THE PROBLEM OF INTERPRETATION AND USE OF RESPONSE EVALUATION TREATMENT

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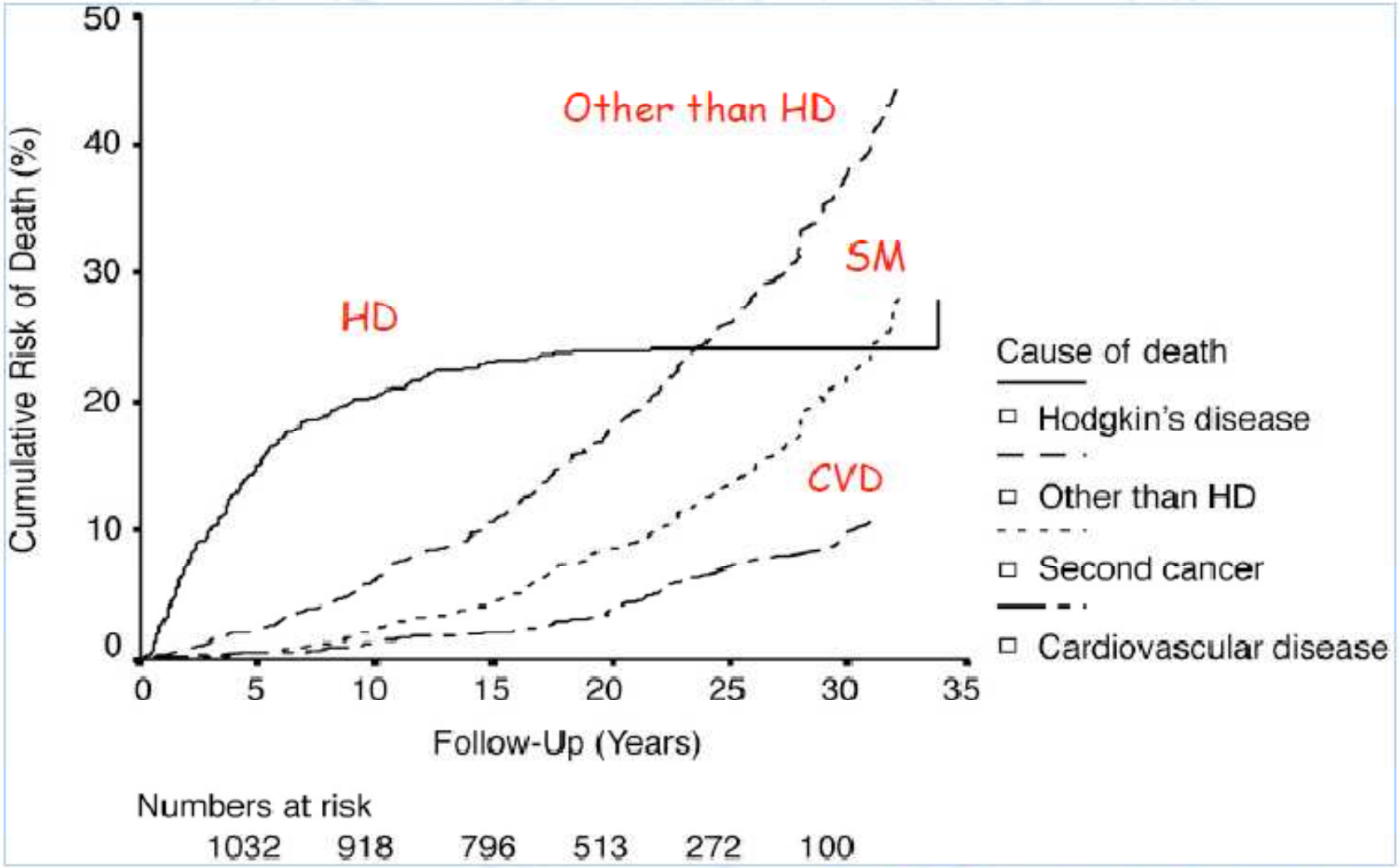
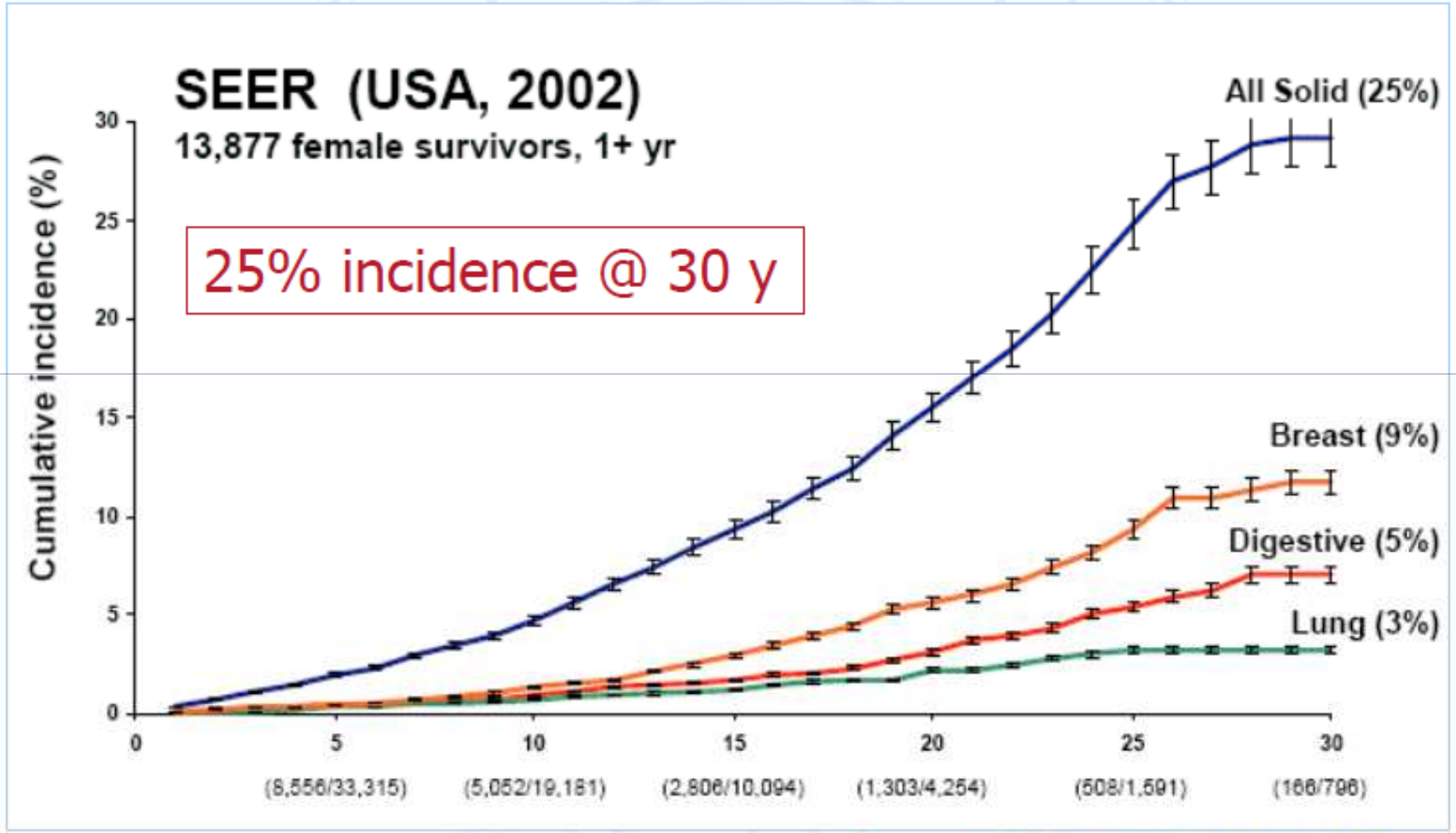
Brescia, May 14th 2010

