

Gastrointestinal Tumours

What is the (optimal) interventional treatment in HCC

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SGH – Surgery

ESMO Asia 2015 Congress
20th Dec 2015, Singapore



Disclosure slide

- Have received honorarium, research grants or consultancy fees from:
 - Sirtex Medical
 - Bayer Pharmaceutical
 - Ipsen
 - OncoSil
 - Glaxo-Smith-Kline
 - Merck Sharp and Dohme
 - Novartis

Rapid Evolution in the Management of HCC

- The *last decade* has seen better approaches and more efficacious therapies for HCC
- Much greater number of options
- The rapid evolution has lead to significant improvement in clinical outcomes
- The challenge for the busy clinician is to adopt a *practical approach* to HCC that incorporates these new advances.



The Choice of **optimal** treatment for an individual with HCC depends on

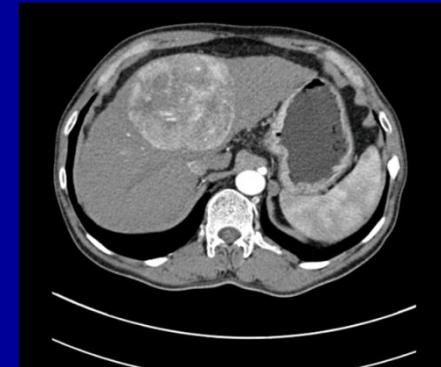
- *the stage of the cancer*
- *the function of the liver and health of the patient*
- *and the availability of expertise and therapeutics*



Stages of Liver Cancer

Early Stage HCC

- Lesions within the Milan Criteria
- criteria:
 - Solitary tumour $\leq 5\text{cm}$ OR ≤ 3 tumours, each $< 3\text{cm}$ AND No invasion of blood vessels and no distant spread



Locally Advanced HCC

- Lesions confined to the liver that are outside of the Milan criteria with or without vascular invasion



Metastatic HCC

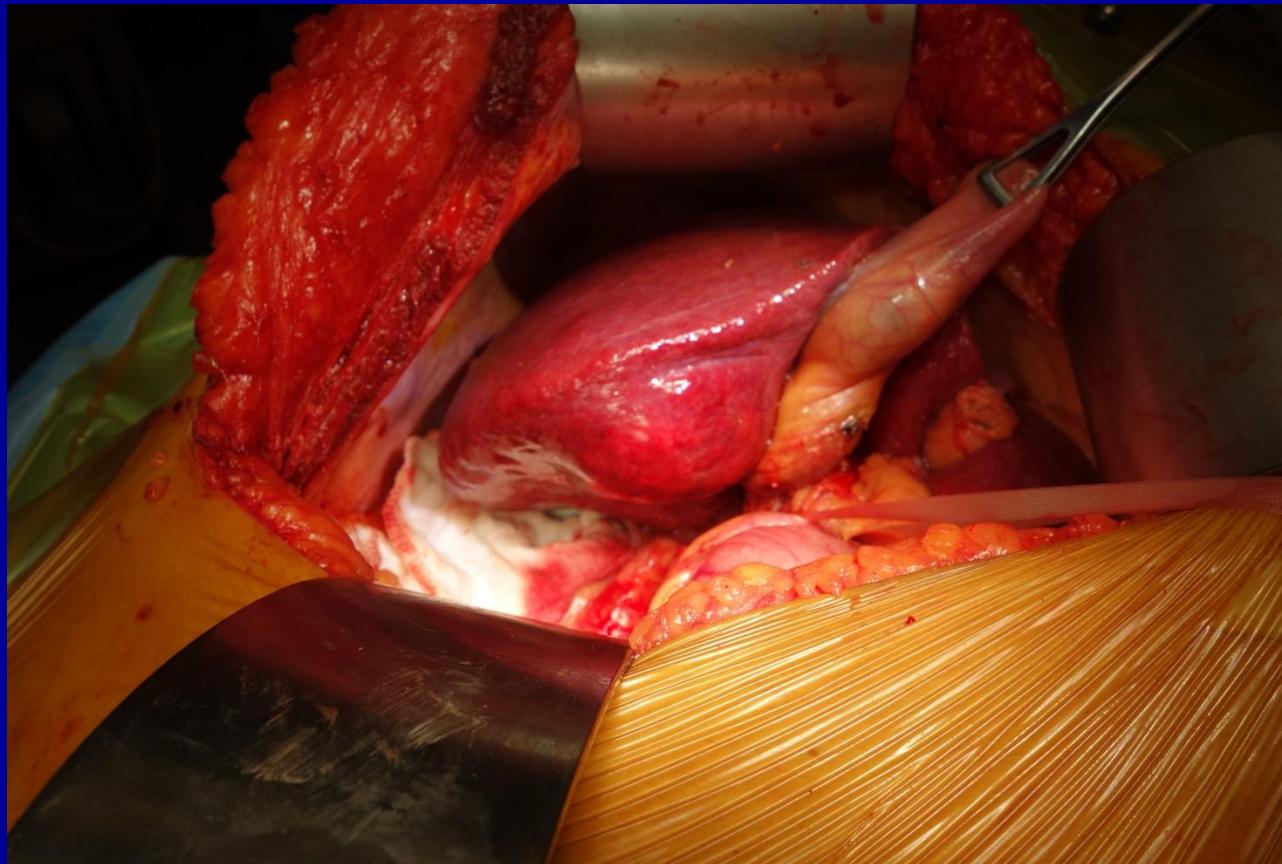
- With good liver function (Child-Pugh A or early B)
- With poor liver function



National Cancer Center Singapore Guidelines on Liver Cancer

http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline_Final Ver to upload PDF 26092014.pdf

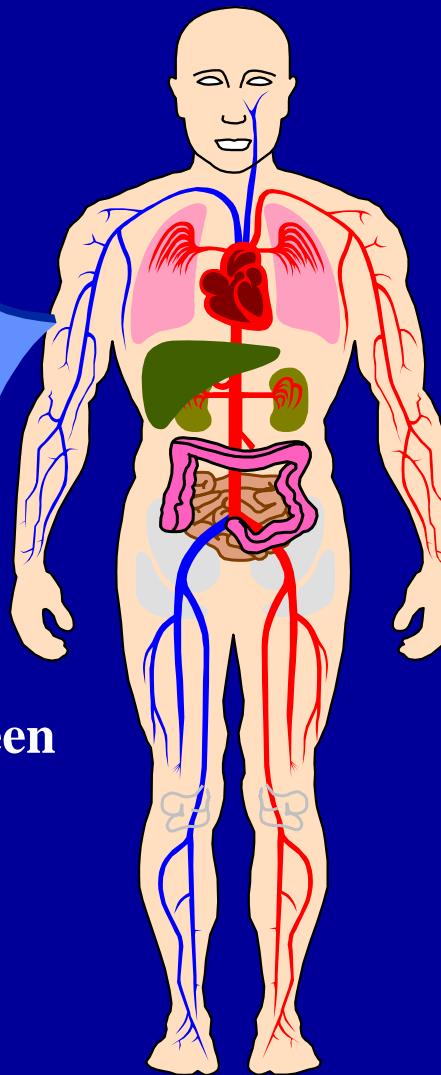
Surgery is potentially curative in Early Stage HCC



- If liver function is good
- If there is adequate future liver remnant

Dynamic Assessment of Function

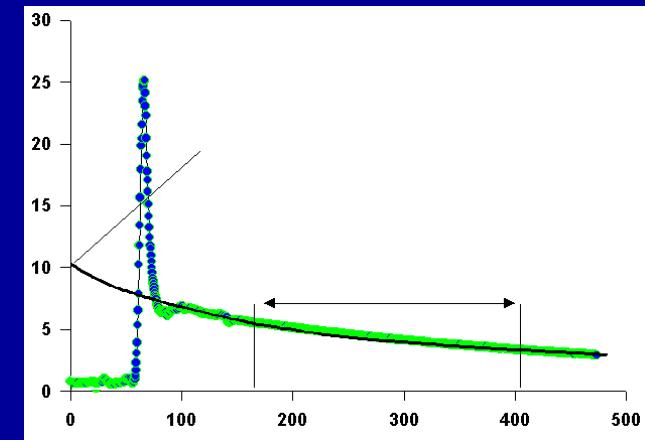
Indo-cyanine green retention test



Indo-cyanine green
retention test

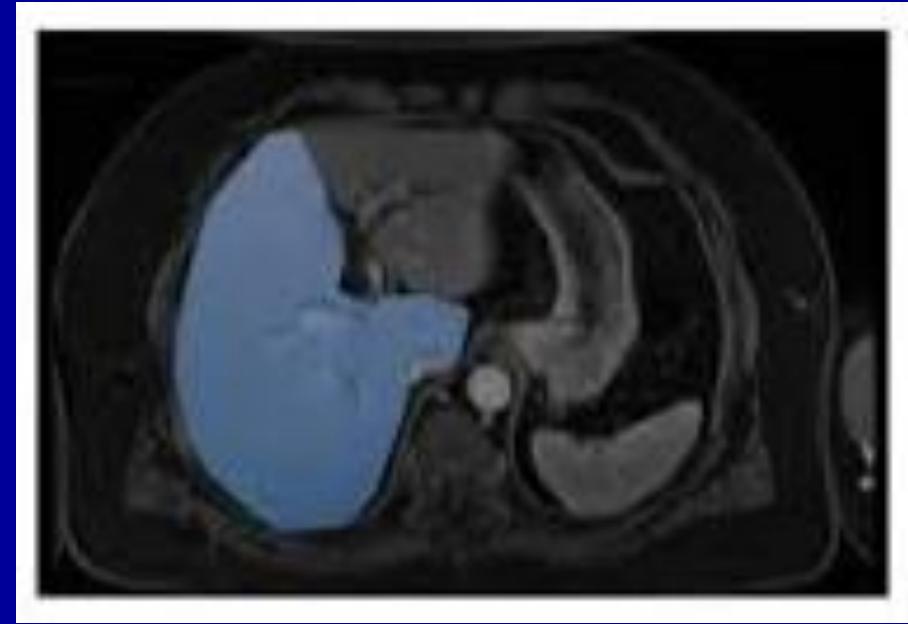
Lau et al 1987: Relative risk of mortality for major hepatectomy increase 3X if ICG retention at 15 min > 14%

