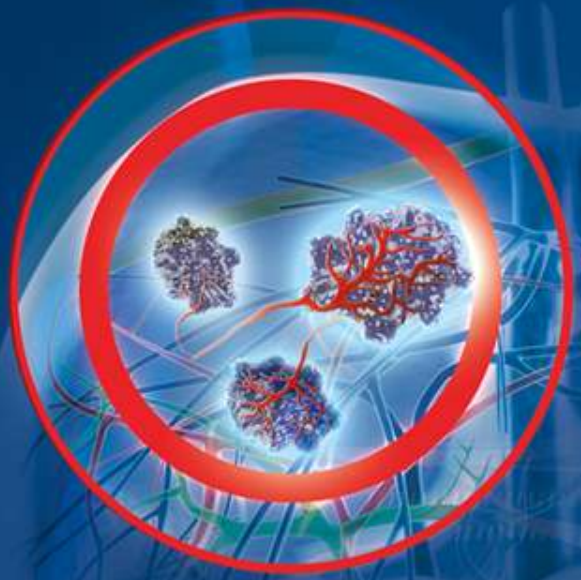
APASL HCC Conference, 2013 Cebu



Therapeutic Response Assessment and Endpoints in HCC

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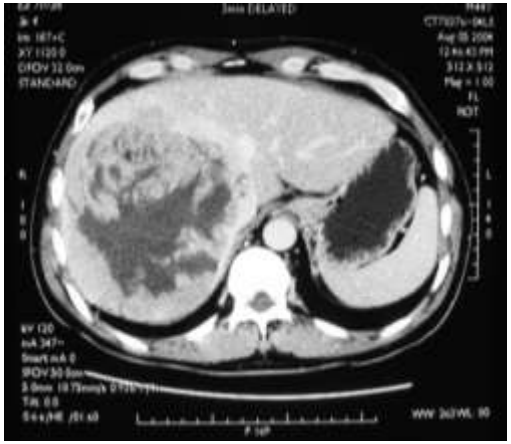
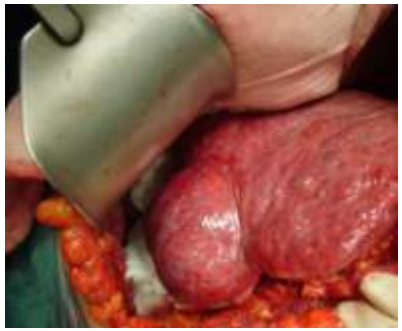
Challenges in Management of HCC

One patient with two diseases



- A highly malignant tumor
  - Rapid growth
    (tumor volume doubling time 3 months)
  - High propensity for venous invasion



- Associated cirrhosis (70-80%)
  Impaired liver function
  Multifocal disease

Majority of patients presented with symptomatic advanced disease in Asia, less than 30% detected by screening in Hong Kong

Chan et al. Ann Surg 2007

Curative Treatments for HCC

- **Surgical resection**: 5-yr survival 55%, high recurrence rate (5-yr 70%)
- **Liver transplantation**: best cure with 5-year survival 75%, only for early HCC, limited graft availability
- **Local ablation**: 5-year survival 50%, overall recurrence rate at 5 years 70-80%

Poon et al. Ann Surg 2001
Ng & Poon. Surg Oncol 2005

Palliative Treatments for HCC

- **Transarterial chemoembolization**: 35-40% response rate, 5 year survival <20%

Poon et al. J Surg Oncol 2000

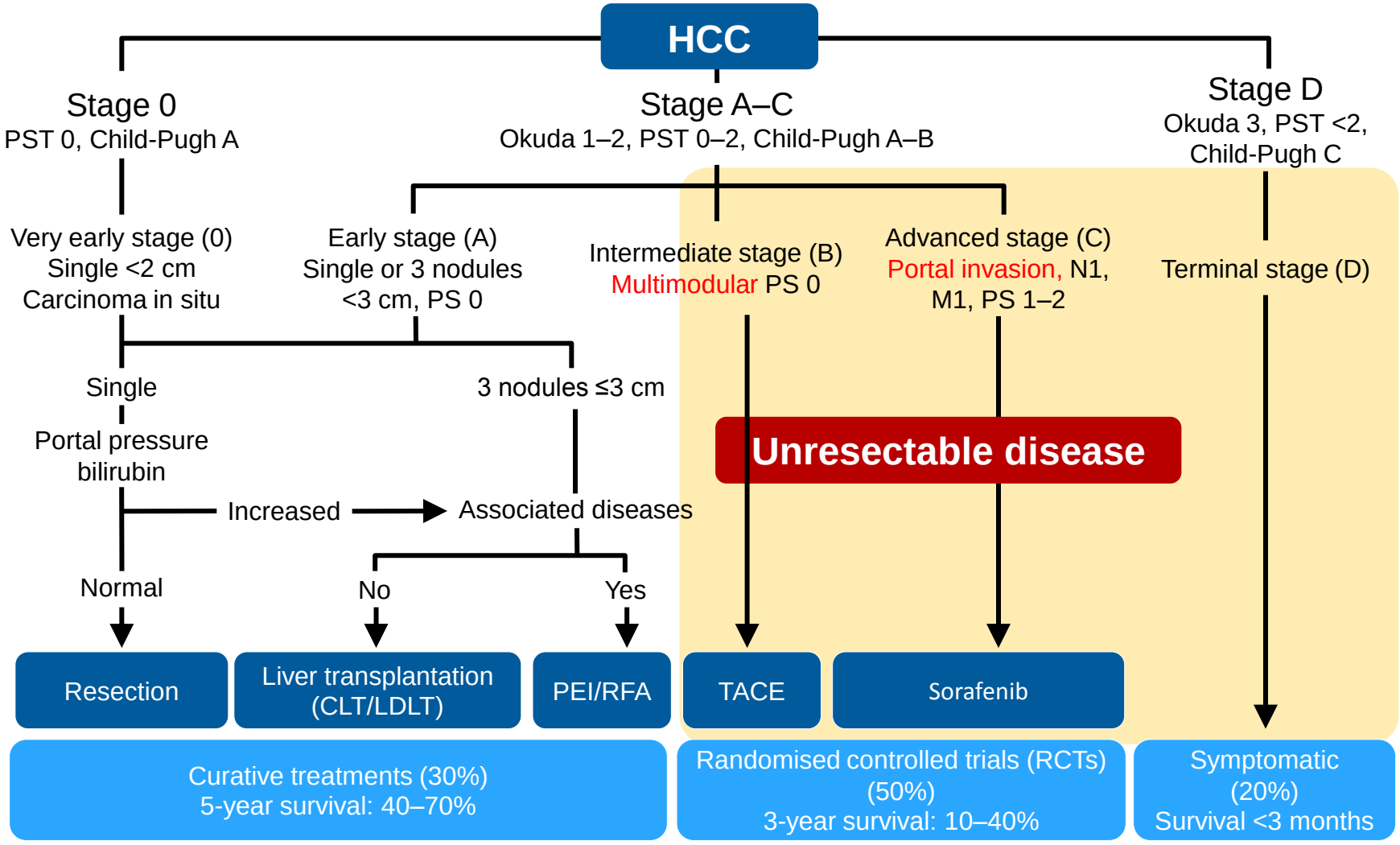
- **Transarterial Y-90 radioembolization**

- **Sorafenib** is the only approved therapy for advanced stage HCC (metastasis or portal vein tumor thrombus):

  - median survival benefit 3 months, response rate < 5%

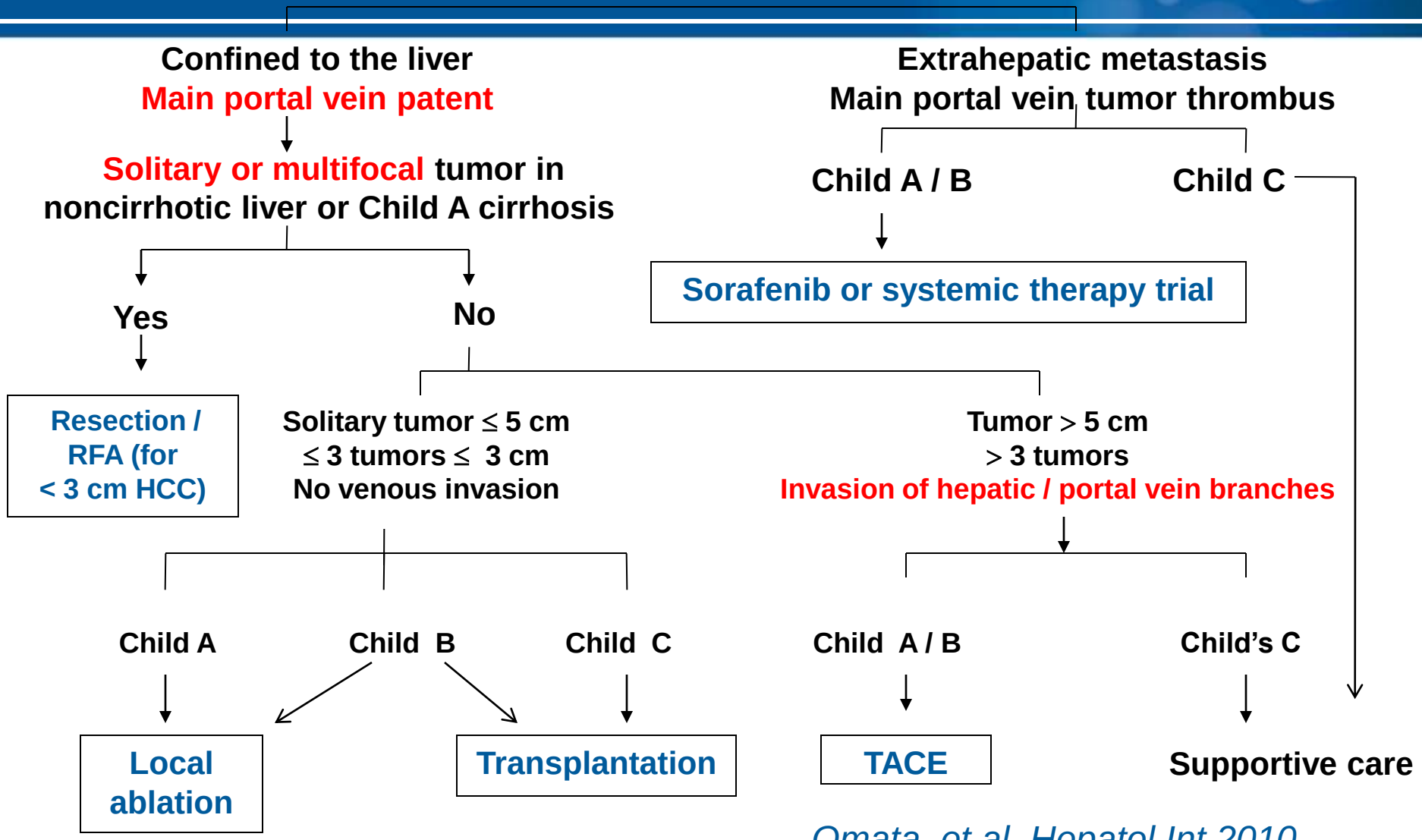
Llovet et al. N Engl J Med 2008

BCLC Staging and Treatment Algorithm



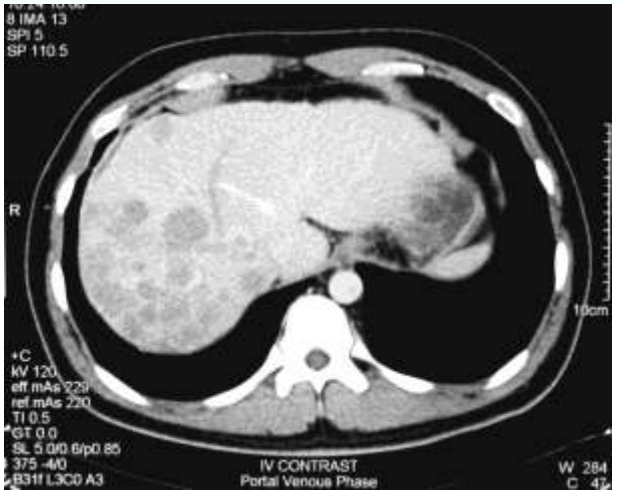
Llovet JM, et al. J Natl Cancer Inst 2008

