After the cure: improving outcomes for young people with cancer

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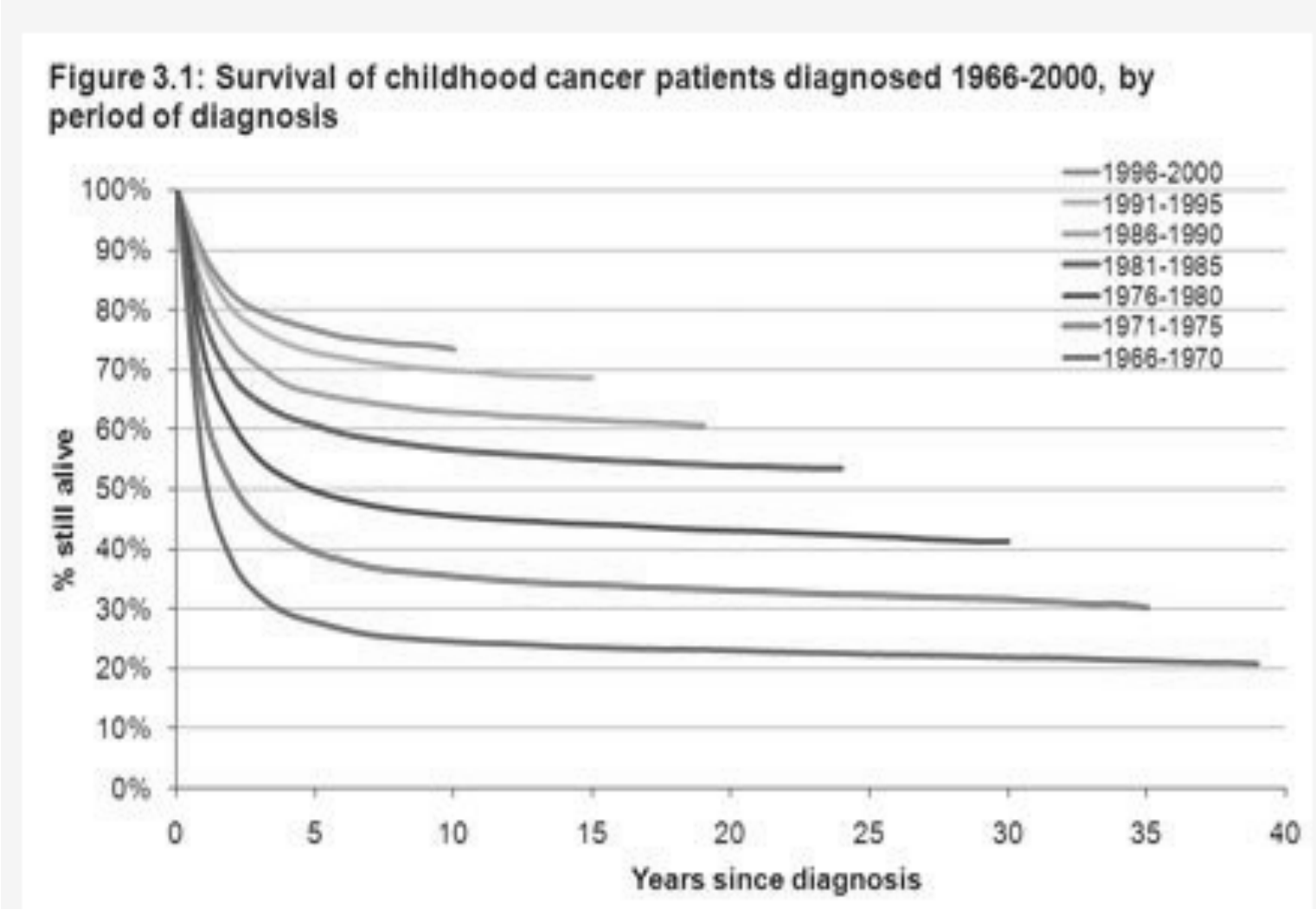
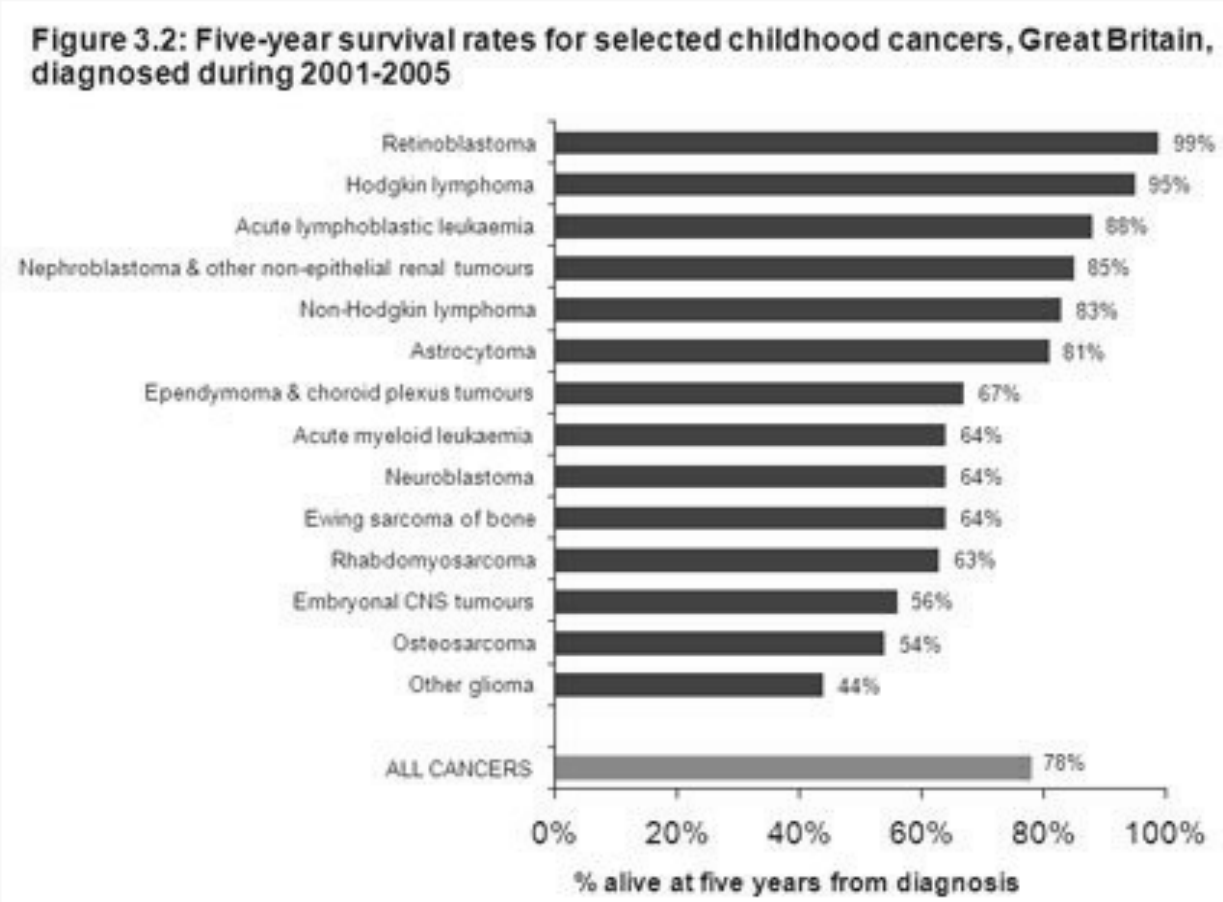
Overview

- Childhood Cancer Survival
- A young patient with Hodgkin's lymphoma
- European Clinical trial for Hodgkin's lymphoma
- Fertility preservation options for young females with cancer
- Hormone replacement therapy for young women with premature ovarian insufficiency

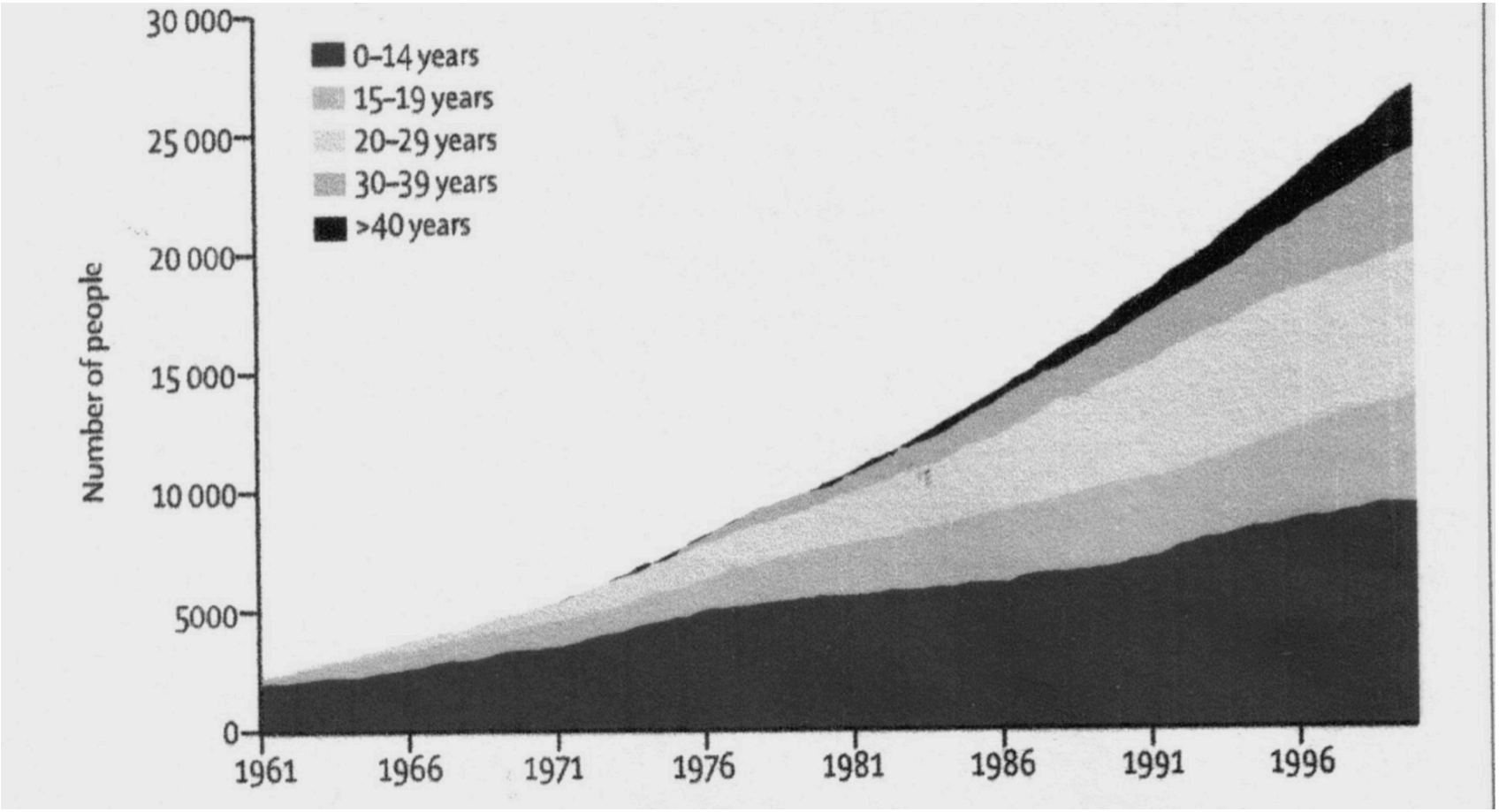
Improved Five Year Survival (1966-2000)



Five year survival – Childhood cancer



Increasing numbers of five year UK survivors by current age



Skinner, Wallace & Levitt , Lancet Oncology, 2006

Morbidity of Survivors

- By 30 years after childhood cancer:
  - 73% survivors with at least one chronic condition
  - 32% with multiple chronic conditions
- Survivors – 8.2 times more likely to have a severe or life-threatening health condition than siblings

Oeffinger et al. (2006) NEJM

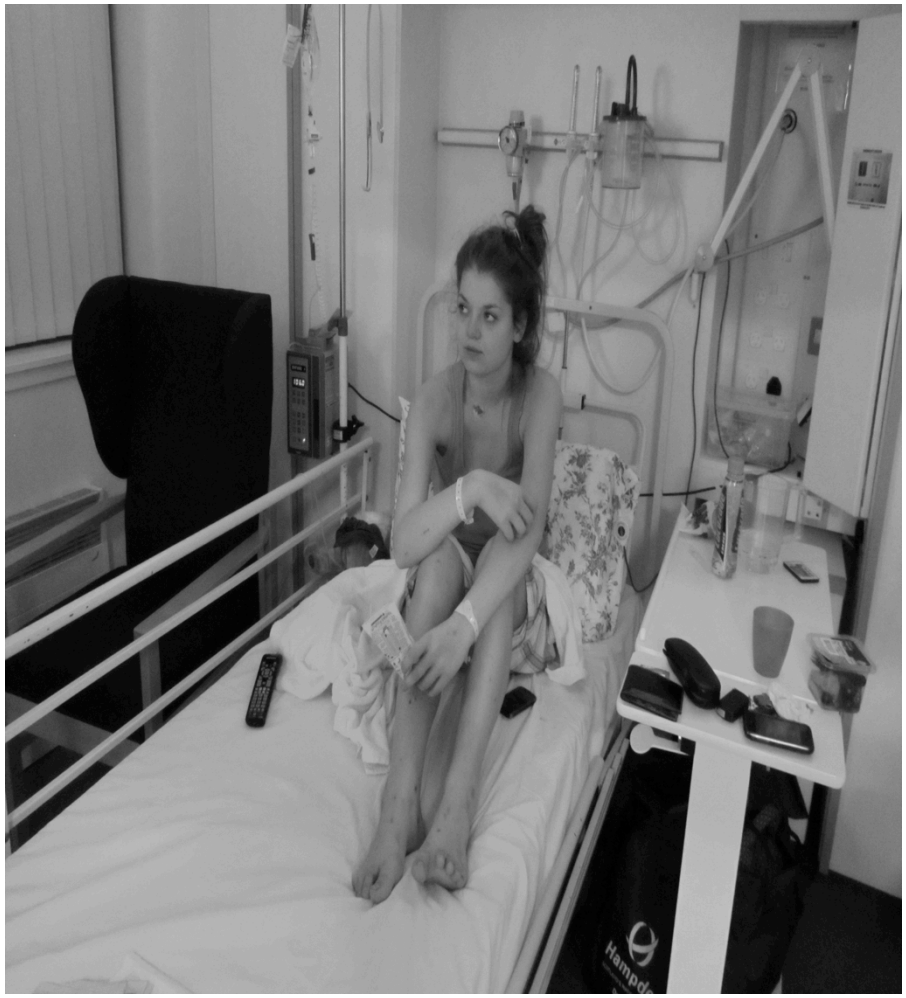
Cure - but at a cost

Sustain survival rates

Minimise late effects

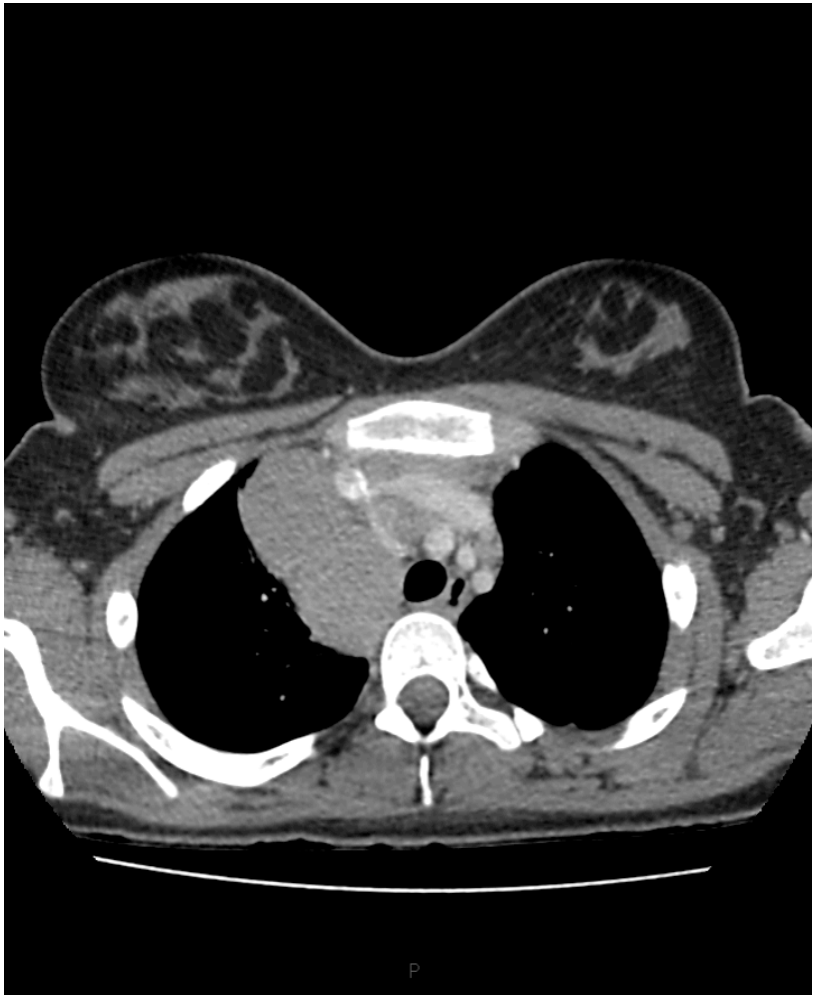
Treatment is in conflict with normal childhood growth and development

