
INDIAN COLLEGE OF RADIATION ONCOLOGY (ICRO)
PG TRAINING PROGRAMME
18TH & 19TH JULY 2015, HYDERABAD

# IRRADIATION IN PAEDIATRIC PATIENTS:

# LATE SEQUELAE AND RISK OF SECOND MALIGNANCIES

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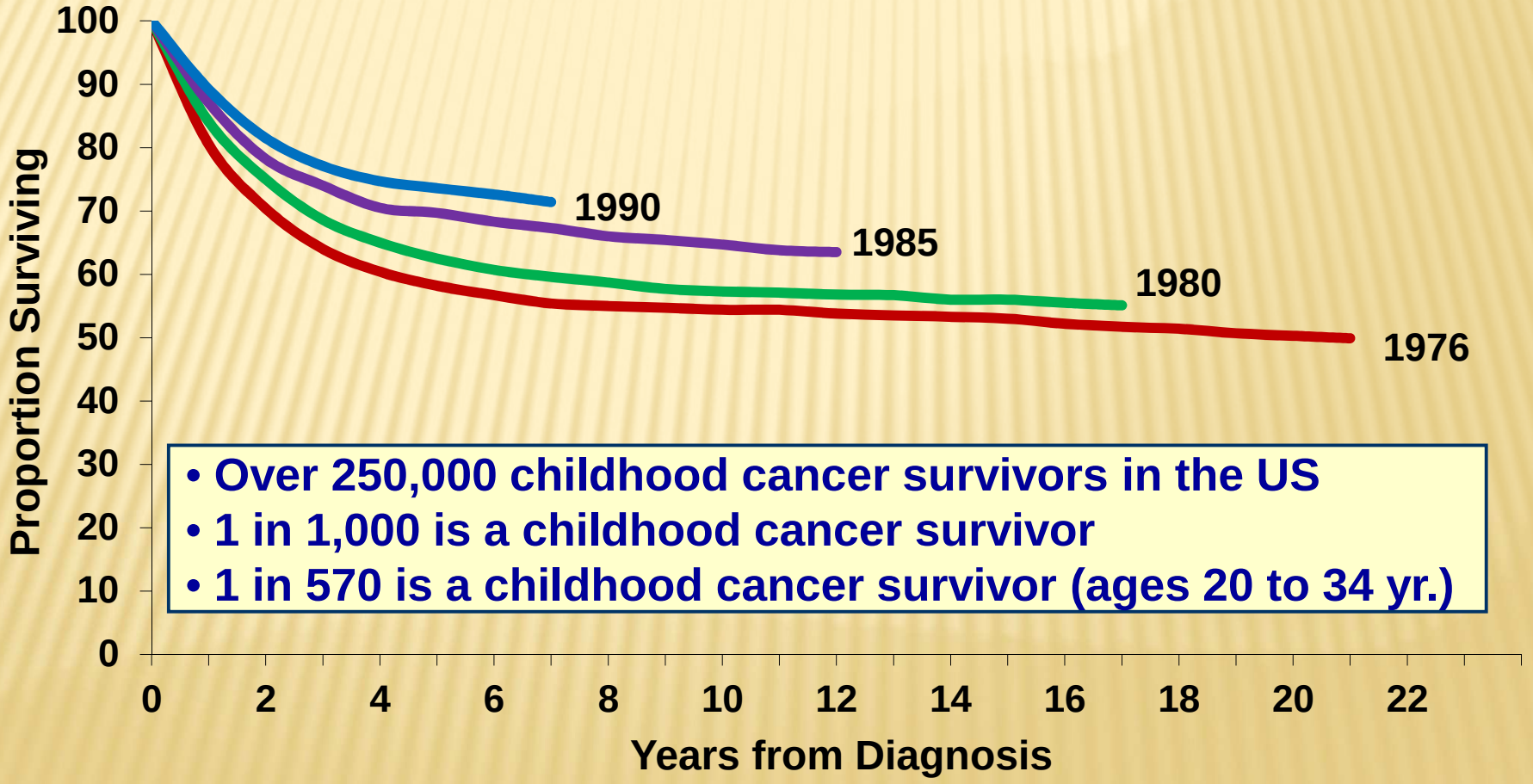
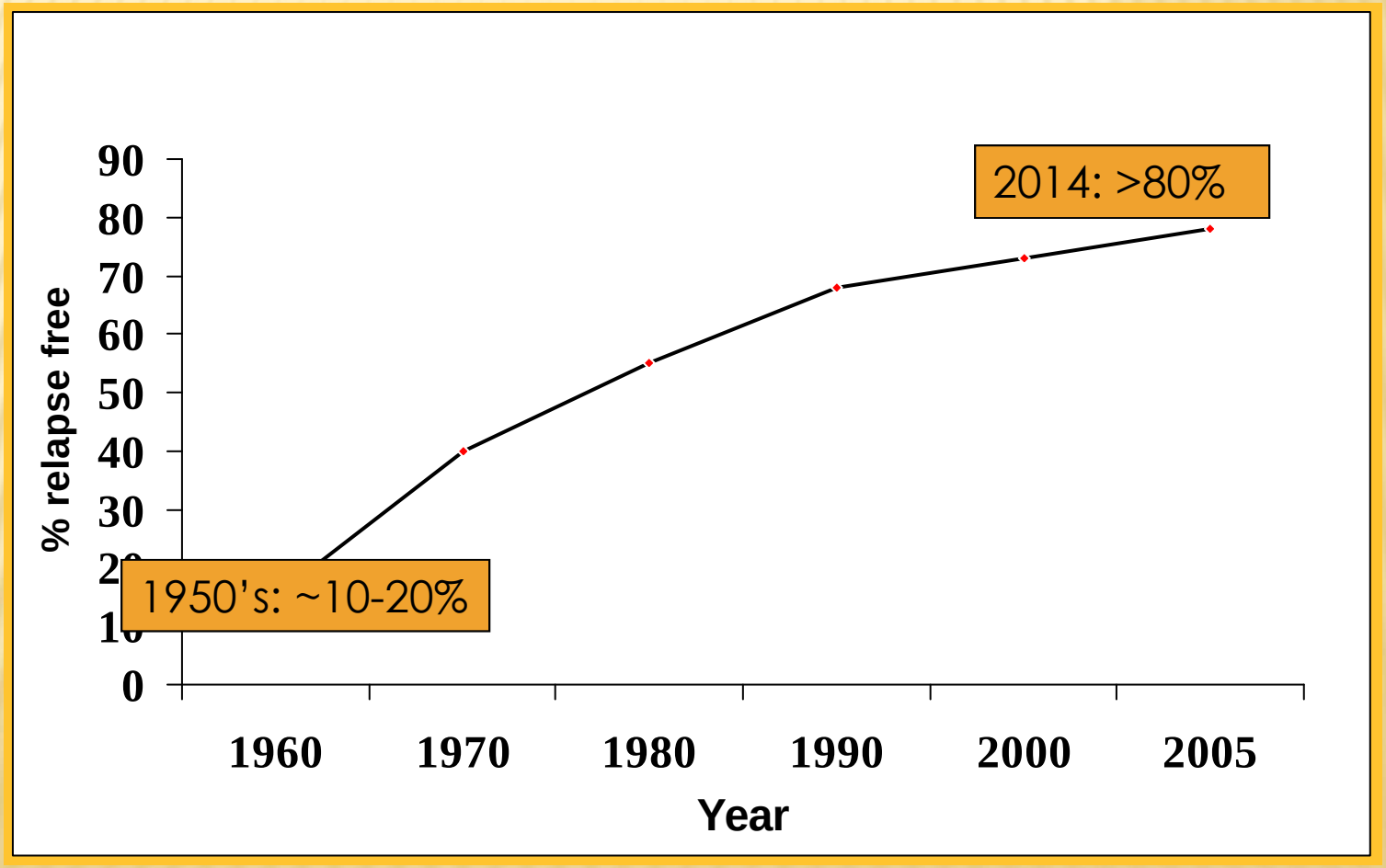
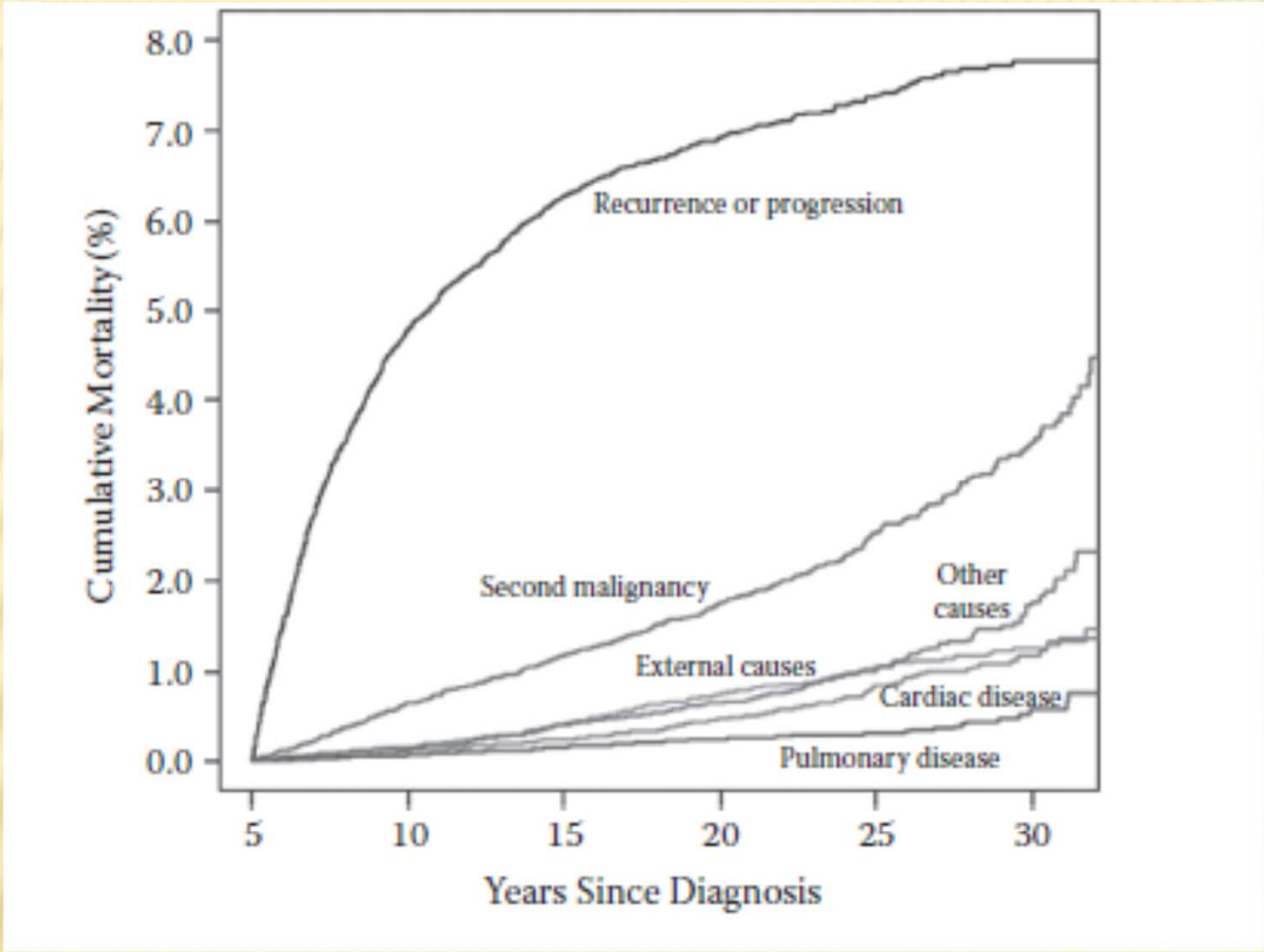
# CANCER SURVIVAL, 0-14 YEARS OF AGE
# SEER PROGRAM 1976-1997




- Over 250,000 childhood cancer survivors in the US
- 1 in 1,000 is a childhood cancer survivor
- 1 in 570 is a childhood cancer survivor (ages 20 to 34 yr.)

