Aggressive Lymphoma Workshop

Bologna, Royal Hotel Carlton

May 8-9, 2023

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI SCIENZE MEDICHE E CHIRURGICHE

POLICLINICO DI SANT'ORSOLA

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Role of Radiotherapy

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President: **Pier Luigi Zinzani**

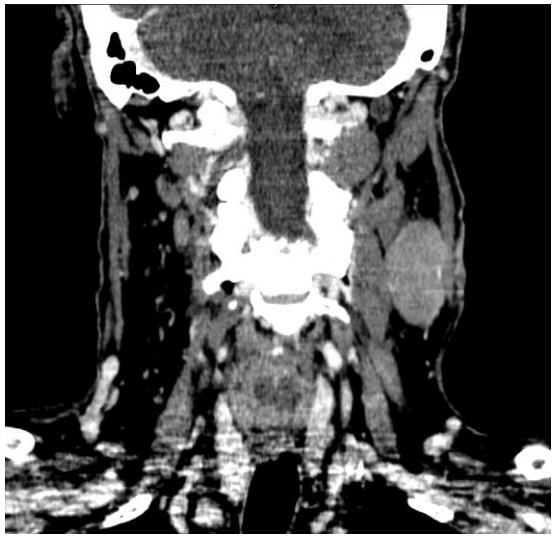
Disclosures of Umberto Ricardi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Astra Zeneca					x	X	
Accuray	x				x		
BrainLab	x						

- CMT has been the standard (with CHOP)

- New era:
  - Rituximab improved PFS & OS
  - PET response assessment
  - Omitting RT in HL (late toxicity)

- Need to re-evaluate role of RT in DLBCL



DLBCL is different from HL

- **Prognosis:**

  HL is highly curable

  DLBCL is curable in 60-65% in **population-based** studies

  Salvage is more successful in HL > DLBCL (especially >RCHOP)

- **Age:** older age group, with median age 60-65

- **Late effects:**

  No evidence of increased risk of **2nd malignancy** in NHL

  Explanation:

  2nd malignancy risk is small @ age > 45

  Competing causes of death: disease-related, co-morbidities


Malignant Lymphomas • Research Paper

Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study

Original Article

Second malignancies after treatment of diffuse large B-cell non-Hodgkin's lymphoma: a GISL cohort study

Stefano Sacchi,[1] Luigi Marcheselli,[1] Alessia Bari,[1] Raffaella Marcheselli,[1] Samantha Pozzi,[1] Paolo G. Gobbi,[2] Francesco Angrilli,[3] Maura Brugiatelli,[4] Pellegrino Musto,[5] and Massimo Federico[1]

The main concern in DLBCL is still curing the disease

Table 2. International prognostic index (IPI)

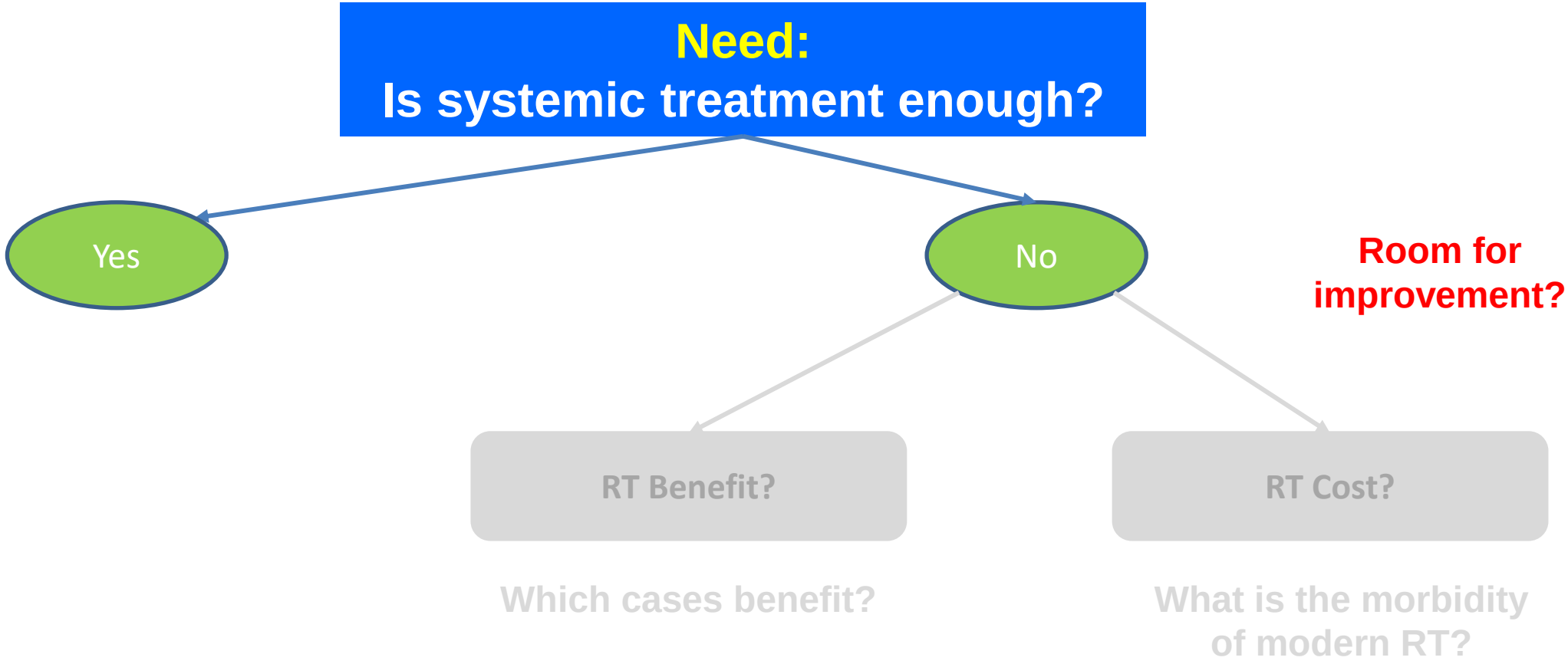
International prognostic index (IPI)			Estimated 3-year overall survival [26–29] (95% CI)
Risk factors	Age >60 years Serum LDH > normal Stage III–IV Performance status 2–4 Extranodal sites >1		
Risk categories	Low	0–1	91 (89–94)
	Low intermediate	2	81 (73–86)
	High intermediate	3	65 (58–73)
	High	4–5	59 (49–69)
Age-adjusted international prognostic index (aaIPI) in patients ≤60 years			
Risk factors	Serum LDH > normal Stage III–IV Performance status 2–4		
Risk categories	Low	0	98 (96–100)
	Low intermediate	1	92 (87–95)
	High intermediate	2	75 (66–82)
	High	3	

clinical practice guidelines

Annals of Oncology 26 (Supplement 5): v116–v125, 2015
doi:10.1093/annonc/mdv304

Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

H. Tilly[1], M. Gomes da Silva[2], U. Vitolo[3], A. Jack[4], M. Meignan[5], A. Lopez-Guillermo[6], J. Walewski[7], M. André[8], P. W. Johnson[9], M. Pfreundschuh[10] & M. Ladetto[11], on behalf of the ESMO Guidelines Committee*

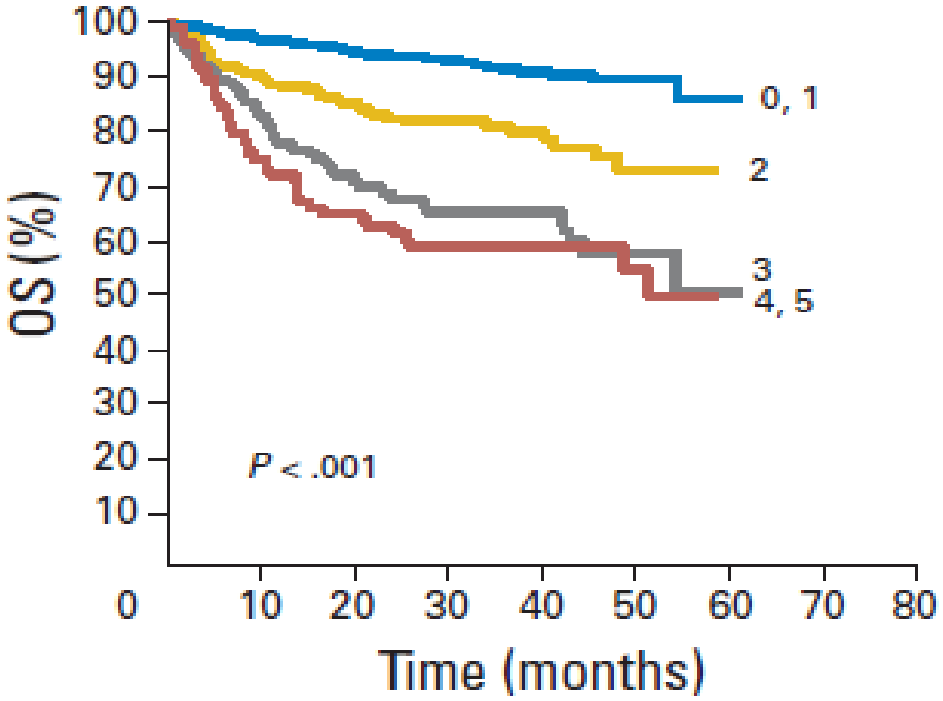

Need:
Is systemic treatment enough?
Yes
No
Room for improvement?
RT Benefit?
RT Cost?
Which cases benefit?
What is the morbidity of modern RT?

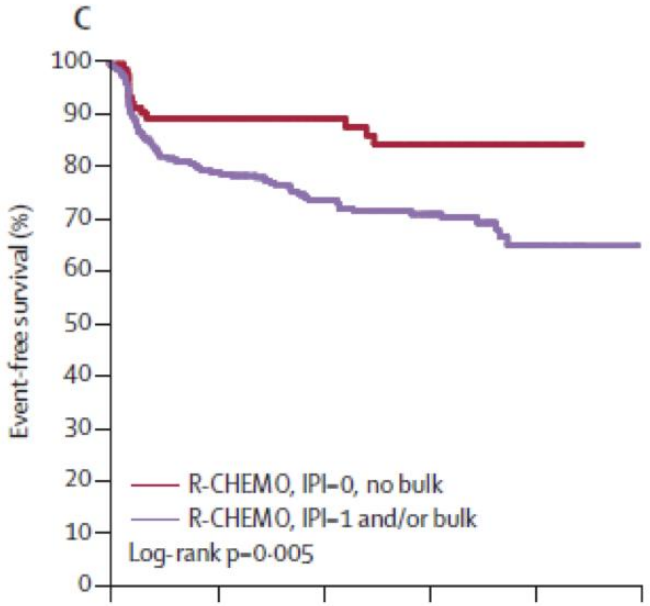
The gold standard is R-CHOP

Significant improvement over CHOP

- Long-term remission 60-70% (lower in population studies than RCTs)
- 30 - 40% of patients are not cured with R-CHOP
- Salvage after R is less effective

  (Relapse >R-CHOP defines a worse prognostic group)
- No significant improvement since R-CHOP



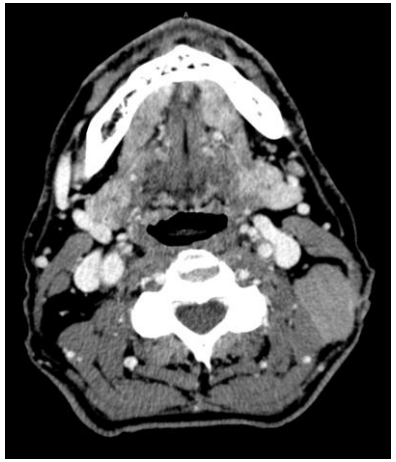


Need:
Is systemic treatment enough?

