The role of end-of-treatment PET in lymphoma management

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Disclosures

I have no conflicts of interest to declare.

End-of-treatment PET in lymphoma

Key objectives

1. **Performance of EoT PET**
2. **Prognostic information**
3. **Therapeutic implications**

End-of-treatment PET in lymphoma

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Positron emission tomography

Increased glucose utilization in lymphomas

Entity	% positive cases	Maximum SUV
Aggressive lymphomas		
HL, DLBCL, PMBCL, BL, PTCL	85 - 100 %	19,6 ± 9,3
Indolent lymphomas		
Mantle cell lymphoma	100 %	8,7 ± 1,3
Follicular lymphoma	95 %	7,7 ± 4,6
Nodal marginal zone lymphoma	100 %	
Splenic MZL	67 %	3,8 ± 1,3
Extranodal MZL (MALT)	55 %	
Waldenstrom's macroglobulinemia	83 %	n.r.
Lymphocytic lymphoma / CLL	83 %	2,5 ± 0,7

Schöder et al, J Clin Oncol 23: 4643, 2005; Weiler-Sagie et al, J Nucl Med 51: 25, 2010;
Karam et al, Nucl Med Comm 30: 770, 2009;
Karam et al, Cancer 107: 175, 2006;
Banwait et al, Am J Hematol 86: 567, 2011

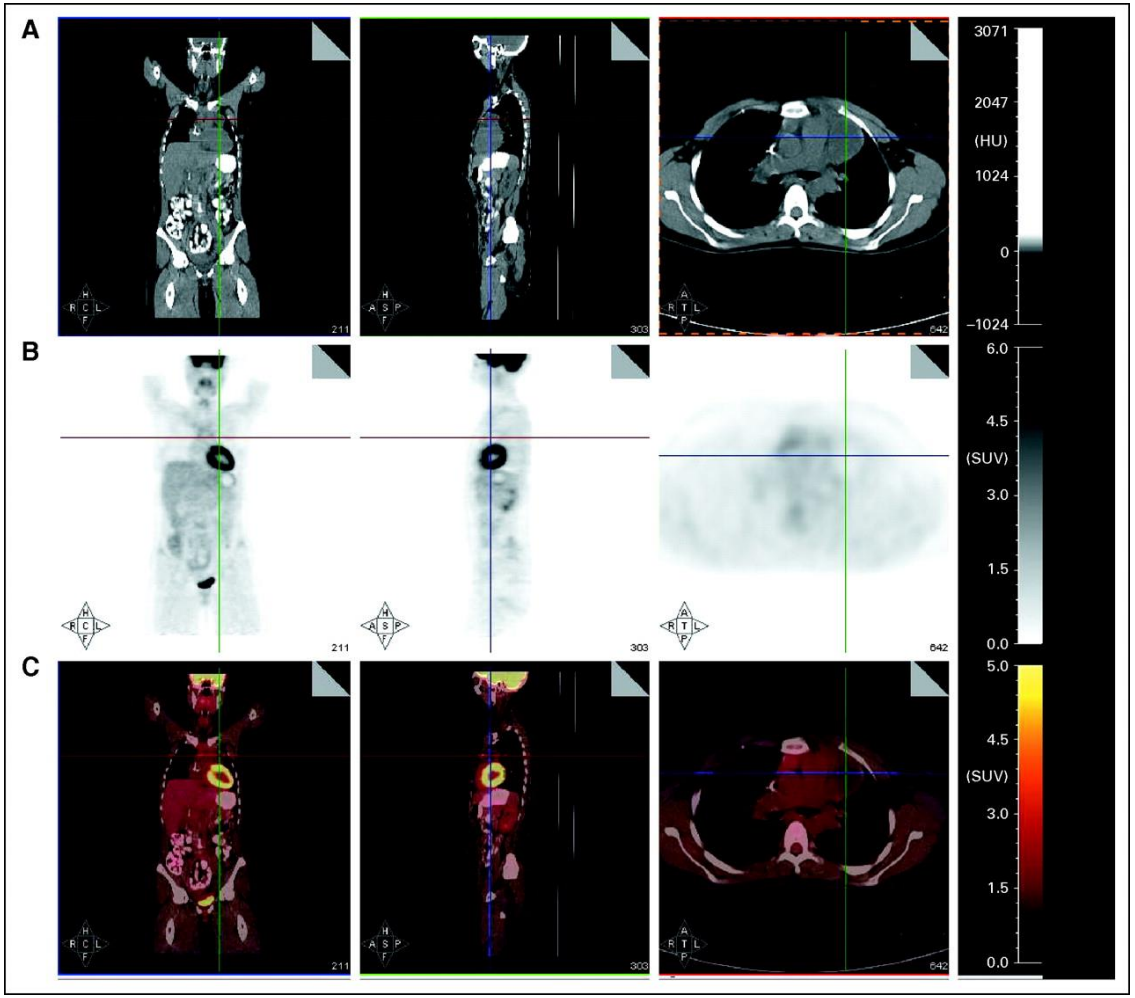
End-of-treatment PET

Comparison with computed tomography

CT

PET

PET/CT



Hodgkin lymphoma

Residual bulk

of 5 x 4 cm

after 6 x ABVD

Viable lymphoma

≠

necrosis or fibrosis

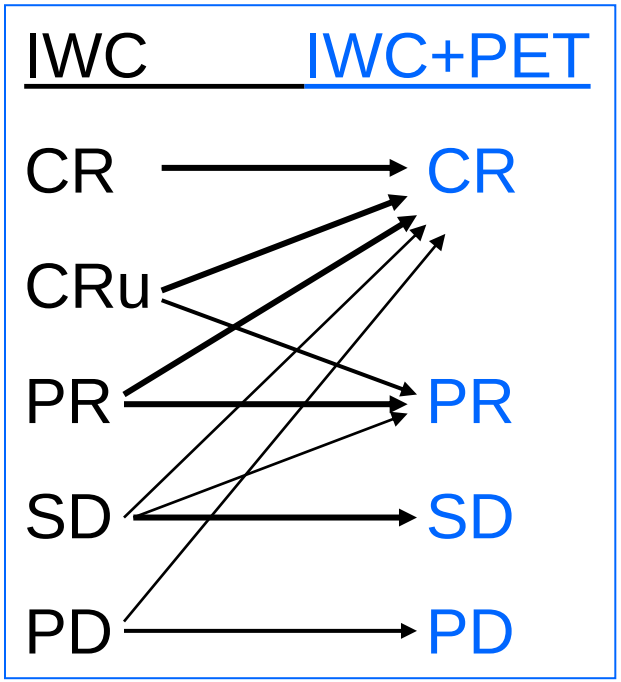
Juweid et al, J Clin Oncol 25: 571, 2007

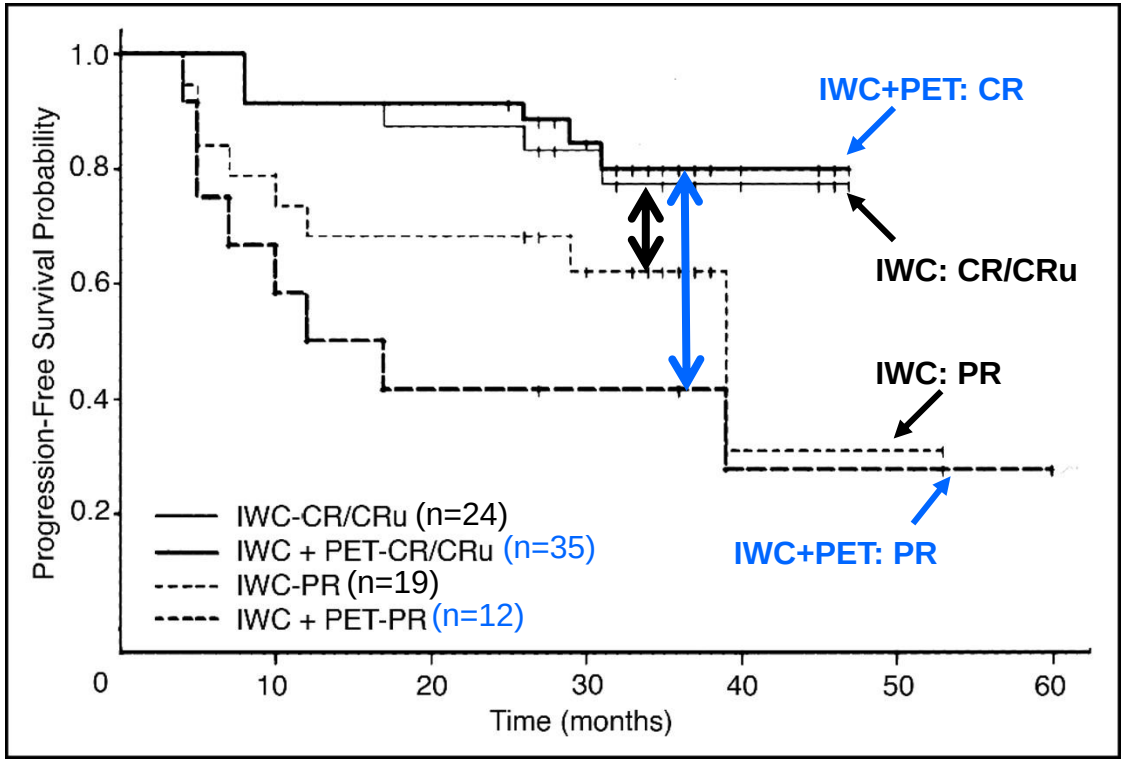
End-of-treatment PET

Superior outcome prediction

EoT PET negative: **always CR (independent of residual mass)**

EoT PET positive: **never CR**





Juweid et al, J Clin Oncol 23: 4652, 2005

End-of-treatment PET

Timing

Lugano recommendations:

6 - 8 weeks	after chemotherapy (minimum of 3 weeks)
2 weeks	after cessation of G-CSF treatment
3 months	after radiotherapy

(avoidance of inflammatory reactions)

Barrington et al, J Clin Oncol 32: 3048, 2014

End-of-treatment PET

Response criteria

Locally developed response criteria

International Harmonization Project (IHP) criteria – 2007

Small lesions	no uptake above background
Lesions ≥ 2 cm	uptake ≤ mediastinal blood pool

Deauville criteria – 2009, 2014

1. no uptake
2. uptake ≤ mediastinal blood pool
3. uptake > mediastinal blood pool, but ≤ liver
4. uptake moderately > liver
5. uptake markedly > liver *or* new lesions

Semiquantitative criteria (SUVmax, MTV, …)

Juweid et al, J Clin Oncol 25: 571, 2007;
Meignan et al, Leuk Lymphoma 50: 1257, 2009;
Barrington et al, J Clin Oncol 32: 3048, 2014

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End-of-treatment PET

Prognostic information

Indolent lymphomas

Follicular lymphoma
Mantle cell lymphoma

Aggressive lymphomas

Diffuse large B-cell lymphoma
Primary mediastinal B-cell lymphoma
Burkitt lymphoma
Hodgkin lymphoma
Peripheral T-cell lymphoma

Indolent lymphomas

Studies reporting the prognostic value of EoT PET

Entity	No. of studies	No. of patients	PET criteria	Prognostic value PFS	OS
Follicular lymphoma	8 6 retrospective **2 prospective**	16 - 202	local IHP D5S	**8 / 8**	**3 / 3**
Mantle cell lymphoma	4 retrospective	28 - 55	IHP	**3 / 4**	**3 / 4**

Follicular lymphoma

Zinzani et al, Clin Lymphoma Myeloma 7: 291, 2007; Bishu et al, Leuk Lymphoma 48: 1548, 2007; Le Dortz et al, Eur J Nucl Med Mol Imaging 37: 2307, 2010; Trotman et al, J Clin Oncol 29: 3194, 2011; Dupuis et al, J Clin Oncol 30: 4317, 2012; Zinzani et al, Am J Hematol 88: E273, 2013; Luminari et al, Ann Oncol 25: 442, 2014; Lu et al, Ann Nucl Med 28: 805, 2014

Mantle cell lymphoma

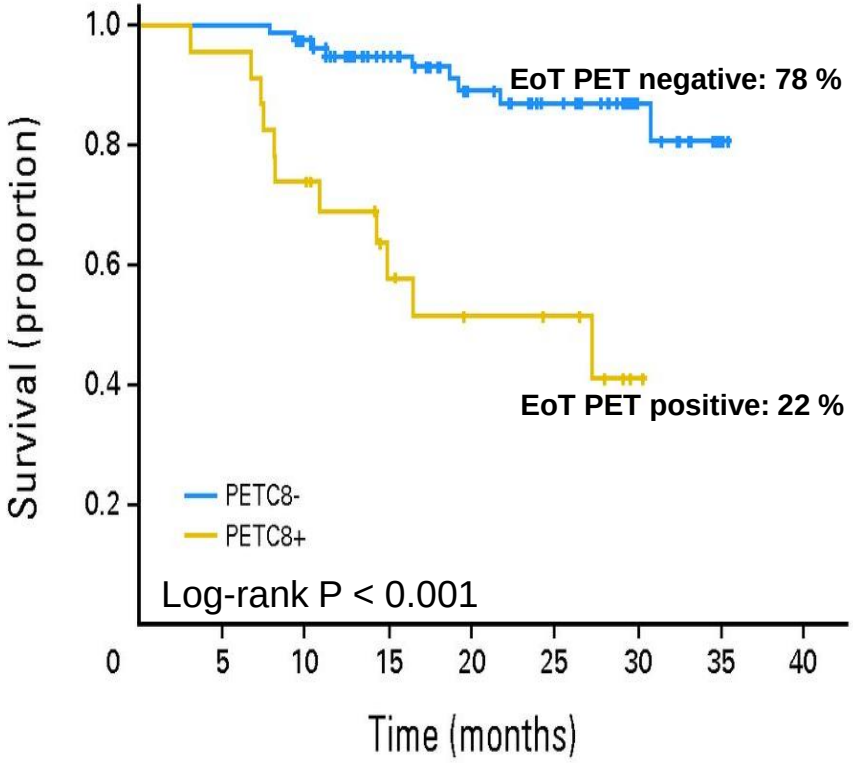
Bodet-Milin et al, Eur J Nucl Med Mol Imaging 37: 1633, 2010; Hosein et al, Am J Hematol 86: 841, 2011; Mato et al, Cancer 118: 3565, 2012; Kedmi et al, Leuk Lymphoma 55 : 2484, 2014

Follicular lymphoma

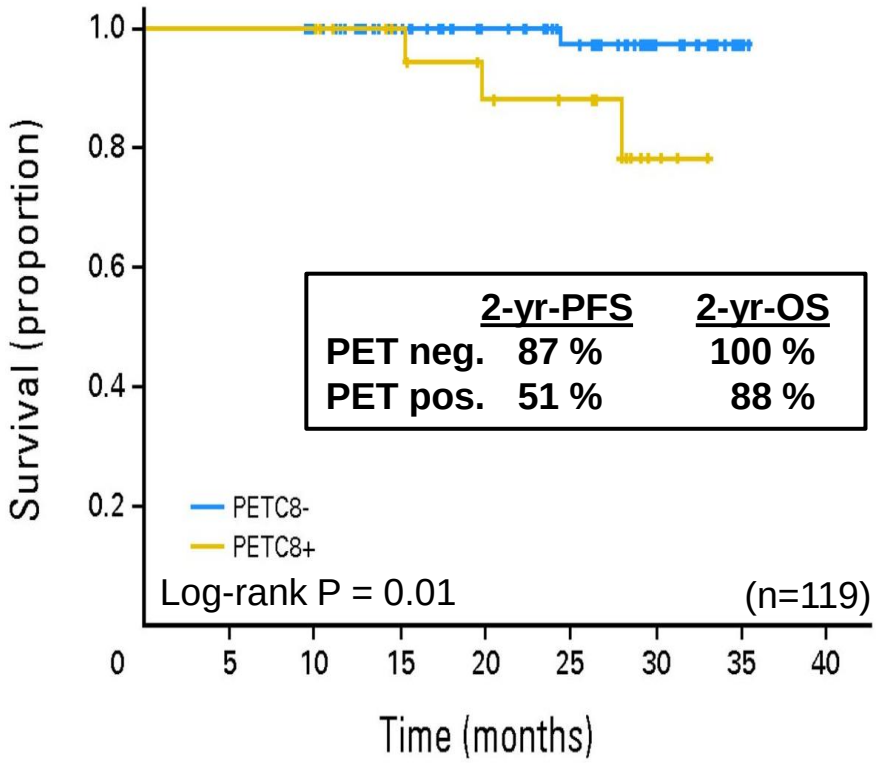
PFS and OS according to EoT PET

6 x R-CHOP + 2 x R → EoT PET → Deauville 1-3 vs. 4+5

Progression-free Survival



Overall Survival



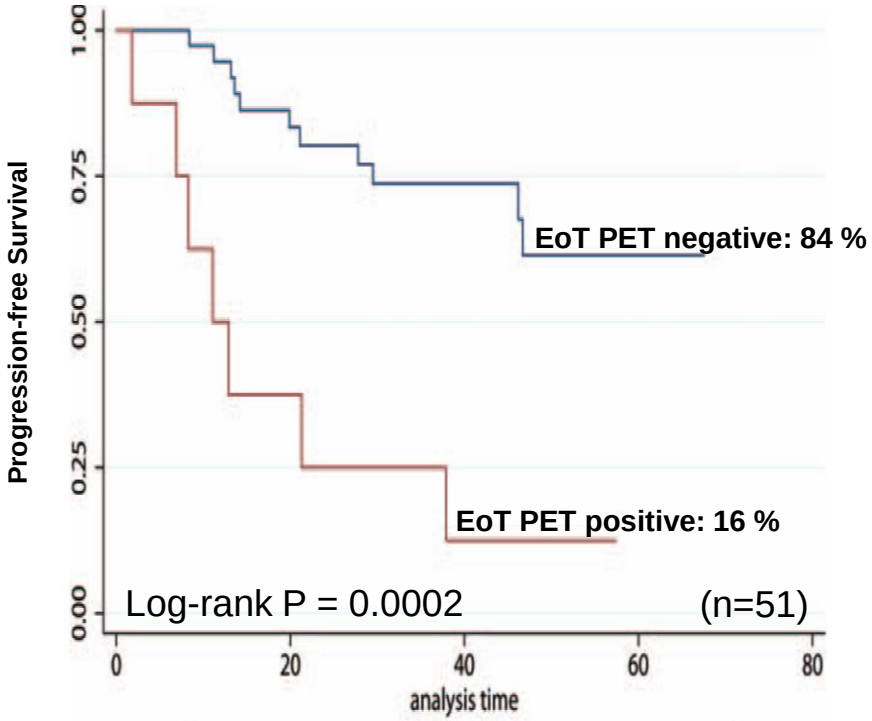
	2-yr-PFS	2-yr-OS
PET neg.	87 %	100 %
PET pos.	51 %	88 %

