Gruppo di studio Linfomi

Torino, 02.10.2019

La Radioterapia nel Linfoma di Hodgkin:

- Advanced stage -

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Background

- The role of consolidation RT to bulky lesions of advanced stage Hodgkin disease is controversial

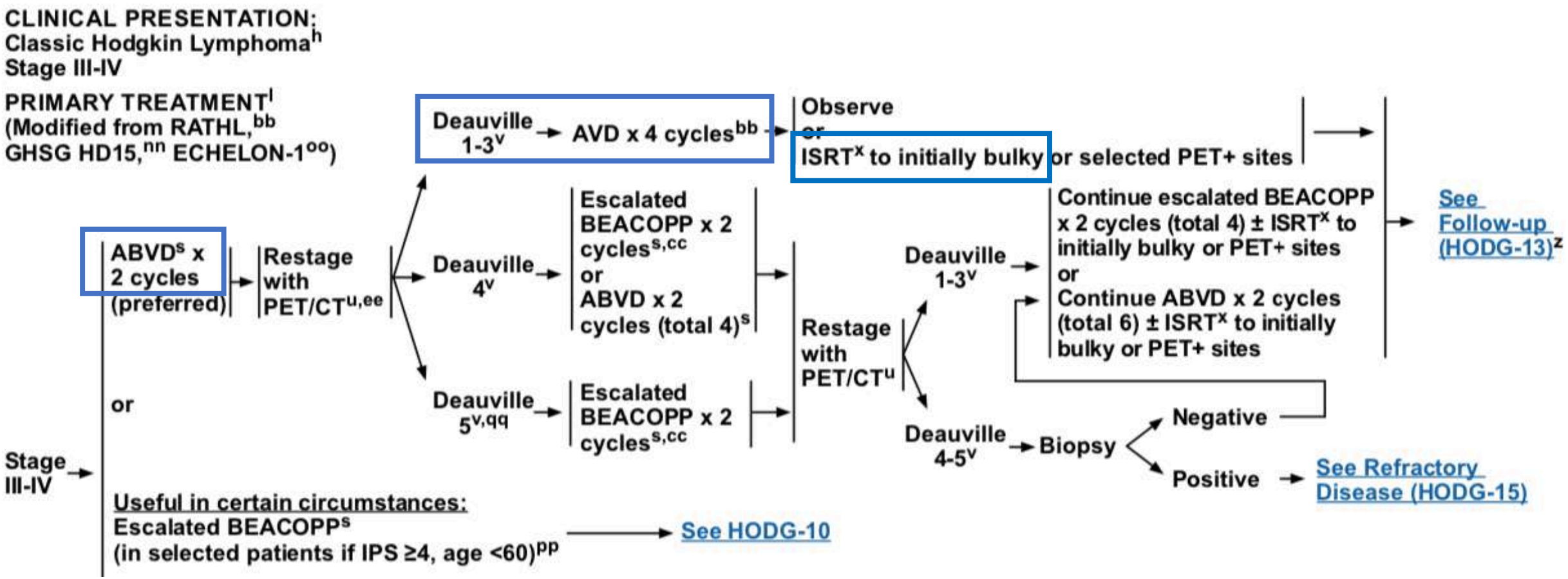
- Several outdated studies have shown the beneficial role of consolidation RT in term of PFS (but not in term of OS). However these results were obtained with outdated RT (dose, fields and techniques) and CT (MOPP, Stanford V…) schedules

- Nowadays the choice to offer consolidation RT to bulky lesions is related to the chemotherapy regimen selected (ABVD vs BEACOPP) and to the metabolic status at the end of it

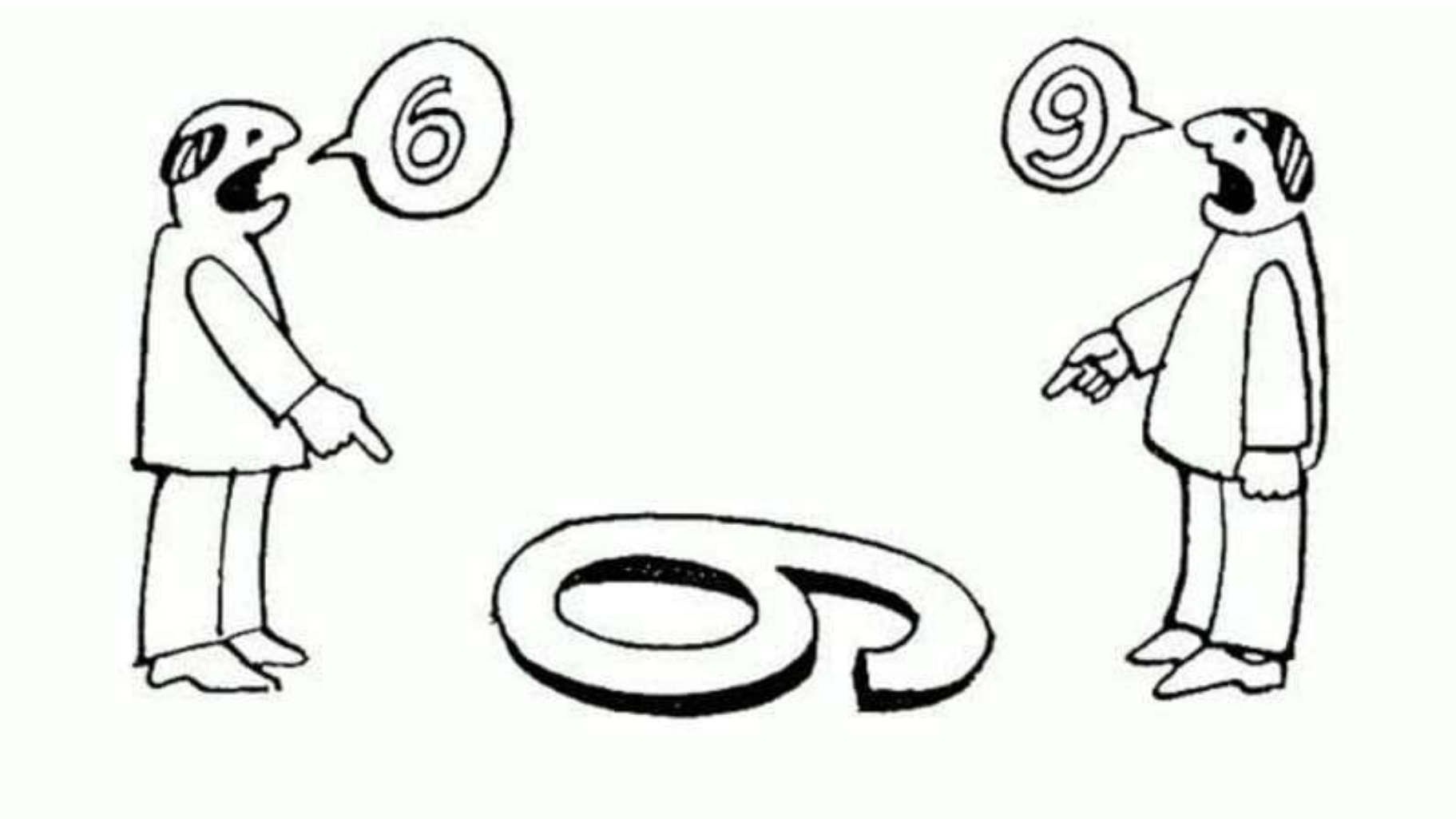
- Consolidation RT was not established but left to the discretion of the treating physicians (bulky lesions or residual disease at the end of chemotherapy) in many recent randomized studies that tested the effect of ABVD regimen (e.g. RATHL study)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Hodgkin Lymphoma (Age ≥18 years)



To radiate or not to radiate…? The big dilemma



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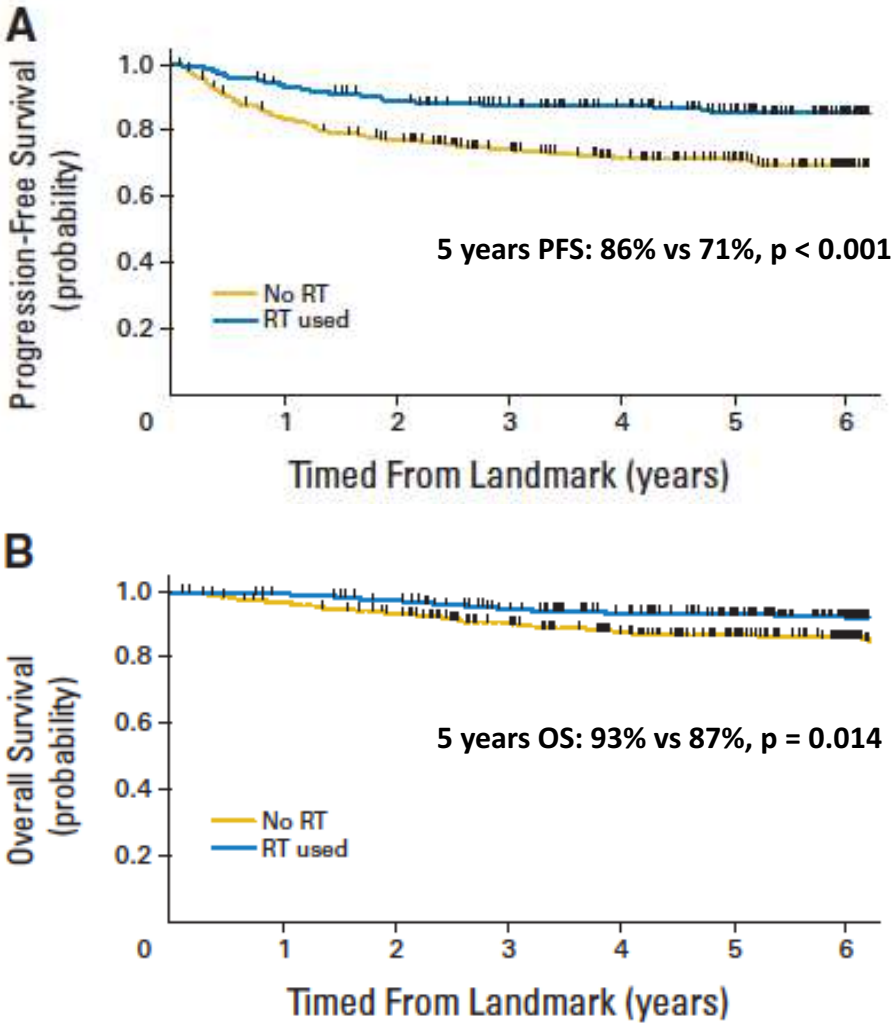
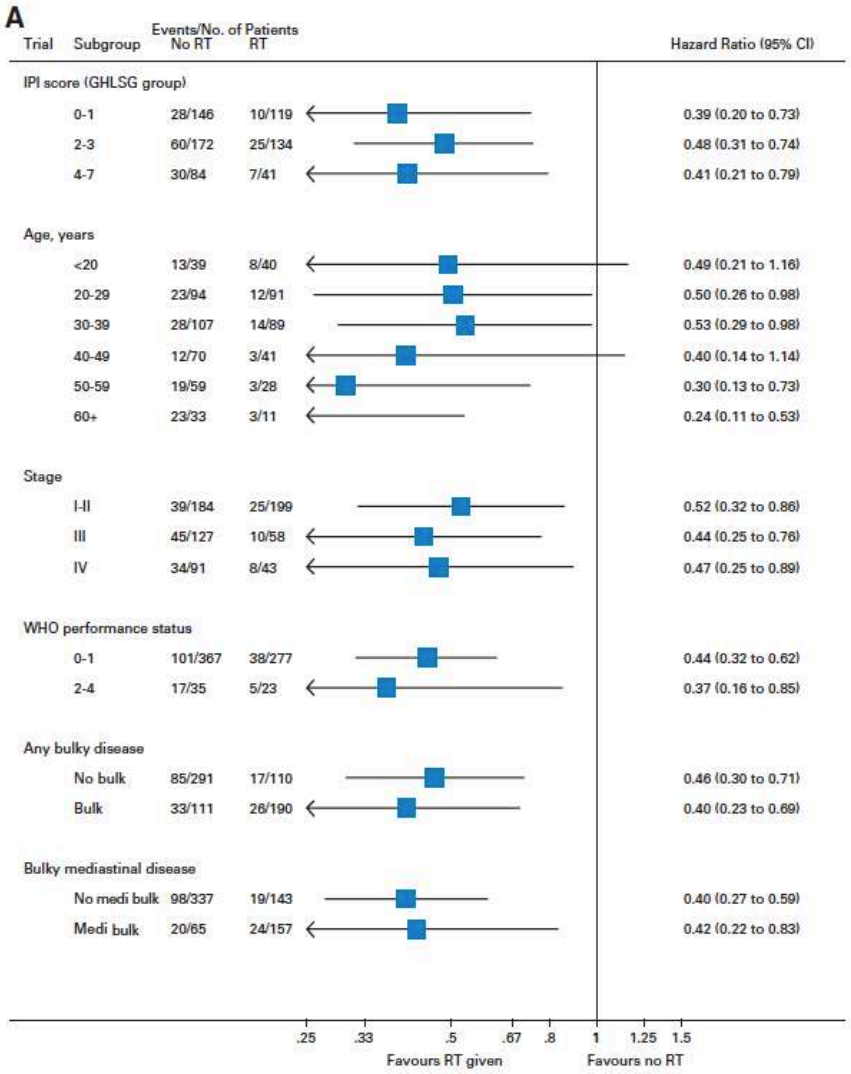
Role of Consolidation RT before the "^{18}FDG-PET era"