A Patient



March 2011 (age 15 years)

- Six month H/O of intense pruritis of her feet
- Three month H/O fever, night sweats, lethargy, pallor, poor appetite and weight loss
- Widespread LN – lower cervical, mediastinum, abdomen



Diagnosis and Staging

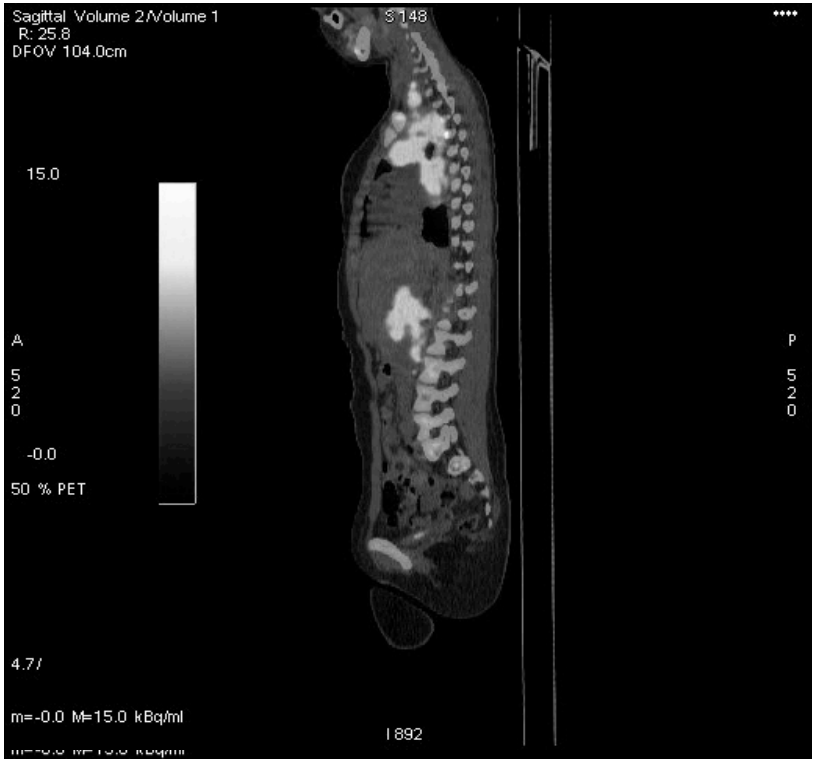
- Mediastinal lymph node biopsy
  - Hodgkin's lymphoma
- Insertion of double lumen portacath

Laparoscopic ovarian biopsy and cryopreservation of ovarian cortical strips

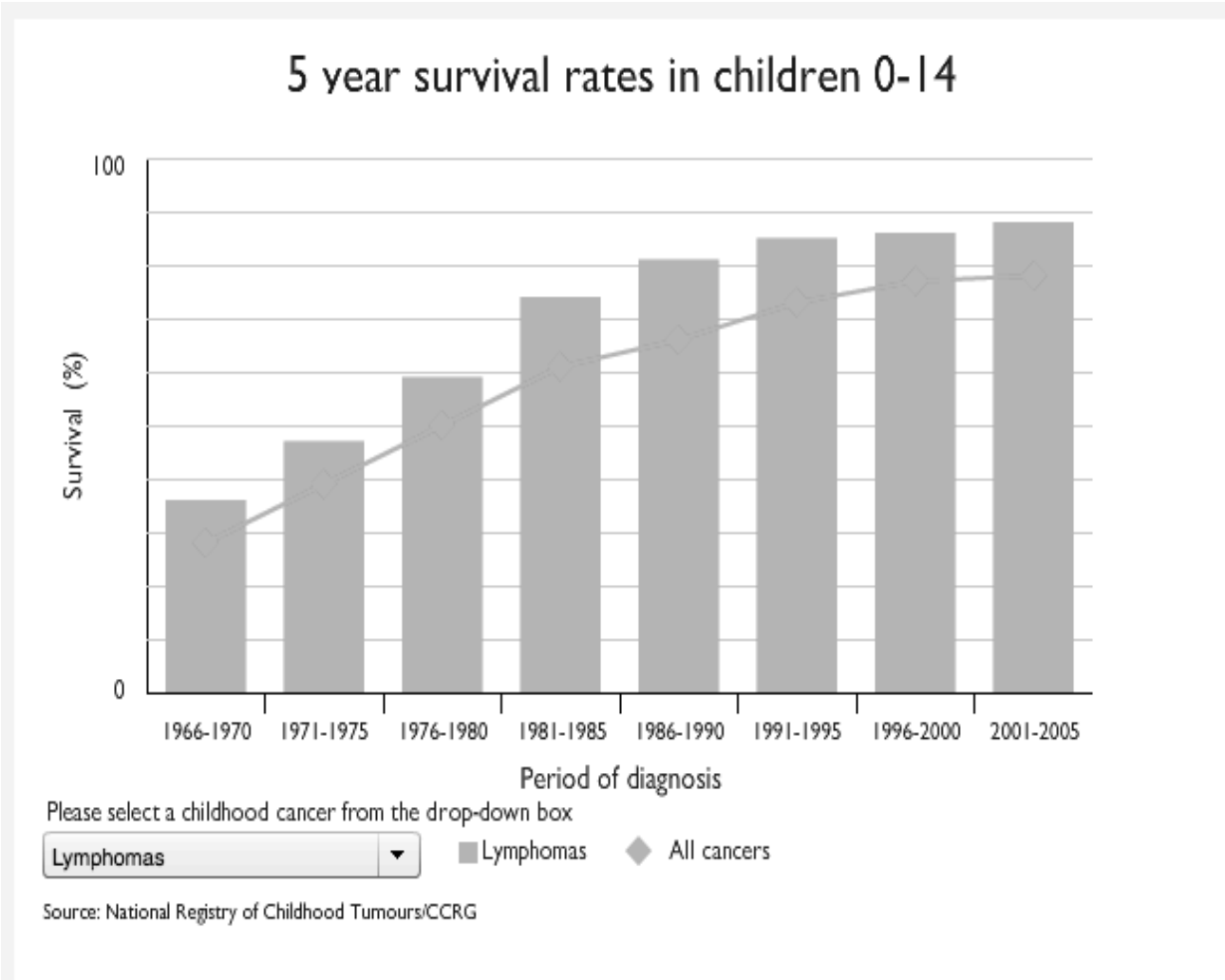
FDG-PET Scan

^{18}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

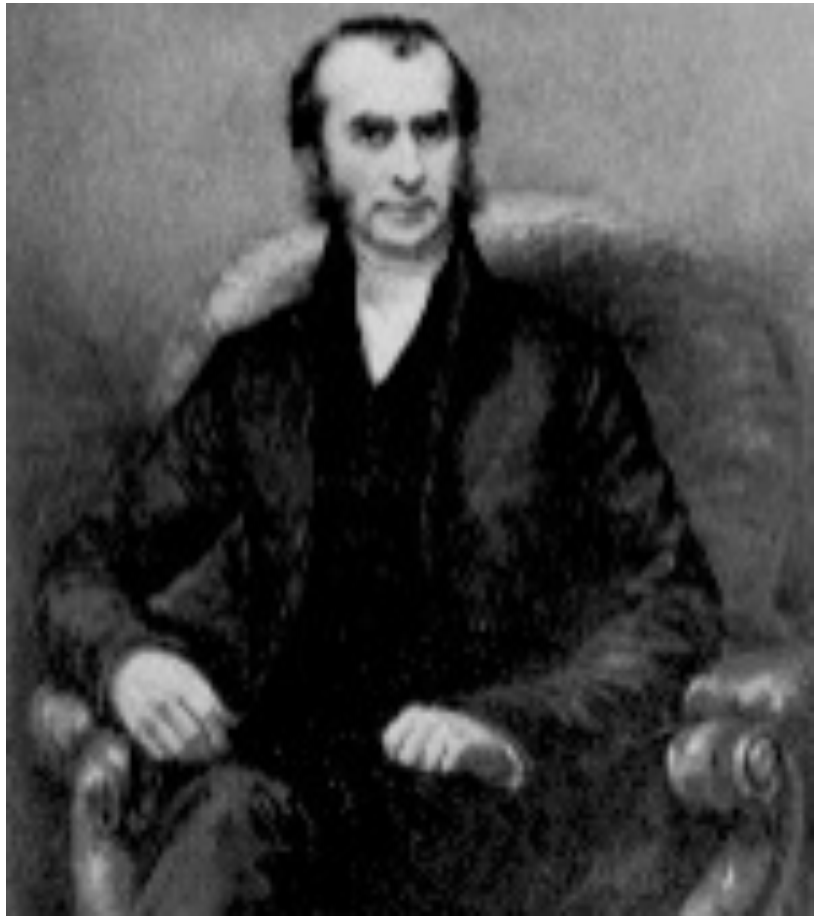


Stage IVB Hodgkin lymphoma



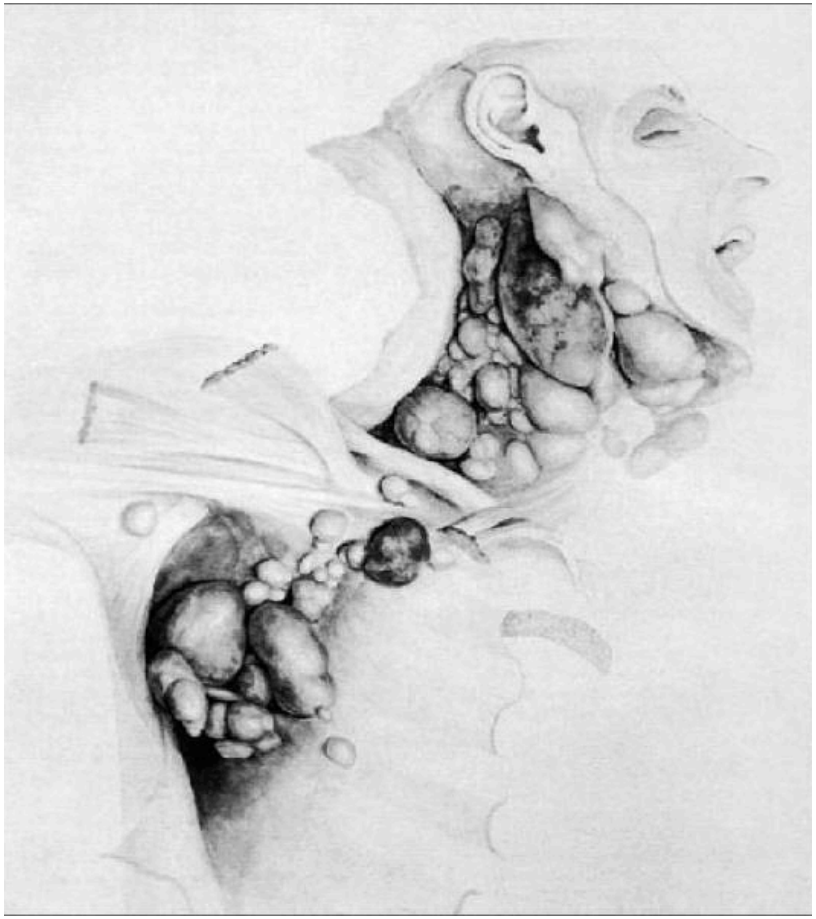
Thomas Hodgkin (1798-1866)

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



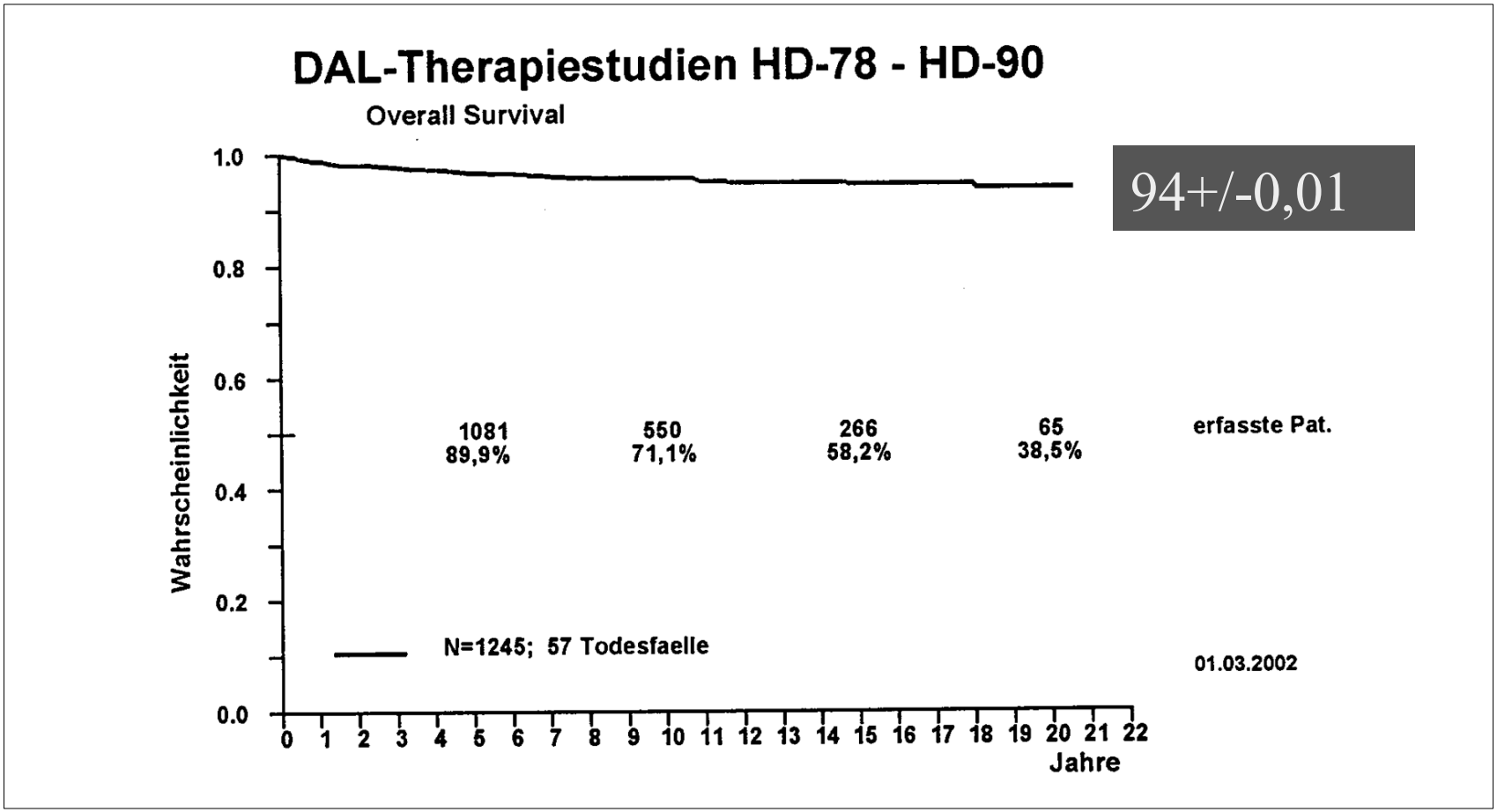
Thomas Hodgkin (1798-1866)

- 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 !



