1st Postgraduate Lymphoma Conference
Session II: Follicular Lymphoma

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FDG PET/CT: the new entry is Follicular Lymphoma

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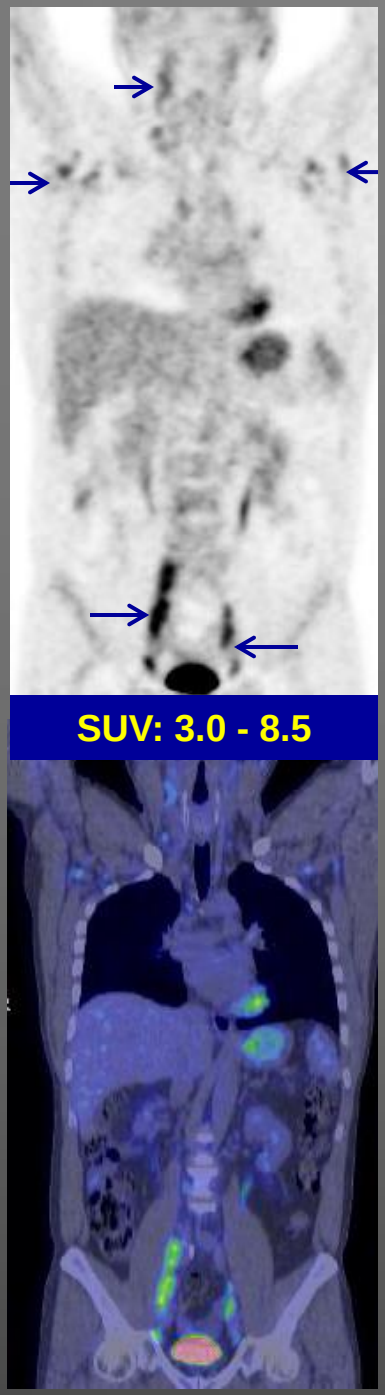
FL Facts

- typically presents with superficial small LNs
- uncommon mediastinal and isolated splenic inv
- BM is involved in 50-60% of the cases
- risk of histologic transformation
- initially sensitive to ICT, recurrent relapses
- FLIPI and FLIPI2, fail to identify pts with a particularly poor outcome
- outcome of FL patients are highly variable
- FDG PET/CT is positive in ~95% of cases



Weiler-Sagie M,. J Nucl Med 2010, Elstrom R Blood. 2003 , Wohrer S, Ann Oncol. 2006, Karam M, Cancer. 2006 , Tsukamoto N,.Cancer ,2007 Wirth A, Int J Radiat Oncol Biol Phys. 2008, Scott A, EJ NM 2009

Current and potential roles of FDG PET/CT in FL

I. At initial presentation

- Staging - YES
- Prognostication - ??
- Risk of transformation – YES
- Therapy decision & RT field-YES

II. After 1st line therapy

- Eval/prediction of response
  - ICT - YES
  - IT - YES
  - incremental role (molecular response) - ??
- Prediction of PFS - YES

  after induction in untreated
  - maintanence
  - no maintanence

III. At relapse

- Prediction of PFS
  - after salvage before ASCT
  - after induction of rel/ref FL
- Prognostication

IV. Follow-up after therapy

PET-CT
Initial Staging of FL

PET-CT - Stage Migration

- FDG PET/CT sensitive for staging FL irrespective of grade
- FDG PET/CT identifies a greater extent of nodal and END sites than std staging with CT in 20-30% of pts

Elstrom R Blood. 2003 , Wohrer S, Ann Oncol. 2006, Karam M, Cancer. 2006 , Tsukamoto N,. Cancer,2007 Wirth A, Int J Radiat Oncol Biol Phys. 2008, Janikova A, Clin Lymph Myeloma. 2008, Scott A, EJ NM 2009, Le Dortz L, EJNM 2010, Luminari S, Ann Oncol. 2013, Smith SD, Blood, 2015

- FDG PET not sensitive for detecting BMI; PET & BMB fair concordance: 60% (κ= 0.2)

Wirth A, Int J Radiat Oncol Biol Phys. 2008, Chen YK, Clin Nucl Med. 2011, Adams H, Skeletal Radiol 2015, Wohrer S, Ann Oncol 2006, Pakos EE, J Nucl Med, 2005, Luminari S, Ann Oncol. 2013

- When PET showed no bone lesions (n=108 pts), BMI 43%

Luminari S, Ann Oncol. 2013

Importance of PET-based Stage Migration

- PET upstages (early to adv stage) in 30 - 62% of FL pts

  Luminari S, Ann Oncol. 2013
  Scott A, EJNM 2009

- Increased accuracy by PET staging probably holds the most benefit in pts with presumed limited stage disease being considered for curative IFRT

- PET-based staging led to a revised RT plan in 34%; shift to palliative-intent in 10%

  Scott A, EJ NM 2009

- In NCCN practice, pts who undergo a PET for initial staging were more likely to receive early therapy

  Abou-Nassar KE, Leuk Lymphoma. 2013

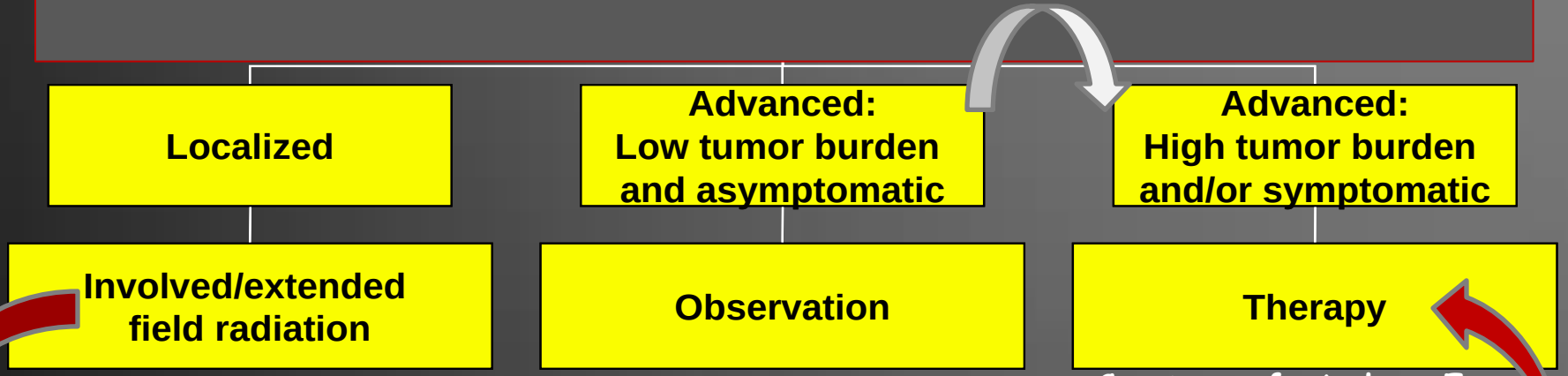
- In adv stage pts, PET detection of more FL sites is clinically less significant; also BMB results proved PET less sensitive

  Luminari S, Ann Oncol. 2013

PET/CT – Initial Management Decisions

- in selected early stage pts, deferred therapy is acceptable; survival of >50% of untreated pts was comparable to that of treated pts

Advani R, JCO 2004;22:1454



Courtesy of Andrew Evens

~50% of early stage pts enjoy durable remission after IFRT

Pugh TJ, Cancer 2010;116:3843

- PET/CT can improve defining margins of RT fields in more extensive local disease in 15%
- identification of multifocal disease may make IFRT futile in 15-30% of pts

Janikova A, Clin Lymph Myeloma 2008, Wirth A, Int J Radiat OncolBiolPhys 2008, Luminari S, Ann Oncol 2013

Determination of risk

- 2 distinct prognostic indices: FLIPI Solal-Celigny P, Blood 2004 & FLIPI2 Federico M , J Clin Oncol 2009 and several prognostic factors - host genetic polymorphisms, tm genomic signatures, microenvironment
- Hard to translate from an academic exercise into a clinical tool

GELF

Any Node > 7cm
3 or more nodes >3cm each
B symptoms
Splenomegaly
Leukocytosis or Leukemic pha
Pleural or peritoneal effusions

