Primary Liver Cancer: An overview

Subtitle

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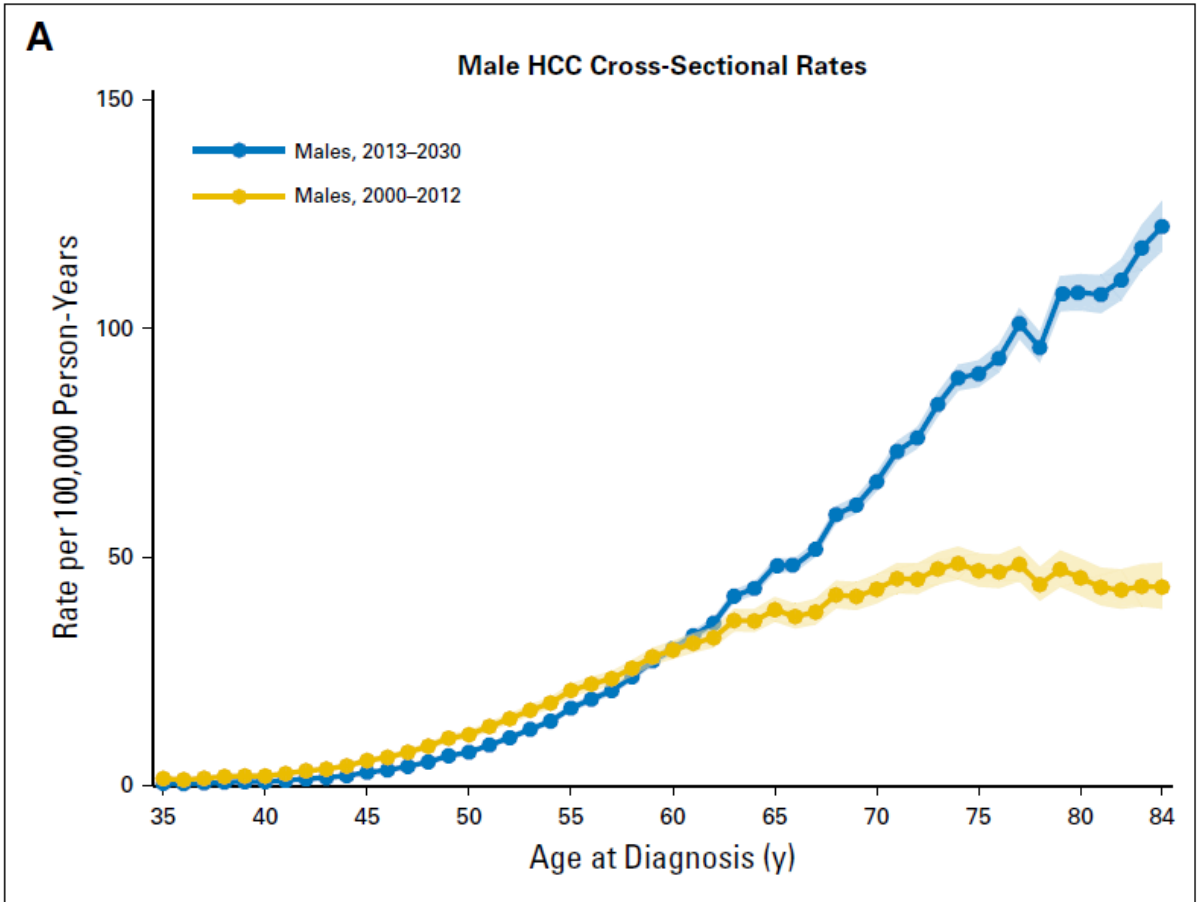
Primary Liver Cancer

- Hepatocellular carcinoma (HCC) & intrahepatic bile duct cancer
- 5th common cause of cancer, 3rd cause of cancer death
- 80% on cirrhotic background

Risk Factors

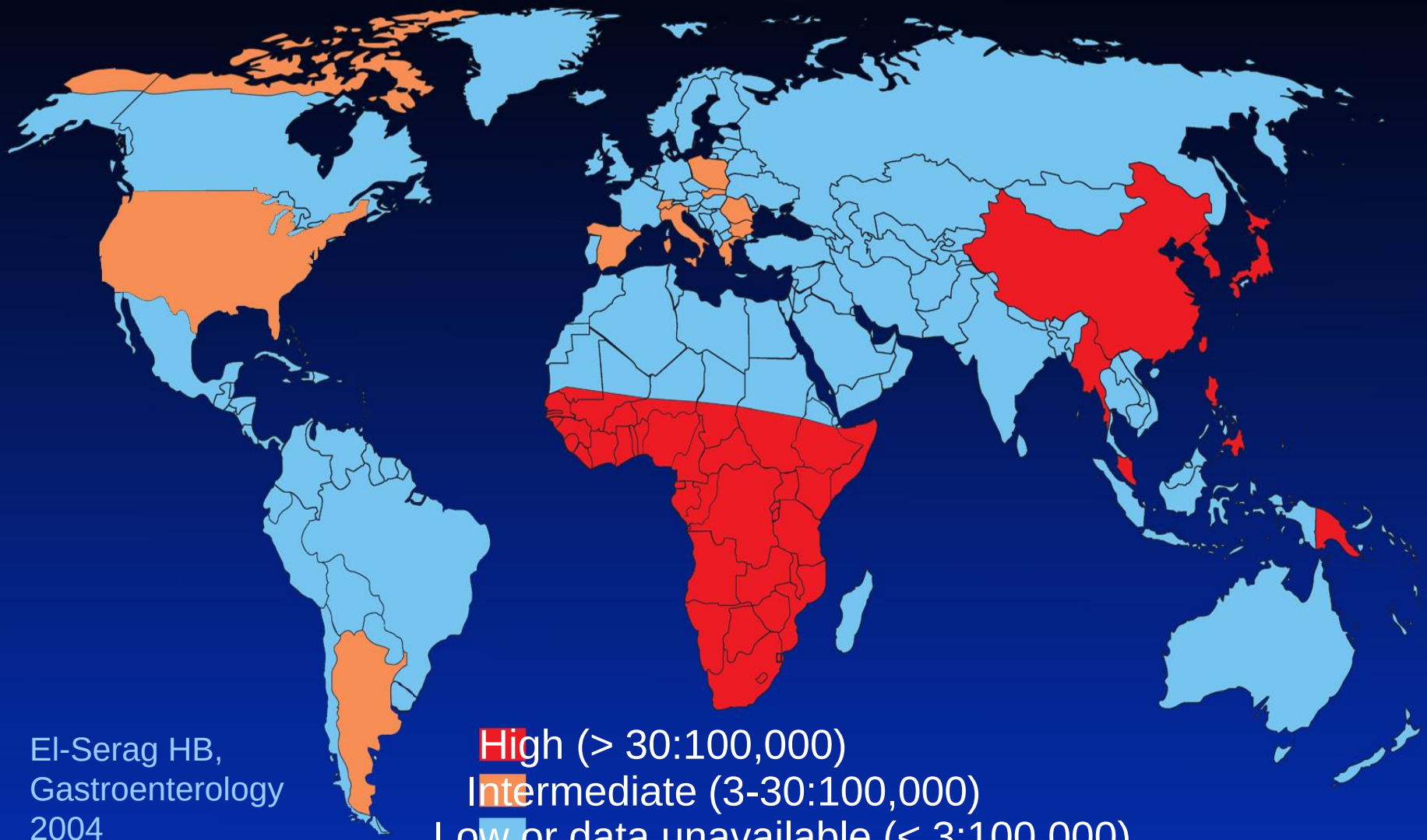
- **Cirrhotic liver**
  - Hepatitis B & C
  - Alcohol excess
  - Metabolic syndrome
  - Haemachromatosis
  - Other – aflatoxin, biliary cirrhosis

