Late effects of childhood cancers

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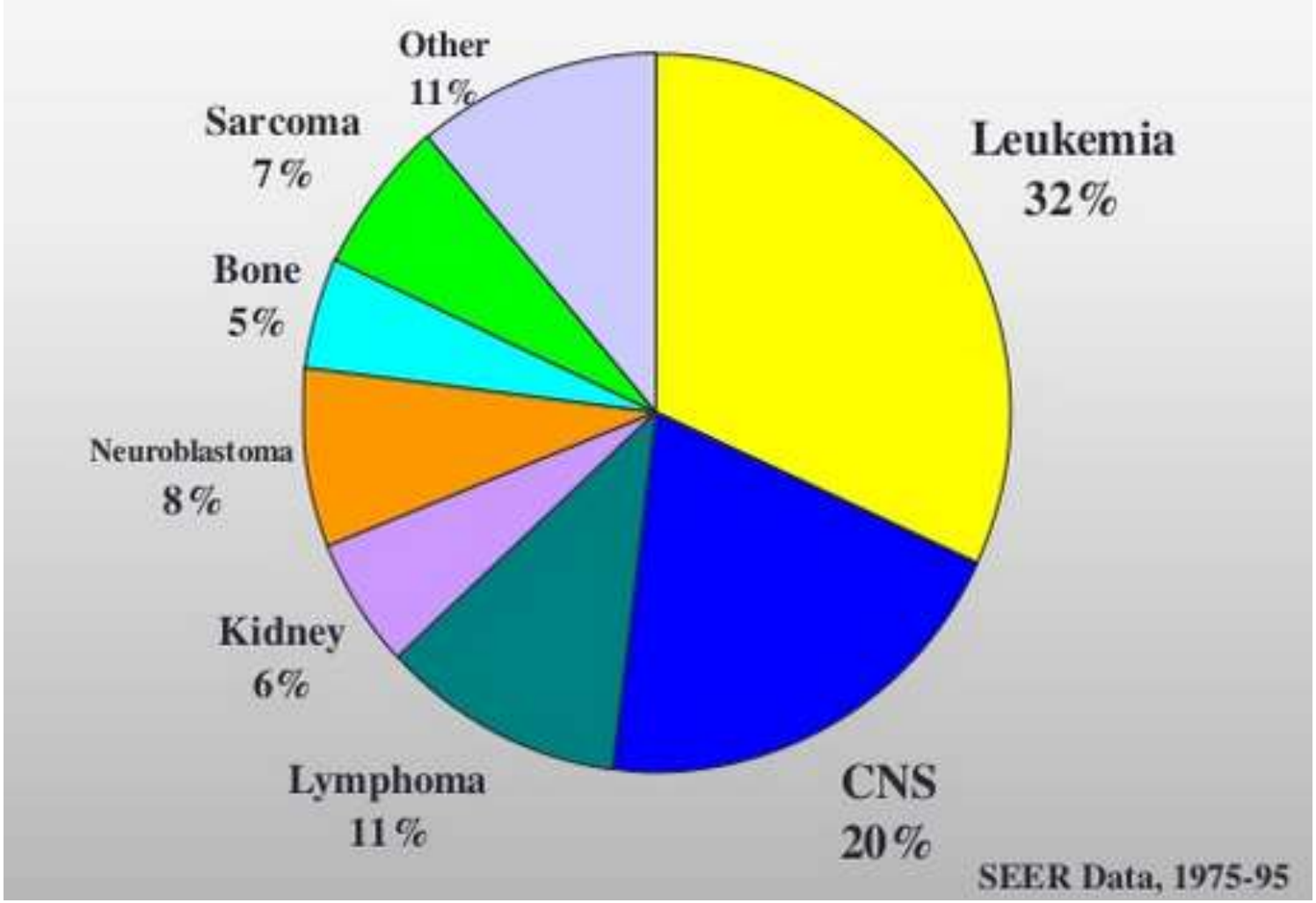
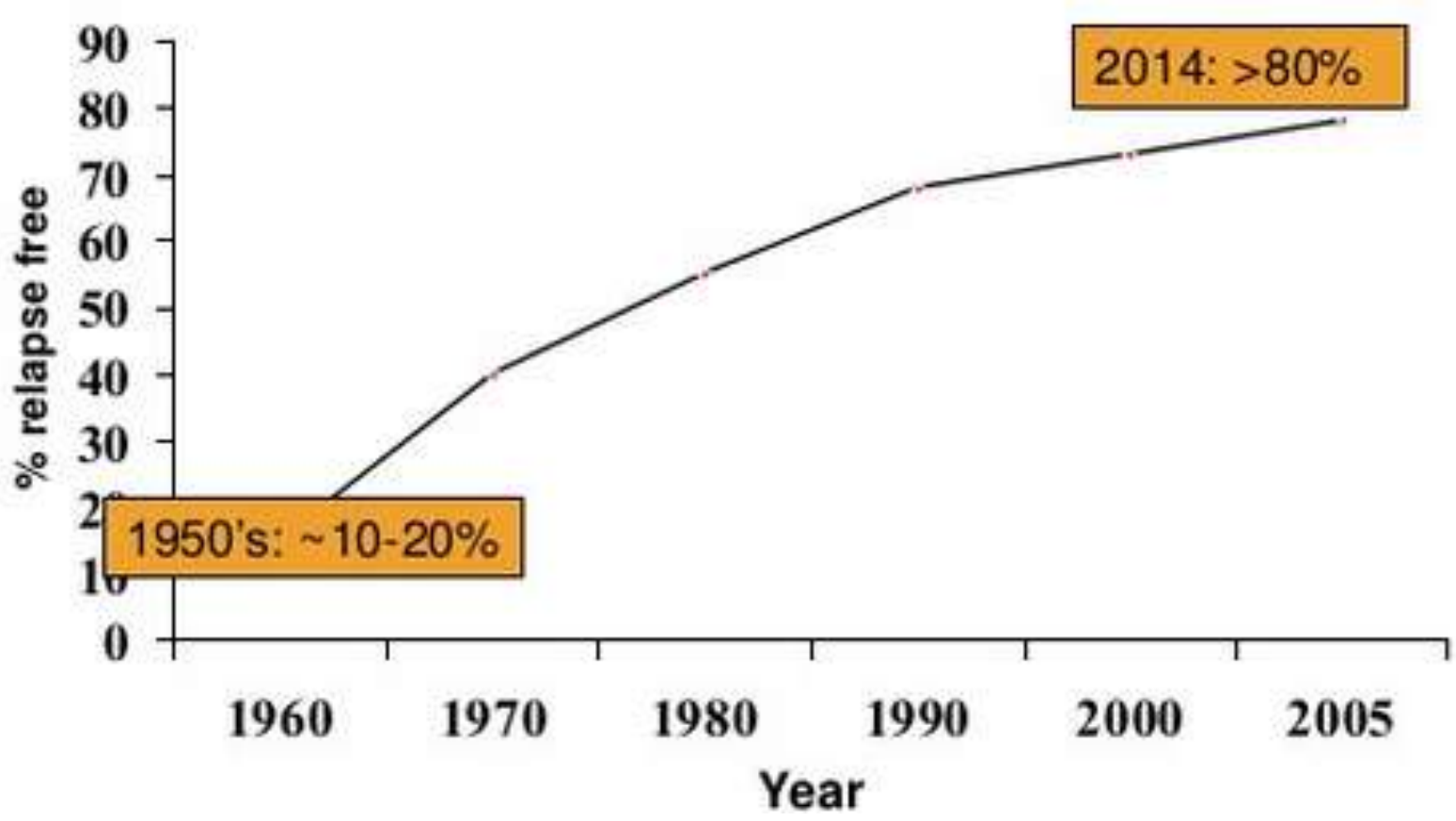
Incidence of childhood cancers

