SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

UNIVERSITÀ DEGLI STUDI DI FERRARA
- EX LABORE FRUCTUS -

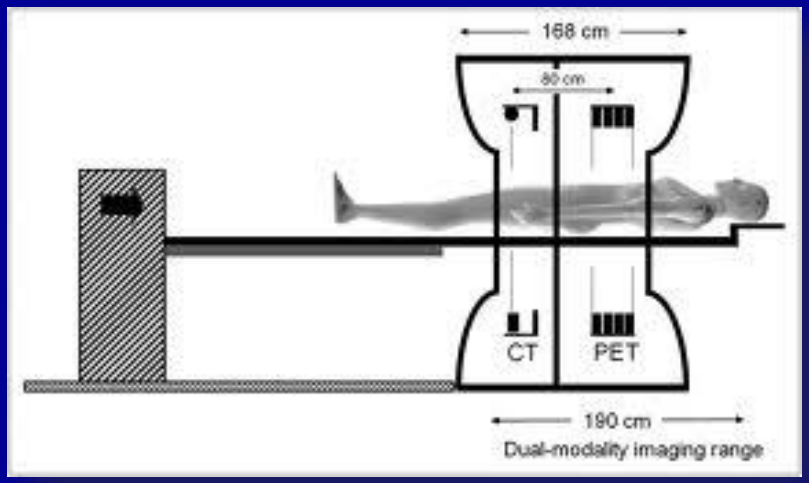
La PET nel Linfoma di Hodgkin in età pediatrica: nuove metodologie per la valutazione della risposta terapeutica

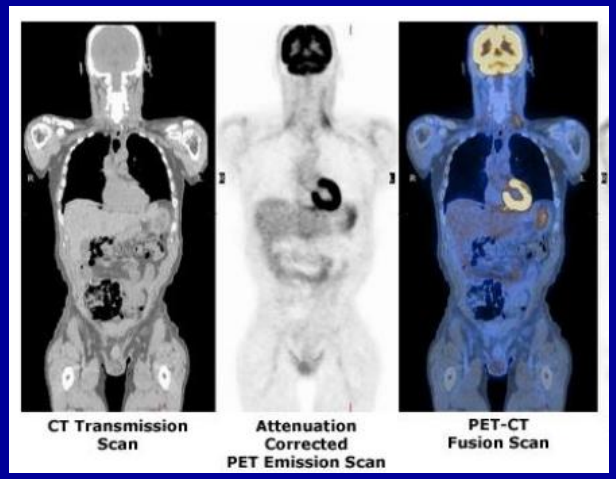
Stefano Panareo
UOC Medicina Nucleare
Azienda Ospedaliero - Universitaria di Ferrara
(Direttore F.F.: Corrado Cittanti)

s.panareo@ospfe.it

Tomografi PET/CT

- Imaging funzionale e morfologico insieme
- Migliore risoluzione spaziale (5 mm)
- Imaging “whole body”
- Tempo di acquisizione limitato (12-15’)
- Minor dose al paziente
- Ridotta esposizione del paziente a radiazioni



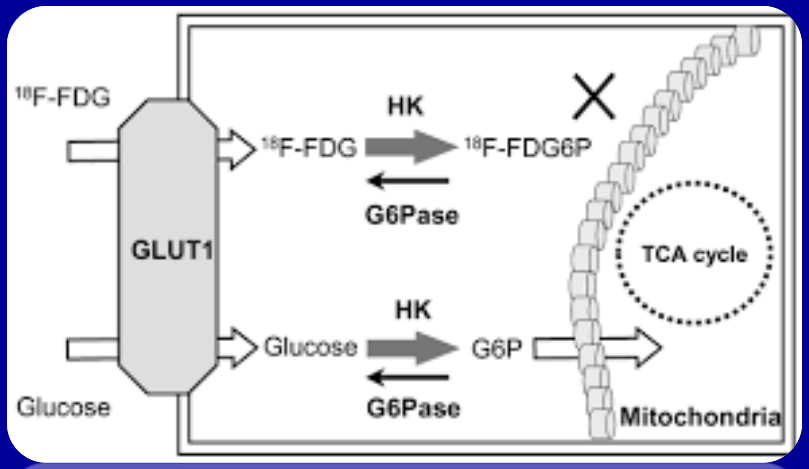


Marcatori biologici nei tumori con PET

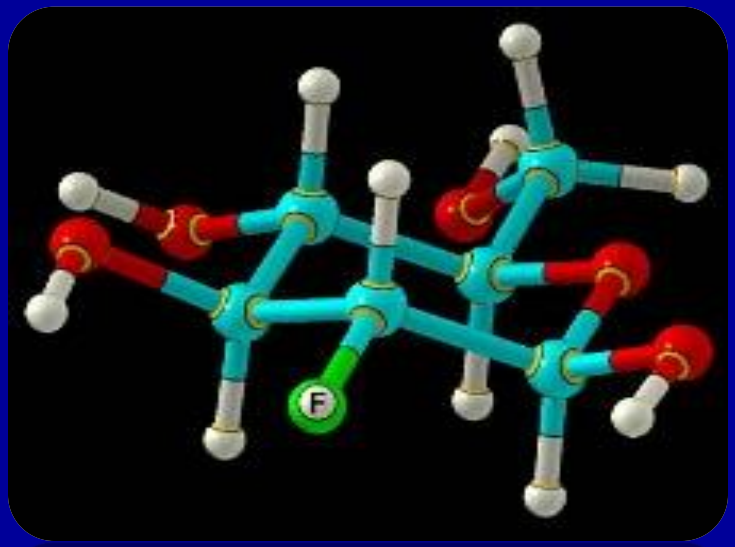
- Perfusione
- Metabolismo ⇒ ^{18}F-FDG
- Ipossia
- Espressione recettoriale
- Sintesi DNA

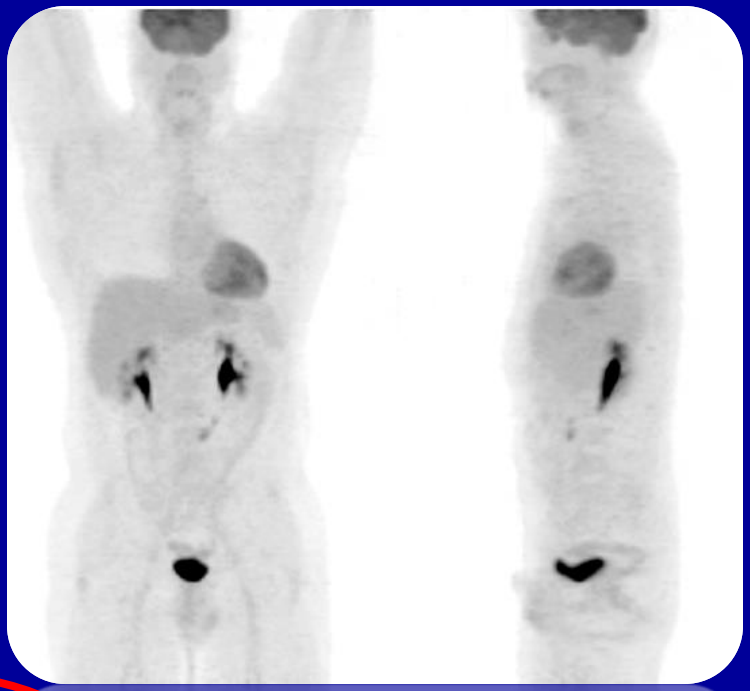
^{18}F-FDG nei tumori

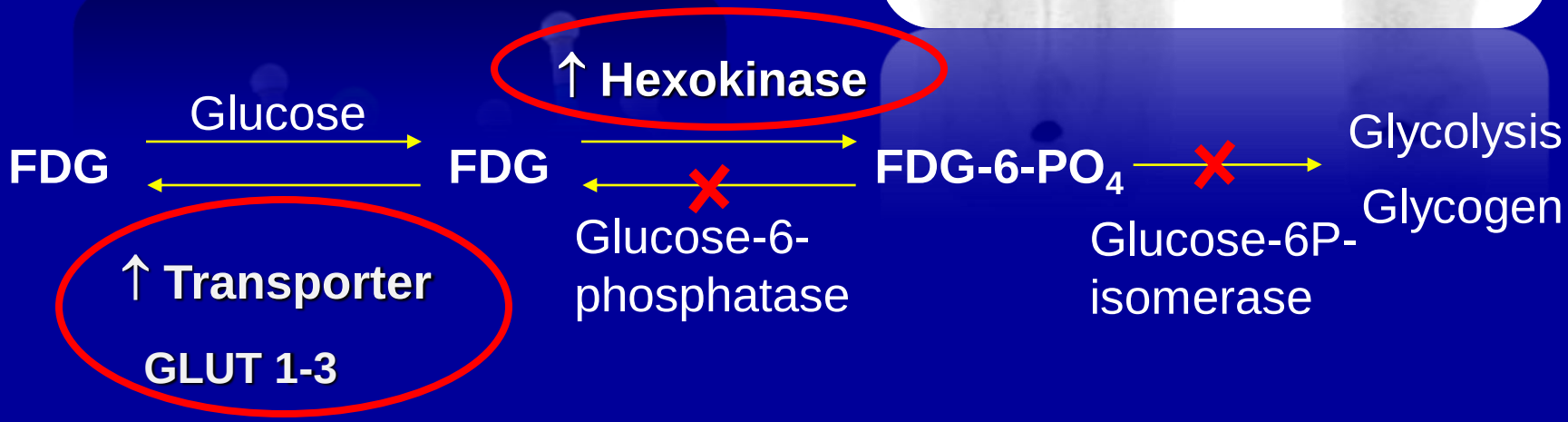
- **La trasformazione maligna della maggior parte delle linee cellulari si associa ad elevato consumo di glucosio:**
  - ***sovraespressione dei trasportatori di glucosio (Glut1 e Glut3)***
  - ***aumento dell'attività esochinasica.***



