April 8-9, 2010
Palais de l'Europe,
Menton

Has the interim-PET retained its prognostic role in lymphoma?

Lale Kostakoglu, M.D., M.P.H.

Mount Sinai School of Medicine
Department of Radiology,
New York, NY, USA

Fact Sheet

HL

- ~90% pts with early-stage HL achieve a CR
- Variable relapse rate of 5-35%

- CR is even higher with more intensive therapies, at a cost of increased toxicity and long term AE

DLBCL

- heterogeneous clinical course, a response profile
- adding R to CHOP improved EFS by ~20%
- Still 20-40% not be cured with RCHOP
- In resistant/refractory cases, salvage treatment may be less effective after RCHOP

Ultimate Goal in Management

Best chance of cure lies with 1st line therapy

- decrease the AE while maintaining therapeutic efficacy in sensitive patients
  - Abbreviation of cycles in early stage HL
  - Avoidance of IFRT in HL
- improve the therapeutic efficacy with an acceptable rate of AEs in refractory patients
  - Early escalation of therapy in HL and DLBCL

Selection of poor-prognosis DLBCL patients

profiling response by interim-PET

response-adapted therapy strategy

Pressing Clinical Questions

Using interim PET as a surrogate marker for chemosensitivity, can we define the eligibility for,

- aggressive front-line therapy, while sparing toxicity/AE for those who can otherwise be cured with conventional treatment?

- avoidance of RT, or abbreviated front-line therapy whose efficacy = conventional treatment?

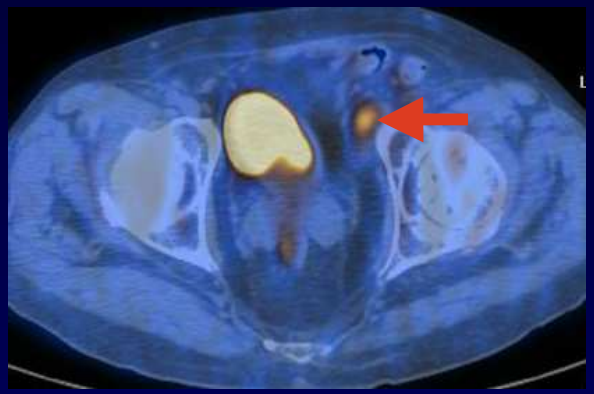
Would adaptive strategy lead to a better outcome?

- Escalated therapy increases survival?
- Escalated therapy leads to better survival than salvage?
- Could inherent drug resistance be overcome by escalated therapy?
- Abbreviated therapy decreases morbidity and increases quality of life?

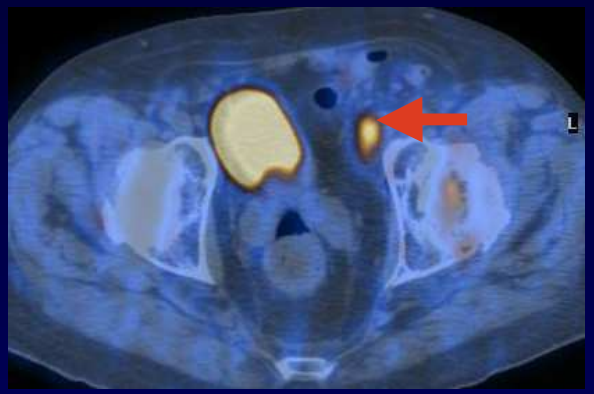
DLBCL

Interim FDG-PET in DLBCL

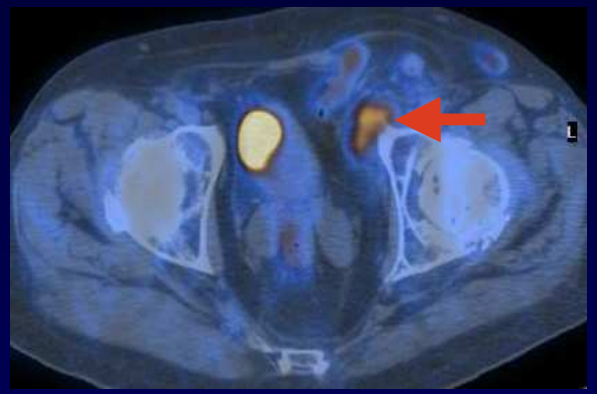
10 mo



After 2 Cycles



After Completion



6 mo After

Interim PET

60-70% NEGATIVE
30-40% POSITIVE

past trials determining the predictive value of interim PET

Interim FDG-PET - DLBCL

obvious heterogeneity of prediction of PFS

	PET-	MRU	PET+	
Spaepen	84	-	0%	(median fu 1107 dys)
Haioun	82	-	43%	(2-year PFS)
Mikhaeel	93	59	30%	(2-year PFS)

PFS for the PET- groups comparable,
PFS for the PET+ group varied from 0 to 43%

	Spaepen	Haioun	Mikhaeel
% progression	51	23	40
% PET+	53	40	43
% DLBCL	67	94	79
% CHOP or rCHOP	80	30	74
% Rituximab	0	41	NR (<74)

Mikhaeel GN, Leukemia & Lymphoma, 2009;50:1931

Interim PET - DLBCL

Author	Year	#	Sens	Spec	+LR	-LR
Spaepen	2002	47	91	100	46	0.1
Mikhaeel	2005	57	68	77	3.0	0.4
Haioun	2005	83	63	73	2.3	0.5
Fruchart	2006	35	90	76	3.8	0.1
Querellou	2006	21	50	93	7.5	0.5
Kostakoglu	2006	24	100	93	10	0.06
Ng	2007	45	67	88	5.3	0.4

Median fu 18-36 mo

sensitivity 50-100% and specificity 73-100%

combined estimates, sensitivity 78% ; specificity 87%

Terasawa, T, et al. J Clin Oncol; 27:1906-1914 2009

Summary Past Interim PET Results DLBCL

frequency of PET- results ranged between 40-60% and PET+ results between 40-53%

frequency of progression varied btw 23-51%

variables impacting NPV and PPV

- timing of PET
- pre-test probability of recurrence based on the population
- differences in efficacy of treatment
- R containing therapy regimens - cytotoxicity ADCC and complement activation (may increase FPs, ~33%)

Han HS et al, Ann Oncol. 2009;2:309.

- different methodology used for interim PET interpretation

Spaepen K et al. Ann Oncol. 2003;14:1155
Mikhaeel NG et al. Ann Oncol. 2005;16:1514

Haioun C et al. Blood. 2005;106:1376.
Mikhaeel NG. Leuk Lymphoma. 2009;50:1931

more recent data determining the predictive value of interim PET

NOT SO PROMISING!!

Early PET Predicts Outcome for Patients with DLBCL

- 112 patients treated on 3 protocols
- RCHOP-21, RACVBP, or RCHOP-14
- All had PET2, 3 point scale (low, intermediate, high)
- PET- Either negative, or "minimally positive in only 1 area
- 75 received planned therapy, 18 SCT consolidation
- AAIPI 0:5%, 1:35%, 2:37%, 3:23%

Safar et al. ASH 2009, Abst 98

Early PET for DLBCL: 4 Year Outcomes by PET Results

PET	PTs	% CR	% PR	% PFS	P	% OS	P
NEG	70	53	10	81	.0001	88	.001
POS	42	16	14	41		62	

RCHOP-21 RACVBP or RCHOP-14

PET	PTs	% PFS	P	%Pts	PFS	P
NEG	33	80	.0006	37	82	.0056
POS	24	40		18	56	

Safar et al. ASH 2009, abst 98.

50 pts with stage III - IV DLCL, RCHOPx6
PET2-3 cycles and at completion

Results: Med fu 15 mo

PET2-3	PET6
NPV 87% and PPV 27%	NPV 92% and PPV 80%
PET2-3 not correlated with PFS	PET6 correlated with PFS

Equivocal scans had outcomes similar to those with negative scans (80% free of relapse vs 92% free of relapse)

Conclusions: In contrast to prior reports in DLCL patients treated with RCHOP, interim PET/CT does not predict PFS

It may be that the dichotomous response criteria, are not useful for interpretation of interim scans

Cashen A, et al. *Blood* 2008 112: Abstract 371

42 DLBCL, Med age 59 yrs, 40% male, bulky 48%, stage III–IV 67%, IPI ≥high-int 21%, extranodal DLBCL 29%

RCHOP-like treatmentx6, PET3, PET6, Conventional IWG

86% CR, med fu 15 mo
2 yr EFS 77%
2 yr OS 78%

	-	+	Sens	Spec	PPV	NPV
PET3	67%	33%	75%	76%	43%	93%
PET6	81%	19%	75%	94%	75%	94%

2 yr EFS PET3- 90% PET3+ 55%, (p=0.01)

64% with PET3+ had a CR after induction treatment, 89% did not relapse

These results do not support an early intensification with a positive interim PET due to risk of overtreatment

Gigli F, et al. *Blood* 2008 112: Abstract 3607

Multicenter phase II study to assess efficacy of ER-CHOP in DLBCL;

Results: 76 pts PET2, PET6
med age 60, male 56% adv stage 80%, elevated LDH 73%, IPI 3-5 50%

PET CR rate after 2 cycles was 79%
PET CR rate after 6 cycles was 90%

Using an ITT analysis, 87% achieved PET CR

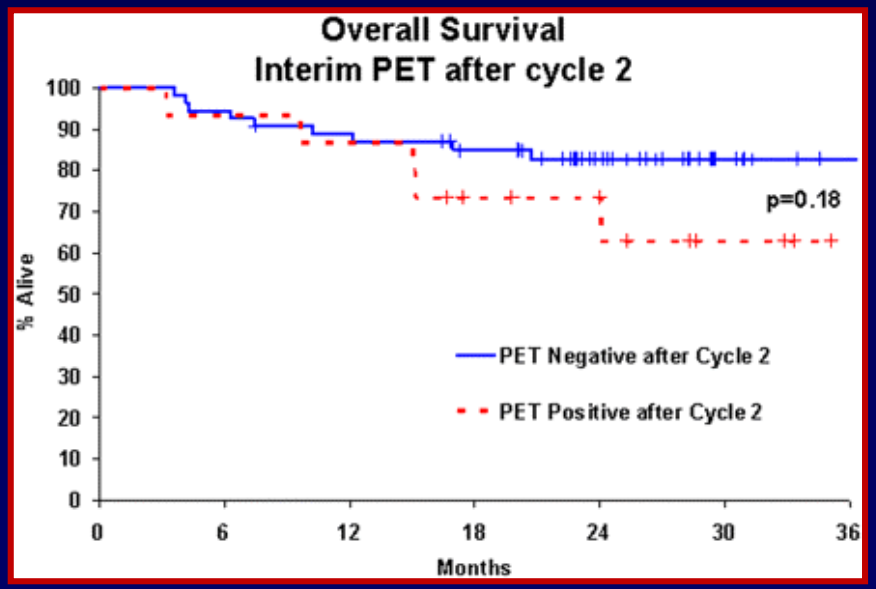
2 yr EFS	PET2-	73%
	PET2+	60% (p=0.25)
2 yr OS	PET2-	83%
	PET2+	73% p=0.17

Micallef I, *Blood* 2009 114: Abstract 137

Predictive ability of PET scan results from Cycle 2 and Cycle 6 of ER-CHOP in relation to 24-months EFS and OS

ER-CHOP cycles	CR rate [1]	PET scan result	24 mos. EF	24 mos. OS
Cycle 2	78%	NEG	73%	83%
		POS	60%	73%
Cycle 6	90%	NEG	80%	92%**
		POS	57%	57%

[1]A PET-negative patient is considered a CR.



