Imaging for immunotherapy management, what you should know for your clinical practice

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Jan 2024 ONC-BE-2300249

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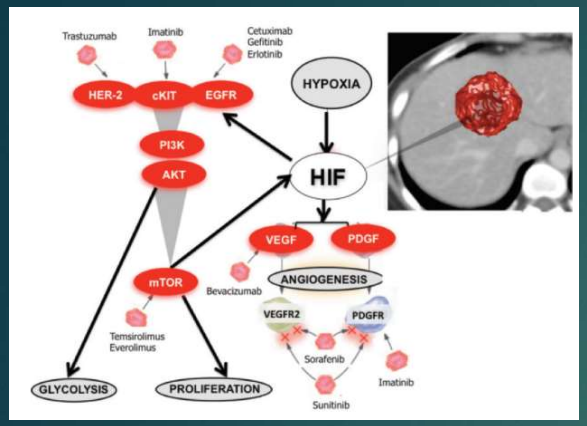
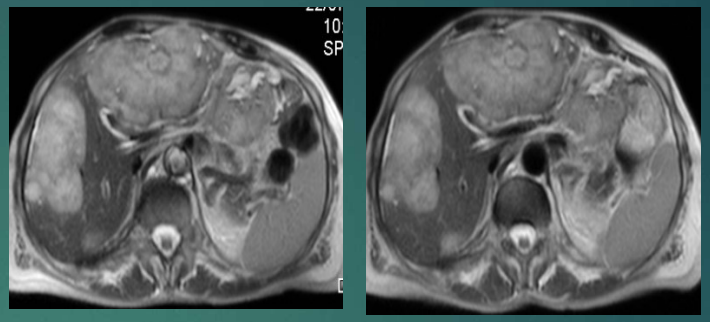
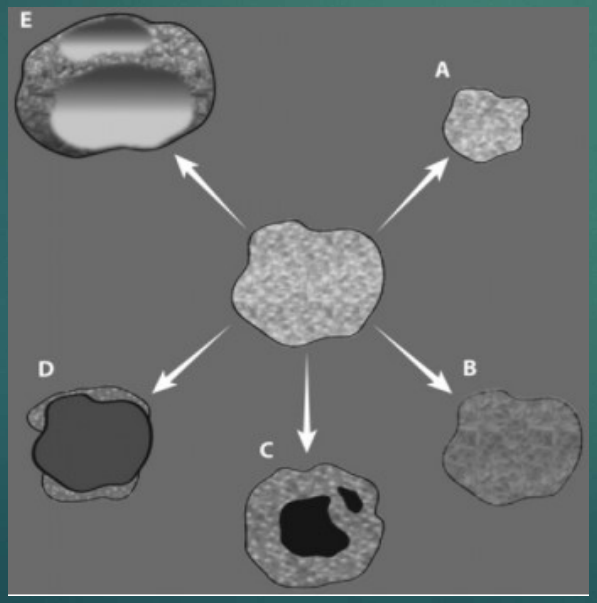
Response assessment of treatment that does not reduce tumour size: Immunotherapy



Figueiras R et al, radiographics 2011



Response?



A. Reduction in tumour size

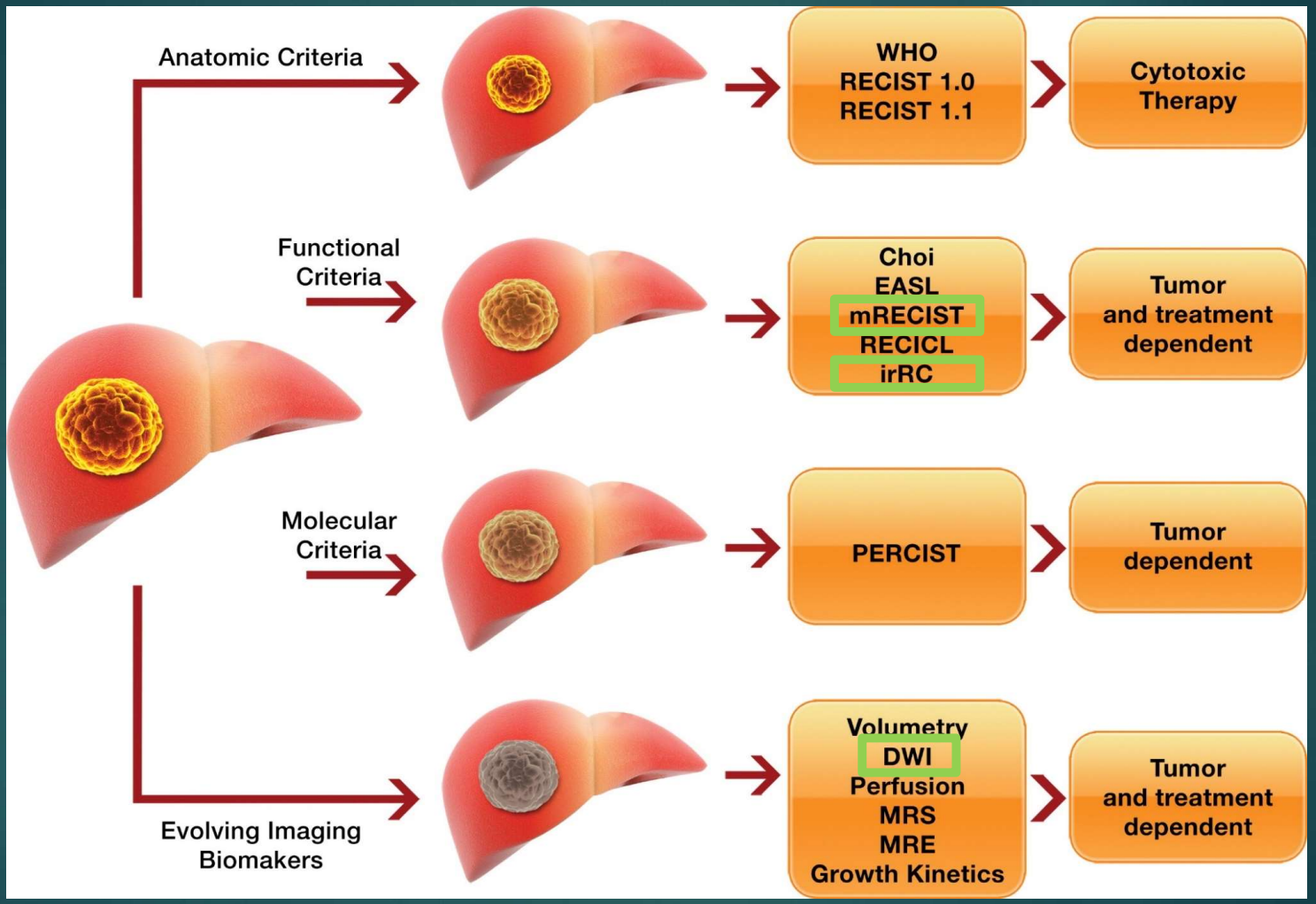
B. Reduction in vascularity ± size reduction

C. Cystic/necrotic change ± size reduction

D. Intratumoral hemorraghe ± size reduction

Figueiras R et al, Radiographics 2011

Response assessment of treatment that does not reduce tumour size: beyond RECIST 1.1

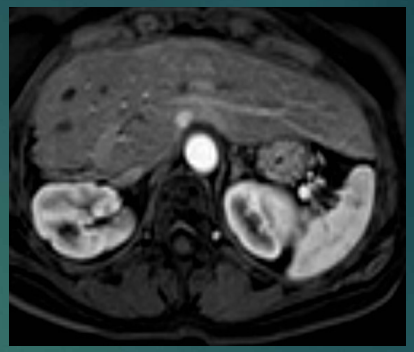


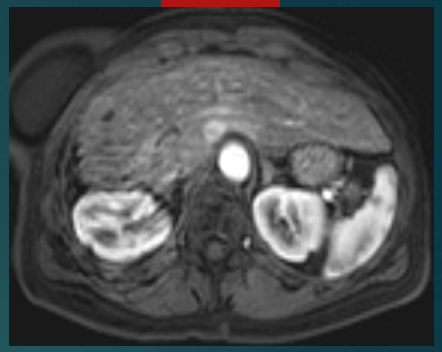
Figueiras R et al, Radiographics 2011

DWI, diffusion-weighted imaging; EASL, European Association for the Study of the Liver; irRC, immune-related response criteria; MR, magnetic resonance; MRE, MR enterography; mRECIST, modified RECIST; MRS, MR spectroscopy; PERCIST, PET Response Criteria in Solid Tumors; RECICL, Response Evaluation Criteria in Cancer of the Liver; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

mRECIST – EASL - RECICL

- Chemo-embolization /SIRT - Immunotherapy
- Represents vascular disruption
  and intratumoral necrosis in absence of tumour size changes





1. European Association for the Study of the Liver (EASL)
   WHO-criteria incorporating viable tissue concept (EASL-criteria)

2. American Association for the Study of Liver diseases
   Modified RECIST (mRECIST) incorporating viable tissue concept

3. Liver Cancer Study Group of Japan
   Response evaluation Criteria in Cancer of the Liver (RECICL)
   -> Includes tumour necrosis in measurements
   -> Timing of measurements
   -> 3 tumour markers : AFP, AFP-L3 and DCP

AFP, a-fetoprotein; AFP L3, lectin-reactive AFP; DCP, des-gamma-carboxyprothrombin; EASL, European Association for the Study of the Liver; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECICL, Response Evaluation Criteria in Cancer of the Liver; SIRT, selective internal radiation therapy; WHO, World Health Organization.

Subbiah V et al, Diagnostics 2017

mRECIST – EASL - RECICL

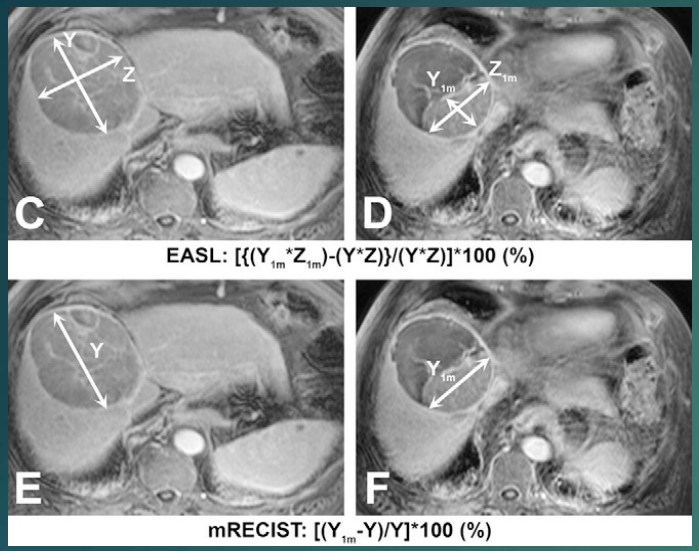


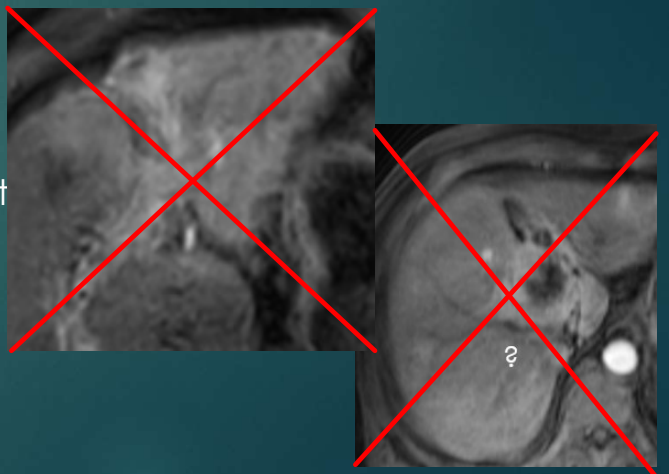
Table 2
Evaluation of Hepatocellular Carcinoma Overall Response According to EASL Criteria, Modified RECIST, and RECICL

Response Category	EASL Criteria*	Modified RECIST†	RECICL‡
Complete response	Disappearance of enhancing tissue in target lesion(s)	Disappearance of intratumoral arterial enhancement and pathologic lymph nodes	Complete tumor necrosis or complete tumor disappearance
Partial response	≥50% decrease in sum of arterial enhancing area	Decrease ≥ 30% in sum of diameters of viable tissue, taking as reference the baseline sum of the diameters	Tumor necrosis or tumor area reduction between 50% and <100%
Stable disease	Neither partial response nor progressive disease	Neither partial response nor progressive disease	Neither partial response nor progressive disease
Progressive disease	≥25% increase in sum of arterial enhancing area or appearance of new lesion(s)	Increase ≥ 20% in sum of diameters of viable tissue, recorded since treatment started	Tumor area growth > 25% regardless of tumor necrosis, or appearance of new lesion

Source.—Adapted, with permission, from reference 31.
*Arterial enhancing area = longest diameter multiplied by longest perpendicular diameter in the enhancing tumor.
†Viable tissue = arterial enhanced part of the lesion.
‡New lesion = new intrahepatic solitary or multiple lesions or vascular invasion/extrahepatic spread.

