

# Rola radioterapii w chłoniakach

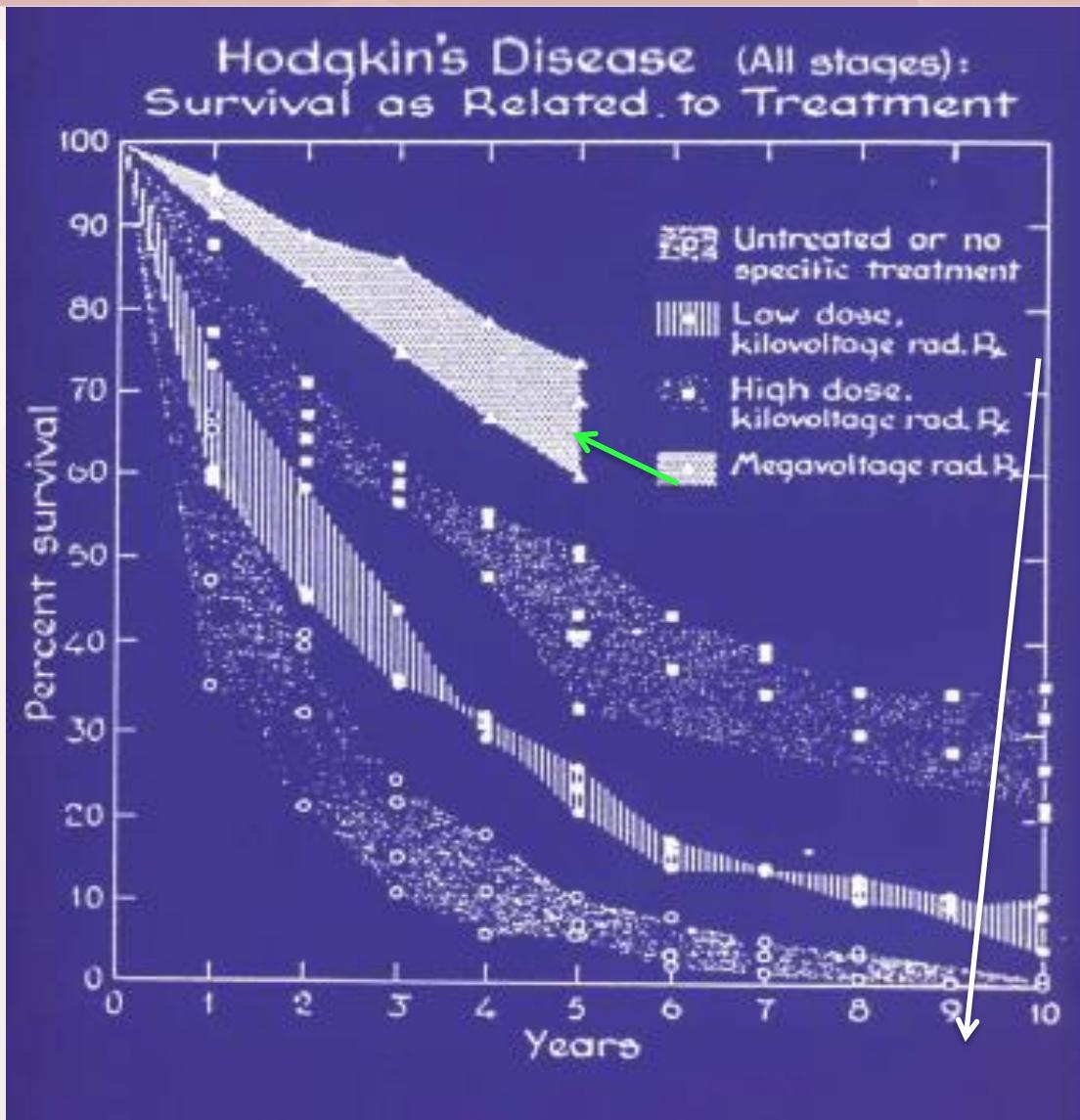
Kraków 04.06.2018

# Radioterapia

- Wykorzystuje cząstki o wysokiej energii (elektrony, protony ) lub promieniowanie np. promieniowanie jonizacyjne celem zniszenia komórek nowotworowych poprzez uszkodzenie ich DNA co prowadzi do apoptozy
- Jest bardzo skuteczne
- Zwykle terapia lokalna (wyjątek TBI)

In 1950-1970

Radiotherapy the domain of HD-Treatment:Cure of localized stages



# Każdy kij ma dwa końce

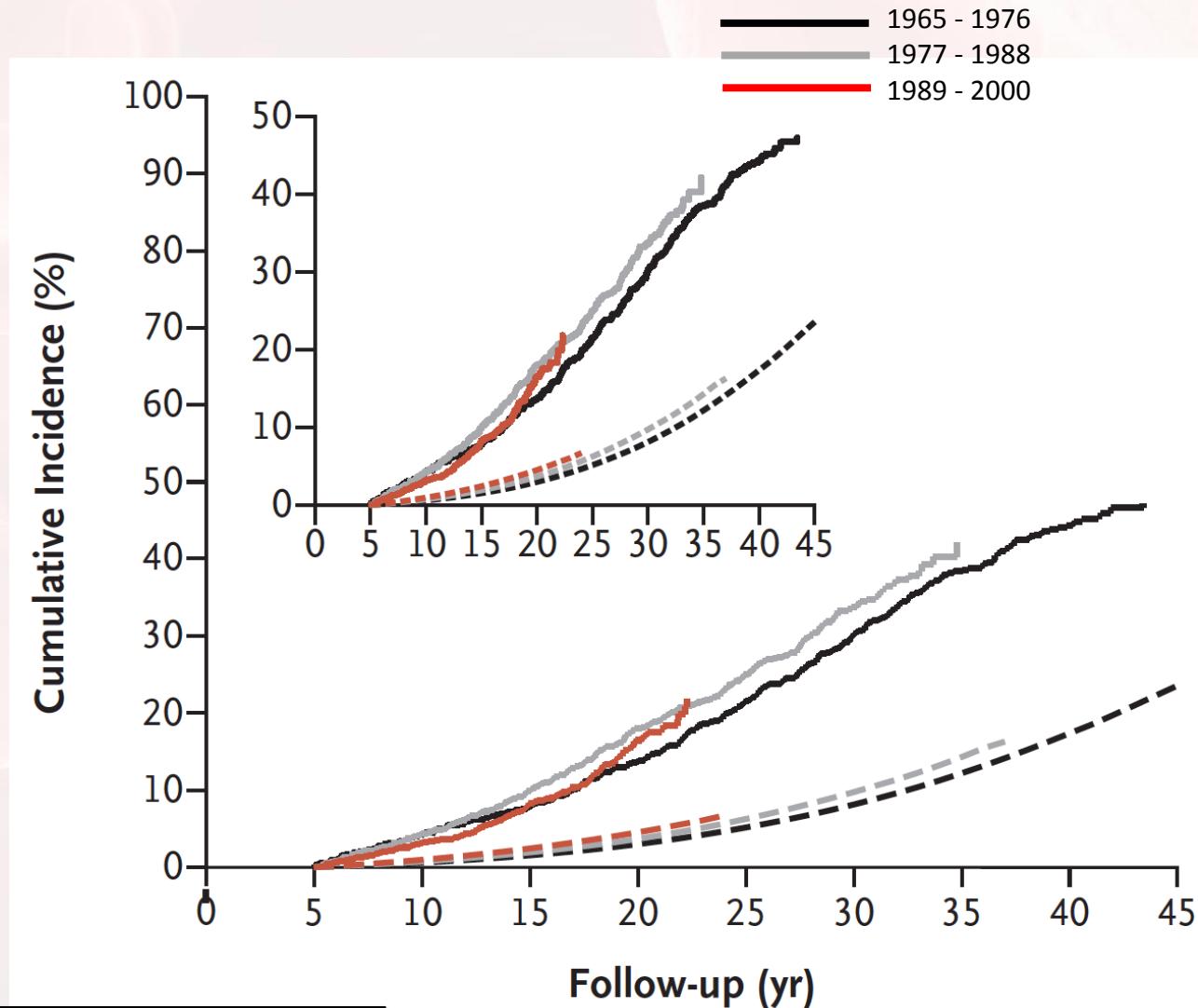


# Radioterapia też ma dwa końce-

- Powikłania ostre (nudności, wymioty, bóle jamy brzusznej, dyzuria, biegunka, suchość w jamie ustnej, dysfagia, zapalenie odbytu)
- Powikłania późne takie jak nekroza kości, bezpłodność, powikłania kardiologiczne,  
**wtórne nowotwory**

# Cumulative incidence of 2nd cancer in 3 different periods

2 <sup>nd</sup> cancer	SIR
Any	4.2
G.I.	4.6
Esophagus	9.5
Lung	6.4
Mesothelioma	15.1
Sarcoma S.T.	12.0
Breast (F)	4.7
Thyroid	14.0
Hemolympho	10.4



**Solid line:** study population

**Dashed line:** normal age-matched population

# Rola radioterapii

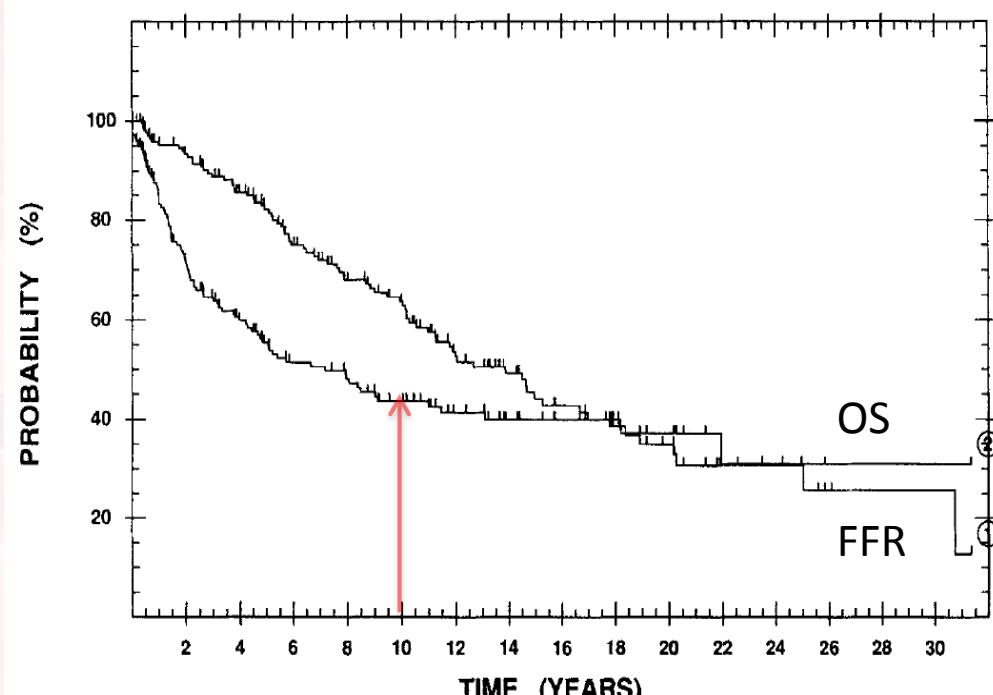
- Jako jedyna opcja leczenia
- W skojarzeniu jednocześnie z chemioterapią
- Jako leczenie konsolidujące po wcześniejszej chemioterapii