- 300,000 children develop cancer each year –WHO statistics

Distribution of childhood cancers – US statistics

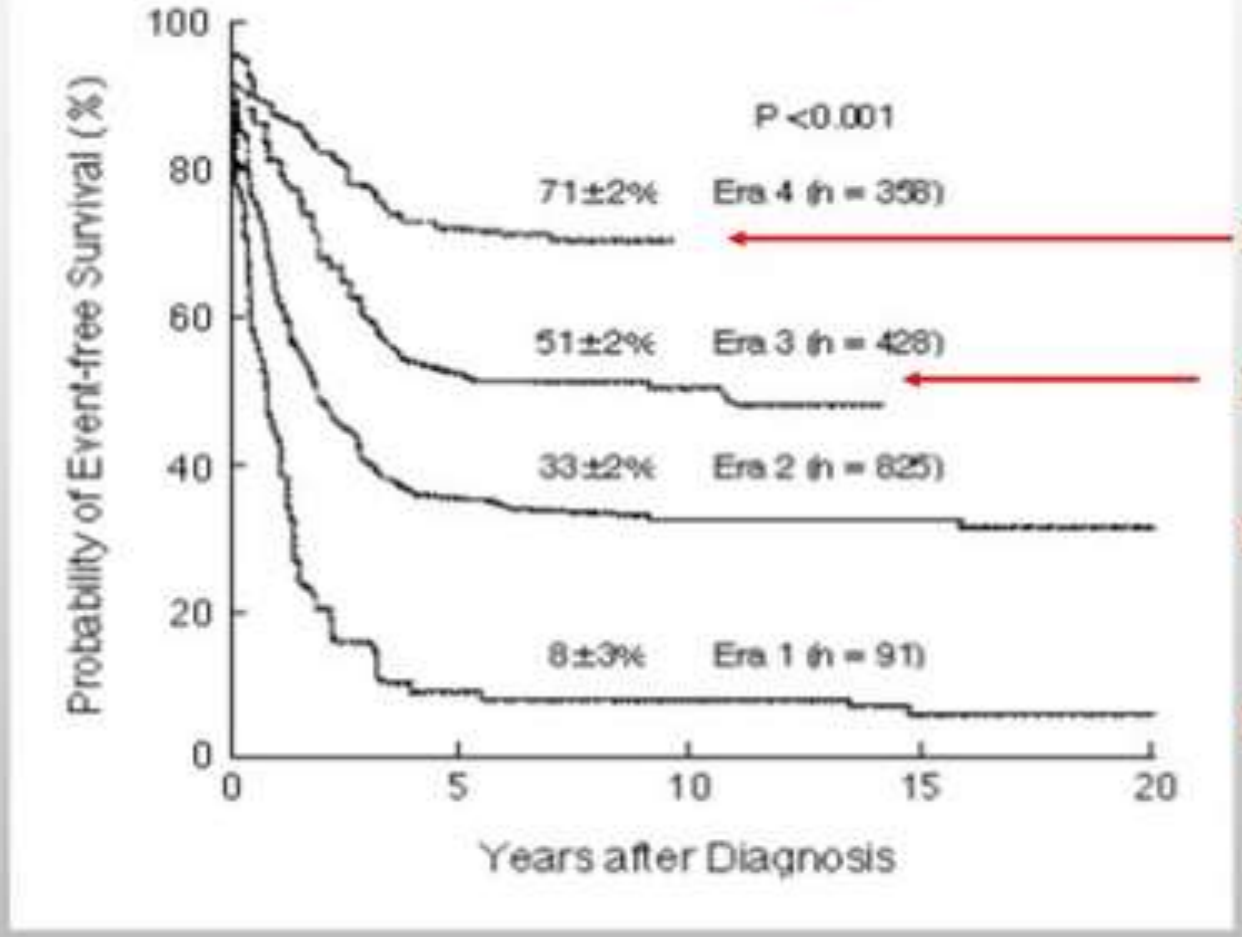


Improvement in Cancer survival



Childhood cancer survivors are living longer - more late effects manifest.

