Was the predictive value of interim PET confirmed by the IVS study with sufficiently robust data in HL patients

International Validation Study of Prognostic role and Interpretation Criteria for Interim-PET Scan in ABVD-treated, Advanced Stage Hodgkin Lymphoma

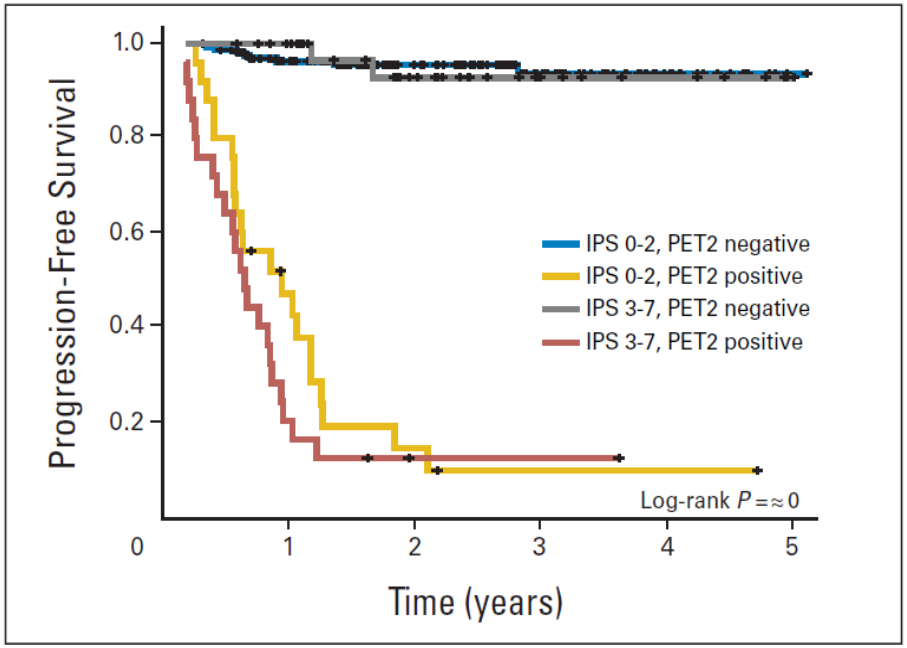
Gallamini A, Barrington S, Biggi A, Chauvie S, Kostakoglu L, Gregianin M, Meignan M, Mikhaeel G, Specht L, Zaucha JM, Seymour J, Hofman M, Rigacci L, Pulsoni A, Coleman M, Dann EJ, Trentin L, Casasnovas O, Rusconi C, Brice P, Bolis S, Viviani S, Salvi F, Luminari S, Roberto E, Cerello P and Hutchings M.

Was the predictive value of iPET confirmed by IVS study with sufficiently robust data in HL ?

Why do we need IVS ?

…interim-PET scan has been proven the most powerful tool to predict treatment outcome in ABVD-treated HL. Despite repeated recommendations (Connors 2011, Gallamini 2012) interim PET is continuously performed early during therapy to guide treatment outside clinical trials. In 2009 in Deauville a retrospective multicenter clinical study was proposed to confirm the predictive role of interim PET and to “validate” retrospectively the 5-PS criteria

What should be validated ?



Gallamini A et al. J Clin Oncol 2007; 25:3746-52.

DEAUVILLE RULES

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 uptake > mediastinum but ≤ liver
- Score 4: moderately ↑uptake > liver
- Score 5 markedly ↑uptake > liver and/or new sites of disease

IVS endpoints

Primary endpoint

- To confirm the 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.

