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# New approaches to Hodgkin's lymphoma as a paradigm for avoiding late effects of treatment

LTFU Symposium, ANZCHOG, Sydney,  
Australia, 31 August, 2010

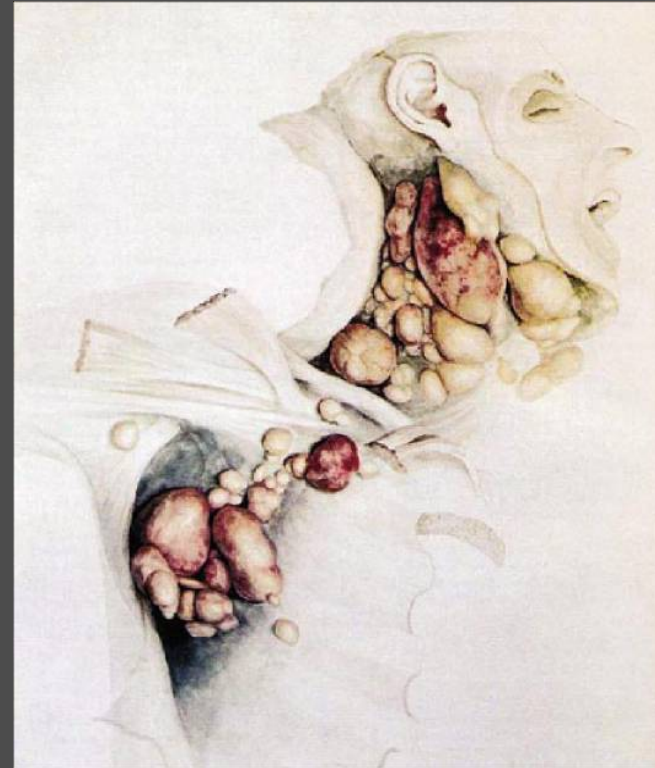
## Thomas Hodgkin (1798-1866)

- English Physician and Pathologist
- 1819: St Thomas's and Guys and Edinburgh
- Qualified Edinburgh 1823



## Thomas Hodgkin (1798-1866)

- 1832- Hodgkin publishes his paper on lymphatic disease "On Some Morbid Appearances of the Absorbent Glands and Spleen"
- In histological re-examinations in 1926, 60 years after the death of Hodgkin, his diagnosis was confirmed in three of seven cases !



# Challenges in managing Hodgkin's Lymphoma in children and teenagers

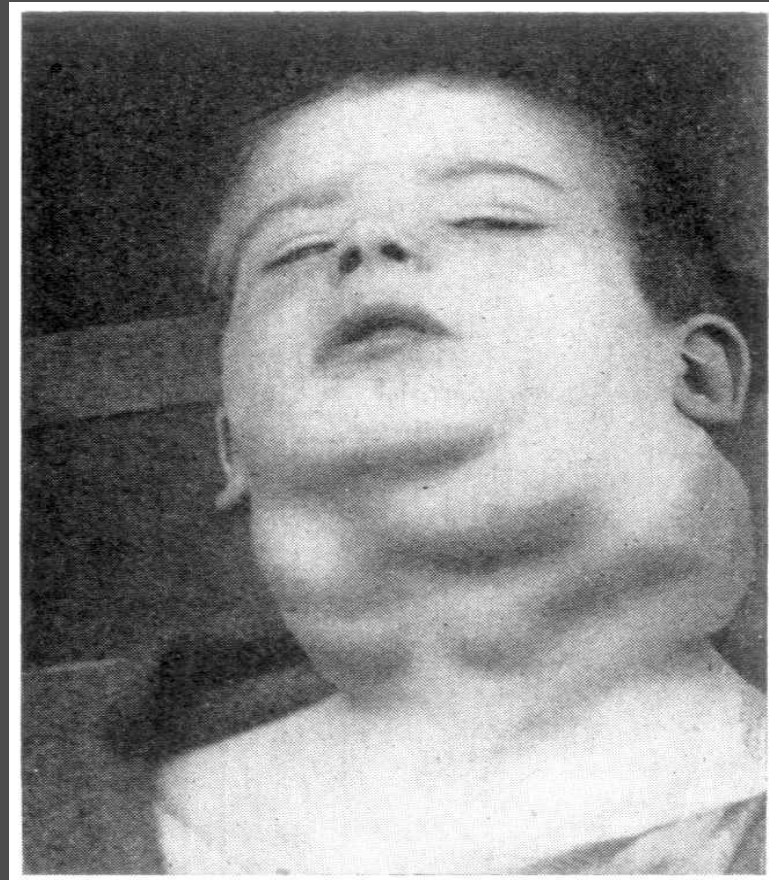
- **Reduction of secondary cancer**  
Avoiding radiotherapy in selected cases
- **Reduction of infertility and premature menopause**  
Avoiding alkylating agent based chemotherapy
- **Seamless care for teenagers and young people**
- **Less intensive treatment of nodular LP HL**
- **European Clinical Trials (EuroNet)**
- **Maintaining event free survival for all > 90%**

# Hodgkin's Lymphoma

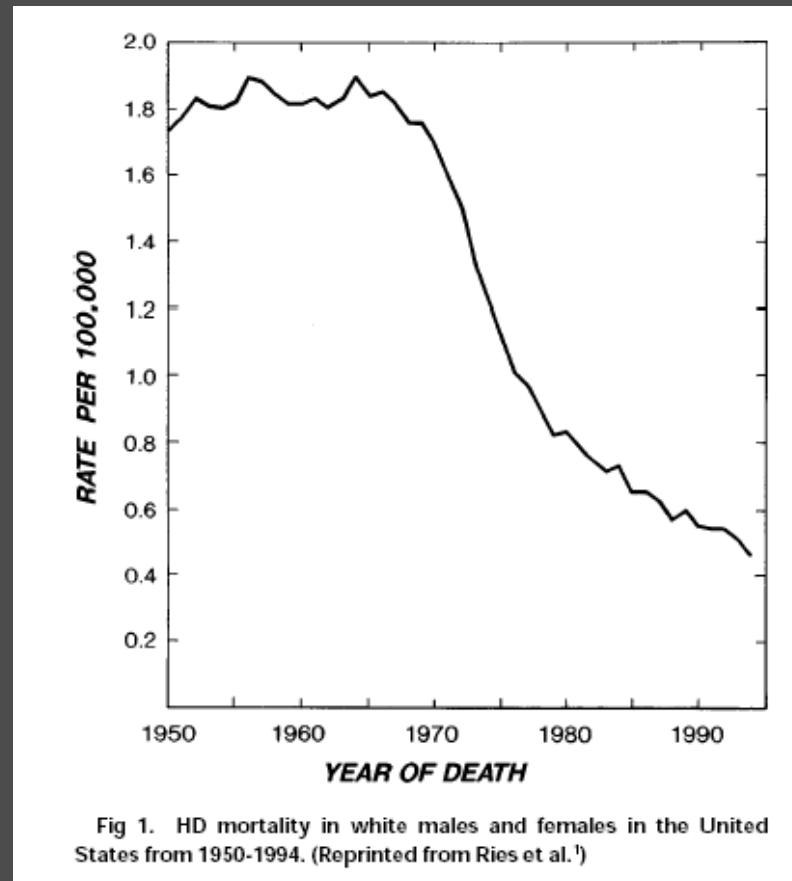
- ◎ 5-6 per million children per year
- ◎ Uncommon <5yrs old
- ◎ Painless cervical lymphadenopathy - 80%
- ◎ Asymptomatic mediastinal disease - 60%
- ◎ 'B' symptoms - 32%
  - night sweats
  - unexplained fever
  - weight loss

# Hodgkin's Lymphoma

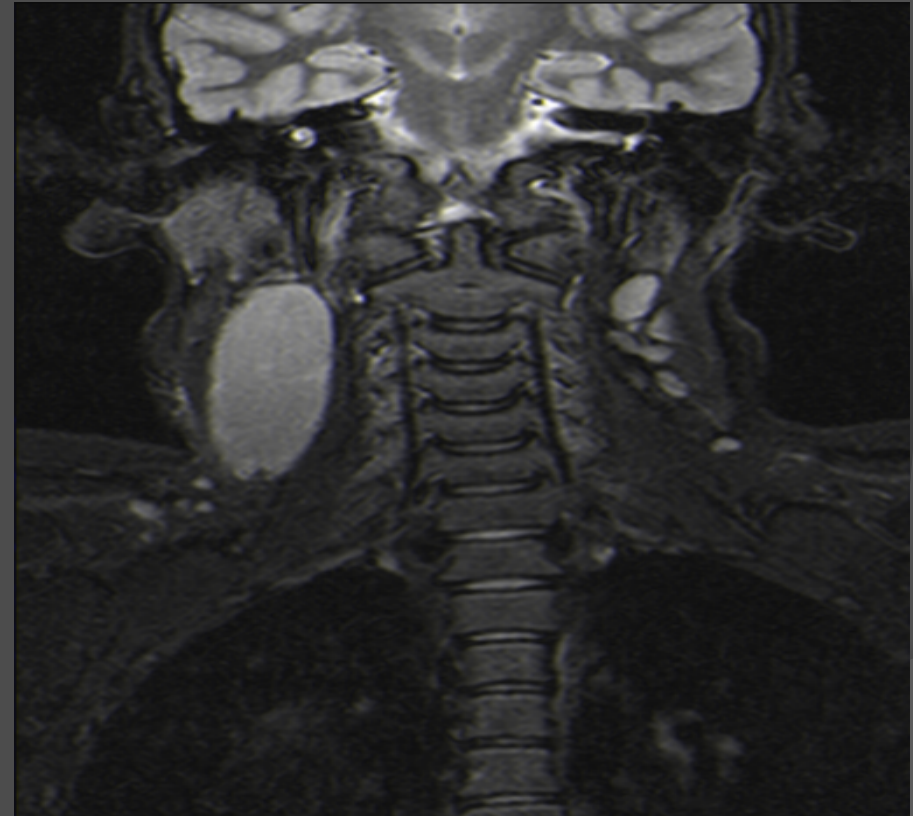
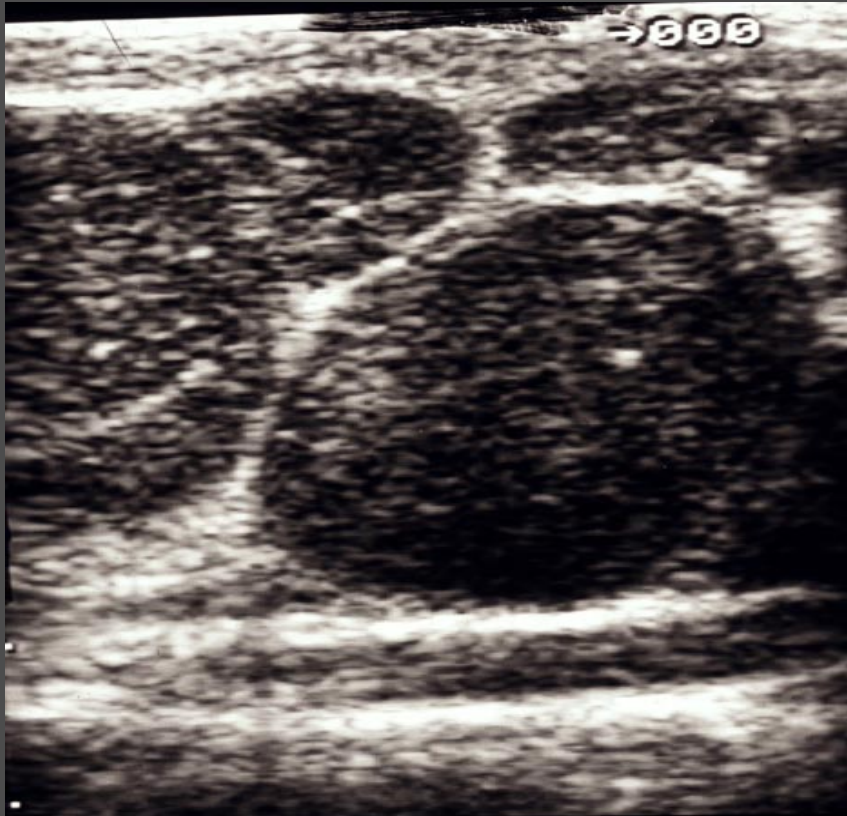
- Taken from Patterson's Sick Children 1944



## Hodgkin's Lymphoma: Mortality (1950-1994)



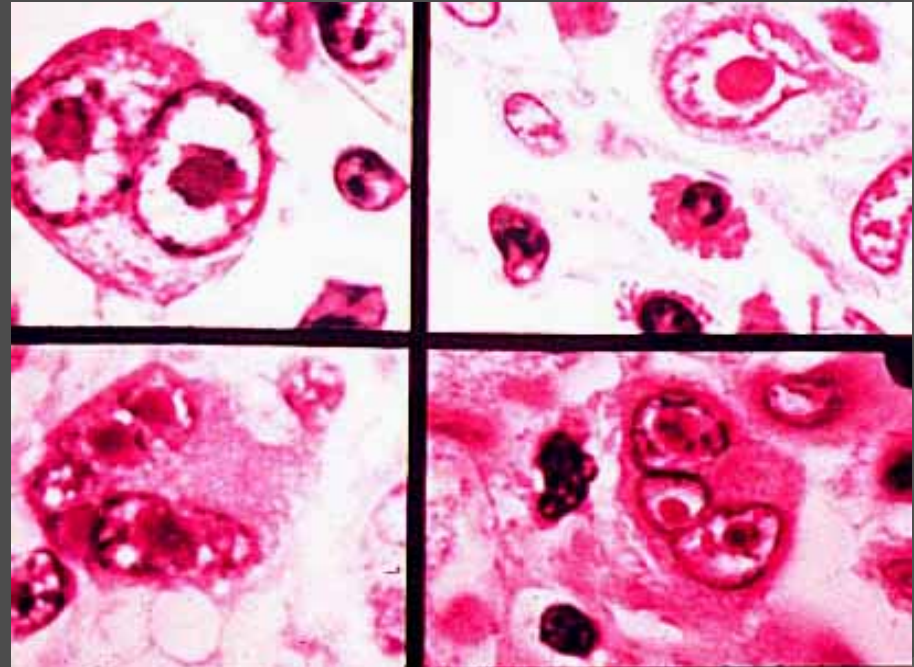
# USS & MRI/CT



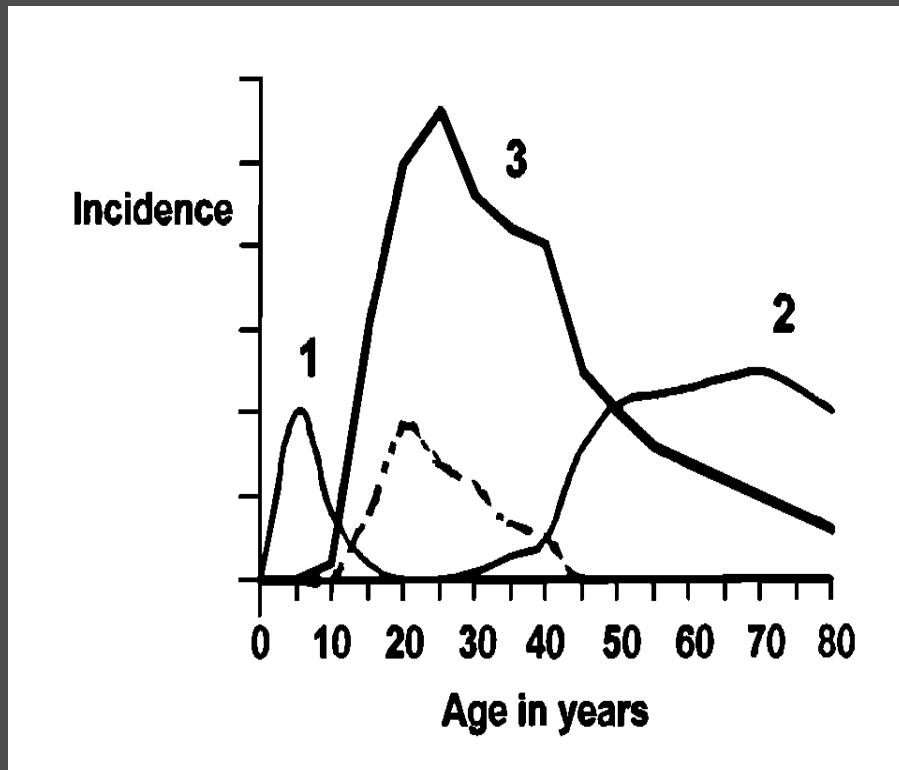


# Hodgkin's Lymphoma

- ⦿ Reed Sternberg cell
- ⦿ now known as **Hodgkin's/Reed/Sternberg** cell (HRS)
- ⦿ HRS cell
  - < 1% of lymph node
  - Cell of origin