UK LY09 trial





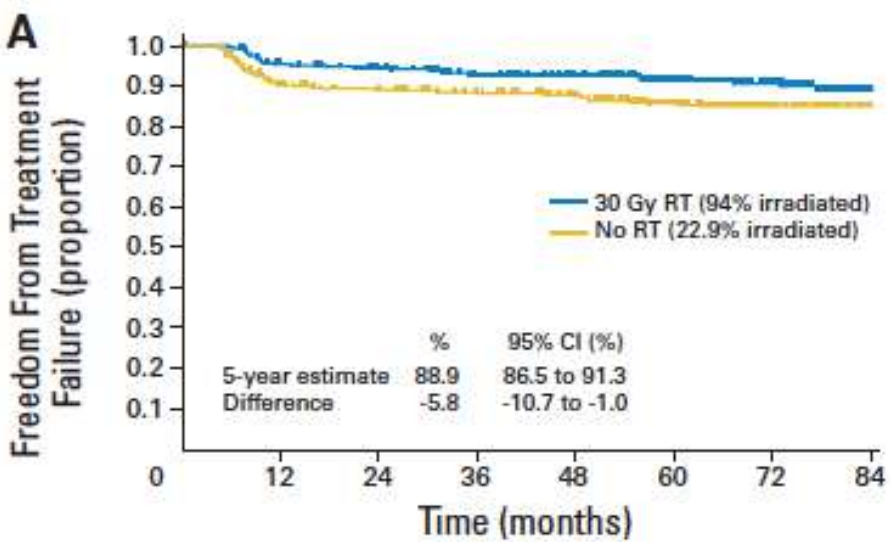
Johnson PWM et al. JCO 2010

More Aggressive Chemotherapy Regimen May Relieve Consolidative RT To Bulky Lesions

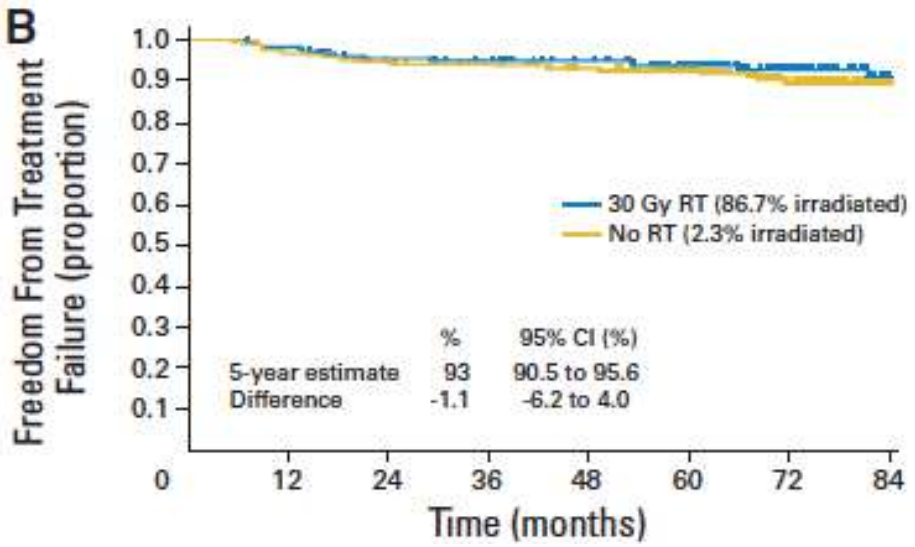
Eight Cycles of Escalated-Dose BEACOPP Compared With Four Cycles of Escalated-Dose BEACOPP Followed by Four Cycles of Baseline-Dose BEACOPP With or Without Radiotherapy in Patients With Advanced-Stage Hodgkin's Lymphoma: Final Analysis of the HD12 Trial of the German Hodgkin Study Group

Additional RT (30 Gy) given to:
- **residual disease > 1.5 cm on CT scan**
- **bulky lesion at baseline**

RESIDUAL DISEASE AFTER CT



BULKY LESIONS



Borchmann P. et al, JCO 2011

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Reduced-Intensity Chemotherapy and PET-guided RT De-escalation TO REDUCE TOXICITY

Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial

PET done after chemotherapy can guide the need for additional radiotherapy in this setting.

HOWEVER:

1) Need for a careful extrapolation of this PET-guided approach to weaker regimens that might need more vigorous additional radiotherapy.

2) PET-guided radiotherapy was not assessed in a randomised fashion.

Engert et al. Lancet 2022

Beacoppescalated Followed By Radiotherapy of Initial Bulk or Residual Disease in Advanced Stage Hodgkin Lymphoma: Long-Term Follow up of the HD9 and HD12 Trials of the German Hodgkin Study Group

Stefanie Kreissl, Bastian von Tresckow, Helen Goergen, Heinz Haverkamp, Stephanie Sasse, Volker Diehl, Andreas Engert and Peter Borchmann

Blood 2016 128:923;

Regarding the HD12 trial:

Amongst the patients with bulk

- **PFS in favor of RT arm** @ 10 years (88.6% vs 83.5%), HR 1.47
- **OS marginally in favor of RT arm** @ 10 years (93% vs 90.2%)

Amongst the patients with residual disease

- **PFS in favor of RT arm** @ 10 years (89.3% vs 83.4%)
- **OS in favor of RT arm** @ 10 years (94.4% vs 88.4%)

No significant difference in terms of second cancer @ 10 years (9.7% vs 6.4%)

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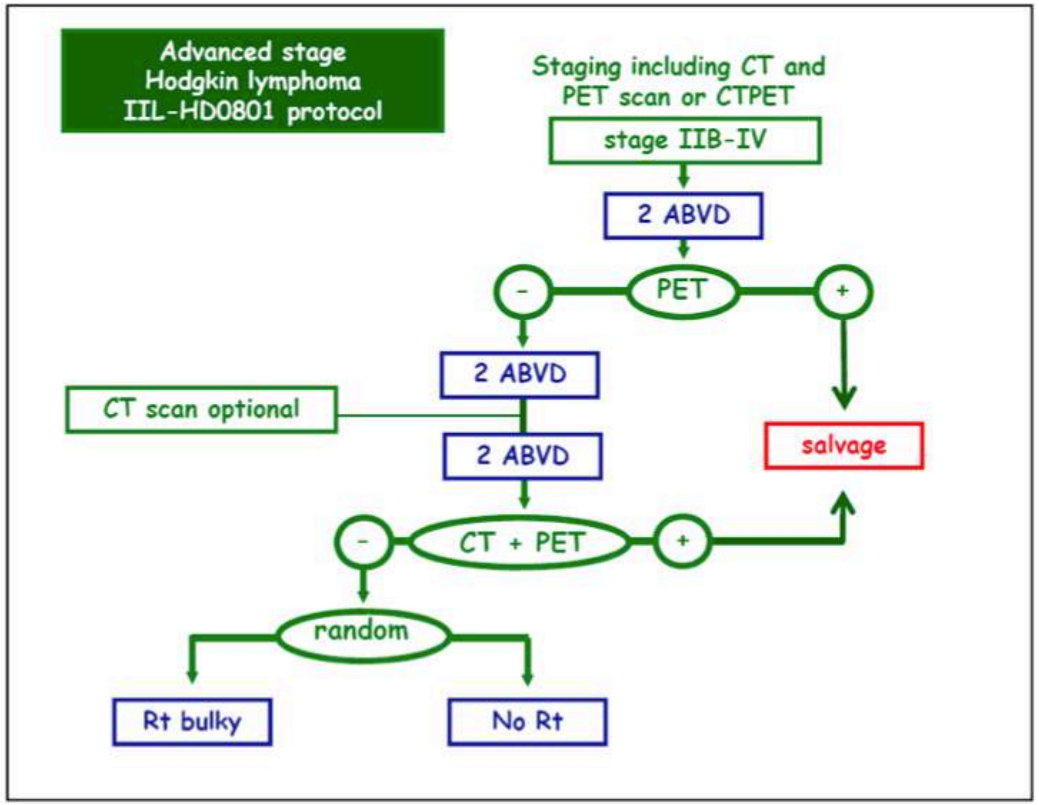
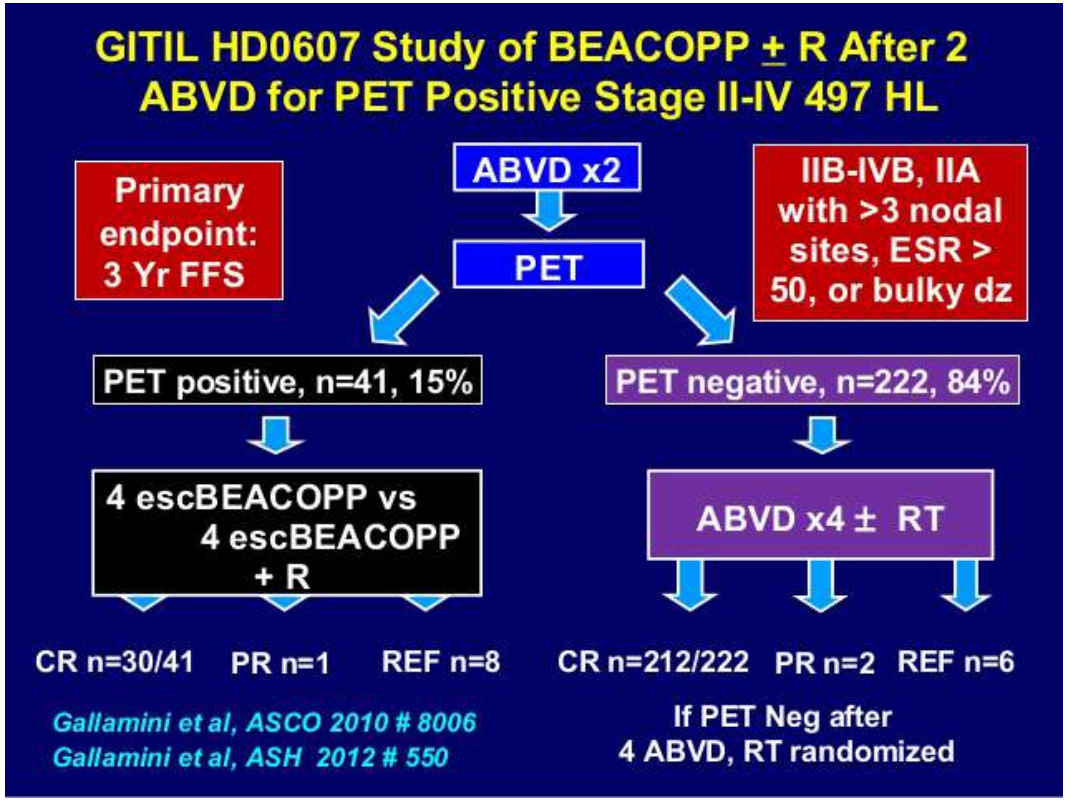
Role of consolidative RT to bulky lesions in the "^{18}FDG-PET AGE"

