ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

THE LUGANO CLASSIFICATION

RECOMMENDATIONS FOR HODGKIN'S AND NON-HODGKIN'S LYMPHOMA: STAGING, RESPONSE ASSESSMENT AND FOLLOW UP

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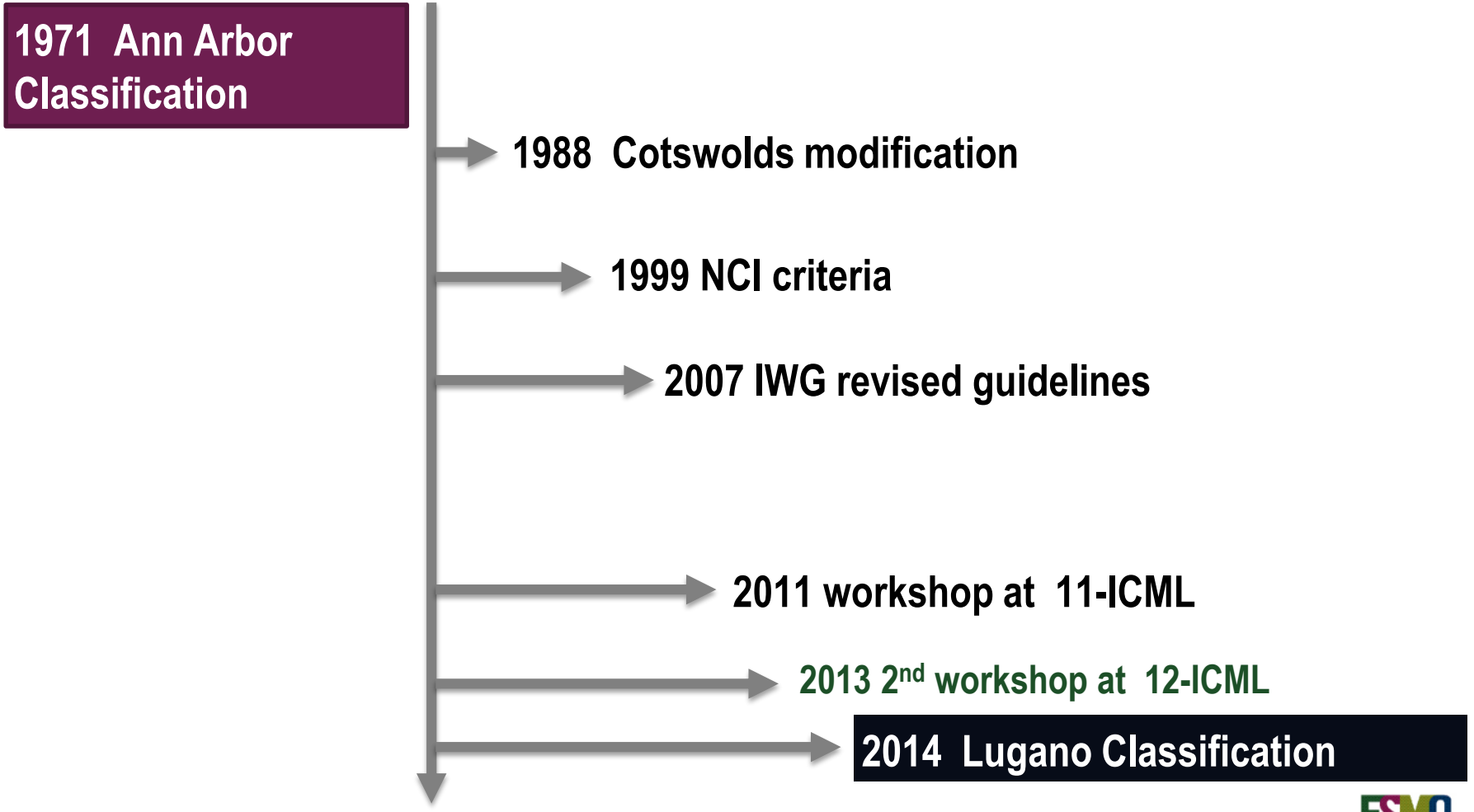
RECOMMENDATIONS: INITIAL EVALUATION

