Cancer Risk and Management in RTS

Webinar Series, #5

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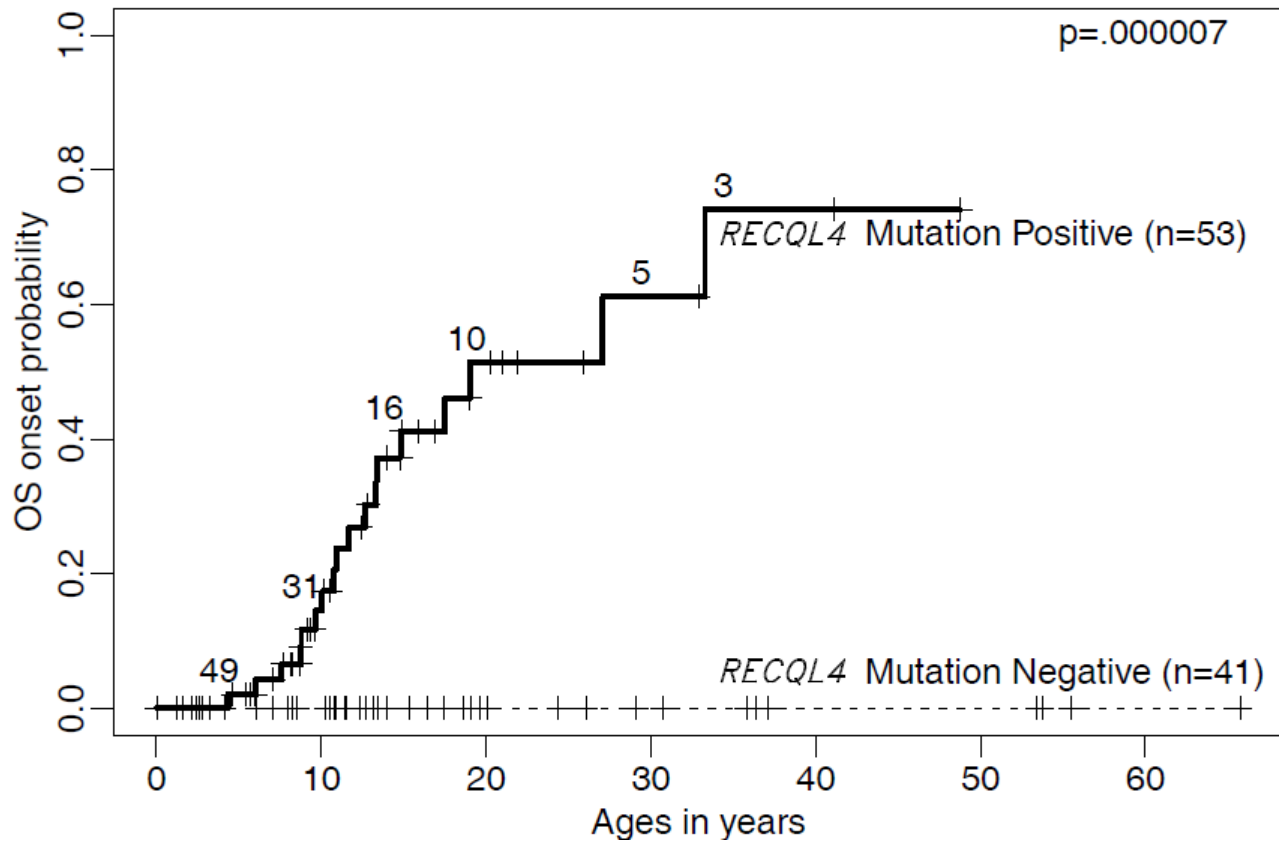
Summary of Clinical Findings in 41 RTS Subjects
Baylor College of Medicine Study

Rash	**41/41**	**100%**
Small stature	**25/38**	**66%**
Skeletal dysplasia	**15/20**	**75%**
Radial ray defect	**8/40**	**20%**
Sparse scalp hair	**15/30**	**50%**
Sparse brows/lashes	**19/26**	**73%**
GI disturbance	**7/41**	**17%**
Cataracts	**2/32**	**6%**
Skin cancer	**1/41**	**2%**
Osteosarcoma	**13/41**	**32%**

Wang *et al* (2001) Am J Med Genet; 102:11-17

Presence of *RECQL4* mutations increases risk of osteosarcoma (OS) in RTS



Type 2 RTS:
RECQL4 mutations

Increased risk of OS compared to Type 1

Type 1 RTS:
No *RECQL4* mutations

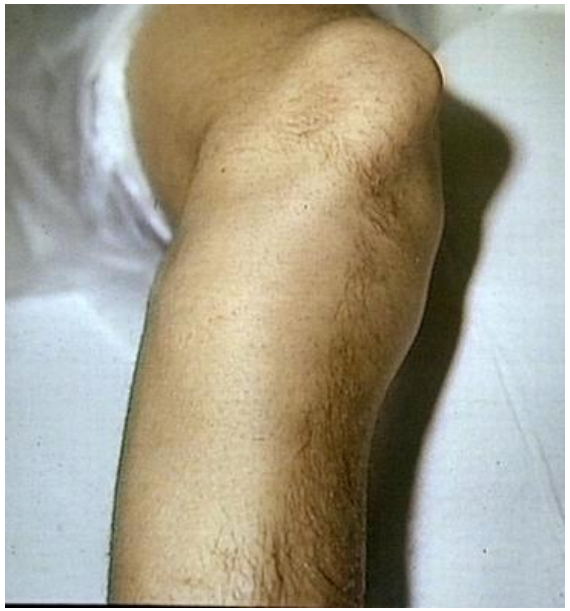
Lu et al, Adv Exp Med Biol. 2014;804:129-45

