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Optimal use of imaging for Lymphoma in 2023

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ILROG 4th International Educational Conference
9-10 September 2023, London, UK

ILROG
INTERNATIONAL LYMPHOMA RADIATION ONCOLOGY GROUP

Lugano Guidelines

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

JCO 2014 32:3048-3058

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Müeller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

JCO 2014 2: 3059-3067

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

ILROG Imaging Guidelines

CME ASTRO

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Critical Review

The Optimal Use of Imaging in Radiation Therapy for Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group (ILROG)

N. George Mikhaeel, FRCR,* Sarah A. Milgrom, MD,† Stephanie Terezakis, MD,‡ Anne Kiil Berthelsen, MD,§ David Hodgson, MD,‖ Hans Theodor Eich, MD,¶ Karin Dieckmann, MD,# Shu-nan Qi, MD, Joachim Yahalom, MD,†† and Lena Specht, MD§**

Note—An online CME test for this article can be taken at https://academy.astro.org.

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Int J Radiation Oncol Biol Phys, Vol. 104, No. 3, pp. 501–512, 2019
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2019.02.001

- New data
- Issues/questions from use of guidelines

Which lymphomas should be imaged with FDG-PET/CT?

Most lymphomas are FDG-avid

	Histology and numbers of patients included in studies	Percentage FDG-avid
B-cell	Hodgkin lymphoma (n = 489)	97 - 100
	Diffuse Large B cell lymphoma (n = 446)	97 - 100
	Follicular lymphoma (n = 622)	91 - 100
	Mantle cell lymphoma (n = 83)	100
	Burkitt lymphoma (n = 24)	100
	Lymphoblastic lymphoma (n = 6)	100
	Marginal zone lymphoma, nodal (n = 14)	100
	MALT marginal zone lymphoma (n = 227)	54 - 81
	Marginal zone lymphoma, splenic (n = 13)	53 - 67
	Marginal zone lymphoma, unspecified (n = 12)	67
	Small lymphocytic lymphoma (n = 49)	47 - 83
T-cell	Peripheral T-cell lymphoma (n = 93)	86 - 98
	Anaplastic large T-cell lymphoma (n = 37)	94 -100 (but only 27% of cutaneous sites)
	Natural killer/T-cell lymphoma (n = 80)	83 - 100
	Angioimmunoblastic T-cell lymphoma (n = 31)	78 - 100
	Enteropathy type T-cell lymphoma (n = 20)	67 - 100
	Mycosis fungoides (n = 24)	83 -100
	Sezary Syndrome (n = 8)	100 (but only 62% of cutaneous sites)
	Primary cutaneous anaplastic large T-cell lymphoma (n =14)	40-60
	Lymphomatoid papulosis (n = 2)	50
	Subcutaneous panniculitis-like T-cell lymphoma (n = 7)	71
	Cutaneous B-cell lymphoma (n = 2)	0

Exceptions

SLL / CLL
EN MZL / MALT

Some cutaneous T-cell

Modified from Weiler-Sagie et al. JNM 51: 25-30, 2010

- Marginal Zone Lymphoma (nodal, EN or splenic)
- Lymphoplasmacytic / Waldenstrom: useful for skeletal or nodal disease
- Cutaneous lymphomas: useful for nodal and visceral dis

Discussion:

- Use for staging
- If staging PET/CT showed uptake → use for response
- Deauville score may not be best ?compare to background and baseline

Can SUVmax predict transformation?

Suspecting high-grade transformation on PET/CT

- De novo FL:
  - Does high SUVmax suggest high-grade? No
  - Should we biopsy high uptake areas? Yes & No

- Follow-up PET: Signs suggesting possible transformation:
  - Increasing uptake during FU
  - Relapse has much higher uptake
  - Rapid progression of disease
  - Necrosis
  - Multiple extra-nodal sites

Can FDG-PET/CT replace BM biopsy?

2014 recommendations

- HL: PET/CT only (BMBx no longer required)

High sensitivity and specificity
Large studies showed: v small % of false -ve but no change in therapy

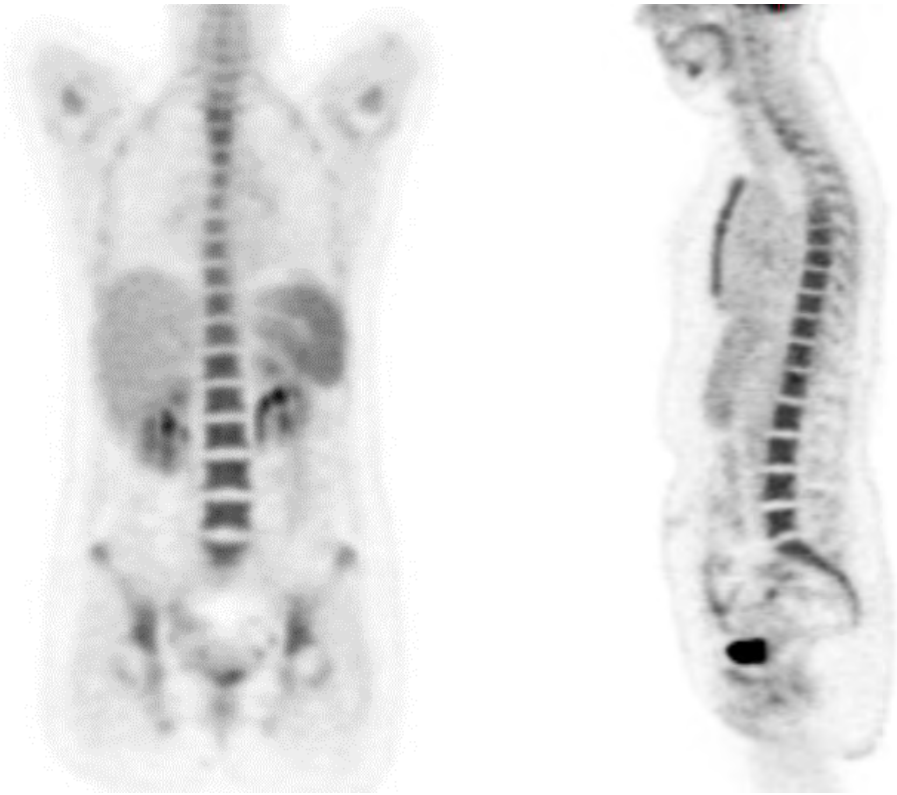
- DLBCL: PET/CT enough in most cases

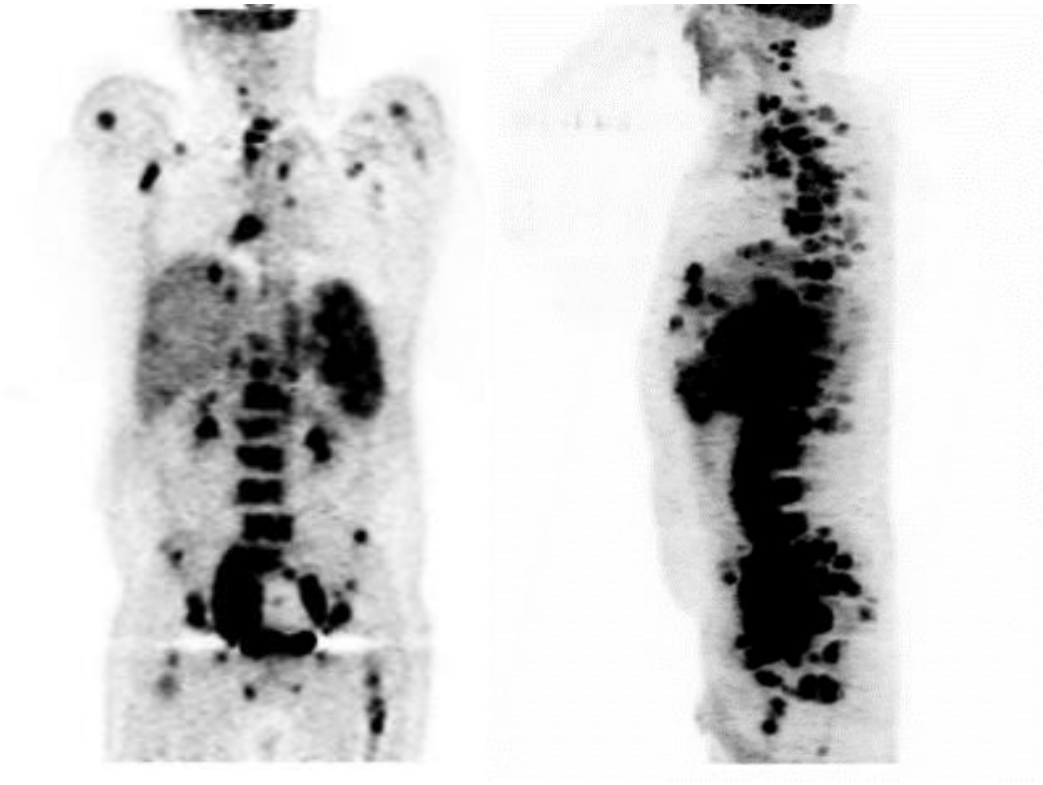
High sensitivity and specificity
But: - small % of **false –ve** (small volume BM involvement 10-20%)
- possibility of missing **LG** component
- Histologically +ve BM may be more **prognostically** important
So BMBx indicated only if result may change management