# IMPROVEMENT IN CANCER SURVIVAL

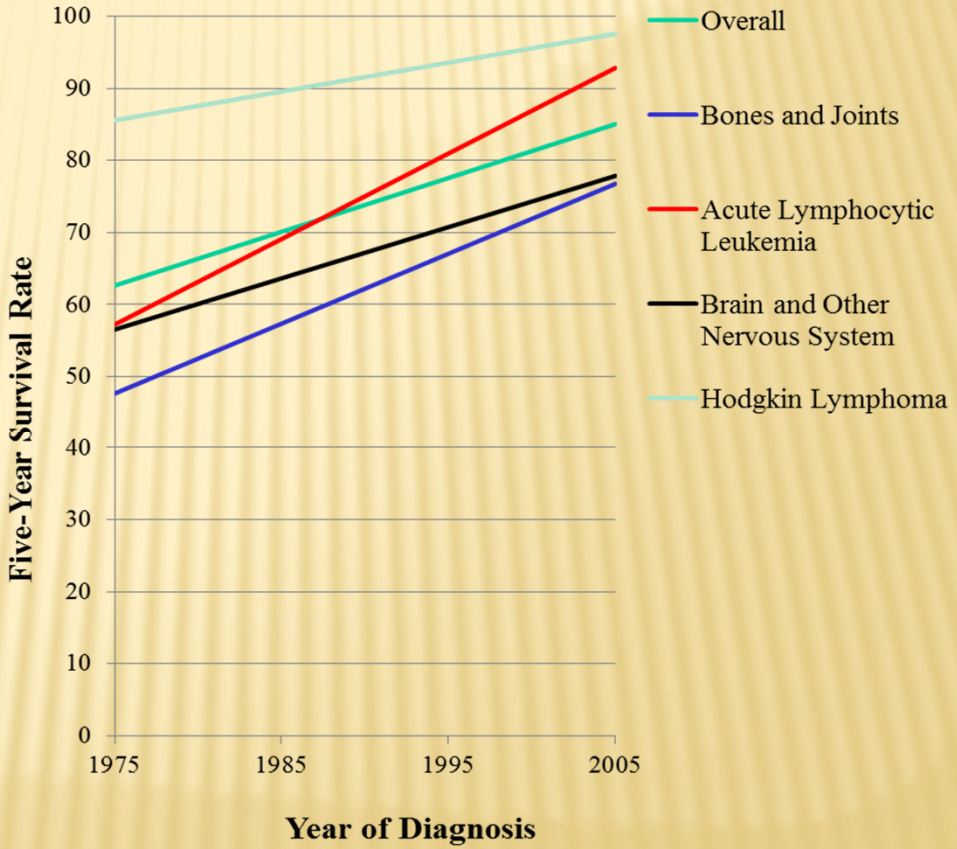





Cumulative mortality of pediatric cancer patients [Mertens et al., Journal National Cancer Institute 100 (19):1368–79, 2008]

# THE FACTS ON CHILDHOOD CANCER SURVIVORSHIP

- 1 /10 Cancer Survivors < 40 yo
- 379,112 Childhood Cancer Survivors are Living in the US Currently
- 1 of Every 539 Young Adults (Ages 20-39) is a Childhood Cancer Survivor

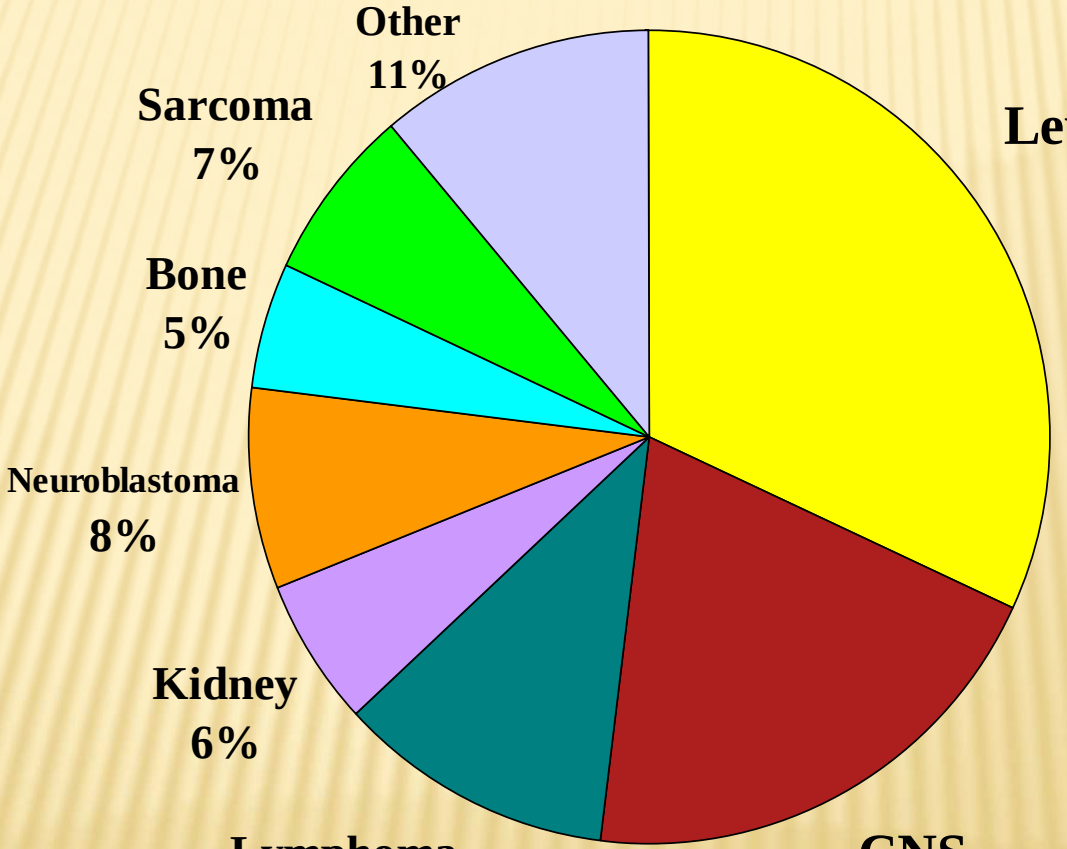



The American Cancer Society's publication, Cancer Facts & Figures 2014.

# IMPROVEMENT IN SURVIVAL IN CHILDHOOD CANCERS IN INDIA (1970s – 2000s)

- ALL : 20% → 60%
- Hodgkin's disease: <70% → >90%
- Non-Hodgkin's lymphoma (NHL): 30% → 70%
- AML: 10% → 40%

# DISTRIBUTION OF CHILDHOOD CANCER IN THE US




SEER Data, 1975-95

# OUR CURRENT APPROACH TO CHILDHOOD CANCER

Maximize Cure

MinimizeToxicities

# ISSUES IN PAEDIATRIC RT DELIVERY

- Children have a lower tolerance to radiation due to growing tissues and therefore likely to suffer more damage.
- Relatively large target volumes compared to the overall body volume.
- Immobilization of young children is a major issue.
- Children below 4-5 years of age may require anaesthesia.
- Presence of additional dose limiting normal tissues compared to adult patients such as growing bones, pituitary, thyroid, heart , lungs,

# ISSUES IN PAEDIATRIC RT DELIVERY

- Risk of producing a radiation-induced second malignancy (SM).
- Modern conformal treatments like IMRT or VMAT may result in a large volume of the treated region receiving unequal small doses of radiation and may result in asymmetric organ growth resulting in bad cosmesis.

# GOOD PRACTICES IN PAEDIATRIC RT DELIVERY

- Immobilization cast preparation and simulation in a child friendly environment with distraction aids
- Treated daily on the same machine so that he / she is familiar with the treating personnel
- Two way communication device during simulation and treatment delivery so that the child does not feel isolated
- Daily set-up verification of portals prior to delivery

# GOOD PRACTICES IN PAEDIATRIC RT DELIVERY

- Target volume definition using defined protocols and using image fusion of diagnostic CT, MRI and PET images.
- Dose prescription should be individualized .
- Delivering dose with fewer non-coplanar beams could be better.
- Growth and development to be continuously monitored
- Sedation required to maintain immobilization. Better idea to use short acting agents such as propofol .

