

# ICML imaging guidelines & the Lugano Classification

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# ICML IMAGING GUIDELINES & THE LUGANO CLASSIFICATION

Two consensus documents in press  
To update 2007 IHP imaging &  
response criteria in lymphoma  
For use in clinical practice and late  
phase trials

Barrington SF et al JCO in press  
Cheson BD et al JCO in press

# RECOMMENDATIONS: STAGING

# 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



# 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

To avoid measurement errors in FDG in reference sites Eg liver, for accurate quantitation, EANM, SNM, RSNA suggest the following sequence for PET-CT during 1 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

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

# BULK

Is prognostic in some lymphomas

Largest tumour diameter should therefore be recorded at staging whenever possible on CT in HL and NHL \*

Measurements of total tumour volume should be explored as potential prognosticators with PET and CT

\* *Term X need no longer be used*

RECOMMENDATIONS:  
RESPONSE  
ASSESSMENT

# 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

Trials are currently evaluating 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

# CT

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)  
 $\geq 3$  months after radiotherapy

# 5 POINT SCALE (DEAUVILLE CRITERIA)

1. no uptake
2. uptake  $\leq$  mediastinum
3. uptake  $>$  mediastinum but  $\leq$  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 probably 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.

# HIGH PHYSIOLOGICAL FDG UPTAKE

can occur in some sites...

e.g. Waldeyers ring , gut, bone marrow after chemotherapy or GCSF treatment with 'physiologic' uptake > normal liver

In this case, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue

# 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

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	<p>Score 4 or 5, with reduced uptake compared with baseline and residual mass(es) of any size.</p> <p><i>At interim</i> , these findings suggest responding disease</p> <p><i>At end of treatment</i> these findings indicate residual disease</p> <p>Bone marrow: Residual marrow uptake &gt; 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.</p>
NMR	Score 4 or 5 with no significant change in uptake from baseline <i>At interim or end of treatment</i>
PMD	Score 4 or 5 with an increase in uptake from baseline and /or New FDG-avid foci consistent with lymphoma <i>At interim or end of treatment</i>

**\* 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

These are also desirable in routine clinical practice

Quantitative assessment including  $\Delta$ SUV, 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

# 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  $>13\text{cm}$
- 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
<b>CR</b>	<p>Target nodes/nodal masses must regress to <math>\leq 1.5</math> cm in LDi            No extralymphatic sites of disease. Any organ enlargement must regress to normal. Bone marrow - normal by morphology; if indeterminate, IHC -ve</p>
<b>PR</b>	<p>50% decrease in SPD of up to 6 target measurable nodes and extranodal sites.            No increase in size of non measured lesions.            Spleen must have regressed by <math>&gt;50\%</math> in length beyond normal</p>
<b>SD</b>	<p><math>&lt; 50\%</math> decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met</p>
<b>PD (at least one)</b>	<p><u>PPD Progression: An individual node must be abnormal with:</u>            LDi <math>&gt; 1.5</math> cm AND Increase by <math>\geq 50\%</math> from PPD nadir AND An increase in LDi or SDi from nadir 0.5 cm for lesions <math>\leq 2</math> cm 1.0 cm for lesions <math>&gt; 2</math> cm            If splenomegaly present, splenic length must increase by <math>&gt; 50\%</math> of the extent of its prior increase beyond baseline (e.g. a 15 cm spleen must increase to <math>&gt;16</math> cm). If no prior splenomegaly, spleen must increase <math>\geq 2</math> 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 <math>&gt; 1.5</math> cm in any axis            A new extranodal site <math>&gt; 1.0</math> 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</p>

# 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 should be used for routine staging of FDG-avid lymphomas

Patients with HL and many with DLBCL can be spared BMB  
PET-CT is recommended for mid-treatment assessment in place of CT, if imaging is clinically indicated and for remission assessment