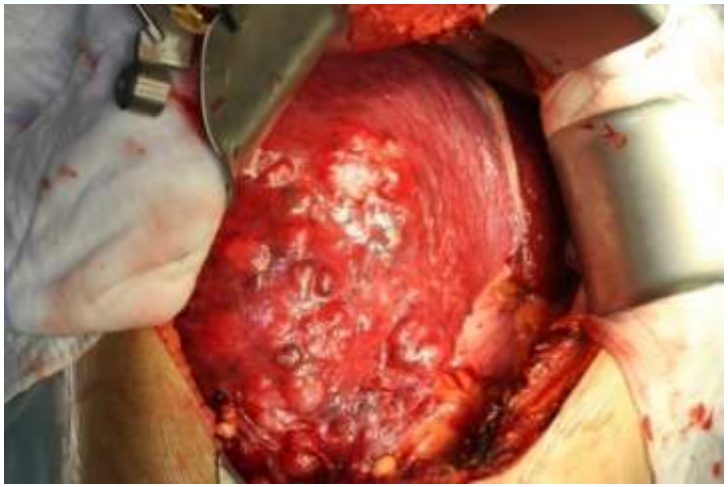
APASL Consensus on Treatment of HCC

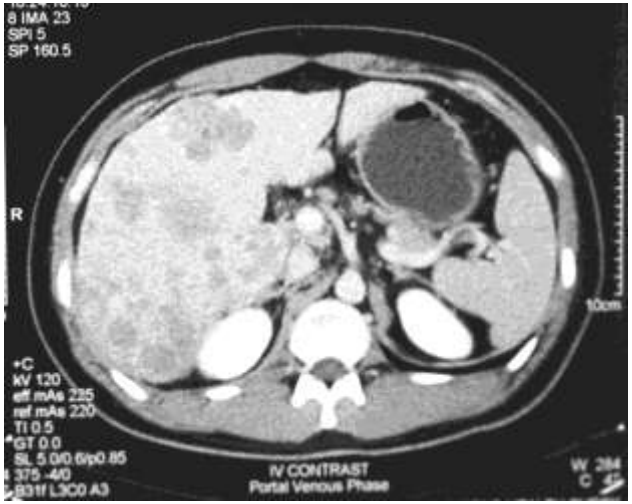


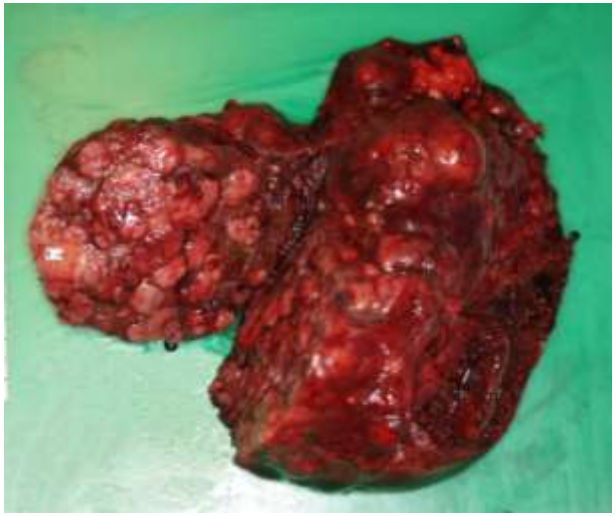
Omata, et al. Hepatol Int 2010

Resection for Multifocal HCC







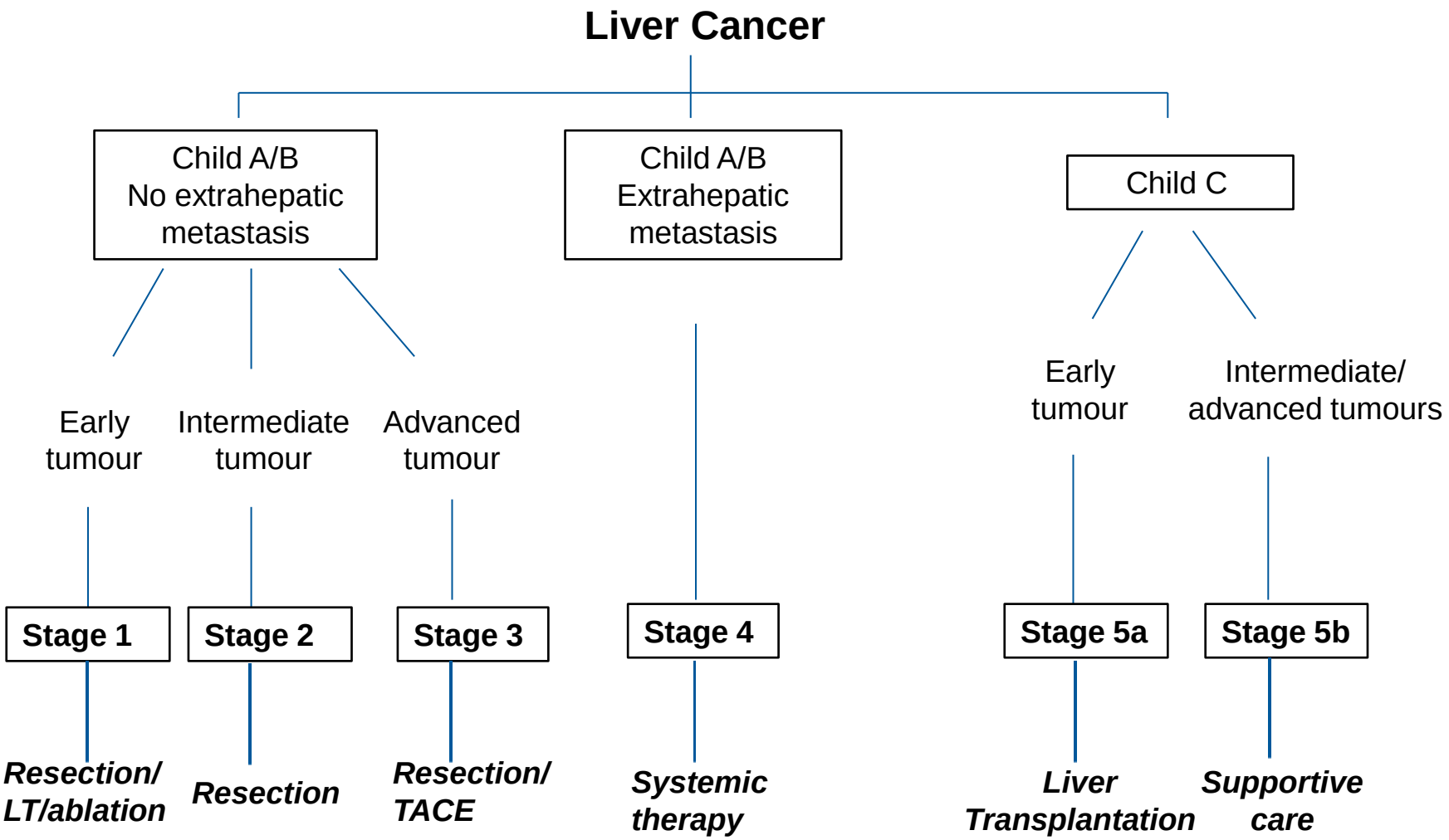


Hong Kong Liver Cancer Staging System

- A new prognostic classification of liver cancer patients based on Cox regression model and classification & regression tree (CART) analysis of 3856 patients treated at QMH between 1995 and 2008

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



Hong Kong Liver Cancer Staging System

- HKLC staging showed significantly better discriminatory ability than BCLC staging

- HKLC staging better stratified patients with intermediate and advanced tumours to different groups, which had better survival outcomes due to more aggressive treatment than what were recommended in BCLC

  - In BCLC-B/HKLC-II patients, the survival benefit of radical curative therapies over TACE was substantial:

    5-year survival: 52% vs 18%; P<0.0001

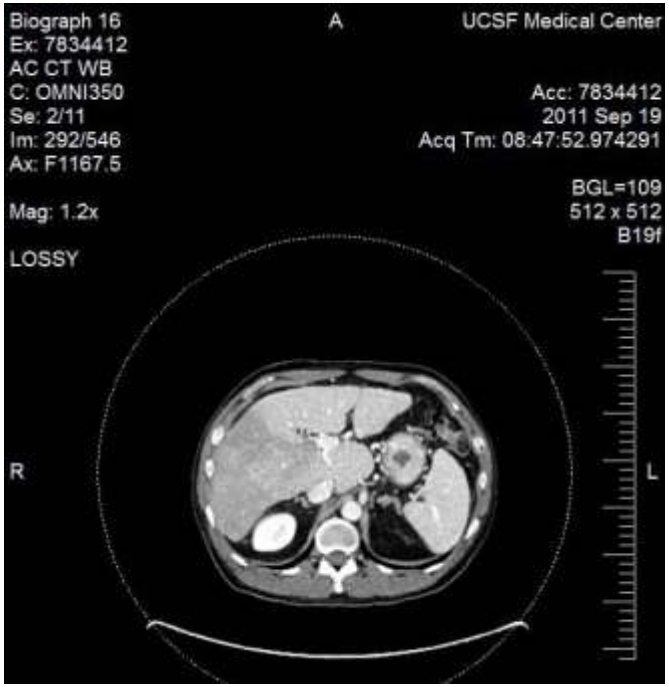
  - In BCLC-C/HKLC-II patients, the survival benefit of radical curative therapies over systemic therapy was even more pronounced:

    5-year survival : 49% vs 0%; P<0.0001

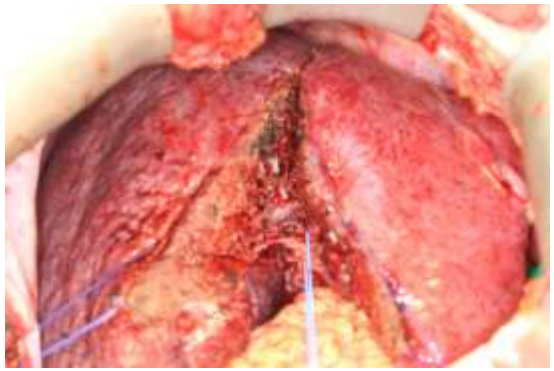
Gastroenterology (in revision)

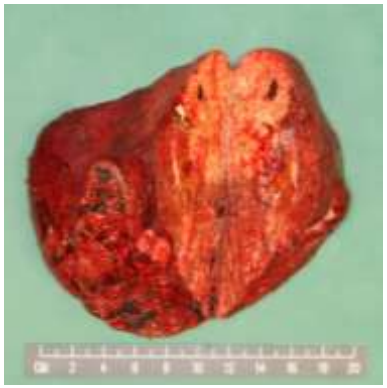
Difference between BLCL and HKLC Staging

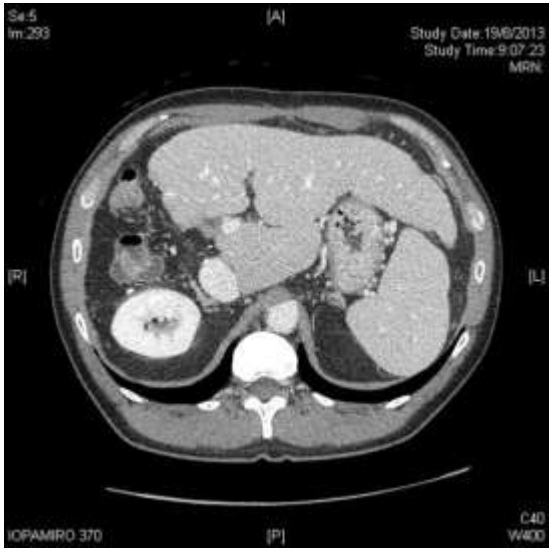
- A 59/M patient from Cebu diagnosed locally advanced liver cancer, deemed inoperable at UCSF, USA due to right portal vein invasion and offered Sorafenib to prolong survival
- Sought second opinion at QMH – extended R hepatectomy performed > 2 years ago, followed by 2 courses of TACE, now disease-free with normal liver function



Preoeprative CT







How to Assess Treatment Outcome for HCC

- Depends on intent of treatment

- Curative

  Resection and liver transplantation – complete extirpation of tumor(s)

  Ablation – complete necrosis of tumor, but a necrotic lesion remains

- Palliative

  Transarterial (TACE or Y-90) – tumor shrinkage and also necrosis

  Targeted therapy – mainly tumor stabilization +/- necrosis

Therapeutic Response Assessment and Endpoints in HCC

- Therapeutic response:
  - complete response (cure)
  - partial response (palliative but potential downstaging to cure)
  - disease stabilization/disease control (palliative)

  Which imaging modality?

  Which imaging criteria?

  What is the role of AFP?

- Endpoints:
  - Time to tumor recurrence/ time to tumor progression (tumor specific)
  - Disease-free survival/ progression-free survival
  - Overall survival

  Death from HCC, cirrhosis and other disease

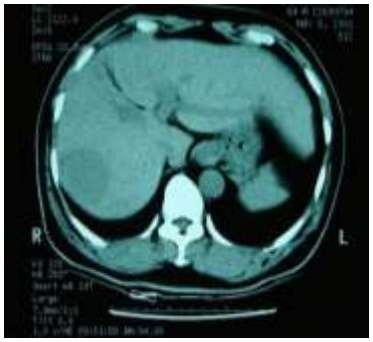
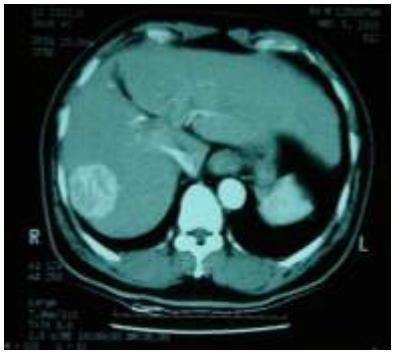
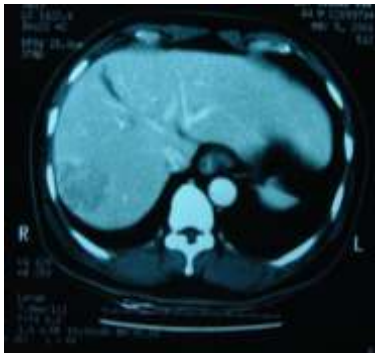
  Which endpoint(s) to use with respect to treatment – resection, ablation, transarterial, systemic therapy

Imaging Techniques for Assessment of HCC Response

- Microbubbles contrast-enhanced USG
- Contrast CT scan
- Contrast MRI scan
- PET scan

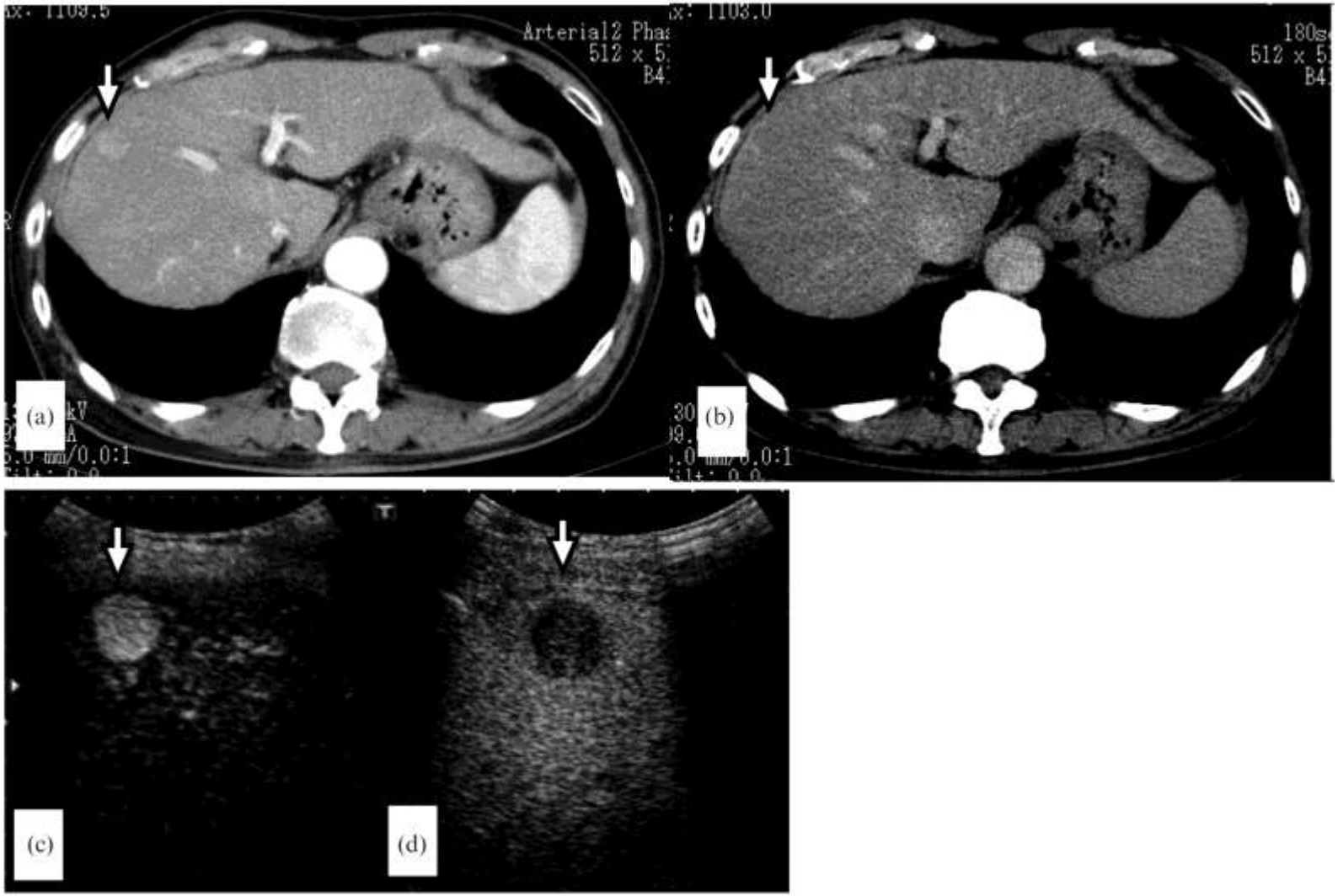
Hallmark of HCC in Imagings

- HCC receives most blood supply from hepatic artery – strong arterial enhancement in contrast-enhanced imagings

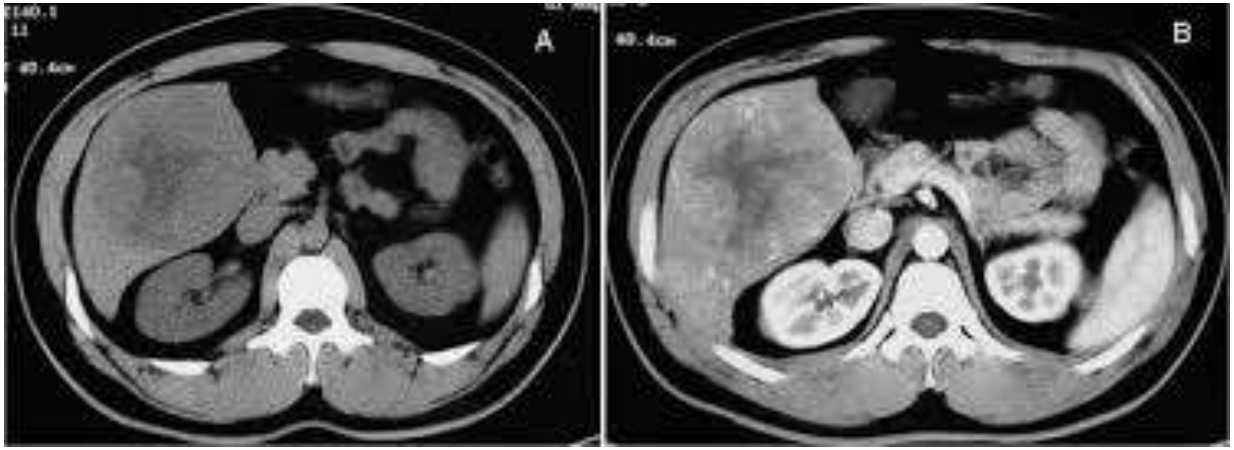




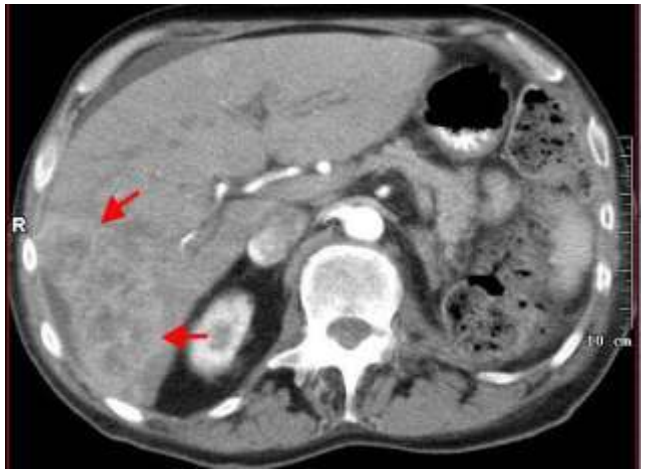
- Assessment of arterial enhancement acceptable as assessment of tumor viability (except hypovascular HCC)

