PET/CT in Lymphoma

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PET-CT in Lymphoma

- Staging
- Response Evaluation
  - During treatment
  - End of treatment
- Surveillance

FDG PET (-CT) in Lymphoma

- PET= whole body imaging
- **Sensitivity** depends on
  - FDG avidity
  - Size
  - Background activity surrounding tissue
- **Specificity**
  - Inflammatory tissue
  - Physiological uptake in brown fat, gut, urinary system
- PET-CT
  - Combination of metabolism and anatomy
  - Increase in sensitivity and specificity

FDG avidity of lymphomas according to WHO classification

Weiler-Sagie et al. JNM Jan 2001

TABLE 1. ^{18}F-FDG Avidity of Lymphoma According to World Health Organization Histopathologic Classification

Histology	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Hodgkin disease	233	233	0	100
Burkitt lymphoma	18	18	0	100
Mantle cell lymphoma	14	14	0	100
Anaplastic large T-cell lymphoma	14	14	0	100
Marginal zone lymphoma, nodal	8	8	0	100
Lymphoblastic lymphoma	6	6	0	100
Angioimmunoblastic T-cell lymphoma	4	4	0	100
Plasmacytoma	3	3	0	100
Natural killer/T-cell lymphoma	2	2	0	100
Diffuse large B-cell lymphoma	222	216	6	97
Follicular lymphoma	140	133	7	95
Peripheral T-cell lymphoma	10	9	1	90
Small lymphocytic lymphoma	29	24	5	83
Enteropathy-type T-cell lymphoma	3	2	1	67
Marginal zone lymphoma, splenic	3	2	1	67
MALT marginal zone lymphoma	50	27	23	54
Lymphomatoid papulosis	2	1	1	50
Primary cutaneous anaplastic large T-cell lymphoma	5	2	3	40
All	766	718	48	94

FDG uptake and grading

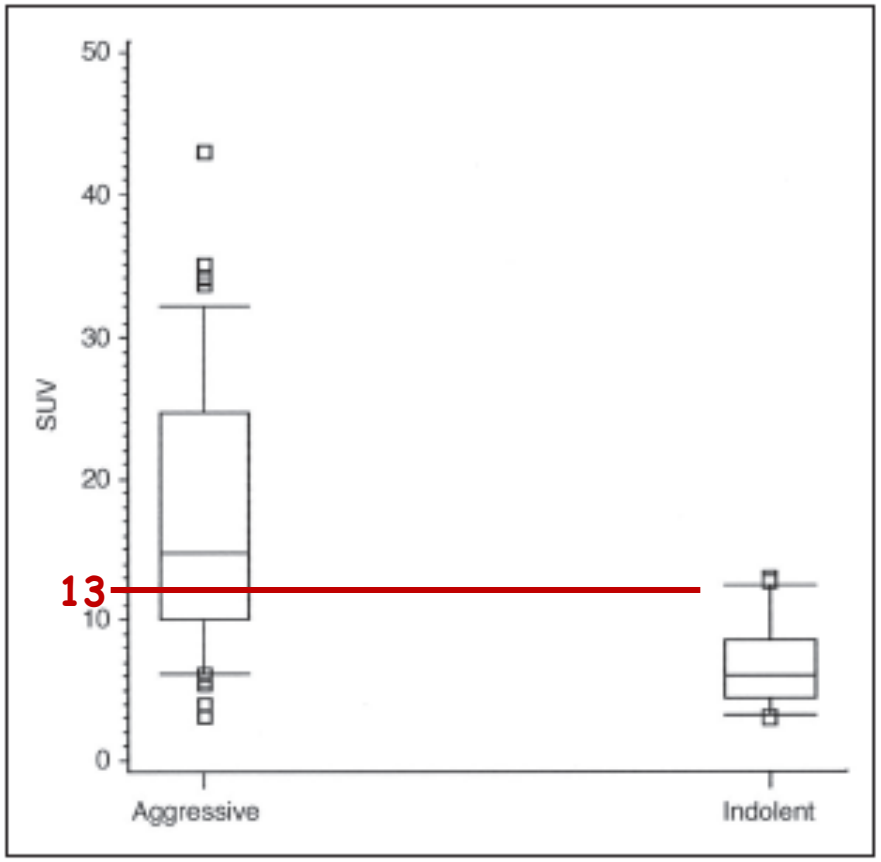


Fig 3. Box plots showing distribution of standard uptake value (SUV) among patients with aggressive and indolent lymphoma. The box represents the lower and upper quartiles and the median is marked with a horizontal line inside the box. The whiskers are the 10th and 90th percentiles with outlying observations individually plotted by squares outside the whiskers.

Schöder et al. JCO 2005

Aggressive N=63

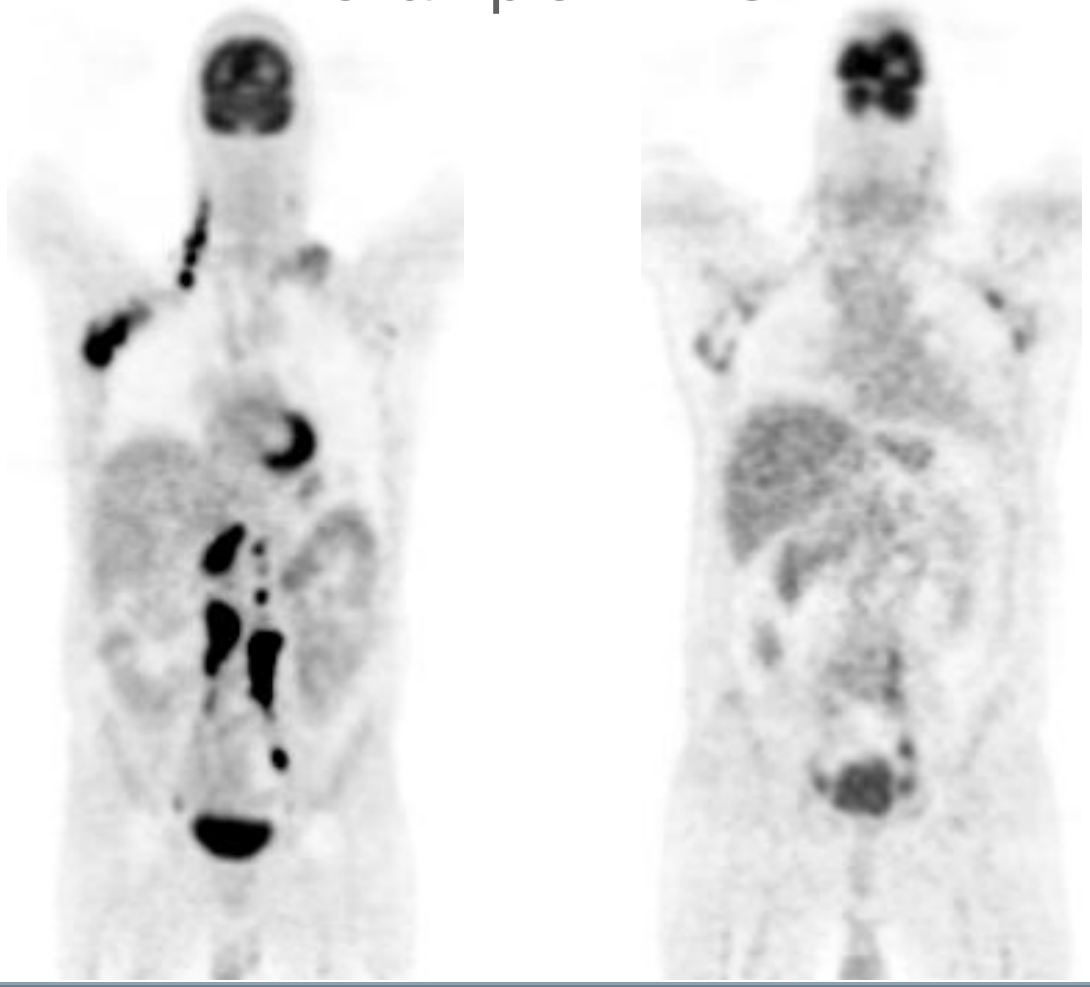
DLBCL	55
FL gr III	7
PTCL	1

Indolent N=28

FL gr I	11
FL gr II	4
MZL	4
small cell	8
lyPl	1

FDG avidity

Variability within same histological subtype: example DLBCL



PET for Staging of Lymphomas

Meta-analysis (Isasi et al. Cancer 2005, 104:1066-1074)
20 studies – 854 patients – 3658 lesions

TABLE 4
Summary True-Positive Rate, False-Positive Rate, and Maximum Joint Sensitivity and Specificity of FDG-PET in the Staging of Patients with Lymphoma (January 1995–June 2004)

	No. of studies	TPR (95% CI)	FPR (95% CI)	Maximum joint sens and specificity (95%
Patient-based data				
All	14	90.9 (88.0–93.4)	10.3 (7.4–13.8)	87.8 (85.0–90.7)
Excluding studies with lowest sensitivity and lowest specificity	12	91.8 (88.8–94.3)	9.5 (6.6–13.1)	89.6 (87.5–91.6)
Hodgkin disease	6	92.6 (88.4–95.6)	13.4 (8.0–20.6)	89.4 (84.5–94.3)
Non-Hodgkin lymphoma	5	89.4 (82.8–94.1)	11.4 (5.6–19.9)	85.0 (78.2–82.0)
Lesion-based data				
All	7	95.6 (93.9–97.0)	1.0 (0.6–1.3)	95.6 (93.1–98.1)
Excluding study with lowest specificity	6	95.1 (93.0–96.7)	1.0 (0.5–1.3)	95.8 (92.0–99.6)

upstaging : median 13.2% (7.7–17.4)
downstaging: median 7.5% (2.3–23.4)

PET for Staging of Lymphomas

Schiepers C, Eur J Nucl Med Mol Imaging. 2003 Jun;30 Suppl 1:S82-8.

Table 1. Overview of recent studies comparing CT and PET for the staging of lymphoma

First author	Year	Ref.	Patients	P	R	Positive lesions	Type	Sensitivity, CT	Sensitivity, PET	Specificity, CT	Specificity, PET	Biopsy
Buchmann	2001	[30]	52	52	–	124 regions	Mixed	84	99	100	100	30%
Jerusalem	2001	[35]	33	29	4	–	HD	73	79	–	–	–
Najjar	2001	[18]	36	21	15	31 sites	HD	90	87	100	100	All 31
Weihrauch	2002	[40]	22	22	–	77 sites	HD	74	88	100	100	–
Wirth	2002	[41]	50	50	–	117 sites	Mixed	68	82	–	–	–
Sasaki	2002	[22]	46	43	3	152 sites	Mixed	65	92	99	99	–

Three studies evaluated patients with Hodgkin's disease (HD), the other 3 had a mix of HD and NHL. When available, the number of sites biopsied is provided

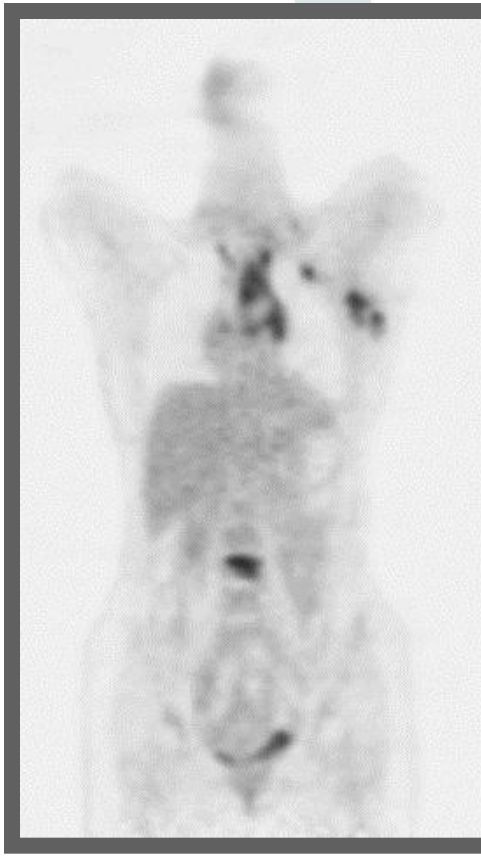
Ref, Reference number; P, number of patients for primary staging; R, number of patients for re-staging

PET/CT for staging HD

Raanani, Annals of Oncology 2006
Comparison of CE-CT with low-dose CT+PET

Table 3. Comparison of staging algorithms based on CT or PET/CT in 35 patients with HD