BACKGROUND


1971 Ann Arbor Classification
1988 Cotswolds modification
1999 NCI criteria
2007 IWG revised guidelines
2011 workshop at 11-ICML
2013 2nd workshop at 12-ICML
2014 Lugano Classification

11-ICML & 12-ICML WORKSHOPS

- Recommendations for initial evaluation, and response assessment of HL and NHL
- To update 2007 IHP criteria
- For use in clinical practice and late phase trials
- Two consensus paper in JCO 2014

SF Barrington
NG Mikhaeel
L Kostakoglu
M Meignan
M Hutchings
S Müeller
LH Schwartz
E Zucca
RI Fisher
J Trotman
OS Hoekstra
RJ Hicks
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A Biggi
BD Cheson

BD Cheson
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SF Barrington
F Cavalli
LH Schwartz
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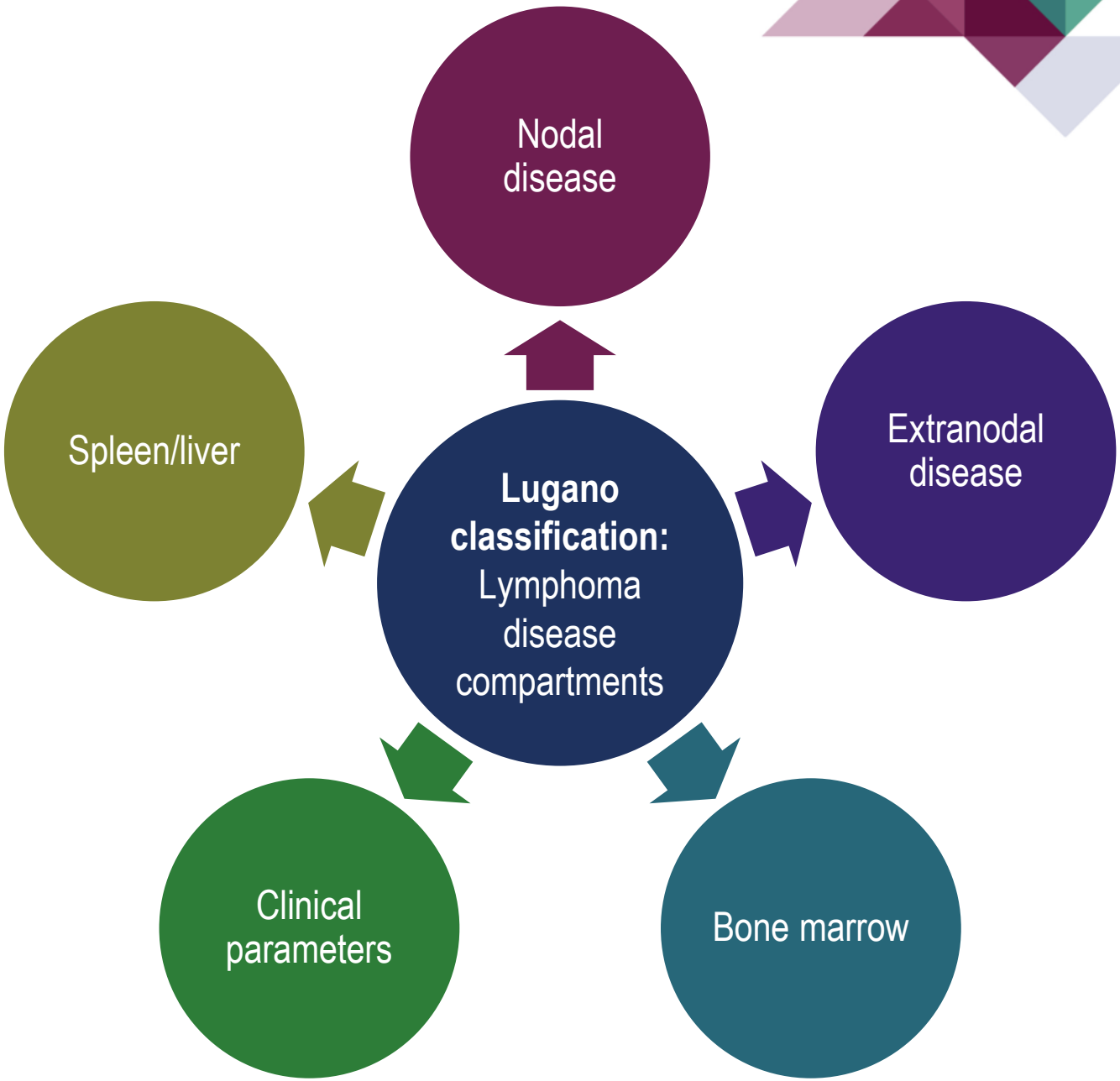
TA Lister

