



Disturbances of female reproductive system in survivors of childhood cancer

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Introduction

- Cancer is the second commonest cause of death in children in developed countries.
- Of all childhood cancers:
 - one third are leukaemias, of which 80% are acute lymphoblastic leukaemia (ALL)
 - 25% are brain and spinal tumours
 - 15% are embryonal tumours (neuroblastoma, retinoblastoma, Wilms' tumour and hepatoblastoma)
 - 11% are lymphomas (Hodgkin's and non-Hodgkin's lymphomas)

The remainder is comprised of bone (osteosarcoma and Ewing's sarcoma), soft tissue tumours (rhabdomyosarcoma), and a variety of more rare tumours.



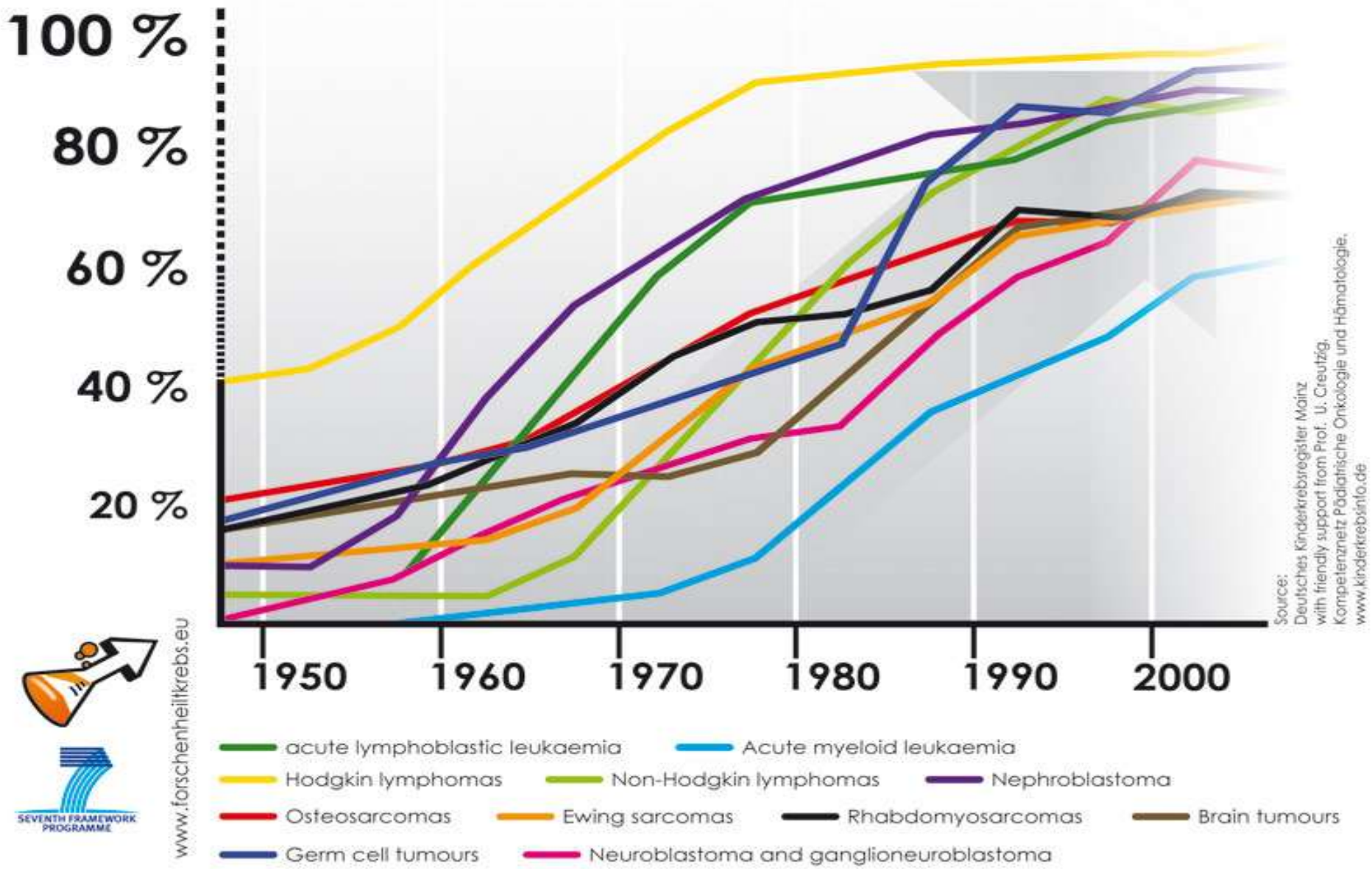
Incidence and prognosis of the most common childhood cancers

	Incidence/100 000 children/year	Cure rate (%)
Acute lymphoblastic leukaemia/ non-Hodgkins lymphoma	5.0 – 6.0	75 - 80
Hodgkins lymphoma	0.4	>90
Brain tumours	4.0	Depends on diagnosis
Wilms' tumour	0.9	80

For all childhood cancers the 5-year survival rate has improved over recent decades due to advances in treatment regimens. Five-year survival rate has increased from around 30% in the 1960s to around 80% for children diagnosed 2001-2005.



Survival Rates of Children and Young Adults Suffering from Cancer



Principles of cancer treatment

Local treatments

- Surgery
- Radiation therapy

Systemic treatment

- Chemotherapy
- Hormone therapy (in case of hormone sensitive tumors)
- Biological therapy (including immunotherapy and gene therapy)

Surgery may impact fertility by removing reproductive organs or damaging structures needed for reproduction.

Chemo- and radiotherapy have toxic effect on the gonads.

The impact of biological therapy on reproduction is largely unknown.



Adverse effects of treatment

- Cancer disease itself, as well as the life saving cancer treatment, may carry with it a risk of immediate and late adverse effects.
- Late effects encompass a range of clinical conditions including neurocognitive deficits, skeletal deformities, cardiopulmonary, renal and hepatic damage, endocrine and reproductive dysfunction.



Disturbances of pubertal development

- Initiation of puberty is the result of reactivation of the hypothalamic-pituitary-gonadal axis.
- GnRH-producing neurones of the hypothalamus are particularly sensitive to the influences of cancer treatment.
- The pituitary gland seems to be relatively resistant to treatment effects.
- Radiotherapy and certain forms of chemotherapy may have deleterious effects on the gonads, particularly on the germ cells.



