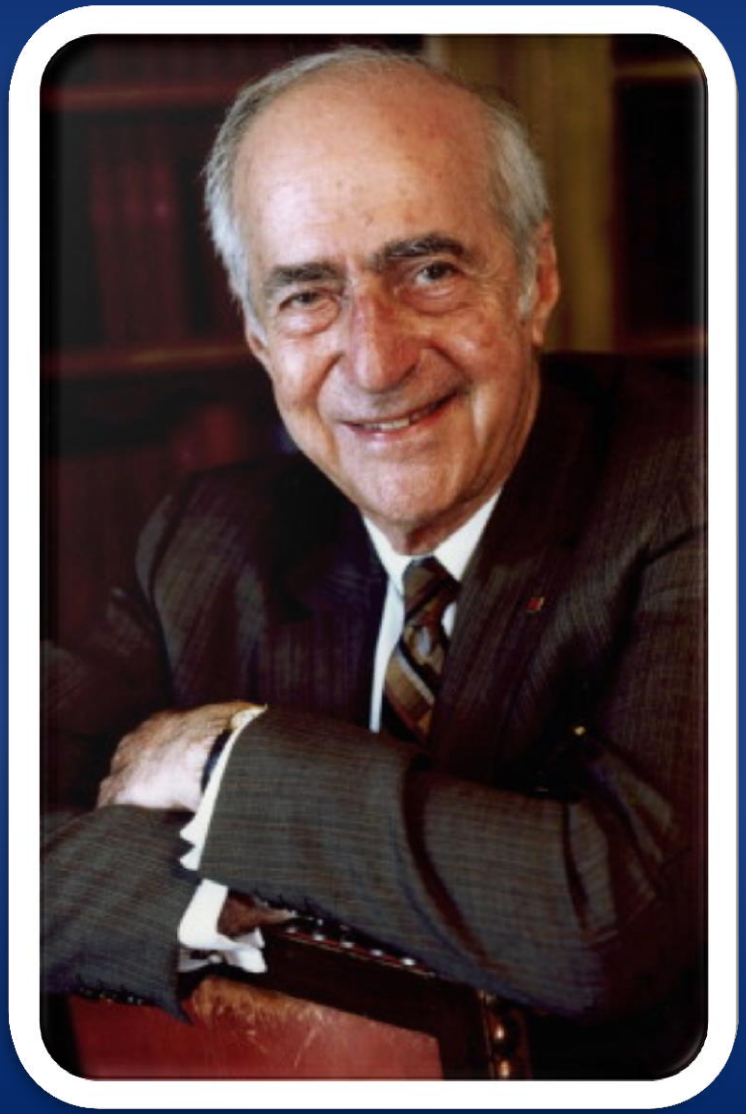
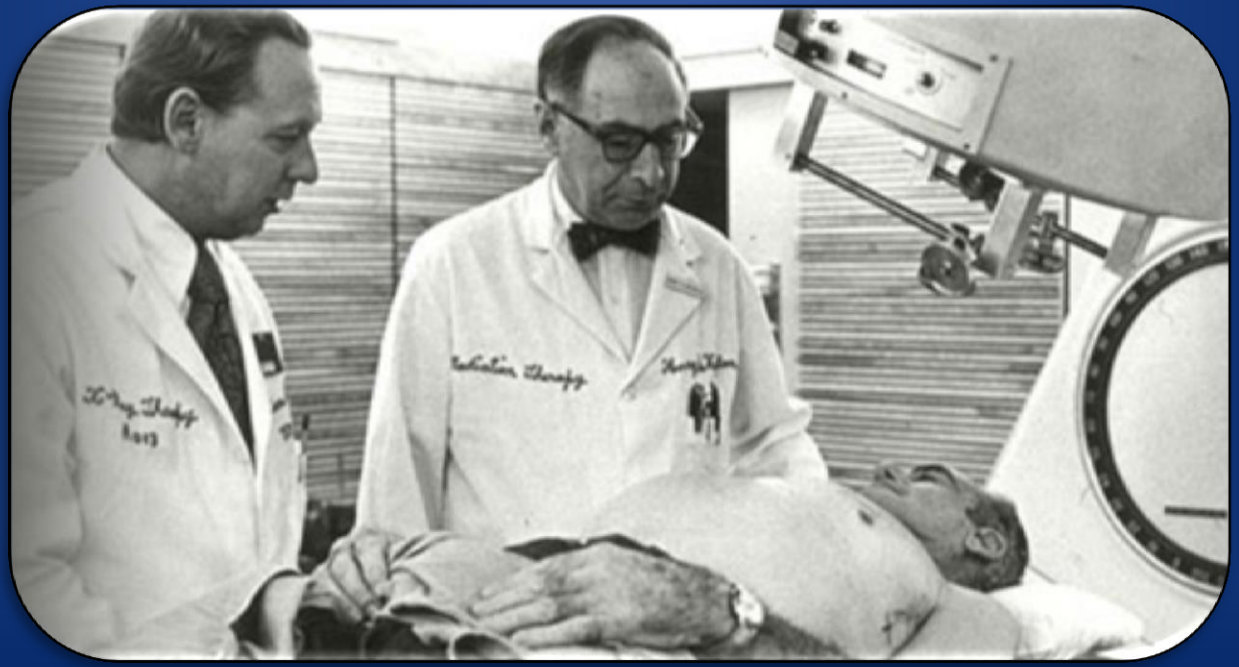
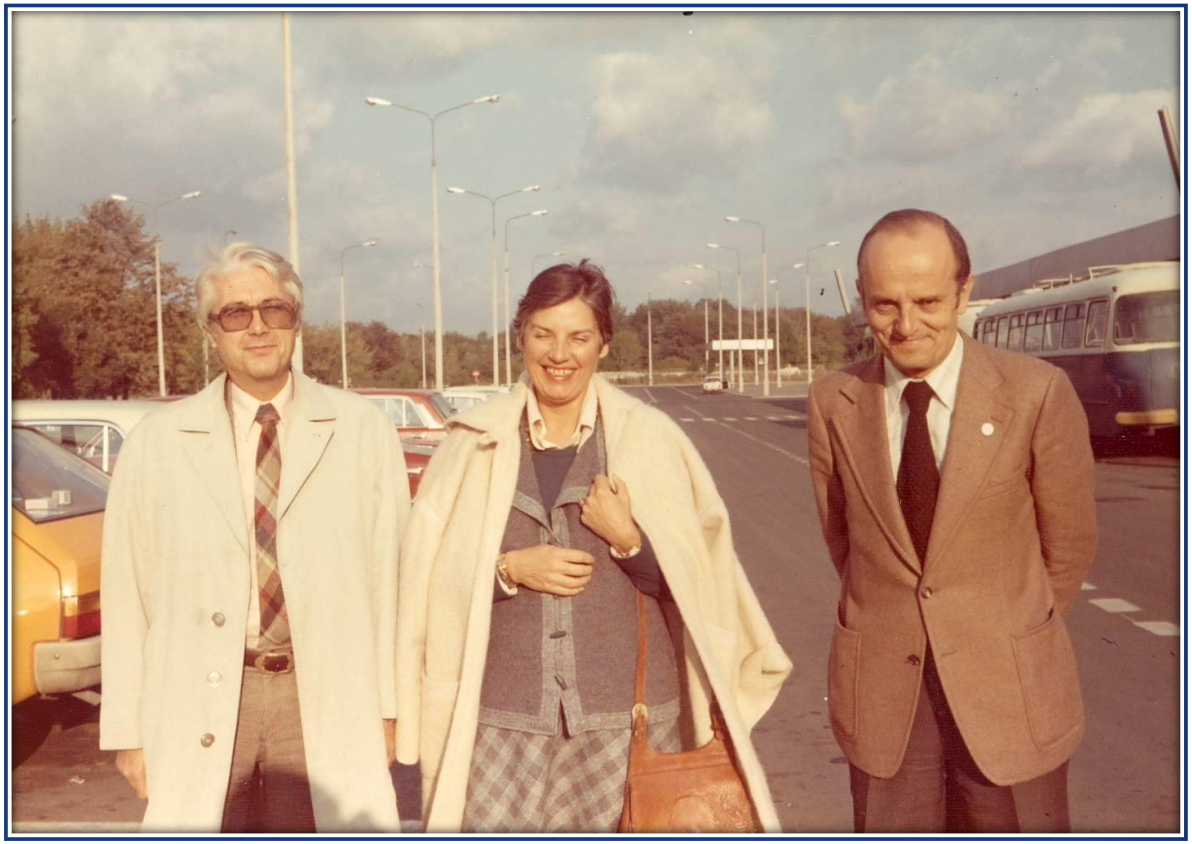
Professor Maurice Tubiana





