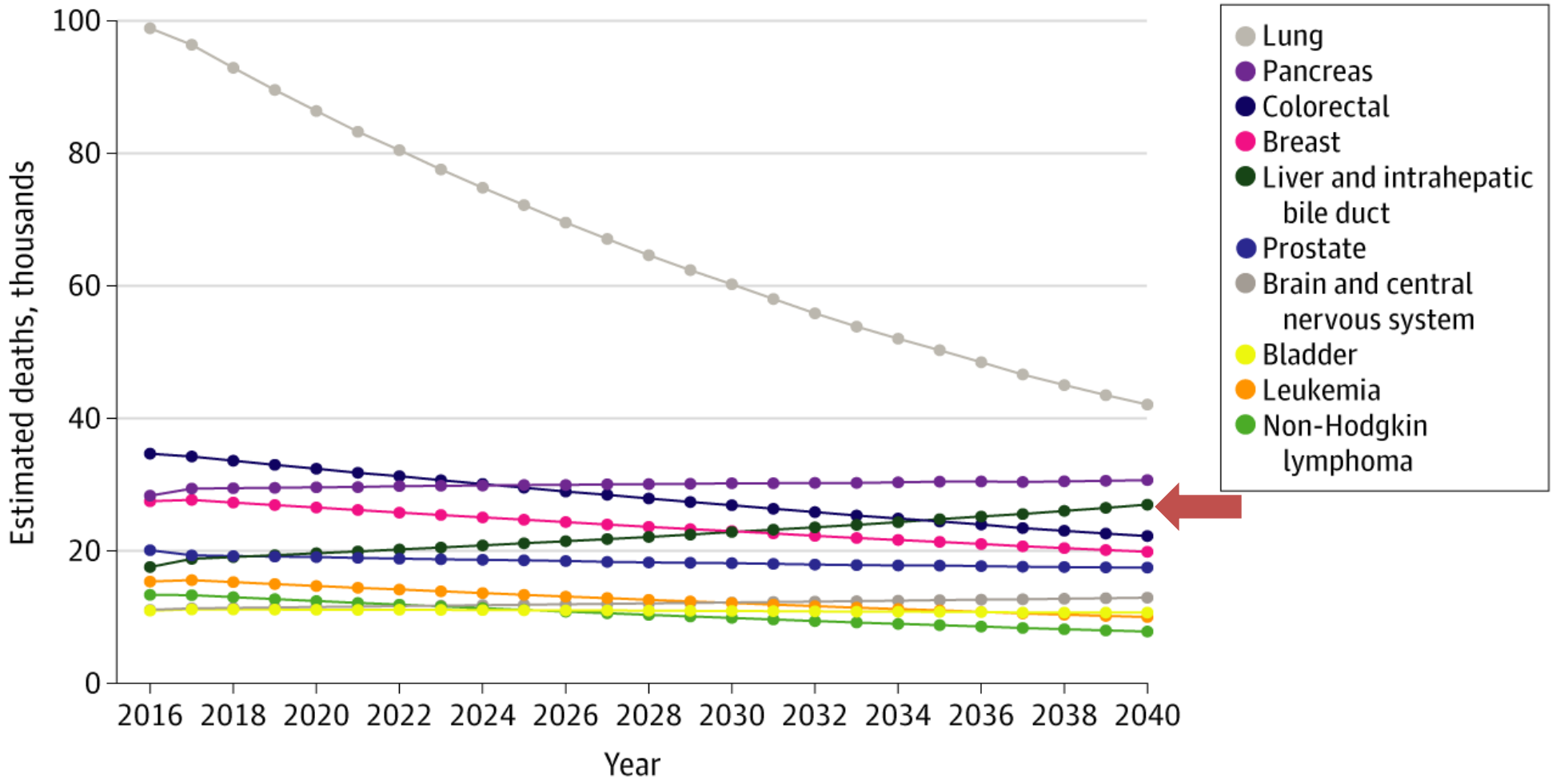
Advances in Treatment of HCC

Amit G. Singal MD MS
Willis C Maddrey Distinguished Chair in Liver Disease
Professor of Medicine, Digestive and Liver Diseases
Chief of Hepatology and Medical Director, Liver Tumor Program
UT Southwestern Medical Center

Disclosures

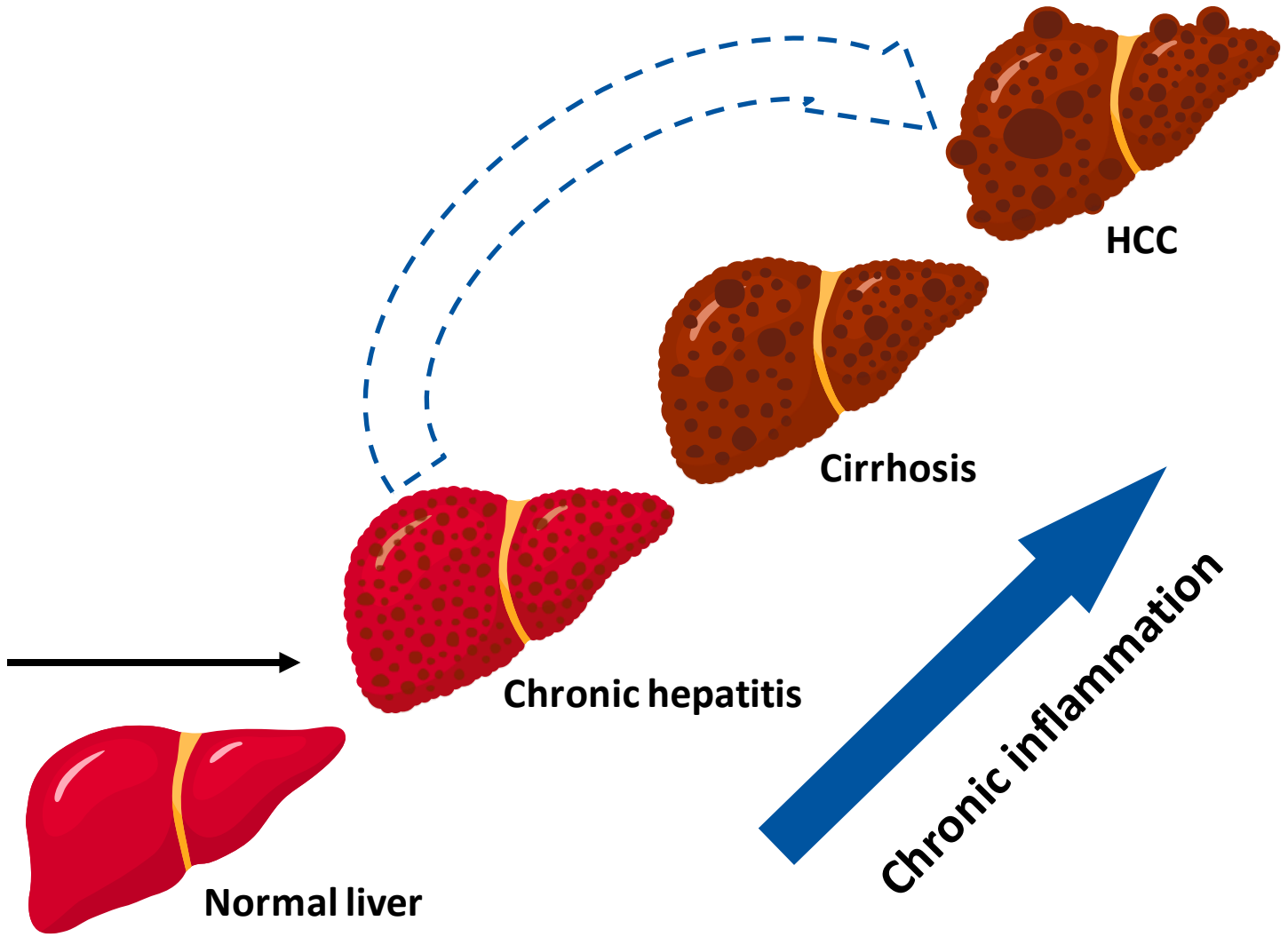
- I have served as a consultant or served on advisory boards for Genentech, AstraZeneca, Bayer, Eisai, Bristol Meyer Squibb, Exelixis, FujiFilm Medical Sciences, Glycotest, Exact Sciences, Roche, and GRAIL

HCC projected to be 3rd leading cause of death in US by 2035

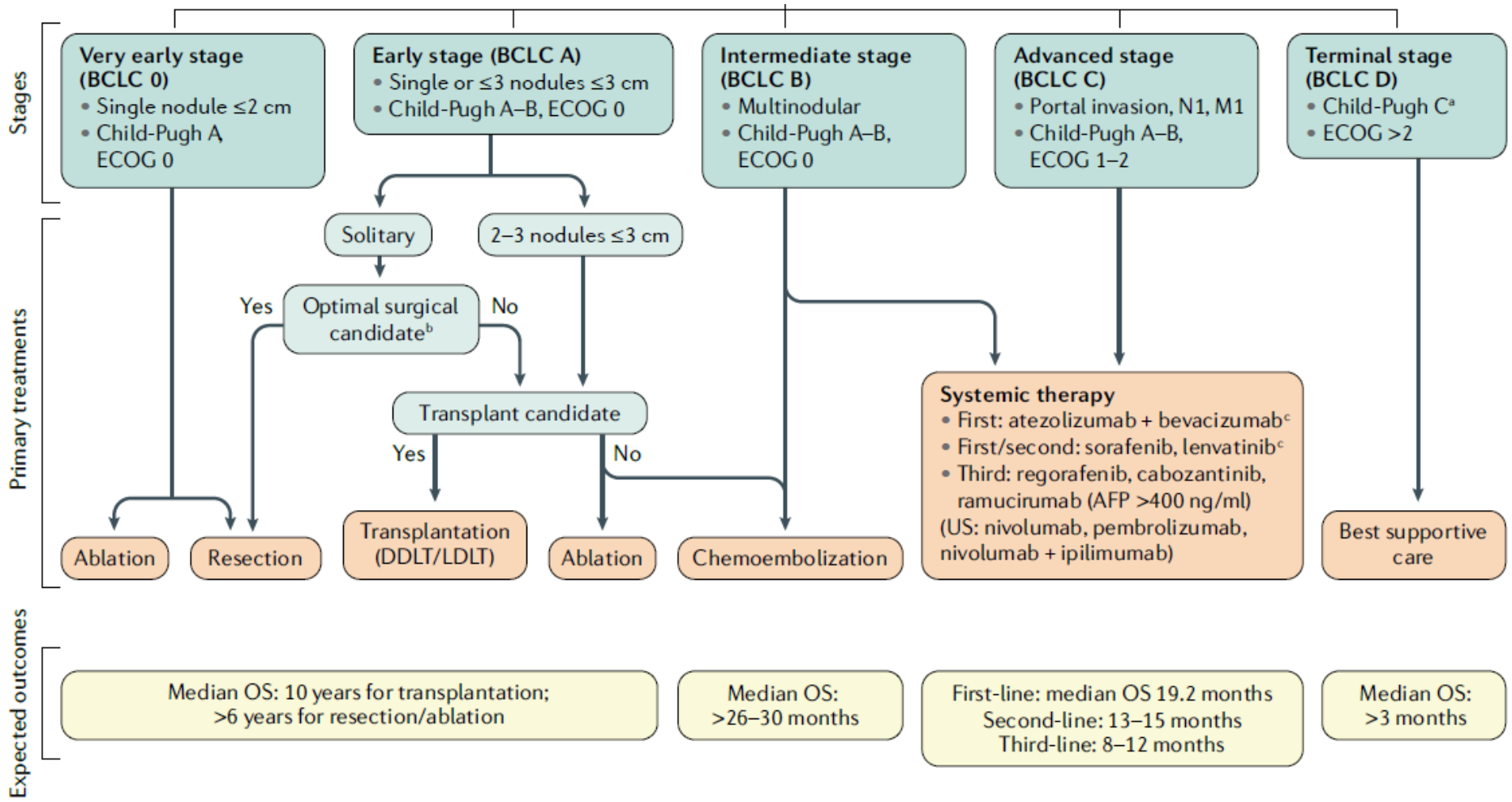


Most HCC occur in the setting of chronic liver disease, if not cirrhosis

Hepatitis B viral infection
Hepatitis C viral infection
Alcohol-associated liver disease
Nonalcoholic steatohepatitis

