PET In Lymphoma - "Beyond Lesion Counting"

IAEA – RAS 6071

TMH, Mumbai 21st Nov 2016

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OVERVIEW

- PET in staging
- End of treatment response
- Interim PET and controversies
- Quantitative PET in Lymphoma
- Pre transplant evaluation

FDG PET/CT in Lymphoma

Diagnosis & staging

- Avidity
- Extent of disease
- Pattern of nodal and extranodal disease.

Impact on clinical management

- Response assessment at completion of treatment
- Early/interim response assessment

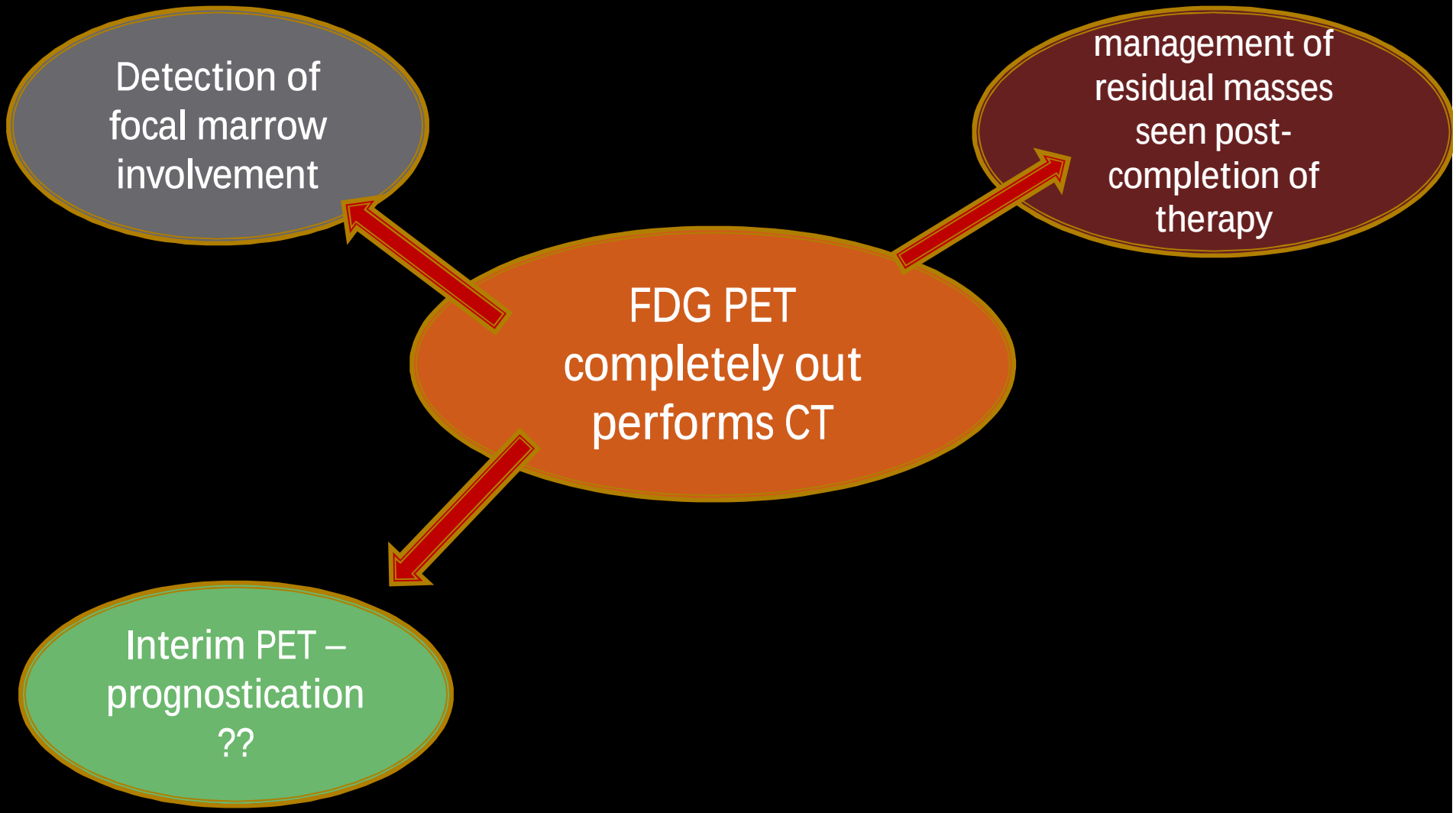
Staging

- FDG-PET is more accurate than CT at initial staging with a sensitivity and specificity of 96%.

- Discordance between PET and CECT findings – 1/3rd patients at initial staging - in favour of PET/CT

J Clin Oncol 25:579-586, 2007
J Clin Oncol 29:1844-1854, 2011
Int J Radiat Oncol Biol Phys 71:213-219, 2008
Eur J Nucl Med Mol Imaging 37:2307-2314, 2010

FDG-PET and CT in Lymphoma



J Clin Oncol 2014 Aug 11

Staging

- PET-CT leads to change in stage in 10% to 30% of patients - more often upstaging.

- But treatment is rarely changed (in very few - up to 15% of patients)

- No evidence that outcome is improved as a result of these data

J Clin Oncol 25:579-586, 2007
J Clin Oncol 29:1844-1854, 2011
Int J Radiat Oncol Biol Phys 71:213-219, 2008
Eur J Nucl Med Mol Imaging 37:2307-2314, 2010