PET/CT	CT				
	I	II	III	IV	NE
I	–	2	–	–	–
II	1	**14**	1	2	–
III	–	5	**2**	–	–
IV	–	3	2	**2**	–
NE	–	1	–	–	–



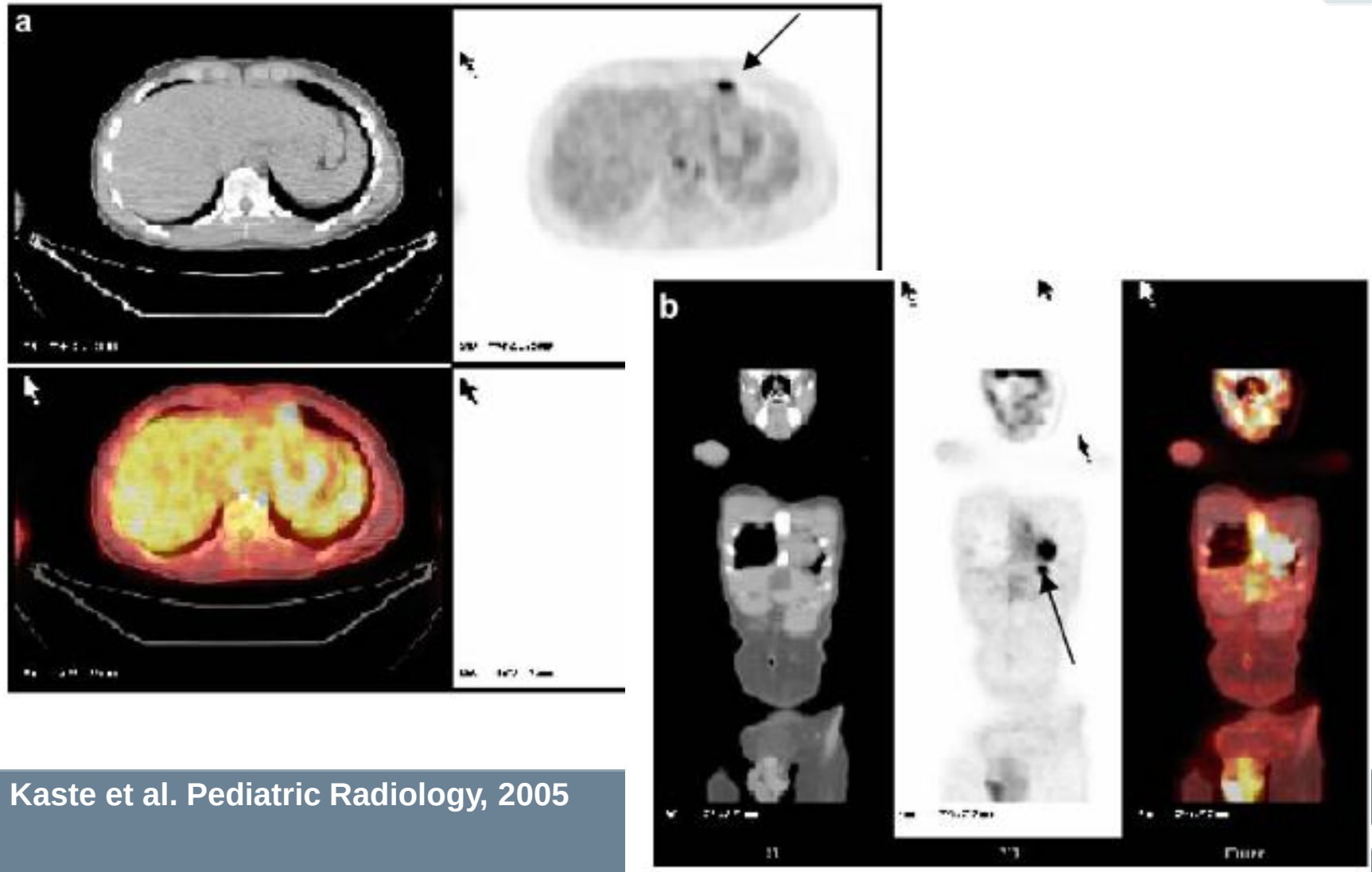
Discordant in 45%

32% upstaging (non-enlarged LN, liver, spleen, bone, thymus)

13% downstaging

PET for staging of Lymphomas

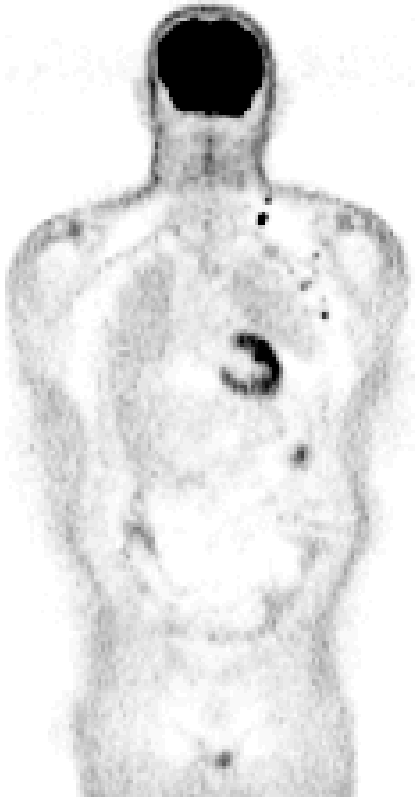
DD lymphoma vs brown fat tissue



Kaste et al. Pediatric Radiology, 2005

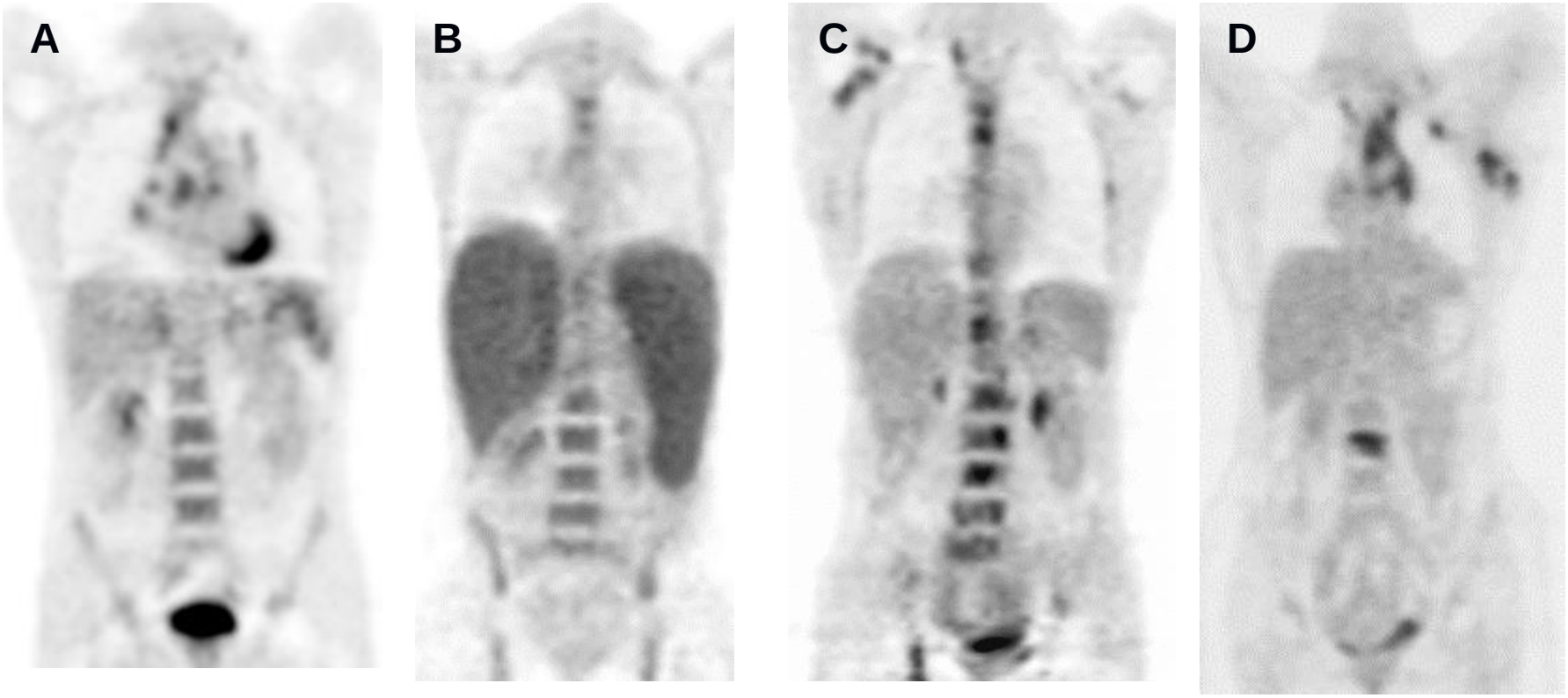
PET for DD enlarged lymph nodes

Toxoplasmosis



DLBCL

PET for staging of Lymphomas



“reactive BM”	BMB+	BMB+	BMB-positive MRI

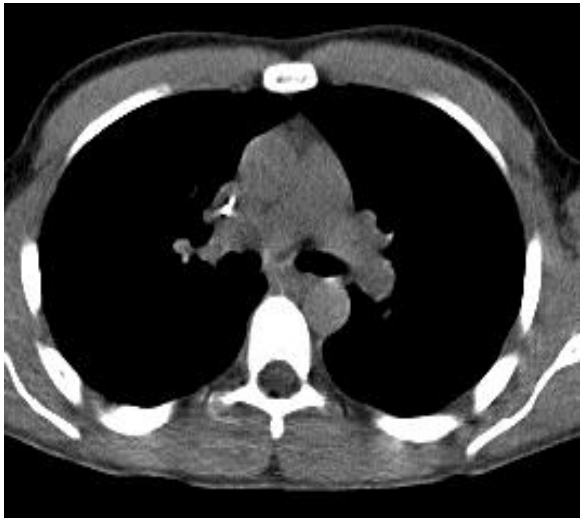
PET for Staging of Lymphomas
Conclusions

- Higher sensitivity and specificity for nodal and extra-nodal disease but false negatives do occur!!!!!!
- Improved accuracy and “certainty of diagnosis” with PET-CT
- Complementary to contrast-enhanced CT
- Complementary to bone marrow aspiration
- Better than gallium scintigraphy
- Change in therapy management in 10%-20%, especially Stage I-II effect on outcome?

→ **Initial staging = CE-CT + BMB + (PET)**

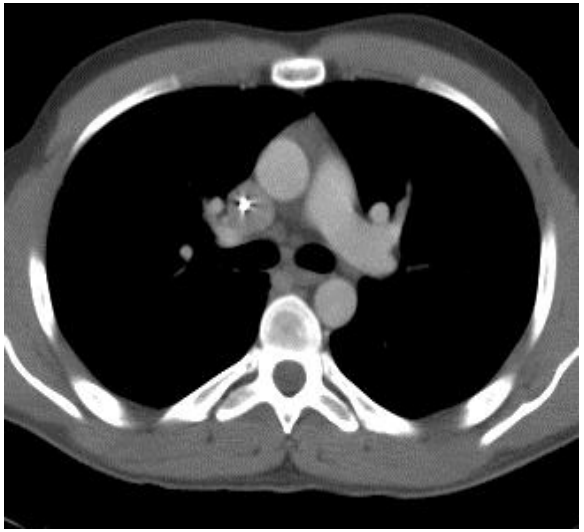
PET-CT in lymphoma

Low dose PET-CT
<30 mAs , no contrast
2 mSv



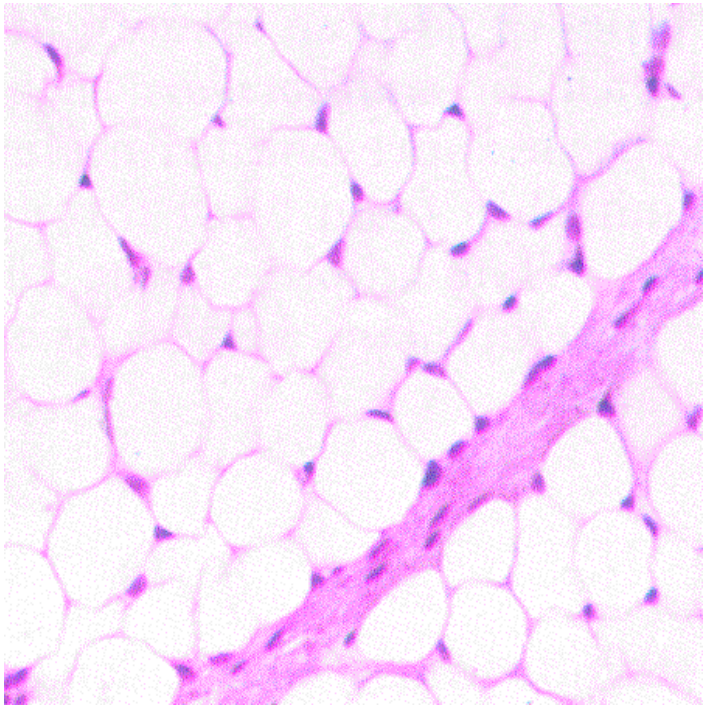
“diagnostic” PET-CT
85 mAs, 120 ml contrast
8 mSv

