# Role of consolidation RT in early and advanced stage DLBCL in the PET era

## 4th ILROG Educational Meeting, London 2023

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ILROG
INTERNATIONAL LYMPHOMA
RADIATION ONCOLOGY GROUP

# Disclosures
# trip to Isle of Skye (Quiraing)

# ILROG MELBOURNE 2017- same enthusiasm, less grey hair

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

DAILY NEWSPAPER OF THE YEAR

# THE TIMES

Monday September 4 2017 | thetimes.co.uk | No 72319

Only £1 to subscribers £1.60

## the game

12-PAGE PULLOUT
HENRY WINTER
ON ENGLAND'S
BIG NIGHT

## How to stay alive in Silicon Valley Times2

**Radiotherapy not needed after CMR to RCHOP for DLBCL**

## May reins in Tory rebels with fear of reshuffle

Matt Chorley Red Box Editor

Theresa May is using the threat of a reshuffle to bring Tory troublemakers into line as she seeks to tighten her grip on Downing Street.

Conservative Campaign Headquarters had expected the prime minister to overhaul jobs in the government after the party conference next month.

However, she is now thought more likely to delay the shake-up, using her ability to reward supporters and punish rebels to reassert her authority after angering some MPs by vowing to lead the party into the next election.

The threat will be seen as an attempt to rein in ministers with whom No10 has clashed, including Sajid Javid, the communities secretary, Andrea Leadsom, the Commons leader, and Liam Fox, the international trade secretary.

Tom Parfitt Moscow

Donald Trump left open last night

best route. "It is of course right to say that all options are on the table,

**The increasingly prevalent view is that RT is unnecessary following a CMR to RCHOP**

***"It's old news, the science is settled …. time to move on!"***

My task is to take a fresh/critical look at this and ask how robust is this conclusion

**I WONT PROVIDE** definitive evidence of benefit of RT (appropriate study yet to be done)

**I HOPE TO SHOW**

- that a benefit from RT has not really been entirely excluded by existing studies
- RT should continue to be considered for selected patients in CMR after RCHOP

1. Set context with brief review evidence for efficacy of RT

   (Nodal disease only – extra nodal disease discussed in a separate lecture)

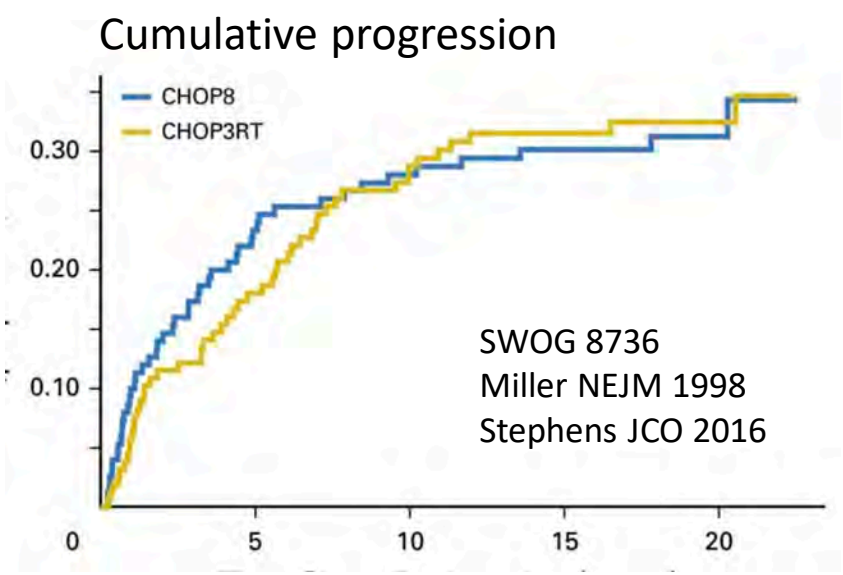
2. Review studies questioning role of RT after PET CMR- potential limitations /uncertainties?

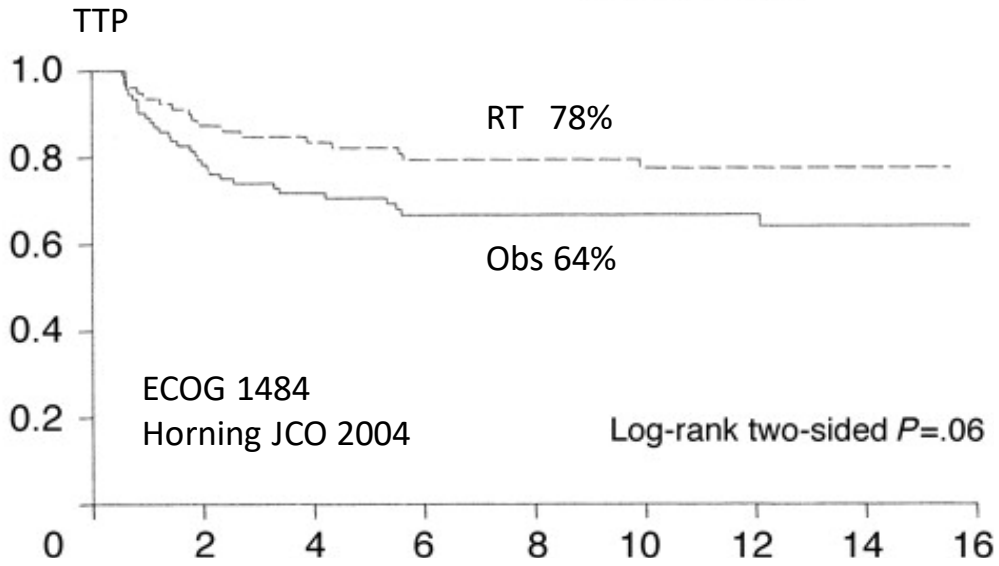
3. Offer an approach to clinical decision making in the face of imperfect data/clinical uncertainty

# Combined modality approach for stage I-II was established in the CHOP era

SWOG 8736: 3 CHOP + RT equivalent efficacy to 8 CHOP with significantly less toxicity

