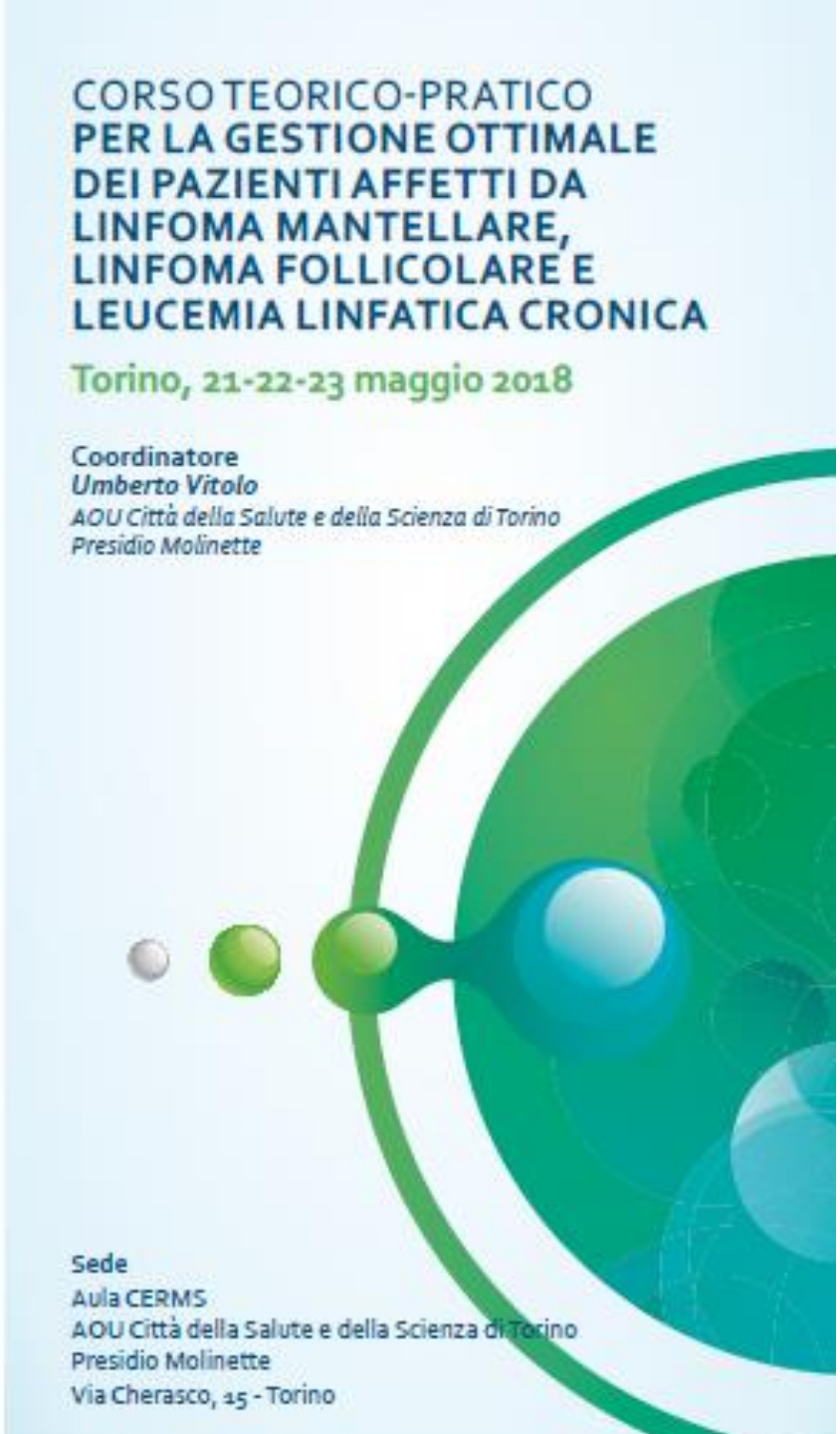


I SESSIONE
Ruolo dell'imaging nelle malattie linfoproliferative

Ruolo della PET

Alberto BIGGI

SC Medicina Nucleare
ASO Santa Croce e Carle
CUNEO

21 maggio 2018

Positron emission tomography

Increased glucose utilization in lymphomas

Entity	% positive	Maximum SUV
Aggressive lymphomas		
HL, DLBCL, PMBCL, BL, PTCL	85 - 100 %	19,6 ± 9,3
Indolent lymphomas		
Mantle cell lymphoma	100 %	8,7 ± 1,3
Follicular lymphoma	95 %	7,7 ± 4,6
Nodal marginal zone lymphoma	100 %	3,8 ± 1,3
Splenic MZL	67 %	
Extranodal MZL (MALT)	55 %	
WM	83 %	k. A.
SLL / CLL	83 %	2,5 ± 0,7

Schöder et al, J Clin Oncol 23: 4643, 2005;
Weiler-Sagie et al, J Nucl Med 51: 25, 2010;
Karam et al, Nucl Med Comm 30: 770, 2009;
Karam et al, Cancer 107: 175, 2006;
Banwait et al, Am J Hematol 86: 567, 2011

Lugano consensus conference (2013)

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

JOURNAL OF CLINICAL ONCOLOGY SPECIAL ARTICLE

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group

Barrington SF: J Clin Oncol. 2014; 32 (27): 3048-58
Cheson BD: J Clin Oncol. 2014; 32 (27)3059-68

Role of PET/CT in lymphoma

- PET/CT should be used for **staging** in clinical practice and clinical trials but is not recommended in lymphomas with low FDG avidity (Type 1)
- If **midtherapy** imaging is performed during treatment in clinical trials/practice , PET/CT is superior to CT alone to assess early response and has the potential to replace CT (Type 1)
- PET/CT is the standard of care for **remission assessment** in FDG avid lymphoma. In presence of residual metabolically active tissue, where salvage treatment is being considered, biopsy is considered (Type1)

Barrington SF: J Clin Oncol. 2014; 32 (27): 3048-58

La PET/CT nel linfoma follicolare

Approccio terapeutico

Early stage - Stadio I-II
(10-20% of pts)

→ Inv. Field RxTherapy

Advanced stage - Stadio III-IV
(80-90% of pts)

→ Watch and Wait

- Sintomi B
- Alta massa tumorale (>7 cm)
- Citopenia da invasione midollare
- Splenomegalia > 16 cm CT
- Leucemizzazione
- Versamento sieroso
- Coinvolgimento d'organo
- Progressione rapida del linfoma
- LDH elevato

→ R-CHOP + 2 yrs R (FOLL5)
R-Benda + 2 yrsR (STILL)

Ruolo della PET/CT nel linfoma follicolare

- **Stadiazione**
- **Valutazione della risposta e prognosi**
- **Mantenimento**

Captazione di FDG alla stadiazione

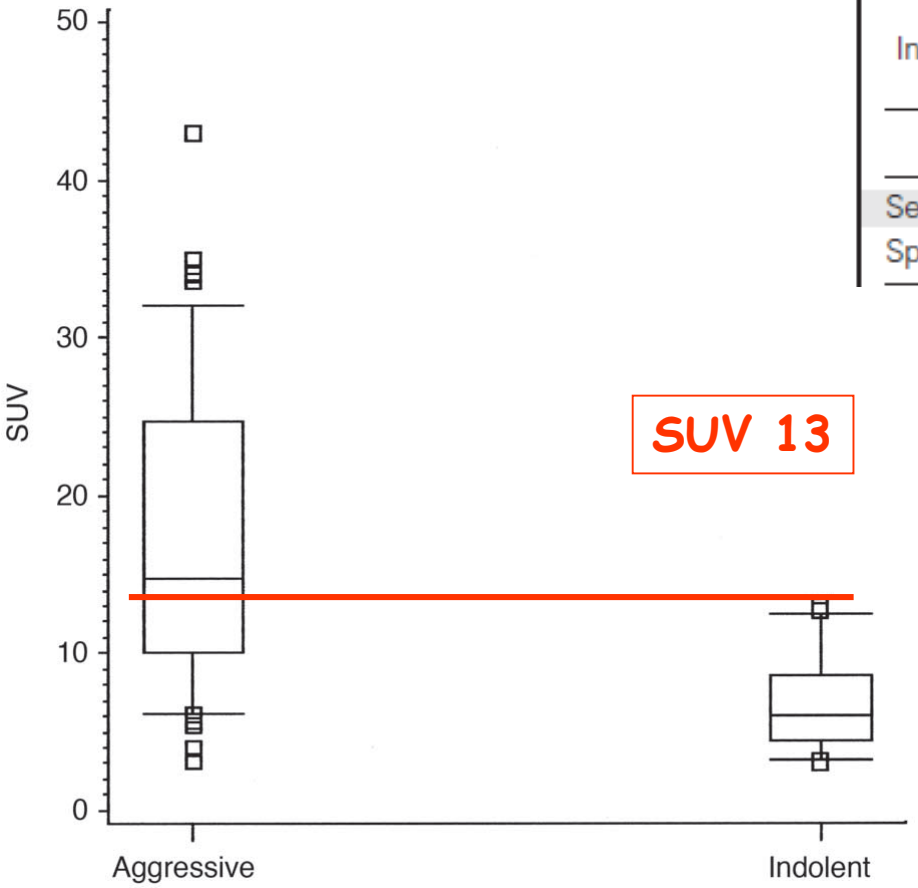
	PRIMA Trotman, JCO 2011	PRIMA Central review. Tychyj-Pinel, Euro J Nuc Med 2013	FOLL05 Luminari, Ann Oncol 2013	PET Folliculaire Dupuis, JCO 2012
Patients	120 Retrospective	59	142 Retrospective	118 Prospective
Treatment	R-CHOP (75%), R-CVP +/- R maintenance		R-CHOP vs. R-CVP vs. R-FM	R-CHOP
% PET+ at diagnosis	99	98	98	99
SUV_{max} range	na	4.6-35.0	na	3.3-35.6
SUV_{max} median	na	10.7 (Higher in mediastinum)	na	9.5
Extranodal	na	52% Bone/spleen/GIT/ skin	46% Bone/spleen/GIT	na

PRIMA = PRimary RItuximab and MAintenance

Intensity of ^{18}Fluorodeoxyglucose Uptake in Positron Emission Tomography Distinguishes Between Indolent and Aggressive Non-Hodgkin's Lymphoma

Heiko Schöder, Ariela Noy, Mithat Gönen, Lijun Weng, David Green, Yusuf E. Erdi, Steven M. Larson,

J Clin Oncol 2005: 23:4643-4651



SUV 13

Table 3. Sensitivity and Specificity of SUV to Distinguish Between Indolent and Aggressive Lymphoma, Based on Biopsies From Site of Highest SUV in the PET Study (n = 69)

SUV	6.4	7.4	8.6	10	12	13.1
Sensitivity	92	85	75	71	63	58
Specificity	50	56	69	81	94	100

Conclusion

- Intensity of FDG uptake correlates with tumor aggressiveness …
- Higher SUV have a higher specificity for the detection of aggressive disease …
- Guide biopsies of lesions with the highest SUV or if there is discordance between biopsy and clinical behaviour

PET/CT e trasformazione

In presenza di dati clinici sospetti per trasformazione (LDH elevato, sedi extranodali, incremento volumetrico lesione nodale, comparsa di sintomi B) può essere effettuato uno studio PET/CT per identificare la sede sospetta da sottoporre ad una biopsia.

The use of FDG-PET in the initial staging of 142 patients with follicular lymphoma: a retrospective study from the FOLL05 randomized trial of the Fondazione Italiana Linfomi

S. Luminari[1]*, I. Biasoli[2], L. Arcaini[3], A. Versari[4], C. Rusconi[5], F. Merli[6], M. Spina[7], A. J. M. Ferreri[8],

Table 2. Number of nodal areas

		Nodal areas			
		CT scan			
		<4	4–7	>7	Total
PET scan	<4	30	10	0	40
	4–7	23	25	5	53
	>7	3	20	26	49
	Total	56	55	31	142
κ	0.37				
Agreement	57%	↑60%		↓33%	

PET, positron emission tomography; CT, computed tomography.

