

The hierarchy of evidence in clinical research



Large randomised placebo-controlled trial

Large randomised controlled trial

Small randomised controlled trial

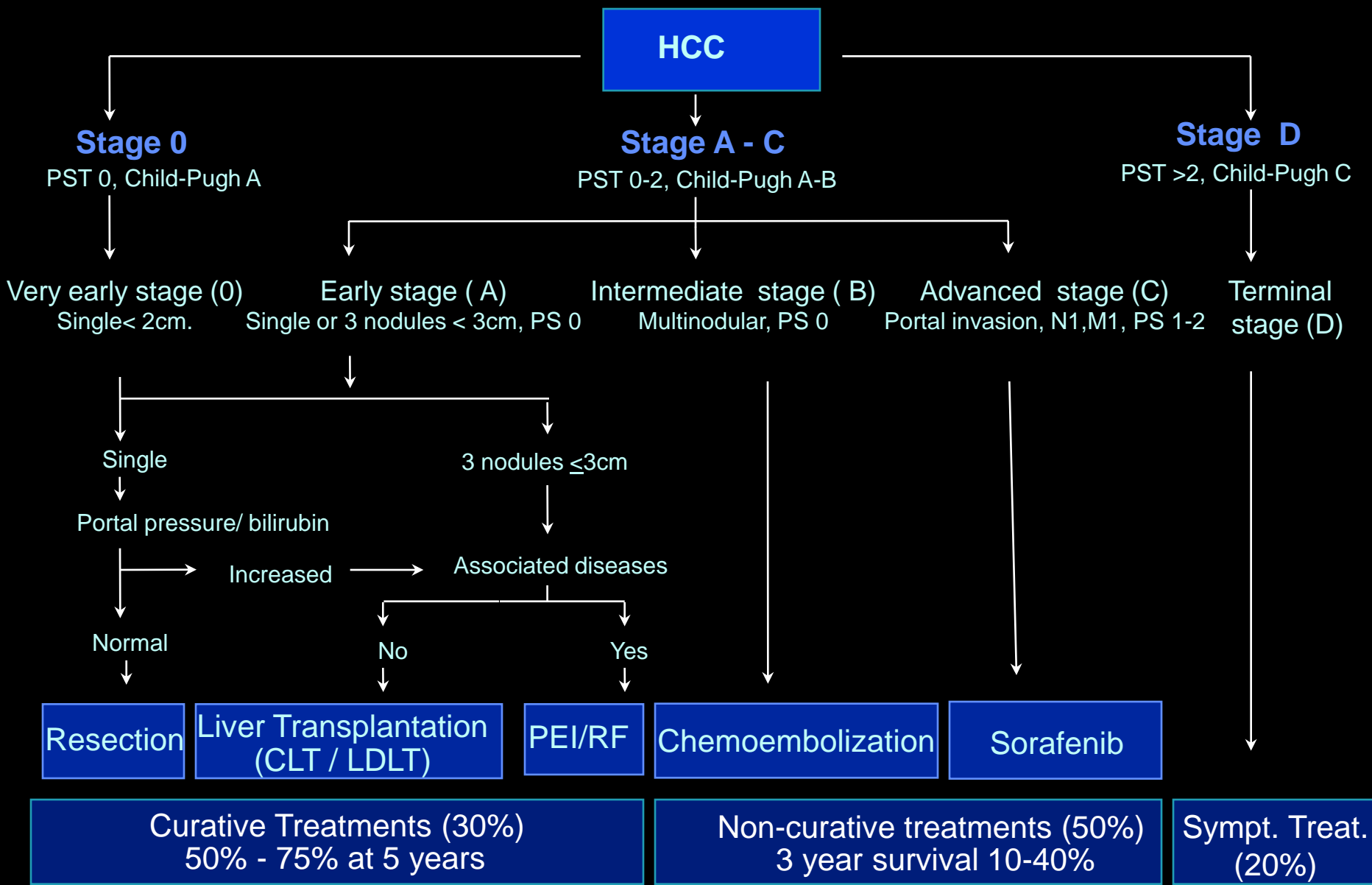
Case control studies

Cohort descriptions (prospective/retrospective)

Small size, selection bias, variable follow-up.

