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A review of the most common pediatric malignancies, short and long-term side effects of treatment. What should we be looking for and how do we support our patients?

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Disclosure

- Nothing to disclose

Objectives

1. Review the most common pediatric malignancies
2. Discuss the overall treatment plan for common pediatric malignancies
3. Review early and late side effects of treatment with monitoring and supportive recommendations

What are the most common pediatric cancers?

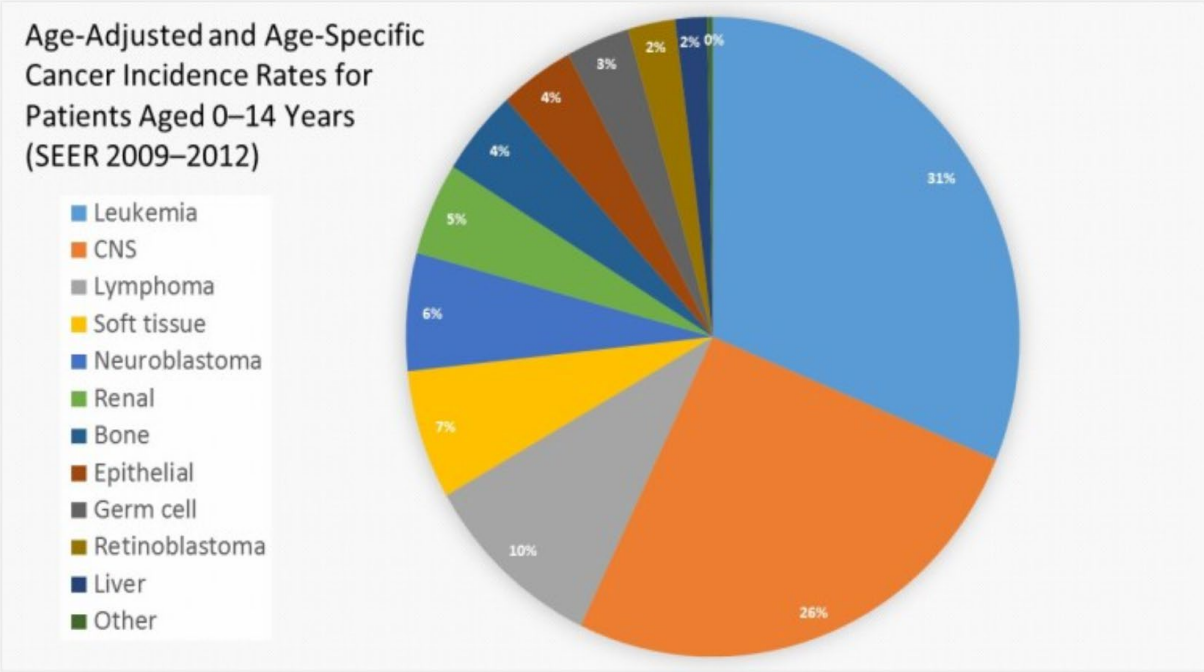

Figure 1. Age-adjusted and age-specific (0–14 years) Surveillance, Epidemiology, and End Results (SEER) cancer incidence rates from 2009 to 2012 by International Classification of Childhood Cancer group and subgroup and age at diagnosis, including myelodysplastic syndrome and group III benign brain/central nervous system tumors for all races, males, and females.

From: Rare Cancers of Childhood Treatment (PDQ®)

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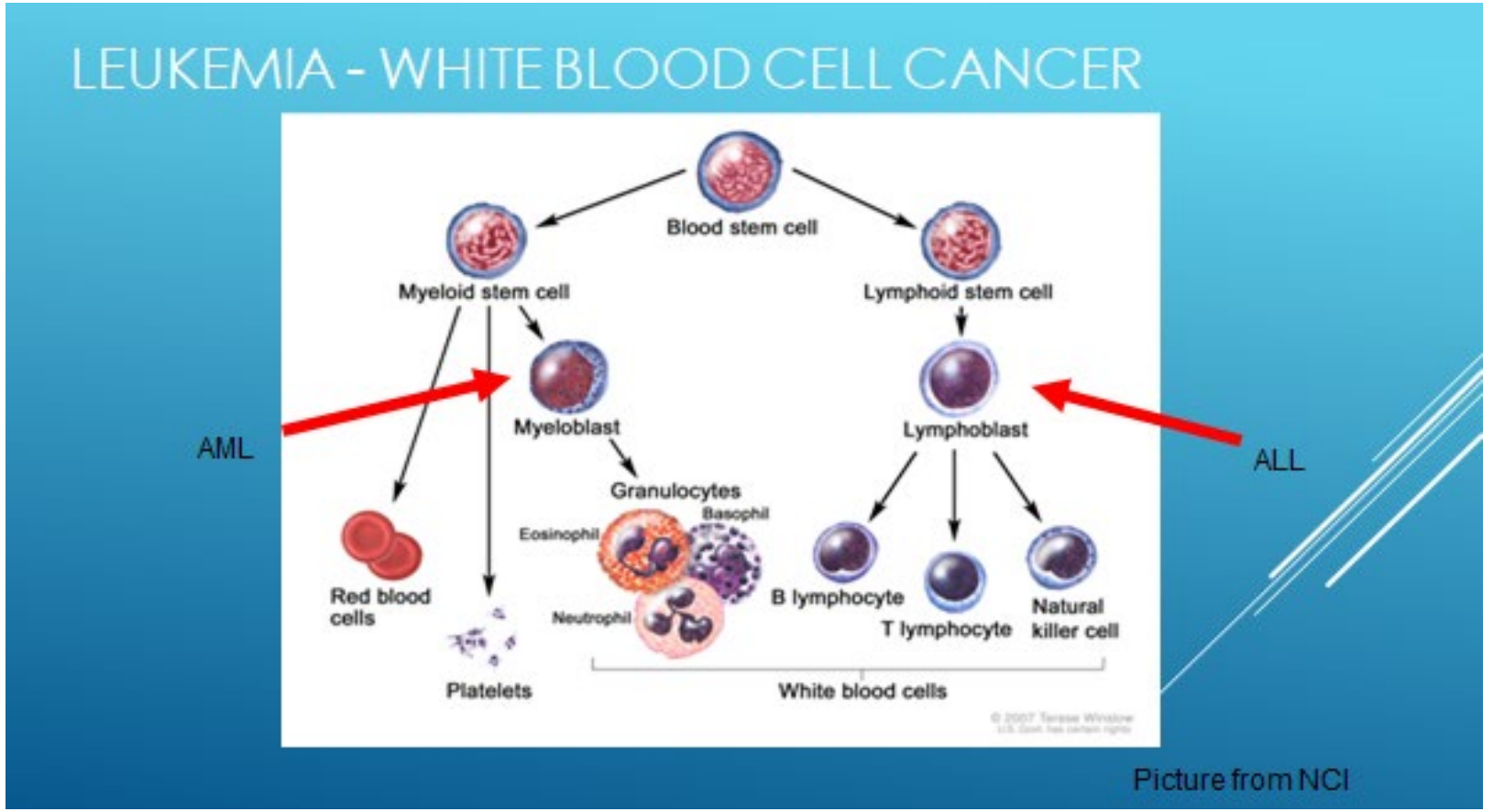
Approximately 60% of pediatric malignancies are solid tumors