# Single curative modality (local treatment)

- Early stage of follicular lymphoma- it is potentially curative- importance of FL staging with PET/CT at diagnosis
- Extranodal (stage IE) lymphomas (some: ocular, skin, stomach)
- Nodular lymphocyte predominant type Hodgkin lymphoma stage I and contiguous II
- Solitary plasmocytoma

# Early stage FL

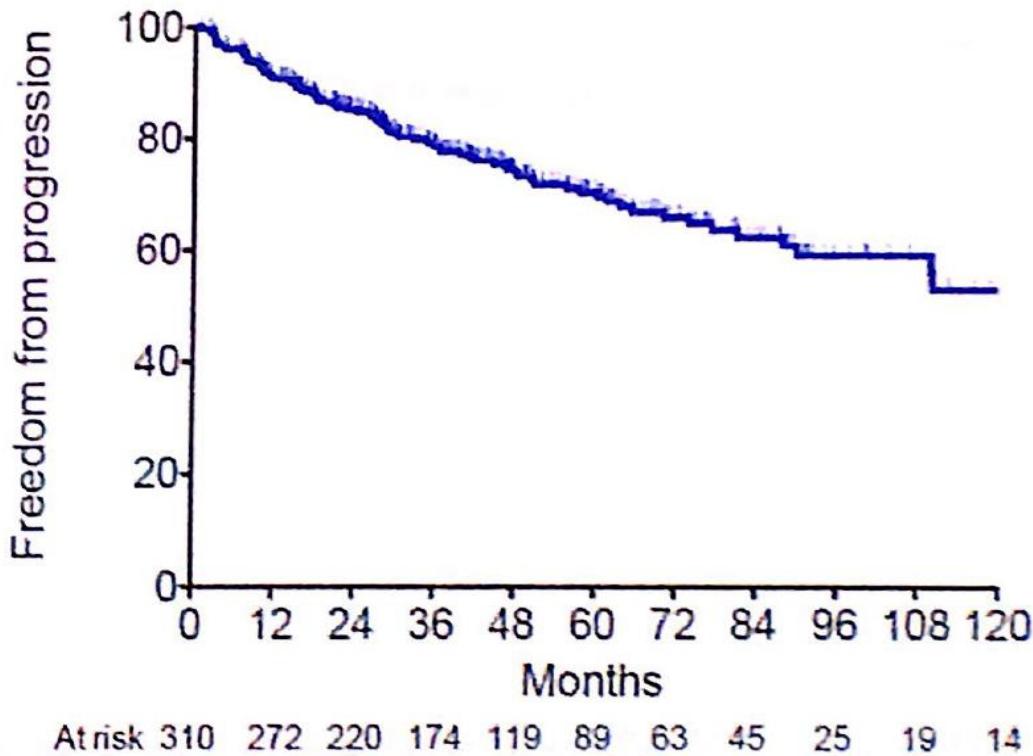
- Early stage of FL- it is potentially curative- 10 year PFS 40-50%
- importance of FL staging with PET/CT at diagnosis- PET/CT upstaged 10-60% of pts
- What is outcome of RT in PET/CT-staged patients?



## Results: FFP and OS

- 5 y FFP = 70.2%  
(from completion of RT)
- 5 y OS = 95.8%.

**Figure 1. Freedom from progression**

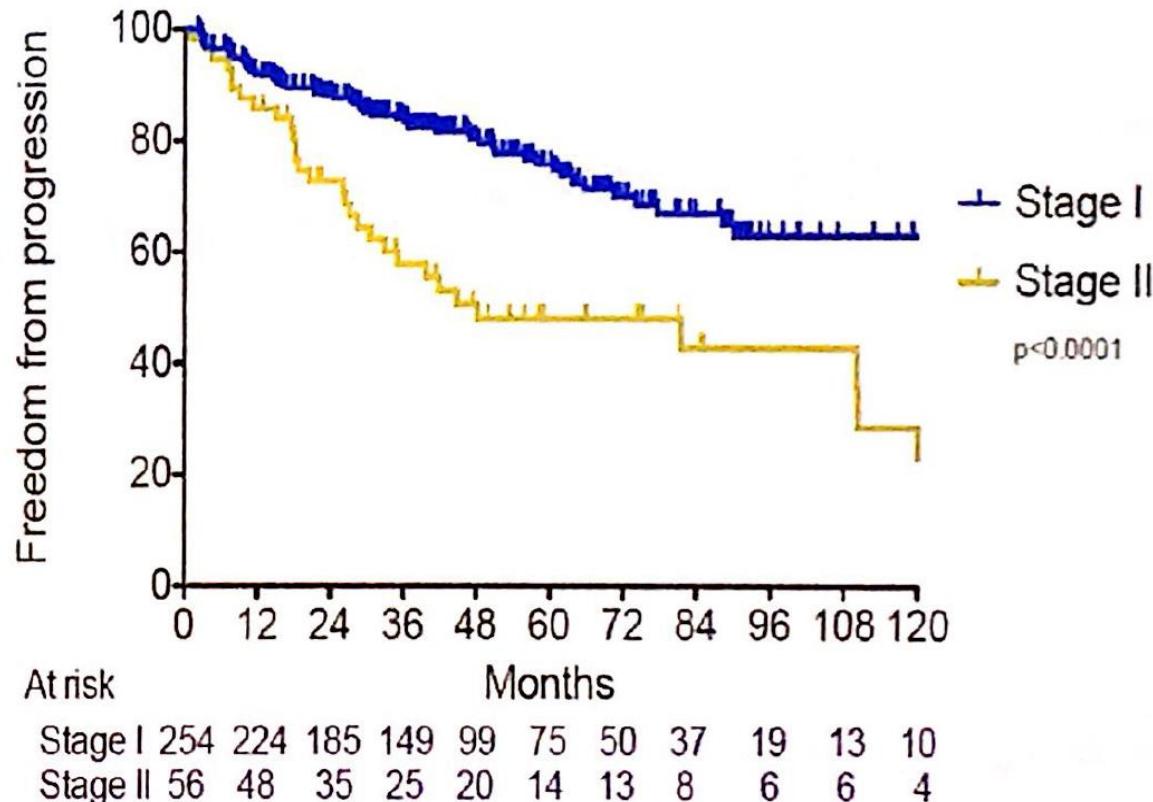


## 5 y FFP by stage

- Stage I = 74.3%
- Stage II = 48.1%

( $p<0.0001$ )

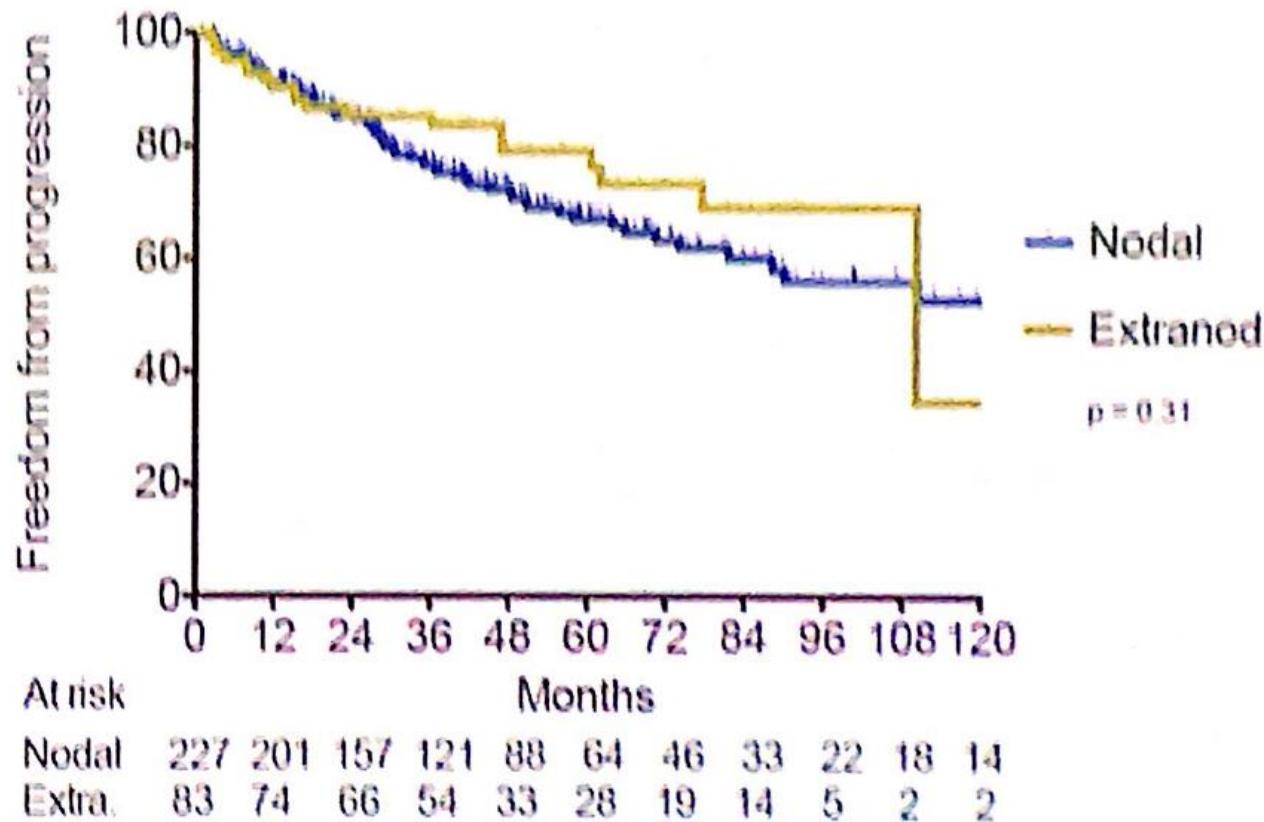
Figure 2. FFP by stage



## 5y FFP by nodal vs extranodal site

No significant difference ( $p=0.23$ ).

Figure 3. FFP by nodal vs extranodal site



## Multivariate analysis of prognostic factors for progression

- Stage II HR= 2,51 (95%CI 1,53-3,77) p=0,0001
- CMR by PET HR= 0,32 (95%CI 0,14-0,74) p=0,0008

Not: Bulk, FLIPI, Extra-nodal disease, age, male sex

## Pattern of relapse

- In-field= 6 pts (1,9%)
- Marginal= 2 pts (0,6%)
- Distant = 80 pts (25,8%) (**90% of all relapses**)

# Jaka dawka RT we wczesnym FL?

2011

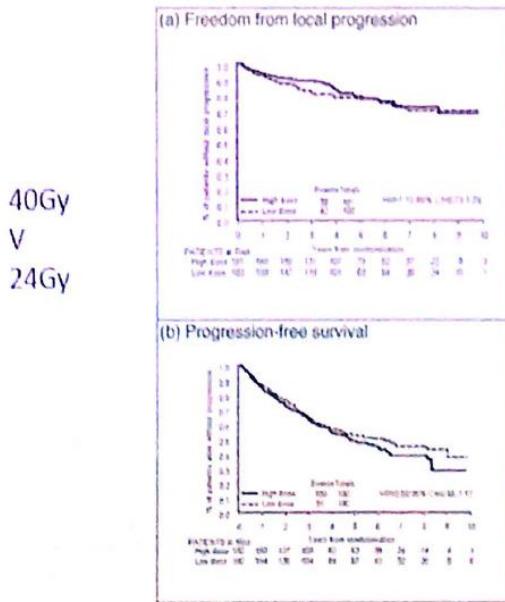


Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma:  
A randomised phase III trial<sup>a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z</sup>