Two Italian trials…

FIL HD 0801

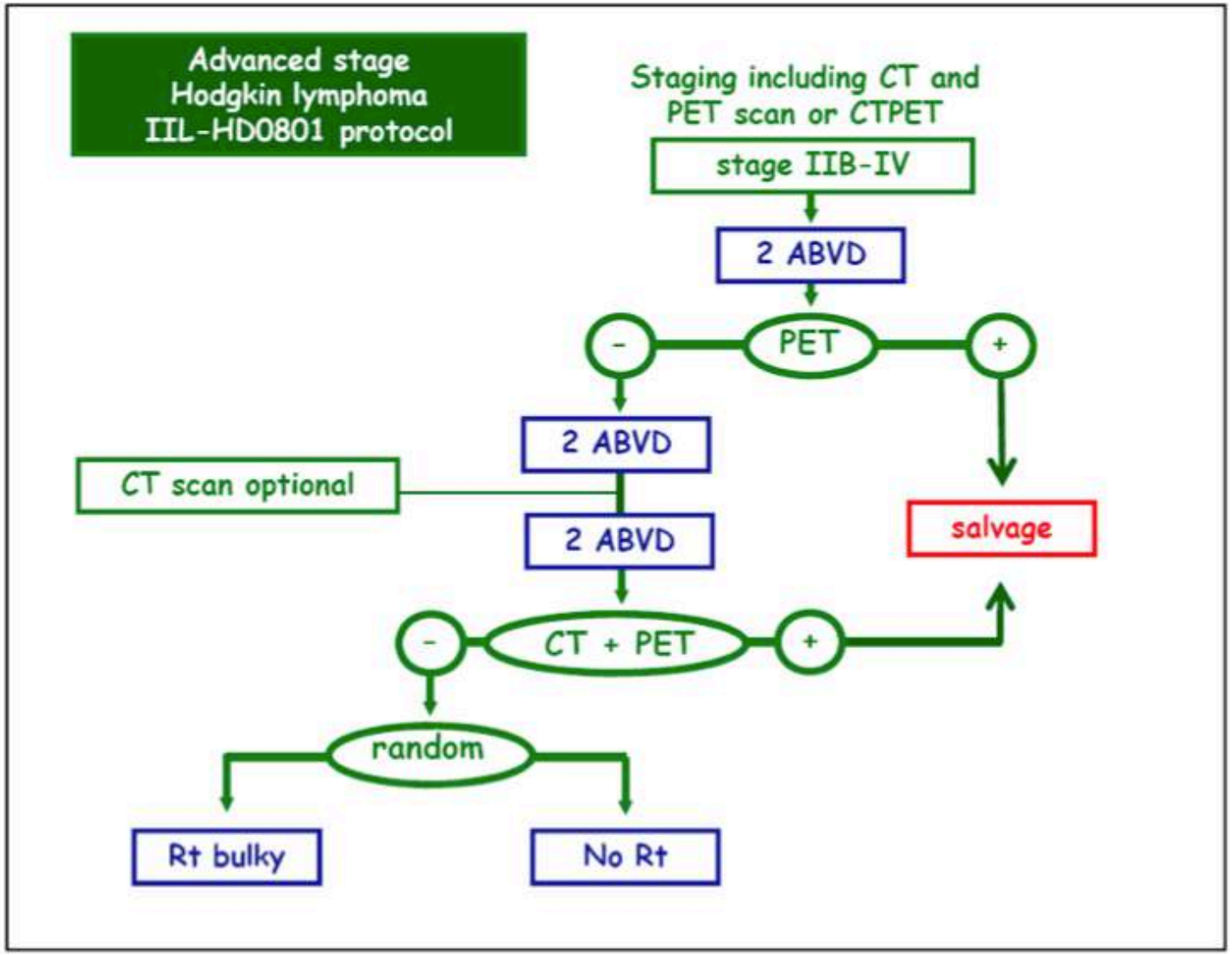


GITIL HD 0607



FONDAZIONE ITALIANA LINFOMI

HD0801 - FLOWCHART



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HD 0801 trial

Phase II part: “early salvage in PET2+ patients”

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

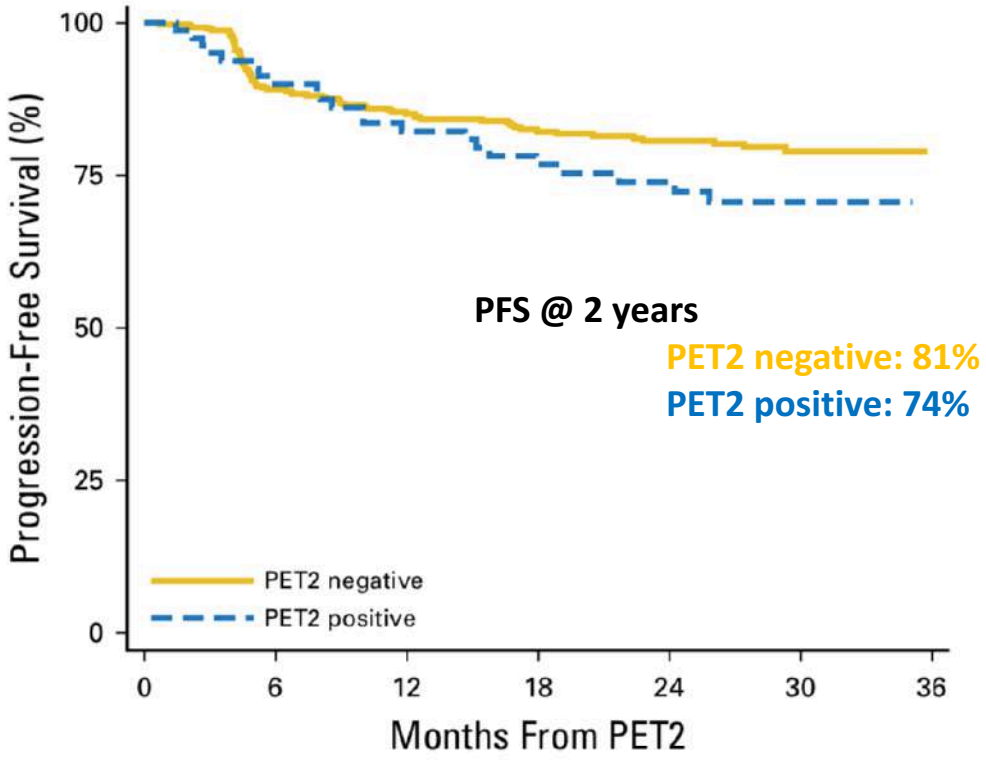
Interim Positron Emission Tomography Response–Adapted Therapy in Advanced-Stage Hodgkin Lymphoma: Final Results of the Phase II Part of the HD0801 Study

- ❑ 519 advanced stage HL patients
- ❑ PET positive if DS 4-5 (central review)
- ❑ Early salvage: IGEV x 4 followed by BEAM + ASCT
- ❑ 81 PET2+ patients underwent early salvage
- ❑ Primary endpoint: 2 years PFS

CONCLUSION:

Advanced-stage HL patients at high risk of relapse may benefit from early salvage with ASCT, with similar 2-year PFS of PET2-negative subgroup.

Per-protocol analysis



PFS @ 2 years

PET2 negative: 81%

PET2 positive: 74%

Zinzani P.L. et al. JCO 2015

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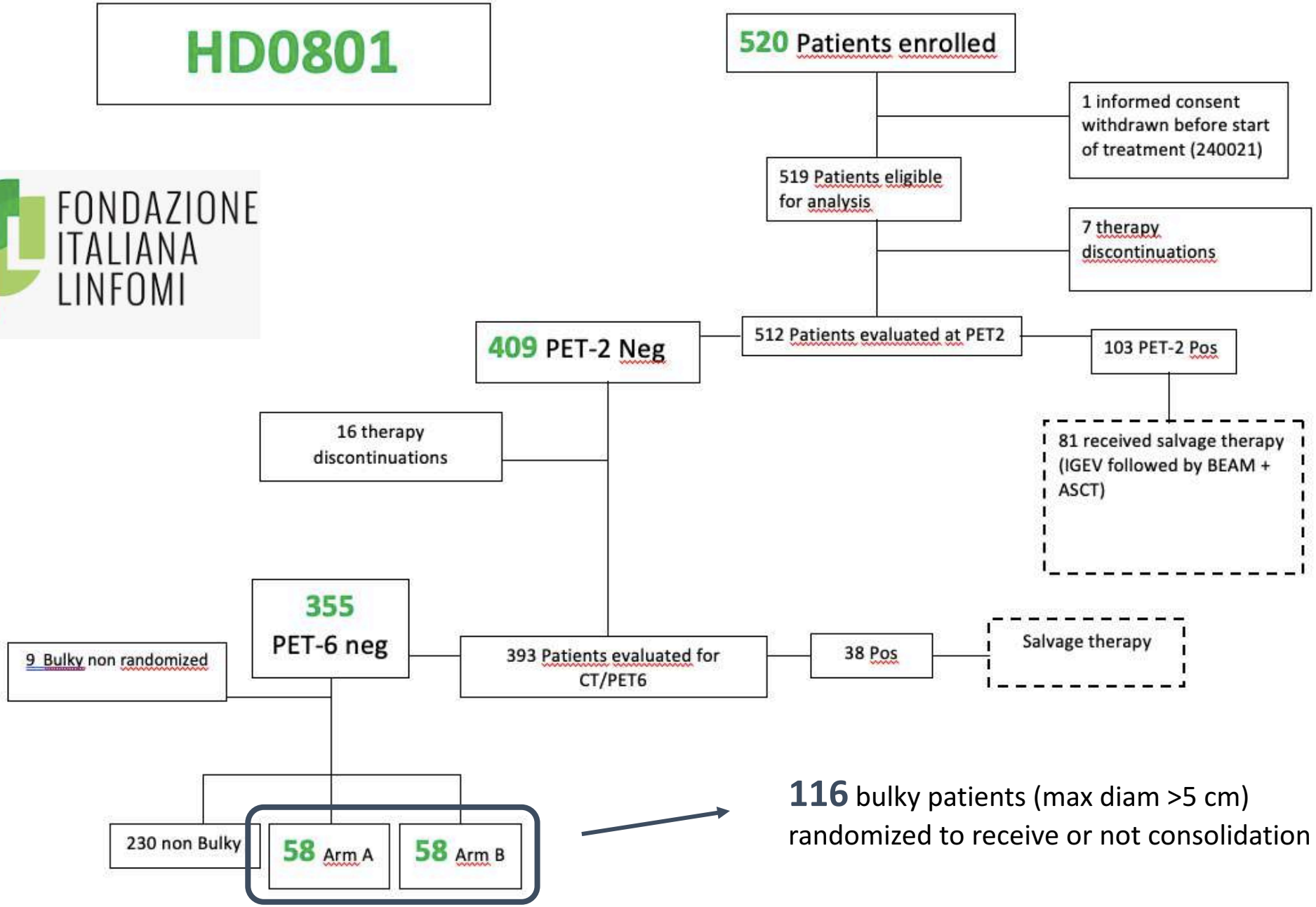
HD0801

