1st Postgraduate Lymphoma Conference
Session I: Hodgkin Lymphoma

Donna Camilla Savelli
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FDG PET/CT and its real role

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Current proven and potential roles of PET/CT in cHL

initial presentation

- Staging
- Directed bx - YES
- Nodal & END - YES
- BMI - YES

- RT planning – developing
- Defining bulk - Unknown
- Prognostication – Unknown

interim therapy response

- Prediction of PFS - YES

end of therapy response

- Prediction of PFS - YES

Follow up-relapse detect-Yes but..

Pre-ASCT evaluation

- Prediction of PFS - YES
  - after salvage before ASCT

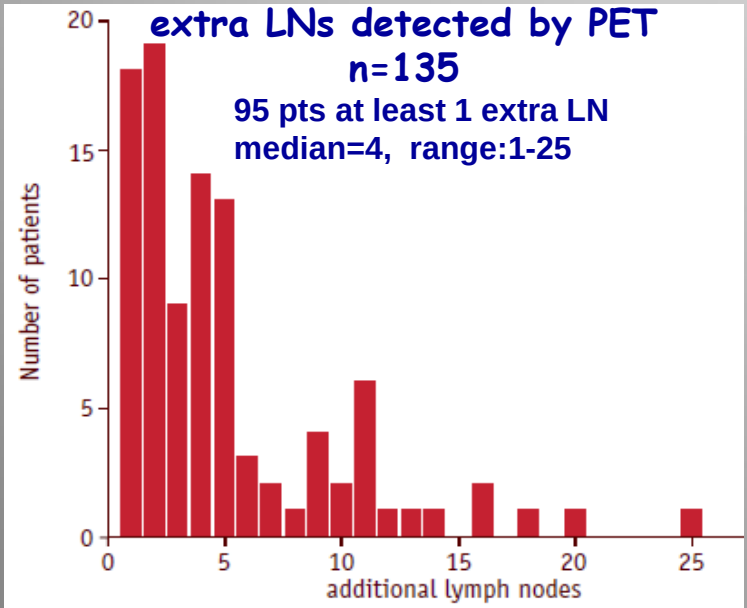
Staging- PET/CT in HL

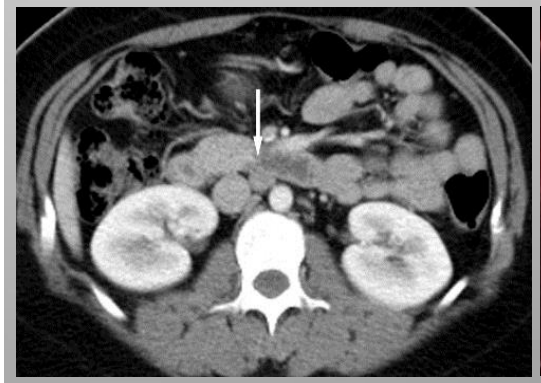
PET-CT is recommended for routine staging of HL as the gold std

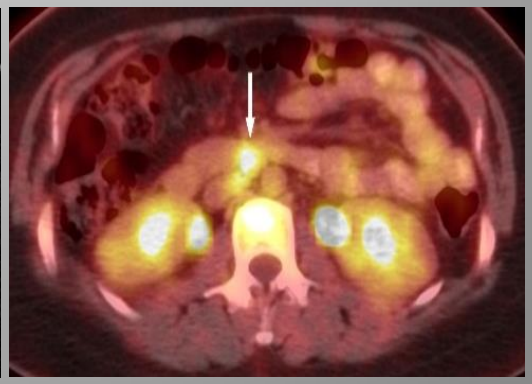
Cheson B, JCO,2014;32:3059

- improves staging accuracy vs CT: stage changes 10-30% pts
- often upstaging; change in management occurs in ~15% pts
- no demonstrated impact on overall outcome
- staging accuracy minimizes under or over-treatment
- important role for staging before RT

EORTC/LYSA/FIL H10 trial







Girinsky T, Int J Radiat Oncol Biol Phy 2014:89;1047

Bone marrow involvement

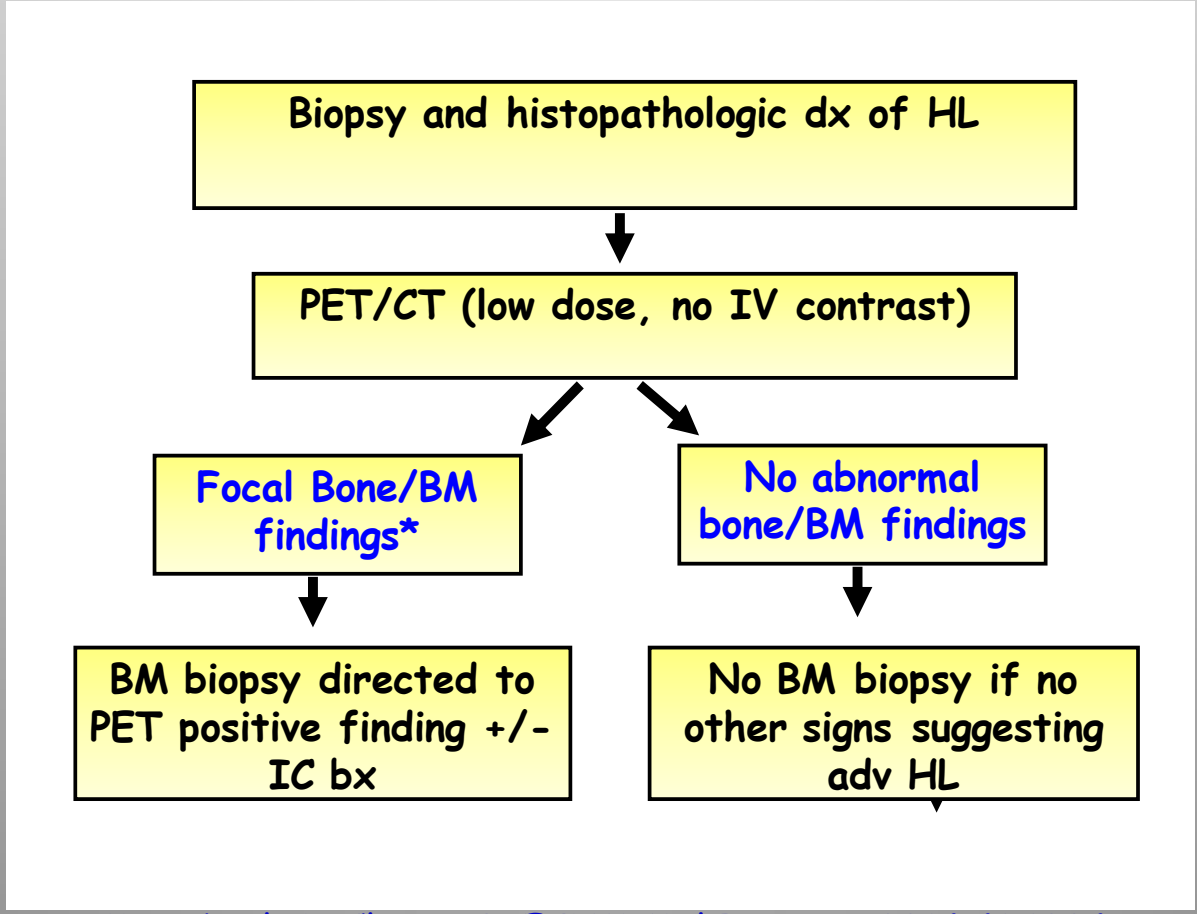
- **Focal FDG uptake in the BM is highly sensitive for BMI**
  Pelosi E, Q J Nucl Med Mol Imaging 2008, Wu LM, Eur J Radiol 2010, Moulin-Romsee G, EJNM 2010, Pakos EE, J Nucl Med 2005, El-Galaly TC, JCO 2012
  - **early HL, BMI is rare with no PET finding, also PET identifies sites distant from iliac bone**
  - **adv HL rarely presents with BMI with no other evidence of adv disease**
  - **in 18% of pts with focal bone lesions on PET, only 6% had +BMB, all adv HL and none would have been allocated to other rx based on BMB**

    El-Galaly TC, JCO 2012

after a staging PET/CT, BMB no longer required for routine evaluation of HL pts Cheson B, JCO 2014

Bone marrow involvement

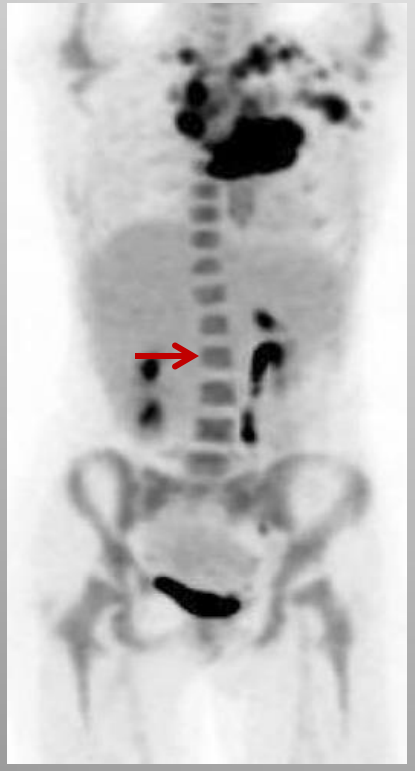
FDG PET should be performed before the BMB, should be used as a guide for BMB, in the case of PET+ results



