INTERNATIONAL IMAGING GUIDELINES IN LYMPHOMA

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Concord Cancer Centre
Concord Hospital
University of Sydney

ALG PI of PET in PRIMA, RATHL, REMARC, RePLY, & IRiC studies
## DISCLOSURES

<table>
<thead>
<tr>
<th>Role</th>
<th>Details</th>
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<tbody>
<tr>
<td>Research Support/P.I.</td>
<td>Celgene funding to ALLG for NHL26 RePLy Study</td>
</tr>
<tr>
<td></td>
<td>Janssen funding to ALLG for NHL29 IRiC study</td>
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<tr>
<td>Consultant</td>
<td>Janssen - Unremunerated</td>
</tr>
<tr>
<td>Speakers Bureau</td>
<td>Janssen, Roche - Unremunerated</td>
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<tr>
<td>Scientific Advisory Board</td>
<td>Roche, Takeda, Janssen, Abbvie, all unremunerated</td>
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ICML imaging guidelines & the Lugano Classification


Abstract

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

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

See accompanying article on page 3048
Two consensus documents: Journal of Clinical Oncology, 2014.
- To update 2007 IHP imaging & response criteria in lymphoma.
- For use both in clinical practice and late phase clinical trials.

Edited slides provided by Sally Barrington for the ICML Imaging Working Group

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

A word of caution re. pre-treatment SUV as a measure of histologic transformation in Follicular Lymphoma

- Early small, single institutional studies, patient and scan heterogeneity
- Poor correlation of $SUV_{\text{max}}$ with histologic grade
  - Wohrer 2006
  - Karam 2006
- Wide range in SUVmax, no correlation with FLIPI or outcome (R-CHOP):
  - Med 9.5 (3.3 - 35.6) PET Folliculaire, Dupuis 2013
  - Med 10 (4 - 35) PRIMA, Tychy Pinel 2014
  - Med 13 (1.5 - 42) MDACC, Ahmed 2015
- No clear cut-off defines transformation
  - $SUV_{\text{max}} < 12$ = indolent disease, $SUV > 17$ usually = transformation
    - Bodet-Milin 2008
- Only 20/40 with biopsy confirmed HT presented with an SUV max >13
  - Noy 2009
- Biopsy the most FDG-avid lesion to detect transformation? Low PPV. Often logistically difficult in abdomen. Relevant if using R-CHOP? Risk exposing too many low risk patients to unnecessary biopsies.
<table>
<thead>
<tr>
<th>Histology (patient numbers)</th>
<th>% FDG-avid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma (489)</td>
<td>97 - 100</td>
</tr>
<tr>
<td>Diffuse Large B cell lymphoma (446)</td>
<td>97 - 100</td>
</tr>
<tr>
<td>Follicular lymphoma (622)</td>
<td>91 - 100</td>
</tr>
<tr>
<td>Mantle cell (83) Burkitt (24) MZL nodal (14) LL (6)</td>
<td>100</td>
</tr>
<tr>
<td>Anaplastic large T-cell lymphoma (37)</td>
<td>94 -100 (27% of cutaneous sites)</td>
</tr>
<tr>
<td>Natural killer/T-cell lymphoma (80)</td>
<td>83 - 100</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma (31)</td>
<td>78 - 100</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma (93)</td>
<td>86 - 98</td>
</tr>
<tr>
<td>MALT (227)</td>
<td>54 - 81</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma (49)</td>
<td>47 - 83</td>
</tr>
<tr>
<td>Enteropathy type T-cell lymphoma (20)</td>
<td>67 - 100</td>
</tr>
<tr>
<td>MZL, splenic (13), unspecified (12)</td>
<td>53 - 67</td>
</tr>
<tr>
<td>Mycosis fungoides (24) and Sezary (8)</td>
<td>83 -100 (62% of cutaneous sites)</td>
</tr>
<tr>
<td>1° cutaneous anaplastic large T-cell (14)</td>
<td>40-60</td>
</tr>
</tbody>
</table>
PET-CT

Scans should be reported with visual assessment. Images scaled to a fixed SUV & colour table
- noting location of foci in nodal & extra-nodal sites
- distinguished from physiological uptake and other disease patterns (inflammation and infection) according to distribution and/or CT characteristics

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

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.

