Incorporating PET into lymphoma trials: U.S. experience

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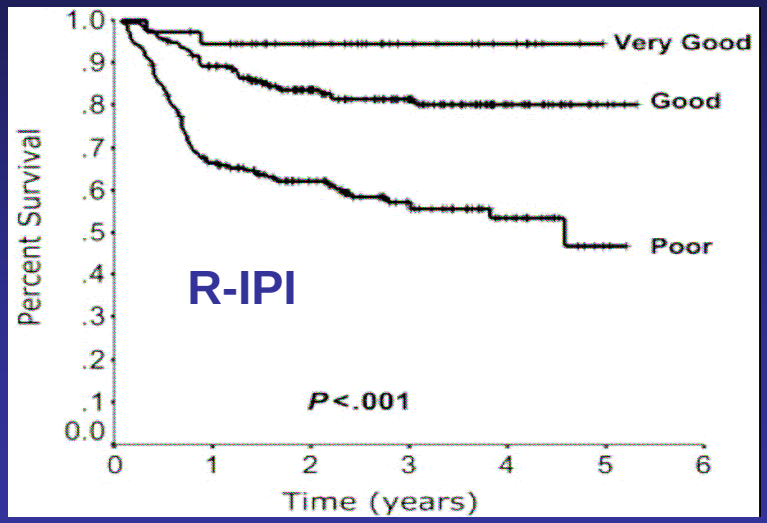
Objectives

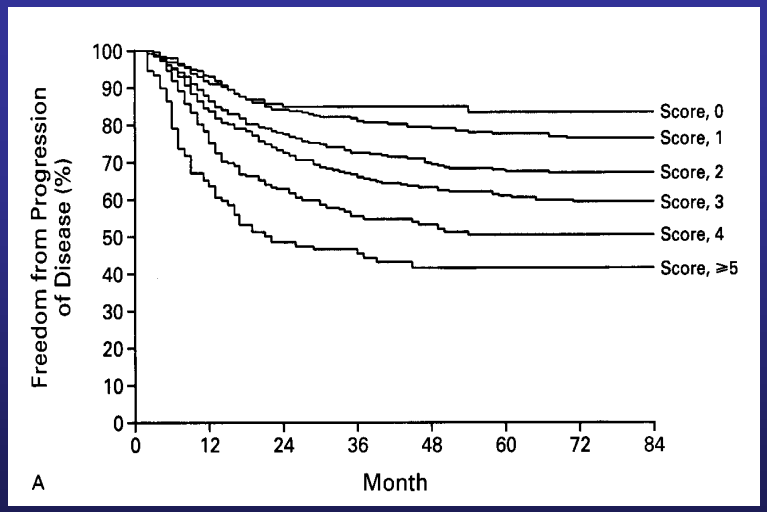
- Describe integration of PET in response-adapted lymphoma trials and other trials (focus on U.S. experience)
- Consider options for managing post-therapy PET results on clinical trials

Traditional risk stratification

- IPI (aggressive NHL)[a,b]
  - **Age > 60**
  - **ECOG performance status ≥ 2**
  - **High LDH**
  - **Stage III or IV**
  - **> 1 extranodal site**

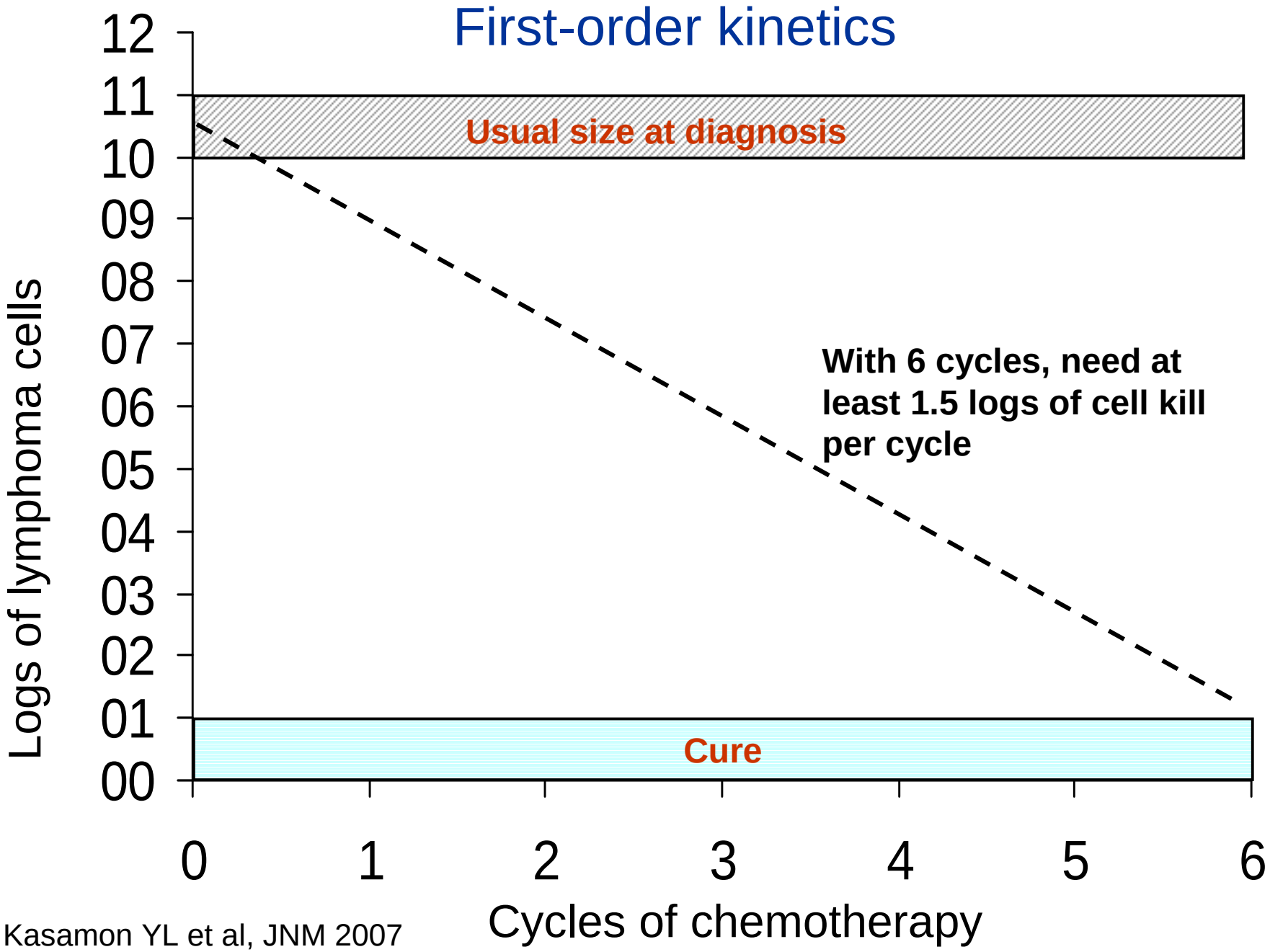


- IPS (advanced Hodgkin's)[c]
  - **Age ≥ 45**
  - **Stage IV**
  - **Male**
  - **Albumin < 4 g/dl**
  - **Hemoglobin < 10.5 g/dl**
  - **WBC > 15,000/mm³**
  - **Lymphopenia**

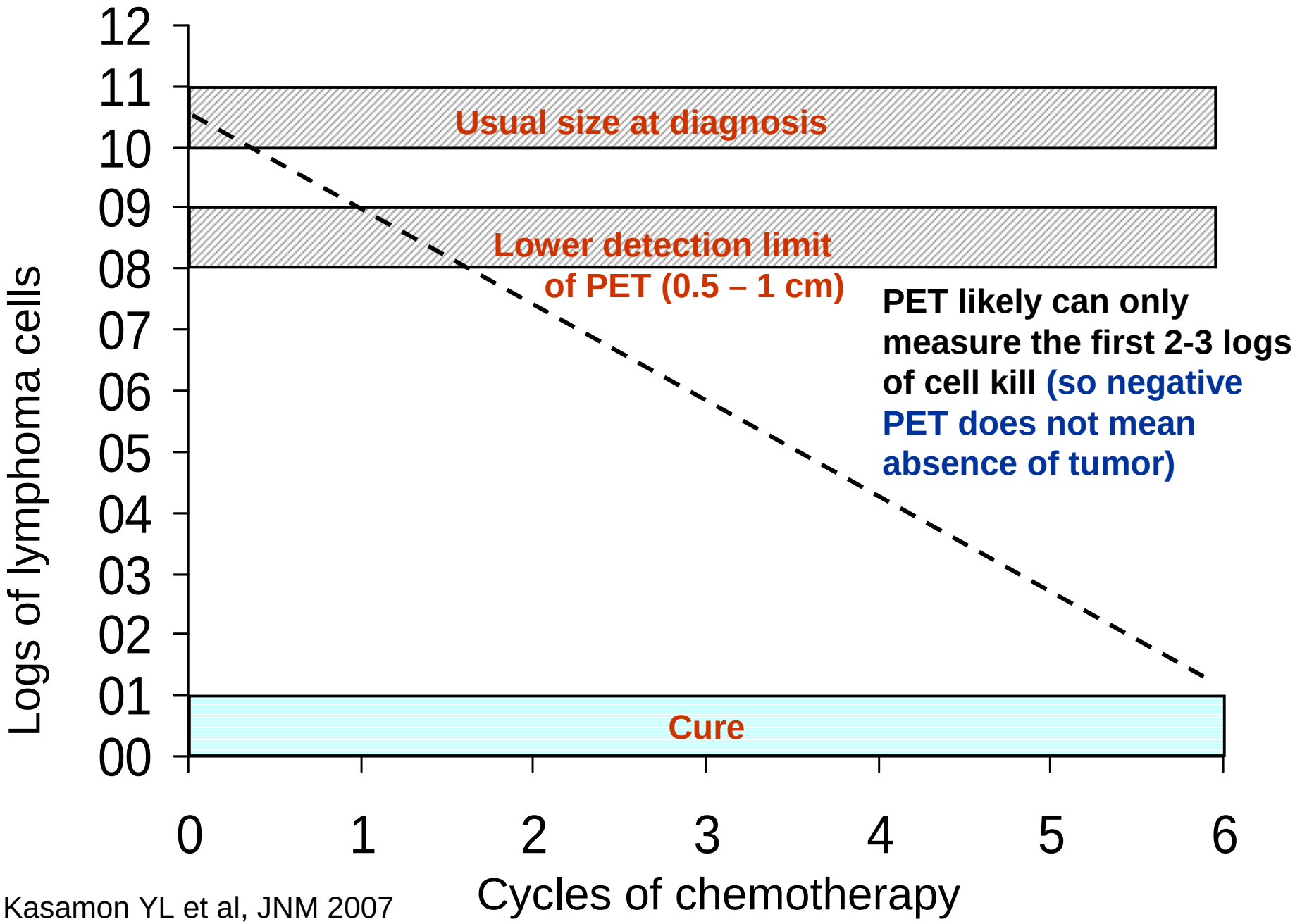


a) NEJM 1993; 329: 987-994 b) Sehn LH et al, Blood 2007;109:1857-1861, Fig 4; c) Hasenclever, Diehl. NEJM 1998;339:1506-14, Fig 1A.

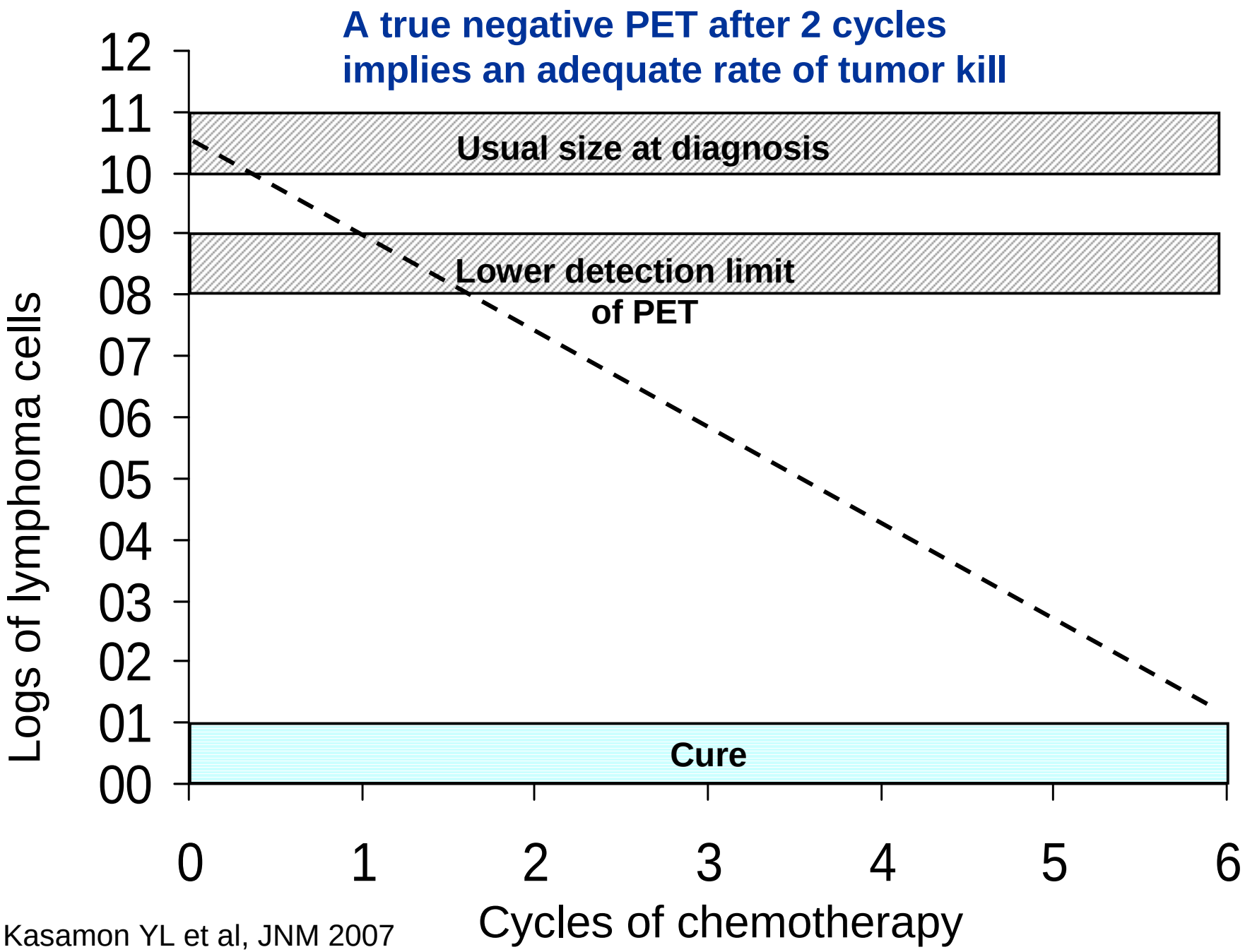
- Prognosis depends not only on whether PET becomes negative, but how quickly this occurs
- In thinking about lymphoma trials, what is the biologic basis of this observation?



