

Radiotherapy in aggressive lymphomas

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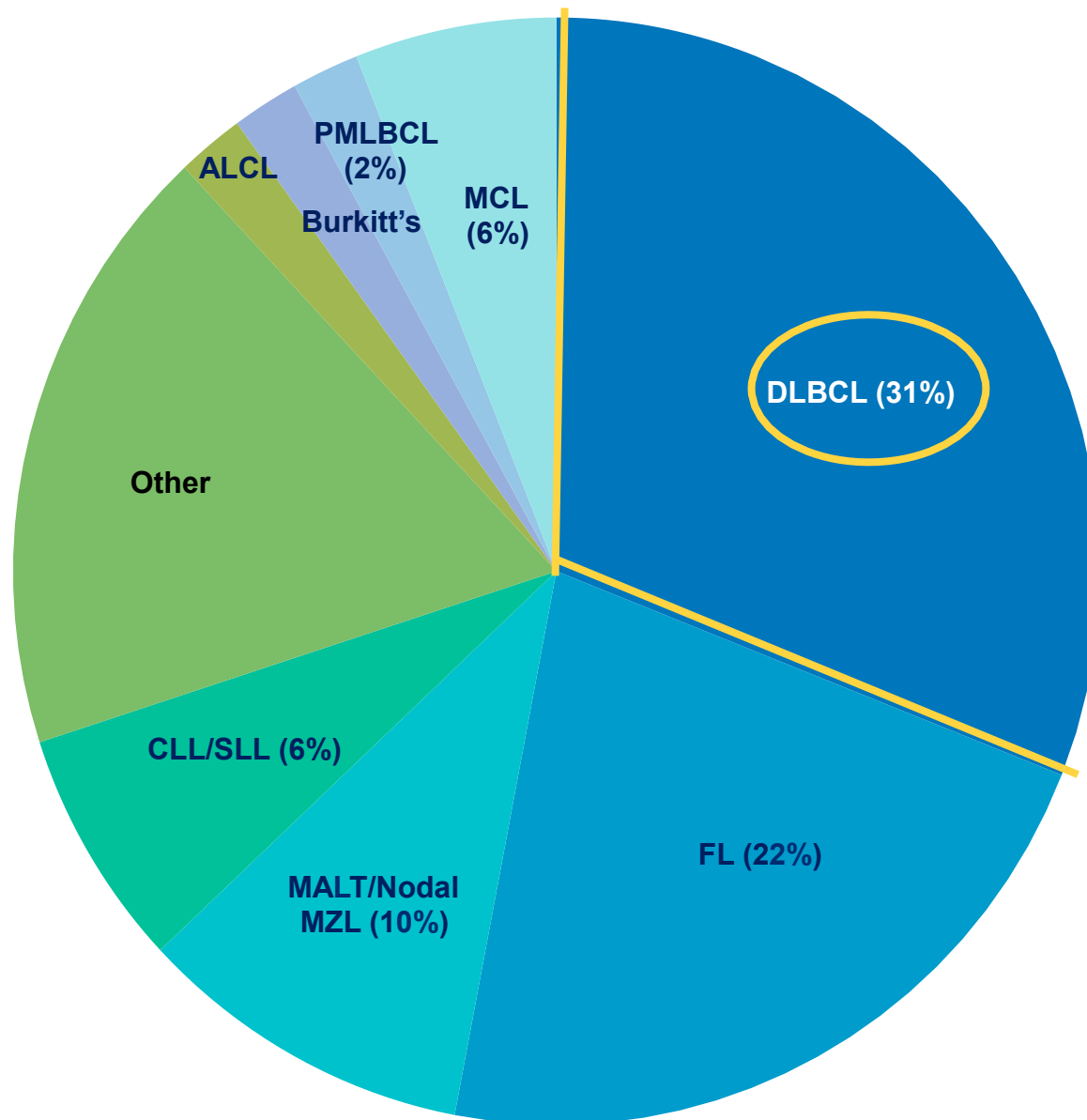
The logo of the University of Turin, featuring a circular emblem with a central figure and the Latin motto "SIGILLUM UNIVERSITATIS TURONENSIS" around the perimeter.

ILROG
INTERNATIONAL LYMPHOMA
RADIATION ONCOLOGY GROUP

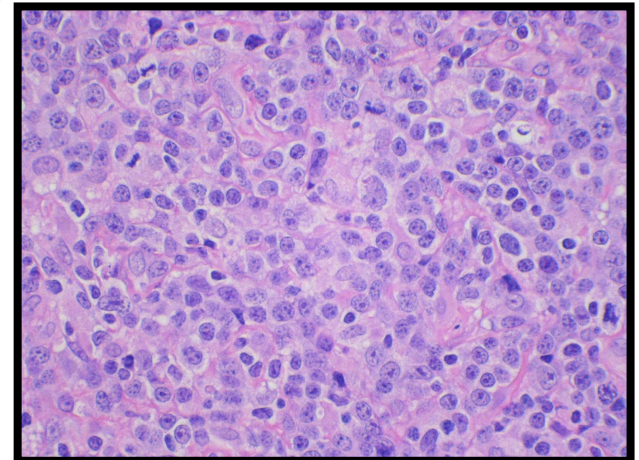
The logo for the International Lymphoma Radiation Oncology Group (ILROG), featuring a stylized human figure with a radiation symbol (a circle with three curved lines) superimposed over it.

Is there (still) a role for Radiation Therapy in DLCL?

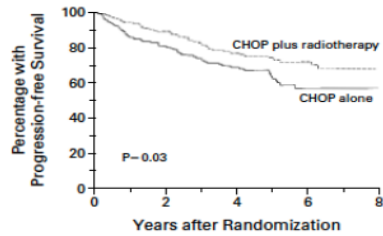
NHL: A Heterogeneous Disease



- 75% of aggressive NHL
- 40%: localized disease
- 40-50%: extranodal disease



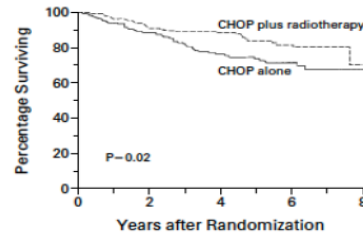
CHOP x 8 vs. CHOP x 3 + IFRT in Stage I/II DLBCL



| NO. AT RISK | 0 | 2 | 4 | 6 | 8 |
|------------------------|-----|-----|-----|----|----|
| CHOP alone | 201 | 172 | 111 | 55 | 14 |
| CHOP plus radiotherapy | 200 | 178 | 119 | 70 | 17 |

Figure 1. Progression-free Survival of 201 Patients Receiving Eight Cycles of CHOP Alone and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

Sixty-five patients in the CHOP-alone group died or had progression of their disease, as compared with 45 patients in the CHOP-plus-radiotherapy group. The estimated rates of progression-free survival at five years were 64 percent and 77 percent, respectively.



| NO. AT RISK | 0 | 2 | 4 | 6 | 8 |
|------------------------|-----|-----|-----|----|----|
| CHOP alone | 201 | 187 | 120 | 61 | 14 |
| CHOP plus radiotherapy | 200 | 185 | 128 | 75 | 17 |

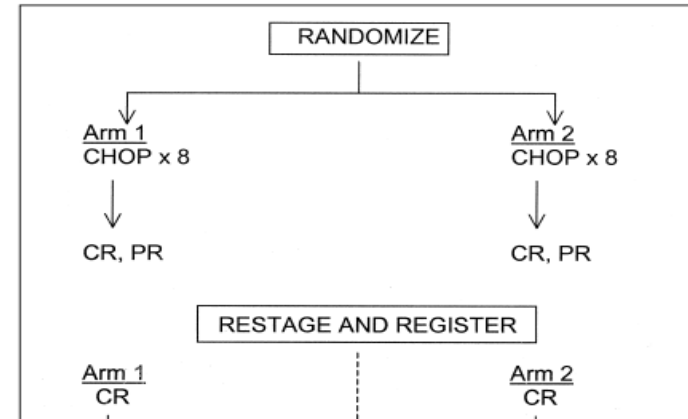
Figure 2. Overall Survival of 201 Patients Receiving Eight Cycles of CHOP and 200 Patients Receiving Three Cycles of CHOP plus Radiotherapy.

There were 51 deaths in the CHOP-alone group, and 32 in the CHOP-plus-radiotherapy group. The estimated rates of survival at five years were 72 percent and 82 percent, respectively.

Miller et al NEJM 1998; 339:21

Chemotherapy With or Without Radiotherapy in Limited-Stage Diffuse Aggressive Non-Hodgkin's Lymphoma: Eastern Cooperative Oncology Group Study 1484

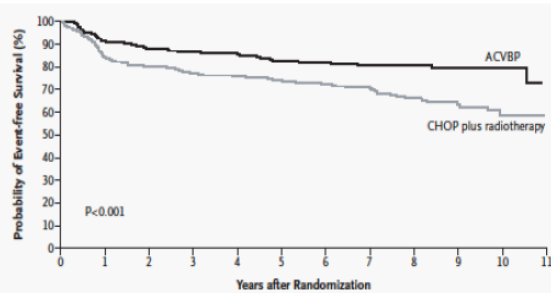
Sandra J. Horning, Edie Weller, KyungMann Kim, John D. Earle, Michael J. O'Connell, Thomas M. Habermann, and John H. Glick



CHOP Alone Compared With CHOP Plus Radiotherapy for Localized Aggressive Lymphoma in Elderly Patients: A Study by the Groupe d'Etude des Lymphomes de l'Adulte

Christophe Bonnet, Georges Fillet, Nicolas Mounier, Gérard Ganem, Thierry Jo Molina, Catherine Thiéblemont, Christophe Fermé, Bruno Quesnel, Claude Martin, Christian Gisselbrecht, Hervé Tilly, and Félix Reyes†

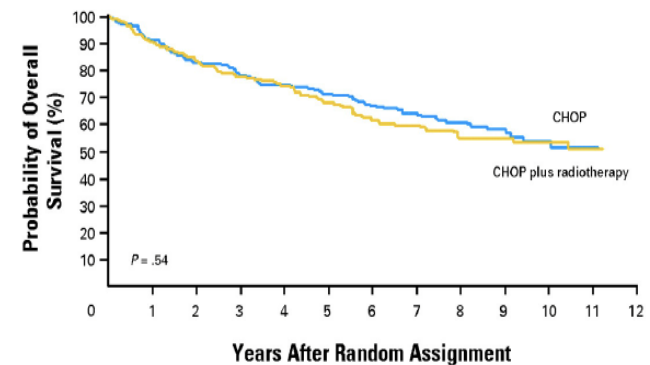
ACVBP vs CHOP + RT in Stage I/II aggressive Lymphoma



| No. at Risk | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|
| ACVBP | 318 | 287 | 278 | 270 | 253 | 217 | 190 | 149 | 117 | 77 | 33 | |
| CHOP plus radiotherapy | 329 | 275 | 262 | 252 | 243 | 209 | 179 | 133 | 94 | 59 | 22 | |

Figure 1. Event-free Survival among 647 Patients Assigned to Chemotherapy Alone with the ACVBP Regimen or to CHOP plus Involved-Field Radiotherapy.