- Prospective study: 127 patients



Adequate Future Liver Remnant (FLR)

- **Normal liver** - FLR of at least 25% is deemed sufficient by most surgeons to prevent postoperative liver failure.
- **Cirrhotic Livers** - a larger FLR of up to 40% should be preserved^{1,2}
- Inadequate FLR is the most common factor precluding curative LR



1. Tanaka K, Shimada H, Matsuo K, et al. Remnant liver regeneration after two-stage hepatectomy for multiple bilobar colorectal metastases. Eur J Surg Oncol. 2007 Apr;33(3):329-35.
2. Hemming AW, Reed AI, Howard RJ, et al. Preoperative portal vein embolization for extended hepatectomy. Ann Surg. 2003 May;237(5):686-91

Systematic review

Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria

K.-C. Lim¹, P. K.-H. Chow^{1,2,3}, J. C. Allen¹, F. J. Siddiqui^{1,4}, E. S.-Y. Chan^{1,4} and S.-B. Tan^{1,4}

¹Centre for Quantitative Medicine, Duke–NUS Graduate Medical School, ²Department of General Surgery, Singapore General Hospital, ³Department of Surgical Oncology, National Cancer Centre, and ⁴Singapore Clinical Research Institute, Singapore

Correspondence to: Professor P. K.-H. Chow, c/o Department of General Surgery, Singapore General Hospital, Outram Road, Singapore 169608
(e-mail: pierce.chow@duke-nus.edu.sg)

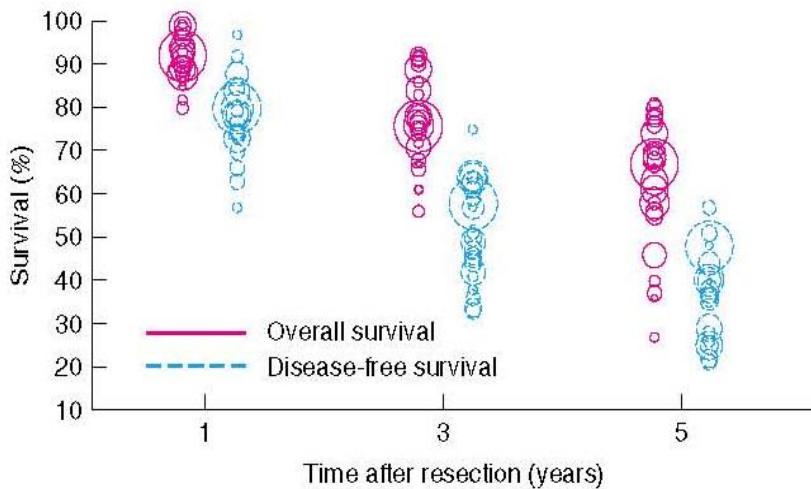


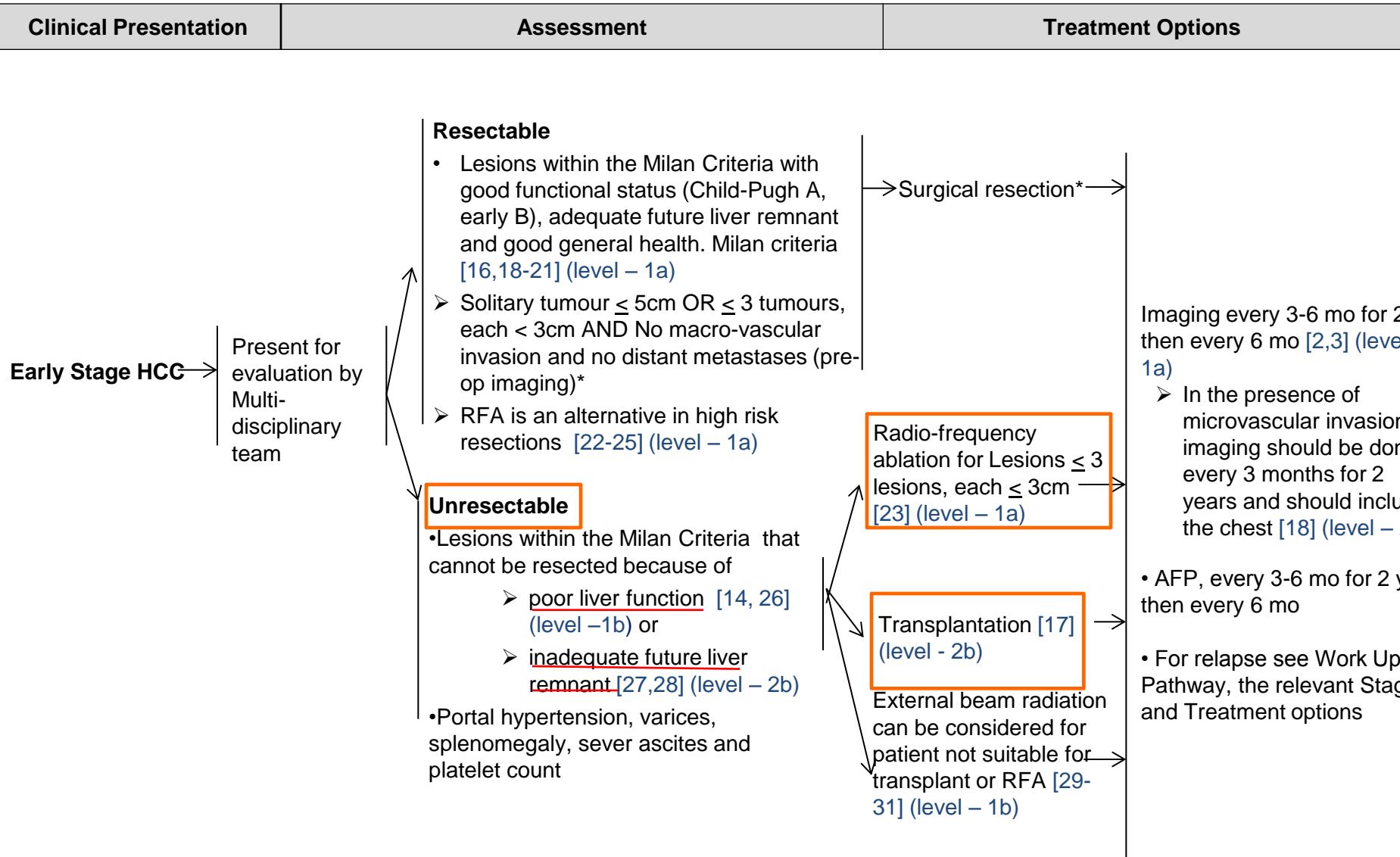
Fig. 2 Bubble plot of overall and disease-free survival from systematic review of outcomes of liver resection for early hepatocellular carcinoma meeting the Milan criteria and with good liver function. Bubble size indicates relative cohort size

2 RCT, 27 retrospective studies
Published between Jan 2000 – Dec 2010
4209 patients
with HCC within **Milan Criteria**
Med tumour size **2.5 – 4.0 cm**

Med operative mortality **0.7% (0 – 5%)**
Med **5-yr overall survival** **67% (27 – 81)**
Med 5-yr disease-free sur **37% (21 – 57)**

Lim, Chow et al BJS 2012

EARLY STAGE HEPATOCELLULAR CANCER

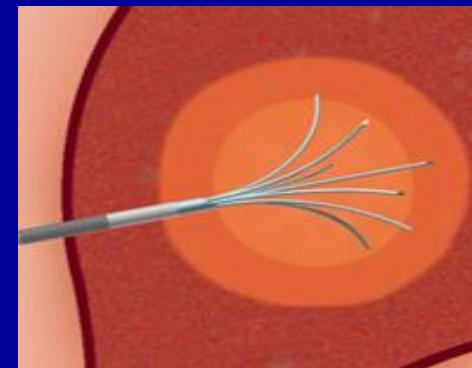


National Cancer Center Singapore Consensus Guidelines on Liver Cancer

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Radio-Frequency Ablation

- *Radiofrequency ablation* (RFA) is most efficacious for small volume HCC
≤ 3 lesions each ≤ 3 cm



