Celsion Symposium

New Paradigms in HCC Staging: **HKLC** vs. **BCLC** Staging

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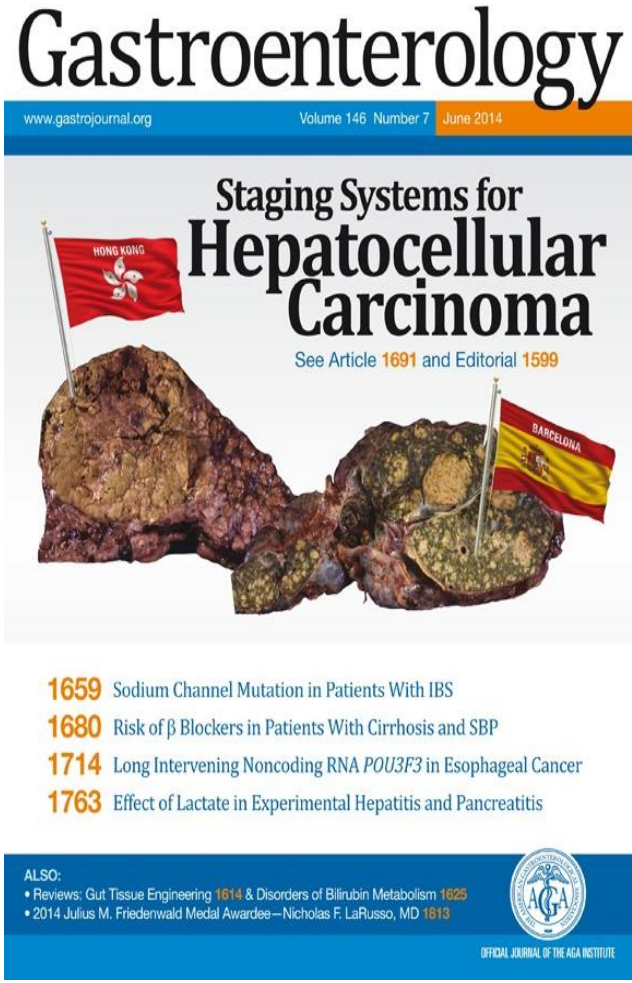
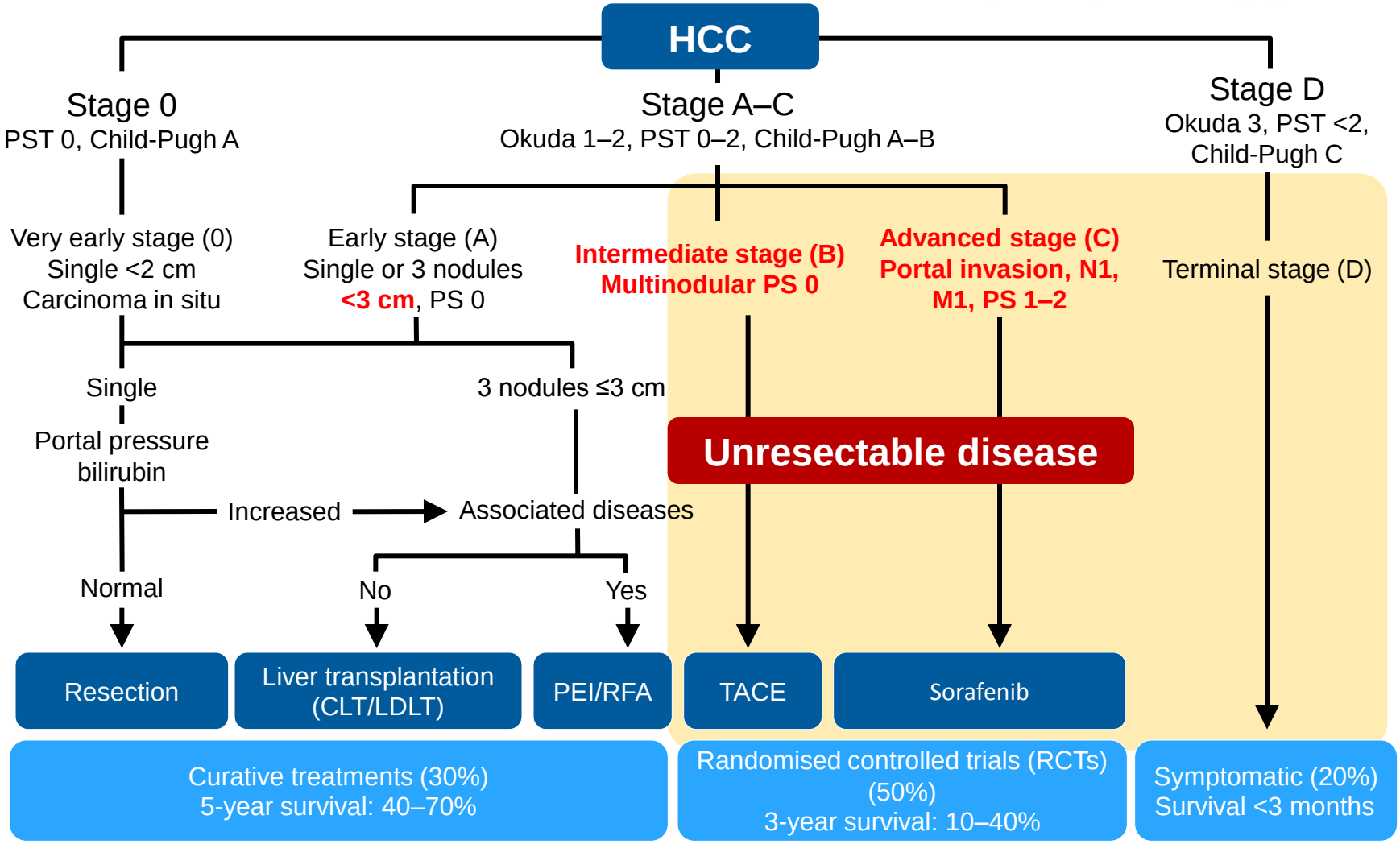
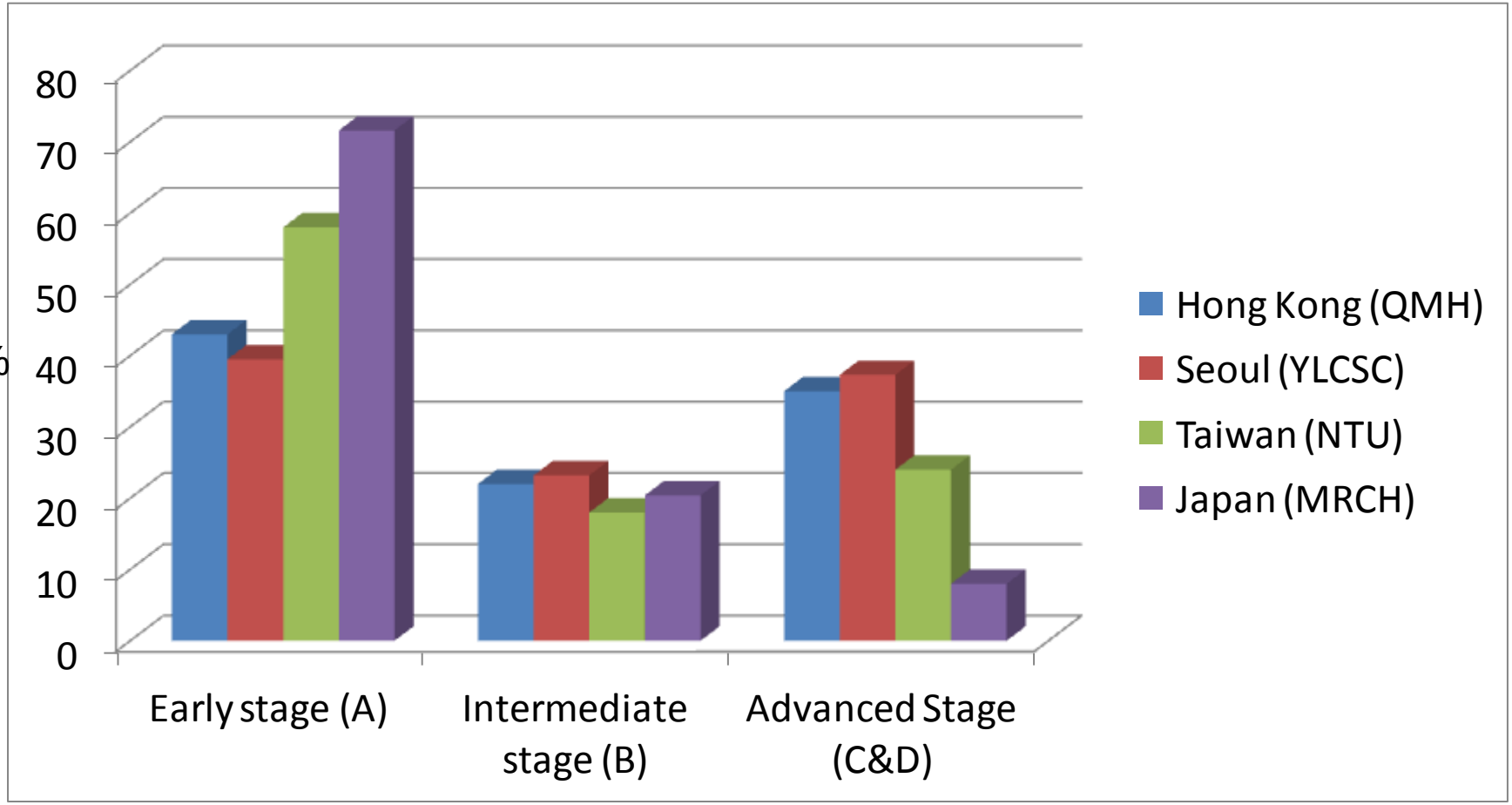


BCLC Staging and Treatment Algorithm



Llovet, et al. J Natl Cancer Inst 2008

BCLC Stage Distribution in Asian Countries



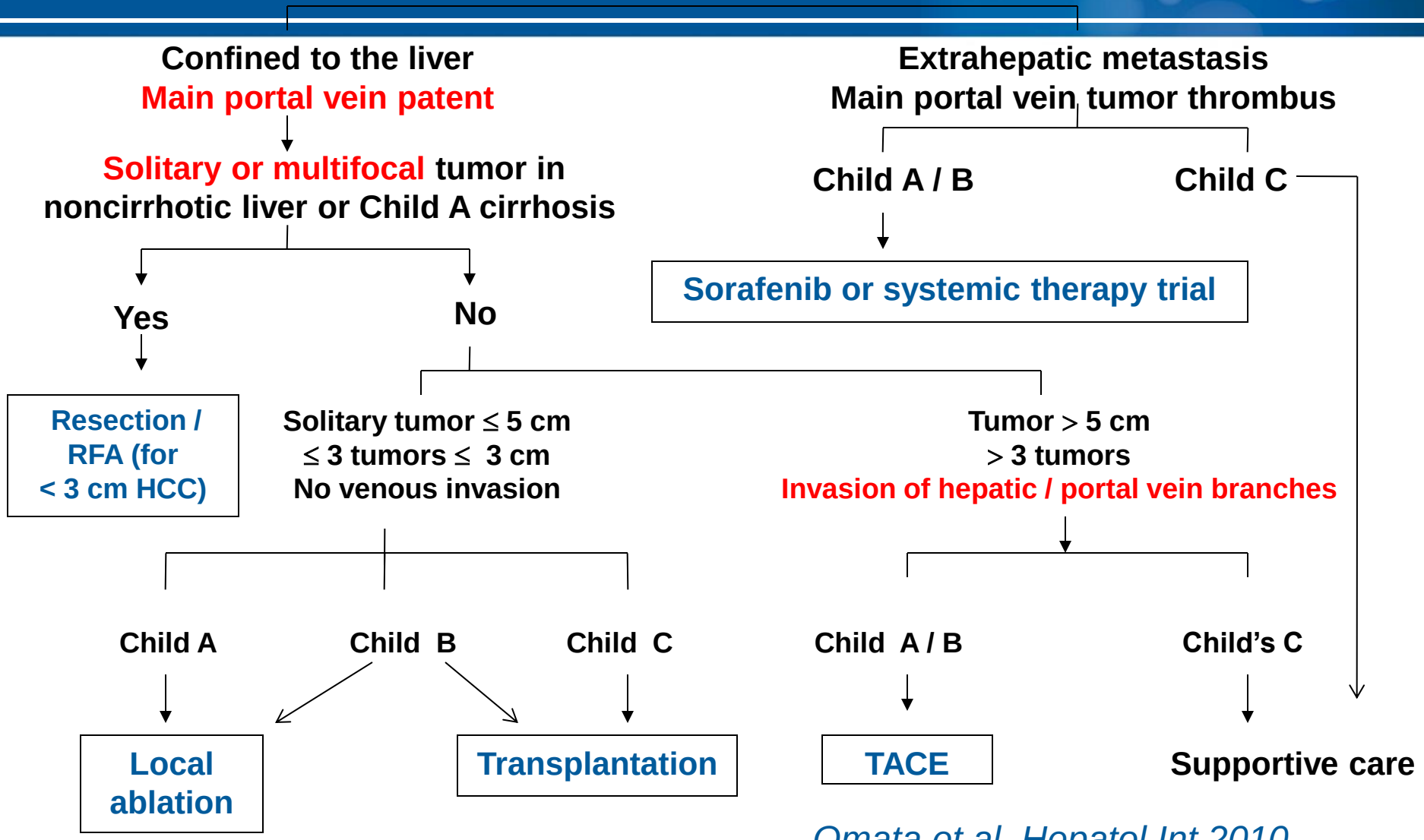
Asia-Pacific Cancer Conference, 2009

BCLC is too Conservative in Treatment Recommendation

Many clinicians especially in the East consider that:

