THE LUGANO LYMPHOMA CLASSIFICATION AND THE NEW CRITERIA FOR PET EVALUATION

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Published Ahead of Print on August 11, 2014 as 10.1200/JCO.2013.54.8800
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.54.8800

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

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

Published Ahead of Print on August 11, 2014 as 10.1200/JCO.2013.53.5229
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.53.5229

JOURNAL OF CLINICAL ONCOLOGY | SPECIAL ARTICLE

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

ICML IMAGING GUIDELINES & THE LUGANO CLASSIFICATION

Two consensus documents:
To update

1. Imaging guidelines for lymphoma

2. Ann Arbor/Cotswolds staging classification and 2007 IHP response criteria in lymphoma

Both for use in clinical practice and late phase trials

Barrington SF et al J Clin Oncol 2014; 32(27): 3048-58.
Cheson BD et al J Clin Oncol 2014; 32(27): 3059-68.

BACKGROUND FOR THE CHANGES

- In most lymphoma subtypes PET/CT is has higher sensitivity and specificity for staging than CT
- There is a general tendency towards upstaging
- PET/CT both during and after chemotherapy is more strongly prognostic than conventional response assessment with CT
- Several studies investigate the role of treatment adaptation based on PET response
- More and more treatment guidelines use PET response to determine the course of treatment

ICML imaging group

SF Barrington, NG Mikhaeel, L Kostakoglu, M Meignan, M Hutchings, S Müeller, LH Schwartz, E Zucca, RI Fisher, J Trotman, OS Hoekstra, RJ Hicks, MJ O'Doherty, R Hustinx, A Biggi, BD Cheson

RECOMMENDATIONS STAGING

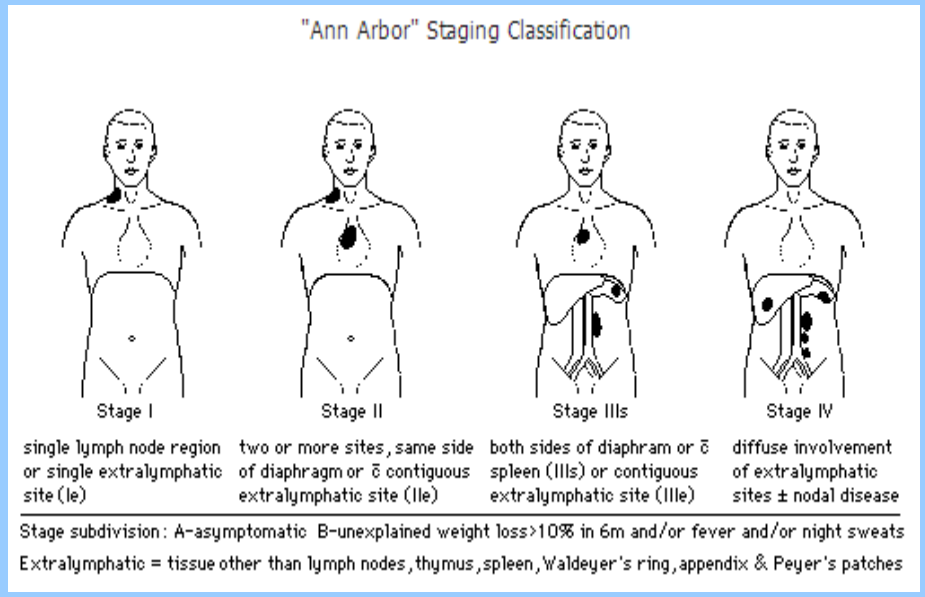
The ICML Imaging Working Group

STAGING

The four stages of Ann Arbor and Cotswolds are not changed

Even though there are much more refined ways of assessing and reporting disease burden

Most evidence and guidelines are based on the stratification of patients with local (I-II) vs. disseminated (III-IV) disease



PET-CT

PET-CT should be used for :

Staging of routinely FDG-avid lymphomas
- can be used to direct biopsy
(especially in case of suspected transformation)

A baseline PET-CT scan is also optimal for subsequent response assessment

Histology (patient numbers)	% FDG-avid
Hodgkin lymphoma (489)	97 - 100
Diffuse Large B cell lymphoma (446)	97 - 100
Follicular lymphoma (622)	91 - 100
Mantle cell (83) Burkitt (24) MZL nodal (14) LL (6)	100
Anaplastic large T-cell lymphoma (37)	94 -100 (27% of cutaneous sites)
Natural killer/T-cell lymphoma (80)	83 - 100
Angioimmunoblastic T-cell lymphoma (31)	78 - 100
Peripheral T-cell lymphoma (93)	86 - 98
MALT (227)	54 - 81
Small lymphocytic lymphoma (49)	47 - 83
Enteropathy type T-cell lymphoma (20)	67 - 100
MZL, splenic (13), unspecified (12)	53 - 67
Mycosis fungoides (24) and Sezary (8)	83 -100 (62% of cutaneous sites)
1° cutaneous anaplastic large T-cell (14)	40-60