Lisa Lowry<sup>a</sup>, Paul Smith<sup>a</sup>, Wendi Qian<sup>b</sup>, Stephen Falk<sup>c</sup>, Kim Benstead<sup>d</sup>, Tim Blidge<sup>e</sup>, David Lynch<sup>f</sup>, Martin Robinson<sup>g</sup>, Andrew Jack<sup>h</sup>, Peter Hesk<sup>i</sup>\*

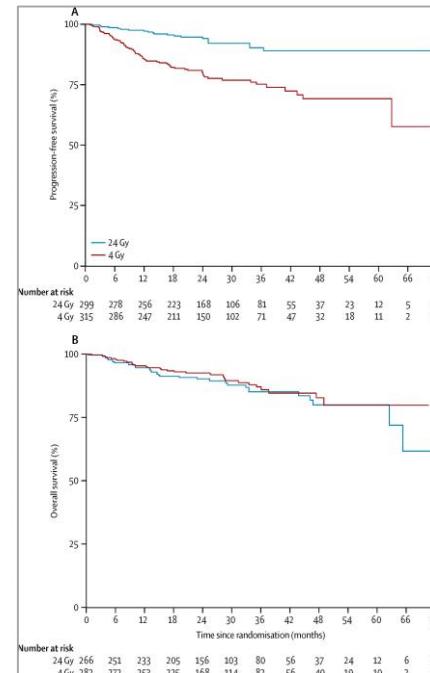
<sup>a</sup>Hematology Dept & Cancer Research Institute, St. George's, UK; <sup>b</sup>MRU, UCL, London, UK; <sup>c</sup>Radiotherapy and Oncology Dept, UCLH, London, UK; <sup>d</sup>Department of Clinical Radiology, University of Bristol, UK; <sup>e</sup>Radiotherapy and Imaging Division, University of Bristol, UK; <sup>f</sup>Centre for Clinical and Academic Excellence in Radiation Oncology, Royal Free Hospital, London, UK; <sup>g</sup>UCLH, UCL, London, UK; <sup>h</sup>Medical Oncology Unit, UCL, London, UK; <sup>i</sup>Department of Radiology, University of Bristol, Bristol, UK; <sup>j</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>k</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>l</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>m</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>n</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>o</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>p</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>q</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>r</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>s</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>t</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>u</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>v</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>w</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>x</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>y</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK; <sup>z</sup>Department of Clinical Oncology, Royal Free Hospital, London, UK



2014

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial

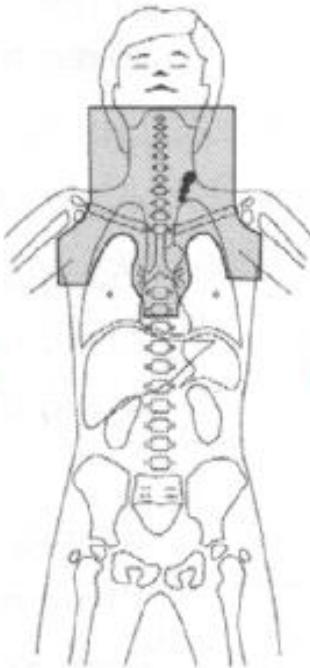
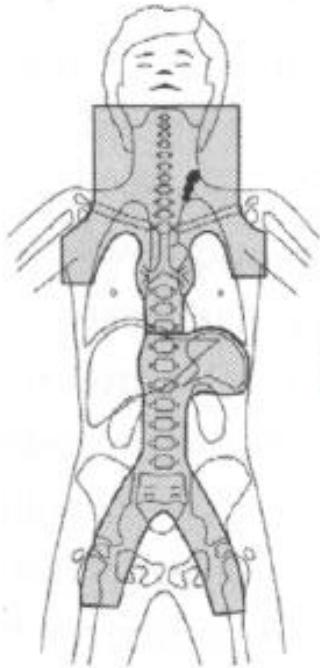
Peter Hesk, Amy Aitkenhead, Debbie Phipps, Paul Smith, Amanda Galloway, Les Gitterman, Steven Allen, Timothy Briggs, Elizabeth Maryhouse, Caroline Branscombe, Pauline Park, Daniel Andrade, Lucy Taylor, Stephen



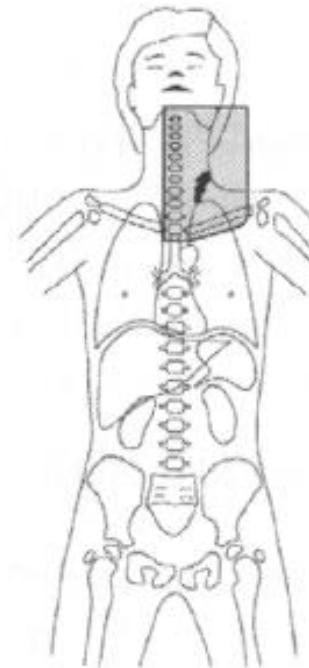
True also for limited marginal zone lymphomas: standard 24Gy in 12 fractions

# What field ?

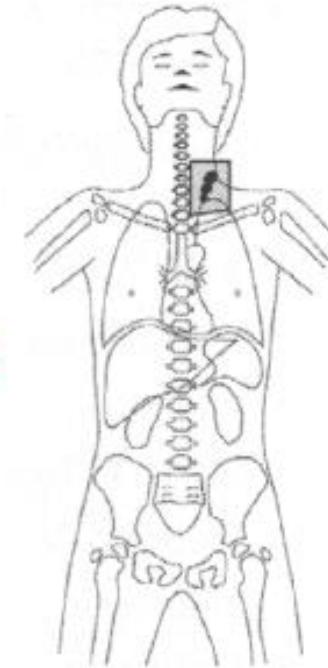
1978



80 % reduction



2010



Total nodal

Regional nodal

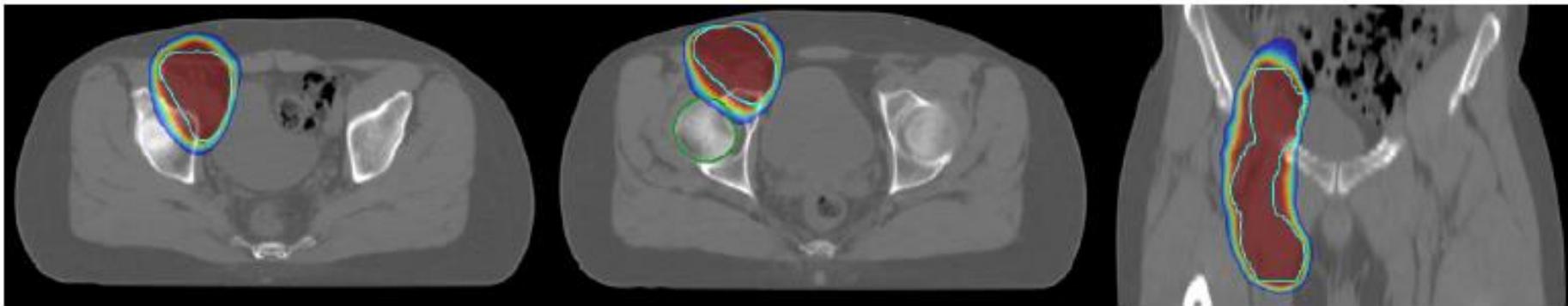
Involved field

Involved node

Unlike classic IFRT, INRT limits the treatment to only pre and post-chemotherapy involved nodal volumes. INRT is based on optimal pre-treatment imaging such as PET/CT. However, the concept of **involved node** was developed for HL as consolidation therapy not as a single modality curative approach.

# Jakie pole napromieniania we wczesnym chłoniaku grudkowym?

- In FL, nodes that are “at risk” (i.e., minimally involved nodes that may be negative on PET imaging but involved by microscopic disease), should be included within radiation volumes
- The International Lymphoma Radiation Oncology Group (ILROG) developed specific consensus guidelines for the delineation of RT volumes for non-Hodgkin’s lymphomas that are slightly different from those developed for HL:
- The new concept, defined as “**involved site radiotherapy**” (ISRT), has been adopted by the NCCN and provides the basis for the current RT protocols.



**Figure 1.** Example of involved site radiotherapy in a case of a 43 years old male patient affected with limited stage FL (right inguinal and central nodes)

[www.mjhid.org](http://www.mjhid.org) *Mediterr J Hematol Infect Dis* 2016; 8; e2016041



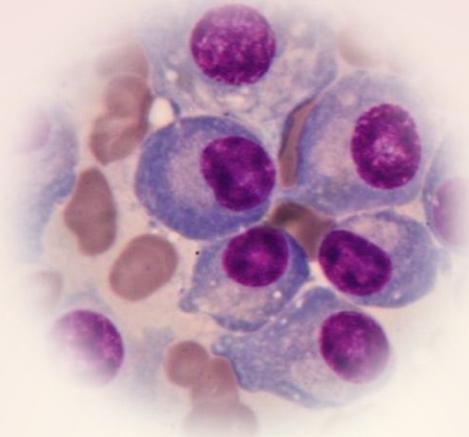
GDAŃSKI UNIWERSYTET MEDYCZNY

# Różnica pomiędzy INRT and ISRT

- INRT= RT should include only the originally involved lymph nodes as defined by the pre-chemotherapy staging PET/CT in treatment position
- ISRT differs from INRT only in the quality and accuracy of the pre-chemotherapy imaging - the extra margins that need to be added to the CTV to compensate for the uncertainties due to suboptimal prechemotherapy imaging= involved and unininvolved regions

# Nodular lymphocyte predominant type Hodgkin lymphoma stage I and contiguous II

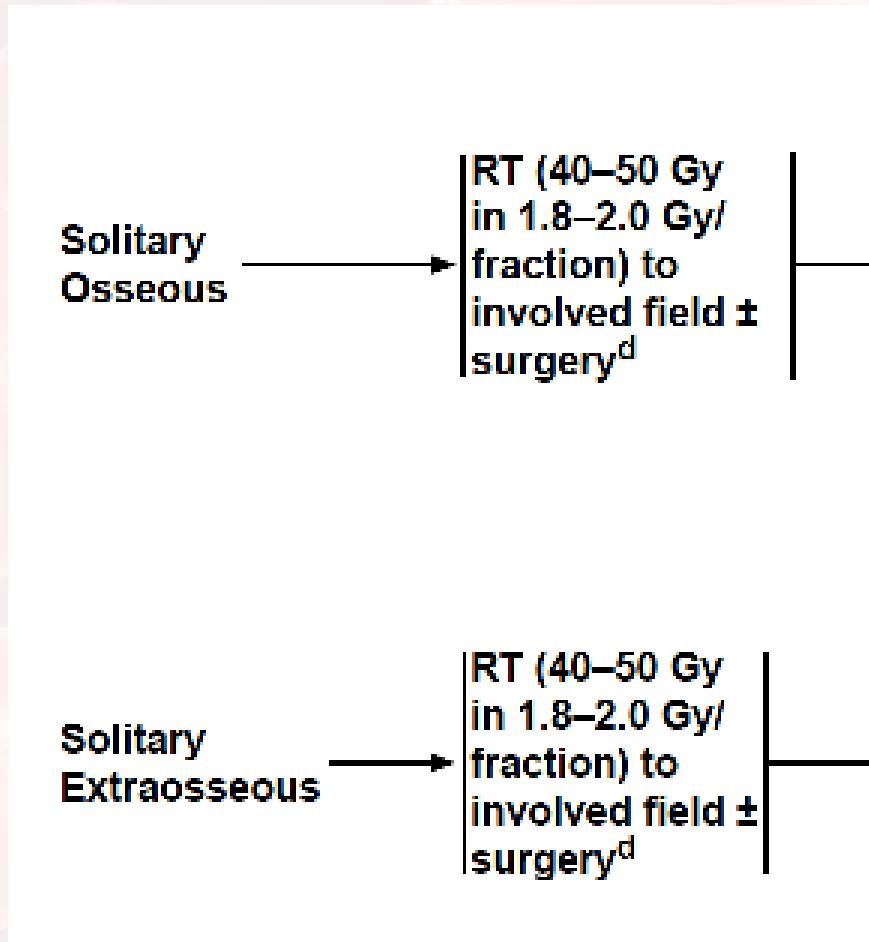
- More than 75% of LPHL early stage, commonly limited to one peripheral site (neck, axilla or groin) involvement of mediastinum is extremely rare
- NCCN recommends for patients without bulky disease and B symptoms involved **site** regional radiation therapy
- Doses of 30 Gy are generally considered sufficient in patients whose nodal disease has been completely excised surgically.
- Uninvolved mediastinum should not be irradiated, avoiding the site most prone to short-term and long term RT related adverse effects
- If B symptoms present search for transformed DLBCL T-cell rich