Dedicated CT
140 mAs, 200 ml contrast
15-20 mSv

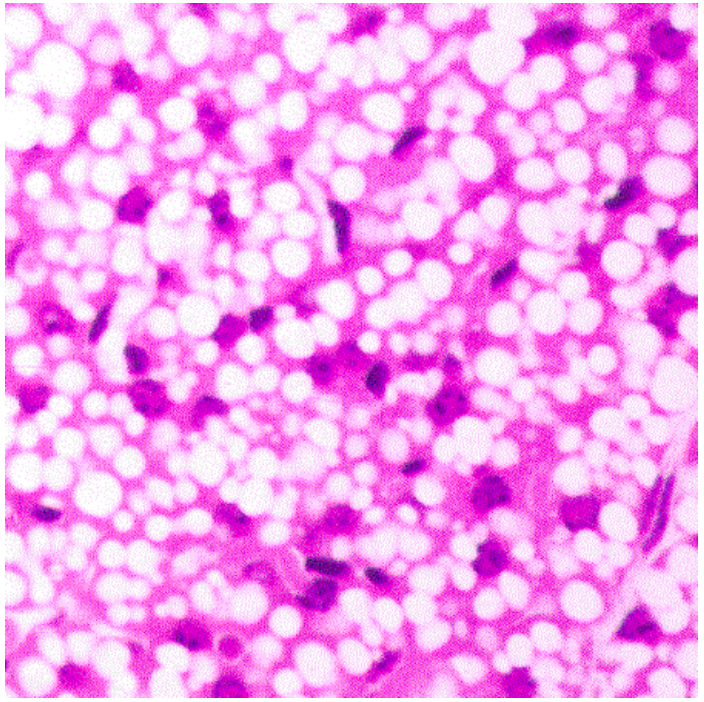


FDG and Brown Fat Uptake

White fat

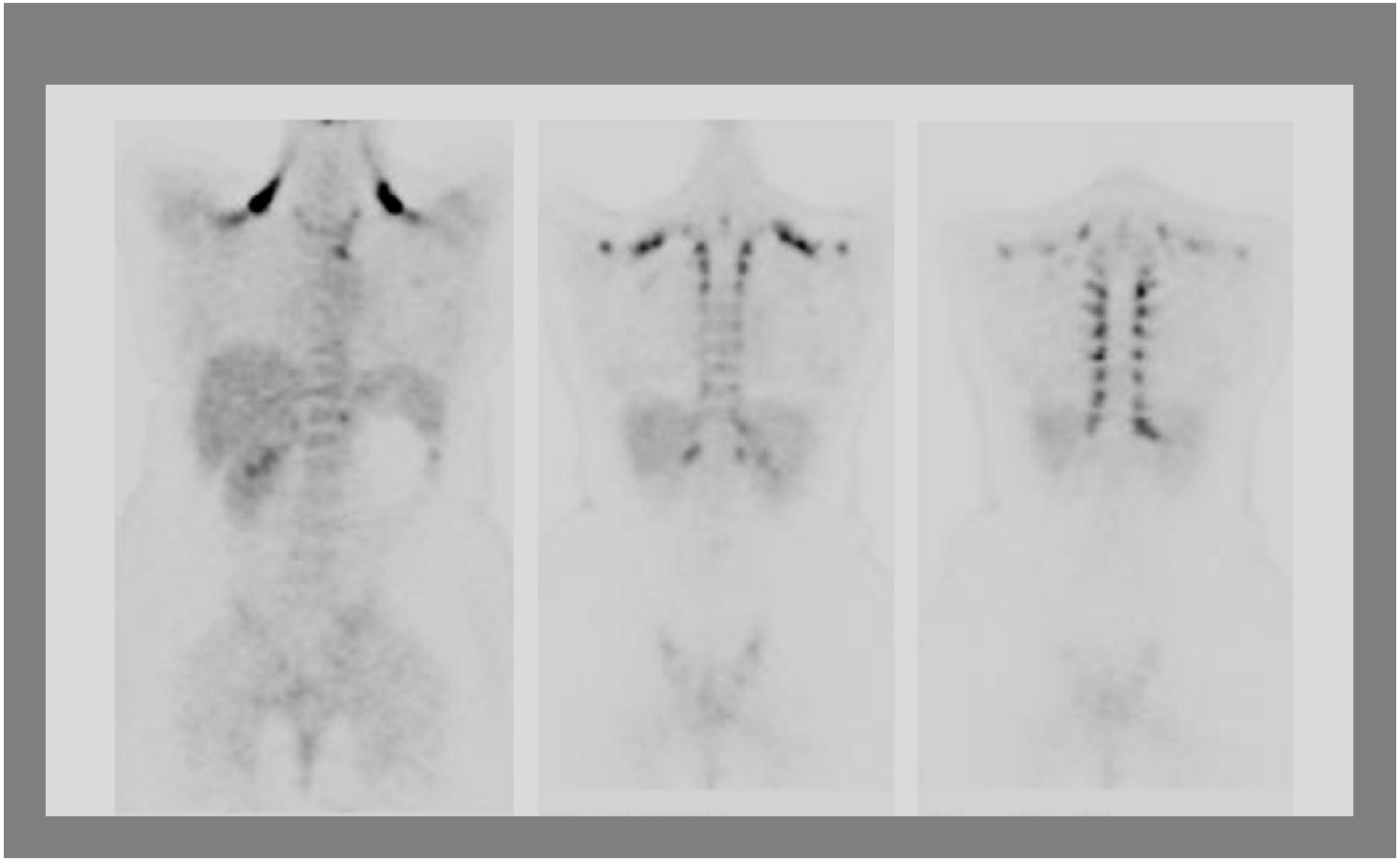


Brown fat



BAT regulates the body temperature by non-shivering thermogenesis
BAT is activated by stimulation of the β Adrenergic receptors and will induce oxidation of free fatty acids.
The energy generated in this process is completely converted to heat.

Pattern



Methods

- Prospective study from January to March 2008
- Inclusion criteria
  - Patient scheduled for a FDG PET-CT examination (Siemens Biograph 2) were randomly assigned to the pre-treatment group or not.
- Exclusion criteria
  - Astma
  - Patients already on beta suppression
- Pre-treatment group received 20 mg Propranolol (Inderal°) 30 min prior to FDG injection.
  - No administration of Diazepam.
  - Patients were kept warm during uptake phase.
- Control of blood pressure and heart rate in all patient
  - on arrival, prior to FDG injection, prior to scan

Data analysis

- Visual scoring (- or +) for different regions
- Statistical analysis of 3 groups (Fisher exact)
  - Control group
  - Pre-treatment with Inderal 20 mg
  - Home medication

Results

330 FDG - PET – CT

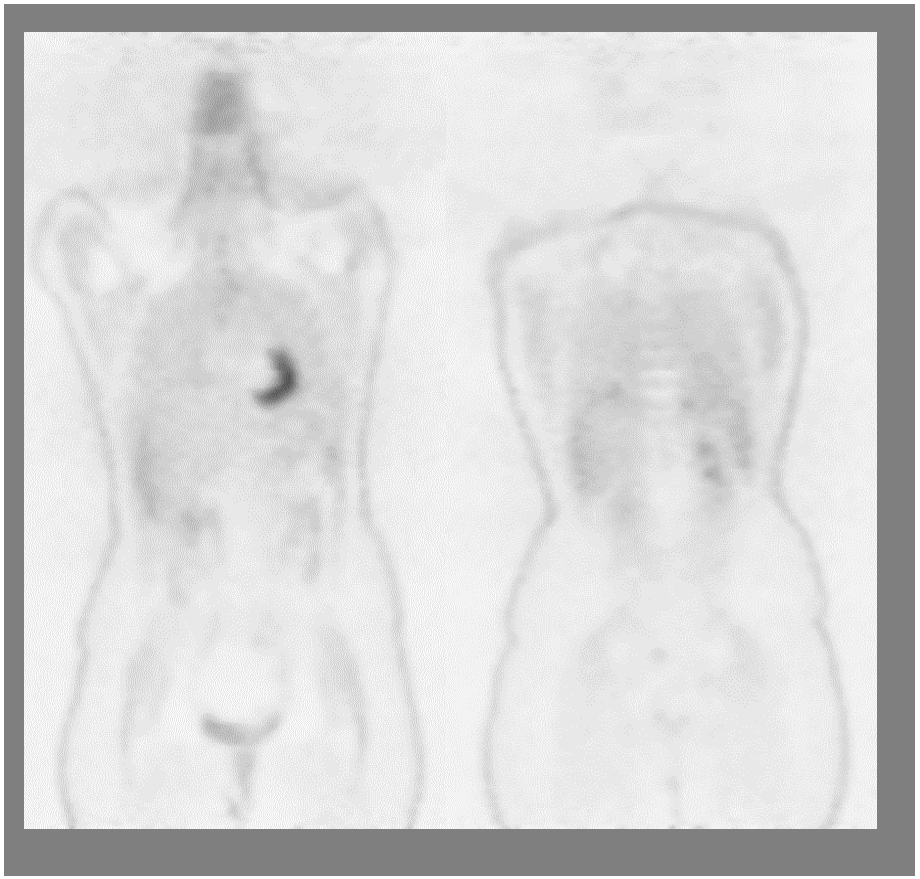
- 190 males - 140 females
- mean age 58 (range 4-89)
- no significant differences between groups with regard to age, gender, diagnosis and BMI
- No effect of low dose inderal on heart rate and BP

Results

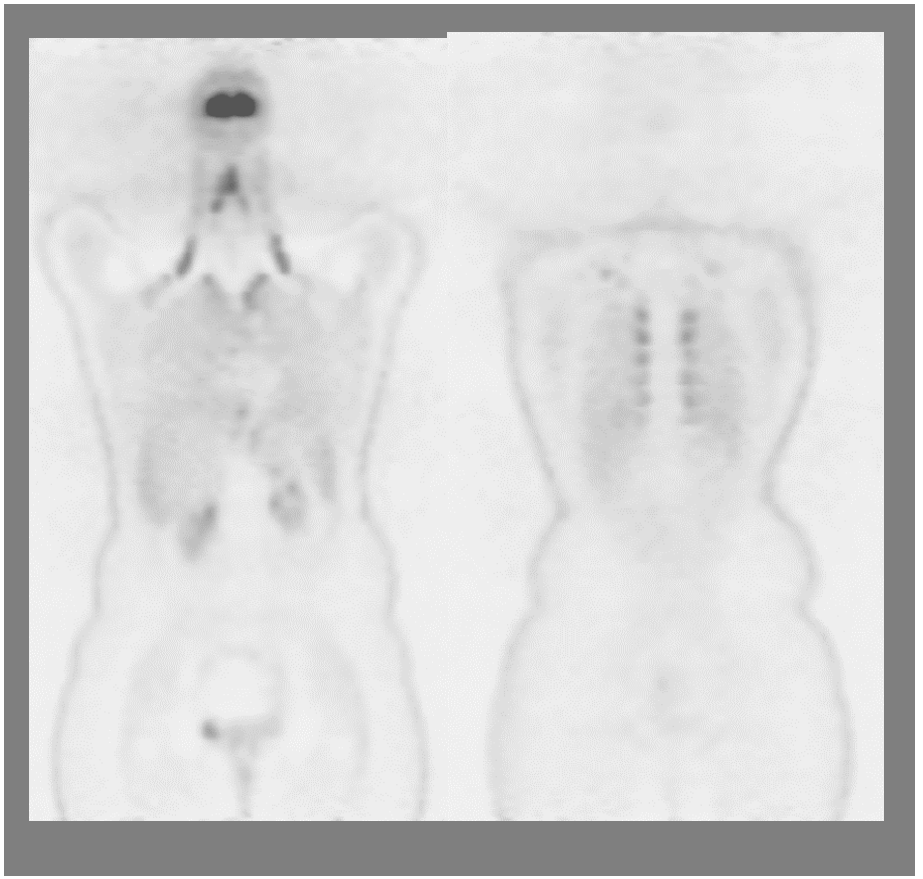
	No patients	Brown fat	No brown fat	
Pre-treated group (propanolol 20mg)	**99**	**3 (3%)**	**96 (97%)**	**P<0.001**
Control group	**160**	**26 (16.3%)**	**134 (83.7%)**	
Beta-blocker (home medication)	**71**	**1 (1.4%)**	**70 (98.6%)**	**P<0.001**
Total	***330***	***30 (9%)***	***300 (91%)***	

Effect on one patient

with Inderal



without Inderal

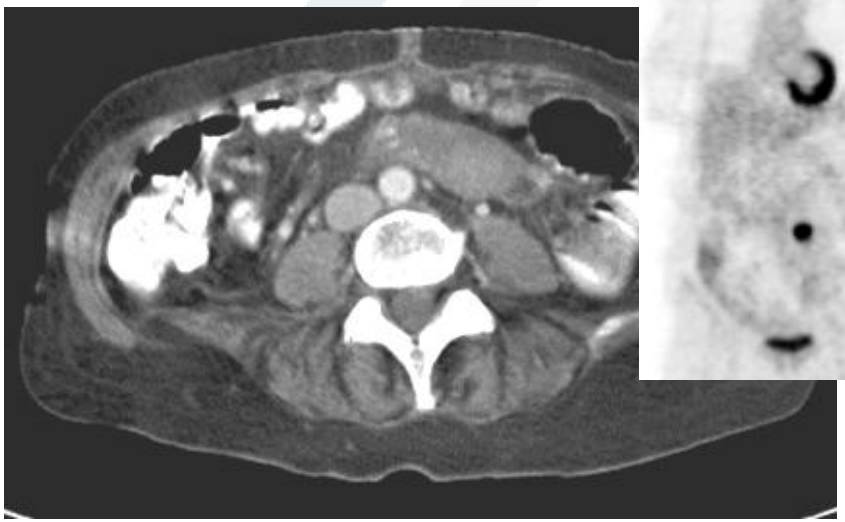


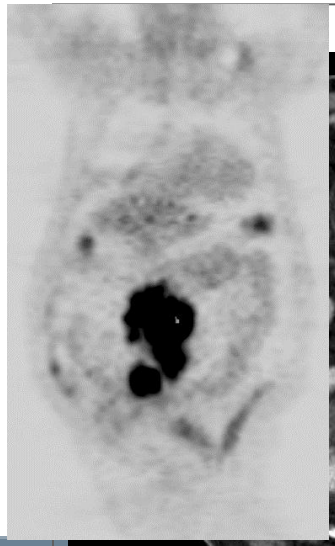
PET for response assessment

- Literature data
  - Impact of histology, treatment, timing
- How to analyse
  - New cheson criteria vs other methods

Patient 1

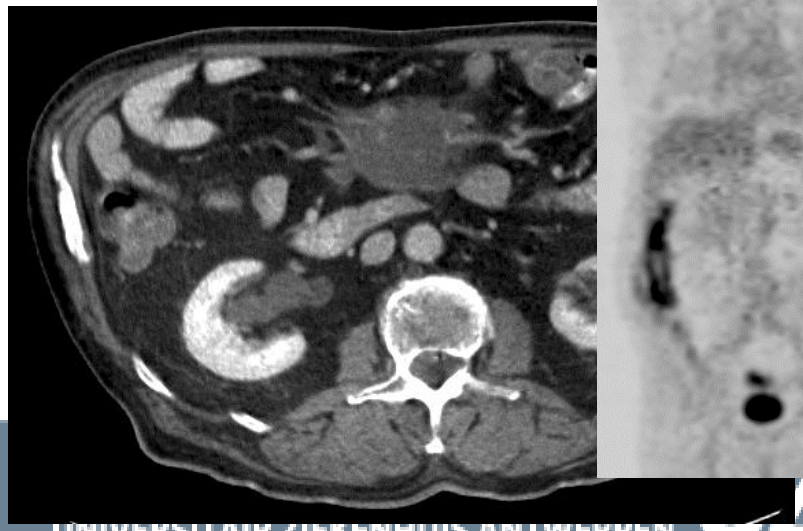
After





Patient 2

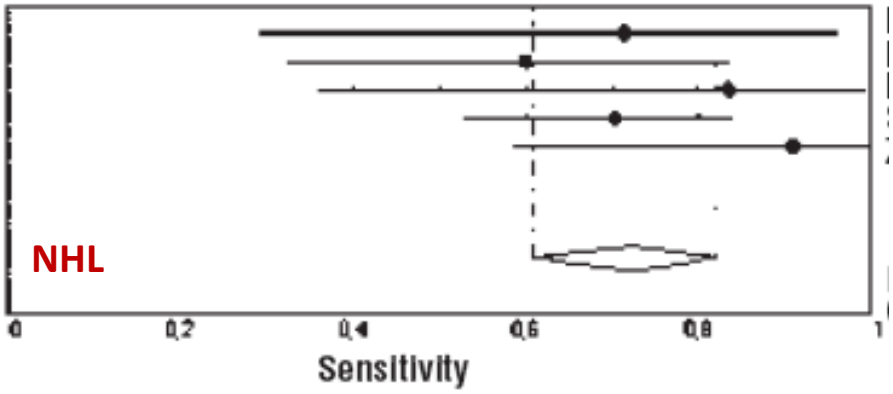
After



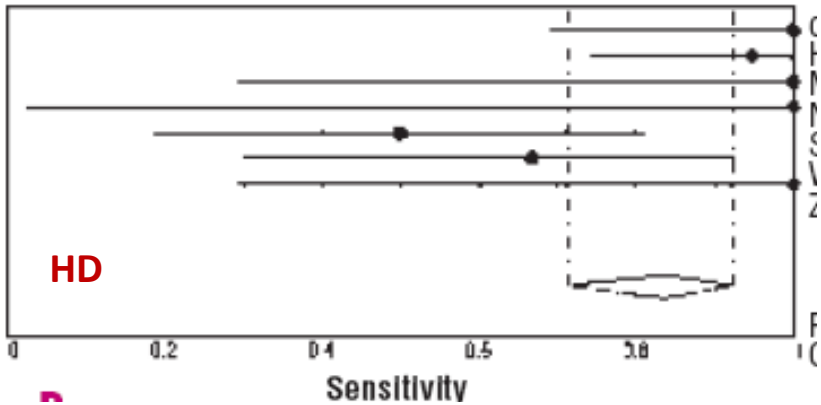
PET at the end of therapy

Systematic review Zijlstra et al, Heamatologica 2006

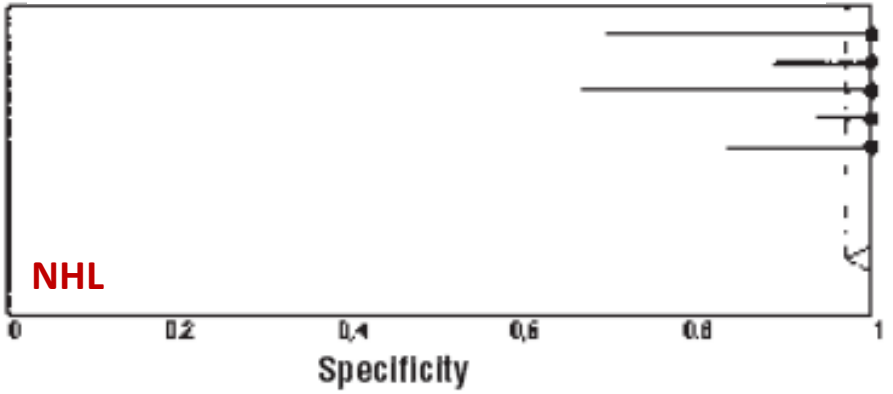
Pooled sensitivity= 0.72 (95% CI 0.61 to 0.82)



