PINTAD
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A clinical perspective on the changing landscape in lymphoma criteria

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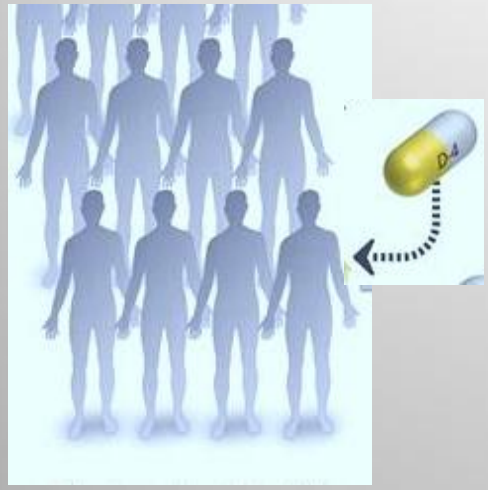
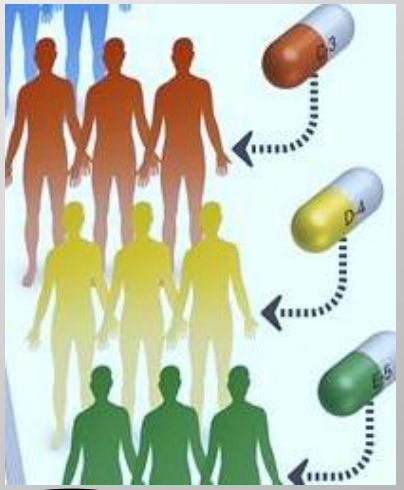
Objectives

- Understand currently used and proposed lymphoma response assessment criteria
  - Lugano
  - RECIL
  - LyRIC
  - Quantitative?

- Discuss challenges to the radiologist

Disease-oriented → **Disease-agnostic Individualized**





Novel criteria are needed that predict prognosis, determine treatment response, of an individual patient for a therapeutic lexicon that benefits the patient outcome

(Inflationary!) Imaging Response Criteria

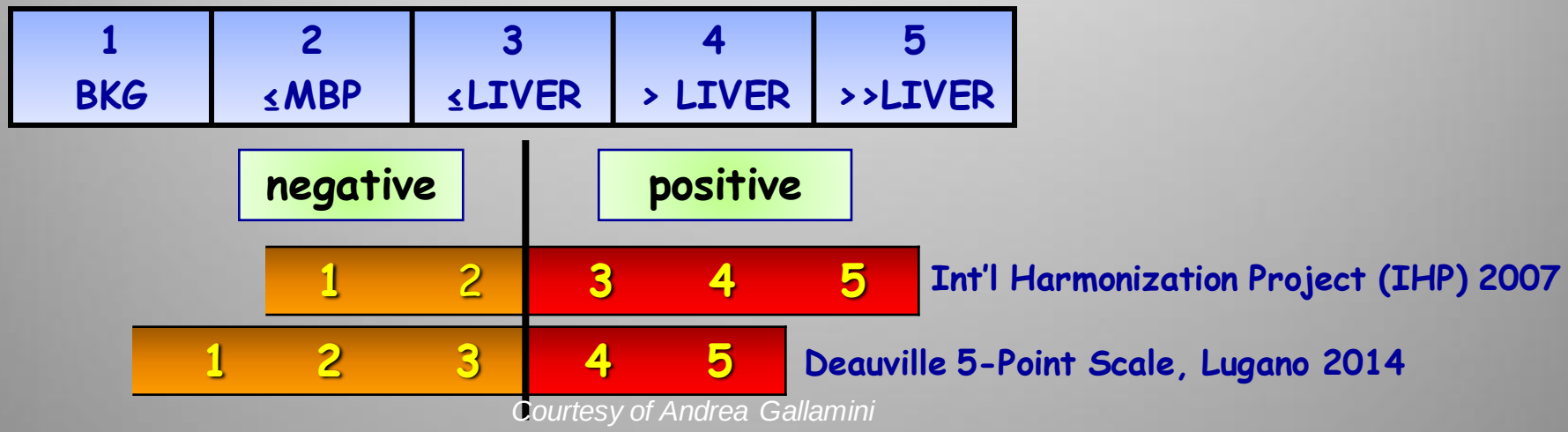
- ❑ **International Working Group (Cheson) Criteria** 2007
- ❑ **Deauville Criteria**
- ❑ **Lugano Recommendations 2014**
- ❑ **RECIST v1.0 (2000)**
- ❑ **RECIST v1.1 (2011)**
- ❑ **Modified RECIST (mRECIST)**
- ❑ **immune RECIST (iRECIST)**
- ❑ **European Org for Research & Treatment of Cancer (EORTC)**
- ❑ **PET Response Criteria in Solid Tumors (PERCIST)**
- ❑ **IMWG myeloma**
- ❑ **McDonald Criteria**
- ❑ **Response Assessment in Neuro-Oncology (RANO)**
- ❑ **MD Anderson Bone Response Criteria (MDA)**
- ❑ **Prostate Cancer Working Group 2 (PCWG2)**
- ❑ **Choi Criteria (2007)** (GIST)
- ❑ **Immune-Related Response Criteria (irRC)**
- ❑ **Size & Attenuation Contrast-enhanced CT (SACT Criteria)** (RCC)
- ❑ **Morphology, Attenuation, Size, Structure (MASS Criteria)** (RCC)

Standard Response Criteria for Malignant Lymphoma Have Evolved with Integration of PET Imaging

	CR	PR	SD	PD
IWC **1999**	Reduction of nodes to normal size	≥50% reduction in size of 6 largest nodes	≤50% reduction or increase in size of nodes	≥50% increase in size of nodes
IWC+PET	CR by IWC plus negative PET scan	CR/PR by IWC plus positive PET scan	SD by IWC plus positive PET scan	PD by IWC plus positive PET scan
International Harmonization Project **2007**	PET− nodes or PET+ nodes of normal size	≥50% reduction in size of 6 largest nodes	New PET+ nodes	New PET+ ≥1.5 cm or ≥50% increase in size of existing nodes
D5PS*	^{18}F-FDG uptake at background level	^{18}F-FDG uptake ≤ mediastinal blood pool/liver activity	Mediastinal blood-pool activity ≤ ^{18}F-FDG uptake ≤ liver activity	^{18}F-FDG uptake > liver activity
Lugano				
PET/CT **2014**	Normalized ^{18}F-FDG uptake (1–3 on D5PS)	Reduced ^{18}F-FDG uptake (4–5 on D5PS)	Unchanged ^{18}F-FDG uptake (4–5 on D5PS)	Increased ^{18}F-FDG uptake (4–5 on D5PS) + new lesions
CT	Reduction of nodes/ organs to normal size	≥50% reduction in size of up to 6 nodes/spleen	<50% reduction in size of up to 6 nodes	≥50% increase in size of node + new lesions

Definition of complete metabolic response has evolved

- Resolution of FDG uptake at initial sites indicates lack of malignant metabolic activity
- *Visual assessment* is the usual method for PET interpretation
- Uptake is defined relative to *an internal reference*: background, mediastinal blood pool (MBP) or liver



Courtesy of Andrea Gallamini

minimal residual uptake, i.e. uptake consistent with a score 3 is usually associated with good outcome

Deauville Criteria: Five Point Scale (5PS) 2014 Response Criteria

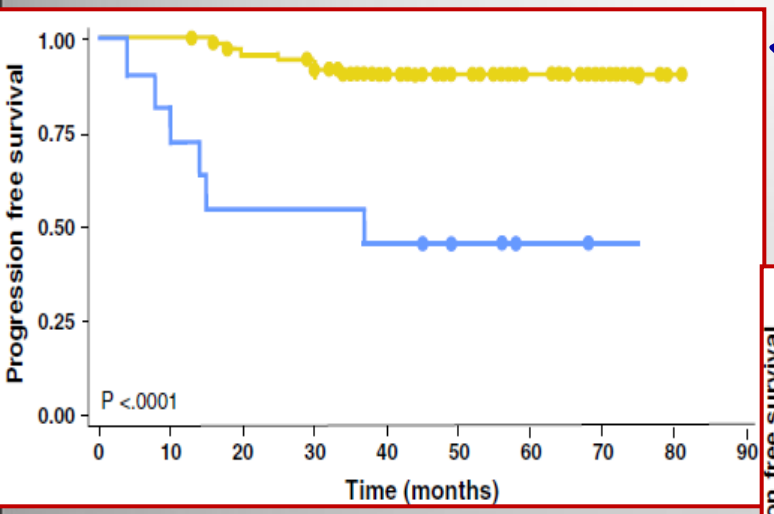
Classification		Description
1	PET-	No uptake above background tissues
2		Uptake less than or equal to mediastinum
3		Uptake greater than mediastinum but less than or equal to liver
4	PET+	Uptake moderately more than liver uptake, at any site
5		Markedly* increased uptake at any site or new sites of disease

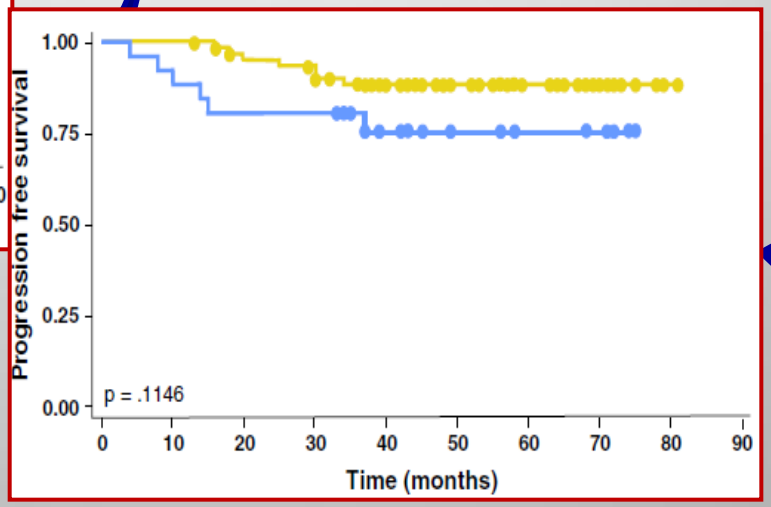
Integrated into ESMO and NCCN Clinical Practice Guidelines for DLBCL

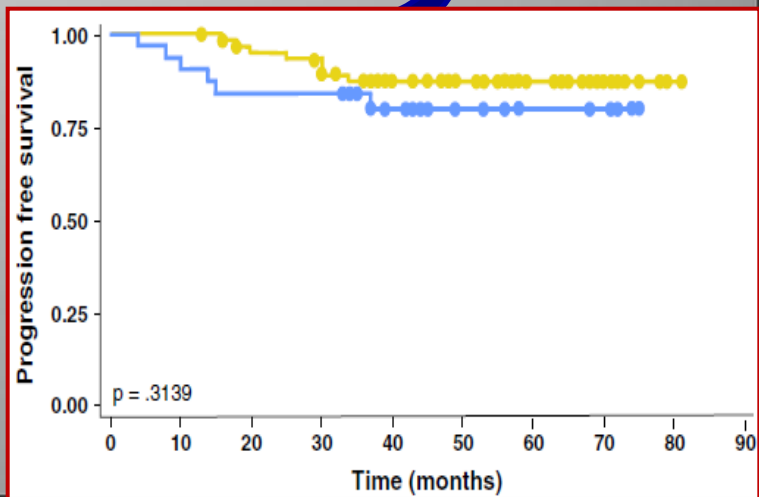
*i.e., maximum standardized uptake value (SUVmax) of the lesion >2x liver uptake

Cheson, J Clin Oncol, 2014; Barrington, J Clin Oncol, 2004

Prognostic value of interim FDG PET/CT in HL patients treated with interim response-adapted strategy: comparison of IHP, and Bckg criteria







- NPV remained very high (95%)
- PPV increased by 25% from 19 to 45%

Le Roux, EJNMMIg 2011;38:1064

Deauville PET- Based Response Criteria

Score 1 or 2	**CMR**	♦ Considered to represent complete metabolic response (CMR) at interim and end of treatment
Score 3	**CMR**	♦ Dependent on the timing of assessment, the clinical context and the treatment ♦ FDG uptake declines during therapy in chemosensitive disease and residual FDG uptake higher than normal liver uptake is frequently seen at interim in patients who achieve CMR at the end of treatment
Score 4 or 5 at interim	**PMR**	♦ Suggests chemosensitive disease provided uptake has reduced from baseline and is considered to represent partial metabolic response
Score 4 or 5 at end of treatment	**PMR**	♦ Represents residual metabolic disease even if the uptake has reduced from baseline

PET Timing:

- **As long as possible after the last chemotherapy administration for int scans**
- **6-8 wks post chemo at EOT ideally (but a min of 3 wks)**
- **≥ 3 mos after RT**

Lugano PET-Based Response Criteria

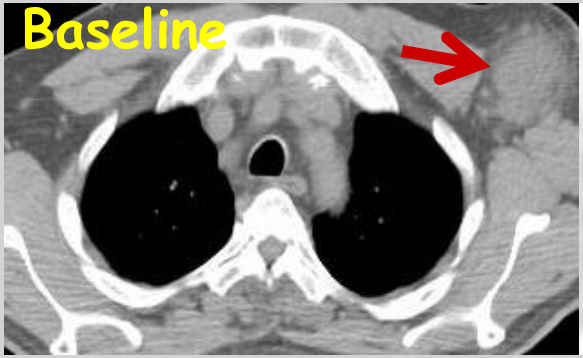
Scores 4 and 5 may be confusing in response categorization

