# Hepatocellular Carcinoma (HCC) Case Study: What You Don't Know Can Hurt Your Patient

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# Our Patient

Katherine Crow, PA-C

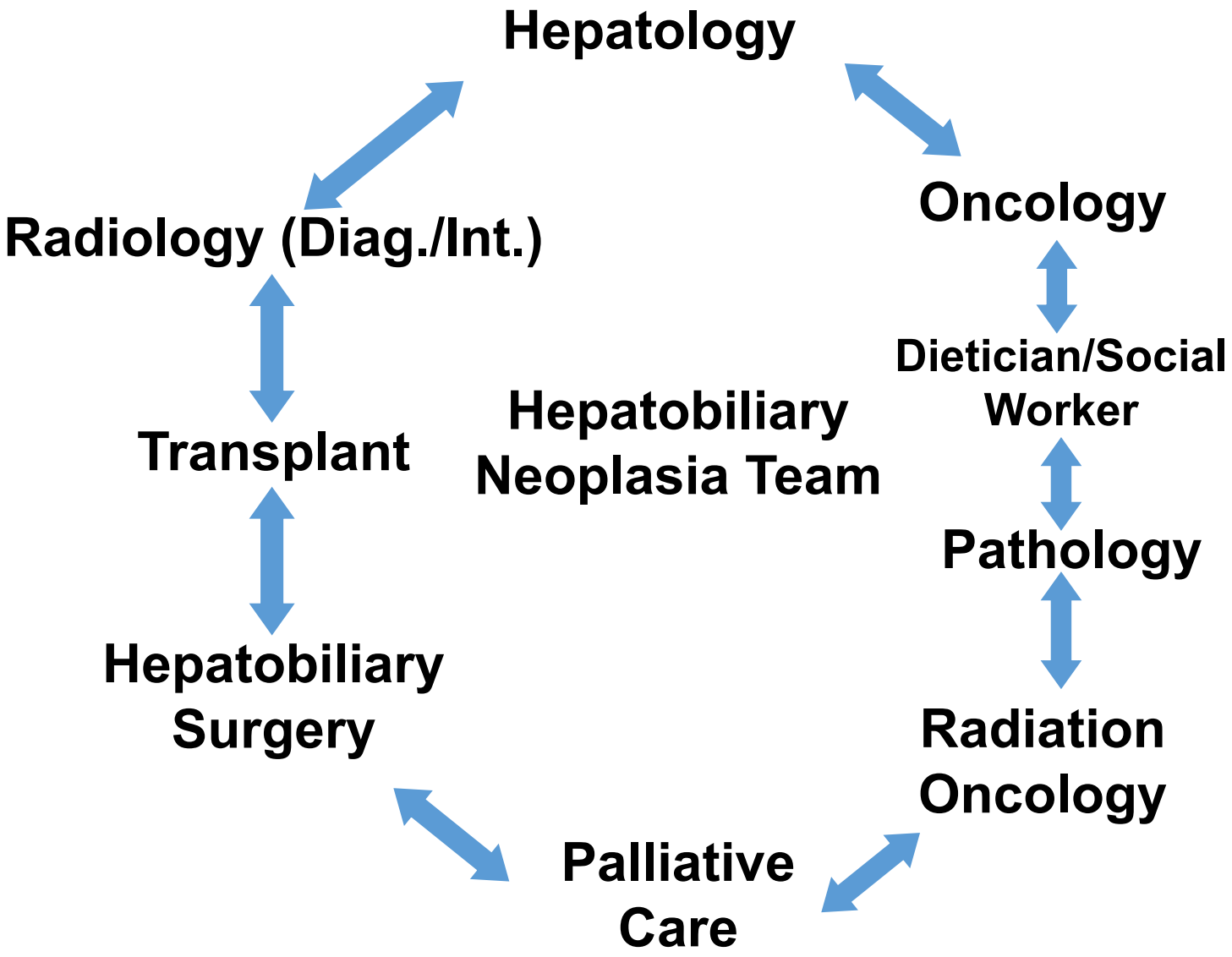
# Meet Mr. Higado Disparo

- 52-year-old Hispanic male with history of moderate alcohol use and hepatitis C, who underwent HCV therapy with DAA and achieved SVR (cure) in 2019.
- Fibroscan and FibroSure revealed probable cirrhosis and patient was placed in HCC surveillance with ultrasound every 6 months.
- Patient was employed as oil field worker and was unable to continue with consistent medical care.
- He stopped alcohol use in 2020 and returned for follow up care in late 2021.
- He was otherwise healthy, and on no medications.
- Imaging and labs were ordered.

# Results

- Ultrasound: 6.5 cm mass in right lobe
- AFP: 87 ng/mL
- CBC:
  - WBC 6.3 x $10^9$/L
  - Hgb: 14.2 g/dL
  - Platelets: 104 x $10^9$/L
- CMP:
  - Bili: 0.8 mg/dL
  - AST: 45 U/L; ALT: 40 U/L
  - ALP 120 U/L
  - Cr 0.8 mg/dL
  - INR 1.1
- Patient is referred to Texas Liver Tumor Center (TLTC) for multidisciplinary care

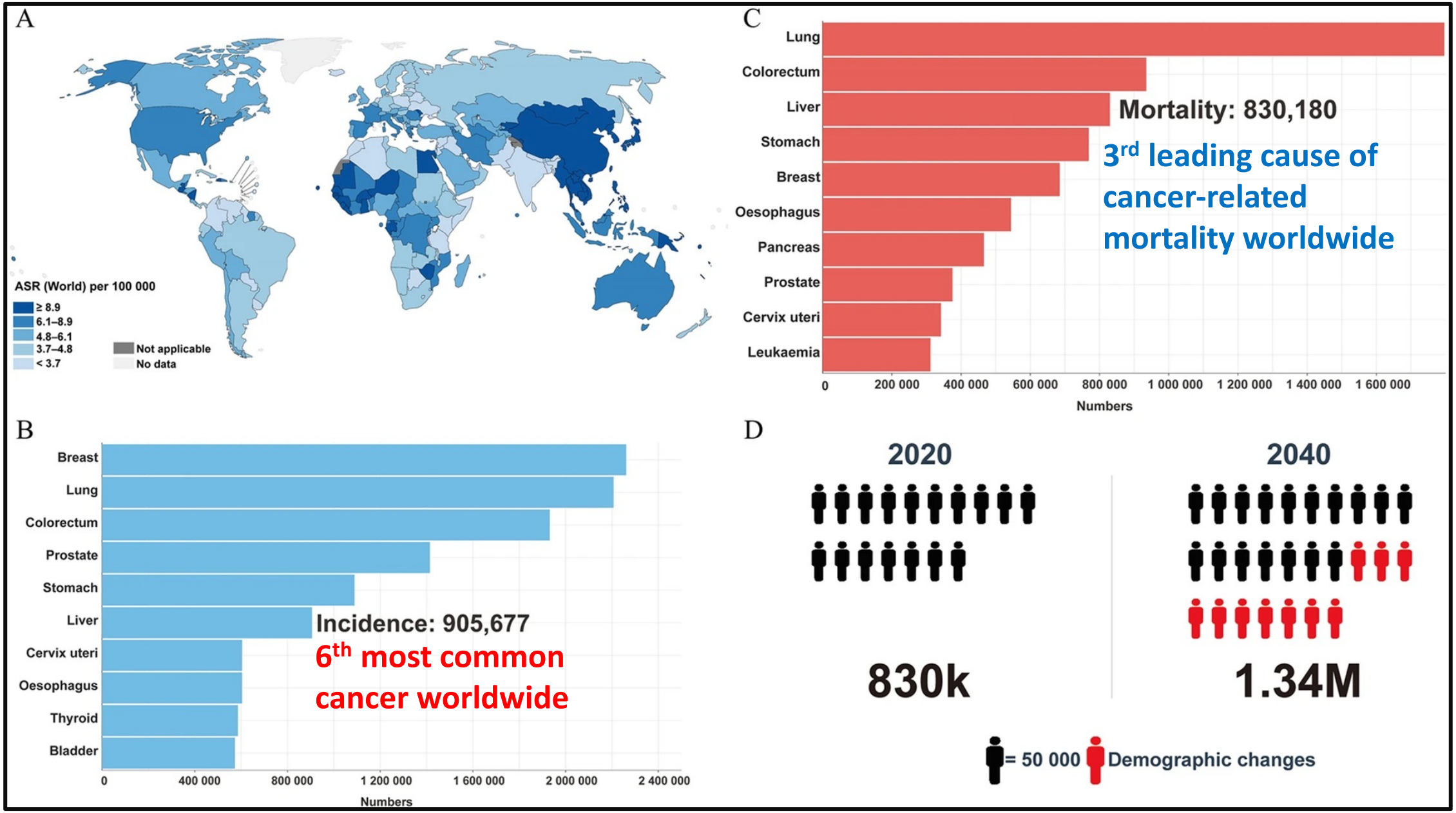
# Multidisciplinary Care



# Texas Liver Tumor Center = Multidisciplinary Care in 1 day

# Epidemiology, Diagnosis and Medical Management Options

Shruti Pandita, MD

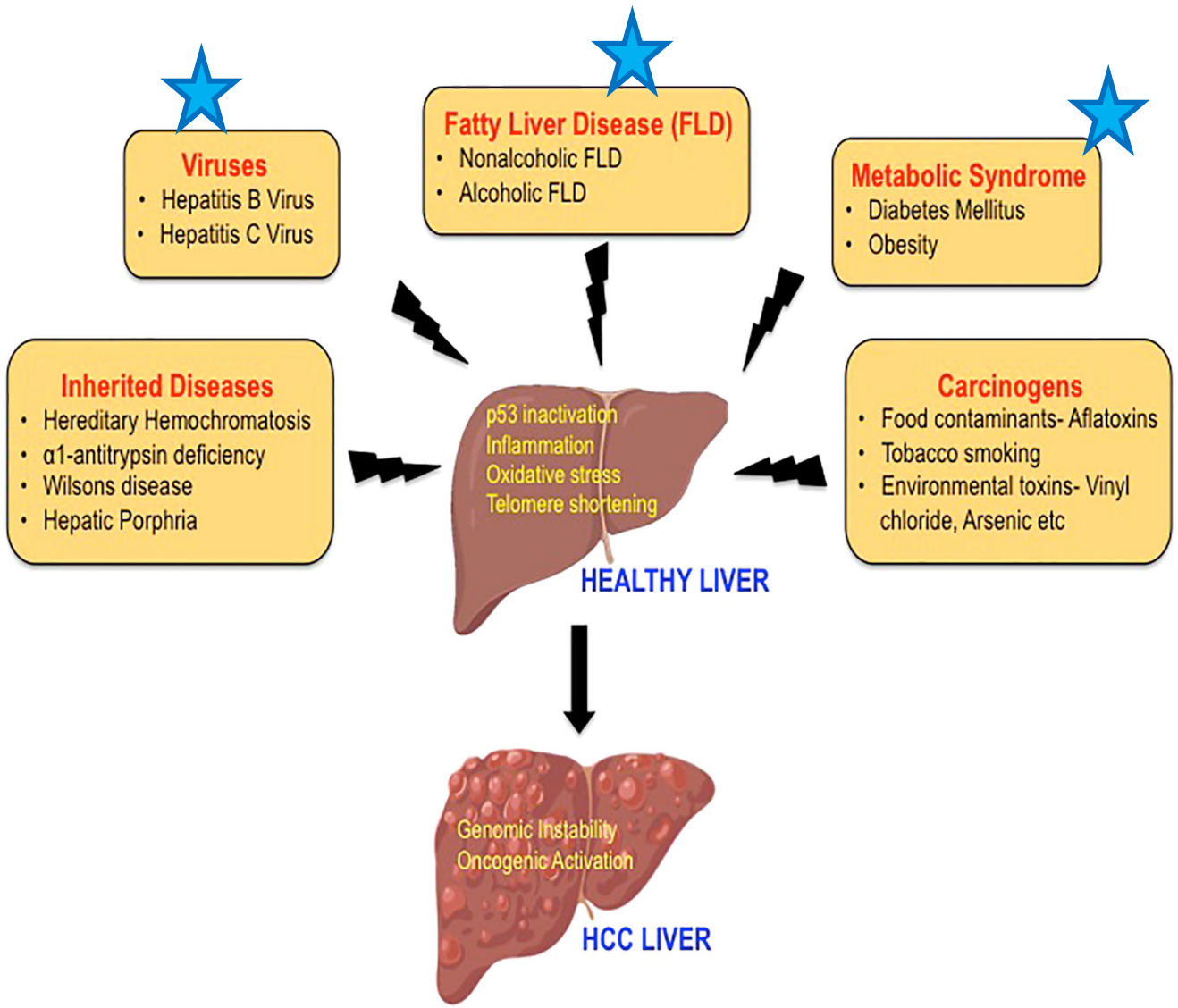

A
ASR (World) per 100 000
≥ 8.9
6.1–8.9
4.8–6.1
3.7–4.8
< 3.7
Not applicable
No data
B
Breast
Lung
Colorectum
Prostate
Stomach
Liver
Cervix uteri
Oesophagus
Thyroid
Bladder
Incidence: 905,677
6th most common cancer worldwide
0
400 000
800 000
1 200 000
1 600 000
2 000 000
2 400 000
Numbers
C
Lung
Colorectum
Liver
Stomach
Breast
Oesophagus
Pancreas
Prostate
Cervix uteri
Leukaemia
Mortality: 830,180
3rd leading cause of cancer-related mortality worldwide
0
200 000
400 000
600 000
800 000
1 000 000
1 200 000
1 400 000
1 600 000
Numbers
D
2020
2040
830k
1.34M
= 50 000
Demographic changes

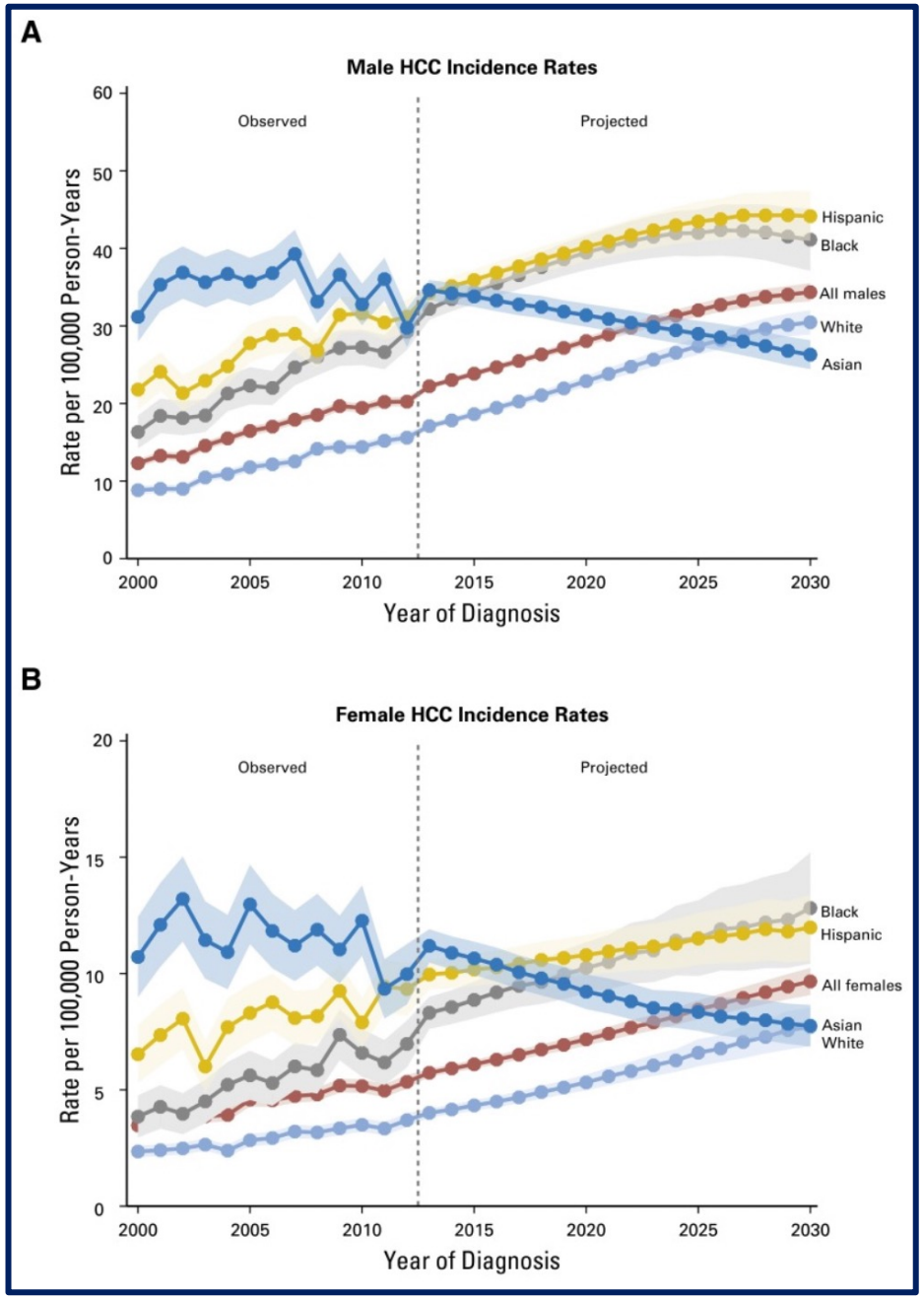
# Risk Factors

- 2022 US liver cancer estimates: 41,260 new diagnoses (73% HCC) and 30,520 deaths

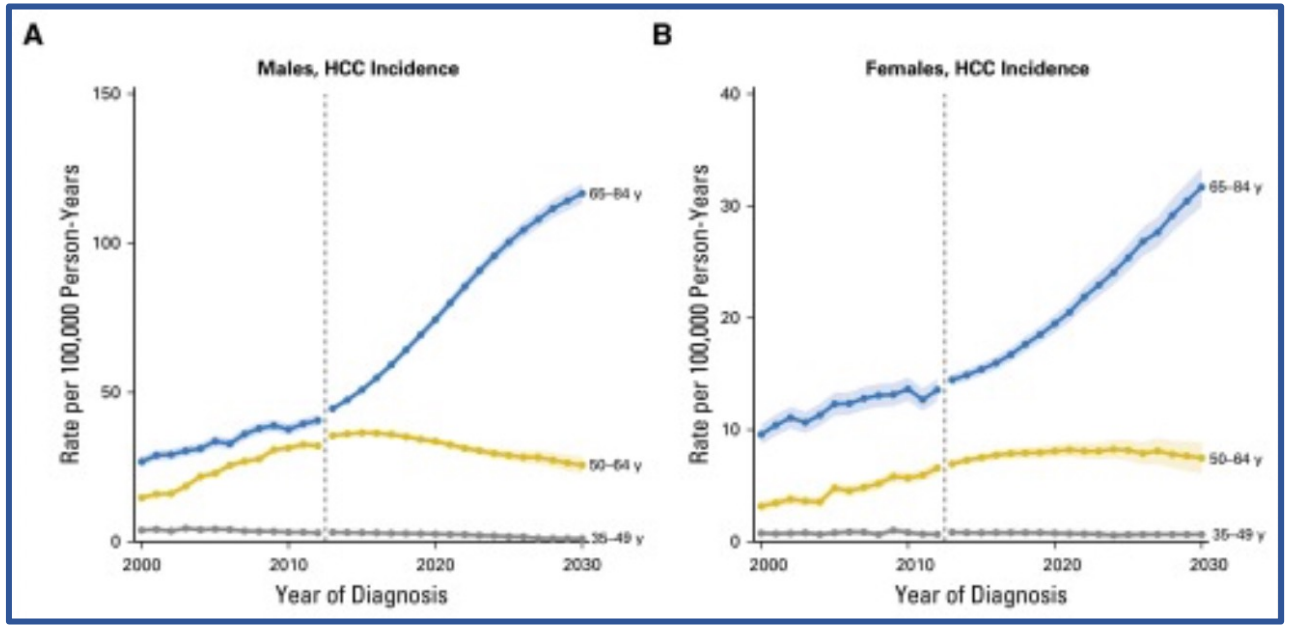
- Most HCC cases occur in patients with antecedent liver cirrhosis
  - Appears 20-30 years following initial insult to liver