Pubertal disorders following treatment for childhood cancer

	Precocious puberty	Delayed puberty/ hypogonadotropic hypogonadism
ALL without cranial irradiation	–	–
ALL with cranial irradiation	+	–
BMT with TBI	–	++
BMT with chemotherapy	–	++
Brain tumours with cranial irradiation	++	+
– not observed; + observed; ++ frequently observed		



Infertility risk

based on common cancers of childhood and adolescence



High risk (>80%)

- Total body irradiation (TBI)
- Localized pelvic radiotherapy
- Chemotherapy conditioning for bone marrow transplantation (BMT)
- Hodgkin's disease: treatment with alkylating drugs
- Soft-tissue sarcoma: stage IV (metastatic)
- Ewing's sarcoma: metastatic



Medium risk

- Acute myeloblastic leukaemia (difficult to quantify)
- Hepatoblastoma
- Osteosarcoma
- Ewing's sarcoma: non-metastatic
- Soft-tissue sarcoma: stage II or III
- Neuroblastoma
- Non-Hodgkin lymphoma
- Hodgkin's disease: alternating treatment
- Brain tumour: craniospinal radiotherapy, cranial irradiation >24 Gy



Low risk (<20%)

- Acute lymphoblastic leukaemia (ALL)
- Wilms' tumor
- Soft-tissue sarcoma: stage I
- Germ-cell tumors (with gonadal preservation and no radiotherapy)
- Retinoblastoma
- Brain tumour: surgery only, cranial irradiation <24Gy



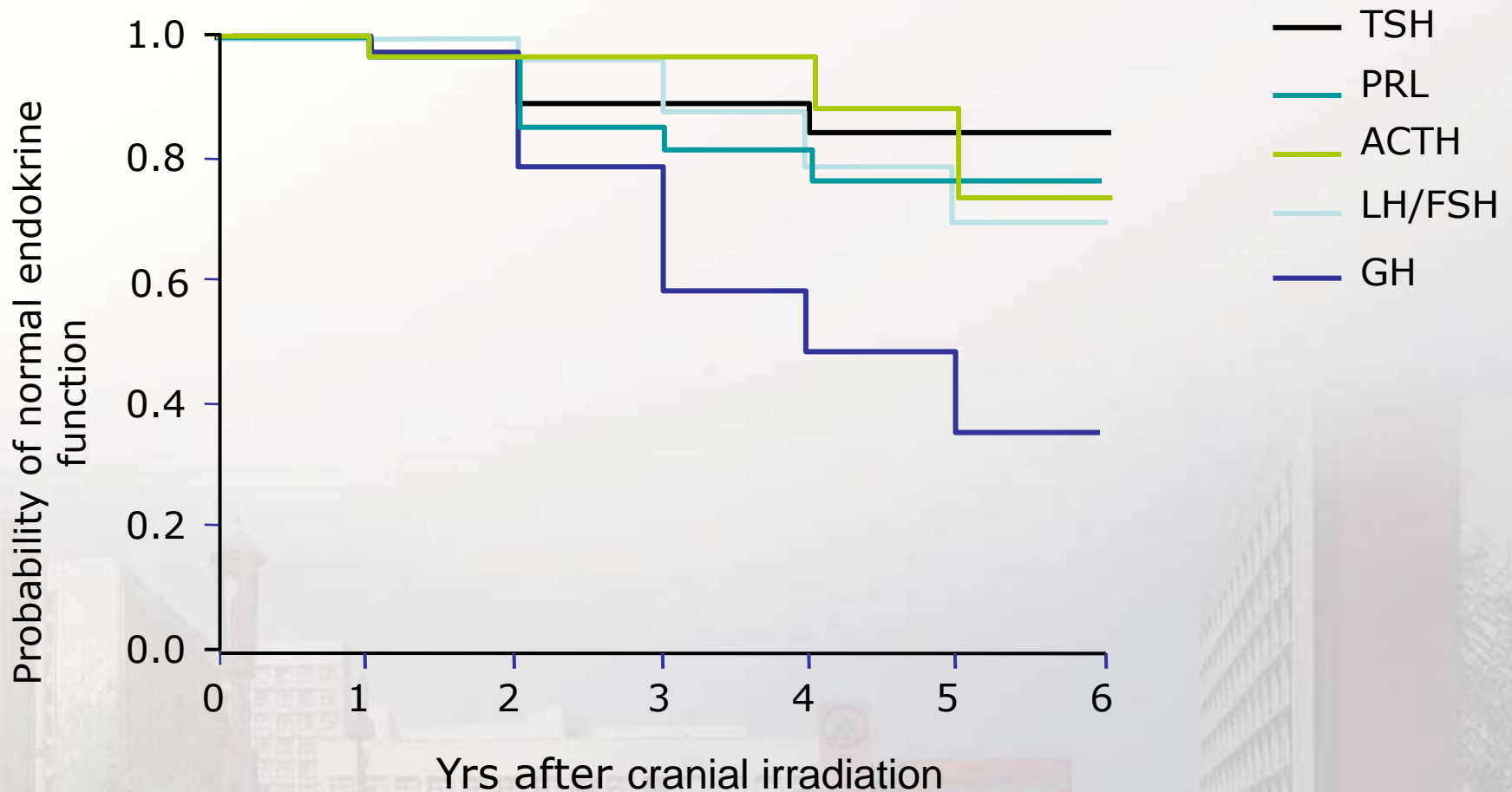
Late effects of **radiotherapy** to female reproductive system



- The impact of radiotherapy on endocrine function is highly dependent on the **age of the child**, the **total dose** of irradiation as well as the **number of fraction** given.
- Radiotherapy doses to the hypothalamic-pituitary area in excess of 30Gy have been shown to cause **early puberty**.
- Children who have received large doses of cranial irradiation are at risk of developing **hypogonadotropic hypogonadism** with time.