Inclusion criteria

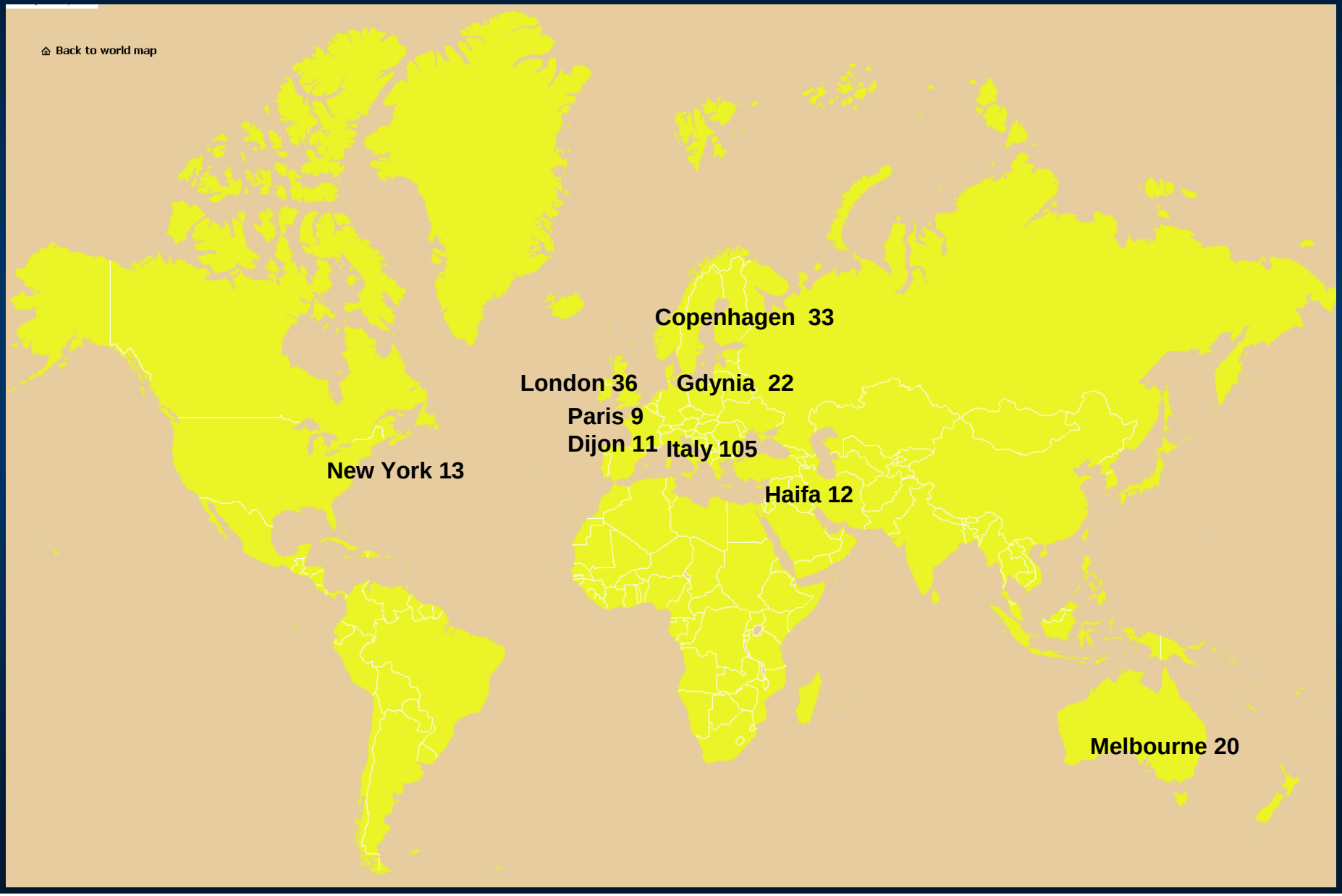
- Advanced-stage (IIB-IVB) or poor-prognosis stage IIA* HL.
- Therapy: ABVD x 6 cycles ± consolidation RT or ABVD x 4 + IFRT
- Staging at baseline and after 2 ABVD with PET-CT(PET-0 and PET-2)
- No treatment change depending on interim-PET results.
- Patients treated with 2-nd line chemotherapy for progressive /resistant lymphoma during ABVD chemotherapy eligible only with **clinical and/or radiological evidence of disease progression.**
- PET-0 and PET-2 performed in the same PET center
- Minimum follow-up of one year after treatment completion

* ≥ 3 nodal sites involved, bulky lesion, ESR > 40 mmHg.

Study population

400 consecutive patients affected by HL from 17 participating centres worldwide diagnosed between January 2002 and December 2009 were considered eligible and retrospectively enrolled, provided they met the inclusion criteria

17 participating centers 261 p. enrolled from 05.11.2001 to 23.11.2009)



Patient selection

400 patients enrolled

336 patients with PET/CT scans uploaded & quality controlled

Reason for PET scan exclusion

•Absence of CT images	22
•Absence of baseline PET	25
•Absence of interim PET	1
•CT slices missing	3
•PET slices missing	10
•Poor quality scans	6
•Miscellaneous	9

260 patients with PET/CT scans approved & sent to review

•**REVIEWERS**
•Sally Barrington – London – UK
•Alberto Biggi- Cuneo – I
•Michele Gregianin – Padova - I
•Martin Hutchings- Copenhagen – DK
•Lale Kostakoglu – New York – USA
•Michel Meignan – Paris – F

KEOSYS Medical Imaging

Review results acquired and statistical analysed

Demographics (N= 260).