Luminari et al. Annals of Oncology. 2013, August

Diagnostic and prognostic impact of ^{18}F-FDG PET/CT in follicular lymphoma

Ludovic Le Dortz · Sophie De Guibert · Sahar Bayat · Anne Devillers · Roch Houot ·

Eur J Nucl Med Mol Imaging (2010) 37:2307-

Diagnostic impact

Localization	Number of lesions on PET/CT		Number of lesions on CT
Lymph nodes (number of areas)	258	+51%	171
Bone marrow	13		2
Spleen	11		6
Liver	5	+67%	5
Lungs, pleura	5		5

		Staging with PET/CT			
		I	II	III	IV
Standard staging	I	3	1	3	1
	II	0	1	1	0
	III	0	0	11	2
	IV	0	0	0	22

50%

Interessamento midollare : PET vs BM

« overall PET and BMB were concordant in 85 of 142 cases with a fair concordance (k=0.2).
In the group of 108 patients without PET detected bone lesions, BM involvement was detected in 43% of patients (46 of 108)»

Annals of Oncology 24: 2108–2112, 2013

Nel LF la BM è necessaria

PET/CT alla stadiazione

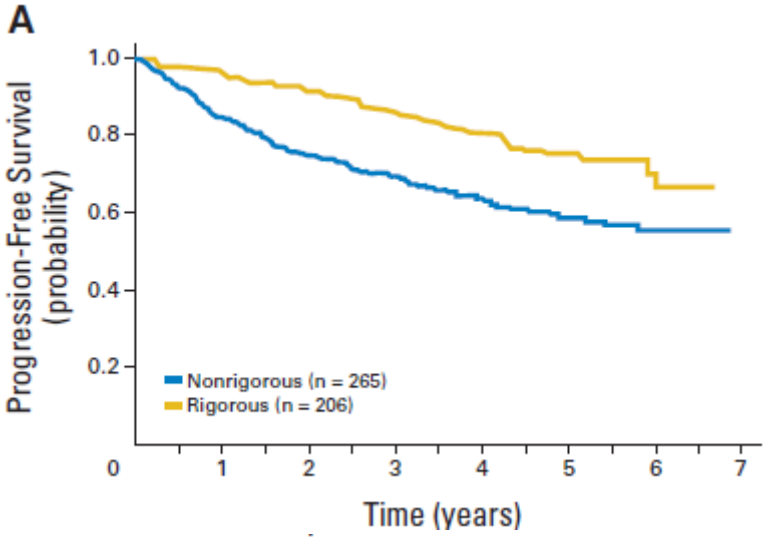
- **Increased sensitivity for nodal and extranodal disease**
- **PET Upstaging:**
  - Overall 18-31%
  - **Early Stage up to 60%**
- **Management change** :
  - Overall 18-29%
  - **Early Stage 45-50%**
- **Limited sensitivity for BM involvement**
  - diffuse and non focal involvement

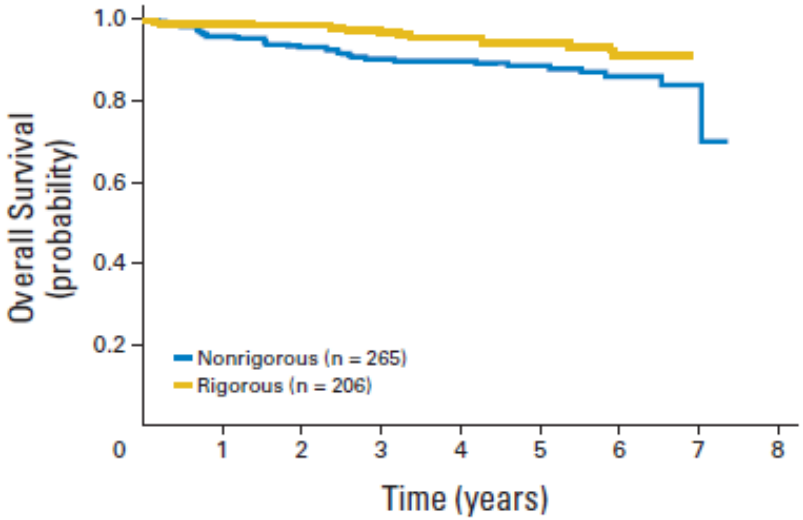
Early vs Advaced : RxT vs chemo

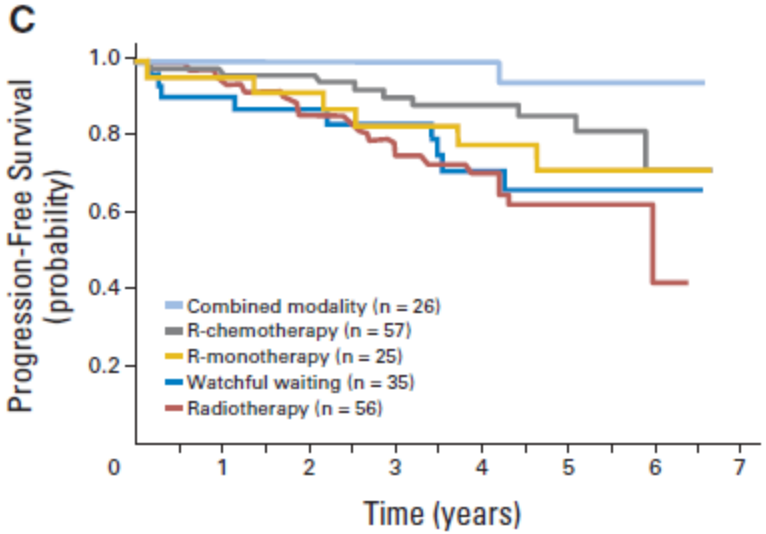
Wohrer S: Annals of Oncology 2006; 17: 780–784.
Karam M: *Cancer* 2006; 107:175–83.
Svoboda J. :Blood 2011; 118: Abstract 4204

Effectiveness of First-Line Management Strategies for Stage I Follicular Lymphoma: Analysis of the National LymphoCare Study

Jonathan W. Friedberg, Michelle Byrtek, Brian K. Link, Christopher Flowers, Michael Taylor, John Hainsworth,



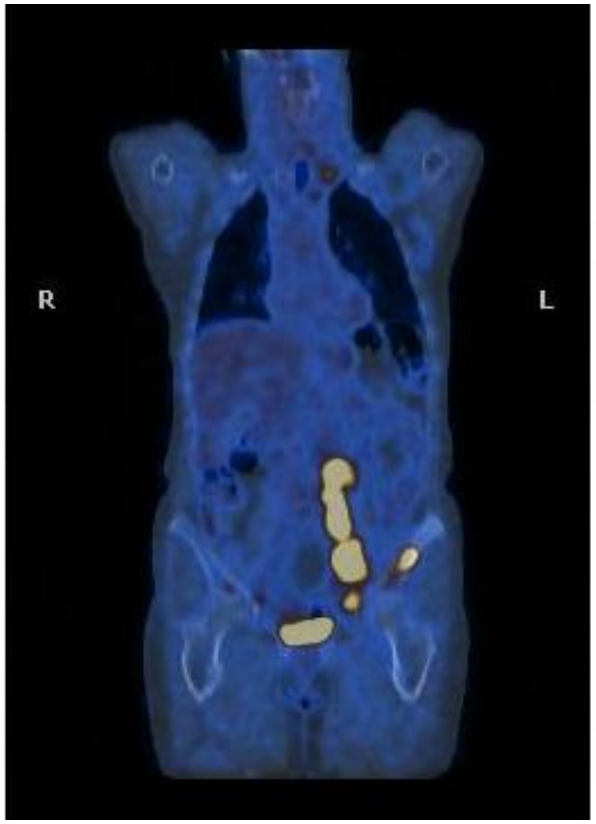




« i pti stadiati in modo più rigoroso ricevono più frequentemente R-chemo o chemo + Rxt»
«diversi tipi di trattamento sono altrettanto efficaci o più efficaci della sola Rxterapia»

J Clin Oncol 30:3368-3375. © 2012


L
R


R
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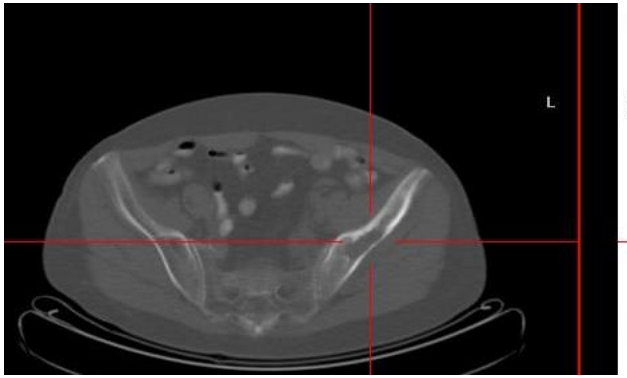
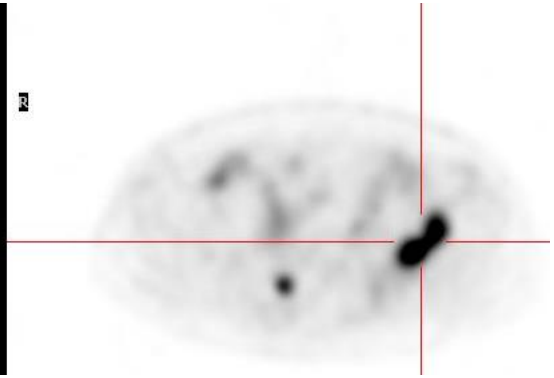

L
R



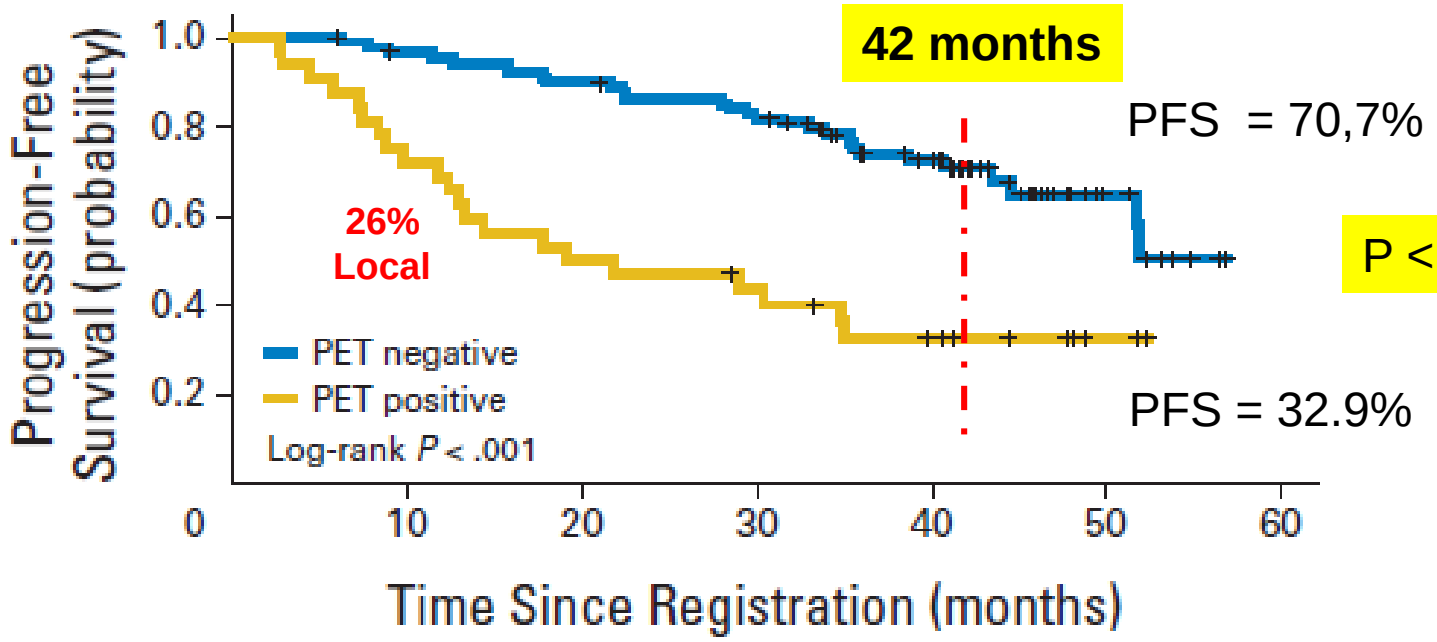
Ruolo della PET/CT nel linfoma follicolare

- Stadiazione
- **Valutazione della risposta e prognosi**
- Mantenimento

Positron Emission Tomography–Computed Tomography (PET-CT) After Induction Therapy Is Highly Predictive of Patient Outcome in Follicular Lymphoma: Analysis of PET-CT in a Subset of PRIMA Trial Participants

Judith Trotman, Marion Fournier, Thierry Lamy, John Francis Seymour, Anne Sonet, Andrea Janikova,

Studio retrospettivo 122 p
R- CHOP or R-CVP
+/- R maintenance



P < 0.001

OS

«PET status but not conventional response according to IWC was an independent predictive factor for lymphoma progression»

«EOT PET should be considered a meaningful clinical end-point in future study»

