

FDG PET for therapy response assessment in lymphoma: Beyond Lugano Classification

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Assess lymphoma response to therapy : Pre-PET era

CAL ONCOLOGY

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Report of an International Workshop to Standardize Response Criteria for Non- Hodgkin's Lymphomas

Bruce D. Cheson, Sandra J. Horning, Bertr Coiffier, Margaret A. Shipp,

JOIOLOGY

Abstract

ABSTRACT: Standardized guidelines for response assessment are needed to ensure disease. Single-photon emission computed tomography **gallium scans are encouraged as a valuable adjunct to assessment of patients with large-cell NHL, but** such scans require appropriate expertise. Flow cytometric, cytogenetic, and molecular

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FDG avidity according to WHO classification

Table 2. FDG Avidity According to WHO Classification

Histology	No. of Patients	FDG Avid (%)
HL	489	97-100
DLBCL	446	97-100
FL	622	91-100
Mantle-cell lymphoma	83	100
Burkitt's lymphoma	24	100
Marginal zone lymphoma, nodal	14	100
Lymphoblastic lymphoma	6	100
Anaplastic large T-cell lymphoma	37	94-100*
NK/T-cell lymphoma	80	83-100
Angioimmunoblastic T-cell lymphoma	31	78-100
Peripheral T-cell lymphoma	93	86-98
MALT marginal zone lymphoma	227	54-81
Small lymphocytic lymphoma	49	47-83
Enteropathy-type T-cell lymphoma	20	67-100
Marginal zone lymphoma, splenic	13	53-67
Marginal zone lymphoma, unspecified	12	67
Mycosis fungoides	24	83-100
Sezary syndrome	8	100†
Primary cutaneous anaplastic large T-cell lymphoma	14	40-60
Lymphomatoid papulosis	2	50
Subcutaneous panniculitis-like T-cell lymphoma	7	71
Cutaneous B-cell lymphoma	2	0

NOTE. Data adapted,⁶⁴ with additional updates.^{18,20,24,65-67}
 Abbreviations: DLBCL, diffuse large B-cell lymphoma; FDG, [¹⁸F]fluorodeoxyglucose; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue; NK, natural killer.
 *Only 27% of cutaneous sites.
 †Only 62% of cutaneous sites.

§ S Barrington. J Clin Oncol 32:3048-3058

§ and

Weiler-Sagie M. (18)F-FDG avidity in lymphoma
 readdressed: A study of 766 patients. J Nucl Med 51:25-30,
 2010

PET era.....

q Numerous validation studies to define the prognostic value of PET/CT at baseline, interim or EOT

q Some published validation study series demonstrated good performance

§ Classical [Haoun C, Blood 2005;106(4):1376–81].

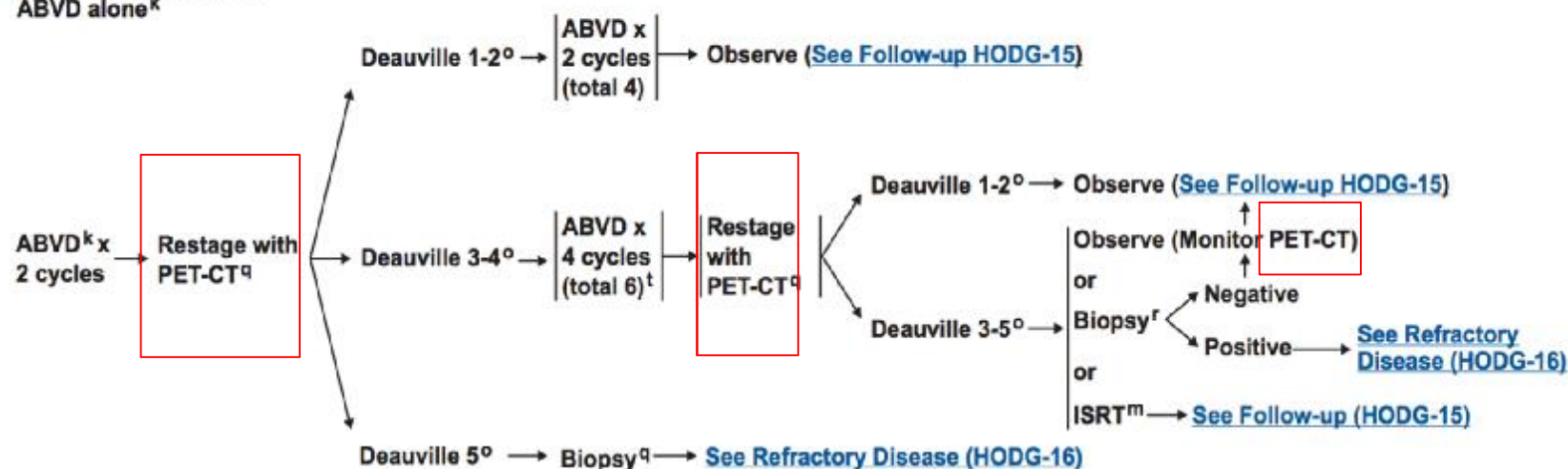
§ 90 patients with newly diagnosed aggressive lymphoma

§ At mid-induction, "early PET" was considered negative in 54 patients and positive in 36. After completion of induction, 83% of PET-negative patients achieved complete remission compared with only 58% of PET-positive patients. The 2-year estimates of EFS reached 82% and 43%, respectively ($P < .001$), and the 2-year estimates of OS reached 90% and 61%, respectively ($P = .006$).

q Therefore.....

PET/CT scan—modality of choice in staging and restaging lymphoma

CLINICAL PRESENTATION:
Classical Hodgkin lymphoma^f
Stage IA, IIA Favorable
(Continued from HODG-2)
PRIMARY TREATMENT^j
ABVD alone^k



International Harmonization Project Criteria

VOLUME 25 • NUMBER 5 • FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revised Response Criteria for Malignant Lymphoma

Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, Randy D. Gascoyne, Lena Specht, Sandra J. Horning,

VOLUME 25 • NUMBER 5 • FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Mottaghy, Markus Dietlein, Ali Guermazi,

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Key points in IHP criteria

- q EOT PET.
- q Mediastinal blood pool is the reference:
 - For residual mass > 2 cm: positive if >
 - For lesions < 2 cm: positive if any uptake > background
- q Category of CRu (unconfirmed) by CT is **eliminated**.

IHP criteria: Far from perfect

- q Using these criteria (MBP is really a quite low threshold in some patients) some studies have reported very high rates of false positivity of EOT PET in NHL with a PPV as low as 26%
- § [Moskowitz CH et al: J Clin Oncol 2010;28(11):1896–903].

Where is Lugano classification from?

Eur J Nucl Med Mol Imaging (2010) 37:1824–1833
DOI 10.1007/s00259-010-1490-5

ORIGINAL ARTICLE

Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma

Sally F. Barrington • Wendi Qian • Edward J. Somer • Antonella Franceschetto •

q 5 points scale using mediastinum and liver as reference proposed—[London Criteria](#).