- 20% of cases occur in patients with non-cirrhotic liver

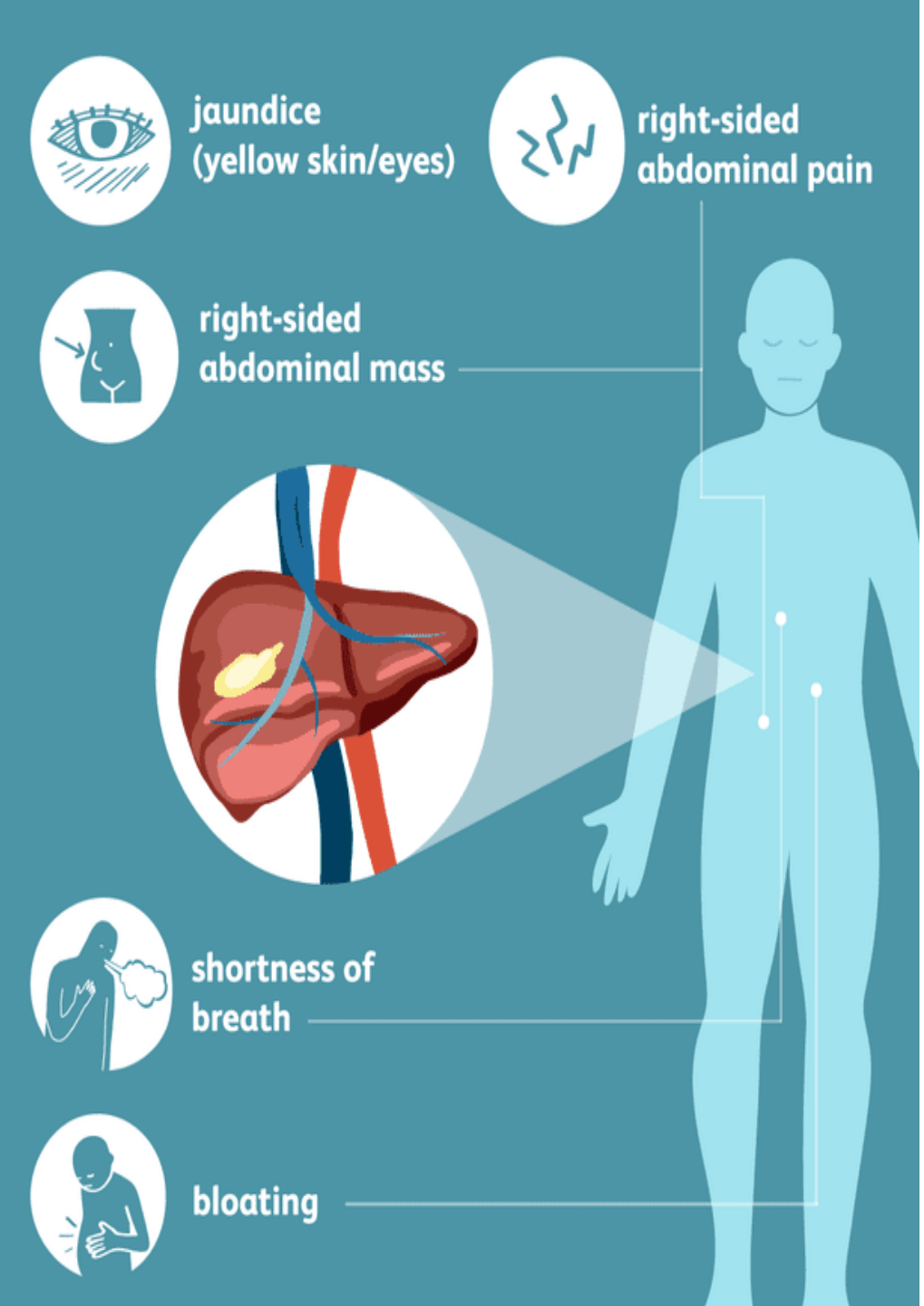





# By 2030: Hispanics and Blacks forecasted to have highest incidence of HCC in the US



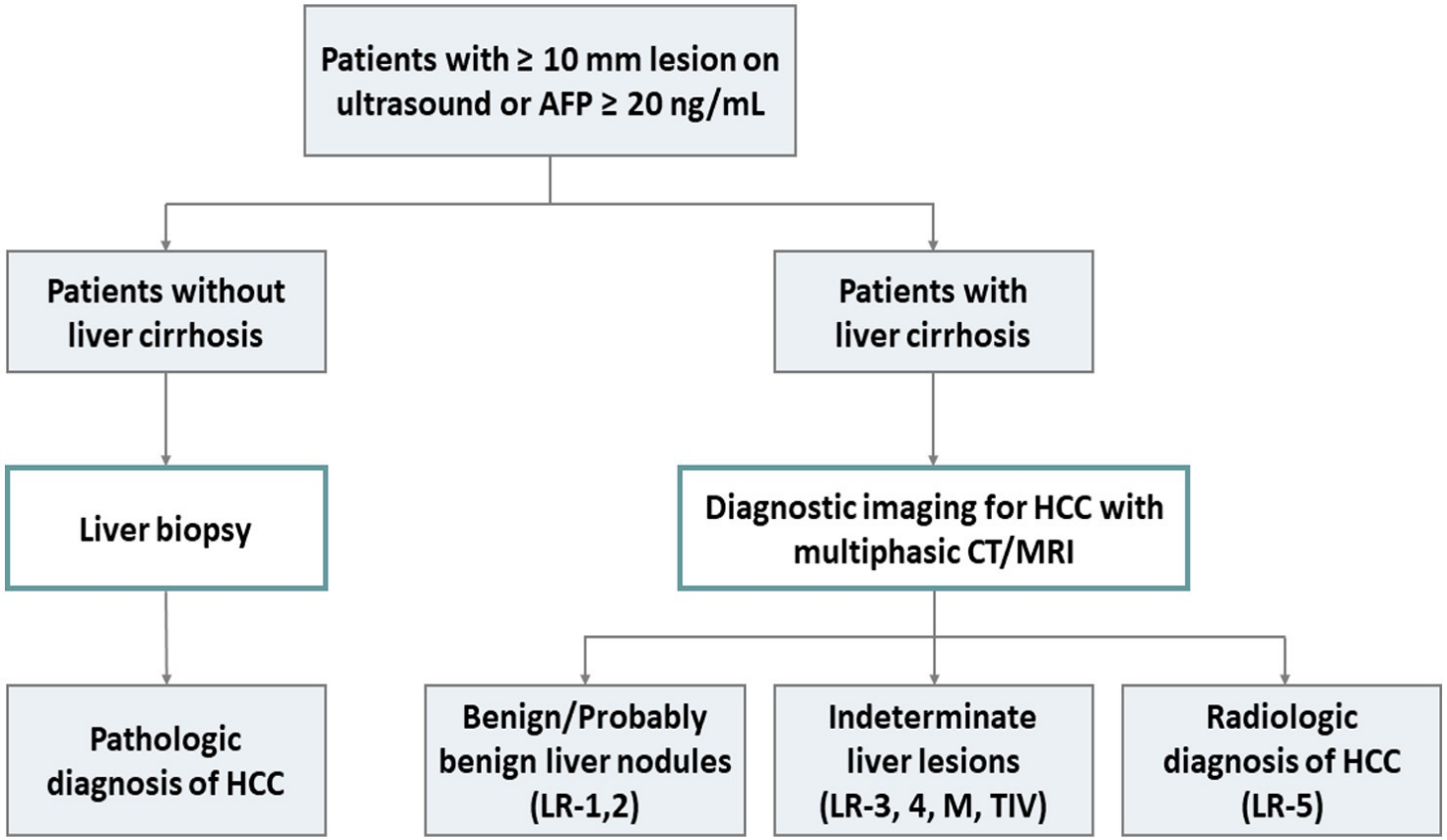

Increasing HCC incidence rates forecasted for those born 1950-1959 (high rates of HCV infection in age cohort)




# Clinical Presentation

- **Incidental finding (asymptomatic)**
- **Liver mass on screening u/s or CT/MRI**
- Locally advanced disease: jaundice, tumor fever, bone pain (d/t metastases), and complications from portal HTN
- Hepatomegaly present in >90% of patients
- 50% of patients: Hepatic arterial bruit or friction rub, ascites, splenomegaly, and jaundice

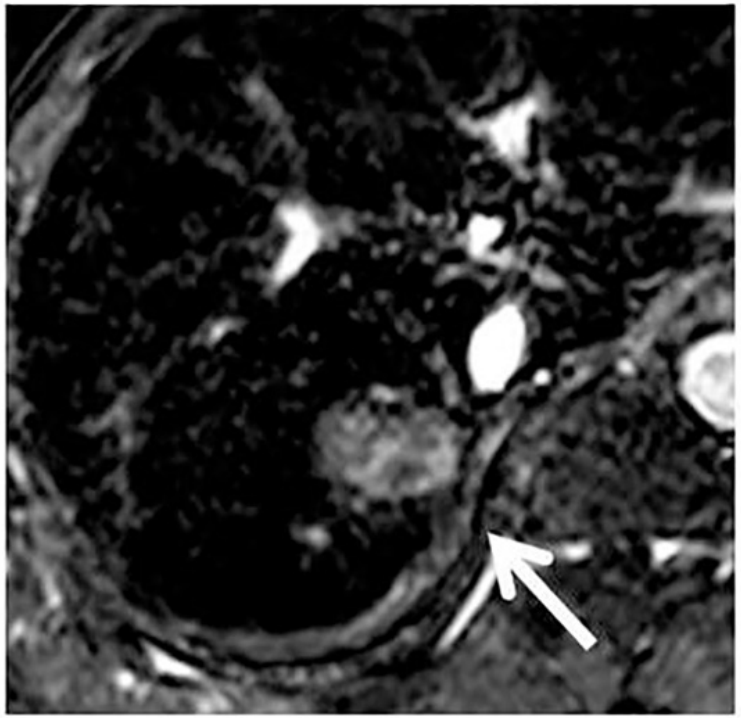
# HCC Diagnosis



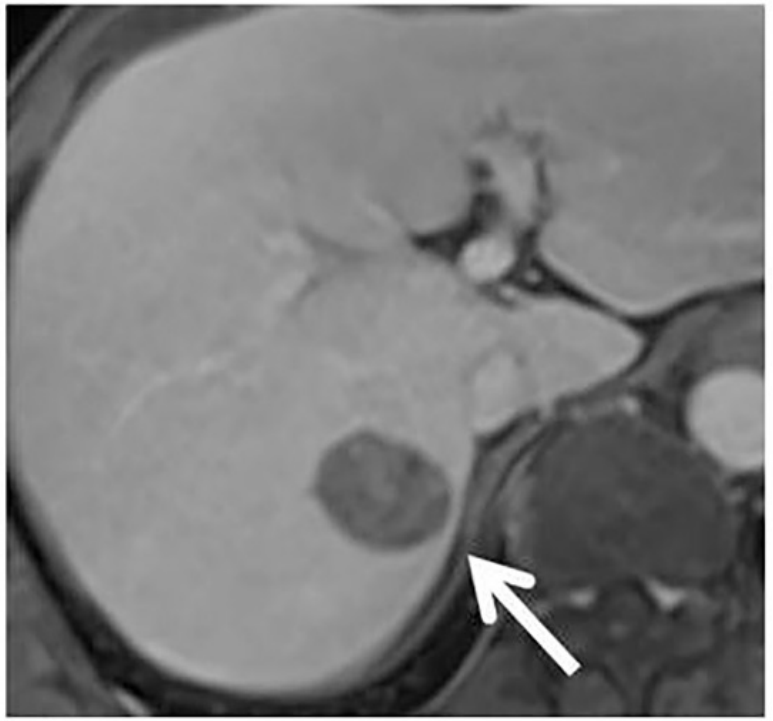

## LI-RADs Major Criteria:

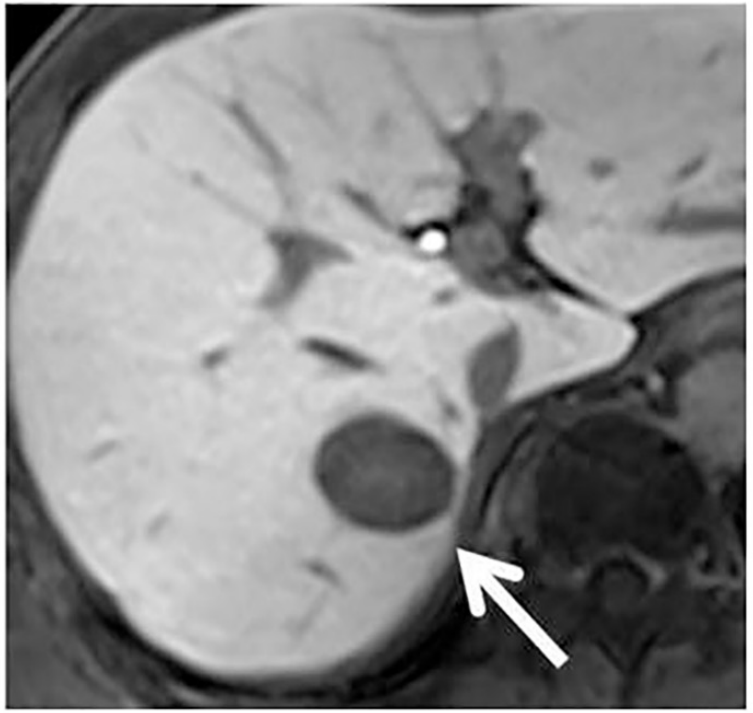
- **Arterial phase hyperenhancement (APHE):** Non-rim arterial hyperenhancement of lesion >> enhancement of liver parenchyma.
- **Non-peripheral washout:** Decrease in attenuation or intensity from earlier to later phase, resulting in hypoenhancement in portal venous or delayed phase
- **Enhancing Capsule:** Smooth, uniform border surrounding all or most of an observation. Increases from early to late contrast phases.
- **Size:** Large lesion >> small lesion has greater chance of being HCC
- **Threshold growth:** Increase in size ≥50% in ≤6 months

# LI-RADS 5 Lesion (HCC)



Arterial subtraction image shows homogeneous enhancement compared to normal liver parenchyma.

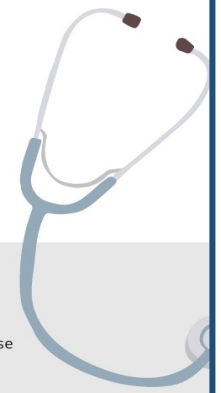




Delayed phase and hepatobiliary phase images show decreased signal intensity in hepatic lesion compared to liver parenchyma.

# ECOG PERFORMANCE SCALE

**Rating a patient's well-being**

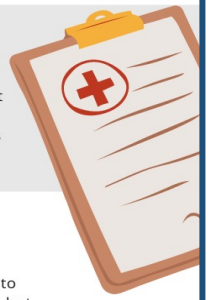


**0** ASYMPTOMATIC

Fully active, able to carry on all pre-disease activities without restriction

**1** SYMPTOMATIC BUT AMBULATORY

Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work



**2** SYMPTOMATIC, <50% IN BED

Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours

**3** SYMPTOMATIC, >50% IN BED

Capable of only limited self-care, confined to bed or chair 50% or more of waking hours, but not bed-bound.

**4** BED BOUND

Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

**5** DECEASED

Patient has passed away.

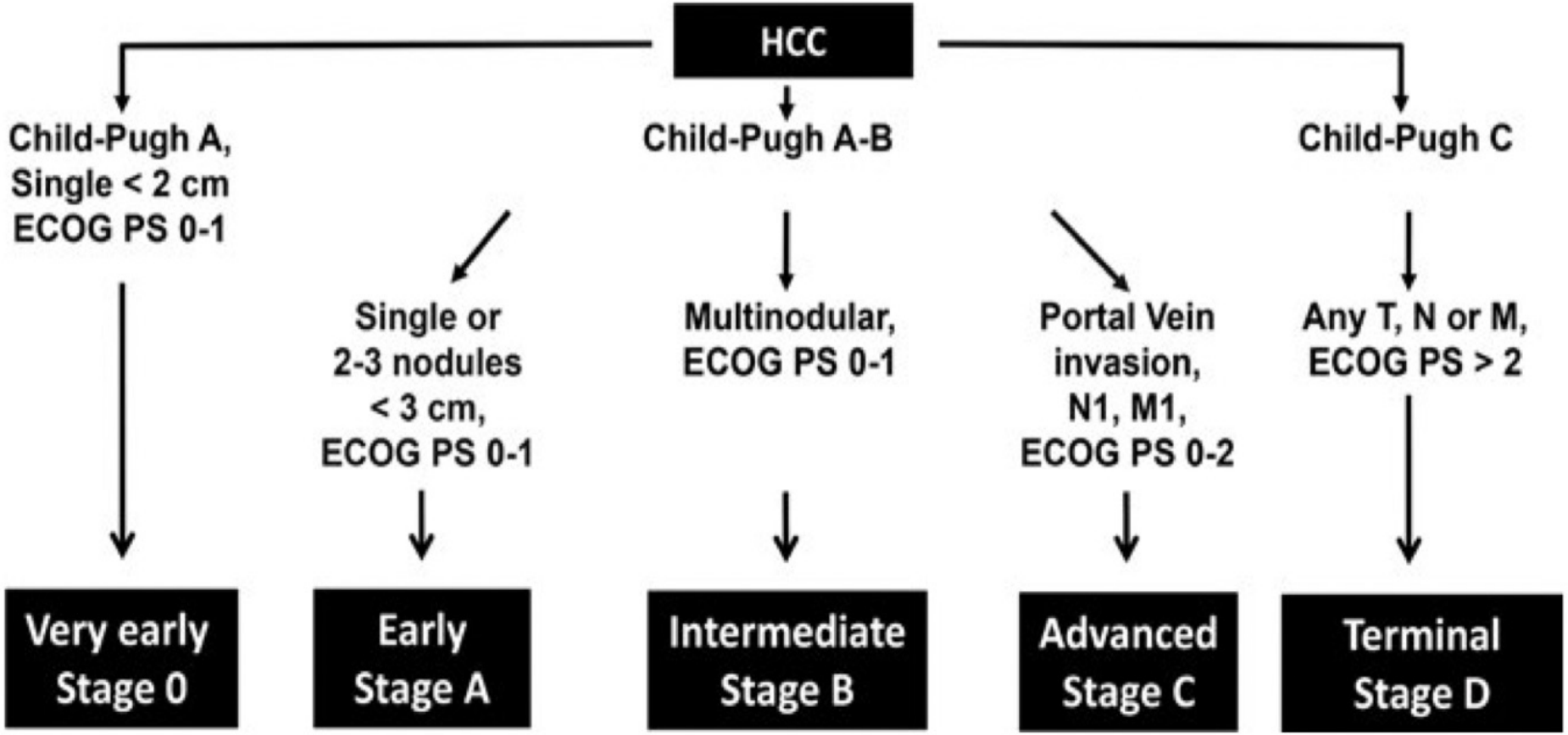
# Child-Pugh Score

| Clinical and Lab Criteria | Points* | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Encephalopathy | None | Mild to moderate (grade 1 or 2) | Severe (grade 3 or 4) |
| Ascites | None | Mild to moderate (diuretic responsive) | Severe (diuretic refractory) |
| Bilirubin (mg/dL) | < 2 | 2-3 | >3 |
| Albumin (g/dL) | > 3.5 | 2.8-3.5 | <2.8 |
| Prothrombin time | | | |
| Seconds prolonged | <4 | 4-6 | >6 |
| International normalized ratio | <1.7 | 1.7-2.3 | >2.3 |

**Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**

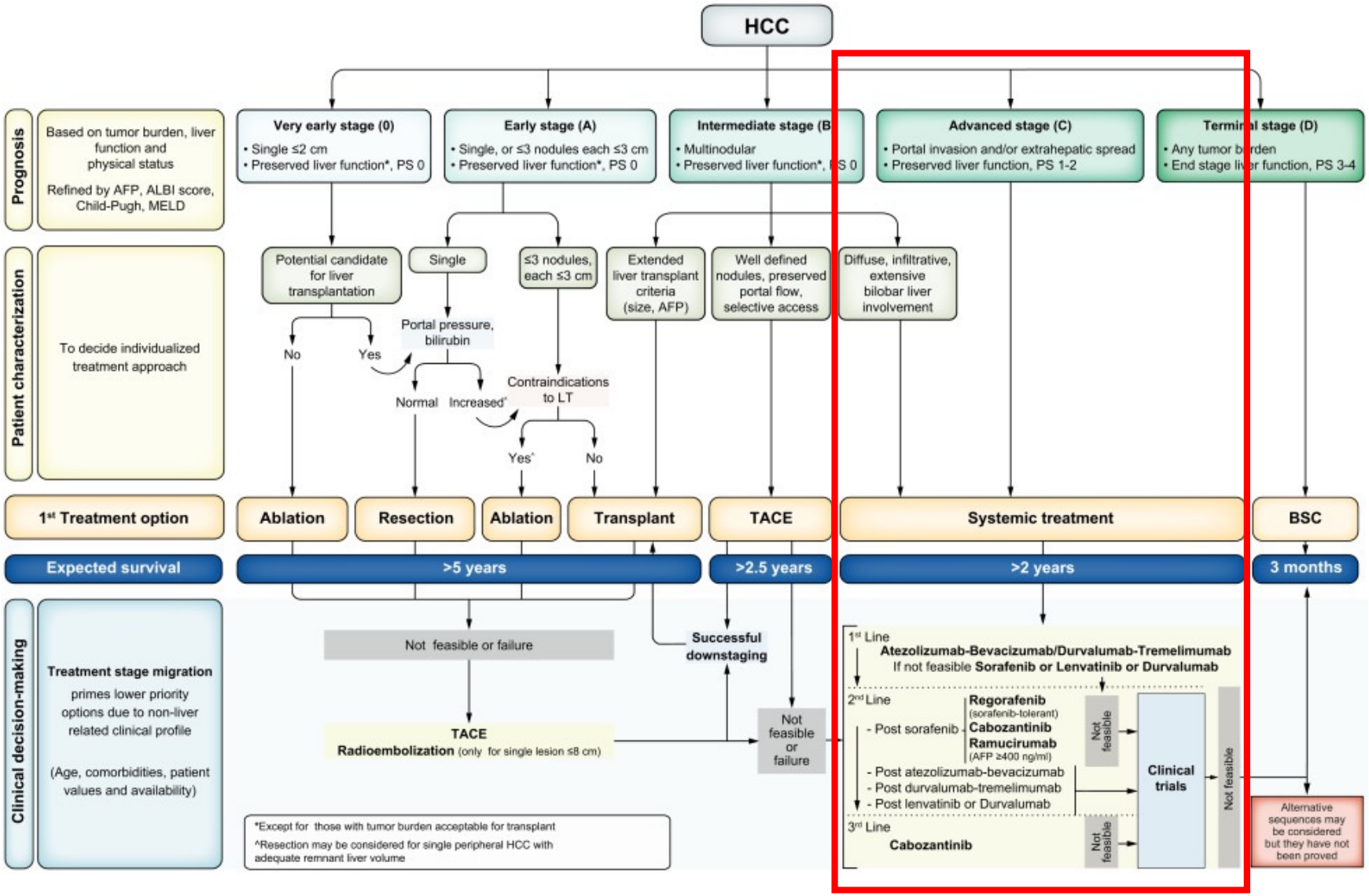
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)

