The Management of Advanced Stage Hepatocellular Carcinoma

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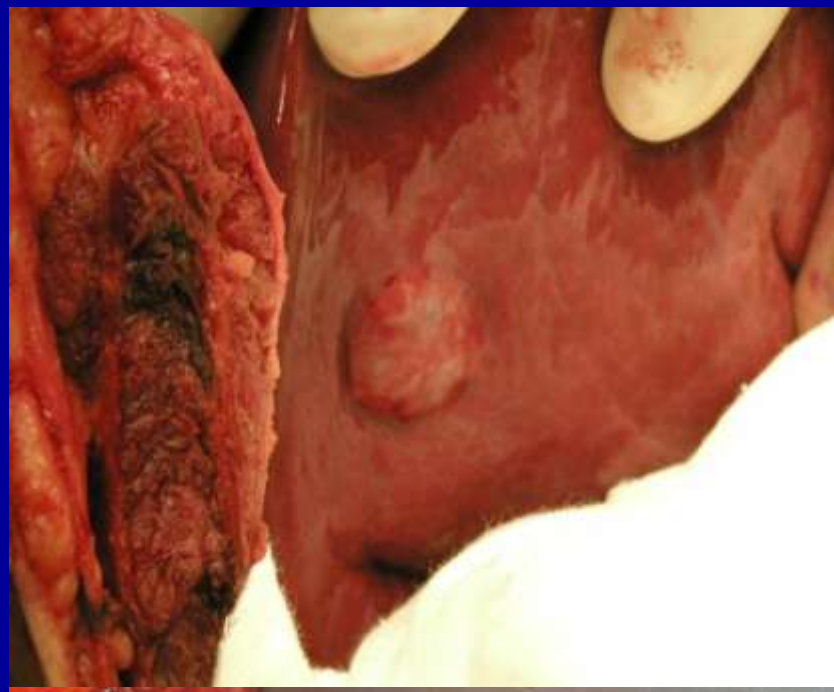
APASL Single Topic Conference on HCC

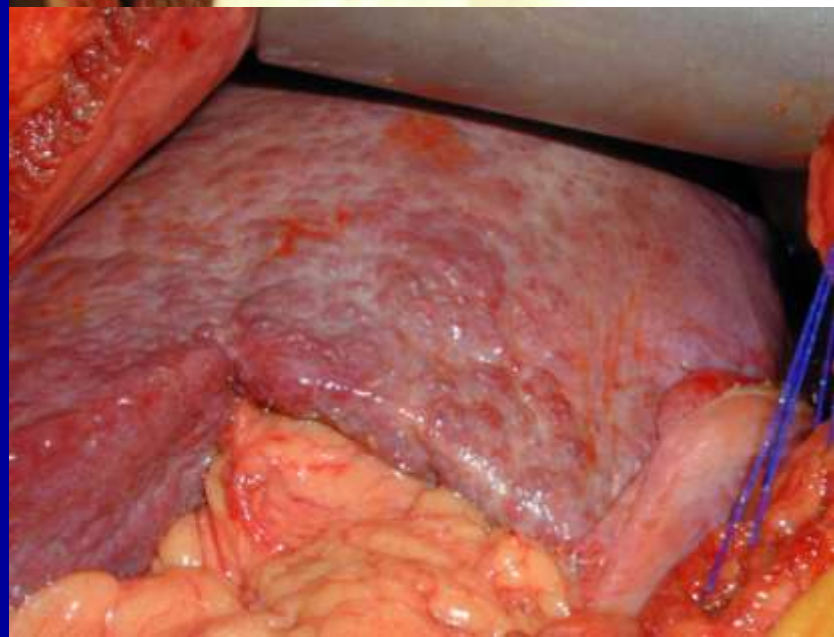
23rd Nov 2013, Cebu

SGH – Surgery

HCC is a difficult Cancer to Treat

- Patients with HCC usually suffer from 2 diseases simultaneously
  - Liver cirrhosis (Chronic Hepatitis B or C)
    - *80% have cirrhosis*
    - *Liver function can be poor*
  - Cancer
    - *Synergistic impact on treatment and outcomes*





What is Advanced Stage HCC?

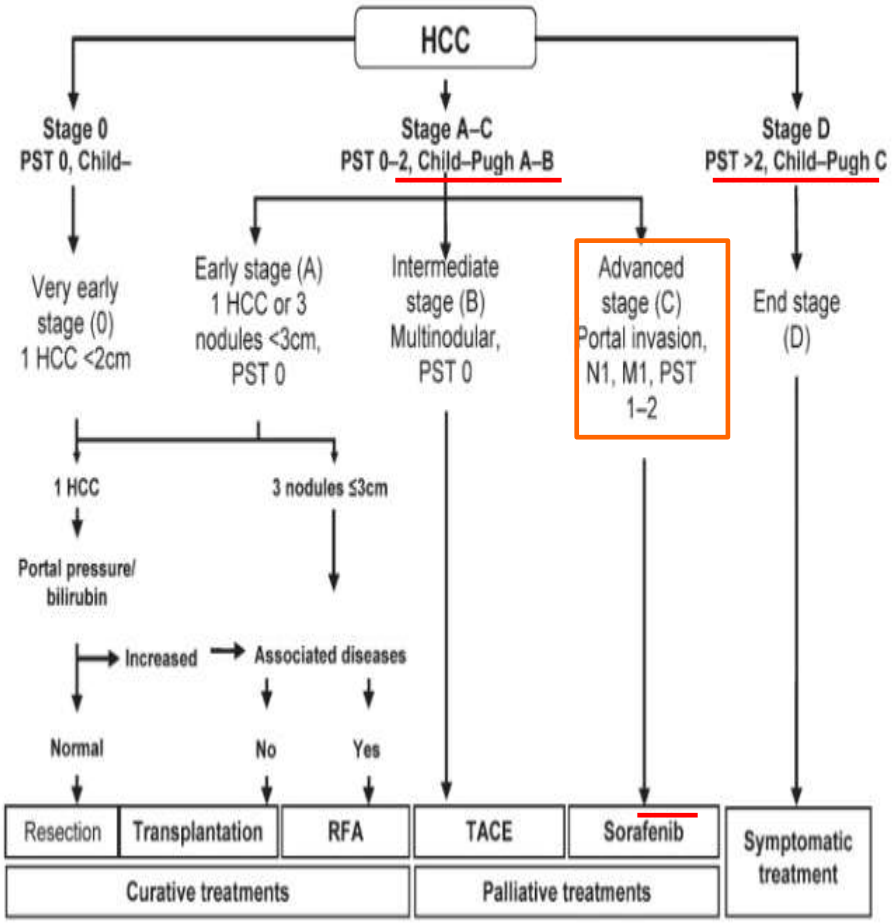
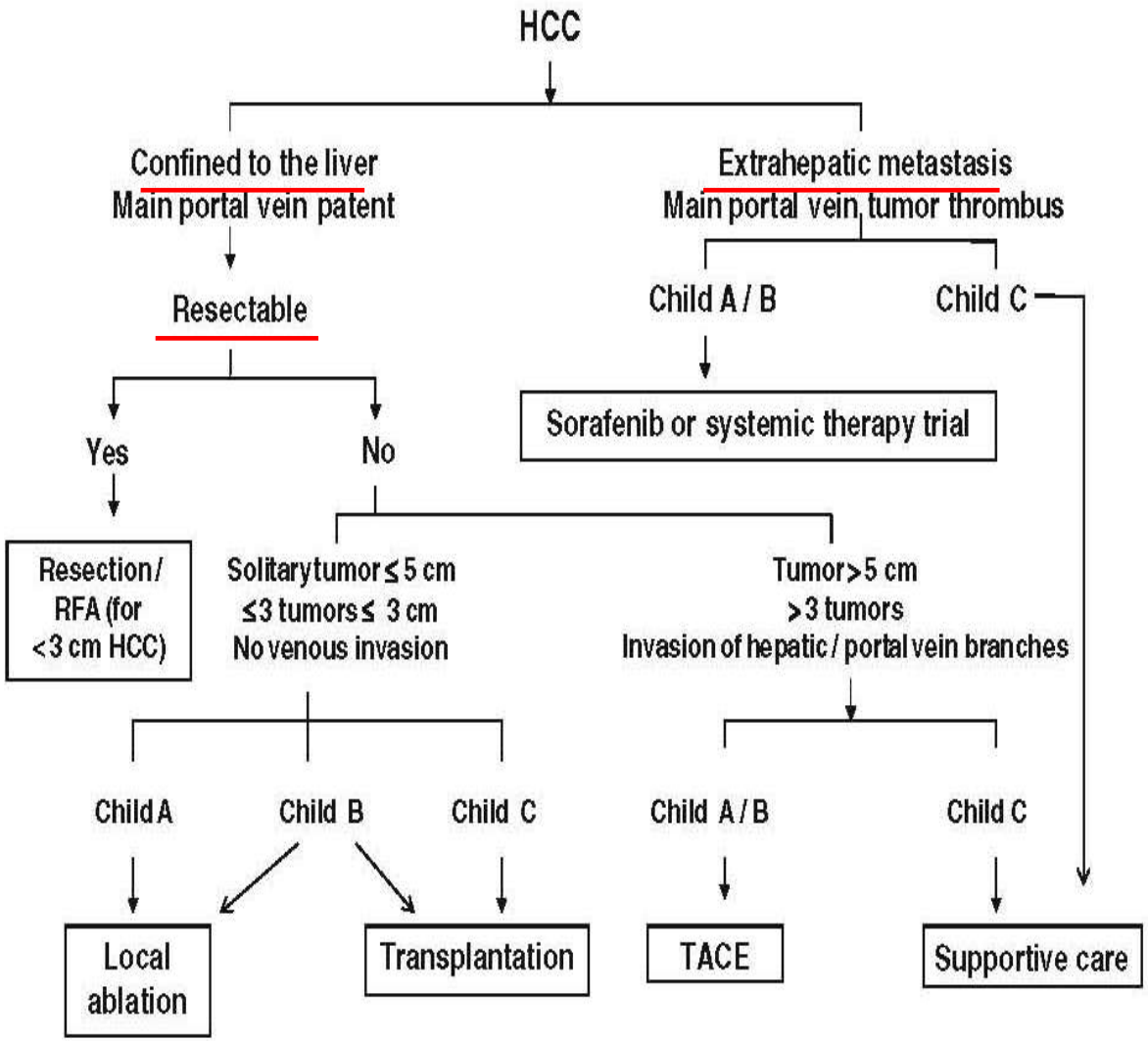


Fig. 2. The BCLC staging system and treatment allocation.