Timing of Endocrinopathy development



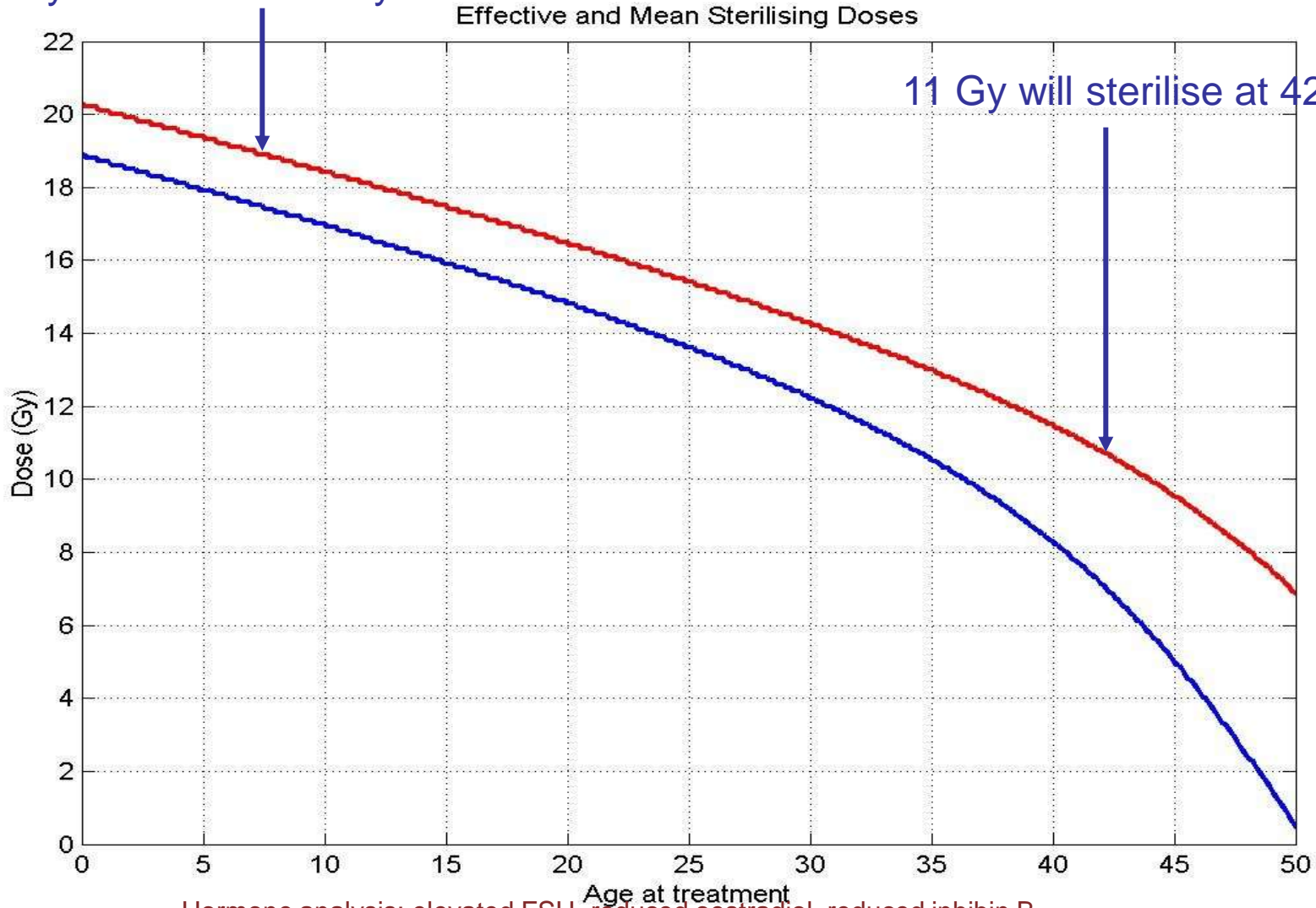
Lam et al. Effects of cranial irradiation on hypothalamic-pituitary function – a five year longitudinal study in patients with nasopharyngeal carcinoma. *Q J Med* 1991; 78:165–76.



Effective sterilising doses of radiation are 20.3Gy at birth, 18.4Gy at 10 years, 16.5Gy at 20 compared to 9.5Gy at 45 years of age.

19 Gy will sterilise at 7 years

11 Gy will sterilise at 42 years



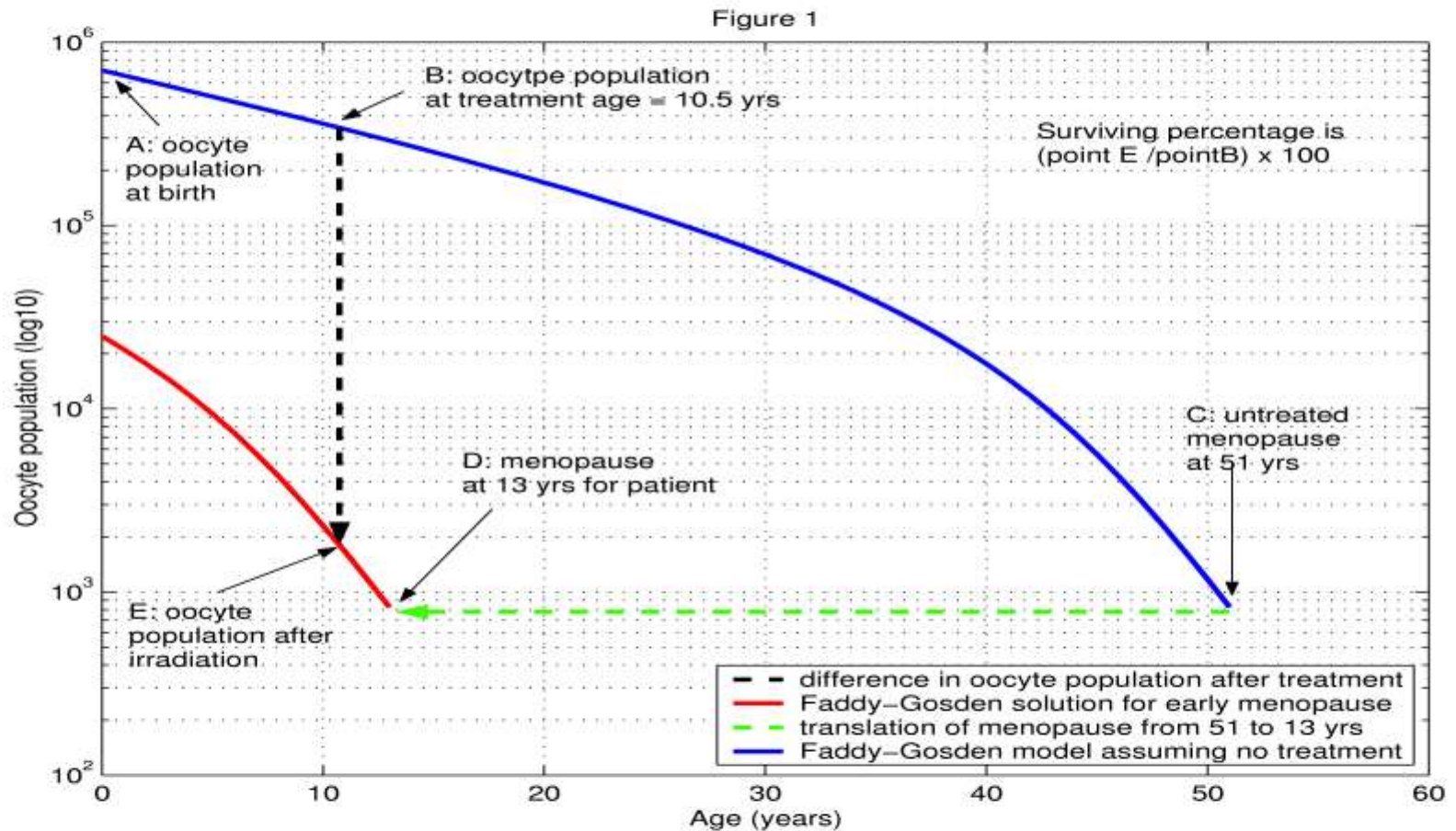
Hormone analysis: elevated FSH, reduced oestradiol, reduced inhibin B

Direct radiotherapy to the ovaries

- The specific risk of premature POF after direct radiation to the ovaries is dose-dependent.
- Premature ovarian failure may take the form of either **acute ovarian failure**, where there is a loss of ovarian function during or shortly after the completion of cancer therapy, or **premature menopause**, defined as menopause younger than 40 years.
- Doses as low as 5Gy to the ovaries have been identified as a significant risk factor for ovarian failure.
- **The LD50** (the radiation dose required to kill 50% of oocytes) of the human oocyte has been estimated at **<2Gy**.