Dupuis et al, J Clin Oncol 30: 4317, 2012

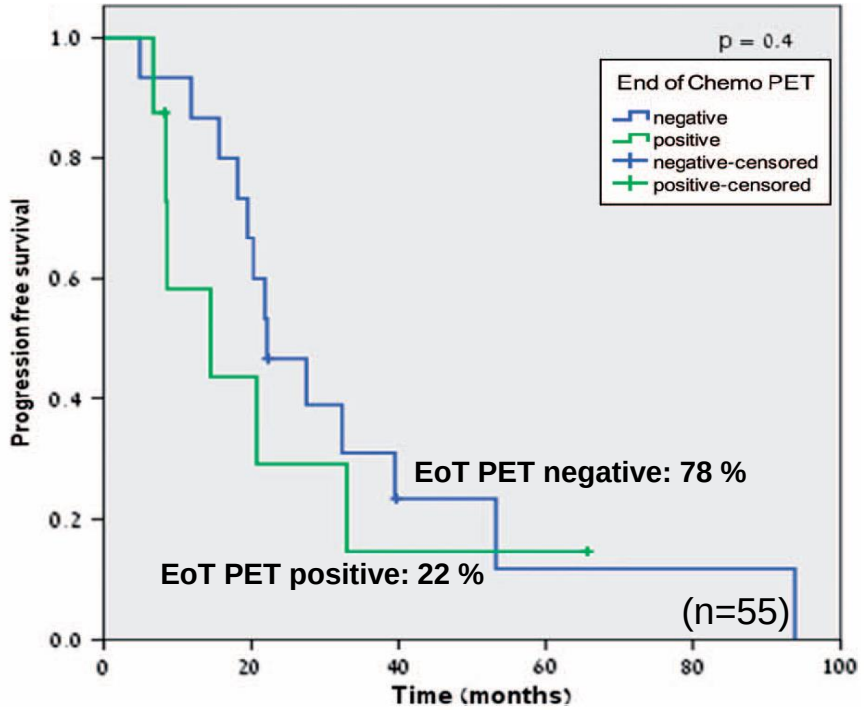
Mantle cell lymphoma

PFS and OS according to EoT PET

R-Hyper-CVAD/MA → IHP
Follow-up: 32 months



R-CHOP ± AutoSCT → IHP
Follow-up: 36 months



Mato et al, Cancer 118: 3565, 2012;
Kedmi et al, Leuk Lymphoma 55: 2484, 2014

Aggressive lymphomas

Studies reporting the prognostic value of EoT PET

Diffuse large B cell lymphoma

Yoo et al, Ann Hematol 90: 797, 2011; Cashen et al, J Nucl Med 52: 386, 2011; Cox et al, Leuk Lymphoma 53: 263, 2012; Pregno et al, Blood 119: 2066, 2012; González-B et al, Nucl Med Comm 34: 946, 2013

Primary mediastinal B cell lymphoma

Martelli et al, J Clin Oncol 32: 1769, 2014; Nagle et al, Cancer Med 4: 7, 2015; Vassilakopoulos et al, Leukemia (in press), 2015

Burkitt lymphoma

Carillo-Cruz et al, Eur J Haematol 94: 23, 2014

Hodgkin lymphoma

Spaepen et al, Br J Haematol 115: 272; 2001; De Wit et al, Ann Oncol 12: 29, 2001; Barnes et al, Ann Oncol 22: 910, 2011; Straus et al, Blood 117: 5314, 2011; Engert et al, Lancet 379: 1791, 2012; Hutchings et al, J Clin Oncol 32: 2705, 2014

Peripheral T cell lymphoma

Cahu et al, Ann Oncol 22: 705, 2011; Li et al, J Nucl Med 54: 507, 2013; Tomita et al, Ann Hematol 94: 431, 2015; El-Galaly et al, Am J Hematol 90: 975, 2015; Fukumoto et al, ASH #3915, 2015

Aggressive lymphomas

Studies reporting the prognostic value of EoT PET

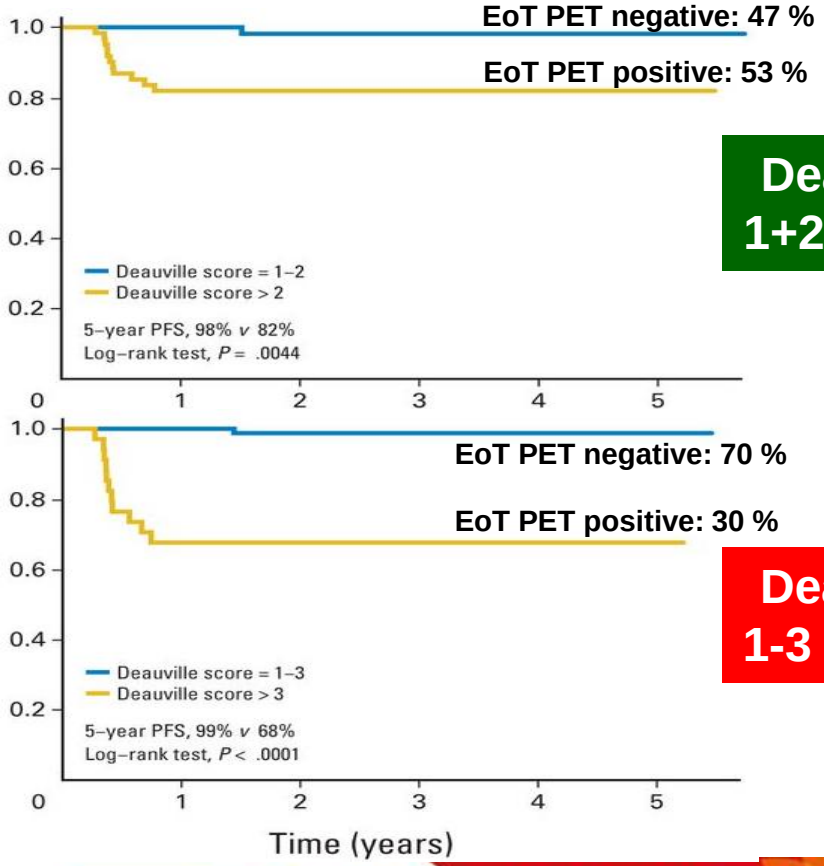
Entity	No. of studies	No. of patients	PET criteria	Prognostic value PFS	Prognostic value OS
Diffuse large B cell lymphoma	5 2 retrospective **3 prospective**	42 - 155	IHP D5S	**5 / 5**	**3 / 3**
Primary mediastinal B cell lymphoma	3 2 retrospective **1 prospective**	27 - 115	IHP D5S SUV	**3 / 3**	**2 / 3**
Burkitt lymphoma	1 retrospective	27	SUV	**1 / 1**	**- - -**
Hodgkin lymphoma	6 3 retrospective **3 prospective**	37 - 739	Local IHP D5S	**6 / 6**	**1 / 2**
Peripheral T cell lymphoma	5 retrospective	31 - 80	IHP D5S	**4 / 5**	**3 / 4**

Primary mediastinal B-cell lymphoma

PFS and OS according to EoT PET

R-M/VACOB-B / R-CHOP → EoT PET → Deauville

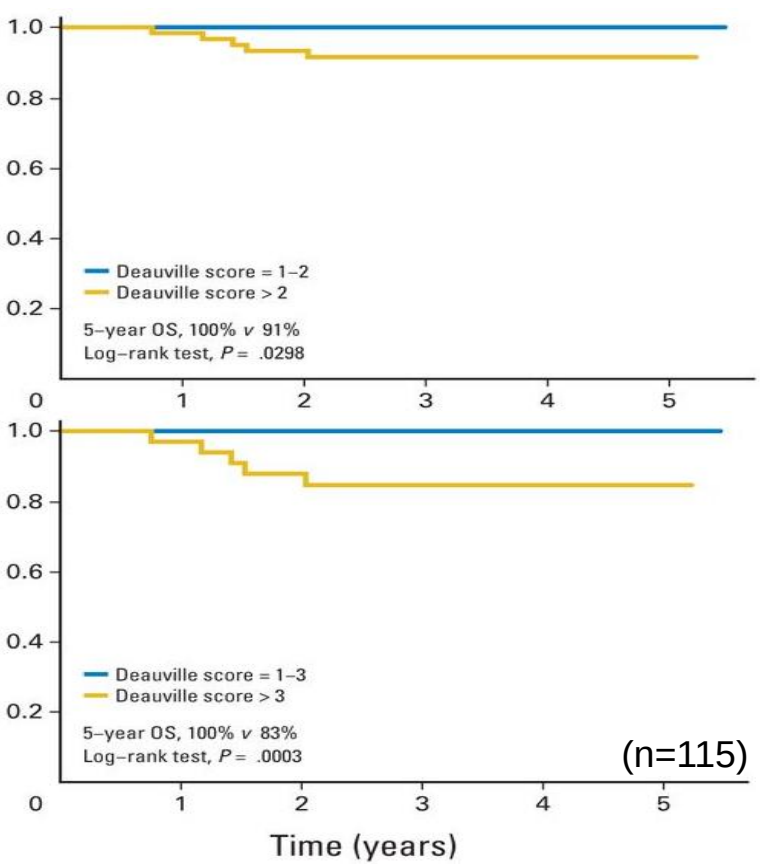
Progression-free Survival



Deauville 1+2 vs. 3-5

Deauville 1-3 vs. 4+5

Overall Survival



(n=115)

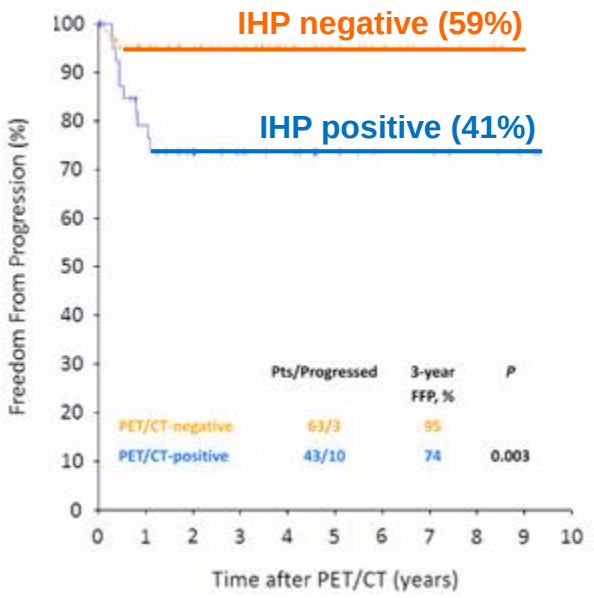
Martelli et al, J Clin Oncol 32: 1769, 2014