A Hepatologist's definition (1)

AASLD 2010

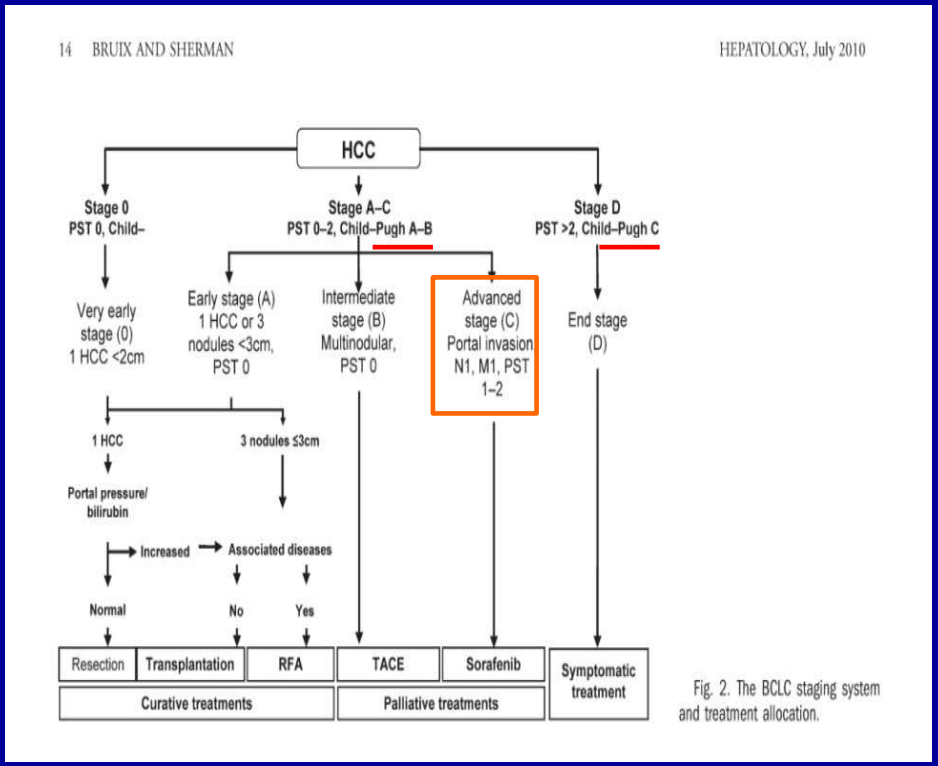
What is Advanced Stage HCC?



Another Hepatologist's definition (2)

APASL 2010

What is Advanced Stage HCC?



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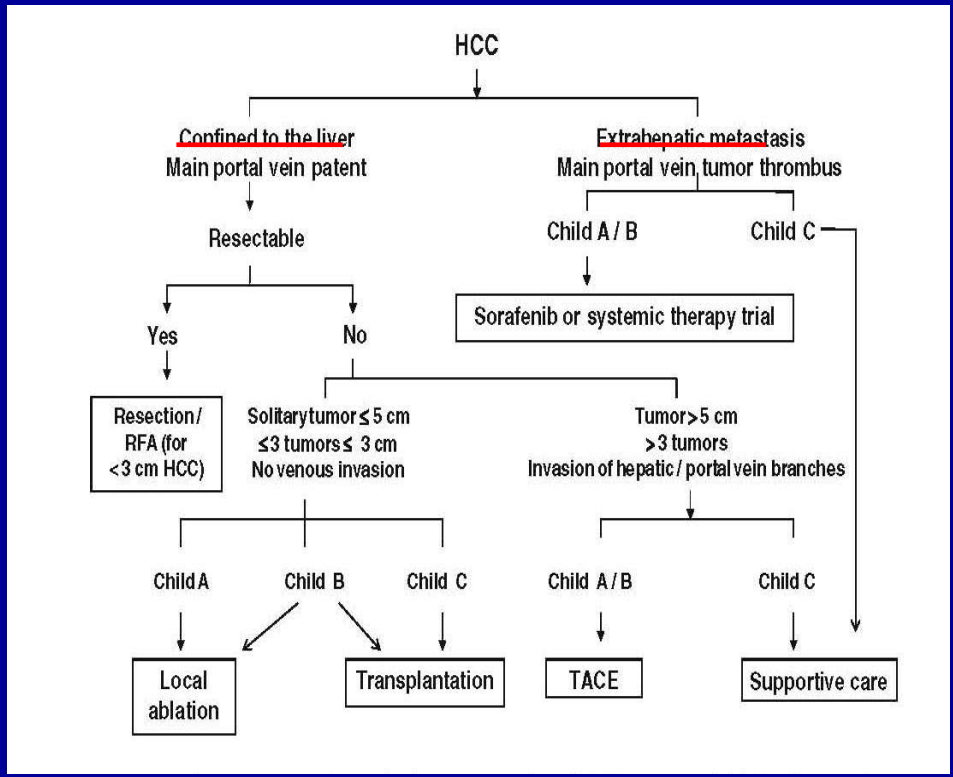
AASLD 2010

