Using Local Therapy Options for HCC: Transplant, resection, or other liver-directed therapy?

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Surgical Management of HCC: Resection and Transplant

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HCC Staging

- TNM alone fails to account for background liver dysfunction and PS
- Prognosis depends on:
  - tumor burden
  - degree of liver dysfunction
  - performance status
- Most commonly accepted staging system is Barcelona Clinic Liver Cancer (BCLC)

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Reig et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update J Hepatol 2022

Treatments

- Curative:
  - **Resection, Ablation, Transplantation**

- Non-curative:
  - TACE, TARE, SBRT, Systemic Chemotherapy

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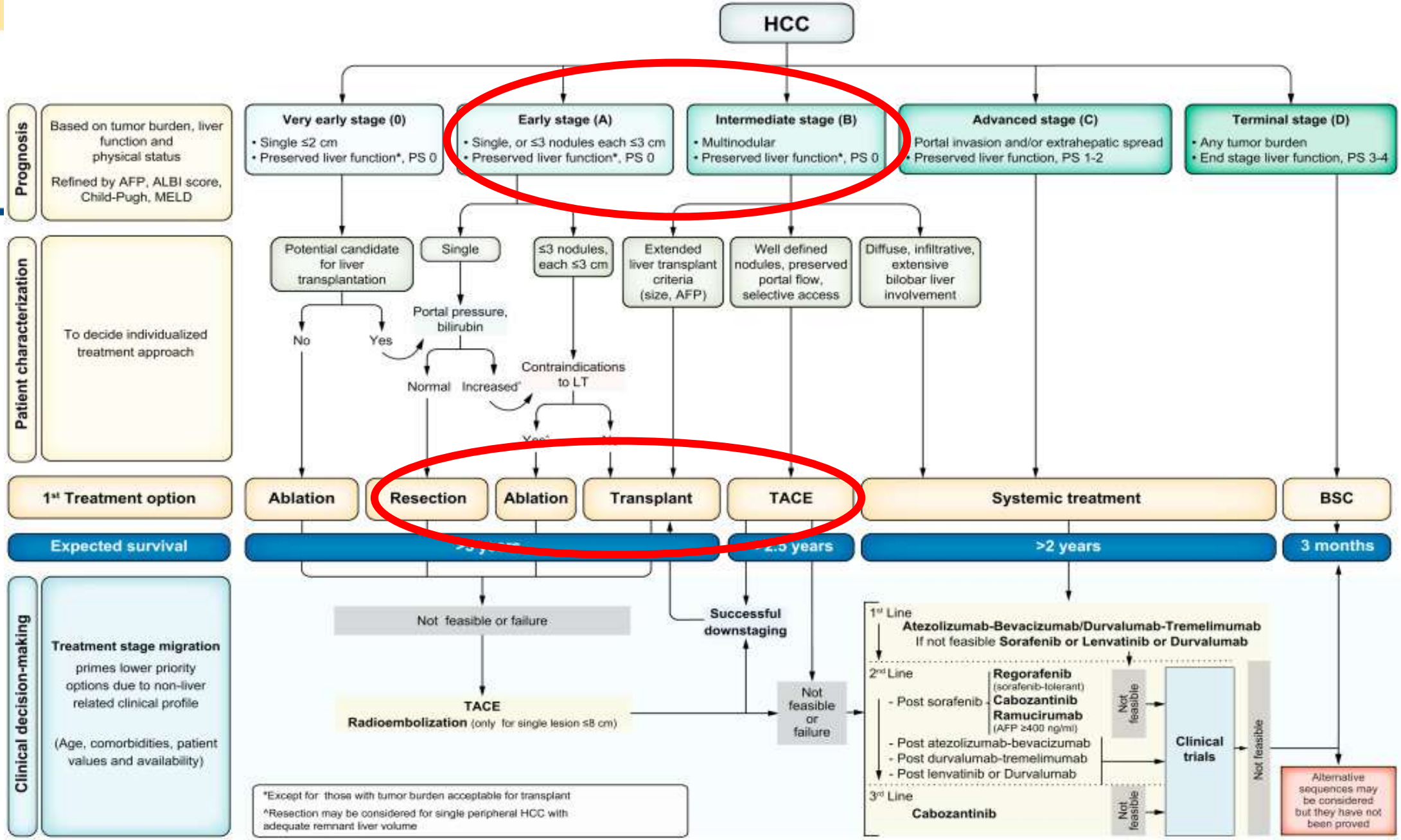

Journal of Hepatology, Volume 76, Issue 3, 681 - 693

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Surgical Resectability of HCC
Balance: Oncologic Benefit vs Risk of PHLF

Tumor Factors

- Solitary
  - Any size
  - No multifocal disease
- No main portal vein TT
- Complete resection
  - Debate regarding margin negative verses anatomic
- Always exceptions but this is standard
  - ie exceptional responders to systemic therapy

Background Liver Factors

- 30% FLR – Non-cirrhotic
- 40% FLR – Cirrhotic (Can PVE)
- ALBI Grade I (grade II if not transplantable)
- Child-Pugh A (Select B's)
- No clinically significant portal HTN
  - Plt >100K
  - Usually assessed biochemically and radiographically
  - Can do direct or indirect portal pressure measurement

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Belghiti et al. HPB. 2005

Resection for Hepatocellular Carcinoma PVTT have poor survival

Surgical Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus.

Shi, Lai, Li, Guo, Xue, Lau, Wu, Cheng. *Ann Surg Oncol. 2010;17(8):2073-80*

- 406 patients resected for HCC with PVTT
- 1- and 3-year overall survival **34.4 and 13.0%**
- 1- and 3-year disease-free survival **13.3 and 4.7%**
- 2° and 3°TT significantly better survival than those with main PVTT

- Portal Tumor thrombus
  - Poor prognosis regardless of treatment modality is acknowledged

- **This may change with effective systemic therapies and well selected patients …..**

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Effect of portal vein embolization on treatment plan prior to major hepatectomy for hepatocellular carcinoma

Benjamin P.T. Loveday, Arash Jaberi, Carol-Anne Moulton, Alice C. Wei, Steven Gallinger, Robert Beecroft, Sandra Fischer, Anand Ghanekar, Ian McGilvray, Gonazolo Sapisochin, Paul D. Greig, Kongteng Tan, Sean P. Cleary

HPB (Oxford). 2019 Feb 20

- PVE for planned major hepatectomy for HCC
- FLR volume increased (median 430–574 cm^3; $p < 0.001$)
- Tumor volume increased (median 161–240 cm^3; $p < 0.001$)

- The treatment plan changed in 50%

- Tumor progression prevented resection in 25%

- **Consideration should be given to further liver directed therapy in the setting of HCC and PVE.**

