How to evaluate tumor response?

Yonsei University College of Medicine
Kim, Beom Kyung

End points in research for solid cancers

- Overall survival (OS)

✓ The most ideal one, but requires long follow-up duration

- Progression (or recurrence)-free survival/
- Shrinkage of tumor burden

✓ Representative surrogates for OS

✓ Decrease in tumor size, or complete and sustained remission after treatment influence OS in the majority of cancers including HCC.

Tumor response criteria
-World Health Organization (WHO) criteria

- Introduced in 1979 (ref: *Miller et al. Cancer 1981*)
- "Measurable lesions" / "non-measurable lesion"
- Bi-dimensional measurement (=long axis x short axis)
- Difference between baseline and after treatment

✓ CR (complete respone): disappearance of all lesions

✓ PR (partial response): ≥50% decrease

✓ SD (stable disease): neither PR nor PD

✓ PD (progressive disease) : ≥25% increase / appearance of new lesions

Tumor response criteria
- RECIST (Response Evaluation Criteria in Solid Tumors)

- Introduced in 2000 (ref: *Therasse et al. J Natl Cancer Inst 2000*)
- Target lesion (measurable) / non-target lesion (measurable or non-measurable)
- Uni-dimensional measurement (longest diameter)
- Difference between baseline and after treatment

✓ CR: disappearance of all lesions

✓ PR: ≥30% decrease

✓ SD: neither PR nor PD

✓ PD: ≥20% increase / appearance of new lesions

Tumor response criteria
- RECIST (Response Evaluation Criteria in Solid Tumors)

- Compared to WHO criteria, RECIST is the simple method with good predictive ability of survival outcome and more detailed recommendation.

- So, now, RECIST is regarded as a standard method in oncology field

Clinical application of size-based criteria for hepatocellular carcinoma

- WHO criteria and RECIST were primarily designed to measure tumor shrinkage through cytotoxic chemotherapy.
- What about hepatocellular carcinoma(HCC)?

Type of treatment Objective response Survival benefit

Conventional treatments in HCC	Objective response	Survival benefit
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

Hudes etl al. N Engl J Med 2007; Shepherd et al. N Engl J Med 2005; Hurwitz et al. N Engl J Med 2004; Llovet etl al. J Clin Oncol 2007

Llovet et al. J Natl Cancer Inst 2008

Problems of size-based criteria for HCC

- Trans-arterial chemoembolization (TACE) or radiofrequency ablation (RFA) are the mainstay of non-surgical locoregional treatment

✓ Tumor necrosis, irrespective of tumor shrinkage, is significantly associated with the better OS, the most solid endpoint.

- Sorafenib

✓ Using sorafenib or other investigational molecular target agents, cytostatic agents, shrinkage of tumor would not be expected (about 2% observed in SHARP trial).

Llovet et al. N Engl J Med 2008

Problems of size-based criteria for HCC

- Therefore, they almost all underestimate the clinical benefit of tumor necrosis but without tumor shrinkage.
- And, most cases with “complete response” are missed using WHO or RECIST guidelines.

- Now, a concept of “viable tumor” should be adopted.

Enhancement criteria for HCC

-European Association for the Study of the Liver (EASL) criteria

- Introduced in 2001 *(ref; Bruix et al. J Hepatol 2001)*
- "Viable lesion" defined as arterialized enhanced portion is assessed, instead of whole mass.
- Lipiodol deposit area or area without arterial enhancement after treatment is regarded as necrotic portion.
- Otherwise, same methods with WHO criteria, bi-dimensional measurement and 4 categorizations (CR, PR, SD, and PD), are applied.

Enhancement criteria for HCC

-European Association for the Study of the Liver (EASL) criteria

CR: Disappearance of any intratumoral arterial enhancement in all measurable arterially-enhancing liver lesions
PR: At least a 50% decrease in the sum of the product of bi-dimensional diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
SD: Any cases that do not qualify for either partial response or progressive disease.
PD: An increase of at least 25% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

Enhancement criteria for HCC
-modified RECIST

- Introduced in 2008 *(ref: Llovet et al. J Natl Cancer Inst 2008 / Lencioni et al. Semin Liver Dis 2010)*
- Same concept of "viable lesion" with EASL criteria
- Almost similar to RECIST, regarding uni-dimensional measurement and 4 categorizations (CR, PR, SD, and PD)

