

► 4-6 September 2015

► Paris, France



ILCA 2015
9th Annual Conference

www.ilca2015.org

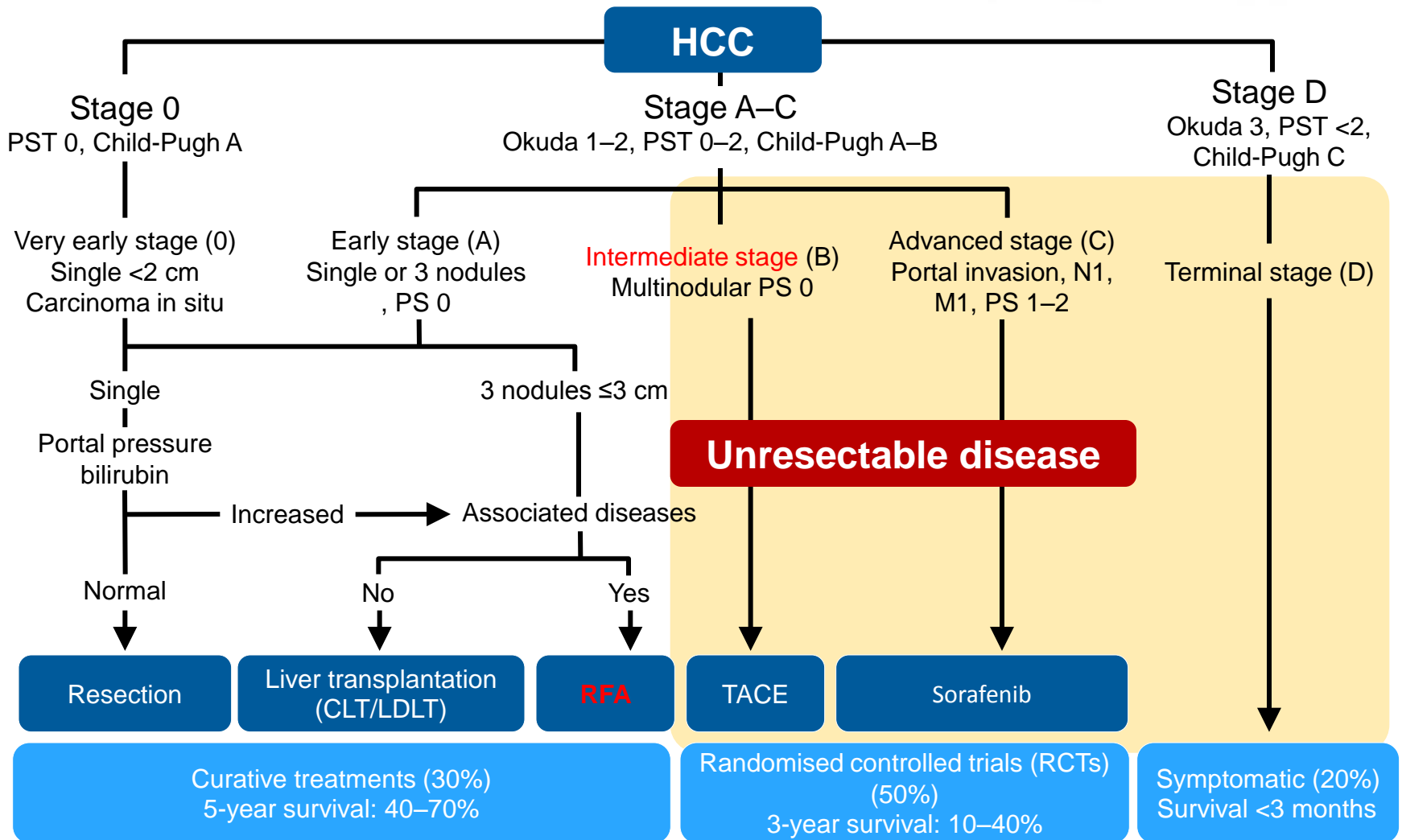
Celsion Symposium

Current Management of Intermediate HCC: Unmet Medical Needs

Prof. Ronnie T.P. Poon

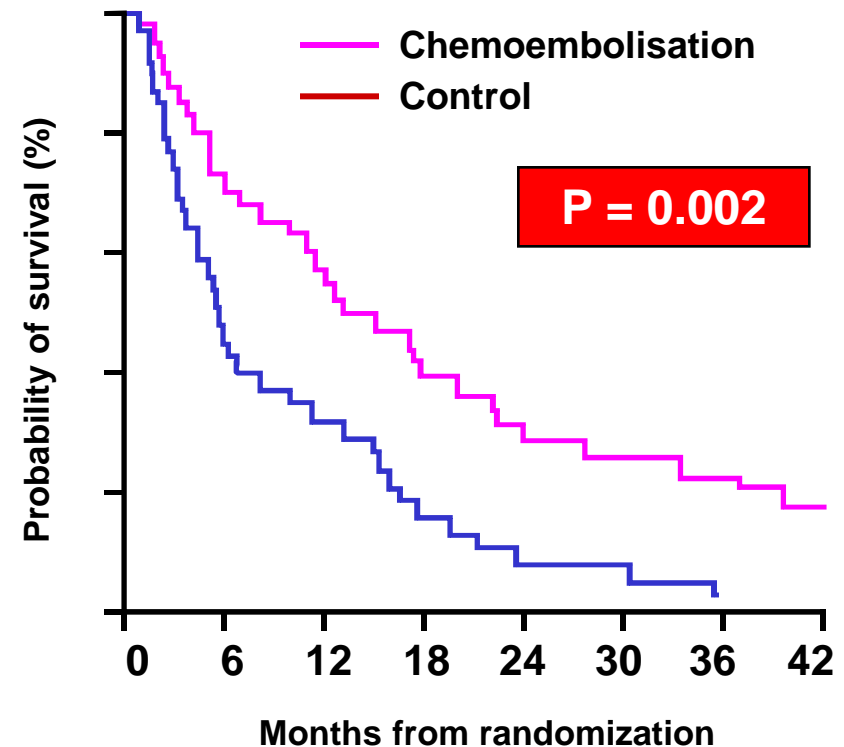
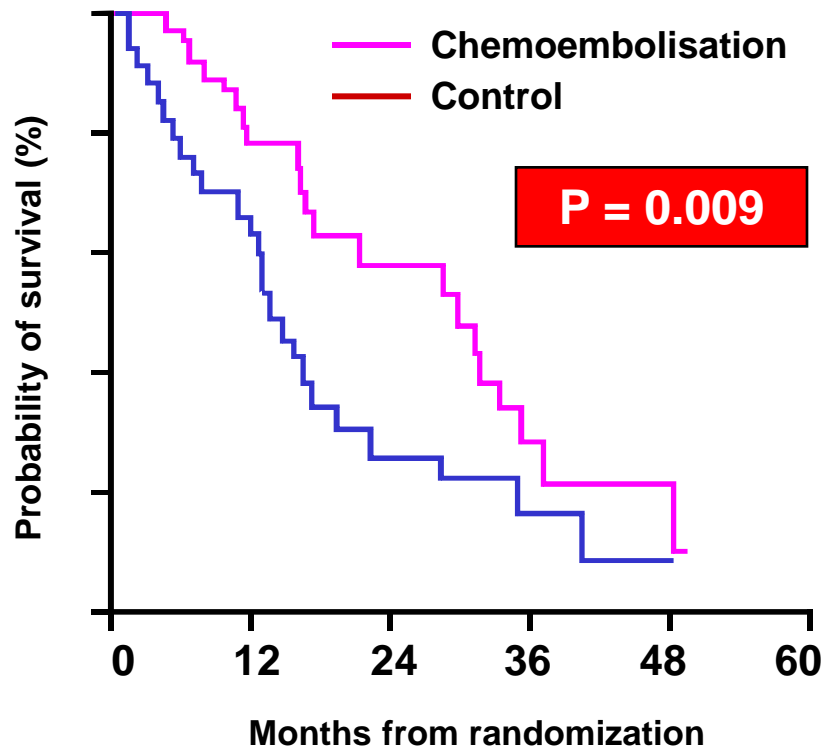
Department of Surgery, The University of Hong Kong

BCLC Staging and Treatment Algorithm



TACE for Intermediate HCC

- **Vascular invasion:** Barcelona: 0%; Hong Kong 27%
- **2-year OS of untreated group:** Barcelona: 27%; Hong-Kong 11%



TACE for HCC

Lipiodol-TACE with cisplatin or doxorubicin

484 patients (1989 - 1997)

- ◆ Response rate: 50%
- ◆ Morbidity: 23%
- ◆ TACE-related Mortality: 4%
- ◆ Survival: 1-yr 49%, 3-yr 23%, 5-yr 17%
- ◆ Adverse prognostic factors:
 - tumor size > 10 cm,
 - serum albumin < 35 g/L



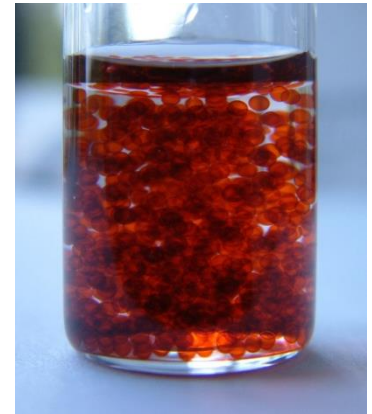
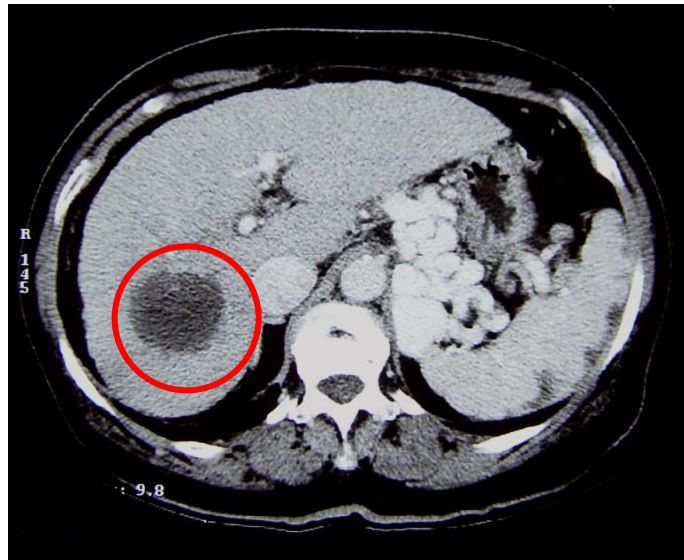
Poon et al. J Surg Oncol 2000

Unmet Needs in Intermediate Stage HCC

- Can we improve results of TACE by better technologies or combination with systemic therapy?
- Is cure possible for intermediate stage HCC by more aggressive treatments such as resection or ablation?