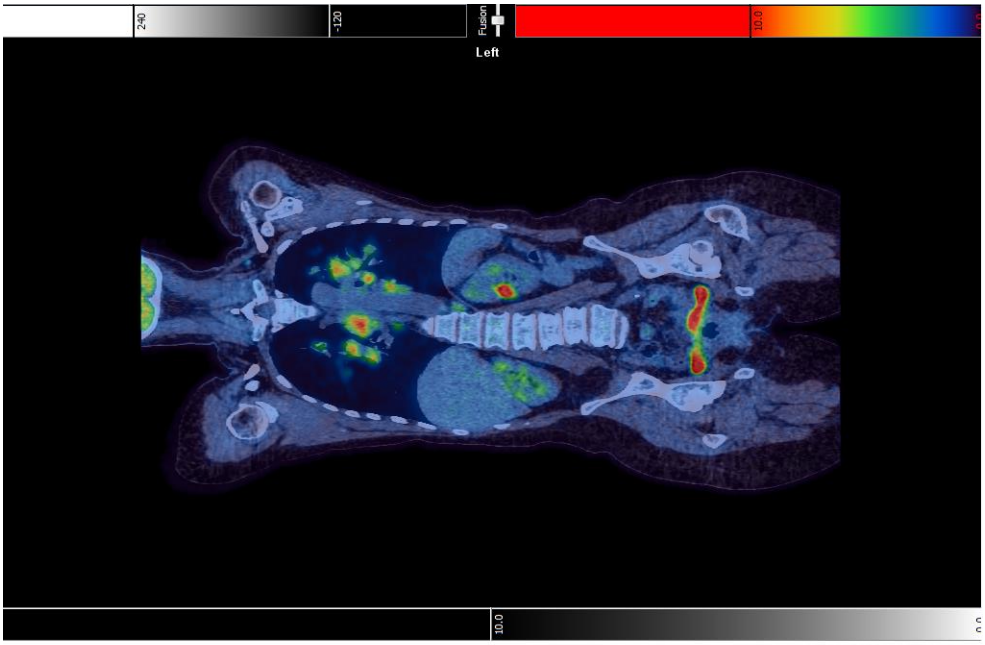
Modified from Weiler-Sagie et al JNM 51: 25-30, 2010

PET-CT

Scans should be reported with visual assessment

Images scaled to a fixed SUV & colour table

- noting location of foci in nodal & extranodal sites
- distinguished from physiological uptake and other patterns of disease according to the distribution and/or CT characteristics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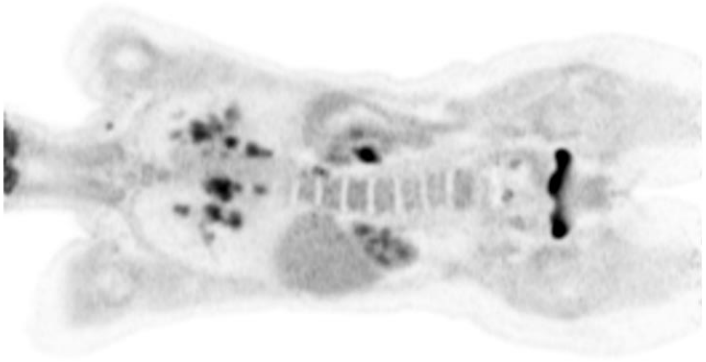

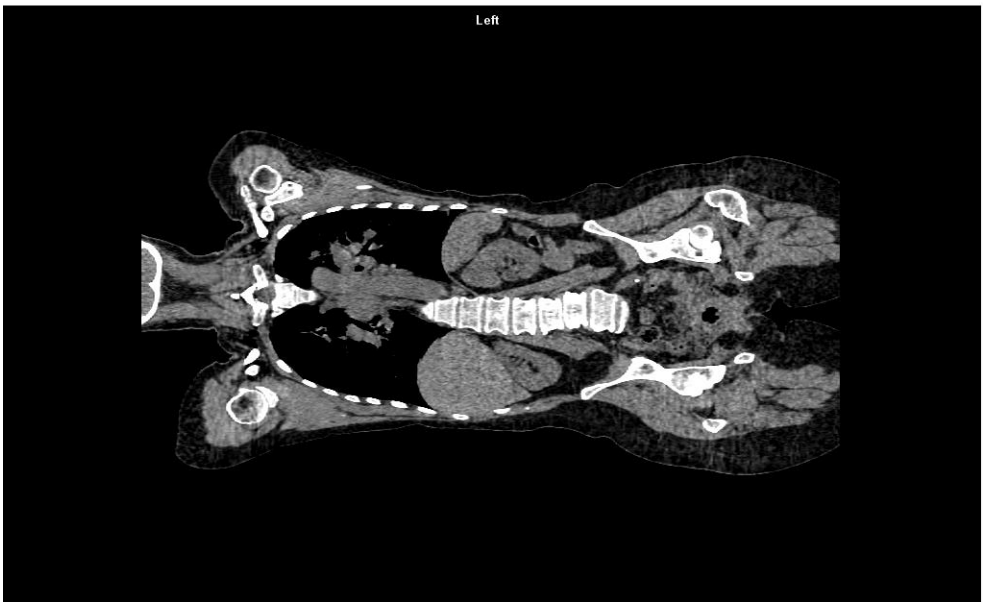
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CONTRAST ENHANCED CT (CECT)

Reserved for

- measurement of nodal size for trials
- radiation planning
- distinguishing bowel from nodes or assessing compression/thrombosis of central/mediastinal vessels if required at staging

CONTRAST ENHANCED CT (CECT)

In practice many patients have separate ceCT before PET-CT.

If not and ceCT is required at staging, it should ideally be combined with PET-CT at a single visit.

Full dose ceCT involves additional radiation, which should be considered when deciding which examination(s) to perform.

CONTRAST ENHANCED CT (CECT)

To avoid measurement errors in FDG in reference sites (e.g. liver) for accurate quantitation, EANM and SNM suggest the following sequence for PET-CT during one visit:

1. low dose CT scan with normal breathing
2. PET scan
3. full dose diagnostic ceCT with repositioning of arms and breath-hold)