Osteosarcoma

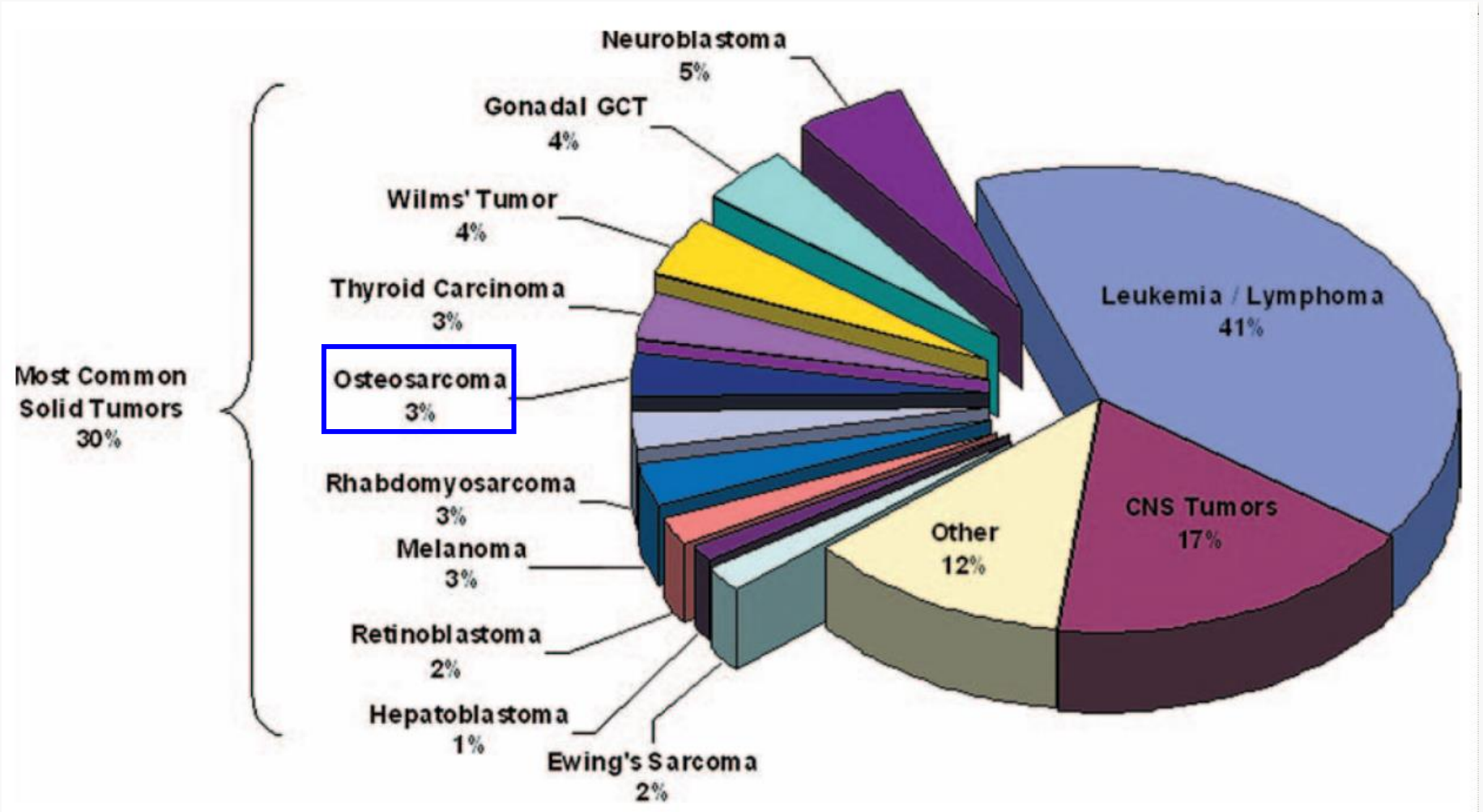
- Known associations
  - Prior irradiation
  - Li-Fraumeni syndrome (*p53*)
  - Bilateral retinoblastoma (*RB*)
  - Adults with Paget's disease
  - Werner syndrome (*WRN*)
  - Rothmund-Thomson syndrome (*RECQL4*)

Sporadic Osteosarcoma

- Most common malignant bone tumor in children and adolescents
- Patients usually present with pain in the affected bone with no systemic symptoms
- Peak age during teenage years