Il prezzo del successo



Aleman B., JCO 21; 18: 3431-3439, 2003

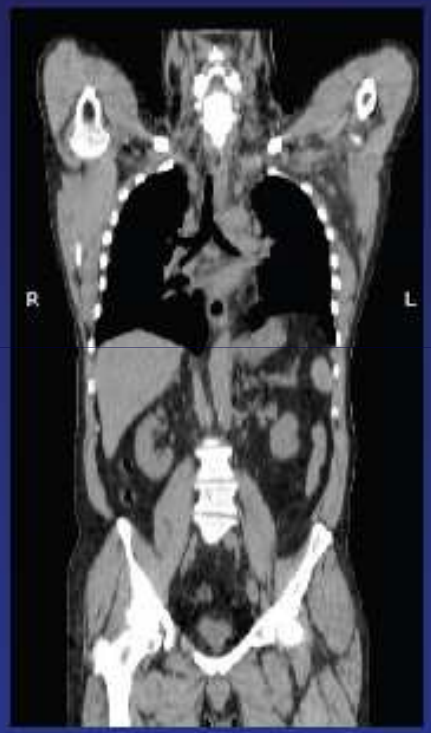
II Cancer Risk dopo LH



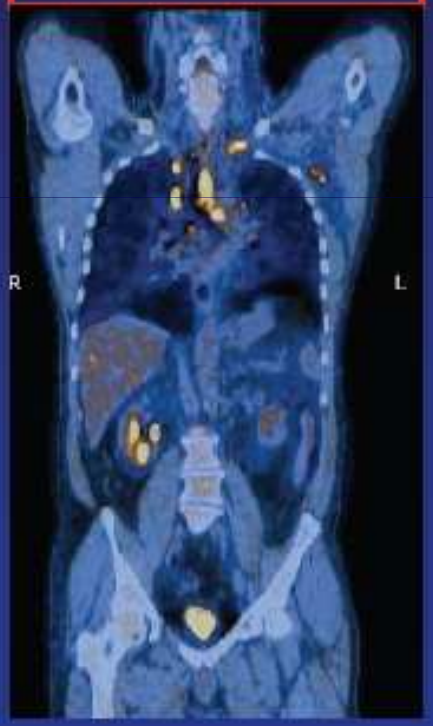
Dores et al JCO 20:3484, 2002

CT-PET: Last-born Imaging technique in Lymphoma management

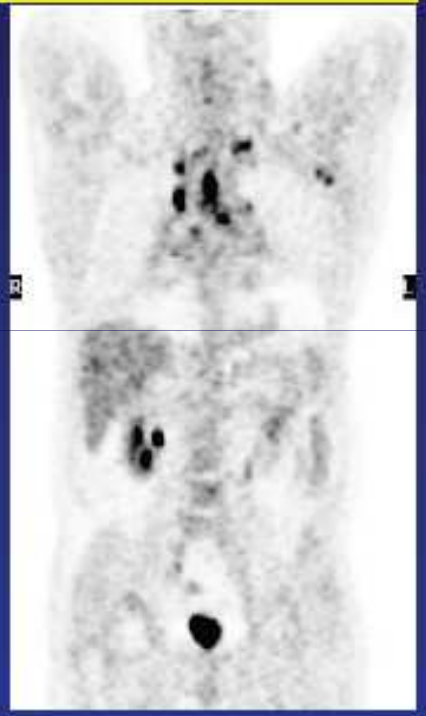
CT: anatomic detail



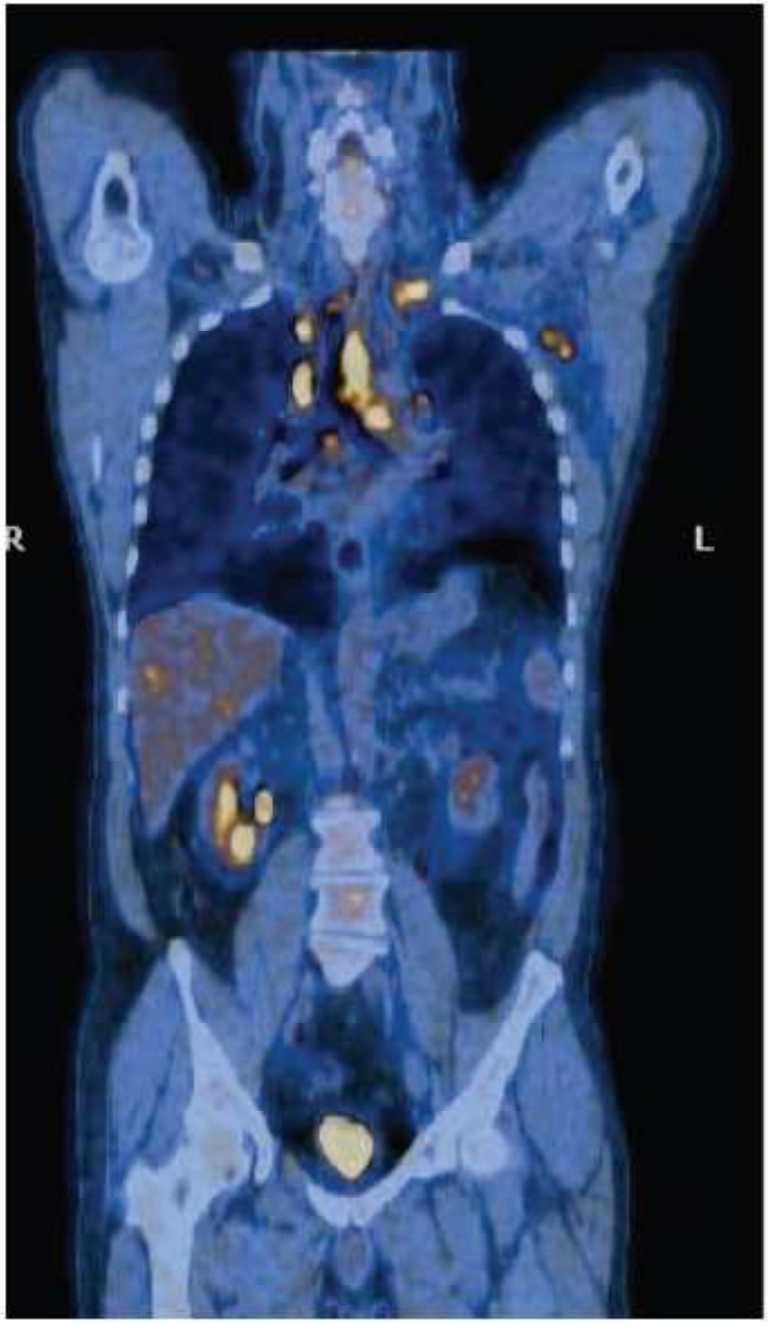
PET - CT



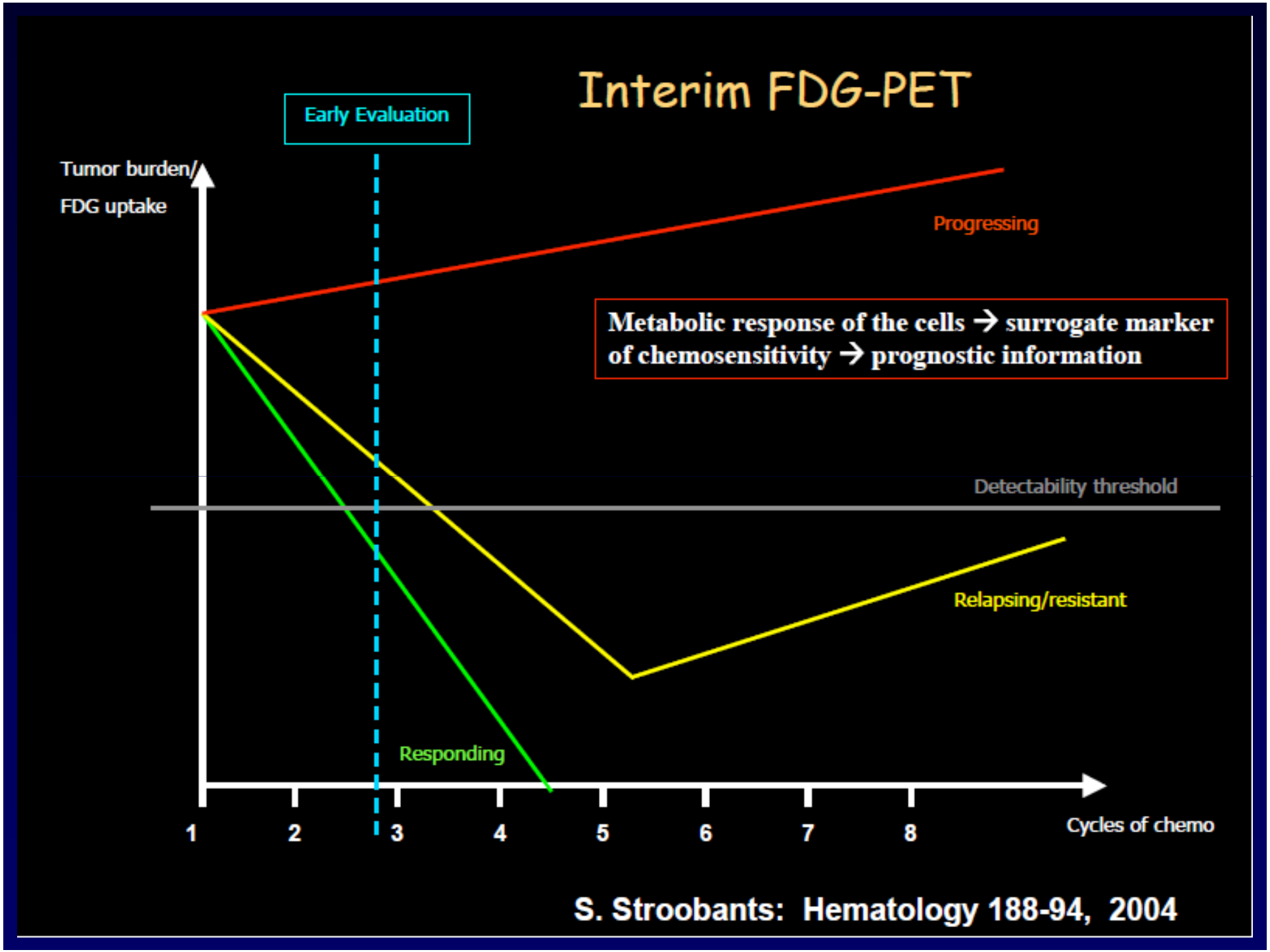
PET: viability of tumor cells

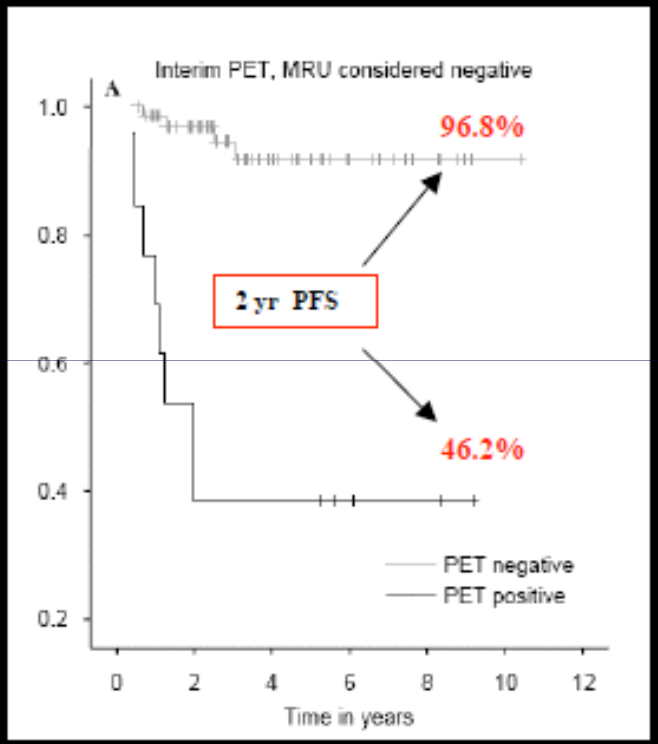


CT-PET= High specificity (CT), high sensitivity (PET)



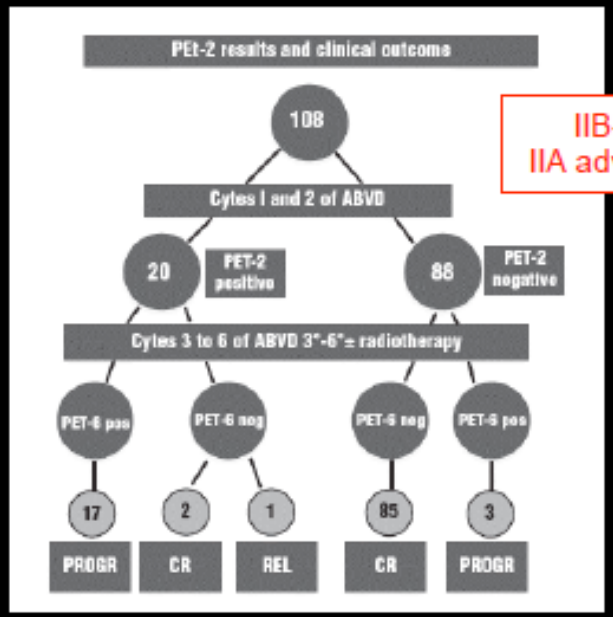
FDG-PET has changed our approach to Hodgkin lymphoma


Interim FDG-PET
Early Evaluation
Tumor burden/
FDG uptake
Progressing
Metabolic response of the cells → surrogate marker of chemosensitivity → prognostic information
Detectability threshold
Relapsing/resistant
Responding
1
2
3
4
5
6
7
8
Cycles of chemo
S. Stroobants: Hematology 188-94, 2004



Annals of Oncology 16: 1160–1168, 2005

85 pts; 20% I-IIA



IIB-IVB
IIA adverse PF

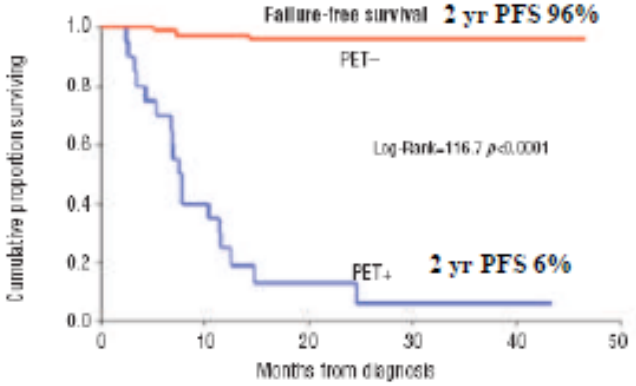


Figure 3. Probability of failure-free survival according to PET-2 results.

Haematologica 2006; 91:475-481

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

Andrea Gallamini, Martin Hutchings, Luigi Rigacci, Lena Specht, Francesco Merli, Mads Hansen, Caterina Patti, Annika Loft, Francesco Di Raimondo, Francesco D'Amore, Alberto Biggi, Umberto Vitolo, Caterina Stelliano, Rosario Sancetta, Livio Trentin, Stefano Luminari, Emilio Iannitto, Simonetta Viviani, Ivana Pierri, and Alessandro Levis

J Clin Oncol 25:3746-3752. © 2007

260 pts IIB-IVB + IIA adverse PF
FU: 2.19 yrs

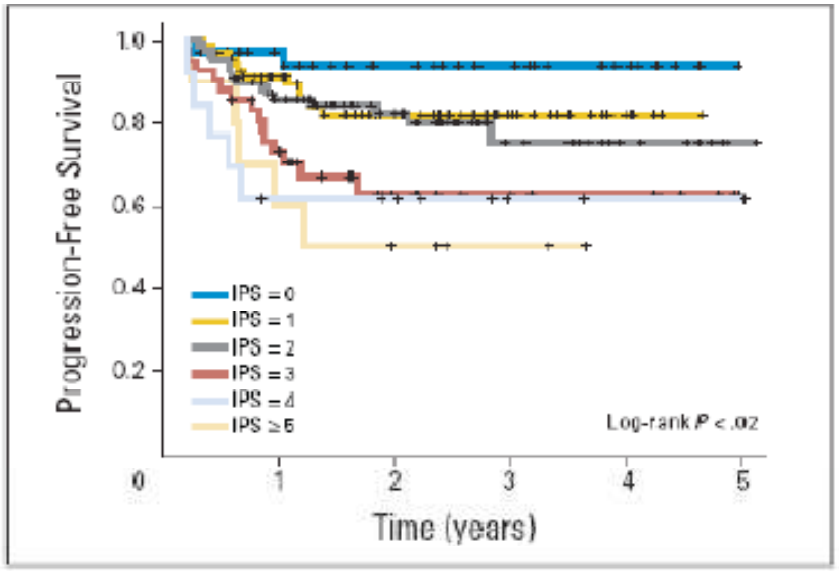


Fig 2. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group.