BONE MARROW ASSESSMENT

Focal FDG uptake in HL and aggressive NHL is sensitive for BM involvement

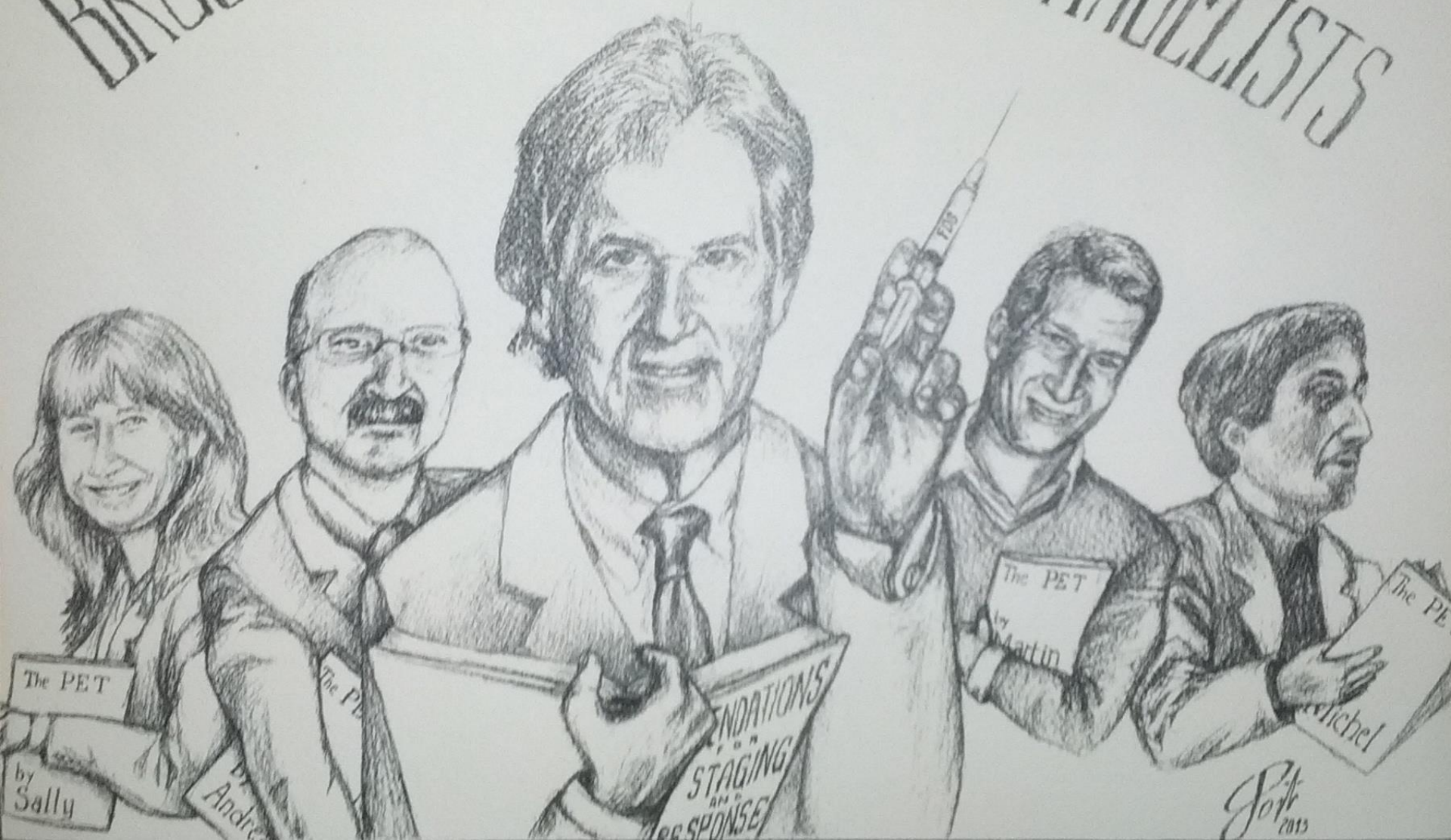
Bone marrow biopsy is no longer indicated for HL

PET may also obviate the need for biopsy in DLBCL unless discordant histology is considered important for management

(as a negative PET does not rule out small cells in the marrow)

Bone marrow biopsy is required for other lymphomas with IHC and flow cytometry

BRUCE AND HIS FOUR EVANGELISTS



RECOMMENDATIONS: RESPONSE ASSESSMENT

The ICML Imaging Working Group

RECOMMENDATIONS: RESPONSE ASSESSMENT PET-BASED EVALUATION

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PET-CT

For FDG-avid lymphomas:

PET-CT is recommended for response assessment using 5-Point Scale (5-PS)

PET-CT is standard of care for remission assessment

If mid therapy imaging is performed, PET-CT is superior to CT

Recent and ongoing trials evaluate the role of PET response adapted therapy

Meantime it is not recommended to change treatment based solely on PET-CT unless there is clear evidence of progression

Most data relate to HL,DLBCL& high tumor burden FL

CONTRAST ENHANCED CT

Contrast enhanced CT is reserved for :

low or variably FDG avid lymphomas

where PET is not available

for evaluation of new agents in multiply relapsed disease

(where data are lacking for PET and where disease control is more relevant than assessment of cure)

TIMING OF PET-CT SCANS

Should be:

as long as possible after the last chemotherapy administration for interim scans

6-8 weeks post chemotherapy at end of treatment ideally (but a minimum of 3 weeks)

≥ 3 months after radiotherapy

5 POINT SCALE (DEAUVILLE CRITERIA)

1. no uptake
2. uptake ≤ mediastinum
3. uptake > mediastinum but ≤ liver
4. moderately increased uptake compared to liver
5. markedly increased uptake compared to liver and/or new lesions