Impact of new chemotherapy in ALL



Pui, NEJM 1995; 332: 1618

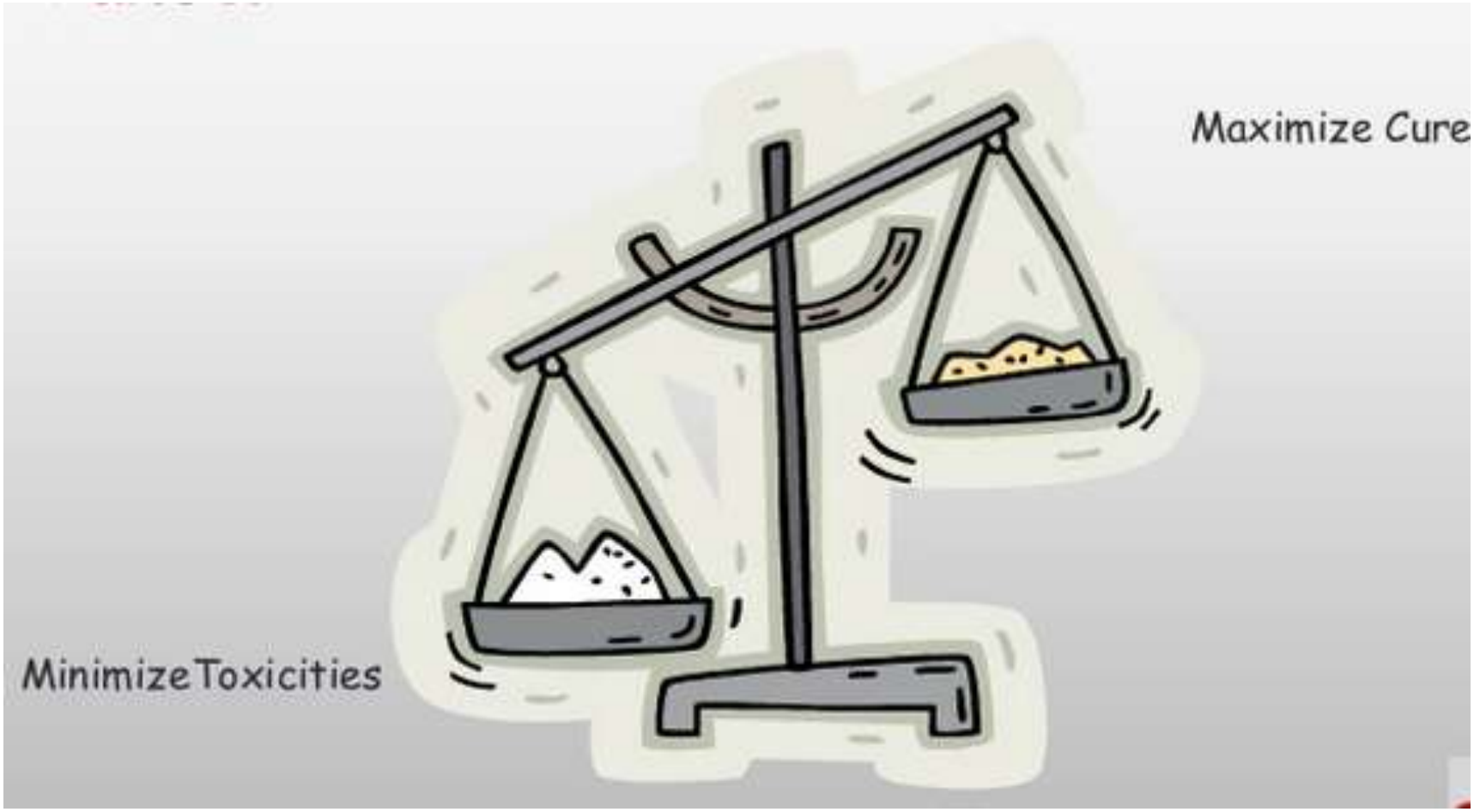
Background

- High income countries – 80% cured
- LMIC -20% cures
- Cure – early diagnosis, multimodal treatment

• Multimodal Cancer directed therapy is toxic
•Children – growing organs – vulnerable
•Preventable/ reduced severity

Oeffinger et al NEJM, 2006

Our current approach to childhood cancers



While most late effects are not life-threatening, they may cause serious problems that affect health and Quality of Life

Late effects – tumor related factors

- Type of cancer.
- Site
- Stage of tumor (adjacent organ involvement)
- Genetic and familial conditions

Late effects – treatment related factors

- Type of surgery.
- Chemotherapy type, dose and schedule
- Type of radiation therapy, part of the body treated, and dose.
- Stem cell transplant.
- Use of two or more types of treatment at the same time.
- Chronic graft versus host disease

Late effects - Patient related factors

- Gender
- Baseline Health
- The child's age at diagnosis.
- Length of time since diagnosis and treatment.
- Immune status and repair capacity

Treatment modality

- Surgery
- Radiotherapy
- Chemotherapy
- Bone marrow transplantation

Each modality has its own acute and late side effects.