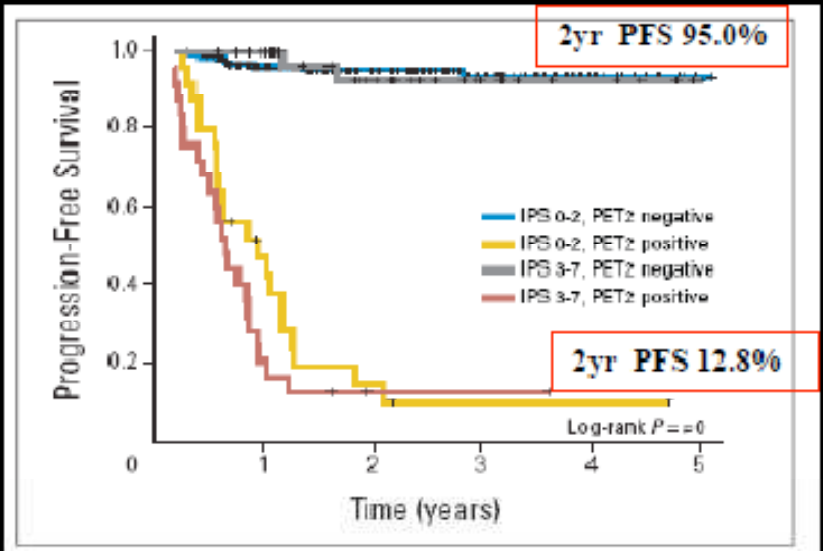


Fig 3. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group and positron emission tomography results after two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).

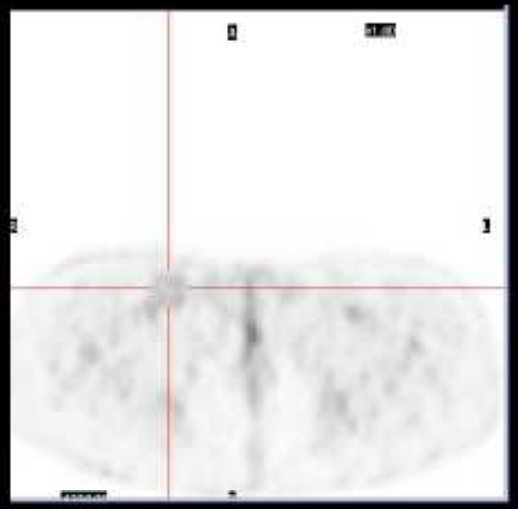
Conclusion
PET-2 overshadows the prognostic value of IPS and emerges as the single most important tool for planning of risk-adapted treatment in advanced HL.

Studies of PET for Interim Response Assessment of malignant lymphoma

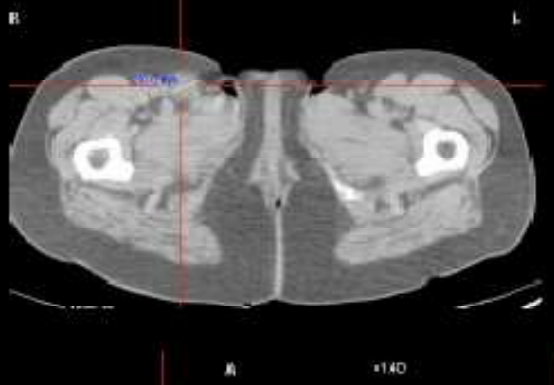
Study	Year	Country	Study Design	No. of Involved institutions	Pts	Sensi-tivity	Speci-ficity
Friedberg et al	2004	USA	Prosp.	3	22	0.80	0.94
Hutchings et al	2005	UK	Retrosp.	1	28	0.67	1.00
Gallamini et al	2006	Italy	Prosp.	11	108	0.86	0.98
Hutchings et al	2006	Denmark	Prosp.	3	46	0.77	0.97
Zinzani et al	2006	Italy	Prosp.	1	40	0.89	1.00
Gallamini et al	2007	Italy+ Denmark	Prosp.	14	106	0.79	0.95

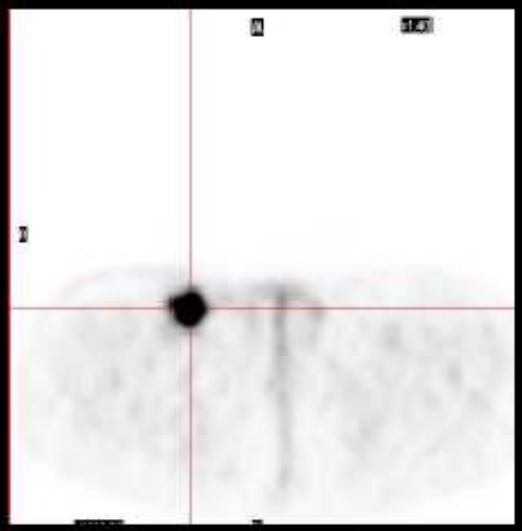
The criteria of interpretation of interim PET/CT **significantly affects** clinical results