** markedly increased uptake is taken to be uptake > 2-3 times the SUV max in normal liver

RESPONSE ACCORDING TO 5-PS

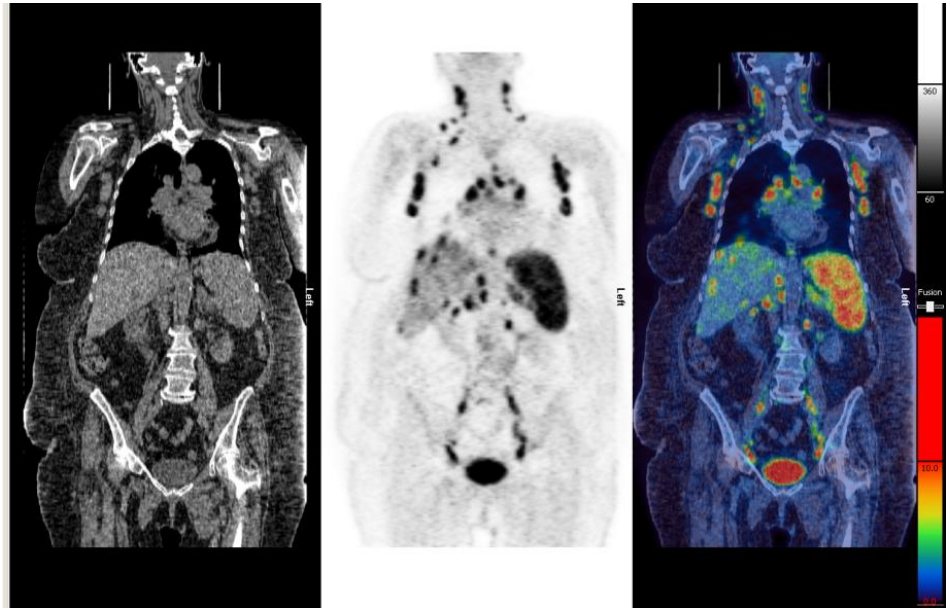
Score 1, 2 is Complete Metabolic Response (CMR)

Score 3 is also CMR with standard treatment

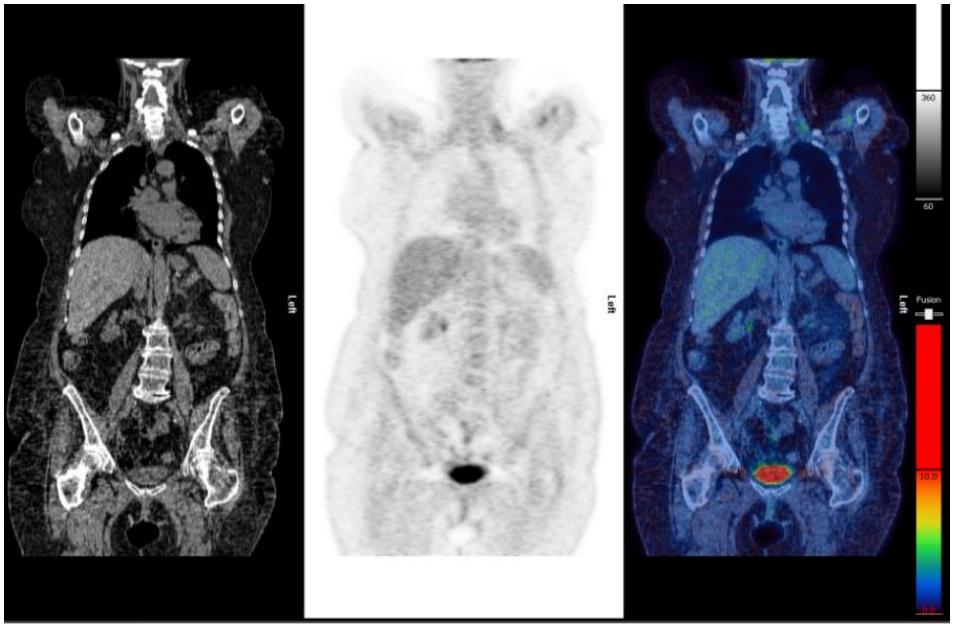
But in response-adapted trials exploring de-escalation, score 3 may be deemed inadequate response to avoid under-treatment

Interpretation of score 3 depends on timing of assessment, clinical context & treatment.

Baseline



Response



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CMR

RESPONSE ACCORDING TO 5-PS

Score 4, 5 with reduced uptake from baseline is partial metabolic response (PMR)

At interim this suggests responding disease

At end of treatment this indicates residual disease

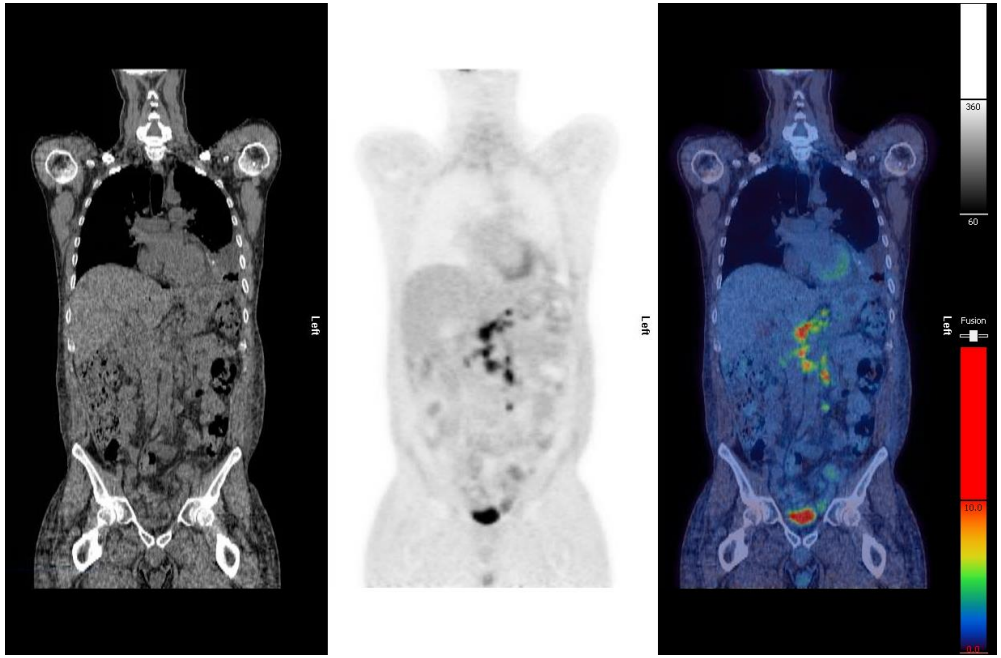
Score 4, 5 with no change in uptake from baseline means no metabolic response (NMR)

Score 4, 5 with an increase in uptake from baseline &/or new lesions is progressive metabolic disease (PMD)

