Early interim PET (PET2) in Hodgkin Lymphoma patients treated with ABVD. An International Validation Study (IVS).

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S. Chauvie	Medical Physics Department, Santa Croce Hospital – Cuneo – Italy
M. Gregianin	PET Imaging centre, Nuclear Medicine Department, Policlinico Universitario, Padova
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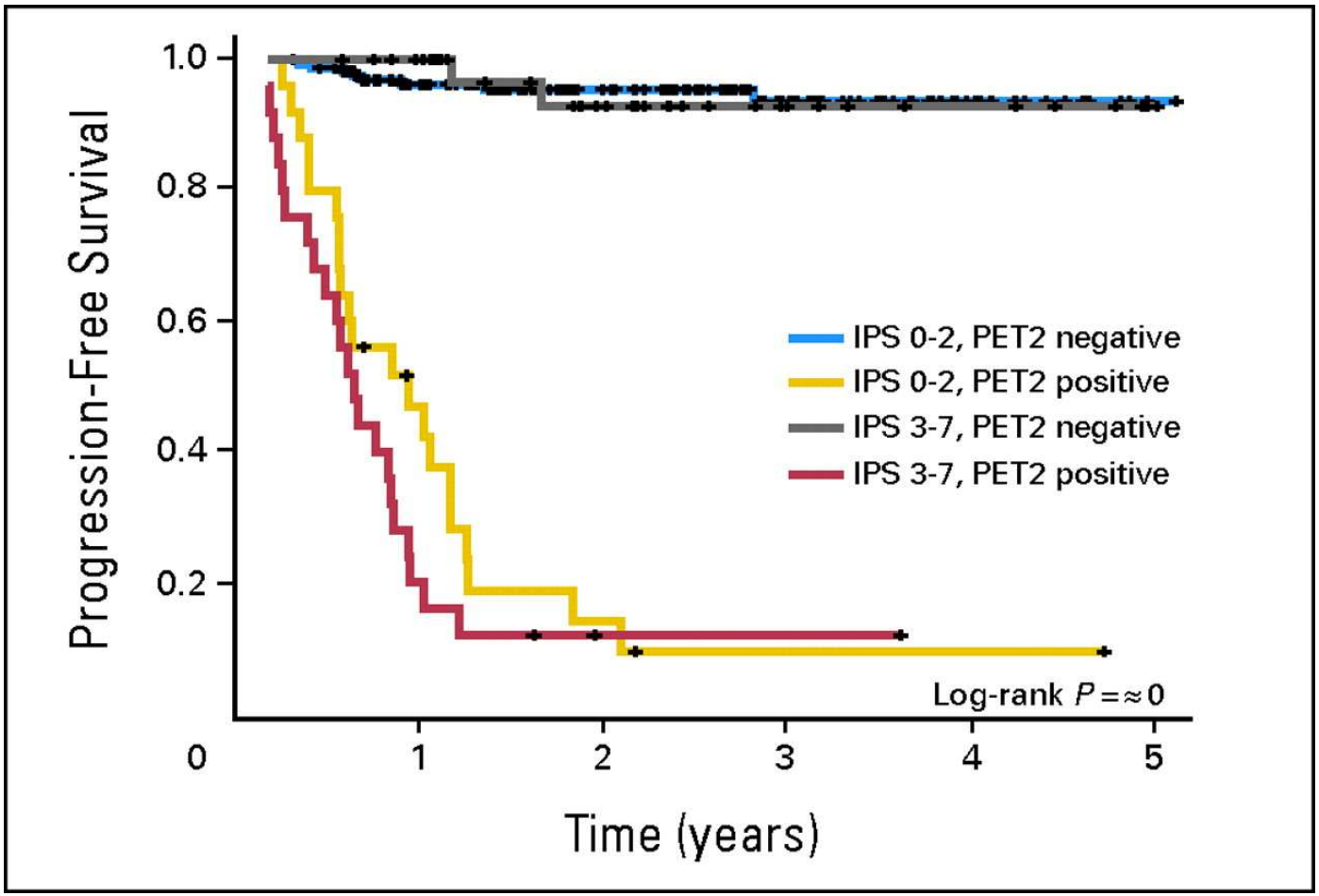
M. Meignan	Nuclear Medicine Department, H. Mondor Hospital, AP-HP/Paris 12 University, Creteil, France