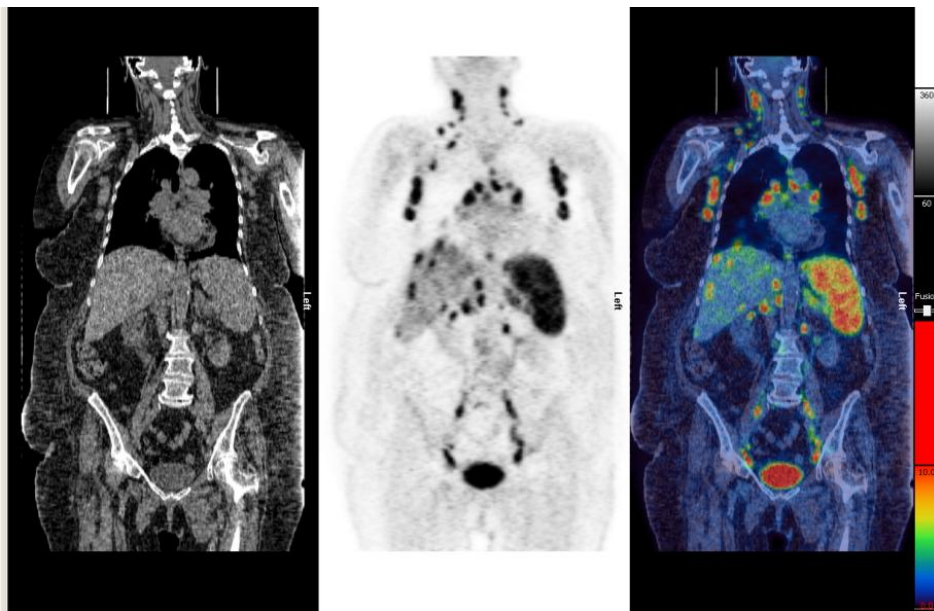
The 5-PS is recommended for reporting response

Quantitative imaging parameters for assessing initial disease burden & response should be explored as prognosticators

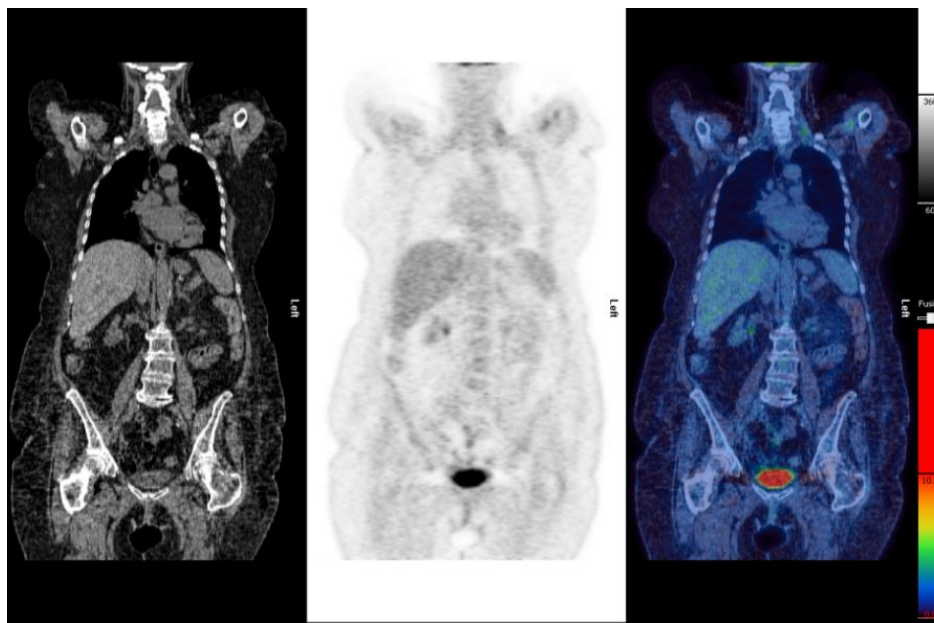
Standardisation of PET-CT methods is mandatory for quantitative analysis and desirable for best clinical practice

