Liver Transplantation for Patients with Hepatocellular Cancer

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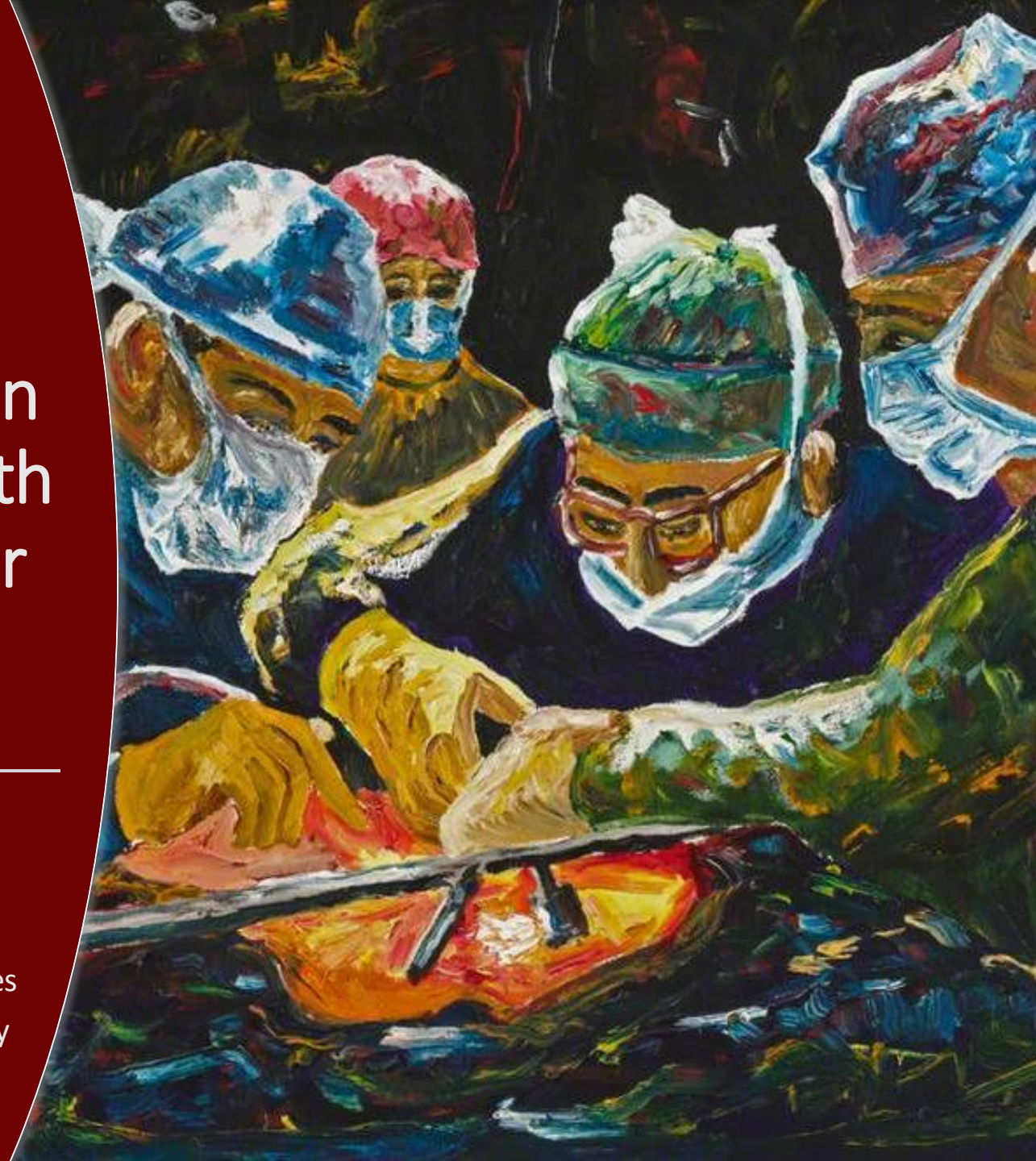
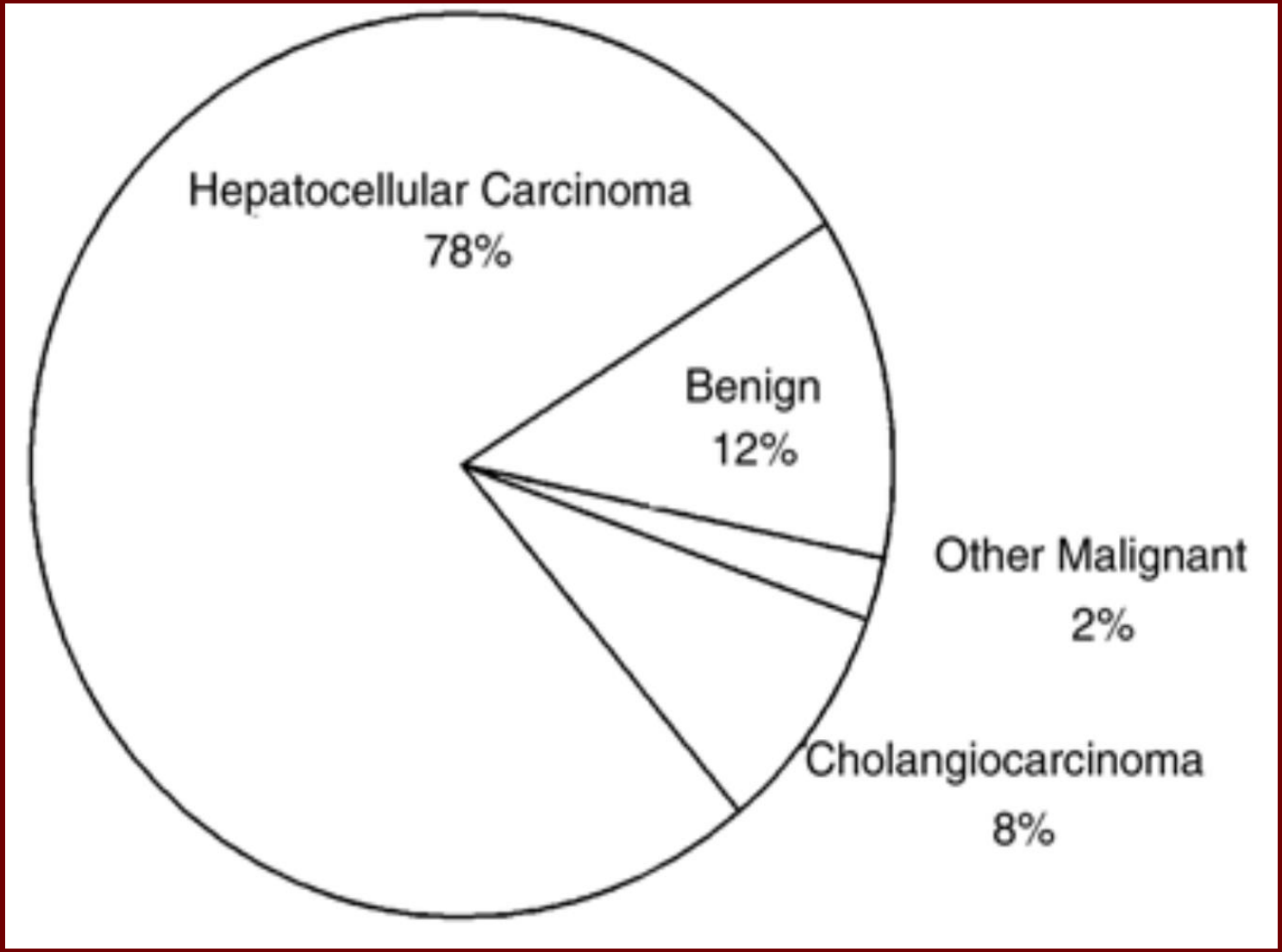
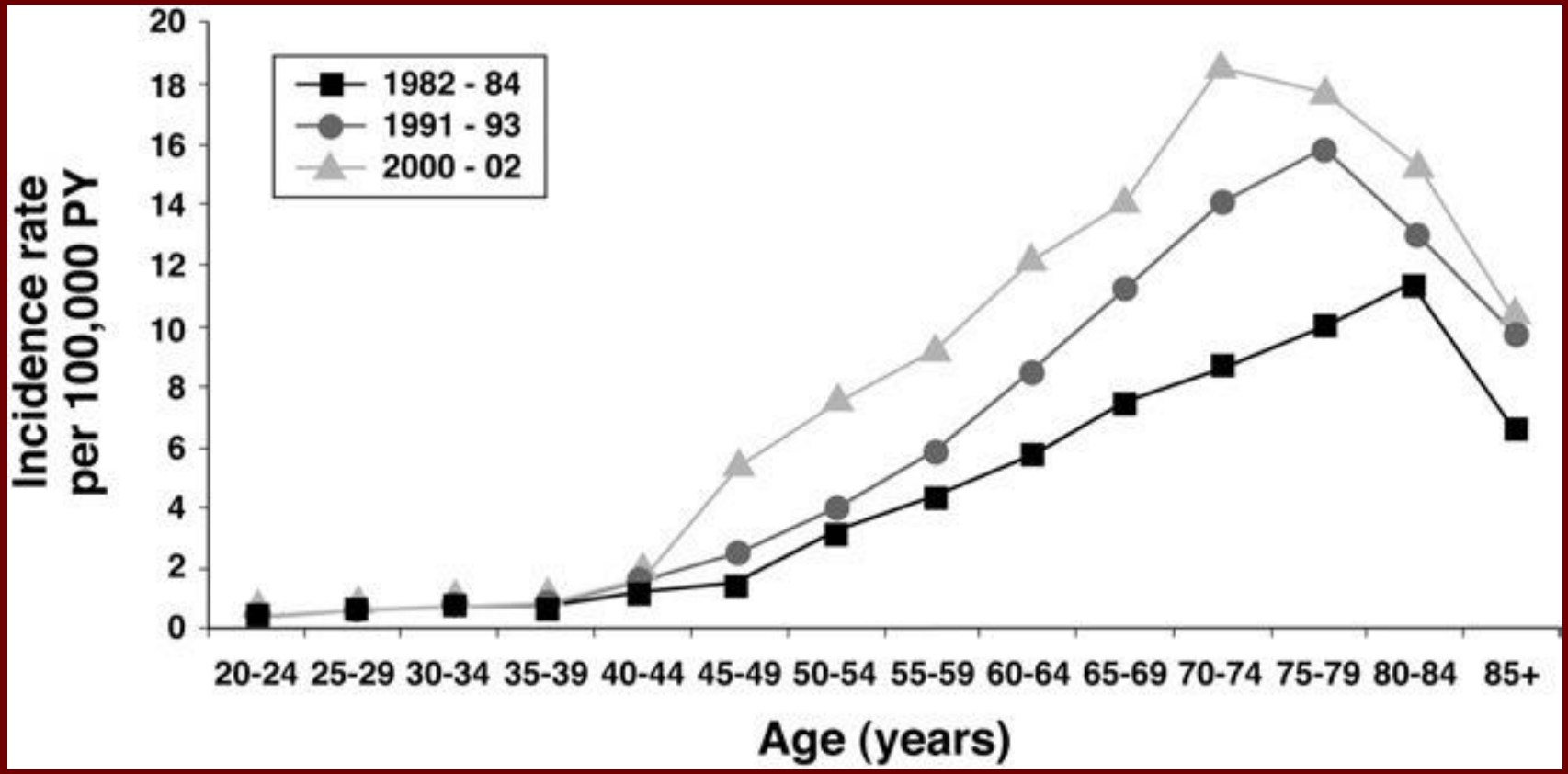