- FL / LG-NHL: BMBx is mandatory

High false negative rate

Interpretation of DIFFUSE marrow uptake





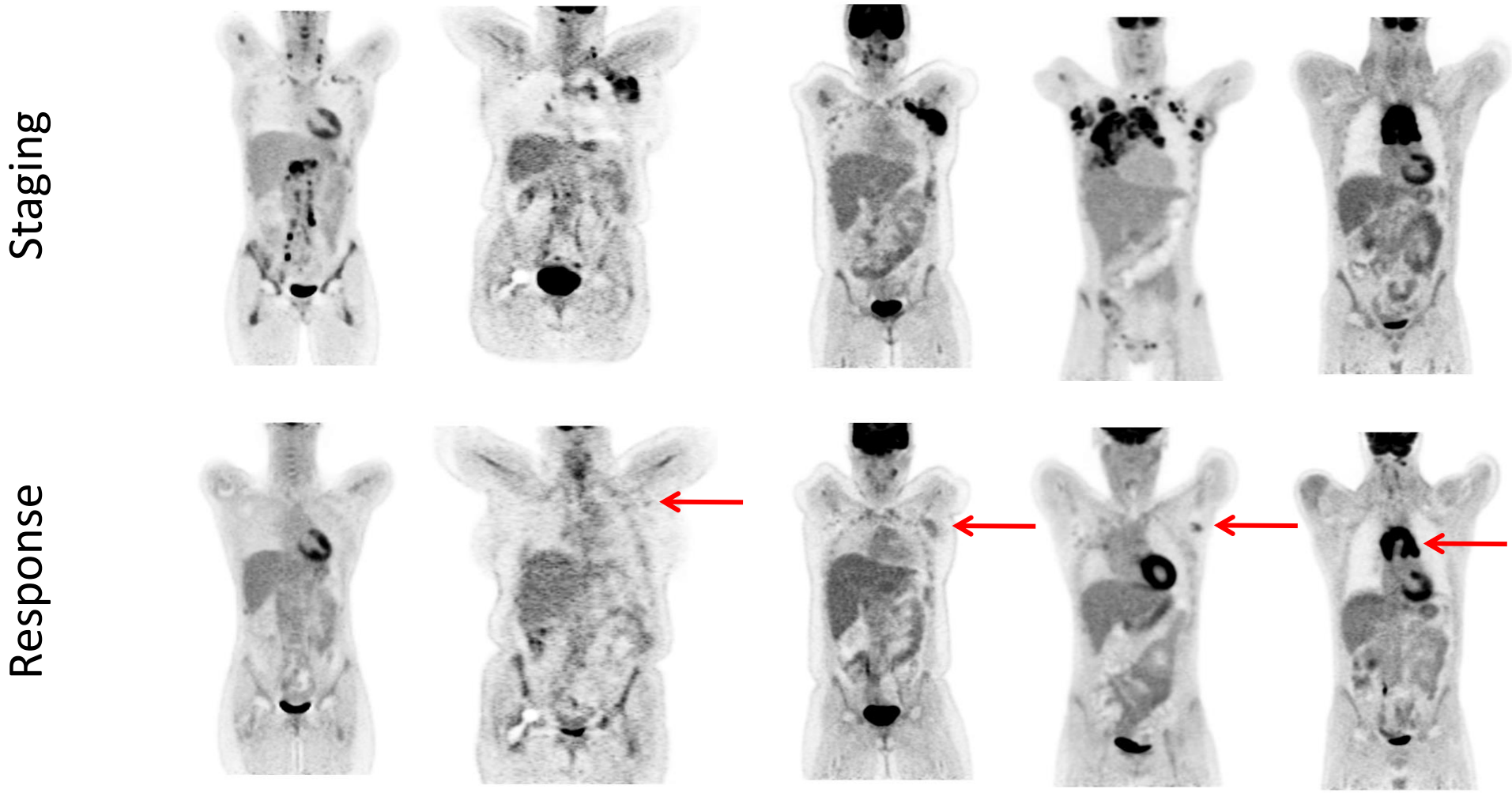
- indicates hyperplasia in HL
- occurs with chemotherapy & GCSF

Extensive BM Involvement

Deauville score or ΔSUVmax for response assessment?

Deauville Score

King's College London & Guy's and St Thomas' PET Centre



ation

Score 1 no uptake

Score 2 uptake ≤ mediastinum

Score 3 uptake > mediastinum but ≤ liver

Score 4 uptake > liver at any site

Score 5 uptake > liver and new sites of disease

***Score X**:*

new areas of uptake unlikely to be related to lymphoma

Negative scan

Positive scan

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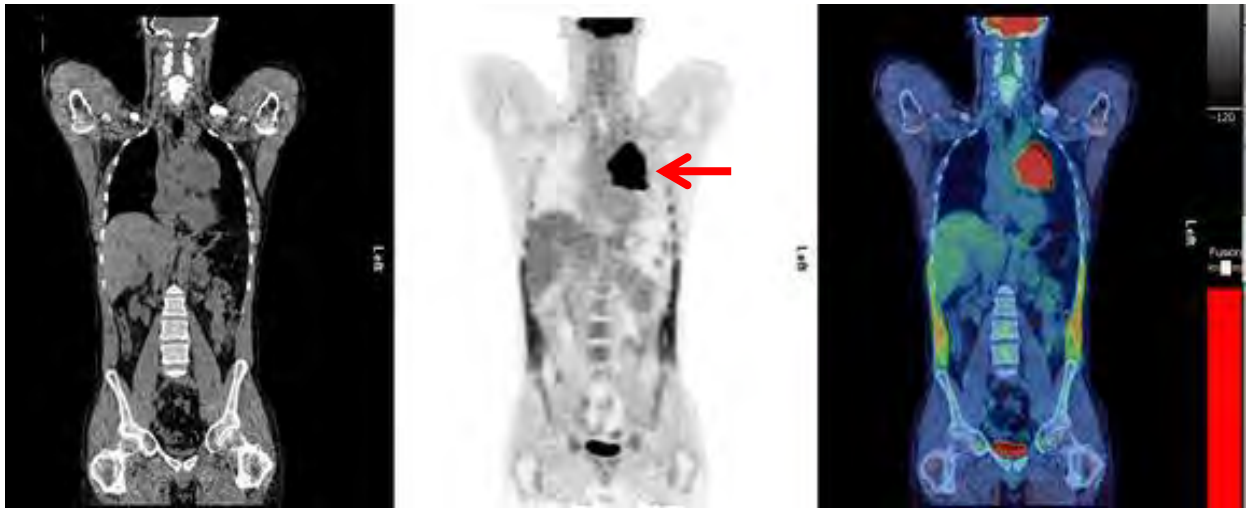
& Guy's and St Thomas'
PET Centre

Metabolic Response Categories		
Response		FDG uptake
Complete Metabolic Response	CMR	DS 1, 2, or 3
Partial Metabolic Response	PMR	DS 4/5 - improvement compared to baseline
Stable Metabolic Disease	SMD	DS 4/5 - No significant change from baseline
Progressive Metabolic Disease	PMD	DS 4/5 - Uptake > baseline or new areas

Baseline



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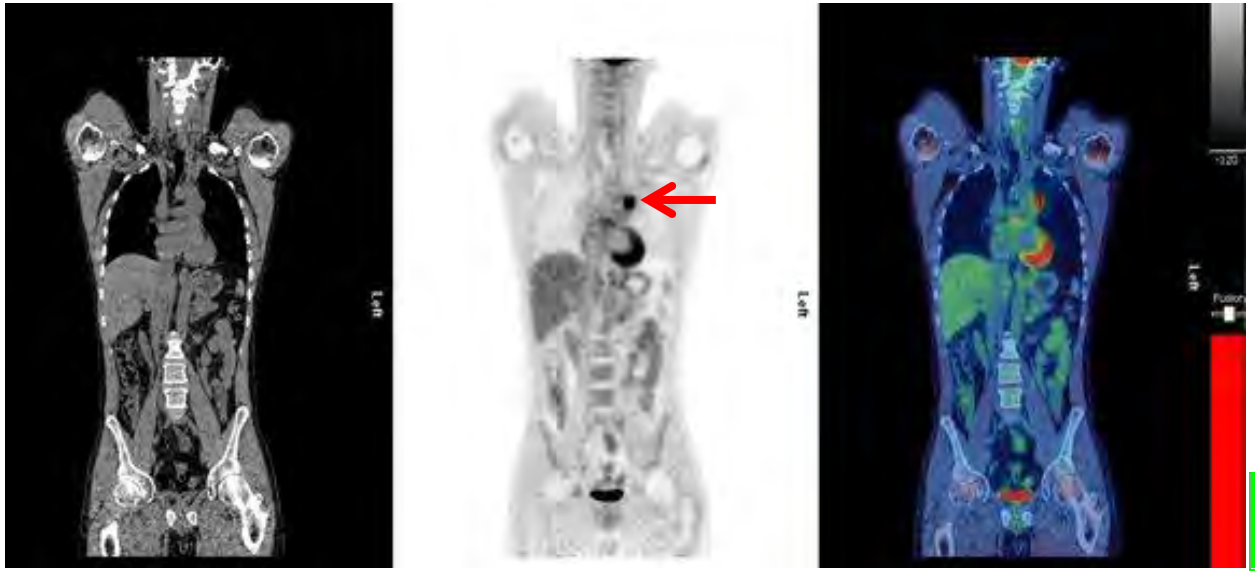
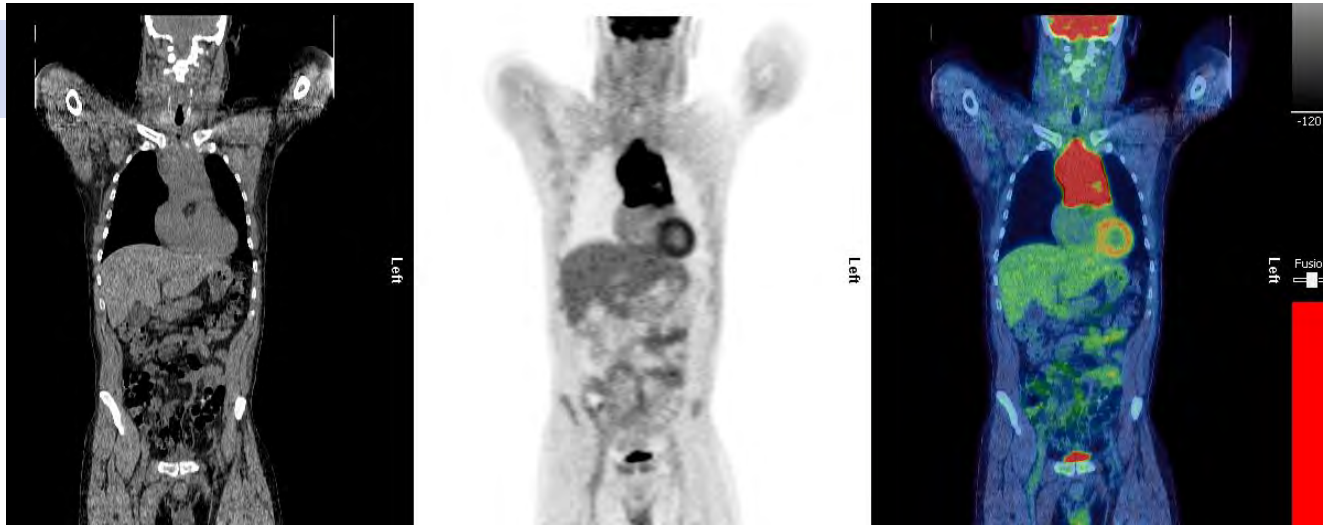