		Stage IIA patients unf.*	Stage IIB patients	Stage III patients	Stage IV patients	All patients
No.		53	60	85	62	260
Gender	male	23 (43.39%)	32 (53.33%)	48 (56%)	36 (58%)	139 (53%)
	female	30 (56.60%)	28 (46.67%)	37 (44%)	26 (42%)	121 (47%)
Follow-up	median	35.5	40.4	34.7	38.4	37.0
	range	7-73.7	1.8-105.3	3.2-109.9	2.5-78.5	1.8-109.9
B-symptoms		0(0%)	60 (100%)	52 (61%)	41 (66%)	152 (58.4%)
Extranodal disease		2 (3.7%)	8 (13%)	18 (21%)	52 (84%)	80 (31%)
Bulky disease		17 (32%)	26 (43%)	21 (25%)	15 (24%)	79 (30%)
IPS	0	--	--	9 (1)	0 (0)	9 (6%)
In parentheses % of PET-2 positive patients	1	--	--	29 (3)	10 (0)	39 (26%)
	2	--	--	26 (3)	19 (4)	45 (31%)
	3	--	--	13 (1)	16 (6)	29 (20%)
	4	--	--	6 (2)	11 (5)	17 (11%)
	≥5	--	--	2 (1)	6 (1)	8 (5%)
Radiotherapy		36 (67.9%)	39 (65%)	15 (17.6%)	(10 (16.1%)	100 (38.5%)

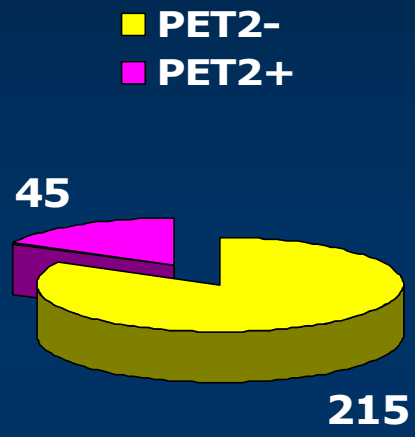
* ≥ 3 nodal sites involved, bulky lesion, ESR > 40 mmHg.

First-line treatment

Treatment consisted of ABVD x 4 plus IFRT for 32 early unfavorable patients or ABVD x 6 ± consolidation RT for 20 early unfavorable and for 208 advanced-stage patients. Consolidation RT was delivered to the site of initial bulky disease in 68 patients. 212 (82.7%) achieved CR and 3 PR; all three converted to CR later. Forty-five (17.3%) had treatment failure: 31 disease progression and 14 disease relapse. Median follow-up was 37.6 months (2-110)

2nd-line chemotherapy

Median follow-up 37.6 months



45/260 (17.3%) patients were PET2 positive

- 33/45 (65%) of them (TP) had a treatment failure
  - 29 had treatment intensification for disease progression
  - 4 had a relapse

215/260 (82.7%) patients were PET2 negative

- 12 (5%) of them (FN) had a treatment failure
  - 7 had treatment intensification for disease progression
  - 5 had a relapse

44 patients changed therapy:

- 39 after a median of 7.86 months (range 2-34) at clinical progression
- 1 after 2 months due to PET findings in isolation
- 3 after 3 months for clinical evidence of disease progression
- 1 after 4 months due to PET findings in isolation.