ECOG1484: RT improved TTP after 8 CHOP

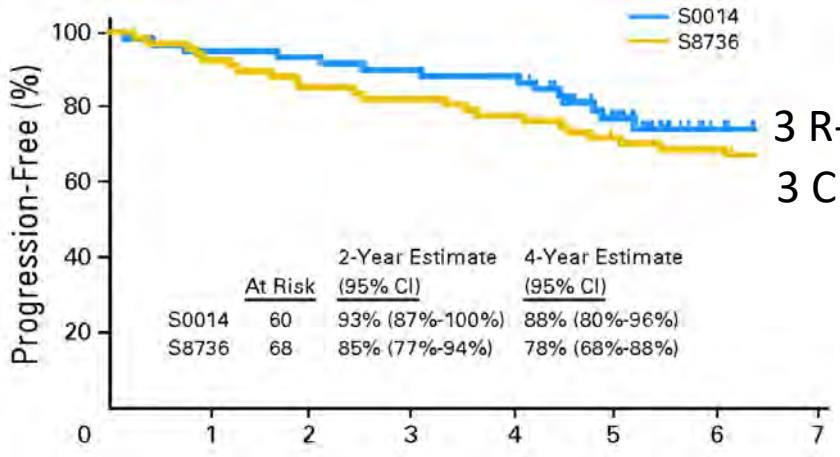


# For favourable disease (stage I-II, non bulky) in the RCHOP era: Two reasonably effective options-80-90% cure rate

3 RCHOP + RT

88% 4 yr PFS



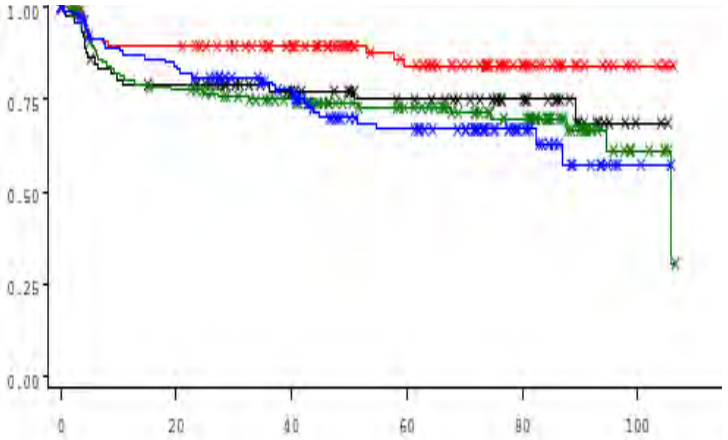

3 R-CHOP + RT

3 CHOP + RT

SWOG 0014 Persky JCO 2008

6 RCHOP

83% 5 yr PFS




< 5 cm , IPI 0

MINT Pfreundschuh 2011

# For bulky/advanced disease: RT after 6 RCHOP

| Study | n | Stage | %PFS/EFS RCHOP + RT | | PFS /EFS HR | MVA | OS HR | P MVA |
|---|---|---|---|---|---|---|---|---|
| UNFOLDER Thurner 2023 | 285 | 1- 4 | **68** | **84** | | **0.0012** | | |
| RICOVER Held 2014 | 113 | 1-4 | **62** | **88** | 0.23 | 0.001 | 0.23 | 0.002 |
| MDACC Phan 2010 | 469 | 1-4 | **68** | **82** | 0.19 | 0.0001 | 0.32 | 0.0001 |
| ILSG Marcheselli 2011 | 182 | 1-4 | **56** | **85** | 0.33 | 0.044 | 0.39 | NS |
| Duke Dorth 2012 | 79 | 3-4 | **65** | **85** | 0.23 | 0.014 | 0.48 | NS |
| Chicago Shi 2013 | 110 | 3-4 | **44** | **85** | 0.10 | 0.024 | 0.17 | NS |
| Seoul Kwon 2015 | 198 | 1-2 | **83** | **94** | 0.23 | 0.021 | 0.15 | 0.014 |

Randomised phase 3

Sequential prospective

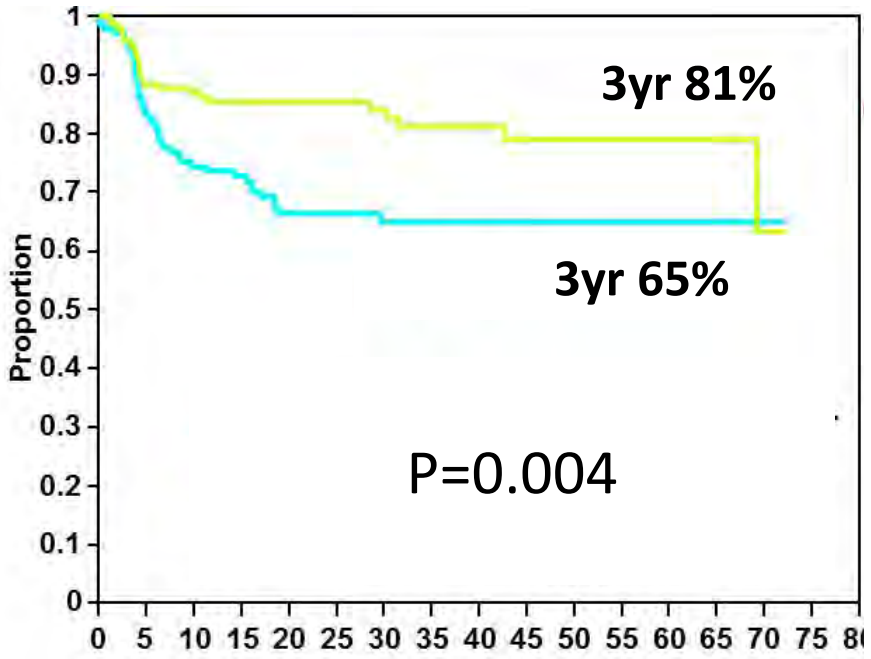
Retrospective

# Prospective randomised “UNFOLDER“ trial- initial report

285 patients, age < 60 yr
IPI 1
IPI 0 + bulk >7.5 cm

6 R-CHOP 14 v 21

Bulk or EN → RT
Bulk or EN → Observation

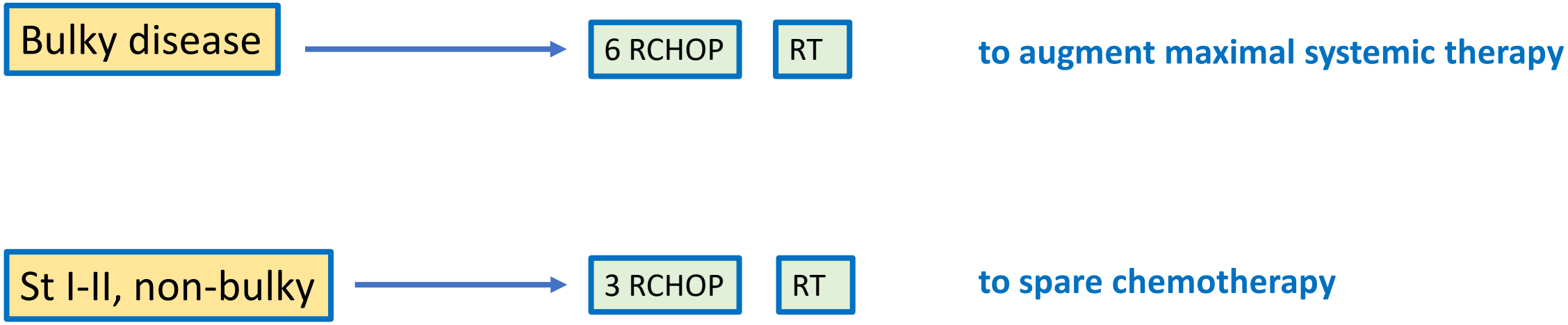



Treatment arms without radiotherapy were closed after planned interim analysis 2012

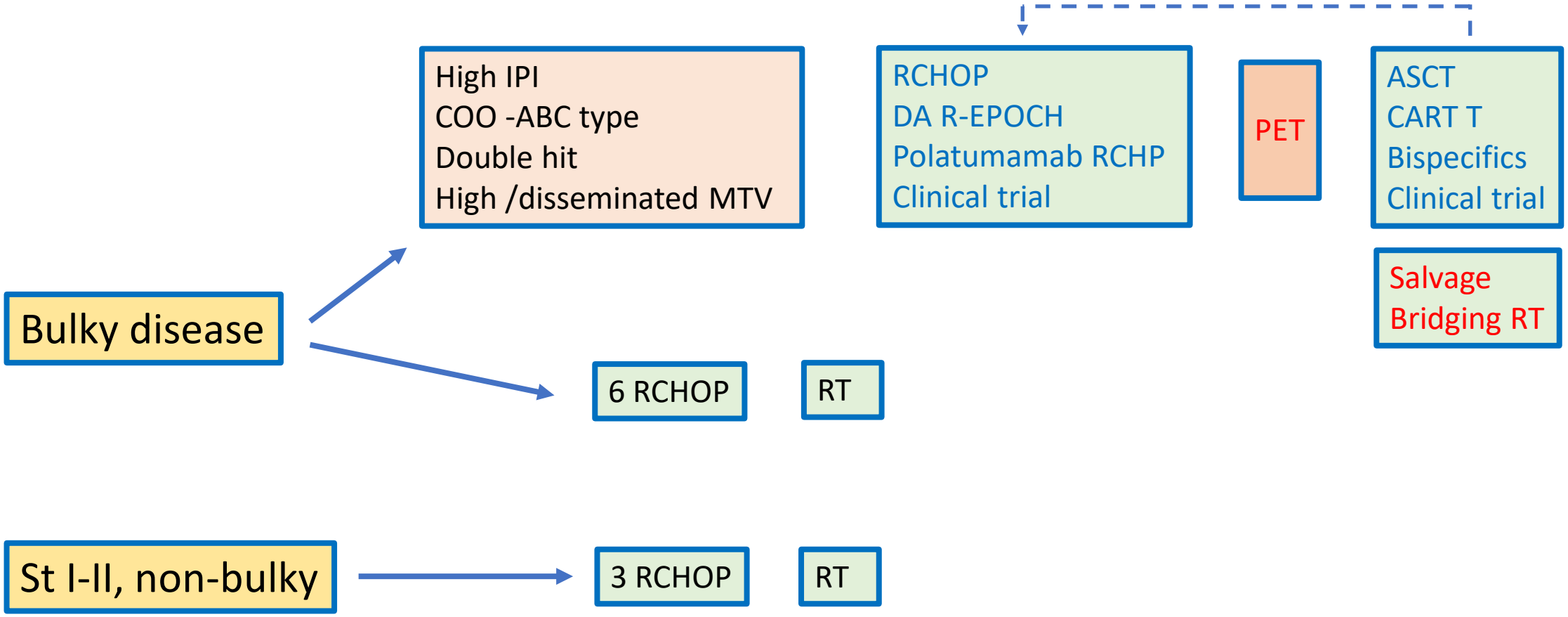
These interim results were interpreted as supporting routine use of adjuvant RT after 6 RCHOP