Barrington SF, *et al.* JCO 2014;32(27):3048-58 - Cheson BD, *et al.* JCO 2014;32(27):3059-68

OVERARCHING GOALS OF THE REVISION:

Lugano Classification 2014

- Universally applicable
- Improve lymphoma patient evaluation
- Eliminate ambiguity
- Facilitate the comparison of patients and results amongst studies
- Simplify the evaluation of new therapies by regulatory agencies


Nodal disease
Extranodal disease
Bone marrow
Clinical parameters
Spleen/liver
Lugano classification: Lymphoma disease compartments

WHAT'S NEW IN THE LUGANO CLASSIFICATION?

- **FDG-PET-CT**
  - Standard staging for FDG-avid lymphomas
  - Response assessment in FDG-avid subtypes using the 5-point scale
- **Progressive disease evaluation**
  - PPD progression of single site defines progression. SPD eliminated for progression
- **Spleen evaluation**
  - Quantified: >13 cm is enlarged on CT
- **Modification of the Ann Arbor Classification**
- **Bone marrow biopsy**
  - No longer indicated for the routine staging of HL and most DLBCL
- **Scan frequency**
  - Routine surveillance scans are discouraged

WHAT'S THE LUGANO CLASSIFICATION DEALING WITH?

- **Initial evaluation**
  - Diagnosis
  - Patient evaluation
  - Anatomic stage
- **Staging criteria revision**
  - Imaging
  - Tumour bulk
  - Spleen liver and bone marrow involvement
- **Prognostic groups**
- **Assessment of response**
- **Follow up and surveillance**

INITIAL DIAGNOSIS

- Fine-needle aspirate is inadequate for initial diagnosis
- Excisional biopsy is recommended
- Core-needle biopsy may suffice when excision not feasible

CRITERIA FOR INVOLVEMENT OF SITE

Tissue site	Clinical	Type	Test	Positive finding
Lymph nodes	Palpable	FDG-avid	PET-CT	Increased FDG uptake
		Non-avid	CT	Unexplained node enlargement
Spleen	Palpable	FDG-avid	PET-CT	Diffuse uptake, solitary mass, miliary lesions, nodules
		Non-avid	CT	>13 cm in vertical length, mass, nodules
Liver	Palpable	FDG-avid	PET-CT	Diffuse uptake, mass, nodules
		Non-avid	CT scan	Mass, nodules

CRITERIA FOR INVOLVEMENT OF SITE

Tissue site	Clinical	Type	Test	Positive finding
Lymph nodes	Palpable	FDG-avid	PET-CT	Increased FDG uptake
		Non-avid	CT	Unexplained node enlargement
Spleen	**Organomegaly is formally defined by CT** **Splenomegaly is quantified >13 cm**			
Liver				

