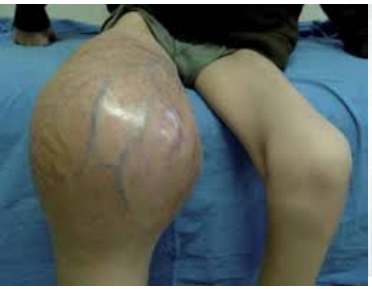
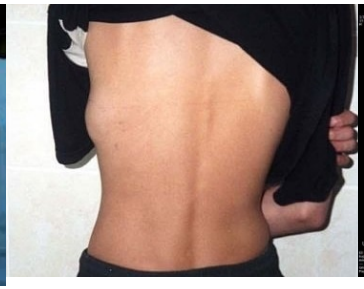
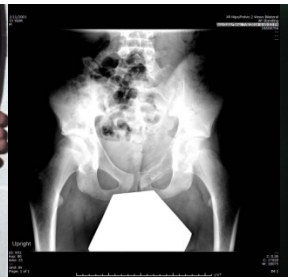
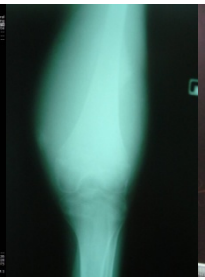
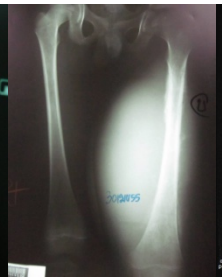
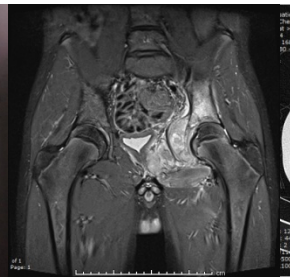
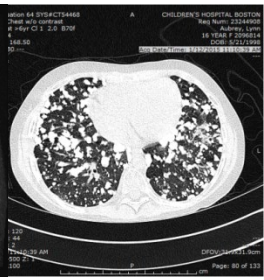
Malignant Bone Tumors in Children

Educational Course for Hematology Trainees 2021

7-8 August, 2021

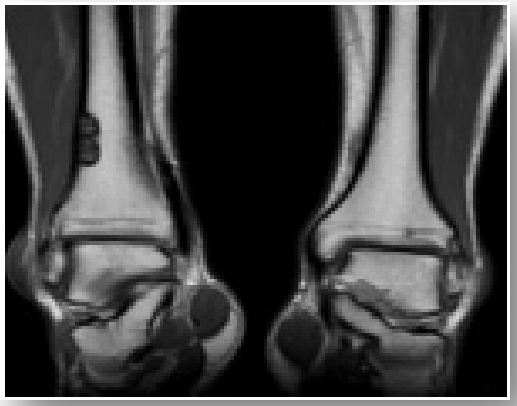
Chalinee Monsereenusorn, M.D.

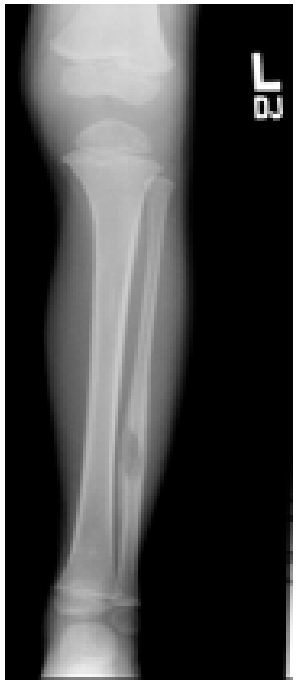
Assistant Professor in Pediatrics
Division of Hematology-Oncology,
Department of Pediatrics, Phramongkutklao Hospital

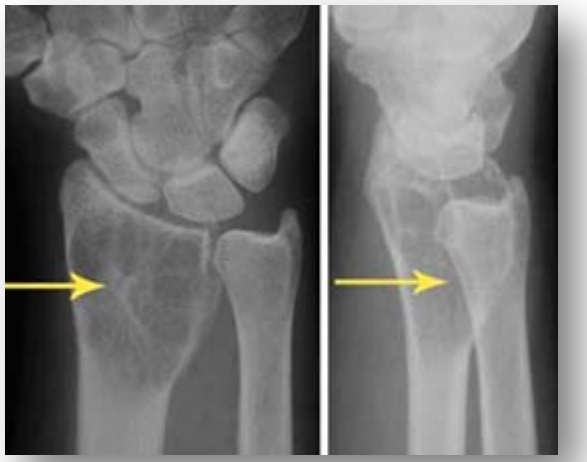
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Bone Tumors in Children

- Only half of bone lesions in children are malignant
- Other half benign or nonneoplastic lesions







Bone Tumors

Malignant	Benign	Non-neoplastic
Osteosarcoma	Osteoid osteoma	Fibrous dysplasia
Ewing's Sarcoma	Osteoblastoma	Fibrous cortical defect
Chondrosarcoma (classical, clear cell, mesenchymal)	Enchondroma	Aneurysmal bone cyst
Undifferentiated pleomorphic sarcoma (formerly MFH)	Chondroblastoma	Myositis ossificans
Isolated Bone Lymphoma	Chondromyxoid fibroma	Avulsion/stress fracture
Metastatic Tumor	Hemangioma	Solitary bone cyst
Intermediate		Osteomyelitis
Langerhans' Cell Histiocytosis		
Giant Cell Tumor		