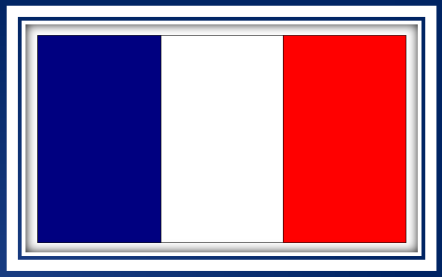
The French way of life

Dr. Odile Schweisguth
Pediatric Radiation Oncology



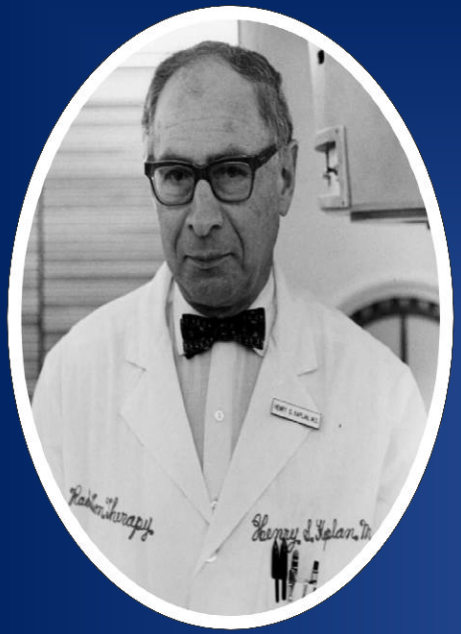
Daniele Sarrazin
Pediatric Radiation Oncology

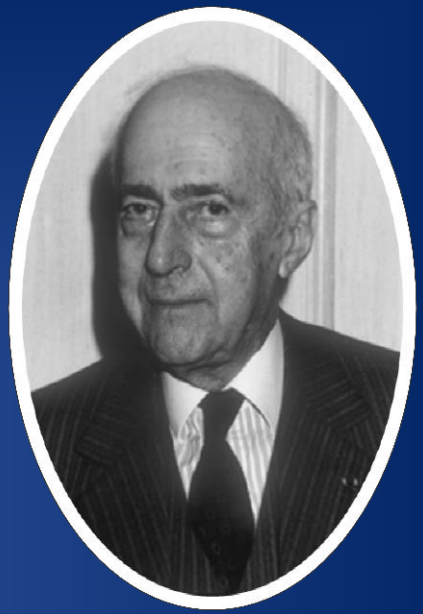
Stanford Visitors from France



A Massiot	1958	Courbevoie	Jean-Marc Cosset	1979	IGR
C Rouquette	1967	IGR	Maurice Tubiana	1979	IGR
Michel Schlienger	1963	IGR	Regis Soleilhac	1980	Ile de la Reunion
Guy Juillard	1958	CAC Nice	Philippe Pouletty	1982	Hopital St Louis
Jean-Pierre Wolff	1968	IGR	Jean Kadouche	1982	Hopital St Louis
Alain Laugier	1968	IGR	Olivier LeFloch	1983	Tours
Le Fur	1969	IGR	Robert Flamant	1983	IGR
Bernard Pierquin	1969	IGR	Francoise Flamant	1983	IGR
M Raynal	1969	IGR	Michele Mangold	1988	Chartres
Henri Pourquier	1964	Montpellier	A Kervazo	1990	Maubeuge
C Vrousos	1972	Grenoble	Bruno Cutuli	1993	Strasbourg
S Schraub	1972	Besançon	Catherine Schumacher	1993	Strasbourg
P Conbes	1972	Toulouse	Nathalie Pinto	1995	Sainte- Etienne
JP Le Bourgeois	1973	Paris	Francoise Mornex	1995	Lyon
Alain Daban	1977	Poitiers	Eric Lartigau	2014	Lille

Lessons Learned





Radiation Therapy
- Large fields
- High doses

Chemotherapy with radiotherapy
- EORTC trials
- Reduction of toxicity

- International cooperation on clinical trials
- Quality Assurance
- Medical education

“A historical glimpse of Hodgkin’s disease and The IGR- Stanford Connection”

Pediatric Hodgkin's Lymphoma

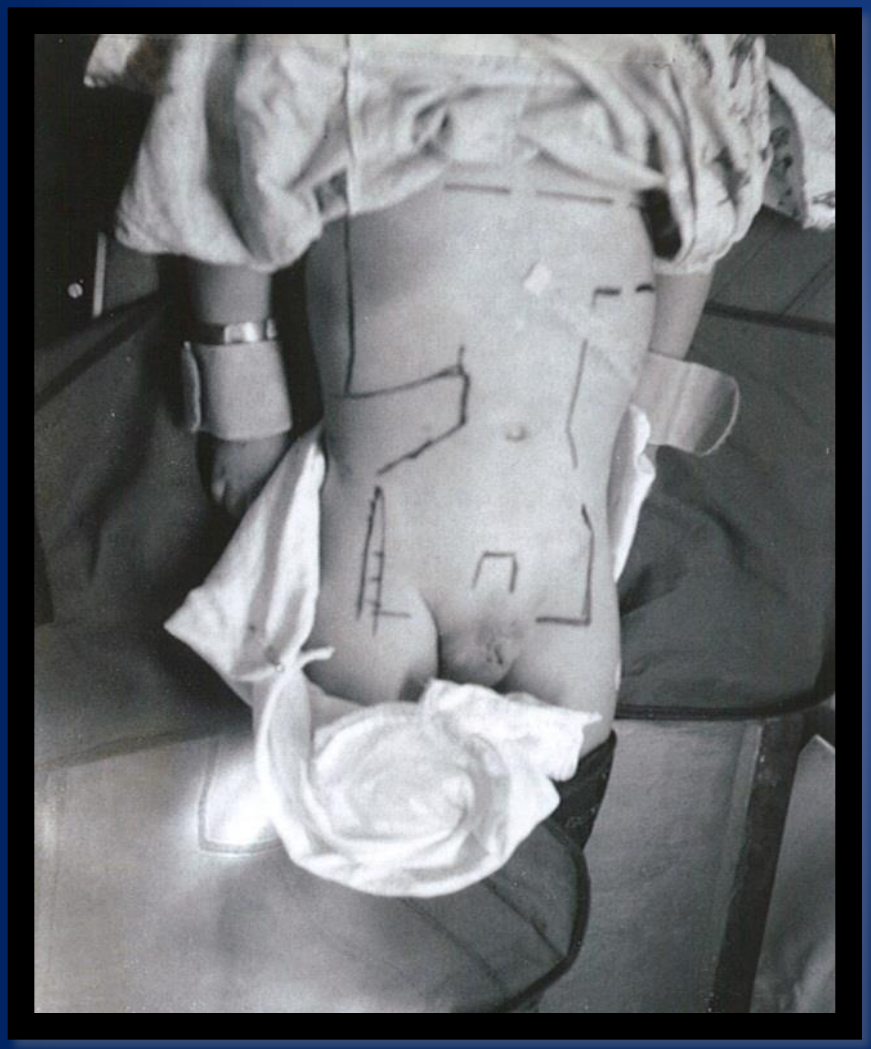
Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care