## Szpiczak odosobniony

# Solitary plasmacytoma

- “multiple” myeloma should be excluded with several blood, bone marrow and imaging tests
- If indeed solitary RT at a dose 40-50Gy is recommended with follow-up interval every 3-6 months



# Jednoczasowo z chemioterapią

- Extranodal NK/T lymphoma nasal type

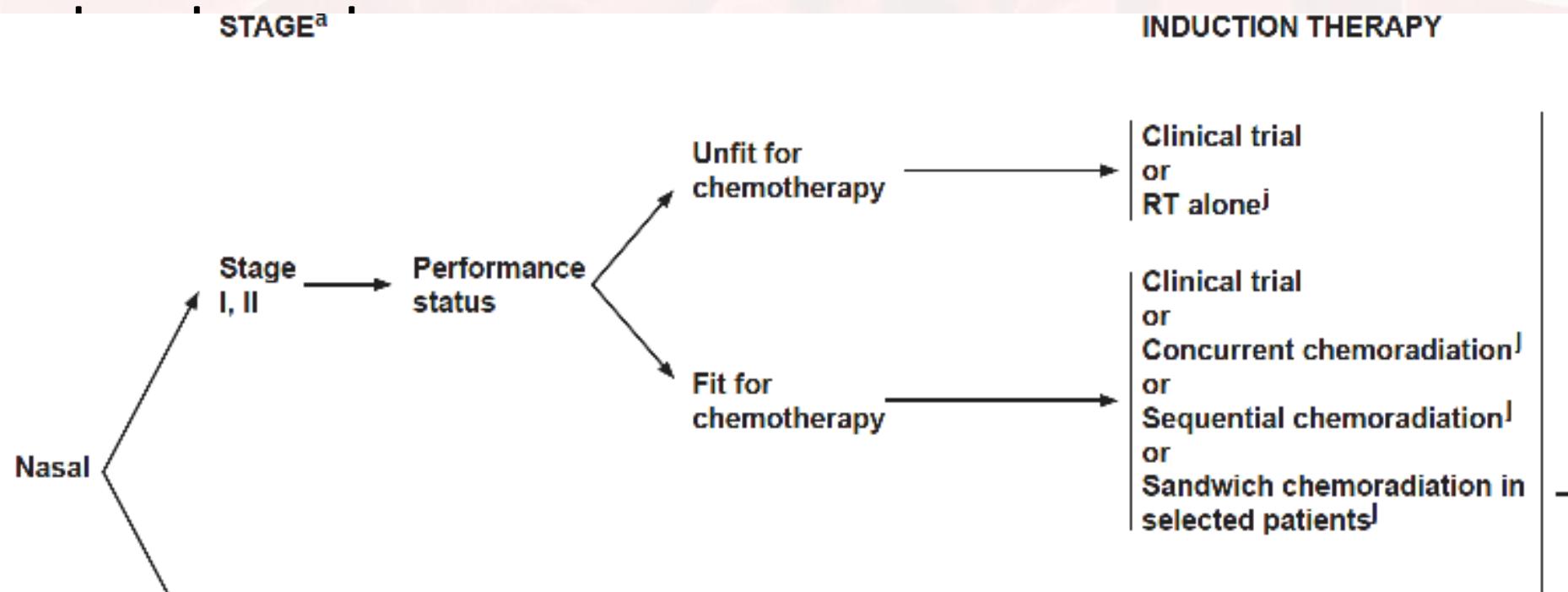


# Extranodal NK/T lymphoma nasal type

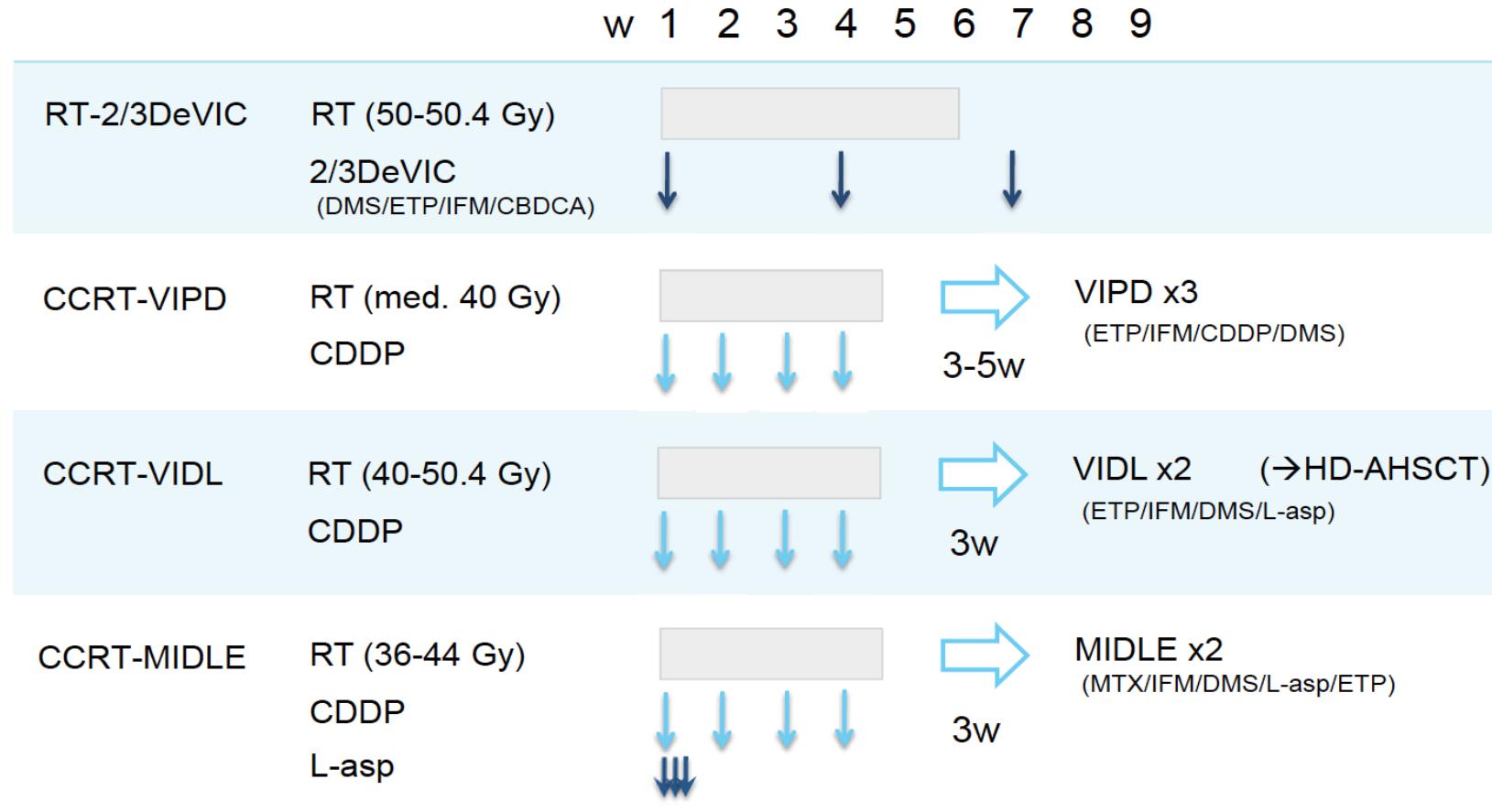
- Very aggressive, although rare in Europa (<1%), more common in Asia and Latin America
- 65% of patients have nasal involvement
- Median age 40-58 years, male sex
- 65% stage I and II
- Of note- it is difficult to identify the tumor extension with CT only due to its low power resolution, is FDG- avid – PET/CT or MRI recommended for staging

# Extranodal NK/T lymphoma nasal type

- For stage I or and contiguous stage II with cervical lymph node involvement RT with concurrent chemotherapy is recommended as first line



# Przykłady schematów terapeutycznych



Journal of clinical and experimental hematopathology  
Vol. 57 No.2, XXX-XXX, 2017

77% OS@5 years 70% (53-82)