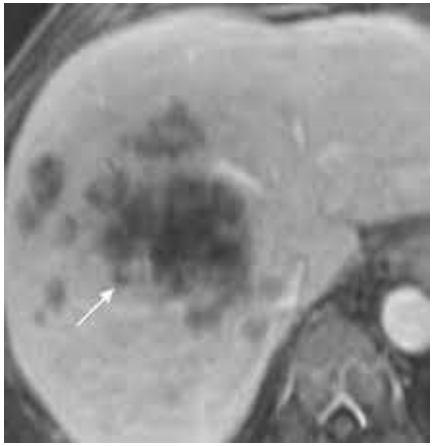
Contrast-enhanced CT Scan and USG



Spontaneous Necrotic Areas in HCC







Comparison with similar pre-treatment imagings critical in treatment response assessment

Ultrasound and Contrast-Enhanced Ultrasound

- CEUS can be used to assess response to locoregional therapy including ablation and TACE:

  - nodules showing no contrast enhancement in the arterial phase correlate with complete necrosis on CT; nodules with persistent arterial vascularization are considered viable tumor deposits

- The potential benefits of CEUS

  - ease of use during or immediately after locoregional therapy
  - high-density iodized oils used in TACE do not limit CEUS interpretation

- Requires instaneous assessment by experienced radiologists

Contrast CT scan

- Mainstay of liver and HCC imaging for both initial tumor characterization and post-treatment follow-up for response assessment

- Quadruple-phase CT preferable for treatment response assessment: -
  - noncontrast images (to characterize residual enhancement in post-treatment cases)
  - arterial phase
  - portal venous phase at 60 or 70 seconds after contrast injection
  - late venous phase (≥ 120 seconds) after contrast injection

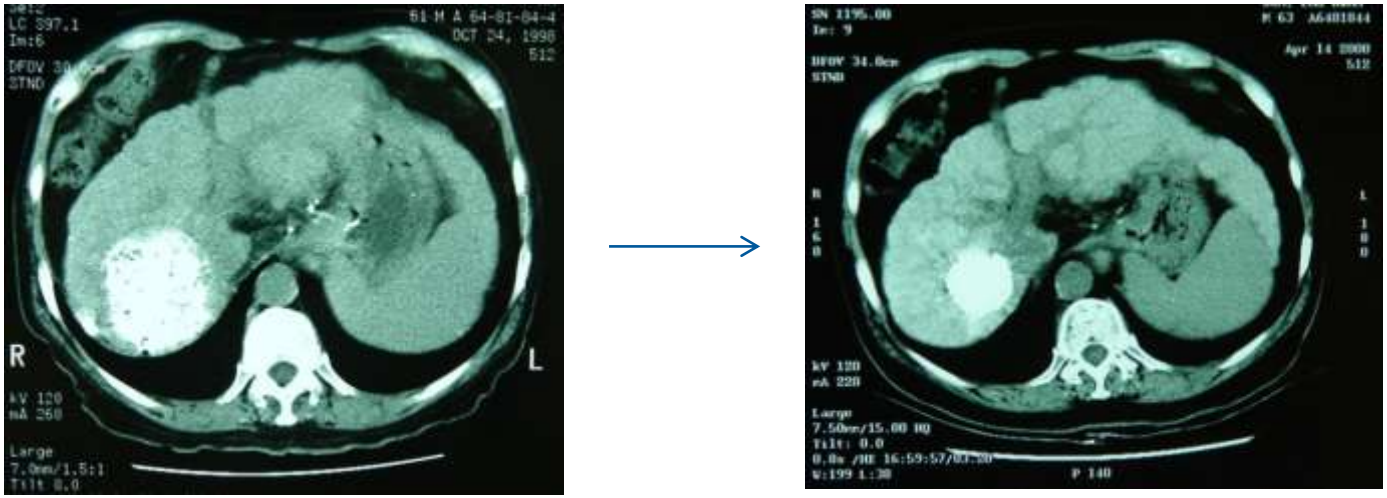
- Dual-energy CT with either two x-ray sources of differing tube voltages or a single source with rapidly alternating tube voltages aids in the detection of residual tumor after locoregional therapy (more sensitive for arterial enhancement)

Lee et al. Invest Radiol 2011

Limitations of Contrast CT scan

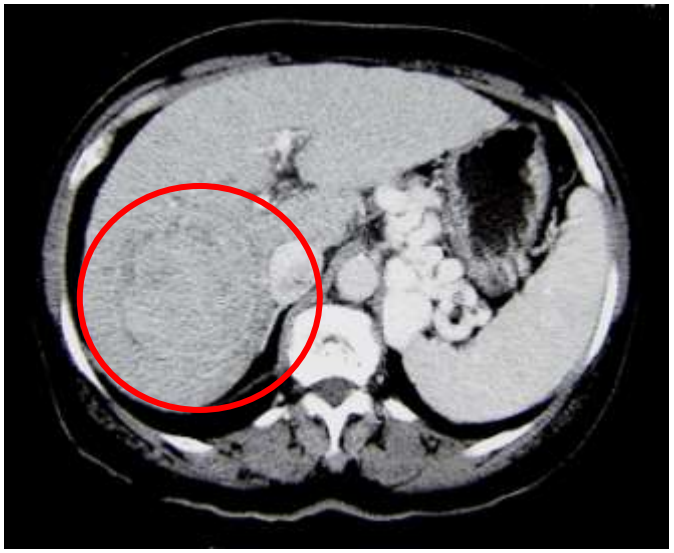
- Hypovascular HCC difficult to differentiate from regenerative/dysplastic nodule

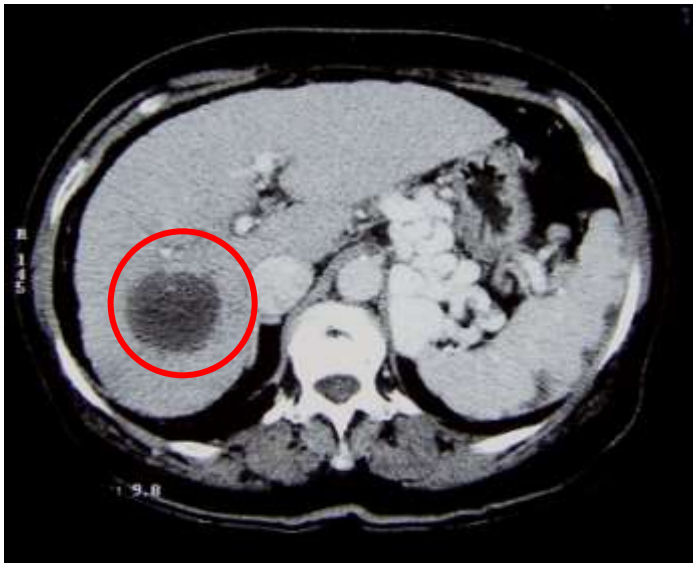
- Lipiodol staining after TACE makes interpretation for tumor necrosis difficult



New TACE without Lipiodol

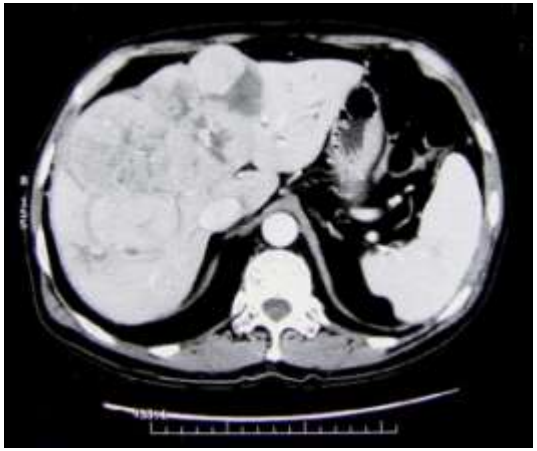
- Doxorubicin eluting beads is a safe and maybe more effective treatment modality for unresectable HCC
- Objective response rate 70% by modified RCIST
- One advantage: no Lipiodol

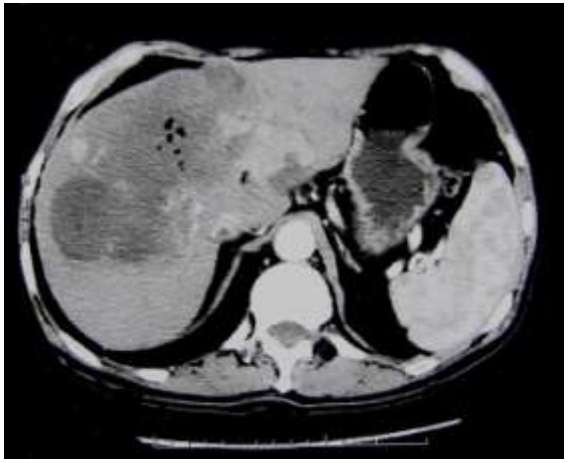


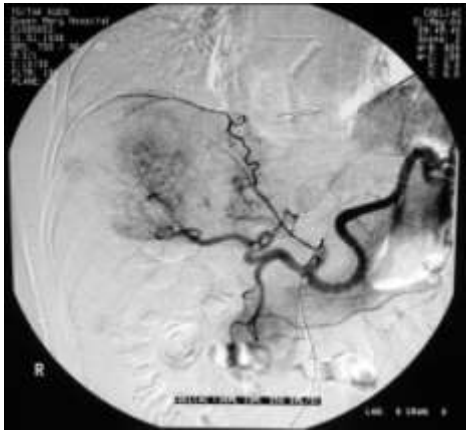


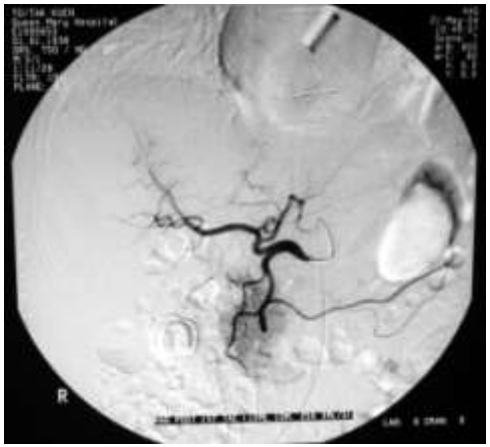
Poon et al. Clin Gastroenterol & Hepatol 2007

TACE with Doxorubicin-eluting Beads









Contrast MRI Scan

- MRI imagings with T1-weighted, T2-weighted, diffusion-weighed imaging (DWI) and T1-weighted imagings before and after dynamic injection of extracellular gadolinium-based contrast agents (GBCAs) or a liver-specific GBCA (e.g. Primovist)

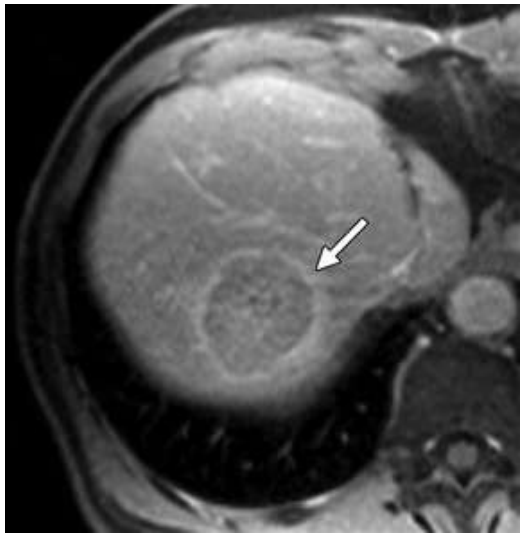
- Contrast-enhanced dynamic T1-weighted imaging with DWI has been shown to be superior to CECT in evaluating patients who have undergone Lipiodol-based TACE as Lipiodol does not adversely affect MR signal-intensity characteristics, so residual enhancement can be detected especially when image subtraction is used

Kloecknor et al. Cardiovasc Intervent Radiol 2010

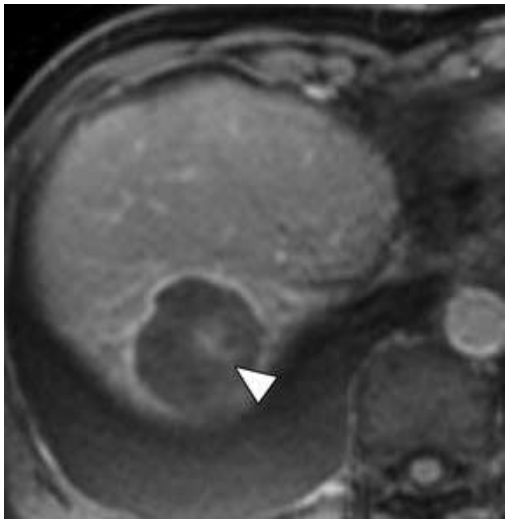
-

MRI Scan

- Lesions treated with RFA or TACE typically undergo coagulative hemorrhagic necrosis that may appear hyperintense on unenhanced T1-weighted imaging, making contrast-enhanced evaluation difficult



Y-90



Central high signal intensity(*arrowhead*) also present on unenhanced T1-weighted image

- Image subtraction techniques with MRI have been shown to be beneficial in depicting residual enhancement, with excellent correlation with histopatho-logic degree of tumor necrosis

Kim et al. Magn Reson Imaging 2010

MRI Scan

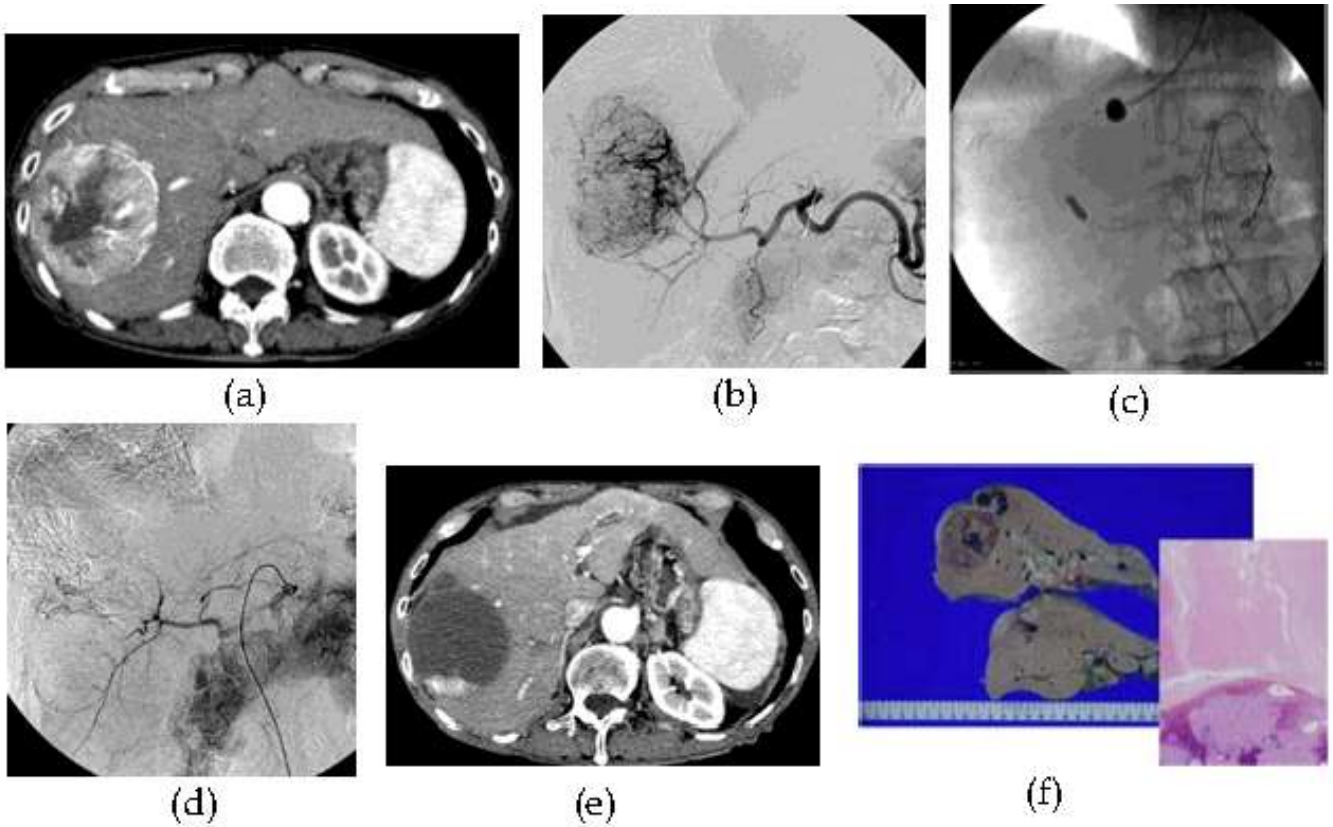
- There is no compelling evidence to use a liver-specific agent such as Primovist for follow-up of treated HCC other than for detecting new tumor foci away from the treated lesion