CRITERIA FOR EXTRANODAL SITES

Tissue site	Clinical	Type	Test	Positive finding
Central nervous system	Signs, symptoms		CT scan	Mass lesion(s)
			MRI	Leptomeningeal infiltration, mass lesions
			CSF assessment	Cytology, flow cytometry
Other (e.g., skin, lung, gastrointestinal tract, bone, bone marrow)	Site-dependent		PET-CT, Biopsy	Lymphoma involvement

REVISED STAGING SYSTEM FOR PRIMARY NODAL LYMPHOMAS

Stage	Involvement	Extranodal status (E)
Limited		
Stage I	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited, contiguous extranodal involvement
Stage II bulky	II as above with bulky disease	N/A

Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.
Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Cheson BD, *et al*. JCO 2014;32(27):3059-68

REVISED STAGING SYSTEM FOR PRIMARY NODAL LYMPHOMAS

Stage	Involvement	Extranodal status (E)
Advanced		
Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	N/A
Stage IV	Additional non-contiguous extranodal involvement	N/A

Cheson BD, *et al.* JCO 2014

ABNORMAL/SUSPECTED DISEASE SITES

Abnormal Nodal Site

LDi >1.5 cm

Abnormal Extranodal Site

Present and consistent with lymphoma

Enlarged Liver

As judged by radiological interpretation on CT

Enlarged Spleen

>13 cm in vertical length (cranial to caudal)

IMAGING EVALUATION

- PET-CT is the standard for FDG-avid lymphomas
- CT is indicated for nonavid histologies
- CT based evaluation is preferred for
  - Histologies with low or variable FDG avidity
  - Regions of the world where PET-CT is unavailable.
- In absence of PET, mass that has decreased in size but persists is a PR
  - Need biopsy documenting absence of lymphoma to upgrade to CR
  - CRu (complete remission unconfirmed) is not a response category in the Lugano classification

FDG AVIDITY ACCORDING TO WHO CLASSIFICATION

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)	100
Burkitt (24)	100
Anaplastic large T-cell lymphoma (37)	94 -100
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

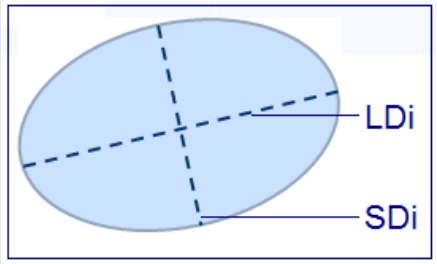
Modified from Weiler-Sagie M, *et al.* J Nucl Med.2010;51(1):25-30

FDG-AVID, NODAL LYMPHOMAS

- All histologies, except
  - Chronic lymphocytic leukaemia/small lymphocytic lymphoma
  - Lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia,
  - Mycosis fungoides,
  - Marginal zone lymphomas

- Unless there is a suspicion of aggressive transformation

DISEASE EVALUATION

Measurable nodal site	Measurable extranodal disease site	Non-measurable disease sites
LDi >1.5 cm	**LDi >1.0 cm**	**All other disease sites:** ♦ Nodal ♦ Extranodal ♦ Assessable disease
Up to 6 measurable nodal/extranodal sites		
♦ Largest target nodes, nodal masses or other lymphomatous lesions ♦ Measurable extranodal disease ♦ Measurable in two diameters (LDi and SDi) ♦ Represent different body regions/overall disease burden ♦ Include mediastinal and retroperitoneal disease, if involved		**Examples:** skin, GI, bone, spleen, liver, kidneys, effusions 

CLINICAL EVALUATION

Systemic symptoms rarely direct treatment,
their recurrence may herald disease relapse

Lugano Classification:

The presence of residual symptoms in the absence of detectable disease by imaging does not preclude the designation CR

RECOMMENDATIONS: STAGING

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)

It rarely alters management, and can be reserved for:

- Measurement of nodal size for trials
- Radiation planning
- Distinguishing bowel from nodes
- Assessing compression/thrombosis of central/mediastinal vessels