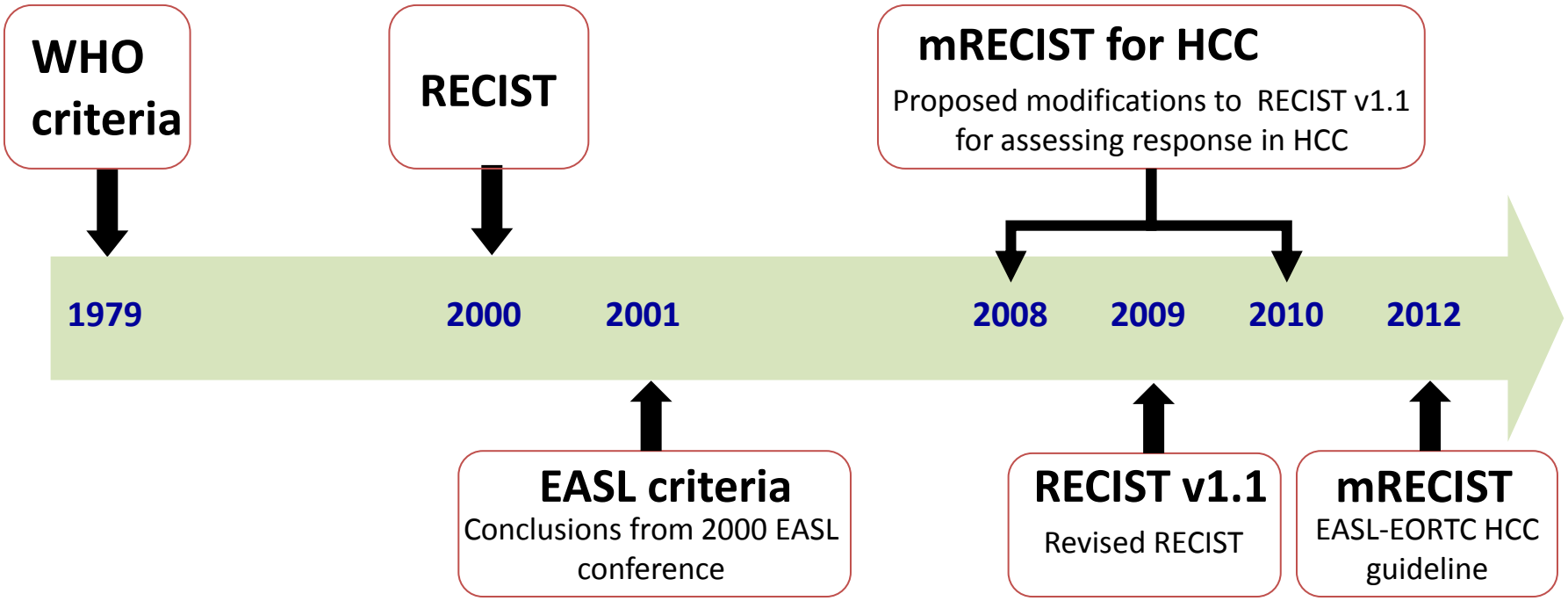
- Compared to EASL criteria,

✓ mRECIST is the simpler.

✓ More importantly, detailed recommendations for response evaluations were addressed.

EASL-EORTC Guidelines. J Hepatology 2012

Brief history of evolution of response evaluation criteria



WHO 1979. Available at: http://whqlibdoc.who.int/offset/WHO_OFFSET_48.pdf / Therasse P, et al. J Natl Cancer Inst 2000;92:205-16 / Bruix J, et al. J Hepatol 2001;35:421-30 / Llovet JM, et al. J Natl Cancer Inst 2008;100:698-791 /Lencioni R, et al. Semin Liver Dis 2010;30:52-60 / Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47 / EASL-EORTC Guidelines. J Hepatology 2012;56:908-43

mRECIST

- Image acquisition

✓ contrast-enhanced spiral CT (preferably with use of multislice scanners contrast) or enhanced dynamic MRI

✓ At least dual-phase (arterial & portal phase) imaging

✓ Contiguous slice

Target lesions for mRECIST

- *Only well-delineated, arterially enhancing lesions* can be selected as target lesions.

✓ Suitable for repeated measurement

✓ The longest diameter ≥ 1cm

✓ LN is categorized as non-target lesion

✓ Number of target lesions: RECIST 1.0 ~ 1.1 may apply

- Compared to target lesions for RECIST

✓ The longest diameter ≥ 1cm

✓ LN > 15 mm in the short diameter

✓ Number of target lesions: RECIST 1.0 (5 per organ, 10 Lesions) to RECIST 1.1 (2 per organ, 5 Lesions)

Target response of mRECIST

CR: disappearance of any intratumoral arterial enhancement in all target lesions
PR: At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD: Any cases that do not qualify for either partial response or progressive disease
PD: An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

Lencioni et al. Semin Liver Dis 2010

Special consideration for target response

- The measurement of viable tumor is not necessarily located in the same scan plane with baseline evaluation.
- The longest diameter of viable tumor should be measured performed when contrast between viable tissue and non-enhancing tissue is the highest.
- The measurement of the viable tumor should not include any major intervening areas of necrosis.

Non-target lesions for mRECIST

- Non-measurable lesions
- Other measurable lesions other than target lesions
- Infiltrative HCC
- Previously treated with locoregional or systemic treatments (if it is poorly demarcated or exhibits atypical enhancement as a result of the previous treatment)

Special consideration for non-target response

- Malignant portal vein thrombosis is non-target lesion.
- Porta hepatis lymph node can be considered as malignant if its short axis is at least 20 mm.
- ✓ Reactive lymph nodes at the porta hepatis is a common finding in patients with cirrhosis.
- Cytopathologic confirmation is necessary for neoplastic nature of any effusion (pleural effusion or ascites).