April 1970

21 mos old
PS III_SB NSHD

Radiotherapy - TLI - 1970

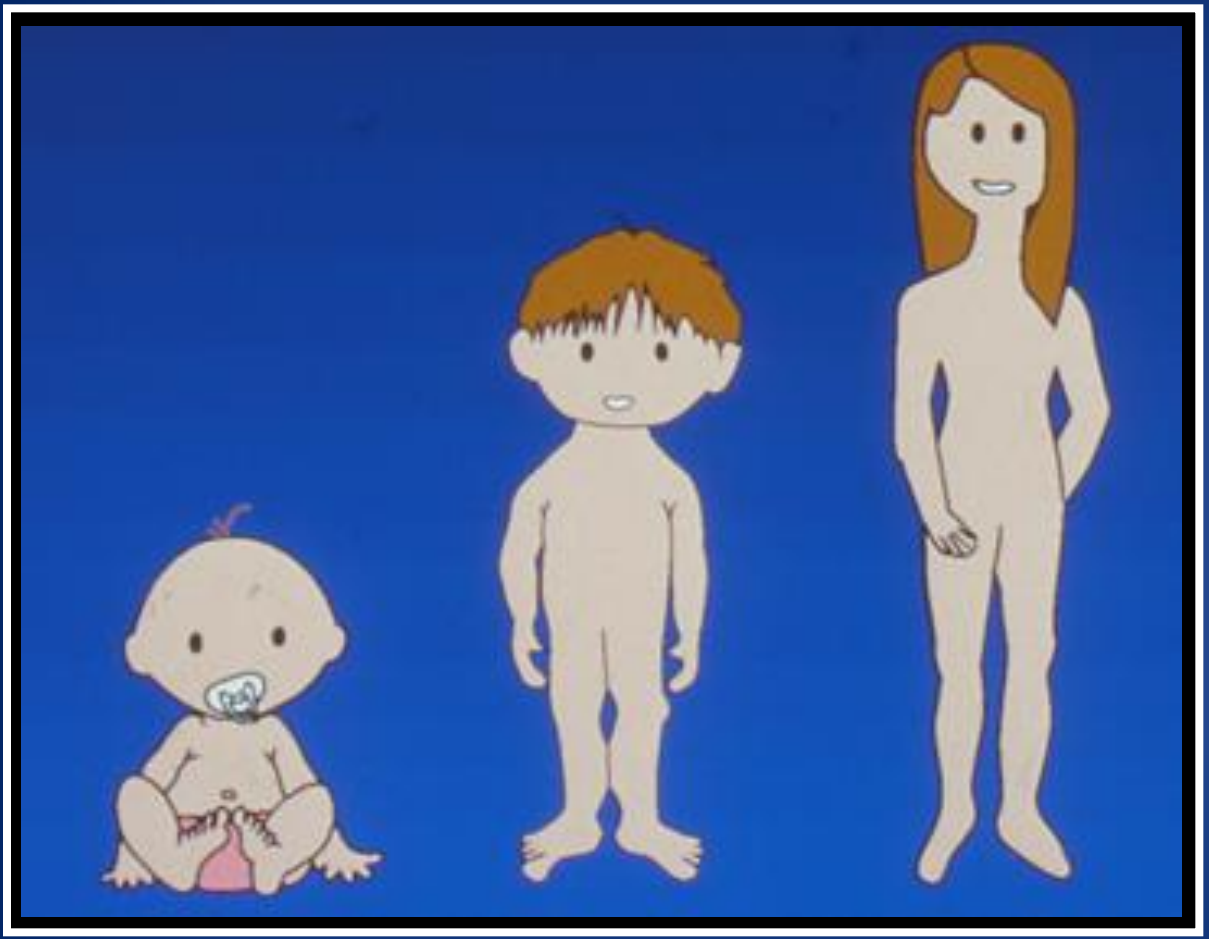


Lessons

1) Be Innovative

- Novel approach - 1500 rads TLI + MOPP
- Success - Cure of HD,
  No growth /development abnormalities

Treatment-Combined Modality Therapy



≤ 5 yrs.	6 – 10 yrs.	11 - 14 yrs.
1500 rads	2000 rads	2500 rads + Boost

Chemotherapy:

- 6 cycles MOPP alternating with radiotherapy

Volumes:

- Involved fields
- Extended ST/TLI fields

Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care

Pediatric HD: Stanford Protocols 1970 -1981

- MOPP x 6 + 15 - 25.5 Gy IFRT
  - for children < 15 years
  - surgical staging
  - all stages included
  - age dependent RT
  - 10 Gy boost to bulky sites

Donaldson et al. J Clin. Oncol. 5, 1987

Low Dose Radiation + MOPP

Pediatric HD: Stanford Protocols 1970 -1981

- MOPP x 6 + 15 - 25.5 Gy IFRT
  - post splenectomy bacteremia and meningitis
  - infertility
  - leukemia

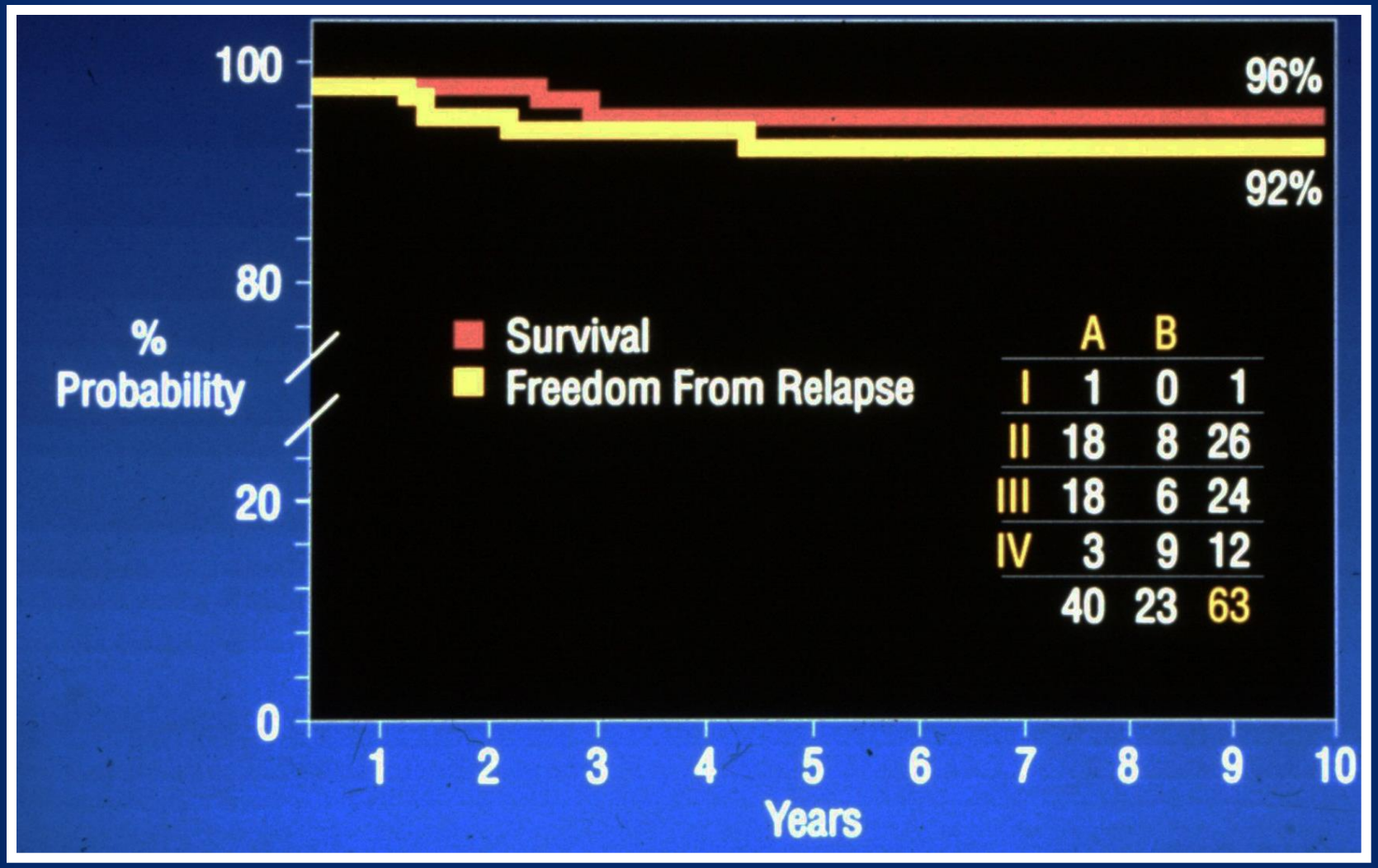
Donaldson et al. J Clin. Oncol. 5:742, 1987

Pediatric HD: Stanford Protocols 1982-1990

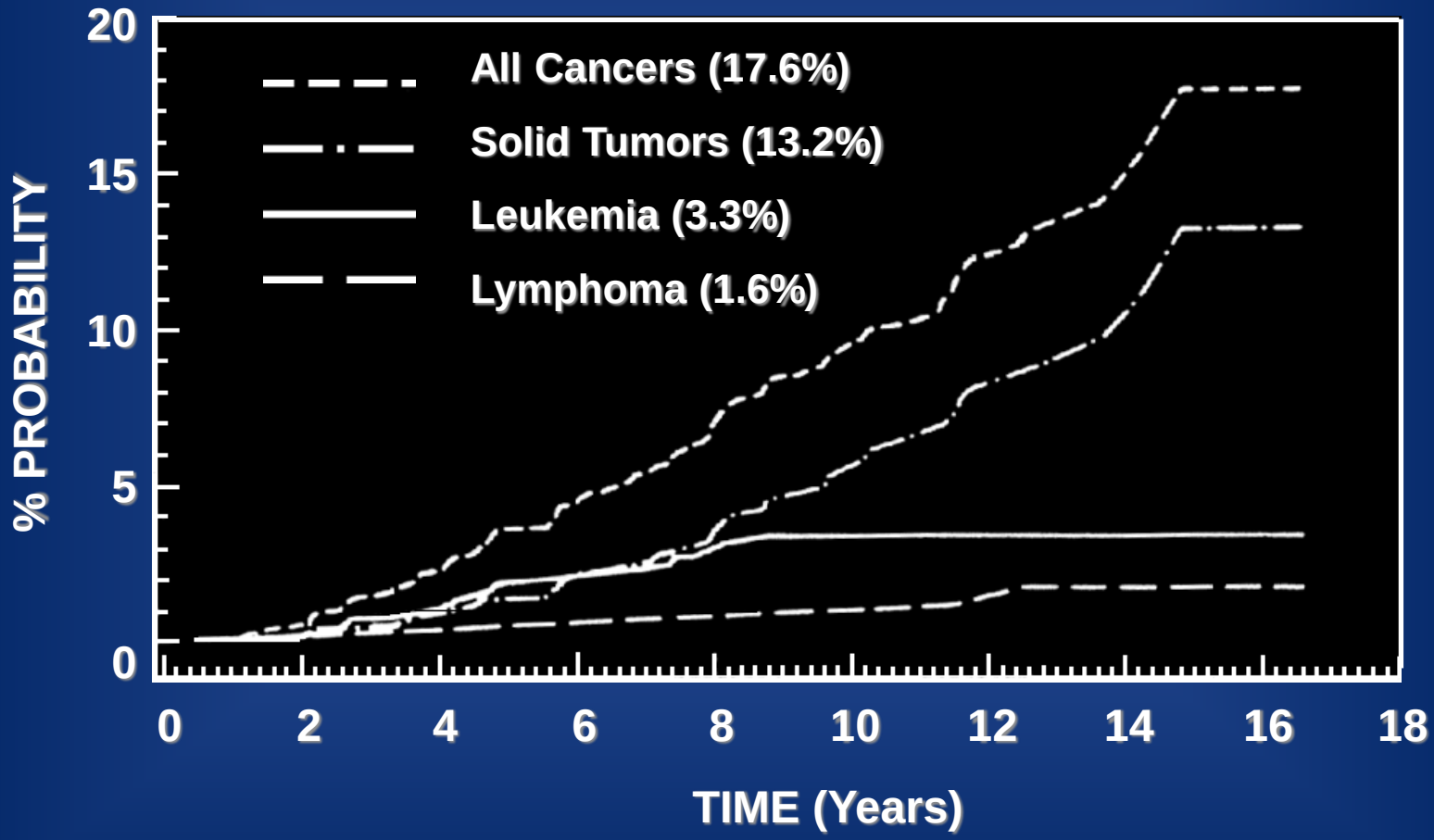
- ABVD/MOPP x 6 + 15 - 25.5 Gy IF RT
  - for children < 16 years
  - clinical staging
  - all stages (except IA LPHD)
  - 15 Gy IF RT
  - 10 Gy boost for PR or bulky disease