Rising Incidence



Petrick JCO 2016

Worldwide Incidence of Hepatocellular Carcinoma



El-Serag HB, Gastroenterology 2004

Screening for HCC: EASL Recommendations

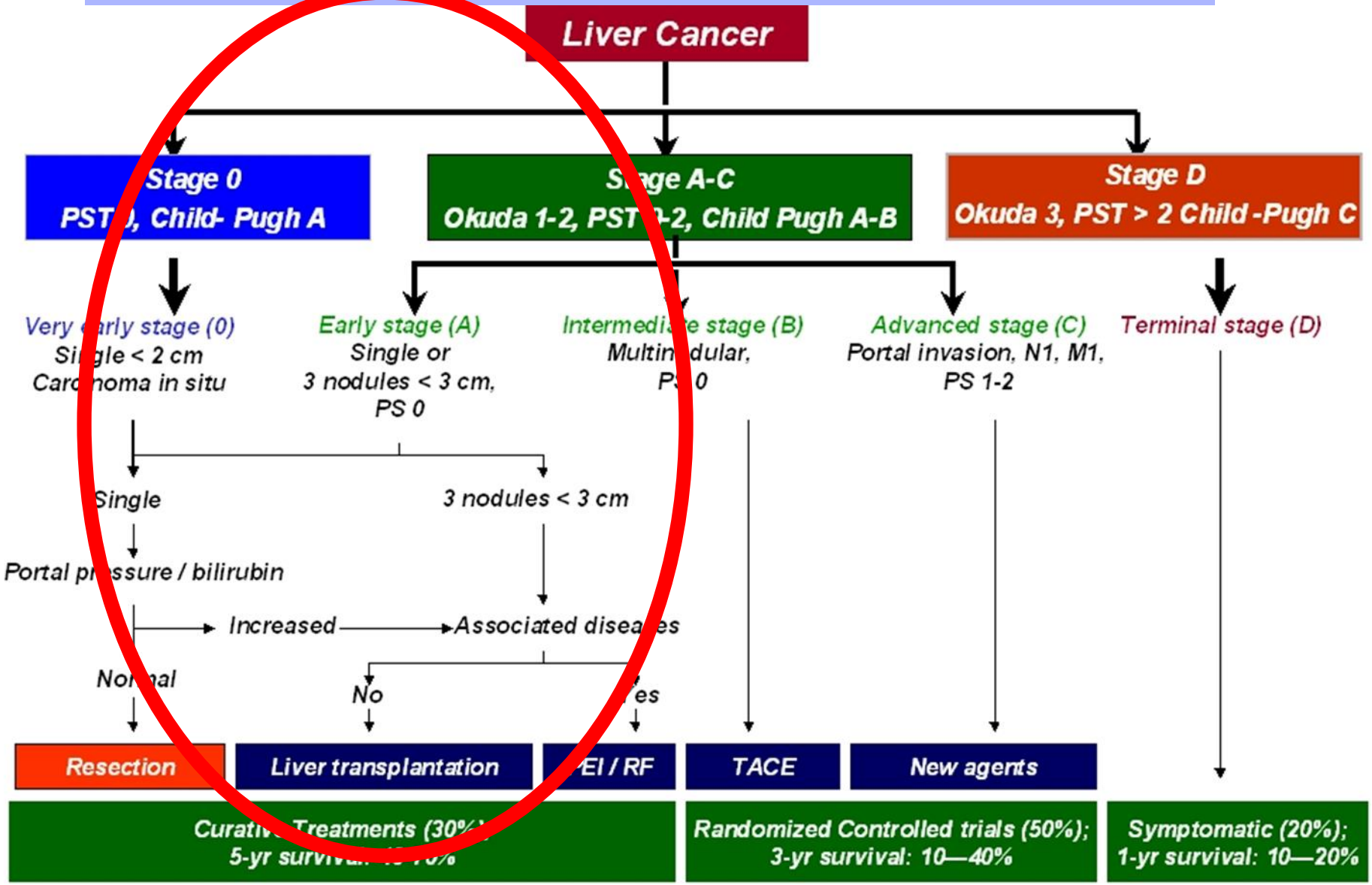
Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.

1.	Cirrhotic patients, Child-Pugh stage A and B*
2.	Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3.	Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4.	Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

- Surveillance for HCC should be performed with

  US + AFP (20 ng/ml → 6-9% improvement).
- Screening should occur every 6 months.
- Shortened recall for patients at higher risk of HCC (ie. suspicious unifocal nodules <1cm sign) – 3 mo.

