


# Redefining Normal: Health Maintenance for Childhood Cancer Survivors



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# Goals



- Scope of problem
- Follow-up guidelines
- Organ-based review of late effects
- Survivor health care

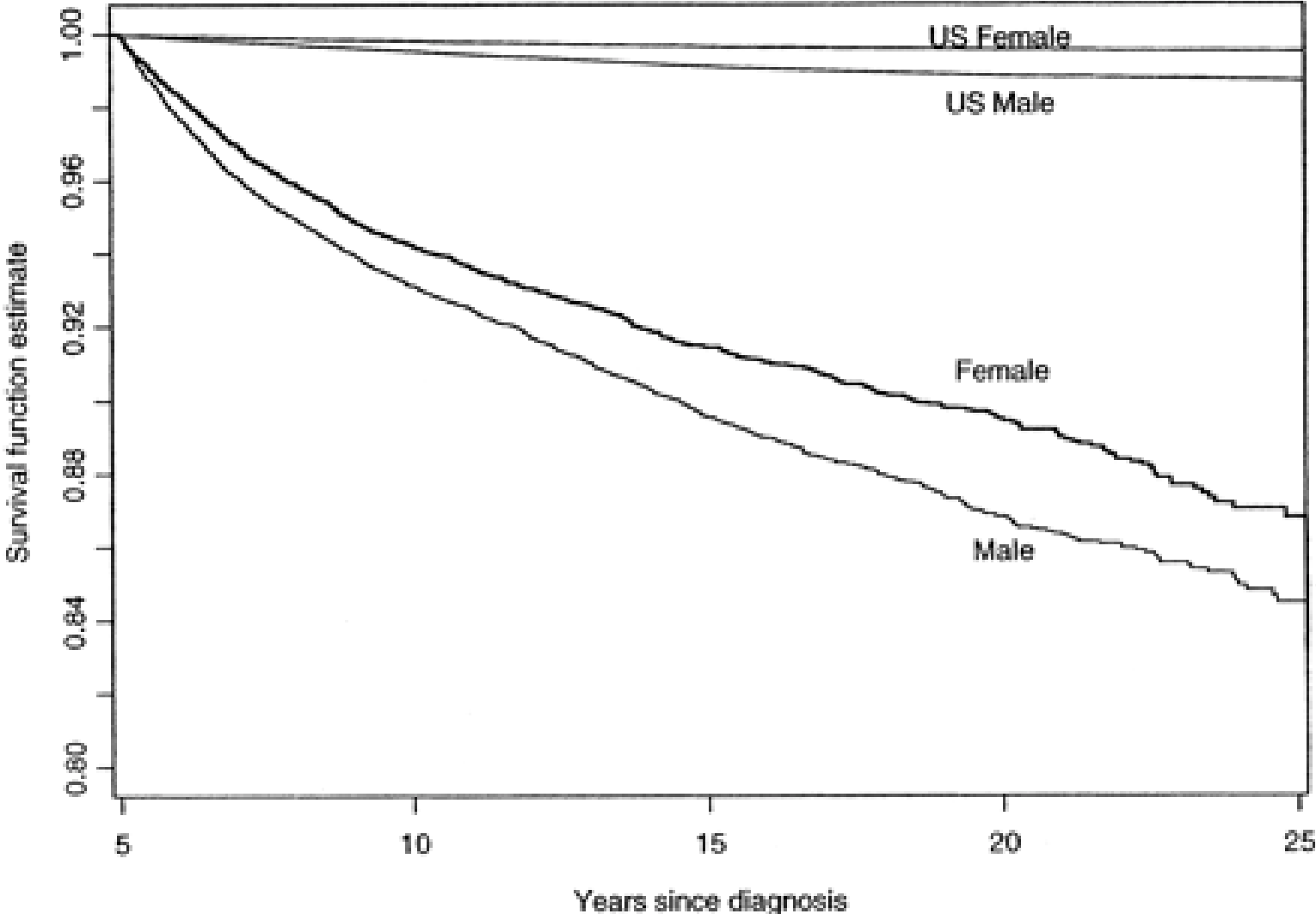