| 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 |

# CRITICAL STRUCTURE RT DOSES IN ADULTS VS CHILDREN

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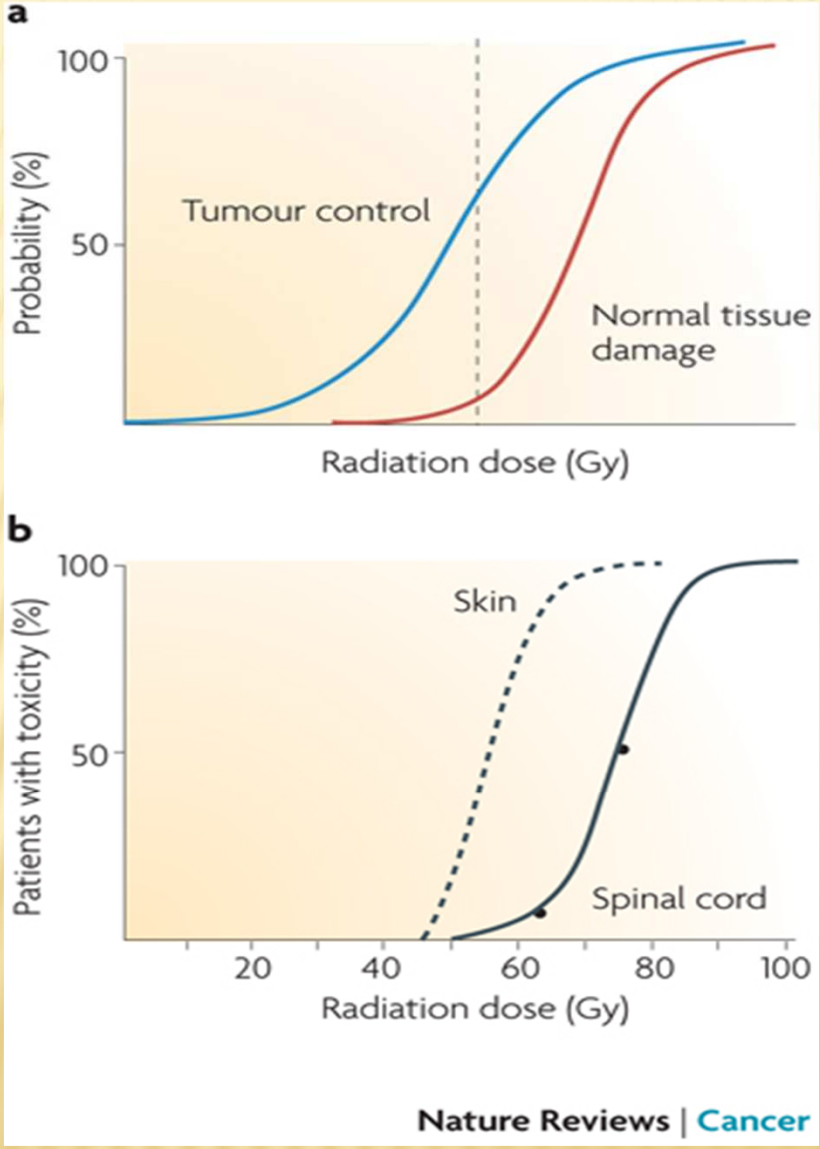
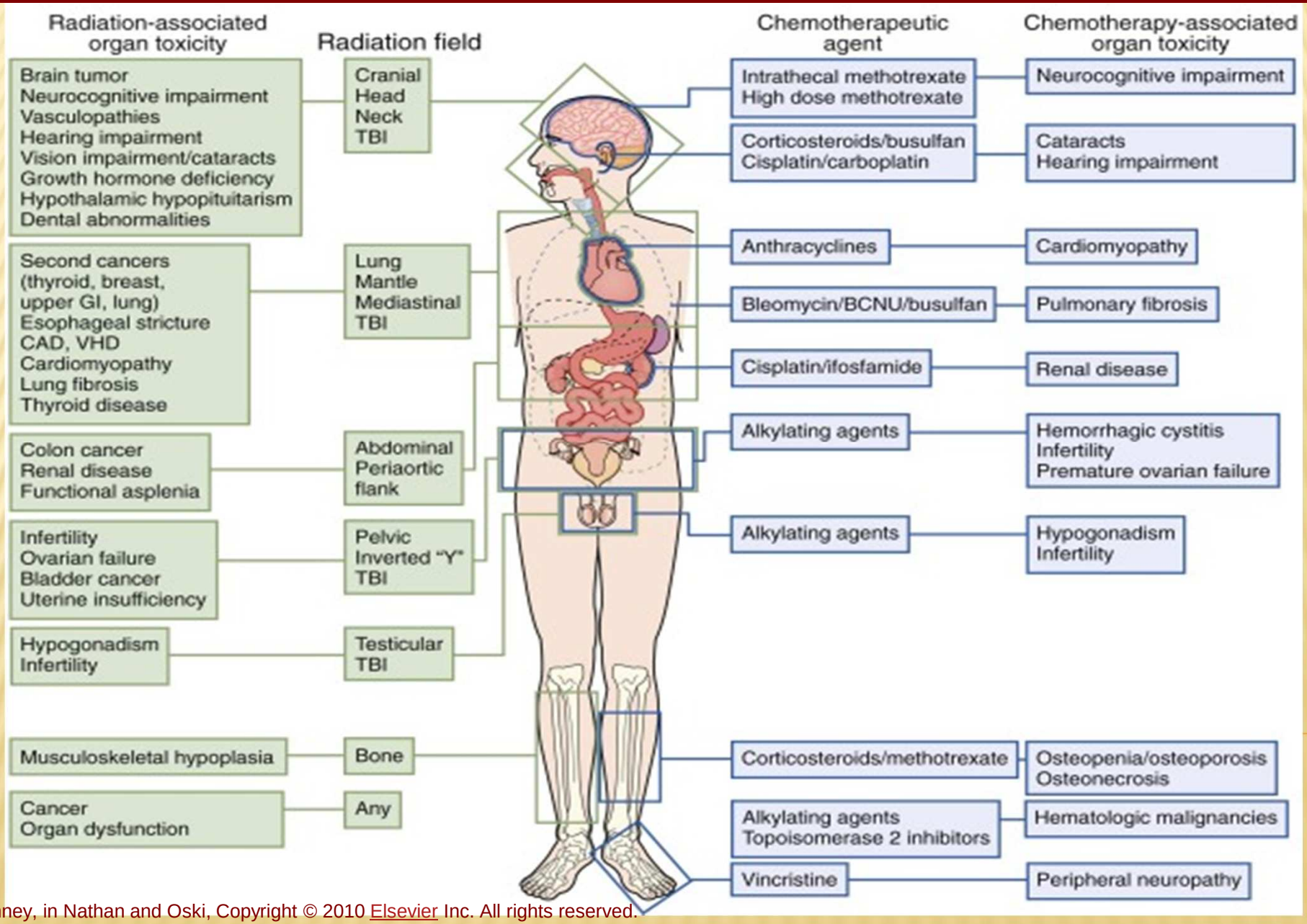


# Treatment Associated Late Effects

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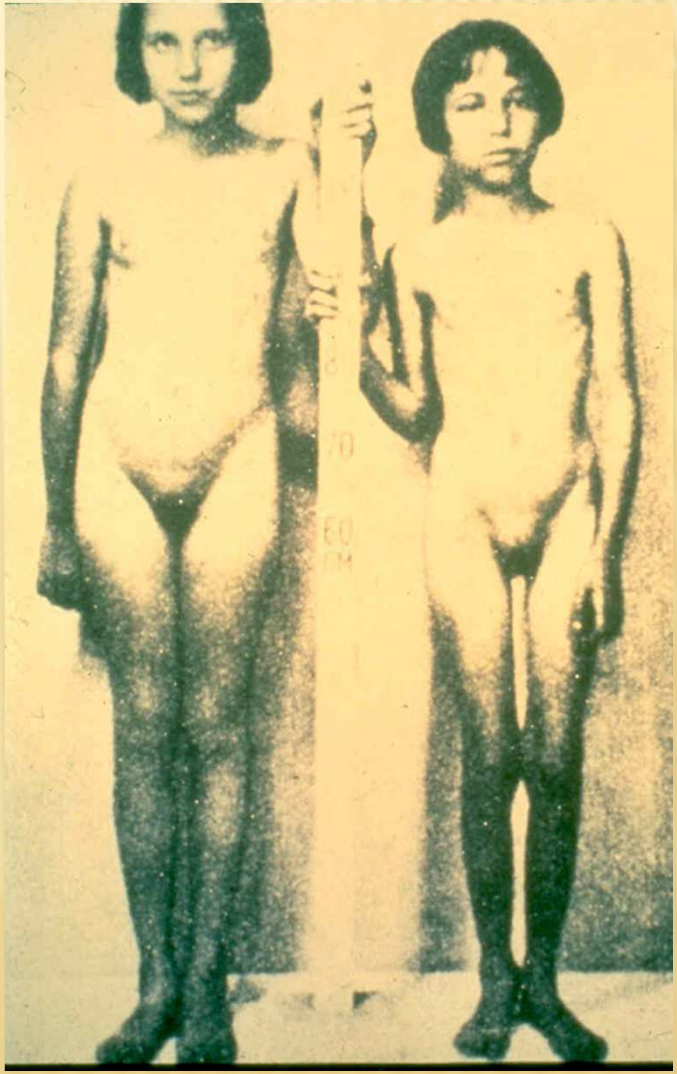
# LATE COMPLICATIONS OF CHILDHOOD CANCER THERAPY

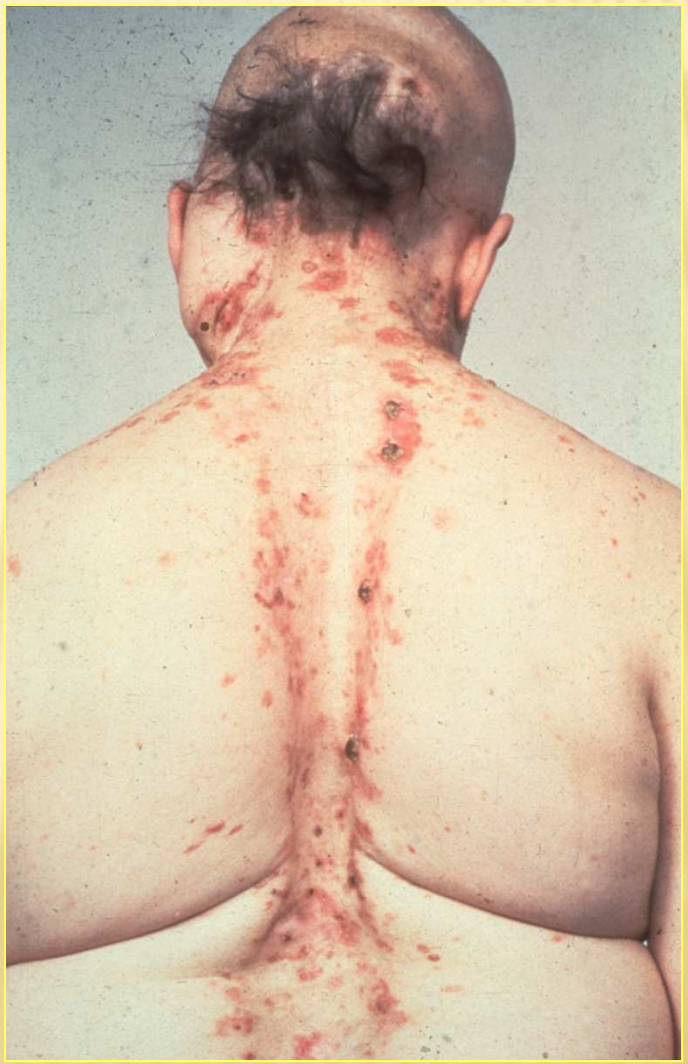
- Growth and Development
  - linear growth
  - intellectual function
  - sexual maturation
- Reproduction
  - fertility
  - health of offspring
- Vital Organ Function
  - cardiac
  - pulmonary
  - renal
  - gastrointestinal
- Second Neoplasms
  - benign
  - malignant
- Psychosocial adjustment

## THE FRANKLIN TWINS

Fig. 1. The Franklin Twins: This is a graphic demonstra



# GORLIN SYNDROME
## Radiation for Medulloblastoma



# GROWTH AND DEVELOPMENT

## Linear Growth

- Dose and age of radiation affect ultimate height attained
- Steep dose–effect relationship for bone growth effects between about 15 and 30 Gy.
- Early onset of puberty is common after cranial radiation, further reducing ultimate height and is dependent inversely with age as well as body mass index
- Age at time of treatment, total dose of radiation, fraction size, and volume treated are all significant predictors of ultimate attained height; as well as effect on the hypothalamic – pituitary axis.

# GROWTH AND DEVELOPMENT

## Hypoplasia (tissue growth)

- Radiation therapy for childhood cancers interferes with physical growth, neurocognitive growth, musculoskeletal growth and, ultimately, pubertal development.
- The effect is direct with resultant growth impairment (termed as hypoplasia) causing cosmetic defects.
- Asymmetric Irradiation fields can cause differential growth of the irradiated part leading to anatomical or functional defects such as scoliosis or organ hypoplasia which may not be immediately apparent but become visible during the child's growth spurt.