* MRI or CT-scan

- Requires dual phase contrast
- Measurements in arterial phase
- Target lesion: measurable according to RECIST, suitable for repeat measurements and shows well-defined arterial enhancement
- 2 target lesions recommended



- Diffuse HCC = non-target lesion; Portal tumoral thrombus = nonmeasurable
- Rim-like lesion = non-measurable

CT, computed tomography; EASL, European Association for the Study of the Liver; HCC; hepatocellular carcinoma; mRECIST, modified RECIST; MRI, magnetic resonance imaging; RECICL, Response Evaluation Criteria in Cancer of the Liver; RECIST, Response Evaluation Criteria in Solid Tumors ; SIRT, selective internal radiation therapy.

Figueiras R et al, Radiographics 2011

mRECIST – EASL – Validated in large patient populations

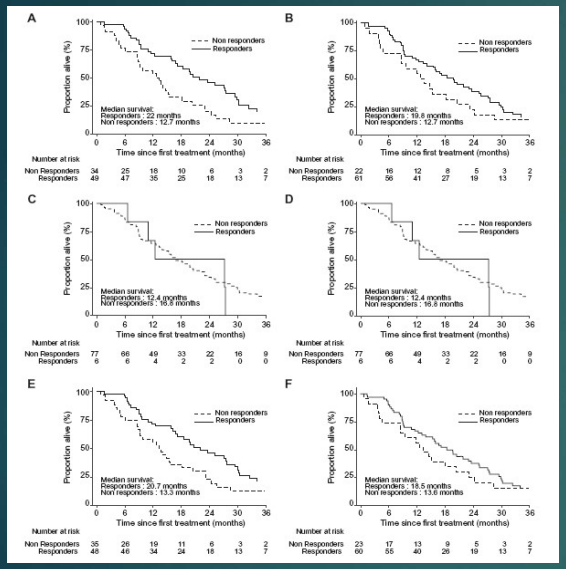
Research Article

EASL JOURNAL OF HEPATOLOGY

EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolisation

Roopinder Gillmore[1], Sam Stuart[2], Amy Kirkwood[3], Ayshea Hameeduddin[2], Nick Woodward[2], Andrew K. Burroughs[4], Tim Meyer[1,5,*]

[1]Department of Oncology, Royal Free Hospital, London, UK; [2]Department of Radiology, Royal Free Hospital, London, UK; [3]Cancer Research UK & UCL Cancer Trials Centre, London, UK; [4]The Royal Free Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK; [5]UCL Cancer Institute, London, UK



Review

JOURNAL OF HEPATOLOGY

mRECIST for HCC: Performance and novel refinements

Josep M. Llovet[1,2,3,*], Riccardo Lencioni[4,5]

Table 1. Assessment of objective response by mRECIST for locoregional and systemic therapies in the setting of phase II and III investigations.

Trial	Arms	n	ORR-mRECIST	ORR-RECIST	Median OS	ORR predicts survival	OS responders *vs.* non responders (HR; *p* value)
TACE							
BRISK-TA	TACE + brivanib	249	48%	n.a.	26.4		
	TACE + placebo	253	42%	n.a.	26.1		
SPACE	TACE + sorafenib	154	55%	n.a.	NR		
	TACE + placebo	153	41%	n.a.	NR		
Meta-analysis (7 studies)	TACE	1,357	62%	n.a.		Yes	0.38 (p <0.0001)
First-line							
BRISK-FL* (10)	Brivanib	577	12%	n.a.	9.5		
	Sorafenib	578	8.80%	n.a.	9.9		
REFLECT* (13)	Lenvatinib	478	24.10%	18.80%	13.6	Yes	22.4 months *vs.* 11.4 months (0.61; p <0.001)
	Sorafenib	476	9.20%	6.50%	12.3		
SILIUS* (18)	Sorafenib + HAIC	103	36.30%	n.a.	11.8		
	Sorafenib	103	17.50%	n.a.	11.5		
BRISK-PS* (19)	Brivanib	263	10%	n.a.	9.4	Yes	14.3 months *vs.* 9.4 months (0.31; p <0.001)
	Placebo	132	1.50%	n.a.	8.2		
Second-line							
RESORCE* (22)	Regorafenib	379	11%	7%	10.6		
	Placebo	194	4.10%	3%	7.8		
Phase II	Nivolumab	145	19%	14%		Yes	NR *vs.* 13.4 months
Phase II	Pembrolizumab	104	15%	17%*			
Phase II	Nintedanib	180	15.60%	4.40%		Yes	16.7 months *vs.* 10.9 months (0.54; p = 0.012)

HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; n.a., not applicable; NR, not reached; ORR, objective response rate; OS, overall survival; TACE, transarterial chemoembolisation.
* Both RECIST and irRECIST.

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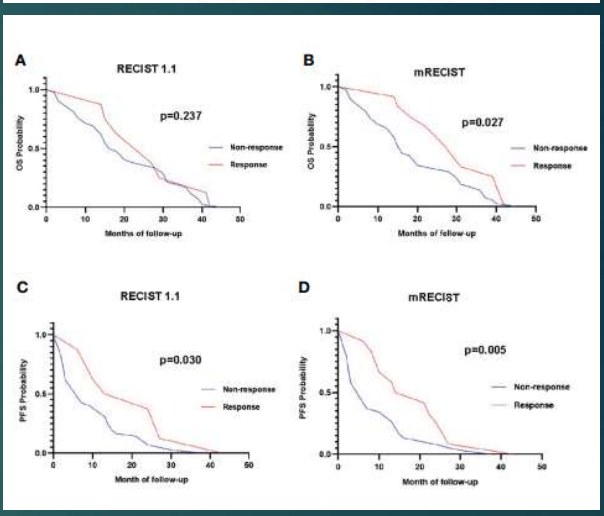
ORIGINAL RESEARCH
published: 09 December 2021
doi: 10.3389/fonc.2021.764189

Response Evaluation and Survival Prediction Following PD-1 Inhibitor in Patients With Advanced Hepatocellular Carcinoma: Comparison of the RECIST 1.1, iRECIST, and mRECIST Criteria

OPEN ACCESS

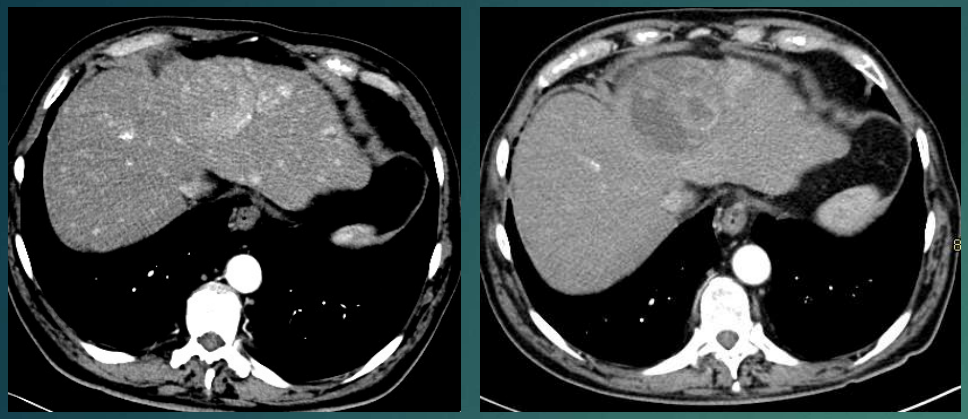
Meng Zhou[†], Chunhui Zhang[†], Jianhua Nie[†], Yajuan Sun[2], Ye Xu[2], Fangfang Wu[1], Yuhong Huang[1], Shun Li[1], Yuan Wang[1], Yang Zhou[2] and Tongsen Zheng[1,3,4*]*



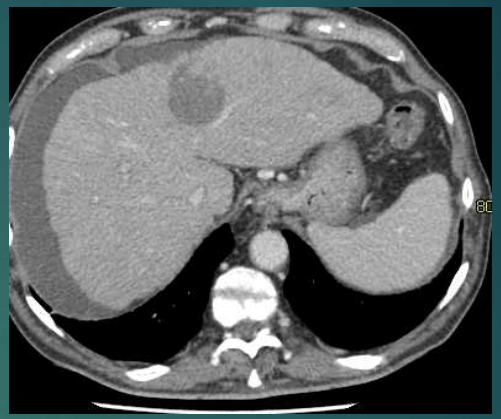
mRECIST better correlation with progression free and overall survival compared to RECIST 1.1

EASL, European Association for the Study of the Liver; HCC; hepatocellular carcinoma; mRECIST, modified RECIST; RECIST, Response Evaluation Criteria in Solid Tumors.

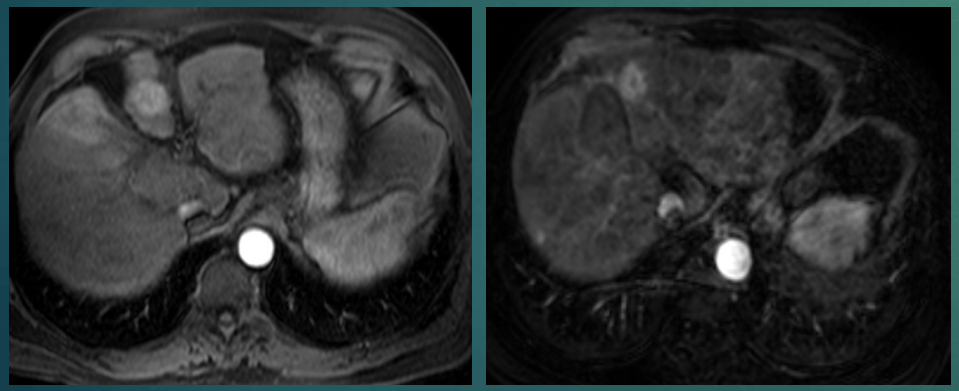
mRECIST



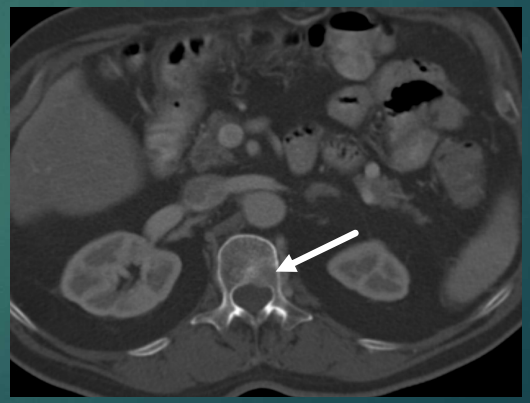
Immunotherapy: mRECIST partial response - RECIST 1.1 stable disease



9 months follow-up since response assessment



Immunotherapy: mRECIST stable disease (non-response)



3 months follow-up since response assessment

EASL, European Association for the Study of the Liver; mRECIST, modified RECIST; RECIST, Response Evaluation Criteria in Solid Tumors.

mRECIST: Difficulties

1/ Arterial enhancement has moderate correlation with tumour pathology and only reflects vascularity!