Management: Barcelona Liver Cancer Clinic Guidelines



Treatment

- Early HCC - curative intent
- Intermediate-Advanced HCC - Curative intent not possible, but not terminal
- Advanced/Terminal HCC - Palliative options only

Patient Pathway at Imperial

- Patients discussed at Multidisciplinary meeting
  - Interventional Radiologist
  - HPB surgeons
  - Hepatologist
  - Oncologist
  - HCC CNS
  - Palliative Care
- Patients then reviewed in Specialist Liver Cancer Clinic
  - Dr Sharma (oncology), Dr Khan (hepatology), Mr Pai (surgeon), CNS, psychologist

Liver Transplantation for Small HCC: Milan Criteria

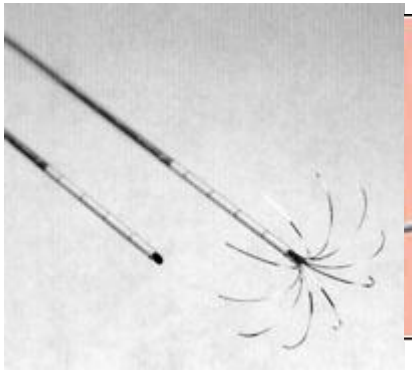
- Single tumors ≤ 5 cm or no more than 3 nodules, ≤ 3 cm
- No vascular invasion
- No distant metastases
- Jointly run with Royal Free Hospital

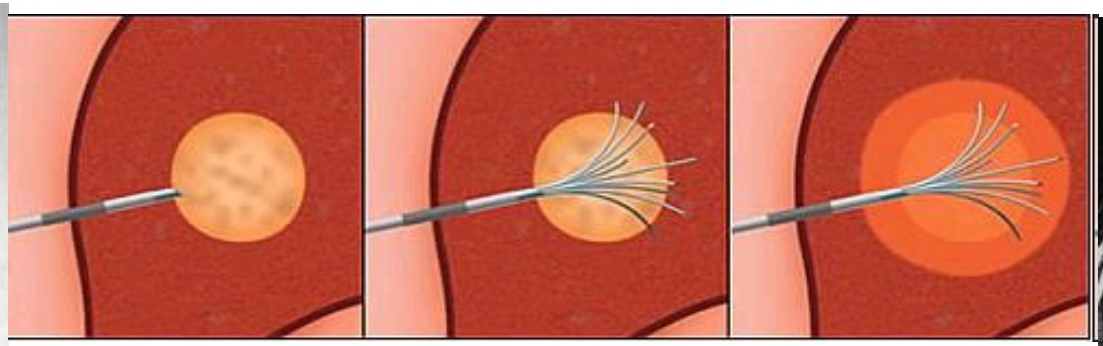
Surgery

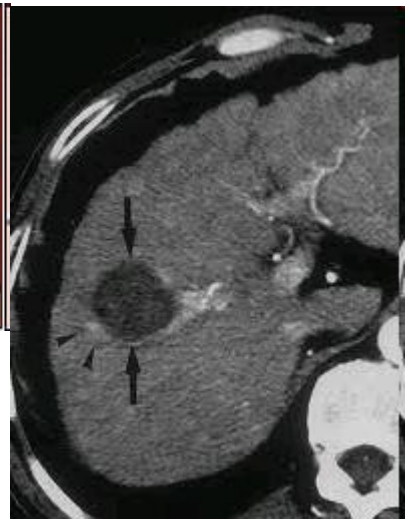
- No cirrhosis
  - Tumors of any size
  - No macrovascular, lymph node, or extrahepatic metastases
  - If technically feasible
- Cirrhosis
  - Child-Pugh A cirrhosis
  - No clinically significant portal hypertension
  - Bilirubin < 1 mg/dl (17 mmol)

Radiofrequency Ablation (RFA)

- High frequency alternating current moves from electrode tip into surrounding tissue
- Ions within tissue attempt to follow change in direction of alternating current resulting in frictional heating of tissue
- Coagulative necrosis
- Microvasculature destroyed