Non-target response of mRECIST

CR	Disapperance of all nontarget lesions
IR (incomplete response)/SD	Persistence of one or more target lesions
PD	Appearance of new lesions Unequivocal progression of existing nontarget lesions

Lencioni et al. Semin Liver Dis 2010

New lesions for mRECIST

- Nodule ≥ 1cm with typical vascular enhancement (hypervascularization in the arterial phase with washout in the portal venous or late venous phase) can be considered as a newly developed lesion (PD).

- Nodule ≥ 1cm without typical vascular enhancement can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.

✓ An individual radiologic event will be adjudicated in retrospect as PD at the time it was “first” detected.

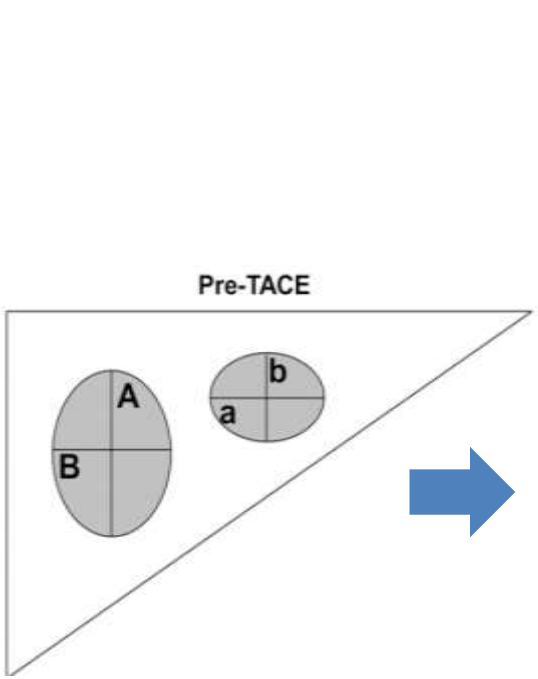
Overall response for mRECIST determined by evaluation of target, non-target, and new lesions

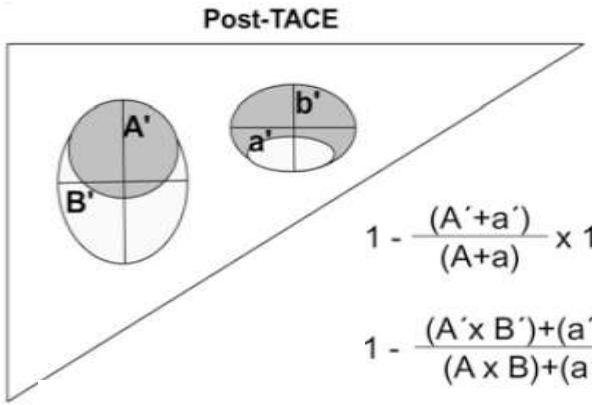
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	Absent	CR
CR	IR/SD	Absent	PR
PR	Non PD	Absent	PR
SD	Non PD	Absent	SD
PD	Any	Present or Absent	PD
Any	PD	Present or Absent	PD
Any	Any	Present	PD

Abbreviations: CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

Lencioni et al. Semin Liver Dis 2010

Overview of schematics

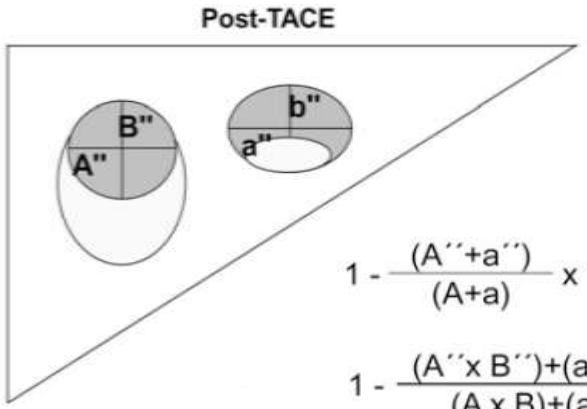




Size criteria

$$1 - \frac{(A'+a')}{(A+a)} \times 100\ (\%)$$ **: by RECIST**

$$1 - \frac{(A' \times B')+(a' \times b')}{(A \times B)+(a \times b)} \times 100\ (\%)$$ **: by WHO**



Enhancement criteria

$$1 - \frac{(A''+a'')}{(A+a)} \times 100\ (\%)$$ **: by mRECIST**

$$1 - \frac{(A'' \times B'')+(a'' \times b'')}{(A \times B)+(a \times b)} \times 100\ (\%)$$ **: by EASL**