# Survivor population

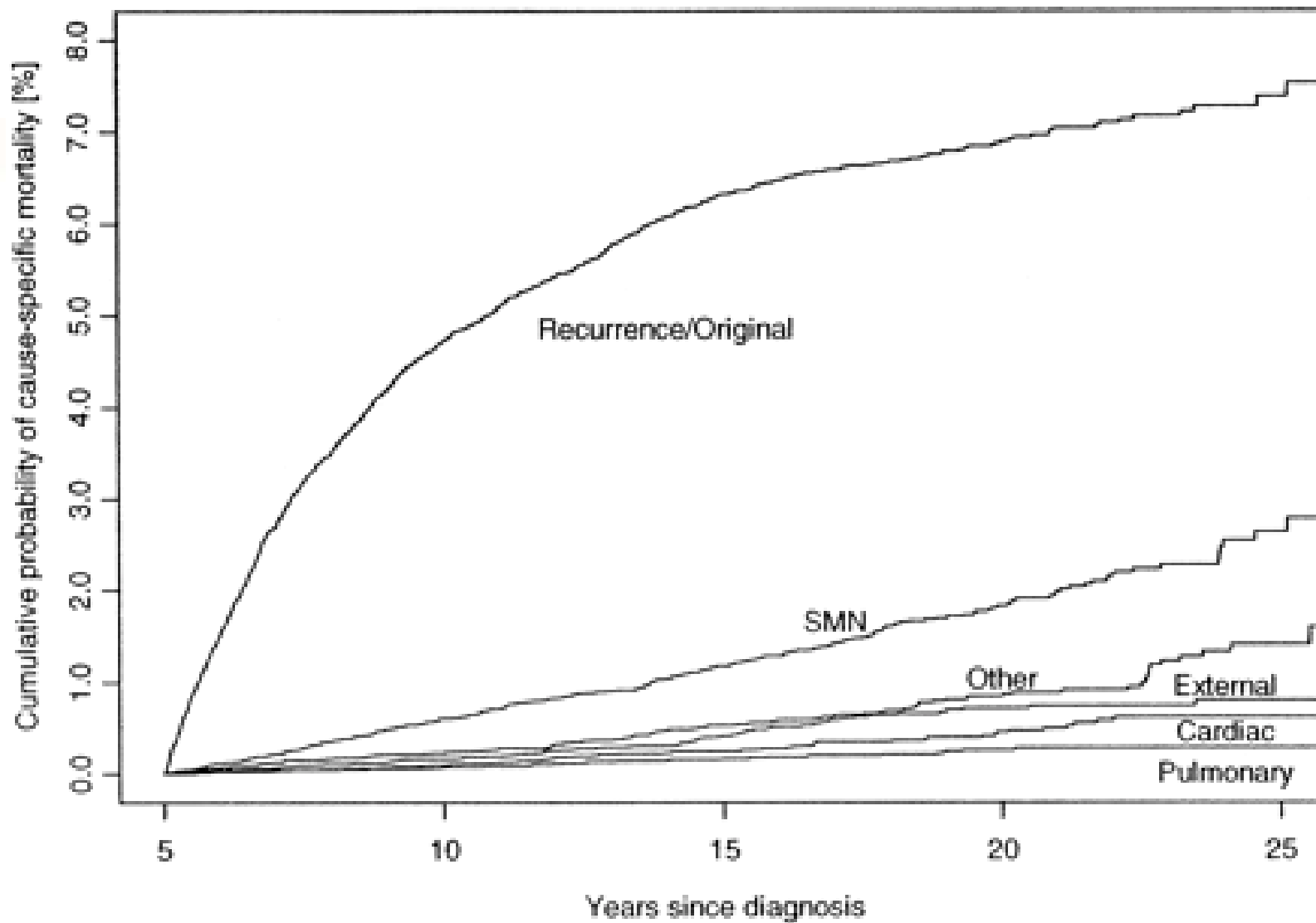
- Between birth and 20 years, 1 in 300 will be diagnosed with cancer
- Cure rates for most malignancies over 70%
- By 2010, 1 in 250 young adults will be survivor of childhood cancer