§ Relatively less variation of mediastinal and liver FDG uptake during course of treatment, therefore ideal as reference organs.

FDG avidity of mediastinum and liver on sequential PET/CT scans in NKT cell lymphoma nasal type.
Xuexian Yan and Zoe Zhang
J Nucl Med May 1, 2016 vol. 57 no. supplement 2
1611

Conclusion: In NKT cell lymphoma nasal type, the FDG avidity of mediastinum and liver on sequential PET/CT scans over the treatment course is relatively stable and comparable.

q Excellent reproducibility of scoring tested in 50 patients -- 47 patient complete consensus over 4 centers

London Criteria -- 5PS

Adopted in Deauville, France, 2009 -- Deauville criteria

Eur J Nucl Med Mol Imaging (2010) 37:1824–1833

Score	PET/CT scan result
1	No uptake above background
2	Uptake \leq mediastinum
3	Uptake $>$ mediastinum but \leq liver
4	Uptake moderately increased compared to the liver at any site
5	Uptake markedly increased compared to the liver at any site
X	New areas of uptake unlikely to be related to lymphoma

Leukemia & Lymphoma, Aug 2009; 50(8): 1257–1260
Leukemia & Lymphoma, Dec 2010; 51(12): 2171–2180
Leukemia & Lymphoma, Oct 2012; 53(10): 1876–1881
Leukemia & Lymphoma, Jan 2014; 55(1): 31–37
Leukemia & Lymphoma, May 2015; 56(5): 1229–1232
Leukemia & Lymphoma, Oct 2016; 58(10): 2298–2303

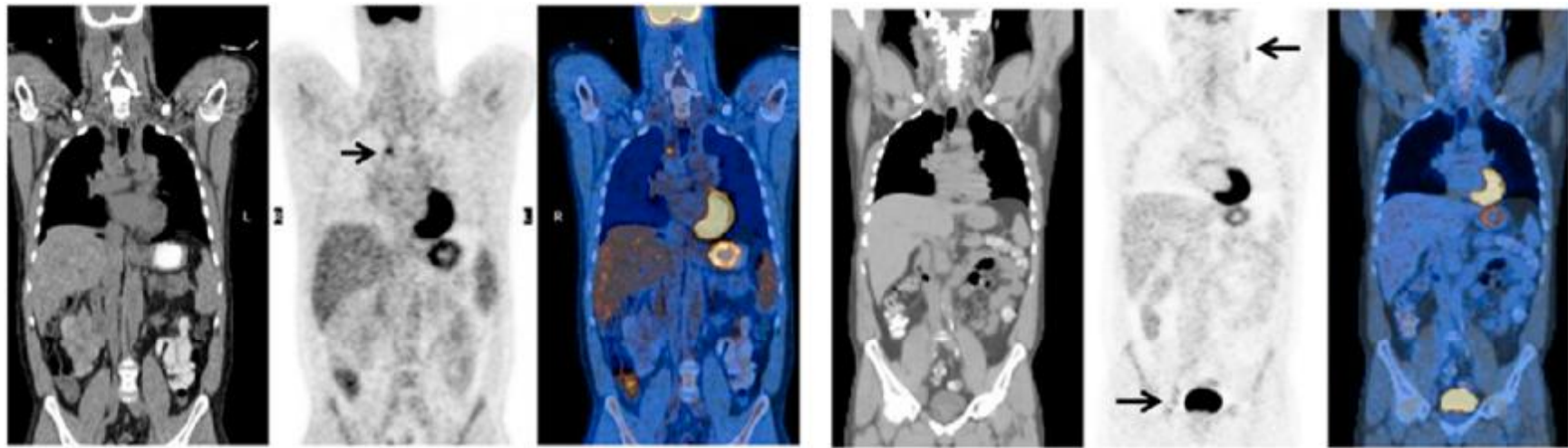


NCCN modification of Deauville criteria:

1 – 5a: previously known lesions

5b: appearance of new lesions likely to be due to lymphoma

Examples



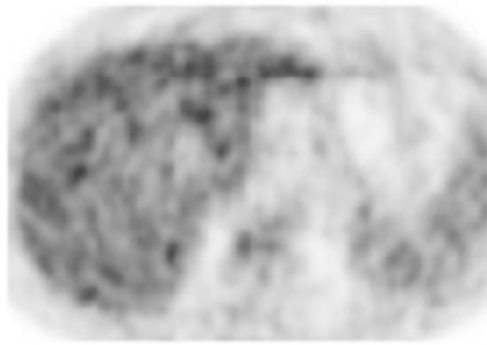
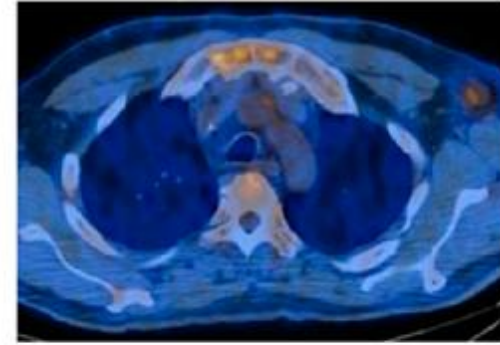
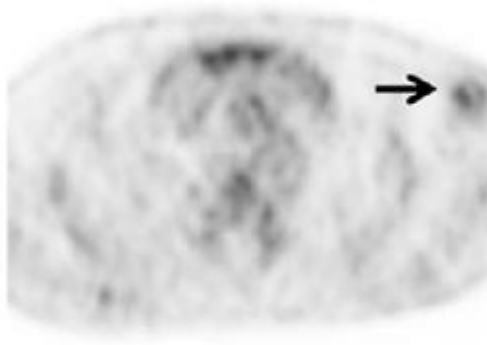
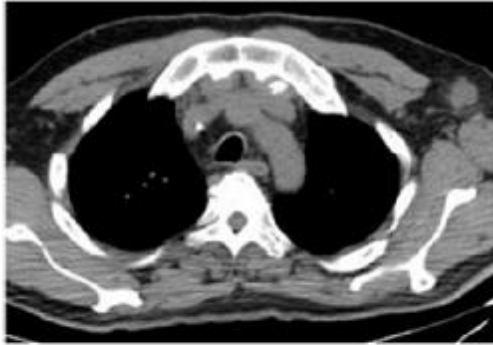
Score 4
Uptake > Liver