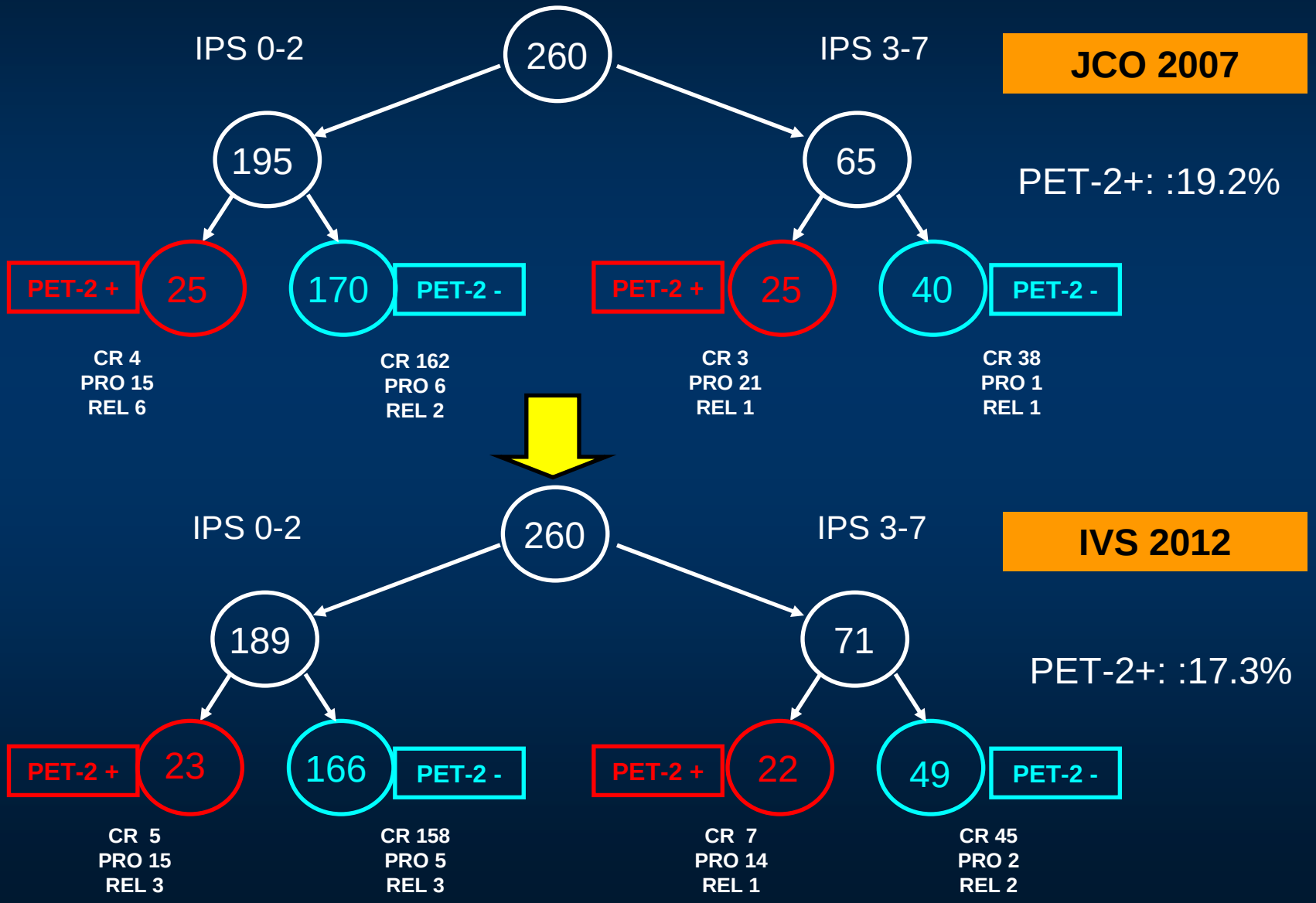
2-nd line treatment outcome (N=45: 17%)

PET-2 positive cohort (n= 33)
- 22 patients attained CR
- 3 patients progressed
- 4 died for disease progression

PET-2 negative cohort (N= 12)
- 10 patients reached CR
- 1 patient progressed
- 1 died for disease progression.

Treatment administered
DHAP (4) , IGEV (4), Unknown (7) HDS (199) followed by ASCT in 25 pts.