- Brain tumors are the most common; ranging from slow growing more indolent tumors to aggressive tumors which require, surgery, chemo and radiation
- Followed by soft tissue tumors and neuroblastoma
- In teenage patients, sarcomas are most common. In younger children, Wilms tumor of the kidney and neuroblastoma
- Most solid tumors require a combination of surgery, chemotherapy and possibly radiation for treatment
- Initial treatment tends to be intensive, but typically less than a year of therapy
- Relapse adds to the length of treatment

40% of pediatric malignancies are leukemia



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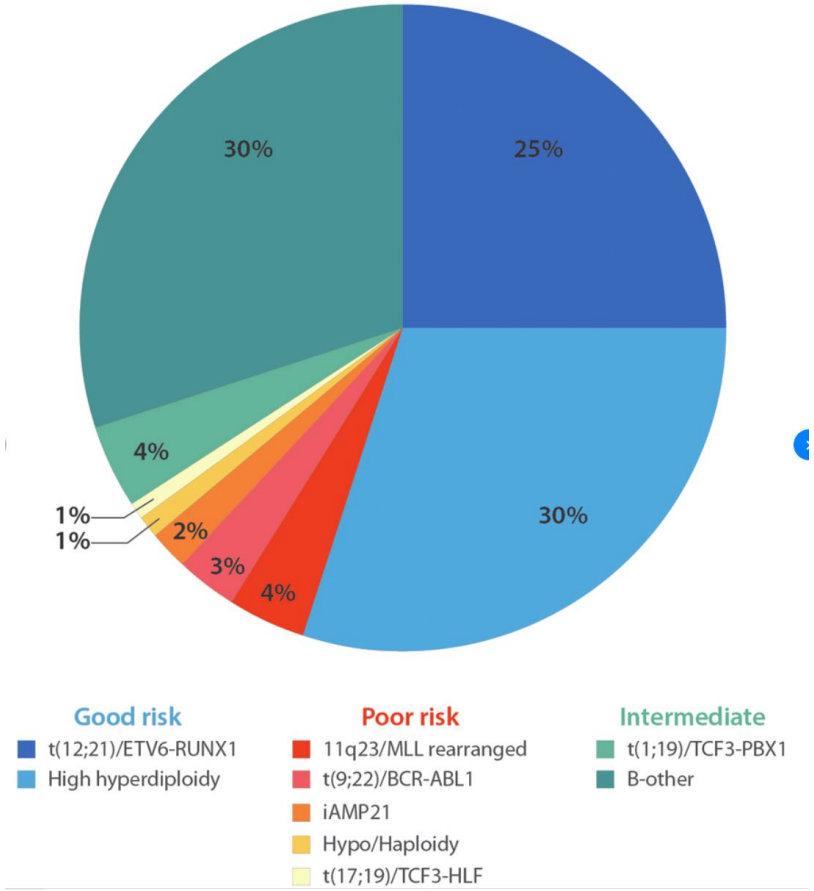
Pediatric Leukemia, most patients are low or standard risk