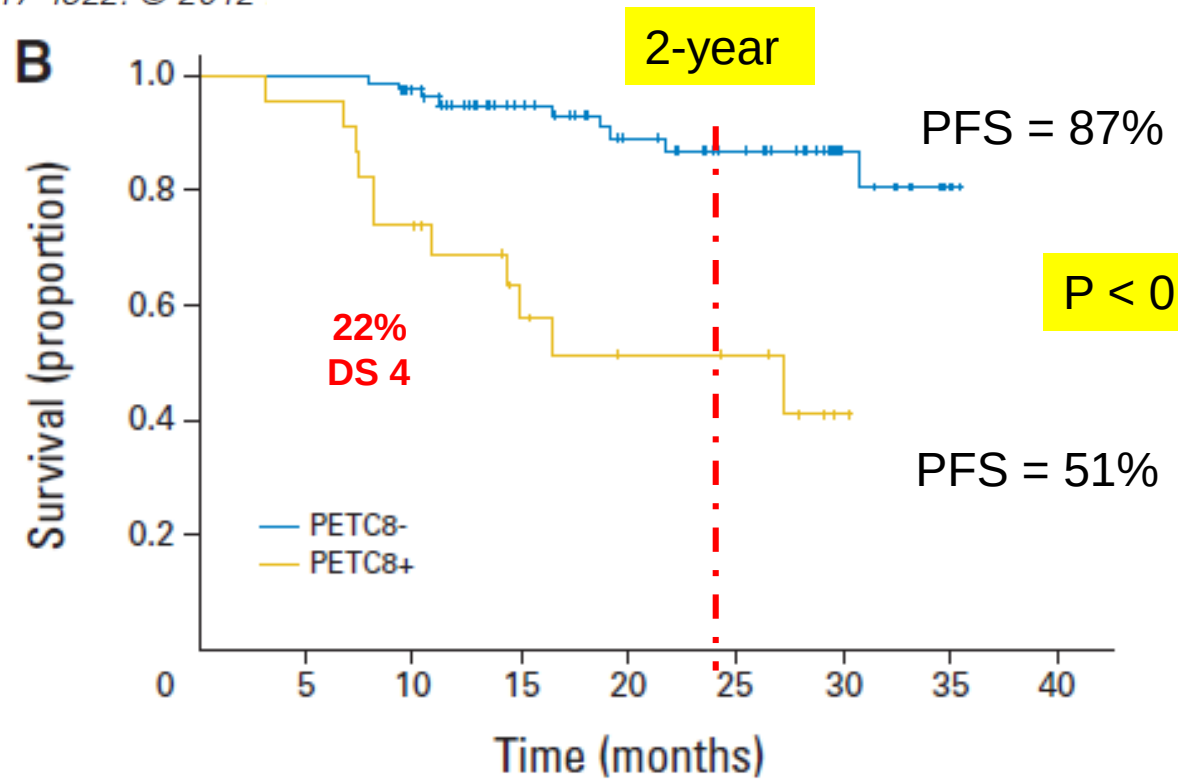
J Clin Oncol 29:3194-3200. © 2011

Impact of [^{18}F]Fluorodeoxyglucose Positron Emission Tomography Response Evaluation in Patients With High–Tumor Burden Follicular Lymphoma Treated With Immunochemotherapy: A Prospective Study From the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS

Jehan Dupuis, Alina Berriolo-Riedinger, Anne Julian, Pauline Brice, Christelle Tychyj-Pinel, Hervé Tilly,

J Clin Oncol 30:4317-4322. © 2012

Studio prospettico 106 p
6 R- CHOP + 2R
No R-maintenance



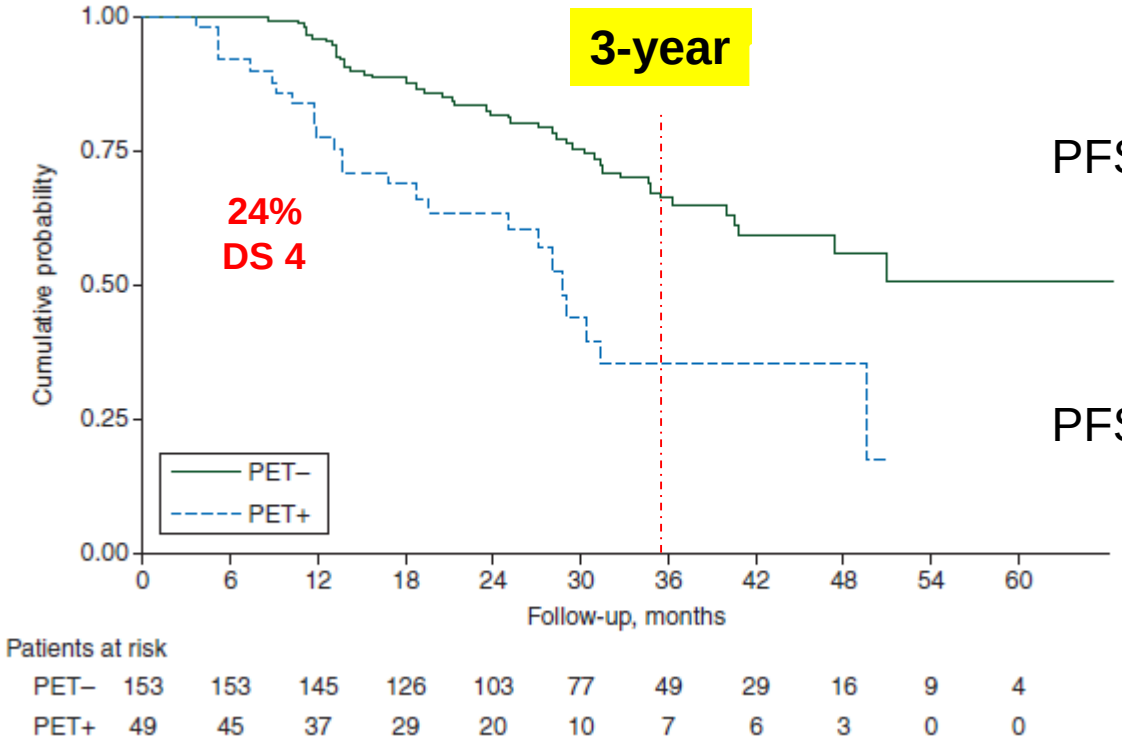
«EOT- PET provide a meaningful surrogate for PFS with a superior predictive power than IWC response»

«Therapeutic intervention based on EOT-PET should be evaluated»

The prognostic role of post-induction FDG-PET in patients with follicular lymphoma: a subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi (FIL)

S. Luminari[1*], I. Biasoli[2], A. Versari[3], S. Rattotti[4,5], C. Bottelli[6], C. Rusconi[7], F. Merli[8], M. Spina[9],

Studio retrospettivo 202 p
R- CHOP or R-CVP or RFM
No maintenance



PFS = 66%

P < 0.001

OS = NS

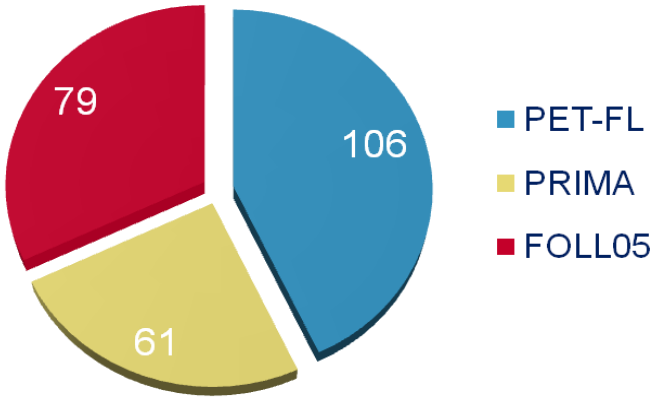
PFS = 35%

«EOT-PET was independent of conventional response and FLIPI and should be considered in further updates of response criteria»

Annals of Oncology 25: 442–447, 2014

Prognostic value of PET-CT after first-line therapy in patients with follicular lymphoma: a pooled analysis of central scan review in three multicentre studies

Trotman et al. Lancet Hematol. 2014, September.



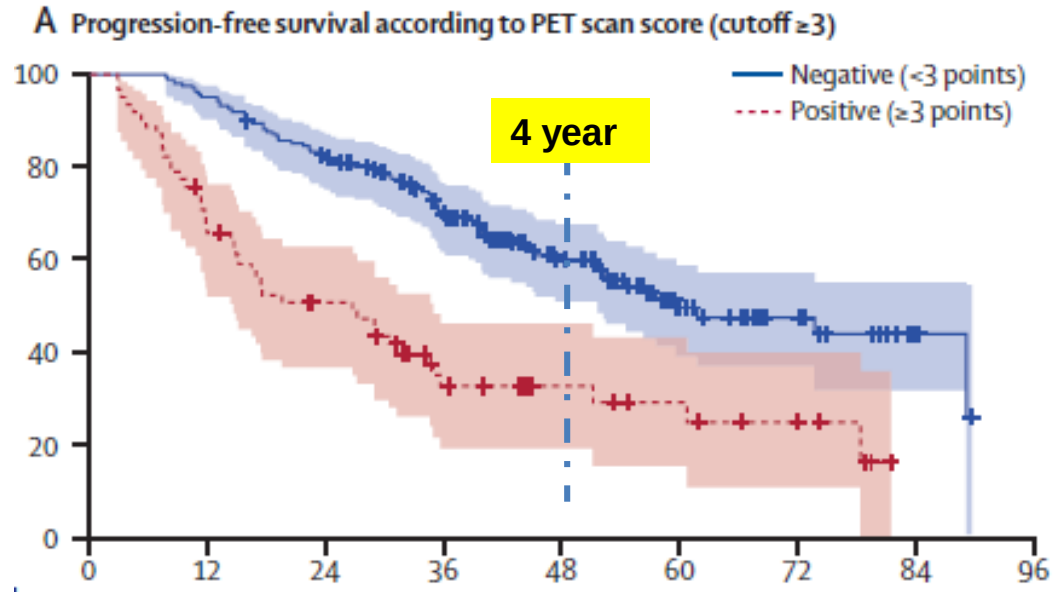
Induction Therapy	Patients n= 246	(%)
R-CHOP	180	74
R-CVP	36	15
R-FM	30	12

- 15% pts Rituximab maintenance
- PET: a median 30 days after last chemotherapy
- PET criteria : DS

Identify the best cut-off for survival when applying the 5PS for response assessment of FDG-avid lymphoma

Provide more precise survival estimates from a larger patient cohort with longer follow-up

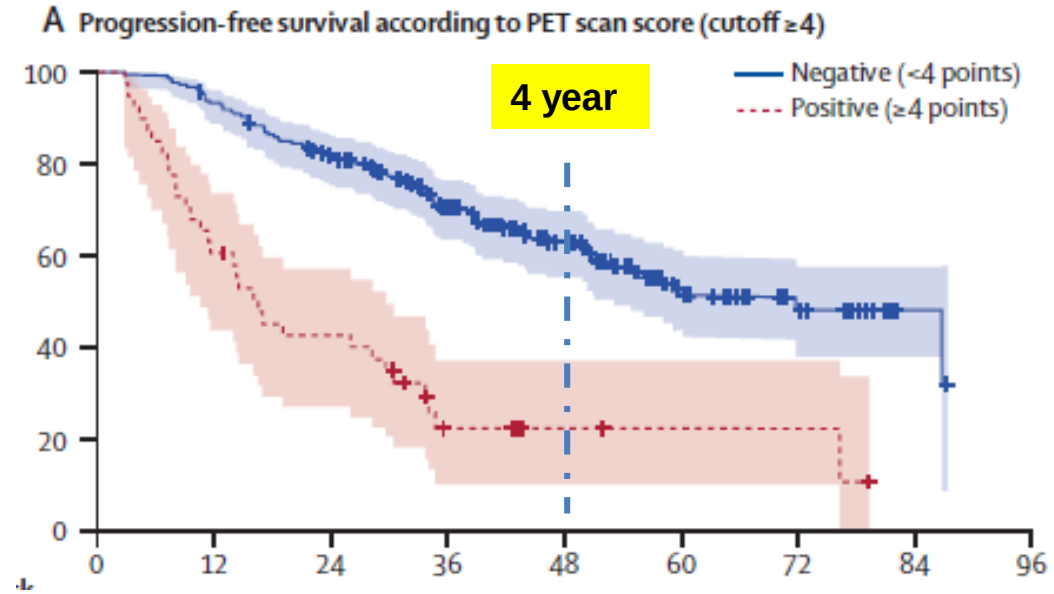
PFS vs DS cut-off ≥ 3 and ≥ 4



Score ≥3 **28%**

4-year PFS
- **PET+ 29.1 %**
- **PET - 74.0%**

p < 0.0001



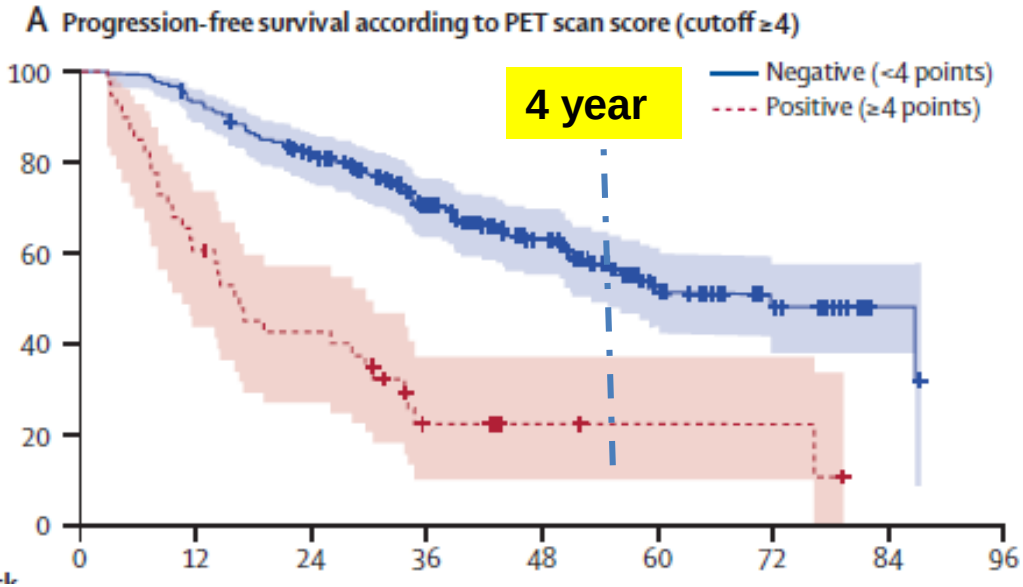
Score ≥4 **17%**

4-year PFS
- **PET+ 16.9 %**
- **PET - 74.0%**

p < 0.0001

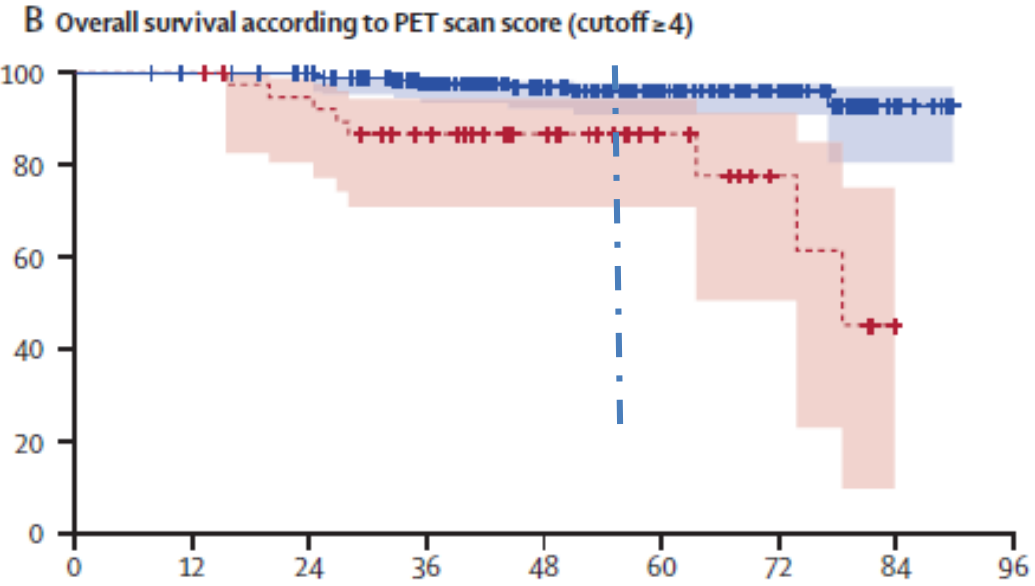
«EOT PET status is a significant predictor of PFS and OS with a superior HRs with a cutoff of 4»