Hunger et al. J Clin. Oncol. 12:2160, 1994

Low Dose Radiation + MOPP/ABVD

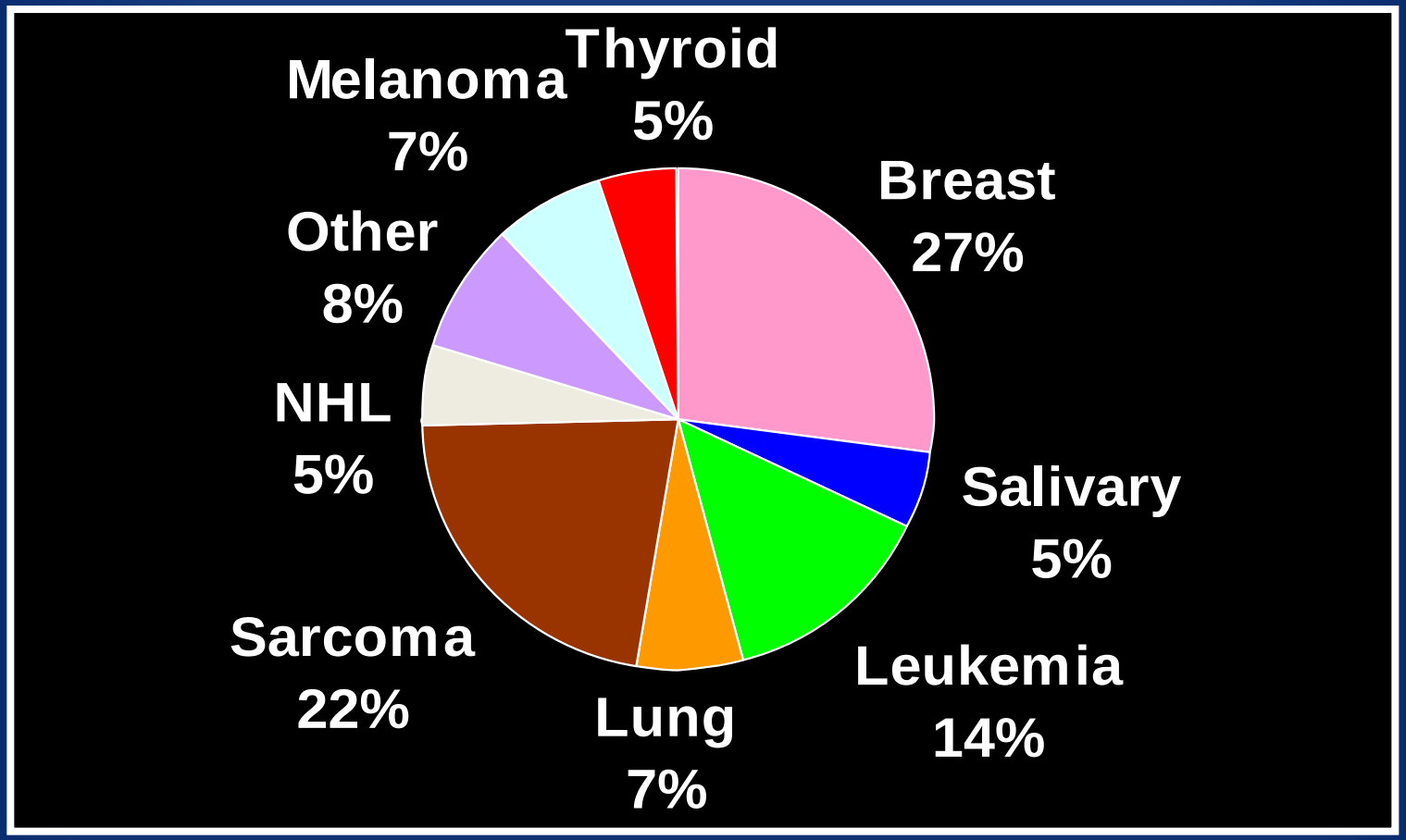


Second cancers
Stanford data 1968 - 84 (n = 1510)



Tucker et al. NEJM 318:76, 1988

New cancers in Pediatric HL patients



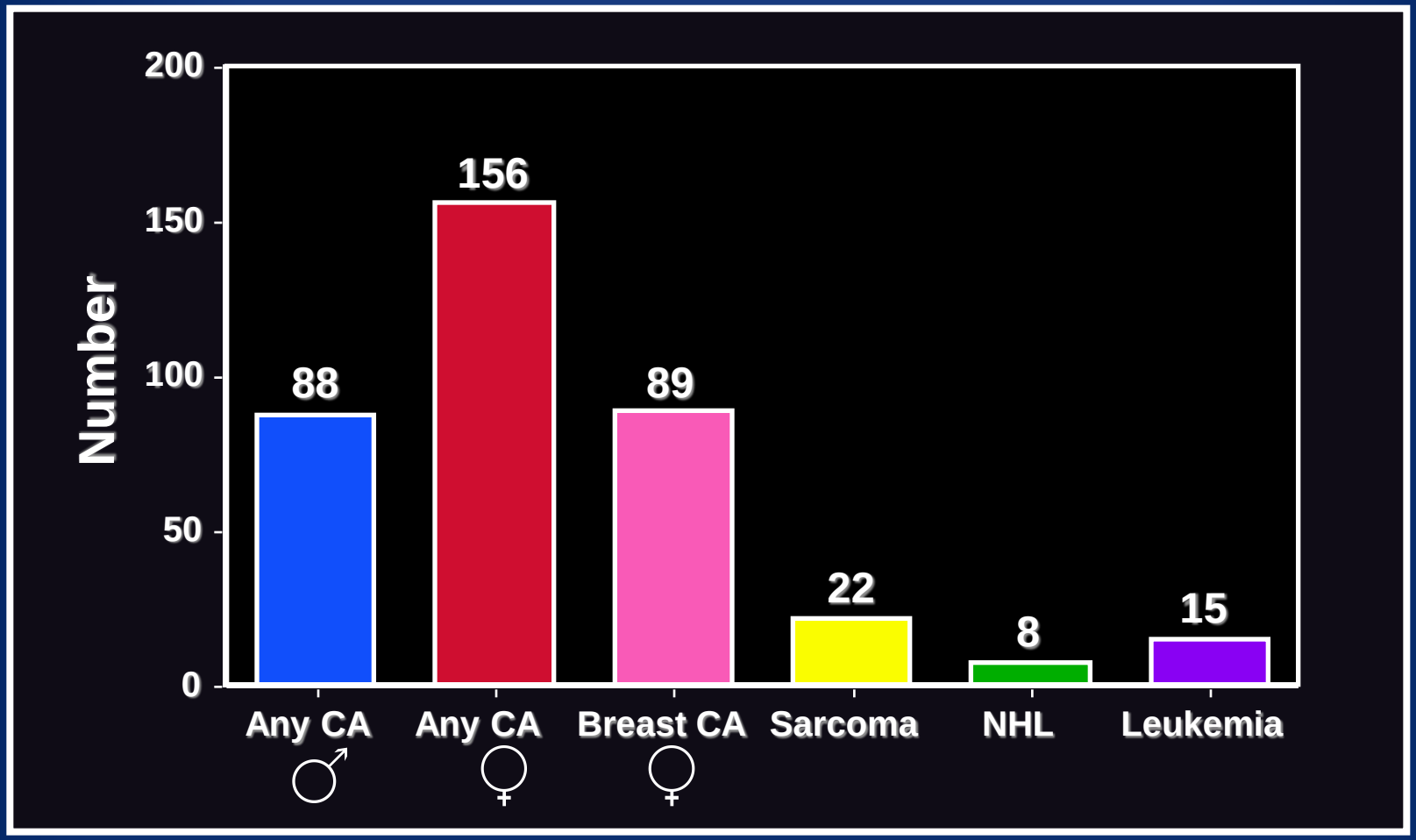
59 cancers in 56 pts

Wolden et al. JCO 16, 1998

Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) **Cure is NOT enough**
4) The greatest rewards come from continuity of care