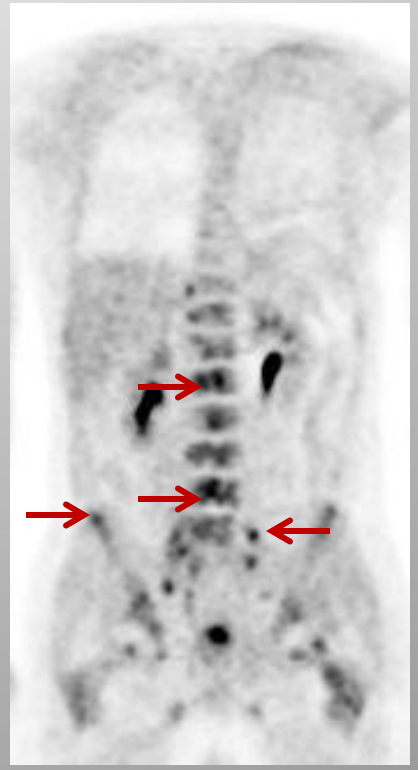
Kostakoglu L, Cheson B, EJNM Mol Imaging, 2014;41:1004

- **Only focally increased BM uptake at baseline should be considered +ve**
- **Diffusely increased BM uptake usually reflects myeloid hyperplasia, particularly for HL**

Shaefer NG. EJNM 2007, Nunez R, Rev Esp Med Nucl 2005, Elstrom RL, Clin Lymphoma. 2004, Salaun PY, EJNM, 2009



myeloid hyperplasia



proven BM involvement

RT Planning - PET/CT in HL

Incorporation of PET into CT-based RT planning for lymphoma results in considerable changes in volume definition, normal tissue dosimetry for a significant number of pts

Terezakis SA, Int J Radiat Oncol Biol Phys 2014;89

Role of FDG-PET in the Implementation of INRT for HL

- **135 pts of EORTC/ LYSA/FIL H10 trial prospectively included**
- **addition of PET to CT led to a CTV increase in 60% of pts**

Conclusions Pre-chemo PET leads to significantly better INRT delineation without necessarily increasing RT volume

Measure	Volume determination with CT scan	Volume determination with PET-CT	% increase*	Paired *t*-test *P* value
Mean (±SD)	501.1 (±331.7)	526.9 (±334.4)	8.8% (±24.0)	<.0001

mean increases in the GTV and CTV were 8.8% and 7.1%, respectively

post-chemotherapy CTV (115 patients)				
Measure	CT scan	PET-CT	% increase**	Paired *t*-test *P* Value
Mean (±SD)	327.2 (±155.2)	350.7 (±171.1)	7.1% (±13.5)	<.0001

Girinsky T, Int J Radiat Oncol Biol Phy 2014:89;1047

Interim response assessment

PET/CT is performed at interim therapy to assess early treatment response to serve as a surrogate for adapted strategies

- PET/CT provided better prognostic info than CT, with a high NPV, 2y PFS of ~95% in PET-ve, and 10-50% in PET +ve pts
- PET found to be an independent predictor superior to other pf's

Interim FDG PET in HL

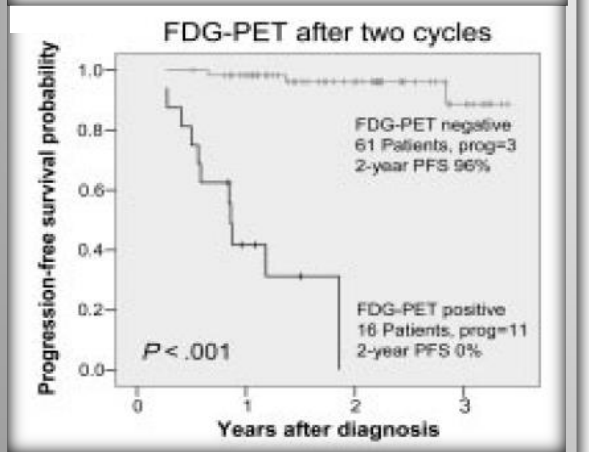
Author	Design	Pts	Stage	IntPET	PPV %	NPV %	PFS (%) PET+	PFS (%) PET-	Med fu (mo)
Gallamini 2006	pros	108	IIA, IIB-IV	2	90	97	6	96	20_m
Hutchings2006	pros	77	I-IV	2	69	95	0	96	23
Zinzani,2006	pros	40	IIB-IV	2	100	100	*	*	18
Gallamini 2007	pros	260	IIA, IIB-IV	2	86	95	13	95	26
Markova 2009	pros	69	IIB-IV^{BEACOPPesc}	4	*	98	78	96	55
Kostakoglu 2012	pros	88	I-IIB	2	46	84	54	88	39
Hutchings 2005	retro	85	I-IV	2-3	61.5	94	46	97	40
Kostakoglu,2006	retro	23	II-IV	1	83	100	17	100	20
Zinzani,2012	retro	304	I-IV	2	72	92	13	95	45
Barnes,2011	retro	96	I-II$^{50\%RT}$	2-4	12	92	87	91	46
Cerci, 2010	retro	104	I-IV	2	53	92	53	90	36
Filippi, 2013	retro	80	I-IIA^{RT}	2	0	98	97	100	36
Biggi, 2013	retro	260	IIB-IV	2			28	95	36

In HL, midtreatment PET, 70-80% int PET -ve

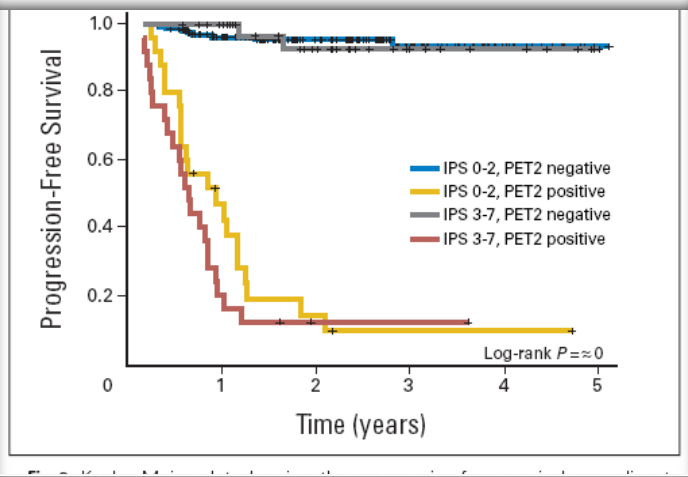
- NPV consistently high at least 95%
- PPV variable, 60 – 90%
- Combined sensitivity 81% and specificity 97%

Terasawa T, JCO 2009;27:1906

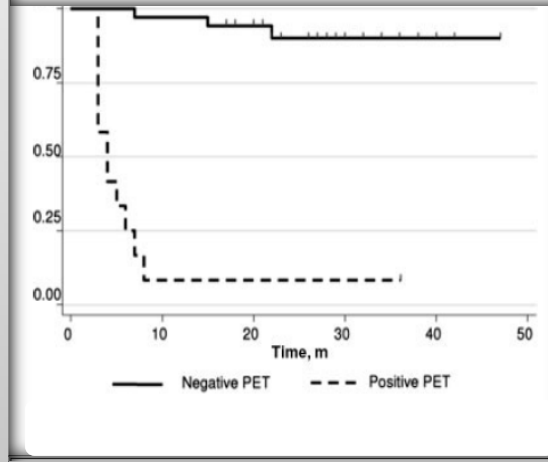
Hutchings et al, Blood 2006



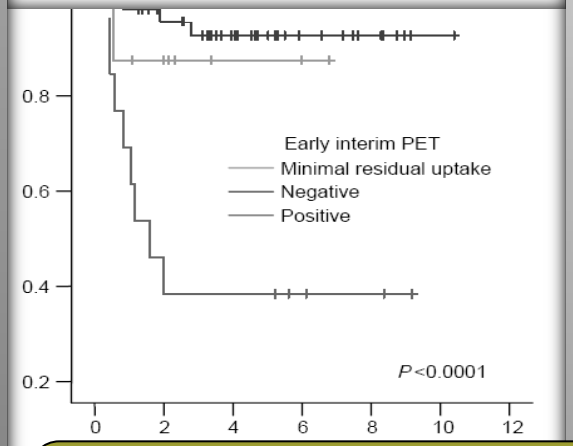
Gallamini et al, JCO 2007



Kostakoglu et al, Cancer 2006



Hutchings et al, Ann Oncol 2005



Gallamini et al, Haematologica 2006

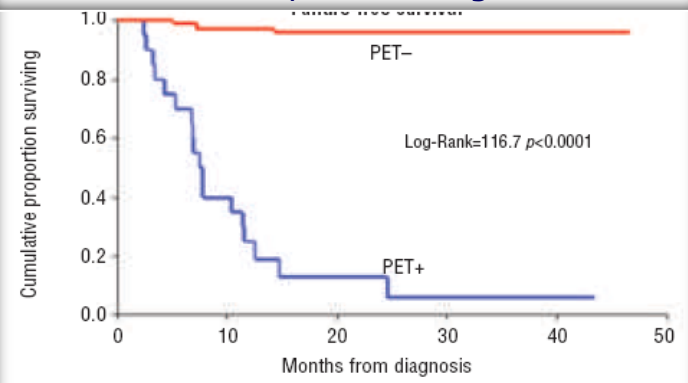
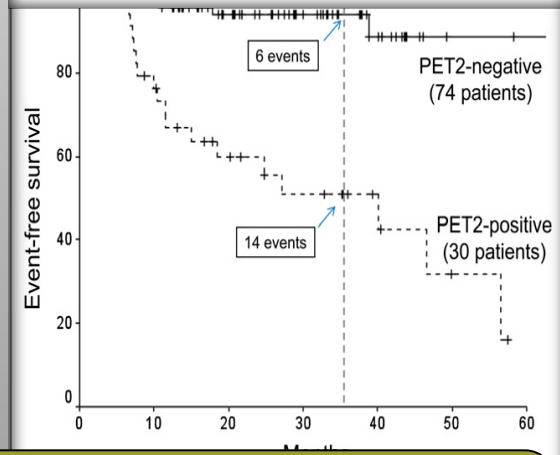