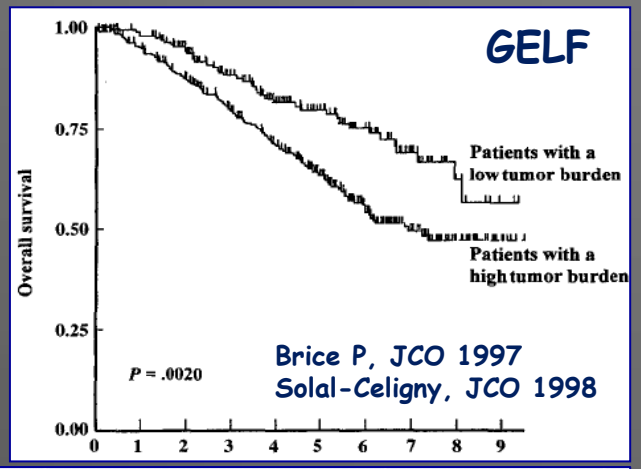
FLIPI

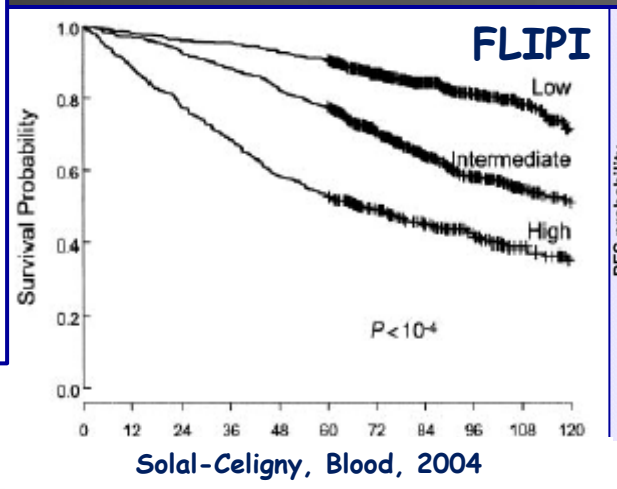
Age >60
Hemoglobin <12g/L
Elevated LDH
Nodal sites >4
Stage III/IV

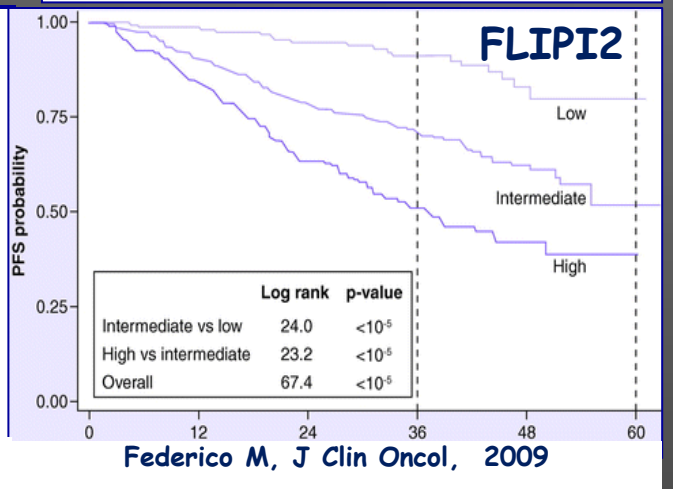
FLIPI2

Age >60
Hemoglobin <12g/L
Elevated β2M
Any node >6cm
Bone Marrow +

Could a PET scoring system improve risk stratification of FL incrementally or independently ?







The need for improvement of prognostication

- Emerging and more effective therapies for FL requires improved and integrated prognostic factors

- Baseline PET found to have a high prognostic value, irrespective of FLIPI

Janikova A, Clin Lymphoma Myeloma 2008;8:287, Le Dortz L, EJNM 2010;37:2307, Hofman MS, Best Pract Res Clin Haematol 2011, Scott AM, EJNM. 2009;36:347

- At NCCN ctrs, among grade I-II FL pts, no difference in FLIPI distribution btw PET-staged and non-PET staged pts

Abou-Nassar KE, Leuk Lymphoma. 2013;54:2155

- No study reported the clinical outcomes in pts in which the therapy was adjusted according to PET staging

PET / CT – Prognosis at initial staging

END, BM uptake, presence of ≥6 nodal sites on staging PET predicted poor outcomes following CIT

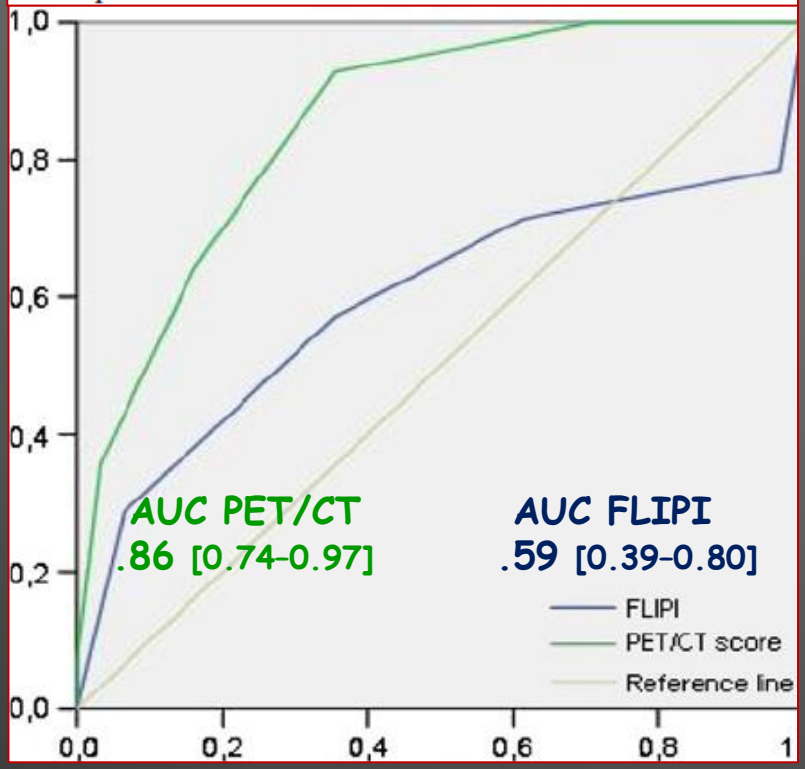
Prognostic factor	*p*
PET extranodal involvement	0.042
PET osteomedullar uptake	0.011
Diffuse uptake	0.16
Focal uptake	0.08
Osteomedullar infiltration	0.61
PET splenic involvement	0.07
PET involvement of at least six nodal areas	0.015
SUV_{max} higher than or equal to 15	0.301
Lesion larger than or equal to 7 cm	0.21
PET liver involvement	0.578
PET pleuropulmonary involvement	0.575

new prognostic models incorporating number, intensity, location of FDG-avid sites should be explored

Le Dortz L, Eur J Nucl Med Mol Imaging. 2010;37:2307

PET/CT score ≥2 correlated with incomplete response or early relapse (p<0.0001)

- 1 point for osteomedullar uptake on PET
- 1 point for $SUV_{max} \geq 15$
- 1 point for extranodal involvement other than bone on PET
- 1 point for largest diameter of lesion ≥7 cm
- 1 point for number of nodal areas affected on PET ≥6



PET / CT – Prognosis at initial staging

- PET/CT resulted in a different FLIPI risk group in 24% of pts: FLIPI score increased in 18% decreased in 6% pts

- PET info contributed to GELF for prompting rx by detecting END sites; this may change approach in a small group of pts

Cautions for PET findings:

- FPs cannot be excluded
- not useful in BMI; no data exist to omit BMB in FL

		FLIPI score			
		CT scan			
		0–1	2	3–5	Total
PET scan	0–1	29	4	2	35
	2	15	39	3	57
	3–5	1	10	39	50
	Total	45	53	44	142

PET

PET

CT

CT

GELF

Any Node > 7cm
3 or more nodes >3cm each
B symptoms
Splenomegaly
Leukocytosis or Leukemic phase
Pleural or peritoneal effusions

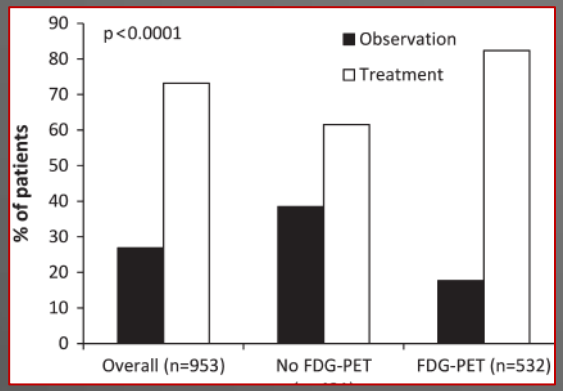
Luminari Ann Oncol 2013;24:2118

PET utilization at initial staging of grade I-II FL at NCCN ctrs n=953

- In the US, use of PET for staging of FL is widespread and associated with a greater proportion of pts receiving early therapy

Table II. Multivariable analysis of the likelihood of early therapy in all patients with grade 1–2 FL.