# Survivor population

- Childhood Cancer Survivor Study
  - Initial cohort of 20,277 5-year survivors diagnosed between 1970 and 1986 under age 21 years
  - SMR of 10.8 for survivors
    - Higher in females, diagnosis before age 5, leukemia or CNS tumor
  - Leading cause of death was recurrence
  - SMR for second malignant neoplasm (SMN) was 19.4, cardiac causes 8.2, pulmonary 9.2, other 3.3

Mertens, J Clin Oncol 2001.





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# COG Guidelines



- Children's Oncology Group (merged CCG and POG) nursing and late effects disciplines
- Evidence-based when available else consensus
- Organized by treatment
- Generally history and physical direct screening

# COG Guidelines



- Currently only available in provider-oriented format although publicly accessible
  - [www-survivorshipguidelines.org](http://www-survivorshipguidelines.org)
  - Full text guidelines
  - Patient/family directed health links
- Each section undergoes review of new evidence every other year

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# Neurologic



- Vincristine or cyclophosphamide can cause acute peripheral neuropathy during treatment which can persist
  - Motor and sensory
- Treatment-induced leukoencephalopathy
  - Radiation and/or methotrexate
  - Correlation mostly with gray matter problems such as memory loss and dementia
  - Link to late neurocognitive problems still under study

# Neurologic

- Radiation changes
  - Moyamoya disease
  - Aneurysm
  - Radiation necrosis and myelopathy can be transient
- Screening based on symptoms

# Neuropsychological

- Radiation and/or methotrexate major risks
  - Majority of survivors at risk after treatment for ALL or brain tumor
- In ALL, outcomes worse with younger age at treatment and higher treatment intensity
- Adverse effects can be delayed and progressive
  - Worse outcomes when tested further out from treatment

# Neuropsychological

- IQ scores remain stable pre and post therapy but declines seen over time in...
  - Arithmetic achievement
  - Verbal fluency
  - Visual-motor skills
  - Executive functioning
- Gender and SES also implicated in some studies
  - Females and lower SES patients at higher risk

# Neuropsychological

- Brain tumor survivors with high risk for social and vocational problems
  - Specific deficits depend on tumor type and treatment
  - Radiation at age <4 years much more susceptible to loss of intellectual function
- Stem cell transplant (SCT) recipients only those treated at age <3 year appear to be at risk
- School intervention very important

# Neuropsychological

- Referral for formal neuropsychological testing recommended at baseline into long-term follow-up then as needed
  - Often not covered by insurance
  - Generally start with request for testing by school if history indicates problems
    - Minor deficits may be missed

# Ocular

- Cataracts
  - Radiation, steroids, busulfan
- Glaucoma
  - Steroids
- Retinopathy
  - Radiation, including late onset
- Dry eyes
  - Radiation, SCT with GvHD



# Ocular

- Recommend ophthalmologic exam yearly if at risk

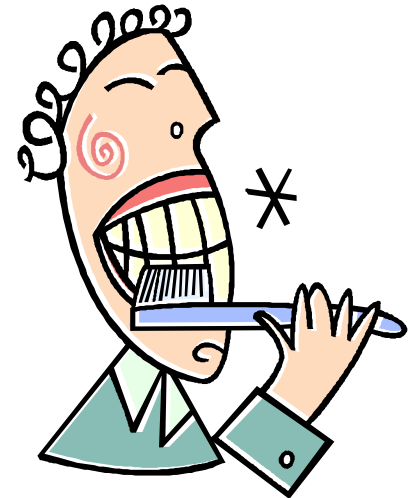


# Hearing

- Primary risks for hearing loss include platinum-based chemotherapy, especially when combined with radiation
- Ifosfamide also a risk factor
- Cytoprotective agents have potential to help prevent hearing loss
  - Amifostine under study
- Screen hearing at baseline, then as indicated by history