Excess cancers per 1000 patients followed 20 years



Wolden et al. JCO 16:536, 1998

Secondary Cancers in Pediatric HL Survivors
Cumulative Incidence

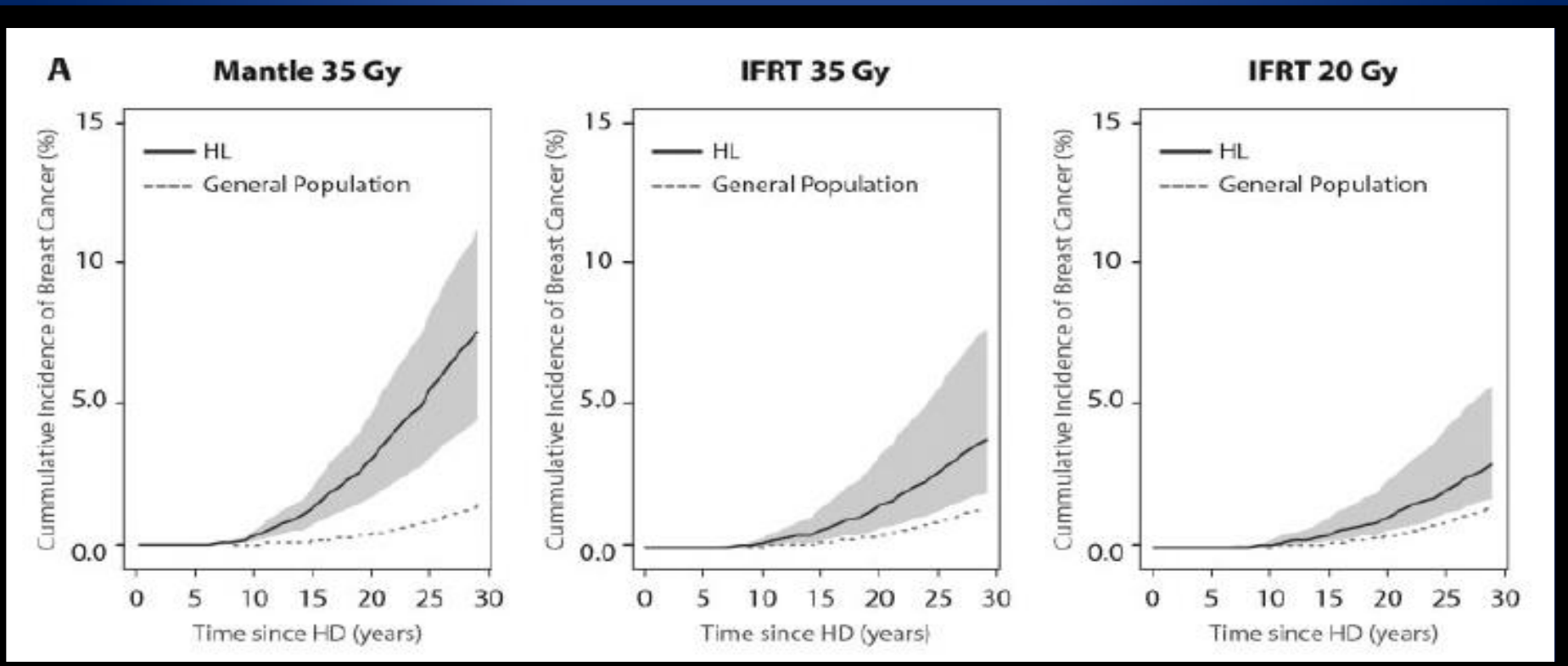
	20 year	30 year
Stanford	17%	29.4%
LESG	9.3%	23.7%
CCSS	7.6%	-
Nordic	6.9%	18%
Roswell Park	12.7%	26.3%

O'Brien et al. J Clin Oncol 28, 2010
Bhatia et al. J Clin Oncol 21, 2003
Neglia et al. J Natl Cancer Inst 93, 2001

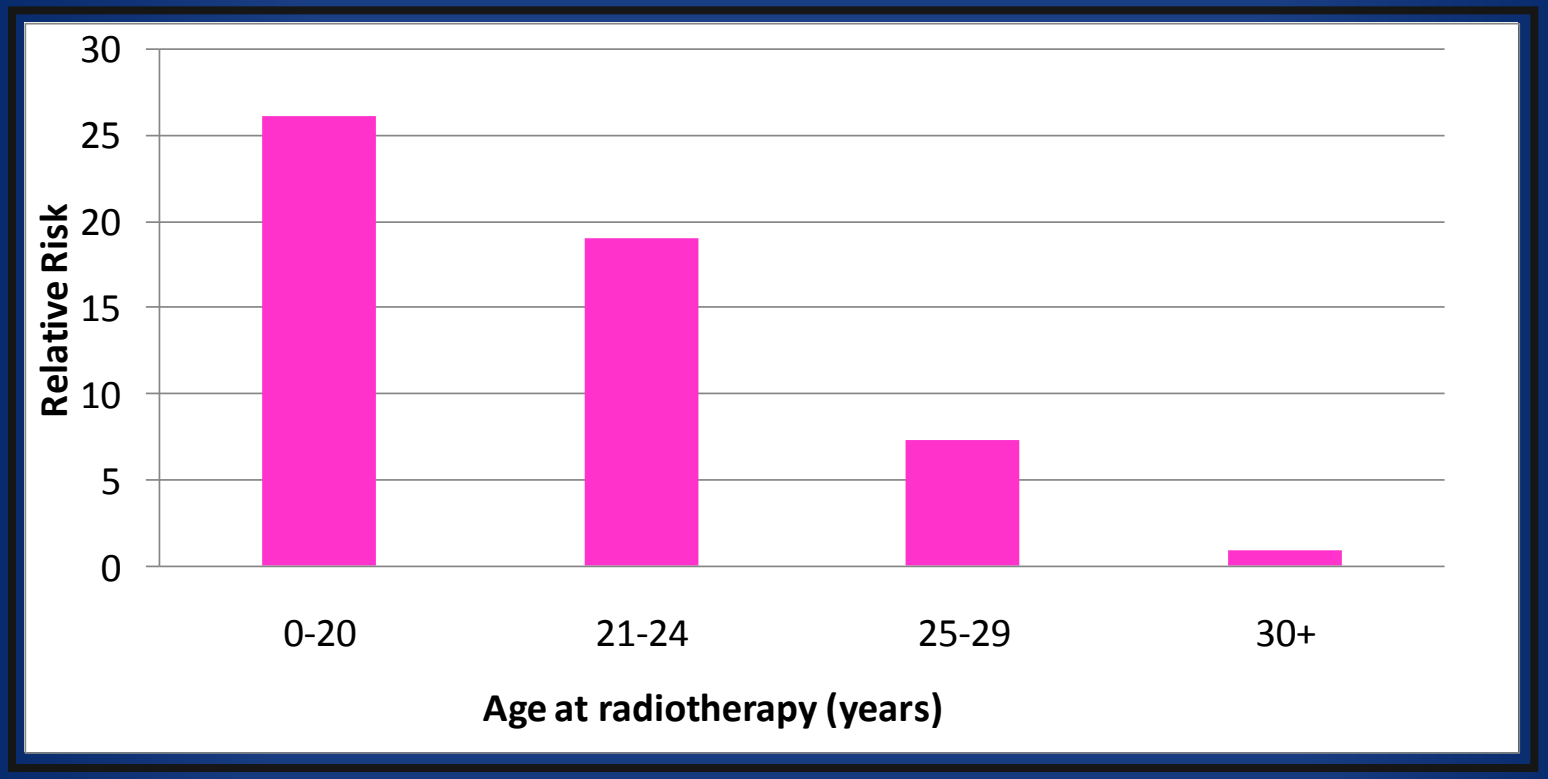
Sankila et al. J Clin Oncol 14, 1996
Green et al. J Clin Oncol 18, 2000