Modern Pathology (2007) **20,** S49–S60. doi:10.1038/modpathol.3800682

Incidence

- Overall, sixth most diagnosed malignancy worldwide & fourth cause of cancer mortality worldwide.
- Highly variable rates (East Asia / Sub-Saharan Africa).
- In US, incidence of 6/100,000 (circa 2010).
- 250 thousand to 1 million deaths annually – second leading cause of CA related death in men, 6th in women.



Expert Rev Gastroenterol Hepatol. 2015 Jun;9(6):765-79.
Gastroenterology. 2007 Jun;132(7):2557-76.

Risk factors

- Age
- Male gender
- Chronic liver disease (viral, alcohol, and metabolic)
- DM
- Tobacco
- Obesity
- Environmental (Aflatoxin B exposure).

Surveillance

- Identify at risk population + screening
- American Association of Liver Diseases algorithm (AASLD) “at risk”.

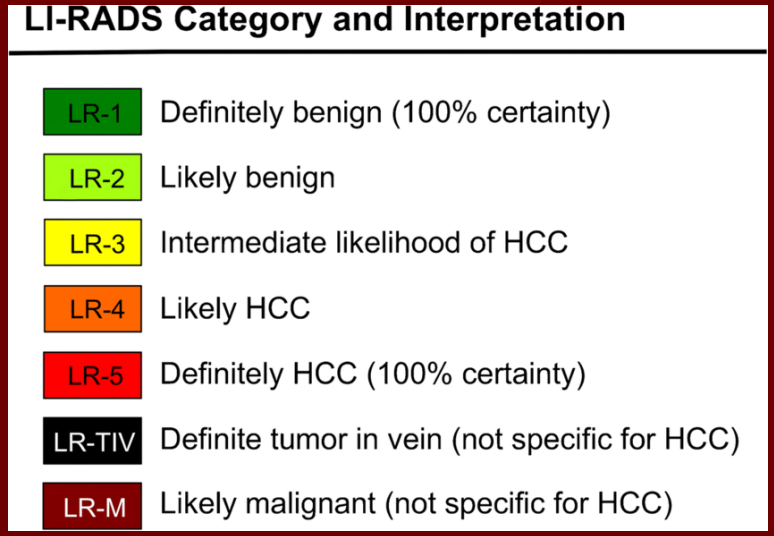
  Cohort with an annual incidence of > 1.5-2%.