Reyes et al NEJM 2005; 352:1107



| No. at risk: | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|
| CHOP | 277 | 249 | 226 | 206 | 178 | 153 | 131 | 102 | 75 | 45 | 22 | 1 | |
| CHOP plus radiotherapy | 299 | 265 | 243 | 211 | 187 | 155 | 123 | 98 | 68 | 50 | 30 | 9 | |

GELA LNH 93-4

Bonnet C et al. JCO 2007;25:787-792

- ❑ Combined modality therapy has been the standard of care for many patients with diffuse large B-cell lymphoma (DLBCL), particularly those with limited stage low risk disease or bulky sites

- ❑ In the modern era the selection of appropriate patients for combined modality therapy has become increasingly complex over the last decade with the transition to
 - **immunochemotherapy**
 - **emergence of functional imaging for response evaluation**

Re-Examining the Role of Radiation Therapy for Diffuse Large B-Cell Lymphoma in the Modern Era

Andrea K. Ng, *Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Bouthaina Shbib Dabaja, *The University of Texas MD Anderson Cancer Center, Houston, TX*

Richard T. Hoppe, *Stanford University School of Medicine, Stanford, CA*

Timothy Illidge, *University of Manchester, Manchester Academic Health Sciences Centre, The Christie National Health Service Foundation Trust, Manchester, United Kingdom*

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



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Radiation Therapy for Diffuse Large B-Cell Lymphoma: Indications, Outcomes, and Controversies

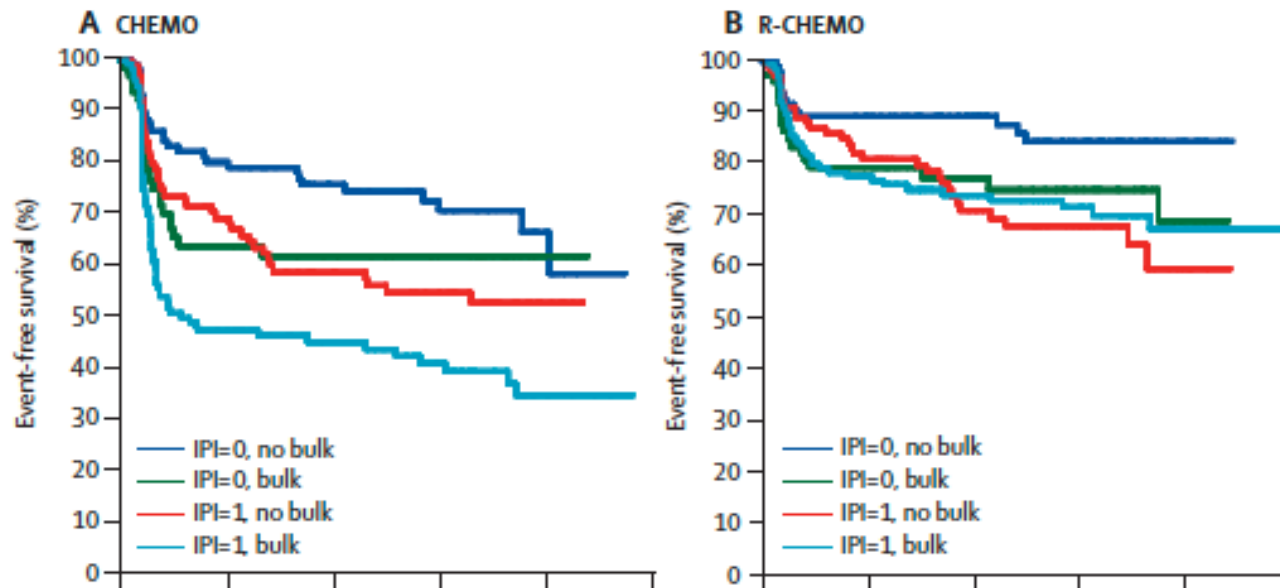
By Chelsea C. Pinnix, MD, PhD, *Associate Editor*

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CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MINT) Group



Michael Pfreundschuh, Evelyn Kuhnt, Lorenz Trümper, Anders Österborg, Marek Trnecny, Lois Shepherd, Devinder S Gill, Jan Walewski, Ruth Pettengell, Ulrich Jaeger, Pier-Luigi Zinzani, Ofer Shpilberg, Stein Kvaloy, Peter de Nully Brown, Rolf Stahel, Noel Milpied, Armando López-Guillermo, Viola Poeschel, Sandra Grass, Markus Loeffler, Niels Murawski, for the MabThera International Trial (MINT) Group*

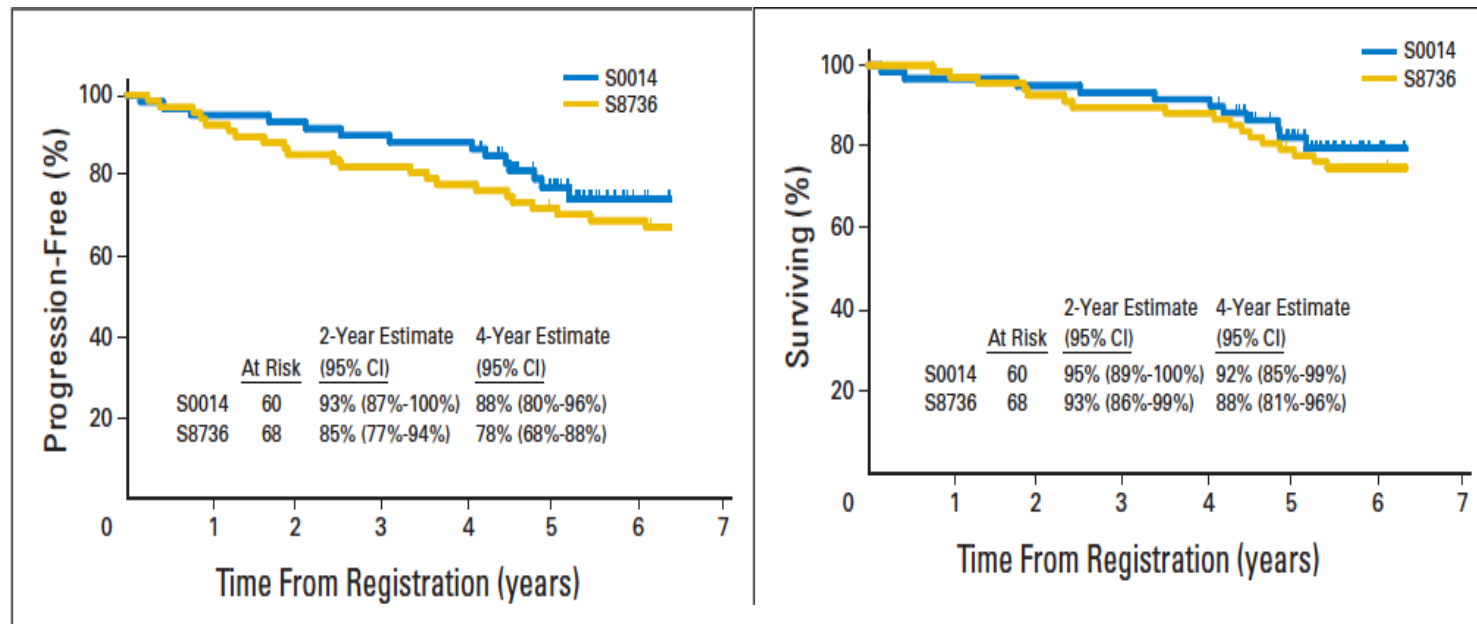


Number at risk

| | | | | | | | | | | | | |
|----------------|-----|----|----|----|---|---|-----|----|----|----|----|---|
| IPI=0, no bulk | 108 | 79 | 56 | 36 | 8 | 0 | 101 | 81 | 60 | 40 | 8 | 0 |
| IPI=0, bulk | 70 | 38 | 28 | 21 | 6 | 0 | 73 | 53 | 37 | 26 | 4 | 0 |
| IPI=1, no bulk | 105 | 62 | 42 | 34 | 6 | 0 | 107 | 78 | 51 | 35 | 4 | 0 |
| IPI=1, bulk | 127 | 54 | 37 | 26 | 5 | 0 | 132 | 93 | 66 | 49 | 14 | 0 |

Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients With Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014

Daniel O. Persky, Joseph M. Unger, Catherine M. Spier, Baldassarre Stea, Michael LeBlanc, Matthew J. McCarty, Lisa M. Rimsza, Richard I. Fisher, and Thomas P. Miller



- Lower impact of R in limited stage (5% vs 15% in advanced stage)
- Biological explanation : molecular fingerprint GCB in 3/4 of cases (demonstrated lower benefit of R)

Benefit of Consolidative Radiation Therapy in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP Chemotherapy

Jack Phan, Ali Mazloom, L. Jeffrey Medeiros, Tony G. Zreik, Christine Wogan, Ferial Shihadeh, Maria Alma Rodriguez, Luis Fayad, Nathan Fowler, Valerie Reed, Patricia Horace, and Bouthaina Shbib Dabaja

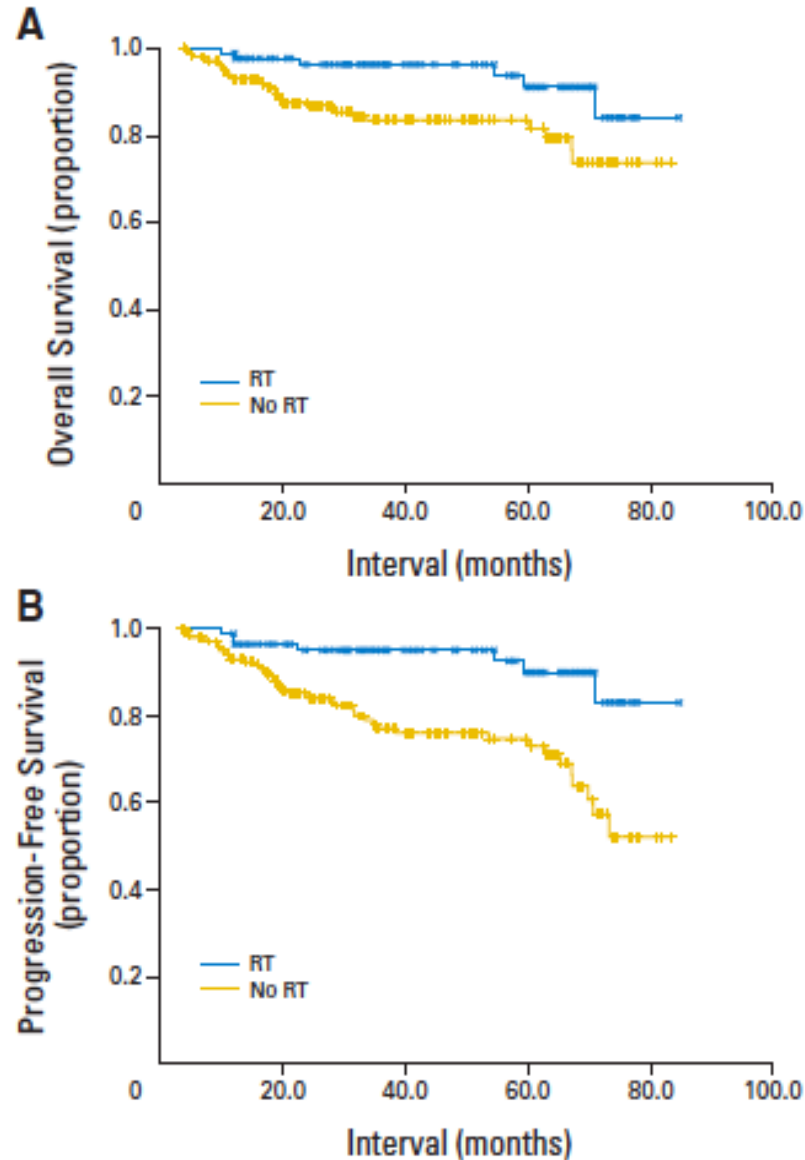



Table 5. Multivariate Analysis of Overall and Progression-Free Survival for All Patients