Process of interpretation interim PET

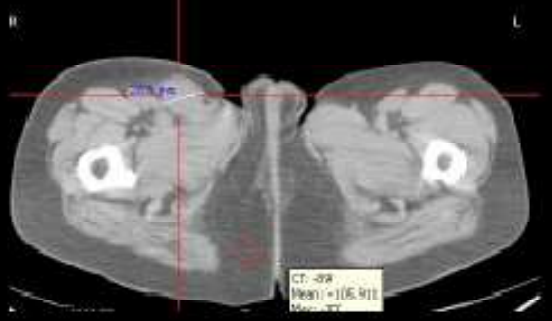


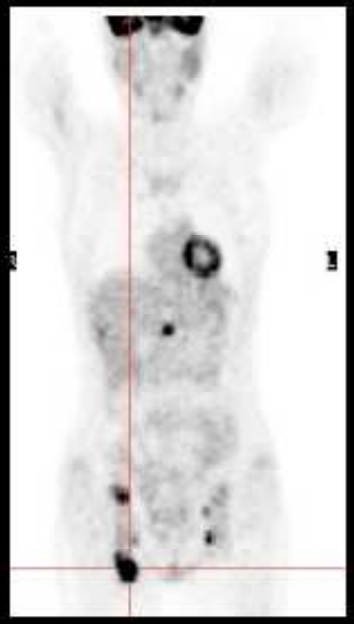
uptake in a residual mass





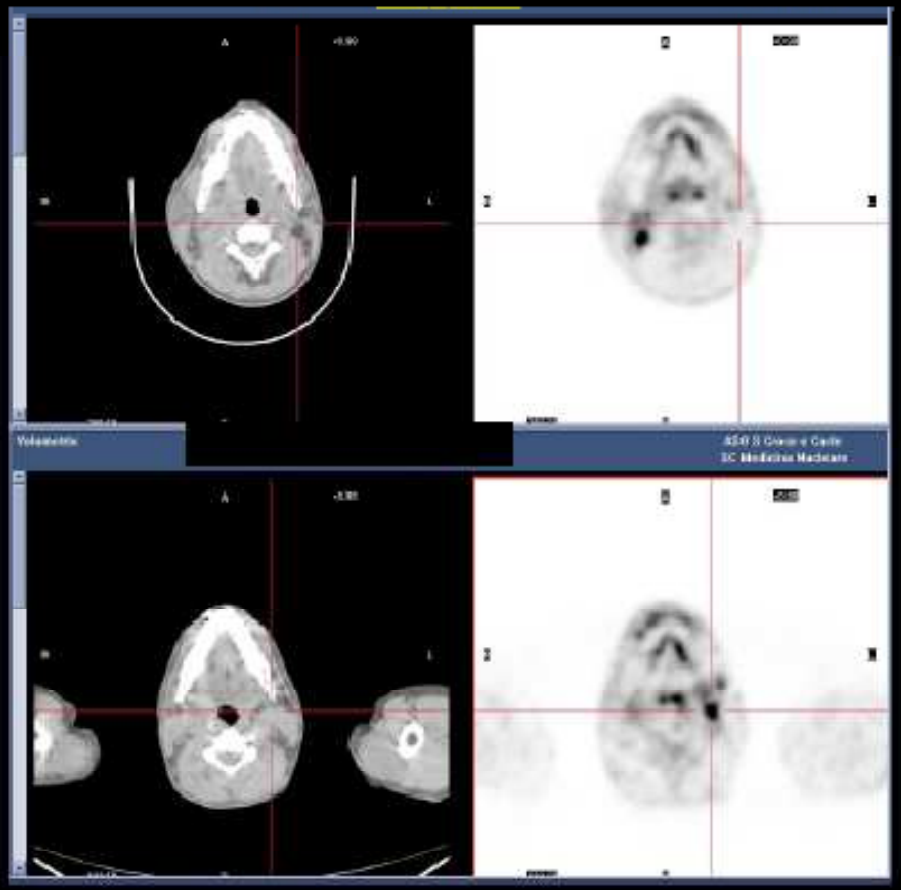
in a site previously involved

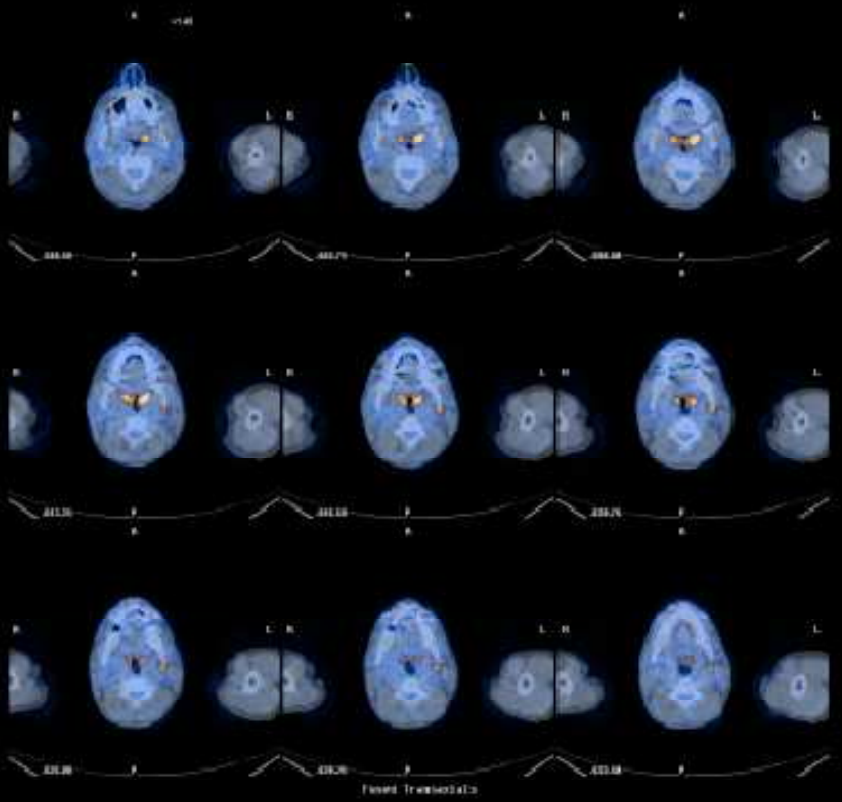




Comparison with a reference organ

New lesion in a site previously uninvolved

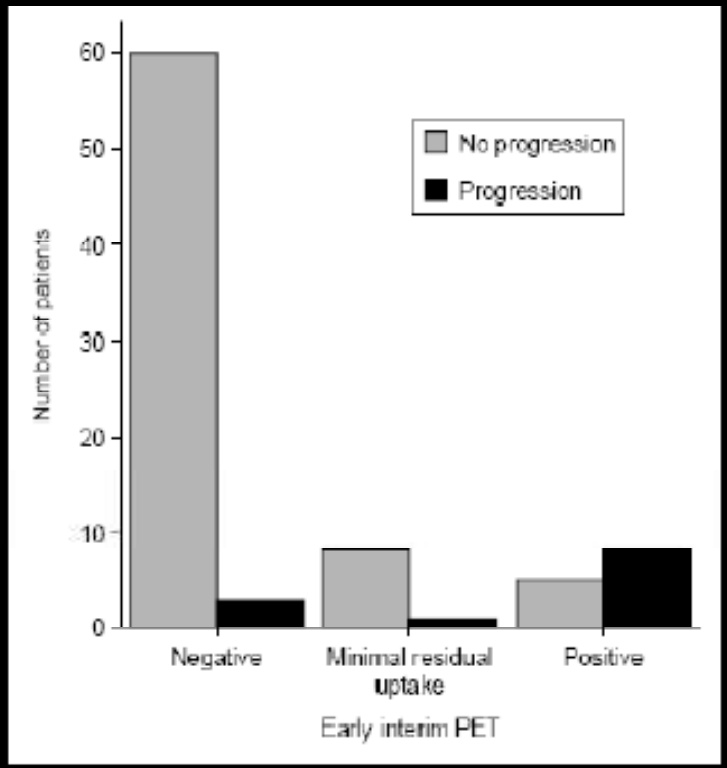




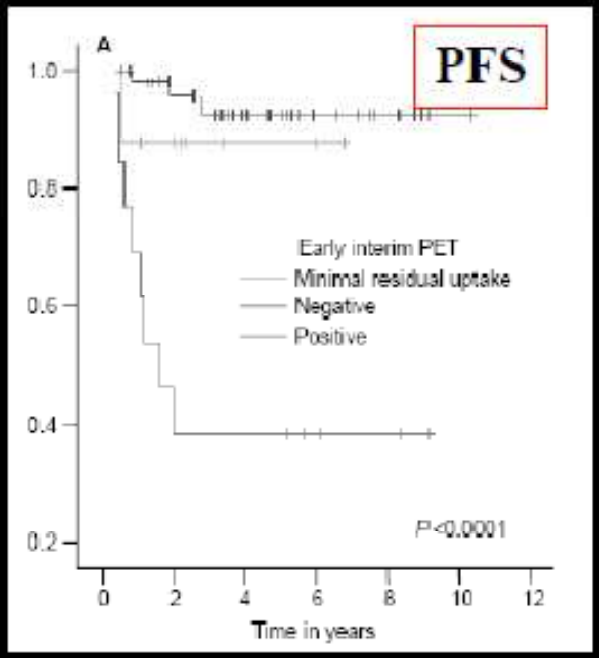
Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma

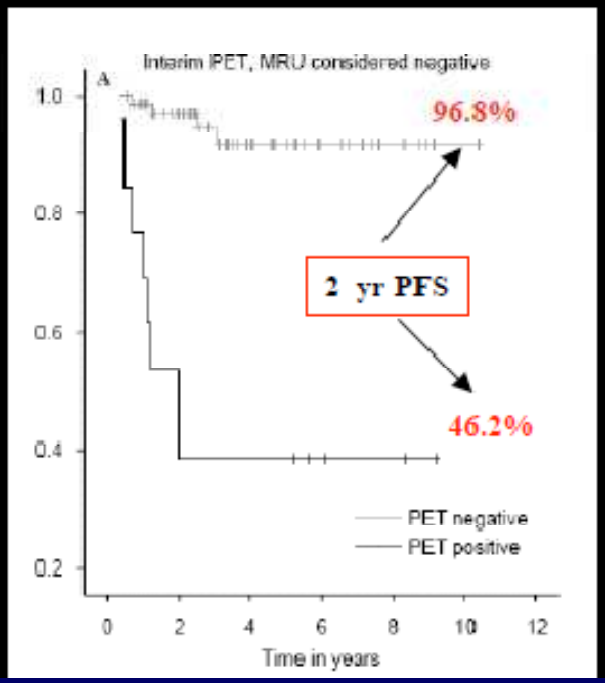
M. Hutchings[1], N. G. Mikhaeel[1]*, P. A. Fields[2], T. Nunan[3] & A. R. Timothy[1]

Annals of Oncology 16: 1160–1168, 2005



"low grade uptake of FDG (just above background) in an area of previously noted disease reported by the nuclear medicine physician as not likely to represent malignancy"





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

Andrea Gallamini, Martin Hutchings, Luigi Rigacci, Lena Specht, Francesco Merli, Mads Hansen,

J Clin Oncol 25:3746-3752. © 2007

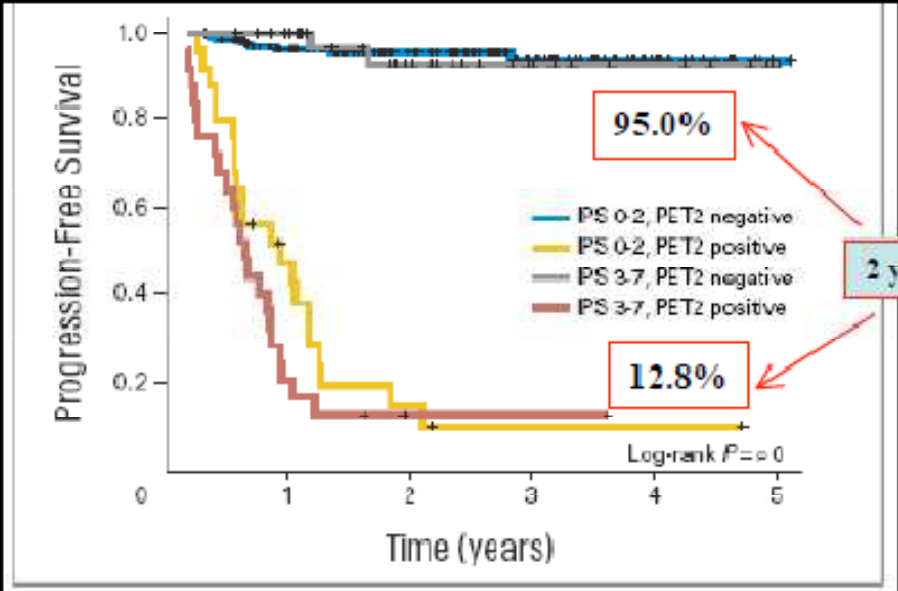
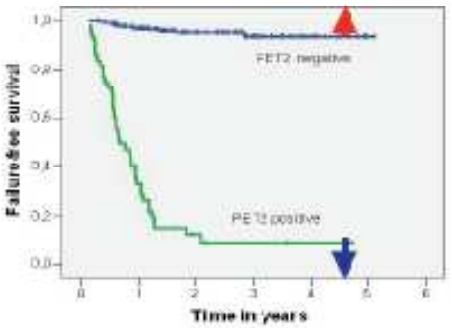


Fig 3. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group and positron emission tomography results after two cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).

"MRU was redefined …as a low grade FDG uptake with avidity lower than, equal to or only slightly higher than the uptake in mediastinal blood pool structure. A standardized uptake value of 2.0-3.5 was regarded as consistent with MRU. Patient with a PET scan showing MRU was considered PET negative for the analysis"

The MRU definition, as the time goes by.