FONDAZIONE ITALIANA LINFOMI



116 bulky patients (max diam >5 cm) randomized to receive or not consolidation RT

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Patients Characteristics

Characteristic	No-RT (N=58)	RT (N=58)	Total (N=116)	p value
Age, median value	29.5 (25;37)	31.5(26;39)	31.0 (25;39)	**ns**
Gender				
Males	30 (52%)	34 (59%)	64 (55%)	**ns**
Females	28 (48%)	24 (41%)	52 (45%)	**ns**
Systemic Symptoms				
A	21 (36%)	14 (24%)	35 (30%)	**ns**
B	37 (64%)	44 (76%)	81 (70%)	**ns**
Performance Status				
0	38 (66%)	35 (60%)	73 (63%)	**ns**
1	17 (29%)	16 (28%)	33 (28%)	**ns**
2	3 (5%)	7 (12%)	10 (9%)	**ns**
Stage				
2	15 (26%)	19 (33%)	34 (29%)	**ns**
3	20 (34%)	21 (36%)	41 (35%)	**ns**
4	23 (40%)	18 (31%)	41 (35%)	**ns**
Extranodal sites number				
0	34 (59%)	39 (67%)	73 (63%)	**ns**
>= 1	24 (41%)	19 (33%)	43 (37%)	**ns**
Bulky sites				
Mediastinum	41 (71%)	39 (67%)	80 (69%)	**ns**
Non-mediastinal sites	17 (29%)	19 (33%)	36 (31%)	**ns**
Bulky nodal sites number				
1	52 (90%)	48 (83%)	100 (86%)	**ns**
2	5 (9%)	6 (10%)	11 (9%)	**ns**
3 or more	1 (2%)	4 (7%)	5 (4%)	**ns**

Bulky Lesions

Arm	Bulky Baseline (cm)			
	Median	25° percentile	75° percentile	Minimum
No RT	8.25	6.5	11	5
RT	8.15	6.5	10	5

Bulky defined as every single mass with a maximum diameter ≥5 cm

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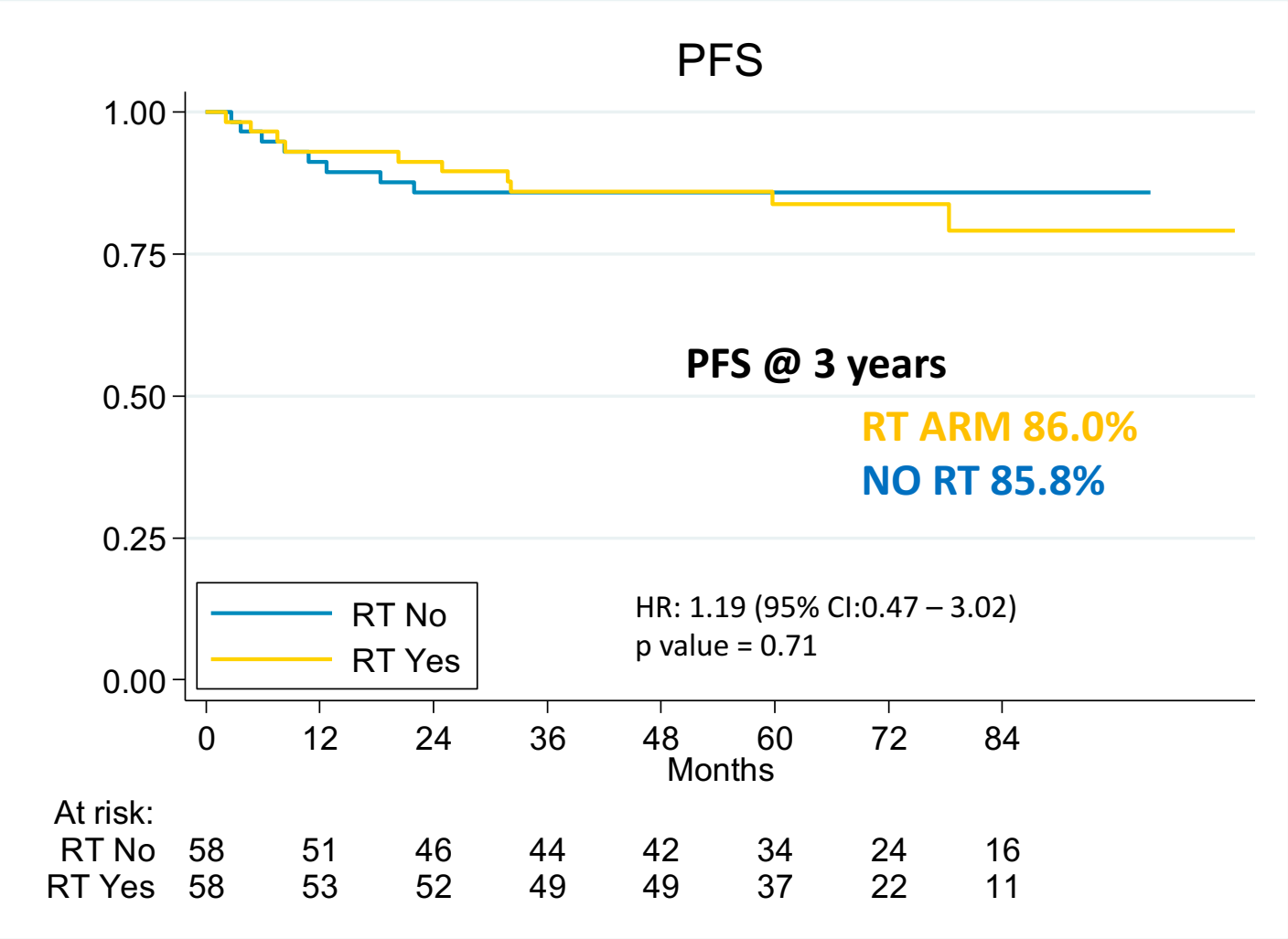
Results

Intention-to-treat analysis



But… 9 patients randomized in the RT arm did NOT receive consolidation treatment

Of these, **5 relapsed**!

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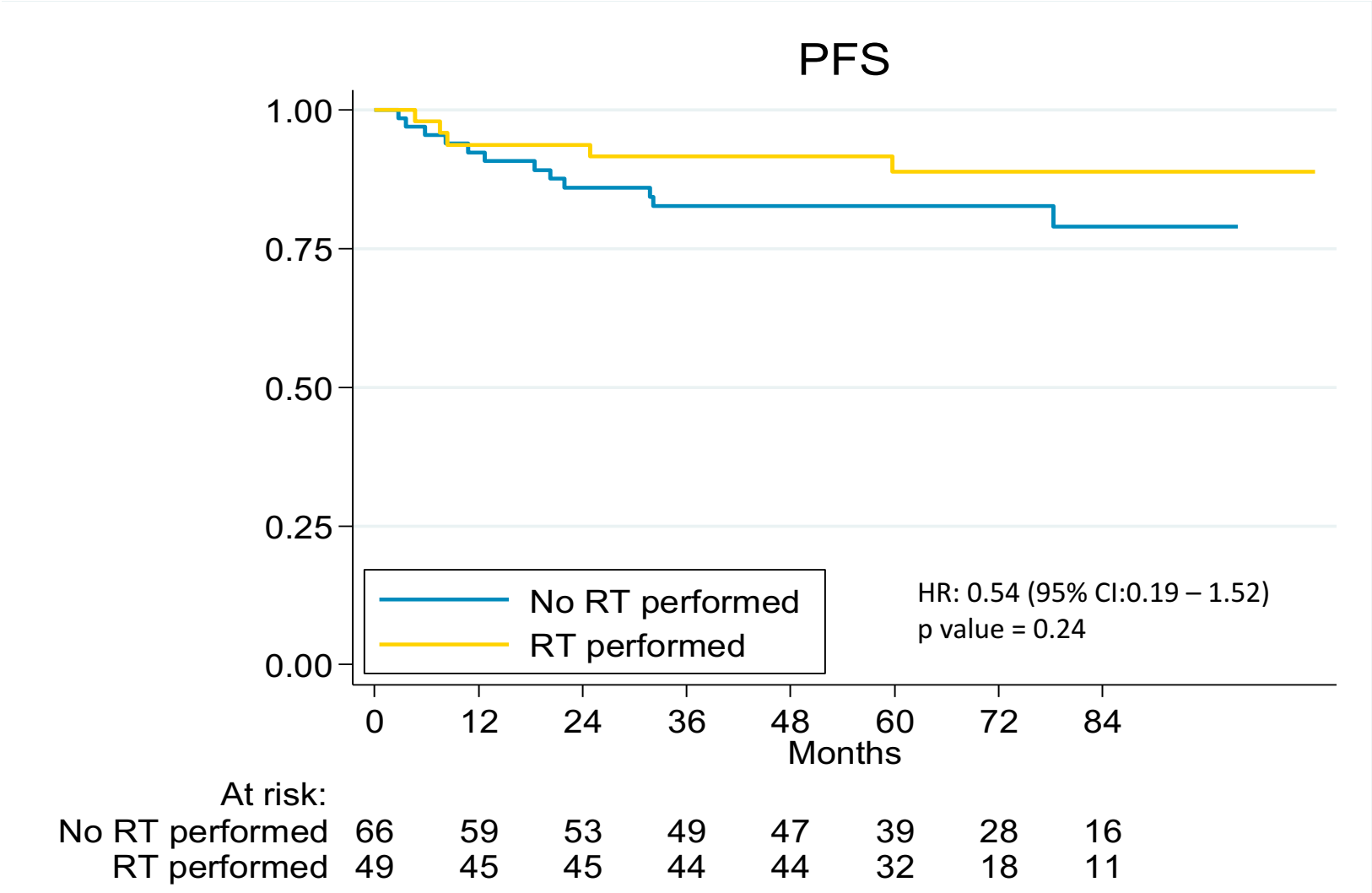
Results

Per-protocol analysis



PFS @ 3 years

RT ARM 91.7%

NO RT 81.4%

(RT benefit: +10.3%)

PFS @ 5 years

RT ARM 88.9%

NO RT 81.4%

(RT benefit: +7.5%)