Yes

No

Room for improvement?



RT Benefit?

RT Cost?

Which cases benefit?

What is the morbidity?

RT in DLBCL: selection of patients who may benefit from its addition

Which cases might benefit from RT?

Reduce toxicity:

early stage disease (CMT with less chemo)

Improve outcome:

Bulk

EN sites

Skeletal sites

Testicular

Residual masses

Incomplete response (PET) to chemo

Salvage

Early stage DLBCL (stage I-II, IPI 0-2: low, low-intermediate risk)

2 options:

- **R-CHOP only (6 cycles)**
- **Short course R-CHOP (3-4 cycles) + ISRT 30 Gy**

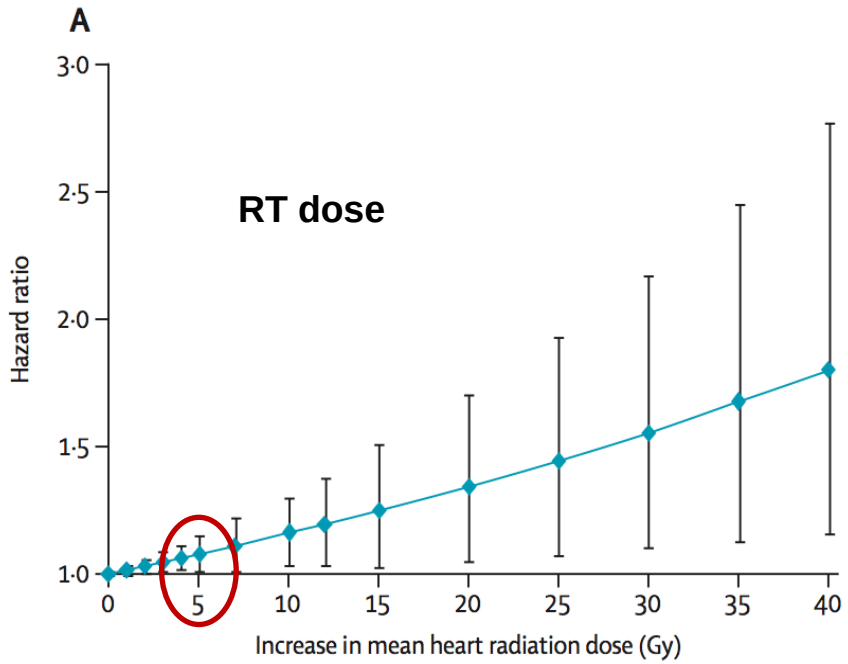
Equivalent oncological outcome – different toxicity

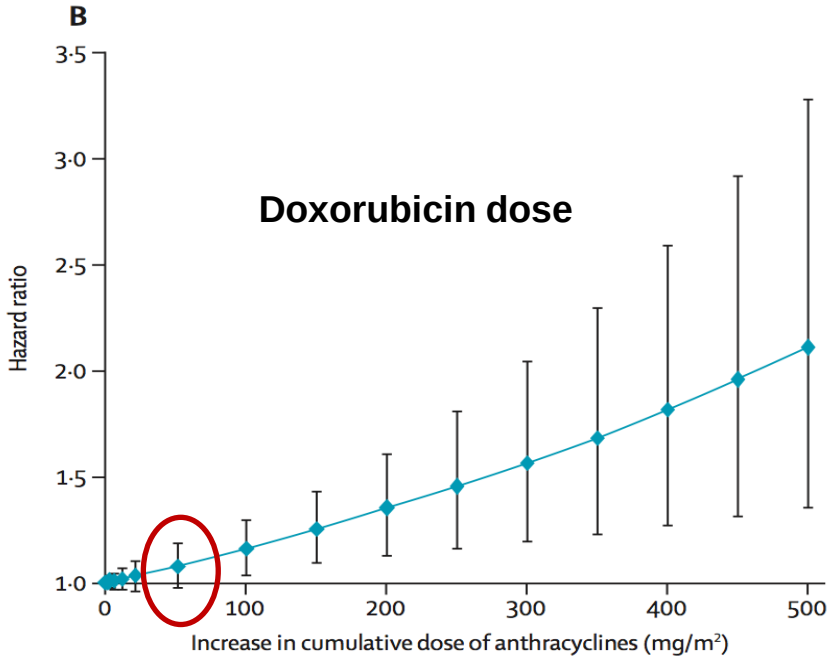
Choice of treatment should be based on expected toxicity

Advantage of CMT: less cardiac and/or haematological toxicity

Toxicity profile

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

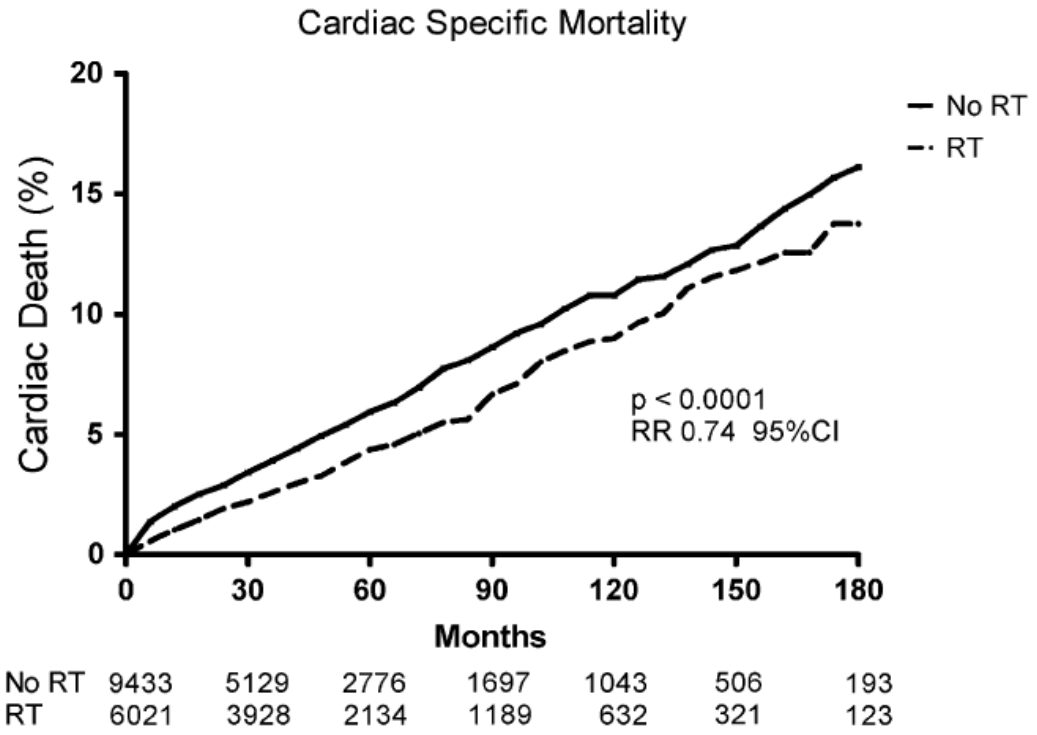




An increase in **mean heart dose of 5 Gy** yields the **same excess risk** of cardiac events as an increase in cumulative **anthracycline dose of 50 mg/m2** (≈ 1 cycle)

Maraldo et al., Lancet Haematol 2015

CARDIAC MORTALITY IN PATIENTS WITH STAGE I AND II DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AND WITHOUT RADIATION: A SURVEILLANCE, EPIDEMIOLOGY, AND END-RESULTS ANALYSIS



Increased Cardiac Death in Patients Treated without RT

SEER study: >65 – ES-DLBCL

Patients:

SEER database, 1541 pts (10 ys) median age 75
Stage 1-2, at least 2 cycles chemo, ±RT

Treatment:

78% RCHOP 30% RT
Pts who had RT: more likely to have
- stage 1
- EN sites
- fewer cycles of chemo (3 vs 6)

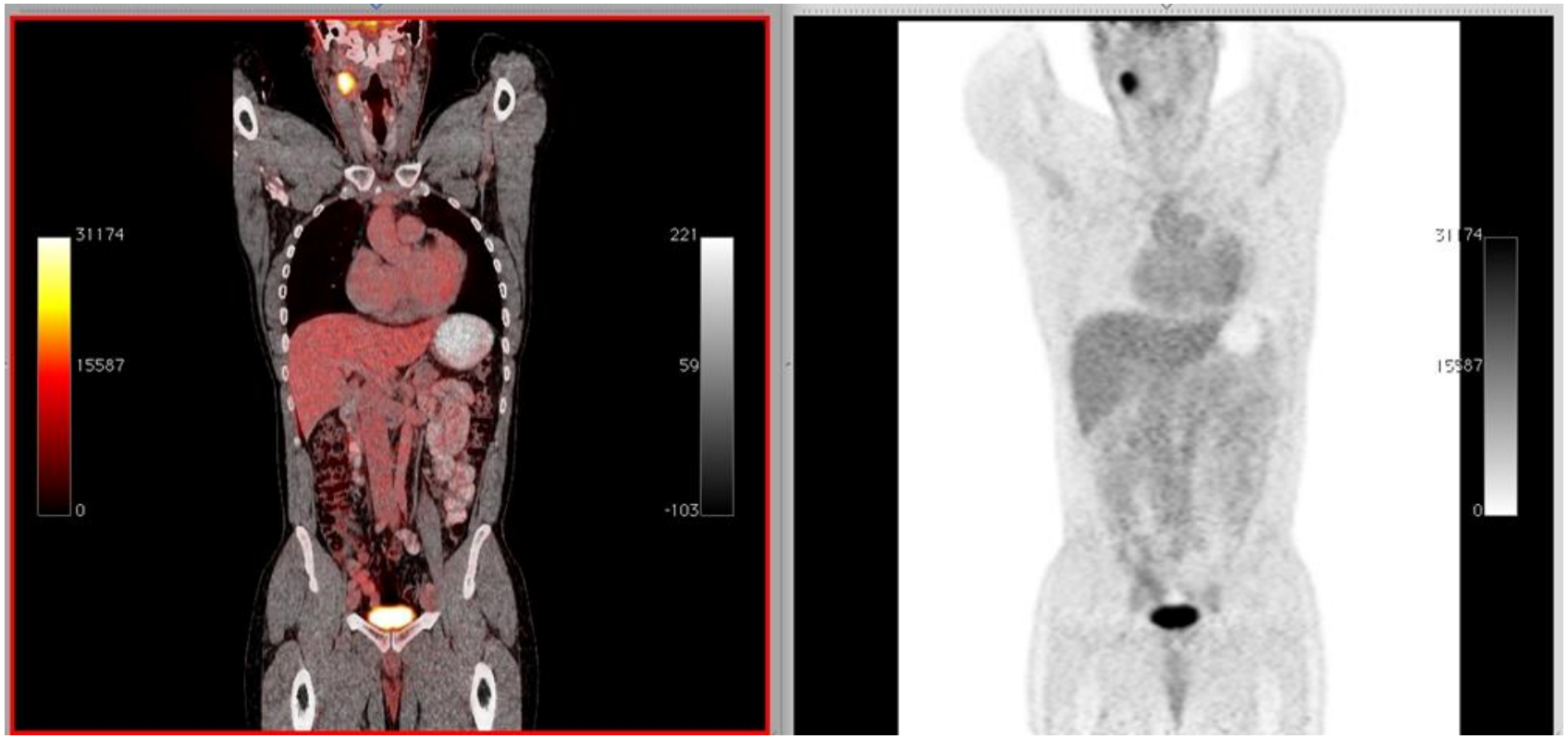
Outcome: pts who had RT:

Less febrile neutropenia
Less hospitalisation
Less thrombocytopenia + neutropenia
Equivalent survival

Elderly pts do better with less chemo and RT

Madden IJROBP 2018

Combined modality OR chemotherapy alone in early stage DLBCL in PET era

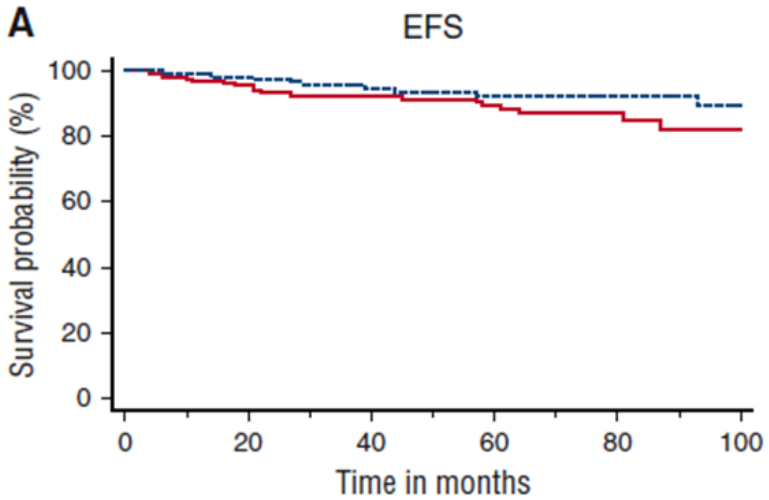


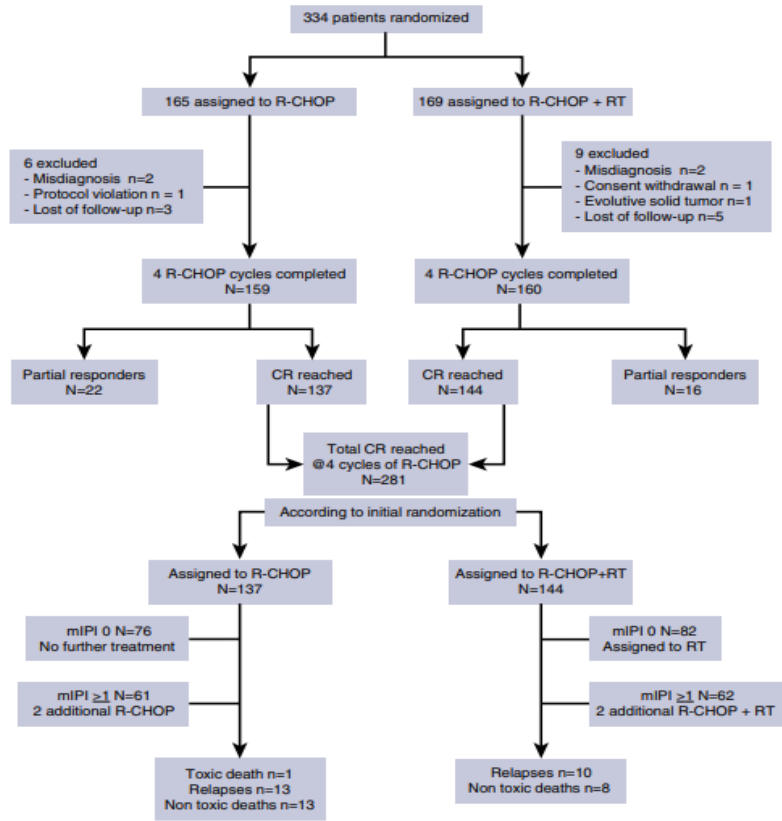
Is there (still) a role for RT in early stage DLBCL ?

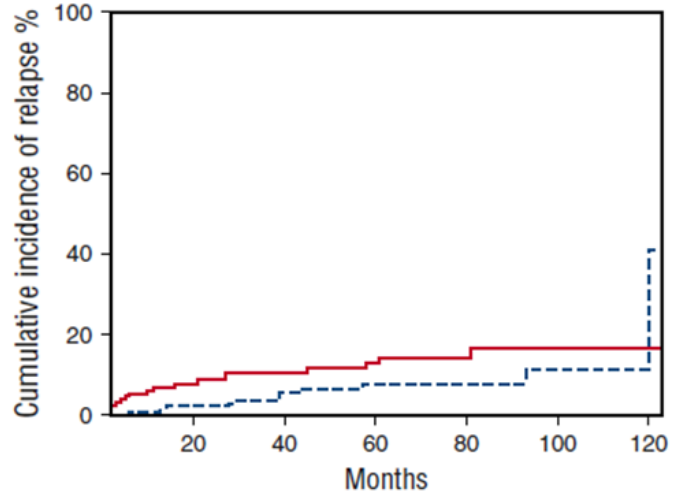
R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma

blood

R-CHOP alone (159 pts) vs. R-CHOP + 40 Gy IFRT (160 pts)







89% in R-CHOP arm vs.
92% in R-CHOP + RT arm
(p 0.18)

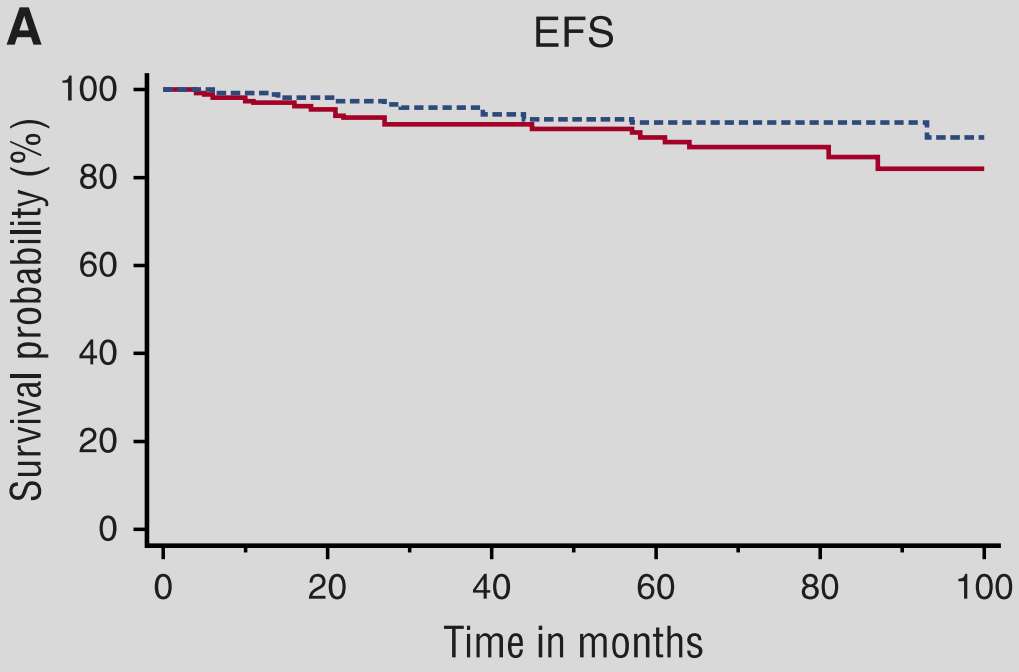
Median time to relapse was 21 months, with no difference between the 2 arms

R-CHOP alone is not inferior to R-CHOP followed by RT in patients with nonbulky limited-stage DLBCL

(Lamy et al., *Blood*, Aug 2018)

Chemotherapy can be safely de-escalated to **4-RCHOP** (without RT) in early stage DLBCL with **FAVOURABLE** features (**IPI 0-1**) achieving a **CMR after chemotherapy**

(Lamy et al., Blood 2018)



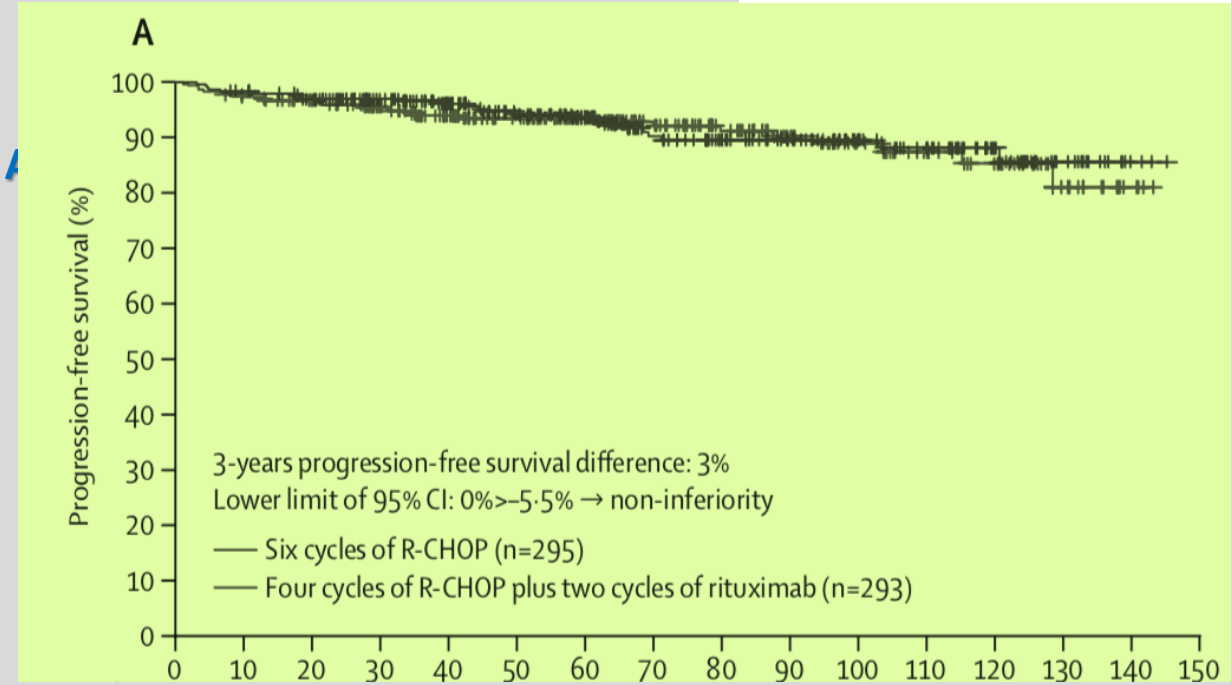
FLYER trial (DSHNHL group)

(Poeschel et al., Lancet 2019)

Very Favorable
(IPI=0, no bulk)