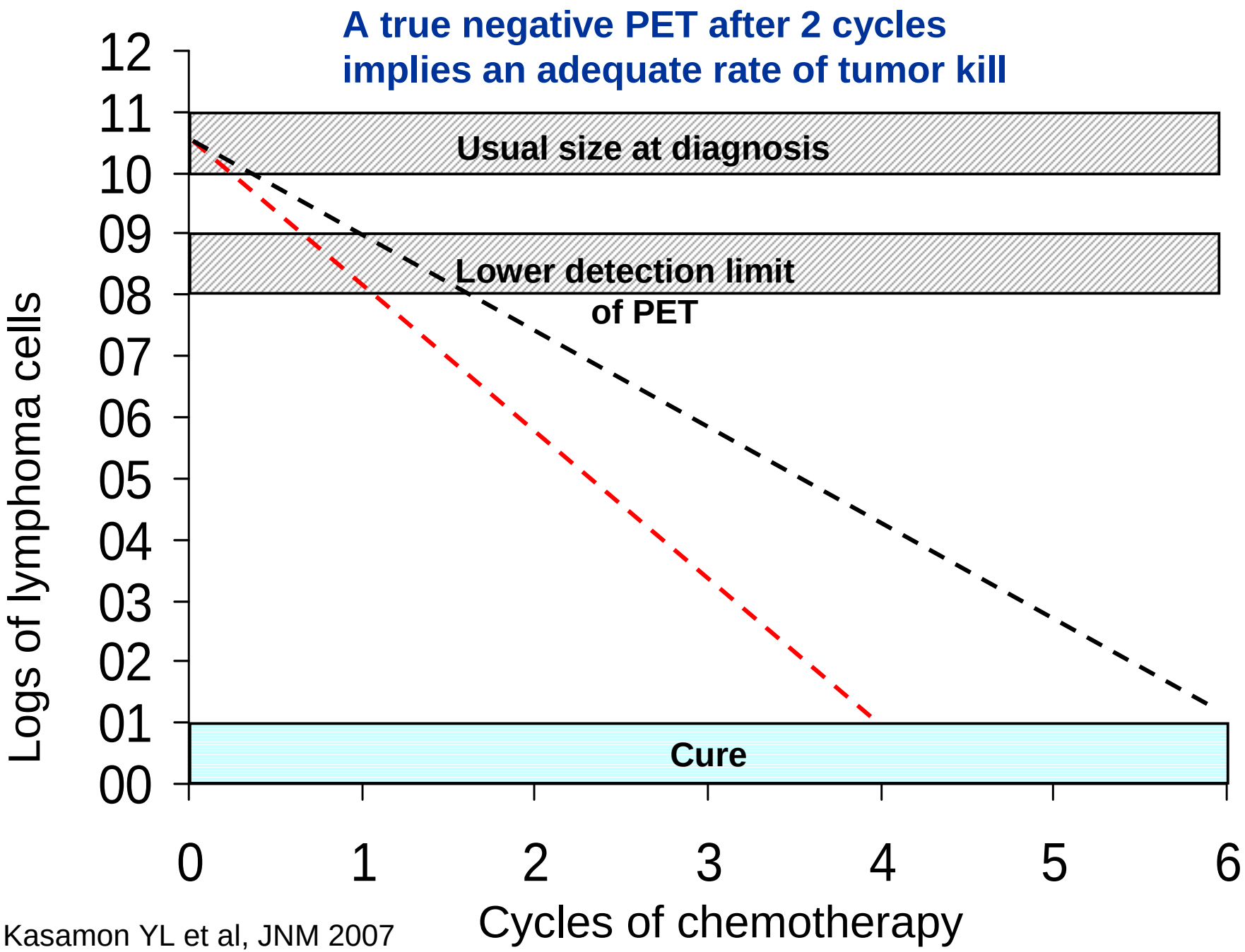
Kasamon YL et al, JNM 2007



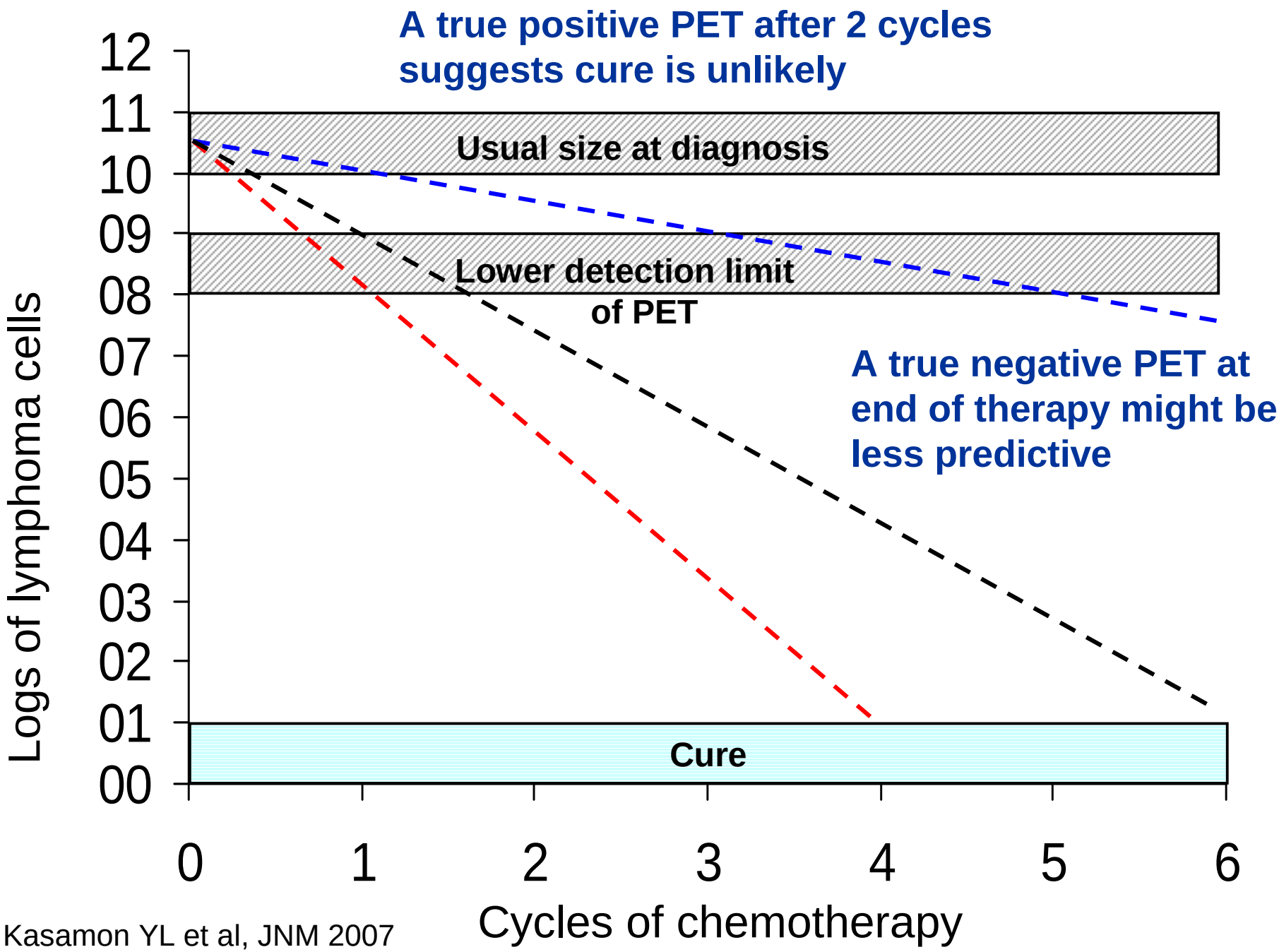
Kasamon YL et al, JNM 2007



Kasamon YL et al, JNM 2007



Kasamon YL et al, JNM 2007



Kasamon YL et al, JNM 2007

Why might midtreatment PET be superior to posttreatment?

Early PET result implies a certain rate of tumor kill

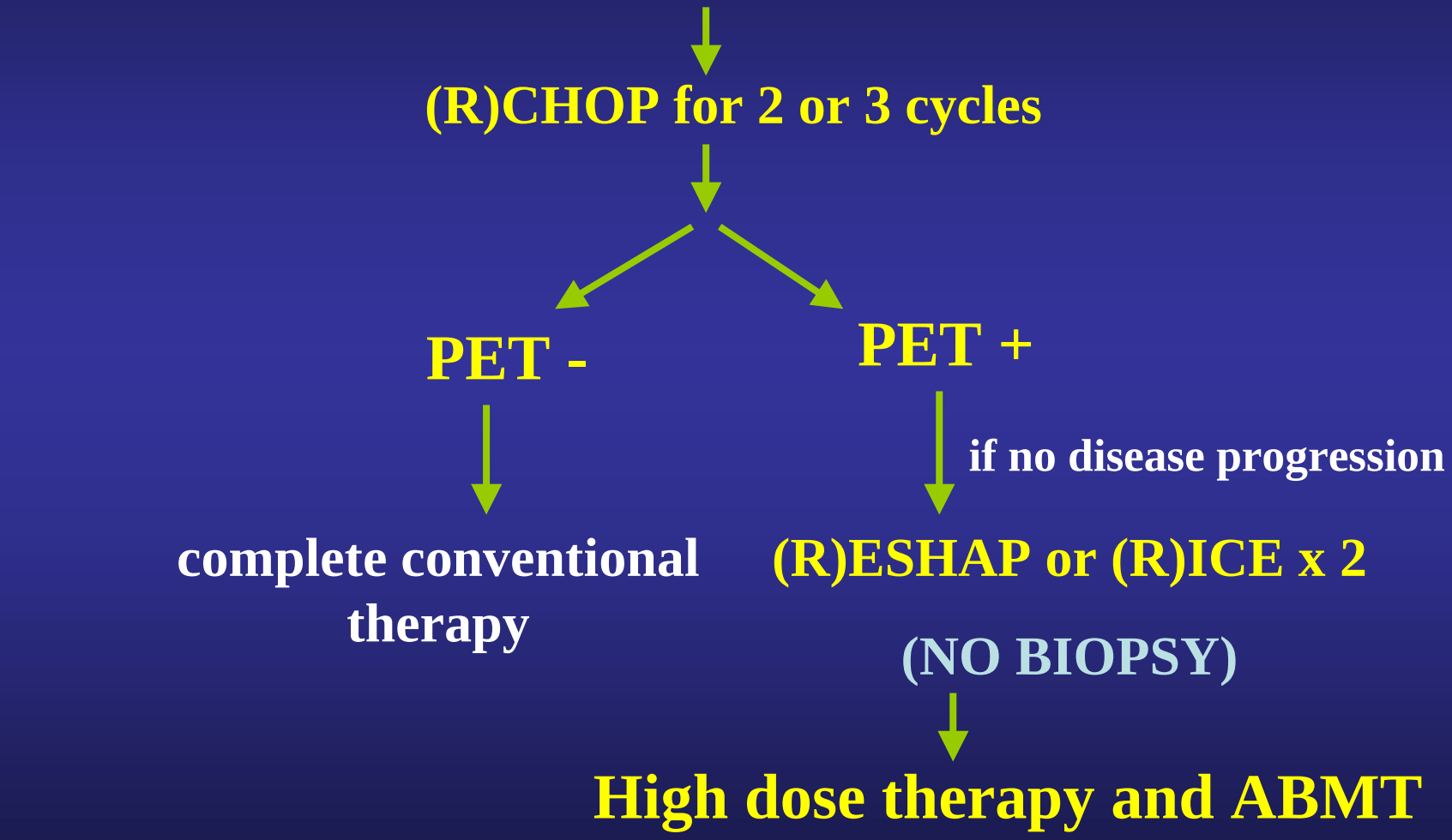
Considerations

- Recently, more variability in outcome than appreciated in previous series
- Subsets with positive interim scans do well – not as clear-cut as previously appeared
- Concern about false positives
- Variability with PET criteria and reproducibility of reads

Response-adapted therapy

- Changing chemotherapy based on early PET
- Using PET to guide # of cycles and to tailor radiation

Johns Hopkins study (2004-2007)



Kasamon YL et al, BBMT 2009;15:242

Johns Hopkins PET assessment

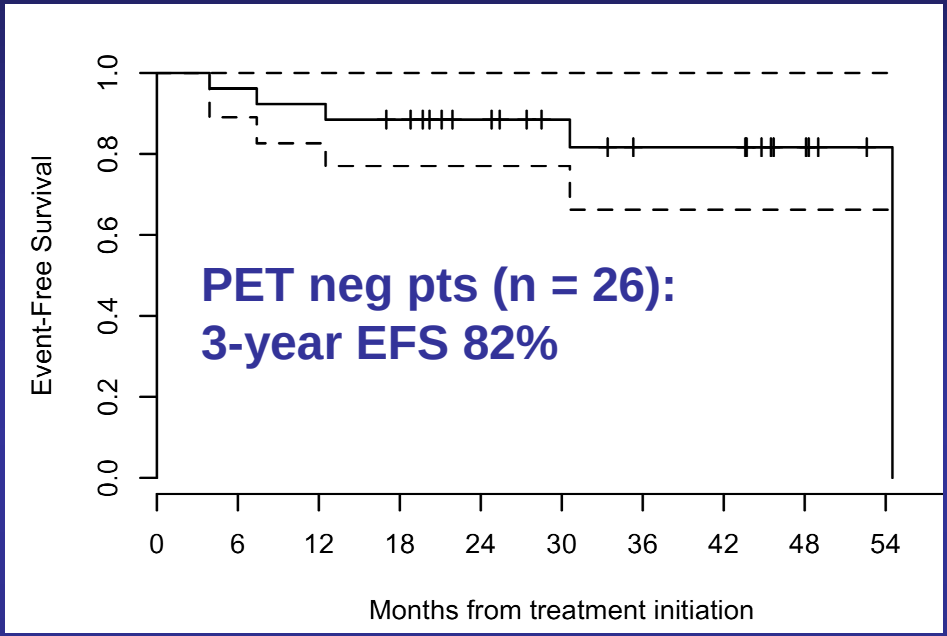
NEGATIVE

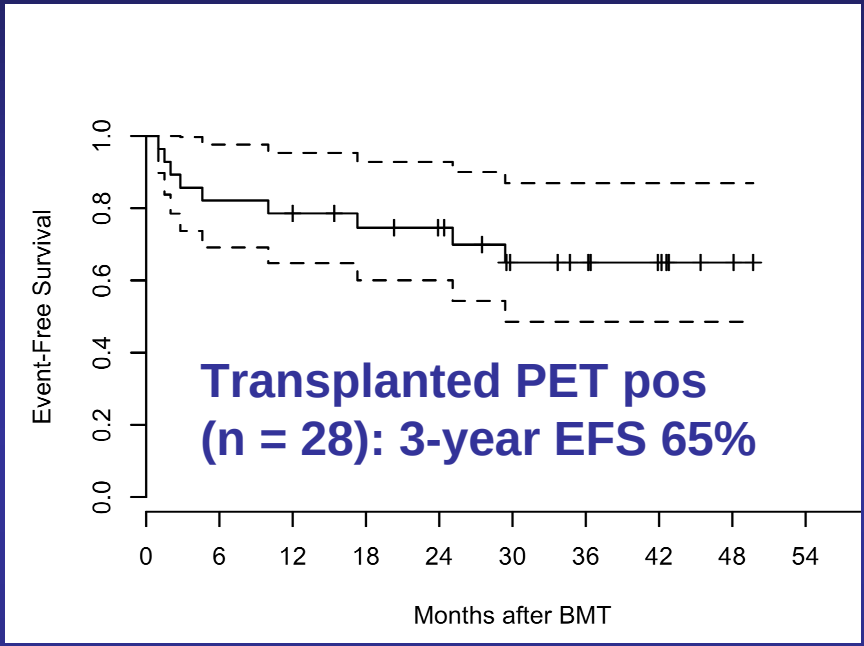
- 0 no abnormal activity (tumor cold)
- 1+ minimal activity (tumor < mediastinal blood pool)
- 2+ equivocal (tumor = or near blood pool)