▲= FN

▼= FP

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

St. criteria, < 2005
Hutchings, 2005
Gallamini, 2007
Barrington, 2008

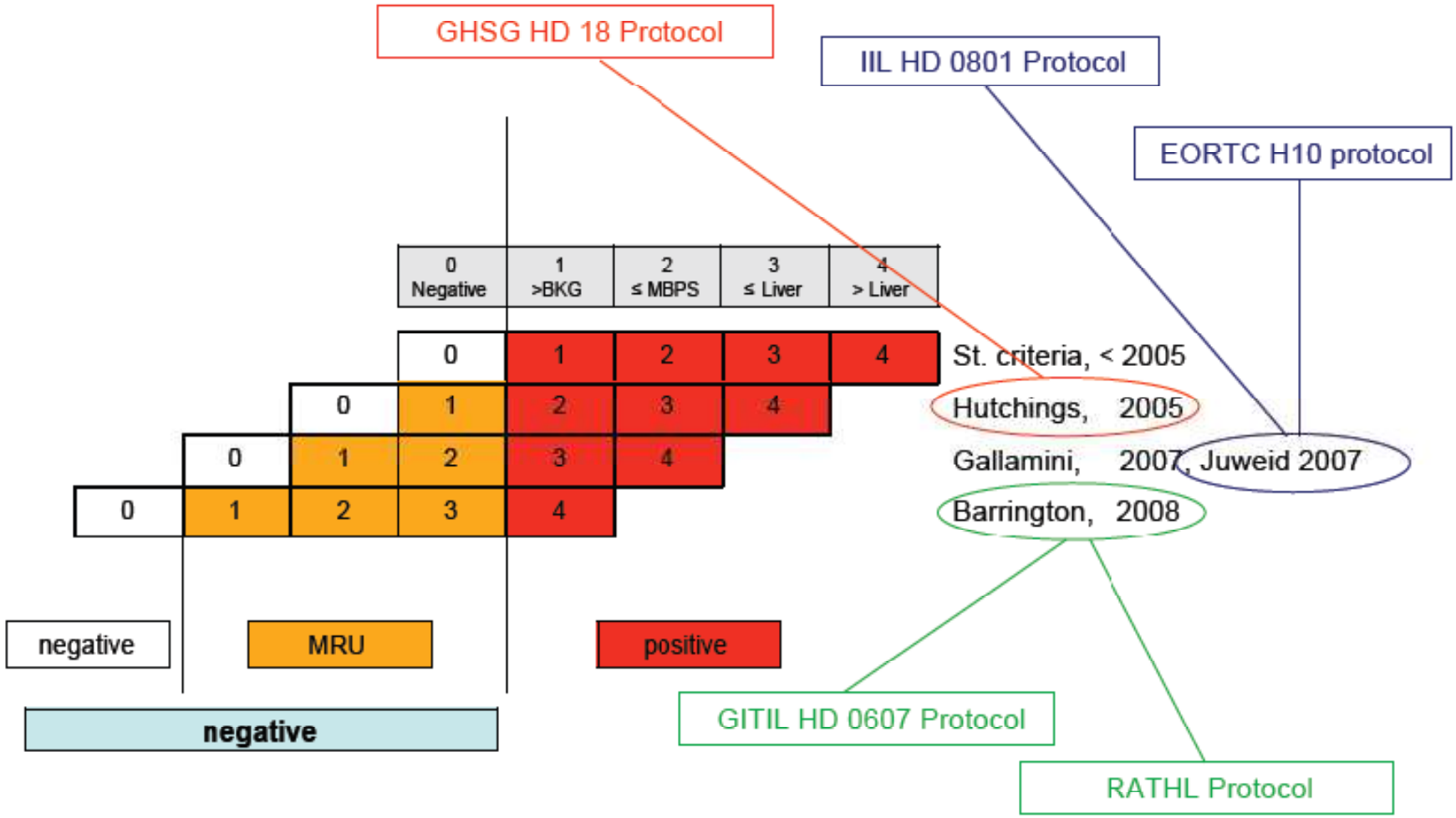
SPECIFICITY

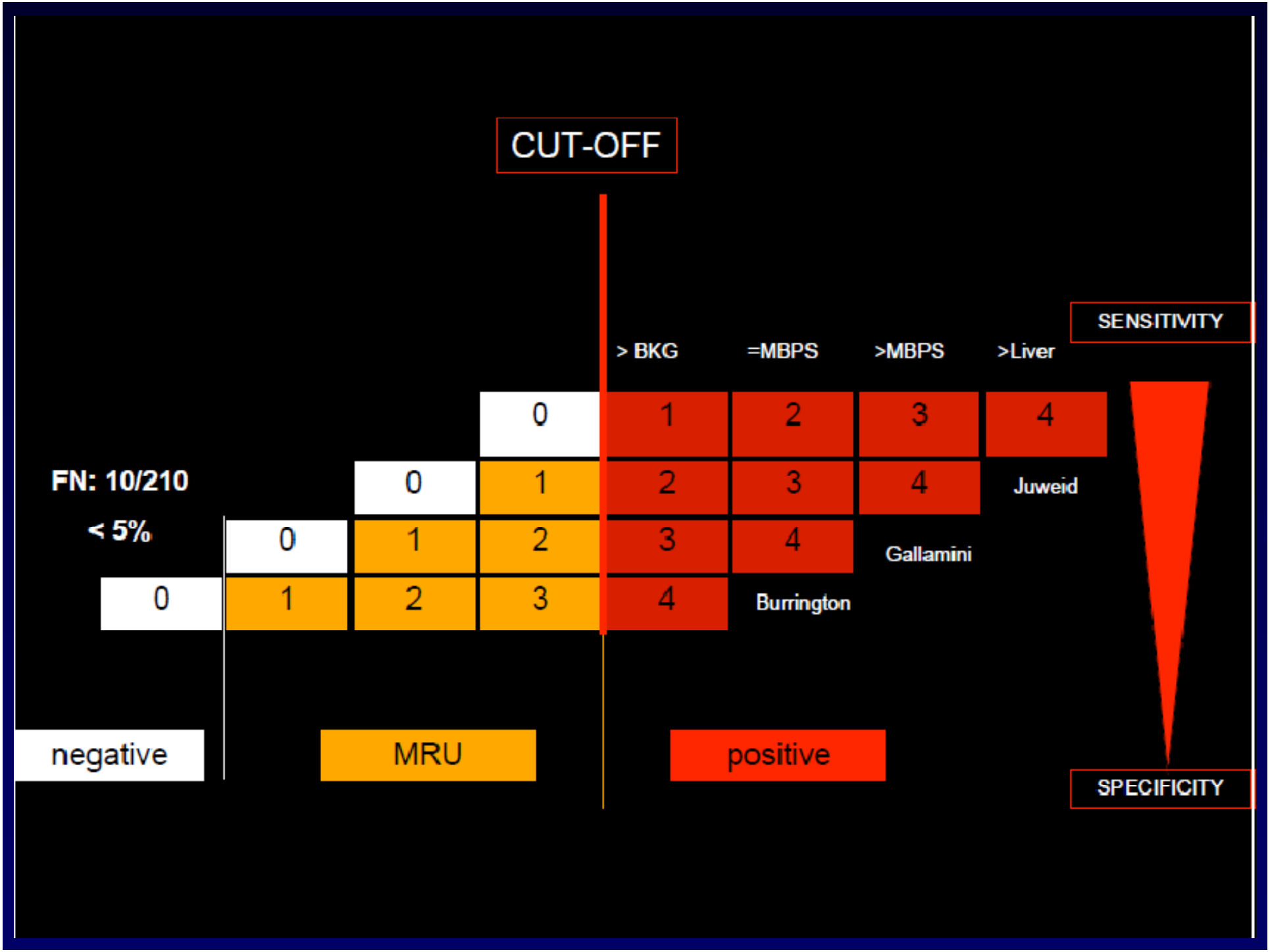
SENSITIVITY

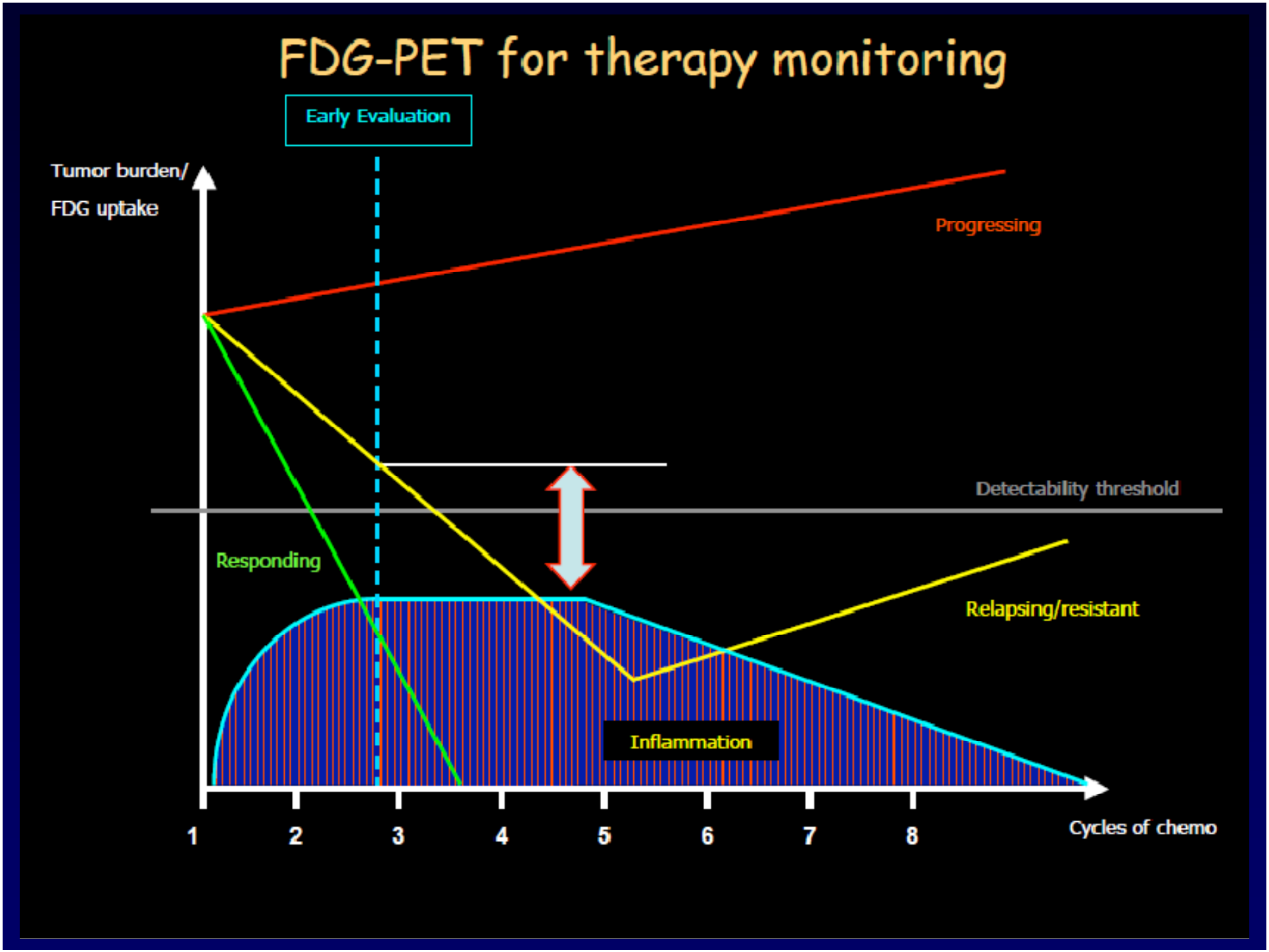
negative | MRU | positive

negative

The MRU definition, as the time goes by.




CUT-OFF
SENSITIVITY
> BKG
=MBPS
>MBPS
>Liver
0
1
2
3
4
FN: 10/210
< 5%
Juweid
Gallamini
Burrington
negative
MRU
positive
SPECIFICITY


FDG-PET for therapy monitoring
Early Evaluation
Tumor burden/
FDG uptake
Progressing
Detectability threshold
Responding
Relapsing/resistant
Inflammation
1
2
3
4
5
6
7
8
Cycles of chemo

Report on the First International Workshop on interim-PET scan in lymphoma

Authors: Michel Meignan [a]; Andrea Gallamini – This workshop was held at Deauville, France from April 3–4, 2009, under the auspices of the GELA.[b]; Corinne Haioun [c]

Leukemia and Lymphoma, 1029-2403, Volume 50, Issue 8, 2009, Pages 1257 – 1260

Because the use of interimPET to assess early response is increasing it is therefore necessary to standardize response criteria for the interim setting

The criteria should be simple, reproducible, easy to implement and relevant for prognosis

These criteria should be validated in a large cohort of patients

PET reporting
- the Deauville criteria

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 new sites of disease

International Validation Study (IVS)

The **primary endpoint**

- to measure overall Accuracy and Predictive Value of interim-PET scan in terms of 2-year failure-free survival

The **secondary endpoint** of the IVS are

- to propose easy and reproducible international rules for early PET interpretation during ABVD chemotherapy for Hodgkin's lymphoma
- to measure concordance rate of reviewers among the members of Central Review Panel

Indicazioni

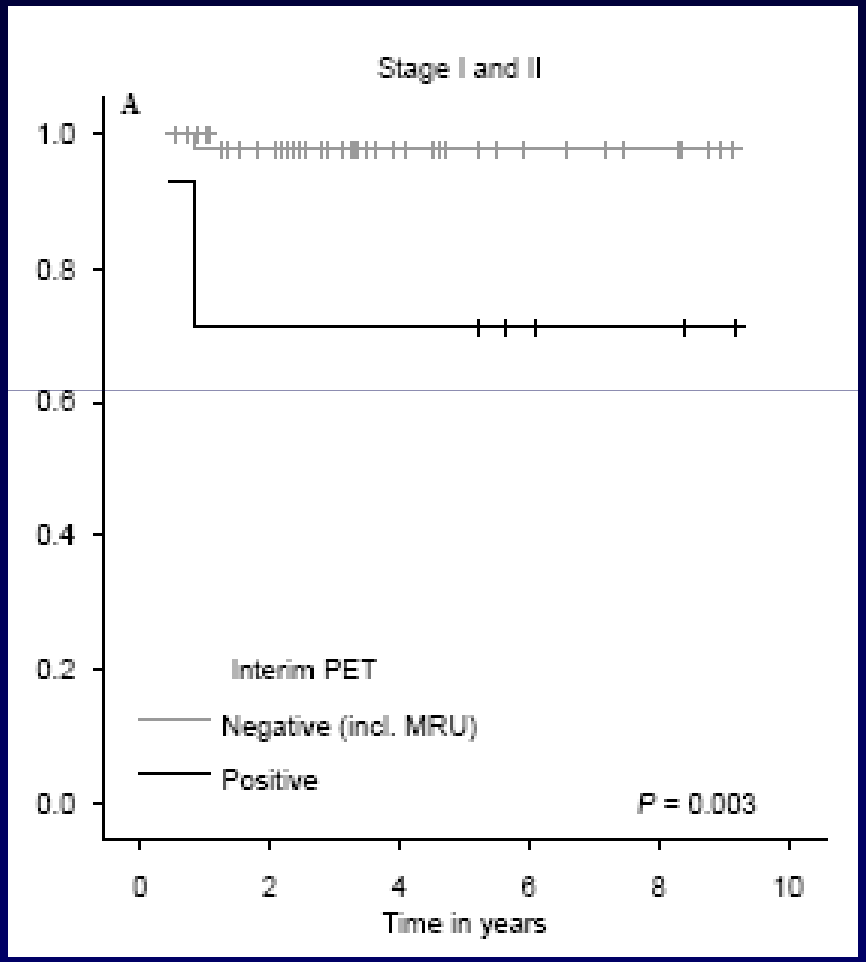
La PET/CT è uno strumento diagnostico estremamente importante che ha consentito una modificazione della strategia terapeutica nel linfoma di Hodgkin avanzato

I risultati della PET/CT sono ottimali quando si applicano criteri di lettura semplici, riproducibili e validati e quando esista una buona collaborazione e una reciproca comprensione tra Medico Nucleare ed Ematologo

La PET/CT non può comunque riflettere completamente la complessità biologica della malattia di Hodgkin per cui esisteranno sempre dei casi in cui i risultati clinici potranno essere difformi dalle dalle previsioni fornite dalla PET

Prognostic value of PET after 2-3 cycles CT in early stage HL (PFS)

- 57 stage I and II patients
- 42/57 had IF RT after CT (mostly ABVD)
- 1/50 PET- relapsed
- 2/7 PET + relapsed



Hutchings et al. Ann Oncol 16: 1160-8, 2005

Intensive CT for Ga/PET+ lesions after 2 cycles standard CT

- Israeli study: Unfavorable early stage or standard risk advanced stage (IPS ≤ 2): 2 cycles standard-dose CT (BEACOPP)
  - Ga/PET - $\rightarrow$ 4 cycles standard dose BEACOPP
  - Ga/PET + $\rightarrow$ 4 cycles escalated BEACOPP
- 69 pts. 5-yr. EFS 84%, OS 90%
  - No difference between cycle 2 Ga/PET – or +

Dann et al. JCO 109: 905-9, 2007

Stage I and II Hodgkin Lymphoma

Intergroup Studies

CALGB 50604 (non-bulky disease)

AVBD x 2 cycles → PET scan

- PET- → 2 more ABVD cycles
- PET+ → 2 cycles escalated BEACOPP + IF RT

CALGB 50801 (bulky disease)