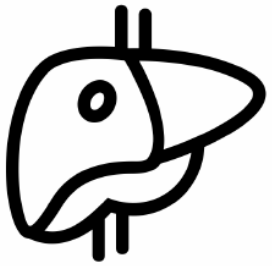


Prognosis strongly associated with tumor stage at diagnosis



HCC surveillance associated with improved survival in cirrhosis

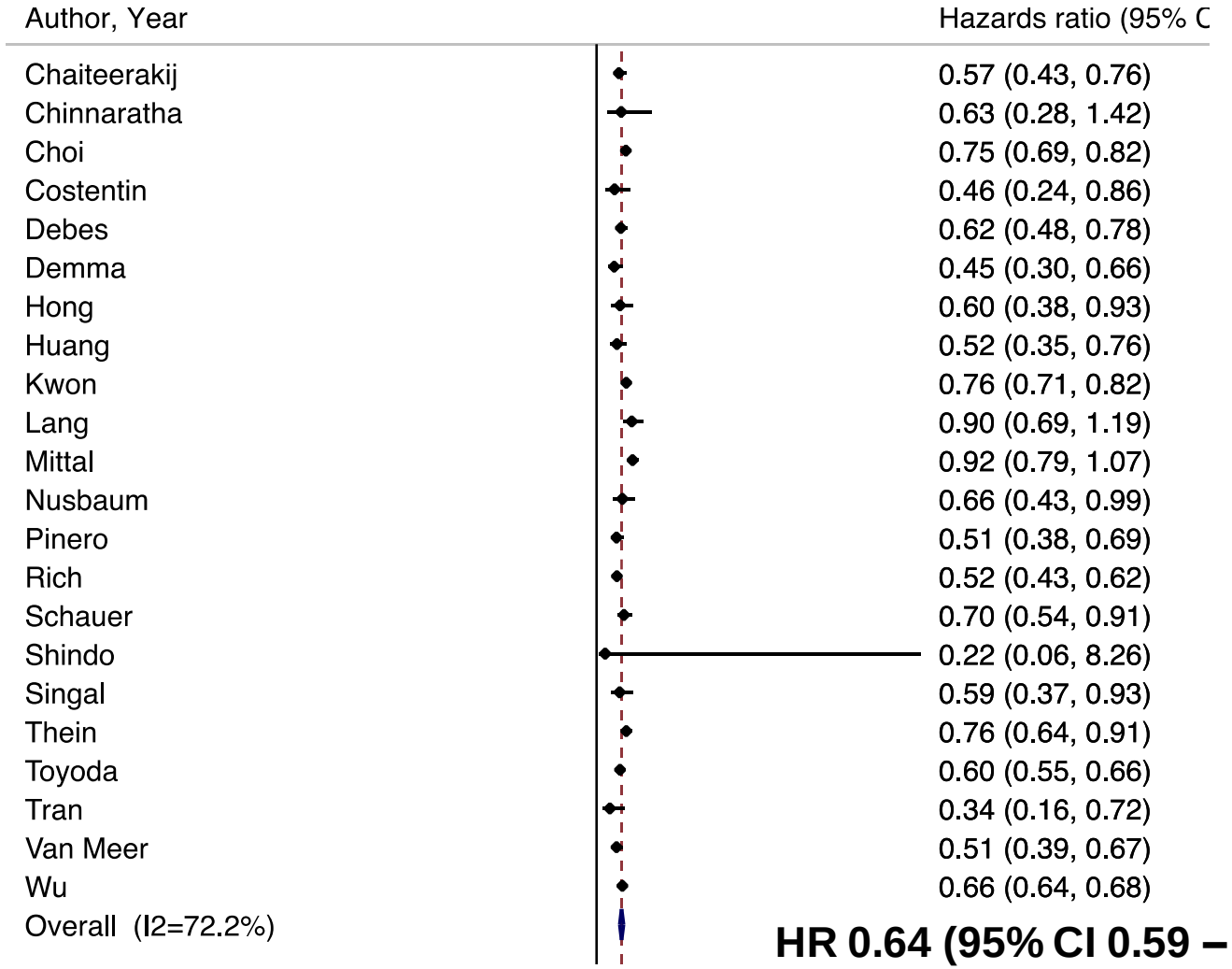
HCC Surveillance associated with:



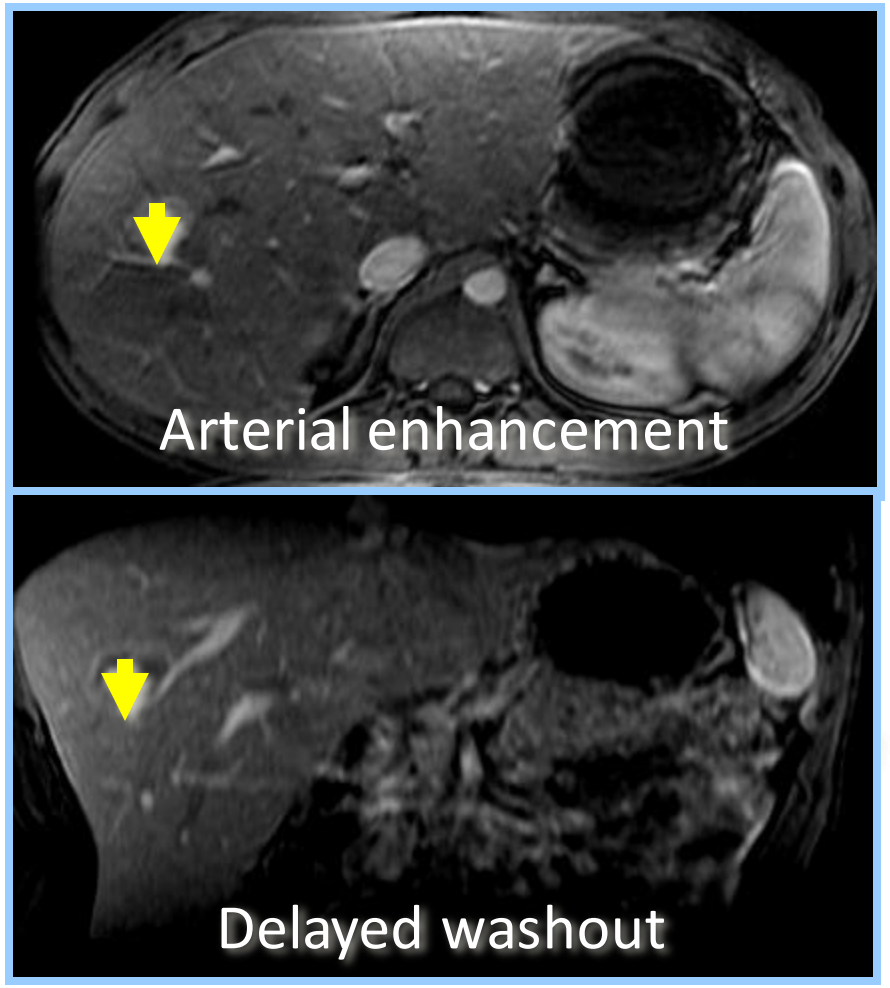
Early stage detection:
OR 1.86, 95%CI 1.73 – 1.98