Second international workshop on interim-PET in lymphoma

Menton (France), Palais de l'Europe, April 8-9th, 2010

Interim PET in ABVD-treated HL patients



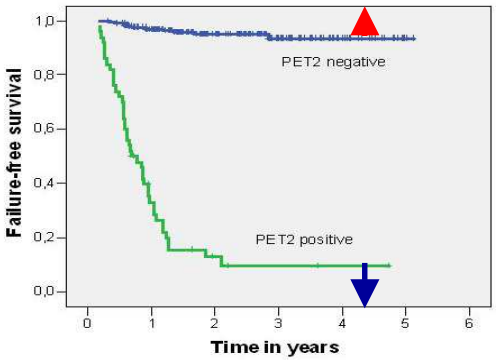
Gallamini, A. et al. J Clin Oncol; 25:3746-3752 2007

Why we need IVS ?

…interim-PET scan has been proven the most powerful tool to predict treatment outcome in ABVD-treated HL patients. We feel now the responsibility with the international scientific community for the consequences of this assumption. We propose simple, reproducible rules for interim PET interpretation, in order to share our results with other teams worldwide.

Joseph Connors, PET conference, Lugano 2008

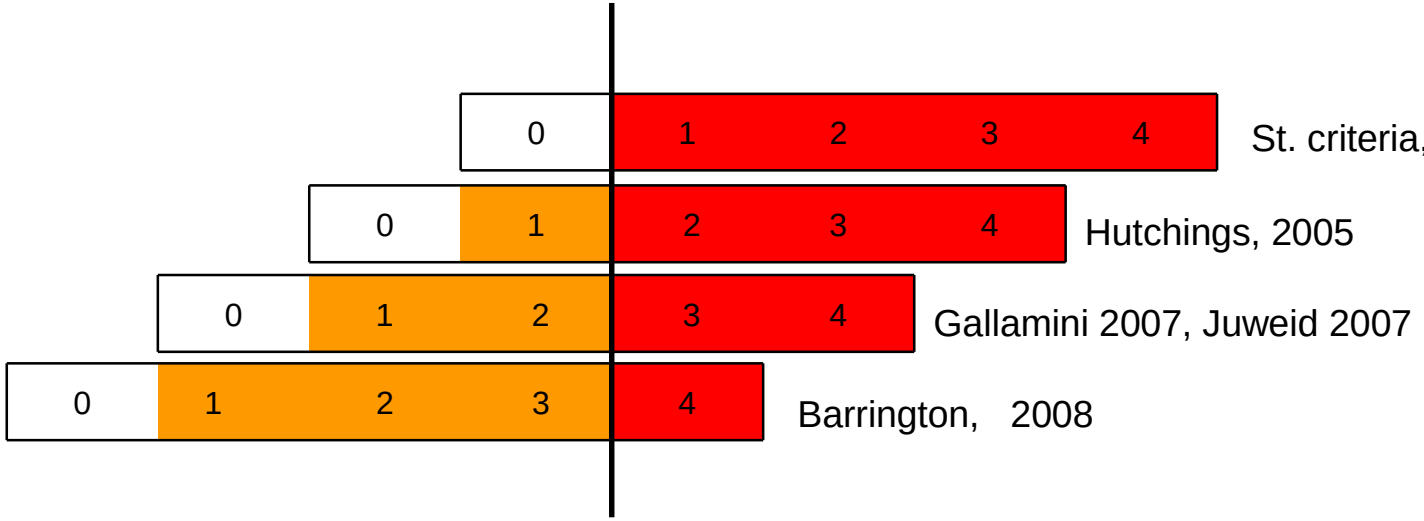
The MRU definition, as the time goes by.