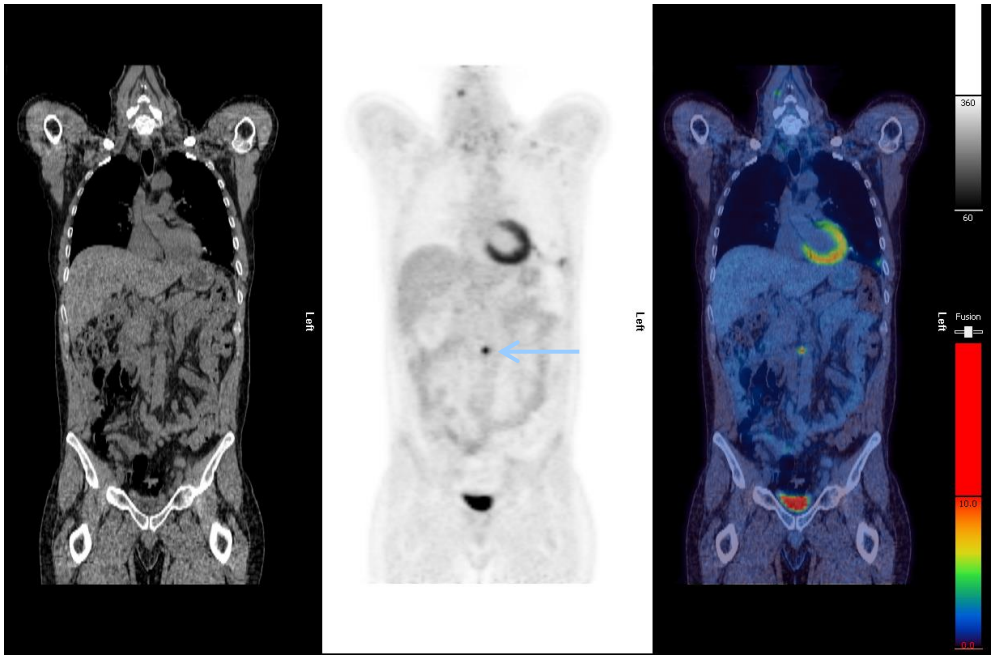
At interim and end of treatment NMR and PMD indicates treatment failure

Deauville score 5 with both metabolic and anatomical regression

Baseline



Response interim



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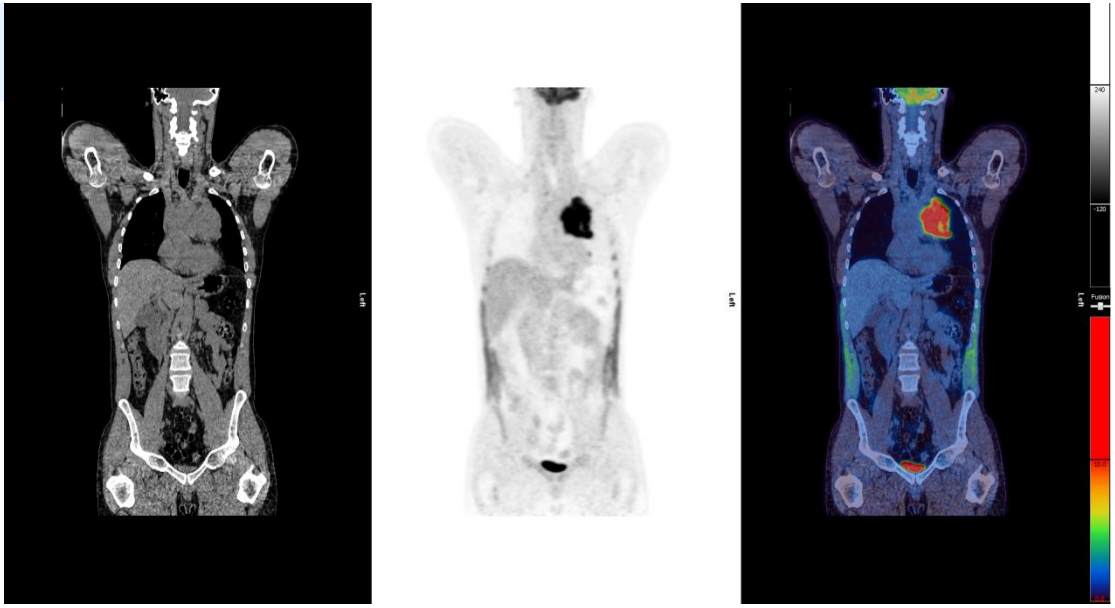
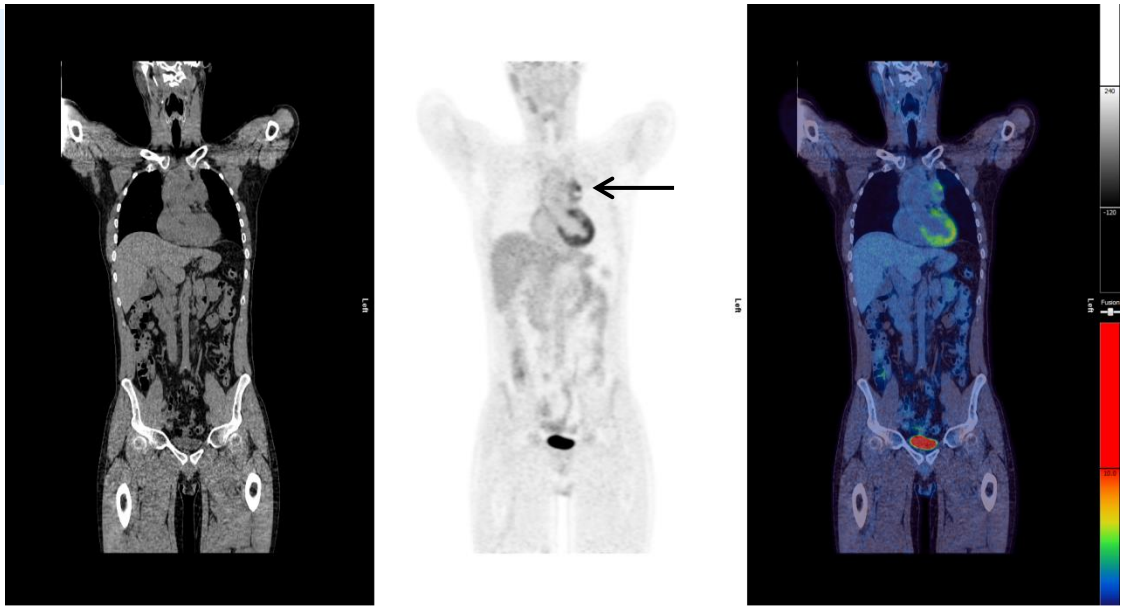
PMR