Human oocyte (primordial follicle) $LD_{50} < 2$ Gy



Wallace et al. (2003) Hum Reprod

Late effects of **chemotherapy** to female reproductive system



Chemotherapy

- Factors affecting the risk of ovarian injury in children treated with chemotherapy include the **specific agent**, the **number of agents**, and the **cumulative dose**.
- Many of chemotherapeutic agents do not affect pubertal development.
- Several chemotherapeutic agents when given at high doses are recognized as toxic to young ovaries.



Estimated risk of gonadal dysfunction with cytotoxic drugs

High risk	Medium risk	Low risk/ No risk
<p>Chemotherapy conditioning for bone marrow transplantation (BMT)</p> <p>Cyclophosphamide</p> <p>Ifosfamide</p> <p>Chlormethine</p> <p>Busulfan</p> <p>Melphalan</p> <p>Procarbazine</p> <p>Chlorambucil</p>	<p>Cisplatin</p> <p>Carboplatin</p> <p>Doxorubicin</p>	<p>Cytarabine</p> <p>Vincristine</p> <p>Methotrexate</p> <p>Dactinomycin</p> <p>Bleomycin</p> <p>Mercaptopurine</p> <p>Vinblastine</p>



Chemotherapy and POF

- Clinically, administration of chemotherapy can have two effects on ovarian function: immediate, or longer term.
- **The immediate effect**, occurring during treatment, is amenorrhea, which results from loss of the growing follicle population. However, if sufficient primordial follicles remain in the resting pool upon the cessation of treatment, the population of growing follicles will then be replenished, and menses resume.
- **Later ovarian failure** is a result of loss of the primordial follicle pool, and results in premature ovarian failure POF.
- Where there is only partial loss of primordial follicles, this longer term effect may not manifest itself until years or even decades after treatment, when the patient then undergoes premature menopause.



Improvement of childhood cancer survival in Lithuania



Dr. Jelena Rascon retrospective analysis

- Period: from 1982 to 2011 (30 years)
- Children's Hospital Affiliate of VUH Santariskiu Klinikos

Comparative analysis of three decades

1982-1991

1992-2001

2002-2011

- Entire study population and 3 disease cohorts

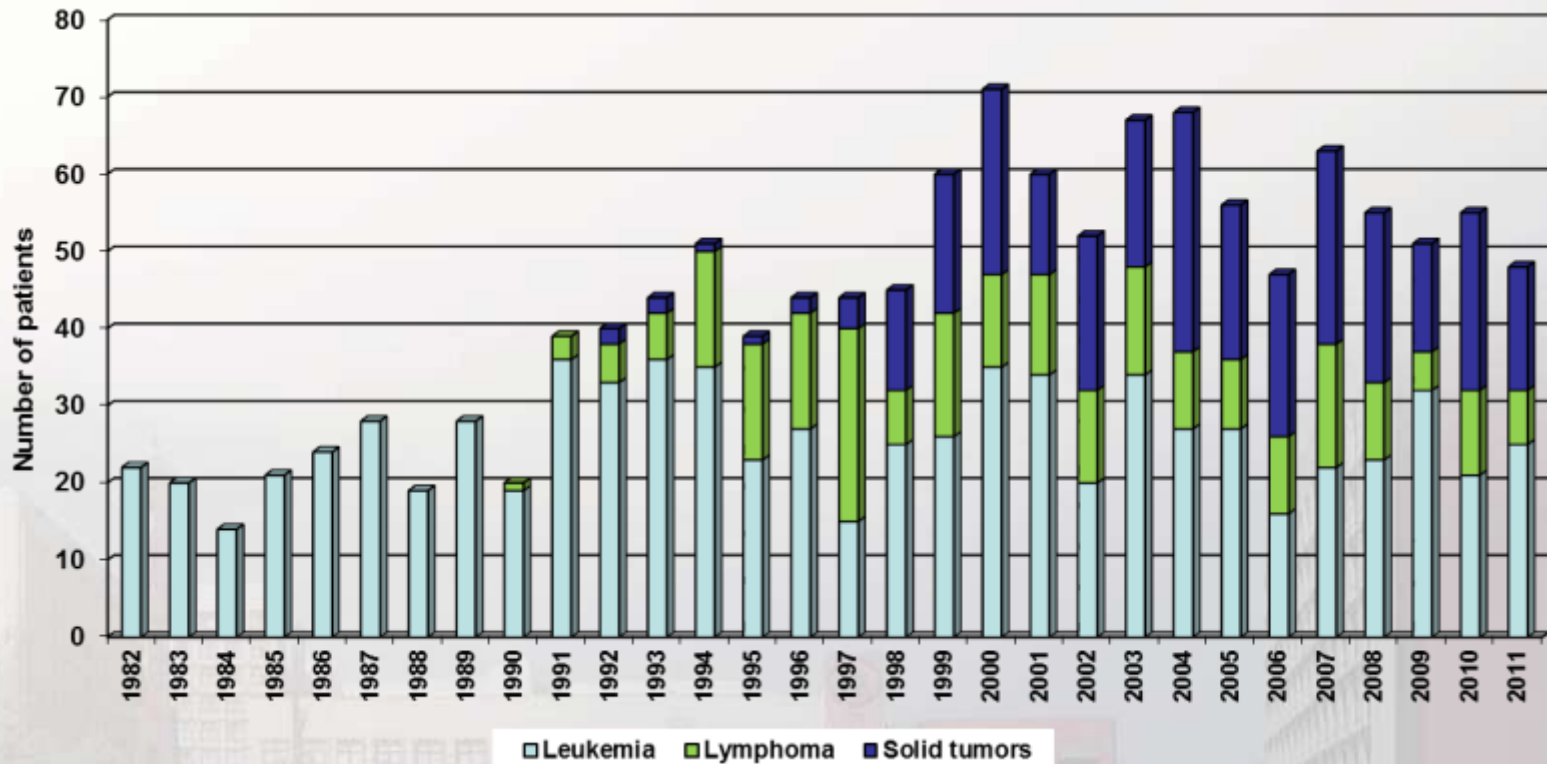
Leukemia

Lymphoma

Solid tumors



Annual number of patients treated from 1982 till 2011 (totally 1294 children)

