PET negative Residual Masses

	RECOMMENDATIONS: RESPONSE ASSESSMENT - VISUAL
1.	The Deauville criteria (DC) are recommended for reporting PET scans at interim and end treatment assessment when using visual assessment of response *(category 1).*
2.	If mid chemotherapy assessment is performed, PET-CT is the best imaging modality and is superior to CT alone *(category 1).*
3.	There is currently insufficient evidence to change standard treatment based solely on interim PET-CT outside clinical trials. Imaging findings on interim scans should be related to the anticipated prognosis, clinical findings and other markers of response *(category 1).*
4.	Further investigation of the significance of PET negative residual masses is warranted (*category 3*). Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).* Residual mass size should be recorded on end of treatment PET-CT report

Further investigation of the *significance* of PET negative residual masses is warranted (*category 3*).

Data should be collected prospectively in clinical trials dividing CR into two categories: Complete Metabolic Response (CMR) and Complete Metabolic Response with a residual mass (CMRr) *(category 3).*

Residual mass size should be recorded on end of treatment PET-CT report.

Rationale

- PET improved characterisation of residual CT masses (PET+ vs PET-).
- Some data suggests that:
  PET- / CT- do better than PET- / CT+ (i.e. PET negative residual mass)
- Some other data suggests no difference
- Significance of residual mass may be disease & treatment specific.
- Needs further Ix, hence CMRr designation.

Supplementary slides

Relevance of PET negative residual CT masses

PET in Lymphoma residual masses

- One of the earliest established indications for PET in response assessment
- First funded indication in USA
- NPV 80-90%
- Transformed response assessment
- Removed CR(u)

Adding PET to IWC for response

Table 3. Concordance of Response Designations Between IWC and IWC+PET (n = 54)

Response Designation	IWC+PET					
	CR	CRu	PR	SD	PD	Total
IWC						
CR	17	0	0	0	0	17
CRu	5	0	2	0	0	7
PR	10	0	9	0	0	19
SD	2	0	1	6	0	9
PD	1	0	0	0	1	2
Total	35	0	12	6	1	54

Abbreviations: IWC, International Workshop Criteria; IWC+PET, IWC plus positron emission tomography; CR, complete response; CRu, unconfirmed complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Juweid et al JCO 2005; 23 (21): 4652

Is IWC+PET better?

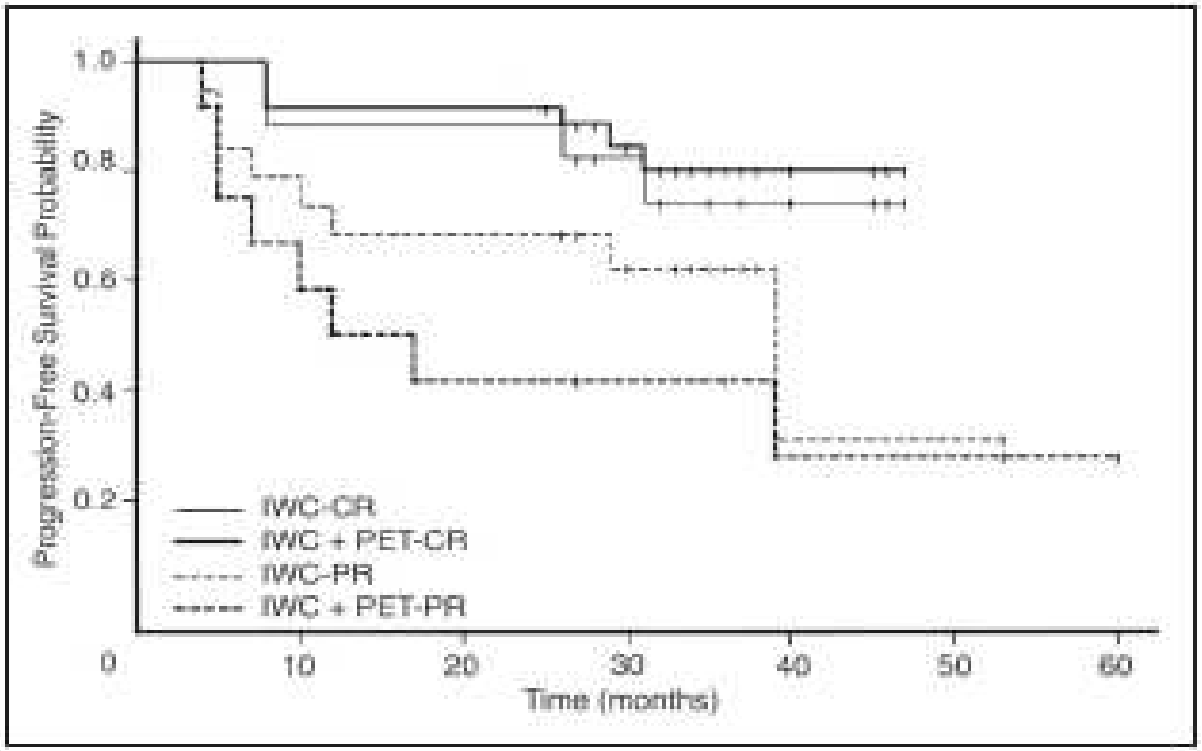


Fig 3. Progression-free survival by International Workshop Criteria (IWC) and IWC plus positron emission tomography (PET) based on the Kaplan-Meier method. (——) Complete response (CR) by IWC (n = 17); (——) CR by IWC+PET (n = 35); (– – – –) partial response (PR) by IWC (n = 19); (– – – –) PR by IWC+PET (n = 12); (|) censored observations.

Juweid et al JCO 2005; 23 (21): 4652

Revised IWC *(Cheson JCO 2007)*

Table 2. Response definitions for clinical trials

Response	Definition	Nodal masses	Spleen, liver	Bone marrow
Complete remission (CR)	Disappearance of all evidence of disease	(a) FDG avid or PET+ before therapy: mass of any size permitted if PET−; (b) variably FDG avid or PET−: regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy, if indeterminate by morphology immunohistochemistry should be negative
Partial remission (PR)	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to six largest dominant masses. No increase in size of other nodes (a) FDG avid or PET+ before therapy: one or more PET+ at previously involved site; (b) variably FDG avid or PET−: regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter), no increase in size of liver or spleen	Irrelevant if positive before therapy, cell type should be specified
Stable disease (SD)	Failure to attain CR/PR or PD	(a) FDG avid or PET+ prior to therapy: PET+ at prior sites of disease and no new sites on CT or PET; (b) variably FDG avid or PET−: no change in size of previous lesions on CT		
Relapsed or progressive disease	Any new lesion or increase from nadir by ≥50% of previously involved sites	Appearance of a new lesion >1.5 cm in any axis ≥50% increase in the longest diameter of a previously identified node >1 cm in short axis or in the SPD of more than one node; lesions PET+ if FDG-avid lymphoma or PET+ before therapy	≥50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

PET is changing Rx Paradigms

HL:

- Early favourable: RAPID study testing omission of RT
- Advanced HL:
  - Pre-PET:
    - **EORTC study:** PR (CT) need RT
    - **UK LY09:** RT improves PFS & OS in all subgps (non-randomised)
  - Post-PET:
    - **GHSG HD15:** RT can be omitted in PET- residual masses (2.5cm) after BEACOPP

DLBCL:

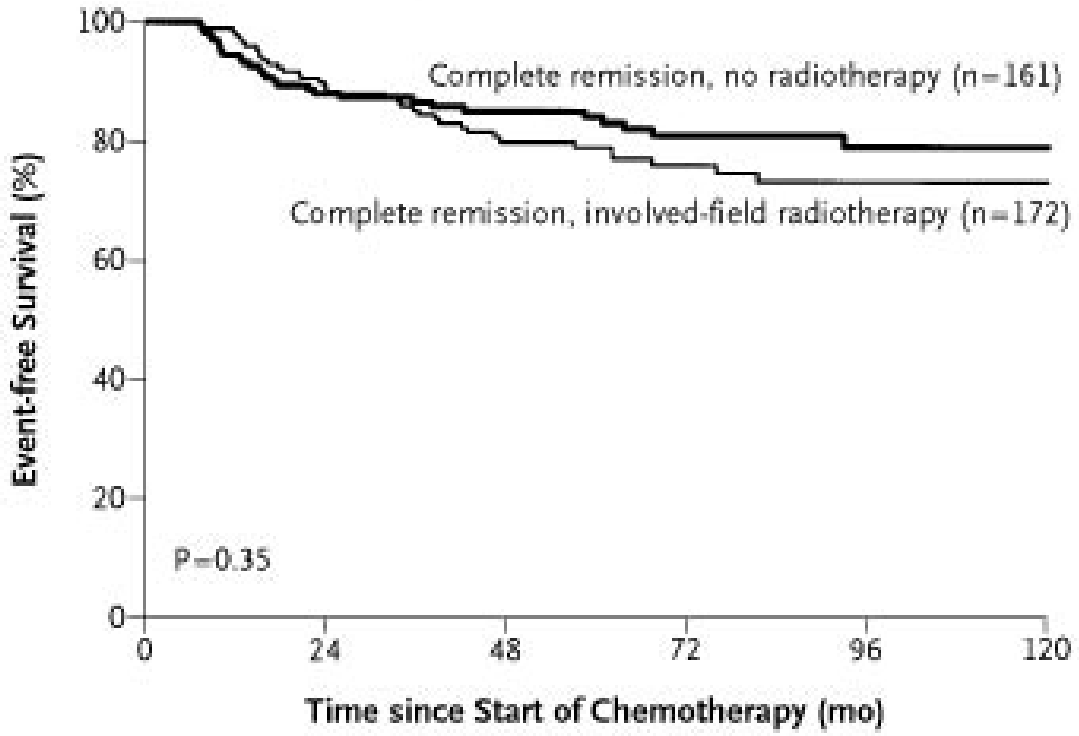
- Pre-PET: Initial bulk receives RT
- Post-PET:
  - Move towards RT only for PET+ residual masses
  - BCCA approach (no RT if PET-)

Randomised Trials of IFRT in advanced HL

Study	CT criteria used for RT	RT dose	% outcome	OS	Median follow-up, y
EORTC 2003[17]	CR*	24 Gy	EFS 79	85	6.6
EORTC 2007[19]	PR	30 Gy	EFS 76	84	7.8
UKLG LY09 2010[20]	PR and/or bulk	30 Gy	PFS 86	93	6.9
UK NCRI 2009[1]					
ABVD	Sites > 5 cm or splenic disease	36 Gy	PFS 76	90	4.3
Stanford V	Sites > 5 cm or splenic disease	36 Gy	PFS 74	92	
NA Intergroup 2010[14,22]					
ABVD	Bulky mediastinal	36 Gy	FFS 85	95	5.47
Stanford V	Sites ≥ 5 cm or splenic disease	36 Gy	FFS 71	87	5.25
GHSG 2008/2009					
HD9[2]	Sites > 5 cm or residual sites ≥ 1.5 cm	30–40 Gy	FFTF 82†	86†	9.25
HD12[3]	PR/residual sites ≥ 2.5 cm	30 Gy	FFTF 87	90	6.5
	PET criteria used for RT				
GHSG (2010)[4]					
HD15	PR or residual sites ≥ 2.5 cm	30 Gy	86	91	3.2

Advani R, ASH educational book 2011

EORTC study
Aleman, NEJM 2003



No. at Risk						
No radiotherapy	161	135	103	73	40	14
Radiotherapy	172	141	101	68	37	19

Figure 2. Kaplan–Meier Estimates of Event-free Survival among Patients in Complete Remission after Chemotherapy Who Were Randomly Assigned to Receive Either No Radiotherapy or Involved-Field Radiotherapy.
There was no significant difference between groups (P=0.35 by the log-rank test).

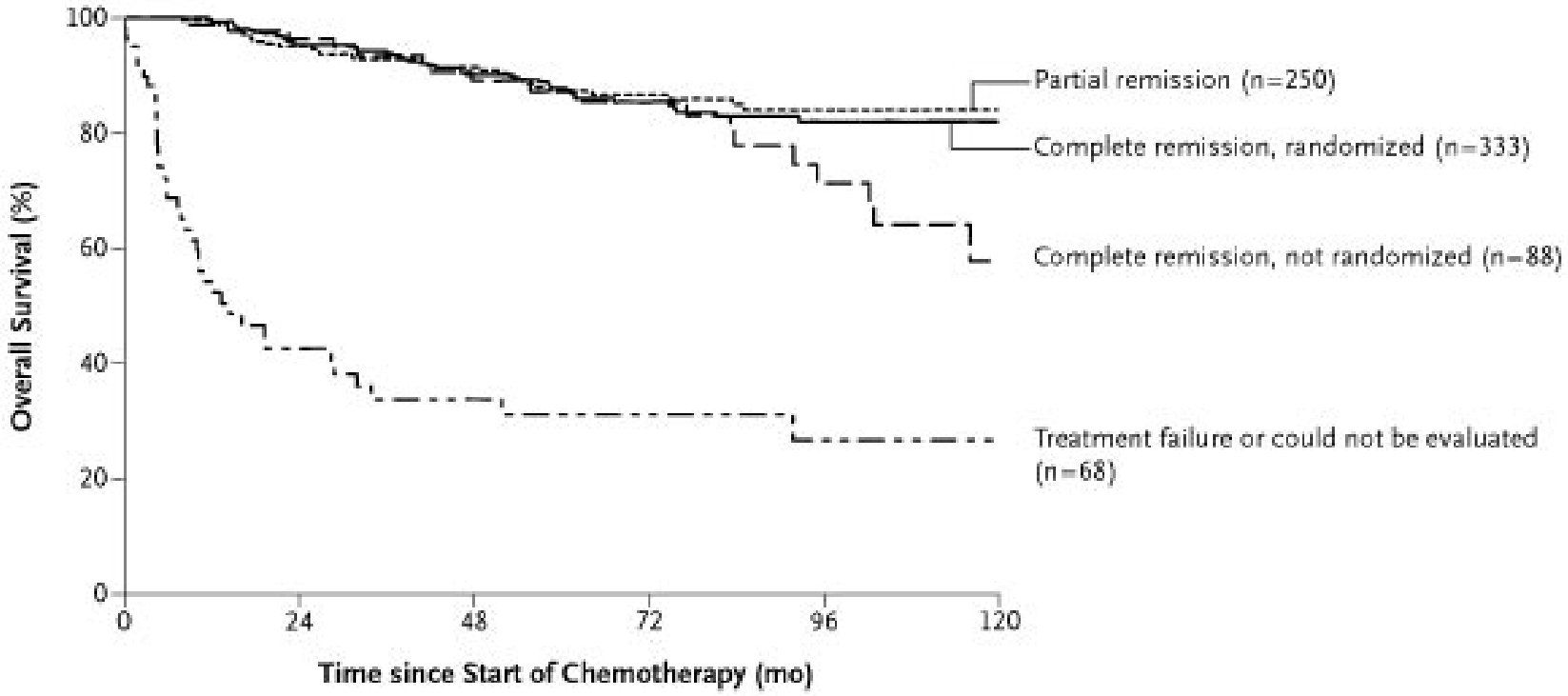


Figure 3. Kaplan–Meier Estimates of Overall Survival According to the Patients' Response to Initial Chemotherapy and to Whether They Underwent Randomization