Contents lists available at SciVerse ScienceDirect

European Journal of Radiology

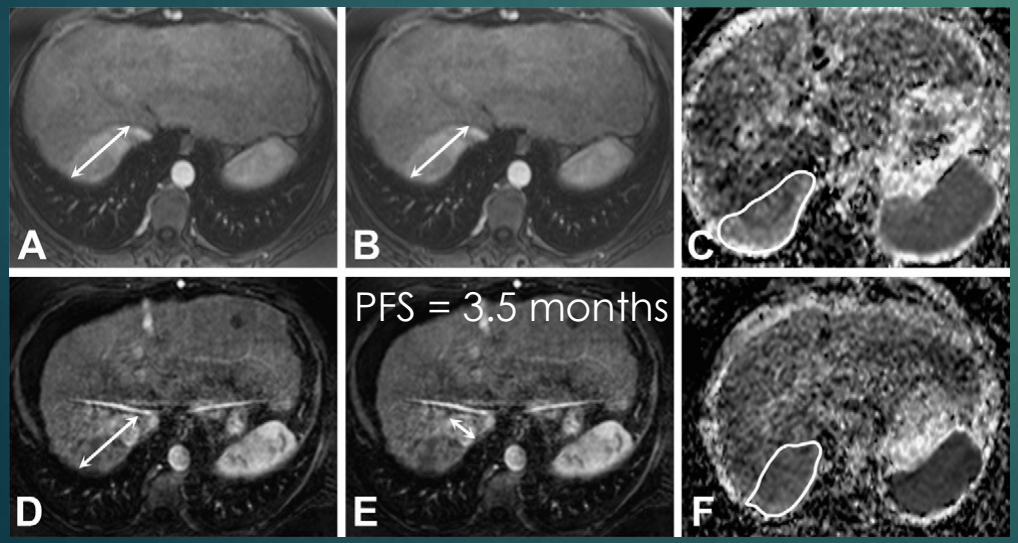
journal homepage: www.elsevier.com/locate/ejrad

Modified RECIST to assess tumor response after transarterial chemoembolization of hepatocellular carcinoma: CT–pathologic correlation in 178 liver explants

Irene Bargellini[a,*], Elena Bozzi[a], Daniela Campani[b], Paola Carrai[c], Paolo De Simone[c], Luca Pollina[b], Roberto Cioni[a], Franco Filipponi[c], Carlo Bartolozzi[a]

CT–pathology correlation: mRECIST versus pathologic necrosis. The overall accuracy of mRECIST was 65.2% (116/178 patients) for target lesion response and 67.4% (120/178 patients) for overall response.

CT (mRECIST)	Patients #	Pathology necrosis (%)		
		100	>50	<50
Target lesion response				
CR	93	51 (54.8%)	41 (44.1%)	1 (1.1%)
PR	60	9 (15%)	41 (68.3%)	10 (16.7%)
SD	23	0 (0%)	1 (4.3%)	22 (95.7%)
PD	2	0 (0%)	0 (0%)	2 (100%)
Overall response				
CR	86	51 (59.3%)	33 (38.4%)	2 (2.3%)
PR	53	9 (17%)	40 (75.5%)	4 (7.5%)
SD	22	0 (0%)	1 (4.6%)	21 (91.4%)
PD	17	0 (0%)	9 (52.9%)	8 (47.1%)



mRECIST, modified Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival.
Vandecaveye V et al, Radiology 2013

frontiers in Oncology

ORIGINAL RESEARCH

Response Evaluation and Survival Prediction Following PD-1 Inhibitor in Patients With Advanced Hepatocellular Carcinoma: Comparison of the RECIST 1.1, iRECIST, and mRECIST Criteria

OPEN ACCESS

Meng Zhou[†], Chunhui Zhang[†], Jianhua Nie[†], Yajuan Sun[2], Ye Xu[2], Fangfang Wu[1], Yuhong Huang[1], Shun Li[1], Yuan Wang[1], Yang Zhou[2*] and Tongsen Zheng[1,3*]

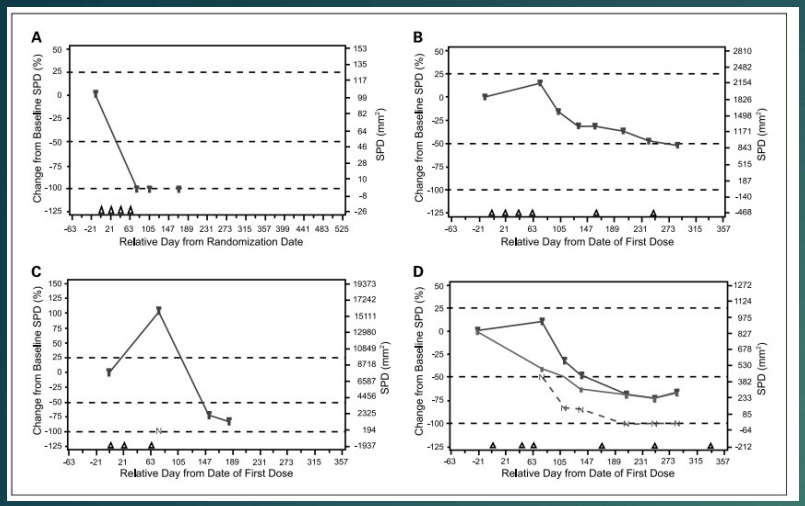
TABLE 7 | Compare the response assessment of two radiologists.

	Kappa	CI 95%
RECIST 1.1	0.534	0.305–0.763
iRECIST	0.438	0.426–0.450
mRECIST	0.363	0.351–0.375

CI, confidence interval.

2/ Interobserver variability increases

iRECIST

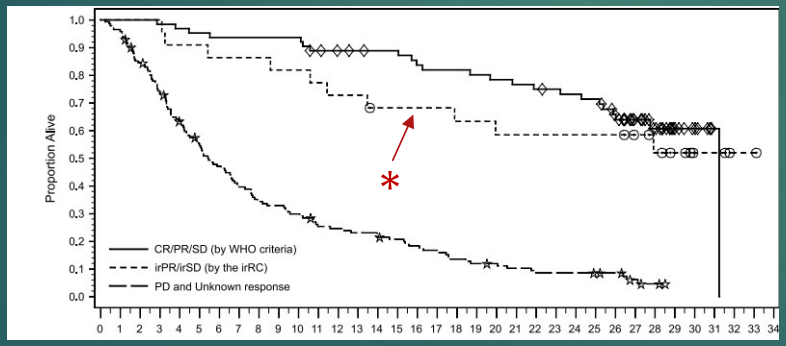


4 patterns of response

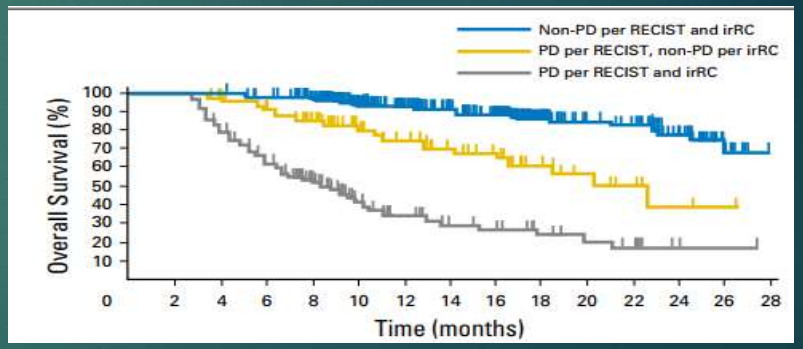
Cancer Therapy: Clinical Clin Cancer Res 2009;15(23) December 1, 2009

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[3] Celeste Lebbé,[5] Michele Maio,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]



ipilimumab phase II program



Validation studies (Hodi F et al, JCO 2016)

iRECIST PR and SD similar survival outcome as RECIST 1.1 PR

iRECIST, immune-related RECIST; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
Vandecaveye V et al, Radiology 2013

iRECIST

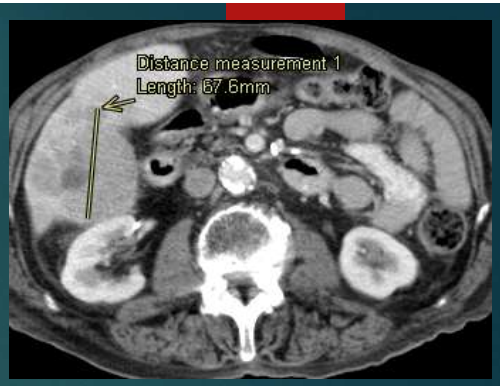
Table 1 Features of criteria for immune-related responses

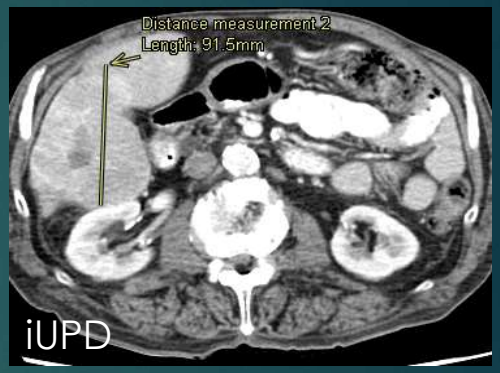
Features	irRC	irRECIST	iRECIST	imRECIST
Source	Wolchok 2009	Nishino 2013	Seymour 2017	Hodi 2018
Model based on	WHO criteria	irRC & RECIST 1.1	RECIST 1.1	irRC & RECIST 1.1
Dimension	Two	One	Same as irRECIST	Same as irRECIST
Progressive disease definition	25% increase from the nadir	20% increase from the nadir	20% increase from the nadir; results in unconfirmed progressive disease; confirmation is necessary for confirmed progressive disease	Same as irRECIST
New lesion	The presence of new lesion(s) does not define progression; the measurements of the new lesion(s) are included in the sum of the measurements	Same as irRC	The presence of new lesion(s) does not define progression; the measurements of the new lesion(s) are not incorporated in tumor burden	Same as irRC
Confirmation	4 weeks	4 weeks	4 weeks; no longer than 8 weeks	4 weeks
Development cohort	Melanoma treated with ipilimumab	Advanced melanoma treated with ipilimumab	Consensus base	Advanced NSCLC and mUC treated with atezolizumab
Outcomes of development cohort	OS	irRC response	Not applicable	OS

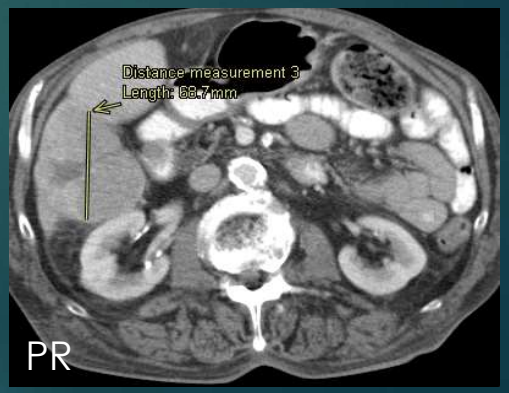
irRC, immune-related response criteria; irRECIST, immune-related response evaluation criteria in solid tumors, iRECIST, immune response evaluation criteria in solid tumors; imRECIST, immune-modified response evaluation criteria in solid tumors; WHO, World Health

Kataoka Y et al, Annals of Translational Medicine 2018

- Imaging modalities, contrast-phase and target lesion selection: as per RECIST 1.1
- Follow-up frequency → 6 -12 weeks
- New definitions : iUPD = unconfirmed progression – iCPD = confirmed progression







iRECIST, immune-related RECIST; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

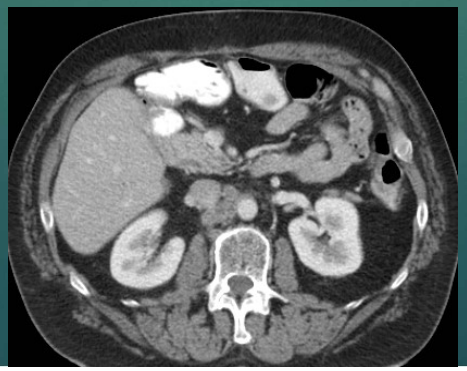
iRECIST

Seymour L, Lancet Oncology 2017

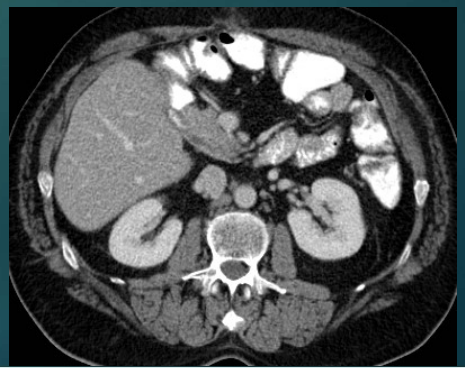
	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1: **Comparison of RECIST 1.1 and iRECIST**