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

SPLEEN AND LIVER EVALUATION

Evaluate spleen and liver by PET-CT

Spleen	Liver
♦ Use single measurement which correlates well with volume ♦ Most studies use 10-12 cm for vertical length (cranial to caudal) ♦ **Lugano recommendation: Splenomegaly >13 cm**	♦ Liver size by physical examination or CT scan not a reliable measure of hepatic involvement by lymphoma ♦ **Diffusely increased or focal uptake, with or without focal or disseminated nodules support liver involvement**

BONE MARROW EVALUATION

- **HL**
  - If PET-CT is performed, bone marrow biopsy no longer indicated for HL
- **DLBCL**
  - Biopsy if the PET is negative and identifying a discordant histology is important for patient management
- **Other subtypes**
  - ~2.5 cm unilateral bone marrow biopsy is recommended, along with immunohistochemistry and flow cytometry at screening/baseline
- **If involved at baseline**
  - Must be normal for CR
  - No evidence of FDG-avid disease in marrow for CMR

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

(FDG-avid lymphomas)

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

5-POINT SCALE
(DEAUVILLE CRITERIA)

Score	18-FDG uptake
1	No uptake
2	≤ Mediastinal blood pool
3	> Mediastinum and ≤ liver
4	Moderately > liver at any site
5	Markedly[1] > liver at any site and/or new sites of disease
X	New areas of uptake unlikely to be related to lymphoma

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

FDG-PET EVALUATION

Score 1 or 2	♦ Considered to represent complete metabolic response (CMR) at interim and end of treatment
Score 3	♦ 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	♦ 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	♦ Represents residual metabolic disease even if the uptake has reduced from baseline

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

FDG-PET EVALUATION

2007 Guidelines	Lugano Classification
♦ PET scans based on visual interpretation and intended for end of treatment evaluation ♦ Used mediastinal blood pool as the comparator	♦ Use the 5-point scale (MBP and liver) ♦ Interim PET-CT to assess early treatment response ♦ end of treatment PET-CT to establish remission status.

CT *VS*. PET: CMR/CR

	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

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

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

RESIDUAL MASSES

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

  → interval scan can be considered where clinical likelihood of disease is low

- 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

PET-CT AND NEW THERAPIES

- Immunomodulatory agents may be associated with tumour flare or pseudo-progressions
- Biopsy or repeat assessment (> 2 weeks) are needed to determine if there is true PD

QUANTITATIVE METHODS FOR RESPONSE ASSESSMENT

- PET-CT quantitative methods (e.g. ΔSUV, MTV & TLG) may improve on visual assessment

  → require further validation in clinical trials

  → should be explored as prognosticators

- Standardisation of PET-CT assessment is mandatory for quantitative analysis of imaging parameters

  → and desirable for best clinical practice

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

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 (e.g. HL, DLBCL) ↓ over time with ↓ likelihood of relapse
- Frequency of FU in **other** lymphoma (e.g. 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

TIMING OF IMAGING EVALUATION

- **Limit the number of scans to which a patient is exposed**
- Clinical trials with time-dependent endpoints (e.g., PFS, EFS):
  - CT scan is determined by the study-designated interval
  - Indolent lymphomas, asymptomatic intra-abdominal or retroperitoneal disease progression may be a concern in patients with residual disease in those areas following therapy
- Published studies fail to support routine surveillance scans, and they are discouraged
- Follow-up scans should be prompted by clinical indications

SUMMARY OF IMAGING RECOMMENDATIONS

NEW since 2007

- PET-CT for staging of FDG-avid lymphomas
- HL and many DLBCL patients can be spared BMB
- PET-CT is recommended for mid-treatment assessment and for remission assessment
- The Deauville 5-PS is recommended for reporting response
- PD can be defined on a single site
- Splenomegaly is defined (13 cm on CT scan)
- Routine surveillance scans are discouraged

Thank you!

REFERENCES

- Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

- Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, Schwartz LH, Zucca E, Fisher RI, Trotman J, Hoekstra OS, Hicks RJ, O'Doherty MJ, Hustinx R, Biggi A, Cheson BD. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014 Sep 20;32(27):3048-58.