TACE with Drug-Eluting Beads – Is It a Significant Improvement?

Phase ½ trial of doxorubicin eluting for HCC:



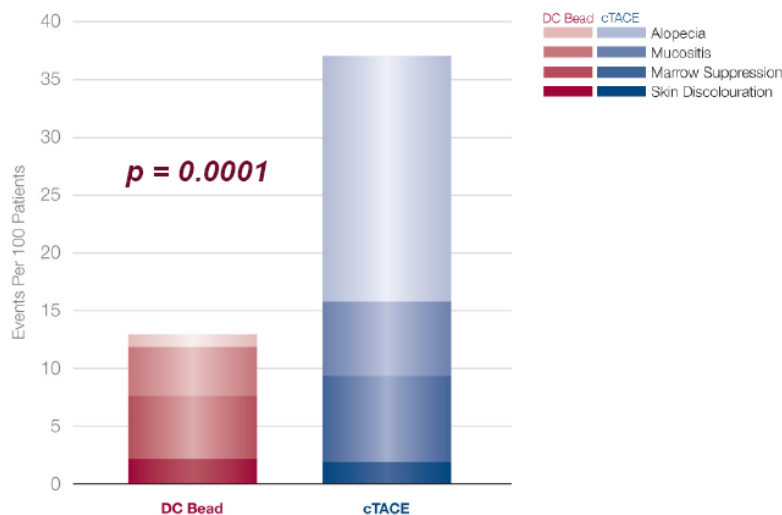
Objective response rate 70% by modified RECIST criteria

Poon et al. Clin Gastroenterol & Hepatol 2007

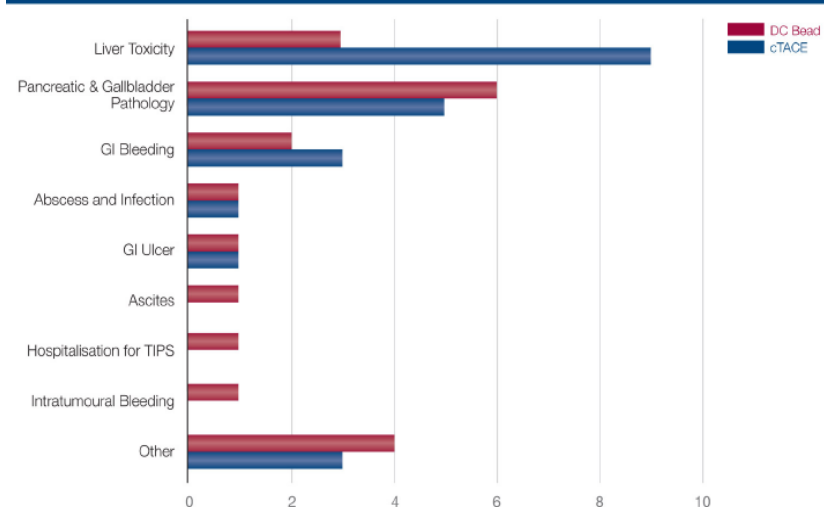
Randomized Controlled Trial of DEB-TACE vs. cTACE

European multi-centre randomized trial to compare safety and efficacy of doxorubicin-eluting bead with conventional TACE using Lipiodol-doxorubicin (100 patients in each arm)

Doxorubicin-Related Side Effects

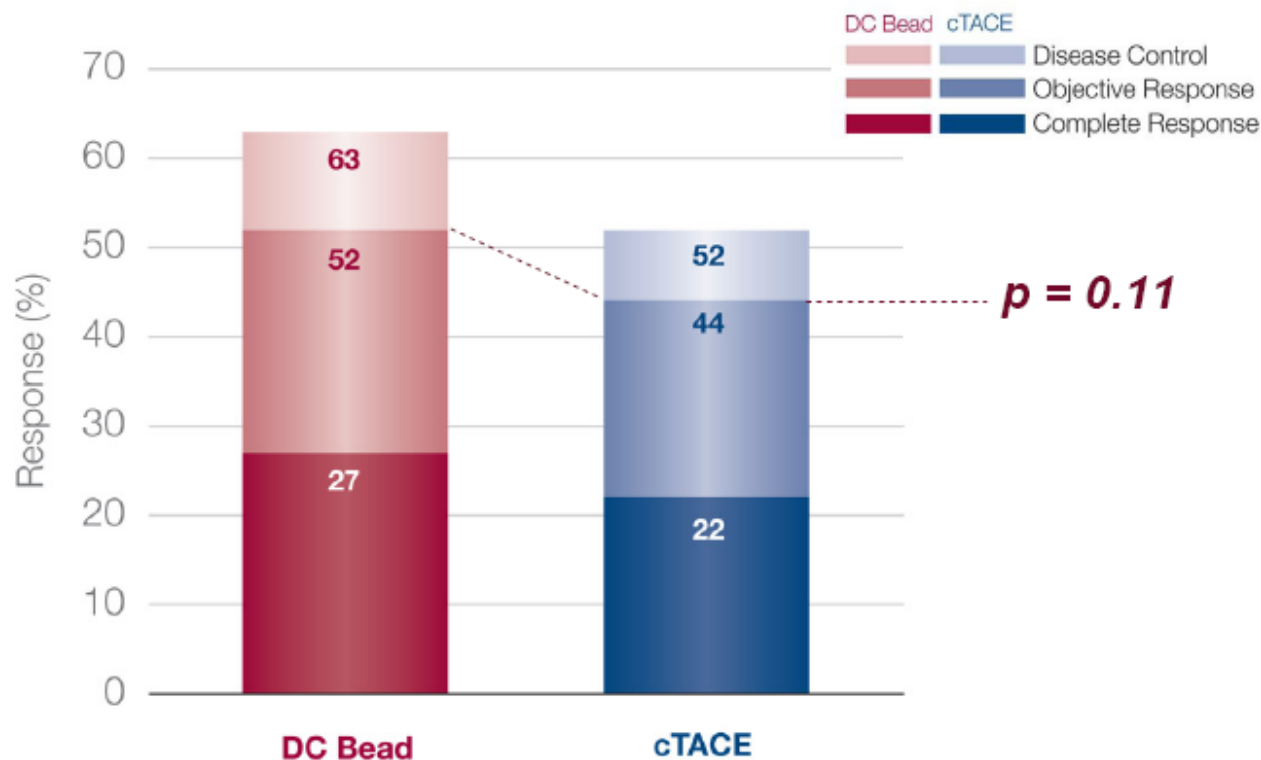


Gastrointestinal and Liver Serious Adverse Events (SAEs)