# GROWTH AND DEVELOPMENT

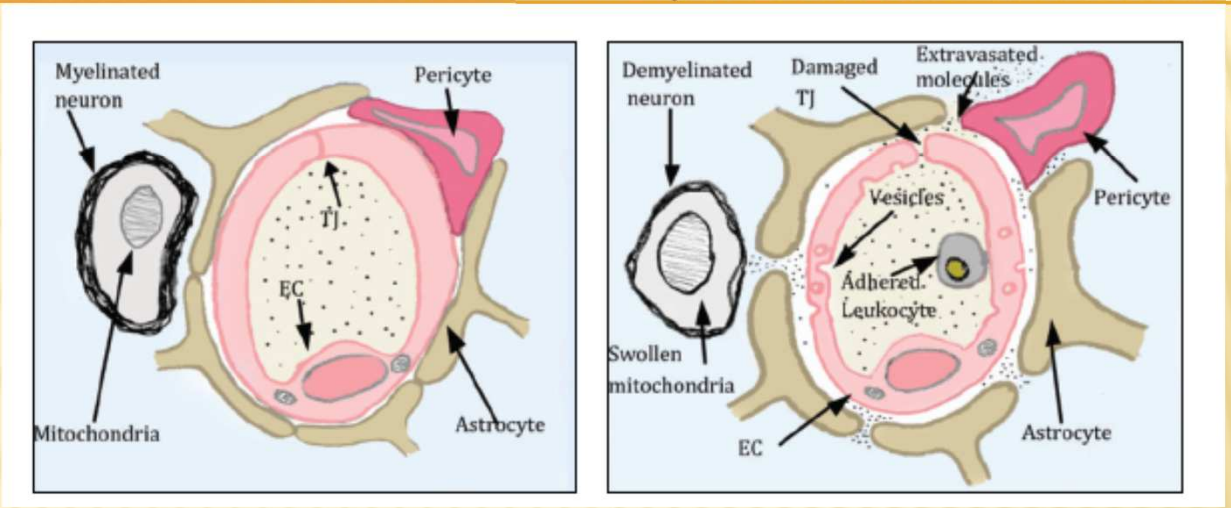
## Hypoplasia (tissue growth)

- Breast asymmetry occurs after unilateral chest radiotherapy prior to maturity.
- It has been seen that at doses beyond 20 Gy there is lack of breast development while hypoplasia occurs after exposure to doses of 10-20 Gy
- Adipose tissue is very sensitive to irradiation and fat distribution may reflect irradiation fields and may cause unequal growth.

# GROWTH AND DEVELOPMENT

## Intellectual function

- Difficulties in reading, language, and arithmetic may arise from impairment of attention capabilities, memory, and visual perceptual motor skills.
- Children receiving higher doses (>36 Gy) for the treatment of brain tumors have significant deficits which if deferred until after age two, cognitive defects may not be as profound.
- Sparing of the hippocampi by limiting dose of radiation to atleast 40-50% of the organ to less than 7.3 Gy and ensuring a limitation of the Dmax to less than 12-15 Gy associated with memory and sensory processing sparing.




- Radiation induced
  - dose related
  - age related
- Chemotherapy induced
  - Methotrexate
  - Intrathecal therapy:
    - Triples > single agent
- Surgical resection

## NEUROCOGNITIVE LATE EFFECTS

# PREVENTION OF COGNITIVE DYSFUNCTION

- Eliminate or reduce cranial irradiation
- Substitute chemotherapy with CNS penetration
- Avoid parenteral methotrexate after radiation
- Monitor educational performance
- Provide early intervention

# GROWTH AND DEVELOPMENT

## Sexual maturation

- Sertoli cells are more sensitive than Leydig cells to radiation and young boys without Leydig cell damage can have normal masculinization even in the face of azoospermia. Such sterile males can usually be assured of potency and normal libido.

- Cranial radiation of girls can also result in secondary gonadal insufficiency by impairment in LH/FSH production and secretion. These children may experience both pubertal delay and amenorrhea. Hormone therapy may be needed to initiate and maintain feminization.

# GONADAL FAILURE

- Males and females are different; Fertility and hormone production are not synchronous in males, unlike females
- Radiation and alkylating agent chemotherapy (cyclophosphamide, ifosfamide, cisplatin, procarbazine, nitrosoureas, mustard) are responsible; doses are critical.
- Ovarian function after radiotherapy stops causing infertility which may be irreversible. The testis is more sensitive with very low doses (2-3 Gy) of radiotherapy causing azoospermia in all males, but late recovery after several years' can happen.

# PREVENTION OF GONADAL TOXICITY

- Eliminate or reduce radiation to the gonads
- Design gender-specific protocols
- For males, avoid or reduce total dose of alkylating agents.
- Oophoropexy is commonly performed to prevent infertility so that ovaries are displaced from the radiation field.
- Hyperprolactinemia is caused by hypothalamic-pituitary (HPA) irradiation; may impair fertility, growth and libido. Treated with bromocriptine and other dopamine agonists.

# CARDIAC LATE EFFECTS

- Anthracyclines
  - Gender
  - Age
  - Dose
  - Latency
- Radiation
  - > 25 - 30 Gy
  - mean left ventricular dose ≥17 Gy : LVEF ↓
  - mean central cardiac dose ≥37 Gy: LVEF ↓

The critical target: endothelial lining of blood vessels

- Cardiomyopathy
- Ventricular dysfunction
- Pericarditis
- Rhythm abnormalities
- Pericardial damage
- CAD

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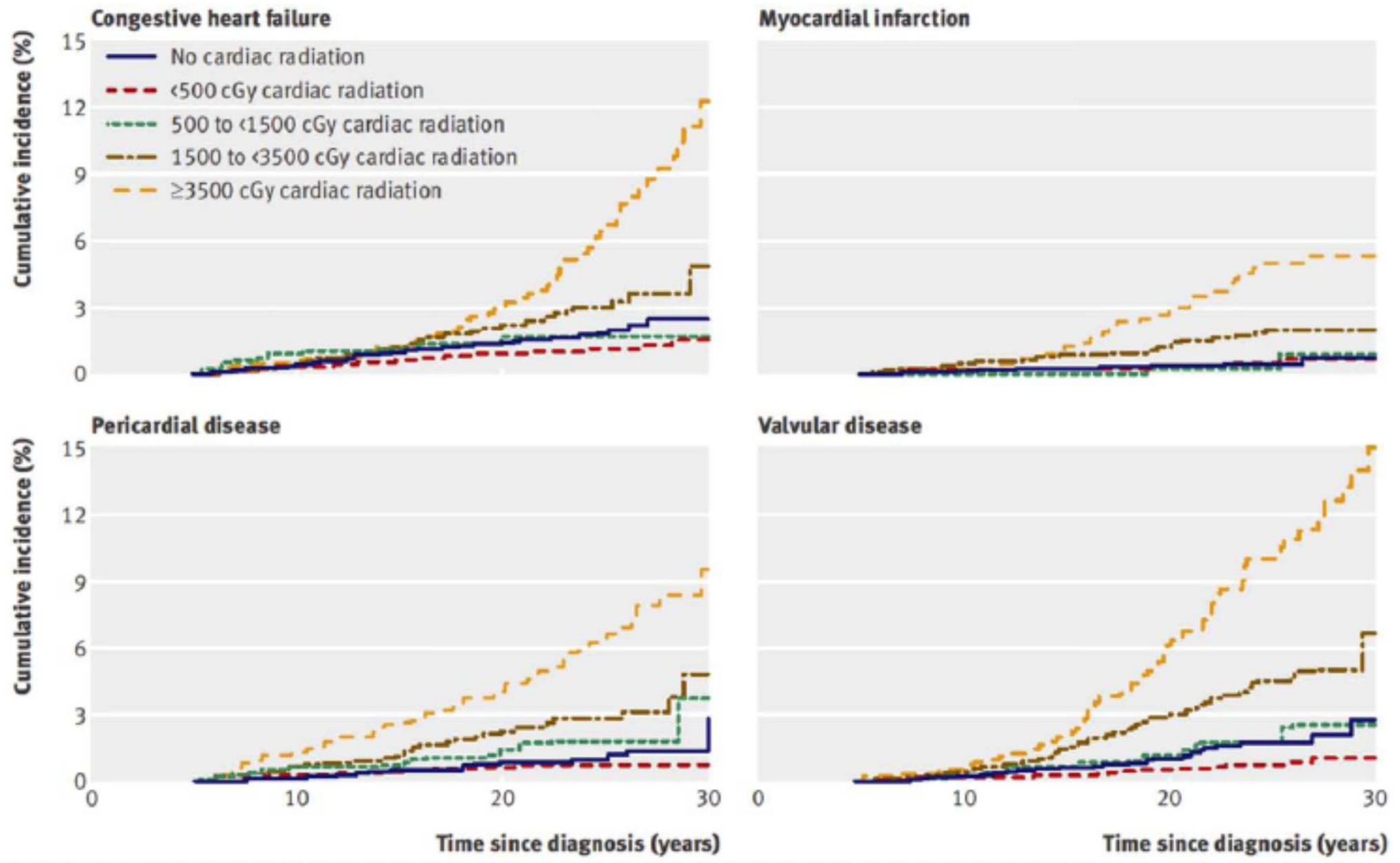

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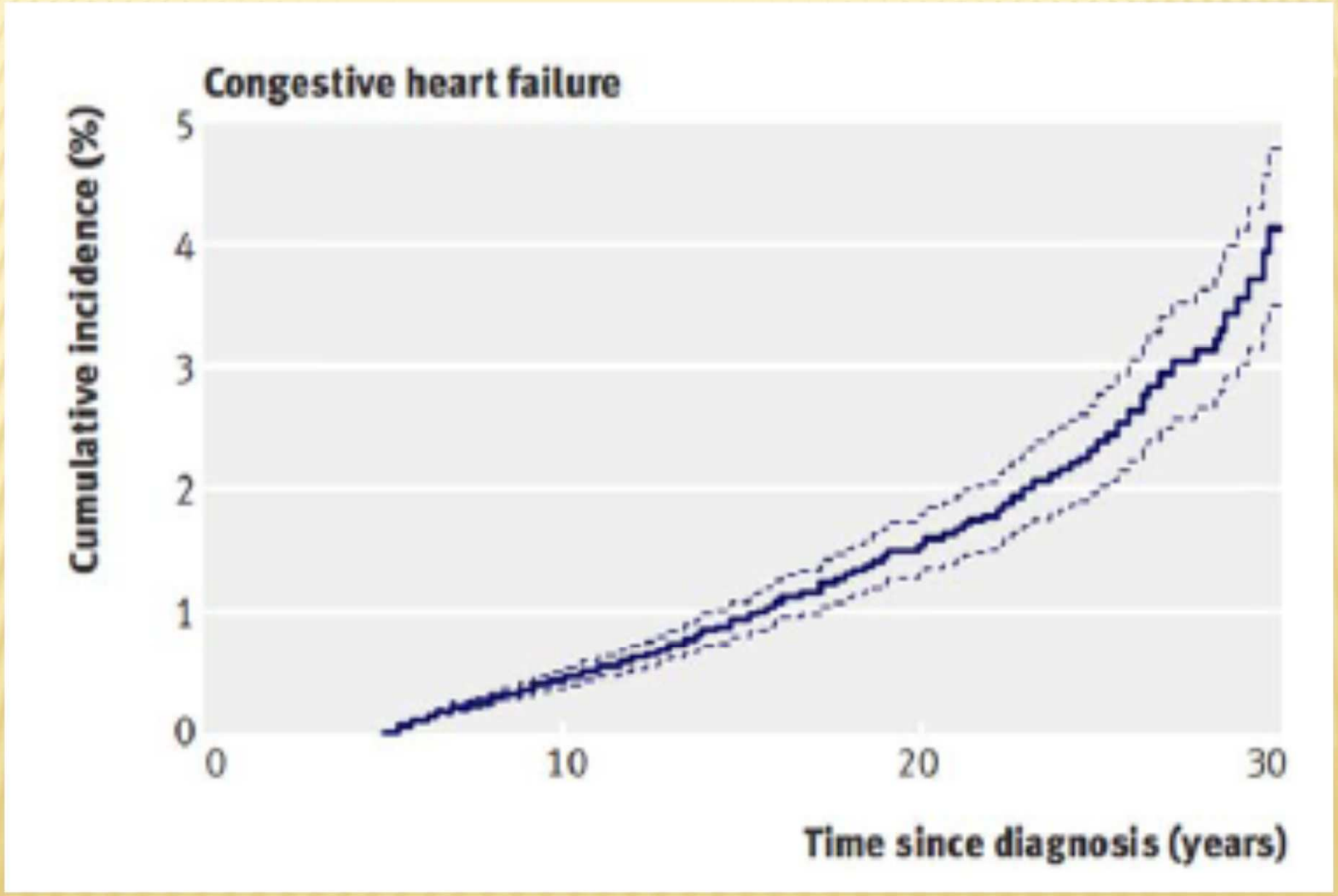

# PREVENTION OF CARDIAC TOXICITY

- Limit total dose of anthracyclines
- Infuse anthracyclines slowly
- Evaluate cardiac function during therapy
- Avoid concomitant radiotherapy
- Use the cardioprotectant dexrazoxane
- RT induced cardiac sequelae decreased by
  - lowering total radiation dose,
  - limiting radiation dose in the lower mediastinum, blocking the heart, avoidance of anteriorly weighted ports,
  - reduction of total tumor dose to <40 Gy and reduction of daily fraction dose to <200 cGy.