PFS and OS in DS ≥ 4



4 yr PFS
- **PET+ 23.2 %**
- **PET - 63.4%**

p < 0.0001

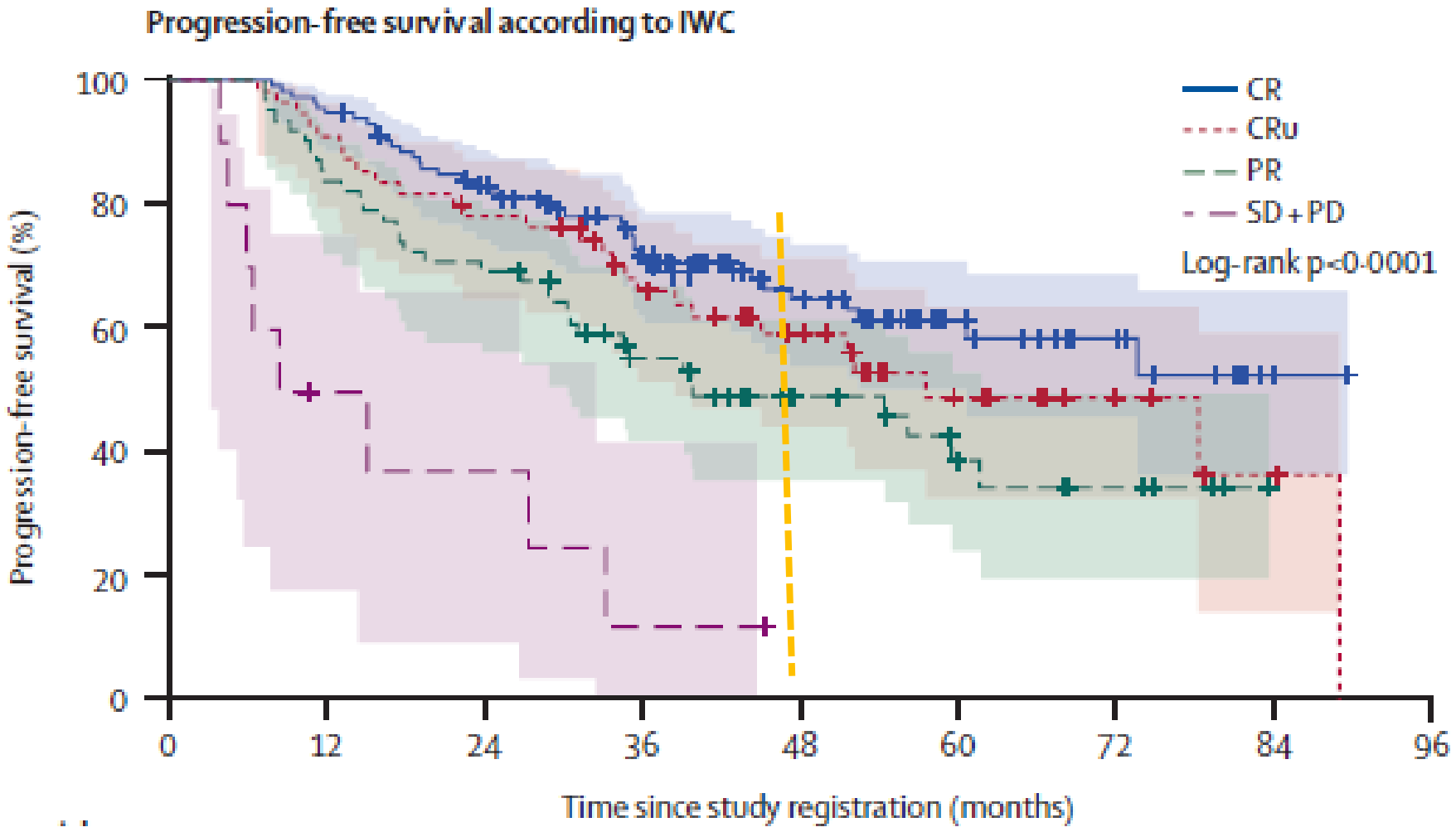


4 yr OS
- **PET+ 87.2 %**
- **PET - 97.1%**

p < 0.0001

«Applying a cutoff of 4, EOT PET identifies a PET+ population of pts who have a high rate of early progression and higher risk of death than in a PET- population »

PFS according to IWC



SD + PD vs CR = 0.0001

CRU + PR vs CR = 0.019

«The improved predictive power of EOT PET reflects PET's capacity as a biomarker to identify residual disease activity in small nodes, and confirm or exclude active disease in persisting masses»

«With the IWC, residual lesion up to 1.5 cm are categorized as complete response. PET is capable of discrimitating within responders 25% of patients with an EOT positive PET»

«PET/CT rather than ce-CT scanning should be considered as a new standard for response assessment of follicular lymphoma in clinical practice, and could be guide response –adapted therapy»

Trotman et al. Lancet Hematol. 2014, September.

Metodiche di valutazione della risposta nel linfoma follicolare : confronto

CT:

- Impatto prognostico più basso rispetto alla PET per PFS, nullo per OS
- Capacità limitata di valutare l'interessamento extranodale
- Difficile utilizzo nella pratica clinica (somma dei diametri perpendicolari)

PET:

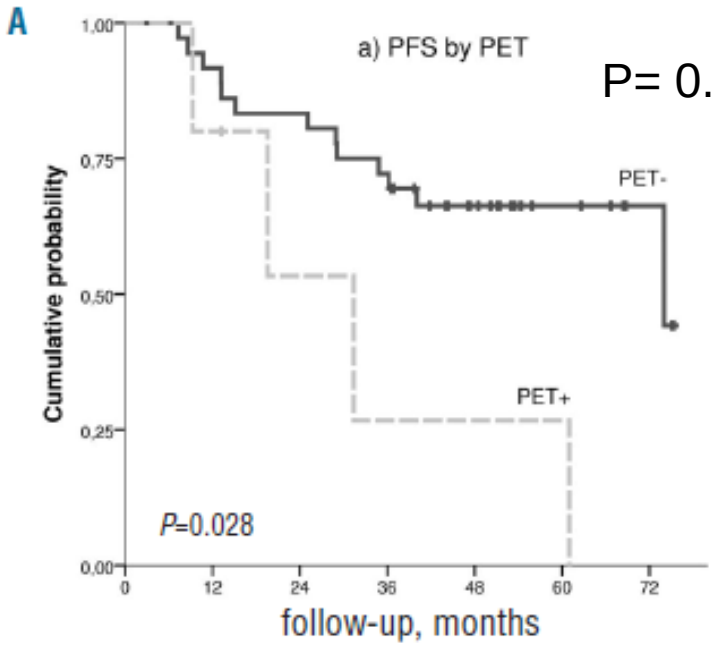
- Ha l'impatto prognostico più elevato su PFS e OS
- E' la metodica raccomandata dai nuovi criteri di valutazione della risposta

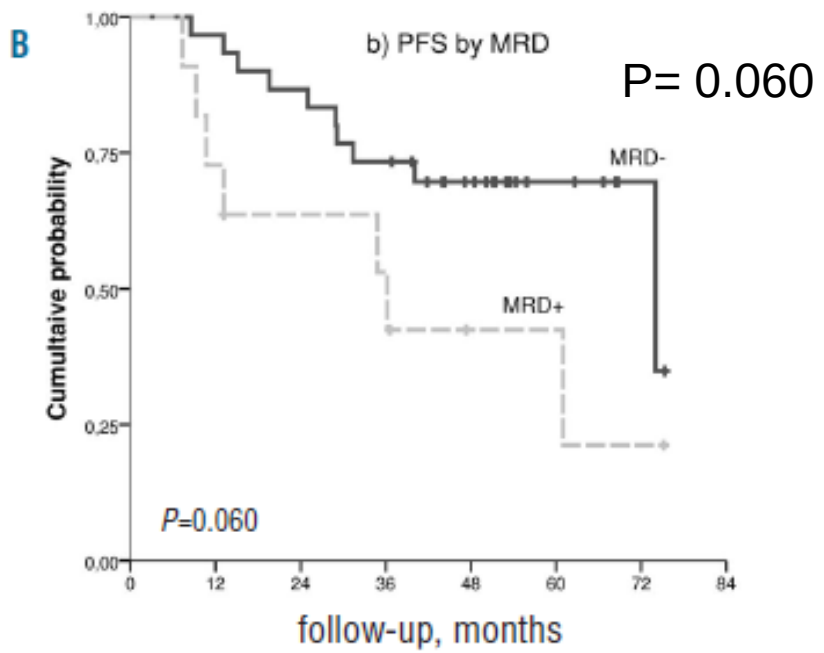
Analisi molecolare

- La presenza di traslocazione t(14;18) ne fa un ottimo modello di valutazione nel linfoma follicolare
- Nella CLL e MCL l'analisi molecolare ha una maggiore sensibilità rispetto alle metodiche disponibili

Positron emission tomography response and minimal residual disease impact on progression-free survival in patients with follicular lymphoma. A subset analysis from the FOLL05 trial of the Fondazione Italiana Linfomi

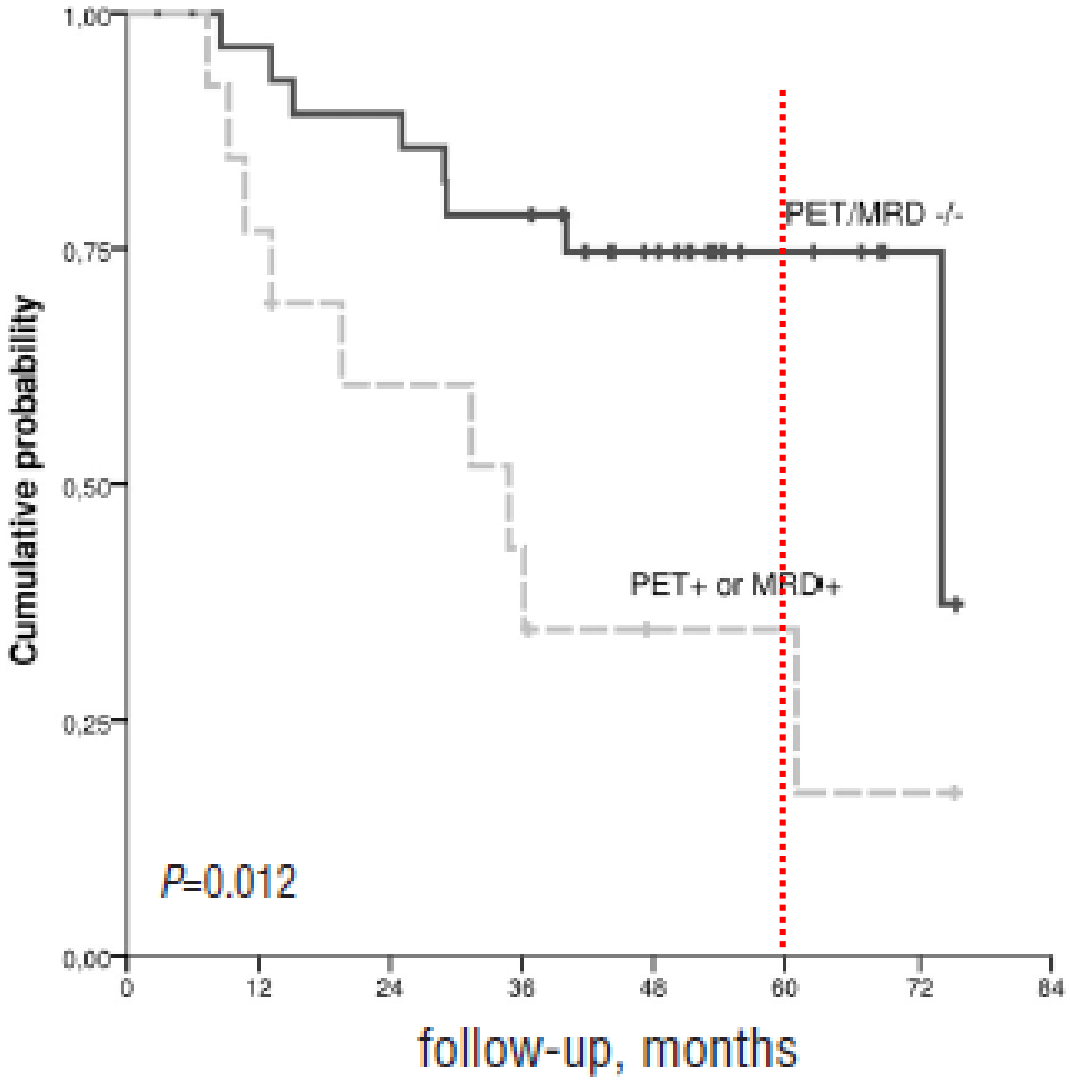
haematologica 2016; 101:e66





	PET negative	PET positive
MRD negative	28 (68%)	2 (5%)
MRD positive	8 (20%)	3 (7%)

