Sarcomas

Living Beyond Cancer A-Z
UT Health San Antonio MD Anderson Cancer Center

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Bone and Soft Tissue Sarcomas

- Rare Tumors
- Different than “carcinoma”
- Cancers that start IN the tissues (cartilage, bone, muscle, tendon, ligaments, blood vessels)
- Unique management focused on multi-disciplinary approach

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Bone and Soft Tissue Sarcomas

- Account for about 1% of all adult malignancies
  - Roughly 12,000 new diagnoses in United States in Adults

- Account for about 10% of all pediatric malignancies
  - Approximately 1,000 new diagnoses in United States

Diagnosis

- Many sarcomas misdiagnosed initially as benign tumors

- Requires pathologist with familiarity in sarcomas
  - 100's of different sarcoma subtypes

- Biopsy should be done under supervision of surgeon that will be the ultimate treating surgeon

Sarcoma Principles

- Biopsies do not make cancers spread to other parts of the body
- Pathology analysis of the tissue can take 10-14 days for definitive results
- After diagnosing "what" it is, the next question: "where is it?"
- Most sarcomas when they metastasize will travel to the lungs
  - Only a few will travel to lymph nodes
  - CT of the Chest along with an MRI of the area of concern are necessary imaging tests

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Sarcoma Principle

All sarcomas should be treated by a multi-disciplinary team and discussed at a specialized tumor board

UT Health Sarcoma Tumor Board

Rajiv Rajani MD, Robert Quinn MD – Orthopaedic Oncology

Frederico Tozzi MD, Mio Kitano MD – Surgical Oncolgy

Elizabeth Bowhay Carnes MD, Vinu Madhusudhanannair-Kunnuparampil MD (Madhu) – Medical Oncology

Aaron Sugalski DO – Pediatric Medical Oncology

Richard Crownover MD – Radiation Oncology

Josephine Heim-Hall MD – Pathology

Michael Tall MD, Michael Davis MD - Radiology

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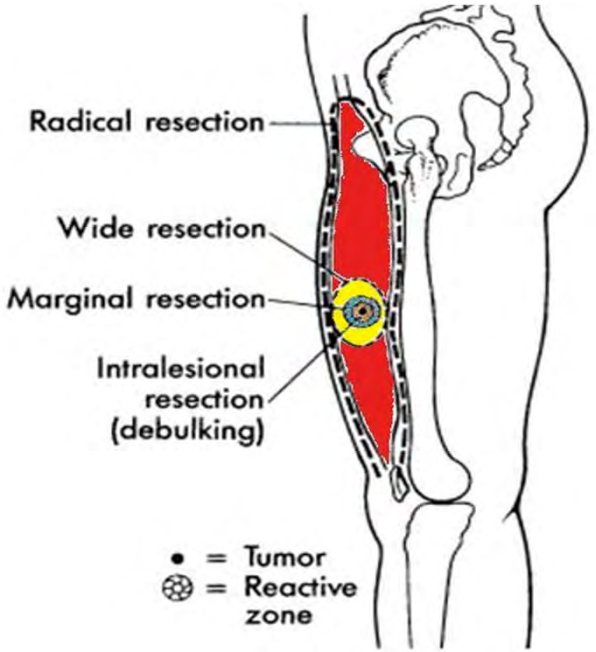
Sarcoma Treatment

Almost all sarcomas receive a surgery that removes the entire tumor

Some patients will receive chemotherapy and radiation therapy based on a variety of factors

- Appearance under microscope
- Present elsewhere
- Size of tumor
- How close to blood vessels, nerves, bone



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Goals of Treatment

- Remove ALL tumor
- Retain highest level of function while minimizing tumor recurrence risk
- Pain free function
- Avoid future complications (fracture, infection, drainage, recurrence)