Initial staging NHL

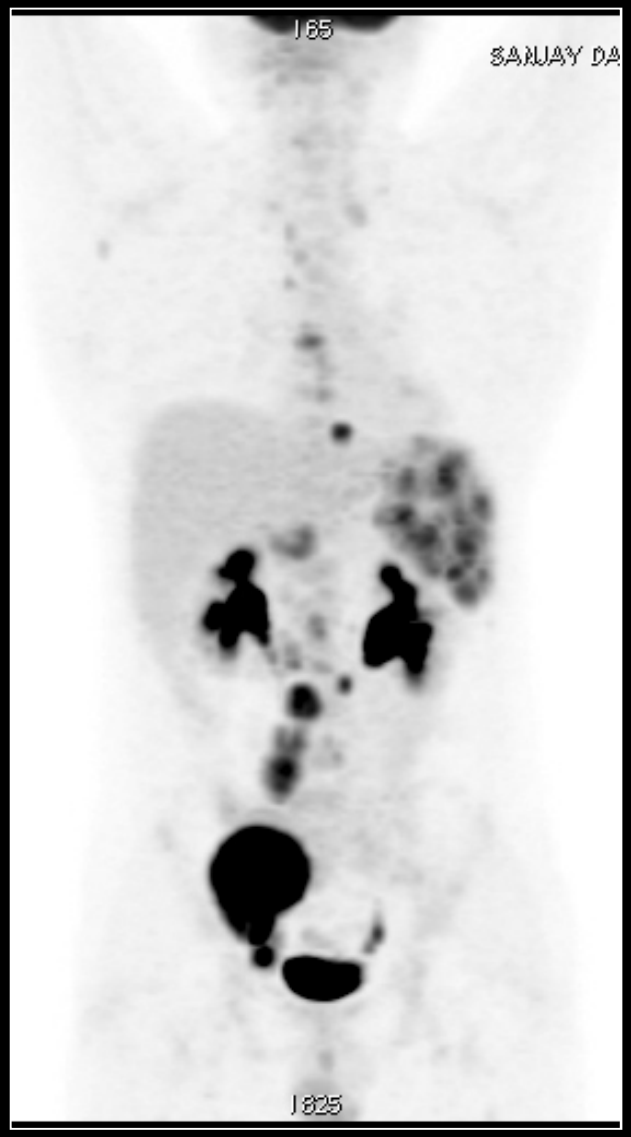
Clinically – left level IB node

Stage – I A

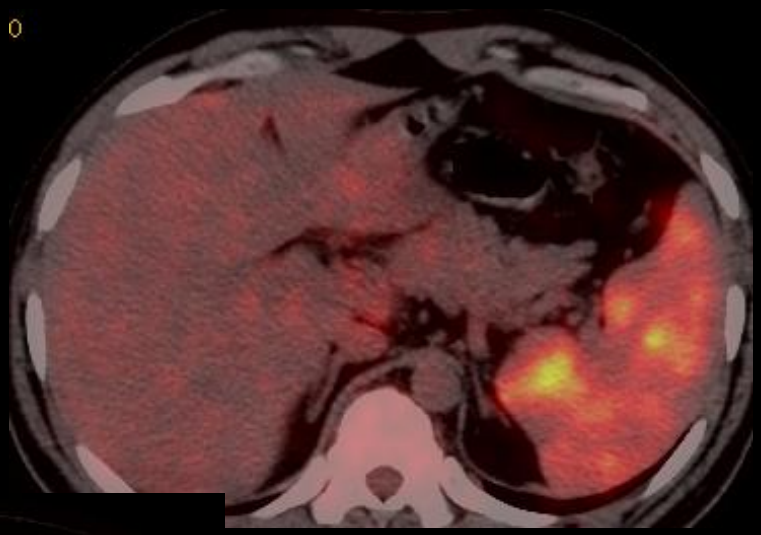
PET CT – retroperitoneal and iliac nodes with a focus in spleen – Upstaged to IIIA

PET-CT leads to upstaging in 10% to 30% of patients

Initial staging – Hodgkin's Disease



Presentation with pelvic adenopathy.
PET CT – multiple foci of uptake in a normal sized spleen.



FDG-PET in Bone Marrow Involvement
BM Biopsy – to be done or not?

In Hodgkin's Lymphoma -

- Patients with early-stage disease rarely have involvement in the absence of a positive PET finding.

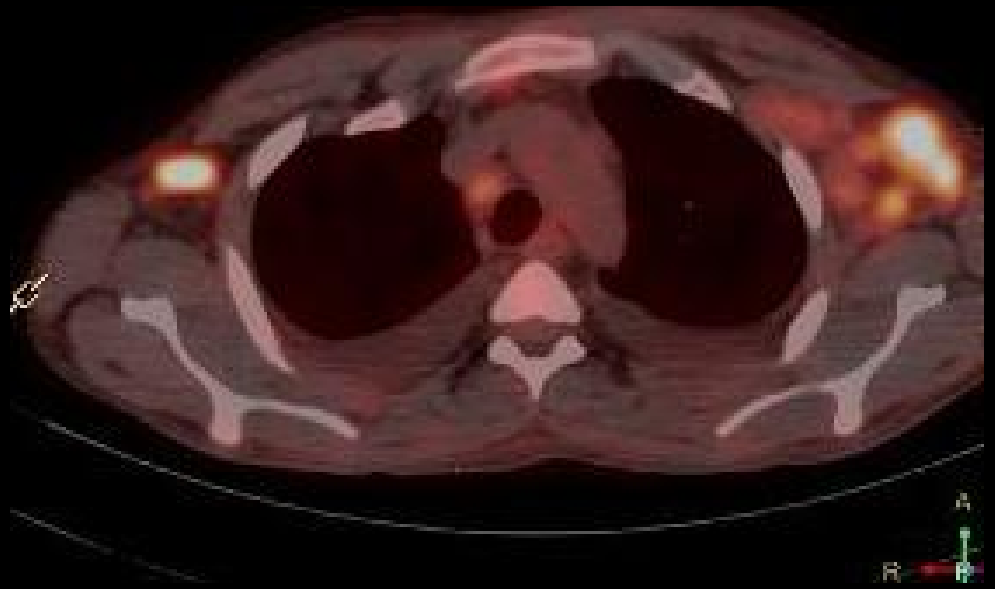
- Advanced-stage disease rarely have involvement in the absence of disease-related symptoms or other evidence of advanced stage disease.

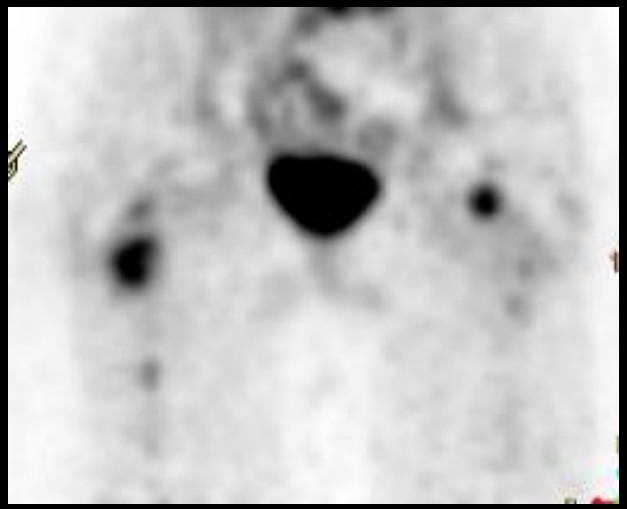
If a PET-CT is performed - a bone marrow aspirate/biopsy is not
required for the routine evaluation of patients with HL.

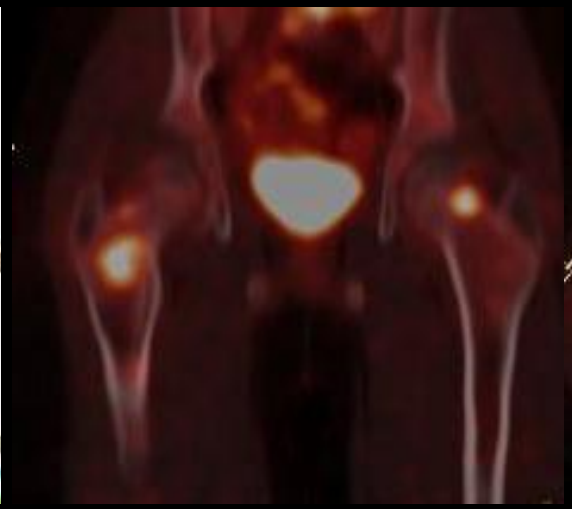
J Clin Oncol 30: 4508-4514, 2012

18 years/ F, Hodgkin's Lymphoma.
BM – uninvolved.