Receipt of curative therapy:
OR 1.83, 95%CI 1.69 – 1.97

Overall survival:
HR 0.64, 95%CI 0.59 – 0.69

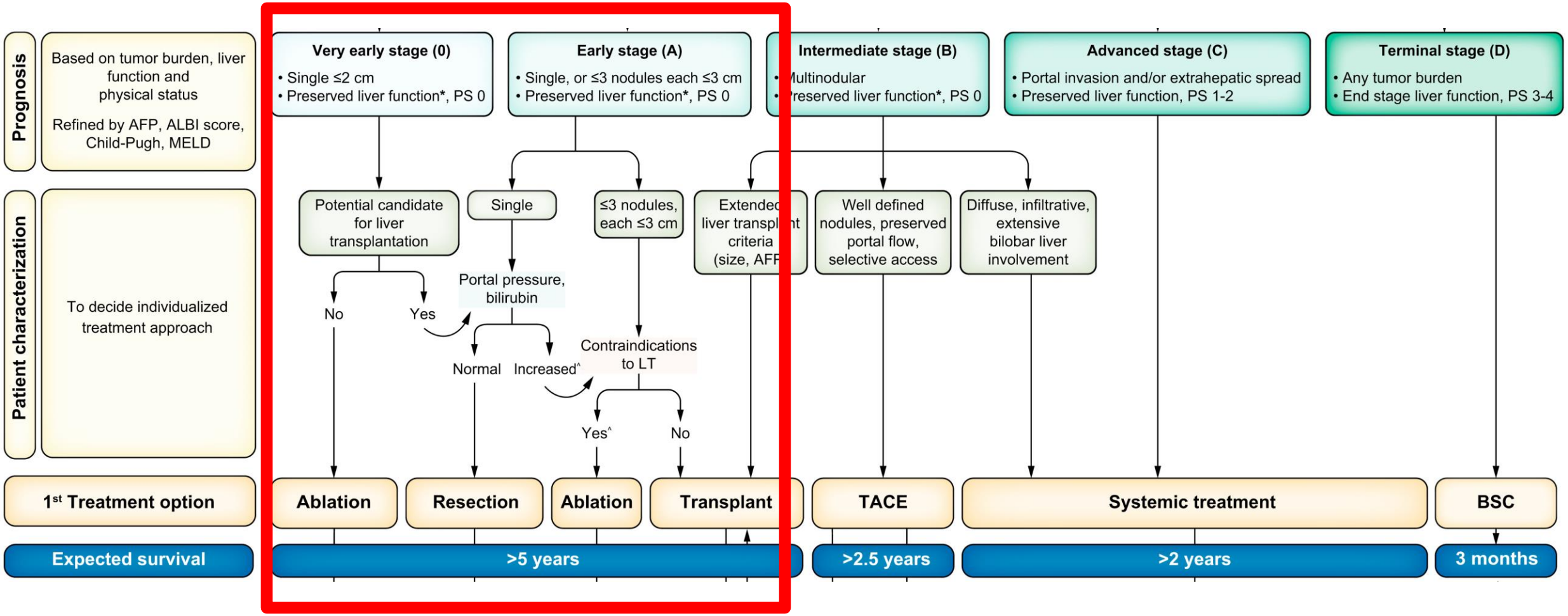


HCC can be diagnosed radiographically with need for biopsy



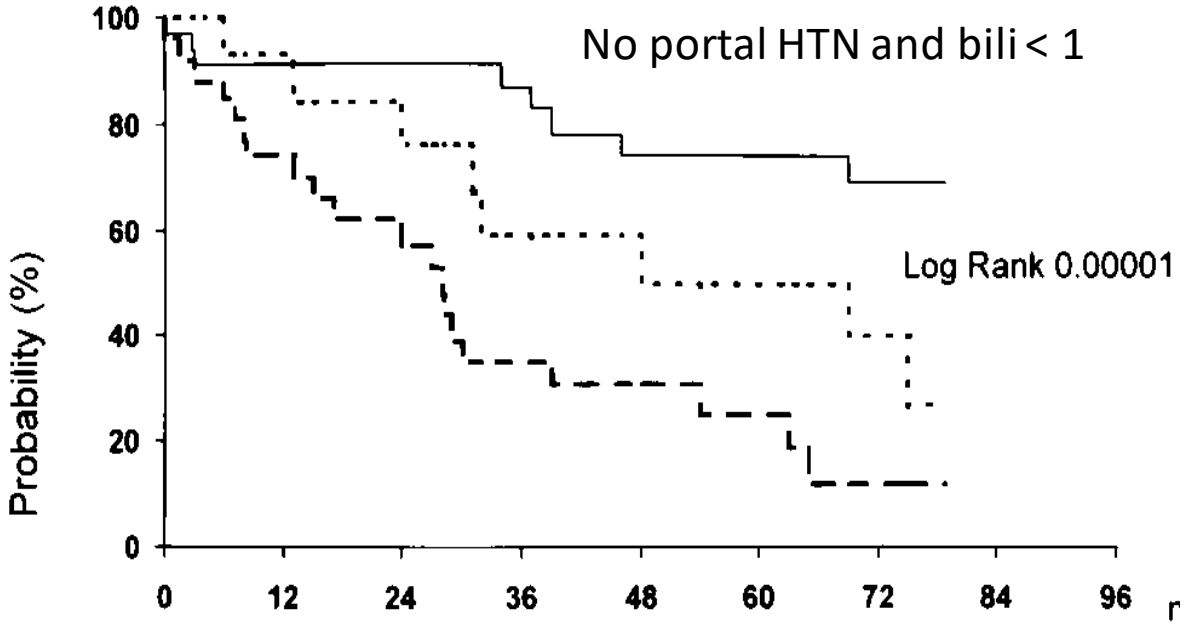
LI-RADS Category	Concept and Definition
LR-1 Definitely Benign	**Concept:** 100% certainty observation is benign. **Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2 Probably Benign	**Concept:** High probability observation is benign. **Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3 Intermediate probability for HCC	**Concept:** Both HCC and benign entity have moderate probability. **Definition:** Observation that does not meet criteria for other LI-RADS categories.
LR-4 Probably HCC	**Concept:** High probability observation is HCC but there is not 100% certainty. **Definition:** Observation with imaging features suggestive but not diagnostic of HCC.
LR-5 Definitely HCC	**Concept:** 100% certainty observation is HCC. **Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V Definitely HCC with Tumor in Vein	**Concept:** 100% certainty that observation is HCC invading vein. **Definition:** Observation with imaging features diagnostic of HCC invading vein.
LR-M Probable malignancy, not specific for HCC	**Concept:** High probability that observation is a malignancy, but imaging features are not specific for HCC. **Definition:** Observation with one or more imaging features that favor non-HCC malignancy.
LR-Treated Treated Observation	**Concept:** Loco-regionally treated observation. **Definition:** Observation that has undergone loco-regional treatment

BCLC Stage A (early-stage HCC)

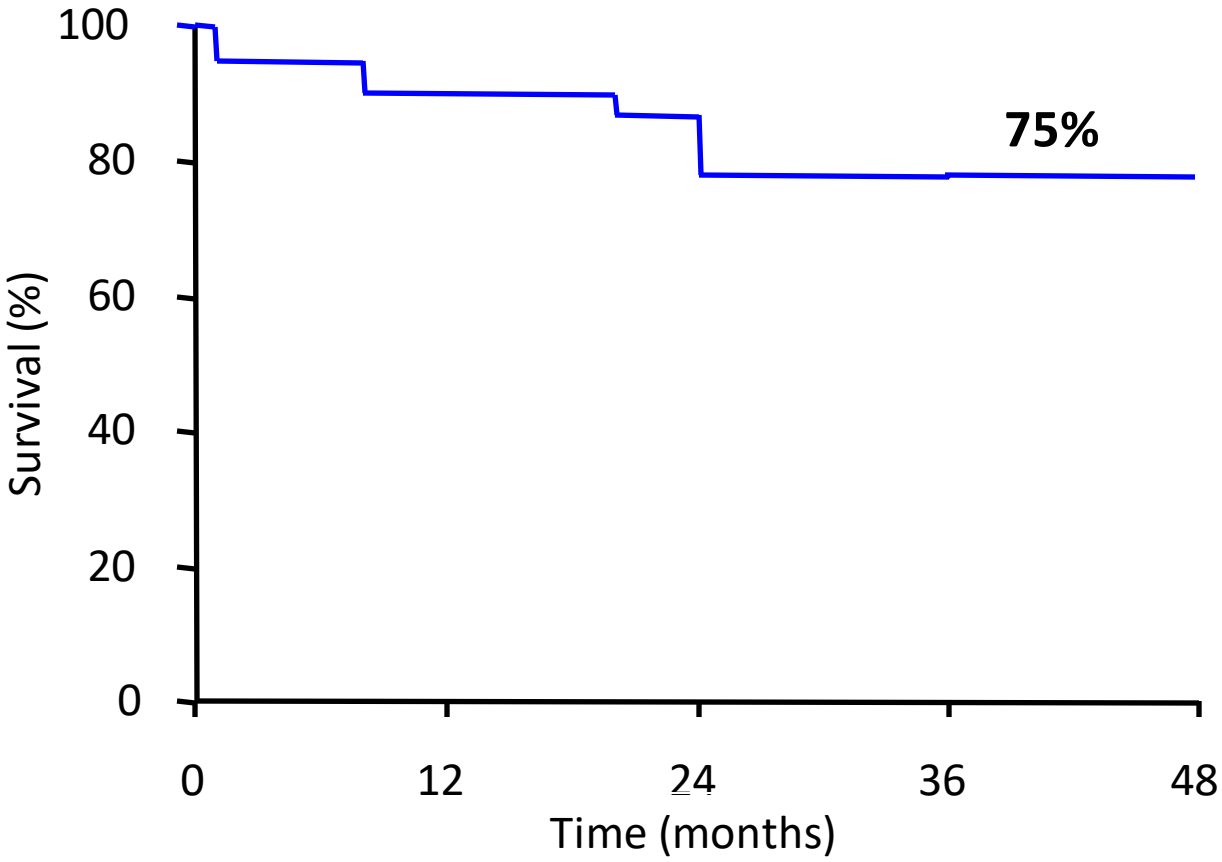


Surgical therapy affords excellent long-term survival for early-stage HCC

Resection



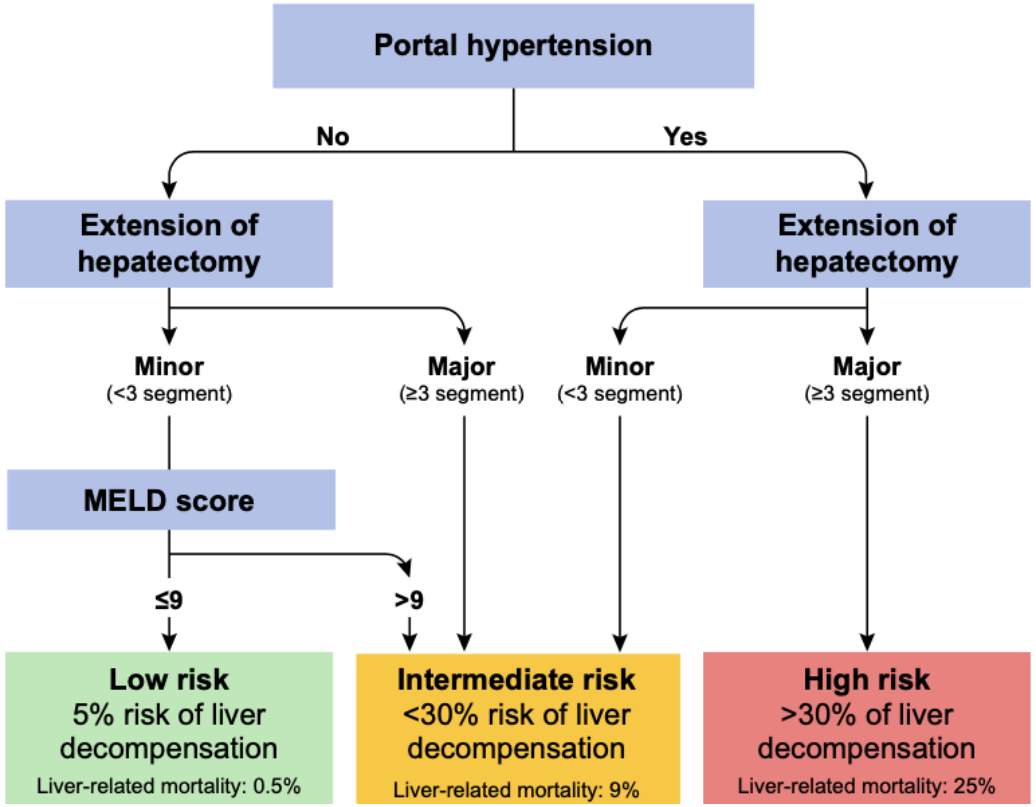
Liver Transplantation



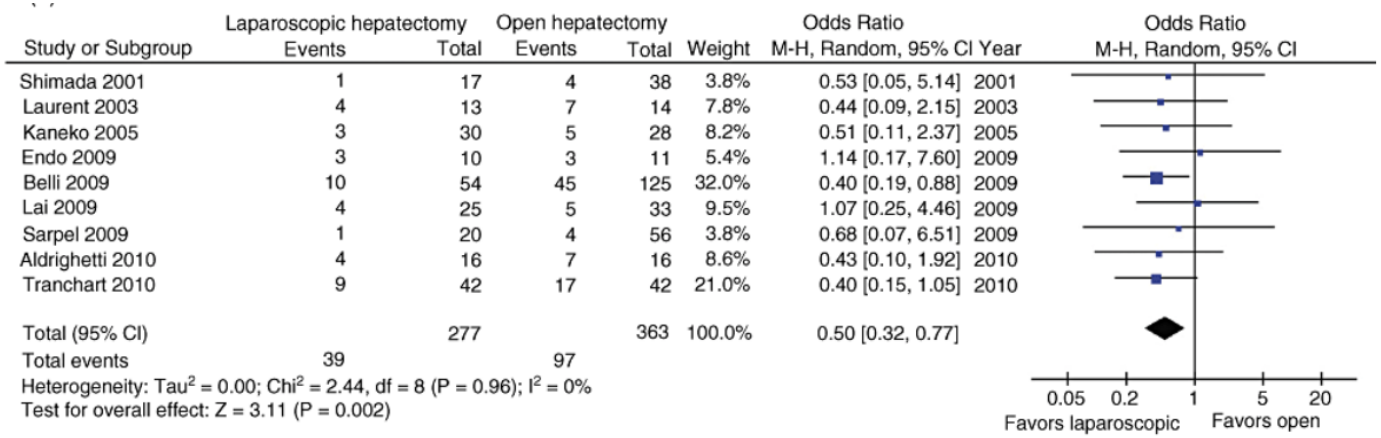
Llovet et al Hepatology 1999

Mazzaferro et al. N Engl J Med. 1996

Laparoscopic techniques allow resection to be used in patients with unifocal BCLC stage A and mild portal HTN