Variable	OR	95% CI	*p*-Value
FLIPI score			
0–1	Ref	Ref	Ref
2	0.96	0.67–1.38	0.83
3–5	2.38	1.45–3.90	0.0006
Initial staging imaging			
No FDG-PET	Ref	Ref	Ref
FDG-PET	1.87	1.31–2.66	0.0006



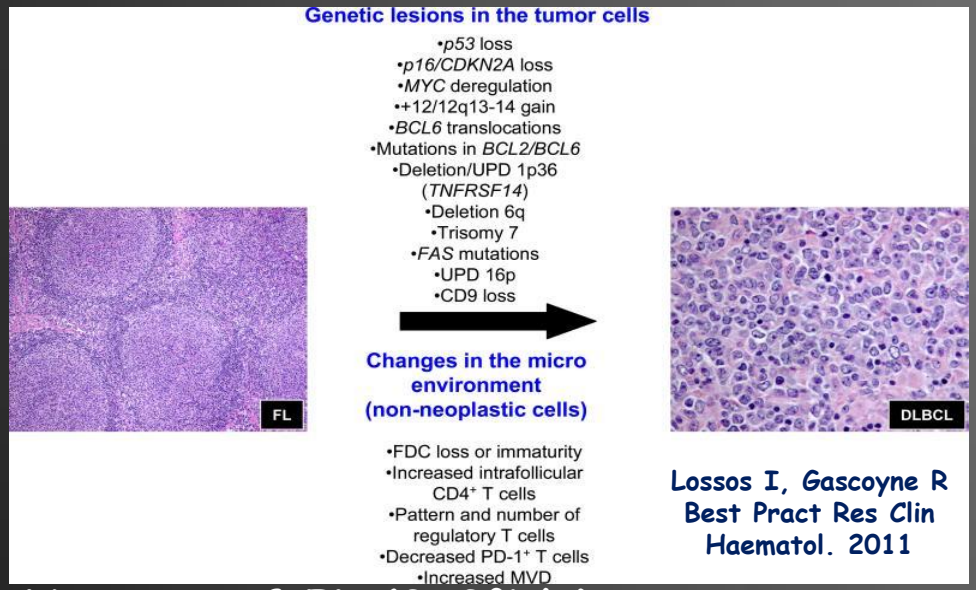
82% PET pts vs. 61.5% non-PET had early therapy

- In stage I FL, only 47% treated with RT alone; the choice of initial rx strategy did not vary significantly by use of PET

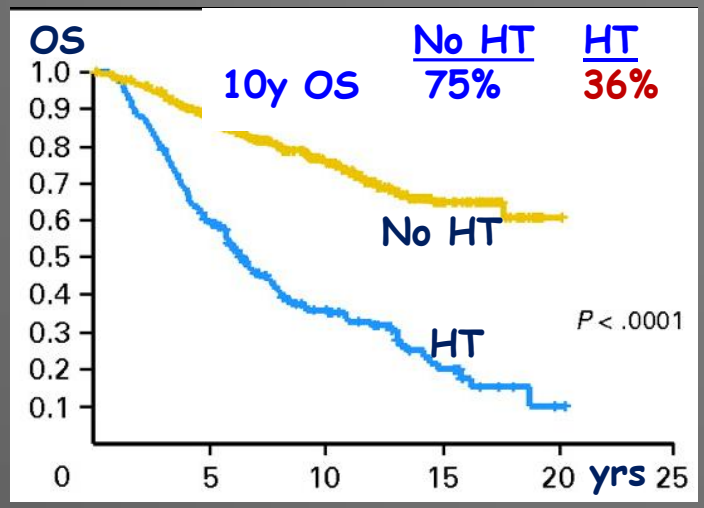
Abou-Nassar KE, Leuk Lymphoma. 2013;54:2155

PET-CT
Risk of histopathologic transformation

Histologic Transformation of FL



has implications for prognosis



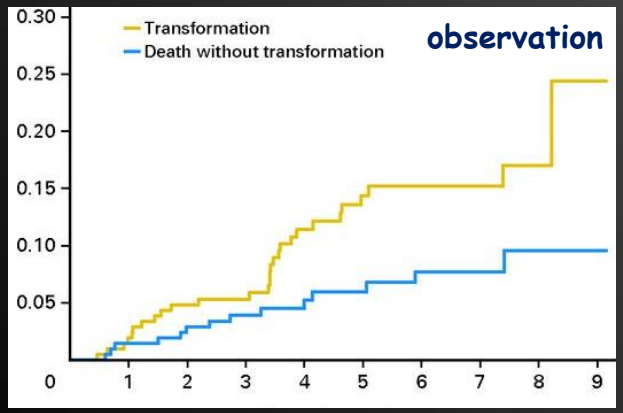
Al-Tourah AJ, JCO 2008;26:5165

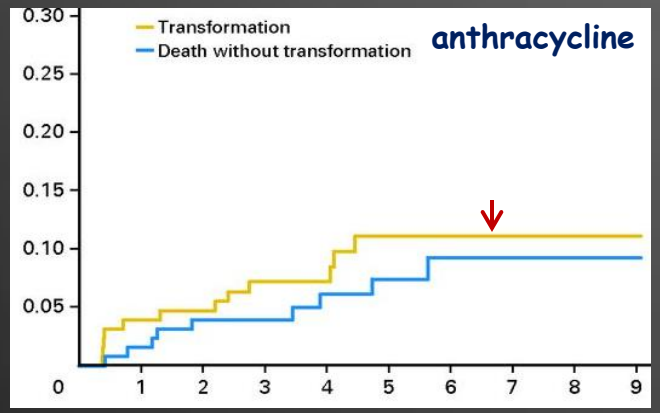
HT rate of FL (2-3%/y)
~11% at 5 y
30% at 10 y