Adapted from Shim JH et al. Radiology 2012

Clinical application of enhancement criteria for HCC

Discrepancies between size-based and enhancement critetria

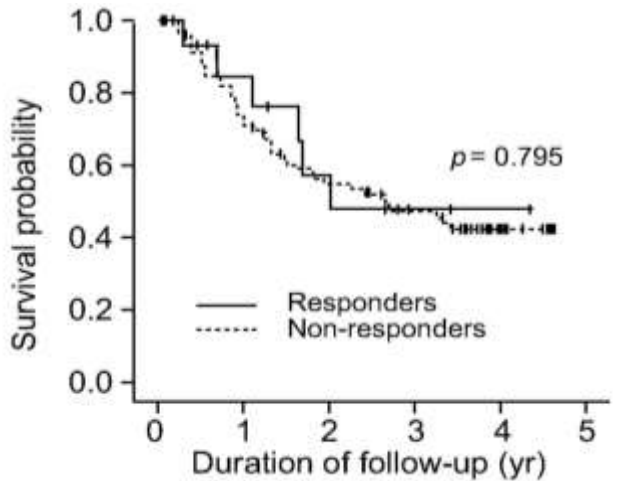
	EASL criteria					mRECIST			
WHO	CR	PR	SD	PD	WHO	CR	PR	SD	PD
CR	1	0	0	0	CR	1	0	0	0
PR	10	4	0	0	PR	10	3	1	0
SD	22	30	22	0	SD	22	25	27	0
PD	1	0	3	5	PD	1	0	3	5
RECIST	CR	PR	SD	PD	**RECIST**	CR	PR	SD	PD
CR	1	0	0	0	CR	1	0	0	0
PR	11	1	0	0	PR	11	1	0	0
SD	21	32	24	0	SD	21	26	30	0
PD	1	1	1	5	PD	1	1	1	5

- There exist substantial discrepancies (*kappa value 0.088-0.122*) in response between enhancement criteria (EASL and mRECIST guidelines) and size-based criteria (WHO and RECIST guidelines).

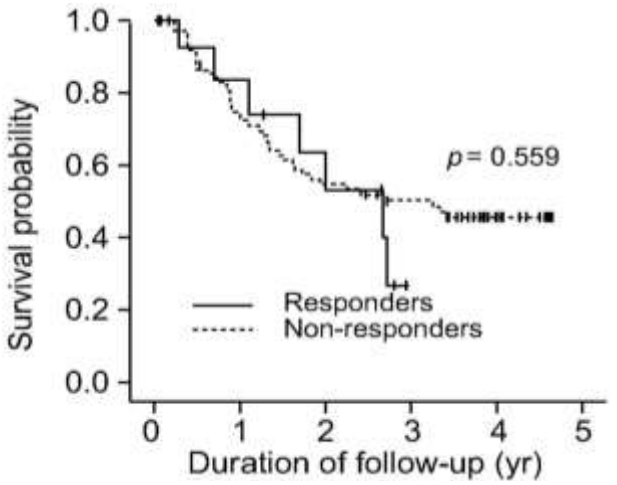
Jung et al. J Hepatol 2013

Enhancement criteria for HCC treated with TACE

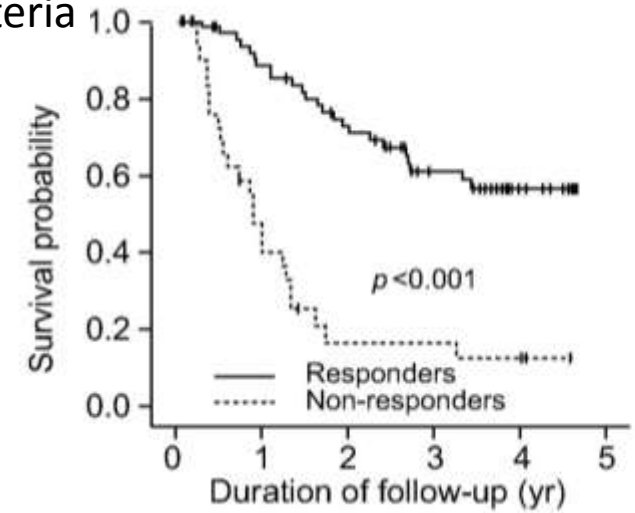
WHO



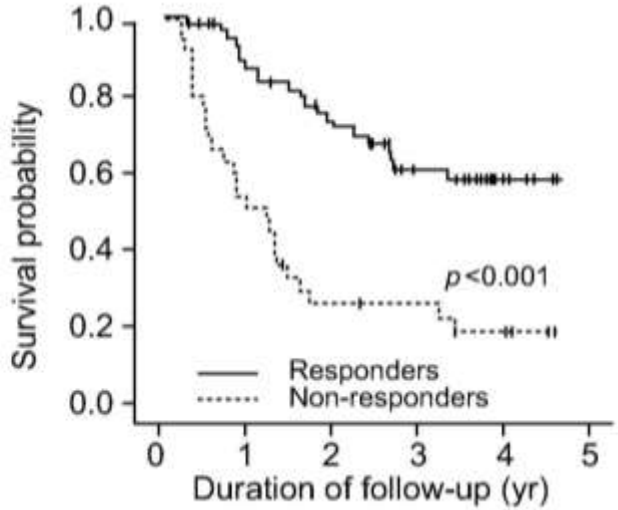
RECIST



EASL criteria



mRECIST



- EASL and mRECIST guidelines have better discriminatory ability for survival than WHO and RECIST guidelines among those treated with TACE.

Jung et al. J Hepatol 2013

Enhancement criteria for HCC treated with sorafenib

- For HCC treated with sorafenib, mRECIST were compared with RECIST.

RECIST 1.1		*mRECIST*
✓ OR: 2%		✓ OR: 23%
✓ SD: 79%	vs.	✓ SD: 57%
✓ PD: 19%		✓ PD: 21%

- Patients with OR according to mRECIST had a longer OS than non-re sponders (median OS 18 vs. 8 months, respectively; P=0.013)
- Among 42 patients with SD according to RECIST, OS differed according to mRECIST; median OS with OR (n = 11), SD (n = 29), and PD (n = 2) was 17, 10 and 4 months, respectively (P = 0.016).