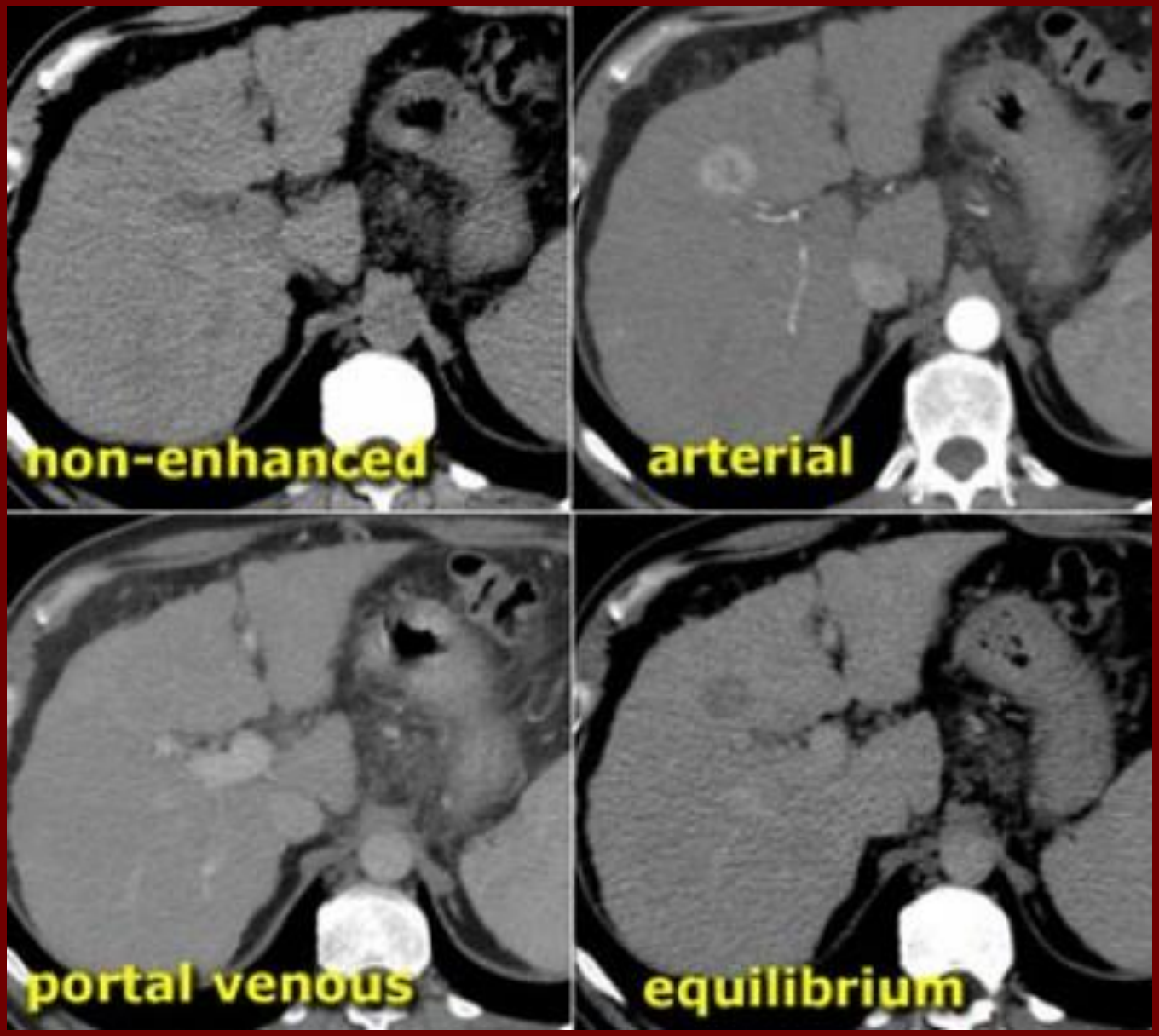
- Other criteria include
  - Chronic hepatitis with or without cirrhosis
  - Cirrhosis of any etiology
  - Anyone actively listed for a liver transplant.

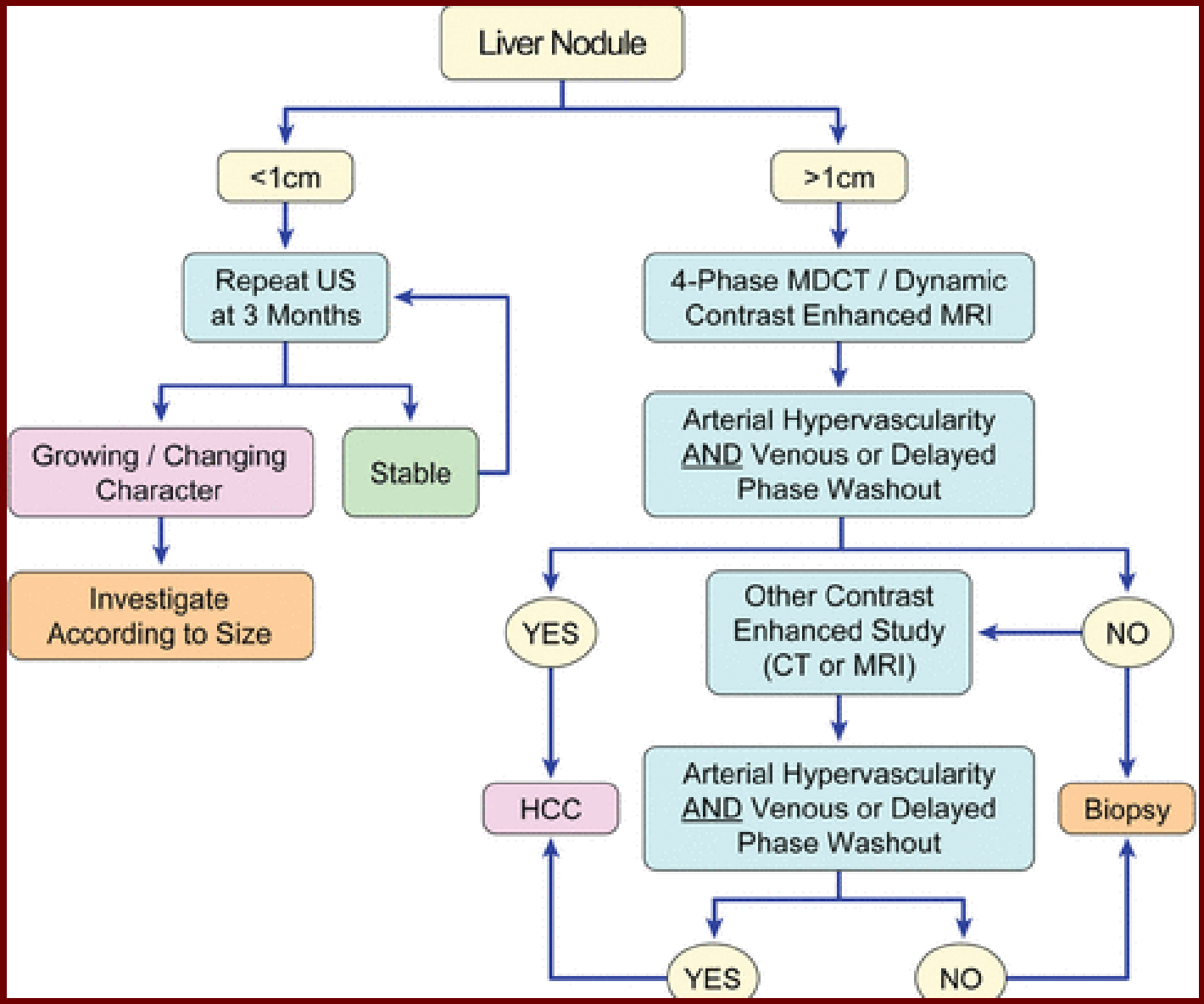
Surveillance recommended		
Population group	**Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)**	**Incidence of HCC**
Asian male hepatitis B carriers over age 40	0.2	0.4-0.6%/year
Asian female hepatitis B carriers over age 50	0.2	0.3-0.6%/year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African/North American Blacks with hepatitis B	0.2	HCC occurs at a younger age
Cirrhotic hepatitis B carriers	0.2-1.5	3-8%/yr
Hepatitis C cirrhosis	1.5	3-5%/yr
Stage 4 primary biliary cirrhosis	1.5	3-5%/yr
Genetic hemachromatosis and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Alpha 1-antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5%/year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	< 0.2%/yr
Hepatitis C and stage 3 fibrosis	1.5	< 1.5%/yr
Non-cirrhotic NAFLD	1.5	< 1.5%/yr