Figure 3. Probability of failure-free survival according to PET-2

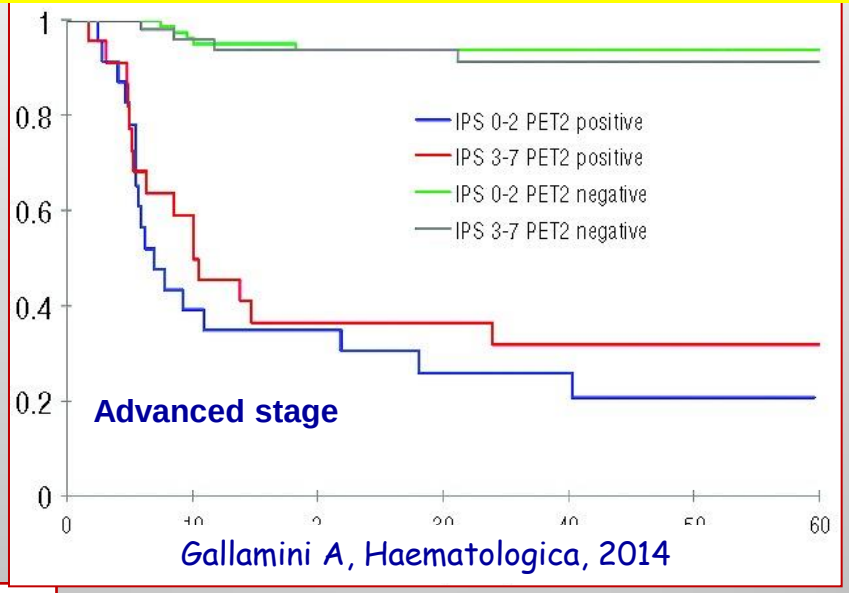
Cerci et al, J Nucl Med, 2010



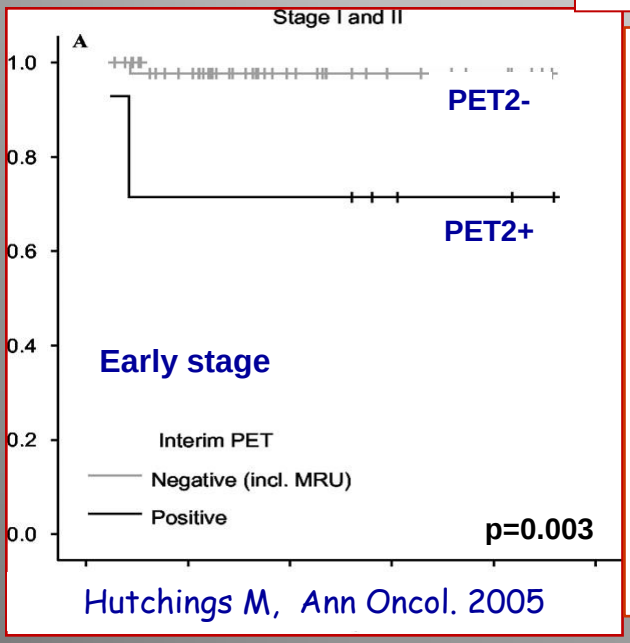
- most powerful prognostic indicator in HL for 1st line rx
- R & non-R can be identified by PET after several chemo cycles

Interim PET is not highly predictive of outcome

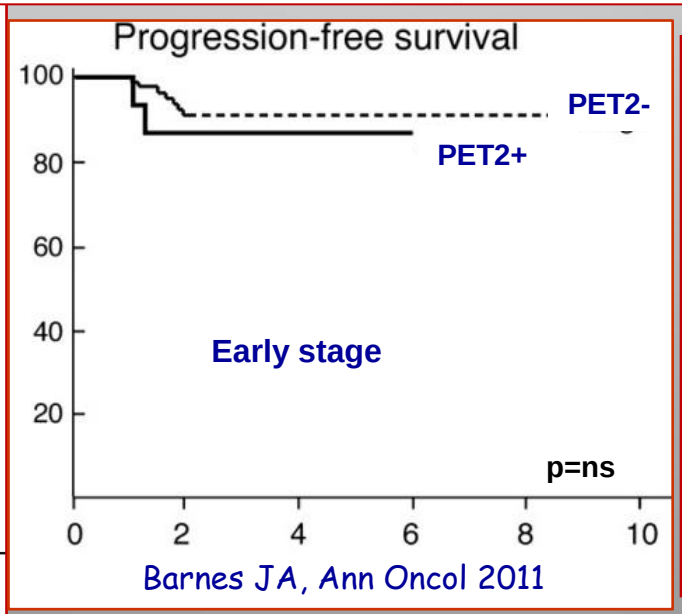
- in early stage (non-bulky) HL pts
- in those pts treated with more effective therapy



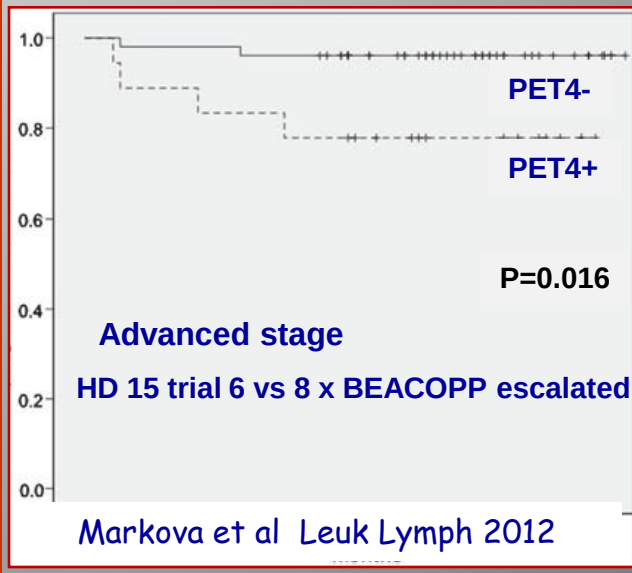
Gallamini A, Haematologica, 2014



Hutchings M, Ann Oncol. 2005



Barnes JA, Ann Oncol 2011



Markova et al Leuk Lymph 2012

DEAUVILLE 5PS

- D 5PS is recommended for reporting PET/CT studies; results should be interpreted in context of prognosis & clinical findings
- D 5PS for reporting improved reproducibility of results

Meignan M. Leuk Lymphoma. 2009, Barrington SF, EJNMMI 2010

NEGATIVE SCAN

Score 1 no uptake
Score 2 uptake ≤ mediastinum
Score 3 uptake > mediastinum, ≤liver