HD, axillary adenopathy.







FDG-PET in Bone Marrow Involvement
BM Biopsy – to be done or not?

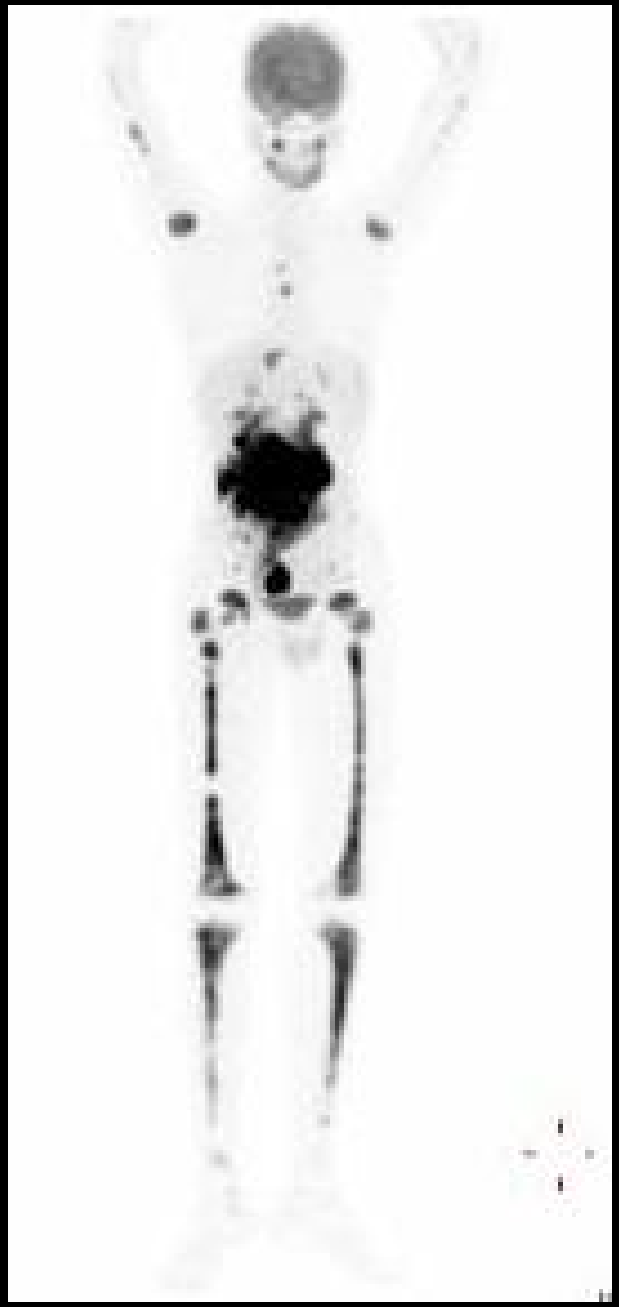
In DLBCL -

- PET-CT is more sensitive than BMB but can miss low-volume diffuse marrow involvement in 10% to 20% .

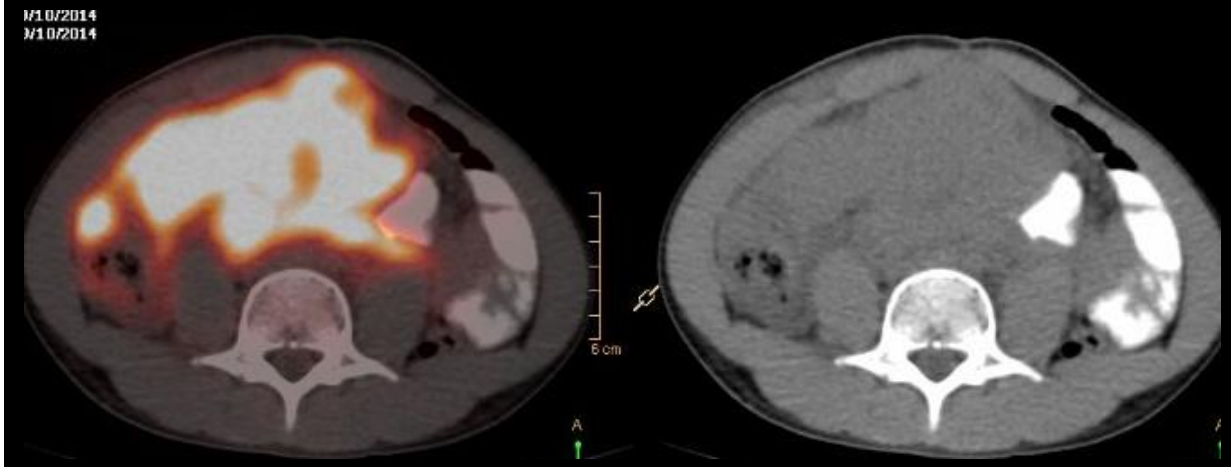
- A positive PET-CT scan indicating bone or marrow involvement is usually sufficient to designate advanced-stage disease and a BMB is not required.

- If the scan is negative a BMB is indicated to identify involvement.

Eur J Nucl Med Mol Imaging 41:565-574, 2014
Eur J Nucl Med Mol Imaging 36:745-750, 2009



20 years/male, NHL. Abdominal mass.



32 years/male, mediastinal mass - PMBCL

Focal marrow involvement in right humerus.

End of treatment response

Evaluation Of Response After Completion Of Therapy

- PET has the ability to distinguish fibrosis or sclerosis from residual active disease – thus has definite role.