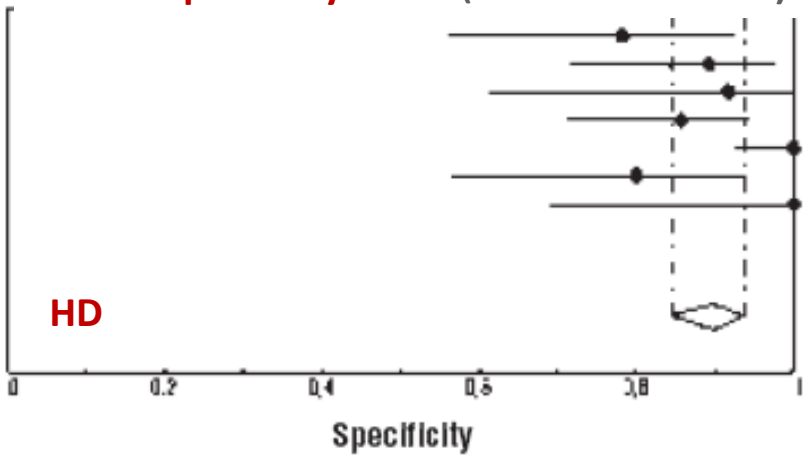
Pooled sensitivity= 0.84 (95% CI 0.71 to 0.92)



Pooled specificity= 1.00 (95% CI 0.97 to 1.00)



Pooled specificity= 0.90 (95% CI 0.84 to 0.94)



Systematic review Terasawa, JNM 2008, accuracy independent of residual mass

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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, Bertrand Coiffier, Richard I. Fisher, Anton Hagenbeek, Emanuele Zucca, Steven T. Rosen, Sigrid Stroobants, T. Andrew Lister, Richard T. Hoppe, Martin Dreyling, Kensei Tobinai, Julie M. Vose, Joseph M. Connors, Massimo Federico, and Volker Diehl

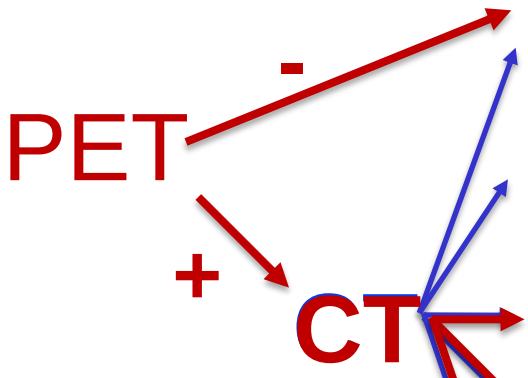
Use of Positron Emission Tomography for Response Assessment of Lymphoma: Consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma

Malik E. Juweid, Sigrid Stroobants, Otto S. Hoekstra, Felix M. Mottaghy, Markus Dietlein, Ali Guermazi, Gregory A. Wiseman, Lale Kostakoglu, Klemens Scheidhauer, Andreas Buck, Ralph Naumann, Karoline Spaepen, Rodney J. Hicks, Wolfgang A. Weber, Sven N. Reske, Markus Schwaiger, Lawrence H. Schwartz, Josee M. Zijlstra, Barry A. Siegel, and Bruce D. Cheson

New Cheson Guidelines for end of treatment evaluation

Cheson et al, JCO 1999 and Cheson et al, JCO 2007

IWG criteria ➔ IWC+PET criteria



Complete remission (**CR**): No more lesions visible

~~*Complete remission unconfirmed* (**CRu**): reduction **>75%**~~

Partial remission (**PR**): reduction **>50%**

Stable disease (**SD**): reduction **<50%**

Progressive disease (**PD**): new lesion or **>50%** increase

Exception New lesion < 1.5 cm and PET – is also PD

Guidelines on procedure and interpretation

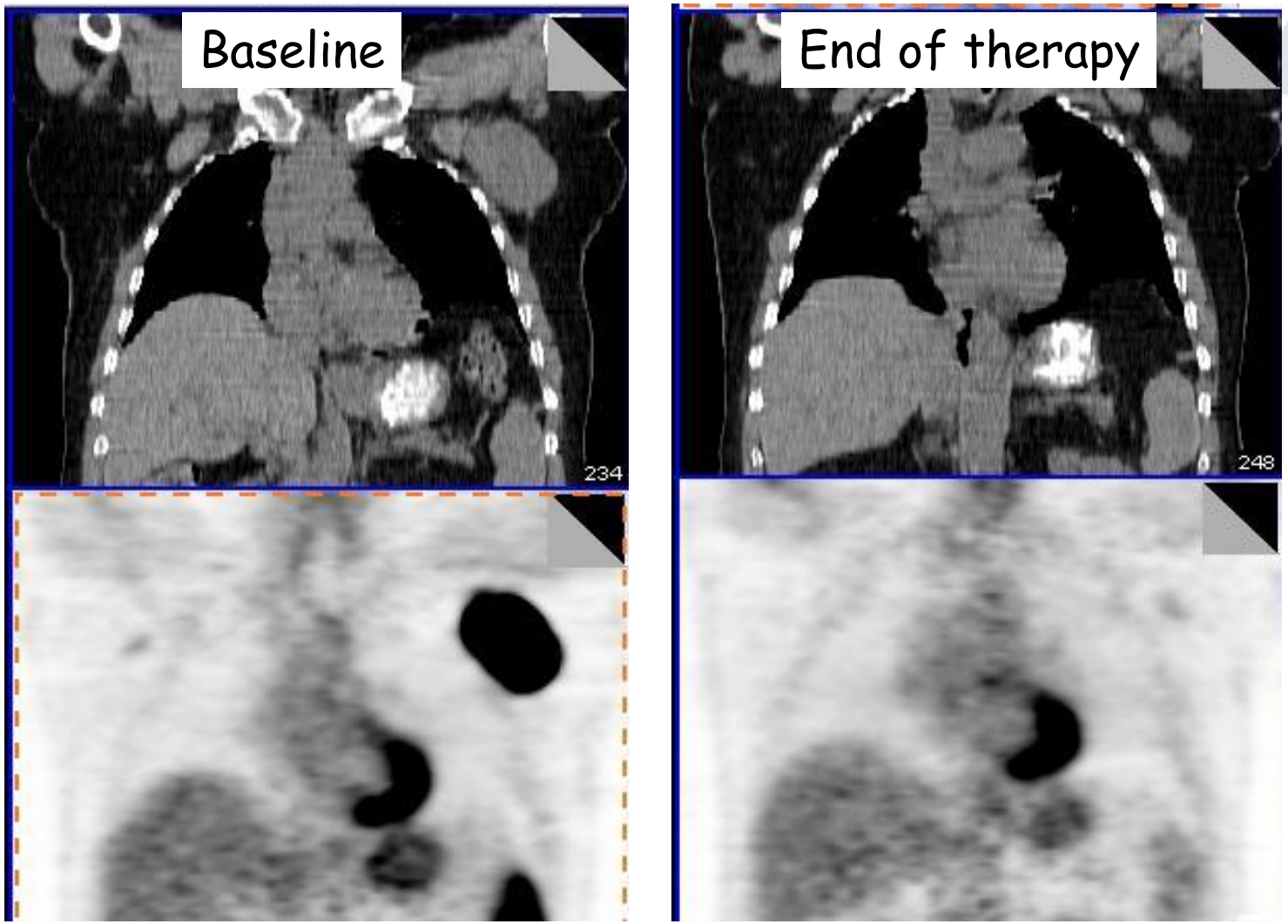
Juweid et al, JCO 2007

- For HD and aggressive NHL at the end of treatment
  - > 3 weeks after last chemotherapy
  - > 12 weeks after end of radiotherapy
- Standardization of acquisition procedure
  - NCI guidelines Shanker et al. JNM 2006
- Visual analysis
  - Residual mass < 2cm ➔ higher than local background
  - Residual mass > 2cm ➔ higher than mediastinal blood pool
  - Special criteria for high background regions like spleen, liver, BM
- EXCLUDE increased FDG uptake in
  - Normal tissue (brown fat, Thymic rebound)
  - Inflammation