▲ = FN

▼ = FP

0	1	2	3	4
Negative	> BKG	≤MBPS	≤LIVER	> LIVER



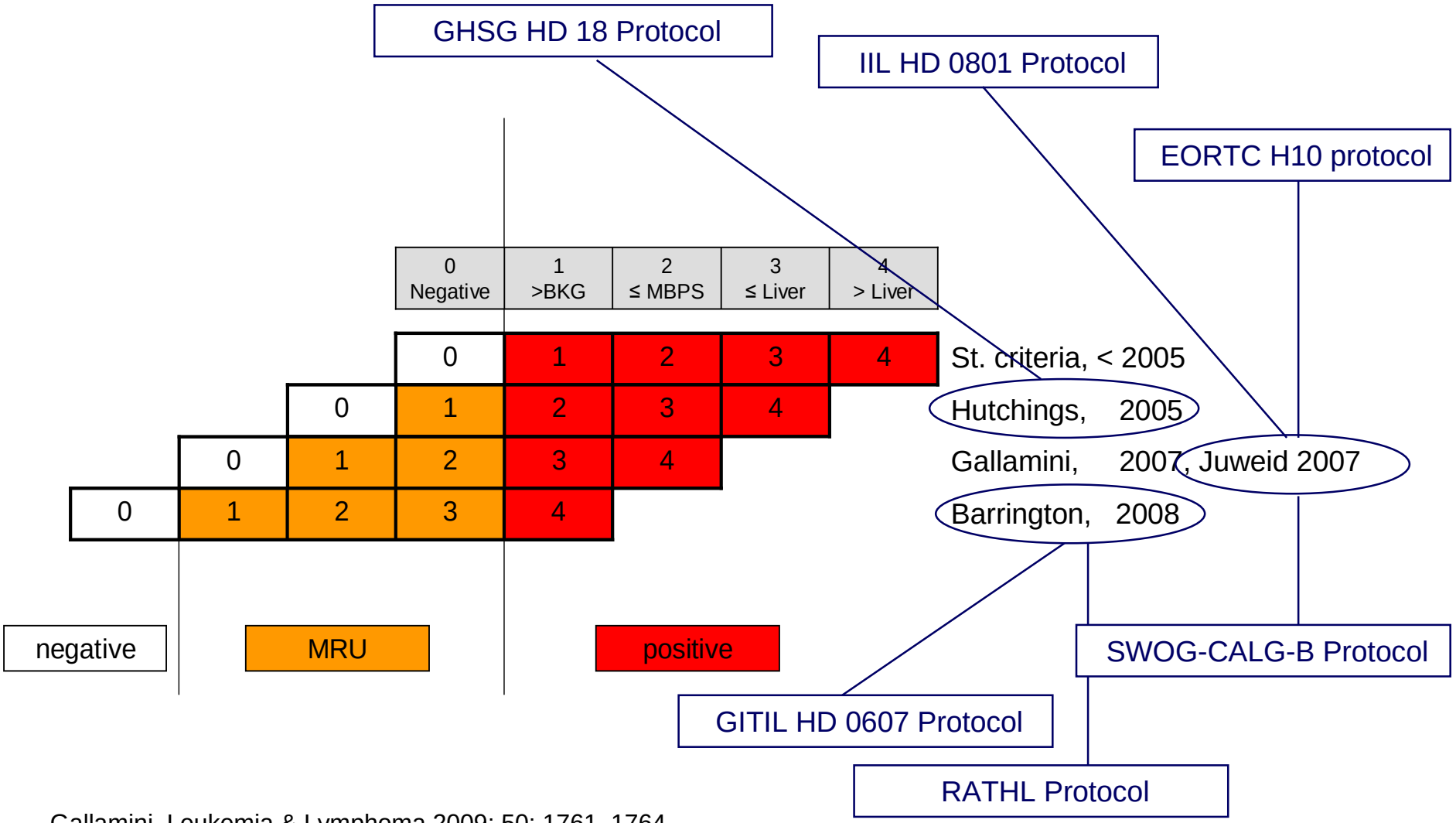
Specificity

False Positive

negative | MRU | positive

Gallamini, Leukemia & Lymphoma 2009; 50: 1761–1764

The MRU definition, and the ongoing clinical trials.



Gallamini, Leukemia & Lymphoma 2009; 50: 1761–1764

Endpoints: what should be validated ?

Primary endpoint	Overall accuracy and Predictive Value of interim-PET scan in terms of 2-year failure-free survival
Secondary endpoints	▪Propose easy reproducible international rules for early PET interpretation during ABVD chemotherapy for Hodgkin lymphoma. ▪Concordance rate of reviewers among he members of Central review panel.

Central panel for PET reviewing:

Sally Barrington – London - UK

Alberto Biggi - Cuneo – Italy

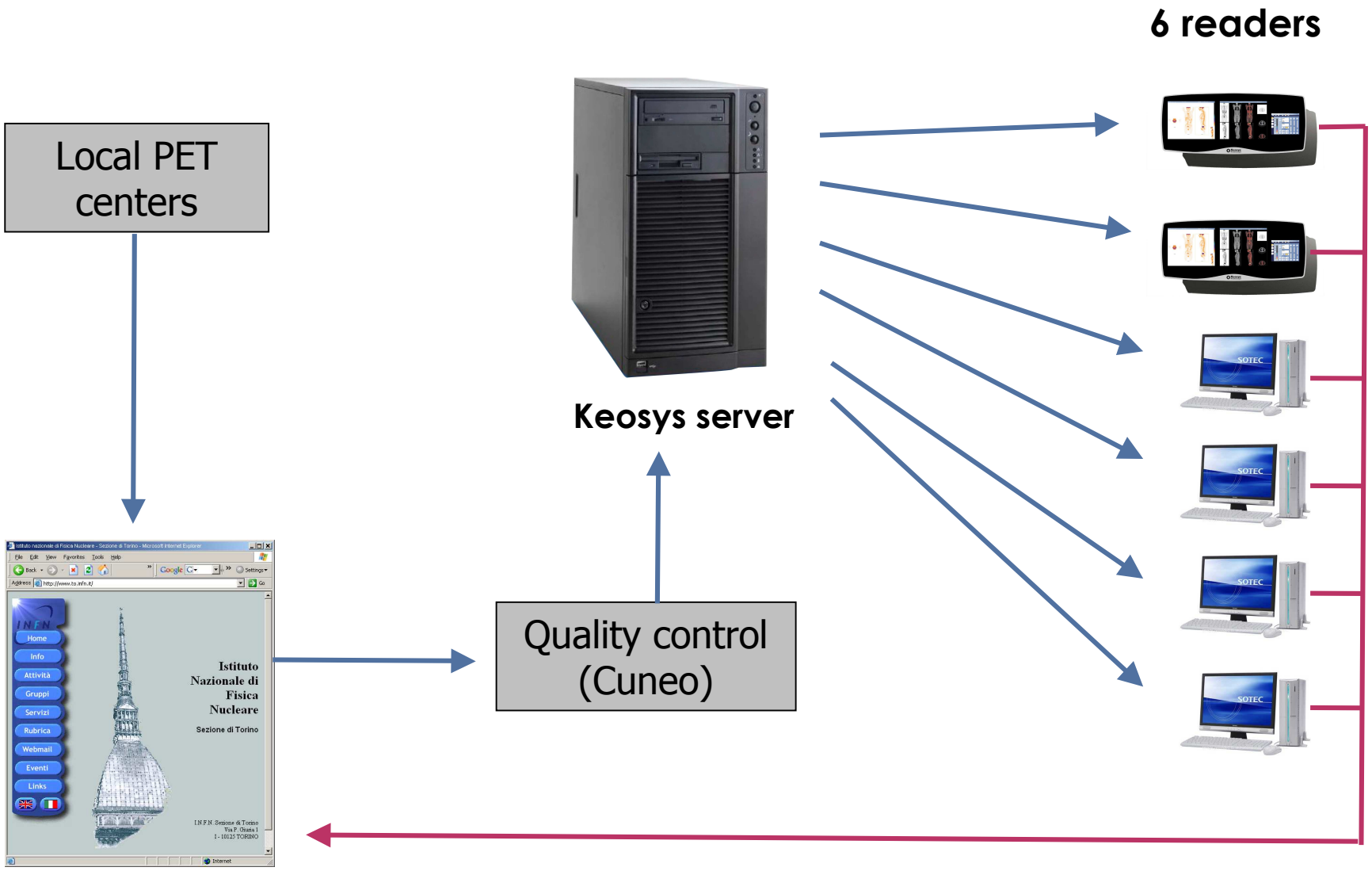
Michele Gregianin - Padua - Italy

Martin Hutchings - Copenhagen – Denmark

Lale Kostakoglu – New York – USA

Michel Meignan – Paris – France

Image transfer for PET reviewing:



http://magic5.to.infn.it/ivs

Inclusion criteria

- Advanced-stage (stage IIB-IVB) Hodgkin Lymphoma or stage IIA with unfavorable prognostic factors
- Therapy: ABVD x 6 cycles with/without consolidation radiotherapy.
- Staging at baseline and after two courses of ABVD with CT-PET (PET-0 and PET-2)
- Patients that have been treated with intensified chemotherapy for progressive /resistant lymphoma during ABVD chemotherapy are eligible only if the treatment change has been decided on clinical and/or radiological evidence of disease progression.
- PET-0 and PET-2 performed with CT-PET technology in the same PET center
- Agreement, by the nuclear team that have performed the scan to submit the studies to the central review panel and to upload the images on dicom format to the dedicated Web site for reviewing.
- Minimum follow-up of one year after treatment completion