# LATE TOXICITY OF THORACIC RADIOTHERAPY

- Growth abnormalities
  - Bone and soft-tissue hypoplasia in prepubertal children
- Thyroid sequela
  - Hypothyroidism
  - Hyperthyroidism
  - Benign and malignant thyroid nodules
  - 17% of children treated with RT dose <26 Gy had thyroid abnormalities compared to 78% with >26 Gy

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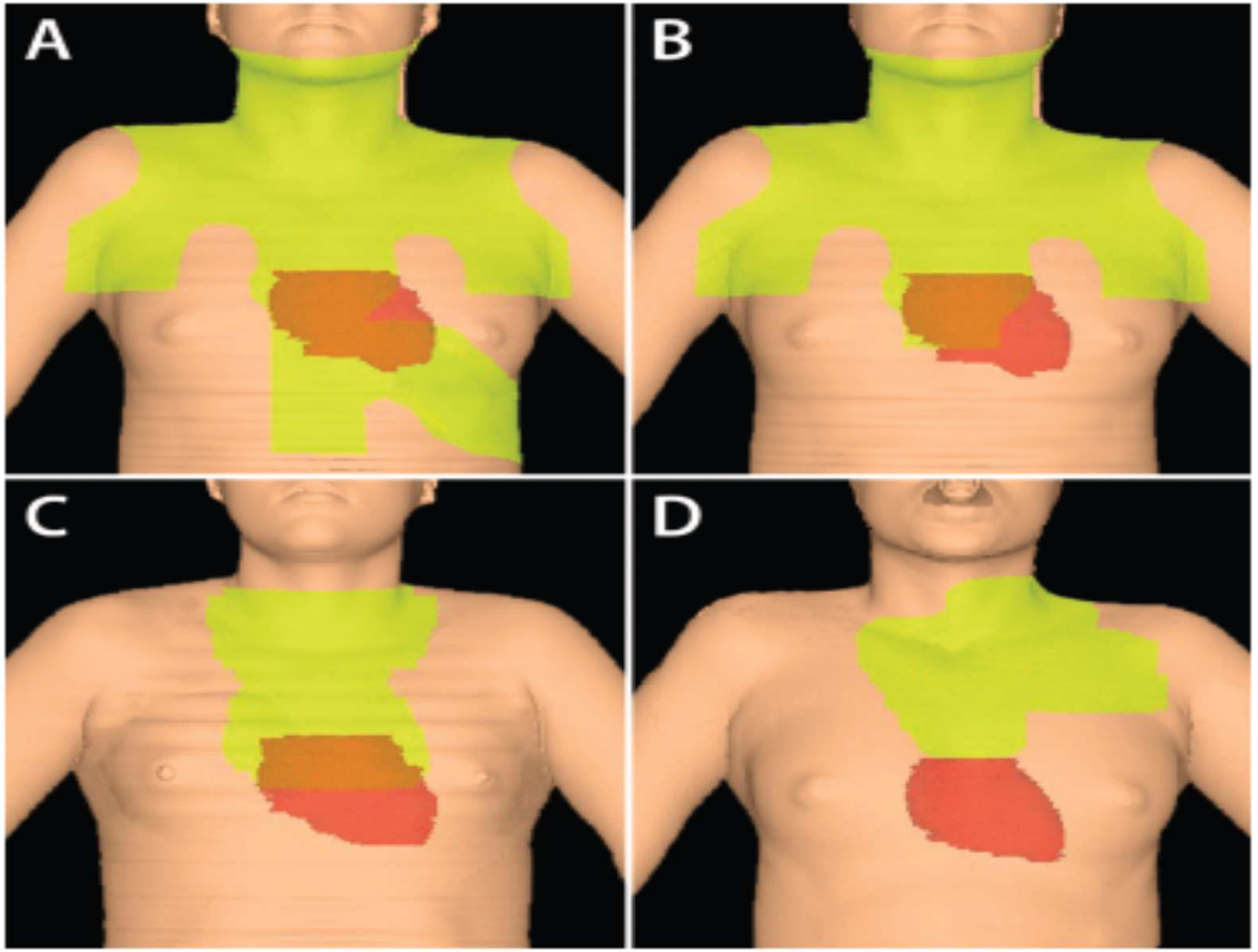
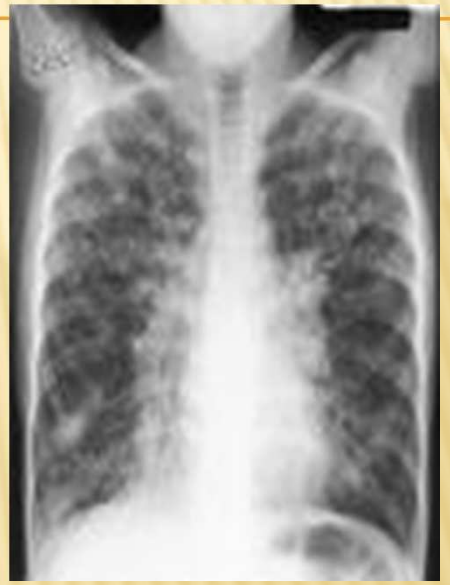


# LUNG & THYROID TOXICITY



- Pulmonary fibrosis is the late phase of radiation-induced lung damage.
- Diffusion capacity (%DLCO) and (FEV1/FVC) can deteriorate in asymptomatic patients.
- Damage to thyroid is common after lower neck or upper mediastinum RT.
- Initially elevation of TSH with normal T3 and T4 which may maintain euthyroid clinical state for some time.
- Treatment with thyroid hormone is recommended.
- Other effects include: benign nodules, Graves' disease, thyroid cancer and Hashimoto's thyroiditis.

# GI & LIVER TOXICITY

- Fibrosis and adhesions are known to occur after radiotherapy to the bowel.
- Manifestations include dysphagia, vomiting, abdominal pain, diarrhea, bleeding and anorexia. Intolerance to fat, milk, gluten, and fiber-containing food occur in abdominally irradiated children and cause growth and weight deficits.
- Beyond tolerated limits (25-30 Gy), both radiation and chemotherapy to liver can cause fibrosis and occlusion of the central veins of the hepatic lobules. Doses below 15 Gy tolerated.
- Symptoms of less severe radiation hepatitis include hepatomegaly, ascites, jaundice, and abdominal pain.

# KIDNEY & BLADDER

- The entire kidney in children appears to tolerate up to 15 Gy in 1.8 Gy daily fractions; total kidney V20 and V30 should be less than 17% and 10%, respectively.
- Tubular damage and hypertension due to renal artery stenosis most common after radiation therapy, with doses above 20 Gy
- Glomerular injury has been seen to recover over time, but tubular injury persists.
- Radiation also induces bladder fibrosis, diminishing capacity, and decreasing contractibility. The severity of the damage caused is proportional to the dose and volume of bladder irradiated

# EFFECT OF ORBITAL IRRADIATION

- ORBITAL BONE
  - "hour glass" appearance,
  - evident by early adolescence, when orbital growth is mostly complete.
  - Bony changes are seen after higher doses (>23 Gy) than soft tissue changes (>6 Gy).
- LACRIMAL GLAND (DRY EYE)
  - in 5-25% of cases receiving doses of 30 to 40 Gy
- CATARACT
  - In healthy eyes, cataracts develop 1 to 3 years after irradiation. With Pd-103 plaques, the cataract rate 90% for lens doses >20Gy, but 30% of patients for 10 to 19 Gy
- RETINOPATHY risk increases at doses above 50 Gy.

# PSYCHOSOCIAL LATE EFFECTS

- Fear of recurrence and death
- Adjustment to physiological late effects
- Sexuality/intimacy issues
- Changes in social support
- Employment discrimination
- Insurance discrimination
- Financial issues
- Quality of life issues

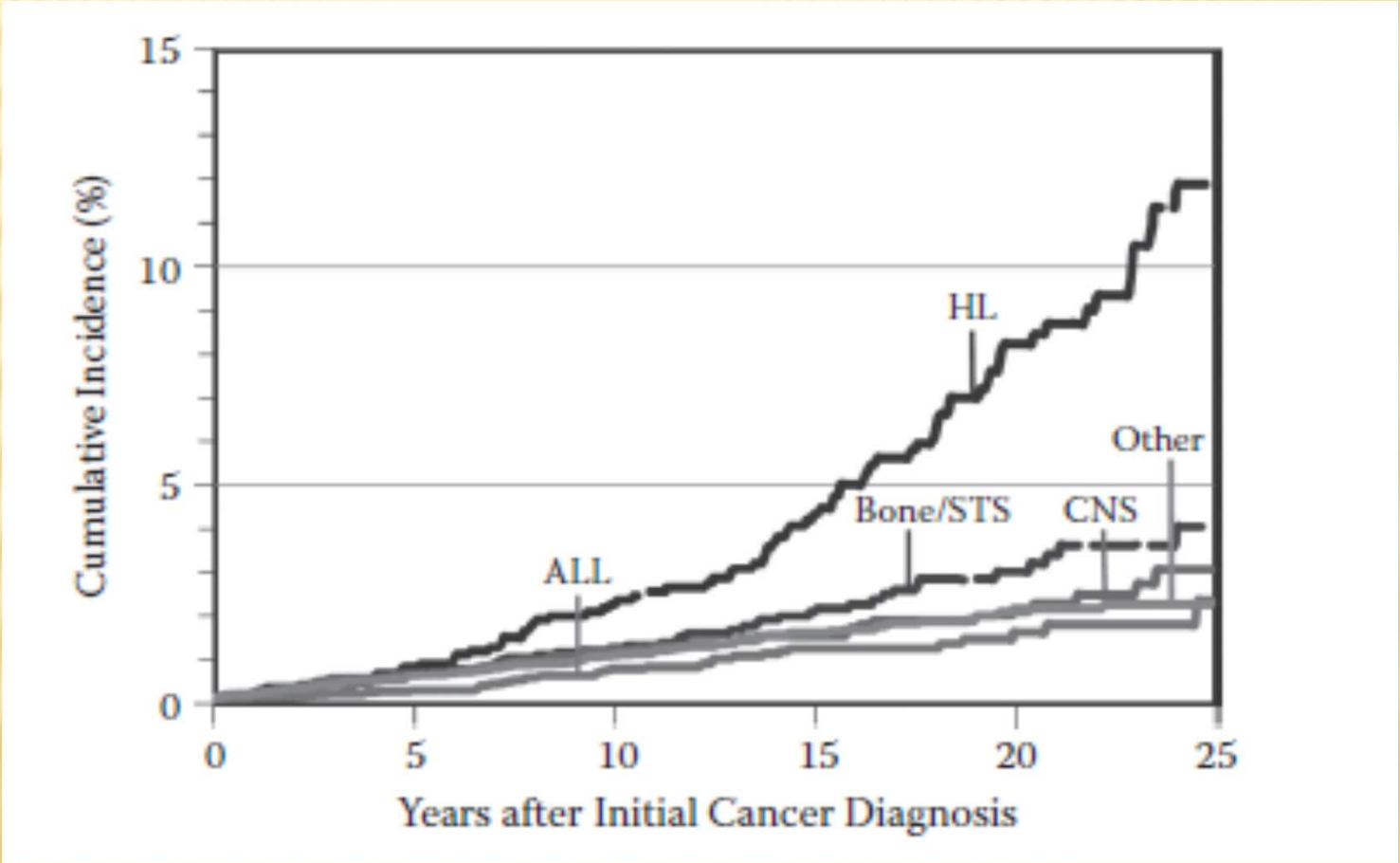
# METHODS OF ELIMINATING OR LIMITING LATE EFFECTS

- omitting or delaying radiotherapy until the child is older,
- decreasing radiotherapy doses and volumes by incorporating chemotherapy in the treatment regimen,
- alteration of radiotherapy fractionation,
- use of novel techniques to spare or minimize radiation dose to surrounding normal tissues, and
- elimination of radiotherapy in favorable subsets of patients.