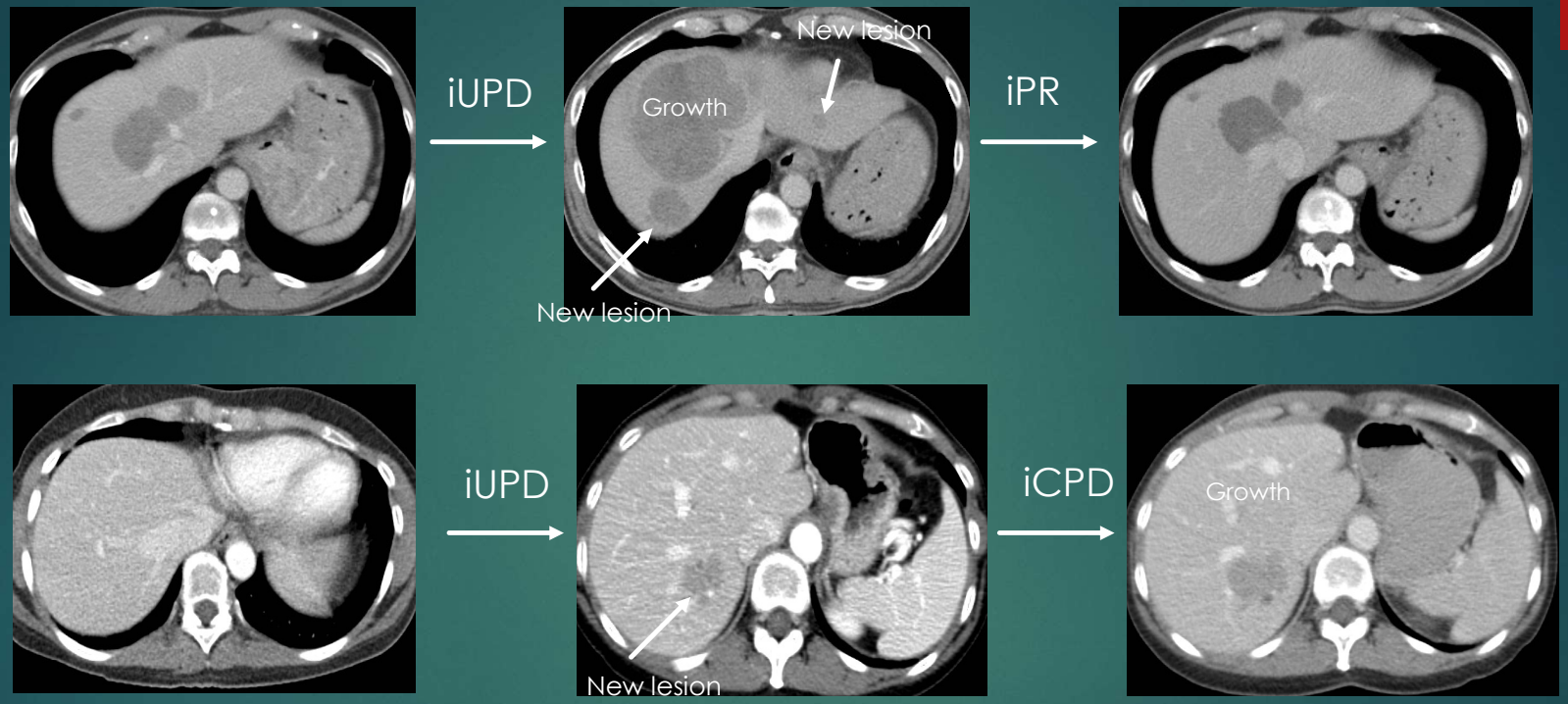


Partial response as per RECIST 1.1



iRECIST, immune-related RECIST;
RECIST, Response Evaluation Criteria in Solid Tumors.

iRECIST – from trial to clinical practice

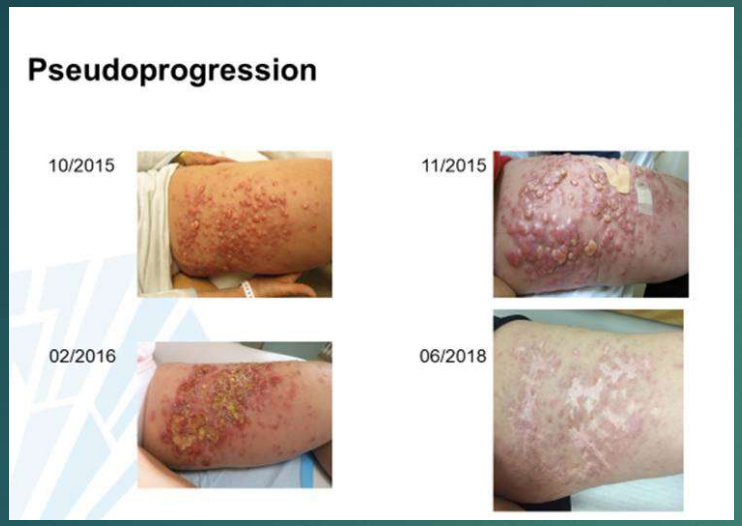


iRECIST response → closer correlation to outcome than RECIST 1.1
Avoiding premature withdrawal of immunotherapy

Clinical trials → drug efficacy
Clinical practice → optimize therapeutic management

iRECIST, immune-related RECIST;
RECIST, Response Evaluation Criteria in Solid Tumors.

iRECIST - Potential difficulties



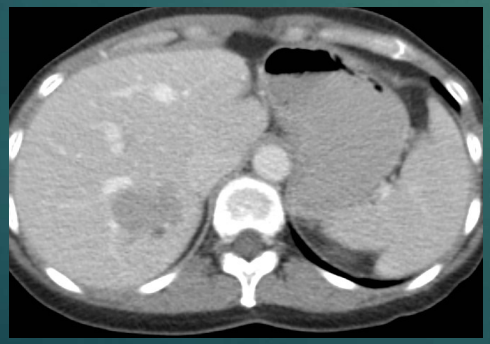
Courtesy of J Dekervel, digestive oncology UZ Leuven

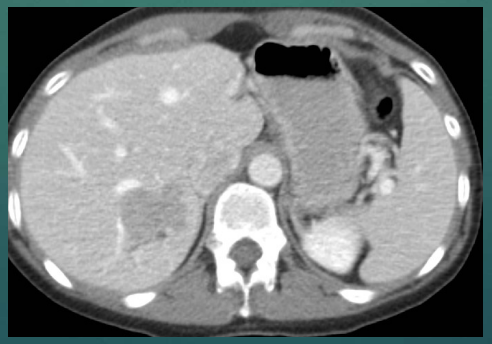
1/
Although potentially an improvement over conventional criteria for immunotherapeutic agents, the iRECIST may still not capture or fully characterize all relevant patterns of clinical activity

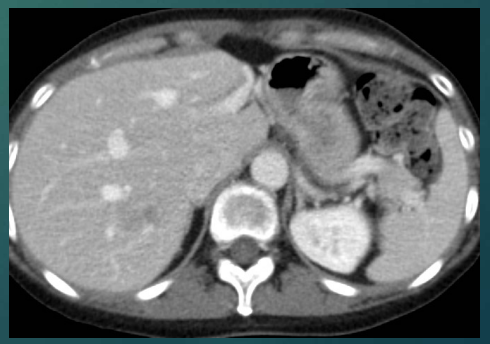
→ Validation in different agents remains necessary

2/
Balancing the adverse effects of premature immunotherapy withdrawal opposed to treatment induced toxicity

Clinical assessment lack of progression?

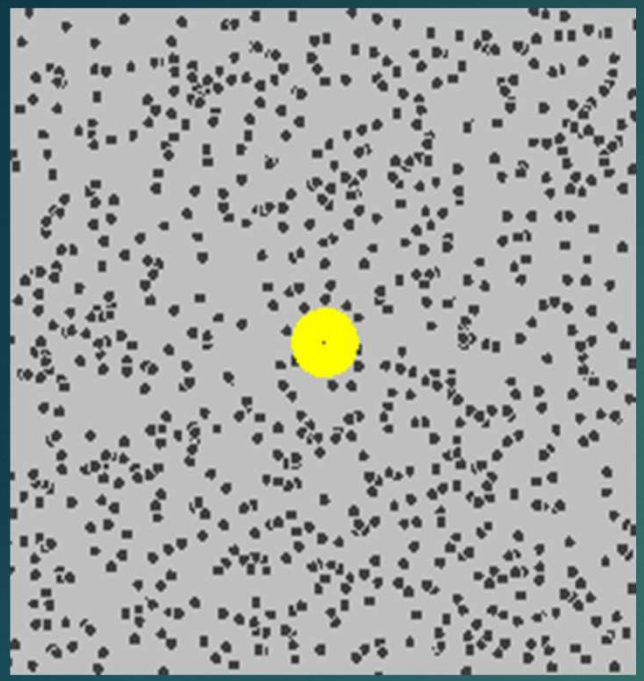




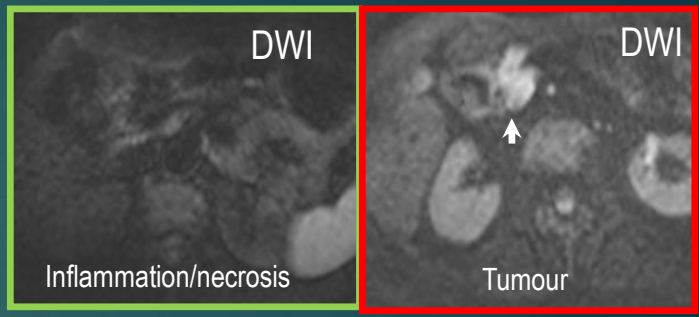


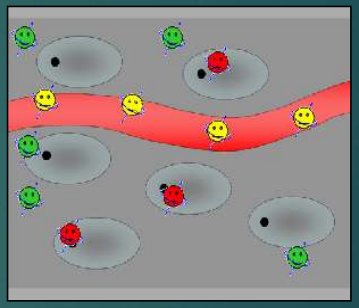
iRECIST, immune-related Response Evaluation Criteria in Solid Tumors.