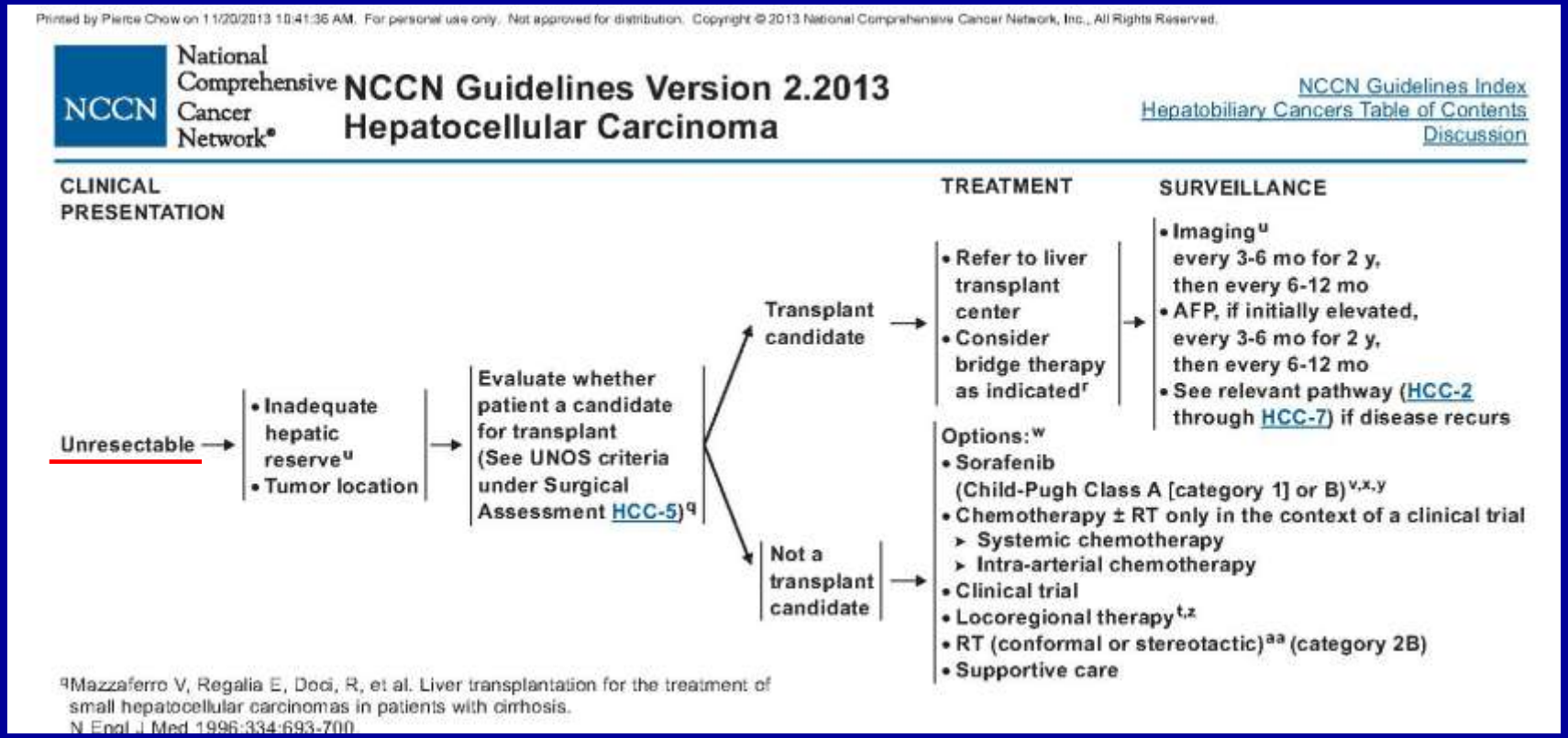
APASL 2010

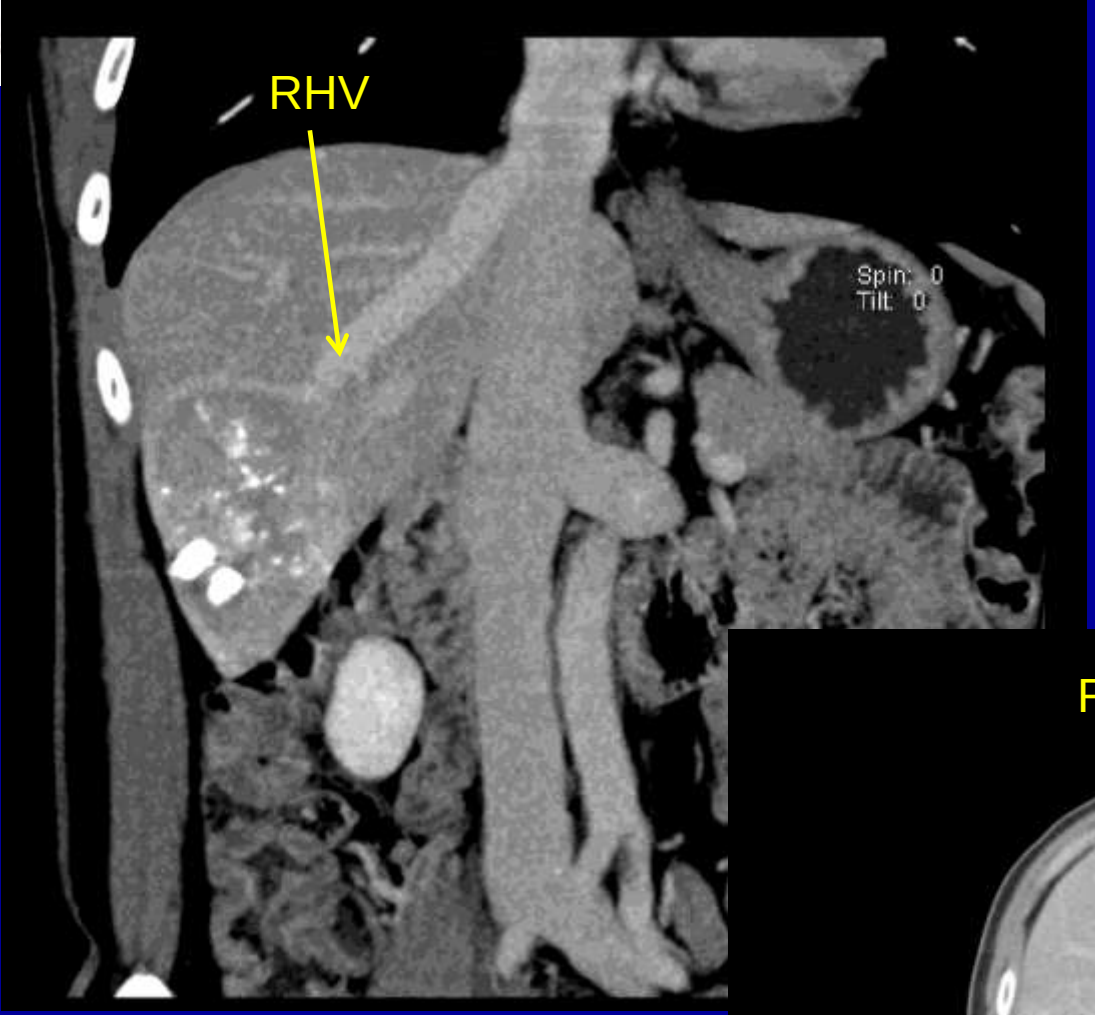


No Staging in APASL Guidelines

What is Advanced Stage HCC?

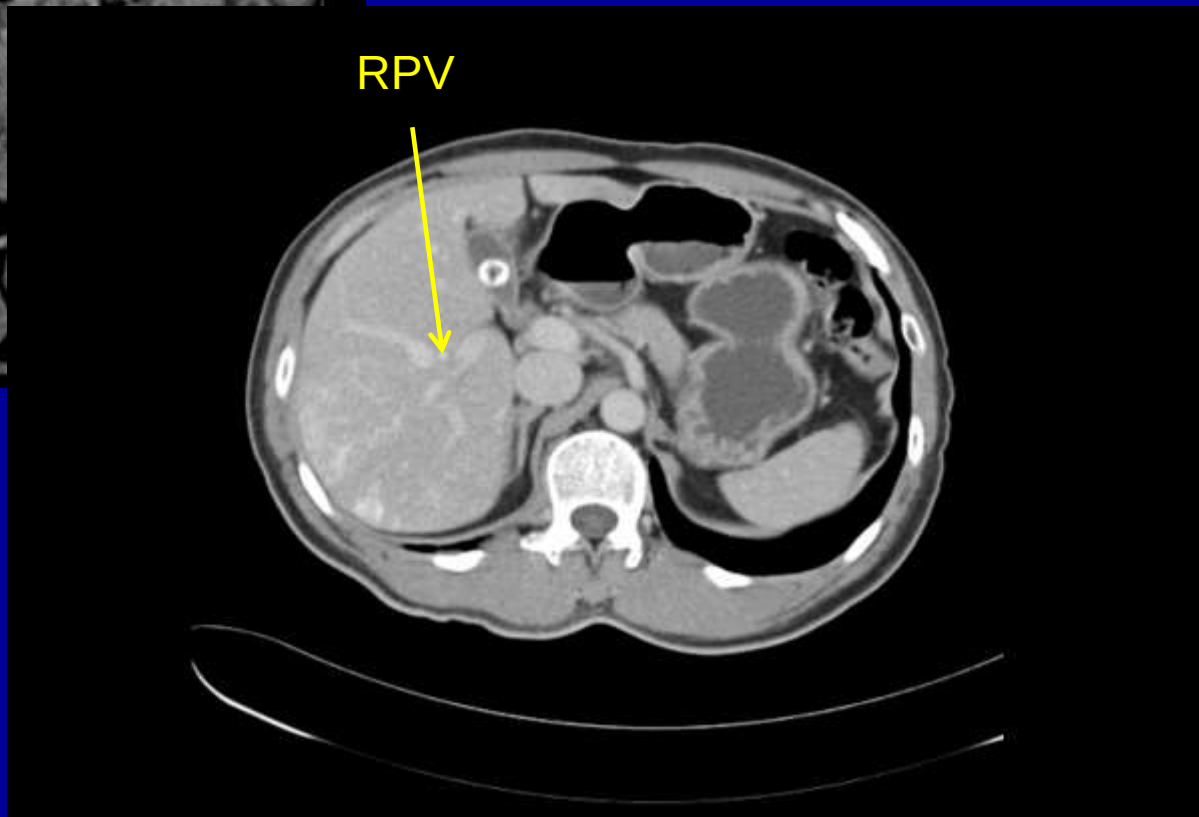
An Oncologist's definition





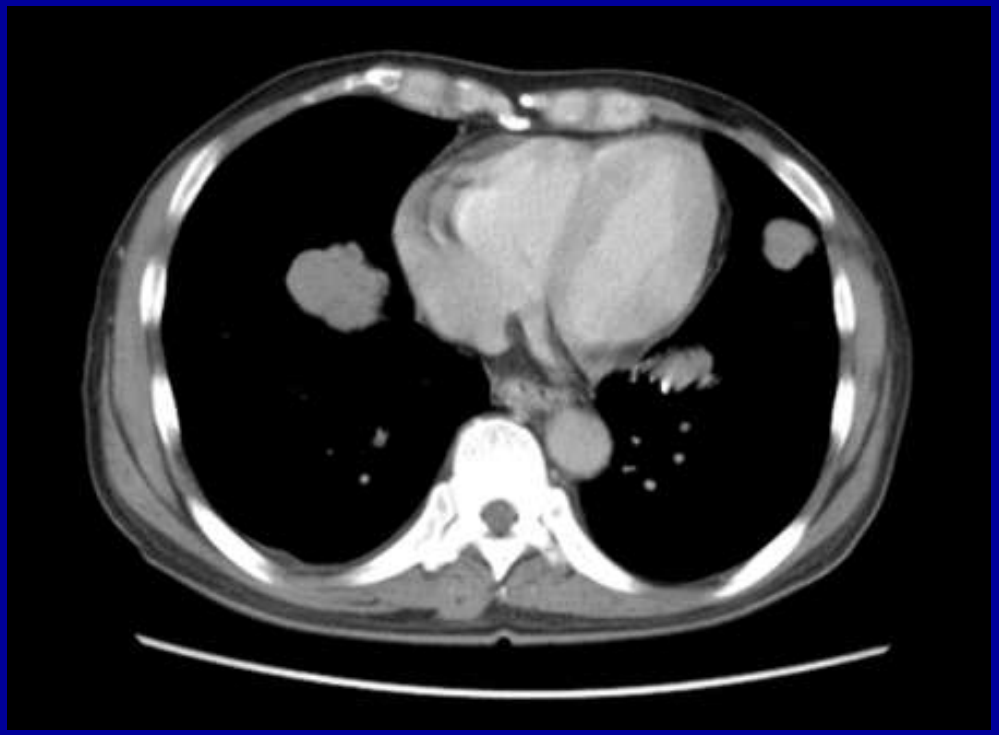
Features of Advanced HCC (1)

Vascular Invasion



Challenge: not synonymous with un-resectable

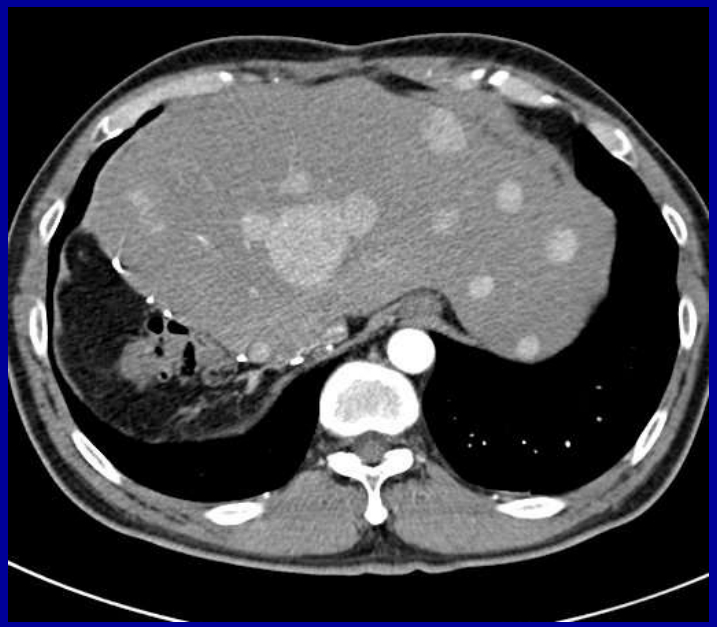
Features of Advanced HCC (2)

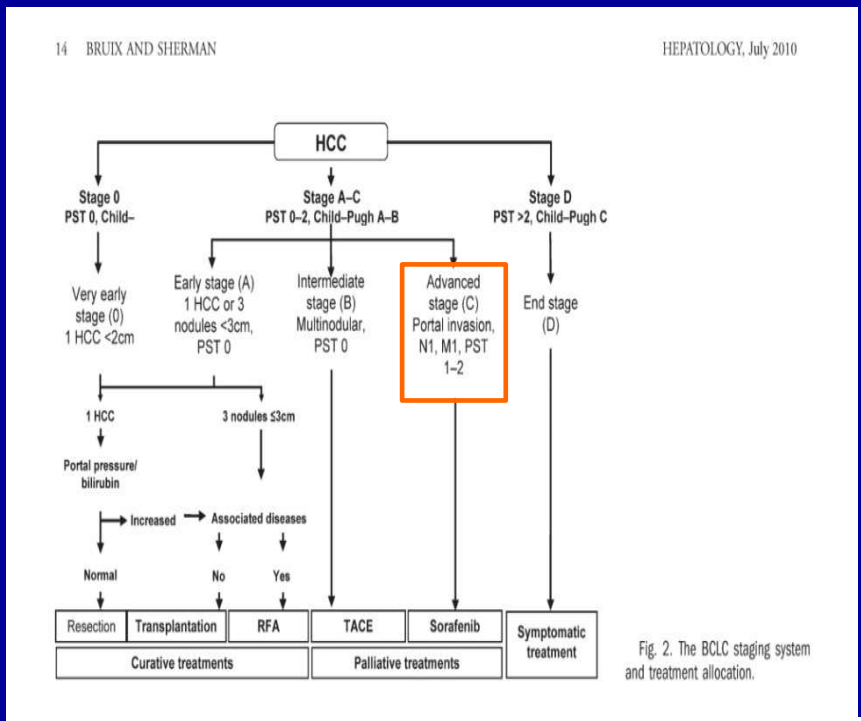


Distant metastases

No Challenge:
un-resectable (especially if synchronous)