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TACE→PVE

Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma

S. Ogata[1], J. Belghiti[1], O. Farges[1], D. Varma[1], A. Sibert[2] and V. Vilgrain[2]

P=0.013

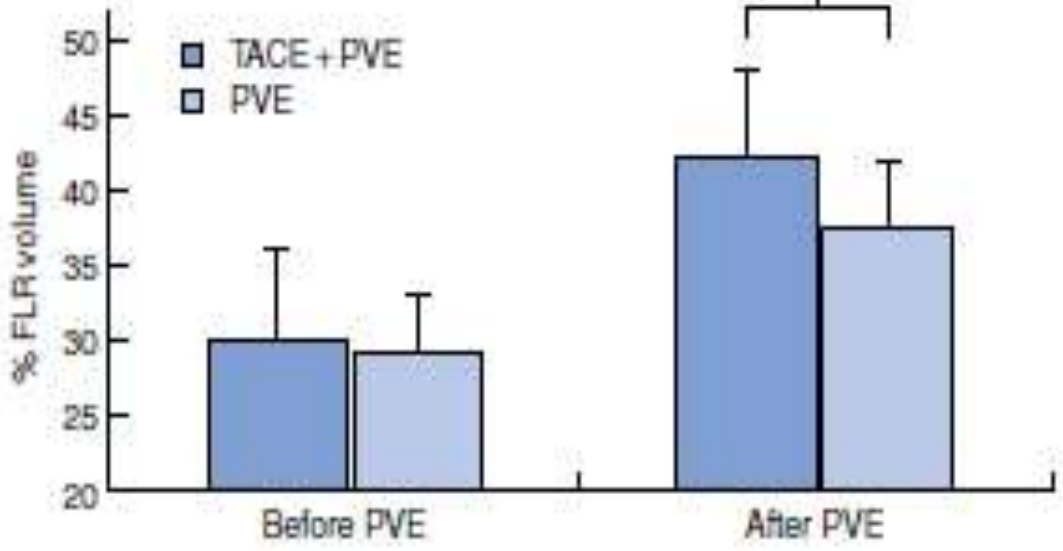
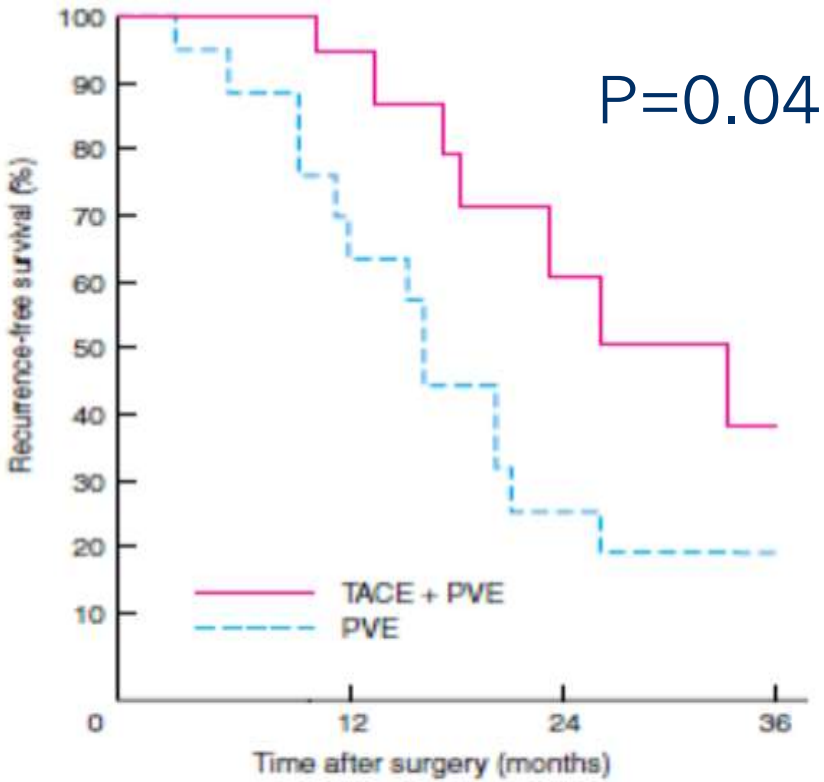


Fig. 2 Change in percentage future liver remnant (FLR) volume in the transarterial chemoembolization (TACE) plus portal vein embolization (PVE) and PVE alone groups. Values are mean(s.d.). *$P = 0.013$ (Student's t test)

P=0.041



No. at risk

TACE + PVE	18	14	9	3
PVE	18	10	5	2

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Outpatient and Ambulatory Extended Recovery Robotic Hepatectomy: Multinational Study of 307 Cases

Park, James O MD, FACS; Lafaro, Kelly MD, MPH; Hagendoorn, Jeroen MD; Melstrom, Laleh MD, MS, FACS; Gerhards, Michael F MD, PhD; Görgec, Burak MD, PhD; Marsman, Hendrik A MD; Thornblade, Lucas W MD, FACS; Pilz da Cunha, Gabriela MD, PhD; Yang, Frank F MD; Labadie, Kevin P MD; Sham, Jonathan G MD, MBEE, FACS; Swijnenburg, Rutger-Jan MD, PhD; He, Jin MD, PhD, FACS; Fong, Yuman MD, FACS

- 307 patients
- Same day and next day discharges
- Readmission 1.6% (n=5)
- Mortality 0%
- Complications 2% (n=6)

- Multiple studies have shown improved postoperative outcomes with minimally invasive liver surgery
- Cirrhotic patients benefit the most from minimally invasive surgery

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Resection for HCC

- Surgical resection is the treatment of choice for resectable HCC in non-cirrhotics
- Surgical resection favored in patients without CS-PH and CP- A
- Ablation is Equivalent to Resection for <3cm HCC
- Technically no size cut-off for Resection
  - Large tumors can be safely resected if sufficient functional liver remnant
- PVE can be utilized to increase FLR
- Systemic therapy (and in combination with local therapies) can be utilized to control/downstage/select locally advanced cases for curative intent resection

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But What About Transplant….

- Most in the US are transplanted within Milan
  - Solitary less 5cm
  - 2-3 less than 3cm
- Expanded criteria
  - UCSF – Solitary ≤ 6.5cm or ≤ 3 tumors ≤ 4.5cm and total tumor diameter ≤ 8cm
  - Extended Toronto Criteria – Any size or number!
    - Exclusions: cancer related symptoms, extrahepatic disease, vascular invasion, poorly differentiated
- Downstaging to within Milan
  - In highly selected cases can have excellent post-transplant outcomes similar to those within Milan
  - Typically for unresectable, particularly due to background liver disease

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Transplantation for HCC

- LT is the treatment of choice for patients with more advanced cirrhosis, CS-PH, hepatic decompensation, and early stage HCC (ie Milan)
- LT should be a primary consideration for multifocal HCC
- LT is a highly effective, efficient therapy for early-stage HCC because it offers optimal treatment of both the underlying liver disease and the tumor.
- LT is associated with excellent long term survival rates for HCC within Milan criteria occurring in the setting of decompensated liver disease.

AASLD. Hepatology 2018, 68

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Transplantation for HCC in the US

The Milan Criteria

- **Mazzaferro** et al, *NEJM 1996; 334(11):693*
  - 48 patients transplanted, 1991 – 1994
  - No vascular invasion or +ve lymph nodes
  - No control group
  - 28 chemoembolization prior to Tx
  - Retrospective analysis based on pathologic staging:

- **Criteria: 1 tumor ≤ 5 cm or ≤ 3 tumors each ≤ 3 cm**

	Overall	Disease-Free
– Survival (4yr):		
• Pathologic staging ≤ Criteria	**85%**	**92%**
– n=35		
• Pathologic staging > Criteria	**50%**	**59%**
– n = 13		

- Subsequent series *Transplant Proc 2001;33:1442*
  - 122 patients 1995 – 2000
  - 5 year survivals **80%** **88%**