To avoid measurement errors in FDG in reference sites, e.g. liver, for accurate quantitation EANM, SNM, RSNA, suggest the following sequence 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.

Impact of iodine on attenuation correction.
Bias is small cf. variability in SUVmax, and mostly in reference organs: e.g. liver (5-10%), rather than in tumours themselves.

Can measure lesion sizes easily with later model PET/CT scans with Time of Flight scanners.

Prospective study: Itti et al 2012
237 PET/CT then 1hr later CECT exams in 163 patients:
- CECT had no clinical impact in 92% (219 cases)
- Positive impact in 3% (diagnosed DVT in 5, upstaging in 2)
- Debatable impact in 5%
  (documentation of PET-negative lesion in 8. No change in Mx)
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.

2.5cm unilateral bone marrow biopsy is required for other lymphomas with IHC and flow cytometry.

In Australia MBS reimbursement for

- Staging of I-IIA indolent NHL with consideration of curative radiotherapy
- Staging of untreated NHL and HL (excl iNHL)
- Assessment of response to first-line therapy NHL and HL (excl iNHL)
- Restaging of suspected recurrence (excl iNHL)
- Assessment of response to second line chemo when SCT is being considered (excl iNHL)
RECOMMENDATIONS: RESPONSE ASSESSMENT

The ICML Imaging Working Group
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 in DLBCL (French LYSA studies, Casasnovas. ALLG NHL21 study, Hertzberg ASH 2015)

Meanwhile, it is not recommended to change treatment based solely on PET-CT unless there is clear evidence of progression*, ... except in HL

*Any mid-therapy proposed change in management should be discussed in the MDT setting.
TIMING OF PET-CT SCANS

Should be:
- as long as possible after the last chemotherapy administration for interim scans
- Ideally 6-8 weeks post-chemotherapy at end of treatment (but a minimum of 3 weeks)
- ≥3 months after radiotherapy

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
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.

Figure 16:  

(a) Pretreatment FDG PET/CT image demonstrates a mesenteric and retroperitoneal mass with an SUV of 23.5 in an 81-year-old woman with diffuse large B cell lymphoma. 

(b) On interim FDG PET/CT scan, the residual mesenteric mass has reduced FDG uptake with an SUV of 5.6. Uptake with an SUV of 5.6 is moderately higher than liver uptake (SUV of 2.3 in this patient); therefore this would be scored as 4 on the five-point scale.
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

HIGH PHYSIOLOGICAL FDG UPTAKE

Can occur in some sites... e.g. Waldeyer’s ring, gut, bone marrow after chemotherapy or g-CSF use 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

Figure 15:  (a) Pretreatment FDG PET/CT image in a 61-year-old woman with diffuse large B cell lymphoma documents retroperitoneal adenopathy with SUV of 16.4 and uptake in the anterior abdominal wall secondary to previous surgery. (b) Interim scan shows resolved retroperitoneal adenopathy with no FDG uptake, consistent with a score of 1 on the five-point scale, as well as improving postsurgical inflammation in the anterior abdominal wall.
### PET-CT based metabolic response

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>Description</th>
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<tbody>
<tr>
<td>CMR</td>
<td>Score 1,2,3* in nodal or extranodal sites with or without a residual mass using 5-PS</td>
</tr>
<tr>
<td>PMR</td>
<td>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 &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.</td>
</tr>
<tr>
<td>NMR</td>
<td>Score 4 or 5 with no significant change in uptake from baseline. At interim or end of treatment.</td>
</tr>
<tr>
<td>PMD</td>
<td>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.</td>
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</table>

* 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.

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Biopsy of residual metabolically active tissue is recommended if salvage treatment is considered or an interval scan performed 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.

Quantitative methods may improve on visual assessment e.g. ΔSUV in DLBCL. Requires proper calibration and standardised methods and matching conditions to be applied for serial image acquisition and analysis. These are also desirable in routine clinical practice.