- There is no clear evidence showing the superiority of MRI or CT for assessing HCC response to therapy except post-Lipiodol TACE - choice of CT or MRI depends on local expertise and availability

- However, MRI with subtraction may be advantageous for the follow-up of patients treated with Lipiodol-based TACE and in patients with questionable areas of residual enhancement on CT after locoregional therapy

Arteriogram

- Vascularization can be assessed with hepatic arteriogram – now only used in transarterial therapy



PET Scan

- FDG PET has limited sensitivity for HCC detection (≈ 60%) and its role in assessing HCC response to therapy is limited

Khan et al. J Hepatol 2000

- Study of 121 HCC patients in Hong Kong with dual-tracer FDG and C-11 acetate PET scan - increases sensitivity for HCC detection to 98% and specificity of 86%

  - 18-FDG detects poorly differentiated HCC

  - 11-acetate detects well- and moderately differentiated HCC

Ho et al. J Nucl Med 2007

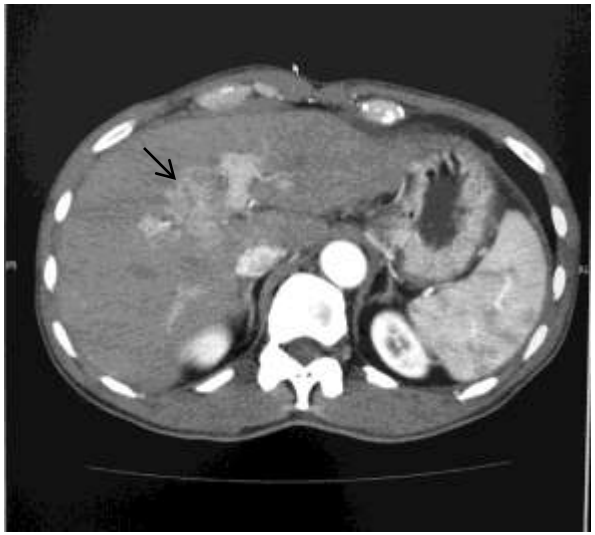
- 58 patients with resection of HCC underwent dual-tracer PET scan:

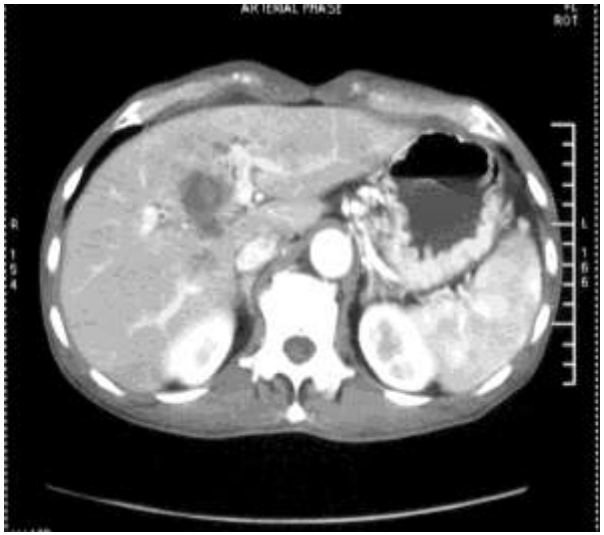
  25 FDG +ve, 56 c-11 acetate +ve

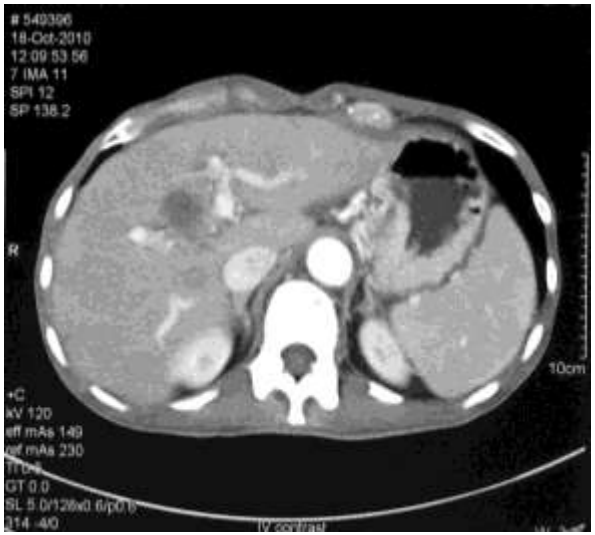
  Preop. FDG uptake predicts microvascular invasion

Cheung et al. Liver Transpl 2011

Dual Tracer PET scan in Treatment Assessment

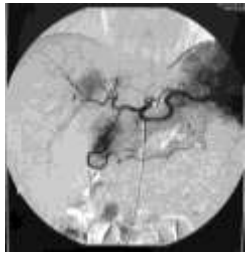






Aug 10
(Dual tracer PET both +ve)

SIRTEX



1 month

3 months
(Dual tracer PET –ve)

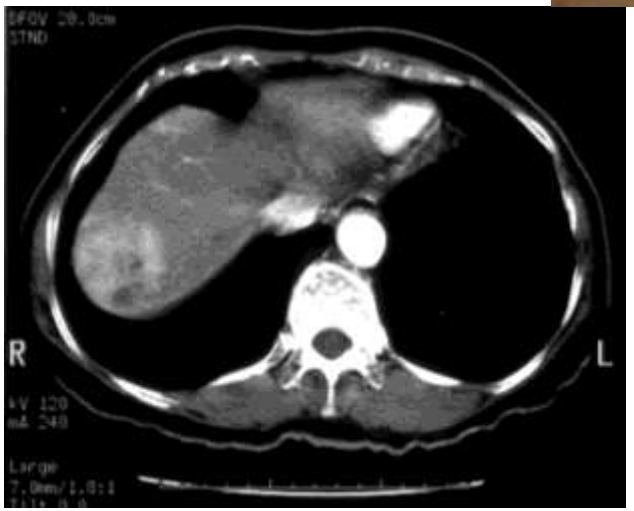
Criteria for Response Assessment in Imagings

- Conventional criteria based on change in tumor size alone:
  - WHO criteria: incorporating bidimensional perpendicular measurements
  - RECIST criteria: incorporating uni-dimensional measurements

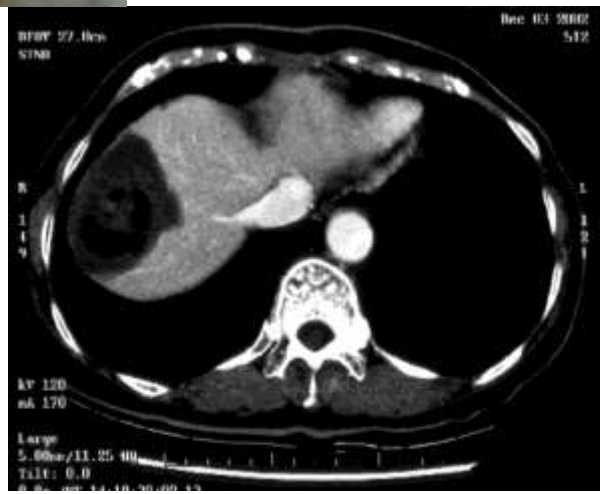
- Intended to evaluate change in tumor size after systemic chemotherapy which induce tumor cell apoptosis, and do not take into account changes in tumor vascularity or necrosis

- Objective of effective locoregional therapy is to obtain tumor necrosis regardless of the presence of changes in size, response based on size changes may not be achieved especially in the first few weeks after therapy, because tumor shrinkage may be delayed.

- After locoregional therapy, a treated HCC can possibly increase in size secondary to intratumoral edema, hemorrhage, or necrosis of surrounding tissues



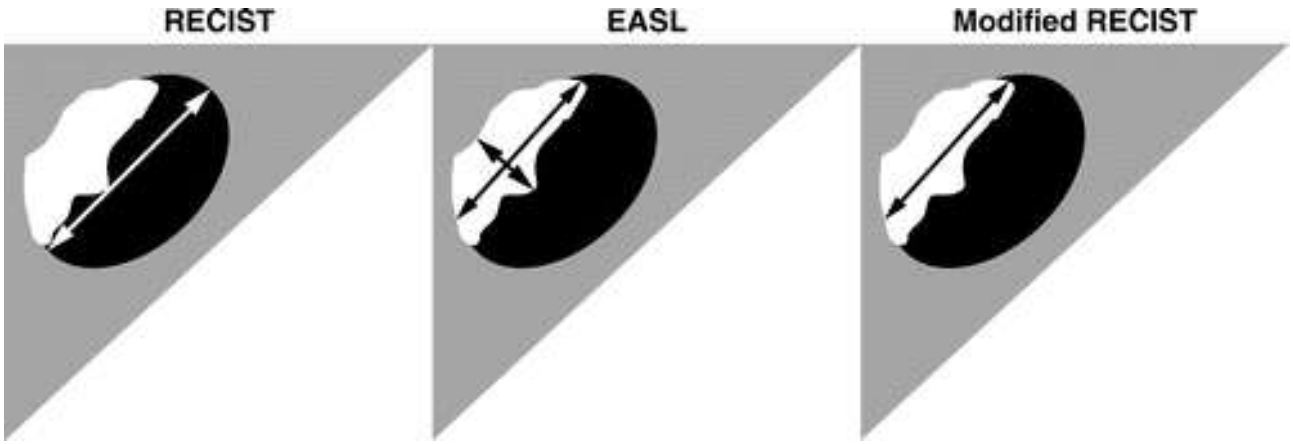
Increase in lesion size but complete necrosis



Criteria for Response Assessment in Imagings

- New criteria take into account tumor necrosis on CT and MRI proposed :

- The criteria proposed by the European Association for the Study of the Liver (EASL) are based on modified WHO bidimensional measurements to estimate tumor response
- Modified RECIST uses the single largest diameter of the viable tumor (defined as the component enhancing during the arterial phase) and is more practical for clinical use



Bruix et al. J Hepatol 2001
Lenioni et al. Semin Liver Dis 2010

EASL vs. Modified RECIST Criteria

Assessment Category	EASL Criteria[a]	Modified RECIST[b]
CR	Disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least 50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart	At least 30% decrease in the sum of diameters of viable target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	At least 25% increase in size of one or more measurable lesions or the appearance of new lesions	At least 20% increase in the sum of the diameters of viable target lesions

Note—Both methods are based on CT or MRI using contrast-enhanced arterial phase images (see also Fig. 1). CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.
[a]Bidimensional measurements.
[b]Unidimensional measurements.

The EASL and European Organisation for Research and Treatment of Cancer (EORTC) have recently endorsed the use of the modified RECIST criteria for the assessment of HCC response based on dynamic CT or MRI performed 1 month after locoregional therapy or systemic therapy.

J Hepatol 2012; 56:908–943

Modified RECIST Criteria – The Current Standard

- Several recent studies have shown modified RECIST to be superior to RECIST in predicting HCC response to TACE :

  - A significant independent association between overall survival after TACE and EASL and modified RECIST responses, whereas there was no significant association between survival and RECIST 1.1 response

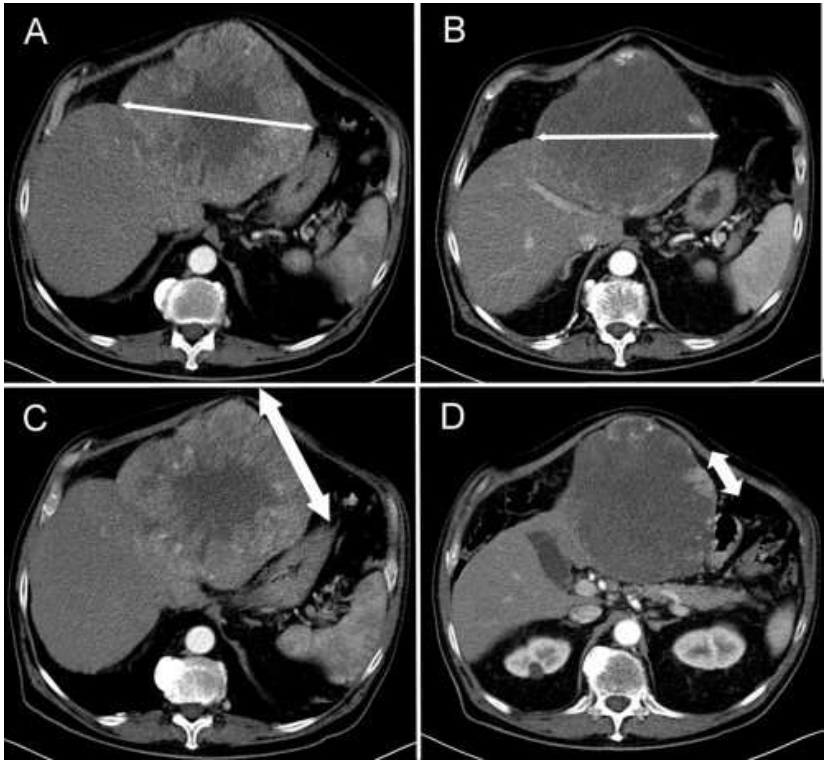
Gillmore et al. J Hepatol 2011
Kim et al. Eur J Cancer 2013

- Response assessments based on EASL criteria and modified RECIST performed approximately 1 month after therapy with TACE using drug-eluting beads have been shown to predict survival, with better performance for the modified RECIST guidelines

Prajapati et al. Ann Oncol 2012

Modified RECIST Criteria in Sorafenib Treatment

- 53 patients who received Sorafenib for advanced HCC underwent a 4-phase CT scan before treatment and repeatedly thereafter
- The rates of objective response 2% according to RECIST and 23% according to mRECIST
- Objective response according to mRECIST predicted better survival, but not according to RECIST



Edeline et al. Cancer 2012

Modified RECIST Criteria – The Current Standard

- Measurements of the two largest target lesions have been shown to be adequate for the assessment of HCC response to TACE when using modified RECIST guidelines

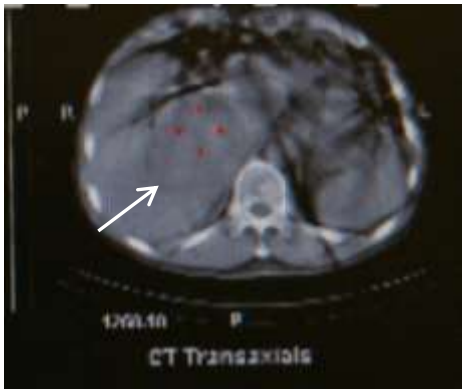
Shim et al. Radiology 2012
Kim et al. Eur J Cancer 2013

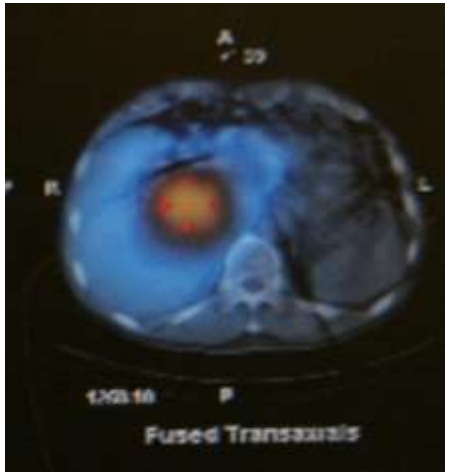
- Limitations: subjective element in choosing the largest diameter of tumor necrosis; it is difficult to measure with confidence in diffusely necrotic lesions with intervening viable components or diffusely infiltrative tumors

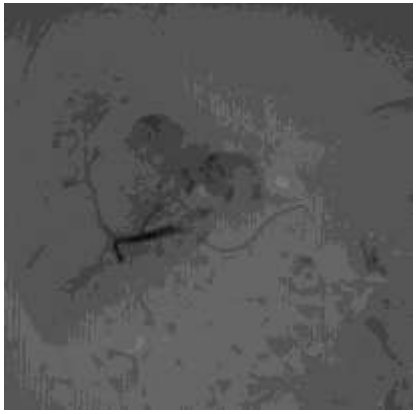
- The modified RECIST criteria have not been validated for assessing HCC after transarterial radioembolization and RFA

Transarterial Yttrium-90 Radioembolization

M/73 patients with previous left hepatectomy for intrahepatic stones, diagnosed 8 cm R lobe HCC

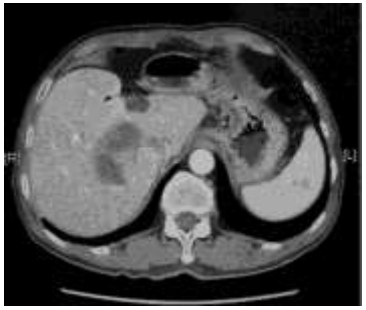


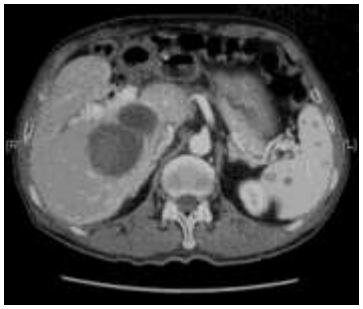


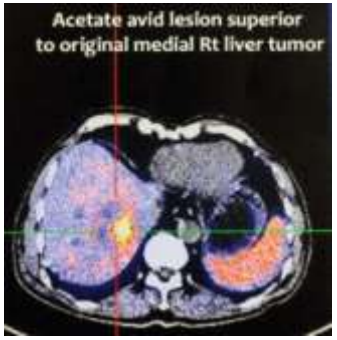


Y-90 therapy

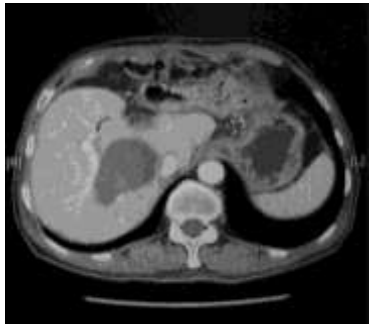
Partial response

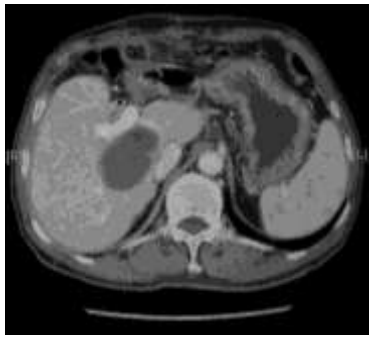






Open RFA





Complete response

Disease-free for 1 year

2D versus 3D Assessment of Tumor Response

- The anatomic imaging biomarkers based on 2D CT or MRI assume that tumors are spherical before and after treatment:

  In modified RECIST, a 30% decrease in diameter of viable tumor, defined as the threshold for partial response, is presumed to correspond to a 65% decrease in viable tumor volume.