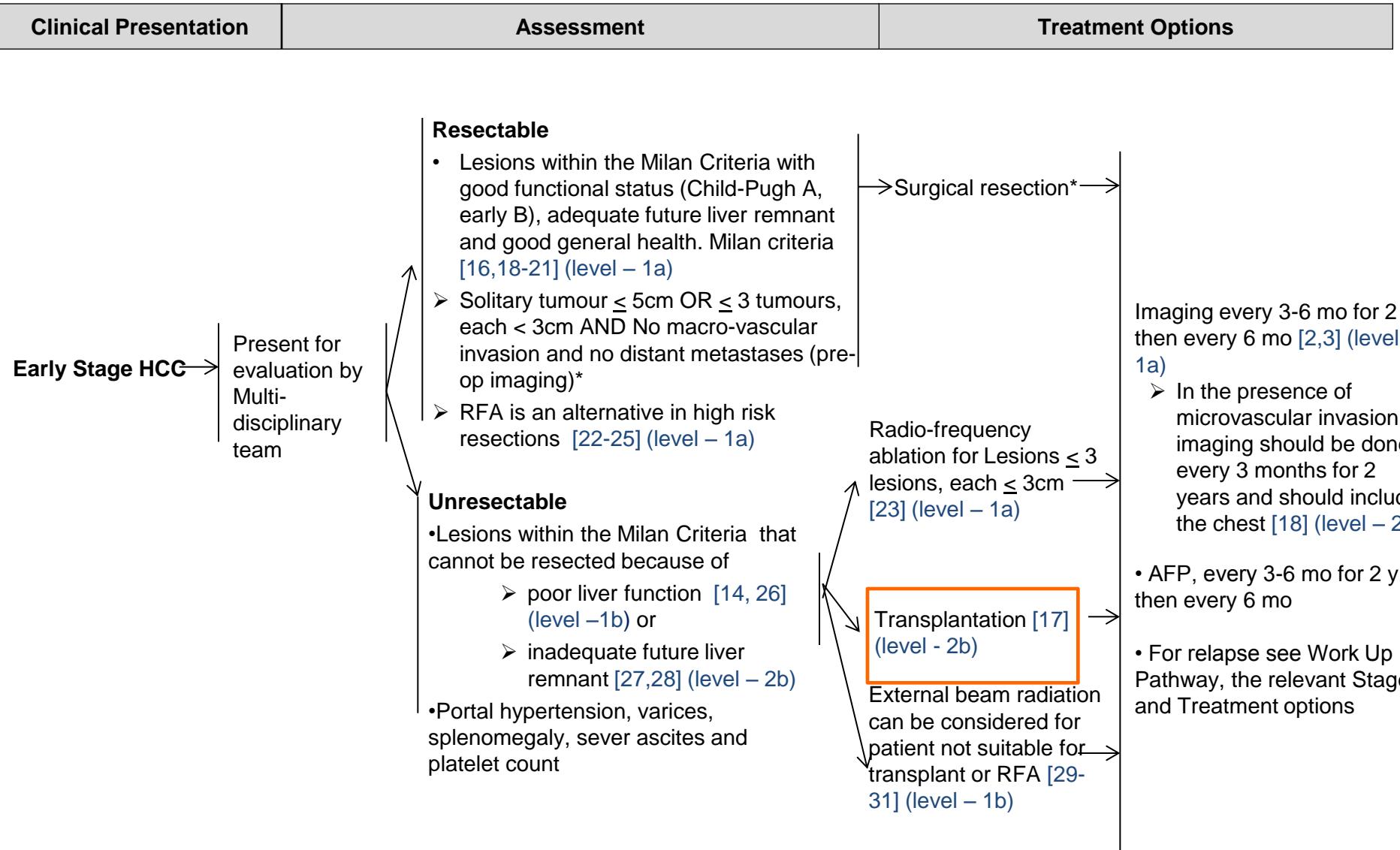
- Mortality: 1.2% Complications: 3 – 7%

Study	n	Tumor Size	Mortality Rate (%)	Major Morbidity Rate (%)	5-Yr Overall Survival (%)	5-Yr Disease-Free Survival (%)
Buscarini et al. ²⁰ 2001	88	≤3.5 cm	0	2.3	33	3
Lencioni et al. ²¹ 2005	187	Mean, 2.8 cm	0	2	48	—
Raut et al. ²² 2005	194	Median, 3.3 cm	1	12	55.4	33.1
Machi et al. ²³ 2005	65	Mean, 3.2 cm	1.2	4.8	39.9	27.9
Tateishi et al. ²⁴ 2005	319	Mean, 2.6 cm	0	4	54.3	—
Cabassa et al. ²⁵ 2006	59	Mean, 3.1 cm	0	1.7	43.1	—
Choi et al. ²⁶ 2007	570	Mean, 2.59 cm	0	1.9	58	21

median 3 cm
5-year OS
33 – 58%

Lau WY 2009

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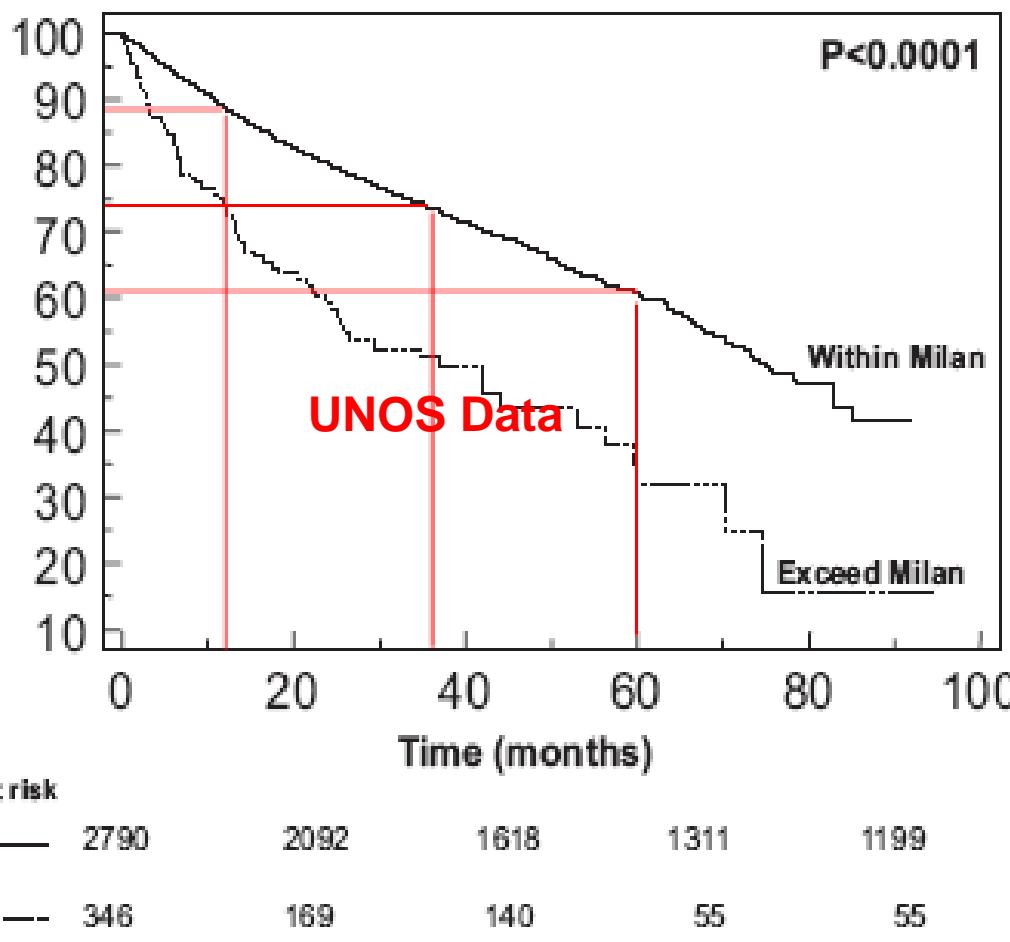


Figure 6. Overall intent-to-treat survival of patients listed for hepatocellular carcinoma according to the utilized criteria. There was a significant difference in survival among those that met the Milan criteria (black line) compared to those who exceeded the Milan criteria (black dotted line). The P value was <0.0001.

5-year OS Transplantation for HCC

4482 patients with HCC
Intention to treat

5 year overall survival

Within Milan	61%
Outside Milan	32%

Actually transplanted

5 year overall survival

Within Milan	65%
Outside Milan	38%

Pelletier et al. 2009,
Liver Transplantation

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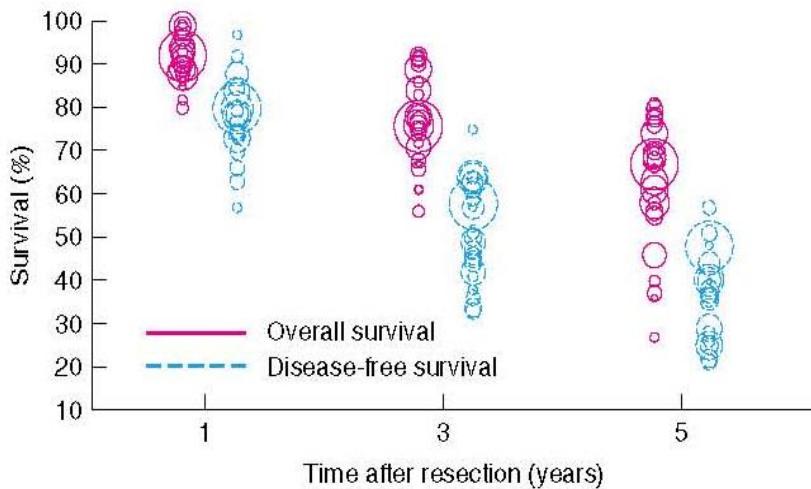
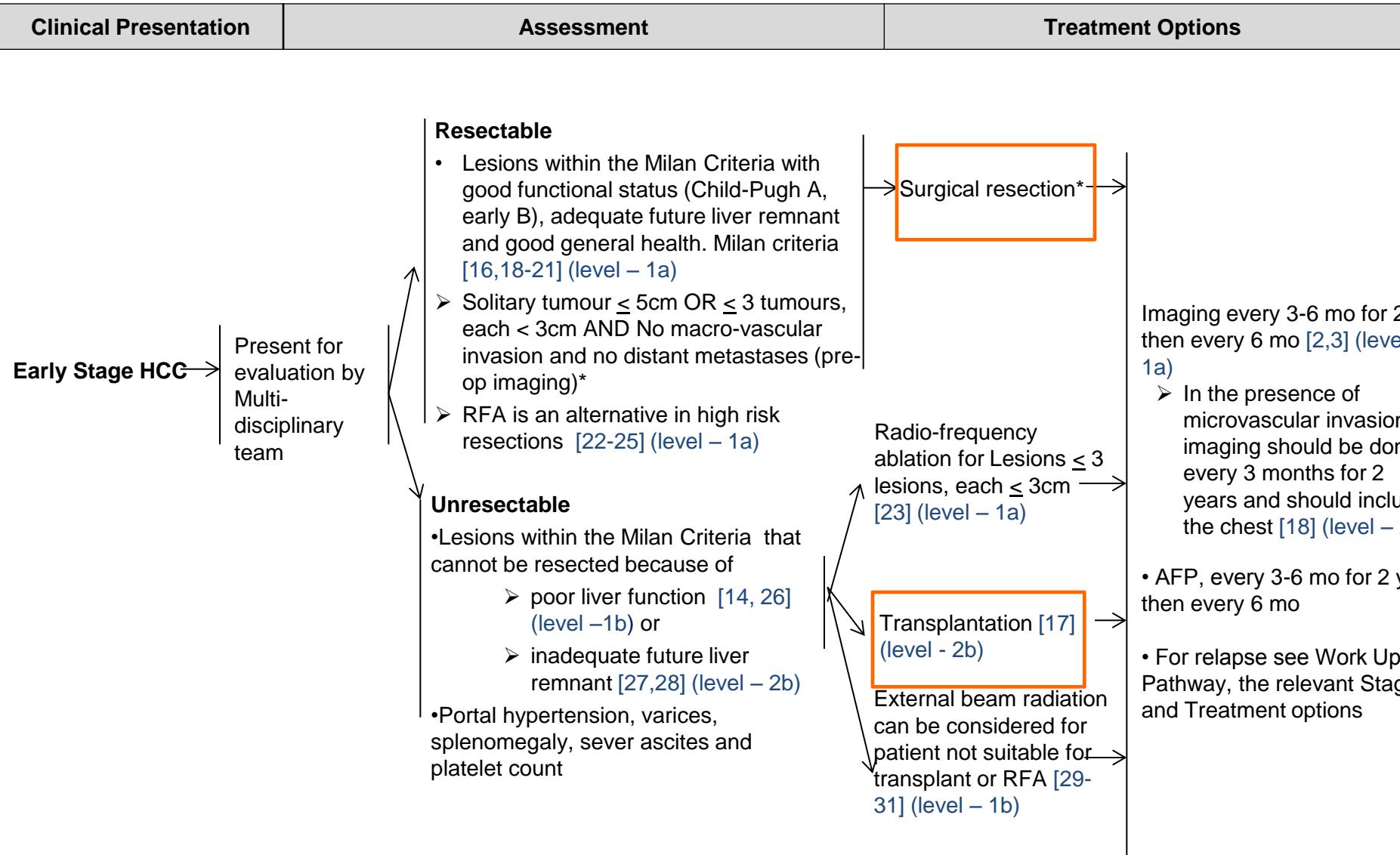