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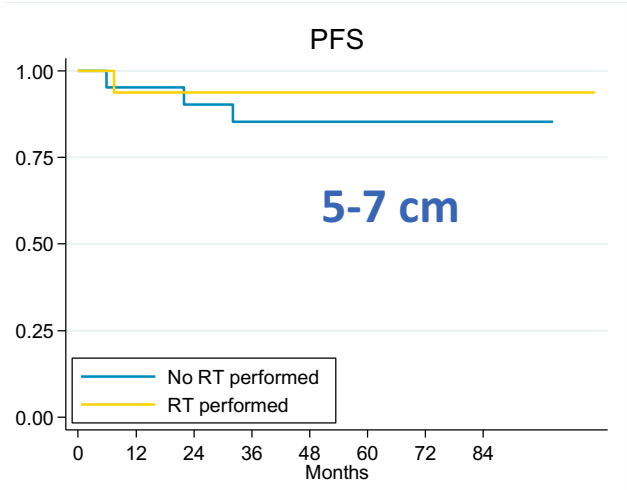
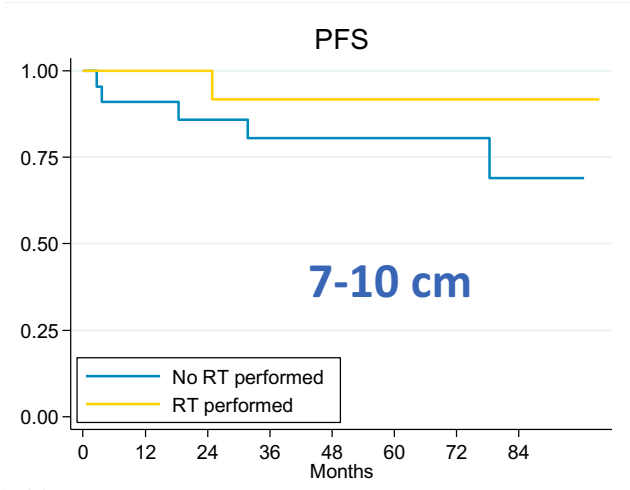
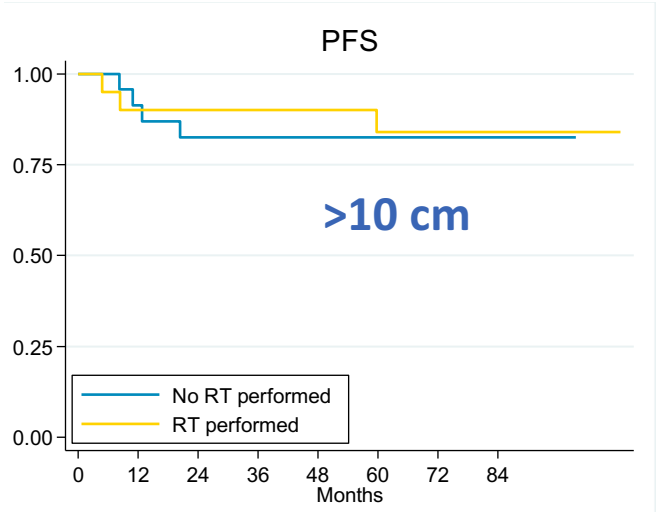
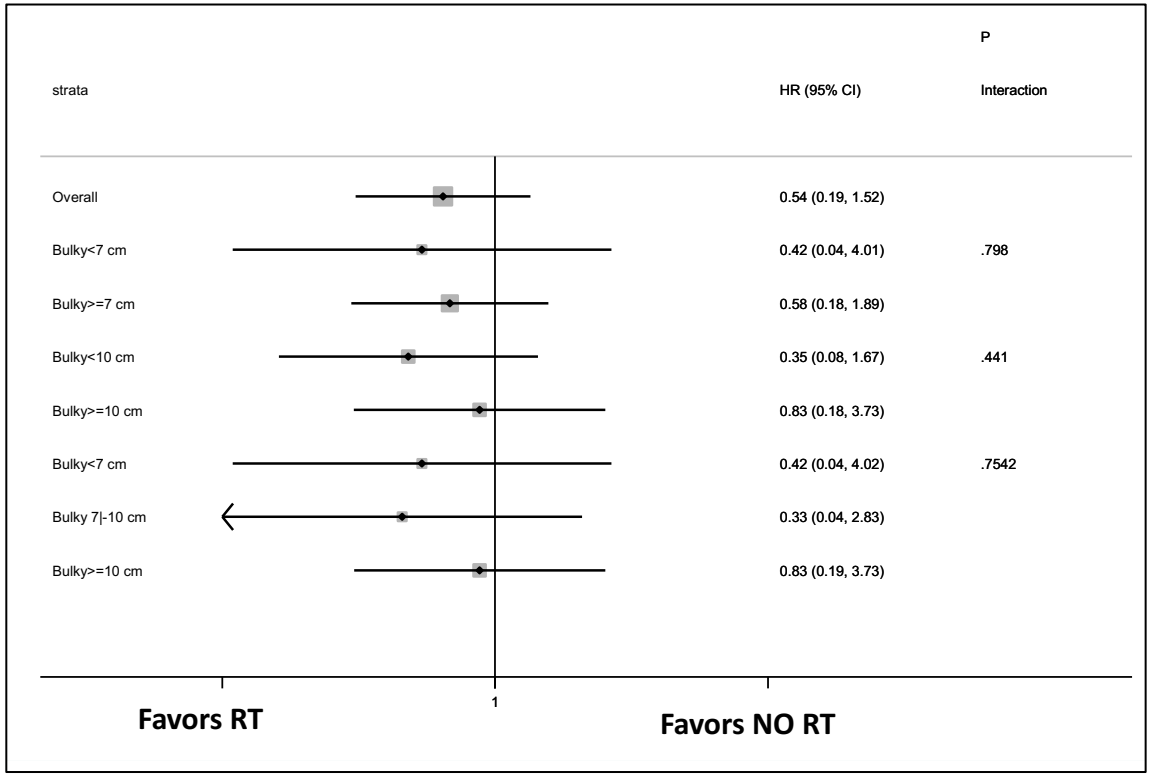
Subgroup analysis for Bulky dimension









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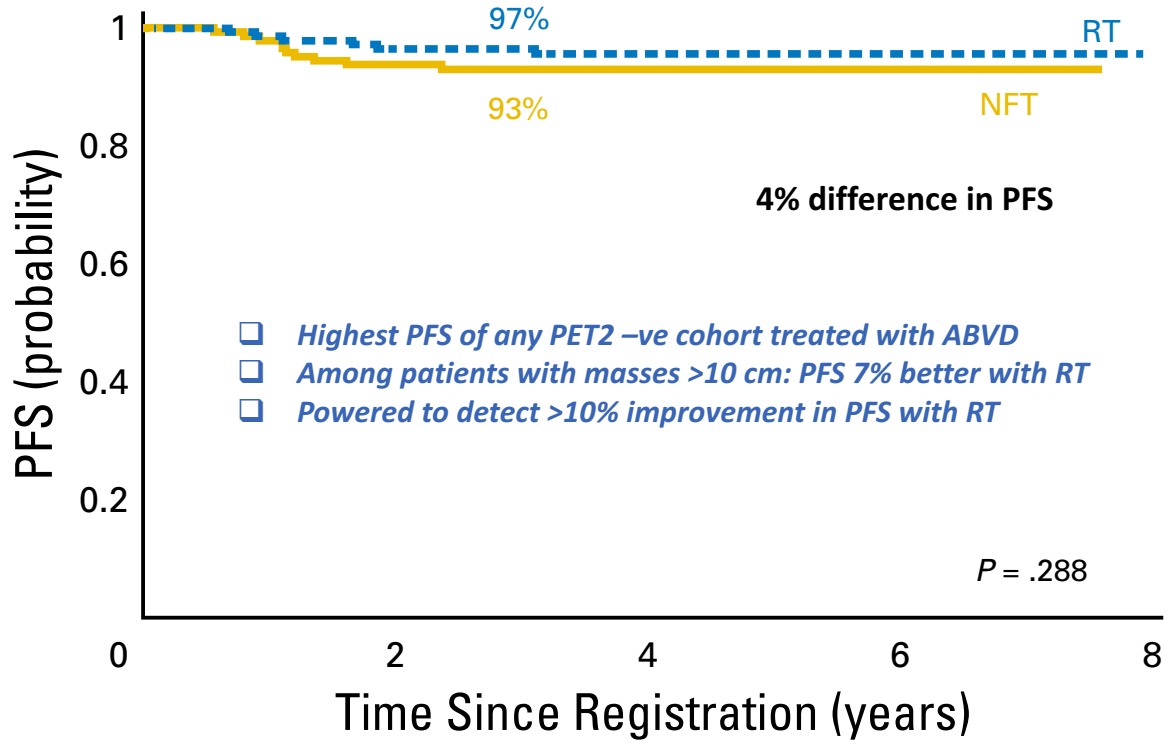
Consolidation RT to Bulky Lesions in Advanced HL after ABVD regimen: "uncertain benefit"

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

GITIL HD0607 trial

Randomization of RT treatment to bulky lesions (>5 cm) of PET2 and PET6 –ve patients



- *Highest PFS of any PET2 –ve cohort treated with ABVD*
- *Among patients with masses >10 cm: PFS 7% better with RT*
- *Powered to detect >10% improvement in PFS with RT*

No. at risk		Events		Events		Events		Events	
NFT	148	9	133	1	35	0	14	0	0
RT	148	5	139	1	39	0	10	0	0

Gallamini A. et al. JCO 2018

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Outcomes in Advanced Stage HL

PET2 Response-adapted ABVD trials

PFS		
	PET2–	**PET2+**
HD0607*#	87% (3-years)	60% (3-years)
RATHL*§	85.7% (3-years)	67.5% (3-years)
SWOG S0816*	76% (5-years)	65% (5-years)
HD0801**	81% (2-years)	74% (2-years)

* PET2+ intensified with eBEACOPP
** PET2+ intensified with IGEV + ASCT
§ 41% of RATHL patients were in stage II
# 36% of HD0607 patients were in stage II

BEACOPP-based trials

PFS	
	Best arm
HD9 (eBEACOPP x 8 + RT)	87% (5-years)
HD12 (eBEACOPP x 8)*	87% (5-years)
HD15 (eBEACOPP x 6)§	90.3% (5-years)
HD18 (eBEACOPP x 4 – only PET-)§	92.2% (2-years)

* RT to residual disease provided a significant PFS benefit (+5.8%)
§ RT given only to residual disease (PET+) at the end of chemotherapy

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Beneficial role of consolidation RT to bulky lesion after ABVD in PET negative patients

Study	PFS		
	Overall population		*RT to bulk*
ABVD studies			
HD0801	81% (3-years)	+ 10% →	91% (3-years)
BEACOPP studies			
HD12	87% (5-years)		90.3% (5-years)
HD15	90.3% (5-years)		NOT PLANNED
HD18	92.2% (5-years)		NOT PLANNED

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Risk of late complications: still a good reason to omit consolidation RT? (SECOND CANCERS)

Intensive treatment strategies in advanced-stage Hodgkin's lymphoma (HD9 and HD12): analysis of long-term survival in two randomised trials