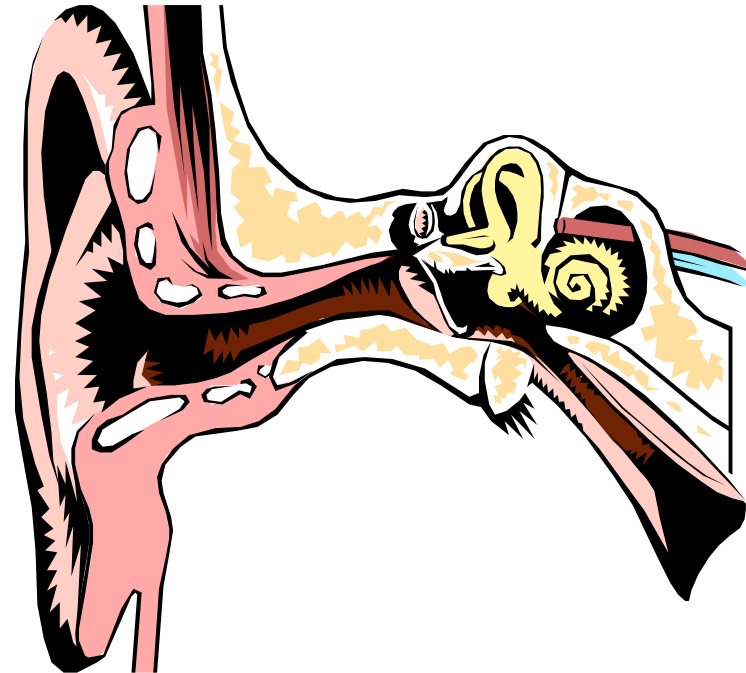
# Dental

- Radiation and chemotherapy can affect enamel growth
  - Young age a risk factor
- Skeletal growth issues from radiation also can affect teeth
- Regular cleanings and surveillance



# Head and neck

- Chronic sinusitis and otitis media have been observed after radiation or surgery