- In early- and advanced-stage patients with HL –
  - NPV of 95 % to 100% and PPV of > 90%

- In aggressive NHL -
  - NPV of 80% to 100% and a lower PPV - from 50% to 100%

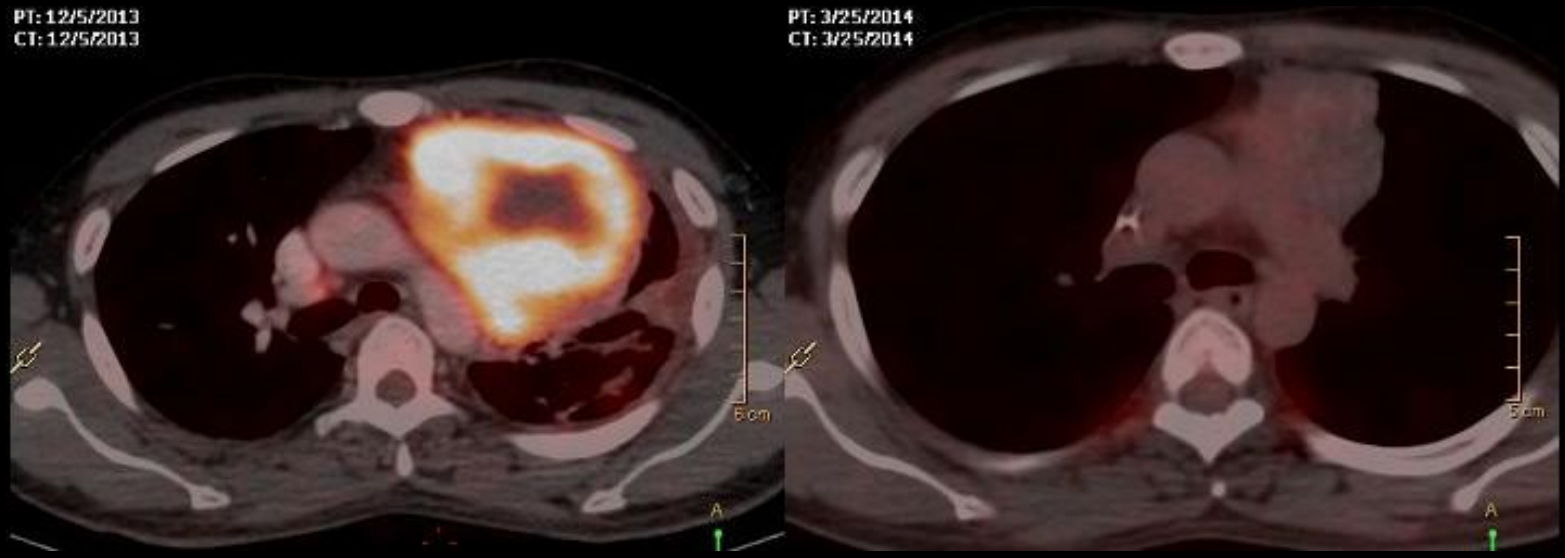
- If further treatment based on residual metabolically active disease on PET/CT is being considered - either biopsy or follow-up scan is advised.

Cheson BD. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

Response evaluation - lymphoma

Pre & Post chemotherapy

Residual mass -post treatment on CT



Complete metabolic response on PET

Burning Questions – interim PET/CT

- Which patient will benefit most from adjuvant RT based on PET/CT imaging?
- Whether it is justified to tailor treatment on the basis of the interim FDG-PET result?
- Whether chemotherapy should be de-escalated based on negative interim scans or intensified in response to positive interim scans?

Interim PET/CT in HL

Hodgkin lymphoma

Trial	No of Patients	Study Summary
Radford et al,[8] 2015 (UK RAPID)	602	PET/CT negativity can be used to forego radiation after ABVD
Raemaekers et al,[10] 2014	1137	PET/CT status cannot be used to obviate radiotherapy
Engert et al,[11] 2012 (HD15)	2182	PET/CT-directed RT after six cycles of eBEACOPP is effective and less toxic
Gallamini et al,[13] 2011	219	Treatment escalation to BEACOPP for PET/CT-positive patients after two cycles of ABVD
RATHL	1214	PET/CT status to determine need for bleomycin in ABVD after two cycles
Israeli H2	356	Interim PET/CT to dictate chemotherapeutic regimen after treatment based on IPS score after two cycles
French LYSA	Ongoing	De-escalation from eBEACOPP to ABVD after negative interim PET/CT

UK RAPID trial

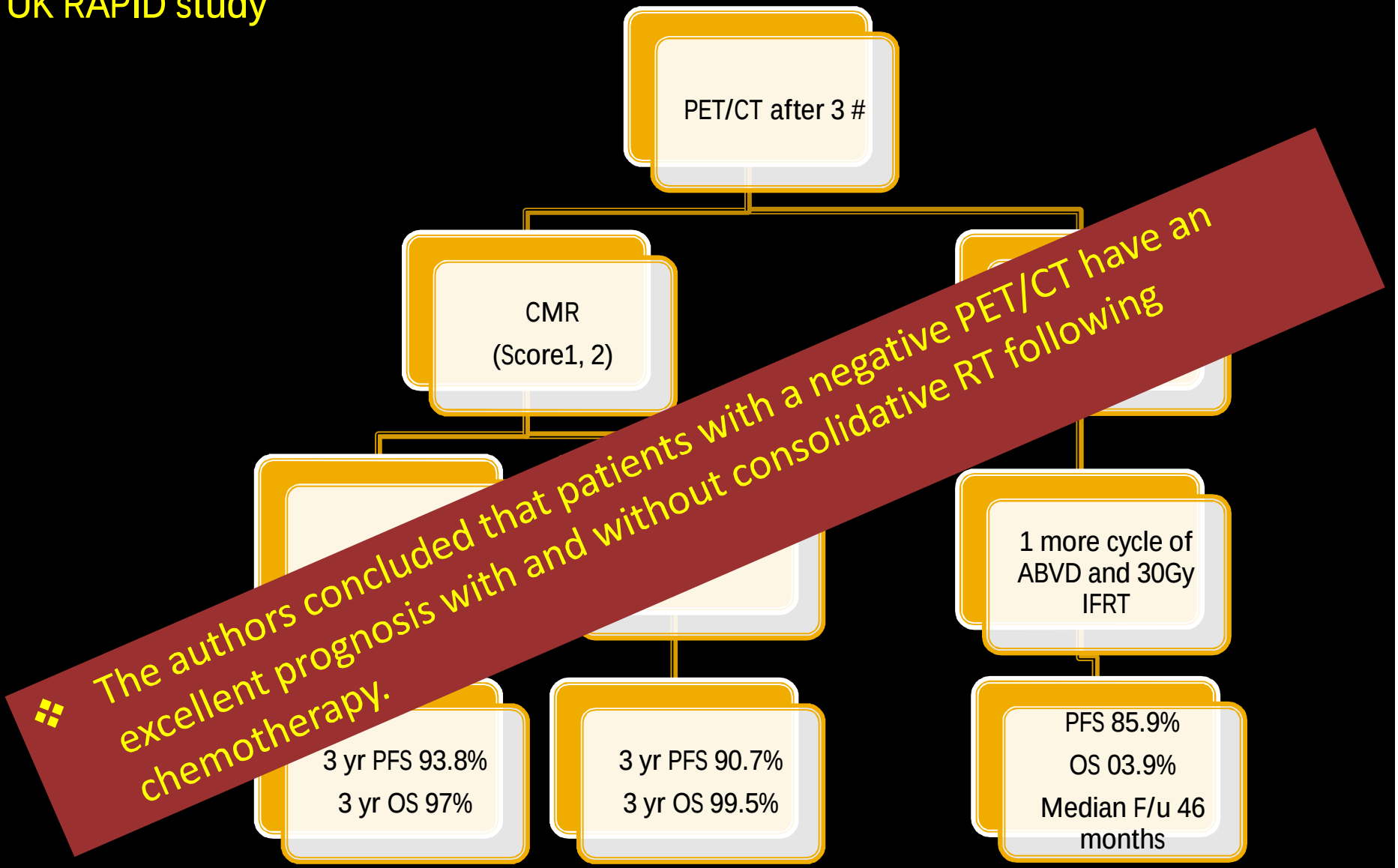
UK RAPID trial –

- 602 patients with HL.
- PET scan performed after 3 cycles of ABVD.
- Non-bulky stage I & IIA disease
- Negative PET were randomized to RT versus no RT
- IHP criteria for defining PET positivity or negativity

- Was designed to exclude a difference of ≥7% between radiotherapy and no further treatment.