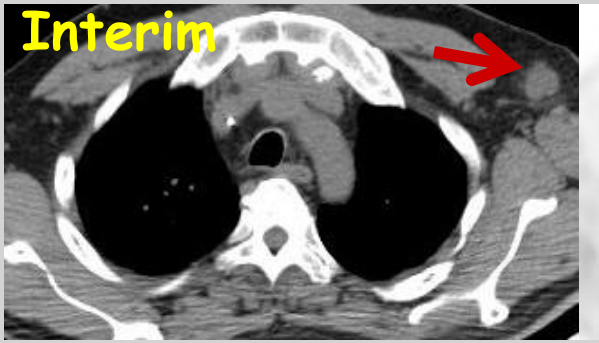
Scores 4 and 5

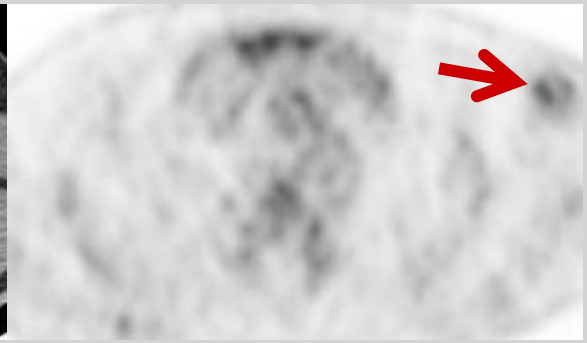
- ❑ reduced uptake from baseline **PMR**
- ❑ no change in uptake from baseline **NMR**
- ❑ increased uptake from baseline &/or new lesions **PMD**

at interim and EOT NMR and PMD indicates treatment failure

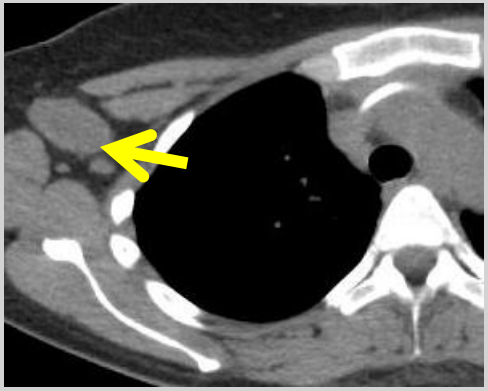
Patient 1

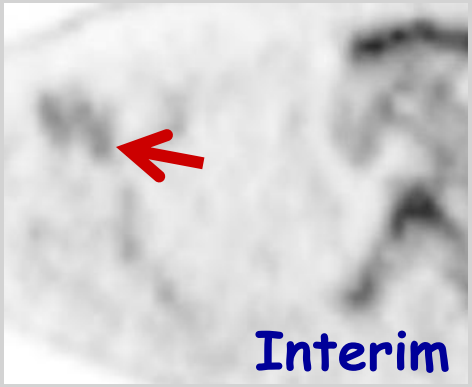




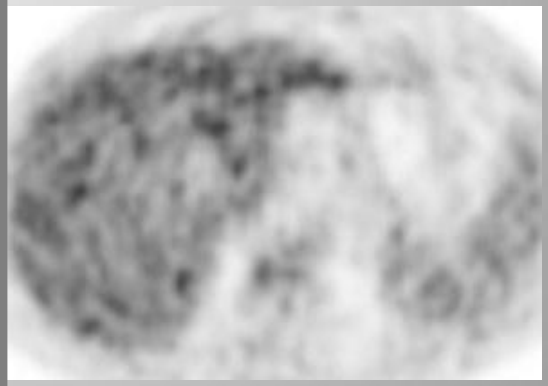


Patient 2





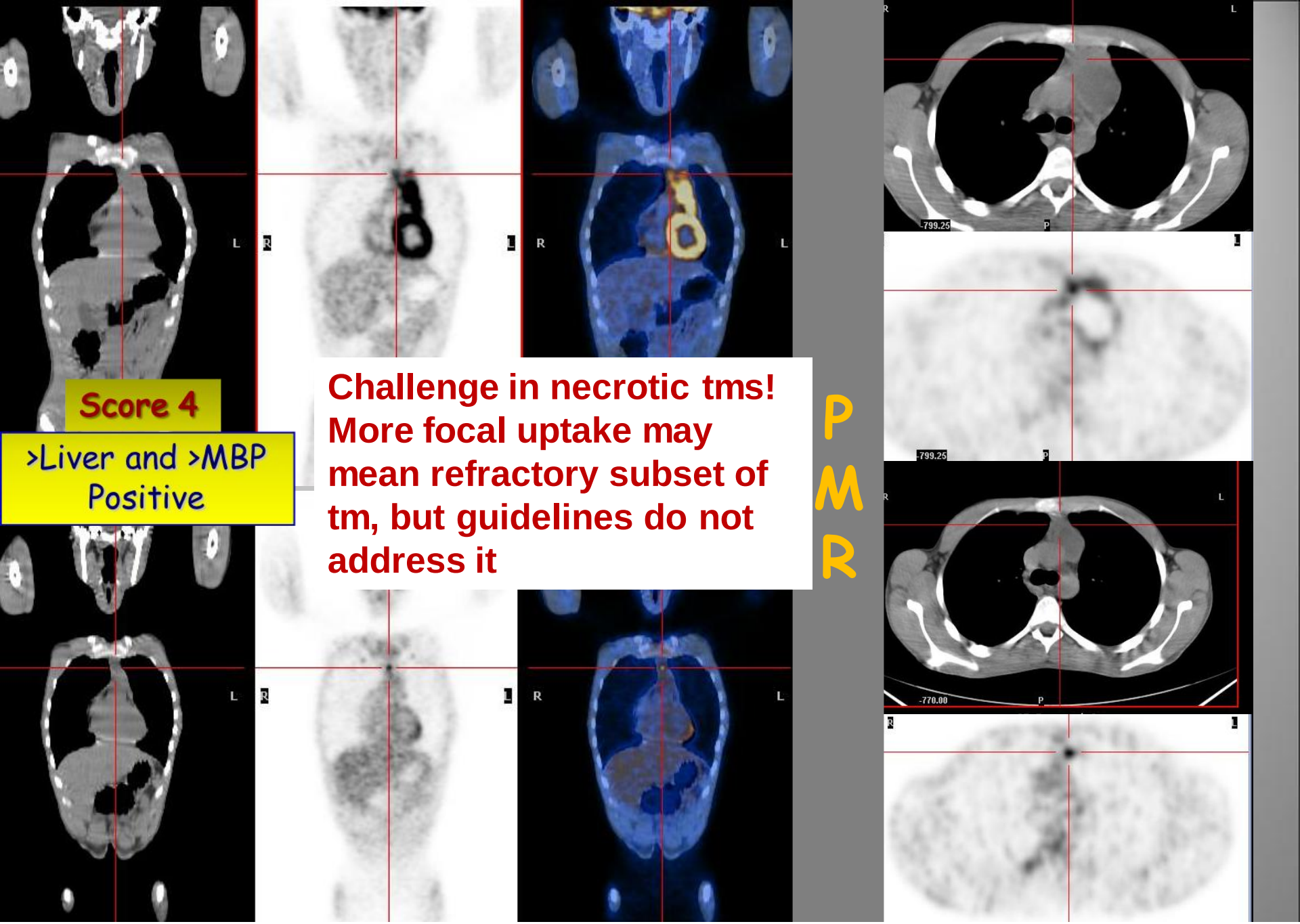
CMR



Score 3

Uptake = Liver and >MBP
Negative

Score 1-3 in nodal or END sites with/without a residual mass



Score 4 - 5, with reduced uptake compared to baseline, residual mass any size

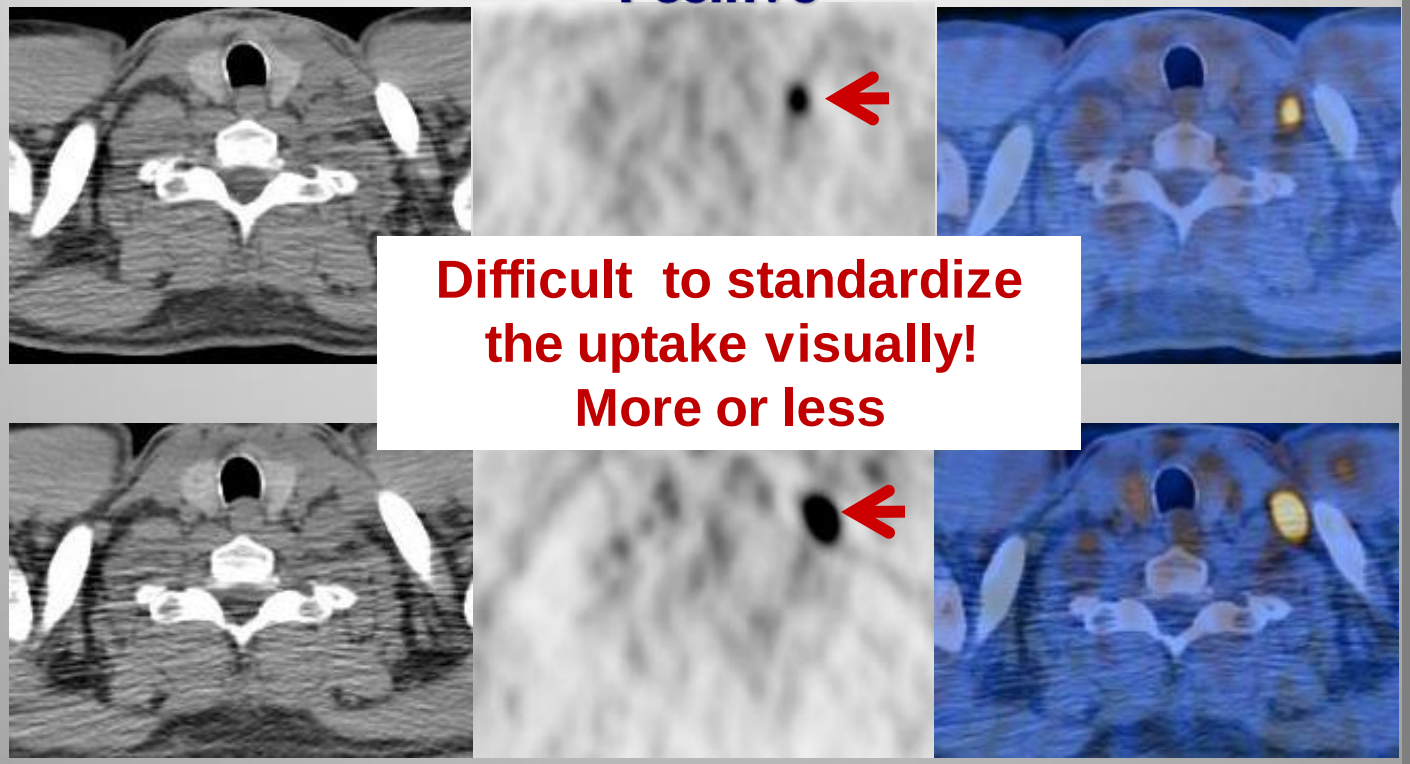
Score 5

>Liver and >MBP

Positive

Baseline

End rx



Difficult to standardize the uptake visually! More or less

PMD

Score of 4 or 5 with intensity that does not change or increases from baseline and/or new foci of lymphoma represents treatment failure at interim and at the end-of-treatment assessment

Lugano PET vs CT-Based Response Criteria

	PET-CT-based response Complete Metabolic Response (CMR)	CT-based response Complete Response (CR) ALL
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Symptoms	Not applicable	Absent

- **Waldeyers ring, BM after GCSF with 'physiologic' uptake > N liver**
- **CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue**

What is New in Lugano Response Criteria

- PET/CT for all FDG-avid histologies
- Deauville 5-PS is the standard
- PET response overrides CT unless no PET available
- Splenomegaly >13cm
- Liver size is not assessed
- Single lesion growth adequate for PD

Lugano Response Categories

CMR/CR	PET-based response	CT-based response
	CMR	CR
Target Nodal/END	Score 1 - 3* by 5-PS with or without a residual mass	Nodal Disease: < 1.5 cm in LDi END: Absent
Non-Target		
Spleen	No involvement (focal or diffuse)	Regress to normal
New lesion	none	none
BM	No FDG-avid BM disease	Normal by morphology; if indeterminate, IHC negative

*Score of 3

- Good prognosis with standard treatment (interim scan)
- De-escalation may consider a score of 3 as inadequate response (to avoid false negatives and undertreatment)

Lugano Response Categories

PMR/PR	PET-based response	CT-based response
	PMR	PR
Target Nodal/END	Score 4-5 by 5-PS with reduced uptake compared to baseline in residual masses*	≥50% decrease from baseline in SPD of all targets
Non-Target		No increase
Spleen	*can be an overall assessment in the patient	≥50% decrease from baseline in enlarged portion of spleen (>13)
New lesion	none	none
BM	• Residual uptake >uptake in N BM but decreased vs. baseline • Persistent focal changes in BM with nodal response • Further evaluation with MRI or bx, or interval scan obtained	