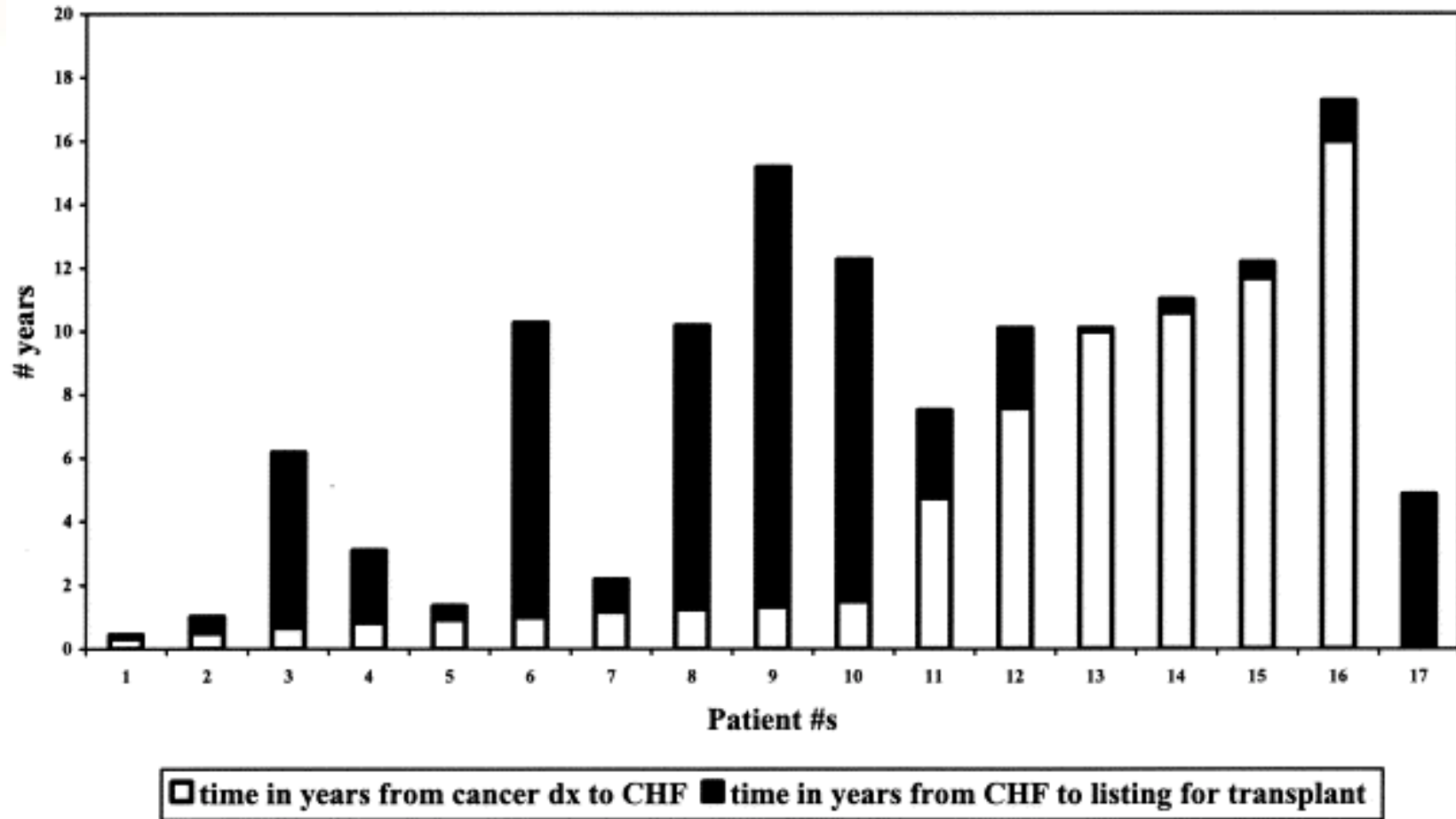
# Cardiac



- Risks include anthracycline treatment (lower risk with alkylating agents and antimetabolites), radiation, young age at treatment, female gender
- In North America >12% of pediatric cardiomyopathy patients had history of treatment for cancer (Lipshultz, Prog Pediatr Cardiol 2000)
- Course variable, toxicity onset can be very late and prevalence and severity increase over time

# Cardiac

## Time Course



Ward, J Heart & Lung Transplant 2004.



# COG Guidelines

RECOMMENDED FREQUENCY OF ECHOCARDIOGRAM OR MUGA SCAN			
Age at Treatment*	Chest Radiation	Anthracycline Dose†	Recommended Frequency
<1 year old	Yes	Any	Every year
	No	<200 mg/m <sup>2</sup>	Every 2 years
		≥200 mg/m <sup>2</sup>	Every year
1-4 years old	Yes	Any	Every year
	No	<100 mg/m <sup>2</sup>	Every 5 years
		≥100 to <300 mg/m <sup>2</sup>	Every 2 years
≥5 years old	Yes	<300 mg/m <sup>2</sup>	Every 2 years
		≥300 mg/m <sup>2</sup>	Every year
	No	<200 mg/m <sup>2</sup>	Every 5 years
		≥200 to <300 mg/m <sup>2</sup>	Every 2 years
		≥300 mg/m <sup>2</sup>	Every year
Any age with decrease in serial function			Every year

\*Age at time of first cardiotoxic therapy (anthracycline or chest irradiation, whichever was given first)

# Cardiac

- Cardioprotective agents available
- EKG at baseline to evaluate for prolonged QTc
- Reassessment with increased cardiac demand, e.g. new exercise routine, pregnancy
- ACE inhibitors, Beta-blockers, transplant

# Cardiac



- Other considerations include risk of vascular disease with concomitant late effects, i.e. growth hormone deficiency, obesity, hyperlipidemia
- Heart-healthy lifestyle important