- Role of surgical resection can be extended to intermediate or locally advanced HCC with intrahepatic venous invasion
- Role of ablation can be extended to tuomr 3-5 cm, or even slightly > 5 cm
- Role of transarterial therapy can be extended to locally advanced HCC with intrahepatic venous invasion

APASL Consensus on Treatment of HCC



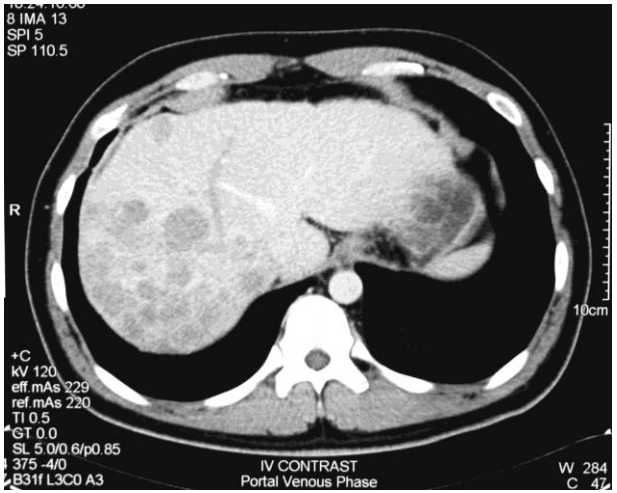
Omata et al. Hepatol Int 2010

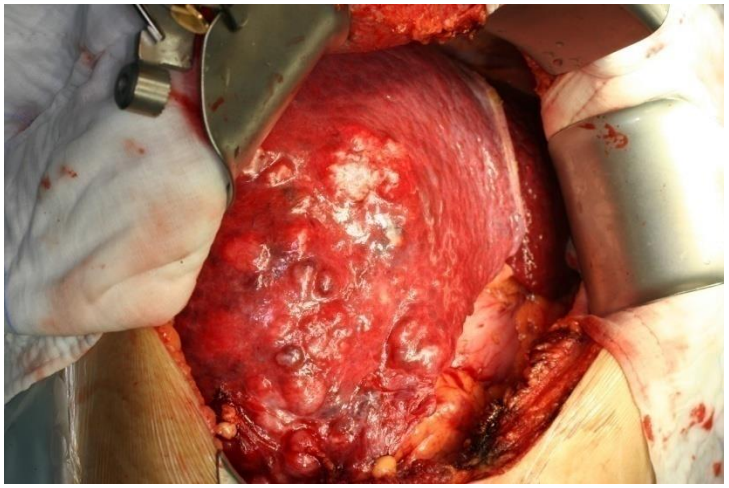
Hepatectomy for HCC at QMH 1995-2011 (1282 Patients)

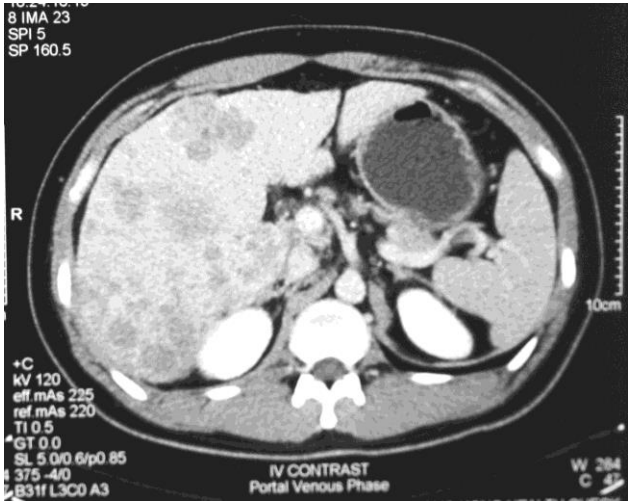
	All patients (n=1282)
Age [Median (Range)]	57 (5-89)
Sex (M:F)	1035:247
Hepatitis B	1092 (85.2%)
Hepatitis C	55 (4.3%)
Cirrhosis	783 (61.1%)
AFP [Median (Range)]	83.5 (1-1,335,900)
Tumor size [Median (Range)]	5.2 (0.7-28.0)
Multiple tumors (BCLC B)	358 (28%)
Macroscopic venous invasion* (BCLC C)	105 (8%)

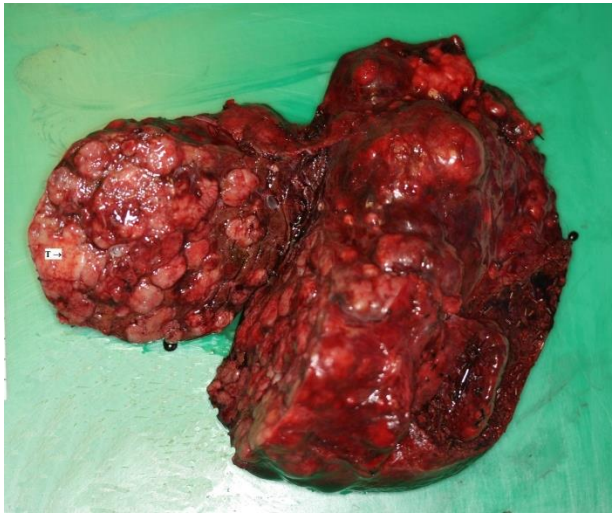
*PV 83; HV 19; IVC 3

Resection for Multifocal HCC

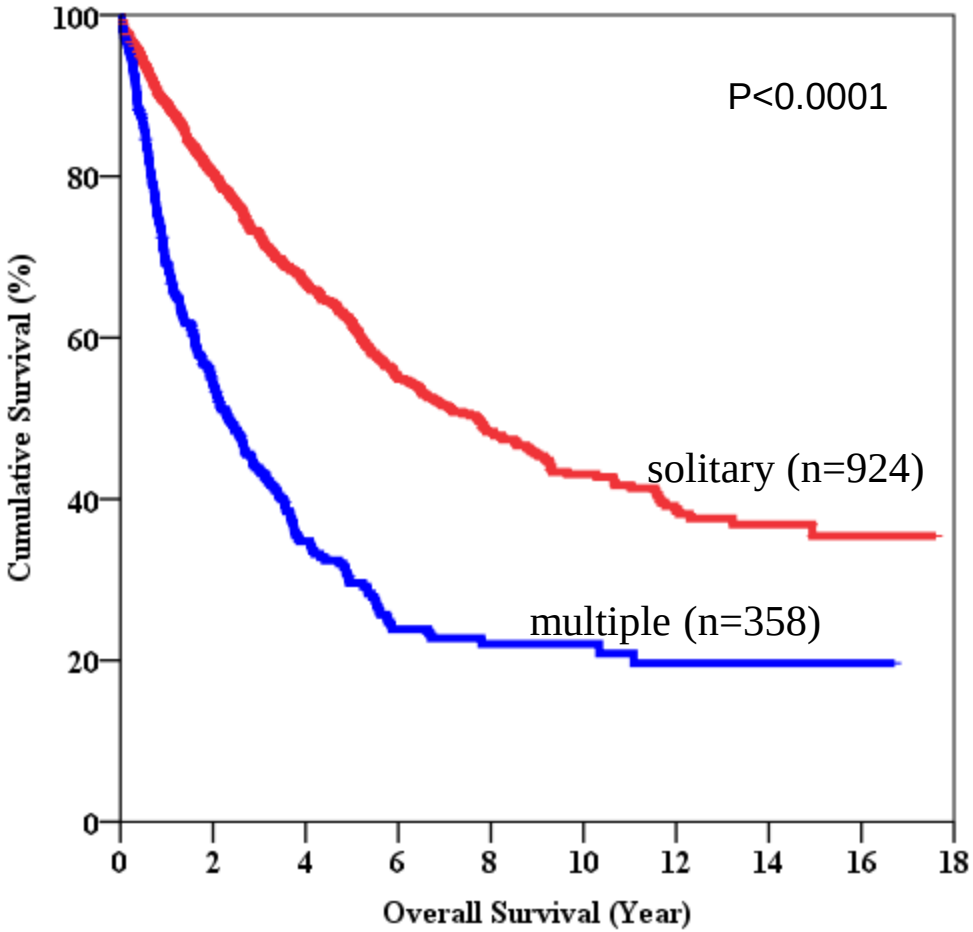






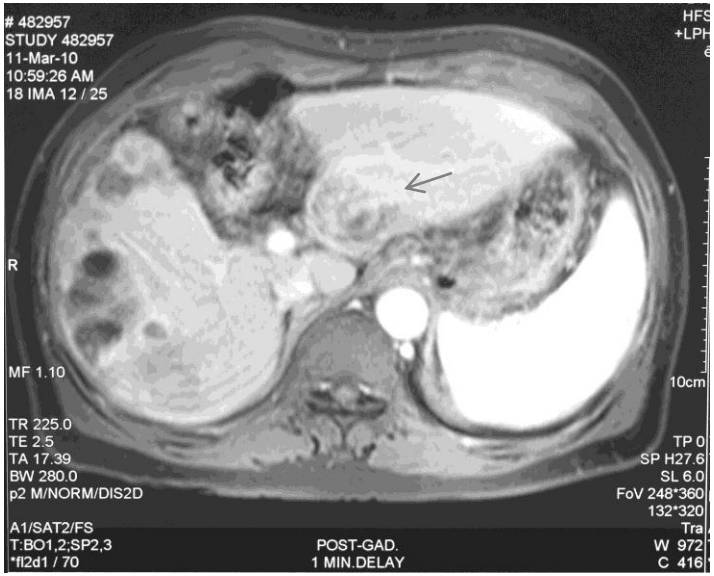


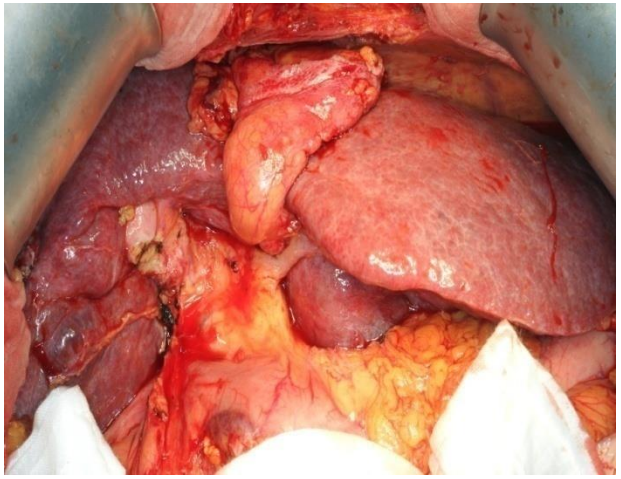
Survival of Patients with Multiple Tumors