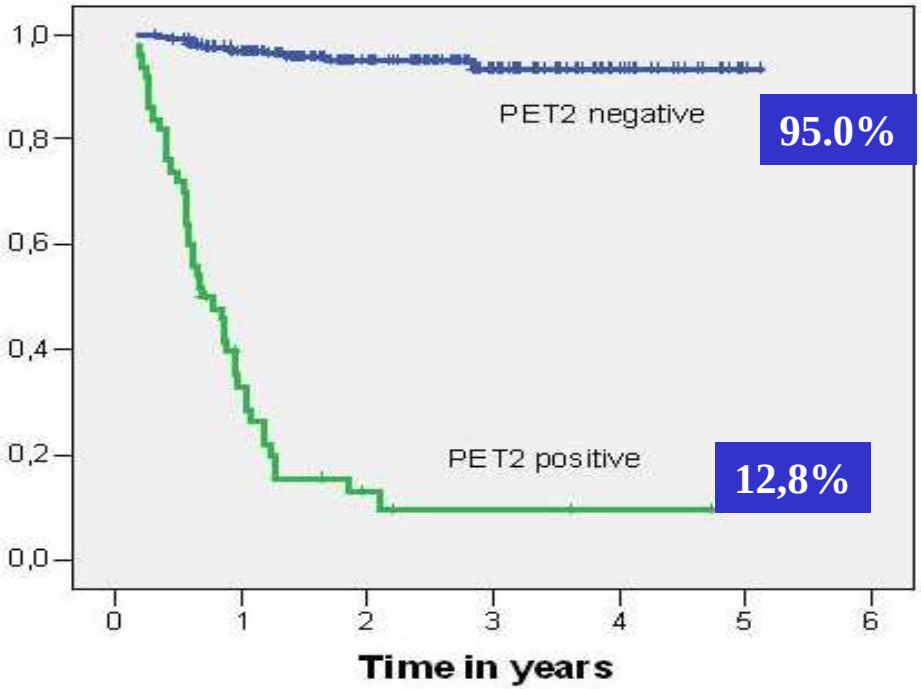
1-st line Tx outcome according to PET-2 and IPS



Predictive value on Tx outcome

Parameter	IVS	JCO
True Positive	33	44
True Negative	203	199
False Positive	12	6
False Negative	12	11
Sensitivity	0.732 [0.678,0.785]	0.81
Specificity	0.927 [0.896,0.959]	0.97
Positive Predictive Value	0.652 [0.594,0.710]	0.93
Negative Predictive Value	0.949 [0.922,0.976]	0.92