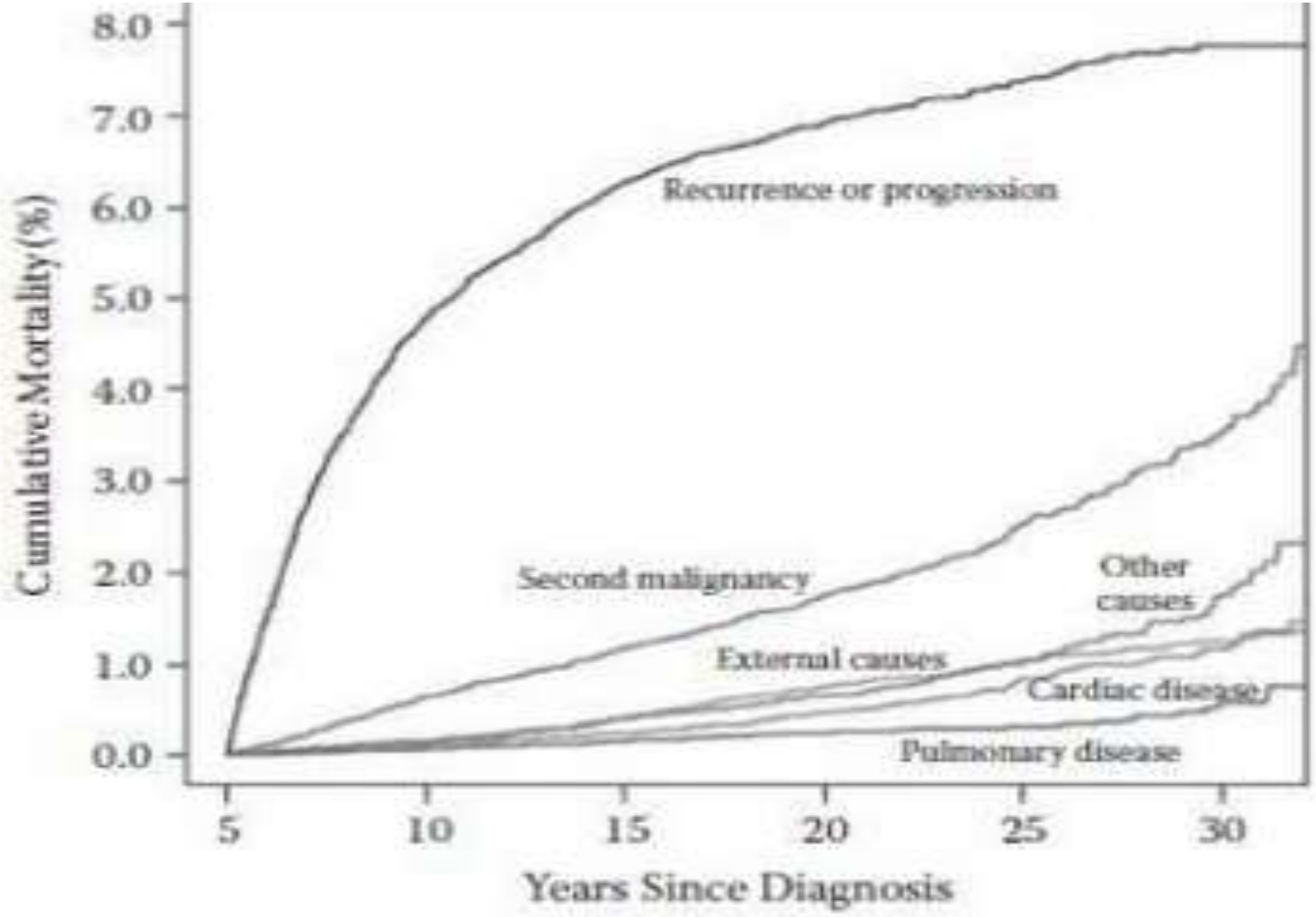
Peculiarities of childhood cancers - radiation

- Children have lower tolerance to radiation due to growing tissues and therefore likely to suffer more damage
- Relatively large target volumes compared the overall body volume
- Immobilization of young children is a major issue
- May require anaesthesia
- Additional dose limits

Dose limits children versus Adults

STRUCTURE	CHILD RT LIMITING DOSE	ADULT RT DOSE LIMIT
Brain	18 Gy	35 Gy
Bones	10 Gy	> 65 Gy
Pituitary (GH)	20 Gy	NA
Ovary / Testes	10 Gy	NA
Breast CA Induction at 40 Gy	RR = 20	RR = 2
Lung MLD	> 9 Gy	17 Gy
Lens (cataract)	> 12-15 Gy	>10-12 Gy
Thyroid	Below 20 Gy up to 14 yrs age	NA

Cumulative mortality of childhood cancers



Survivorship – Living beyond cancer

- 2-5 years off therapy and free of disease
- Long term/ late effects of illness for the child
- Long term effects of treatment
- What family (parents and sibling) experience - rehabilitation

Mullan's survivorship seasons

Acute | Extended | Permanent

Late effects

- Unrecognized toxicities that are absent or subclinical at the end of therapy – manifest later with unmasking of hitherto unseen injury
- Why does it manifest now?