- Thus, mRECIST may be generally reliable in HCCs treated with TACE or sorafenib.

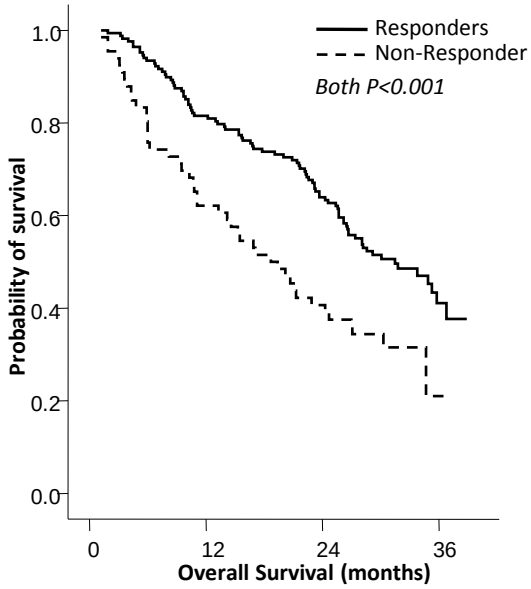
Edeline J, et al. Cancer. 2012 Jan 1;118(1):147-56

Which is the better between EASL and mRECIST guideline?

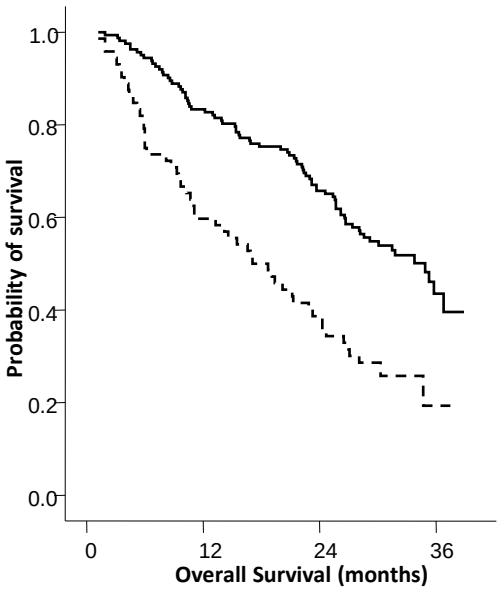
EASL criteria	mRECIST			
	CR	PR	SD	PD
CR	113	0	0	0
PR	4	87	15	0
SD	0	6	56	0
PD	0	0	2	9

Kappa value 0.863

EASL criteria



mRECIST



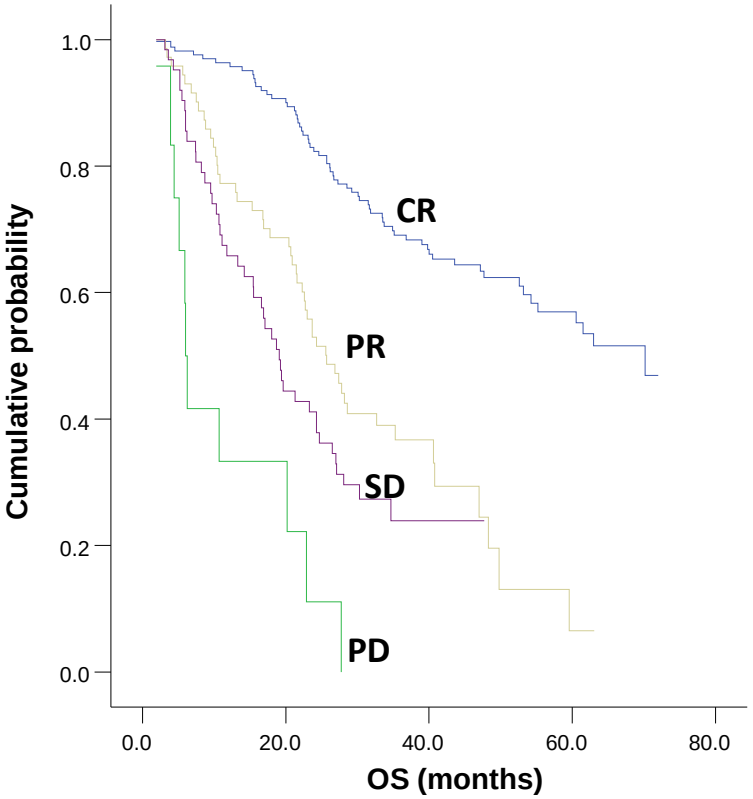
- mRECIST, a simpler method, provided prognostic values for predicting OS equivalent to EASL criteria in patients with HCC undergoing TACE as an initial treatment modality.