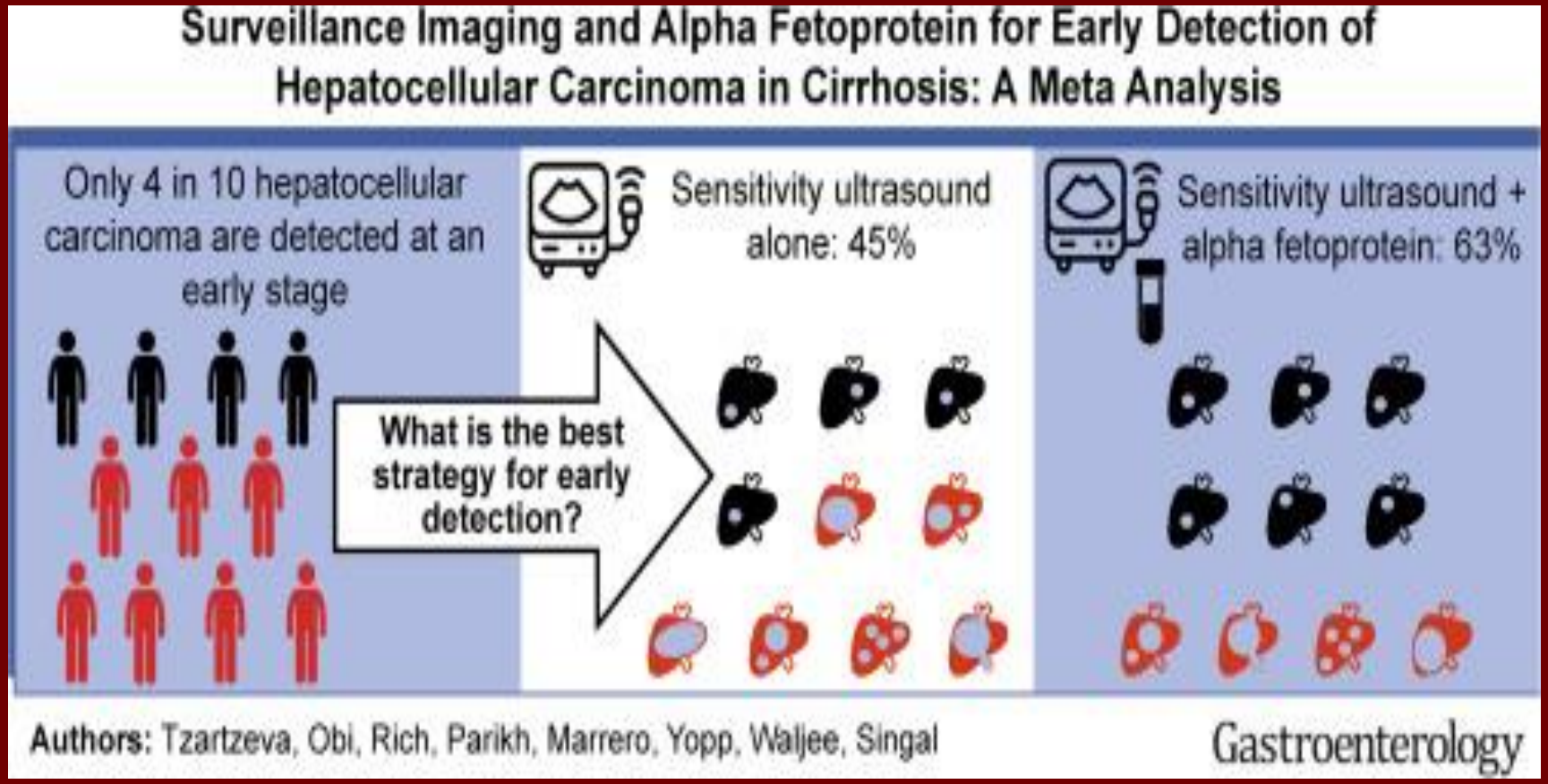
Screening

- No single ideal technique
- Multimodal
  - Imaging
    - US
    - CT / MRI
  - AFP 20ng / mL
    - **Chronic liver disease =** Sensitivity 58-68%, Specificity 80-94%
    - **General population = 25% PPV**




non-enhanced
arterial
portal venous
equilibrium


Liver Nodule
<1cm
>1cm
Repeat US at 3 Months
4-Phase MDCT / Dynamic Contrast Enhanced MRI
Growing / Changing Character
Stable
Arterial Hypervascularity AND Venous or Delayed Phase Washout
Investigate According to Size
YES
Other Contrast Enhanced Study (CT or MRI)
NO
HCC
Arterial Hypervascularity AND Venous or Delayed Phase Washout
Biopsy
YES
NO