Complications



EASL guidelines; Li et al *Hepatology Res* 2012

SBRT has increasing data supporting role in HCC treatment

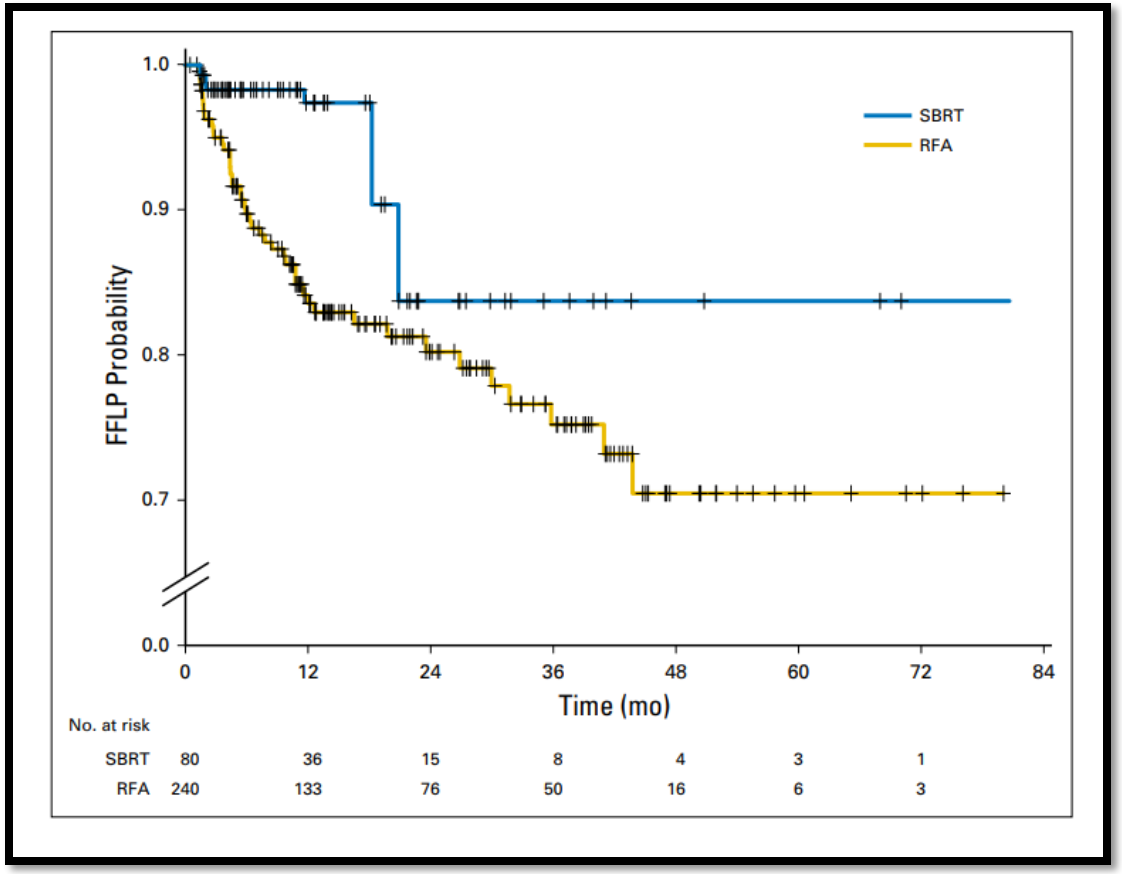


Table 3. Multivariate Cox Proportional Hazards Analysis of Factors Associated With Local Progression

	HR	95% CI	*P*
Treatment			
RFA *v* SBRT	3.84	1.62 to 9.09	.002
Age	1.01	0.97 to 1.06	.514
Tumor size	1.35	0.99 to 1.84	.055
Child-Pugh score	0.95	0.74 to 1.22	.703
AFP	1.12	0.97 to 1.30	.130
No. prior treatments	1.25	1.00 to 1.56	.055

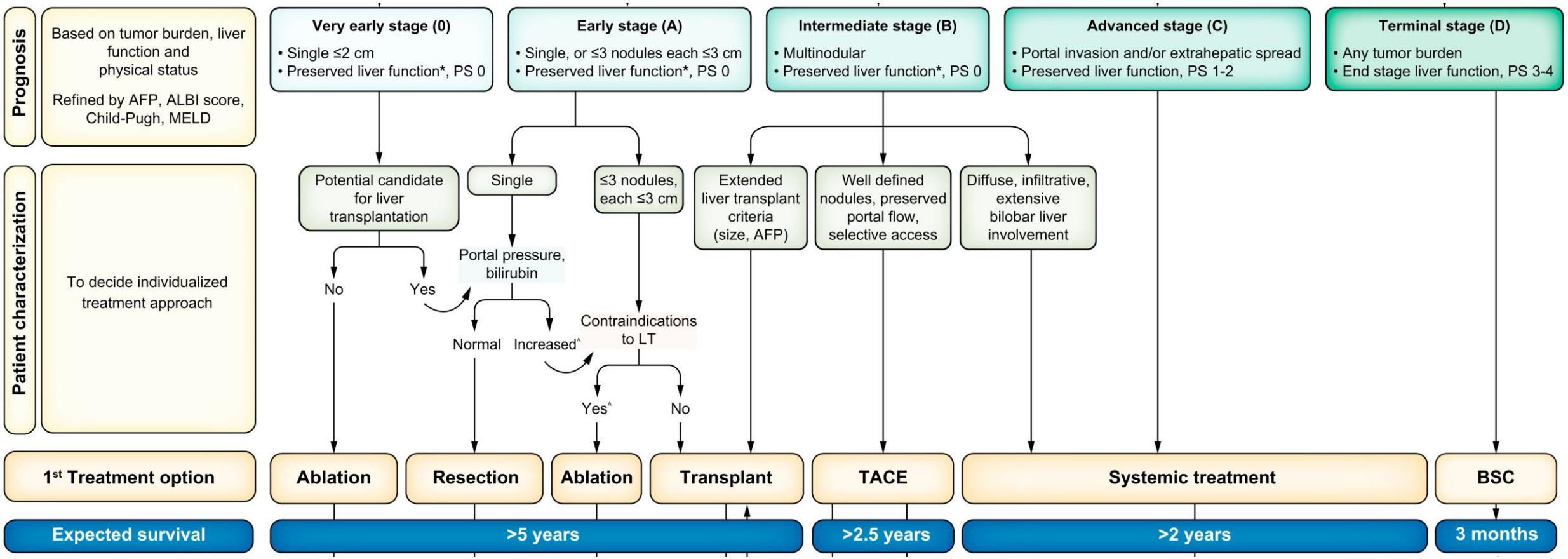
NOTE. Age (per year), tumor size (per cm), Child-Pugh score (per point), AFP (per doubling) and No. prior treatments (per treatment) were treated as continuous variables.

Abbreviations: AFP, alpha-fetoprotein; HR, hazard ratio; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

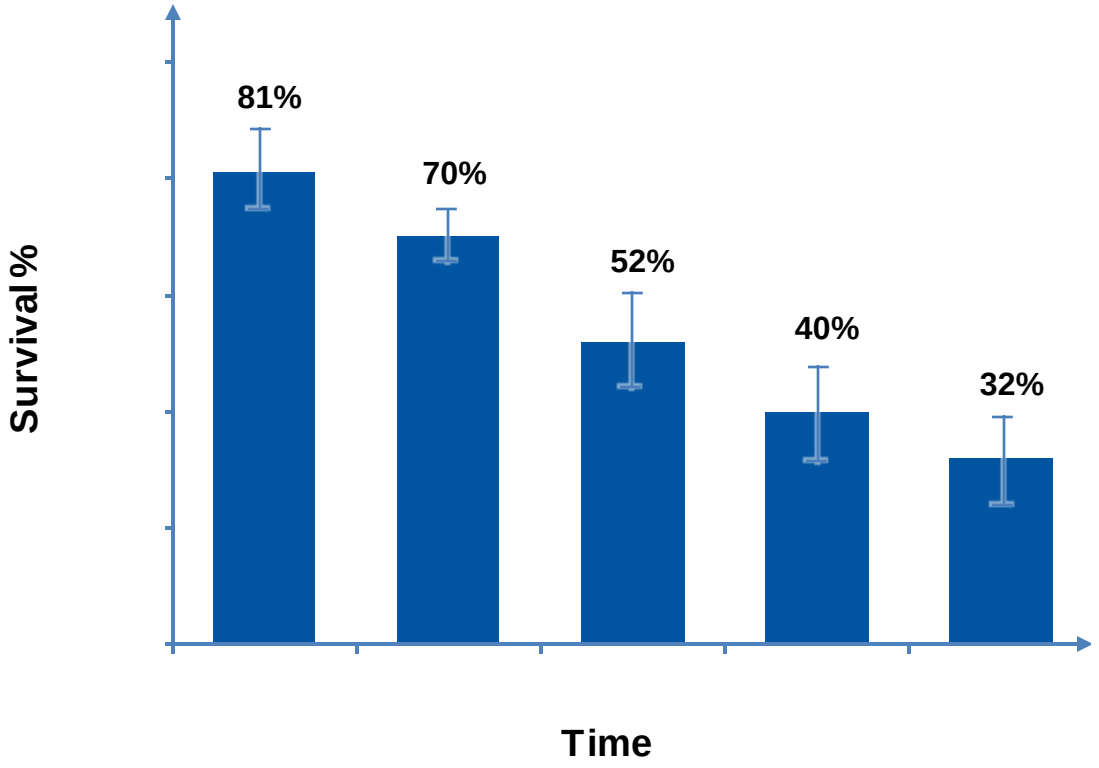
SBRT associated with better outcomes than RFA for HCC > 2cm in propensity matched analyses

Wahl et al *JCO* 2016

BCLC Stage B (intermediate-stage HCC)



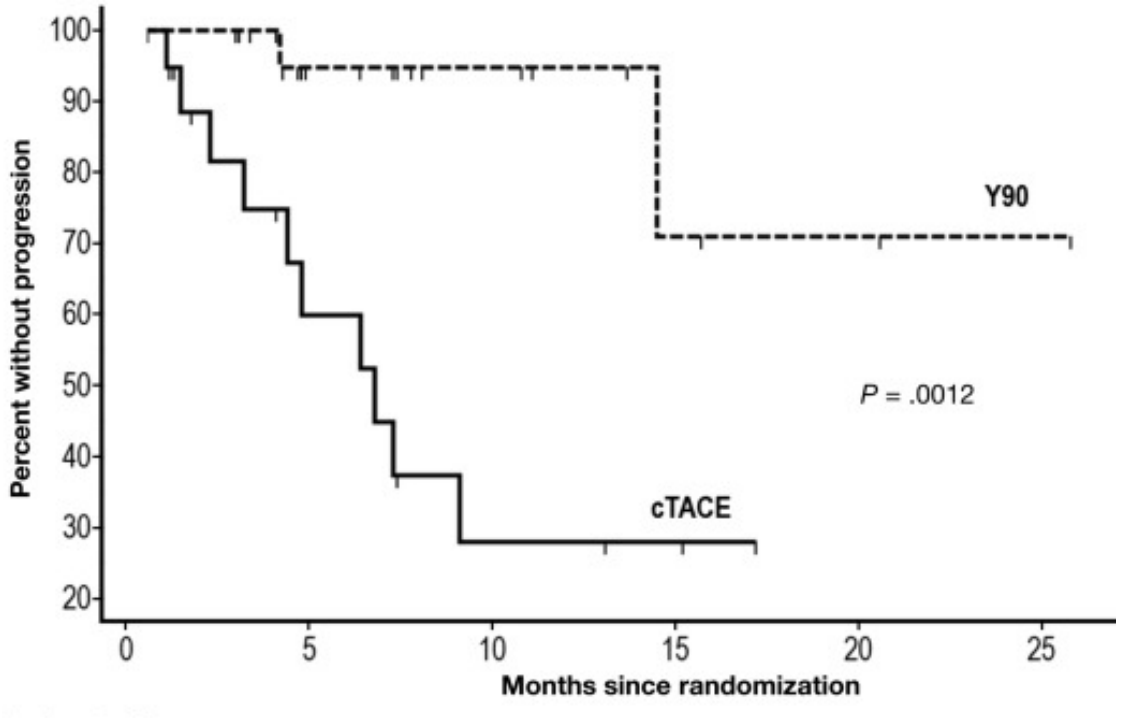
TACE provides high response rate and improves survival



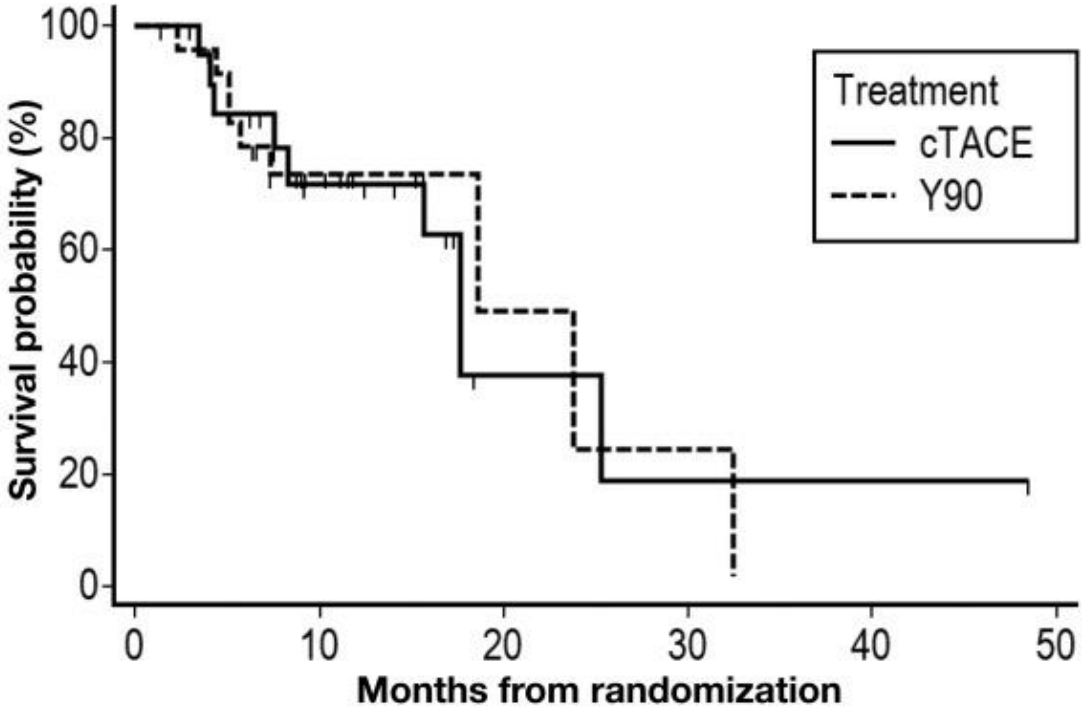
Pooled ORR was 52% and median survival ~19 months