^{18}F-FDG nei tumori



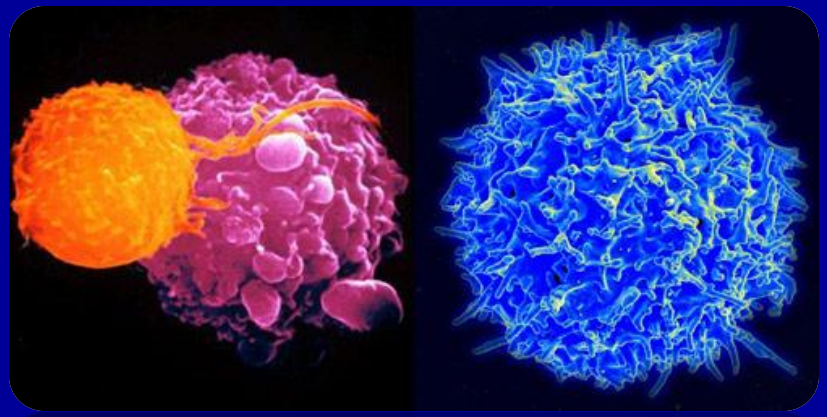




^{18}F-FDG nei tumori

- Maggiore accumulo di FDG nelle lesioni a più rapida crescita e/o nei tumori più aggressivi.
- FDG rispecchia il numero di cellule tumorali vitali.

L'accumulo di FDG nei tumori in vivo dipende anche da vari parametri fisiologici (es. ossigenazione, flusso ematico, flogosi peritumorale)

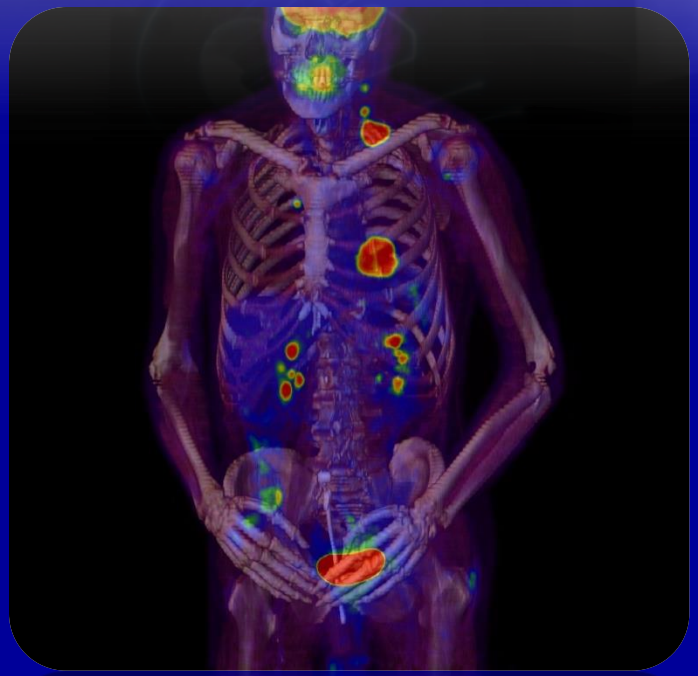


^{18}F-FDG E METABOLISMO

- ^{18}F-FDG captato da cellule in attiva proliferazione.
- fornisce caratteristiche di crescita e di metabolismo tumorale piuttosto che di morfologia della neoplasia (TC, RM).
- descrive estensione locale o a distanza del tumore.
- *riesce a predire ed interpretare le modificazioni che si hanno in seguito a trattamenti terapeutici.*

^{18}F-FDG PET

Indication	%
Lung	24,2%
Head/neck/chest	14,5%
Lymphoma	14,2%
Colorectal	10,1%
Thyroid	8,4%
Gynecological/breast	7,7%
Other	6,6%
Liver	2,8%
Sarcoma	2,7%
Esophageal	2,7%
Testicular/prostate	2,6%
Melanoma	1,7%
Brain	0,9%
Unknown primary	0,8%
Total	**99,9%**



Ricostruzione 3D

FDG PET/CT IN ONCOLOGIA

- **Sensibilità 92-94%**
- **Specificità 93%**
- **Accuratezza diagnostica 93%**

Tab. IX – Sensibilità diagnostica di PET e TC nella rivelazione di ripresa di malattia nelle diverse sedi.

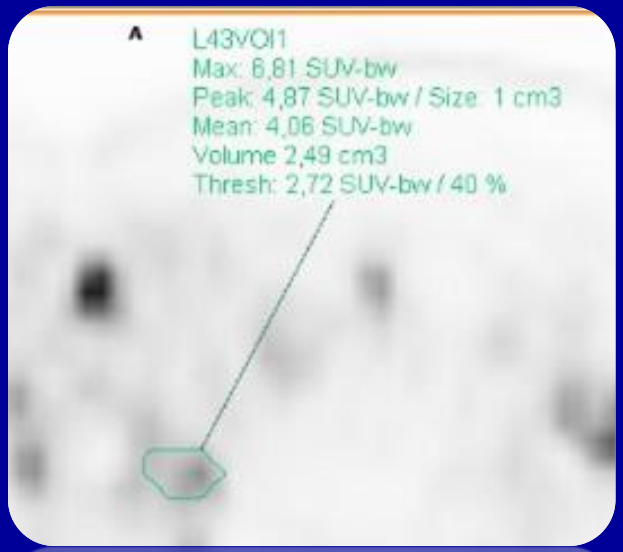
Sede	PET	TC	Differenze (95% intervallo di confidenza)
Fegato	54/57 (95%)	48/57 (84%)	11% (1-22%)
Pelvi	30/31 (97%)	21/31 (68%)	29% (9-49%)
Addome	22/28 (79%)	13/28 (46%)	33% (11-54%)
Retroperitoneo	12/12 (100%)	7/12 (58%)	42% (10-74%)
Polmone	16/17 (94%)	16/17 (94%)	0% (19-19%)
Altre sedi*	12/12 (100%)	4/12 (33%)	67% (36-98%)
Totale	**146/157 (93%)**	**106/157 (69%)**	**24% (16-32%)**

* Altre sedi = 4 ilo e mediastino; 4 osso; 2 parete addominale; 2 ghiandole surrenali.

PET in oncologia – Linee Guida AIMN

SUV
(*Standardized Uptake Value*)

- Indice semiquantitativo che misura la intensità di captazione tumorale del radiofarmaco.
- SUV alto è espressione di elevato metabolismo.
- I tumori con elevato SUV sono più proliferanti e maggiormente aggressivi.
- *SUV come valore prognostico (risposta alla terapia).*



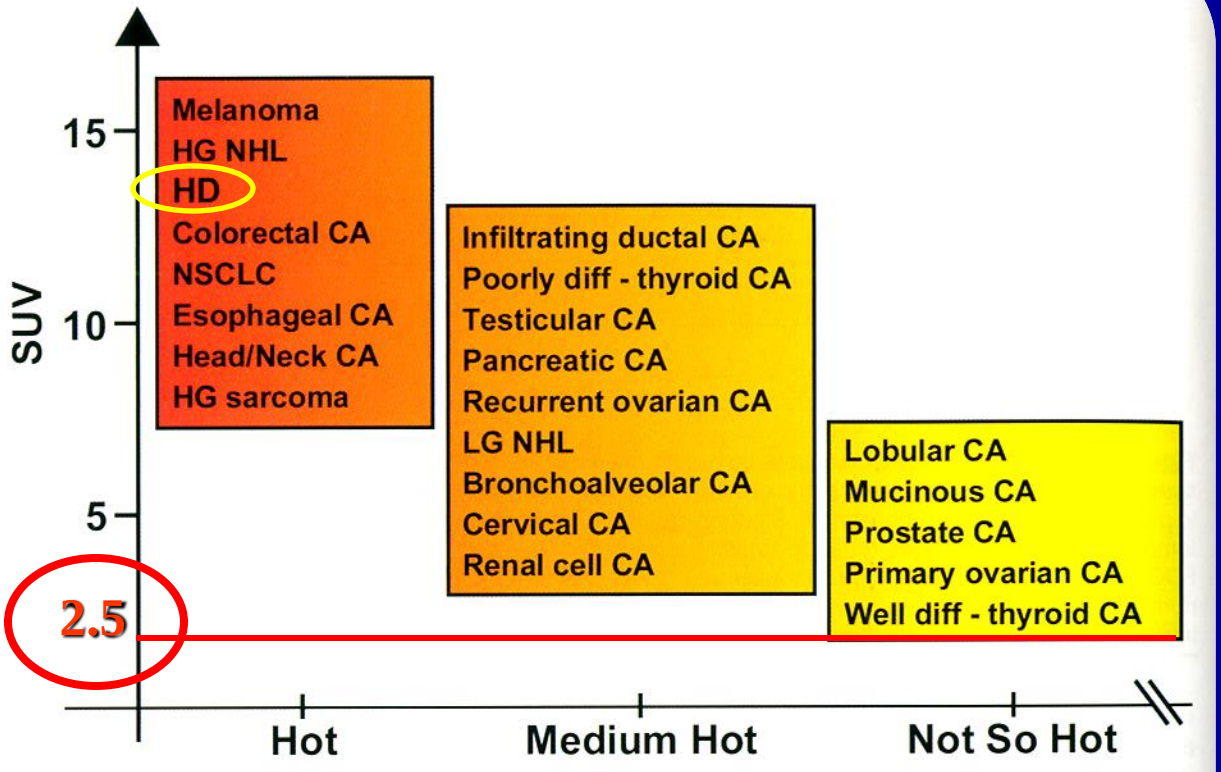


Figure 3. The degree of FDG uptake varies between different cancer types. Note that high grade (HG) tumors generally exhibit higher FDG uptake than low grade (LG) tumors. For instance, poorly differentiated (diff) thyroid cancer shows moderately or severely increased FDG uptake while well differentiated thyroid cancer is frequently low in FDG uptake. Functional features of tumors also determine FDG uptake. For instance, mucinous carcinoma (CA) generally exhibit very low FDG uptake.
Tumor morphology is also an important predictor FDG uptake. For instance, primary ovarian cancer frequently consists of large cystic portions resulting in poor FDG uptake.