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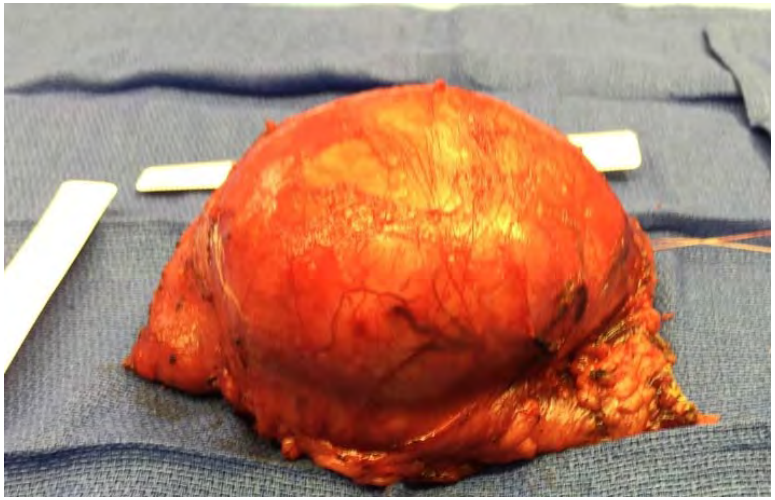
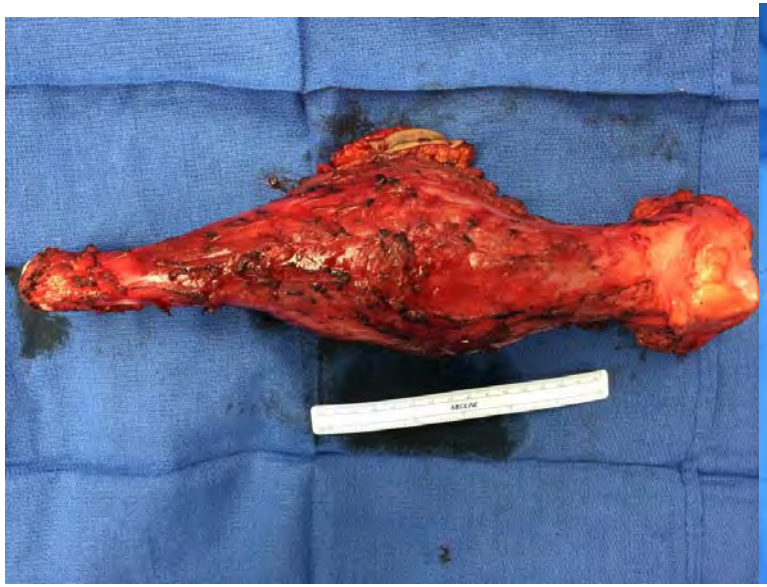
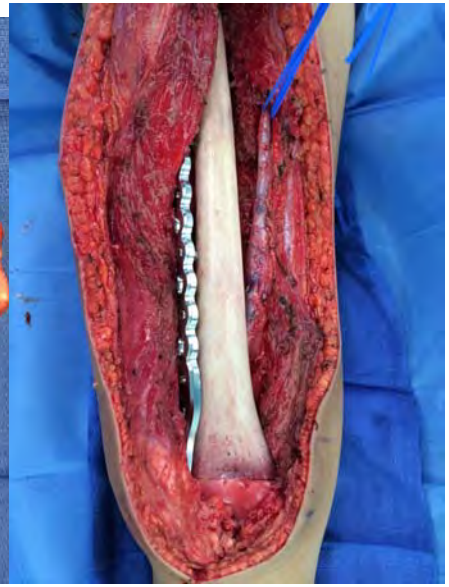
Examples







New Drug Development

- Standard cytotoxic chemotherapy includes Ifosfamide, Doxorubicin, Cisplatin, Methotrexate, Etoposide, etc.
- Genomics and tumor profiling has led to development of more molecular targeted therapies and precision medicine trials