	No. of Studies	Estimate	Lower 95% CI	Upper 95% CI
Median, mo				
≤2002	19	18.5	14.6	22.4
>2002	44	19.8	15.5	24.1
1-year, %				
≤2002	19	70.7	63.2	78.3
>2002	71	70.4	65.2	75.5
2-year, %				
≤2002	21	51.1	37.1	65.1
>2002	50	52.0	43.9	60.2
3-year, %				
≤2002	13	27.8	18.3	37.4
>2002	53	43.4	34.9	51.8

TARE likely has role in treatment of BCLC stage B HCC



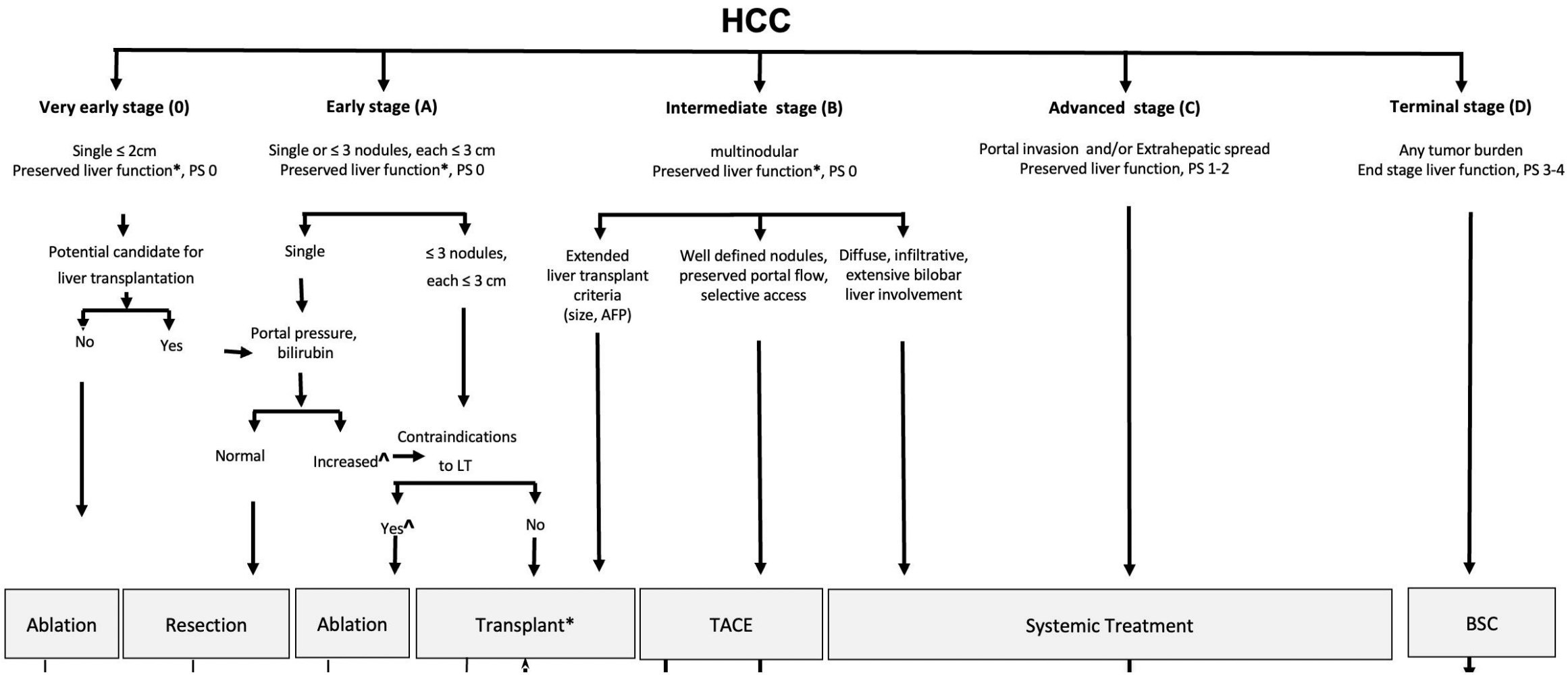
TTP: >26 vs.6.8 months
(HR 0.12, 95%CI 0.03-0.56)



Median survival: 17.7 vs. 18.6 mo
(p=0.99)

Salem et al *Gastro* 2016

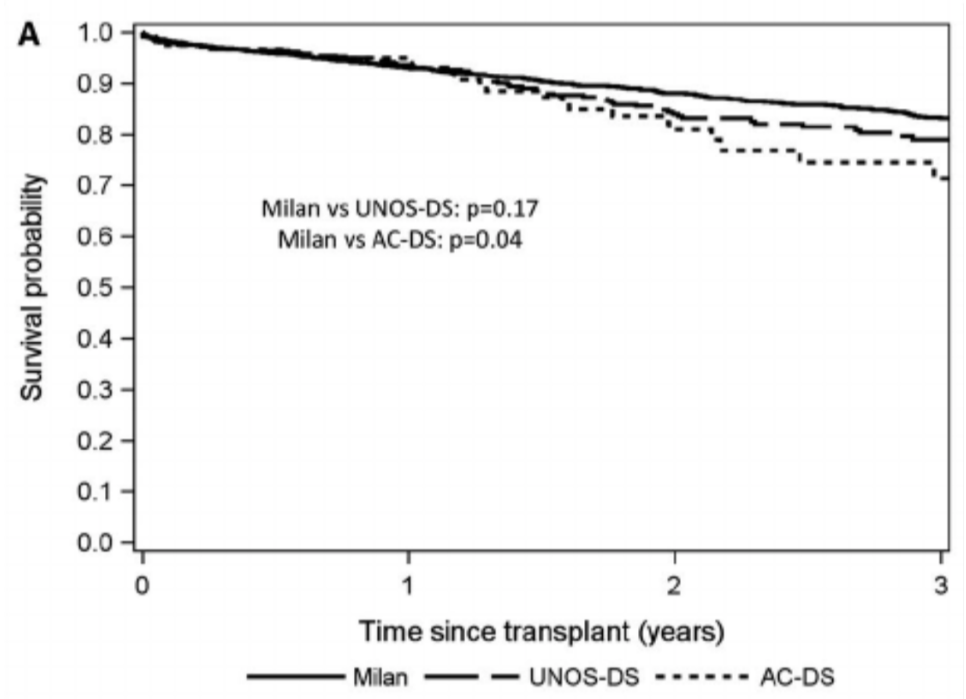
BCLC stage B HCC has heterogeneous prognosis

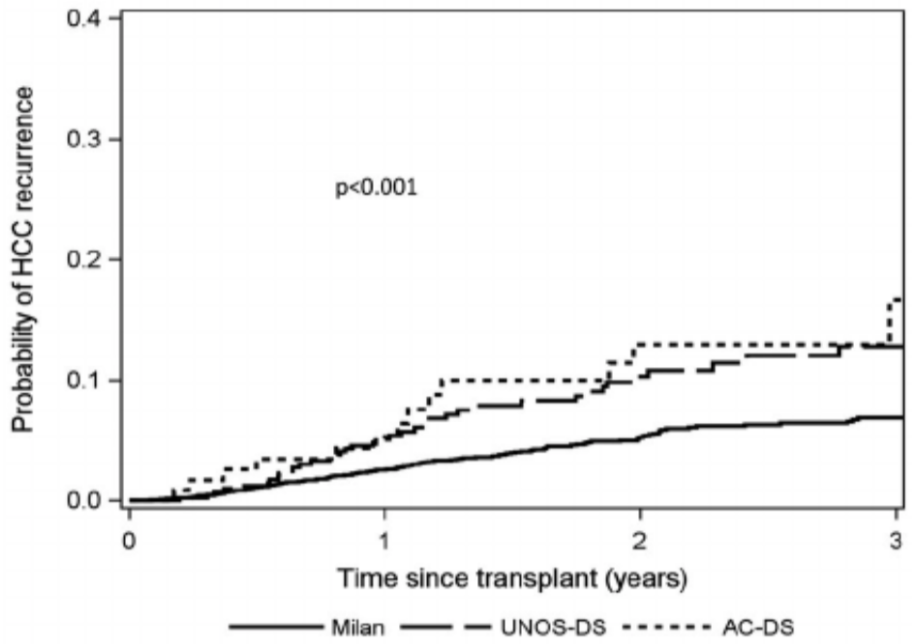


Patients within UNOS-DS can achieve good survival with transplant

Downstaged patients (n=422) vs. within Milan (n=3276) vs. beyond Milan (n=121) post LT from 2012-2015

UNOS-DS: One HCC >5 and ≤8 cm, two to three HCC >3 cm and ≤5 cm and diameter ≤8 cm, or four to five lesions each ≤3 cm and diameter ≤8 cm



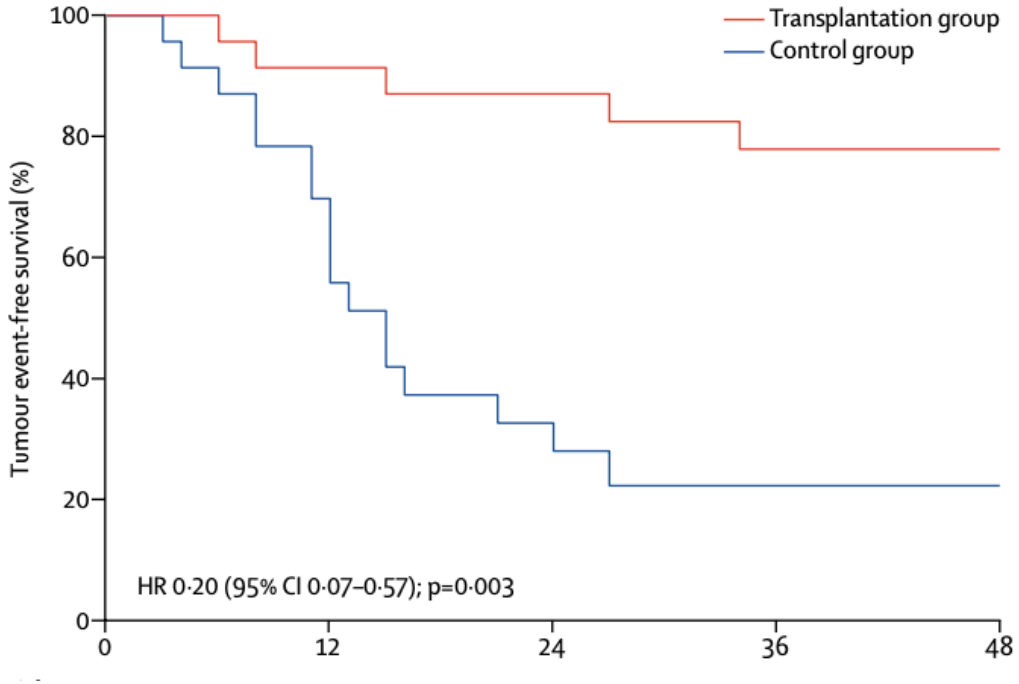


Those beyond UNOS-DS do not get exception points but can undergo LT via living donor (or natural MELD)