Longterm survival after Hodgkin lymphoma

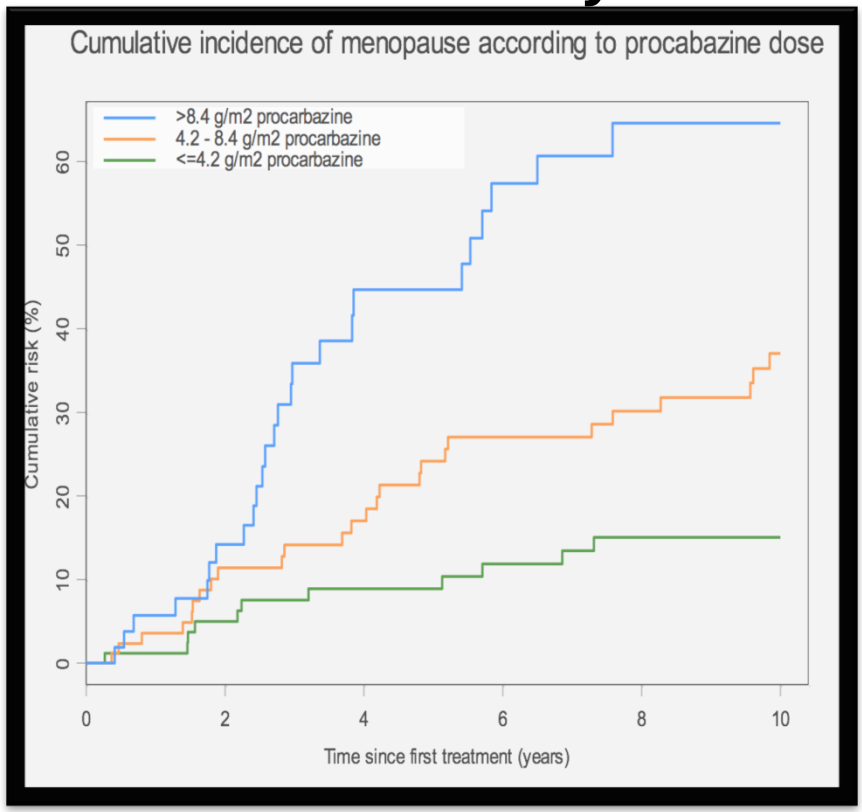
Results of the DAL78 - 90 studies



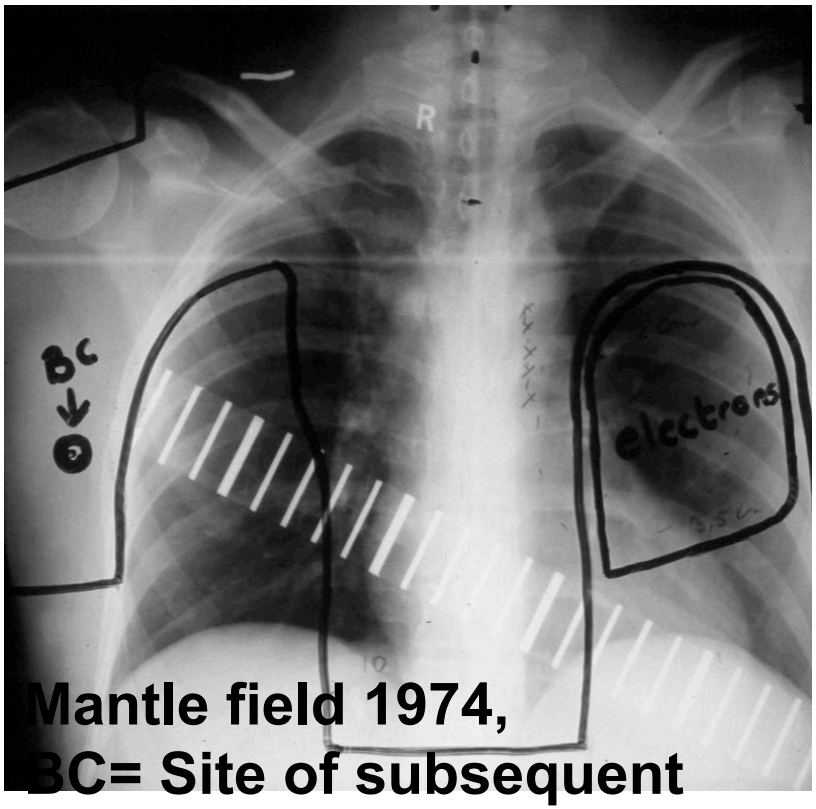
Prof. Schellong (late effects report)

Late effects (Hodgkin lymphoma)

Premature ovarian insufficiency



Secondary solid (breast) cancer



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

A new Europe wide study and collaboration

Aims of EuroNet Hodgkin group

- Reduction of secondary cancer
  Avoiding radiotherapy in selected cases
- Reduction of infertility and premature ovarian insufficiency
  Replacement of procarbazine by dacarbazine

EURONET-PHL-C1

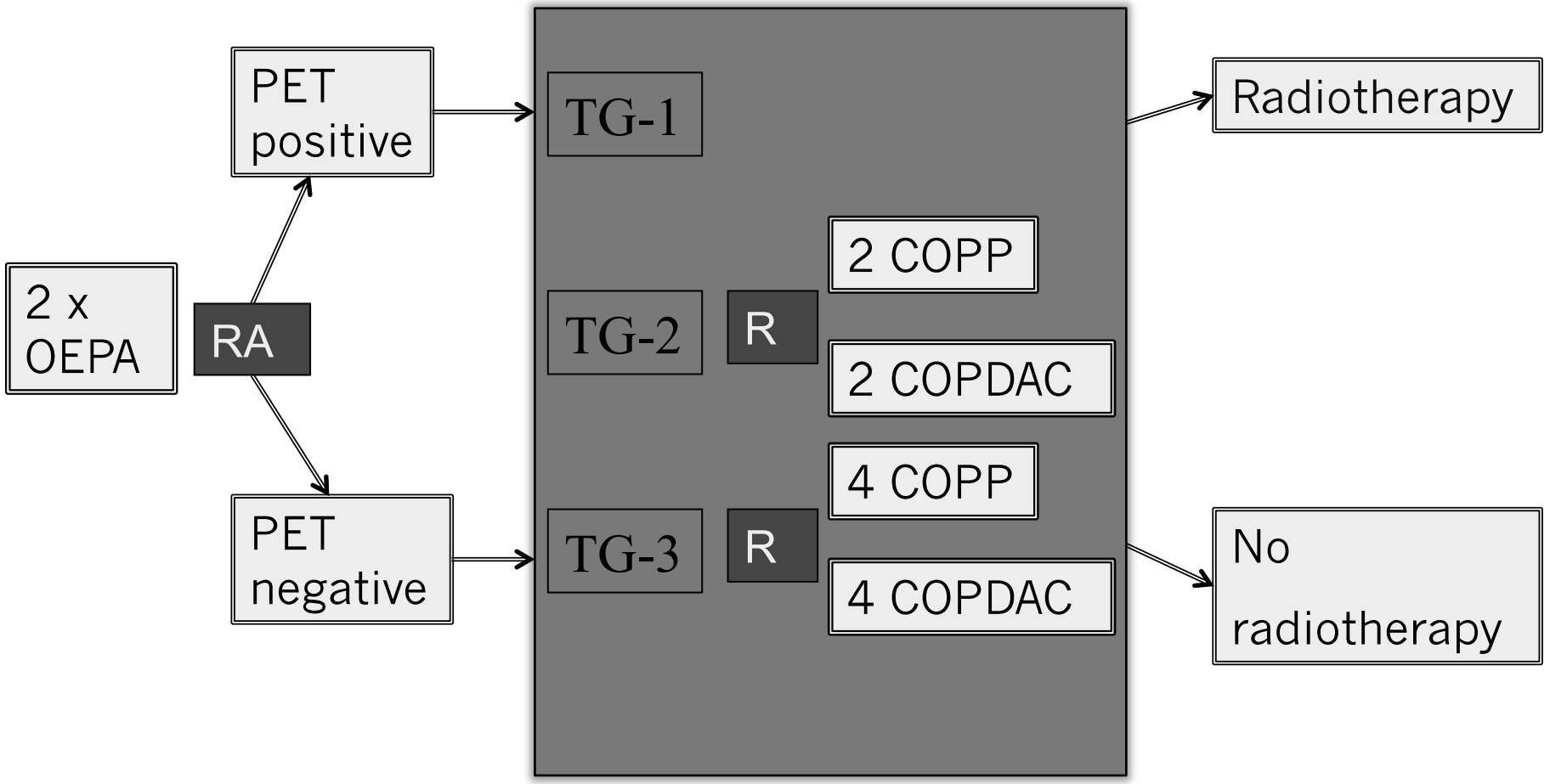
Aims

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?