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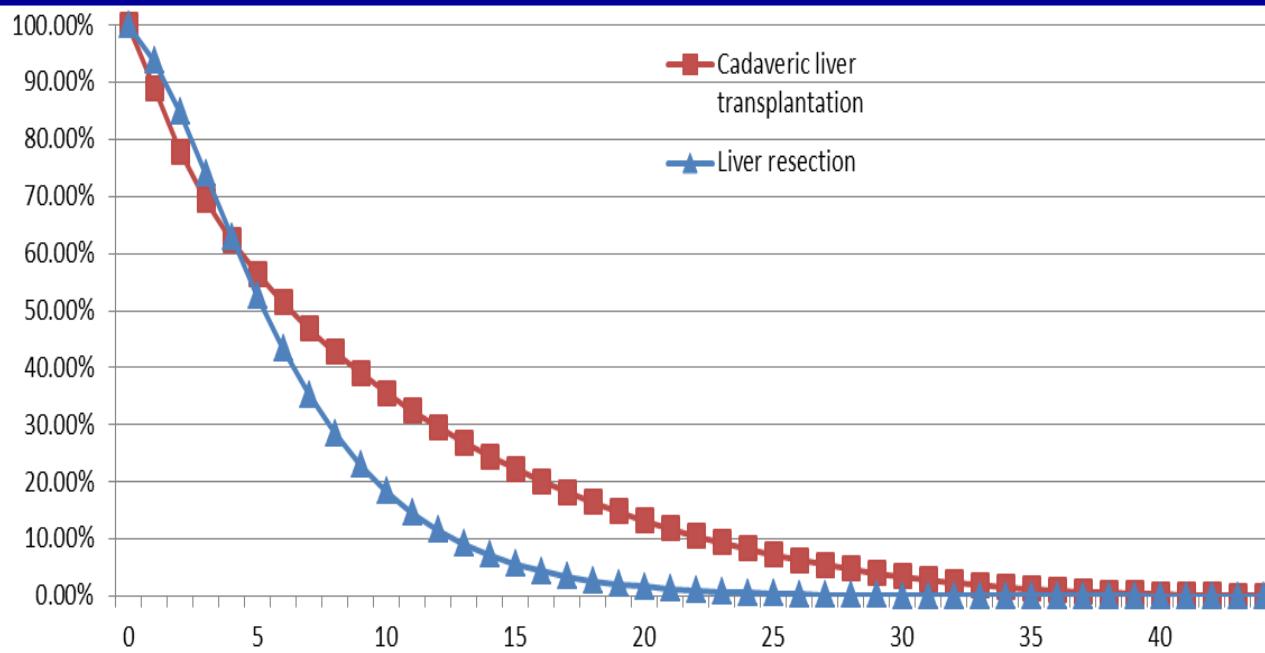
Cost-Effectiveness Analysis of Liver Resection Versus Transplantation for Early Hepatocellular Carcinoma Within the Milan Criteria

Kheng Choon Lim,^{1,2,*} Vivian W. Wang,^{3,*} Fahad J. Siddiqui,^{1,4} Luming Shi,^{2,5} Edwin S.Y. Chan,^{1,2,4}
Hong Choon Oh,³ Say Beng Tan,^{1,2} and Pierce K.H. Chow^{2,6,7}

Both liver resection (LR) and cadaveric liver transplantation (CLT) are potentially curative treatments for patients with hepatocellular carcinoma (HCC) within the Milan criteria and with adequate liver function. Adopting either as a first-line therapy carries major cost and resource implications. The objective of this study was to estimate the relative cost-effectiveness of LR against CLT for patients with HCC within the Milan criteria using a decision analytic model. A Markov cohort model was developed to simulate a cohort of patients aged 55 years with HCC within the Milan criteria and Child-Pugh A/B cirrhosis, undergoing LR or CLT, and followed up over their remaining life expect-

Hepatology 2014
Lim et al

In early liver cancer with good liver function, resection is more cost effective in the US, Switzerland, Singapore



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LOCALLY ADVANCED HEPATOCELLULAR CARCINOMA

Clinical Presentation	Treatment Options
<p>Locally Advanced HCC</p> <p>Good liver function</p> <p>Poor liver function</p> <ul style="list-style-type: none">➤ - Palliative treatment➤ - Consider Clinical Trial➤ - Transplant within UCSF <p>Present for evaluation by multi-disciplinary team</p>	<p>→ Consider Clinical Trial</p> <p>→ Surgical resection for carefully selected cases after multidisciplinary board evaluation</p> <p>LOCOREGIONAL THERAPY</p> <p>No Vascular Invasion*</p> <ul style="list-style-type: none">➤ Transarterial chemoembolisation (TACE) ± DC-Beads [32,33] (level – 1b)➤ Selective Internal Radiation Therapy (SIRT) [34-36] (level – 2b)➤ External beam RT (alone or as part of combined modality)➤ Sorafenib [32-35] (level – 1b) <p>With Vascular Invasion</p> <ul style="list-style-type: none">➤ Sorafenib [37-40] (level – 1b)➤ Selective Internal Radiation Therapy (SIRT) [34-36] (level – 2b)➤ External beam RT (alone or as part of combined modality) [41,42] (level – 2a) <p>→ Transplantation is a consideration for HCC within the UCSF expanded criteria (single tumours < 6.5cm or 2-3 tumours < 4.5cm at the most, with a total tumour diameter < 8cm) after assessment by a multi-disciplinary tumour board [43,44] (level – 2b)</p>

*Sorafenib may also be considered when local regional therapy is not feasible or fails [40] (level - 2b)

National Cancer Center Singapore Consensus Guidelines on Liver Cancer

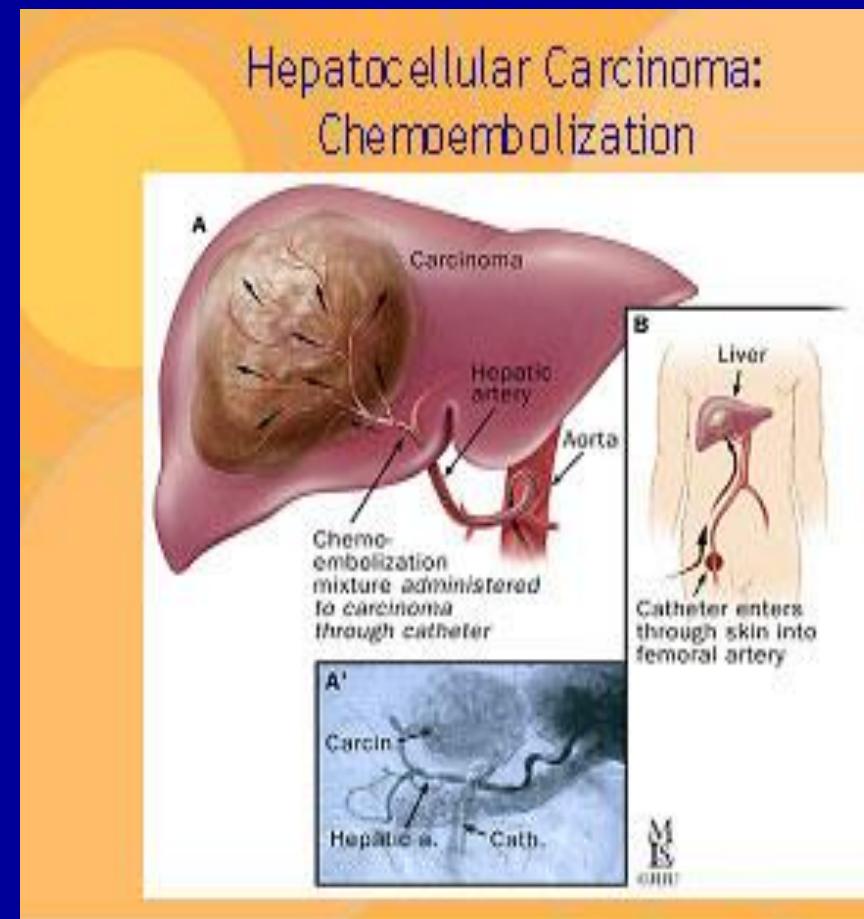
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Main Loco-regional Therapies