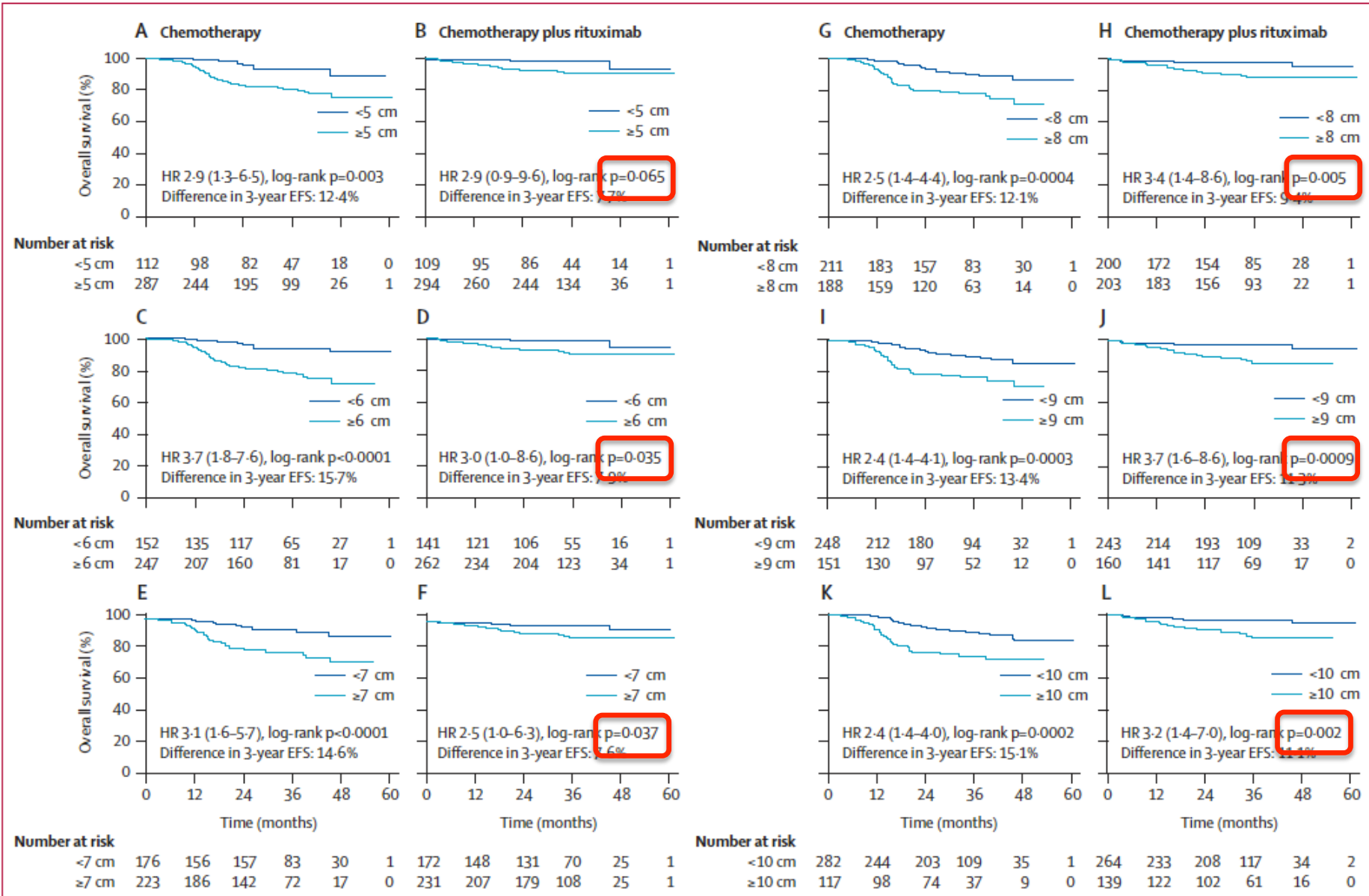
| Variable | Hazard Ratio | 95% CI | P | Hazard Ratio | 95% CI | P |
|------------------------|--------------|---------------|---------|--------------|--------------|---------|
| Age, years | | | | | | |
| ≤ 60 | 1.00 | | .051 | 1.00 | | .010 |
| > 60 | 1.34 | 0.98 to 2.02 | | 1.42 | 1.00 to 2.15 | |
| Chemotherapy | | | | | | |
| 6-8 cycles of R-CHOP | 0.42 | 0.27 to 0.65 | < .0001 | 0.57 | 0.39 to 0.84 | .0050 |
| Other | 1.00 | | | 1.00 | | |
| Radiotherapy | | | | | | |
| No | 1.00 | | < .0001 | 1.00 | | < .0001 |
| Yes | 0.19 | 0.10 to 0.38 | | 0.32 | 0.17 to 0.51 | |
| Triple negative | | | | | | |
| No | 1.00 | | .025 | 1.00 | | .038 |
| Yes | 0.16 | 0.03 to 0.79 | | 0.24 | 0.06 to 0.92 | |
| Triple positive | | | | | | |
| No | 1.00 | | .006 | 1.00 | | .037 |
| Yes | 4.96 | 1.58 to 15.61 | | 1.39 | 1.58 to 9.87 | |
| IPI score | | | | | | |
| 0 | 1.00 | | | 1.00 | | |
| 1-2 | 2.53 | 1.32 to 4.84 | .005 | 2.12 | 1.34 to 3.69 | .001 |
| ≥ 3 | 5.41 | 2.24 to 8.28 | .001 | 6.03 | 3.11 to 9.19 | .001 |
| Response | | | | | | |
| No response | 1.00 | | | 1.00 | | |
| Partial remission | 1.96 | 0.91 to 2.05 | < .0001 | 0.27 | 0.16 to 0.56 | < .0001 |
| Complete remission | 3.35 | 2.33 to 4.59 | < .001 | 0.42 | 0.33 to 0.72 | .0055 |

Prognostic significance of maximum tumour (bulk) diameter ➔ 
in young patients with good-prognosis diffuse large-B-cell
lymphoma treated with CHOP-like chemotherapy with or
without rituximab: an exploratory analysis of the MabThera
International Trial Group (MInT) study

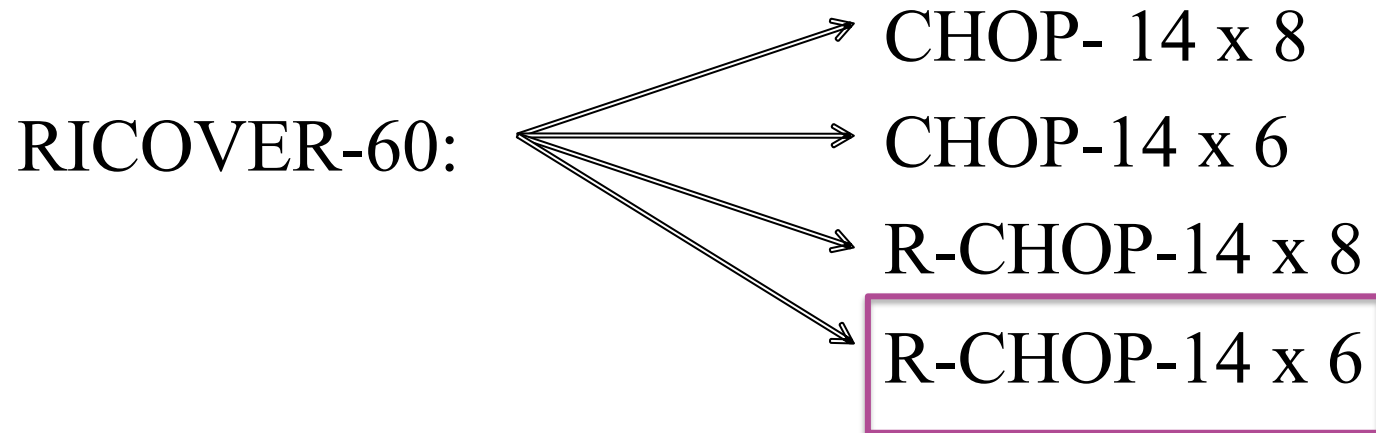
*Michael Pfreundschuh, Anthony D Ho, Eva Cavallin-Stahl, Max Wolf, Ruth Pettengell, Ingrid Vasova, Andrew Belch, Jan Walewski,
Pier-Luigi Zinzani, Walter Mingrone, Stein Kvaloy, Ofer Shpilberg, Ulrich Jaeger, Mads Hansen, Claudia Corrado, Adriana Scheliga, Markus Loeffler,
Evelyn Kuhnt, for the MabThera International Trial (MInT) Group*

Lancet Oncol 2008; 9: 435-44

- Linear prognostic effect of tumor diameter on OS, which is decreased (but not eliminated) by the addition of rituximab



Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma (n=1,222)

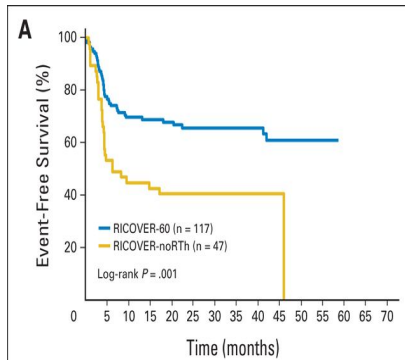


Retrospective subgroup analysis of pts with bulky disease (≥ 7.5 cm) from the R-CHOP14 x 6 arm treated with or without RT (RICOVER-noRT)

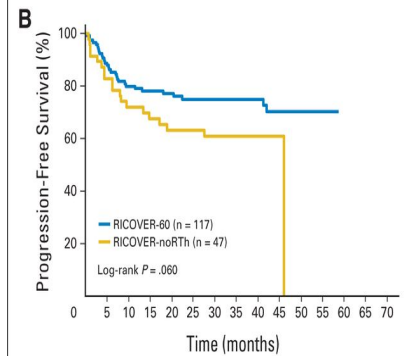
Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Intent-To-Treat Analysis:

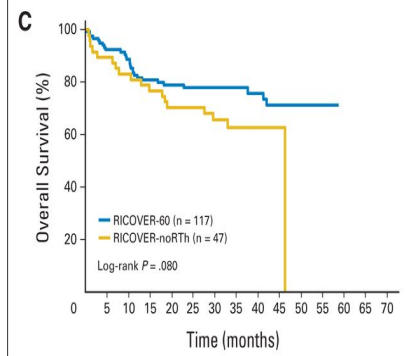
EFS



PFS

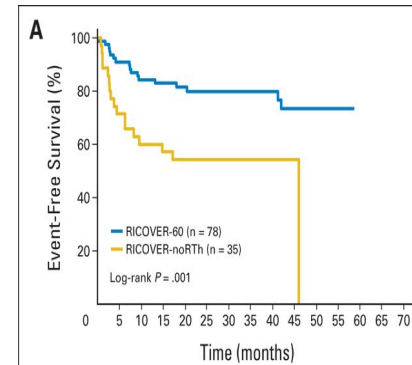


OS

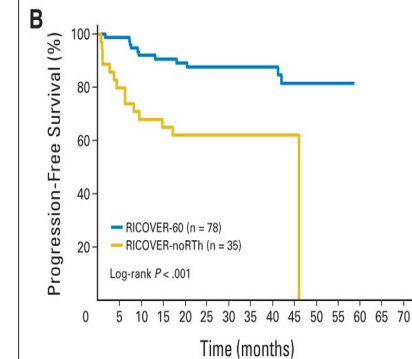


Per-Protocol Analysis:

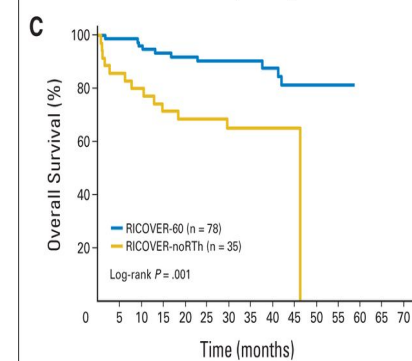
EFS



PFS



OS



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

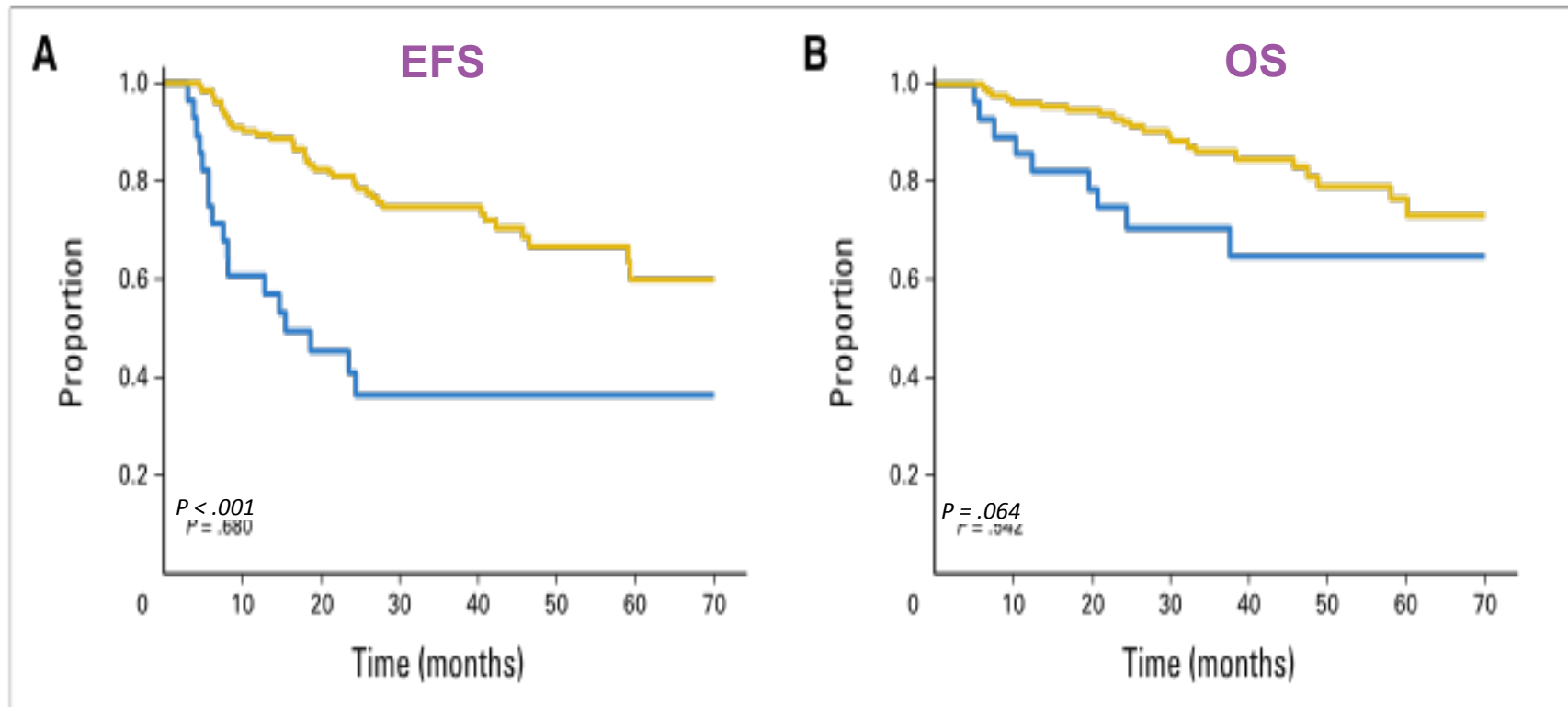
Multivariable analysis (per protocol)

PROGRESSION-FREE SURVIVAL

| Factor | Relative risk | P-value | 95% CI |
|-------------------------------|---------------|--------------|---------------------|
| <i>RT vs no RT</i> | <i>4.4</i> | <i>0.001</i> | <i>(1.8 – 10.6)</i> |
| <i>LDH Elevated</i> | <i>0.6</i> | <i>0.391</i> | <i>(0.2 – 1.7)</i> |
| <i>ECOG >1</i> | <i>1.6</i> | <i>0.439</i> | <i>(0.5 – 4.9)</i> |
| <i>Extranodal Involvement</i> | <i>0.8</i> | <i>0.664</i> | <i>(0.3 – 2.4)</i> |
| <i>Stage III/IV</i> | <i>1.2</i> | <i>0.662</i> | <i>(0.5 – 3.4)</i> |
| <i>Age > 70 years</i> | <i>1.6</i> | <i>0.271</i> | <i>(0.7 – 3.9)</i> |

Impact of Rituximab and Radiotherapy on Outcome of Patients With Aggressive B-Cell Lymphoma and Skeletal Involvement

— Radiotherapy
— NO Radiotherapy

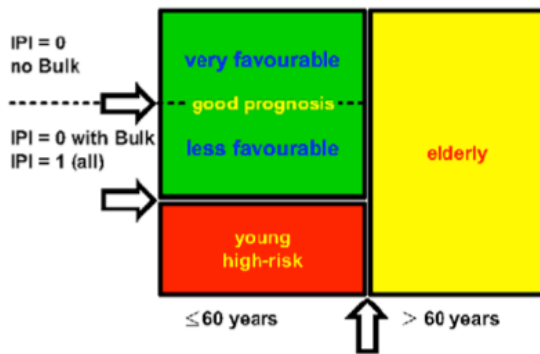


3-year EFS:
75% RT; 36% NO RT

3-year OS:
86% RT; 71% NO RT

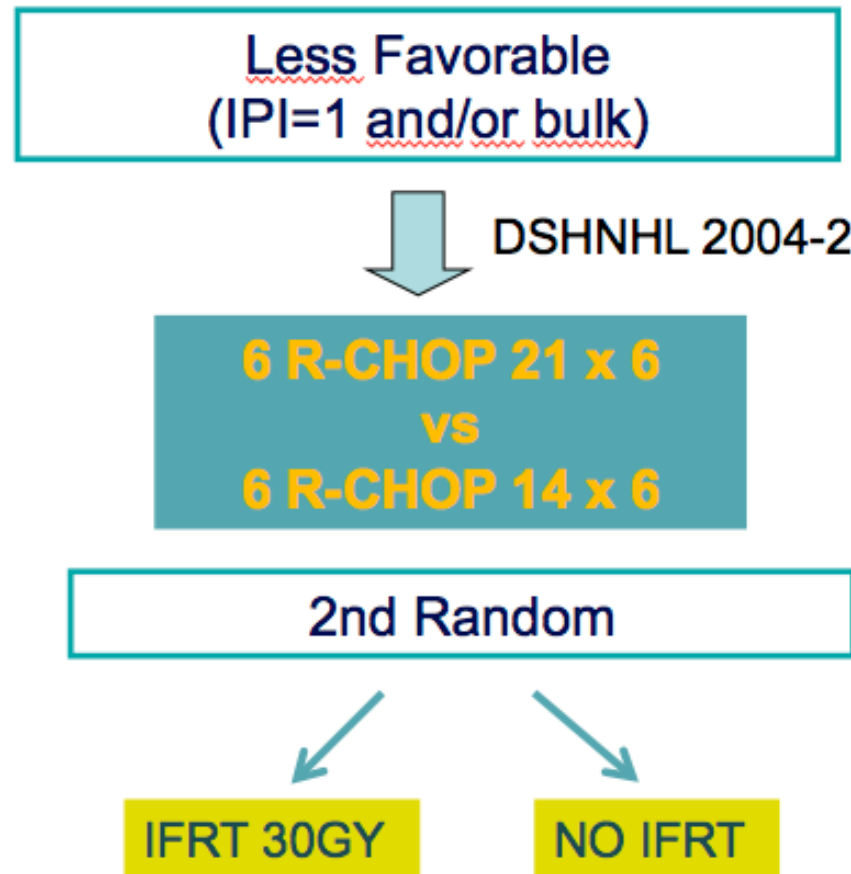
Held et al. JCO 2013;31(32):4115-4122





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

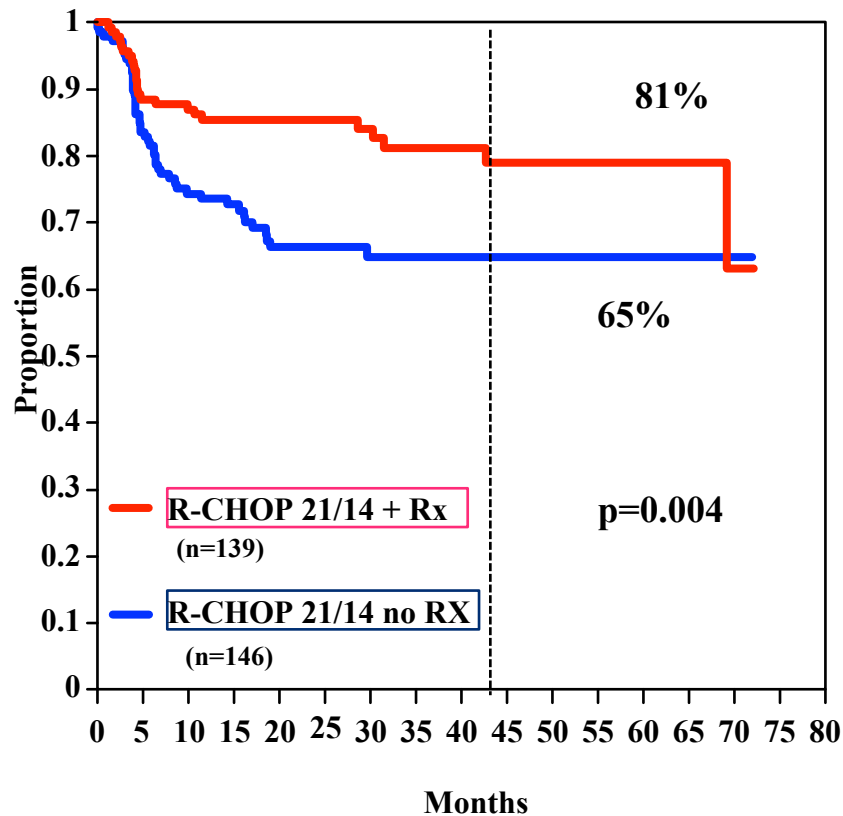
*(supported by Deutsche Krebshilfe)



Patients with extranodal and/or bulky disease (>7.5 cm) were eligible for the RT randomization

UNFOLDER phase 3 study: preliminary results

Patients 18- 60 years, aalPI=0 with bulk or aalPI=1, ITT (n=443)
 Patients randomised to 4 arms (n=285)



GERMAN HIGH-GRADE NHL
 STUDY GROUP (DSHNHL)
www.lymphome.de/en/Groups/DSHNHL



~20% PMBCL

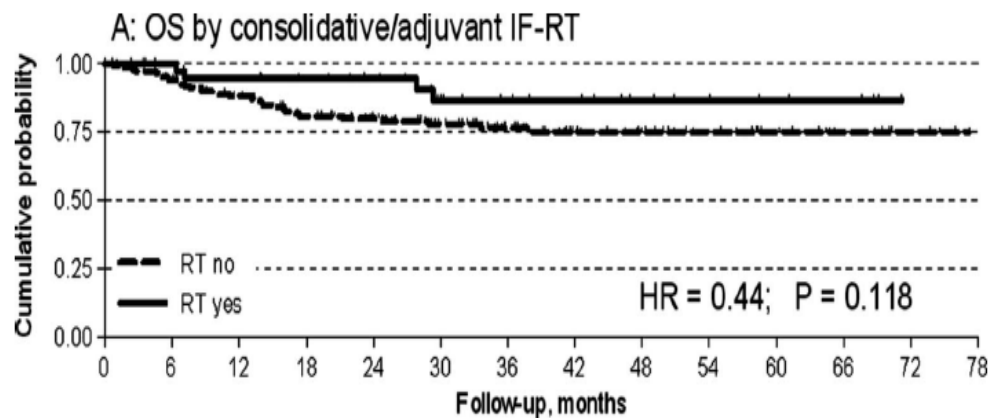
Patients randomized
 to receive or not IFRT
 irrespectively of PET response

Discontinuation of the no RT arms due to evident benefit for IFRT in bulky disease

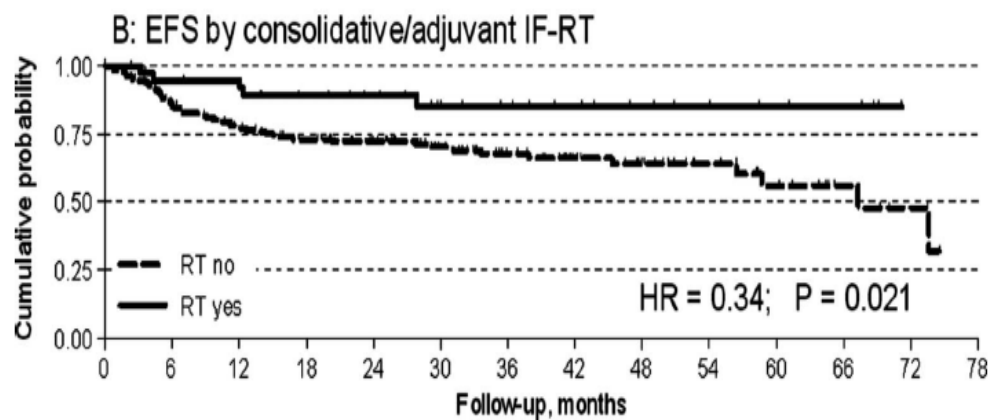
Patients and methods:

- Retrospective analysis of 216 patients treated in 2 trials from GISL with 6 x R-CHOP
- Consolidative/adjuvant IFRT was allowed, at the treating physician's discretion, in patients CR/PR on CT
- Treatment period: 2003-2007
- Stage III-IV: 65%
- 182 patients achieved CR/PR on CT
- Stage I-II: 33% received IFRT
- Stage III-IV: 16% received IFRT

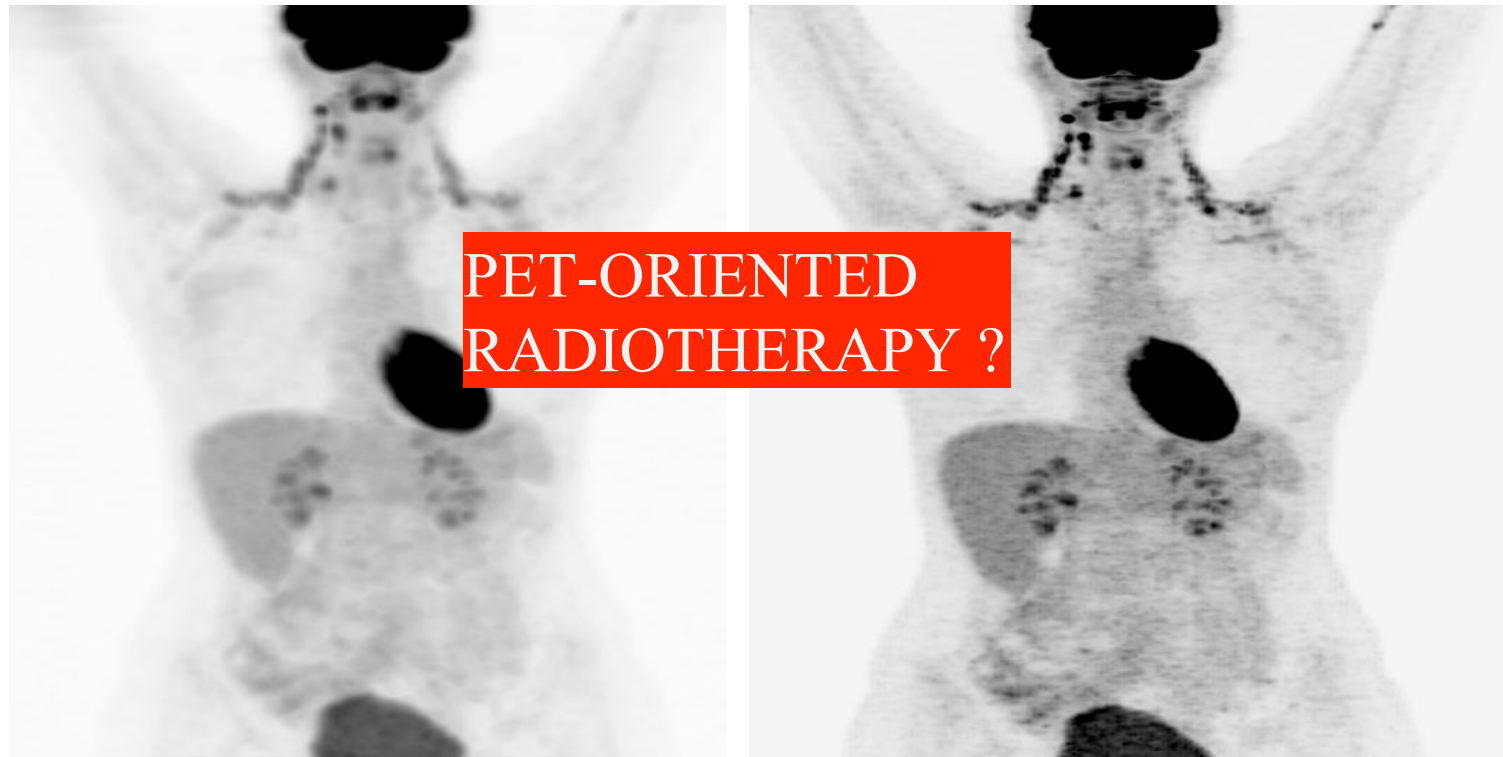
OS and EFS of patients in CR or PR by consolidative/adjuvant IFRT



Median follow up 30 months



To irradiate or not to irradiate ?





The ghost you're trying to reach is currently unavailable.
Please leave a message after the beep.



The Deauville score (5PS)

1 no uptake

2 uptake \leq mediastinum

3 uptake $>$ mediastinum but \leq liver

4 moderately increased uptake compared to liver

5 markedly increased uptake compared to liver and/or new lesion(s)

PET-oriented RT: BCCA experience

N=50 ; stage I-II ; no B symptoms; mass < 10 cm

Median FU 17 months

R-CHOP 21 x 3 → PET

↓

| | N | Terapia | Recidive | 2yFFP | <i>p</i> |
|-----------|------|----------|----------|-------|------------|
| PET neg → | 37 → | CHOP x 1 | 1 | 97% | .09 |
| PET pos → | 13 → | IFRT | 3 | 75% | |

Sehn, ASH 2007

Duke Experience

Results multivariate analysis:

- No RT associated with significantly higher infield failure ($HR=8$, $p=0.01$) and event rates ($HR=4.3$, $p=0.01$)

Conclusion:

- Consolidation RT appears to decrease the risk of local disease progression and overall relapse rates in patients with advanced DLBCL having negative functional imaging after chemotherapy

- The Lysa/Goelams Group recently presented preliminary results of a phase III trial comparing RT versus no RT after 4-6 cycles R-CHOP in patients with nonbulky (<7 cm), stages I and II DLBCL, showing no differences in 5-year event-free (91% v 87%) and OS rates (95% v 90%)
- However, patients with residual fluorodeoxyglucose-avid disease after four cycles of R-CHOP were recommended RT regardless of randomization
- These patients achieved similarly favorable outcome to those with a PET CR after R-CHOP with or without RT, suggesting a role for RT in patients who achieve only a PR to chemotherapy

DLCL 10 IPI = 0 bulk, 1 and/or bulk (7.5 cm) (less favourable according MInT)

PET -1

R-CHOP 14 x 2

PET -2

R-CHOP 14 x 2

CT-4

R-CHOP 14 x 2

CT/PET-6

NR-SD

POS

NEG

Off-study

Single area in previous
involved site (PR)

Multiple areas

Follow-up

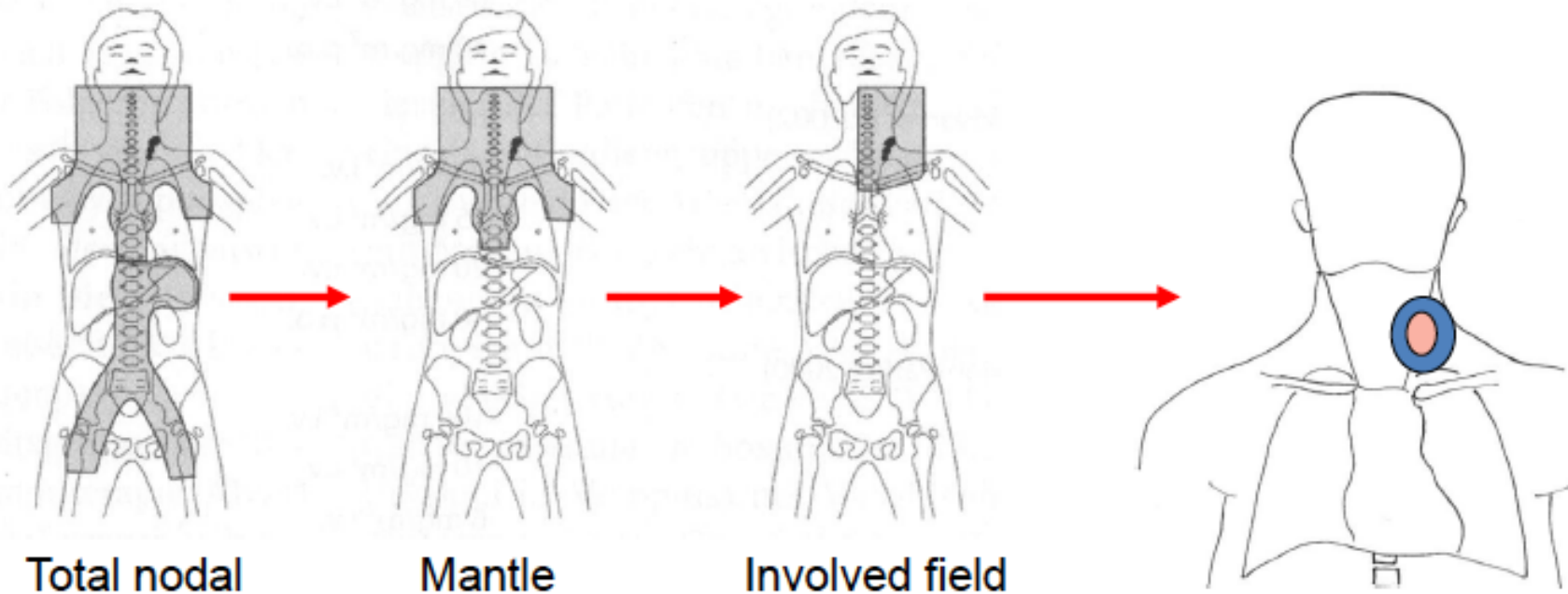
Salvage therapy

ISRT

Modern RT in lymphoma

- Radiation therapy has changed dramatically over the last few decades in terms of both irradiated volumes and dose
- Smaller treatment volumes, lower radiation dose and advanced conformal radiotherapy can certainly allow a safer radiation delivery