Un-resectable but not Advanced HCC by AASLD





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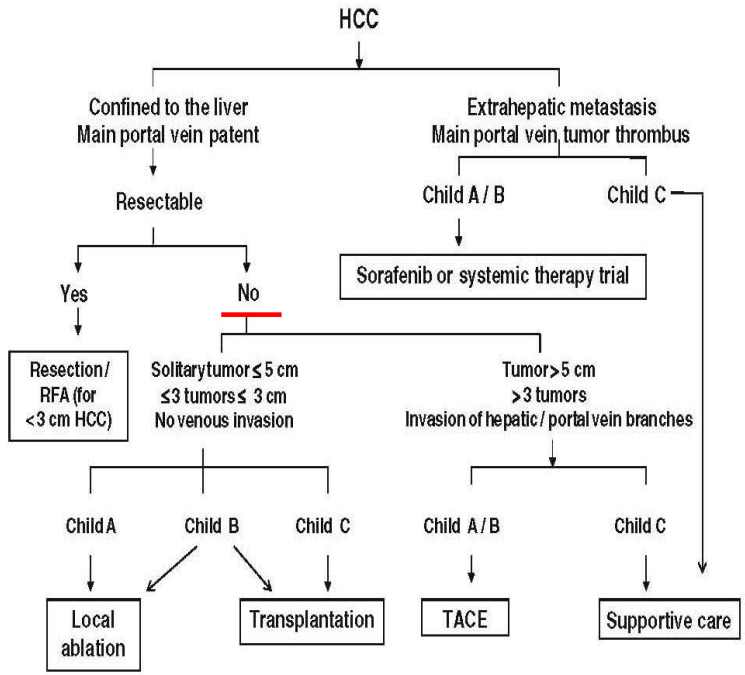


Categories of Advanced HCC

- The current practice in the Asia-Pacific is that **AASLD** stage does not always dictate **APASL** practice recommendations

- Broad categories of Advanced HCC
  - ***Metastatic disease***
  - ***Locally advanced disease with vascular invasion***

Oncology Guidelines: HCC not amendable to resection, transplantation, RFA

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013
Hepatocellular Carcinoma

NCCN Guidelines Index
Hepatobiliary Cancers Table of Contents
Discussion

CLINICAL PRESENTATION	TREATMENT
Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only	Options:[w] • Sorafenib (Child-Pugh Class A [category 1] or B)[v,x,y] • Clinical trial • Locoregional therapy[t] • RT (conformal or stereotactic)[aa] (category 2B) • Supportive care
Metastatic disease or Extensive liver tumor burden	Options:[w] • Sorafenib (Child-Pugh Class A [category 1] or B)[v,x,y] • Supportive care • Clinical trial

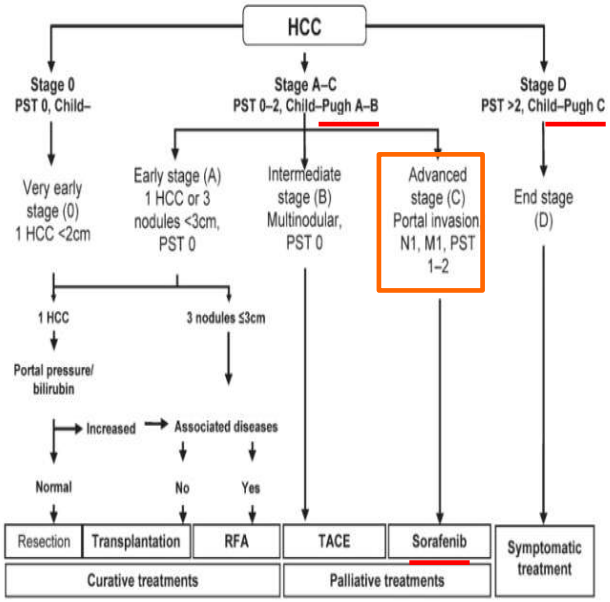
The management of metastatic HCC

- Systemic therapy required if there is adequate liver function

- ***Metastatic HCC and Child-Pugh A (or early B)***
  - ***Sorafenib*** *is the standard of care*
  - *Enrolment in* ***clinical trial***
- ***Metastatic HCC and Child-Pugh late B or C***
  - *Best supportive care*

Pierce Chow FRCSE PhD

Management of metastatic HCC



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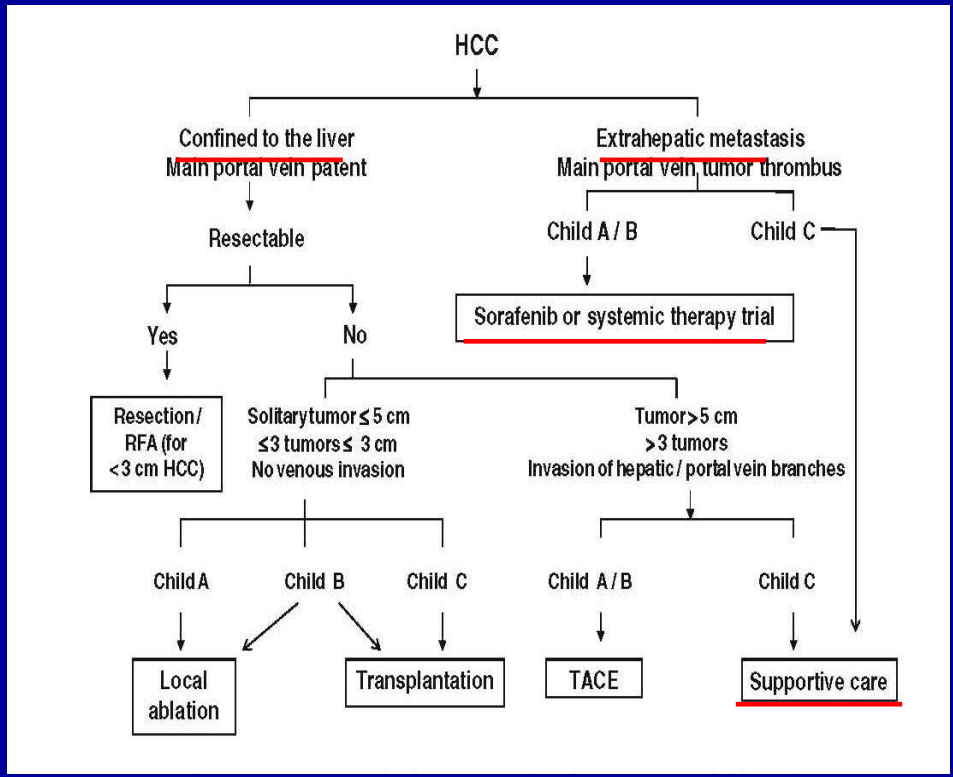
AASLD 2010

APASL 2010



The management of HCC with Vascular Invasion continues to evolve

- Generally poor prognosis
- **Poor liver function**
  - *supportive management*
- **Good liver function**
  - ***Surgical resection*** (some centers especially in Asia)
  - *Selective Internal Radiation Therapy* with yttrium-90
  - *Sorafenib*
  - *External beam radiation*
  - *TACE* (a relative contraindication)

Outcomes of surgical resection for HCC with PVT

Table 1. Survival outcomes for patients with HCC and PVTT following hepatic resection

Study	PVTT status[a]	Number	Survival[b]		
			median months	1-year %	3-year %
Chen et al. [13] (2006)	First-order	286	18.8	58.7	22.7
	Main	152	10.1	39.5	5.7
Shi et al. [14] (2010)	Second-order	139	NR	52.1	25.1
	First-order	169		38.2	17.7
	Main	78		24.7	3.6
	Beyond main	20		18.3	0
Lin et al. [15] (2011)	Second- and first-order	63	NR	52.1	16
	Main	5		33.1	0

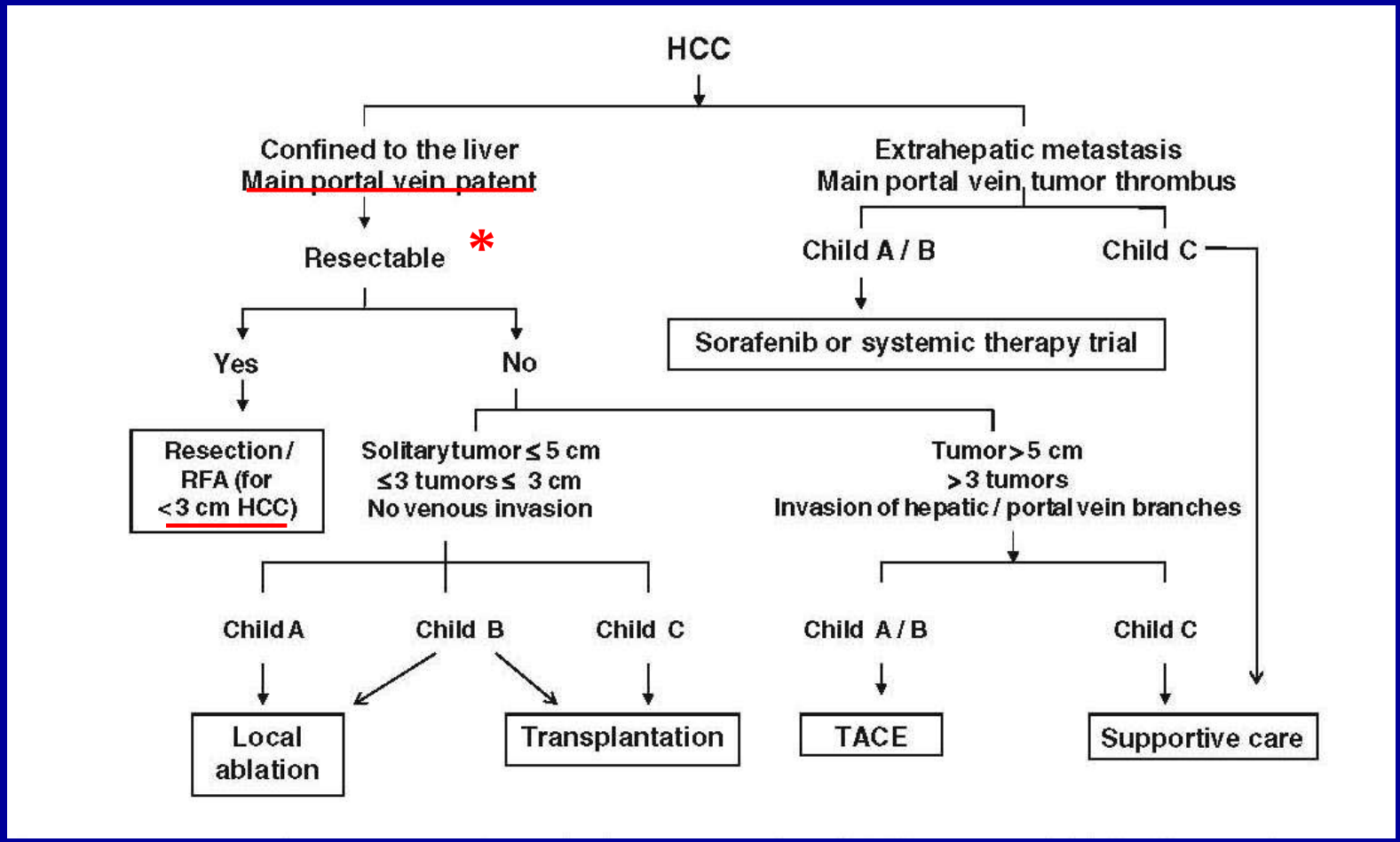
NR = Not reported.