Although works in some scenarios, does not work in all and not reproducible

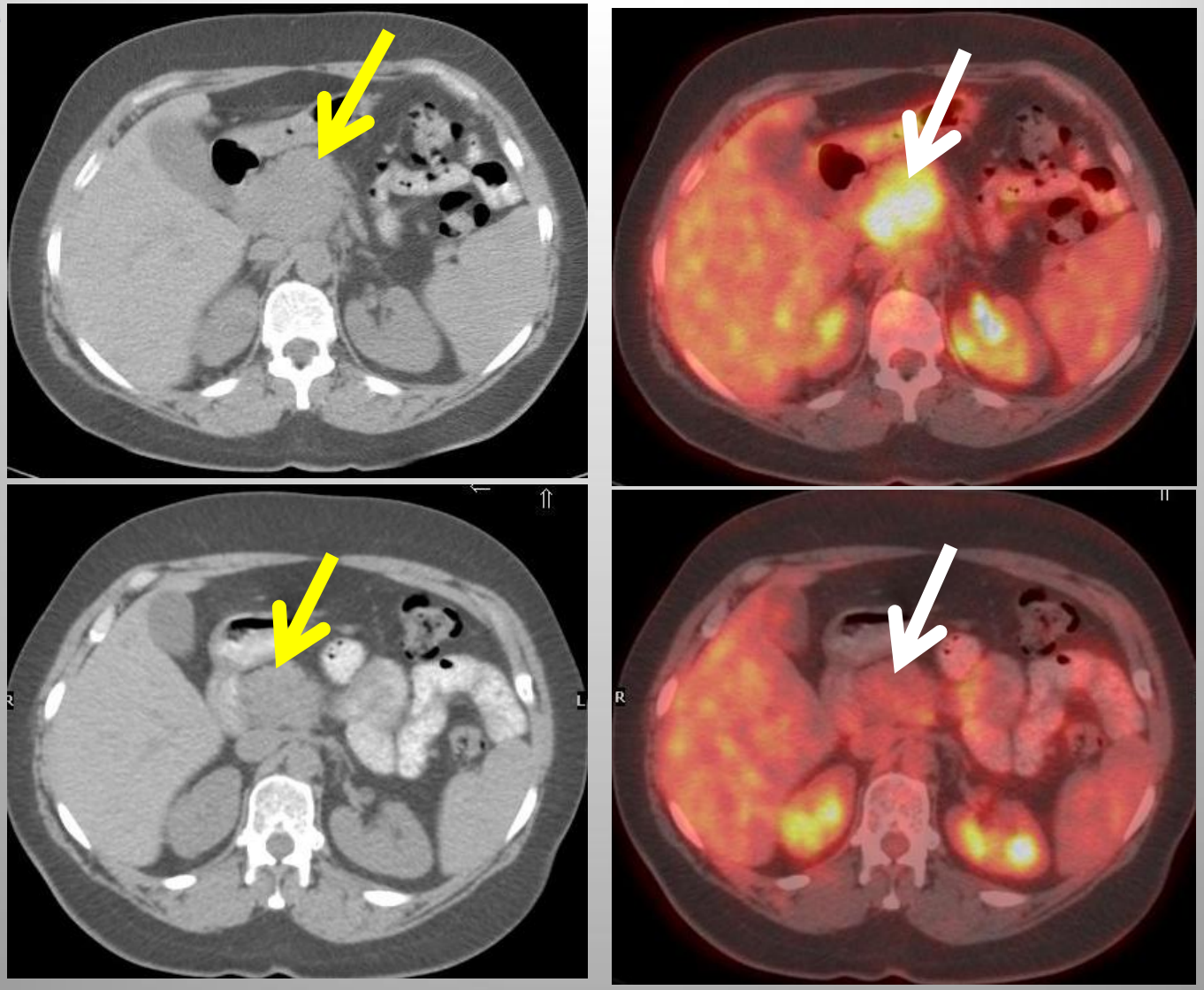
*Depends on the disease under study (risk: benefit analysis), patient characteristics and goal of rx

Lugano Response Categories

PMD/PD	PET-based response	CT-based response
	PMD	PD
Target Nodal/END	• Score 4 or 5 with increased uptake compared to the nadir • New FDG-avid foci consistent with lymphoma • Consider bx or interval scan if findings are of uncertain etiology	An individual node/lesion with: •LDi >1.5 cm and •Increase by >= 50% from PPD nadir and •an increase in LDi or SDi from nadir • ≥ 0.5cm, lesions ≤ 2cm • ≥ 1.0 cm, lesions >2 cm
Non-Target		Unequivocally progressed
Spleen		• Progression of existing SPLM • New or recurrent SPLM
New lesion	Not clear how to code uncertain findings in a standardized fashion	• Regrowth of prior resolved lesions • New LN > 1.5 cm in any axis • New END site >1.0 cm in any axis • New END site < 1.0 cm in any axis or unequivocal/attributable to LYPM • Any size assessable disease unequivocal/attributable to LYPM
BM		New recurrent BM involvement

Baseline

TP1

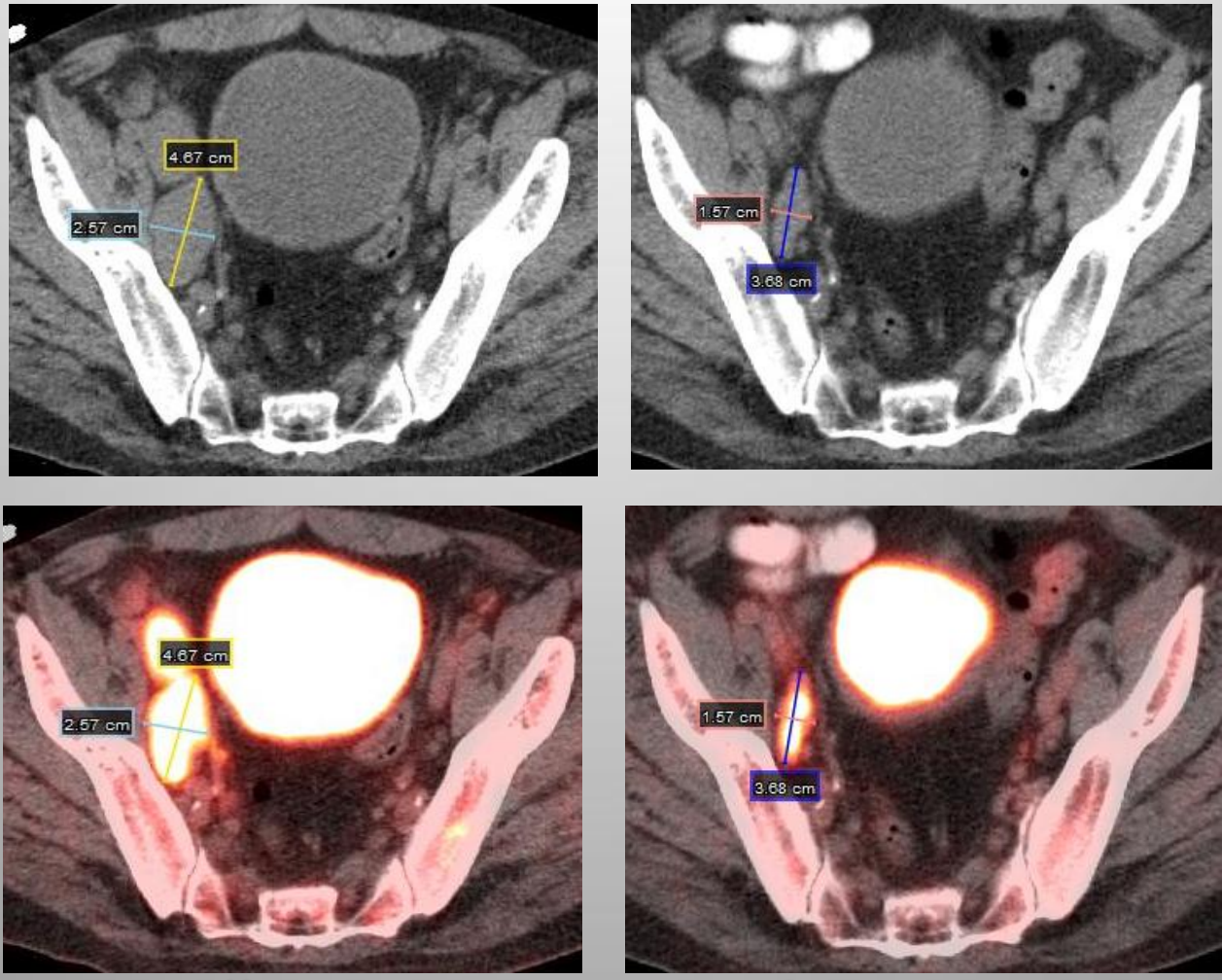


Deauville: CMR

CT-based: SD (SPD -30%)

Overall Lugano: CR

Baseline **TP1**

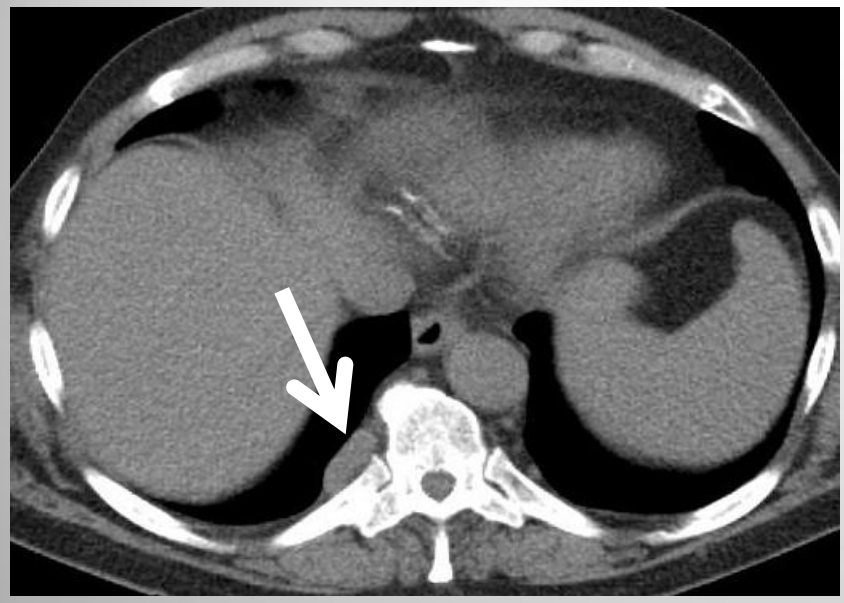


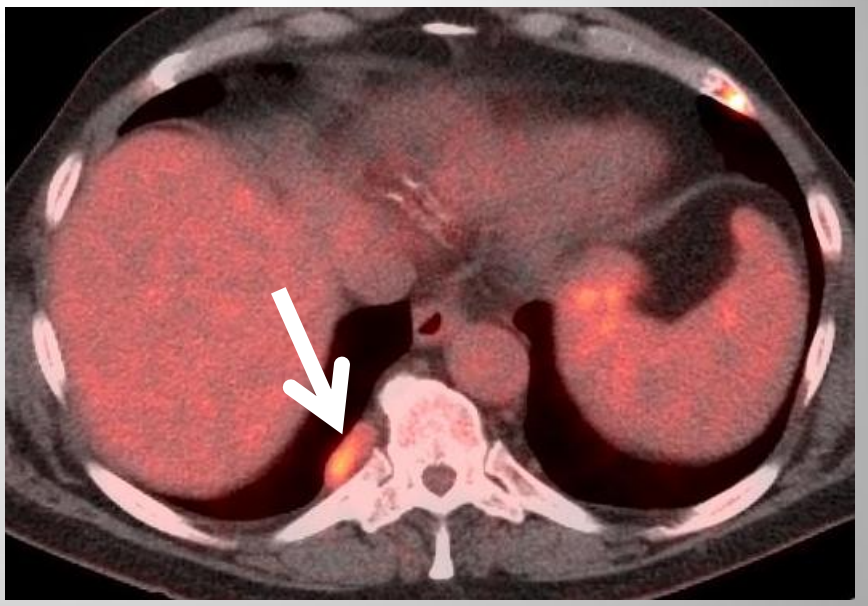
Deauville: Score 5 → 4 PMR

CT-based: PR (≥50% decrease in SPD)