# Pulmonary

- Radiotherapy, bleomycin are main risks, although other chemotherapeutic agents can also have pulmonary toxicity
- Radiation pneumonitis presents 1-3 months from radiation as cough/dyspnea/pain/low-grade fever
- Fibrotic phase can follow
- Chemotherapy potentiates radiation injury

# Pulmonary



- Bleomycin-induced interstitial pneumonitis is dose-related
- SCT also can have major pulmonary complications, including interstitial pneumonitis (accounting for >40% of transplant-related mortality) or bronchiolitis obliterans
- Long-term restrictive or obstructive deficits after acute side effects are a concern

# COG Guidelines

- After whole lung radiation or SCT, baseline CXR and PFTs including DLco (diffusion capacity of carbon monoxide), repeat as clinically indicated
  - Divers should be cleared by specialist
  - Influenza and pneumococcal vaccines indicated
- Also recommend baseline PFTs after bleomycin or busulfan

# Kidney

- Nephrotoxicity may result from tumor, surgery, radiation, chemotherapy
- May be irreversible
- Ifosfamide tends to cause Fanconi syndrome (affects proximal tubule)
- Platinum agents tend to cause tubular damage and hypomagnesemia

# Bladder

- Acutely can have cystitis from radiation or chemotherapy
  - Mesna can help prevent chemotherapy-related hemorrhagic cystitis
  - Can get fibrosis and diminished bladder volume/function chronically
- Bladder cancer is a potential SMN
  - Screening urinalysis

# Gastrointestinal

- Obesity epidemic in survivors as well as general population
  - Brain tumors risk from central damage
  - ALL risks include cranial radiation at young age (girls <4y higher incidence than untreated sibs) as well as decreased physical activity even after treatment complete
- Mainstay is prevention/treatment via healthy lifestyle, especially need to increase habitual physical activity

# Gastrointestinal

- Surgical complications, radiation enteritis and GvHD can all affect GI tract
- Uncommon complications late, although exact incidence unclear
- Maintain high clinical index of suspicion for problems, no other routine screening
- Some older survivors with Hep C post-transfusion

# Endocrine: growth

- Risk factors for growth hormone deficiency
  - Treatment before reaching adult height
  - Cranial radiation  $>1800$  cGy
  - TBI –  $>1000$  cGy single fraction or  $>1200$  cGy fractionated
  - Surgery to suprasellar region
  - Longer time from treatment, more GH deficiency

# Pituitary

- Lower doses cranial radiation (1800-2500 cGy) can cause isolated GH deficiency
  - Often normal baselines with abnormal response to stimulation or and atypical release in puberty
- Higher doses (such as for brain tumors) can cause multiple pituitary deficits
- Younger age at treatment means more vulnerable
- Cranial radiation also associated with earlier onset of puberty, limiting growth potential

# Treatment issues

- Options
  - GnRH agonist in early puberty
  - GH replacement, including into adulthood for body composition benefits
- Controversies
  - Sklar study (J Clin Endocrinol Metab 2002) showing GH treated patients had no increased risk of tumor recurrence, but RR 3.21 for secondary malignancy (also potentially attributable to radiation or alkylating agents)
  - GH registry no increased incidence of tumors

# Endocrine: thyroid

- Hypothyroidism or hyperthyroidism main risk is cervical radiation
  - Screen with TSH, free T4 yearly at dose >20 Gy
  - Incidence of hypothyroidism as high as 30-50% after neck irradiation
- Thyroid nodules and cancer also a risk
  - Other factors include length of TSH elevation, female sex, young age and dose
  - Current recommendations are for imaging or biopsy only if abnormal physical exam or possibly if abnormal TFTs

# Fertility



- Female issues
  - Central dysfunction after cranial irradiation
  - Ovarian dysfunction after cyclophosphamide or abdominal radiation
  - Uterine insufficiency after radiation, surgical loss of reproductive organs
- Male issues
  - Alkylating agents, antimetabolites gonadotoxic as well as radiation
  - Azospermia can be reversible