# BCLC Staging

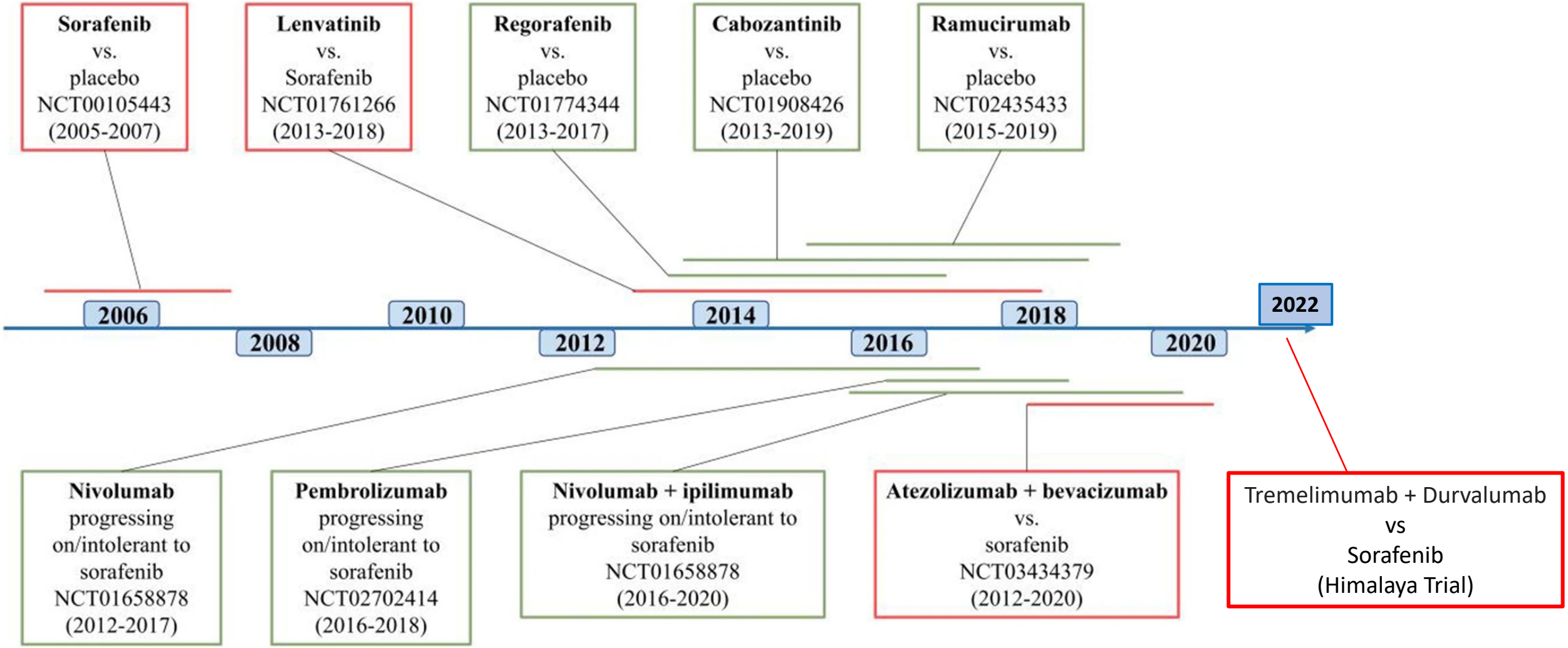



- **Complete staging workup: CT or MRI liver protocol + CT Chest/Pelvis with contrast**
- **Bone scan if clinically indicated (symptomatic)**

# HCC: Treatment Paradigm



# From TKI Era to Combination Therapy



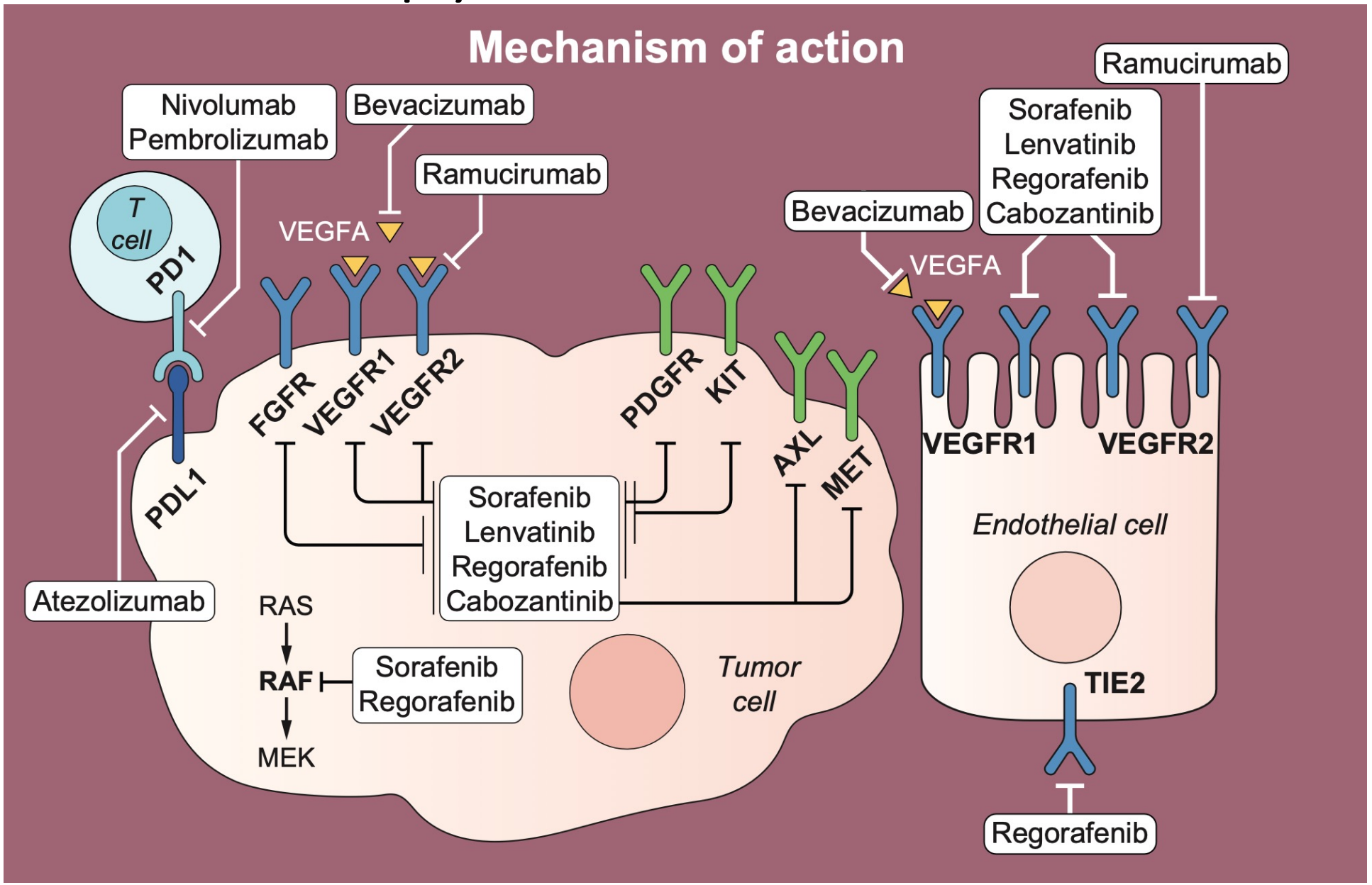
# Efficacy & Safety Data: First-line therapy

| Trial | Target | OS | ORR | G3/4 AEs |
|---|---|---|---|---|
| SHARP:<br>**Sorafenib** vs Placebo<br><br>**CP: A, B7** | VEGFR, PDGFR, c-Kit, RET, BRAF, FGFR | **10.7** vs 7.9 months | 2% vs 1%<br><br>CR: 0% | **45%** (diarrhea, weight loss, fatigue, HFS, HTN)<br><br>11% stopped d/t AEs |
| REFLECT:<br>**Lenvatinib** vs Sorafenib<br><br>**CP: A** | VEGFR, PDGFR, c-Kit, RET, BRAF, FGFR | **13.6** vs 12.4 months | **19%** vs 7%<br><br>CR: <1% | 57% vs 49% (HSR, HTN)<br><br>9% vs 7% stopped d/t AEs |
| IMbrave150:<br>**Atezolizumab/Bevacizumab** vs Sorafenib<br><br>**CP: A** | PD-L1, VEGFA | **19.2** vs 13.4 months | **30%** vs 11%<br><br>**CR: 8%** vs 1% | 46% vs 47% (HTN, proteinuria, hepatotoxicity)<br><br>7% vs 10% stopped d/t AEs |
| HIMALAYA:<br>**Tremelimumab + Durvalumab vs Sorafenib**<br><br>**CP: A** | CTLA-4, PD-L1 | **16.4** vs 13.8 months | **20%** vs 5% | 26% vs 37% (no new safety signals)<br><br>8% vs 11% stopped d/t AEs |

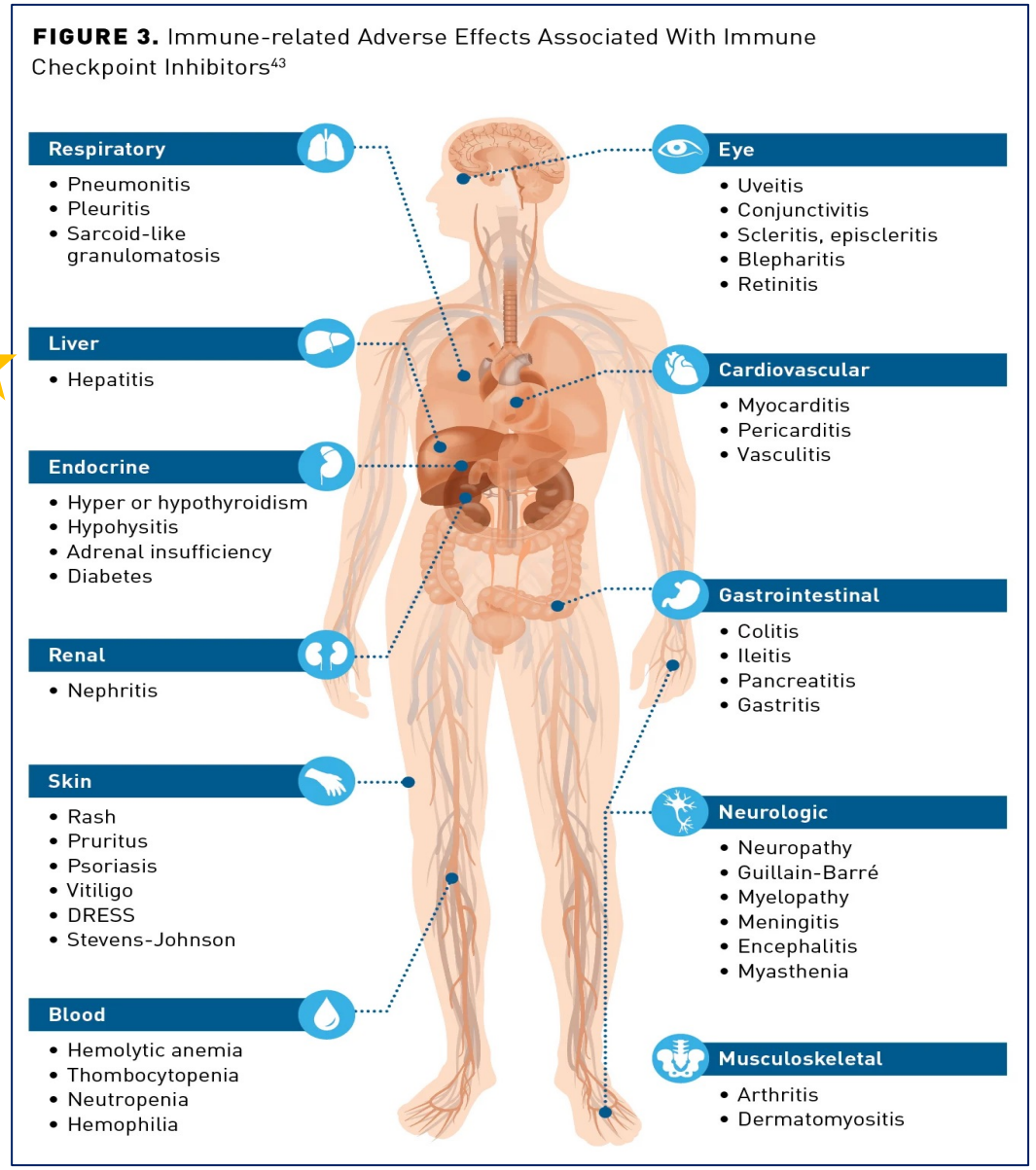
# 2nd-line therapy

| Trial | Target | OS | ORR |
|---|---|---|---|
| RESORCE:<br>**Regorafenib** vs Placebo<br>**CP: A** | VEGFR 1-3, TIE2, KIT; PDGFRα/β, FGFR, KIT, RET, RAF | **10.6** vs 7.8 months | 11% |
| CELESTIAL:<br>**Cabozantinib** vs Placebo<br>**CP: A** | VEGFR 1-3, MET, AXL | **10.2** vs 8 months | 4% |
| REACH-2:<br>**Ramucirumab** vs Placebo<br>**CP: A, AFP ≥400** | VEGFR2; VEGF-A/C/D | **8.5** vs 7.3 months | 5% |
| CHECKMATE 040 (Phase 1/2):<br>**Nivolumab**<br>**CP: A or B** | PD-1 | **15 months** | 14% |
| KEYNOTE 224:<br>**Pembrolizumab**<br>**CP: A** | PD-1 | **12.9 months** | 17% |
| CHECKMATE 040:<br>**Nivolumab + Ipilimumab**<br>**CP: A** | PD-1, CTLA-4 | **23 months** | **33%**<br><br>**CR: 8%** |

# Systemic Therapy: MOA



# Potential Toxicities



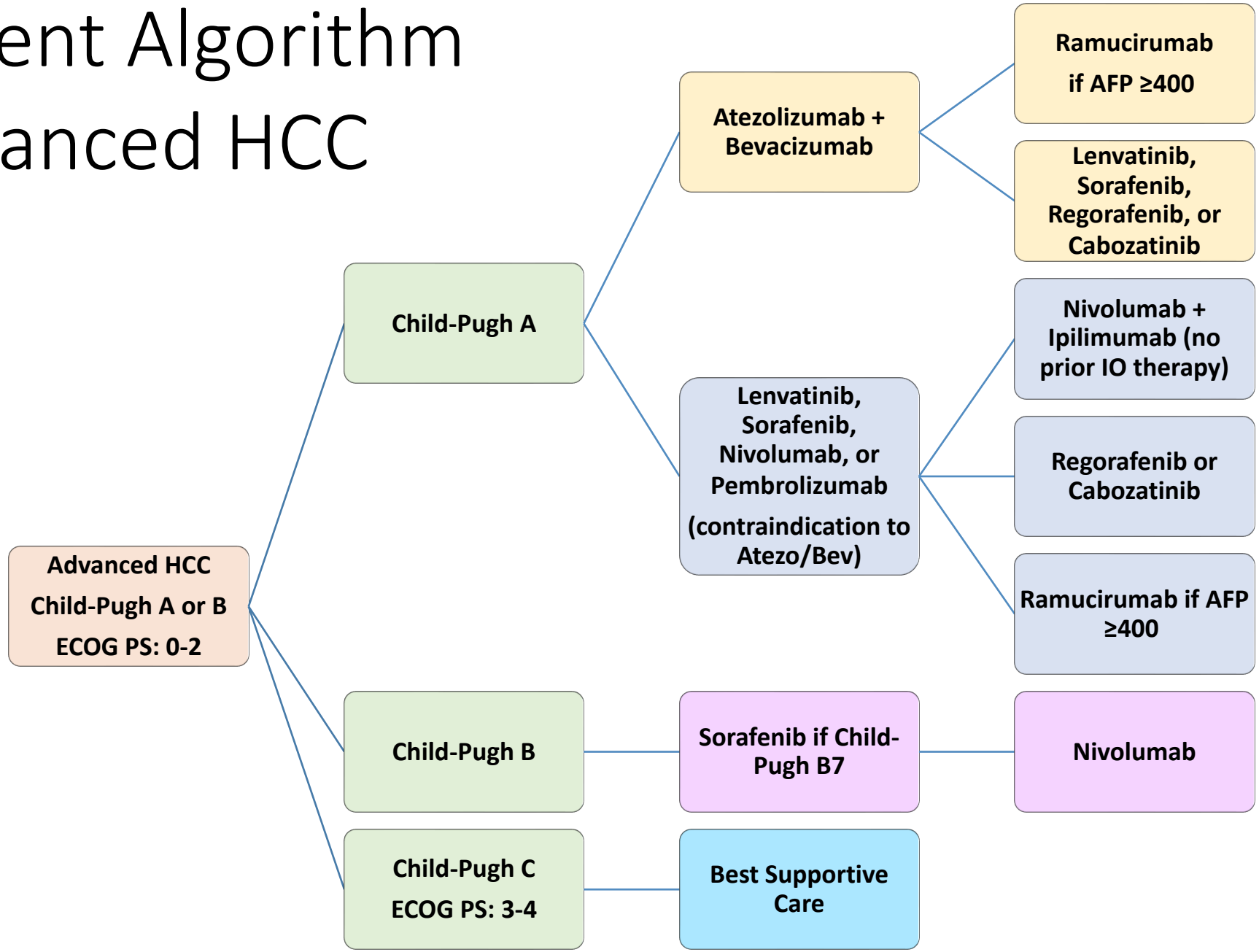

**Atezolizumab + Bevacizumab:**

- GIB
- Fistula formation, delayed wound healing
- HTN, proteinuria
- Stroke, VTE
- Untreated viral hepatitis (B/C): hepatotoxicity, AI hepatitis
- Avoid: autoimmune disease, post-solid organ transplant

**TKIs:**

- Avoid: vascular disease, hx of stroke
- Poorly controlled HTN

# Treatment Algorithm for Advanced HCC



# Back to Mr. Disparo…

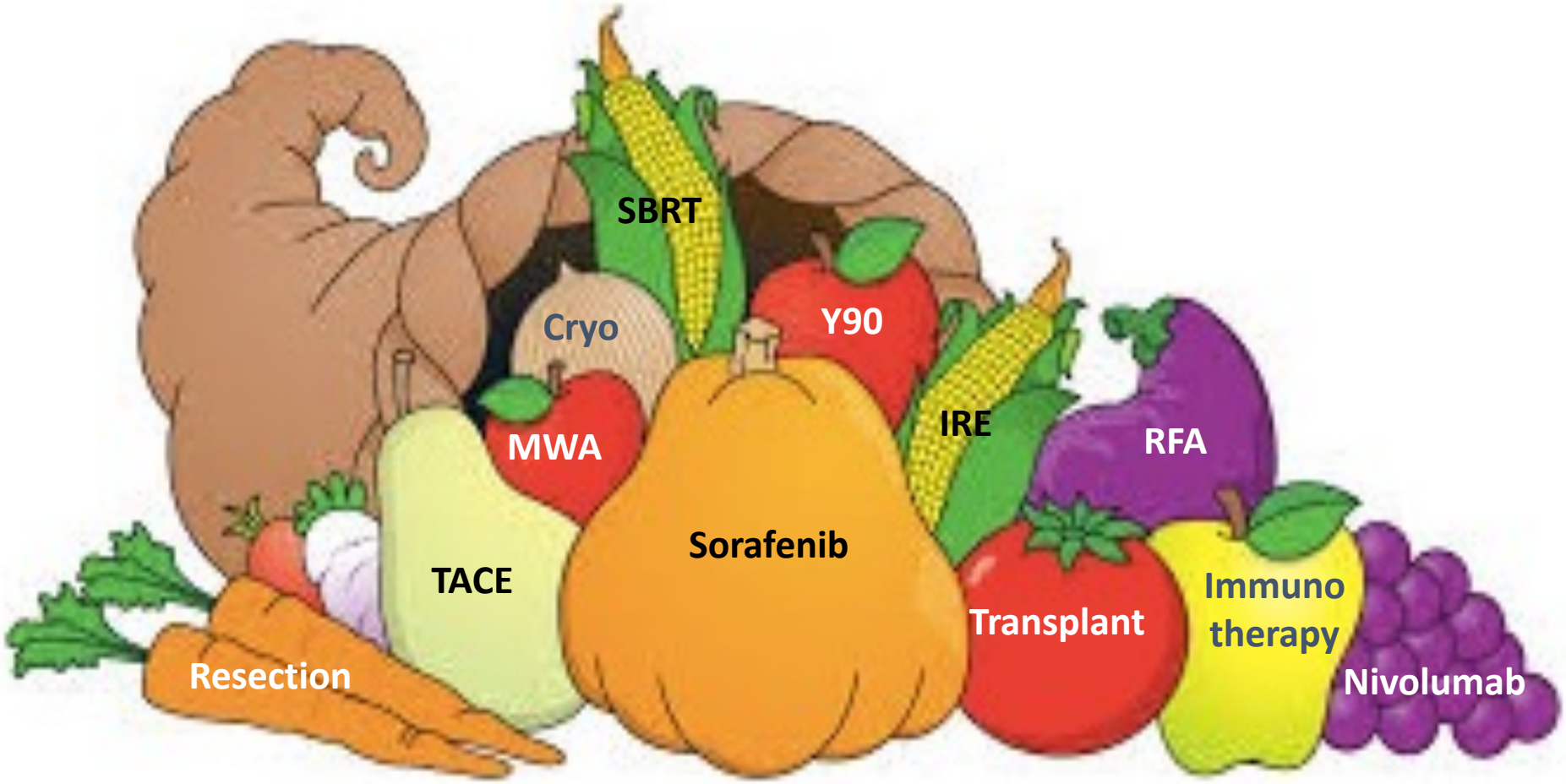
Staging Workup:

- Solitary tumor (6.5 cm) in right hepatic lobe
- No extrahepatic disease or macrovascular involvement
- Child-Pugh Score: A5, BCLC Stage B
- **Patient referred to liver transplant team for transplant evaluation**

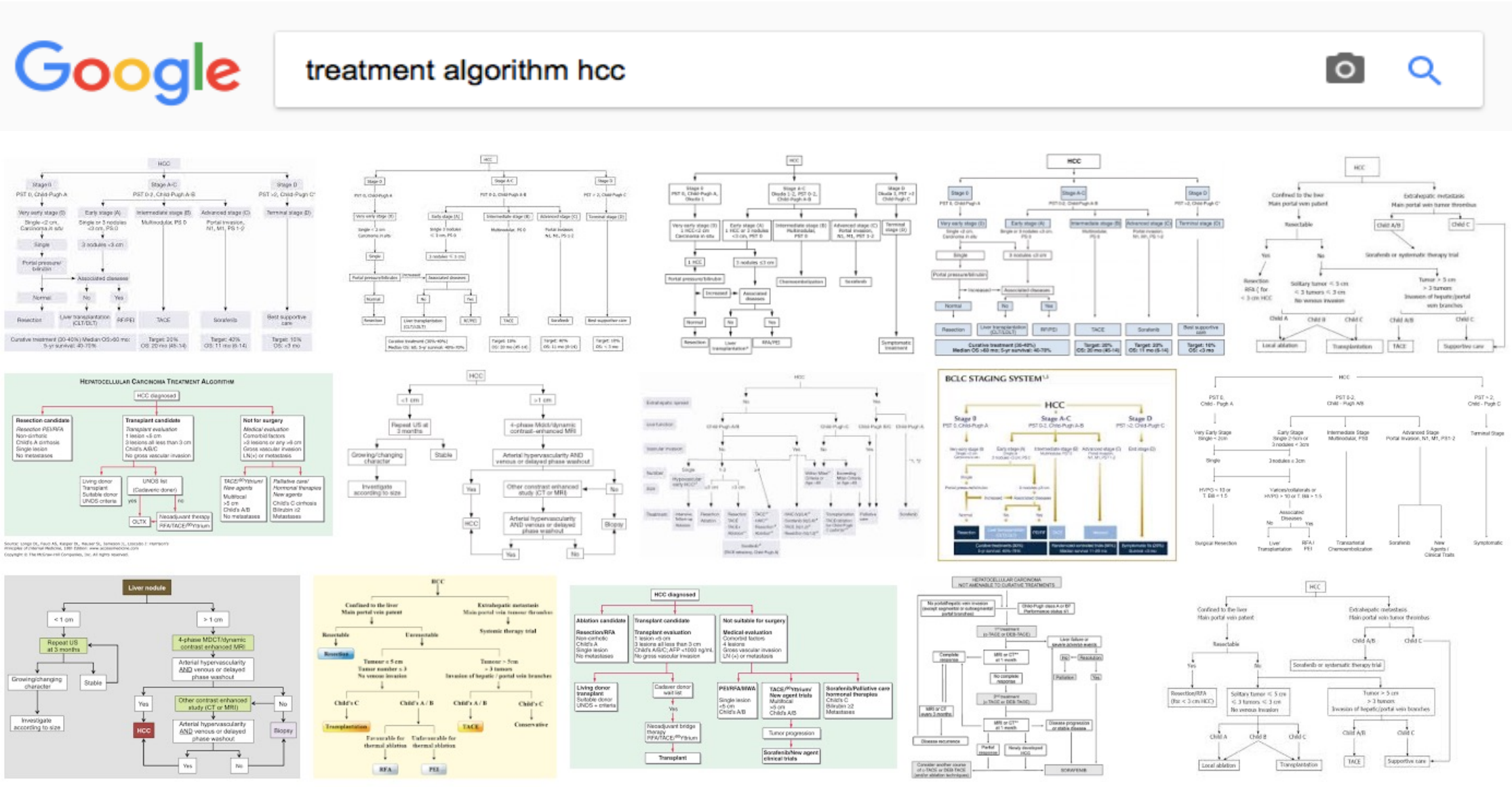
# Surgery is Often the Best Therapy

Danielle Fritze, MD

# Good News


SBRT
Cryo
Y90
MWA
IRE
RFA
TACE
Sorafenib
Transplant
Immuno therapy
Nivolumab
Resection

# Bad (?) News

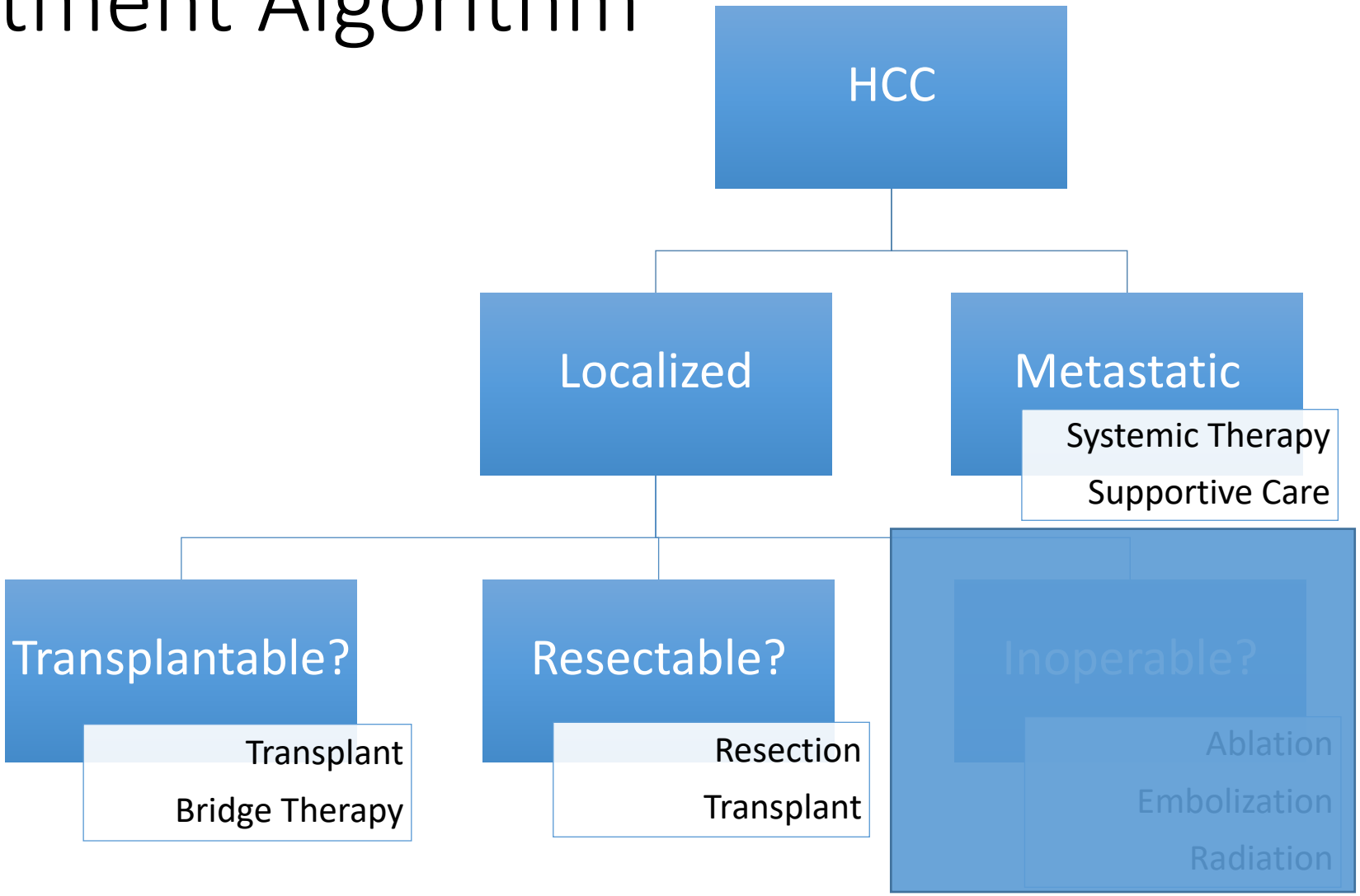

Google
treatment algorithm hcc
HCC
Stage 0
Stage A-C
Stage D
Very early stage (0)
Early stage (A)
Intermediate stage (B)
Advanced stage (C)
Terminal stage (D)
Resection
Liver transplantation (OLT/DLT)
RFA/PEI
TACE
Sorafenib
Best supportive care
Hepatocellular Carcinoma Treatment Algorithm
HCC diagnosed
Resection candidate
Transplant candidate
Not for surgery
Repeat US at 3 months
Growing/changing character
Stable
Investigate according to size
4-phase MDCT/dynamic contrast-enhanced MRI
Arterial hypervascularity AND venous or delayed phase washout
Other contrast enhanced study (CT or MRI)
Biopsy
BCLC STAGING SYSTEM
Liver nodule
< 1 cm
> 1 cm
Confined to the liver
Main portal vein patent
Extrahepatic metastasis
Resectable
Unresectable
Systemic therapy trial
Child's C
Child's A / B
Transplantation
TACE
Conservative
RFA
PEI
Ablation candidate
Transplant candidate
Not suitable for surgery
Resection/RFA
Transplant evaluation
Medical evaluation
Cadaver donor wait list
Neoadjuvant bridge therapy
Transplant
Tumor progression
Sorafenib/New agent clinical trials
HEPATOCELLULAR CARCINOMA NOT AMENABLE TO CURATIVE TREATMENTS
Sorafenib or systemic therapy trial
Local ablation

# Objectives

*To better understand…*

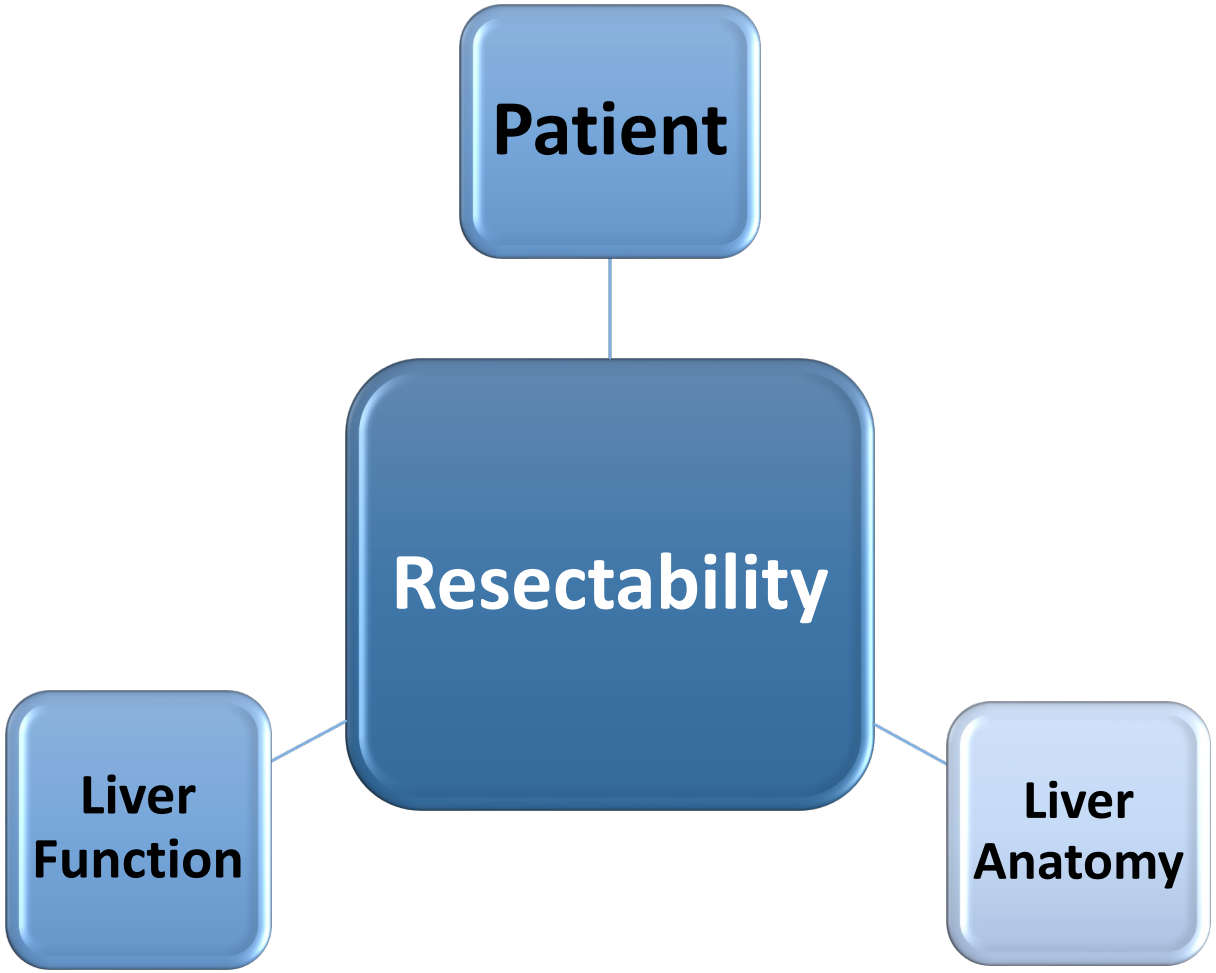
- The place of surgical resection and transplantation in HCC treatment algorithms
- Determinants of candidacy for resectional surgery and transplantation
- Oncologic outcomes of resection and transplantation
- Our patient’s next steps in evaluation and treatment options

# HCC Treatment Algorithm



# HCC: Resection

- Can it be done?
- Can it be done safely for the liver?
- Can it be done safely for the patient?

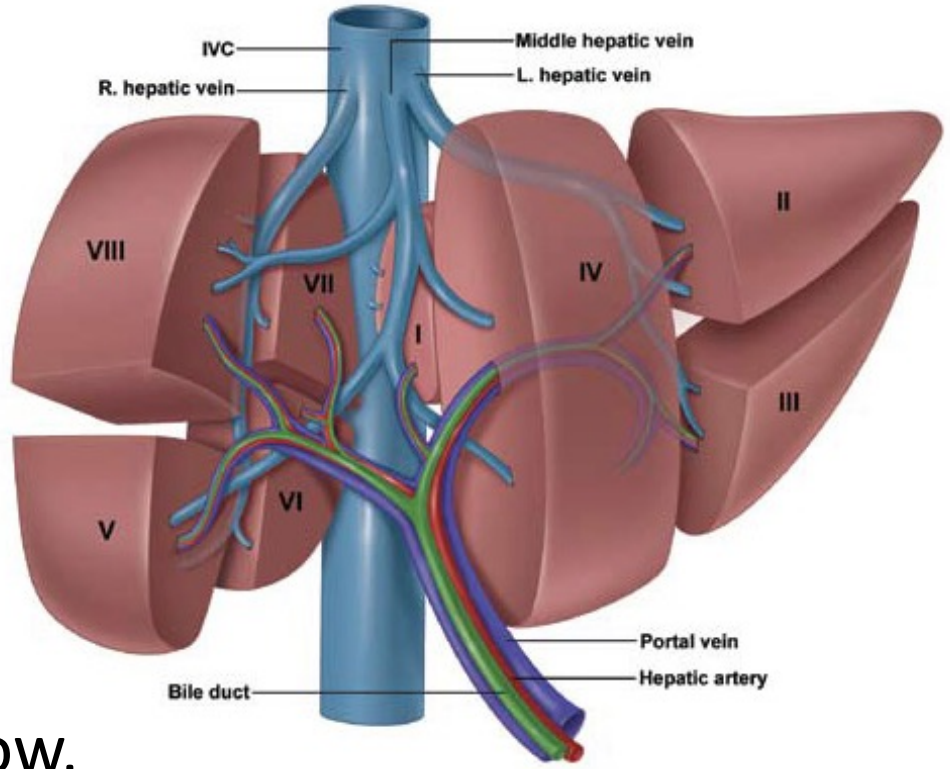



- *Should it be done?*
- *Is there a safer or more effective alternative?*

# HCC Resection: *Can It Be Done?*

## Anatomy

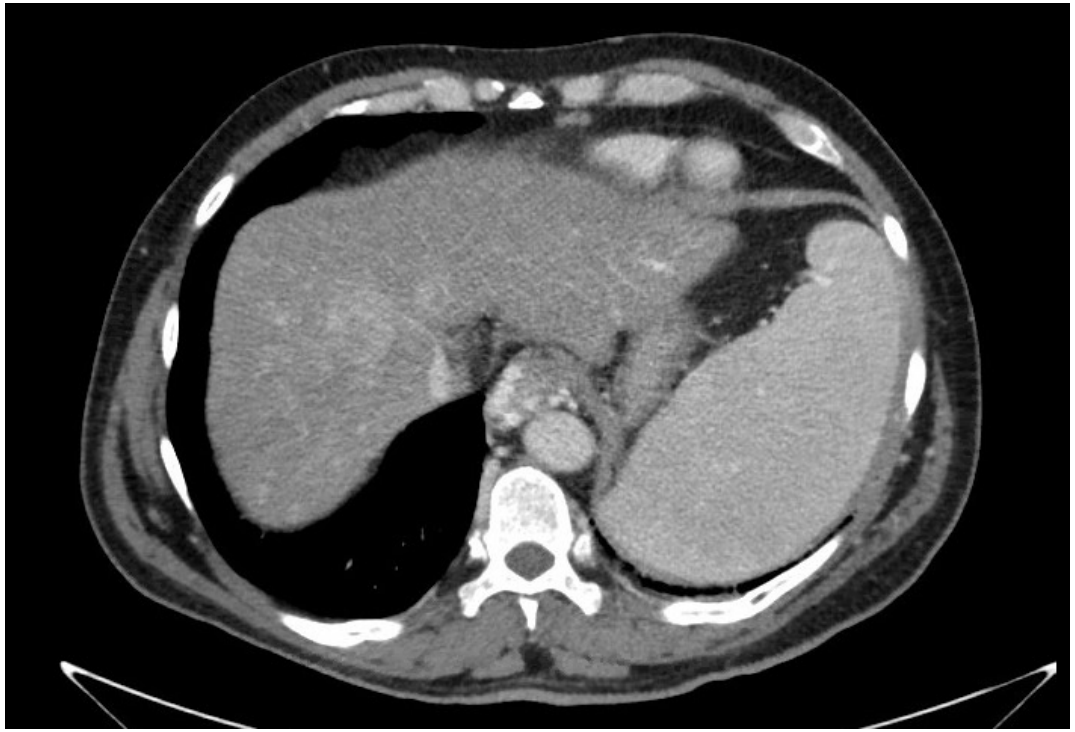
- Segments requiring resection
- Relationship to major vascular structures
- Ability to achieve negative margins
- Preservation of arterial and portal venous inflow, venous outflow, and biliary drainage to the remaining segments