Malagari et al. Cardiovasc Intervent Radiol 2010

Overall 6-Month Tumour Response Rates

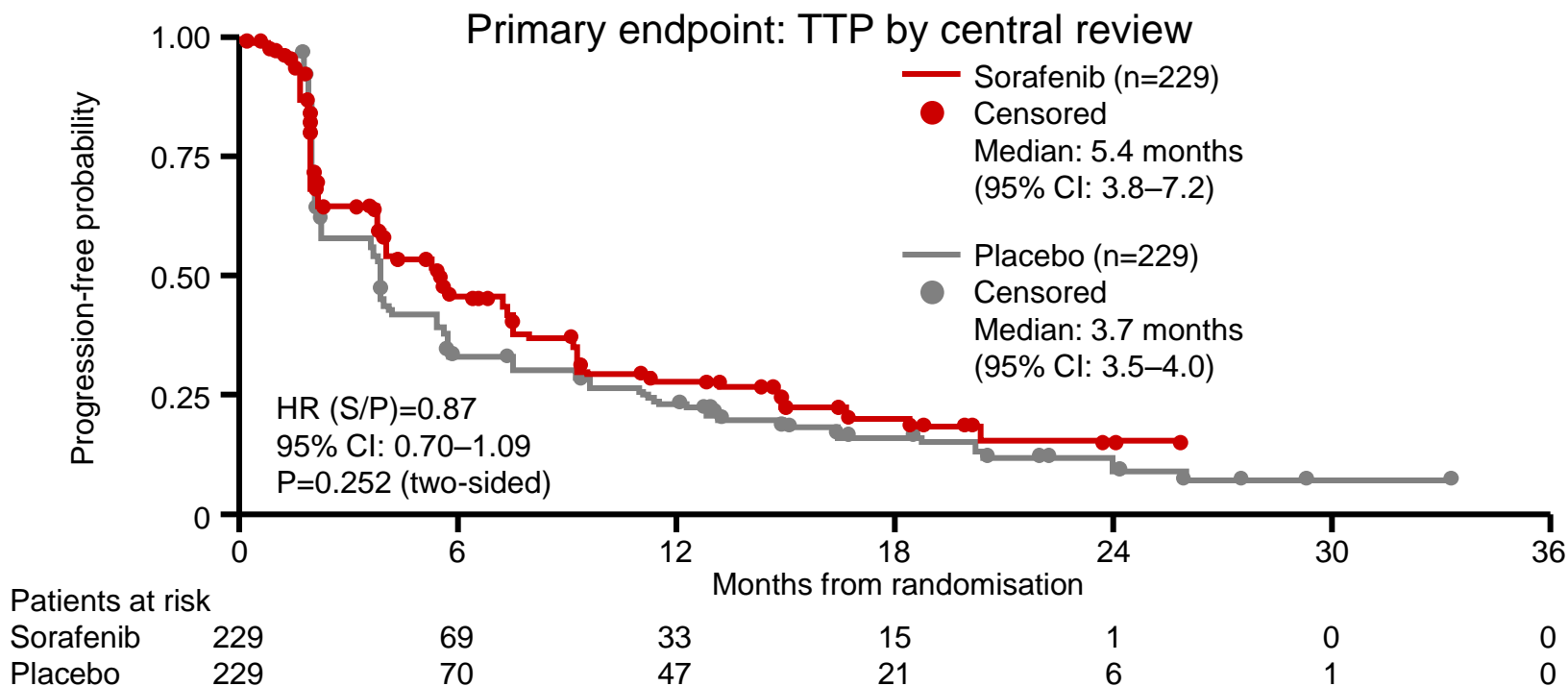


Disease Control = Objective Response + Stable Disease

Objective Response = Complete Response + Partial Response

No significant difference in objective response rate

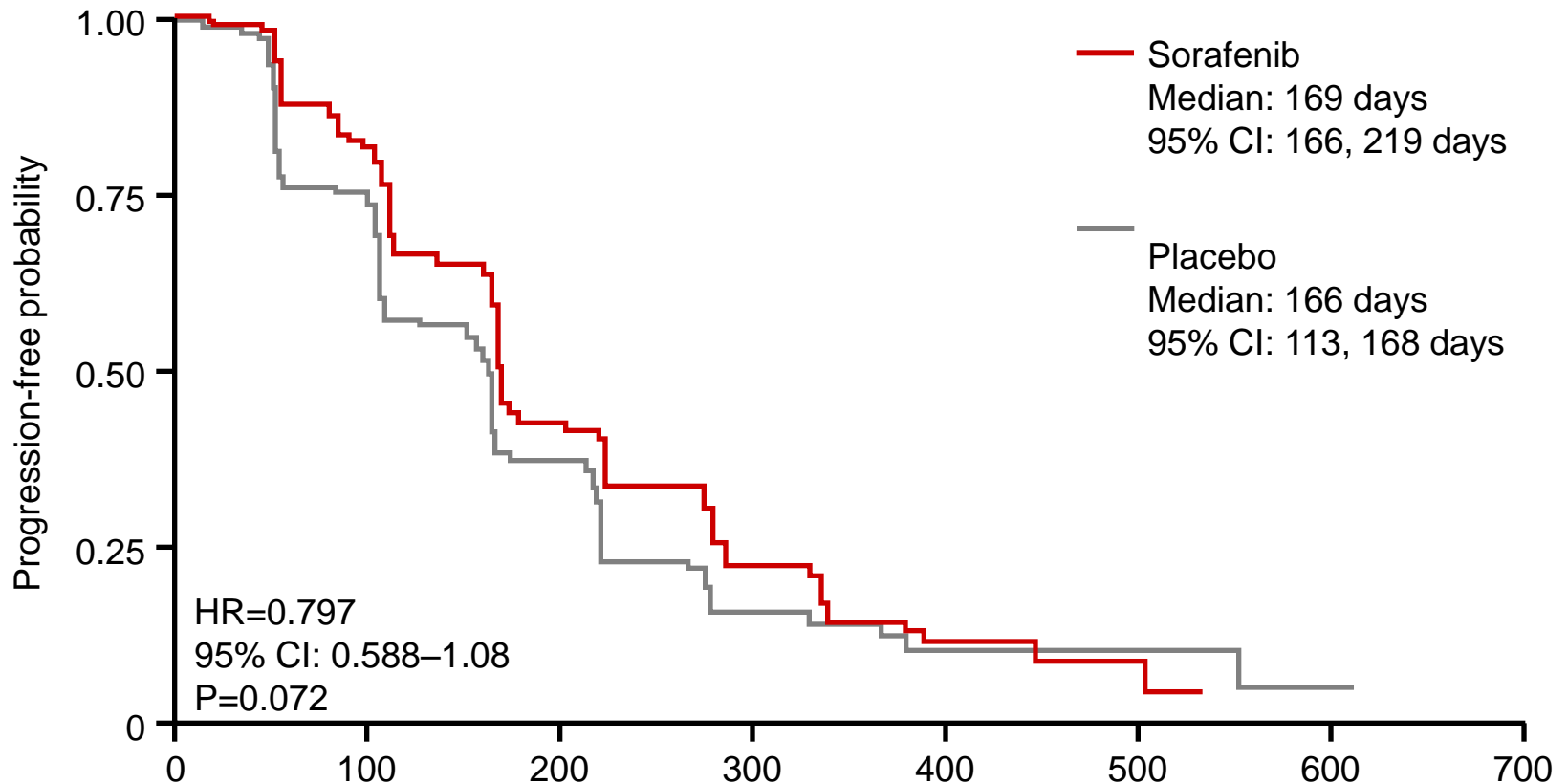
Combining TACE with Sorafenib



Outcome, median months	Sorafenib (n=229)	Placebo (n=229)	HR (P)
TTP by central review ^a	5.4	3.7	0.87 (0.252)
TTP by investigator ^b	7.2	5.3	0.79 (0.049)
OS	29.7	Not reached	1.06 (0.790)

^aPrimary endpoint; ^bExploratory analysis
CI = confidence interval; HR = hazard ratio

SPACE Trial (Concurrent Sorafenib + TACE)



Patients at risk

Sorafenib 154

86

33

10

5

2

0

Placebo 153

91

33

12

5

4

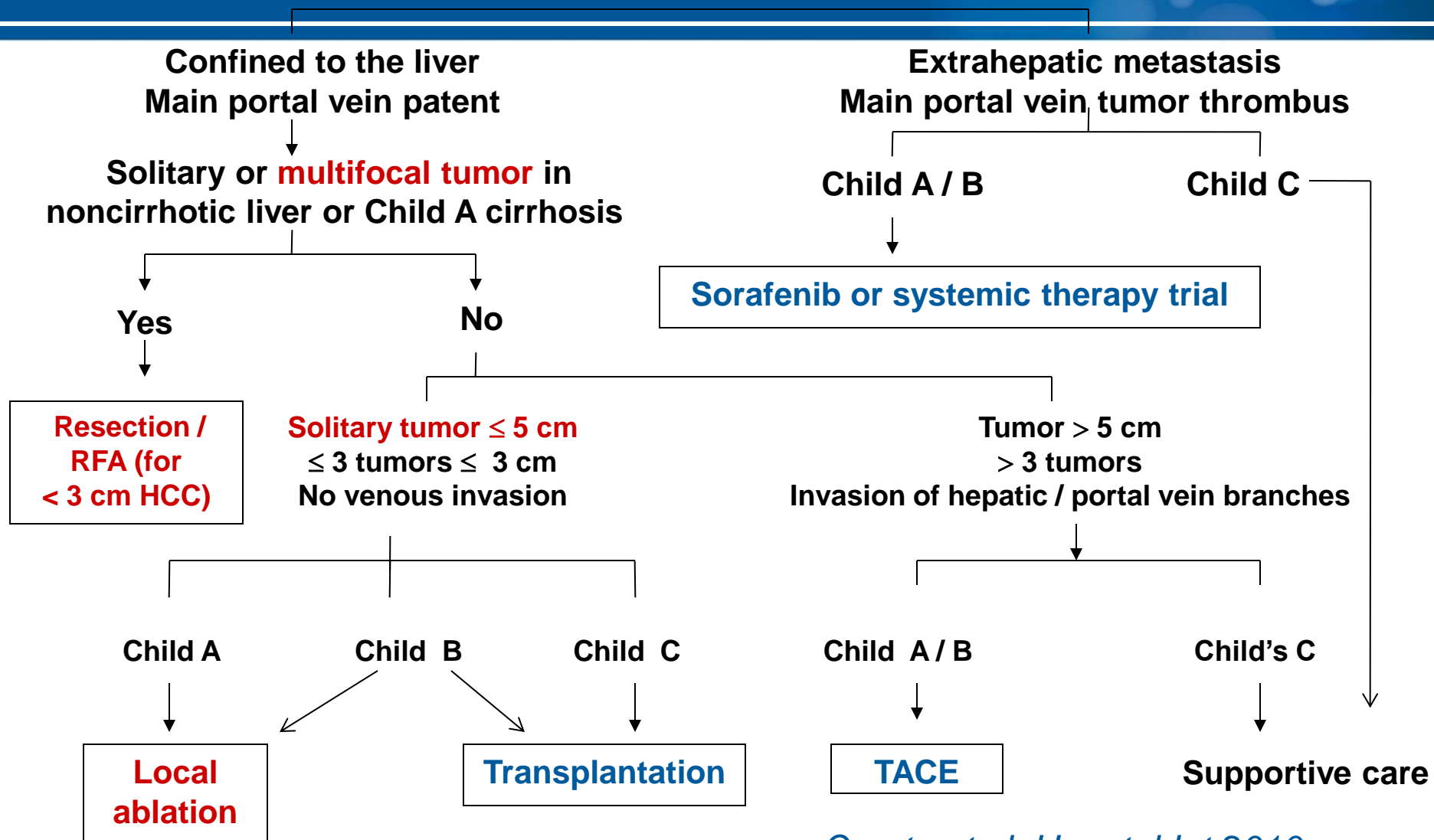
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BCLC is Conservative in Treatment Recommendation for Intermediate Stage HCC

Many clinicians especially in the East consider that:

- Role of surgical resection can be extended to intermediate HCC
- Role of ablation can be extended to larger tumors > 3 cm, or even > 5 cm

APASL Consensus on Treatment of HCC



Omata et al. Hepatol Int 2010

Hong Kong Liver Cancer Staging System with Treatment Stratification for HCC

Prospectively collected data (2026 variables covering demographic, clinical, laboratory, treatment, and survival data) from **3856** patients with HCC (predominantly HBV-related) treated at Queen Mary Hospital from 1995- 2008

Cox regression was used to account for the relative effects of factors in predicting overall survival times

Classification and regression tree (CART) analyses were used to classify disparate treatment decision rules

All patients were allocated randomly into a training set or a test set in 1:1 ratio

Gastroenterology

www.gastrojournal.org

Volume 146 Number 7 June 2014



1659 Sodium Channel Mutation in Patients With IBS

1680 Risk of β Blockers in Patients With Cirrhosis and SBP

1714 Long Intervening Noncoding RNA *POU3F3* in Esophageal Cancer

1763 Effect of Lactate in Experimental Hepatitis and Pancreatitis

ALSO:

- Reviews: Gut Tissue Engineering **1614** & Disorders of Bilirubin Metabolism **1625**
- 2014 Julius M. Friedenwald Medal Awardee—Nicholas F. LaRusso, MD **1813**



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Yau et al. Gastroenterology 2014