ABVD x 2 cycles → PET scan

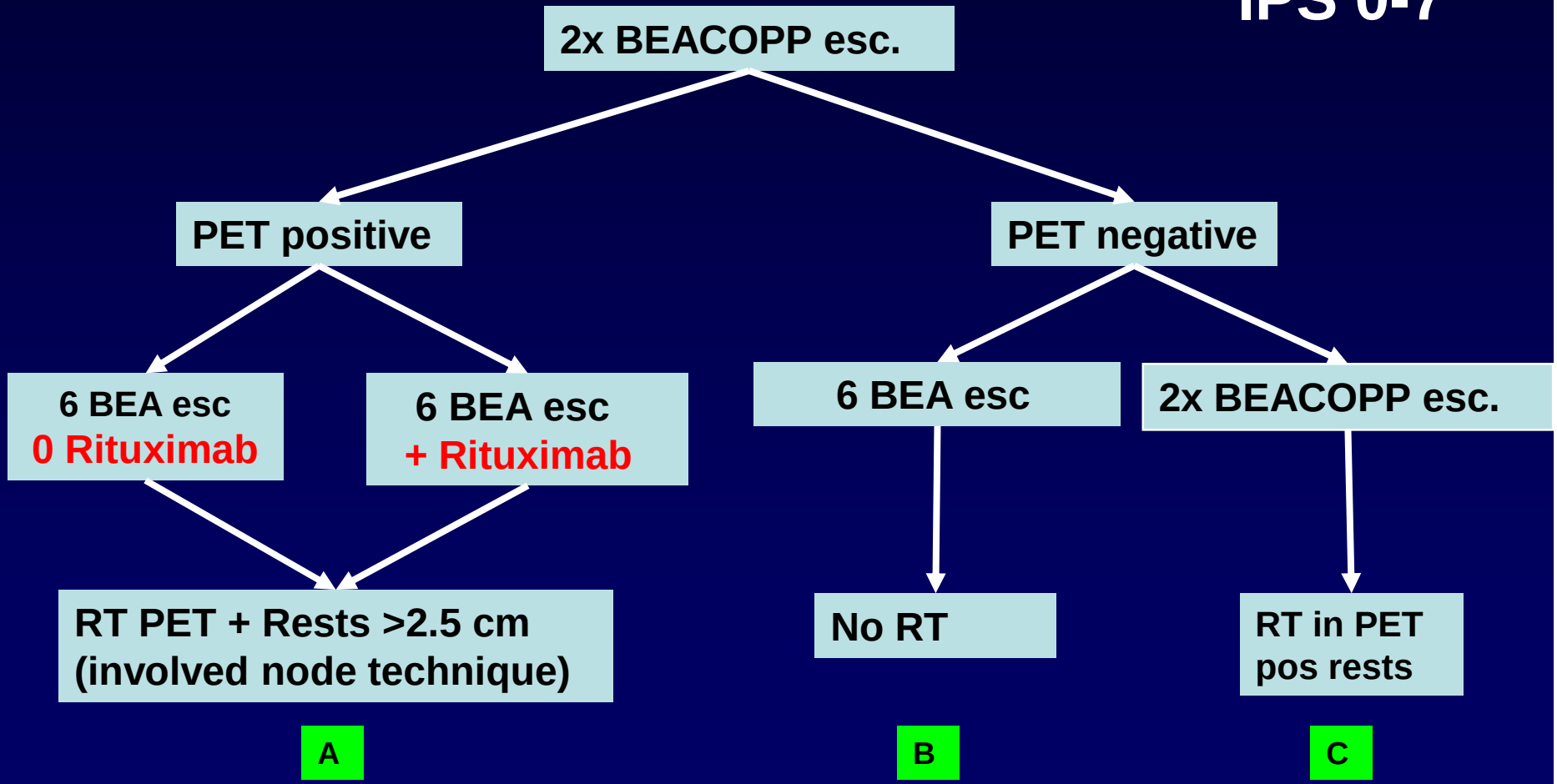
- PET - → 4 more ABVD cycles
- PET+ → 4 cycles escalated BEACOPP + IF RT

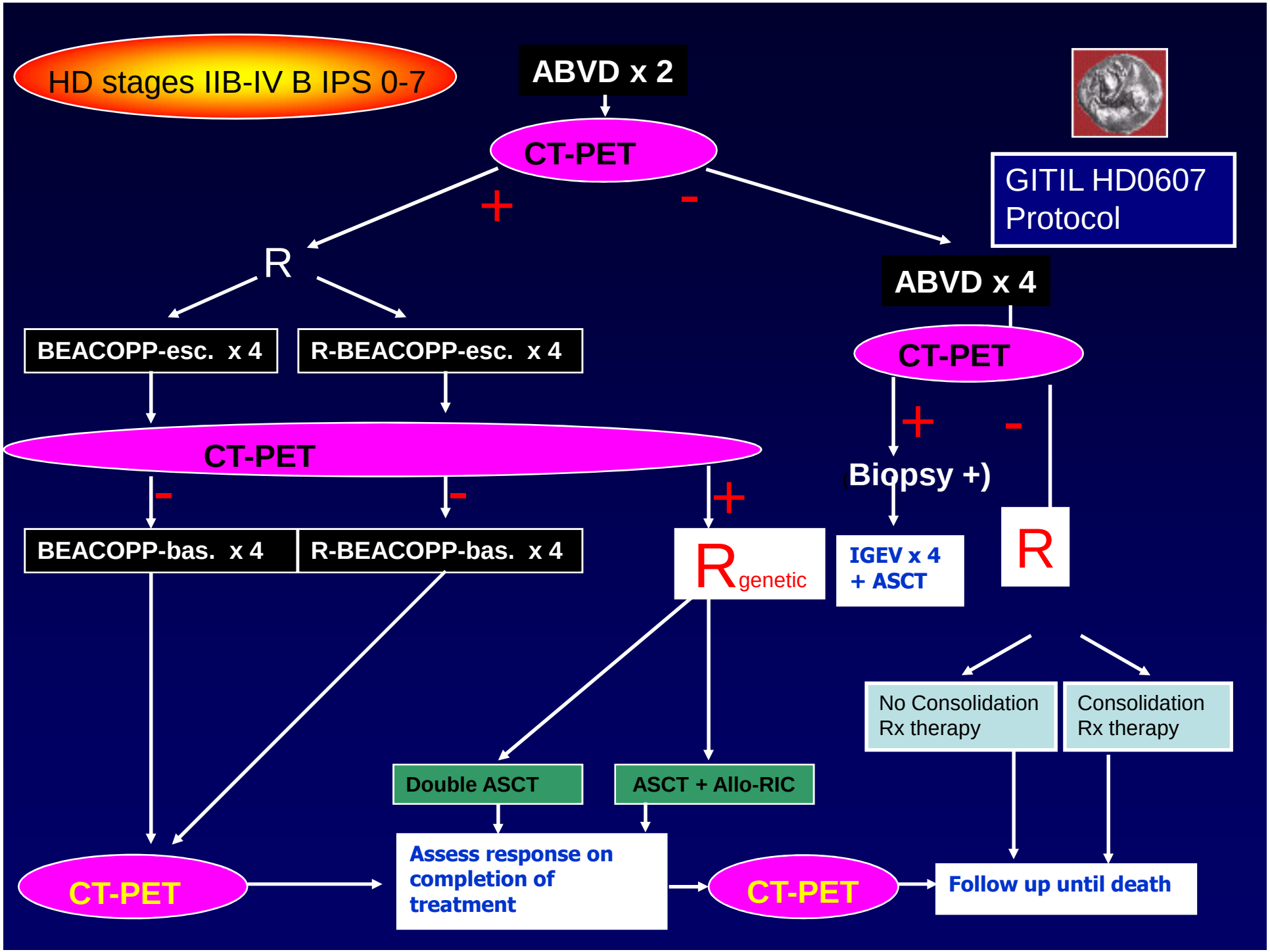
New Treatment Strategies for Advanced Hodgkin Lymphoma

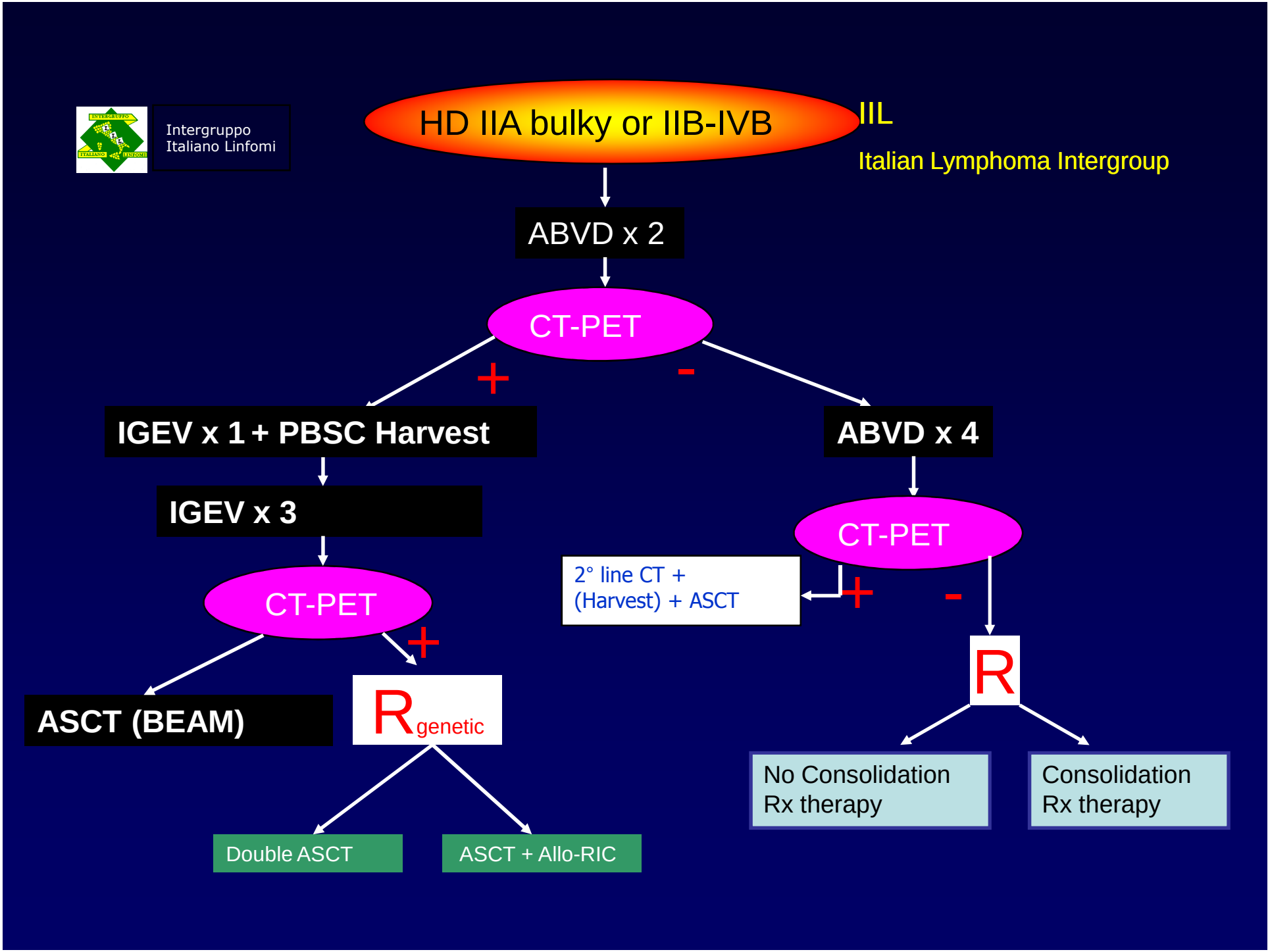
Global Studies
Ongoing or to Be Launched Soon!!