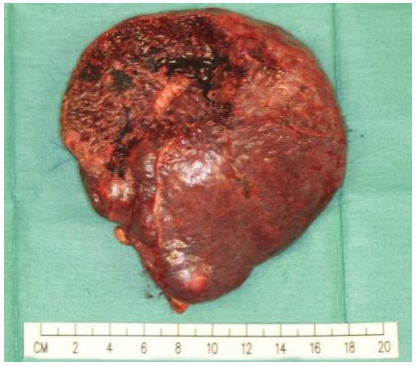


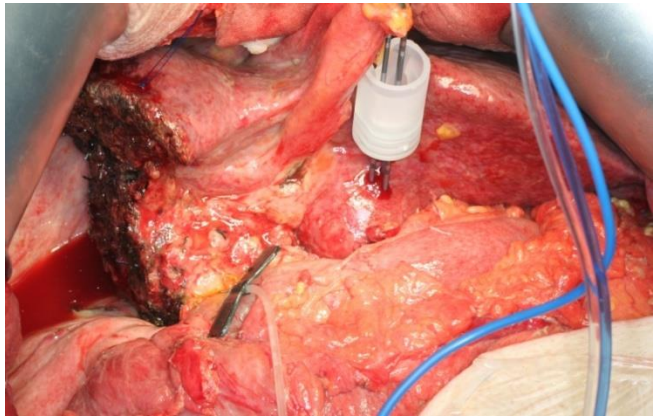
	Solitary (n=924)	Multiple (n=358)	P-value
Overall Survival			<0.001
Median (mths)	92.6	28.0	
1-year	89%	69%	
3-year	73%	44%	
5-year	62%	30%	

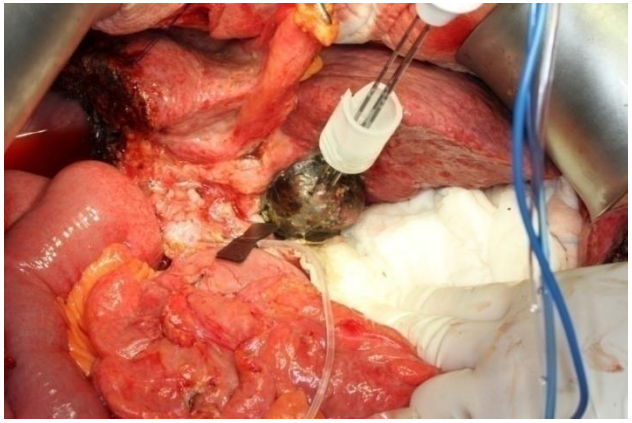
Combined Resection and Ablation











Combined Resection and RFA for Multifocal HCC at QMH

- 19 patients with multiple HCCs and no major venous invasion received hepatectomy in combination with RFA with curative intent (combined treatment group)

- 54 patients with multifocal HCC undergoing hepatectomy alone in the same period were selected as case control (resection alone group)

Cheung et al. World J Gastroenterol 2010

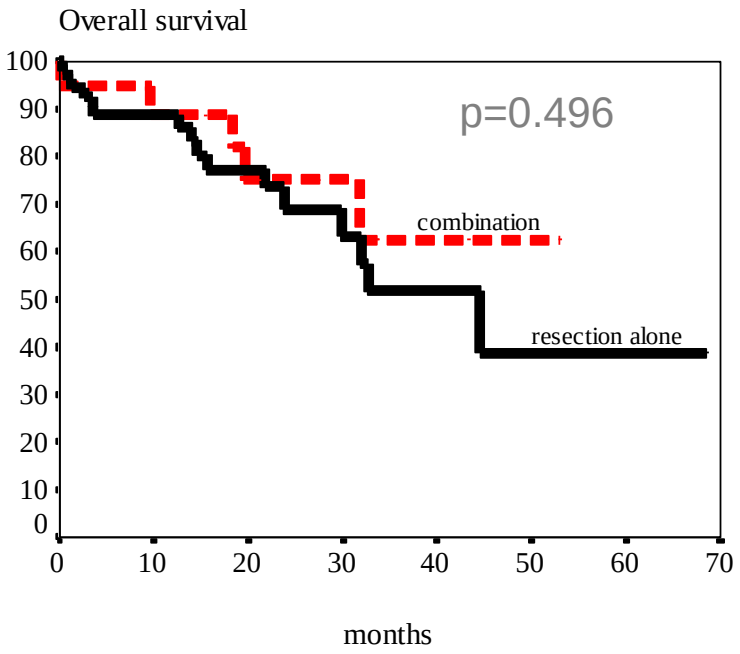
Overall Survival Results

Combined treatment vs. resection alone

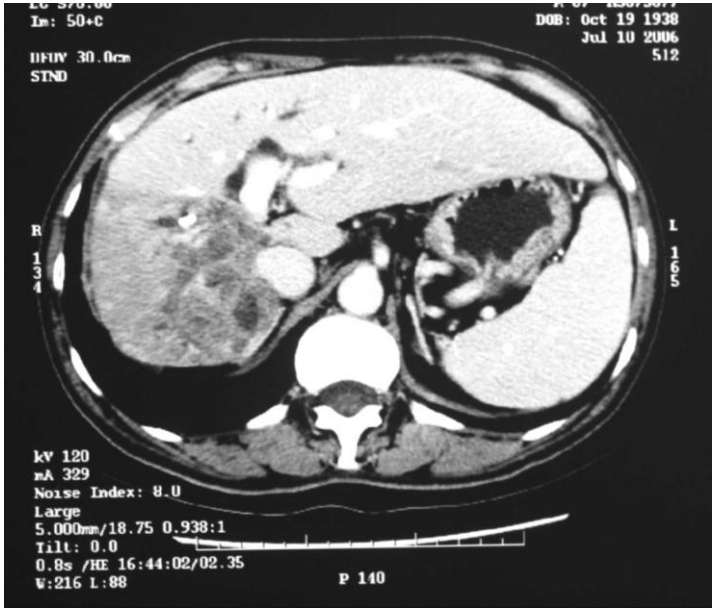
- No hospital mortality in both groups

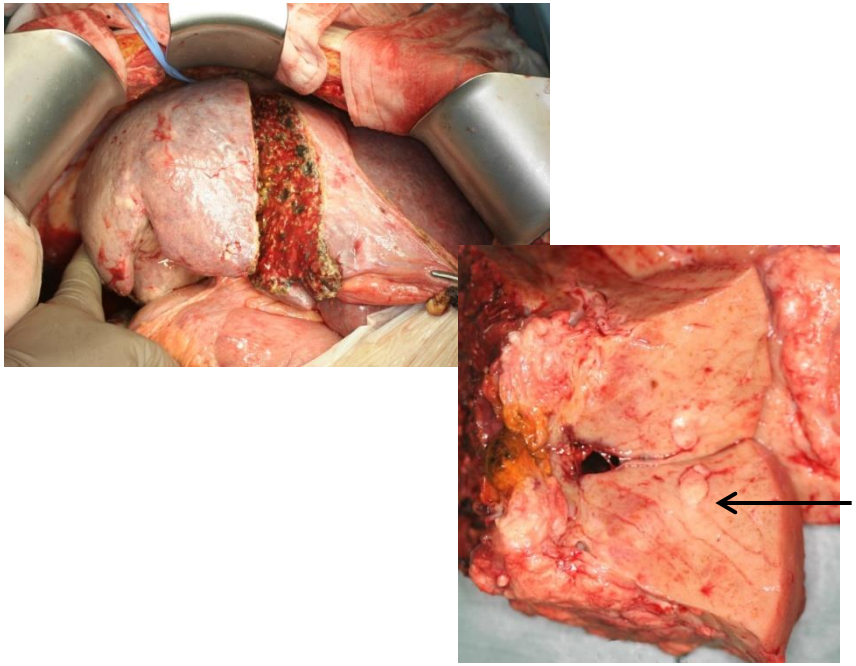
- Median survival:

  53.0 vs. 44.5 months



HCC with Macroscopic Venous Invasion

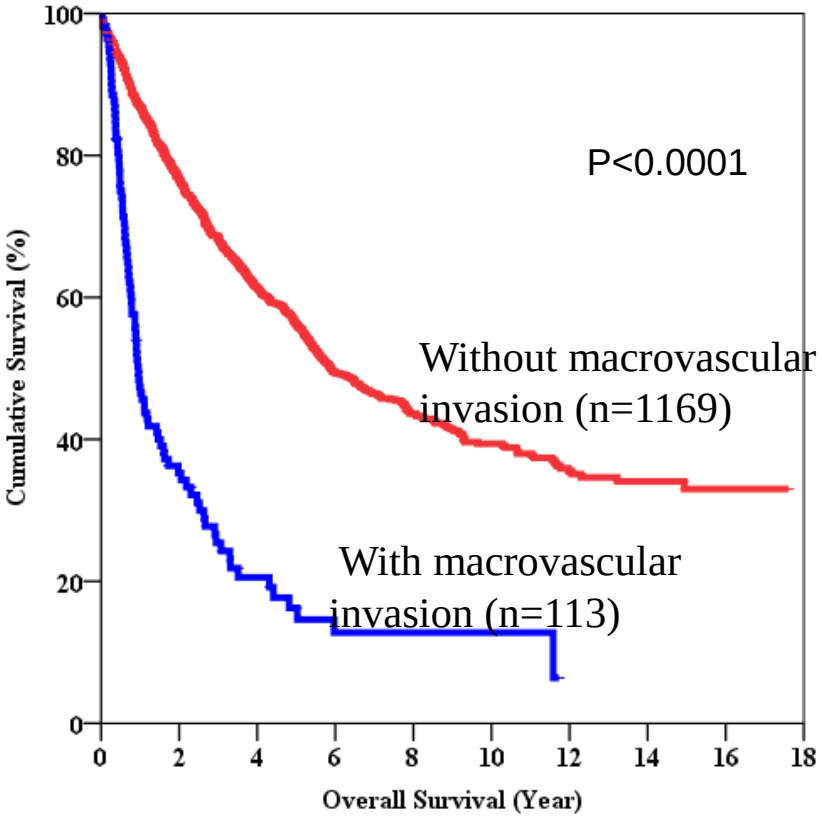




PVTT

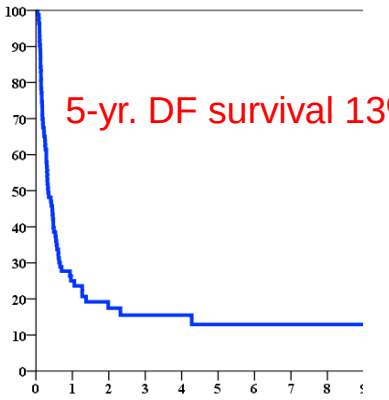
Disease-free for > 6 years after resection

Survival of Patients with Macroscopic Venous Invasion



	Without macro-vascular invasion (n=1169)	With macro-vascular invasion (n=113)	P-value
Overall Survival Median (mths)	70	12	<0.0001
1-year	87%	28%	
3-year	68%	18%	
5-year	58%	15%	

Disease-free survival



Resection for HCC with Macroscopic Venous Invasion – Taiwan Experience

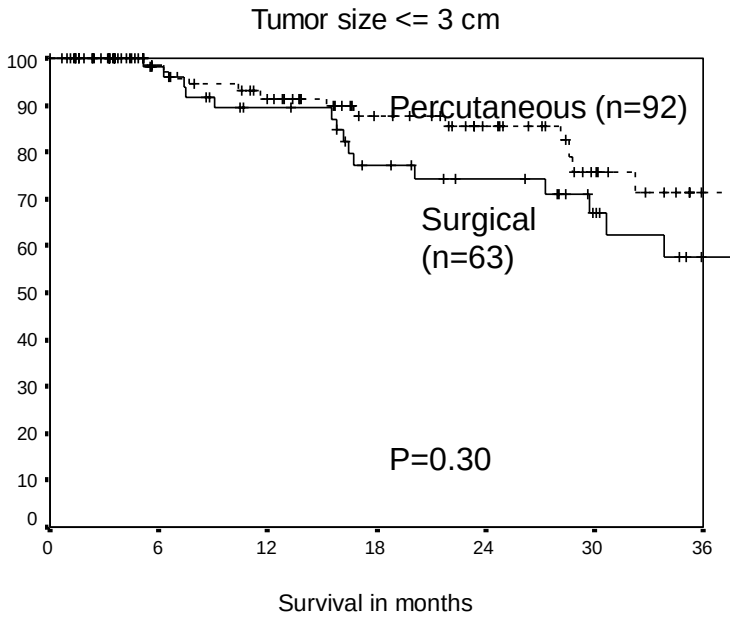
112 patients with HCC with portal vein tumor thrombus underwent curative resection, including 15 patients who underwent a concomitant portal vein resection owing to extension of tumor thrombi to the portal bifurcation