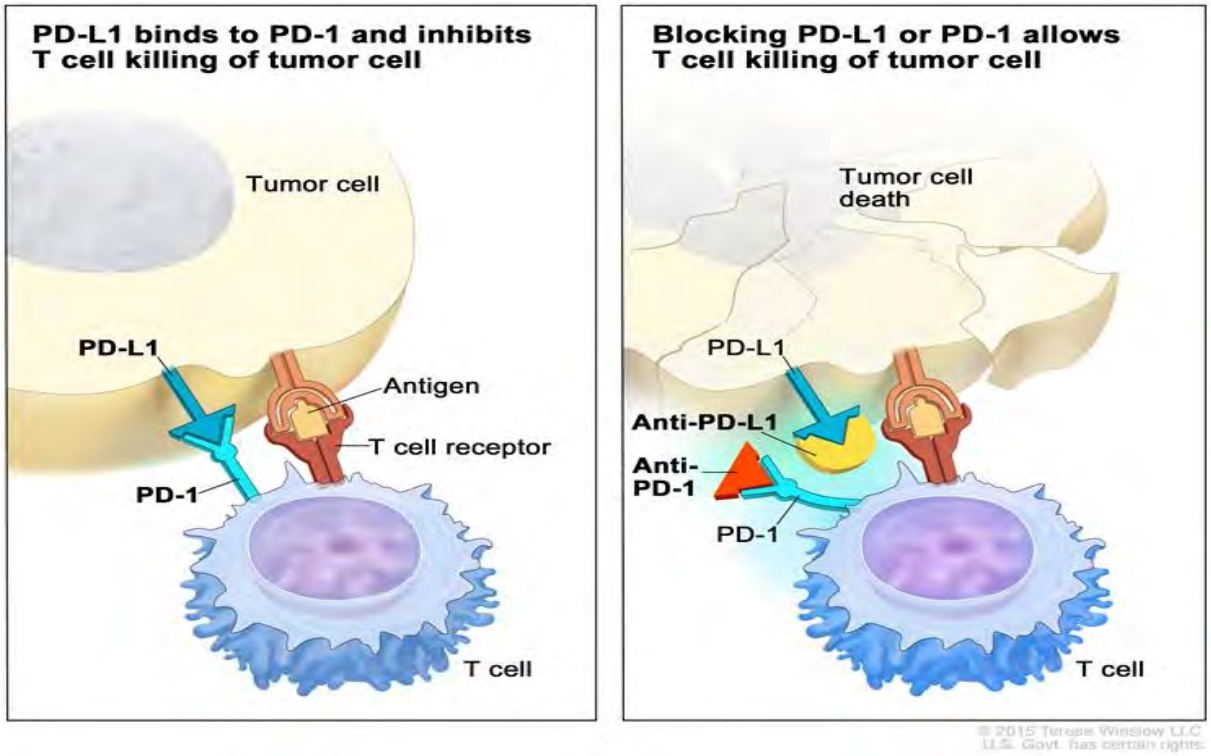
- Anti-Angiogenic Drugs
  - Pazopanib – VEGFR, PDGFR, other TKIs
    - First FDA approved molecular targeted therapy for STS
  - Sunitinib (ASPS), Sorafenib, Regorafenib
- Monocolonal Antibody - Olaratumab (PDGFR -)
  - Recent FDA approval for relapse disease
- Anti-mitotic agent - Eribulin – advanced liposarcoma

New Drug Development

- DNA binding block – Trabectidin- advanced liposarcoma or leiomyosarcoma
- mTOR inhibitors – sirolimus, everolimus, temsirolimus
- ALK (anaplastic lymphoma kinase) inhibitor
  - Crizotinib – Inflammatory myofibroblastic tumor (IMT)
- TRK fusion inhibitor
  - Larotrectinib – STS with identified TRK
- Insulin-like growth factor 1 inhibitor – Trial for Ewing Sarcoma ongoing
- RANK ligand inhibitor – Denosumab for giant cell tumor