Development of RT volumes



Total nodal

Mantle

Involved field

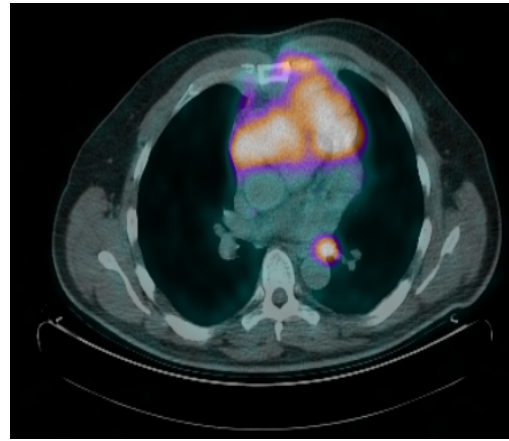
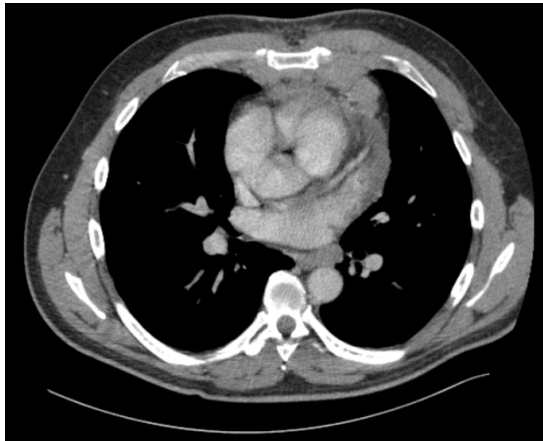
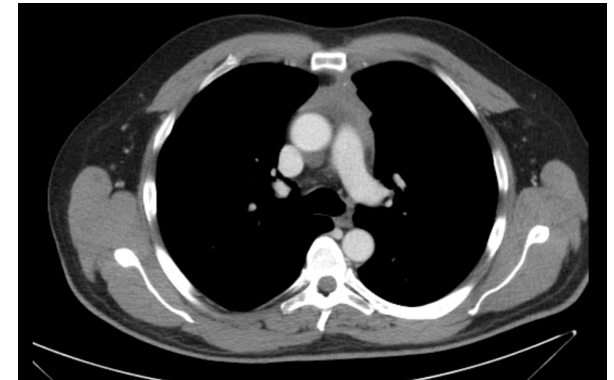
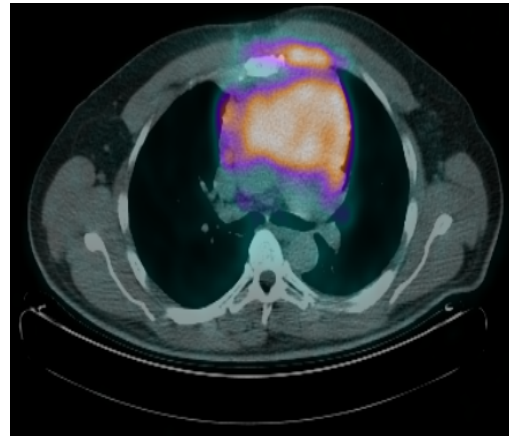
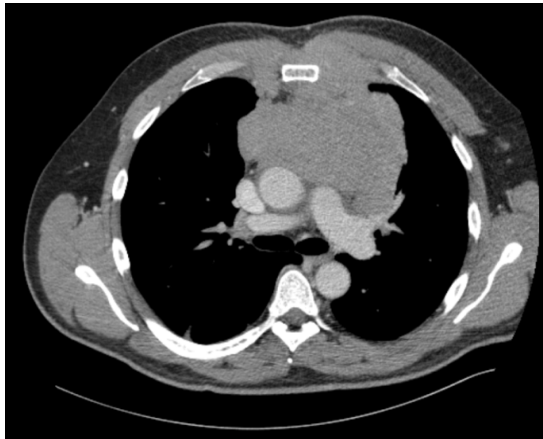
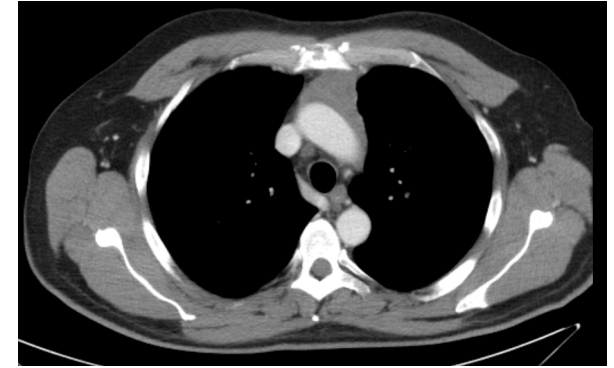
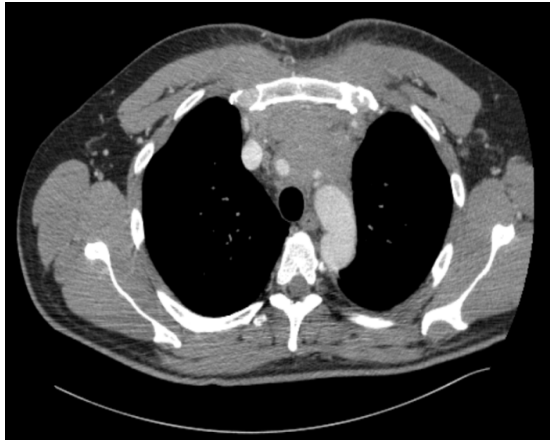
2D planning, based on bony landmarks

Involved node

3D planning, based on lymphoma volume

Gross tumor volume (GTV) (ICRU 83)

- Gross demonstrable extent and location of the tumor (lymphoma)
- Original (before any treatment) lymphoma: pre-chemo GTV
 - Seen on CT: pre-chemo GTV(CT)
 - Seen on FDG-PET: pre-chemo GTV(PET)
- Residual (after systemic treatment) lymphoma: post-chemo GTV
 - Seen on CT: post-chemo GTV(CT)
 - Seen on FDG-PET: postchemo GTV(PET)



Clinical target volume (CTV) (ICRU 83)

- Volume of tissue that contains a demonstrable GTV and/or subclinical malignant disease with a certain probability of occurrence considered relevant for therapy
- Encompasses the original (before any treatment) lymphoma (pre-chemo GTV), modified to account for anatomic changes if treated with chemotherapy up front
- Normal structures (e.g., lungs, kidneys, muscles) that were clearly uninvolved should be excluded
- Residual lymphoma (post-chemo GTV) is always part of the CTV

Clinical Investigation: Lymphoma and Leukemia

Modern Radiation Therapy for Nodal Non-Hodgkin Lymphoma—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Tim Illidge, MD, PhD,^{*} Lena Specht, MD,[†] Joachim Yahalom, MD,[‡]
Berthe Aleman, MD, PhD,[§] Anne Kiil Berthelsen, MD,^{||} Louis Constine, MD,[¶]
Bouthaina Dabaja, MD,[#] Kavita Dharmarajan, MD,[‡] Andrea Ng, MD,^{**}
Umberto Ricardi, MD,^{††} and Andrew Wirth, MD,^{‡‡}, on behalf of the International Lymphoma Radiation Oncology Group

EORTC Lymphoma Group pioneered conformal RT for HL:
Involved node radiotherapy (INRT)

Requirements:

- Good pre-chemo imaging with PET/CT in treatment position
- Image fusion with post-chemo planning CT
- Contouring target volume of tissue which contained lymphoma at presentation



Involved Site Radiotherapy (ISRT)

- Detailed pre-chemotherapy information and imaging is not always optimal in standard clinical practice
- Compared to INRT slightly larger volumes needed to ensure irradiation of all initially involved tissue volumes, but the same principles apply
- In most situations, ISRT will include significantly smaller volumes than IFRT

Hypothesis: Is more dose better?



Phase III Trial on RT Dose

640 Sites of Aggressive NHL

82% DLBCL

86 % stage III-IV

80% as post-chemo consolidative RT

10% received Rituximab

30 Gy in 15 fractions

40-45 Gy in 20-23 fractions

30 Gy vs 40-45 Gy

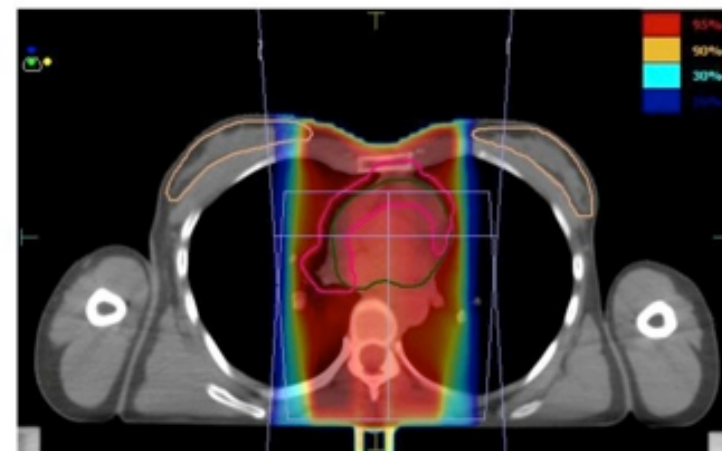
- Median f/u 5.6 years

| | 30 Gy (n=319) | 40-45 Gy (n=321) | P- value |
|---------|------------------|---------------------|-------------|
| 5y FFLP | 82% | 85% | 0.66 |
| 5y OS | 64% | 68% | 0.29 |

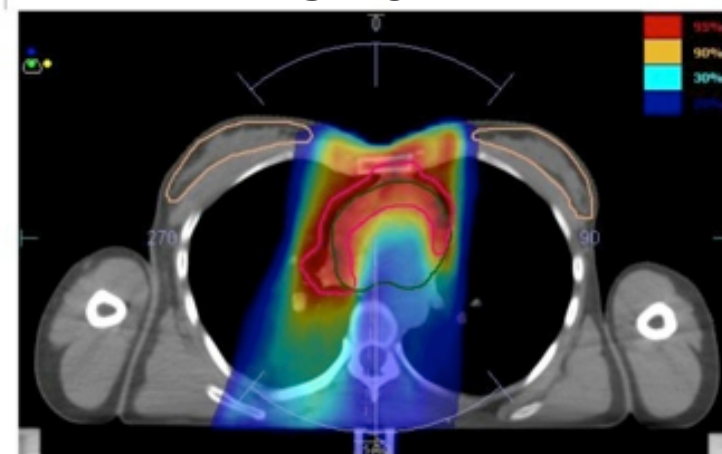
FFLP: Freedom from local progression; OS: Overall Survival

Highly conformal RT

- Only the target volume is treated to the full dose
- Better sparing of normal tissues
- Low-dose bath to the surrounding normal tissues



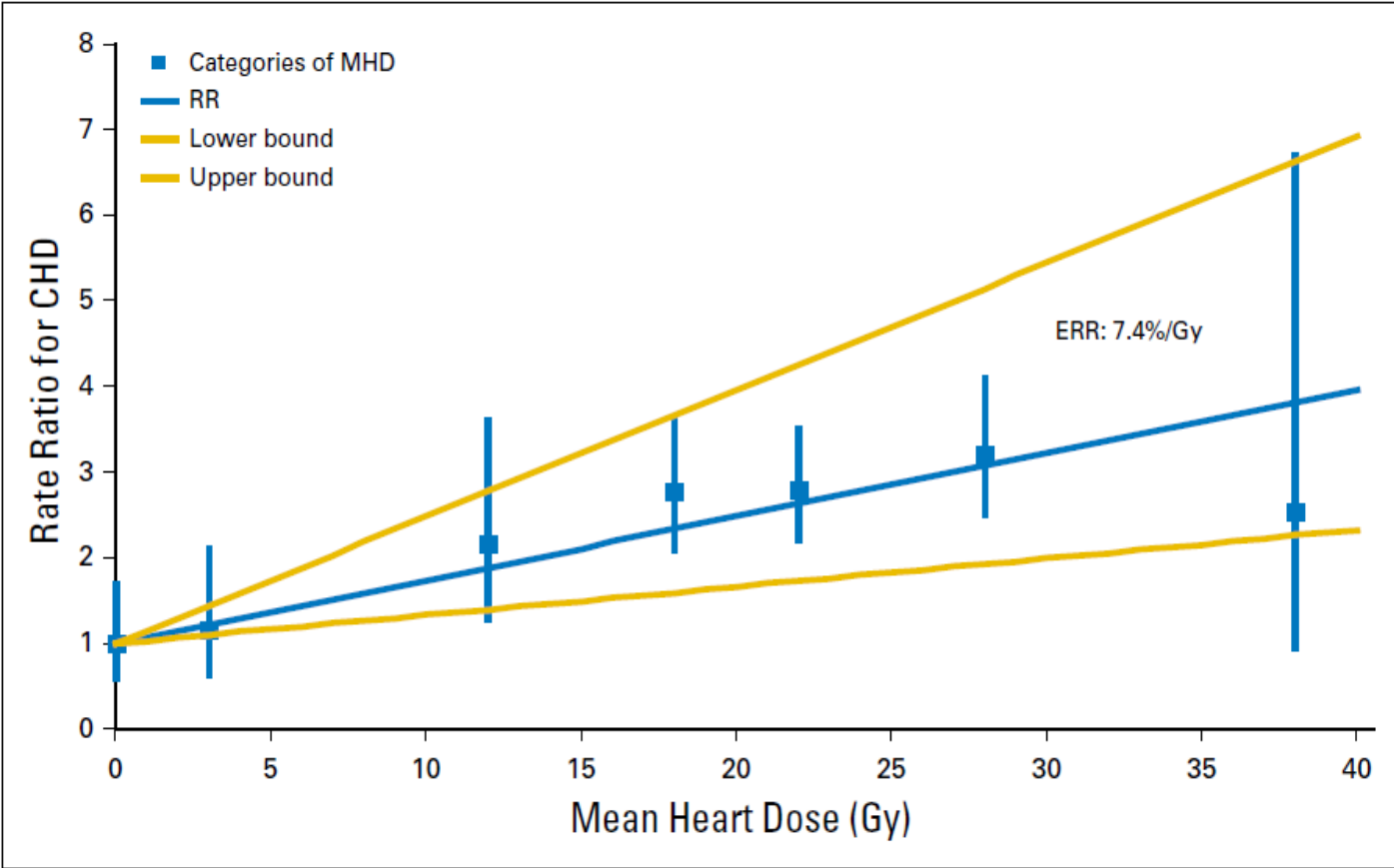
3D-CRT



IMRT (VMAT)