- Operative mortality 2.7%
- 5-year survival 26.4% in patients with PV resection, 28.5% in patients without PV resection
- 5-year disease-free survival 21.6% in patients with PV resection, 20.4% in patients without PV resection

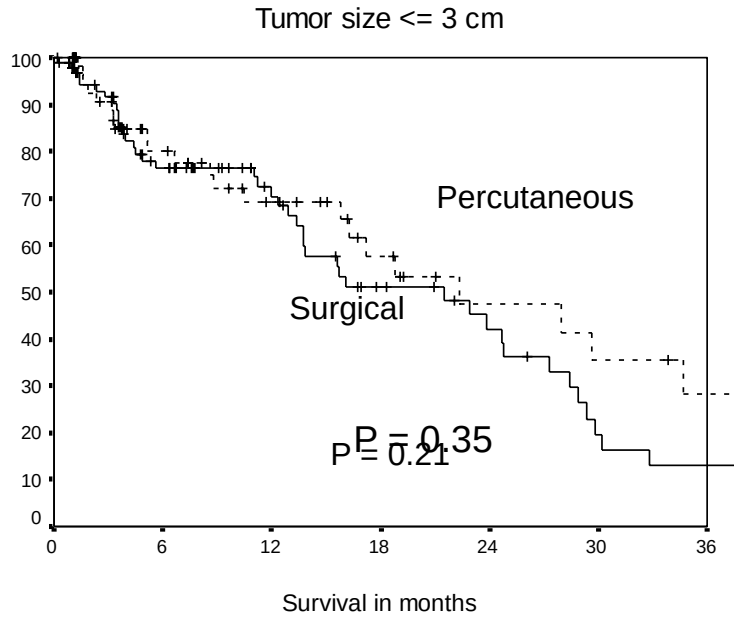
Wu et al. Arch Surg 2000

RFA for HCC: < 3 cm

Tumor size ≤ 3 cm: complete ablation rate 95% in each group



Overall survival

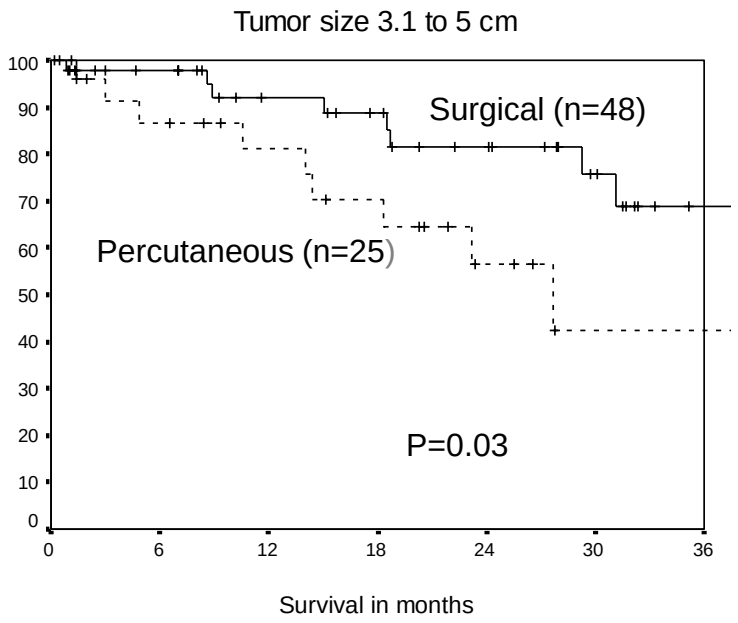


Recurrence-free survival

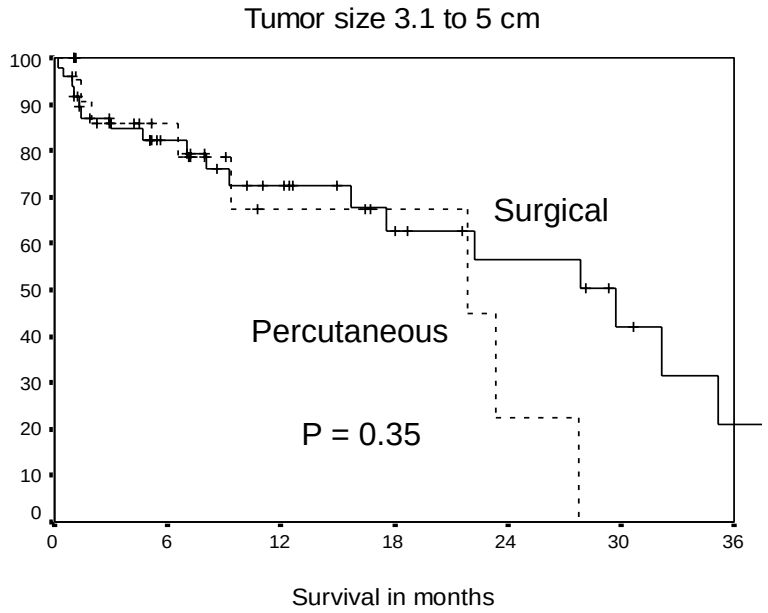
Khan, Poon et al, Arch Surg 2008

RFA for HCC 3-5 cm

Tumor size > 3 cm: complete ablation rate 95% vs 92%



Overall survival



Recurrence-free survival

? Role of RFA for Large HCC > 5 cm

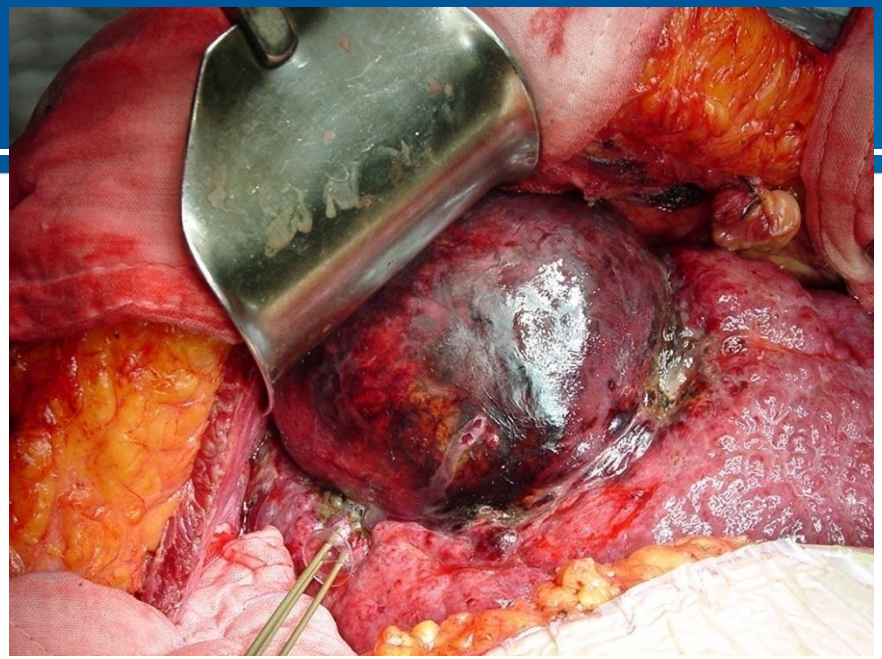
- Percutaneous RFA for HCC > 5 cm:
  Complete ablation rate < 50%
  (compared with 90% for HCC < 3 cm)

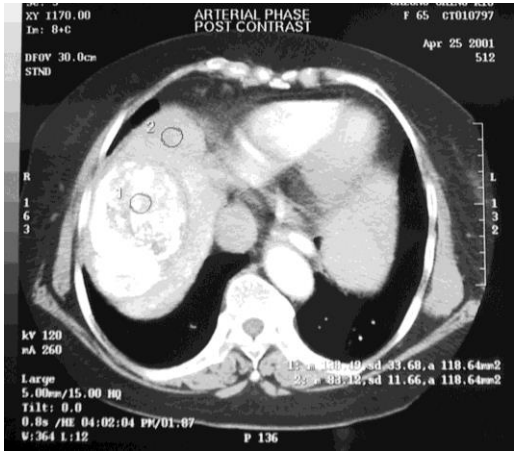
  Livraghi et al, Radiology 2000

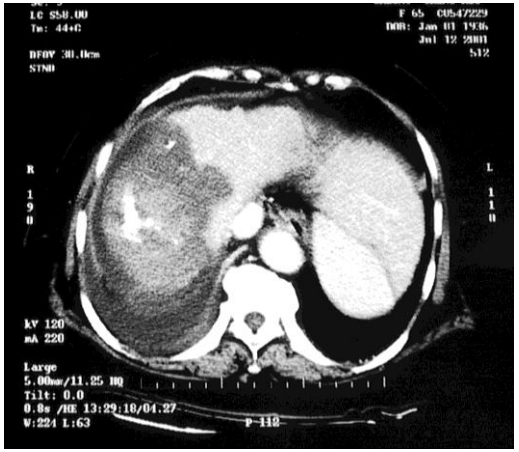
  Guglielmi et al, Hepatogastroenterology 2003

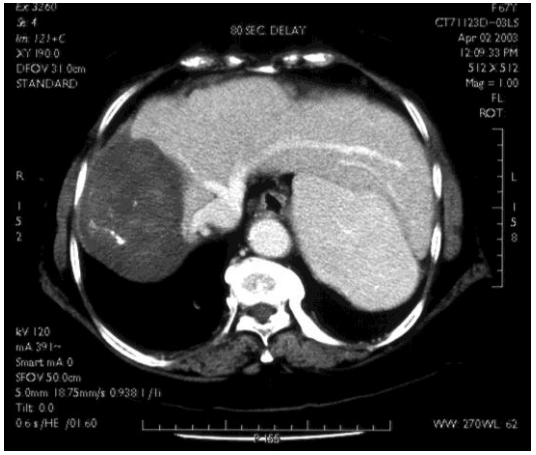
- Open RFA for HCC > 5 cm:
  Complete ablation rate 83% (vs. 96% for HCC < 3 cm)