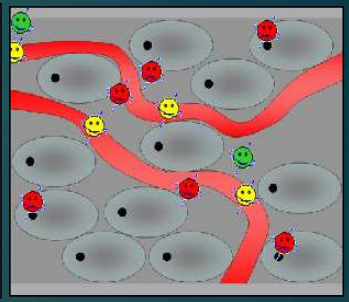
Functional: diffusion-weighted MRI

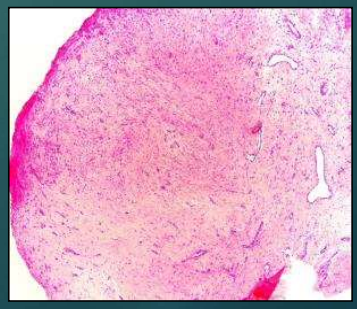


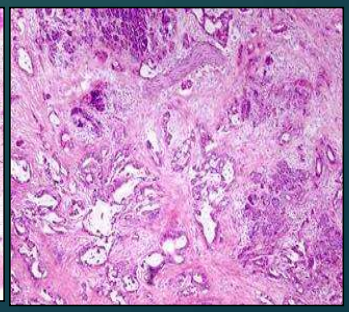
Helsinki museum of art

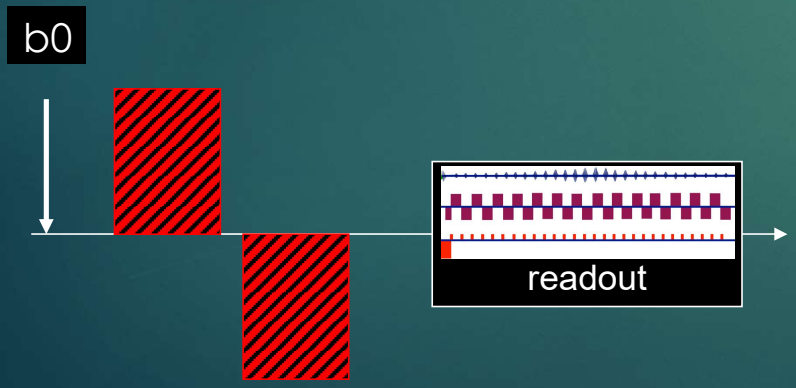






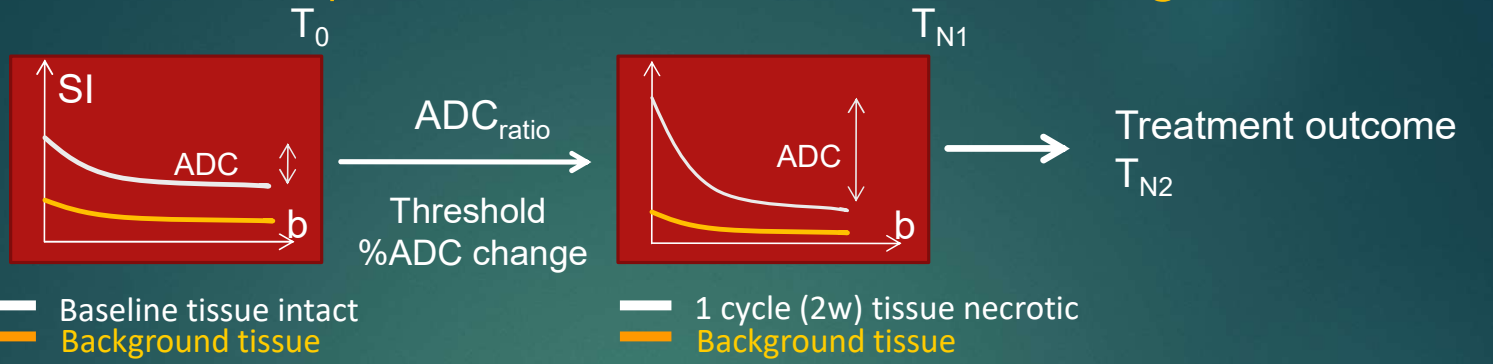


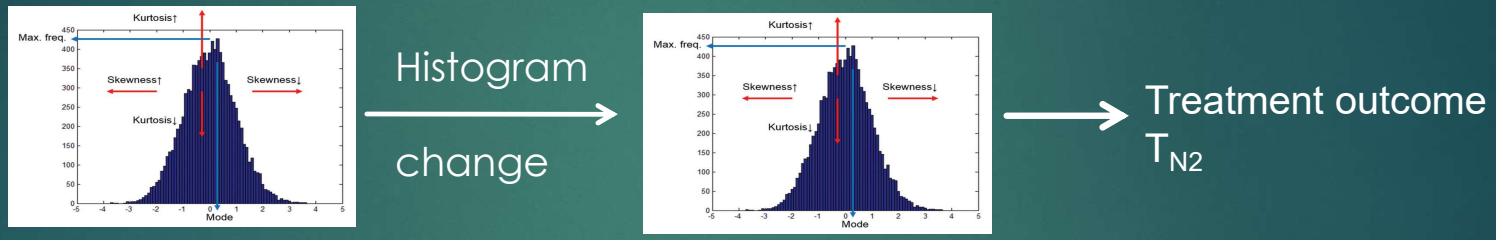


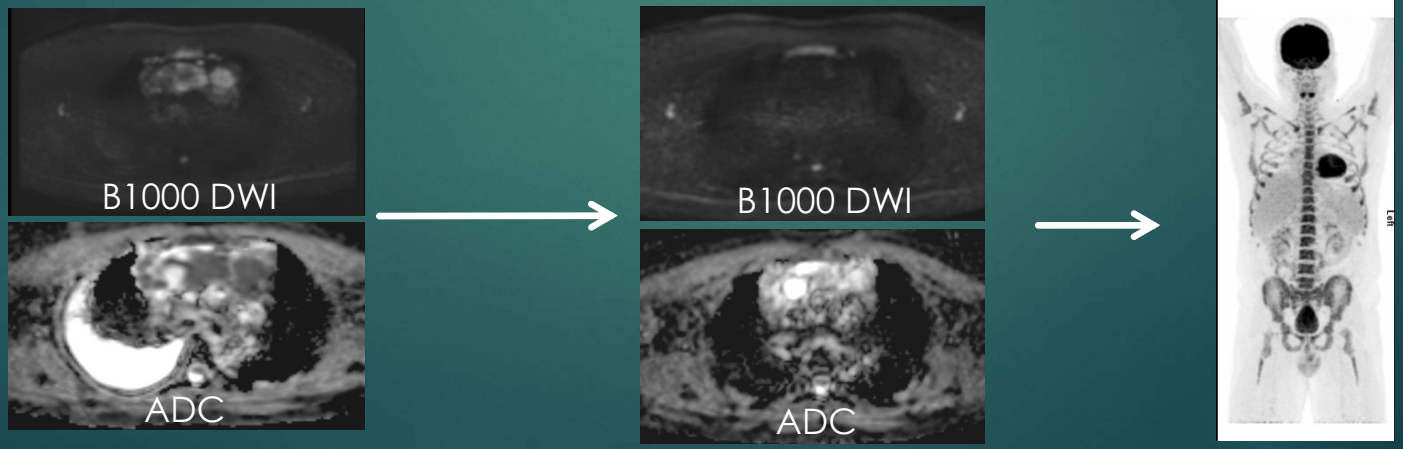


DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging.

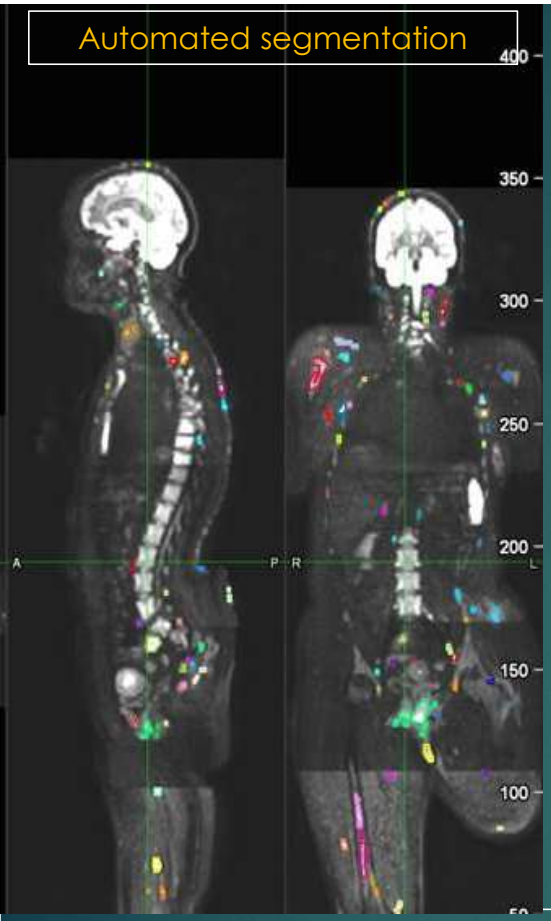
Functional response assessment : diffusion-weighted MRI



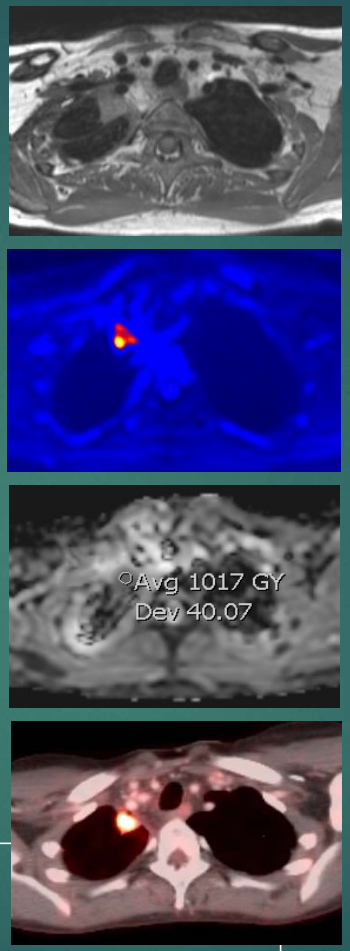




ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; SI, signal intensity.

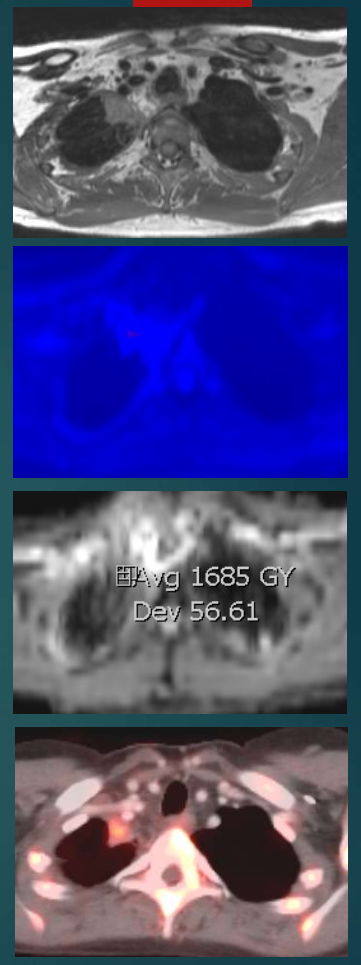


Functional: diffusion-weighted MRI



Chemotherapy
+
Immunotherapy

ADC change = 40%
Threshold = 24%



- **If manual segmentation: up to 5 lesions/organ system**
- **$ADC_{ratio} = [(ADC_{fu} – ADC_{base})/ADC_{base}] \times 100\%$**
- **Threshold ADC_{ratio}, variable (!) = 15% for HCC, 0% for NET, 24% for lymphoma**
- **Lowest responding lesion = index lesion for total response**

DWI not influenced by inflammation

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; NET, neuroendocrine tumor.

Radiology: Imaging Cancer

ORIGINAL RESEARCH

Quantitative Whole-Body Diffusion-weighted MRI after One Treatment Cycle for Aggressive Non-Hodgkin Lymphoma Is an Independent Prognostic Factor of Outcome

Katja N. De Paepe, MD, PhD • Cidka-Anne Van Keerberghen, MD • Giorgio M. Agazzi, MD • Frederik De Keyzer, MSc • Olivier Gheysens, MD, PhD • Oliver Bechter, MD, PhD • Pascal Wolter, MD • Daan Dierickx, MD, PhD • Ann Janssens, MD, PhD • Gregor Verhoef, MD, PhD • Raymond Oyen, MD, PhD • Michel Koole, MSc, PhD • Vincent Vandecaveye, MD, PhD

LYMPHOMA: INTERIM DWI-RESPONSE ASSESSMENT

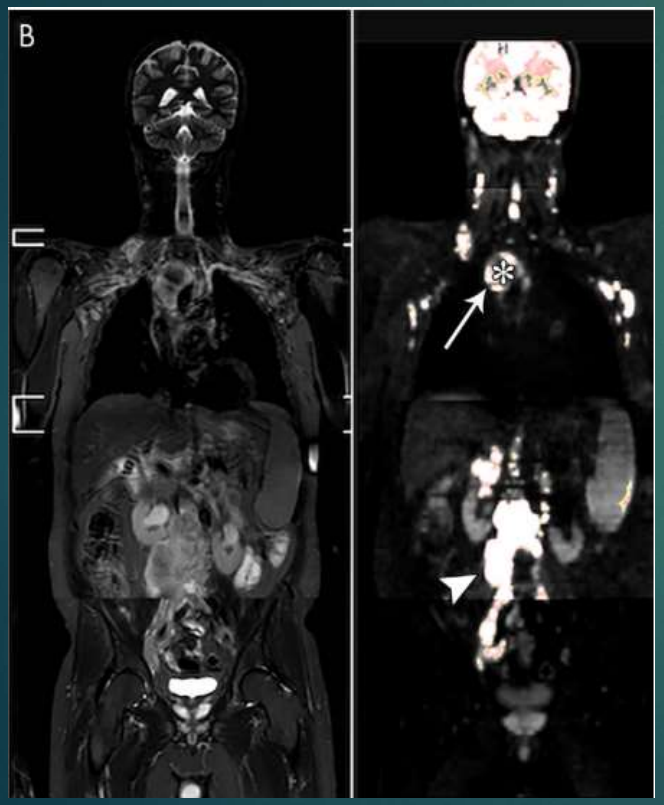
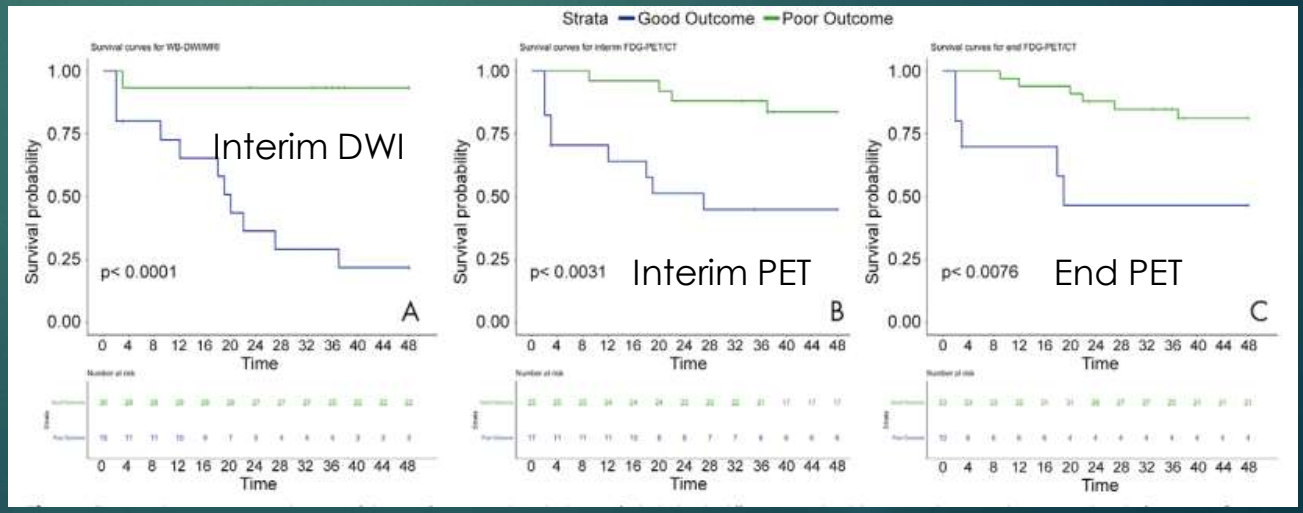