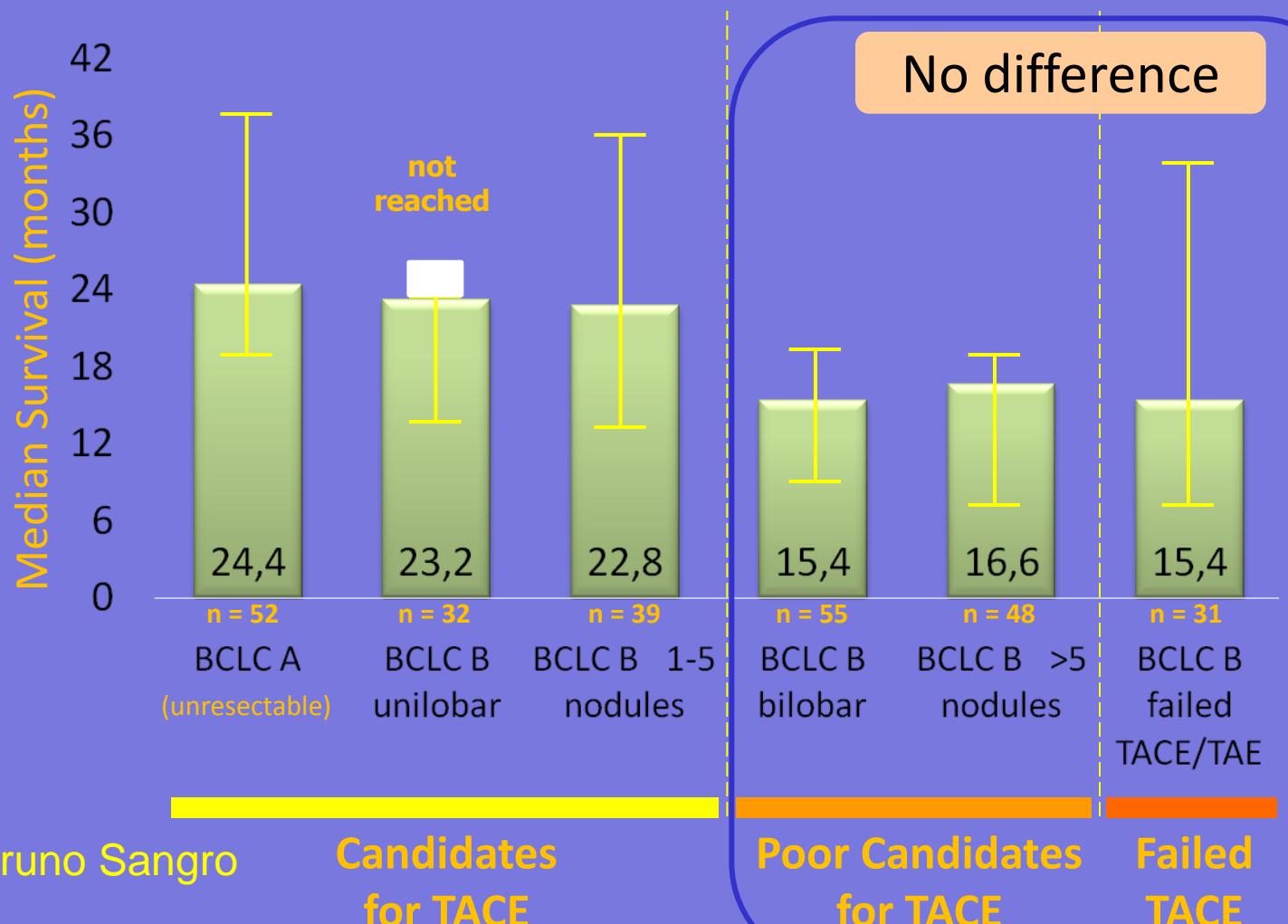
- **Trans-arterial chemo-embolisation (TACE):**
 - widely used - disease control **approx 40%**
 - used mainly in *HCC, NETs* (includes DC Beads)
- **Selective Internal Radiation Therapy (SIRT):**
 - higher disease control (**approx 80%**)
 - SIR-Sphere®, Thera-Sphere®

Trans-arterial chemo-embolization

- Injecting *chemotherapy* (*doxorubicin, cisplatin, mitomycin*) via femoral -> hepatic artery (with *embolization*)
- Requires good liver function (Child's A)
- complete regression (CR) uncommon (2%).
- Contraindicated in PVT



Patient Outcomes According to Suitability for TACE in the ENRY Series



Courtesy Bruno Sangro

Candidates
for TACEPoor Candidates
for TACEFailed
TACE

Main Loco-regional Therapies

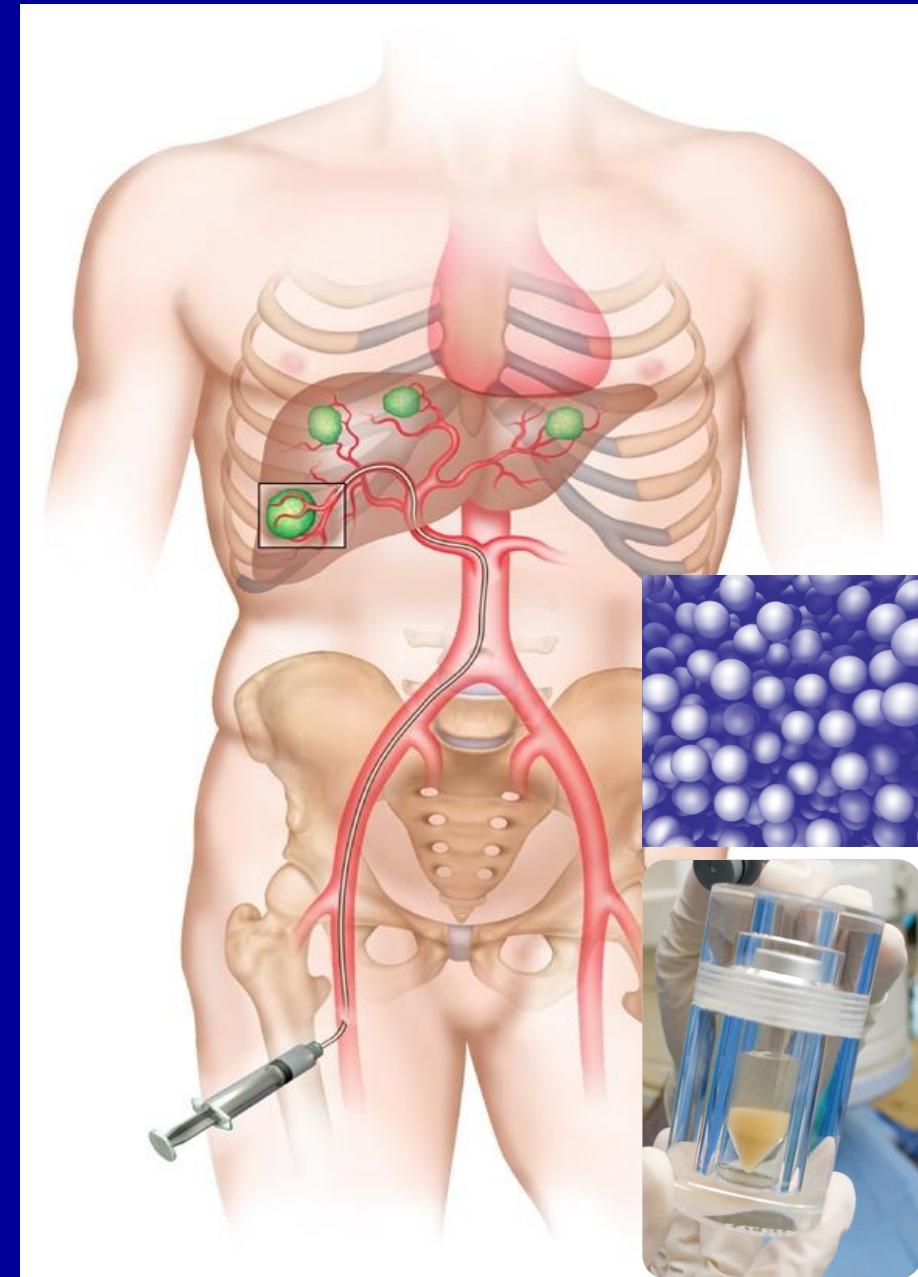
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Trans-arterial Route