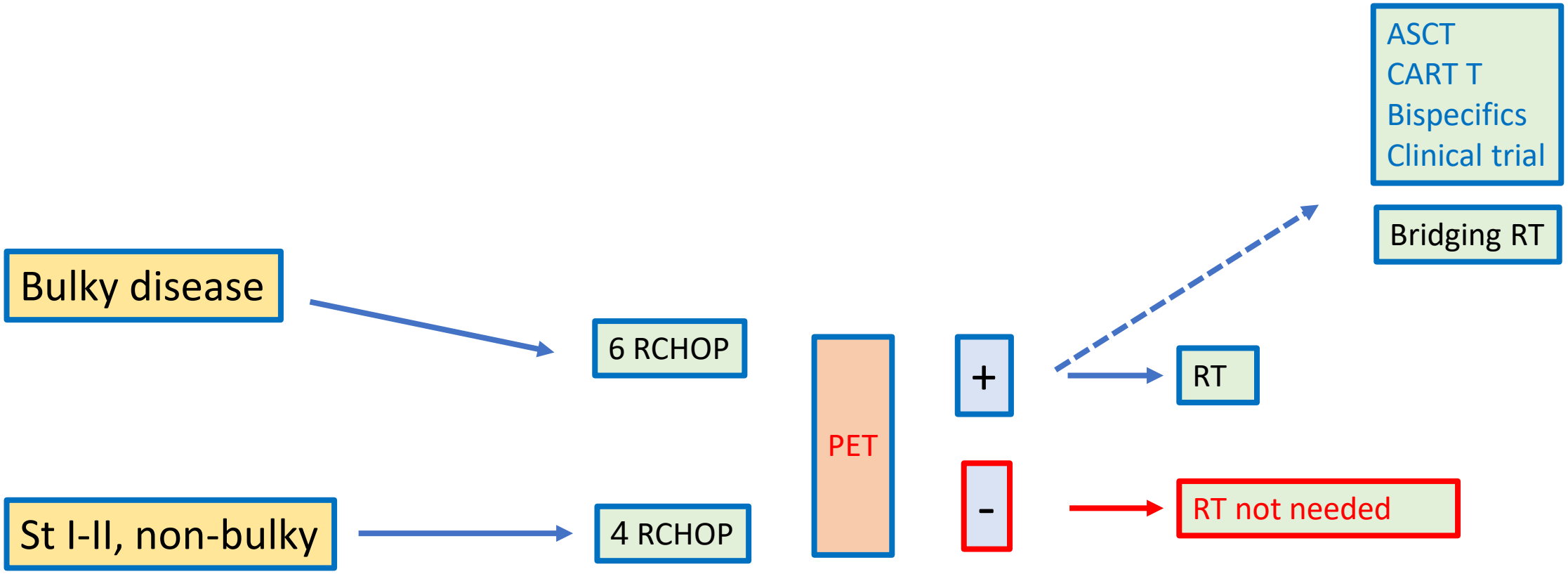
Previous status quo

RT had an accepted role in two settings (though not unquestioned)

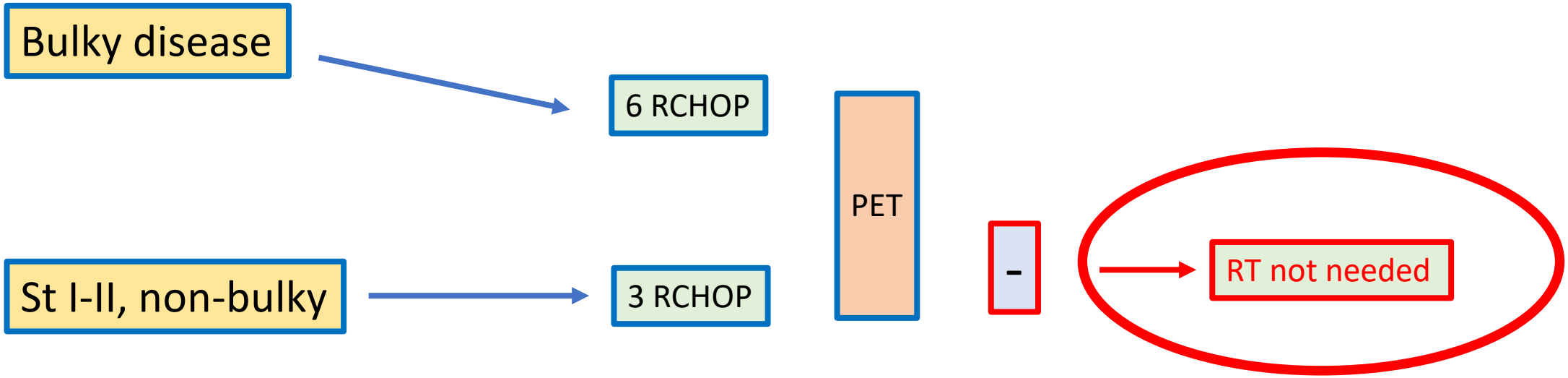


# The current management landscape has become more complex with better prognostic tools, more first-line options, more salvage options and PET




Bulky disease
St I-II, non-bulky
6 RCHOP
4 RCHOP
PET
+
-
ASCT
CART T
Bispecifics
Clinical trial
Bridging RT
RT
RT not needed

What is evidence regarding RT in PET -ve patients?



Favourable st I-II

Motivation was to minimize toxicity by avoiding RT and reducing RCHOP exposure

Five key studies asked whether 4 RCHOP alone sufficient

# *Five key studies*

| Study | Question addressed/design | Treatment |
|---|---|---|
| FLYER<br>Poeschel 2018 | Is 4 RCHOP = 6 RCHOP<br>*Randomised* | 4 RCHOP + 2R (No PET)<br>6 RCHOP |
| LYSA LNH 091B<br>Bologna 2021 (abstr) | | 4-6 RCHOP (PET guided)<br>6 RCHOP |
| Vancouver<br>Sehn 2019 (abstr) | Is 4 RCHOP "good enough"<br>*Prospective policy or protocol* | 4 RCHOP (PET-)<br>3 RCHOP +RT (PET+) |
| Intergroup S1001<br>Persky 2020 | | 4 RCHOP (PET-)<br>3 RCHOP +RT/RIT (PET+) |
| LYSA/GOELAMS 0203<br>Lamy 2018 | Is RT beneficial after CMR to 4-6 RCHOP<br>*Randomised* | 4-6 RCHOP 14 (PET-)<br>+/- RT |

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# *Five key studies*

| Study | Question addressed/design | Treatment | N | Size | PET CR |
|---|---|---|---|---|---|
| FLYER<br>Poeschel 2018 | Is 4 RCHOP = 6 RCHOP<br>*Randomised* | 4 RCHOP + 2R (No PET)<br>6 RCHOP | 297<br>295 | 7.5 cm | n/a |
| LYSA LNH 091B<br>Bologna 2021 (abstr) | | 4-6 RCHOP (PET guided)<br>6 RCHOP | 319<br>331 | 10 cm | DS 1-3<br>cycle 2 |
| Vancouver<br>Sehn 2019 (abstr) | Is 4 RCHOP "good enough"<br>*Prospective policy or protocol* | 4 RCHOP (PET-)<br>3 RCHOP +RT (PET+) | 254<br>59 | 10 cm | DS 1-2<br>cycle 3 |
| Intergroup S1001<br>Persky 2020 | | 4 RCHOP (PET-)<br>3 RCHOP +RT/RIT (PET+) | 111<br>12 | 10 cm | DS 1-3<br>cycle 3 |
| LYSA/GOELAMS 0203<br>Lamy 2018 | Is RT beneficial after CMR to 4-6 RCHOP<br>*Randomised* | 4-6 RCHOP 14 (PET-)<br>+/- RT | 137<br>144 | 7 cm | qual<br>cycle 4 |