# Epstein-Barr Virus + Hodgkin's Lymphoma



## Peak 1

- EBV associated
- mainly MC
- high in low socioeconomic

## Peak 2

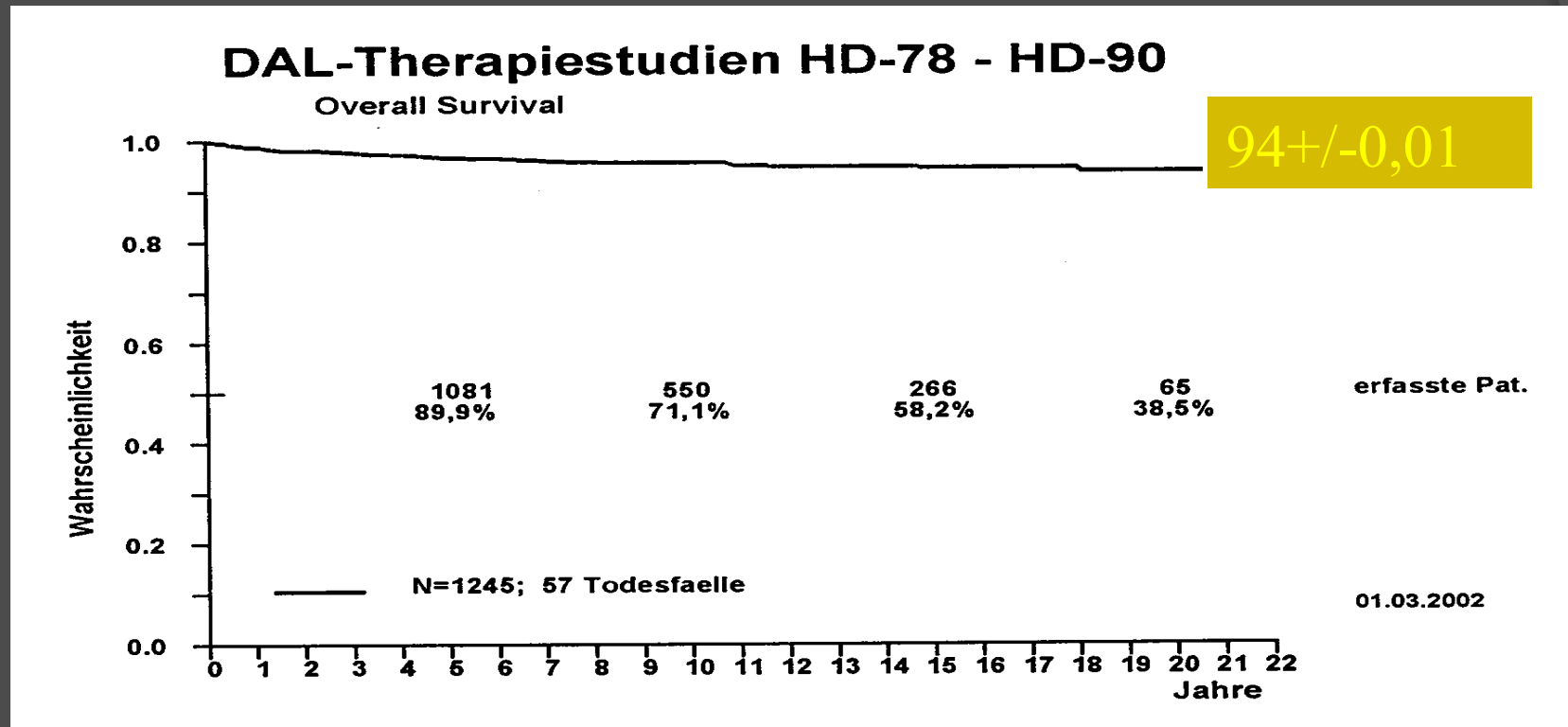
- older adults
- EBV associated
- mainly MC
- less geographical variation

## Peak 3

- Not EBV associated
- mainly NS
- high in high socioeconomic

# Long term survival after HD

## Results of the DAL78 - 90 studies



Prof. Schellong (late effects report)

# Hodgkin`s lymphoma

- Treatment concept of the GPOH-HD study group -

TG-1  
IA/B, IIA



TG-2  
IE, IIB,  
IIE, IIIA



TG-3  
IIBE, IIIA  
E,  
IIIB IV



Involved field RT  
Except: CR in TG-1



# GPOH-HD-95

TG1

TG2+3

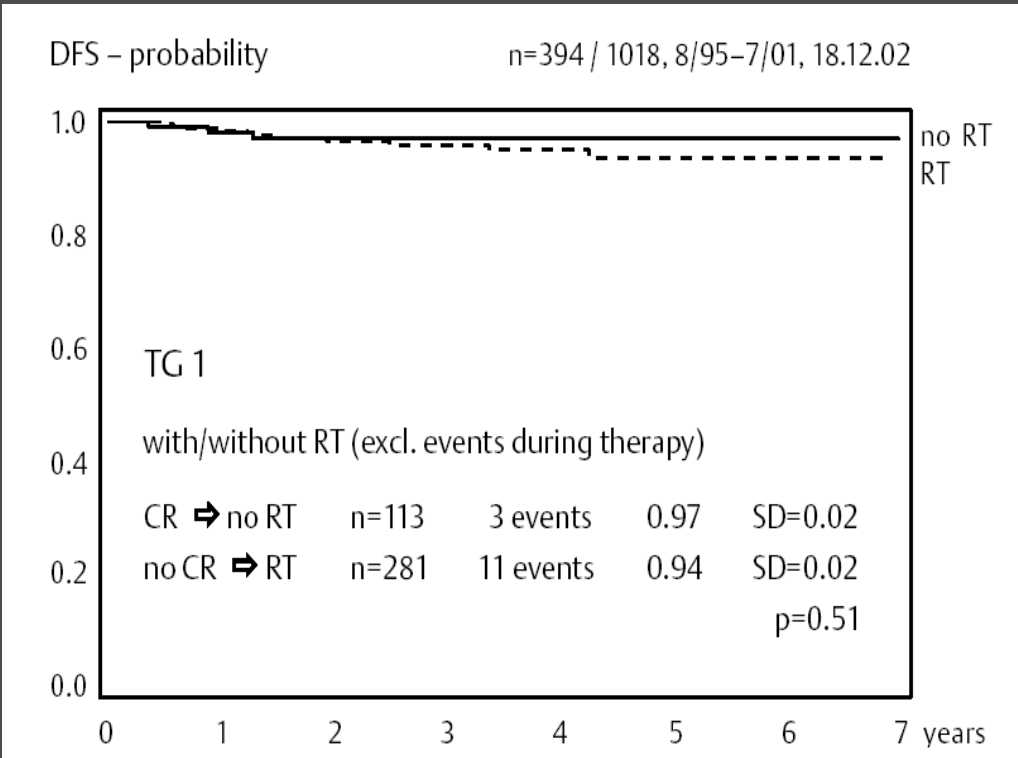


Fig. 4 GPOH-HD 95, 5-year disease-free survival for irradiated vs. non irradiated patients, TG 1 only.

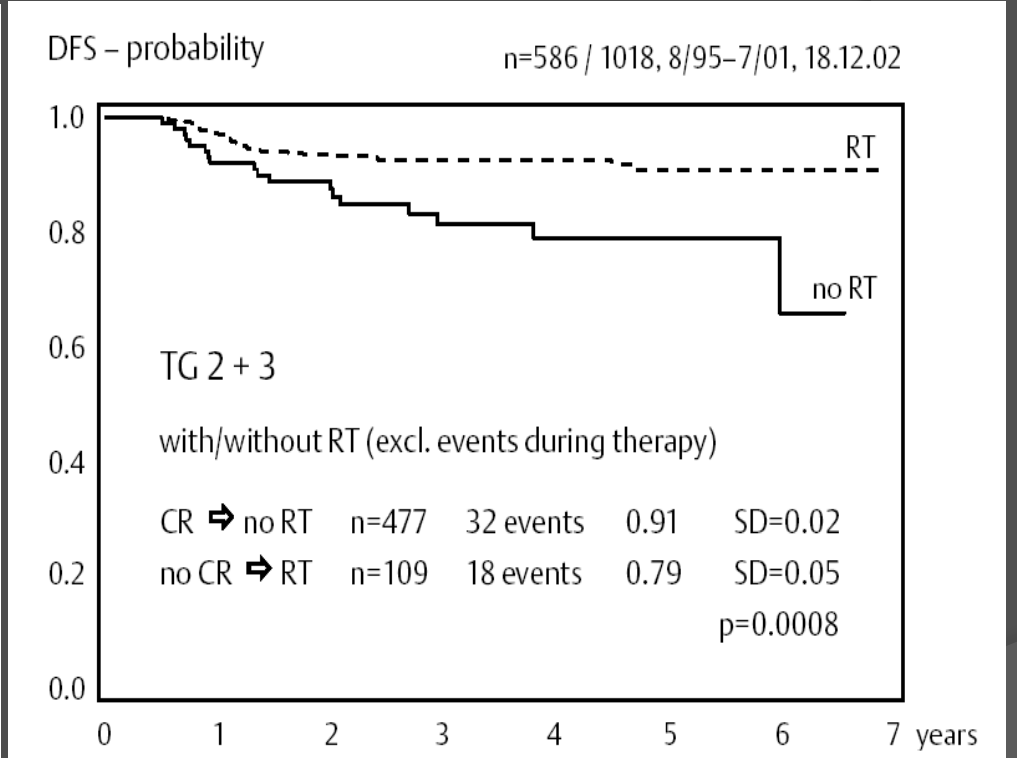


Fig. 5 GPOH-HD 95, 5-year disease-free survival for irradiated vs. non irradiated patients, TG 2 + TG 3 grouped together.

# Nachman et al. JCO 2002;20:3765-71.

- ⦿ Randomised comparison of low dose involved field RT and No RT for children with HL who achieve a complete remission
- ⦿ All stages
- ⦿ Risk adapted CT (COPP/ABV or multi agent CT)
- ⦿ 3 yr EFS 92% for IFRT versus 87% NFT.
- ⦿ No survival advantage, follow up is short.

# Residual masses after treatment

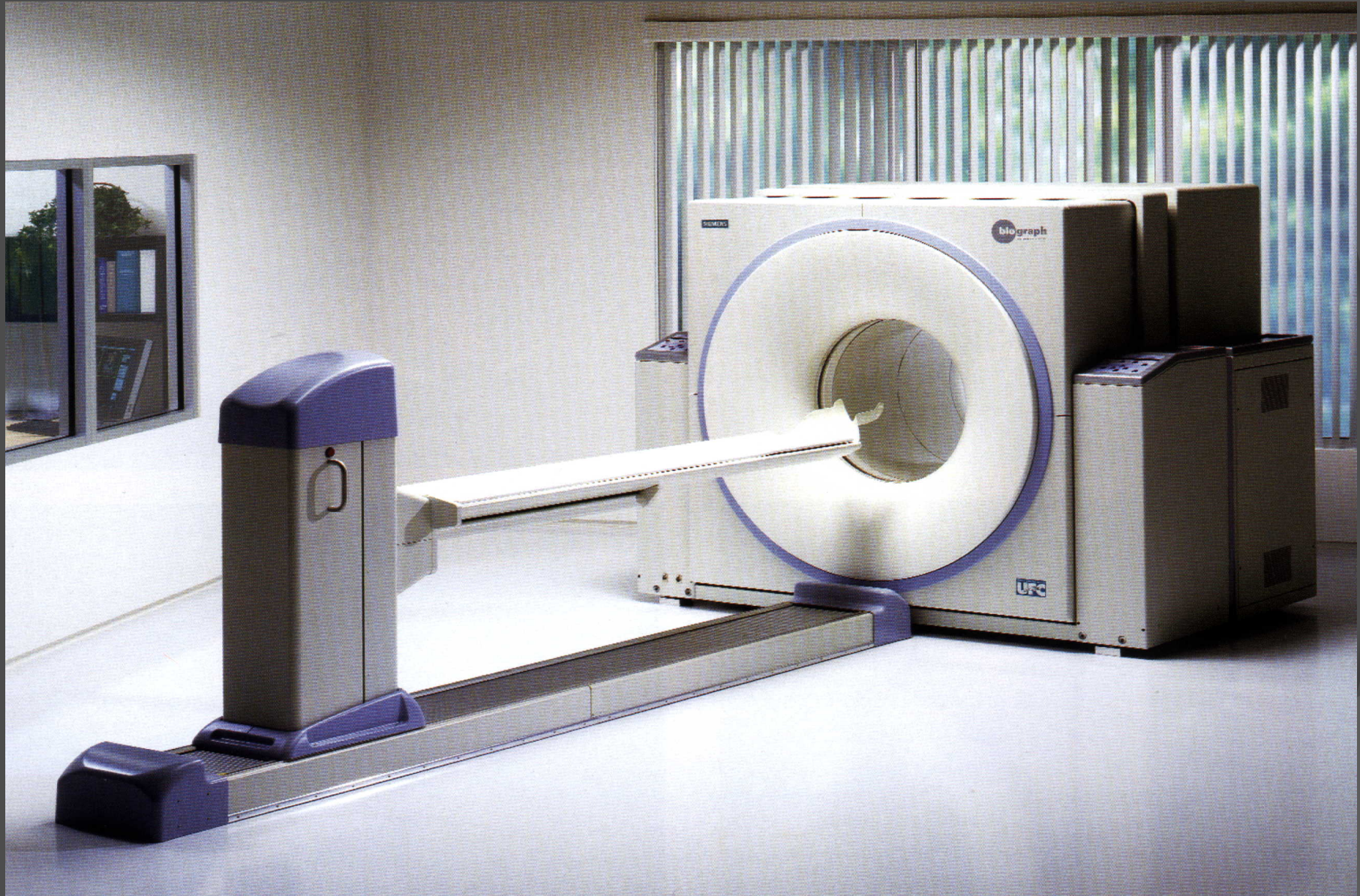
- ~60-70% of patients with HL have a residual mass at the end of treatment
- ~20% of these patients will relapse
- **Can FDG-PET help evaluate residual abnormalities after chemotherapy?**