Research Gate

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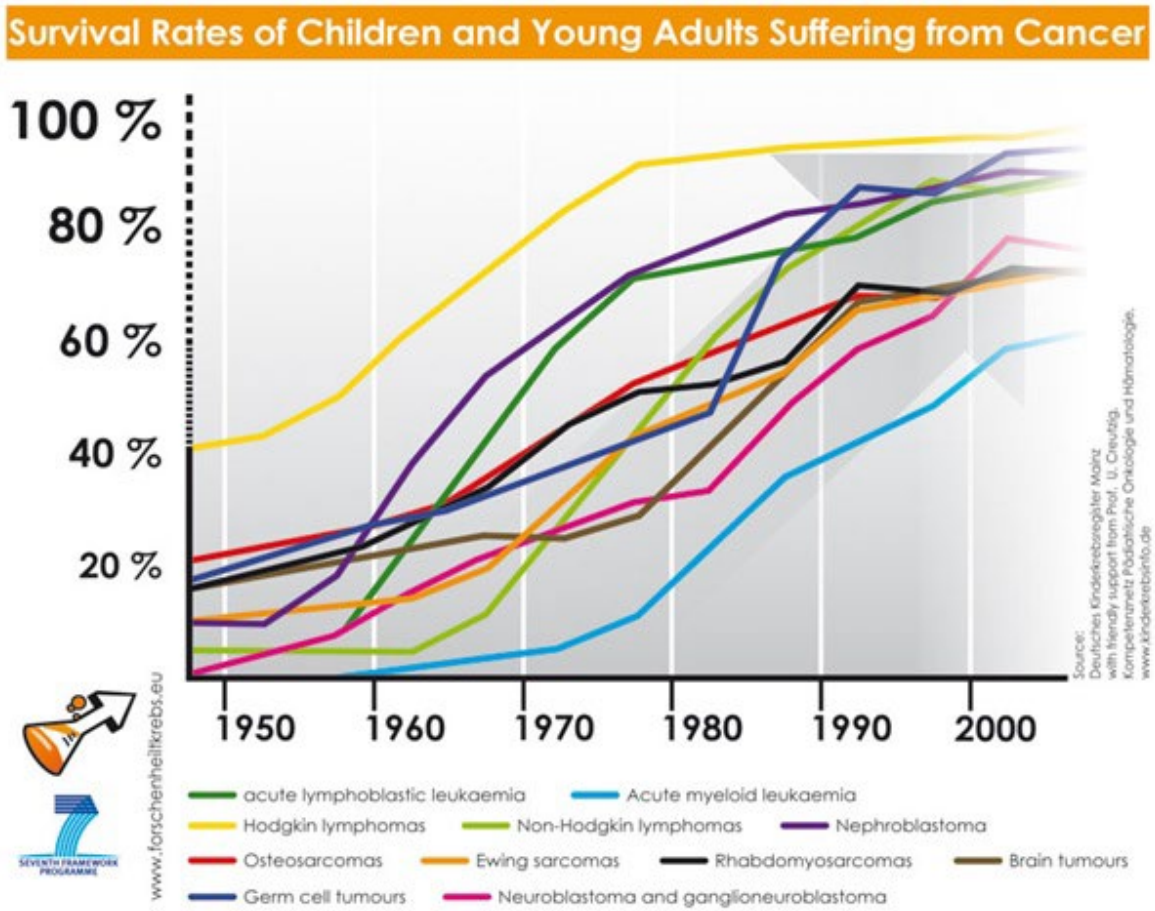
Treatment for Pediatric Leukemia varies with leukemia type and response to treatment

- Treatment for AML is dose intensive inpatient chemotherapy and in some cases stem cell transplant. Typically, a year or less of intensive treatment if no relapse or refractory disease. AML treatment does not typically include radiation
- ALL is 2-3 years of treatment. Depending on type, can be mostly outpatient after first 6-9 months of treatment
- For ALL treatment, hair grows back during "maintenance chemotherapy" and many kids "look normal" but remain at high risk for complications of treatment, infections and require ongoing monitoring and chemotherapy
- High risk and T cell ALL protocols may include CNS radiation
- Relapsed or refractory patients require "re-induction" chemotherapy, stem cell transplant or CAR-T
- Stem cell transplant involves prolonged hospitalization and intensive medical management for at least a year

Pediatric cancer survival rates have improved dramatically in the last few decades



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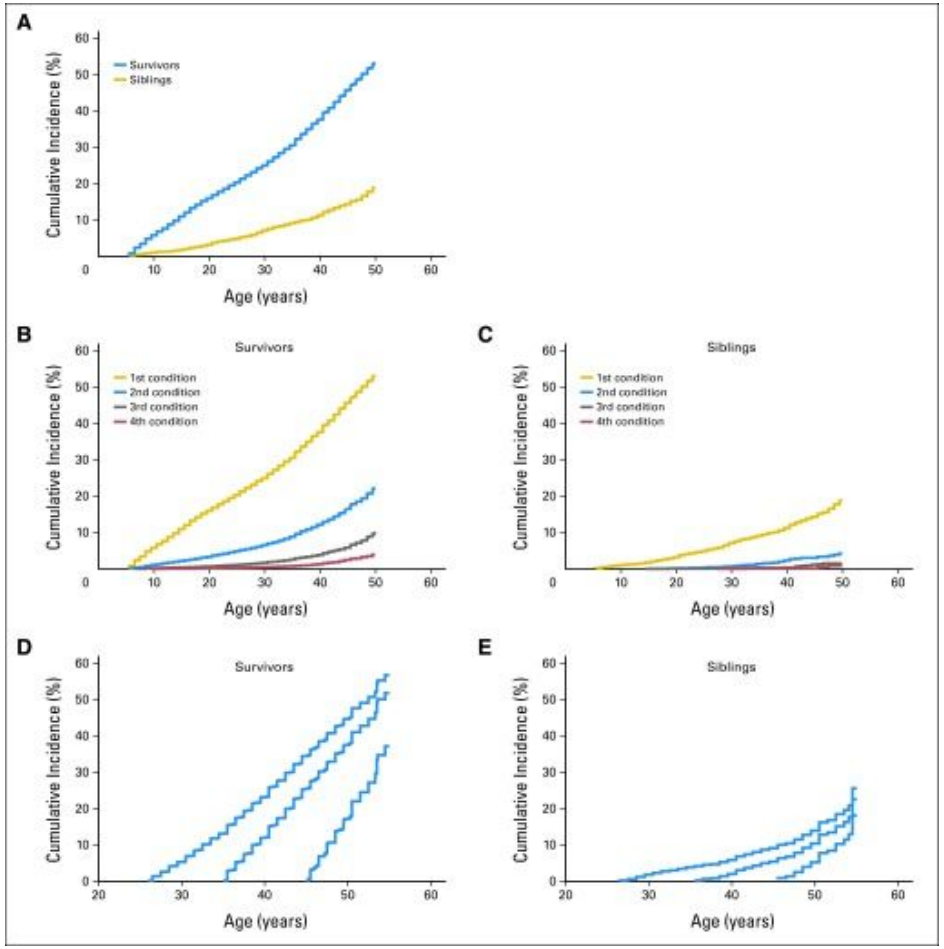
However, “successful” treatment comes at a cost The Childhood Cancer Survivorship Study Data:



By age 50, the cumulative incidence of a self-reported severe, disabling or life-threatening health condition was 53.6% among survivors, compared with 19.8% among a sibling control group.

Among survivors who reached age 35 without a previous severe, disabling, life-threatening health condition, 25.9% experienced a new grade 3 to grade 5 health condition within 10 years, compared with 6.0% of healthy siblings

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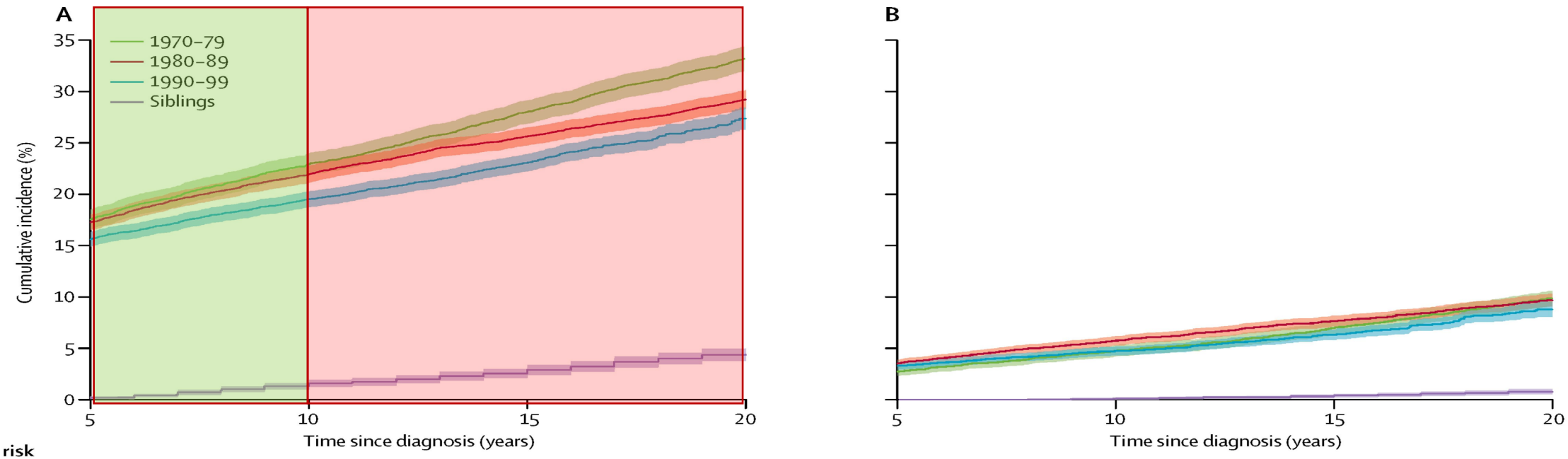

Number at risk (number censored)								
1970–79	6197 (0)	4546 (0)	4152 (1)	3611 (211)	6222 (0)	5606 (0)	5328 (4)	4809 (273)
1980–89	9373 (0)	6948 (102)	6009 (663)	4698 (1642)	9420 (0)	8421 (120)	7462 (802)	6036 (1979)
1990–99	7929 (0)	5942 (103)	3471 (2287)	702 (4922)	7956 (0)	7167 (140)	4251 (2859)	872 (6119)
Siblings	4905 (0)	4772 (62)	4355 (420)	3492 (1207)	5046 (0)	4966 (65)	4582 (437)	3734 (1263)

Cumulative incidence of grade 3–5 chronic health conditions in 5-year survivors of childhood cancer by diagnosis decade and siblings. (A) Cumulative incidence of a first grade 3–5 condition. (B) Cumulative incidence of two or more grade 3–5 conditions.

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Most common treatment modalities in pediatric oncology

• Surgical resection or “debulking”	• Risk of adhesions, strictures, altered physical appearance, single kidney
• “Conventional” Chemotherapy	• Long-term organ, endocrine, neuro-cognitive effects
• “Targeted” therapy such as TKIs for CML	• Endocrine and pulmonary effects
• Immunotherapy such as Rituximab	• Immunodeficiency
• Stem cell transplant or CAR-T	• Endocrine, immunodeficiency, secondary malignancy
• Radiation	• Endocrine, secondary malignancy

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For chemotherapy and radiation, the risk for late effects is related to drug, dose, and age of patient at time of administration