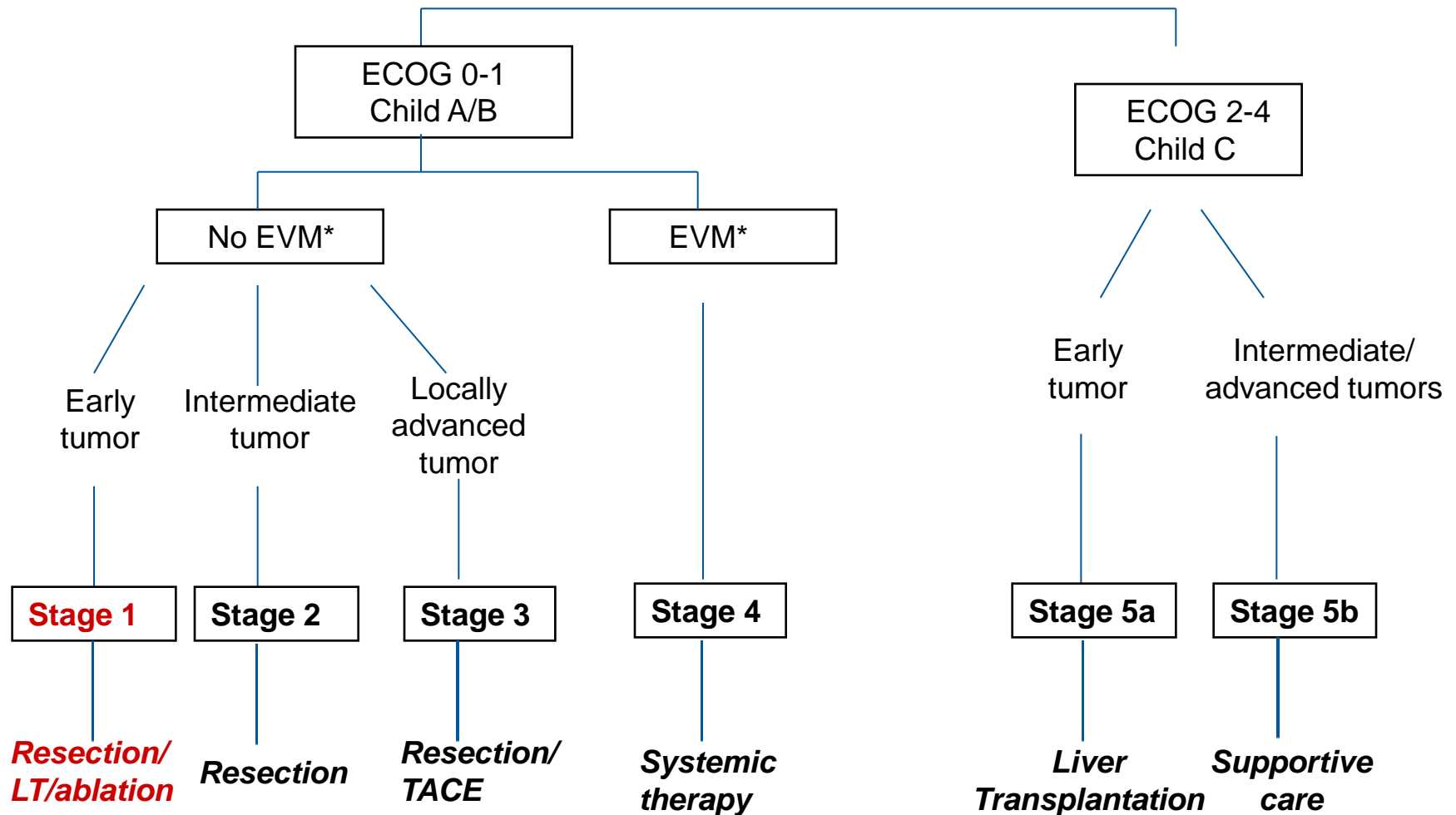
Hong Kong Liver Cancer Staging System

- Tumors in the liver classified into early, intermediate and advanced based on 0, 1 or ≥ 2 adverse prognostic factors :

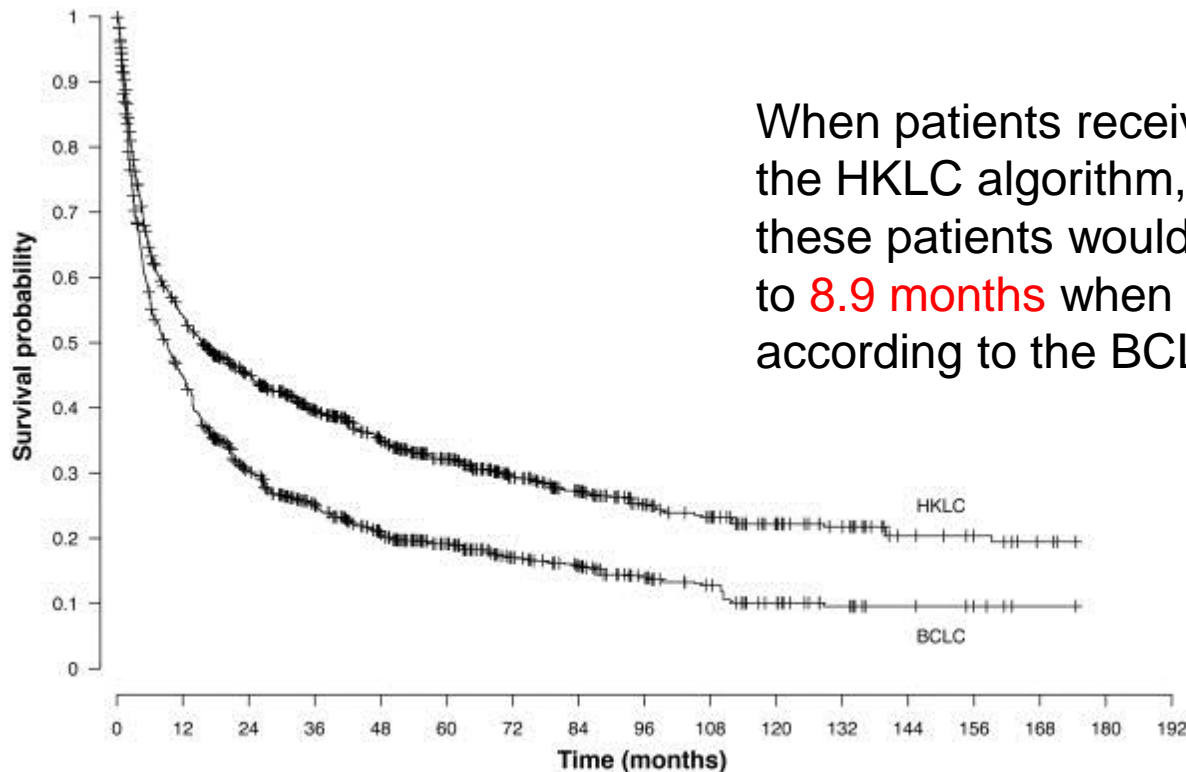
Liver tumor status	Size	Number of nodules	Intrahepatic Venous Invasion
Early	≤ 5 cm	≤ 3	No
Intermediate	≤ 5 cm	≤ 3	Yes
	≤ 5 cm	> 3	No
	> 5 cm	≤ 3	No
Locally-advanced	≤ 5 cm	> 3	Yes
	> 5 cm	≤ 3	Yes
	> 5 cm	> 3	Any
	Diffuse	Any	Any

Hong Kong Liver Cancer Staging System

HCC



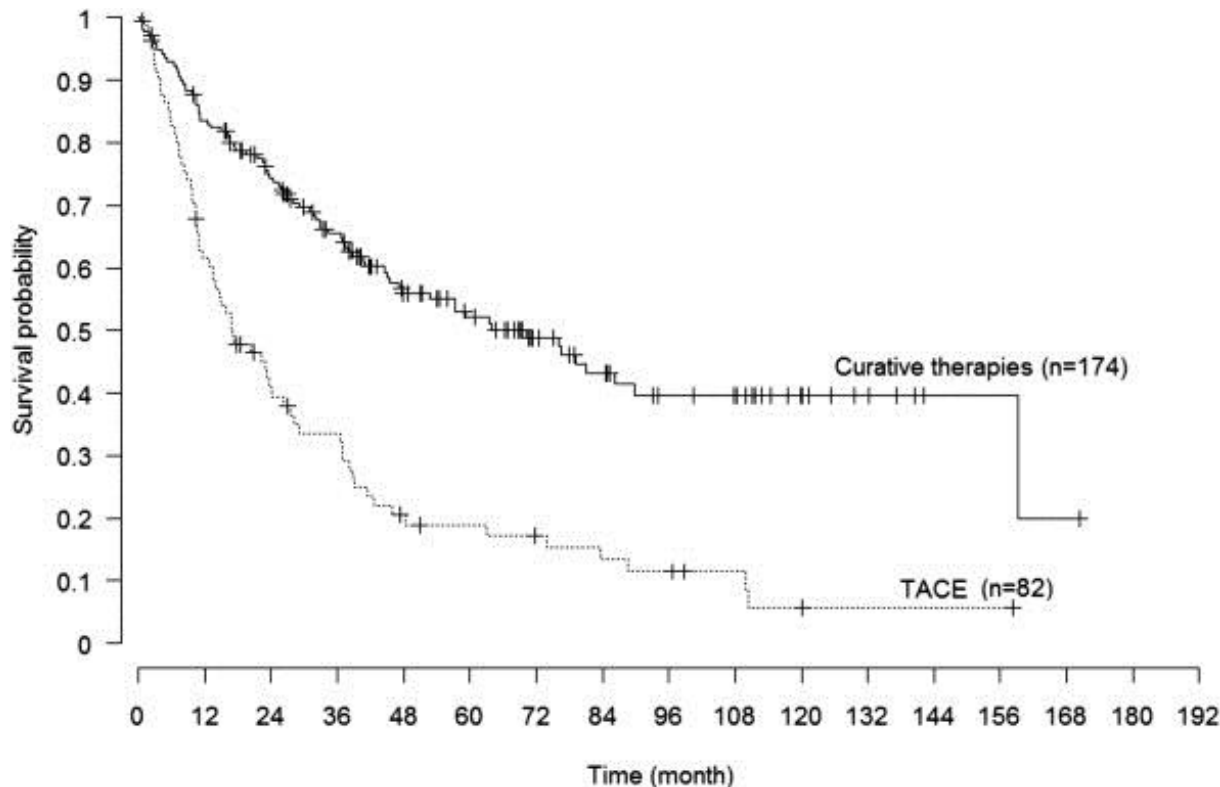
Comparison of HKLC and BCLC Staging System