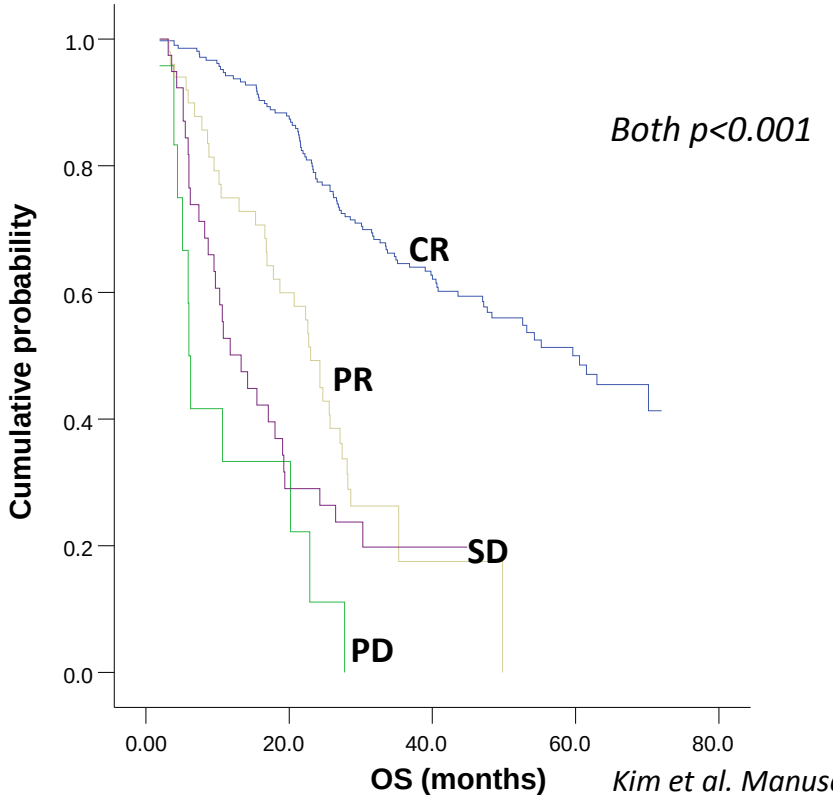
Kim et al. Eur J Cancer 2012

Timing of assessment

- More than half required repeated TACE session to achieve CR.
- Early vs. best response by mRECIST during “on-demand” TACE sessions from Yonsei experience

✓ Both initial and best response well predicted OS, respectively.

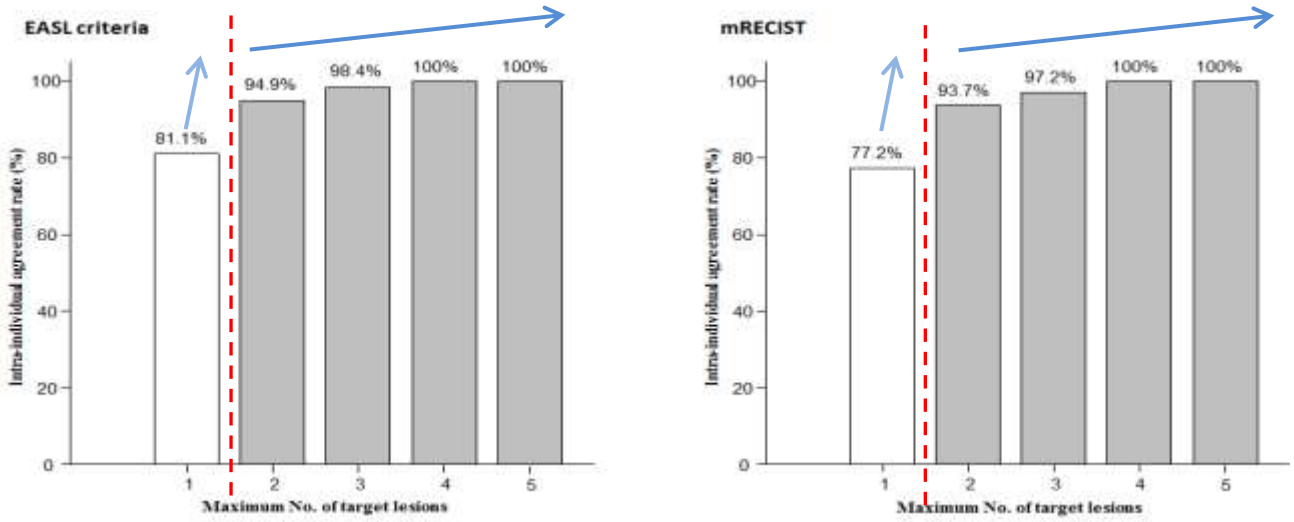




Both p<0.001

Kim et al. Manuscript submitted

Optimal number of target lesions with reference to responses assessing all target lesions



Prognostic value for OS of EASL and mRECIST guidelines

Maximum No. of targets	C-index for OS	
	EASL criteria	mRECIST
Up to 1	0.739	0.750
Up to 2	0.744	0.759
Up to 3	0.744	0.755
Up to 4	0.749	0.750
Up to 5	0.749	0.750
All targets	0.749	0.750

- Prognostic values for OS were similar regardless of number of target lesions.
- However, assessing two targets could be recommended considering high concordances from cross-sectional analyses

Kim et al. Clin Cancer Res 2013

Further consideration of mRECIST

- mRECIST is a reliable method for assessing tumor response in HCC.
- Adequate skills and expertise were required in terms of inter-observer and intra-observer variability.

✓ Education and training

- Standardized software/ hardware protocols were required for reproducibility and reliable comparisons.