•Development process
•Failure of compensatory mechanism
•Organ senescence

Long term side effects –persistence of effects that appear during therapy and continue there after

Late effects – effects that appear months and years after treatment

Types of late effects

System specific – organ damage or failure

Recurrent/ cancer assoc with primary

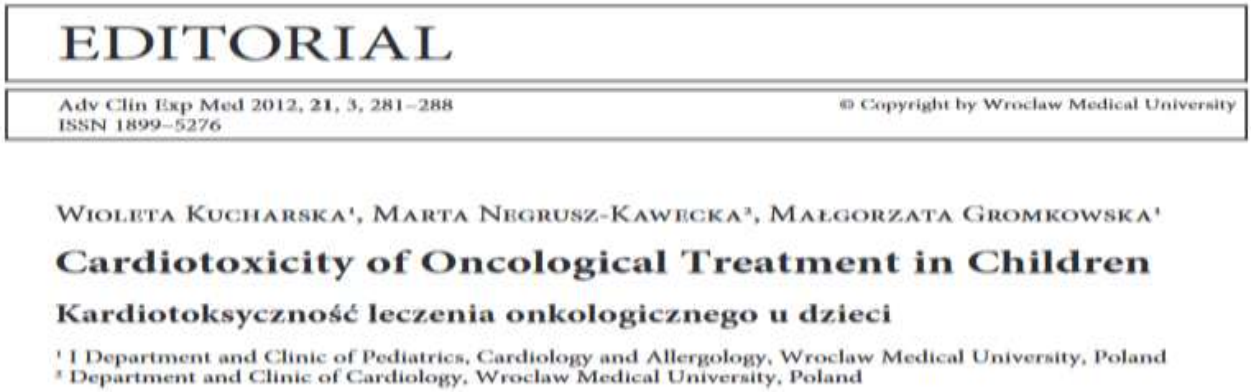
Second Malignant neoplasm

Cancer assoc with therapy

Functional changes

Cardiac late effects

Chemotherapy	Myocardial damage; CHF
Radiotherapy	Atherosclerosis, Valvular disease, Pericardiac effusions/ consrtictive disease



EDITORIAL

Adv Clin Exp Med 2012, 21, 3, 281–288
ISSN 1899–5276

Wioleta Kucharska[1], Marta Negrusz-Kawecka[2], Małgorzata Gromkowska[1]

Cardiotoxicity of Oncological Treatment in Children

Kardiotoksyczność leczenia onkologicznego u dzieci

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[2] Department and Clinic of Cardiology, Wroclaw Medical University, Poland

Anthracycline → Kill myocyte → ↓ Cardiac function
Arrhythmia
Heart failure

Dose dependence

Median time of onset – 7 years

Neuro cognitive late effects

Whole Brain

Intra-thecal Methotrexate

- High risk
- Higher dose
- Younger age <6yrs
- Females

Destruction of white matter

Reduced scholastic performance

Onset – several years → Progressive

Educational issues

Radiotherapy to brain & chemotherapy	Affect learning
Radiation treatment	Short term memory loss – decline in scholastic performance
Absence from school; avoidance of peers	Diminished performance

Psychogical issues

- 1/5th – Post traumatic stress disorders
- 1/4th – Depression/anxiety
- 1/3rd – Long term psychological issues; suicidal ideations

- Fear of recurrences
- Adjustment of late effects
- Financial issues
- Sexual issues
- QOL issues

Pulmonary late effects

Chemotherapy (Bleomycin)	Dose dependent Pulmonary scarring
Radiotherapy (Dose dependent)	

Combination (CT+RT) aggravates

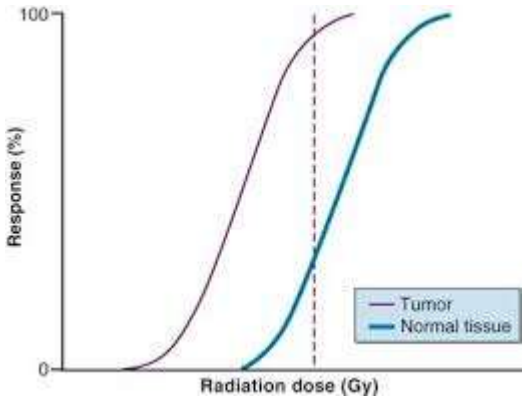
Infection, Intra-operative Oxygen, Age

Premature respiratory insufficiency

Onset 1to 7 years

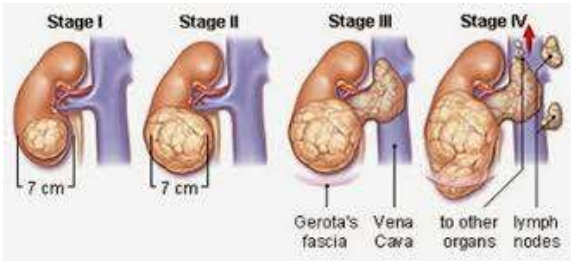
Growth and development

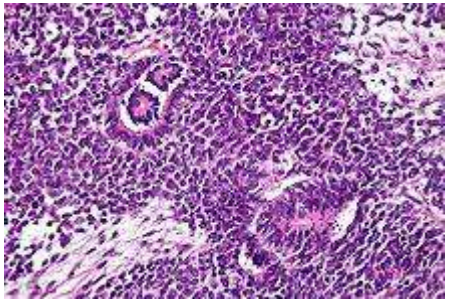
- Total dose, fraction size, volume treated and age of radiation treatment affect ultimate height
- Steep dose-effect relation ship for bone growth – between 15-30Gy
- Cranial irradiation – early puberty – reduce ultimate height