➔ PET-CT, baseline scan, clinical history

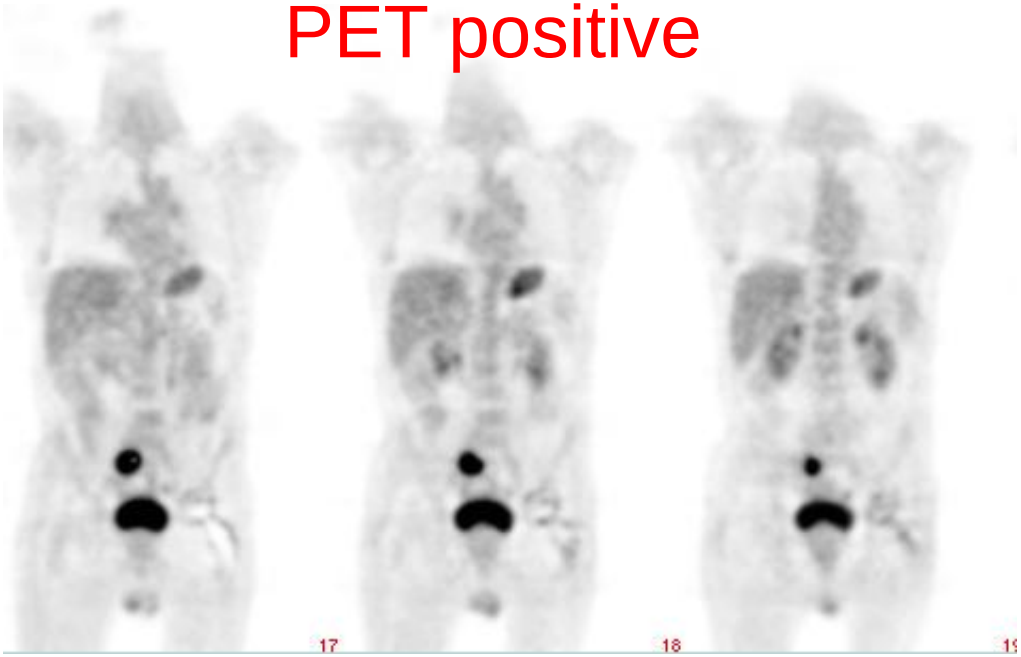
➔ **EXPERIENCE**

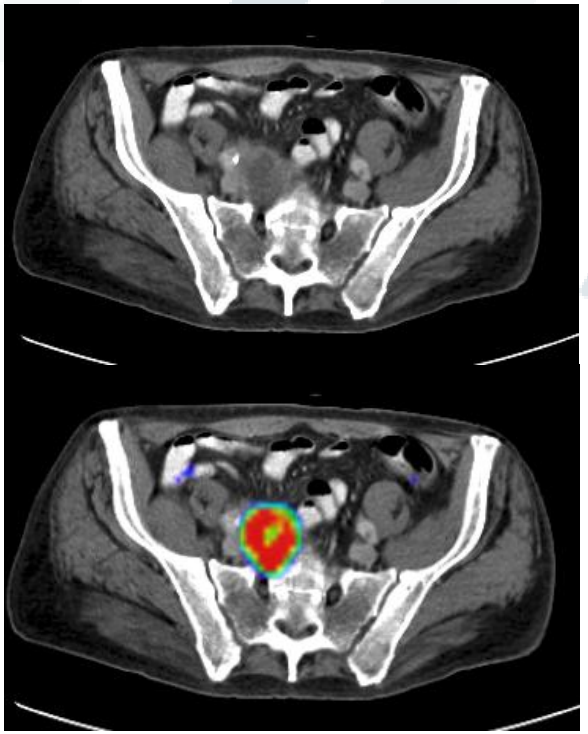
New PET-CT response criteria

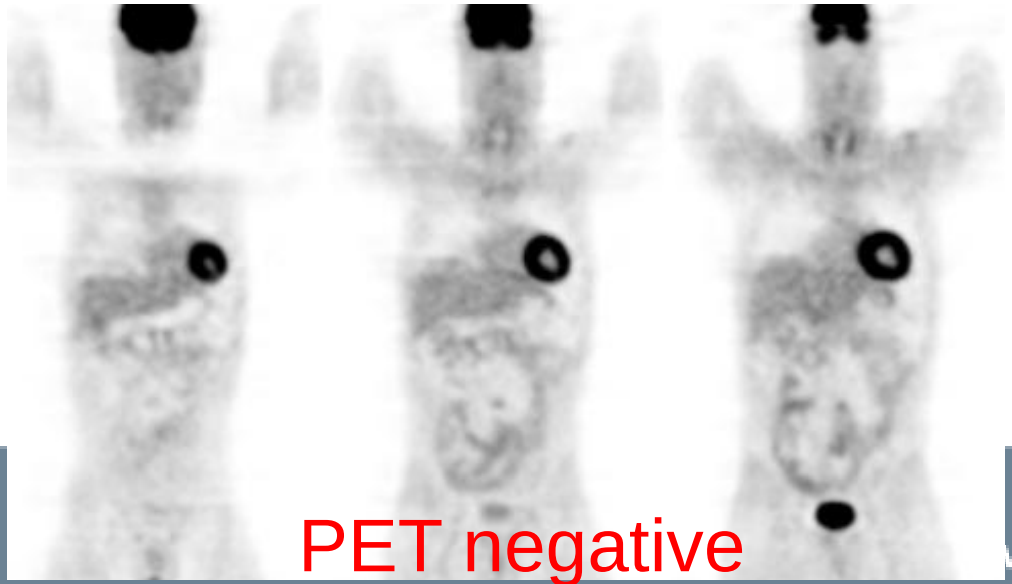


Courtesy of Juweid Malik

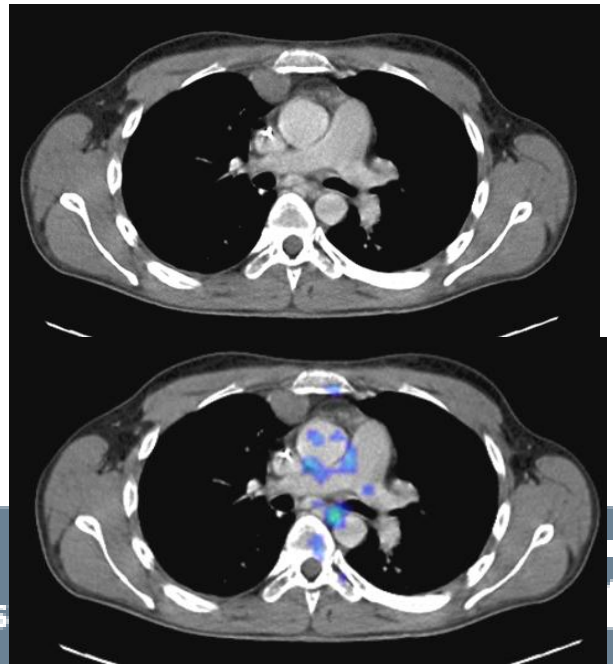
PET positive







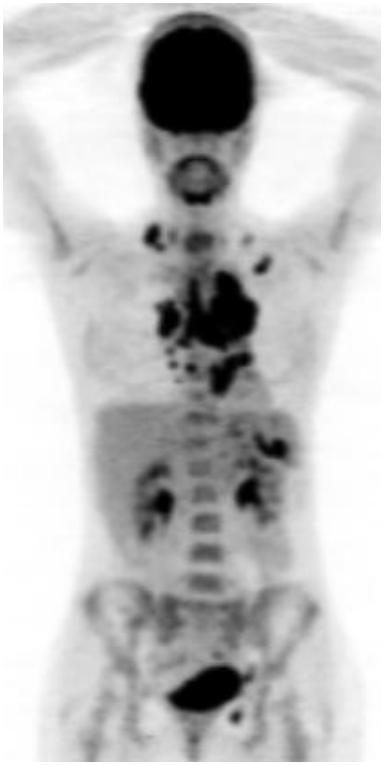
PET negative

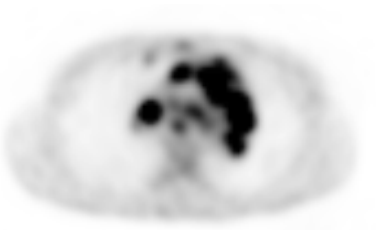


Baseline
HL, Stage III

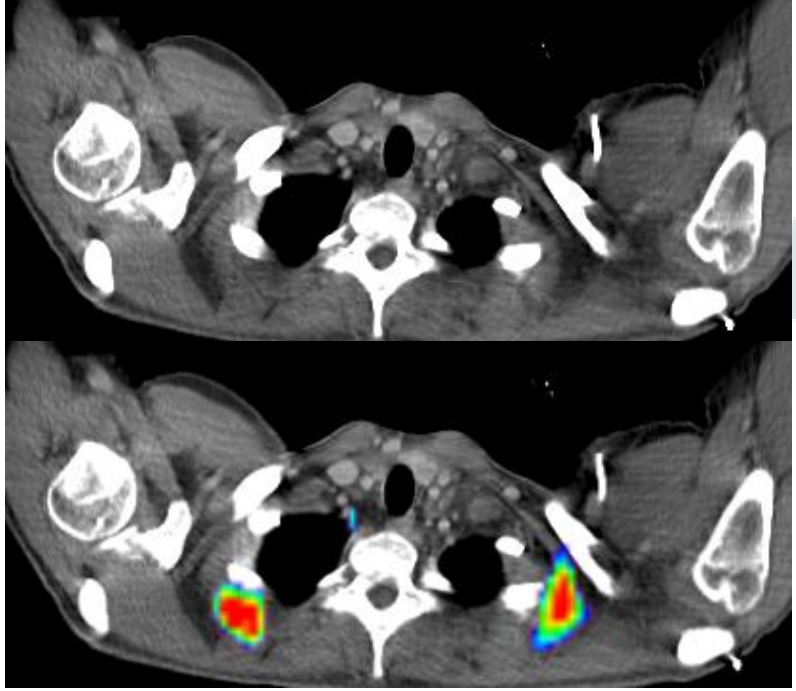
After
6x ABVD

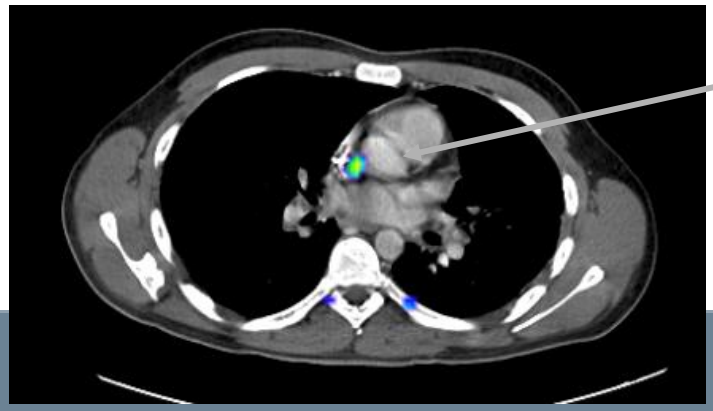
Relapse
6 months FU





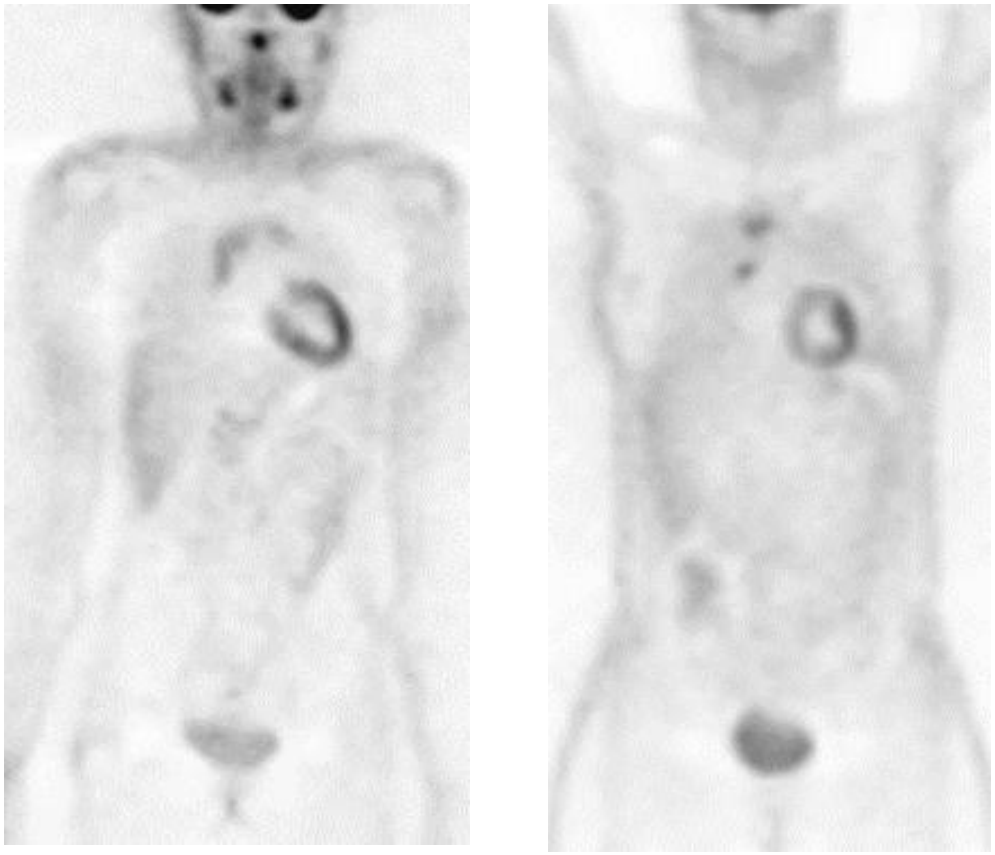
Baseline

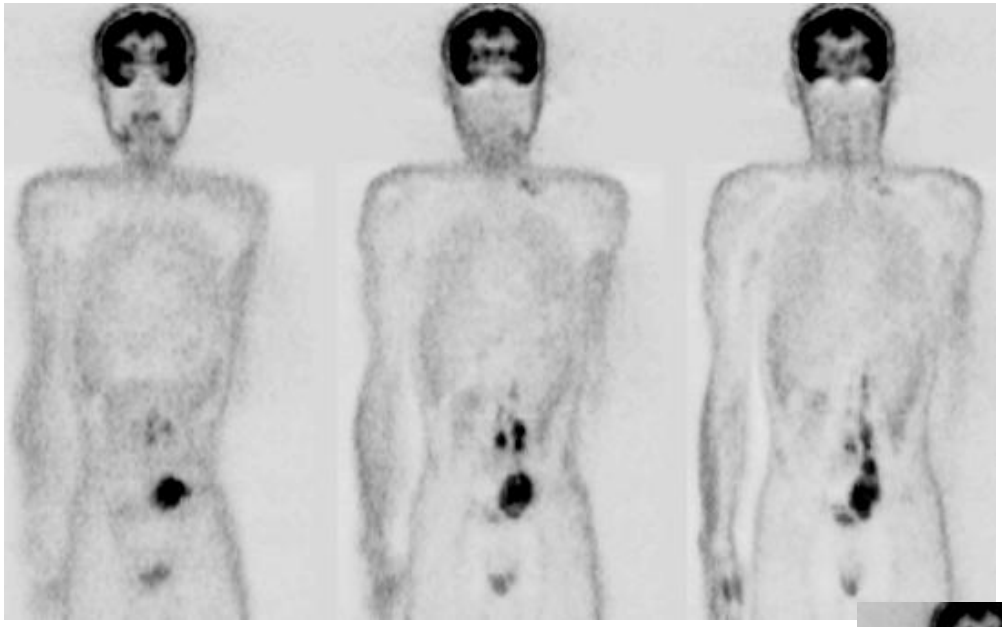




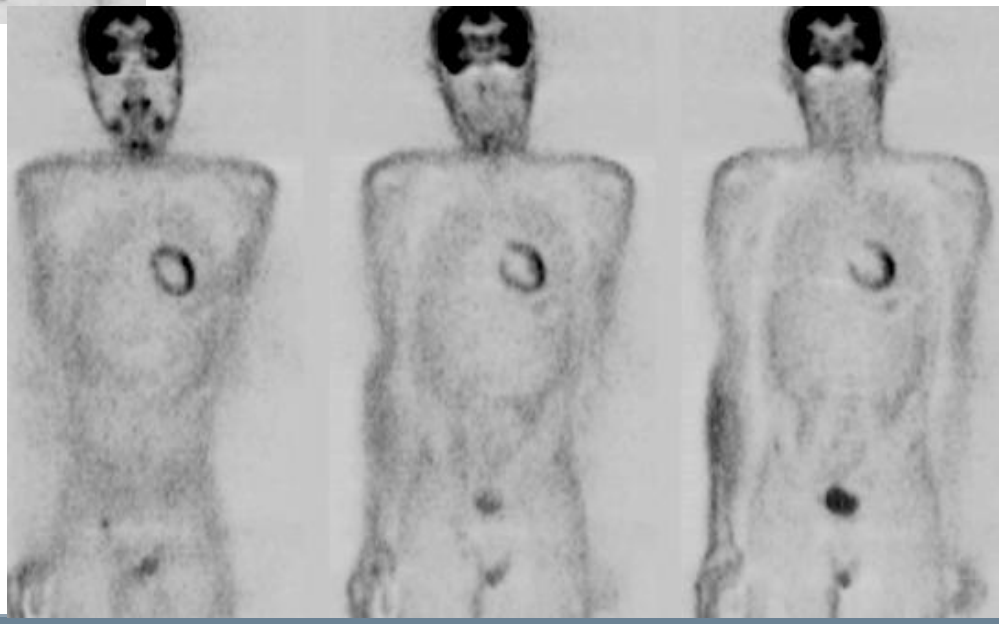
End of R/

PET for detection of residual disease
Thymus Hyperplasia





FL, stage III
PET after 6x CHOP



inflammatory inguinal LN
due to erysipelas

Are new Cheson criteria a better predictor of outcome?