Late effects vary between drug classes

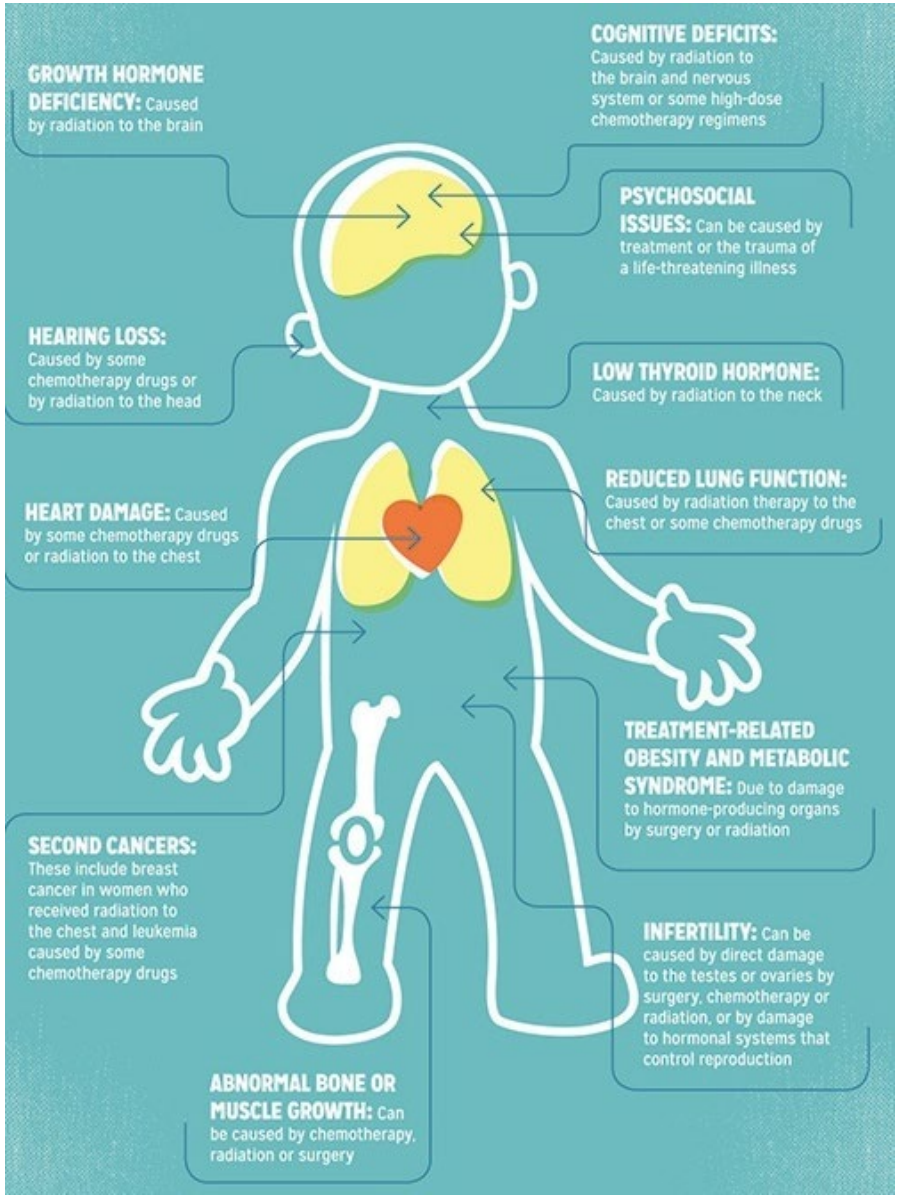
- Anthracyclines and Cytoxan = cardiac toxicity
- Cyclophosphamide and alkylators such as Busulfan = infertility, gonadal deficiency, premature ovarian failure
- Platinum based chemotherapy = oto-toxicity
- Corticosteroids = endocrinopathies, cataracts, osteopenia
- Alkylators, Etoposide and Radiation = secondary malignancy
- Bleomycin, Cyclophosphamide, Dasatinib, Gemcitabine, Brentuximab, Radiation to the chest = pulmonary toxicity
- Bortezomib, vinca alkaloids, taxanes, platinum-based chemotherapy= neuropathy

Dosing caps have been set for many drugs/radiation to reduce risk of severe long-term effects

- Anthracyclines
- Cyclophosphamide
- Alkylators
- Platinum-based chemotherapy
- Radiation

Age at time of administration

- Often times, younger age increases the risk
- For children less than 5 years of age:
- Increased risk of cardiac toxicity from anthracyclines
- Increased risk of neurocognitive late effects for CNS radiation
- Increased risk of ototoxicity from platinum chemotherapy
- Increased endocrine dysfunction from CNS radiation



Early identification and modification of risk factors may improve outcomes

Screening

Risk Reduction

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Cardiac

- Anthracycline induced cardiac toxicity is dose related.
- 1 in 10 Patients who receive more than 300mg/m2 total cumulative anthracycline dose will develop congestive heart failure
- Dose higher than 400mg/m2 are avoided unless extreme circumstances (multiply relapsed)
- Can be early onset within one year of treatment or up to 30 years later
- Younger age, female biologic sex, concomitant radiotherapy and genetic factors may increase risk
- Risk may be reduced with use of chelating agents such as Dexrazoxane (DRZ) to reduce free radical exposure

Close collaboration with cardiology

Echo, EKG and in some cases cardiac MRI, Blood pressure and lipid monitoring (frequency depends on dose exposure/risk)

Risk can be adapted with:

- Early recognition and treatment of hypertension
- Encouraging exercise, "heart-healthy" diets and avoiding obesity
- Early identification and treatment of elevated cholesterol or Triglycerides
- Avoiding smoking
- In some case, preemptive heart failure medications (ACE inhibitors and beta blockers) may be initialed to slow progression