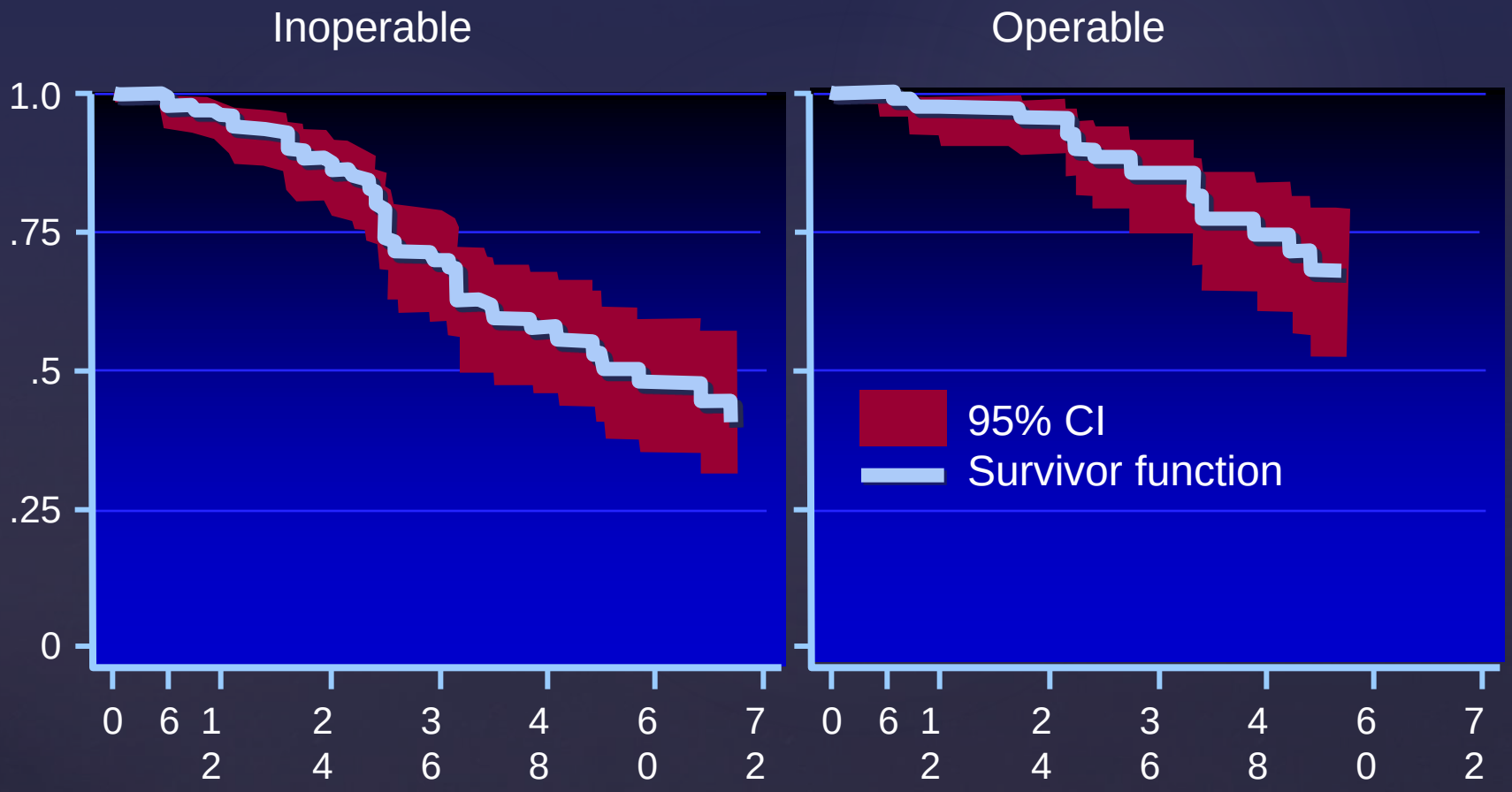






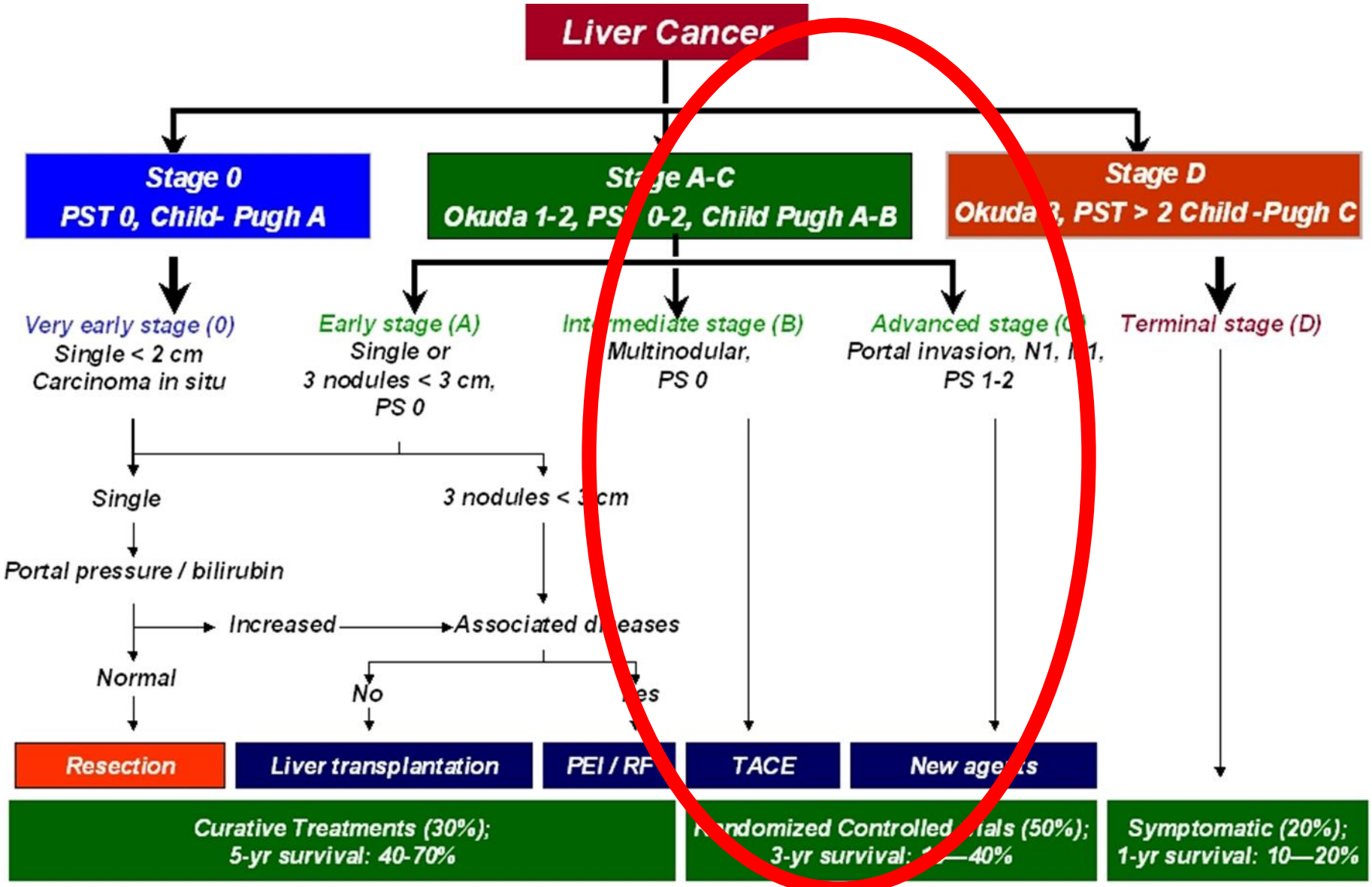
Prospective Study of RFA in Early HCC

Kaplan-Meier survival estimates, by operability
5y OS: 69%. HCC Child A < 2 cm



97% complete response upon a median F/U time of 31 mo

Livraghi T, et al. Hepatology. 2008; 47:429

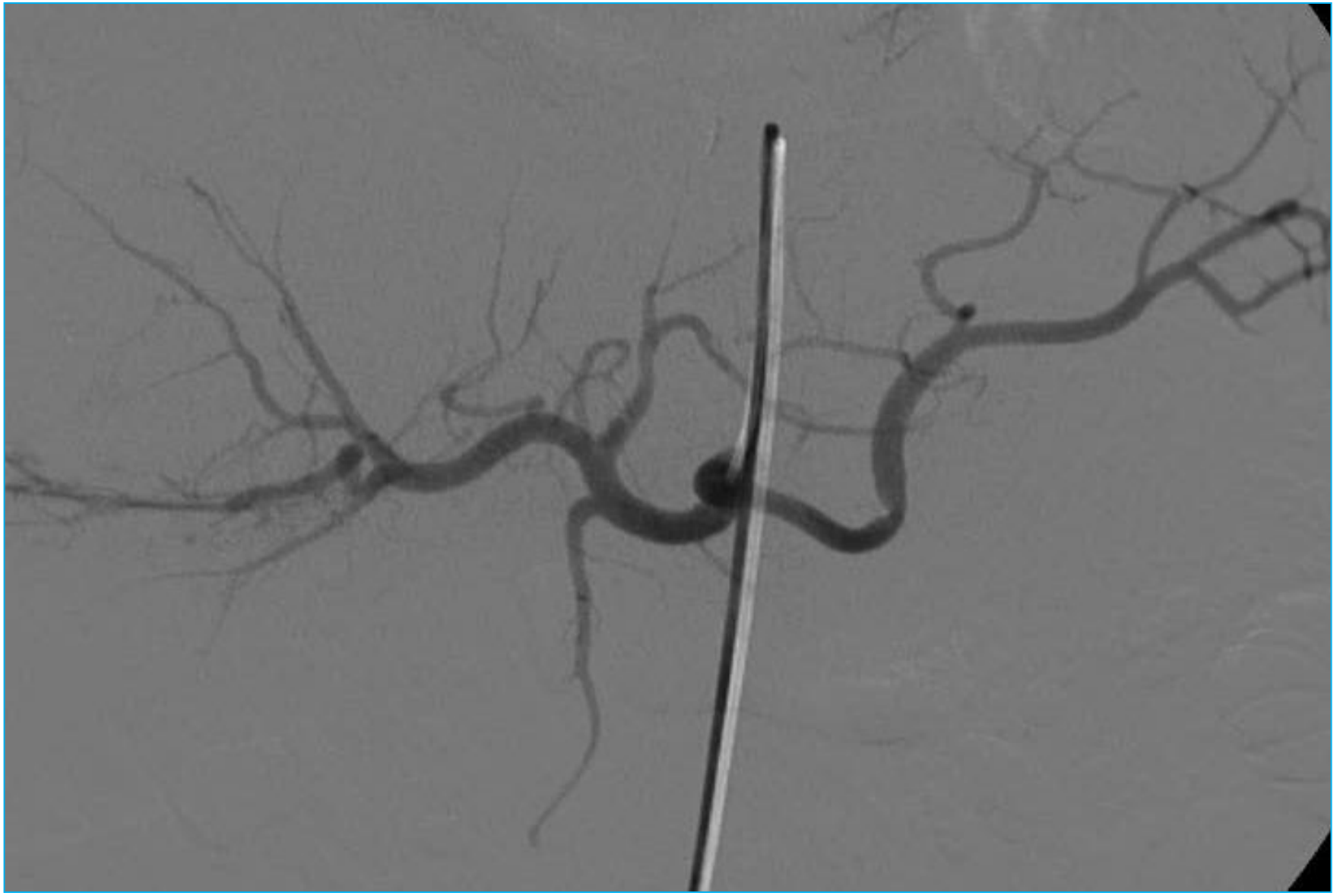

Liver Cancer
Stage 0
PST 0, Child- Pugh A
Stage A-C
Okuda 1-2, PS 0-2, Child Pugh A-B
Stage D
Okuda , PST > 2 Child -Pugh C
Very early stage (0)
Single < 2 cm
Carcinoma in situ
Early stage (A)