When patients received treatment according to the HKLC algorithm, the median OS time of these patients would be **16.6 months**, in contrast to **8.9 months** when they received treatment according to the BCLC algorithm

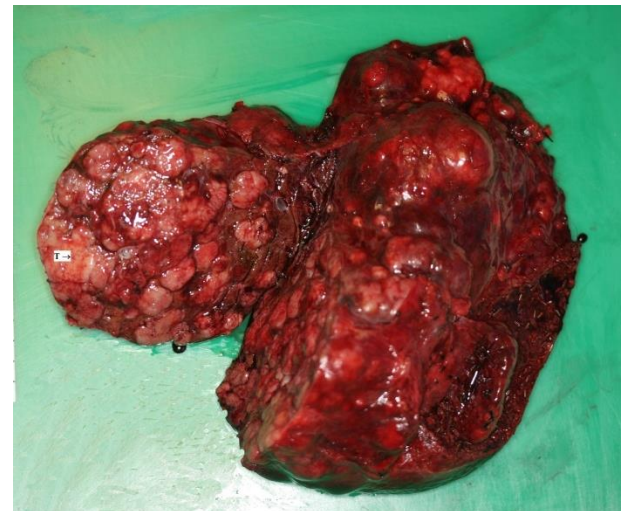
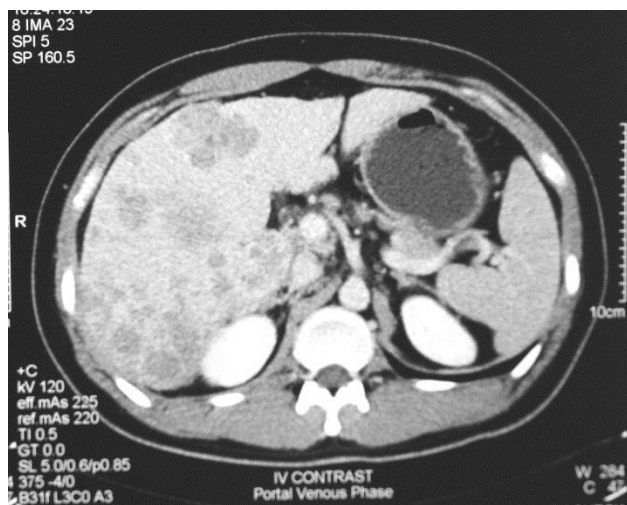
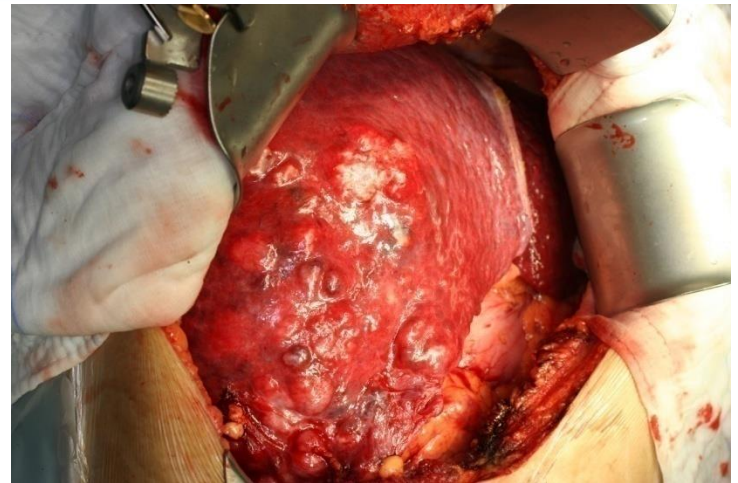
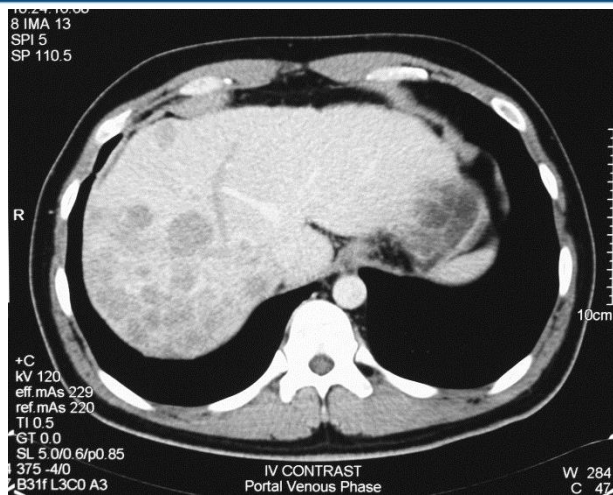
Hypothetical Kaplan–Meier estimated overall survival curves of the HKLC scheme and the BCLC scheme. The survival data of patients who were not treated with HKLC-recommended treatments were substituted by a random draw from the group of patients who had a similar prognosis and were treated according to HKLC recommendations. The BCLC curve was created in a similar way.

Comparison of HKLC and BCLC Staging System

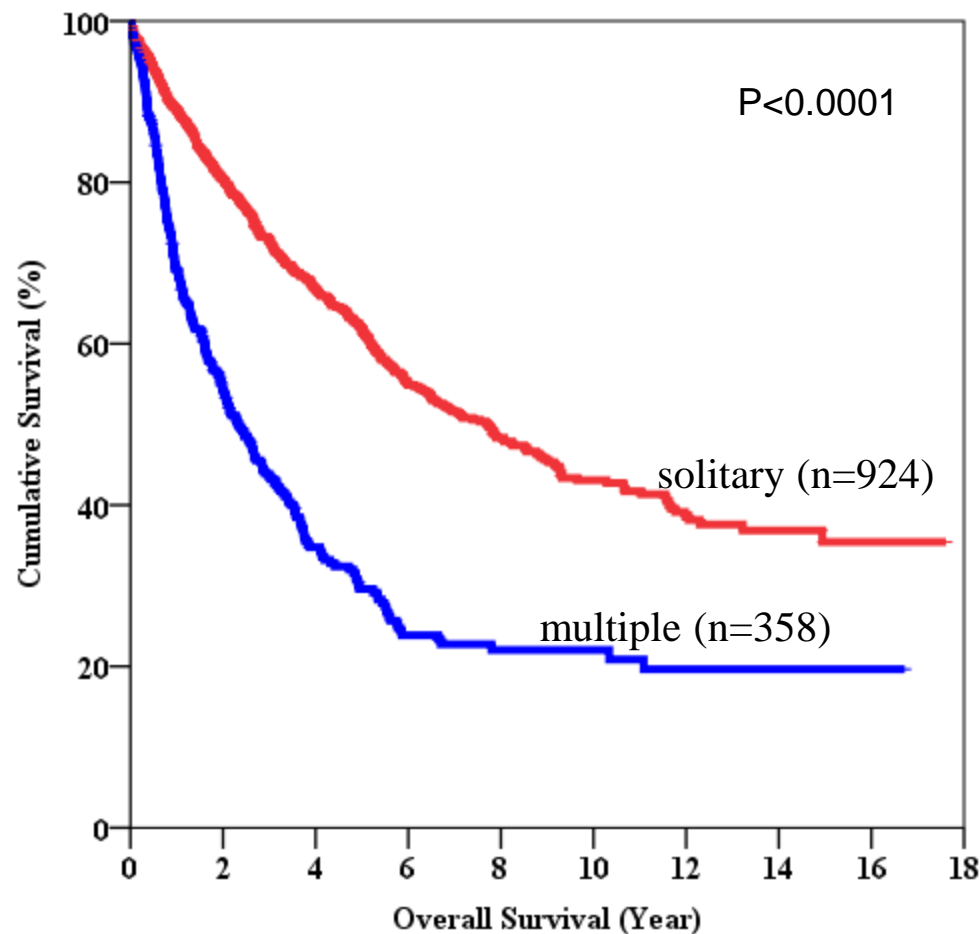


Of BCLC-B patients classified as HKLC-II, the survival benefit of radical therapies (*resection or RFA*), compared with TACE, was substantial (5-year survival, **52.1% vs 18.7%**; $P < .0001$)

Resection for Multifocal HCC



Survival of Patients with Multiple Tumors – QMH Experience 2000-2011



	Solitary (n=924)	Multiple (n=358)	P-value
Overall Survival Median (mths)	92.6	28.0	<0.001
1-year	89%	69%	
3-year	73%	44%	
5-year	62%	32%	

5-yr disease-free survival after
resection of multifocal HCC **21%**

Resection for BCLC Stage B HCC

- An East-West Multicenter Study

2046 patients with HCC resection studied: 746 (36%) from the 3 Asian centers; 307 (15%) from the 3 American centers; and 993 (49%) from the 4 European centers