  Poon et al, Arch Surg 2004




ARTERIAL PHASE
POST CONTRAST
Apr 25 2001
512
kV 120
mA 260

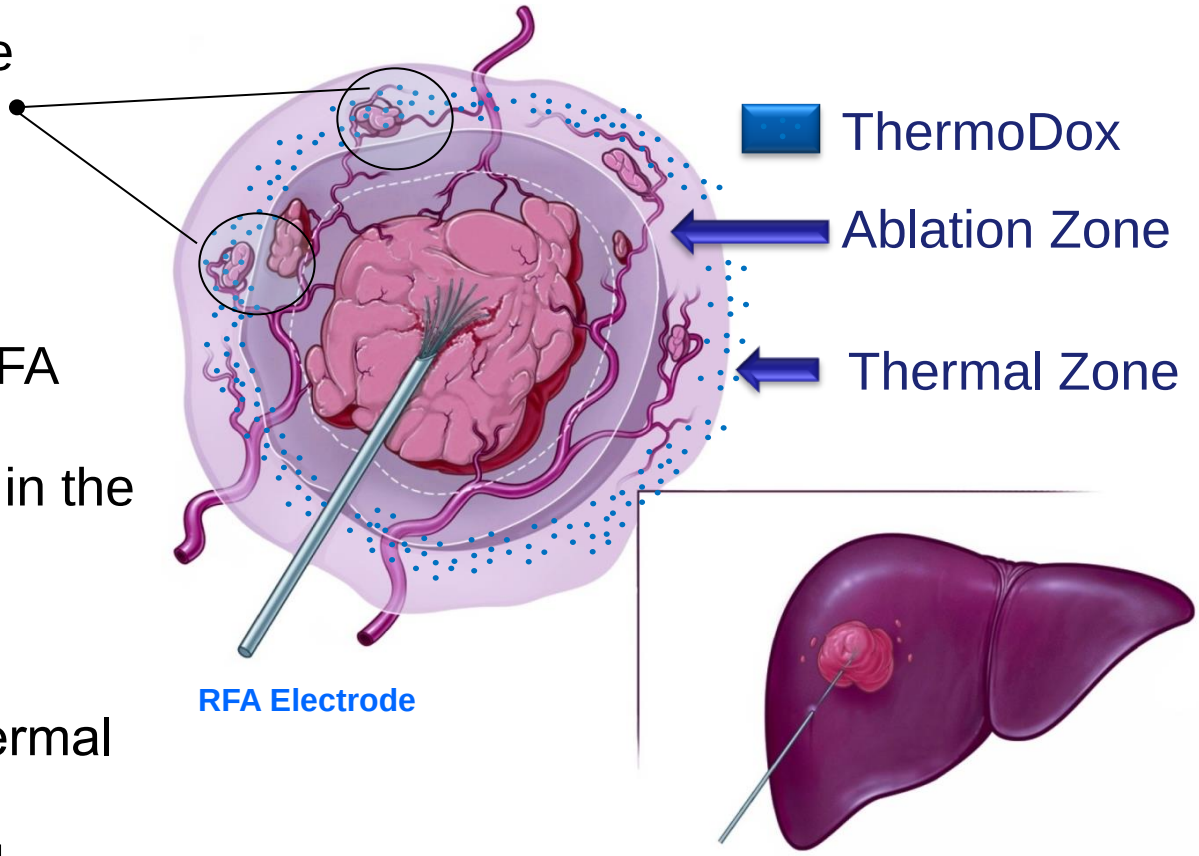

kV 120
mA 220


80 SEC. DELAY
STANDARD
kV 120

RF Liver Ablation + ThermoDox

Expanding the Treatment Zone

- RFA misses micro-metastases outside ablation zone
- RFA+Thermodox: Infuse Thermodox ~15 min. prior to RFA
- Drug concentrates in the “Thermal Zone”
- Ablation releases doxorubicin in “Thermal Zone” expanding treatment area and destroying micro-metastases



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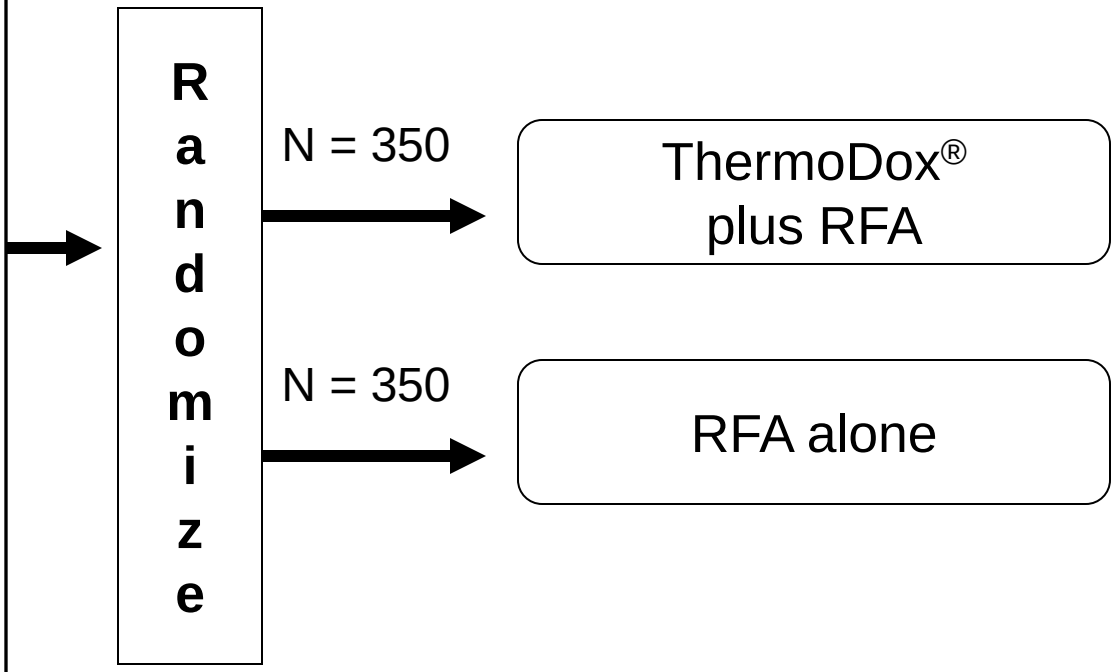
HEAT Study

General Eligibility:
- Non-resectable HCC
- No more than 4 lesions
- At least 1 lesion ≥ 3cm and none > 7cm
- No previous treatment
- Child-Pugh A or B

Stratification:
- Lesion size: 3-5 vs >5-7 cm
- RFA technique:
  - open surgical
  - laparoscopic or
  - percutaneous



Endpoints

Primary: PFS (Progression Free Survival)
Secondary: OS (Overall Survival), TTLR (Time to Local Recurrence), Safety, PRO (Time to Definite Worsening)

Poon et al. ILCA 2013

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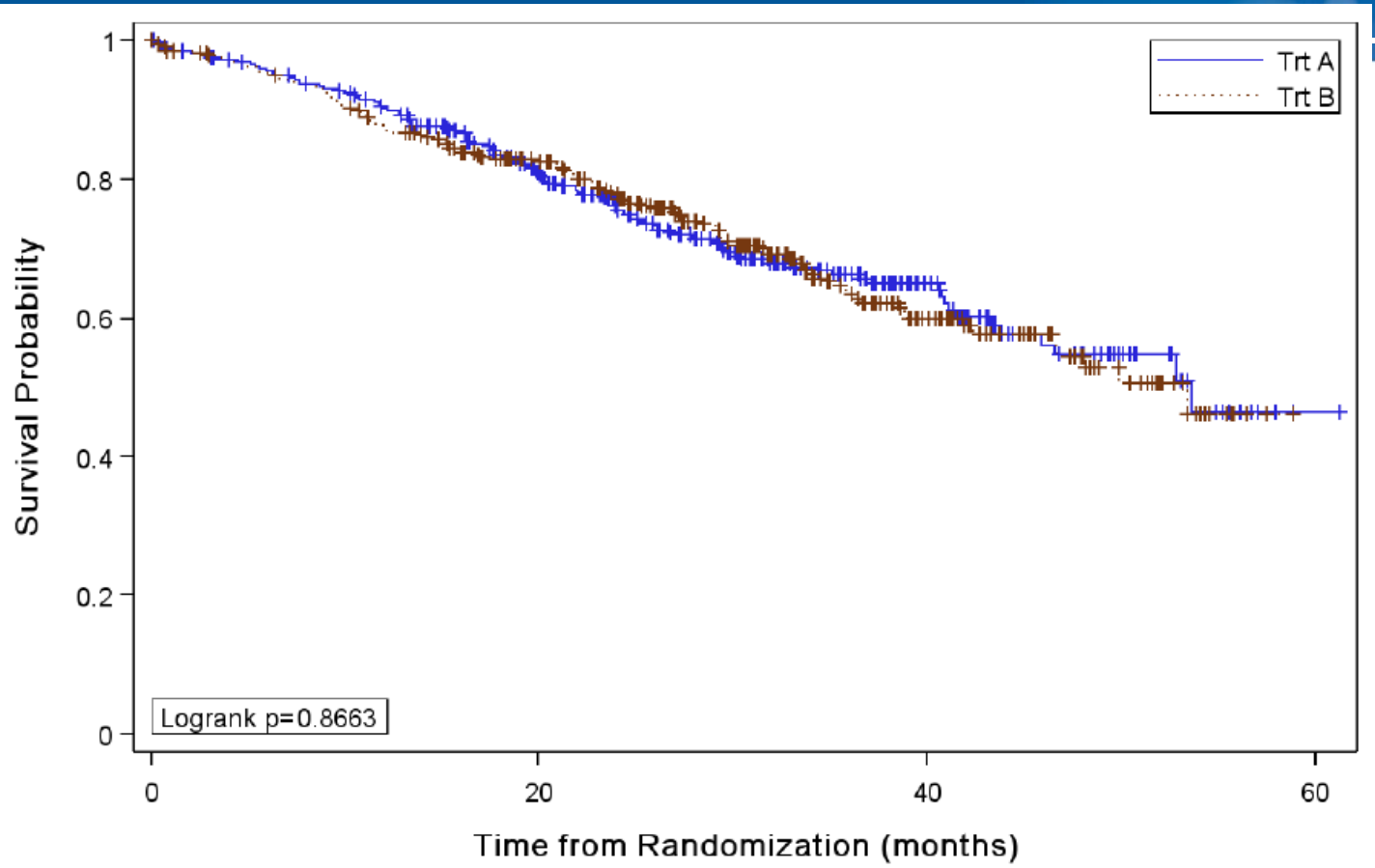
Overall Survival



Median Time to OS event RFA + TDox:	**53.66 mos.**
RFA Alone:	**53.40 mos.**
Hazard Ratio (Trt A/Trt B):	**1.011 (CI 0.761, 1.286)**

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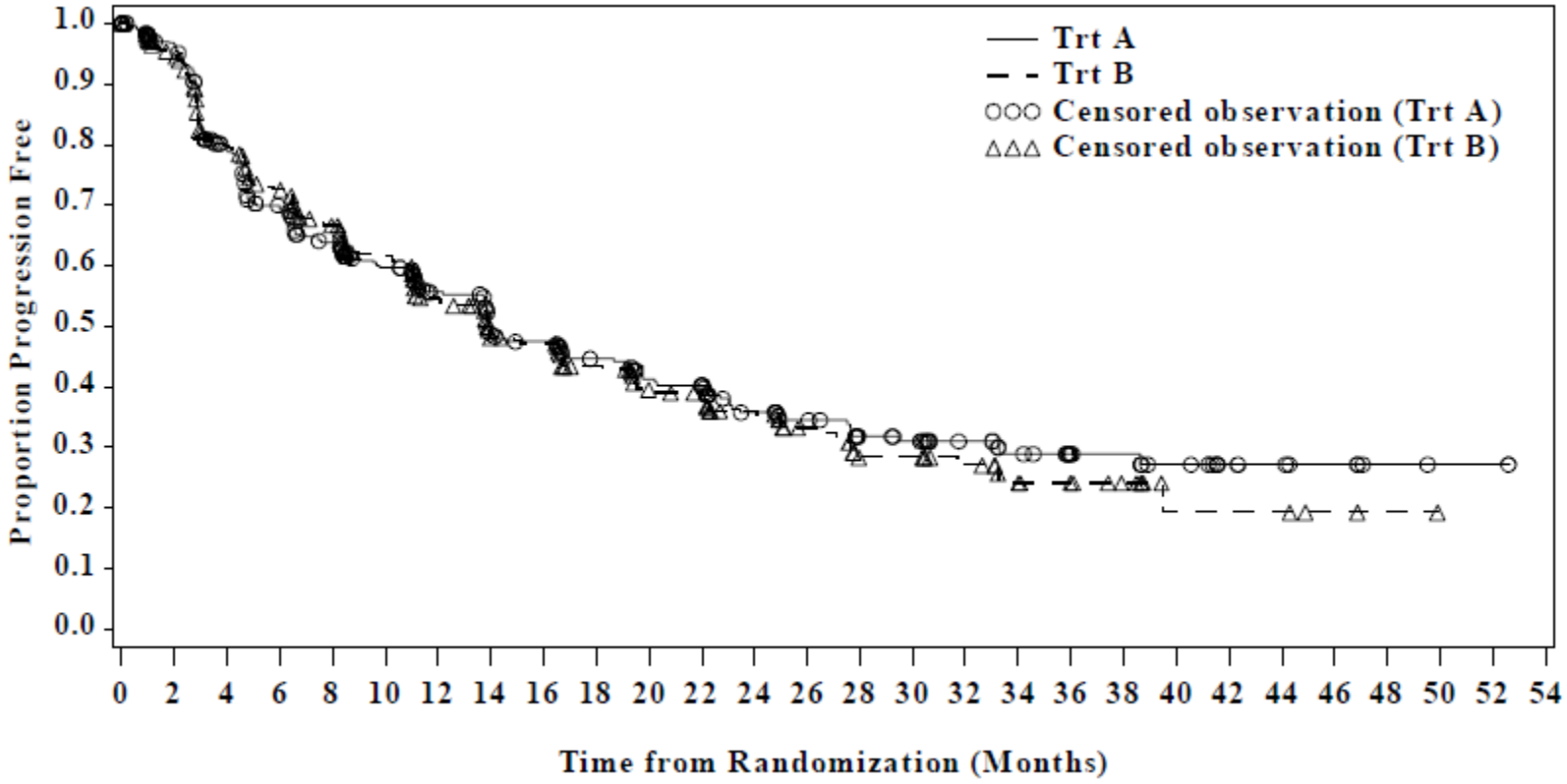
Progression Free Survival



