

# Primary Mediastinal B-cell Lymphomas

*To Radiate or Not to Radiate*

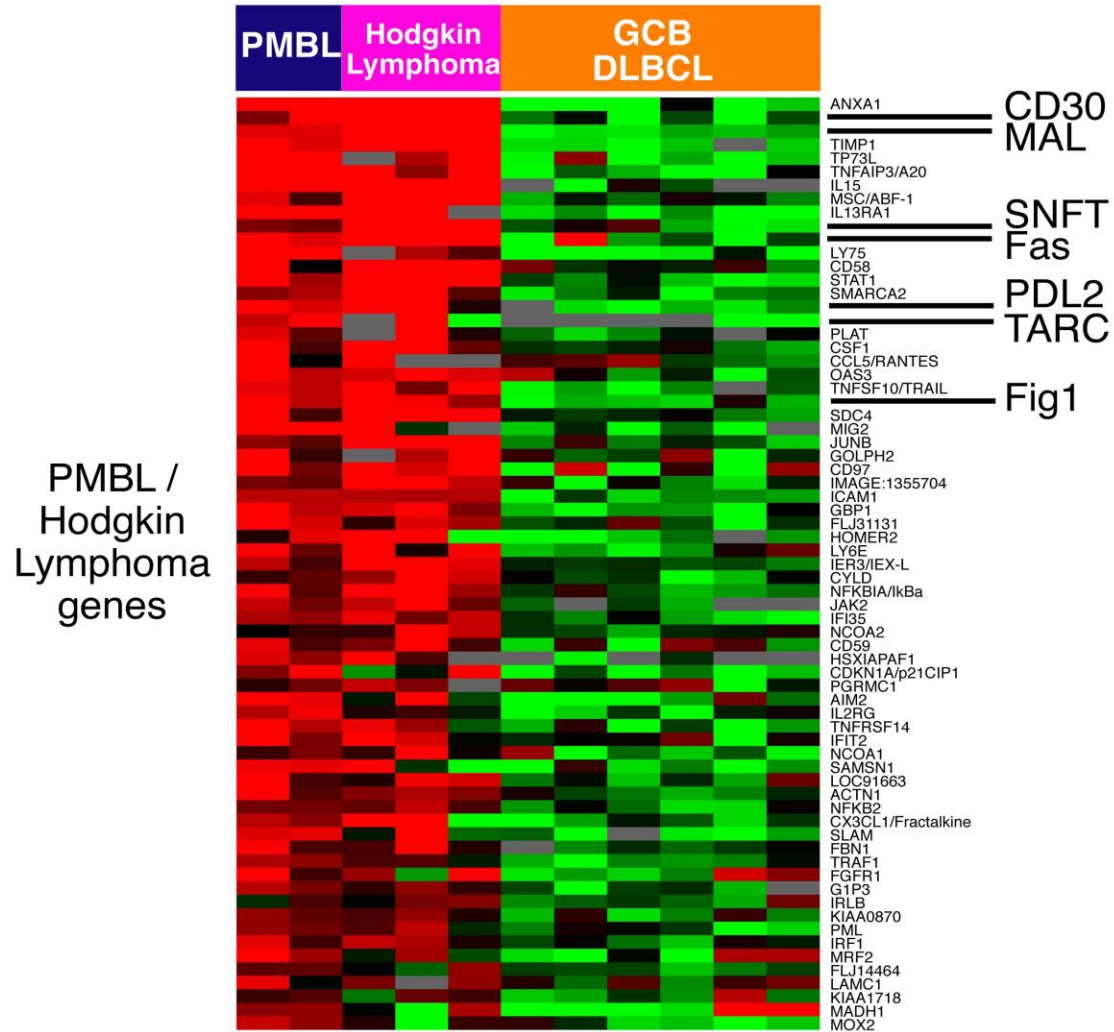
Wyndham H. Wilson, MD, PhD

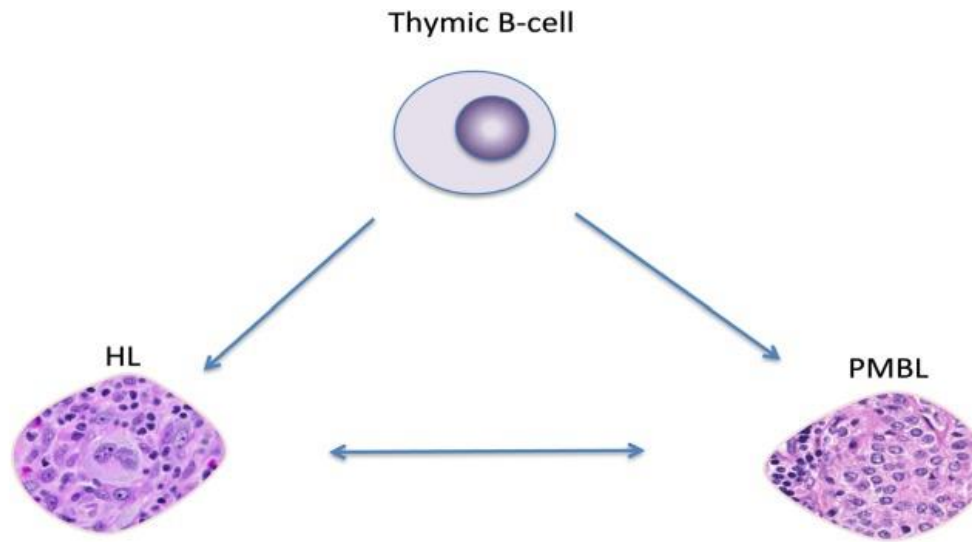
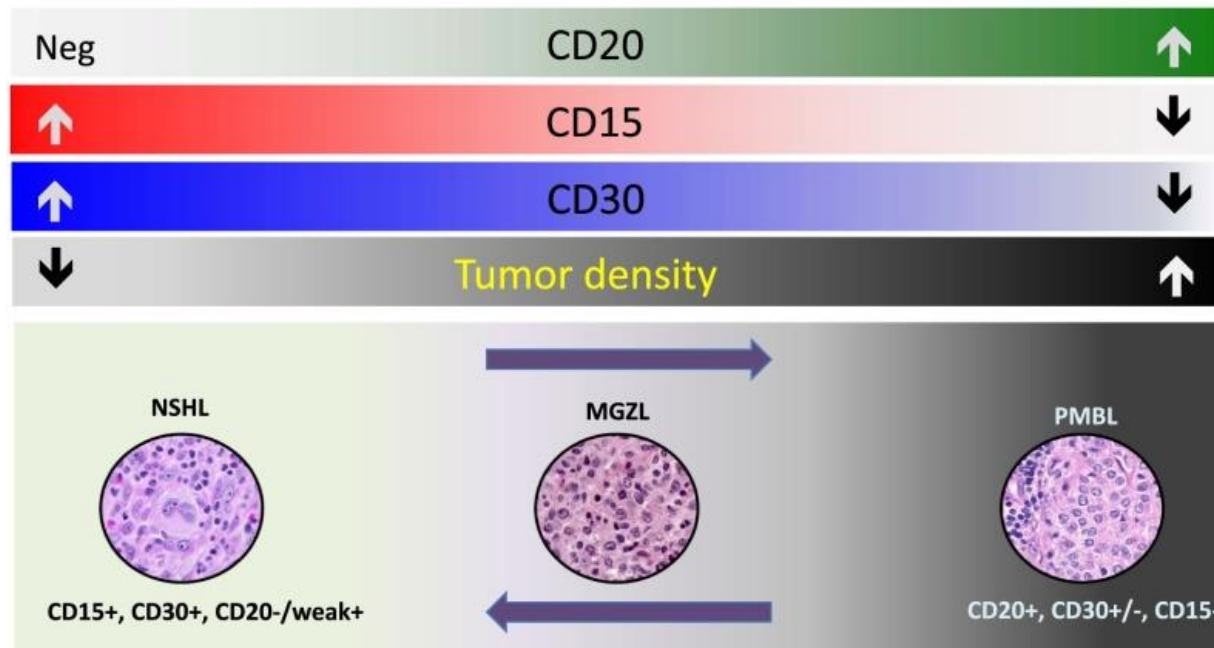