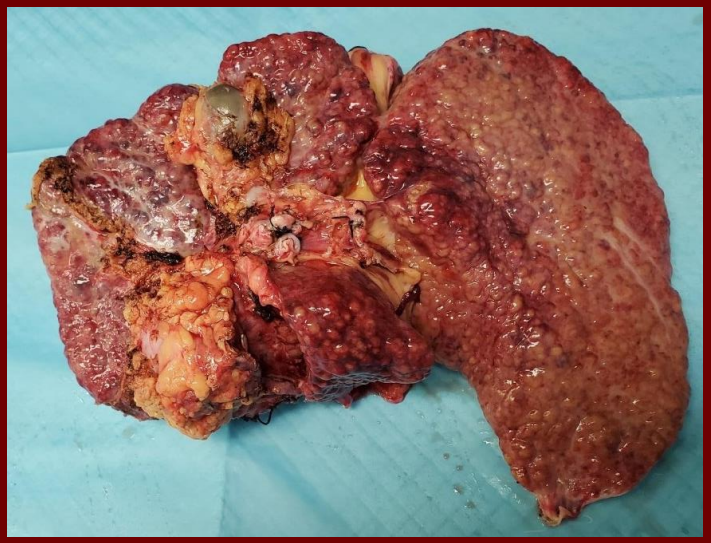

Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Cirrhosis: A Meta Analysis
Only 4 in 10 hepatocellular carcinoma are detected at an early stage
What is the best strategy for early detection?
Sensitivity ultrasound alone: 45%
Sensitivity ultrasound + alpha fetoprotein: 63%
Authors: Tzartzeva, Obi, Rich, Parikh, Marrero, Yopp, Waljee, Singal
Gastroenterology

Presentation

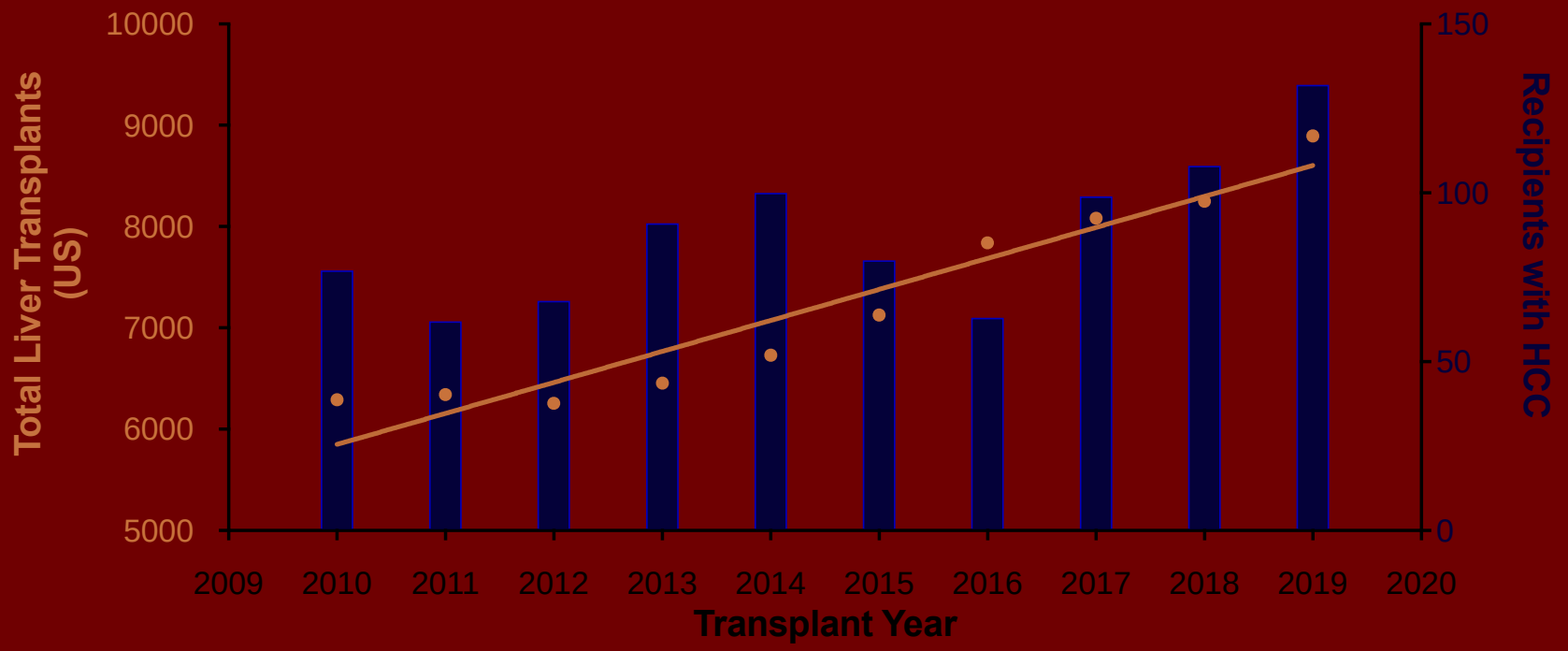
- No pathognomonic symptoms.
- Vague = weight loss, upper abdominal pain, satiety, or abdominal mass.
- Bone pain, intraperitoneal bleed / rupture = rare
  - Rupture = severe abdominal pain, free fluid, hypotension.
- Primary sx related to liver disease = must have high suspicion.
- Majority = diagnosed late.
- Labs = nonspecific (usually related to cirrhosis).

Liver Transplantation for HCC

- Gold standard for unresectable HCC
  - Tumor location, number, and size
  - Underlying cirrhosis
- Eligible recipients are prioritized based on wait time
- Pretransplant locoregional therapy (LRT) mitigates risk of tumor progression
  - Timing in relation to listing and transplant
- Patients with well-compensated disease & single < 3cm HCC with LRT response have reduced urgency