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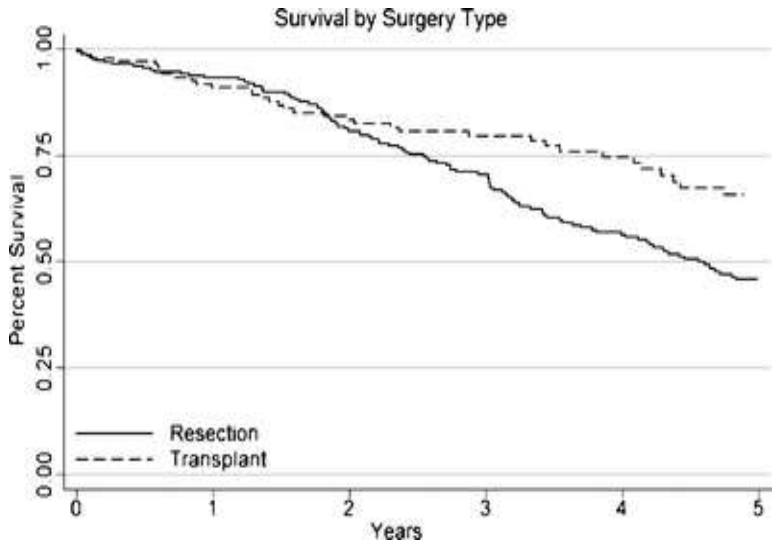
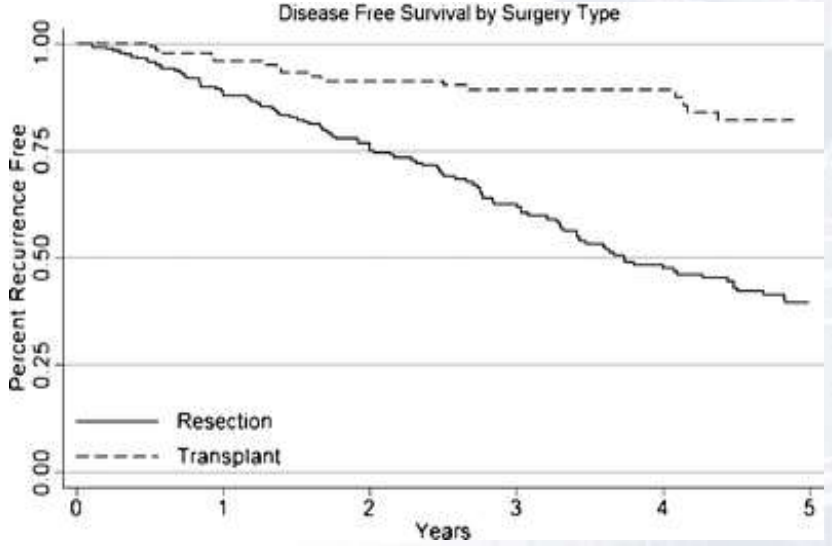
Options for early HCC (within Milan Criteria)

Surgical Management of Early-Stage Hepatocellular Carcinoma: Resection or Transplantation?

Bellavance et al., 2011





Overall Survival (%)	1 yr	3 yrs	5 yrs	P value
Transplant	91	79	66	<.001
Resection	93	71	46	

DF Survival (%)	1 yr	3 yrs	5 yrs	P value
Transplant	96	89	82	<.001
Resection	88	62	40	

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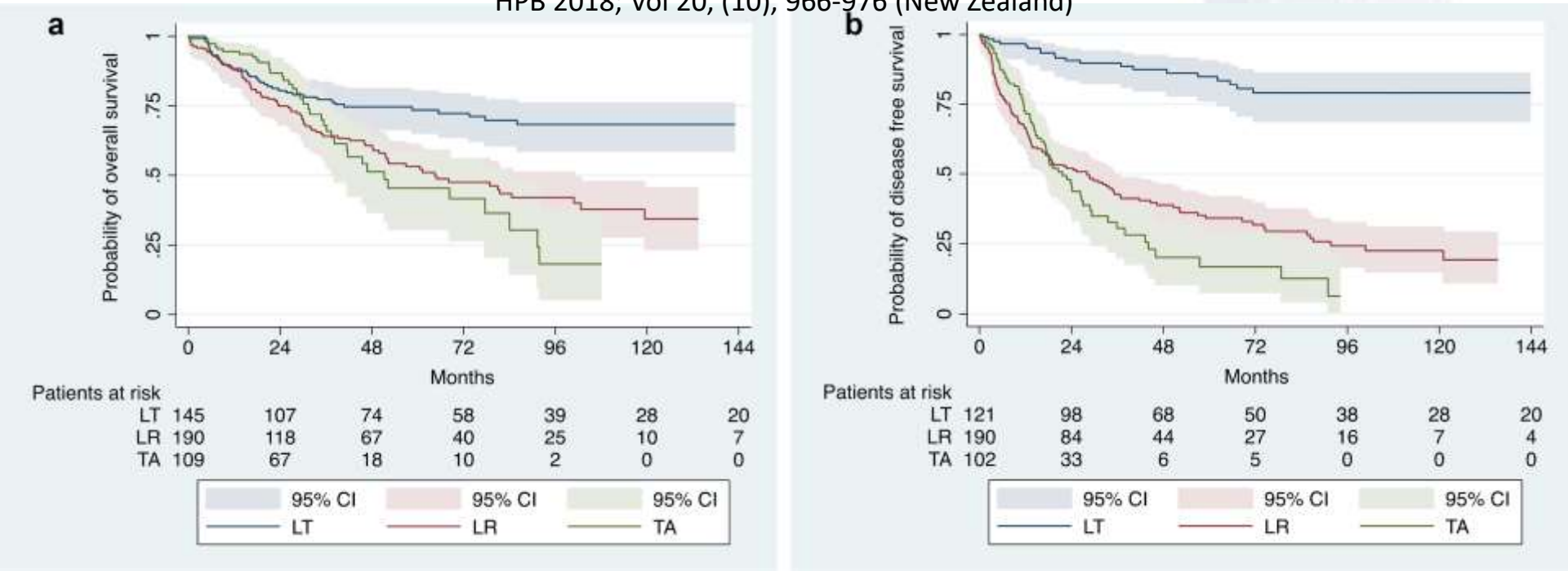
Options for early HCC (within Milan Criteria)

Intention-to-treat analysis of liver transplantation, resection and thermal ablation for hepatocellular carcinoma

HPB 2018; Vol 20, (10), 966-976 (New Zealand)



Intention-to-treat overall survival among the 444 HCC patients treated with curative intent. (b) Per treatment disease-free survival of 413 HCC patients who underwent LT, LR or TA. Twenty-three LT delisted patients, 1 peri-operative LT death and 7 incomplete TA patients excluded