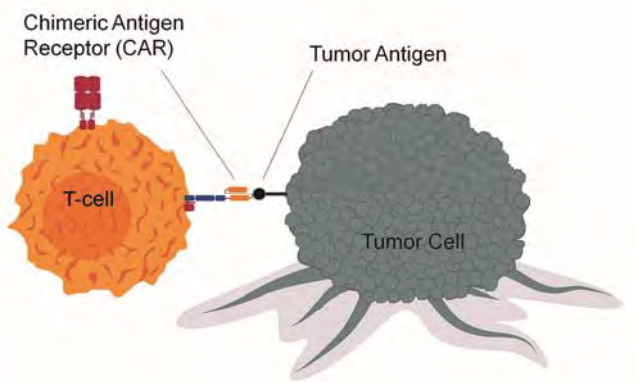
Immunotherapy Drug Development

- Checkpoint inhibitors (PD-1/PD-L1, CTLA-4) –
  - "Taking the brakes off the immune system"
  - Thought to be beneficial in tumors with high expression of PD-L1 or high mutational burden
  - Limited success at this point besides in undifferentiated pleomorphic sarcoma (UPS) or dedifferentiated liposarcoma
  - Pembrolizumab, Nivolumab, Ipilimumab, others



Immunotherapy Drug Development

- Genetically Engineered Specific T Cells
  - NY-ESO-1 - synovial sarcoma; myxoid/round cell liposarcoma
- Chimeric Antigen Receptor (CAR) T cell – Target HER2 (osteosarcoma)



- Vaccines – utilize tumor-specific fragment to trigger immune system to target cancer cells
  - NY-ESO-1 trials; SYT-SSX for synovial sarcoma
  - Early stages of development and likely need to be combined with other therapies (radiation, chemotherapy, checkpoint inhibitors)

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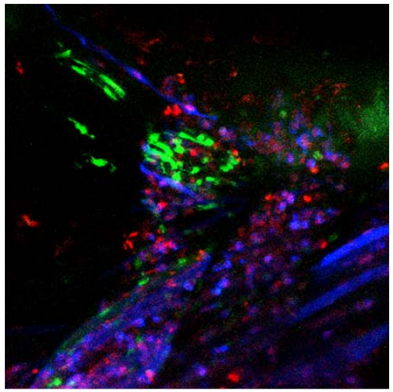
Greehey Children's Cancer Research Center (GCCRI) Sarcoma Team

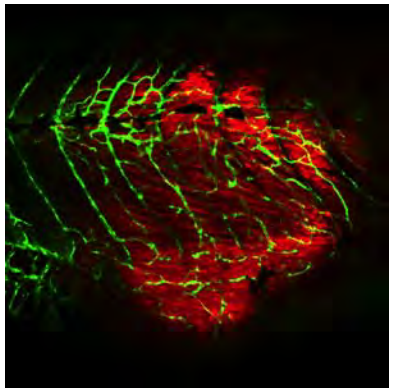
- **Alex Bishop** – Ewing sarcoma DNA Damage Repair.
- **Peter Houghton** – Insulin-like Growth Factors and Developmental Therapeutics Ewing sarcoma and rhabdomyosarcoma.
- **Raushan Kurmasheva** – Ewing sarcoma, Developmental Therapeutics .
- **Yuzuru Shiio** – Biology of Ewing and Synovial Sarcoma.
- **Manjeet Rao** – Osteosarcoma.
- **David Libich** – Fusion oncogenes, Ewing and synovial sarcoma.