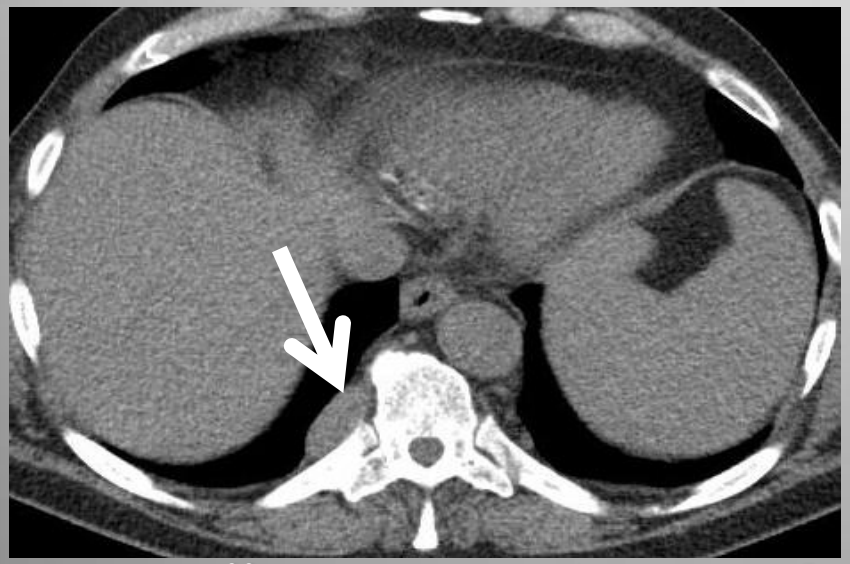
Overall Lugano: PR

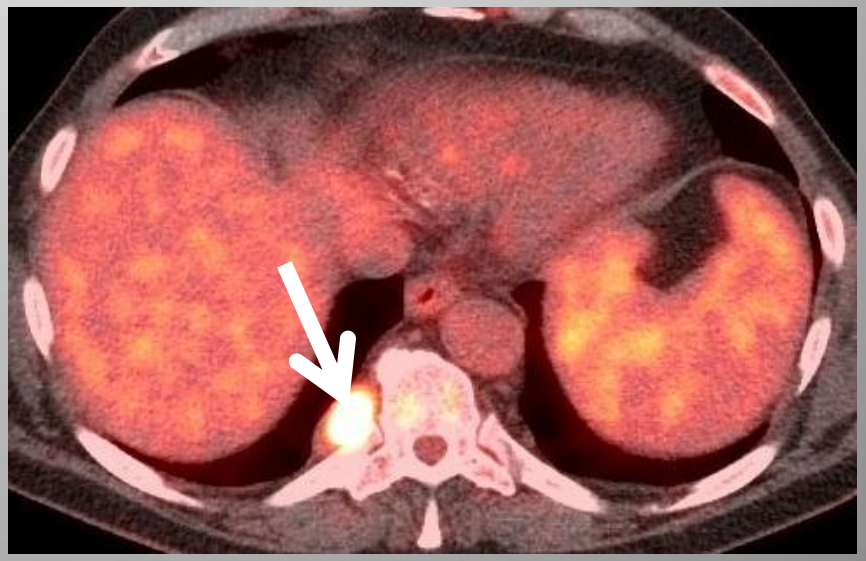
Baseline





TP1



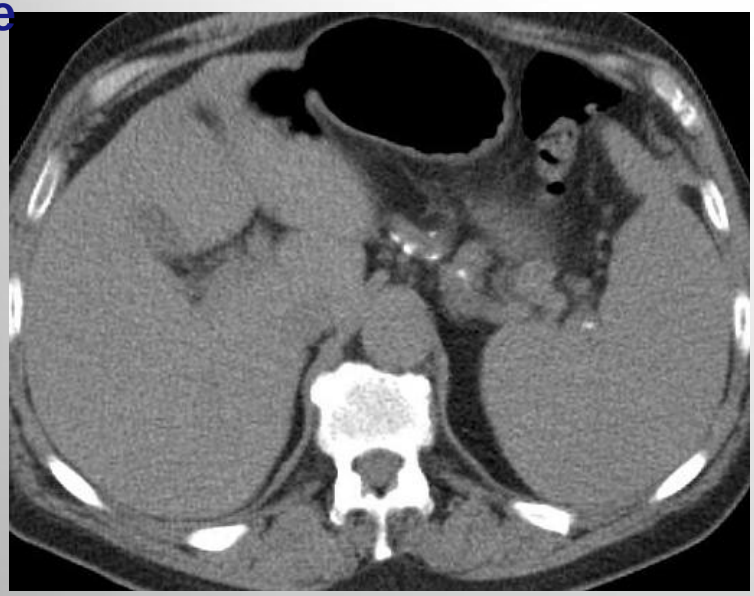


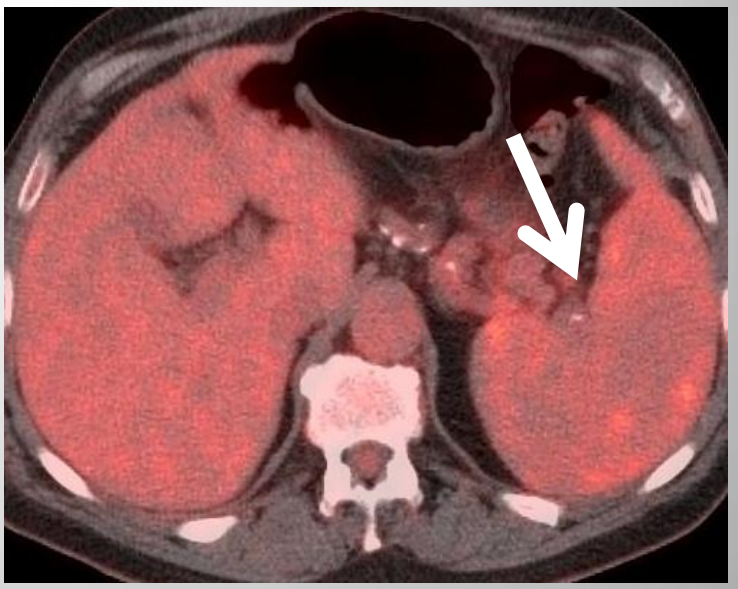
Deauville: Score 4 → 5 PMD

CT-based: SD (<50% decrease or increase in SPD)

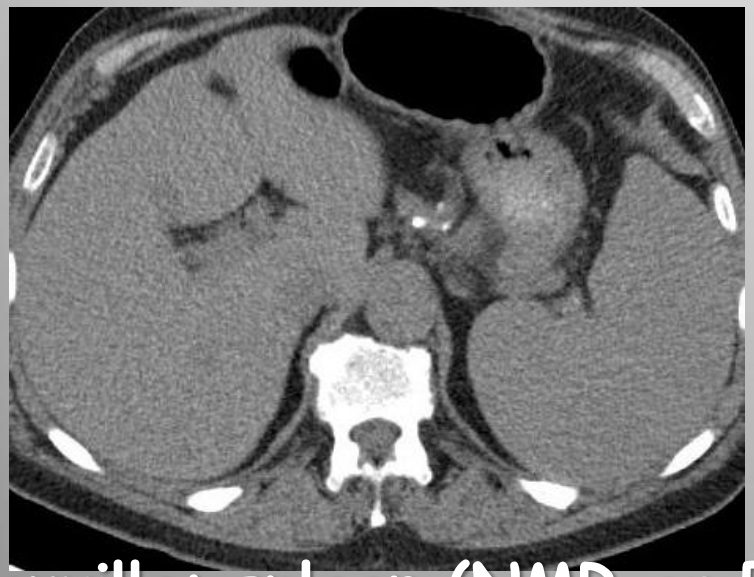
Overall Lugano: PD

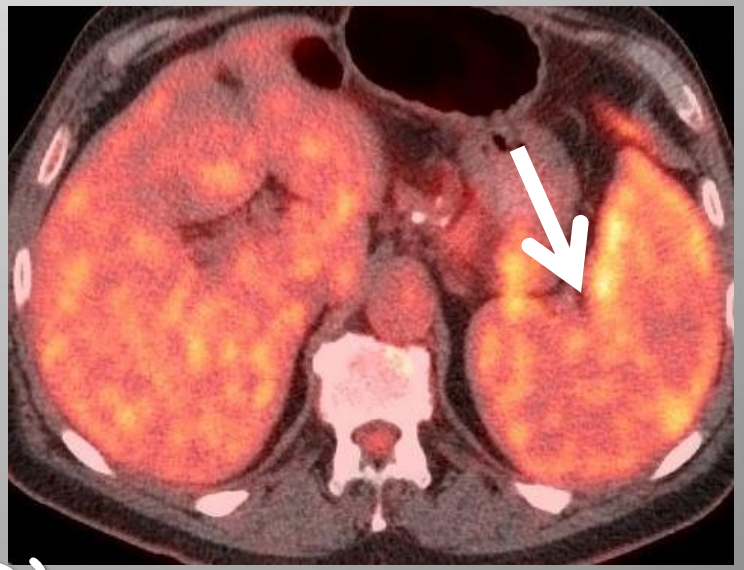
Baseline





TP1

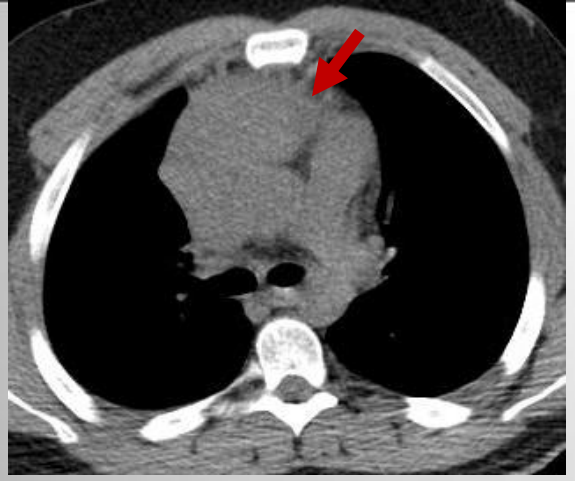


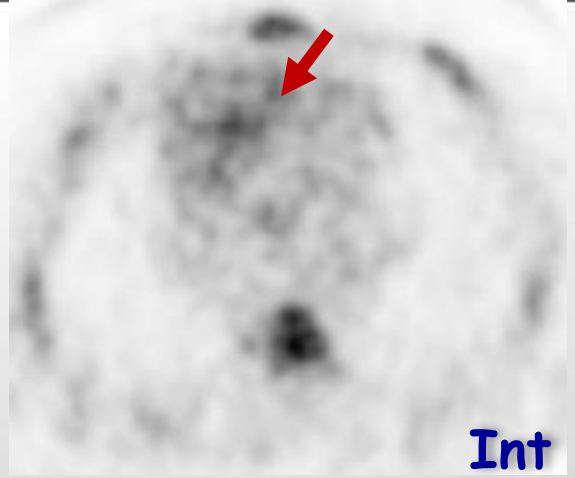


Deauville: spleen (NMR or PMD)

CT-based: PD (>50% of the extent of its prior increase beyond baseline)

Overall Lugano: PD

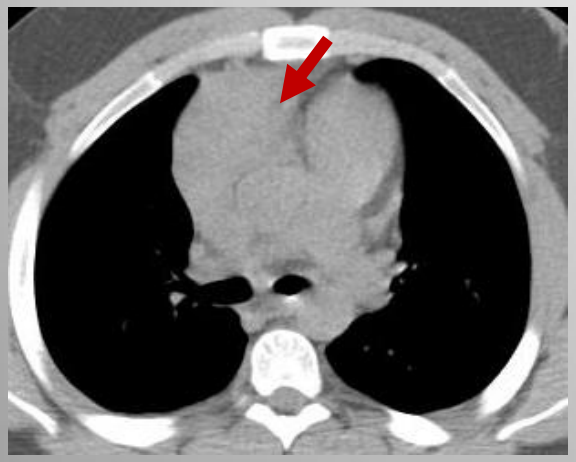




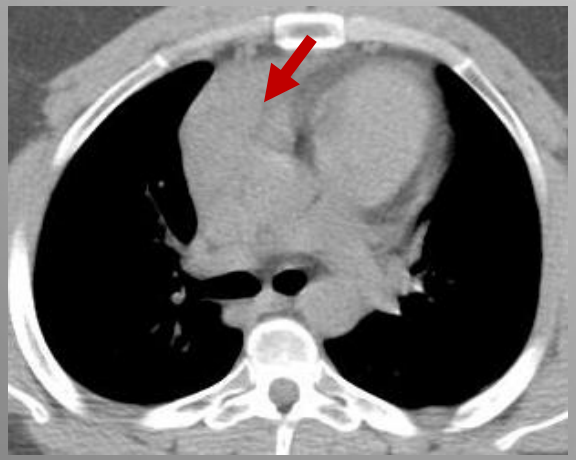
Int

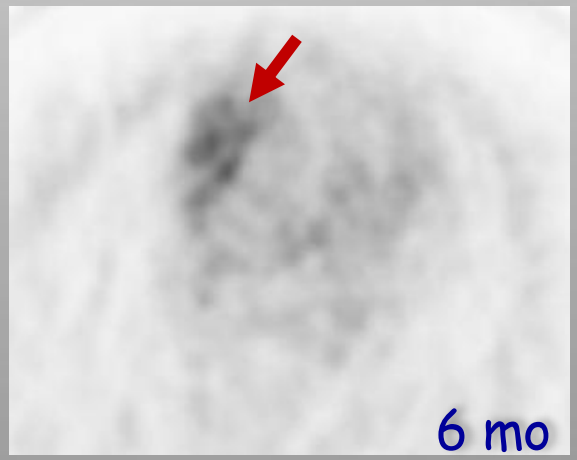
DLBCL

Score 4
Uptake > Liver



but I would override & read as negative b/o frequent association of inflammation in bulky masses!