# Primary Mediastinal B-cell Lymphomas

## Molecular Subtype of DLBCL

Extensive Gene Expression Overlap Between Hodgkin Lymphoma and Primary Mediastinal Large B Cell Lymphoma

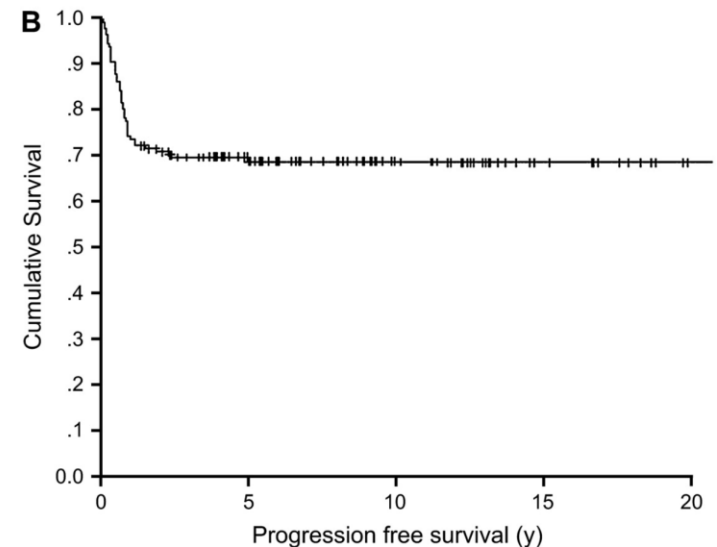
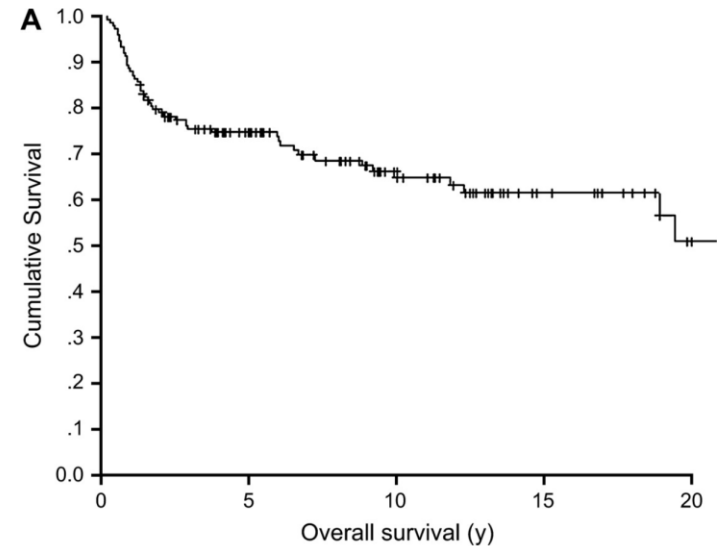


**A****B**

# R-CHOP is Not Adequate for PMBL

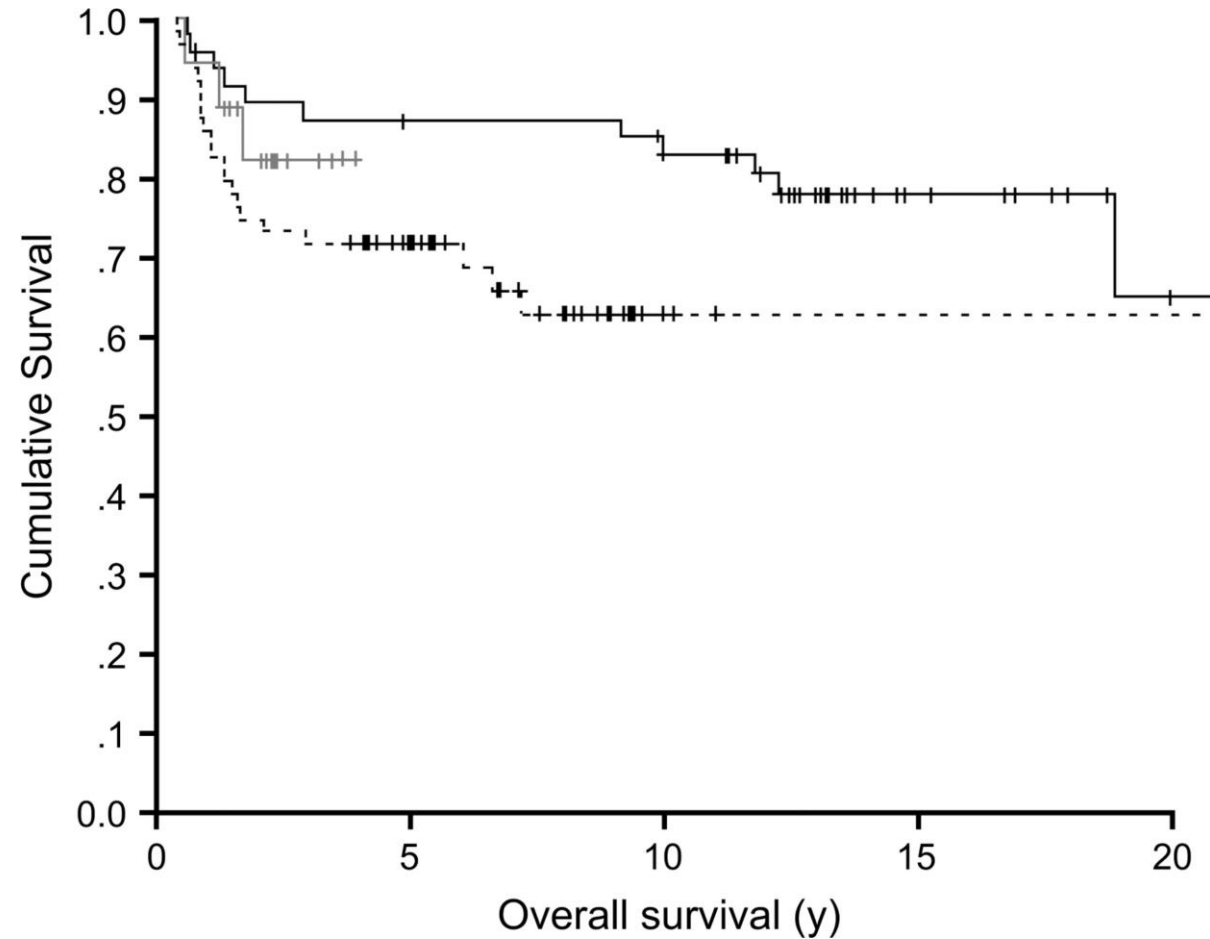
## The British Columbia experience

- 153 patients
- Median age 37 years
- Bulky  $\geq 10$  cm 75%
- Radiotherapy upfront 39%
- Median follow-up 9 years