UK LY09

Initial Bulk: >1/3 Thoracic diameter or >10 cm

Residual disease:

thorax

- CR < 1.0 cm
- CRu 1.1 to 2.0 cm
- PR > 2.1 cm

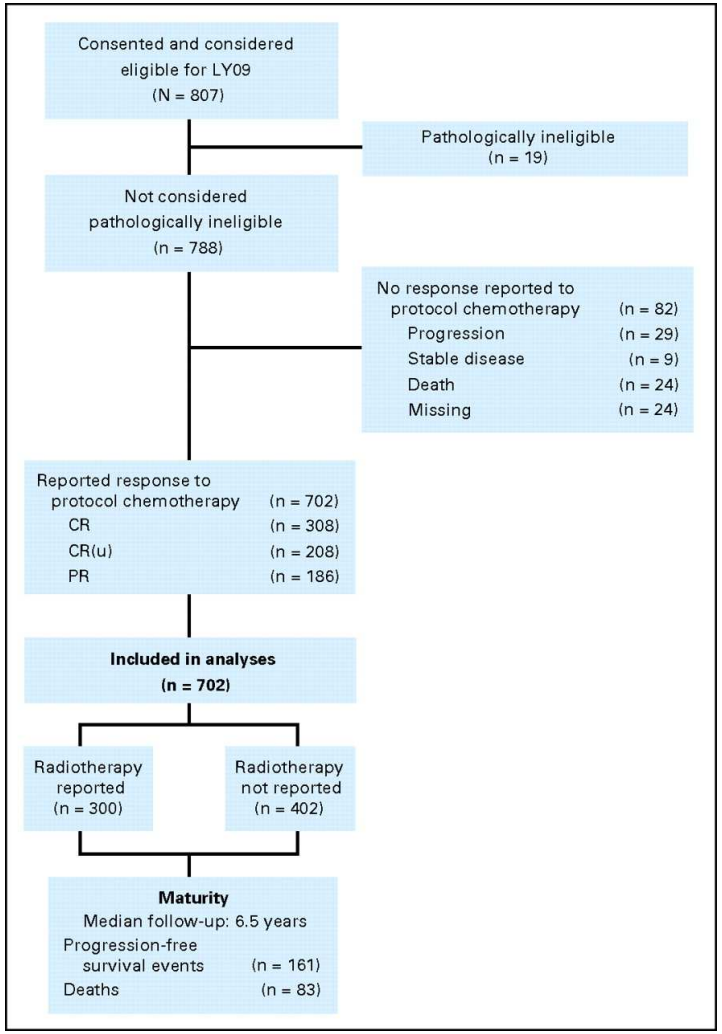
retrocrural space

- CR < 0.6 cm;
- CRu 0.7 to 1.6 cm
- PR > 1.7 cm

abdomen

- CR < 1.5 cm
- CRu 1.6 to 2.5 cm
- PR > 2.6 cm

CONSORT diagram.

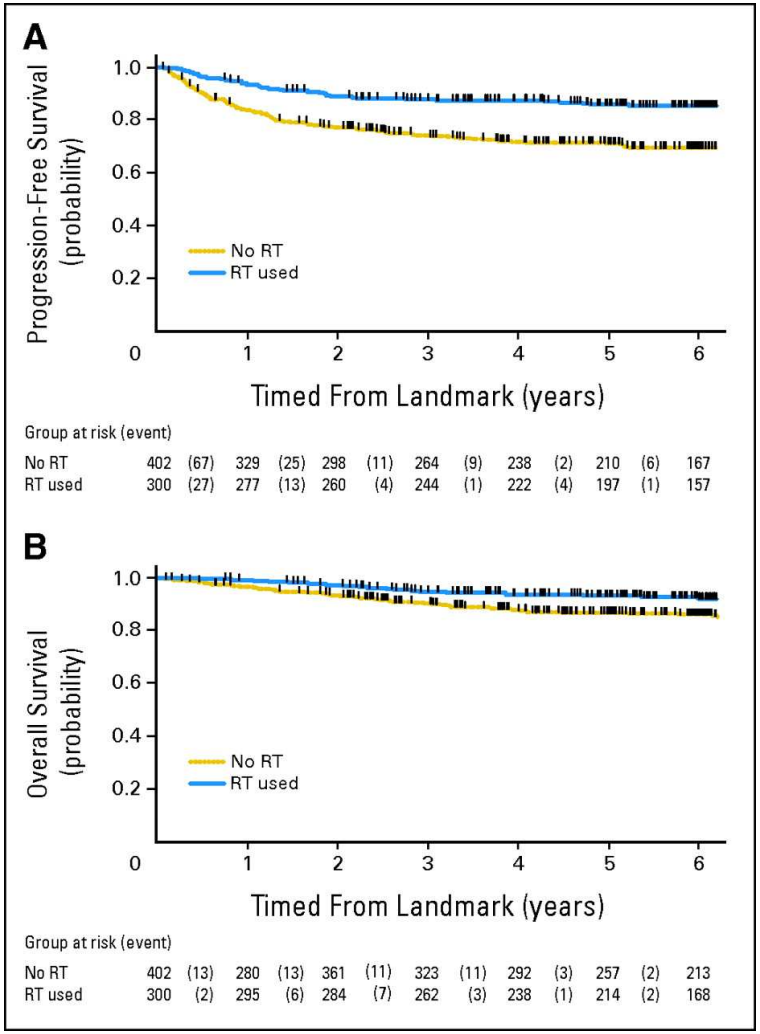


Johnson P W et al. JCO 2010;28:3352-3359

©2010 by American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY

Kaplan-Meier plots of survival by radiotherapy (RT).

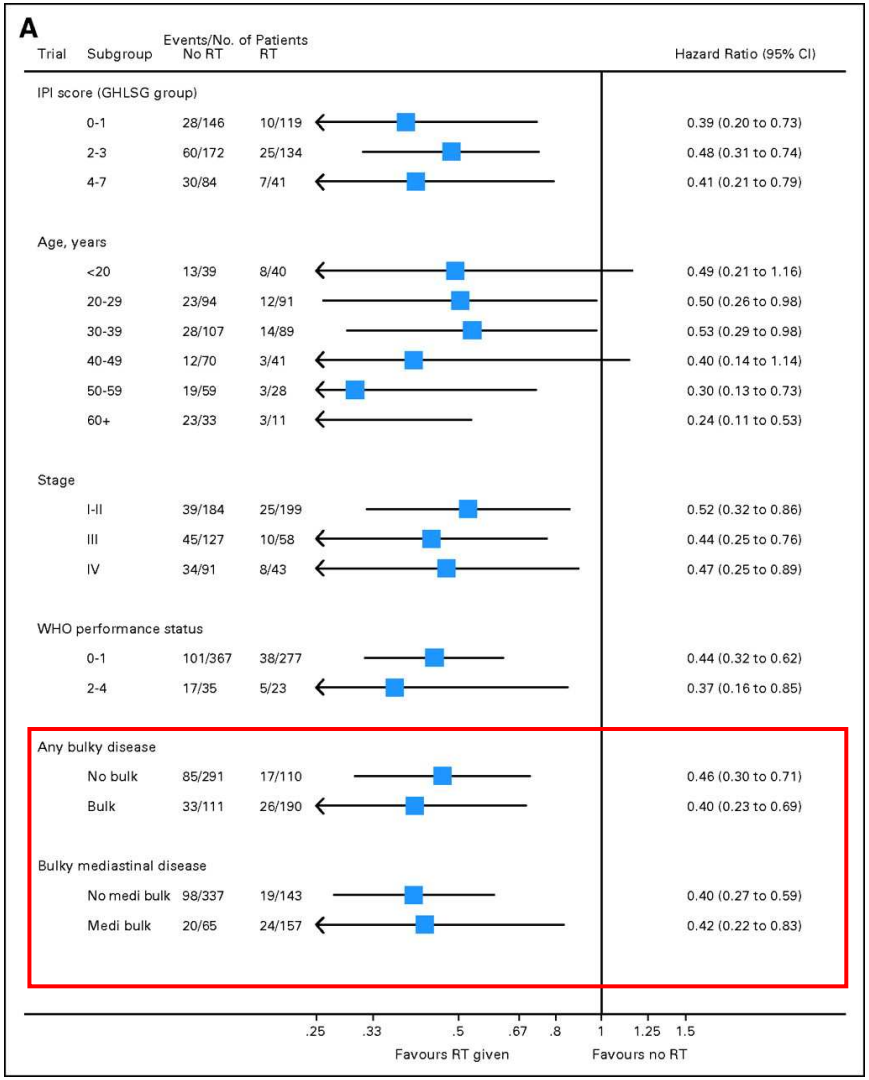


Johnson P W et al. JCO 2010;28:3352-3359

JOURNAL OF CLINICAL ONCOLOGY

©2010 by American Society of Clinical Oncology

Forest plots of effect of radiotherapy (RT) in subgroups: (A) treatment characteristics; (B) baseline characteristics.