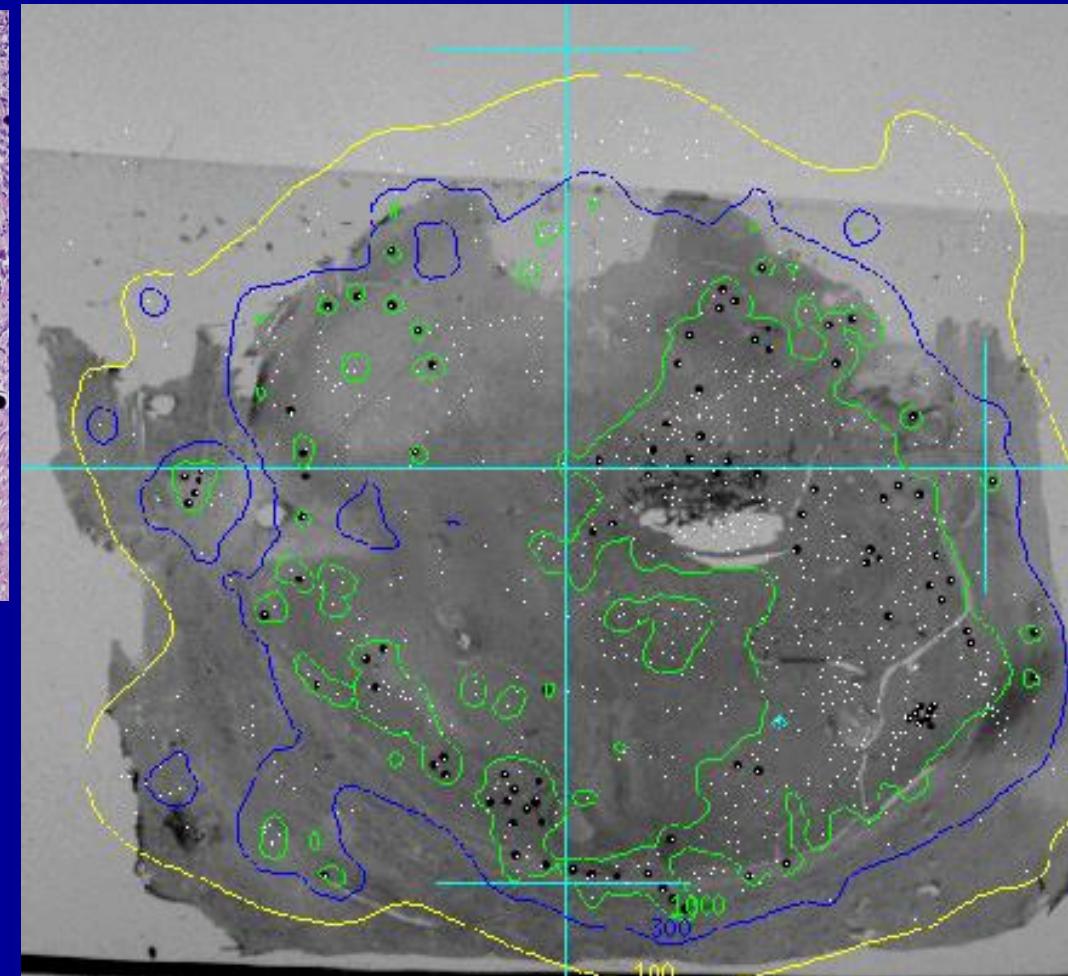
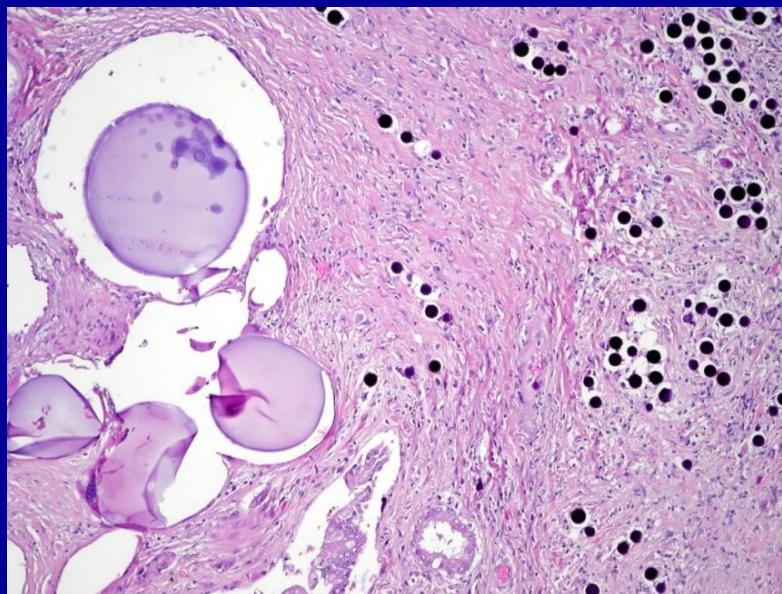
Yttrium-90 on microspheres :

- 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



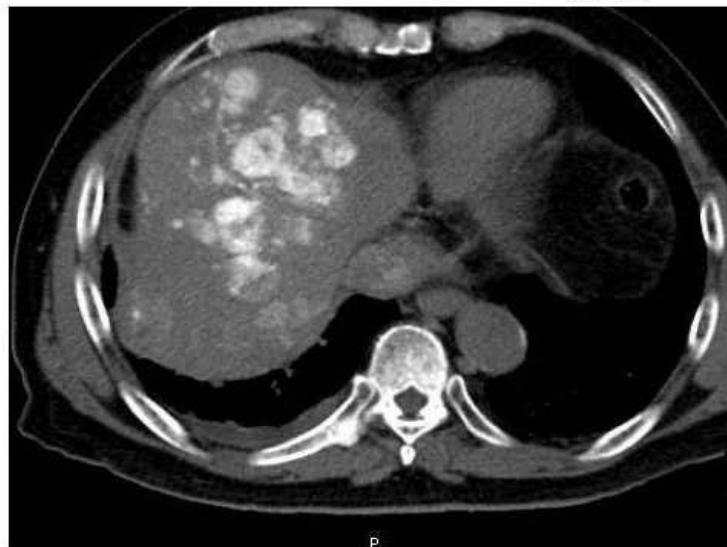
Implantation of SIR-Spheres microspheres in pre-capillary vessels



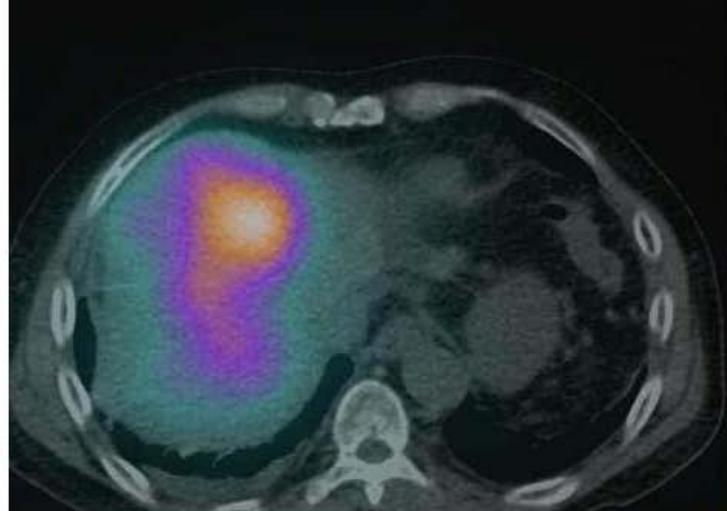
Kennedy AS, Nutting C, Coldwell D, et al. Pathologic response and microdosimetry of (90)Y microspheres in man: review of four explanted whole livers. Int J Radiat Oncol Biol Phys. 2004; 60:1552-63.