Future GHSG Study: HD18 Advanced HL

IPS 0-7




HD stages IIB-IV B IPS 0-7
ABVD x 2
CT-PET
+
-
R
BEACOPP-esc. x 4
R-BEACOPP-esc. x 4
CT-PET
-
-
BEACOPP-bas. x 4
R-BEACOPP-bas. x 4
+
Rgenetic
GITIL HD0607 Protocol
ABVD x 4
CT-PET
+
-
Biopsy +)
IGEV x 4 + ASCT
R
No Consolidation Rx therapy
Consolidation Rx therapy
Double ASCT
ASCT + Allo-RIC
CT-PET
Assess response on completion of treatment
CT-PET
Follow up until death


Intergruppo
Italiano Linfomi
HD IIA bulky or IIB-IVB
IIL
Italian Lymphoma Intergroup
ABVD x 2
CT-PET
+
-
IGEV x 1 + PBSC Harvest
ABVD x 4
IGEV x 3
CT-PET
2° line CT +
(Harvest) + ASCT
+
-
CT-PET
+
R
ASCT (BEAM)
R genetic
No Consolidation
Rx therapy
Consolidation
Rx therapy
Double ASCT
ASCT + Allo-RIC

USA- Cooperative Group Trial
Advanced Hodgkin Lymphoma

IPS: 0-7

2 ABVD→PET

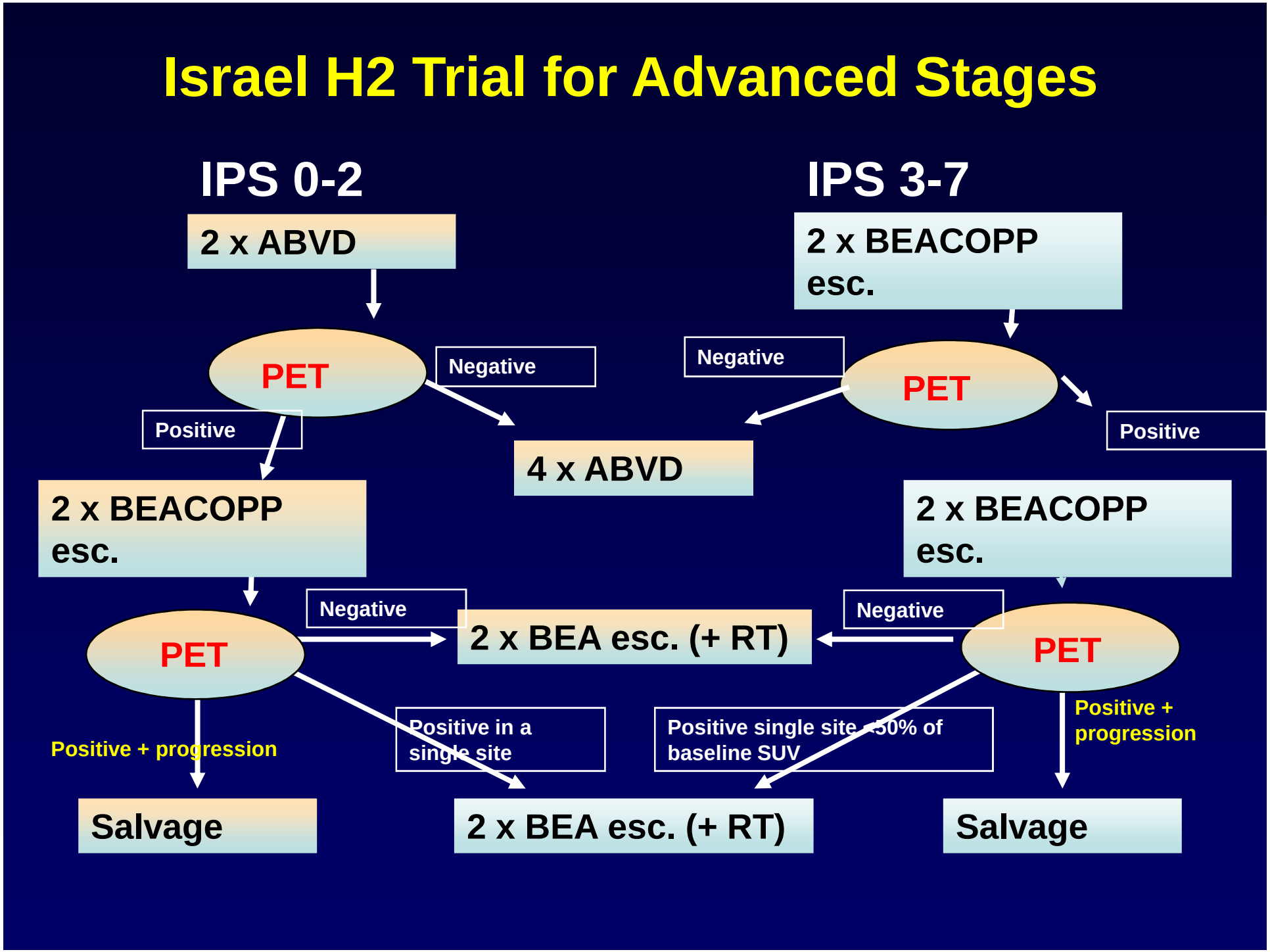
- Neg→ ABVD x 4 no RT
- Pos→ BEACOPP esc x 6+IFRT??

Caveat: BEACOPPesc 8 weeks too late!!

Better for IPS > 3 RFs: 2 esc BEACOPP→PET neg:6 ABVD

→ PET pos:4 BEAesc

Israel H2 Trial for Advanced Stages



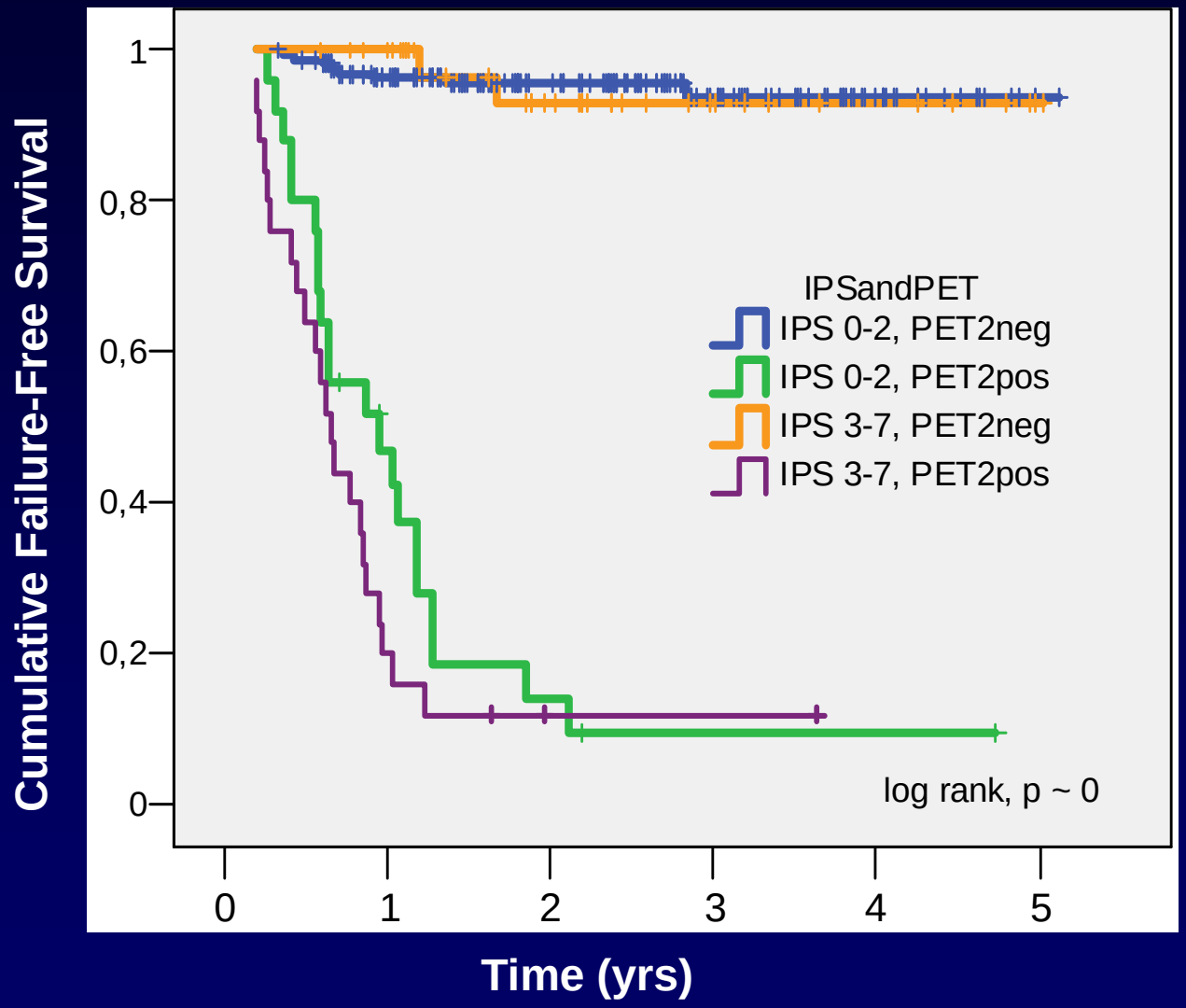
Open Questions

- How to identify the good and bad risk groups at diagnosis?

Open Questions:

- Does PET discriminate between a good and a bad micro-environment in Hodgkin lymphoma?
- Do we need the IPS for risk adaptation?

260 Patients – PET vs. IPS



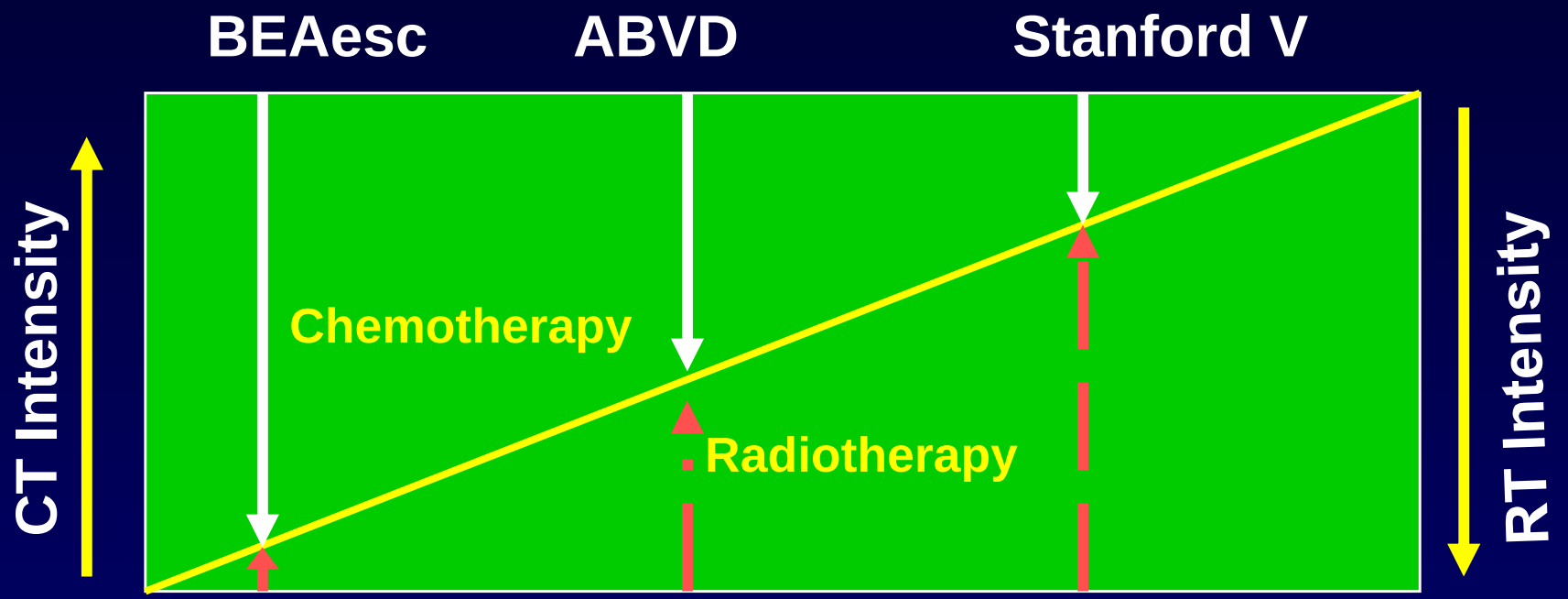
Reprinted with permission from the American Society of Clinical Oncology. Gallamini et al. JCO. 2007.