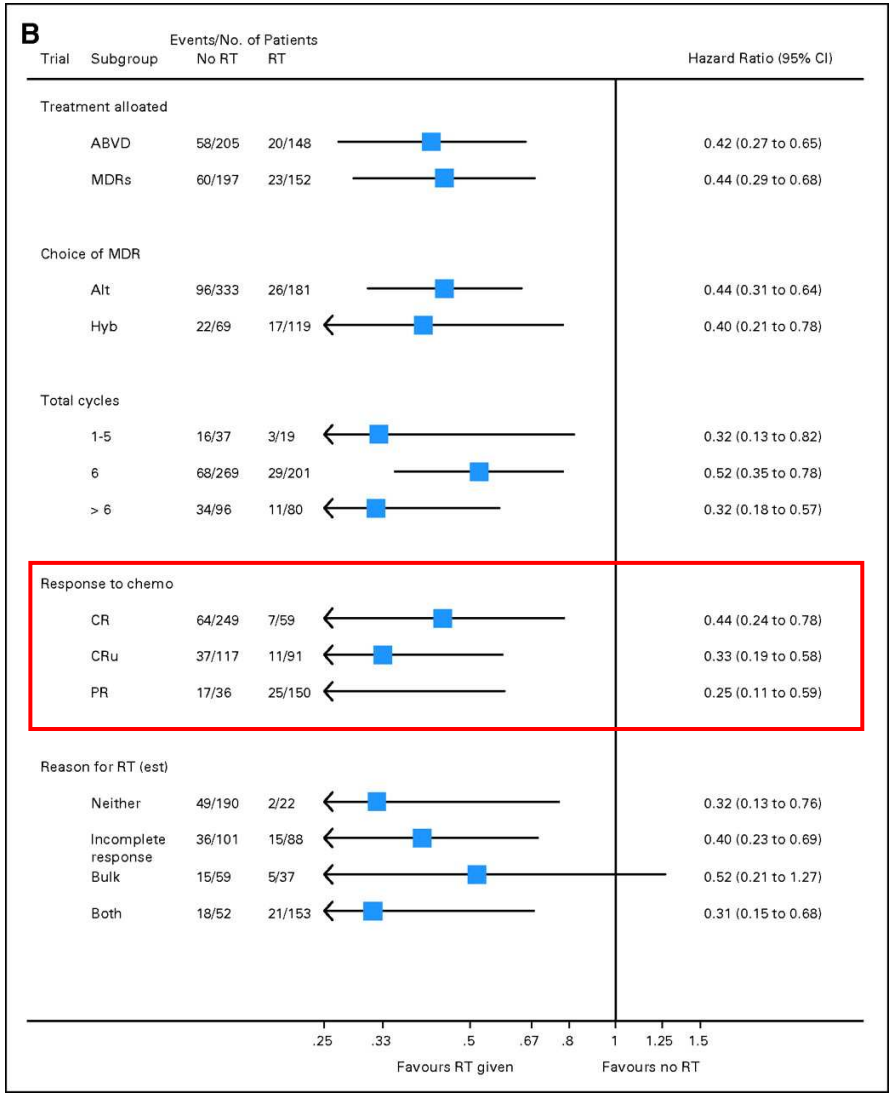


Johnson P W et al. JCO 2010;28:3352-3359

JOURNAL OF CLINICAL ONCOLOGY

©2010 by American Society of Clinical Oncology

Forest plots of effect of radiotherapy (RT) in subgroups: (A) treatment characteristics; (B) baseline characteristics.

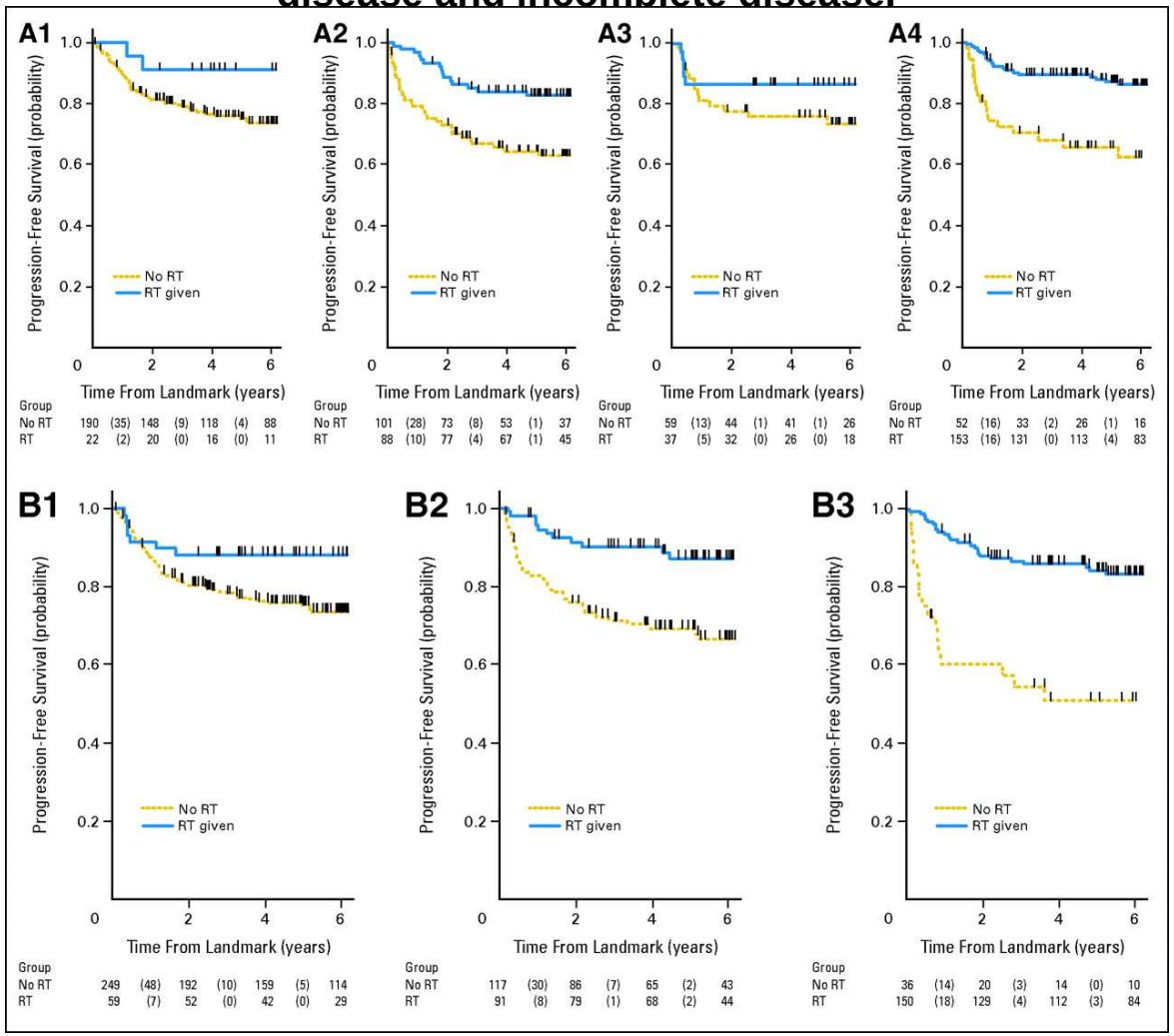


Johnson P W et al. JCO 2010;28:3352-3359

JOURNAL OF CLINICAL ONCOLOGY

©2010 by American Society of Clinical Oncology

Kaplan-Meier plot of progression-free survival (PFS) (A) by use of radiotherapy (RT) and indication for RT. (A1) no indication; (A2) incomplete response; (A3) bulky disease; (A4) bulky disease and incomplete disease.