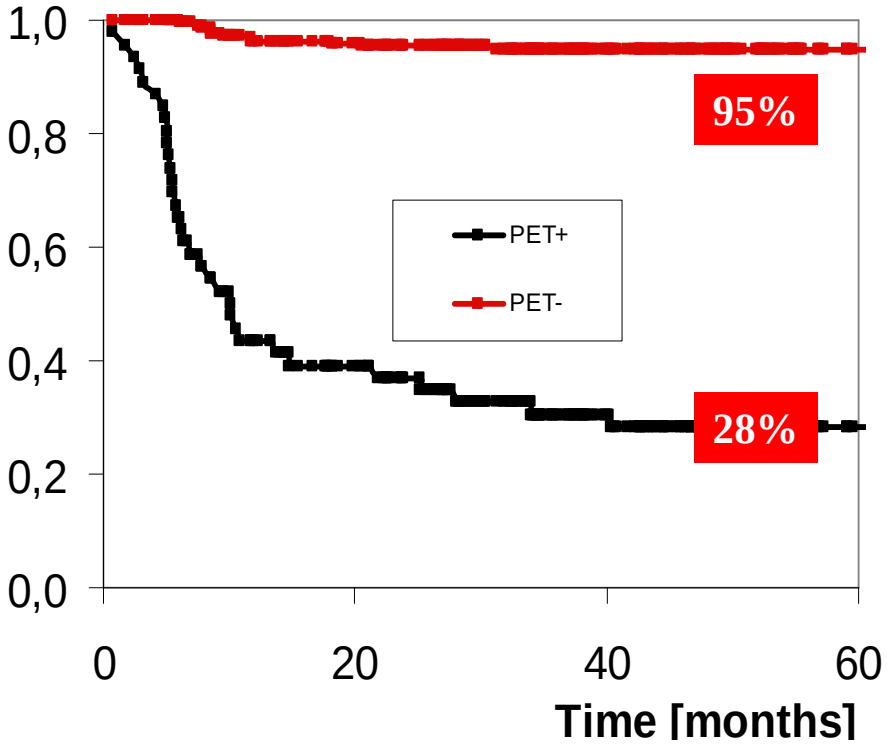
2 yrs PFS



Gallamini A.: J Clin Oncol 2007; 25, 2235-2248

PPV 93% - NPV 92%.
SE 81% ; SP 97% ; ACC 92%

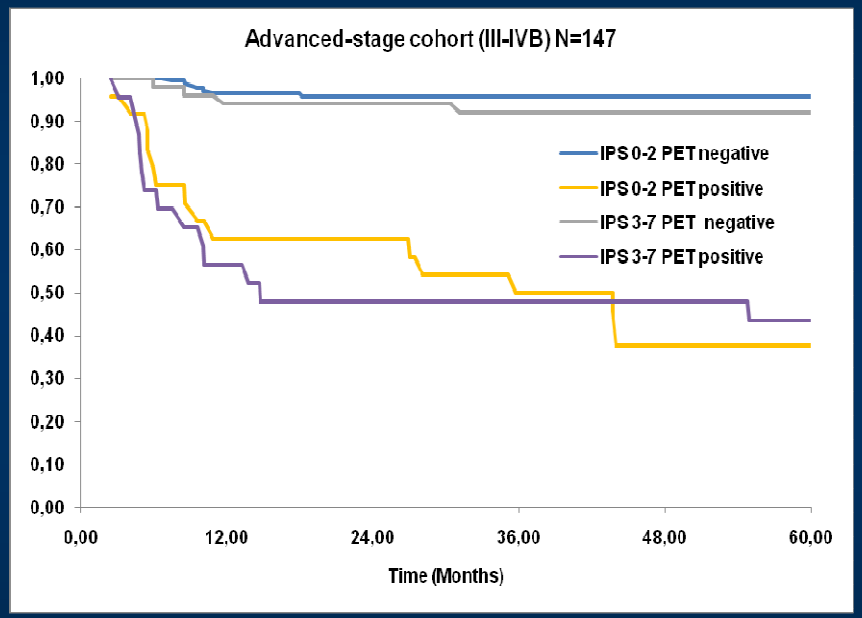
3 yrs PFS



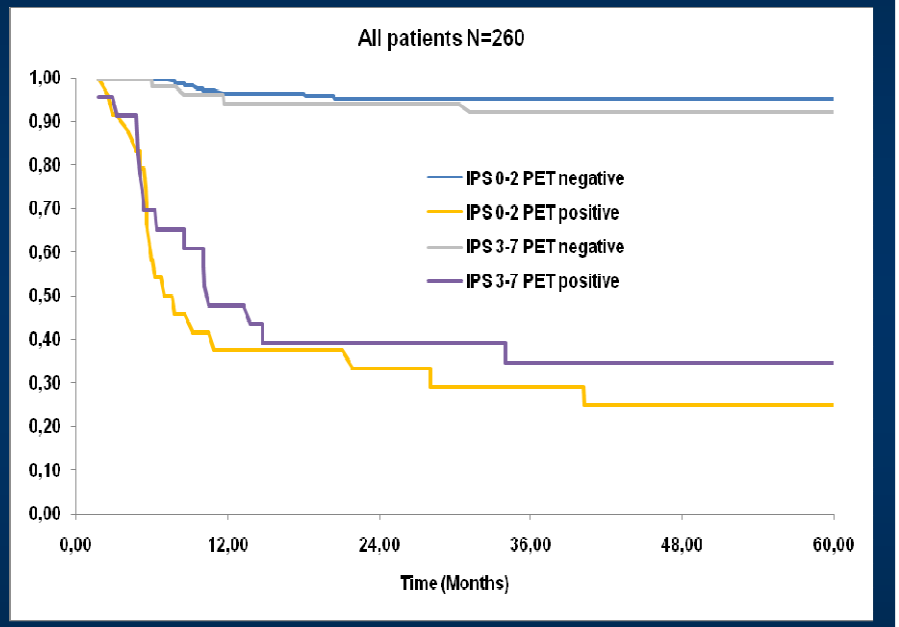
Biggi A. : SNM 2012

PPV 73% - NPV 94%
SE 73% ; SP 94%; ACC 91%

3-y PFS according to PET-2 and IPS in stage III_IV B and all patients



Stage IIIA-IV B (N =147)



All patients (N= 260)