# Recent reports of SM in large studies of childhood cancer survivors

| Group | Number of Children | Number of SM Reported[a] | Reference |
|---|---|---|---|
| Nordic countries | 25,120 | 196 | Svahn-Tapper et al. 2006 |
| Germany | 24,203 | 238 | Klein 2003 |
| SEER (NCI) | 23,819 | 352 | SEER 1973–2000 |
| CCSS | 20,720 | 677 | Bassal et al. 2006 |
| Great Britain | 16,541 | 278 | Jenkinson et al. 2004 |
| France, Great Britain | 4401 | 124 | Nguyen et al. 2008 |
| LESG | 1380 (HD) | 212 | Bhatia et al. 2003 |

# Cumulative incidence of developing a second cancer among children with selected primary cancers



# MOST COMMON SECOND MALIGNANCIES

| Second Malignancy | First Malignancy |
|---|---|
| Bone tumors | RB, other bone tumors, Ewing's sarcoma, STS, ALL |
| Soft-tissue sarcoma | RB, STS, HD, Wilms' tumor, bone tumors, ALL |
| Breast cancer | HD, bone tumors, STS, ALL, brain tumors, Wilms' tumor, NHL |
| Thyroid cancer | ALL, HD, NB, STS, bone tumors, NHL |
| Brain tumors | ALL, brain tumors, HD |
| Carcinomas | ALL, HD, NB, STS |
| AML/ALL | ALL, HD, bone tumors |
| **Legend**: Retinoblastoma (RB); heritable type. STS, soft-tissue sarcoma; HD, Hodgkin disease; NB, neuroblastoma; NHL, non-Hodgkin lymphoma; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia. | |

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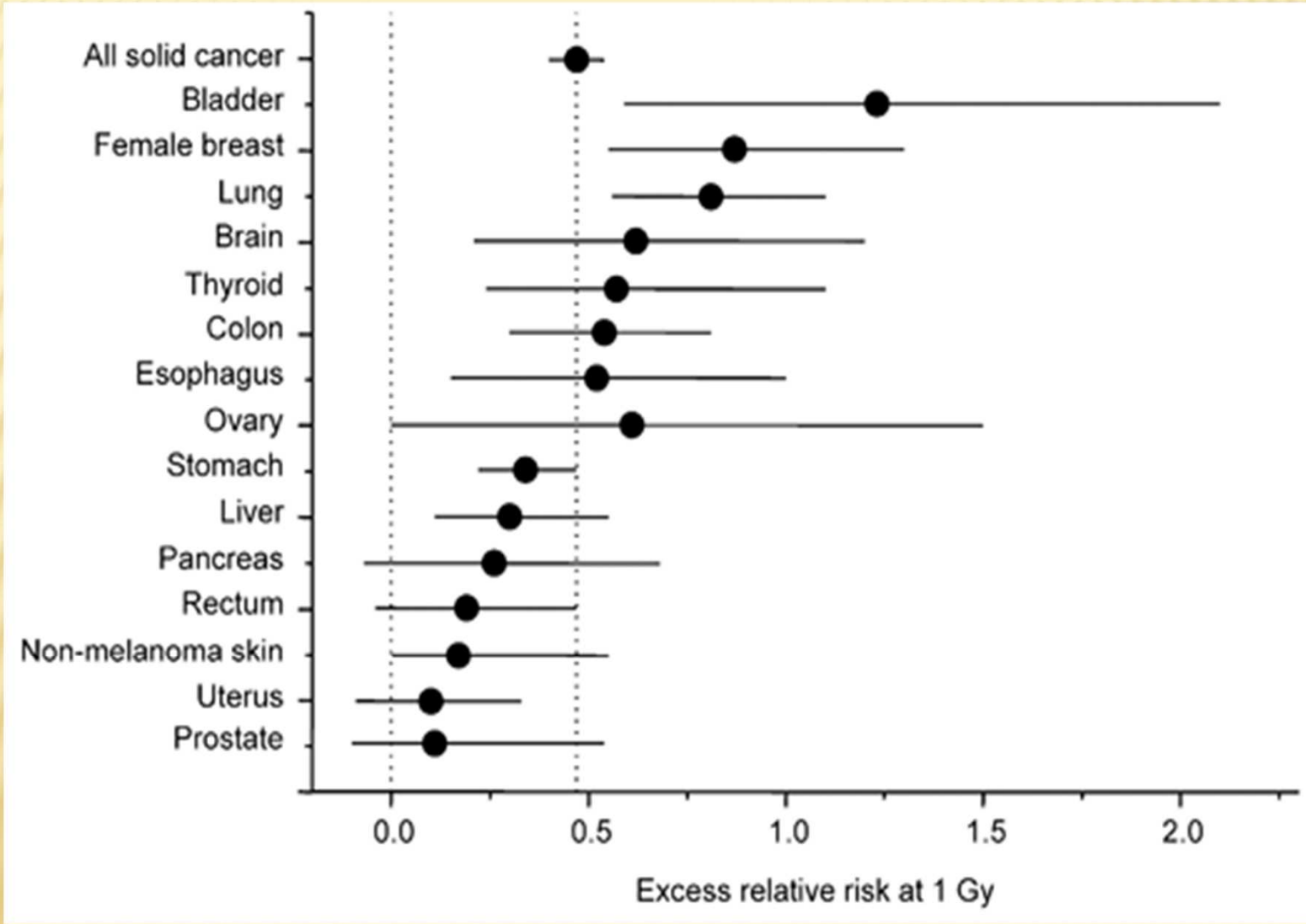


# SECOND MALIGNANCIES (SM)

- Overall rate 3.5% at 25 years.
- Bone & soft tissue sarcomas most common SM
- Chemo used with RT increases risk
- Average latency period 15 yrs.
- Solid tumours 81% of all SM
- RR after Hodgkin's Disease RT is 12% at 25 yrs
- RR after brain RT is 3% at 20 yrs
- Risk dose linear relation; increase with time period.
- survivors of childhood cancer 3-6 fold higher risk of SM than the general population

# MECHANISM OF OCCURRENCE

- Radiation induced cancer is thought to arise in regions distant from the target volume which would have received low doses because higher doses would have killed off any transformed cells before they could develop into cancer.
- **Cell sterilization hypothesis** was given by **Louis Gray** in 1964.
- *Present research: risk increases proportionate to the dose received at the site of the second malignancy*.
- This theory explained by accelerated repopulation during and after radiation treatment → compensates for cell losses due to cell killing, and showing greater effect in areas receiving higher doses.

# FACTORS PREDISPOSING TO SECOND NEOPLASMS

- Treatment
  - radiation therapy
  - chemotherapy: alkylating agents; epipodophyllotoxins
- Genetic Conditions
  - genetic retinoblastoma
  - neurofibromatosis
  - Li-Fraumeni Syndrome

# EFFECT OF RT TECHNIQUE

- Traditionally IMRT / VMAT associated with higher risk.
- Hall extrapolated increase in incidence from 1% → 1.75% by IMRT → due to multiple beams; spreading large areas with lower doses (increased integral dose.)
- This theory disproven by many researchers; IMRT not shown to cause increased integral or peripheral dose due to larger beams.
- SM occur mainly in high dose area with dose – risk linear relation. (65% of SM in high dose area, 20% in edge area. 5% distant.)
- Means that higher head leakage & more MUs / beam-on time increase risk of SM.

# RADIATION THERAPY AND SECOND NEOPLASMS

- Bone and soft tissue sarcomas
  - doses >40Gy; adolescents; mean doses for risk of sarcomatous SM is 25-28 Gy while it is between 15-20 Gy for other SMs.
  - most commonly seen in treated patients of retinoblastoma (RB), Ewing's sarcoma, and Hodgkin lymphoma (HL);
  - cumulative risk at 20 years → 20% for Ewings' Sarcoma and 5-7% for other tumours

# RADIATION THERAPY AND SECOND NEOPLASMS

- CNS SMs
  - 11-25% of all SMs
  - cumulative incidence is 2-3% at 20 years
  - noted in children having received PCI for leukaemias
  - cranial RT of 50 Gy or more higher cumulative incidence of SM within the CNS at 7.1% at 25 years
  - Risk has linear relation with dose and volume parameters.

# RADIATION THERAPY AND SECOND NEOPLASMS

- Carcinomas of the breast
  - most common after irradiation for Hodgkin's Lymphoma
  - doses >30Gy; Girls entering or just beyond puberty most at risk.
  - most SMs within the field or near the field edge
- Thyroid SMs
  - Most in leukemia or HD survivors; young children at highest risk
  - Dose-effect seen