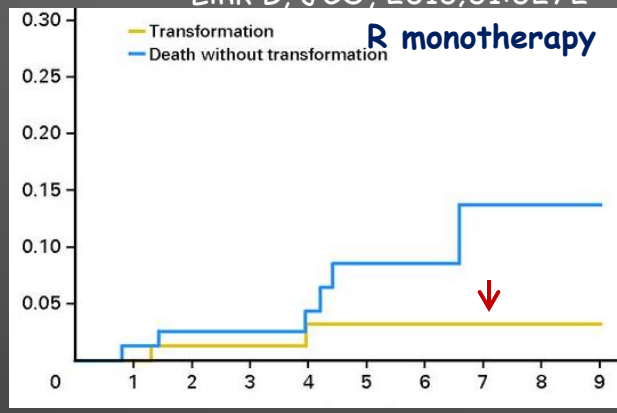
Link B, JCO, 2013;31:3272

Al-Tourah AJ, JCO 2008;26:5165

Link B, JCO, 2013;31:3272







PET-CT – Transformation of FL

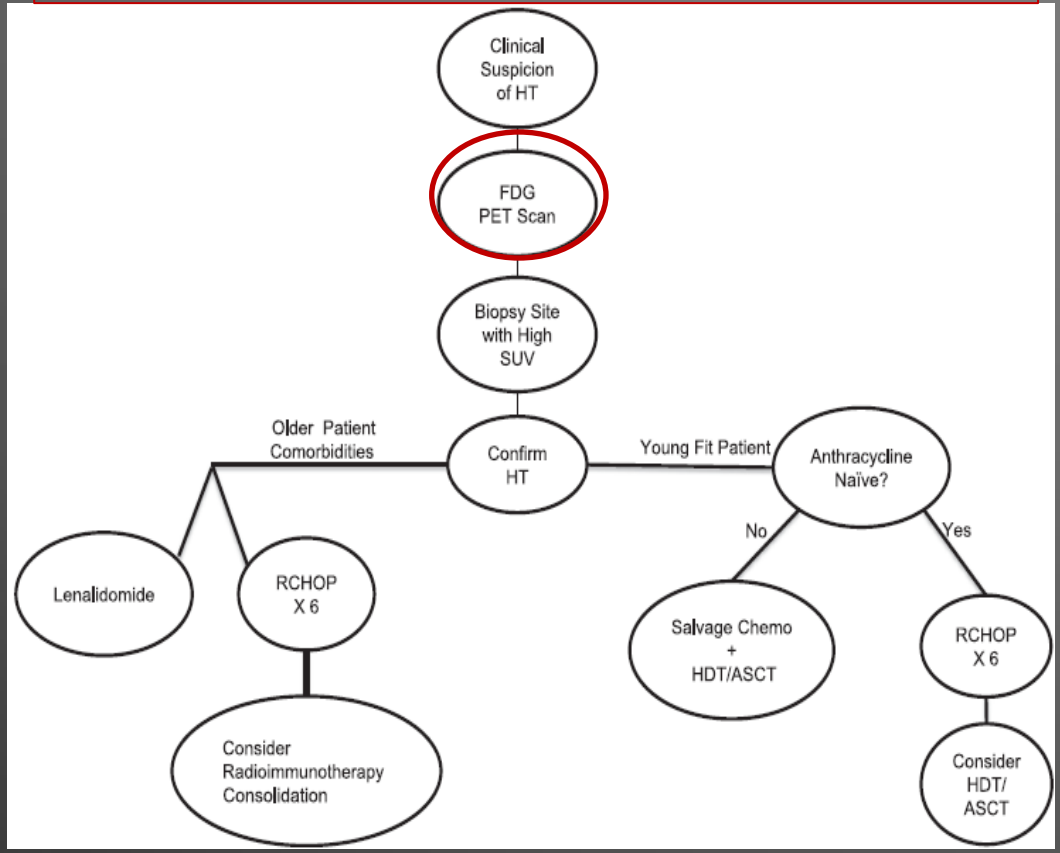
- SUVs > 10 reliably predicted aNHL with a specificity of 80%; SUV >13 did so with 90% certainty

  Schoder H, J Clin Oncol. 2005, Noy A, Ann Oncol 2009, Moskowitz CH, Blood. 2012.

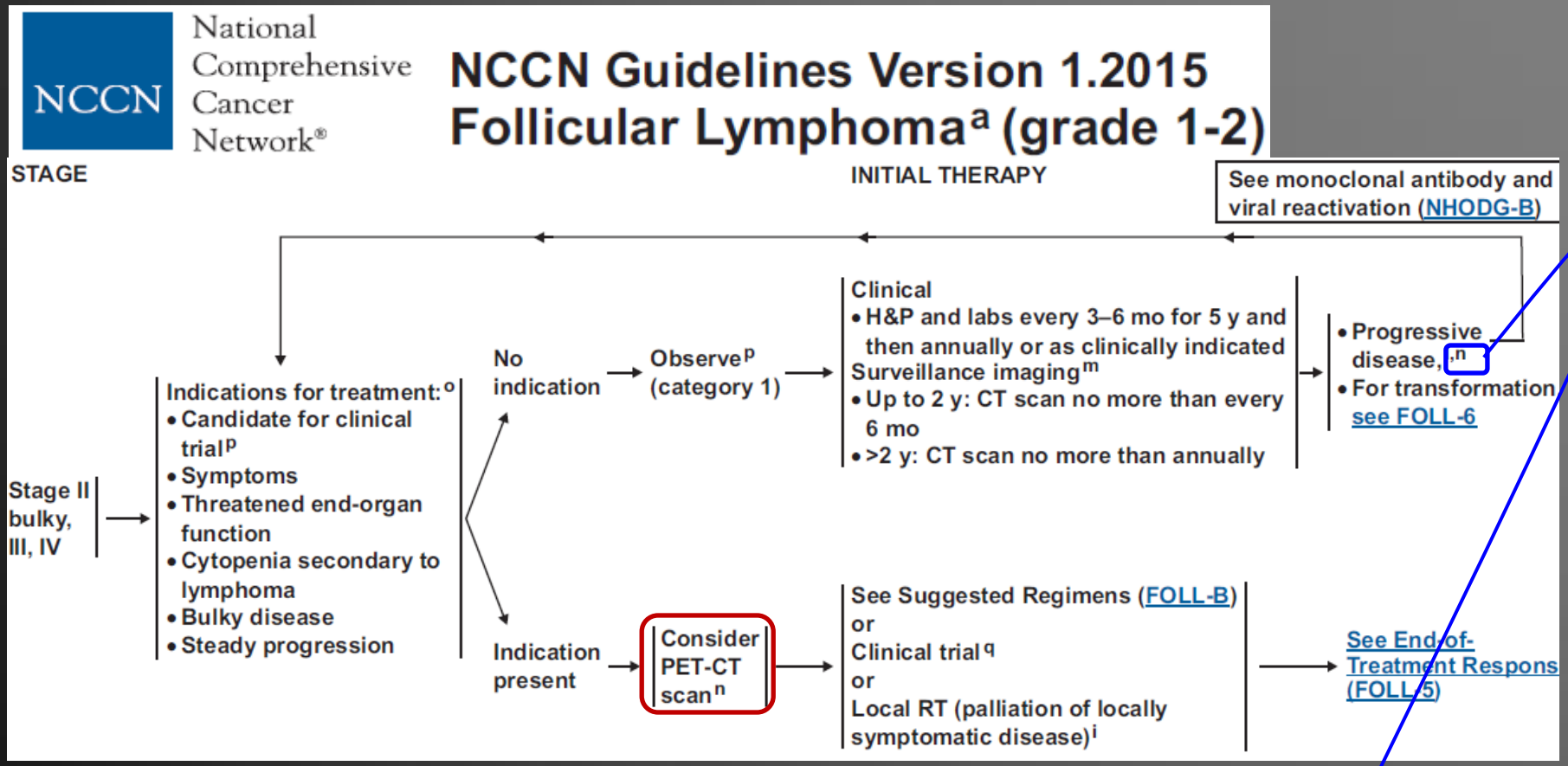
- Among pts with SUV >17, PPV of PET for detecting HT was 100% ; SUV < 11.7 associated with low risk of HT

  Bodet-Milin C, Haematologica. 2008

Considering the overlap in SUVs btw indolent and transformed FL PET is not deemed to replace biopsy to confirm HT

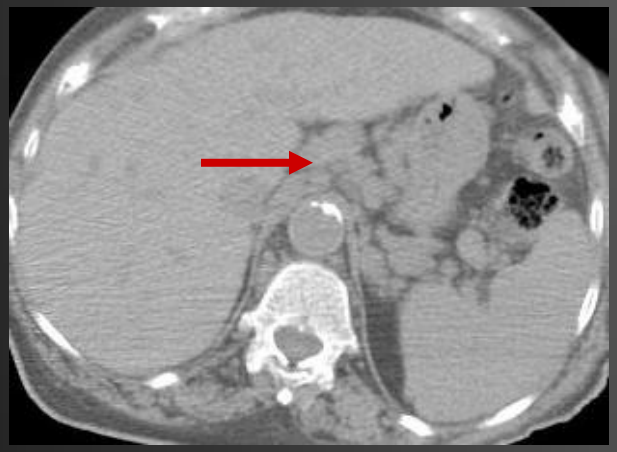


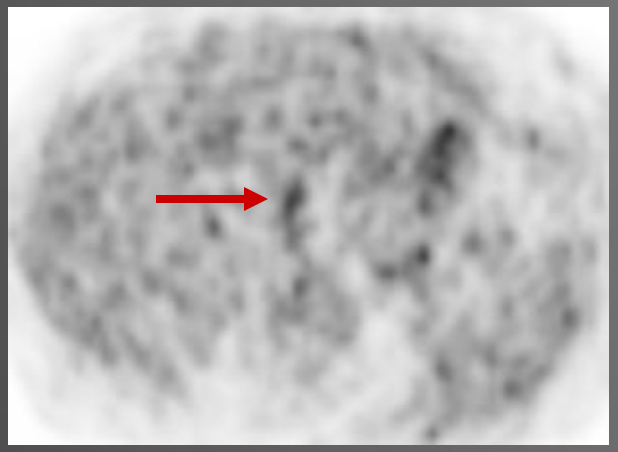
Casulo C, Blood 2015;125:40

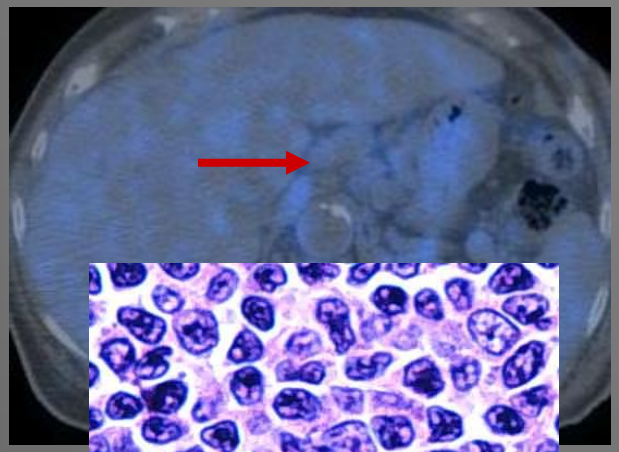


[n] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy.