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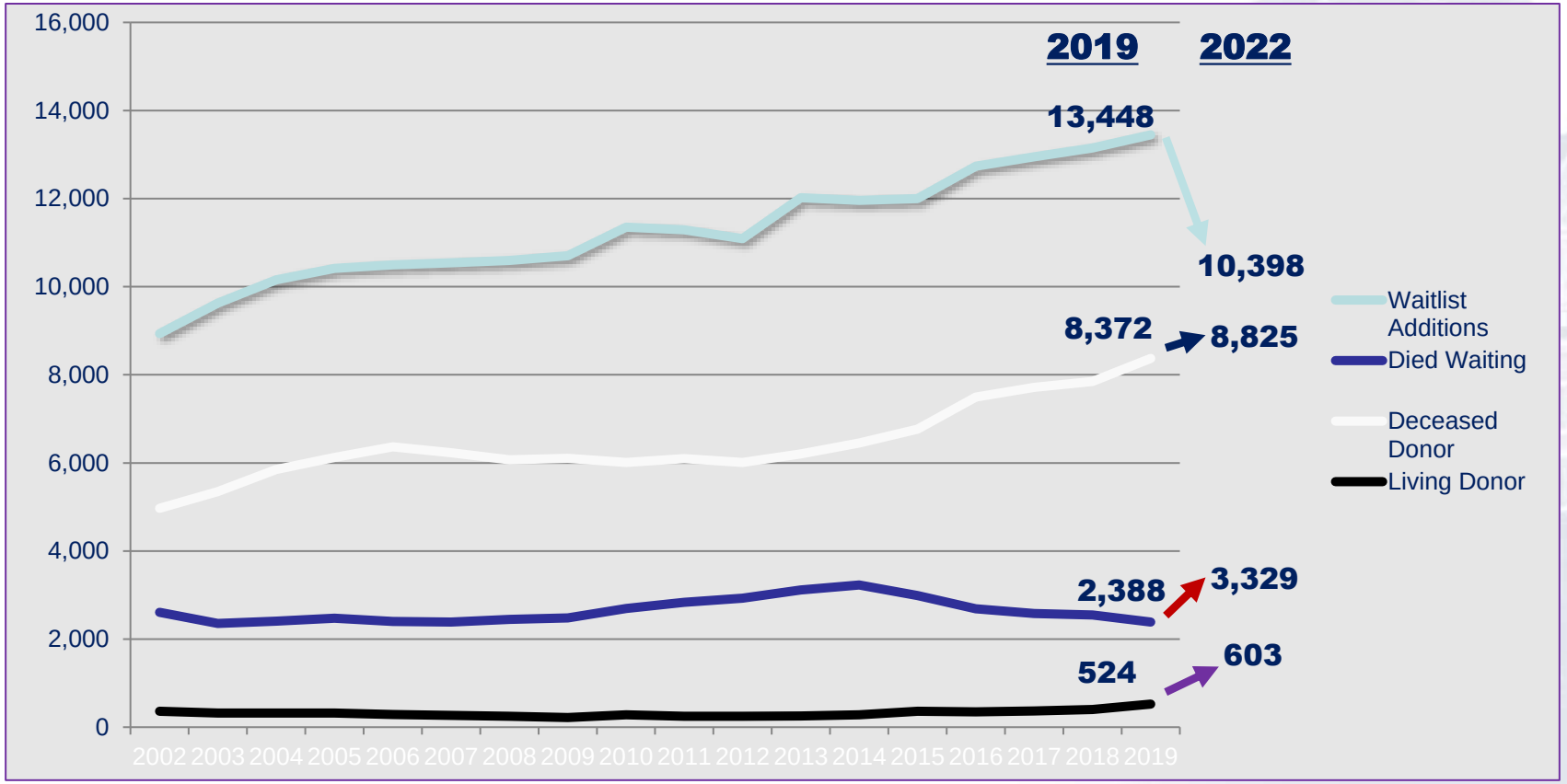
Waitlist Additions, Transplants and Deaths on Waitlist

18% of the patients on the waitlist die before getting transplanted



Data from Organ Procurement and Transplantation Network (OPTN)

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Allocation Prioritization in the US uses MELD score

MELD Scoring System UNOS Modifications

Prognostic Factor	Regression Coefficient	P Value
Serum Creatinine (Log_e value)	0.957	<0.01
Serum bilirubin (Log_e value)	0.378	<0.01
INR (Log_e value)	1.12	<0.01

[0.957 x Log_e(Cr) + 0.378 x Log_e(bili) + 1.120 x Log_e (INR) + 0.643] x 10 *

- Maximum Creatinine is 4 mg/dl
- Patients on dialysis – Creatinine = 4mg/dl
- Lowest score is 6, maximum for allocation is 40
- Serum Na+ has since been added to MELD (MELD-Na) for allocation.

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Patrick Kamath et al. Hepatology 2001; 33(2): 464-470

How do HCC patients with low MELD scores get transplanted?

UNOS Automatic HCC Exception Points

Exception points:

- Mean Transplant MELD Score for the centers within 150 miles of the donor hospital minus 3 (MTS-3)
- Stage T2 HCC (LI-RADS 5 or biopsy proven) = “Milan Criteria”
  - One lesion >2 cm and <5 cm
  - Two or three lesions >1 cm and <3 cm in size)
- Waiting time of 6 months from submission request before MTS – 3 kicks in.
- Patients with HCC beyond standard down-staging criteria who are able to be successfully downstaged to T2 may be appropriate for MELD exception
  - No evidence of metastasis
  - No macrovascular invasion
  - AFP < 1,000

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Conclusions

- Surgery, ablation and liver transplant- curative intent
- Surgery for solitary lesions not within transplant criteria
- MUST access FLR before surgery

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Thank You

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Using Local Therapy Options for HCC: Transplant, resection, or other *liver-directed therapy?*

Kelvin Hong
Interventional Radiology
Johns Hopkins University

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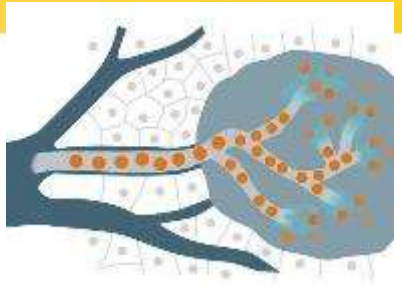
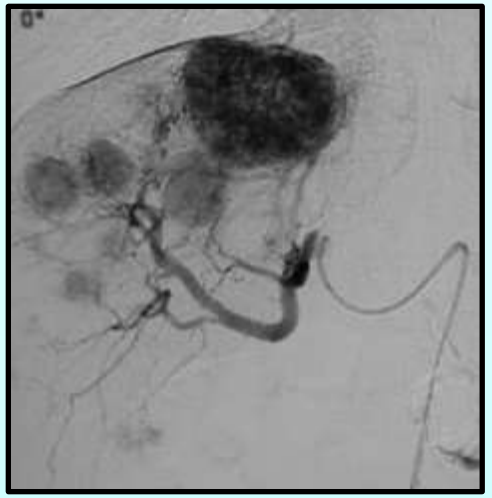
Interventional Radiology in HCC



- Long history in Dx and Mx since 1970's
- Supportive roles in Cirrhosis: TIPS, Ascites management
- Early days: HCC dismal options, 2 diseases
- IR:
  1. Ablation
  2. Chemoembolization TACE
  3. Radioembolization TARE
  4. Combination therapies