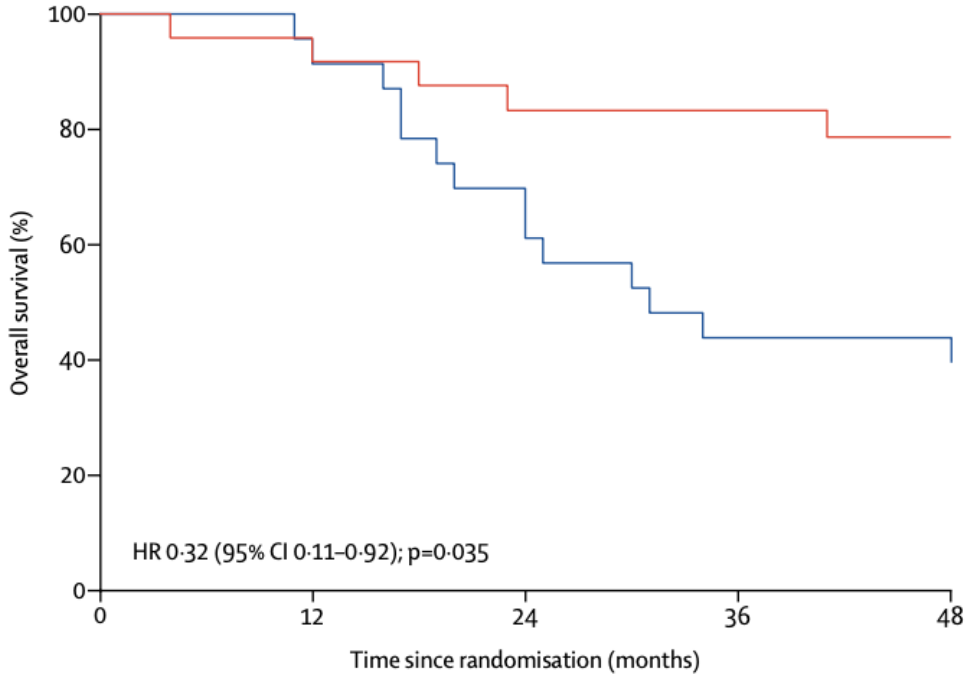
Benefits of downstaging: The XXL Trial

Open-label, multicenter phase 2/3 RCT among patients with liver-localized HCC beyond Milan Criteria
Patients with response after downstaging therapies were randomized to liver transplant or non-transplant therapy
After 29 patients failed downstaging, 45 patients randomized to transplant vs. non-transplant therapy

5-year HCC-free survival: 76.8% vs. 18.3%

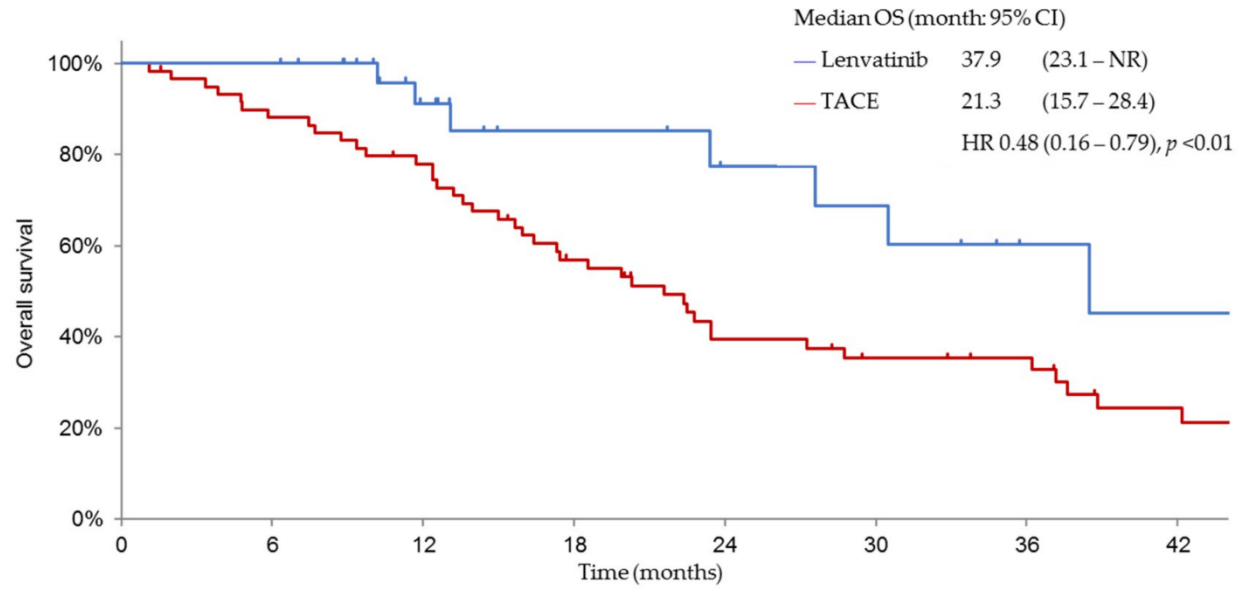


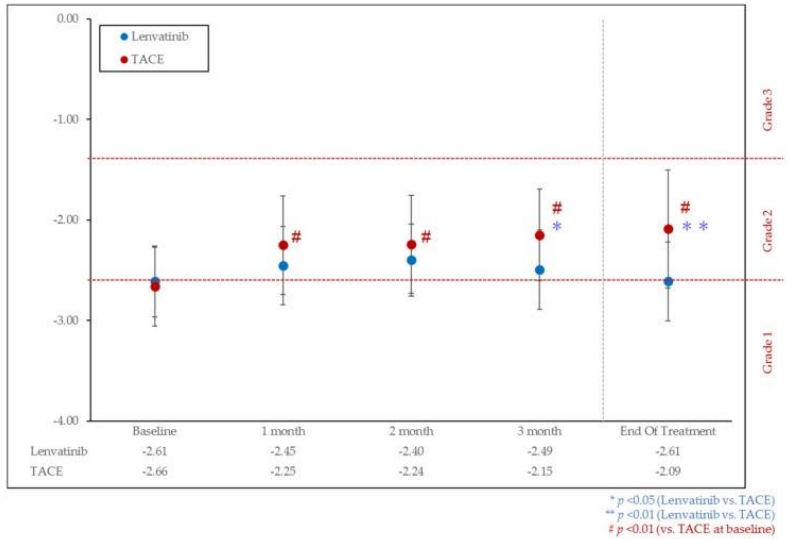
5-year overall survival: 77.5% vs. 31.2%



Mazzaferro et al. Lancet Oncology 2020

Patients with large BCLC B HCC may be achieve better outcomes with systemic than locoregional therapy





ABC-HCC Trial: Randomized, multi-center open-label, phase 3 study

- Multifocal HCC beyond Milan
- No massive multinodular pattern precluding TACE (e.g., infiltrative HCC)
- No portal vein thrombosis or metastases
- ≥1 measurable target lesion per mRECIST
- Child–Pugh A
- ECOG PS 0
- EGD within 6 months and varices treated per local standard of care
- Adequate organ function

N = 434 R

Atezolizumab and bevacizumab q3 weeks (n = 217)

cTACE or DEB-TACE (n = 217)

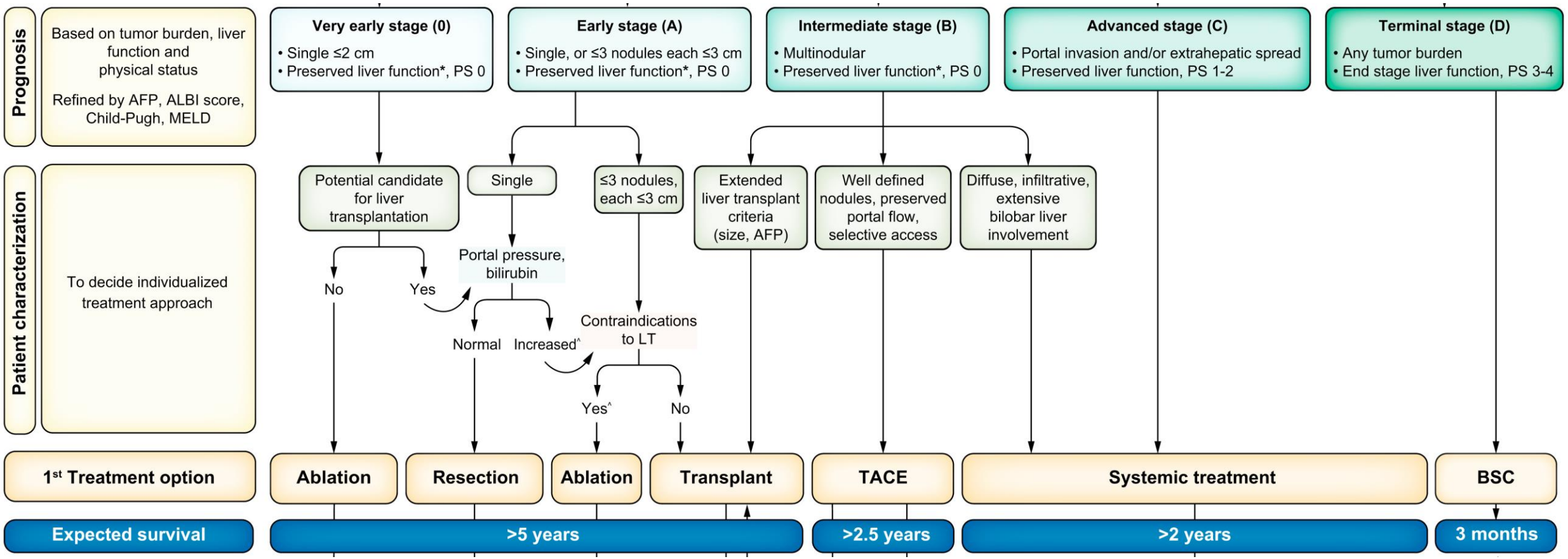
Asia-Pacific Expert Consensus Statement for TACE unsuitability