Positive by Deauville 5PS

Score 3
Uptake \leq Liver

Negative by Deauville 5PS

Kostakoglu, Gallamini, JNM 2013; 54: 1082-93



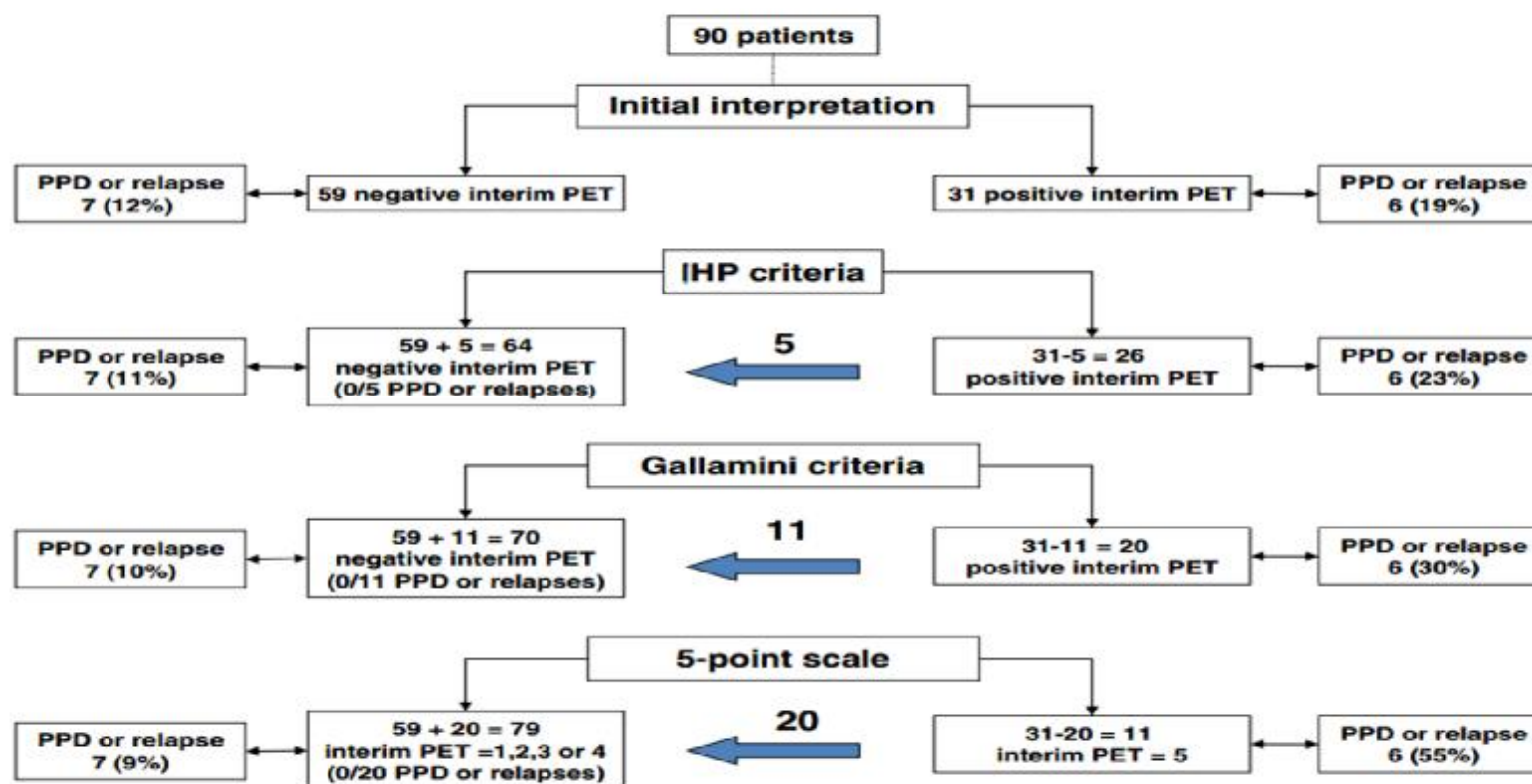
Uptake \leq Liver and $>$ MBP

Negative result by Deauville 5PS
Positive result by IHP criteria

Prognostic value of interim FDG PET/CT in Hodgkin's lymphoma patients treated with interim response-adapted strategy: comparison of International Harmonization Project (IHP), Gallamini and London criteria

Pierre-Yves Le Roux • Thomas Gastinne • Steven Le Gouill • Emmanuel Nowak •

Eur J Nucl Med Mol Imaging (2011) 38:1064–1071



PPD: Primary progressive disease.