New Cheson Criteria in NHL

Brepoels, Stroobants et al., Leuk Lymphoma 2007;48:1522-1530

- **Materials and methods**
  - → Data Spaepen, JCO 2000,

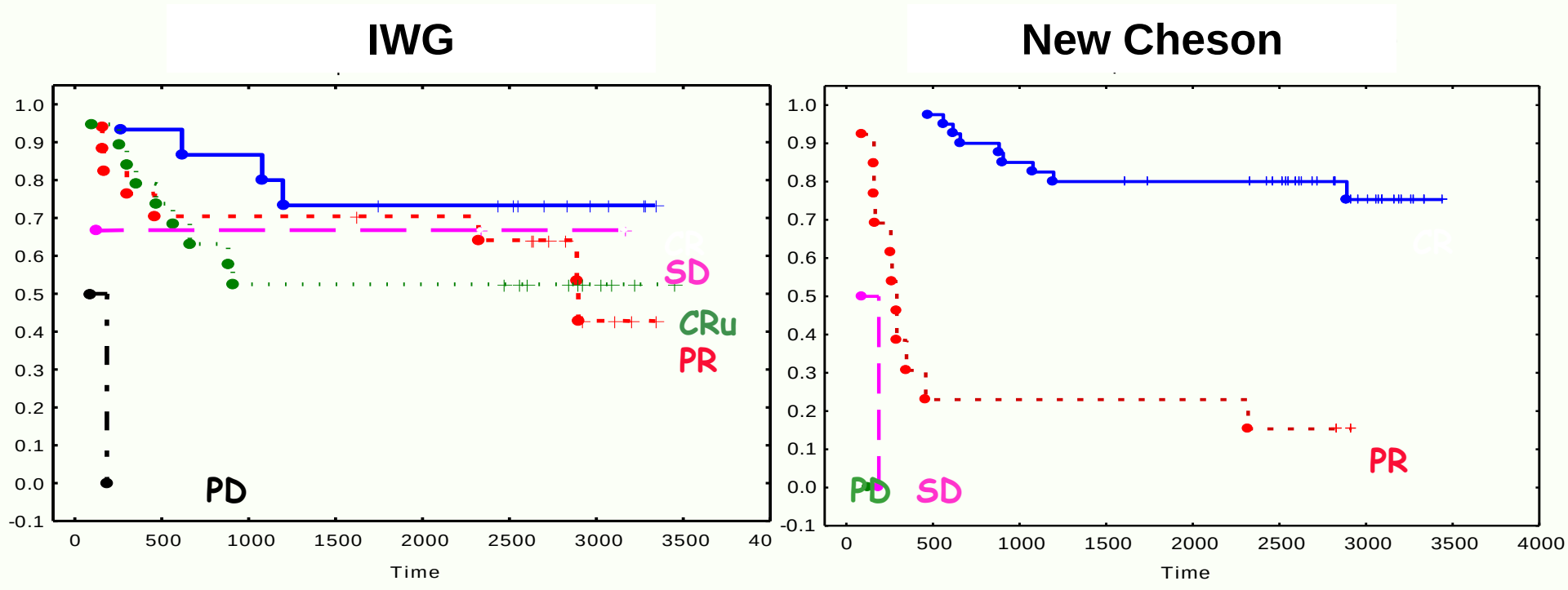
    69 pts with NHL after CHOP like therapy
  - → Revision of PET and CT images following IWG and new Cheson criteria
  - → Correlation with updated outcome
- **2 analyses**
  - → Potentially curable lymphoma
  - → Considered incurable lymphoma

Table III.1. Patient Characteristics

Characteristic	No. of patients	Percentage
Age of diagnosis (years)		
Mean	52	
Range	15-72	
Ann-Arbor clinical stage		
I/II	26	38
III/IV	43	62
Histology		
Group A		
Diffuse large B-cell	41	59
Anaplastic large cell	12	17
Burkitt's lymphoma	2	3
Group B		
Follicle-center lymphoma	8	12
Mantle-cell lymphoma	4	6
Marginal-zone B-cell	2	3
International Prognostic Index (IPI)		
Low	33	48
Low intermediate	19	28
High intermediate	13	19
High	4	6

New Cheson criteria in Aggressive NHL

Brepoels, Stroobants et al., Leuk Lymphoma 2007;48:1522-1530

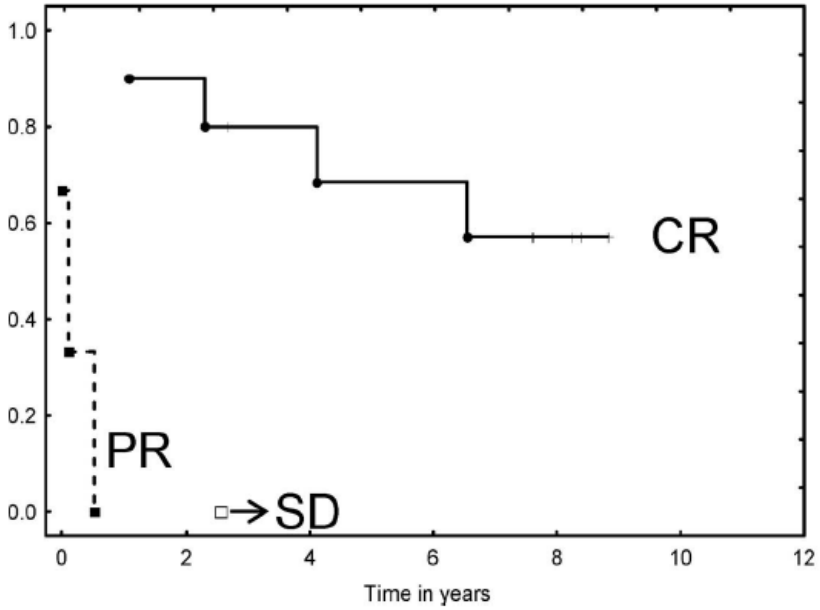


Data Spaepen, JCO 2000, PET after first line R/
Updated and IWC + PET response
in 55 pts with routinely FDG-avid and potentially curable (aggressive) NHL

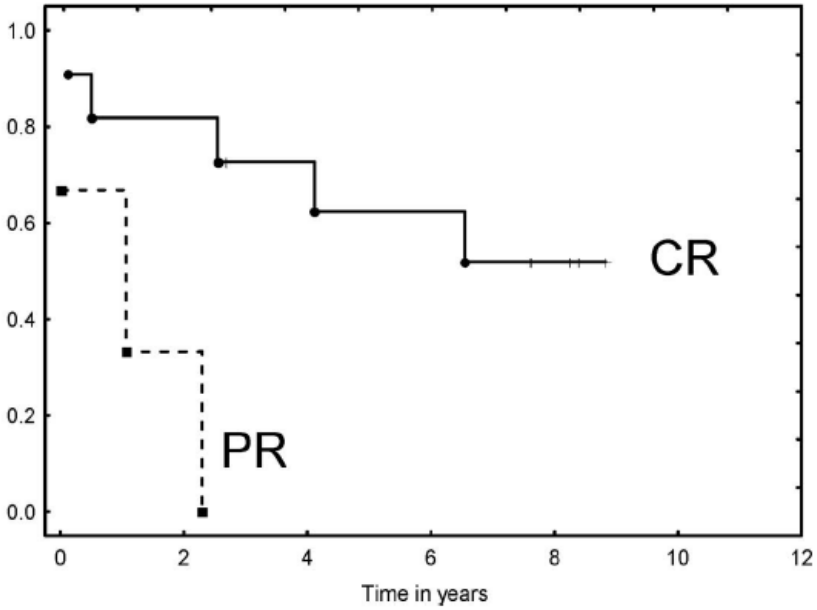
New Cheson criteria in Indolent NHL

Brepoels, Stroobants et al., Leuk Lymphoma 2007;48:1522-1530

IWG



New Cheson



Data Spaepen, JCO 2000 , PET after first line R/
Updated and IWC + PET response
in 14 pts **with not-routinely**
FDG-avid and incurable NHL (8 FL, 4 MCL, 2 MZL)

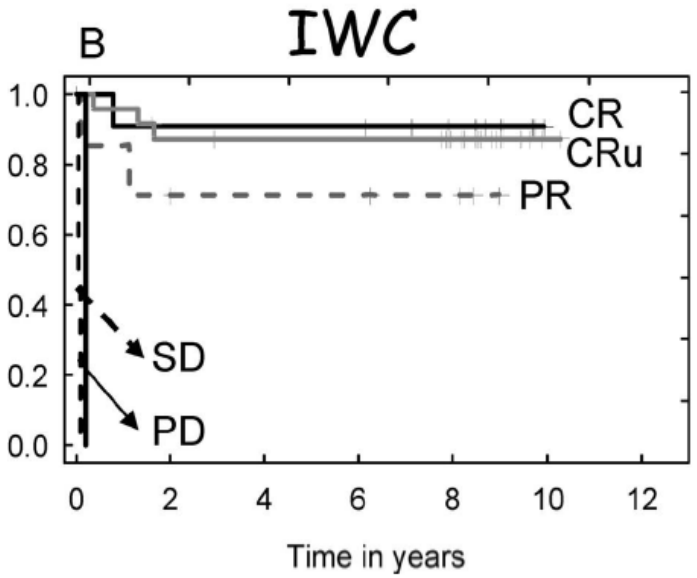
New Cheson criteria in Hodgkin

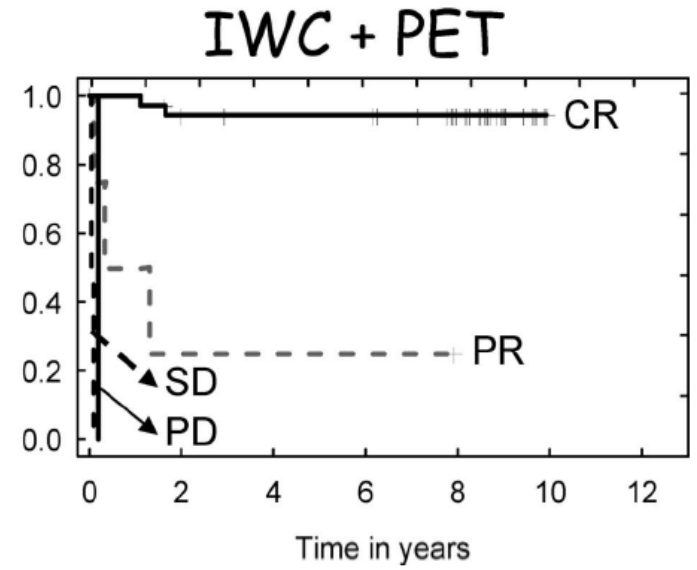
Brepoels, Stroobants et al. Leuk Lymphoma 2007:1539-1547

Data Spaepen, Br J Haematol. 2001
Updated and IWC + PET response in 56 HD
PET at the end of first line R/ (after RT)

Table II.1. Patient Characteristics

Characteristic		No. of patients (n=56)	relapse (n=5)	immediately second line (n=4)
Age of diagnosis	Median	32	25	36
	Range	9-70	15-44	35-39
Follow-up (months)	Median	107	13	
	Range	24-138	2-20	
Sex	Men	30	2	2
	Women	30	3	2
Ann-Arbor clinical stage	I/II	24		
	III/IV	32	5	4
B-symptoms	no	30		2
	yes	26	5	2
Bulky disease	no	34	1	1
	yes	22	4	3
Histology	Nodular sclerosis	42	3	4
	Mixed cellularity	9	2	
	Lymphocyte predominance	3		
	Unclassifiable	2		
Chemotherapy	Stanford V	19	3	3
	MOPP/ABV	37	2	1





Can RT be omitted in PET negative patients?

Kobe te al. Blood. 2008 November: 3989–3994.

Patients included in HD15 trial: PET after 6 or 8 x BEACOPP in advanced HD, RT in PET+ only

Interim analysis on patient with FU >12m (n=275)

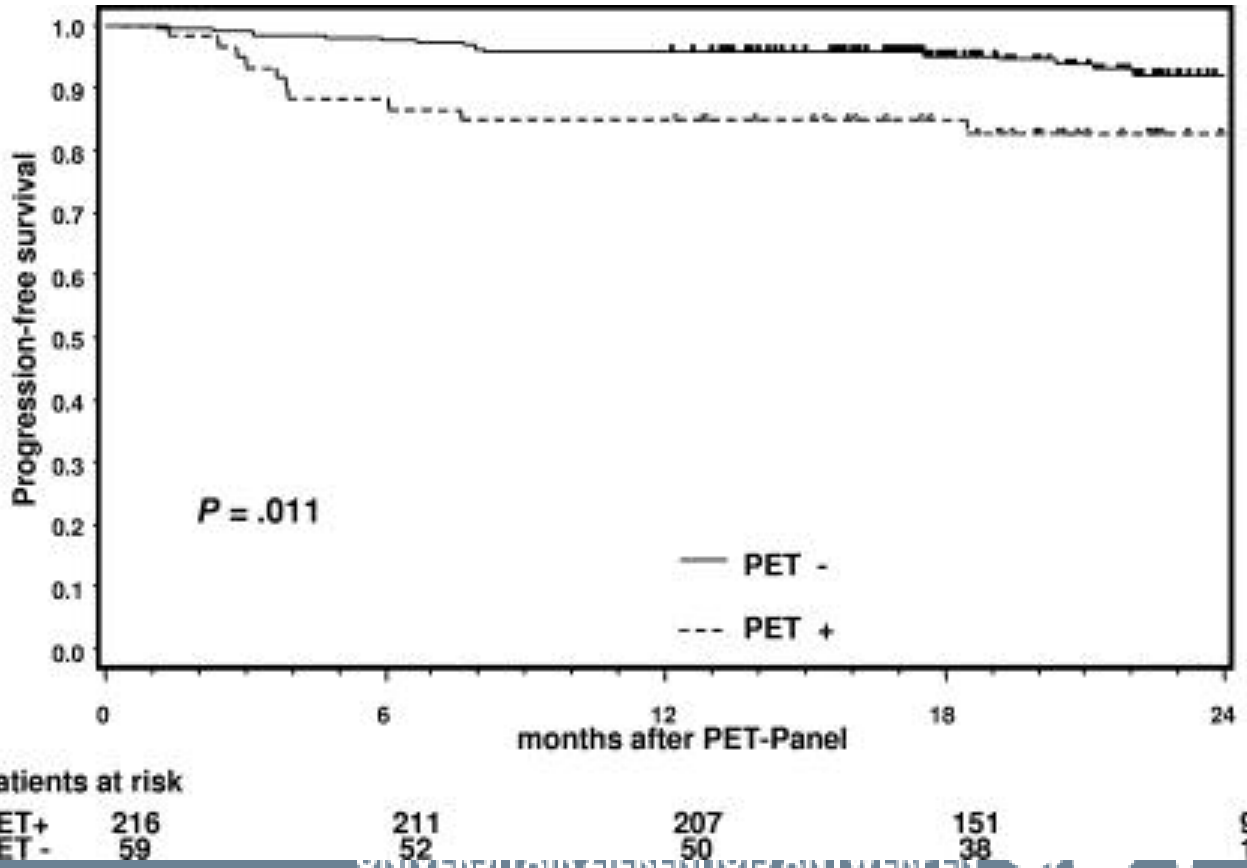
PET+ ~ new Cheson criteria

Relapse rate

PET negative 9/216 (4%)

PET positive 9/59 (15%)

NPV= 94%



Use of PET for during treatment for outcome prediction

PET during first-line therapy

Brepoels L, Stroobants S, Verhoef G. Leuk Lymphoma. 2007;48:270-282. Review.