POSITIVE

- 3+ moderate activity (tumor clearly > blood pool)
- 4+ strong activity (tumor much greater than blood pool)

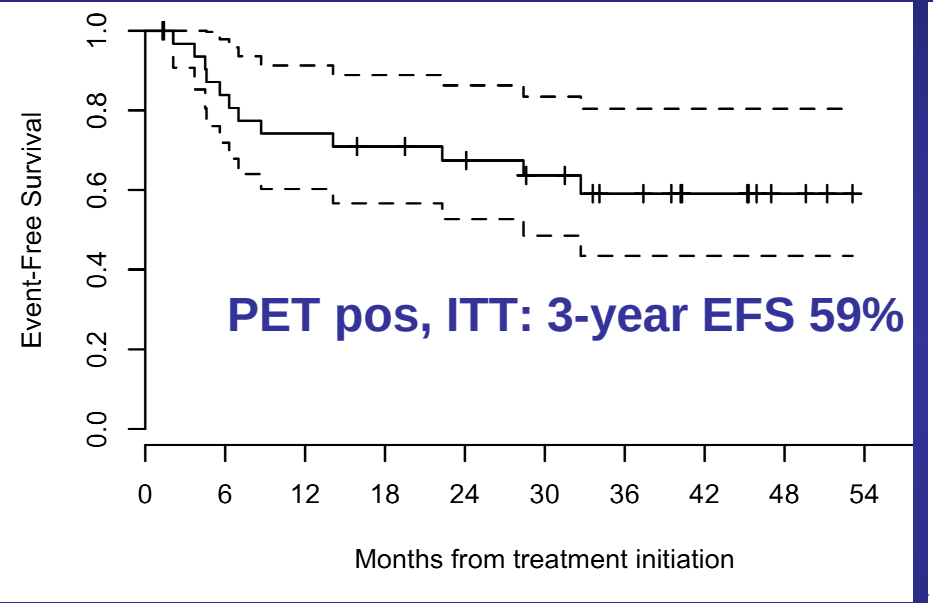
JHH trial: EFS by interim PET

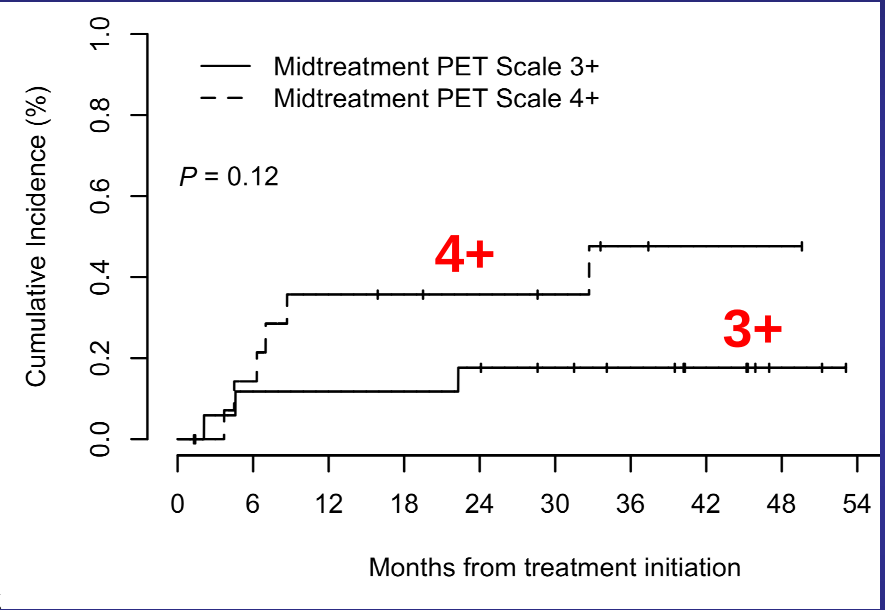




Kasamon YL et al, BBMT 2009;15:242-248

JHH trial: disease outcomes and impact of PET scale





All PET pos pts (n = 33): EFS by intention to treat

(3 pts with early progression, 2 consent withdrawals)

All PET pos pts: cumulative incidence of relapse/progression

Kasamon YL et al, BBMT 2009;15:242-248

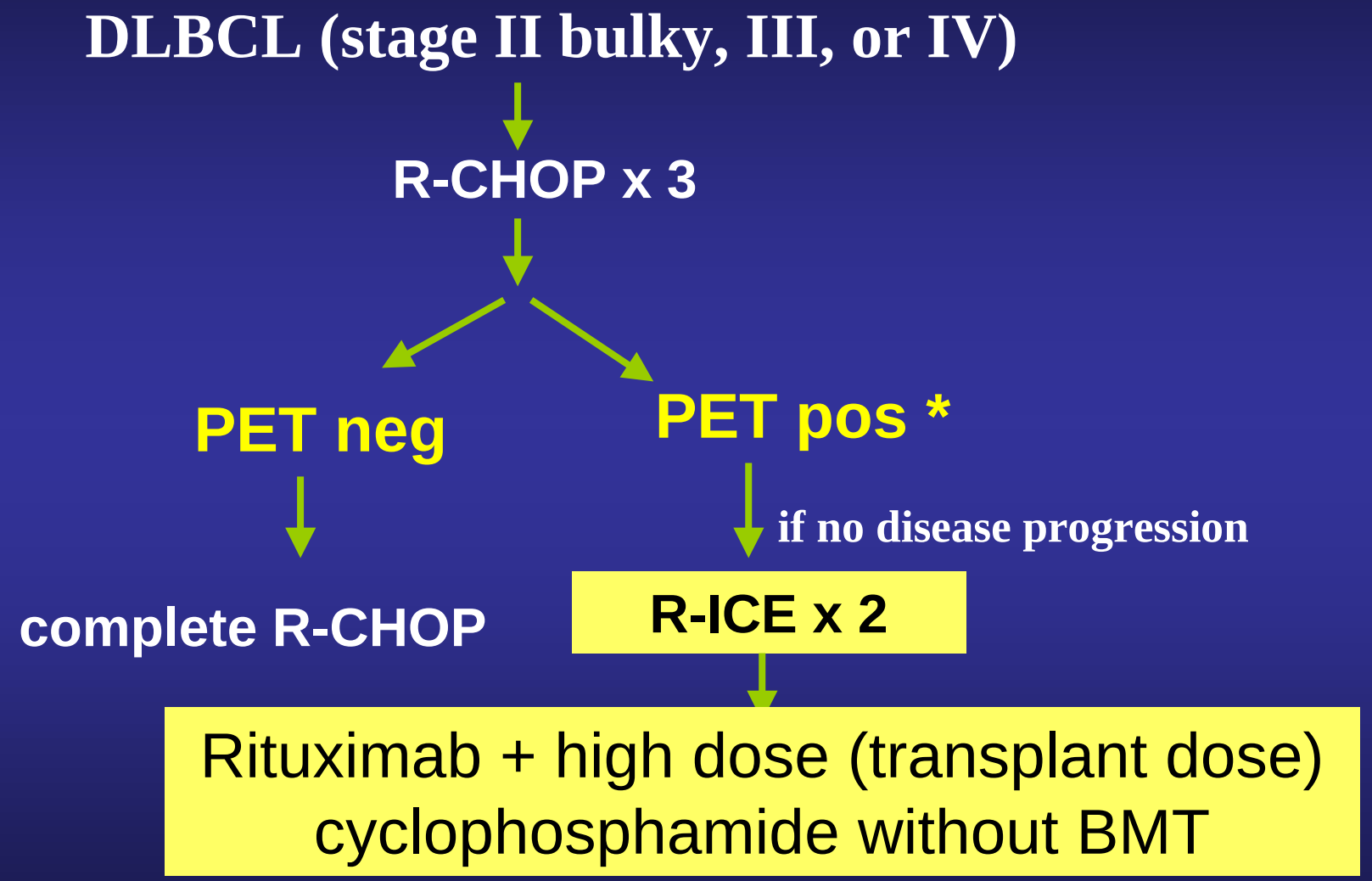
IPI and midtreatment PET

- No association between interim PET and IPI (0-2 vs 3-5); P = 0.99
- If mid PET pos, tendency toward greater relapse risk with IPI ≥ 3 (HR 3.6, P = 0.07)

Johns Hopkins experience

- Early treatment intensification on basis of midtreatment PET is feasible in most pts
- Advantages of this approach, compared with conventional therapy, remain to be defined
- Relative contribution of BMT, compared with platinum- and etoposide-based salvage regimens, is uncertain
- Gradations of FDG uptake may be prognostic