Post-therapy Bremsstrahlung

Catheter-directed CT Hepatic Angiogram

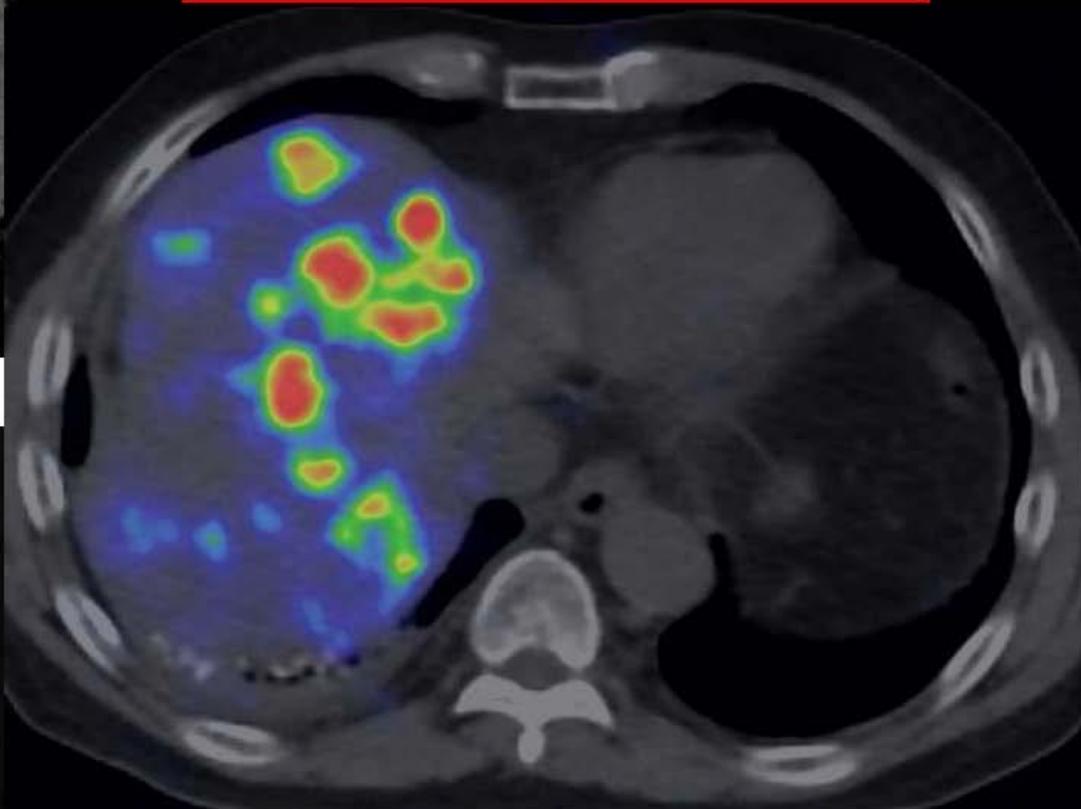


Bremsstrahlung SPECT/CT



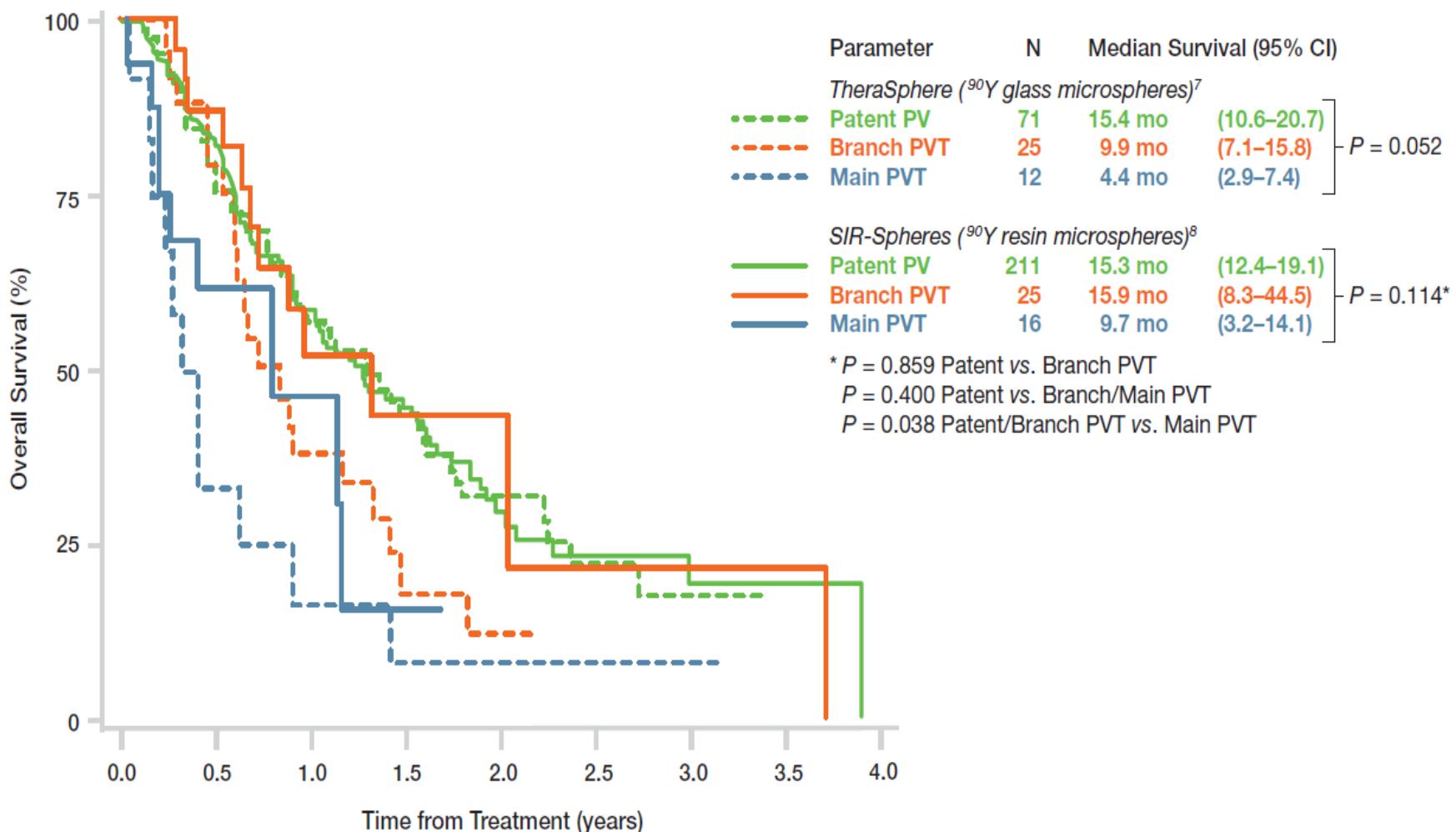
8/16

Yttrium-90 time-of-flight PET/CT has superior spatial resolution than bremsstrahlung SPECT/CT



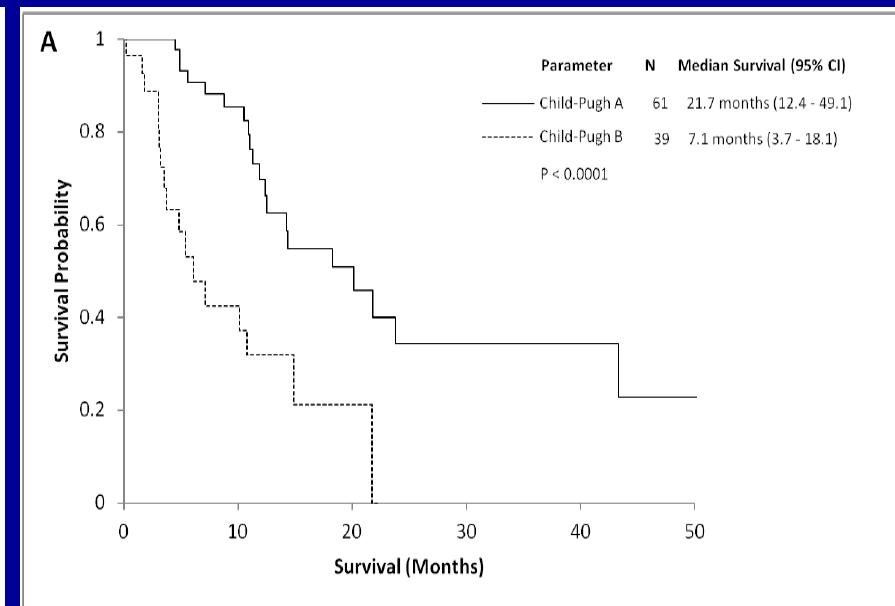
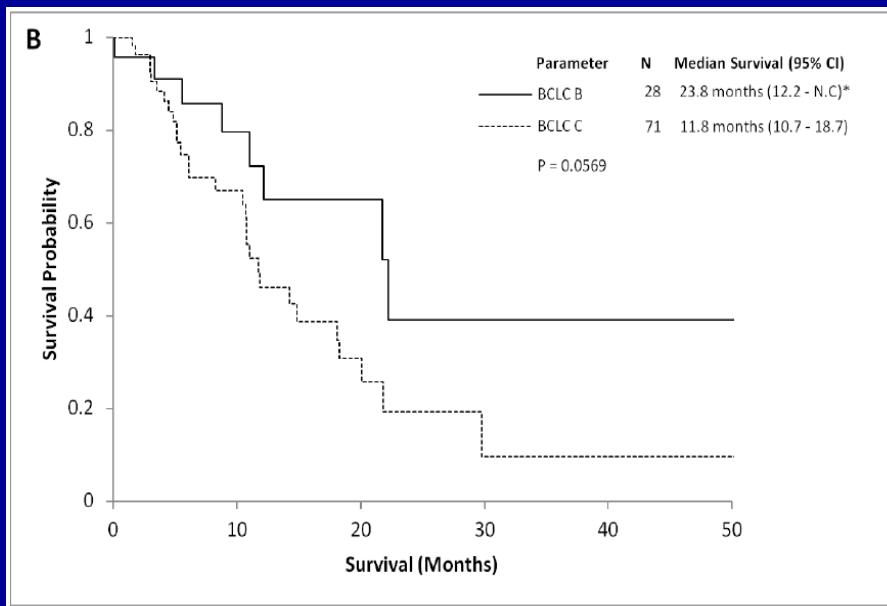
⁹⁰Y microspheres in Patients with HCC and PVT

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



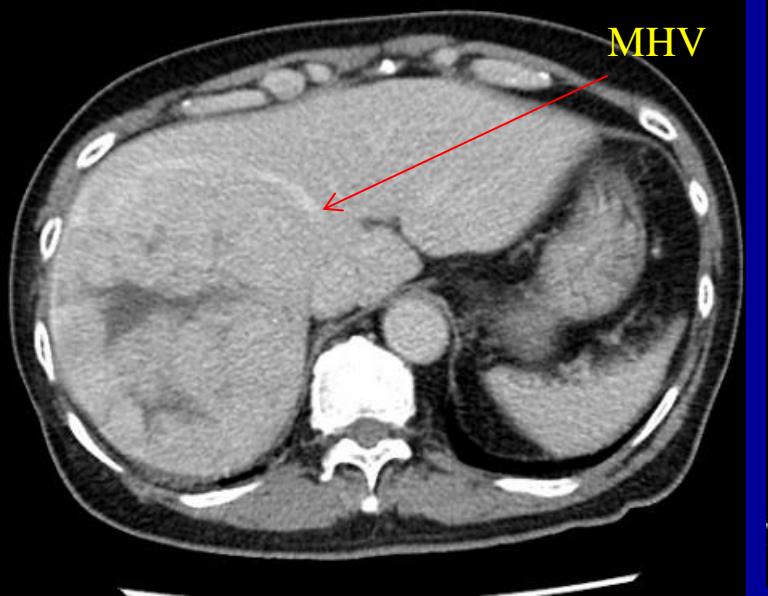
Kulik LM, Carr BI, Mulcahy MF et al. Safety and efficacy of ⁹⁰Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology* 2008; **47**: 71–81.

Sangro B, Carpenese L, Ezzidin S et al. Nodularity is a strong predictor of survival following treatment with radioembolisation using ⁹⁰Y-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.



- Mainly Hepatitis B
- Median Survival: **14.4 months** (95% CI, 11.0 – 2.2)
 - BCLC B: **23.8 months**
 - BCLC C: **11.8 months**
- Failed or progressed on prior therapy **55.4%**
 - Trans-arterial therapy **17.5%**
 - Surgery/transplantation **14.6%**
 - Percutaneous ablative therapy **12.6%**
 - Chemotherapy **10.7%**

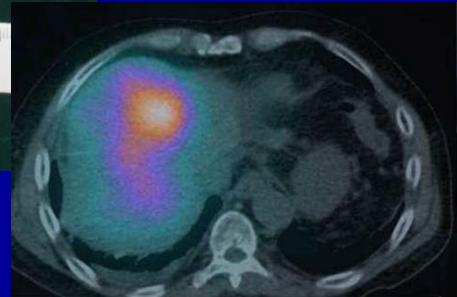
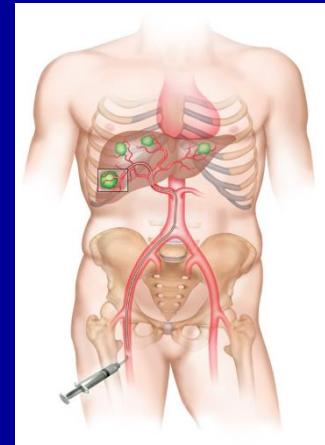
Down-
staging to
surgery
With
yttrium-90



CT July 09



CT Apr 10



Residual HCC 7 cm diameter (from 13 cm)