Score 5

PMR

Baseline



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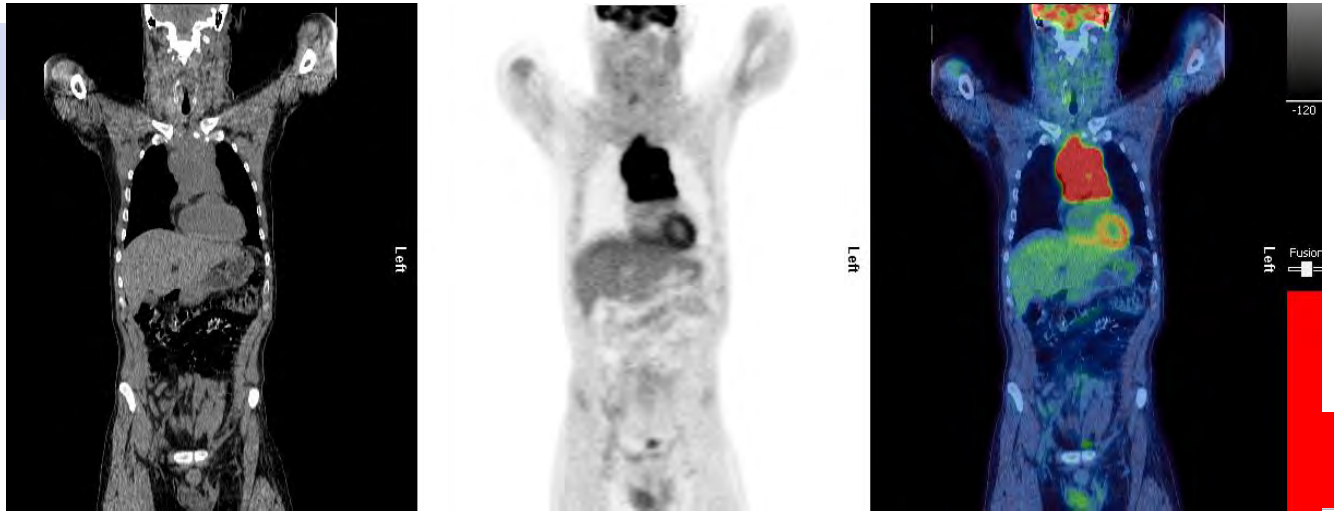
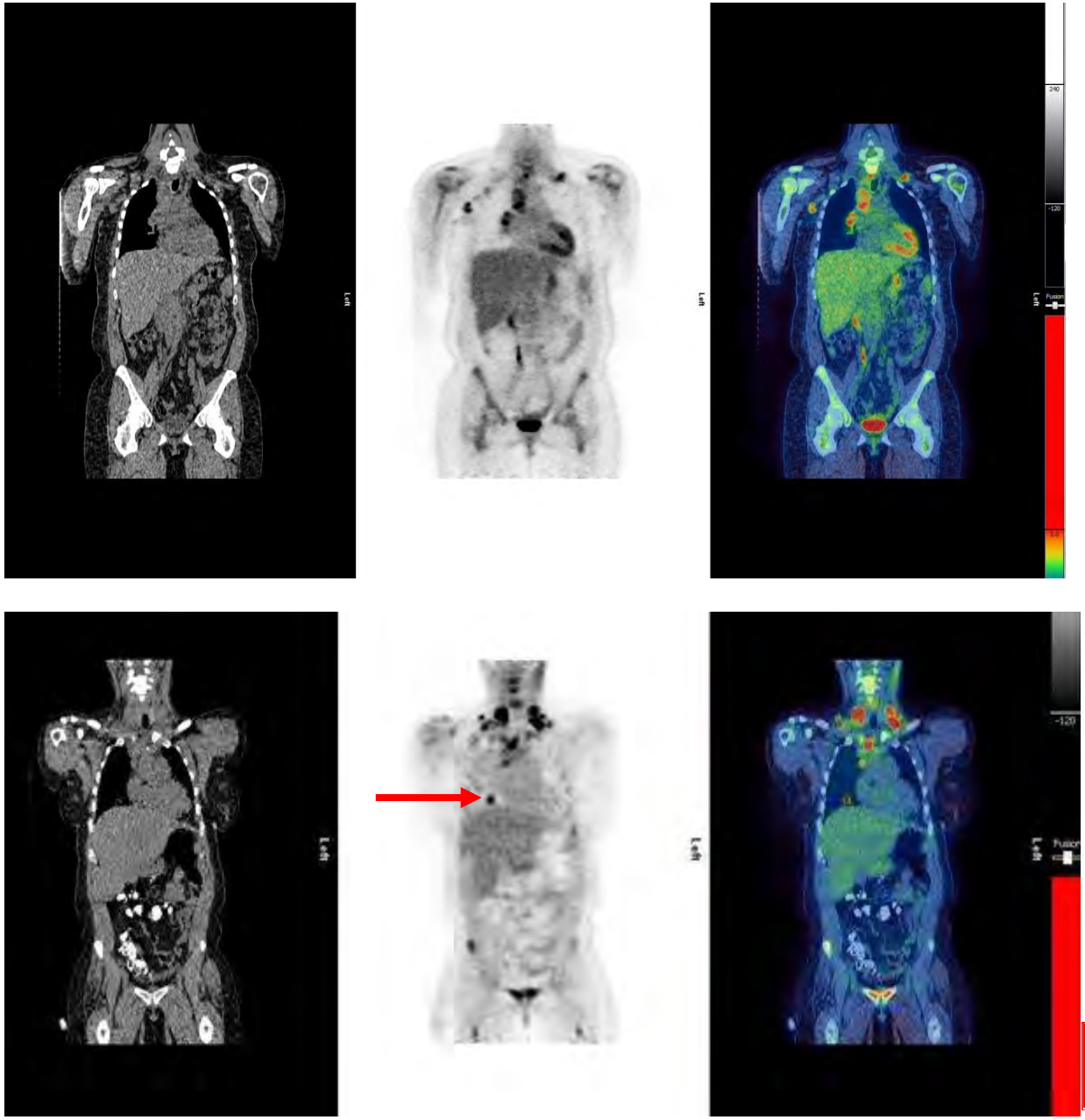


Score 5

NMR



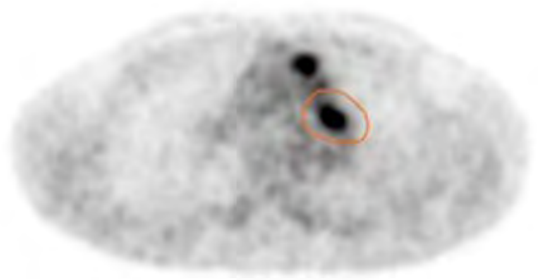
Score 5

PMD

Quantitative response assessment: ΔSUVmax

$$\text{SUV (Standardised Uptake Value)} = \frac{\text{activity per unit volume of a region of interest (ROI)}}{\text{activity per unit whole body volume}}$$

$$\Delta\text{SUVmax} = \frac{\text{max SUV in hottest lesion in response scan - baseline}}{\text{max SUV in hottest lesion in baseline scan}}$$

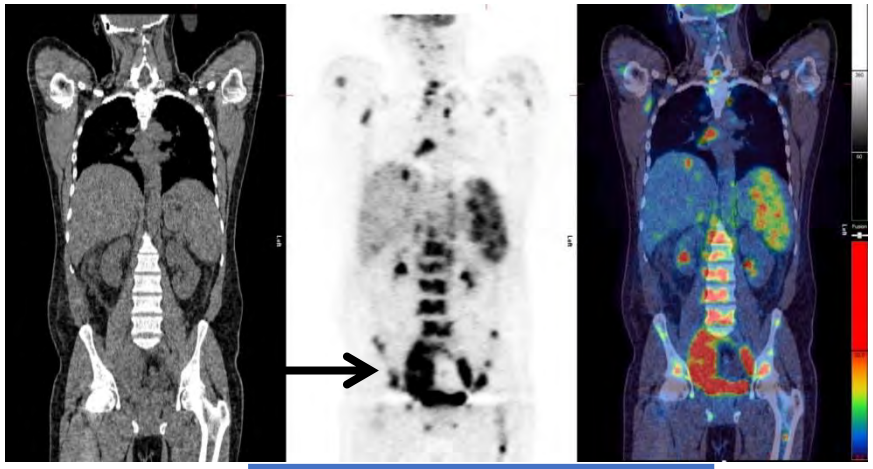


Relatively easy but requires accurate measurement:

- Scanner calibration
- Same scanner
- Exact injected activity recording
- Same injection-to-scan time
- Serum glucose level?

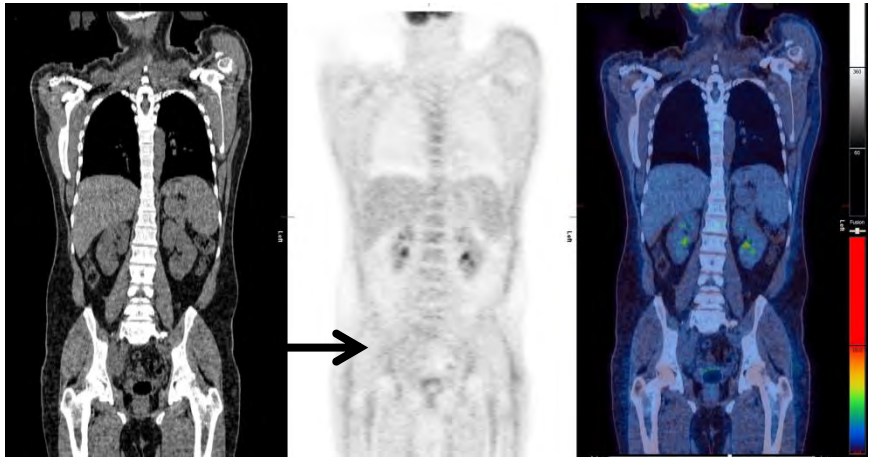
Use of Δ SUVmax

Staging



SUV = 25.0

Response



SUV = 2.5

ΔSUV 90%

- Different cut-off for different lymphomas and time of response assessment
- Example: DLBCL

  Cut-off 66% at 2 cycles ; 70% at 4 cycles

Qualitative or Quantitative

- DS easy, widely used, still requires expertise
- ΔSUVmax requires QA
- Different performance
  - Lymphoma type
  - Interim vs end-of-treatment (EOT)
  - NPV vs PPV
- Hodgkin: DS (both iPET & EOT-PET)
- DLBCL:
  - EOT: DS
  - iPET: PPV highest with DS-5 > ΔSUVmax > DS4-5

DLBCL

Table 2. PPV and NPV using DS4-5, DS5, or ΔSUV_{max} to assign a PET-positive result at I-PET2 and I-PET4

	I-PET criteria	PPV (95% CI)	NPV (95% CI)
I-PET2	DS1-3 vs DS4-5	30.5 (26.2-33.8)	82.9 (80.0-85.7)
	DS1-4 vs DS5	68.5 (56.6-80.3)	80.0 (77.5-82.5)
	ΔSUV_{max}	45.7 (37.3-54.1)	80.6 (78.1-83.2)
I-PET4	DS1-3 vs DS4-5	42.6 (33.0-52.3)	84.7 (81.1-88.3)
	DS1-4 vs DS5	70.0 (51.7-88.3)	81.5 (77.9-85.0)
	ΔSUV_{max}	57.4 (41.2-73.5)	82.2 (78.0-86.4)

Eertink, Blood advances 2021
1692 patients

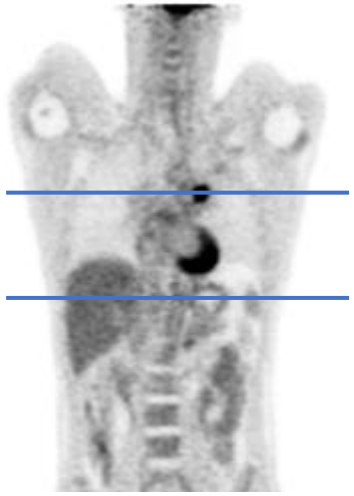
Clinical application of DS

- Is DS completely visual?
- Is DS-3 CMR?
- Is DS-5 different from 4?
- Effect of improvement in PET technology on DS
- How best to define DS-4?

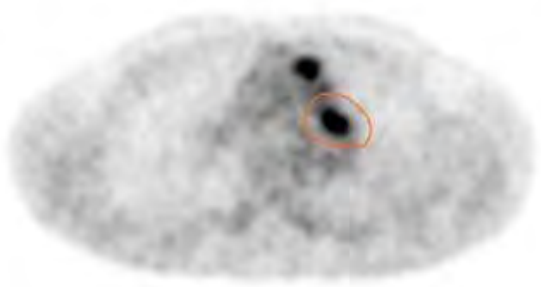
Is Deauville score completely visual?