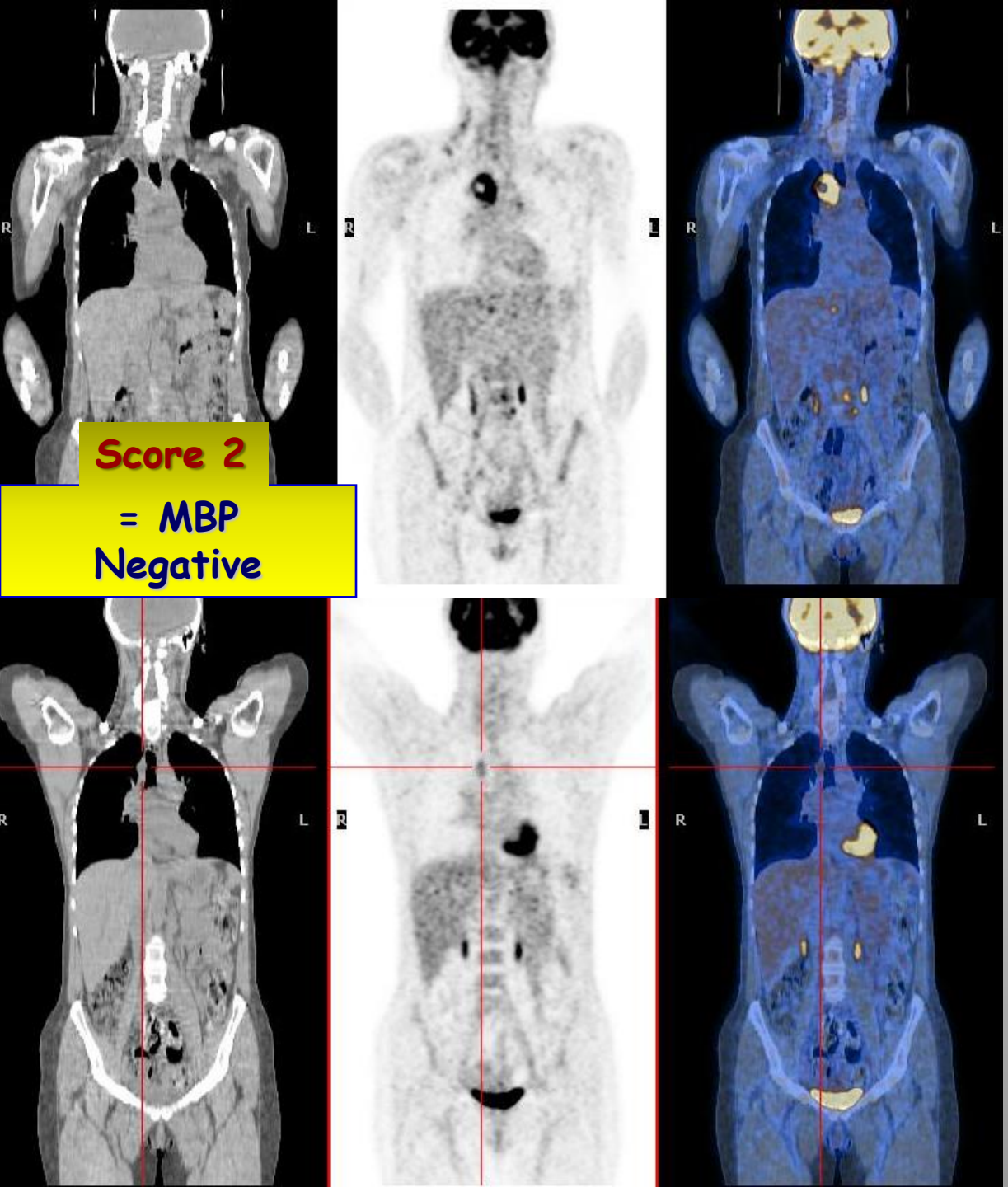
POSITIVE SCAN

Score 4 moderately ↑ uptake > liver
Score 5 markedly ↑ uptake > liver

Score X: new areas of uptake unlikely to be related to lymphoma

Category	Metabolic response by Lugano Criteria
CMR	Score 1,2,3* in nodal or extranodal sites with or without a residual mass using 5-PS
PMR	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-treatment,* these findings indicate residual disease Bone marrow: Residual BM uptake > normal BM but reduced from baseline (diffuse changes allowed). If there are persistent focal changes in BM with a nodal response, consider MRI, biopsy or interval scan
NMR	Score 4 or 5 with no significant change in uptake from baseline *at interim or end of treatment*
PMD	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*

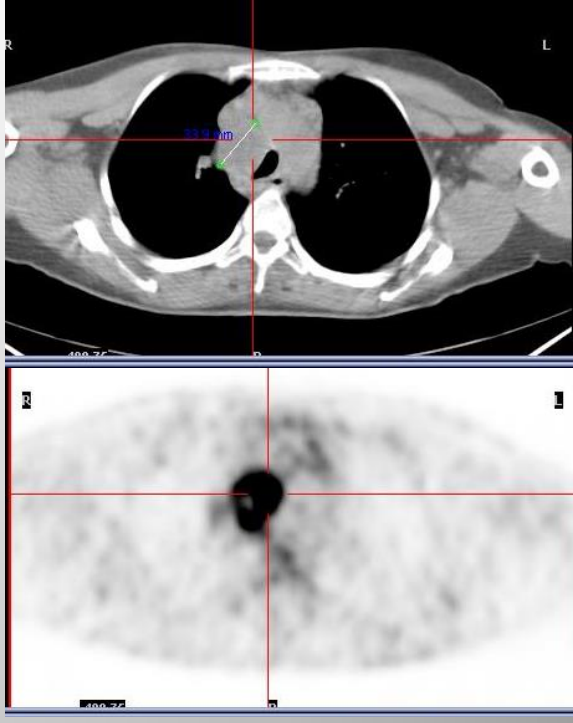
*Score 3 indicates a good prognosis with std rx. However in PET-adapted de-escalation trials, score 3 may be preferable to represent inadequate response to avoid under-treatment