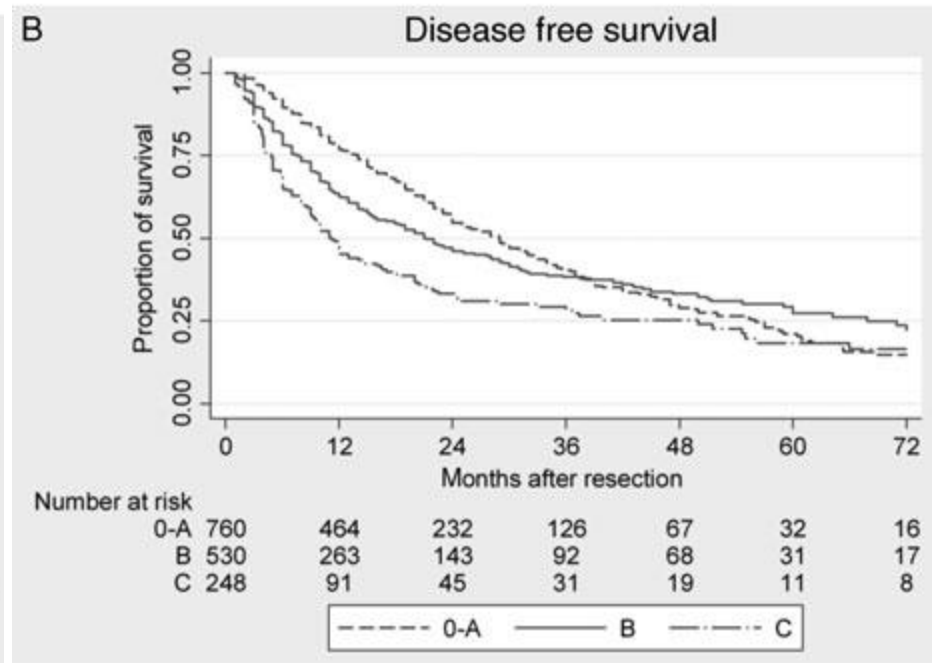
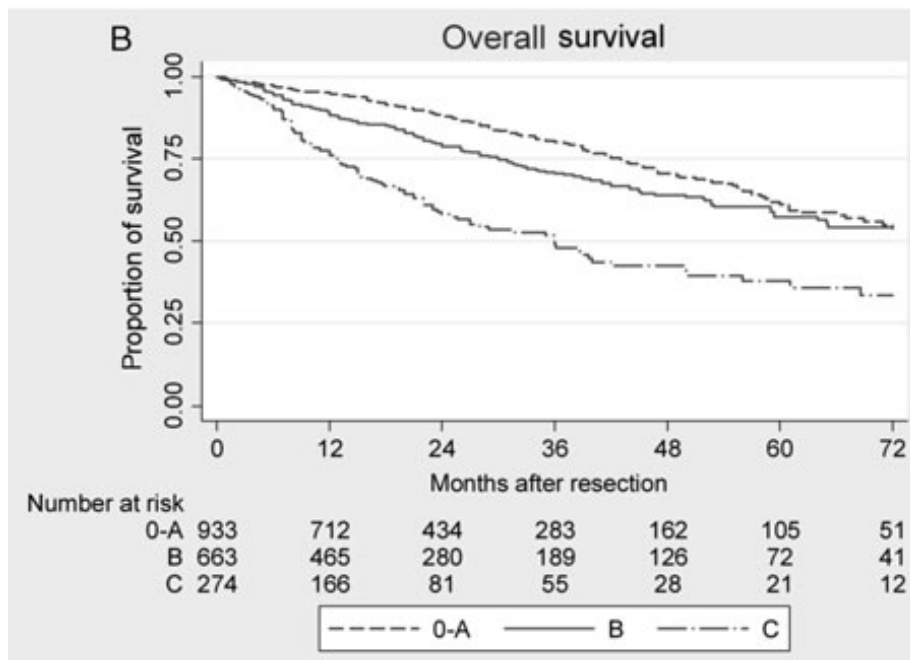
- 1012 (50%) were BCLC 0-A (451 from the eastern centers and 561 from the western centers), 737 (36%)* **BCLC B** (226 from the eastern centers and 511 from the western centers), and 297 (14%) BCLC C (69 from the eastern centers and 228 from the western centers)

Torzilli et al. Ann Surg 2014

Survival after Resection by BCLC classification

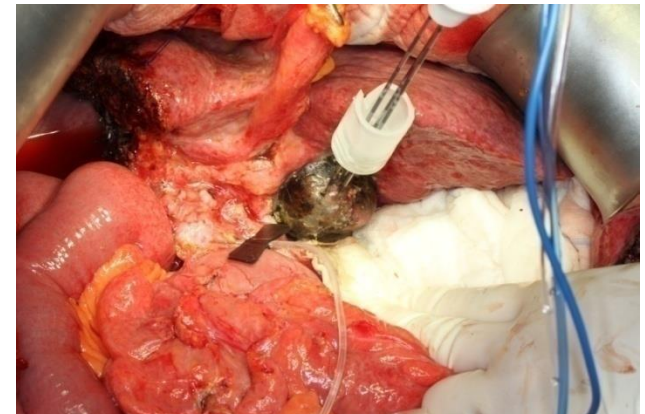
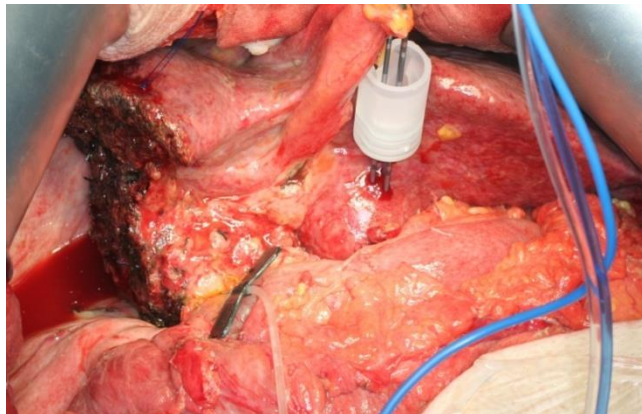
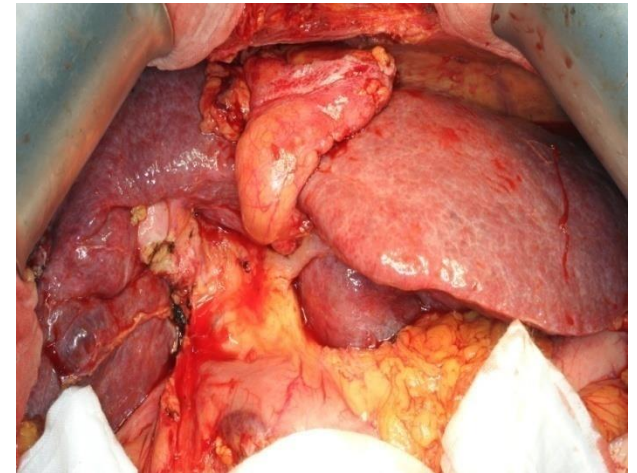
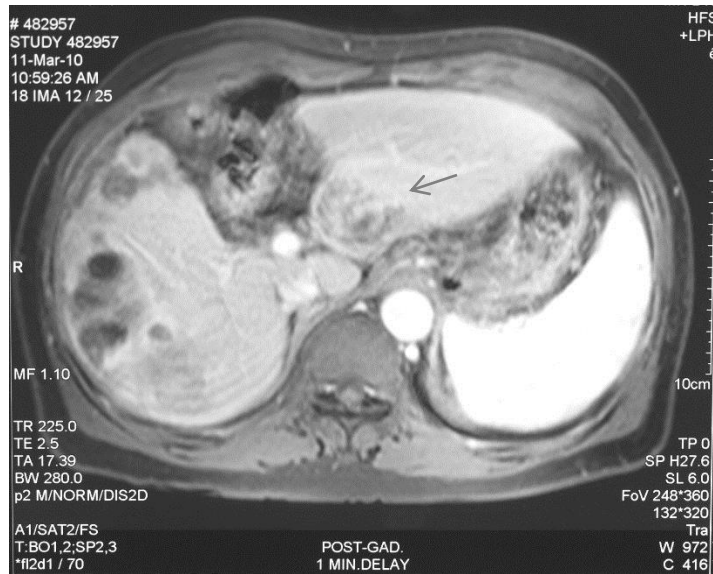
Overall operative mortality 2.3% (BCLC A 1.6%, B 3.1% and C 2.5%)

Overall 5-yr survival 56% (BCLC A 61%, **B 57%** and C 38%)



5-yr disease-free survival: BCLC A 31%, **B 27%**, C 18%)

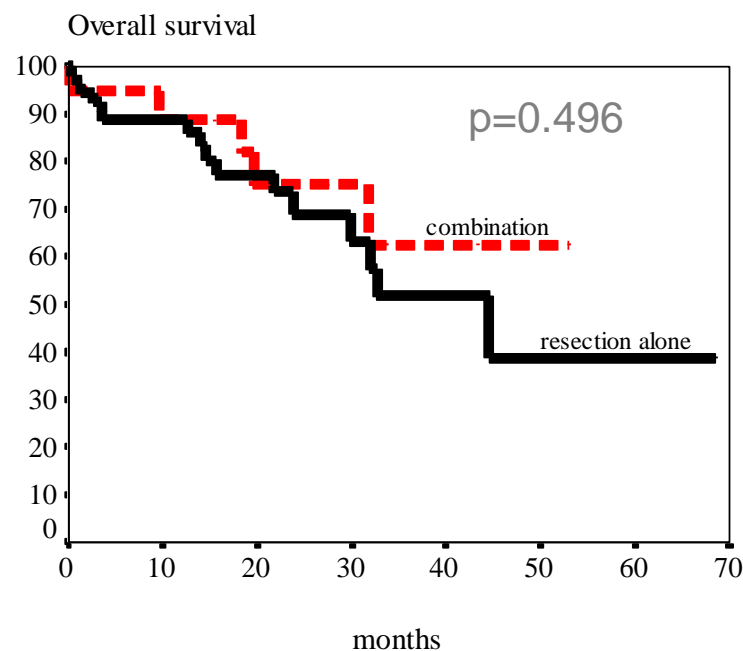
Combined Resection and Ablation



Overall Survival Results

Combined treatment vs.
resection alone

- No hospital mortality in both groups
- Median survival:
53.0 vs. 44.5 months



Long-term Results of RFA for HCC

Study	No. of patients	Mean /Median FU (m)	Recurrence rate	5-year survival	5-year disease-free survival
Rossi 1996	39	22.6	41%	40%	NA
Lencioni 2005	187	24	50%	48%	NA
Machi 2005	65	24.8	57%	40%	28%
Cabassa 2006	59	24.1	58%	43%	17% (3-year)
Choi 2007	570	30.7	52%	58%	NA
Ng 2008	207	26	81%	42%	28%

Local Recurrence after RFA for HCC

- Incomplete necrosis of tumor cells in ablated lesion
 - Complete necrosis only in 29 of 38 (83%) tumors ablated by RFA followed by liver transplantation based on histological examination of explants
- Lu et al. Radiology 2005
- Untreated microsatellite nodules adjacent to tumor
 - Risk factors of local recurrence by meta-analysis of 5224 liver tumors treated by RFA from 95 series in the literature:
 - tumor size > 3 cm ($p < 0.001$)
 - percutaneous vs. surgical approach ($p < 0.001$)