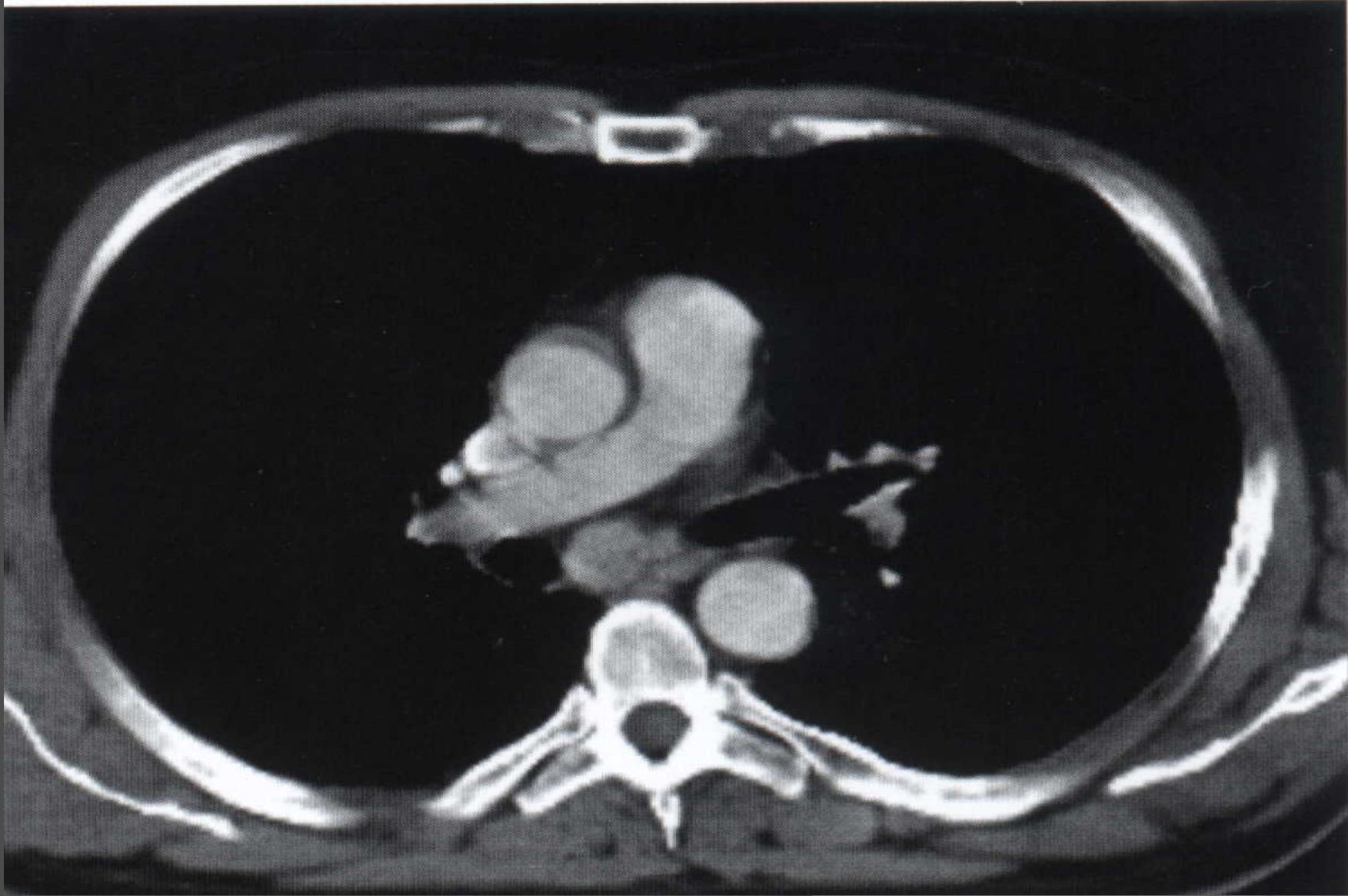
POSITRON EMISSION TOMOGRAPHY  
(PET)  
IN HODGKIN LYMPHOMA

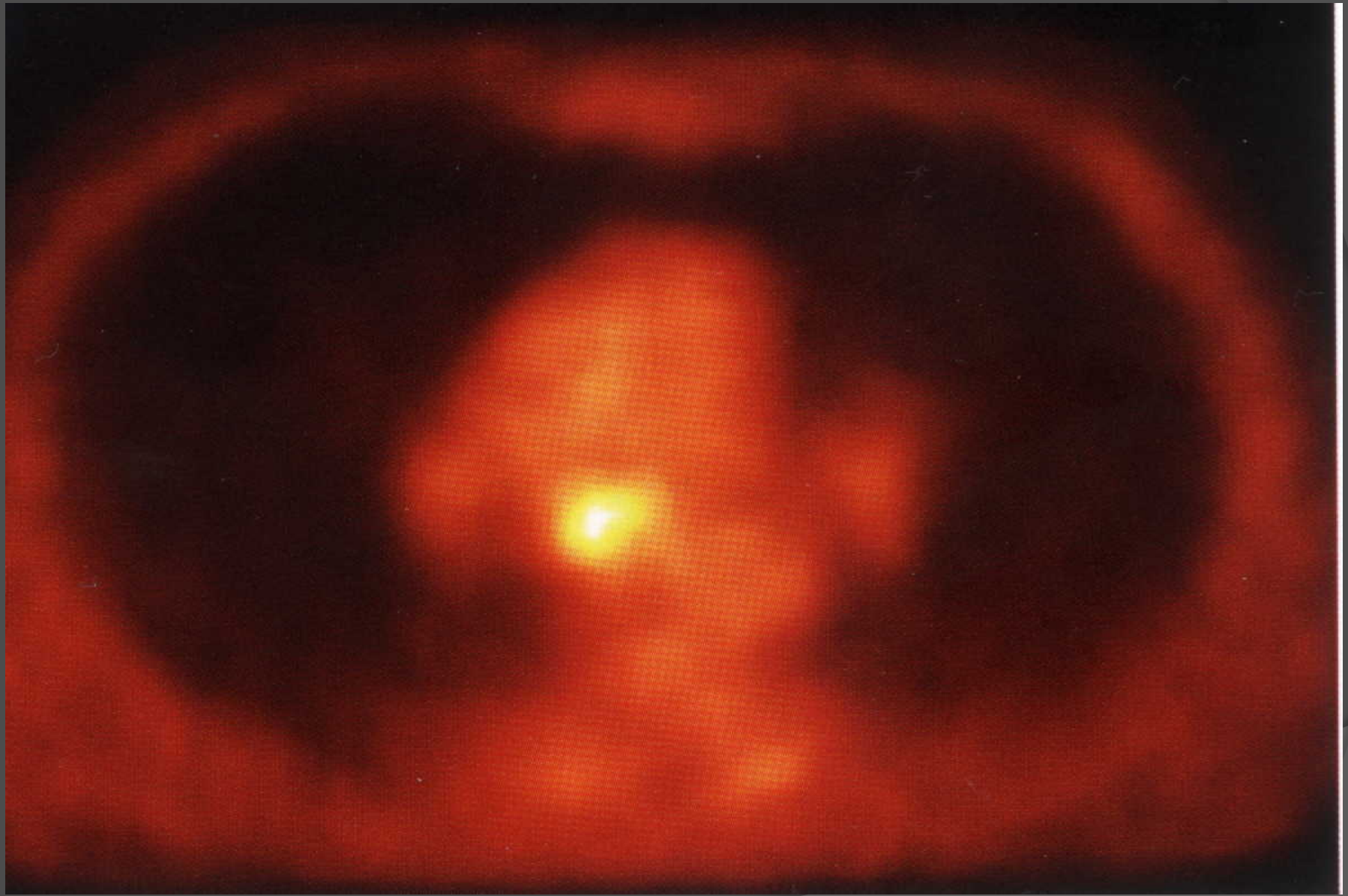


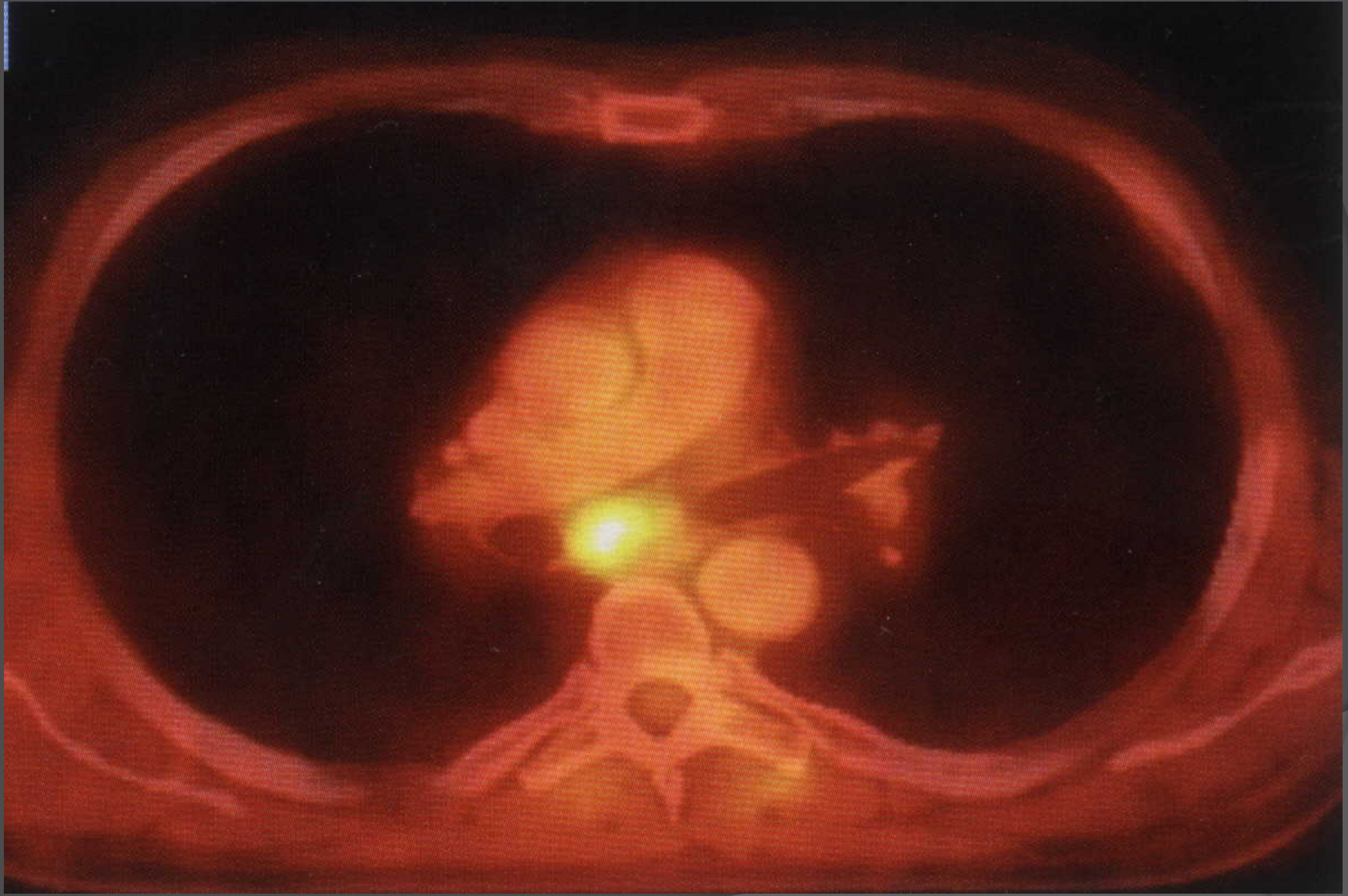
# $^{18}\text{F}$ - fluorodeoxyglucose (FDG)

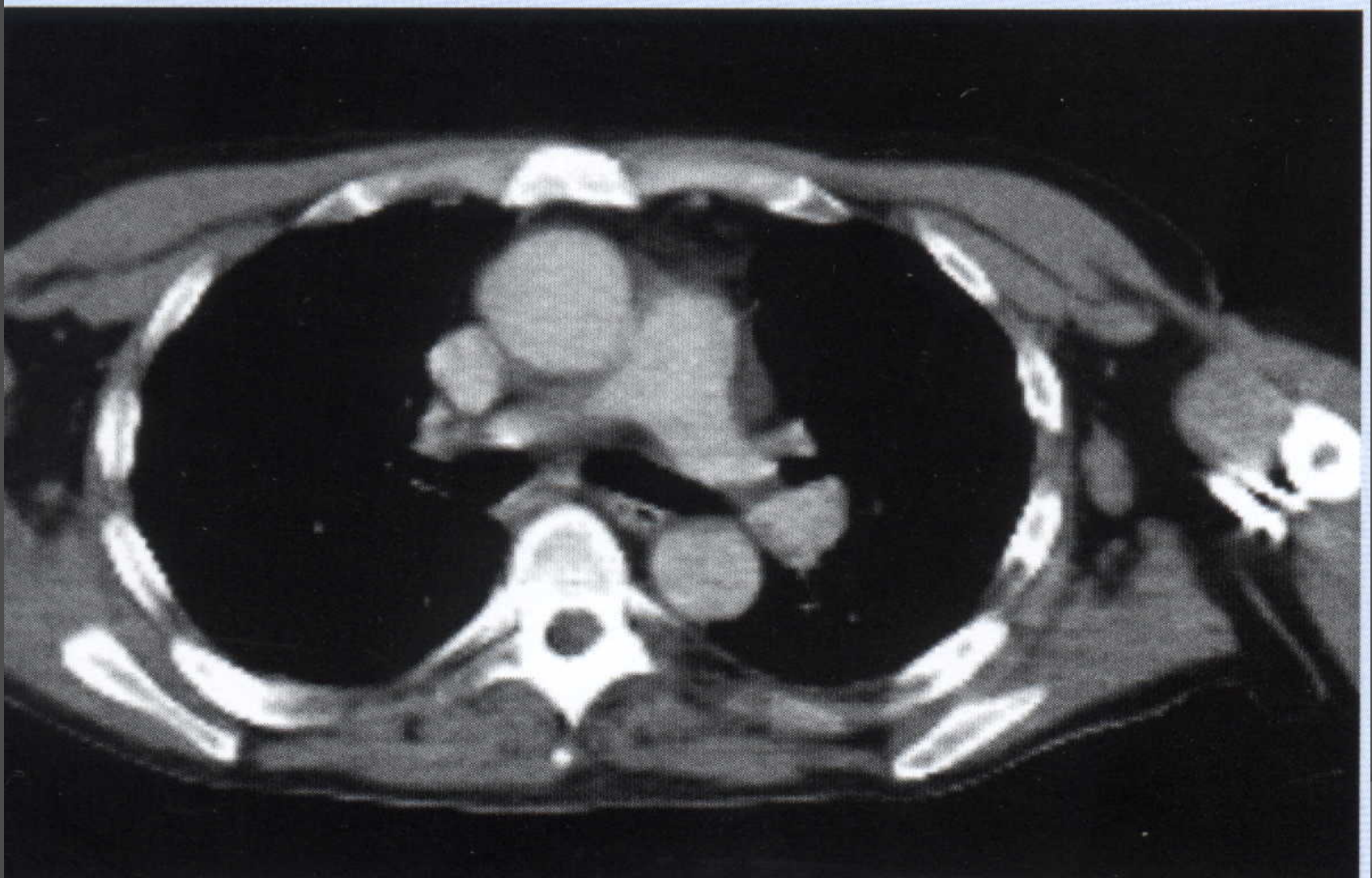
- ⦿ Glucose analogue
- ⦿ Cell membrane transport
- ⦿ Intracellular phosphorylation - FDG-6P
- ⦿ Not metabolised further, trapped within cell
- ⦿ FDG uptake reflects metabolic activity
- ⦿ Scan takes 30 - 45 minutes