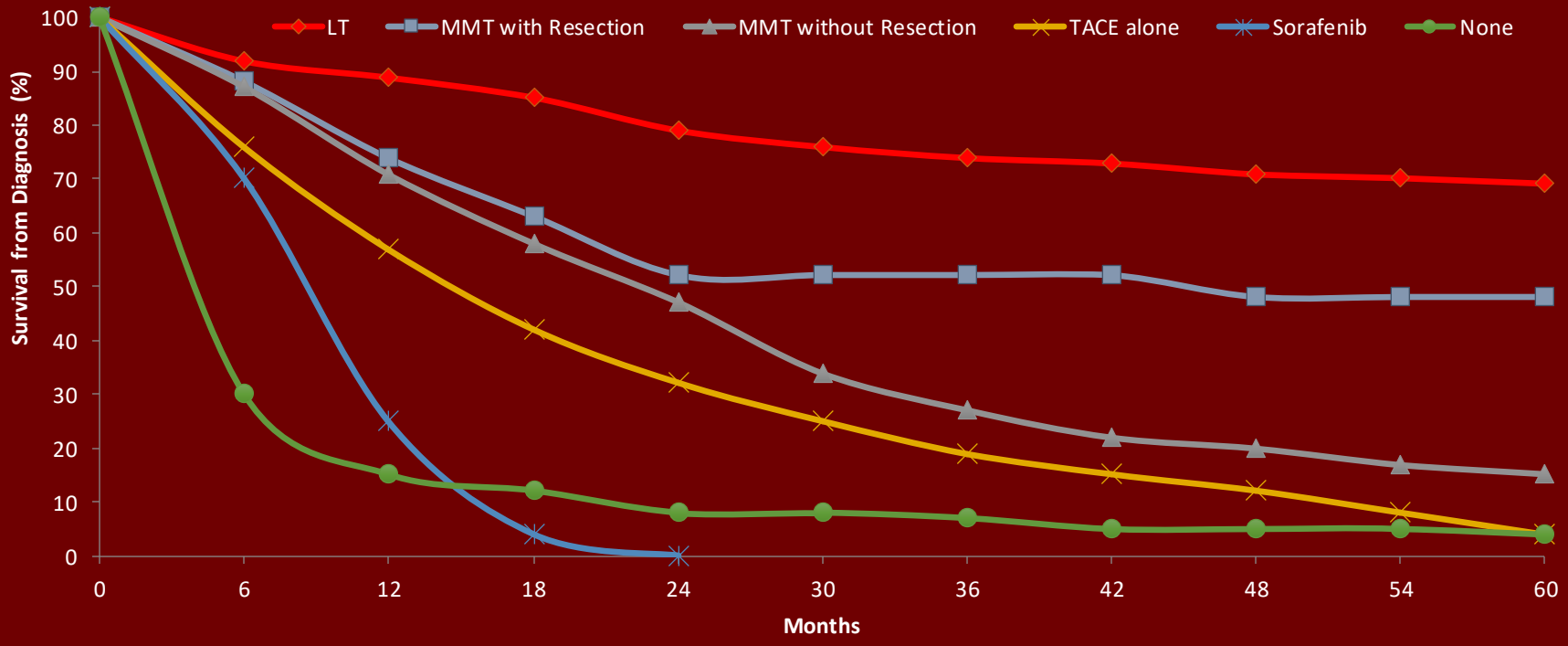


Incidence



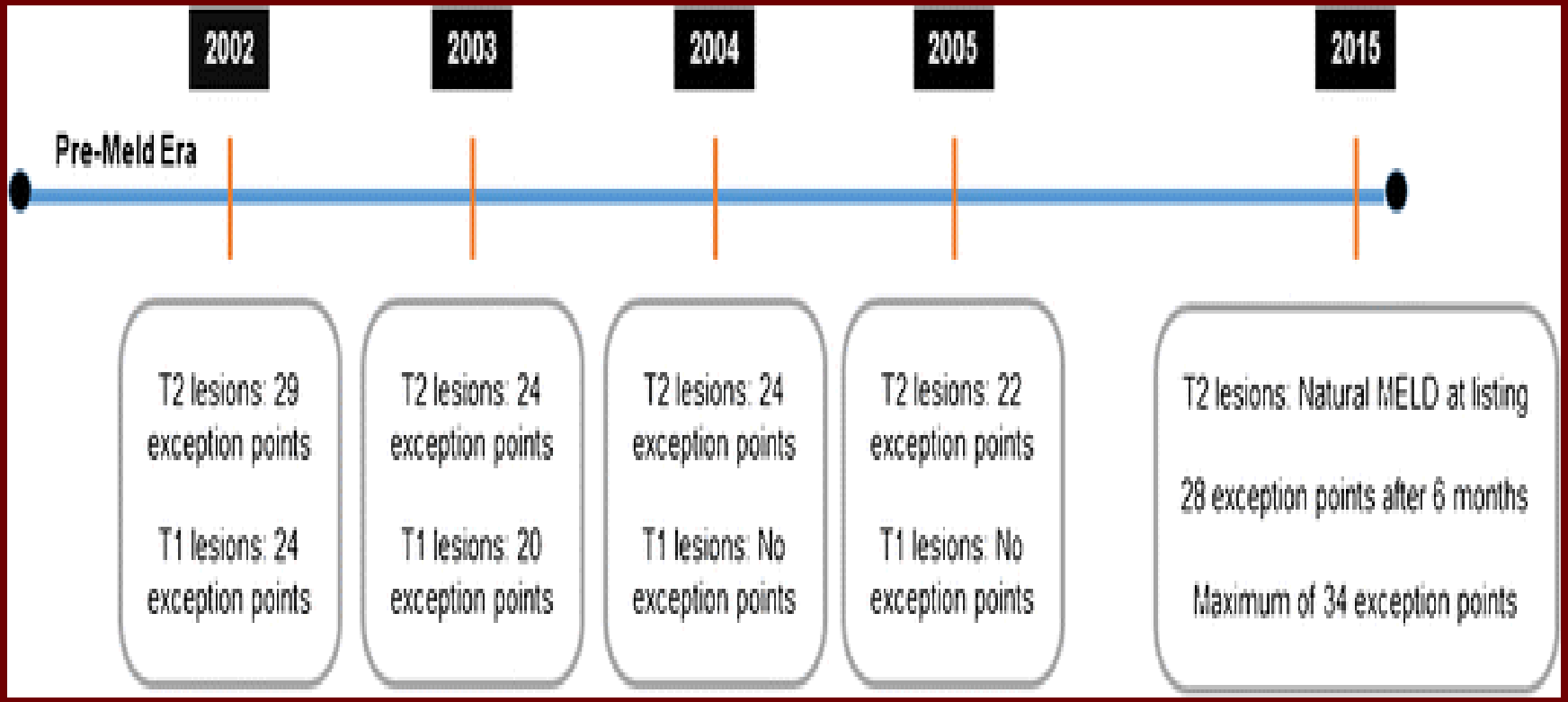
Adapted from: PLoS One. 2020 Sep 18;15(9) and OPTN Data Reports: https://optn.transplant.hrsa.gov/data/view-data-reports/

The Gold Standard



Adapted from Rajesh 2014 Transplantation

DDLT & HCC MELD Points



Since 2019, after 6m median meld of DST [donor service area] -3 points

DDLT HCC "within" cirteria

Group	Criteria	Definition	Survival	Recurrence
Mazzaferro	Milan	Solitary tumor ≤ 5 cm or total ≤ 3 tumors and each tumor ≤ 3 cm	4-yr 75%	4-yr RFS 83%
Yao	UCSF	Solitary tumor ≤ 6.5 cm or total ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm	5-yr 75.2%	5-yr RR: 17%
Takada	Kyoto	Tumor number ≤ 10 and maximal diameter of each tumor ≤ 5 cm and serum des-gamma-carboxy prothrombin levels ≤ 400 mAU/mL	5-yr 87%	5-yr RR: 5%
Mazzaferro	Up-to-Seven	Sum of number of tumors ≤ 7 and max size of the largest tumor ≤ 7cm	5-yr 71.2%	5-yr RR: 9.1%

Adapted from: World J Gastrointest Surg. 2021 May 27;13(5):392-405

DDLT HCC Criteria

AFP can be prognostic of more advanced disease and potential recurrence

- >400 ng/mL associated with worse transplant outcomes
- increase >50 ng/mL or over 15 ng/mL per month: increased risk of recurrence

Change in AFP can indicate response to locoregional therapy or chemotherapy

High AFP (>1000 ng/mL) in general associated with worse outcomes

Adapted from: World J Gastrointest Surg. 2021 May 27;13(5):392-405

DDLT HCC Criteria

6 months after listing, the following pts are eligible for MELD Exception (MMAT-3 at listing center)

- **Within Milan and AFP < 500 prior to LRT**
  - 1 lesion 2-5 cm (T1)
  - 2-3 lesions 1-3 cm (T2)
- **Downstaging with LRT**
  - 1 lesion 5-8cm
  - 2-3 lesions ≤5cm (sum less than 8cm)
  - 4-5 lesions ≤3cm (sum less than 8cm)
  - AFP≥1000 with decrease to ≤500