Breast Cancer in Young Women with Hodgkin's Lymphoma

Cumulative Incidence



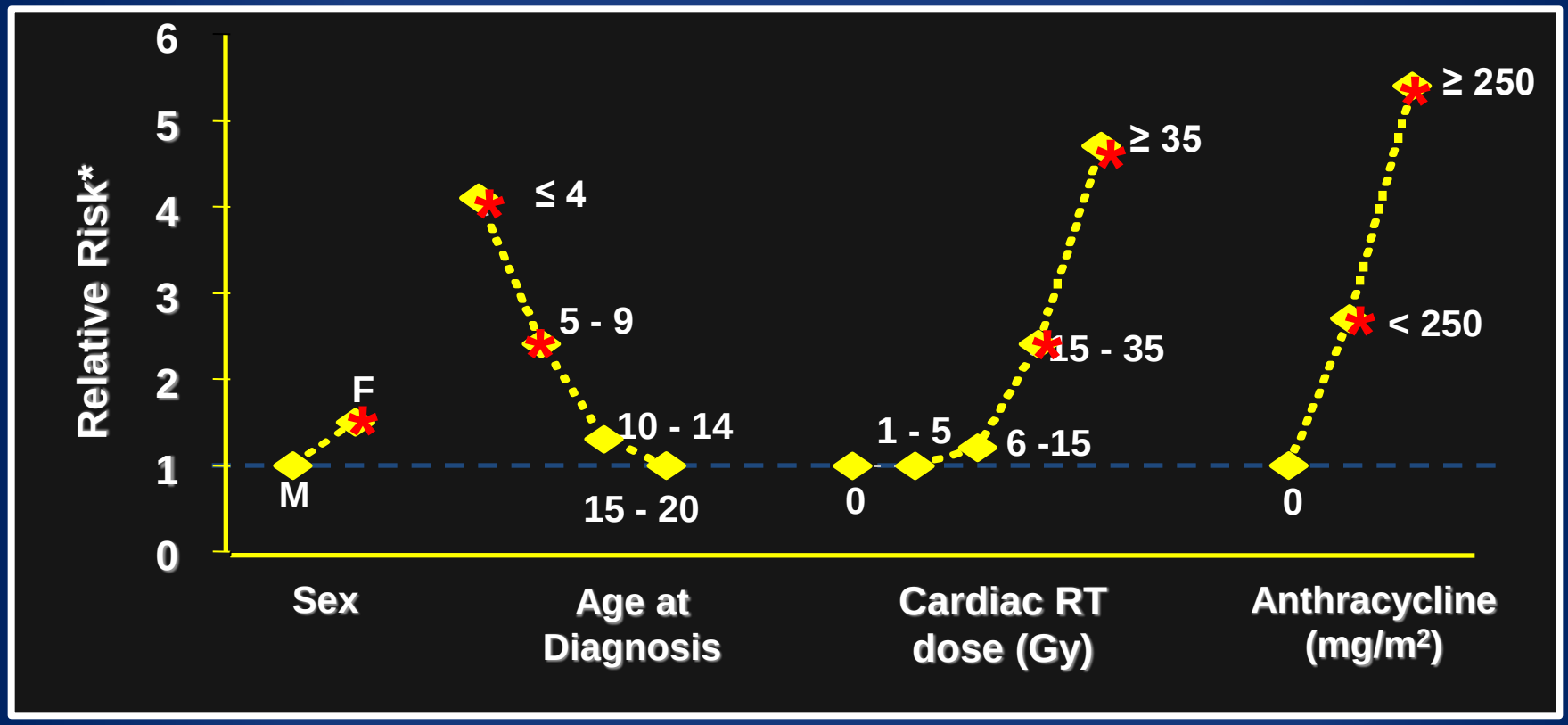
Relative risk of breast cancer by age



Hancock et al, JNCI 85:1, 1993
Wolden et al. JCO16:536, 1998

Risk of Congestive Heart Failure Multivariate Analysis

CCSS
An NCI-funded Resource

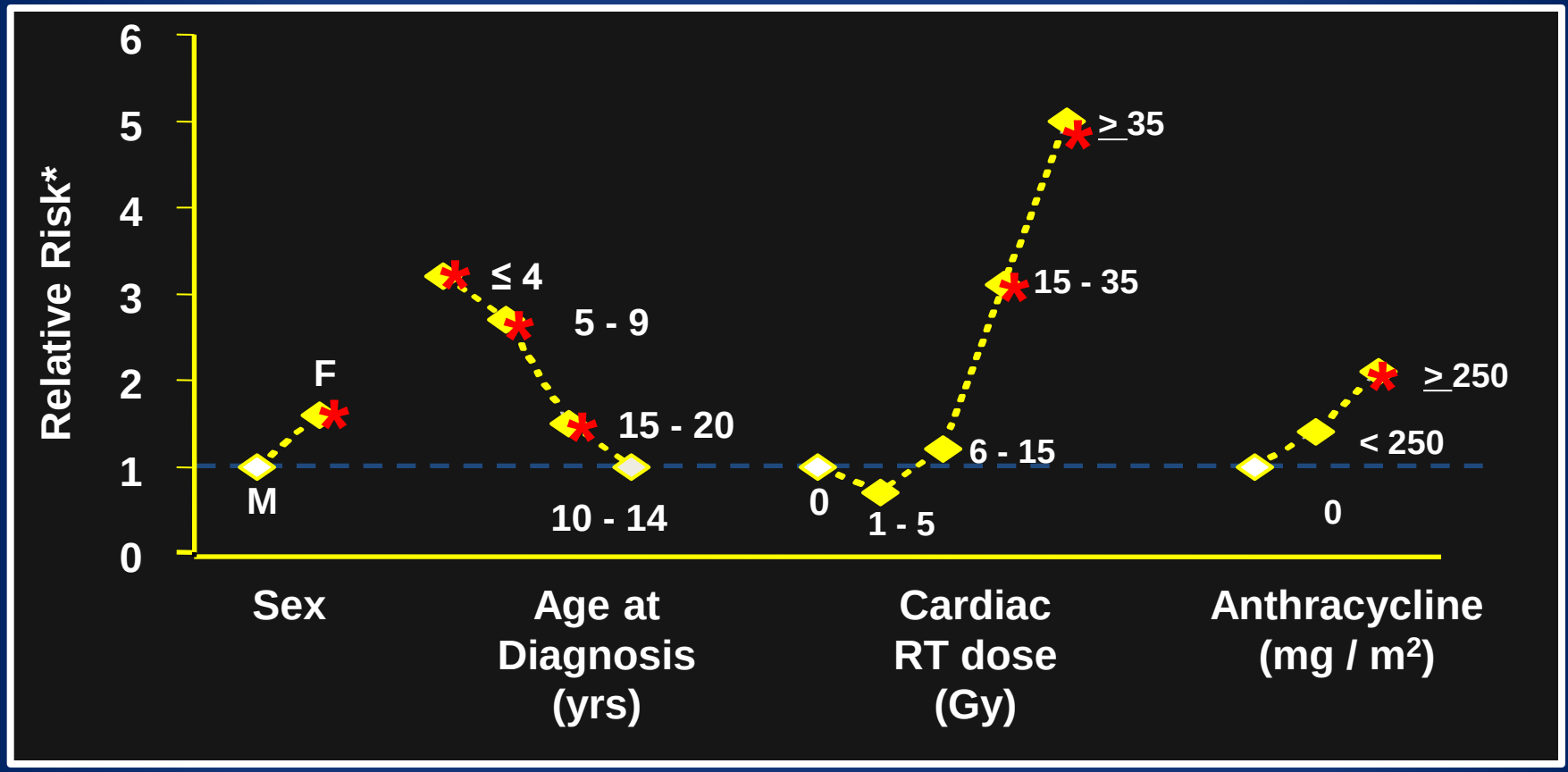


* P < 0.05 * Adjusted for race, BMI, income, education, smoking, treatment era

Mulrooney BMJ 2009

Risk of Valvular Disease Multivariate Analysis

CCSS
An NCI-funded Resource



*P <0.05 * Adjusted for race, BMI, income, education, smoking, treatment era

Mulrooney BMJ 2009

Is there curative treatment for children that is free of toxicity?