# Impact of Dose-Intensity Treatment

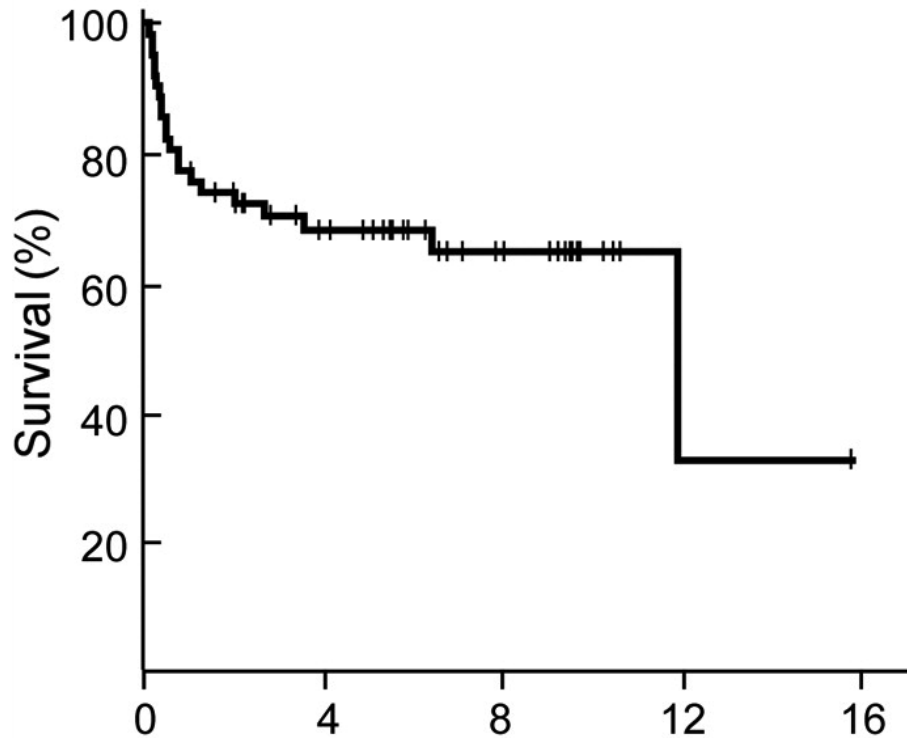
- **Effect of treatment**
  - MACOPB/VACOPB
  - CHOP-R
  - CHOP



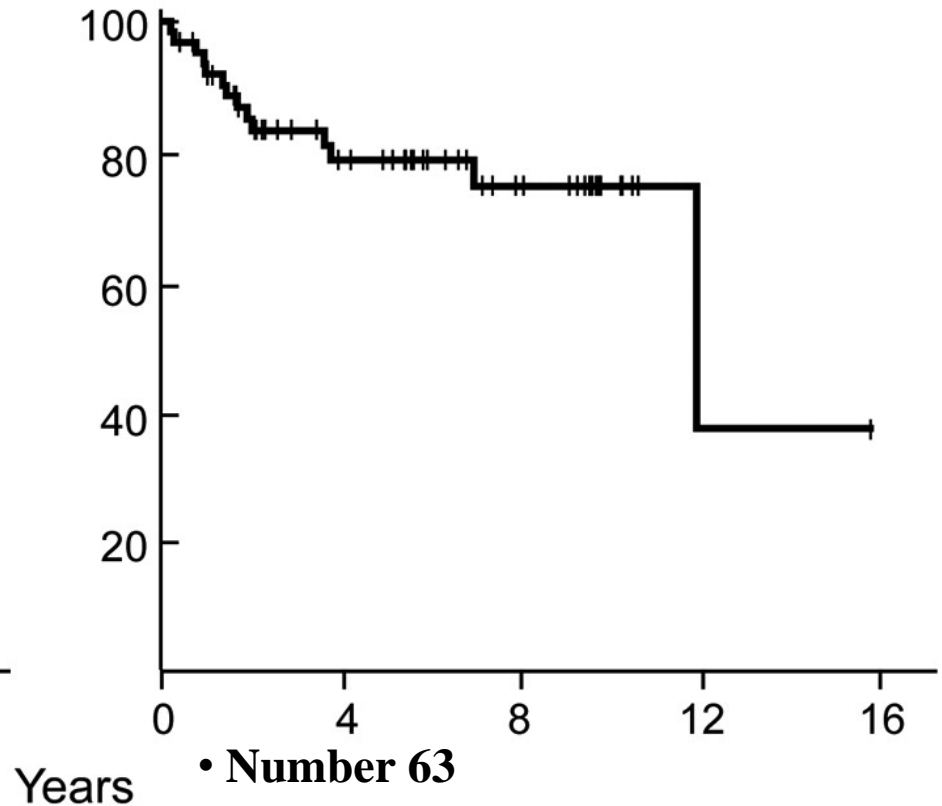
# R-CHOP is Not Adequate for PMBL

## The Harvard Experience

**(A)** Progression-free survival



**(B)** Overall survival



- **Number 63**
- **Median age 37 years**
- **Median mass 11 cm**
- **Radiation in responding patients 77%**
- **Median follow-up 69 months**

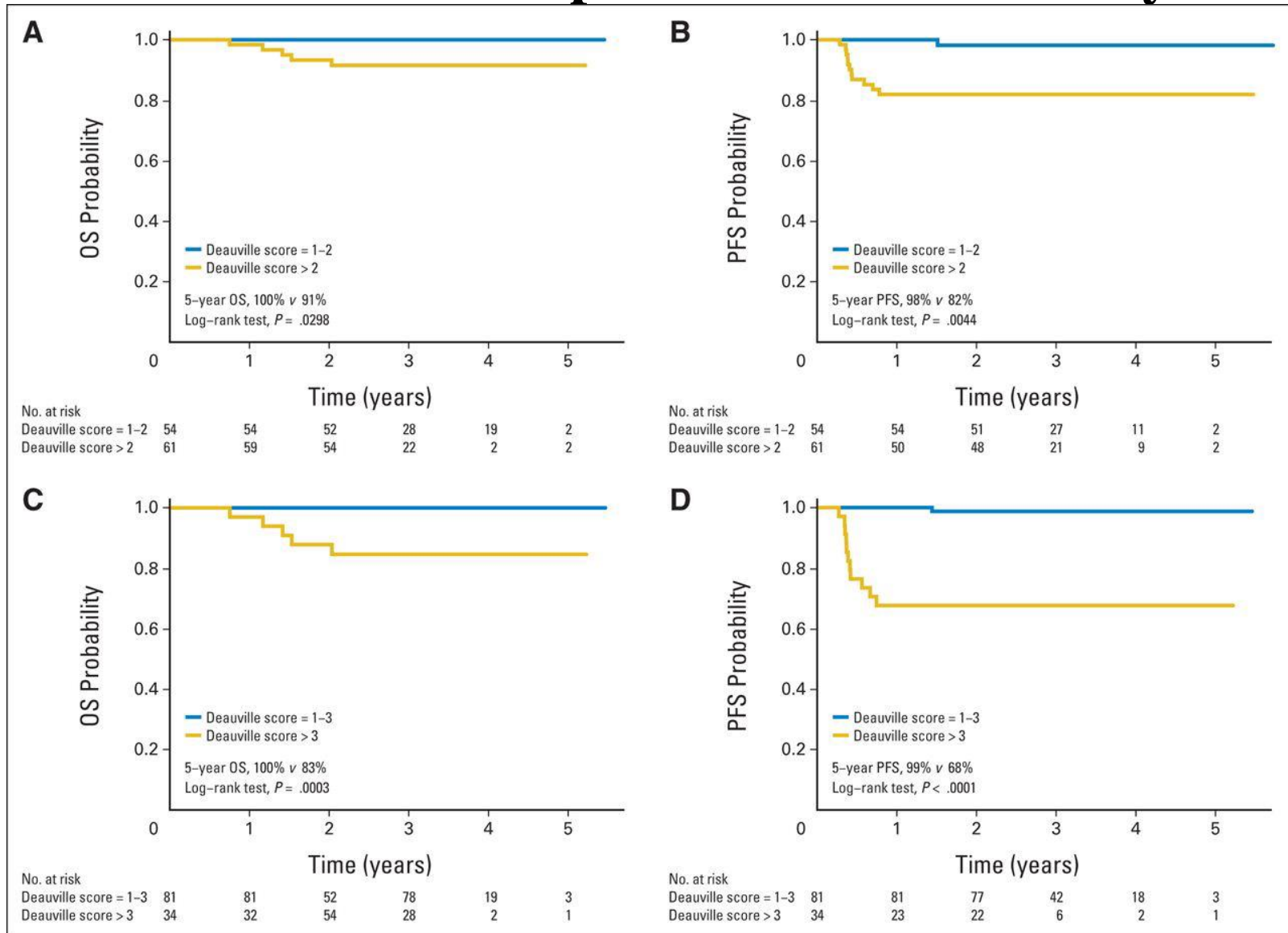
# **EGF PET Predicts Survival in PMBL**

## **Results of Prospective IELSG26 Study**

- 125 patients
- Median age 33 years
- Bulky > 10 cm 52%
- Treatment
  - MACOP-B-R 71
  - VACOP-B-R 34
  - CHOP-R 14
- Consolidation RT allowed