- **Contraindications to transplant**
  - Macrovascular invasion of main PV or HV
  - Extrahepatic disease
  - Ruptured HCC
  - Lesion <2cm
- **Caveat: Ruptured HCC and portal vein branch invasion may be considered if stable >12 months**

LDLT for HCC

Current schema leaves many without a viable DDLT (19.6% in 2008, 16.9% in 2018)

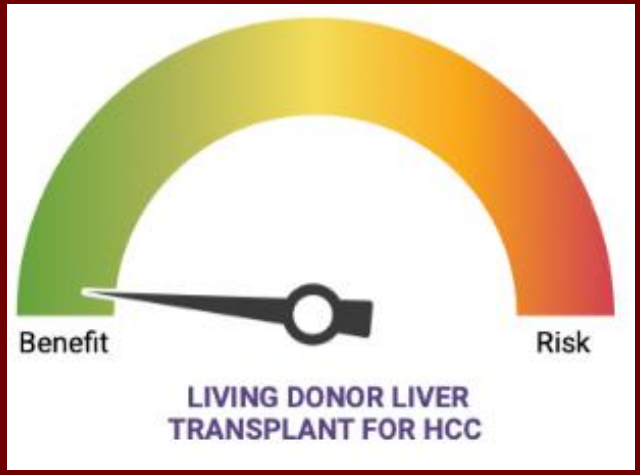
Up to 30% of patients drop out

LDLT affords these patients an alternate option

Offers a “no competition” perspective, thus shifted ethical paradigm

Often incorporates expanded criteria

- Donors outside Milan
- Prior to the requisite wait time



LDLT for HCC

Often utilized for patients with less access to DDLT

Highest utilization was prior to 2002 (pre MELD exception)

Increased rates post 2015, after capping of points @ 34

Older data suggested worse outcomes for LDLT in HCC

Newer analysis shows no difference between DDLT & LDLT for HCC

- When segregated for in-criteria patients
- Especially beneficial for HCC patients with MELD $\geq$ 15

LDLT & double equipoise

Donor risk must be justified by an acceptable outcome for the recipient

Extremes should be avoided;

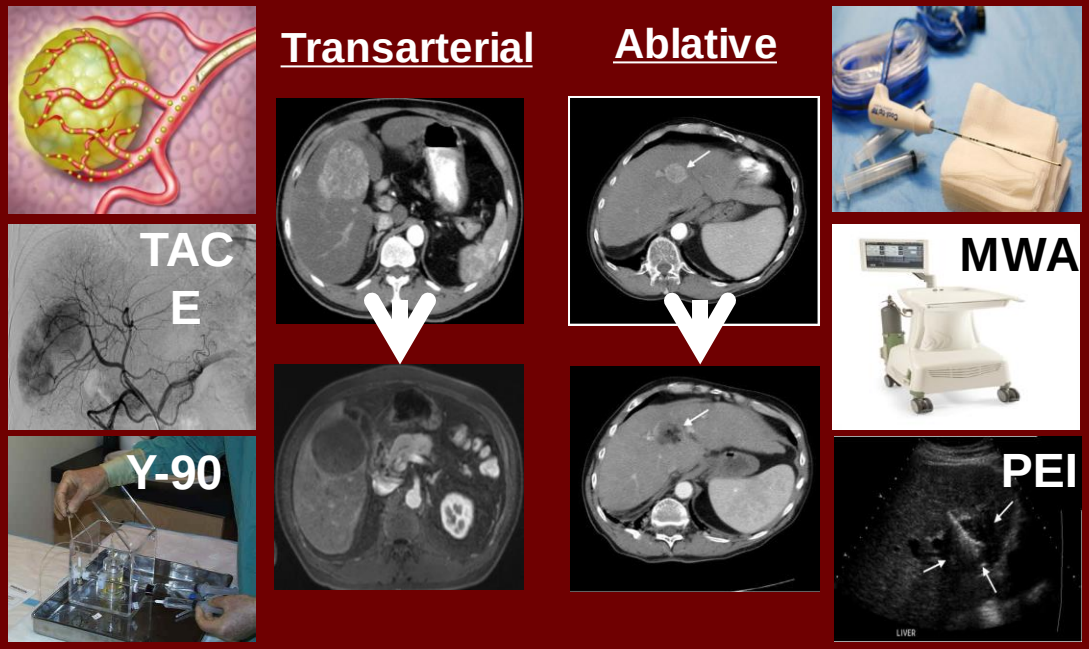
- **Small well treated tumor in a well-compensated patient**
  - **Wait for DDLT or avoid transplant completely**
- **Patient with large tumor & aggressive biology**
  - **Outcome cannot justify risk to the donor**

Recommended benchmark

- **5-year post LDLT survival > 60%**
- **<5% severe post-operative complications (Clavien 3/4)**