Primary mediastinal B-cell lymphoma

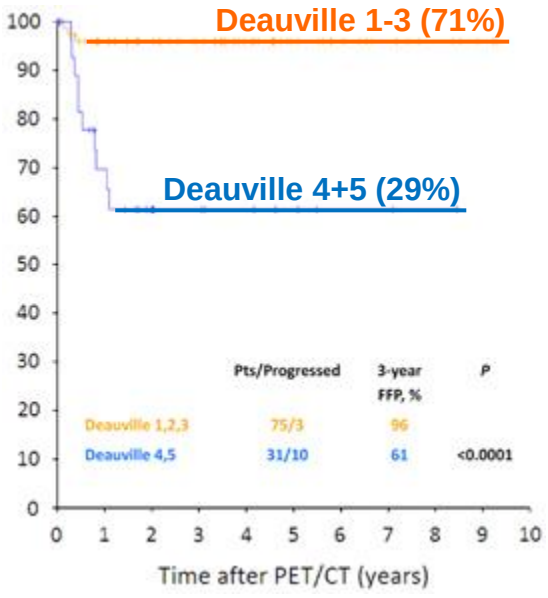
PFS and OS according to EoT PET

R-CHOP → EoT PET → IHP / Deauville / SUVmax

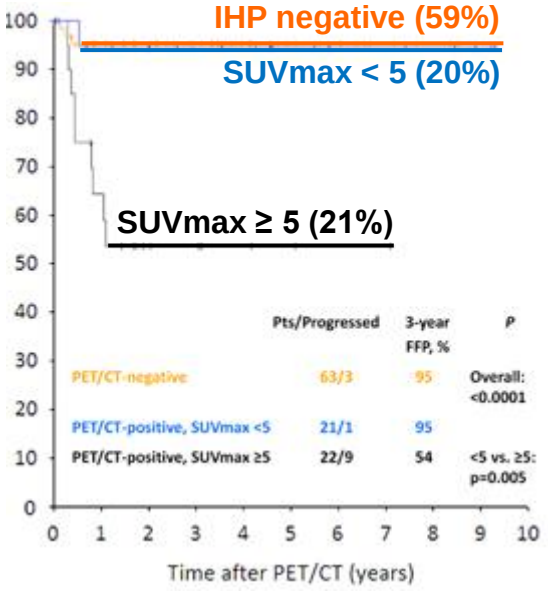
IHP



Deauville 1-3 vs. 4+5



SUVmax < 5 vs. ≥ 5



Vassilakopoulos et al, Leukemia (in press), 2015

End-of-treatment PET in lymphoma

Negative and positive predictive values (PFS)

Entity	NPV	PPV
Follicular lymphoma	91 – 100 %	75 – 92 %
Mantle cell lymphoma	100 %	63 %
Diffuse large B-cell lymphoma	90 – 100 %	50 – 82 %
Peripheral T-cell lymphoma	59 – 64 %	33 – 89 %
Hodgkin lymphoma	94 – 100 %	46 – 91 %
Primary mediastinal B-cell lymphoma	98 – 100 %	32 – 63 %

High **Low**

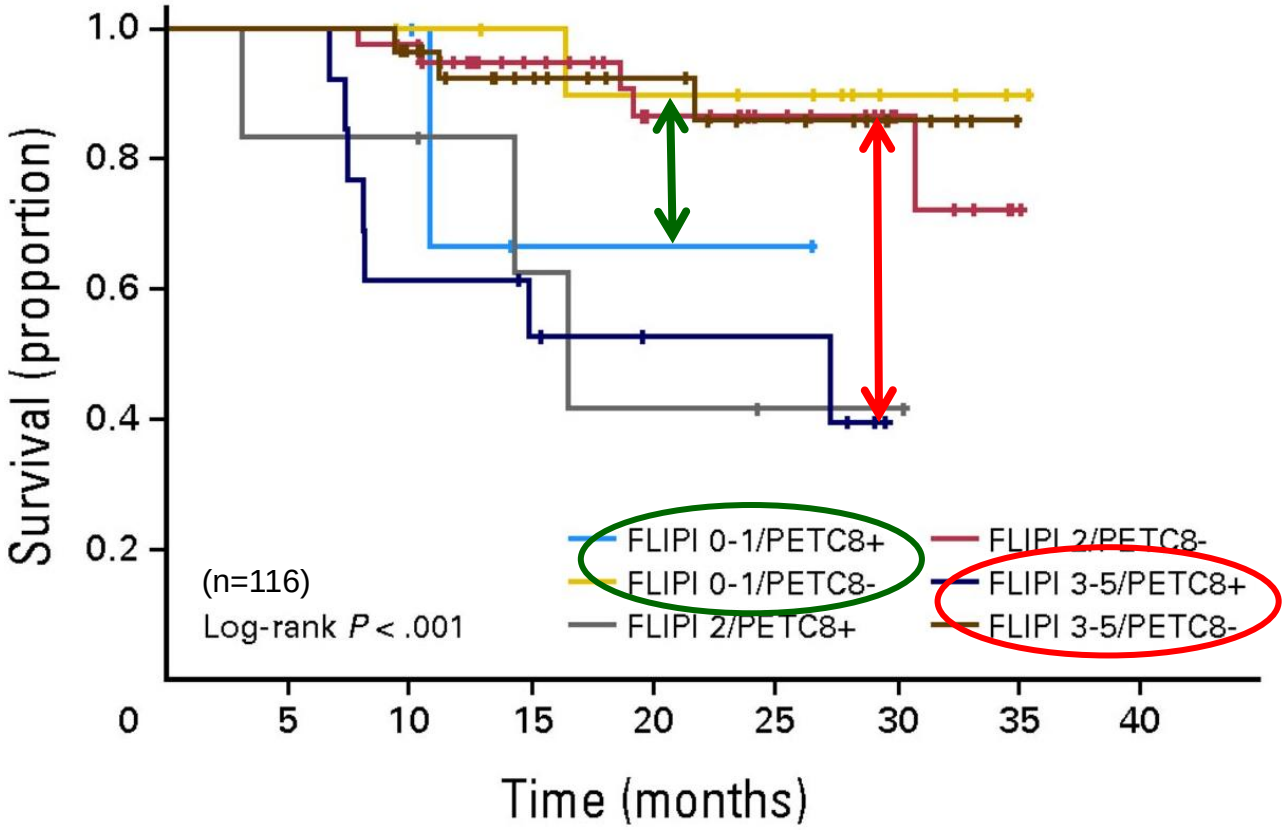
Bishu et al, Leuk Lymphoma 48: 1548, 2007; Le Dortz et al, Eur J Nucl Med Mol Imaging 37: 2307, 2010; Bodet-Milin, Eur J Nucl Med Mol Imaging 37: 1633, 2010; Cahu et al, Ann Oncol 22: 705, 2011; Li et al, J Nucl Med 54: 507, 2013; Tomita et al, Ann Hematol 94: 431, 2015; Martelli et al, J Clin Oncol 32: 1769, 2014; Nagle et al, Cancer Med 4: 7, 2015; Barrington et al, J Clin Oncol 32: 3048, 2014

End-of-treatment PET in lymphoma

Independence of IPI, FLIPI, MIPI, IPS, PIT, …

Follicular Lymphoma

Progression-free Survival according to FLIPI and EoT PET



Dupuis et al, J Clin Oncol 30: 4317, 2012

End-of-treatment PET in lymphoma

Key objectives

1. Performance of EoT PET
2. Prognostic information
3. **Therapeutic implications**

End-of-treatment PET in lymphoma

Possible therapeutic implications

EoT PET negative	Omission of maintenance therapy
	Omission of radiotherapy
EoT PET positive	**Biopsy**
	Radiotherapy
	Radioimmunotherapy
	Alternative chemotherapy
	High-dose therapy
	Allogeneic transplantation
	Experimental treatment