Johnson P W et al. JCO 2010;28:3352-3359

©2010 by American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY

PET is changing Rx Paradigms

HL:

- Early favourable: RAPID study testing omission of RT
- Advanced HL:
  - Pre-PET:
    - **EORTC study:** PR (CT) need RT
    - **UK LY09:** RT improves PFS & OS in all subgps (non-randomised)
  - Post-PET:
    - **GHSG HD15:** RT can be omitted in PET- residual masses (2.5cm) after BEACOPP

DLBCL:

- Pre-PET: Initial bulk receives RT
- Post-PET:
  - Move towards RT only for PET+ residual masses
  - BCCA approach (no RT if PET-)

HD15

Aim:

- Reduce intensity (& toxicity) of 8 cycles of BEACOPPesc while maintaining the improved disease control with an OS of 92% and FTTF of 88% at 5 years.

Trial:

- 8-B-esc v 6-B-esc v 8-B-14 cycles
- PET question:

  End of treatment PET for patients with CT residual >2.5 cm:

  – +ve RT
  – -ve no RT

Result:

- NPV of 94% (@ 12 months) after 6 to 8 cycles of BEACOPP for PET− patients

Lancet. 2012 Apr 3. [Epub ahead of print]

PET is changing Rx Paradigms

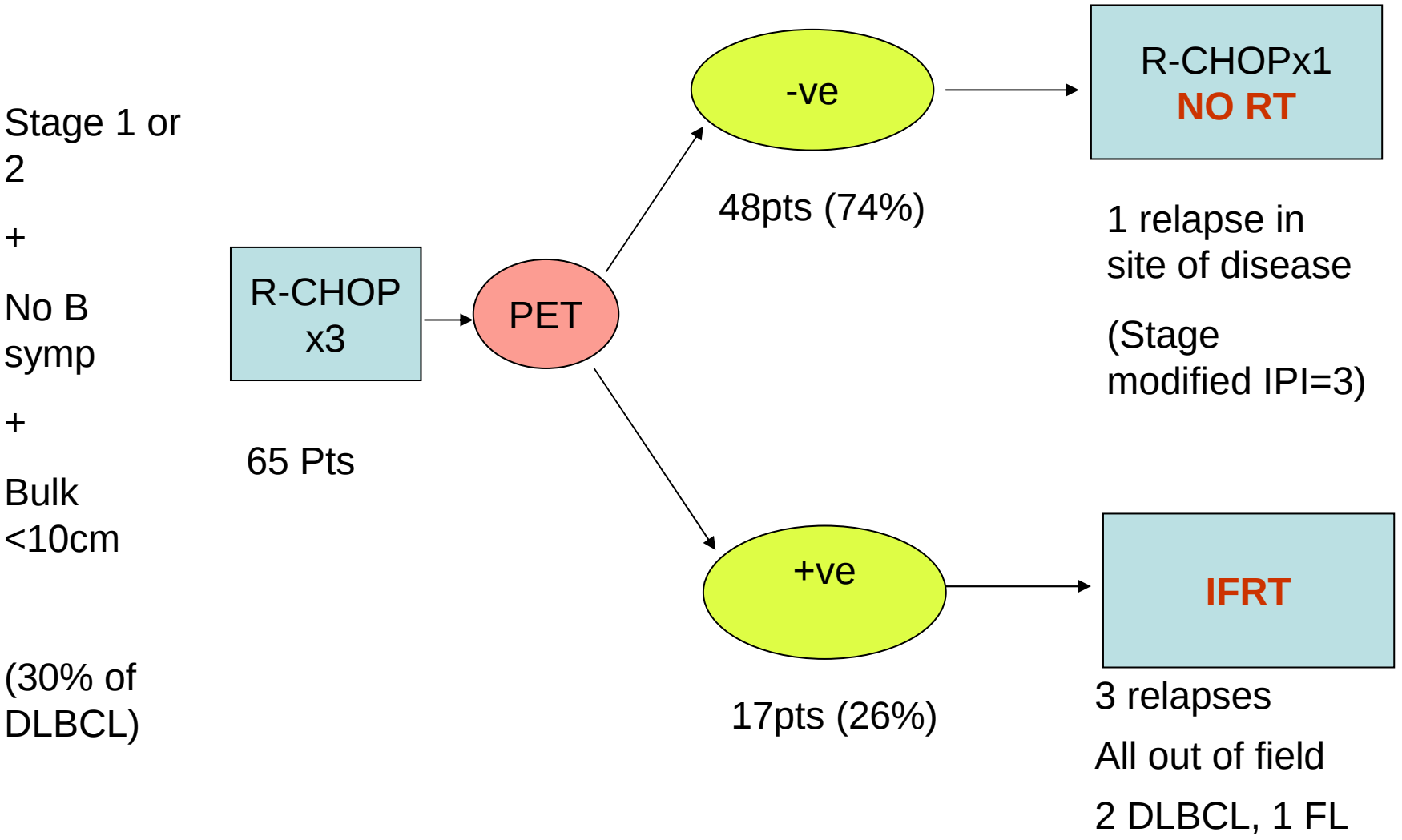
HL:

- Early favourable: RAPID study testing omission of RT
- Advanced HL:
  - Pre-PET:
    - **EORTC study:** PR (CT) need RT
    - **UK LY09:** RT improves PFS & OS in all subgps (non-randomised)
  - Post-PET:
    - **GHSG HD15:** RT can be omitted in PET- residual masses (2.5cm) after BEACOPP

DLBCL:

- Pre-PET: Initial bulk receives RT
- Post-PET:
  - Move towards RT only for PET+ residual masses
  - BCCA approach (no RT if PET-)

British Columbia (Lugano 2008)



What is new?

- Accumulating evidence that PET- with residual CT mass have a worse prognosis than PET- / CT- patients.
- Therapeutic implication: additional RT to residual masses or even salvage Rx
- Significance may be dependent on lymphoma type and treatment type.

DLBCL

Clinical Implications of Residual mass on CT scan with Negative PET at Completion of Chemotherapy in Patients with DLBCL

Bouthaina S. Dabaja, MD[1], Jack Phan, MD PhD[1], L. Jeffrey Medeiros, MD[3], Fu-When Liang, MS[4], Carol Etzel PhD[4], Osama Mawlawi, PhD[5,] F.B. Hagemeister, MD[2], Hubert Chuang, MD[5], Luis Fayad, MD[2], Ferial Shihadeh, MD[1], Pamela Allen, PhD[1], Christine Wogan, MS[1] and Maria A. Rodriguez, MD[2]

[1]Departments of Radiation Oncology, [2]Medical Oncology and [3]Hematopathology, [4]Biostatistics, and Radiology[5].The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Demographics of 300 patients subjects of this study