Single or
3 nodules < 3 cm,
PS 0
Intermediate stage (B)
Multinodular,
PS 0
Advanced stage (C)
Portal invasion, N1,
PS 1-2
Terminal stage (D)
Single
3 nodules < cm
Portal pressure / bilirubin
Increased
Associated diseases
Normal
No
Resection
Liver transplantation
PEI / RF
TACE
New agents
Curative Treatments (30%);
5-yr survival: 40-70%
Randomized Controlled Trials (50%);
3-yr survival: —40%
Symptomatic (20%);
1-yr survival: 10—20%

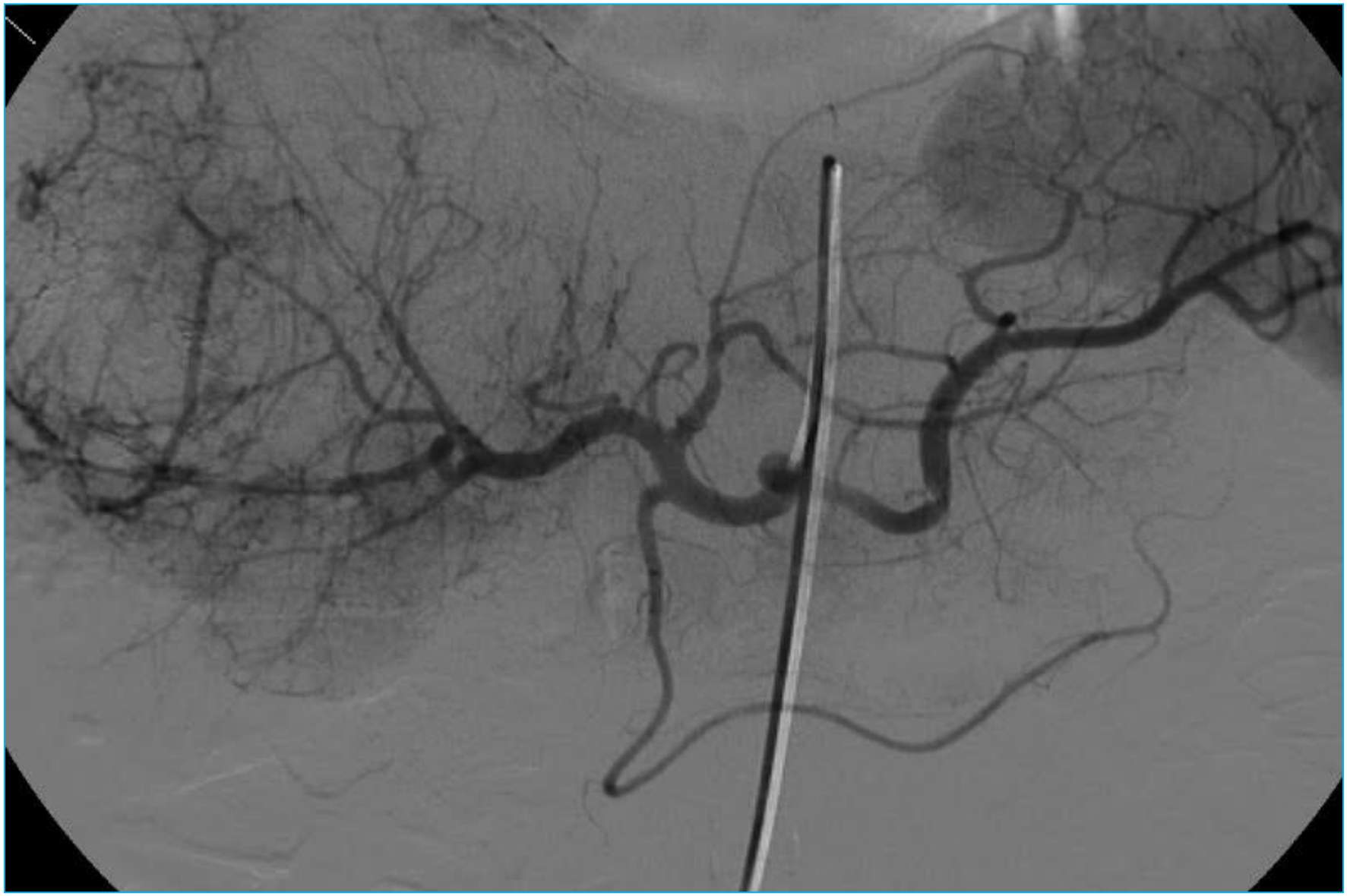
Trans-arterial Chemoembolization (TACE) for Hepatocellular Cancer