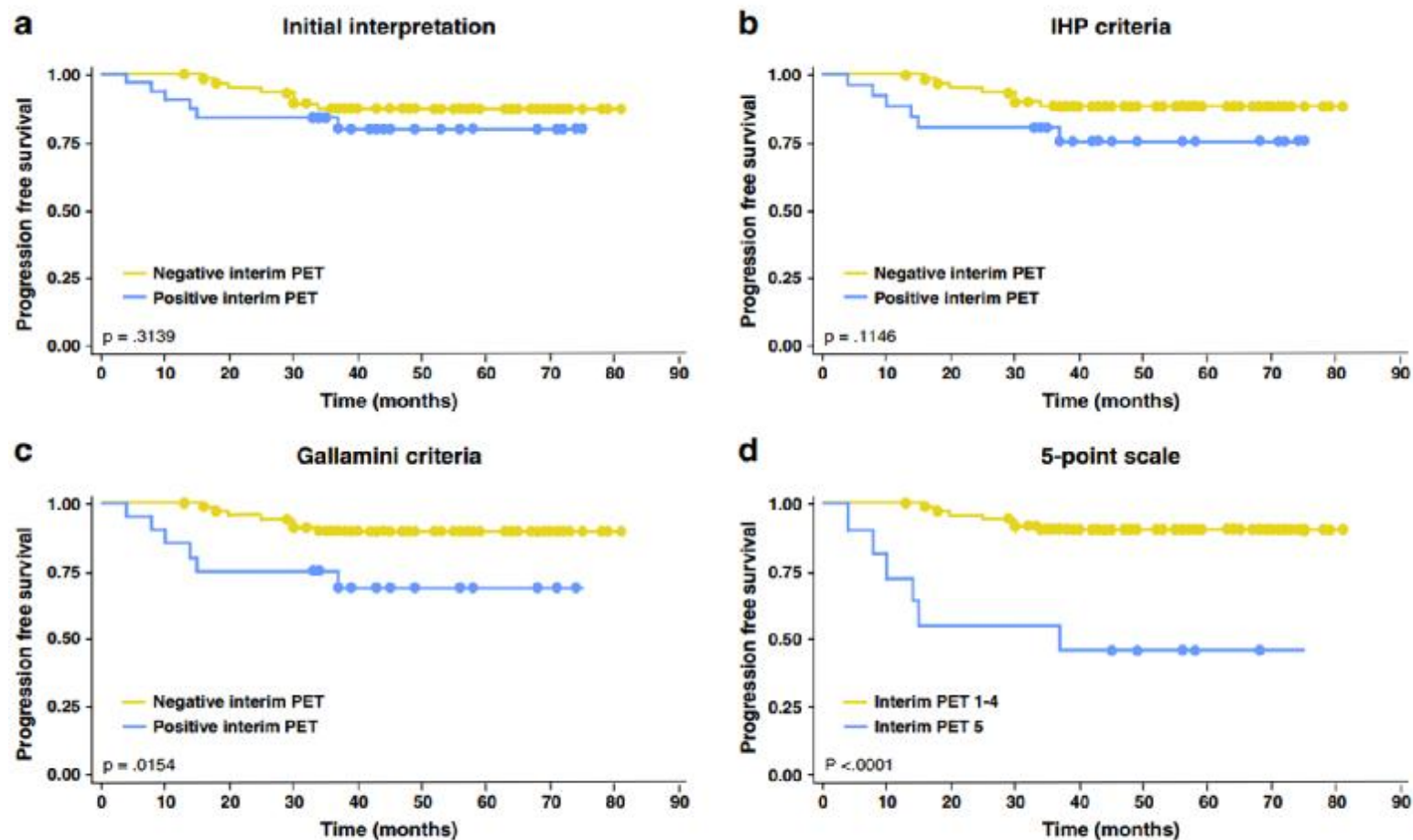


Fig. 4 Kaplan-Meier survival curves showing the PFS according to interim PET/CT results using initial criteria (a), IHP criteria (b), Gallamini criteria (c) and the 5-point scale (d)

The Lugano Classification

VOLUME 32 • NUMBER 27 • SEPTEMBER 20, 2014

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,

VOLUME 32 • NUMBER 27 • SEPTEMBER 20, 2014

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,

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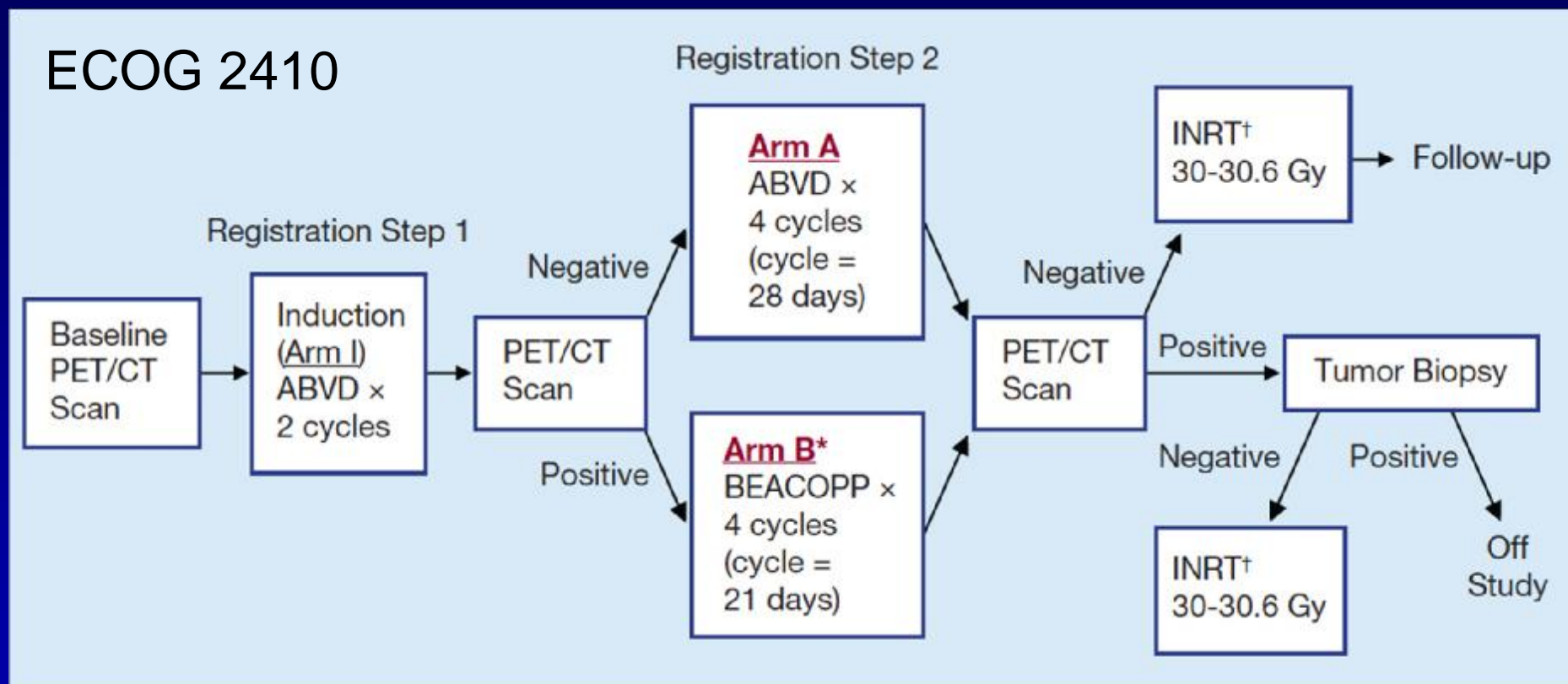


Summary

- q Deauville 5PS applicable to FDG-avid nodal lymphomas essentially all histologic types, both iPET and EOT.
- q iPET is less predictive for response with immunochemotherapy. It is not recommended to change treatment solely on basis of interim PET-CT
- q EOT PET-CT is standard of care and a much better predictor, especially for HD, NHL, and FL; (-) with high NPP, (+) needs biopsy if salvage considered.

Hodgkin Lymphoma

Adaptive Chemotherapy



OBJECTIVE: To evaluate the PFS at 36 months for patients who are PET-negative after 2 courses of chemotherapy, and receive 4 additional courses of ABVD followed by involved-nodal radiotherapy (INRT) of 30-30.6 Gy.

Courtesy: Prof. Terry Wong, NUC

Things not mentioned in Lugano classification

q Deauville 5 PS is not applicable to the following histology types:

§ The following FDG variable subtypes:

- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma
- Lymphoplasmocytic lymphoma
- Waldenstrom macroglobulinemia
- Marginal zone lymphoma

§ Cutaneous/subcutaneous lymphoma including mycosis fungoides/Sezary syndrome.

§ Primary extranodal lymphoma which have separate criteria.