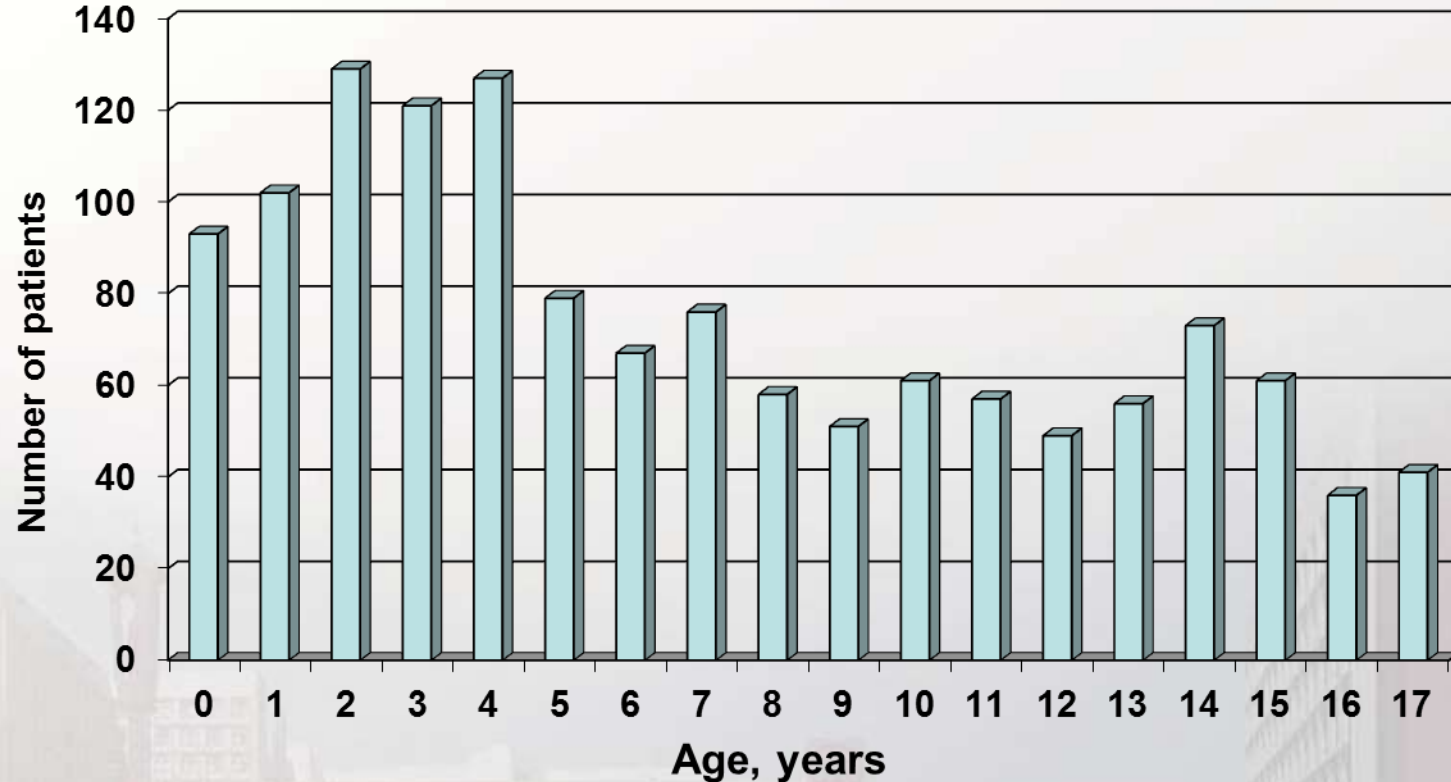


Median 51 new cancer cases per year (range from 39 to 71)