Radford J, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598–607.

UK RAPID study



Radford J, et al. Results of a trial of PET-directed therapy for early-stage Hodgkin's lymphoma. N Engl J Med 2015;372:1598–607.

In contrast, Raemaekers and colleagues,

- Demonstrated early treatment failure without RT in patients with negative PET/CT.
- Aim was to determine whether RT could be omitted in patients with stage I/II HL with favourable or unfavourable risk factors who attained a negative early PET scan.
- 1137 patients, negative PET/CT after 2 cycles of ABVD.

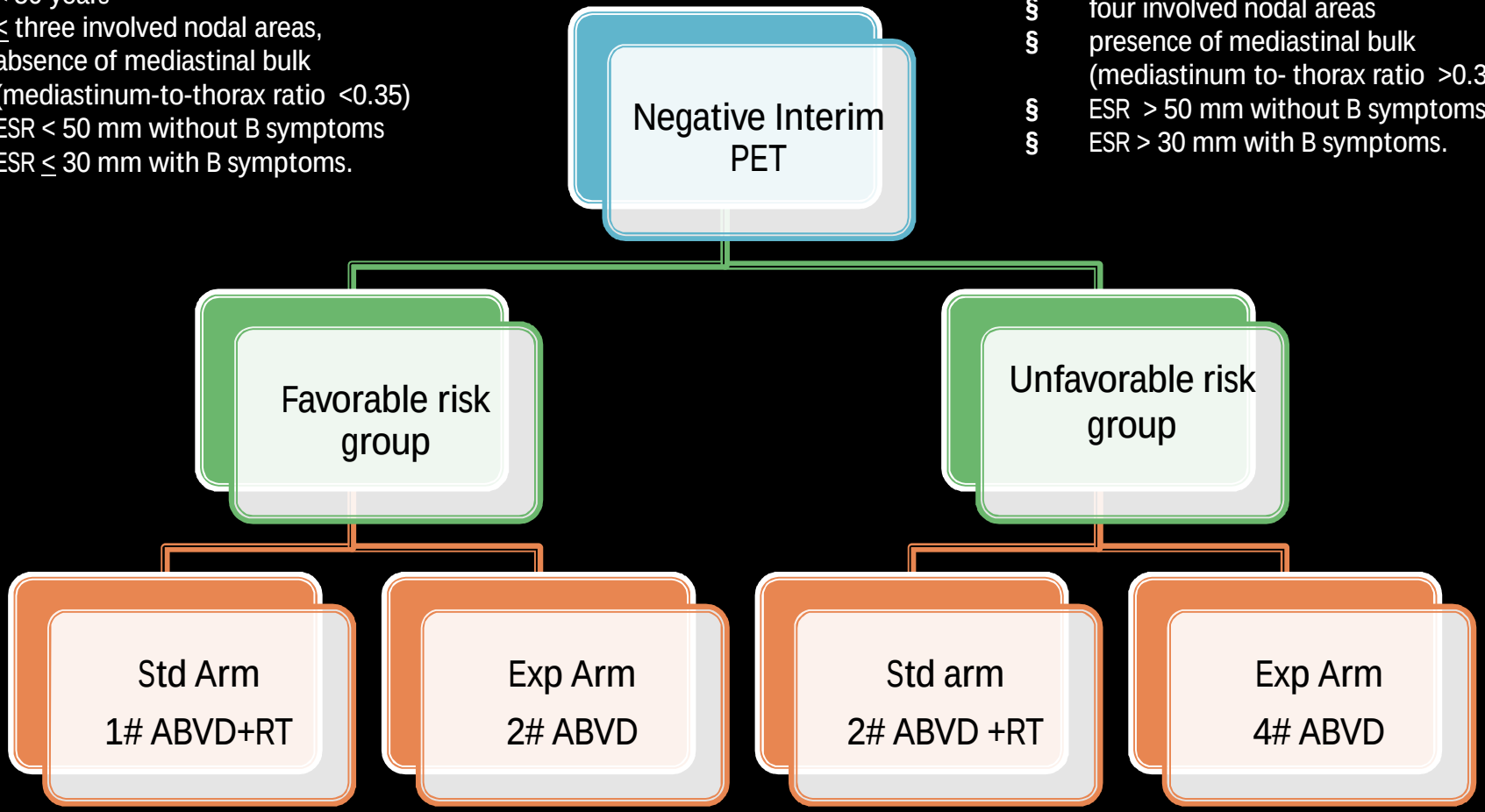
Raemaekers JM, et al. J Clin Oncol 2014;32:1188–94.

Favorable risk

- < 50 years
- ≤ three involved nodal areas,
- absence of mediastinal bulk (mediastinum-to-thorax ratio <0.35)
- ESR < 50 mm without B symptoms
- ESR ≤ 30 mm with B symptoms.

Unfavorable risk –

- >50 years
- four involved nodal areas
- presence of mediastinal bulk (mediastinum to- thorax ratio >0.35)
- ESR > 50 mm without B symptoms
- ESR > 30 mm with B symptoms.



Raemaekers JM, et al. J Clin Oncol 2014;32:1188–94.

Disease progression	Std arm	Investigational arm
Favorable risk	0.5%	4.6%
Unfavorable risk	2.8%	6.0%

Concluded –

- Risk of early relapse in patients not undergoing RT was significantly higher
- Interim FDG-PET was not found useful for early detection of patients who do not need radiation therapy

Raemaekers JM, et al. J Clin Oncol 2014;32:1188–94.