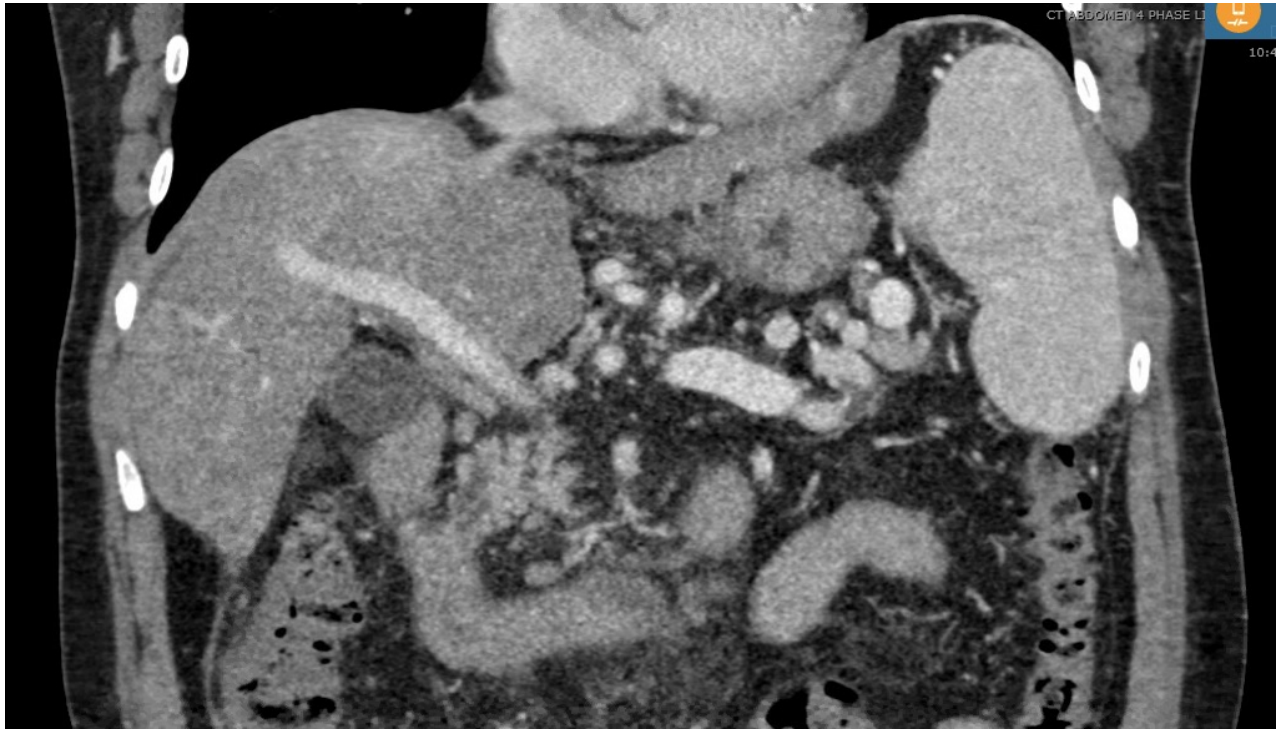


# HCC Resection: *Can It Be Done?*

## Anatomic Assessment

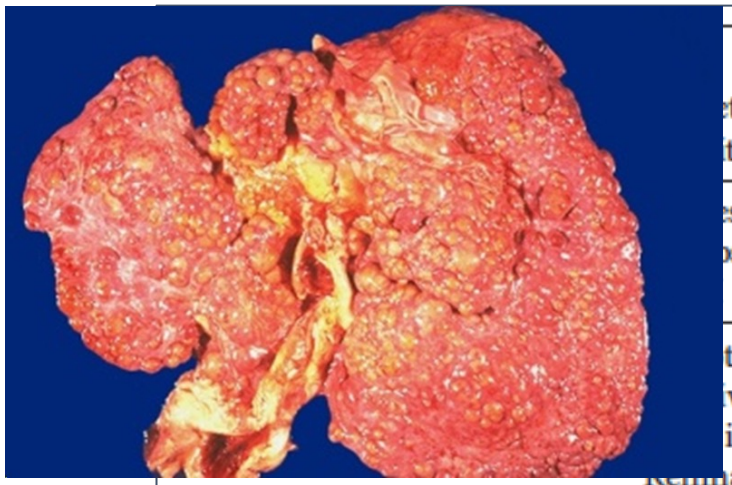
- 4-phase CT or contrast-enhanced liver MR

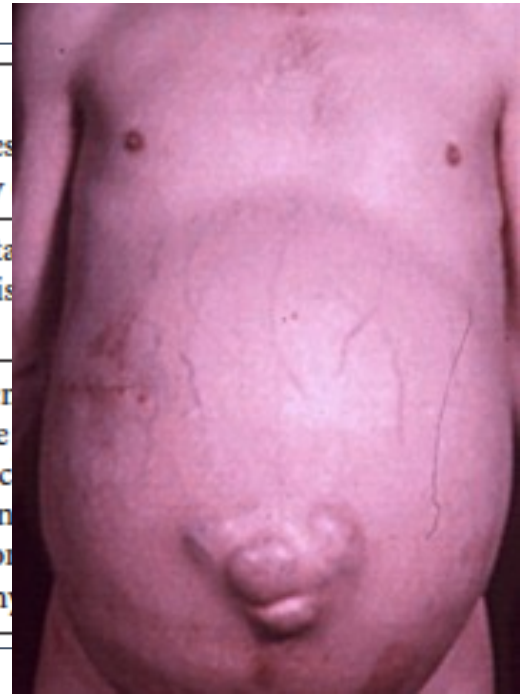




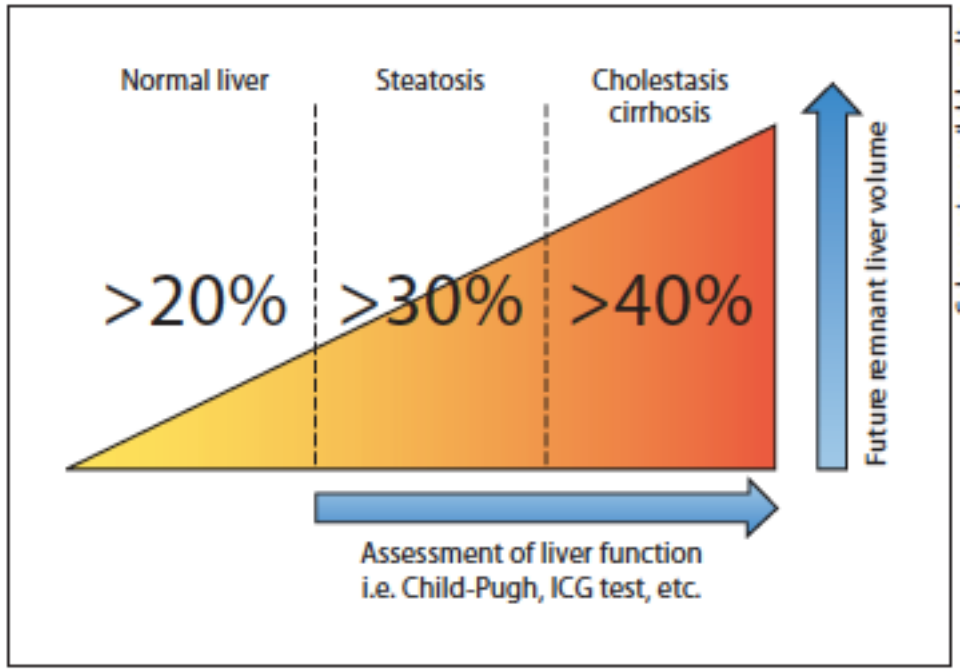
# HCC Resection:
# *Can It Be Done Safely For The Liver?*

## Risk for Post-op Hepatic Failure





## Remnant Adequacy




Dig Surg 2012;29:6–17

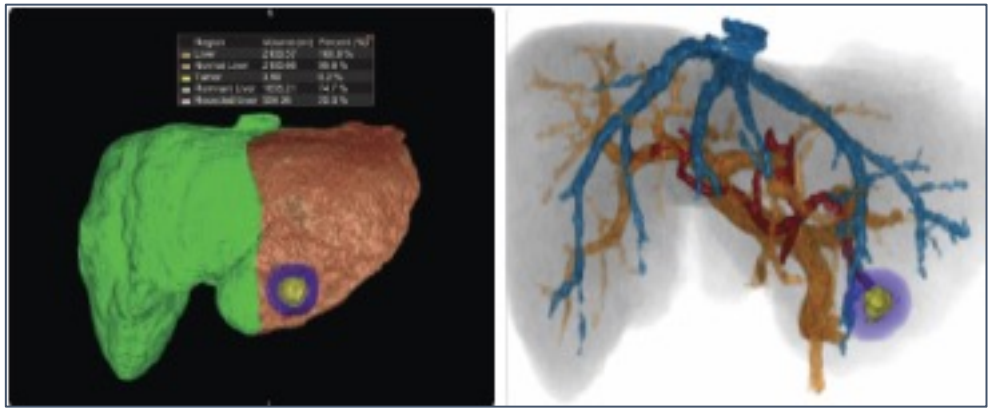
# HCC Resection:
# *Can It Be Done Safely For The Liver?*

## Risk for Post-op Hepatic Failure

- Formal Hepatology Assessment
  - History and Physical Exam
  - Labs
    - Liver enzymes
    - Bilirubin
    - Coags
  - Liver biopsy
  - Portal Manometry

## Remnant Adequacy

- Advanced imaging + volumetrics



- Surgical Plan

*Tropical Gastroenterology 2010;31(3):213–216;* Vitalimages.com

# HCC Resection:
# *Can It Be Done Safely For The Patient?*

## Patient Considerations

- Global patient suitability for surgery
  - Age
  - Functional capacity
  - Cardiopulmonary reserve
  - Comorbidities
  - Nutrition
  - EtOH
  - Patient preference

# HCC Resection: Outcomes

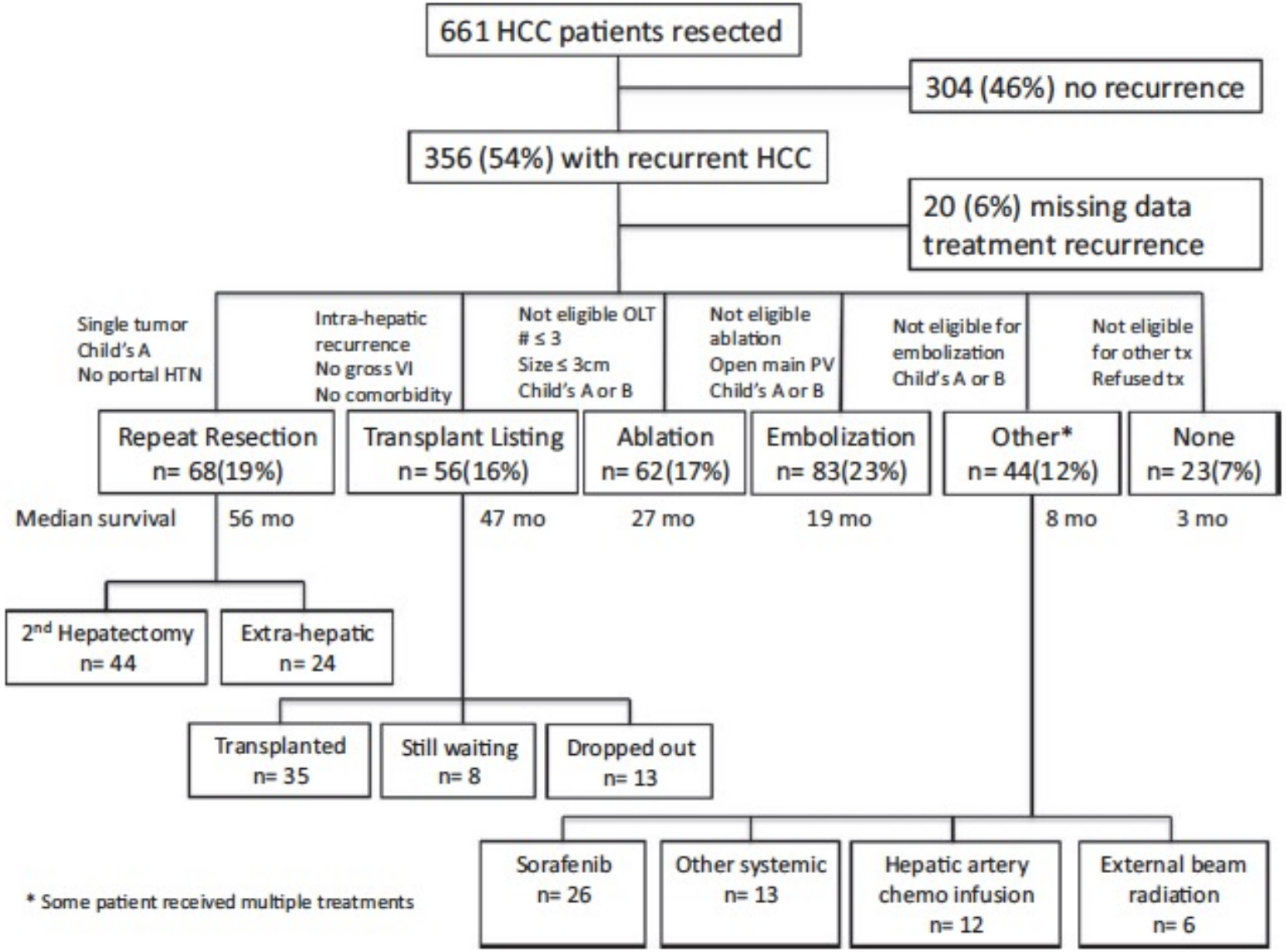
- Risk for Recurrence: >50%

  (up to 70% in some studies)

- Of patients with recurrence
  - 19% - Repeat Resection
  - 12% - Transplanted or Awaiting Transplant

**High recurrence rates**

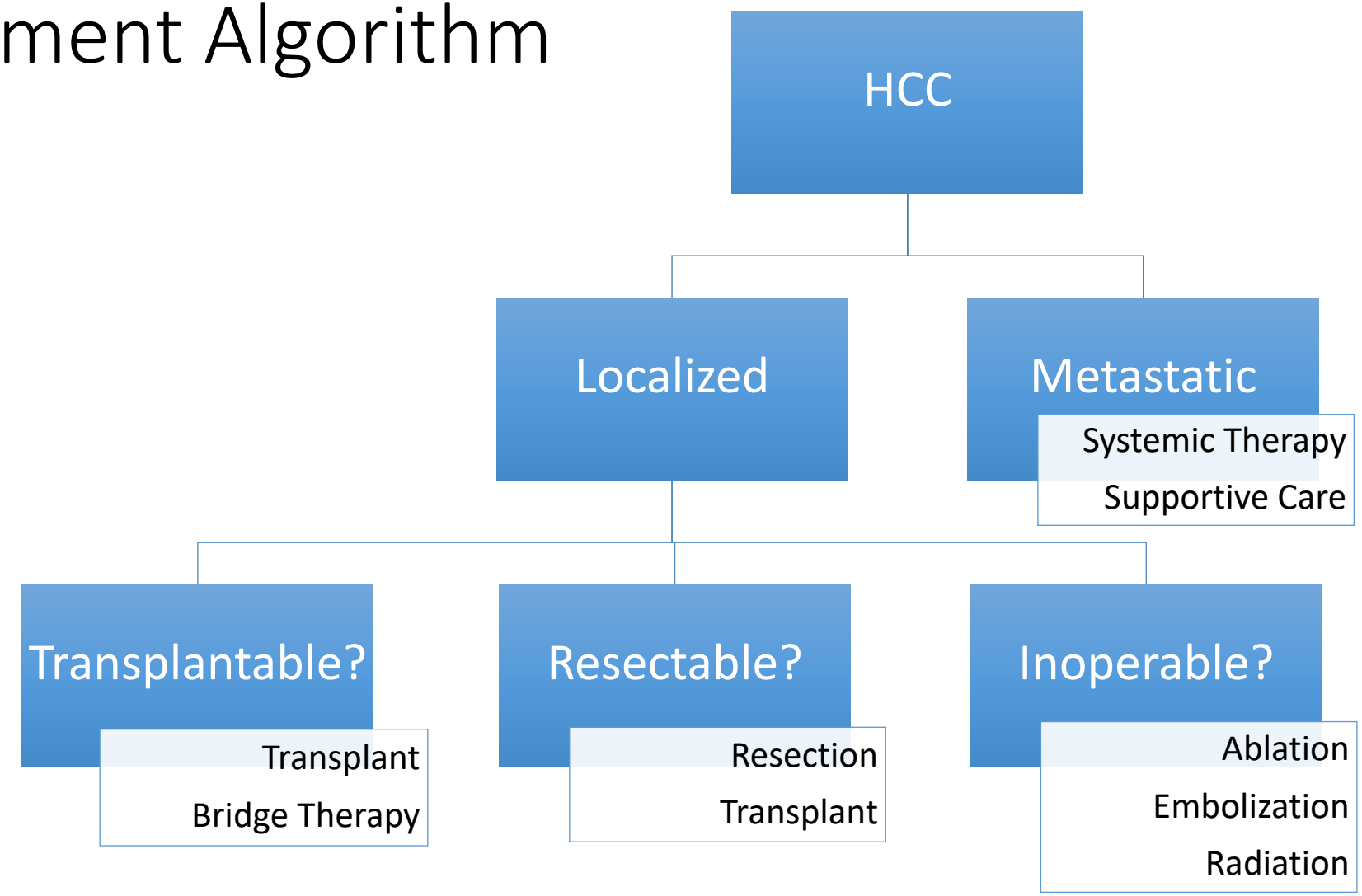
- <1/3 pts with recurrence undergo surgical treatment




(*Ann Surg* 2015;261:947–955)

FIGURE 1. Flow diagram of patients included in the study.

# HCC Treatment Algorithm



# Transplantation

## The Ideal Oncologic Approach?

- Complete (radical) resection of existing tumors

- Addresses the field defect by removing the entire at-risk liver

## With a major bonus:

- Corrects the underlying cirrhosis & portal hypertension

## And a major caveat:

- Cancer is a contra-indication to transplantation

# Transplantation

- First transplants in HCC patients were performed in those with locally advanced, unresectable disease

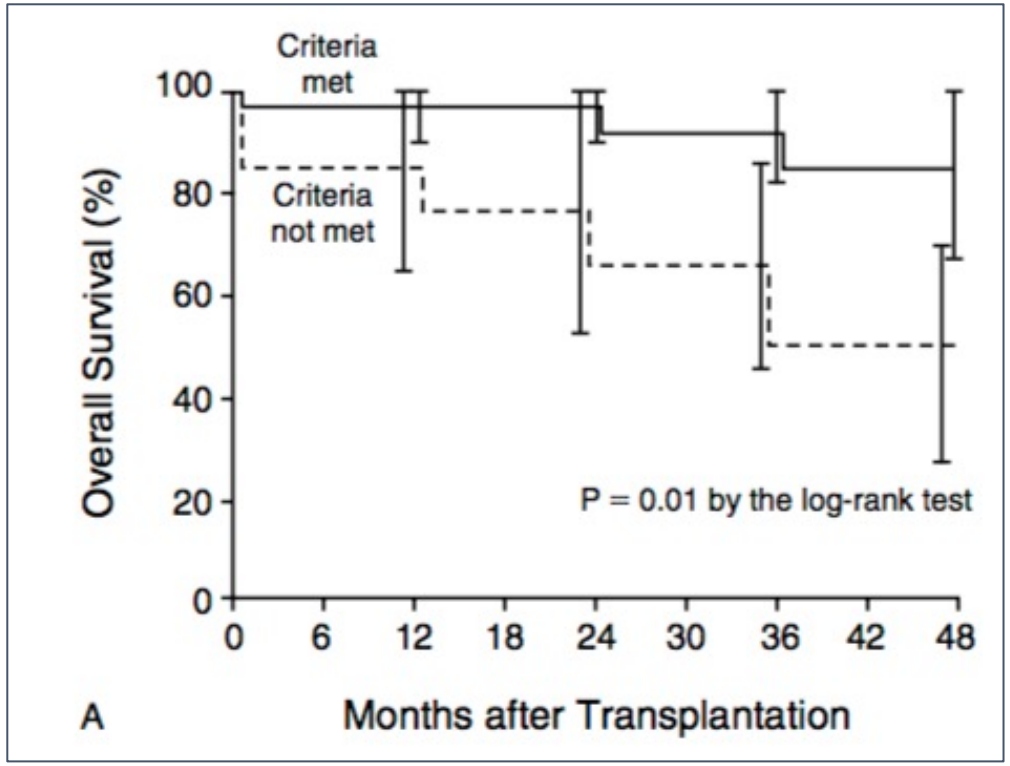
- Outcomes were terrible; transplant for HCC was largely abandoned
  - 1986: HHS Moratorium on Liver Transplantation for HCC

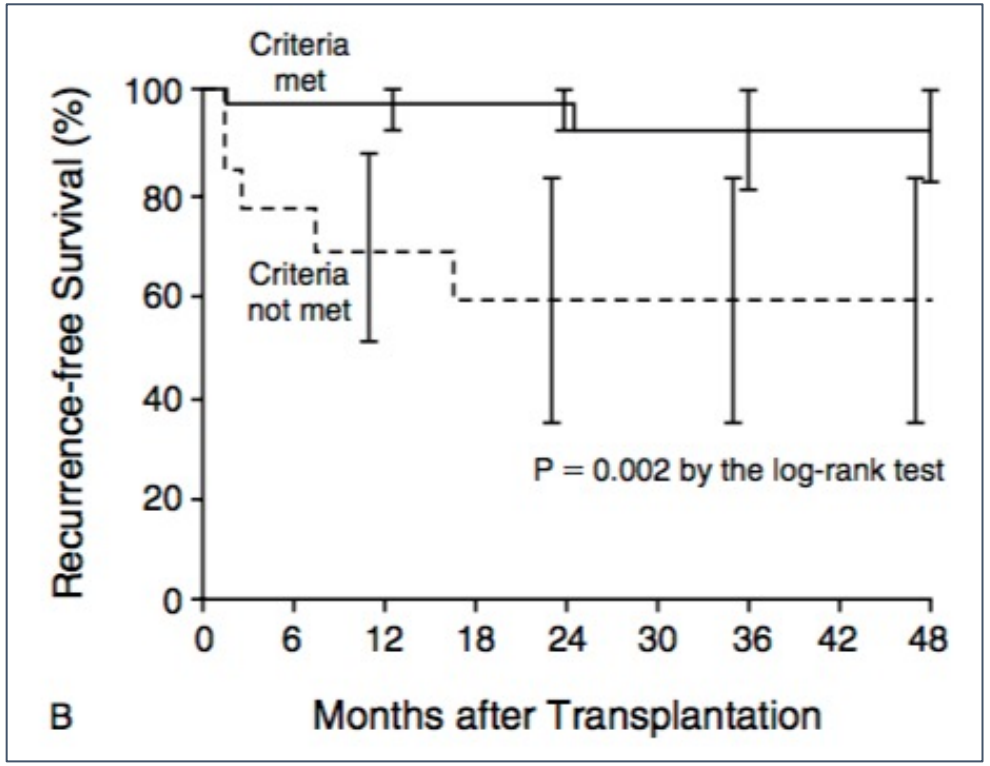
- Glimmer of hope:
  - Patients transplanted for other indications, but incidental HCC discovered on explant path do well