✓ Uniform image acquisition parameters

✓ Quality control

✓ Blinded assessments

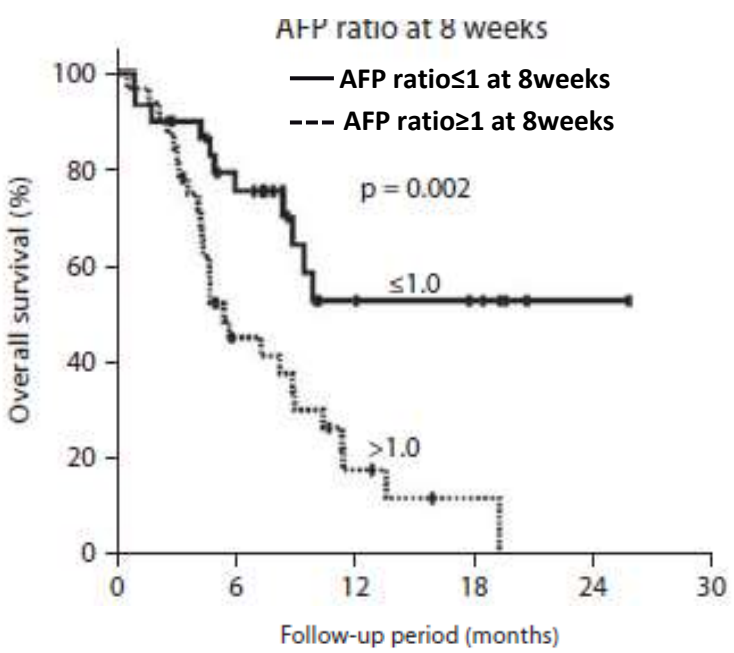
- The use of changes in serum levels of biomarkers (i.e. AFP levels) along with radiological response in HCC is under investigation.

Lencioni R, Llovet JM. Semin Liver Dis. 2010;30:52-60. / EASL–EORTC Clinical Practice Guidelines. J Hepatology 2012;56:908-43

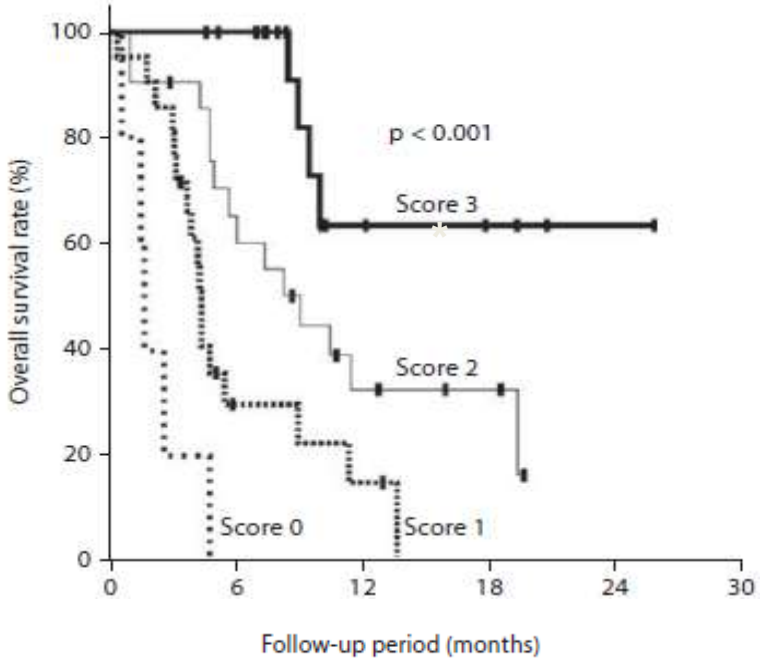
Combination of radiological response and biomarkers response

-AFP change & mRECIST -

OS according to AFP ratio



OS according to mRECIST, Child-Pugh, AFP ratio



- The combination of mRECIST and AFP ratio is useful for the assessment of prognosis of patients with advanced HCC treated with sorafenib.

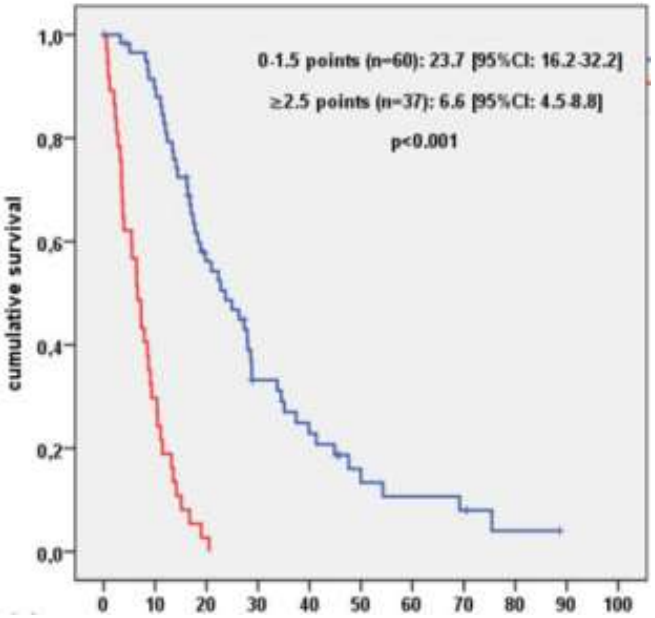
* : score was calculated as sum of the response by mRECIST (PD:0, CR or PR of SD:1), Child-Pugh score (B:0, A:1) and AFP ratio at 8 weeks from the start of the treatment (>1:0, ≤1:1)