PET in Bleomycin toxicity

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2016 VOL. 374 NO. 25

Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma

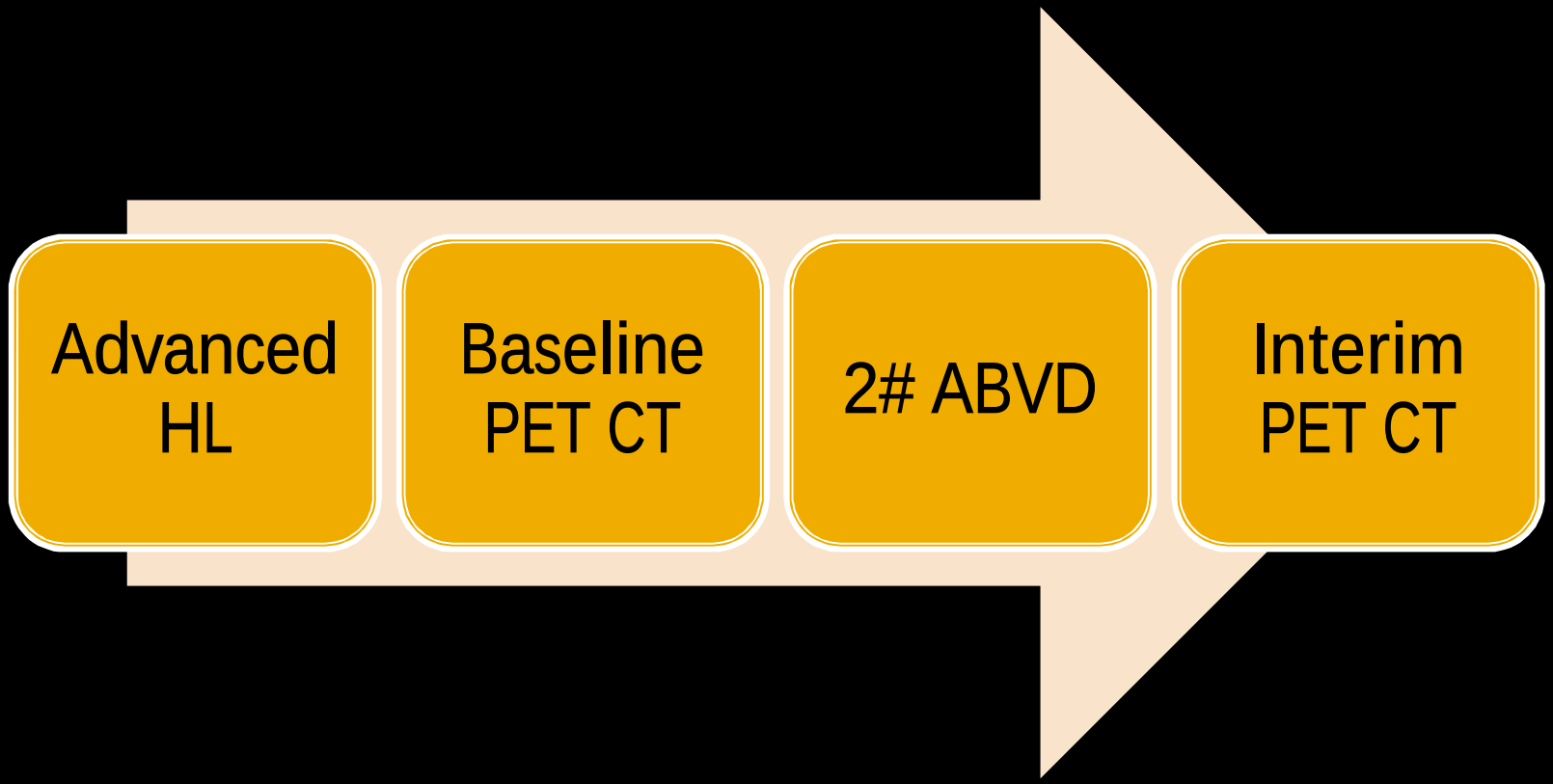
PET in Bleomycin toxicity

- Aim –
  - whether an interim FDG-PET scan could be used to guide the de-escalation of therapy for patients with a high probability of cure after ABVD therapy and
  - escalation for those at higher risk for treatment failure.

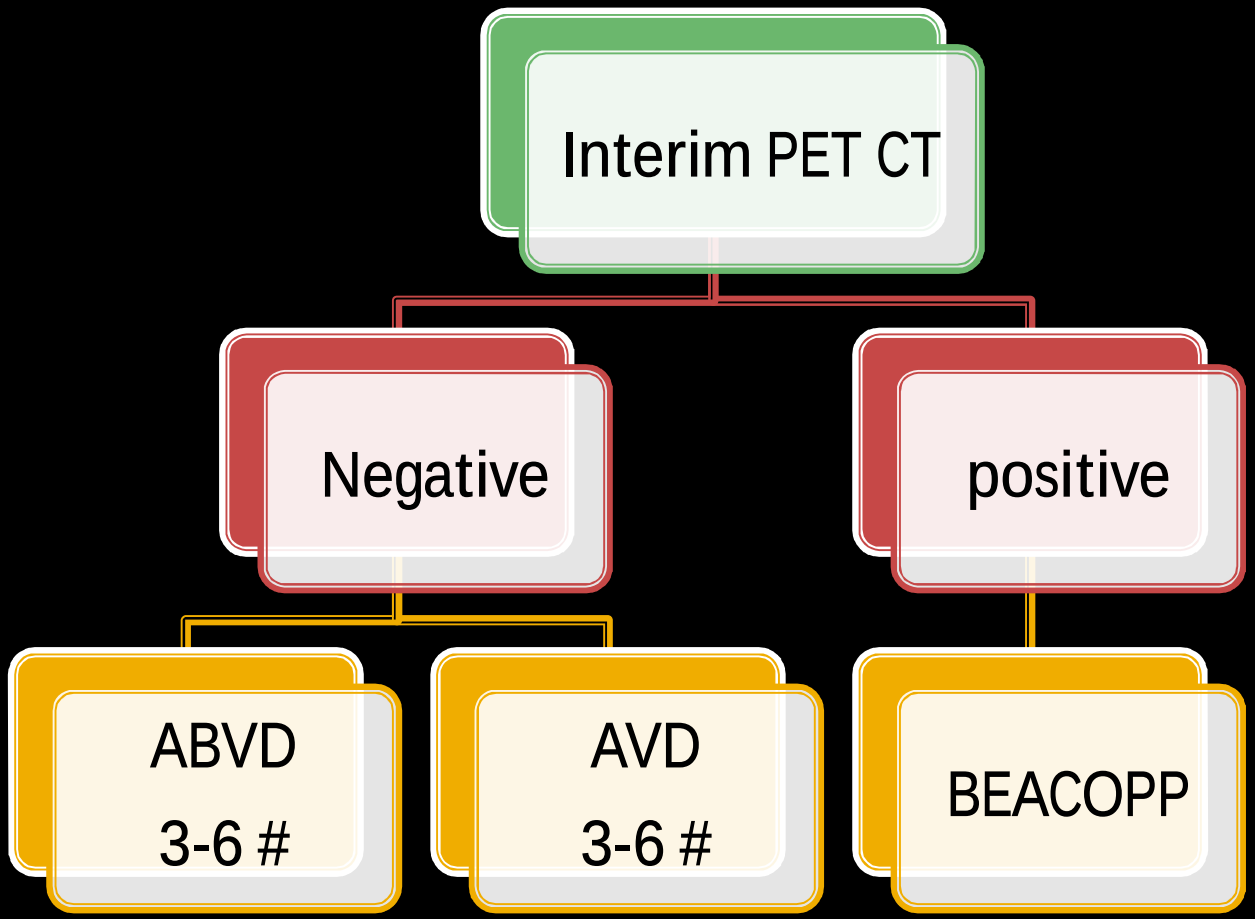
- The intention was to reserve more intensive treatment for patients whose poor prognosis justified the added risk.