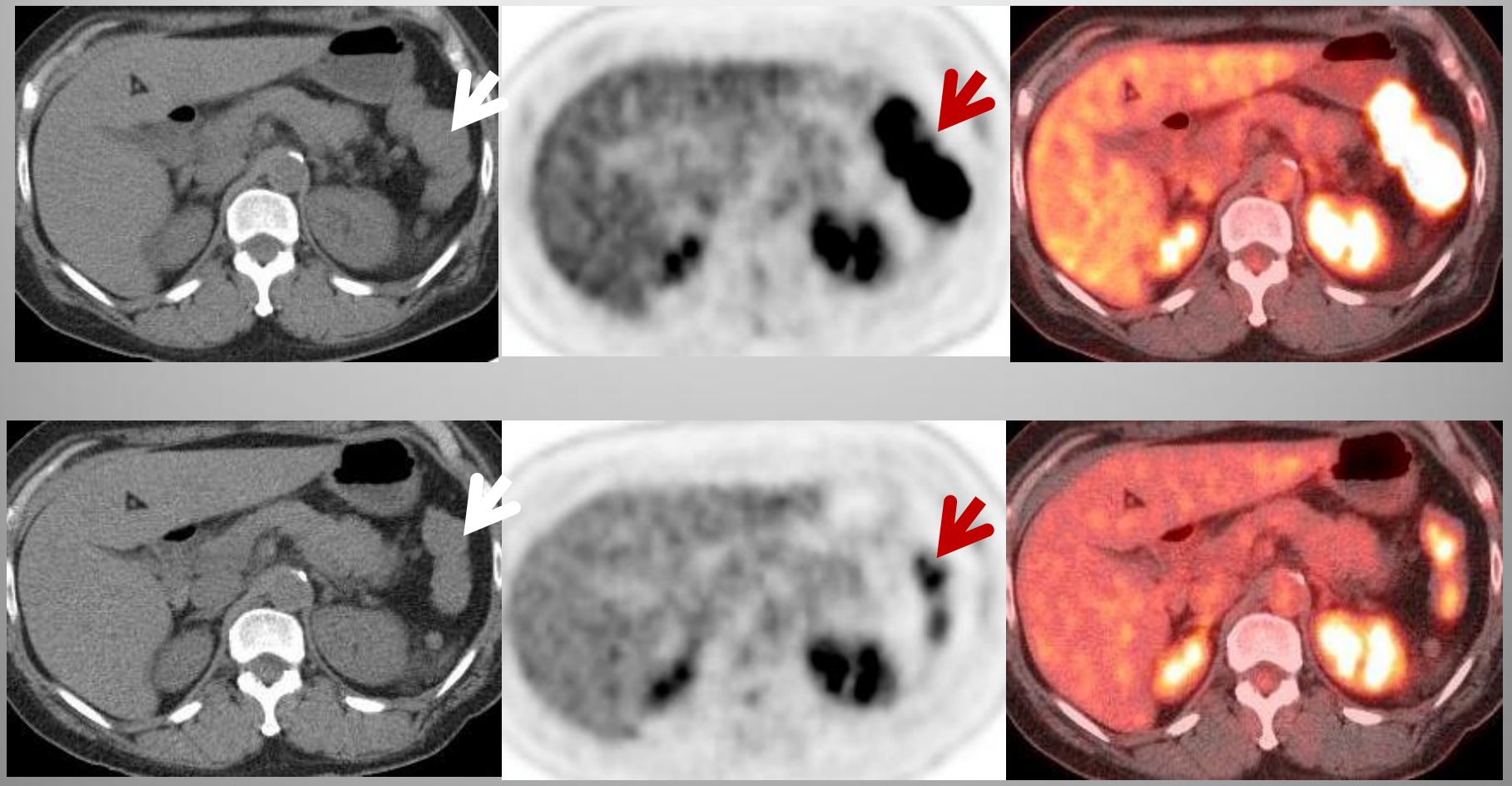


6 mo

Score 4 was FP

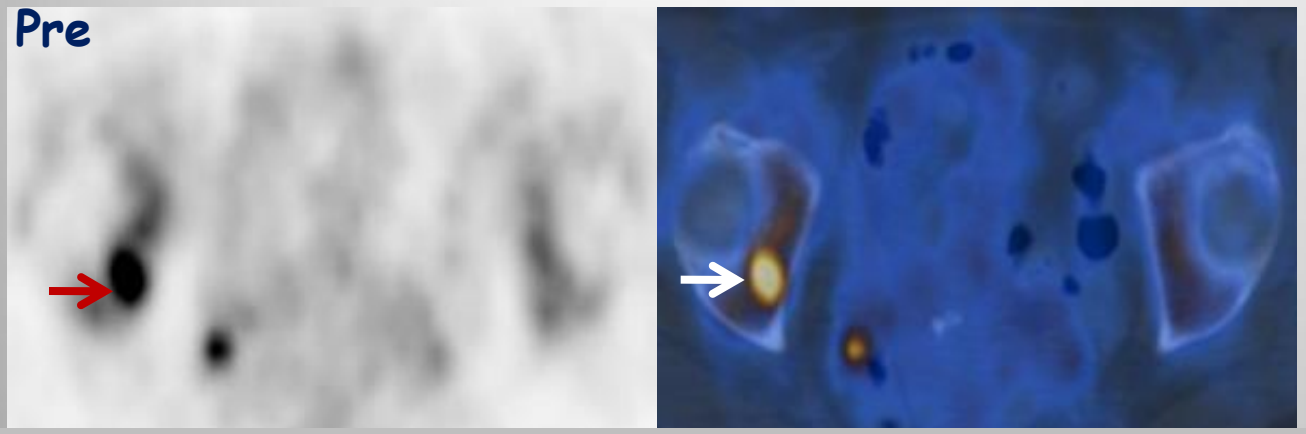
CR, f-u 46 mo

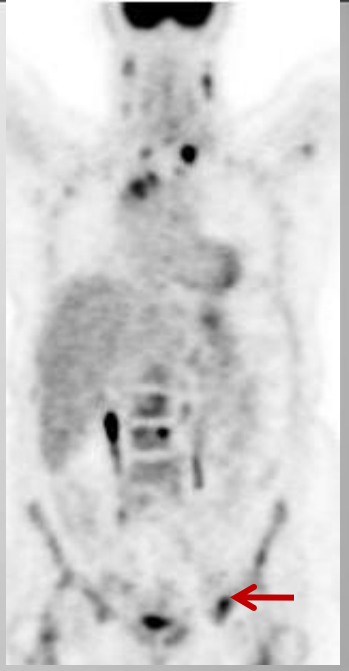
Bowel lymphoma always challenging



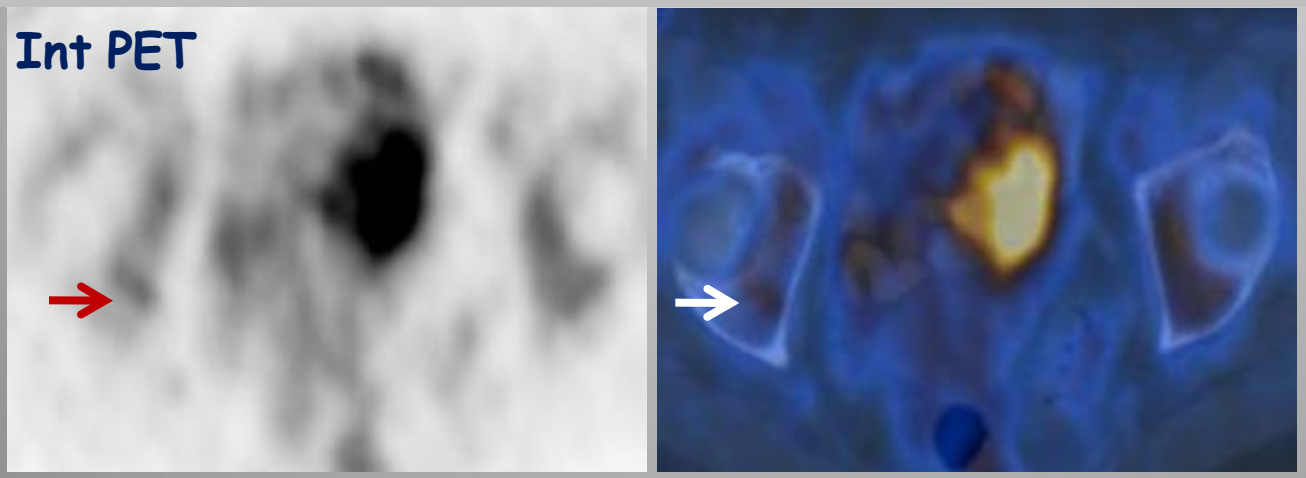
CMR

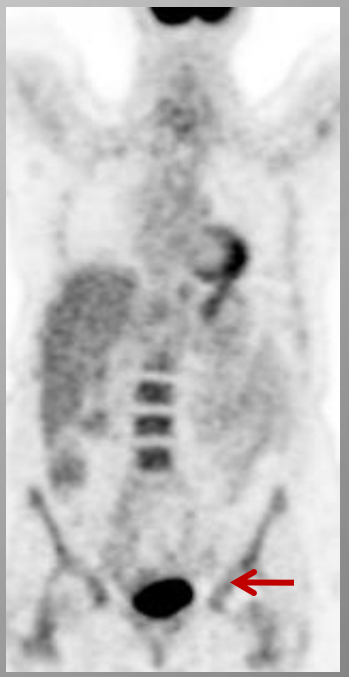
Only focally increased BM uptake at baseline should be evaluated for response





CMR: ≤ BM and decreased from baseline & = normal BM

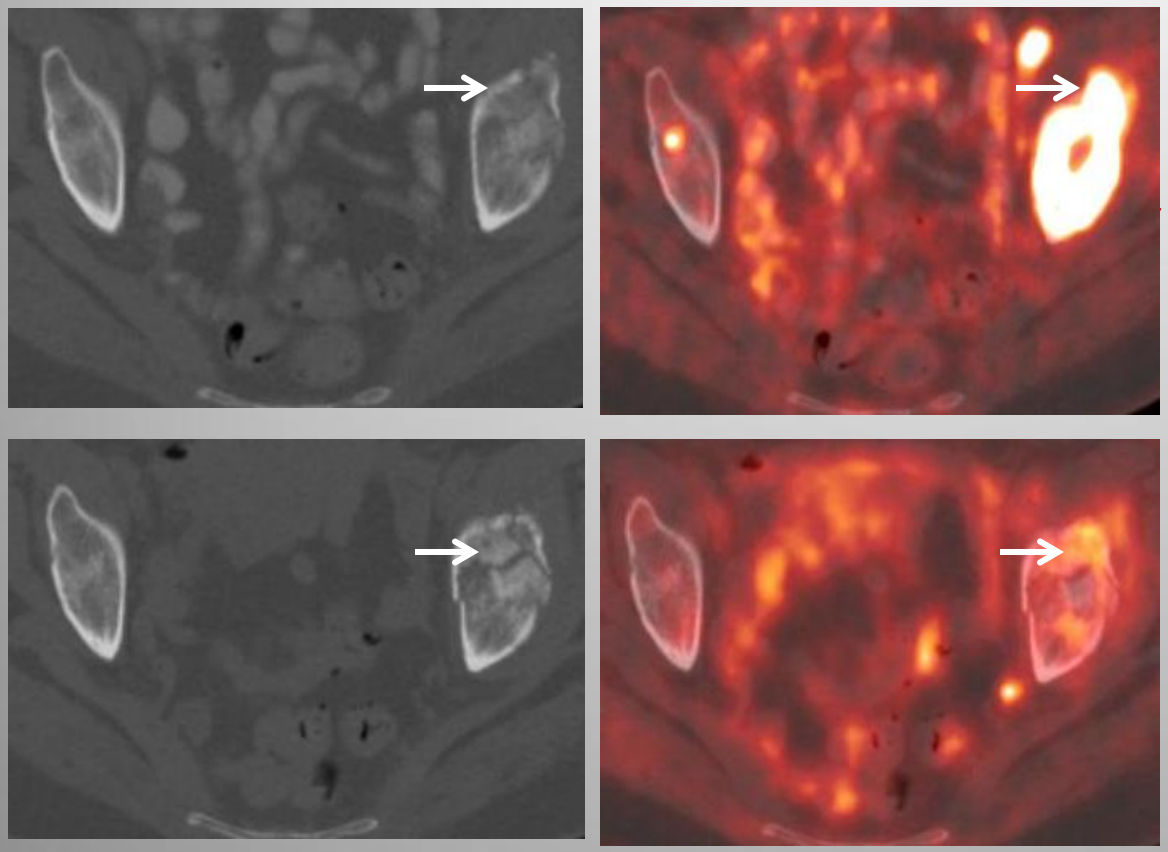


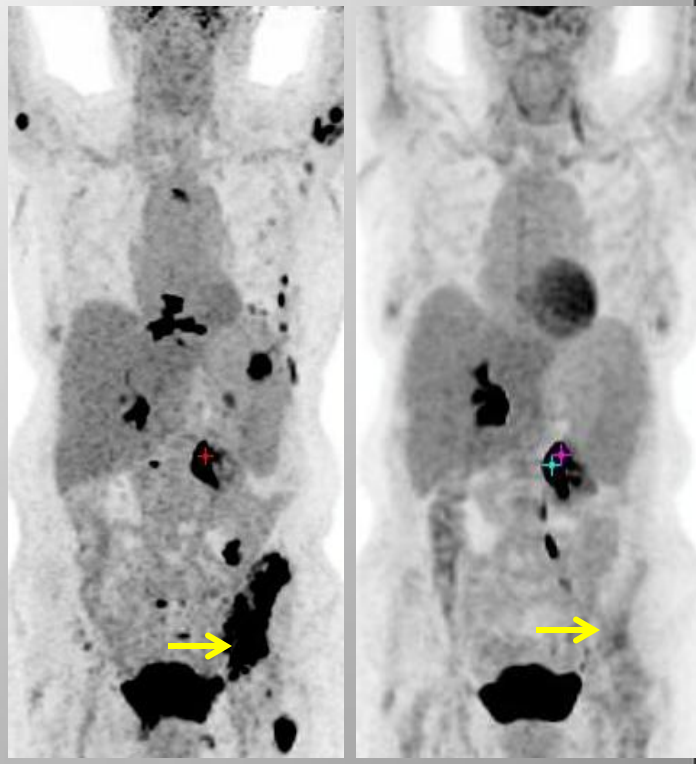


Involved bone marrow

- Must be normal for CR (when all other sites are CR
- No evidence of focal FDG-avid disease in the BM