Exclusion criteria

- Blood fasting levels before scan > 200 mg/dl.
- Interim PET (PET-2) performed after different ABVD courses than the second.
- Treatment change based on interim-PET results.
- Non CT-PET technology.
- Therapy intensification after PET-2 for a different reason than disease progression
- PET-0 and PET-2 not performed in the same PET center
- Unavailability/low-quality of dicom images.
- Inadequate follow-up

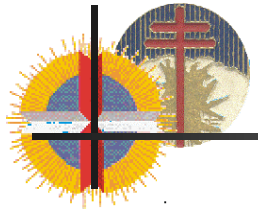
Accrual

Sygehushospitalet Aalborg (DK):	2
Ospedale S. Antonio & Biagio Alessandria (I):	4
Ospedale Policlinico Ferrarotto, Catania (I):	24
Ospedale S. Croce, Cuneo (I):	22
Centre Hospitalier Universitaire Dijon (F):	20
Policlinico Universitario Careggi, Firenze (I):	33
Gdynia University, Gdansk (PL):	33
St. Thomas Hospital London (UK):	42
Peter Mc Callum Center, Melbourne (AUS):	28
Istituto Nazionale Tumori Milano (I):	37
Ospedale Niguarda Milano (I):	11
Ospedale Policlinico Modena (I):	13
Ospedale S. Gerardo, Monza (I):	10
Mount Sinai Medical Center, New York (US):	15
Universitetshospital Odense (DK):	15
Policlinico Universitario, Padova (I):	29
Ospedale V. Cervello, Palermo (I):	27
Righospitalet Copenhagen (DK):	40
Rambam Medical Center – Haifa (IL):	14
Policlinico Melacrino Reggio Calabria (I):	10
Hopital Saint Louis – Paris (F):	18
Ospedale Molinette Torino (I):	12

Total: 459 patients

Patients exclusion

▪Stage I at diagnosis:	7
▪Stage IIA without unfavorable prognostic factors:	8
▪No ABVD therapy:	4
▪PET-0 or PET-2 not done:	10
▪Interim PET after 1° ABVD cycle	3
▪No PET Image available:	34
▪Therapy changed only on PET-2 results	4
PATIENTS EXCLUDED FROM ANALYSIS:	70
PATIENTS WITH MISSING DATA:	14
PATIENTS ENROLLED:	375