Bishop Houghton Kurmasheva Libich Shiio Rao

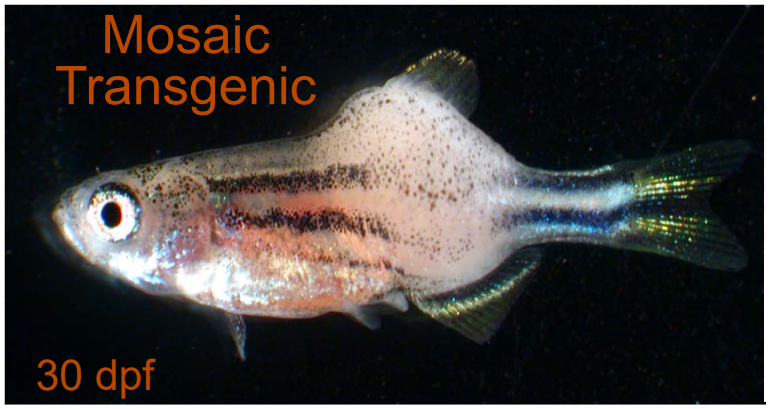
Zebrafish Models of Cancer/Sarcoma

In vivo
Imaging



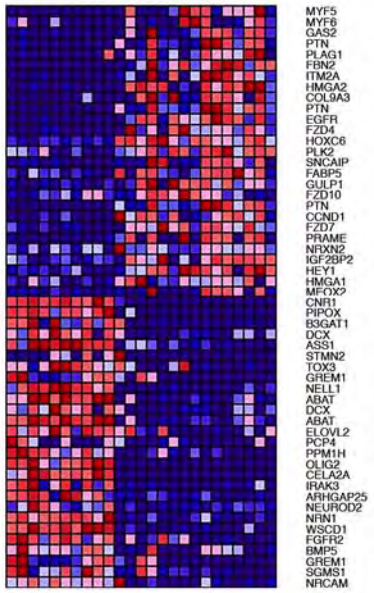


Relapse assays:
High-throughput
Cell Transplantation



Zebrafish Models Sarcoma

Bioinformatics
Approaches



Genetic approaches:
- Transgenesis
- Loss-of-function

Chemical Genetic
Approaches

November 12-13, 2018 • Merck Research Laboratories
33 Avenue Louis Pasteur Boston, MA

PAWS FOR A CURE RESEARCH SYMPOSIUM

Translational Potential Of Comparative Approaches To Accelerate Drug Development In Shared Childhood & Canine Cancers

WHO SHOULD ATTEND:

- Pediatric oncologists
- Veterinary oncologists
- Translational research scientists in academia and in industry
- Pharma and biotech professionals in preclinical research, drug development, oncology and animal health
- Nonprofit and other funders interested in learning about comparative and translational approaches to accelerate development of new and better medicines for the treatment of cancer, particularly devastating shared childhood and canine cancers.

Co-hosted by

Canines-N-Kids FOUNDATION
Finding a cure for pediatric and canine cancers... together

MERCK
INVENTING FOR LIFE

EARLY BIRD **REGISTRATION SAVINGS** AVAILABLE!

ADVANCING RESEARCH IN PEDIATRIC CANCER TREATMENTS has unique challenges, and progress toward better medicines and a cure has been limited. Intriguingly, BOTH children and our canine companions spontaneously develop a number of cancers with remarkable similarities, including osteosarcoma, certain brain/CNS cancers, lymphoma and leukemia. Speakers, panelists and participants will discuss challenges and progress in accelerating cancer drug development using comparative approaches, including:

- The state of the art in comparative and novel translational cancer research
- Ongoing preclinical, translational and clinical projects leveraging the canine patient model.
- The most promising prospects for future scientific exploration, collaboration and funding.
- Life journey presentations by childhood cancer survivors and advocates.

Sarcoma Survivorship

- Sarcoma treatment is combination of surgery, radiation, chemotherapy, or immunotherapy.
- Requires follow up in multi-disciplinary clinic for long term effects of treatment

Journal of Surgical Oncology 2015;111:648–655

Survivorship

DOUGLAS J. HARRISON, MD* AND CINDY SCHWARTZ, MD, MPH
Division of Pediatrics, MD Anderson Cancer Center, Houston, Texas

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TABLE I. Late Effects in the STS Survivor by Exposure

Exposure		Organ system	Specific late effect
Chemotherapy	Doxorubicin	Cardiotoxicity	Pediatric:Dilated followed by restrictive cardiomyopathy Adult:Dilated cardiomyopathy Arrhytmia
			Diabetes, HTN, lipid disorders, CAD
	Ifosfamide	Renal toxicity	Fanconi syndrome; growth inhibition; Nephrogenic Rickets
		Secondary malignancy (SMN)	Secondary leukemia at high cumulative dose as well as secondary solid malignancy in rare instances
		Fertility complications	
	Cisplatin	Hearing Loss	
	Methotrexate	Renal Toxicity, Neurotoxicity	
	Cyclophosphamide	Renal Toxicity	
	Etoposide	Secondary Malignancy	
	Any	Anxiety, Depression	

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TABLE I. Late Effects in the STS Survivor by Exposure