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

High PPV of postinduction PET in HL and DLBCL has driven assessment of interim PET in clinical trials...
INTERIM PET in HL

- 2 ABVD then iPET: 2yr PFS in PET+ 20% cf. 95% in iPET-
  Gallamini, JCO 2007

Now good data to support changing from ABVD to escBEACOPP if iPET+ in AS HL.

- Phase 2 study:
  If change to Esc BEACOPP for 154 iPET+ patients ↑2yr PFS to 65%.
  Gallamini, Br J Haem 2011
Response-adapted Therapy Based on Interim FDG-PET Scans in Advanced Hodgkin Lymphoma

First Analysis of the Safety of De-escalation and Efficacy of Escalation in the International RATHL Study


ICML Lugano 2015, Manuscript under review
Stage II (adverse), III, IV, IPS 0-7, Over 18, PS 0-3

PET 1 (Staging)

2 cycles ABVD
Full dose, on schedule

PET 2

PET 2 +ve

4 cycles BEACOPP-14
or 3 eBEACOPP

PET 3

PET 3 +ve

RT or salvage regimen

PET 3 -ve

2 cycles BEACOPP-14 or 1 eBEACOPP
No RT

PET 2 -ve

Randomise

4 cycles ABVD
4 cycles AVD

Follow-up (no RT)

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Results for patients with positive PET2

3 year PFS
BEACOPP-14: 66% (55 – 75)
eBEACOPP: 71% (59 – 80)

3 year OS
BEACOPP-14: 90% (80 – 95)
eBEACOPP: 83% (71 – 90)
Primary Endpoint: PFS for PET2-negative randomized, eligible patients  
(Median follow up 36 months)

Intention to treat analysis:

- HR 1.11 (0.79 – 1.54), p = 0.53
- 3yr PFS, ABVD 85% (95% CI: 82 - 89)
- 3yr PFS, AVD 84% (95% CI: 82 - 88)

Per protocol analysis:

- HR 1.09 (0.78 – 1.53), p = 0.59
- 3yr PFS, ABVD 85% (95% CI: 82 - 88)
- 3yr PFS, AVD 85% (95% CI: 81 - 88)

ABVD-AVD = 1.4% (-3.6 - +5.2)
Overall survival: PET2 negative patients

3 year OS%
ABVD 97 (95 – 98)
AVD 97 (95 – 99)
Postinduction and Interim PET in DLBCL

• Refining the definition of PET +/- every few years creates challenges with comparability and limited reproducibility of studies
PFS by International Workshop Criteria (IWC) and IWC PET in 54 patients treated with R-CHOP for DLBCL

Malik E. Juweid et al. JCO 2005;23:4652-4661

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Swiss Study in DLBCL
EFS by local PET assessment:
Lesion/s scored as positive when SUVmax was higher than SUVmax of the mediastinum

138 patients:
evaluated during & after 6 R-CHOP-14

A. iPET after 2 R-CHOP
B. iPET after 4 R-CHOP
C. ePET after 6 R-CHOP

EFS- 25 patients received RT or HD MTX prophylaxis defined as an event

Mamot et al. JCO 2015;33:2523-2529

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EFS by central review using the Deauville criteria (cutoff at 1-3 [negative] vs 4-5 points [positive]).

(A) iPET after 2 R-CHOP-14;  
(B) iPET after 4 cycles  
(C) End-of-treatment PET/CT.

Mamot et al. JCO 2015;33:2523-2529

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OS for PET/CT after 2 cycles of R-CHOP 14

A. Local assessment;
B. Central review using Deauville criteria
C. Post hoc $\Delta$SUV$_{\text{max}}$ evaluation with a cutoff of 66%

Mamot et al. JCO 2015;33:2523-2529
Early Treatment Intensification with R-ICE Chemotherapy and Zevalin-BEAM ASCT for Poor Prognosis Diffuse Large B-Cell Lymphoma as Identified by Interim PET/CT Performed After 4 Cycles of R-CHOP-14:

ALLG NHL21 Phase II Trial


Supported in part by: Roche Products Australia Pty Ltd Amgen Australia Pty Ltd, Bayer Pharmaceuticals Pty Ltd
DLBCL: L-I to H risk, LR + bulk (≥ 7.5 cm) Age ≤70; fit for HDT

R-CHOP-14 x 4

iPET/CT*

iPET-pos

R-ICE x 3

Zevalin-Beam HDT

iPET-neg

R-CHOP-14 x 2 + R x 2

Observation

*Delay C5 chemotherapy by 7 days: PET d17-d20 Assessed centrally, IHP criteria using MBP
PFS is equivalent: iPET- vs. iPET+

n=143: Median follow up: 35 m

\[ P = 0.32 \]
OS is equivalent: iPET- vs. iPET+

n=143: Median follow up: 35 m

\[ P = 0.11 \]

Number at risk

<table>
<thead>
<tr>
<th>PET positive</th>
<th>PET negative</th>
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<tbody>
<tr>
<td>42</td>
<td>101</td>
</tr>
</tbody>
</table>

Time since initial PET scan (months)
iPET+
Deauville Score 4 vs. 5

PFS

OS

Score 4

Score 5

Score 4

Score 5

PFS

OS

Number at risk
Deauville = 4 27 22 22 17 9 6
Deauville = 5 15 5 5 5 2 1

Number at risk
Deauville = 4 27 22 22 17 9 6
Deauville = 5 15 7 5 5 2 1

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Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies

Judith Trotman, Stefano Luminari, Sami Boussetta, Annibale Versari, Jehan Dupuis, Christelle Tychyj, Luigi Marcheselli, Alina Berriolo-Riedinger, Antonella Franceschetto, Anne Julian, Fabien Ricard, Luca Guerra, Corinne Haïoun, Irene Biasoli, Hervé Tilly, Massimo Federico, Gilles Salles, Michel Meignan

Summary
Background The value of 18F-fluorodeoxyglucose (FDG) PET-CT (PET) imaging in response assessment after first-line rituximab chemotherapy for follicular lymphoma has been documented. We analysed the application of the five-point Deauville scale (5PS; used to score FDG uptake on PET images) in a large cohort derived from three studies, to assess the correlation between post-induction PET status and survival in patients with follicular lymphoma.
Postinduction PET status:
3 blinded central reviewers applying 5PS
(246 patients)

68 (28%) PET+ with cut-off ≥3
(uptake > mediastinum)

41 (17%) PET+ with cut-off ≥4
(uptake moderately > liver)
Both PET cut-offs predictive of PFS

Score ≥3

Score ≥4

HR 3.9 (95% CI 2.5-5.9), p<.0001
Med PFS: 17 (11-31) vs. 74 mo (55-NR)

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Postinduction PET status (cut-off ≥4) and Overall Survival

HR 6.7, 95% CI 2.4-18.5, p=0.0002
Median OS: 79 months vs. NR
Conclusions

Independent review of 246 scans and median 4.6 years follow-up after first-line rituximab-chemotherapy for follicular lymphoma confirms:

• Postinduction PET-CT status is strongly predictive of survival:
  - 4yr PFS 23% vs. 67%
  - 4yr OS 87% vs. 97%

• Conventional CT assessment provides limited additional value

• PET-CT applying the 5PS (cut-off ≥4) should be the new gold standard for therapeutic response assessment in FL
Post-induction PET-CT status

Caveats:

• Insufficient data in context of Rituximab maintenance
• No data yet on patients receiving Bendamustine
  GALLIUM study: Obinutuzumab–chemo vs. Rituximab–chemo. Paired pre- & post-induction PETs in 600 FL patients with ~70% receiving Bendamustine chemotherapy in RCT. First results in 2016?
• No data yet for Rituximab - Lenalidomide RELEVANCE study
Postinduction PET-CT: a platform to study response-adapted therapy

- Achieving PET- status better reassures patients, esp. those otherwise in CRu/PR

- The inferior survival of patients remaining PET+ warrants study of PET-response adapted approaches
  - **FIL FOLL12** study of Zevalin consolidation
  - **ALLG NHL26: RePLy** study
    \( R^2 \) consolidation in patients remaining PET Positive after treatment of relapsed Follicular Lymphoma.
  