Semi-quantitative DS

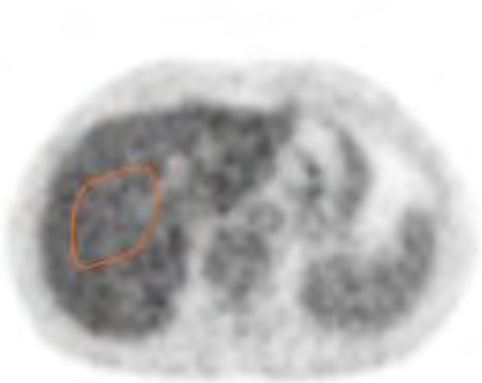
King's College London & Guy's and St Thomas' PET Centre



Score 5



SUVmax lesion 8.51

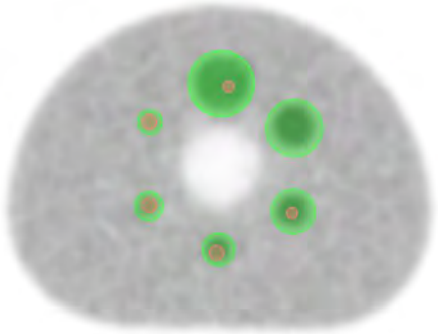


SUVmax liver 2.44

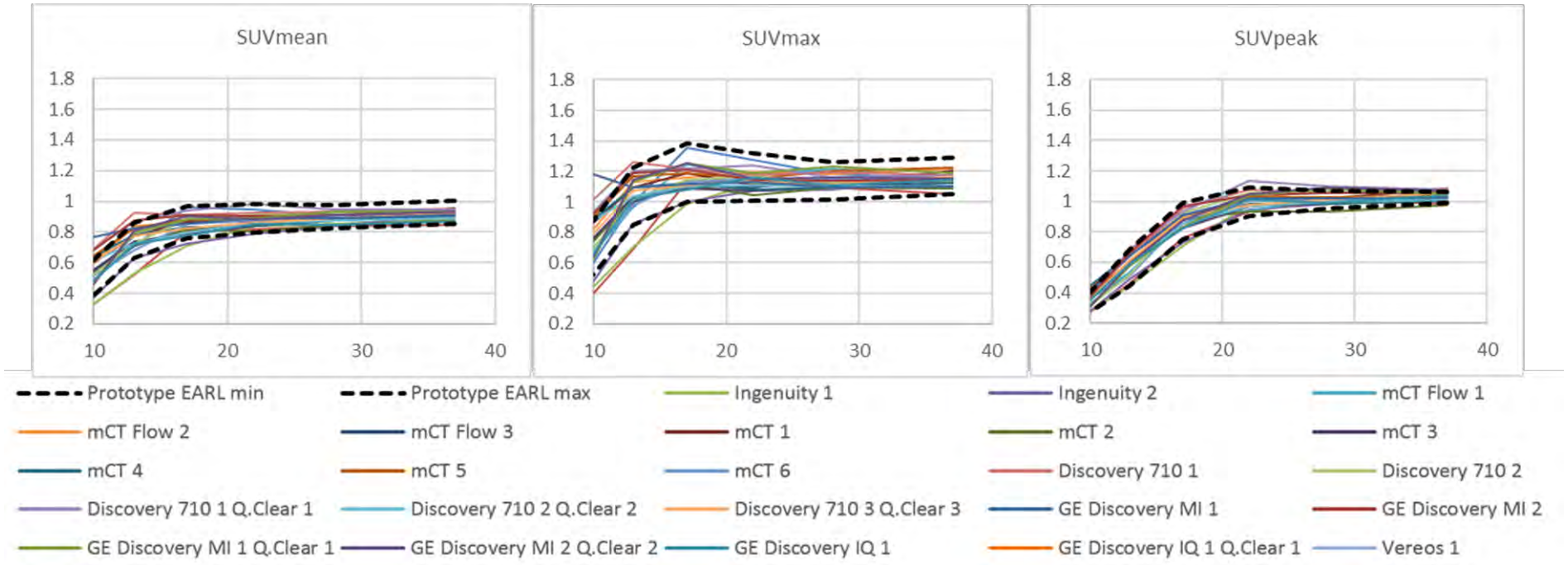
Posterior

Lesion > 3x liver

Other SUV metrics



Prospective independent test data from 23 PET sites



SUVmax = the single pixel with the highest uptake
SUVpeak = the average uptake in the hottest 1cm3 (less sensitive to image noise)
SUVmean = the average uptake in a region

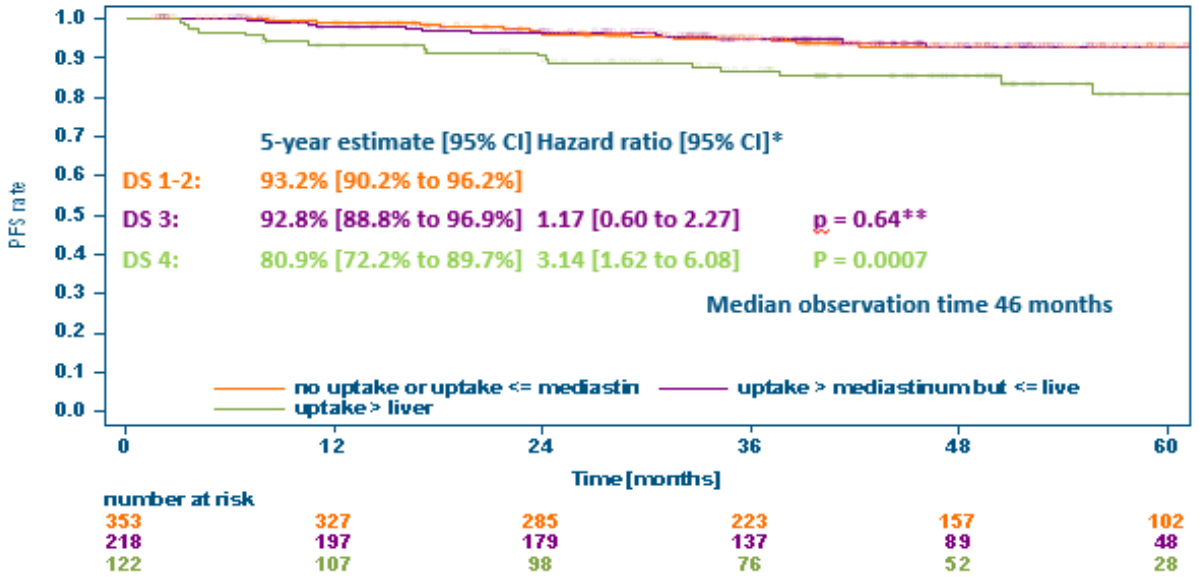
Is DS-3 CMR?

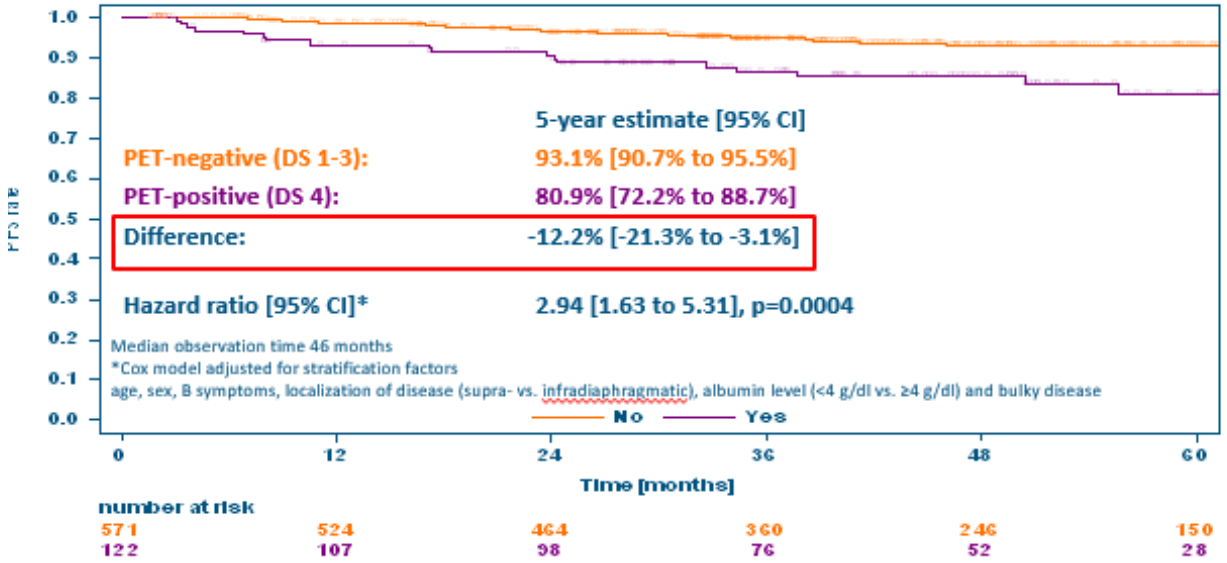
Is DS-3 CMR?

- Many Hodgkin lymphoma studies considered DS-3 as not CMR (iPET):
  - RAPID
  - HD-16 (GHSG)
  - HD-17 (GHSG)
  - (H10)

- Subsequent analysis suggested that DS-3 has same prognosis as DS1-2

Example: HD-16 study





**PFS after DS1-2 and DS3 very similar

Deauville 2009

Leukemia & Lymphoma, August 2009; 50(8): 1257–1260

informa
healthcare

REVIEW

Report on the First International Workshop on interim-PET scan in lymphoma

Statement 4 (scoring).

The 5-point scale.

1. No uptake.
2. Uptake ≤mediastinum.
3. Uptake > mediastinum but ≤liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and new sites of disease.

Lugano 2014

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Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

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The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

- 1. No uptake
- 2. Uptake ≤ mediastinum
- 3. Uptake > mediastinum but ≤ liver
- 4. Uptake moderately higher than liver
- 5. Uptake markedly higher than liver and/or new lesions
- X. New areas of uptake unlikely to be related to lymphoma

Is prognosis of DS-5 different from 4?

DS-5

- Multiple studies show it has worse prognosis > DS-4
- Defined in original DS as: “markedly above the liver” &/or “new lesions.
- Some groups use 2 and others 3 times SUVmax of liver
- Identifies ***refractory disease***
- Mixed bag:
  - >2/3 times liver + responding or no change or worse
  - New lesions
- Suggestion to divide DS-5 to
  - 5a - Uptake markedly greater than liver *(residual refractory dis)*
  - 5b - Presence of new lesions attributed to lymphoma

2023 suggestion

Response	Change from baseline/previous scan
CMR	DS 1-3 (DS 1 usually assigned where lesion is no longer visible on CT)
PMR	DS 4 or 5a with *responding disease* meaning: reduced intensity* or extent¥ of lymphoma
SMD	DS 4 or 5a and intensity and extent of lymphoma *stable*
PMD	DS 5a with increased intensity * &/or increased extent of lymphoma DS 5b new lesions due to lymphoma

* Increase in uptake in a single lesion constitutes PMD, even if there has been a response in lesions elsewhere (sometimes referred to as 'mixed' metabolic response)

¥ extent = number of lesions and/or areas of uptake

Effect of improvements of technology on DS?