Abbreviations: NHL: Non-Hodgkin Lymphoma; HD: Hodgkin's Disease.

^{18}F-FDG Avidity in Lymphoma Readdressed: A Study of 766 Patients

J Nucl Med 2010; 51:25–30

Michal Weiler-Sagie[1], Olga Bushelev[2], Ron Epelbaum[2,3], Eldad J. Dann[2,4,5], Nissim Haim[2,3], Irit Avivi[2,5], Ayelet Ben-Barak[6], Yehudit Ben-Arie[2,7], Rachel Bar-Shalom[1,2], and Ora Israel[1,2]

[1]Department of Nuclear Medicine, Rambam Health Care Campus, Haifa, Israel; [2]Ruth and Bruce Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel; [3]Department of Oncology, Rambam Health Care Campus, Haifa, Israel; [4]Blood Bank and Apheresis Unit, Rambam Health Care Campus, Haifa, Israel; [5]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel; [6]Department of Pediatric Hematology-Oncology, Meyer Children's Hospital, Rambam Health Care Campus, Haifa, Israel; and [7]Department of Pathology, Rambam Health Care Campus, Haifa, Israel

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

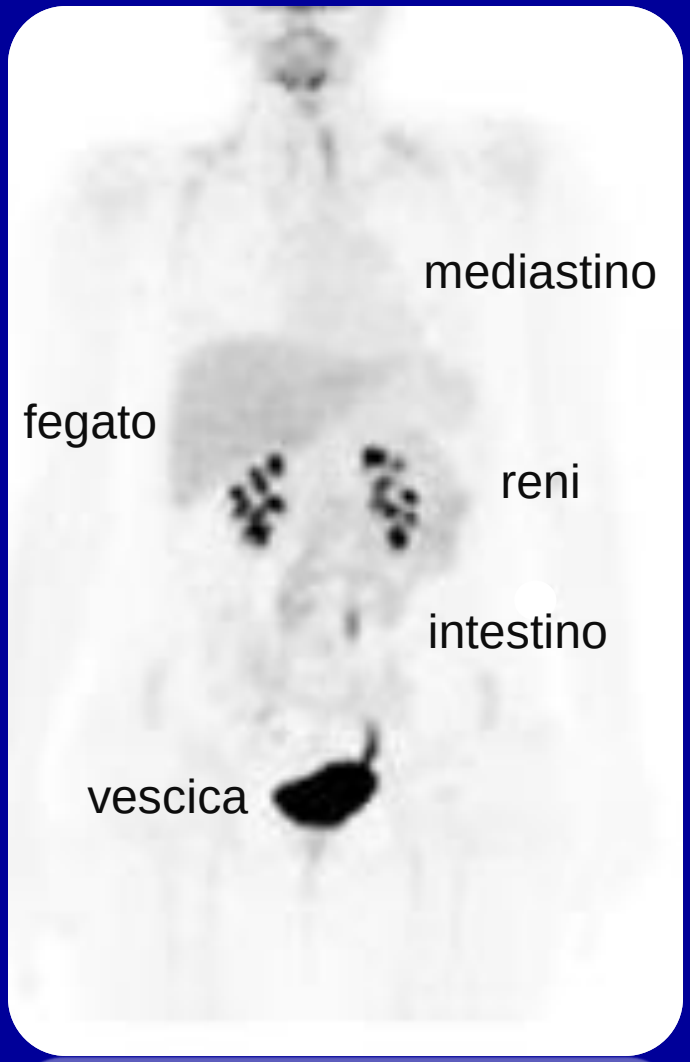
Histology	*n*	^{18}F-FDG–avid	Negative	% ^{18}F-FDG avidity
Hodgkin disease	233	233	0	100
Burkitt lymphoma	18	18	0	100
Mantle cell lymphoma	14	14	0	100
Anaplastic large T-cell lymphoma	14	14	0	100
Marginal zone lymphoma, nodal	8	8	0	100
Lymphoblastic lymphoma	6	6	0	100
Angioimmunoblastic T-cell lymphoma	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

Guidelines for PET scanning

Table 6. Guidelines for Conduct of FDG-PET Scans

Parameter	Recommendations
Patient preparation	Fast overnight, or at least 6 hours Hydrate with > 500 mL post-FDG injection Mild sedation as needed
Blood glucose	Not to exceed 200 mg/dL
Patient imaging	60 ± 10 minutes after FDG injection
Timing of PET scan	Pretreatment scans required if post-treatment to be performed, within 2 weeks of therapy Post-treatment scans at least 6-8 weeks after chemo(immuno)therapy
FDG dose	3.5-8 MBq/kg body weight, minimum 185 MBq
Acquisition	Base of skull to mid-thigh unless other areas of concern

BIODISTRIBUTION



INDICATIONS

- PRE-TREATMENT STAGING
- ***RESTAGING:***
  - ***END-TREATMENT***
  - ***INTERIM/MID-TREATMENT***
- FOLLOW-UP
- Further indications:
  - Pre and post transplant
  - Pre and post Radio Immunotherapy (RIT)
  - Aggressive transformation
  - Radiotherapy planning

False positive

FDG is taken up in any process with increased glycolysis:

- INFLAMMATION
- INFECTION
- NECROSIS
- GRANULOMATOUS DISEASE (including sarcoidosis)
- THYMIC HYPERPLASIA
- BROWN FAT

FP occures with the use of RITUXIMAB [Han et al]

False negative

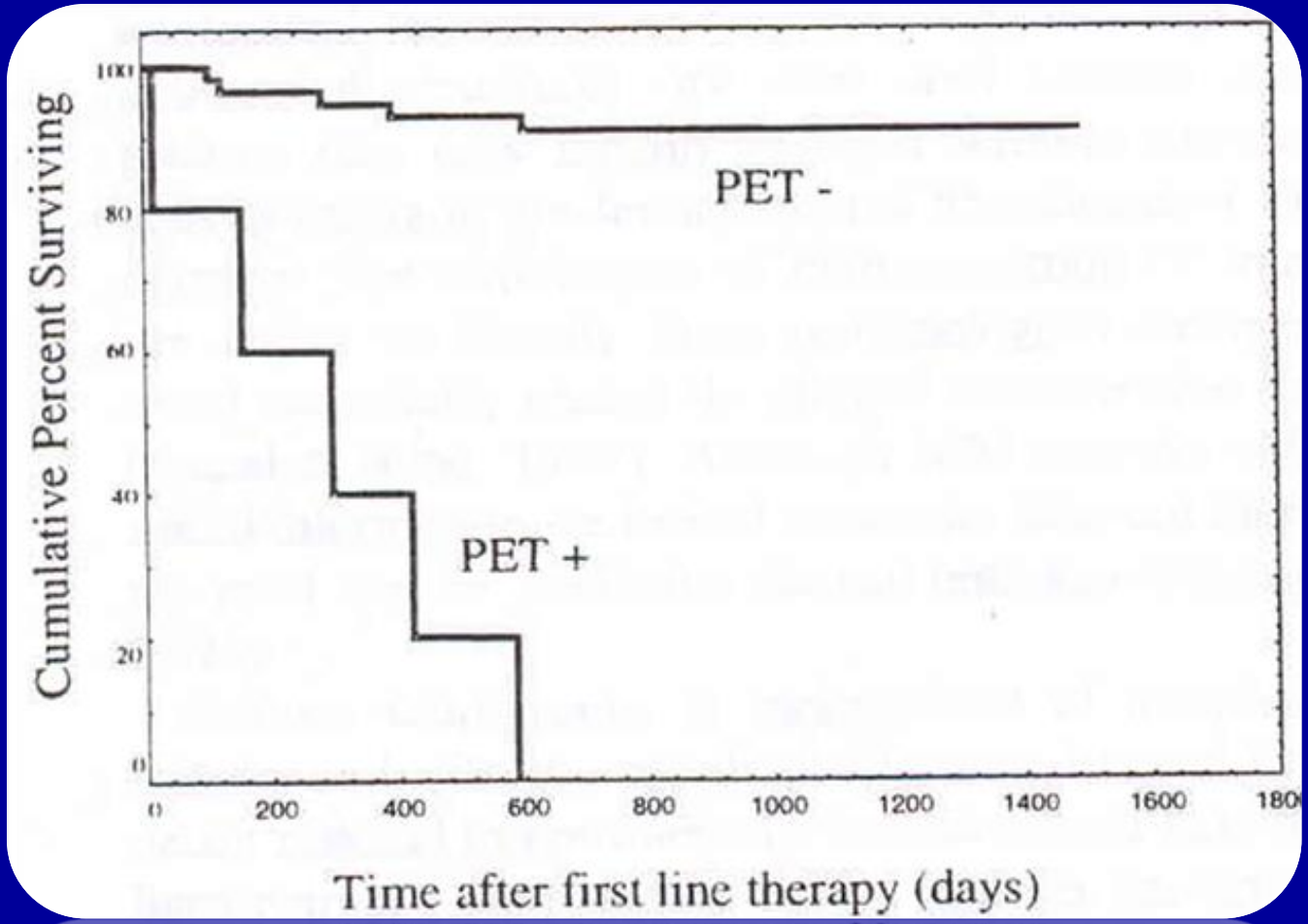
- NON FDG AVID HISTOLOGIES
- SMALL DIMENSION (< 5mm)
- UNCORRECT TIMING OF PET SCANNING
- POST CHEMOTHERAPY STUNNING