# IMAGE EXAMPLES

Baseline

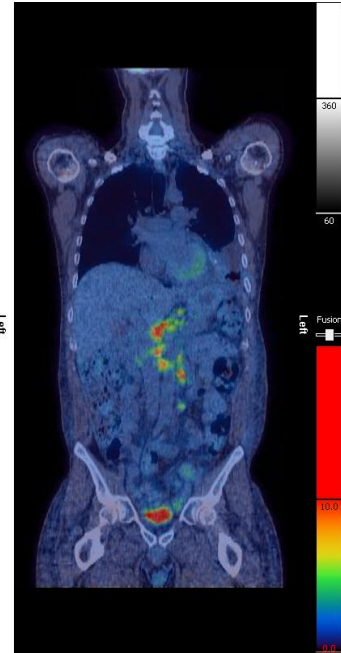


Response

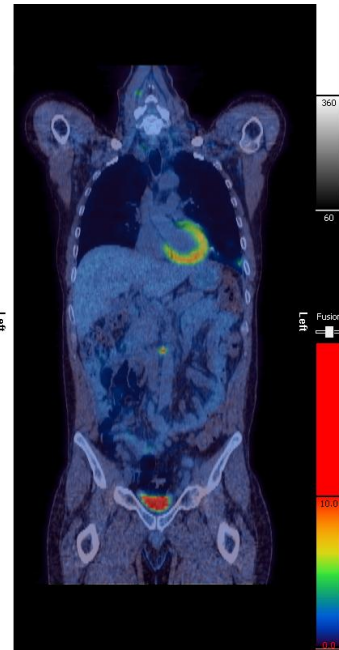
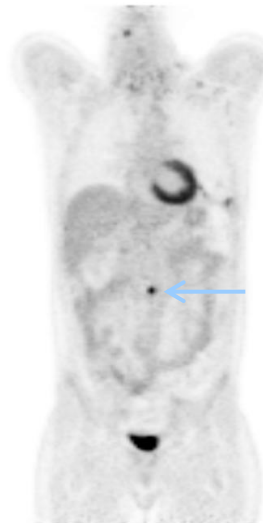