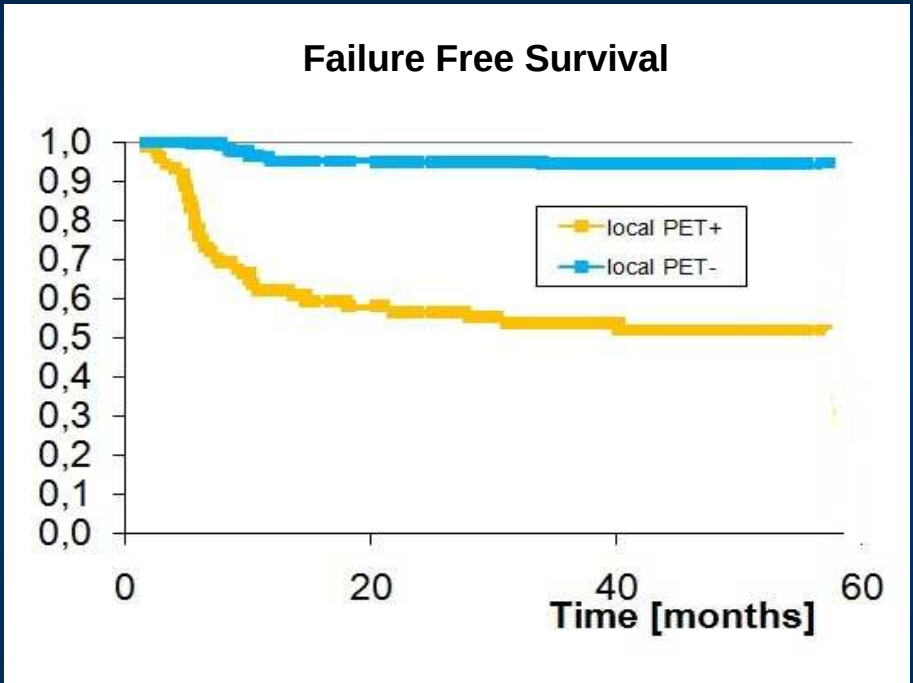
Univariate & Multivariate analysis for 3-Y PFS

Univariate analysis	p Value	Sig.	95,0% CI for Exp(B)	
			Lower	Upper
Bulky	<0.01	0,048	1,000	1,710
Lymphocyte	<0.01	0,007	1,000	1,000
Albumin	<0.01	0,000	0,950	0,970
WBC	<0.01	0,000	1,000	1,000
IPS 0-2 vs.≥ 3	<0.01	0,008	0,790	0,970
CR vs no CR	<0.01	0,000	4,070	7,650
LDH	<0.01	0,031	0,999	1,000
BM	<0.01	0,000	1,090	1,330
PET-2	<0.01	0,000	1,630	3,110
Multivariate analysis (COX)	**p Value**	**Sig.**	**95,0% CI for Exp(B)**	
			Lower	**Upper**
Bone Marrow Involvement	<0.01	0,001	1,107	1,513
PET-2	<0.01	0,000	3,136	7,917

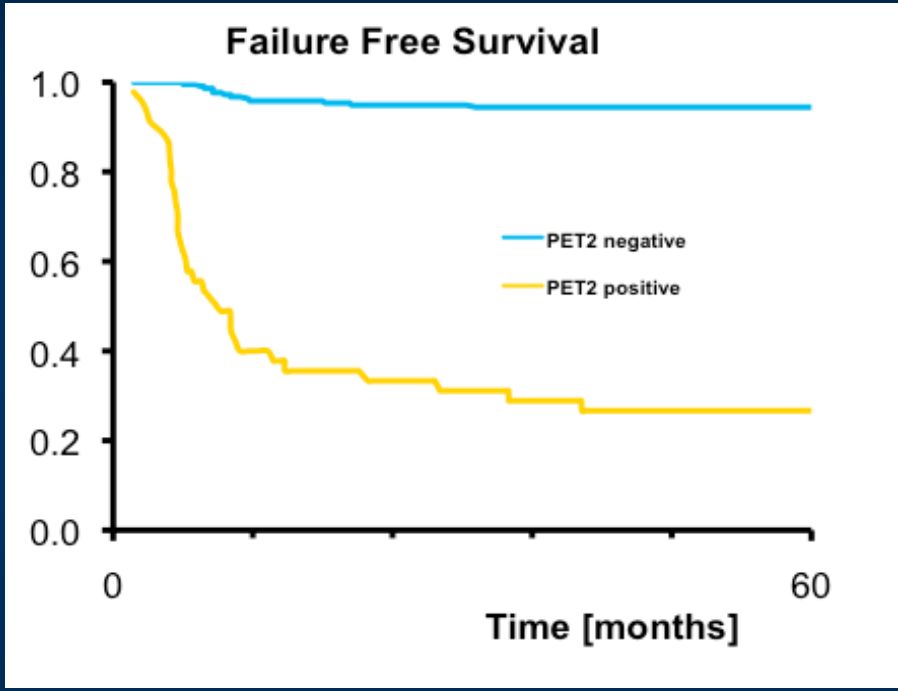
What is the lesson from a retrospective multicenter clinical trial ?