# EGF PET Predicts Survival in PMBL

## Results of Prospective IELSG26 Study





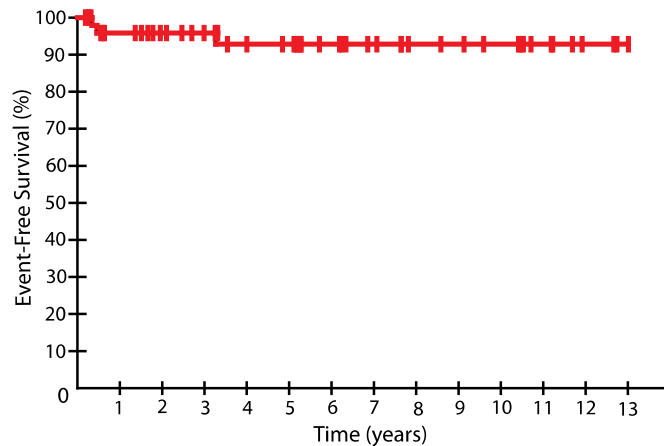
# DA-EPOCH-R in PMBL

## No Need for Radiation

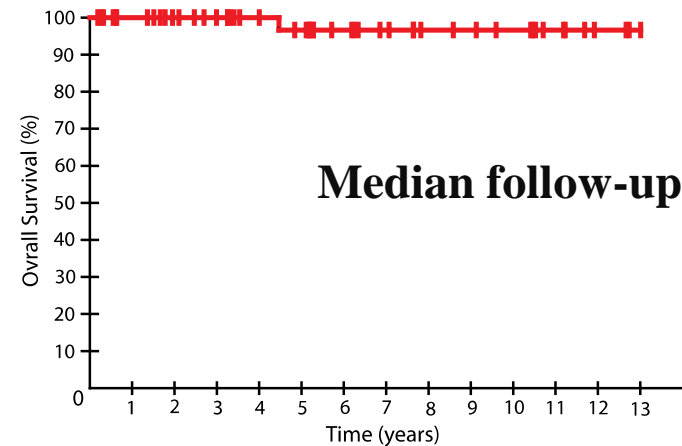
<b>Characteristics</b>	<b>National Cancer Institute Phase II Study DA-EPOCH-R (%)</b>	<b>Stanford Medical Center Retrospective Study DA-EPOCH-R (%)</b>
Total Patients	51	16
Female Gender	30 (59%)	9 (56%)
Age years median [range]	30 [19-52]	33 [23-68]
Bulky Tumor $\geq$ 10 cm [range]	33 (65%) [5-18]	9 (56%) [7-18]
Stage IV disease	15 (29%)	7 (44%)
Lactate Dehydrogenase > Normal	40 (78%)	11 (69%)
Extranodal site	27 (53%)	3 (19%)
Pleural effusion	24 (47%)	10 (63%)
CD20+ malignant cells	51 (100%)	16 (100%)
BCL-6+ malignant cells	33/37 (89%)	Not Done