1214 patients

RATHL study



London criteria for response assessment



- Radiotherapy was not recommended for patients with negative findings on interim scans.
- The primary outcome was the difference in the 3-year PFS rate between randomized groups.

	ABVD	AVD
3 yr PFS	85.7 %	84.4 %
OS	97.2 %	97.6 %
Respiratory adverse events	severe	moderate

Concluded –

- No difference in the proportion of patients who achieved PFS at 3 years in the group treated with Bleomycin compared with without Bleomycin
- Omission of Bleomycin from the ABVD regimen after negative interim PET resulted in a lower incidence of pulmonary toxic effects.

bjh research paper

Prognostic value of interim FDG-PET in Hodgkin lymphoma: systematic review and meta-analysis

British Journal of Haematology, 2015, 170, 356–366

- To analyze the value of interim FDG PET in predicting treatment failure in Hodgkin lymphoma.

- 10 studies, 1389 patients with Hodgkin lymphoma
- Interim FDG-PET (after 1 to 4 cycles) after initiation of first-line chemotherapy.

Prediction of outcome	Pooled Sn	Pooled Sp
Interim PET	71 %	90 %

A negative interim FDG-PET scan appears to be less accurate for excluding treatment failure than a positive interim FDG-PET scan to identify treatment failure.

DIFFUSE LARGE B-CELL LYMPHOMA

Interim PET/CT in DLBCL

- In contrast to HL - the prognostic utility of interim PET/CT imaging is not supported in clinical practice at this time.

- Before the inclusion of rituximab in DLBCL management - literature supported a strong correlation between interim PET/CT and outcomes.

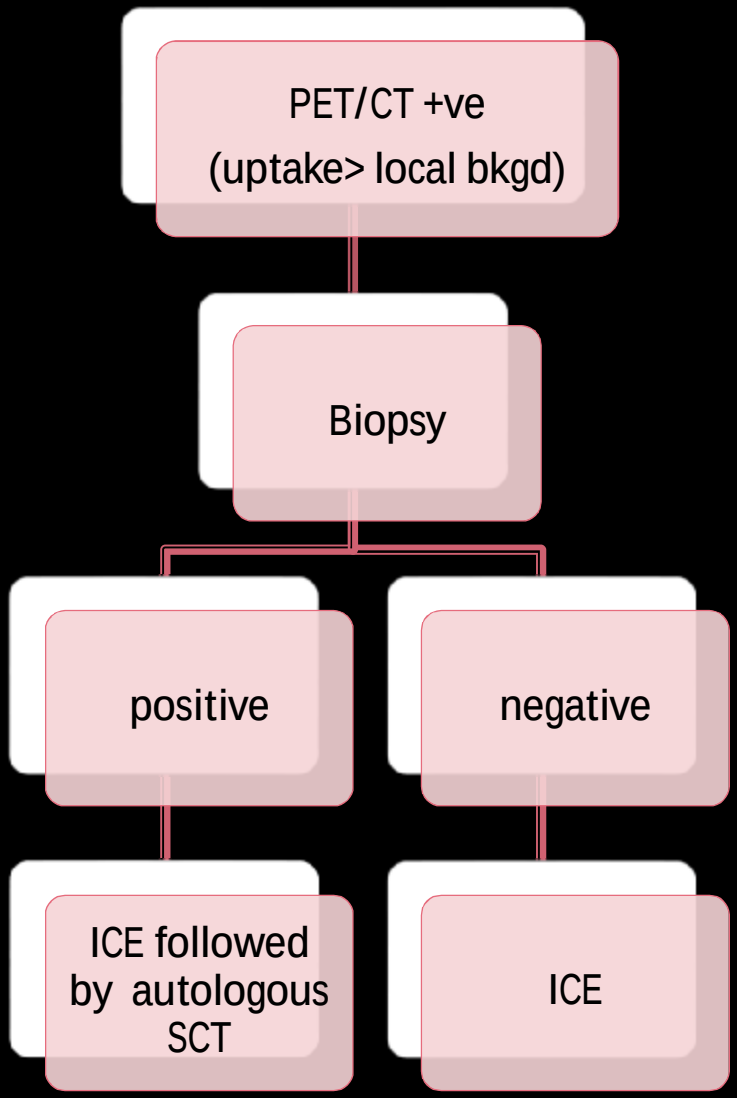
- More recently - the data suggest a high false-positive rate for interim PET/CT scans in DLBCL - rituximab-treated patients

- Possibly because of an exaggerated inflammatory response following rituximab exposure.

J Clin Oncol 2014;32:3059–68.
Ann Oncol 2009;20:309–18.

Trial	No. of patients	Study summary
Moskowitz et al	98	Interim or post-treatment FDG-PET evaluation did not predict outcome
PETAL	851	Escalation to B-ALL protocol for positive interim PET/CT does not improve efficacy

- Moskowitz and colleagues (2010) MSKCC.
- 98 patients - 4 cycles of R-CHOP - interim PET/CT was performed.



J Clin Oncol 2010; 28:1896–903.

At 44 months –

- Survival was identical between -
- PET-negative and PET-positive/biopsy negative groups - suggesting that interim PET/CT positivity in itself does not independently carry predictive power.