End-treatment

Spaepen, B.J. Haemat., 2001

60 HL.

Follow-up: 3 years



End-treatment

Table 4. PET(CT) in Restaging of Lymphoma

Study	No. of Patients	PPV (%)	NPV (%)
NHL			
Bangerter[20]	89	90	98
Jerusalem[42]	35	42.9	100
Zinzani[47]	31	92.9	100
Mikhaeel[44]	45	60	100
Naumann[48]	15	85.7	88.2
Spaepen[45]	93	70.3	100
Cashen[50]	50	80	92
Gigli[49]	42	75	94
HL			
Spaepen[46]	60	100	91
Engert[51]	728	NA	94.6
Cerci[52]	130	92.3	100

- High NPV: 90% (similar to spiral CT)

10-20% FN
inability to detect microscopic disease resulting in relapse

- Lower and more variable PPV:
  75% in NHL (vs 40% CT)
  65% in HL (vs 20% CT) → FP post radiation inflammatory changes
  FP thymic hyperplasia in younger patients

End-treatment

Whole-Body Positron Emission Tomography Using ^{18}F-Fluorodeoxyglucose for Posttreatment Evaluation in Hodgkin's Disease and Non-Hodgkin's Lymphoma Has Higher Diagnostic and Prognostic Value Than Classical Computed Tomography Scan Imaging

Blood, Vol 94, No 2 (July 15), 1999: pp 429-433

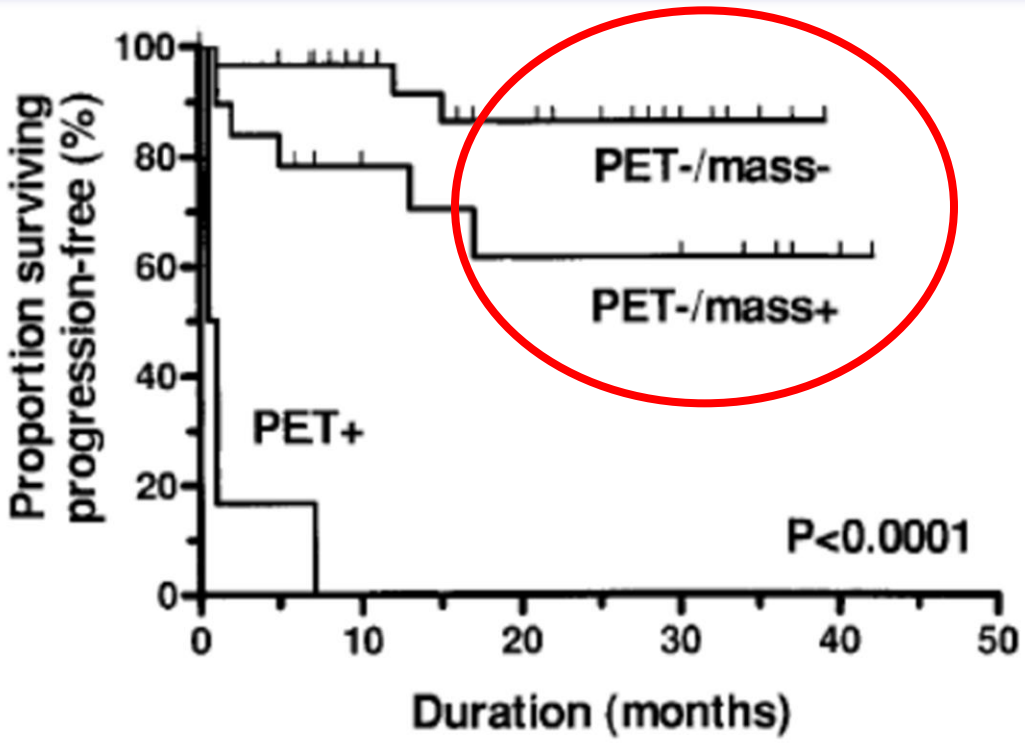


Fig 5. Kaplan-Meier estimate of PFS in 29 patients with negative PET and CT scans compared with 19 patients with positive CT but negative PET and 6 patients with positive PET ($P < .0001$).

End-treatment

Computed tomography and ^{18}F-FDG positron emission tomography for therapy control of Hodgkin's and non-Hodgkin's lymphoma patients: when do we really need FDG-PET?

M. J. Reinhardt[1,2]*, C. Herkel[2], C. Altehoefer[3], J. Finke[4] & E. Moser[2]

Annals of Oncology 16: 1524–1529, 2005
doi:10.1093/annonc/mdi271
Published online 9 June 2005

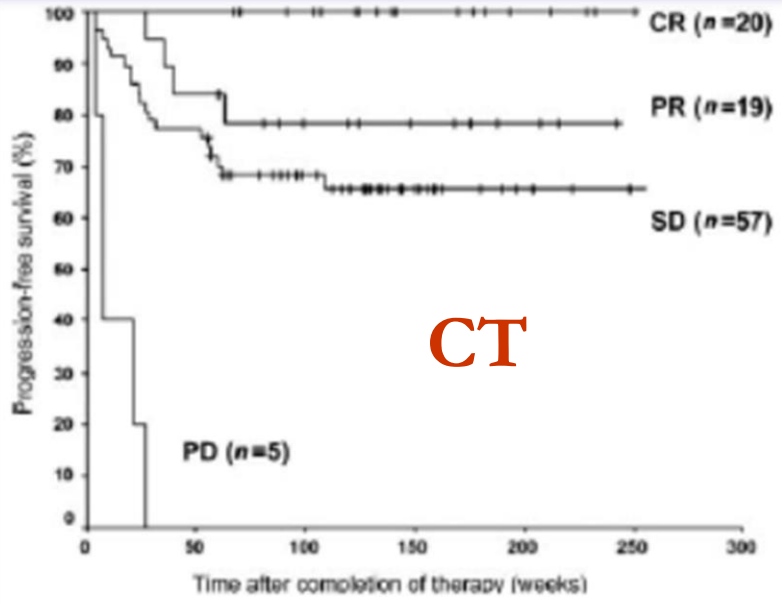


Figure 1. Kaplan–Meier estimates of progression-free survival in 101 lymphoma patients in dependence on CT imaging results after completion of therapy. Significance values were: CR versus PR, $P = 0.029$; CR versus SD, $P = 0.004$; CR versus PD, $P < 0.00001$; PR versus SD, $P = 0.281$; PR versus PD, $P < 0.00001$; SD versus PD, $P < 0.00001$. CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease.