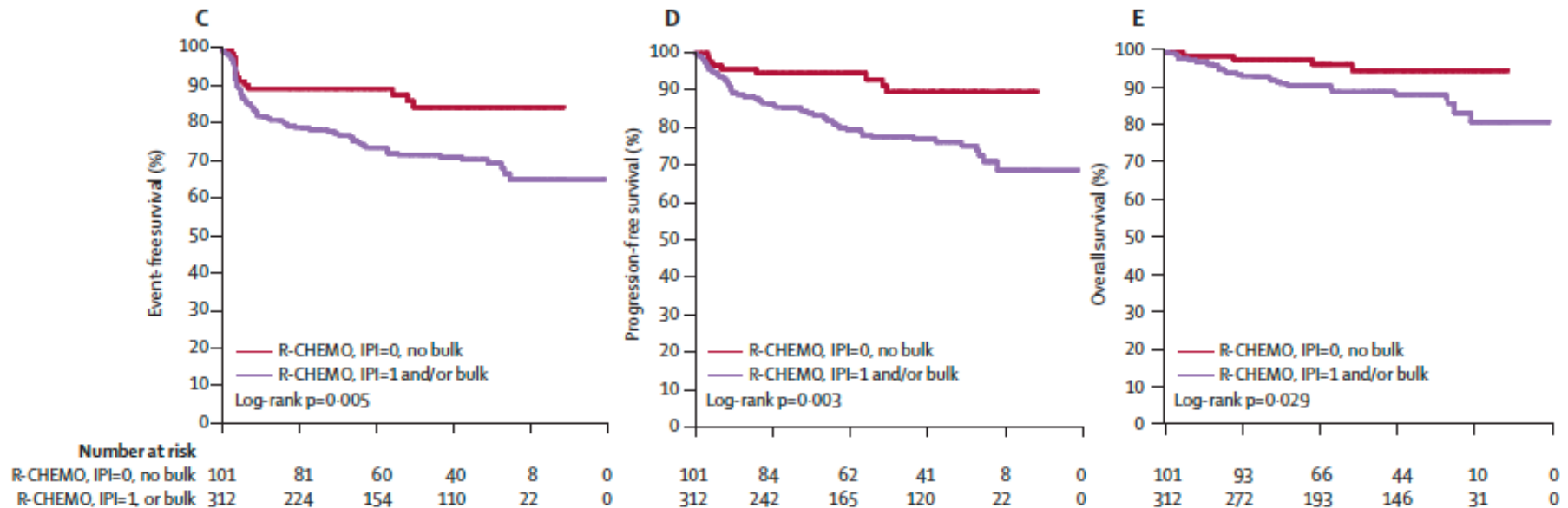
Dose response for CAD

Dose-Response for Coronary Heart Disease After HL



Van Nimwegen et al, JCO 2015

- Given the favorable toxicity profile of RT to 30 Gy administered with modern RT techniques to involved sites, coupled with the suboptimal outcomes for patients with DLBCL, it is difficult to justify withholding a treatment that can positively influence PFS and possibly OS



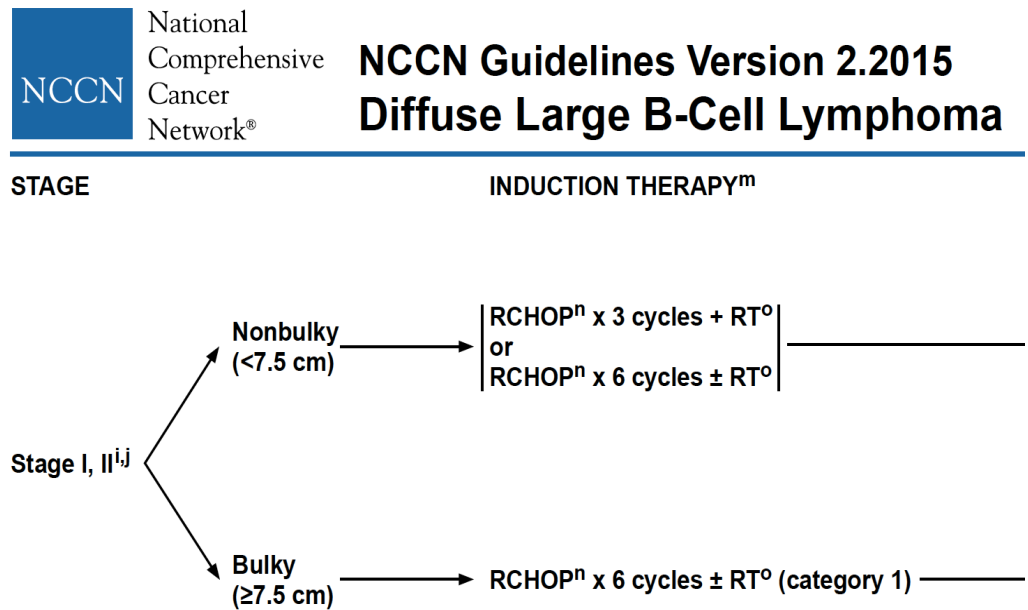
- Late Effects of RT: Distinct Considerations for DLBCL

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

- Although long-term follow-up was limited, secondary malignancies were noted in 5% of the RICOVER-noRT and 6% of the RICOVER-60 trial populations, suggesting that RT did not increase that risk

- Clearly, the issue of treatment consolidation after R-CHOP with IFRT, or alternatively with more chemotherapy, has not been resolved
- In an attempt to satisfy all opinions, NCCN guidelines recommend three cycles of R-CHOP + IFRT for early-stage, non bulky disease, but also allow the administration of six cycles of R-CHOP, with or without IFRT
- 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)

Radiation Therapy after R-CHOP for Diffuse Large B-Cell Lymphoma: the Gain remains

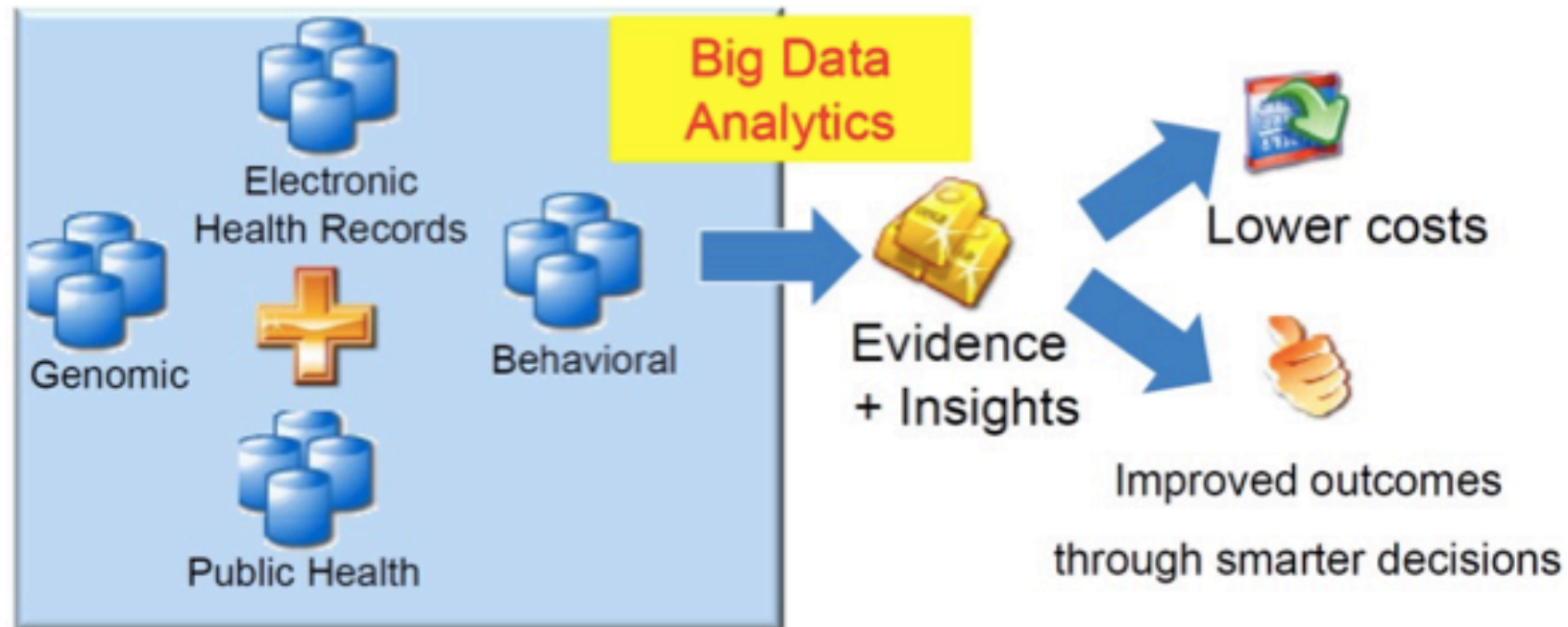


“Big Data”

- **Big data** is a term for data sets that are so large or complex that traditional data processing applications are inadequate.
- Challenges include analysis, capture, data curation, search, sharing, storage, transfer, visualization, querying and information privacy.