Exposure	Organ system	Specific late effect
Radiation	Renal toxicity	Radiation induced Nephropathy (Dose 20–25 Gy)
	Fertility complications	STS patients unlikely to receive primary gonadal radiation but azospermia is documented at doses above 4 Gy in men and ovarian failure at doses above 8 Gy in women
	Secondary malignancies	STS patients are at increased risk for solid tumors in the field of radiation
Radiation, continued	Musculoskeletal complications	Pediatrics:Growth arrest at doses above 10–20 Gy if epiphyseal growth plate is within the radiation field; Spinal deformity, craniofacial defects, slipped capital femoral epiphysis, limb length discrepancy depending on dose, volume, and field of radiation ALL:Osteopenia: Muscle, bone, and soft tissue hypoplasia; Strength deficit, Rarely muscle atrophy and edema which can lead to long term fibrosis and chronic pain
Surgery	Functional and musculoskeletal complications	Dependent on area and extent of resection

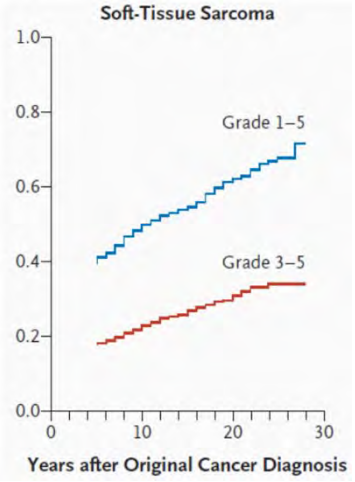
Oeffinger et al., NEJM, 2006

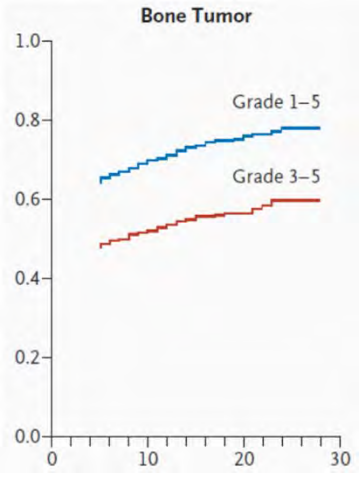
Chronic Health Conditions in Adult Survivors of Childhood Cancer

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D., Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D., Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P., Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D., and Leslie L. Robison, Ph.D., for the Childhood Cancer Survivor Study*

Table 3. Relative Risk of Selected Severe (Grade 3) or Life-Threatening or Disabling (Grade 4) Health Conditions among Cancer Survivors, as Compared with Siblings.

Condition	Survivors (N=10,397)	Siblings (N=3034)	Relative Risk (95% CI)
	percent		
Major joint replacement*	1.61	0.03	54.0 (7.6–386.3)
Congestive heart failure	1.24	0.10	15.1 (4.8–47.9)
Second malignant neoplasm†	2.38	0.33	14.8 (7.2–30.4)
Cognitive dysfunction, severe	0.65	0.10	10.5 (2.6–43.0)
Coronary artery disease	1.11	0.20	10.4 (4.1–25.9)
Cerebrovascular accident	1.56	0.20	9.3 (4.1–21.2)
Renal failure or dialysis	0.52	0.07	8.9 (2.2–36.6)
Hearing loss not corrected by aid	1.96	0.36	6.3 (3.3–11.8)
Legally blind or loss of an eye	2.92	0.69	5.8 (3.5–9.5)
Ovarian failure†	2.79	0.99	3.5 (2.7–5.2)





Slide adapted from Dr. Gregory Aune

Bhakta et al, Lancet, 2017.

