver transplants performed between 1987 and 2001, 985 of which were done for HCC

Survival Non HCC	Waiting time	Survival %	Period
71	37	25%	1987 to 1991
71	103	47%	1992 to 1995
71	215	61%	1996 to 2001

Survival was improved due to:

- Improved patient selection.
- Improved post-transplant care.

Patient Survival of HCV LT recipients with HCC and without HCC



Cabrera R et al. American Journal of Clinical Oncology. 2012 Aug;35(4):345-50.

Conclusion

&

Home

Messages

Conclusion & Home Messages

* LTx is an ideal treatment for HCC because it not only resects HCCs but it also treats cirrhosis and its complications.

* The Milan criteria remain the corner stone to select candidates for LDLT to achieve optimal long-term results (regarding survival and recurrence).

*All new models of expansion should be compared to the Milan Model (Metro-ticket).

* Down-staging acts as a " Bridge " to give more chance to HCC patients.

* The specific precautions in the surgical techniques in LDLT surgery must be assured to decrease recurrence rate (Non touch technique, Hilum first ....).

Conclusion & Home Messages

* Immunosuppression protocol after Ltx for HCC (CNIs to be reduced & m TORs may be of benefit as anti-carcinogenic to decrease recurrence.

* Treatment of HCV in HCV/ HCC liver transplant recipient is the same like Non HCC recipients.

* The dilemma DAAs & HCC should not led the transplant physician to delay HCV treatment impairing the outcome of LTx.

* The global outcome of LTx in HCC in nearly similar to non-malignant causes after good selection.

… And now .. Again … !

… Does One Size Fit All .. ??

Thank You ..