	HD9			HD12			
	8×COPP/ABVD plus RT (n=261)	8×bBEACOPP plus RT (n=469)	8×eBEACOPP plus RT (n=466)	8×eBEACOPP plus RT (n=392)	8×eBEACOPP (n=395)	4×eBEACOPP plus 4×bBEACOPP plus RT (n=393)	4×eBEACOPP plus 4×bBEACOPP (n=394)
Second primary malignant neoplasm*							
Acute leukaemia or MDS	1 (<1%)	8 (2%)†	15 (3%)	10 (3%)	5 (1%)	4 (1%)	7 (2%)
Non-Hodgkin lymphoma or myeloma	8 (3%)	12 (3%)	8 (2%)	8 (2%)	6 (2%)	5 (1%)	3 (1%)
Solid tumour	10 (4%)	28 (6%)	27 (6%)	18 (5%)	14 (4%)	14 (4%)	14 (4%)
Total	19 (7%)	48 (10%)	50 (11%)	36 (9%)	25 (6%)	23 (6%)	24 (6%)
10-year cumulative incidence (95% CI)	5·2% (2·4–8·0)	7·6% (5·0–10·2)	6·5% (4·1–8·9)	9·7% (6·2–13·3)	8·8% (5·2–12·4)	6·4% (3·8–9·1)	6·4% (3·3–9·5)
15-year cumulative incidence (95% CI)	7·2% (3·7–10·7)	13·0% (9·1–16·9)	11·4% (7·6–15·1)	ND	ND	ND	ND
Standardised incidence ratio (95% CI)	2·0 (1·2–3·2)	2·6 (1·9–3·4)	2·6 (1·9–3·4)	3·2 (2·2–4·4)	2·4 (1·5–3·5)	2·5 (1·6–3·7)	2·3 (1·5–3·4)

von Tresckow B. et al. Lancet Haematol 2018

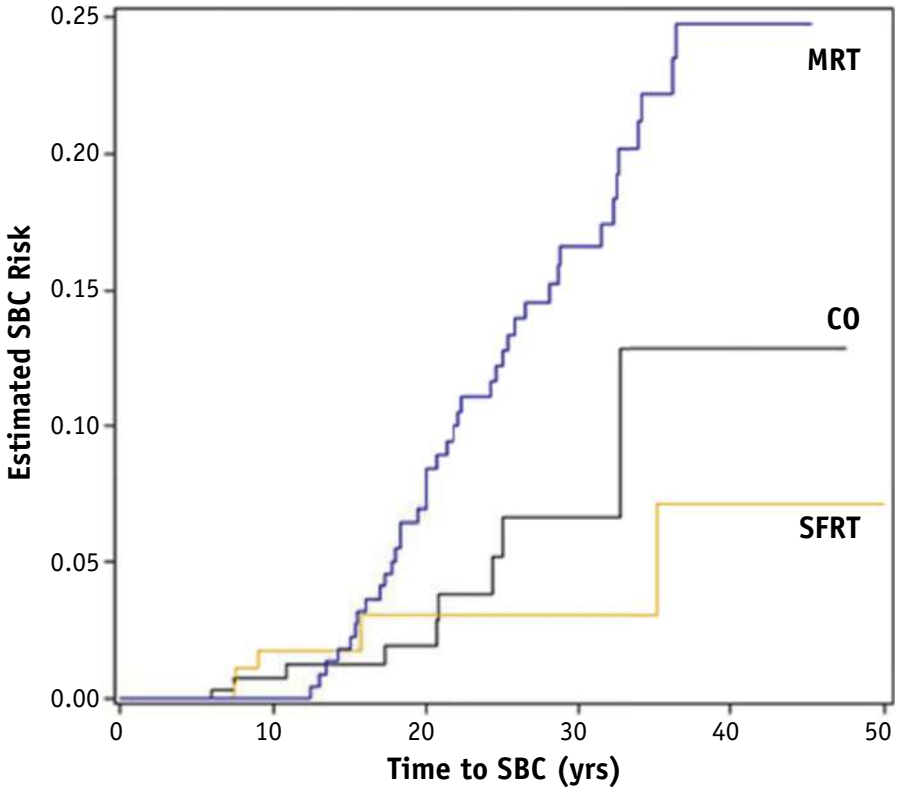
Secondary breast cancer risk of Modern RT fields

- ***Period of analysis: 1961-2009 (>5 years of follow up)***
- ***Median RT dose: 35 Gy***
- ***Median follow up: 18 years***
- ***Total population: 734 patients***
  - ***Mantle Field RT (MFR) = 231 pts***
  - ***Small Fields RT (SFRT) = 185 pts***
  - ***Chemotherapy only (CO) = 318 pts***
- ***N.B: SFRT = IFRT; ISRT; INRT***

Clinical Investigation

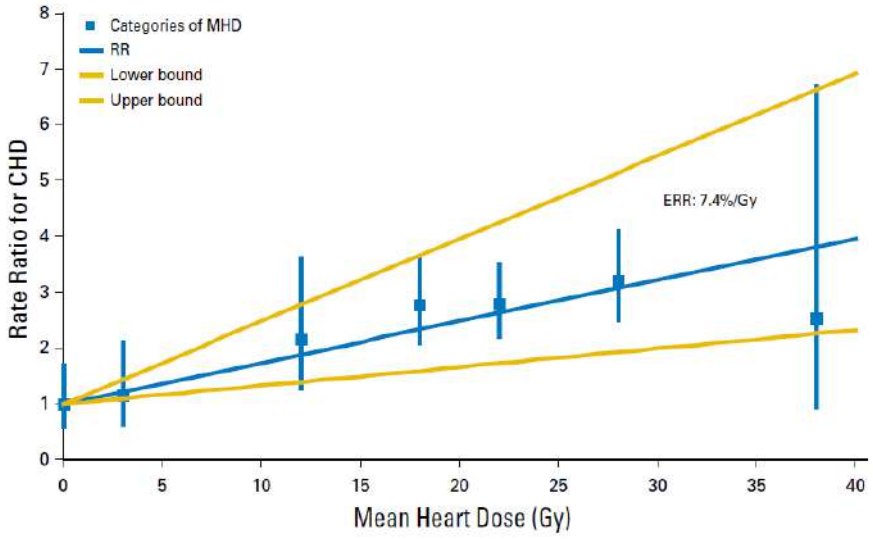
Secondary Breast Cancer Risk by Radiation Volume in Women With Hodgkin Lymphoma

Jessica L. Conway, MD,*,† Joseph M. Connors, MD,*
Scott Tyldesley, MD,*,† Kerry J. Savage, MD,*
Belinda A. Campbell, MD,‡ Yvonne Y. Zheng, MEng, MSc,§
Jeremy Hamm, MSc,§ and Tom Pickles, MD*,†



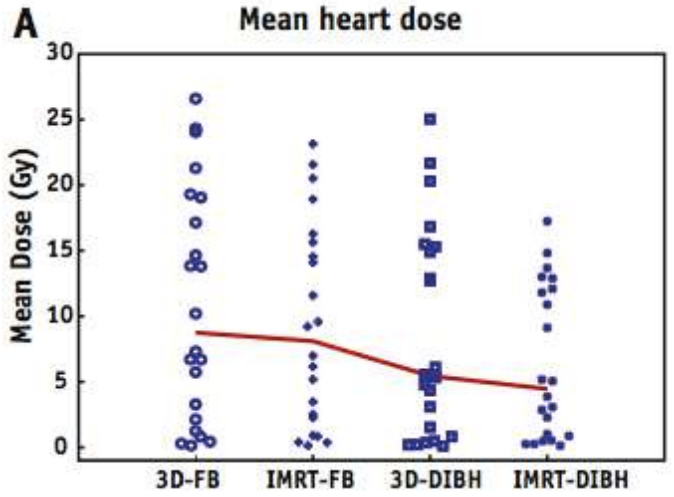
Risk of late complications: still a good reason to omit consolidation RT? (CARDIAC TOXICITY)

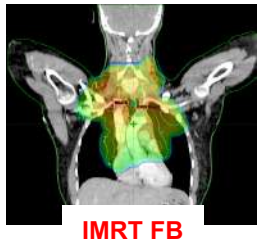
Linear correlation between mean heart dose and the risk of developing coronary artery disease



van Nimwegen et al. JCO 2016

Minimizing Late Effects for Patients With Mediastinal Hodgkin Lymphoma: Deep Inspiration Breath-Hold, IMRT, or Both?



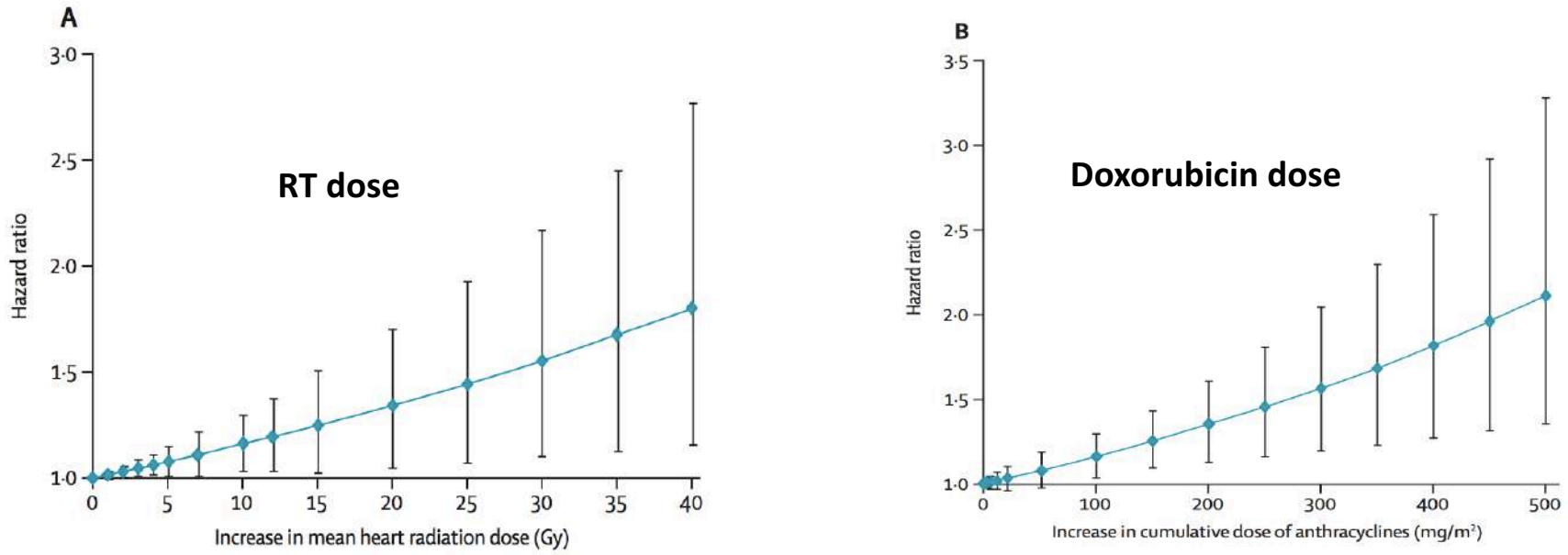

IMRT FB


IMRT DIBH

Aznar M. et al. IJROBP 2015

Why not to give more chemotherapy to avoid RT…

Estimated HR for cardiovascular events according to mean heart RT dose and cumulative dose of anthracyclines



Example: an increase in **mean heart dose of 5 Gy** yields the **same excess risk** of cardiac events as an increase in cumulative **anthracycline dose of 50 mg/m2** (≈1 cycle of ABVD or R-CHOP)

WARNING

HD0801 conclusions:

1. Patients affected with advanced stage HL and achieving a mCR after ABVD chemotherapy may benefit from the addition of consolidation RT to bulky sites (PFS benefit of 10% at 3 years)

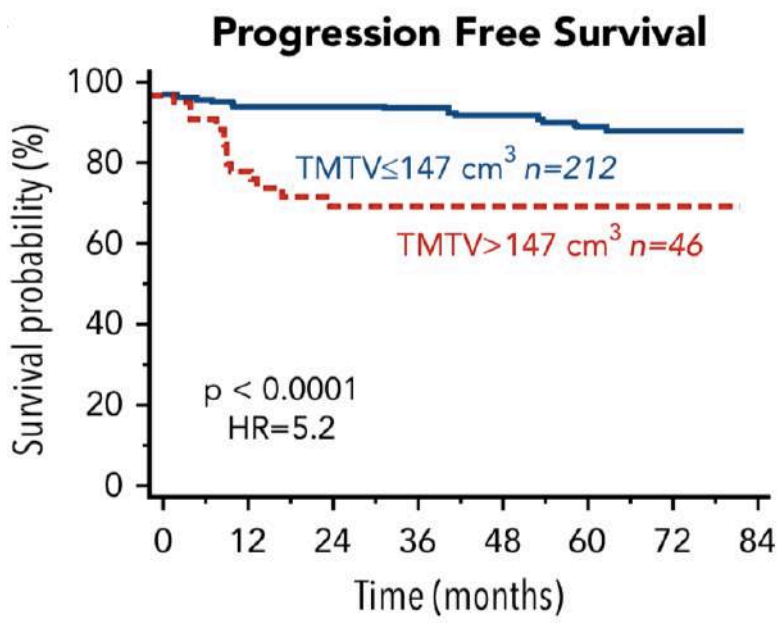
2. The results of this trial do not provide definitive evidence on the role of radiotherapy in this setting, given the limited numbers (statistical robustness)

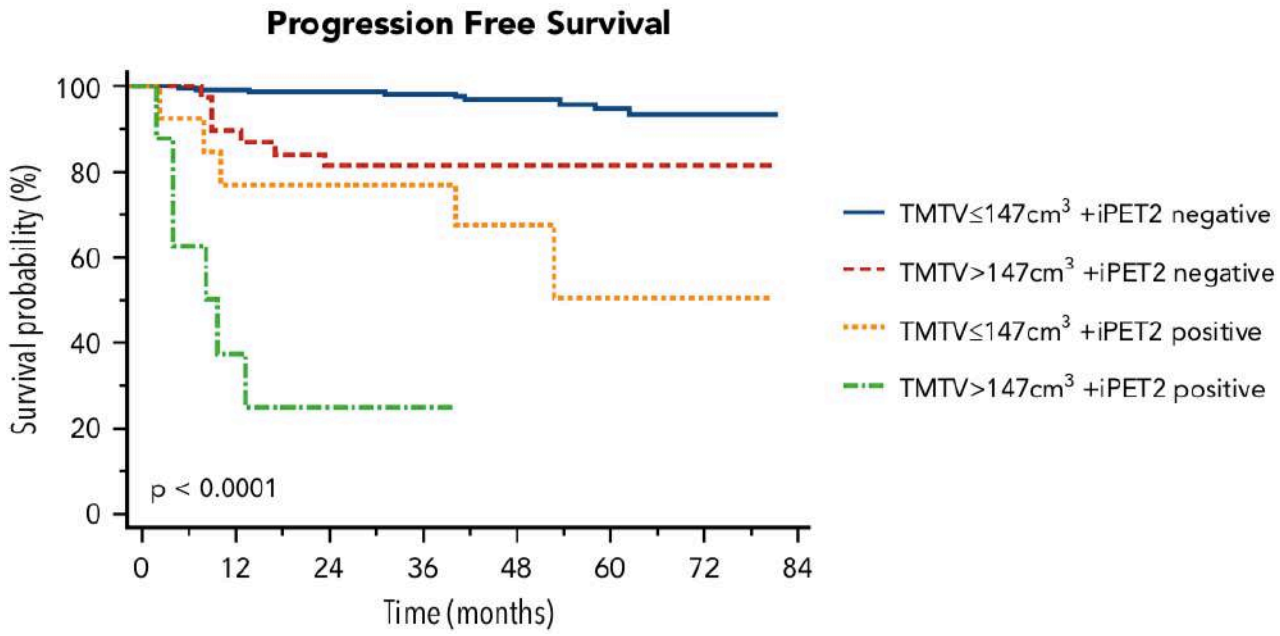
3. To date, a multidisciplinary discussion is strongly recommended to offer the best treatment solution to each patient (pros/cons of RT consolidation)

4. Next steps:
   - ❑ meta-analysis of this and similar randomised trials
   - ❑ New prognosticators for a better selection of patients

Future Perspectives: Innovative metabolic markers ?

Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial





Conclusion: the present study point out the outstanding prognostic value of TMTV, an imaging biomarker available at diagnosis. The combination of TMTV and PET/CT response after 2 cycles assessed with Deauville score improves the predictive value of interim PET

Cottereau A-S et al. Blood 2018

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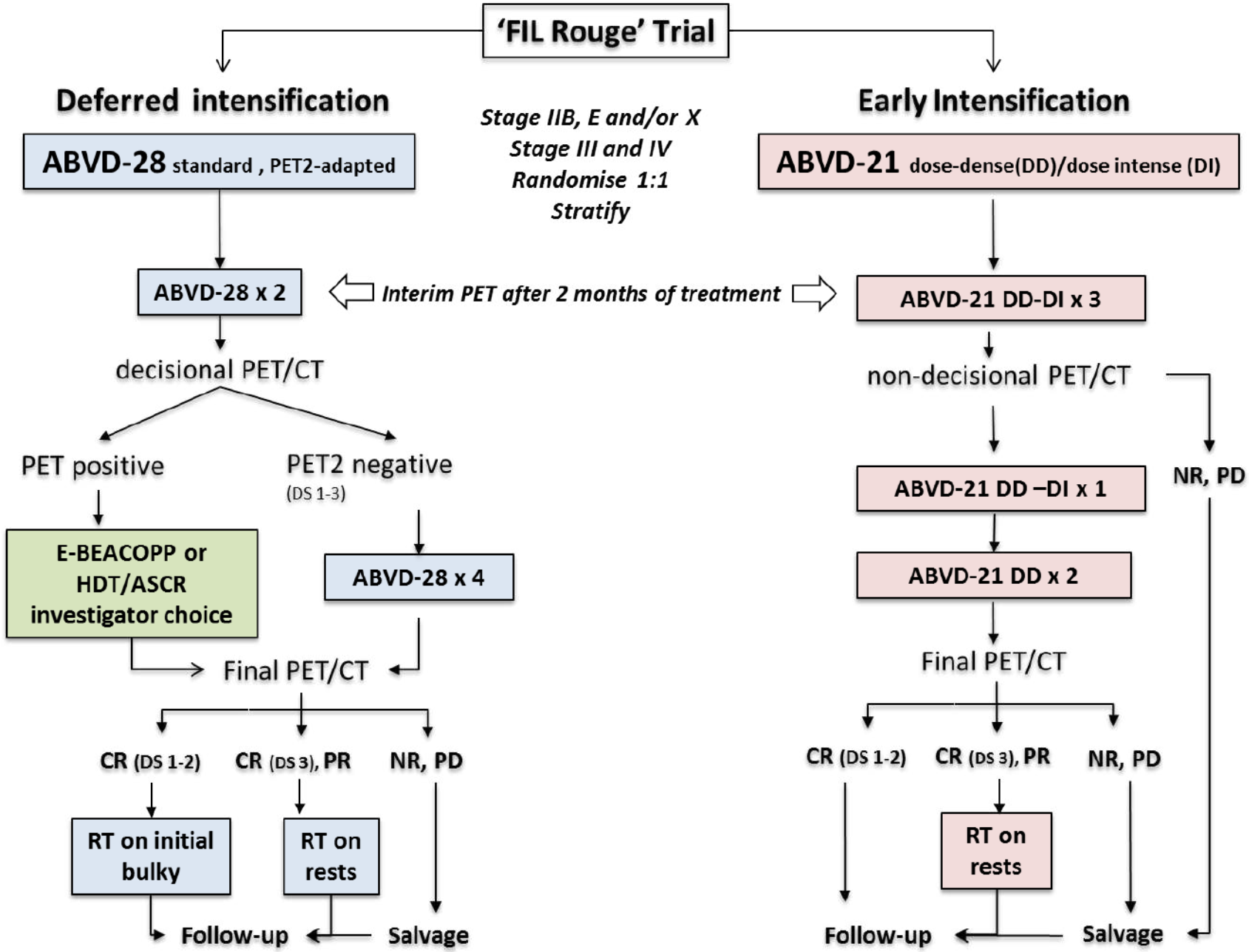
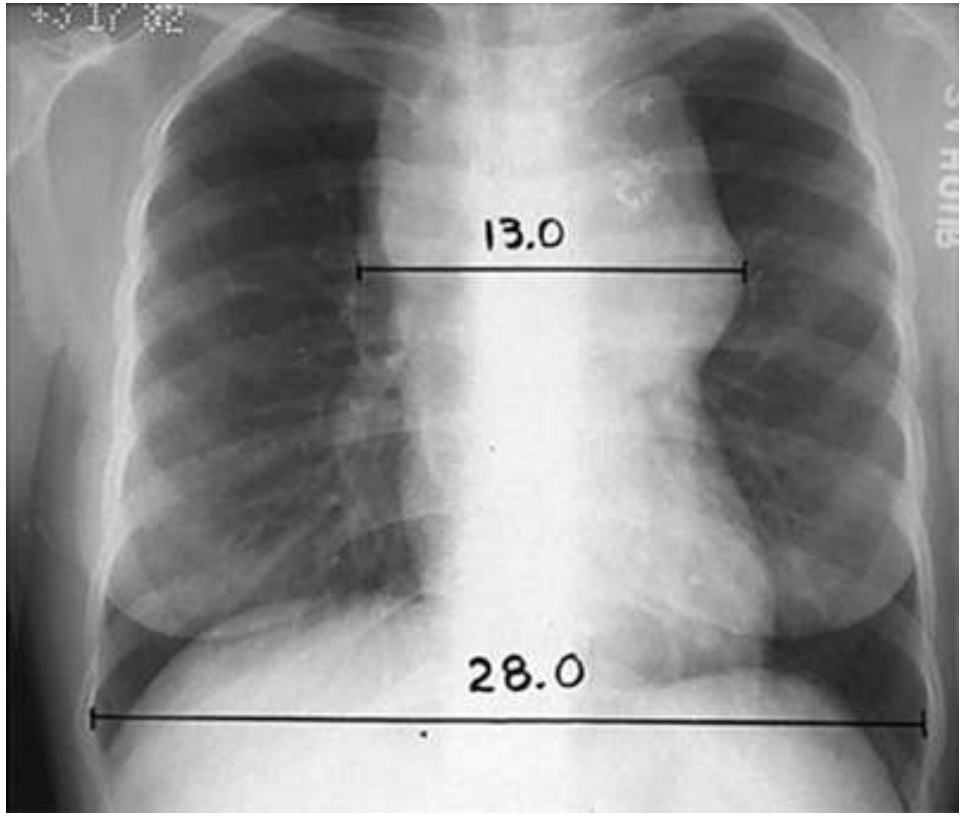