- ***New strategy***
  - Identify patients with lower oncologic risk, thus more likely to survive long-term after transplantation

# Transplantation: Milan Criteria

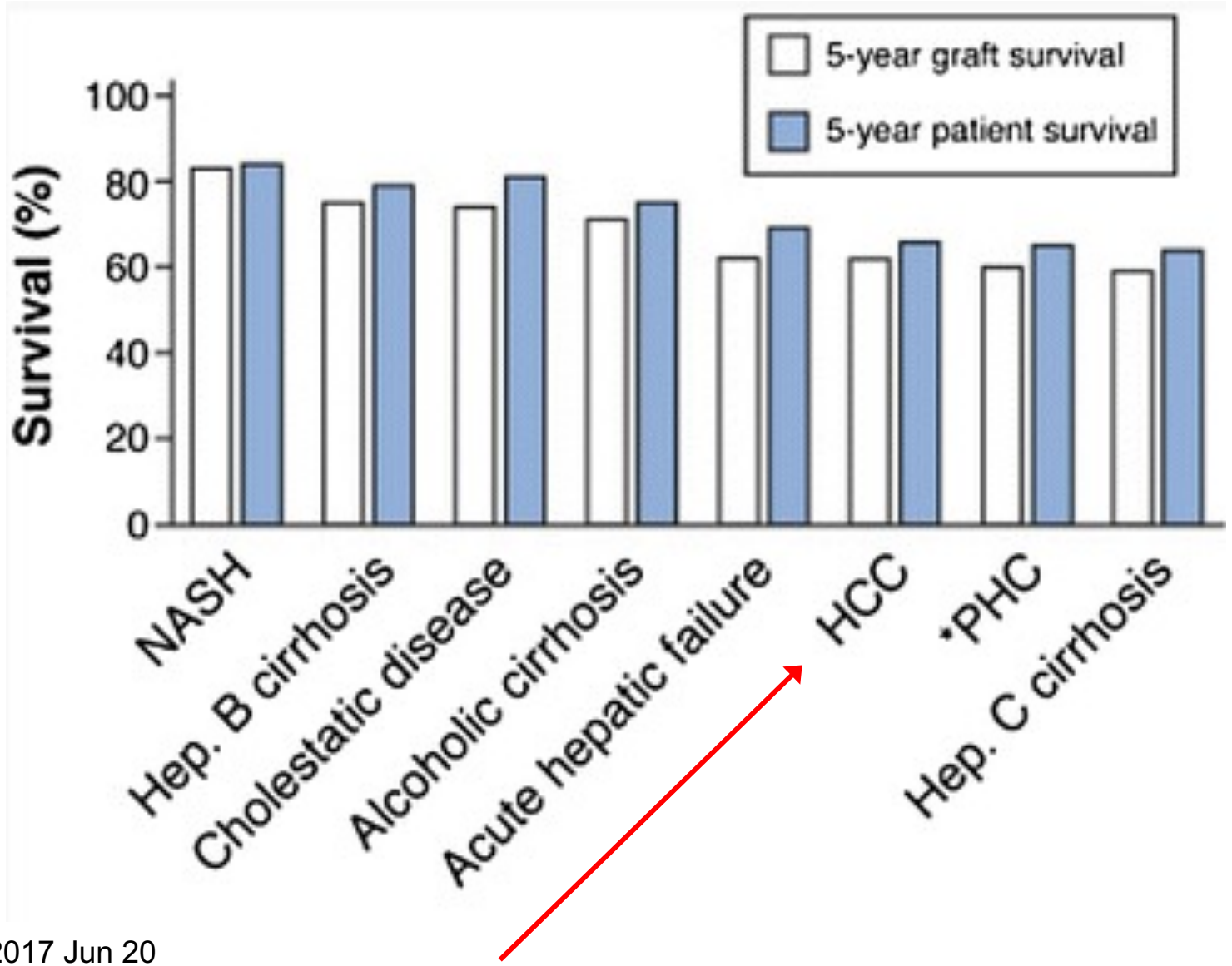
- 1 tumor <5cm
- 3 tumors <3cm each
- No macrovascular invasion or extra-hepatic spread




*N Engl J Med.* 1996 Mar 14;334(11):693-9.

# Transplantation: Current Outcomes




Abdom Radiol (NY). 2017 Jun 20

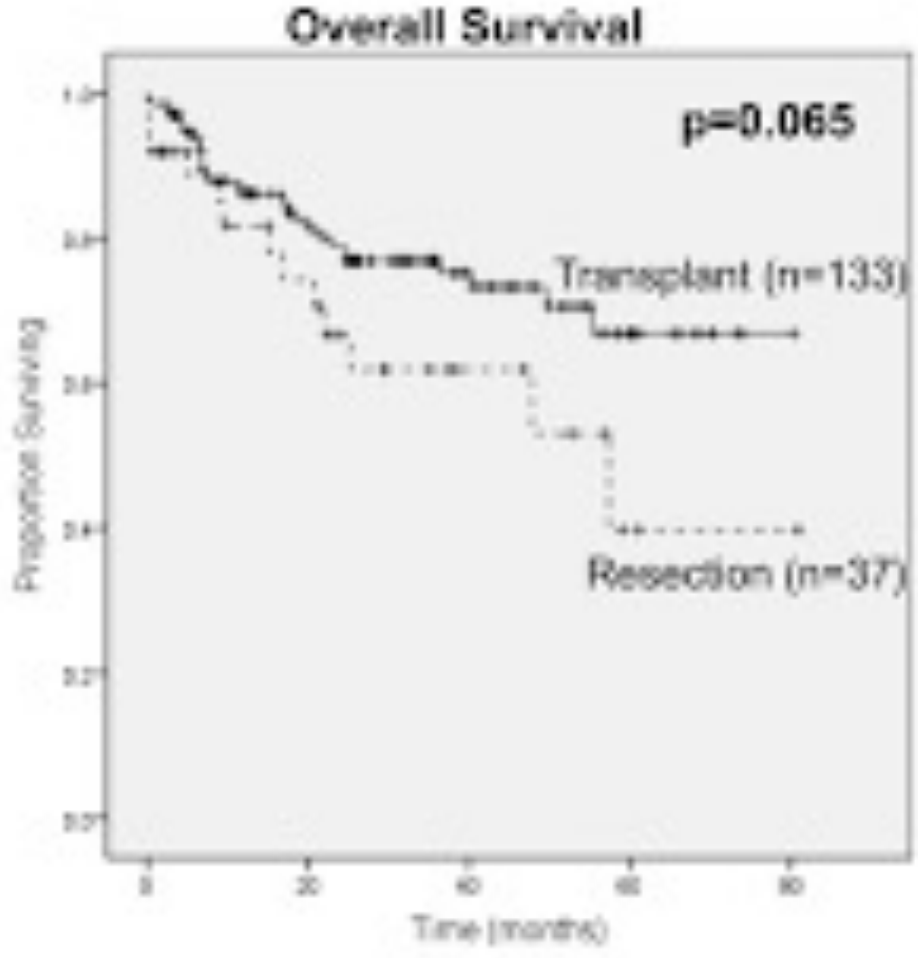
# Transplantation for HCC: Candidacy

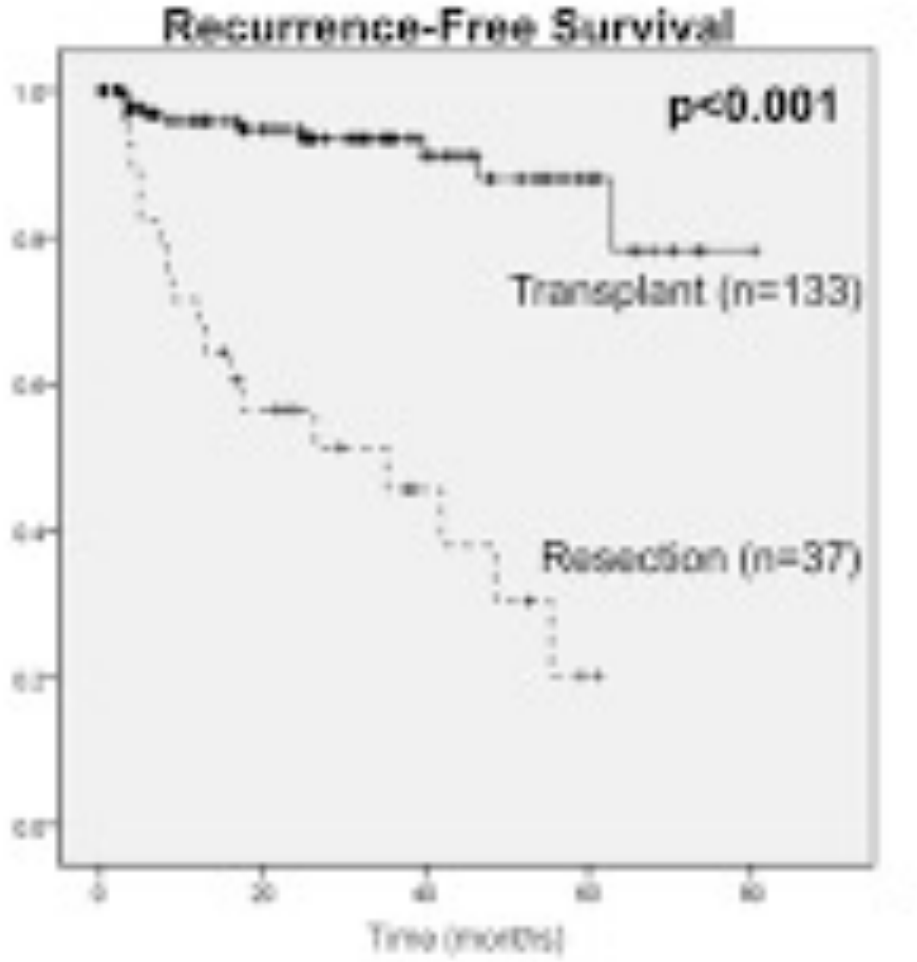
- General Transplant Candidacy
  - Physiologic reserve
  - Cardiopulmonary health
  - Anatomically suitable
  - Nutrition
  - Support

- HCC Criteria
  - Milan criteria (single tumor <5cm or up to 3 <3cm)
  - **Downstaged** to Milan Criteria
  - AFP <1000
  - No metastatic disease

- **Average time to transplantation for HCC: 18 months**

# Transplantation vs Resection

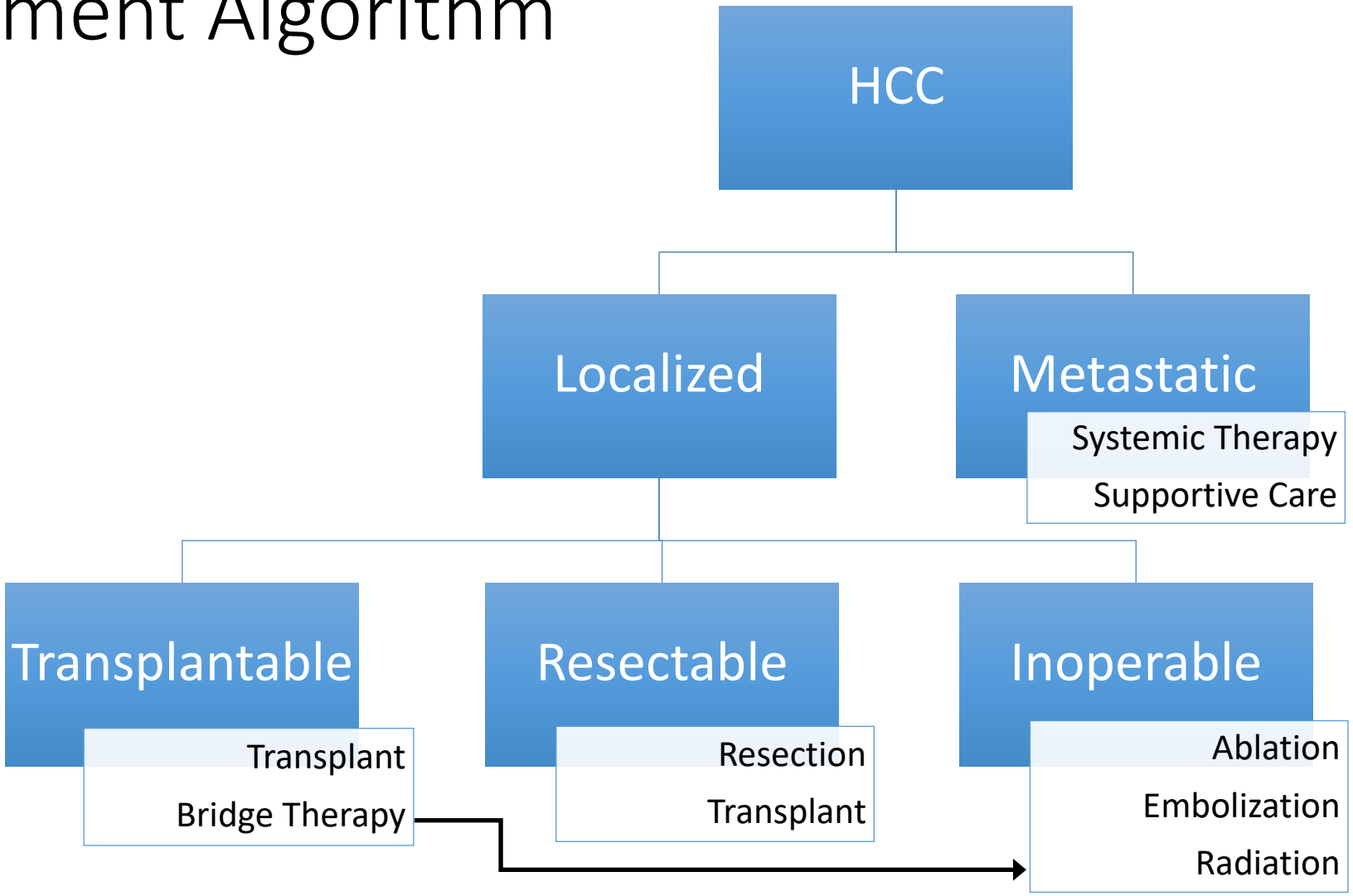


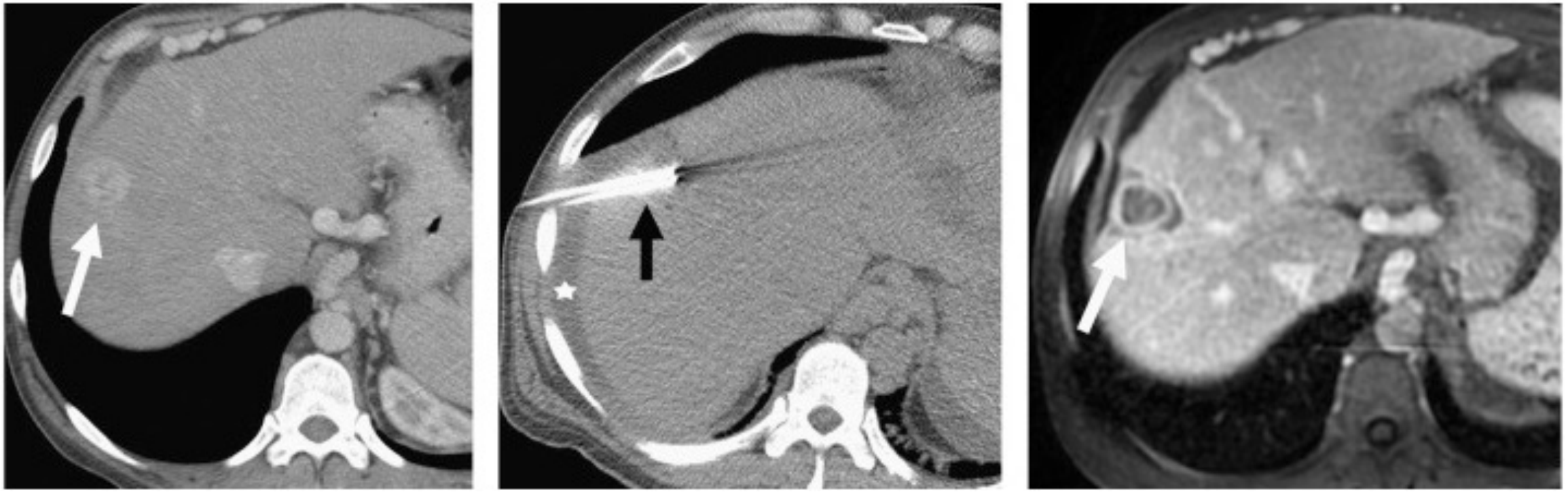

**Transplant Versus Resection for the Management of Hepatocellular Carcinoma in the Post-2006 MELD Exception Era At a Single Institution in the Southeast UNOS Region**

*Malcolm H. Squires*[*1], *Steven Hanish*[2], *Sarah B. Fisher*[1], *Cristen Garrett*[2], *David Kooby*[1], *Juan M. Sarmiento*[3],

# HCC Treatment Algorithm



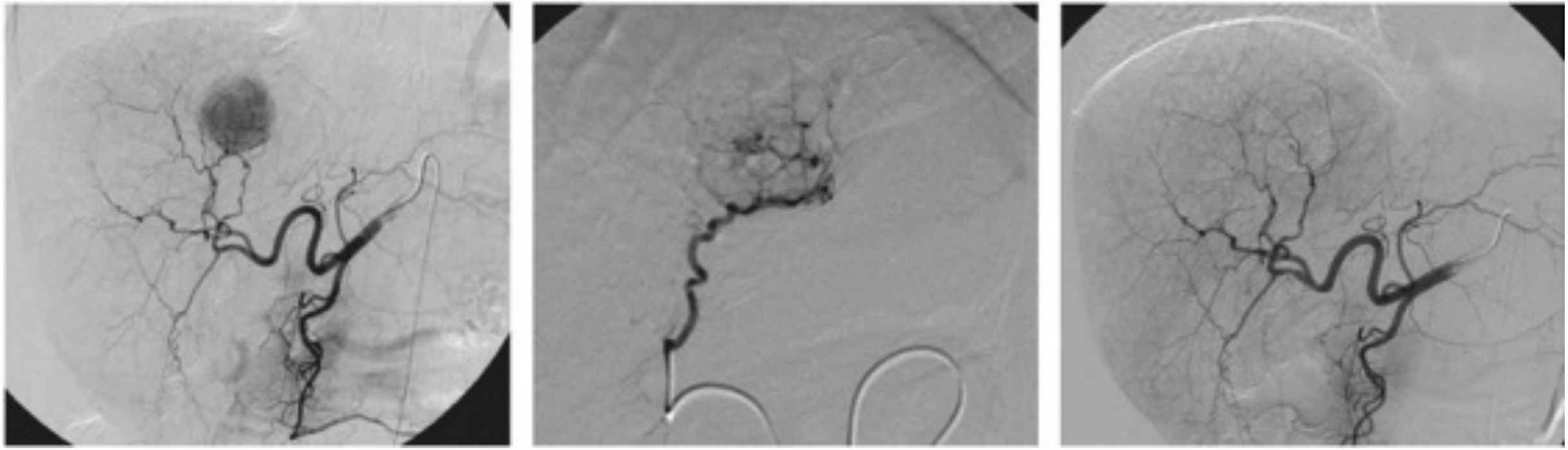
# Liver Directed Therapies: Ablation



Radiofrequency (RFA)
Microwave (MWA)
Cryoablation

Semin Intervent Radiol. 2013 Mar; 30(1): 49–55.