# Consistent finding of around 90% 3-5 year PFS

Common take-away message:
"4 RCHOP without RT is sufficient for non-bulky st I-II DLBCL in CMR"

Does this apply to all non bulky cases?

| Study | Treatment | %PFS | |
|---|---|---|---|
| FLYER | 4 RCHOP + 2R (No PET)<br>6 RCHOP | 96% 3y<br>93% 3y | |
| LYSA LNH 091B | 4-6 RCHOP (PET guided)<br>6 RCHOP | 92% 3y<br>89% 3y | Abstract only |
| Vancouver | 4 RCHOP (PET-)<br>3 RCHOP +RT (PET+) | 88% 5y<br>74% 5y | Abstract only |
| Intergroup S1001 | 4 RCHOP (PET-)<br>3 RCHOP +RT/RIT (PET+) | 89% 5y<br>86% 5y | |
| LYSA/GOELAMS 0203 | 4-6 RCHOP 14 (PET-)<br>+/- RT | 89% 5y<br>92% 5y | |

# Several potential study limitations – 2 key issues

Tumour size

- Were tumours at the upper end of the eligibility range (5-7 or 10 cm) represented in trials?
- If not, can results be extrapolated to these larger (but still “non-bulky”) tumours ?

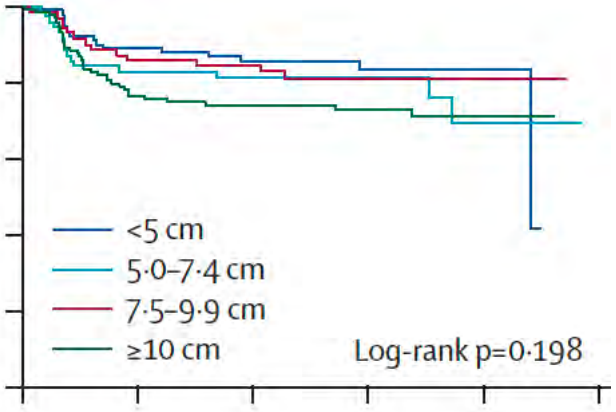
Treatment received

- Did many patients receive more than just 4 RCHOP?
- If not, do results apply to patients receiving only 4 cycles?

# Tumour size matters for DLBCL in the “non-bulky” range

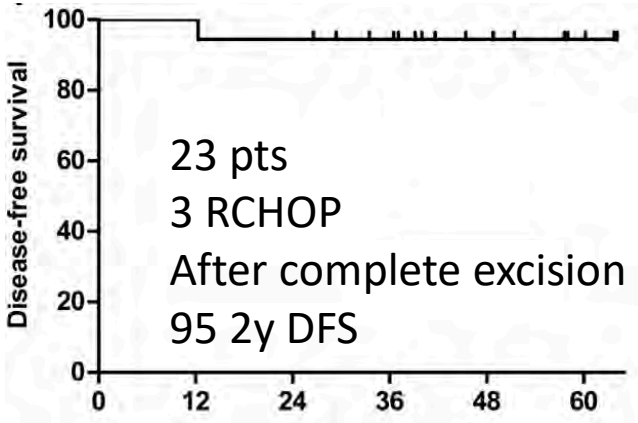
Tumour size continuous variable > 5 cm

HR 1.044 per cm

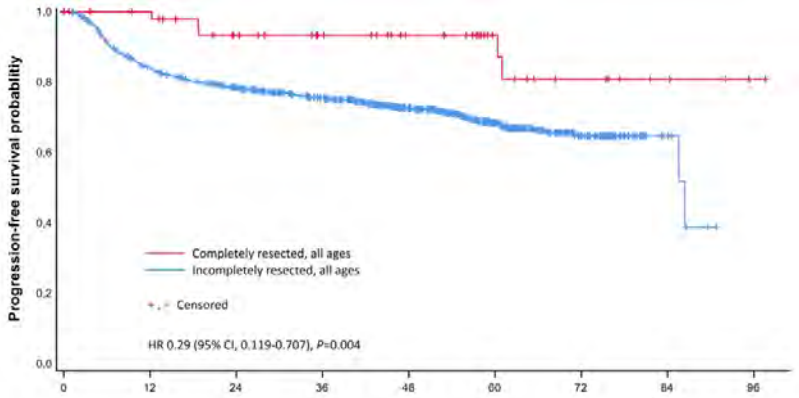



MINT Pfreundschuh
Lancet Oncol 2008

Patients with no macroscopic disease do exceptionally well with limited RCHOP




Yoon Oncotarget 2017




Schmitz Cancer Med 2020 (PETAL)

# With those issues in mind, a closer look at the only randomized trial evaluating RT for patients in CMR after RCHOP

| Study | Question addressed/design | Treatment | %PFS |
|---|---|---|---|
| LYSA/GOELAMS 0203<br>Lamy 2018 | Is RT beneficial after 4-6 RCHOP (PET -)<br>*Randomised* | 4-6 RCHOP 14 (PET-)<br>+/- RT | 89% 5y<br>92% 5y |

# LYSA GOELEMS 0203

## Lamy Blood 2018

Main outcome: 3% difference, non-significant
Conclusions: “no benefit from RT”

334 pts, st I-II, up to 7 cm, age < 75

Exclude: CNS, skin, testis, ovary, breast, GI

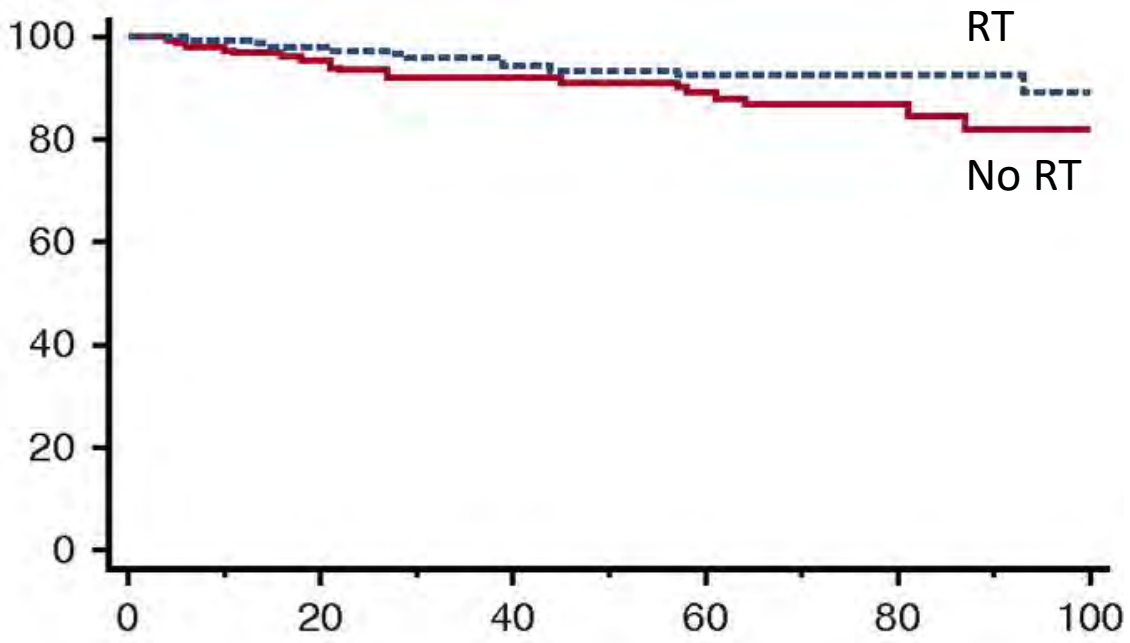
4-6 RCHOP - if iPET –ve, randomised +/- RT 40 Gy

Note: 4 RCHOP if normal LDH, st I, PS 0, age < 60

Otherwise 6 RCHOP

If PET +ve, further treatment /RT

5 y EFS 92 v 89%



# LYSA GOELEMS 0203- comments/limitations

Patient population

- 19% had no evident disease at study entry
- No information on tumour size for other 81%  (? 1-5 cm v 5-7 cm)