Rationale: excellent data for Lenalidomide + rituximab in relapsed FL.

Leonard JCO 2015

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In Australia MBS reimbursement for

- Staging of I-IIA indolent NHL with consideration of curative radiotherapy
- Staging of untreated NHL and HL (excl iNHL)
- Assessment of response to first-line therapy NHL and HL (excl iNHL)
- Restaging of suspected recurrence (excl iNHL)
- Assessment of response to second line chemo when SCT is being considered (excl iNHL)

Whole body FDG PET study for the initial staging of indolent non–Hodgkin’s lymphoma where clinical, pathological and imaging findings indicate that the stage is I or II A and the proposed management is definitive radiotherapy with curative intent. (R)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Fee</th>
<th>Benefit 1</th>
<th>Benefit 2</th>
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<tbody>
<tr>
<td>61616</td>
<td>Whole body FDG PET study for the initial staging of indolent non–Hodgkin’s lymphoma where clinical, pathological and imaging findings indicate that the stage is I or II A and the proposed management is definitive radiotherapy with curative intent. (R)</td>
<td>$953.00</td>
<td>75% = $714.75</td>
<td>85% = $874.60</td>
</tr>
<tr>
<td>61620</td>
<td>Whole body FDG PET study for the initial staging of newly diagnosed or previously untreated Hodgkin’s or non-Hodgkin’s lymphoma (excluding indolent non-Hodgkin’s lymphoma). (R)</td>
<td>$953.00</td>
<td>75% = $714.75</td>
<td>85% = $874.60</td>
</tr>
<tr>
<td>61622</td>
<td>Whole body FDG PET study to assess response to first line therapy either during treatment or within three months of completing definitive first line treatment for Hodgkin’s or non-Hodgkin’s lymphoma (excluding indolent non-Hodgkin’s lymphoma). (R)</td>
<td>$953.00</td>
<td>75% = $714.75</td>
<td>85% = $874.60</td>
</tr>
<tr>
<td>61628</td>
<td>Whole body FDG PET study for restaging following confirmation of recurrence of Hodgkin’s or non-Hodgkin’s lymphoma (excluding indolent non-Hodgkin’s lymphoma). (R)</td>
<td>$953.00</td>
<td>75% = $714.75</td>
<td>85% = $874.60</td>
</tr>
<tr>
<td>61632</td>
<td>Whole body FDG PET study to assess response to second-line chemotherapy when stem cell transplantation is being considered, for Hodgkin’s or non-Hodgkin’s lymphoma (excluding indolent non-Hodgkin’s lymphoma). (R)</td>
<td>$953.00</td>
<td>75% = $714.75</td>
<td>85% = $874.60</td>
</tr>
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</table>
FOLLOW UP

- Clinical judgement, history & examination are the 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.
  (q3/12 for 2 years, q6/12 for 3 years, then annually thereafter for late relapse and treatment related AEs)

SURVEILLANCE IMAGING

Surveillance scans should be discouraged.
Caveat: In the indolent lymphomas, asymptomatic intra-abdominal or retroperitoneal disease progression may be a concern in patients with residual disease in these areas after therapy.

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

Clinical Trials: CT scanning by study-designated interval - but attempts should be made to limit the number of scans to which a patient is exposed

PET-CT should be used to stage FDG-avid lymphomas. Patients with HL & 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

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
THE ONE SLIDE SUMMARY

PET-CT should be used to stage FDG-avid lymphomas. Patients with HL & 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

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PET-CT should be used to stage FDG-avid lymphomas. Patients with HL & 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.
Variable international access to…

- Excisional biopsies
- Quality anatomical pathology review
- PET-CT
  - Access limitations
    - Financial
    - Distance
- CT

- Documented MDT peer review of lymphoma imaging / care.
THANK-YOU!!

Refer patients to the ALLG IRiC Study:

Phase II Study of Ibrutinib, Rituximab and mini-CHOP therapy in truly elderly patients with newly diagnosed DLBCL

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