Renal

- Childhood cancer survivors have a nine-fold increased risk of renal failure compared to siblings
- Renal toxicity can be secondary to chemotherapy, platinum-based, ifosfamide, cyclophosphamide
- Radiation to the flank/abdomen
- Single kidney following resection

- At least annual basic metabolic panel, Blood pressure monitoring and urinalysis
- Maintaining adequate hydration, avoiding renal toxic medications, smoking, compounding risk factors such as hypertension or diabetes

Pulmonary

- Secondary to chemotherapy, radiation to the chest or post-op thoracotomy, VATS
- Can have restrictive lung disease
- Can present while in treatment or months to years later
- Pulmonary Function Testing for high- risk patients
- Avoiding smoking/smoke exposure, avoid occupational risks, cardiopulmonary exercise, adequate control of asthma, avoiding obesity
- PCV, COVID and flu vaccination

Hepatic

- Most often due to high dose of radiation to the abdomen or graft vs host disease post BMT
- long-term hepatic dysfunction due to chemotherapy less likely in pediatrics unless other risk factors such as iron overload
- Annual hepatic panel with albumin
- Avoiding excess alcohol use, hepatitis, treating iron overload

Endocrine

- Metabolic syndrome
- Obesity
- Elevated cholesterol/Triglycerides
- Infertility
- Gonadal dysfunction/delayed or premature puberty
- Growth Hormone deficiency
- Hypothyroid
- Osteopenia

- Screening: TSH, T4, Vitamin D levels, Fasting lipid panel, Tanner staging, If delayed menses/puberty: LH, FSH, Estrogen, Testosterone, bone age if delayed growth or puberty concerns
- If growth delay/puberty concern: Endocrinology referral

- Maintain healthy weight, exercise and lipid levels

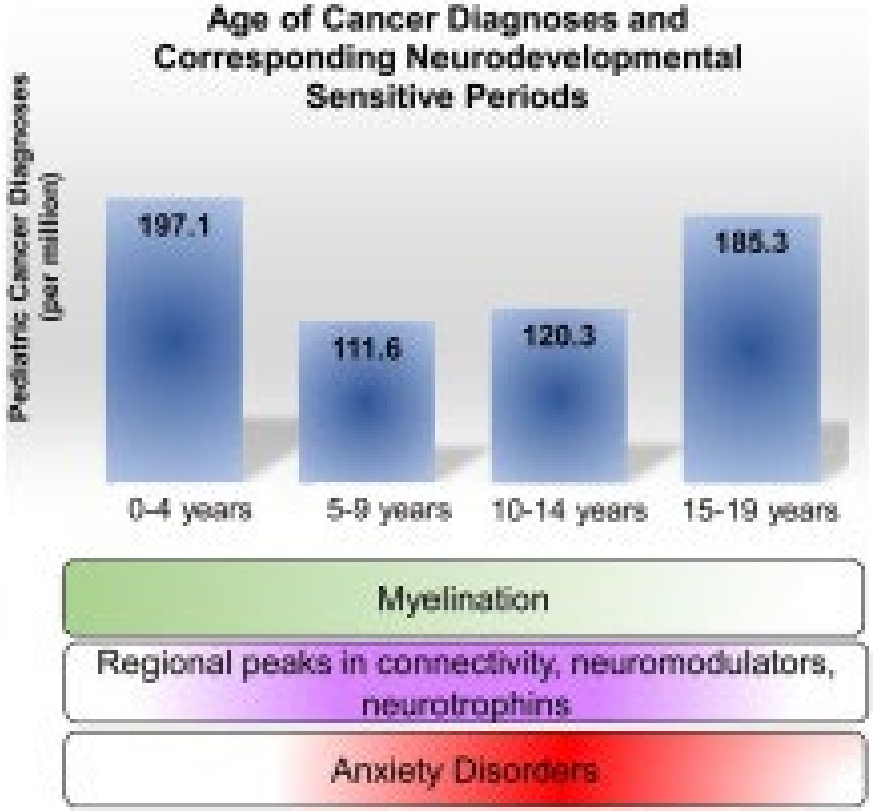
Overweight/Obesity is very common in childhood cancer survivors

- In a study of nearly 2,000 pediatric cancer survivors, 36.2% of childhood have a BMI >30
- 14% higher than peers
- 47% of survivors who received CNS radiation were obese
- Survivors treated at <4 years of age or with steroids were at increased risk
- Genetics may play a role, variations in *FAM155A*, *SOX11*, *CDH18* and *GLRA3* with increased risk
- Monitoring growth curve, weight and BMI
- Pre-emptive diet and exercise education, "healthy lifestyles" programs, limiting screen-time

Cognitive/Psychosocial

- Neurocognitive delay or school concerns especially common in Leukemia or CNS malignancy survivors
- Increased absentee rates very common in survivors
- Difficulties in short-term memory or processing common
- “Chemo brain” compounded by environmental and psychologic factors
- Depression and anxiety common in survivors
- Difficulty in re-establishing peer relationships
- PTSD vs post traumatic growth

Neurodevelopmental outcomes



- **Age at presentation/during treatment has a key effect**
- **Younger age may have higher risk of oto-toxicity and Neurocognitive delay**
- **Older patients are higher risk for anxiety**

Fig. 1. **Diagnoses and treatment for pediatric and adolescent cancer coincides with periods of massive neurodevelopmental change**. Blue bars represent the incidence of pediatric cancer across development (Steliarova-Foucher et al., 2017). During normal development, myelination in the brain peaks during early childhood, while synapses, neuromodulators and neurotrophins, as well as anxiety disorders, peak during early adolescence (Lee et al., 2014). How treatment regimens may shift these normal developmental patterns of myelination, neural connectivity, or emerging psychopathology is of interest to the developmental neuroscience community.