# DA-EPOCH-R Obviates the Need for Radiation in PMBL

A. DA-EPOCH-R [NCI series]

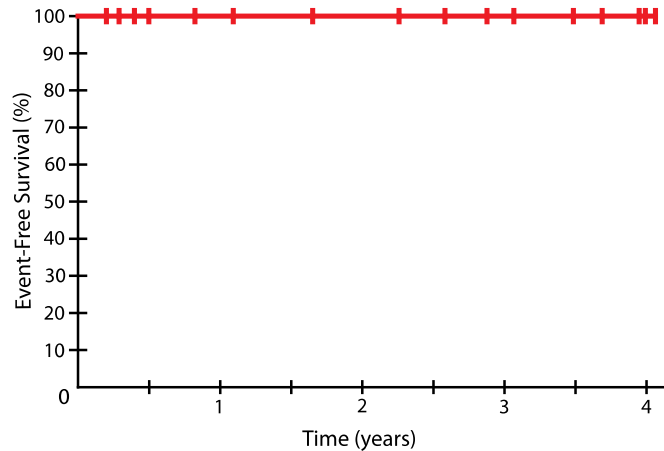


B. DA-EPOCH-R [NCI series]

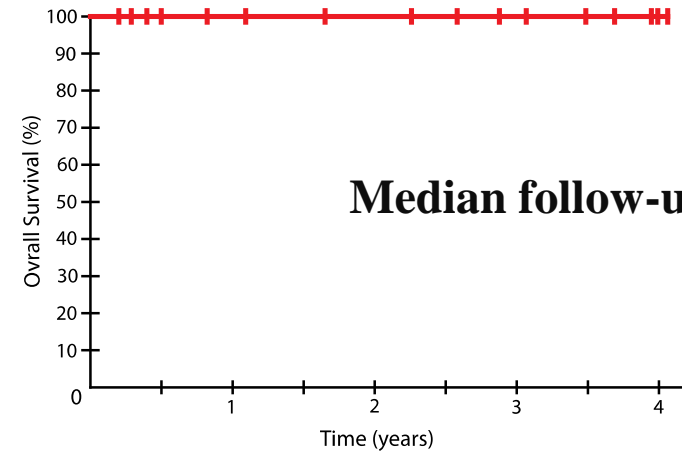


**Median follow-up 5 years**

C. DA-EPOCH-R [Stanford series]



D. DA-EPOCH-R [Stanford series]



**Median follow-up 3 years**

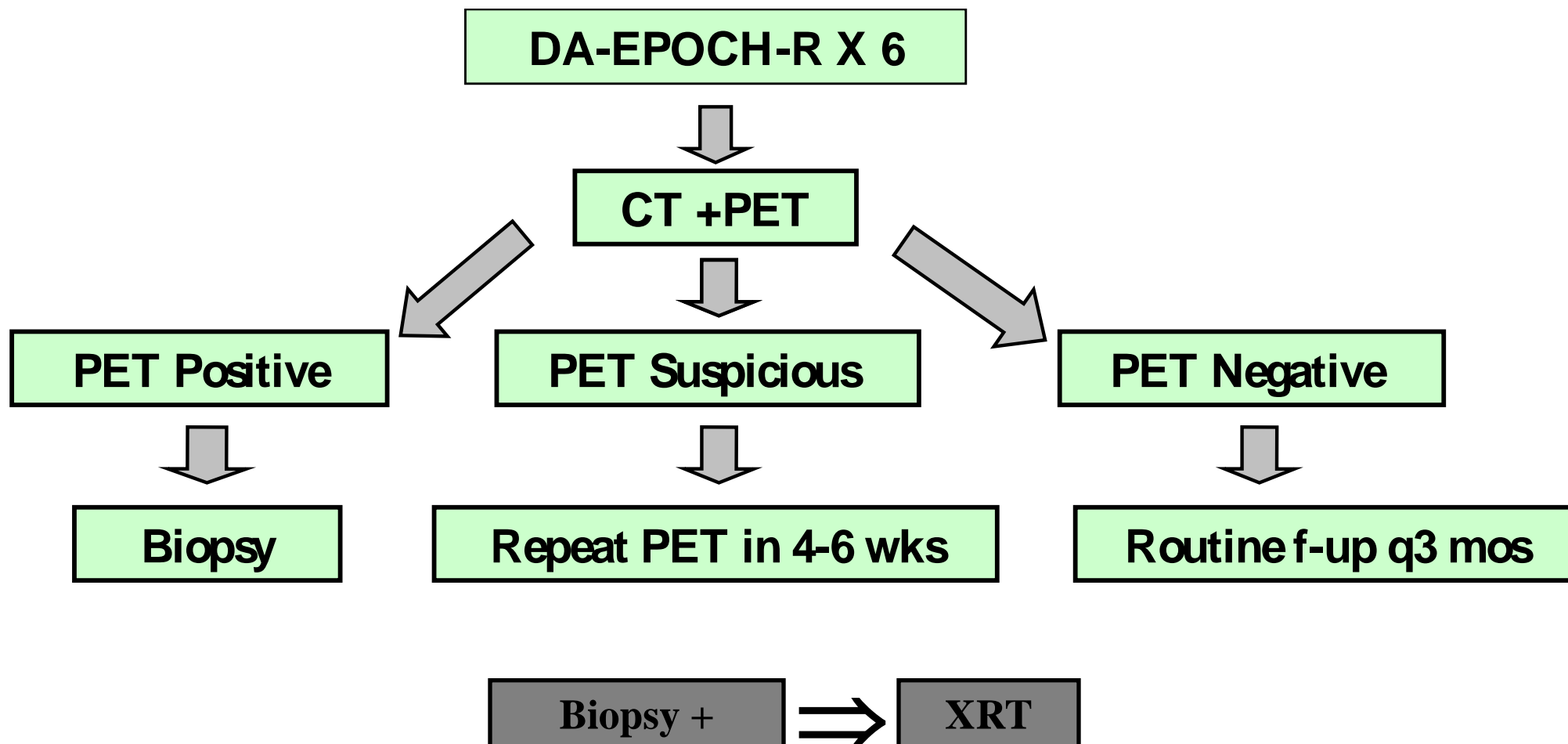
# **EOT FDG-PET with DA-EPOCH-R**

- **Untreated PMBL patients received DA-EPOCH-R without RT (N=93)**
- **Prospective NCI (N = 58); Retrospective Stanford (N = 34)**
- **EOT FDG-PET assessed by 2 independent nuclear medicine physicians blinded to clinical outcome**

<sup>1</sup>Dunleavy, K., et al. *NEJM*. 2013.

<sup>2</sup>Meignan, M., *Leuk Lymphoma*. 2009.

# Treatment Paradigm

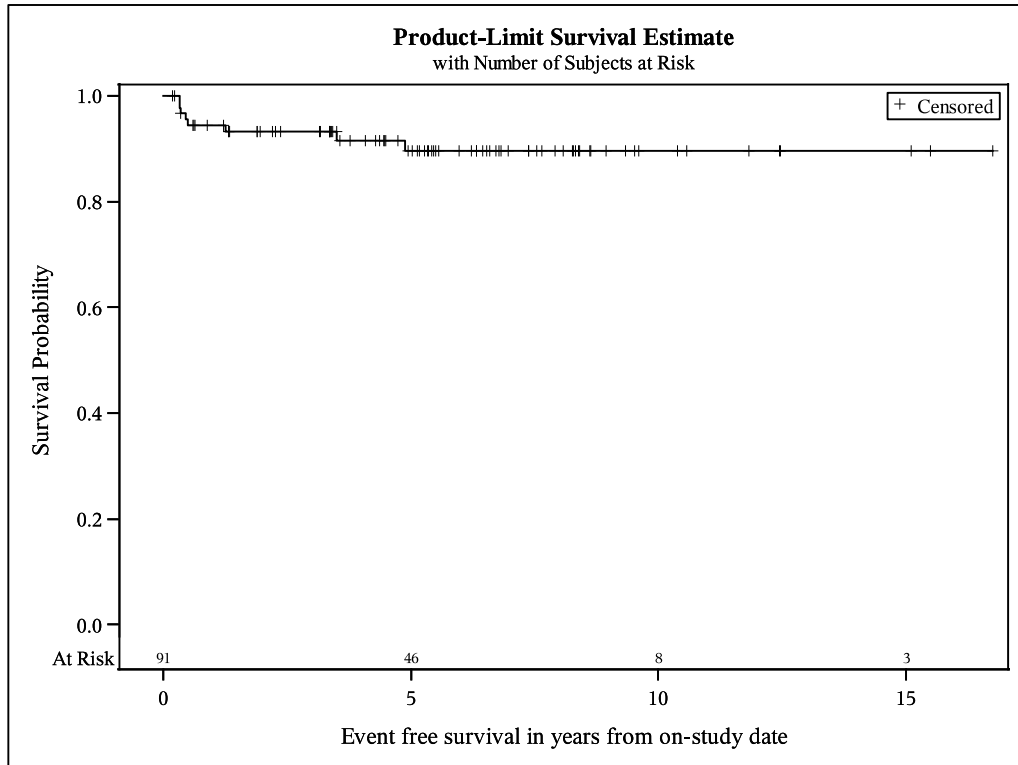


Characteristic	Total Cohort (N = 93)	Evaluable EOT FDG-PET (N = 83)	Prospective NCI Cohort (N = 59)	Retrospective Stanford Cohort (N = 34)
Female sex- no. (%)	55 (59)	47 (57)	35 (59)	20 (59)
Age- yr.				
Median	31	31	30	32.5
Range	18-68	18-68	19-54	18-68
Bulky tumor, $\geq 10$ cm				
Patients- no. (%)	54 (59) <sup>a</sup>	52 (63) <sup>b*</sup>	36 (61)	18 (55) <sup>c</sup>
Maximal diameter range- cm	4-18.3	4.9-18.3*	4-18	4.9-18.3
Stage IV disease- no. (%)	18 (19)	15 (18)	14 (24)	4 (12)
International prognostic index (IPI)- no. (%)				
Low (0-1)	60 (65)	55 (66)	37 (63)	23 (68)
Low-intermediate (2)	22 (24)	18 (22)	15 (25)	7 (21)
Intermediate-high (3)	8 (9)	8 (10)	6 (10)	2 (6)
High (4-5)	3 (3)	2 (2)	1 (2)	2 (6)
ECOG- no. (%)				
0-1	81 (87)	72 (87)	57 (97)*	24 (71)*
2-3	12 (13)	11 (13)	2 (3)*	10 (29)*
Elevated LDH- no. (%)	68 (74) <sup>a</sup>	61 (74) <sup>b</sup>	46 (78)	22 (65) <sup>c</sup>
Extranodal site- no. (%)				
0-1	80 (86)	71 (86)	50 (85)	30 (88)
$\geq 2$	13 (14)	12 (14)	9 (15)	4 (12)
Any	38 (41)	32 (39)	27 (46)	11 (32)
Pleural effusion- no. (%)	45 (48)	42 (51)	27 (46)	18 (53)
Pericardial effusion- no. (%)	38 (41)	36 (43)	21 (36)	17 (50)