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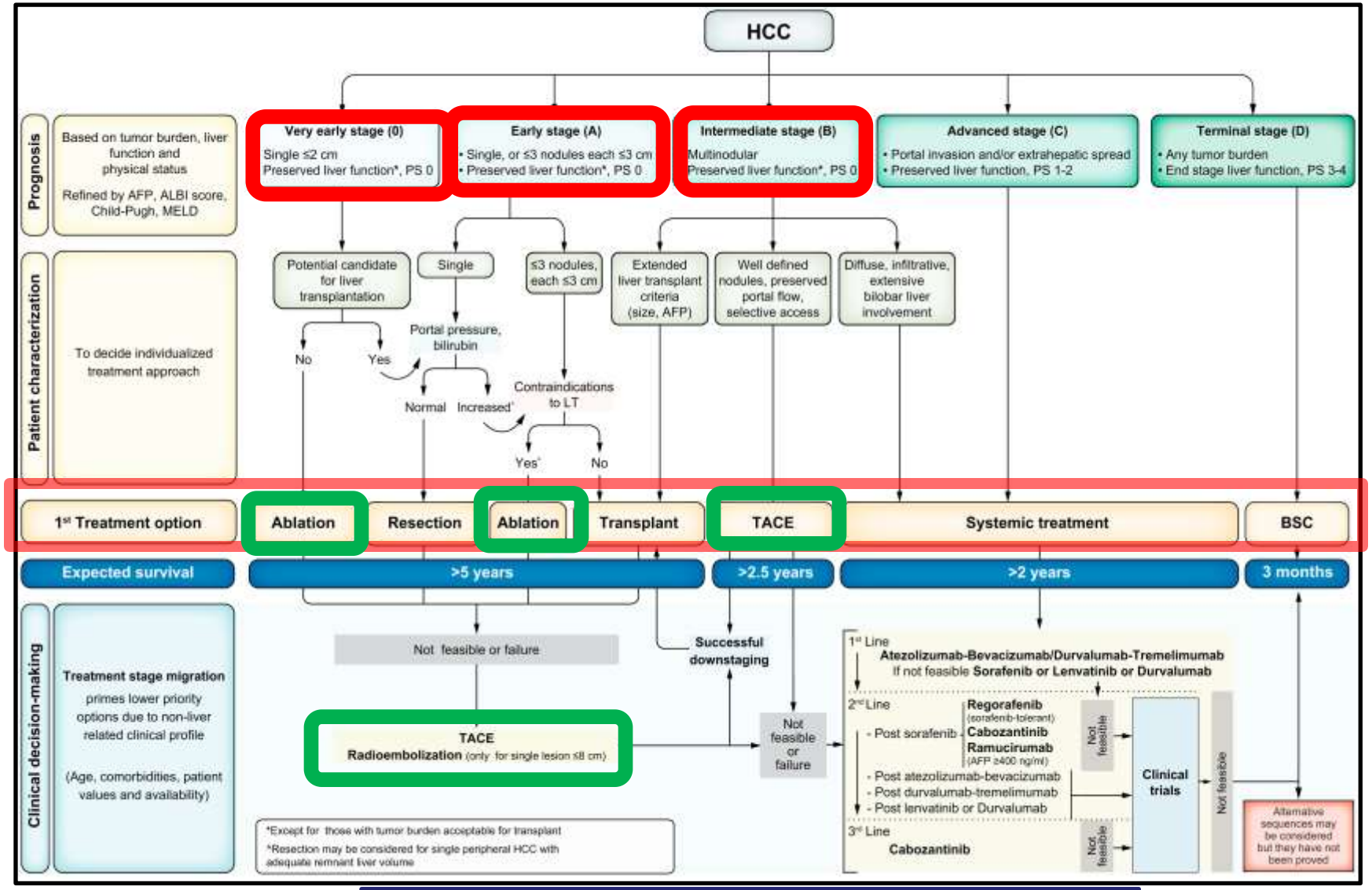
2022 BCLC staging treatment recommendations



Local therapies in Interventional Radiology

Maria Reig, et al. BCLC strategy for prognosis prediction and treatment recommendation:
The 2022 update,Journal of Hepatology,Volume 76, Issue 3,2022,Pages 681-693,ISSN 0168-8278,
https://doi.org/10.1016/j.jhep.2021.11.018.

HCC： Curative therapies

Potentially curative therapies, in Very Early(0) and Early Stage (A)

1. Transplantation
2. Surgical resection
3. Ablation

Maria Reig, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update,Journal of Hepatology,Volume 76, Issue 3,2022,Pages 681-693,ISSN 0168-8278, https://doi.org/10.1016/j.jhep.2021.11.018.

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HCC : Thermal Ablation

Curative therapies, in Early Stage (A)

Best for: Small HCCs, <3 cm, < 3 in number

Randomized clinical trials demonstrating equivalent long-term 5-year survival rates compared with surgical resection

Maria Reig, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update, Journal of Hepatology,Volume 76, Issue 3,2022,Pages 681-693,

Chen M S, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(03):321–328

Feng K, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol.* 2012;57(04):794–802

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Thermal Ablation: curative for non resectable early stage HCC

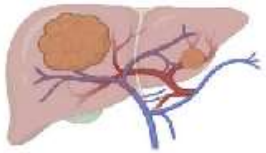
Original Article
J Liver Cancer 2024;24(1):71-80
pISSN 2288-6128 • eISSN 2383-5001
https://doi.org/10.17998/jlc.2023.09.11

JOURNAL OF LIVER CANCER

Treatment options for solitary hepatocellular carcinoma ≤5 cm: surgery vs. ablation: a multicenter retrospective study

Kazuya Kariyama[1], Kazuhiro Nouso[2], Atsushi Hiraoka[2], Hidenori Toyoda[3], Toshifumi Tada[4], Kunihiko Tsuji[5], Toru Ishikawa[6], Takeshi Hatanaka[7], Ei Itobayashi[8], Koichi Takaguchi[9], Akemi Tsutsui[9], Atsushi Naganuma[10], Satoshi Yasuda[3], Satoru Kakizaki[11], Akiko Wakuta[3], Shohei Shiota[1], Masatoshi Kudo[12], Takashi Kumada[13]

Patients



2067 patients with solitary ≤ 5cm hepatocellular carcinoma

Ablation (N=1248)

Surgery (N=819)

1:1 propensity score matching

Results

	Size of HCC		
	≤2 cm	>2 cm and ≤3 cm	>3 cm and ≤5 cm
Surgery vs Ablation	OS: similar (13.7 years vs 11.2 years) RFS: similar (5.9 years vs 6.0 years)	OS: similar (11.0 years vs 7.2 years) RFS: similar (4.9 years vs 3.0 years)	OS: similar (6.7 years vs 6.0 years) RFS: Surgery is better (3.6 years vs 2.0 years)

Conclusion

- Surgery and ablation could be equally used as a treatment for solitary HCC ≤3 cm.
- For HCCs measuring 3–5 cm, the OS was not different between therapies, Thus, ablation and less invasive therapy can be considered a treatment option; however, special caution should be taken to prevent recurrence.

JOURNAL OF LIVER CANCER

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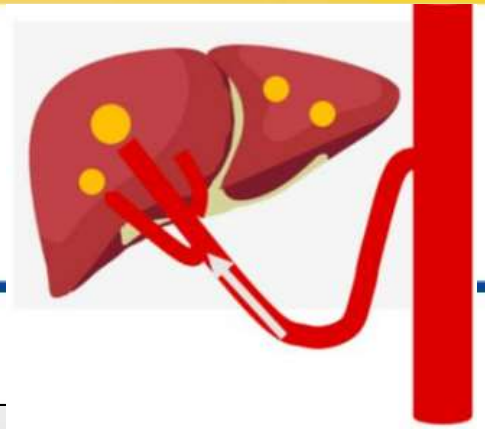
Cureus. 2024 Aug; 16(8): e67938.
Published online 2024 Aug 27. doi: 10.7759/cureus.67938
PMCID: PMC11426338
PMID: 39328664

Comparison of Radiofrequency Ablation and Microwave Ablation for the Management of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Monitoring Editor: Alexander Muacevic and John R Adler

- systematic review
- 6 randomized controlled trials, including 826 patients
- MWA resulted in lower LTP and higher complication rates compared to RFA
- NO difference in OS rates
- similar local tumor recurrence-free survival rates
- Both techniques appear to be effective and safe

Intra-arterial treatments



1. Chemoembolization (TACE)
   - *Drug-eluting Bead TACE*
   - *Bland Embolization TAE*

2. Radioembolization (TARE)

Kung JWC, Ng KKC. Role of locoregional therapies in the management of patients with hepatocellular carcinoma. *Hepatoma Res* 2022;8:17. http://dx.doi.org/10.20517/2394-5079.2021.138