Effect of improvement in PET technology on DS

Since Lugano 2014:

- Advances in PET hardware
  - digital PET scanners
  - smaller detectors
  - higher spatial resolution
  - larger axial field of view

- New image reconstruction software

→ changing image characteristics → change in DS designation

→ increased the variability of visual and semi-quantitative assessments between imaging centres

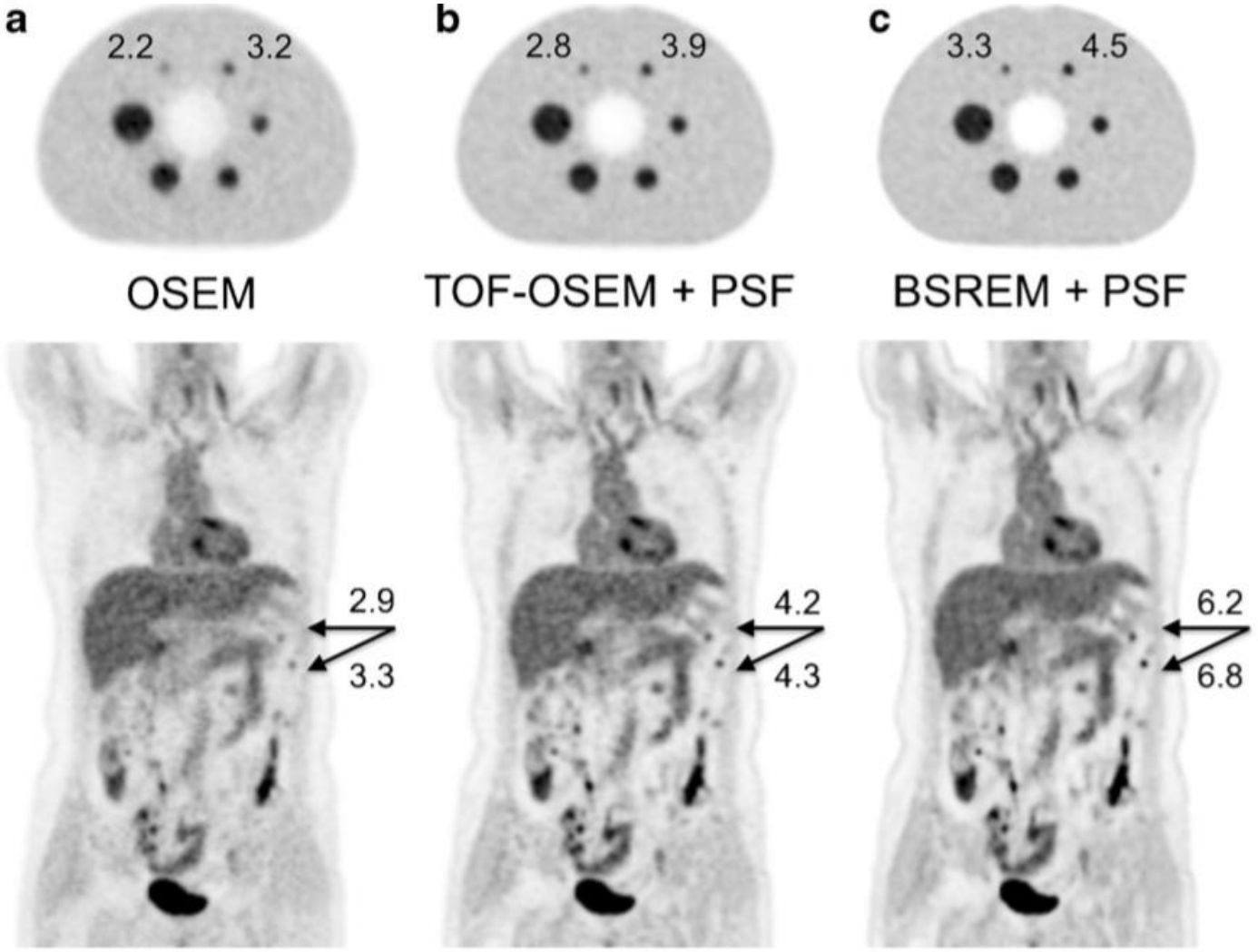
Eur J Nucl Med Mol Imaging (2017) 44 (Suppl 1):S4–S16
DOI 10.1007/s00259-017-3727-z

REVIEW ARTICLE

Quantification, improvement, and harmonization of small lesion detection with state-of-the-art PET

Charlotte S. van der Vos[1,2] · Daniëlle Koopman[2,3] · Sjoerd Rijnsdorp[4] · Albert J. Arends[4] · Ronald Boellaard[5,6] · Jorn A. van Dalen[3,7] · Mark Lubberink[8,9] · Antoon T. M. Willemsen[5] · Eric P. Visser[1]

Reconstruction methods



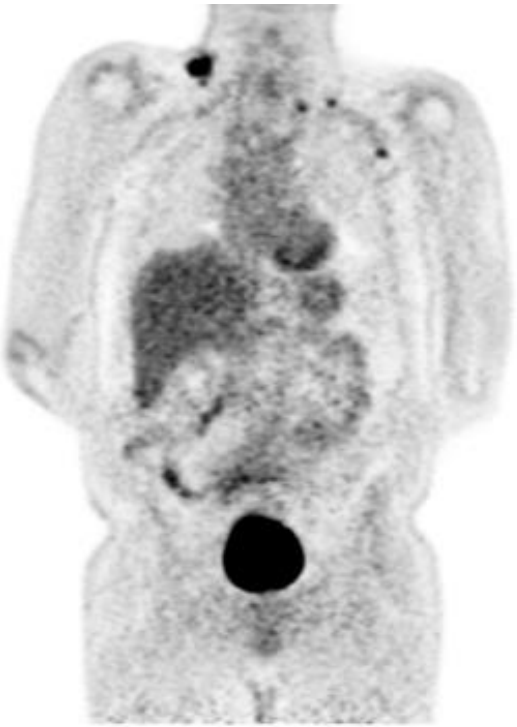
OSEM = Ordered Subset Expectation Maximisation

TOF = Time of Flight

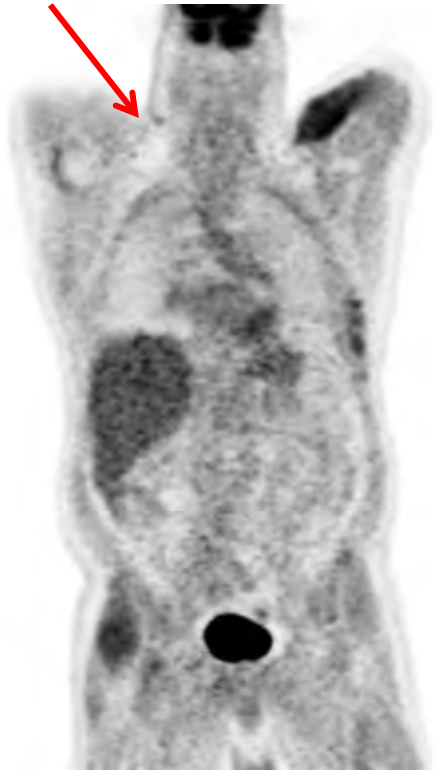
PSF = Point Spread Function

BSREM = Block-Sequential Regularized Expectation Maximization (Q clear)

Attention: Reconstruction algorithm can change Deauville score

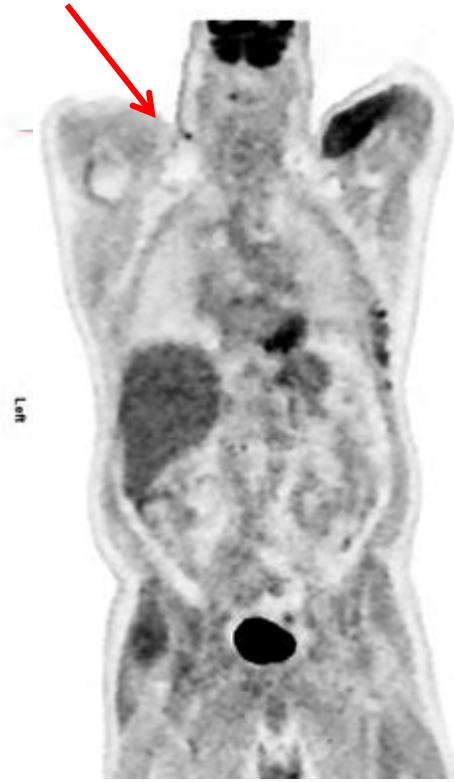


Staging



Response

Score 2



qCLEAR

Score 4

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& Guy's and St Thomas'
PET Centre

Clinical Radiology 78 (2023) e89–e98

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

The frequency of change in five-point scale score with a Bayesian penalised likelihood PET reconstruction algorithm on interim FDG PET-CT and its potential implications for therapy decisions in Hodgkin's lymphoma

M. Subesinghe [a,b,*], H. Ilyas [c], J.T. Dunn [a,b], N. Mir [d], A. Duran [d], N.G. Mikhaeel [e,f,†], S.F. Barrington [a,b,†]

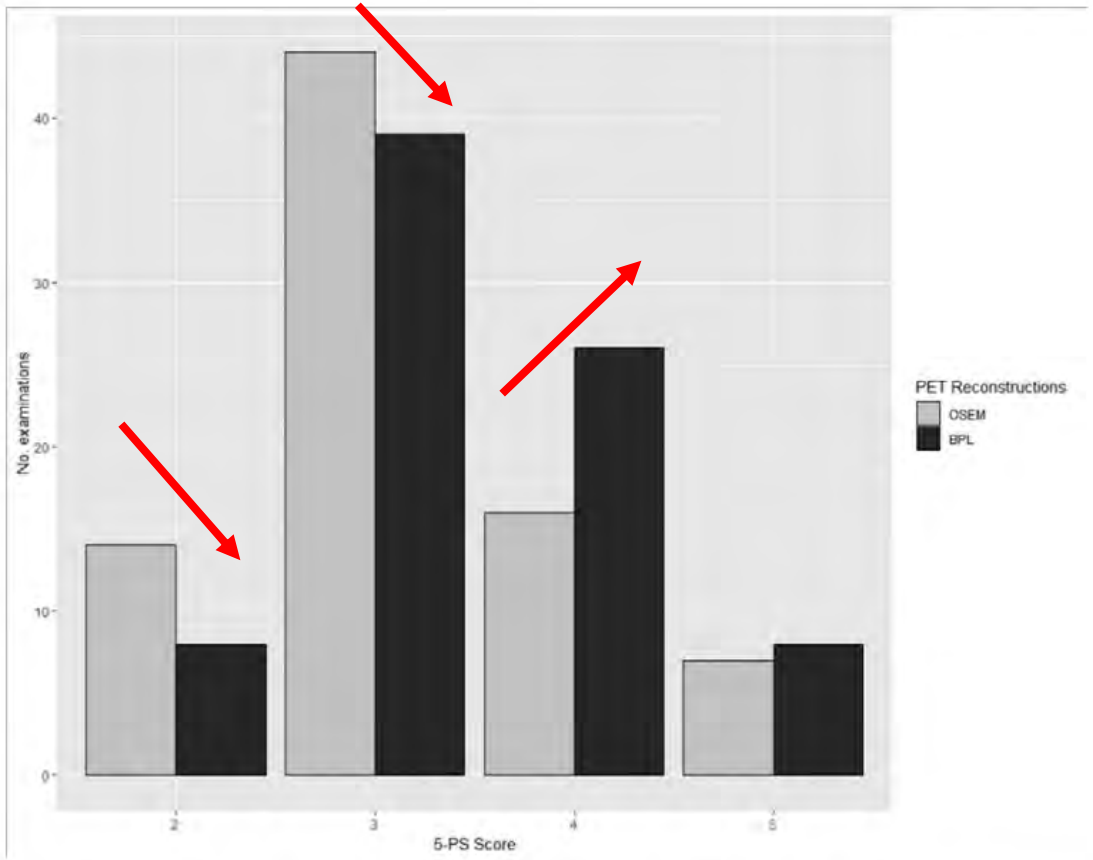


Figure 1 Frequency histogram comparing the 5-PS score between OSEM and BPL PET reconstructions.