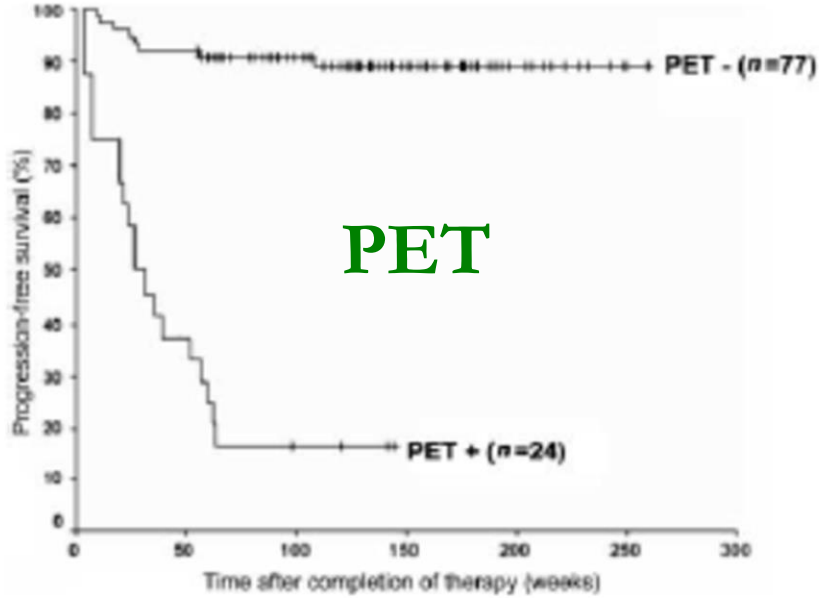
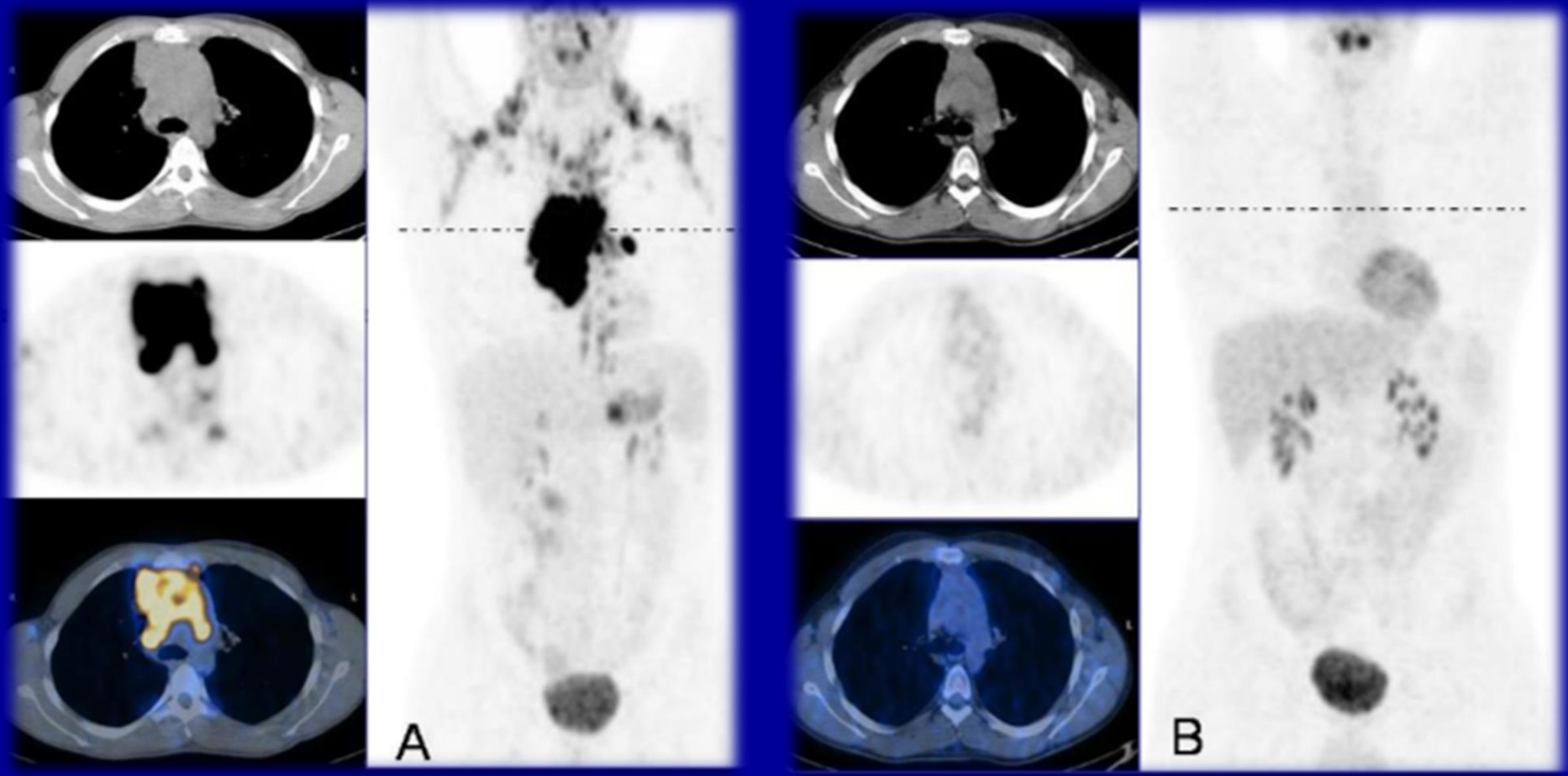


Figure 2. Kaplan–Meier estimates of progression-free survival in 101 lymphoma patients in dependence on [^{18}F]fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) imaging results after completion of therapy. The difference between PET negative (PET–) and PET positive (PET+) was significant ($P < 0.00001$).

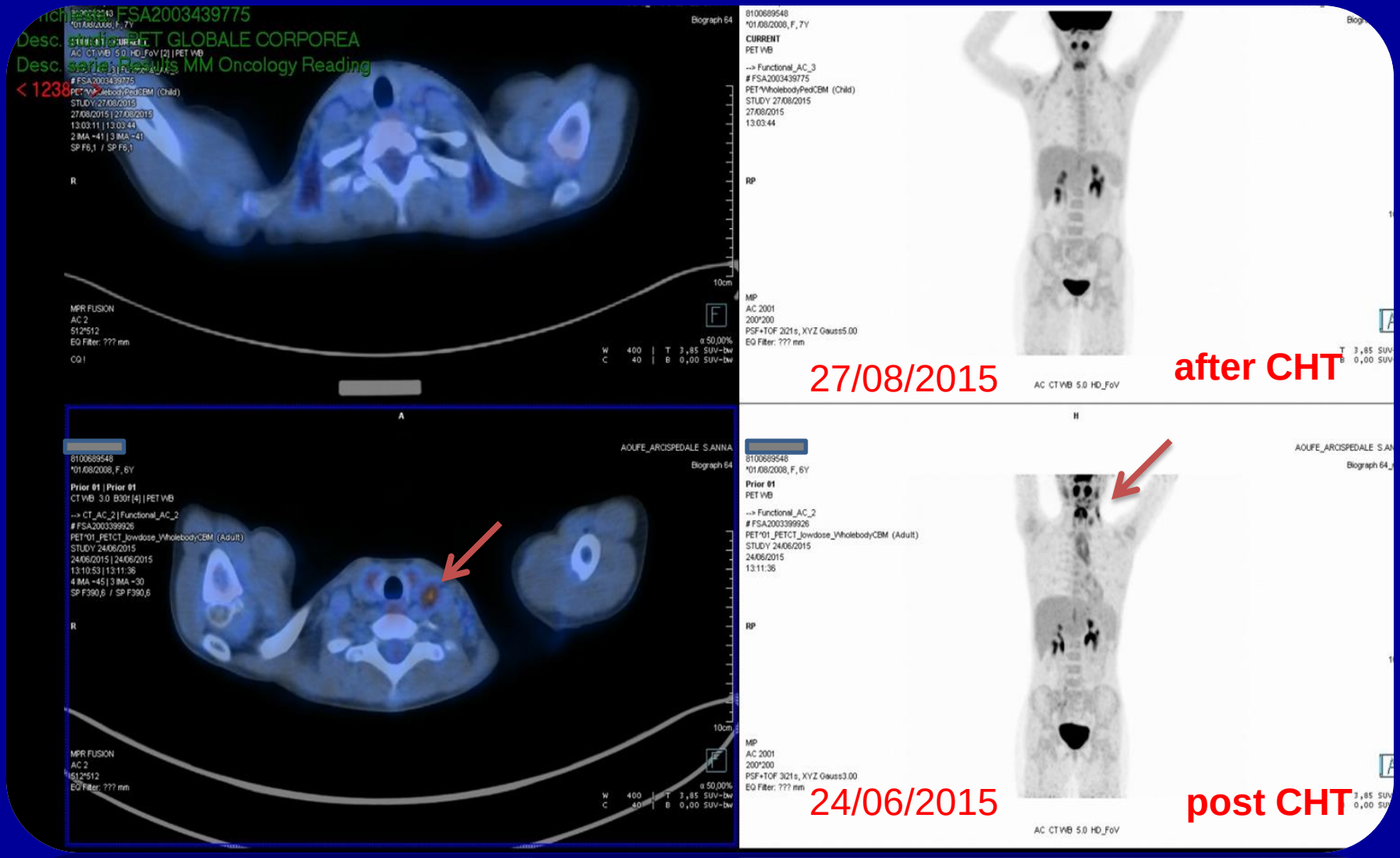
End-treatment



HL nodular sclerosis (stage III): A) after CHT, B) post CHT

End-treatment

Female, 7yo, HL (lymphocytic prevalence) CHT: CVP



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

J Clin Oncol 25:579-586. © 2007 by American Society of Clinical Oncology

Response assessment at therapy conclusion is typically performed:

- **At least 3 WEEKS AFTER CHEMOTHERAPY (6-8)**
- **8-12 WEEKS AFTER RADIOTHERAPY**

Initial staging with PET, for assessment of response after treatment:

- **Not mandatory but strongly recommended for:**
  HL, DLBCL, FL, MCL (routinely FDG avid)
- Mandatory for:
  T-cell lymphomas and indolent NHL other than FL (variably FDG avid)
  PET+ at all disease sites >1.5cm in diameter noted by CECT

Table 2. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identifed node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

New criteria validated by **Juweid et al, Brepoels et al, Dupuis et al:**

- PET doubles the number of CRs and eliminates the CR-unconfirmed
- Enhances the difference in PFS between CR and PR
- IWC+PET is the only statistically significant indipendent predictor of PFS

^{18}F-FDG PET After 2 Cycles of ABVD Predicts Event-Free Survival in Early and Advanced Hodgkin Lymphoma

Juliano J. Cerci[1], Luís F. Pracchia[2], Camila C.G. Linardi[2], Felipe A. Pitella[1], Dominique Delbeke[3], Marisa Izaki[1], Evelinda Trindade[4], José Soares Junior[1], Valeria Buccheri[2], and José C. Meneghetti[1]

Interim

TABLE 5. Major Studies Evaluating Prognostic Impact of PET2 in HL

Study	Year	Number of cycles	Number of patients	EFS		Follow-up (mo)
				PET-positive	PET-negative	
Hutchings et al. (*12*)	2005	2 or 3	85	46%	96%	6–125
Hutchings et al. (*11*)	2006	2	77	0%	96%	2–41
Gallamini et al. (*13*)	2006	2	108	6%	96%	2–47
Gallamini et al. (*14**)	2007	2	97	13%	95%	4–62
Present study	2009	2	104	24%	90%	28–40
Total			471	18%	95%	

[Gallamini et al] and [Cerci et al]:

Interim PET (dynamic) is the most important prognostic factor, more powerful than the IPS (static)

	ALBUMIN	Hb	SEX	AGE	STAGE	WBC count	Lympho cyte
IPS	<4 g/dl	<10.5 g/dl	Male	>45y	IV	>15000/ mm2	<600/m m2 or <8%wbc

Eur J Nucl Med Mol Imaging. 2012 Jan;39(1):4-12. Epub 2011 Sep 6.