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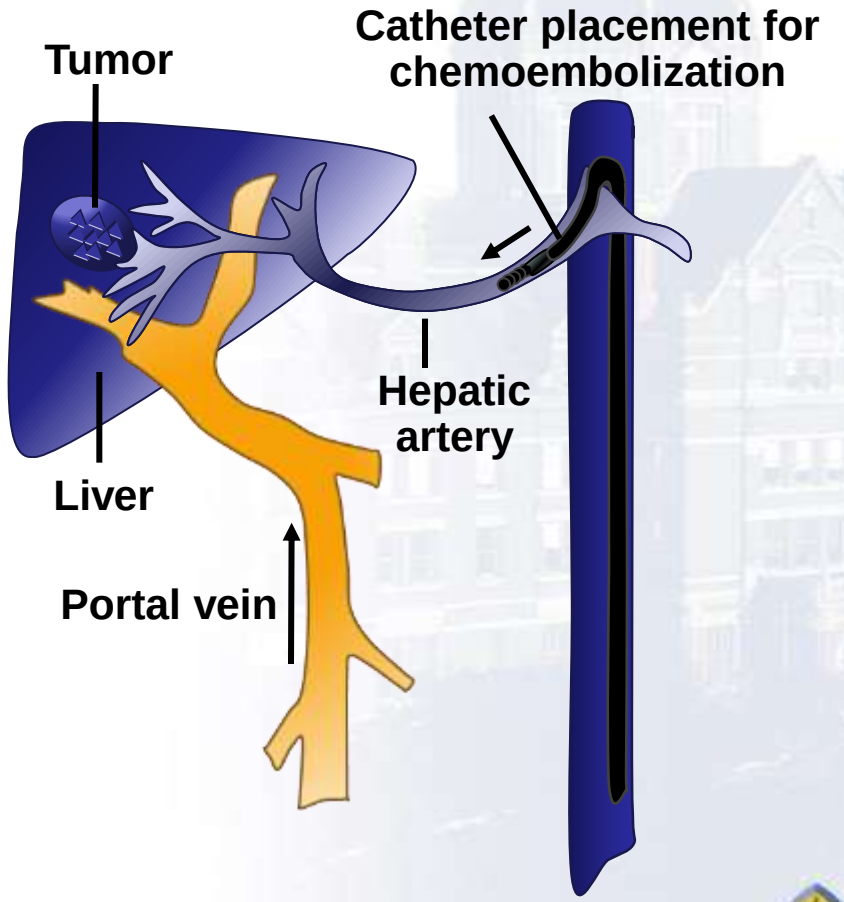
Treatment: Chemoembolization

- Normal liver gets 75% supply from **portal vein** and 25% from hepatic artery
- Tumor receives most from the hepatic artery
- Injection into the hepatic artery spares most of the normal liver
- Embolization of the hepatic artery prevents systemic absorption of chemotherapy agents and induces ischemic necrosis of tumor



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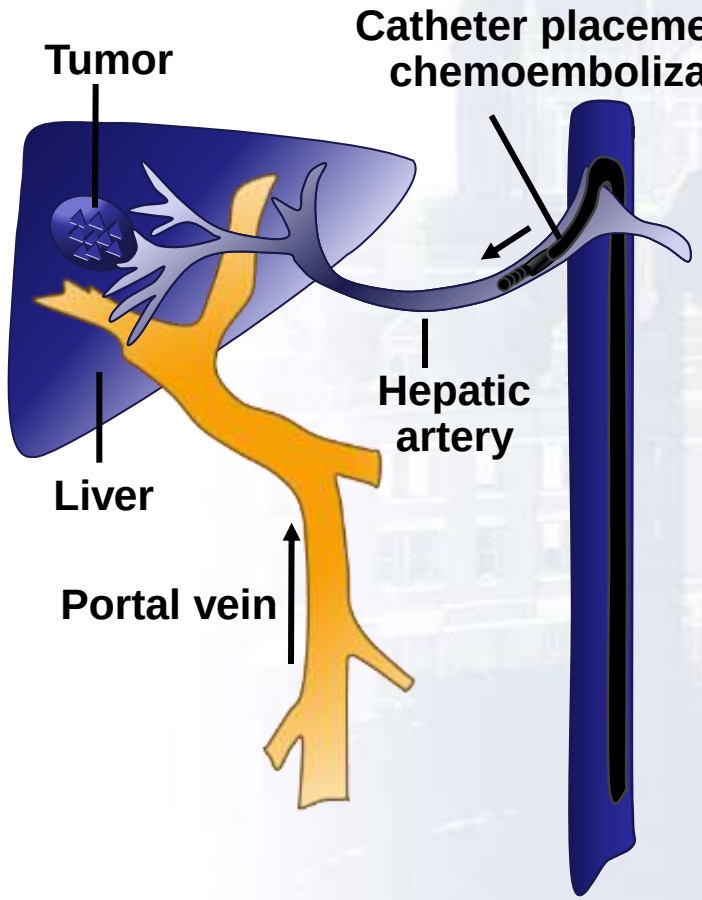
Chemoembolization (TACE) Modern Roles

1. Intermediate stage BCLC B: multifocal disease
2. Bridge to Transplantation
3. Pre-transplant downstaging
4. Pre-resection downstaging
5. Advanced disease palliation in combination with systemic
6. Combination therapies stage migration



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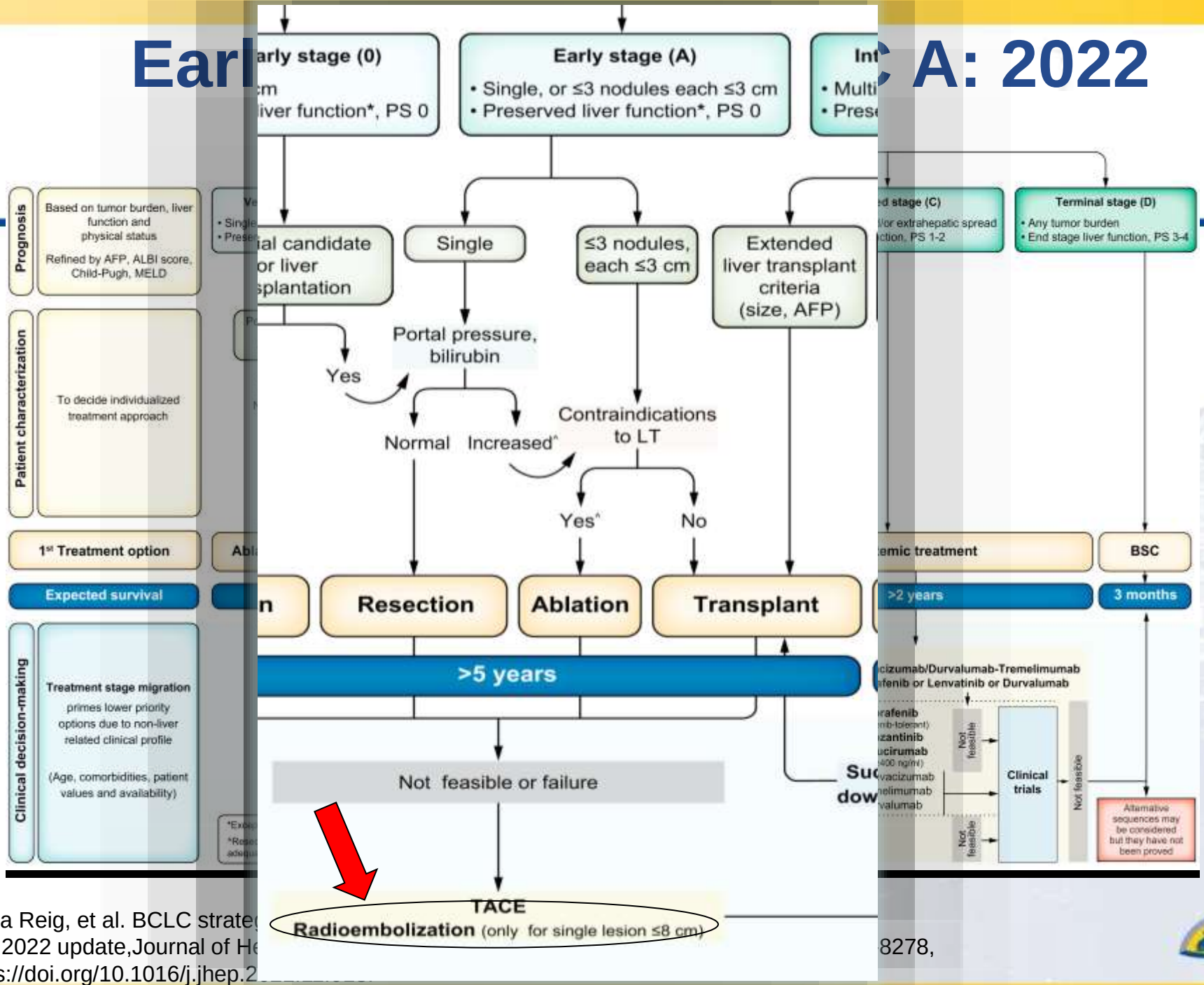
Earl C A: 2022