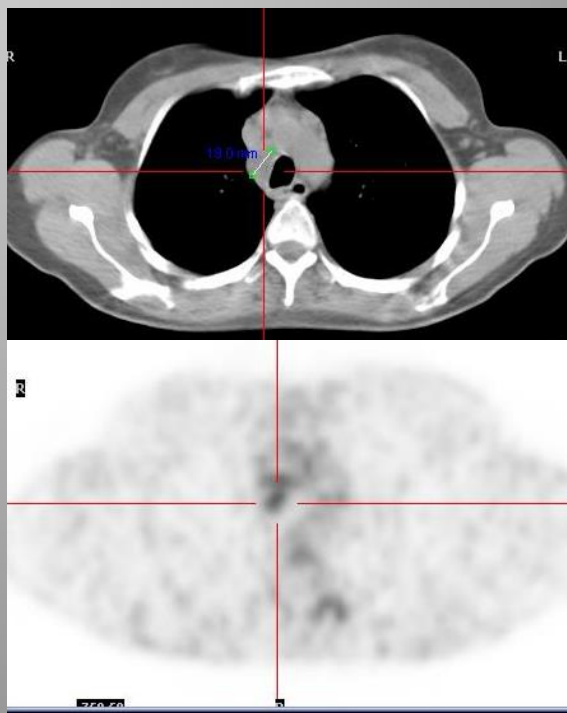


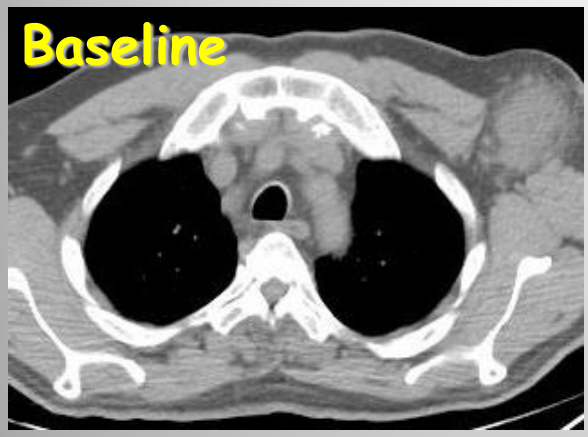
Score 2

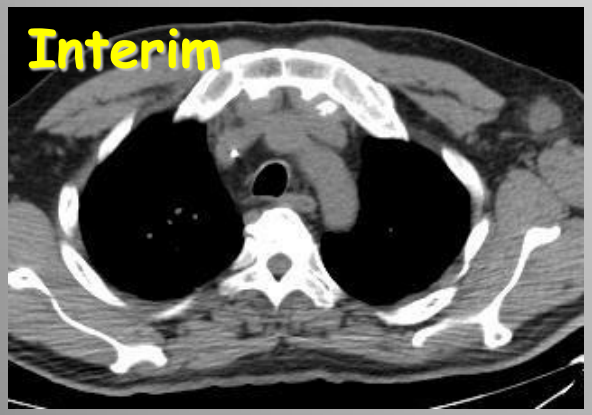
= MBP Negative

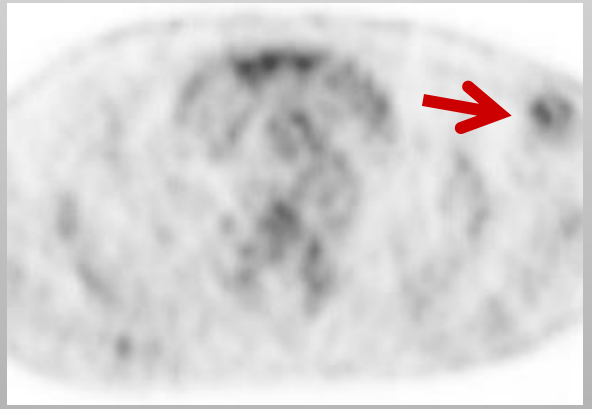
CMR





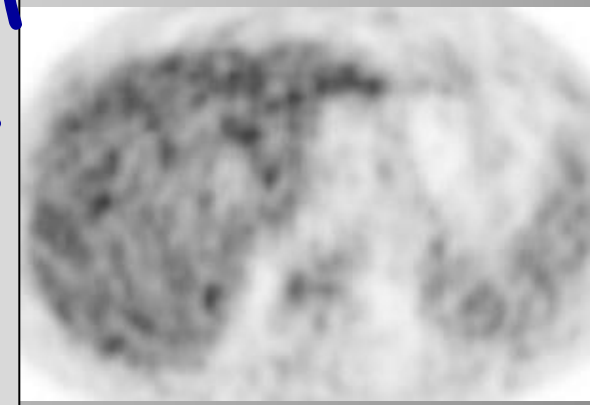






CMR

PFS: 24 mo



Score 3

Uptake = Liver
Negative

Score 1,2,3 in nodal or END sites with or without a residual mass

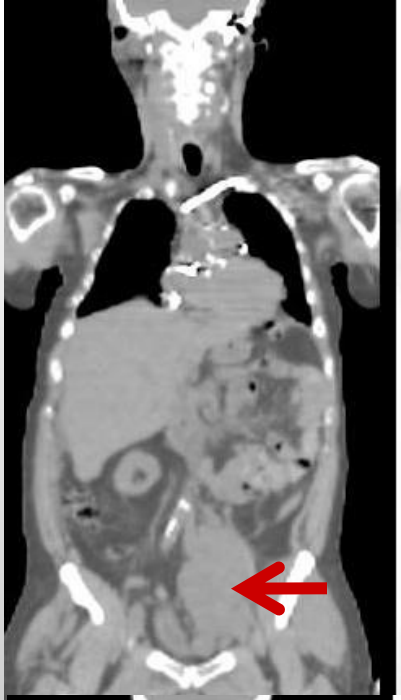
PMR

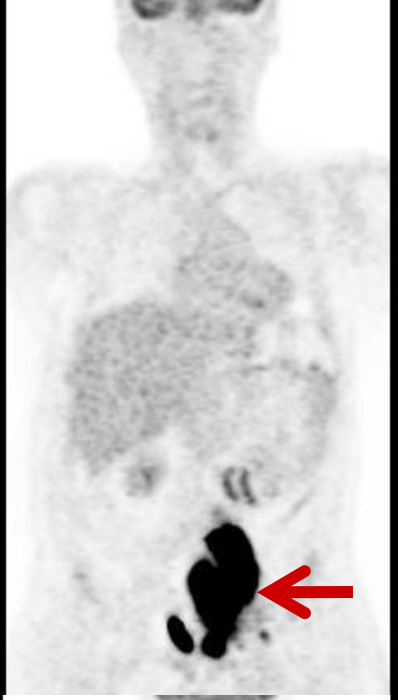
Score 4

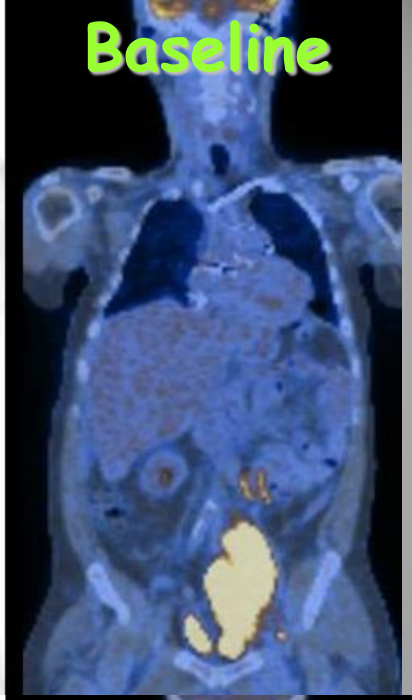
Uptake >Liver

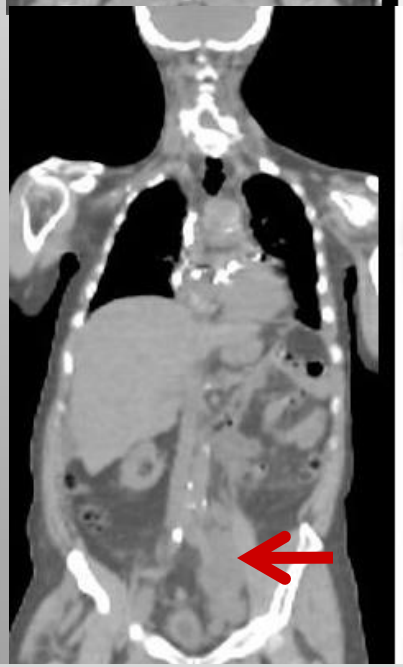
Positive

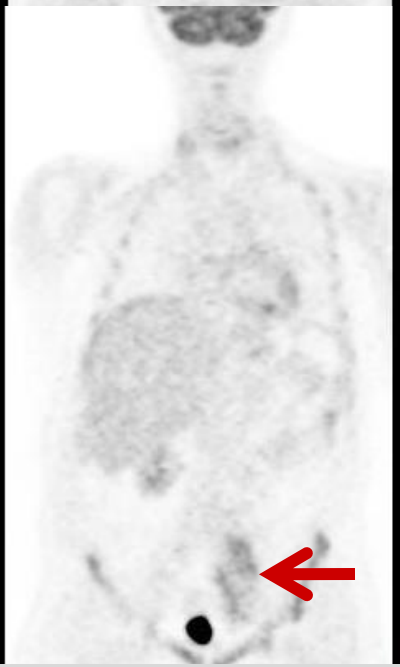
PFS: 9 mo

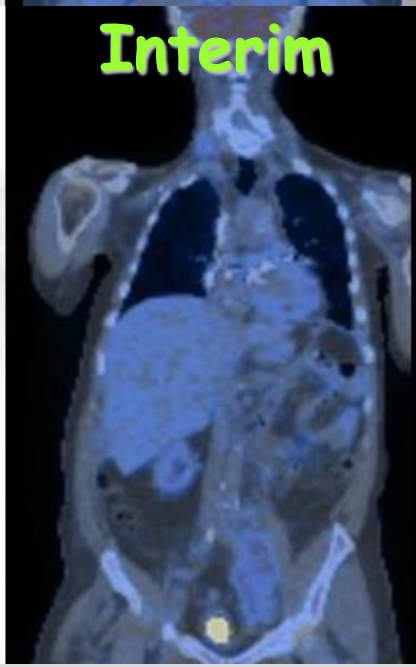












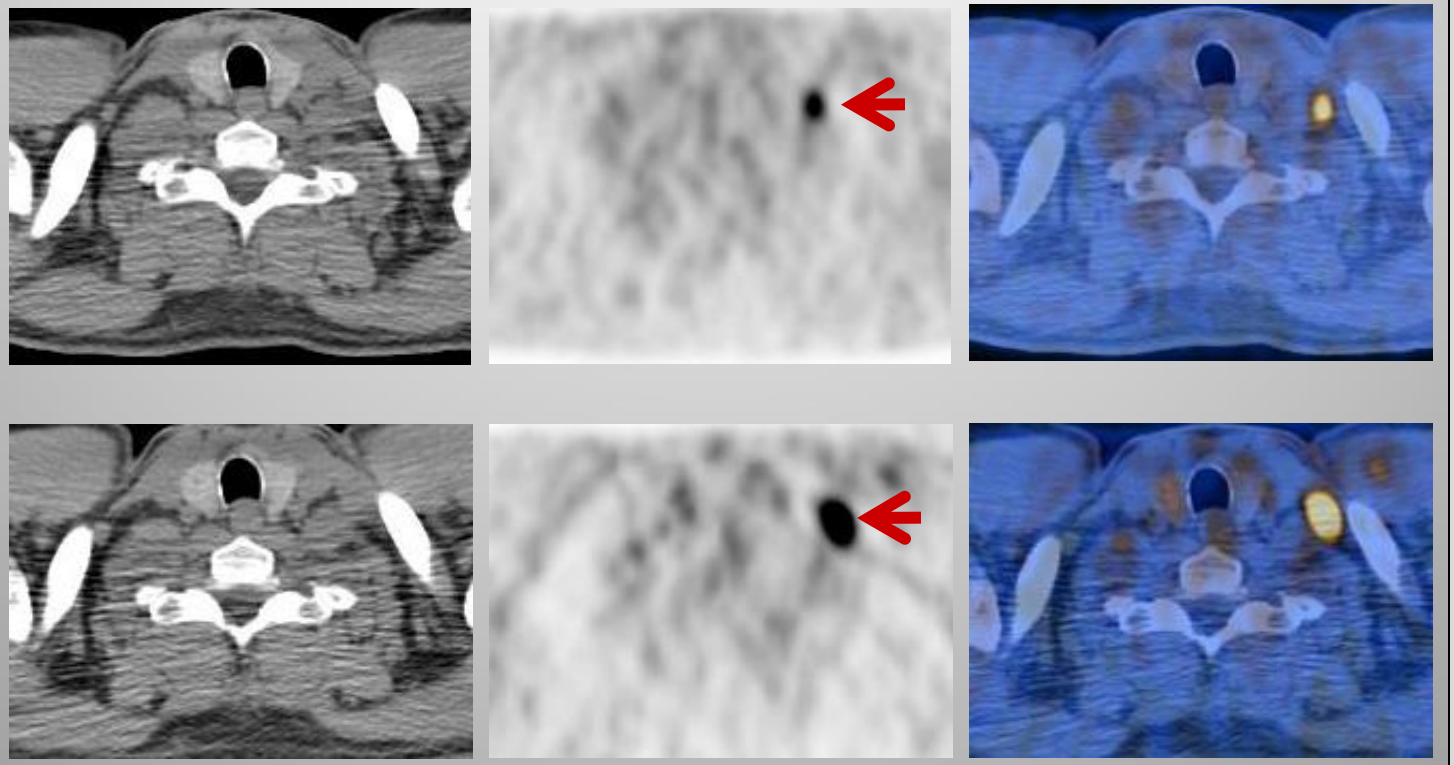
Score 4 or 5, with reduced uptake compared with baseline