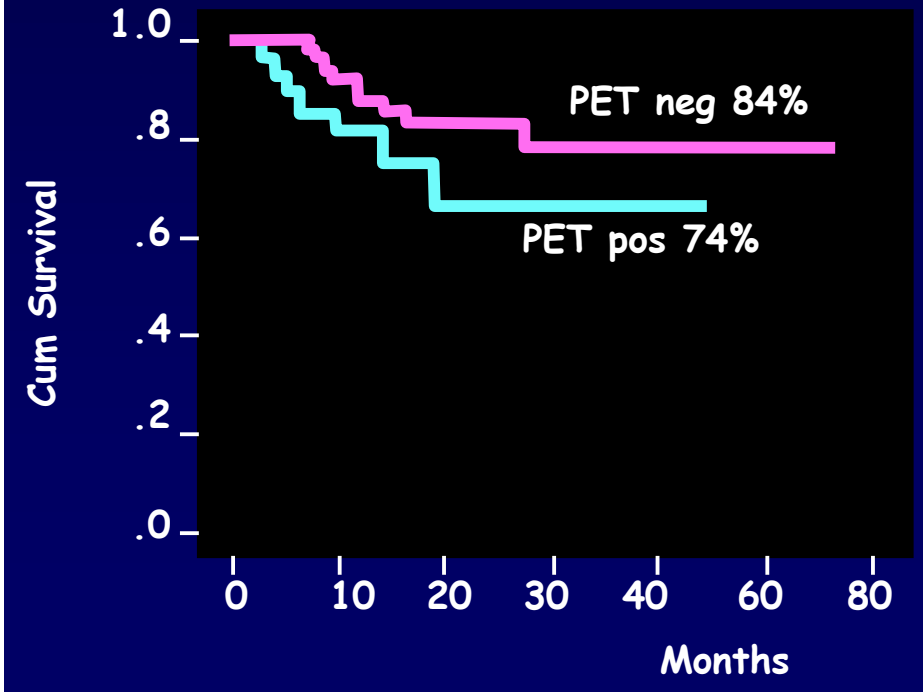
- Early PET scan during therapy does not significantly predict outcome
- Achievement of PET negativity by completion of therapy is associated with a good outcome

Micallef IN, *Blood* 2009 114: Abstract 137

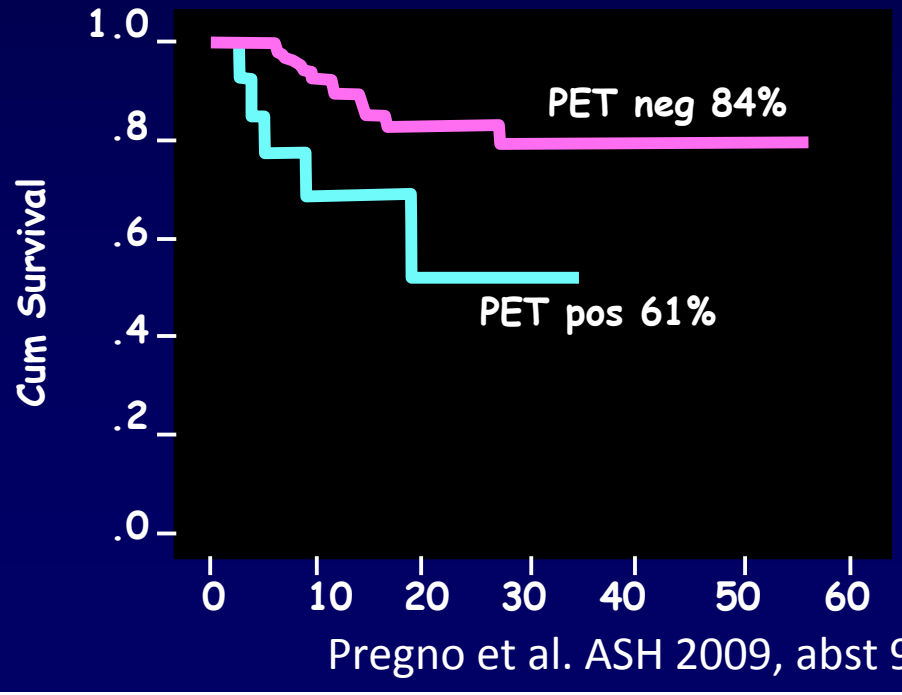
Interim PET Fails to Predict 1.5 Year PFS for DLBCL Treated with RCHOP

- 82 DLBCL,6-8 cycles RCHOP (14 or 21) in 5 Italian centers
  - IPI: L-LI in 47, HI-H in 35
- PET2, PET3, PET4 ,
- CR rate predicted by interim PET results
  - 96% if PET negative
  - 74% if positive (p=.004)

Interim PET Evaluation



Final PET Evaluation



Pregno et al. ASH 2009, abst 99.

published trials modifying therapy
based on interim PET

Autologous BMT for aNHL Based on Early FDG-PET

Primary Goal: To determine the outcome of early treatment intensification for midtreatment PET+ disease, a phase II trial of risk-adapted therapy was conducted

Kasamon YL, et al. Biol Blood Marrow Transplant 2009;15: 242

Autologous BMT for aNHL Based on Early FDG-PET

detect an absolute 25% increase in 2yr EFS in mid PET+ pts, assuming a 2yr EFS of 20% historically in mid PET+ pts who did not receive early ASCT

Median fu after ASCT 34.1 mo

Mid PET+ in 56%; 85% received ASCT, actuarial 2-yr EFS 75%

No association between the IPI and the mid PET result

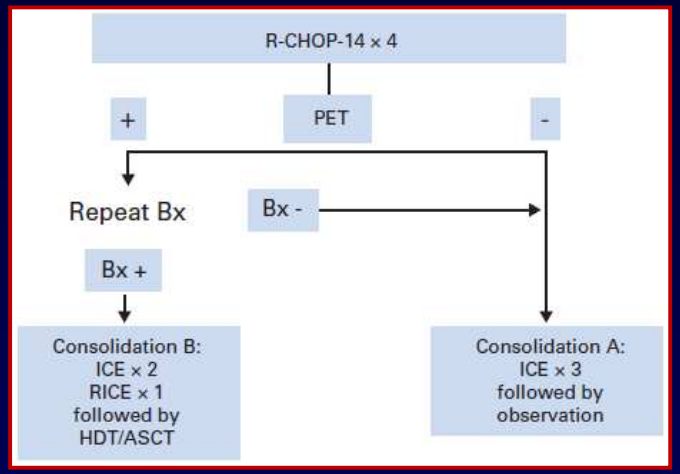
Favorable outcome achieved in historically poor-risk pts warrants more definitive investigation of treatment modification based on early PET

Kasamon YL, et al. Biol Blood Marrow Transplant 2009;15: 242

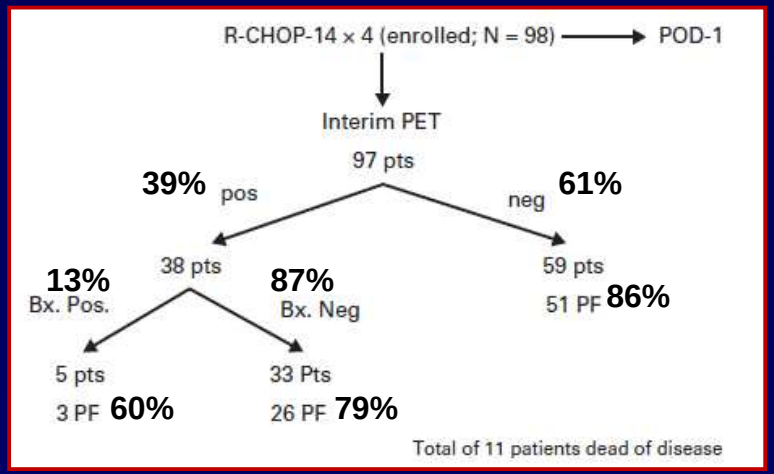
Risk-Adapted Dose-Dense Immunochemotherapy Determined by Interim FDG-PET in Advanced-Stage DLBCL