Change of DS	18/81 = 22%	
Change from DS 3 → 4	11/81 = 14%	(25% of DS 3)

How best to define DS-4?

How best to define DS-4?

- DS-4 = any uptake > the liver ⟷ 2/3 times > the liver
- CMR / no CMR = 1-3 v 4-5

- Issues:
  - Inter-observer variation
  - Visual or semi-quantitative
  - Is “any” uptake > liver significant?

- Some studies: 1.3 – 1.4 > liver (e.g. if liver SUVmax is 3, DS-4 is > 3.9)

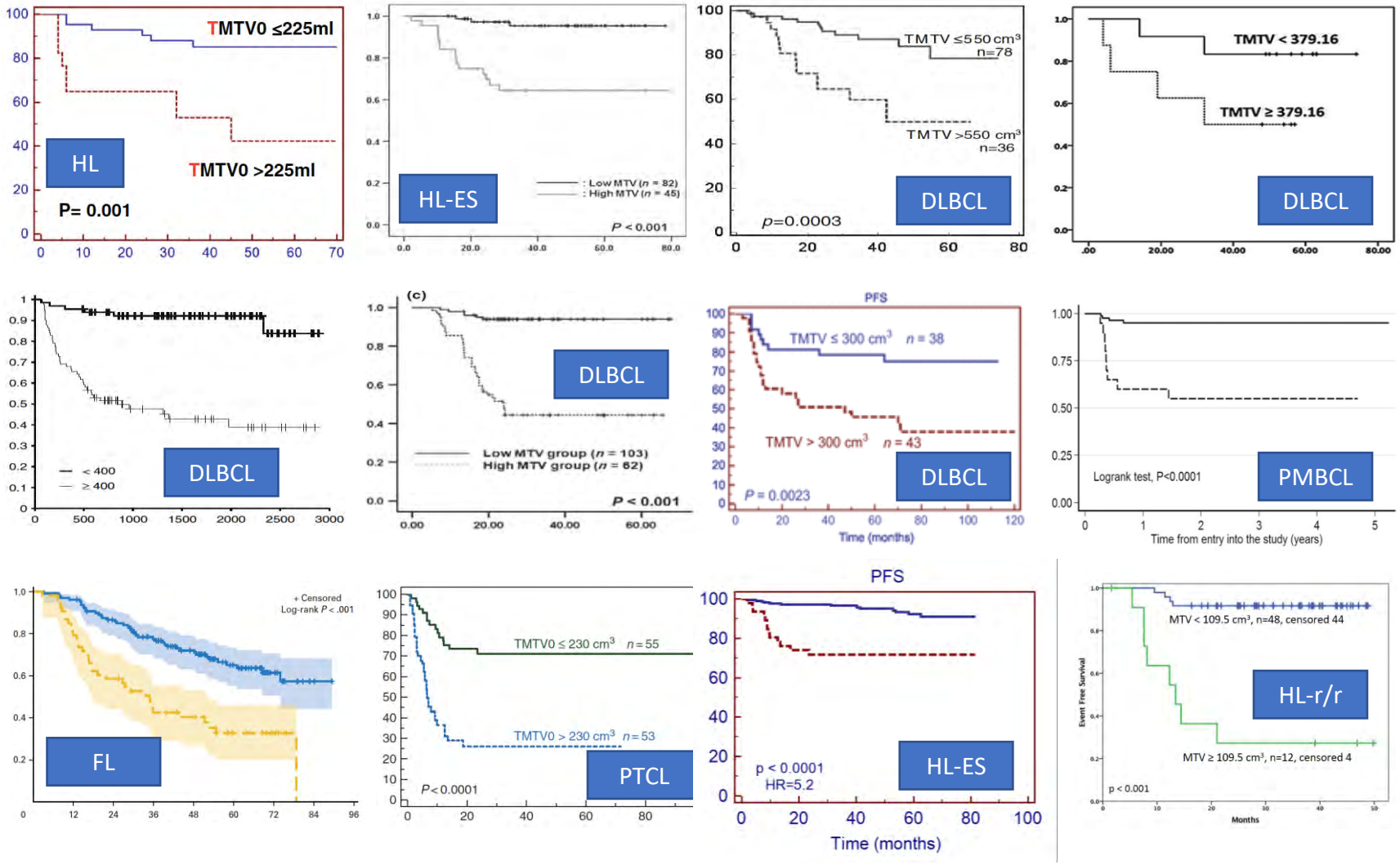
- Optimal definition may depend on: type, time and purpose of scan

Is MTV ready for clinical use?

Is MTV ready for clinical use?

- Is it prognostic?
- Do we have consensus on how to measure it?
  - Software
  - Threshold for measurement
  - Cut-off for prognosis
- Is it reproducible and readily available in clinic?
- How should we use it?
  - In addition to prognostic indices
  - Replace
  - incorporate

Consistently prognostic across many lymphoma types



Different MTV cut-off defining low/high MTV

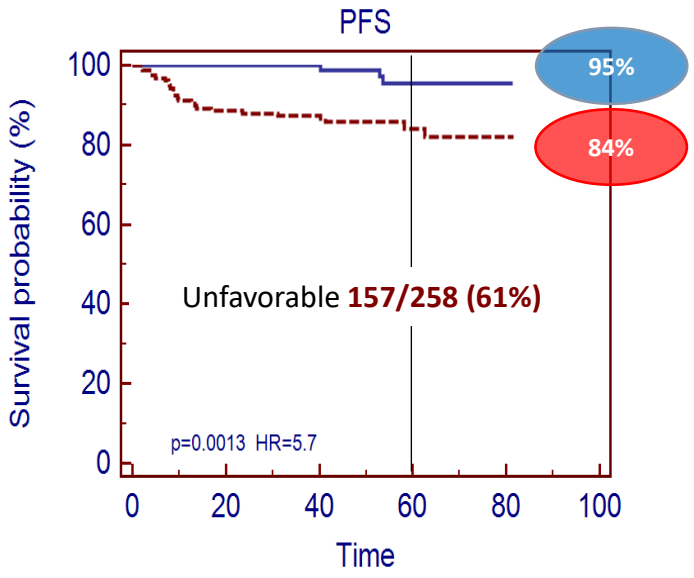
Kanoun EJNMMI 2014; 41: 1735-43
Song Cancer Sci 2013; 104, 1656-61
Sassanelli EJNMMI 2014; 41:2017-22
Esfahani AJNMMI 2013; 3(3):2q72-81

Mikhaeel EJNMMI 2016; 43, 1209-19
Song Cancer Sci; 2012; 103, 477-82
Cottereau AS Clin Cancer Res 2016;22:3801-9
Ceriani Blood 2015; 126(8), 950-6

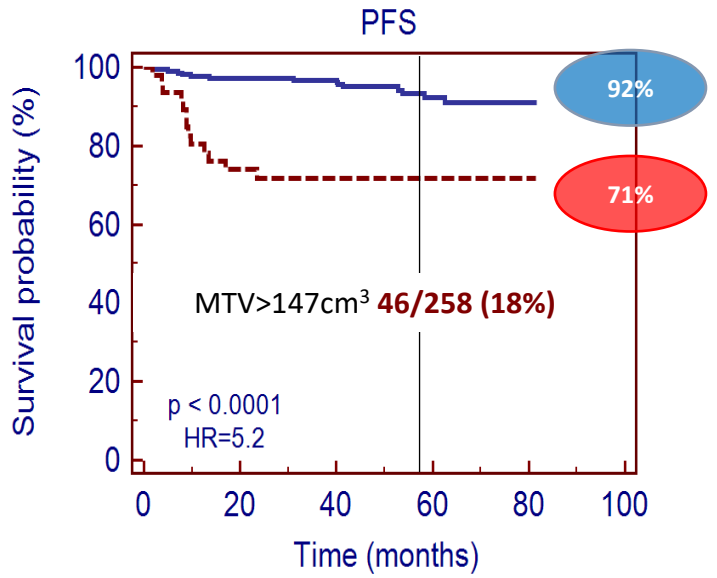
Meignan JCO 2016; 34
Cottereau Ann Oncol. 2016 (4):719-24
Cottereau Hematol Oncol 2015; 35(S2), 35
Moskowitz AJ: Blood 2017-06788877 [epub]

MTV vs EORTC classification in ES-HL

EORTC criteria: F Vs. UF



MTV Low Vs. High



In a cohort of 258 early stage HL included in the standard arm of the H10 trial:

- MTV was able to select a much smaller portion of patients compared to EORTC criteria (46 Vs. 157)
- with a lower 3y PFS compared to unfavorable ES-HL patients: 71% Vs. 84%

Cottereau AS: Blood 2018: 131: 1456-63.

Consistently prognostic regardless of methods (tools and SUV threshold)

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-3953-z

ORIGINAL ARTICLE

Defining the optimal method for measuring baseline metabolic tumour volume in diffuse large B cell lymphoma

Hajira Ilyas[1] · N. George Mikhaeel[2] · Joel T. Dunn[3] · Fareen Rahman[2] · Henrik Møller[4] · Daniel Smith[2] · Sally F. Barrington[3]

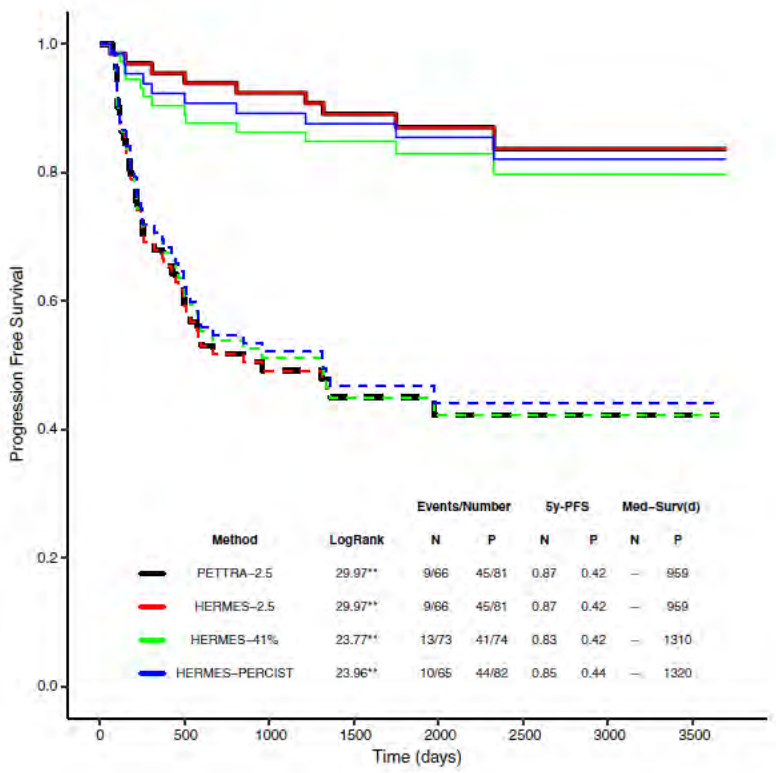
Received: 7 August 2017 / Accepted: 16 January 2018