Distribution of age at diagnosis

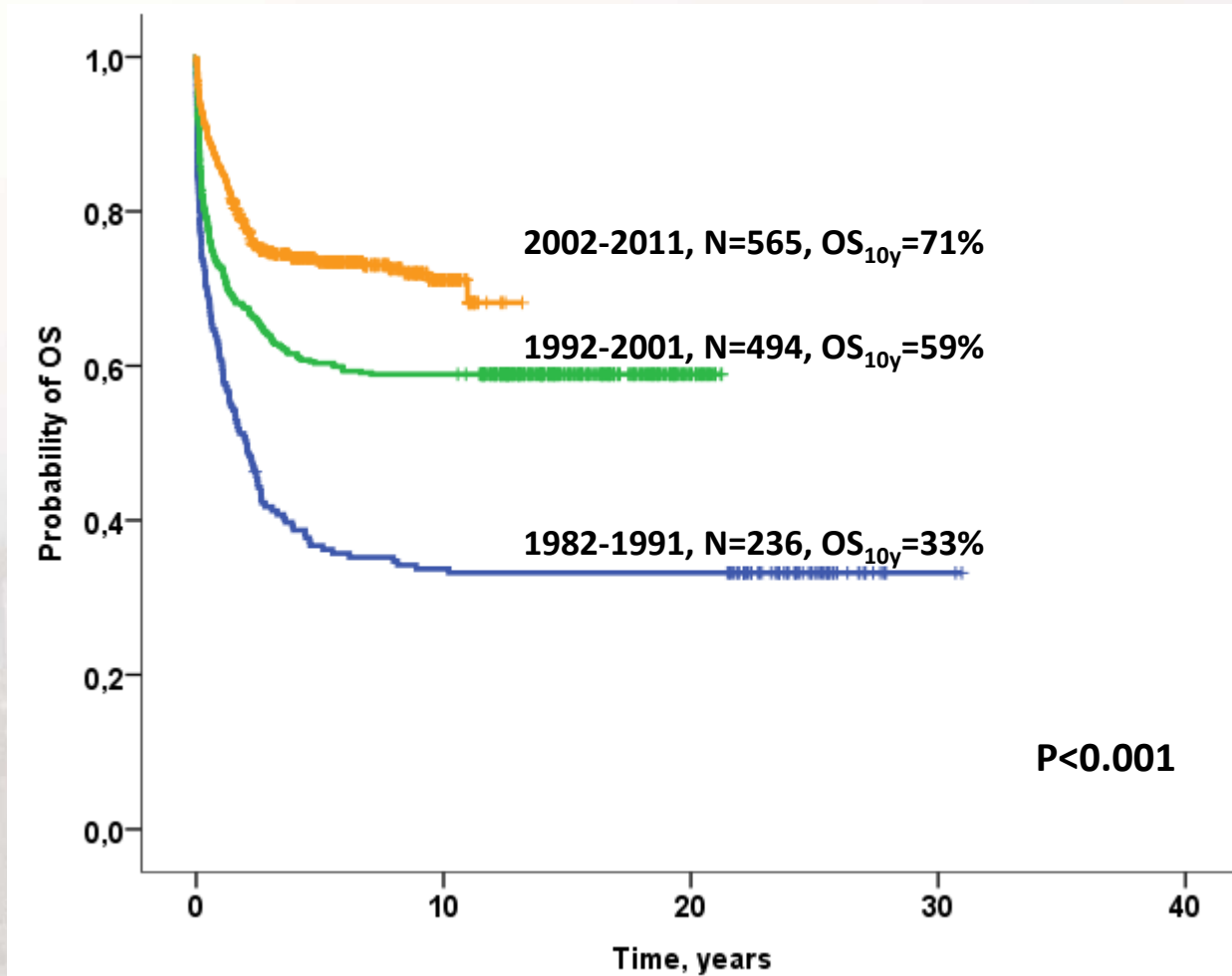
n=1294



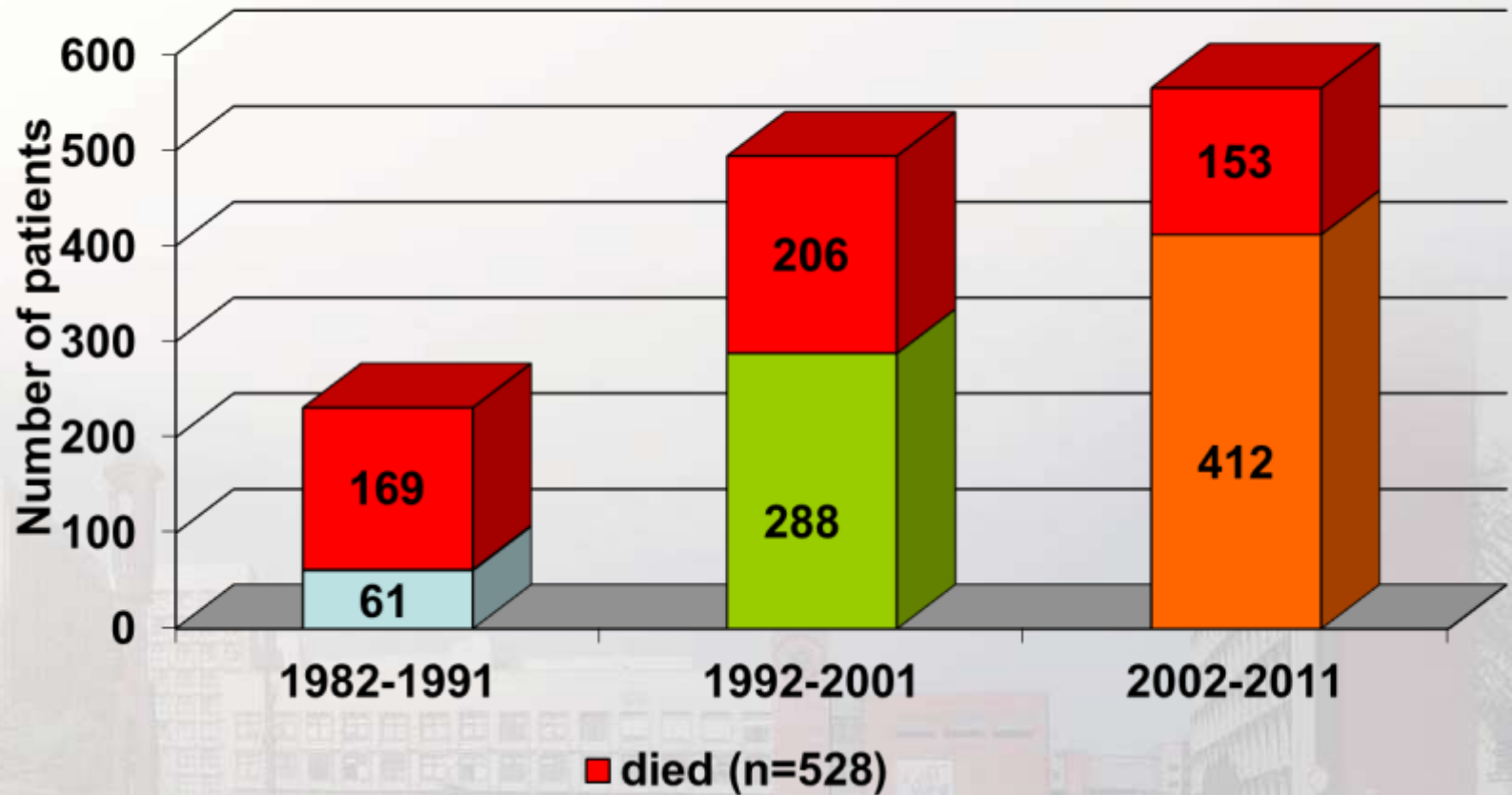
Median age 6 years (range from 0 to 17 years)