Deauville score 4 with both metabolic and anatomical regression

Baseline



Response interim



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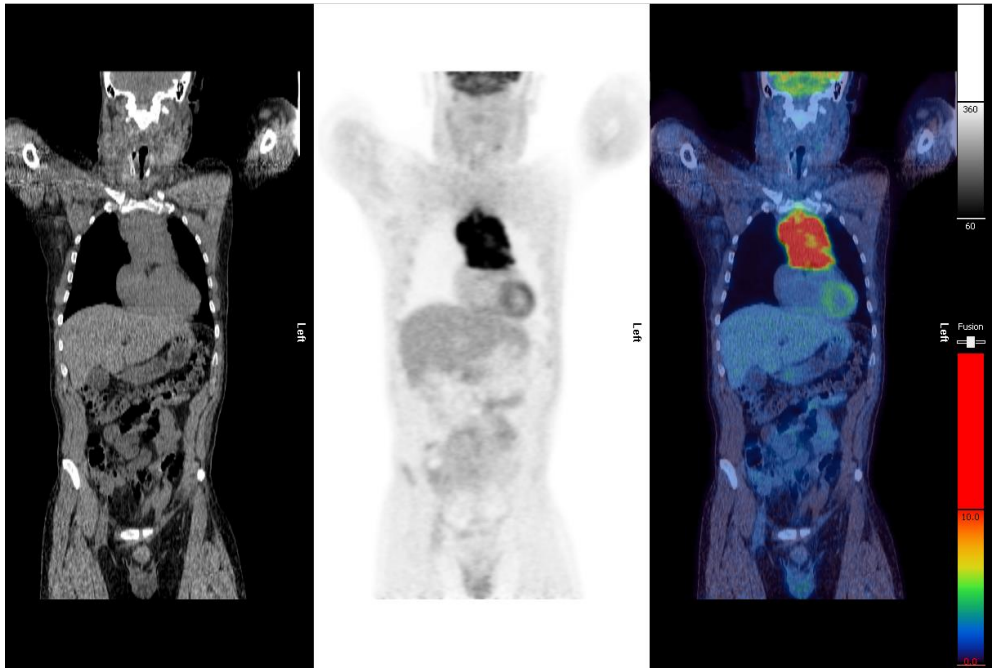
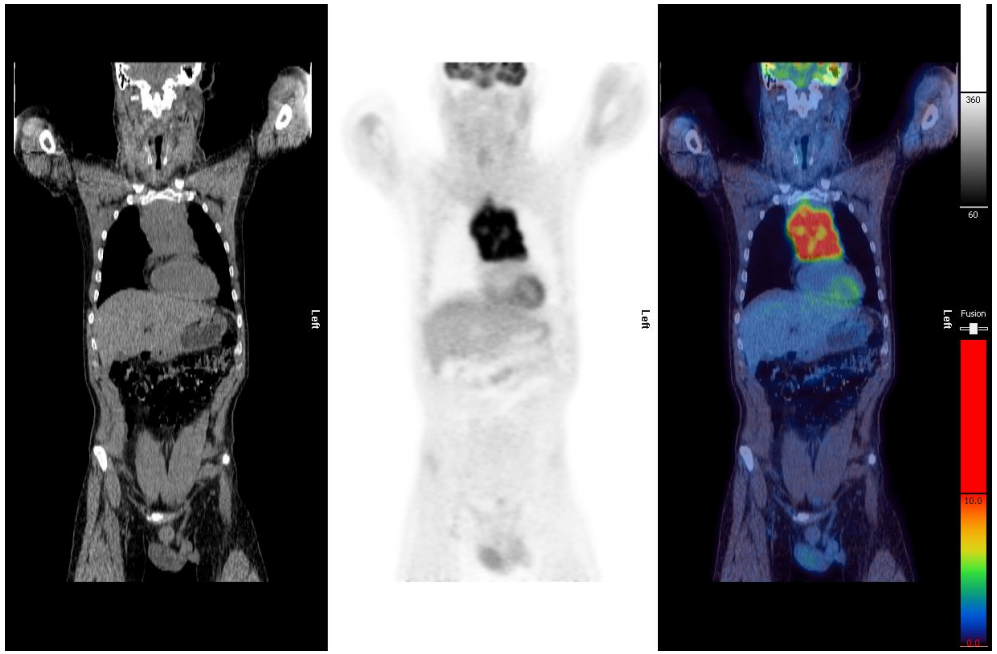
PMR

Deauville score 5 with no regression and no change in FDG uptake

Baseline



Response



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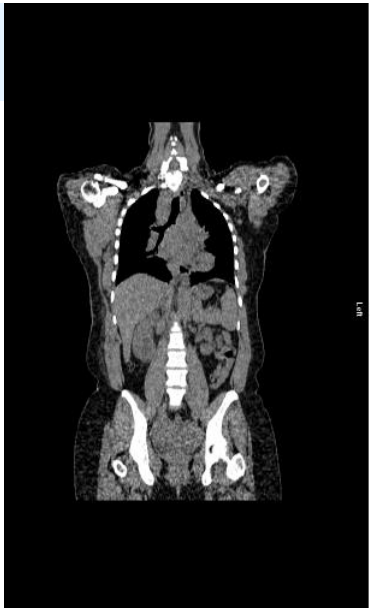
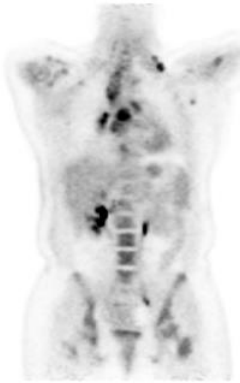
NMR