A. Conditions that easily become refractory to TACE:
- Beyond up-to-seven criteria

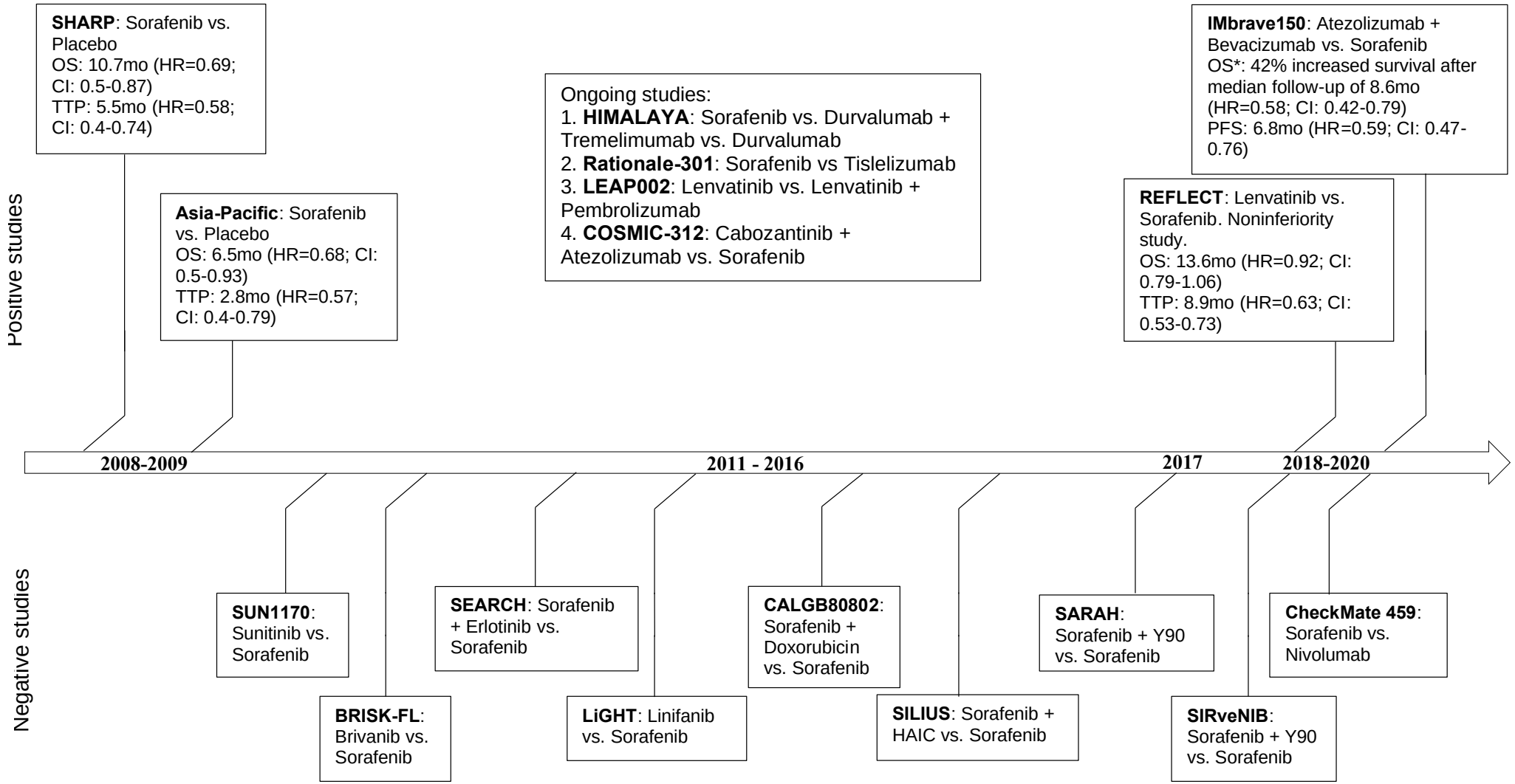
B. Conditions in which TACE causes deterioration of liver function to Child-Pugh class B:
- Beyond up-to-seven criteria
- ALBI grade 2

C. Conditions that are unlikely to respond to TACE (TACE-resistant tumor):
- Simple nodular type tumor with extranodular growth
- Confluent multinodular type tumor
- Massive type tumor
- Poorly differentiated HCC
- Intrahepatic multifocal metastasis
- Sarcomatous change caused by TACE

BCLC Stage C (advanced-stage HCC)



Notable advances in treatment options for advanced stage HCC

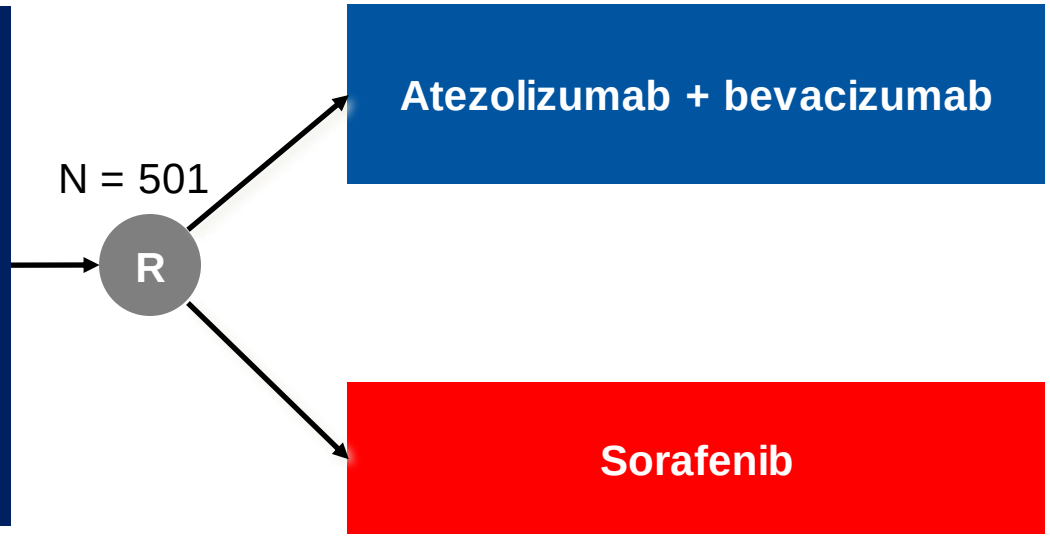


Ferrante et al. Gastro Hep 2020

IMBrave150: Atezolizumab/Bevacizumab vs. Sorafenib

Key eligibility criteria

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy for HCC
- ≥1 measurable untreated lesion
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function
- Child–Pugh class A

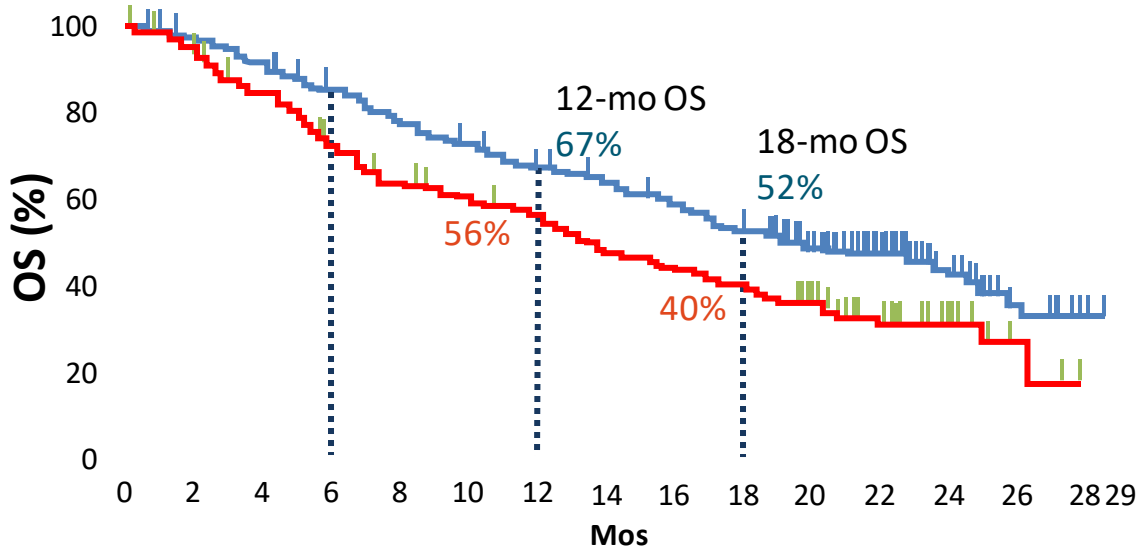


- **Primary endpoints:** PFS and OS

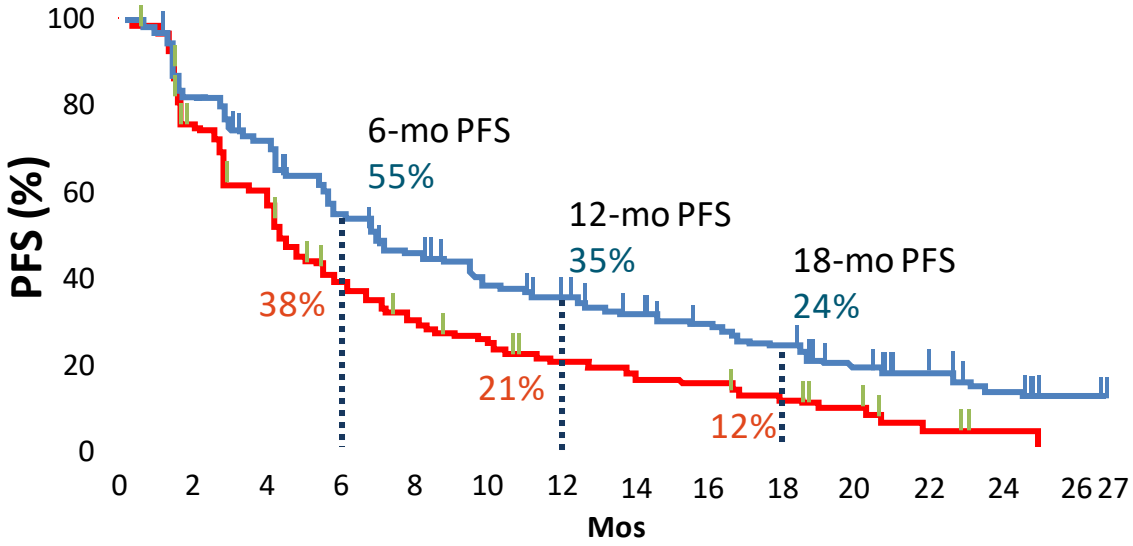
All patients were required to have recent EGD to risk stratify risk of bleeding

Atezolizumab and bevacizumab improves survival for patients with advanced-stage HCC

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, mos	**19.2**	**13.4**
Stratified HR (95% CI)	0.66 (0.52-0.85)	

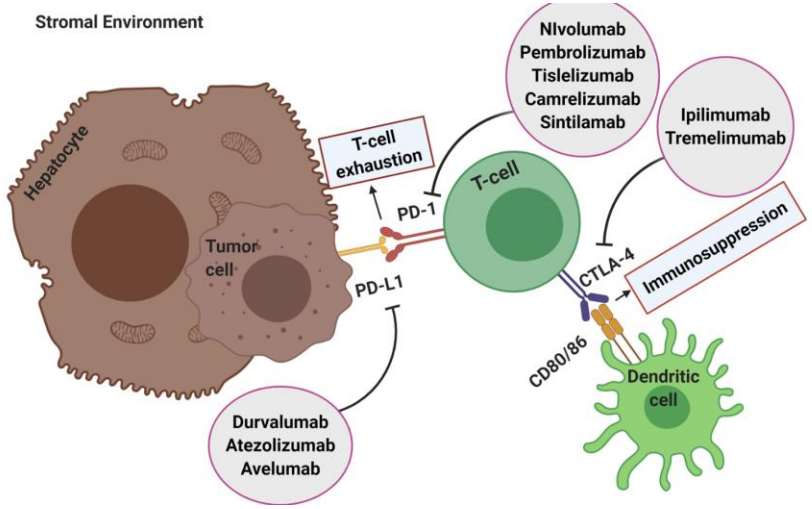


	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, mos	**6.9**	**4.3**
Stratified HR (95% CI)	0.65 (0.53-0.81)	

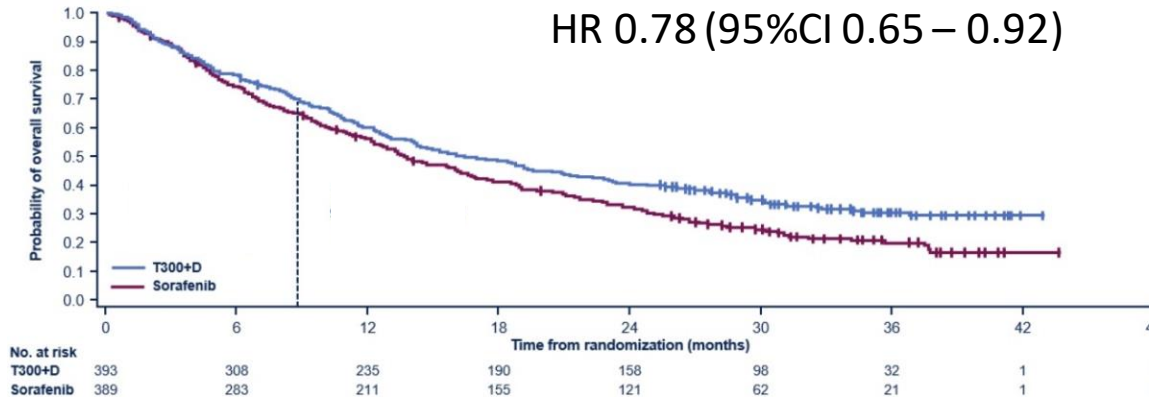


Finn et al New Eng J Med 2020

Durvalumab + Tremelimumab improves survival in front-line setting for advanced stage HCC