Treatment and outcome

- 44% had 6 RCHOP -do conclusions apply to subset who had 4 RCHOP?
- 6% patients assigned RT did not receive it – no as treated analysis
- No local failure in RT arm but  5/13 local relapses after RCHOP alone
- 3% difference not significant – what was statistical power after excluding NED, 6 RCHOP and PET +ve

Uncertain whether this study excludes a benefit from RT after 4 RCHOP

# Missing data on tumour characteristics

| Study | Eligibility | Tumour dimensions | | Additional treatment |
|---|---|---|---|---|
| | | All removed | Size distribution | |
| SWOG 8736<br>Stephens 2016 | < 10 cm | **29%** | | |
| FLYER<br>Poeschel 2018 | < 7.5 cm | **?** | **?** | **12%** |
| Vancouver<br>Sehn 2019 | < 10 cm | **?** | **63% < 5 cm** | **?** |
| LYSA LNH 091B<br>Bologna 2021 | < 10 cm | **?** | **?** | **?** |
| Intergroup S1001<br>Persky 2020 | < 10 cm | **10%** | **Med 3.5cm** | |
| LYSA/GOELAMS 0203<br>Lamy 2018 | < 7 cm | **19%** | **?** | **45% 6 RCHOP** |

# Caveats on 5 key studies

- Tumour size of patients entered into key studies is not well described and where described was mainly at lower end of size range
- A proportion of patients had no evident disease at study entry - a population known to do well without RT
- A proportion of patients had more than 4 RCHOP
- Only one of the 5 studies evaluated RT
- Warrant caution in withholding RT for tumours at the upper end of the eligible size range (say, > 5 cm) having only 4 RCHOP

# Other potentially relevant factors adversely affecting outcome in st I-II

- PET DS (S1001 trial DS 3 worse outcome than 1-2)
- Cell of origin
- Double expressor/hit
- IPI
- Transformed/ Low grade component

Small numbers/conflicting results –tentative and need further study

Rosenwald NEJM 2002, Watanabe J Cancer Ther 2013, Scott JCO 2015, Persky JCO 2020, Tumati IJROBP 2018, Grass Leuk Lymphoma 2019, Lamy Blood 2018, Grass Leuk Lymphoma 2019

# Unfavourable DLBCL

Even more challenging to assess the role of RT for PET CMR

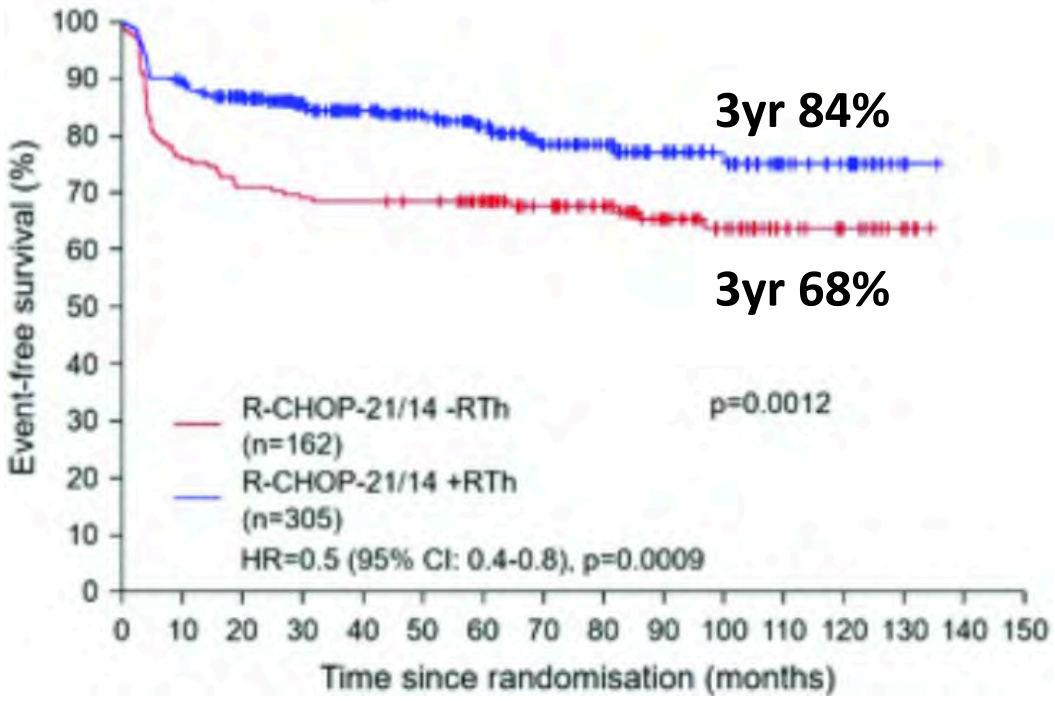
- More heterogeneous population
- No randomized study RCHOP +/- RT

Three commonly cited studies that suggest withholding RT after CMR to 6 RCHOP

| | |
|---|---|
| Final analysis of UNFOLDER | (Thurner, Hemasphere 2023) |
| BC PET guided treatment policy | (Freeman, Blood 2021) |
| Optimal trial: | (Pfreundschuh, JCO 2017 abstract only) |

# Final analysis of the UNFOLDER trial “hot off the press” July 2023

Thurner Hemasphere July 2023




Confirmed the 16% improvement in 3-years EFS in the radiotherapy-arm (*P* = 0.0012) – the same as at interim analysis which led to closure of chemotherapy-only arms

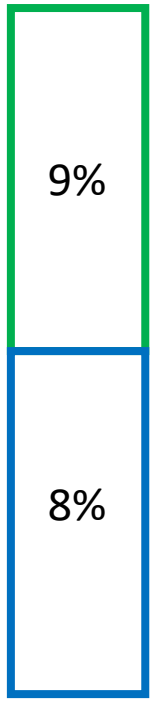
*Yet concludes: “…can be spared from radiotherapy without compromising their outcome…”*

Why the altered interpretation?

# Why was the 16% improvement in EFS not considered important?

Authors divide EFS into:

PRs- reduced by 9% (2% v 11%)




Benefit questioned/dismissed as cannot be sure what residual masses represent without PET

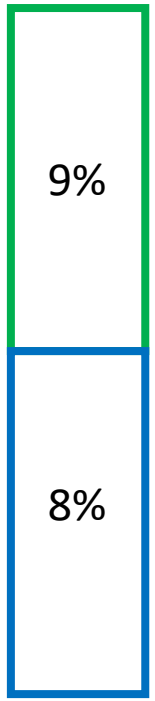
PFS- improved by 8% (89% vs. 81%)

Benefit dismissed as (in isolation) not statistically significant (p = 0.221) – **but study underpowered for this "sub" endpoint**

# Is there another reasonable interpretation of the data?

PRs- reduced by 9% (2% v 11%)

PFS- improved by 8% (89% vs. 81%)




% no disease

% PET +ve disease

% PET -ve disease

Some of the PR cases may have had PET –ve residual disease

Plausibly > 8 % benefited from RT

This is plausible but speculative – we cant know for sure

LYMPHOID NEOPLASIA

# Long-term results of PET-guided radiation in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP

Freeman, Blood 2021

723 pts, DLBCL, 2005-2017

75% st 3-4

45% B

½ IPI 4-5

6 R-CHOP plus end of therapy PET

517 (72%) PET-NEG were observed

206 (28%) PET-POS RT when feasible

Key findings in PET -ve patients:

- 3 yr FFP 83% for all PET –ve patients
- Bulky disease doesn't do worse (infer no need to irradiate)

Conclude that a PET-guided approach to omitting RT "…is feasible and appears to be associated with favourable outcomes"

# Focus on bulky disease in CMR - should we irradiate

285 pt with bulky disease (>10 cm)