Mulier et al. Ann Surg 2005

Role of RFA for Large HCC > 5 cm

- Percutaneous RFA for HCC > 5 cm:

Complete ablation rate < 50%

(compared with 90% for HCC < 3 cm)

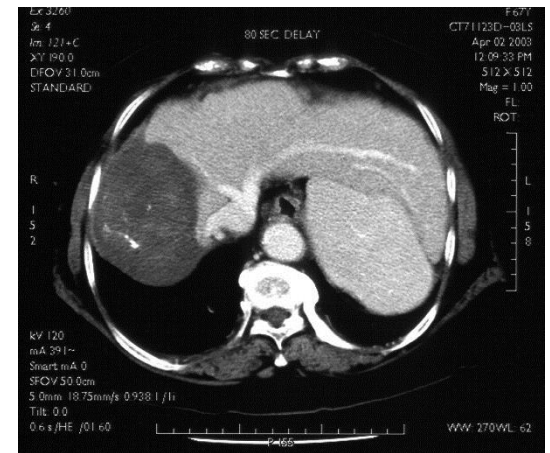
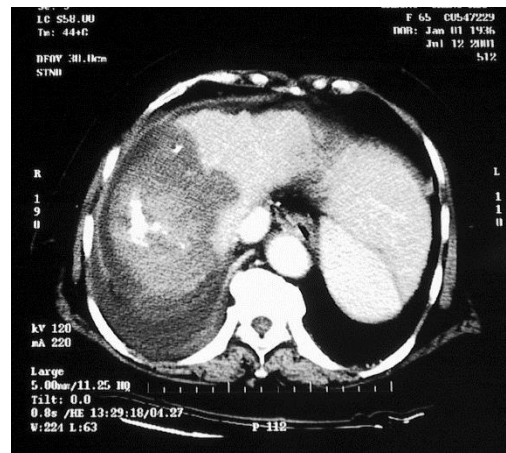
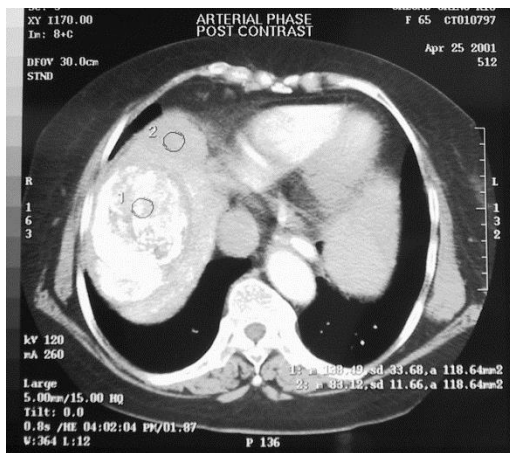
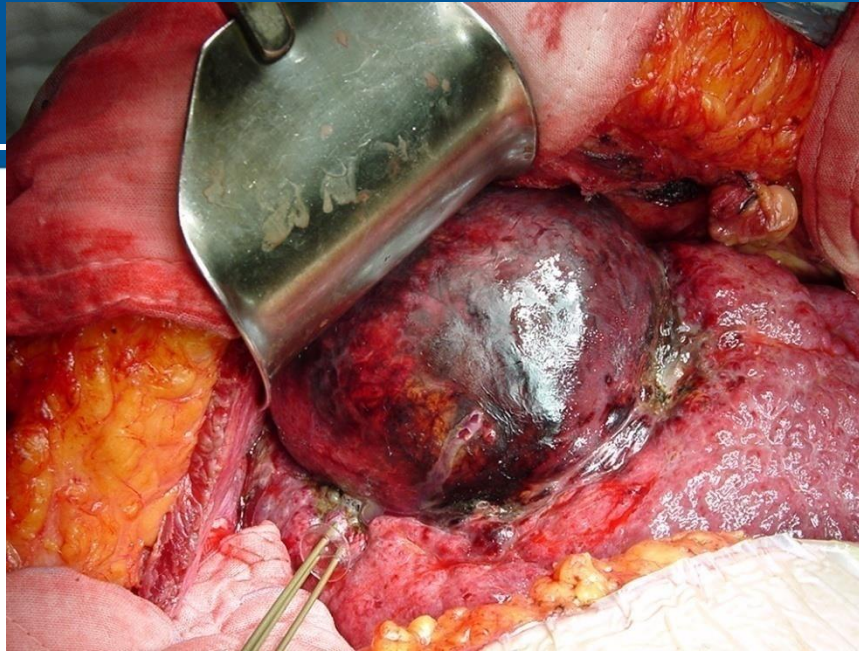
Livraghi et al, Radiology 2000

Guglielmi et al, Hepatogastroenterology 2003

- Open RFA for HCC > 5 cm:

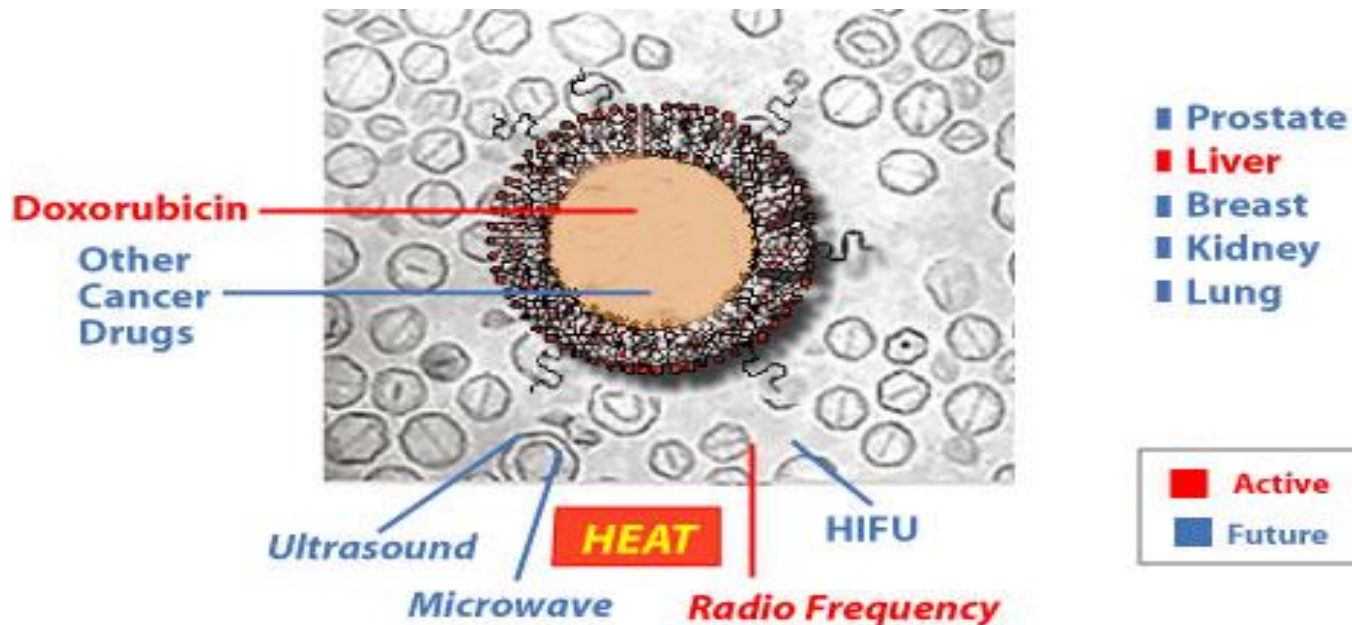
Complete ablation rate 83% (vs. 96% for HCC < 3 cm)

Poon et al, Arch Surg 2004



Reducing Recurrence after RFA

- ThermoDox® (doxorubicin encapsulated in heat-activated liposome)



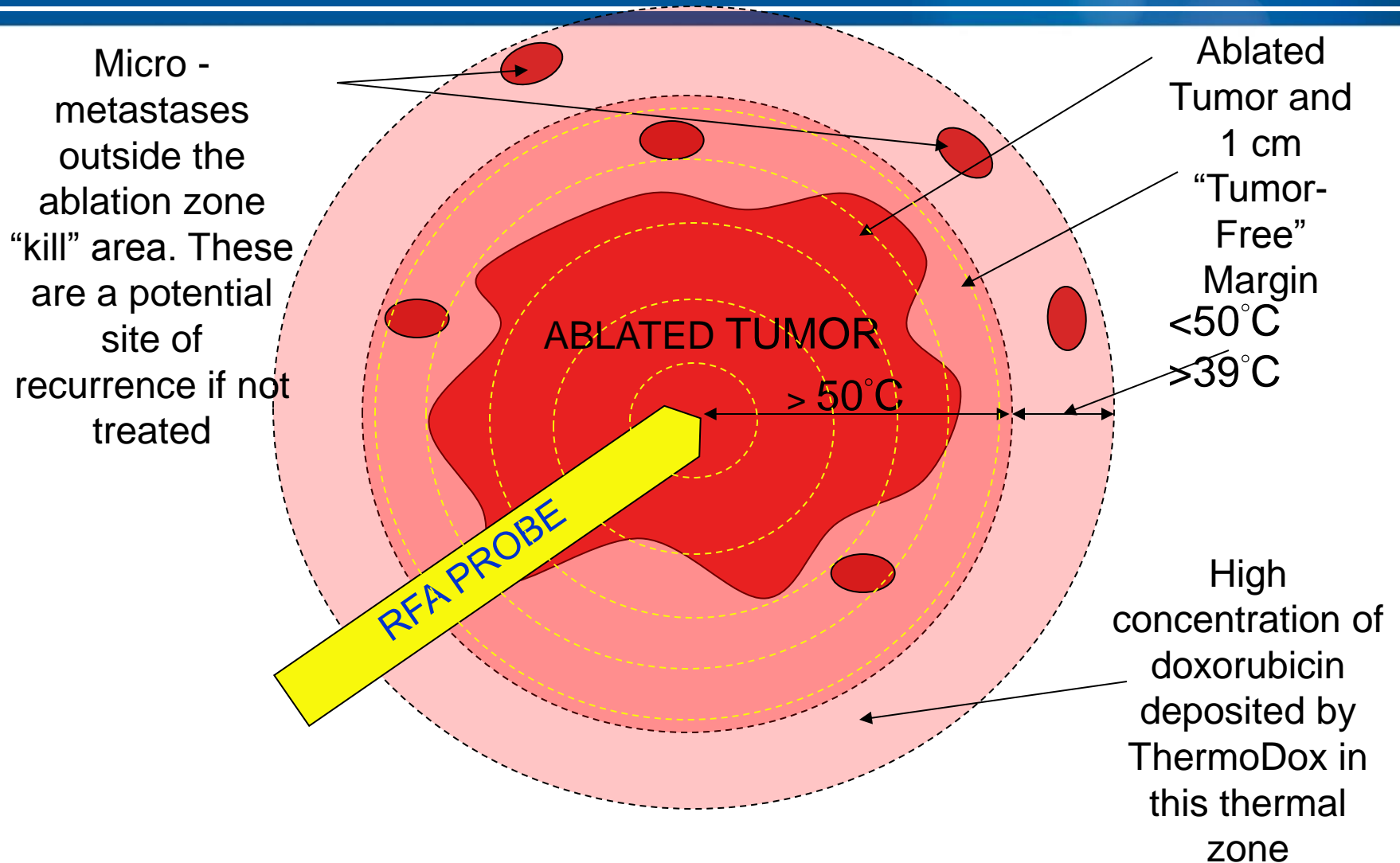
Mode of Action for ThermoDox

- Local tissue concentration $\approx 10\times$ that of standard free doxorubicin, higher cancer cytotoxicity and reduced systemic toxicity
- Direct toxicity to tumor vasculature