Maintaining event free survival for all > 90%

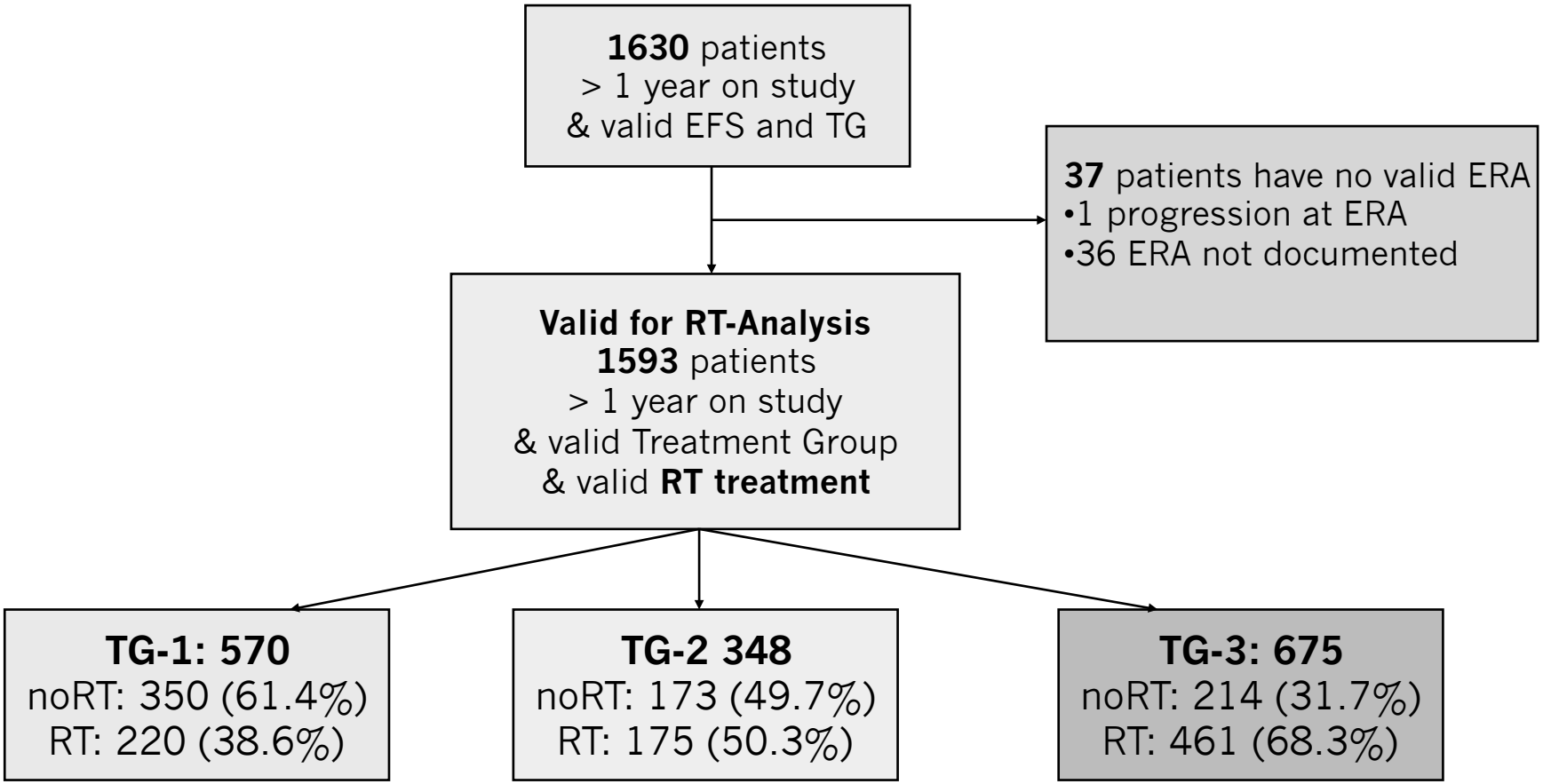
EuroNet-PHL-C-1



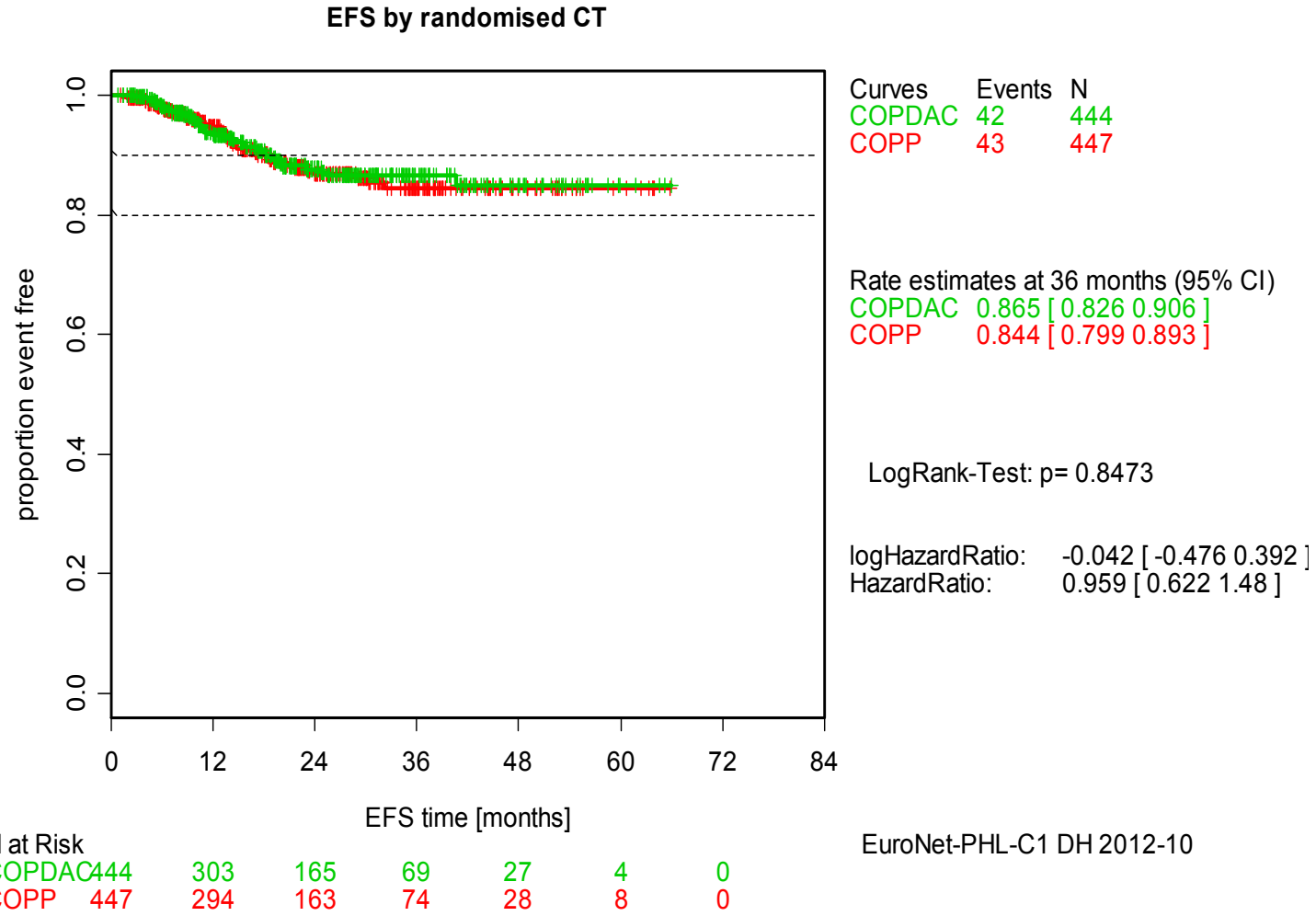
Wallace WH Chief Investigator

CRUK support 400K

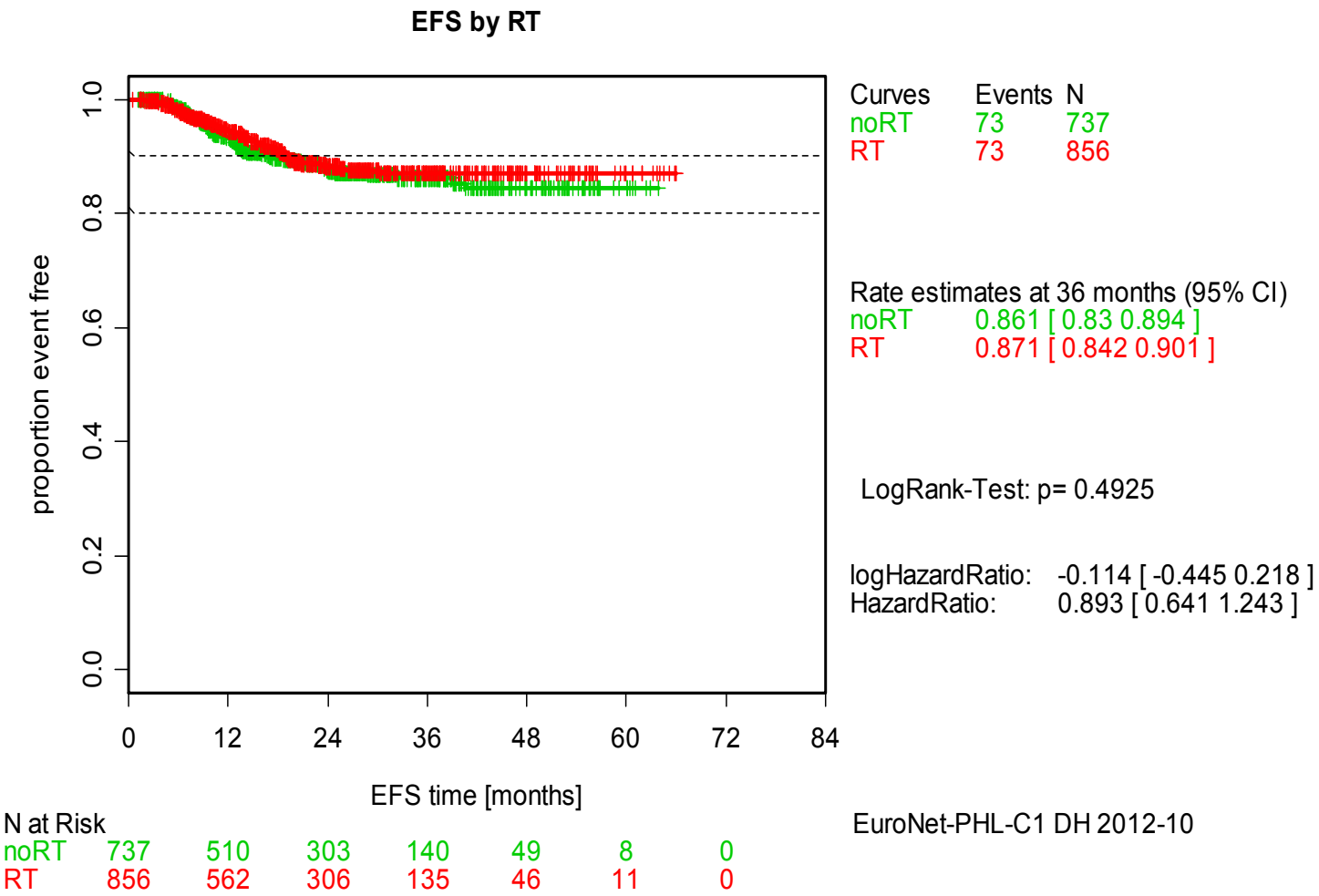
EuroNet-PHL-C1 (Interim analysis October 2012)



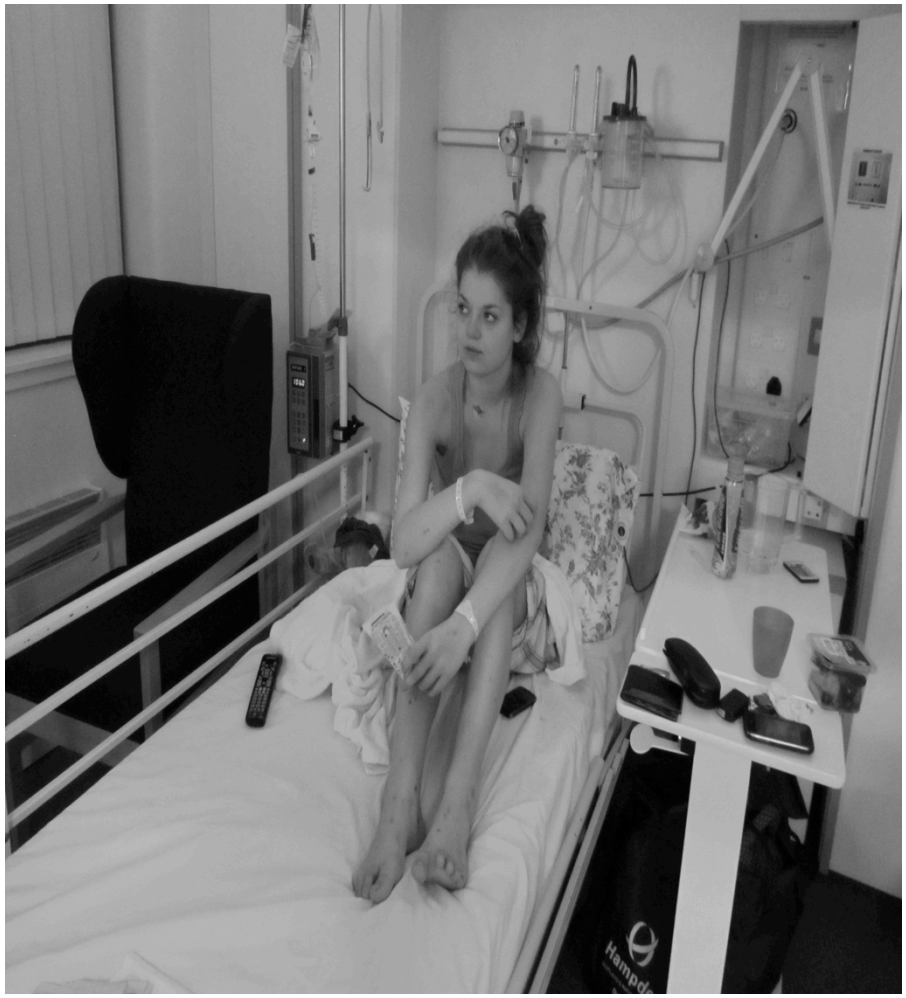
EuroNet-PHL-C1
Chemotherapy question



EuroNet-PHL-C1
Radiotherapy question

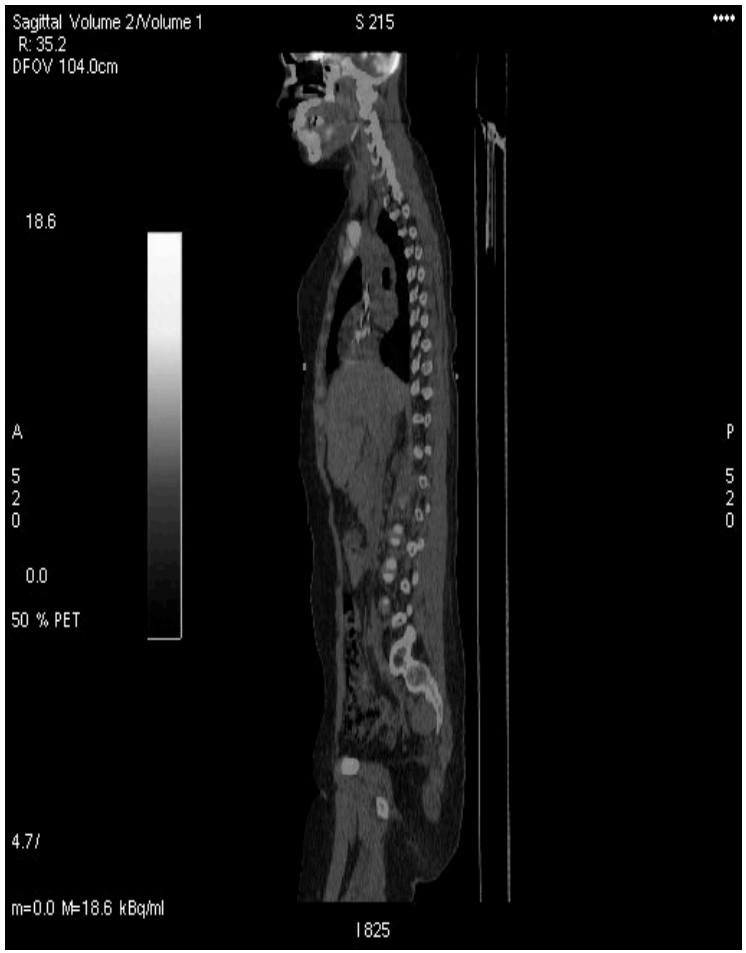


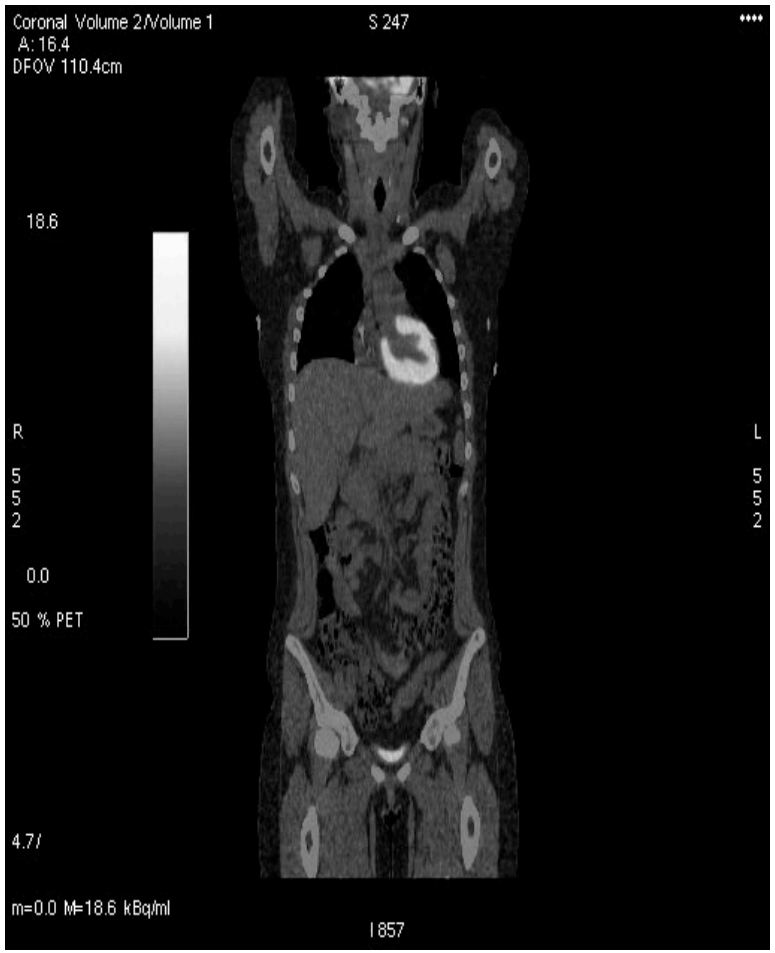
Laura



- EuroNet-PHL-C1 Protocol:
- Treatment Group 3 (TG3)
- Two cycles of OEPA
- Four cycles of COPDAC