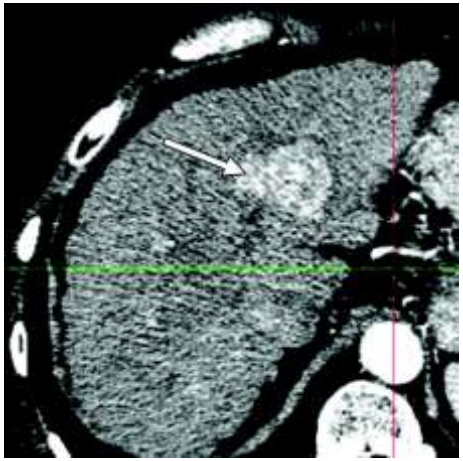
  Similarly, a 20% increase in diameter of viable tumor, which defines the threshold for defining disease progression, corresponds to an approximately 73% increase in spherical volume.

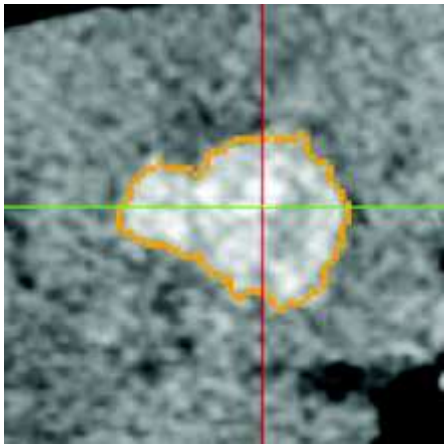
- Limitations: most tumors not spherical; prone to interobserver measurement variability with 2D measurements

- In a retrospective study of 45 HCCs, diameter based on 3D measurements was significantly different from diameter based on conventional 2D measurements

Galizia et al. Acta Radiol 2011

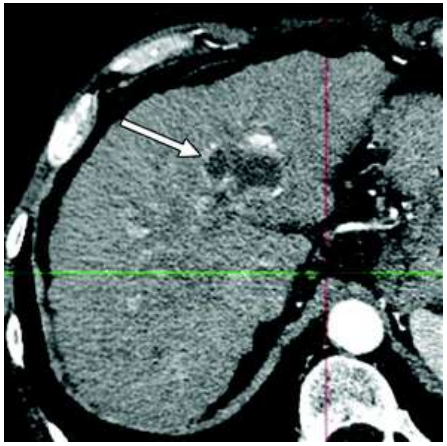
Volumetric Tumor Response Assessment

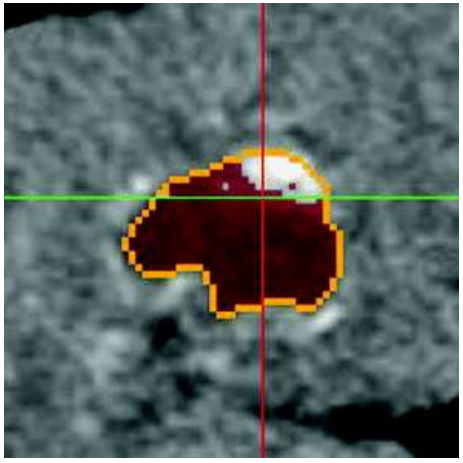




HCC measures 40.5 mm in maximum dimension; volume 15.5 mL after semiautomated segmentation in Voxel-by-voxel volumetric analysis in CT scan

Y90 treatment





Maximum size of viable tumor is 33.9 mm. Decrease of 16% should be considered stable disease according to RECIST. However, tumor volume has decreased to 8.66 mL (–44%) and residual enhancing component (viable tumor) constitutes only 7.7% of tumor.

Yaghmai et al. AJR 2013

Volumetric Tumor Response Assessment

Volumetric functional magnetic resonance (MR) results 3-4 weeks after initial intraarterial therapy using 2 parameters in 143 patients with HCC :

- 25% or more increase in apparent diffusion coefficient
- 65% or more decrease in enhancement

- OS of dual-parameter responders significantly better than single-parameter responders (P = .01), and of single-parameter responders significantly better than those with SD (P = .001)
- RECIST, mRECIST, and EASL stratification was short of significant; most lesions were classified as stable
- Volumetric functional MR was superior to current imaging criteria (RECIST, mRECIST, and EASL)

Bonekamp et al. Radiology 2013

Volumetric Tumor Response Assessment

- Volumetric evaluation of HCC and its necrotic component eliminates limitation of modified RECIST and offers the most comprehensive anatomic evaluation for determining treatment response

- Volumetric quantification is particularly helpful in cases in which necrosis is heterogeneously distributed in HCC and cannot be assessed using modified RECIST

- However, volumetric measurement is not easily feasible in the routine clinical setting and is still not included in tumor response criteria

Chalian et al. Radiology 2012

-

Role of AFP in Therapeutic Response Assessment

- AFP not recommended as an endpoint for assessment of therapeutic response in clinical trial

  -- fluctuations of AFP levels can result from flares of viral reactivation that are unrelated to cancer development

  Llovet et al. J Nat Inst Cancer 2008

- Viral reactivation common after surgical resection (about 20%) and TACE for HCC

  Huang et al. J Gastroenterol Hepatol 2012
  Jang et al. J Hepatol 2004

- Effective antiviral therapy for HBV reduces fluctuation of AFP level due to viral reactivation from treatment

Role of AFP in Therapeutic Response Assessment

- After resection of HCC with raised preoperative AFP, patients who normalized AFP had a lower risk of tumor recurrence (both early and late) in comparison with the remaining patients (hazard ratio 0.3, 95% CI: 0.15–0.48; P < .0001). On average, AFP returned to normal values within 2 months.

Mazzaferro et al. Hepatology 2006

- Study of 173 patients with HCC treated by intra-arterial therapy:

  - AFP responders versus AFP nonresponders had decreased risk of death (HR = 0.36, P = .002), whereas RECIST, mRECIST, and EASL stratification was short of significant; most lesions were classified as stable disease

Bonekamp et al. Radiology 2013

AFP is useful in following patients receiving curative or palliative treatments for HCC, complementary to imagings in treatment decision

AFP Change as Early Predictor of Response/Benefit in Sorafenib Treatment for HCC

- Serum AFP collected prospectively at baseline and subsequent follow-up visits in parallel with imaging and survival outcomes in 94 patients with advanced HCC and elevated AFP treated by Sorafenib at QMH

- AFP response was defined as a *relative drop of AFP >20% of the baseline level after 6 weeks of sorafenib*

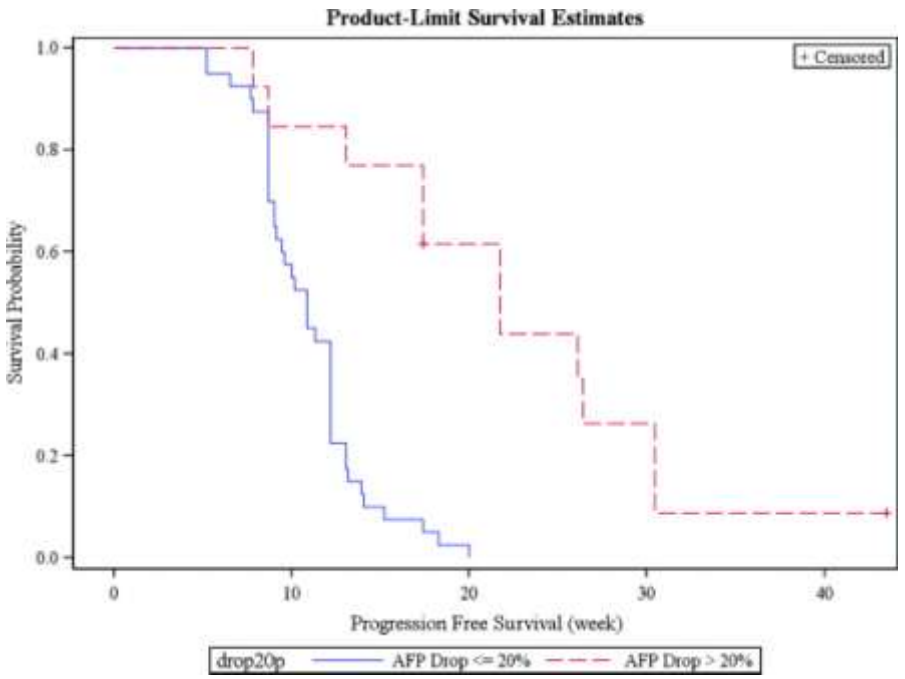
- Clinical benefit (CB) defined as having a best response of complete response, PR, or SD according to imaging by RECIST 1.0 criteria

- AFP response ($p = .04$) was significantly associated with CB rate at 12 weeks: relative chance of CB for AFP responders (44.4%) vs. AFP nonresponders (12.9%) was estimated to be 3.4 (95% CI, 1.1–11.1)

Yau et al. oncologist 2011

AFP Change as Early Predictor of Response/Benefit in Sorafenib Treatment for HCC

- The AFP response was highly associated with progression-free survival ($p < .001$)
- Notably, the use of antivirus therapy did not seem to affect the prognostic value of AFP response on progression-free survival
- Multivariate analysis indicated AFP response was independent prognostic factor associated with better PFS and OS



Yau et al. oncologist 2011

AFP Response in Sorafenib Treatment

- In 66 patients with advanced HCC treated with sorafenib, response to treatment was evaluated by RECIST, mRECIST and changes in AFP
- The response by RECIST and mRECIST were 3.0 and 9.0%, respectively; assessment by mRECIST of overall survival provided a better stratification of the patients than RECIST ($p = 0.09$)
- Overall survival by a change in AFP ratio of ≤ 1 at 8 weeks was better than that of >1 at 8 weeks ($p = 0.002$)
- Multivariate analysis identified mRECIST response and AFP ratio at 8 weeks as independent prognostic factors – can be combined in assessment of response to Sorafenib

Kawaoka et al. Oncology 2012

Endpoints in HCC Treatment

- Difference according to treatments:
  curative vs. locoregional palliative vs. systemic therapy

- Difference between clinical use vs. clinical trial design

Endpoint of Surgical Resection of HCC

- Mainstay of curative treatment for HCC

- 5-year **overall survival** rate is the standard primary endpoint in surgical treatment of cancer:

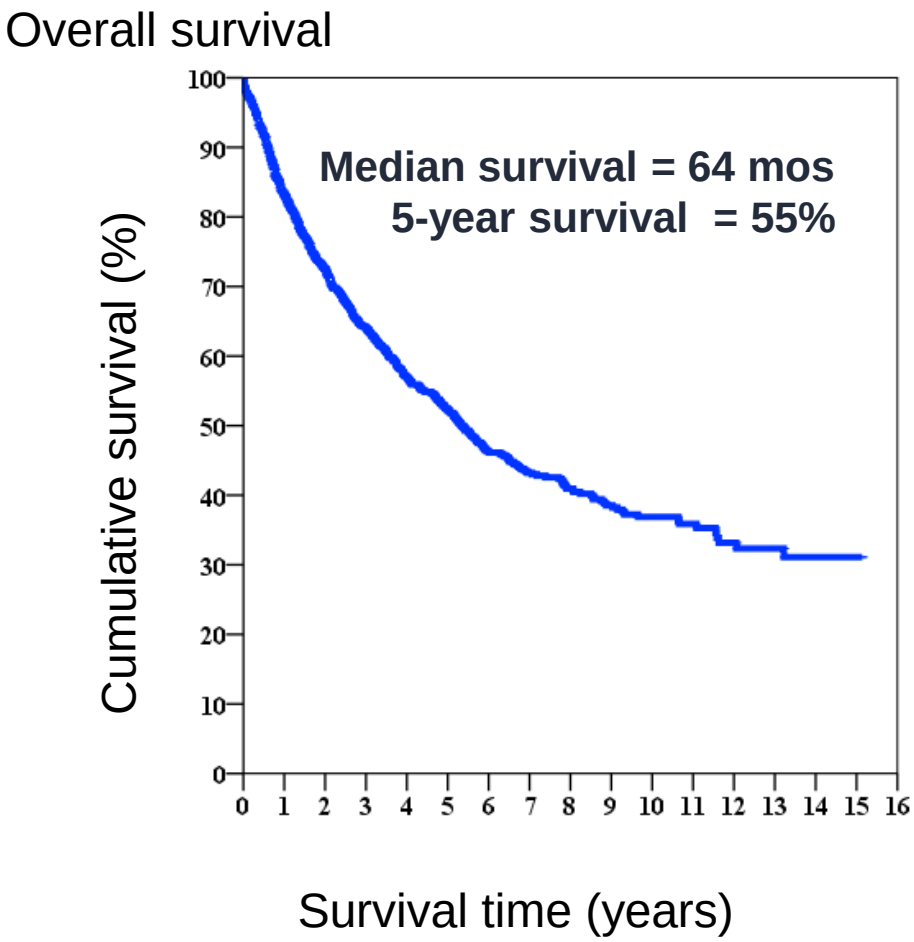
  Time from treatment to death from cancer or any other causes - patients alive at the end of follow-up are censored

- **Median survival** provides easier interpretation when comparing results

Hepatectomy for HCC 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)
Solitary: Multiple	924:358
Macroscopic venous invasion*	105 (8%)

Long-term Survival Results



Overall Survival versus Cancer-Specific Survival

- Overall survival: all deaths from cancer recurrence and all other causes are considered for survival analysis

- Cancer-specific survival: only deaths due to cancer are considered for survival analysis and non–cancer-related deaths are censored

- Cancer-specific survival theoretically better reflect outcome of cancer-specific intervention, however, overall survival is preferable in resection or other treatments of HCC because:

  1. Hepatic resection or other intervention can cause deterioration of liver function, and death from liver failure should be taken into account
  2. In cirrhotic patients who have cancer recurrence, it is often difficult to differentiate death from cancer and liver failure

Resection Endpoint - Time to Recurrence

- Time from treatment to radiological recurrence - deaths during follow-up without evidence of radiological recurrence are censored.