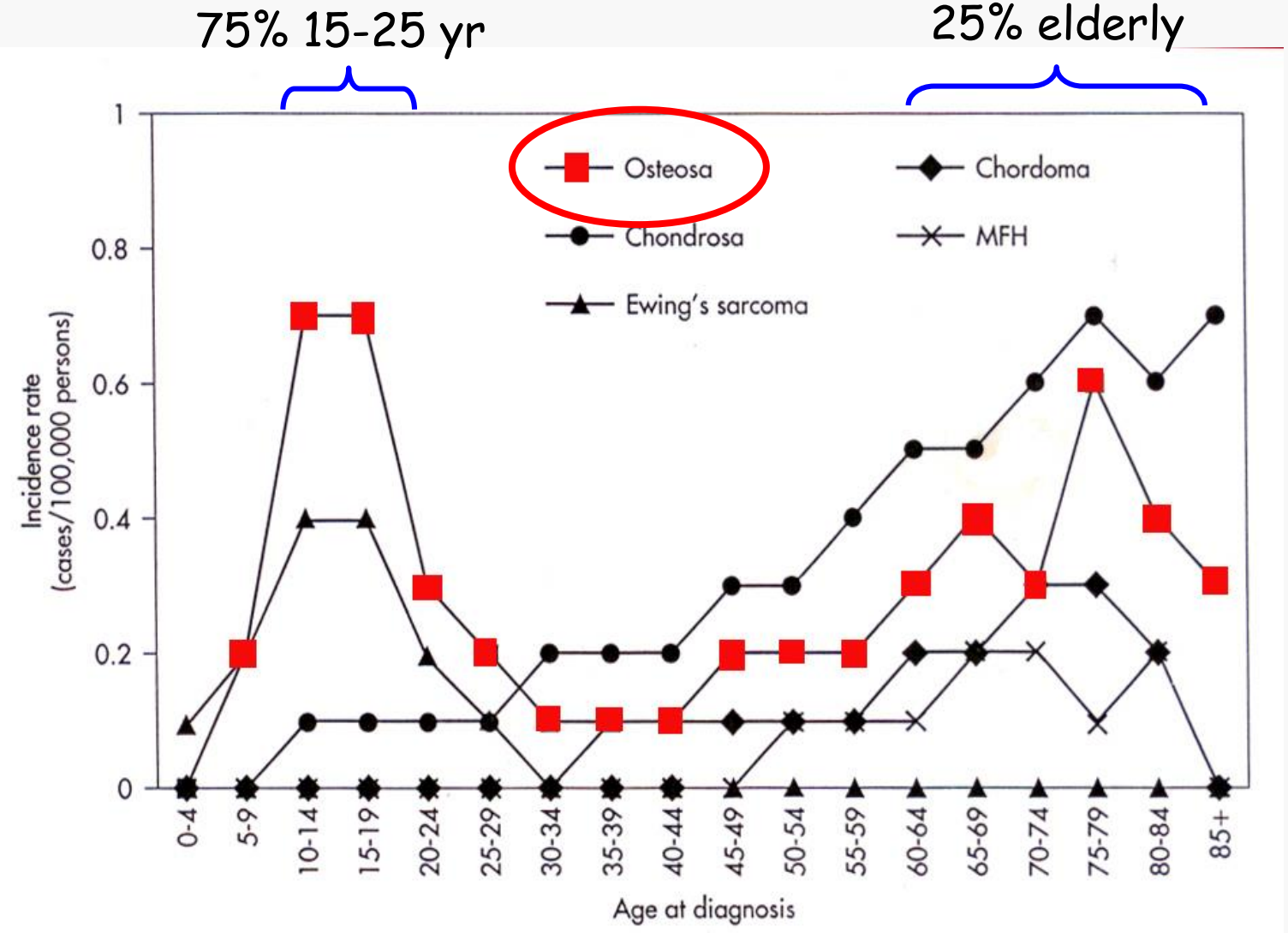


Distribution of pediatric tumors under the age of 20 years
SEER 1986-1995



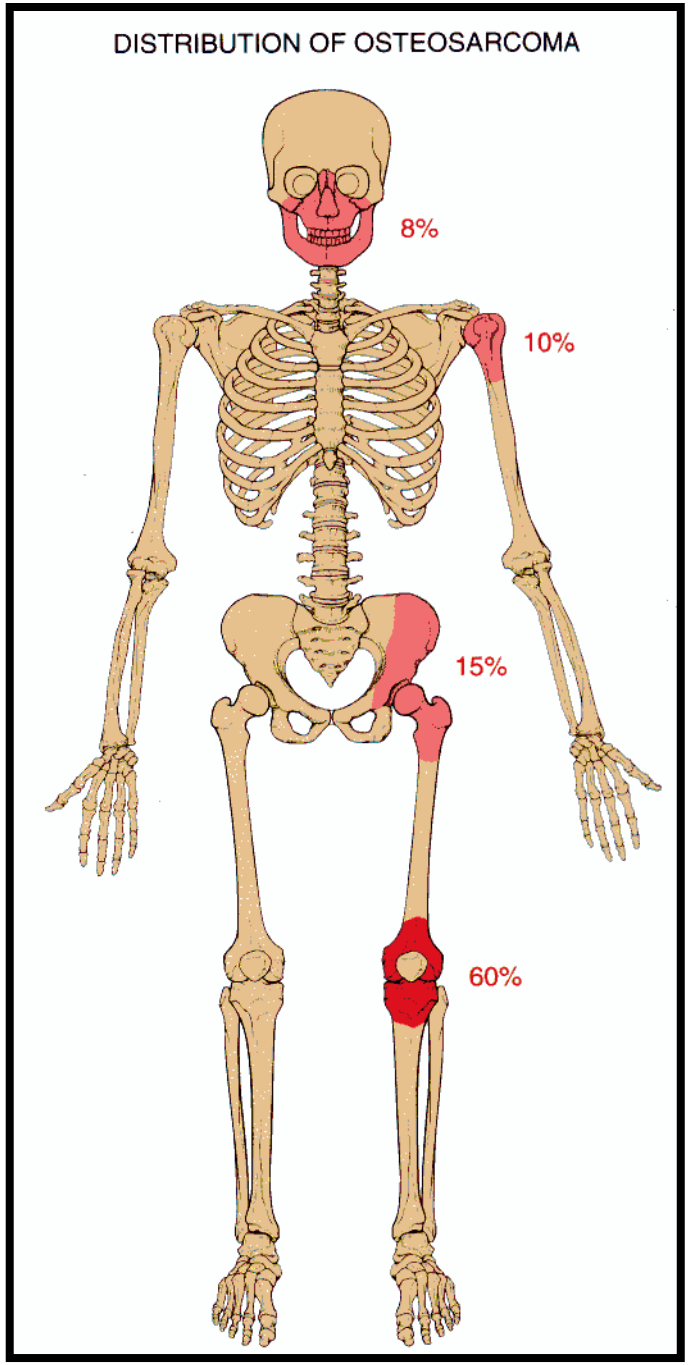
Osteosarcoma: Epidemiology

- Bimodal age distribution



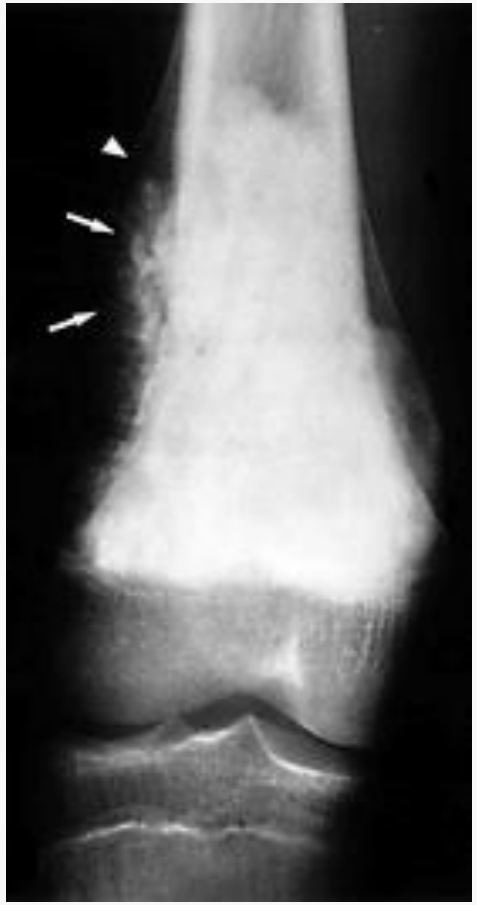
Distribution of Osteosarcoma in children

- 2/3rds occur around knee
- Distal femur > proximal tibia > proximal femur > proximal humerus
- Axial lesions less common
- Metastases to lungs and other bones: 25% at diagnosis