CMR

Baseline

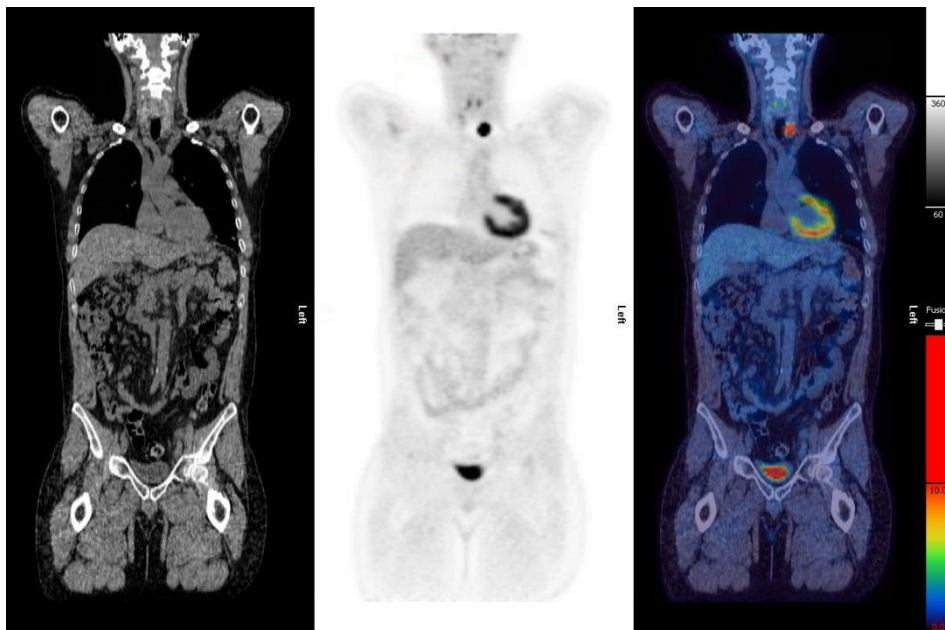


Response interim



PMR

Response  
End



CMR



Baseline



Response interim



PMR



Interim

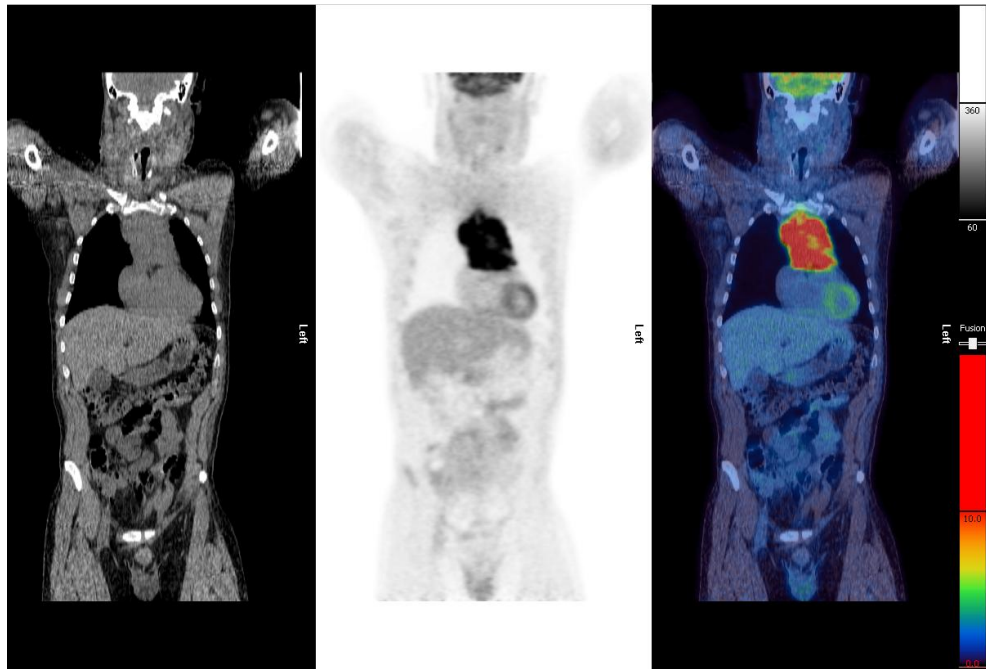


Response  
End

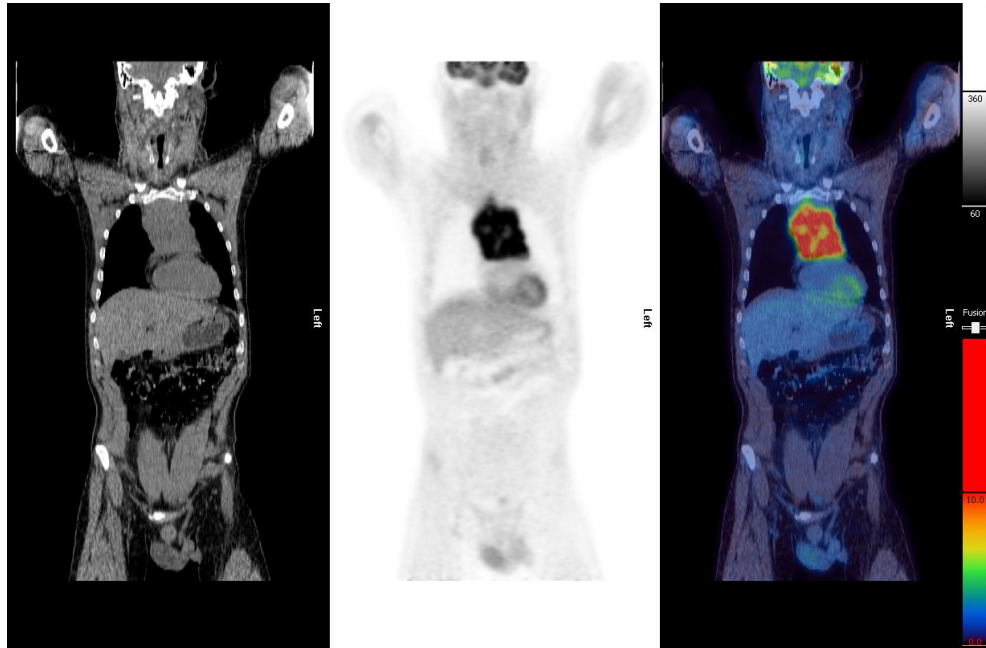


PMR=  
residual  
metabolic  