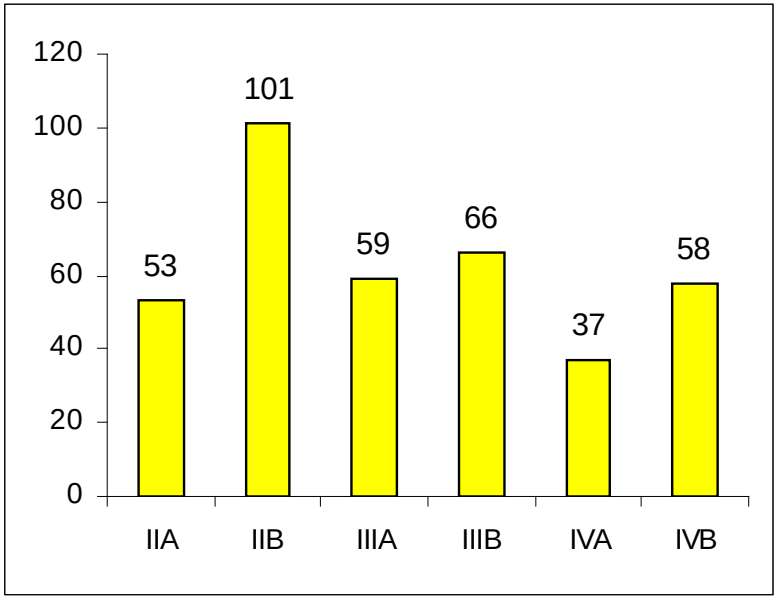


Patient characteristics

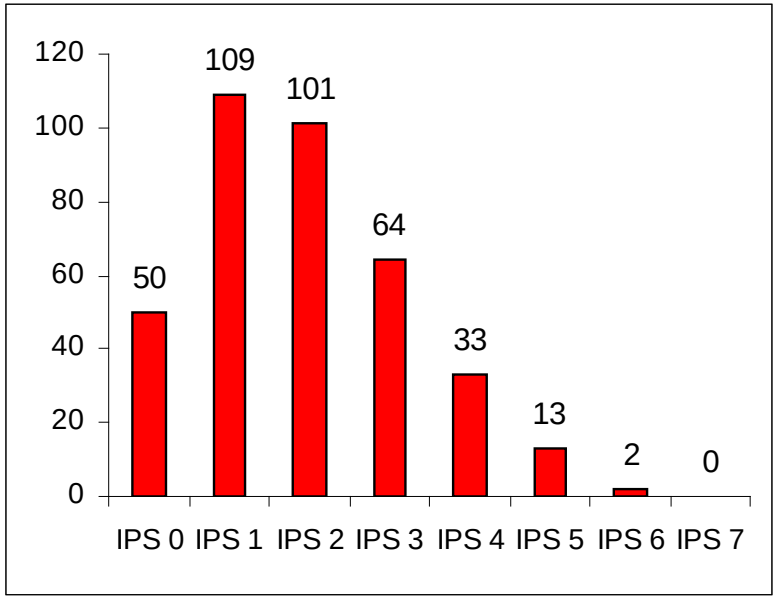
Patients enrolled	375
Mean follow-up (months)	26 (2-93)
Mean age (years)	35 (9-77)
Sex (m/f)	202/173
Histopathology:	
Classical-LR	35
NS	225
LP	46
MC	48
LD	4
NAS	17
B symptoms (no/y)	146/229
Bulky (no/y)	241/133
Extra-Nodal sites (n 0, 1, 2, 3, unknown)	214, 74, 17, 12, 58

Patient characteristics 2

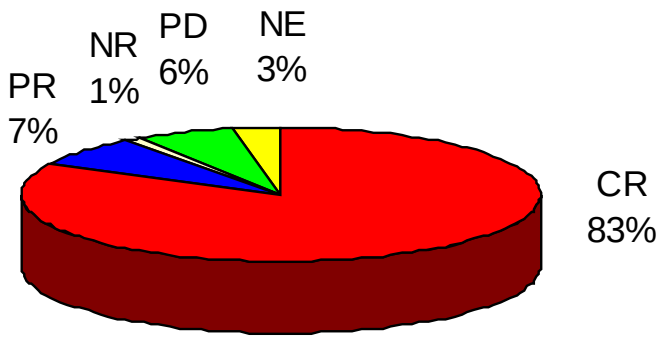
Stage (Ann Arbor)



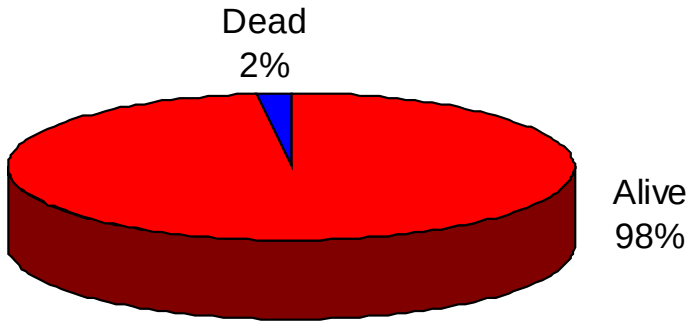
IPS (Hasenclever)



ABVD response



Status



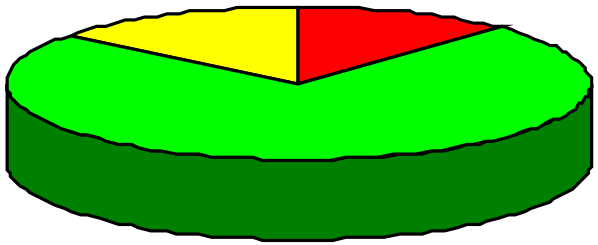
Early interim PET results according to local PET center

15/52 (29%) patients changed their therapy at clinical progression at a median of 7 months from diagnosis (range 4-28)

29/45 (64%) patients changed their therapy at clinical progression at a median of 6 months from diagnosis (range 3-17)