'FIL Rouge' Trial
Deferred intensification
Stage IIB, E and/or X
Stage III and IV
Randomise 1:1
Stratify
Early Intensification
ABVD-28 standard , PET2-adapted
ABVD-21 dose-dense(DD)/dose intense (DI)
ABVD-28 x 2
Interim PET after 2 months of treatment
ABVD-21 DD-DI x 3
decisional PET/CT
non-decisional PET/CT
PET positive
PET2 negative
(DS 1-3)
NR, PD
E-BEACOPP or
HDT/ASCR
investigator choice
ABVD-28 x 4
ABVD-21 DD –DI x 1
ABVD-21 DD x 2
Final PET/CT
Final PET/CT
CR (DS 1-2)
CR (DS 3), PR
NR, PD
CR (DS 1-2)
CR (DS 3), PR
NR, PD
RT on initial
bulky
RT on
rests
RT on
rests
Follow-up
Salvage
Follow-up
Salvage

Bulky Lesion Definition



The definition of bulk has evolved as imaging modalities have changed.
The most common one is based on results of a chest X-ray, and bulky disease is defined based on the ratio of the maximum width of the mediastinal mass and the maximum intrathoracic diameter on standing posterior-anterior X-ray (mediastinal mass ratio [MMR] > 0.33)

Definition of bulky disease in early stage Hodgkin lymphoma in computed tomography era: prognostic significance of measurements in the coronal and transverse planes

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EUROPEAN HEMATOLOGY ASSOCIATION

- ***Training cohort***: (MSK) 185 early stage HL patients
- ***Validation cohort***: (MAYO/DANA FARBER) 38 patients
- **Aim**: to assess the prognostic significance of the largest nodal mass measured in either the transverse and coronal planes using CT scan
- A range of potential cut-off points (in cm) based upon the distribution of the data (between 10° and 90° percentiles) were identified and then examined to test their significance level for RFS using log rank test

Figure 1. Representative images of the longest diameters measured using calipers of a right cervical mass in (A) transverse plane, 2.6 cm and (B) coronal plane, 12.1 cm.

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Roughly 30% of bulky patients were identified only using coronal reformations

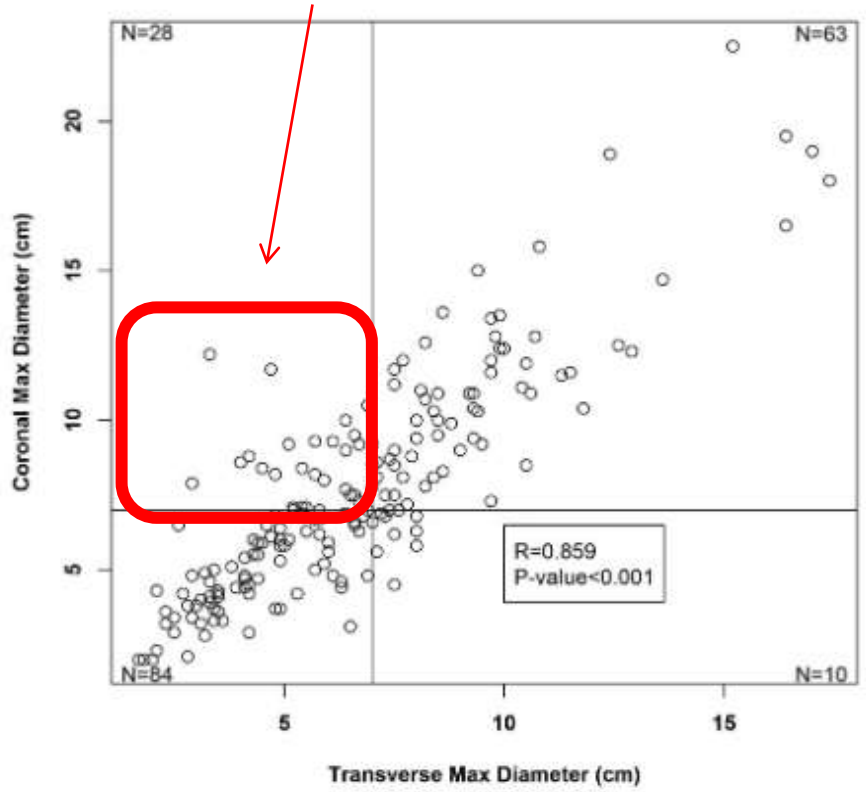
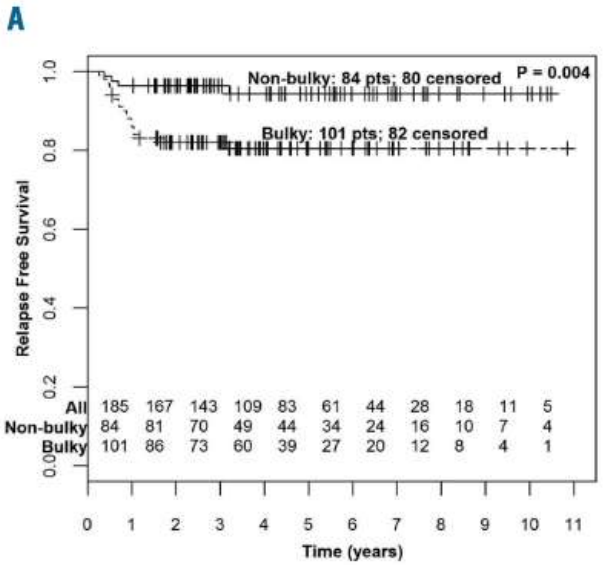
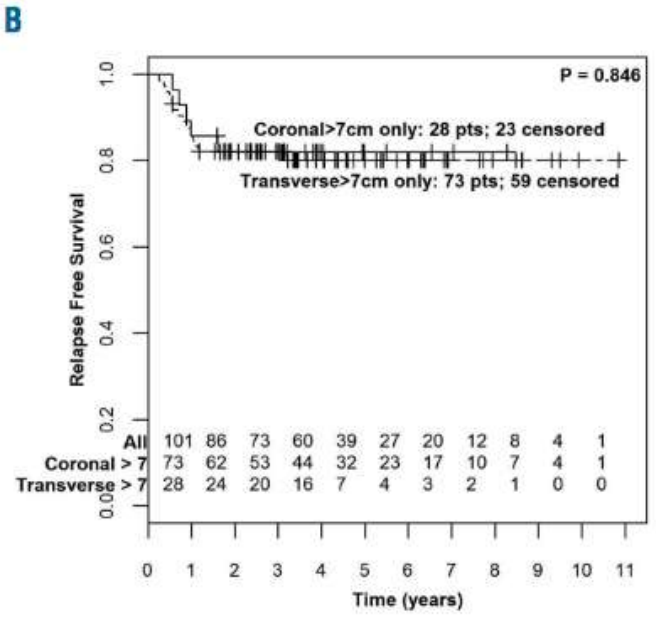


Figure 2. Correlation between maximal transverse and coronal measurements with lines for the 7 cm maximal transverse and coronal cut-offs for disease bulk.





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The Prognostic Role Of Bulky Lesion Is Essential In Patients Treated With Chemotherapy Alone

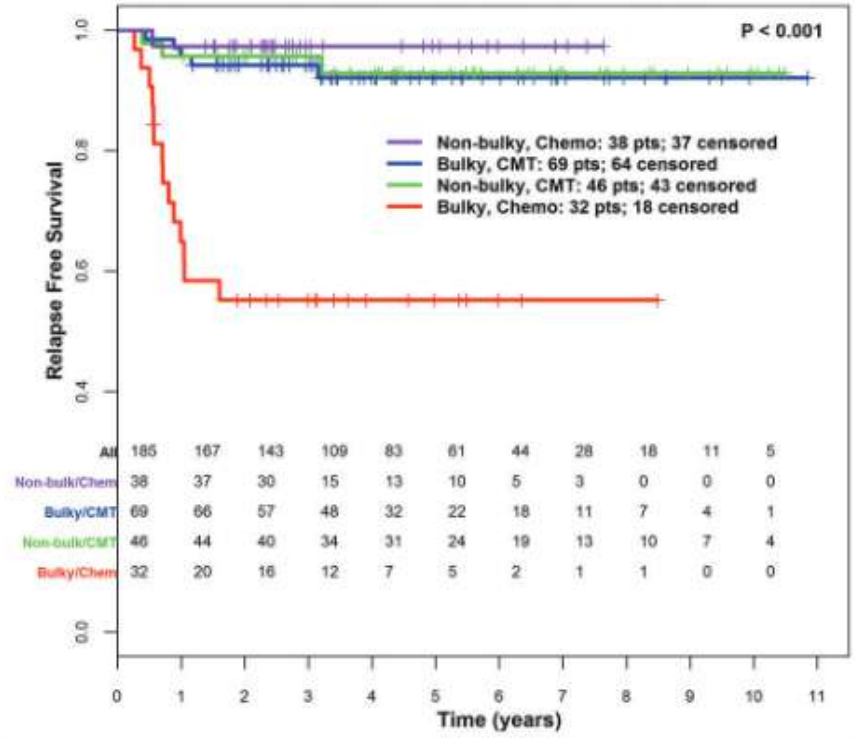

Figure 4. Relapse-free survival by presence of bulky disease (transverse or coronal max, diameter > 7cm) and treatment [chemotherapy alone (Chemo) *vs.* combined modality therapy (CMT)].

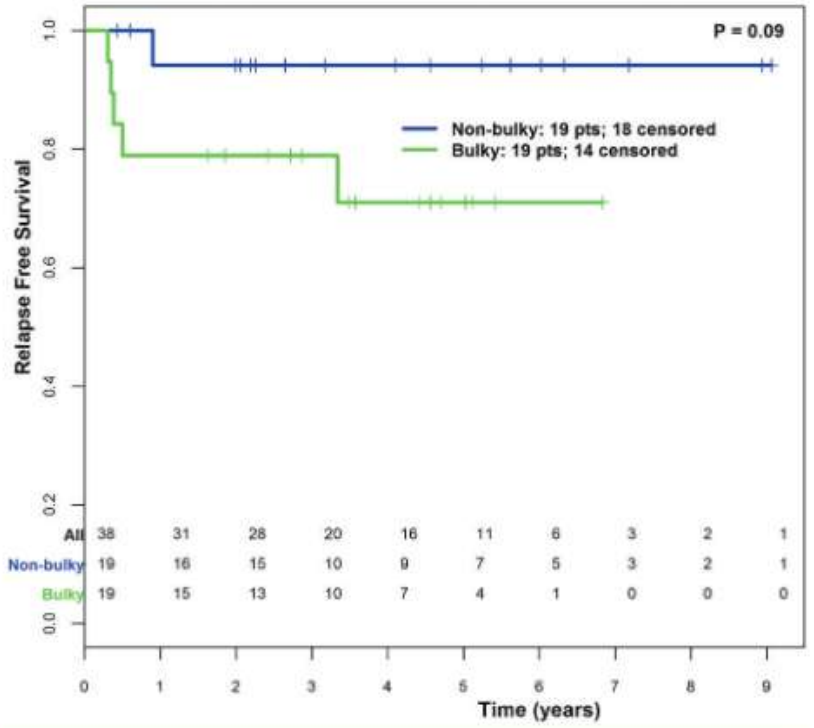

Figure 5. Relapse-free survival by presence of bulky disease (transverse or coronal max, diameter > 7cm) in validation cohort patients (n=38) treated with chemotherapy alone.

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