«PET and MRD are not strongly correlated with each other, and can be used as complementary tecniques at the end of therapy»



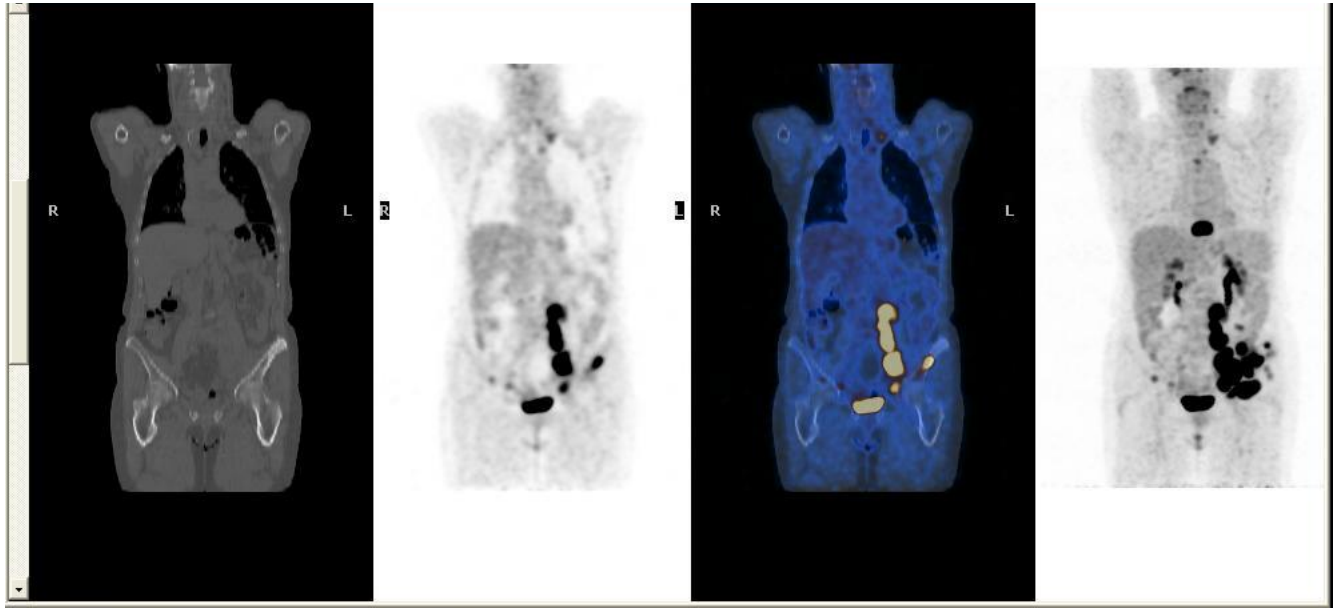
5 yr PFS 75%

P=0.012

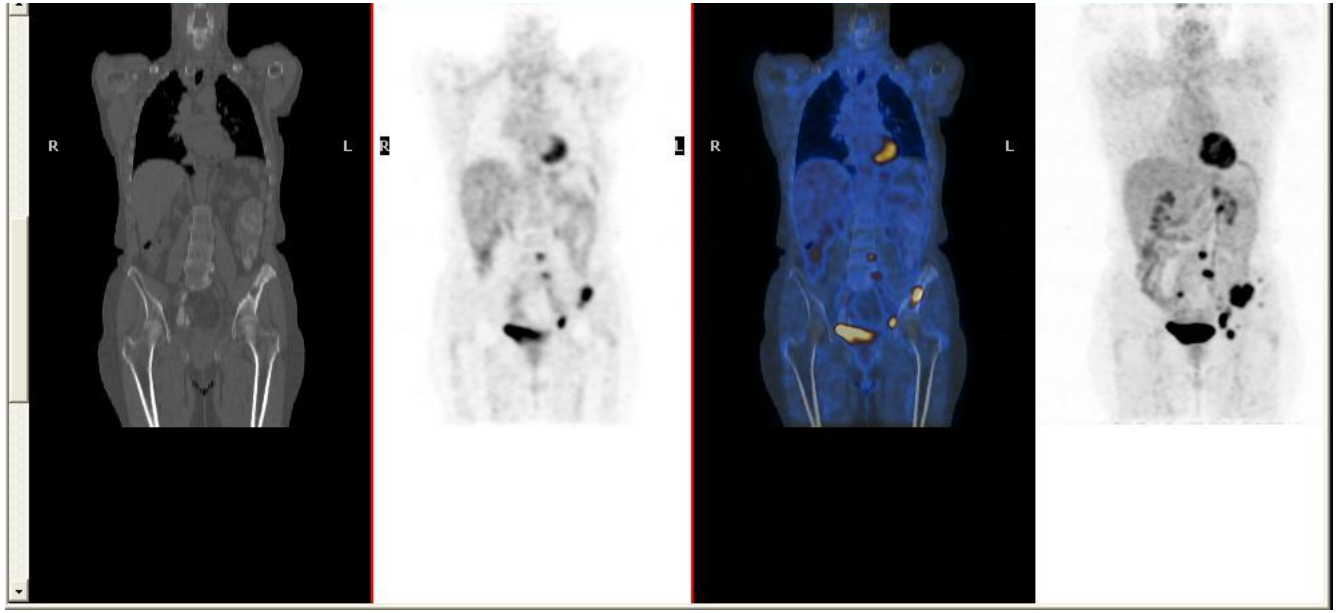
5 yr PFS 35%

«…combining both EOT PET and MRD analysis may improve the ability to predict risk progression, and provide the rationale to design response adapted trial to tailor post-induction therapy to the real risk of progression…»

Baseline



End of treatment



Ruolo della PET/CT nel linfoma follicolare

- Stadiazione
- Valutazione della risposta e prognosi
- **Mantenimento**

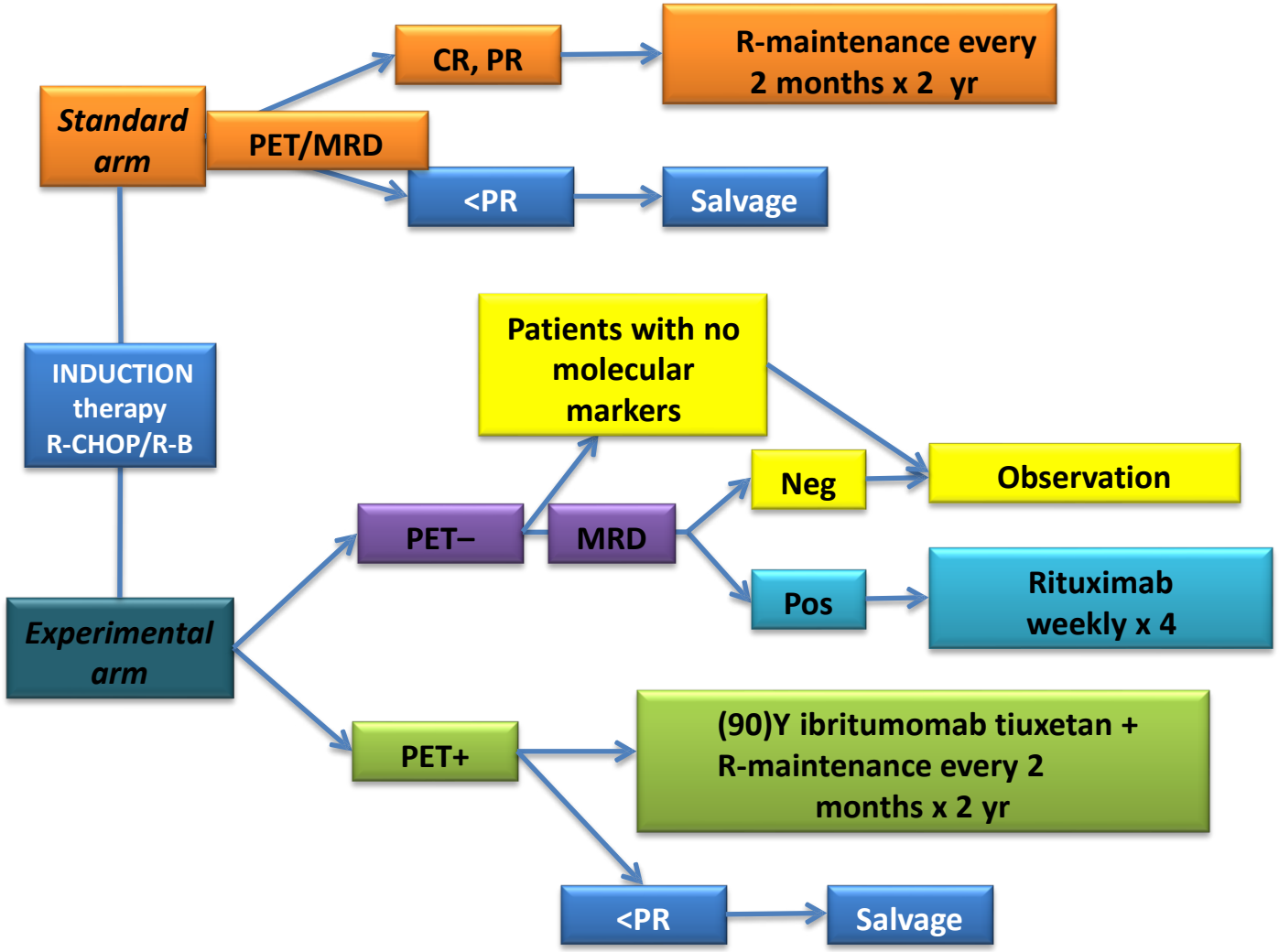
FOLL 12: PRIMARY OBJECTIVE

Evaluate whether

a **PET** and **MRD response-based maintenance** therapy is **not less effective** in terms of PFS than a standard maintenance therapy with R in patients with untreated, advanced FL

FOLL12 TRIAL DESIGN (EudraCT Number: 2012-003170-60)
1° line, stage II–IV, FL (P.I. M. Federico)

FOLLICULAR NHL
Grade I–II–IIIa
Age 18–75
Stage II–IV
Active disease
FLIPI2≥1



Ruolo della PET nel linfoma follicolare

- La PET-CT è indicata nella stadiazione iniziale e nella valutazione della risposta alla terapia

- La risposta metabolica e molecolare sono utili fattori prognostici

- I risultati dello studio prospettico FOLL12 ci forniranno elementi per meglio selezionare i pazienti che debbono effettuare una terapia di mantenimento combinando PET e MRD a fine terapia.