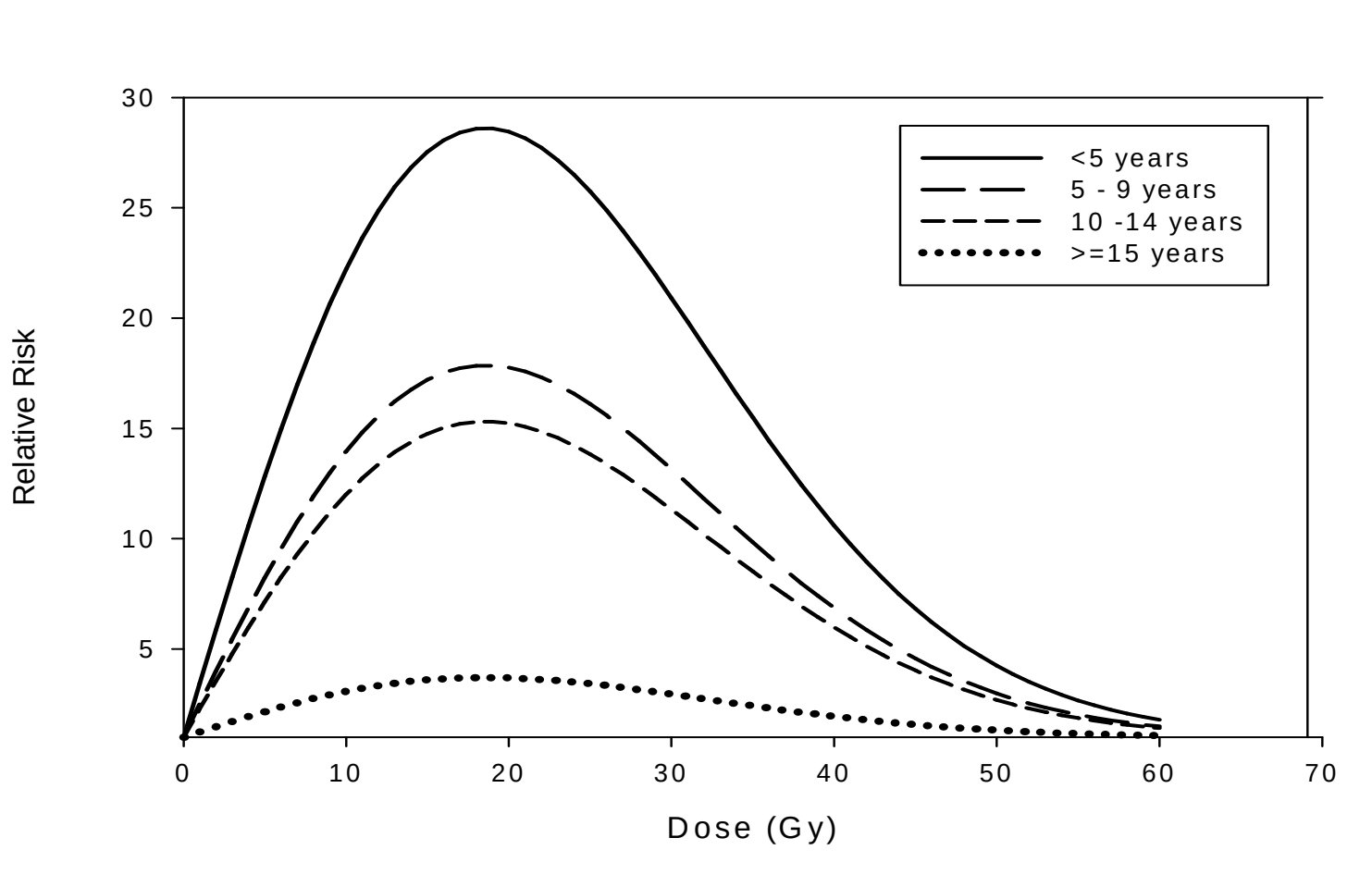
# BREAST CANCER AFTER THORACIC RADIATION IN CHILDHOOD

- MEDLINE, EMBASE, Cochrane Library and CINAHL search – 1966 to 2008
- Cumulative incidence 40-45 years 13-20%
- SIR 13.3-55.5
- Incidence increased linearly with RT dose
- ~13% Bilateral; most metachronous
- Benefits of targeted surveillance screening

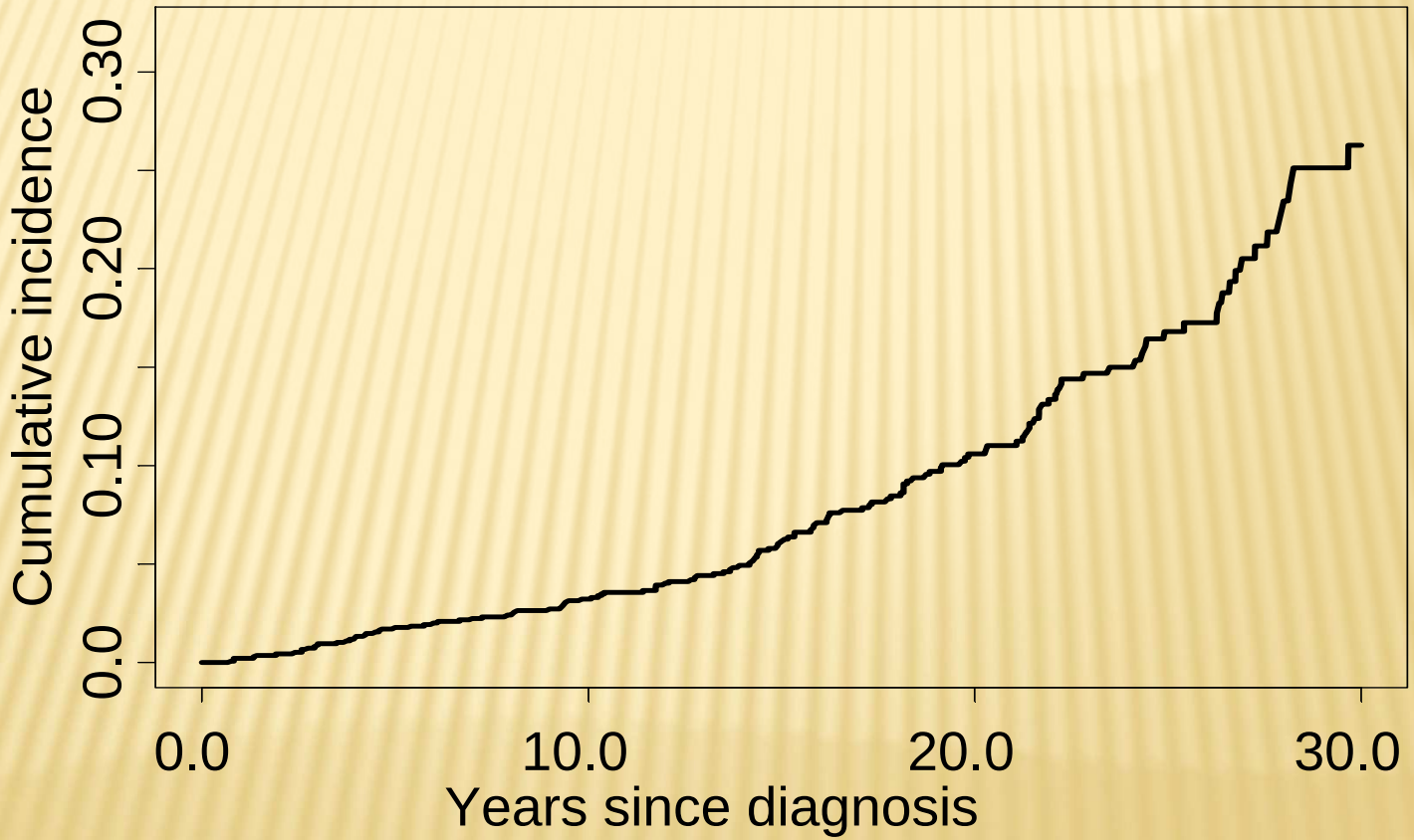
# RADIATION THERAPY AND SECOND NEOPLASMS

- Carcinomas
  - elevated risks of renal cell carcinoma among patients with neuroblastoma; gastrointestinal carcinomas among patients with Wilms' tumor and Hodgkin lymphoma; and head and neck carcinomas among patients with leukemia, neuroblastoma, and soft-tissue sarcoma
- Leukaemias
  - one of the first reported SMs
  - Frequently after HL, followed by non-Hodgkin lymphoma (NHL), Wilms' tumor, and neuroblastoma with an overall relative risk of about 7
  - Leukaemias in about 3 to 6 years after irradiation, compared to beyond 10 years for most secondary solid tumors. Dose-risk effect plateaus after 16 Gy.