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School performance is an area of great concern for many survivors and their families

- Cognitive functioning, working and episodic memory, processing speed, executive functioning, and attention most impacted in survivors
- One study found more than 50% of survivors reported decreased school performance
- >90% for children treated at less than 5 years of age
- In some children, IQ drops by as much as 3 to 4 points per year
- Brain calcifications, leukoencephalopathy and decreased white matter volume correlates with this decline
- Neuro-psych testing, depression and anxiety screening
- early intervention with IEP, Neuro-psych rehabilitation, educational support services early referral to psychology services
- Psychology and Peer support groups

Heavy metal, ie Platinum based chemotherapy can lead to ototoxicity, neurotoxicity and nephrotoxicity

- Ototoxicity due to degeneration of hair cells of the ear which cannot regenerate
- Typically bilateral, sensorineural and permanent
- Higher frequency >4000Hz effected first
- Damage may continue to develop even after platinum-based chemo is stopped so ongoing Audiology evaluations and monitoring for speech delay are needed
- Carboplatin is less toxic than cisplatin due to greater stability but is also less efficacious and therefore requires a higher dose
- Highest risk of ototoxicity for pediatric patients at cumulative exposure of >400mg/m2 Cisplatin.
- Children under 5 years of age are at increased risk
- Concomitant CNS radiation or ototoxic medications can increase risk

Immune dysfunction/increased infectious risk

- Severity/Frequency depends on chemotherapy/radiation regimen
- For example, B cell aplasia is an expected outcome following CAR-T and patients often require years of IVIG repletion
- Patients treated with Rituximab are at risk for hypogammaglobulinemia
- B cell aplasia, low B cell subsets and low T cell numbers/function can result in reduced response to infection and vaccination
- Gradual immune reconstitution is common following bone marrow transplant; many patients remain on prophylactic antimicrobials especially if ongoing graft-vs-host disease and immunosuppression
- Vaccinating siblings, parents can reduce exposure risk

What about re-vaccination?

- Some patients are at increased risk for not maintaining serologic immunity to childhood vaccinations
- In particular, survivors of lymphoid leukemia, Burkitt's lymphoma, bone marrow transplant patients and patients who received prior Rituximab may be at risk for vaccination preventable illness
- Revaccination may be indicated based on titers
- Treatment summary should include indication for titers/risk
- Typically, we do not check titers until evidence of immune recovery, ie improved B cell subsets and IgG >400 off IVIG

Ophthalmologic/Dental

- Screening for cataracts, especially for children with prior corticosteroids or radiation to the orbits
- Dental caries, gingival issues very common post treatment
- Radiation to the face can impact jaw growth and tooth eruption

- Twice yearly dental evaluation and annual dilated eye/retinal exams
- Adequate fluoride and dental care, recognition and management of dental/gingival disease, UV blocking sunglasses

Secondary Cancer

- Leukemia or MDS associated with alkylators and etoposide, typically in the first 10 years following treatment
- Thyroid cancer following radiation to the thyroid
- Secondary brain, breast or bone tumors following radiation, usually occur a decade post treatment
- Skin Cancer

- Children are followed with:
- CBCs (annually or with new symptoms of fatigue, bleeding, frequent infections)
- Annual Thyroid ultrasound, Breast mammogram/MRI (starting 5 years post exposure)
- Dermatology annual evaluation/mole mapping for at risk patients

- Avoid tanning beds, sunburns, smoking, HPV vaccination, healthy diet/exercise

Orthopedic

Avascular Necrosis and Osteopenia

- Most common in patients who have received multiple courses of corticosteroids, methotrexate, CNIs post BMT, TKIs.
- Risk compounded by Gonadal insufficiency
- Chronic joint/limb pain = obtain plain films to evaluate for AVN.
- Screening DXA scan for high-risk patients
- Optimizing Vitamin D levels and adequate Calcium
- Weight baring exercise

Limb length discrepancies

- Following radiation/surgical resection

Foot Drop

- Most common following Vincristine
- Physical Therapy and bracing/casting very effective in treating