Score 5

>Liver and >MBP Positive

Baseline

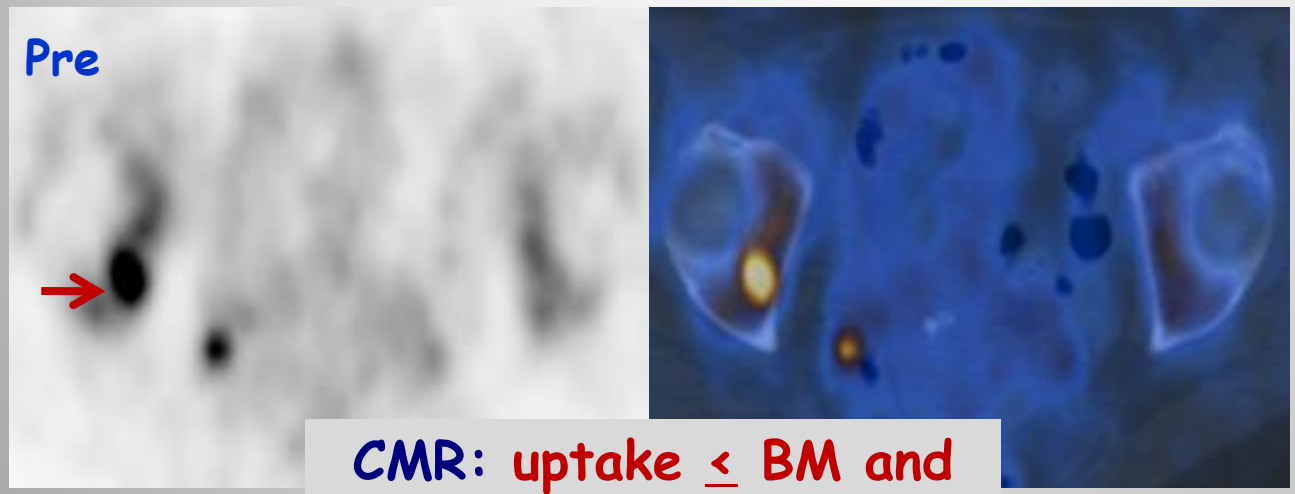
End rx

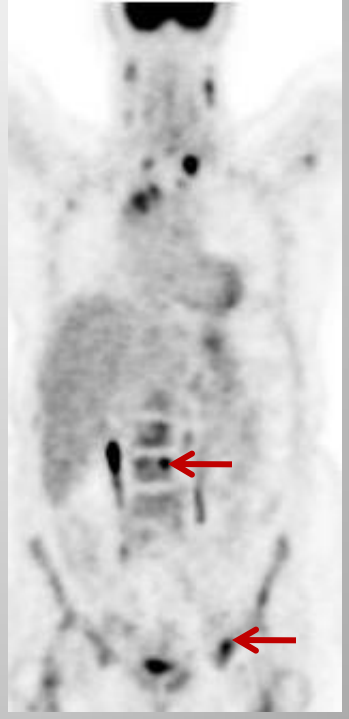


PMD

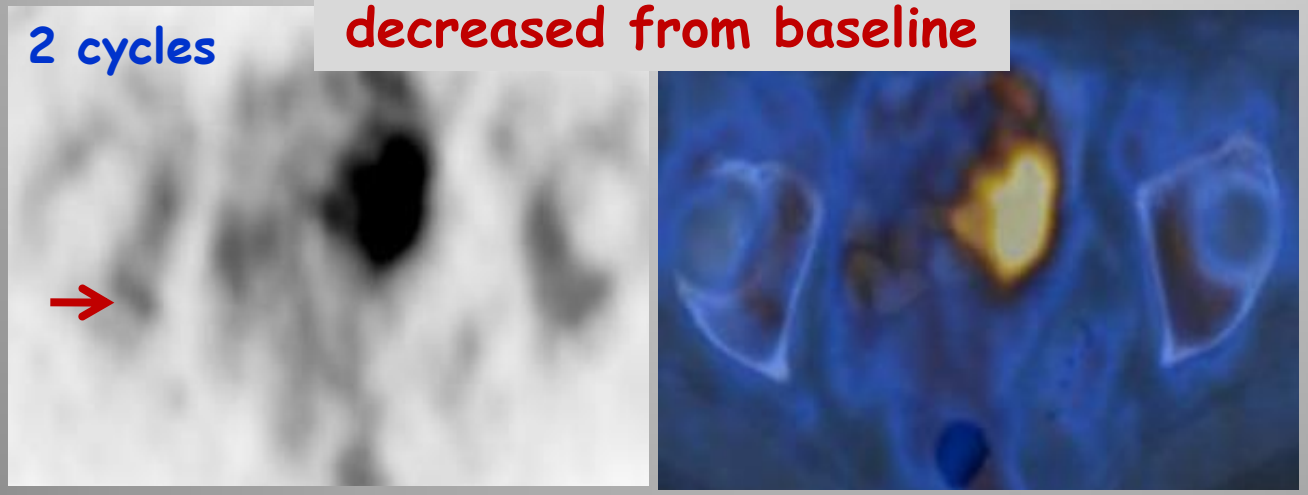
score of 4 or 5 with intensity that does not change or increases from baseline and/or new foci of lymphoma represents treatment failure at interim and at the end-of-treatment assessment

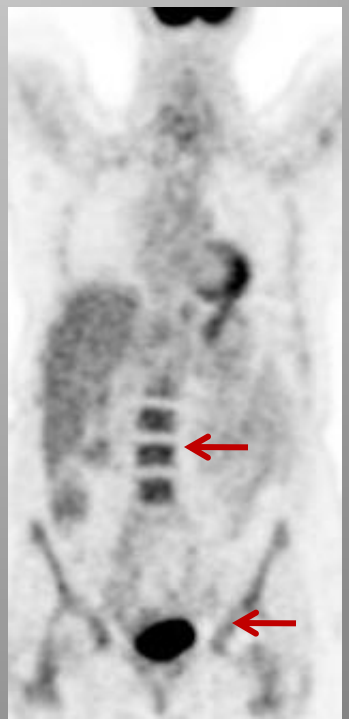
Only focally increased BM uptake at baseline should be evaluated for response





CMR: uptake ≤ BM and decreased from baseline





PMR Residual BM uptake > normal marrow but reduced from baseline

If persistent focal changes in BM with a nodal response, consider MRI, biopsy or interval scan

PET-adapted therapy

Goal:

-select low risk (PET-ve) pts to de-intensify treatment; shorter courses or obviate RT

-select high risk pts to intensify treatment

Response adapted Trials in Early Stage HL

Table 1. Prospective noncontrolled response-adapted studies in adult early-stage (I-II) HL

Trial	Patients	Treatment	Number	Interim PET$^+$	PPV	NPV	Survival
Le Roux et al, 2011[28]	Stages I-IV	ABVD × 4 (FDG-PET): I/II nonbulky: PET$^-$ and/or CR on CT IFRT; PET$^+$ SCT II bulky/III/IV: PET$^-$ ABVD × 4; PET$^+$ SCT	90 (45 stage I/II)	34% (all patients)	16% (all patients)	95% (all patients)	NA
Dann et al, 2013[40]	Stage I-IIA-B nonbulky	ABVD × 2 (FDG-PET): favorable: PET$^-$ INRT; PET$^+$ ABVD × 2 + INRT (PET 4)* Unfavorable: PET$^-$ ABVD × 2 + INRT; PET$^+$ ABVD × 4 + INRT (PET 4)*	350/350†	13%	26%	93%	2-y PFS 94%
CALGB 50604 (NCT01132807)	Stage I/IIA-B nonbulky	ABVD × 2 (FDG-PET): PET$^-$ ABVD × 2 PET$^+$ BEACOPP-escalated × 2 + 30Gy IFRT	160/160	Accrual completed February 2013; preliminary results expected 2015			
CALGB 50801 (NCT01118026)	Stage I/IIA-B bulky	ABVD × 2 (FDG-PET): PET$^-$ ABVD × 4 PET$^+$ BEACOPP-escalated × 4 + 30Gy IFRT	53/123†	NA			

Table 2. Randomized phase 3 response-adapted studies in adult early-stage (I-II) HL*