Table 3: Per-Patient Diagnostic Accuracy of WB-DW MRI, Interim, and End-of-Treatment ^{18}F-FDG PET/CT with Overview of Discordance between Different Techniques

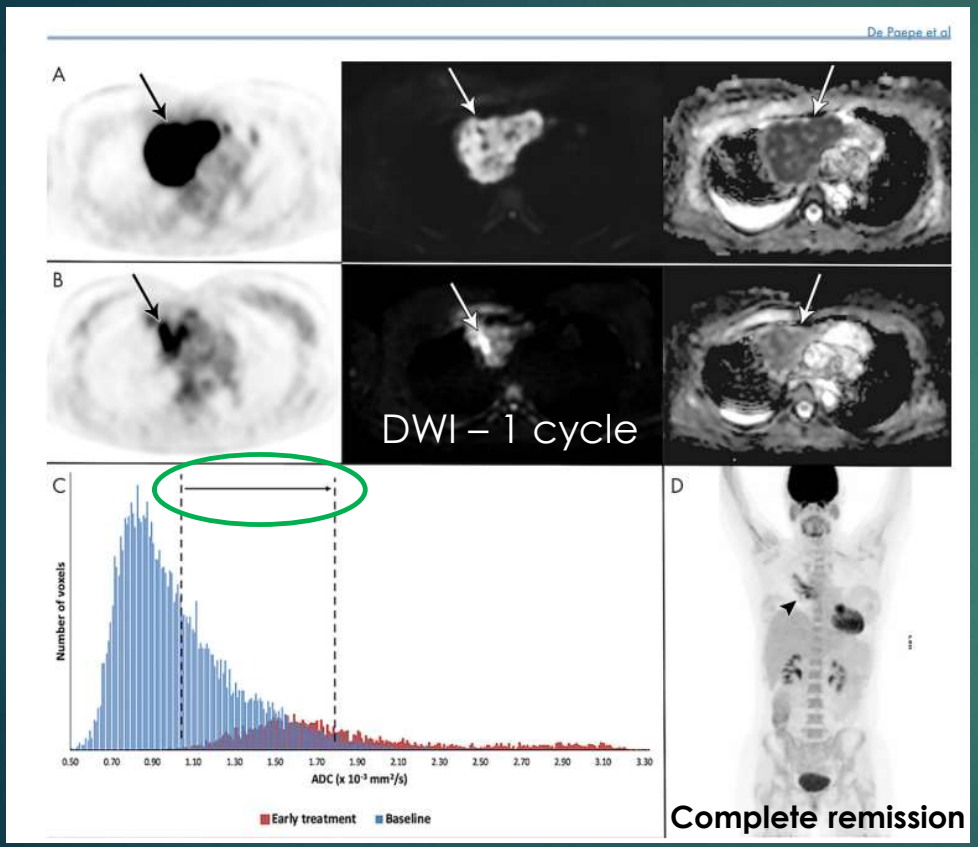
	WB-DW MRI		Interim ^{18}F-FDG PET/CT		End ^{18}F-FDG PET/CT	
Parameter	Value (%)	95% CI	Value (%)	95% CI	Value (%)	95% CI
Accuracy	86.7 (39/45)	(73.2, 95.0)	71.4 (30/42)	(55.4, 84.3)	73.8 (31/42)	(58,0, 86.1)
Sensitivity	84.6 (11/13)	(54.6, 98.1)	69.2 (9/13)	(38.6, 90.9)	45.5 (5/11)	(16.8, 76.6)
Specificity	87.5 (28/32)	(71.0, 96.5)	72.4 (21/29)	(52.8, 87.3)	83.9 (26/31)	(66.3, 94.6)
PPV	73.3 (11/15)	(51.7, 87.6)	52.9 (9/17)	(36.0, 69.2)	50.0 (5/10)	(26.3, 73.7)
NPV	93.3 (28/30)	(79.5, 98.1)	84.0 (21/25)	(69.3, 92.4)	81.3 (26/32)	(71.2, 88.4)

Early WB-DWI improves PET/CT for prediction of outcome

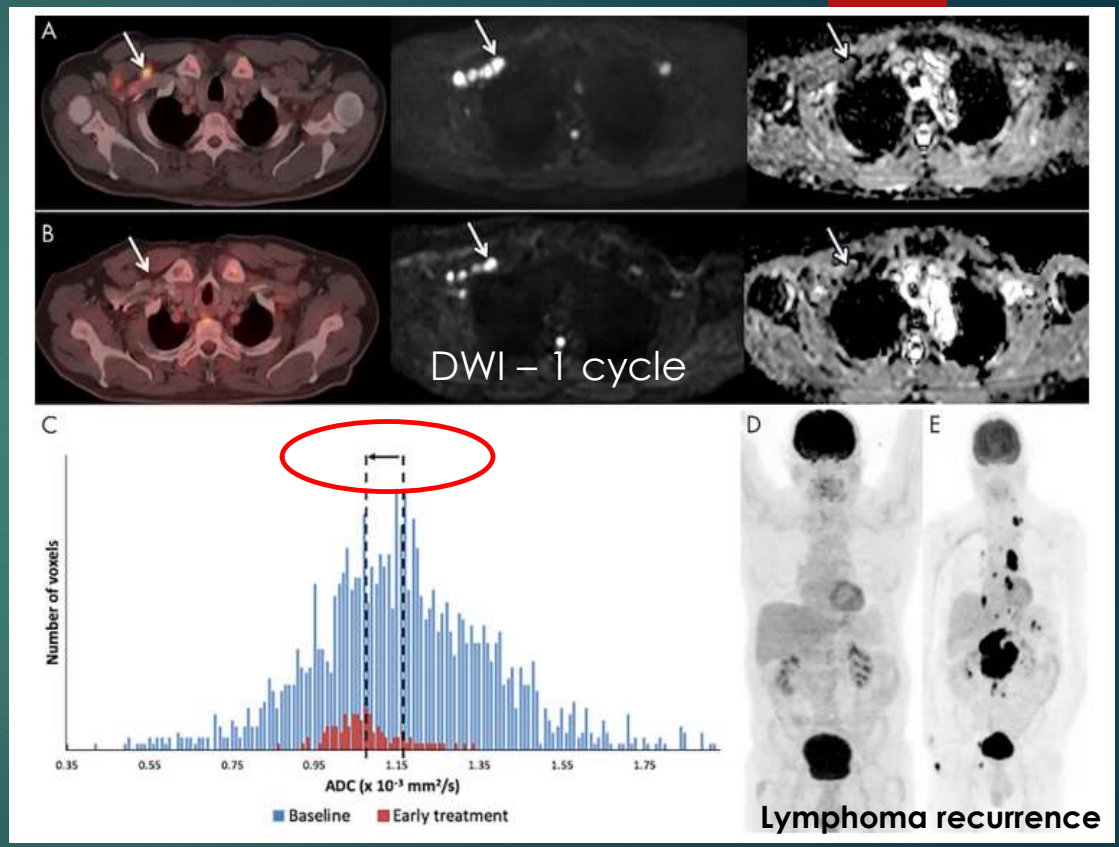


CT, computed tomography; DWI, diffusion-weighted imaging; PET, positron emission tomography; WB , whole body.

DWI: EARLY RESPONSE ASSESSMENT AFTER 1 TREATMENT CYCLE FOR LYMPHOMA



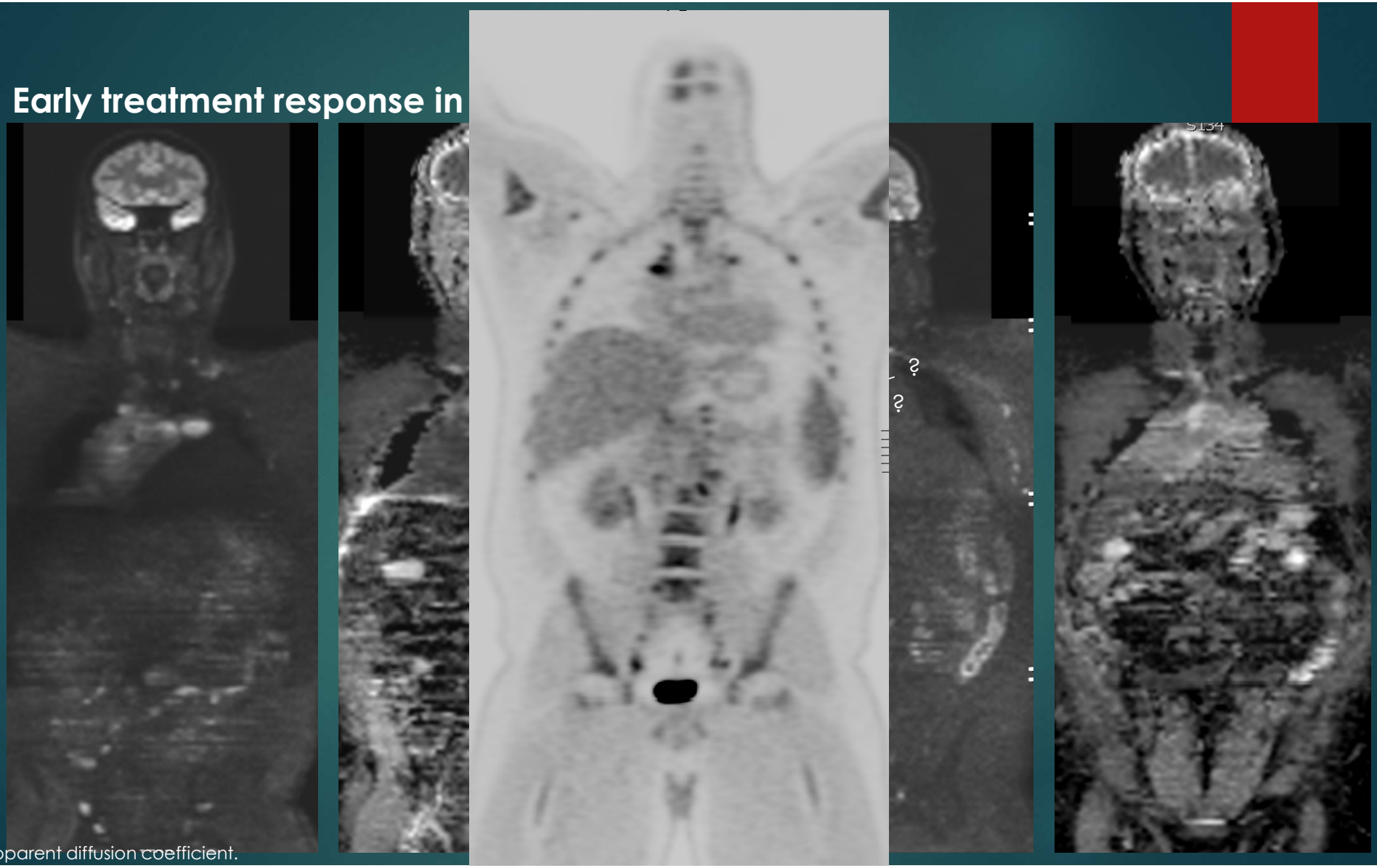
Responder



Non-Responder

DWI, diffusion-weighted imaging.