- Recurrence is a relevant patient outcome as it indicates failure of “curative intent”, majority (>80%) deaths after resection of HCC from tumor recurrence

Poon et al. Ann Surg 2001

- Problems:

1. Difficulty in differentiating between a true recurrent tumors vs. dysplastic nodules in cirrhosis, and often no histological proof due to difficulty in biopsy
2. Difficulty in differentiating between metastatic vs. multicentric recurrence (important in evaluating efficacy of adjuvant therapy)

Metastatic vs. Multicentric Recurrence

- In 25 HCC nodules from 11 patients with multiple HCCs, the clonal relationships of the nodules within individual patients were determined using DNA fingerprinting with loss of heterozygosity (LOH) assay, comparative genomic hybridization (CGH), and hepatitis B virus (HBV) integration pattern

- In 36% of the patients, the multiple HCCs had different clonalities and hence were of multicentric origin, whereas in the remaining 64% patients, the multiple HCCs had similar clonal relationships and were intrahepatic metastases

  Ng et al. J Pathol 2003

- Early recurrence within first two years more likely intrahepatic metastasis, whereas recurrence beyond two years more likely multicentric recurrence based on risk factor analysis

  Poon et al. Cancer 2000

Relevance of Metastatic vs. Multicentric Occurrence in Outcome Analysis of Treatment

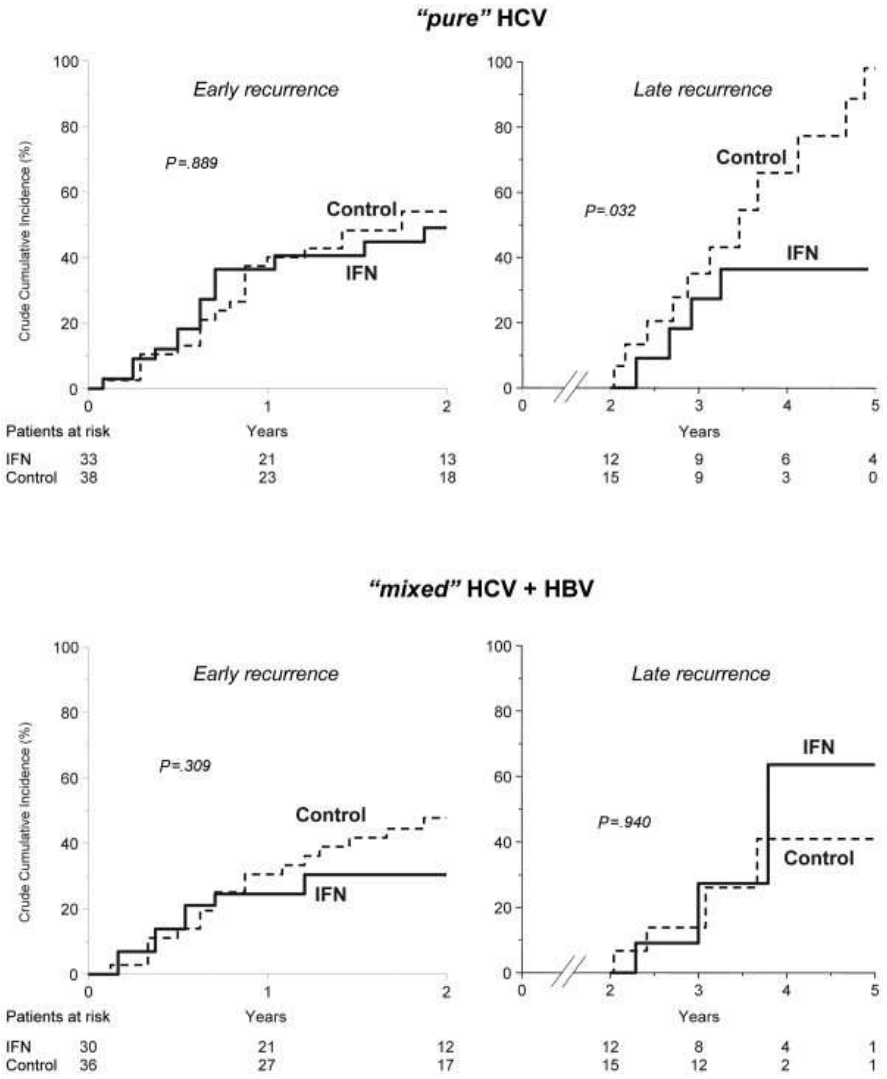
- Adjuvant chemotherapy or molecular targeted therapy should theoretically affects metastatic recurrence but less likely multicentric recurrence

- Antiviral therapy or chemopreventive drugs (e.g. interferon, retinoid) should theoretically affects multicentric recurrence

Differentiation of the two helps in evaluation of treatment effects of different adjuvant therapies

Effect of Interferon on Time-to-Recurrence after Resection of HCV-related HCC

- 150 HCV RNA–positive patients undergoing resection of BCLC early- to intermediate-stage HCC randomized to adjuvant interferon therapy vs. control
- Interferon resulted in significant reduction of late recurrence > 2 yrs. post- resection in HCV pure group by 50%, but no effect on early recurrence
- Likely chemopreventive effect on HCV-related carcinogenesis

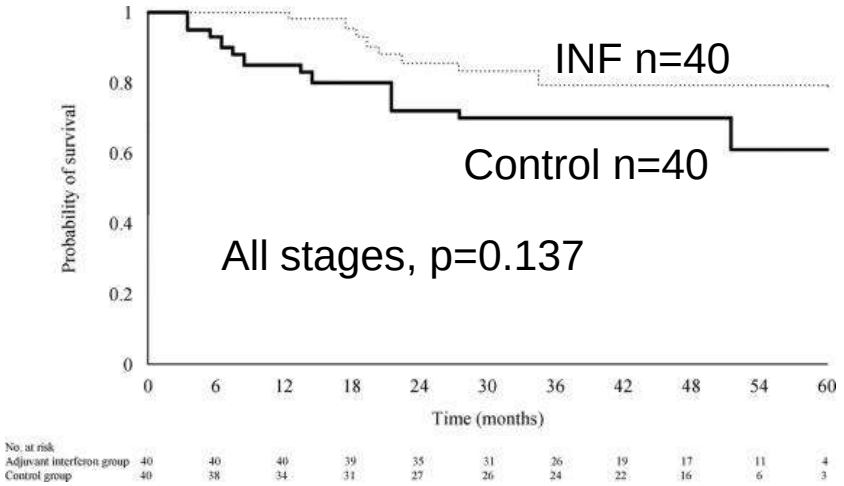


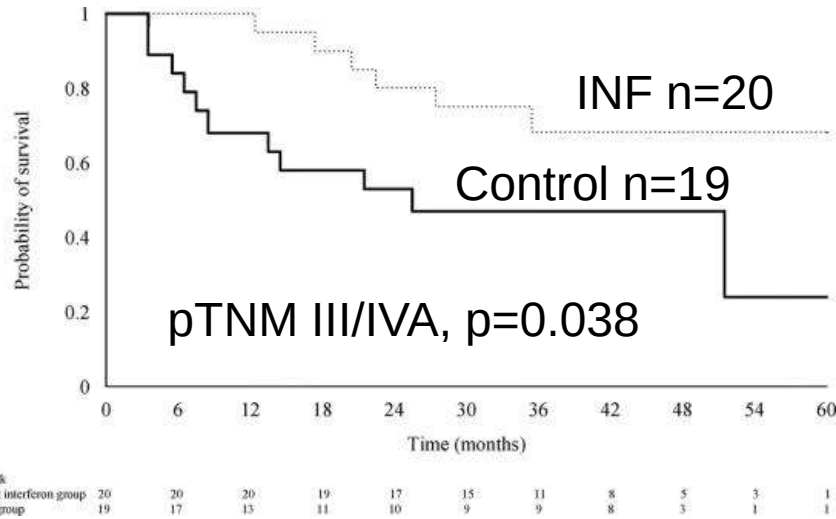
Mazaffero et al. Hepatology 2006

Effect of Interferon on Time-to-Recurrence after Resection of HBV-related HCC

- 80 patients with HCC resection at QMH randomized to interferon vs. control
- 90% HBV+ve, only 3.75% HCV+ve
- No significant difference in overall survival (5-yr. survival 79% in INF group vs. 61% control group)
- Subgroup analysis suggested survival benefit in pTNM stage III/IVA patients

Lo et al. Ann Surg 2007





Effect of Interferon on Time-to-Recurrence after Resection of Predominantly HBV-related HCC

TABLE 4. Comparison of Cumulative Number of Recurrence by Treatment Groups

	Duration of Follow-up (mo)						
	6	12	18	24	36	48	60
All patients							
Control group (n = 40)	10*	12	16	18	20	21	22
IFN-I group (n = 40)	3	9	16	17	20	20	21
pTNM stage I/II							
Control group (n = 21)	2	3	5	5	6	7	7
IFN-I group (n = 20)	1	3	4	5	6	6	7
pTNM stage III/IVA							
Control group (n = 19)	8†	9	11	13	14	14	15
IFN-I group (n = 20)	2	6	12	12	14	14	14

*P = 0.034, comparing control group to IFN-I group.
†P = 0.031, comparing control group to IFN-I group.
pTNM indicates pathologic tumor node metastasis.

There were significantly fewer early recurrences at 6 months after surgery in the IFN-I group (10 of 40 patients vs. 3 of 40 patients; P = 0.034), and this difference in early recurrence rate seen only in patients with pTNM stage III/IVA

Interferon may act as anticancer agent rather than chemopreventive agent

Disease-free Survival after Resection of HCC

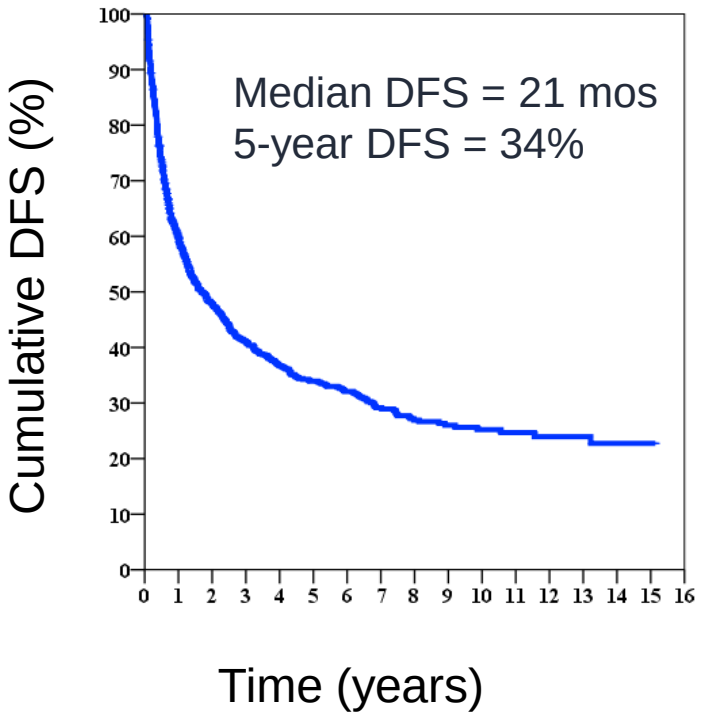
- Composite endpoints that include two types of variables:

  death and evidence of radiological recurrence

- Commonly used clinical endpoint to show “curative” effect of surgical resection

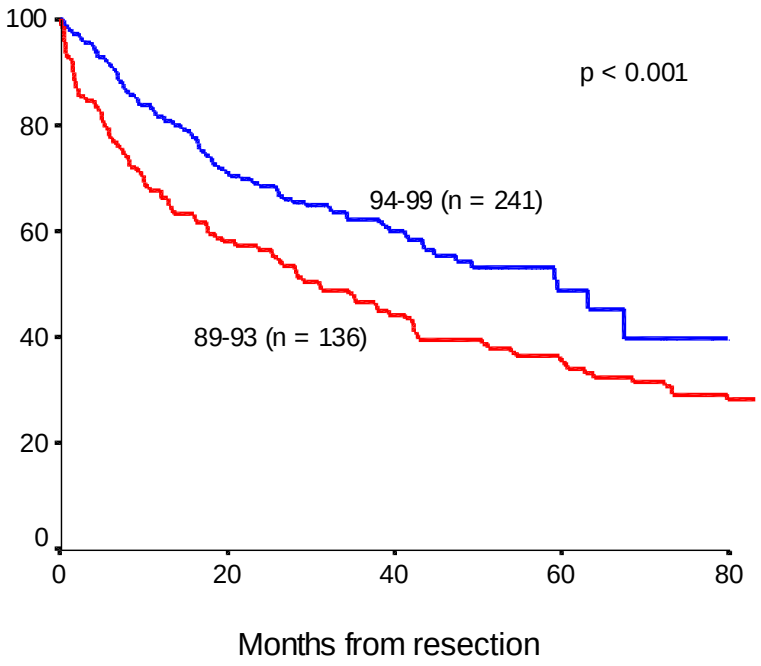
- Disease-free survival is not supported for assessment of adjuvant therapies after resection because of the confounding composite nature of this endpoint

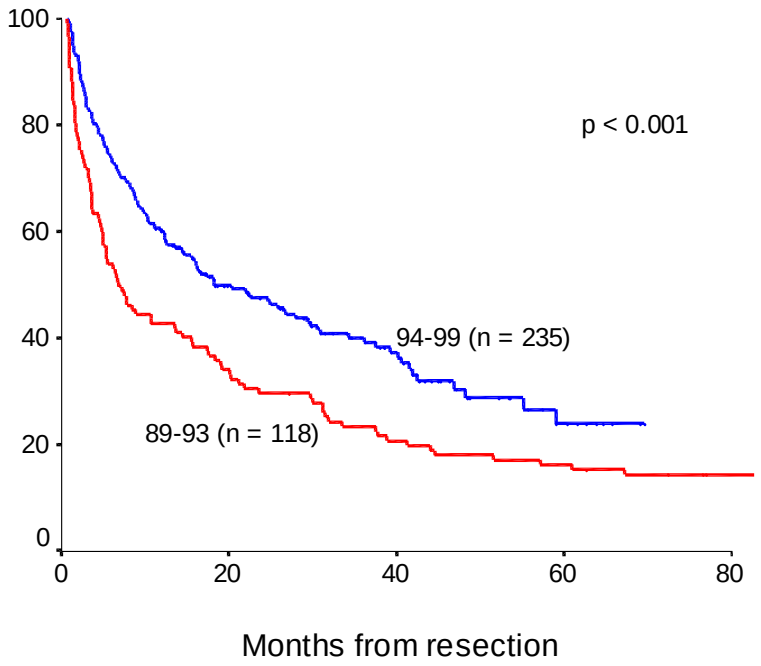
Llovet et al. J Nat Inst Cancer 2008



Disease-free survival after resection of HCC in 1282 patients at QMH

Disease-free Survival – Comparison of Two Periods





5-yr overall survival improved from 37% vs. 50%

5-yr. disease-free survival improved from 16% to 25%

Two independent factors for improved survival:

-Reduced blood loss and perioperative blood transfusion

-Earlier diagnosis of HCC by screening

Poon et al. Annals of Surgery 2001

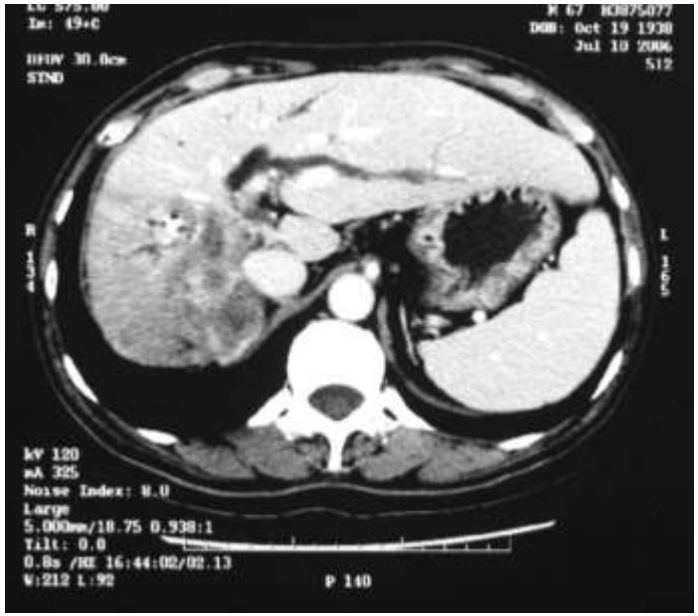
Is Resection of HCC with Macroscopic Venous Invasion Justified?