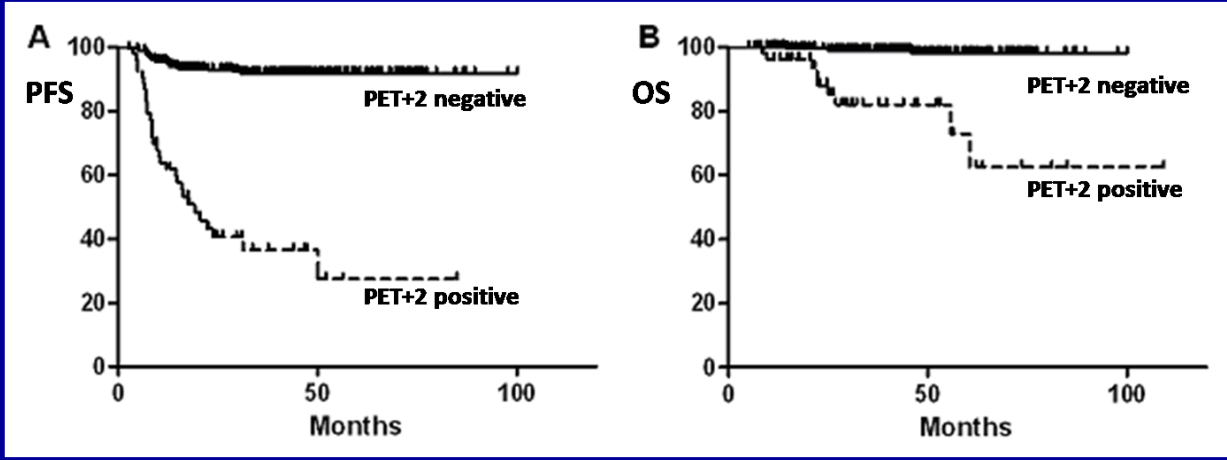
Early interim 18F-FDG PET in Hodgkin's lymphoma: evaluation on 304 patients.

Zinzani PL, Rigacci L, Stefoni V, Broccoli A, Puccini B, Castagnoli A, Vaggelli L, Zanoni L, Argnani L, Baccarani M, Fanti S.

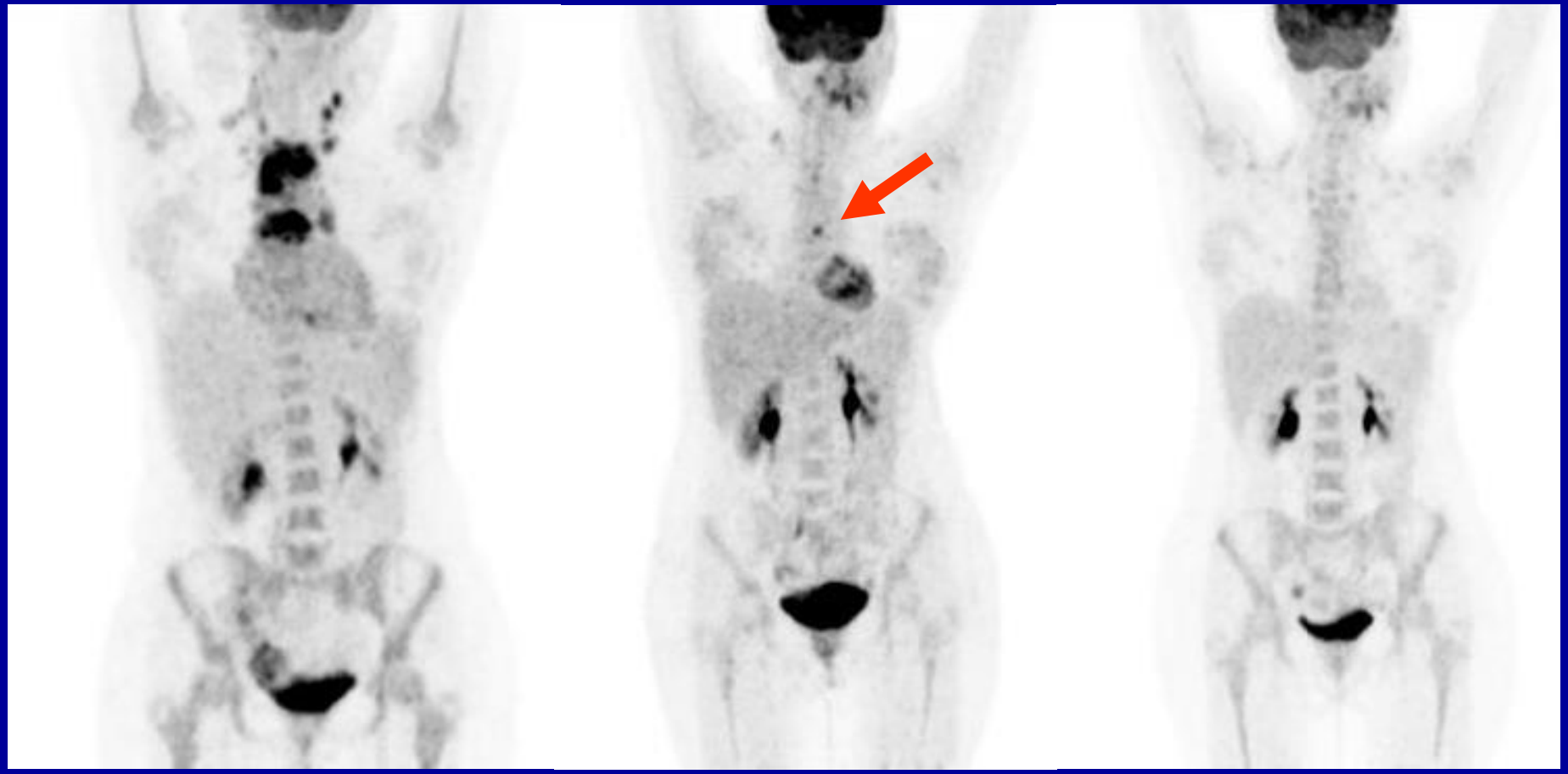
METHODS: Between June 1997 and June 2009, 304 patients with newly diagnosed HL (147 early stage and 157 advanced stage) were treated with the ABVD regimen at two Italian institutions. Patients underwent PET staging and restaging at baseline, after two cycles of therapy and at the end of the treatment.

RESULTS: Of the 304 patients, 53 showed a positive interim PET scan and of these only 13 (24.5%) achieved continuous complete remission (CCR), whereas 251 patients showed a negative PET scan and of these 231 (92%) achieved CCR. Comparison between interim PET-positive and interim PET-negative patients indicated a significant association between PET findings and 9-year progression-free survival and 9-year overall survival, with a median follow-up of 31 months. Among the early-stage patients, 19 had a positive interim PET scan and only 4 (21%) achieved CCR; among the 128 patients with a negative interim PET scan, 122 (97.6%) achieved CCR. Among the advanced-stage patients, 34 showed a persistently positive PET scan with only 9 (26.4%) achieving CCR, whereas 123 showed a negative interim PET scan with 109 (88.6%) achieving CCR.

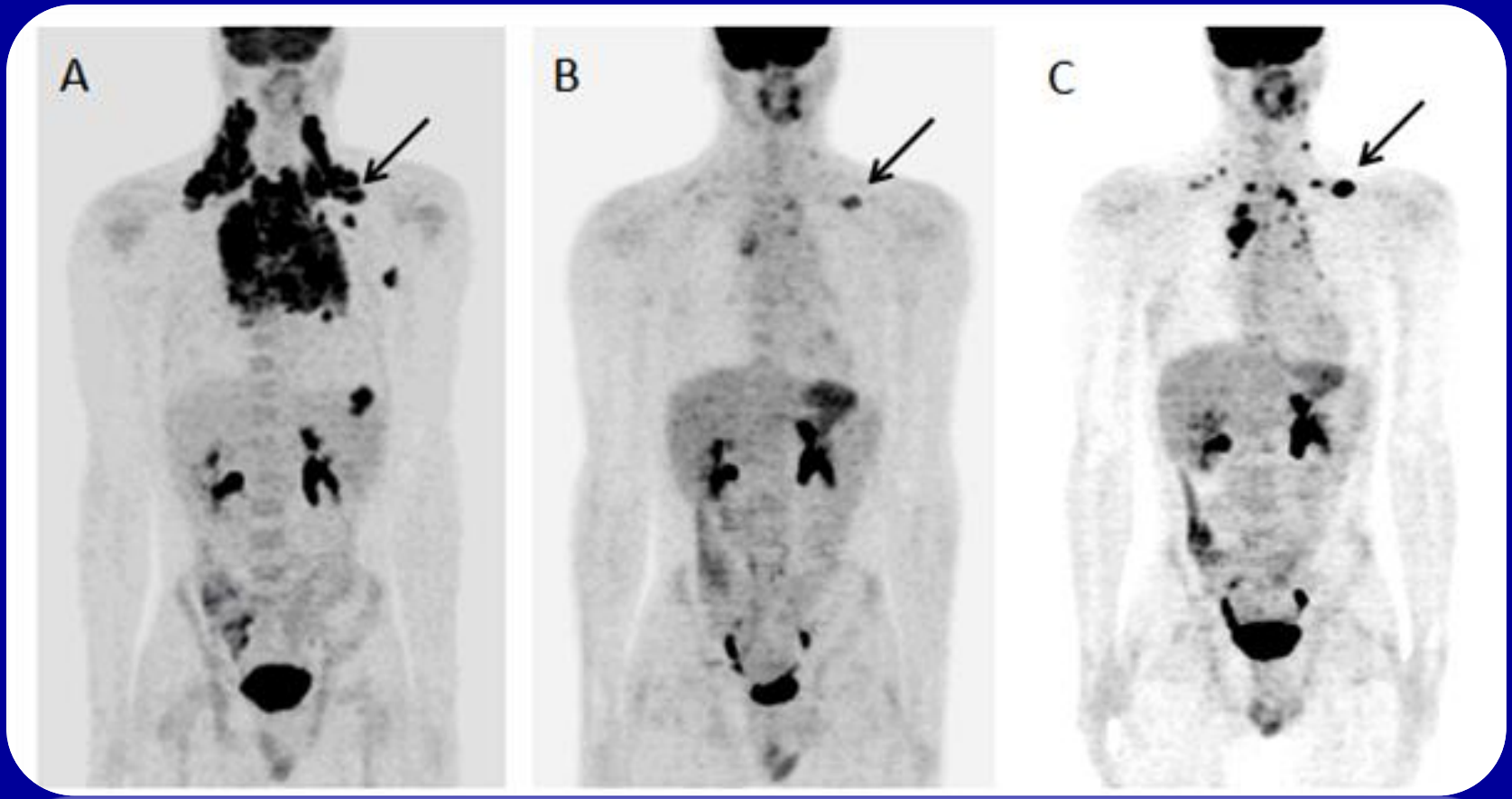
9y PFS:
PET- 94,7%
vs
PET+ 31,3%
(p=0,0000)