2 software tools
3 SUV thresholds

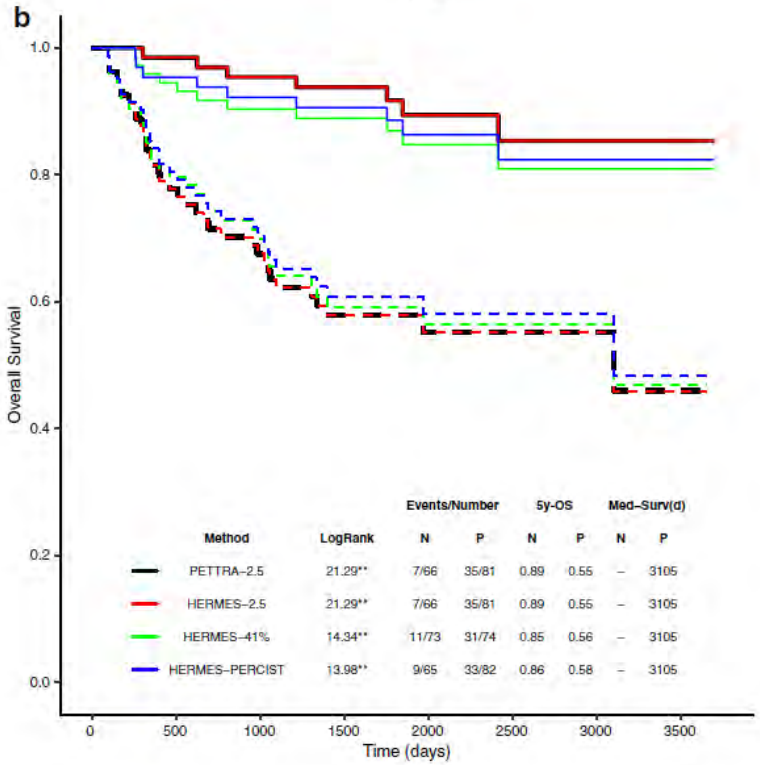
147 DLBCL pts

Method	AUC(95%CI)	Thr(cc)	Spec	Sens
PETTRA–2.5	0.76(0.68–0.84)	396.1	0.61	0.85
HERMES–2.5	0.76(0.68–0.84)	401.4	0.61	0.85
HERMES–41%	0.74(0.65–0.82)	165.7	0.64	0.77
HERMES–PERCIST	0.75(0.66–0.83)	327.4	0.59	0.83

Different MTV cut-off defining low/high MTV



PFS



OS

SUV 4

Automated Segmentation of Baseline Metabolic Total Tumor Burden in Diffuse Large B-Cell Lymphoma: Which Method Is Most Successful? A Study on Behalf of the PETRA Consortium

Sally F. Barrington[1], Ben G.J.C. Zwezerijnen[2], Henrica C.W. de Vet[3], Martijn W. Heymans[3], N. George Mikhaeel[4], Coreline N. Burggraaff[5], Jakoba J. Eertink[5], Lucy C. Pike[1], Otto S. Hoekstra[2], Josée M. Zijlstra[5], and Ronald Boellaard[2]

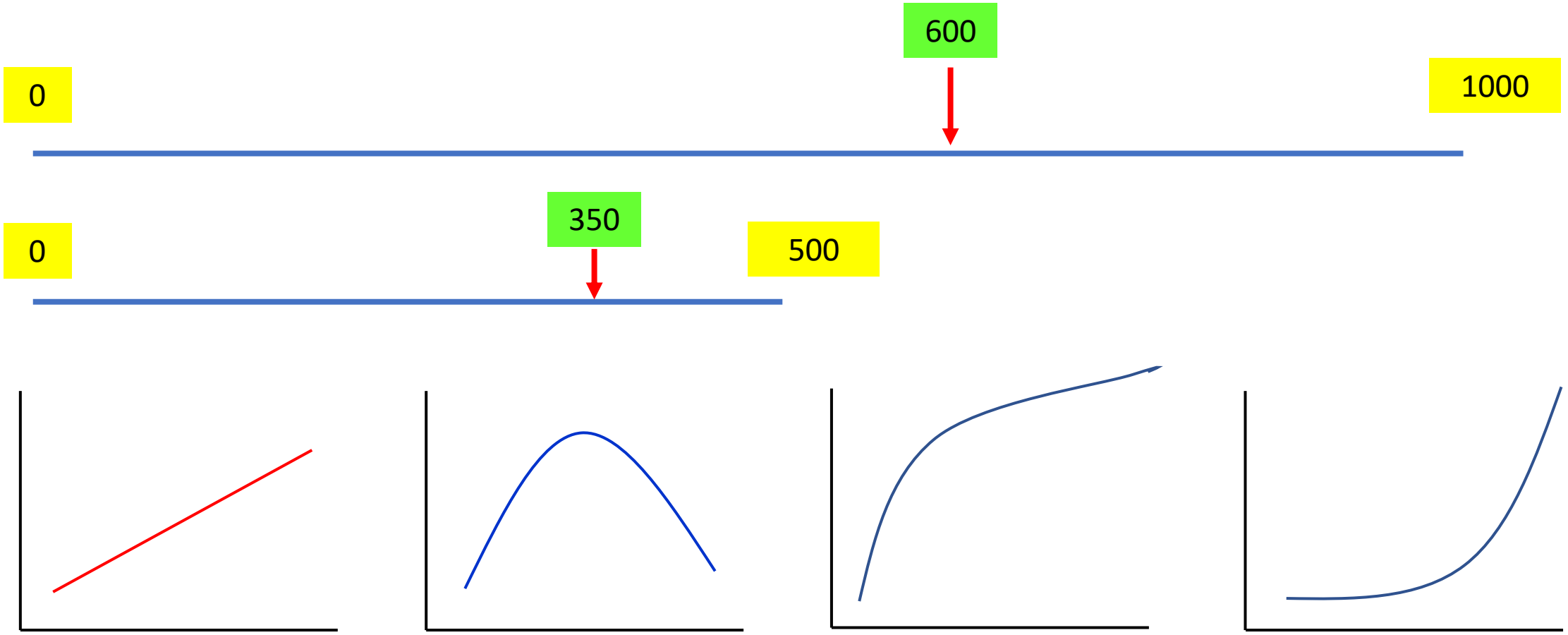
J Nucl Med 2021; 62:332–337
DOI: 10.2967/jnumed.119.238923

TABLE 2
Pairwise Tests of Segmentation Methods Using SUV4.0 as Reference

Segmentation method	Success	Failure	Editing required
SUV4.0	105	6	27
MV2	102	10	26
MV3	90	40*	8
41%	82*	45*	11
A50P	75*	57*	6
SUV2.5	51*	57*	30

*$P < 0.005$, compared with SUV4.0.

Single cut-off for continuous variables!



ASCO

Journal of Clinical Oncology

original reports

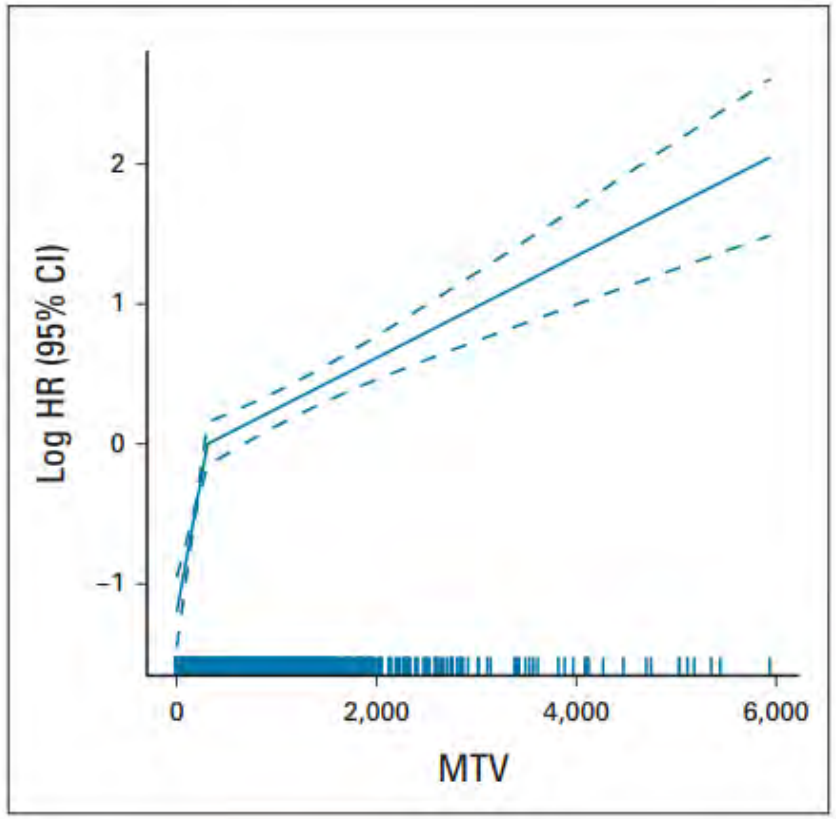
Proposed New Dynamic Prognostic Index for Diffuse Large B-Cell Lymphoma: International Metabolic Prognostic Index

N. George Mikhaeel, MD[1]; Martijn W. Heymans, PhD[2]; Jakoba J. Eertink, PhD[3]; Henrica C.W. de Vet, PhD[2]; Ronald Boellaard, PhD[4]; Ulrich Dührsen, MD[5]; Luca Ceriani, MD[6,7]; Christine Schmitz, MD[5]; Sanne E. Wiegers, PhD[3]; Andreas Hüttmann, MD[5]; Pieternella J. Lugtenburg, MD[8]; Emanuele Zucca, MD[6,7]; Gerben J.C. Zwezerijnen, MD[4]; Otto S. Hoekstra, MD[4]; Josée M. Zijlstra, MD[3]; and Sally F. Barrington, MD[9]

MTV & survival:

Not a linear relationship

Linear-Spline Function with 1-not



JCO 2022

IMPI

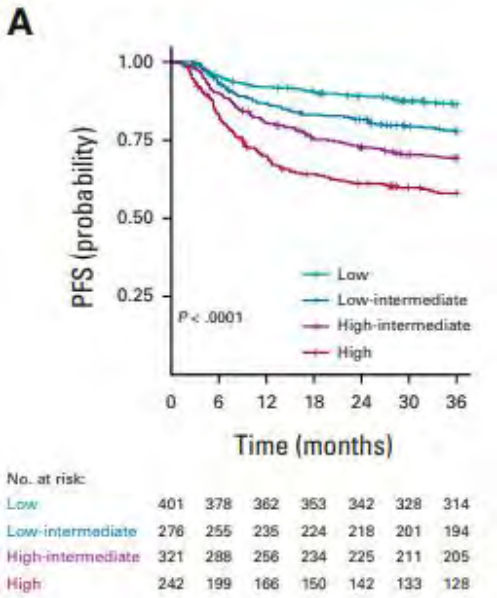
International Metabolic Prognostic Index