Synergistic effects

- Cytotoxic effect enhanced by heat (doxorubicin binding to tumor DNA)
- Reduction of ablation threshold temperature – enhanced lesion size

RF Ablation / ThermoDox Combination



Phase I Study of Thermodox at NCI (USA) and QMH (HK)

- A total of 24 patients were treated (3, 6, 6, 6, 3 patients at doses of 20, 30, 40, 50 and 60 mg/m², respectively)
- Median tumor size 3.7 cm (range 1.7-6.5 cm), and totally 28 tumors treated
- The MTD was determined in this study as 50 mg/m²
- No severe adverse events (grade 1 alopecia, transient neutropenis)
- Complete ablation rate 88%; enlarged ablation zone

Brad & Poon, Clin Cancer Res 2010

Phase III Randomized Blinded Trial - HEAT

Eligibility:

- non-resectable HCC
- no more than 4 lesions
- at least 1 lesion ≥ 3 cm and none > 7 cm
- no previous treatment
- Child-Pugh A or B

Stratification

- lesion size: 3-5 vs $>5-7$ cm and RFA technique:
 - open surgical
 - laparoscopic or
 - percutaneous

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1 : 1

n= 350

ThermoDox[®]
plus RFA

n= 350

RFA alone

End Points:

Primary: PFS (Progression Free Survival)

designed to show a 33% improvement in PFS with 80% power and a p-value = 0.05

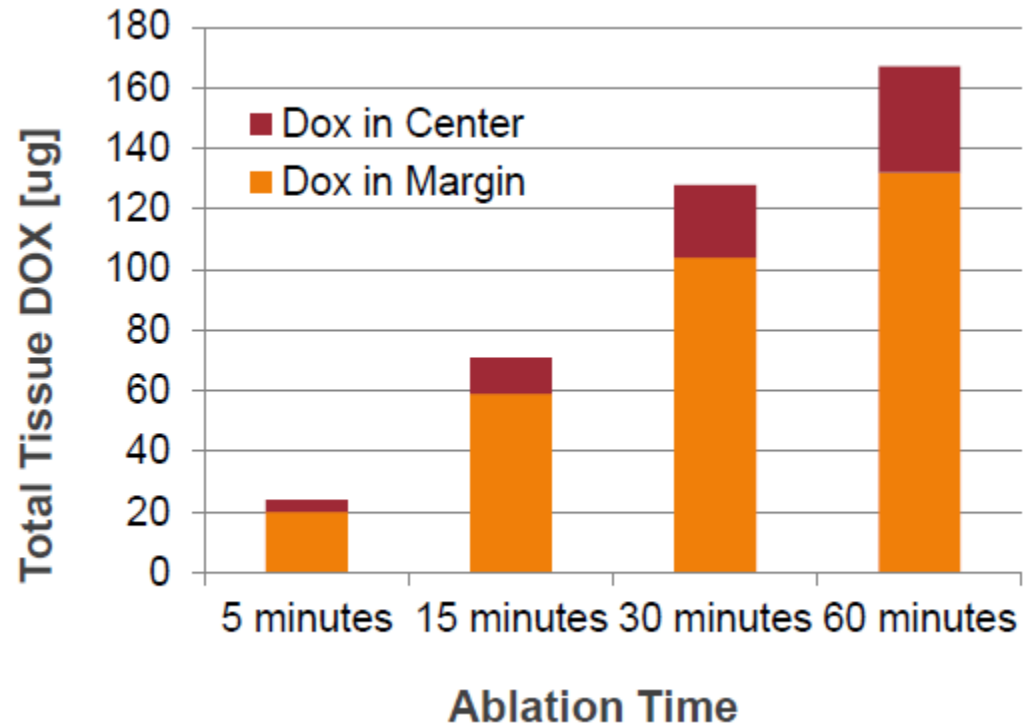
32 Secondary: OS (Overall Survival), TTLR (time to local recurrence), Safety

Results of HEAT Study

- ThermoDox® in combination with RFA did not meet the primary endpoint of the Phase III HEAT Study in patients with HCC; ThermoDox® was well-tolerated with no unexpected serious adverse events
- Greatest benefit in patients that had RFA > 45 mins
 - Single lesion patients (65% of population)
 - Consistent in both PFS & OS analysis

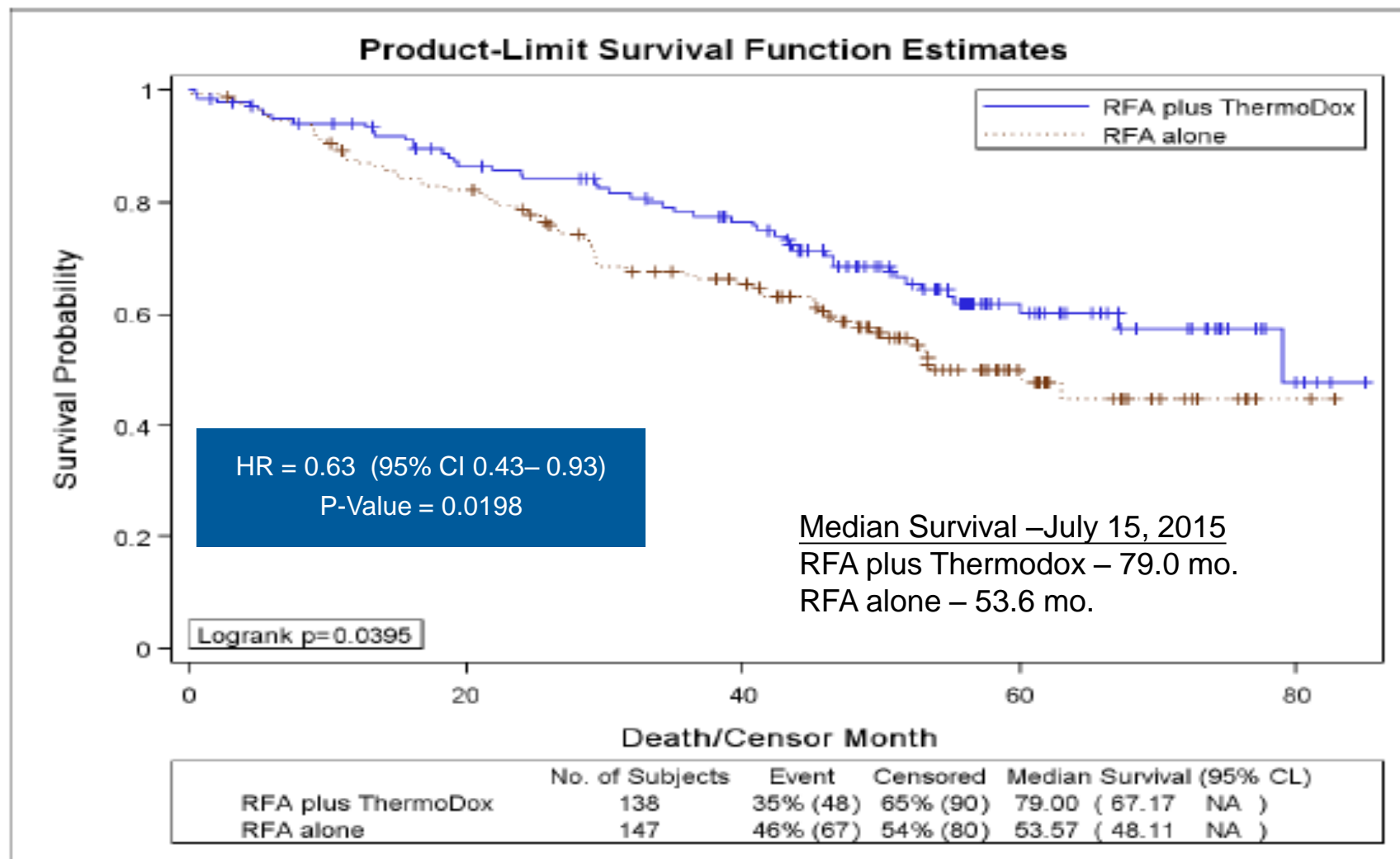
Post Hoc Analysis

- Ablation time or strategy was not mandated in HEAT Study
 - High degree of variability exists with ablation cycles and treatment time by lesion size
- Recent simulation studies show that prolonged heating > 45 min. is required in order to achieve optimal tissue concentrations of doxorubicin
- Patients with single lesion with optimized RFA duration may be the best strategy



Overall Survival Subgroup Analysis

Patients with RFA ≥ 45 mins. (n=285 patients)



Conclusions

- More aggressive treatment of HCC including resection and RFA may lead to improved long-term survival and possible cure in patients with intermediate stage HCC
- TACE remains mainstay of palliative treatment for intermediate HCC in patients whose liver function reserve is not adequate for surgical treatment - but little improvement over the past three decades
- Need for effective combination strategy to further improve long-term outcome of patients with intermediate HCC



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