La PET/CT nel linfoma mantellare

Ruolo della PET/CT nel linfoma mantellare

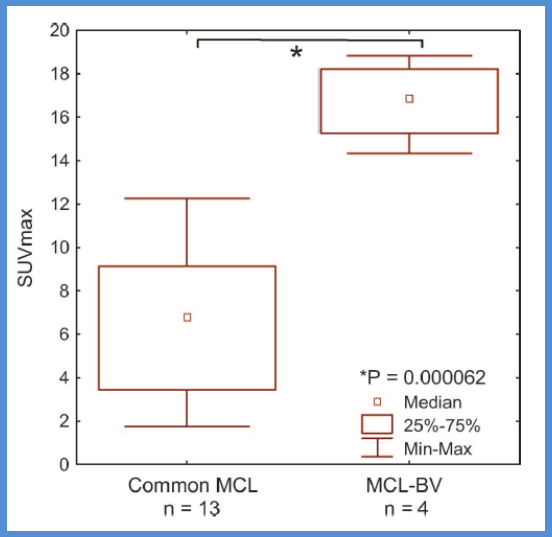
- Stadiazione
- Valutazione della risposta al termine della terapia

FDG-PET alla stadiazione

Study	N	Sensitivity	SUVmax range
Brepoels **Leukemia & lymphoma 2008**	**37**	**100%**	**~1.8-19**
Karam **Nucl. Med. Commun. 2009**	**81**	**100%**	**< ou = 5: n=20**
Gill **Clinical Lymphoma & Myeloma 2008**	**28**	**100%**	**Not performed**
Schaffel **Blood (ASH Annual Meeting) 2009**	**75**	**95%**	**Not performed**
Bodet-Milin **Eur journal of nuclear medicine 2010**	**44**	**100%**	**1.7-18.8**
Mato **Cancer 2012**	**53**	**92%**	**2.5-36.7**

- Elevata sensibilità per le sedi nodali e per la milza.
- Bassa sensibilità per le sedi midollari e gastro-intestinali (non modifiche dello stadio)
- Valori di SUVMax variabili

PET/CT complementare all'imaging convenzionale : BM e biopsie GI mandatorie

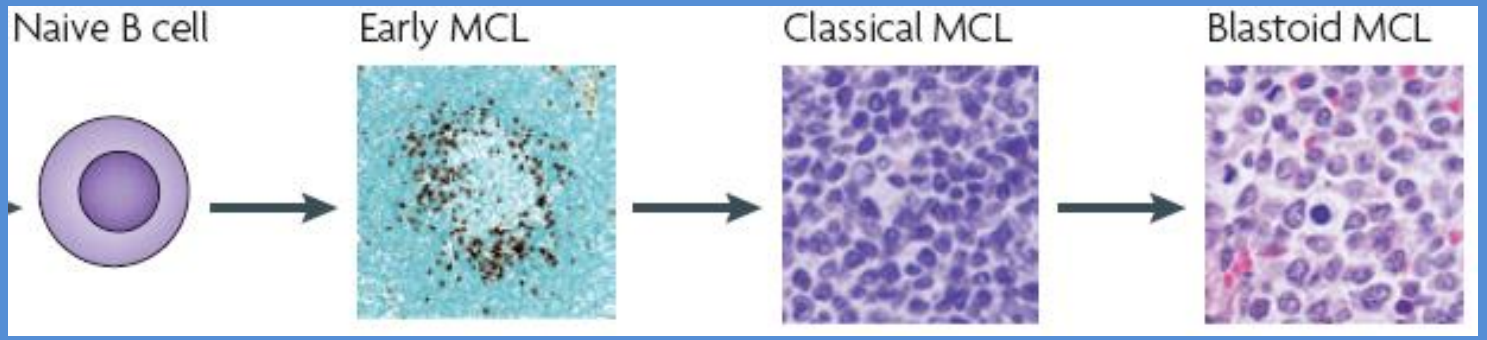


SUV max value

KI67 + cells

t(11:14)

ONCOGENIC events (P53, MYC, ATM, BCL-2…)



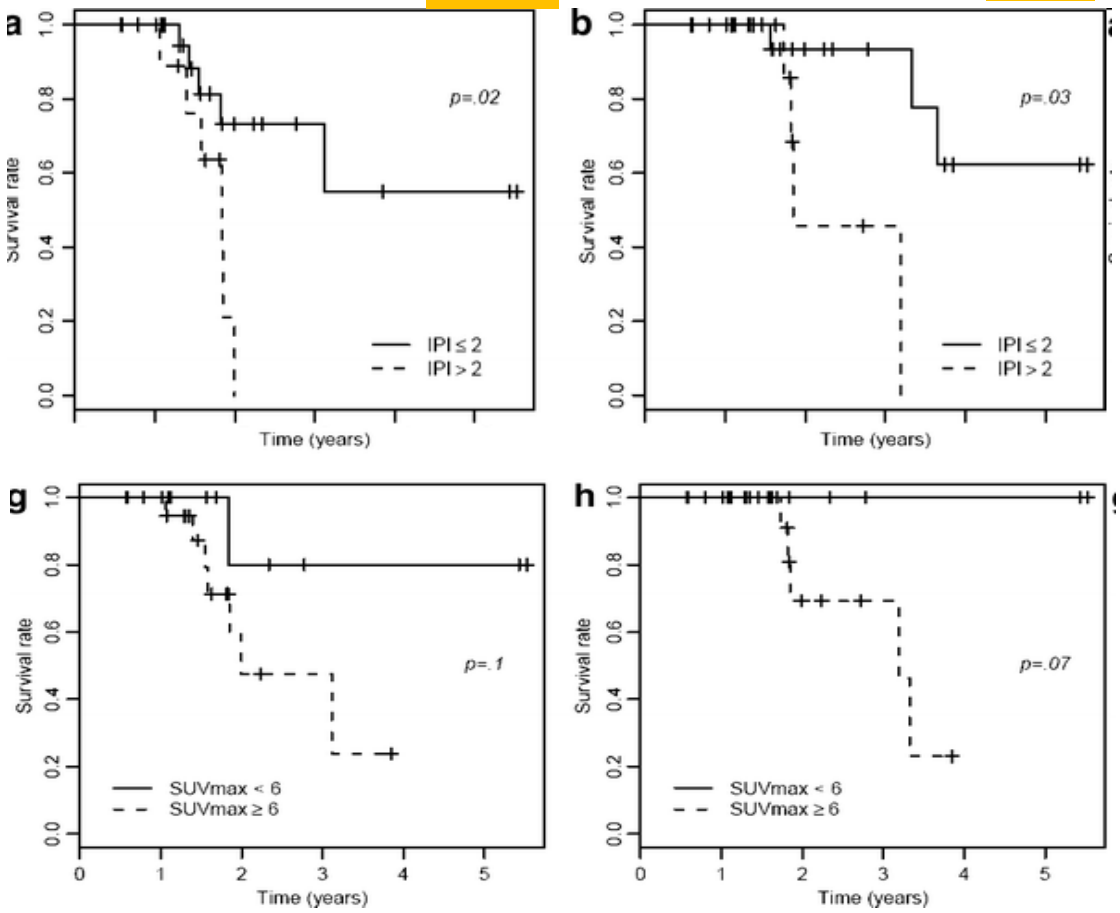
Prognostic impact of ^{18}F-fluoro-deoxyglucose positron emission tomography in untreated mantle cell lymphoma: a retrospective study from the GOELAMS group