# RT JAKO LECZENIE KONSOLIDUJĄCE PO CHEMIOTERAPII

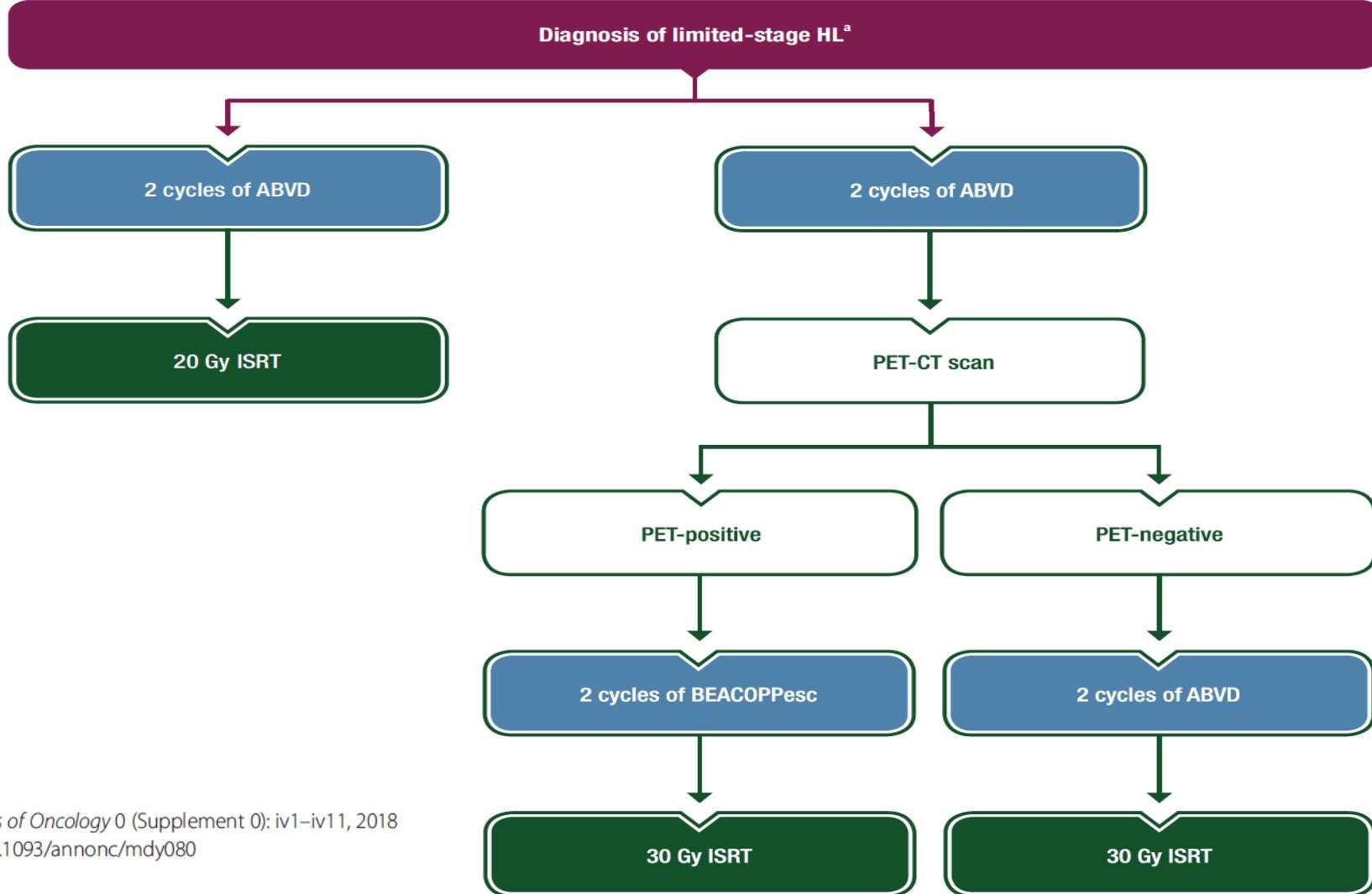
Early and advanced HL, DLBCL

Role of end therapy PET in selecting patients for RT

# Standard leczenia wczesnej postaci HL

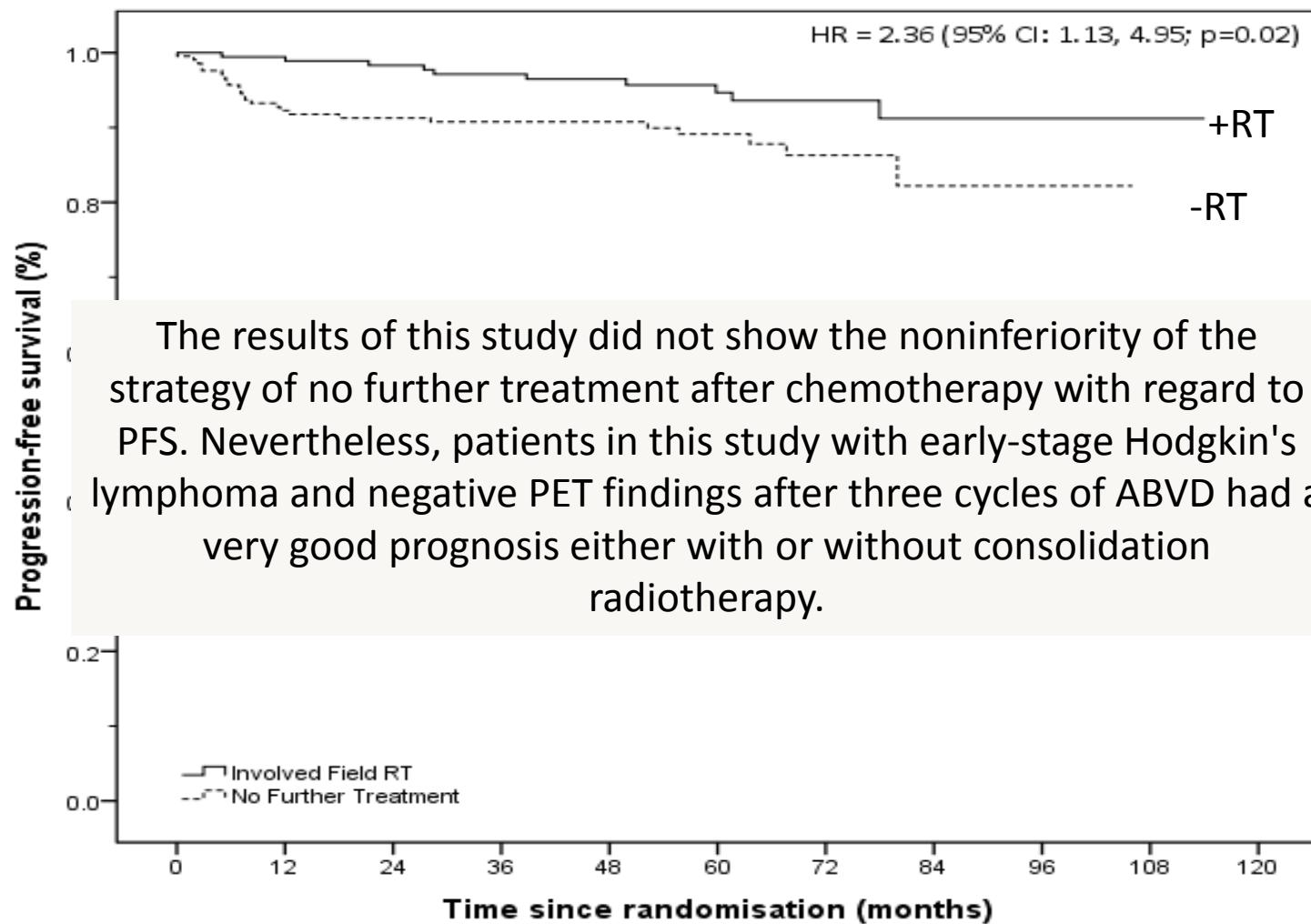
Annals of Oncology

Clinical Practice Guidelines



Annals of Oncology 0 (Supplement 0): iv1–iv11, 2018  
doi:10.1093/annonc/mdy080

# *PFS in the randomised PET -ve population (per protocol analysis, n=392)*



3 year PFS 97.1% (94.7%, 99.6%) vs 90.8% (86.8%, 94.7%)

## Guidelines for the first line management of classical Hodgkin lymphoma

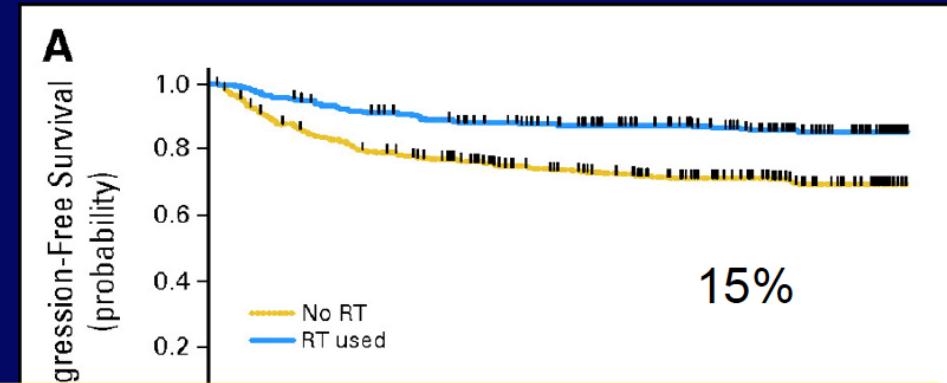
George A. Follows,<sup>1</sup> Kirit M. Ardeshta,<sup>2</sup> Sally F. Barrington,<sup>3</sup> Dominic J. Culligan,<sup>4</sup> Peter J. Hoskin,<sup>5</sup> David Linch,<sup>2,6</sup> Shalal Sadullah,<sup>7</sup> Michael V. Williams<sup>8</sup> and Jennifer Z. Wimperis<sup>9</sup> for the British Committee for Standards in Haematology

### Recommendations:

**The decision to omit RT from the management of IA/IIA non-bulky patients should involve discussion with a radiation oncologist (1B) and patients choosing to omit RT need to be aware of the balance of risks between RT and additional cycles of chemotherapy. (1B)**

*'It is recommended therefore that **score 1 or 2** is used to define a complete metabolic response (CMR) if omission of 'standard' radiotherapy treatment is being considered in discussion with patients.'*

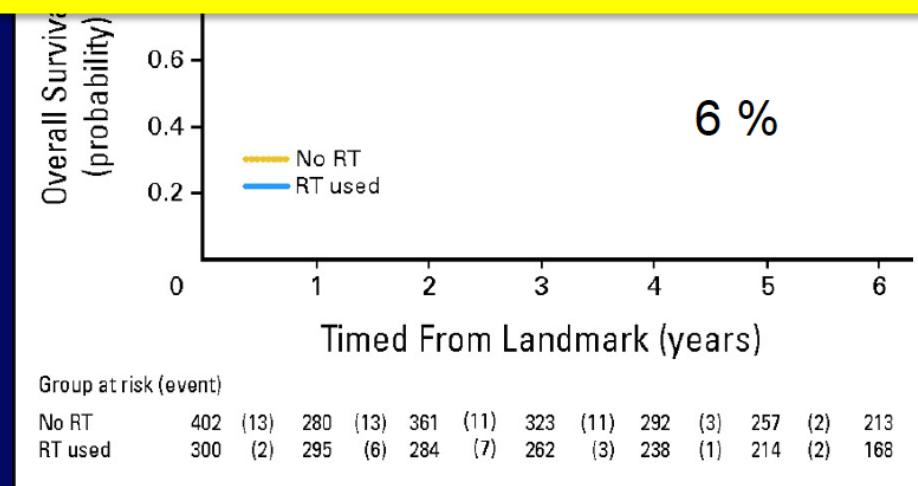
# Consolidation Radiotherapy Is Associated with Improved Outcomes after Chemotherapy for Advanced Hodgkin Lymphoma : Analysis of Results from the UKLG LY09 Trial



This suggests that RT contributes significantly to the cure rate for advanced HL, although patient selection for combined modality treatment requires better definition in prospective trials.

pts no RT. Improved 5 yr OS : 93%  
in pts given RT, 87% in pts with no RT.

- A similar magnitude of effect seen for RT irrespective of subgroups divided by bulk, baseline IPS, or chemotherapy



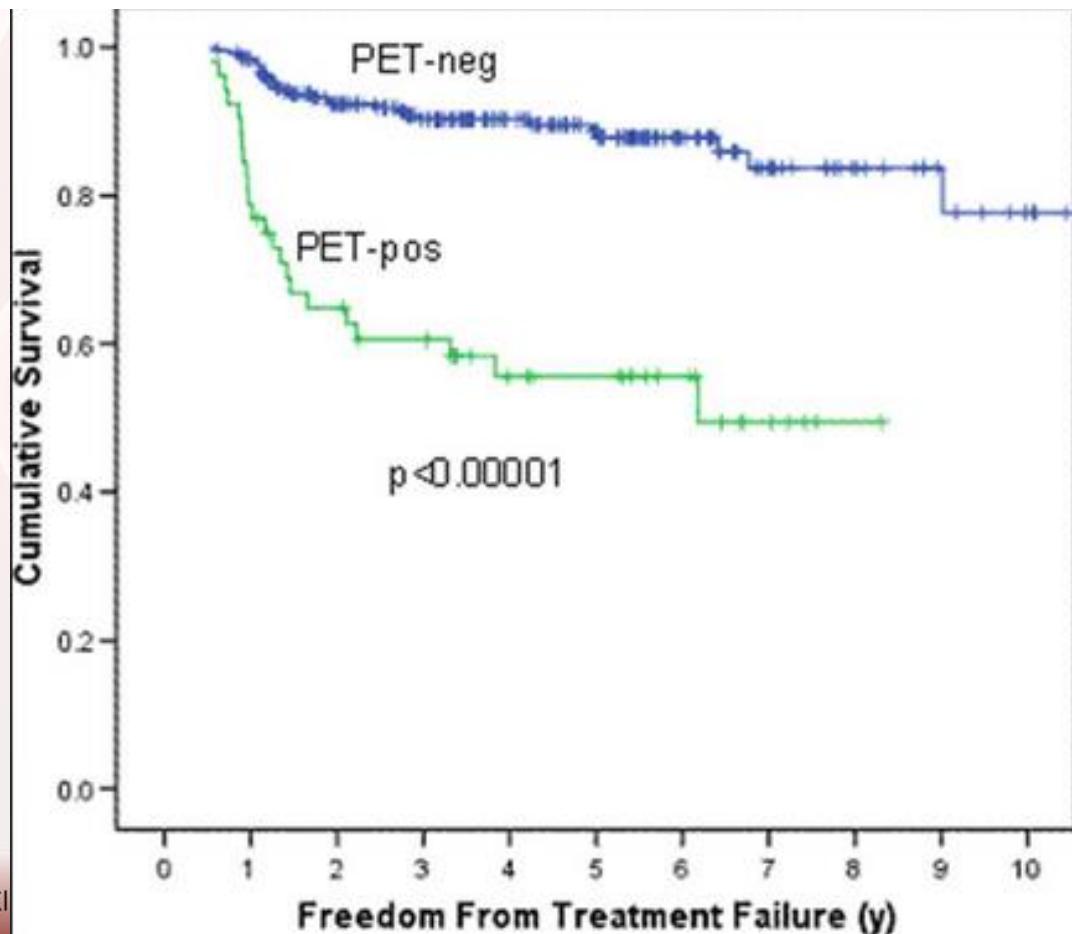
# **SHOULD WE USE END-THERAPY PET IN ADVANCED HL TO SELECT PATIENTS FOR CONSOLIDATION RT ?**