DSHNHL 2004-2

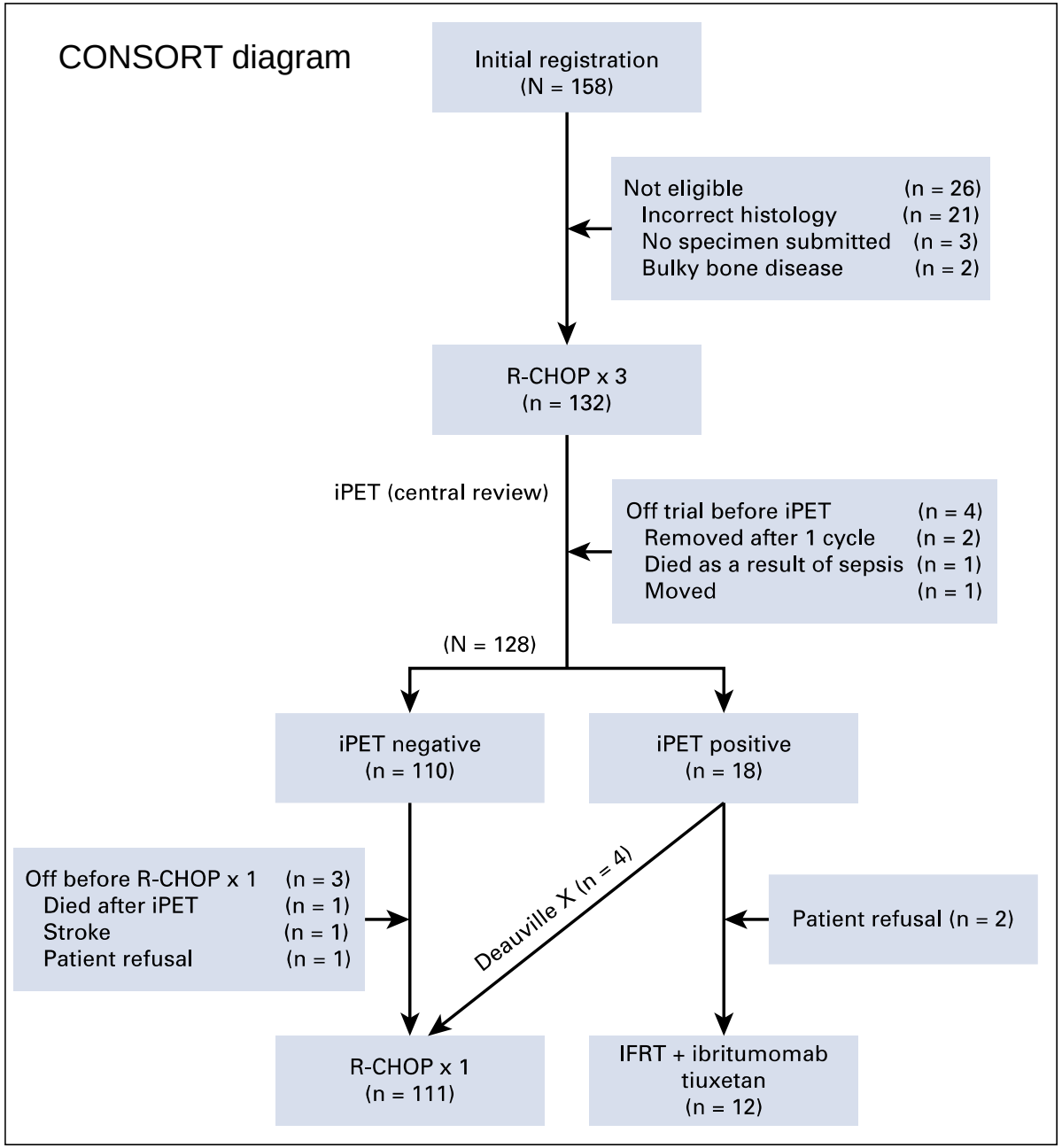
6 R-CHOP-21 x 4
vs
6 R-CHOP-21 x 6



ADDITIONAL BENEFIT FROM RT SEEMS UNLIKELY

Positron Emission Tomography–Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001

- 158 Stage I-II DLBCL
- Non-bulky disease (<10 cm)
- iPET after 3 cycles:
  - PET – patients → 1 more R-CHOP
  - PET + patients → IFRT + ibritumomab
- Primary endpoint: 5-year PFS
- Secondary endpoint: 5-year OS



Persky DO et al., JCO 2020

Positron Emission Tomography–Directed Therapy for Patients With Limited-Stage Diffuse Large B-Cell Lymphoma: Results of Intergroup National Clinical Trials Network Study S1001

CONCLUSION

To our knowledge, S1001 is the largest prospective study in the United States of limited-stage DLBCL in the rituximab era, with the best NCTN results in this disease subset. With PET-directed therapy, 89% of the patients with a negative iPET received R-CHOP × 4, and only 11% had a positive iPET and required radiation, with both groups having excellent outcomes. The trial establishes R-CHOP × 4 alone as the new standard approach to limited-stage disease for the absolute majority of patients.

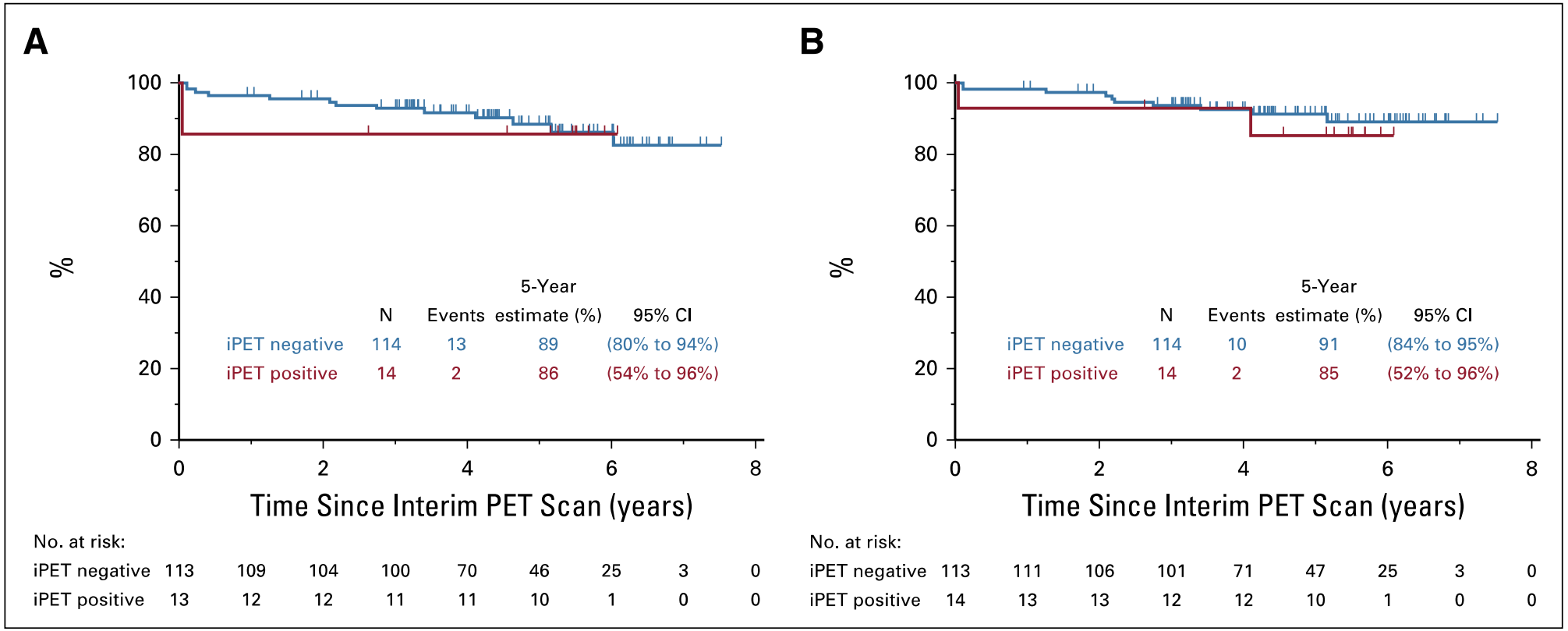


FIG 3. Landmark analysis at interim positron emission tomography (iPET)/computed tomography scan. (A) Progression-free survival. (B) Overall survival.

Persky DO et al. JCO 2020

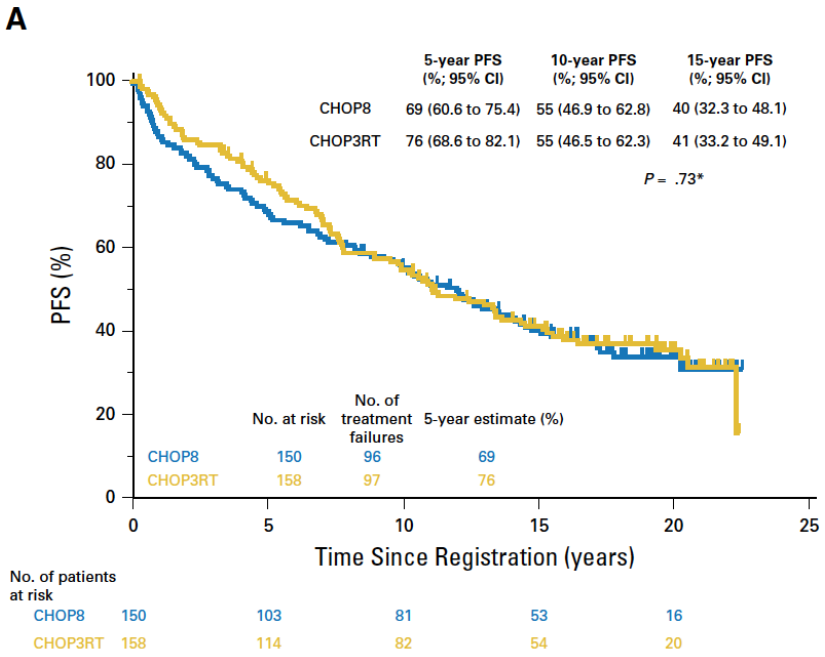
Conclusion: 4 R-CHOP alone is the new standard approach to limited stage DLBCL achieving complete metabolic response

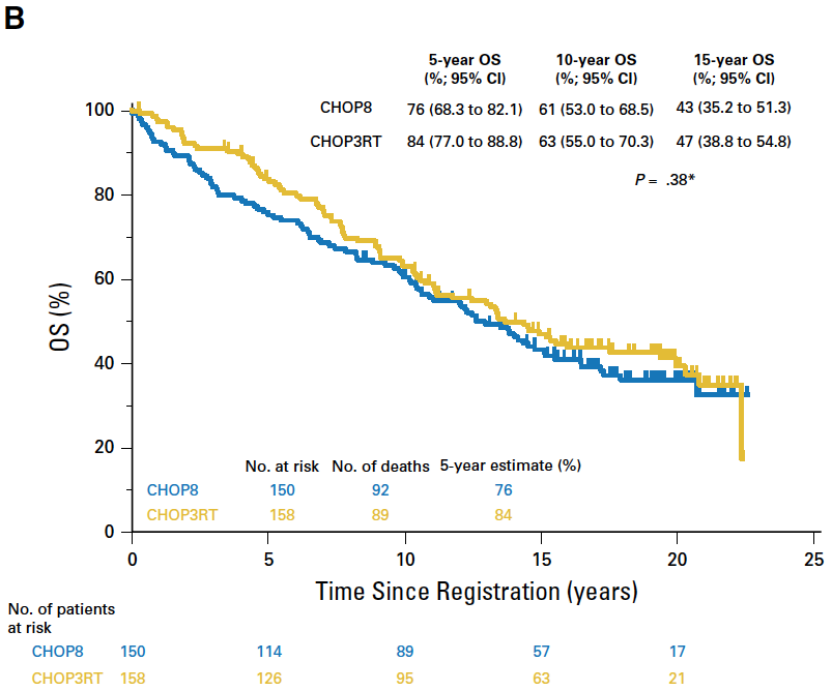
Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736