9y OS:
PET- 100%
vs
PET+ 85,2%
(p=0,0001)



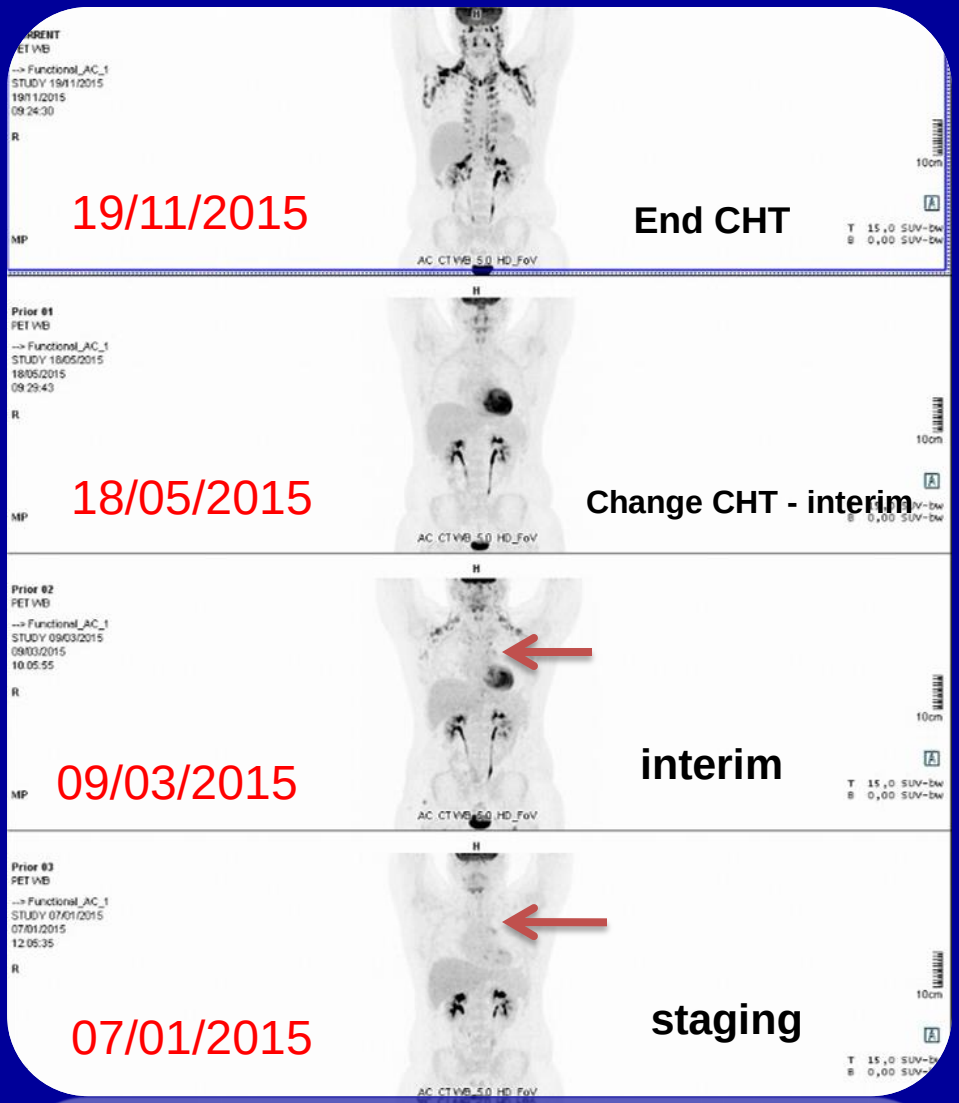
HL
(A) STAGING: IV (spleen + bone marrow)
(B) PET interim: P.R.
(C) PET end-treatment: MRU.
2 year-follow up: C.R.



Male, 26yo patient diagnosed with HL.
A: Initial staging FDG-PET present multiple bilateral cervical, bilateral supraclavicular, left axilary, mediastinum lymph nodes and also spleen lesions.
B: After 2 cycles of ABVD patient was submitted to interim FDG-PET, with partial metabolic response, with markedly reduced metabolism in all lymph node chains.
C: After four cycles of ABVD patient was reevaluated and presented progressive disease (PD).

HL: clinical case

Male, 16yo, HL (nodular sclerosis)
CTH: first l. COPP/ABV + 2 cycles IEP; second l. OPPA + DHAP



Interim PET in lymphoma: a step towards standardization

Michel Meignan

Eur J Nucl Med Mol Imaging (2010) 37:1821–1823

2007:

- **[JUWEID ET AL.]** CONSENSUS OF THE IMAGING SUBCOMMITTEE OF INTERNATIONAL HARMONIZATION PROJECT **(IHP)**
- **[CHESON ET AL.]** **REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA**

F^{18}FDG uptake in mediastinal blood pool as comparator[7,8]

2009:

- **[GALLAMINI et al.]** THE EDUCATION PROGRAM FOR THE ANNUAL CONGRESS OF THE EUROPEAN HEMATOLOGY ASSOCIATION

F^{18}FDG uptake in liver blood pool as comparator[9]

A functional dynamic scoring model to elucidate the significance of post-induction interim fluorine-18-fluorodeoxyglucose positron emission tomography findings in patients with Hodgkin's lymphoma

Eldad J. Dann,[1,5] Rachel Bar-Shalom,[3,5] Ada Tamir,[5] Ron Epelbaum,[2,5] Irit Avivi,[1,5] Menachem Ben-Shachar,[2] Diana Gaitini,[4] and Jacob M. Rowe[1,5]

Haematologica 2010;95:1198-1206

Dynamic visual score

N° and intensity residual sites relative to baseline scan

ble 2. Summary of four scoring systems used to define metabolic response on interim F^{18}FDG PET/CT.

Static visual score	Score	Dynamic visual score (current study)	F^{18}FDG uptake in mediastinal blood pool as comparator[7,8]	F^{18}FDG uptake in liver blood pool as comparator[9]
No abnormal F^{18}FDG uptake	0	No abnormal F^{18}FDG uptake	No abnormal F^{18}FDG uptake	No abnormal F^{18}FDG uptake
	1	A single residual focus of abnormal F^{18}FDG uptake. If only a single site on baseline: a markedly decreased intensity compared to baseline	**Residual mass ≥2 cm:** Lesion uptake < mediastinum	**Residual mass ≥2 cm:** Lesion uptake < liver uptake
	2	More than one site of residual uptake but with a marked decrease in number of disease sites compared to baseline.	**Residual mass ≥2 cm:** Lesion uptake=mediastinum	**Residual mass ≥2 cm:** Lesion uptake=liver uptake
Any focus of abnormal F^{18}FDG uptake (not related to physiological or benign tracer uptake).	3	Reduced intensity of uptake with no change in their number compared to baseline	**Residual mass ≥2 cm:** Moderately increased uptake compared with mediastinum OR Residual mass <2 cm: any focus of abnormal F^{18}FDG uptake (not related to physiological or benign uptake)	**Residual mass ≥2 cm:** Lesion uptake moderately increased compared with liver uptake OR Residual mass <2 cm: any focus of abnormal F^{18}FDG uptake (not related to physiological or benign uptake)
	4	No change in either number or intensity of sites or the appearance of new sites of disease	**Residual mass ≥2 cm:** Markedly increased uptake compared with mediastinum **OR** **Residual mass <2 cm:** any focus of abnormal F^{18}FDG uptake (not related to physiological or benign uptake)	**Residual mass ≥2 cm:** Lesion uptake markedly increased compared with liver uptake **OR** **Residual mass <2 cm:** Any focus of abnormal F^{18}FDG uptake (not related to physiological or benign uptake)
	Negative Positive FDG-PET/CT	Score 0-2 Score ≥3	Score 0-2 Score ≥3	Score 0-2 Score ≥3