Median Time to Progression RFA + TDox:	**13.97 mos.**
RFA Alone:	**13.87 mos.**
Hazard Ratio (Trt A/Trt B):	**0.957 (CI 0.780, 1.170)**

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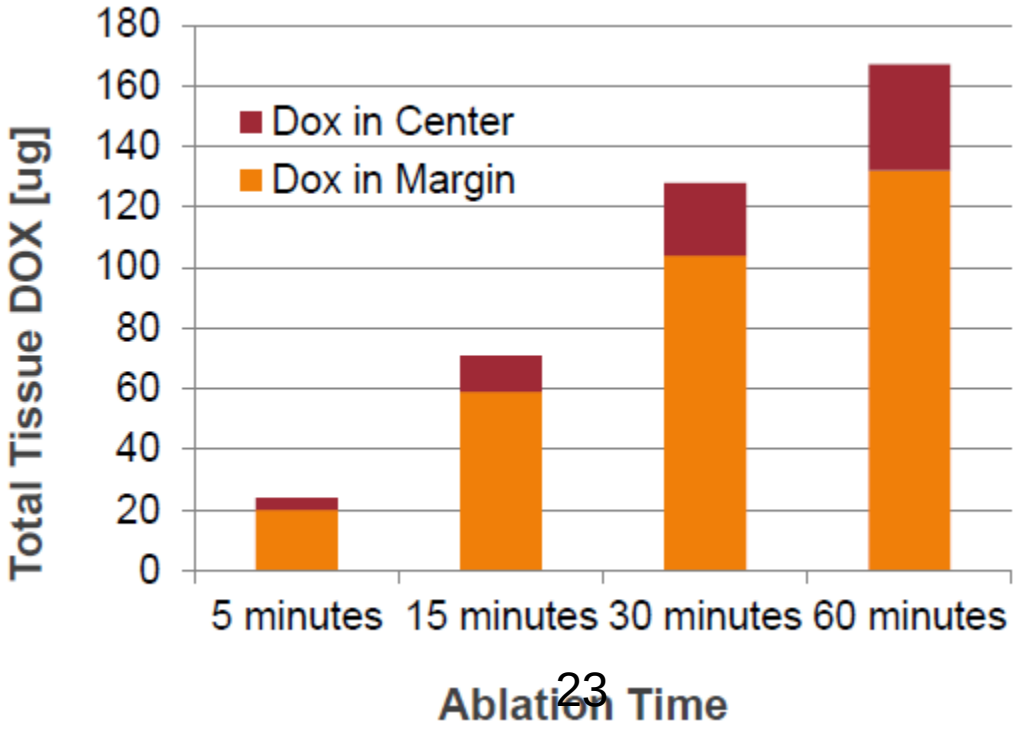
Post Hoc Analysis

- 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



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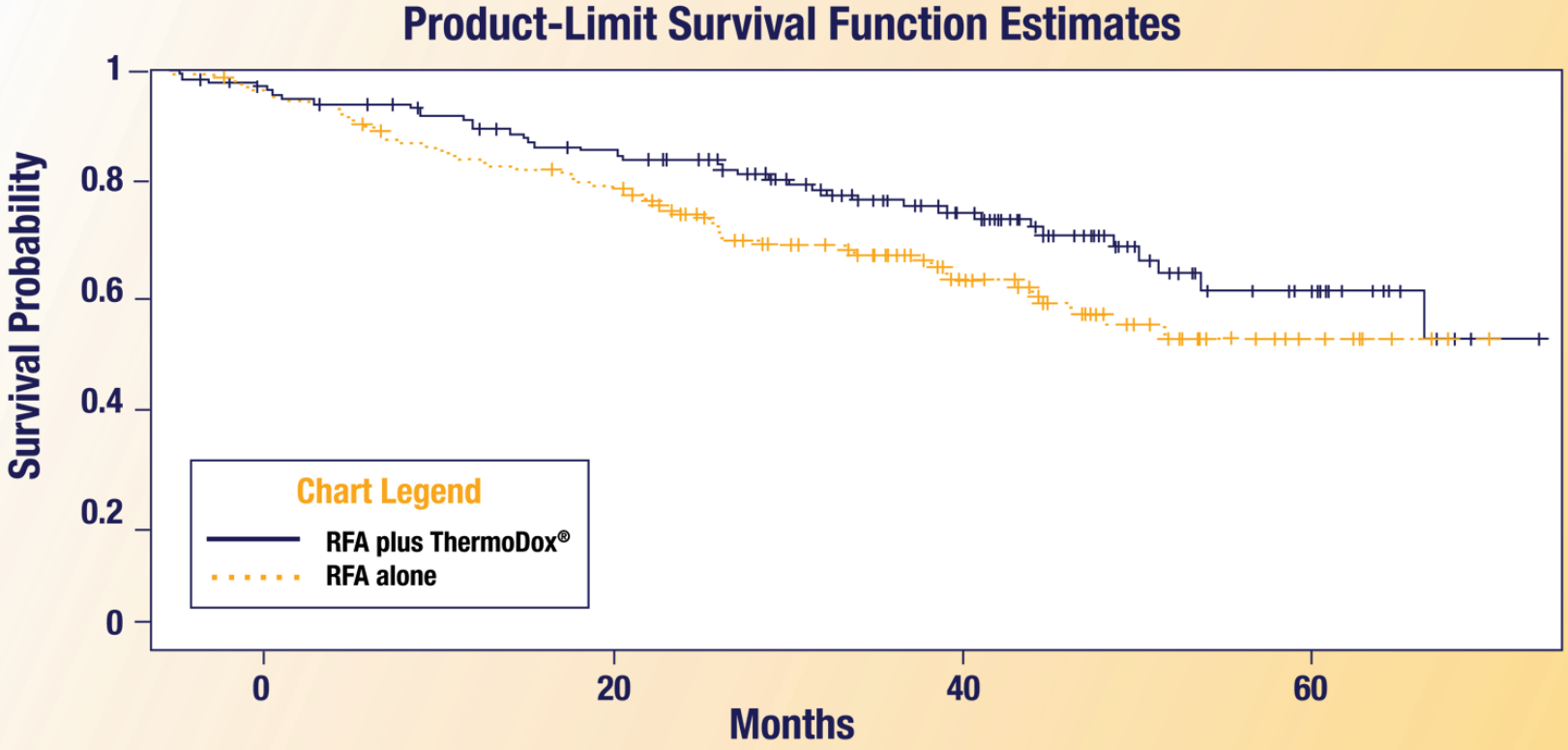
Sub-Group Analysis of HEAT Study Data:

- 285 Patients with Optimized RFA (>45 mins)



Overall Survival as of 6/30/2014	HR=0.639 (95% CI 0.419–0.974) *P* Value=0.037

OPTIMA Phase 3 RCT of Thermodox - Optimizing both RFA & Chemotherapy

- **Optimized thermal ablation**
  (by requiring multiple overlapping RFA ablation cycles)

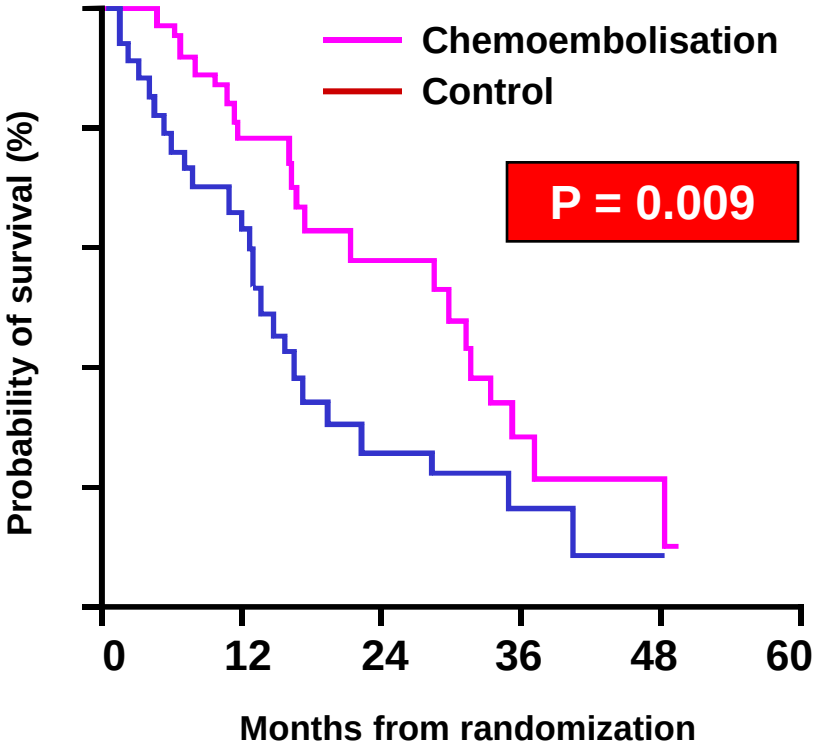
- **Optimized doxorubicin tumor tissue concentration**
  (by heating the target area for at least 45 minutes to concentrate
  a therapeutic amount of
  doxorubicin in tumor tissue)

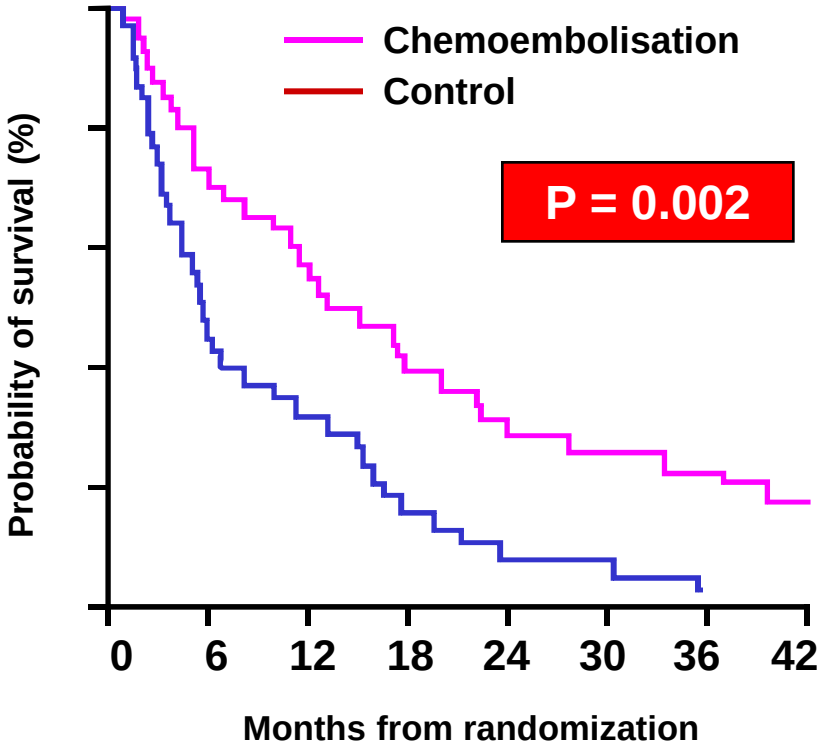
- **Eligibility limited to patients with a single HCC lesion**