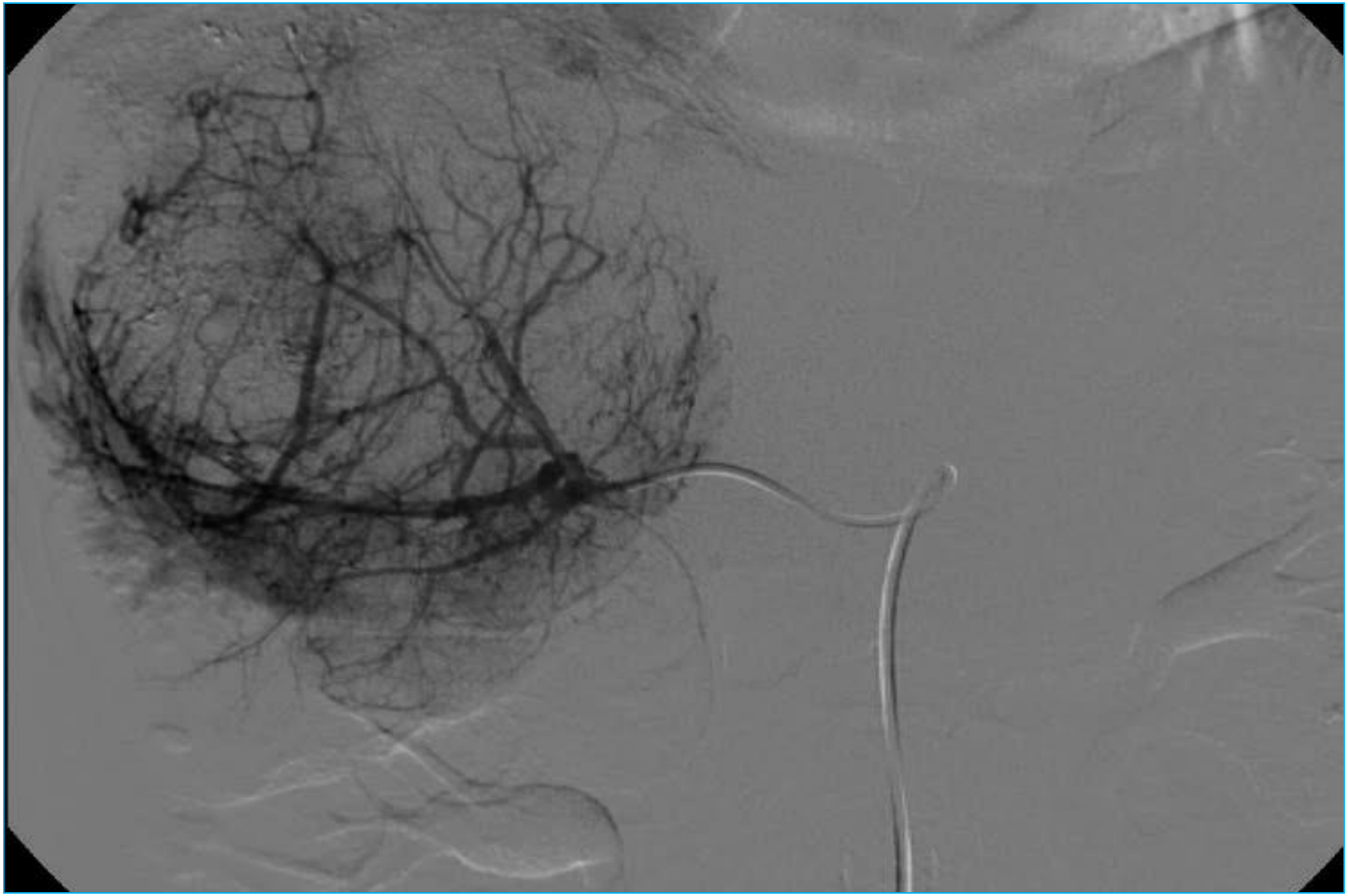
- Treatment of choice for large unifocal (>5cm), or multifocal, liver confined HCCs.
- Chemotherapy (adriamycin, cisplatin or mitomycin) is suspended in lipiodol agent (oil).
- Embolization (gelfoam, microbeads).

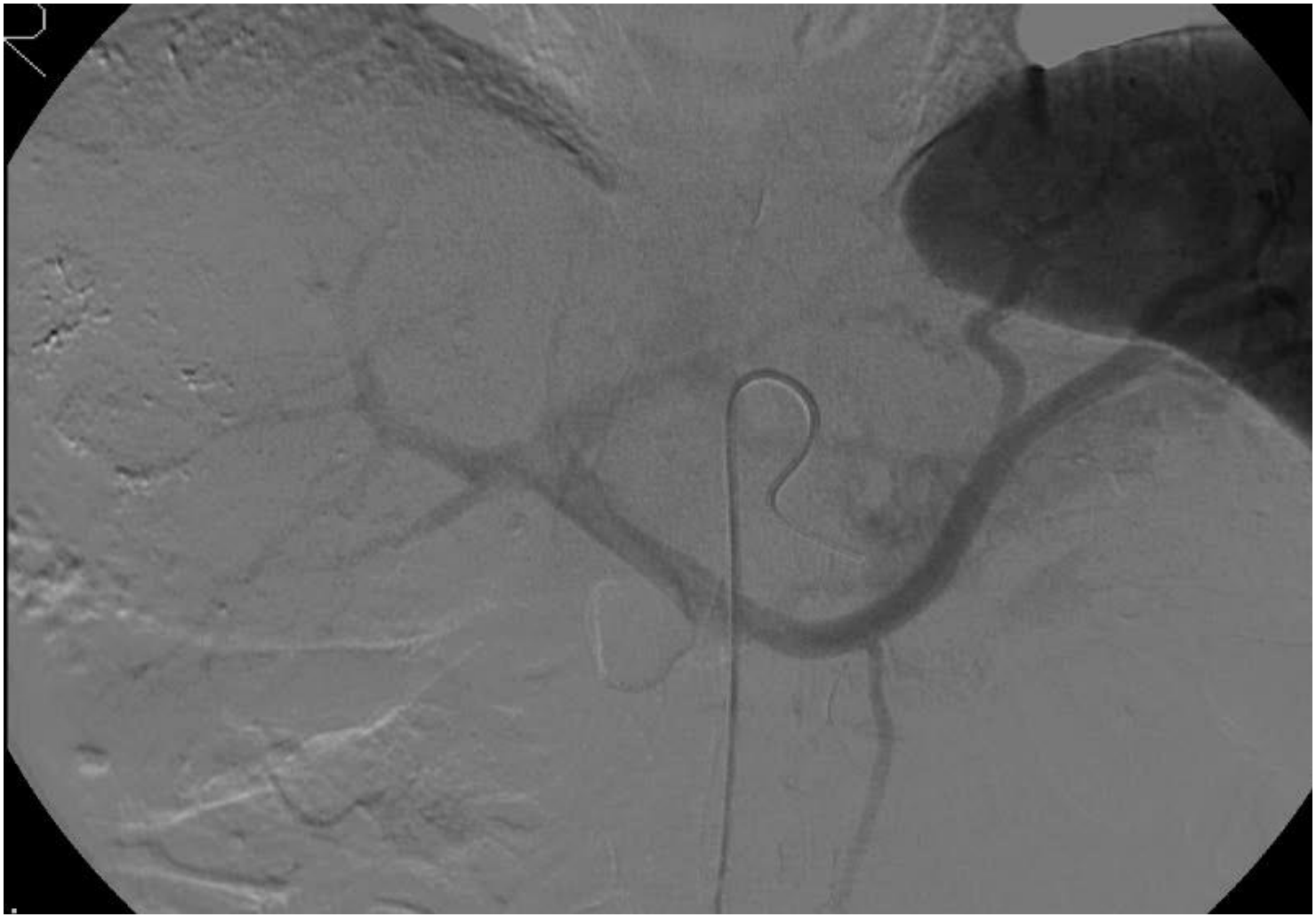
Contraindications: PVT, BCLC stage C or D.