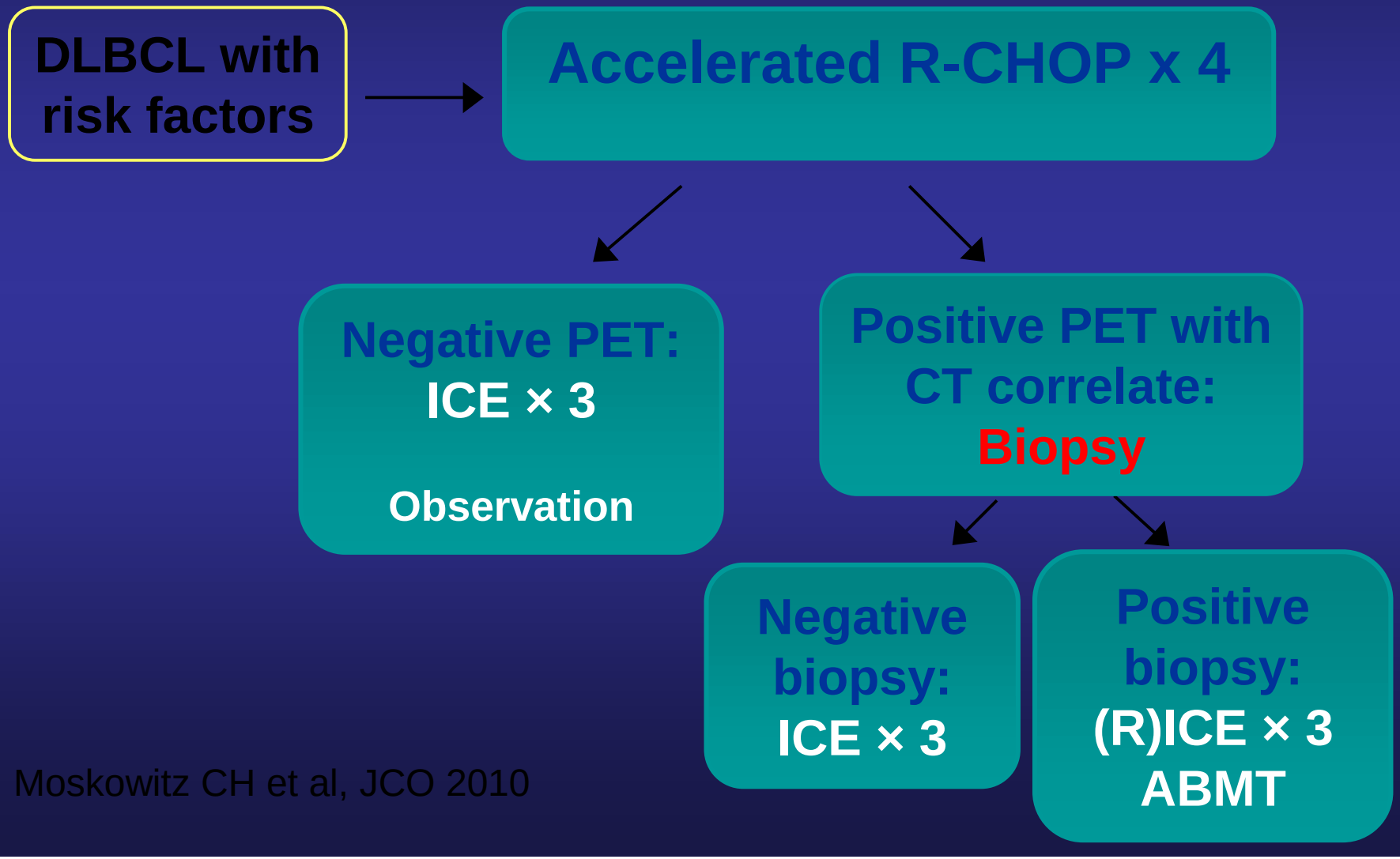
Ongoing Johns Hopkins study



* 5-point scale with blood pool and liver references

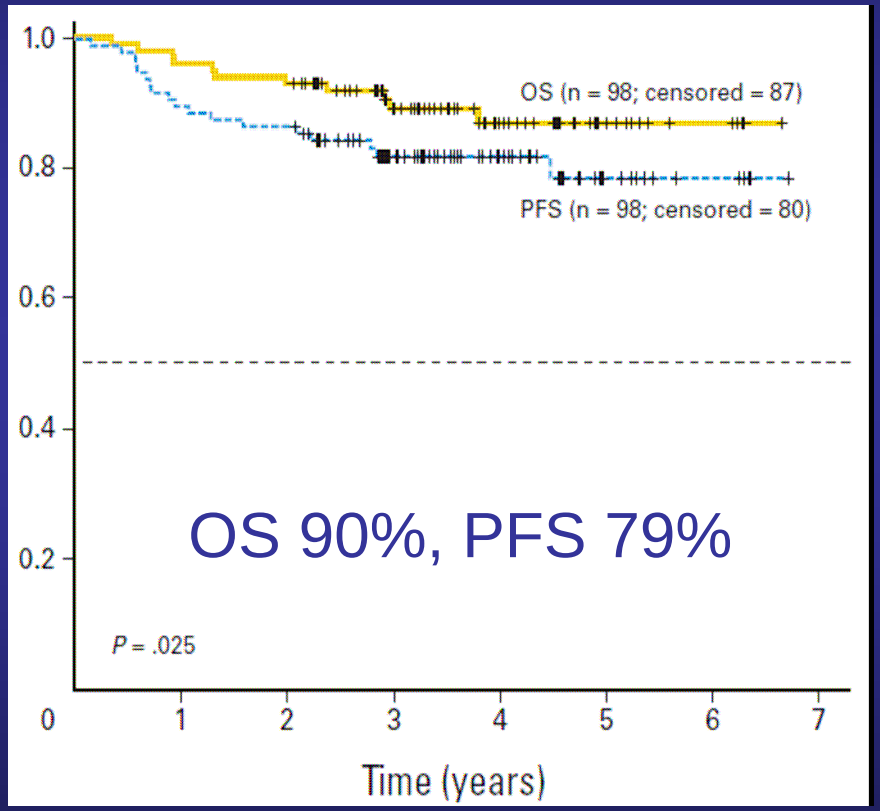
PI: Lode Swinnen

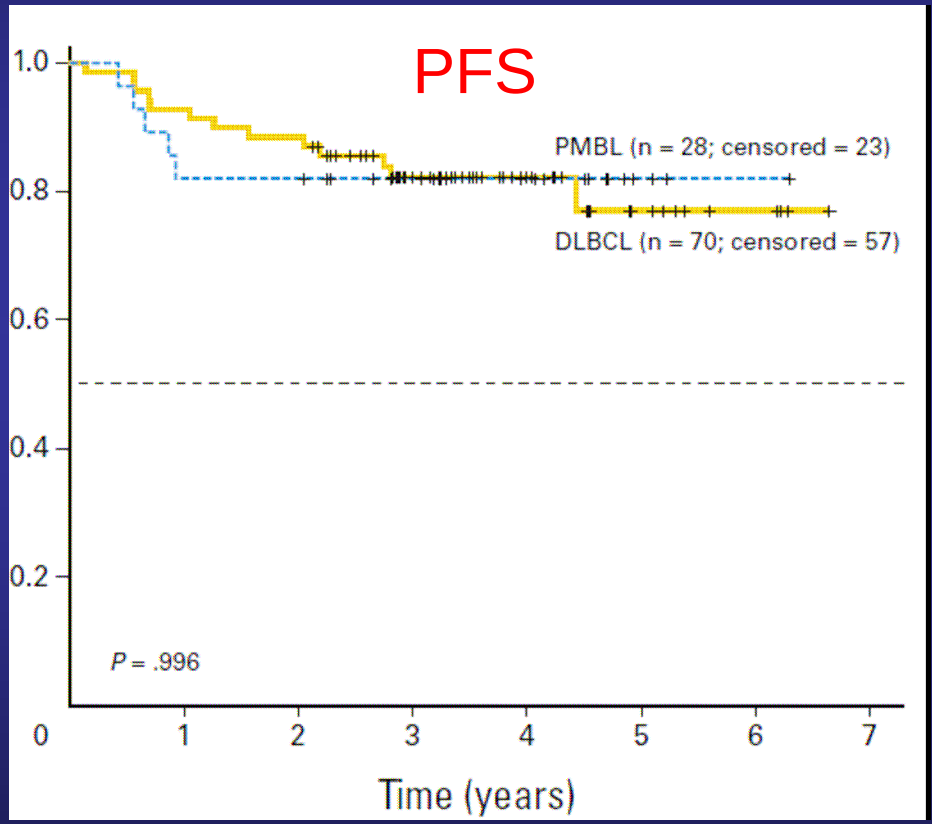
MSKCC: Risk-Adapted Therapy for DLBCL



Moskowitz CH et al, JCO 2010

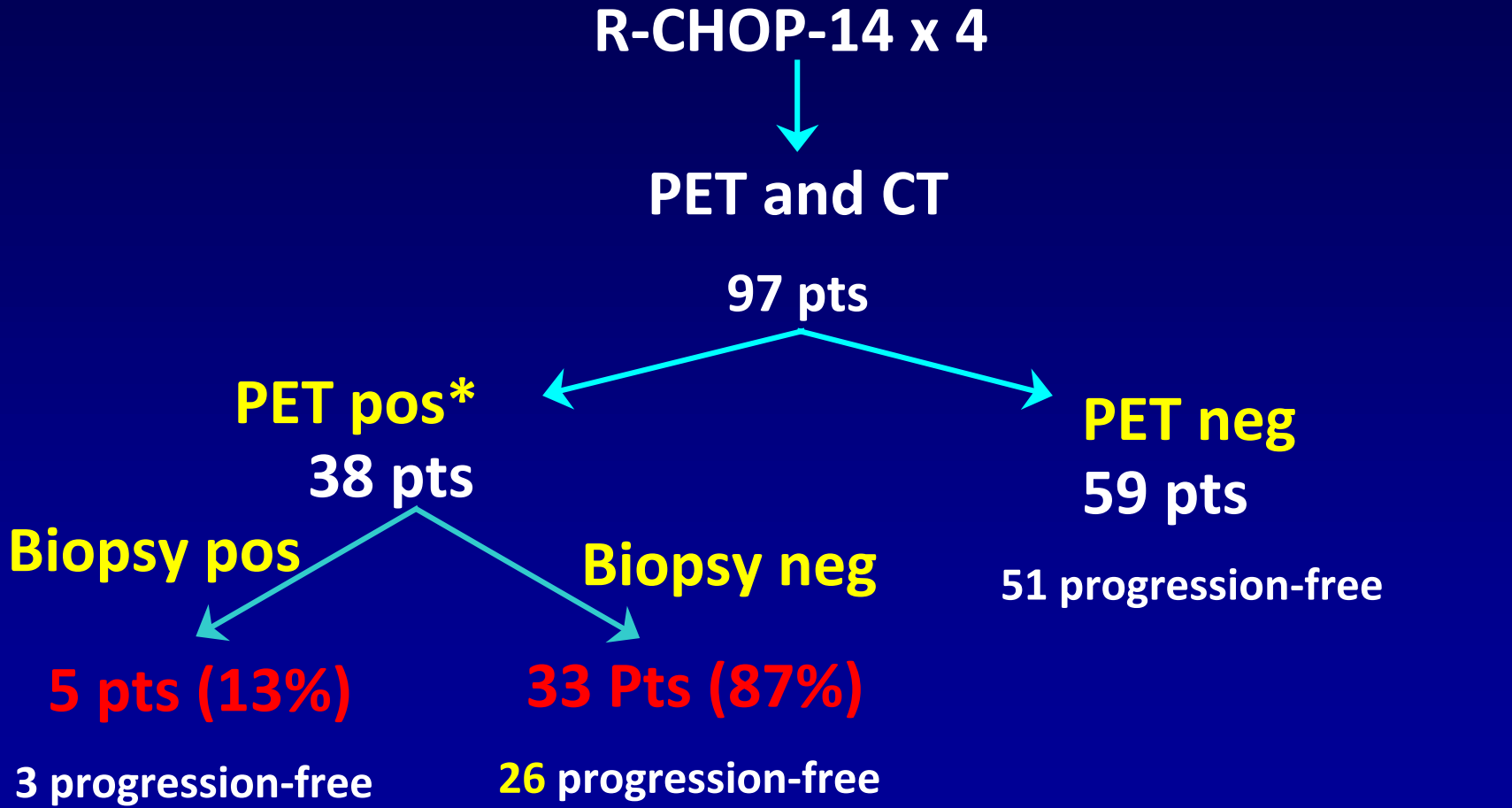
MSKCC: overall outcomes





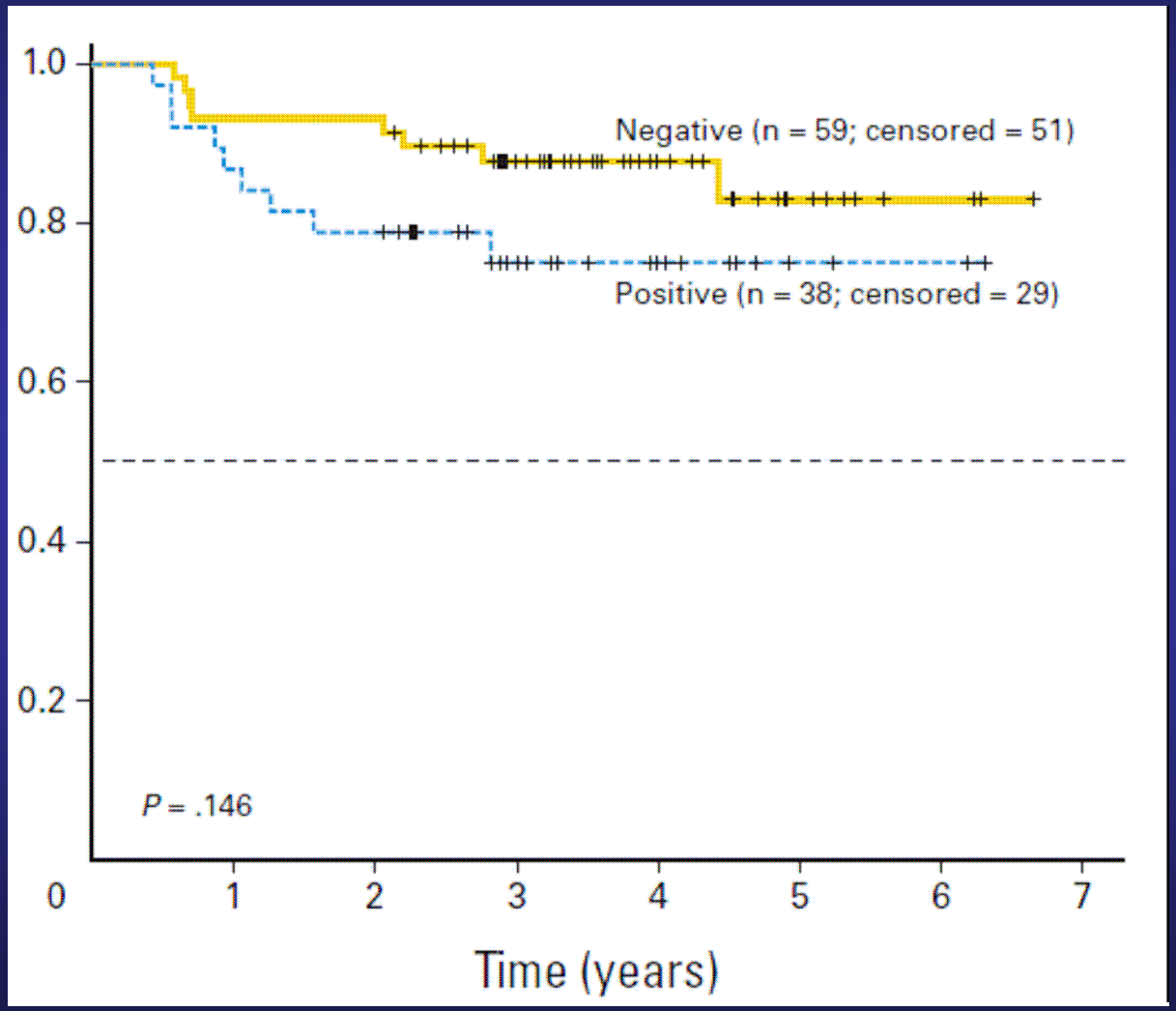
Moskowitz CH et al, JCO 2010

Separation by PET and Biopsy Results



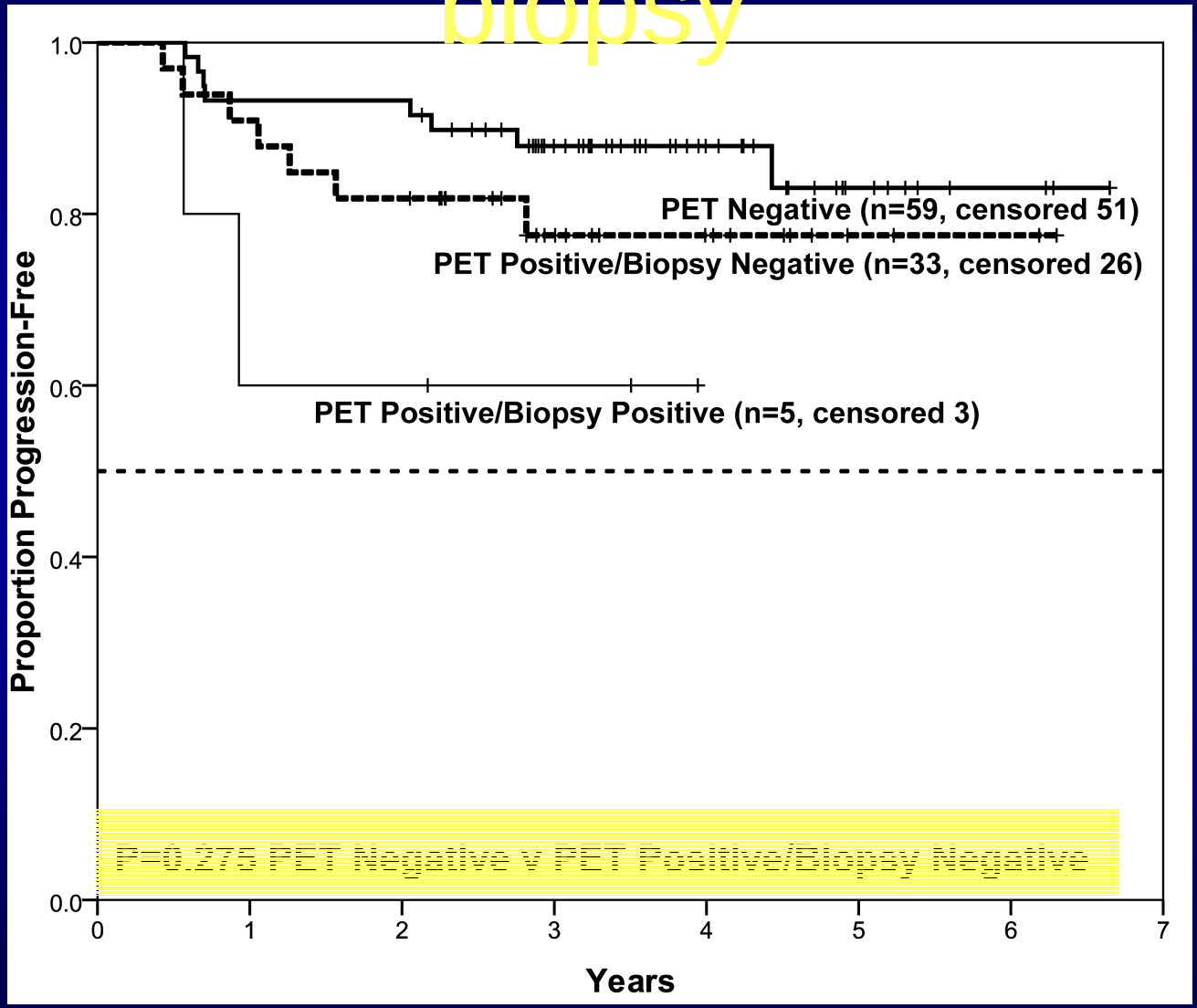
* Uptake > local background, with CT abnormality

PFS according to interim PET



Moskowitz CH et al, JCO 2010

PFS according to PET and biopsy



Moskowitz CH et al, JCO 2010

SUV in relation to biopsy result

Table 3. Correlation Between SUV and Biopsy Result

	Highest SUV at Biopsy Site (Interim PET scan)			Ratio SUV*		
Biopsy Result	Median	Minimum	Maximum	Median	Minimum	Maximum
Negative (n = 33)	3.4	1.5	11.5	1.46	−0.2	3
Positive (n = 5)	5.4	2	14	1.3	0.2	1.7
P (Wilcoxon test)		.25			.36	