PET / CT – Transformation of FL

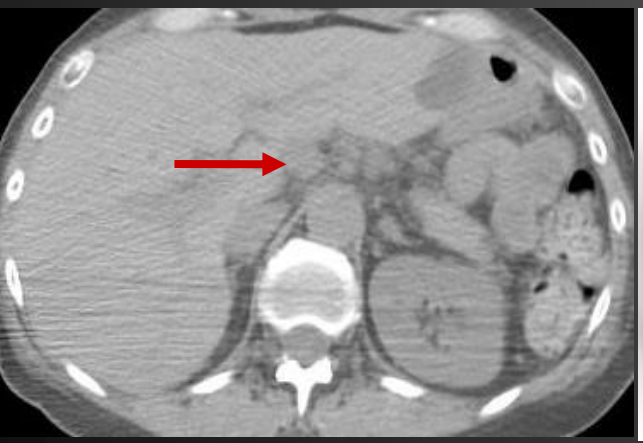


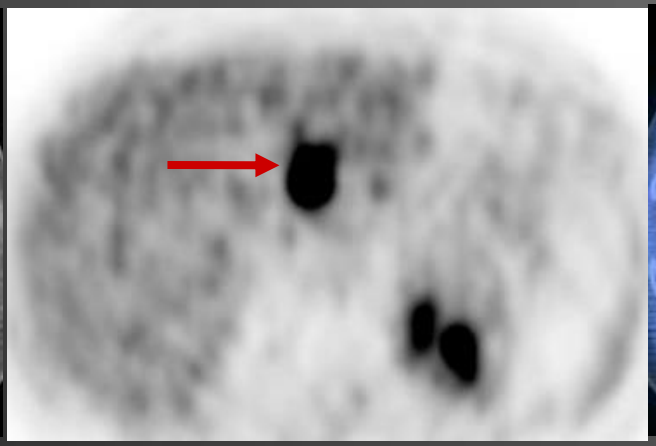


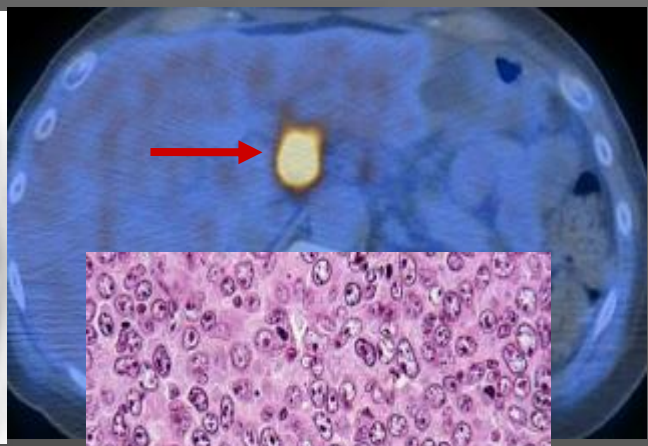


Non-transformed

SUV 5.0







Transformed

SUV 18

PET / CT - Post-inductin Response Evaluation of FL

FL Facts – after 1st line therapy

optimal management should consider the quality of response at the end of induction treatmen

Lugano recommendations

PET-CT should be used for response assessment in FDG-avid histologies, using the 5-point scale

A CMR even with a persistent mass is considered a CR

A PR requires a decrease by >50% in the sum of the product of the perpendicular diameters of up to six nodes or extranodal lesions

Prog disease by CT criteria only requires an increase in the PPDs of a single node by 50%

Cheson B, JCO 2014:*32:3059*

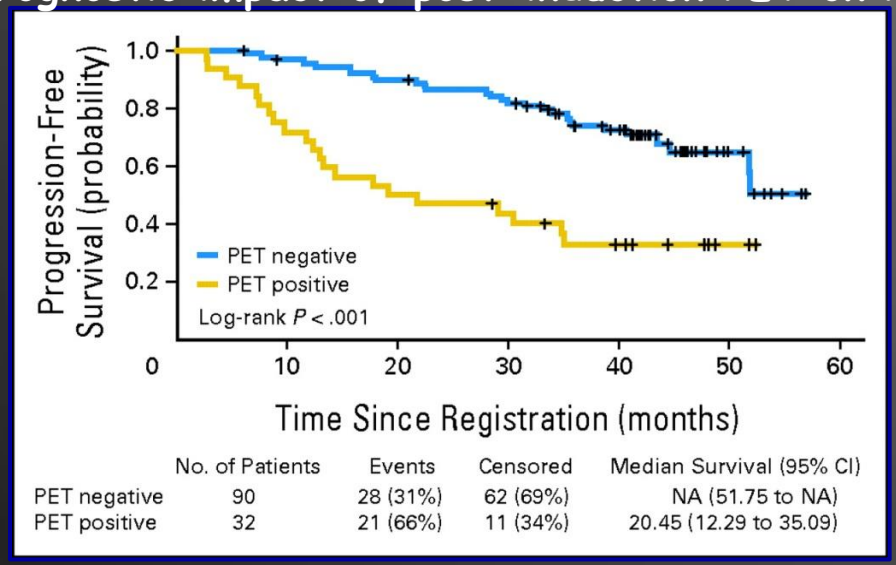
FL – prediction of PFS
PET after induction therapy

	PFS	PET+	PET-	Key points
Le Dortz,2010 Bishu, 2007	median [1,2]	17.2 m	48 m	retro analysis showing utility of PET/CT for prognosis of FL patients
Trotman,2011	42 m [3*] (n=122)	33%	71% p<0.001	utility of EOT PET in high-burden FL supported by prospective data from Primary Rituximab and Maintenance (PRIMA) study - GELA
Dupuis, 2012	24 m [4**] (n=121)	51%	87% p<0.001	

*maintenance therapy; **no maintenance therapy

EOT = end of treatment

Prognostic impact of post-induction PET on PFS[3]

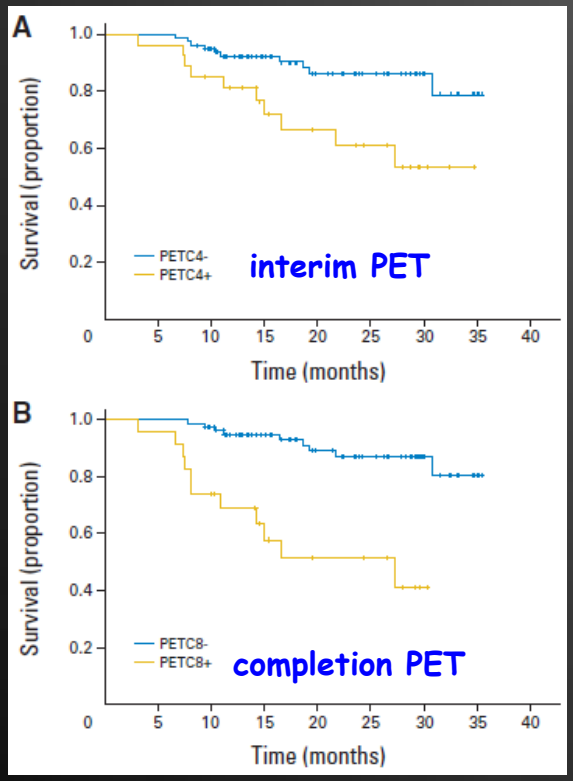


[1]Le Dortz. EJNM 2010;
[2]Bishu S. Leuk Lymphoma 2007
[3]Trotman J. JCO 2011
[4]Dupuis J. J Clin Oncol 2012