Characteristic	No. of Patients (%)	CR by Both PET and CT No. (%)	CR by PET Only No. (%)	PR by Both PET and CT No. (%)	P Value*
Sex					0.496
Female	142 (47.3)	74 (47.7)	47 (50.5)	21 (40.4)	
Male	158 (52.7)	81 (52.3)	46 (49.5)	31 (59.6)	
Disease stage					0.009
I	36 (12.0)	22 (14.2)	9 (9.7)	5 (9.6)	
II	45 (15.0)	24 (15.5)	12 (12.9)	9 (17.3)	
III	60 (20.0)	24 (15.5)	31 (33.3)	5 (9.6)	
IV	159 (53.0)	85 (54.8)	41 (44.1)	33 (63.5)	
Chemotherapy					0.204
R-CHOP ≤ 4	26 (8.7)	11 (7.1)	7 (7.5)	8 (15.4)	
R-CHOP ≥ 6	218 (72.7)	120 (77.4)	68 (73.1)	30 (57.7)	
R-HCVAD	41 (13.7)	17 (11.0)	13 (14.0)	11 (21.2)	
Others	15 (5.0)	7 (4.5)	5 (5.4)	3 (5.8)	
Bulky disease					0.070
≤ 5 cm	177 (59.0)	101 (65.6)	50 (54.3)	26 (50.0)	
> 5 cm	121 (40.3)	53 (34.4)	42 (45.7)	26 (50.0)	
Missing	2 (0.7)				
PET standardized uptake values					0.009
≤ 13	179 (59.7)	105 (68.6)	46 (50.0)	28 (53.8)	
> 13	118 (39.3)	48 (31.4)	46 (50.0)	28 (46.2)	
Missing	3 (1.0)				
Ki-67 expression					0.165
< 50%	54 (18.0)	33 (30.8)	12 (17.9)	9 (27.3)	
≥ 50%	153 (51.0)	74 (69.2)	55 (82.1)	24 (72.7)	
Missing	93 (31.0)				
Triple					0.004
Others	150 (72.5)	78 (72.9)	46 (68.7)	26 (78.8)	
Positive	29 (14.0)	8 (7.5)	14 (20.9)	7 (21.2)	
Negative	28 (13.5)	21 (19.6)	7 (10.4)	0 (0)	
Missing	93 (31.0)				
International Prognostic Index score					0.093
0-1	37 (12.3)	21 (13.5)	13 (14.0)	3 (5.8)	
1-2	181 (60.3)	99 (63.9)	47 (50.5)	35 (67.3)	
≥ 3	82 (27.3)	35 (22.6)	33 (35.5)	14 (26.9)	
Size of residual sites					<.0001
No residual	156 (52.0)	155 (100.0)	1 (1.1)	0	
≤ 2 cm	86 (28.7)	0	62 (66.7)	24 (46.1)	
2-5 cm	47 (15.7)	0	26 (28.0)	21 (40.4)	
> 5 cm	11 (3.6)	0	4 (4.3)	7 (13.5)	
Number of residual sites					<.0001
No	156 (52.0)	155 (100.0)	1 (1.1)	0	
1 site	57 (19.0)	0	50 (53.8)	7 (13.5)	
2-3 sites	56 (18.7)	0	32 (34.4)	24 (46.1)	
> 3 sites	31 (10.3)	0	10 (10.7)	21 (40.4)	

Multivariate Analysis

	OS			*PFS*		
Variable	**Hazard Ratio**	**95% CI**	***P* value**	**Hazard Ratio**	**95% CI**	***P* value**
Response			<.0001			<.0001
CR PET/CR CT	Ref.			Ref.		
CR PET/ PR CT	1.70	0.84-3.45		1.88	0.96-3.69	
PR PET/PR CT	5.92	2.98-11.74		5.05	2.61-9.77	
Triple-positive			0.0413			0.0475
No	Ref.			Ref.		
Yes	2.07	1.03-4.15		1.93	1.01-3.71	
Chemotherapy			<.0001			0.0010
R-CHOP ≤ 4	Ref.			Ref.		
R-CHOP ≥ 6	0.18	0.08-0.41		0.25	0.12-0.55	
R-HCVAD	0.36	0.13-0.99		0.26	0.09-0.76	
Others	1.23	0.38-3.97		0.96	0.27-3.34	
IPI score			0.0010			0.0075
0	Ref.			Ref.		
1-2	5.40	1.28-22.86		5.93	1.41-24.89	
≥ 3	11.80	2.71-51.44		9.47	2.19-40.99	

Results

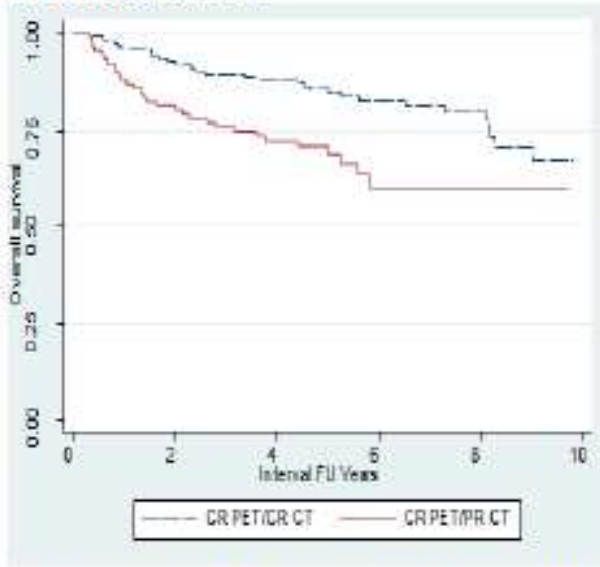
Predictors of OS and PFS

- Univariate Analysis worse outcome:
  - < 6 RCHOP,high IPI score
  - triple positive status
  - end of therapy response less than CR by both PET and CT
  - > 3 sites number of residual sites
  - size of residual mass on CT > 2cm.

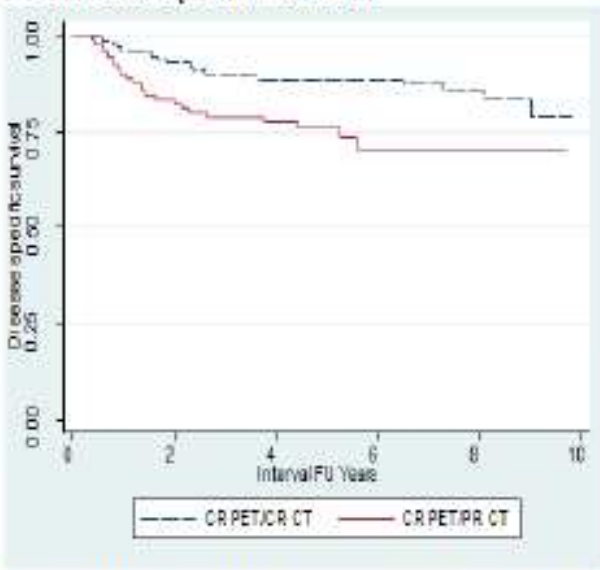
- Multivariate analysis showed worse outcome associated with:

  - High IPI score, suboptimal chemotherapy (< 6 RCHOP), and residual mass > 2 cm on CT.

2.1 Overall survival



2.2 Disease specific survival



2.3 Progression free survival

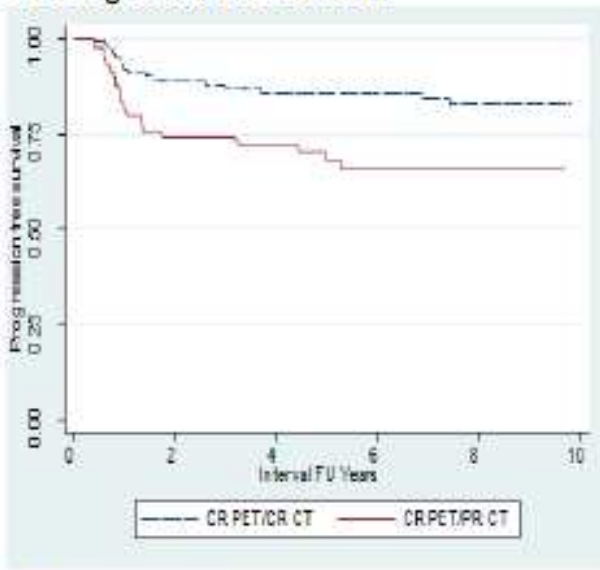


Figure 2. Probability of survival for 248 patients (excluding patients with progressive disease) by response