Caroline Bodet-Milin · Cyrille Touzeau · Christophe Leux · Mehmet Sahin ·

Eur J Nucl Med 2010, 37,1633

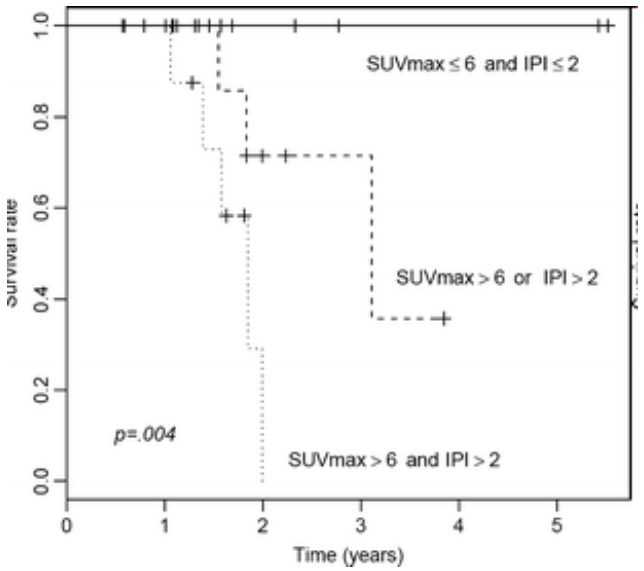
PFS

OS



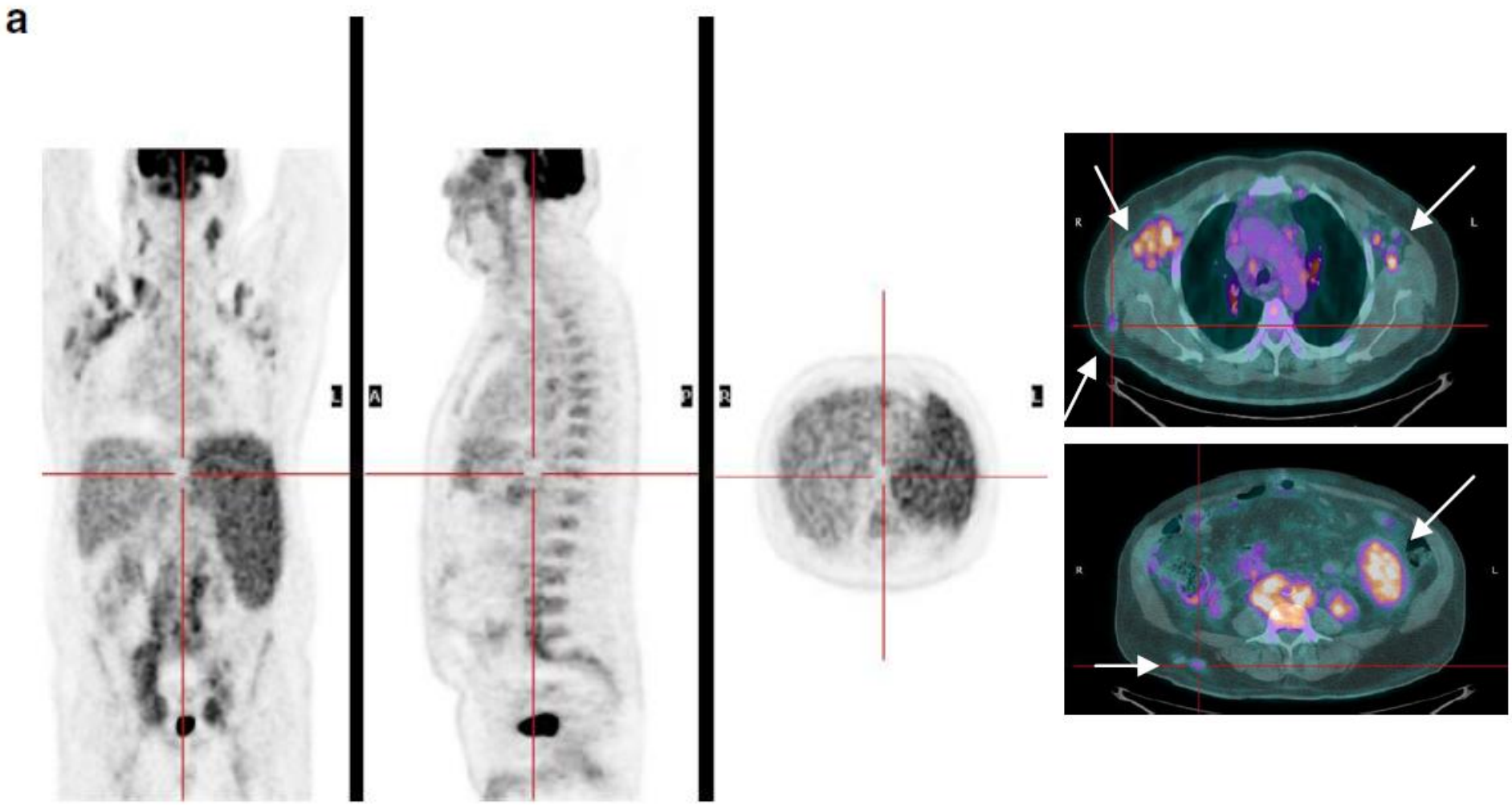
Retrospettivo – 44 pts

PFS

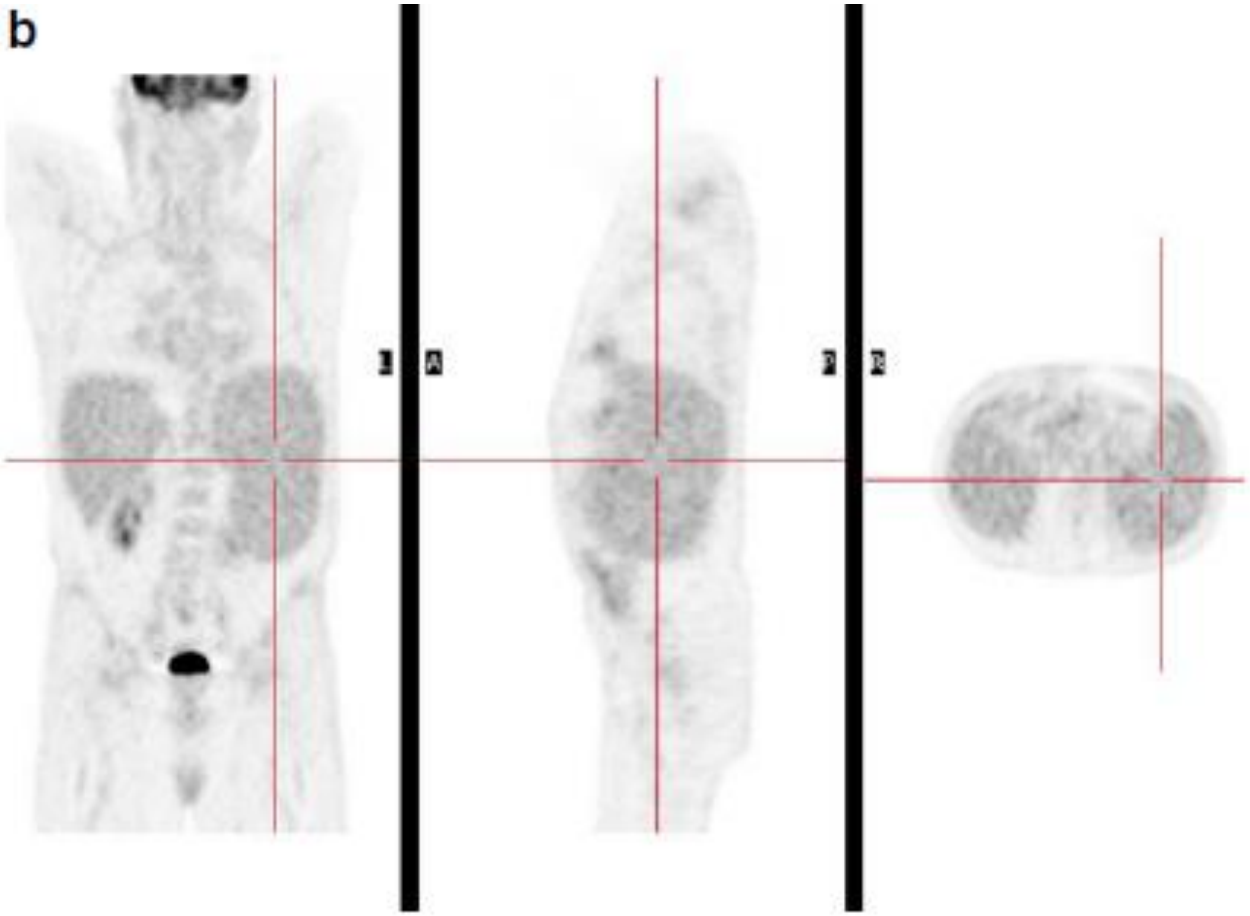


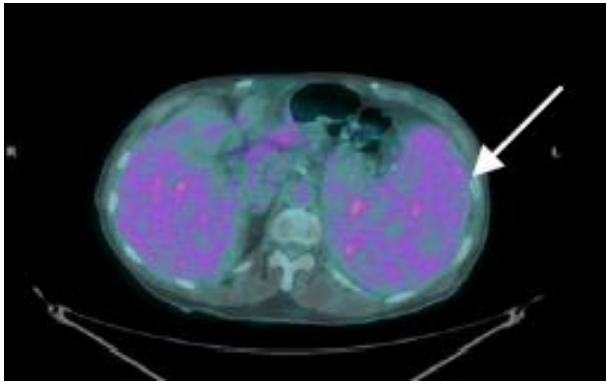
«IPI and PET criteria at diagnosis are highly efficient to identify patients with high risk for early relapse. A prognostic index combining IPI and SUVMax at diagnosis may give an accurate prediction of patient outcome»

Baseline PET



Baseline PET





Ruolo della PET/CT nel linfoma mantellare

- Stadiazione
- Valutazione della risposta al termine della terapia

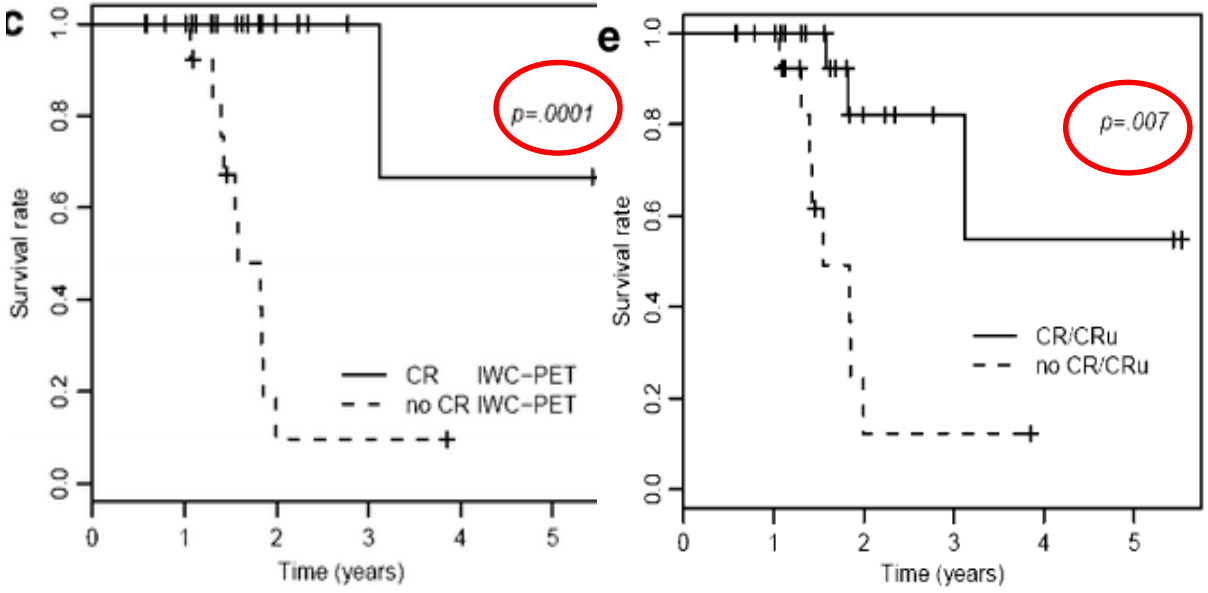
Prognostic impact of ^{18}F-fluoro-deoxyglucose positron emission tomography in untreated mantle cell lymphoma: a retrospective study from the GOELAMS group

Caroline Bodet-Milin · Cyrille Touzeau · Christophe Leux · Mehmet Sahin ·

Eur J Nucl Med 2010, 37,1633

IWC+PET	CR	PR	PD	Total
IWC				
CR/CRu	20	2	-	22
PR	3	9	2	14
Total	23	11	2	36

19%

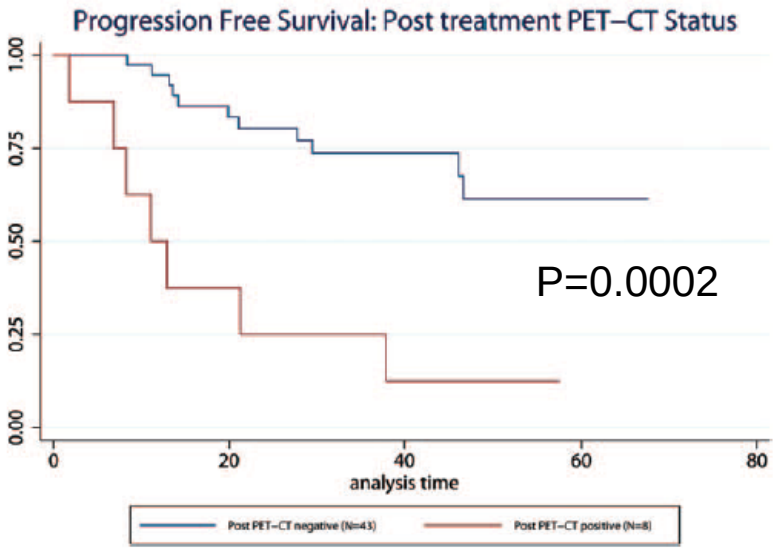


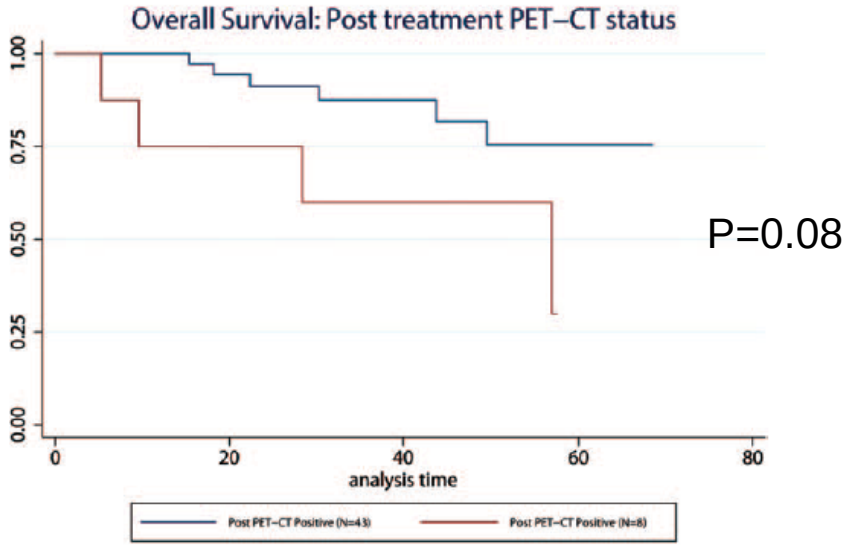
EOT PET is more accurate than IWC criteria to predict outcome

Post-Treatment (Not Interim) Positron Emission Tomography-Computed Tomography Scan Status Is Highly Predictive of Outcome in Mantle Cell Lymphoma Patients Treated With R-HyperCVAD

Cancer 2012;118:3565-70.

Anthony R. Mato, MD[1]; Jakub Svoboda, MD[2]; Tatyana Feldman, MD[1]; Tania Zielonka, RDC[1]; Harry Agress, MD[1];

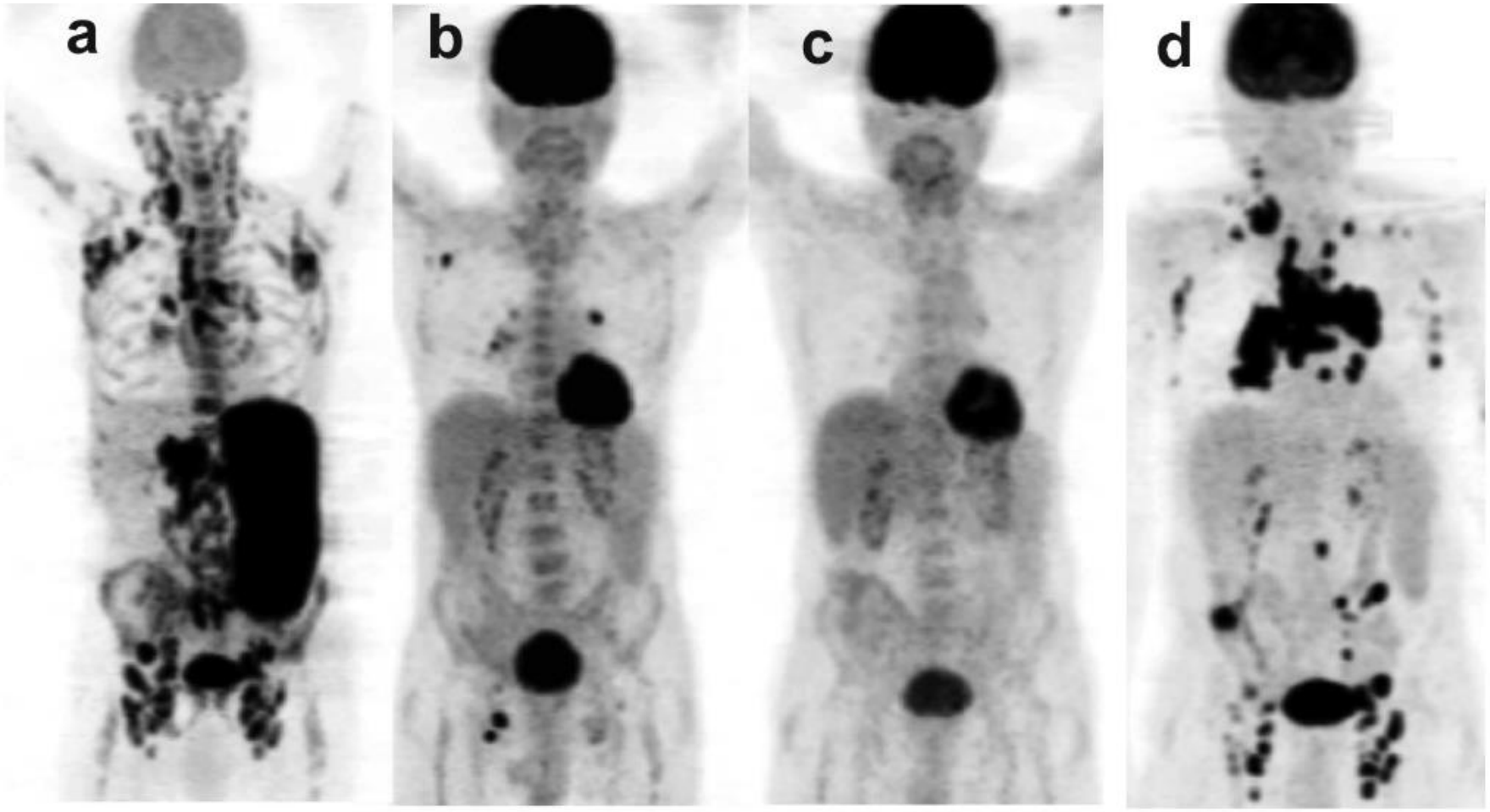




«Achievement of a complete response vs partial response according to IWC was not significantly associated with PFS»

EOT PET/CT is and independent predictor of PFS with a trend toward predicting OS in MCL patients»

Stage IV Mantle Cell Lymphoma



Baseline Interim End of therapy Restaging

Ruolo della PET/CT nel linfoma mantellare

Utilizzo non così consolidato come in altri tipi di linfomi – 5% NHL

Stadiazione

- Captazione di FDG variabile, più elevata nelle forme aggressive → utile per identificare sede da sottoporre a biopsia
- Complementare alla CT ma non sostituisce BOM e biopsie GI

Ristadiazione a fine trattamento (risk of early relapse)

- La PET a fine terapia ha significato prognostico.
- La maggioranza degli studi, ma non tutti, indicano una superiorità della PET rispetto alla valutazione CT.