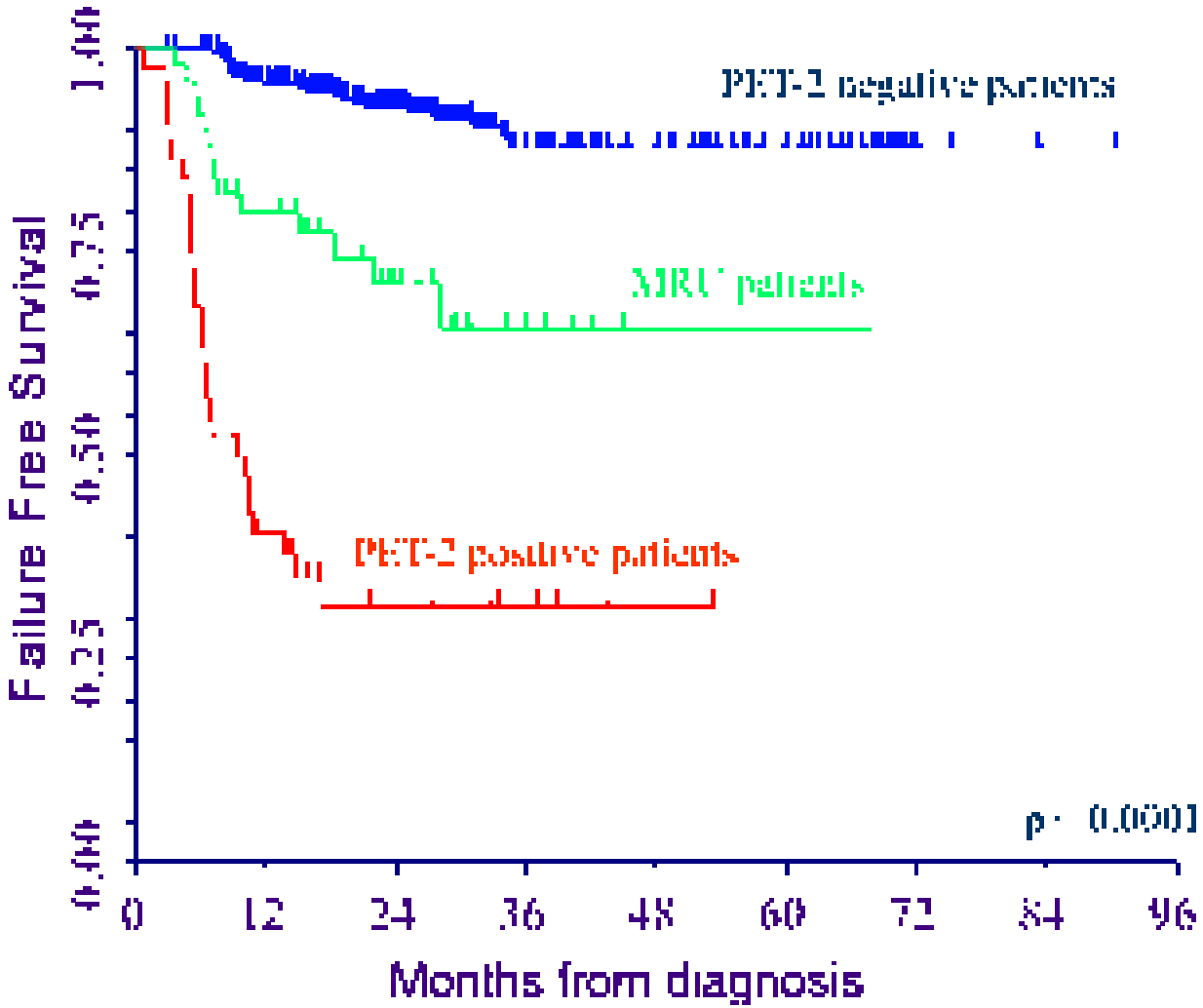
Minimal residual uptake 14%

Positive 12%



Negative 74%

Time to ABVD failure (375 p.)