interim FDG+ disease within a risk-adapted sequential immunochemotherapy program

N=98 pts



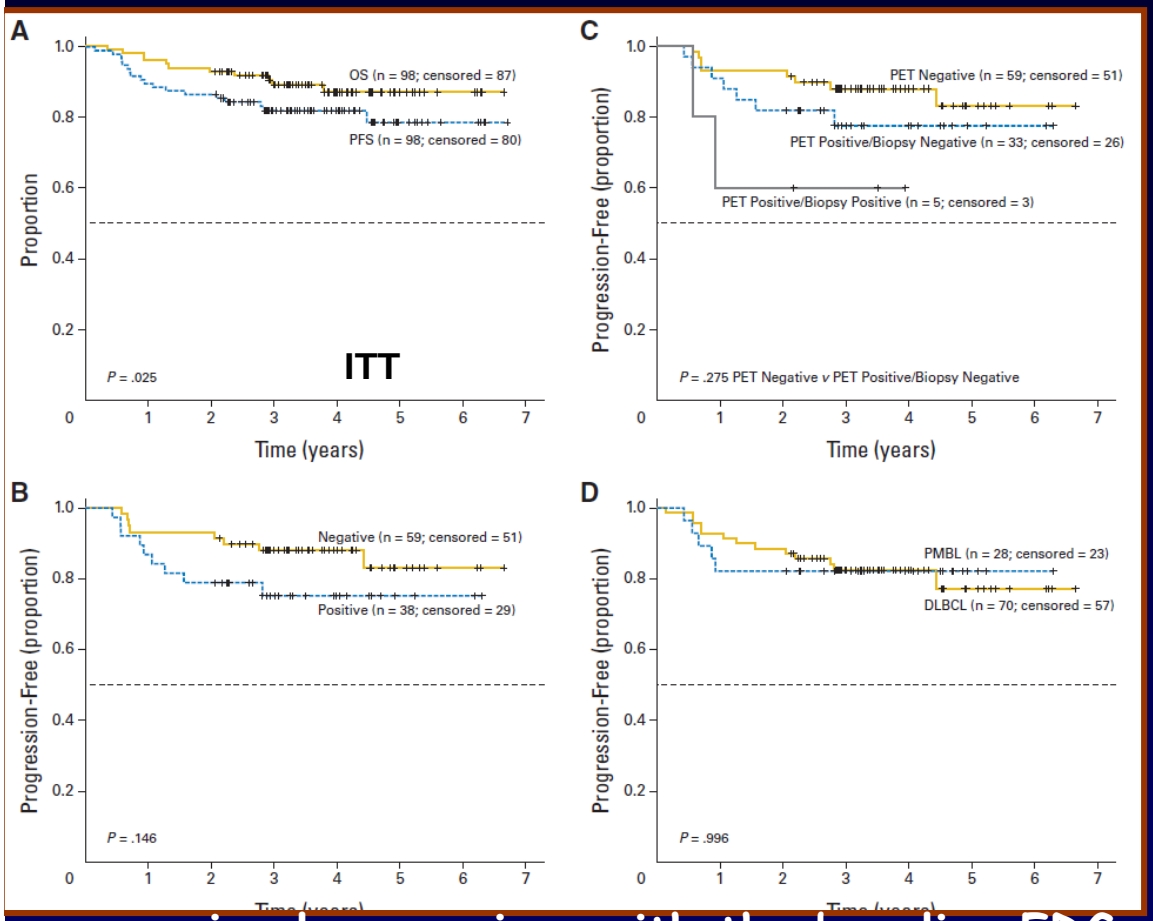
At a med fu 44 mo, PFS 79%, OS 90%,
86% PET4- and 76% PET4+ were progression free



PFS was not different between PET4- and PET4+ groups (P = .27)

Moskowitz CH J Clin Oncol. 2010 Mar 8. [Epub ahead of print]

Risk-Adapted Dose-Dense Immunochemotherapy Determined by Interim FDG-PET in Advanced-Stage DLBCL



	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	

visual comparison with the baseline FDG uptake and uptake in surrounding normal tissue at interim

Interim or post-treatment FDG-PET did not predict outcome with this dose-dense, sequential immunochemotherapy program

Moskowitz CH J Clin Oncol. 2010 Mar 8. [Epub ahead of print]

Interim FDG PET in DLBCL
Summary

- The role of an interim PET to early identify response to chemo is unproven with recent data raising doubt on the value of interim

- Data have significant heterogeneity in patient risk groups , timing and therapy choice

- Some reports show better correlation of post-therapy PET with PFS than interim PET

- More data necessary to test predictive value of PET in homogeneous populations with standardized methodology and criteria

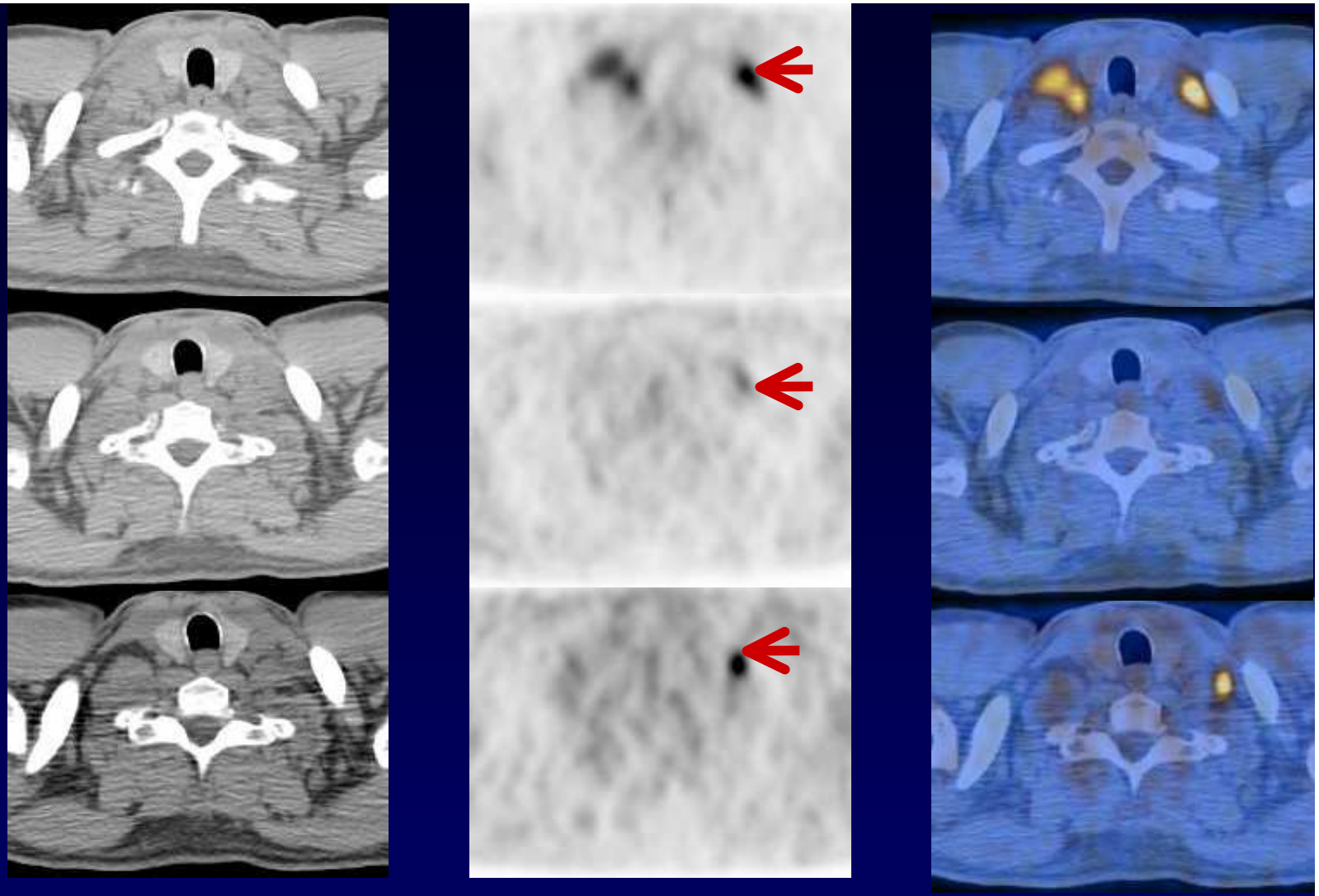
- Is it time to move into novel agents??

HL

Baseline

One cycle

Completion



- 70-80% NEGATIVE interim PET
- 20-30% POSITIVE interim PET
  - ✓25-30% will have mild uptake

If mild uptake is considered "-" then 80-90% PET2-

Evaluation of Response During Therapy- HD

Author	Cycles	#	PPV	NPV	Endpoint		Responder FDG -	Non-R FDG +
Friedberg	3	22	80	94	PFS	2 yr	-	-
Hutchings	2-3	85	62	94	PFS	2 yr	85%	4%
Kostakoglu	1	23	83	100	PFS	1.5 yr	85%	15%
Hutchings	2	77	69	95	PFS	2 yr	85%	4%
Gallamini	2	260	86	95	PFS	2 yr	81%	19%

Median follow 23-40 months

NPV of midtreatment PET has been consistently high at least 95%

However, PPV quite variable, 60 – 90% depending on stage

Interim FDG PET - Response Evaluation in HL

	Year	#	Prog or Relapse (%)	Sens	Spec	+LR	-LR
Friedberg	2004	22	23	0.80	0.94	13.6	0.21
Hutchings	2005	28	32	0.67	1.00	26.0	0.36
Gallamini	2006	108	19	0.86	0.98	37.3	0.15
Hutchings	2006	46	28	0.77	0.97	25.4	0.24
Kostakoglu	2006	10	50	1.00	1.00	11.0	0.09
Zinzani	2006	40	23	0.89	1.00	54.4	0.15
Gallamini	2007	106	20	0.79	0.95	17.2	0.22

NPV of midtreatment PET has been consistently high at least 95%

However, PPV quite variable, 60 – 90%

Terasawa, T. et al. J Clin Oncol; 27:1906-1914 2009

Interim FDG PET
Advanced Stage HL

In a systematical review to evaluate the prognostic accuracy of FDG PET for early interim response assessment in untreated advanced stage HL (n=360)

combined sensitivity 81% and specificity 97%

Terasawa T, et al. J Clin Oncol 2009;27:1906.