Trial	Patients	Enrollment†	Results
EORTC/LYSA/FIL H10F[41]	Favorable group	761/761† (381 PET$^-$ patients)	1-y PFS rates 100.0% and 94.9% in standard and experimental arms, respectively; estimated HR = 9.36 (79.6% CI, 2.45-35.73)
EORTC/LYSA/FIL H10U[41]	Unfavorable/intermediate group	1191/1191† (519 PET$^-$ patients)	1-y PFS rates 97.3% and 94.7% in standard and experimental arms, respectively; estimated HR = 2.42 (80.4% CI, 1.35-4.36)
UK NCRI RAPID[42]	Favorable and unfavorable/intermediate groups combined (nonbulky)	602/602	3-y PFS for no RT versus IFRT in PET$^-$ patients: 91% versus 95% by ITT (P = .23) and 91% versus 97% by protocol analysis (P = .03); 3-y PFS for PET$^+$ 85%
GHSG HD16 (NCT01356680)	Favorable group	686/1100‡	NA
GHSG HD17 (NCT00736320)	Unfavorable/intermediate group	283/1100‡	NA

Evens A, Blood;2014:124:3356

Cochrane Central Register of Controlled Trials and MEDLINE Systematic Review (H10, RAPID, Picardi) n=1480

Key results

- PFS shorter with PET-adapted rx than std rx in early HL
- insufficient data of the effect of PET-adapted rx on OS
- no robust data on QoL, short- and long-term AEs
- uncertain whether PET+ pts benefit from PET-adapted approach and the effect of such an approach in adv HL

In 1000 pts over 4 years,

222 prog or death in PET-adapted vs. 100 in std rx

Sickinger MT, Cochrane Database Syst Rev. 2015 Jan 9;1

H10 Results of futility analysis in early PET- patients (n=1137)

Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

Subset	No. of Patients	No. of Observed Events	HR	Adjusted CI*	P†	1-Year PFS	
						%	Adjusted CI*
Favorable					.017		
Standard	188	1	1.00			100.00	
Experimental	193	9	9.36	2.45 to 35.73		94.93	91.89 to 96.85
Unfavorable					.026		
Standard	251	7	1.00			97.28	95.17 to 98.48
Experimental	268	16	2.42	1.35 to 4.36		94.70	92.11 to 96.46

Raemaekers, J Clin Oncol 2014;32:1188

RAPID Results

PFS in the randomised PET –ve population (intention to treat) n=420

3 y PFS per protocol

PET –ve IFRT	PET –ve, NFT
94.5%	90.8%

HR 1.51 in favour of IFRT, p=0.23

*1 death from cardiac failure in a pt who had IFRT

PFS in the randomised PET -ve population (per protocol analysis) n=392

3 y PFS per protocol

PET –ve IFRT	PET –ve, NFT
97%	90.7%

HR 2.39 in favour of IFRT, p=0.03

3.7% (ITT) and 6.3% (PP) improvements in 3 y PFS are obtained at the cost of irradiating all pts most of whom would not need it

Courtesy, Radford J, et al. Cologne 2013.

Success of CMT in disease control is well recognized in early-stage HL, however, this has not translated to an improvement in OS

Laskar S, J Clin Oncol, Hay AE, Ann Oncol. 2013, Wolden SL, J Clin Oncol. 2012

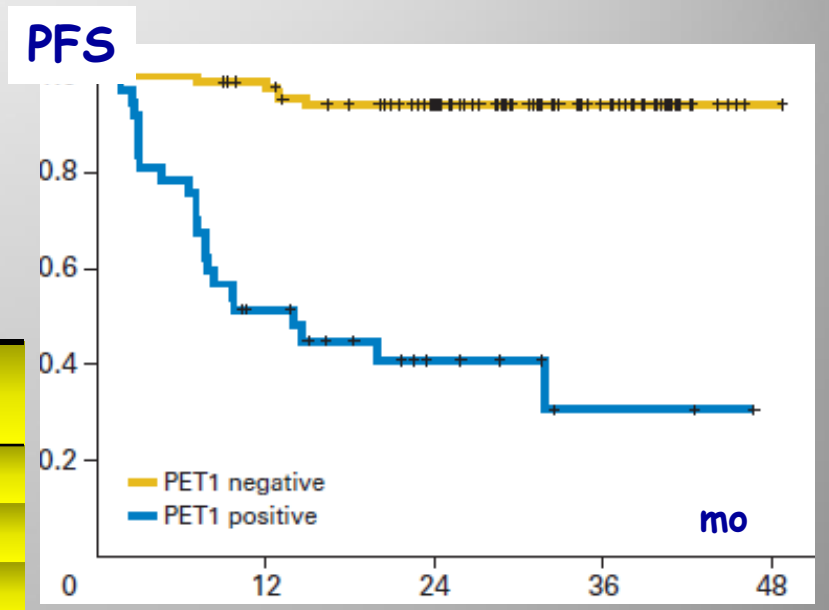
Late adverse effects e.g. CVD and secondary cancers should be seriously considered Meyer RM, N Engl J Med. 2012,

PET after 1 cycle vs 2 cycles in HL

PFS according to interim PET results

		All pts	Limited (I-IIA)	Advanced (IIB-IV)
No.		126	44	82
2-y PFS	PET1 pos	40.8%	50%	37.1%
	PET1 neg	94.1%	100%	90.3%
3-y PFS	PET1 pos	30.6%	25%	37.1%
	PET1 neg	94.1%	100%	90.3%

N=89 PET1 and PET2		PET1	PET2
	NPV	98.4%	90.8%
	PPV	63.0%	84.6%
	Sensitivity	94.4%	61.1%
	Specificity	85.9%	97.2%



In the absence of precise pretherapeutic predictive markers, PET1 is the best method for response-adapted strategies designed to select patients for less intensive treatment

Hutchings M, J Clin Oncol 2014;32:2705

Response Adapted Trials in Advanced Stage HL

HD 0607 (Gallamini)	450	IIB-IV	ABVDx2 → PET	- ABVDx4 + eBEACOPPx4, sBEACOPPx4
SWOG 0816 CALGB (Press)	371	III-IV	ABVDx2 → PET	- ABVDx4 + eBEACOPPx6
AHL 2011 (Casasnovas)	798	III-IV or IIB*	eBEACOPPx2 → PET	- ABVDx2 + eBEACOPPx2
RATHL (Johnson)	1,200	II-IV †	ABVDx2 → PET	- ABVDx4 or AVDx4 + eBEACOPPx4
HD18 (Engert)	1,500	IIB-IV	eBEACOPPx2 → PET	- eBEACOPPx6 or eBEACOPPx2 + eBEACOPPx6 or BEACOPPx6 + rituximab
HD0801 (Levis)	300	IIB-IV	ABVDx2→ PET	- ABVDx4 + IGEVx4 + ASCT
ISRA2432_CTIL (Dann)	660‡	III-IV IPS 0-2	ABVDx2 → PET	- ABVDx4 + eBEACOPPx2 + eBEACOPPx2 + INRT^{PET-4-}
		II-IV IPS 3-7	eBEACOPPx2 → PET	- ABVDx4 + eBEACOPPx2 + eBEACOPPx2 + INRT^{PET-4-}

Slide courtesy, Oliver Press

Recommendation for Interim PET

- If midtherapy imaging is planned,PET-CT is superior to CT alone to assess early response
- Trials are evaluating the role of PET–adapted treatment strategies
- Currently, changing treatment solely on the basis of iPET-CT is not recommended, unless there is clear evidence of progression

Barrington S, J Clin Oncol 2014;32

FDG PET/CT Assessment Pre-ASCT

PET response in stem cell transplantation (SCT)

PET-ve pts before ASCT were significantly more likely to be cured

Pre-SCT PET-vity is one of the strongest predictors of outcome after HDT/ASCT for pts with rel/refrac HL

Moskowitz AJ, *Blood* 2010, Gentzler RD, *Br J Haematol* 2014, Akhtar S, *Bone Marrow Transplant*, Devillier R, *Haematologica* 2012, Smeltzer JP, *Biol Blood Marrow Transplant* 2011, Mocikova H, *Leuk Lymphoma* 2011, Jabbour E, *Cancer* 2007

No difference in outcome for pts btw two salvage regimens and one, provided that the pre-ASCT PET is -ve

Moskowitz CH, *Blood* 2012; 119:1665.