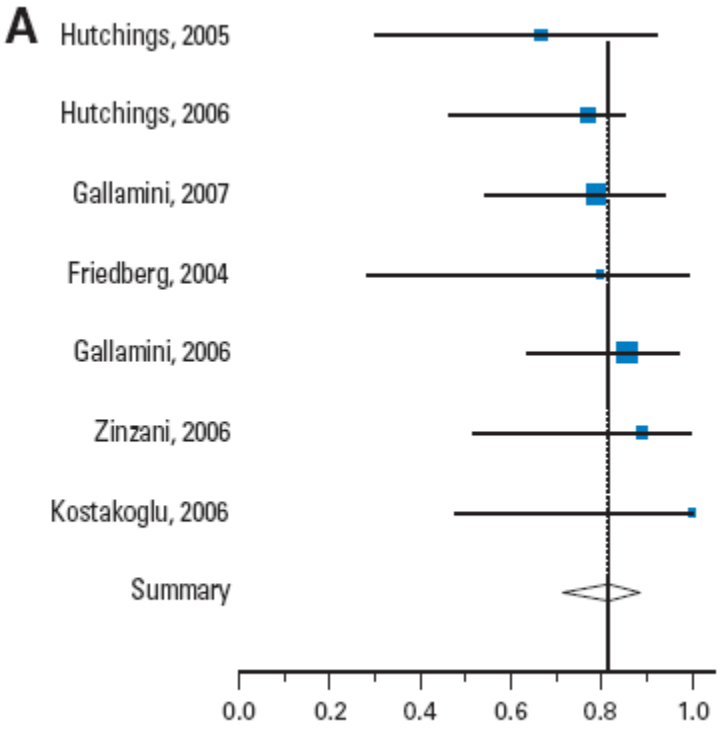
Table III. Prognostic value of PET for early response assessment during first-line or induction treatment.

Author	Number of patients	Histology	Timing PET (cycles)	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %
Jerusalem et al. [47]	28	NHL	2–5	42	100	73	100	67
Mikhaeel et al. [11]	23	NHL	2–4	100	94	96	88	100
Mikhaeel et al. [48]	32	HD	2–3	75	100	94	100	92
Kostakoglu et al. [49]	30	HD/NHL	1	87	87	87	87	87
Spaepen et al. [50]	70	NHL	3–4	85	100	91	100	84
Zijlstra et al. [51]	26	NHL	2	64	75	69	75	75
Torizuka et al. [52]	20	HD/NHL	1–2	87	50	80	87	50
Friedberg et al. [24]	22	HD	3	80	94	91	80	94
Haioun et al. [53]	90	NHL	2	63	71	68	55	77
Mikhaeel et al. [54]	121	NHL	2–3	5-year PFS of 16.2% when PET+, 88.8% when PET−, 59.3% for MRU				
Hutchings et al. [55]	85	HD	2–3	5-year PFS of 38.5% when PET+, 91.5% when PET−, MRU considered PET-				
Hutchings et al. [56]	77	HD	2	79	92	90	69	95
Gallamini et al. [57]	108	HD	2	86	98	95	90	97

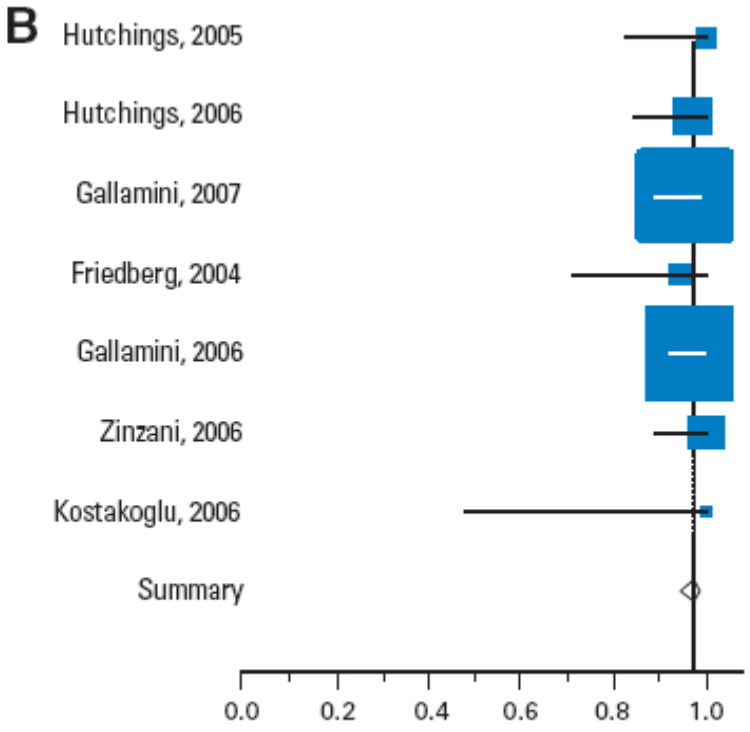
PPV: positive predictivive predictive value, HD: Hodgkin's disease; NHL: Non-Hodgkin's lymphoma; PFS: progression-free survival; PET+: PET positive; PET negative; MRU: minim

PET at during first line therapy

Meta analysis Terasawa et al, J Clin Oncology 2009



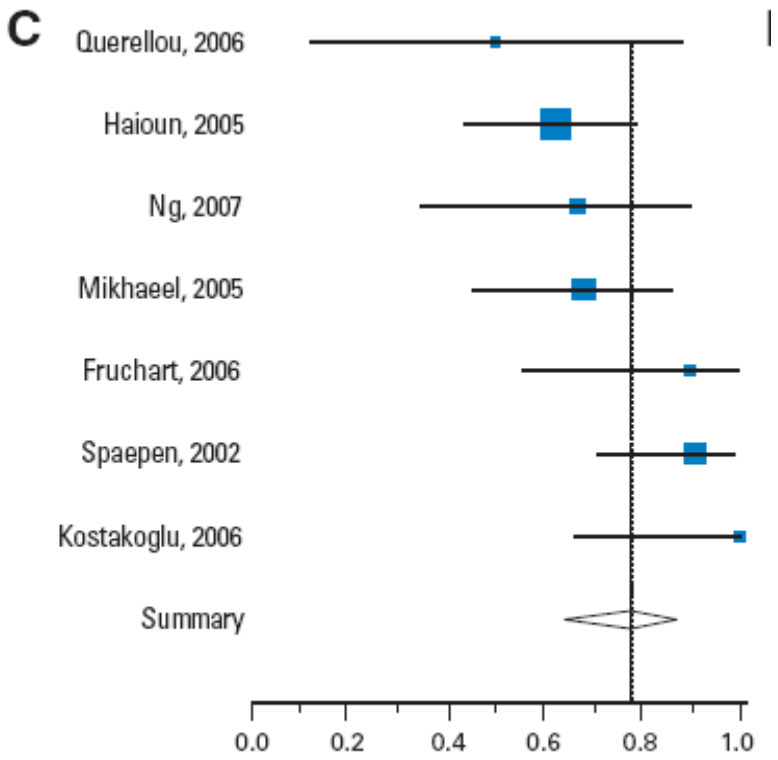
HD Pooled sens= 0.81 (95% CI 0.72 to 0.89)



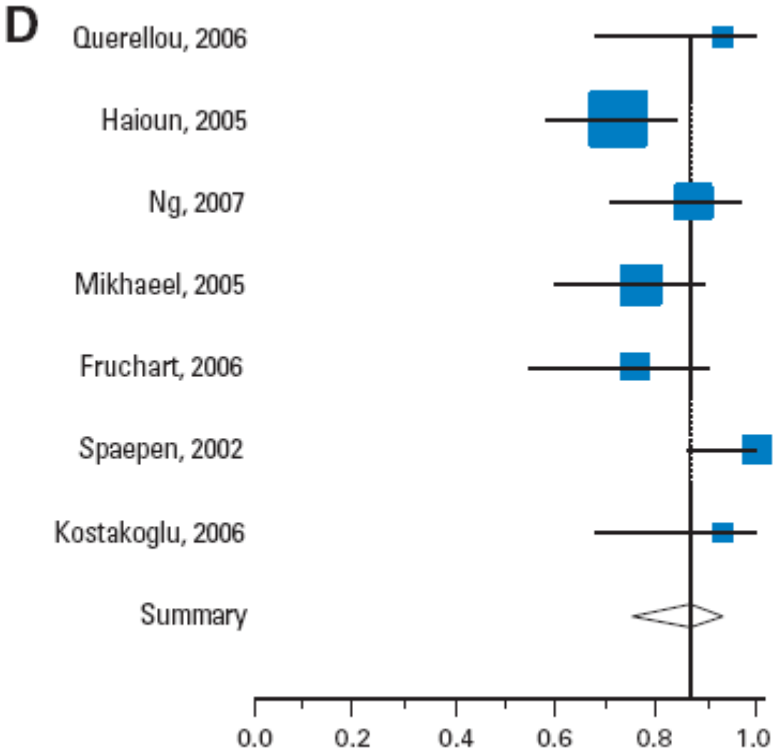
HD Pooled spec= 0.97 (95% CI 0.94 to 0.99)

PET at during first line therapy

Meta analysis Terasawa et al, J Clin Oncology 2009



NHL Pooled sens= 0.78 (95% CI 0.64 to 0.87)



NHL Pooled spec= 0.87 (95% CI 0.95 to 0.93)

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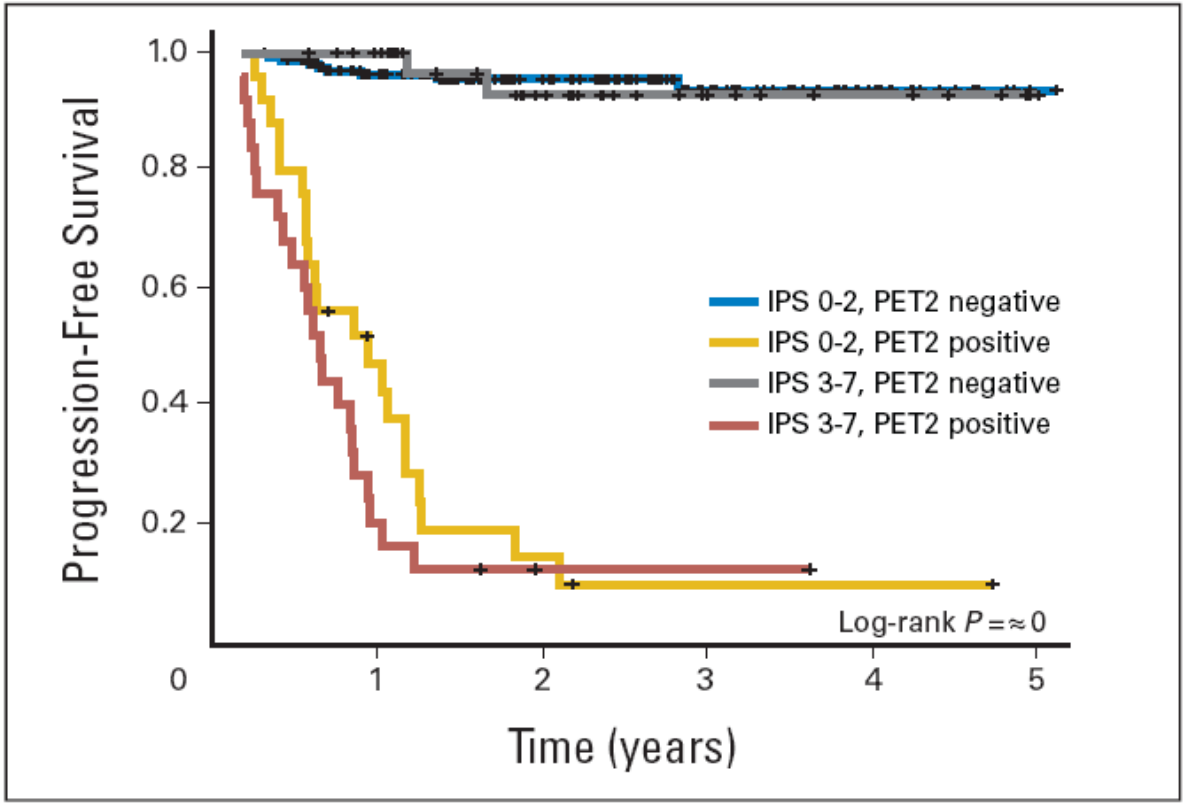
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Interim 2-[^{18}F]Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Is Prognostically Superior to International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: A Report From a Joint Italian-Danish Study

N=260

Andrea Gallamini, Martin Hutchings, Caterina Patti, Annika Loft, Francesco Caterina Stelitano, Rosario Sancetta, I Ivana Pierri, and Alessandro Levis



PET in DLBCL after more intensified treatment or in combination with Retuximab

Haioun et al, Blood 2005

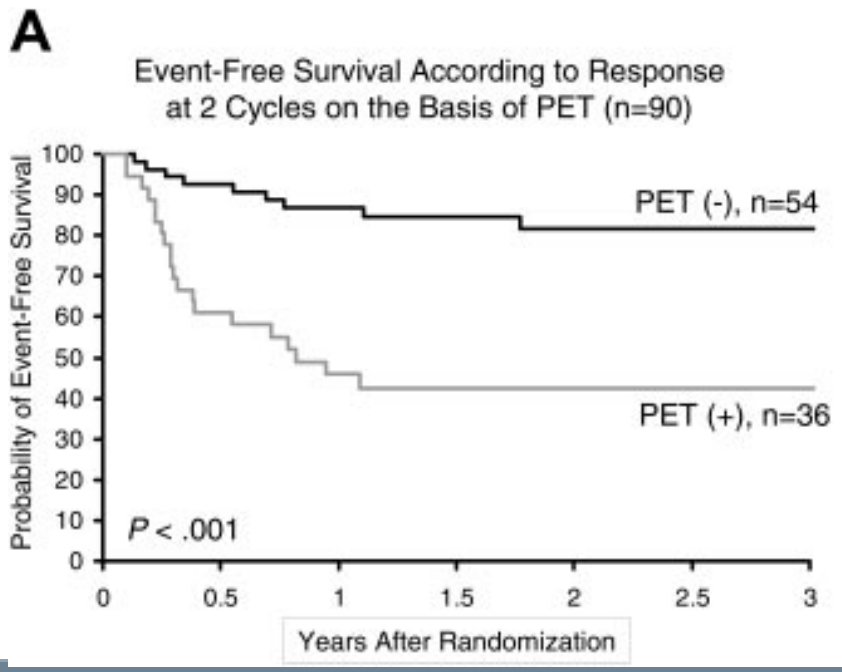
Induction Chemotherapy (4 cycles)
(R)-CHOP/3w (> 60y)
R-ACVPB/2w
ACVBP/ACE