- Post TACE syndrome is seen in 50% of patients, consist of fever, RUQ pain, and ileus.
- RR 15-60%
- Survival 20-60%







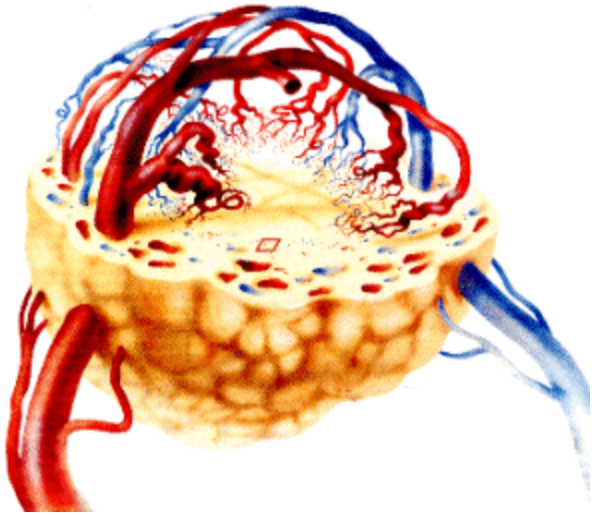


Angiogenesis

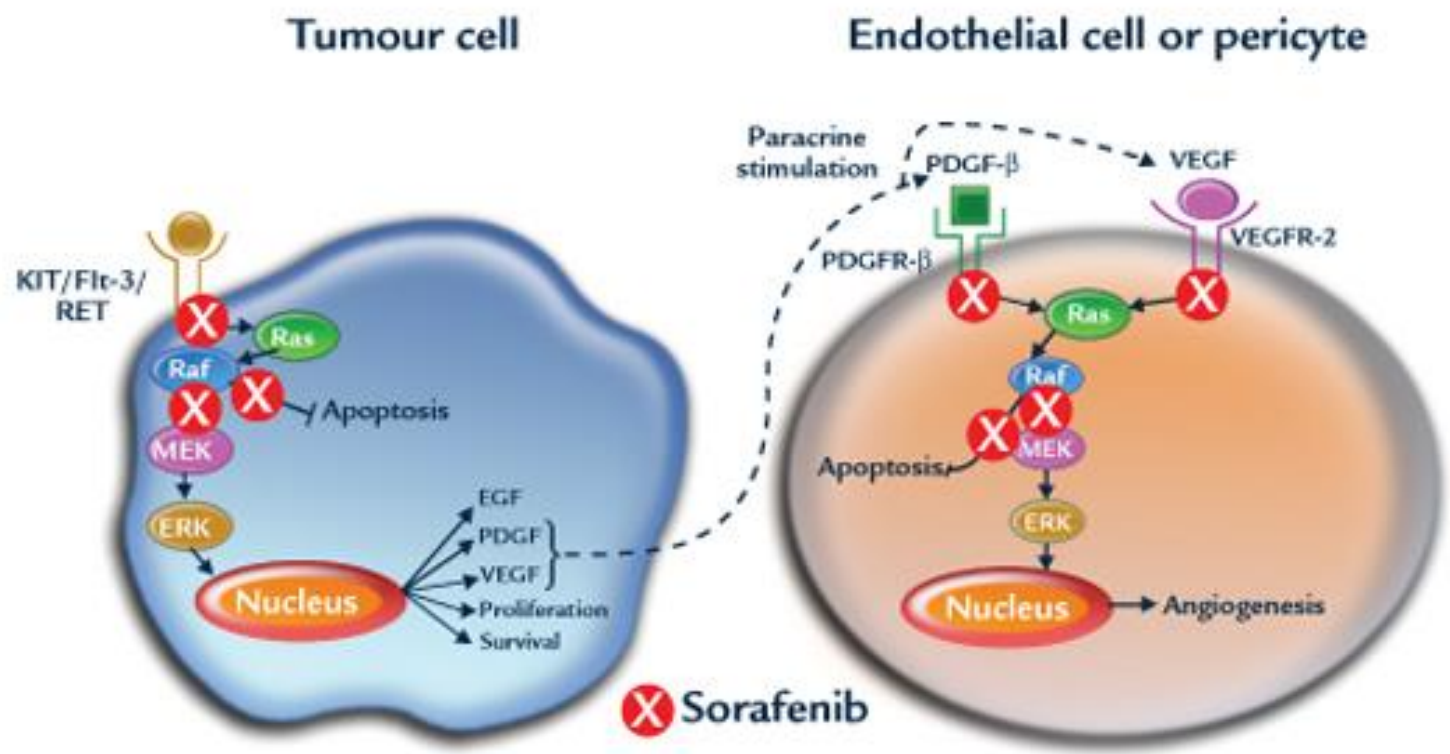
Highly vascular organ

Balance between pro- & anti-angiogenic factors

Balance disturbed in HCC



Sorafenib


Tumour cell
Endothelial cell or pericyte
KIT/Flt-3/
RET
Ras
Raf
Apoptosis
MEK
ERK
Nucleus
EGF
PDGF
VEGF
Proliferation
Survival
Paracrine
stimulation
PDGF-β
VEGF
PDGFR-β
VEGFR-2
Ras
Raf
Apoptosis
MEK
ERK
Nucleus
Angiogenesis
Sorafenib