# COG Guidelines

- Recommend screen LH, FSH, estrogen in girls not spontaneously undergoing puberty by age 13 then prn
  - Yearly for life if cranial radiation > 30 Gy
- LH, FSH, testosterone in boys age 14 if pubertal delay then prn
  - Yearly for life if cranial radiation > 30 Gy
- Sperm analysis if desired for family planning

# Fertility preservation

- Limited options for females undergoing gonadotoxic therapy
  - Some adult studies banking ovarian tissue as oocytes not able to be preserved in isolation
- Sperm banking for males
  - Working on options for prepubertal

# Fertility

- Current evidence suggests higher incidence of somatic gene defects in cancer survivors (Rice, Cancer Research 2004)
- However, pregnancy outcomes data has not yet identified significant birth defect risk (Green, Am J Obstet Gynecol 2002)
- Significant risk of low birth weight to mothers after pelvic irradiation

# Osteopenia/Osteoporosis

- Risks include malignancy (i.e. ALL), steroid treatment, methotrexate, estrogen deficiency, GH deficiency, cranial radiation
- Lifestyle also important
  - Calcium intake
  - Weight-bearing exercise
- Screen those at risk with DEXA or quantitative CT when present to long-term follow-up or earlier if clinically indicated

# Musculoskeletal

- Abnormal bone growth reported in SCT survivors (Taitz, *Pediatr Blood Cancer* 2004)
  - Postulated secondary to TBI, still not well understood
- Other effects can be related to surgery and radiation
  - Amputations
  - Poor skeletal growth
    - Obesity if inadequate height growth
    - Extremity growth impairment

# Skin

- Late effects include
  - GvHD in SCT
  - Relapse or SMN of skin
    - Mole surveillance important
  - Alopecia



# Second malignant neoplasms

- CCSS demonstrated 6.4 fold increased risk in survivors of developing second cancer (Neglia, J Natl Cancer Inst 2001)
- Hereditary retinoblastoma, Hodgkin's disease and soft tissue sarcoma are primary malignancies after which a SMN is most likely
- Radiation, younger age, female sex associated with higher SMN incidence except myelodysplasia/AML

# Second malignant neoplasms

- Chemotherapy at older age increases risk of myelodysplasia/AML
  - Most common pediatric SMN
  - At risk patients screened with yearly CBC
- Breast cancer after HD therapy relatively common due to radiation
  - Counseling on breast health important
- Other SMNs as previously mentioned plus non-melanoma skin cancer, brain tumors, osteosarcoma, lung cancer

# Quality of life

- Cancer survivors age 8-12 years report health-related quality of life (HRQL) higher than healthy controls (Shankar, Pediatrics 2005)
- HRQL generally lower for brain tumor survivors

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# Survivor healthcare

- Risk-based care including counseling and screening is indicated (Oeffinger, CA 2004).
- Health promotion including avoidance of risky behaviors
  - Smoking initiation among survivors lower than general population but still important target given risk of SMN
  - Healthy diet and activity important as previously mentioned

# Survivor healthcare

- Education of survivor regarding treatment and long-term risks
  - Knowledge deficits about treatment history (Kadan-Lottick, JAMA 2002)
  - Primary care physician lack of knowledge about long-term risks

# Quality Survivorship Care

- IOM definition includes (Natl Acad Press 2003)...
  - Provide a range of direct services to survivors to identify, prevent, treat and ameliorate late effects
  - Bridge the realms of primary and specialty health care with education and outreach
  - Coordinate medical care with educational and occupational services
  - Conduct research to better understand late effects and their prevention

# Models of care

- STAR (Survivors Taking Action and Responsibility) is example of specialty follow-up clinic
- Alternative models would include care by community providers with education of patient/provider through some form of electronic communication with oncology or late effects team
  - STILL NEED CONTACT FOR EPIDEMIOLOGY

# Resources

- Late Effects of Childhood Cancer, ed Hamish Wallace and Daniel Green. Oxford University Press 2004.
- [www.curesearch.org](http://www.curesearch.org)
- Childhood Cancer Survivorship: Improving Care and Quality of Life, Institute of Medicine National Research Council. National Academies Press 2003.