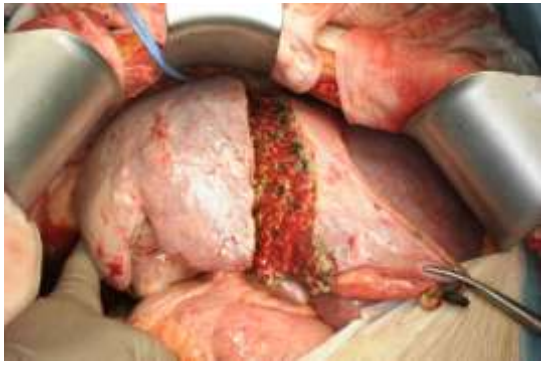
Both overall and disease-free survival important in evaluation of surgical treatment

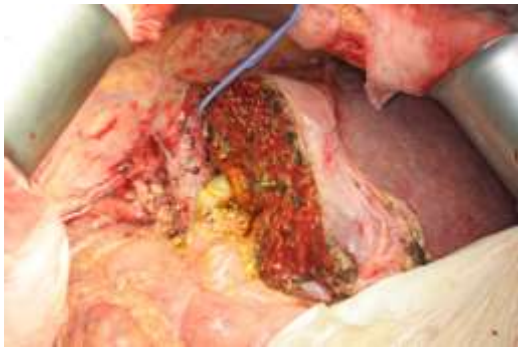
	All patients (n=1282)
Age [Median (Range)]	57 (5-89)
Sex (M:F)	1035:247
Hepatitis B	1092 (85.2%)
Hepatitis C	55 (4.3%)
Cirrhosis	783 (61.1%)
AFP [Median (Range)]	83.5 (1-1,335,900)
Tumor size [Median (Range)]	5.2 (0.7-28.0)
Solitary: Multiple	924:358
Macroscopic venous invasion*	105 (8%)

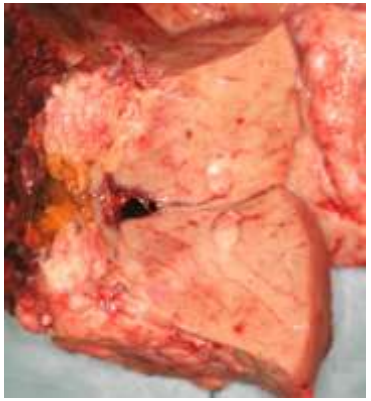
*PV 83; HV 19; IVC 3

Surgical Resection of HCC with Macroscopic Venous Invasion







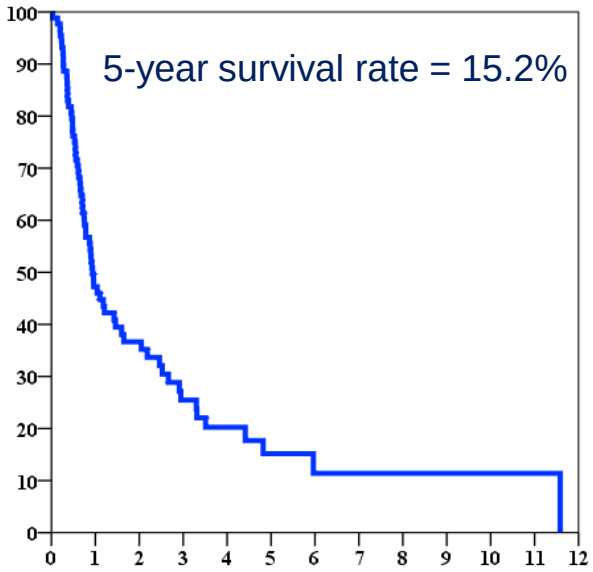


Right hepatectomy + excision of bile duct + left hepaticojejunostomy July 06
Latest CT scan in Feb 2013 – no recurrence

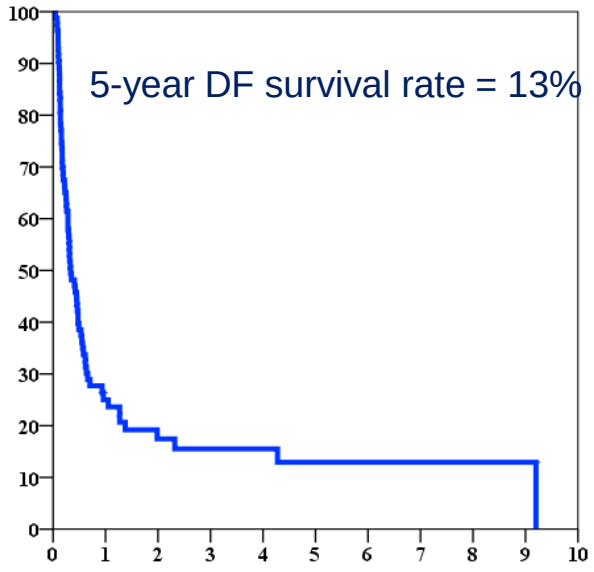
Long-term Results of Resection for HCC with Macroscopic Venous Invasion

105 patients with macroscopic portal vein invasion underwent liver resection

Overall survival



Disease-free survival



Endpoints for Ablation of HCC - Complete Ablation Rate

Study	No. of patients	Route of RFA	Complete ablation
Curley 2000	110	Percut (76) Lap (31) Open (3)	100%
Giovannini 03	53	Percut	92.8%
Vivarelli 04	79	Percut	87%
Poon 04	86	Percut (35) Lap (3) Open (48)	93%

Endpoints in Ablation of HCC - Local Recurrence

Local recurrence means technical failure due to inadequate cancer cell killing or ablation margin

Study	No. of patients	Median follow-up (months)	Local recurrence
Buscarini 01	88	34	14%
Giovannini 03	56	14	7%
Vivarelli 04	79	15.6	15%
Poon 04	86	11.5	6.2%
Lencioni 05	187	24	5.3%
Marchi 05	65	20	17%
Ng 08	207	26	14.5%

Long-term Results of RFA for HCC

Study	No. of patients	Mean / Median FU (mo)	Recurrence rate	5-year survival	5-year disease-free survival
Rossi 1996	39	22.6	41%	40%	NA
Buscarini 2001	88	34	29%	33%	3%
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%

Endpoints in Resection vs. RFA Randomized Trial

180 patients with solitary HCC < 5 cm randomized to either percutaneous local ablation therapy or resection

	Ablation group	Resection group	P value
Major complications	4.2%	55.6%	<0.05
Hospital mortality	0%	1.1%	NS
Survival			NS
1-year	95.8%	93.3%	
2-year	82.1%	82.3%	
3-year	71.4%	73.4%	
4-year	67.9%	64.0%	

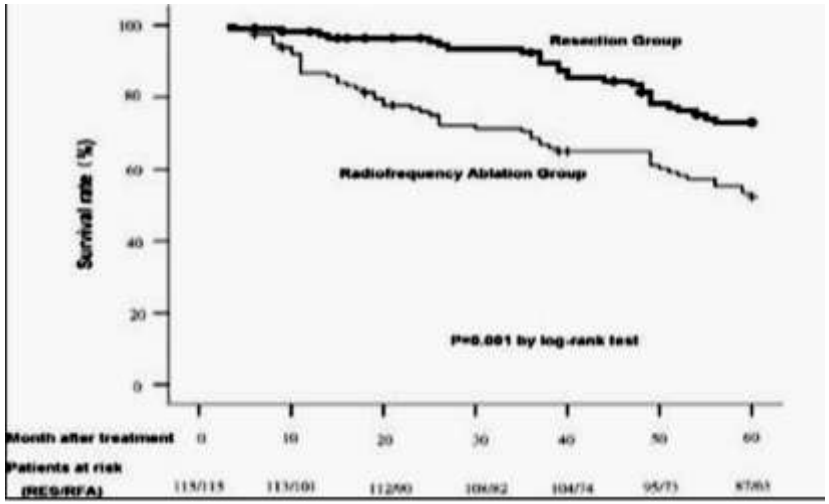
Chen et al. Ann Surg 2006

Resection vs. RFA Randomized Trial

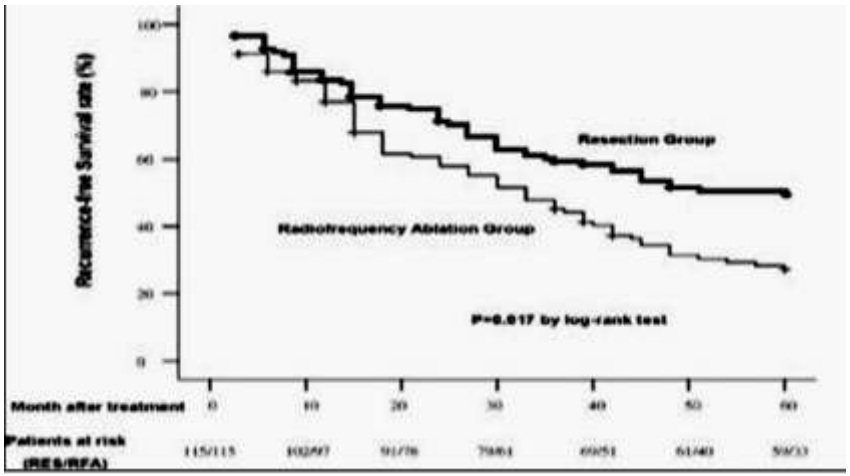
	Ablation (n = 115)	Resection (n = 115)	P value
Complications	4.3%	27.8%	<0.05
Hospital mortality	0%	0%	NS
Overall survival 3-year 5-year	 69.6% 54.8%	 92.2% 75.7%	0.001
Recurrence-free survival 3-year 5-year	 46.1% 28.7%	 60.9% 51.3%	0.007

Huang et al. Ann Surg 2010

Overall and Recurrence-Free Survival



5-year OS = 76% in surgical resection group vs 55% in the radiofrequency ablation group P<0.05



5-year RFS = 51% in surgical resection group vs 29% in the radiofrequency ablation group P<0.05

Resection versus RFA Randomized Trial

- A total of 168 patients with small HCC with nodular diameters of less than 4 cm and up to two nodules were randomly divided into resection (n=84) and RFA groups (n=84)

- The 1-, 2-, and 3-year survival rates:

  Resection - 96.0%, 87.6%, 74.8%

  RFA - 93.1%, 83.1%, 67.2% (p=0.342)

- The corresponding recurrence-free survival rates:

  Resection: 90.6%, 76.7%, 61.1%

  RFA: 86.2%, 66.6%, 49.6% (p=0.122)

Feng et al. J Hepatol 2012

Meta-analysis of Resection vs. RFA Randomized Trials

- Three randomized controlled trials were included in meta-analysis – all patients met the Milan criteria

- Hepatic resection was superior to radiofrequency ablation for the improvement of overall survival [HR=1.41; 95% confidence interval (CI), 1.06-1.89; P=0.02] and recurrence-free survival (HR=1.41; 95% CI, 1.14-1.74; P=0.001).

Xingshun et al. J Clin Gastroenterol 2013

Transarterial Chemoembolization

- Palliative treatment aiming at tumor necrosis or tumor shrinkage

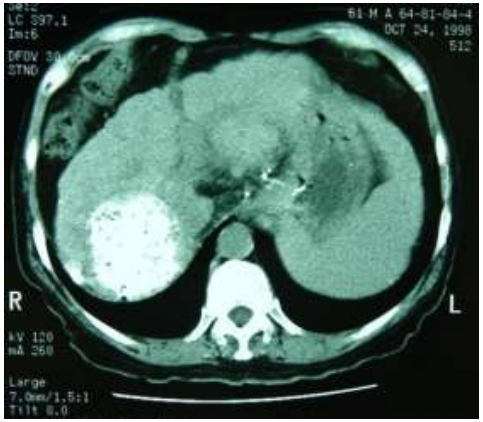
- Important endpoints:
  - Tumor response rate by imaging criteria
  - Time to progression
  - Progression-free survival
  - Overall survival

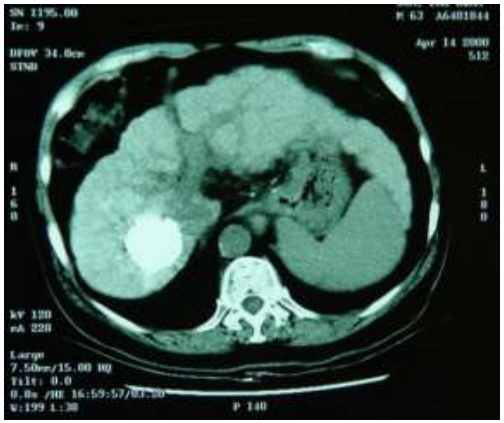
TACE for Unresectable HCC

Lipiodol-TACE with cisplatin or doxorubicin

484 patients (1989 - 1997)

- Response rate by RECIST: 40-50%
- Survival: 1-yr 49%, 3-yr 23%, 5-yr 17%
- Adverse prognostic factor for tumor response and survival:
  - tumor size > 10 cm,
  - serum albumin < 35 g/L





Poon et al. J Surg Oncol 2000

Endpoints in Transarterial Therapies

- ***Tumor response*** – important for patient management decision; studies applying Cox proportional hazards analysis in HCC research suggest that this endpoint is consistently associated with survival in transarterial therapies

  Llovet et al. Lancet 2002

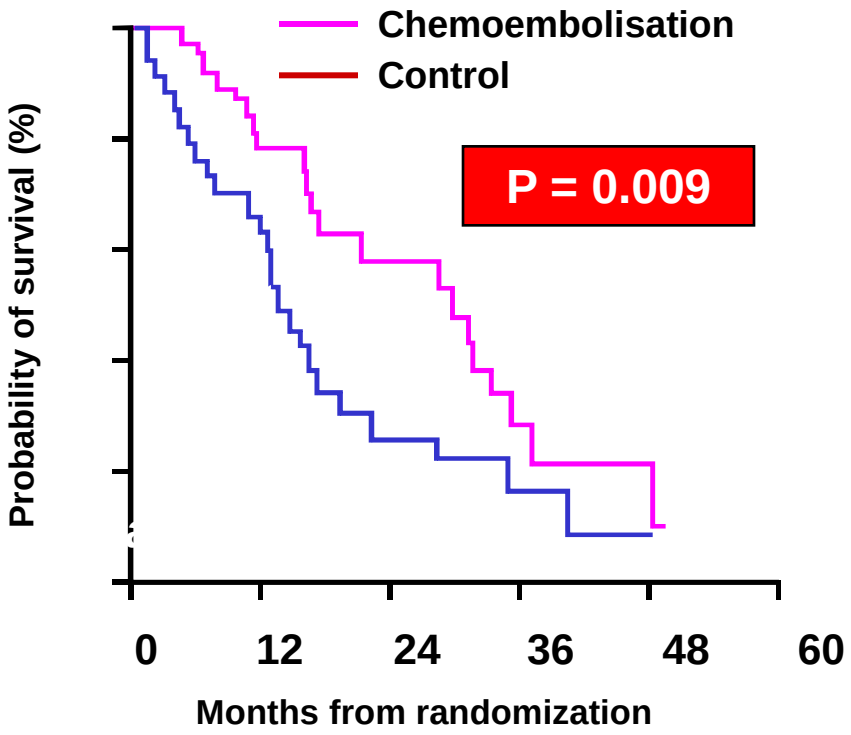
- ***Time-to-progression*** can reflect efficacy of treatment in controlling tumor growth, affected by interval of imaging (optimum is every 6-8 weeks), and also problem with untreated new tumor lesions

- ***Progression-free survival*** is composite endpoint including death and evidence of radiological progression

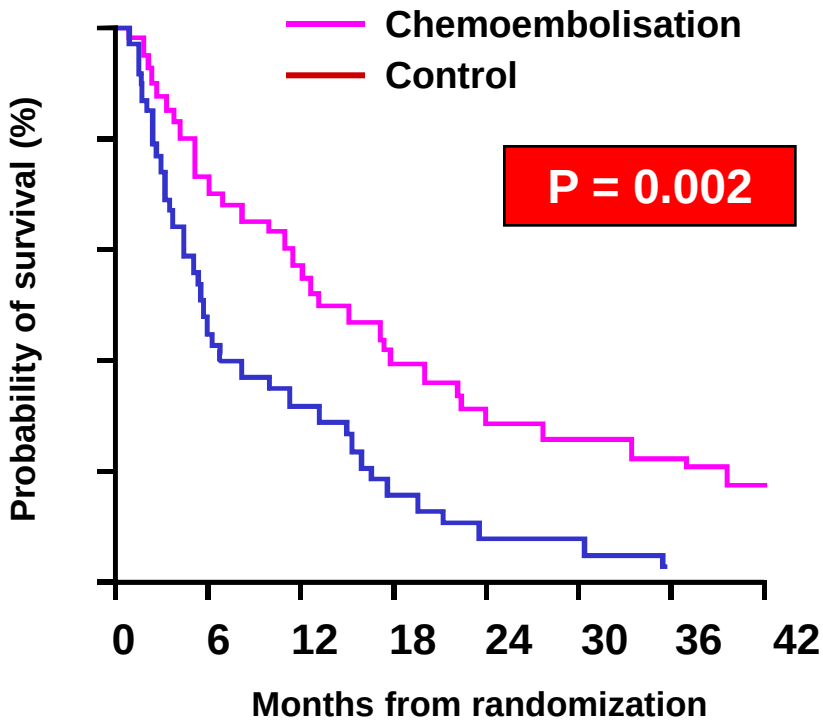
  - deaths resulting from the natural history of cirrhosis might confound potential benefits from treatment
  - useful in patients with well-preserved liver function because it will capture death from treatment-induced liver failure