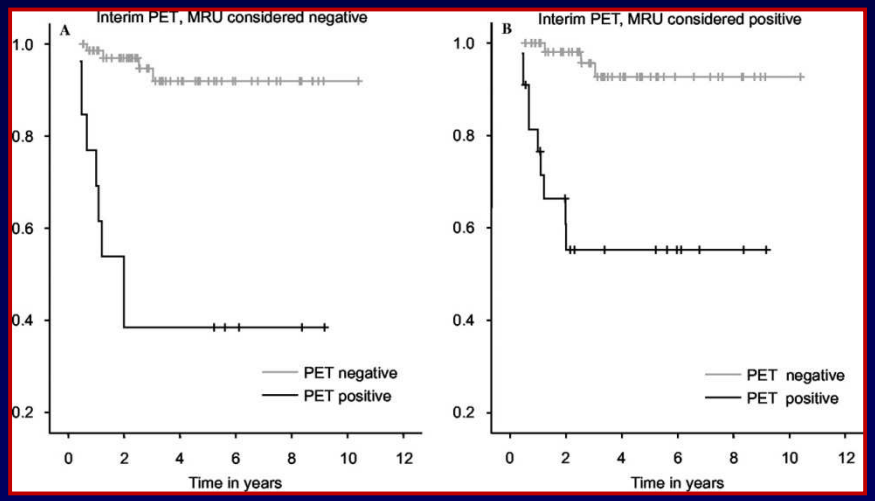
past trials determining the predictive value of interim PET

FDG-PET After 2-3 Cycles

85 pts, med fu 40 mo, Med age 37, 50% male, stage I-II 67%, END 23.5%, B symp 31%, NLP 14%

After 2-3 cycles, 95% PET- pts achieved CR
90% MRU achieved CR
69% PET + pts progressed

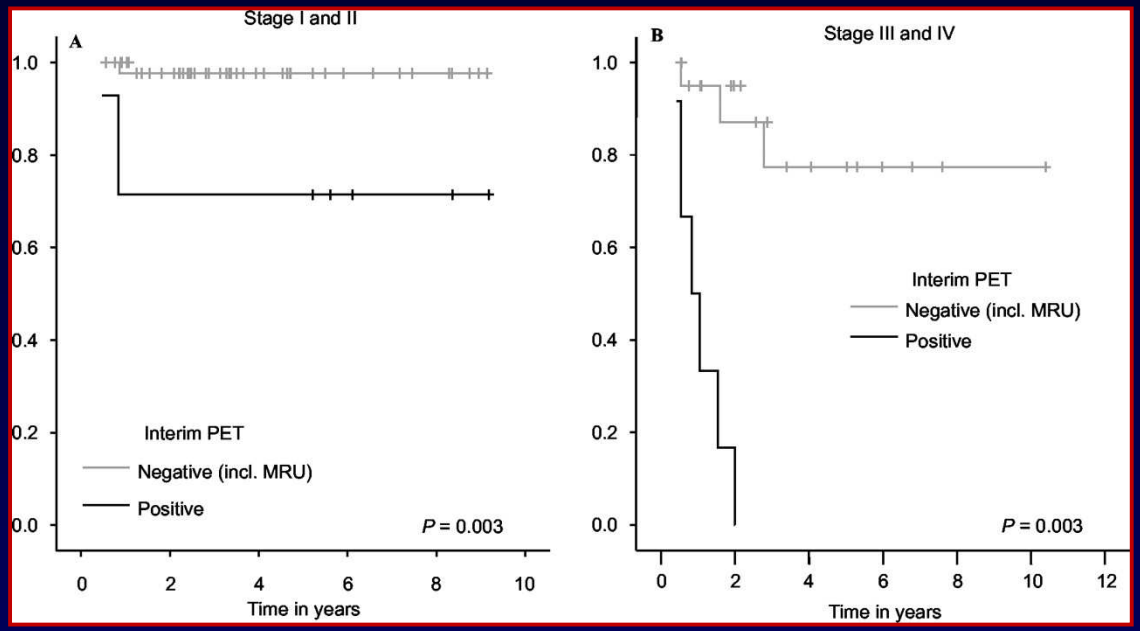
Best predictive value is obtained if MRU is regarded as PET-



	Interim PET+	Interim PET-	
2 yr PFS	46.2%	96.8%	MRU considered -
5 yr PFS	38.5%	91.5%	

Hutchings M et al Ann Oncol. 2005; 16:1160

PFS according to the outcome of early interim FDG-PET for (A) stage I–II patients and (B) stage III–IV patients



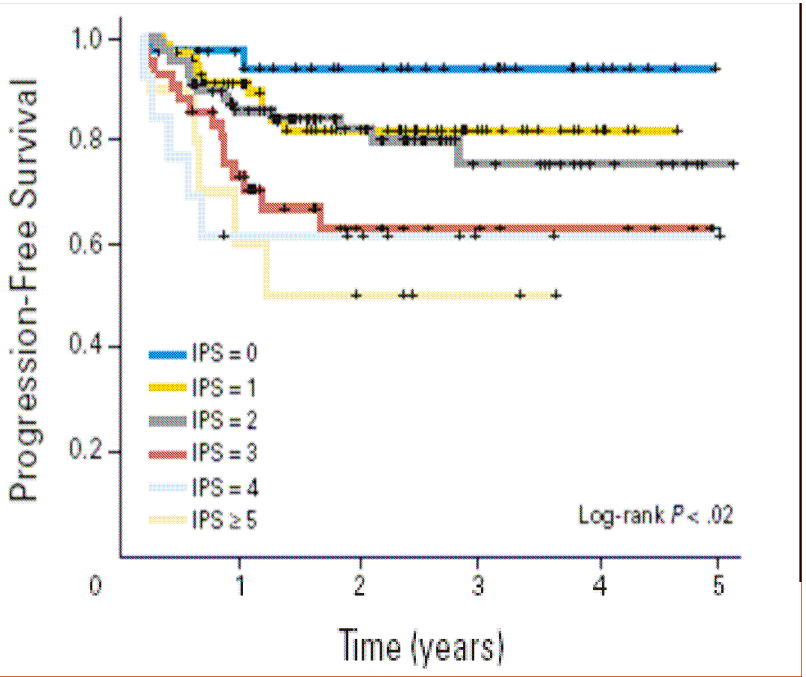
Overall	PPV:	61%
	NPV:	100%
Early stage	PPV:	25-28%
	NPV:	100%
Adv stage	PPV:	91-100%
	NPV:	91-100%

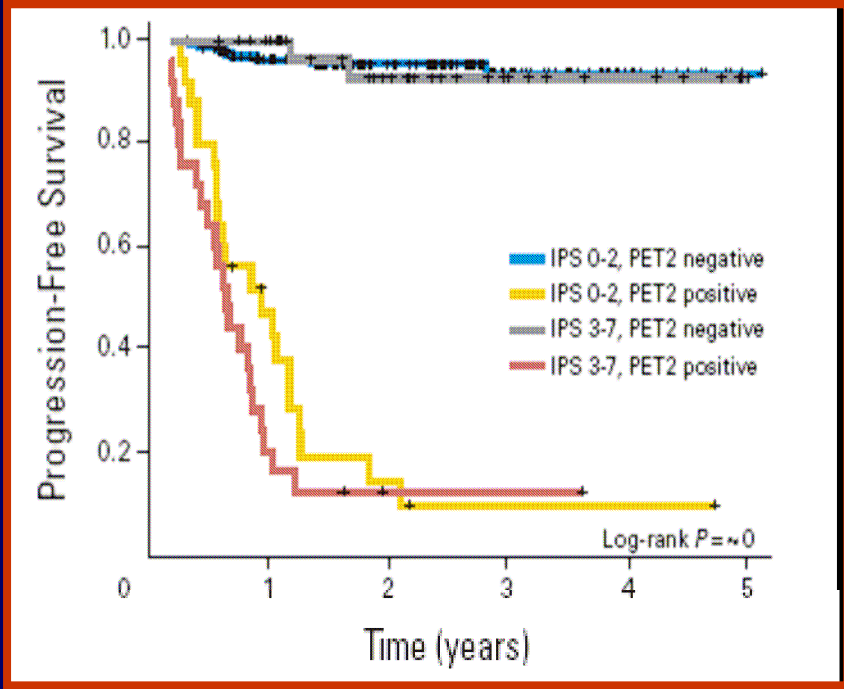
Hutchings M et al Blood. 2006;107:52
Hutchings M et al Ann Oncol. 2005; 16:1160

Advanced Stage HL

- 260 HL patients
  - unfavorable stage IIA 26%
  - stage IIB 27%
  - stage III-IVB 47%
- End-point: 2yr PFS, med f/u 2.2 yrs
- 79% CR; 16% progressed < 6 mo; 4% relapsed after CR
- PET2+ in 19% PPV 86% ; FP 14%
- PET2- in 81% NPV 95% ; FN 5%
- Sens and spec: 81% and 97%
- 2-yr PFS for PET2- vs PET2+
  95% vs 13%,

Positive PET: uptake > MBP
- Negative PET: no pathological FDG uptake at any site





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

FDG-PET After 1 Cycle

Aim: assess the value of FDG-PET after 1 cycle of chemoRx for prediction of PFS in HD and NHL

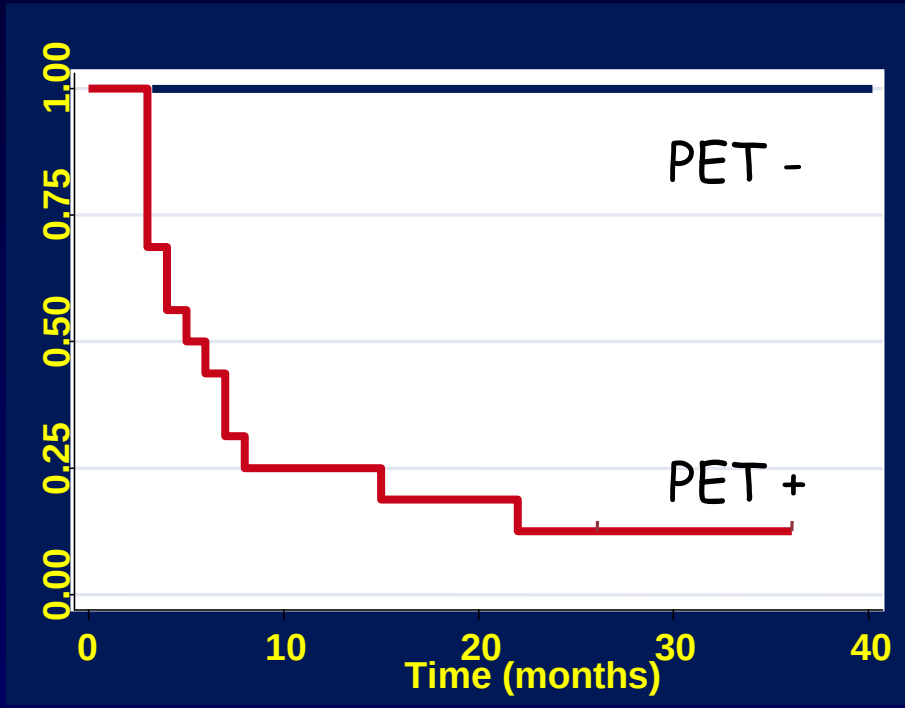
47 newly dx'ed (HD=23; NHL=24), PET post 1, 6 cycles

Results: Med f/u 28 mo

- Post 1 cycle, 87.5% PET– pts CR
  100% PET+ pts prog

- Strong association between PET after 1 cycle and PFS ($P < 0.01$)

2-year PFS	PET1	PET6
PET1–	100.0%	90%
PET1+	12.5%	8.3%



Kostakoglu L, et al Cancer. 2006; 107:2678

recent trials determining the predictive value of interim PET

Validation of the International Harmonization Project (IHP) Guidelines in Early Stage Hodgkin Lymphoma (HL) Treated with Adriamycin, Vinblastine and Gemcitabine (AVG) (CALGB 50203)