End-of-treatment PET

Therapeutic implications investigated

Omission of radiotherapy

Hodgkin lymphoma

Primary mediastinal B-cell lymphoma

Addition of radiotherapy

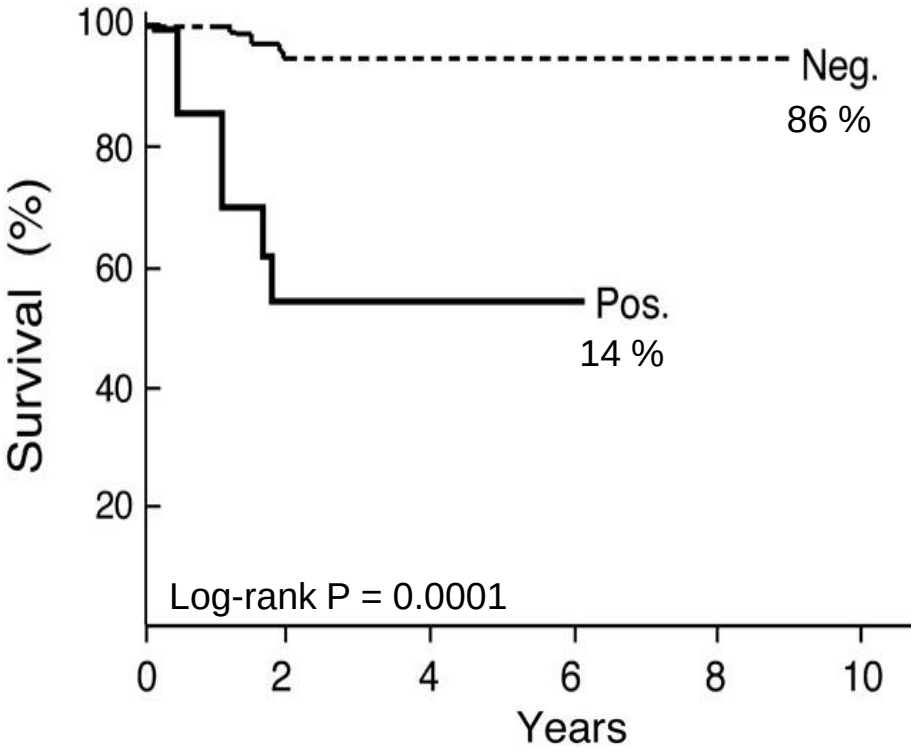
Diffuse large B cell lymphoma

Hodgkin lymphoma

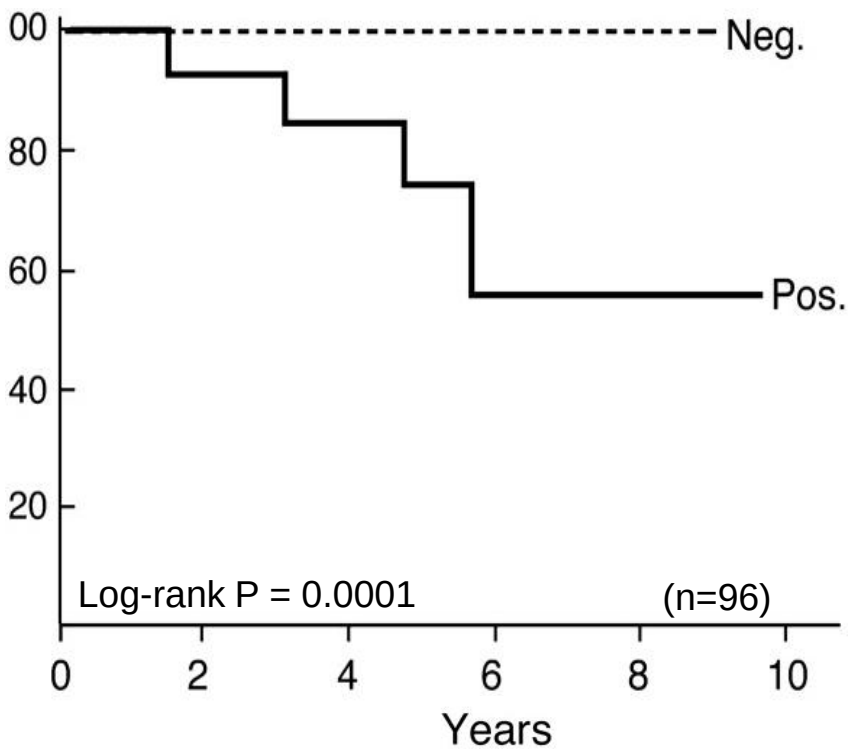
PFS and OS according to EoT PET

4-6 x ABVD ± IFRT → EoT PET → local 4-point scale

Progression-free Survival



Overall Survival

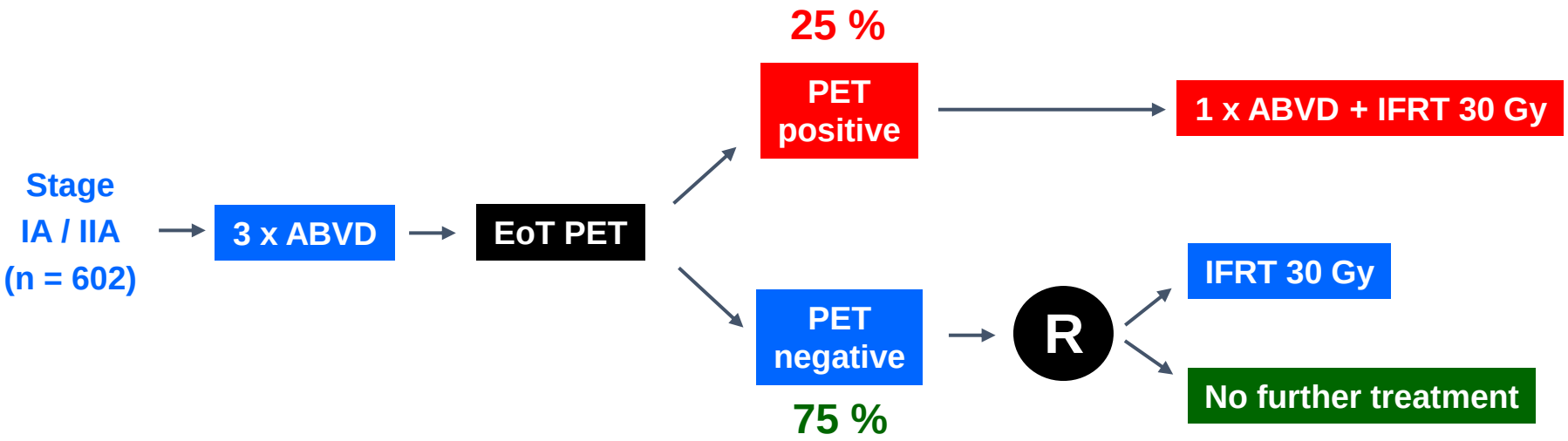


Barnes et al, Ann Oncol 22: 910, 2011

Hodgkin lymphoma, early stages

British standard: 3 x ABVD + IFRT

Can radiotherapy be omitted in EoT PET-negative patients ?



Non-inferiority no further treatment vs. standard IFRT :

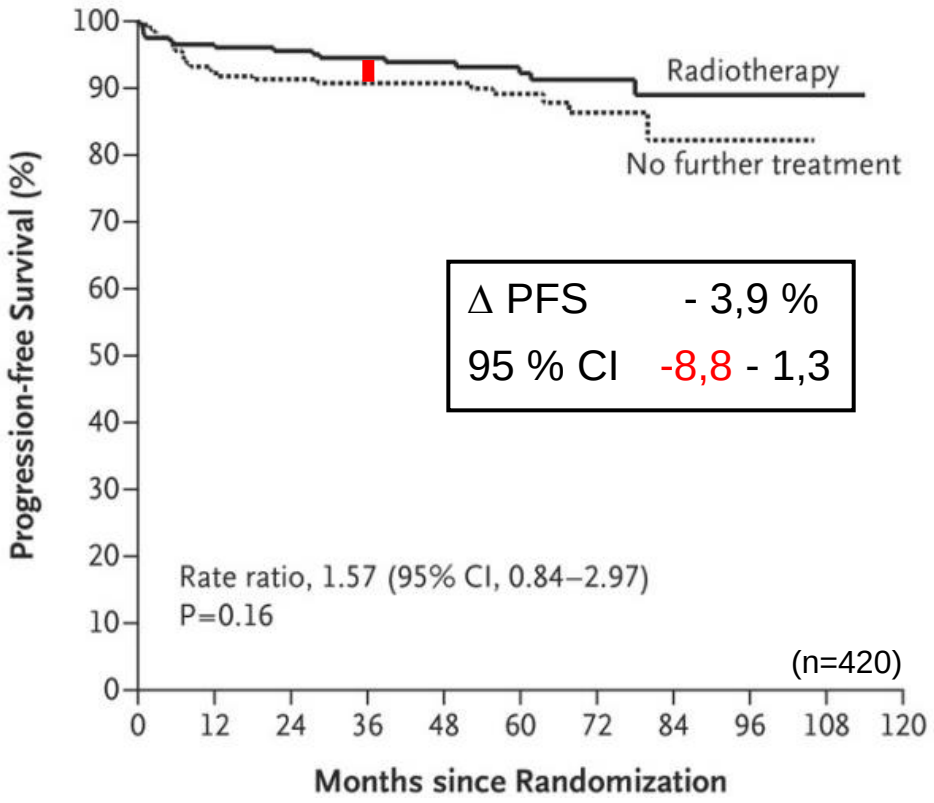
Difference in 3-year PFS ≤ 7 %

Radford et al, N Engl J Med 372: 1598, 2015

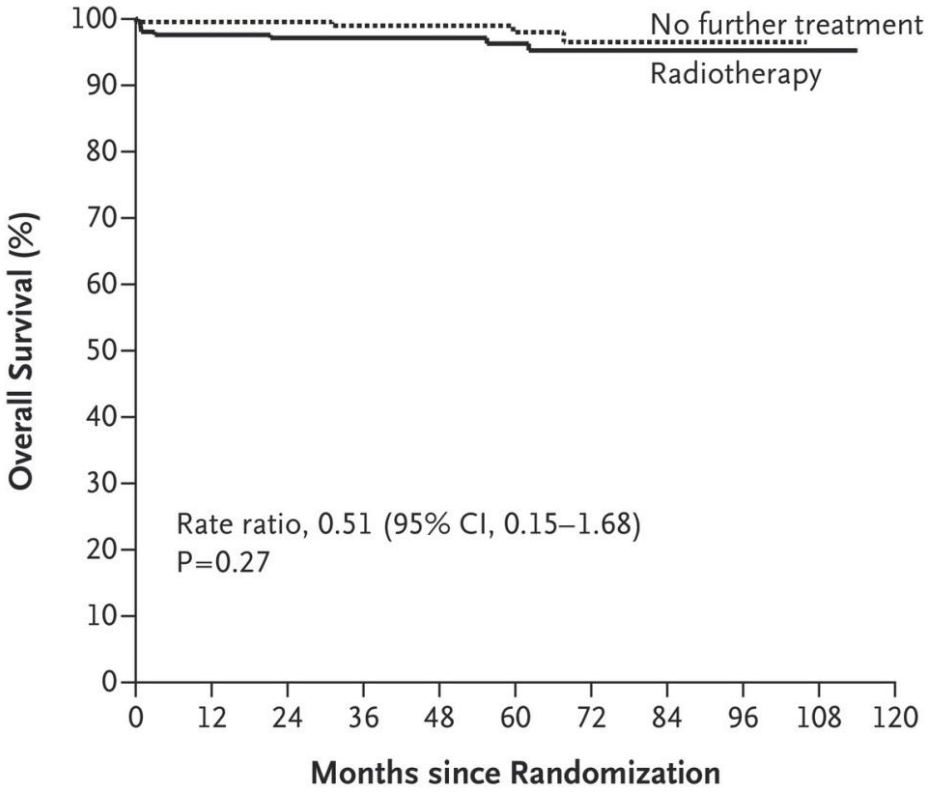
Hodgkin lymphoma, early stages

No radiotherapy ?