Do we need

Consolidative Radiation

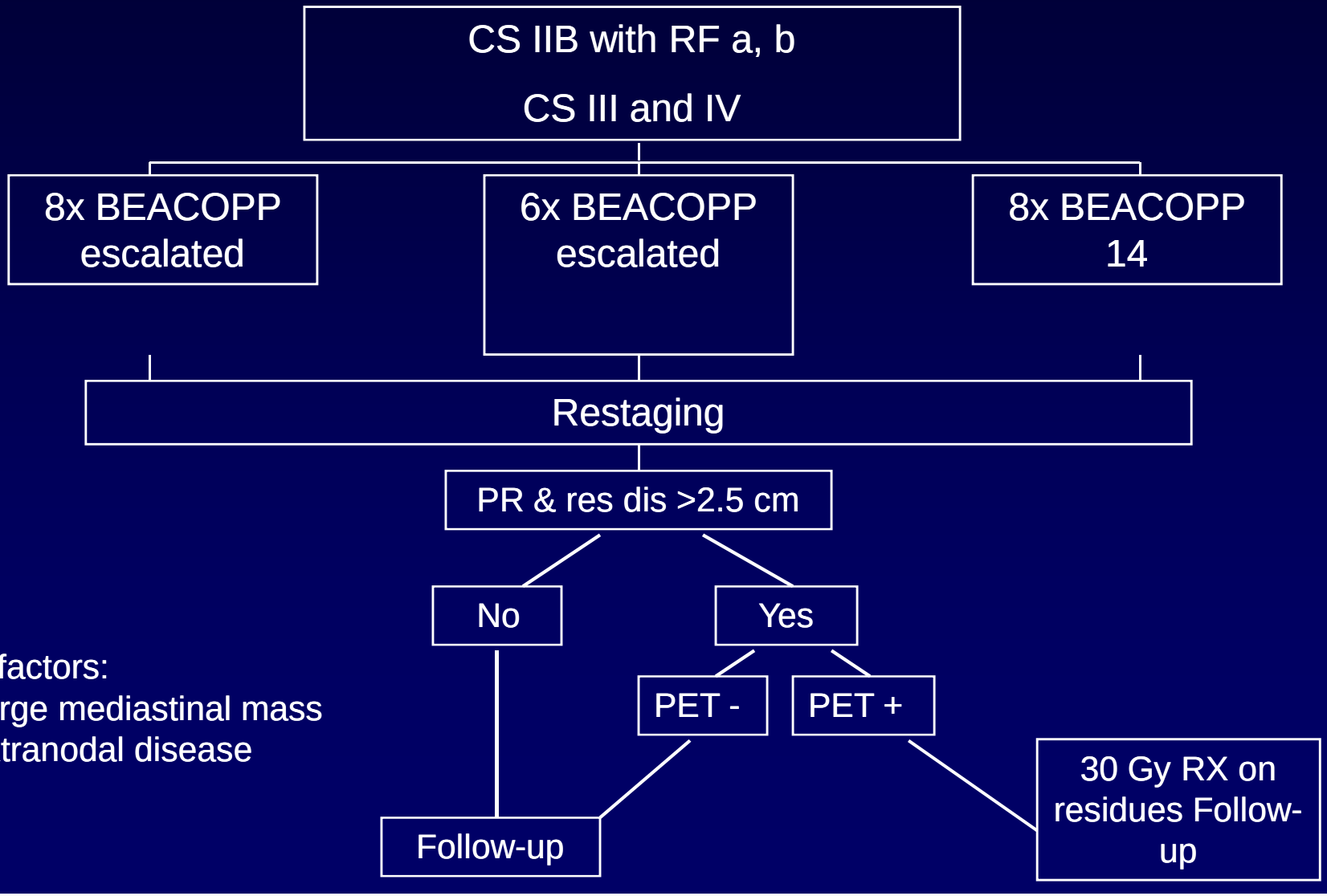
after effective Chemotherapy??

Advanced HL: How Much Radiation With:



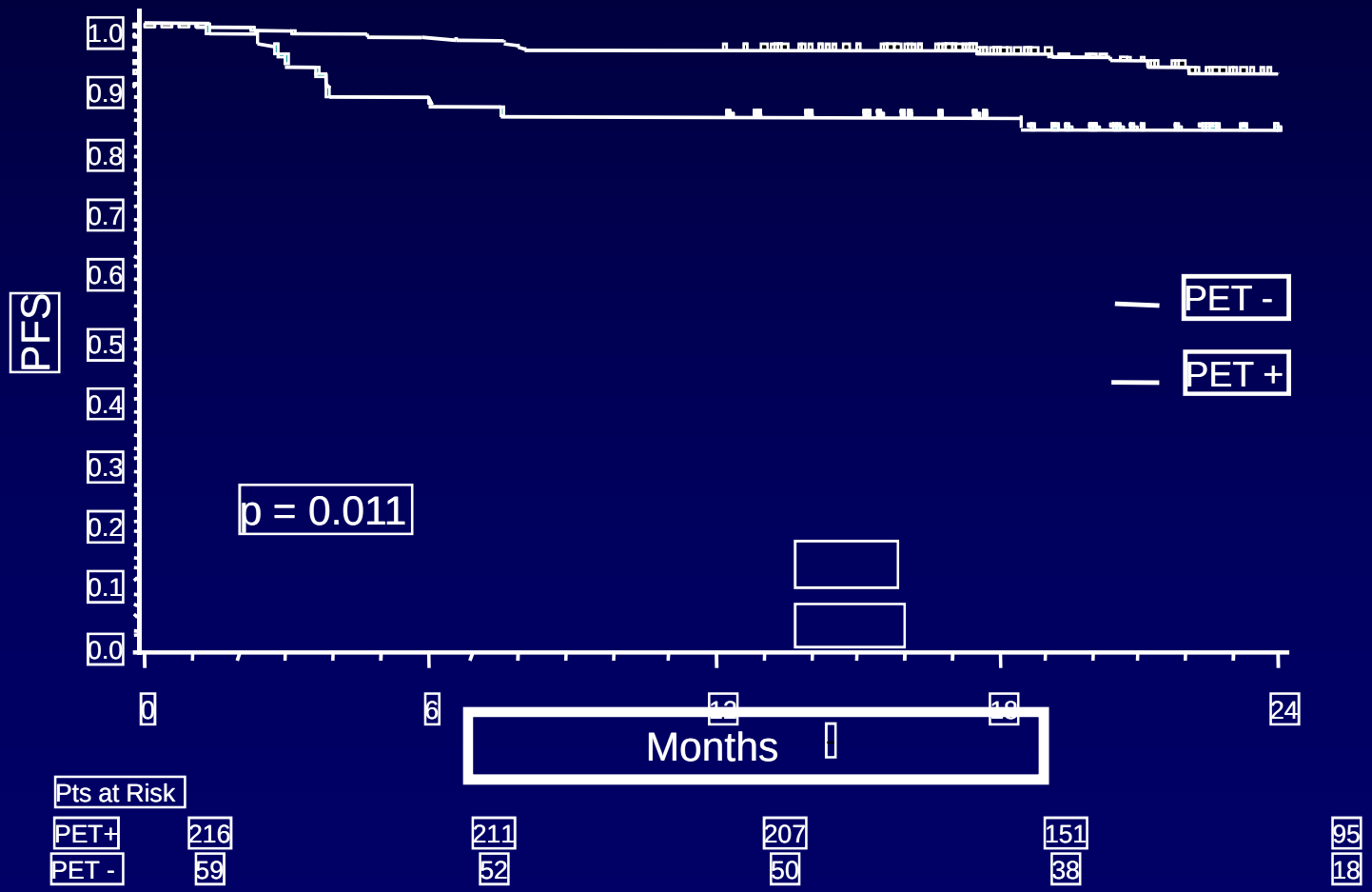
Need for RT: (12%) (45%) (90%)

GHSG ongoing study for advanced stages (HD15)



HD15-PET trial for advanced-stage HL

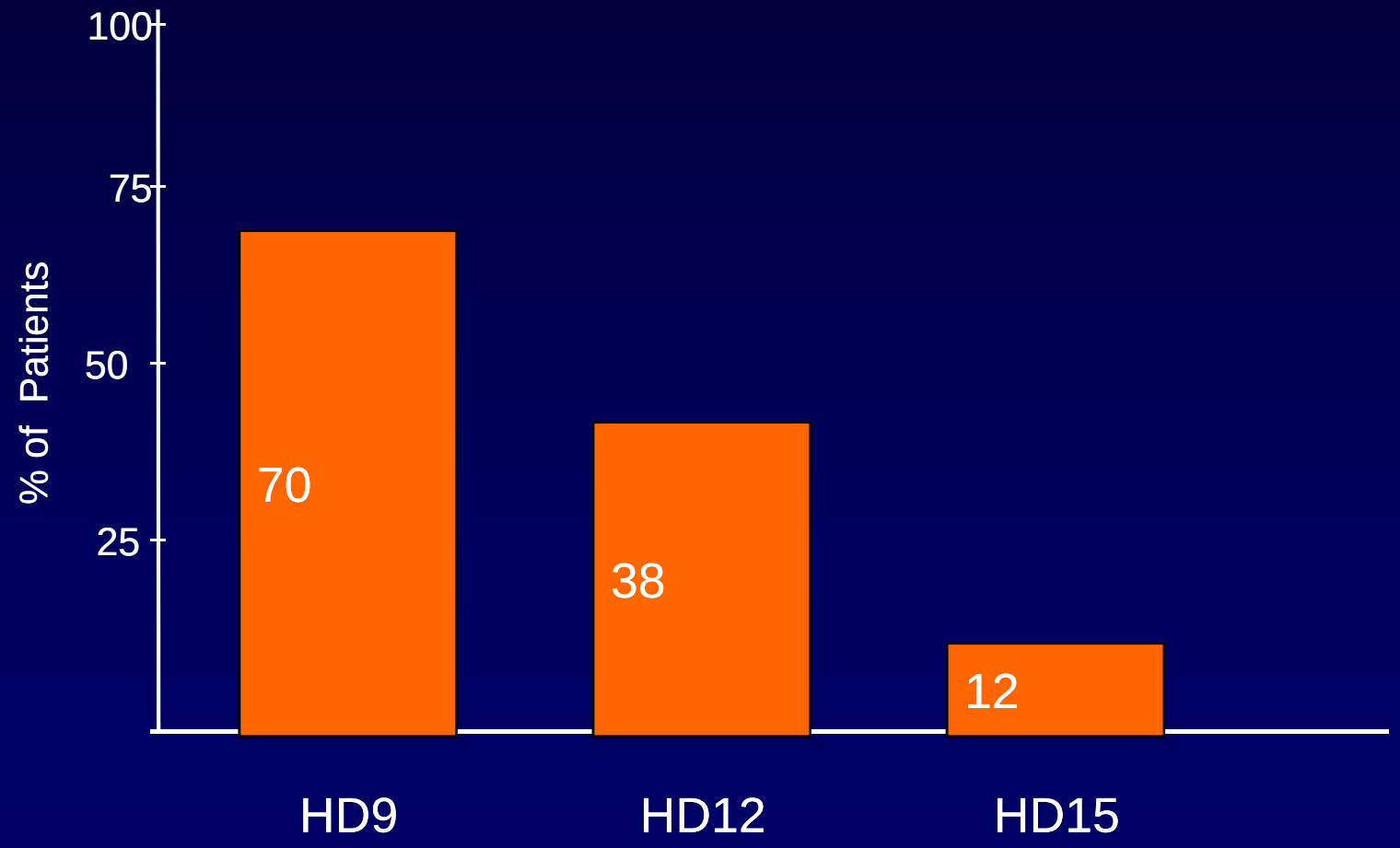
PFS in pts with PET^{+} and PET^{-} residues (n=275)



GHSG 2007

Additional RT after chemo in advanced stages

GHSG studies HD9, HD12 and HD15 (% of all pts)



Symposium article

Annals of Oncology 13 (Supplement 1): 75–78, 2002
DOI: 10.1093/annonc/mdf615

The disappearance of prognostic factors in Hodgkin's disease

D. Hasenclever*

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…Prognostic factors gradually loose their predictive power as treatment is successfully adapted to disease burden….

December 2002

Five years later

…the re-appearance of prognostic factor in Hodgkin's lymphoma….

Interim PET emerges as the single most important tool for planning of risk-adapted treatment in advanced HL.

August 2007

…The re-appearance of prognostic factors in Hodgkin's lymphoma

Next five years….

…to reduce the toxic effects of the therapy