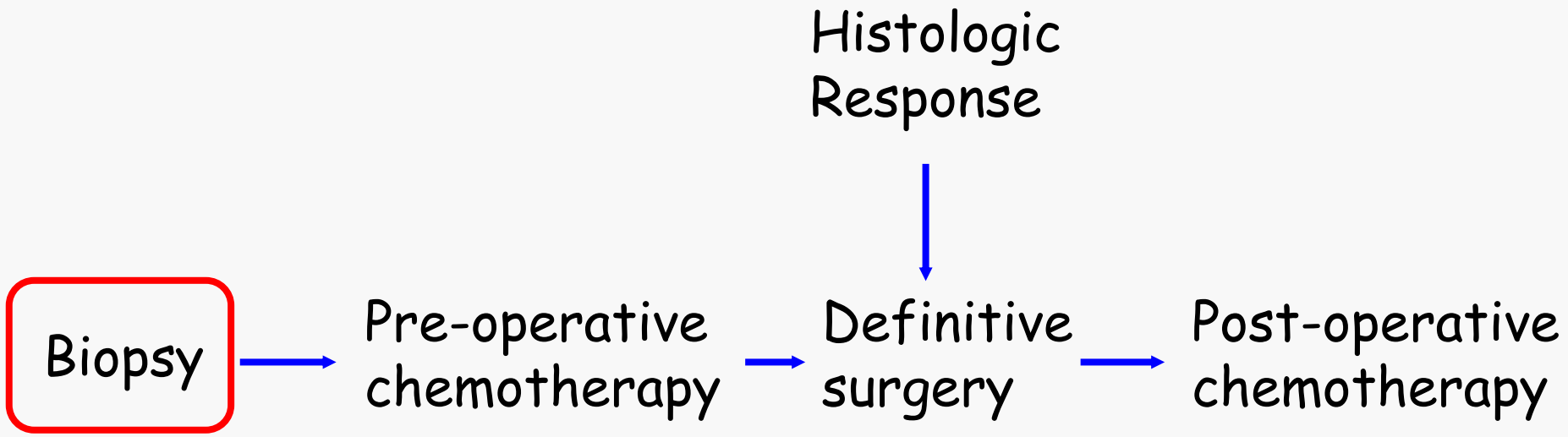


Osteosarcoma: Radiology

- Mixed lytic/blastic
- Cortical breakthrough “Codman’s triangle”
- Radial ossification “sunburst”

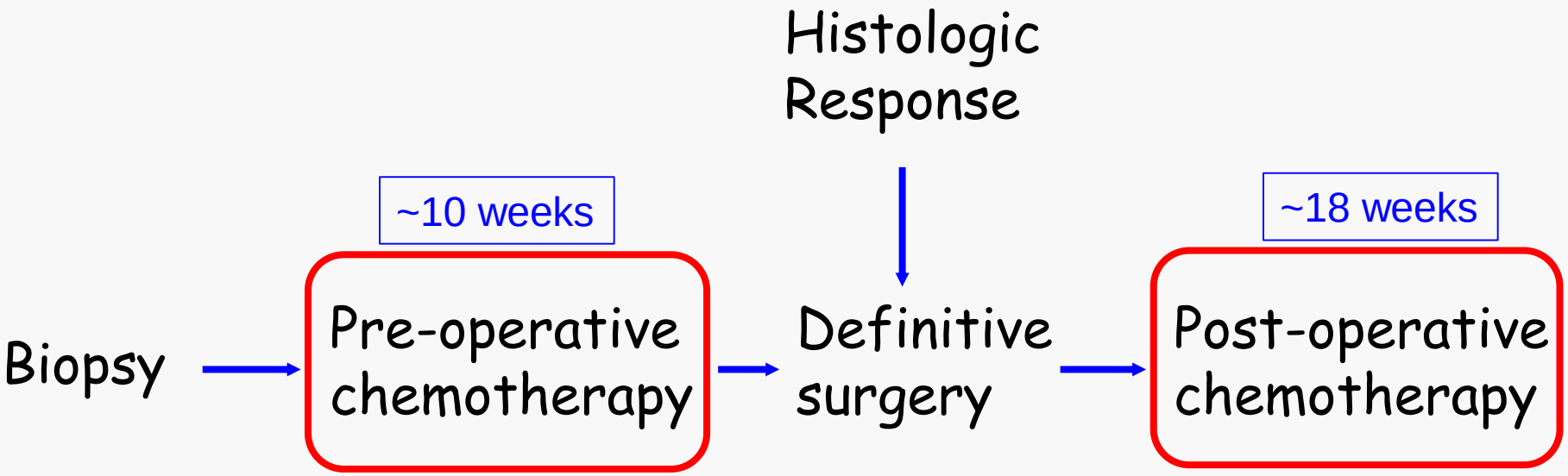


Osteosarcoma: Management Schema



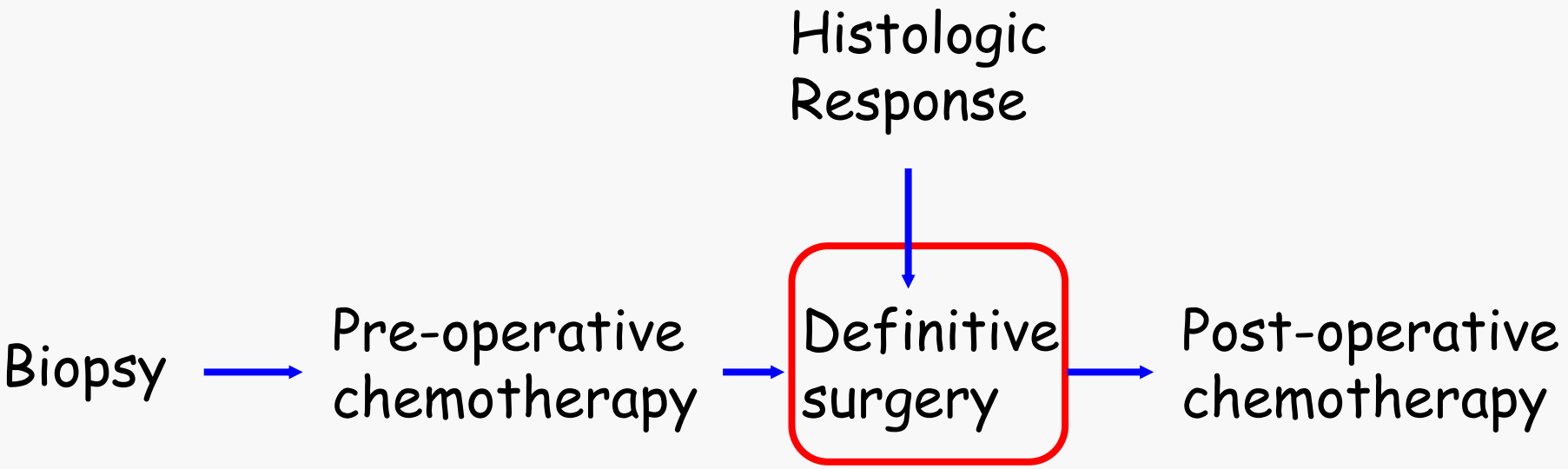
- Diagnosis must be made by biopsy
- Staging to determine metastases
- Treatment consists of surgery and chemotherapy