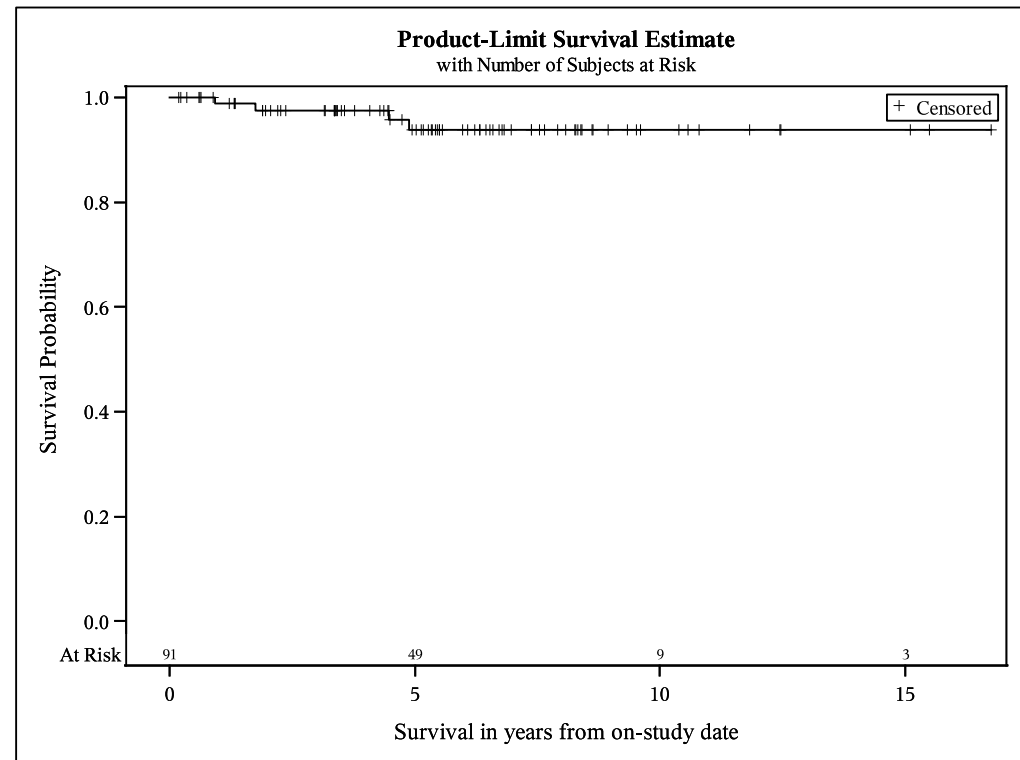
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# EFS and OS for the Entire Cohort

## Event-Free Survival (EFS)



## Overall Survival (OS)



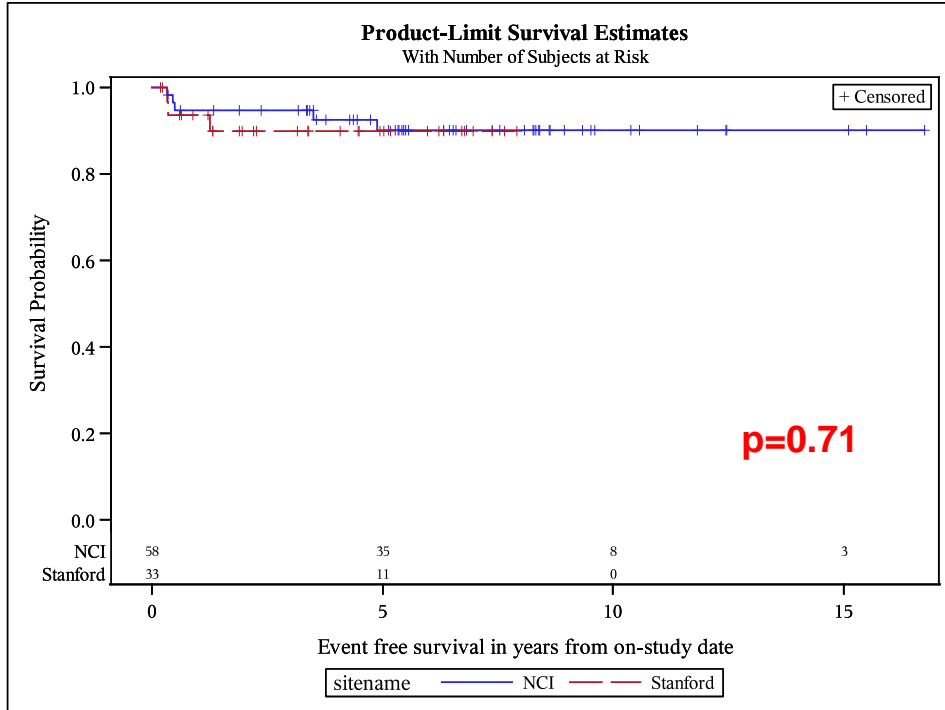
7-year EFS: 89.6% (95% CI: 80.0-94.8%)

7-year OS: 93.9% (95% CI: 84.2-97.7%)

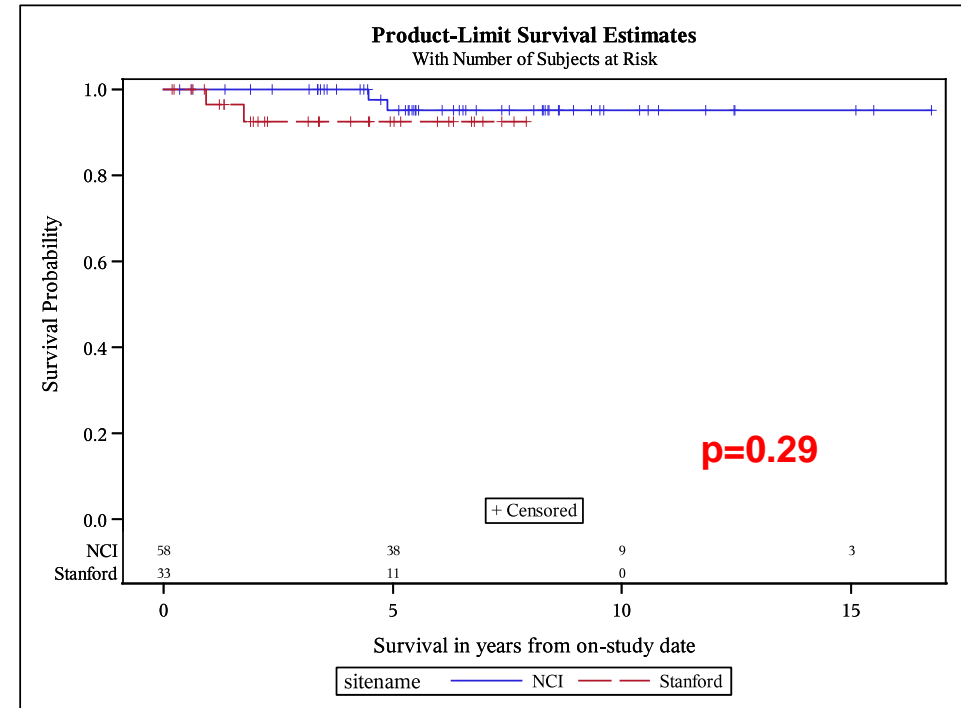
# EFS and OS by Institution

Median potential follow-up = 7.0 years

## Event-Free Survival (EFS)



## Overall Survival (OS)



### 7-year EFS:

NCI: 90.0% (95% CI: 77.3-95.8%)

Stanford: 89.8% (95% CI: 71.5-96.6%)