Median survival 16.4 vs. 13.8 months
HR 0.78 (95%CI 0.65 – 0.92)

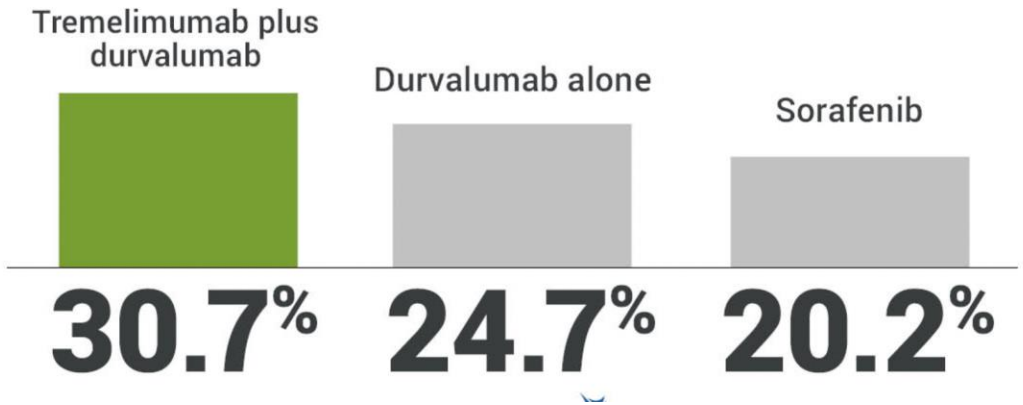


- Unresectable HCC not eligible for LRTs
- BCLC stage B or C
- Child–Pugh A
- No prior systemic therapy

N = ~1,200

R

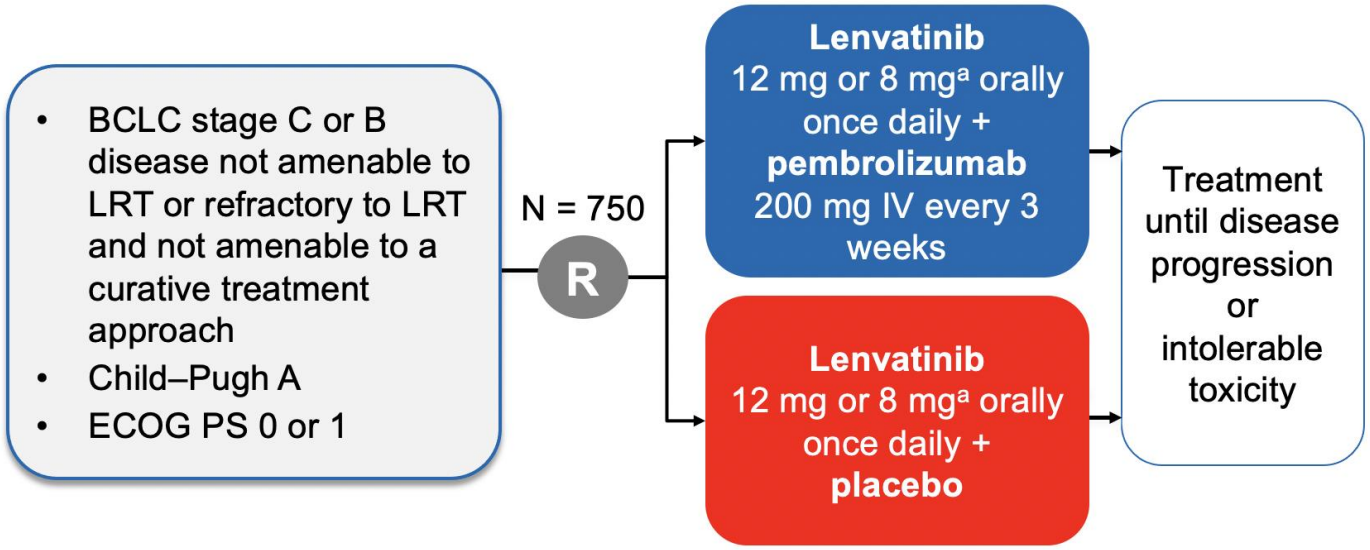
- **Durvalumab 1,500 mg Q4W**
- **Durvalumab 1,500 mg Q4W + Tremelimumab 75 mg x 4 dose**
- **Durvalumab 1,500 mg Q4W + Tremelimumab 300 mg x 4 dose**
- **Sorafenib**



LEAP-002 Trial Evaluating Lenvatinib + Pembrolizumab

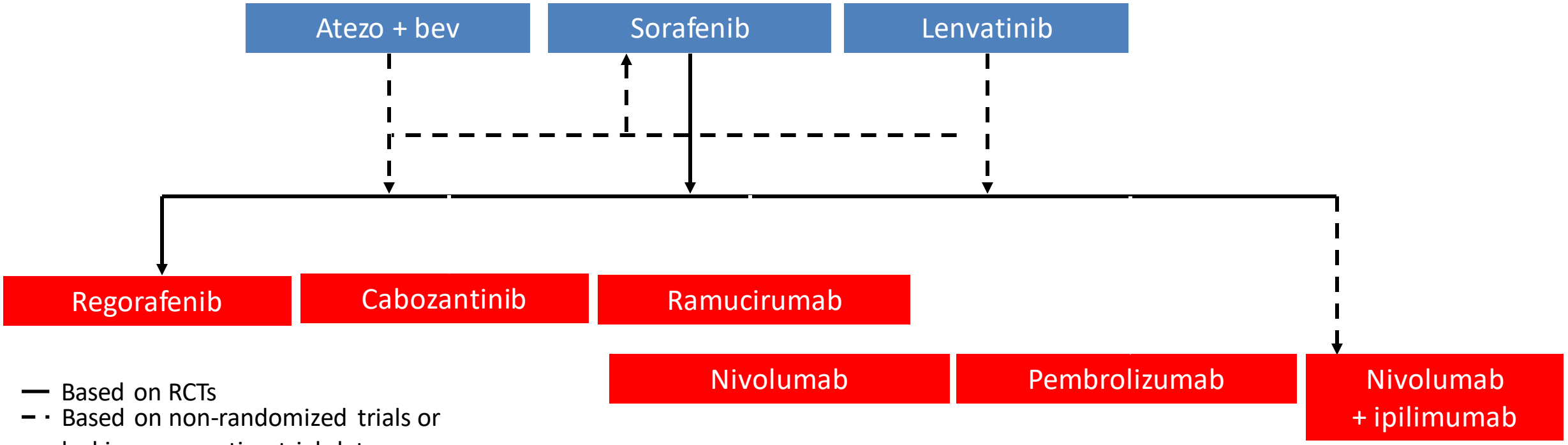
Endpoint/ Outcome	mRECIST per IIR	RECIST v1.1 per IIR	mRECIST per Investigator Review
ORR, n (%)	46 (46)	36 (36)	41 (41)
Median DOR, mo (95% CI)	8.6 (6.9-NE)	12.6 (6.9-NE)	12.6 (6.2-18.7)
Median time to response, mo (range)	1.9 (1.2-5.5)	2.8 (1.2-7.7)	2.7 (1.2-11.8)
Disease control rate, n (%)	88 (88)	88 (88)	86 (86)
95% CI	80.0-93.6	80.0-93.6	77.6-92.1
Most common grade ≥3 TRAE was hypertension (17% of pts)			

Median PFS 9 months and OS 22 months

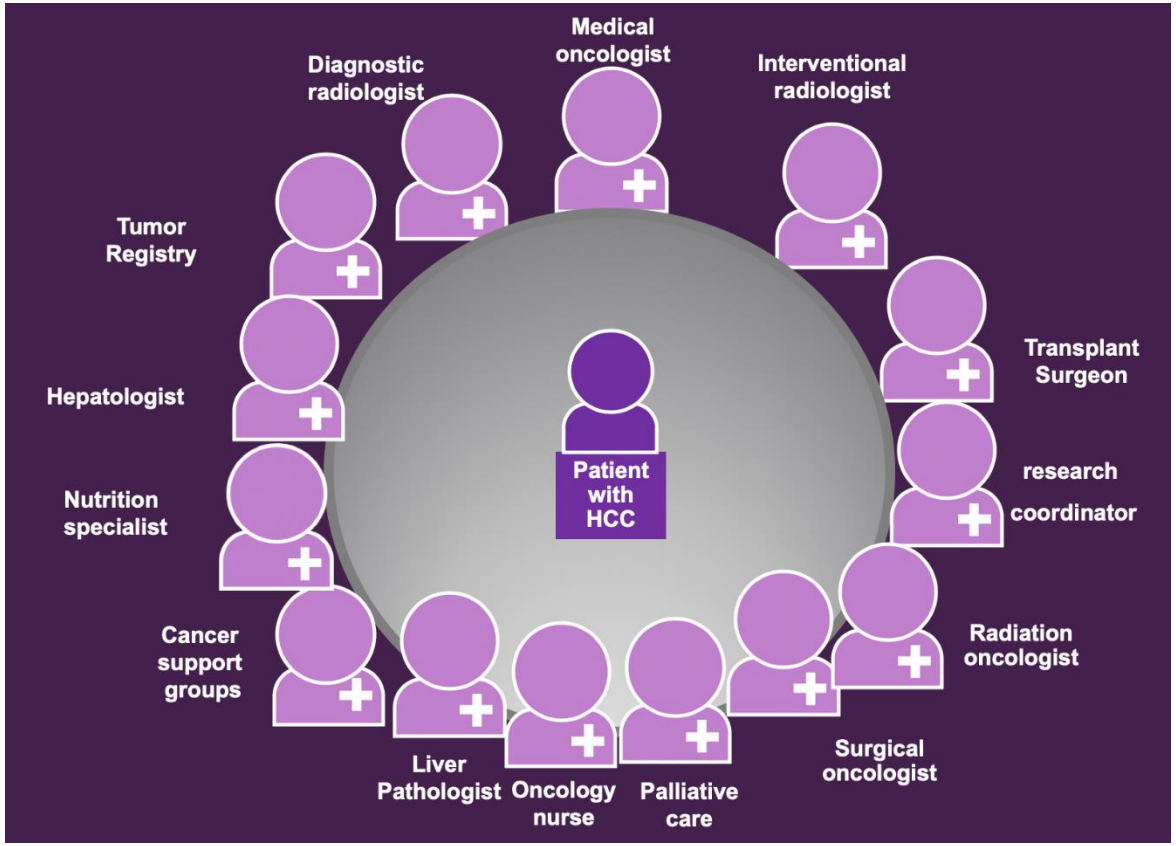


- **Primary endpoints:** OS and PFS
- **Secondary endpoints:** ORR, DOR, DCR, and safety

There are sequential systemic therapy options available



Multidisciplinary care improves HCC outcomes



Study	Description	Outcomes
Serper 2017 (n=3988)	Multi-specialty evaluation or tumor board	Increase HCC treatment receipt and improve survival
Yopp 2014 (n=355)	Single day MDT clinic and conference	Improve early detection, curative treatment, time to treatment, and survival
Zhang 2013 (n=343)	Single day MDT clinic	Changed imaging/pathology interpretation and therapy plan
Chang 2008 (n=183)	Fluid referrals and joint conference	Improve early detection, curative treatment, and survival

Serper et al. Gastro 2017; Yopp et al *Ann Surg Onc*. 2014; Chang et al *HPB* 2008; Zhang et al *Curr Oncol* 2013

Summary

- Best survival observed in patients with early-stage HCC given curative options including surgical resection, liver transplantation, and local ablation
  - Highlights importance of surveillance and early referral
- TACE and TARE are primary therapies for intermediate stage HCC
  - Important to consider downstaging for patients with extended criteria
- There are a growing number of systemic treatment options for advanced HCC
  - 1st line: Atezolizumab/bevacizumab, Durvalumab/tremelimumab, Sorafenib, or Levantinib
  - 2nd line: Regorafenib, Cabozantinib, Ramucirumab, Pembrolizumab, Ipilimumab/Nivolumab
- Multidisciplinary care improves outcomes for patients with HCC, particularly as treatment landscape evolves

Liver Cancer Awareness Month
October