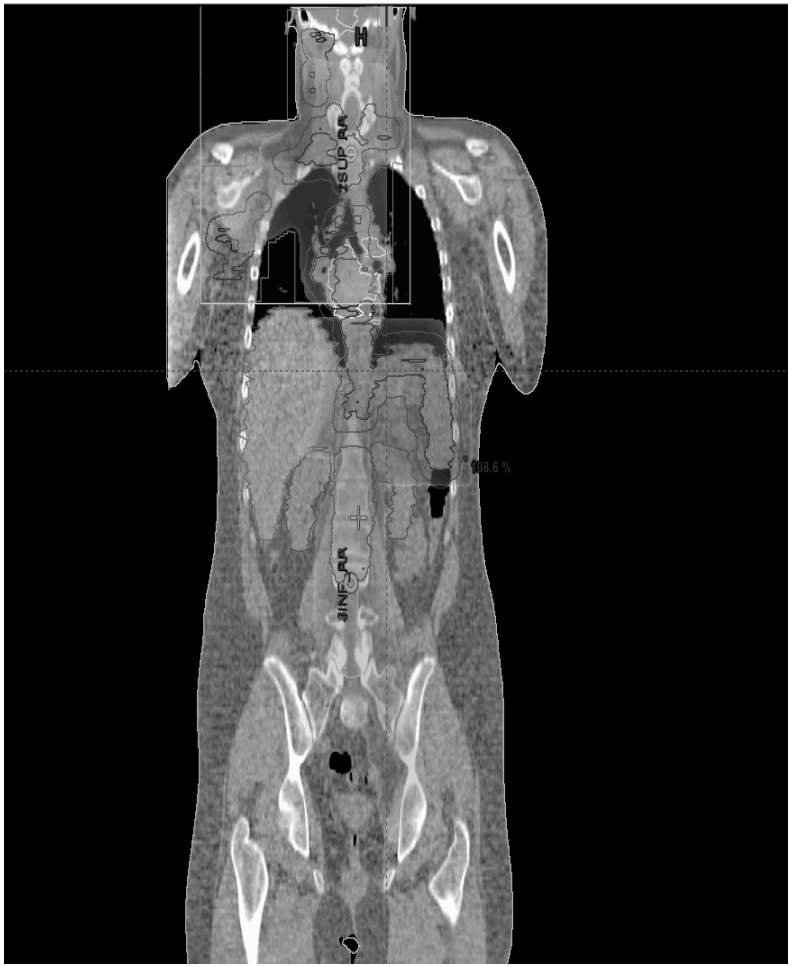
Early Response Assessment PET scan





Radiotherapy Field and estimated doses to organs at risk

Organs at risk		
	Maximium dose received	Mean Dose
- spinal cord	2139.7 cGy	1916.2 cGy
- heart	2116.1 cGy	1701.4 cGy
- left kidney	2169.1 cGy	1439.8 cGy
- right kidney	2022.2 cGy	639.3 cGy
- lung	2148.5 cGy	1168.9 cGy
- right breast	2195.1 cGy	476.7 cGy
- left breast	2156.4 cGy	654.6 cGy
- liver	2153.4 cGy	830.2 cGy
- thyroid	2047.2 cGy	1999.0 cGy



Fertility Preservation?

Risk assessment for fertility preservation

- Intrinsic factors
  - Heath status of patient
  - Consent (Patient/Parent)
  - Assessment of ovarian reserve
- Extrinsic factors
  - Nature of predicted treatment
    - High/Medium/Low/Uncertain Risk
  - Time available
  - Expertise available

Wallace WH, Critchley HOD & Anderson RA. JCO, 2012

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Wallace WH, Critchley HOD & Anderson RA. JCO, 2012

Infertility - Risk Factors

- RT to HPA or a field that includes testes/ ovaries
- Busulphan
- BCNU
- CCNU
- Cyclophosphamide
- Ifosfamide
- Melphalan
- Mustine
- Nitrogen mustard
- Procarbazine
- Thiotepa
- Chlorambucil
- Cytarabine

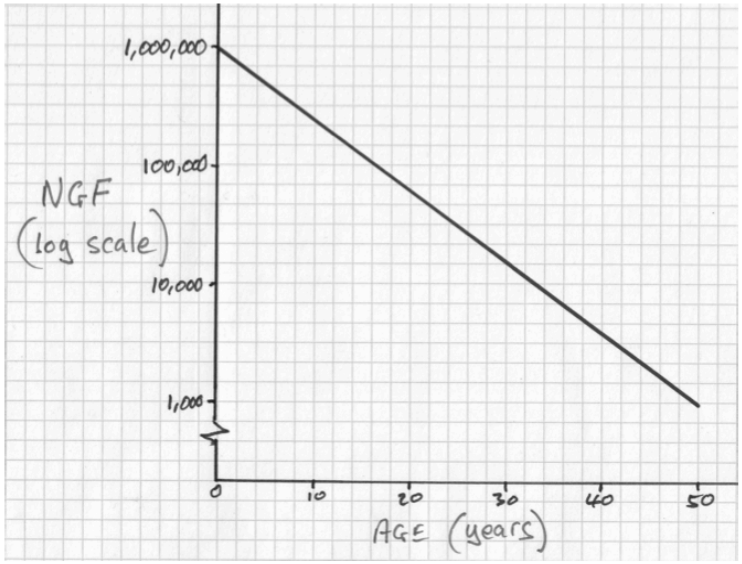
The pre-pubertal gonad is not protected

Risk of infertility

Low risk (<20%)	**Medium risk**	**High risk (>80%)**
ALL Wilms' tumour Brain tumour Sx, RT < 24Gy Soft tissue sarcoma (stage1) **Hodgkin's Lymphoma** **HL(Low stage)**	AML Osteosarcoma Ewing's sarcoma STS: stage II/III Neuroblastoma NHL Brain tumour RT>24Gy **HL (High Stage)**	Total Body Irradiation Pelvic/testes RT Chemo pre BMT Metastatic Ewing's **HL (Pelvic RT)**

Wallace, Anderson, Irvine. Lancet Oncology 2005

Radiation-induced Ovarian Damage



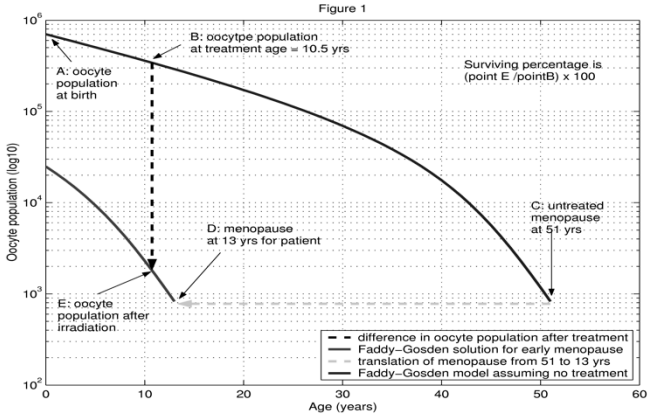
- LD_{50} < 4 Gy
- Wallace et al (1989) Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. BJR

Serendipity

Radiation-induced ovarian damage

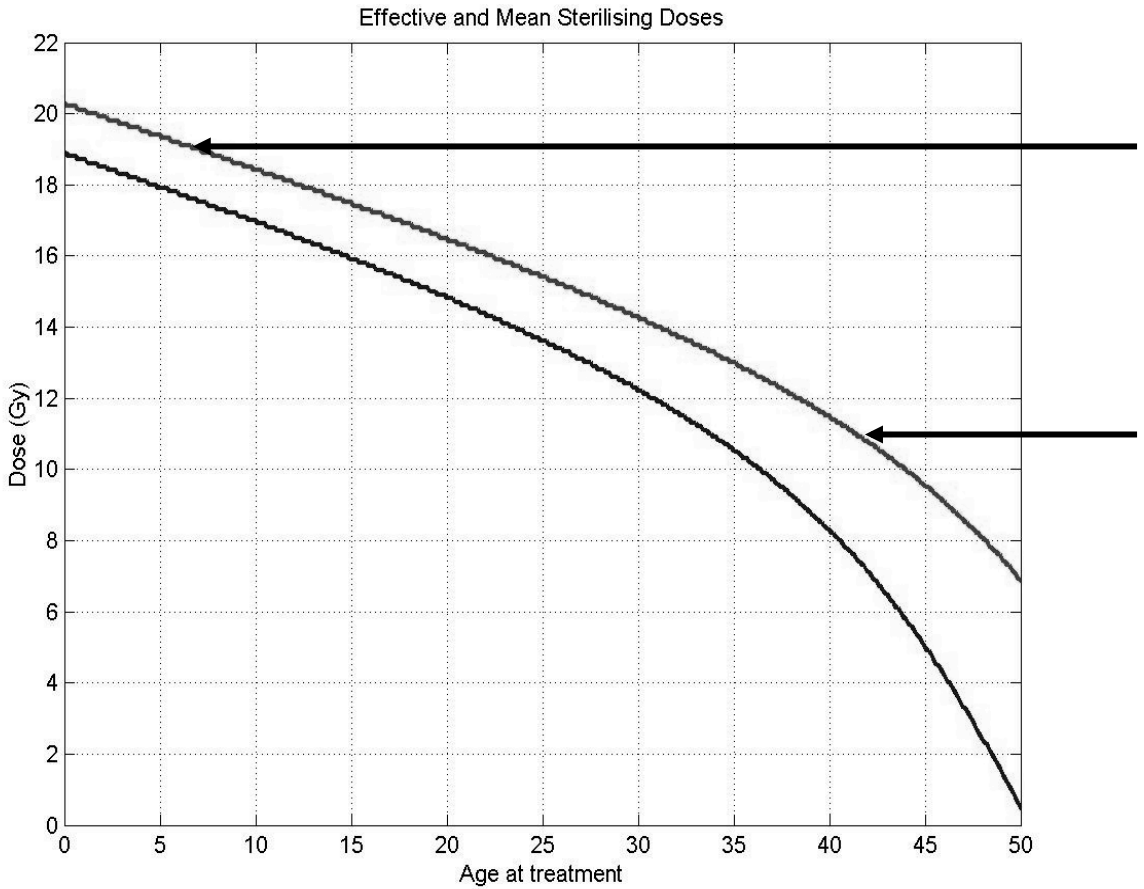
Human oocyte
(Primordial follicle)

- $LD_{50} < 2$ Gy



Wallace, Thomson, Kelsey. (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)

Ovarian Reserve?

Risk assessment for Fertility preservation

- Intrinsic factors
  - Heath status of patient
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  - Assessment of ovarian reserve
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  - Nature of predicted treatment
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  - Time available
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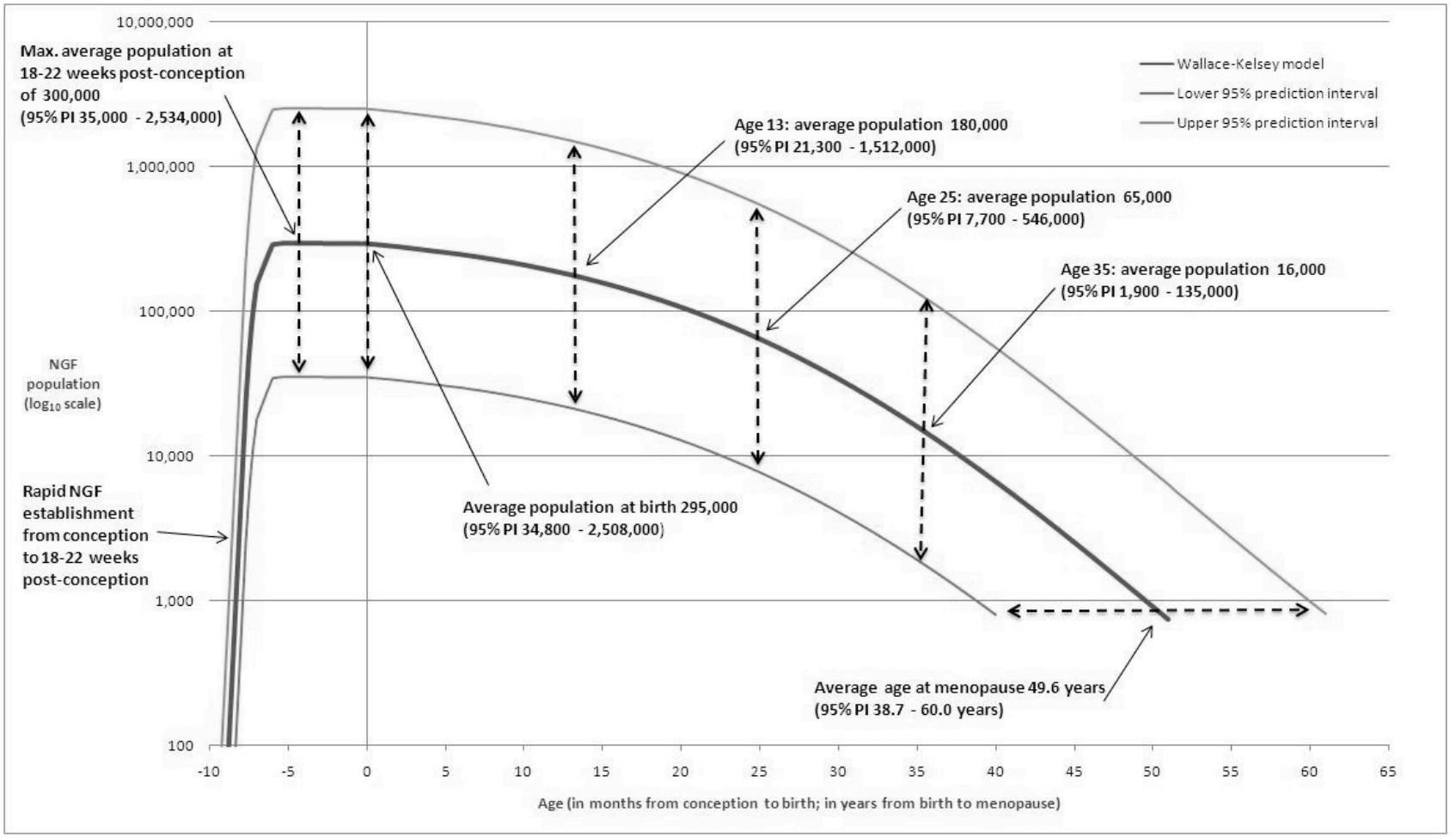
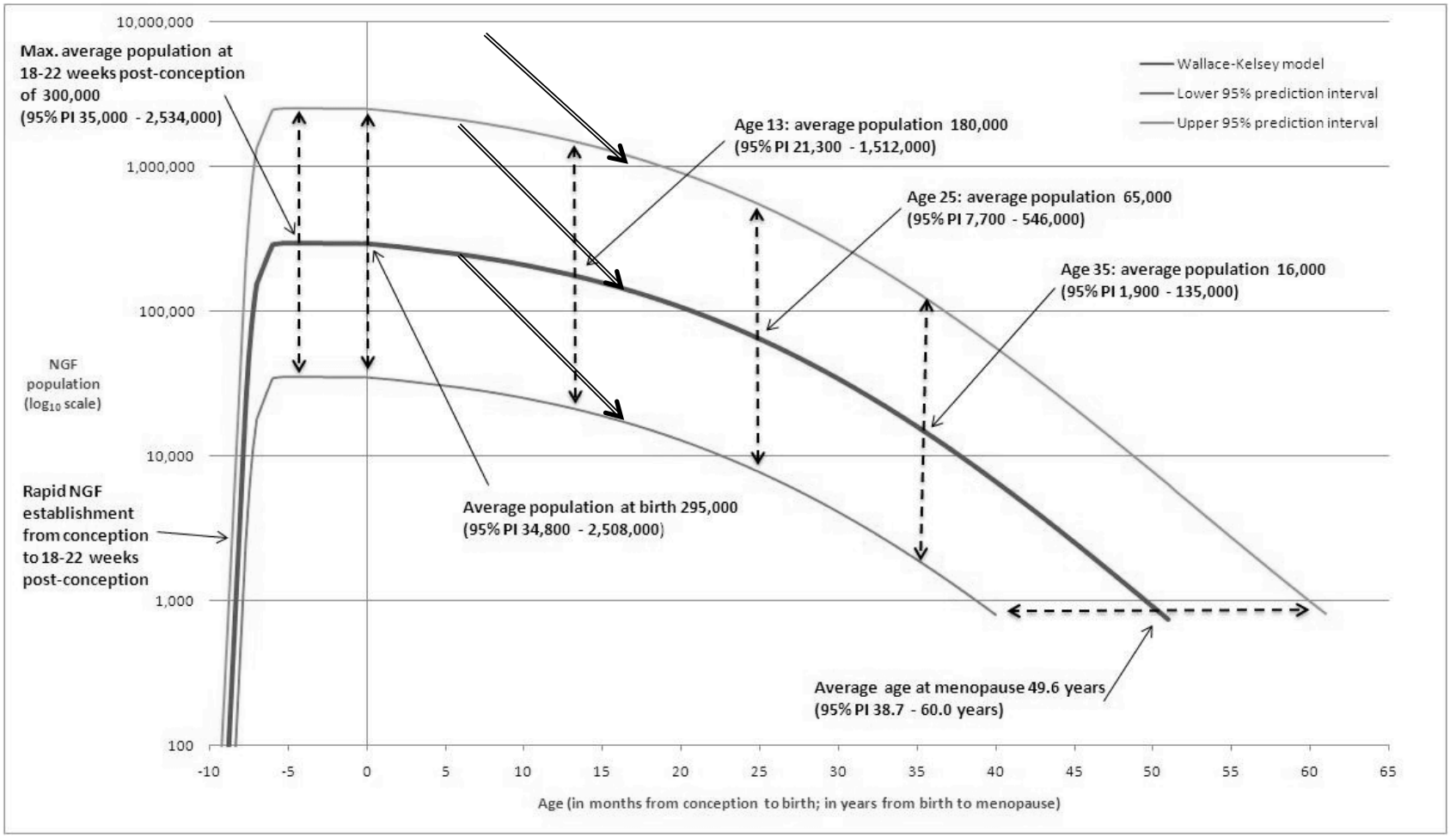
Wallace WH, Critchley HOD & Anderson RA. JCO, 2012