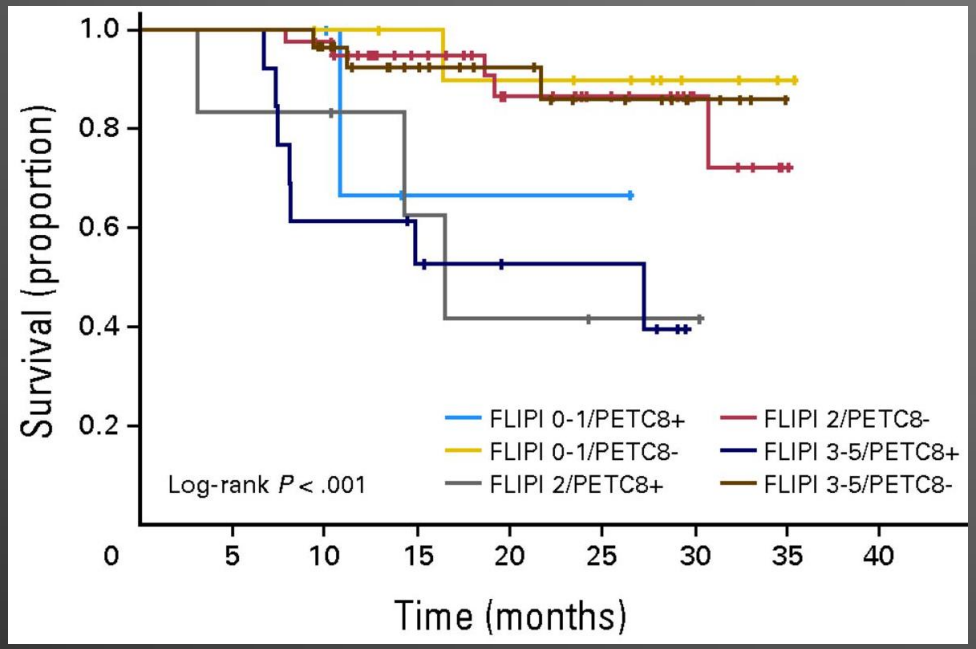
PFS by FLIPI score and final PET/CT

prospective,121 pts with high tm burden FL, PET after 4 cycles and at the end of therapy, RCHOP, Deauville 5PS -

	int PET-	PET+	endPET-	endPET+
2 year PFS	86%	61%	87%	51%
		p=0.0046		p=0.001
2-year OS			100%	88%
				p=0.0128



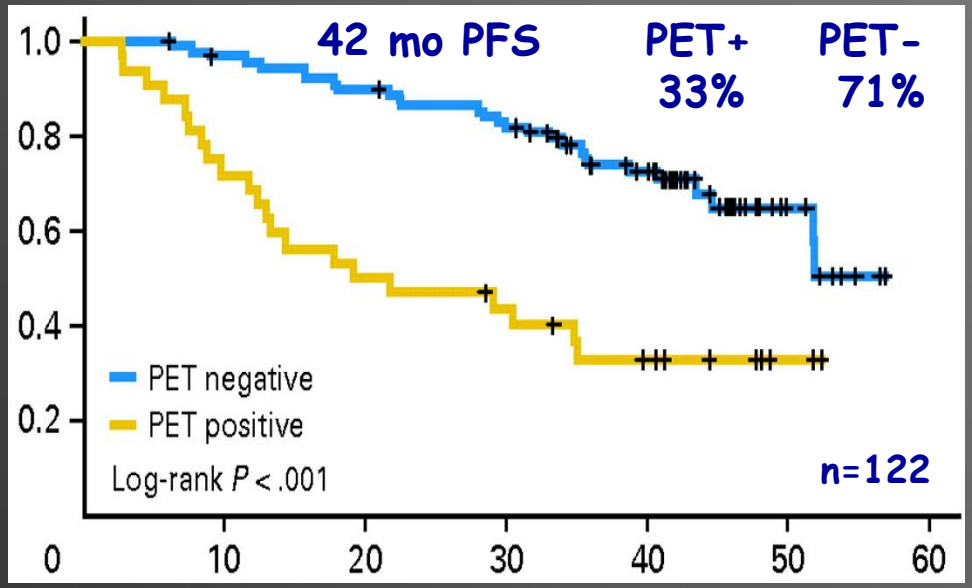
PFS by FLIPI and final PET



Dupuis J et al. JCO 2012;30:4317

PET / CT - post induction therapy PRIMA

Prognostic impact of post-induction PET on PFS



- PET status, was an independent predictive factor for progression
- Risk of death increased in PET+ pts (HR 7.0; *P*= .0011)
- PET-CT status at end of CIT induction is strongly predictive of outcome and should be a clinical end-point

Trotman J et al. *JCO* 2011;29:3194-3200

PET / CT – post induction therapy FOLL05

Conventional response assessment with CT modified by PET

	CR, $n = 145$ (%)	PR, $n = 48$ (%)	SD/PD, $n = 9$ (%)
PI-PET negative	123 (85)	27 (56)	3 (33)
PI-PET positive	22 (15)	21 (44)	6 (67)

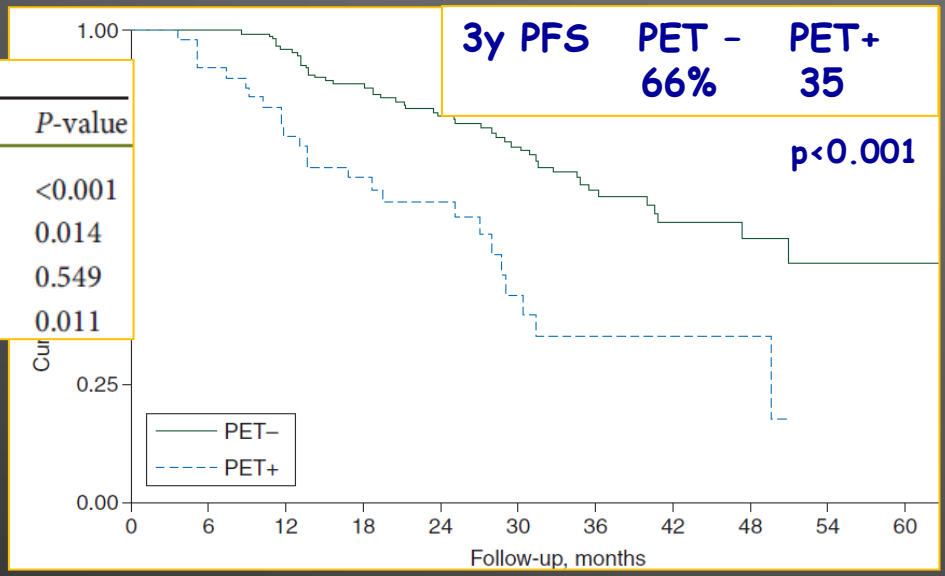
pi-PET substantially modifies response assessment and strongly predictive for the progression risk

Luminari S, Ann Oncol. 2014;25: 442

pi-PET was independent of conventional response, FLIPI and treatment arm

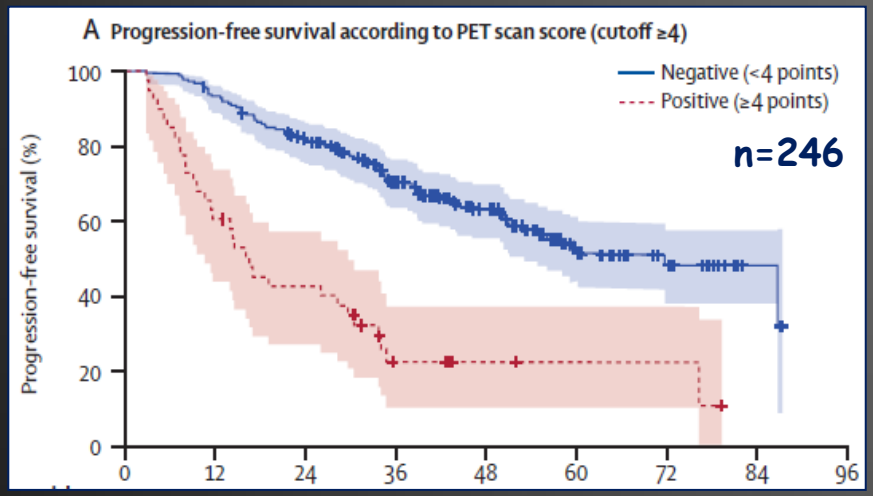
multivariate analysis	PFS ($n = 202$) HR	95% CI	*P*-value
PI-PET +	2.57	1.52–4.34	<0.001
FLIPI 3–5	1.80	1.13–2.89	0.014
Response <CR (CT only)	1.17	0.70–1.95	0.549
R-CVP[a]	1.84	1.15–2.95	0.011