RCTs of TACE vs Best Supportive Care

- **Portal vein invasion:** Barcelona: 0%; Hong Kong 27% (portal vein tumor thrombus makes response evaluation more difficult)
- **2-year OS of untreated group**: Barcelona: 27%; Hong-Kong 11%



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



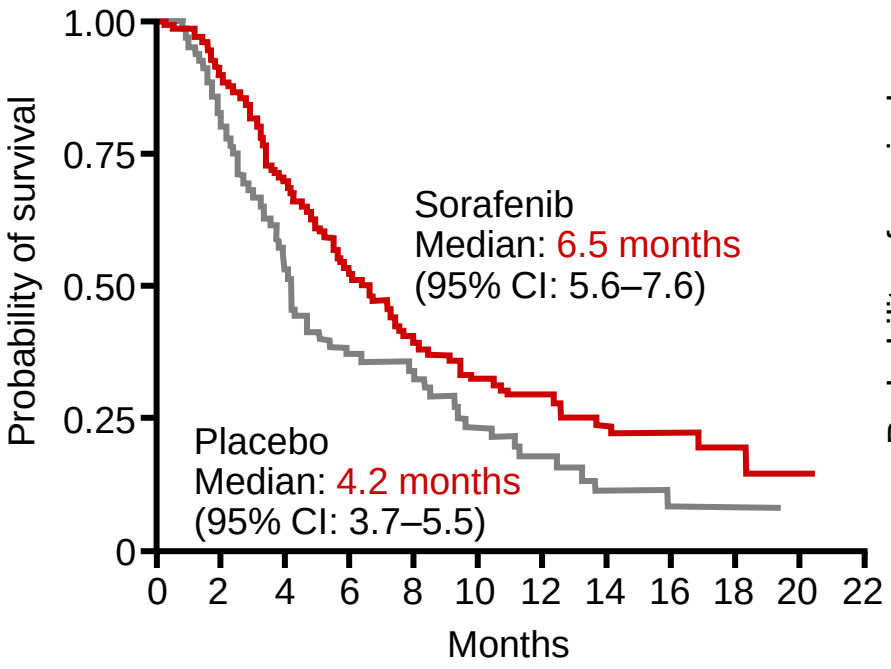
Lo CM et al. Hepatology 2002;35:1164–71

Overall survival is the best endpoint in clinical trials

Endpoints in Targeted Therapy for HCC

Asian trial on Sorafenib

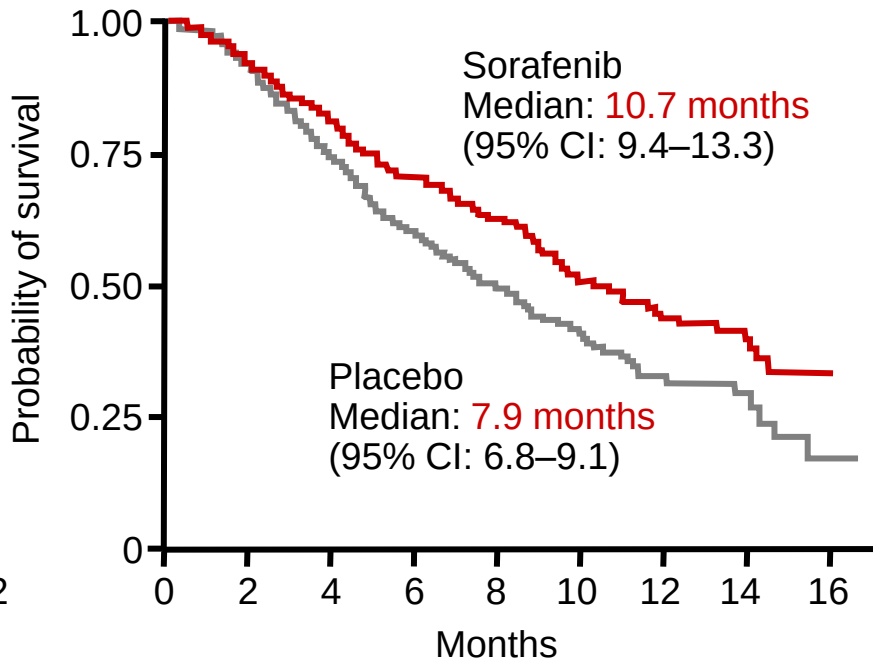
HR (S/P): 0.68 (95% CI: 0.50–0.93) P=0.014



Cheng AL, et al. Lancet Oncol 2009;10:25–34

SHARP trial

HR (S/P): 0.69 (95% CI: 0.55–0.87) P<0.001



Llovet JM, et al. N Engl J Med 2008;359:378–90

Sorafenib in HCC: SHARP and Asia-Pacific Studies

	SHARP[1]		Asia-Pacific[2]	
	Sorafenib vs placebo		Sorafenib vs placebo	
Endpoint	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
OS	10.7 vs 7.9 months 0.69 (0.55-0.87)	<.001	6.5 vs 4.2 months 0.68 (0.50-0.93)	.014
TTSP	1.08 (0.88-1.31)	.768	0.90 (0.67-1.22)	.50
TTP	5.5 vs 2.8 months 0.58 (0.45-0.74)	<.001	2.8 vs 1.4 months 0.57 (0.42-0.79)	<.001
RR	2% vs. 1%		3.3% vs 1.3%	

TTSP = time to symptomatic progression; TTP = time to progression; RR = response rate

[1]Llovet J, et al. N Engl J Med. 2008;359(4):378-90; [2]Cheng A, et al. Lancet Oncol. 2009;10(1):25-34

Endpoints in Targeted Therapies

- Molecular targeted therapies aim at disease-stabilization rather than tumor shrinkage, can produce survival benefit without tumor response

Table 2
Change in the paradigm for designing clinical trials in hepatocellular carcinoma

Type of treatment	Objective response	Survival benefit
Conventional treatments in HCC		
Local ablative therapies (RF ablation and/or PEI)	70–80% (CR)	Yes
Chemoembolization	35–40% (PR)	Yes
Internal radiation (I131, Y90)	20–30% (PR)	Unknown
Intraarterial chemotherapy	15–20% (PR)	Unknown
Systemic chemotherapy	~10% (PR)	No
Molecular targeted therapies in oncological practice†		
Small-molecule kinase inhibitors		
EGFR: erlotinib (NSCLC) (41)	9% (PR)	Yes
Raf/VEGFR: sorafenib (HCC) (18)	2.7% (PR)	Yes
mTOR: temsirolimus (RCC) (42)	8% (PR)	Yes
Monoclonal antibodies		
Anti-VEGF: bevacizumab (metastatic CRC) (43)	10% (PR)	Yes

Llovet et al, J Nat Cancer Inst 2008

Endpoints in Targeted Therapies

- Apart from overall survival, time to progression as measured by modified RECIST criteria is a useful endpoint reflecting antitumor efficacy of targeted drugs that induce tumor necrosis

- Quality of life is an important endpoint especially with significant side effect of targeted drugs, but this not frequently evaluated

  e.g. EORTC quality-of-life questionnaire (QLQ)-HCC18 has been cross-validated internationally

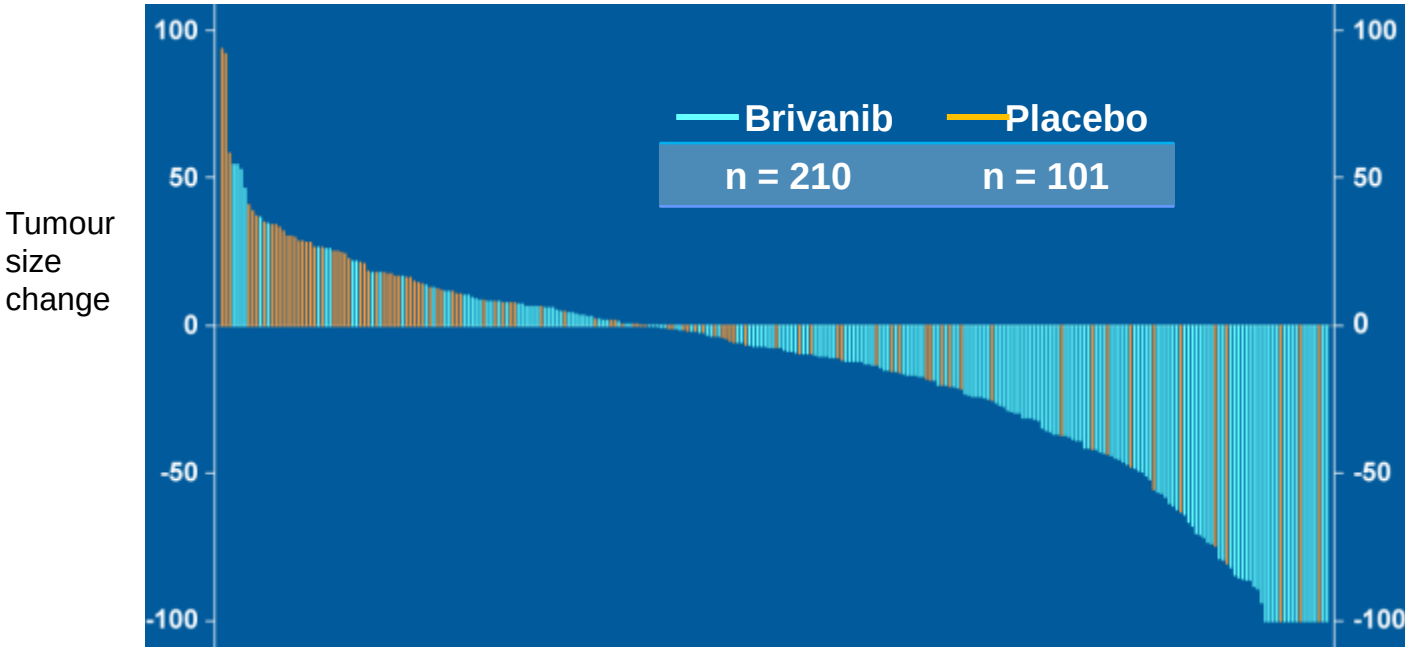
  Chie et al. Hepatology 2012

- Time to symptomatic progression is a composite score capturing both tumor progression and drug-related toxicity

Phase 3 Trial of an Agent Targeting both VEGF and FGF

Brivanib is a drug targeting both VEGF and bFBF receptors in HCC

International multicentre phase 3 double-blinded clinical trial of Brivanib vs. placebo in liver cancer patients with progression after Sorafenib



Llovet et al. J Clin Oncol 2013

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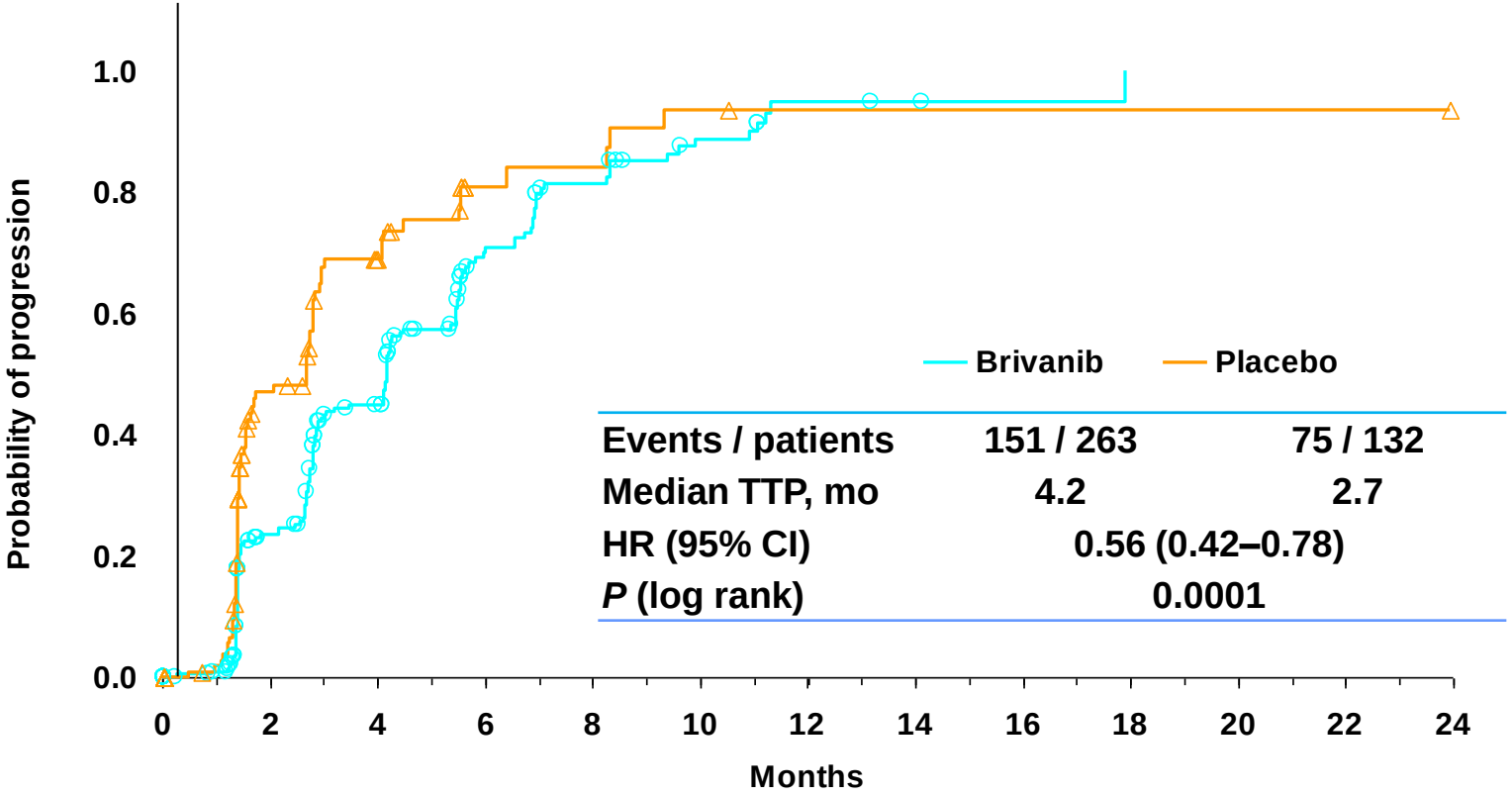
Time to Tumor Progression vs. Overall Survival



Brivanib slowed down tumor growth with significantly longer time to tumor progression (p=0.0001)

Median overall survival 9.4 months in Brivanib vs. 8.2 months in placebo (p=0.104)

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Summary – Therapeutic Response Assessment

- Imagings: Contrast CT scan or MRI scan is the current standard to assess tumor recurrence or progression
- Serum AFP level useful in patients with elevated AFP, complementary to imagings
- Modified RECIST criteria is the most widely recommended in imaging theraputic response assessmeny

Summary - Endpoints In Clinical Practice

- Curative treatment (resection/transplantation/ablation)
  - *Tumor recurrence* by imaging and AFP surveillance is an important endpoint for management decision
  - *Recurrence-free survival and overall survival* both reflect efficacy of treatment
- Transarterial locoregional therapies
  - *Tumor response by modified RECIST criteria* and *AFP change* important in management decision
  - *Time to progression and overall survival* reflect treatment efficacy and toxicity
- Targeted therapies
  - *Tumor response by modified RECIST criteria* and *AFP change* important in management decision
  - *Progression-free survival* and *overall survival* reflect treatment efficacy/toxicity

Summary - Endpoints In Clinical Trial Design

- Adjuvant therapy for curative treatment
  - *Time to recurrence* in phase 2 studies to detect signal of treatment efficacy
  - *Overall survival* should be the primary endpoint in phase 3 trials

- Palliative locoregional or systemic targeted therapies
  - *Time to tumor progression* in phase 2 studies to detect signal of efficacy
  - *Progression-free survival* can be used in phase 2 studies if only patients with preserved liver function are recruited (can detect drug toxicity)
  - *Overall survival* in phase 3 trials

Future Directions

- Therapeutic response assessment:
  - Tumor volumetric assessment
  - Molecular functional imagings
  - New biomarkers e.g. AFP mRNA levels

- Further studies to validate surrogate endpoints that can be used instead of overall survival in clinical trial designs may help to select potential candidate drugs in early phase trials for phase 3 randomized trials

Thank you!