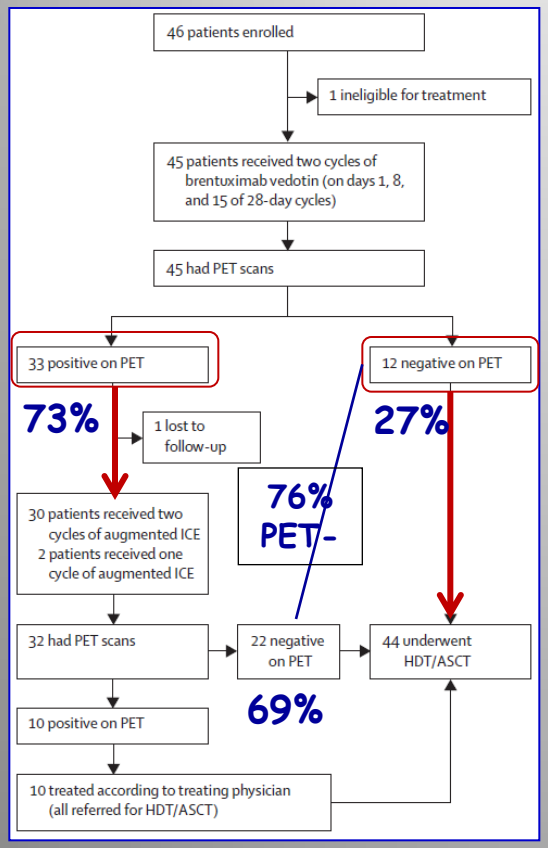
	CT-based	PET-based
CR	17- 21%	54 - 60%

Santoro A , Haematologica, 2007, Moskowitz CH, *Blood* 2012

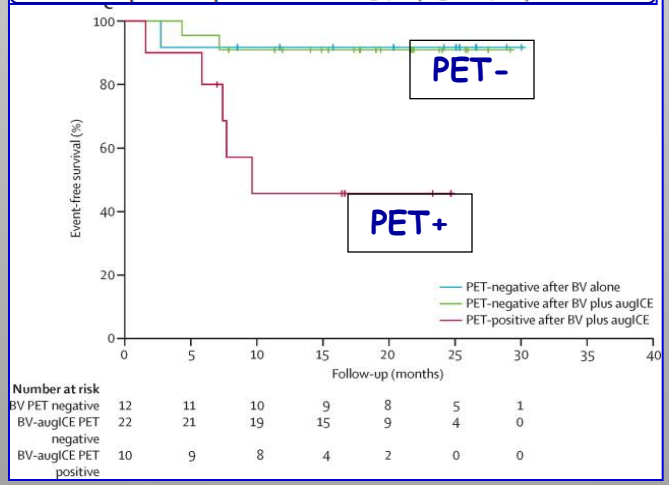
	PET+ve	PET-ve
PFS or EFS	23 – 52%	69 – 85%

Gentzler RD, *Br J Haematol* 2014, Akhtar S, *Bone Marrow Transplant* 2013, Devillier R, *Haematologica* 2012, Smeltzer JP, *Biol Blood Marrow Transplant* 2011, Mocikova H, *Leuk Lymphoma* 2011, Jabbour E, *Cancer* 2007

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ICE for relapsed/refractory HL: a non-randomised, open-label, single-centre, phase 2 study



	HR (95% CI)	p value
Univariate analysis		
Age ≥45 years	3·15 (0·79–12·60)	0·09
B symptoms at relapse	3·00 (0·72–12·60)	0·12
Refractory	6·25 (0·77–50·90)	0·05
Refractory or relapse within 1 year	1·75 (0·22–14·22)	0·60
Advanced stage at relapse	3·63 (0·73–17·97)	0·09
Extranodal disease at relapse	1·58 (0·39–6·31)	0·50
Bulk disease ≥5 cm at relapse	1·02 (0·20–5·26)	0·98
Positive PET pre-transplantation	6·73 (1·60–28·30)	0·003
Multivariate analysis		
Refractory	5·00 (0·60–41·40)	0·130
Positive PET pre-transplantation	5·70 (1·30–24·10)	0·02



PET-adapted (score 1 or 2 -ve) sequential salvage rx with BV followed by augICE resulted in a high rate of PET-vity,

This approach could optimize the chance of cure after HDT/ASCT in rel/ref HL

Moskowitz AJ. Lancet 2015;16:284

End-therapy response assessment

FDG PET/CT is performed at end of treatment to establish remission status

Most defined role for PET/CT is in the response assessment of HL and DLBCL after therapy

- End-of-treatment assessment is more accurate with PET/CT, especially for pts with residual masses a/o CT-based PR

Cheson JCO 2007, Juweid ME, JCO, 2005, Cerci JJ, JCO, 2010, Wiedmann E, Leuk Lymphoma, 1999, Hueltenschmidt B, Cancer, 2001, Bishu S, Leuk Lymphoma. 2007.

- In early- and adv-stage HL pts, a NPV of 95-100% have been consistently reported

	# studies	# pts	Sens	Spec	PPV	NPV
HL	15	408	84	90	60	97
aNHL	13	350	72	100	97	78

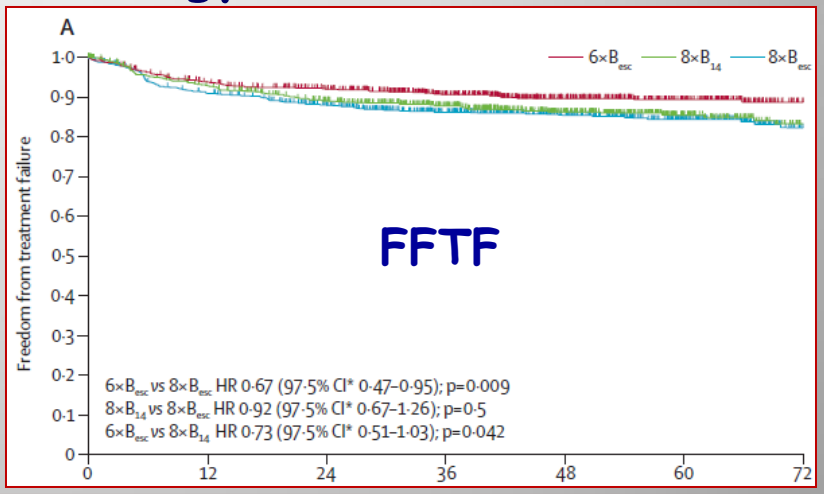
Zijlstra JM, et al. Haematologica. 2006;91:522

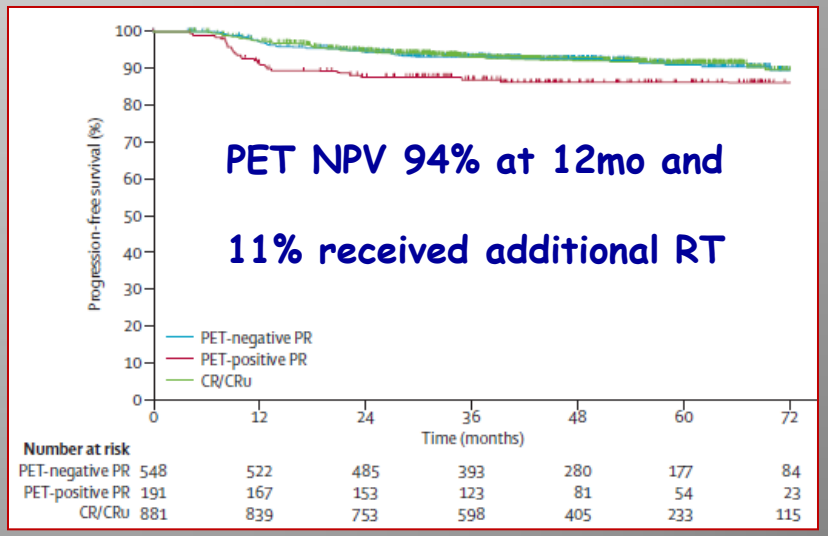
Higher PPV for aNHL; Higher NPV for HL
HL is more curable than aNHL

PET-guided Consolidation RT

Using end PET to select those with residual masses and PMR needing cRT appears to be a good strategy

- GHSG HL 15, randomized trial comparing 2 reduced-intensity BEACOPP variants with std regimen
- 2182 adv stage HL randomly assigned to 3 arms
- 6-8 x chemo followed by PET-guided 30 Gy RT to persistent mass >2.5cm
- 6xBEACOPP$_{esc}$ followed by PET-guided RT, more effective and less toxic than 8x in terms of FFTF
- PET after chemo can guide the need for additional RT in this setting





Engert A, Lancet 2012;379:1791.

Recommendation End-therapy

- PET-CT is the SOC for remission assessment in HL
- In the presence of residual metabolically active tissue, where salvage rx is being considered, a bx is recommended (HL and DLBCL)
- Significance of a residual mass if CMR is achieved is unclear
  - it is proposed that the size of the residual mass be recorded, and relapses should be evaluated with respect to the residual mass
  - investigation of the significance of PET -ve residual masses should be collected prospectively in clinical trials

Barrington S, J Clin Oncol 2014;32

Follow up and Relapse

- **Follow-up scans should be prompted by clinical indications: symptoms are the most effective means of detecting a recurrence**

Radford JA, BMJ. 1997;314:343, Cheson B, JCO, 2014:32;3059

- **Routine PET or CT holds little value in identifying relapses and cannot be recommended in pts achieving a -ve interim or end-of-treatment PET/CT**

Dryver ET, Br J Cancer. 2003;89:482, Dann EJ, Br J Haematol. 2014;164:694.

- **FP rate with PET scans is 20-30%, leading to unnecessary investigations, rad exposure, bx's, expense, and anxiety**

Summary

- PET/CT
  - the recommended modality for staging HL
  - may be used to select the best site to biopsy
  - obviates the need for BM biopsy
- Std PET protocols, reading, quantitative methods necessary
  - D 5PS is recommended for reporting PET/CT
- PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT
- effective in determining chemosensitivity during therapy
  predictive value of interim PET
  - is high in advanced stage HL
  - not as high in early stage HL and mitigated with PET-adapted escalated therapies
- Mature data from adaptive studies will establish the role of interim PET

Potential roles for PET/CT under investigation

- Quantitative PET
  - Prognostication at staging
  - Definition of tumor bulk refinement
  - Early response assessment
- Size measurements on PET/CT
- PET based RT planning
- PET-guided consolidation RT

Molte Grazie !