# Patients with advanced stages

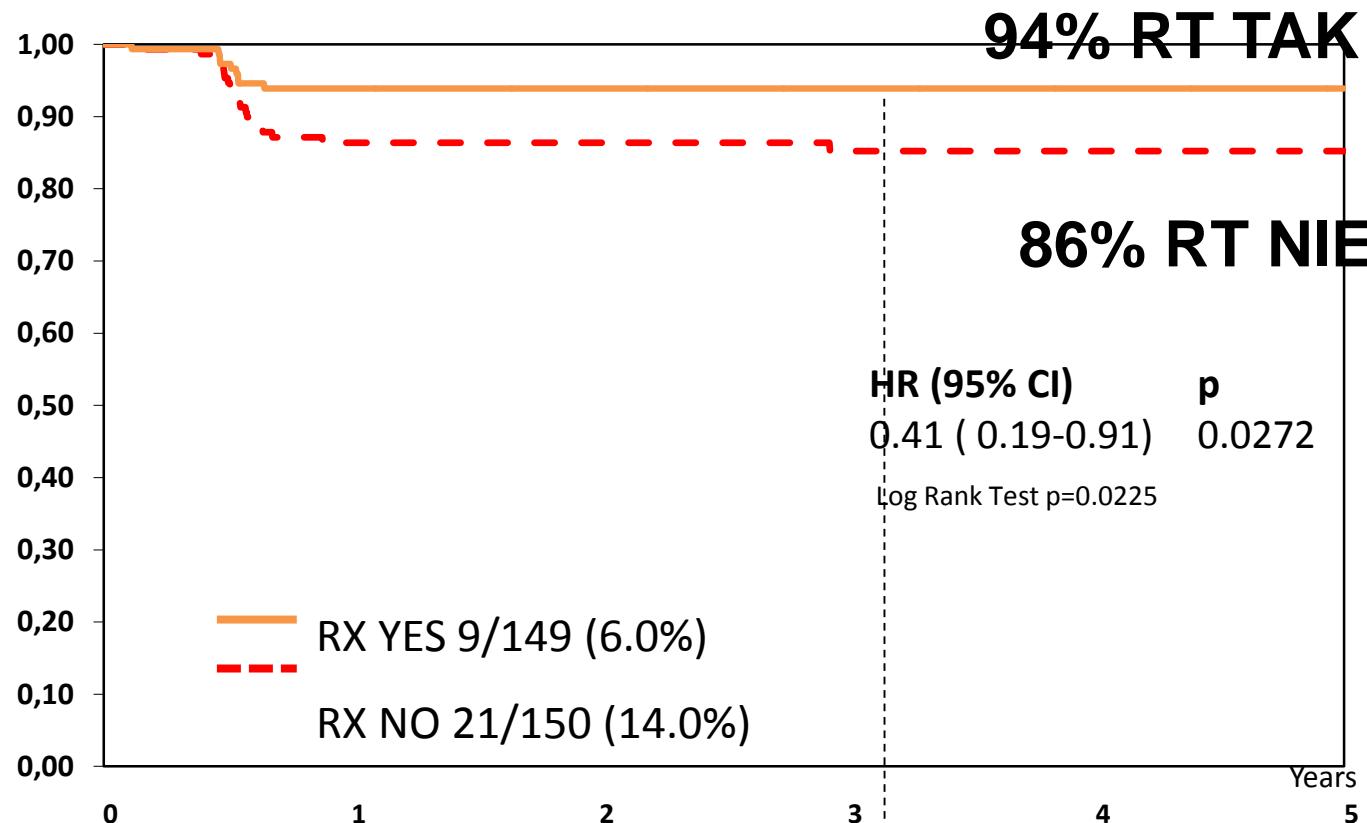
Advanced Stage Classical Hodgkin Lymphoma Patients with a Negative PET-Scan Following Treatment with ABVD Have Excellent Outcomes without the Need for Consolidative Radiotherapy Regardless of Disease Bulk at Presentation

Kerry J. Savage, MDMSc<sup>1,2</sup>, Joseph M. Connors, MD<sup>1</sup>, Diego R Villa, MDMPH\*<sup>1</sup>, Greg Hapgood, MD<sup>1</sup>, Alina S Gerrie, MD<sup>1</sup>, Tamara N Shenkier, MD\*<sup>3</sup>, David W Scott, MBChB, PhD\*<sup>4</sup>, Randy D. Gascoyne<sup>5</sup>, Francois Benard, MD\*<sup>6</sup>, James Morris, MD\*<sup>7</sup>, Tom Pickles, MD\*<sup>7</sup>, Christina Parsons, MD\*<sup>7</sup>, Don Wilson, MD\*<sup>6</sup>, and Laurie H. Sehn<sup>1</sup>

+ Author Affiliations



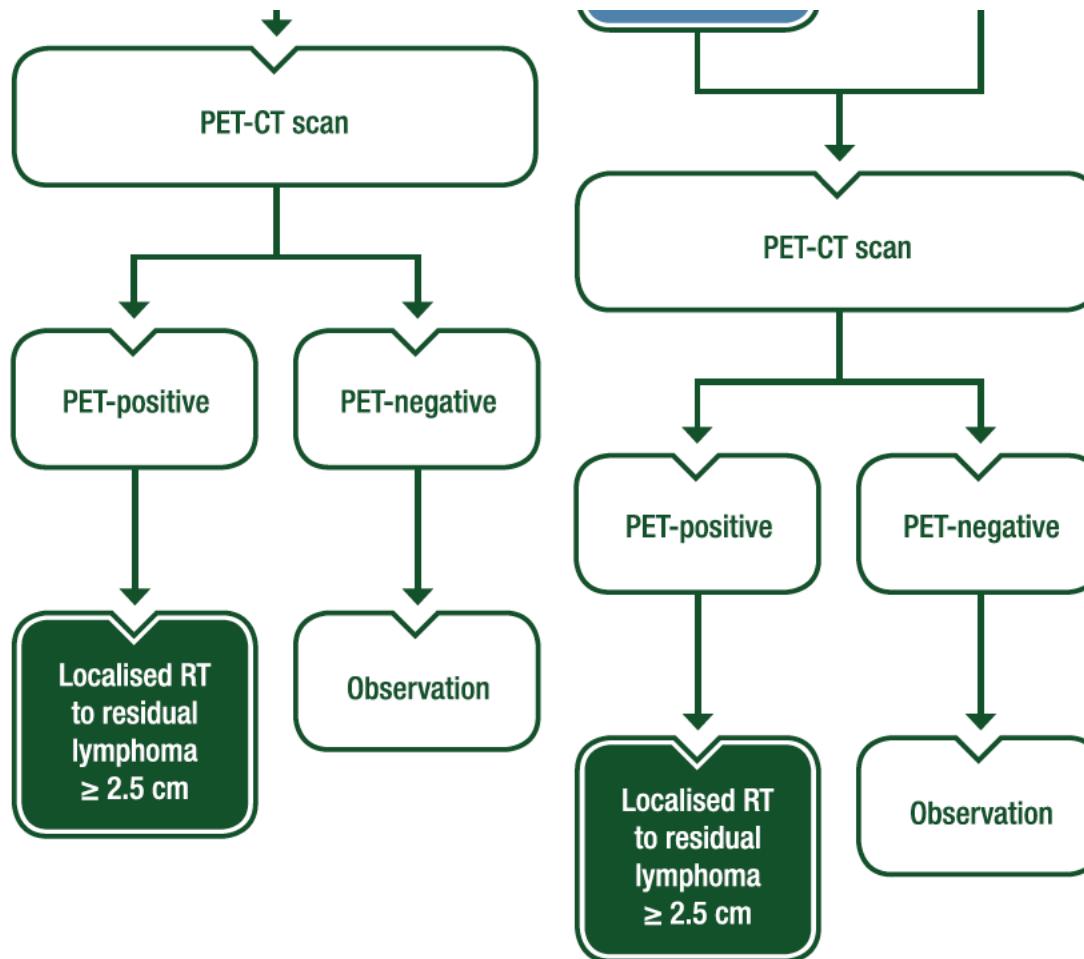
# Przeżycie wolne od niepowodzeń u chorych PET-2(-) w zależności od stosowania RT (N=299) Badanie włoskie



Patients at risk (Events)

RX NO	150	(7)	143	(13)	119	(0)	111	(0)	104	(0)	91	(1)	69	(0)	40	(0)	10	(0)	3	(0)
RX YES	149	(4)	144	)	129	(0)	123	(0)	111	(0)	99	(0)	82	(0)	63	(0)	21	(0)	6	(0)