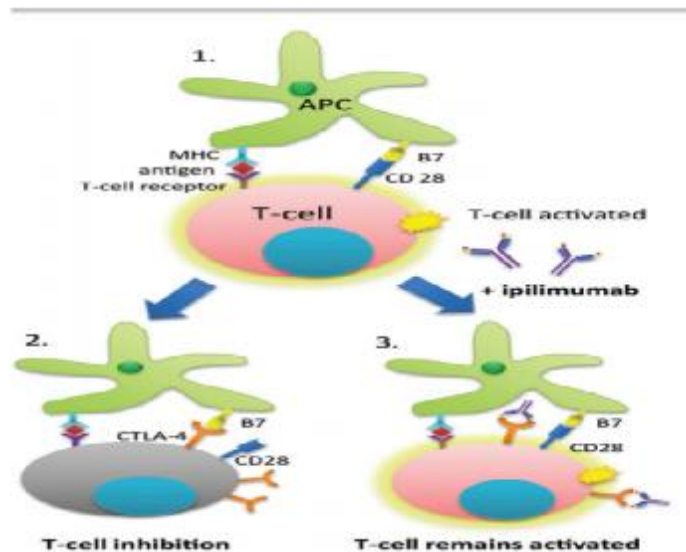
- Olsen EA et al. J Clin Oncol. 2011 Jun 20;29(18):2598-607.
- Zinzani PL et al. Haematologica. 2008 Sep;93(9):1364-71.

q Score 5 = more than 2-3 times higher than liver by SUVmax

q What's special for response assessment in patients with immunochemotherapy??

Era of immunomodulatory therapy

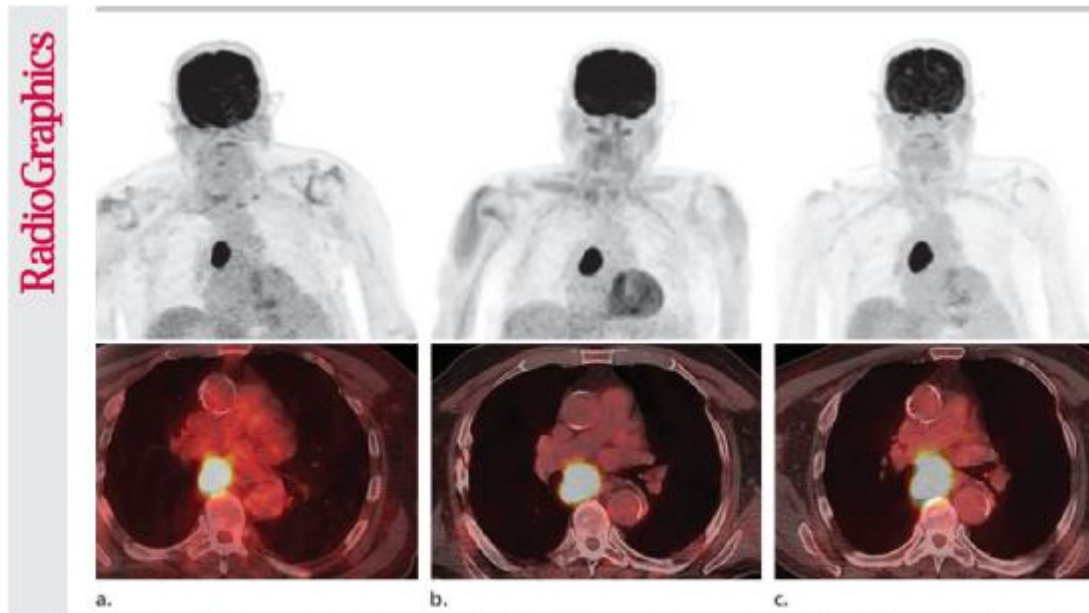
- q Immunomodulatory monoclonal antibodies that are directed against CTLA-4, the programmed death protein 1 (PD-1)/programmed death receptor ligand 1 (PD-L1) of T-cells
- q Ipilimumab, tremelimumab, nivolumab, Pembrolizumab
- q FDA approval of nivolumab, Pembrolizumab for patients with relapsed and refractory Hodgkin lymphoma



New patterns of treatment response of immunotherapy

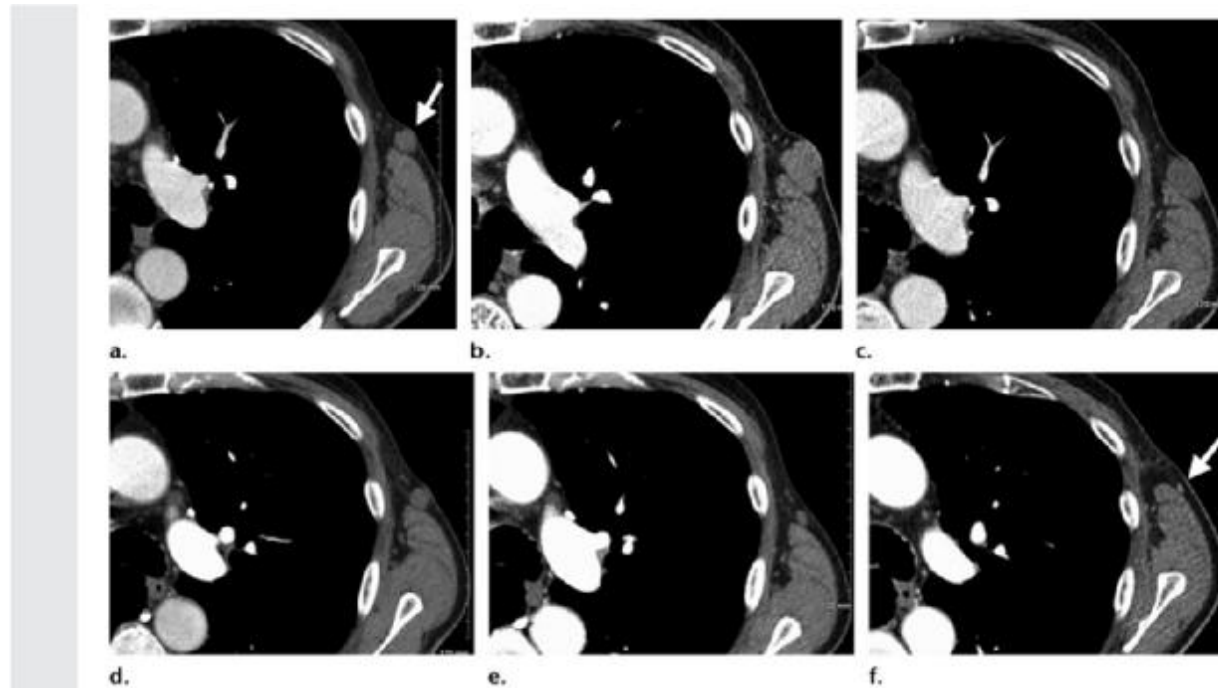
- § The first new pattern of response is clinically stable disease after completion of treatment followed by an eventual decline in tumor burden.

Jennifer J. Kwak, MD et al.
Radiographics Volume 35, Issue 2, 2015



7 months

§ The 2nd new pattern is a delayed tumor response to treatment after an initial increase in tumor burden that manifests as an increase in tumor size



Jennifer J. Kwak, MD et al.
Radiographics Volume 35, Issue 2, 2015

§ The 3rd new pattern of response is the appearance of new lesions after the completion of treatment that precede a decrease in tumor burden at subsequent follow-up examinations. The appearance of new lesions may represent an interval increase in the size of micrometastases.