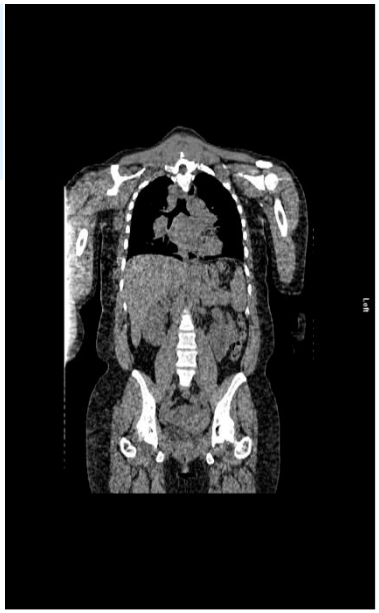
Deauville score 5 and new site in the right axilla

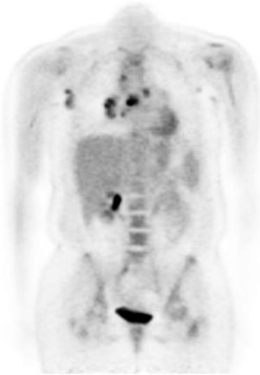
Baseline

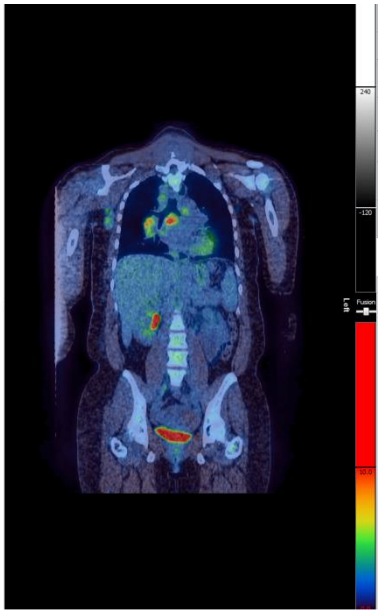




Interim Post 2







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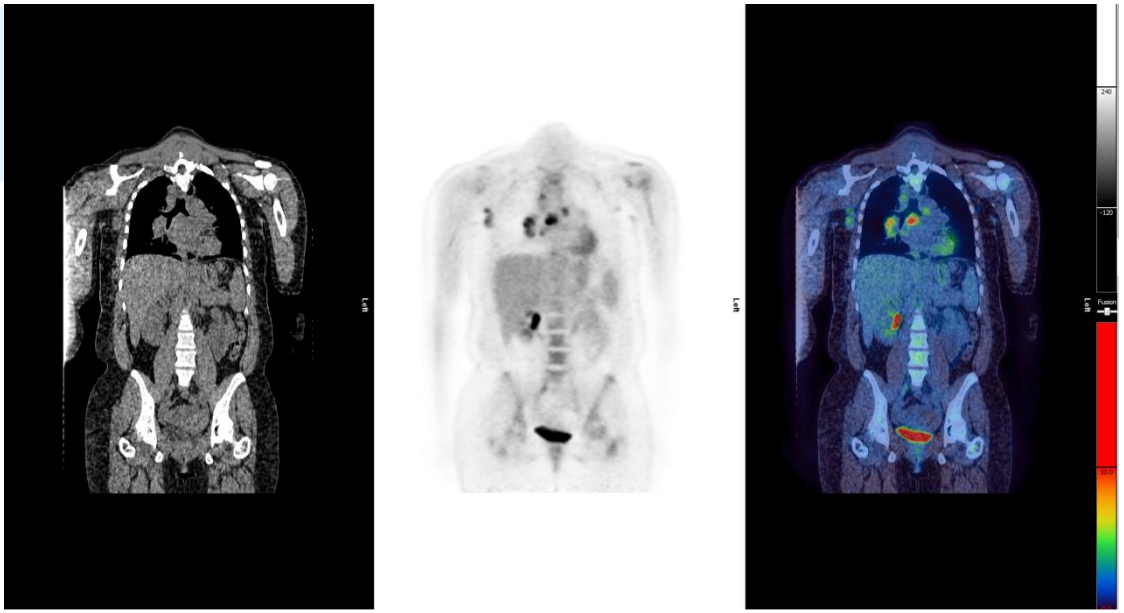
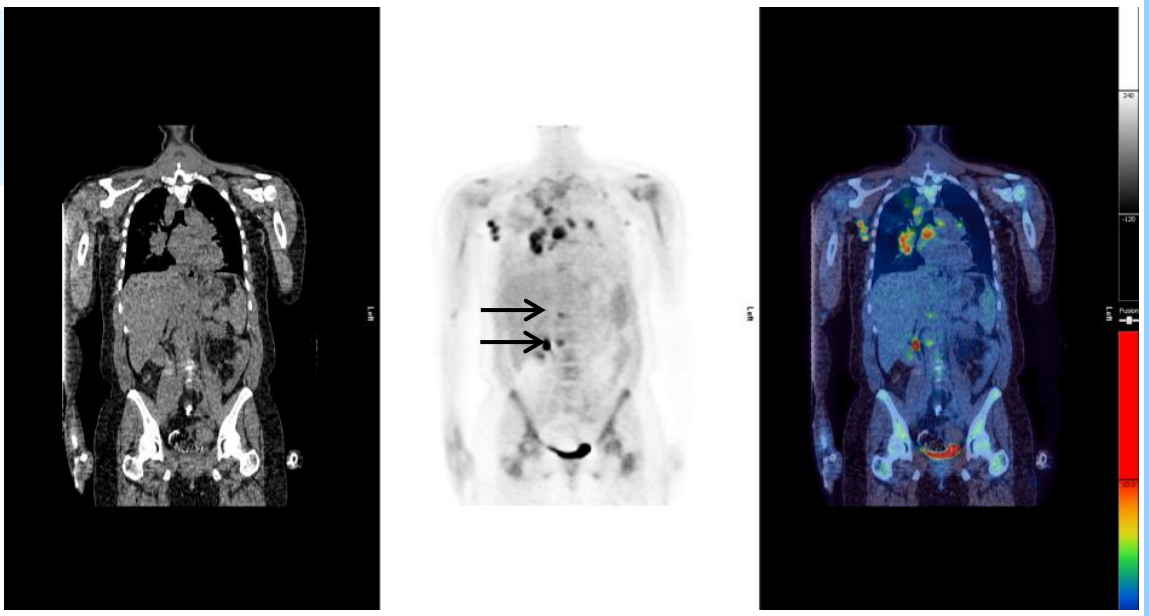
PMD ?