Progression-free Survival



Overall Survival

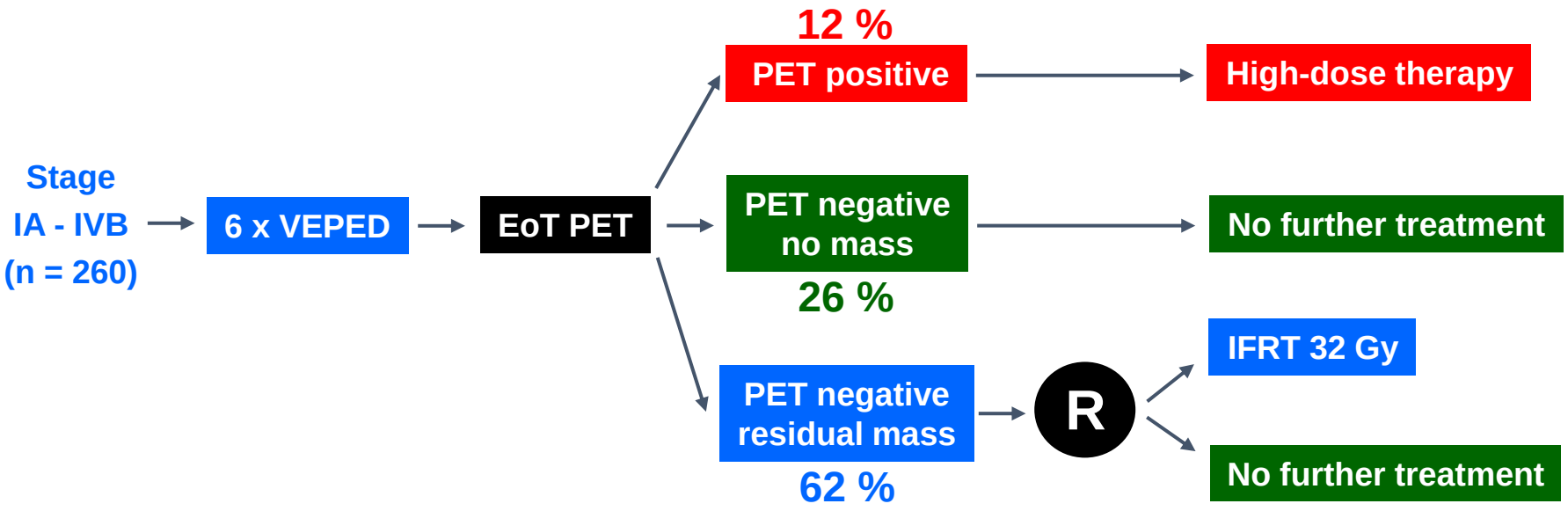


Radford et al, N Engl J Med 372: 1598, 2015

Hodgkin lymphoma, bulky disease

Italian standard: 6 x VEPED + IFRT

Can radiotherapy be omitted in EoT PET-negative patients ?



Superiority standard IFRT vs. no further treatment :

Difference in EFS ≥ 10 %

Picardi et al, Leuk Lymphoma 48: 1721, 2007

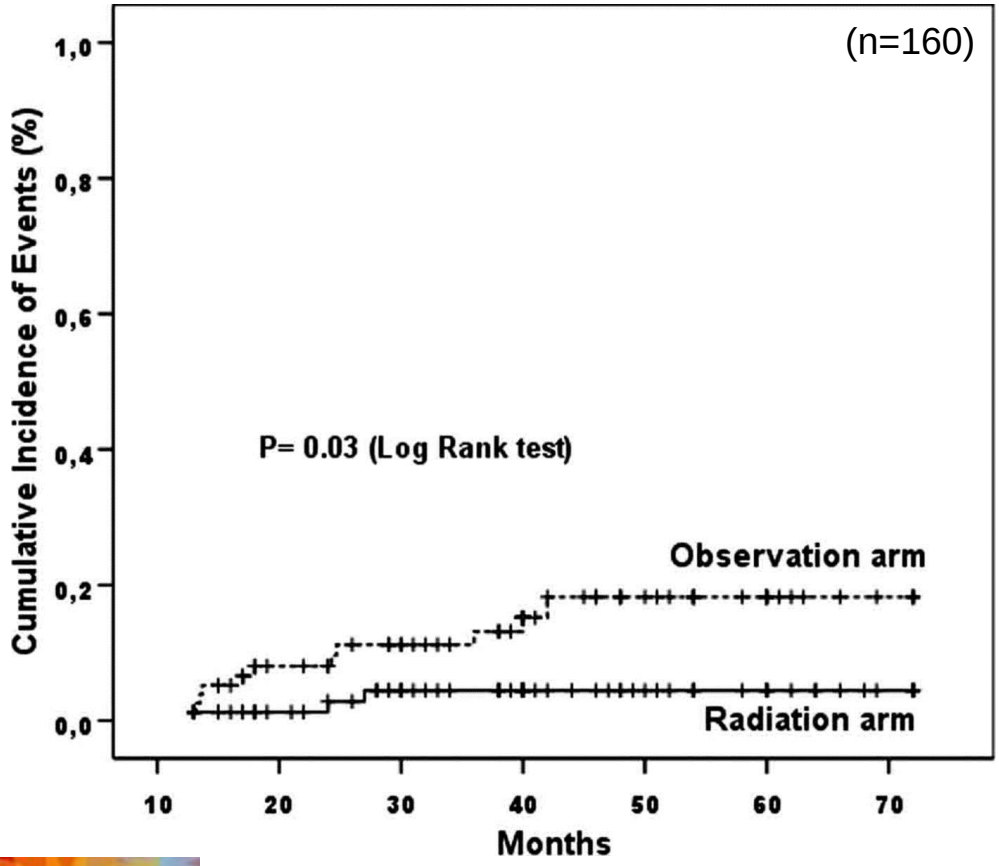
Hodgkin lymphoma, bulky disease

No radiotherapy ?

	EFS (40 mo.)
PET positive	50 %
PET negative, no mass	88 %
Randomisation: PET negative, residual mass	
Observation	86 %
Radiotherapy	96 %

Δ 10 %

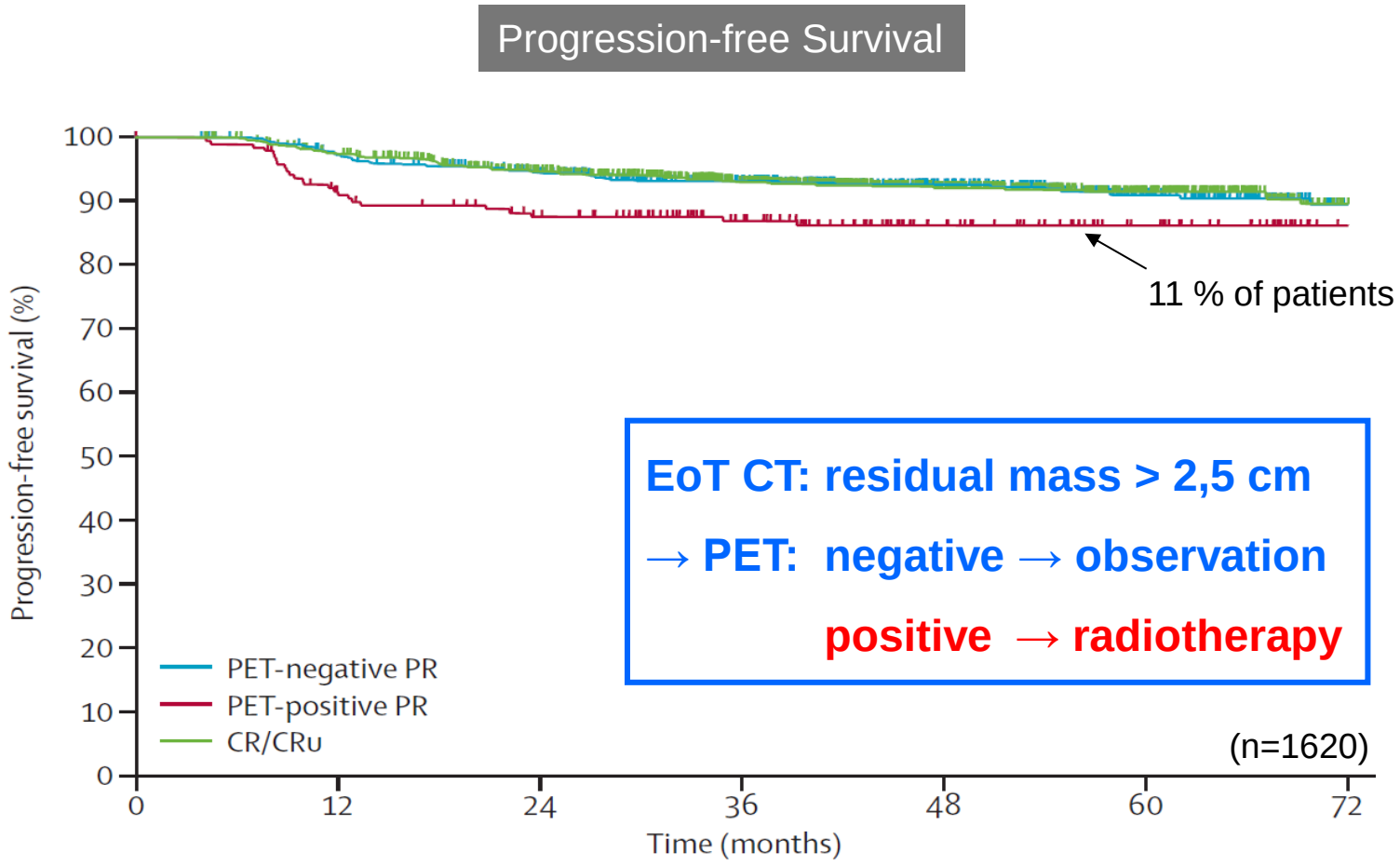
Relapses in EoT PET-negative patients with a residual mass