Maria Reig, et al. BCLC strate
The 2022 update,Journal of He 8278,
https://doi.org/10.1016/j.jhep.2

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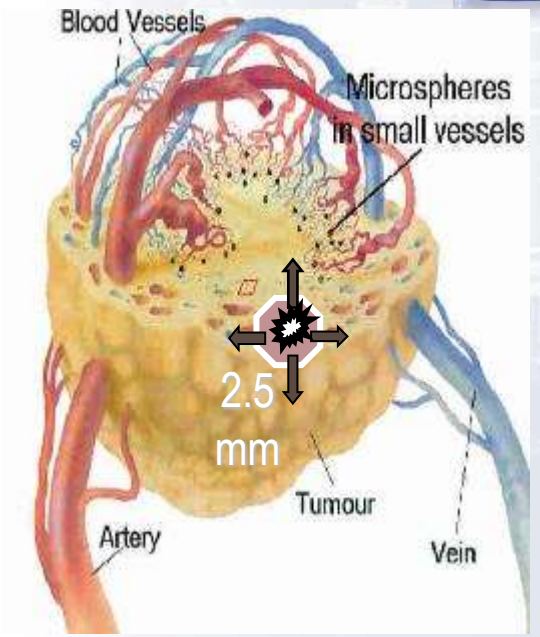
Y90 Radioembolization (TARE)

- High interest in USA sites, FDA approved in 1999 including PVT
- high therapeutic efficacy and low rates of adverse events
- Higher doses of radiation to smaller volumes and greater tumoricidal effect
- Insoluble glass or resin microspheres. Beta radiation; half-life 64 hrs
- Minimization of damage to non-tumor tissue: injected into angiosome
- Mean penetration: 2.5 mm
- Patient ease: outpatient procedure; Well tolerated
- Single treatment step
- Need up to 3 months to determine effect



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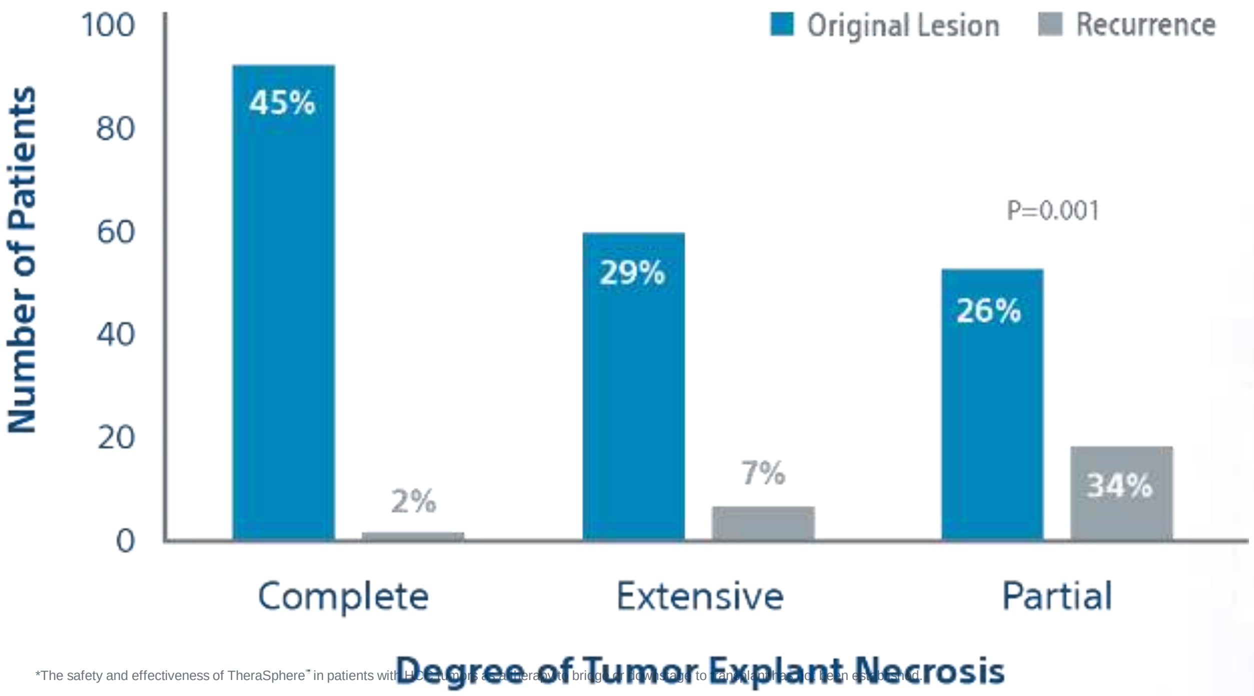
TARE: Downstage and Bridging:

High level of tumor explant necrosis

Histopathology and Recurrence Rate



*The safety and effectiveness of TheraSphere™ in patients with HCC tumors as a therapy to bridge or downstage to transplant has not been established.

74% of patients showed complete or extensive tumor necrosis

Median recurrence-free survival following liver transplant of 10 years

Gabr A, Salem R et al. Liver Transplantation Following Yttrium-90 Radioembolization: 15-Year Experience in 207-Patient Cohort. Hepatology. 2021 Mar;73(3):998-1010. doi: 10.1002/hep.31318. PMID: 32416631.

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TARE: Legacy study pivotal study

- **multicenter**, single-arm, retrospective study three site
- BCLC: A and C (39.5%) but no PVT thrombosis
- Single lesion Median 2.6 cm
- Follow up: 29.9 months
- Bridge to transplantation 21.0% (34 of 162)
- Or Resection 6.8% (11 of 162), Primary treatment 72.2% (117 of 162)

Salem R, et alA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable HCC: The LEGACY Study. Hepatology. 2021 Nov;74(5):2342-2352. PMID: 33739462; PMCID: PMC8596669.