- Risk adapted non-toxic chemotherapy with low dose, small volume XRT to optimize the therapeutic ratio
- Cure without toxicity

1990
Stanford, Dana Farber, St Jude

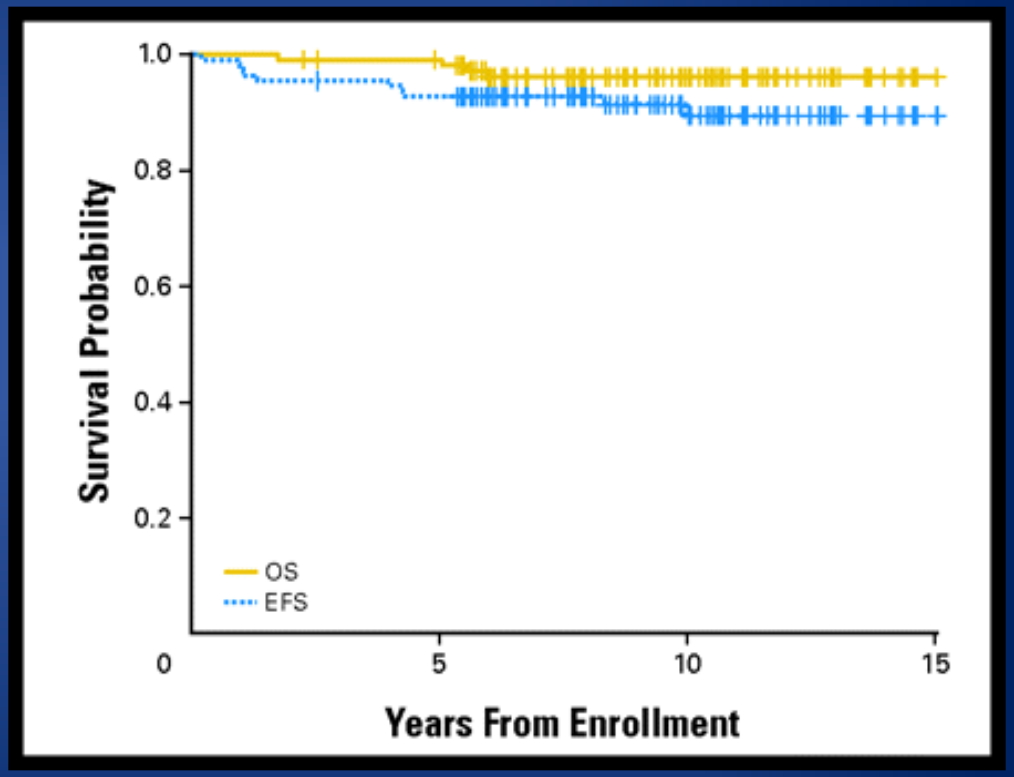
Risk adapted, response driven therapy

Early Stage, Favorable
Stanford, Dana Farber, St. Jude

- VAMP x 4 + 15-25.5 Gy IF RT
  - Velban, Adria, Mtx, Prednisone
  - for children < 18 yrs.
  - CS I-II A/B, non-bulky
  - RT after VAMP x 2
  - RT dose dependent on response
    - 15 Gy CR
    - 25.5 Gy PR

Early Stage, Favorable
Stanford, Dana Farber, St. Jude

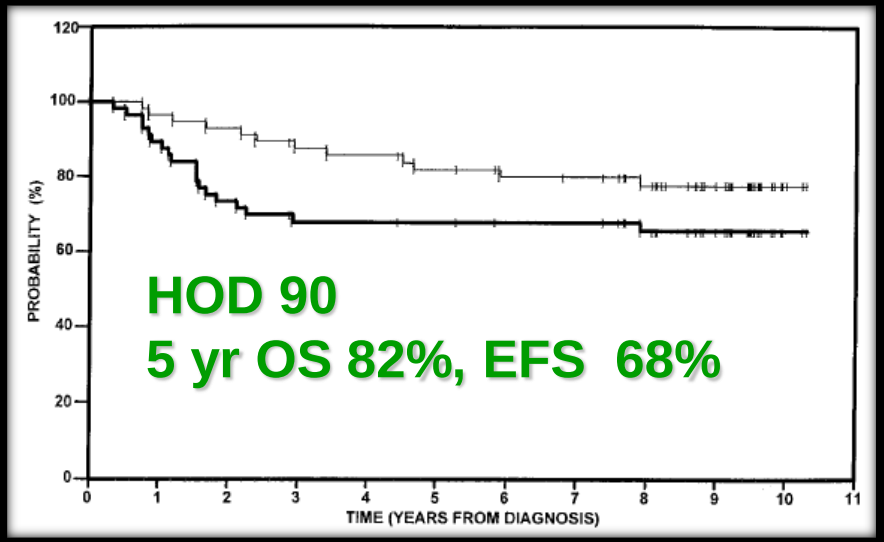
- Stage I-II A, non-bulky, < 3 sites involved
- VAMP x 4
  - Vinblastine, doxorubicin, methotrexate, prednisone
- 110 children
- Response based IFRT
  - Assessed after cycle 2
  - CR: 15 Gy (7%)
  - PR: 25.5 Gy (92%)
- Results
  - Median follow-up: 9.6 years
  - **10 year EFS 89%**
  - **10 year OS 96%**