- I linfomi mantellari hanno elevata incidenza di relapse nonostante la buona risposta al trattamento iniziale e quindi il riconoscimento di malattia residua può essere meno importante

I principali trial della FIL

Aperti

- TRIANGLE
- R2-B

Chiusi

- RBCA500
- LEN-DEX MCL7
- MCL0208

I principali trial della LYSA

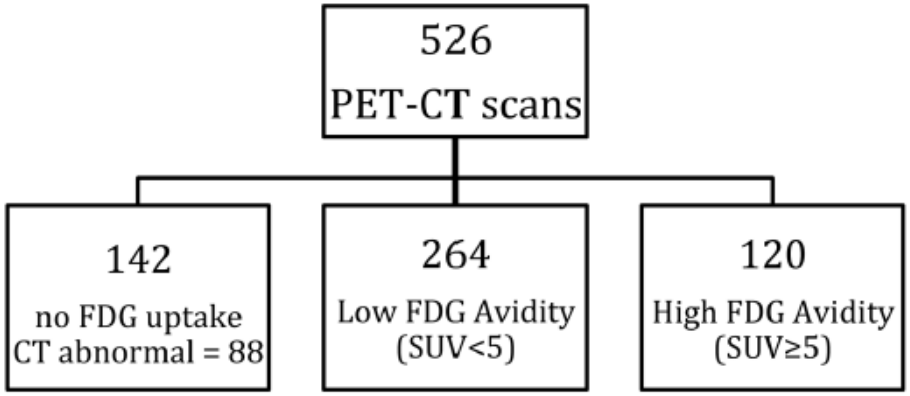
- LyMA-101
- MCL R2 elderly

Non hanno previsto l'utilizzo della PET

La PET nella leucosi linfatica cronica

Use of Positron Emission Tomography-Computerized Tomography (PET-CT) in the Management of Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL)

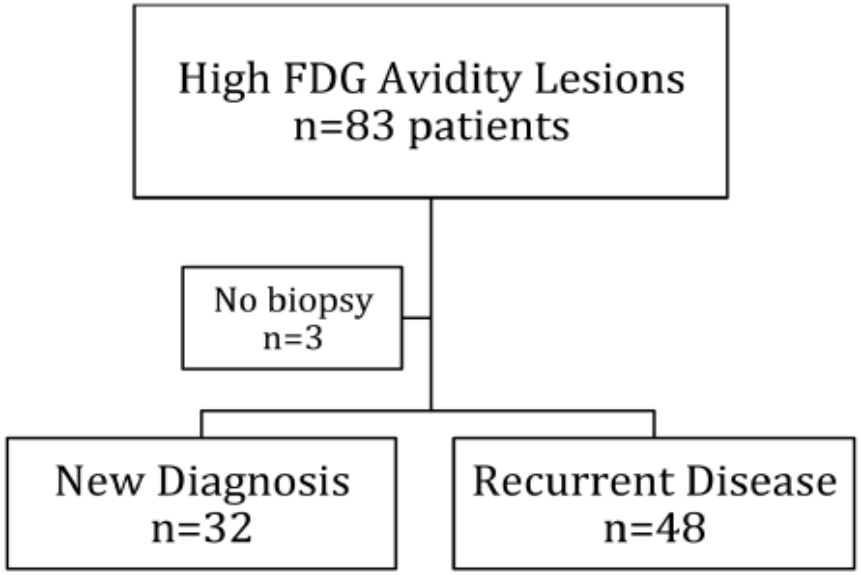
Michael J. Conte[1], Deborah A. Bowen[1], Gregory A. Wiseman[2], Kari G. Rabe[3],



27%

50%

23%
83 pti



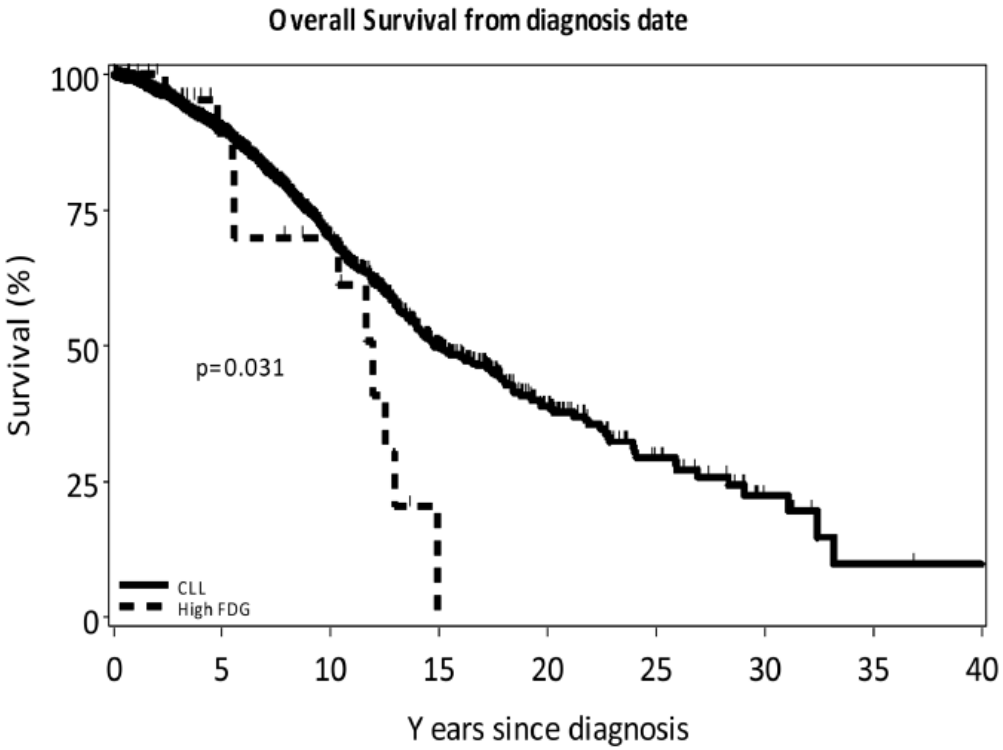
13 pts DLBCL
8 pts other malignan.
4 pts HL
1 pts herpes symplex, granuloma, cellulitis, EBV
1 pts thyroid, colon aden., pneumonia

27 pts CLL
21 pts non CLL
(14 pts other malign
6 pts DLBCL
1 pt HL)

Leuk Lymphoma. 2014 September ; 55(9): 2079–2084.

«PET is indicated in evaluation of pts with CLL with clinical findings suggestive of trasformation, second malignancies or serious infection but should not be used for routine management of CLL (positive patients 23%) »

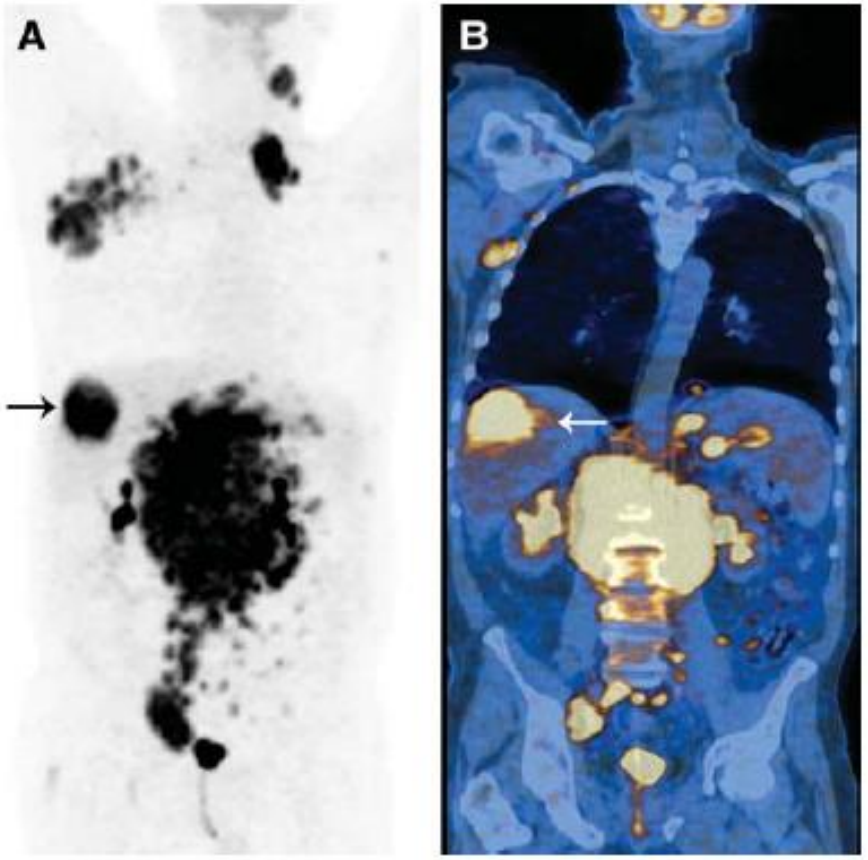
« high FDG uptake in patients with a CLL is non-specific and includes aggressive lymphomas, non-hematological malignancies, infection and inflammation of solid organs. A definitive diagnosis using surgical biopsy is necessary. Pts with low FD uptake have a low probability of these complications »



« Pts with high FDG uptake and CLL had a shorter OS compared to the rest of CLL population»

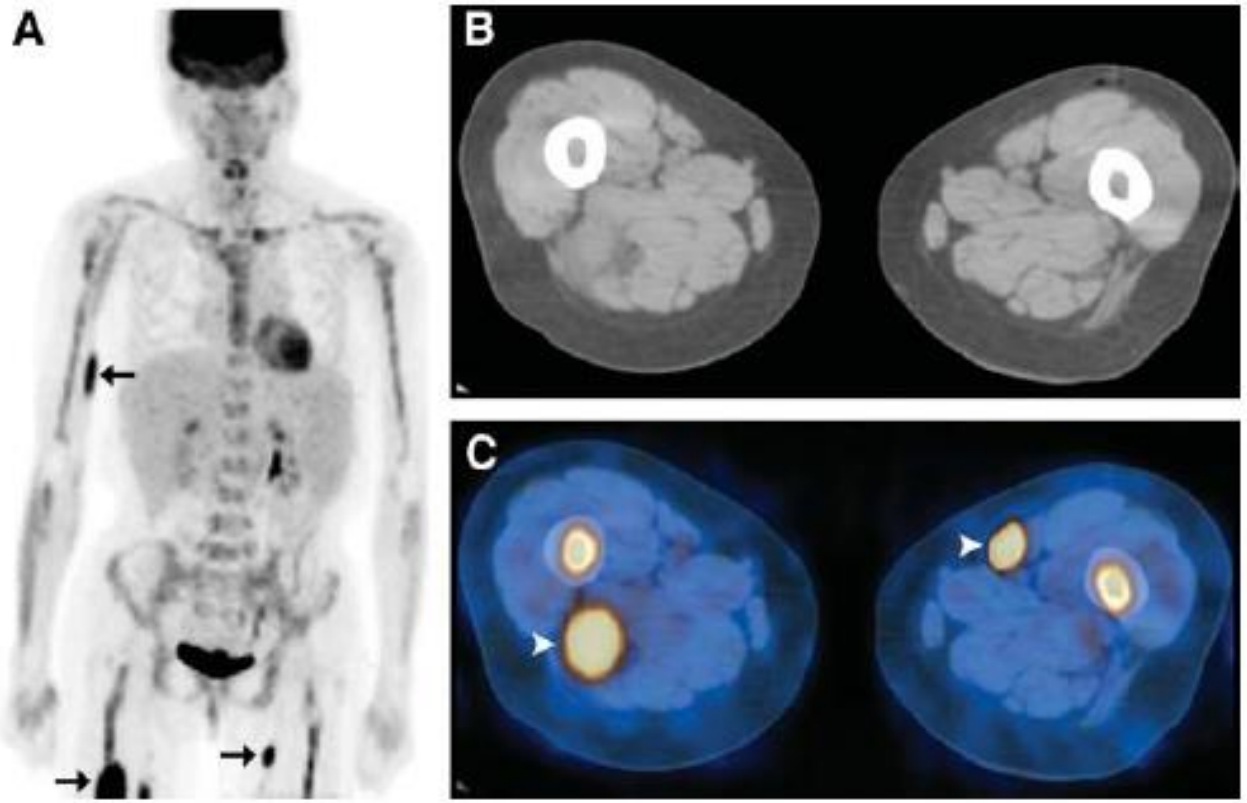
Detection of Richter's Transformation of Chronic Lymphocytic Leukemia by PET/CT

John F. Bruzzi[1], Homer Macapinlac[1], Apostolia M. Tsimberidou[2], Mylene T. Truong[1], Michael J. Keating[2],



LLC da 1 aa., completata la chemioterapia. Esegue PET per dolore addominale e sospetti sintomi di trasformazione

J Nucl Med 2006; 47:1267–1273



LLC da 8 aa. responsiva alla chemioterapia. Massa dura al braccio dx. sospetta per ematoma da carenza piastrinica.

J Nucl Med 2006; 47:1267–1273

Ruolo della PET/CT nella LLC

- Non è indicata nello studio di routine dei pazienti con LLC

- Può utilmente integrare la stratificazione prognostica dei pazienti con LLC basata su fattori biologici ed ha un ruolo rilevante in pazienti con sospetto clinico di trasformazione in forme aggressive di linfoma (Richter), di una seconda neoplasia o di infezioni sistemiche

- In presenza di questo sospetto clinico una PET negativa (SUVMax <5) rende poco probabile la presenza di una di queste complicazioni mentre una PET positiva identifica la sede per una successiva biopsia.

GRAZIE PER L'ATTENZIONE