SHARP study

RCT, double blind

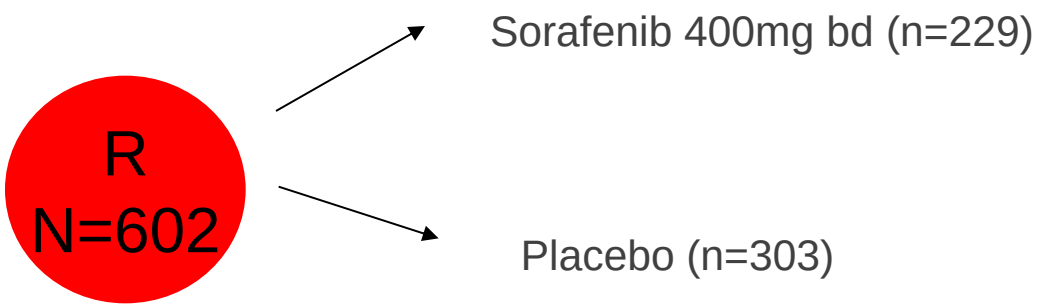
Improved OS 3months: 7.9 to 10.7months

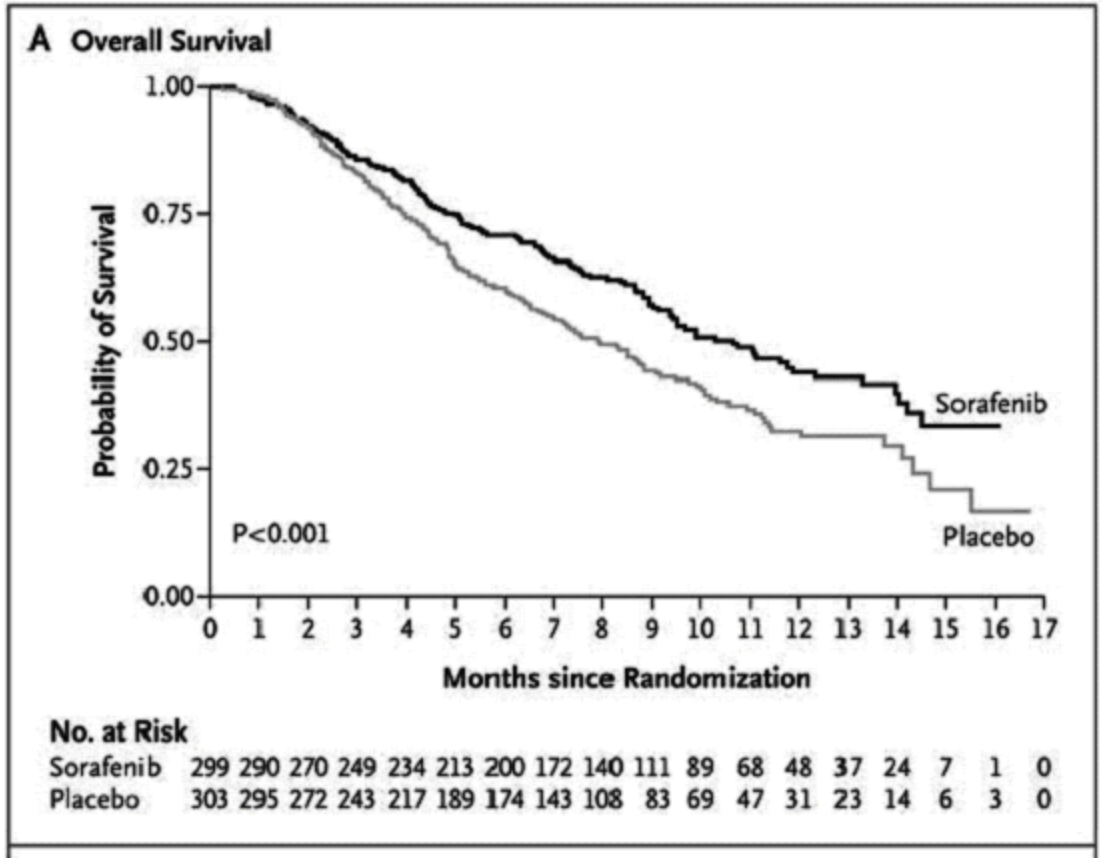
Improved TTP: 5.5 vs 2.8months

HR 0.69 (95% CI 0.55 – 0.86), P<0.01

Approved 1st line

Childs Pugh A or good B




A Overall Survival
1.00
0.75
0.50
0.25
0.00
Probability of Survival
P<0.001
Sorafenib
Placebo
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
Months since Randomization
No. at Risk
Sorafenib 299 290 270 249 234 213 200 172 140 111 89 68 48 37 24 7 1 0
Placebo 303 295 272 243 217 189 174 143 108 83 69 47 31 23 14 6 3 0

SHARP: Adverse events

Adverse Event	Sorafenib (N=297)			Placebo (N=302)			P Value	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3 or 4
	percent							
Overall incidence	80			52				
Constitutional symptoms								
Fatigue	22	3	1	16	3	<1	0.07	1.00
Weight loss	9	2	0	1	0	0	<0.001	0.03
Dermatologic events								
Alopecia	14	0	0	2	0	0	<0.001	NA
Dry skin	8	0	0	4	0	0	0.04	NA
Hand–foot skin reaction	21	8	0	3	<1	0	<0.001	<0.001
Pruritus	8	0	0	7	<1	0	0.65	1.0
Rash or desquamation	16	1	0	11	0	0	0.12	0.12
Other	5	1	0	1	0	0	<0.001	0.12
Gastrointestinal events								
Anorexia	14	<1	0	3	1	0	<0.001	1.00
Diarrhea	39	8	0	11	2	0	<0.001	<0.001
Nausea	11	<1	0	8	1	0	0.16	0.62
Vomiting	5	1	0	3	1	0	0.14	0.68
Voice changes	6	0	0	1	0	0	<0.001	NA
Hypertension	5	2	0	2	1	0	0.05	0.28
Liver dysfunction	<1	<1	0	0	0	0	0.50	0.50
Abdominal pain not otherwise specified	8	2	0	3	1	0	0.007	0.17
Bleeding	7	1	0	4	1	<1	0.07	1.00

Thank you!