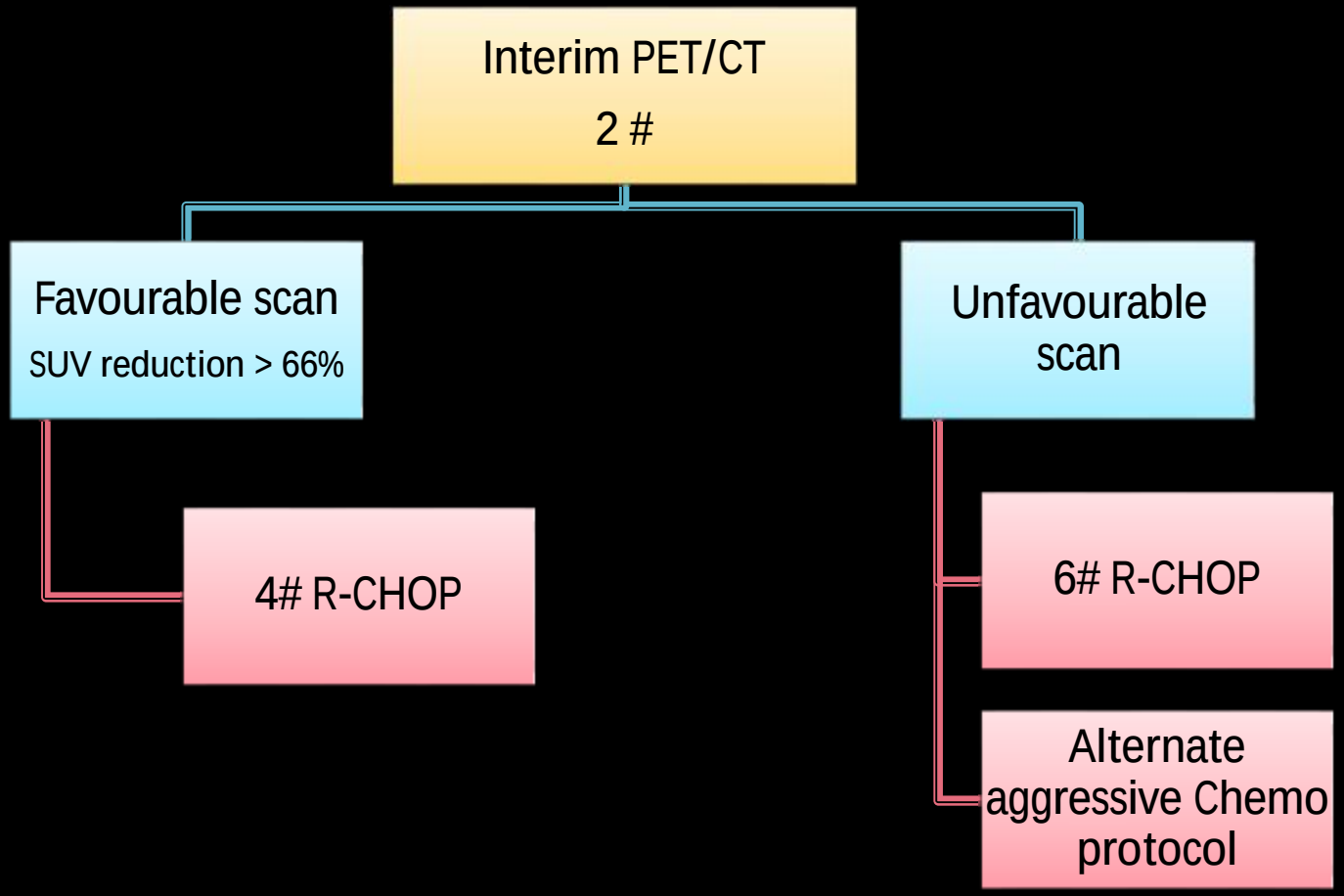
Concluded –

Interim or post-treatment FDG-PET evaluation did not predict outcome with this dose-dense, sequential immunochemotherapy program.

J Clin Oncol 2010; 28:1896–903.

The PETAL trial evaluated 851 patients in an intent-to-treat analysis to determine the utility in treatment escalation for patients with unfavourable PET/CT scans.

PET Guided Therapy of Aggressive NHL



Leuk Lymphoma 2009;50:1757–60.

- The authors found –
  - No statistically significant difference in time to treatment failure or OS between patients with favourable and unfavourable PET/CT.
  - No improved outcomes with alternate intensified regimen.
  - Patients who received intensified treatment suffered more severe leukopenia with comparable deaths with the R-CHOP cohort.

Leuk Lymphoma 2009;50:1757–60.

Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 648572, 8 pages
http://dx.doi.org/10.1155/2015/648572

Hindawi

Review Article

Predictive Value of Interim PET/CT in DLBCL Treated with R-CHOP: Meta-Analysis

Na Sun, Jinhua Zhao, Wenli Qiao, and Taisong Wang

Department of Nuclear Medicine, Shanghai First People's Hospital, Shanghai Jiao Tong University, Shanghai 200080, China

- 605 DLBCL patients
- Interim PET/CT - after 2–4 cycles of first-line chemotherapy (R-CHOP).
- PFS with or without OS was chosen as the endpoint to evaluate the prognostic significance of interim PET/CT.
- Follow-up period ranged from 12 to 81 months.

RESULTS

Interim PET in DLBCL	Pooled Sn	Pooled Sp
	52.4%	67.8%

- Sn and Sp of interim PET/CT in predicting the outcome of DLBCL patients treated with R-CHOP chemotherapy were not satisfactory

Quantitative PET in Lymphoma

- Quantitation to improve on visual assessment has been explored in DLBCL.

- Change in the maximum SUV (ɗ SUVmax) in tumor before and after treatment has been evaluated as a measure of response.

- The ɗ SUVmax analysis is being prospectively applied in few trials –

  - PETAL and GAINED studies exploring response-adapted treatment with immunochemotherapy.

Leuk Lymphoma 55:773-780, 2014
Blood 118:37-43, 2011
The PETAL trial. Leuk Lymphoma 50:1757-1760, 2009

- Changes in the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are being evaluated - less sensitive to noise and resolution and possibly more reproducible.

- But preliminary reports have suggested changes in MTV and TLG are not predictive in DLBCL.

Cancer 119:1195-1202, 2013
Ann Hematol 91:697-703, 2012

Assessment Before High-dose Chemotherapy And Autologous Stem-cell Transplantation

- PET-CT using FDG is prognostic in patients with relapsed or refractory HL or DLBCL after salvage chemotherapy before high-dose chemotherapy and ASCT.

- Three-year PFS and EFS rates of –
  - 31% to 41% have been reported for patients with PET-positive scans compared with
  - 75% to 82% for patients with PET-negative scans.

Blood 116:4934-4937, 2010
Biol Blood Marrow Transplant 17:1646-1652, 2011
Ann Hematol 90:1329-1336, 2011

Assessment Before High-dose Chemotherapy And Autologous Stem-cell Transplantation

- PET may have a role in selecting patients for high-dose chemotherapy and ASCT after salvage treatment and in identifying patients with poor prognosis who could benefit from alternative regimens or consolidation.

- Assessment with PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT but additional studies are warranted.

Blood 116:4934-4937, 2010
Biol Blood Marrow Transplant 17:1646-1652, 2011
Ann Hematol 90:1329-1336, 2011

To sum up .....

Beyond lesion counting FDG PET/CT –

- BM biopsy - Obviates the need for one in HL and in positive DLBCL.

- End of treatment response – high NPV and PPV in HL. High NPV but low PPV for DLBCL .
  - Treatment for residual metabolically active disease on PET/CT – needs a biopsy correlation.

- Interim PET – Still questionable whether it is justified to tailor treatment on the basis of the interim FDG-PET.

- Before ASCT - Is prognostic.
  - Identifies patients with poor prognosis who could benefit from alternative regimens or consolidation.


Thank
you