[a] First-order = Right and/or left portal vein; main = main portal vein trunk; second-order = segmental branches of portal vein or above; beyond main = extending to superior mesenteric vein.

[b] Treatments for HCC recurrences after resection included transarterial chemoembolization, radiofrequency ablation and percutaneous ethanol injection.

Lau WY et al 2013
Oncology

APASL 2010


HCC
Confined to the liver
Main portal vein patent
Extrahepatic metastasis
Main portal vein tumor thrombus
Resectable
*
Child A / B
Child C
Sorafenib or systemic therapy trial
Yes
No
Resection / RFA (for <3 cm HCC)
Solitary tumor ≤ 5 cm
≤3 tumors ≤ 3 cm
No venous invasion
Tumor >5 cm
>3 tumors
Invasion of hepatic / portal vein branches
Child A
Child B
Child C
Child A / B
Child C
Local ablation
Transplantation
TACE
Supportive care

The management of HCC with vascular invasion continues to evolve

- Generally poor prognosis
- **Poor liver function**
  - supportive management
- **Good liver function**
  - *Surgical resection* (some centers especially in Asia)
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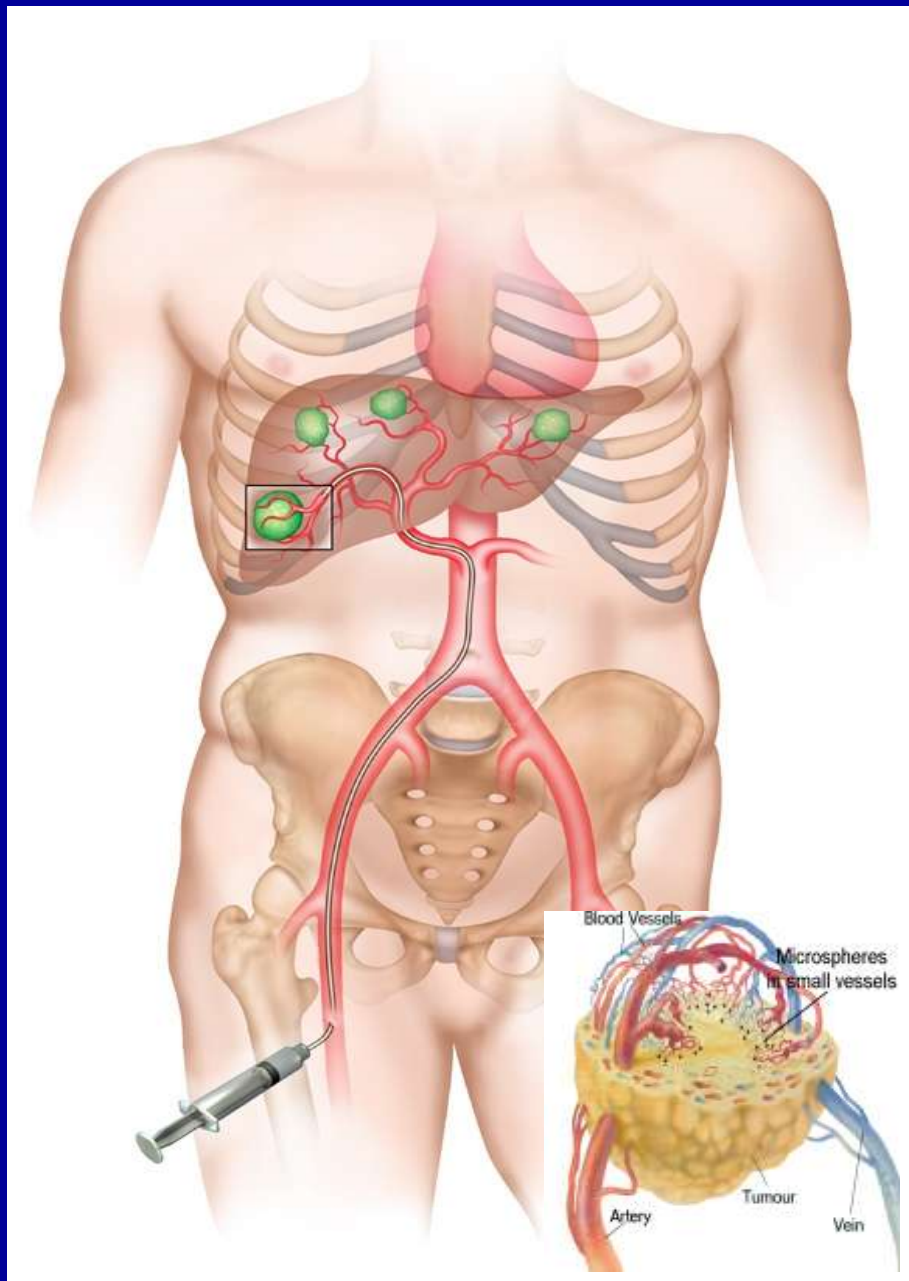
Selective Internal Radiation Therapy

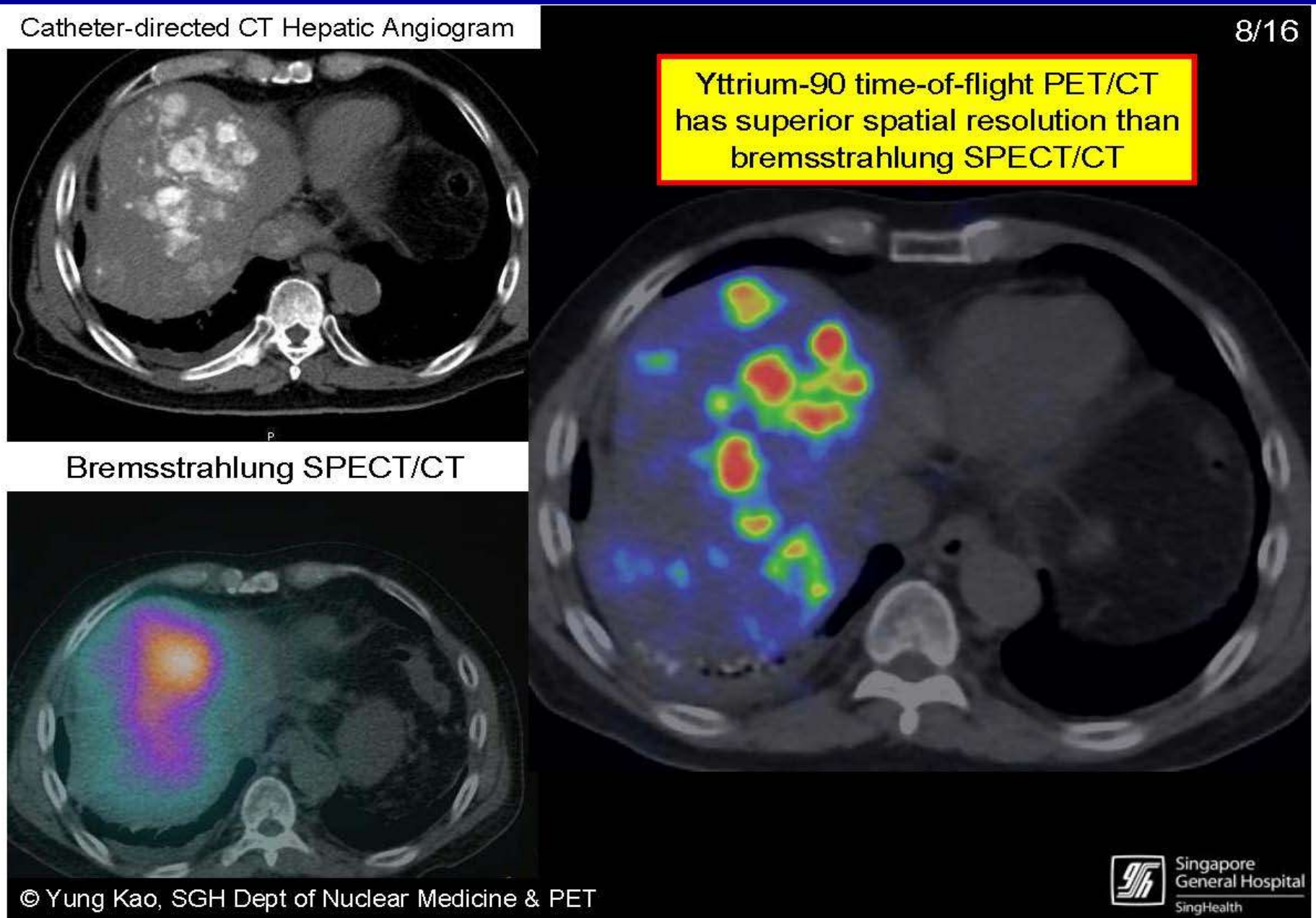
SIR-Spheres:

- 20 – 40 μm diameter
- High-energy beta rays 0.9367 MeV
- 64.2 hrs (2.67 days) half-life
- Penetration:
  - average penetration 2.5mm
  - maximum range 11.0mm