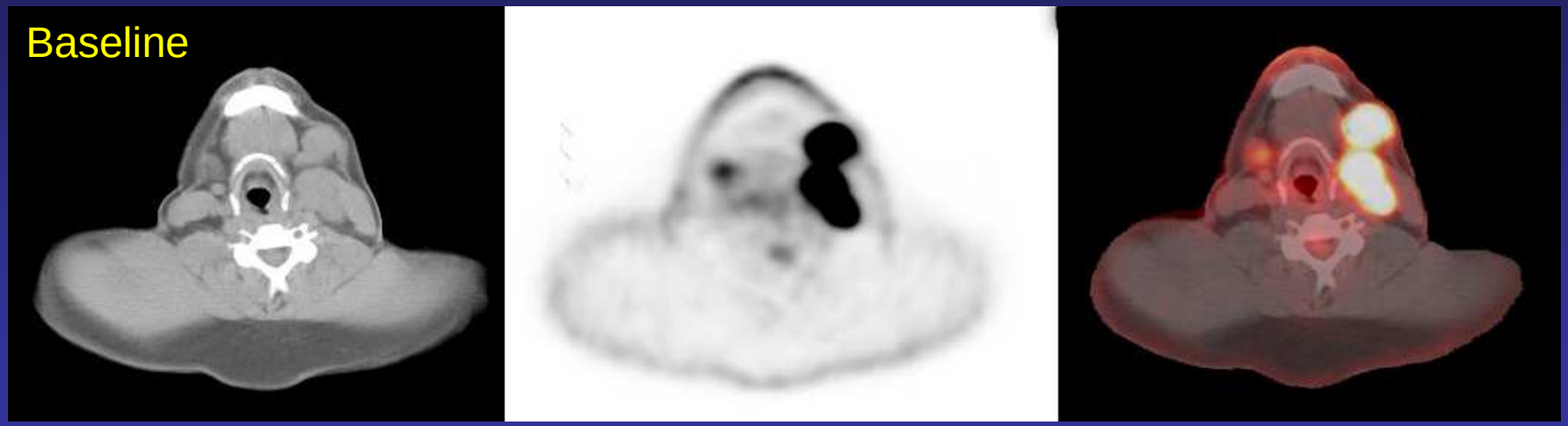
*Ratio SUV = Log (initial SUV max at biopsy site / interim SUV max at biopsy site)

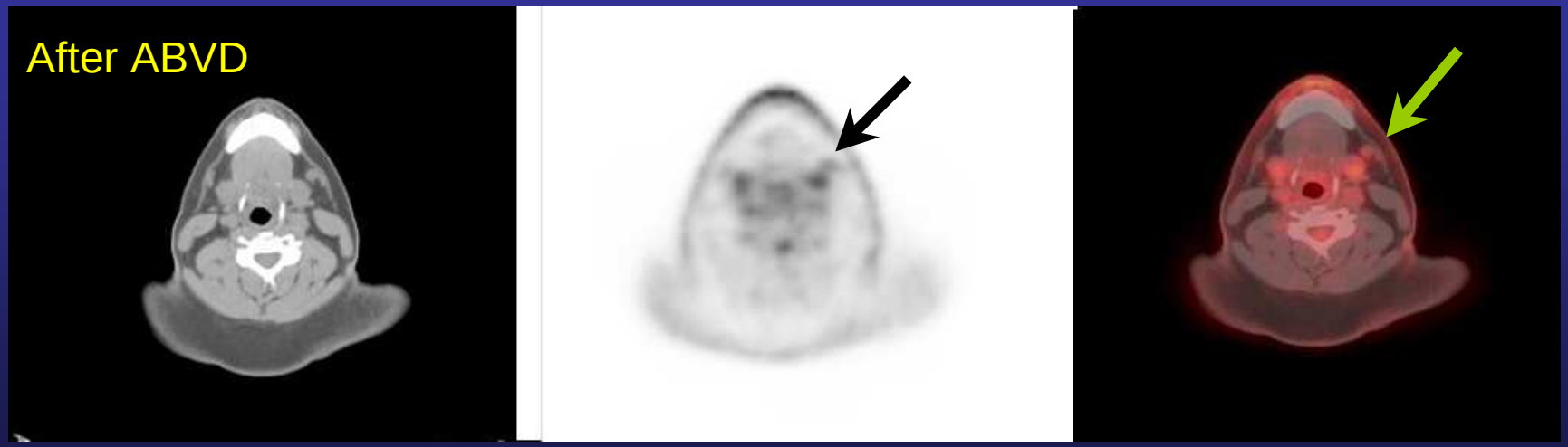
Moskowitz CH et al, JCO 2010

Considerations in trial planning

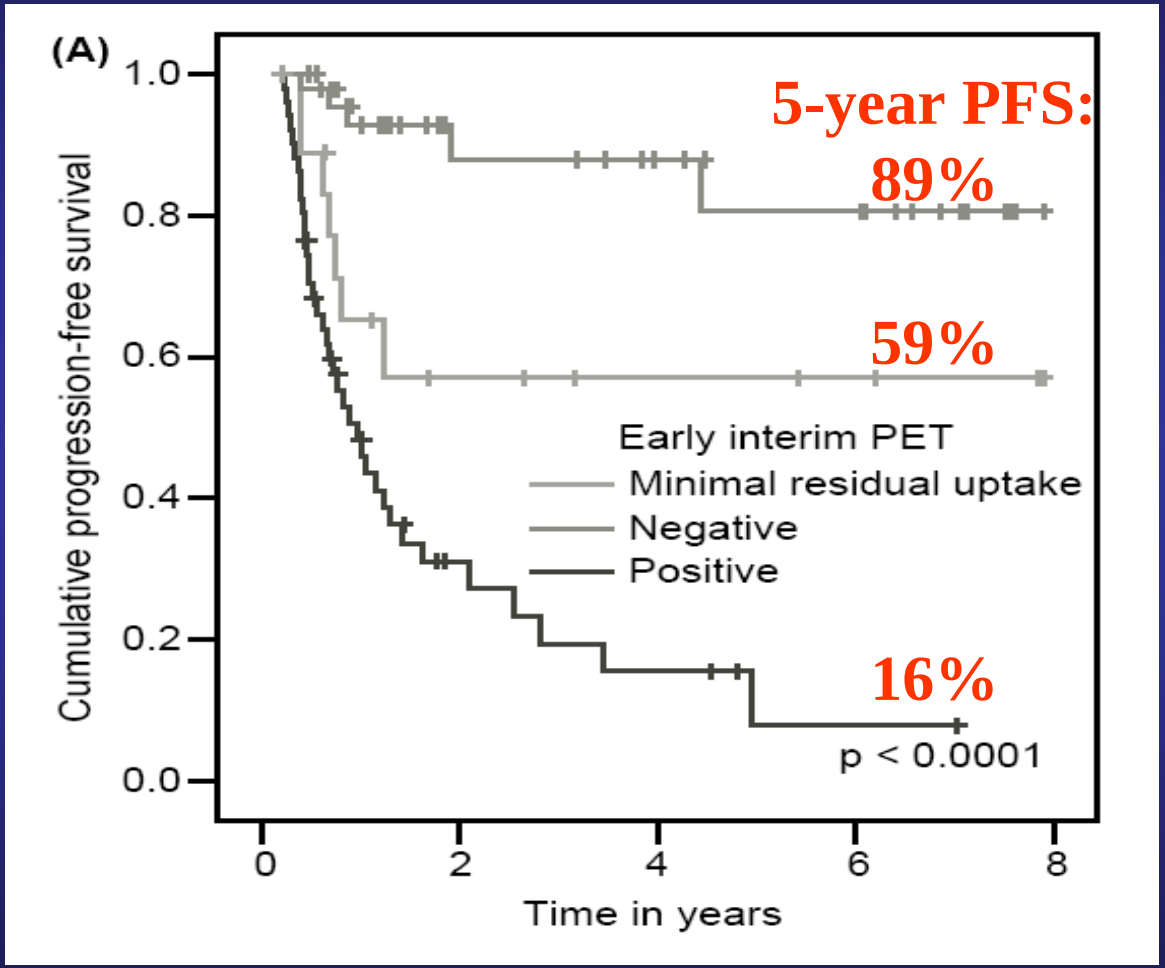
- Impact of regimen
  - IPI, revised IPI were also not prognostic
  - A moving target?
- Role of biopsy
  - Prognostic significance of PET previously established without use of biopsy
  - Limited prognostic data on midtreatment biopsy
  - Sampling error
  - All biopsies showed inflammation and/or necrosis

How positive is “positive”?





How positive is “positive”?



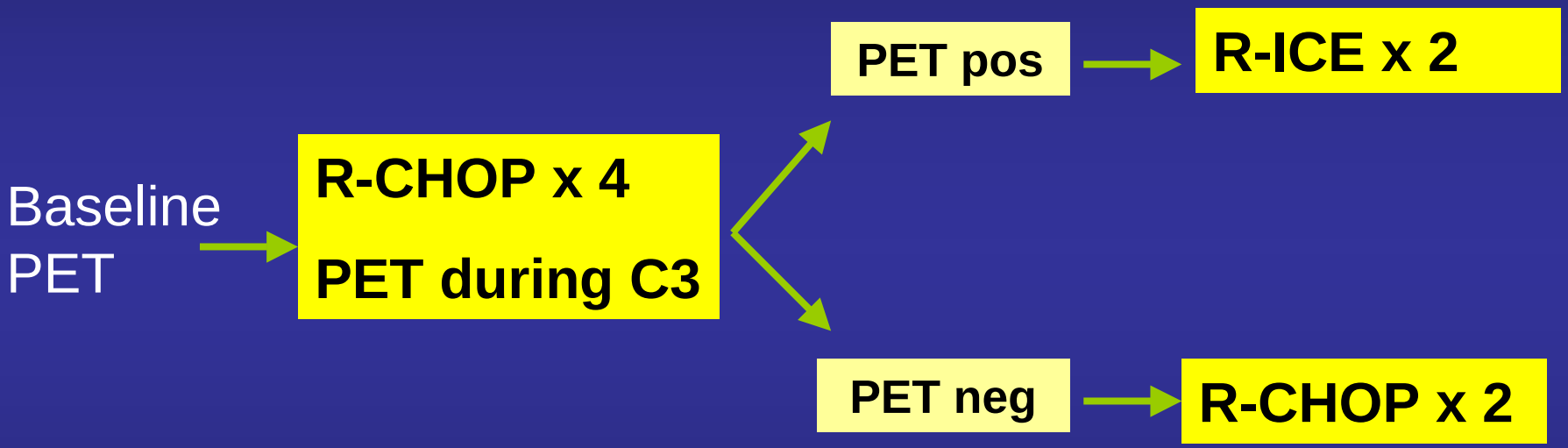
2 yr median follow-up

Mikhaeel NG et al, Ann Oncol 2005;16:1514-1523, Fig 3A

Considerations in trial planning

- Reproducibility of reads in context of risk-adapted trials

E3404: Phase II Study of Response-Adapted Therapy for DLBCL



Central review of interim PET;
designated + or – by visual assessment

PI: Lode Swinnen

ECOG criteria for interim PET (binary result)

- Evaluate only sites abnormal at baseline
- Pos sites must have anatomic correlate
- Abnormal = focal appearance and intensity > liver
- Marrow, spleen abnormal only if focal and clear
- Symmetric foci in chest abnormal only if remaining scan is pos
- New foci considered pos only if remaining scan is pos, or if new lesion is focal, very intense, and has CT correlate

E3404: PET read reproducibility

68-72% agreement (k: 0.4 – 0.5)

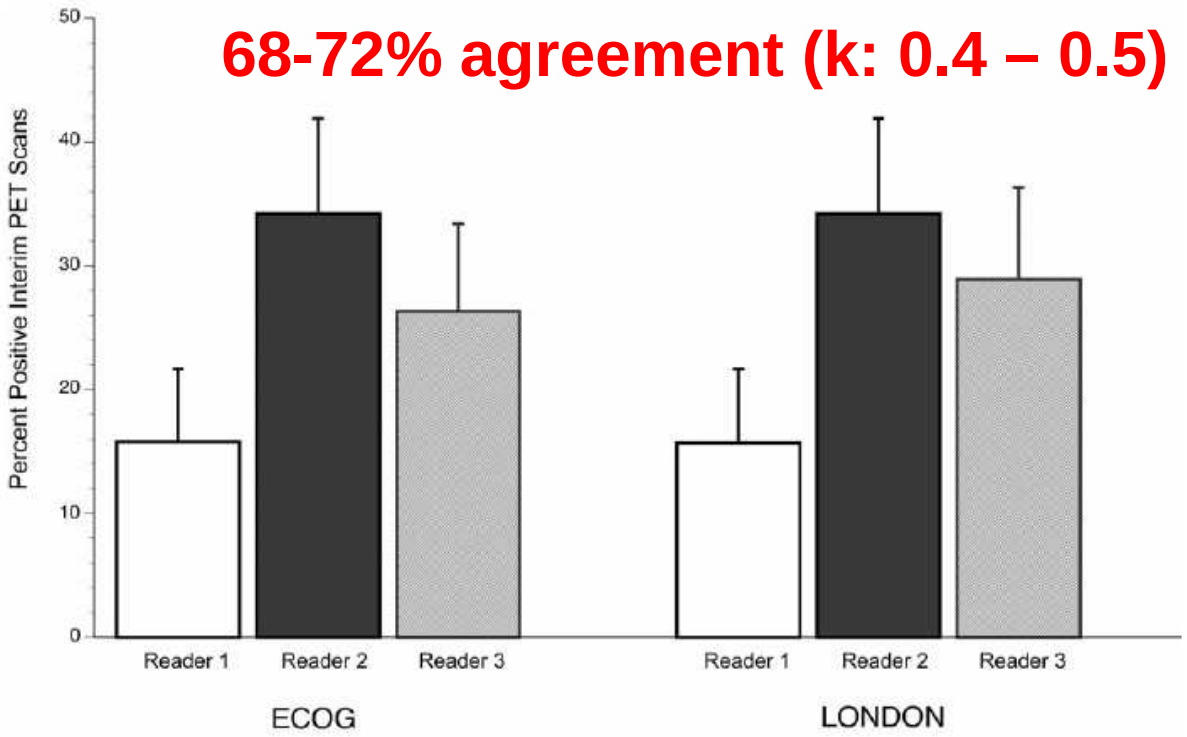


Figure 1. Proportion of interim-PET cases interpreted as positive by reader, according to the ECOG and London criteria. Error bar represents 1 SE for the proportion.