- **Overall Survival is the primary endpoint**

TACE for HCC with PV Invasion

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



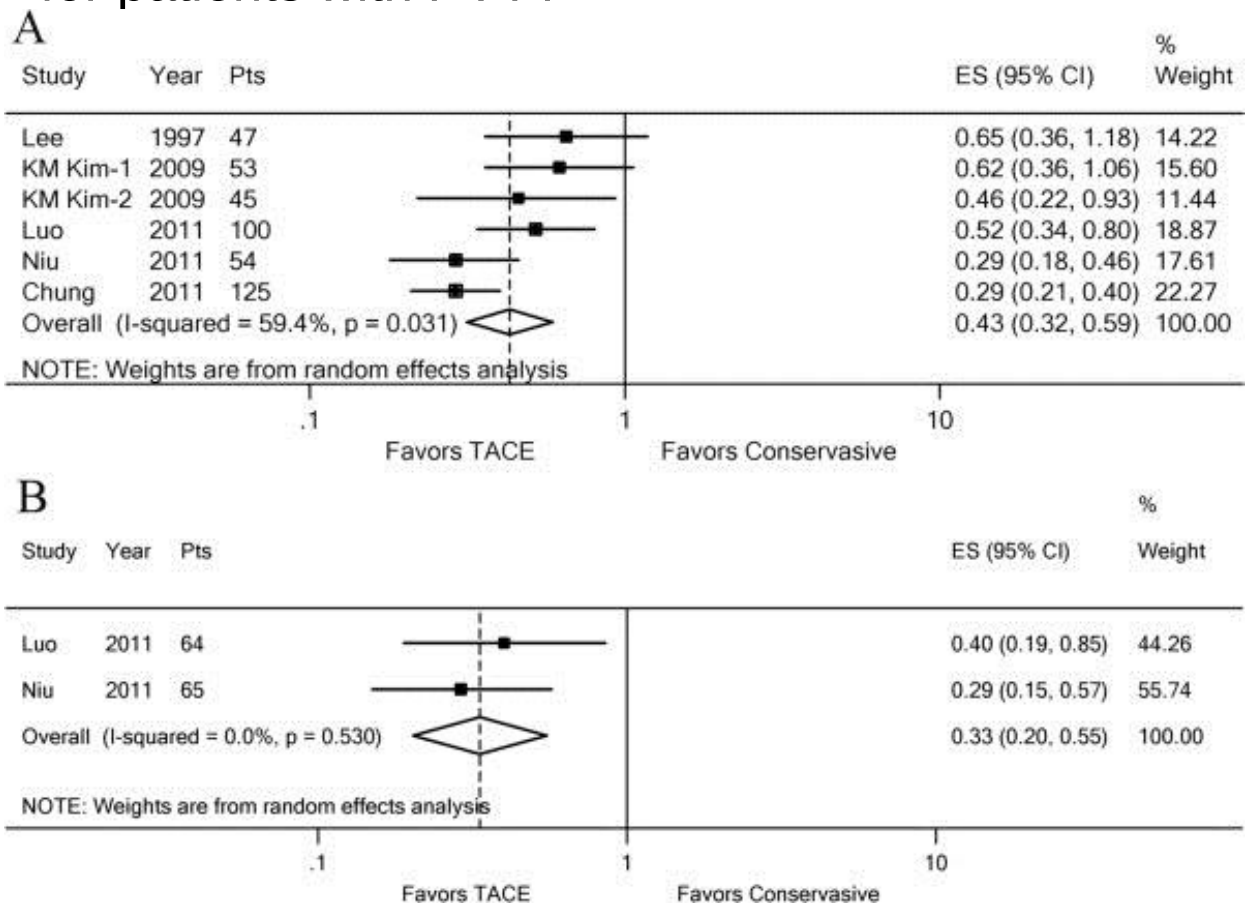


Llovet JM et al. Lancet 2002;359:1734–9

Lo CM et al. Hepatology 2002;35:1164–71

TACE for Patients with PV Tumor Thrombosis

- Meta-analysis of 6 prospective (n=3) or retrospective (n= 3) trials of TACE for patients with PVTT



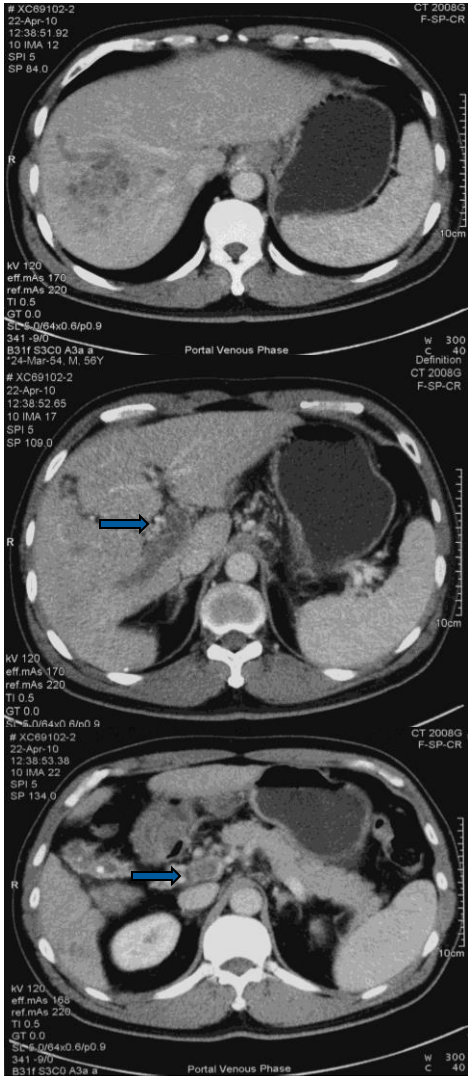
Forest plots of the favored effect of TACE for 6-month OS

(A)Subgroup analysis in HCC with MPV

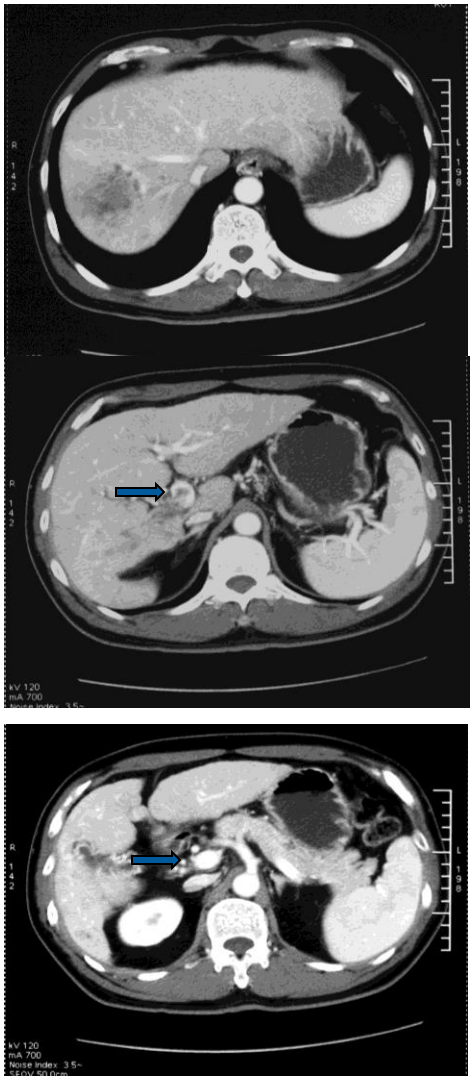
(B) Subgroup analysis in HCC with segmental PVTT

Xue et al. BMC Gastroenterol 2013

Transarterial Yttrium-90 for PV Tumor Thrombus

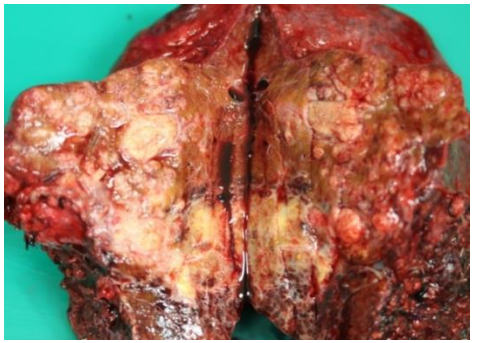


Y-90



M/50 HBsAg +, Child A cirrhosis
Right lobe HCC with PV tumor thrombus extending to SMV

Transarterial Yttrium-90 radioemebolization induced partial response and regression of PV tumor thrombus