Score 4 but actually CMR according to expert review





CMR: uptake ≤ BM and decreased from baseline & = normal BM

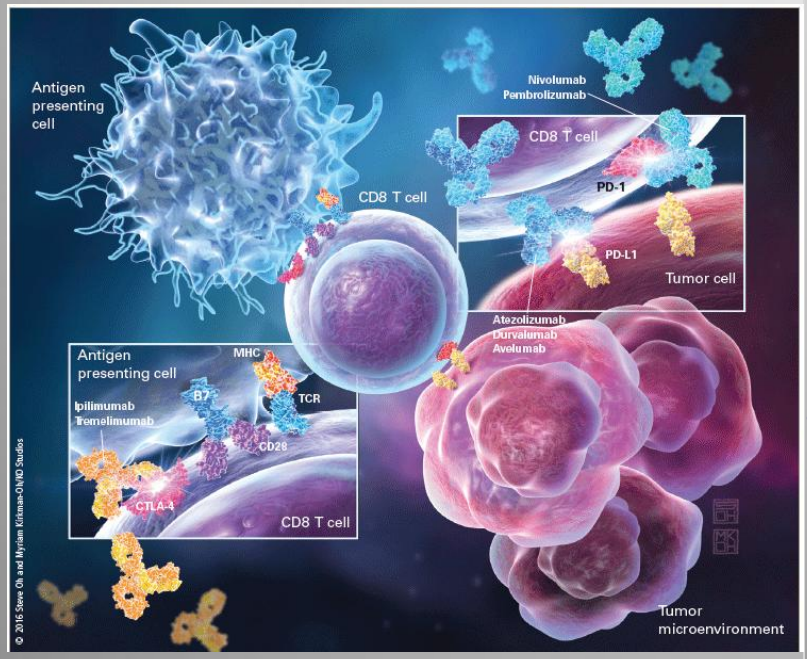
Involved bone marrow
- Must be normal for CR (when all other sites are CR
- No evidence of focal FDG-avid disease in the BM

More recently

Immunomodulating agents, new immunotherapies, i.e. immune check point inhibitors, antigen receptor engineered T cells can be associated with early "pseudo-progression" with a subsequent response through recruitment of immune cells to disease site

Goy A, J Clin Oncol 2013, Witzig TE, Ann Oncol 2011, Bollard CM, J Clin Oncol 2014, Younes A, Lancet Oncol 2016

Refinement of Lugano response criteria in the era of immunomodulatory therapy: LYmphoma response to immunomodulatory therapy criteria



CR PR	PD
LYRIC	Same as with Lugano with following exceptions: **Immune response**
	IR1: ≥50% increase in overall tm burden (SPD) of up to 6 lesions in the 1st 12 wks with no clinical deterioration
Same as Lugano	**IR2**: <50% increase in SPD with • New lesion(s), or • ≥50% increase in PPD of a lesion/set of lesions during rx
	IR3: Increase in FDG upt in ≥1 lesions without concomitant increase in lesion size or number to meet criteria for PD

Cheson BD, Blood, 2016;128:2489

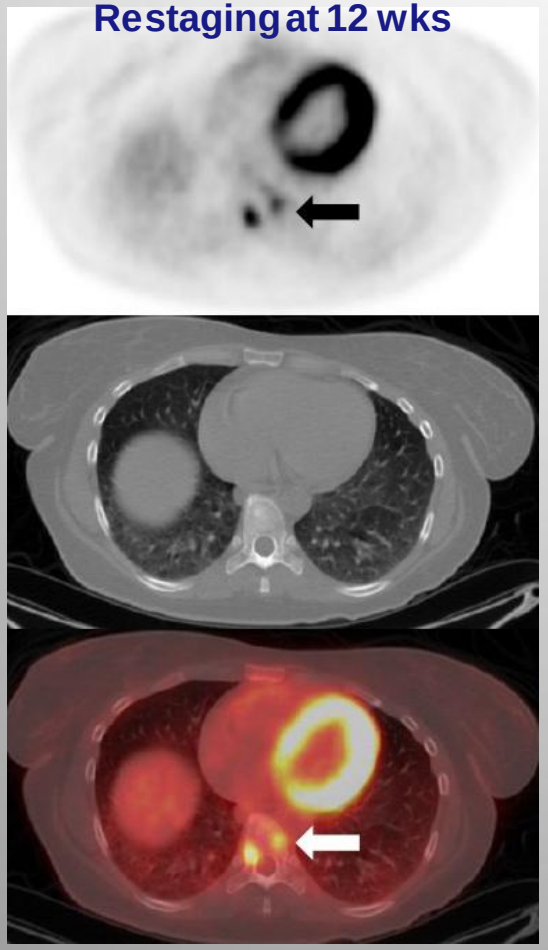
SPD, sum of the perpendicular diameters
PPD, product of the perpendicular diameters

Refinement of Lugano response criteria in the era of immunomodulatory therapy: LYmphoma response to immunomodulatory therapy criteria LYRIC

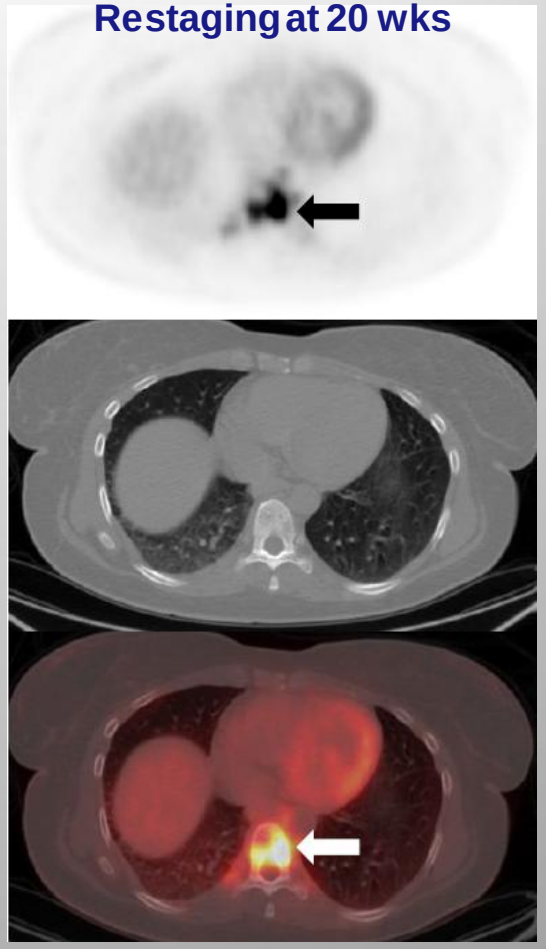
Indeterminate Response (IR)

- Provisional term
- To identify lesions that may be flare vs PD
- Does not make direct reference to underlying mechanism
- Allows appropriate patients to remain on treatment until reassessment to confirm or refute PD – or bx proven disease

Restaging at 12 wks

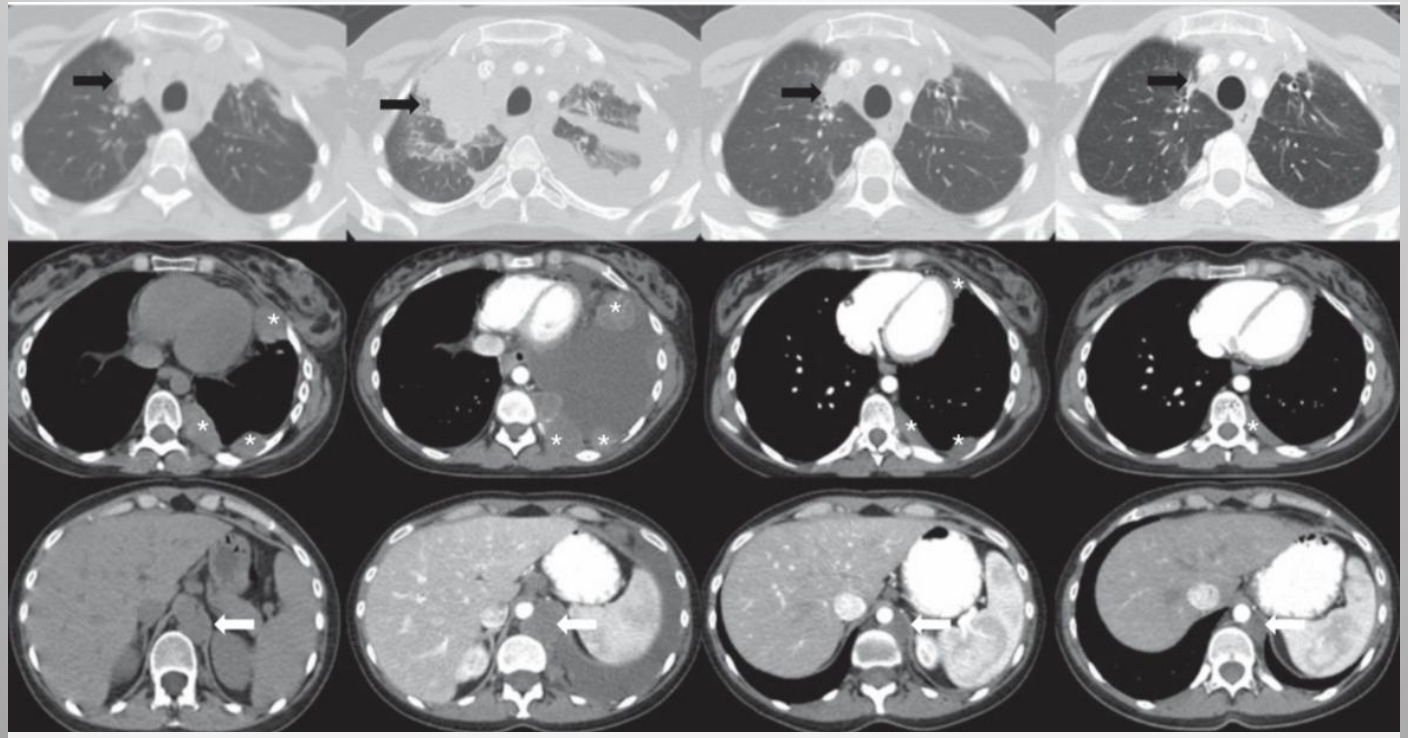


Restaging at 20 wks



Serial imaging should confirm that the prior increase in tm size was related to disease progression rather than a tumor flare time of progression

IR1: ≥50% increase in overall tm burden (SPD) of up to 6 lesions in the 1st 12 wks with no clinical deterioration



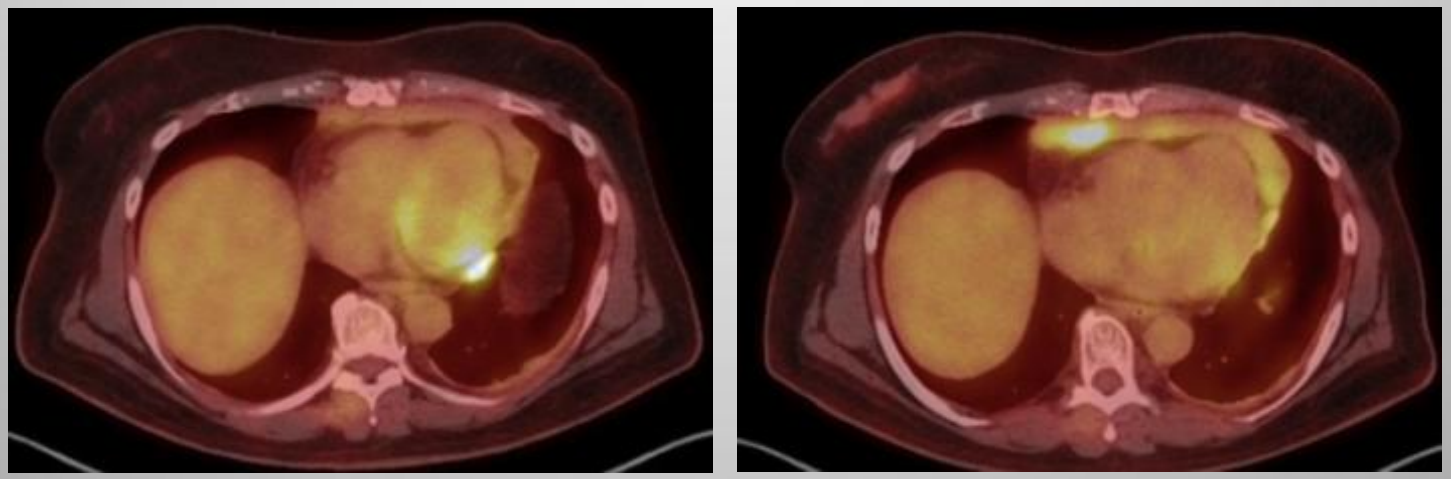
Baseline CT | Restaging CT 1- 3w | Restaging CT 2- 7w | Restaging CT 3-13 w

Cheson BD, Blood, 2016;128:2489

Repeat scan in 12 wks (earlier if indicated)

- PD if:
  - IR1 – further increase in SPD
  - IR2 – new lesion added to SPD and, if >50% increase
  - IR3 – PD if increase in size or new lesions

IR3: increase in FDG upt in ≥1 lesions without concomitant increase in lesion size or number to meet criteria for PD



increase in uptake in a paracardiac LN without a concomitant increase in size that meets PD criteria

Repeat scan in 12 wks (earlier if indicated)

- PD if:
  - IR1 – further increase in SPD
  - IR2 – new lesion added to SPD and, if >50% increase
  - IR3 – PD if increase in size or new lesions

Cheson BD, Blood, 2016;128:2489

Novel Therapies and New Response Criteria
RECIL

	% Change in sum of diameters of target lesions from nadir				
	CR	**PR**	**MR[a]**	**SD**	**PD**
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10mm. • ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauvile score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [^{18}F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.