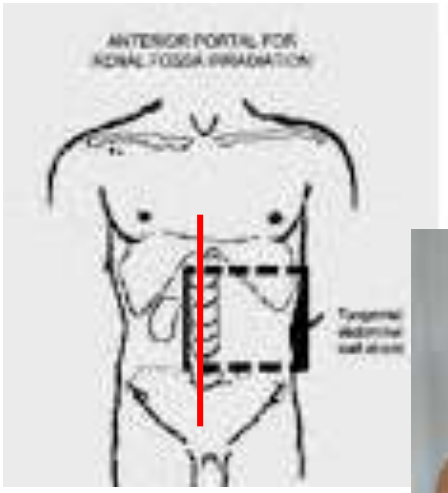


An example – Wilms Tumor

- Flank RT – 1080cGy/6fr – Stage III disease







Endocrine issues

Obesity – dose dependent effect of cranial irradiation
Hypothyroid
Osteoporosis
Growth hormone deficiency

Thyroid –
HNC, HD RT
40-90% cases at 20yrs in doses >15Gy

Cranial irradiation - early onset of puberty
Poor linear growth – short stature
10 -15% survivors – below 5th percentile

Urinary effects

Chemotherapy	Cisplatin, Ifosphamde, Methotrexate, NU
Radiotherapy (Flank)	Hypertension due to RT to the kidney

- Glomerular injury recovers
- Tubular injury persists –HT
- Radiation > 20Gy – tubular damage
  - shrunken bladder
- CT+RT dysfunction cutoff 10-15Gy

Fertility issues

Chemotherapy (Alkylating agents)	Reduced sperm production/ ovarian function
Radiotherapy (Abdominal RT)	Uterine shrinkage; Ovarian failure
Surgery (RPLND)	Retrograde ejacluation

- Delayed or impaired puberty
- Infertility
- Miscarriage
- Still birth
- Low birth weight babies

Gonadal failure or Infertility –
May be transient in males – dose dependent
Ovarian function recovery is poor

TABLE 6.1. Possible late effects of radiotherapy and chemotherapy.

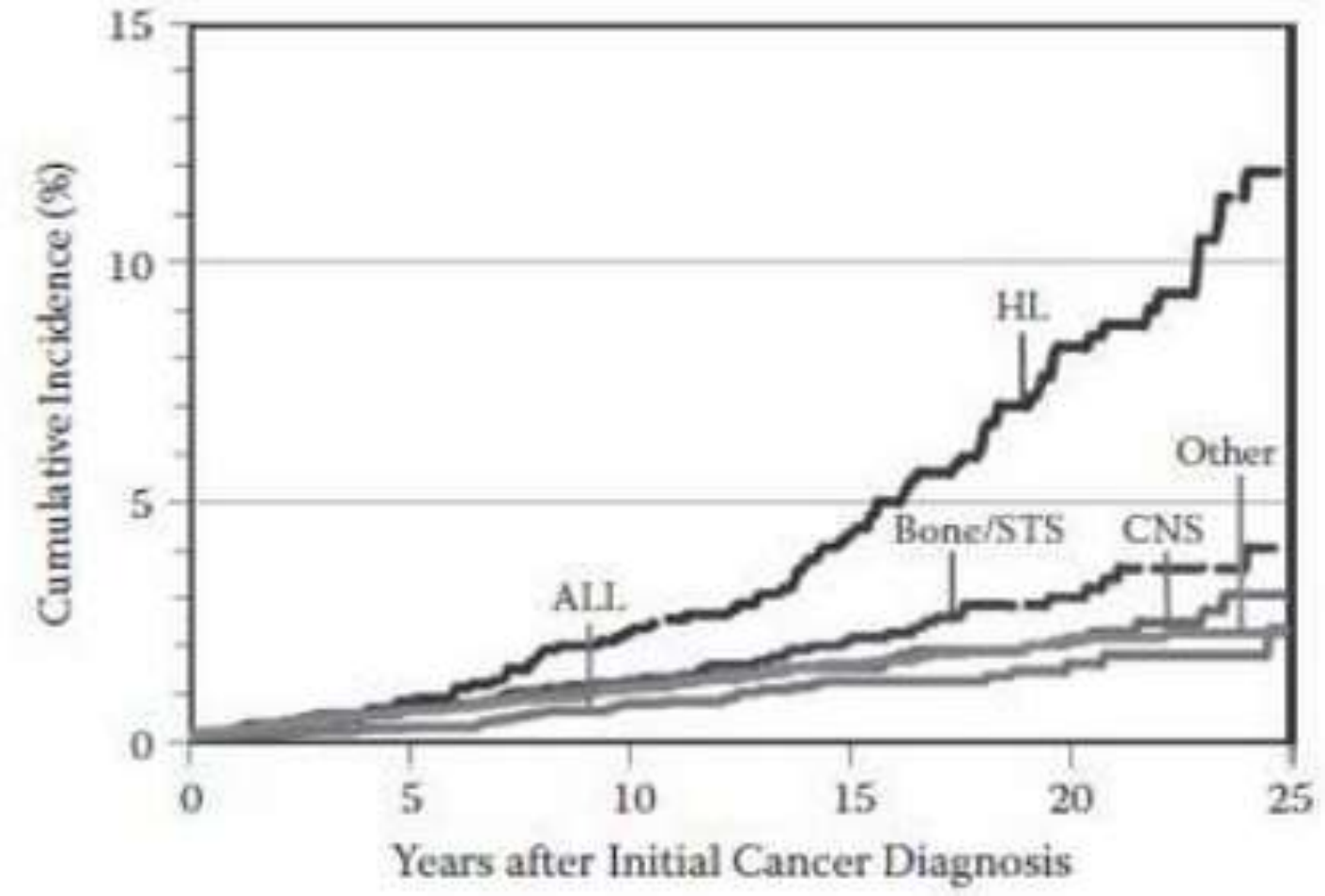
Organ system	*Late effects/sequelae of radiotherapy*	*Late effects/sequelae of chemotherapy*	*Chemotherapeutic drugs responsible*
Bone and soft tissues	Short stature; atrophy, fibrosis, osteonecrosis	Avascular necrosis	Steroids
Cardiovascular	Pericardial effusion; pericarditis; CAD	Cardiomyopathy; CHF	Anthracylines Cyclophosphamide
Pulmonary	Pulmonary fibrosis; decreased lung volumes	Pulmonary fibrosis; interstitial pneumonitis	Bleomycin, BCNU Methotrexate, adriamycin
Central nervous system (CNS)	Neuropsychologic deficits, structural changes, hemorrhage	Neuropsychologic deficits, structural changes Hemiplegia; seizure	Methotrexate
Peripheral nervous system		Peripheral neuropathy; hearing loss	Cisplatin, vinca alkaloids
Hematologic	Cytopenia, myelodysplasia	Myelodyplastic syndromes	Alkylating agents
Renal	Decreased creatinine clearance Hypertension	Decreased creatinine clearance Increased creatinine Renal filtration Delayed renal filtration	Cisplatin Methotrexate Nitrosoureas
Genitourinary	Bladder fibrosis, contractures	Bladder fibrosis; hemorrhagic cystitis	Cyclophosphamide
Gastrointestinal	Malabsorption; stricture; abnormal LFT	Abnormal LFT; hepatic fibrosis; cirrhosis	Methotrexate, BCNU
Pituitary	Growth hormone deficiency; pituitary deficiency		
Thyroid	Hypothyroidism; nodules		
Gonadal	Men: risk of sterility, Leydig cell dysfunction. Women: ovarian failure, early menopause	Men: sterility Women: sterility, premature menopause	Alkylating agents Procarbazine
Dental/oral health	Poor enamel and root formation; dry mouth		
Opthalmologic	Cataracts; retinopathy	Cataracts	Steroids