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

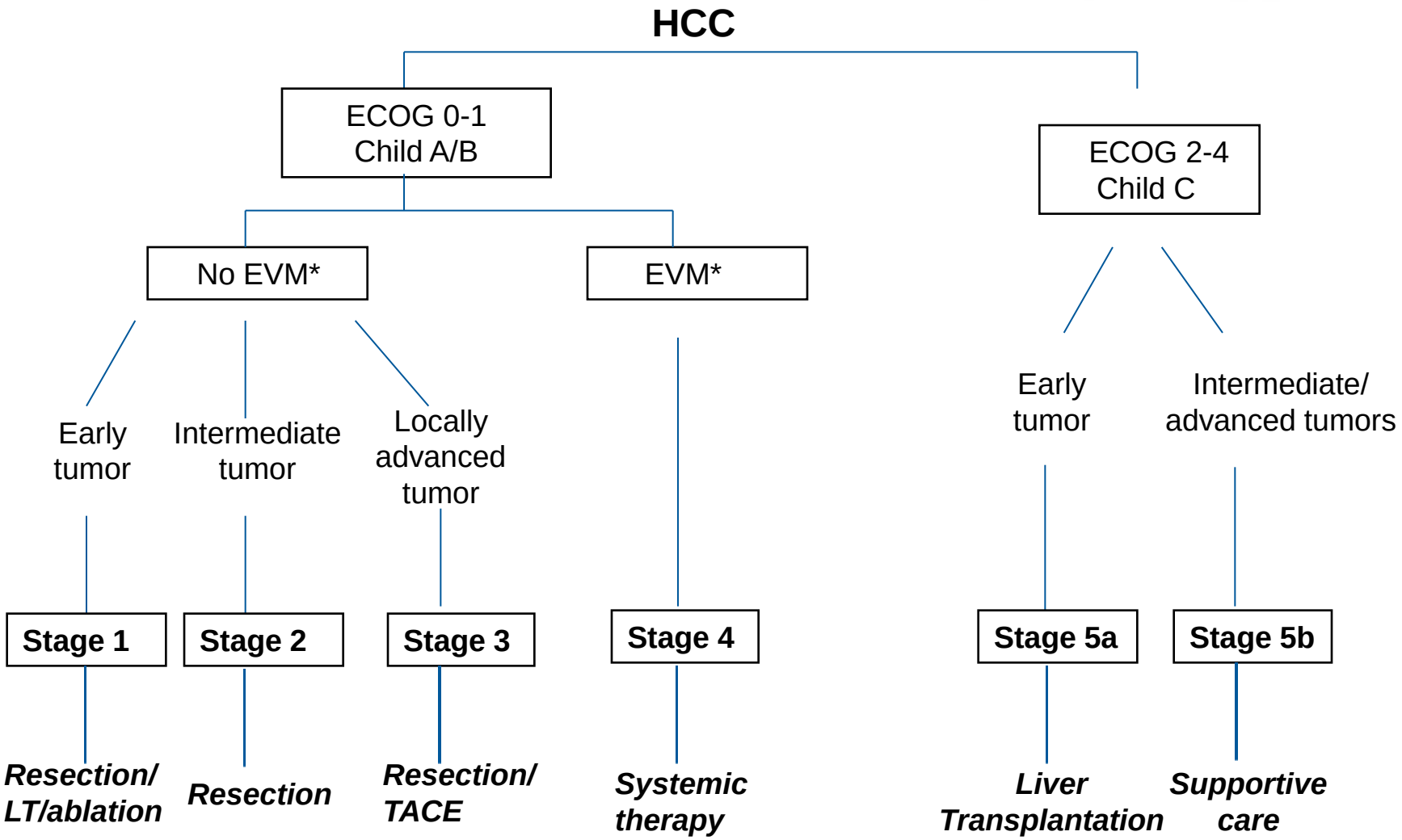
Yau et al. Gastroenterology 2014

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



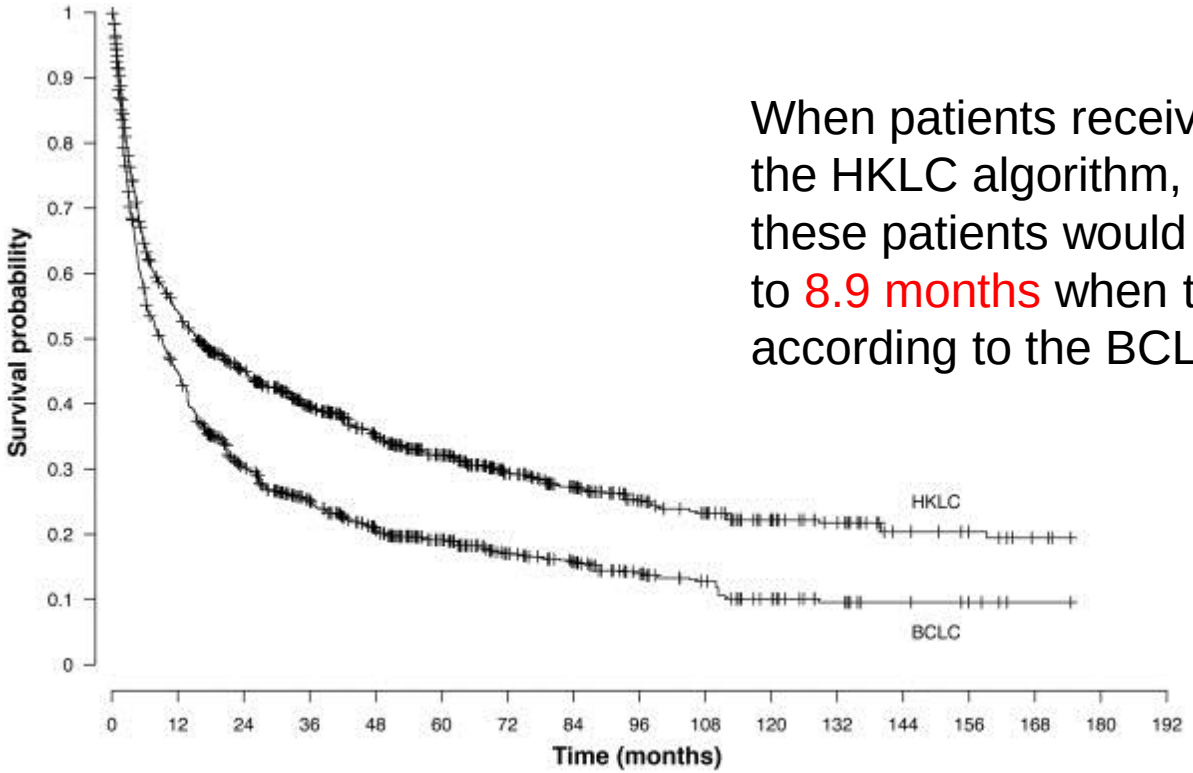
*EVM, extrahepatic vascular invasion/metastasis

Comparison of HKLC and BCLC Staging System

- The HKLC system has significantly better ability than the BCLC system to distinguish between patients with specific overall survival times (area under the receiver operating characteristic curve values, approximately 0.84 vs 0.80; concordance index, 0.74 vs 0.70)

- HKLC identifies subsets of BCLC intermediate- and advanced-stage patients for more aggressive treatments than what were recommended by the BCLC system, which improved survival outcomes

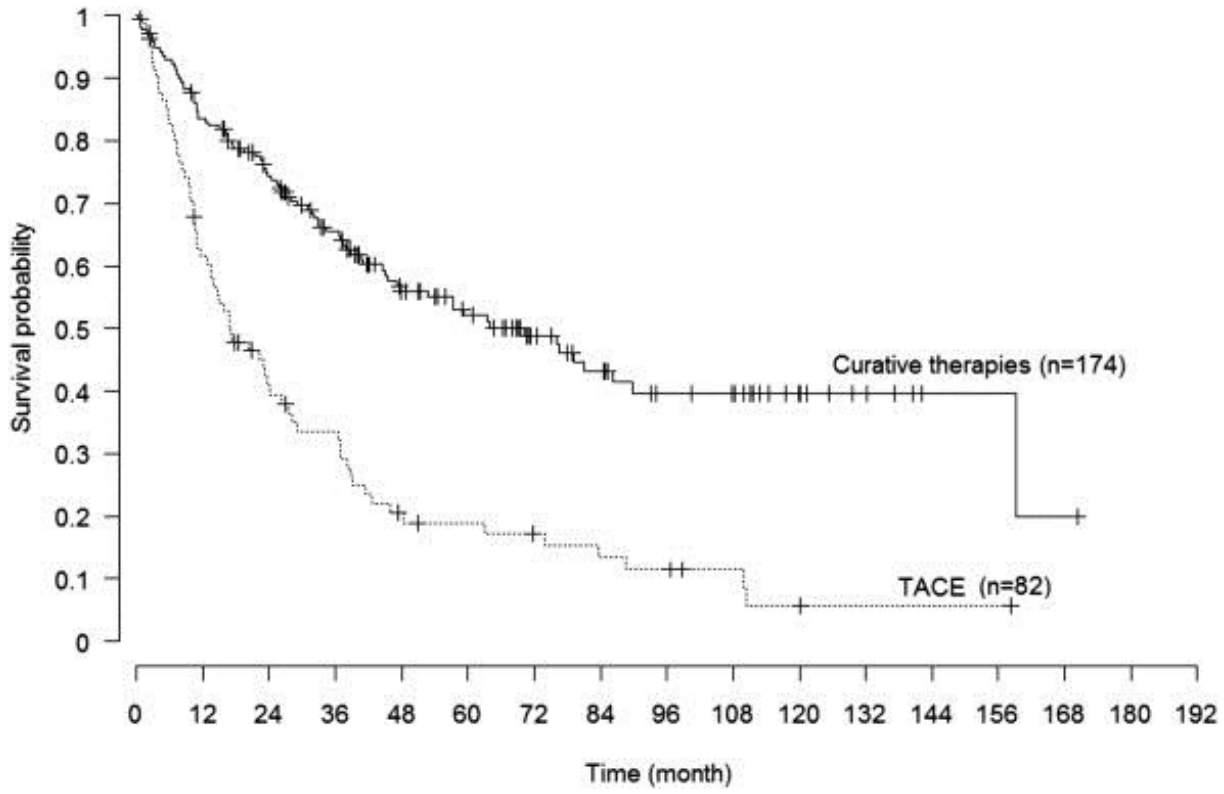
Comparison of HKLC and BCLC Staging System



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

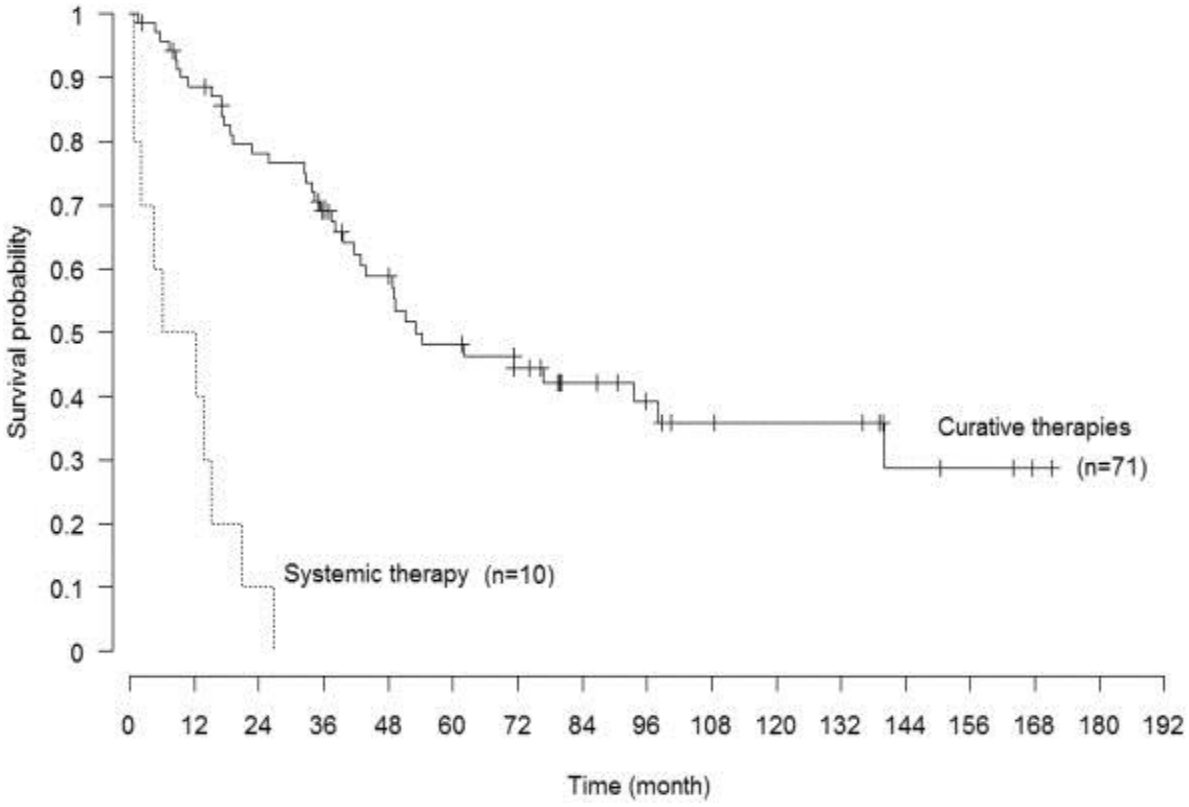
Hypothetical Kaplan–Meier estimated overall survival curves of the HKLC scheme and the BCLC scheme. The survival data of patients who were not treated with HKLC-recommended treatments were substituted by a random draw from the group of patients who had a similar prognosis and were treated according to 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, compared with TACE, was substantial (5-year survival, 52.1% vs 18.7%; P < .0001)

Comparison of HKLC and BCLC Staging System



In BCLC-C patients classified as HKLC-II, the survival benefit of radical therapies compared with systemic therapy was pronounced (5-year survival probability, 48.6% vs 0.0%; P < .0001).

Key Differences between HKLC and BCLC - Staging Classification

HKLC Staging:

- **Combine ECOG 0 and 1** into one category to reflect clinical practice – patients with symptoms should not be excluded from radical treatment

- Refined stratification of local tumor(s) in the liver using the triad of **tumor size** (5 cm as cut-off diameter**), tumor number**, and **macroscopic vascular invasion**

- Separate classification **of locally advanced tumor (stage 3b)** and **tumor with extehepatic venous invasion or metastasis (stage 4)**

- Unique stage Va for **transplantable early HCC associated with Child C cirrhosis** and ECOG >1

Key Differences between HKLC and BCLC - Treatment Recommendation

- Multifocal tumors or intrahepatic vascular invasion NOT considered contraindication for surgical resection
- Ablation recommended for tumor up to 5 cm
- Intrahepatic vascular invasion NOT considered contraindication for transarterial therapies

More aggressive treatments give better survival outcomes, provided with careful patient selection in terms of liver function reserve

HEPATOCELLULAR CARCINOMA

Have we finally found the ultimate staging system for HCC?

Julius Chapiro and Jean-François Geschwind

A staging system capable of addressing the real issues facing patients with hepatocellular carcinoma has long been overdue. The new Hong Kong Liver Cancer staging system might do just that because it deals effectively with the limitations of previous staging systems.

Chapiro, J. & Geschwind J.-F. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 6 May 2014; corrected online 8 May 2014; doi:10.1038/nrgastro.2014.67

…….It is possible (if not likely) that the HKLC system will become the new standard and accepted universally.

Conclusions

- HKLC provides a more refined staging and more aggressive treatment algorithm than BCLC
- Surgical resection plays an important role in prolonging survival in patients with intermediate or even locally advanced HCC with good liver function reserve, and it offers the only hope of CURE for such patients
- RFA offers an alternative curative treatment for early HCC as well as intermediate stage HCC with tumors up to 5 cm
- TACE or transarterial Y90 may prolong survival in patients with portal vein tumor thrombus and good liver function
- More aggressive treatments in HKLC staging give better overall survival than in BCLC staging

Thank you!