- 16 – 29% interim scans read as positive
- Consensus reached in 3 of 12 discordant cases

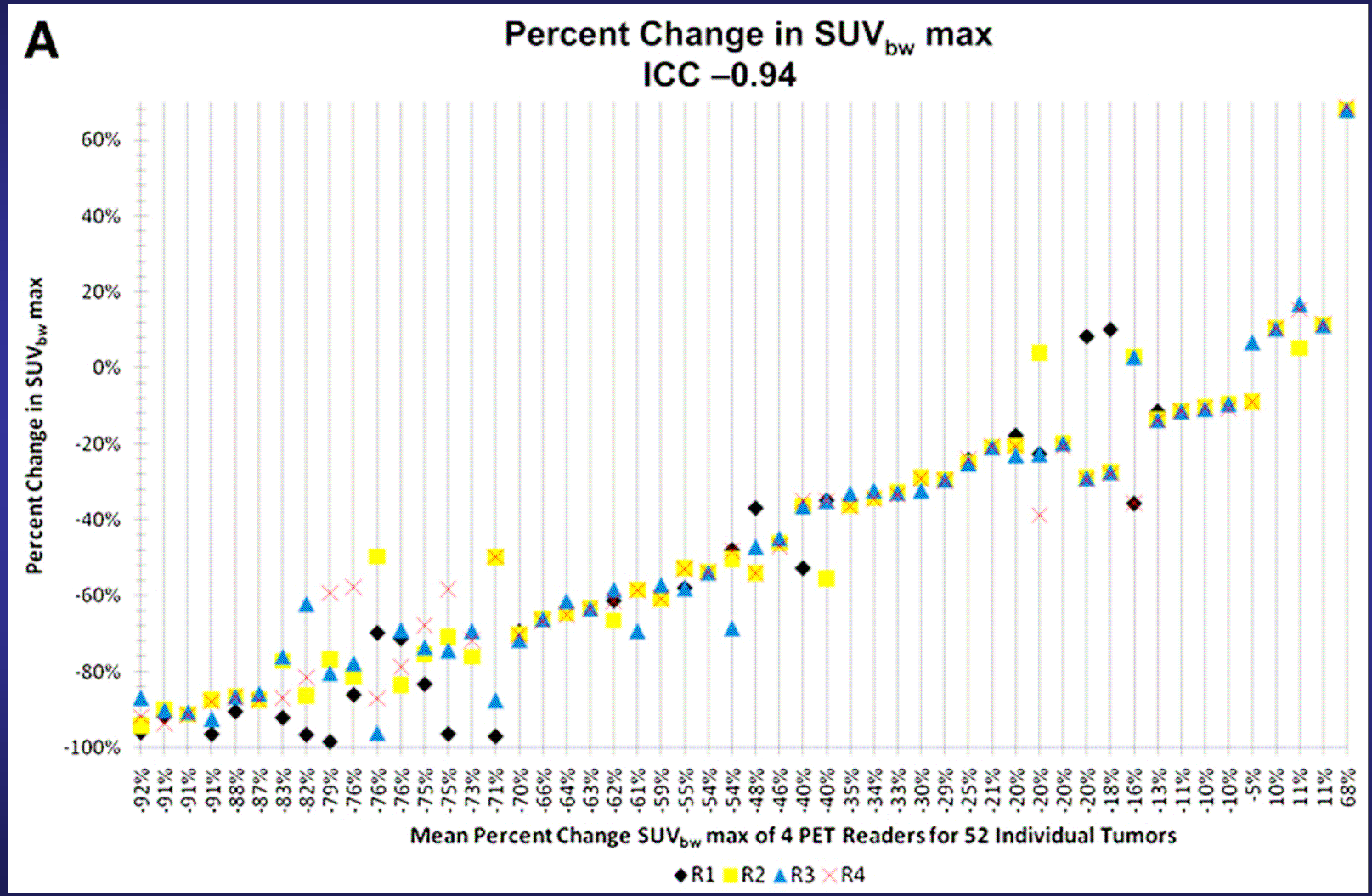
Horning SJ et al, Blood 2010;115:775

E3404: PET read reproducibility

- Similar reproducibility of ECOG & London criteria
- Sources of disagreement
  - Para-aortic, spleen, bone
  - CT correlates of residual “positive” sites often absent or equivocal

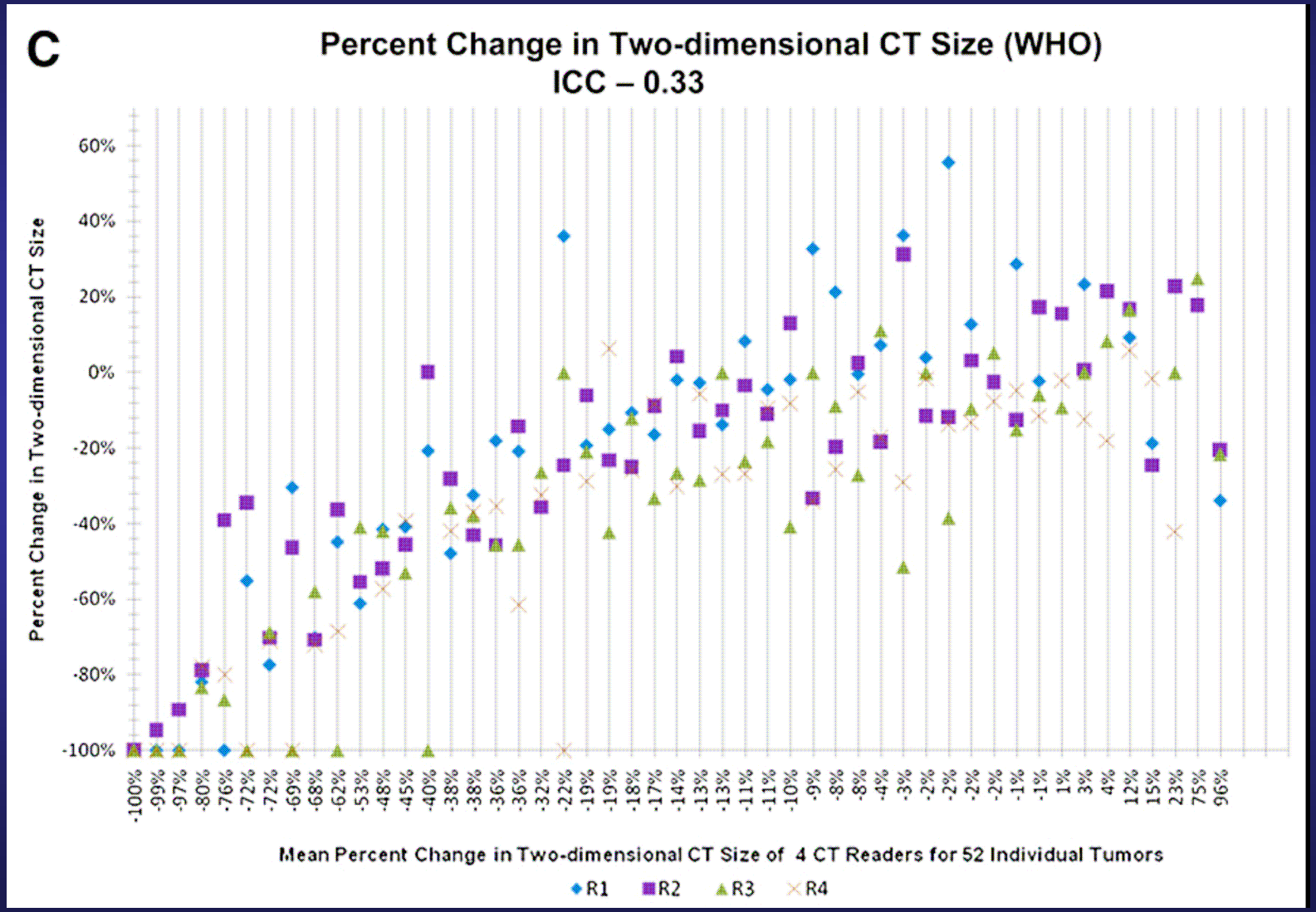
Horning SJ et al, Blood 2010;115:775

SUV vs. CT measurements



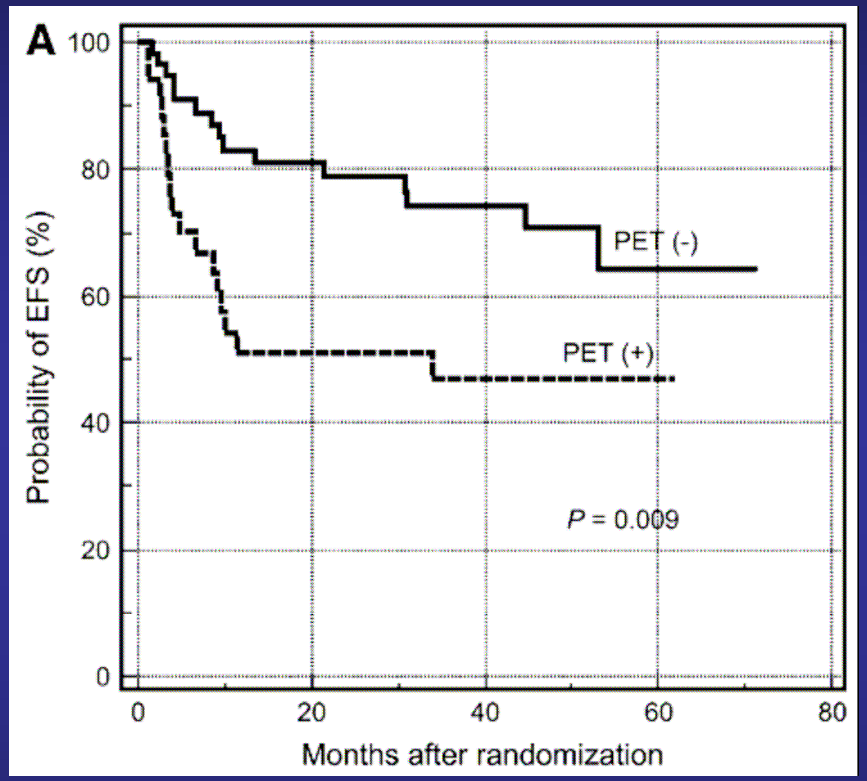
Jacene HA et al, JNM 2009;50:1760

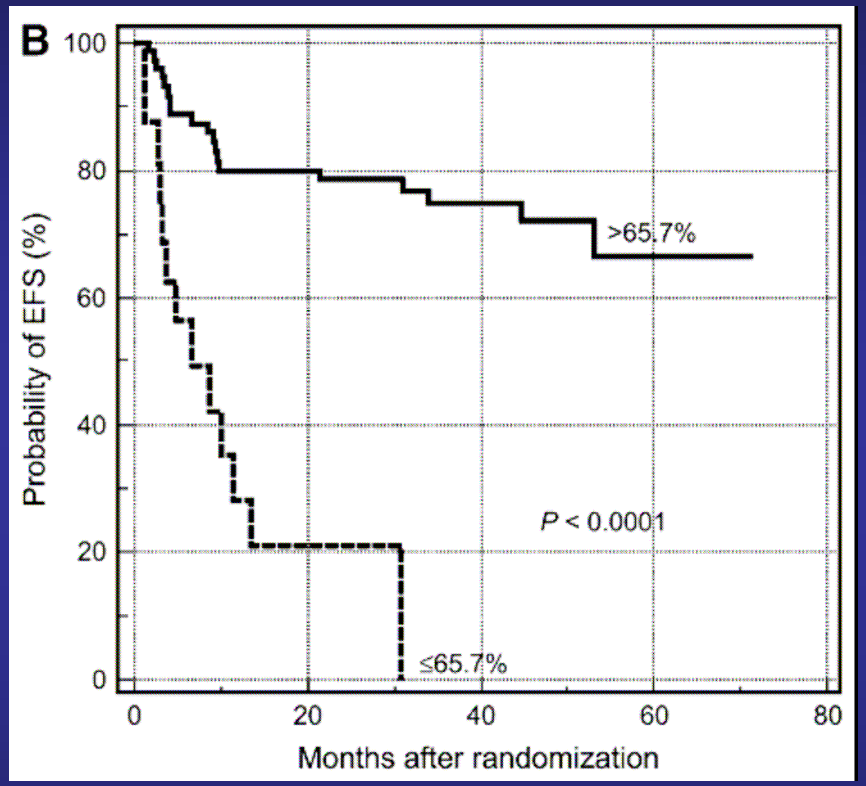
SUV vs. CT measurements



Jacene HA, JNM 2009;50:1760

Cycle 2 PET in DLBCL





3-point visual scale
(65% accuracy)

Change in SUV max
(76% accuracy)

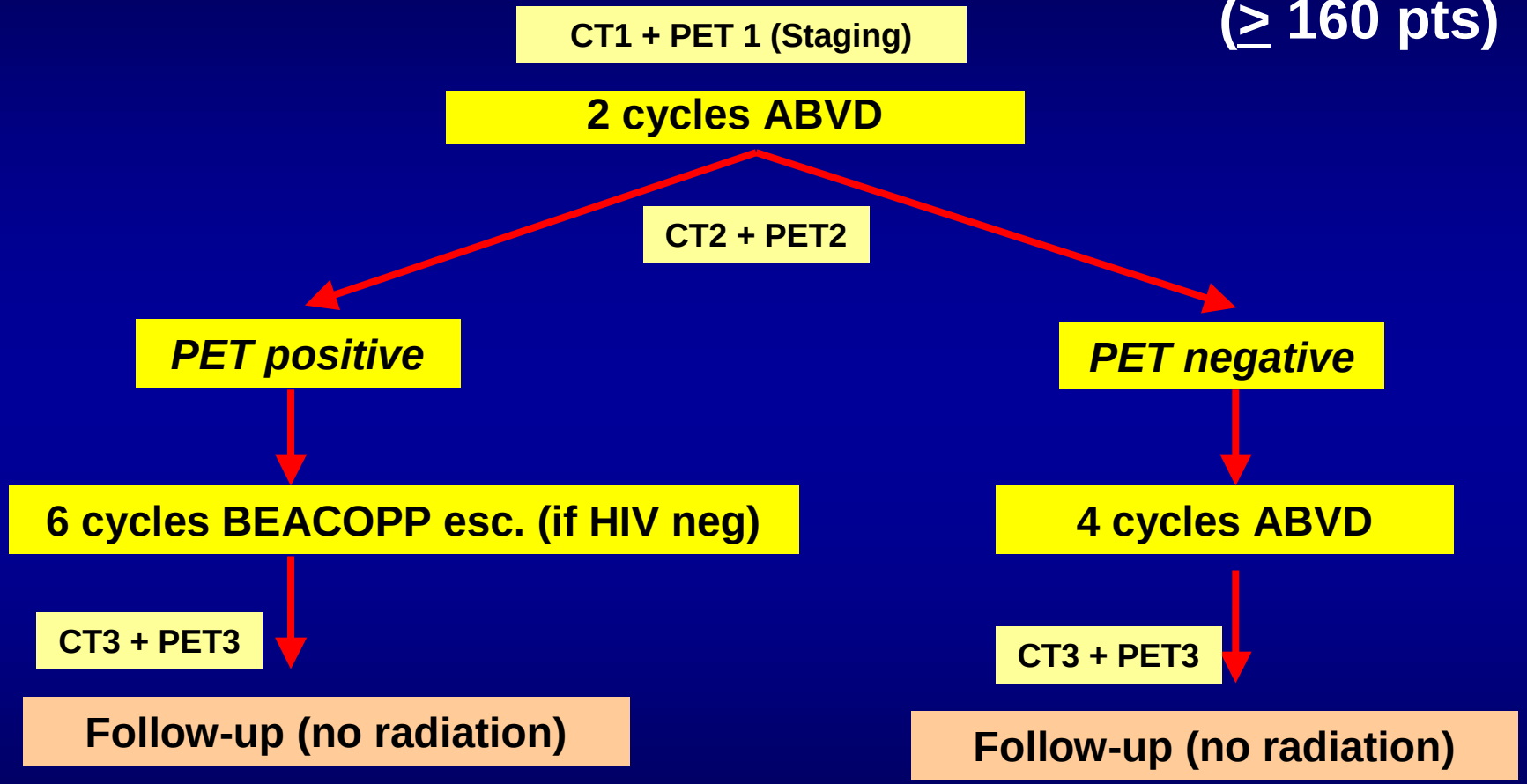
Lin C et al, JNM 2007;48;1626

SUV analyses

- Potential for greater reproducibility
- Standardization critical
- Although no clear “cut-off”, further prospective studies are warranted – particularly correlating with visual criteria
- May help in prognosticating “minimal residual uptake”?