Ideal for Brachy-therapy

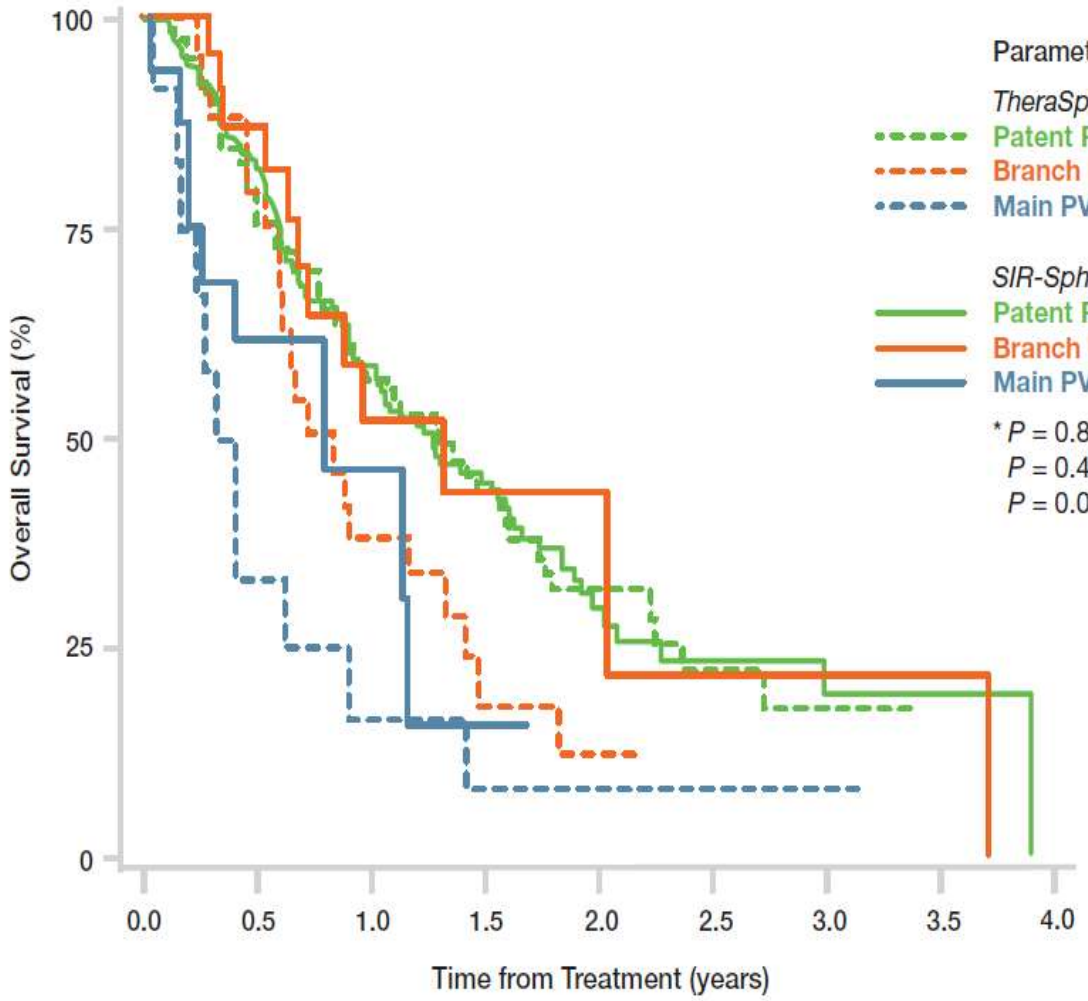


Post-therapy Bremsstrahlung



^{90}Y microspheres in Patients with HCC and PVT

Kaplan-Meier survival analysis of HCC patients treated with ^{90}Y glass or resin microspheres stratified by portal vein status[7,8]



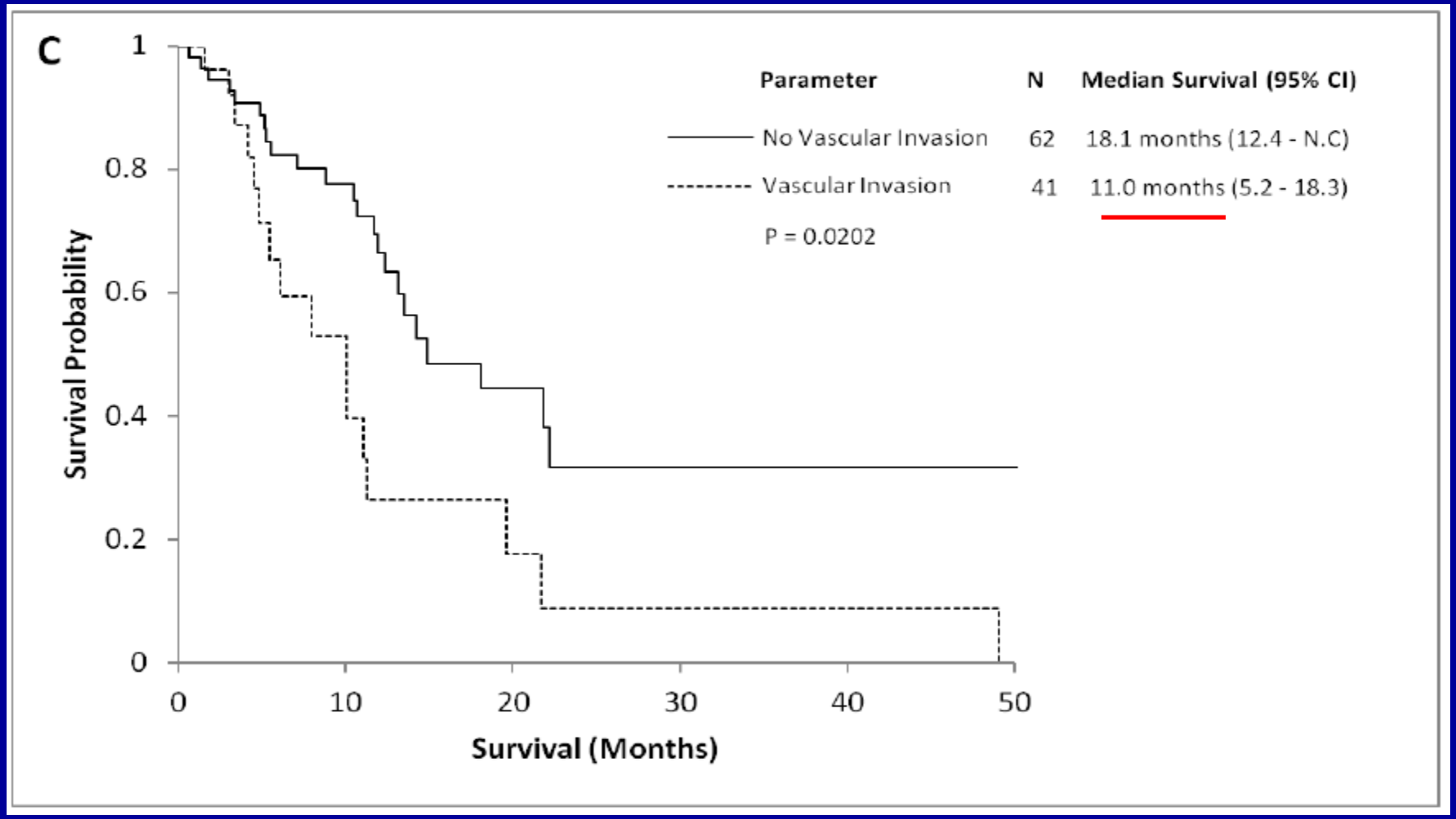
Parameter	N	Median Survival (95% CI)	
TheraSphere (^{90}Y glass microspheres)[7]			
Patent PV	71	15.4 mo	(10.6–20.7)
Branch PVT	25	9.9 mo	(7.1–15.8)
Main PVT	12	4.4 mo	(2.9–7.4)
			$P = 0.052$
SIR-Spheres (^{90}Y resin microspheres)[8]			
Patent PV	211	15.3 mo	(12.4–19.1)
Branch PVT	25	15.9 mo	(8.3–44.5)
Main PVT	16	9.7 mo	(3.2–14.1)
			$P = 0.114$*

* $P = 0.859$ Patent *vs.* Branch PVT
$P = 0.400$ Patent *vs.* Branch/Main PVT
$P = 0.038$ Patent/Branch PVT *vs.* Main PVT

Kulik LM, Carr BI, Mulcahy MF *et al.* Safety and efficacy of ^{90}Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008; **47**: 71–81.

Sangro B, Carpenese L, Ezzidin S *et al.* Nodularity is a strong predictor of survival following treatment with radioembolisation using ^{90}Y-labelled resin microspheres in unresectable hepatocellular carcinoma: Preliminary results from a European multi-centre evaluation. *3rd International Liver Cancer Association (ILCA) meeting* 2009; Abs. P-129.

^{90}Y microspheres in Patients with HCC and PVT



Data from 103 patients (not enrolled in clinical trials from Singapore General Hospital/National Cancer Center Singapore