PMD confirmed after additional therapy

Interim Post 2



Interim Post 3



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PMD confirmed

CATEGORY	PET – CT based metabolic response
CMR	**Score 1,2,3*** in nodal or extranodal sites with or without a residual mass using 5-PS
PMR	**Score 4 or 5, with reduced uptake** compared with baseline and residual mass(es) of any size. *At interim* , these findings suggest responding disease *At end of treatment* these findings indicate residual disease Bone marrow: Residual marrow uptake > normal marrow but reduced compared with baseline (diffuse changes from chemotherapy allowed). If there are persistent focal changes in marrow with a nodal response, consideration should be given to MRI, biopsy or interval scan.
NMR	**Score 4 or 5 with no significant change in uptake** from baseline *At interim or end of treatment*
PMD	**Score 4 or 5 with an increase in uptake** from baseline and /or New FDG-avid foci consistent with lymphoma *At interim or end of treatment*

* **Score 3 in many patients indicates a good prognosis with standard treatment. However in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as inadequate response to avoid under-treatment**

RESIDUAL MASSES

Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered

or an interval scan where clinical likelihood of disease is low to decide on treatment (or not)

Residual size mass and location should be recorded in PET-CT reports where possible

as significance of the size of masses is unclear but may be complementary to metabolic information and data should be collected prospectively in clinical trials

QUANTITATIVE METHODS FOR RESPONSE ASSESSMENT

Quantitative methods may improve on visual assessment e.g. delta SUV in DLBCL

Requires standardised methods to be applied for PET-CT for image acquisition and analysis

These are also desirable in routine clinical practice

Quantitative assessment including ΔSUV, MTV & TLG require further validation in clinical trials

PET-CT ROLE IN ASCT

PET-CT is prognostic in refractory & relapsed HL & DLBCL after salvage chemotherapy prior to HD chemotherapy & ASCT

PET-CT could be used :
to select patients for HD chemotherapy & ASCT
to identify poor prognosis patients
as a surrogate endpoint to test novel therapies to current re-induction regimes

RECOMMENDATIONS: RESPONSE ASSESSMENT CT-BASED EVALUATION

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CHANGES TO CT RESPONSE FROM 2007

- If a confluent mass splits into discrete nodes when disease is responding, the perpendicular diameters of the nodes should be summed and the combined PPD compared with the PPD of the initial mass
- If nodes later grow the nadir of each node is used to determine progression (or not)
- If target nodes become a confluent mass when disease is progressing, the diameters of those target nodes should be added and the combined PPD compared with the PPD of the subsequent mass
- Splenic enlargement defined as >13cm
- In relapsed disease, CT criteria for PD can be based on increase in a single lesion. SPD eliminated for PD.
- Agents associated with flare reactions may require biopsy or repeat assessment > 2 weeks to determine if there is PD

CATEGORY	CT based anatomical response
CR	**Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi** No extralymphatic sites of disease. Any organ enlargement must regress to normal. Bone marrow - normal by morphology; if indeterminate, IHC -ve
PR	**50% decrease in SPD** of up to 6 target measureable nodes and extranodal sites. No increase in size of non measured lesions. Spleen must have regressed by >50% in length beyond normal
SD	**< 50% decrease from baseline in SPD** of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
PD (at least one)	PPD Progression: An individual node must be abnormal with: LDi > 1.5 cm AND **Increase by ≥ 50% from PPD nadir** AND An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm If splenomegaly present, splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g. a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, spleen must increase ≥ 2 cm from baseline New or recurrent splenomegaly **New or clear progression of pre-existing non-measured lesions** Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis if less than 1.0 cm in any axis, its presence must be unequivocal and attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma New or recurrent bone marrow involvement

FOLLOW UP

Clinical judgement, history & examination are cornerstones of FU

FU is determined by histology, if patient is within a trial (or not) & clinical setting

Frequency in curable lymphoma (eg HL, DLBCL) ↓ over time with ↓ likelihood of relapse

Frequency of FU in other lymphoma (eg FL, MCL) ↑ over time as ↑ likelihood of recurrence

Surveillance scans should be discouraged

FP rate > 20% for surveillance PET leads to unnecessary investigations, radiation , biopsies, cost and anxiety

SUMMARY OF IMAGING RECOMMENDATIONS

- PET-CT used for routine staging of FDG-avid lymphomas
- Patients with HL and many with DLBCL can be spared BMB PET-CT is recommended for interim assessment (if imaging is clinically indicated) and for remission assessment
- The 5-PS is recommended for reporting response, and metabolic response replaces anatomical response in FDG-avid lymphomas
- Quantitative imaging parameters for assessing initial disease burden & response should be explored as prognosticators
- Standardisation of PET-CT methods is mandatory for quantitative analysis and desirable for best clinical practice

6th International Workshop on PET in Lymphoma
Palais de l'Europe, Menton (France), September 20-21, 2016