AVN

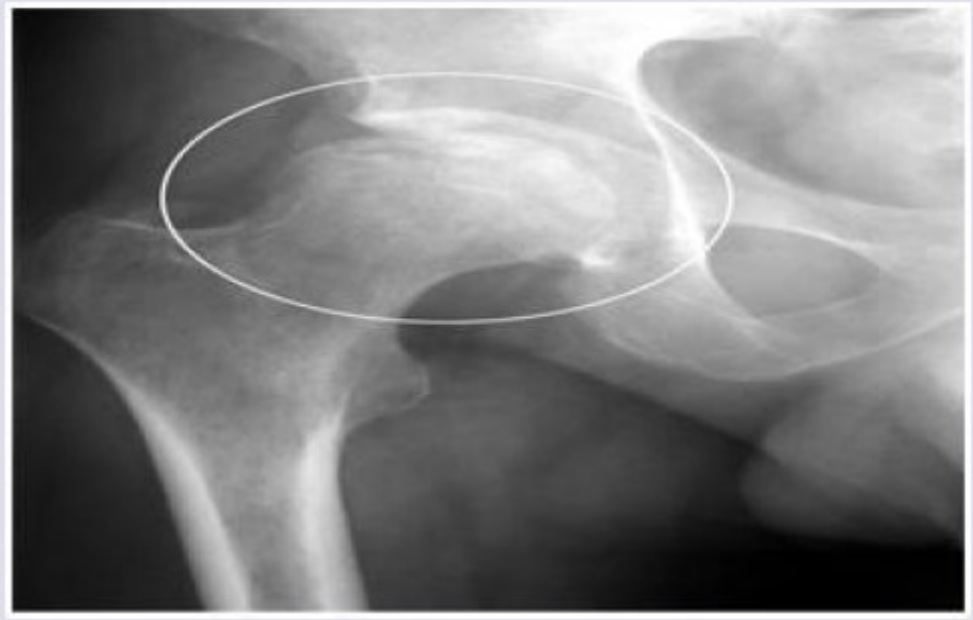
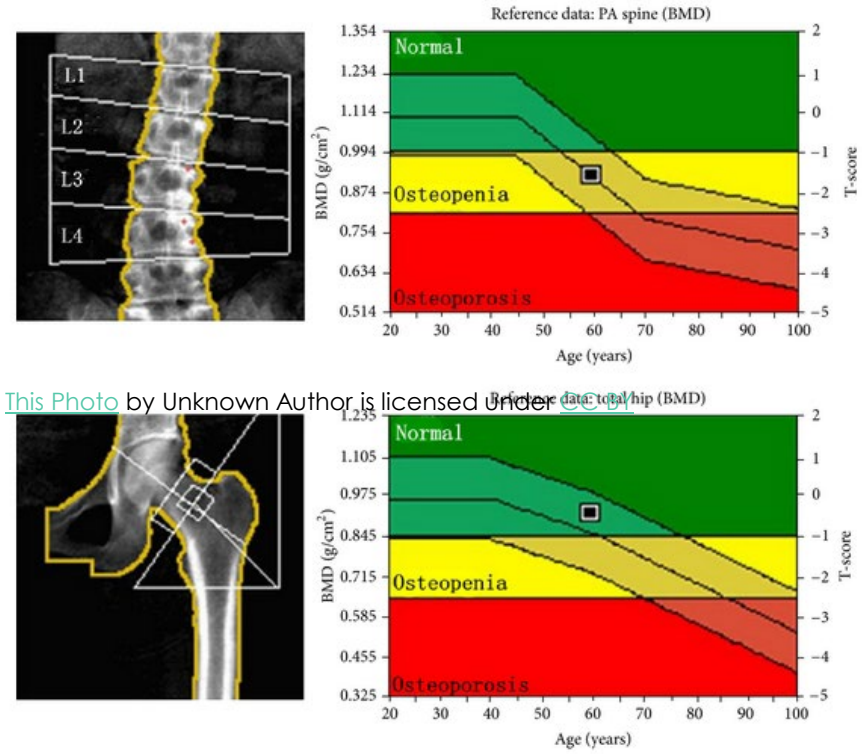


Figure 2: X- ray AP view of the right hip with features of AVN-FH.

Osteopenia



Resources

https://childrensoncologygroup.org/survivorshipguidelines

- Survivorship clinic at SZ campus as well as the Montgomery county ROC
- Treatment summary is a helpful tool for patients, families and providers
- Education liaisons, excellent resources for coordinating with local schools
- After school enrichment programs through community based Philanthropic groups
- Psychosocial team
- Survivorship/AYA support groups

Prevention is the best medicine

- Goal is to reduce treatment intensity while maintaining excellent outcomes
- In “Low Risk ALL”, reducing duration and intensity of treatment
- Reducing radiation exposure or delaying until older age for solid tumors and leukemia
- Fertility preservation options, discussion at diagnosis
- Surgical protection of gonads
- Chelation therapy for anthracyclines
- Hydration, Mesna to reduce GU toxicity
- Possibly STS for ototoxicity

Summary

- Survivorship rates have improved dramatically for many pediatric cancers
- However, treatment can "come at a high cost"
- Many current treatment protocols and ongoing studies focus on reducing treatment burden
- Early screening and intervention can delay or prevent late effects
- Close collaboration between primary care, oncology, schools, psycho-social support services is crucial to improving outcomes

- Thank you! Any questions?

References

Cancer PDQ
CCDD
COG Survivorship guidelines
Pediatric Anthracycline-induced Cardiotoxicity. A Tripaydonia, R. Conyers and D. Eilliot. Clinical Pharmacology and Therapeutics. 2019

Assessment and Management of platinum-related ototoxicity in children treated for cancer. A. Romano, M. Capozza and A. Ruggiero. Cancers. 2020

Late renal toxicity of treatment for childhood malignancy. R. Skinner. Pediatric Nephrology 2018

Cisplatin- induced nephrotoxicity in children: what is the best protective strategy? A. Ruggiero. J Oncol Pharm Pract. 2021

References Continued

Future considerations for pediatric cancer survivorship: Translational perspectives from developmental neuroscience. Rebecca M. Jones, Siobhan S. Pattwell, Developmental Cognitive Neuroscience, PBC Volume 38, 2019

Childhood cancer treatment and age influence obesity risk for childhood cancer survivors - St. Jude Children's Research Hospital (stjude.org)

Neuropsychological Sequelae of Childhood Cancer
Matthew C. Hocking,Melissa A. Alderfe Wiley 2012

Askins MA, Moore BD 3rd. Preventing neurocognitive late effects in childhood cancer survivors. J Child Neurol. 2008 Oct;23(10):1160-71. doi: 10.1177/0883073808321065. PMID: 18952582; PMCID: PMC3674758.

Q & A

Thank You!