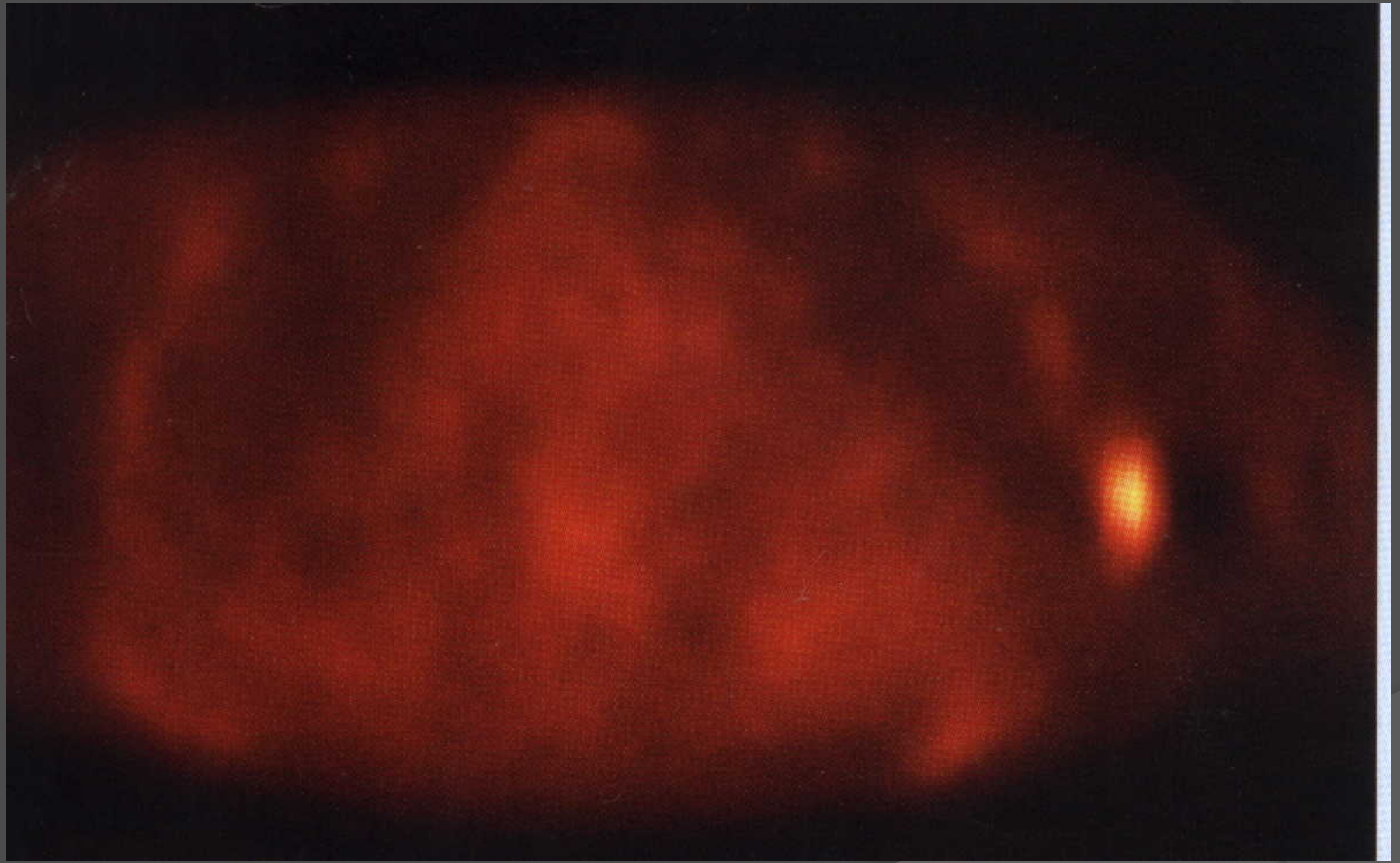


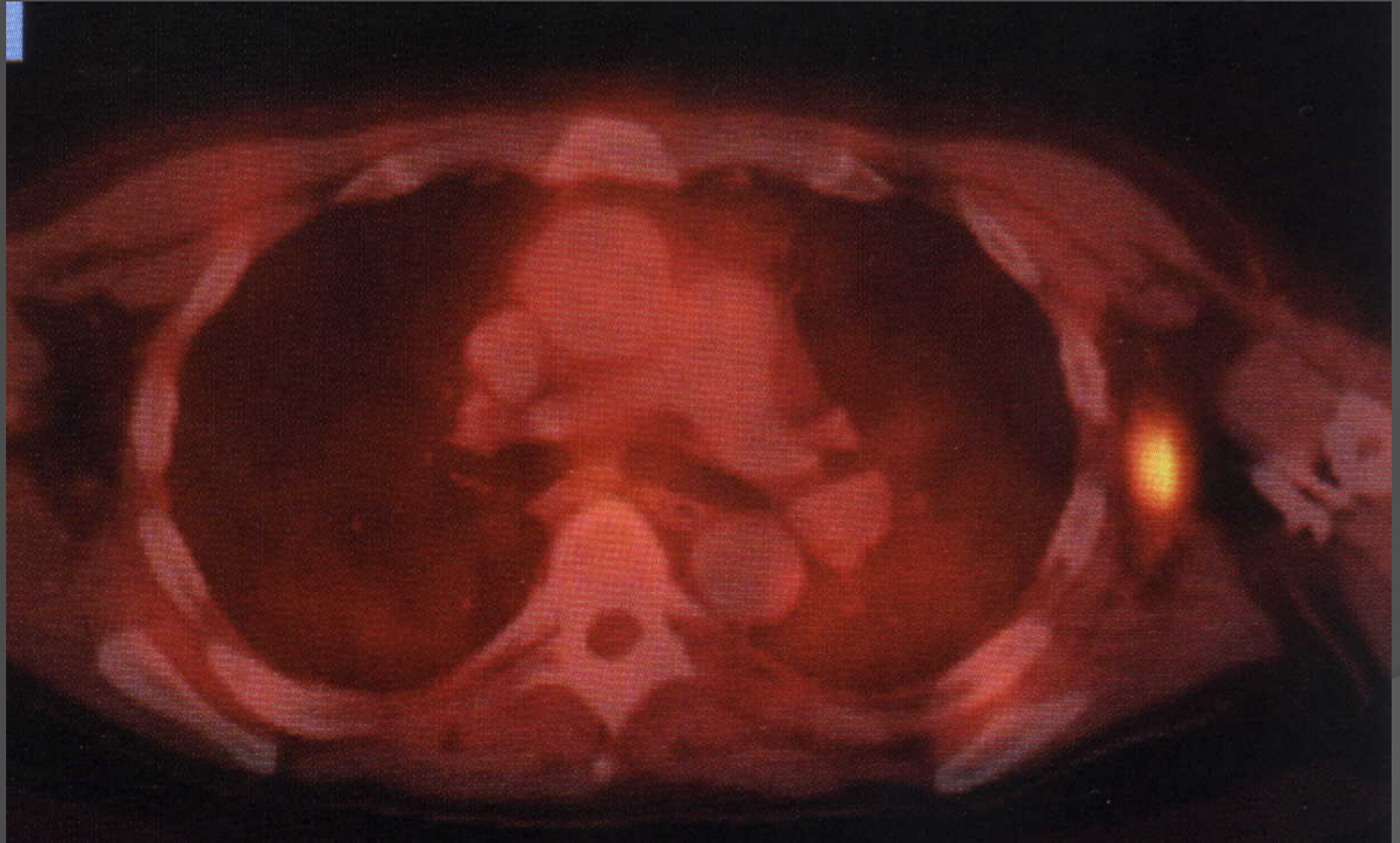
















# FDG-PET scans

- ⦿ Negative predictive value (81-100%) is consistently reported
- ⦿ Clearly identifying patients with an excellent prognosis

## Question:

- ⦿ Can RT be safely omitted after first line chemotherapy in patients with a negative PET scan?

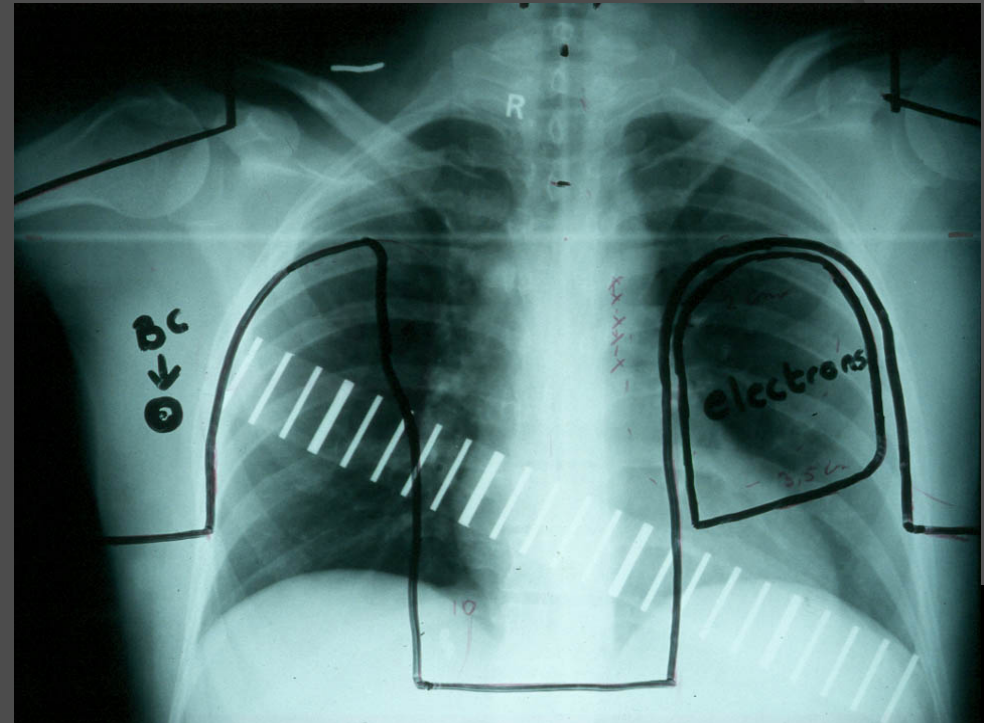
## Current aims of EuroNet-PHL group

- Reduction of secondary cancer  
Avoiding radiotherapy in selected cases
- Reduction of infertility and premature menopause  
Replacement of procarbazine by dacarbazine
- Maintaining event free survival for all > 90%

# Breast cancer after RT for HL

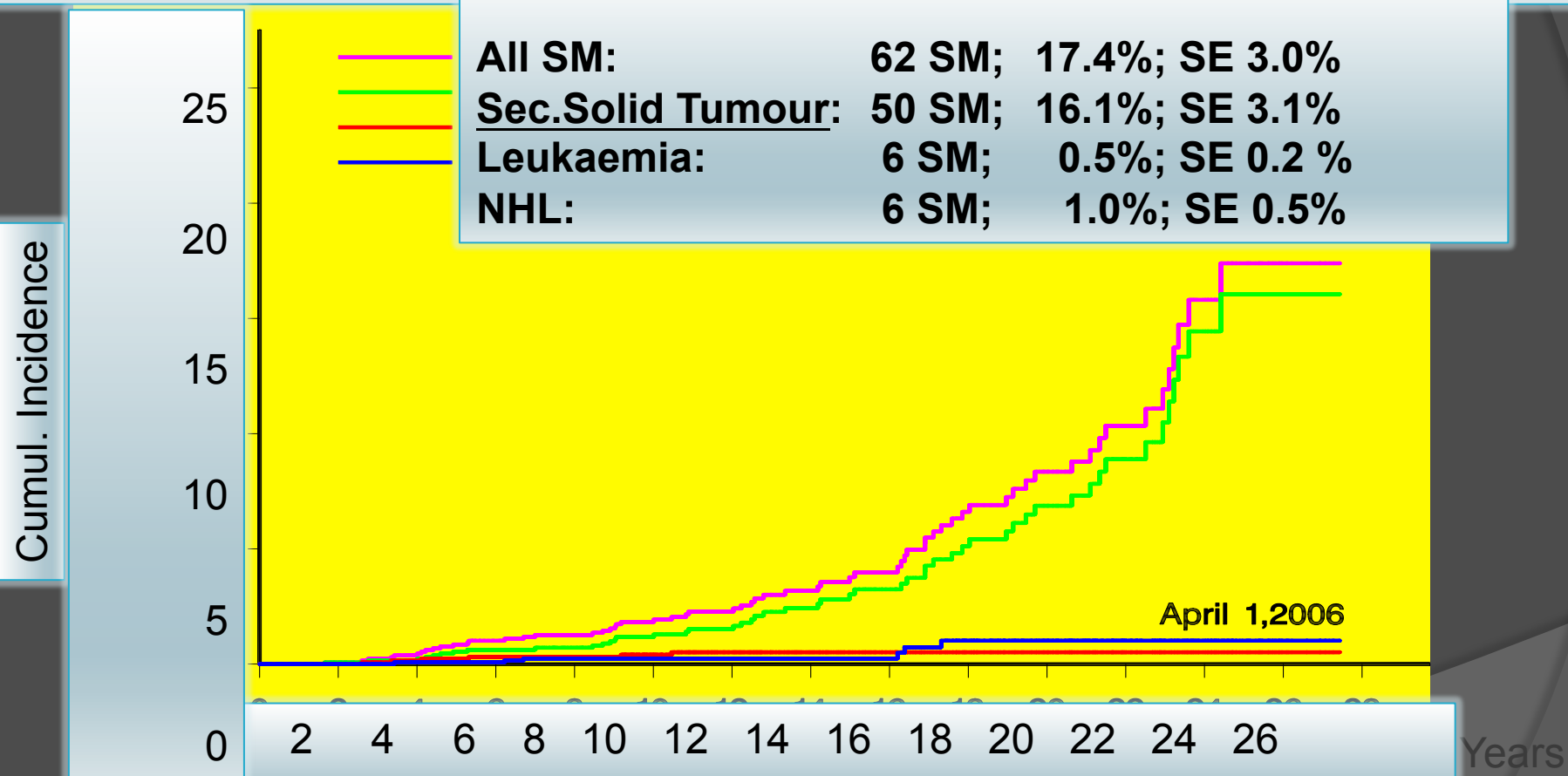


**Mantle field RT**



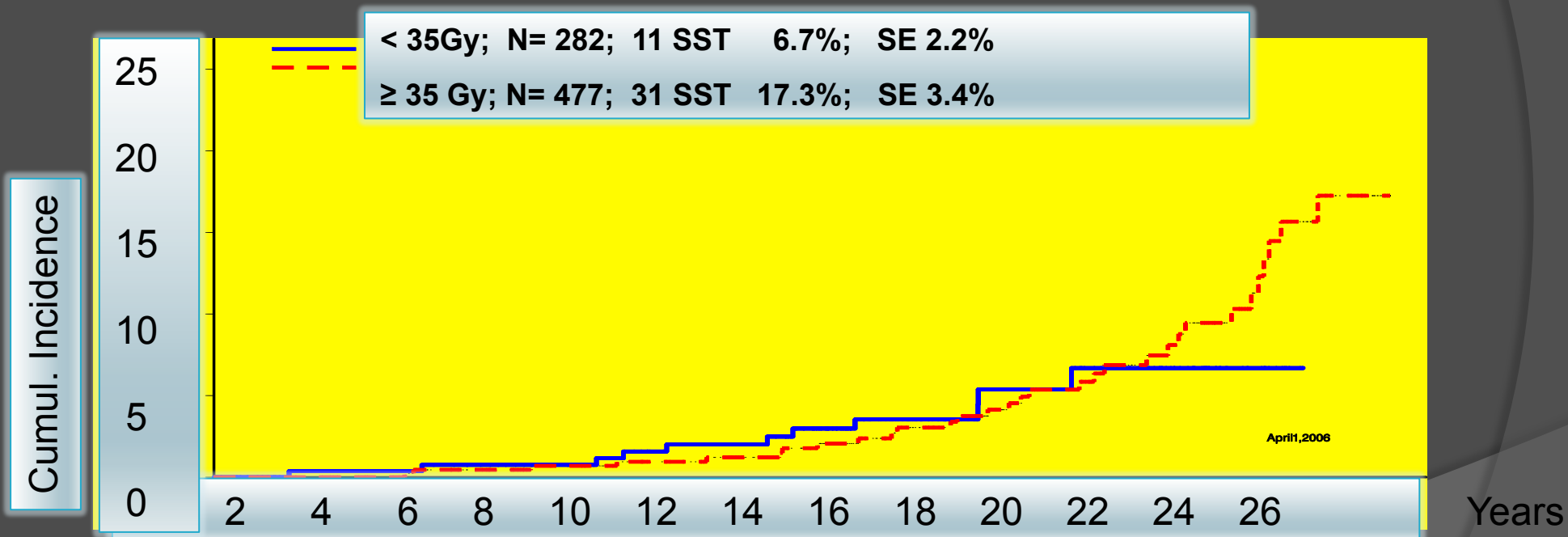
**Mantle field 1974,  
BC= Site of subsequent  
breast cancer 2002**