OS: Management Schema



- OS is relatively radio-resistant
- Active agents: doxorubicin, cisplatin, methotrexate, ifosfamide

Osteosarcoma: Management Schema



- Determine histologic response at time of definitive surgery
- Amputation vs. limb salvage

Osteosarcoma: Outcomes

- Non-metastatic

  Overall ~65% cure rate

- Metastatic

  < 20 % cure rate

- No significant improvements in cure rates for either group in the past 30 years

Treatment of OS in RTS

Questions:

- Can RTS patients who develop OS be treated the same as OS patients without RTS?
- Will RTS patients have more toxicities from chemotherapy?
- Are their clinical outcomes the same?

OS in RTS: Clinicopathologic Features

- Age at diagnosis of OS
- Location of OS
- Histologic subtype
- Tumor response to chemotherapy
- Toxicities to chemotherapy
- Overall patient outcomes

OS in RTS: Clinicopathologic Features

- 12 subjects with RTS; age range 4–20 years; 7 males, 5 females
- 7 subjects diagnosed with RTS prior to OS; 5 subjects diagnosed with RTS after OS
- Median age at diagnosis of OS: 10 years
- All subjects received chemotherapy and surgery

Hicks et al. J Clin Oncol 2007; 25:370-375

OS in RTS: Results

- Location of OS: similar to general population, distal long bones, around the knee (~75%)
- Histologic subtype: similar to general population; “conventional” OS most common (~75%, osteoblastic, chondroblastic, fibroblastic)

Hicks et al. J Clin Oncol 2007; 25:370-375

OS in RTS: Results

- Histologic (Tumor) Response to Chemotherapy: similar to general population: about 45% have good response
- Overall patient outcomes: 9 patients alive and disease-free--similar to general population: ~65% survival

Hicks et al. J Clin Oncol 2007; 25:370-375

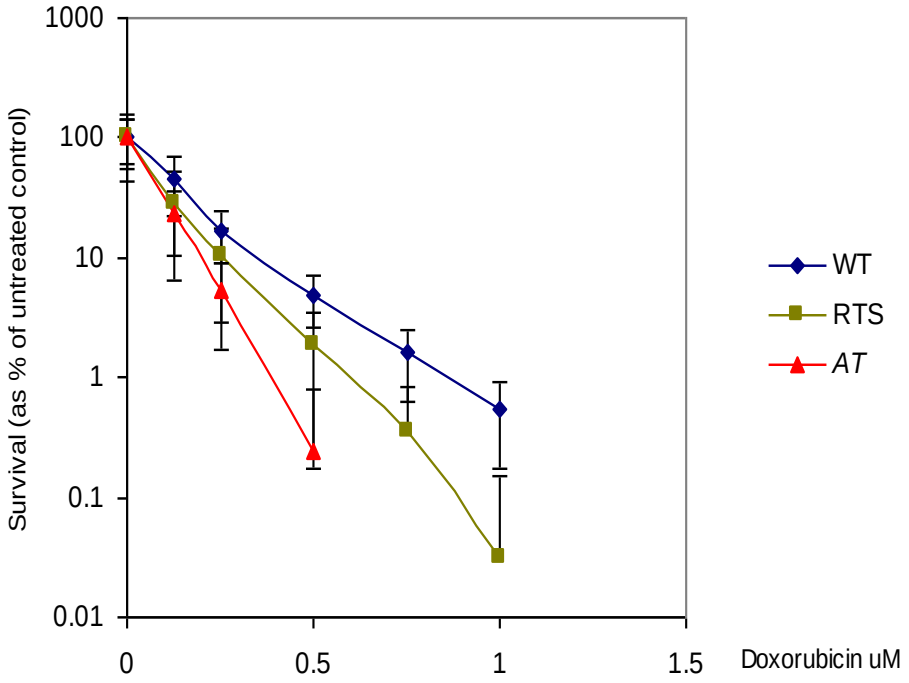
OS in RTS: Results

- Toxicities to chemotherapy:
  - 5 subjects had toxicities without modifications
  - 4 had toxicities to doxorubicin requiring modifications (maximum 25% dose reduction)
  - 2 subjects were started at lower doses of chemotherapy up front
  - 2 subjects no treatment data was available