Phase II US Intergroup trial (S0816): stage III-IV HL

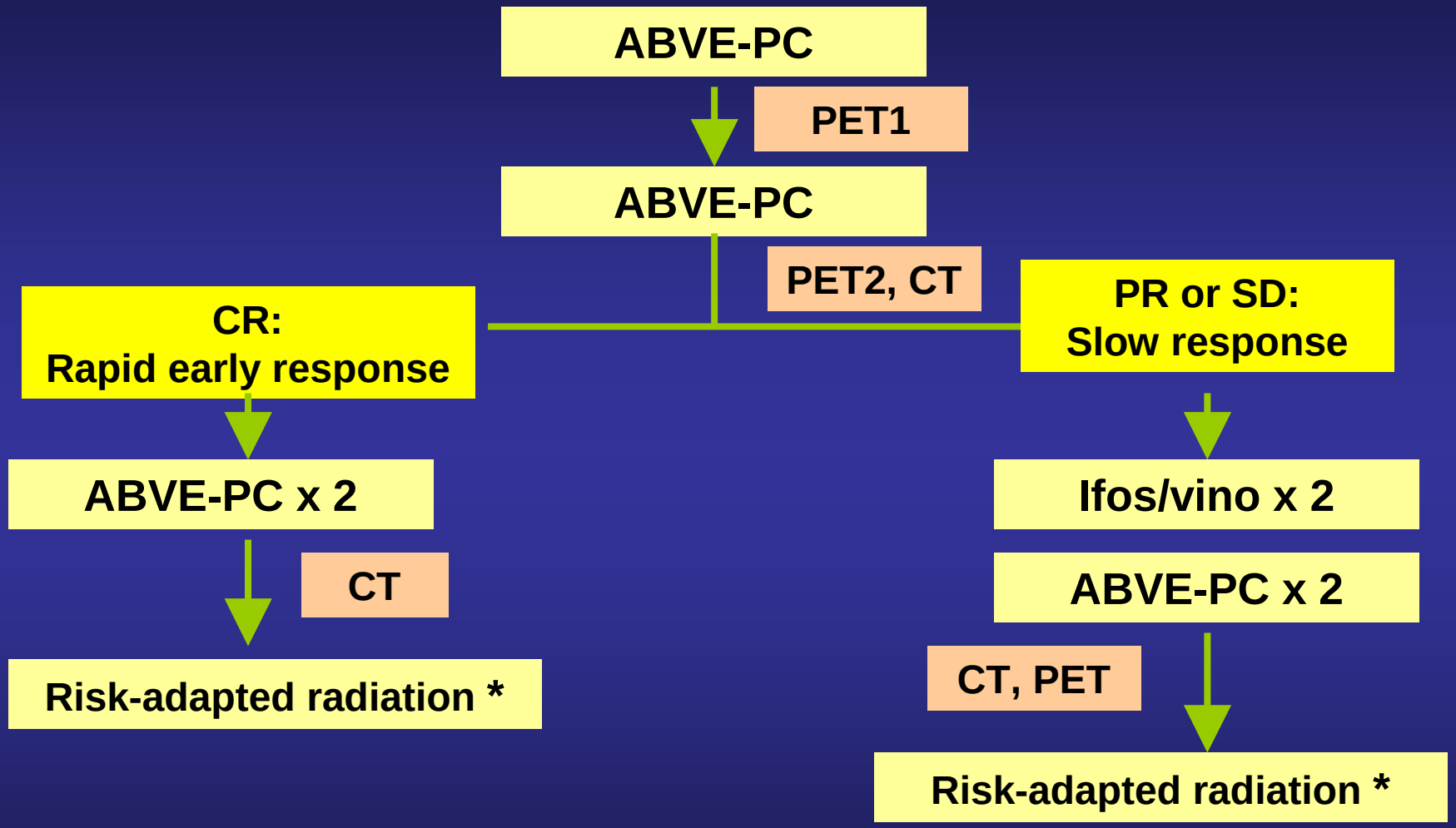
IPS 0-7
(≥ 160 pts)



5-point scale, with exploratory SUV studies

Soon to open: CALGB risk-adapted trial in HL

COG study: high-risk pediatric HL



* Initial bulk disease, nonbulk disease with slow response

COG study: high-risk pediatric HL

- Response criteria
  - Modification of revised IWG criteria
    - CR: nodal size criteria and PET neg
    - PR: nodal size criteria, either PET neg or pos
- Endpoints
  - Maintain comparable overall survival in rapid and slow responders through risk-adapted therapy
  - Investigate whether PET1 identifies group distinct from “rapid early responders” (e.g. PET1+, PET2-), who might require augmented therapy

U.S. observational studies: example

- CALGB imaging protocol for de novo DLBCL
- Centralized PET review: 5-point visual scale and SUVs

Baseline PET/CT → R-CHOP vs R-EPOCH → PET/CT post cycle 2 and cycle 6 (no intervention)

Negative

- 0 no abnormal activity (tumor cold)
- 1+ minimal activity (tumor < background)
- 2+ equivocal (tumor = background)

Positive

- 3+ moderate activity (tumor > background)
- 4+ marked activity

Managing a positive post-therapy PET

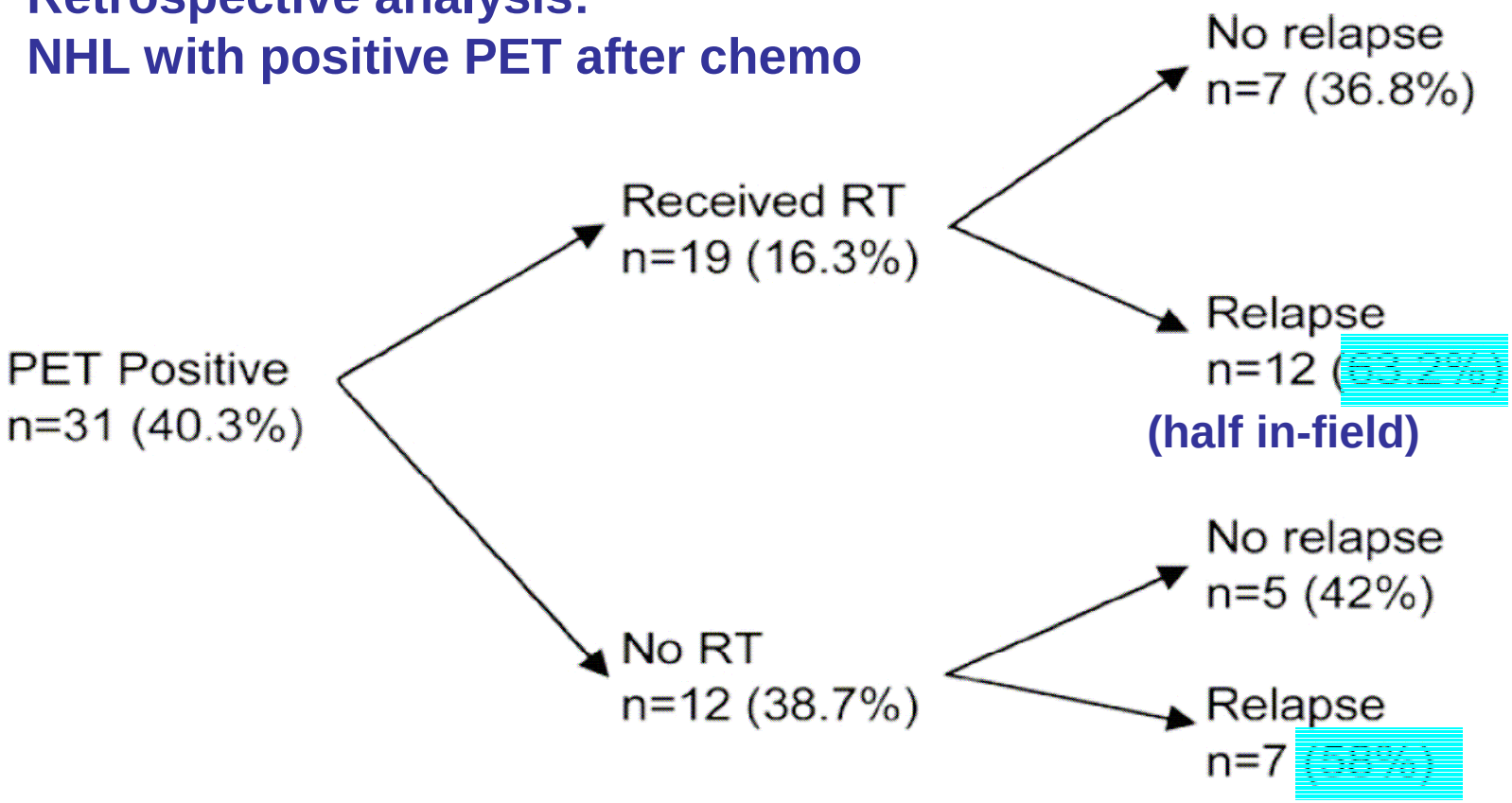
- Extending course of chemotherapy?
  - Doubtful that additional cycles of same chemo will help, even if brisk CT response

Managing a positive post-therapy PET

- Extending course of chemotherapy?
- Adding radiation?
  - Radiation may complicate future therapies
  - Chemoresistance and radioresistance often coexist
  - Should not assume radiation is natural next step
  - Positive PET may identify subset who stand NOT to benefit from radiation

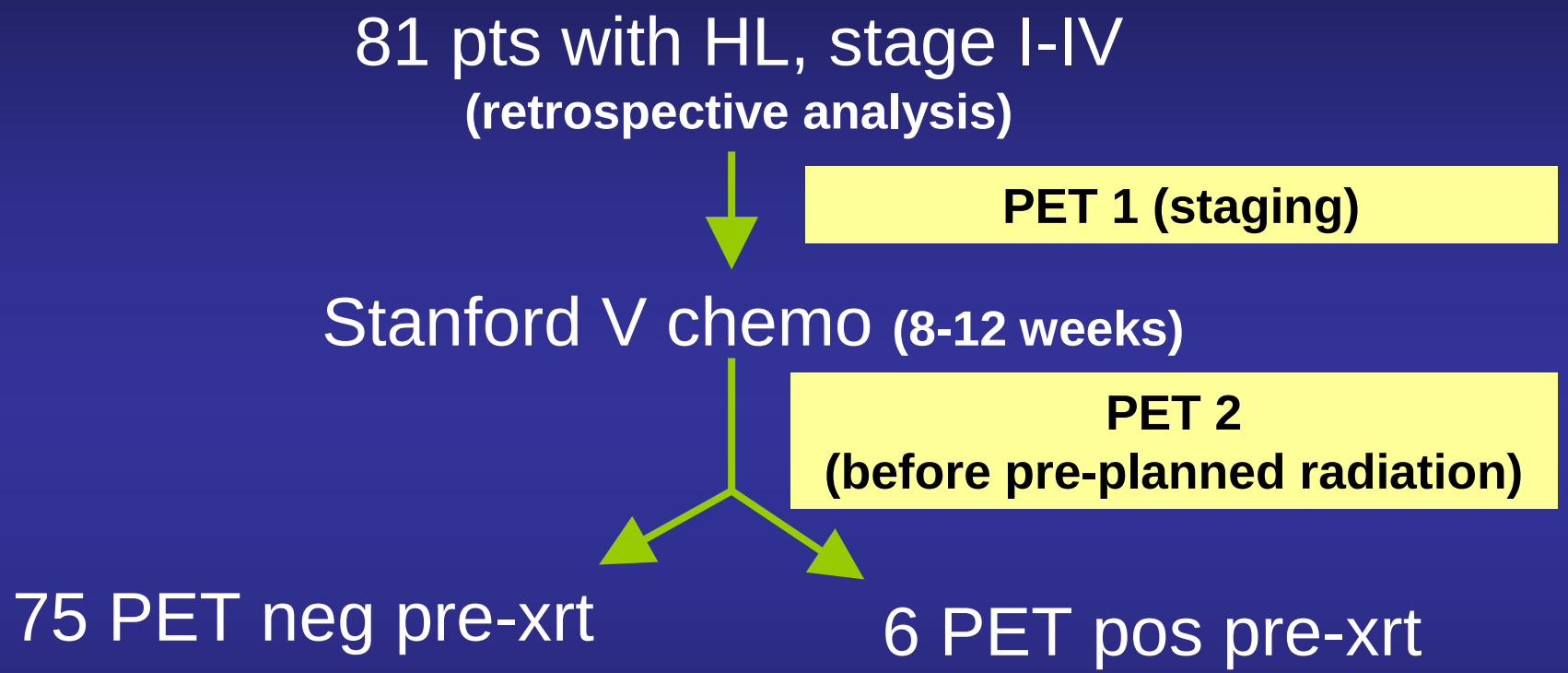
Radiation in residually PET+ pts

Retrospective analysis:
NHL with positive PET after chemo



Kahn et al, Int J Rad Onc Biol Phys 2006; 66: 961-965

Hodgkin's: PET and radiation



Advani R et al, JCO 2007;25:3902

Hodgkin's: PET and radiation

81 pts with HL, stage I-IV
(retrospective analysis)

PET 1 (staging)

Stanford V chemo (8-12 weeks)

PET 2
(before pre-planned radiation)

75 PET neg pre-xrt

3 relapses

6 PET pos pre-xrt

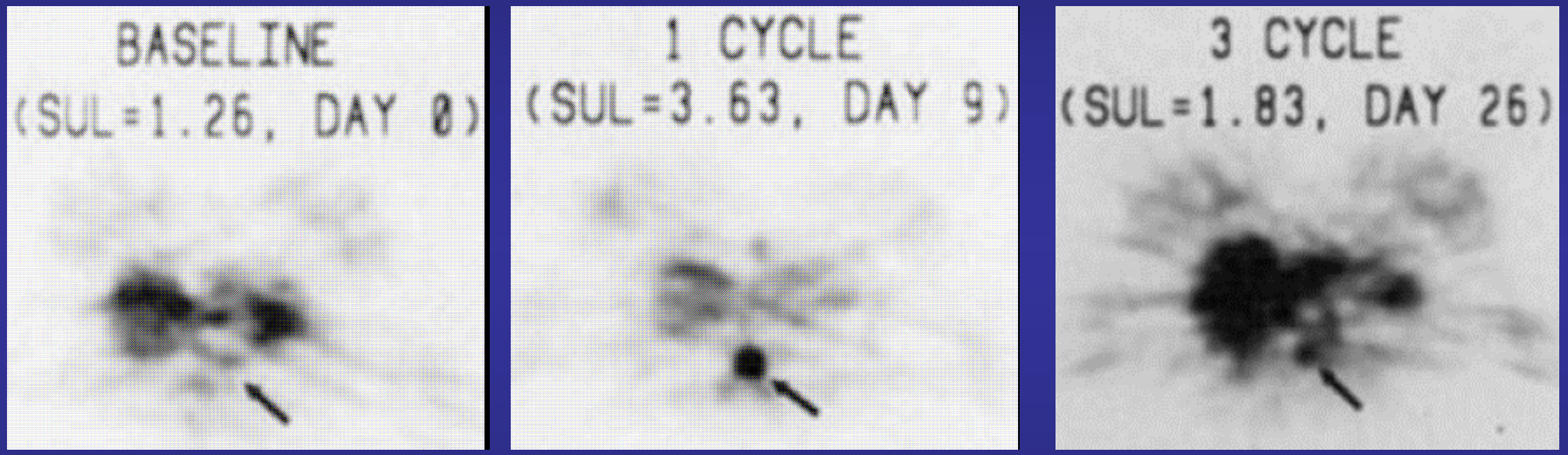
4 relapses:
3 in-field, 1 at margin

Advani R et al, JCO 2007;25:3902

Managing a positive post-therapy PET

- Extending course of chemotherapy?
- Adding radiation?
- Intensifying treatment, possibly with BMT?
  - Before considering escalating therapy, outside a trial, confirm disease persistence