# DAL Therapy Studies HD-78 - HD-90; N=1387, Sec. Malignancies (SM), Cumulative Incidence (26 years)



# Therapy Studies HD-78 – HD-87

## Secondary Solid Tumours (SST) by Radiation Dose

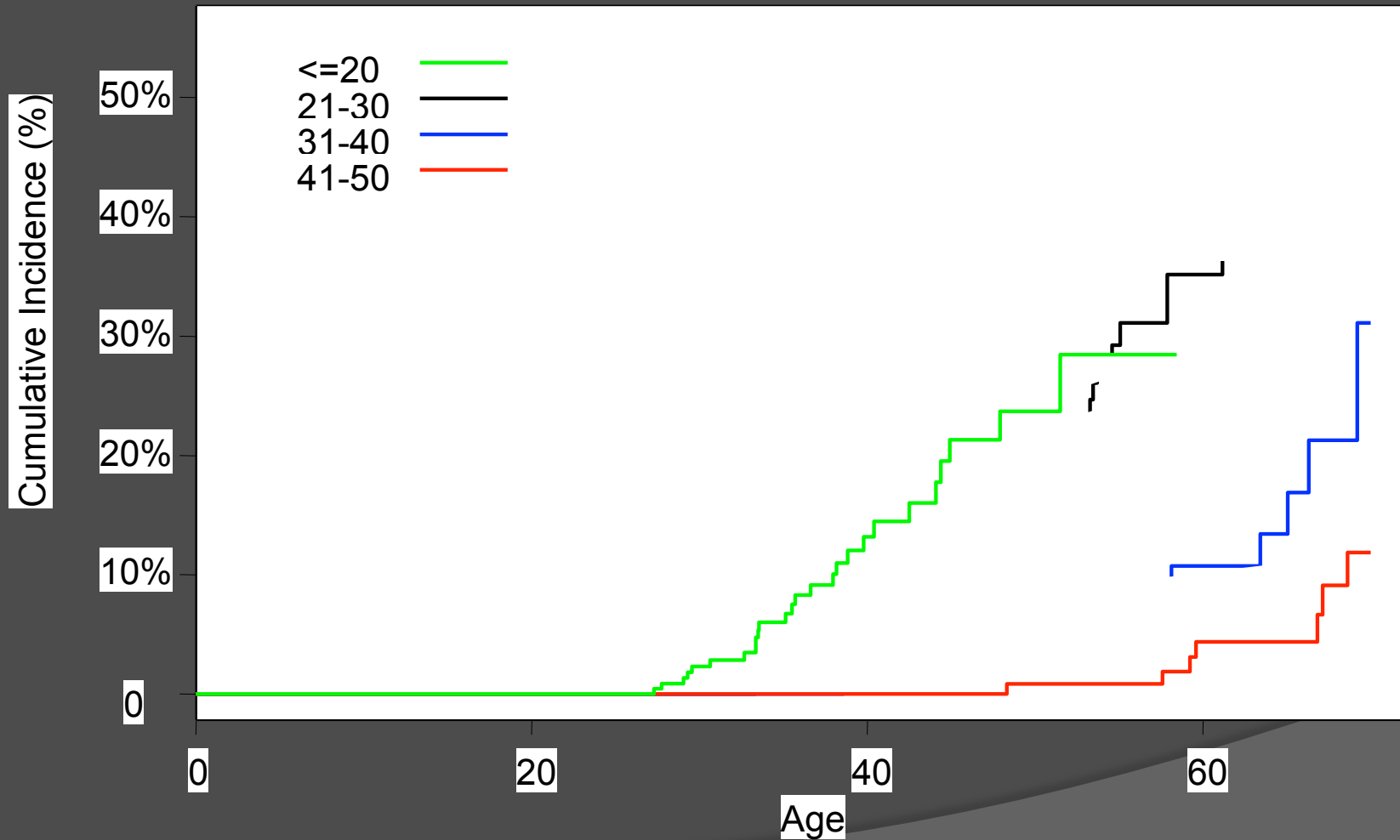


# Breast cancer following Hodgkin's lymphoma

	cases	controls	OR	(95% CI)
<b>Radiation dose in Gy (median) to affected breast area</b>				
< 4 Gy (3.6)	9	47	1.0	(ref)
4-24 Gy (15.5)	10	39	1.11	(0.32-3.85)
24-38.5 Gy (30.2)	14	44	4.20	(0.99-17.8)
≥ 38.5 Gy (40.7)	15	45	5.16	(1.27-21.0)
			p trend <0.001	
<b>Overall treatment</b>				
RT only	30	68	1.0	(ref)
RT + CT	18	104	0.45	(0.22-0.91)