The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE)

Nickhill Bhakta, Qi Liu, Kirsten K Ness, Malek Baassiri, Hesham Eissa, Frederick Yeo, Wassim Chemaitilly, Matthew J Ehrhardt, Johnnie Bass, Michael W Bishop, Kyla Shelton, Lu Lu, Sujuan Huang, Zhenghong Li, Eric Caron, Jennifer Lanctot, Carrie Howell, Timothy Folse, Vijaya Joshi, Daniel M Green, Daniel A Mulrooney, Gregory T Armstrong, Kevin R Krull, Tara M Brinkman, Raja B Khan, Deo K Srivastava, Melissa M Hudson, Yutaka Yasui*, Leslie L Robison*

Studied 5,522 Survivors >18 years old and > 10 years form diagnosis

<u>On average:</u>

- 17.1 chronic health conditions grade 1-5 by age 50
- 4.7 chronic health conditions grade 3-5 by age 50

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Slide adapted from Dr. Gregory Aune

Cumulative burden of chronic health conditions by disease

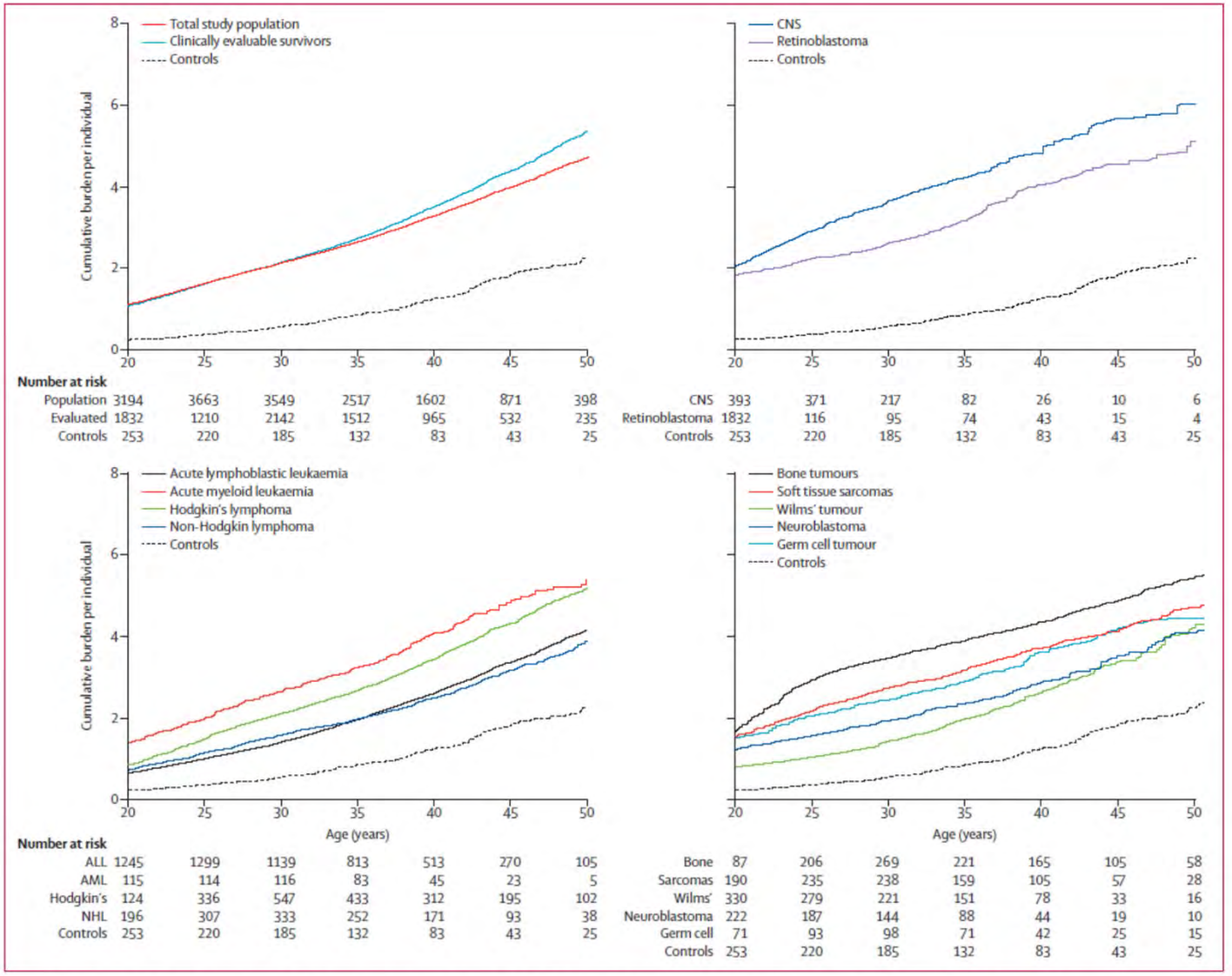

Figure 3: **Cumulative burden of severe (grade 3–5) chronic health conditions in St Jude Lifetime Cohort Study survivors of childhood cancer and in community controls**

Bhakta et al, Lancet, 2017.