# Liver Directed Therapies: Embolization



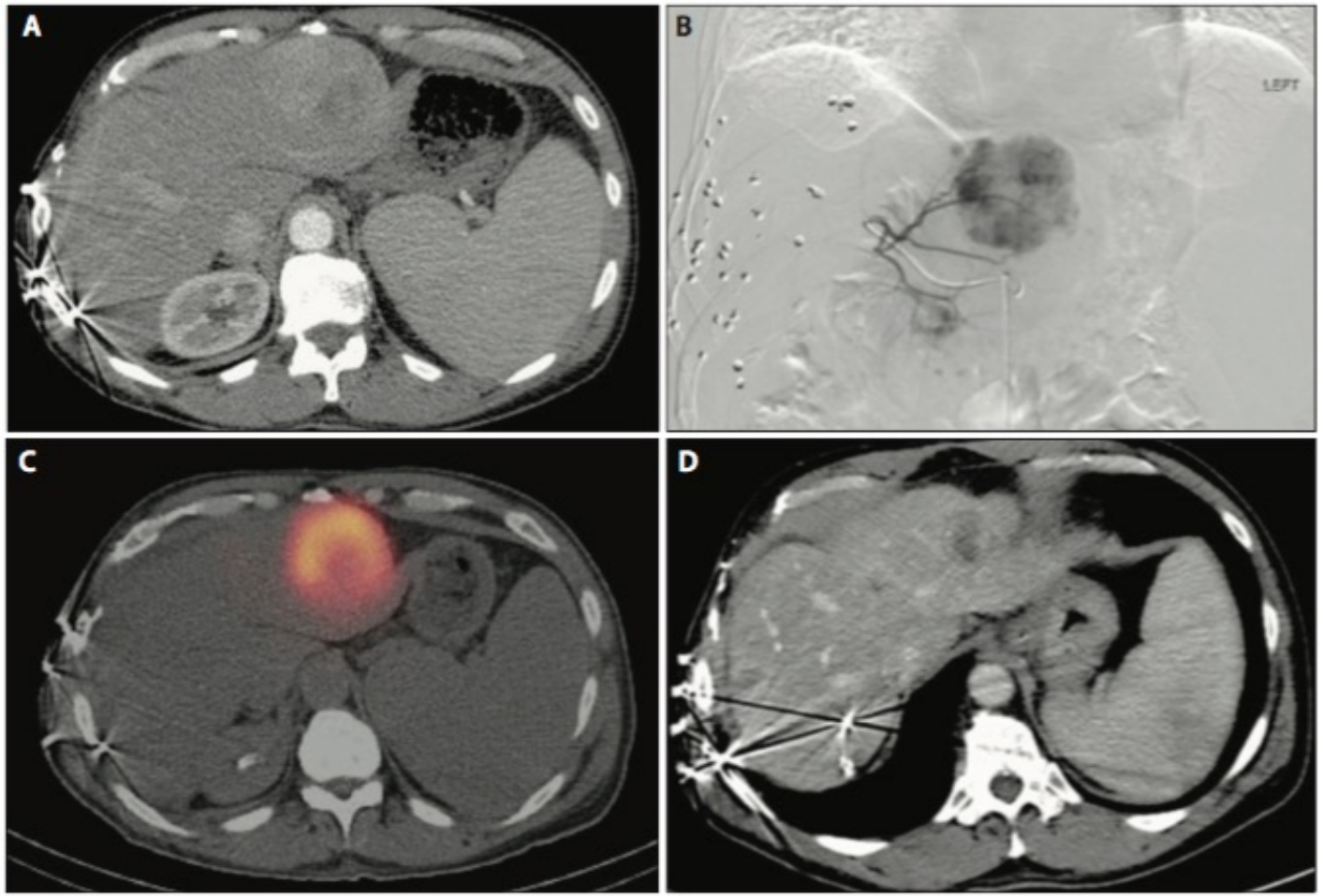
Bland Embolization

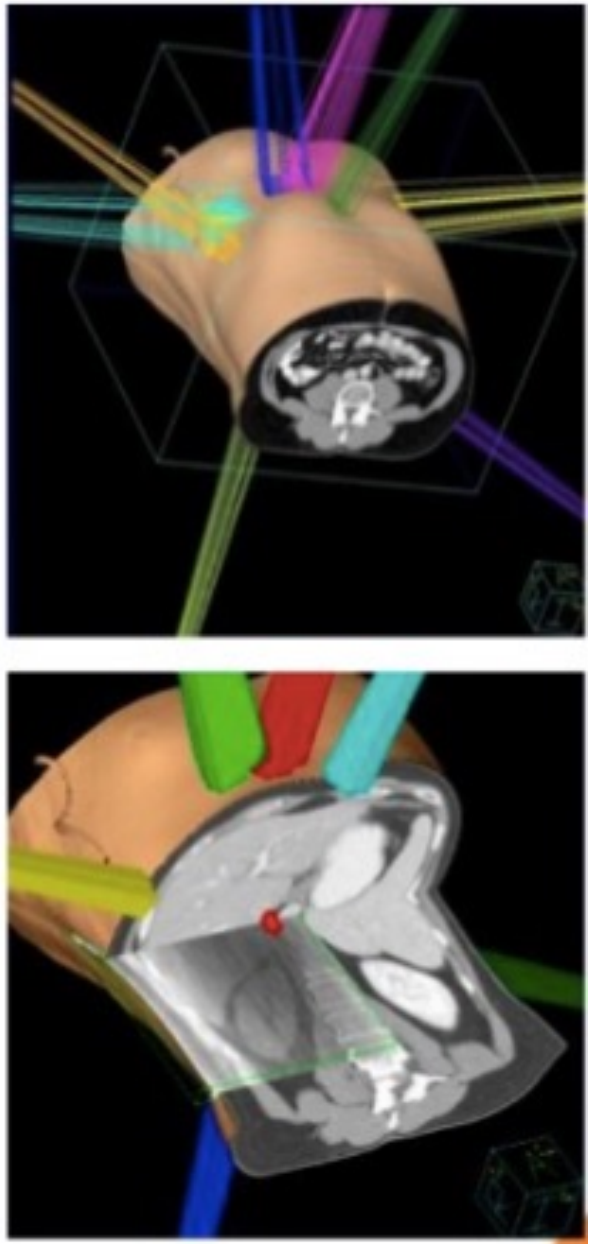
Trans-arterial Chemo-embolization (TACE)

European Society of Radiology; http://blog.myesr.org/endovascular-procedures-in-hcc-treatment/

# Liver Directed Therapies: Radiation

**Trans-arterial Radio-embolization (TARE)**



**Stereotactic Body Radiation Therapy (SBRT)**

Endovasc Tod. 2015 Oct; 78-86; Vellayappan B. *Latest advances in radiotherapy for hepatocellular carcinoma.* HPBA Singapore 09/27/2014.

# Mr. Disparo

- Comprehensive tumor center evaluation (AM)
  - Hepatology, Oncology, Social Work, Dietitian
  - Labs
  - Imaging: CT chest/abdomen/pelvis including 4 phase liver

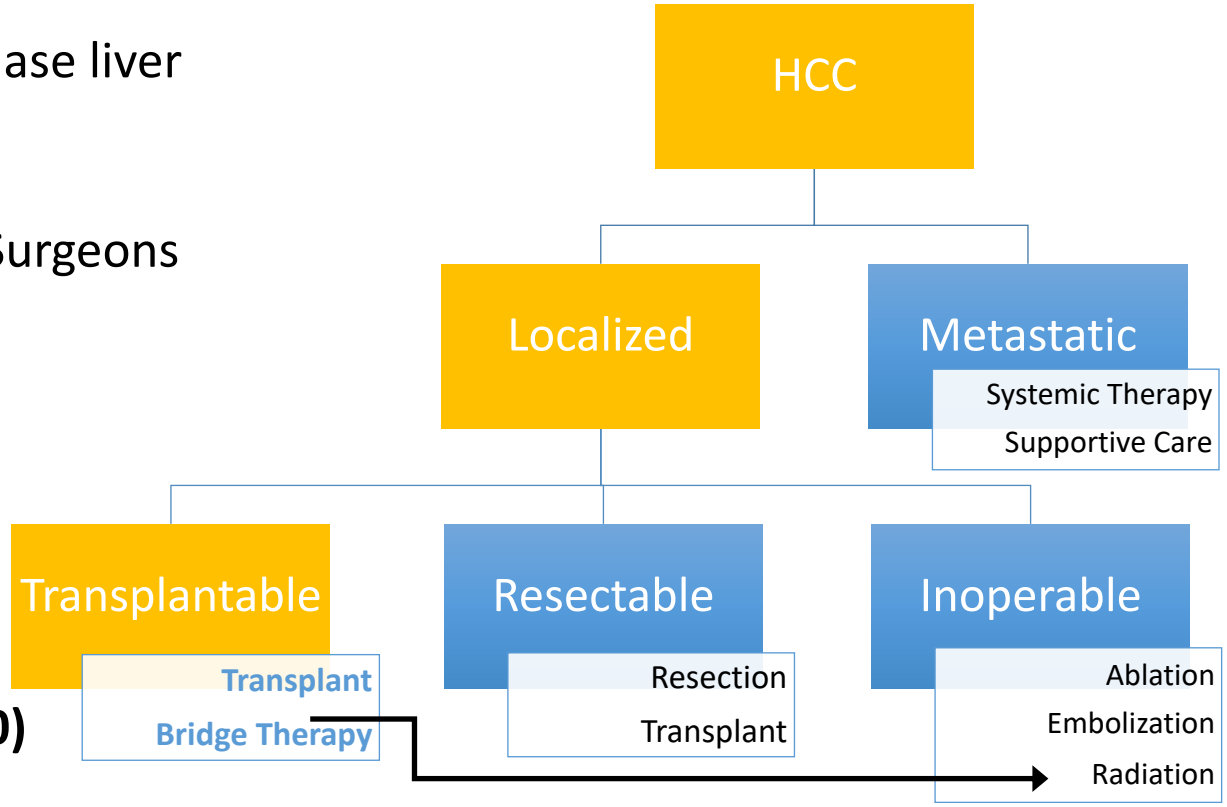
- Tumor Board Review (noon)
  - Hepatology, Onc, RadOnc, Radiology, Pathology, Surgeons

  - 6.5cm HCC, no metastatic disease
  - Cirrhosis with portal HTN
  - Otherwise healthy

- **Recommendations:**
  - **Evaluation for liver transplant**
  - **Downstaging with radio-embolization (TARE/Y90)**

- Treatment Planning (PM)
  - Meeting with transplant surgeon and interventional radiologist
  - Schedule next steps in treatment

# HCC Treatment Algorithm



# HCC: Our Disease

***Our*** patients
***Our*** community

Our ***opportunity***
to study and understand

Our ***responsibility***
to treat HCC better here than anywhere else

UT Health
San Antonio

# Sometimes Two Surgeries Are Better Than One

Seiji Yamaguchi, MD

# What is Living Donor Liver Transplantation (LDLT)?

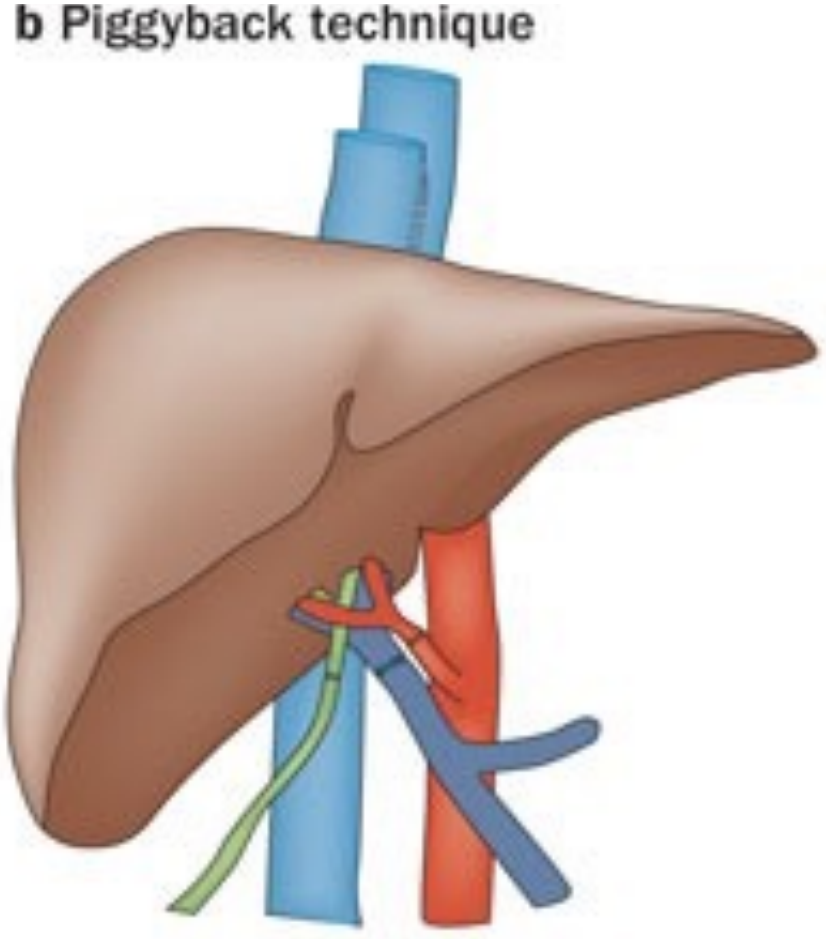
- As opposed to deceased donor liver transplant, the transplanted liver comes from a **healthy live patient and there could essentially be no wait time**

- **Since it's a live donor, only part of the donor's liver can be used for transplant, and only segmental arteries, veins and bile ducts can be included** with the partial liver graft

- The concept of **double equipoise** is crucial in evaluating a pair (donor and recipient) for live donor transplantation

- Donor and their initially intended recipient do not necessarily have to be compatible to make LDLT happen, as **pairs can participate in paired exchanges or chains.**

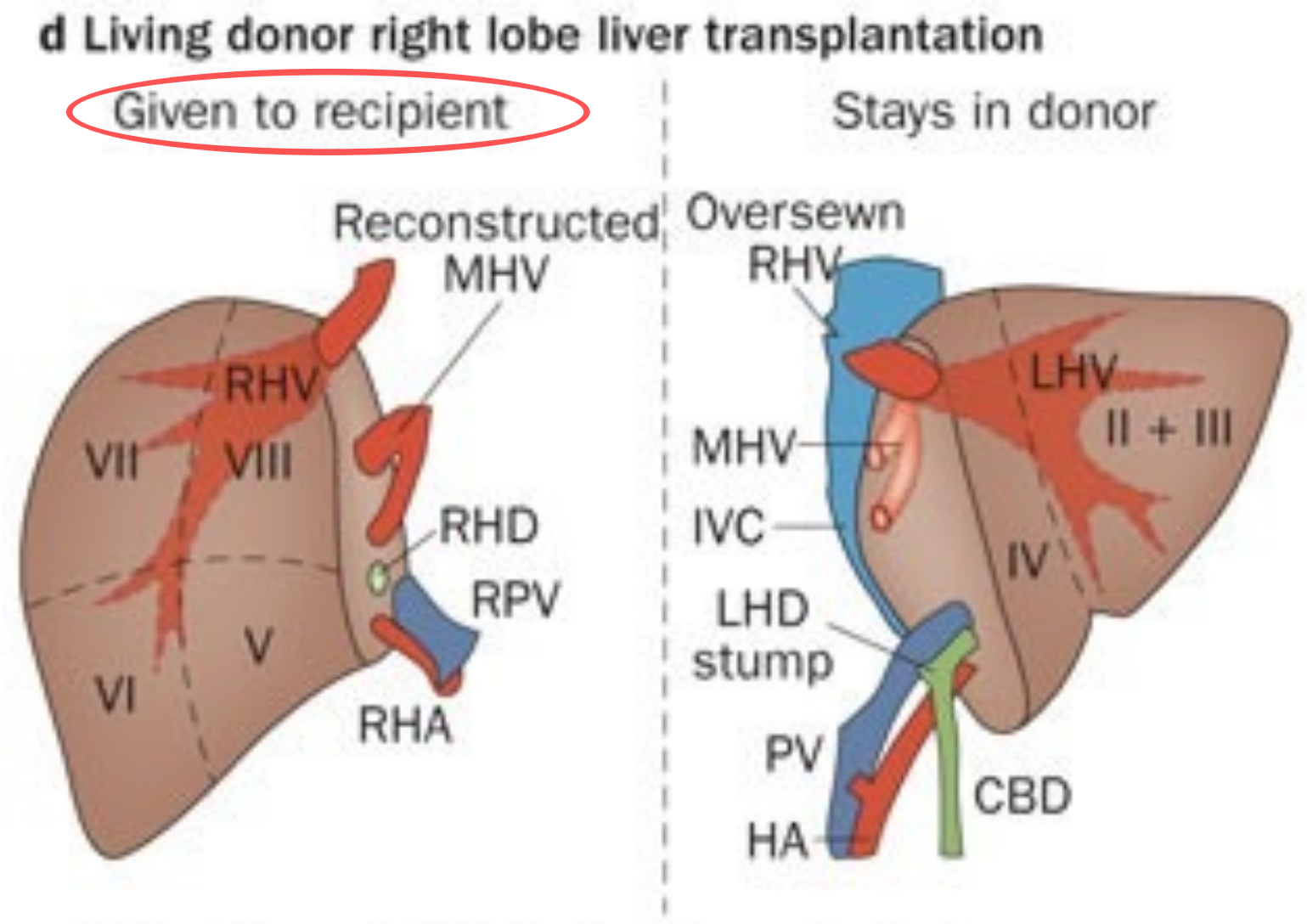
# Conventional Deceased Donor Liver Transplantation (Whole Liver Typically)




| | |
|---|---|
| IVC | inferior vena cava |
| HA | hepatic artery |
| PV | portal vein |
| CBD | common bile duct |
| LHA | left hepatic artery |
| LPV | left portal vein |
| LHD | left hepatic duct |
| LHV | left hepatic vein |
| RHA | right hepatic artery |
| RPV | right portal vein |
| RHD | right hepatic duct |
| RHV | right hepatic vein |
| MHV | middle hepatic vein |

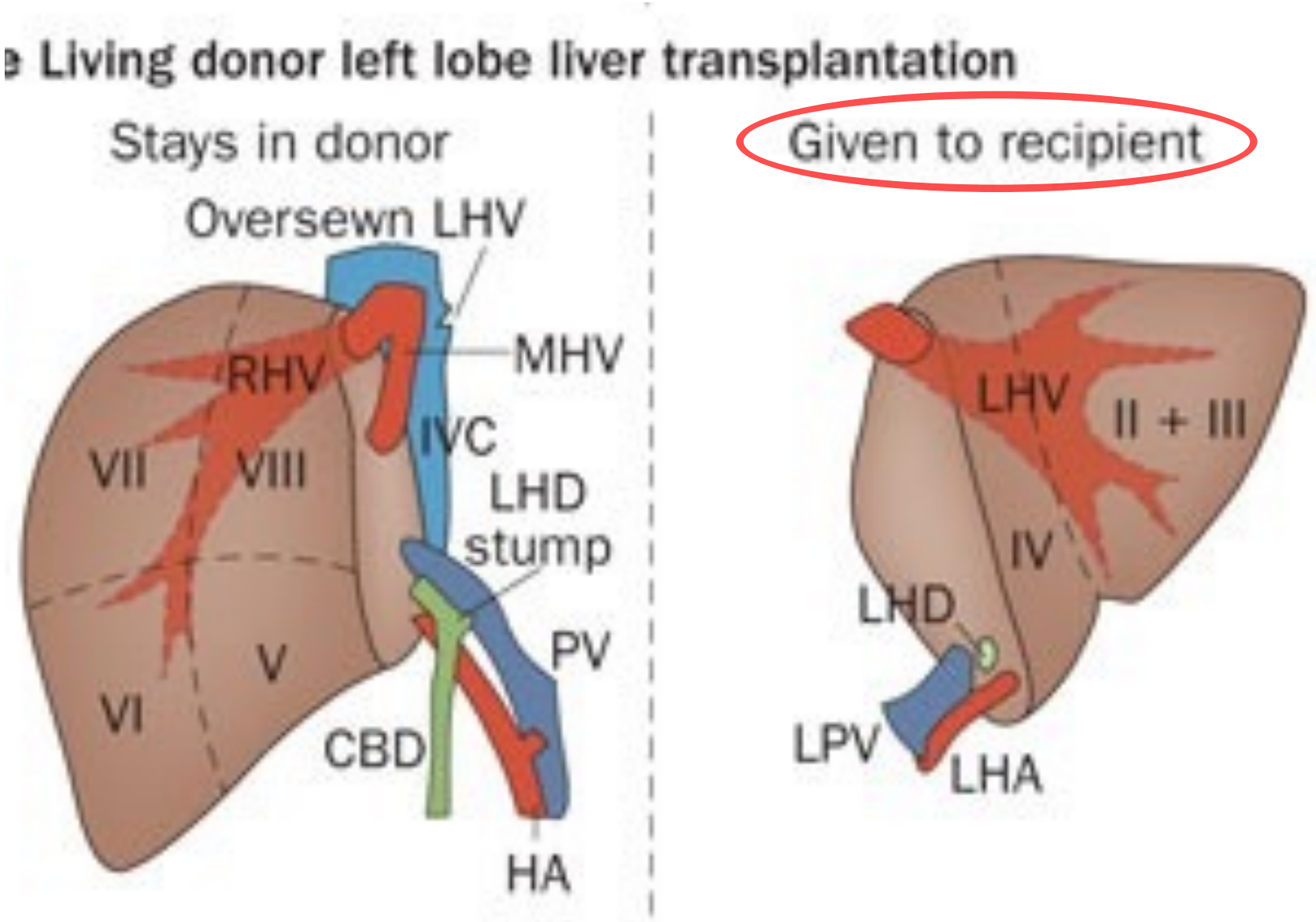
Zarrinpar, A. & Busuttil, R. W. *Nat. Rev. Gastroenterol. Hepatol.* 10, 434–440 (2013); published online 11 June 2013; doi:10.1038/nrgastro.2013.88