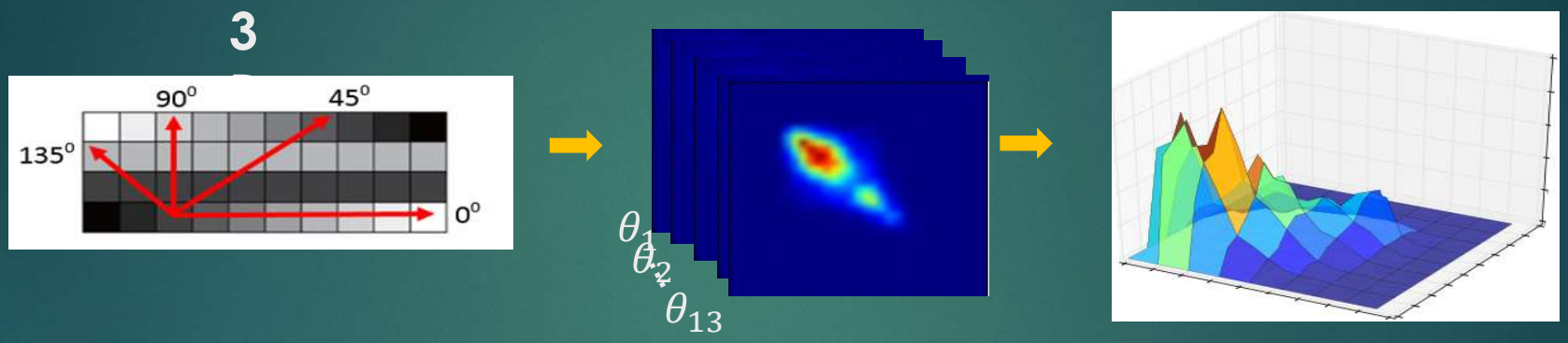
Early treatment response in

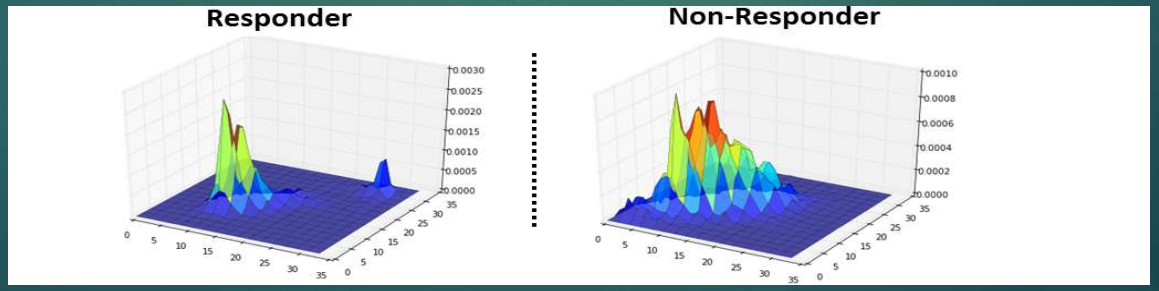


ADC, apparent diffusion coefficient.

Beyond ADC

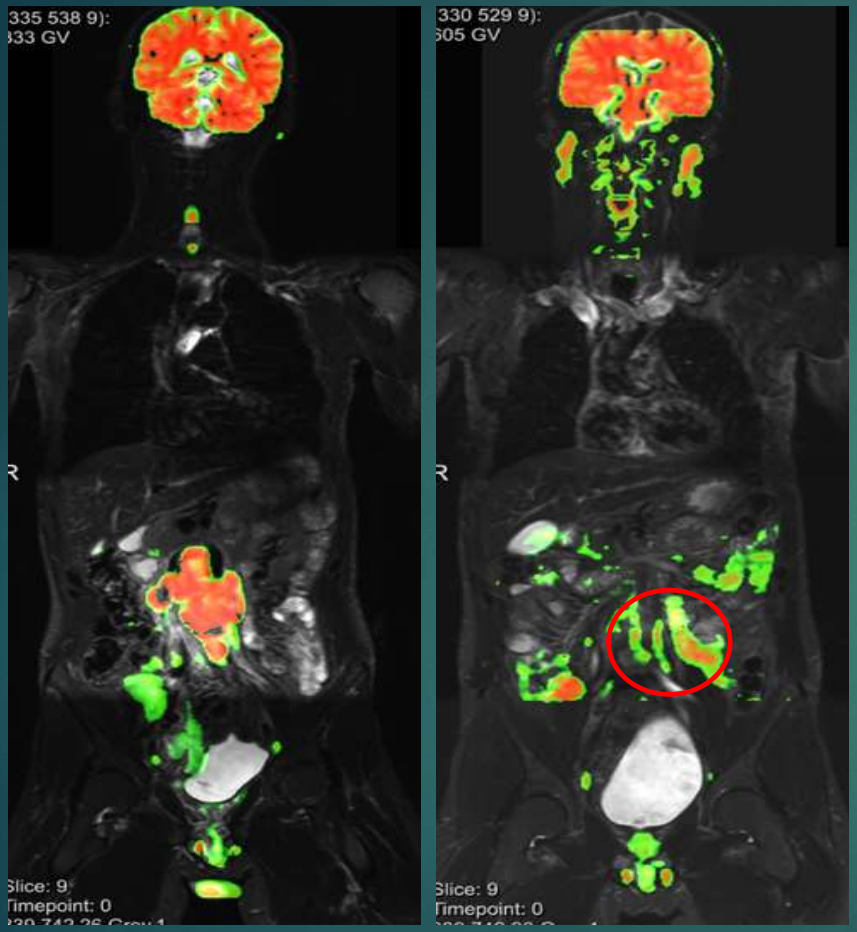
Second Order Statistic (SOS) using 2D histogram based on Gray Level Coocurrence matrix (GLCM)

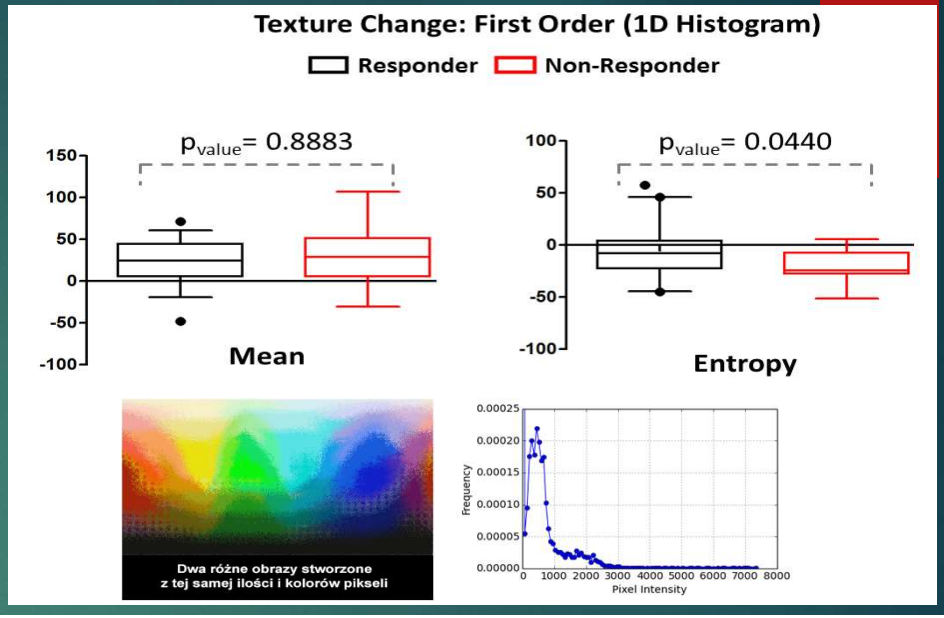


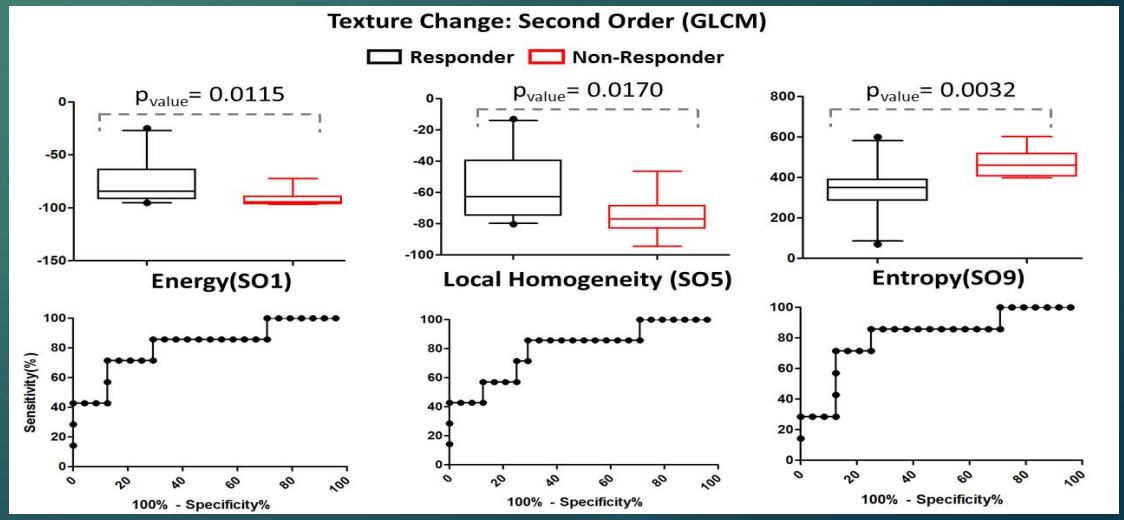


ADC, apparent diffusion coefficient.

Hodgkin lymphoma: non-responder







Overcoming failure of standard DWI analysis → Texture metrics

DWI, diffusion-weighted imaging.

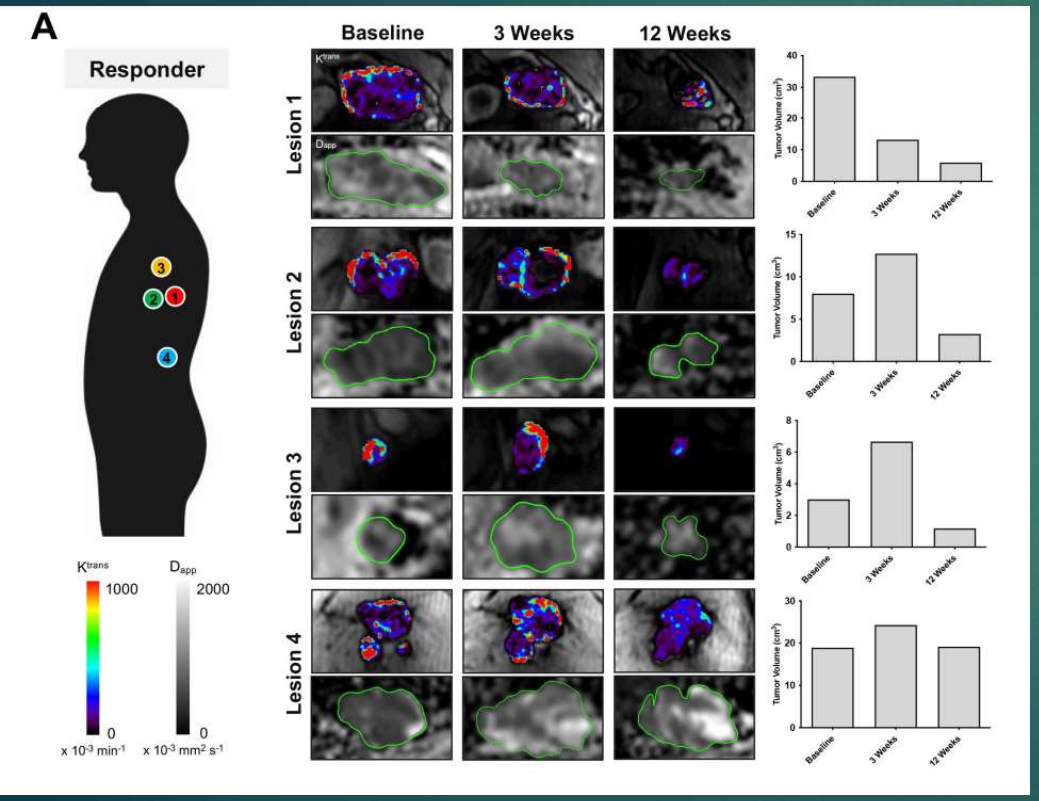
DWI enables identification of pseudoprogression