Picardi et al, Leuk Lymphoma 48: 1721, 2007

Hodgkin lymphoma, advanced stages

German standard: 6 x BEACOPPesc + IFRT (residual m.)

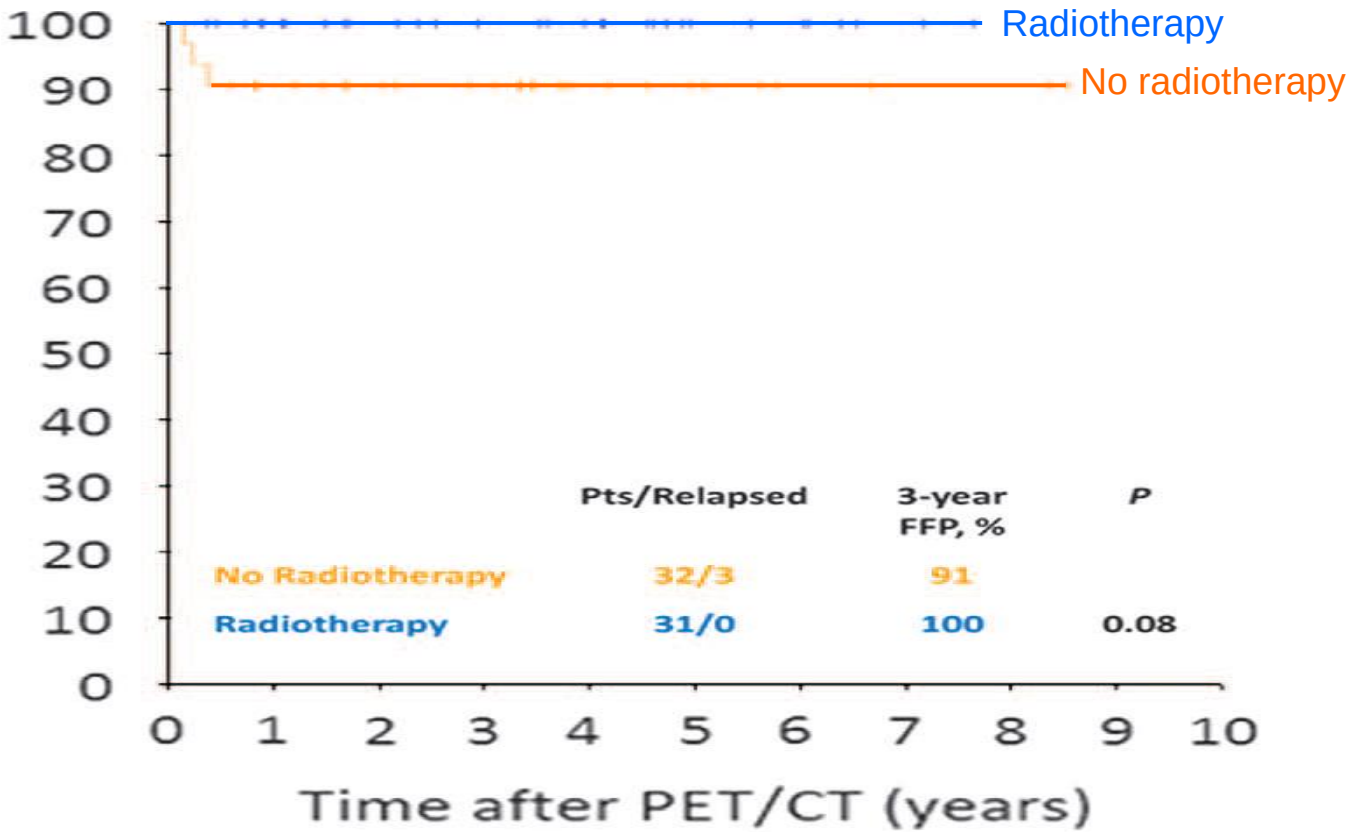


Engert et al, Lancet 379: 1791-99, 2012

Primary mediastinal B-cell lymphoma

Is radiotherapy required in EoT PET-negative patients ?

Freedom from Progression
in EoT PET-negative patients



Vassilakopoulos et al, Leukemia (in press), 2015

Primary mediastinal B-cell lymphoma

Canadian standard: 6 x R-CHOP + IFRT

Recommendation in British Columbia:

EoT → PET → negative → observation

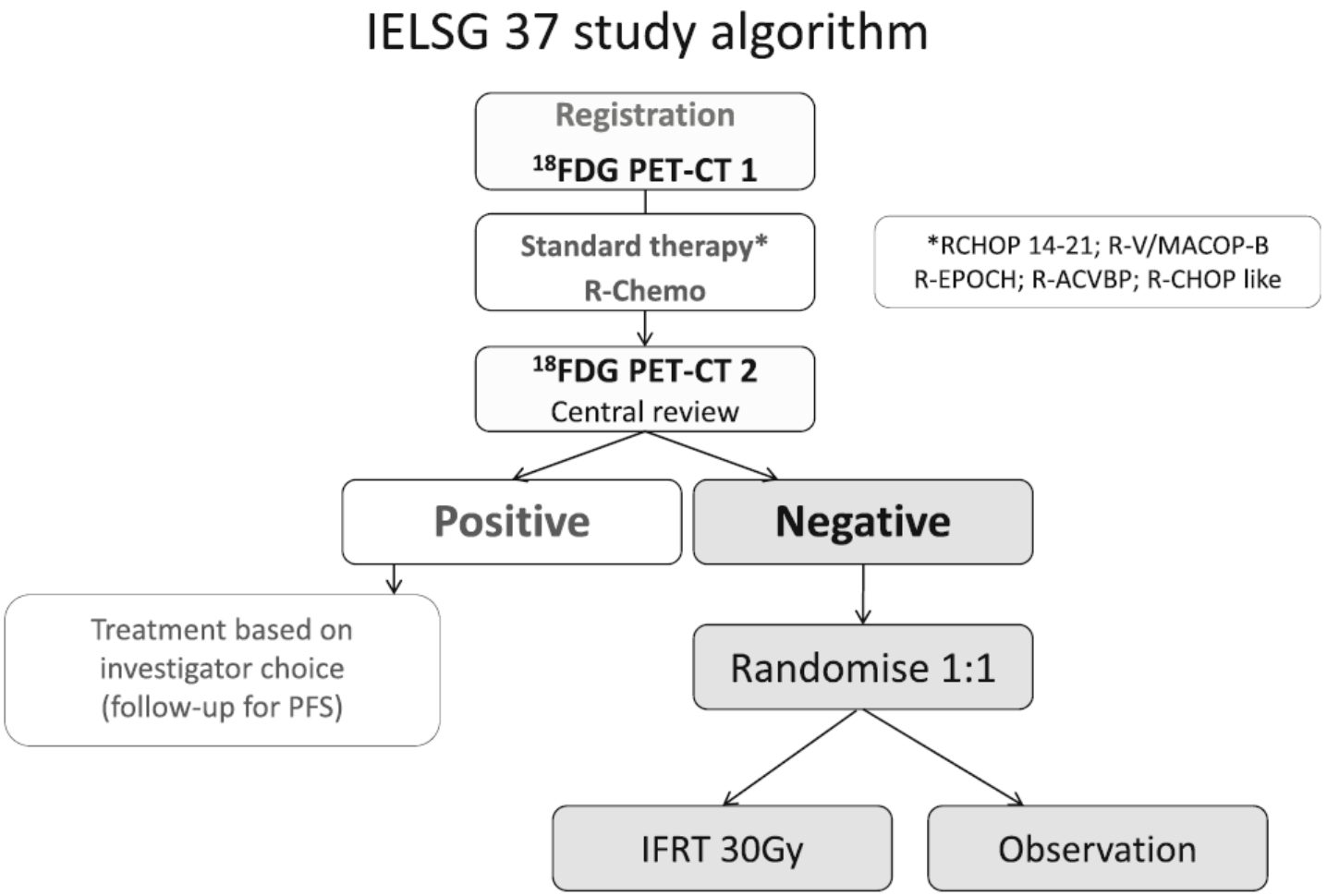
→ positive → radiotherapy

EoT PET	Patients	Radiotherapy	5-year TTP	5-year OS
Negative	35	6 %	78 %	89 %
Positive	24	95 %	83 %	95 %

Savage et al, ASH #303, 2012

Primary mediastinal B-cell lymphoma

Can radiotherapy be omitted in PET-negative patients ?