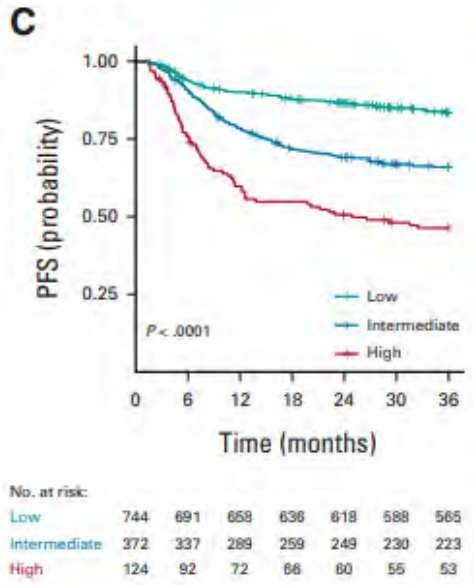
1241 patients

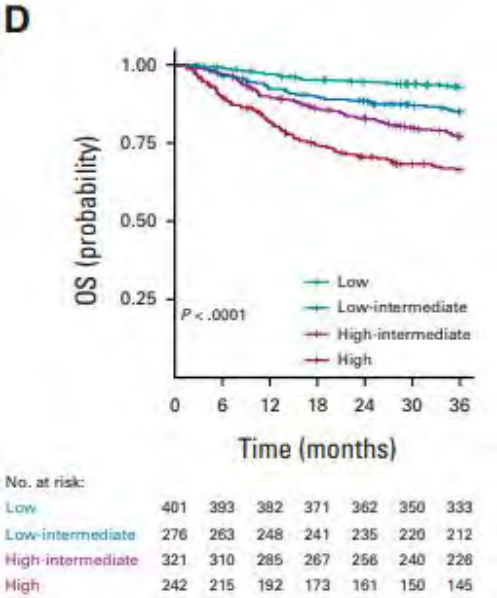
3 factors (continuous):

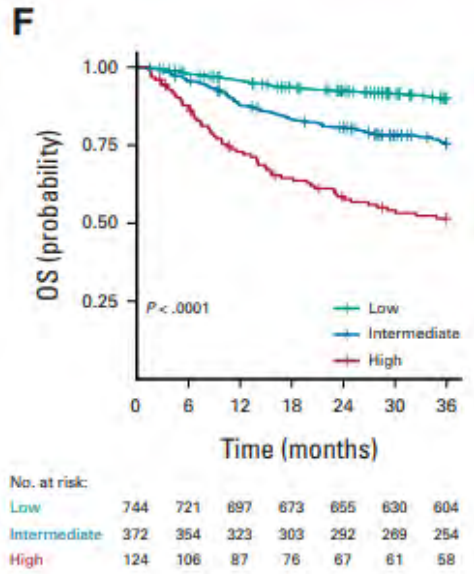
- **Age**
- **Stage**
- **MTV**

Mikhaeel et al, JCO 2022





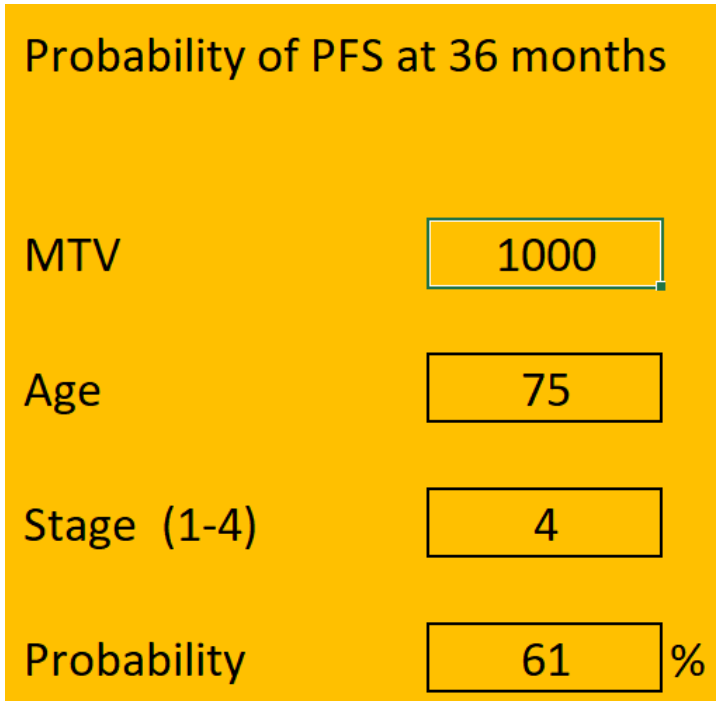




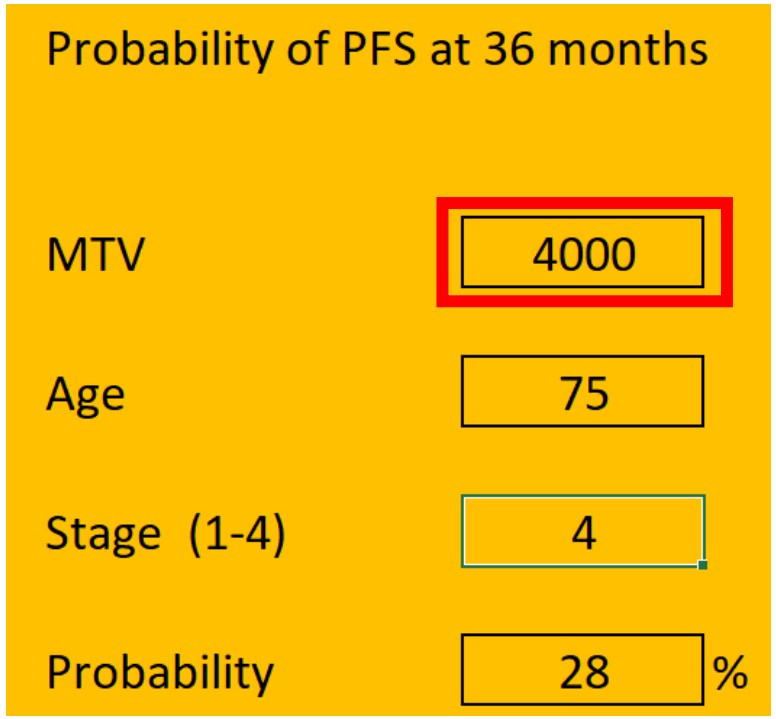
IPI

IMPI

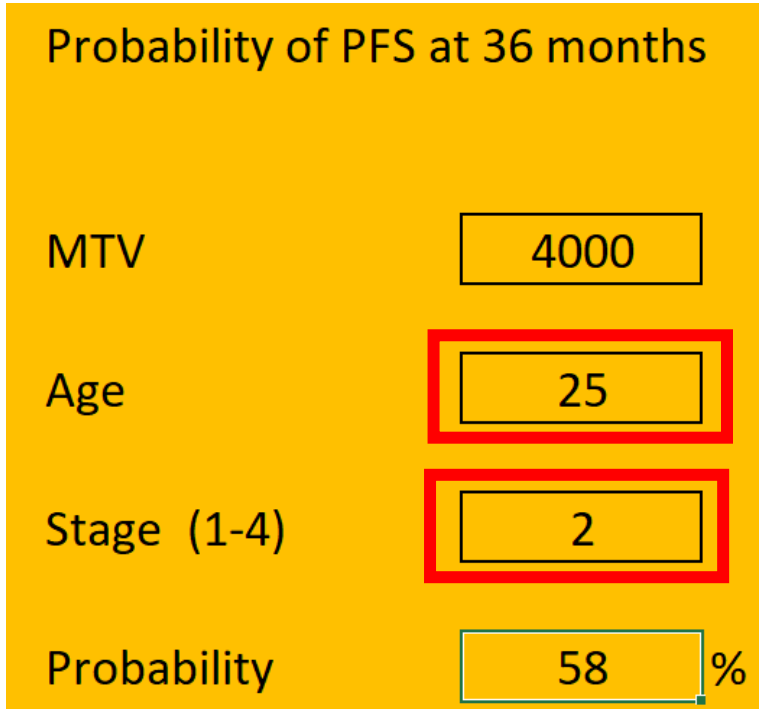
IMPI – Individual PFS calculator



75 y.o. + stage 4 + MTV 1000ml
= 3y PFS **61%**



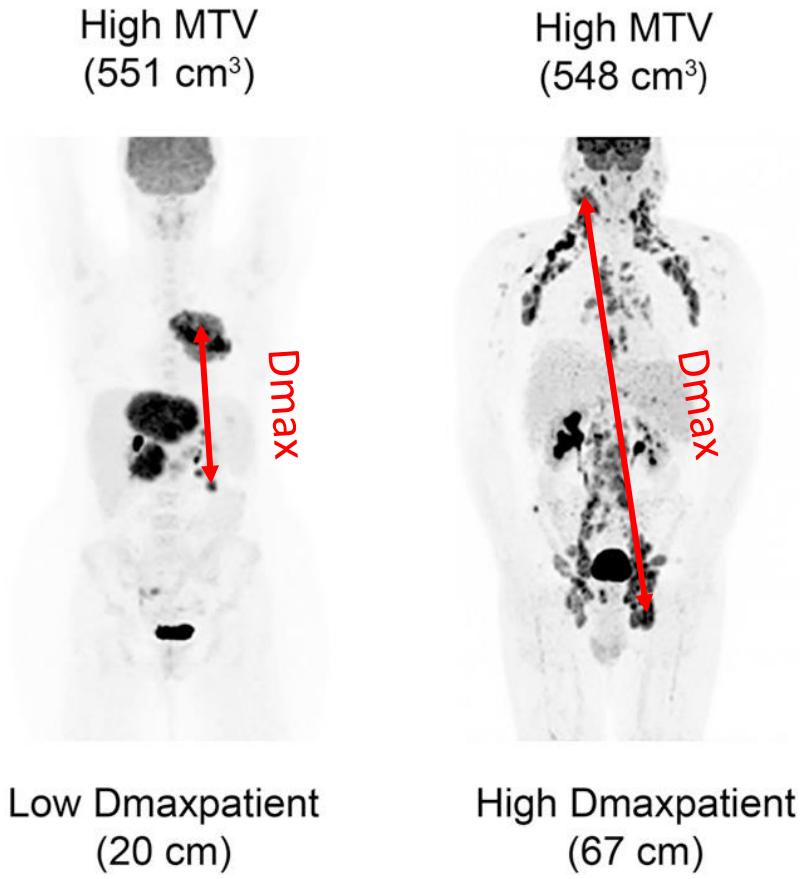
75 y.o. + stage 4 + MTV 4000ml
= 3y PFS **28%**



25 y.o. + stage 2 + MTV 4000ml
= 3y PFS **58%**

https://petralymphoma.org/impi/

Radiomics: Max distance between lesions



Cottereau AS et al J Nucl Med 2020; 61: 40-45

Conclusions

- Modern lymphoma management is heavily dependent on imaging

- Clinicians need to know:
  - Optimal use of imaging
  - Limitations
  - Performance of imaging in their institution

Thank you
Any questions?

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