Jennifer J. Kwak, MD et al.
Radiographics Volume 35, Issue 2, 2015

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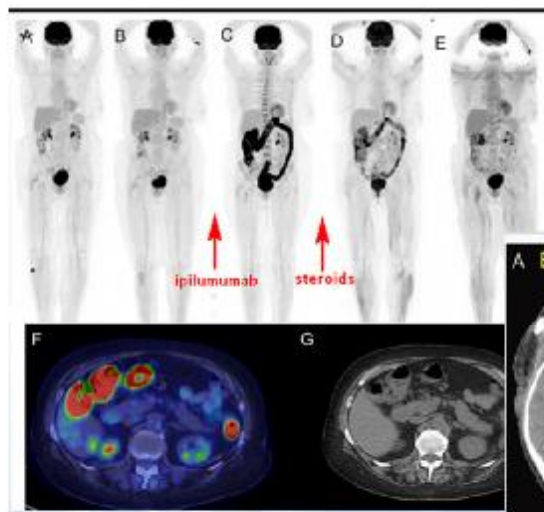
Patterns of an irR on FDG PET

- Reactive nodal uptake in drainage basin of metastases
- For mediastinal / hilar nodes: symmetry
- Reactive diffuse splenic uptake
- High tonsillar +/- para-appendiceal uptake (lymphoid hyperplasia)

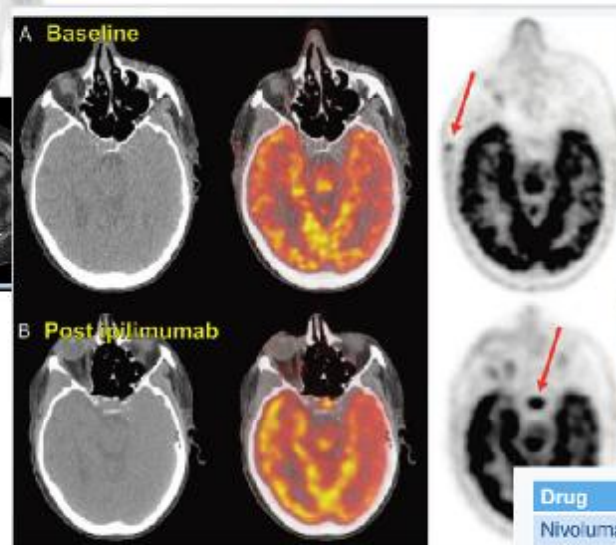
Imaging Findings of Immune-related Adverse Events

- § Imaging Findings of Immune-related Adverse Events It is important for the imager to recognize the unique adverse events associated with immunotherapy to guide appropriate treatment and avoid potential imaging pitfalls that could be mistaken for metastatic progression of disease.





Colitis



Hypophysitis

Stats

Drug	Immune related AE	No
Nivolumab	pan-enteritis	1
	thyroiditis	1
	systemic fasciitis	1
Pembrolizumab	colitis/duodenitis	5 / 1
	pneumonitis	3
	thyroiditis (hypothyroidism)	5
	polymyalgia rheumatic	1
	pancreatitis	1
	seronegative inflammatory arthritis	1
Ipilimumab	colitis	1
	sarcoidosis	1
	adrenallitis / autoimmune hypophysitis	1
pembrolizumab+ ipilimumab	pneumonitis	1
	dermatologic (lichen planus)	1
153 patients (236 PET scans): 30 pt (20%) had irAEs detected		

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IRRC -- immune-related response criteria

q Key points of the immune-related response criteria are as follows:

- § Because of a potentially delayed response to immunotherapy treatment, imaging assessment of treatment response or disease progression after completion of treatment should be made with two consecutive follow-up imaging studies performed at least 4 weeks apart
- § New or enlarging lesions do not necessarily represent progression of disease immediately after completion of treatment. Because of this, follow-up imaging should be performed at least 4 weeks later to assess for further changes in tumor burden.

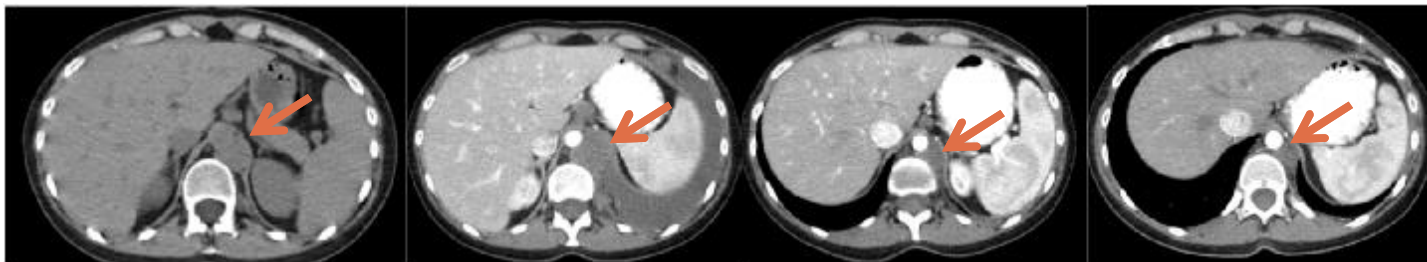
Hodi FS. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol 2016

Evolution still continuing.....

LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC)

- § Tumor flare or pseudo-progression has been well described with checkpoint blockade therapy in lymphoma.
- § **Provisional** “Indeterminate Response” (IR) was introduced in order to identify such lesions until confirmed as flare/pseudoprogression or true PD
- § “Tumor flare” occurs, generally during the first two to three weeks of treatment – acute inflammatory reaction
- § These criteria were proposed to overcome the limitations of the Lugano classification

- q **IR(1)**: Increase in overall tumor burden (as assessed by SPD) of $\geq 50\%$ of up to 6 measurable lesions in the first 12 weeks of therapy, without clinical deterioration repeat imaging in 4-8 weeks of the original IR(1) time point