### 7-year OS:

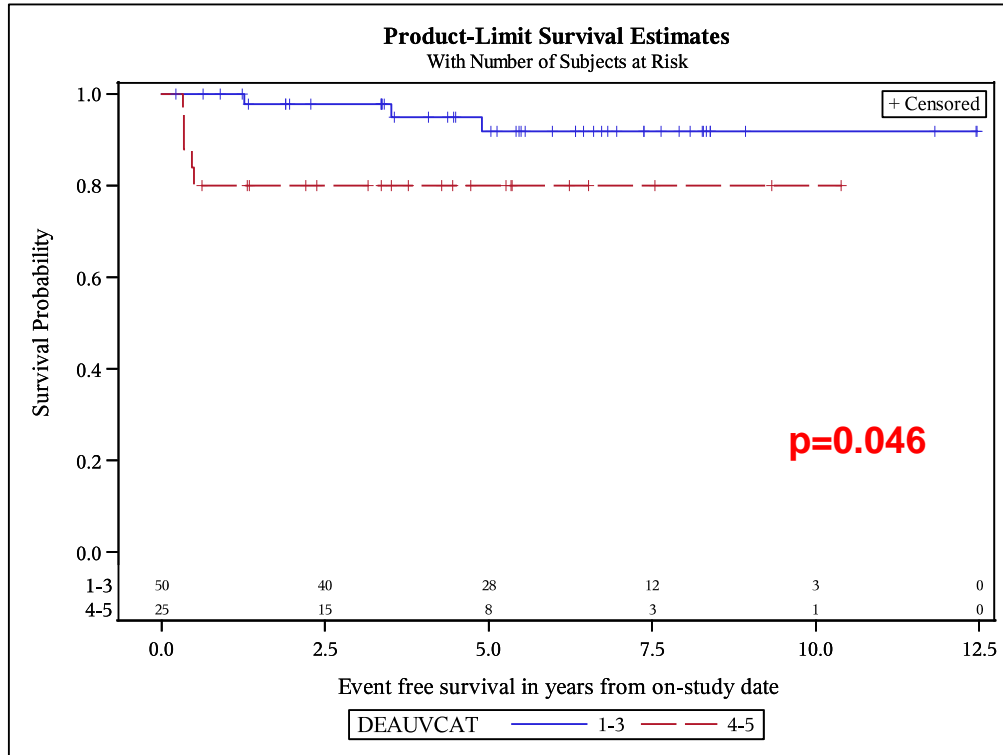
NCI: 95.1% (95% CI: 83.9-99.7%)

Stanford: 92.4% (95% CI: 72.8-98.1%)



# EFS and OS Based on EOT FDG-PET

## Event-Free Survival (EFS)

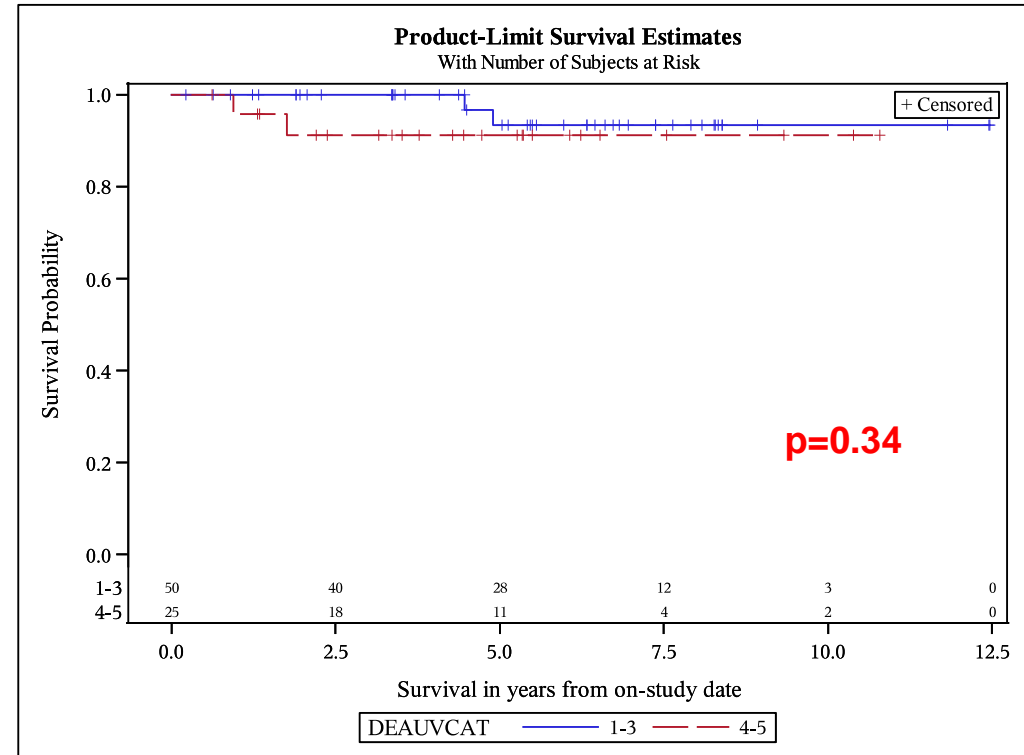


### 7-year EFS:

**Deauville 1-3: 91.8%**

**Deauville 4-5: 80.0%**

## Overall Survival (OS)



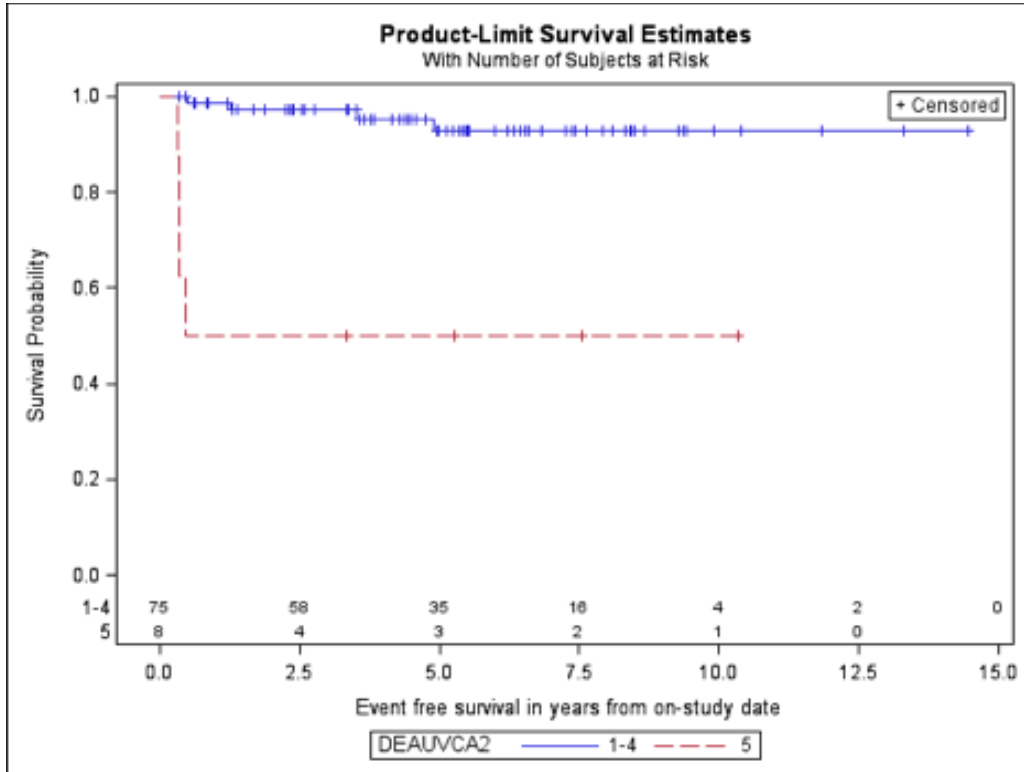
### 7-year OS:

**Deauville 1-3: 93.4%**

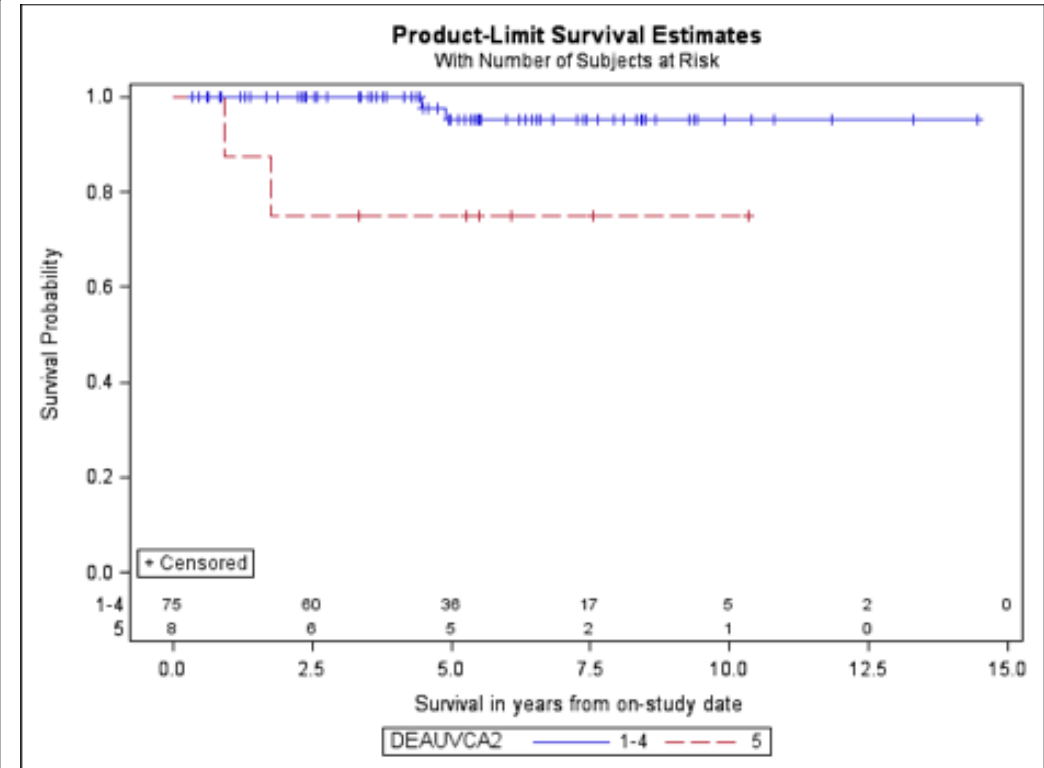
**Deauville 4-5: 91.3%**

# EOT FDG-PET Deauville 1-4 v 5

## Event-Free Survival (EFS)



## Overall Survival (OS)

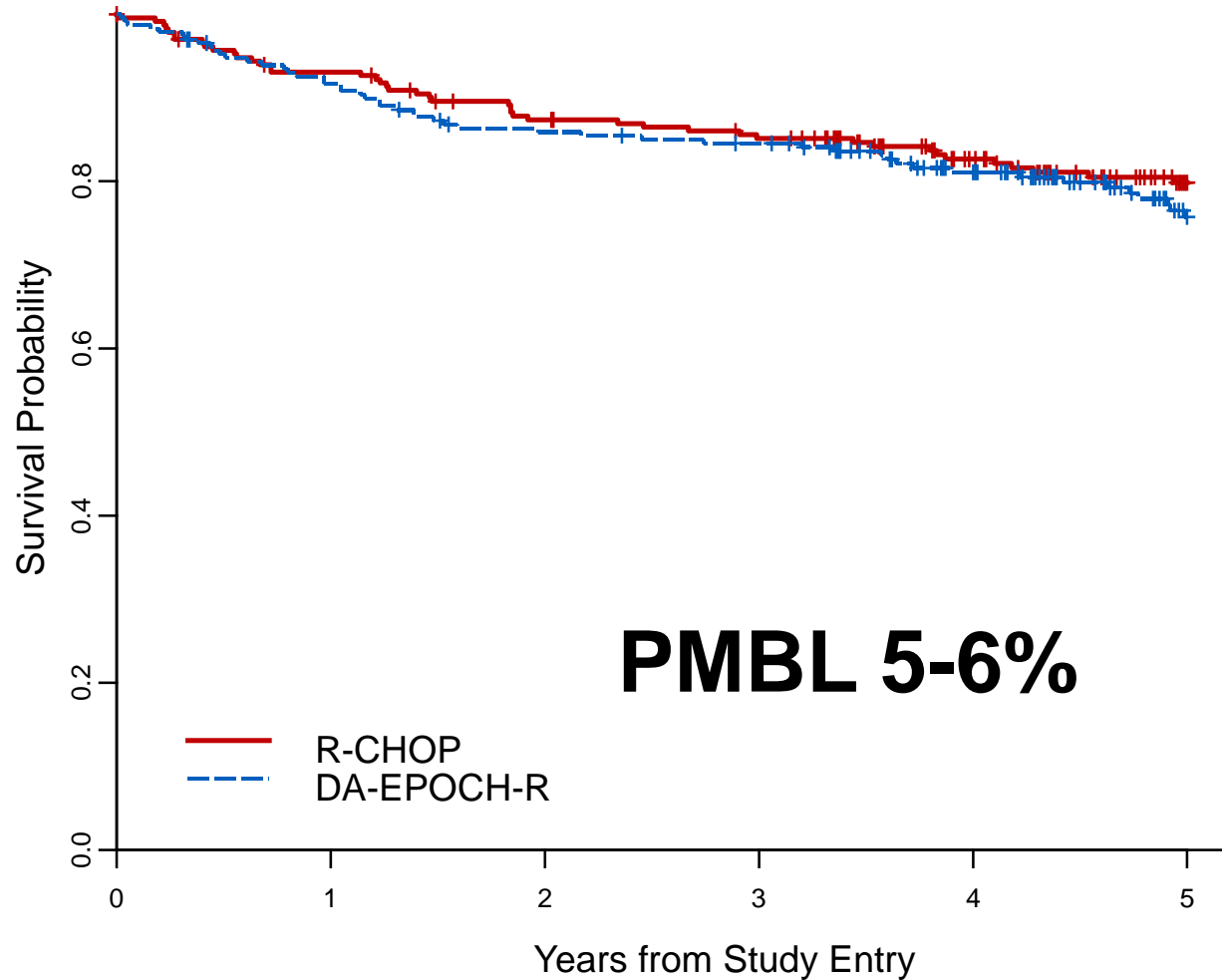


# EOT FDG-PET Performance

<b>EOT FDG-PET Performance</b>	<b>Percent</b>
<b>Sensitivity</b>	<b>83%</b>
<b>Specificity</b>	<b>77%</b>
<b>Positive Predictive Value (PPV)</b>	<b>22%</b>
<b>Negative Predictive Value (NPV)</b>	<b>98%</b>

# Randomized R-CHOP versus DA-EPOCH-R

## Not Relevant to PMBL



# Problems with the Study

- **Poor compliance with DA-EPOCH-R**

	R-CHOP	DA-EPOCH-R	P-value
Completed per protocol*	85.9%	79%	0.037
PD during treatment	2.7%	1.5%	0.361
Early discontinuation due to AE	1.5%	6.5%	0.004

## Max DA-EPOCH-R Dose level

1			28%	
2	20% ↑		20%	
3	44% ↑		23%	
4	73% ↑		17%	
5	107% ↑		9%	
6	149% ↑		2%	
7	200% ↑		<1%	

# Problems with the Study

## IPI outcome in DA-EPOCH-R

	% of Pts	ALL	R-CHOP	DA-EPOCH-R	P-value
Age					0.073
≤ 60	59	71%	73%	70%	
> 60	41	63%	65%	61%	
IPI					<0.001
0-1	27	82%	90%	72%	
2	38	70%	72%	68%	
3	25	55%	50%	61%	
4-5	10	53%	40%	60%	

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# Conclusions

- **DA-EPOCH-R obviates need for RT with EFS 90% and OS 94% 7-year median potential follow-up**

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- **RT associated with late toxicity and combined modality treatment is more costly than DA-EPOCH-R alone**

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- Totality of data indicates PMBL like nsHL benefits from dose-intensive treatment
- Totality of data with R-CHOP indicates need for RT in a significant subset
- RT associated with late toxicity and combined modality treatment is more costly than DA-EPOCH-R alone
- **DA-EPOCH-R should be the standard for PMBL**

# Acknowledgements

## National Cancer Institute

- Wyndham H. Wilson
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