Standardization is mandatory !

3-y PFS according to local or blindend independent central review

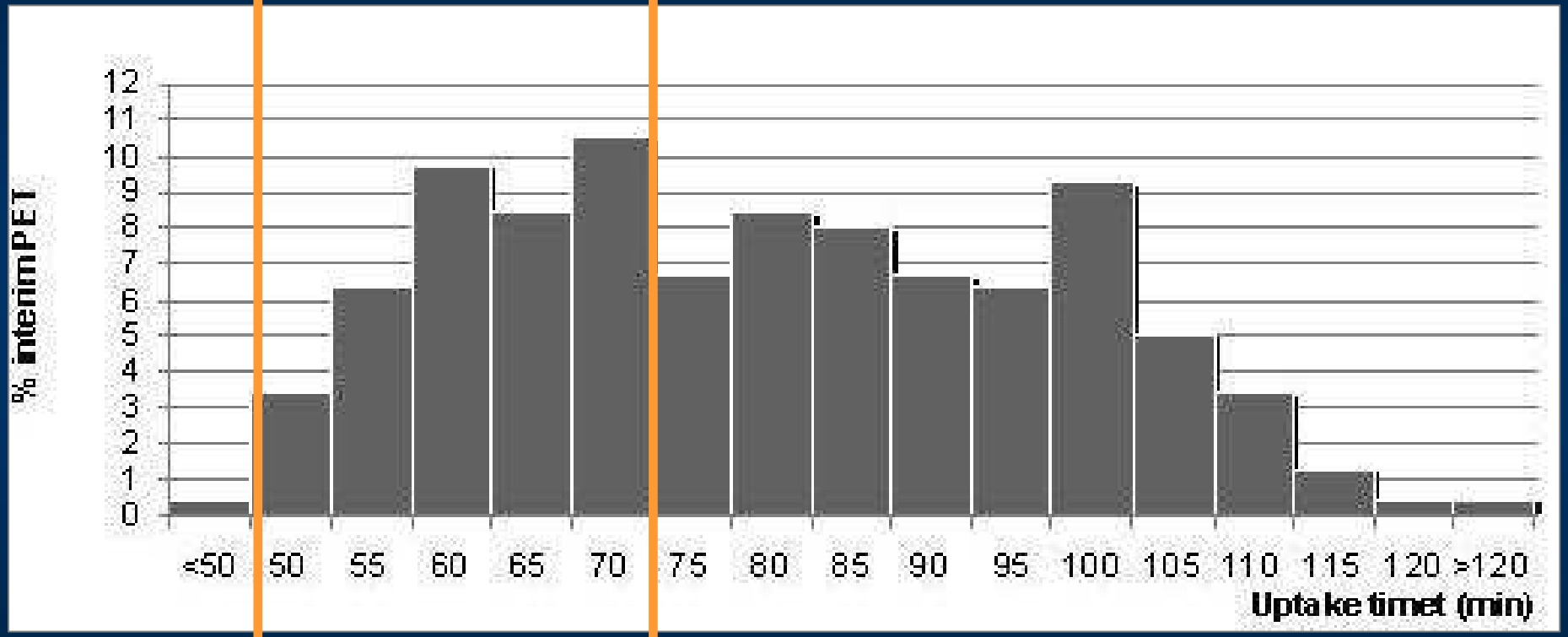


Local centre interpretation



BICR

Uptake time



Standard range

101/260 patients (38%)

Conclusions

- Predictive role of iPET was confirmed in multicenter retrospective study: 3-Y PFS for iPET-neg and iPET-pos. of 95% and 28%, respectively,
- IPS prognostic role was overridden by iPET both in " truly advanced" and in all patient series
- The PPV was 73% in IVS and 93% in Italian Danish study. The lower value probably is accounted by the different methodology or review process (blinded vs. consensus)
- Deauville 5-PS turned out robust enough as interpretation key (Cohen k 0.69-0.84: good-very good; Krippendorf alpha 0.76 : excellent)

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