Mehta et al., Transplantation. 2020 Jun; 104(6): 1136-1142

Locoregional Therapies & tumor downstaging in LDLT



Locoregional Therapies & tumor downstaging in LDLT

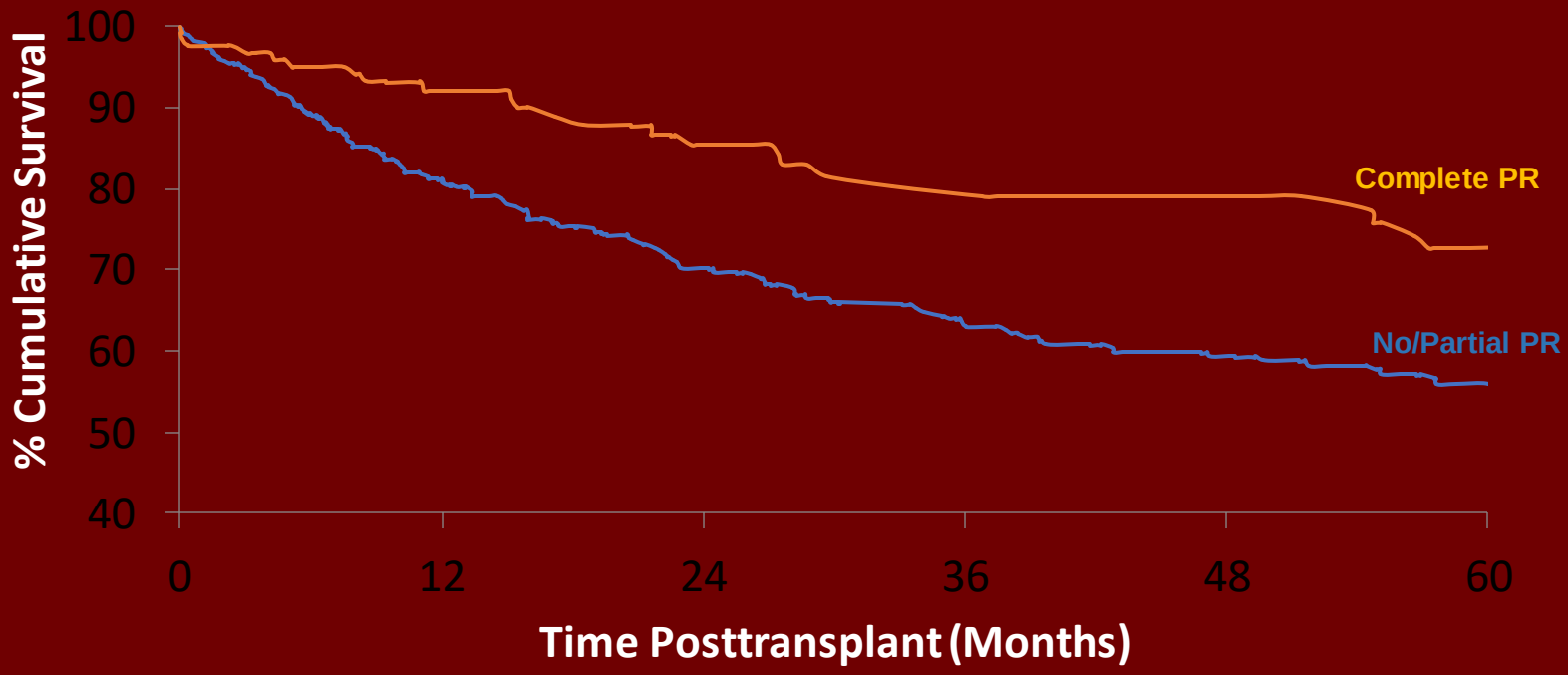
Typically performed for DDLT

~60% of patients with HCC considered "all-comers" can be successfully downstaged to within Milan.

ILTS guidelines recommend LRT to within UCSF with AFP < 500 ng/mL + observation period of at least 3 months before LDLT

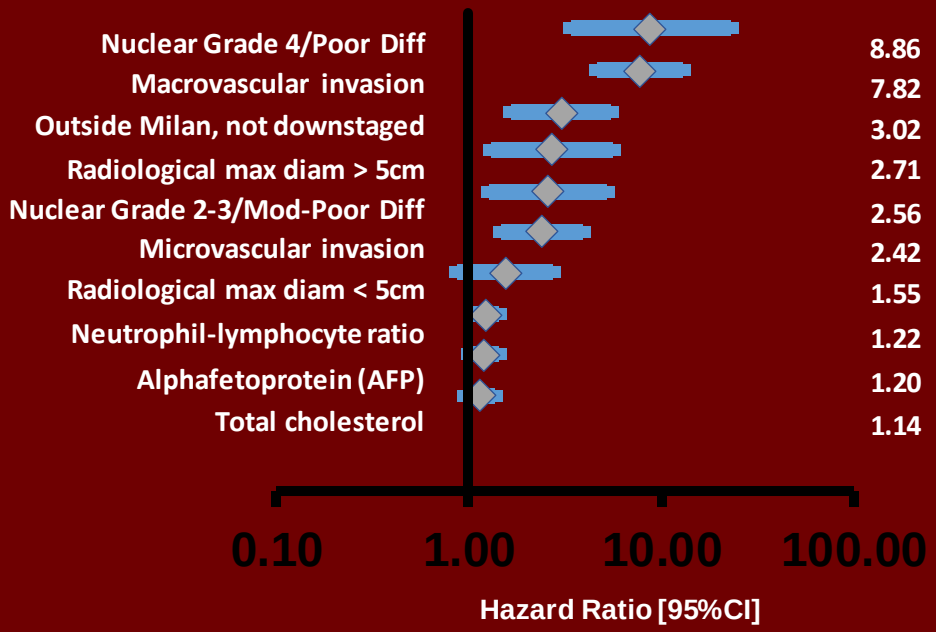
Locoregional Therapies

Recurrence Free Survival following Liver Transplantation for HCC



Adapted from: Agopian et al., Ann Surg. 2015 Sep; 262(3): 536-45.

HCC & DDLT Prognostic factors



Adapted from: Agopian et al., Ann Surg. 2015 Sep; 262(3): 536-45

HCC & LDLT Prognostic factors

Similar to DDLT

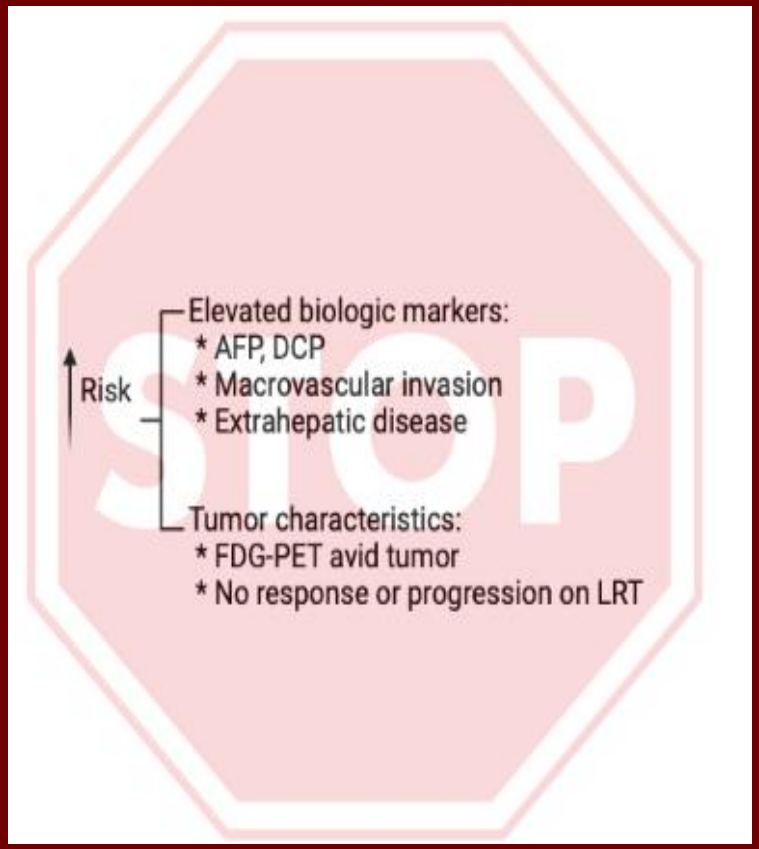
Should generally stray from expanded criteria

Validated criteria include

- AFP and DCP cutoffs (<400 ng/mL, <7.5ng/mL)
- F-FDG PET
- Response to LRT to ensure acceptable tumor biology
- No extra-hepatic disease
- No macro-vascular invasion

Conclusion

- Excellent long-term outcomes for certain patients
- Recipient selection criteria should include
  - Tumor biology: signs of increased risk
  - Probability of waitlist and post-LT survival
  - Center factors: organ availability/ waitlist composition



TEAM EFFORT

Thank You

Liver Transplantation. 2022;28:1144–1157.

Transplantation ■ June 2020 ■ Volume 104 ■ Number 6

HepatoBiliary Surg Nutr 2016;5(2):133-140

American Journal of Transplantation 2015; 15: 17–38

Session Survey

Kambiz Etesami, MD | April 20th 10:00 AM-10:30 AM