# Zalecenia ESMO 2018- postać zaawansowana



n = 739 PR ≥  
2.5cm

## HL advanced stage HD15

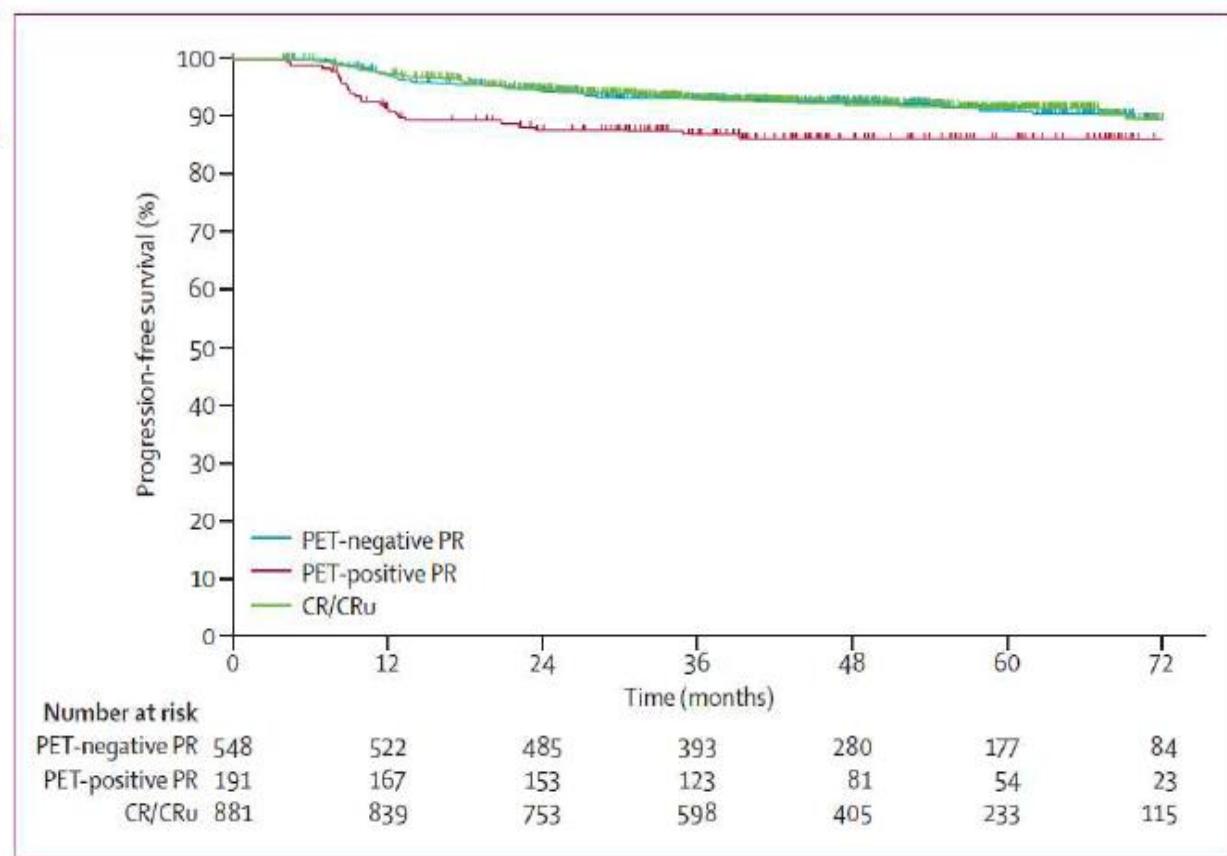
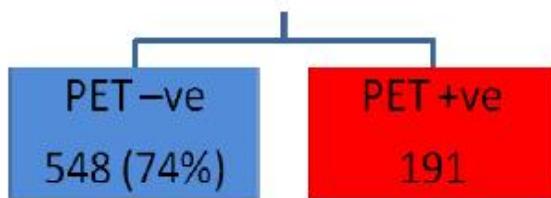


Figure 3: Progression free survival for PET study objective

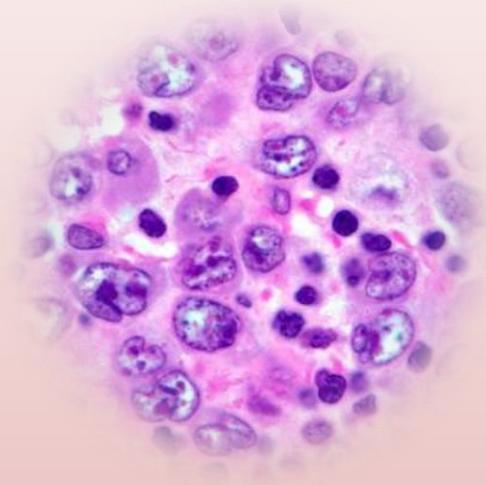
PR=partial remission at the end of chemotherapy. CR/Cru=complete remission without or with residual abnormalities at the end of chemotherapy.

11% had RT

Originally published by the Lancet  
[Engert A et al 2012 379(9828), May 12 pp1791-9]

# Current standard (2018)

- RT- ISRT (30Gy) is still recommended for ABVD treated patients to selected PET positive sites
- For BEACOPPesc treated patients RT is recommended only to end therapy PET positive sites regardless of the size of residual mass



**DLBCL**

---

# The role of RT in DLBCL

## *Before the Rituximab era:*

- *Favor RT*
  - 8 CHOP vs 8 CHOP + RT (ECOG, JCO 2004)
  - 3 CHOP + RT vs 8 CHOP (SWOG, NEJM 1999)  
but not confirmed with 17 yr Fup (JCO 2016)
- *Favor Chemo alone*
  - 3 CHOP + RT vs ACVBP (GELA, NEJM 2005)
  - 4 CHOP vs 4 CHOP + RT (GELA, JCO 2007)

# The role of RT in DLBCL

- Limited DLBCL non-bulky – ?
- Advanced DLBCL + bulky- ?

# **R-CHOP with or without Radiotherapy in non-bulky limited-stage diffuse large B cell Lymphoma (DLBCL): Final results of the prospective randomized phase III 02-03 trial from the LYSA/GOELAMS-FILO**

Lugano 2017

Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K,

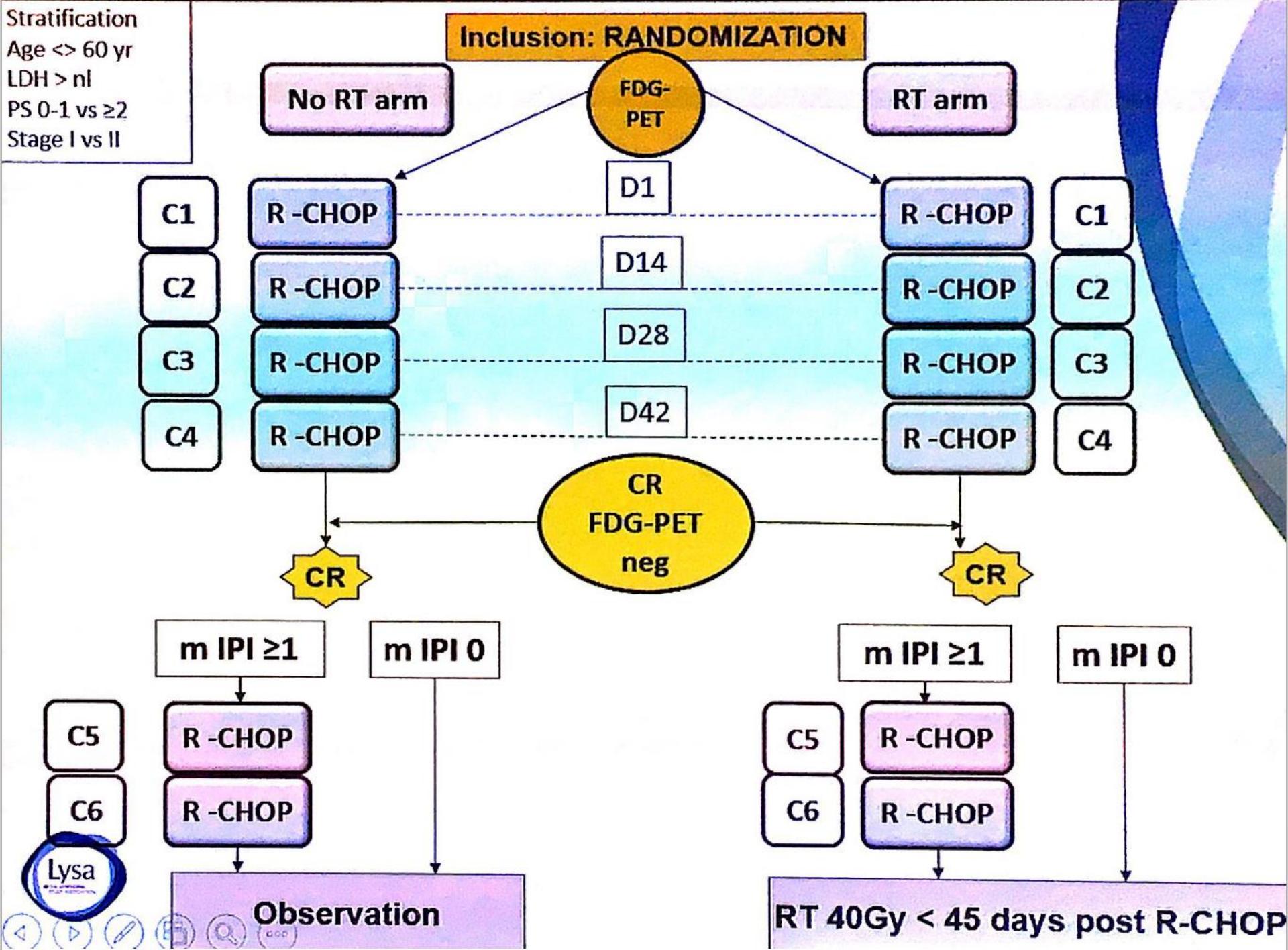
## **AIM OF THE 02-03 STUDY**

**To assess the role of additional RT in non bulky limited stage DLBCL in CR after 4-6 R-CHOP**

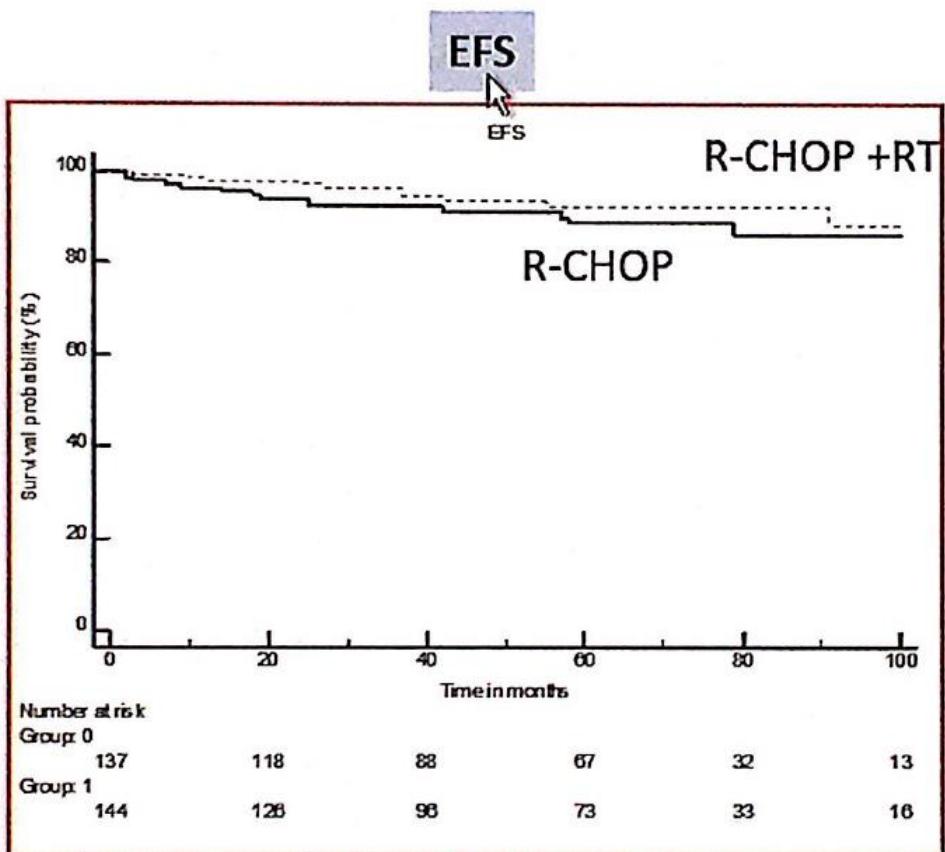
## **Inclusion Criteria**

- **18 to 75 years**
- **Histologically proven (central review) CD20+ DLBCL**
- **Ann Arbor stage I/II (based on CT-scan/ FDG-PET)**
- **non bulky (< 7cm)**
- **Not involving CNS, GI tract, testis, skin**
- **Previously untreated**