2008:

• **[GUY'S et al.] LONDON FDG UPTAKE 5-POINT SCALE**:

1. No uptake

2. Uptake > mediastinum

3. Uptake > mediastinum but <liver

4. Uptake moderately increased compared to the liver at any site

5. Uptake markedly increased compared to the liver at any site or/and new sites of disease

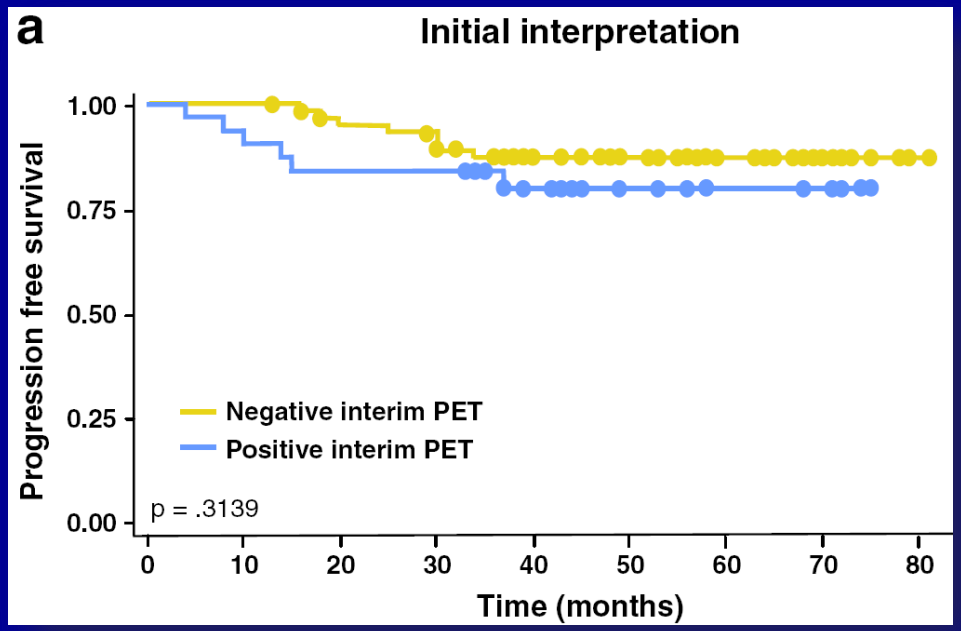
2009:

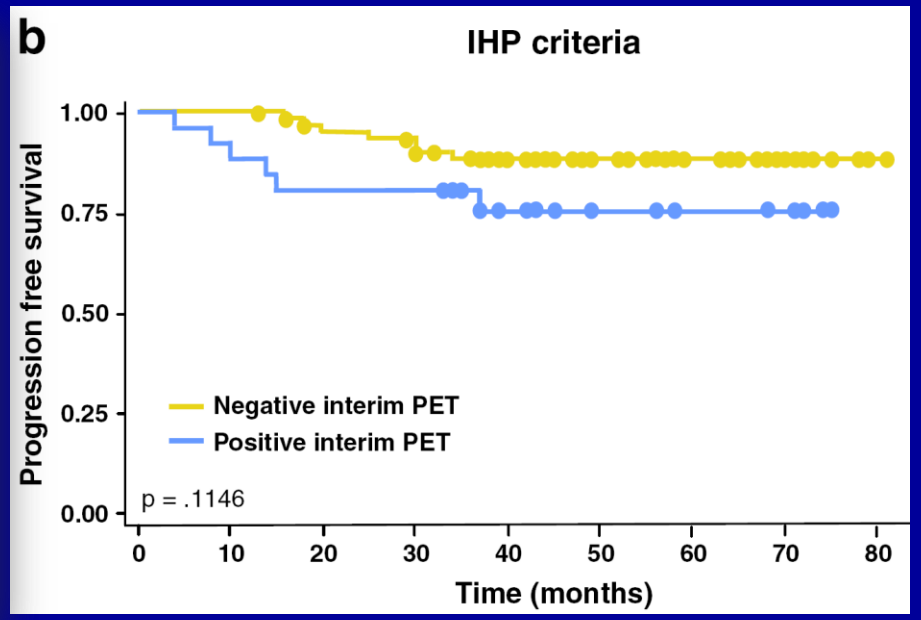
• FIRST INTERNATIONAL WORKSHOP ON INTERIM PET IN LYMPHOMA: validation **5-point scale** as **DEAUVILLE SCORE**

2010:

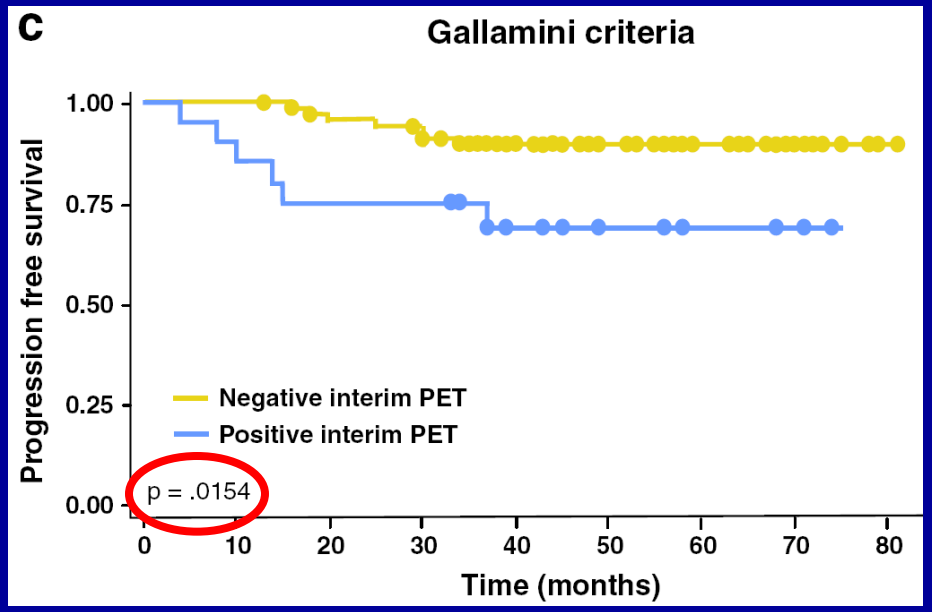
• Criteria publication by **[BARRINGTON et al] and [MEIGNAN et al]** after the SECOND INTERNATIONAL WORKSHOP (in Menton -France)

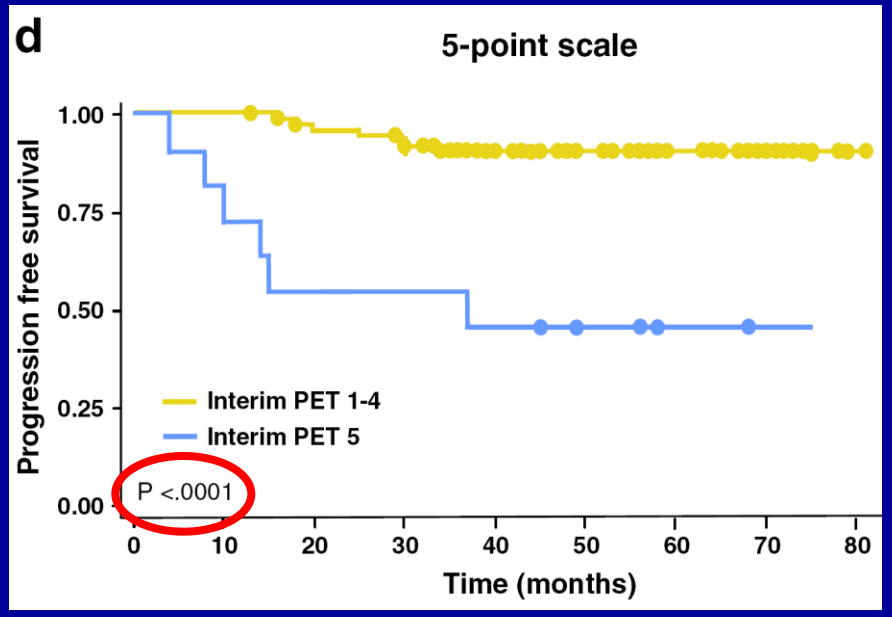
A score of 4 or more was the positivity threshold





Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-011-1741-0





ISSN 1591-223X
DOSSIER 227 - 2012
Regione Emilia-Romagna
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

LINFOMA DI HODGKIN

Ballini L, Maltoni S, Vignatelli L, Negro A, Trimaglio F. Criteria for appropriate use of FDG-PET in in malignant lymphoma. Dossier 227 - Agenzia sanitaria e sociale regionale, Regione Emilia-Romagna. 2012.

- stadiazione del linfoma di Hodgkin -
  Appropriato (livello di evidenza: moderato)
- definizione del *dose painting* nella radioterapia *involved-field* nel linfoma di Hodgkin -
  Indeterminato a causa della mancanza di studi
- valutazione, durante il trattamento, della risposta precoce alla terapia del linfoma di Hodgkin -
  Appropriato (livello di evidenza: moderato)
- valutazione della risposta alla fine del trattamento del linfoma di Hodgkin -
  Appropriato (livello di evidenza: moderato)
- *follow up* dei pazienti trattati per linfoma di Hodgkin senza sospetto di ricaduta -
  Inappropriato (livello di evidenza: basso)
- stadiazione della ricaduta nei pazienti trattati per linfoma di Hodgkin -
  Appropriato (livello di evidenza: molto basso)

Grazie dell'attenzione