88 pts, newly dx, stage I-IIB, NONBULKY
med fu 3.3 yrs

Patients: Med age 36 yrs, male 47%, >40 yrs 42%, Stage IIB 20%, favorable 28% (CTIC/EORTC)

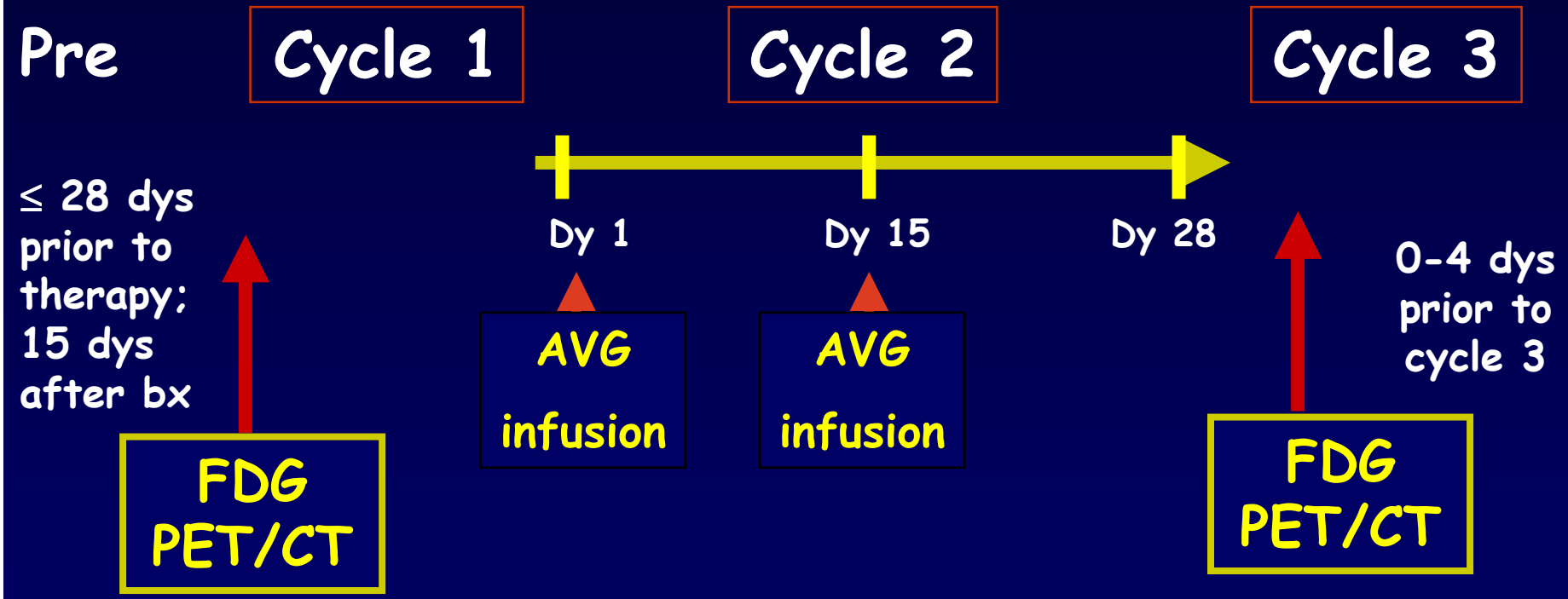
IHP-based PET interpretation was also compared with CT-based lesion size changes

Results: 73% CR/Cru, 3 yr PFS 77%

21 patients progressed

73% PET- 27% PET2+ by IHP criteria

FDG PET Imaging Timelines



CALGB 50203
PET/CT after 2 cycles n=88

Med fu 3.3 yrs, 73% CR/Cru, 3 yr PFS 77%

50% of stage IIB pts achieved a CR/CRu (50%) compared to 60% who were not Stage IIB (p=0.59)

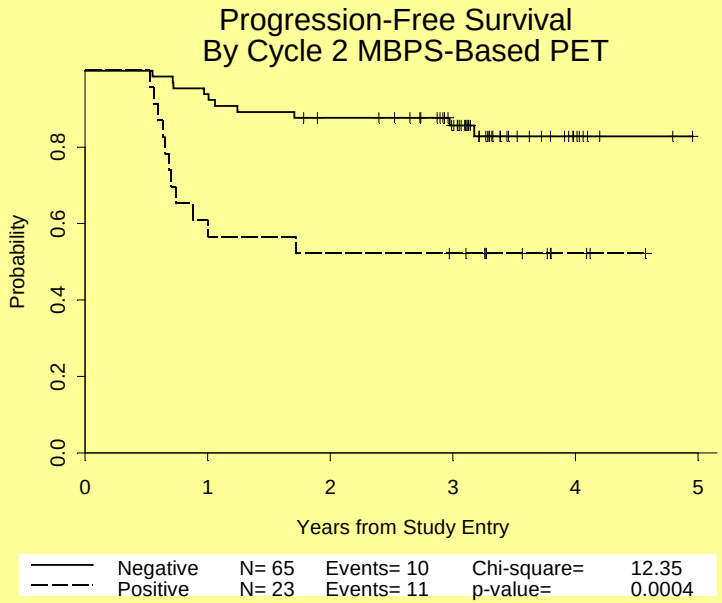
IHP-based

12% with CR/Cru were PET2+ vs 49% in those with SD or PR (p=0.0004)

Liver-based

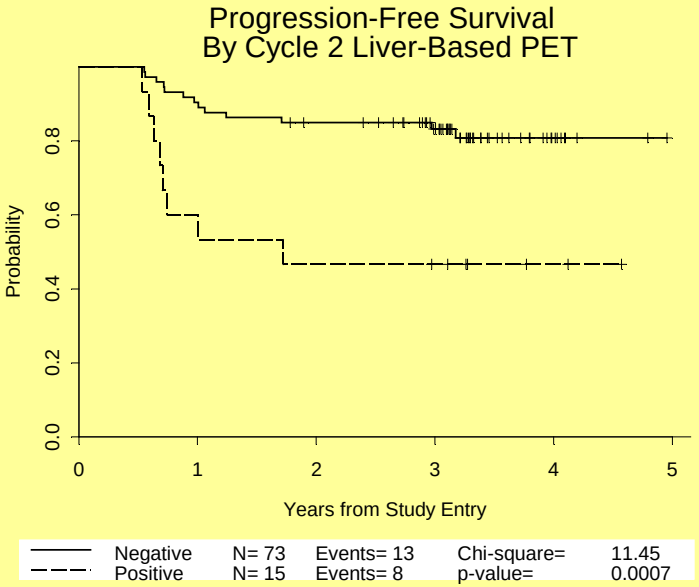
10% with CR/Cru were PET2+ vs 30% in those with SD or PR, (p=0.024)

Estimated 2-year probability of PFS (n=88)



PET –ve: 0.88, 95% CI (0.77,0.94)
PET +ve: 0.54, 95% CI (0.33,0.71)
PET+ HR: 3.8 95% CI (1.6,9.1)
p < 0.0001

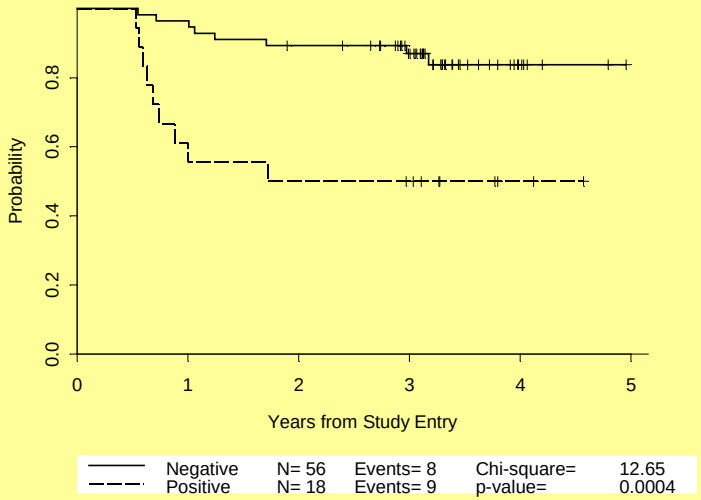
PPV: 46%
NPV: 84%
Sensitivity: 52%
Specificity: 81%



PET –ve: 0.85, 95% CI (0.74,0.91)
PET +ve: 0.50, 95% CI (0.25,0.71)
PET+ HR: 3.6, 95% CI (1.5,8.8)
p < 0.0001

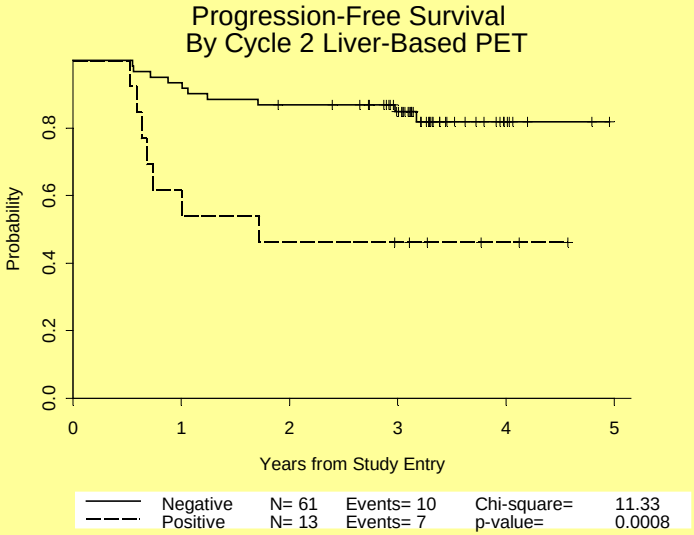
PPV: 50%
NPV: 82%
Sensitivity: 38%
Specificity: 88%

Estimated 2-year probability of PFS for PET/CT only (n=74)



PET –ve: 0.89 , 95% CI (0.78.0.95)
PET +ve: 0.50 , 95% CI (0.26,0.70)
PET+ HR: 4.8 95% CI (1.8,12.5)
p < 0.0004