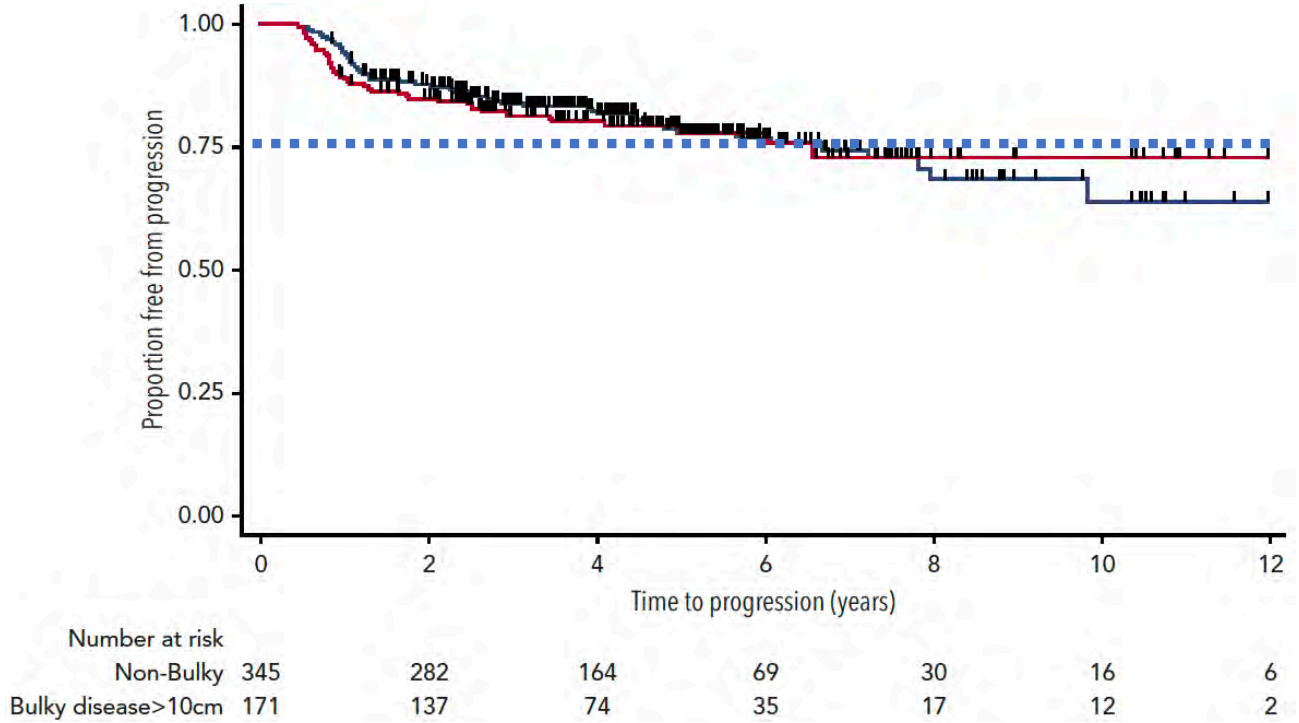
172 (60%) became PET-NEG

3-year FFP 82% bulky v 84% non-bulky

Also note < 75% FFP

Bulky disease didn't do more poorly
So inferred that local RT not needed?

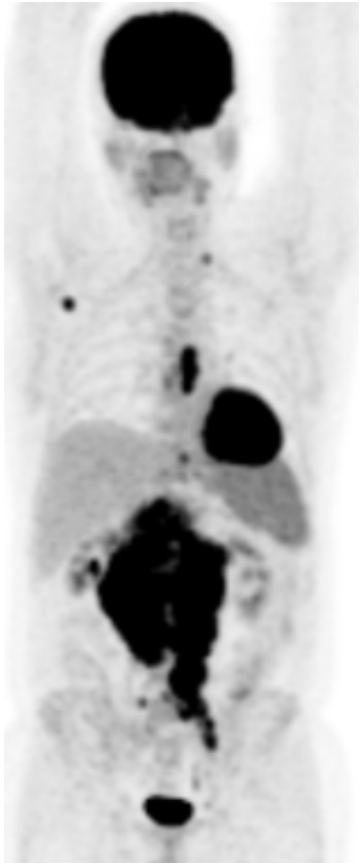
Is this a valid interpretation?



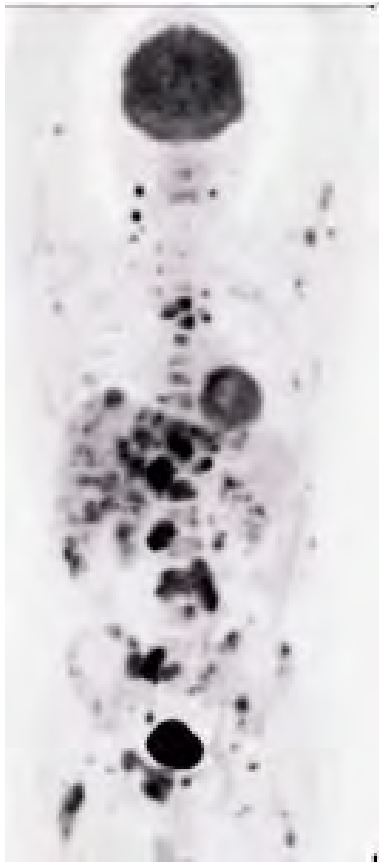

Freeman Blood 2021

# Is bulk a prognostic or predictive factor?

Bulky disease



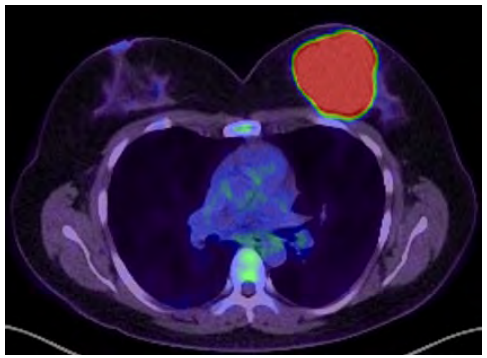
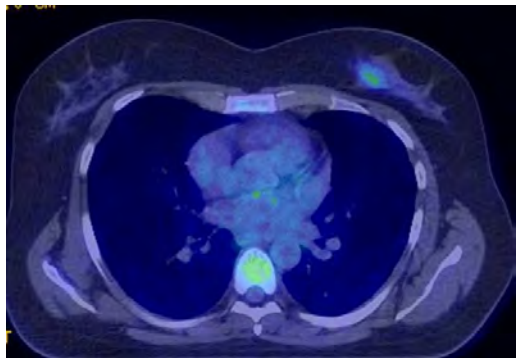
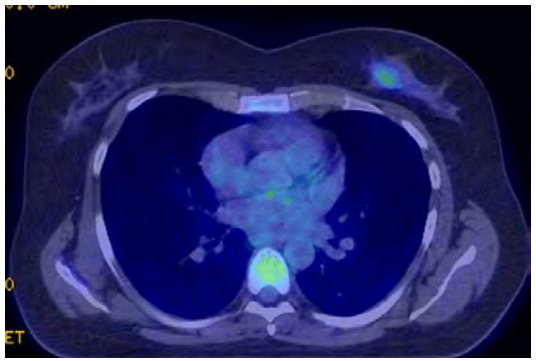
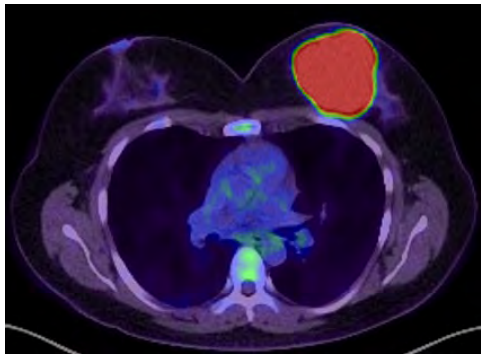
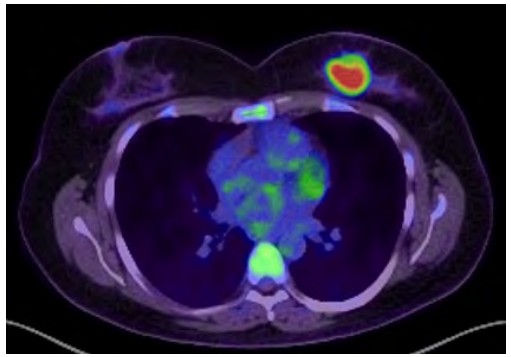
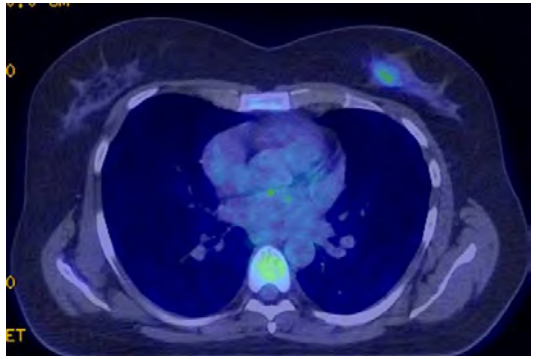
Non bulky disease