Second malignancy

- Chemotherapy (Alkylating agents; Epipodophyllotoxins)
- Radiotherapy
- Combination increases the risk further
- Genetic predisposition – HNPCC gene etc
- IMRT increases integral dose – Higher risk of SM

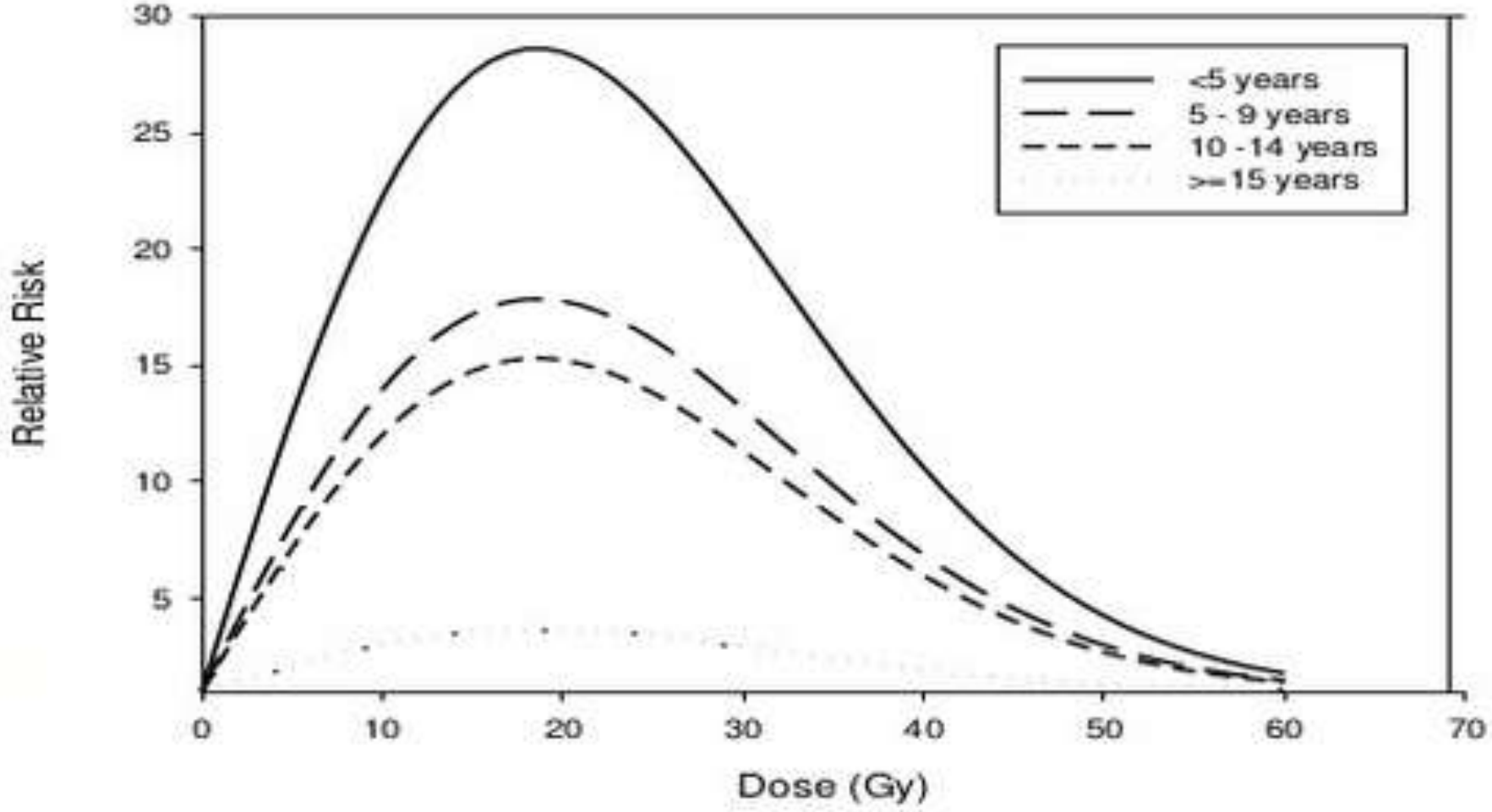
- Skin cancers, Bone and ST tumors - common
- Secondary leukemias, Colon cancers, Breast cancers – less common
- Average latency report – 15years
- Increases with time