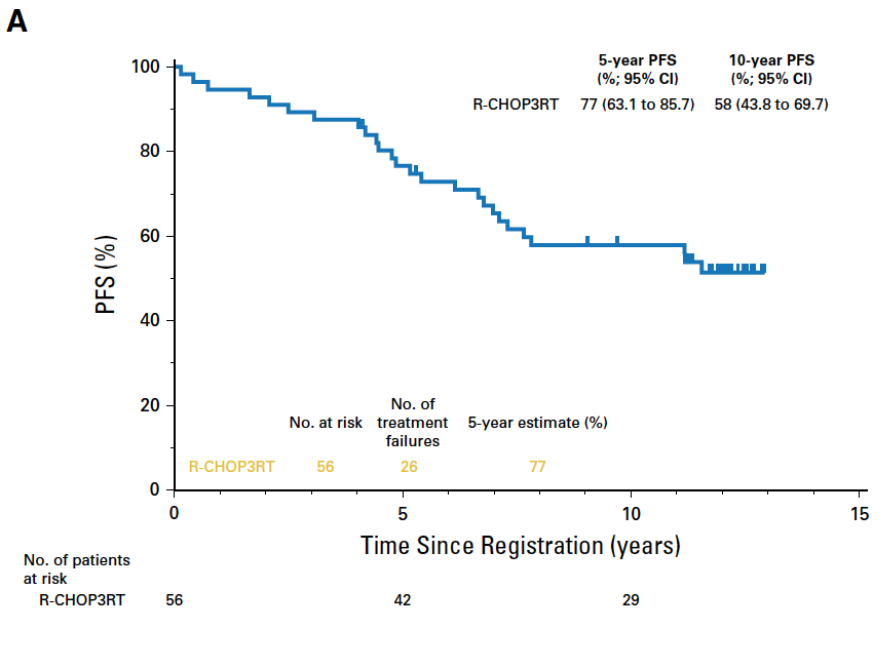
Deborah M. Stephens,

VOLUME 34 · NUMBER 25 · SEPTEMBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY







Conclusion

Although 5-year PFS and OS were improved after early analysis in patients with limited-stage DLBCL receiving CHOP3RT versus CHOP8, extended survival data showed similar PFS and OS, with continuous treatment failure. The addition of rituximab (S0014) to combined-modality therapy did not mitigate the continued relapse risk, underscoring the value of prolonged clinical trial patient observation and possible unique biology of limited-stage DLBCL.

Mean follow up:

- **FLYER: 66 months**
- **S1011: 58 months**

Which cases might benefit from RT?

Improve outcome:

- **Bulky disease**
- EN sites
  - Skeletal sites
  - Testicular
- Residual masses
- Incomplete response (PET) to chemo
- Salvage

Is Bulk still important in Rituximab era?

Bulk was significant at any cut off between 5 – 10 cm

Pfreundschuh 2008

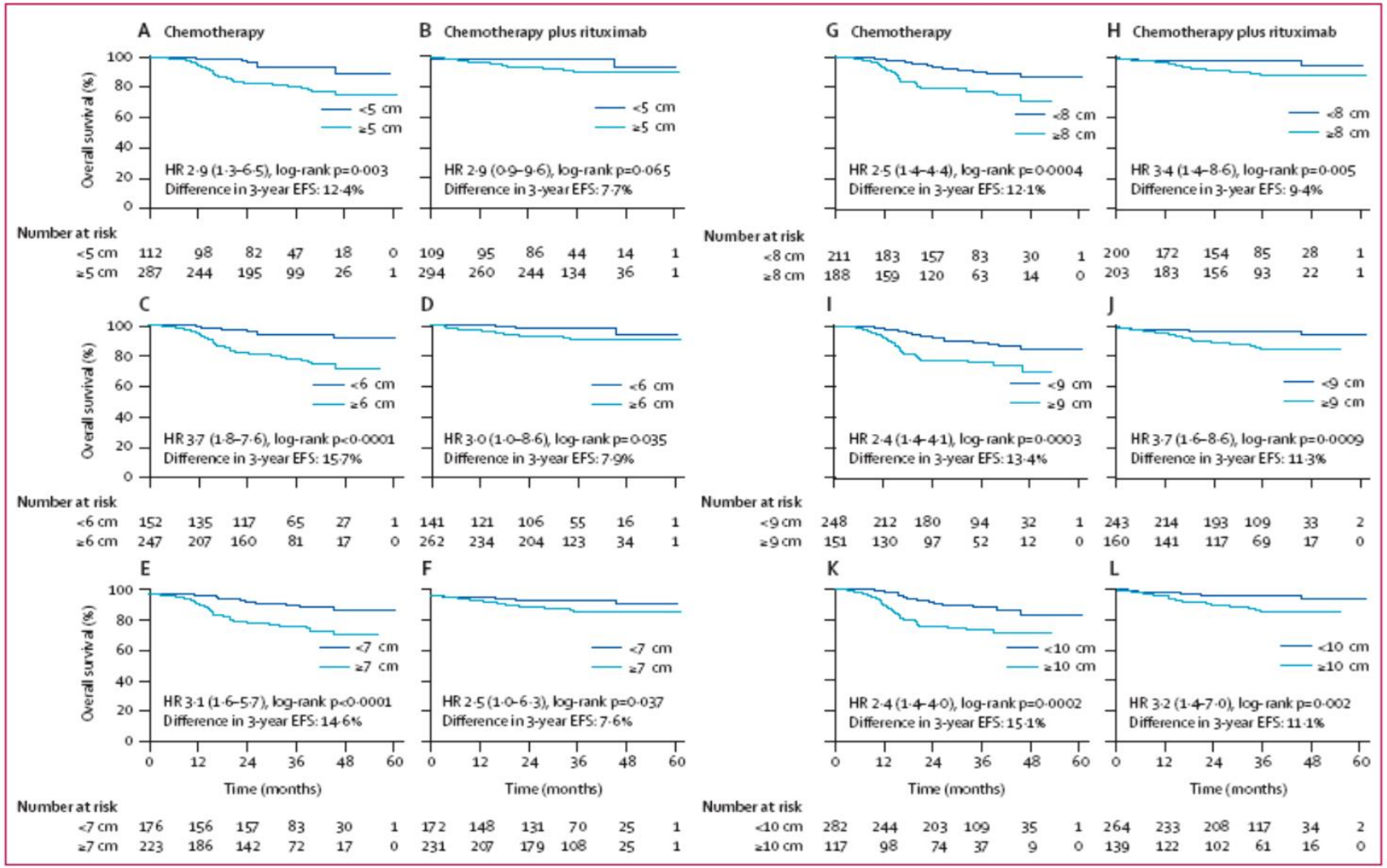
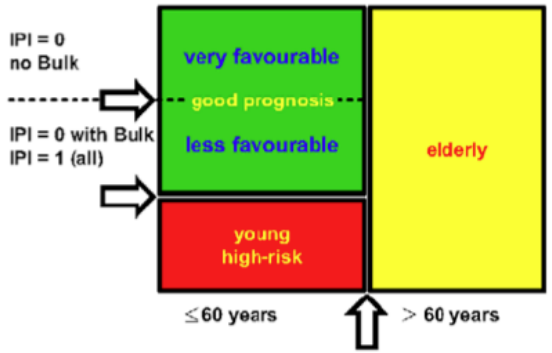


Figure 3: Overall survival of patients without bulky disease according to different cut-off points
The differences in overall survival between the bulky and non-bulky population after chemotherapy only (A, C, E, G, I, K) and after chemotherapy plus rituximab (B, D, F, H, J, L) are shown for cut-off points at 5 cm (A, B), 6 cm (C, D), 7 cm (E,F), 8 cm (G, H), 9 cm (I, J), and 10 cm (K, L).



Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: Results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA.

Less Favorable
(IPI=1 and/or bulk)

DSHNHL 2004-2

6 R-CHOP 21 x 6
vs
6 R-CHOP 14 x 6

2nd Random

IFRT 30GY

NO IFRT

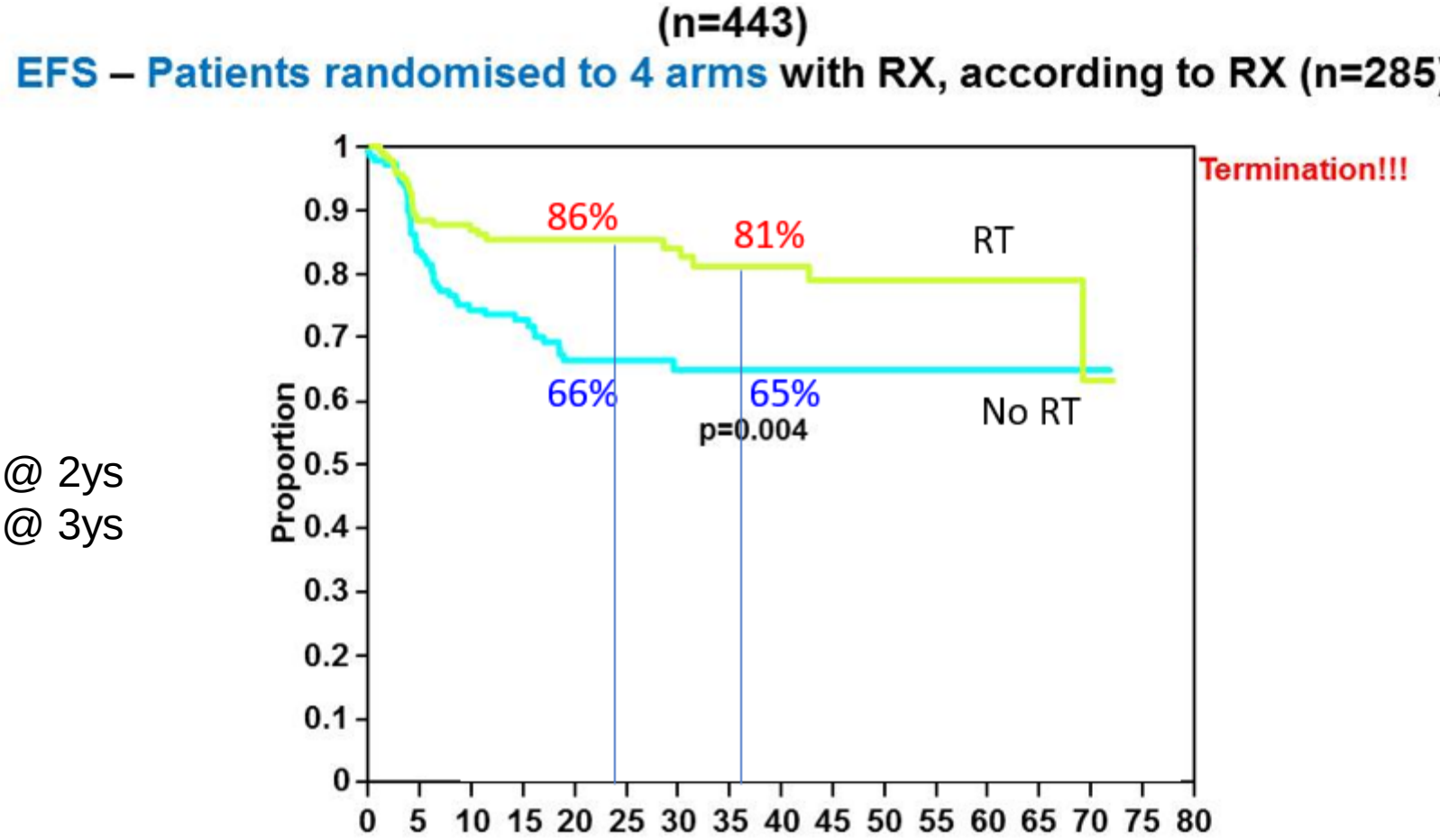
GERMAN HIGH-GRADE NON-HODGKIN'S LYMPHOMA STUDY GROUP*

* (supported by Deutsche Krebshilfe)