Both cases may have <u>same prognosis</u>

Doesn’t exclude a benefit from RT to bulky site

# Significance of timing of PET response:
# Do these patients have the same likelihood of relapse?

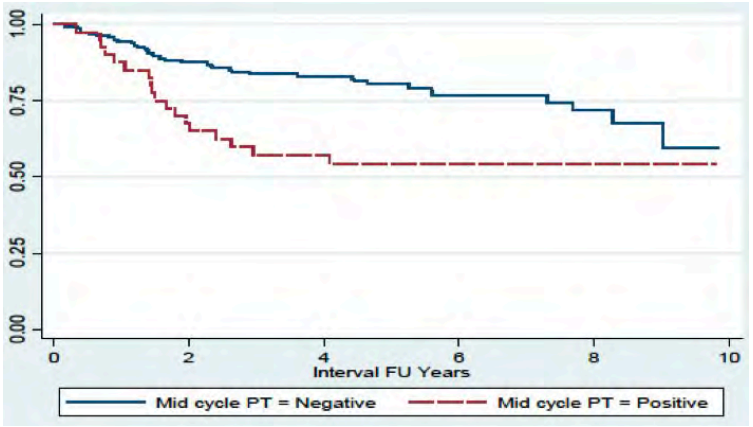
| | Baseline | Cycle 3 | Cycle 6 |
|---|---|---|---|
| Patient A |  |  |  |
| Patient B |  |  |  |

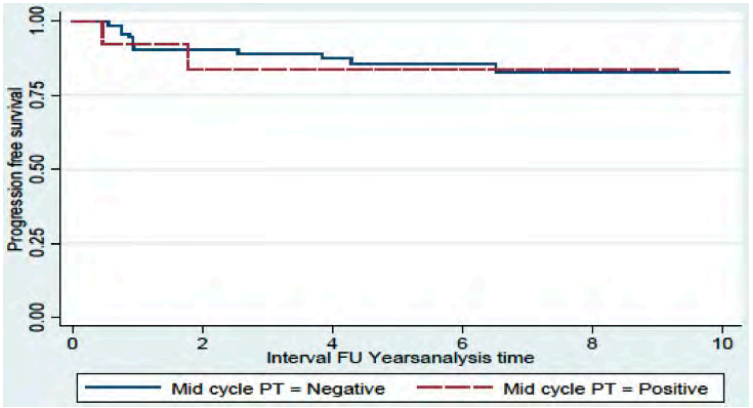
# Significance of timing of PET response

Spaepen Ann Oncol 2002

Patients who were interim PET +ve at cycle three and achieved PET CR all relapsed at interim PET + sites

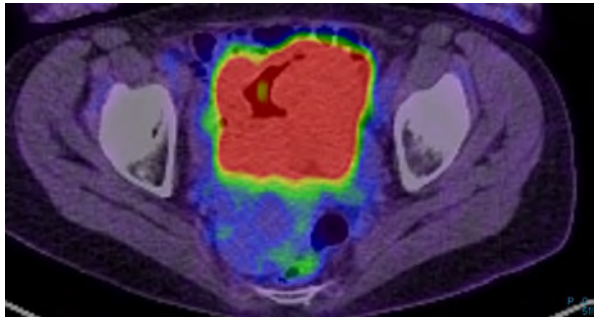
Dabaja, IJROBP 2012



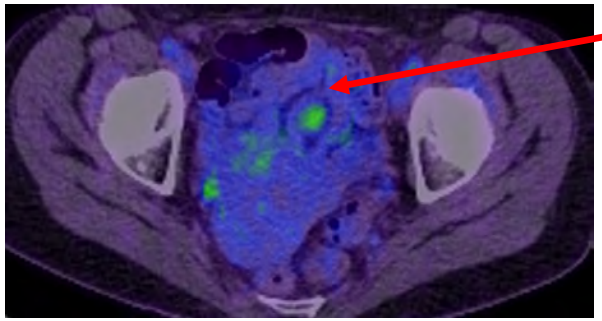




RT

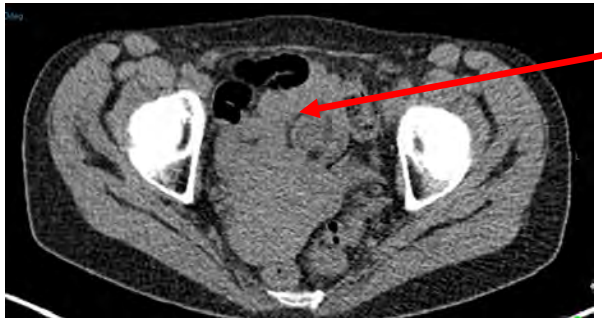
# Beyond metabolic response: ? Significance of residual mass