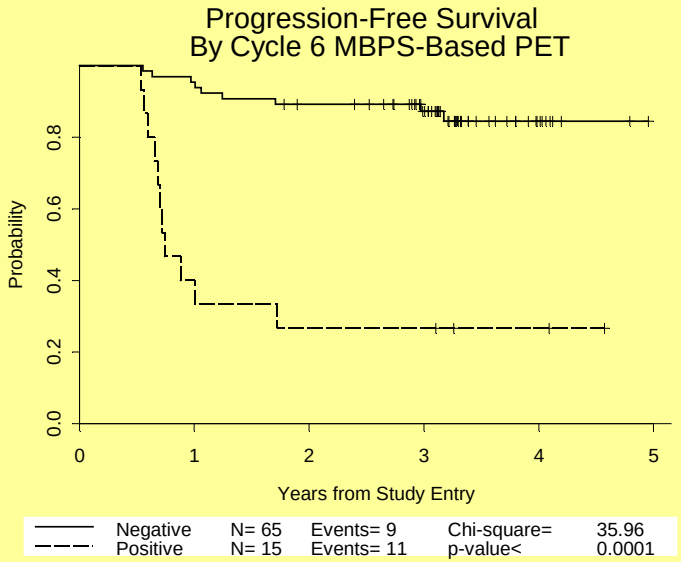
PPV: 50%
NPV: 86%
Sensitivity: 53%
Specificity: 84%



PET –ve: 0.87, 95% CI (0.75.0.93)
PET +ve: 0.46, 95% CI (0.19.0.70)
PET+ HR: 4.6, 95% CI (1.7,12.0)
p < 0.0001

PPV: 54%
NPV: 84%
Sensitivity: 41%
Specificity: 89%

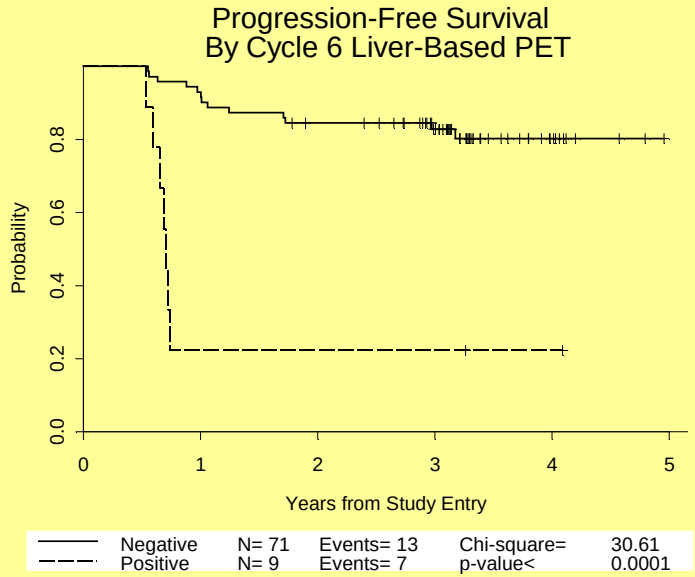
Estimated 2-year probability of PFS (n=88)



PET –ve: 0.89, 95% CI (0.79,0.95)
PET +ve: 0.27, 95% CI (0.08,0.50)
PET+ HR: 9.6, 95% CI (3.9,23.8)
p < 0.0001

PPV: 73%
NPV: 86%
Sensitivity: 55%
Specificity: 93%

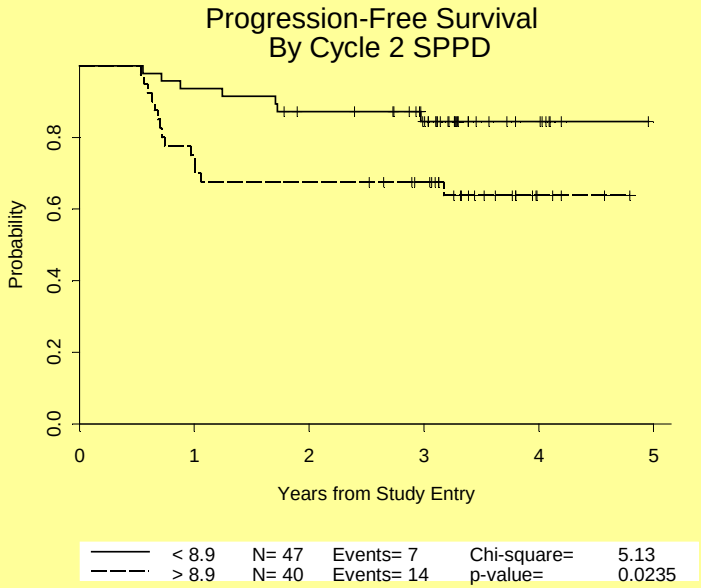
10 of 23 (43%) PET2+ became PET6- and 1/10 progressed



PET –ve: 0.85, 95% CI (0.74,0.91)
PET +ve: 0.22, 95% CI (0.04,0.51)
PET+ HR: 9.3, 95% CI (3.6,24.1)
p < 0.0001

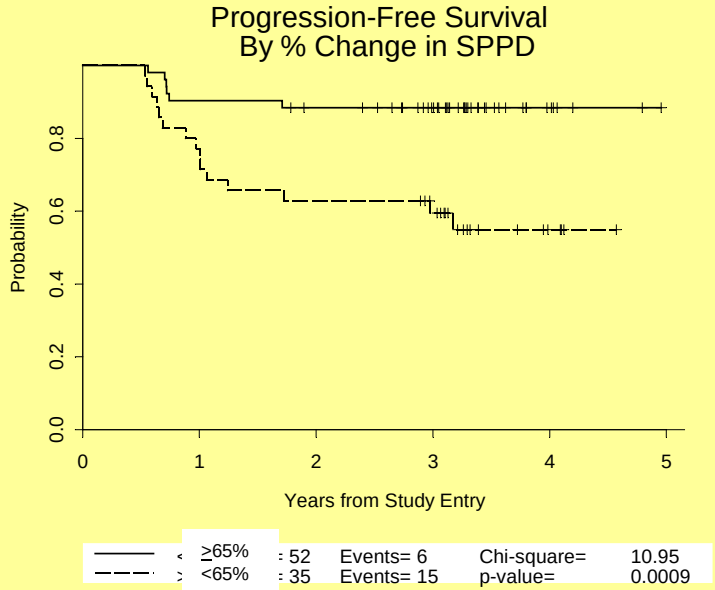
PPV: 78%
NPV: 82%
Sensitivity: 35%
Specificity: 97%

CT Measurements
Estimated 2-year probability of PFS (n=88)



SPPD<8.9 : 0.87, 95% CI (0.74,0.94)
SPPD≥8.9 : 0.68, 95% CI (0.51,0.80)
PET+ HR: 2.7, 95% CI (1.1,6.8)

PPV: 35%
NPV: 85%
Sensitivity: 67%
Specificity: 61%



%Δ≥65% : 0.88, 95% CI (0.76,0.95)
%Δ<65% : 0.63, 95% CI (0.45,0.76)
PET+ HR: 4.3, 95% CI (1.7,11.2)

PPV: 43%
NPV: 88.5%
Sensitivity:68%
Specificity:70%

2-Year PFS Probabilities

Group	#	Probability	95% CI	# Prog	% Prog
Qualitative					
PET2- / ≥ 65%	46	0.91	0.78,0.97	4	8.7%
PET2- / < 65%	25	0.72	0.50,0.86	9	36.0%
PET2+ / ≥ 65%	6	0.67	0.19,0.90	2	33.3%
PET2+ / < 65%	10	0.40	0.12,0.67	6	60.0%
Qual and CR/noCR					
PET2- / CR	46	0.89	0.76,0.95	7	15.2%
PET2- / no CR	26	0.77	0.55,0.89	6	23.1%
PET2+ / CR	5	0.80	0.20,0.97	1	20.0%
PET2+ / no CR	11	0.36	0.11,0.63	7	63.6%

Conclusion

FDG PET yields a high correlation with 2-yr PFS

IHP-based and liver-based interpretation yielded similar results after 2 cycles of chemo

The prediction of PFS using FDG-PET is superior to %SPPD change after 2 cycles of therapy

However in PET+ cases % change in SPPD may streamline the true positive population

Ongoing studies will prospectively define the role of interim FDG PET in tailoring treatment to optimize benefits and minimize risks

Multicenter, 163 HL, stage I-IIA, PET2 and PET6
3-4 course of ABVD followed by IFRT 30 Gy
No treatment variation based only on PET-2 allowed

Patients:
med age 33 yrs, 48% male, 91% stage II, bulky 28%
91% treated with chemoRT

Results:
90% CR, 10% chemoresistant: 56% prog, 44% relapse

PET2+ 14%: 52% rel/prog and 48% in CR
PET2- 86%: 7% rel/prog and 93% in CR

Sensitivity	Specificity	PPV	NPV
55%	92%	52%	93%

2-yr FFS for PET2- 94% and PET2+ 58%

65% of prog during Rx or within 12 mo after CR, PET2+

Rigacci L, et al. EHA, 14th Congress, June 4-7, Berlin, 2009. 0087

Methods: 178 pts HL, PET2
med age 33, 48% male, 63% stage I-II,B-symp 46%, bulky 30%, ABVD 97%, 3% BEACOPP,
revised IWG

Results: med fu 42 mo, 85% CR; 4% PR; 2% SD; 9% PD/dead
39 pts had ASCT following 1st line

PET2- 84%
PET2+ 16% (93% PR, 3.5% SD, 3.5% PD)