[a]A provisional category.

Younes A, Ann Oncol, 2017:28

- **PD measured from nadir after initial response**
- **Immunomodulatory agents may be associated with tm flare or pseudo-progressions**
- **Bx or repeat assessment confirmation of PD on two consecutive scans at least *4 wks apart***

	Lugano	RECIL 2017
Number of target lesions	Up to 6	Up to 3
Measurement method	Bi-dimensional: perpendicular diameters	Uni-dimensional: long diameter of any target lesion
Incorporates PET results to describe CR	Yes	Yes
Minor response	No	Yes, reduction in sum of long diameters between ≥10% and <30%
Stable disease	−50% to + 50%	decrease <10% to increase ≤20%
PD	Increase in the sum of products of perpendicular diameters by > 50%, or any single lesion by > 50%	Increase in sum of the longest diameters by 20%. For relapse from CR, at least one lesion should measure 2 cm in the long axis with or without PET activity

Conducive to non-reproducibility with current software measurement systems to measure this small difference

Challenges of Readers

- Lack of clear guidance on charters; which can be rather confusing and at times wrong
- Non-uniformity among readers with target selection
- Alternating PET, CT , MRI at various TPs
- Missing images, lack of MIP, lack of display 2 or 3 TPs at the same time
- Lack of good quality CT and/or PET
- Artificial environment; Lack of relevant clinical info which is always a good guide to do the right diagnosis
- Forced to follow criteria, strictly!!

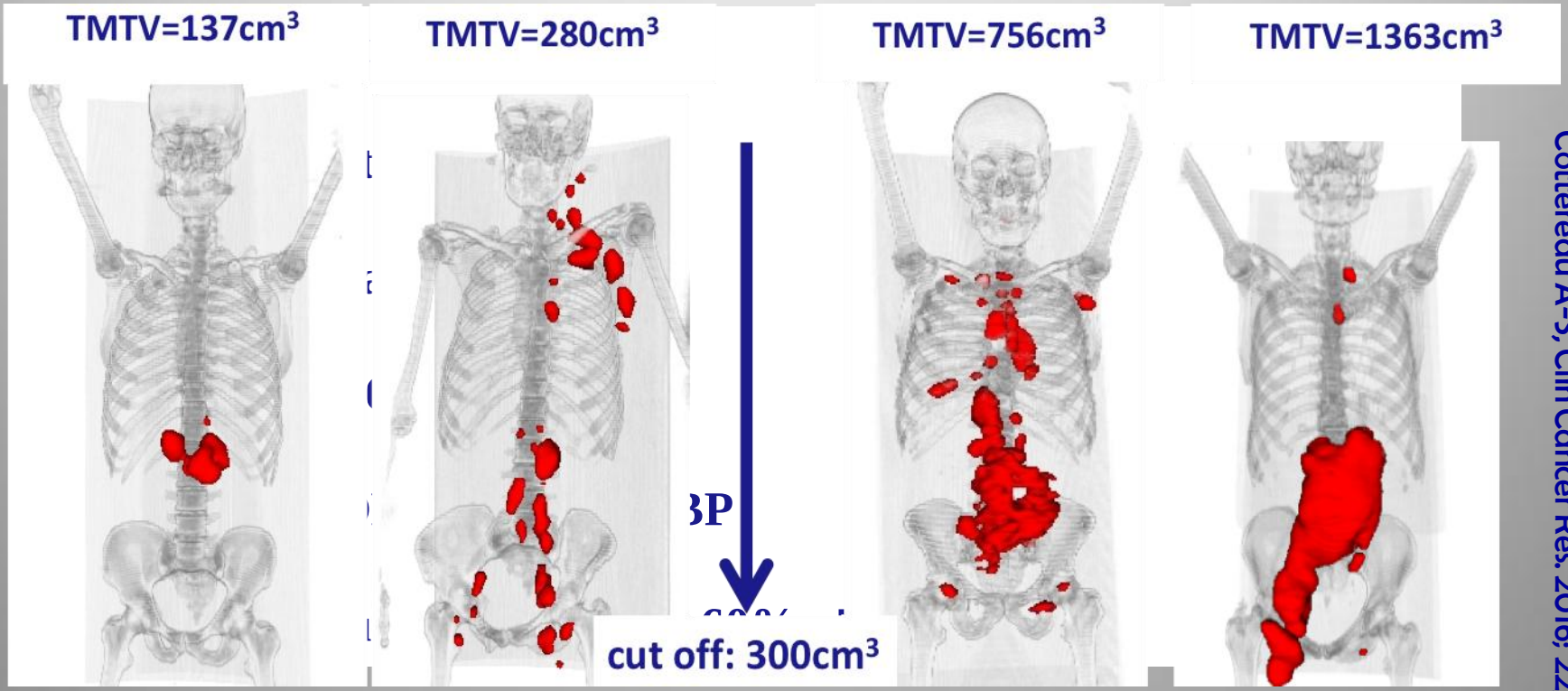
Works in Progress

Quantitative assessment of response

- Δ SUV
- Metabolic tumor volume
- Radiomics
- Combined modality approaches
- Contribution of the microenvironment

Can Combination of Molecular Profile and TMTV Improve Risk Classification at Diagnosis for Patients with DLBCL?

There was a continuous increased of risk with TMTV for PFS and OS with a Cox model p=0.043 and p=0.031, respectively



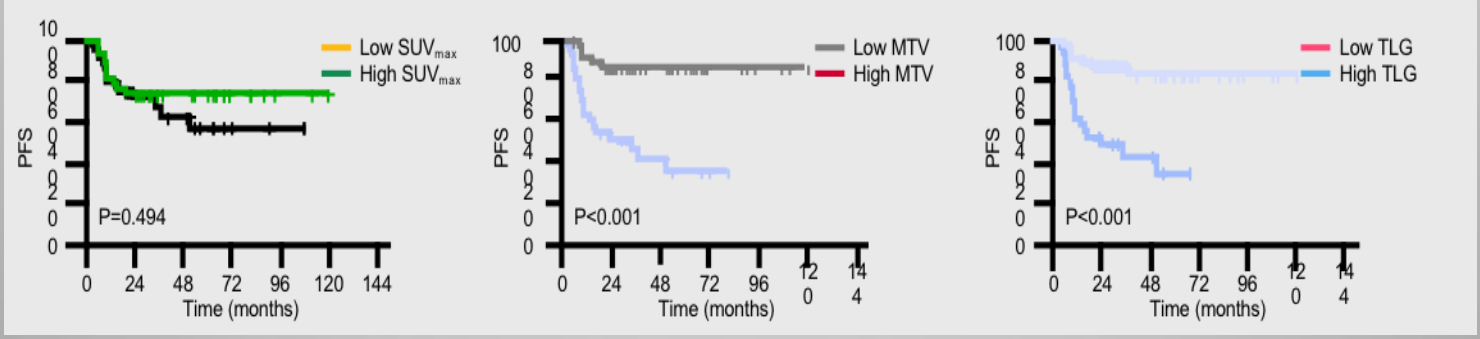
300 cm³ cutoff	sensitivity	specificity
PFS	73.5%	64%
OS	74%	62%

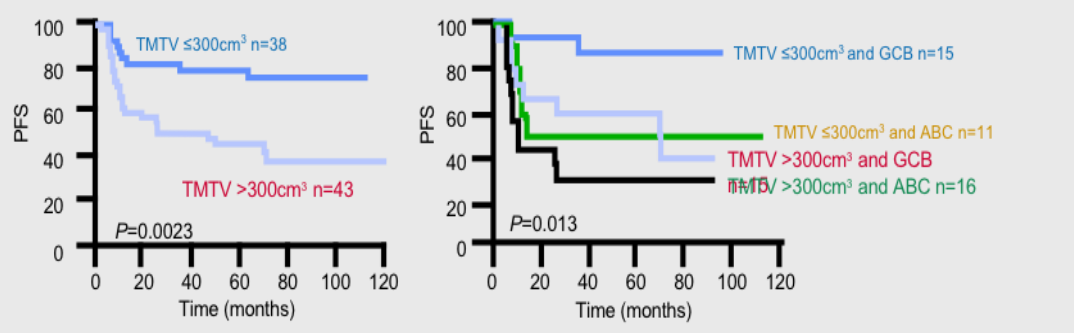
*segmentation 41% SUV_{max}

Cottereau A-S, Clin Cancer Res. 2016; 22; 3801

Measurement of whole body disease burden can be used as a risk stratification tool – DLBCL

- Baseline high MTV found to predict poor PFS and OS in DLBCL
- A study (n=91) confirmed that baseline TLG was the only independent predictor for PFS (HR=5.2, p<0.001) and OS (HR=9.1, p=0.002)[6]



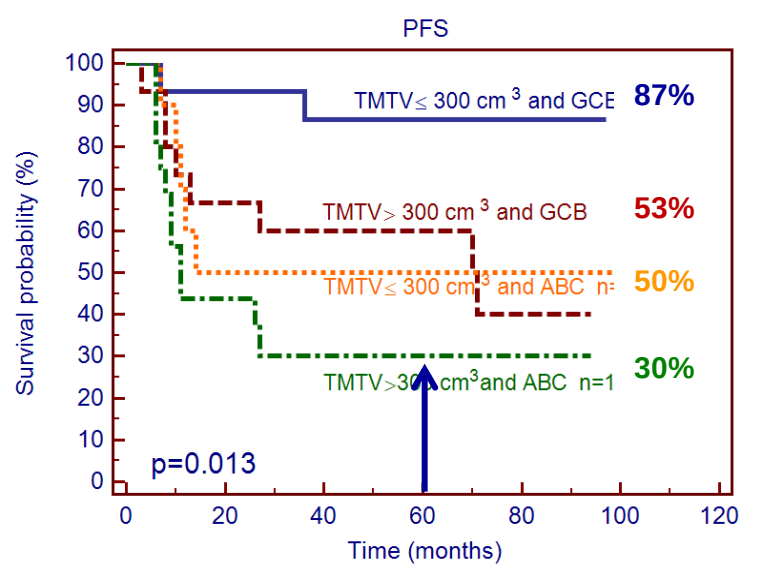


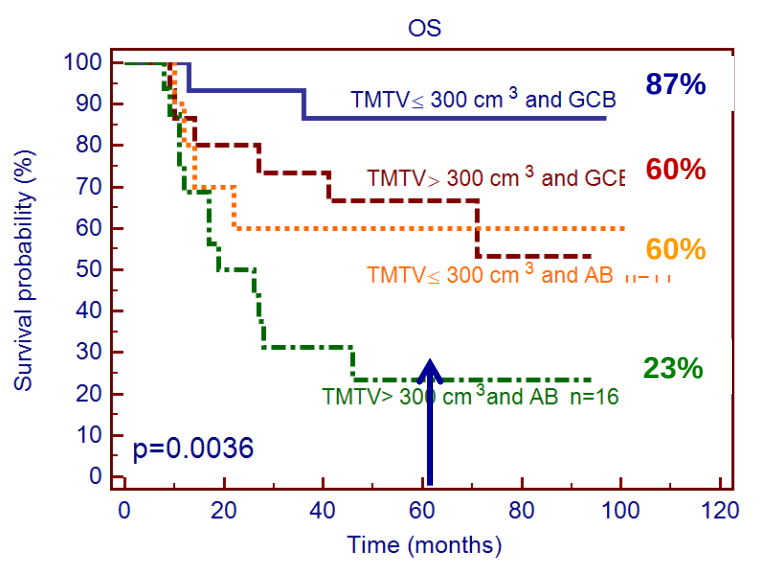
- MTV (n=81), improved risk stratification when combined with COO phenotype