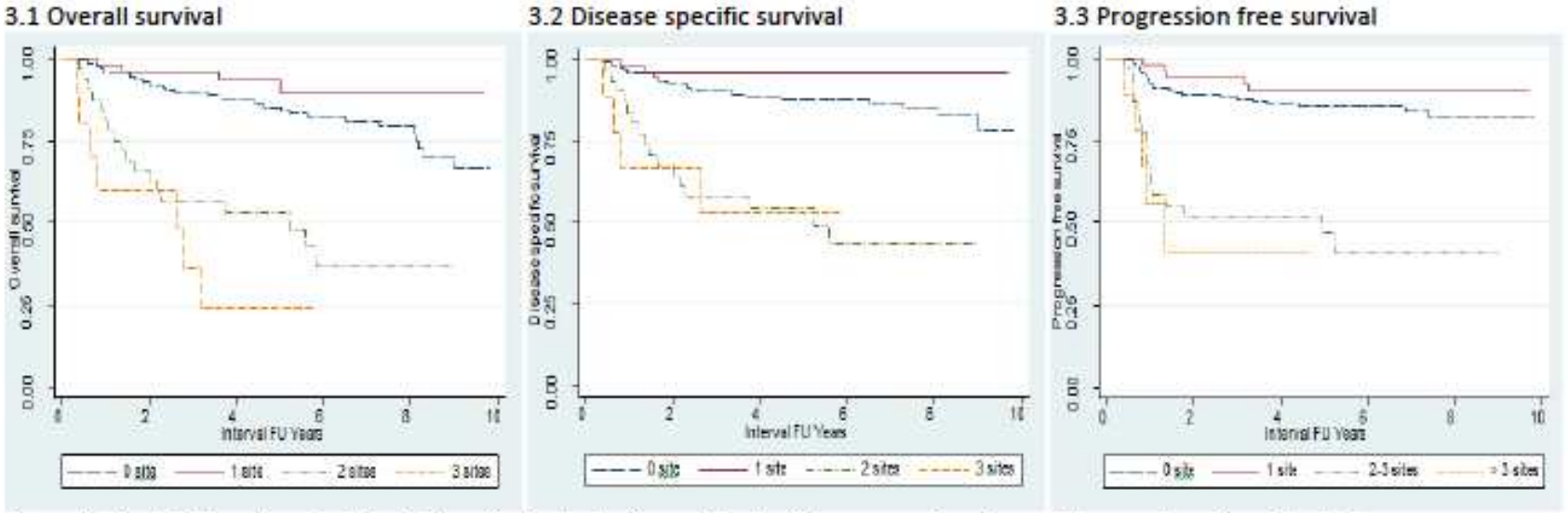


Figure 3. Probability of survival for 248 patients (excluding patients with progressive disease) by number of residual sites

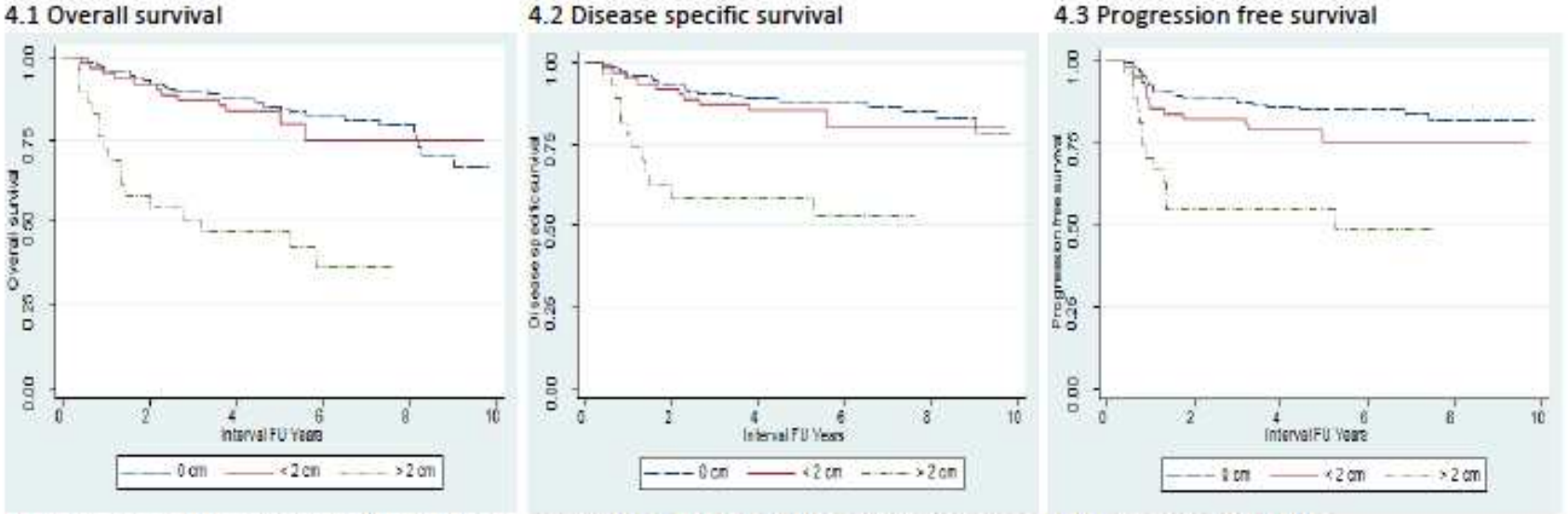


Figure 4. Probability of survival for 248 patients (excluding patients with progressive disease) by size of residual sites

Hodgkin

Dimension of Residual CT Scan Mass in Hodgkin's Lymphoma (HL) is a Negative Prognostic Factor in Patients with PET Negative After Chemo +/- Radiotherapy

Massimo Magagnoli, Katia Marzo, **Monica Balzarotti,** Marcello Rodari, Rita Mazza, Laura Giordano, Sara Gandolfi, Stefania Bramanti, Antonella Anastasia, Fabio Romano Lutman, Michele Spina, Arturo Chiti, Armando Santoro

Hematology and Nuclear Medicine Unit
Humanitas Cancer Center Rozzano – Milano - Italy
Oncologia Medica A, CRO Aviano - Italy

Sunday, December 11 2011

PATIENT CHARACTERISTICS

Observation period: May 2001 – August 2009			
N^ patients		105	
Median age (range)		33	17-75
Gender	M F	62 43	
Bulky disease	Yes No	41 64	37 mediastinum
Symptoms	A B	80 25	
Phase of disease	1st diagnosis 1st relapse	74 31	