28

AHCC06 : SIRT versus Sorafenib in patients with locally advanced HCC SIRveNIB

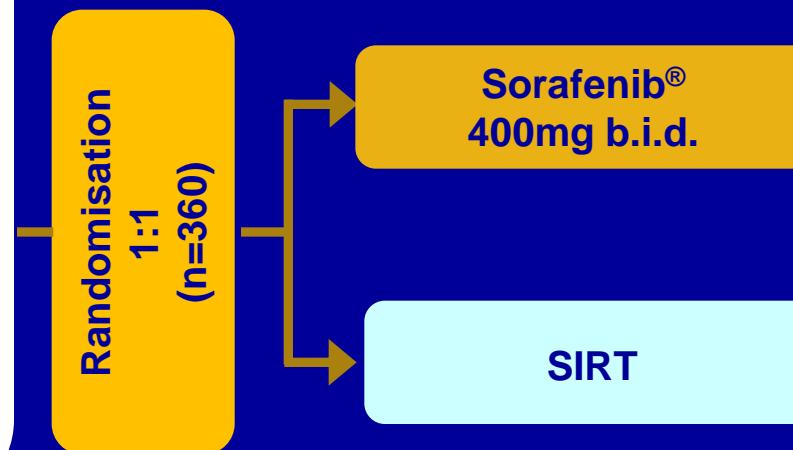
Asia-Pacific, Phase III, open-label, open-labelled study

Eligibility criteria

- Locally advanced HCC
- Child–Pugh <8 pts
- ECOG PS 0 – 1

Exclusion criteria

- Distant metastases
- Complete main portal vein thrombosis



Endpoints

Primary

- OS

Secondary

- TTP
- QoL
- Downstaging to curative therapies

ECOG PS = Eastern Cooperative Oncology Group Performance Status
OS = overall survival; TTP = time to tumour progression

Eligible: Previous surgery, RFA, TACE

Asia-Pacific HCC Trials Group 2015

SIRveNIB

Ulaan Baator

Yangon

Bangkok

Penang

Kuala Lumpur

Singapore

Jakarta

Bali

Seoul,
Bundang

Taipei
Hong Kong

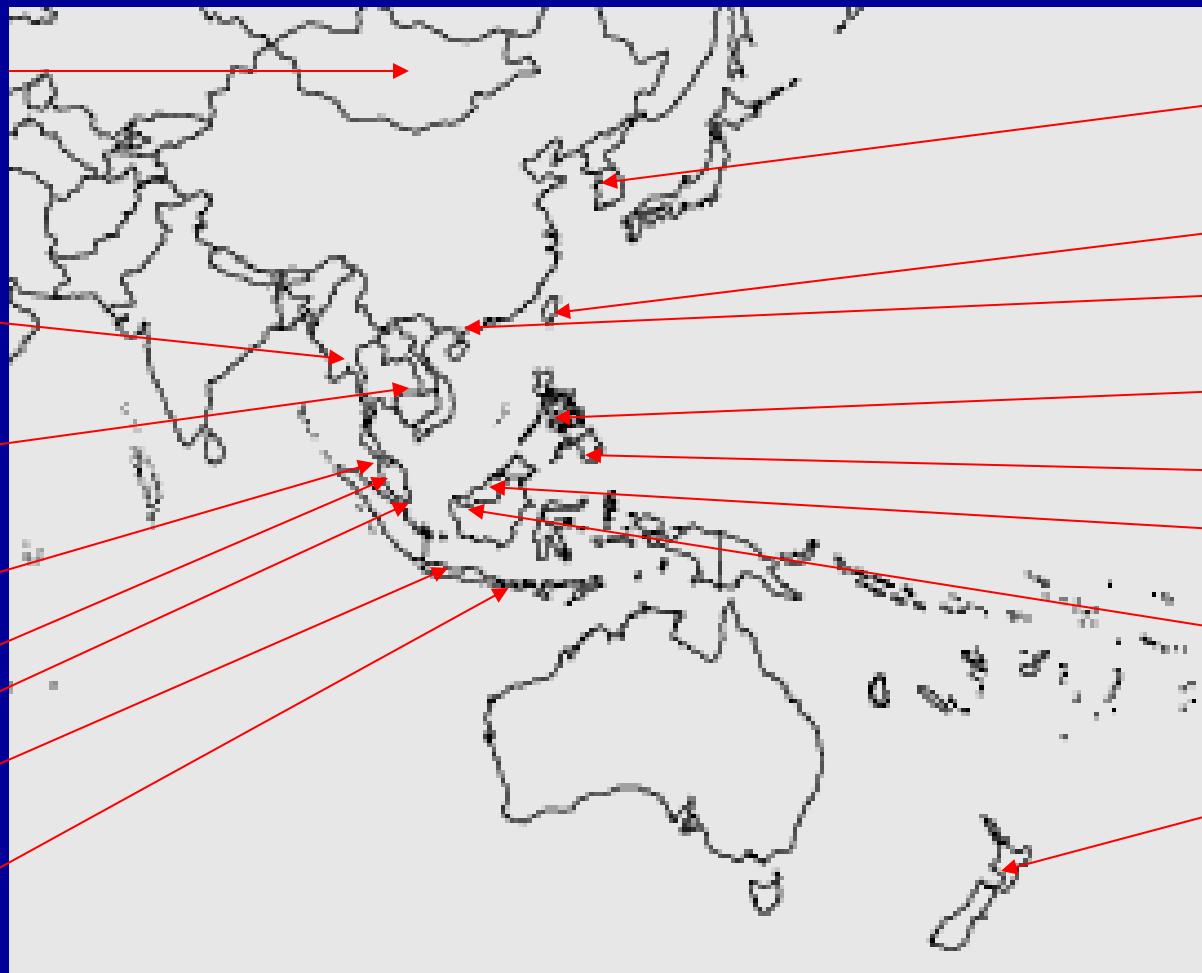
Manila

Davao

Brunei

Kuching

Auckland



28 centers 12 Countries

The SARAH Study

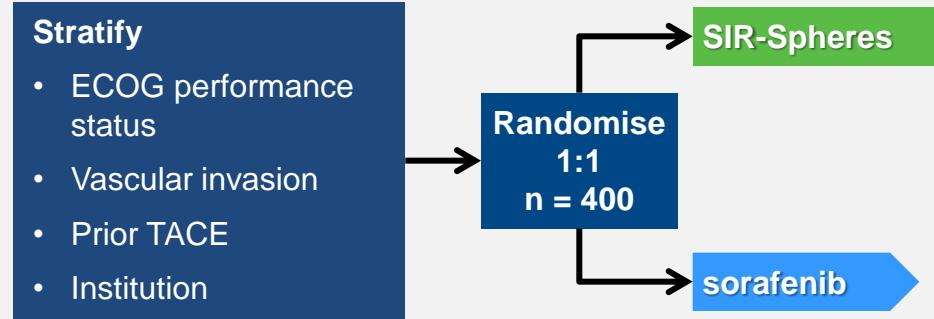
To determine whether radioembolisation with SIR-Spheres® microspheres is more effective on overall survival in advanced HCC than sorafenib

Design: Prospective open-label, multi-centre, national (France) RCT



Eligible Patients:

- Unresectable HCC
- BCCL stage C or
- BCCL stage A/B:
 - New lesions post-radical therapy and unsuitable for further radical therapy or
 - No objective response after ≤ 2 TACE sessions
- Child-Pugh class A or B ≤ 7 points
- ECOG performance status 0–1
- Fit for sorafenib and SIRT



Primary endpoint: Overall survival

Sponsor: Assistance Publique – Hôpitaux de Paris (AP-HP)

PI: Prof. Valérie Vilgrain

Status: Currently enrolling

Secondary endpoints: Safety and toxicity

Quality of life

Healthcare costs

Progression-free survival at 6 months

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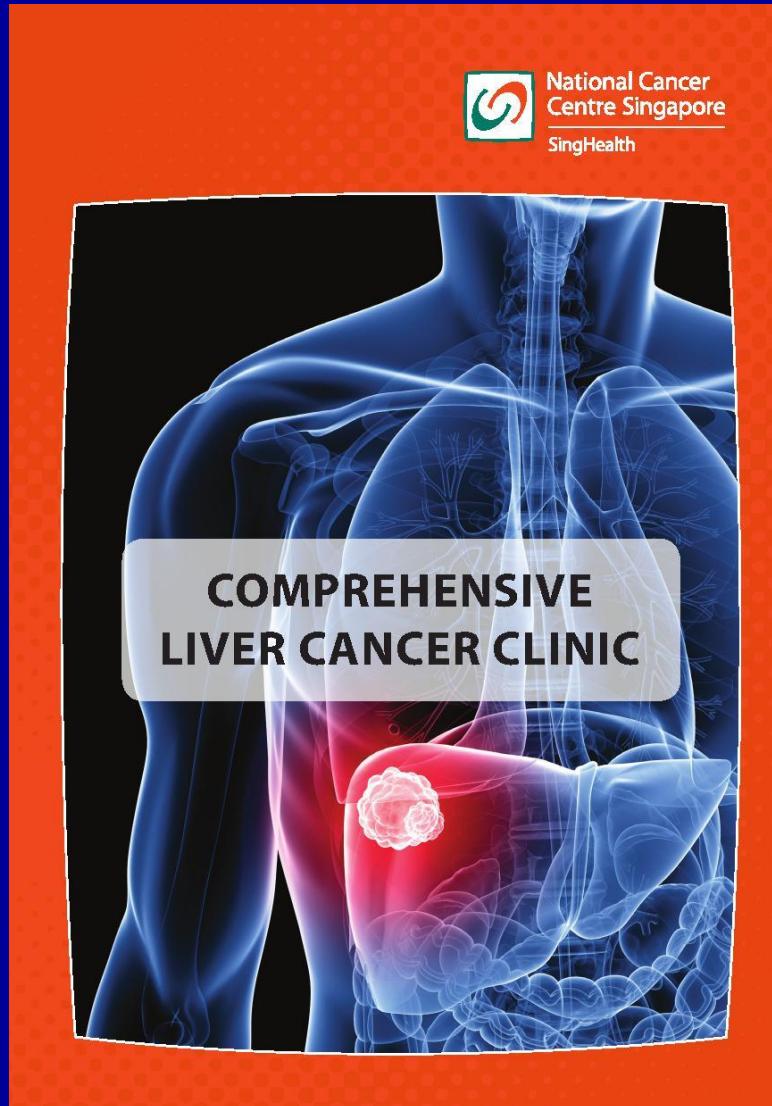


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Thank
You!

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