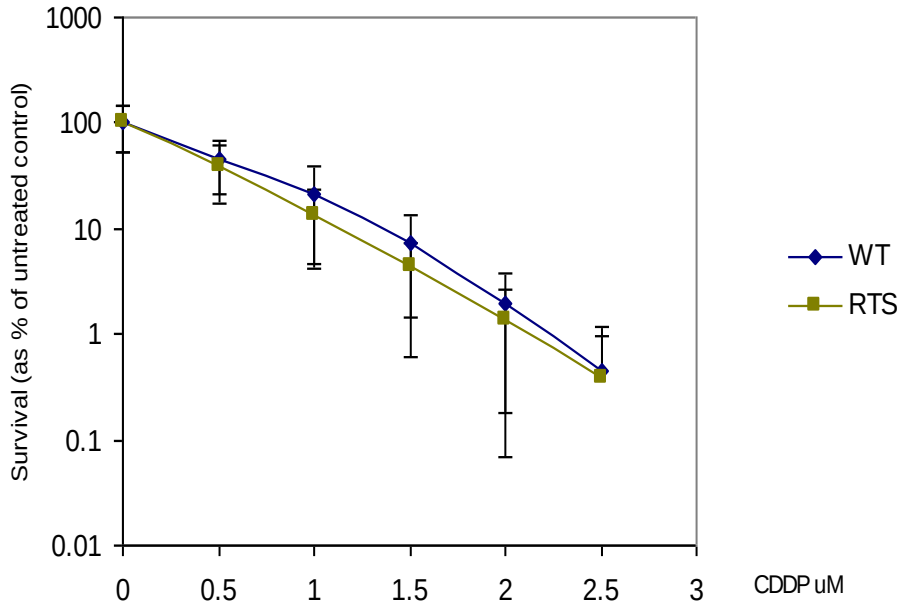
Hicks et al. J Clin Oncol 2007; 25:370-375

Cellular Sensitivity

Doxorubicin



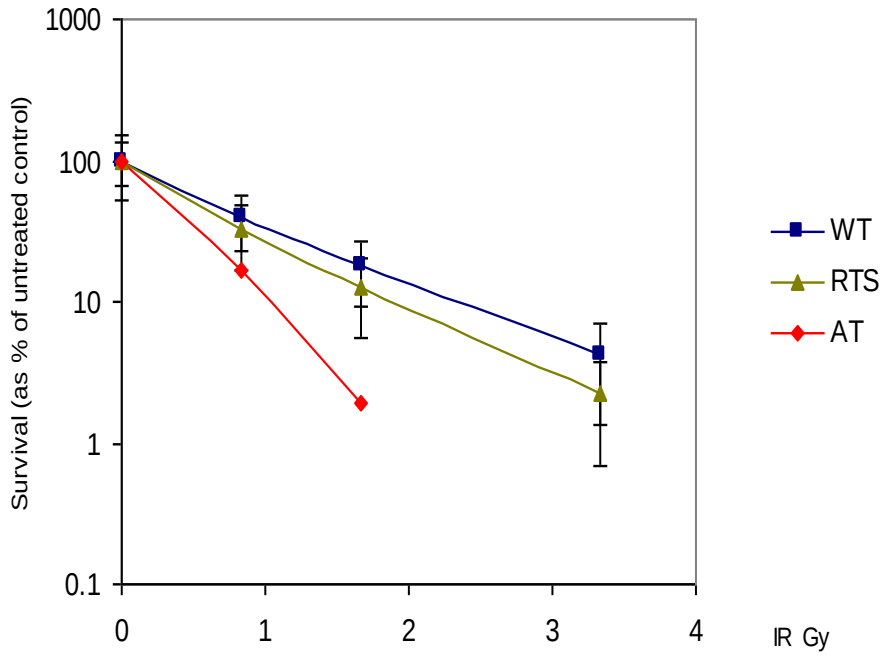
Cisplatin



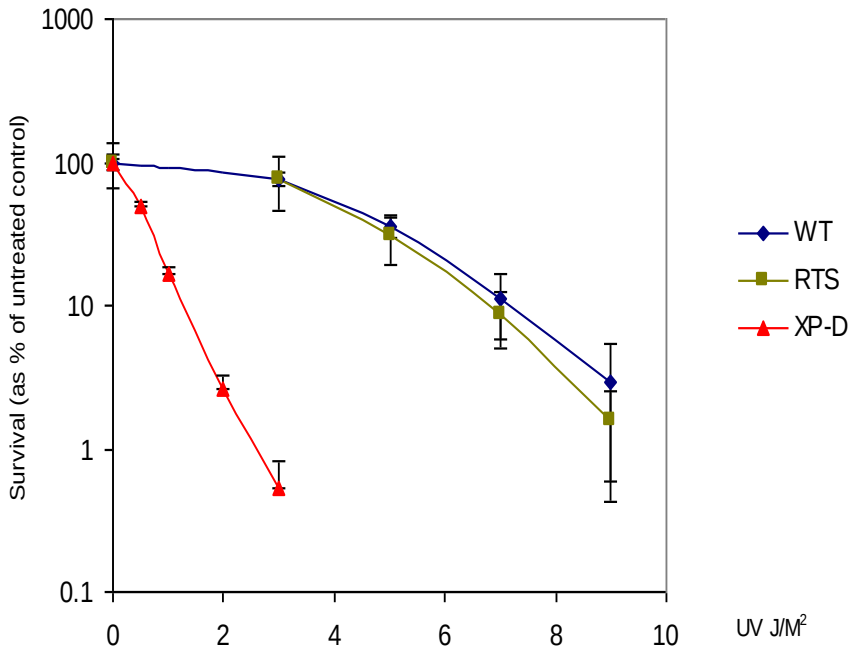
Jin et al. Hum Genet 2008; 123(6):643-653