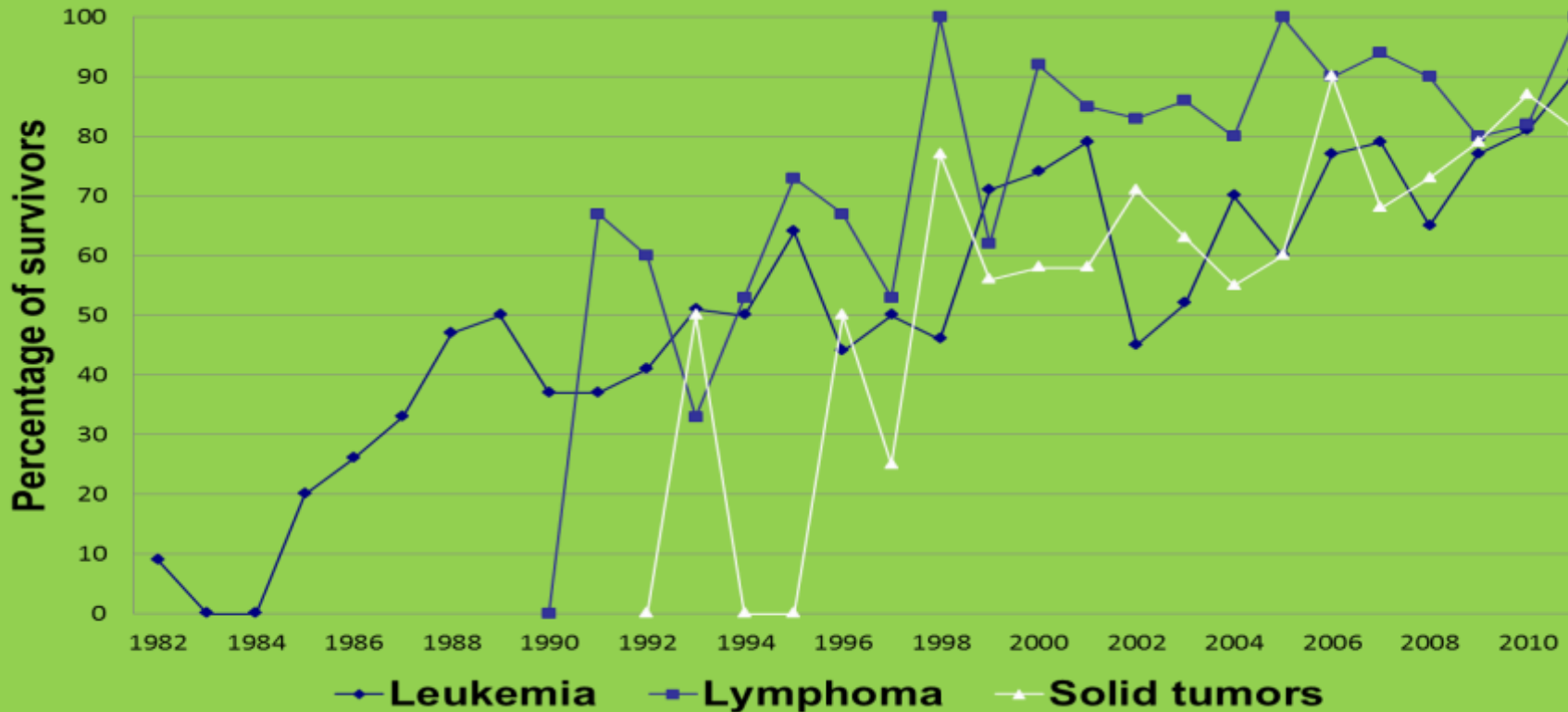
Overall survival of the entire cohort (n=1294)



Number of survivors in each decade (n=761)



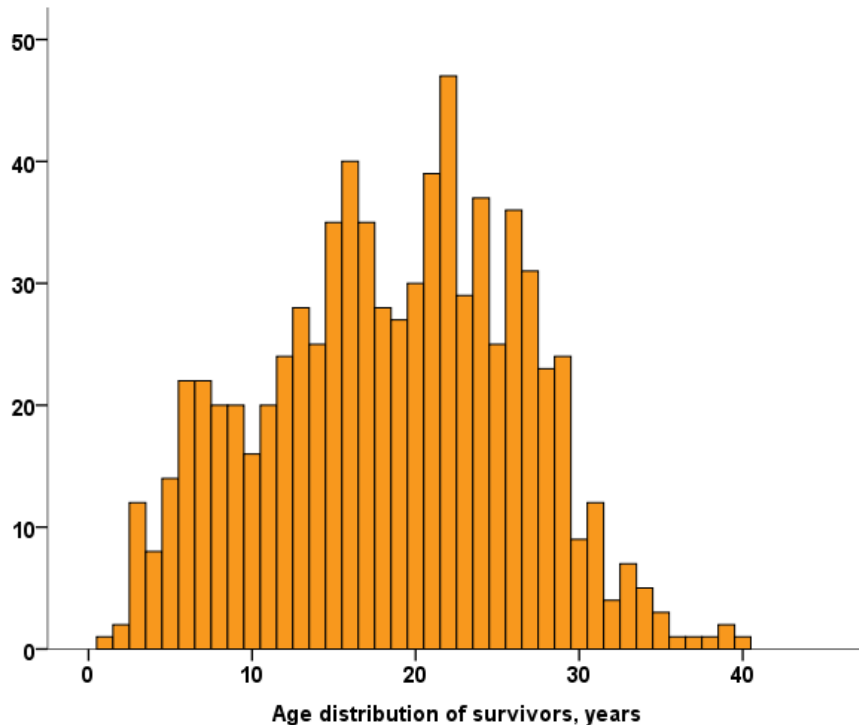
Survival rates of children suffering from cancer in Lithuania



This increased survival rate has led to a rapidly increasing population of adult survivors of childhood cancer.



Survivors treated from 1982 to 2011 (n=761)



Age

- Median **19** years
(range from 2 to 40 years)
25-75 % - **13-24** years

Follow-up

- Median 10.6 years
(range from 1.4 to 31.0 years)

Protecting fertility



Ovarian status

- Progressing normal puberty
- Normal concentration of gonadotropins and estradiol
- Ovarian status could not be determined in children younger than 12 years, because the measurement of gonadotropins and estradiol in girls younger than 12 years is not a reliable measure of ovarian function.
- Premature ovarian insufficiency: amenorrhea >4 months, FSH >25 IU/L, low estradiol.



Assessment of ovarian reserve

- Ovarian reserve refers to the number and quality of oocytes that, at any given age, are available to produce a dominant follicle late in the follicular phase of the menstrual cycle.
- A small proportion of primordial follicles are constantly entering the growth phase throughout life, including in childhood.
- Accurate measurement of the ovarian reserve is not possible.



Assessment of ovarian reserve

- **AMH** is a product of growing ovarian follicles and is a useful biomarker in children, because it is measurable in girls of all ages and shows a progressive rise through childhood and adolescence, with a peak at age 24.5 years followed by a steady decline thereafter.
- **Transvaginal ultrasound** assessments of total ovarian volume and antral follicle count (AFC) are noninvasive and accurate tests of ovarian reserve.
- **AFC (antral follicle count)** is defined as the number of follicles smaller than 10mm in diameter detected by TVS in the early follicular phase. AFC has also been shown to correlate tightly with plasma levels of AMH.



Risk assessment for fertility preservation

Pre-treatment assessment of an individual patient for invasive fertility preservation techniques requires evaluation of

Intrinsic factors:

- Health status of patient
- Consent (patient/parent)
- Assessment of ovarian reserve in girls/young women

Extrinsic factors:

- Nature of predicted treatment (high/medium/low/uncertain risk)
- Time available
- Expertise available