*pi-PET done at a med of 36 d (range 10–92) after last dose ICT



PET-CT – Response Evaluation of FL

In a pooled analysis of 246 high tm burden pts from 3 trials, it was confirmed that post-ind PET highly predictive of both PS or OS, when PET+ status was defined by D-5PS (score≥4)



4 y PFS

PET+	PET-	
23%	63%	p<0.0001

4-y OS

PET+	PET-	
87%	97%	p<0 · 0001

Multivariate analysis of prognostic factors

med f-u 54.8 mo

	FLIPI		FLIPI2	
	HR (95% CI)	p value	HR (95% CI)	p value
FLIPI score of 3–5	1·056 (0·703–1·585)	0·7934	1·837 (1·153–2·926)	0·0105
Positive postinduction PET scan*	3·045 (1·888–4·939)	<0·0001	3·492 (1·977–6·166)	<0·0001
Response		0·0020†		0·0679†
PR	1·564 (1·027–2·381)	0·0370	1·754 (1·085–2·835)	0·0220
SD or PD	3·677 (1·660–8·145)	0·0013	1·573 (0·450–5·496)	0·4778

25%PRIMA, 43% PET-FL, 32% FOLL05

Trotman J, Lancet Haematol 2014 ; 1 : e17

PET/CT – Response Evaluation - RIT

- phase II INITIAL (n=68) pts with FL; med 4 yr f-u after ^{131}I-ritux RIT in conjunction with ritux, followed by 1y maintenance rx

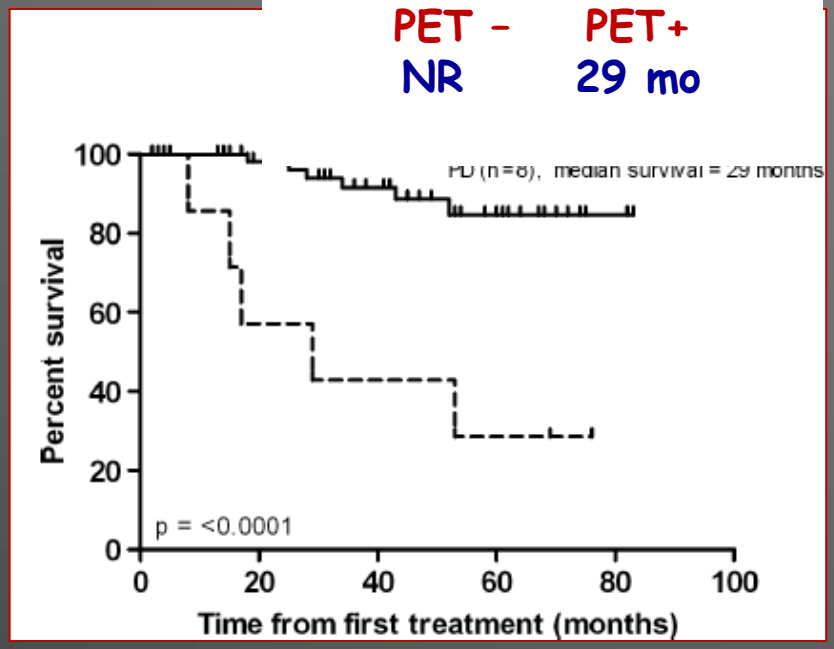
- IWG ^{2007} RR 99%
- D 5PS RR 88% (score 1-3)

- Response assessment at 3 mo by FDG PET D-5PS permits prognostic stratification

- ^{131}I-ritux RIT in newly diagnosed, adv stage, symptomatic FL is an effective, alternative to existing chemo with durable remissions

med time-to-next-rx

PET –	PET+
NR	29 mo



McQuillan AD, Leuk Lymphoma 2014

PET / CT – End therapy Response

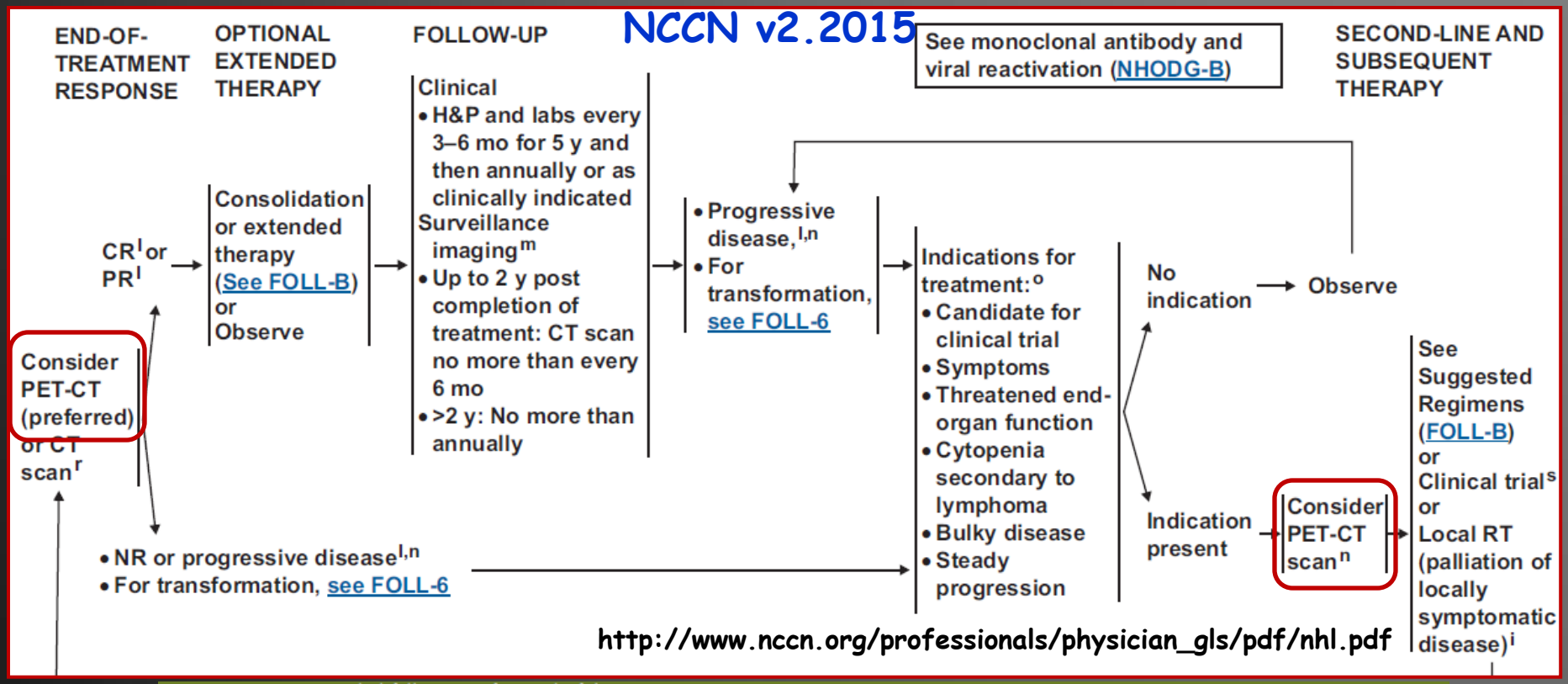


Table 6. Recommended follow-up after end of therapy **ESMO 2014**

Examination	Details	Year 1–2	Year 3–5	Year >5
History	B symptoms	Every 3 months	Twice annually	Annually
Physical examination	Particular: peripheral lymph nodes, liver, spleen	Every 3 months	Twice annually	Annually
Laboratory work-up	Blood and differential count	Every 3 months	Twice annually	Annually
	LDH	Every 3 months	Twice annually	Annually
Imaging	Abdominal ultrasound	Twice annually	Every 12 months	If progress suspected
	CT neck, chest, abdomen, pelvis	Optional: twice annually	Optional: every 12 months	If progress suspected