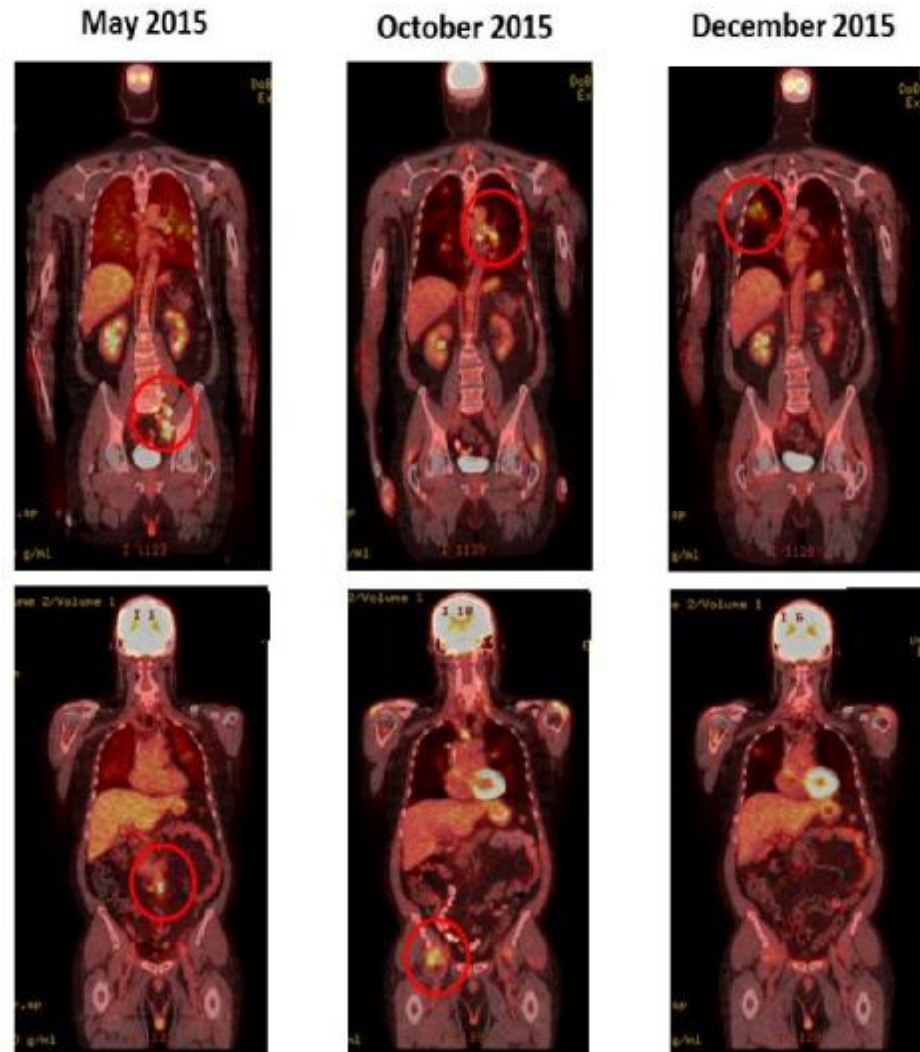
Baseline CT

Restaging CT 1

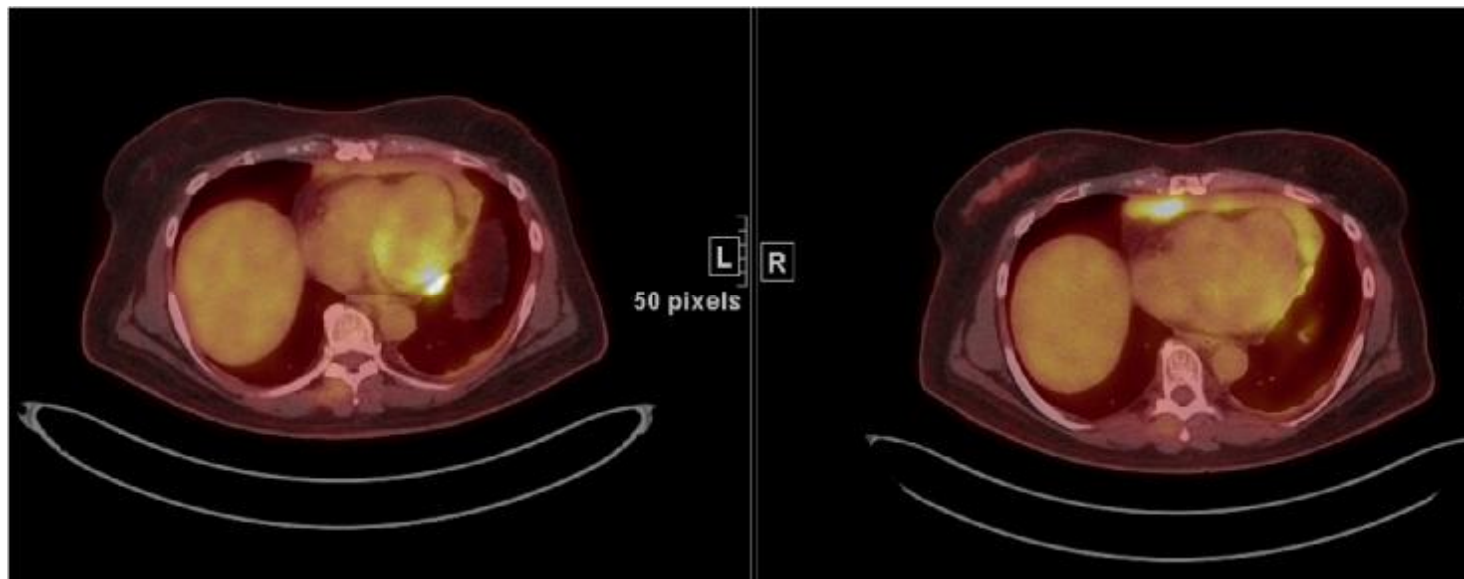
Restaging CT 2

Restaging CT 3

- q **IR(2)**: Appearance of new lesions; or growth of one or more existing lesion(s) $\geq 50\%$; at any time during treatment; occurring in the context of lack of overall progression ($< 50\%$ increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment a biopsy is strongly encouraged in such cases.



- q **IR(3)**: Increase in FDG uptake of one or more lesion(s) without a concomitant increase in lesion size or number an increase in FDG avidity of one or more lesions suggestive of lymphoma, without a concomitant increase in size of those lesions meeting PD criteria does not constitute PD.



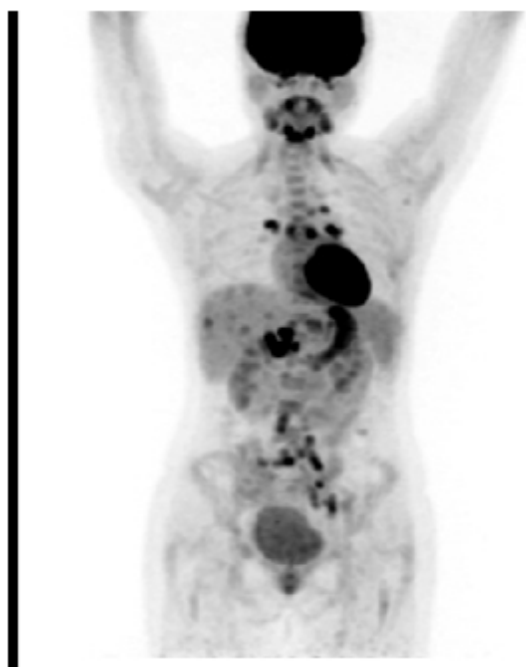
In summary

As with Lugano with the following exceptions
IR1: $\geq 50\%$ increase in SPD in first 12 weeks
IR2a: $< 50\%$ increase in SPD with new lesion(s)
IR2b: $< 50\%$ increase in SPD with $\geq 50\%$ increase in PPD of a lesion or set of lesions at any time during treatment
IR3: Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