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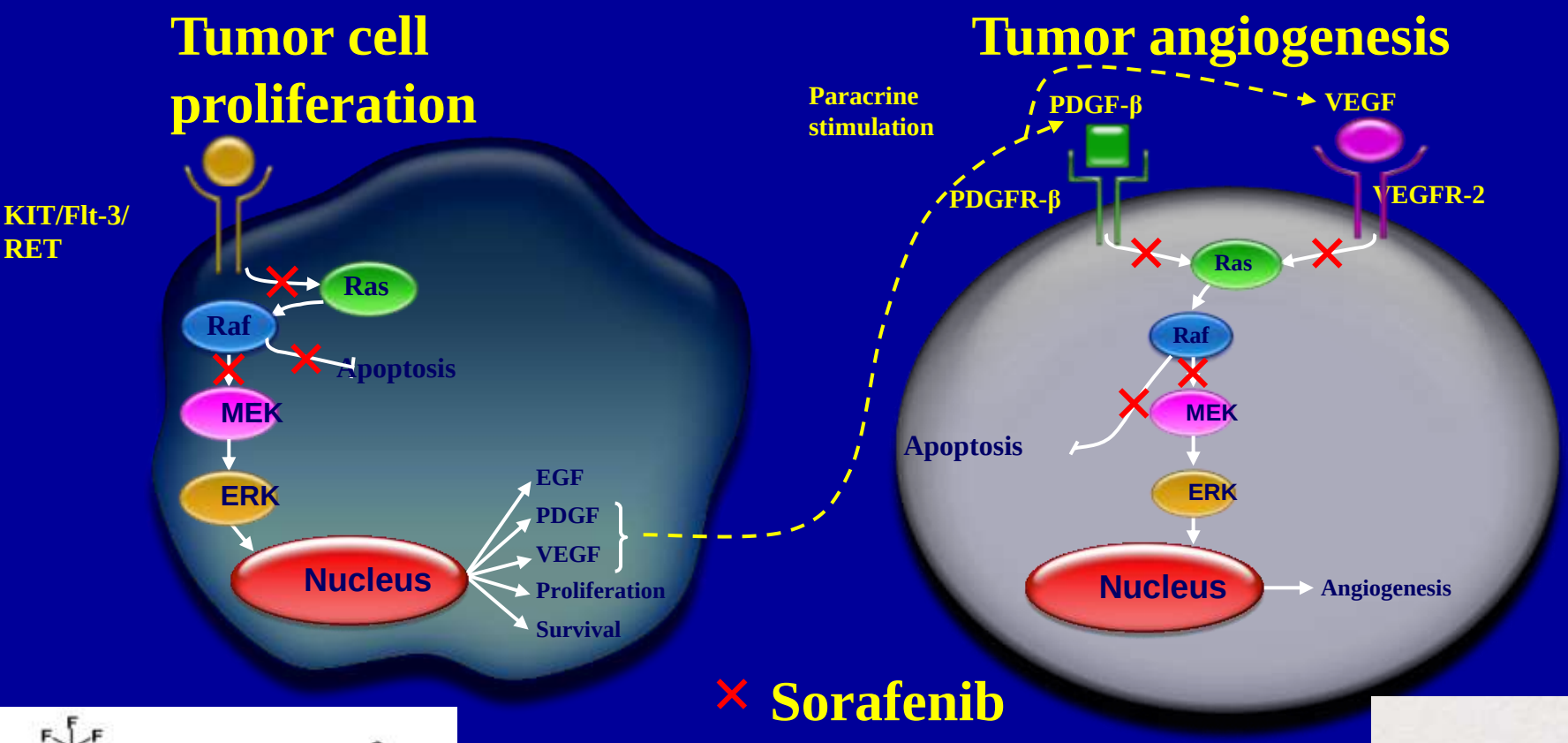
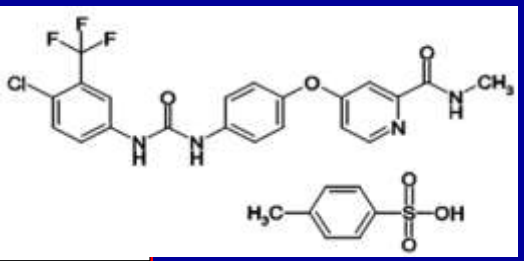
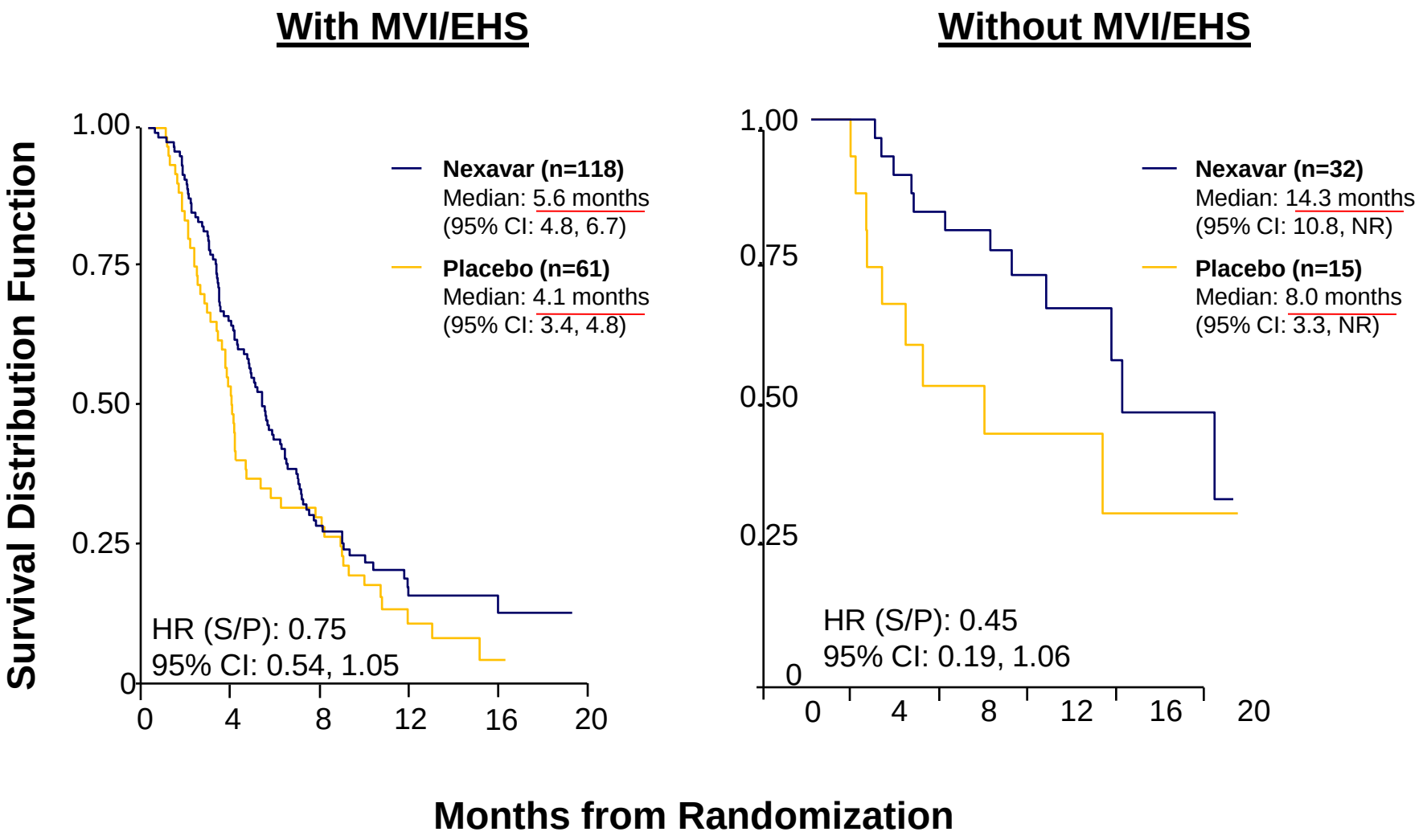
Sorafenib: proposed mechanism





Wilhelm SM et al. Cancer Res 2004

Asia-Pacific Sorafenib Trial: Overall Survival with/without MVI and/or EHS



Adapted from Khang, et al. Presented at AASLD 2008 Annual Meeting. Oct 31 - Nov 4; San Francisco, CA, USA.

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Pierce Chow FRCS, PhD

Stereotactic Radiotherapy for PVT

Xi et al PLOS One 2013

OPEN ACCESS Freely available online

PLOS ONE

Effectiveness of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Portal Vein and/or Inferior Vena Cava Tumor Thrombosis

Mian Xi[☯], Li Zhang[☯], Lei Zhao, Qiao-Qiao Li, Su-Ping Guo, Zi-Zhen Feng, Xiao-Wu Deng, Xiao-Yan Huang, Meng-Zhong Liu*

State Key Laboratory of Oncology in Southern China, Department of Radiation Oncology, Cancer Center, Sun Yat-sen University, Guangzhou, China

Abstract

Background: To report the feasibility, efficacy, and toxicity of stereotactic body radiotherapy (SBRT) for the treatment of portal vein tumor thrombosis (PVTT) and/or inferior vena cava tumor thrombosis (IVCTT) in patients with advanced hepatocellular carcinoma (HCC).

Materials and methods: Forty-one patients treated with SBRT using volumetric modulated arc therapy (VMAT) for HCC with PVTT/IVCTT between July 2010 and May 2012 were analyzed. Of these, 33 had PVTT and 8 had IVCTT. SBRT was designed to target the tumor thrombosis and deliver a median total dose of 36 Gy (range, 30–48 Gy) in six fractions during two weeks.

Results: The median follow-up was 10.0 months. At the time of analysis, 15 (36.6%) achieved complete response, 16 (39.0%) achieved partial response, 7 (17.1%) patients were stable, and three (7.3%) patients showed progressive disease. No treatment-related Grade 4/5 toxicity was seen within three months after SBRT. One patient had Grade 3 elevation of bilirubin. The one-year overall survival rate was 50.3%, with a median survival of 13.0 months. The only independent predictive factor associated with better survival was response to radiotherapy.

Conclusions: VMAT-based SBRT is a safe and effective treatment option for PVTT/IVCTT in HCC. Prospective randomized controlled trials are warranted to validate the role of SBRT in these patients.

Citation: Xi M, Zhang L, Zhao L, Li Q-Q, Guo S-P, et al. (2013) Effectiveness of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Portal Vein and/or Inferior Vena Cava Tumor Thrombosis. PLoS ONE 8(5): e63864. doi:10.1371/journal.pone.0063864

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☯ These authors contributed equally to this work.

Introduction

Portal vein tumor thrombosis (PVTT) and inferior vena cava tumor thrombosis (IVCTT) are common complications in patients with advanced hepatocellular carcinoma (HCC). Despite improvement in the survival of HCC, the prognosis of patients with PVTT/IVCTT remains poor, with a median survival of only approximately three months without treatment [1,2]. PVTT is commonly associated with portal vein hypertension, tumor dissemination, and deterioration of liver function, which then limits the application of surgical resection or transarterial chemoembolization (TACE) on HCC [3,4].

As no standard treatment modality has been established for HCC with tumor thrombosis, radiotherapy can be considered as an alternative treatment. With the development of radiation techniques such as three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and stereotactic body radiotherapy (SBRT), high-dose radiation can be safely delivered to liver tumors without resulting in serious complications [5]. Several studies have reported the application of 3DCRT in the treatment of HCC with PVTT, which has shown encouraging results in local control and survival [6–13]. However, few studies have investigated the efficacy of SBRT for the treatment of PVTT/IVCTT. In addition, the published reports have been limited to small case series, making it difficult to carry out reliable analysis [14,15].

The purpose of the current study was to report our institutional experience with a relatively large group of patients and to evaluate the feasibility, efficacy, and toxicity of SBRT for PVTT/IVCTT in HCC.

Materials and Methods

Ethics statement

This study was approved by our Institutional Review Boards (IRBs) for Cancer Center, Sun Yat-sen University. Written informed consents were obtained from all the patients in accordance with the regulations of IRBs.