Cumulative incidence of developing SM with selected cancers



8-10% risk of developing SMN within 20yrs of primary diagnosis

Relative risk of Thyroid cancer by age & Radiation dose



Late recurrence

- A reality - different for different tumor types
- Fear lurks!
- 4.4% at 10yrs
- 5.6% at 15 yrs
- 6.2% at 20 yrs

Childhood cancer survivor study report. Wasilewski et al JNCI2009

How to limit late effects

- Delay or omit Radiotherapy till the child is older
- Decrease Radiotherapy doses if possible
- Decrease volume of Radiotherapy portals

Incorporate chemotherapy

Alteration of Radiotherapy fractionation
Use of novel techniques

Grading of late toxicity

- To systematically monitor the development/ progression of late effects
- Impede development of toxicity related interventions
- Comparison between Institutions/ across clinical trials

NCI Common toxicity criteria
- Both acute and late effects
- Effects due to multimodal therapy
- Duration of an effect

Need follow up

Why follow up?

- Timely diagnosis of long term complications of cancer treatment
- Institute preventive strategies
- Screening and early detection of second malignancy
- Detection of Functional/Physical/ Psychological disability

How and what-follow up

- Regular physical examination and screening
- Physical growth
- Neurocognitive development
- Hormonal imbalance - puberty

VOLUME 34 · NUMBER 27 · SEPTEMBER 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

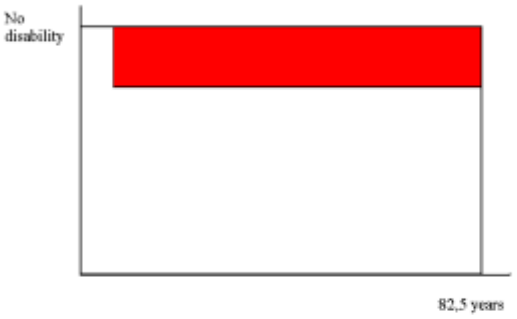
EDITORIAL

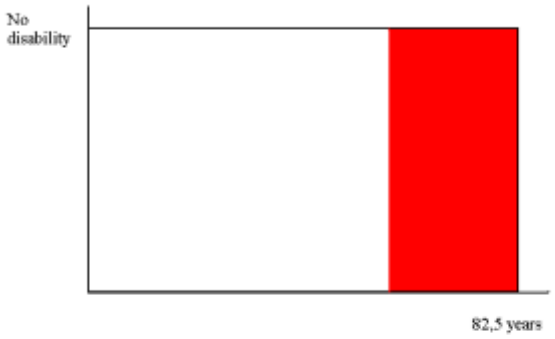
When Do Late Effects in Childhood Cancer Survivors Cease Emerging? The Endocrine Answer

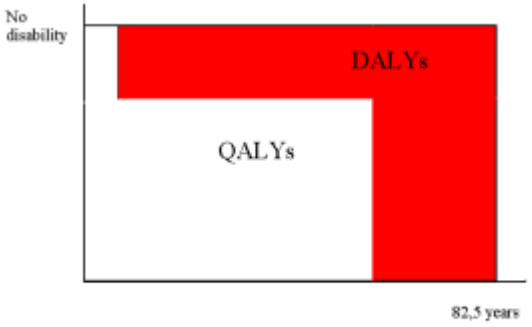
Mark L. Greenberg, *The Hospital for Sick Children, The University of Toronto; and Pediatric Oncology Group of Ontario, Toronto, Ontario, Canada*

DALY - Disability adjusted life years

- Common measurement unit for morbidity and mortality
- Comparisons of health outcomes
- Burden and Cost effectiveness
- Selection of intervention
- QOL reduced due to disability (QALY – Quality adjusted life years) OR
- Lifetime lost due to premature mortality







Out look of survivor children

- Greater appreciation of life
- Lesser degree of aggression, antisocial behavior, substance abuse

Cure is not enough

Dr. Giulo D'Angio

- Aronyatesh Ganguly, cancer survivor won a gold medal

8-year-old cancer survivor bags gold in Moscow

Sumati Yengkhom | TNN | Updated: Jul 15, 2019, 17:38 IST

A- A+

Summary

- Late effects are price that we pay to cure cancer
- Late effects are not “One size fits all”
- Today’s treatment strategies/ techniques look into the probability of late effects and how to decrease them

Thank you