PET2- 90% continuous CR
PET2+ 0% CR

In this unfavorable group, 32% durable CR after ASCT

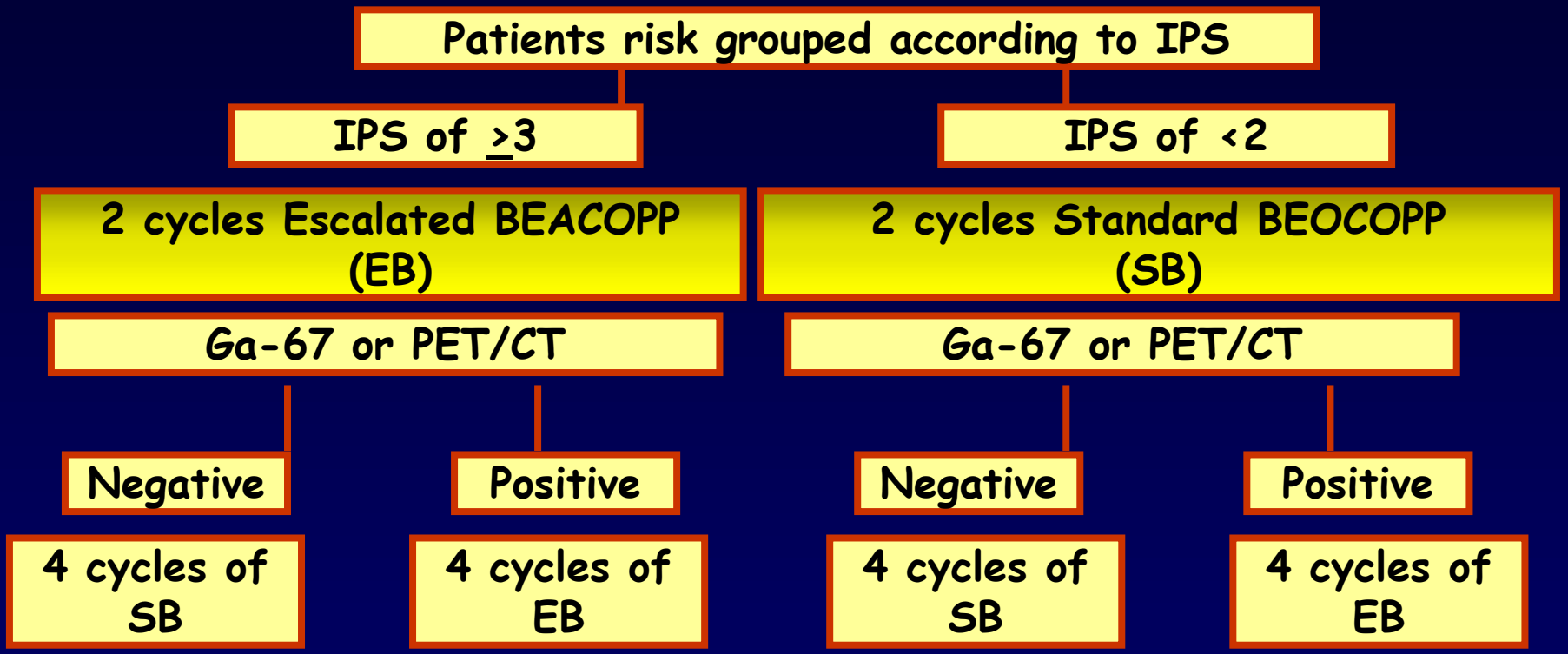
Conclusions:
- High NPV of PET2 in HL
- There may a potential role for ASCT in inducing a CR early during therapy in those pts who have a PET2+

Stefoni V et al. *Blood* 2009 114: Abstract 1659

published trials modifying therapy
based on interim PET

Phase II Risk Adapted Therapy in Advanced HD

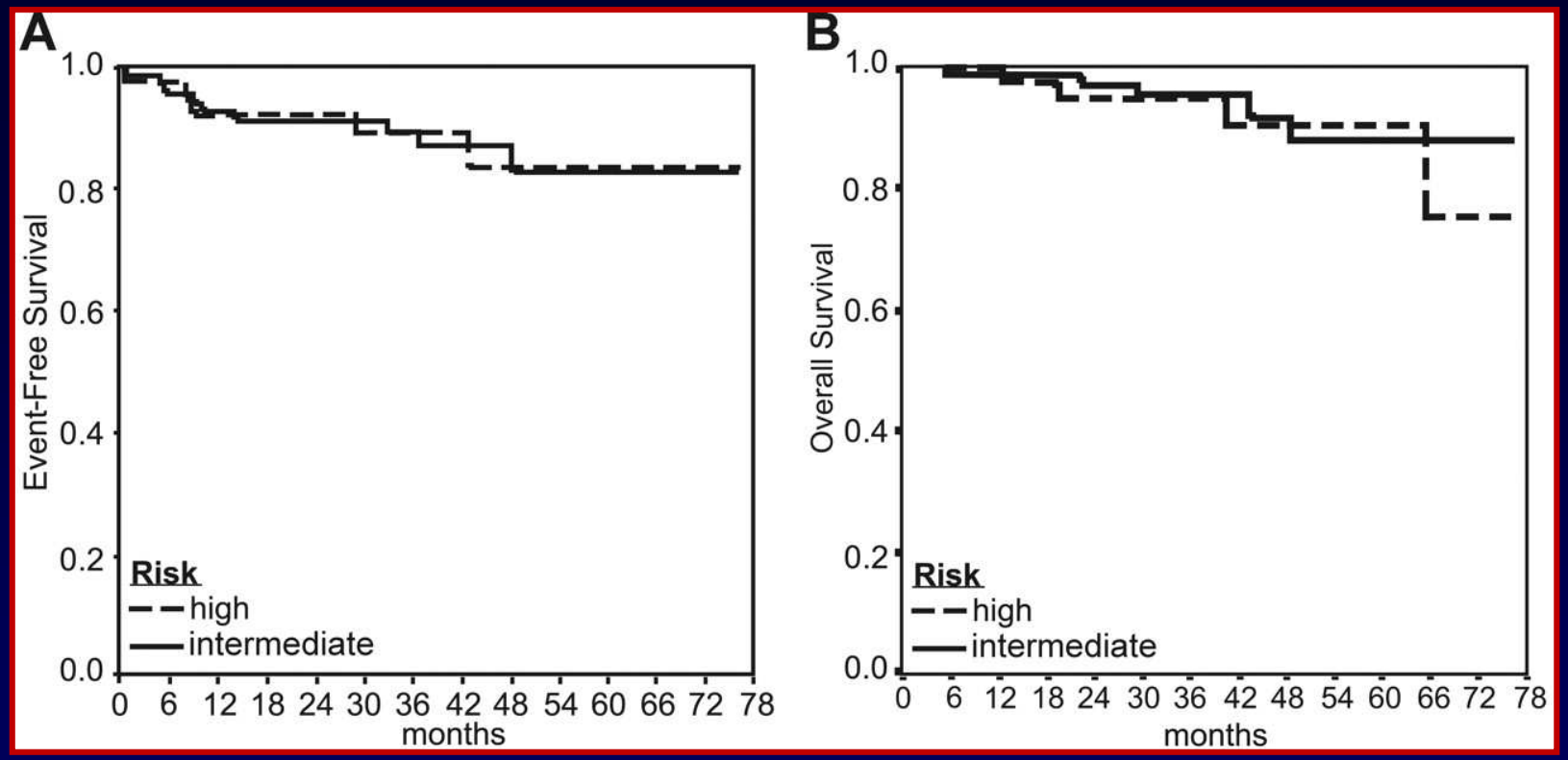
108 HD patients with adverse prognostic factors prospectively evaluated



- Similar EFS and OS observed for both risk groups

Dann EJ et al , Blood. 2007;109:905.

EFS and OS according to patient risk groups - med fu 47mo



5-year EFS for all patients: 85%

5-year EFS for early unfavorable and I risk versus H risk pts were 84% and 85%, respectively.

OS from diagnosis: 90%

5-year OS for early unfavorable and intermediate risk versus high risk pts were 90% and 91%, respectively.

Dann EJ, et al.: Blood. 2007;109:905

For Standard and High-Risk HL Patients, Six Cycles of Tailored BEACOPP, Based On Interim Scintigraphy, Effective and Female Fertility Is Preserved

5-y FFS and OS were 92% and 97%, respectively at a med fu 56 mo

94% with PET2- had no disease progression during the fu, while 17% of patients with PET2+ progressed

38 females < 40 years old treated with tailored BEACOPP assessed for fertility status. 26 were co-treated with the GnRH agonist, concomitantly with chemo. 19 conceived during fu

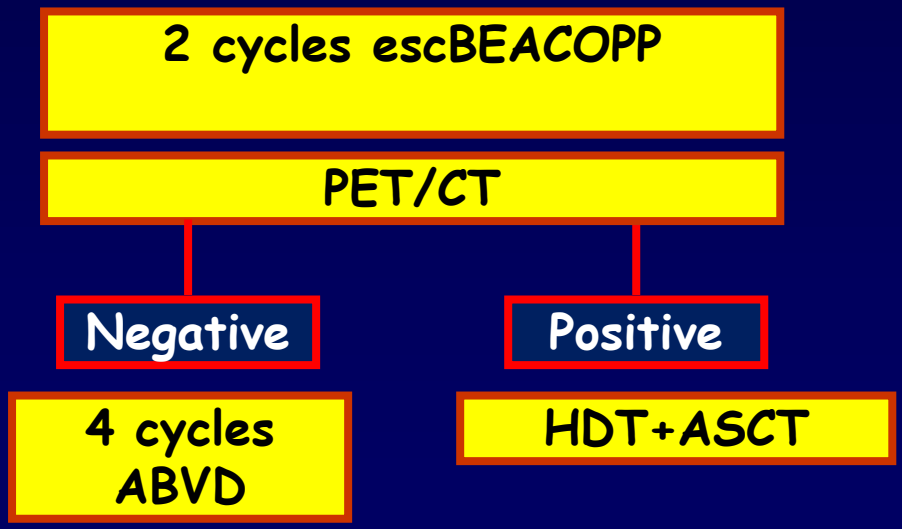
Use of tailored therapy enables reduction of cumulative chemotherapy and preservation of fertility in the majority of young female patients

Dann EJ, et al, *Blood* 2009 114: Abstract 1552

Risk Adapted Therapy in Advanced HL

This study conducted in an attempt to reduce the toxicity of the original schedule, while attempting to preserve improved initial control

44 newly diagnosed patients with adv-stage HL and IPS≥ 3



Avigdor A et al, Ann Oncol. 2009;21:126

PET2+ 29.5% and had ASCT
PET2- 70.5% treated with ABVD x4

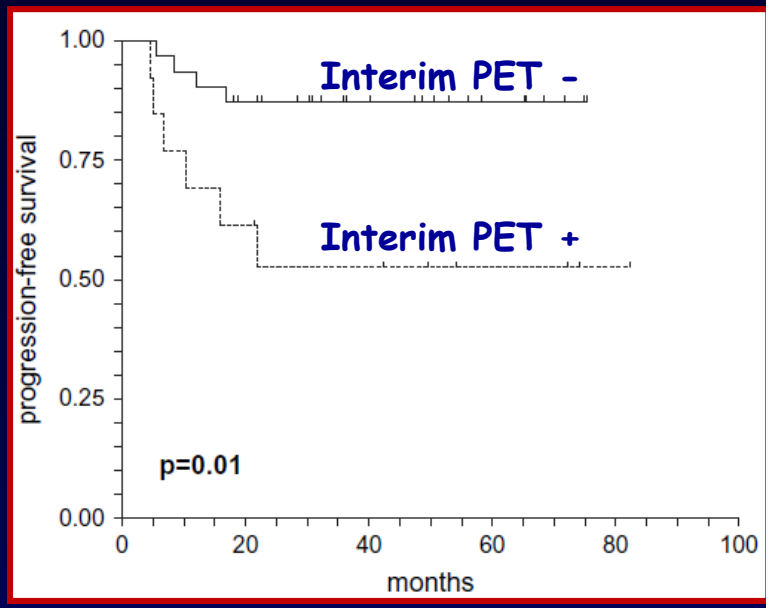
mean fu of 48 mo,
PFS 78% and the OS 95%

Results:

At the end of all therapy (revised IWG)

OR	CR	PR	Prog
100%	89%	7%	4%

4-year PFS	PET2-	PET2+	
	87%	53%	(P = 0.01)



Combined escBEACOPP-ABVD may improve outcome in HR adv HL

The potential benefit of early-interim PET as a guide to therapy merits further studies

Avigdor A et al, Ann Oncol. 2009;21:126

PET is Quantitative

Interim PET SUV Based Assessment

- Can SUVs help to improve the prognostic value of FDG PET compared with visual analysis?