Personal opinions

BCLC Staging and Treatment Strategy

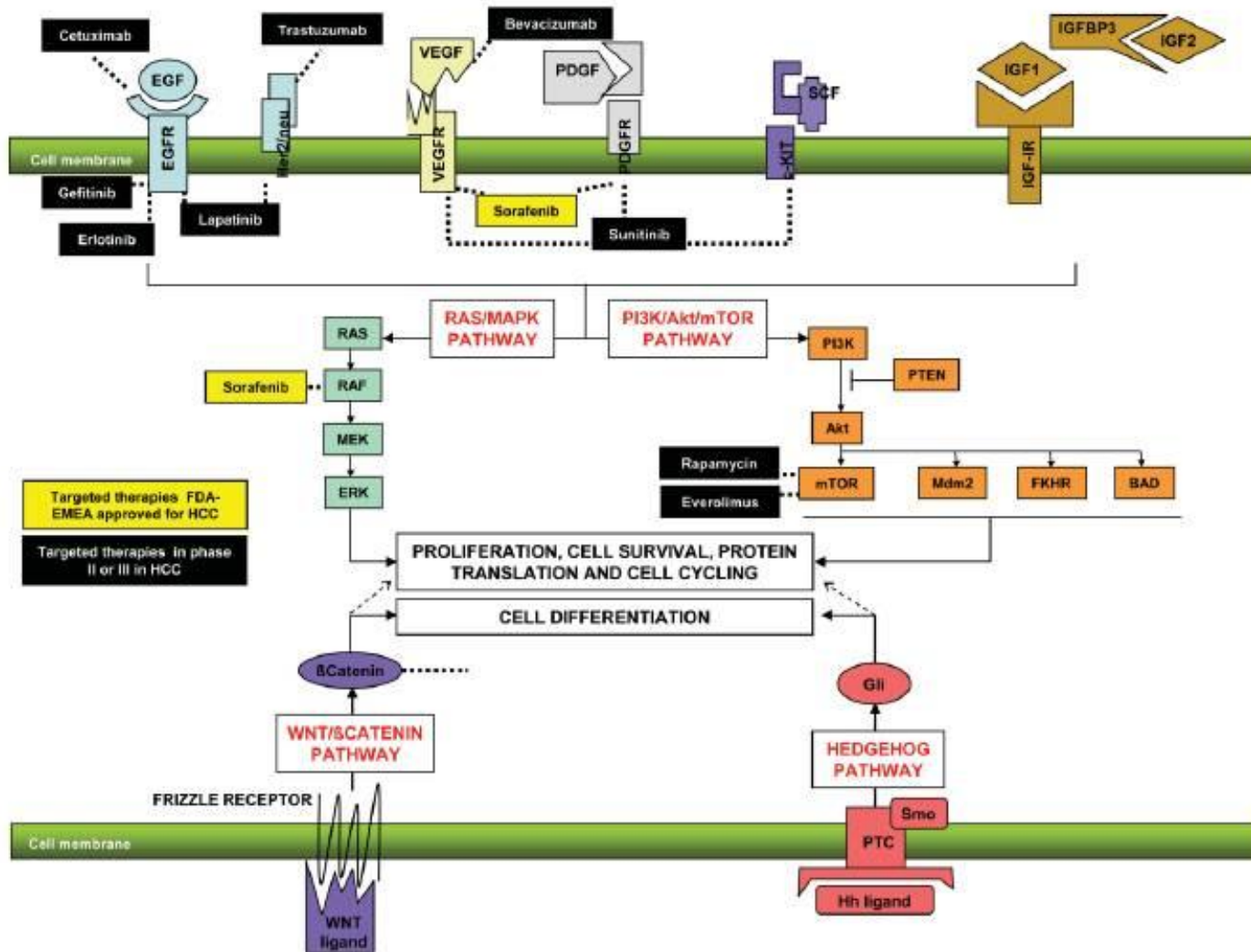


Treatment of advanced HCC

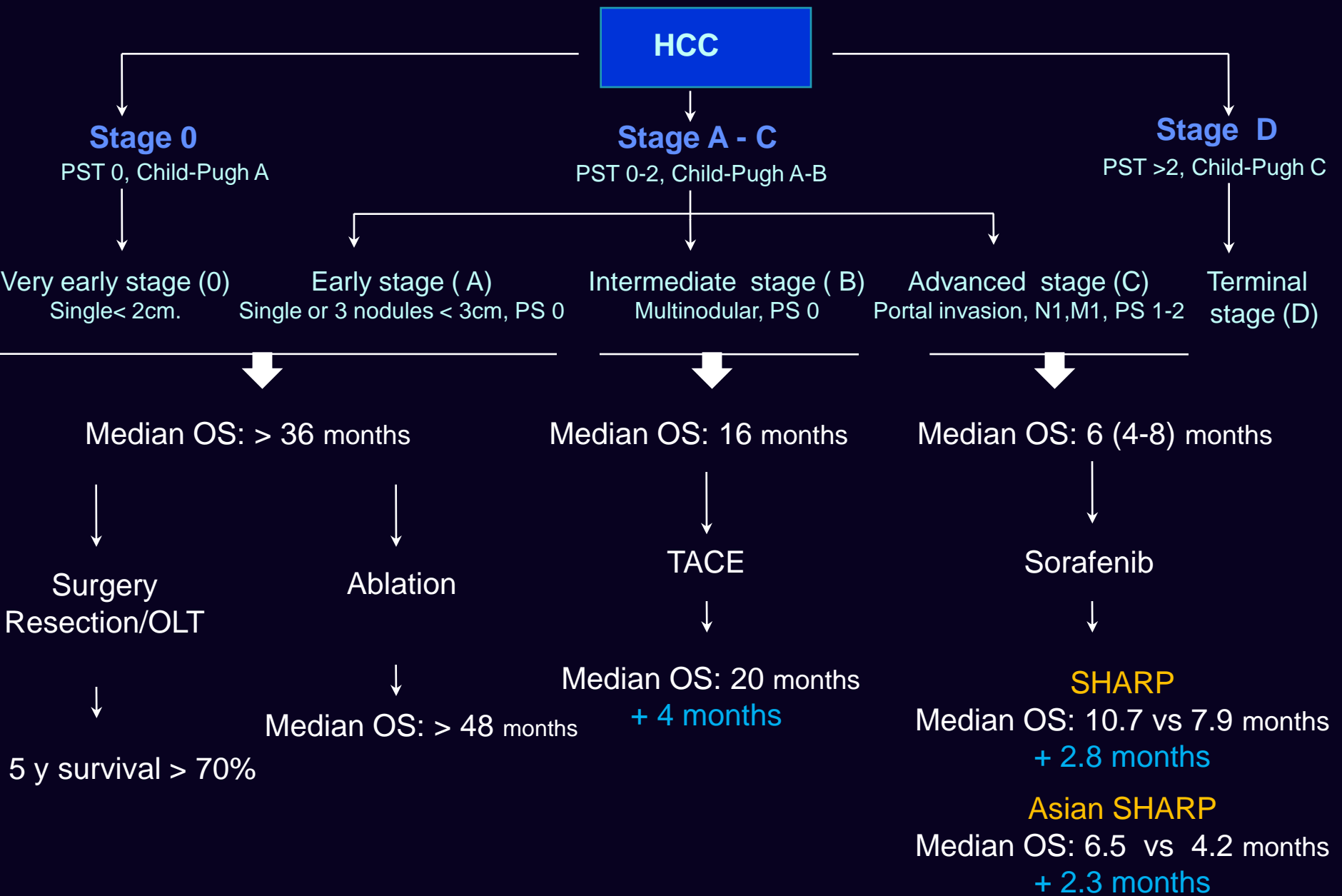
Phase II/III studies with systemic treatments

Treatments	Studies	N	Objective response
Systemic chemotherapy			
Doxorubicin as single agent	Phase II/III	>1000	10-18%
Doxorubicin combination (PIAF)	Phase II/III	144	26%
Cisplatin	Phase II	48	10%
Epirubicin	Phase II	62	11%
Mitoxantrone	Phase II	118	16%
5-FU, Paclitaxel, iridotecan, gemcitabine	Phase II/III	<10%
Anti-androgen	Phase III	376	<10%
Interferon	Phase III	60	<10%
Tamoxifen	Phase III	>1000	< 5%
Octreotide	Phase III	60	<5%
Seocalcitol	Phase III	746	<5%

Molecular-targeted therapies in HCC



Gains in life expectancy according to stage and treatment



Critical issues in combination therapy

- Selection of best partner for sorafenib
- Optimal dosage for efficacy and safety

Underlying cirrhosis: variceal bleeding, renal failure, ascites, encephalopathy, HBV/HCV flares

- How to define efficacy: RR by RECIST (No meaning), TTP?

New definitions/categories for progression: nodules vs M1, treatable?

- Transition from phase 1 into phase 2. RCT phase 2.

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Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma

Josep M. Llovet, Adrian M. Di Bisceglie, Jordi Bruix, Barnett S. Kramer, Riccardo Lencioni, Andrew X. Zhu, Morris Sherman, Myron Schwartz, Michael Lotze, Jayant Talwalkar, Gregory J. Gores; for the Panel of Experts in HCC-Design Clinical Trials

Current trials (1st and 2nd line)

(Ethics, background, feasibility)

- Sorafenib- Erlotinib vs Sorafenib (Phase 3)
- Sunitinib vs Sorafenib (Phase 3)
- Brivanib vs Sorafenib (Phase 3)
- Erlotinib Bevacizumab vs Sorafenib (Phase 3)
- 2nd line Brivanib vs Placebo (Phase 3)
- Radiation + Sorafenib (Phase 2)
- Rad001 Sorafenib vs Sorafenib (Phase 1-2)
- C-met inhibitor Sorafenib vs Sorafenib (Phase 1-2)