# Living Donor Liver Transplantation (LDLT) – RIGHT Lobe

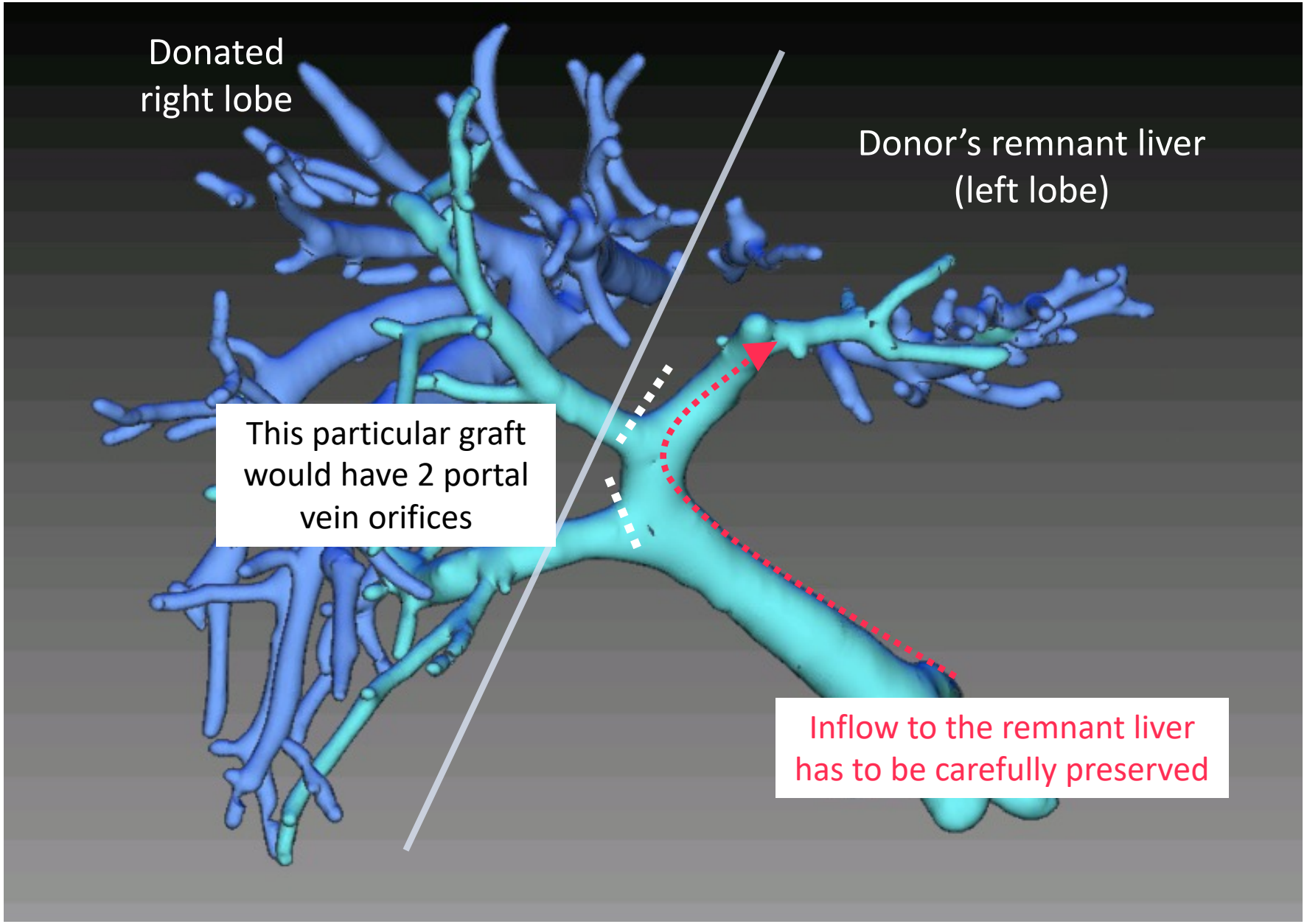



Zarrinpar, A. & Busuttil, R. W. *Nat. Rev. Gastroenterol. Hepatol.* 10, 434–440 (2013); published online 11 June 2013; doi:10.1038/nrgastro.2013.88

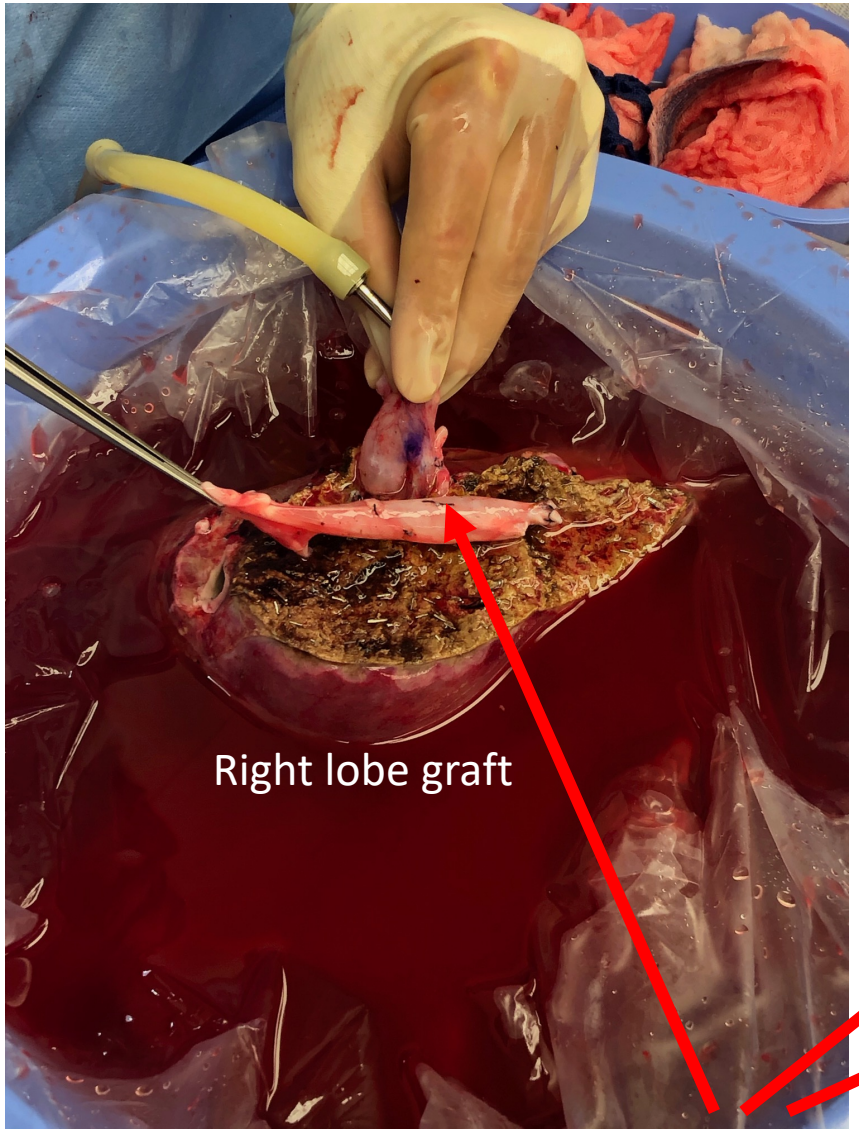
# Living Donor Liver Transplantation (LDLT) – LEFT lobe

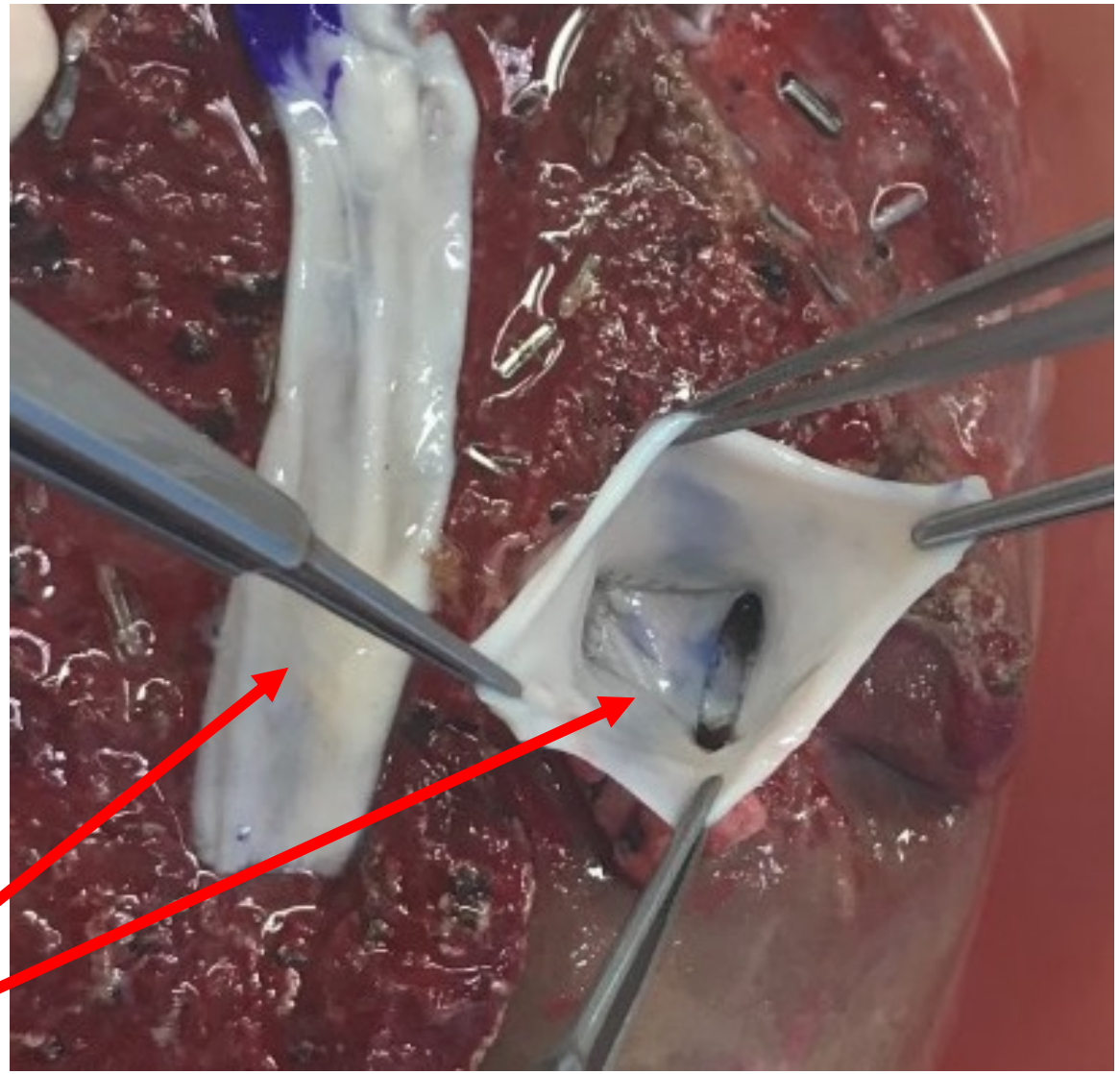



Zarrinpar, A. & Busuttil, R. W. *Nat. Rev. Gastroenterol. Hepatol.* 10, 434–440 (2013); published online 11 June 2013; doi:10.1038/nrgastro.2013.88

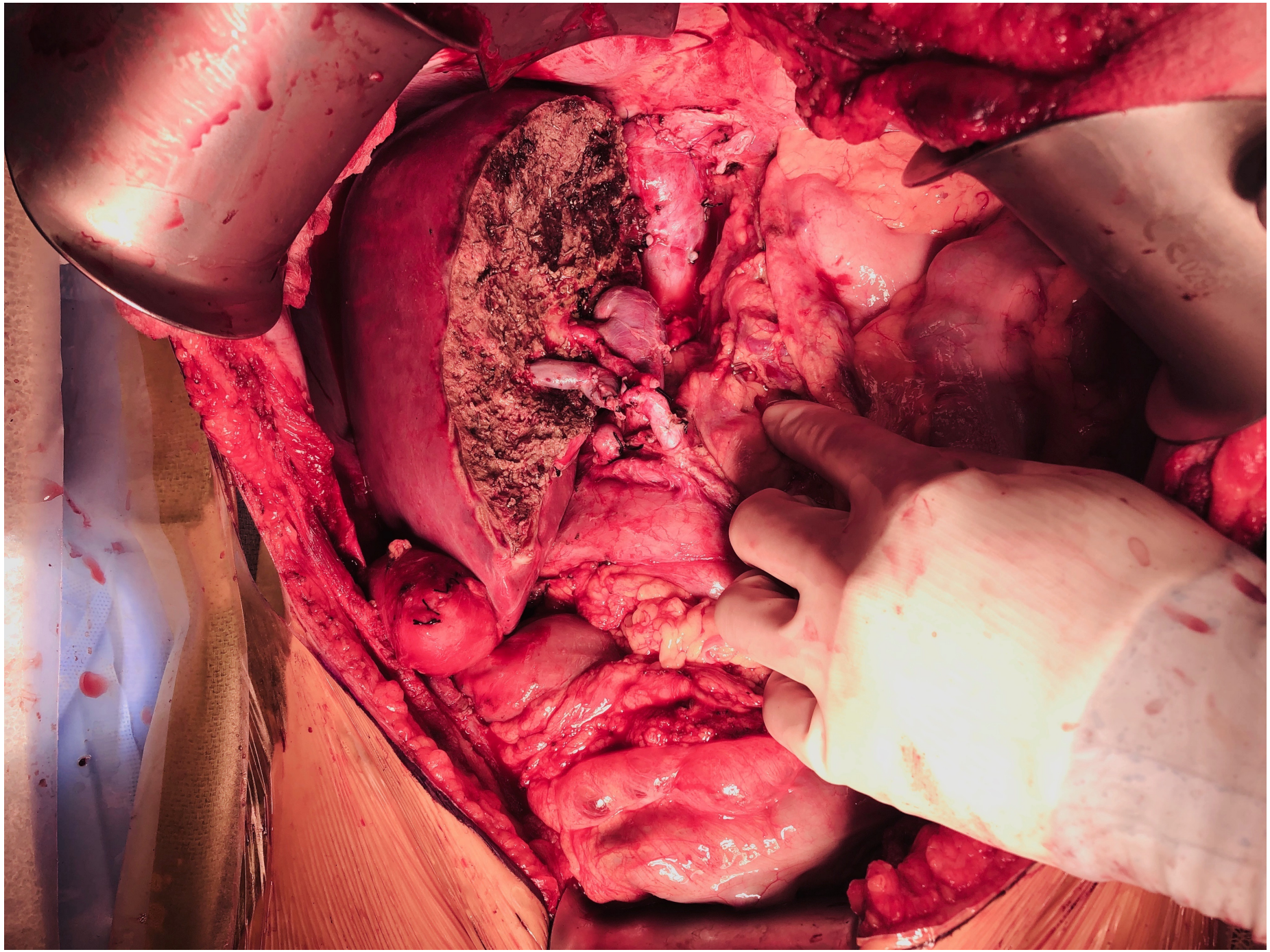



Aberrant anatomy and required considerations

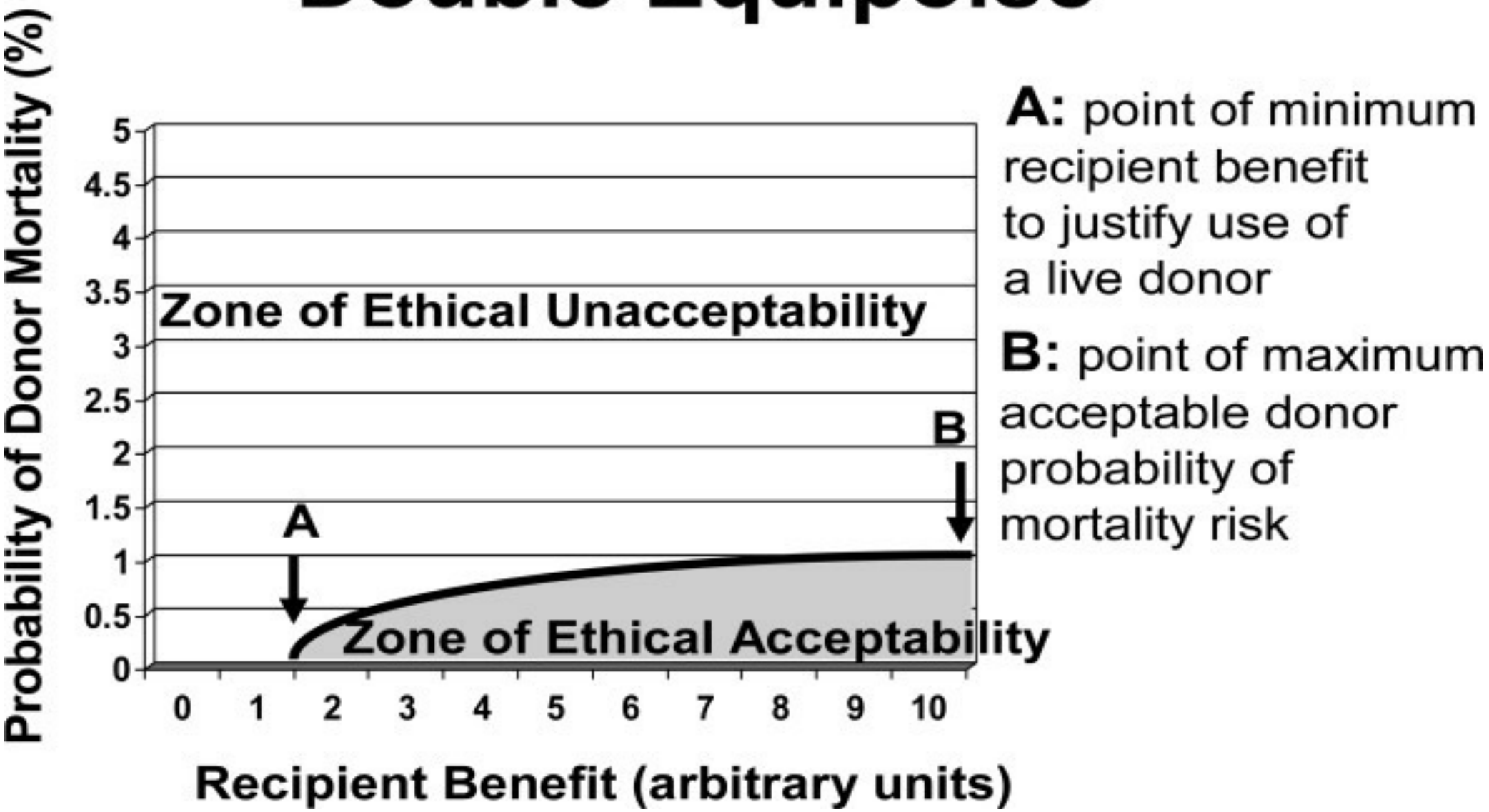


Extra deceased donor vessels that have been banked previously, or autologous vessels, are used to reconstruct donor graft vessel ends to make the split liver more suitable for implantation



# Double Equipoise




Recipient deaths during donor surgery: A new ethical problem in living donor liver transplantation (LDLT); *Liver Transplantation,* Volume: 12, Issue: 3, Pages: 358-360, First published: 23 February 2006, DOI: (10.1002/lt.20670)

# What Criteria Make a Patient a Good Candidate for LDLT

- Higher physiologic reserve
- Generally, a lower MELD (less than 35, though most are much less than 30)
  - MELD > 35 should be able to get relatively good deceased donor offers in our area
  - Highest MELD and sickest patients (especially patients requiring ICU-level care) may need a whole liver and not a partial liver
  - MELD 40+ patients who may even be marginal candidates for DDLT may fall out of “zone of ethical acceptability” for the donor
- Adequate vascular inflow options (arterial and portal venous or mesenteric venous)
- Good candidate for OLT in general: good performance status, low cardiac risk, low risk for having a hostile surgical abdomen, low chance of disseminated malignancy, appropriate for induction of immunosuppression, medically compliant, good social support

# Why Mr. Disparo is a Good Candidate for LDLT

- Very low MELD: ~7
  - Very poor access to deceased donor liver transplantation until he can receive exception points
  - Should have enough reserve to tolerate split-liver transplantation

- Great physiologic reserve and no other major co-morbidities

- HCC status:
  - One lesion in right lobe with maximal diameter of **6.5cm**
  - **AFP 87** ng/mL (much lower than ideal of <300; requirement <1000 or downstaged to <500)
  - Potentially favorable tumor biology but at HCC size, may be at risk of dropout with current poor access to DDLT and expected long wait time without LDLT

# Hospitalization Time for Donor and Recipient

Donor:

Left lateral segment: 4 days

Left lobe: 5 days

Right lobe: 5 days

Recipient:

Required: 7 days

Typical: 7-14 days

Occasionally: > 14 days

Rarely: >1 month

# Follow-up and Long-term Prognosis for Mr. Disparo

## Donor:

Clinic visit at 2 weeks post-op

Labs (CBC, CMP, INR) at 6, 12, 24 months post-op

Mortality*: 0.08 - 0.5%

Morbidity*: 9 - 67%

*Varies extensively by the series, experience of the institution(s) at that time, and what is actually reported by the surgeons/programs as a complication

## Recipient:

Outpatient follow-up frequent at first but eventually can be spaced to monthly to yearly

Recurrence surveillance can by guided by RETREAT score

MELD-era, with exception points and when within Milan criteria:

**5-year survival 70-80% with DDLT**

LDLT outcomes for HCC approaching this

(but overall less data, and varies between centers, especially as centers transplant outside of Milan criteria)

# Summary

- Early HCC treated locoregionally. Consider liver transplant evaluation.
- In advanced HCC, dual agent therapy with atezolizumab + bevacizumab is first line. Child Pugh A. EGD needed within 6 months.
- Localized HCC, consider surgical resection or transplant evaluation.
- Resection requires careful evaluation of risk for post op hepatic failure. Remnant must be adequate. Patient must be a suitable candidate for resection (cardiovascular, comorbidities, nutrition)
- Risk of recurrence of HCC after resection: >50%.

# Summary

- Milan criteria for transplant: 1 tumor <5 cm; 3 tumors <3 cm each; no macrovascular invasion or extrahepatic spread.
- Tumors can be downstaged. AFP <1000.
- Liver directed therapies: microwave ablation, TACE, Y90 can bridge to transplant or resection.

# Summary

- Reduced wait time for living donor liver transplant (LDLT)
- Donor and recipient do not have to be compatible. Pairs can participate in paired exchanges or chains.
- Low MELD score is preferred for LDLT. Very sick patients may need a whole liver.
- Maintain strict criteria for LDLT donors and recipients.