Cellular Sensitivity

IR



UV



Jin et al. Hum Genet 2008; 123(6):643-653

Osteosarcoma in RTS Patients

- Conclusions
  - OS in RTS patients occurs at a younger median age (10 years) compared to the general population.
  - The locations and histologic subtypes of OS in RTS patients do not differ greatly from that in the general population.

Osteosarcoma in RTS Patients

- Conclusions
  - Some RTS patients (33%) had enhanced sensitivity to doxorubicin in the form of severe mucositis, while others tolerated it well.
  - No way to predict *a priori* who will have more sensitivity

Osteosarcoma in RTS Patients

Recommendations:

- Counsel RTS patients with *RECQL4* mutations for awareness of OS risk
- Obtain baseline skeletal survey to define underlying bone abnormalities
- Treat OS with standard chemotherapy with no up-front reductions
- Modify chemotherapy only as dictated by clinical course of the individual patient

Screening for Osteosarcoma in Type 2 RTS

CCR PEDIATRIC ONCOLOGY SERIES

Recommendations for Childhood Cancer Screening and Surveillance in DNA Repair Disorders

Michael F. Walsh[1], Vivian Y. Chang[2], Wendy K. Kohlmann[3], Hamish S. Scott[4], Christopher Cunniff[5], Franck Bourdeaut[6], Jan J. Molenaar[7], Christopher C. Porter[8], John T. Sandlund[9], Sharon E. Plon[10], Lisa L. Wang[10], and Sharon A. Savage[11]

Abstract

DNA repair syndromes are heterogeneous disorders caused by pathogenic variants in genes encoding proteins key in DNA replication and/or the cellular response to DNA damage. The majority of these syndromes are inherited in an autosomal-recessive manner, but autosomal-dominant and X-linked recessive disorders also exist. The clinical features of patients with DNA repair syndromes are highly varied and dependent on the underlying genetic cause. Notably, all patients have elevated risks of syndrome-associated cancers, and many of these cancers present in childhood. Although it is clear that the risk of cancer is around the world to discuss and develop cancer surveillance guidelines for children with cancer-prone disorders. Herein, we focus on the more common of the rare DNA repair disorders: ataxia telangiectasia, Bloom syndrome, Fanconi anemia, dyskeratosis congenita, Nijmegen breakage syndrome, Rothmund–Thomson syndrome, and Xeroderma pigmentosum. Dedicated syndrome registries and a combination of basic science and clinical research have led to important insights into the underlying biology of these disorders. Given the rarity of these disorders, it is recommended that centralized

Walsh et al., *Clinical Cancer Research* 2017

Surveillance in Type 2 RTS

			Dental: biannual exam
Rothmund–Thomson syndrome	Genetic testing	Osteosarcoma, basal cell carcinoma, skin SCC	Oncology: avoid ionizing radiation, consider imaging for osteosarcoma risk, HPV vaccine per AAP guidelines Dermatology: avoid excessive UV; use sunscreen annual exam and early treatment of lesions Ophthalmology: annual evaluation and cataract treatment as needed Endocrine: management for osteopenia Orthopedics: baseline skeletal survey Dental: biannual evaluation with proper care for hypoplastic teeth, enamel defects
Xeroderma pigmentosa	Genetic testing	Melanoma, basal cell carcinoma, skin SCC, leukemia, brain and spinal cord tumors	Oncology: beginning at diagnosis, avoid excessive sunlight and ionizing radiation; early identification and treatment of skin lesions; exam for ocular and ENT neoplasms every 6–12 months Dermatology: thorough skin evaluation every 3 months Gastroenterology/nutrition: evaluate swallowing function, nutritional support as needed Ophthalmology: exam every 6–12 months Neurology: evaluation for developmental delay or progressive neurologic changes Orthopedics: annual scoliosis evaluation ENT: baseline hearing evaluation and as needed cancer screening every 6–12 months

Abbreviations: AAP, American Academy of Pediatrics; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; AVM, arteriovenous malformations; CBC, complete blood count; DEB, diepoxybutane; ENT, ear, nose and throat; HPV, human papillomavirus; IVIg, intravenous immunoglobulin; MDS, myelodysplastic syndrome; MMC, mitomycin C; PHA, phytohemagglutinin; SCC, squamous cell carcinoma.

- Annual skin checks for **skin cancer**; sunscreen
- No formal screening recommended for **osteosarcoma**
- Increased awareness and understanding of the disease
- Prompt attention to symptoms and signs
- Baseline skeletal survey for comparison