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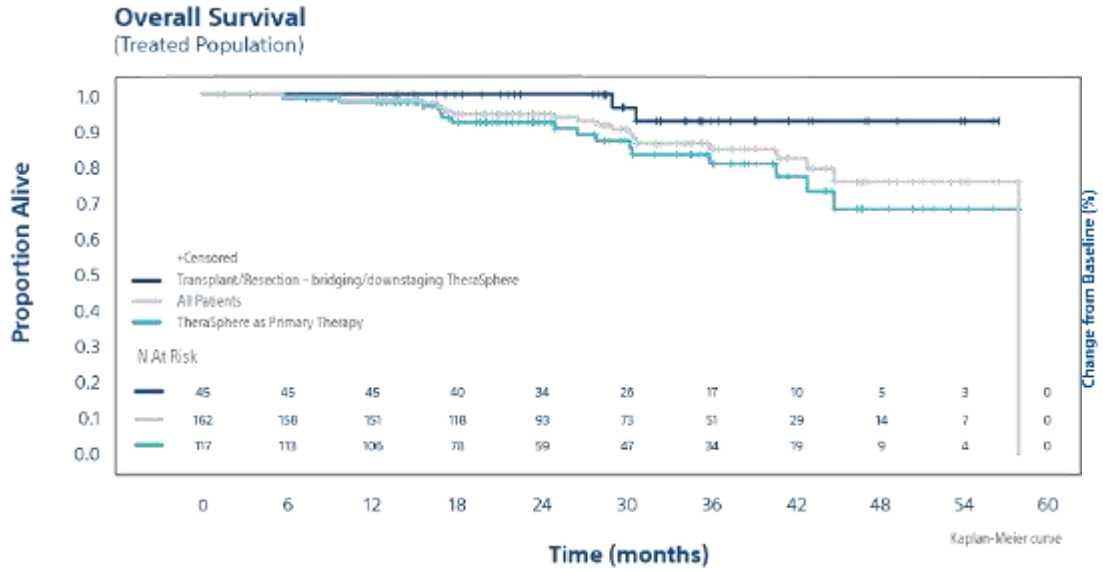
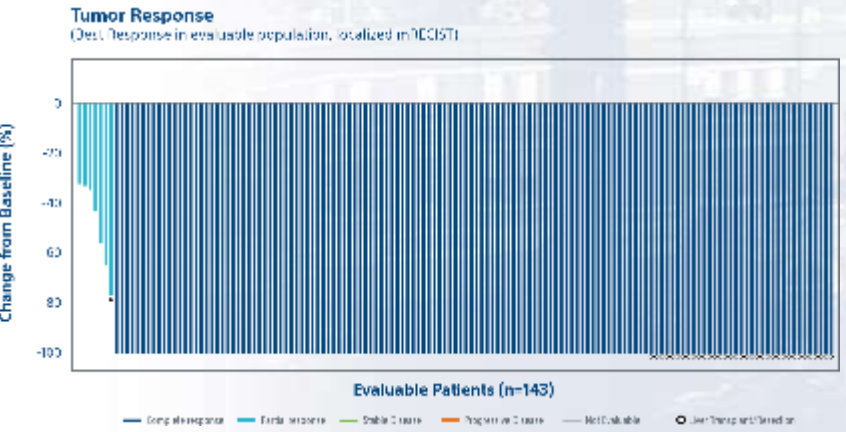
TARE: Legacy study pivotal study Durable and high response

- 93% OS rate in neoadjuvant at 3 years
- 84% OS rate in primary therapy at 3 years
- 96.8% single treatment,100% with 2





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Conclusion:

- Interventional Radiology treatments spans the breadth of HCC staging (BCLC A to C)
- Cemented in national and international guidelines
- Ablation (curative), TACE, TARE (segmentectomy)
- HCC best treated in MDC setting

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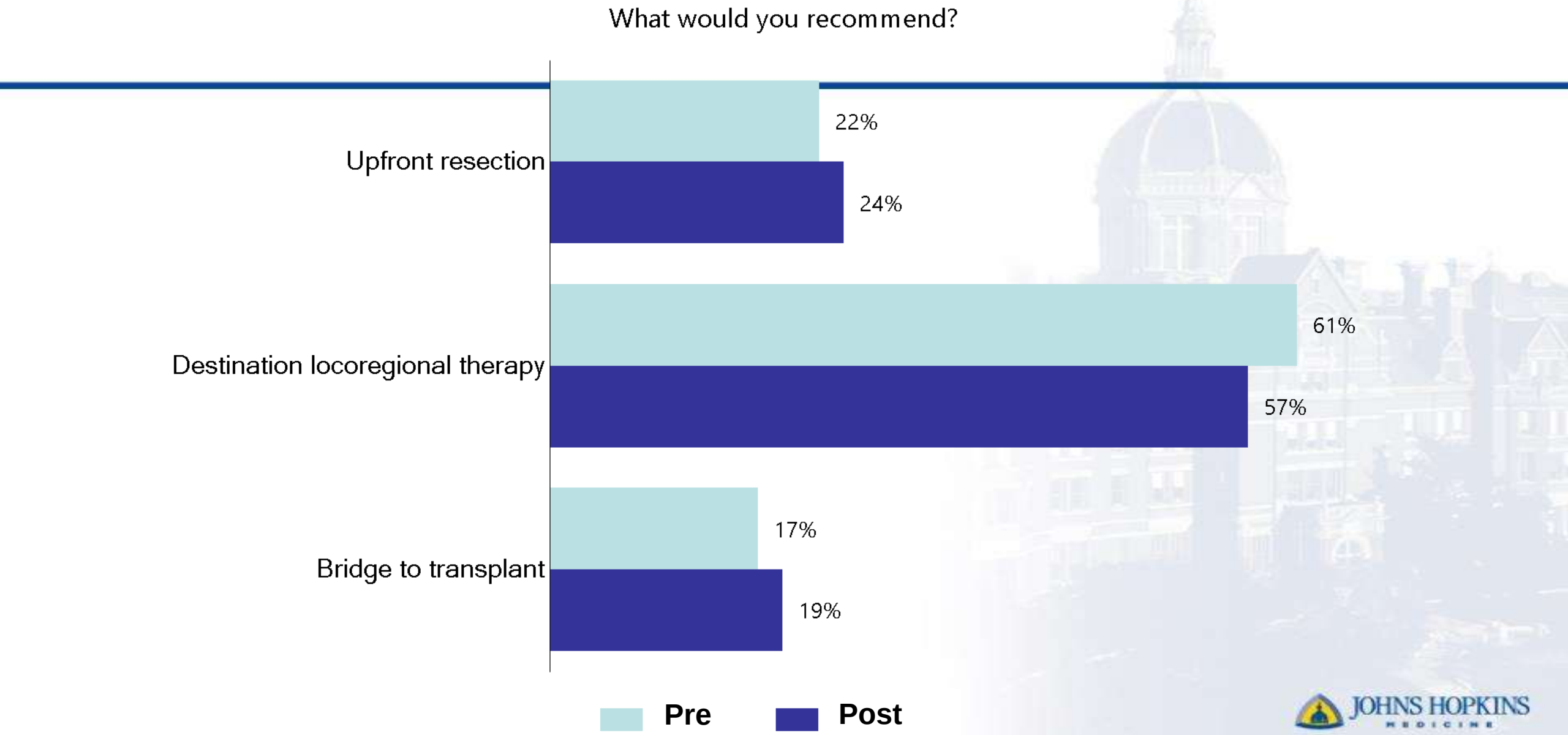
What would you recommend?
Upfront resection
22%
24%
Destination locoregional therapy
61%
57%
Bridge to transplant
17%
19%
Pre
Post