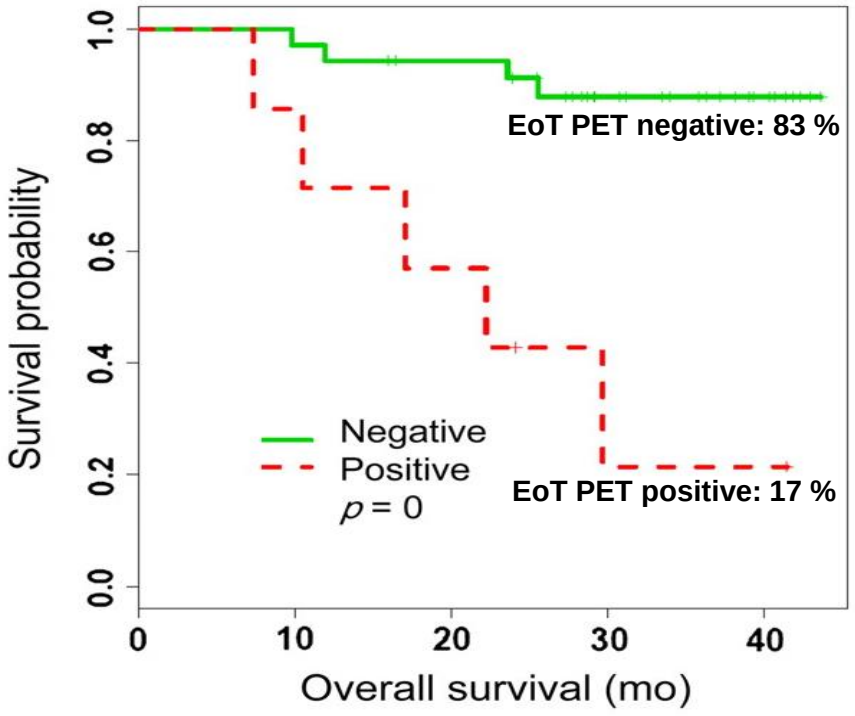
ClinicalTrials.gov: NCT01599559

Diffuse large B-cell lymphoma

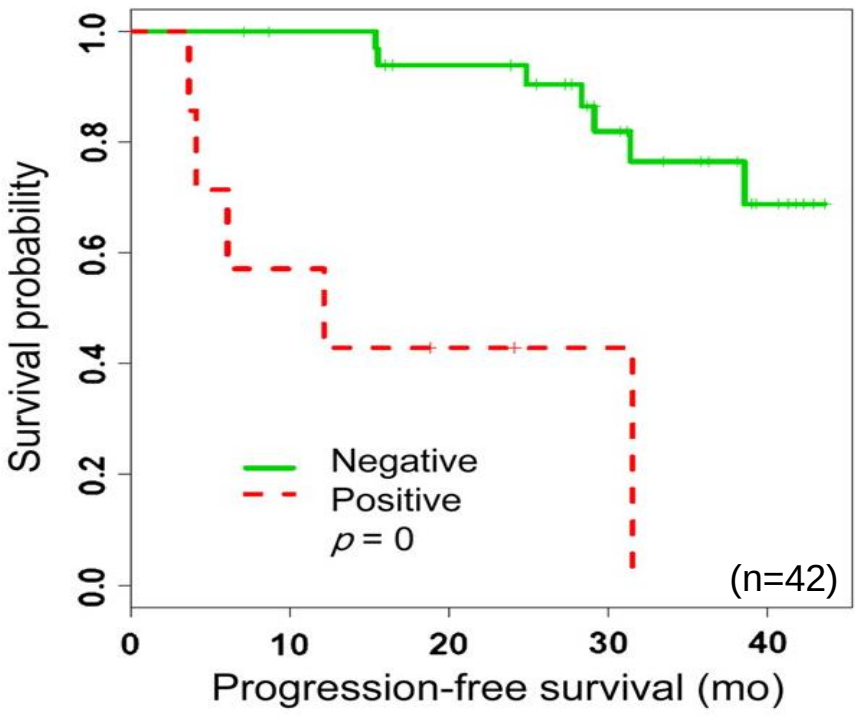
PFS and OS according to EoT PET

6 x R-CHOP → EoT PET → IHP

Progression-free Survival



Overall Survival



Cashen et al, J Nucl Med 52: 386, 2011

Diffuse large B-cell lymphoma

Should radiotherapy be given to EoT PET-positive sites ?

Recommendation in British Columbia:

EoT CT: residual mass > 2,0 cm → PET → negative → observation

→ positive → radiotherapy

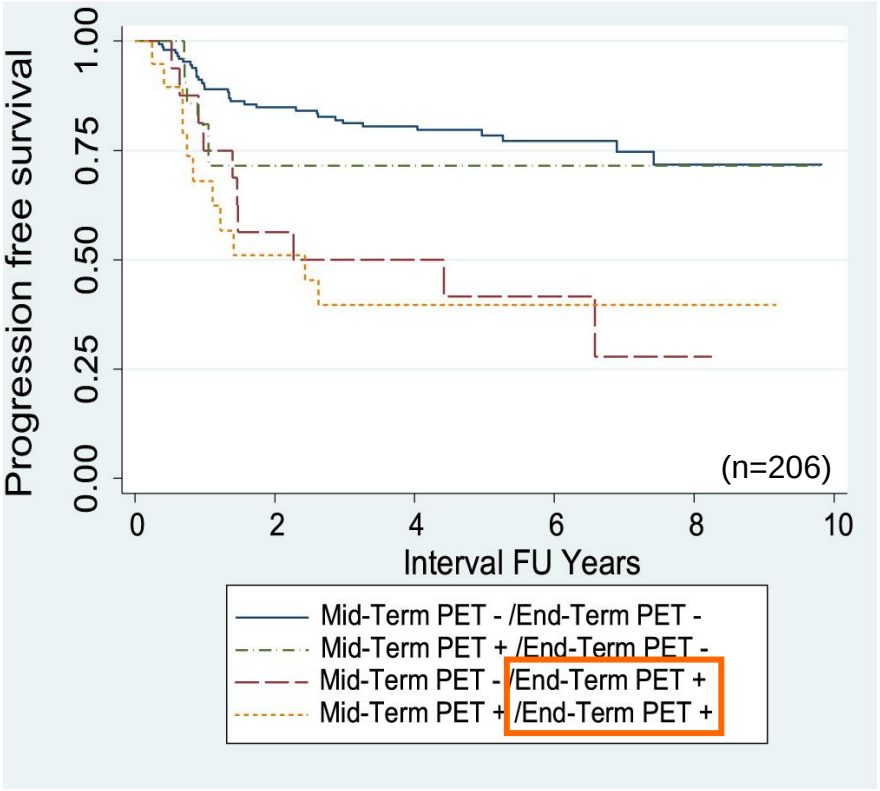
EoT PET	Patients	Radiotherapy	4-year TTP	4-year OS
Negative	167	1 %	74 %	83 %
Positive	82	Yes: 73 % No: 27 %	81 % 33 %	85 % 30 %

Sehn et al,
Hematol Oncol 31 (suppl 1): abstr 123, 2013

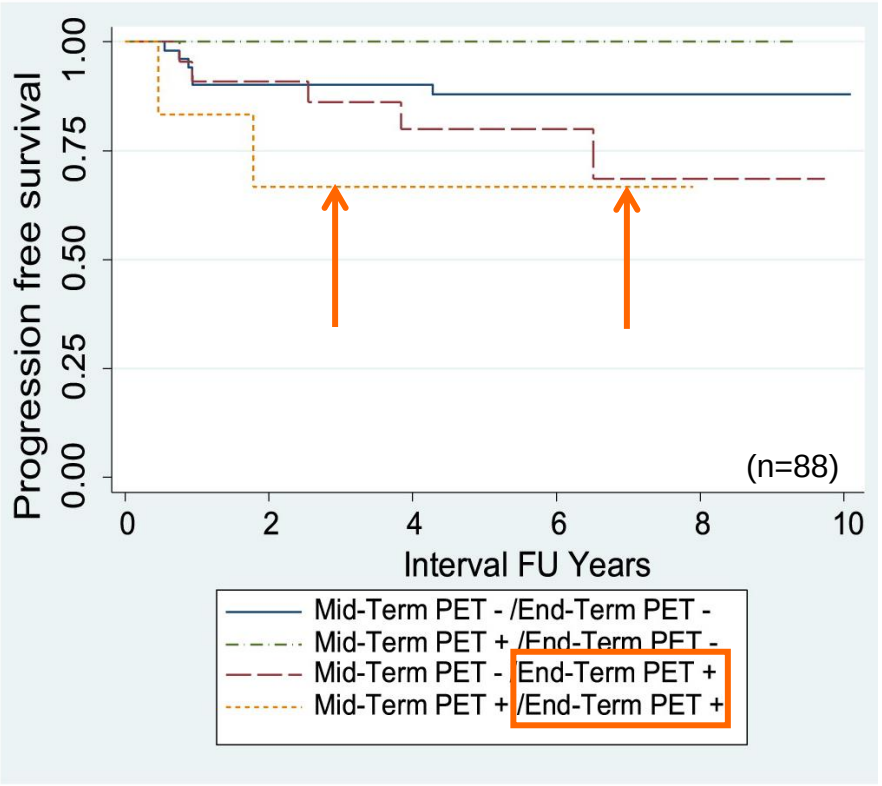
Diffuse large B-cell lymphoma

Should radiotherapy be given to EoT PET-positive sites ?

Chemotherapy only



Chemotherapy + radiotherapy



Dabaja et al,
Int J Radiation Oncol Biol Phys 89: 384, 2014

End-of-treatment PET in lymphoma

Key objectives

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2. Prognostic information
3. **Therapeutic implications**

must be based on prospective trials !