Conception to Menopause
NGF population



Wallace & Kelsey (2010) PloS ONE

Ovarian reserve:
A Validated model from Conception to Menopause
(NGF population)



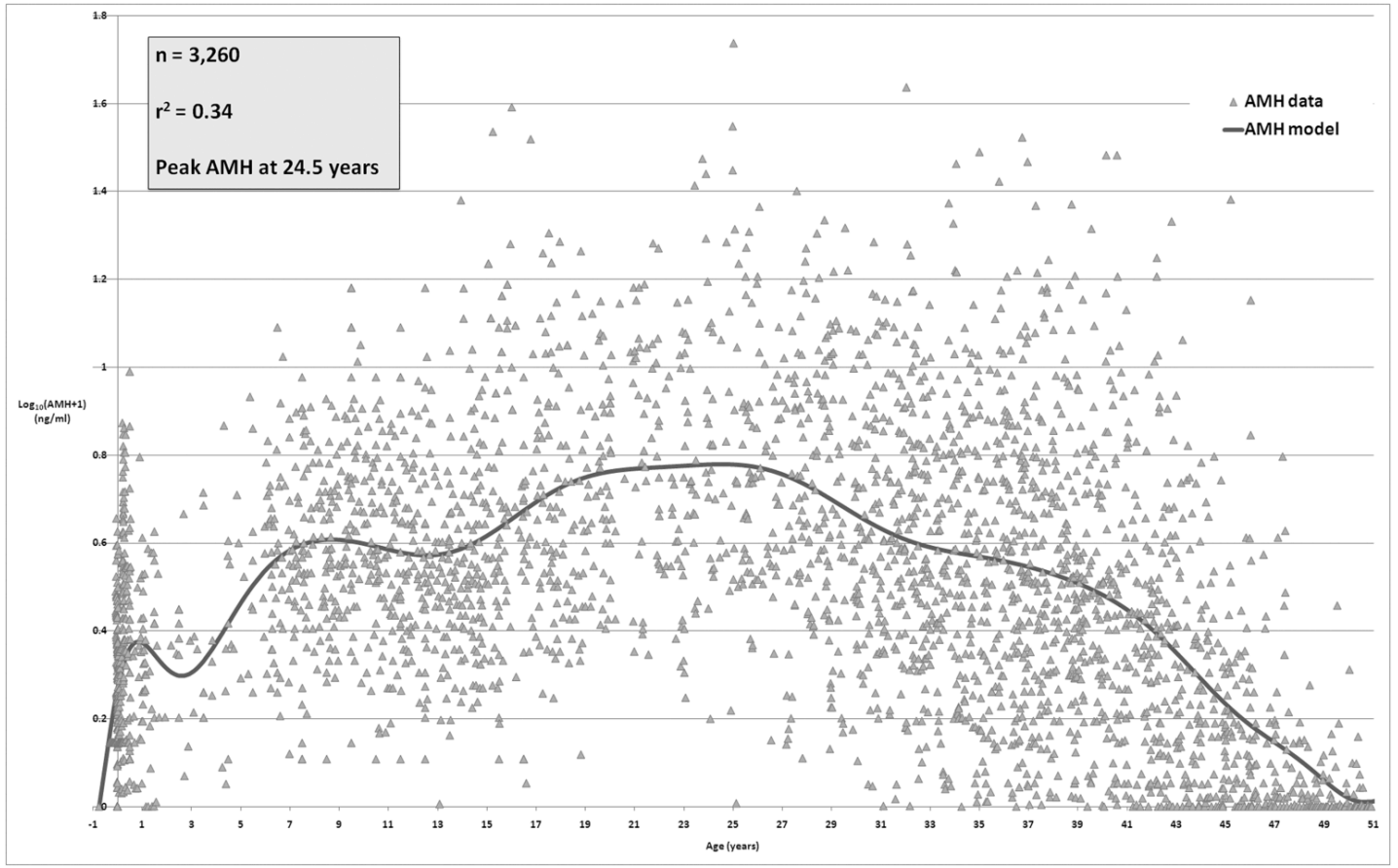
Wallace &Kelsey (2010) PloS ONE

Prediction of Ovarian Reserve (AMH)

- Anti Mullerian Hormone (AMH) is an important product of the adult ovary, produced by the granulosa cells of small growing follicles
- AMH has little variation across and between menstrual cycles
- AMH is the best currently available marker of the number of small-growing follicles in the ovary
- But there was no validated reference model for AMH available

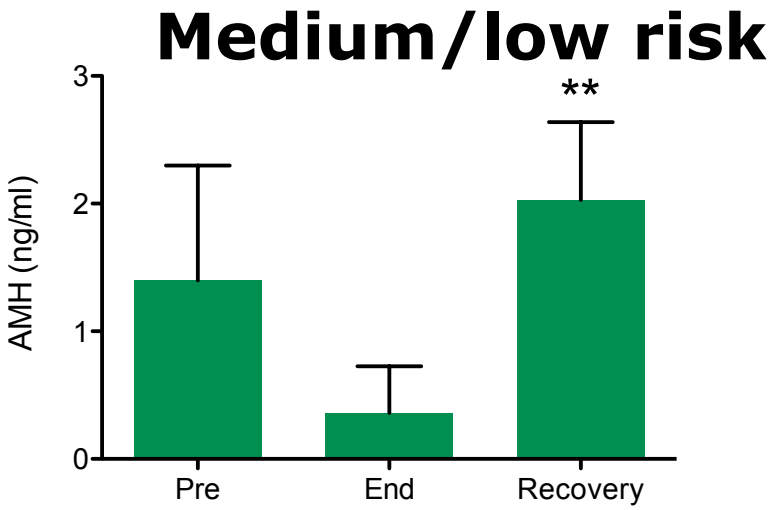
Anderson, Nelson, Wallace (2011) Maturitas

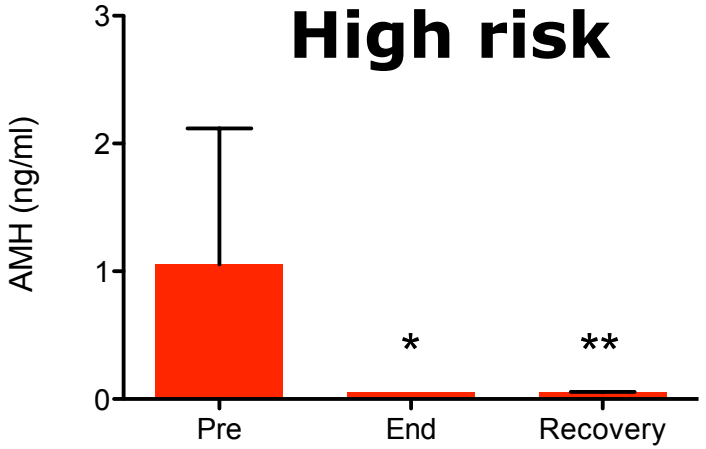
A validated model of serum anti-Mullerian hormone from conception to menopause



Kelsey et al. PLoS ONE 2011

AMH in childhood cancer





22 girls age 0.3-15yr
17 prepubertal

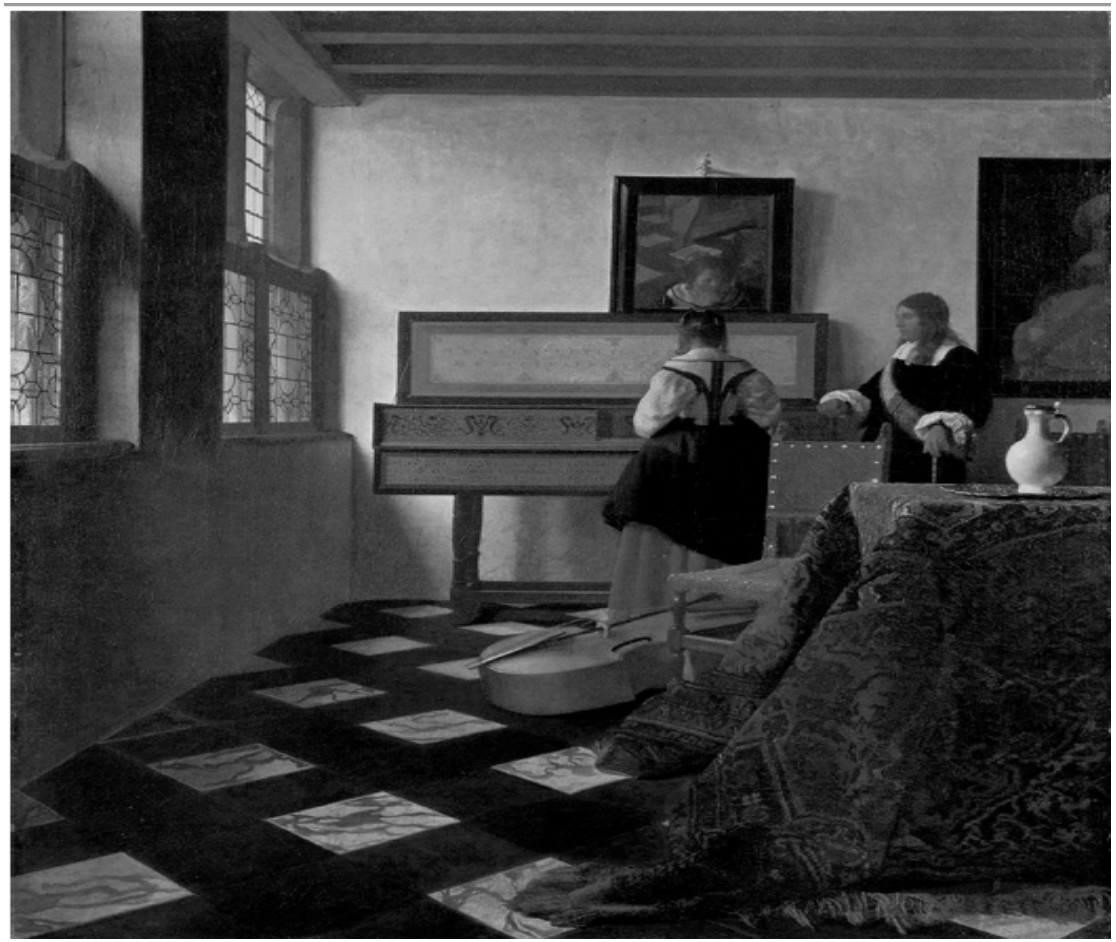
Brougham et al 2012 JCE&M

Summary

- AMH is detectable before puberty
- AMH falls rapidly during cancer treatment in both pre-pubertal and pubertal girls
- AMH levels recover in those patients at low/ medium risk of gonadotoxicity
- AMH fails to recover in those at high risk. This could be indicative of future reproductive impairment

Brougham et al 2012 JCE&M

Sex steroid replacement therapy for young women with POI?



Physiological versus standard sex steroid replacement in young women with POI

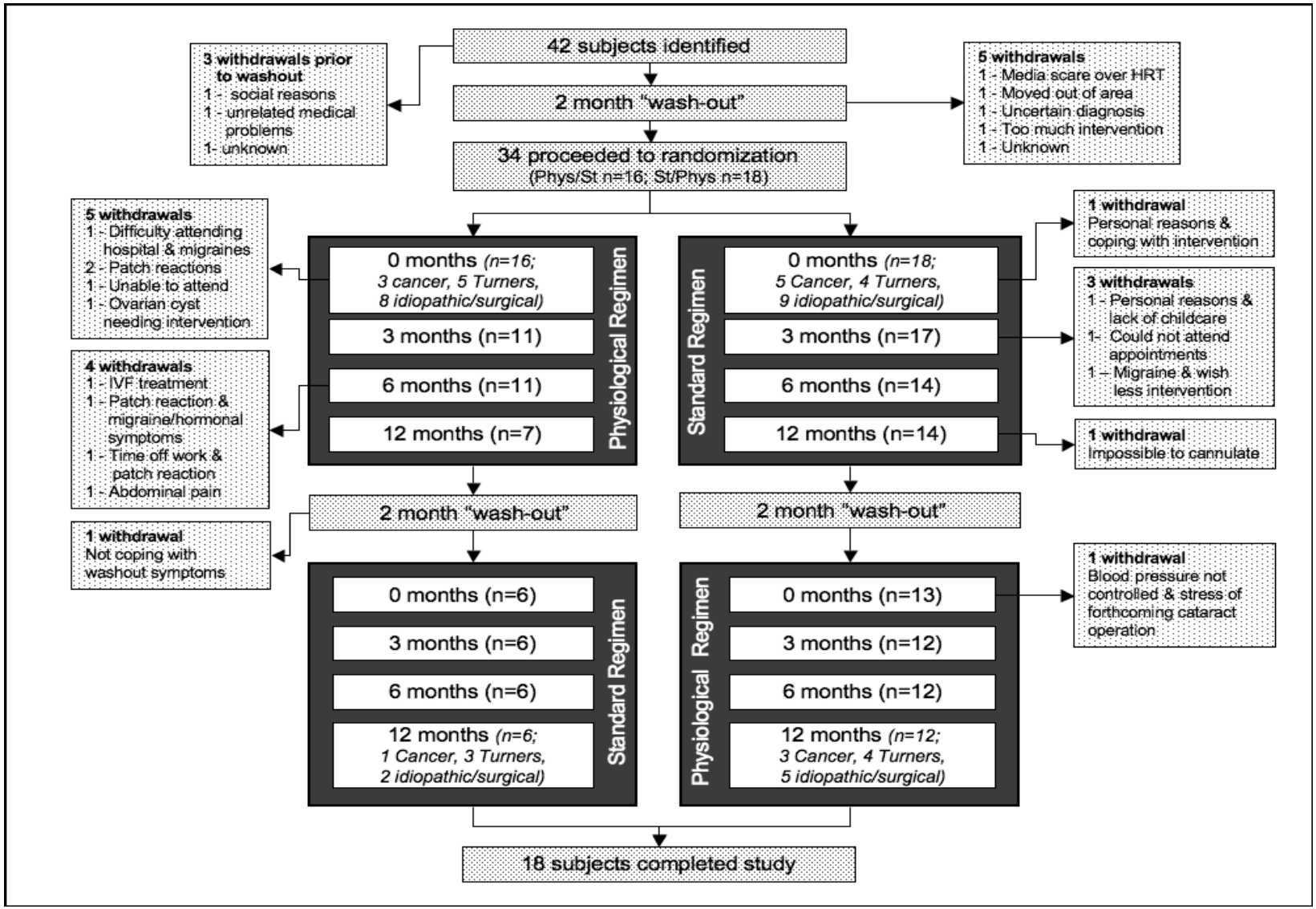
Physiological versus standard sex steroid replacement in young women with POI

- Eligibility
- Documented premature ovarian insufficiency <40 yrs.
- Aim:
- To establish whether we can improve skeletal, cardiovascular and uterine health with a physiological regimen of SSR in young women with premature ovarian insufficiency.