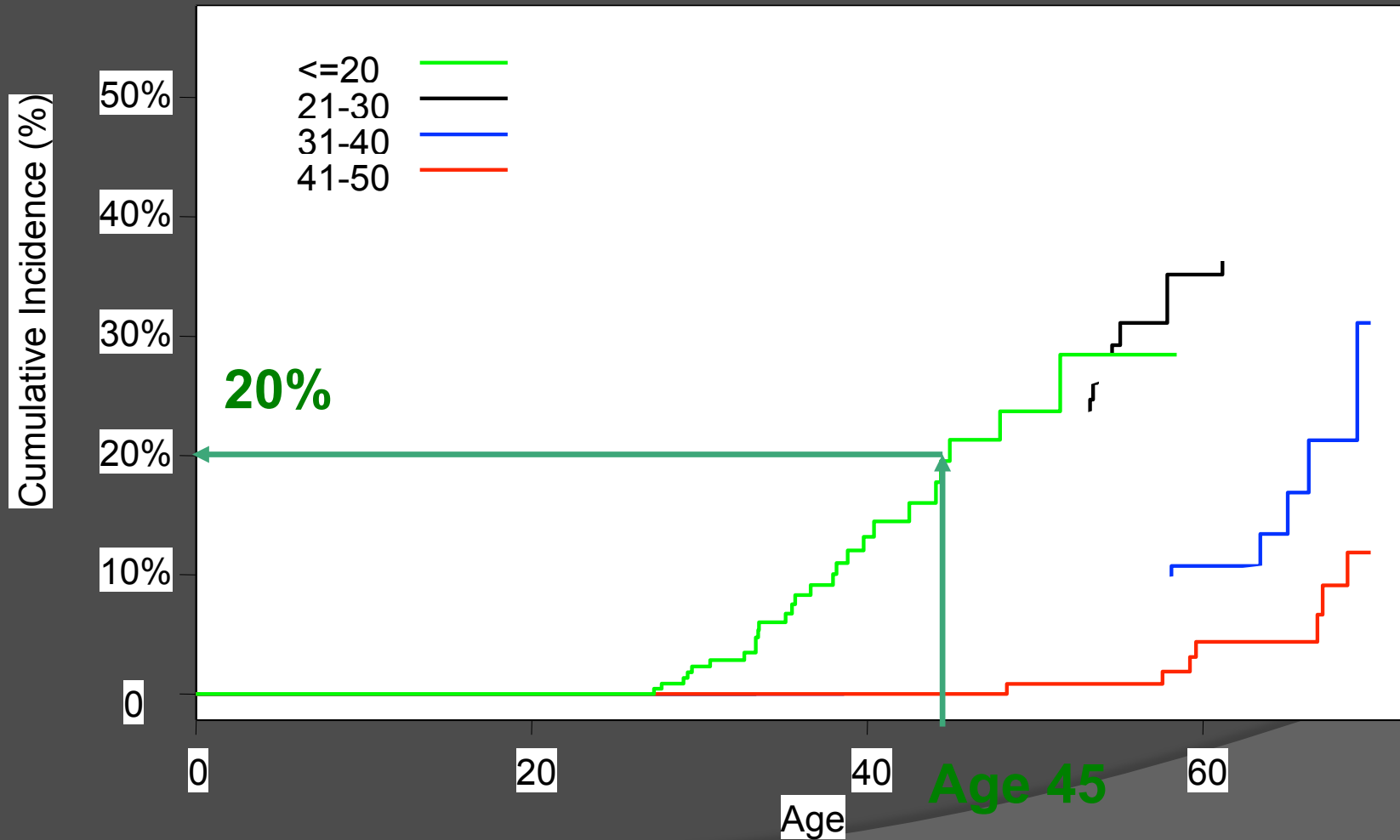
- Dose-response effect

# Cumulative incidence of breast cancer according to age at first treatment



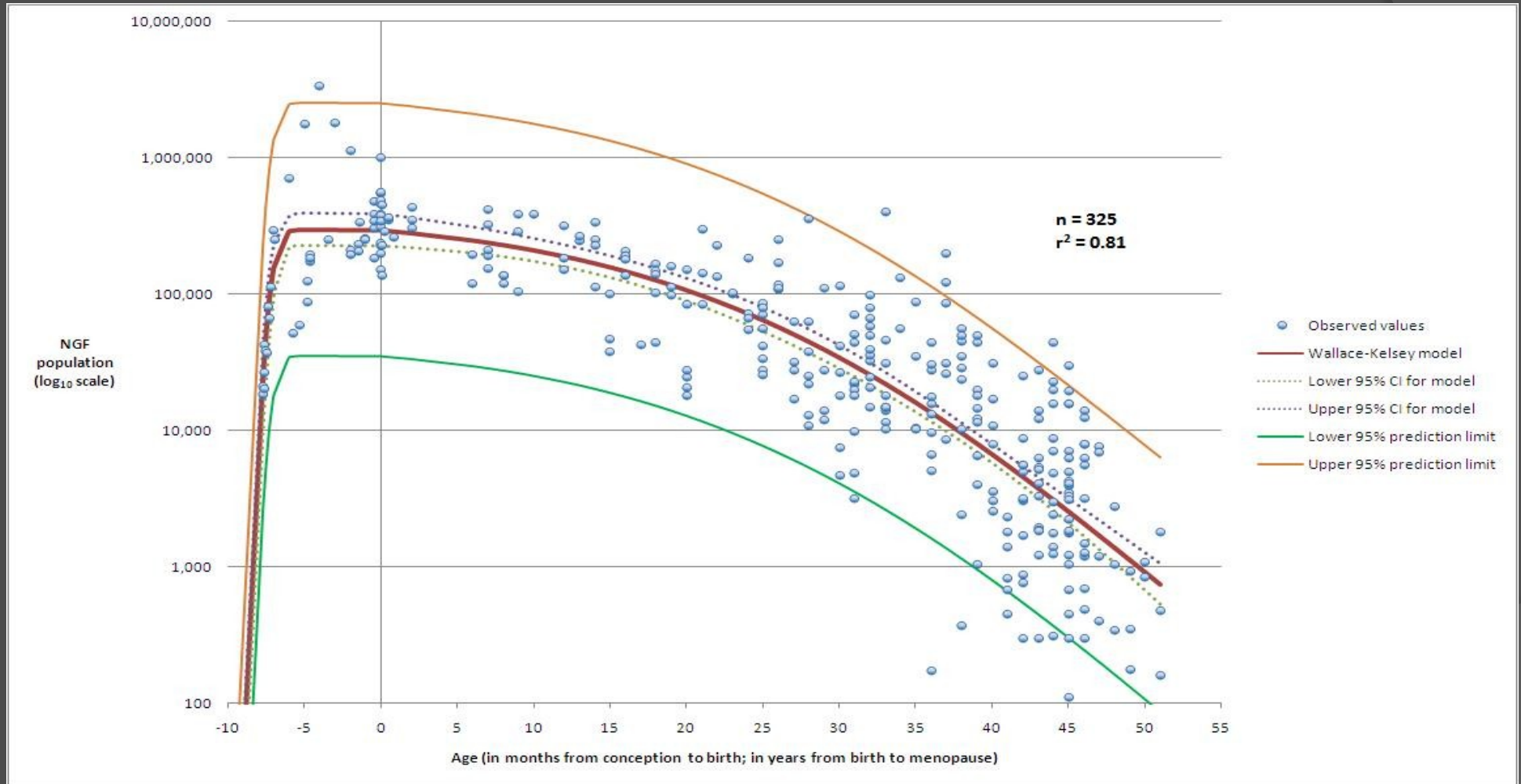


# Cumulative incidence of breast cancer according to age at first treatment



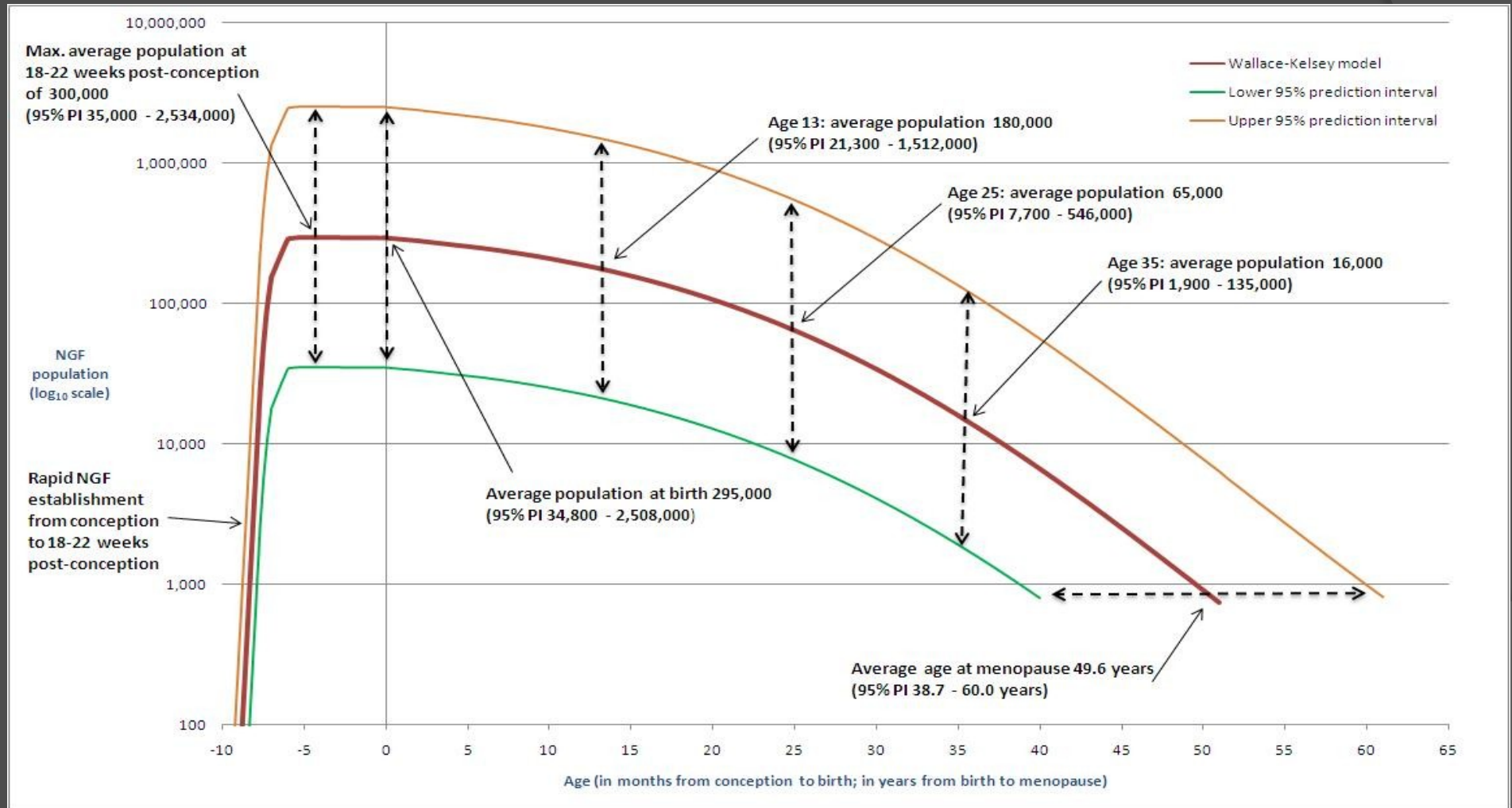


# Ovarian reserve:conception to menopause



Wallace & Kelsey, PloS ONE, 2010

# Ovarian reserve: Conception to Menopause (NGF population)

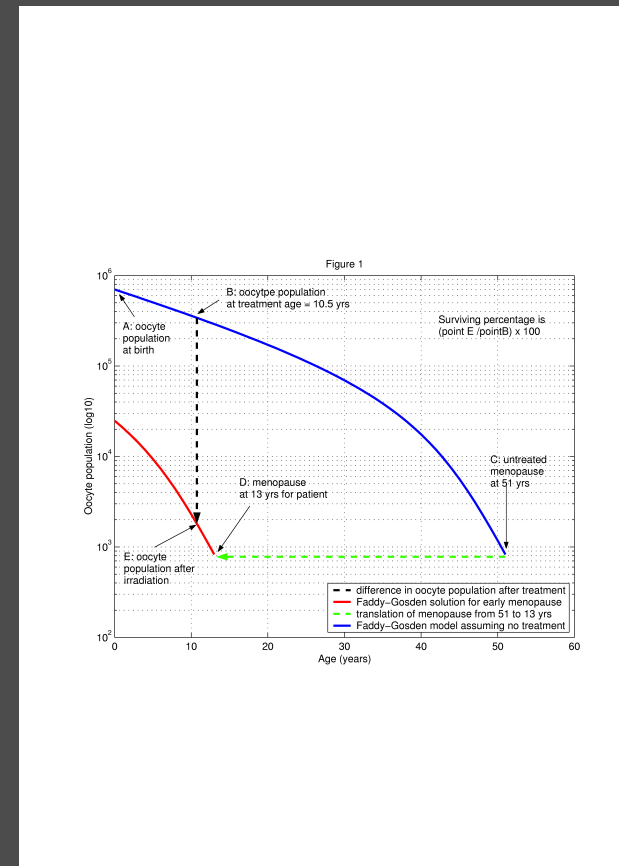


# Radiation-induced ovarian damage

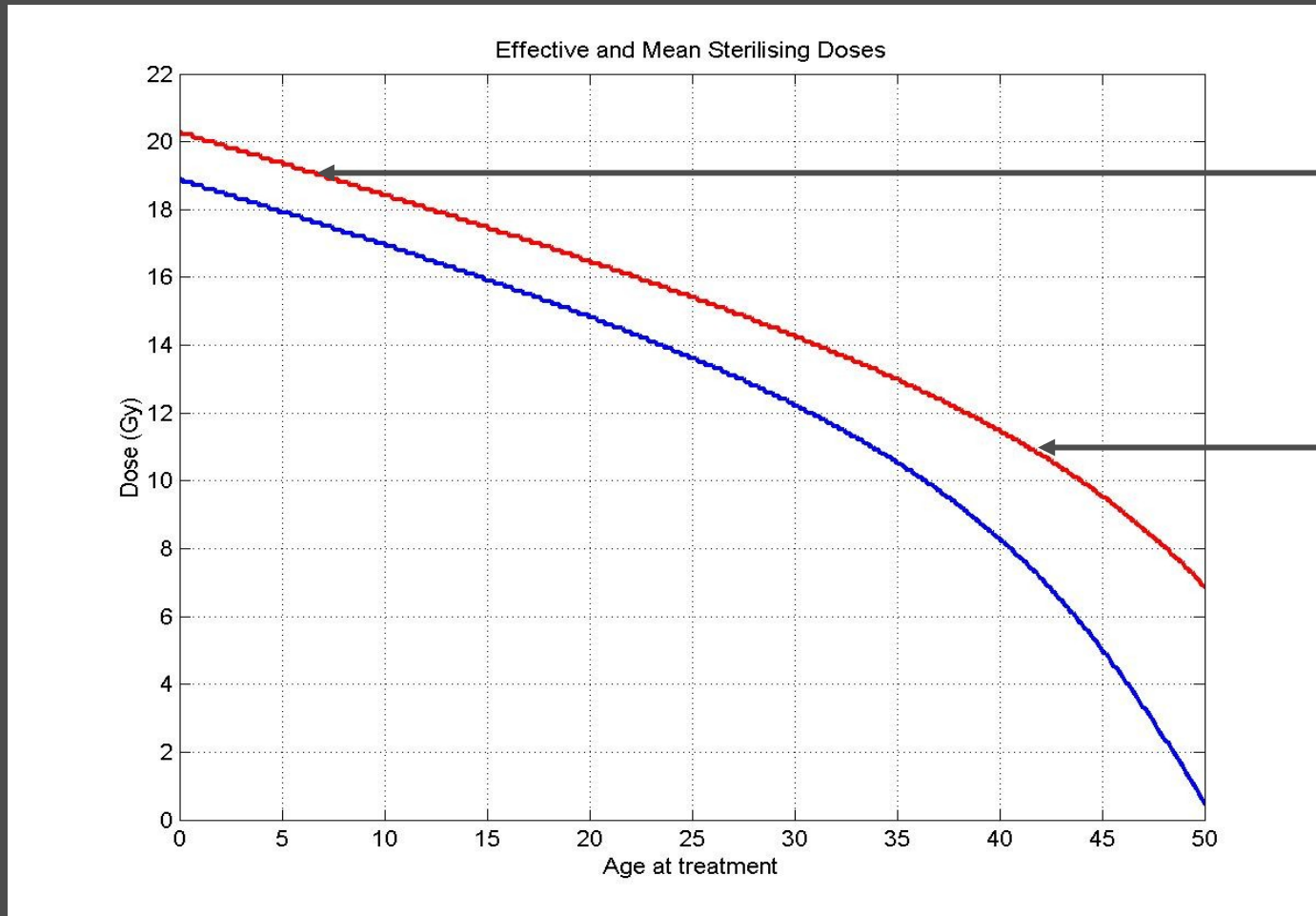
Human oocyte  
(Primordial follicle)

⦿  $LD_{50} < 2 \text{ Gy}$

Wallace et al. (2003) Hum Reprod.



# Effective and mean ovarian sterilizing doses of radiotherapy at increasing age



19 Gy will sterilize at 7 years

11 Gy will sterilize at 42 years

Wallace WH et al. IJRBP (2005)

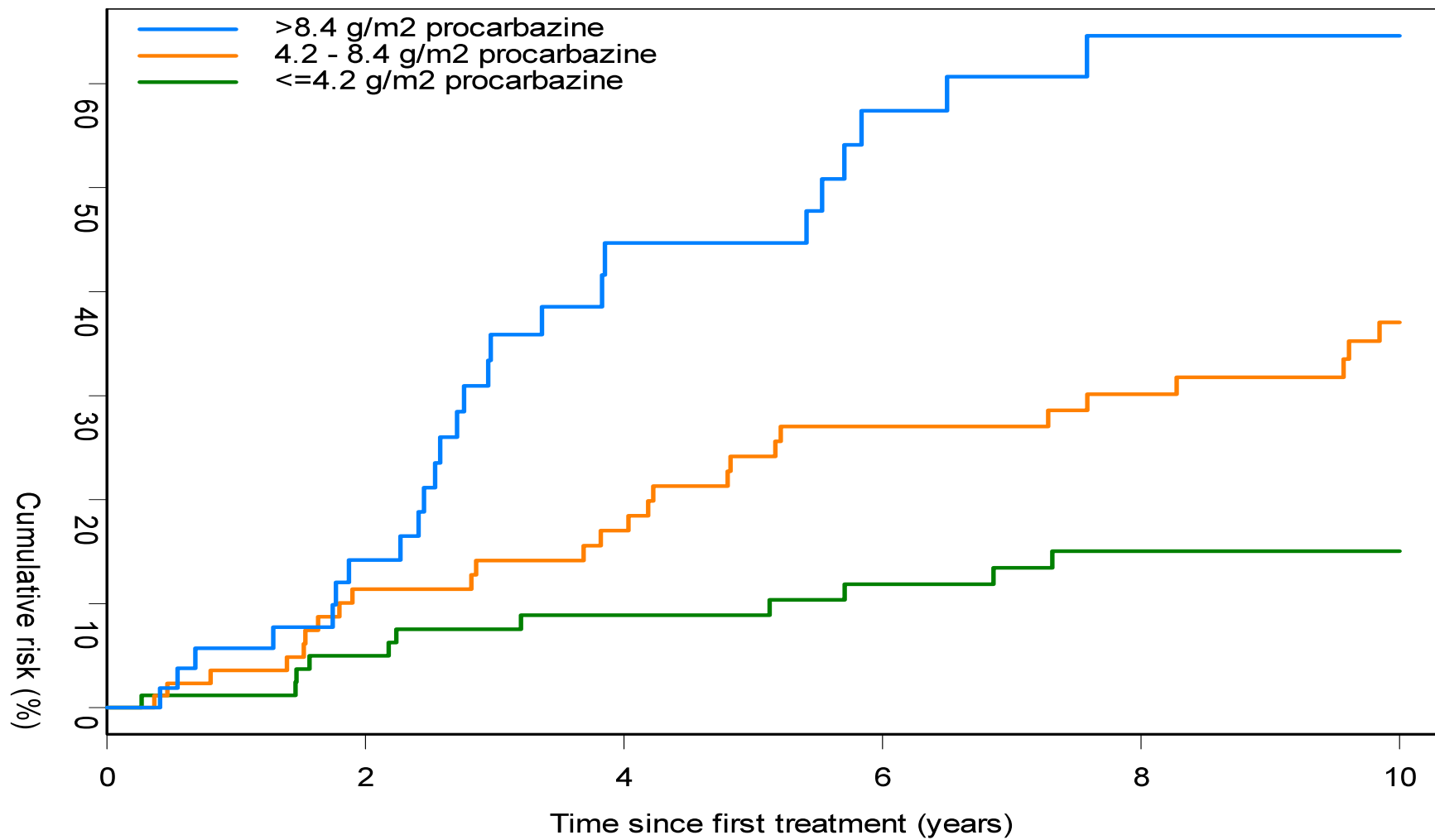
# Premature menopause in survivors of childhood cancer

## Childhood Cancer Survivor Study (CCSS)

- ⊙ Diagnosed cancer <21 yrs, 1970-86, Five year survivors.
- ⊙ 2819 eligible subjects, 1065 sibling controls
- ⊙ Non-surgical menopause: Cumulative Incidence 8% vs 0.8 % (RR 13.21)
- ⊙ Risk factors:
  - attained Age
  - Increasing doses of radiation to the ovaries
  - Increasing alkylating agent score (dose )
  - Hodgkin's Lymphoma

Sklar et al. JNCI 2006;98:890-6

## Cumulative incidence of menopause according to procarbazine dose





## Risk of premature menopause (PM<40) according to mutually exclusive chemotherapy categories

	Patients (n=518)	PM (n=97)	HR <sub>adjusted</sub> * (95% CI)
no CT	289	6	1 (ref)
non-alkylating CT only	45	1	0.8 (0.1 - 6.9)
alkylating CT, no procarbazine	46	5	<b>5.4 (1.6-18.2)</b>
alkylating CT, ≤ 8.4g/m <sup>2</sup> procarbazine	183	44	<b>10.9 (4.6-26.1)</b>
alkylating CT, > 8.4g/m <sup>2</sup> procarbazine	48	26	<b>41.5 (16.9-102 )</b>

\* Adjusted for smoking, OC-use, radiotherapy



## Pathologic FSH-Values in Postpubertal Boys by Cumulative Doses of Procarbazine

	Chemotherapy	Procarbazine (mg/m <sup>2</sup> )	Therapy Study	Pathologic FSH-Values
TG 1	2 O <sup>P</sup> PA	3000	HD - 78/82	28,9%
	2 OPA	0	HD - 85	0%
	2 OEPA	0	HD - 90	0%
TG 2	2 O <sup>P</sup> PA / 2 CO <sup>P</sup> P	5800	HD - 78/82	45,5%
	2 OPA / 2 COMP	0	HD - 85	0%
	2 OEPA / 2 CO <sup>P</sup> P	3000	HD - 90	37,5%
TG 3	2 O <sup>P</sup> PA / 4-6 CO <sup>P</sup> P	8600-11400	HD - 78/82	62,5%
	2 OPA / 4 COMP	0	HD - 85	0%
	2 OEPA / 4 CO <sup>P</sup> P	6000	HD - 90	36,4%

# OVERVIEW OF EURONET-PHL-C-1

# EURONET-PHL-C1

## Aims

Can involved field RT be omitted in FDG-PET scan negative patients after two courses of OEPA in all treatment groups?

Can procarbazine be substituted for intermediate and advanced stage disease groups by Dacarbazine?