Esfahani SA, Am J Nucl Med Mol Imaging 2013;3:272; Kim TM, Cancer 2013;119:1195; Mikhaeel NG,. Eur J Nucl Med Mol Imaging 2016;43:1209; Song MK, Leuk Res 2016;42:1; Sasanelli M, Eur J Nucl Med Mol Imaging 2014;41:2017; Zhou M, Oncotarget. 2016;7:83544; Cottereau AS, Clin Cancer Res 2016;22:3801; Xie M, Hematology 2016;21:99. Malek E, Blood Cancer J. 2015;5:e326

TMTV and ABC/GCB phenotype

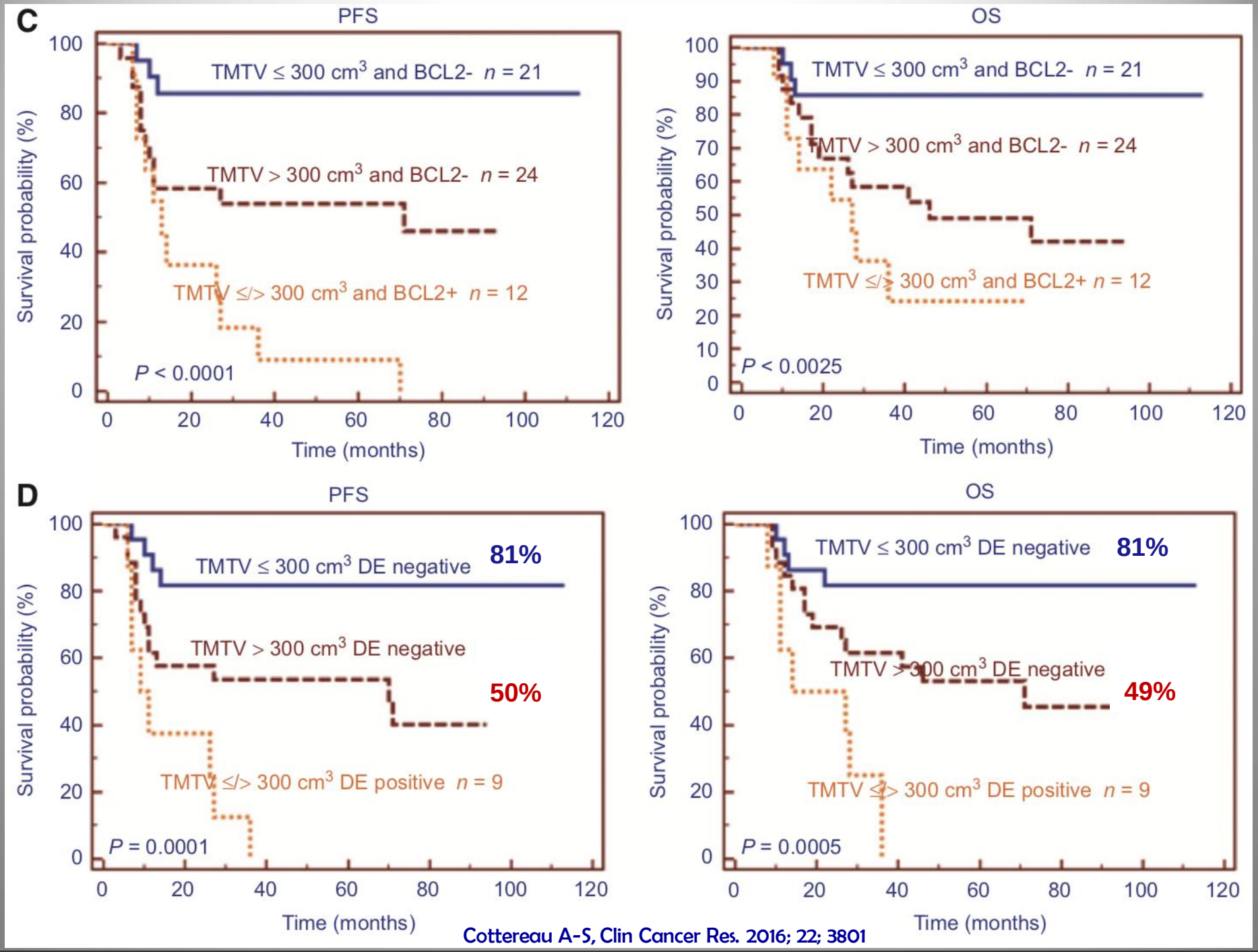
TMTV with ABC/GCB





High MTV individualized in molecular low risk pts a group with a poor outcome

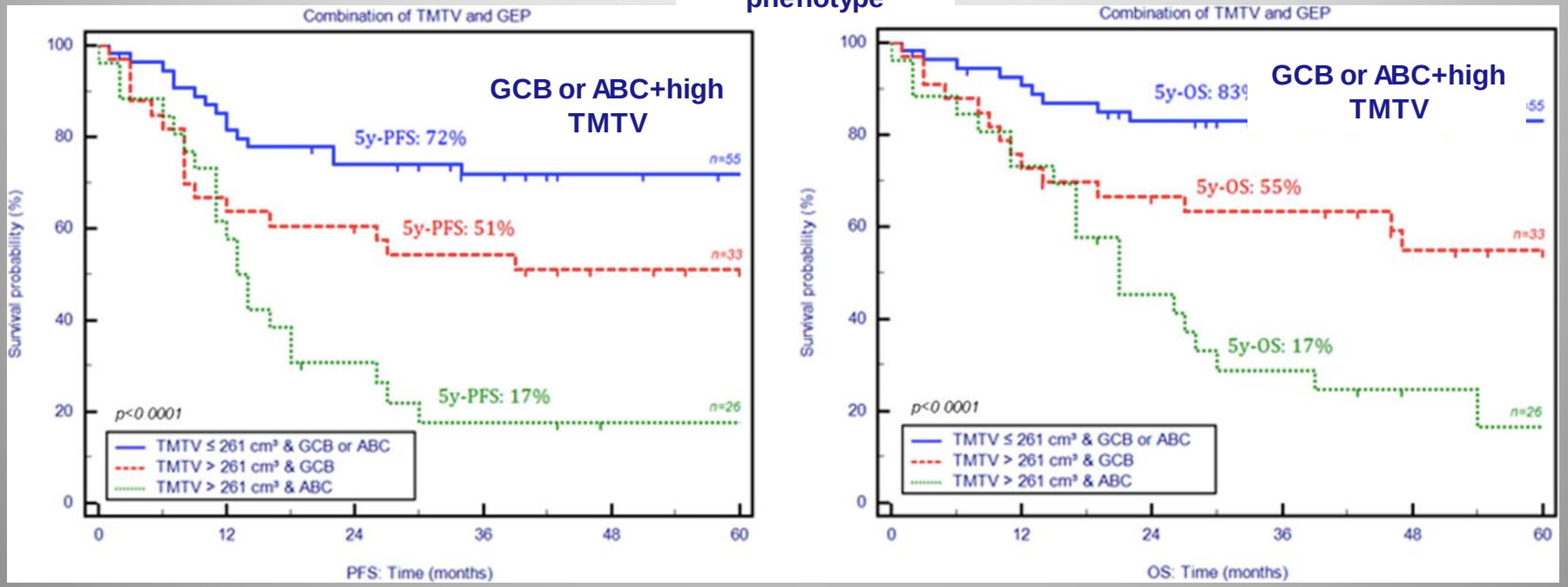
Cottereau A-S, Clin Cancer Res. 2016; 22; 3801



Cottereau A-S, Clin Cancer Res. 2016; 22; 3801

Combination of baseline TMTV and GEP have a predictive value

regardless of phenotype



Combination of TMTV and GEP identified 3 distinct risk groups

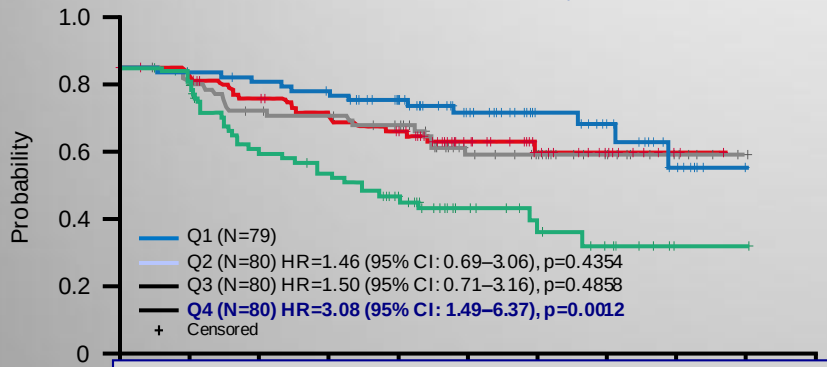
This integrated risk model could lead to more accurate patient selection that would allow better individualization of therapy

Toledano MN, EJNMMI,2018;45:680.

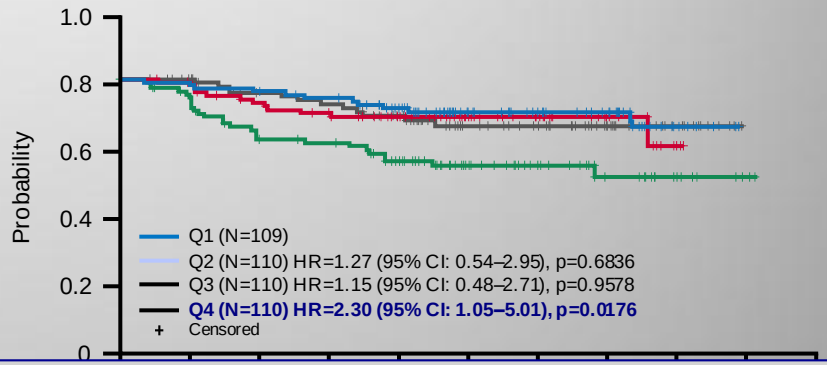
GOYA study: Prognostic value of baseline TMTV for PFS by COO

- High MTV at baseline predicts poorer outcome
- SUV_{max} was not predictive for PFS or OS

ABC/Unclassified



GCB



Better differentiation of outcome in ABC/unclassified DLBCL vs GCB

Multivariate analysis	HR	Wald 95% CI	P-value
TMTV Q4 vs Q1	1.91	1.10–3.30	0.0211
COO *ABC vs GCB*	2.09	1.44–3.03	0.0001
IPI High vs low-intermediate	1.86	1.17–2.96	0.0088

*COO assessed using the NanoString Research Use Only Lymphoma Subtyping (LST) gene expression assay (NanoString Technologies Inc., Seattle, WA, USA)

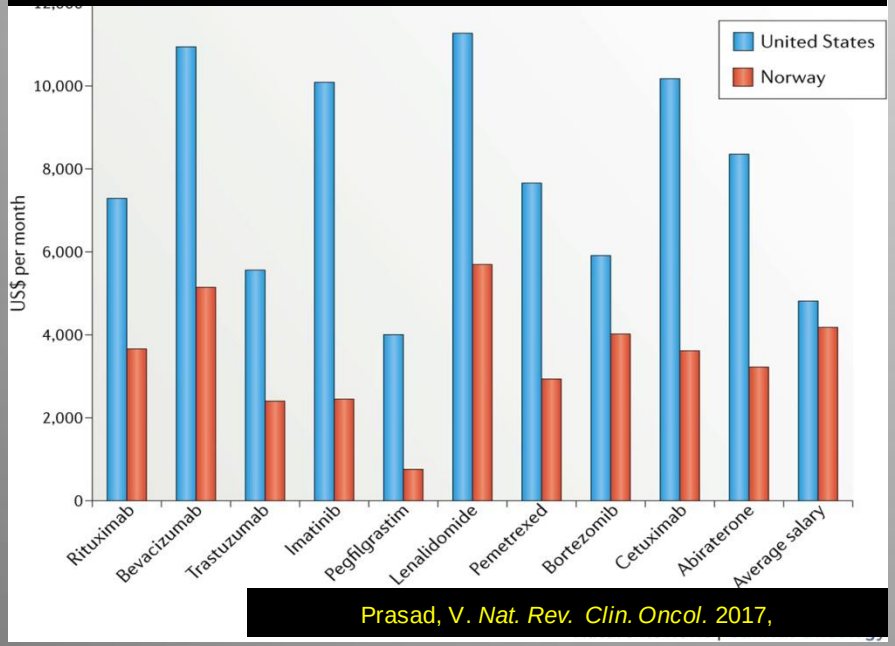
L Kostakoglu , ASH 2017

We are in a phase of expansion in the availability of novel biologic treatments

"We have a problem; the rising cost of anti cancer therapies and the current regulatory environment have helped to create an unsustainable (and unacceptable) situation"

Romero D, Nat Rev Clin Oncol 2018:15:397

Cost of 1mo of rx with top 10 bestselling anticancer drugs in USA & Norway



Prasad, V. *Nat. Rev. Clin. Oncol.* 2017,

there is an urgent need to define biomarkers which can reliably assess response, predict outcome, and thus avoid the AEs and high cost of these new agents in pts who will not benefit from therapy

THANK YOU!