- Physiological
- transdermal Oestradiol

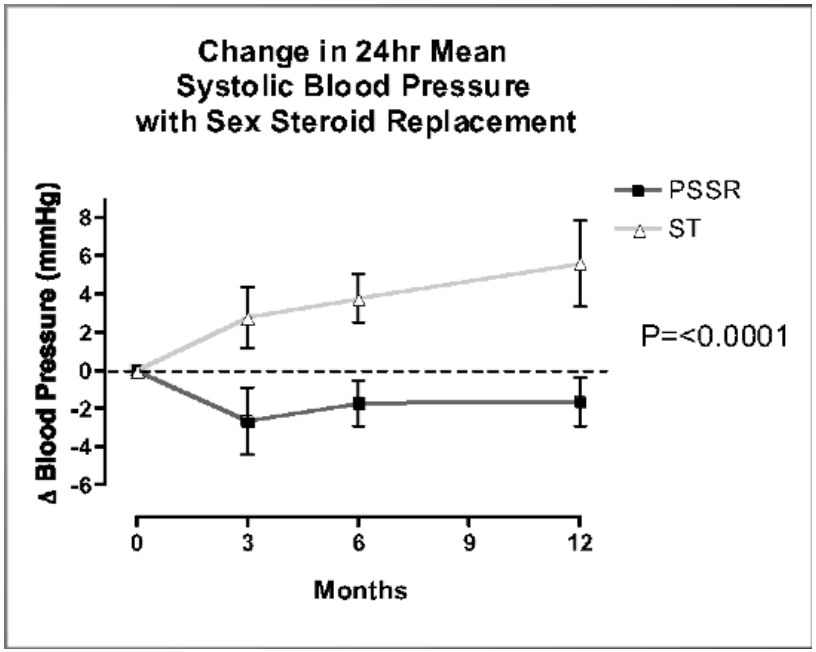
- Standard
- Loestrin 30

Consort flow chart of study participants



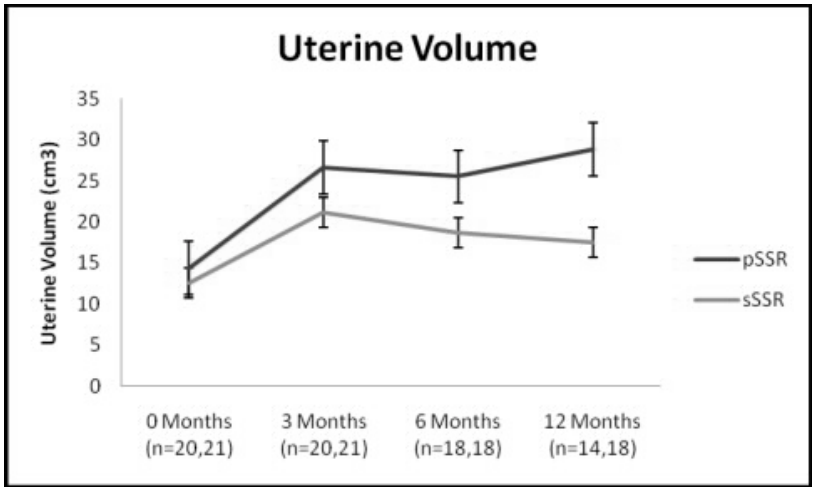
Haemodynamic (Blood Pressure)

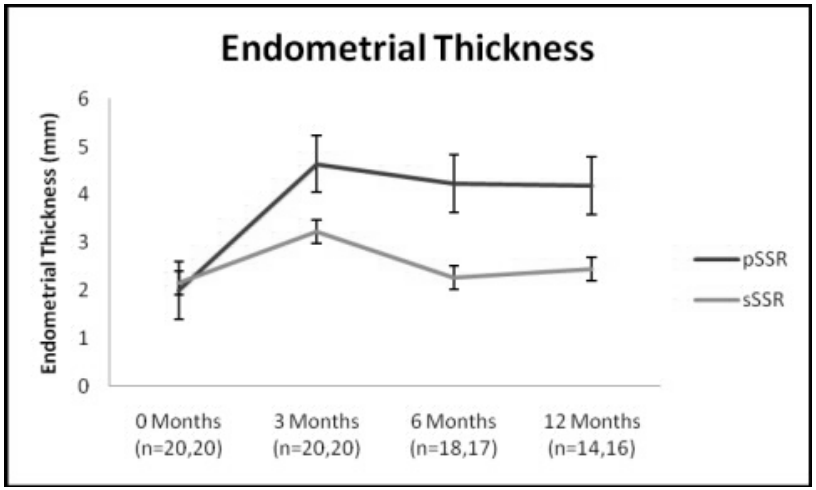
- 1.6mmHg reduction with PSSR (SBP)
- 5.6mmHg increase with ST (SBP)
- **OVERALL 7.2mmHg SBP benefit with physiological sex steroid replacement**



Langrish, Mills, Bath, Warner, Webb, Kelnar, Critchley, Newby, Wallace (2009) Hypertension

Uterine volume and function





P=0.096

P=0.02

O'Donnell, Warner, Lee, Walker, Bath, Kelnar, Wallace Critchley. (2012) Human Reproduction

Fertility preservation options: established and experimental

Key features of the 3 options for fertility preservation for women

- Embryo cryopreservation
  - Established but require time and a partner
- Oocyte cryopreservation
  - Established but require time and hormone stimulation (success rate per oocyte low)
- Ovarian tissue cryopreservation
  - Minimal delay
  - No lower age limit
  - Surgical procedure
  - Allows for future developments

Ovarian cortical strips

- rich in primordial follicles
- survive cryopreservation
- technique validated in sheep

Baird & Gosden (1994) Human Reproduction

Cryopreservation: World-wide experience

* At least 20 pregnancies worldwide after othotopic reimplantation of frozen–thawed ovarian cortex
* Success rate is unclear as the denominator is unknown
* No pregnancies reported following the reimplantation of ovarian tissue harvested pre-pubertally
* Young children are potentially ideal candidates

Anderson & Wallace (2011) Clin Endo

Technology or evidence led?

- In the field of fertility preservation there is a dearth of well-designed studies to fully evaluate exciting new techniques
- Unlikely to be feasible or ethical to perform an RCT in a well characterized group of young women to test laparoscopic collection of ovarian cortex versus either dummy laparoscopy or no intervention
- It is highly unlikely that IRBs would pass such a study, or that such a randomized study would be able to recruit sufficient patients

Technology or evidence led?

- When there is uncertainty about a new experimental procedure, it is important for it to be evaluated in IRB-approved clinical trial
- The ASCO guideline recommends that ovarian cryopreservation and transplantation procedures should only be performed in centres with the necessary expertise under IRB-approved protocols that include follow-up for recurrent cancer

Lee et al. (2006) J Clin Oncology
Loren et al (2013) J Clin Oncology

Ovarian Cryopreservation & Ovarian Function

Edinburgh experience in children (< 18 yrs)

1996-2012

Cryopreservation of ovarian cortical tissue – Edinburgh criteria

Selection criteria (1995,modified 2000)

- Age < 30 years
- No previous chemotherapy/radiotherapy if age >15 years
- Mild, non gonadotoxic chemotherapy if < 15 years
- A realistic chance of surviving five years
- A high risk of ovarian failure
- Informed consent (parent and where possible patient)
- Negative HIV and Hepatitis serology
- No existing children

Consent

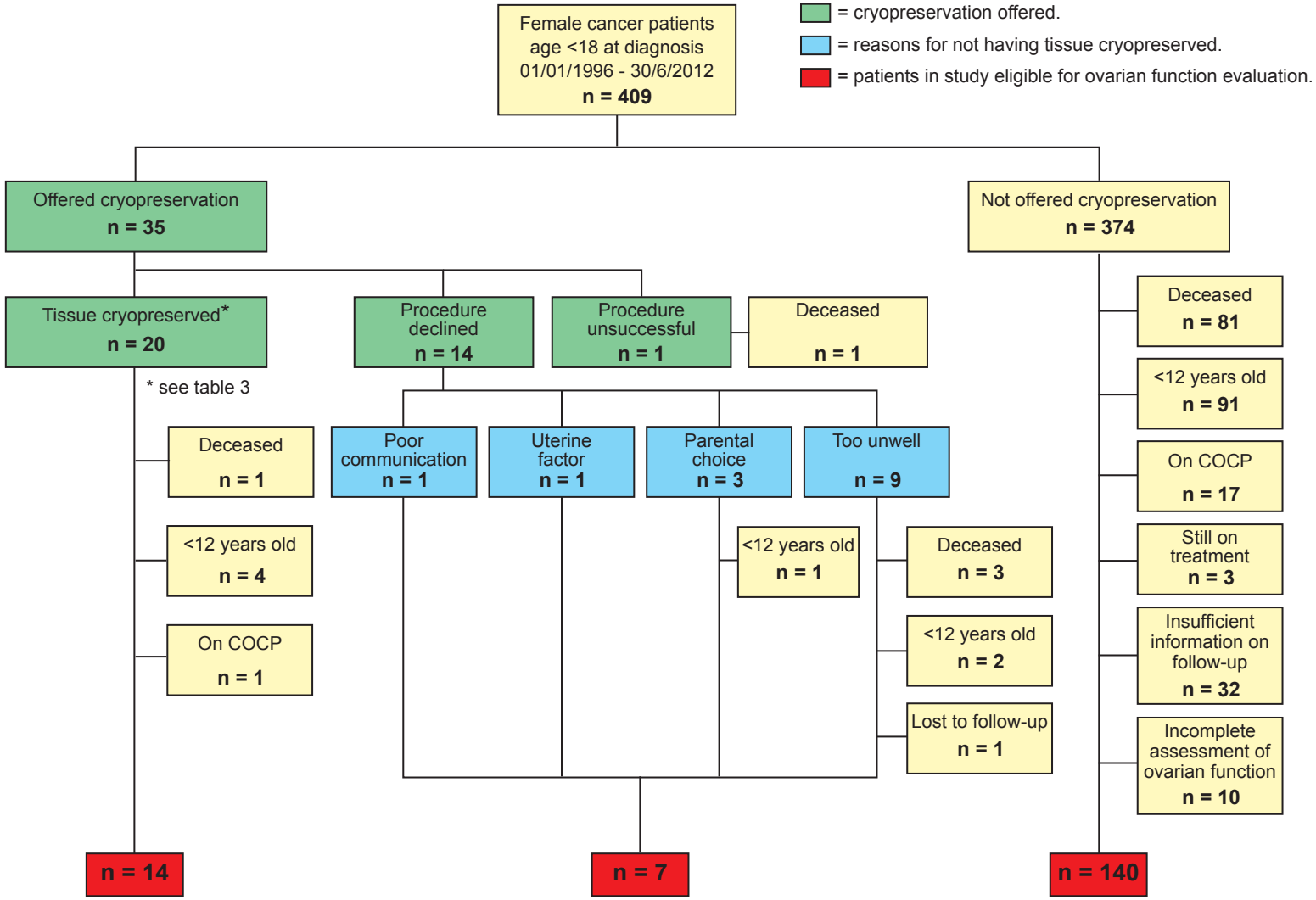
- We emphasize in the information sheet that the procedure is voluntary and experimental, and not part of routine practice
- We obtain informed consent for disposal of ovarian tissue if it is no longer required or the patient dies
- Separately, we ask if an additional small amount can be taken at the time of collection for research studies
- Our practice constitutes research and has been approved by the local institutional review board (IRB)

Wallace (2011) Cancer

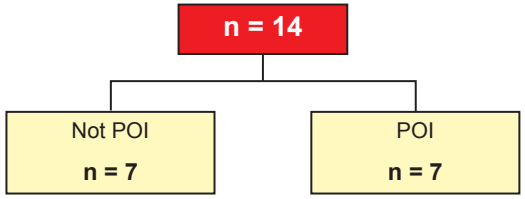
Edinburgh Paediatric Experience

Table 3: Patients that had ovarian tissue cryopreserved

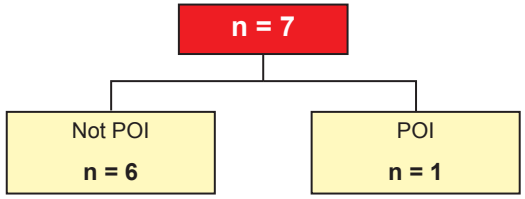
Patient No.	Diagnosis	Age at procedure	Method	Complications
1	Hodgkin's lymphoma¤	14.9	Laproscopic Cortical Strip	None
2	Ewing's sarcoma of pubic bone	14.9	Laproscopic Cortical Strip	None
3	Sacral ependymoma	11.3	Laproscopic Cortical Strip	None
4	Hodgkin's lymphoma	13.7	Laproscopic Cortical Strip	None
5	Hodgkin's lymphoma	11.0	Laproscopic Cortical Strip	None
6	Chronic granulocytic leukaemia	9.9	Laproscopic Cortical Strip	None
7	Rhabdomyosarcoma	5.3	Laproscopic Cortical Strip	None
8	Ewing's sarcoma (pelvic)	9.8	Laproscopic Cortical Strip	None
9	Uterine Cervix Rhabdomyosarcoma*	16.5	Laproscopic Cortical Strip	None
10	Hodgkin's lymphoma°	14.1	Laproscopic Cortical Strip	None
11	Abdominal embryonal Rhabdomyosarcoma	7.9	Laproscopic Cortical Strip	None
12	Ewing's sarcoma	12.1	Laproscopic Cortical Strip†	None
13	Hodgkin's lymphoma	12.7	Laproscopic Cortical Strip	None
14	Metastatic Medulloblastoma	8.1	Laproscopic Cortical Strip	None
15	Hodgkin's lymphoma	15.2	Laproscopic Cortical Strip	None
16	Alveolar Rhabdomyosarcoma	10.5	Laproscopic Cortical Strip	None
17	Embryonal Rhabdomyosarcoma	3.0	Oophorectomy	None
18	Ewing's Sarcoma	12.0	Laproscopic Cortical Strip	None
19	Undifferentiated Sarcoma	12.3	Laproscopic Cortical Strip†	None
20	Wilm's Tumour	1.2	Oophorectomy	None