Sarcoma Survivorship at UT Health San Antonio

- Pediatric, Adolescent and Young Adult (AYA) Diagnosis
  - Musculoskeletal Tumor Follow-up Clinic
  - Multidisciplinary visit seen by Pediatric Oncologist, Orthopedic Oncologist, Prosthetist, Psychologist.
  - Screened with recommended Imaging, ECHO/EKG, Audiogram and Laboratory Assessments
  - Appropriate referrals completed
  - Research Studies offered through Children's Oncology Group
    - ALTE11C2 - Health Effects after Anthracycline and Radiation Therapy (HEART)
    - ALTE1621- Pharmacologic Reversal of Ventricular Remodeling: A Phase 2b Randomized Placebo-Controlled (Carvedilol) Trial
    - ALTE16C1- Effects of Modern Chemotherapy Regimens on Spermatogenesis and Steroidogenesis in Adolescent and Young Adult (AYA) Survivors of Osteosarcoma

Sarah Lea[1] | Ana Martins[1] | Matt Bassett[2] | Maria Cable[3] | Gary Doig[2] | Lorna A. Fern[1,4] | Sue Morgan[5] | Louise Soanes[1] | Sam Smith[2] | Michael Whelan[3] | Rachel M. Taylor[1]

Eur J Cancer Care. 2018;27:e12972.

TABLE 3 Sources of information and support for young people with cancer at the end of active treatment

Source	Key things recommended or identified as sources of support/information
Hospital/medical team	• Post-treatment support provided by the hospital, by professionals such as social workers and specialist nurses (Moody et al., 2015) • Preparation for end of treatment, provision of information, follow-up and service referrals after treatment ends; longer consultations than older cancer patients (Brédart et al., 2015) • Sleep screening to identify disturbances and better support to adolescents and young adults (AYA) after completion of cancer therapy are important to reduce impact of poor sleep (Daniel et al., 2017) • Provision of a summary at the end of treatment, to facilitate AYA when telling others about their cancer when they return to school (Choquette et al., 2016) • Effective communication between the school and hospital before active treatment ends, to assist smooth reintegration to school (Thompson et al., 2009)
Family and existing friends and peers	• Maintaining peer groups or close friendships throughout treatment (Choquette et al., 2016; Pini et al., 2013) • Family was reported by healthcare professionals as one of the main sources of support for young people after treatment ends (Moody et al., 2015)
Peers with cancer	• Opportunities and mechanisms for peer-to-peer support and to connect with other AYA living with and beyond cancer, for example support groups specifically for AYA, peer-to-peer counselling (Moody et al., 2015; Roper et al., 2013; Thompson et al., 2009)
Online	• Access to cancer websites and social media groups online to access social support (Moody et al., 2015; Shen et al., 2016)
Specific services	• Programmes targeting health behaviour, which covered nutrition and exercise, were used immediately after treatment and popularity increased at 6 months after treatment (Roper et al., 2013) • A rehabilitation programme providing psycho-education targeted at giving AYA tools to cope with the challenges of cancer survivorship (Hauken & Viken, 2015) • Use of cognitive therapy to help AYA cope with negative thoughts, emotions and behaviours (Hauken & Viken, 2015)
Education/work	• Encouragement from teachers; in addition to maintaining relationships with school personnel throughout their treatment (Choquette et al., 2016; Pini et al., 2013) • Having a reduced school workload to help AYA transition back to school (Choquette et al., 2016) • Transitional care planning to assist AYA to reintegrate through return-to-work assistance and occupational rehabilitation (Thompson et al., 2009)