TREATMENT and RESPONSE EVALUATION

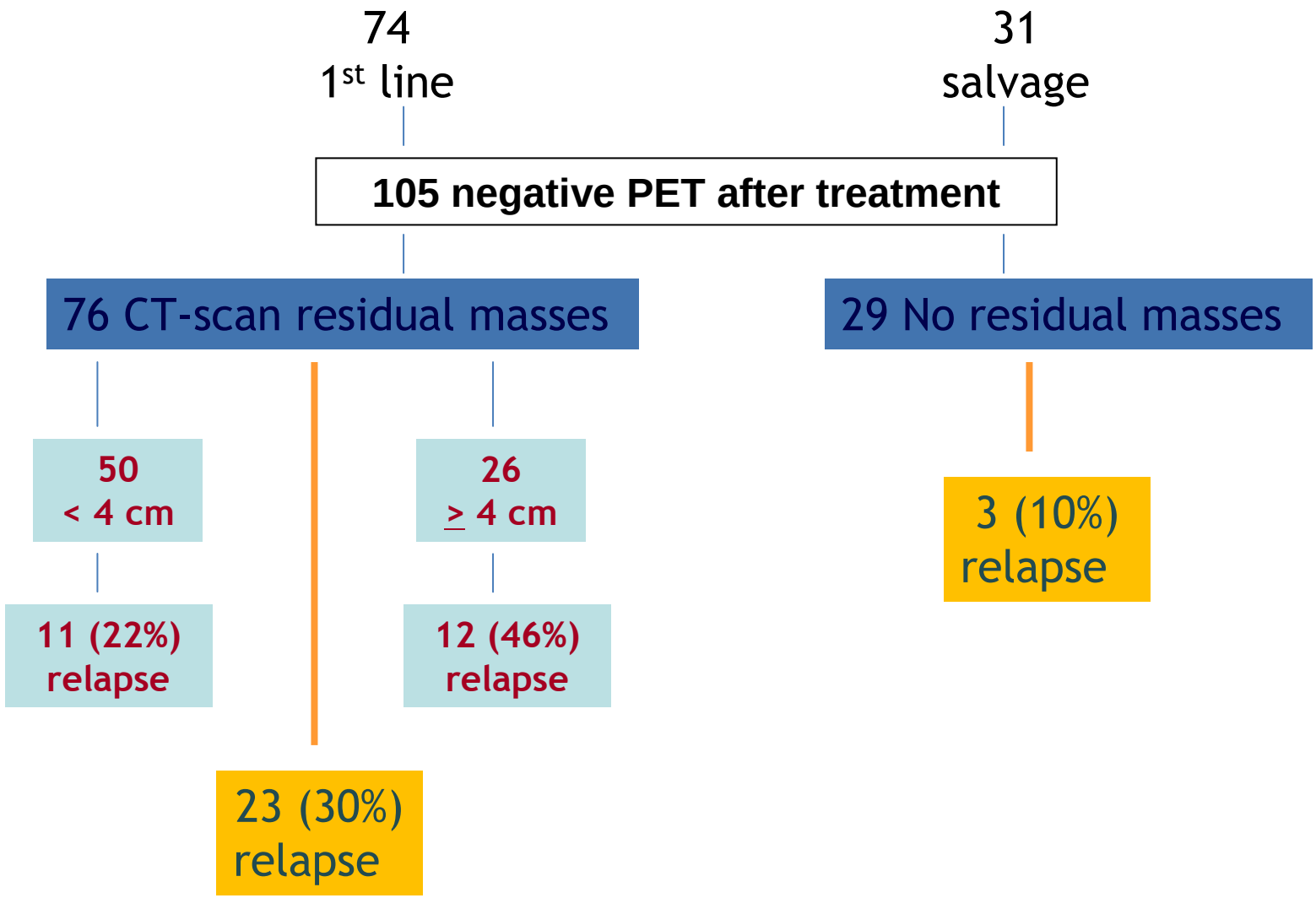
First line		74	34 ABVD 40 VEBEP
Second line		31	IGEV and ASCT
Radiotherapy	Yes No	57 48	
Median days treatment - PET (range)		21 (11-63)	

ABVD: Doxorubicin, Bleomycin,Vinblastin, Dacarbazine
VEBEP: Vinorelbine, Cyclophosphamide, Bleomycin, Epirubicin, Prednisone
IGEV: Ifosfamide, Gemcitabine, Vinorelbine, Prednisone
ASCT: Autologous Stem Cell Transplantation

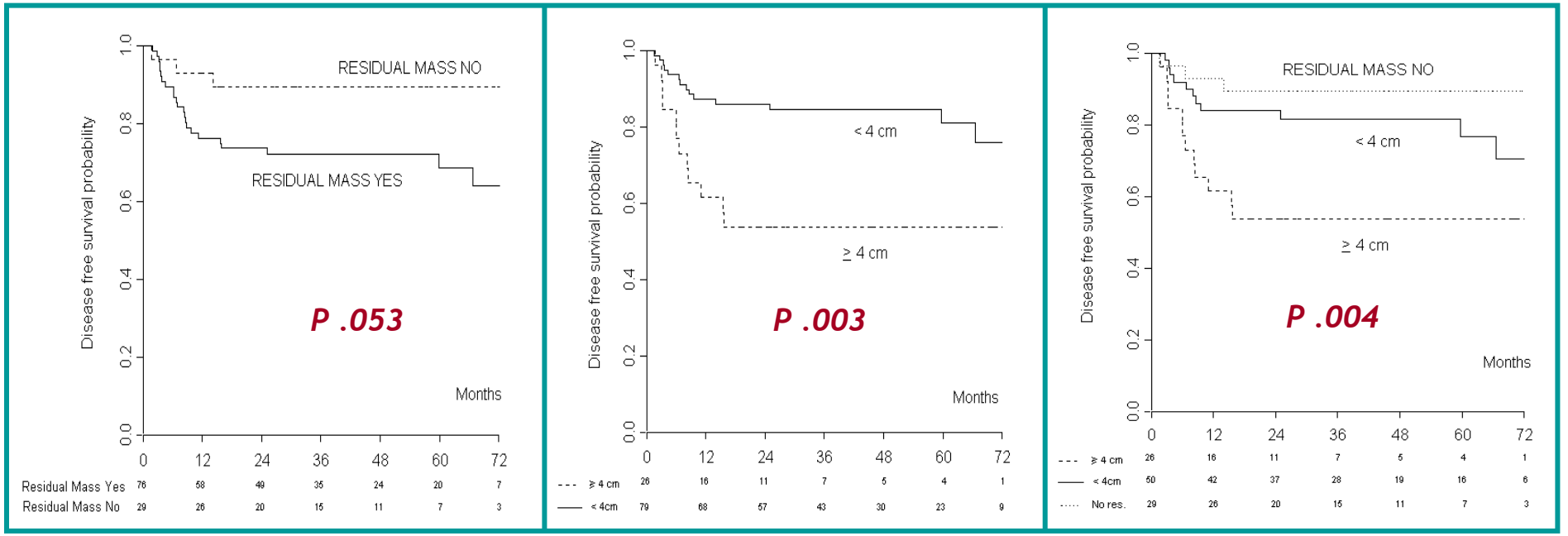
IMPACT of RESIDUAL

Median follow-up: 45 months					
		% 5-yr DFS	*p*	% 5-yr OS	*p*
All		74		88	
Gender	M F	76 72	*.316*	93 75	.352
Symptoms	A B	77 65	*.297*	89 85	.367
Bulky	Yes No	77 70	*.451*	85 92	.717
Phase of disease	1st diagnosis 1st relapse	77 67	*.860*	93 75	.079
CT residual	Yes No	69 89	*0.053*	90 87	.802

SUMMARY


74
1st line
31
salvage
105 negative PET after treatment
76 CT-scan residual masses
29 No residual masses
50
< 4 cm
26
≥ 4 cm
3 (10%)
relapse
11 (22%)
relapse
12 (46%)
relapse
23 (30%)
relapse

DFS↔ RESIDUAL



IMPACT of RESIDUAL SIZE

- ✓ The larger the residual mass, the lower the DFS (*p* value: **0.007**)
- ✓ Cut off at 4 cm (arbitrary) separated two prognostic categories

		% 5-yr DFS	*p*
Residual size	< 4 cm ≥ 4 cm	81 54	*.0029*

Questions

- Is likelihood of residual mass related to
  - initial bulk
  - Initial FDG avidity (e.g. SUVmax)
  - IPI

- Does it have an independent prognostic significance?

Conclusions, Thoughts & Questions

- Residual CT masses are relevant even if PET negative

- Paradigm shift?
  - FROM: role of negative PET in residual CT mass
  - TO: role of residual CT mass in negative PET?

- Prognosis may be divided (good to bad):
  - PET- / CT-
  - PET- / CT+
  - PET+ / CT-
  - PET+ / CT+

Conclusions, Thoughts & Questions - 2

- Necessity of reporting SIZE of residual CT masses on PET/CT
- What size cut-off is relevant?
- What research can/need to be done to confirm?
- How do we account for this in any “response criteria”?

How do we account for this in any “response criteria”?

Options:

- Reintroduce CRu
- Divide CR into;
  - CMR (complete metabolic response)
  - CAR (complete anatomical response)

  OR
  - CMR
  - CMR with residual mass