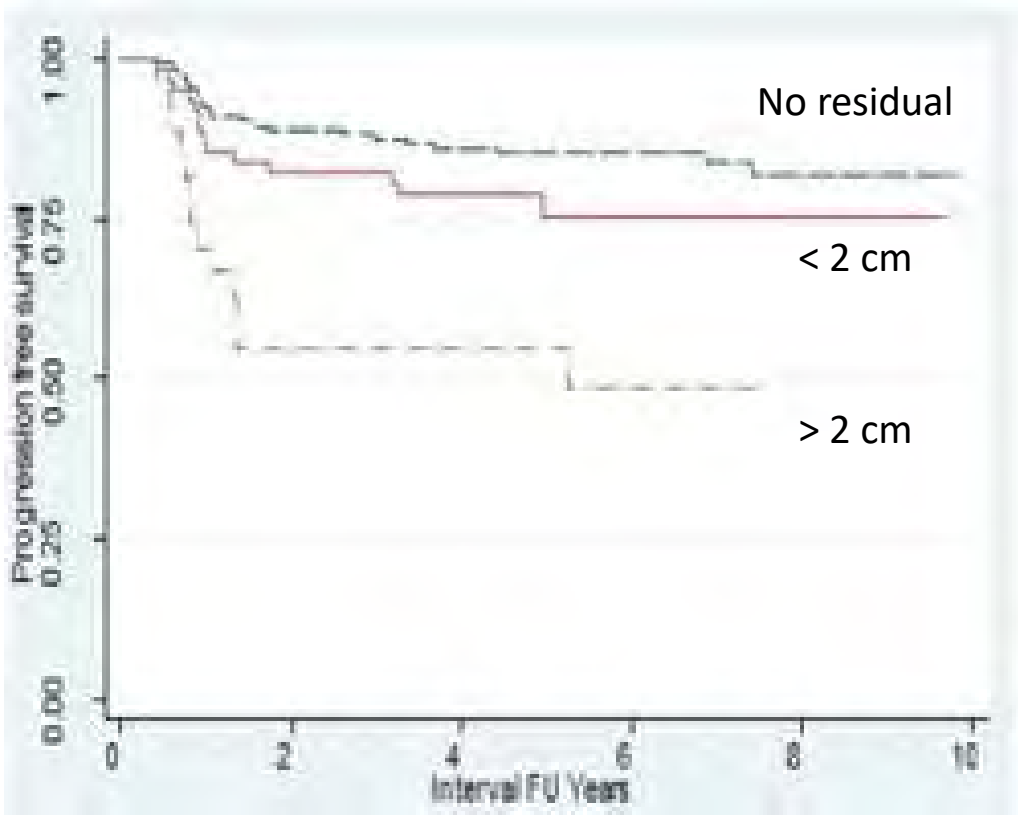


CMR



Residual soft tissue



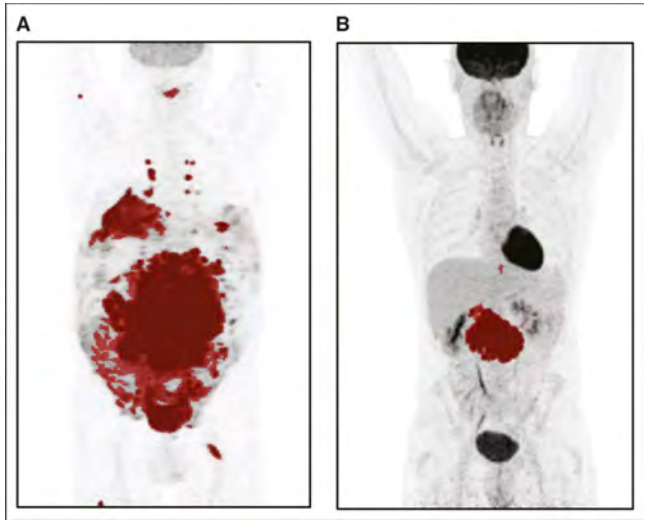



Dabaja Leukemia & Lymphoma 2013

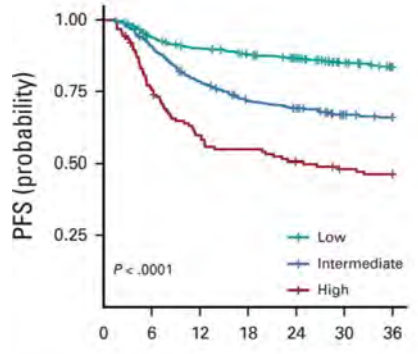
Many emerging PET radiomic parameters predict outcomes:

*Could a combination of PET parameters identify patients more likely to benefit from RT?*

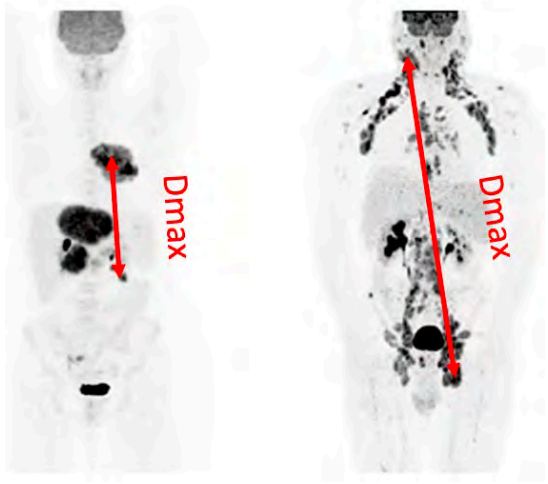
## Metabolic tumour volume



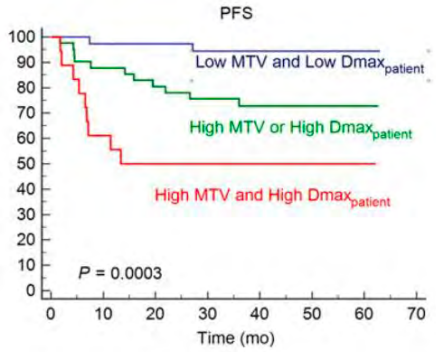

Mikhaeel JCO 2022



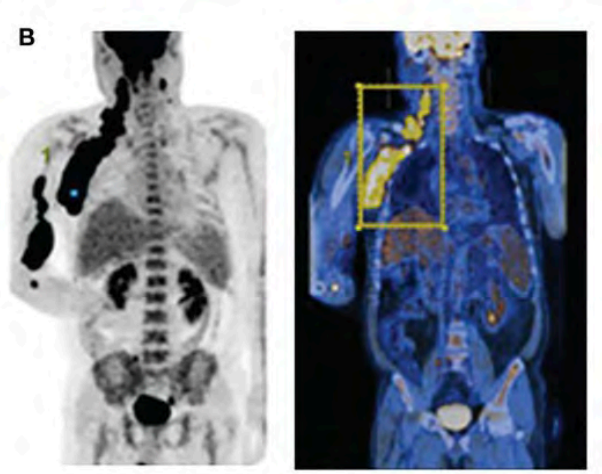

## Tumour dissemination



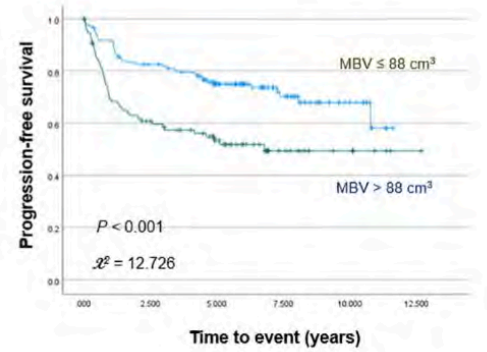

Cottereau J Nucl Med 2020




## MTV of largest lesion




Jin Front. Oncol. 2023



# Risk / benefit of RT

What is magnitude of benefit for patients in CMR?

We don’t really know- speculative – very difficult to discuss with patients (and colleagues)

? between 3% (LYSA)  and 16% (UNFOLDER)

take conservative approach when discussing with patients - 5-7% (maybe 10%)

What is risk?

Acute toxicity of 30 Gy ISRT - minimal in UNFOLDER/LYSA using 40Gy IFRT

Second malignancy- minimal incremental risk for older patients (DLBCL demographic)

# In summary: PET response is just one of many potentially relevant factors

**End of therapy**

- Structural response
- **PET response**

**Clinical features**

- Stage
- Bulk
- Disease distribution
- Extra-nodal primary
- Prognostic scores -IPI

?

?

Clinical decision

?

?

?

**Novel radiomic parameters**

- Baseline MTV
- SUV
- Indices of disease distribution
- Response kinetics/interim PET

**Pathology**

WHO 5 sub-type
Cell of origin
Molecular features: MYC BCL2 BCL6

**Patient factors**

- Age, sex, comorbidities
- Toxicity risks
- Salvage options
- Preferences

# When to consider adjuvant RT (one approach!)

Chemotherapy alone

4 RCHOP if < 5 cm

6 RCHOP If < 7(?10) cm

…in the absence of other risk factors

Consider RT

Larger tumours
Residual mass > 2cm
Interim PET + after 2-3 cycles
For st III-IV if dominant mass

ABC/DH/transformed (if not intensified)
PET response (DS 3)

Potential for emerging radiomic features

Patient centred

Benefit
toxicity
salvage options
For individual

Discuss with patients
elicit preferences

# Concluding thoughts

PET CMR predicts improved prognosis and a proportion of PET –ve cases will do well without RT

However

- benefit from RT after PET CMR has not been excluded in an appropriately designed and powered study
- may disadvantage our patients by withholding potential benefit of RT based on PET response alone

Further research needed to integrate PET, clinical factors and biological factors to guide use of RT


Thank you

# RT Toxicity

Acute

UNFOLDER Thurner Hemasphere 2023. 39.6 Gy

"radiotherapy generally very well tolerated" 1%–3% CTC grade 3 of 4 acute toxicities

LYSA/GOELAMS 0203 Lamy 2018 40 Gy

2 cases grade 3 mucositis, 1 jaw radionecrosis/160 pts

| | No RT | | | | RT | | | |
|---|---|---|---|---|---|---|---|---|
| **age** | <25 | 25-49 | 50-74 | >74 | <25 | 25-49 | 50-74 | >74 |
| | | | | | | | | |
| **All ca** | 2.1 | 1.8 | 1.1 | 0.9 | 4.5 | 2 | 1.1 | 0.9 |
| **lung** | 0 | 2.3 | 1.4 | 0.8 | 0 | 2.4 | 1.3 | 0.7 |
| **breast** | 0 | 0.8 | 0.8 | 0.7 | 5 | 1.2 | 0.9 | 1.1 |

SEER data 77000 pts and 5600 malignancies
Tward Cancer 2006

Optimal > 60  Pfreundschuh Abstract ASCO 2017

**OPTIMAL > 60 study**

6 x R chemo
166 pts with bulk-PET guided use of RT

80 +ve:  62 had RT

86 –ve: no RT

2y pfs 79%

RICOVER -60 RT
Held 2014

6 x R chemo
All 117 pt with bulk had RT

2y pfs 75%

Historical comparison 166 patients (half had RT) to an historical cohort 117 patients (all had RT)

**Conclusion:** ”RT can be spared in bulky disease PET-negative after chemotherapy…without compromising the outcome”

Places a lot of weight on 86 cases PET –ve cases not receving RT
(? different staging, histol assessment and exclusions in the two treatment eras)

Difficult to draw definitive conclusions about need for  RT- await final publication