→ **Consolidation/salvage Treatment (CT based)**
R-ACVPB
High Dose + AutoSTx

Baseline | PET 2 N=90 | PET 4 N=80

Comparison of PET results after 2 and 4 cycles

13 patients PET2 positive → PET4 negative
Patients that were PET negative after 2 remained PET negative after 4



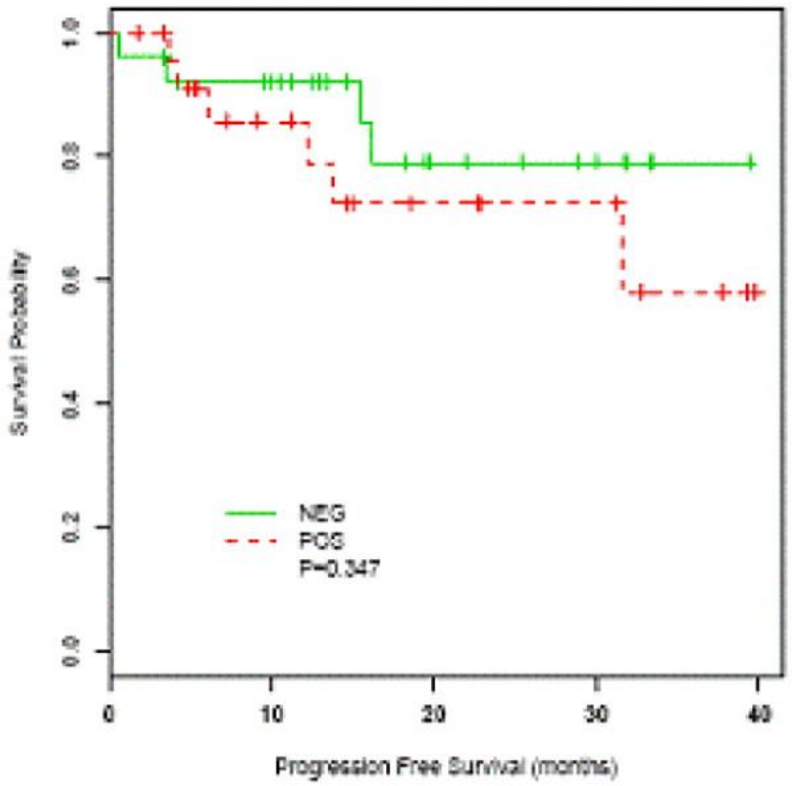
Poor Predictive Value of FDG-PET/CT Performed after 2 Cycles of R-CHOP standard in Patients with Diffuse Large B-Cell Lymphoma (DLCL)

Amanda Cashen, M.D., Farrokh Dehdashti, M.D.*, Jingqin Luo, Ph.D.* and Nancy L. Bartlett, MD
Washington University School of Medicine, Saint Louis, MO, USA

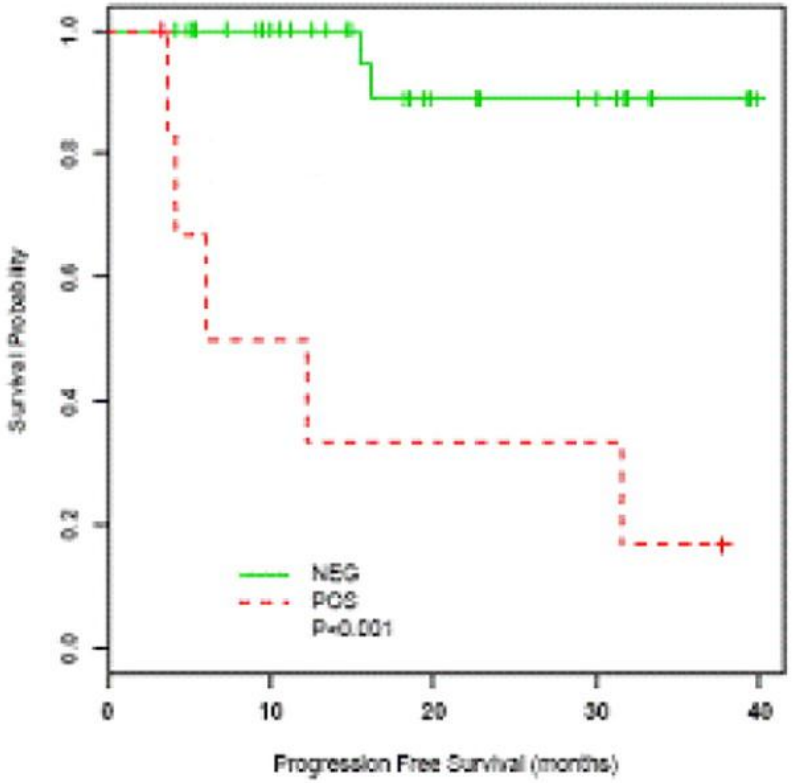
ASH 2008, abstract 371

PET response based on new Cheson guidelines

After 2 or 3 cycles



After 6 cycles



How to evaluate early PET

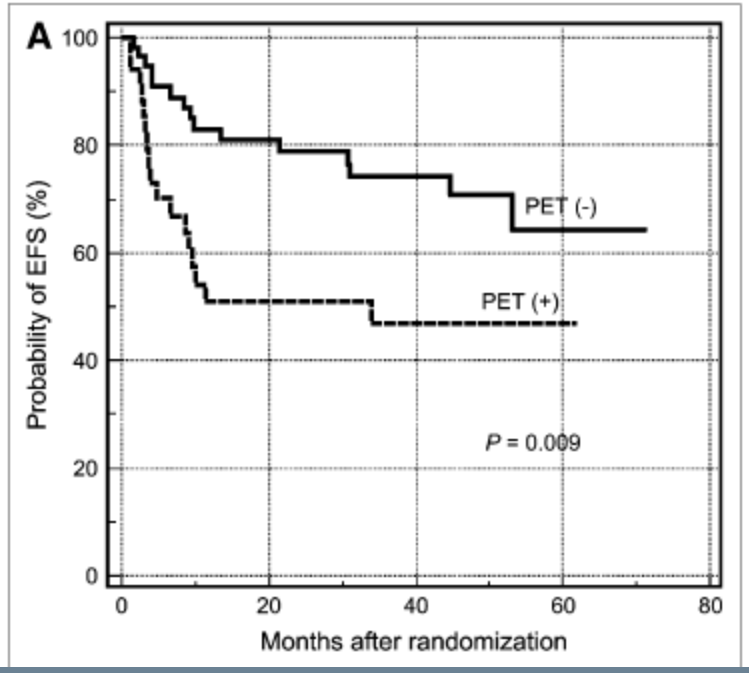
Lin, Itti, Haioun et al, JNM 2007

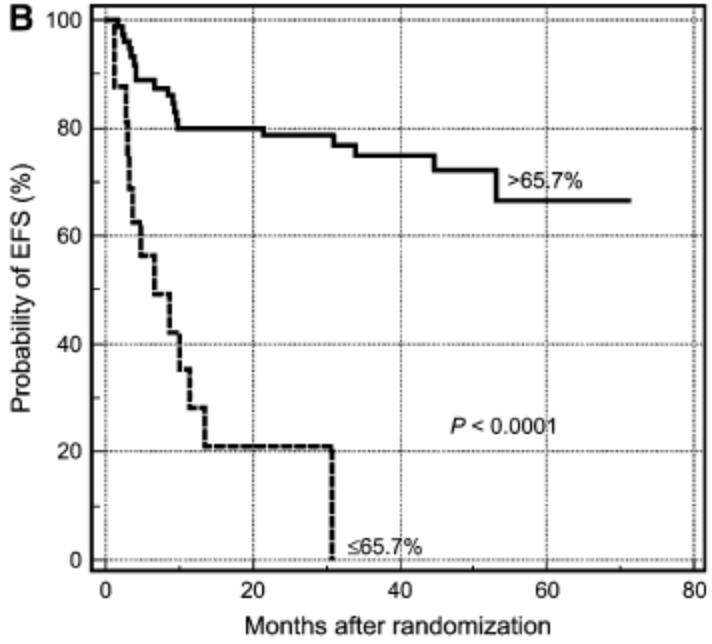
Induction Chemotherapy (4 cycles)
(R)-CHOP/3w (> 60y)
R-ACVPB/2w
ACVBP/ACE

Consolidation/salvage Treatment (CT based)
R-ACVPB
High Dose + AutoSTx

Baseline

PET 2





Baseline	+ D 7	Mid R/	End of R/	
				→ Refractory Disease (PA+)
				→ NED FU 29m

PET prior to stem cell transplantation

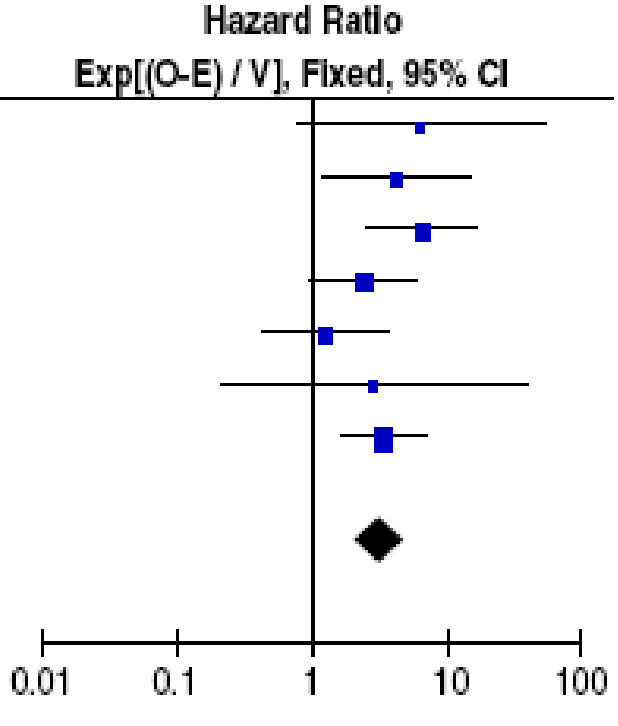
Meta analysis Poulou et al, EJNMMI 2010

a

Study or Subgroup	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Cremerius U,2002	3.8%	6.43 [0.78, 53.19]
Crocchiolo R, 2008	10.2%	4.23 [1.17, 15.27]
Derenzini E, 2008	18.4%	6.56 [2.52, 17.06]
Hoppe BS, 2009	20.1%	2.44 [0.98, 6.08]
Schot BW, 2003	14.8%	1.25 [0.43, 3.64]
Spaepen K, 2003	2.4%	2.87 [0.21, 39.36]
Svoboda J, 2006	30.3%	3.40 [1.61, 7.16]
Total (95% CI)	**100.0%**	**3.23 [2.14, 4.87]**
Total events		

Heterogeneity: $Chi^2 = 6.12$, $df = 6$ ($P = 0.41$); $I^2 = 2\%$

Test for overall effect: $Z = 5.61$ ($P < 0.00001$)



PET for surveillance

- Limited data

- Jerusalem et al. (Annals of Oncology 2003)
  - 36 HD
  - PET every 4-6 months during 3y
  - 11 positive PETs – 5 relapses (FPR 55%)

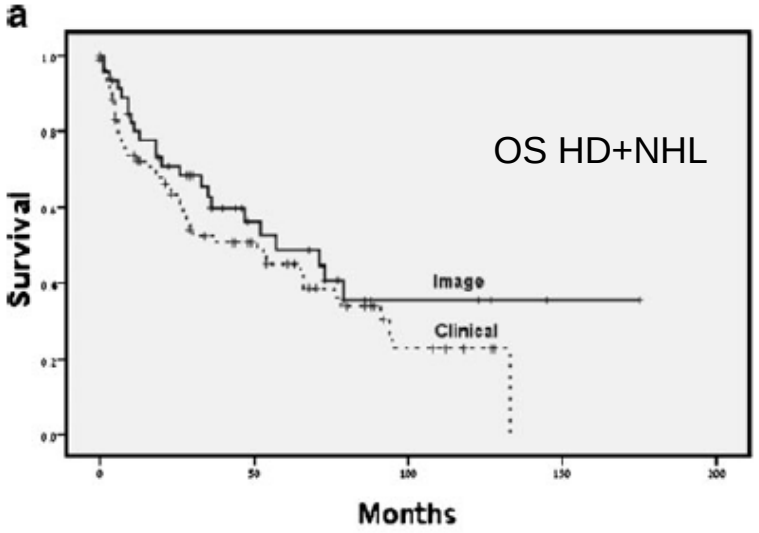
- Mocikova et al. (Abstract Int. Symposium on HL, Cologne, 2007)
  - 82 HD, 301 PETs, mean FU 39 months
  - 70 patients were PET- after treatment
    - 31/70 became PET+ but transient non-specific in 19 pts (61,3%)
  - 12 patients were PET+ after treatment
    - 5 primary resistant HD
    - 7 non-specific and transient (1 biopsy: reactive changes)

PET for surveillance

- Goldschmidt et al, Ann Hematology 2010
  - Retrospective analysis of 125 patients who relapsed > 1m after end of therapy

Table 2 Pretreatment characteristics versus the modality of relapse detection

	Clinical (%)	Image (%)
Histology[a]*		
HL	20 (16.0)	22 (17.6)
A-NHL	58 (46.4)	25 (20.0)
Period of diagnosis[b]		
HL*		
1993–2000	15 (35.7)	9 (21.4)
2001–2009	5 (11.9)	13 (31.0)
A-NHL		
1993–2000	28 (33.7)	11 (13.3)
2001–2009	30 (36.1)	14 (16.9)
All		
1993–2000	43 (34.4)	20 (16.0)
2001–2009	35 (28.0)	27 (21.6)



PET and PET-CT in lymphoma
When and how to use?

- **Baseline PET**
  - PET/CT most accurate test
  - Strongly encouraged if PET response assessment will be done
  - ? Outcome
- **PET during treatment**
  - Promising but only on in trials (impact on outcome?)
  - Optimal Timing? What is PET positive?
- **End of treatment PET**
  - Routine use in aggressive NHL and HD ➔ new response criteria
  - No detection of MRD; Sensitive enough to omit radiotherapy?
  - Exclude false positive uptake!
- **PET for surveillance**
  - Limited data, high false positive rate ➔ no routine use, histology!
  - Better than clinical FU?