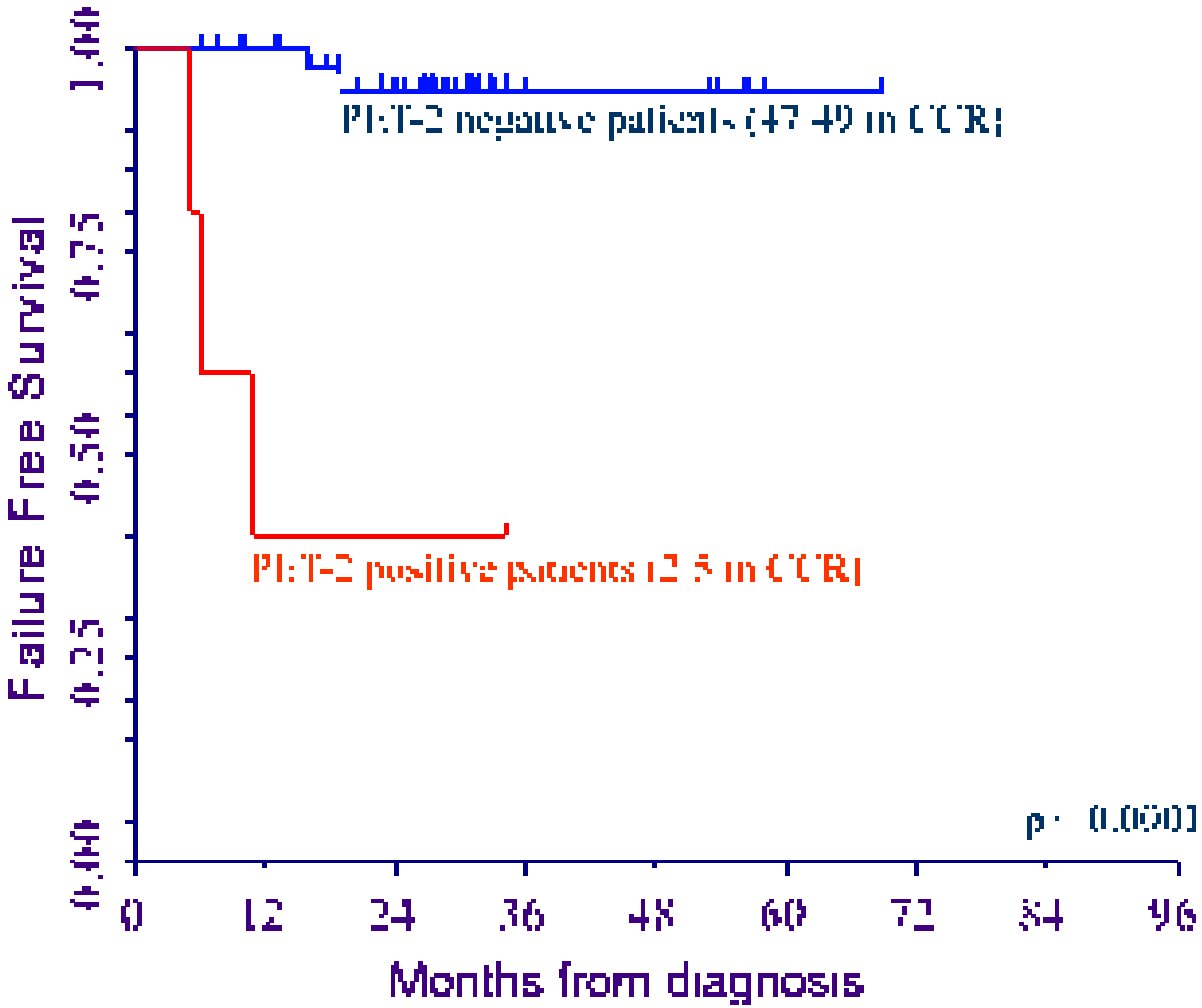
PET review (54 p.)

N	Local PET Center	Review Panel	Tx Outcome
46	Negative	Negative	44 RCC; 2 Pro
2	Negative	Positive	2 RCC (f-up 3 yrs)
3	MRU	Negative	3 RCC (f-up 34, 30, 68 m)
3	Positive	Positive	3 Pro (11, 6, 5 m after Dx)

PET-2: reviews not correlating with treatment outcome

UPN	REVIEW	CENTER	Tx Outcome	Notes
131	Positive	Cuneo	RCC (F-up 36 m.)	Stage IIA bulky; 2-point PET-2 with a decreasing SUV
191	Positive	H. St. Louis	RCC (F-up 34 m.)	Stage IV without bulky; IPS 4
255	Negative	Modena	Rel	17 y. old. Relapse 19 months after Dx on clinical grounds and PET surveillance; treated with Rx therapy. In RCC after 8 months.
317	Negative	Melbourne	Rel	Relapse 16 month after dx; clinical + CT + PET) Tx BEACOPP; RCC 10 month after failure

Time to ABVD failure (54 pts.).



Concordance among reviewers (54 pts.)

1	0.48	0.67	0.77	0.70	0.36
0.48	1	0.53	0.71	0.78	0.54
0.67	0.53	1	1.00	0.80	0.52
0.77	0.71	1.00	1	0.89	0.52
0.70	0.78	0.80	0.89	1	0.67
0.36	0.54	0.52	0.52	0.67	1

CONCORDANCE

- Almost perfect
- Substantial
- Moderate
- Poor

Binary concordance: K Cohen

Perspectives

- PET reviewing is supposed to end by September 2010
- A second meeting of the expert reviewers panel should take place in July to comment the scans of the first 250 cases reviewed, and to discuss on discordant cases
- A preliminary abstract could be sent to ASH meeting 2010
- The final report is supposed to be presented at Lugano meeting, June 2011