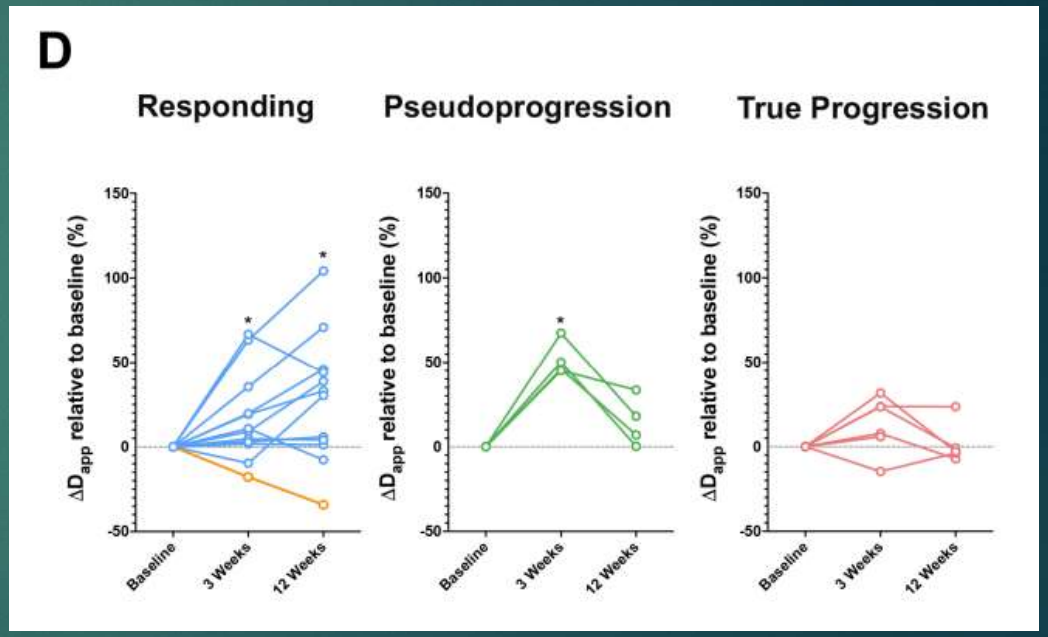
Open access Original research

Journal for ImmunoTherapy of Cancer

Multiparametric MRI of early tumor response to immune checkpoint blockade in metastatic melanoma

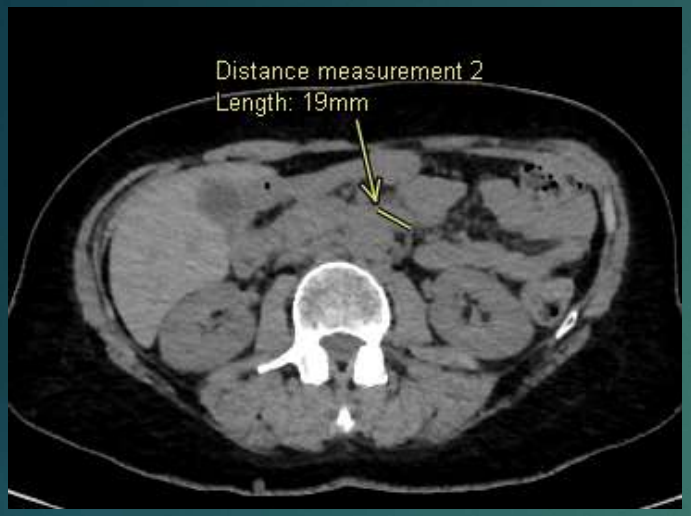
Doreen Lau ,[1,2] Mary A McLean ,[1,2] Andrew N Priest ,[1,3] Andrew B Gill ,[1,2] Francis Scott,[1] Ilse Patterson,[3] Bruno Carmo,[3] Frank Riemer,[1] Joshua D Kaggie,[1] Amy Frary,[1] Doreen Milne,[4] Catherine Booth,[4] Arthur Lewis,[5] Michal Sulikowski,[5] Lee Brown,[5] Jean-Martin Lapointe ,[5] Luigi Aloj,[1,6] Martin J Graves,[1,3] Kevin M Brindle,[7] Pippa G Corrie ,[4] Ferdia A Gallagher [1,2]

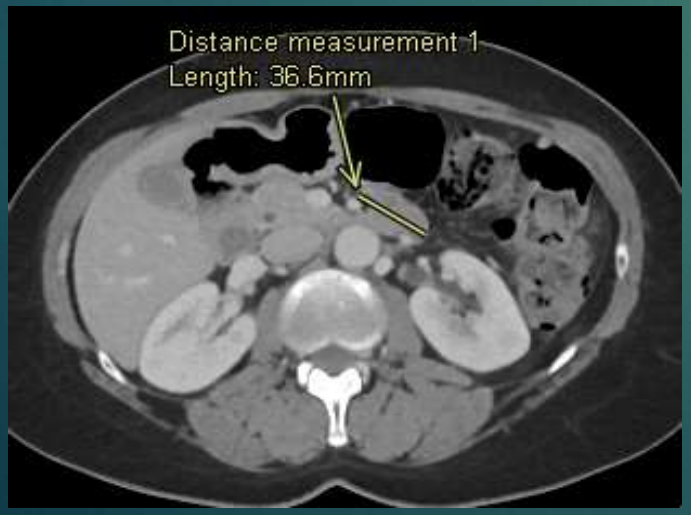


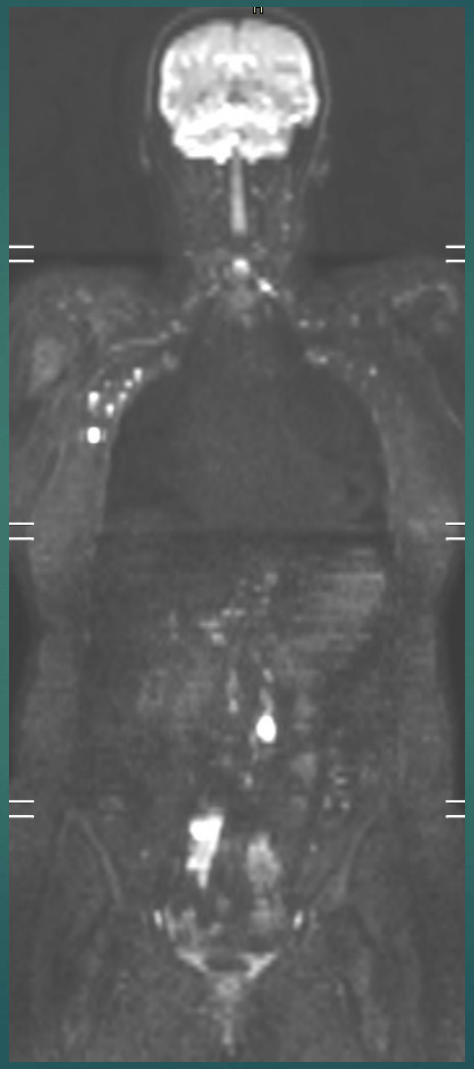


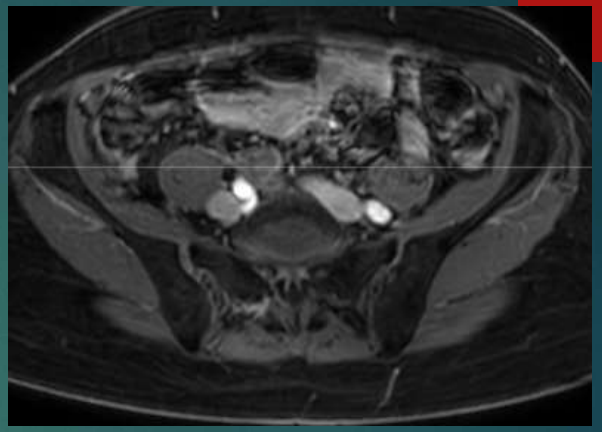
DWI, diffusion-weighted imaging.

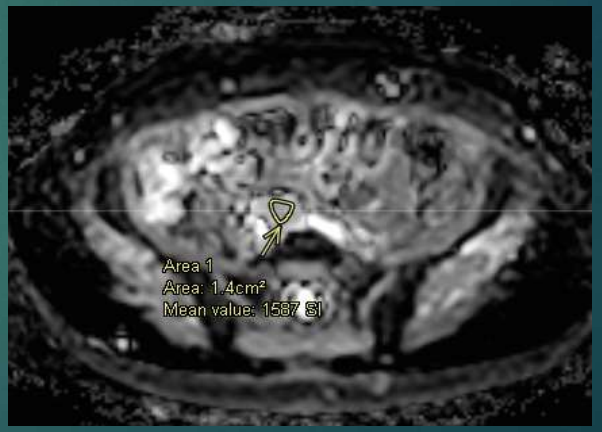
DWI enables identification of pseudoprogression: clinical case colon cancer





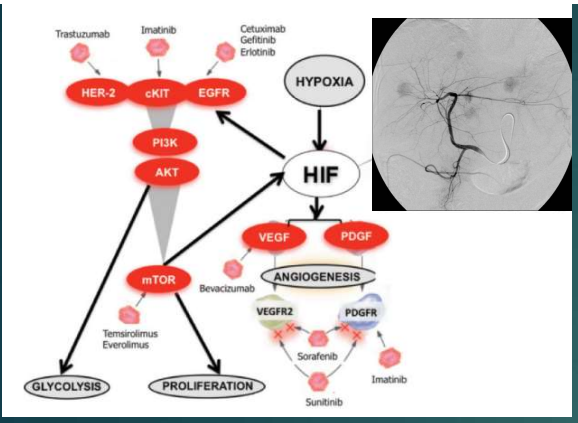






ADC > 0,00140 → inflammation/necrosis
Complete remission for 4 years

ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging.

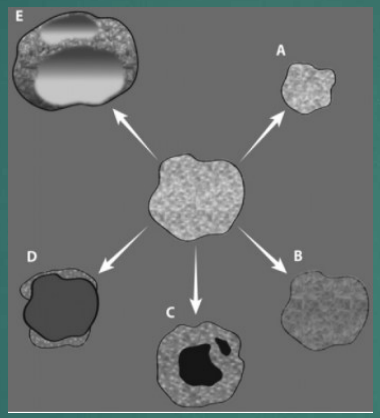


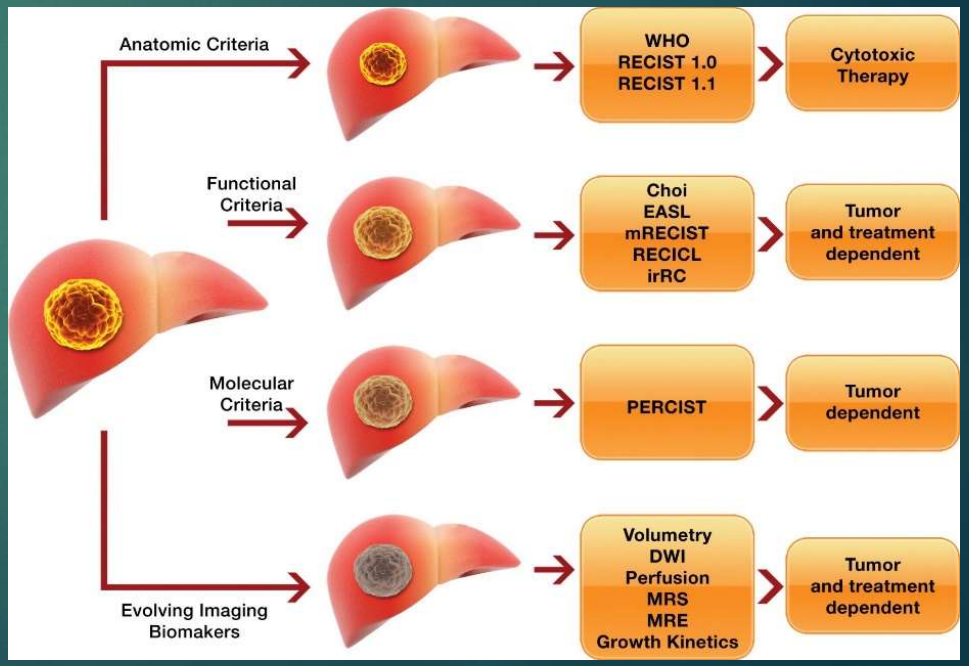
Take home messages

Alternative RECIST criteria

Improved marker for outcome then RECIST

Likely do not capture disease activity as functional imaging





Functional MRI criteria

Improved marker for outcome then RECIST/FDG-PET

Requires further build-up of data

FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; Response Evaluation Criteria in Solid Tumors.