Kawaoka T, et al. Oncology 2012

Combination of radiological response and biomarkers response

-CP score change, AST change & EASL criteria -

Variable		Overall Survival HR	95% CI	B	ART Score Points*	P-value (Cox Regression)
Child-Pugh score increase	Absent	1			-	
	+ 1 point	2.0	1.2-3.5	0.71	1.5	
	+ ≥2 points	4.4	2.0-9.6	1.49	3	<0.001
AST increase >25%	Absent	1			-	
	Present	8.4	4.5-15.5	2.13	4	<0.001
Radiologic tumor response	Present	1			-	
	Absent	1.7	1.1-2.6	0.51	1	0.026



- An ART (Assessment for Retreatment with TACE) score of ≥2.5 prior the second TACE identifies patients with a dismal prognosis who may not profit from further TACE sessions.

Sieghart et al. Hepatology 2013

Alternative evaluation methods

- Choi criteria

✓ Introduced in 2007 *(Ref: Choi et al. J Clin Oncol 2007)*

✓ To resolve the limitation of RECIST for patients undergoing imatinib for GastroIntestinal Stromal Tumor

✓ Tumor density, using CT attenuation coefficient (Hounsfield unit [HU]), was applied to reflect areas of tumors with reduced vascularization.

✓ Combination of size criteria (long diameter) and tumor density

Alternative evaluation methods

- Choi criteria

✓ 4 categorization

- CR: Disappearance of all lesions

- PR: Decrease in size of ≥10% or decrease in tumor density (HU) ≥15% on CT

- SD: Does not meet criteria for CR, PR, or PD

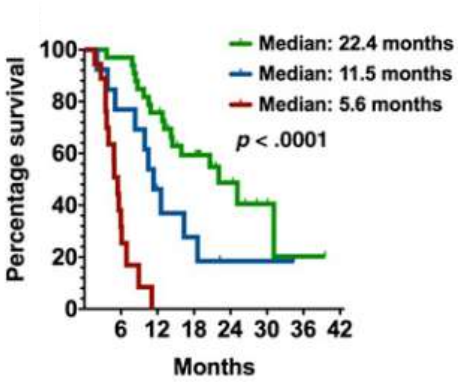
- PD: Increase in tumor size of ≥10% and does not meet criteria of PR by tumor density (HU) on CT/ New lesions

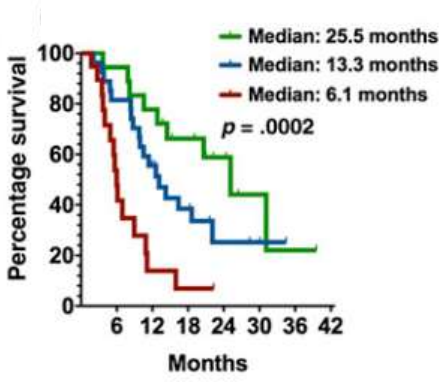
Alternative evaluation methods

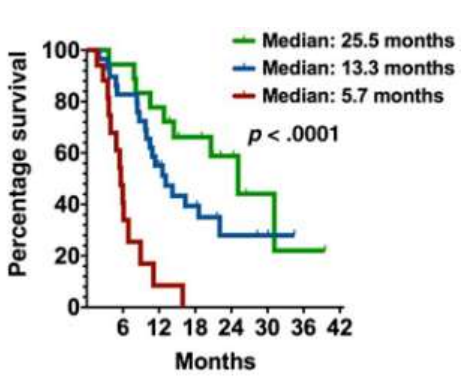
- Choi criteria

✓ Also tried for HCC with good discrimination of OS

	Choi criteria	EASL criteria	mRECIST	RECIST 1.1
OR	32	13	12	2
SD	15	31	34	41
PD	17	19	17	20







Ronot et al. Oncologist 2014

Future perspectives

- Metabolic response by differences between standardized uptake values from PET scans

✓ PET+ RECIST → PERCIST *Wahl et al. J Nucl Med. 2009*

- 3D-Volumetric criteria (automated methods)

- Functional imaging using diffusion weighted MR

- Development of “new” biomarkers and combinations with radiological response

Future perspectives

- For the newer treatment modalities (drug-eluting bead TACE and TARE) and other investigational drugs, conventional assessment tools should be validated accordingly.

- For infiltrative HCC or HCC with atypical enhancement patterns, more optimized methods other than categorizing into “non-target lesions” are required.

Take home messages

- Enhancement criteria are now standard tools for HCC.
- So far, mRECIST provides equivalent efficacy, more convenience with a simpler method and detailed recommendation, compared to EASL criteria.

- Advances in imaging technologies will allow the better assessment protocol.
- Newer treatment modalities will require modification of current assessment tools.

경청해 주셔서 감사합니다~