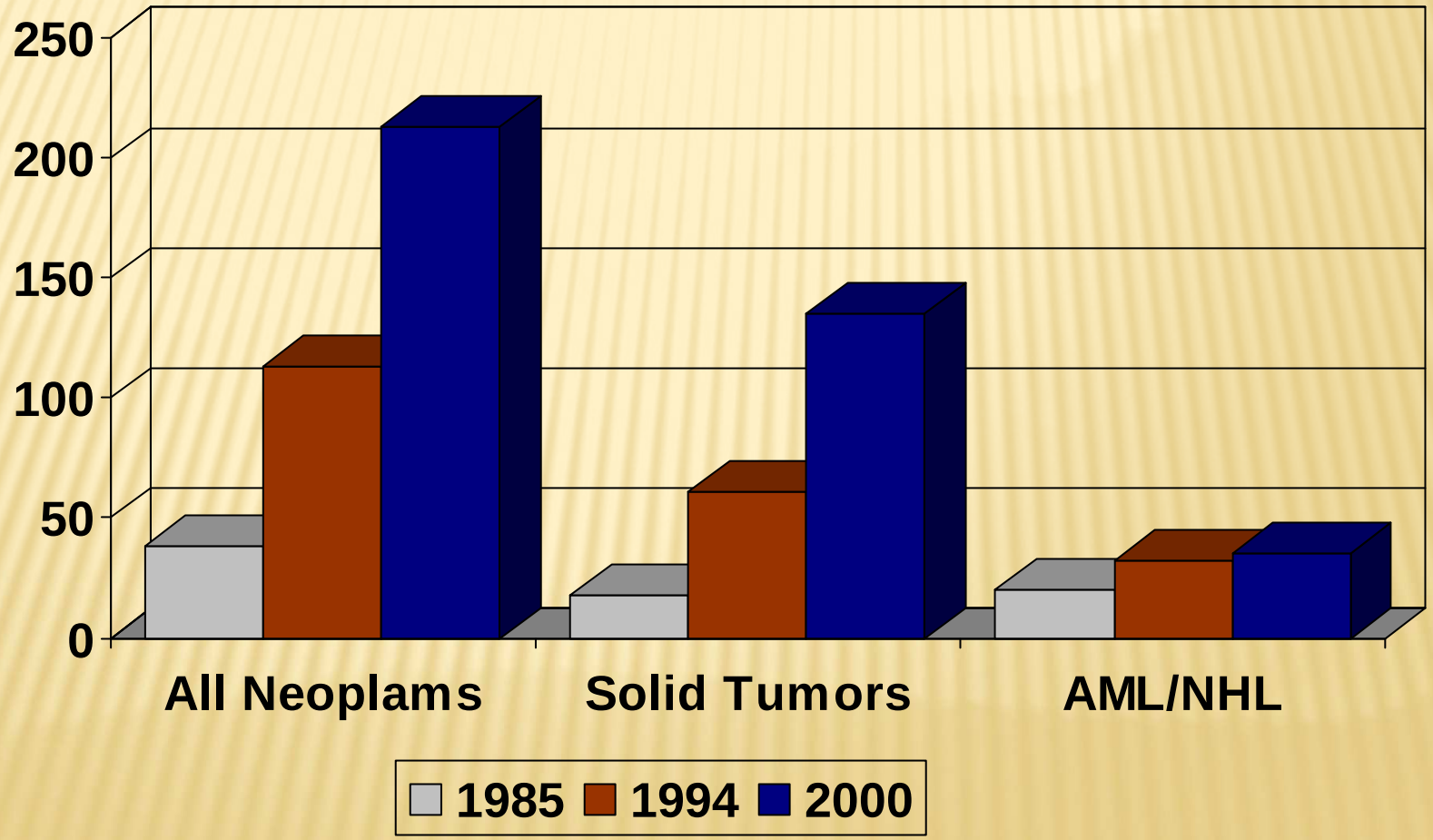
# RELATIVE RISK OF THYROID CANCER BY AGE AND RADIATION DOSE



# LESG - SECOND MALIGNANT NEOPLASMS



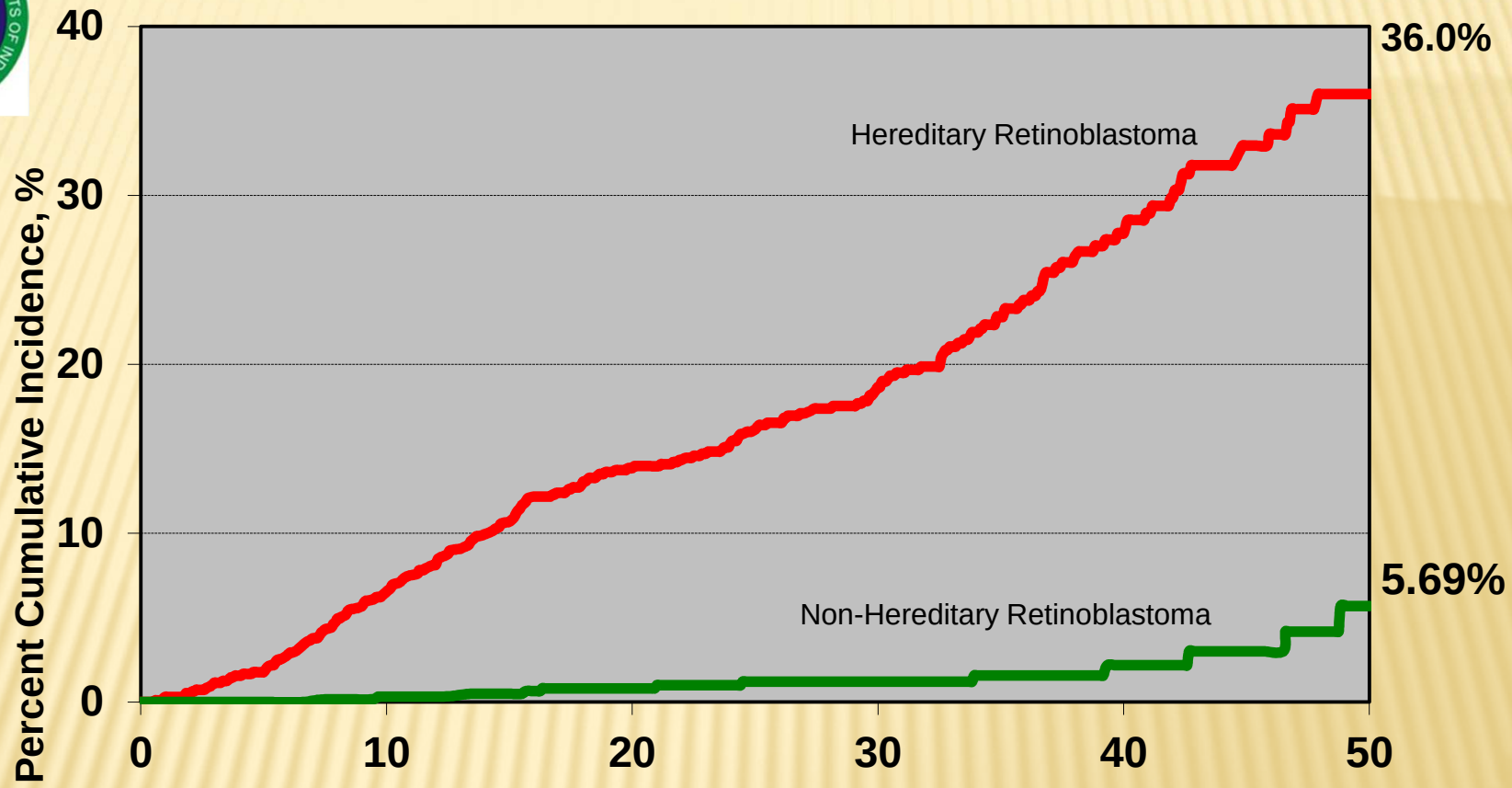
# SUBSEQUENT NEOPLASMS FOLLOWING UPDATE OF LESG COHORT



# SECOND CANCERS IN GENETIC RETINOBLASTOMA

- Pineal gland
  - familial cases at greater risk
- Bone and soft tissue sarcomas
  - 6 to 10% up to 20 years without radiation
  - increasing frequency with time after radiation
- Malignant melanoma; leiomyosarcoma

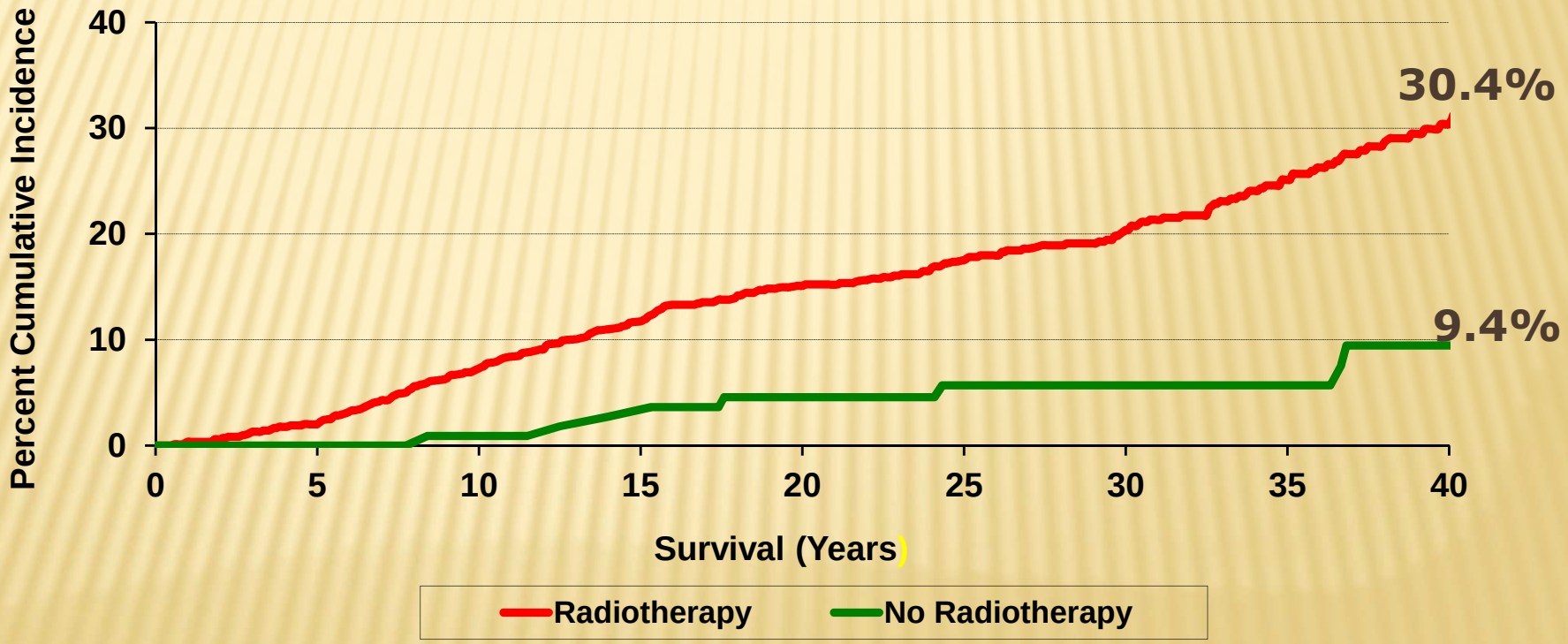
# Cumulative Incidence of a Second Cancer




| | | | | | | |
|---|---|---|---|---|---|---|
| Hereditary | 963 | 760 | 615 | 401 | 147 | 30 |
| Non-Hereditary | 638 | 570 | 500 | 317 | 134 | 46 |

Number of Patients at Risk

# Cumulative Incidence of a Second Cancer Following Hereditary Rb



# THE OFFSPRING OF CHILDHOOD CANCER SURVIVORS

- **Offspring do not demonstrate an increased risk of cancer!!!**
  - Green et al (CCSS)
    - 4029 pregnancies in 1915 survivors
    - No evidence of adverse outcomes
- Genetic predisposition is the exception
  - Wilm's Tumor, Retinoblastoma, Li-Fraumeni

# SURVIVORS' NEEDS

- Education
  - Treatment
  - Risk factors
  - Surveillance
- Surveillance
  - Early detection of problems
  - Anticipatory guidance
  - Modifiable risk factors
- Empowerment/Advocacy
  - Education
  - Awareness

# IDEAL FOLLOW-UP PROGRAM

- Coordinated, comprehensive care
- Multidisciplinary; culturally and socially appropriate
- Health education and anticipatory guidance based on therapy and other risk factors
- Transition to adult health care system

# SURVIVOR INTERVENTION TO REDUCE LATE EFFECTS

- Health education re: exercise, diet, sun, smoking cessation
- Reproductive counseling
- Psychosocial support
- Education regarding previous disease history
- Discussion of risks associated with treatment

# PROVIDER EDUCATION TO REDUCE LATE EFFECTS

- Increase knowledge of late effects of cancer therapy
- Improve ability to recognize and treat subclinical late effects
- Detect second cancers early
  - Screening of high risk patients for RT-associated cancers
  - Counseling of survivors with genetic predisposition

- Presently it is suggested that childhood cancer survivors should be encouraged to prevent exposure to known carcinogens such as tobacco, limited exposure to alcohol, sun protection, reduced fat intake, and maximal intake of fruits and vegetables.

- surveillance techniques for detecting cancer in the general population (breast self-examination, mammography, testicular examination, examination of stools for blood, and evaluations of the rectum and colon) should be performed regularly.

**Table 1.** Organ-specific late effects of cancer therapy and screening methodology

| Organ | Therapy | Screening tests |
|---|---|---|
| Musculoskeletal | Radiotherapy (RT) | Physical exam, scoliosis exam (annually if growing), x-ray prn |
| Breast | Mediastinal RT | Breast exam, mammography beginning age 25-30 |
| CNS | Cranial RT | Neurocognitive testing (baseline, q 3-5 yrs prn), MRI (baseline) |
| Neuroendocrine | Hypothalamic-pituitary RT | Growth curve q yr, bone age (age 9)<br>GH stimulation test<br>TSH, Free T4,T3 (baseline q 3-5 yr prn)<br>LH, FSH, test/est, prolactin (baseline, prn)<br>8 am cortisol (baseline, prn) |
| Cardiac | Anthracyclines<br>mediastinal/<br>T-spine RT | ECHO/EKG<br>(baseline for all; q 3-5 yr after anthracycline)<br>Holter q 5 yrs prn (high-dose anthracycline)<br>Stress test/dobutamine stress echo prn<br>(after RT) |
| Pulmonary | RT<br>Bleomycin, CCNU/BCNU | PFT baseline, q 3-5 yrs prn |
| Ovary | Alkylating agents<br>RT | Menstrual Hx annually,<br>LH, FSH, estradiol baseline (age >12) and prn |
| Testes | Alkylating agents<br>RT | LH, FSH, testos baseline (age >12) and prn<br>Spermatoanalysis prn |
| Renal | Cisplatin (carboplatin),<br>Ifosfamide,<br>RT | Creatinine, Mg q 1-2 yrs<br>Creatinine clearance baseline and q 3-5 yrs prn<br>Urinalysis (RT, ifosfamide)<br>Ifosfamide: serum phospate, urine glucose, protein |
| Bladder | Cyclophosphamide,<br>Ifosfamide, RT | Urinalysis annually for heme |
| Thyroid | RT to neck, mediastinum | TSH, Free T4, T3 q yr X 10<br>Scans (U/S) prn |
| Liver | 6-MP, MTX, Act-d, RT | Liver function tests every 1-3 yrs |
| GI | Intestinal RT | Stool guiac q yr, colonoscopy (ACS) |

**INDIAN COLLEGE OF RADIATION ONCOLOGY (ICRO)**
**PG TRAINING PROGRAMME**
**18th & 19th JULY 2015, HYDERABAD**


# THANK YOU