Patient population

We retrospectively reviewed the records of 41 advanced HCC patients with PVTT and/or IVCTT who had received SBRT

Factor	N	Median survival (month; 95% CI)	*P* values	
			Univariate	Multivariate
Sex				
Male	37	13.0 (6.5–19.4)	0.756	
Female	4	10.2 (8.1–12.3)		
Age, y				
<54	17	16.6 (6.2–27.1)	0.847	
≥54	24	13.0 (8.3–17.7)		
AFP				
<400	21	10.9 (7.1–18.8)	0.956	
≥400	20	13.0 (5.2–20.8)		
Intrahepatic tumor type				
None/solitary	18	23.9 (17.0–30.8)	<0.0001	0.610
Multiple	23	8.9 (7.7–10.1)		
Intrahepatic lesion control				
Well-controlled	8	17.6 (15.9–19.2)	0.013	0.532
Uncontrolled	33	10.0 (7.9–12.1)		
Abdominal LNM				
Yes	11	8.2 (6.0–10.4)	<0.0001	0.295
No	30	18.0 (11.8–24.1)		
Site of tumor thrombosis				
Portal vein branch	16	23.9 (14.6–33.3)	<0.0001	0.879
Portal vein trunk	17	9.1 (5.1–13.0)		
Inferior vena cava	8	9.2 (2.6–15.8)		
Combined with sorafenib				
Yes	14	16.6 (10.1–23.1)	0.755	
No	27	10.9 (5.7–16.1)		

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  - supportive management
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  - *Surgical resection* (some centers especially in Asia)
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A prospective comparative study of TACE in PVT in Asia

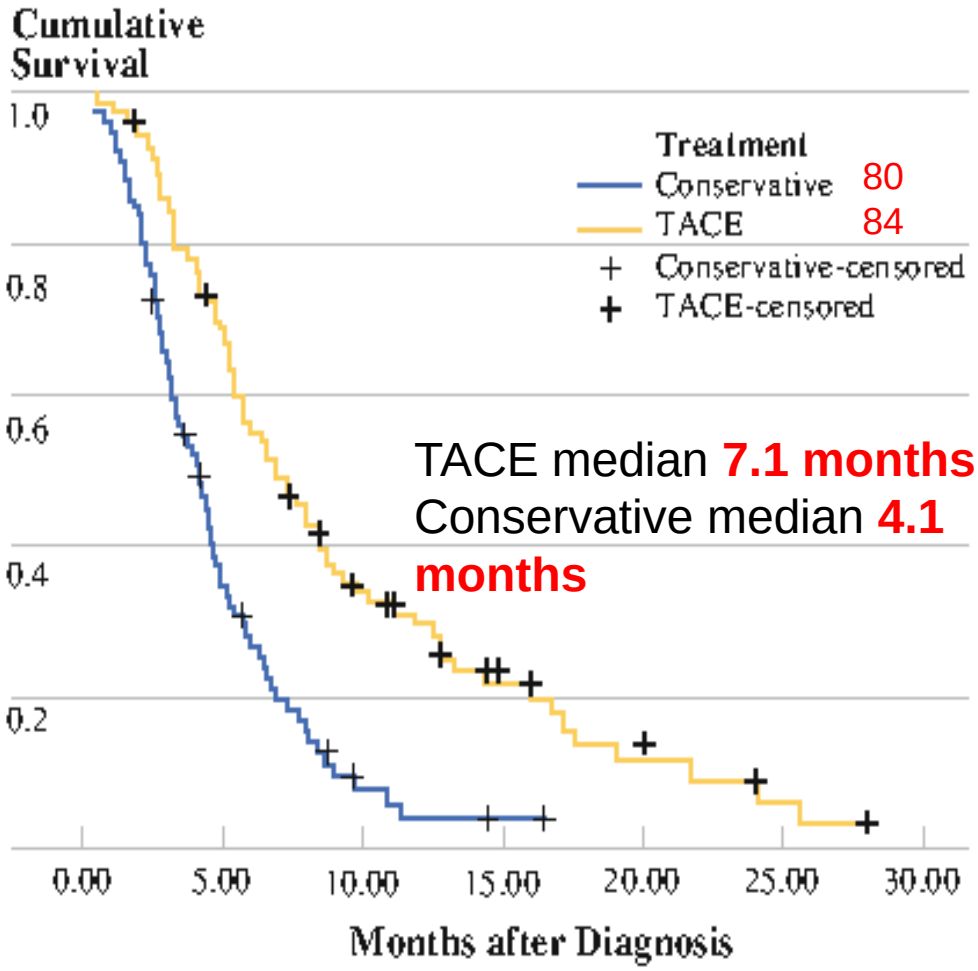
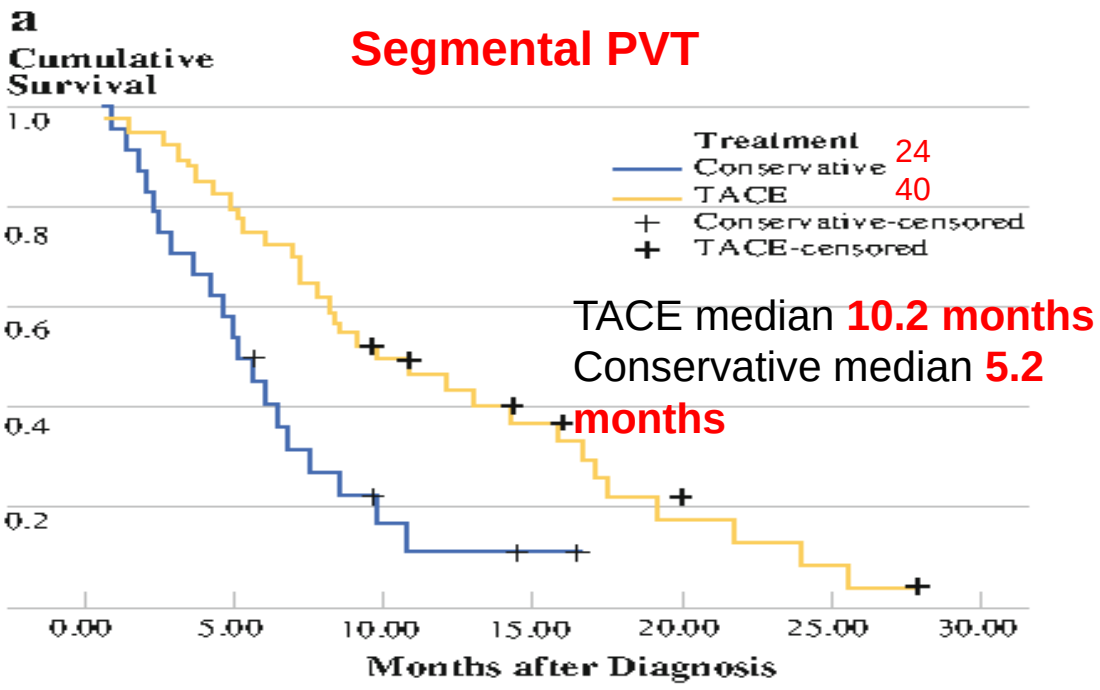
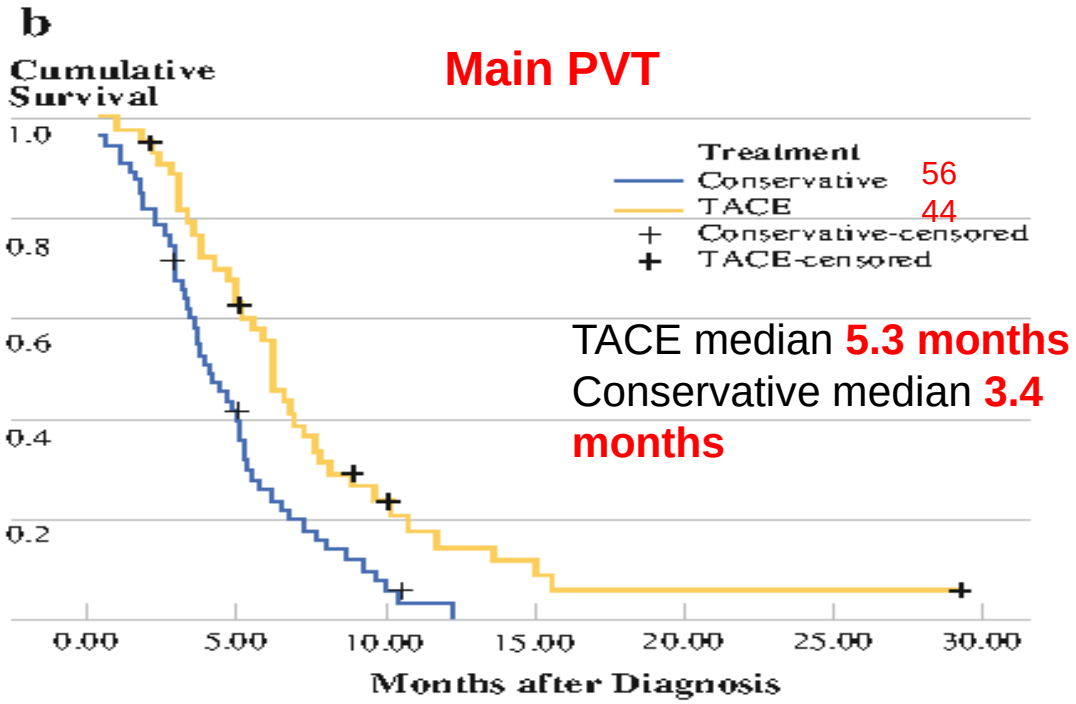


FIG. 1 Comparison of survival rates between the TACE and conservative treatment groups. The 3-, 6-, 12-, and 24-month overall survival rates for the TACE and conservative groups were 85.6%, 56.4%, 30.9%, 9.2%, and 63.6%, 28%, 3.8%, 0%, respectively ($P < 0.001$)

Luo et al 2011
Ann Surg Onc

A prospective comparative study of TACE in PVT in Asia





Luo et al 2011
Ann Surg Onc

Comparative Median Survival for Vascular Invasion

Modality	Surgery	Yttrium-90 (SIRT)	Sorafenib	Stereotatic radiotherapy	TACE
IVC	-	-	-	9.2 mo	-
Branch PVT	18.8	15.9 mo	-	23.9 mo	10.2 mo
Main PVT	10.8	9.7 mo	5.3 mo (MVI/EHD)	9.1 mo	5.3 mo

Randomized Controlled Trials are required

How should clinicians decide on what the most appropriate treatment for a patient with advance HCC in the absence of phase III data

The choice of the best treatment depends on:

- *the stage of the cancer*
- *the general health of the patient*
- *and the availability of cutting edge expertise and therapeutics*

The rapid evolution of new therapeutic modalities makes it increasingly challenging to deliver optimal care with the patient being managed sequentially by individual specialists

Multi-Disciplinary Tumor–Board delivered treatment

Oncologic Radiologist

Medical Oncologist

Surgical Oncologist

Pathologist

Radiation Oncologist

Liver Surgeon

Nuclear Medicine

Multi-Disciplinary Tumor–Board delivered treatment

Oncologic Radiologist

Medical Oncologist

Surgical Oncologist

Nuclear Medicine

Pathologist

Radiation Oncologist

Liver Surgeon

Thank You!