- Between PET0 and PET2, a 66% reduction in SUVmax predicted EFS in DLBCL patients

Lin et al, J Nucl Med 2007;48:1626–1632

- Between PET0 and PET4, a 73% reduction in SUVmax yielded a 2yr estimate for EFS in 79% of pts vs. 32% in those with reduction of 73% or less ($P < 0.0001$)

Itti E, et al. J Nucl Med. 2009;50:527.

45 pts, RCHOP or CHOP-like reg, FDG PET at 2 cycles

-IHP criteria (PET+ if >MBP)
-Liver as a reference (PET+ if >liver)

-SUV_{max} cut-off 65% by ROC

Results: med fu 25 mo
med age 50 yrs, 73% <61 yo, age-adjusted IPI, 2-3 49%, 13% rel/prog and 4 died from prog

	PET2+	PET2-
IHP	64%	36%
2 yr PFS	83%	93% (p=0.3)
Liver	44%	56%
2 yr PFS	75%	95% (p=0.04)
SUV_{max} 65%	20%	80%
2 yr PFS	56%	94% (p=0.0009)

Casasnovas RO, et al. *Blood* 2009 114: Abstract 2931

Interim PET After 2 cycles in HL

- Interim PET has a high NPV for PFS, OS
- Therapy efficacy, patient risk categories and scan reading heterogeneity negatively impact the high NPV
- Interpretation standardization is yet to be established
- Value of SUV should be explored
- More data from ongoing randomized studies will establish the role of interim PET
- Oncologists should agree on a consensus to establish an acceptable FP rate to take on risk

Pressing Clinical Questions

1.Using interim PET as a surrogate marker for chemosensitivity, can we define the eligibility for,

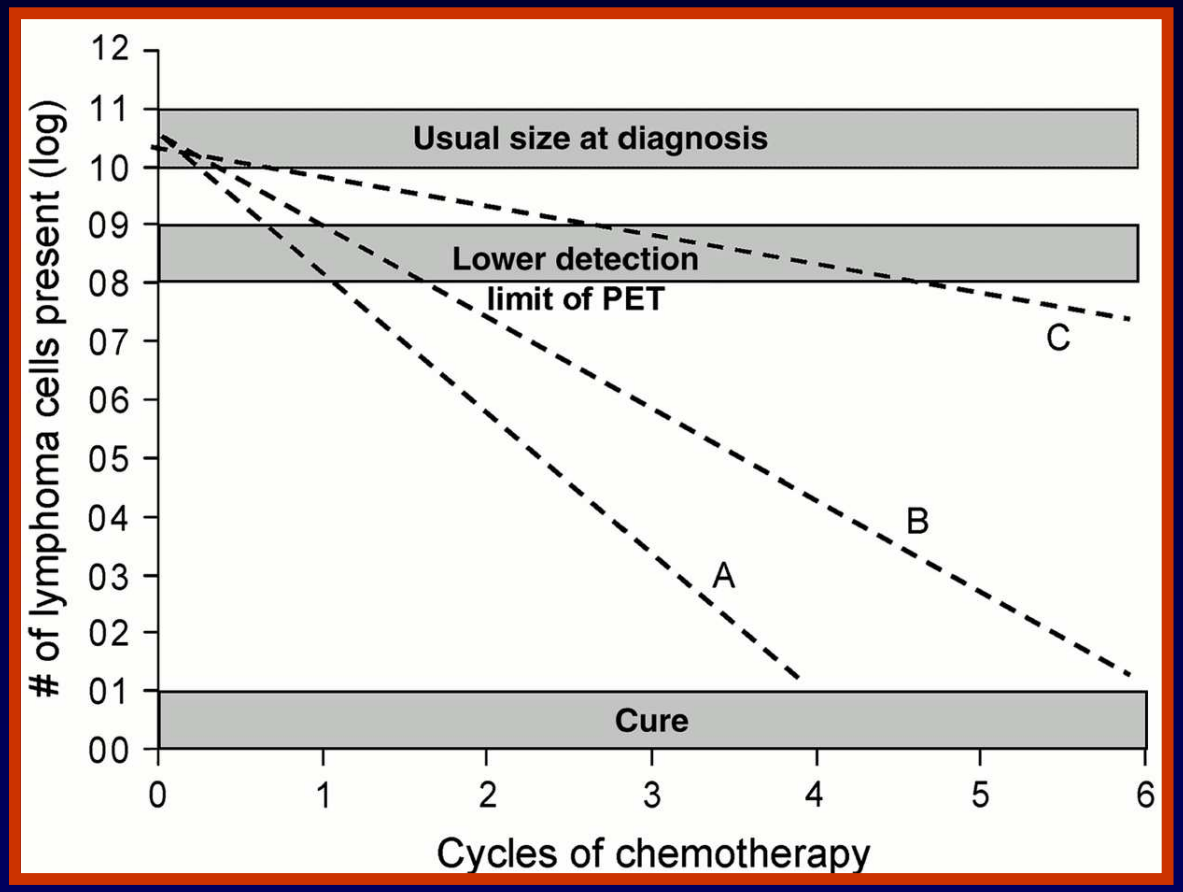
- aggressive front-line therapy, while sparing toxicity/AE for those who can otherwise be cured with conventional treatment? ONGOING

- avoidance of RT, or abbreviated front-line therapy whose efficacy = conventional treatment? ONGOING

2.Would adaptive strategy lead to a better outcome?

- Escalated therapy increases survival? ONGOING
- Escalated therapy leads to better survival than salvage??
- Could inherent drug resistance be overcome by escalated therapy??
- Abbreviated therapy increases quality of life??

Kinetics of Cell Kill vs PET

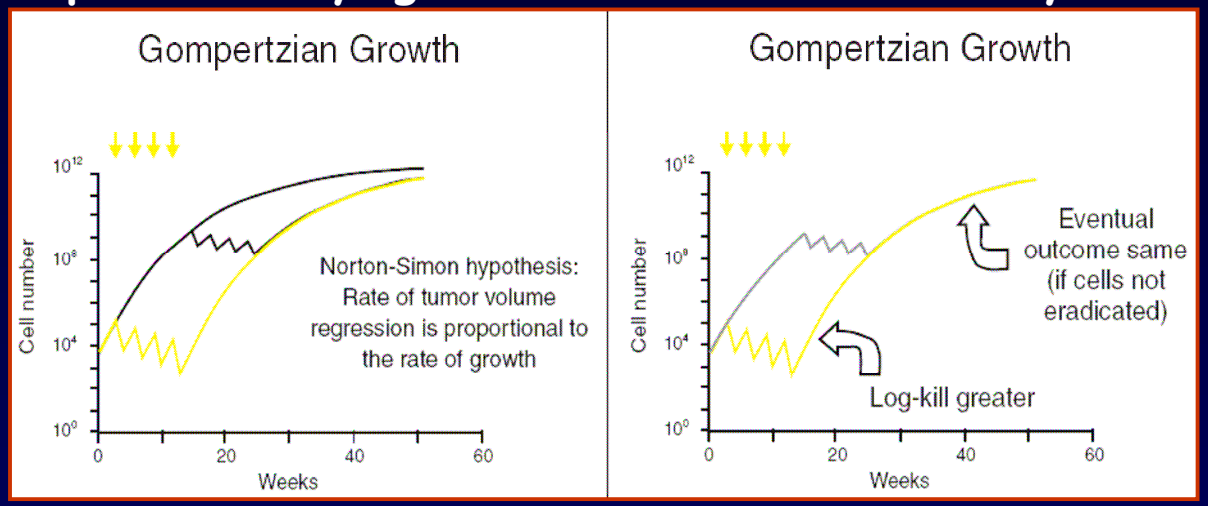


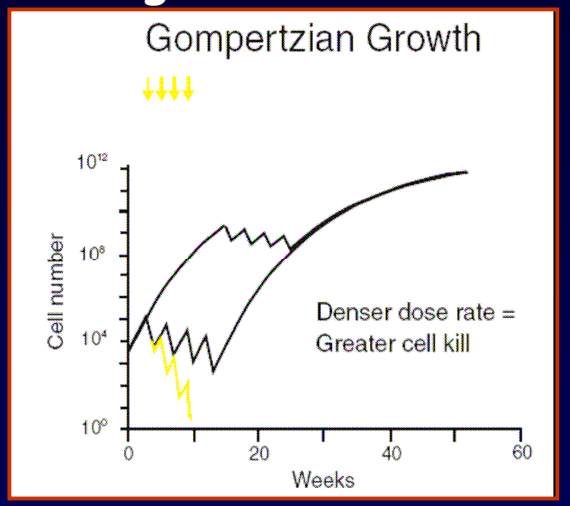
- Line B: min rate of tm cell killing that would lead to cure
- Line A: more brisk response that would produce cure after 4 cycles
- Both lines would be associated with negative PET results after 2 cycles
- Line C: rate of tm cell killing associated with negative PET after 4–6 cycles but would not produce cure
- PET results for line C would be positive after 2 or 3 cycles

Kasamon Y et al J Nucl Med. 2007 Jan;48 Suppl 1:19S.

Mathematical Modeling
Norton-Simon Hypothesis

- Mathematical modeling of tm cell kill clinically validated to show the impact of varying doses and intensities of cytoreductive agents





- It is a reasonable assumption that the rate of cell killing by chemo is proportional to tumor growth rates;

  - smaller tms are more easily eradicated than larger tms
  - if the tms are given less time to resume their growth between treatments they are more likely to be destroyed
  - this is the basis of dose-dense therapy ; may also serve as a basis for administration of salvage therapy early during the course of therapy before the progressing tumor attains a large volume

Norton L. A. Cancer Res 1988;48:7067
Norton L, Simon R. Cancer Treat Rep 1986;70:163