**Without reduction in EFS**

# EURONET-PHL-C1

Inclusion: 0-18 Yrs

TG1:

- Stage 1A/B and 11A

TG2:

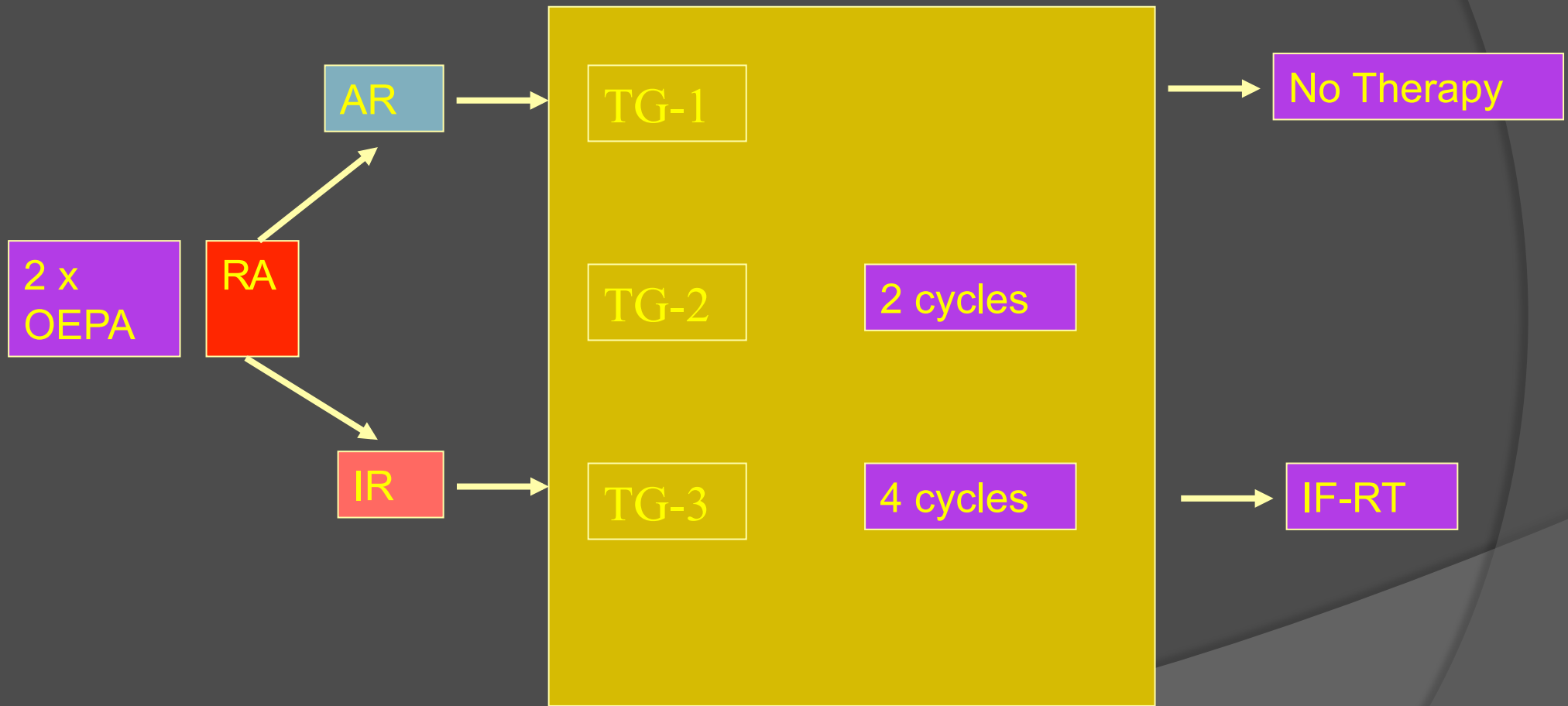
- Stage 11B, 11AE, 111A, 1E

TG3:

- Stage 111B, 111E, 11BE, 1VA/B

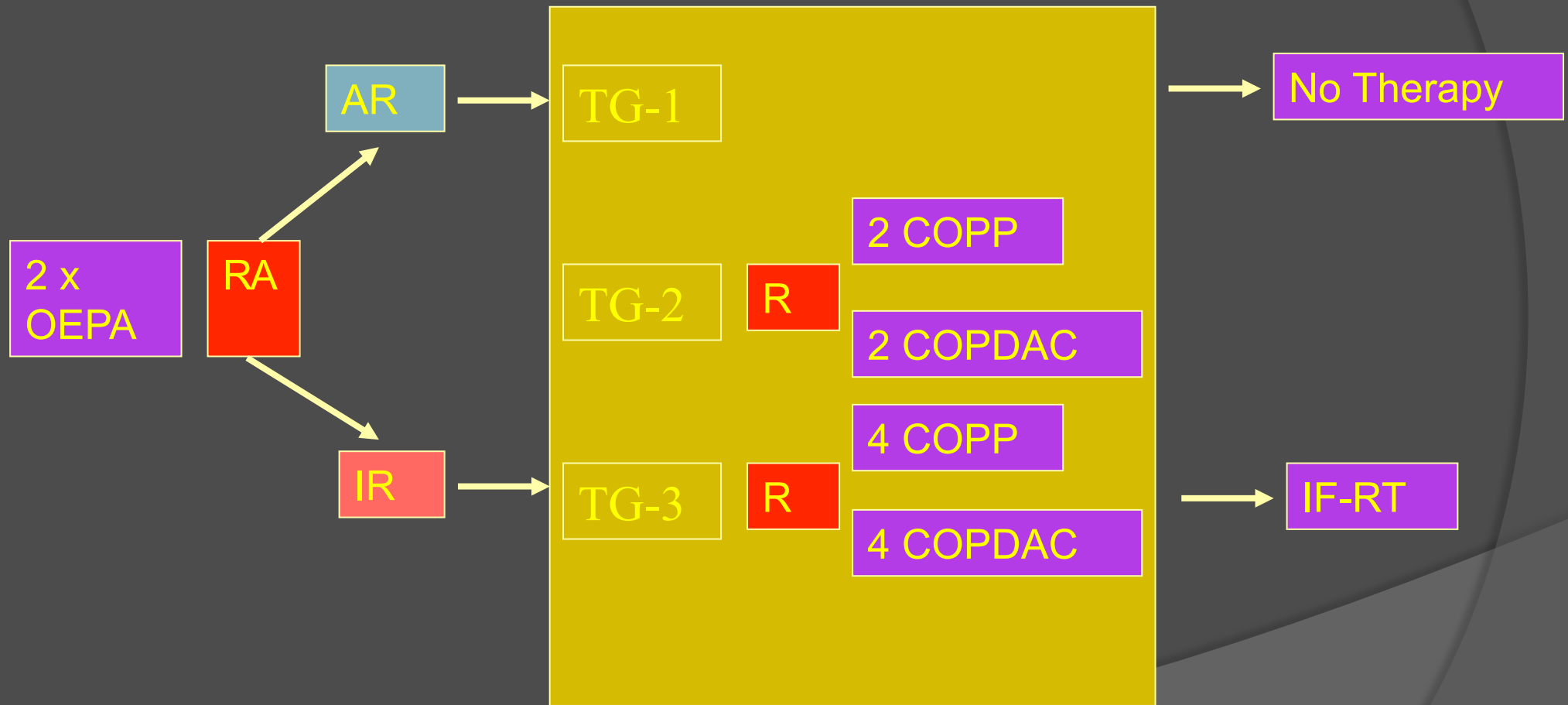
# EuroNet-PHL-C-1

## Response-adapted Therapy



# EuroNet-PHL-C-1

## Chemotherapy randomisation



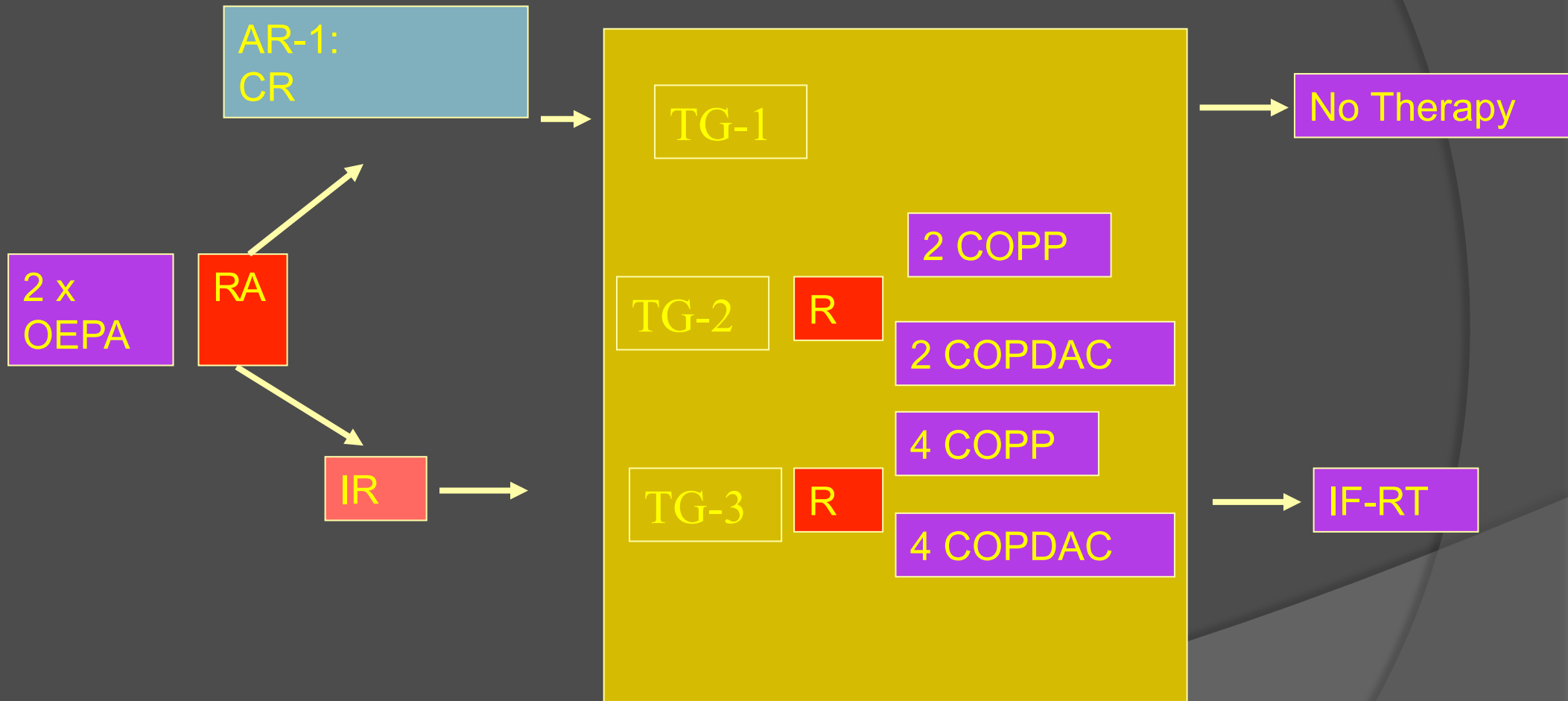


## Replacement of procarbazine (COPP) by Dacarbazine (COPDAC)

<b>COPDAC</b>	<b>COPP</b>
Vincristin 6 mg/m <sup>2</sup>	Vincristine 6 mg/m <sup>2</sup>
Dacarbazine 250 mg/m <sup>2</sup> (three)	Procarbazine 3000 mg/m <sup>2</sup>
Prednisolone 1200 mg/m <sup>2</sup>	Prednisolone 1200 mg/m <sup>2</sup>
Cyclophosphamide 2000 mg/ m <sup>2</sup>	Cyclophosphamide 2000 mg/ m <sup>2</sup>