= cryopreservation offered.
= reasons for not having tissue cryopreserved.
= patients in study eligible for ovarian function evaluation.
Female cancer patients age <18 at diagnosis 01/01/1996 - 30/6/2012 n = 409
Offered cryopreservation n = 35
Not offered cryopreservation n = 374
Tissue cryopreserved* n = 20
Procedure declined n = 14
Procedure unsuccessful n = 1
Deceased n = 1
* see table 3
Deceased n = 1
<12 years old n = 4
On COCP n = 1
Poor communication n = 1
Uterine factor n = 1
Parental choice n = 3
Too unwell n = 9
<12 years old n = 1
Deceased n = 3
<12 years old n = 2
Lost to follow-up n = 1
Deceased n = 81
<12 years old n = 91
On COCP n = 17
Still on treatment n = 3
Insufficient information on follow-up n = 32
Incomplete assessment of ovarian function n = 10
n = 14
n = 7
n = 140

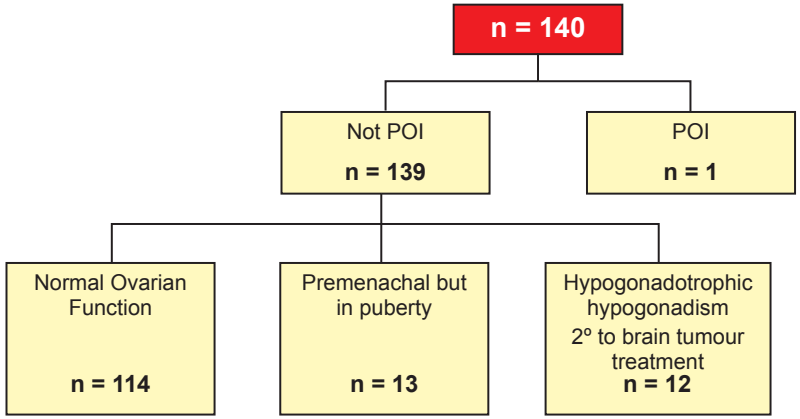
CRYOPRESERVED



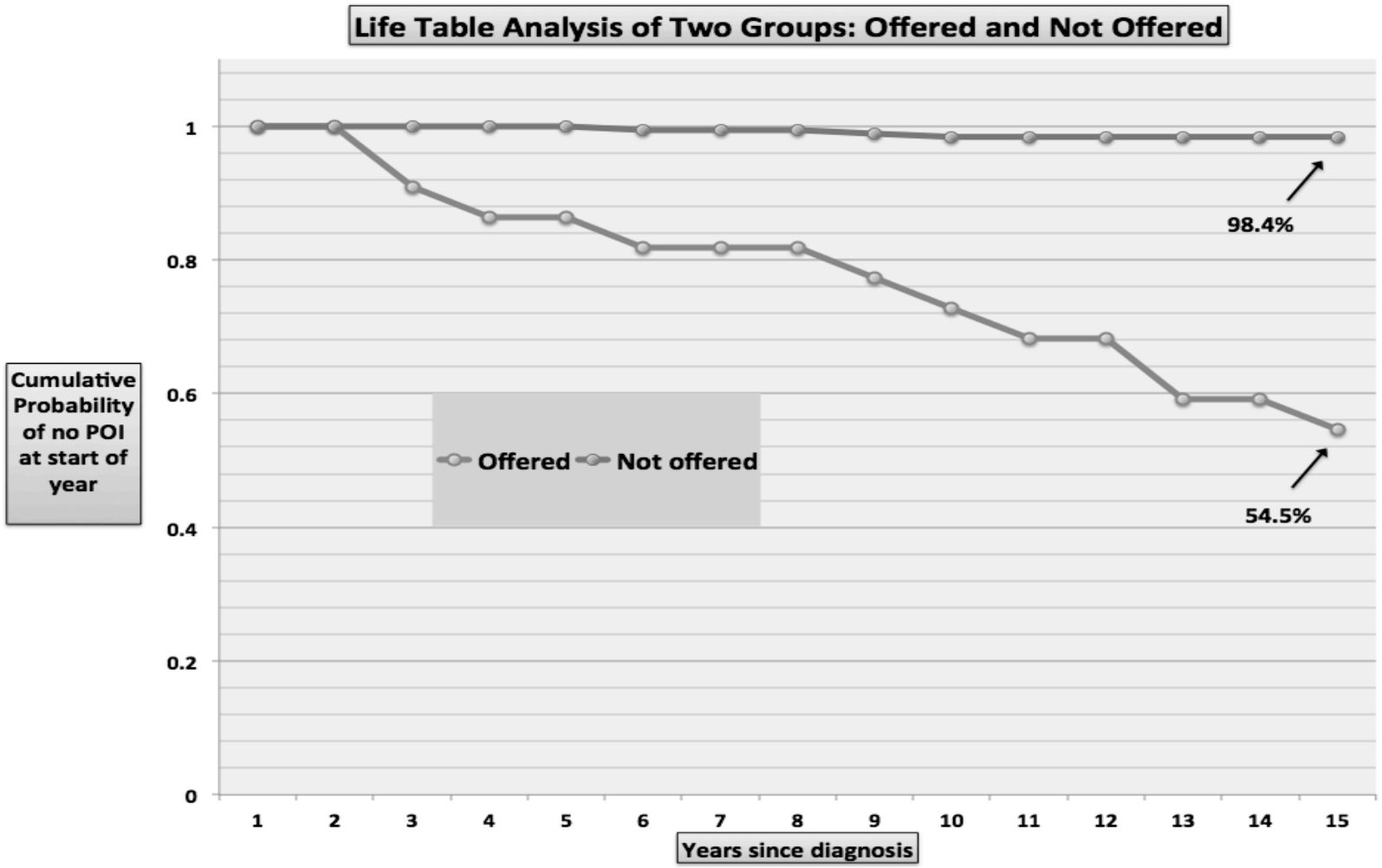
OFFERED CRYOPRESERVATION - procedure declined



NOT OFFERED CRYOPRESERVATION



Life Table Analysis of POI



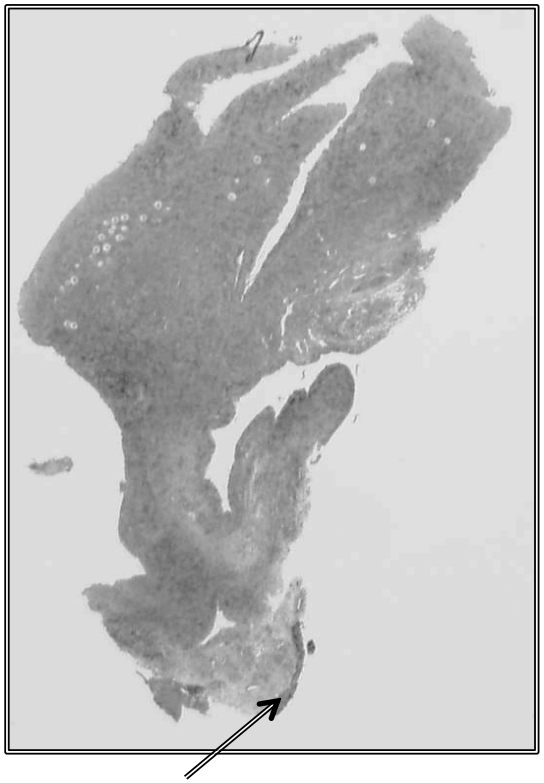
Summary

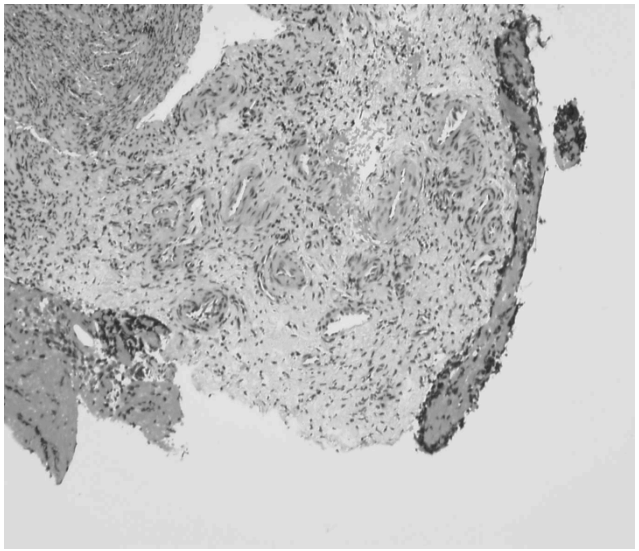
- Ovarian cryopreservation was offered to 9% of our patients, and performed in 5%
- The procedure was safe and without complications
- No patients have asked for re-implantation of their tissue – to date (15.7 [1.3-30.9] yrs)
- All patients who have thus far (bar one) developed premature ovarian insufficiency were identified
- The Edinburgh Selection Criteria have proved to be helpful and accurate in determining the correct patients for ovarian cryopreservation

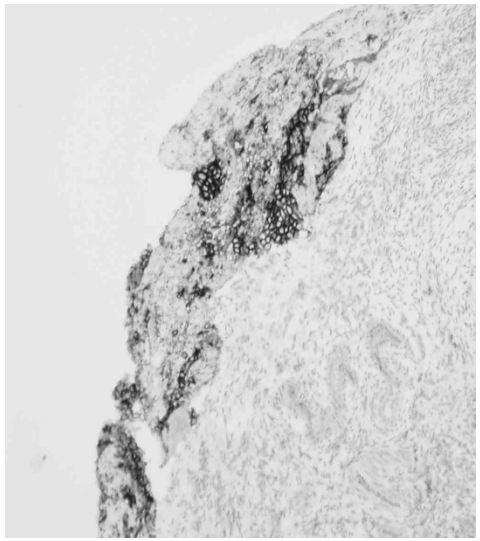
Reimplantation?

- It is important to be aware that reimplantation of ovarian cortical tissue is a separate procedure at a time distant from the treatment of the original cancer
- Consent for harvesting ovarian tissue from children often will have been obtained from their parents
- Informed consent for reimplantation can be obtained from the patients at a much later date when they are competent to assess the complex issues themselves.

Ewings sarcoma localised T 7 Vertebrae (Age 12) – unexpected contamination of ovarian biopsy







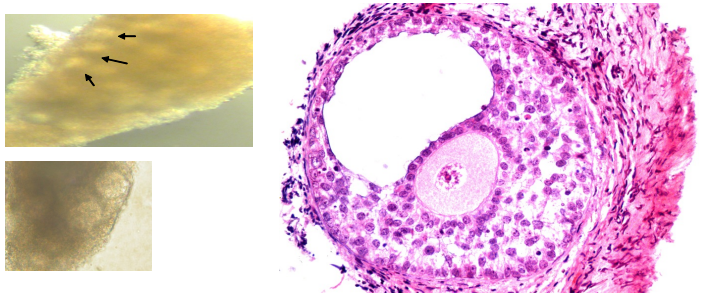
CD99

Re-implantation or IVG and maturation?

- Contamination of the cryopreserved tissue with malignant cells, particularly in haematological malignant disease – shown in a rodent lymphoma model – to cause recrudescence of the original disease

- Oocyte maturation in vitro, followed by IVF, would eliminate this risk

Antral development from *in vitro* grown human primordial follicles within 10 days



Telfer et al., 2008: A two step serum free culture system supports development of human oocytes from primordial follicles in the presence of activin. **Human Reproduction** 23: 1151-1158

Telfer et al. (2008) Human Reproduction

Cancer Risk in Children Born after Assisted Conception

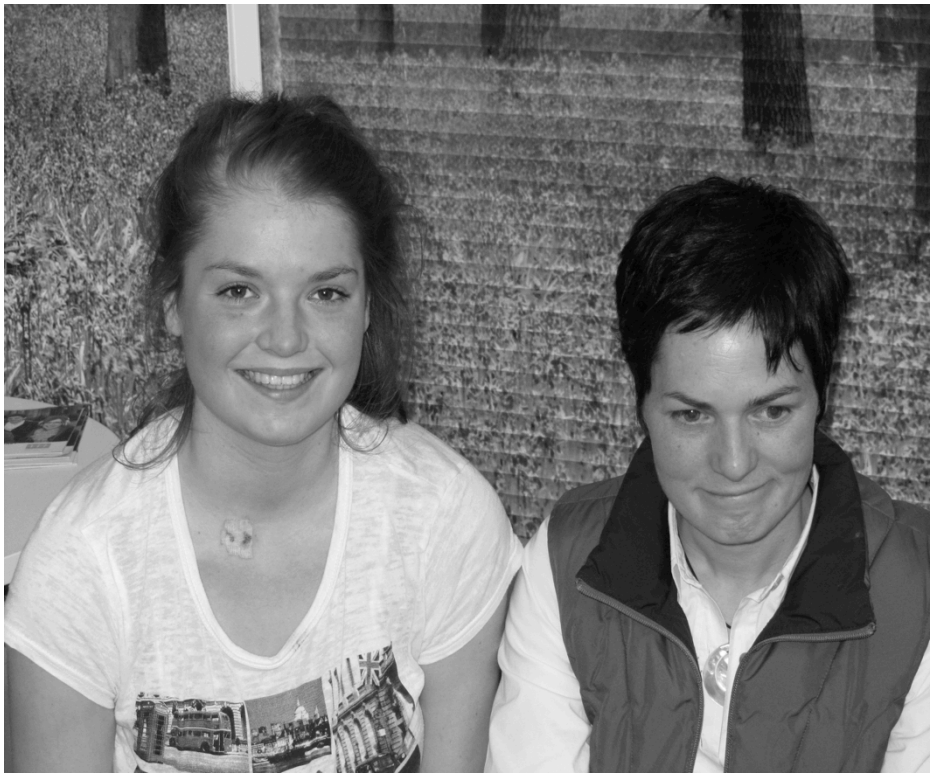
- Records of all children born in Great Britain between 1992 and 2008 after assisted conception without donor involvement were linked to the United Kingdom National Registry of Childhood Tumors to determine the number who subsequently developed cancer by 15 years of age.
- Overall, 108 cancers were identified compared to 109.7 expected (Standardized Incidence Ratio (SIR), 0.98; 95% Confidence Interval (CI), 0.81-1.19; P=0.87)
- There was **no overall increased risk of cancer** in British children born after assisted conception over this 17 year period

Williams CL et al. NEJM (in press)

An important future development

- Cryopreservation of pre-pubertal testicular tissue for preservation of fertility in young boys with cancer
- CI Dr Rod Mitchell (RCPCH Young Investigator of the Year 2013)
- This proposal involves starting to offer testicular tissue cryopreservation to appropriate pre-pubertal male patients

After Treatment:
with a famous guest!



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