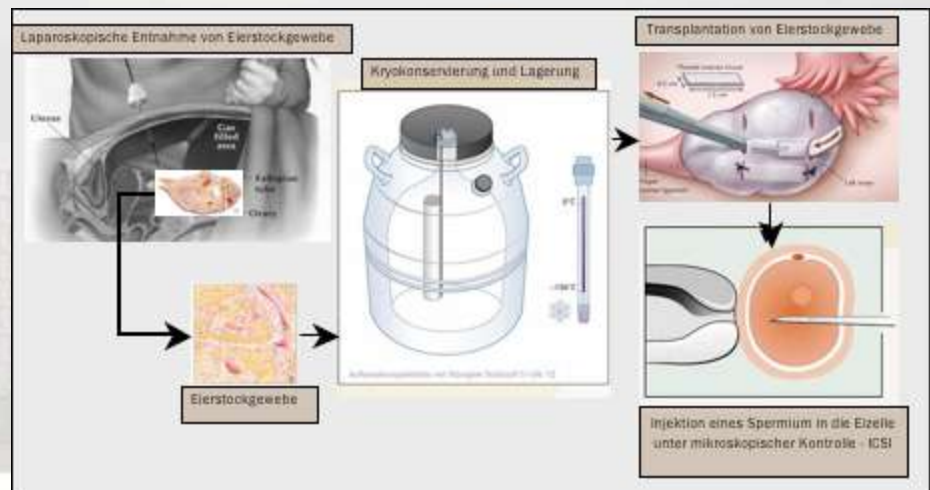
SIGN (Scottish Intercollegiate Guidelines Network): SIGN 132 • Long term follow up of survivors of childhood cancer (March 2013)



Options for fertility preservation

There are two main approaches to preserving fertility in female childhood cancer survivors:

1. cryopreservation of ovarian tissue, oocytes,
2. interventions to minimise the effects of cancer therapies on the ovaries.



Patient selection is crucial ...

- Evidence from case series has suggested that the collection of ovarian tissue for freezing by laparoscopy under a general anaesthetic is safe and feasible in prepubertal girls without delaying cancer treatment, but this approach remains experimental (level of evidence 4).
- The procedure is invasive, and can carry an unacceptable risk in some children with cancer who might be immunocompromised and pancytopenic (increased risk of bleeding and infection).
- Unknown effectiveness of the procedure for the restoration of fertility (30 pregnancies after reimplantation have been reported in adults, but the total number of women in whom frozen ovarian tissue has been reimplanted is unknown).
- These problems dictate that patient selection is crucial.



The Edinburgh selection criteria

- Age younger than 35 years
- No previous chemotherapy or radiotherapy (patients aged 15 years with previous low-risk chemotherapy should be considered)
- Realistic chance of surviving for 5 years
- High risk of premature ovarian insufficiency (>50%)
- Informed consent from patient or from parents
- Negative serology results for HIV, syphilis, hepatitis B
- No pregnant and no existing children



Oocyte cryopreservation

- Oocyte cryopreservation is increasingly used for fertility preservation in adult women.
- This may also be an option in post-pubertal girls.
- The method requires the use of ovarian stimulation and its success is dependent on the total number of oocytes retrieved (<10 oocytes is associated with minimal chance of pregnancy), which is often difficult in sexually immature patients.
- This process also requires at least one cycle of ovarian stimulation which may not be possible when chemotherapy needs to be commenced immediately or where stimulation is contraindicated due to hormone-sensitive tumours.



Ovarian tissue cryopreservation (1)

- The option has greater fertility potential in prepubertal girls due to a greater density of primordial follicles in the harvested tissue.
- Cryopreservation of ovarian tissue should be considered in girls at high risk of premature ovarian insufficiency. (Grade D)
- This process has the added advantage of endogenous hormone production by the ovarian tissue.
- Risks of OTC include the surgical risks associated with the invasive procedure. An additional concern is reimplantation of the primary tumour and/or malignant transformation of reimplanted tissue, which is possible with leukaemias, neuroblastoma, and Burkitt's lymphoma which are common during childhood and metastasise to the ovaries.

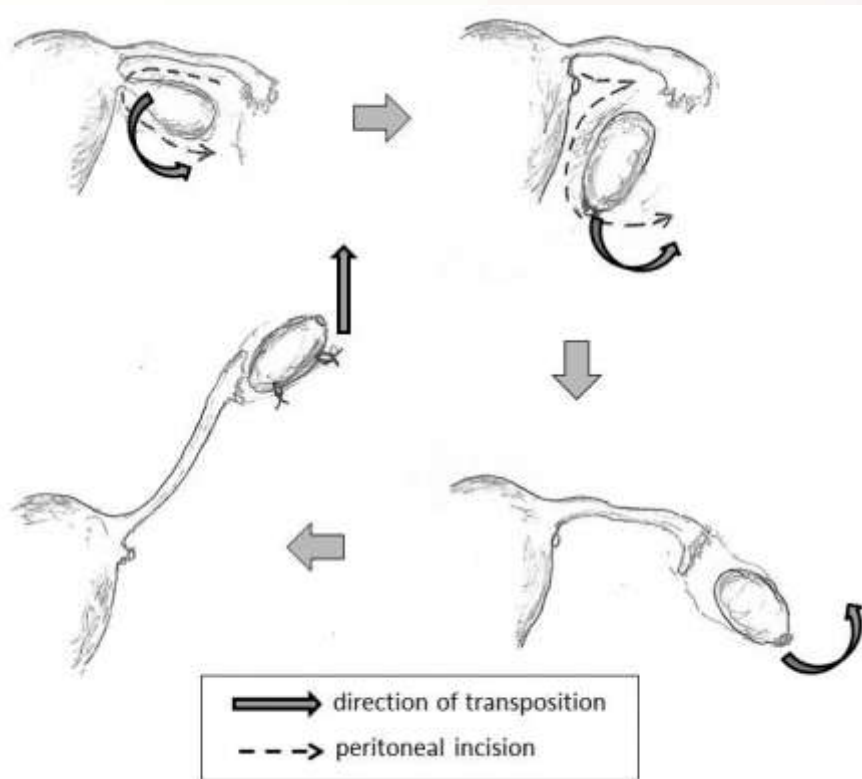


Ovarian tissue cryopreservation (2)

- No cases have been reported of pregnancy after ovarian tissue cryopreservation in childhood or adolescence.
- Two case reports have described the replacement of ovarian tissue in adolescents for the purpose of estrogen production for pubertal induction. The evidence of successful suggest that follicular development is possible, potentially allowing for oocyte maturation, ovulation, and fertility.



Interventions to minimise damage caused by cancer therapies (1)



- Ovarian transposition (**oophoropexy**) has been used in adults to move the ovaries out of a proposed radiation field.
- There are no data on the efficacy of this approach in girls and adolescents. (level of evidence 4)

Interventions to minimise damage caused by cancer therapies (2)

Hormonal suppression of ovarian activity by **GnRH analogues** to protect the ovary against cytotoxic insult has been proposed in adults.

Randomised controlled trials in adults have produced conflicting results and there are no data demonstrating efficacy in girls and adolescents (level of evidence 1+).

Conclusions



Counseling

- Girls and their families should be counseled regarding the possibility of abnormal pubertal progression, menstrual dysfunction and options for fertility preservation.
- Young women who are at risk of premature ovarian failure should be advised to not delay their childbearing, have assessment of ovarian reserve with referral for specialist fertility consultation as required.
- Pregnant survivors should be managed in a high-risk obstetric unit.





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