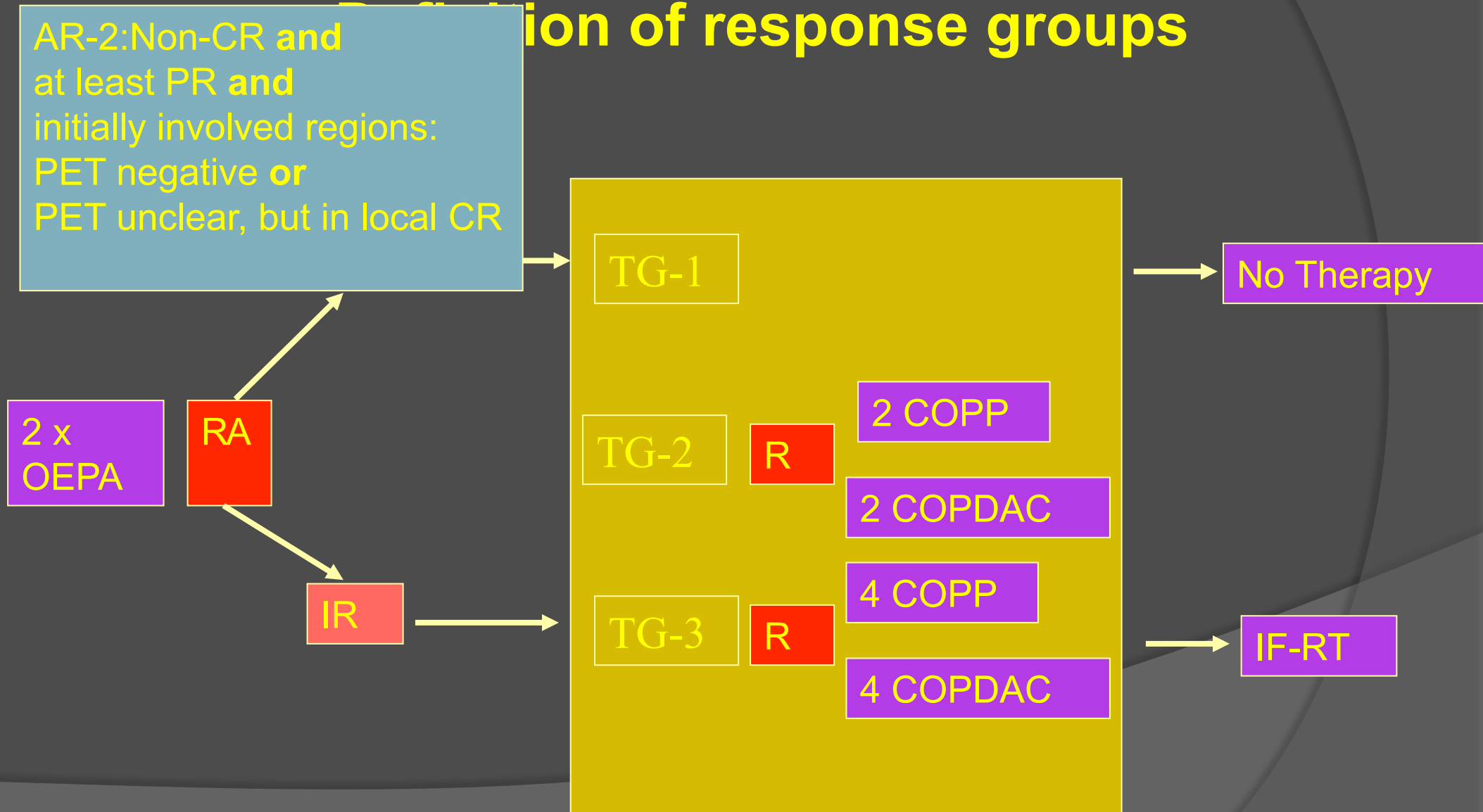
# EuroNet-PHL-C-1

## Definition of response groups



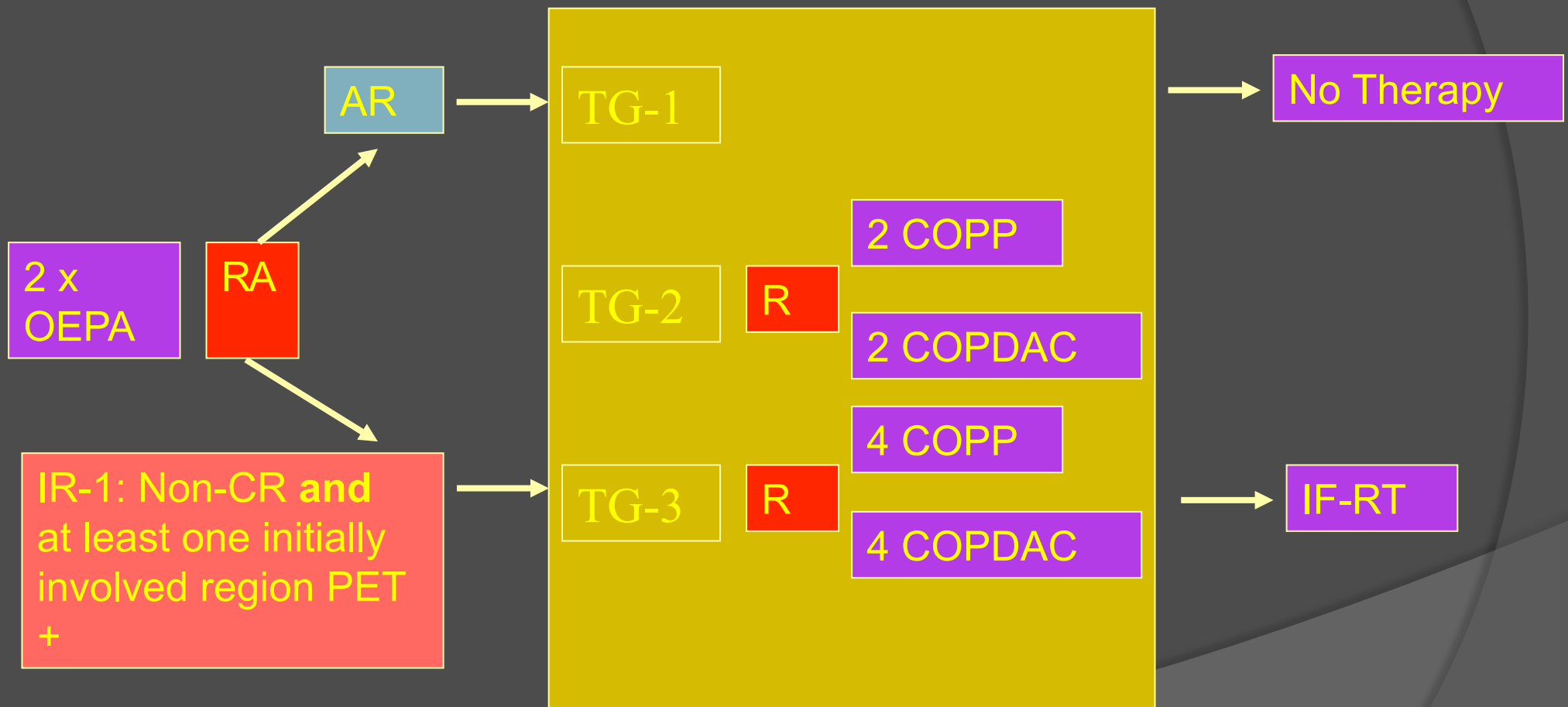
# EuroNet-PHL-C-1

## Definition of response groups



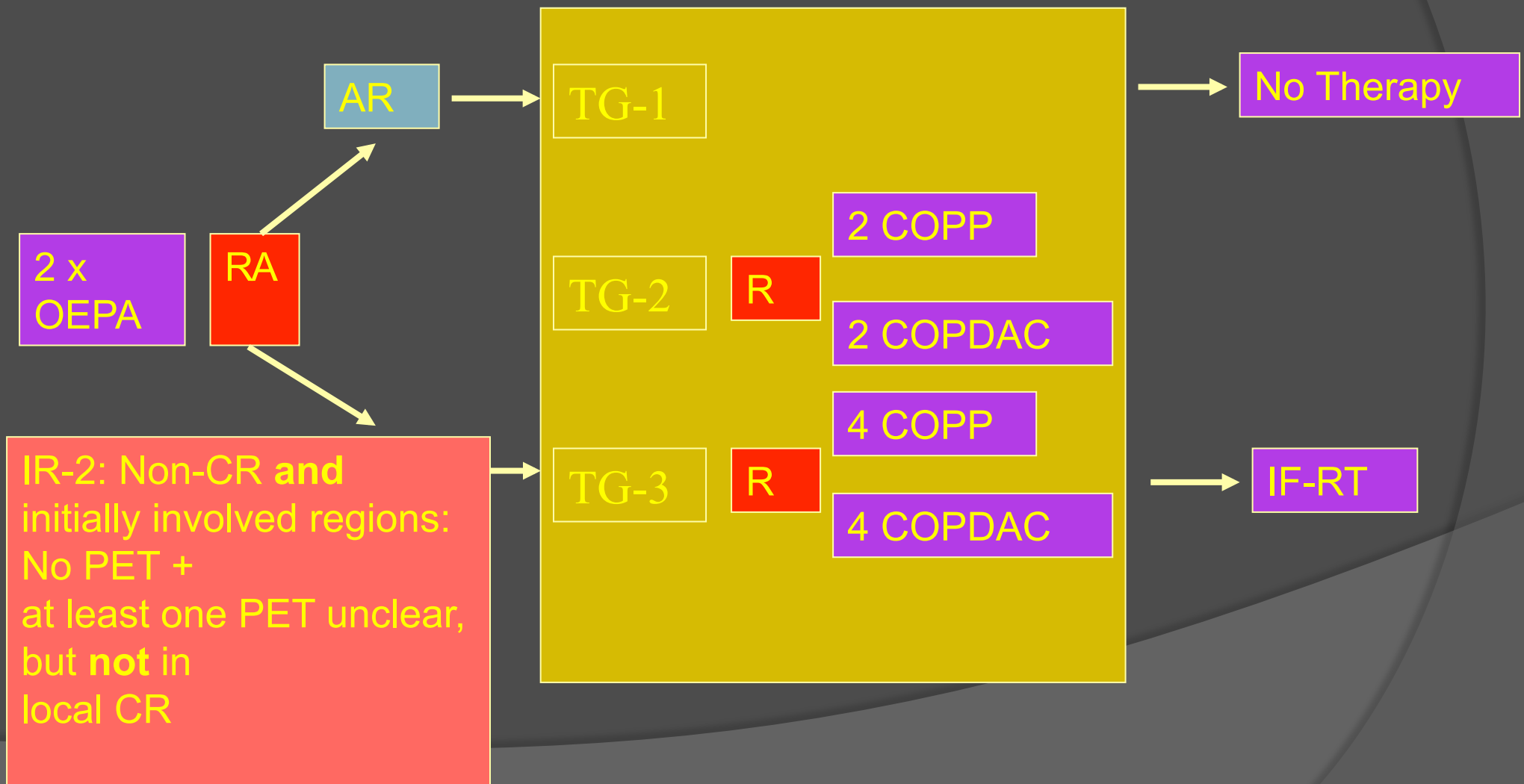
# EuroNet-PHL-C-1

## Chemotherapy randomisation



# EuroNet-PHL-C-1

## Chemotherapy randomisation

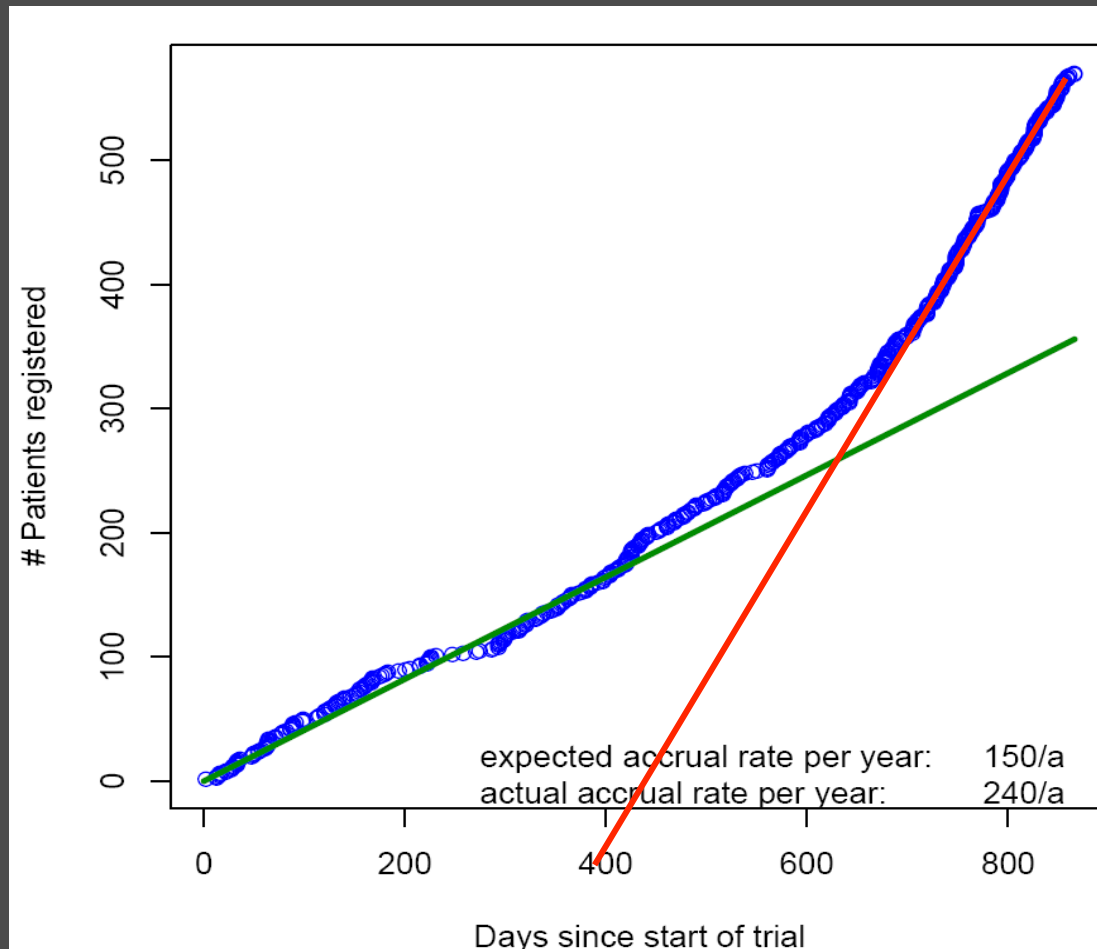


FDG-PET after 2 cycles  
Data from the GPOH-Pilot paediatric study

After 2 cycles	TG1	TG2	TG3	TG2+3
PET-negative	27/41 (66%)	5/16	8/23	13/39 (33%)

- ~ 30% of TG1 Patients will require IFRT
- ~ 60% of TG 2 & 3 patients will require IFRT

# Accrual EuroNet-PHL-C1



N=**570** as of Jun 15th 2009

Last 6 months  
~ accrual 450/a

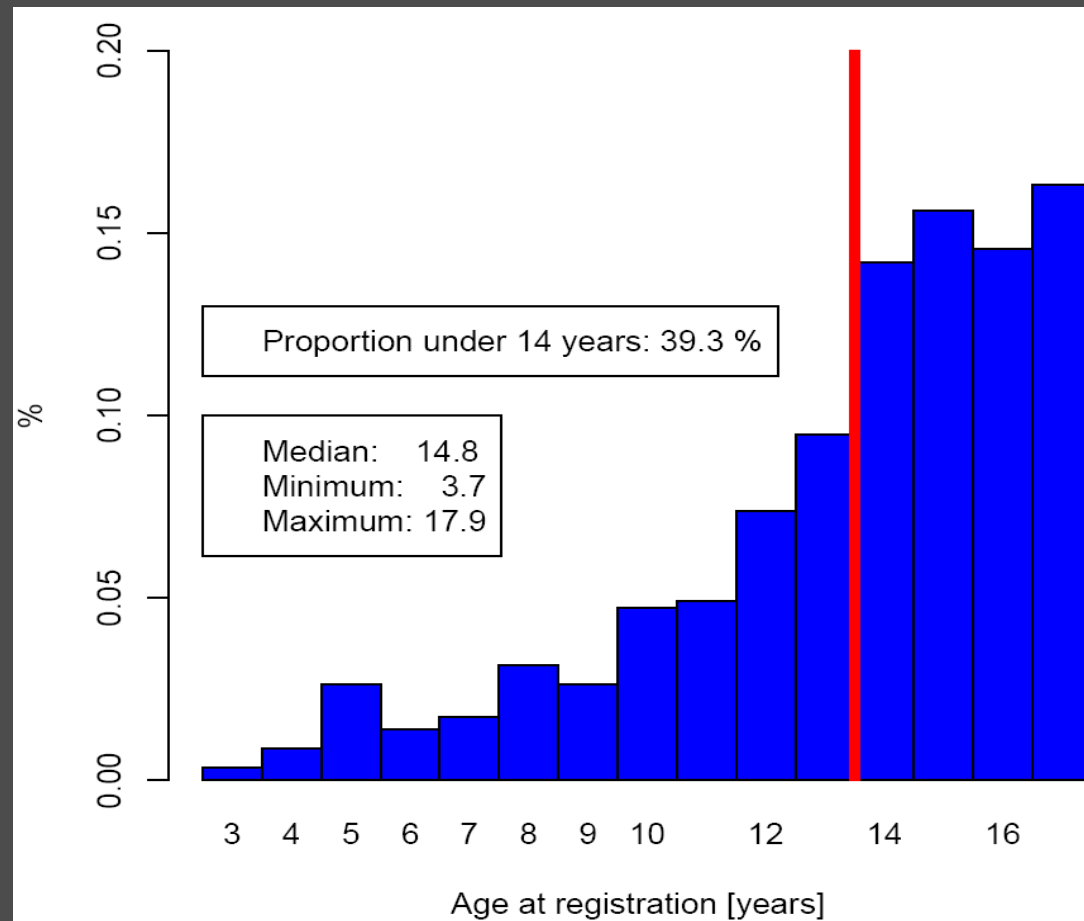
**Projection**  
End of study 2013  
N~2000  
**(planned (protocol) > 1900)**

# Accrual by Country – 2009-06-15

	N
Germany	345
France	68
Great Britain	34
Austria	29
Czech Republic	19
Spain	19
Switzerland	18
Sweden	16
Norway	13
Ireland	7
Denmark	2
Sum	570



# Age distribution



# Treatment groups

	observed	expected
TG1	37.7	36.0
TG2	23.1	28.0
TG3	39.2	36.0

# Randomisation in TG2+3

	randomized			chosen		
	COPP	COPDAC	Sum	COPP	COPDAC	Sum
TG2	47	49	96	6	4	10
TG3	70	72	142	17	19	36
Sum	117	121	238	23	23	46

Randomisation rate: **83.8%** (+1.1% since Paris)

# Treatment chosen by gender

	COPP	COPDAC	Sum
male	10	21	31
female	13	2	15
Sum	23	23	46

**p = 0.0012** (Fisher's exact Test)

**Boys prefer COPDAC**  
**Girls opt for “safe” standard**

# Inadequate response at ERA (IFRT)

	No RT	in %	RT required	PRO(gress)	Sum
TG1	93	62.8	55	0	148
TG2	46	50.5	45	0	91
TG3	48	32.2	100	1	149
Sum	187	48.2	200	1	388

THANK YOU



**From: Thomas Hodgkin (1798-1866)**

**To: Howard Hodgkin**