disease

Baseline

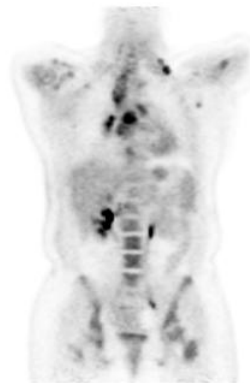


Response

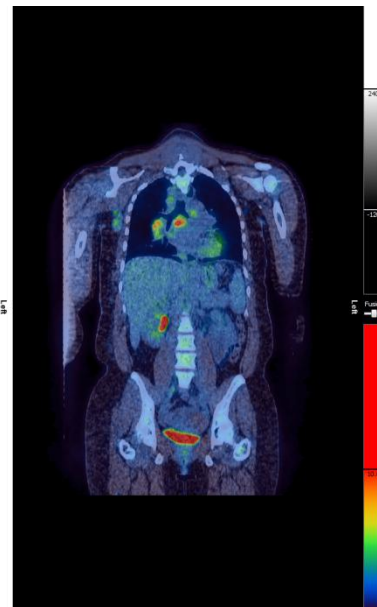


NMR

Baseline

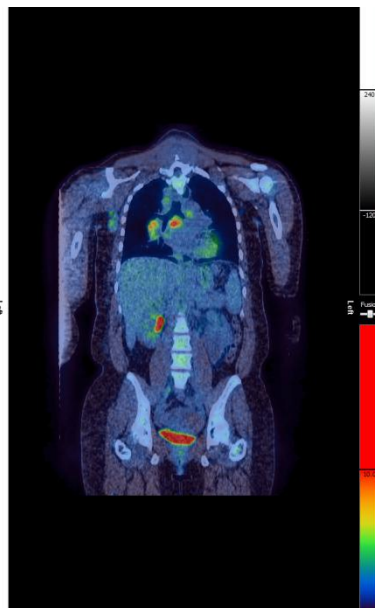


Interim  
Post 2

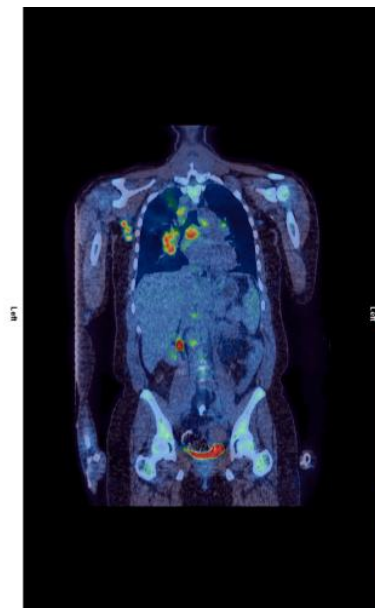


PMD ?

Interim  
Post 2



Interim  
Post 3



PMD  
confirmed