Dreyling M, Ann Oncol 2014;25:iii76-iii82

PET-CT
prediction of PFS at relapse

Prognosis
PET/CT after salvage before ASCT

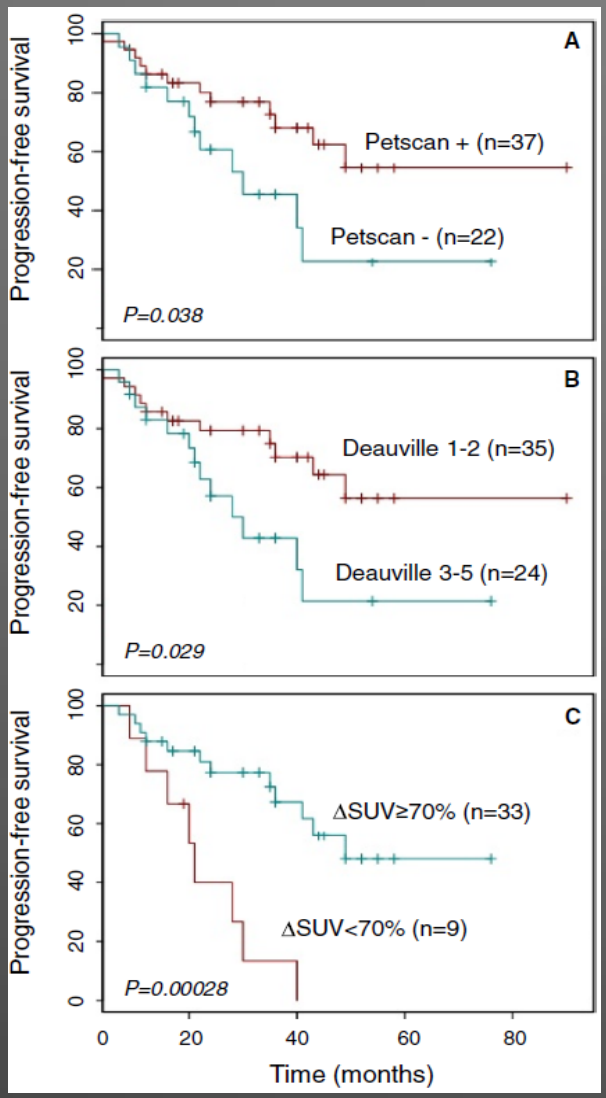
- Retro, 59 pts, ref/rel FL after 1st-line R-CHOP who were chemosensitive (by CT) to salvage rx before ASCT

3 y PFS	3y OS
63 %	90.5 %

did not differ according to FLIPI at relapse, conditioning regimen, or type of salvage

3 y PFS

- rIHP criteria — 45.5% vs 73%; p = 0.04
- D 5PS score≥3 — 75% vs 43%; p = 0.02
- ≥70 % ΔSUV_{max} — 72% vs 13%; p < 0.0001
- PET/CT findings before ASCT independently correlated with PFS

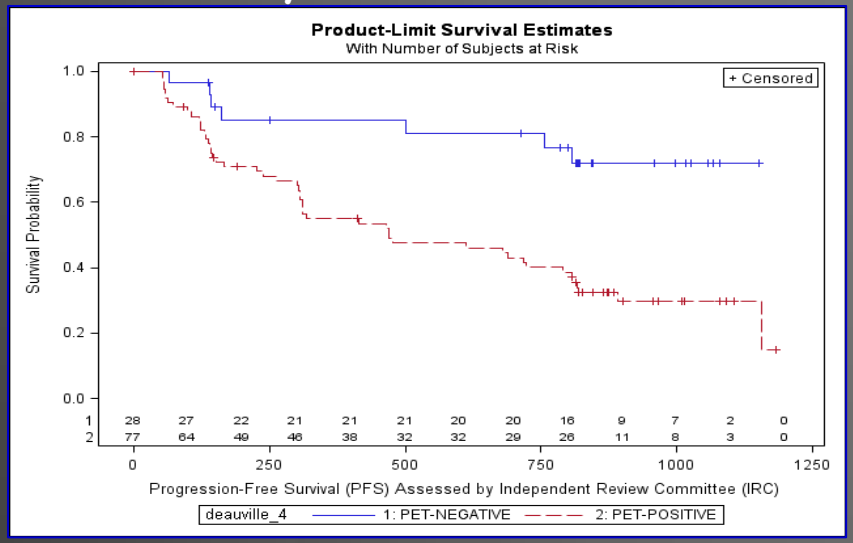


Alcantara M, Eur J Nucl Med Mol Imaging. 2015 ;42:215

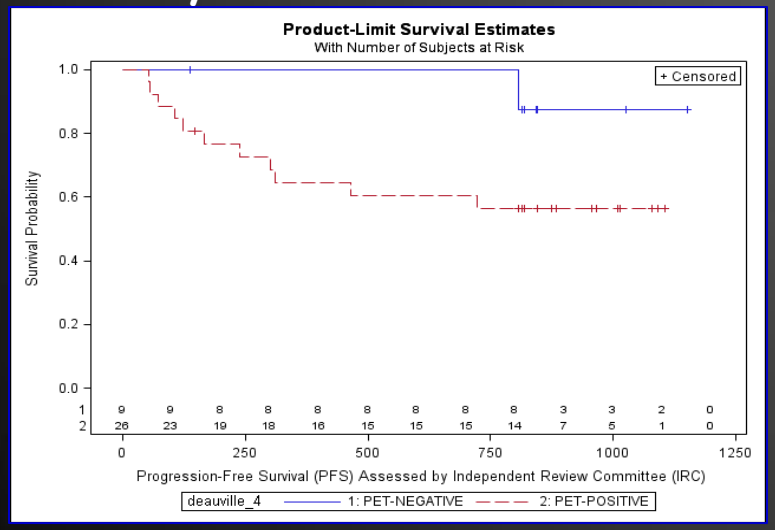
Improved PFS prediction by PET
PET at end of IT provides added value to clinical response

GAUSS: Randomized phase II trial comparing GA101 (obinutuzumab) with rituximab in relapsed CD20+ indolent B-cell NHL

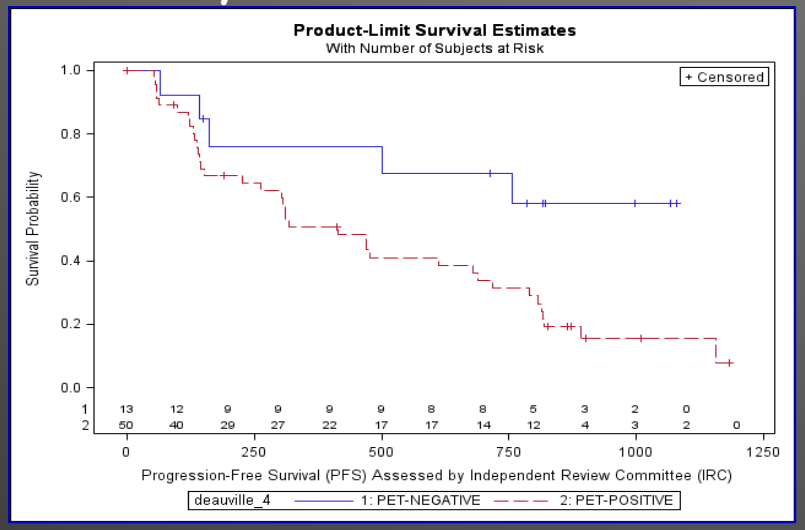
PFS by D 5PS+ vs D 5PS-



PFS by PR / D 5PS+ vs D 5PS-



PFS by SD/D 5PS+ vs D 5PS-



Kostakoglu L, EHA, 2014

Summary – Role of PET in FL

STAGING

- In limited stage FL, PET-based detection of otherwise unknown disease may translate to improved disease control and survival by changing IRFT plans

- In adv stage FL, PET-based staging may not have sign. management change but still necessary for assessment of post-IT response

- PET not sensitive to detect BMI; BMB holds its importance

POST-THERAPY

- Emerging data support the use of PET-CT after rituximab-containing chemotherapy in high–tumor burden FL

- Studies are warranted to confirm this finding in patients receiving maintenance therapy

- Using PET as a response assessment tool should encourage a new generation of clinical trials aiming to increase the efficacy of ITs

Cheson B, JCO 2014

Molte Grazie !