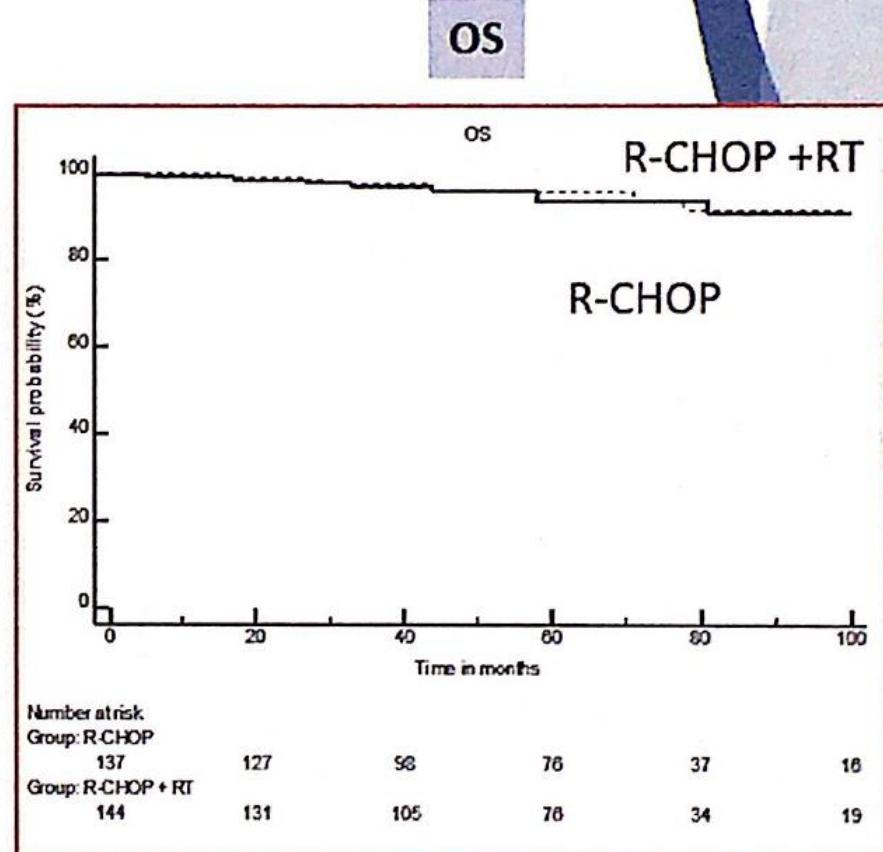
**Stratification**  
Age <> 60 yr  
LDH > nl  
PS 0-1 vs ≥2  
Stage I vs II



# EFS and OS for patients in CR at C4



5y EFS  $93 \pm 2.3\%$  vs  $91 \pm 3.5\%$



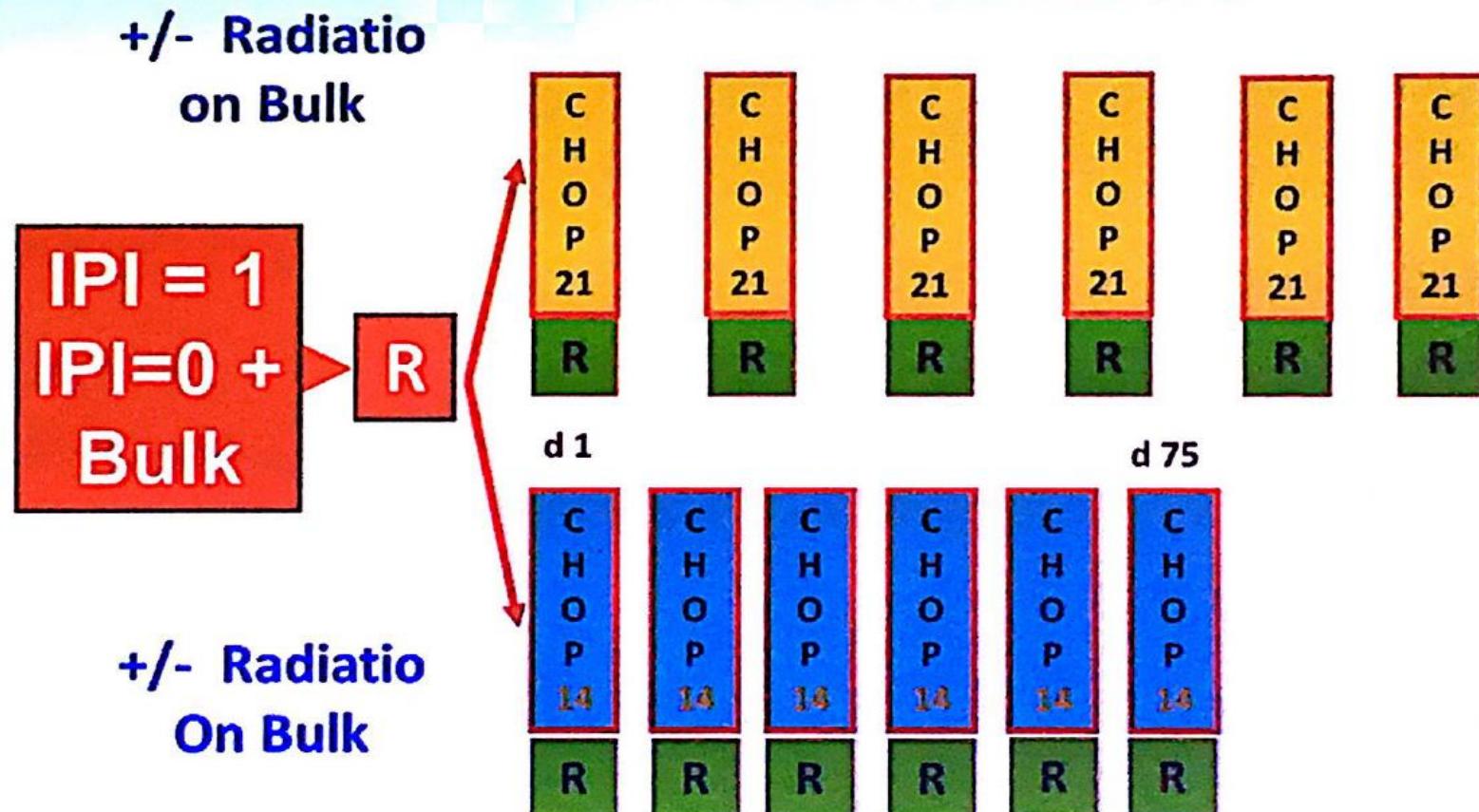
5y OS  $94 \pm 2\%$  vs  $93 \pm 2.5\%$

## CONCLUSIONS

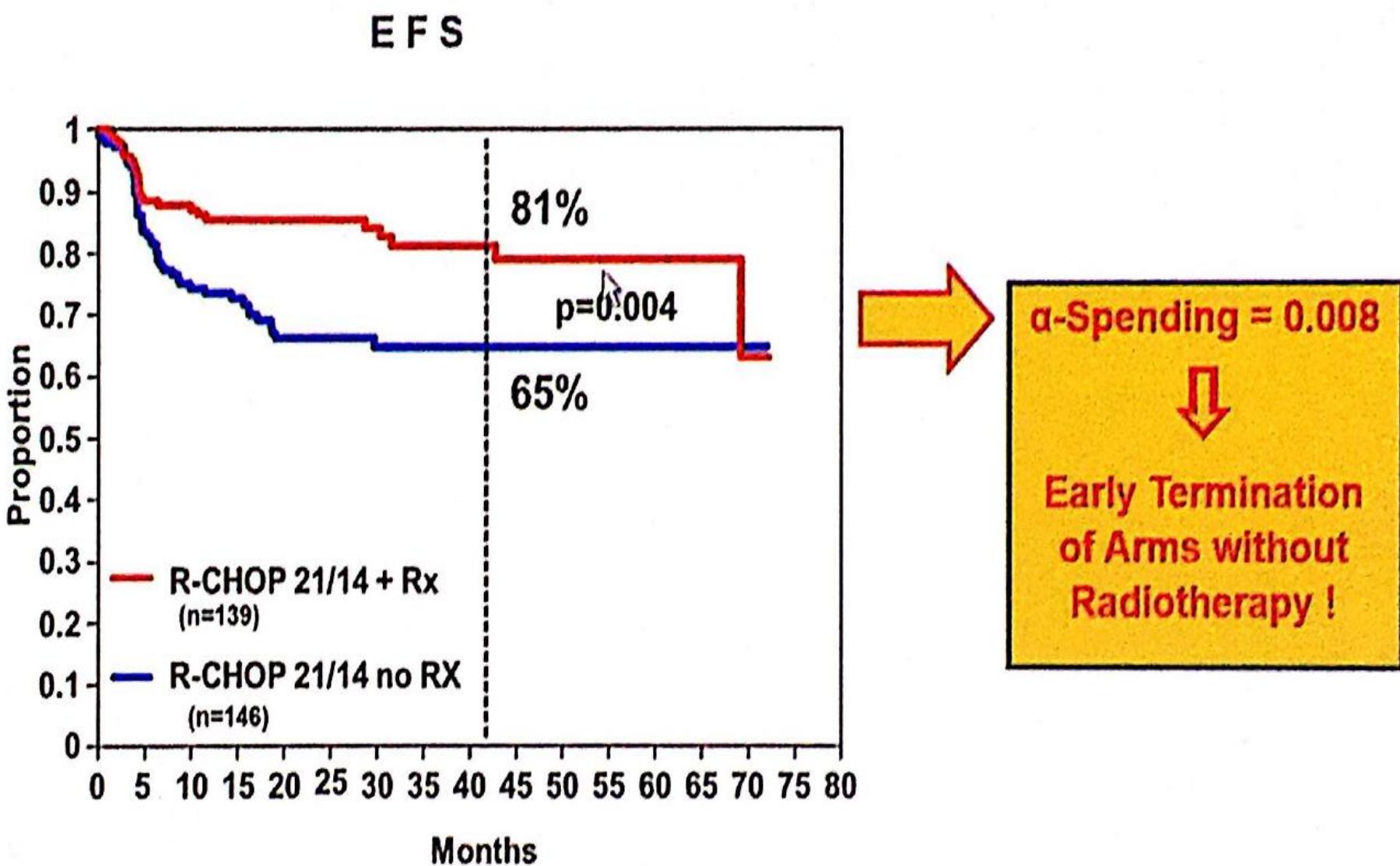
- Excellent prognosis of limited stage non bulky DLBCL
- No advantage for adding RT after 4 or 6 cycles of R-CHOP for CR PET neg patients (EFS > 92% at 5 years)
- After 4 cycles of R-CHOP, adding 2 cycles + RT for PR patients induces similar outcome as compared to CR patients.

# The role of RT in advanced DLBCL in R era

## Rx to Bulky Disease in Young DLBCL: UNFOLDER: Study Design



# UNFOLDER Study: Interim Analysis



# Current standard of RT in DLBCL (2018)

- Limited DLBCL non-bulky –no role of adding RT for CR PET(-) patients, for PR patients addition of RT improves results – comparable to CR pts
- Limited DLBCL bulky- R-CHOP  $6 \pm$  RT
- Advanced DLBCL non bulky – if CR consider RT only in isolated skeletal sites, if PR consider RT in elderly instead of second line chemotherapy
- Advanced DLBCL + bulky- to all young patients, in elderly only to PET(+) pts