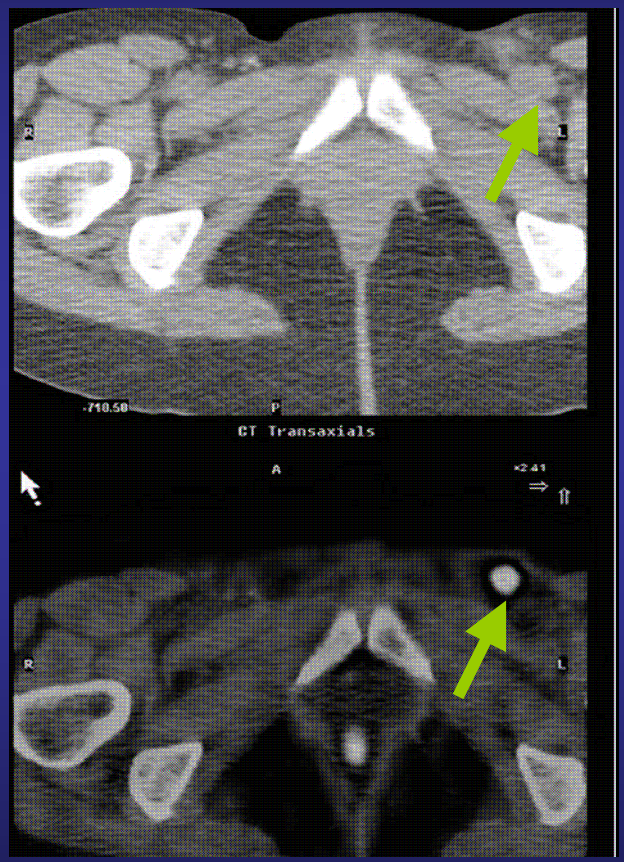
False positives: implications for trial planning



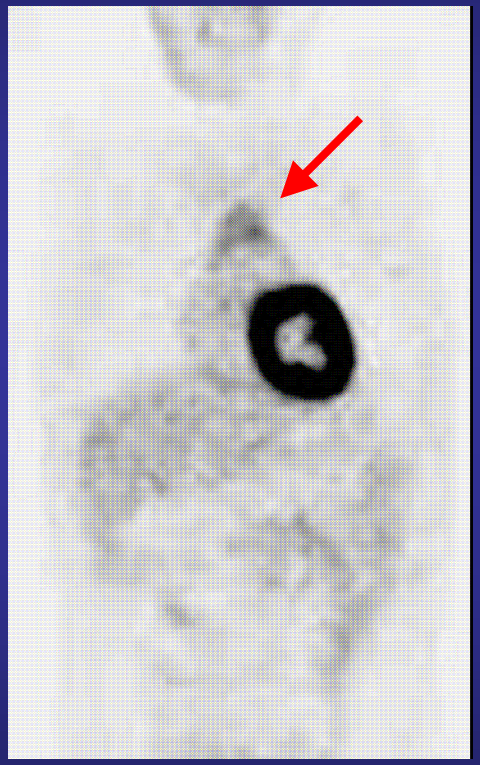
Transverse PET, lower thoracic region

Sugawara Y et al, JCO 1998; 16: 173

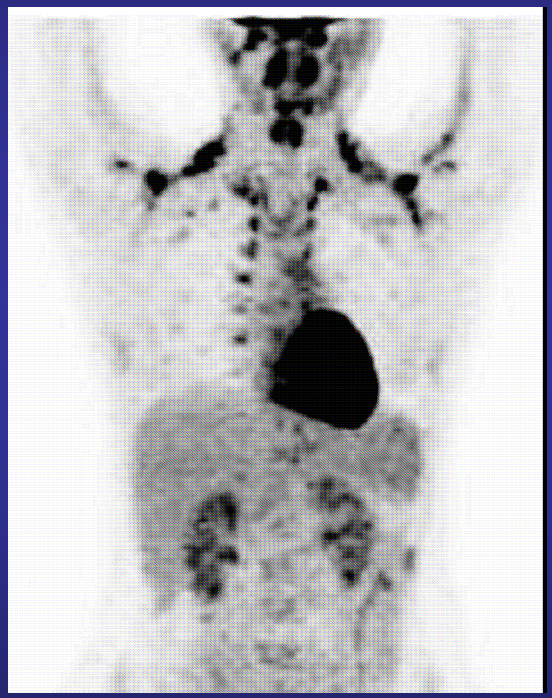
False positives after Hodgkin's therapy: implications for trial planning



Inflammatory node
(SUV 9.4)



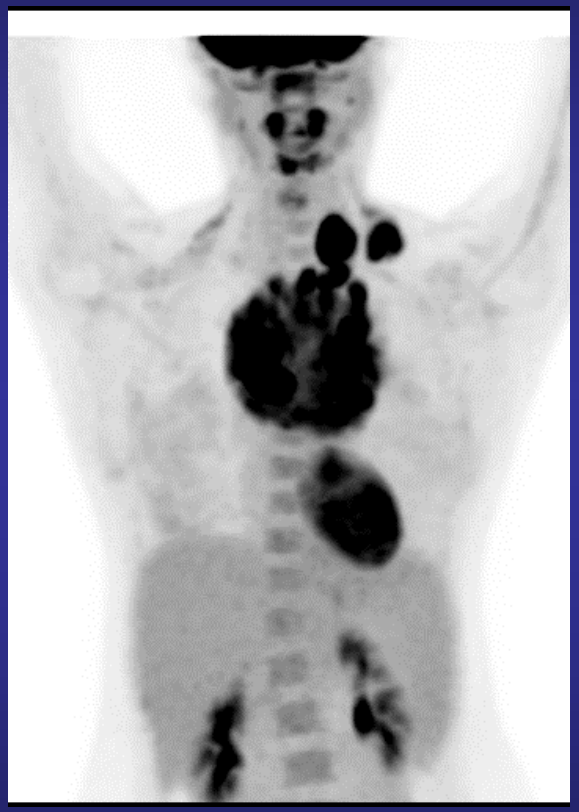
Thymic hyperplasia
(SUV 3.7)



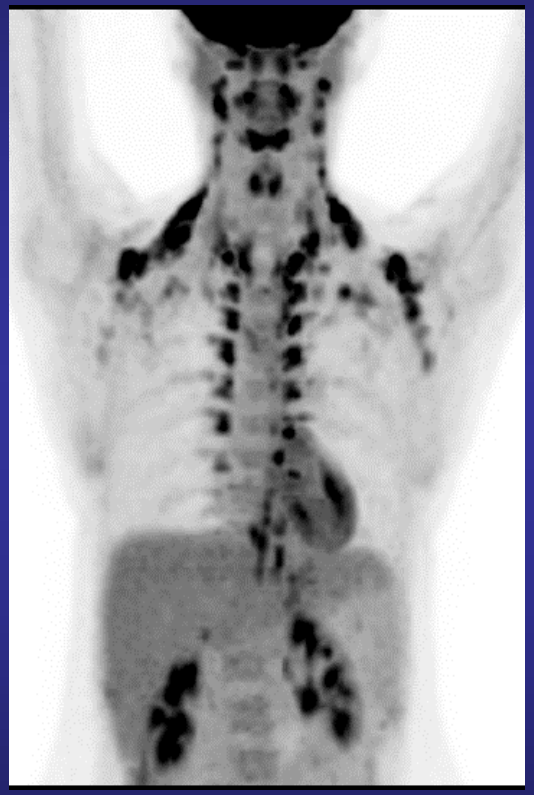
Brown fat
(SUV 13)

Castellucci P, Nuc Med Commun 2005; 26: 689

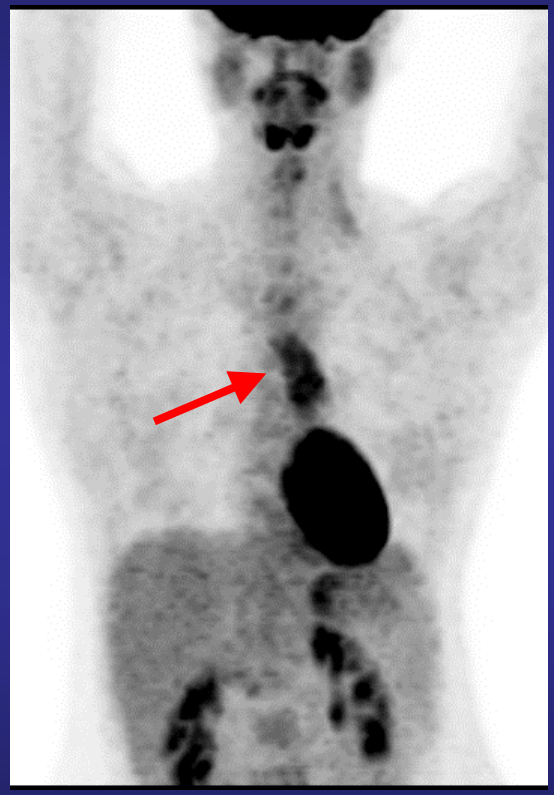
An 18 year old with HL



Baseline



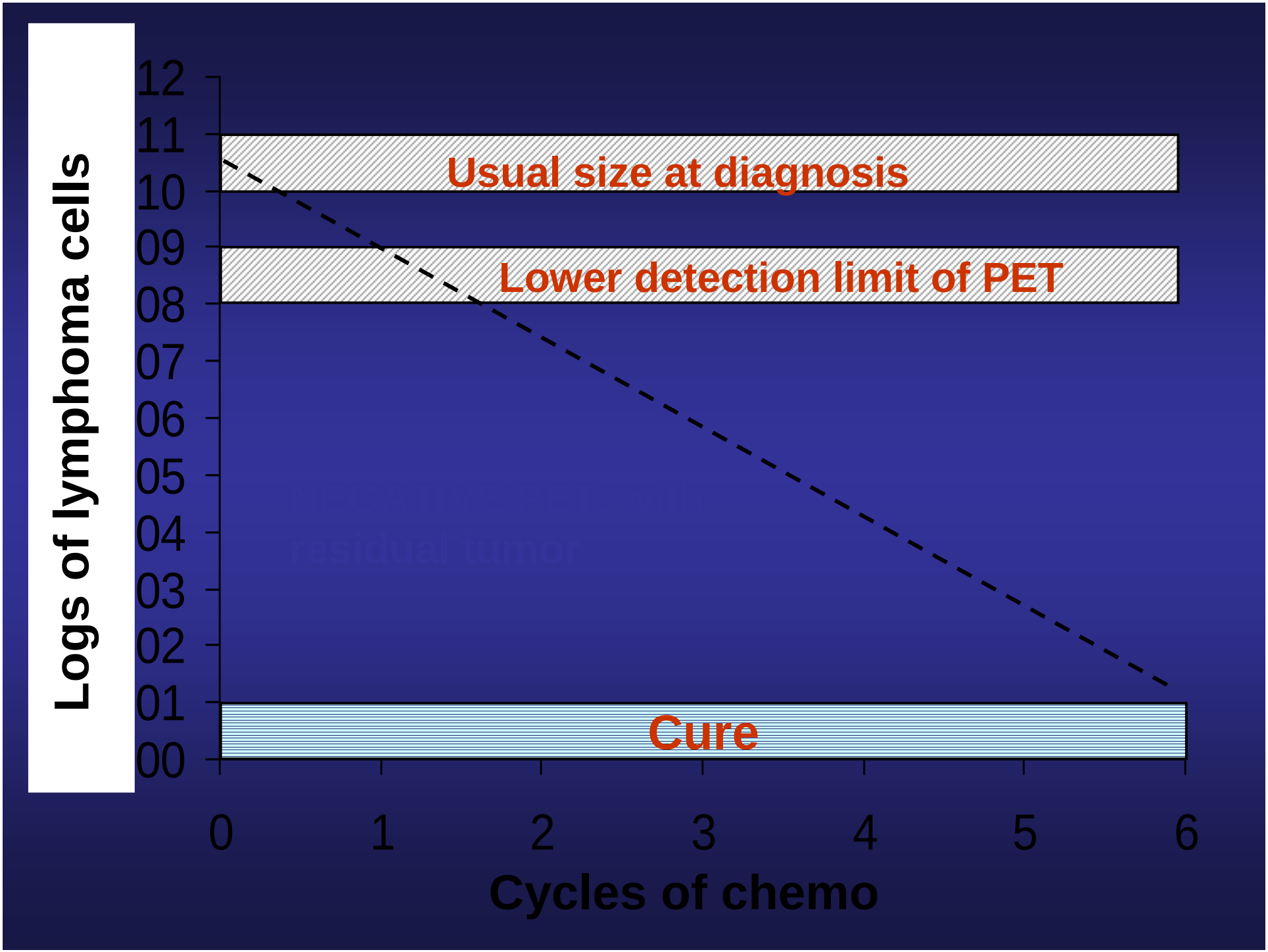
End of chemo



3 mo after chemo

Negative mid-PET: de-escalate therapy?

- Studying this makes sense but…
- A true negative PET may not mean ultimate eradication of disease
- Caution with early cessation of chemo (many logs of tumor may remain, depending in part on timing of PET)
- (For same reason, focusing radiation on residual PET+ foci, while reducing toxicity, may be ineffective)


Logs of lymphoma cells
12
11
10
09
08
07
06
05
04
03
02
01
00
Usual size at diagnosis
Lower detection limit of PET
Cure
0
1
2
3
4
5
6
Cycles of chemo

Considerations: trial design

- Potential to more precisely tailor treatment to the individual patient
  - Changing definition of disease response
  - Changing risk stratification
- Prognostic significance not as clear-cut as earlier series suggested
- Prognostic value may reflect efficacy of the chemotherapy regimen

Considerations: trial design

- Investigation of SUV criteria: prospective analysis, comparison to visual criteria
- Threshold for treatment modification
- Role of biopsy
- Reproducibility of reads
- Conservative strategy best outside of a trial