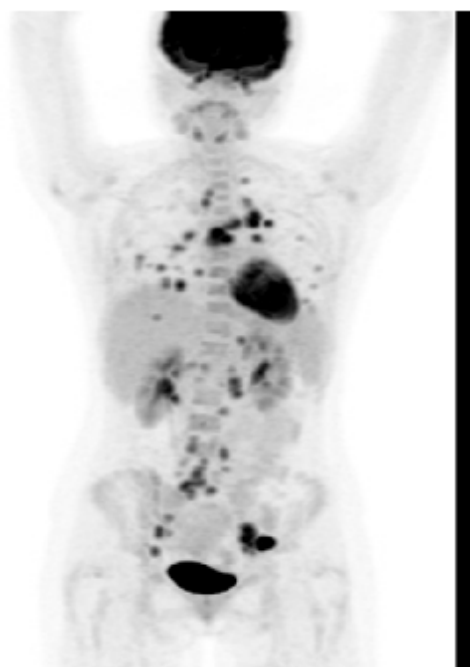
Follow-up of IR

- Repeat scan in 12 wks (earlier if indicated)
- PD if:
 - IR1 – further increase in SPD
 - IR2 – new lesion added to SPD (unless benign) and, if $\geq 50\%$ increase – PD
 - IR3 – PD if increase in size or new lesions

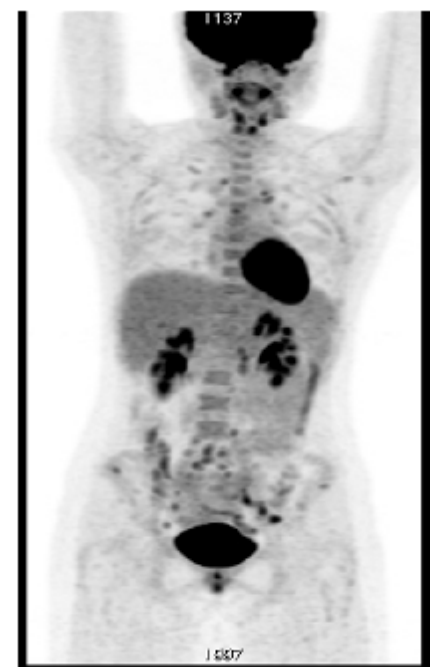
q 26 yom, HL, s/p ABVD and ICE, Kaytruda 03/16-05/16



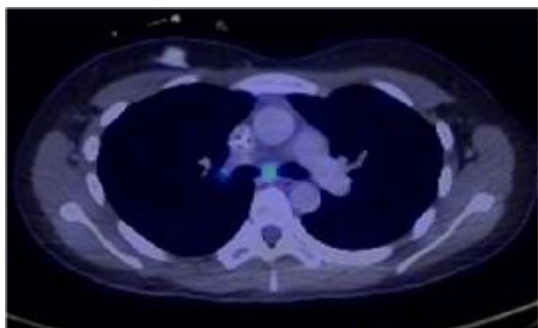
02/2016



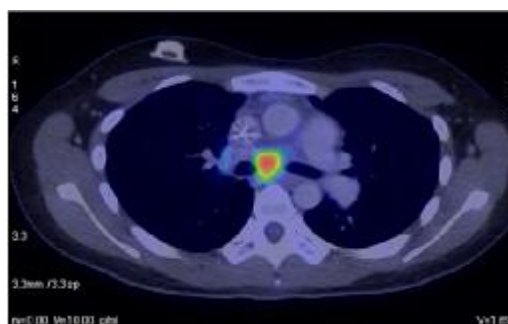
05/2016



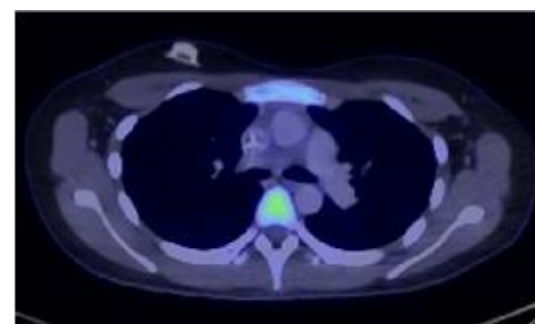
09/2016



02/2016



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09/2016



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PET and CT-scan Detect New Imaging Patterns of Response and Progression in Patients with Hodgkin Lymphoma Treated by Anti-PD1 Immune Checkpoint Inhibitor

Journal of Nuclear Medicine, published on June 8, 2017 as doi:10.2967/jnumed.117.193011

- q 5/16 patients (31%) displayed new imaging patterns related to antiPD1; we observed two transient progressions consistent with indeterminate response according to the LYRIC 2016 criteria (IR2b at 14 months and IR3 at 18 months), and three patients with new lesions associated with immune-related adverse events.
- q Indeed, the persistence of 18F-FDG PET positive lesions at 3-month does not preclude a prolonged clinical benefit.

- q Interestingly, healthy spleen tissue ^{18}F -FDG uptake appears significantly increase in responders suggesting a favorable immunological reconstitution.

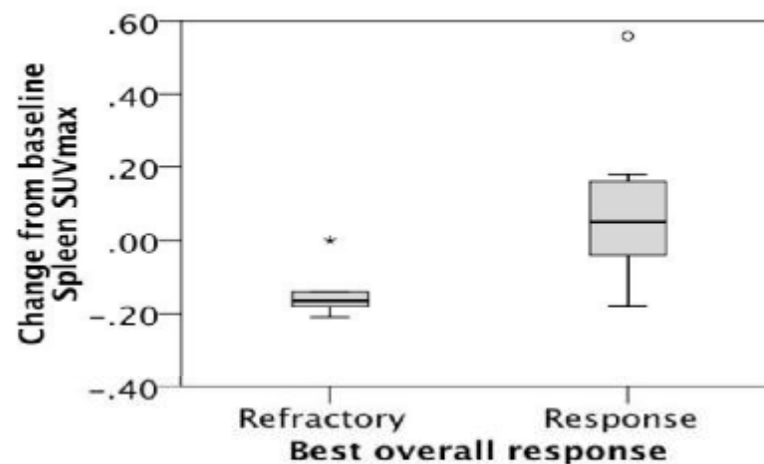


Figure 3. Responders have an increase in spleen metabolism (delta-SUVspleen) at 3 months

Take home message

- q Assessing treatment response in lymphoma with FDG PET has been a concerted effort for decades.
- q Lugano classification applies to most subtypes under traditional or salvage therapy but does not work well for patients on novel immunomodulatory therapy, particularly for iPET.
- q Lyric is proposed for assessment of PD in lymphoma patients on immunomodulatory therapy with three 'IR' categories described.
- q The key to deal with 'IR' is repeated scan in 3 months.

q Thank you!

q I love Nanjing!

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