UNFOLDER – Trial initial results- RT v no RT

EFS

20% difference @ 2ys
16% difference @ 3ys



DSHNHL 01.07.12

Pfreundschuh, ASCO 2018

VOLUME 32 · NUMBER 11 · APRIL 10 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Gerhard Held, Niels Murawski, Marita Ziepert, Jochen Fleckenstein, Viola Pöschel, Carsten Zwick, Jörg Bittenbring, Mathias Hänel, Sibylla Wilhelm, Jörg Schubert, Norbert Schmitz, Markus Löffler, Christian Rübe, and Michael Pfreundschuh

no PET

COMPARISON between

RICOVER-60 -> RCHOP-14 x 6 + 2R + RT on bulky ≥ 7.5 cm

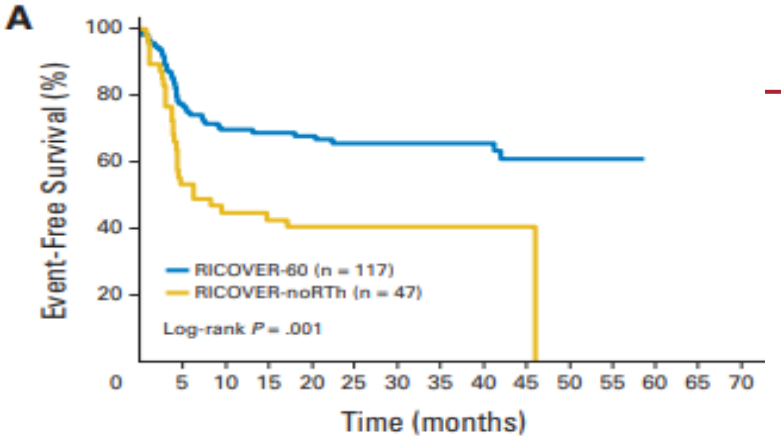
vs

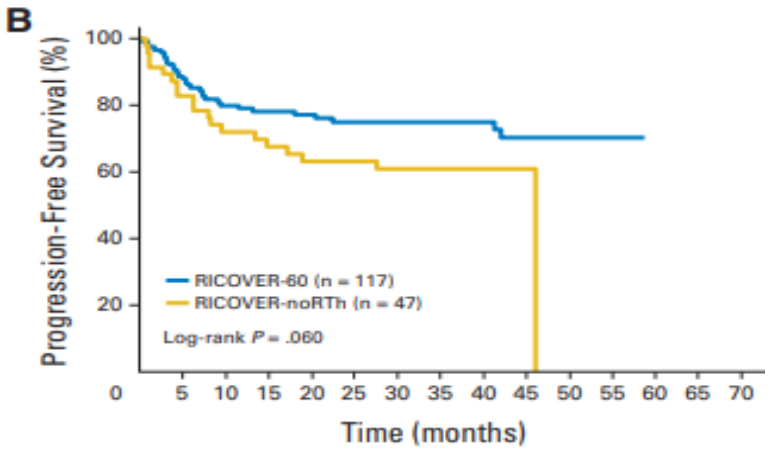
RICOVER-noRTh→ RCHOP14 x 6 + 2R – no RT

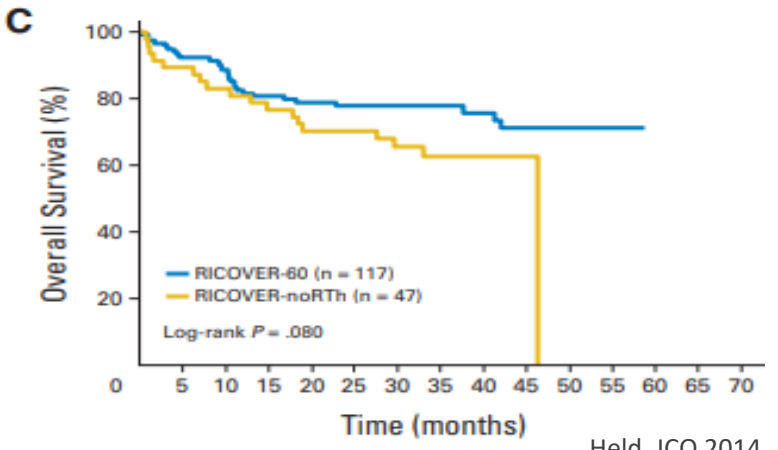
Table 3. Multivariable Per-Protocol Analysis of Patients With Bulky Disease

Variable	EFS HR	EFS 95% CI	EFS *P*	PFS HR	PFS 95% CI	PFS *P*	OS HR	OS 95% CI	OS *P*
RICOVER-noRTh *v* RICOVER-60	2.7	1.3 to 5.9	.011	4.4	1.8 to 10.6	.001	4.3	1.7 to 11.1	.002
LDH > normal	0.9	0.4 to 2.0	.728	0.6	0.2 to 1.7	.391	0.5	0.2 to 1.3	.161
ECOG PS > 1	1.4	0.6 to 3.4	.465	1.6	0.5 to 4.9	.439	1.0	0.3 to 3.5	.949
Extralymphatic involvement > one	1.3	0.5 to 3.4	.561	0.8	0.3 to 2.4	.664	0.9	0.3 to 2.8	.850
Stage III to IV disease	0.8	0.4 to 2.0	.684	1.2	0.5 to 3.4	.662	1.9	0.7 to 5.6	.230
Age > 70 years	2.2	1.1 to 4.5	.033	1.6	0.7 to 3.9	.271	1.8	0.7 to 4.6	.196

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; noRTh, no radiotherapy; OS, overall survival; PFS, progression-free survival; RICOVER-60, six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas.





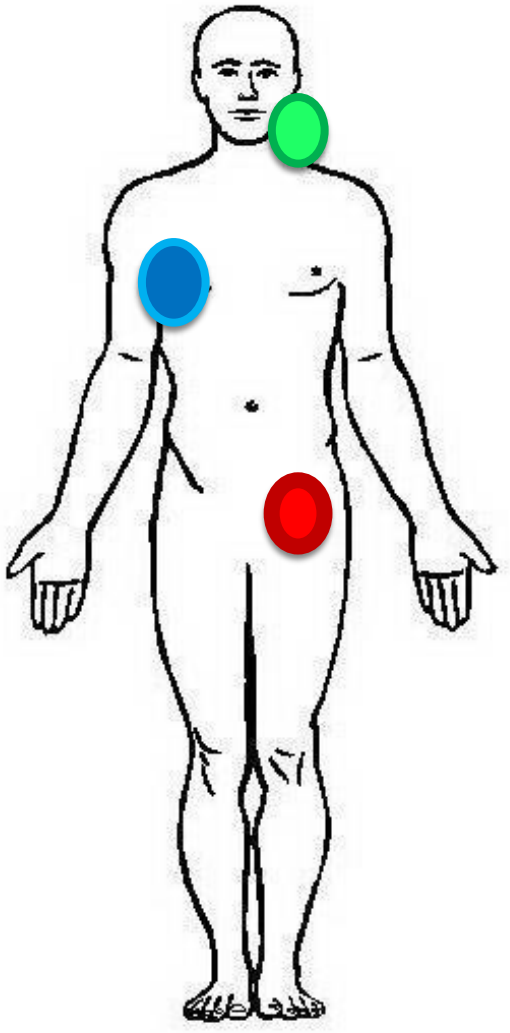


Held, JCO 2014

Some reasons for we should always consider consolidation ISRT to bulky sites

- Increases clinical outcomes according to the available retrospective literature data (LC, PFS and probably also OS)

Study	No of patients	% CR by PET	% receiving RT	Local Control		PFS / EFS		OS	
				RT	No RT	RT	No RT	RT	No RT
Emory Univ. (Shi 2013)	110	86%	13%	92%	49%	85%	44%	92%	69%
Duke Univ. (Dorth 2012)	79	83%	48%	92%	69%	85%	65%	85%	78%
MDACC (Phan 2010)	469	100%	30%	100%	NA	82%	59%	91%	68%



- Toxicity is modest for the following reasons:
  - Modern RT (ISRT concept, lower doses, modern techniques)
  - Anatomical sites of bulky disease in DLBCL

Which cases might benefit from RT?

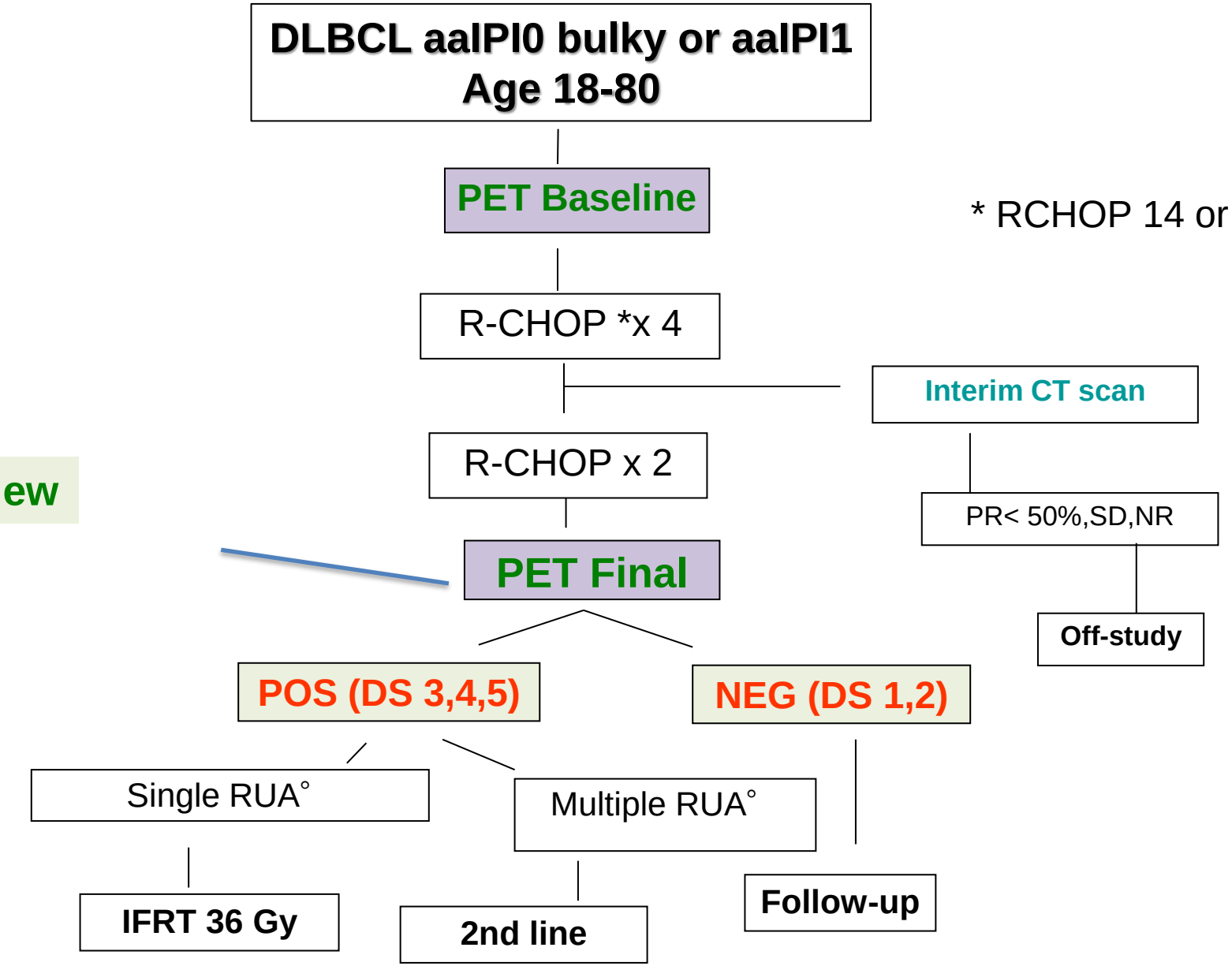
Improve outcome:

- Bulk
- EN sites
  - Skeletal sites
  - Testicular
- Residual masses
- **Incomplete response (PET) to chemo**
- Salvage

PET-driven radiotherapy (RT) in patients with low risk diffuse large B cell lymphoma (DLBCL): the DLCL10 multicenter phase 2 trial by **Fondazione Italiana Linfomi** (FIL)

Monica Balzarotti, Umberto Ricardi, Michele Spina, Andrea Evangelista, Alessandra Tucci, Federica Cavallo, Manuela Zanni, Annalisa Arcari, Vittorio Zilioli, Roberto Sartori, Francesco Merli, Francesca Re, Umberto Vitolo, Luca Melis, Maria Assunta Deidda, Gianluca Gaidano, Daniela Dessì, Marcello Rodari, Armando Santoro, Giovannino Ciccone, Stephane Chauvie, Maria Giuseppina Cabras

DLCL10 trial design



PET Central Review

* RCHOP 14 or RCHOP-21

° RUA = residual uptake area

Patient characteristics

Enrolled 115, **evaluable 110** not eligible 5
(1 consent withdrawal, 1 HBV+, 1 unsuitable IPI, 2 missing)

	IPI 0 bulky (N =16)	IPI 1 (+/- bulky) (N= 94)	Total (N=110)	
Median age	57.5	58	58 (22-78)	
Age >= 60	8	41	48	
Age >= 70	1	12	13	
Gender M/F	10/6	51/43	61/49	
AA stage I/ II/ III-IV (%)	5/11/0 (31/69/0)	15/23/56 (16/25/59)	20/34/56 (18/31/51)	
Bulky no/yes	0/**16**	75/**19**	75/ **35**	**Bulky 32%**
LDHr < 1/ > 1	15/1	79/24	84/25	1 missing
R-CHOP14/R-CHOP21	13/3	60/34	73/37	
Extranodal involvement	6	42	48	

Accrual period January 2012 – December 2017

RADIOTHERAPY

in 17 pts with single residual uptake site

POST-RT RESPONSE (N= 17, Bulky 13)			
PET post RT	IPI 0 bulky (N=8)	IPI 1 (N=9)	Total (N=17)
Negative	6 (71)	9 (100)	15 (88)
Positive	1 (14)	0	1 (6)
Not done	1 (14)	0	1 (6)

Radiotherapy was spared in approximately 50% of patients with bulky disease, on the basis of negative post-induction PET

Consolidation RT in patients with focal residual PET positivity allows an excellent prognosis

No relapse occurred in patients irradiated on single residual uptake area

Balancing the Therapeutic Ratio in DLBCL Requires Appropriate, Individualized Patient Selection Rather Than Broad Elimination of Radiation Therapy

Campbell, IJROBP 2022

Study	Eligibility	Study design	Treatment groups	Primary endpoint	Other notable findings
LYSA/GOELAMS trial 02-03(1)	PET-staged stage I or limited Stage II, and non-bulky (<7cm) DLBCL, age 18-75 years	Prospective, Phase 3, randomized, non-inferiority study (upper limit of 8%)	All patients received 4 cycles of R-CHOP-14 followed by a PET scan. Randomized to: (a) RT: 40Gy/20# consolidation IFRT, (b) No RT. For patients who did not achieve CMR after cycle 4: 2 additional cycles of R-CHOP+RT were delivered (both study arms).	5-year EFS: R-CHOP alone was not inferior to R-CHOP + RT (89% vs 92%, HR 0.61 CI, 0.3-1.2; P = 0.18).	5-year OS: not statistically different for R-CHOP alone vs R-CHOP + RT (92% vs 96%, HR 0.62; 95% CI, 0.3-1.5; P = 0.28). No local failures after RT. Severe acute toxicities were less common from RT than R-CHOP.
National Clinical Trials Network study S1001(13)	PET-staged stage I or II non-bulky (<10cm) high grade B-cell lymphoma.	Prospective, Phase 2, non-randomized study	All patients received 3 cycles of R-CHOP followed by iPET: (a) iPET-negative: 1 additional cycle of R-CHOP, (b) iPET-positive: IFRT plus ibritumomab tiuxetan and rituximab.	5-year PFS: similar for iPET-negative and iPET-positive (89% vs 86%).	5-year OS: similar outcomes for iPET-negative and iPET positive (91% vs 85%). No local failures after RT. No severe RT toxicities reported.
BC Cancer retrospective study(16)	Non-PET staged, advanced DLBCL: stage III/IV or stages I/II with B symptoms and/or bulky disease (≥10cm).	Retrospective analysis of a protocol-driven, population-based treatment strategy.	All patients received ≥6 cycles of R-CHOP, and EOT PET: (a) PET-negative: no further treatment, (b) PET-positive: considered. for consolidation ISRT (received by 53%)	3-year TTP: favored the PET-negative group, 83% vs 56% for PET-positive (p<0.001).	3-year OS: favored the PET-negative group, 87% vs 64% for PET-positive (p<0.001). PET-positive patients who received RT had similar outcomes to PET-negative patients, but poorer outcomes were observed for PET-positive patients who did not receive RT (3-year OS, 80% vs 87% vs 44%, respectively). No toxicity data reported.

Which cases might benefit from RT?

Improve outcome:

- Bulk
- EN sites
  - Skeletal sites
  - Testicular
- Residual masses
- Incomplete response (PET) to chemo
- **Salvage**

John Plastaras

ILROG Multicenter Retrospective Review of CAR T Therapy and Radiotherapy for r/r BCL

Eligibility: Patients with r/r aggressive B-cell lymphoma undergoing leukapheresis for commercial CAR T therapy at any of the participating institutions between 01/2018 and 12/2020, either treated with or without bridging radiotherapy (RT)

- Penn, Moffitt, UCSF, UW, City of Hope, Minnesota, MSK, MDACC, Wash U, URMC, Ohio State (DUA pending)

Main Cohorts:

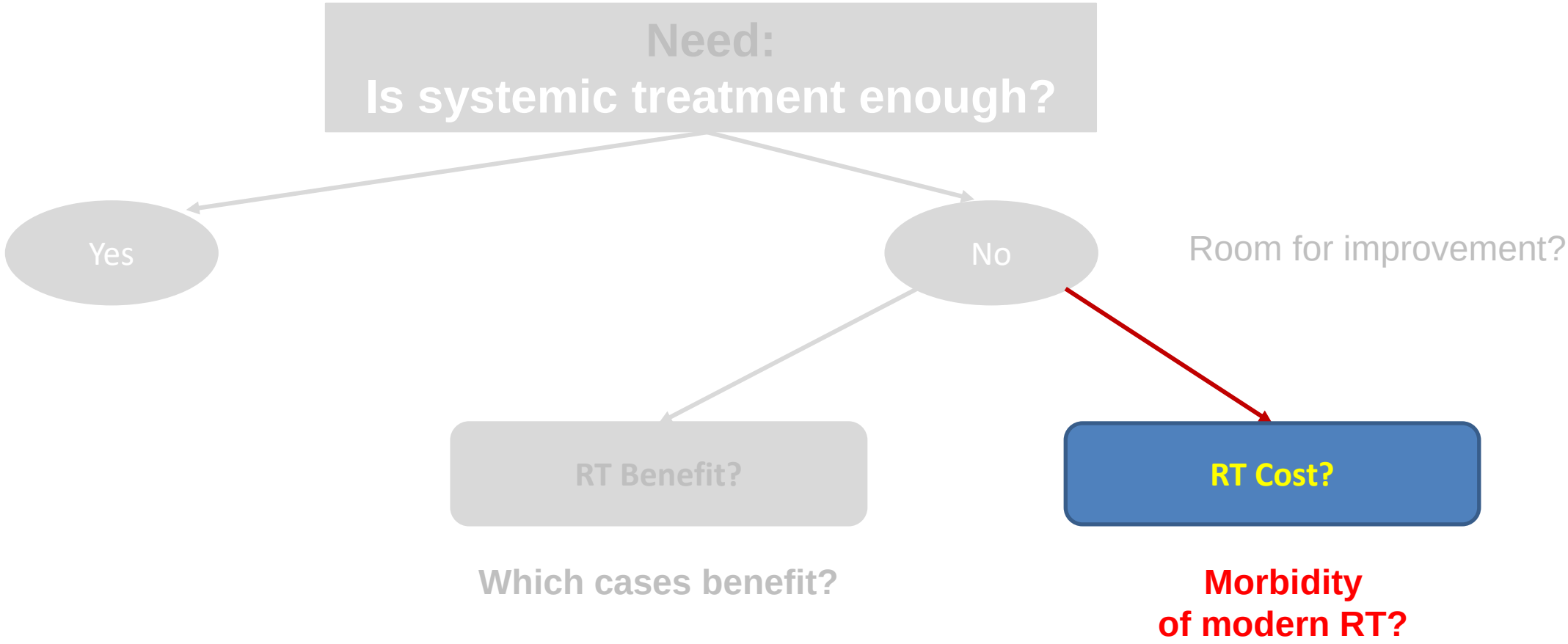
1. **Patients who received CART with bridging RT** (within 30d of leukapheresis)
2. Patients who received CART with or without bridging RT – more challenging to collect non-RT pts

Presentations:

- ASH 2022 abstract, Cohort 1 - 77 pts from 4 institutions (Penn, Moffitt, UCSF, UW)
- ASTRO 2023 abstract (submitted), Cohort 1 – 115 pts from 6 institutions (the above + City of Hope, Minnesota)

Timeline:

- Hope to pool data from remaining centers by 06/2023, prior to publication


Need:
Is systemic treatment enough?
Yes
No
Room for improvement?
RT Benefit?
RT Cost?
Which cases benefit?
Morbidity
of modern RT?