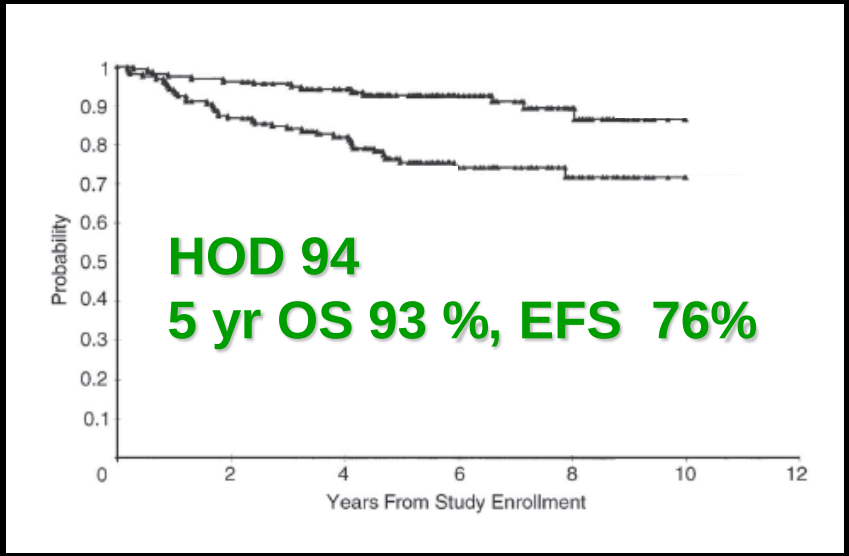
Donaldson et al. JCO, 2007

Advanced Stage Pediatric Hodgkin's Disease

HOD 90 – VEPA x 6 + LD IFRT



HOD 94 – VAMP/COP x 6 +LD IFRT



- but the outcome was disappointing
- we needed improved therapy

Current Pediatric Hodgkin Lymphoma Protocols

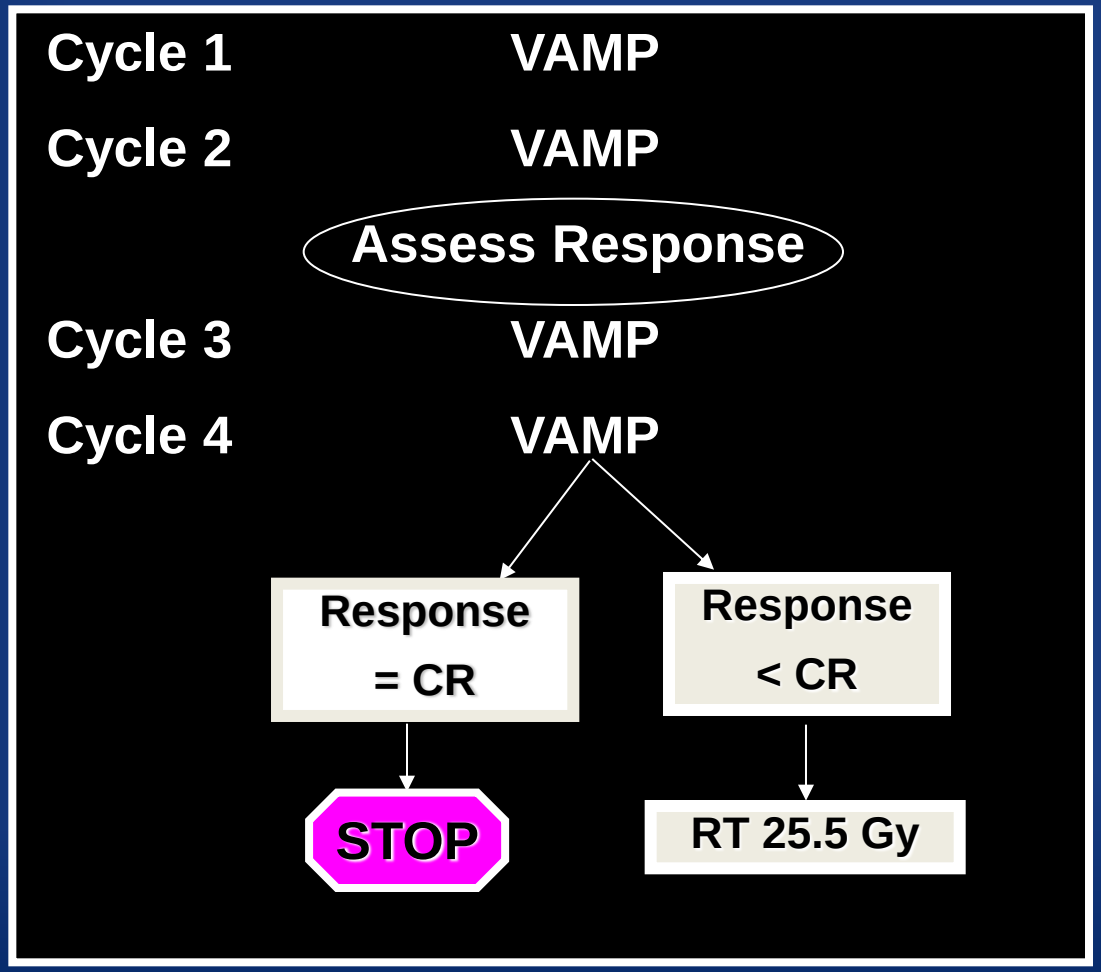
Low Risk

Intermediate Risk

High Risk

Pediatric Hodgkin's Lymphoma

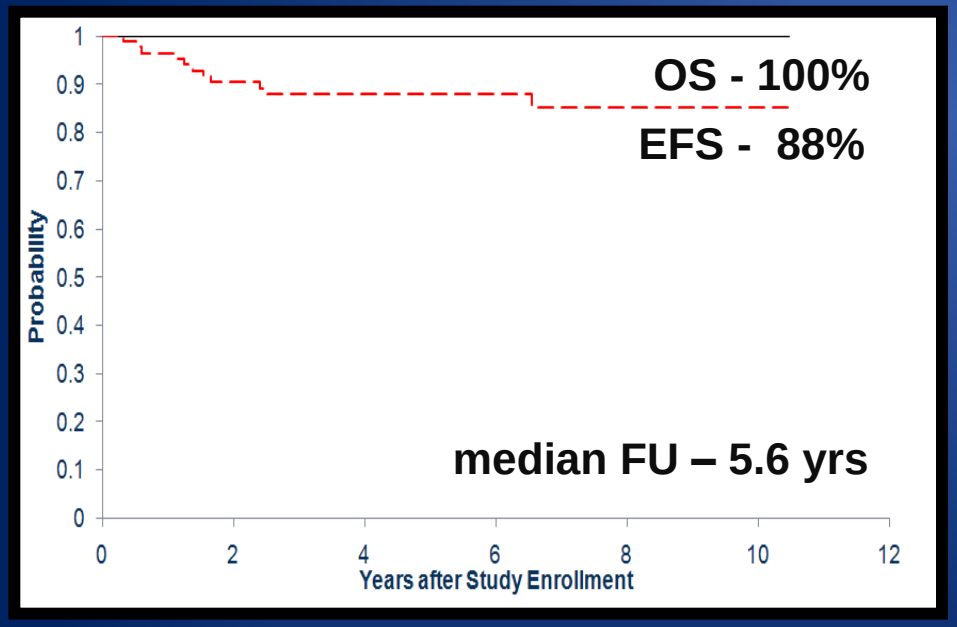
Low risk - IA / IIA, Non-Bulky, < 3 nodal regions



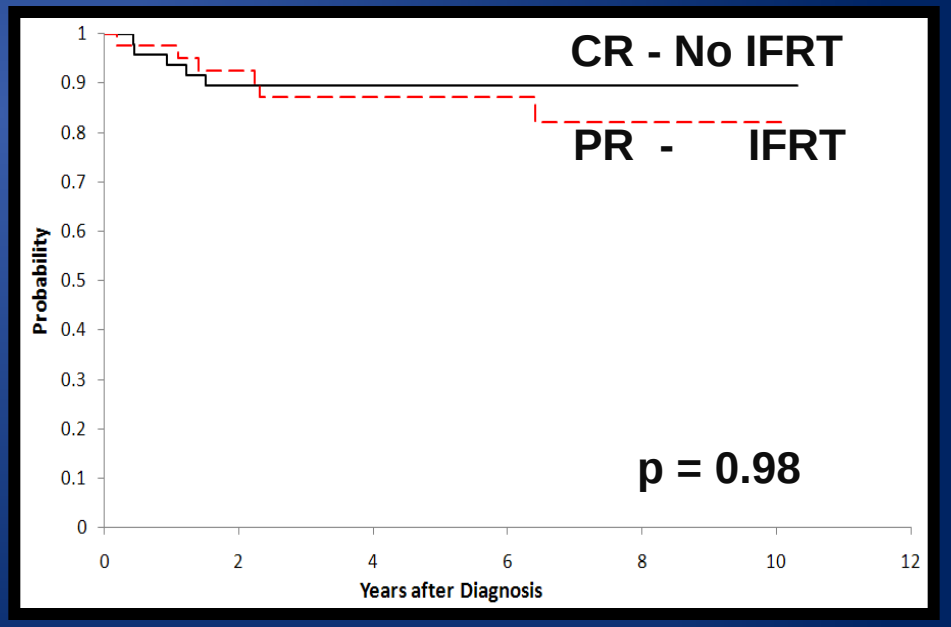
Pediatric Hodgkin's Lymphoma

Low risk - IA / IIA, Non-Bulky, < 3 nodal regions

5 yr OS & EFS



5 yr EFS



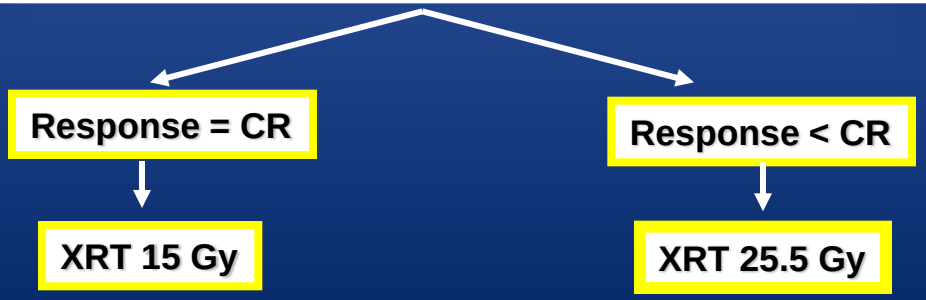
Metzger , M et al. JAMA, 307, 2012

Intermediate and Unfavorable Hodgkin's Disease: Stanford V + IF XRT

Vinblastine, Doxorubicin, Nitrogen Mustard,
Vincristine, Bleomycin, Prednisone
} 8 wks

Assess Response

Vinblastine, Doxorubicin, Nitrogen Mustard
Vinblastine, Bleomycin, Doxorubicin, Etoposide
} 4 wks



Intermediate / High Risk Pediatric HL

Protocol	Therapy	EFS (3 yrs)	OS (3 yrs)
HOD 99	Stanford V + LD IFRT	79%	98%
POG 8725	MOPP/ABVD x 8 + TNI MOPP/ABVD x 8	81% 83%	98% 87%
POG 9425	ABVE-PCx3 (+ABVE-PC x2) + RT	88% (2)	
CCG 5942	Ara-C/VP - 16 + COPP/ABV + CHOP + RT Ara-C/VP - 16 + COPP/ABV + CHOP	90% 81%	100% 94%
CCG-59704	BEACOPP x4 + ABVD x2 + IFRT BEACOPP x4 + COPP/ABV x 4	95 %	98%
GPOH - HD 2002	(boys) OEPA / COPDAC + IFRT (girls) OEPA / COPDAC + IFRT	91% 88%	98%

Lessons from the Children

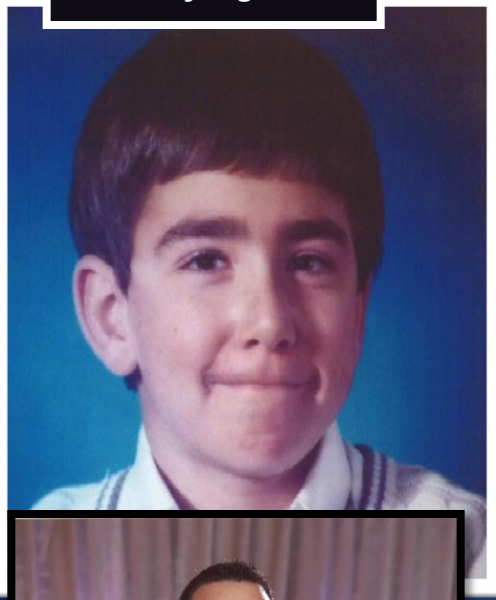
- Need large clinical trials to find answers – ie. multiple institutions or country-wide trials
- Need many years of FU to prove efficacy, especially when the goal is to maintain high cure rates and also to reduce toxicity

Pediatric Hodgkin Lymphoma
SEER 5 -Yr Relative Survival

Lessons

1) Be Innovative
2) Test your ideas in a clinical trial
3) Cure is NOT enough
4) The greatest rewards come from continuity of care

Teddy Age 10



Teddy Age 34

Rosemarie Age 5

Rosemarie age 35

Tammy Age 17

Tammy Age 50