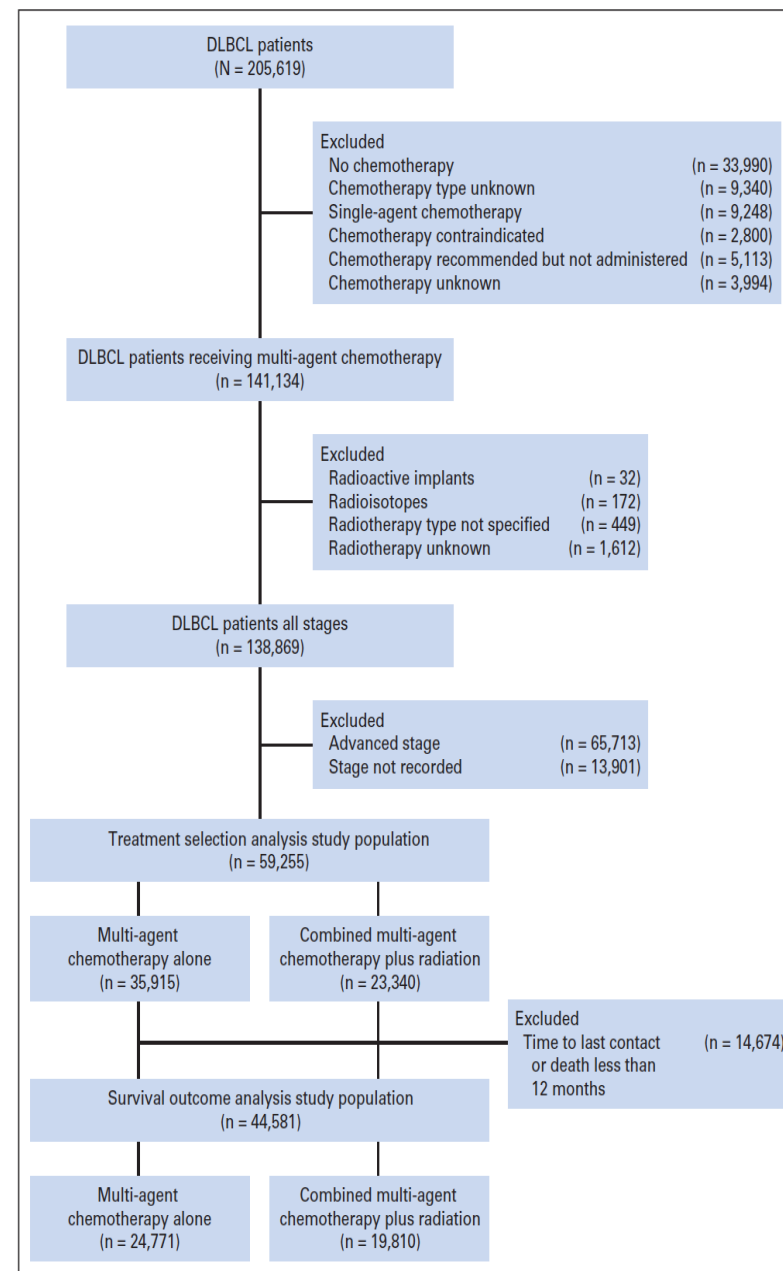
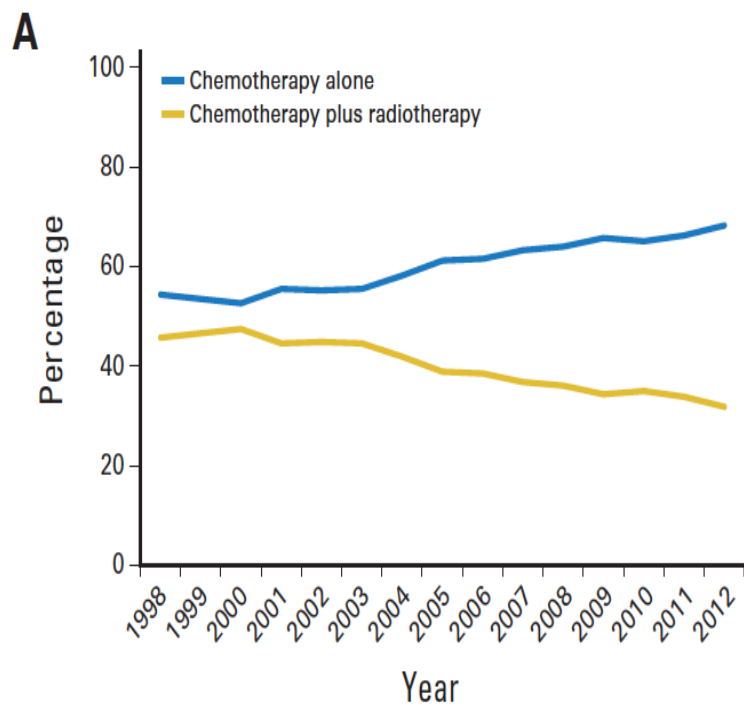
Overall Goals of Big Data Analytics in Healthcare



- Take advantage of the massive amounts of data and provide right intervention to the right patient at the right time.
- Personalized care to the patient.
- Potentially benefit all the components of a healthcare system
i.e., provider, patient, payer (*when applicable*) and management.)

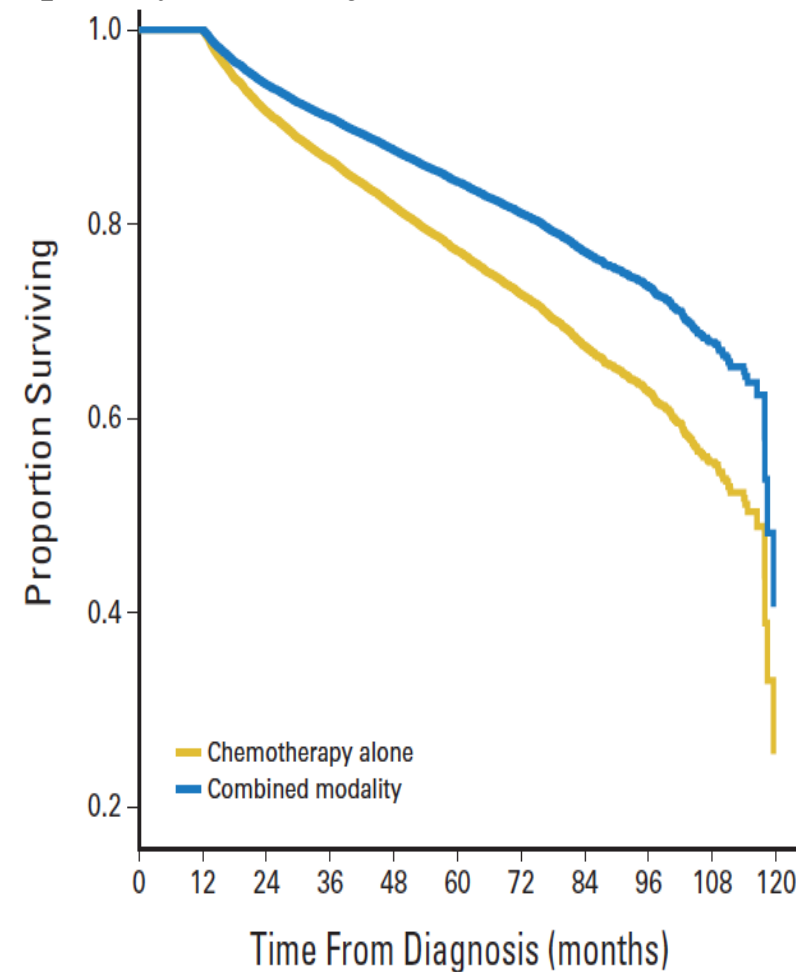
Treatment Selection and Survival Outcomes in Early-Stage Diffuse Large B-Cell Lymphoma: Do We Still Need Consolidative Radiotherapy?

John A. Vargo, Beant S. Gill, Goundappa K. Balasubramani, and Sushil Beriwal



Receipt of RT is associated with a 34% reduction in mortality on multivariable analysis with propensity score adjustment

| Cox Model With Propensity Score | | |
|---------------------------------|---------------------|--------|
| Treatment strategy | | |
| Chemotherapy alone | Reference | |
| Combined modality | 0.66 (0.61 to 0.71) | < .001 |
| Sex | | |
| Male | Reference | |
| Female | 0.87 (0.82 to 0.92) | < .001 |
| Income, US dollars | | |
| < 30,000 | Reference | |
| 30,000 to 35,000 | 0.98 (0.88 to 1.10) | .78 |
| 35,000 to 45,999 | 0.94 (0.85 to 1.03) | .19 |
| ≥ 46,000 | 0.81 (0.74 to 0.89) | < .001 |
| Extranodal disease | | |
| Absent | Reference | |
| Present | 1.11 (1.05 to 1.18) | < .001 |
| Propensity score (IPW)* | 1.09 (1.02 to 1.15) | .008 |



Conclusion

Use of consolidative RT after multiagent chemotherapy in DLBCL is decreasing in the modern era. Selection of treatment strategy is affected by both classical prognostic features and socioeconomic factors. Abandonment of combined-modality therapy in favor of chemotherapy alone negatively affects patient survival.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

Combined-Modality Therapy for Early-Stage Diffuse Large B-Cell Lymphoma: Knowing When to Quit

Dan L. Longo, *Harvard Medical School, Brigham and Women's Hospital, Boston, MA*

See accompanying article doi:10.1200/JCO.2015.61.7654

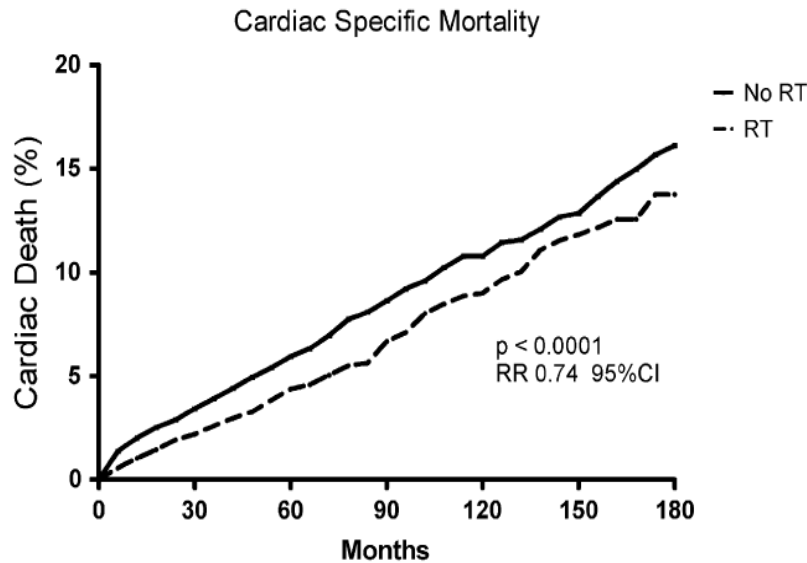
Until we have better evidence for changing our current approach, oncologists should stop using radiation therapy as routine treatment in all patients with stage I and II diffuse large B-cell lymphoma

We should stop arguing and agree that current evidence does not support the use of radiation therapy in all of these patients

Rather, we should focus on conducting prospective clinical trials on selected subsets of patients for whom there may be a reasonable chance of demonstrating improved outcomes with radiation therapy

It is important to know when to quit

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

| | | | | | | | |
|-------|------|------|------|------|------|-----|-----|
| No RT | 9433 | 5129 | 2776 | 1697 | 1043 | 506 | 193 |
| RT | 6021 | 3928 | 2134 | 1189 | 632 | 321 | 123 |

Fig. 1. Cardiac death in patients with stage I–II DLBCL. A comparison between patients treated with and without RT.

A SEER-Medicare analysis on the risk of congestive heart failure in patients with DLBCL age > 65 years showed that any doxorubicin exposure was associated with a 29% (HR, 1.29; 95% CI, 1.02 to 1.62) increased risk of congestive heart failure, and the increased risk rose to 47% (HR, 1.47; 95% CI, 1.13 to 1.9) after six or more cycles of R-CHOP (Hershman, JCO 2008)

- ❑ General suggestions that RT no longer has a role in treating early-stage lymphomas should thus be reexamined carefully

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

H. Tilly¹, M. Gomes da Silva², U. Vitolo³, A. Jack⁴, M. Meignan⁵, A. Lopez-Guillermo⁶, J. Walewski⁷, M. André⁸, P. W. Johnson⁹, M. Pfreundschuh¹⁰ & M. Ladetto¹¹, on behalf of the ESMO Guidelines Committee*

Table 3. Recommended treatment strategies in diffuse large B-cell lymphoma

| Patients ≤60 years | | |
|--|---|---|
| IPI low risk (aaIPI = 0) and no bulk | IPI low risk (aaIPI = 0) with bulk or IPI low-intermediate risk (aaIPI = 1) | IPI intermediate-high risk or IPI high risk (aaIPI = 2, 3) |
| R-CHOP21 × 6 | R-ACVBP and sequential consolidation or R-CHOP21 × 6 + IF-RT on bulk | R-CHOP21 × 6–8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens in selected patients: R-CHOEP14 × 6 or R-CHOP or R-ACVBP plus HDCT with ASCT |
| Consider CNS prophylaxis in patients at risk for CNS progression | | |
| Elderly >60 years | | |
| Fit, 60–80 years | >80 years without cardiac dysfunction | Unfit or frail or >60 years with cardiac dysfunction |
| R-CHOP21 × 6–8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R | Attenuated regimens: R-miniCHOP21 × 6 | Doxorubicin substitution with gemcitabine, etoposide or liposomal doxorubicin or others: R-C(X)OP21 × 6 or palliative care |
| Consider CNS prophylaxis in patients at risk | | |

The treatment of patients with DLBCL requires
multidisciplinary collaboration
to ensure optimal outcome

- ❑ On the basis of currently available data, indications for radiotherapy in patients with DLBCL include bulky disease (> 7.5 cm), skeletal involvement, and partial response to immunochemotherapy among patients with non bulky disease

- ❑ Patients with low risk disease may also benefit from abbreviated chemotherapy and RT instead of prolonged chemotherapy

- ❑ We eagerly await mature results of modern randomized trials that use contemporary immunochemotherapy and functional imaging for response assessment

”There is no doubt that radiation remains the most active single modality in the treatment of most types of lymphoma”

James O. Armitage