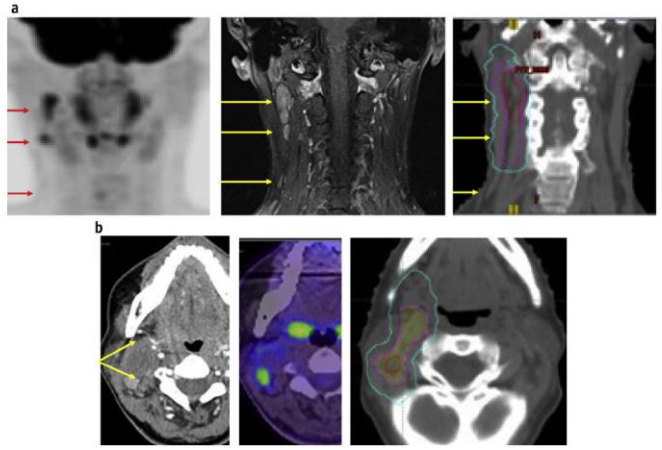
Modern RT

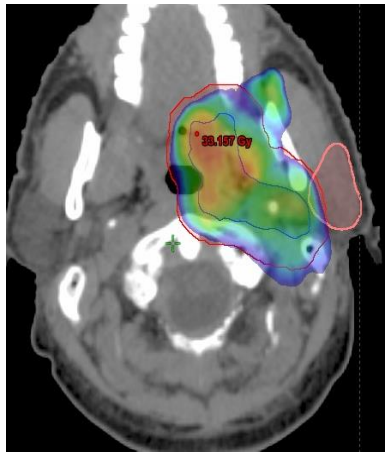
Smaller volumes: ISRT (as defined by ILROG guidelines)

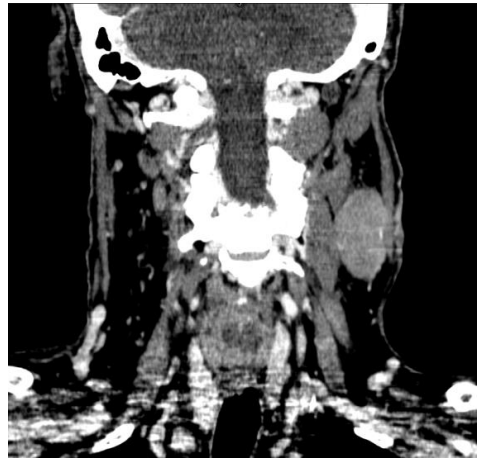
Lower doses: 30 Gy (compared to old doses of 40-45 Gy)

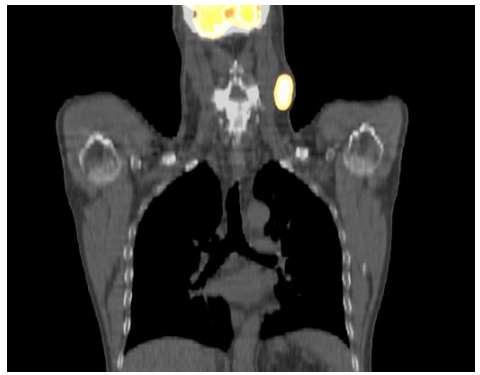
More targeted: IMRT and IGRT

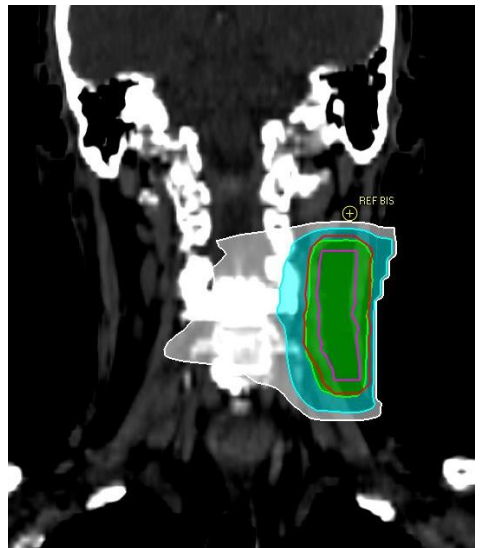
less doses to organs-at-risk









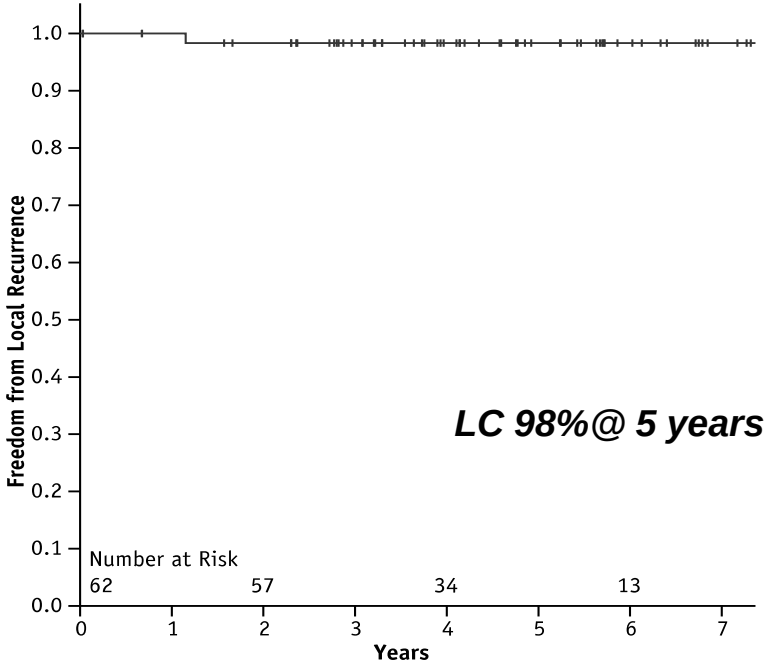


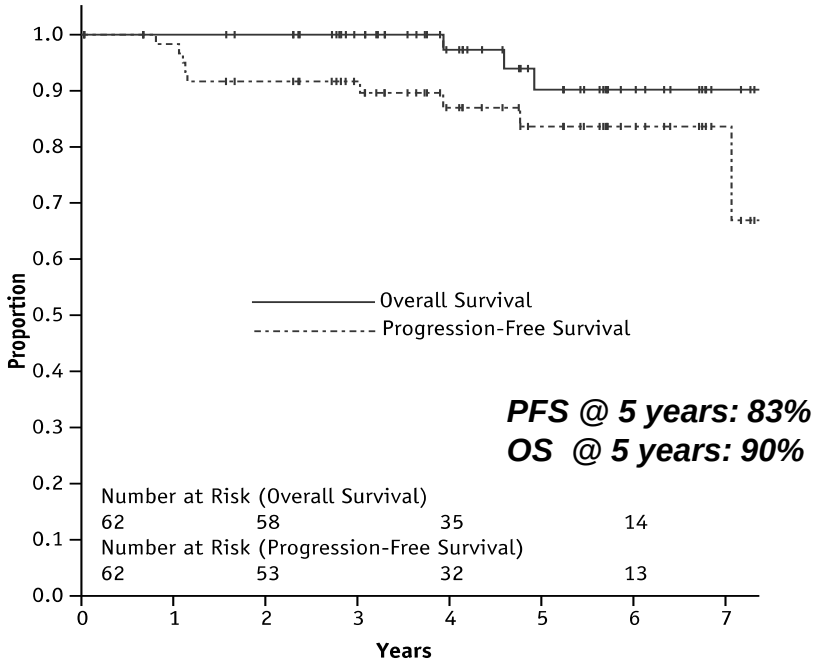
More accurate & safer

…further reduction of consolidation RT dose (20 Gy)

Phase 2 Study of Dose-Reduced Consolidation Radiation Therapy in Diffuse Large B-Cell Lymphoma

- 62 DLBCL/PMBCL patients (stage I-IV)
  - 50 (81%)
  - 12 (19%)
- >3 cycles of R-CHOP (median: 6)
- Median tumor size: 5.7 cm
  - Bulky >7.5 cm: n = 23 (40%)
  - Bulky >10 cm: n = 16 (28%)
- **RT dose: 20 Gy**
- Primary endpoint: LC
- Secondary endpoints: PFS, OS





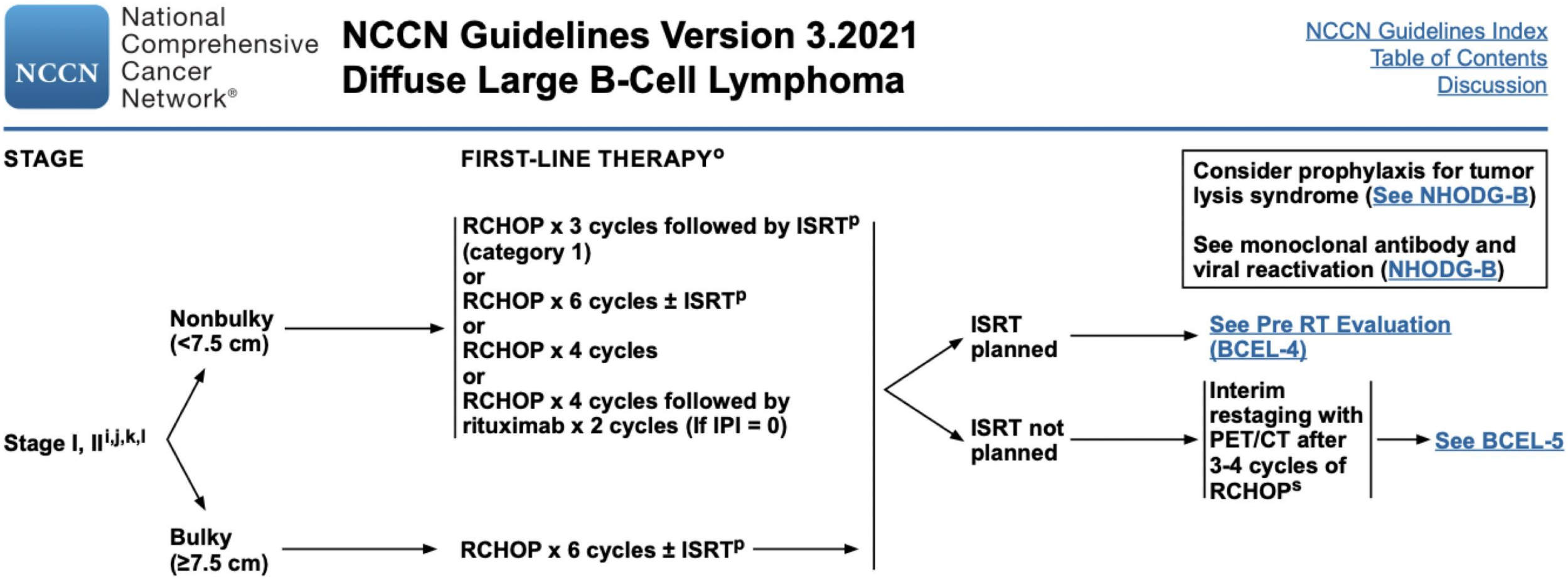
Kelsey et al. IJROBP 2019

Phase II study of Dose-Reduced Consolidation Radiation Therapy in Patients with Diffuse Large B-cell Lymphoma

- ❑Single arm study
- ❑Population: DLBCL (not PMBCL)
- ❑Accrual goal: **240 patients**
- ❑Complete metabolic response after R-CHOP (DS 1-3)
- ❑Dose of ISRT: **20 Gy**
- ❑Primary endpoint: LC
- ❑Secondary endpoints: PFS, OS

- **Duke University**
- **SingHealth**
- **Dana Farber/BWH**
- **Mayo Clinics**
- **MD Anderson Cancer Center**
- **Yonsei University (Korea)**
- **Juntendo University (Japan)**
- **Wilmot Cancer Center**
- **Turin University**

Which is the current Treatment Strategy?



Radiation Therapy After R-CHOP for Diffuse Large B-Cell Lymphoma: The Gain Remains

Joachim Yahalom, *Memorial Sloan-Kettering Cancer Center, New York, NY*

JOURNAL OF CLINICAL ONCOLOGY

- This variety of options in the NCCN guidelines may make everybody happy, but it could be confusing to the nonexpert

- In reality, many hematologists/oncologists simply extend the chemotherapy course and omit radiotherapy (RT)

Treatment of patients with DLBCL requires multidisciplinary collaboration to ensure optimal outcome (with patient selection and treatment personalization being the key)

Primary indications for RT in first-line management of DLBCL

- Consolidation RT as a chemotherapy minimization strategy
- Consolidation RT to sites at higher risk of local recurrence (bulky, EN disease)
- Consolidation RT to convert incomplete metabolic responses to complete responses