Distinguishing Benign vs Malignant Bone Lesions

History

- Age
- Pain
- Trauma
- Duration of symptoms
- Swelling
- Rate of growth

Physical Examination

- Constitutional symptoms
- Tenderness
- Swelling
- Associated soft tissue mass
- Deformity
- Range of motion

Malignant bone tumors

- 6th most common neoplasms in children
- 3rd most common in adolescents and young adults
- 8.7 cases per million per year in the US (< 20 years age)

Most common types

- Osteosarcoma
- Ewing sarcoma family of tumors (ESFT)
- Chondrosarcoma
  - Mesenchymal – *HEY1-NCOA2 fusion, late recurrences*
- Other
  - Undifferentiated pleomorphic sarcoma of bone (formerly MFH)

Management of Sarcomas

BONE SARCOMAS

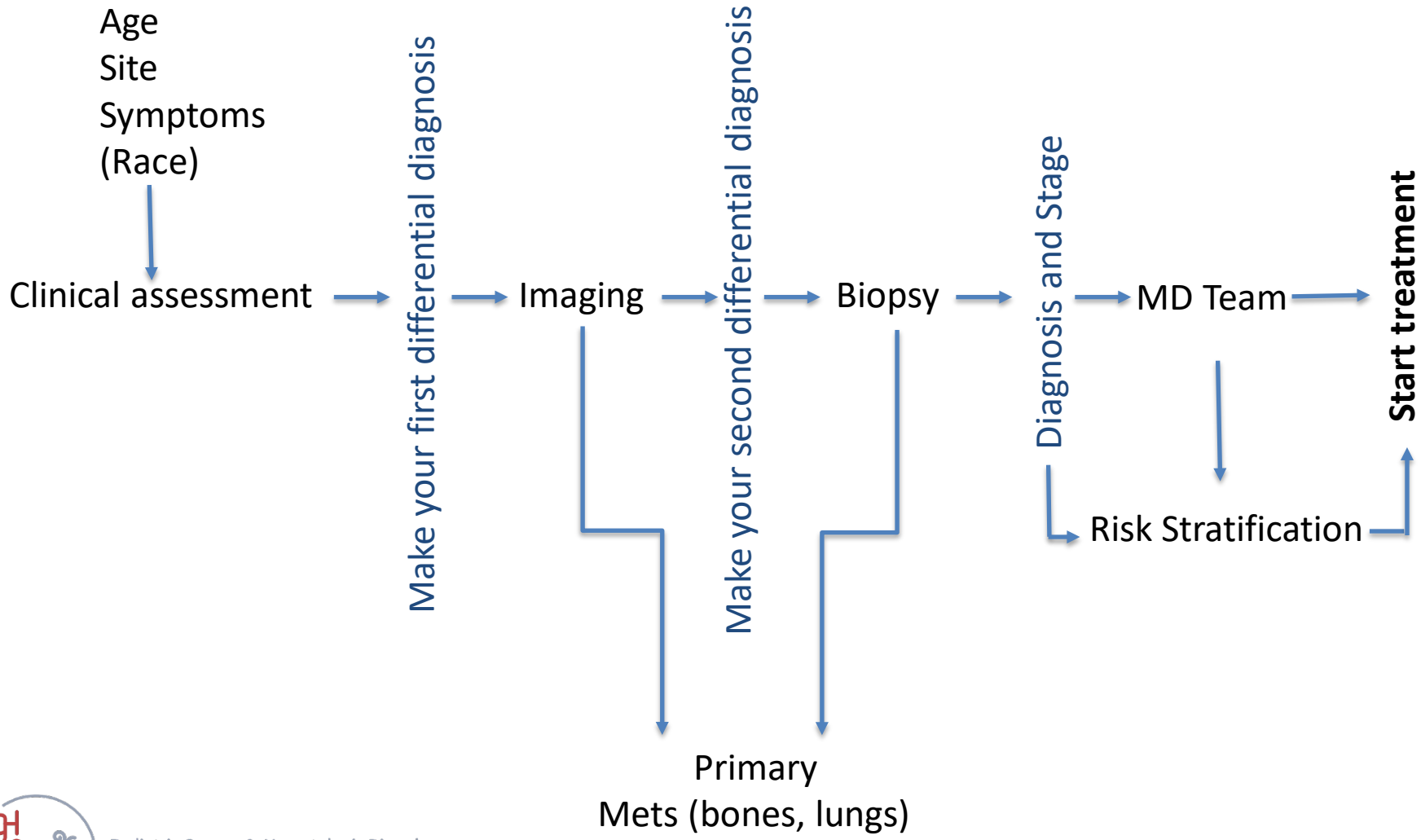
- Ewing Sarcoma
- Osteosarcoma

SOFT TISSUE SARCOMAS

- Rhabdomyosarcoma
- Soft Tissue Sarcomas

MULTIDISCIPLINARY CARE

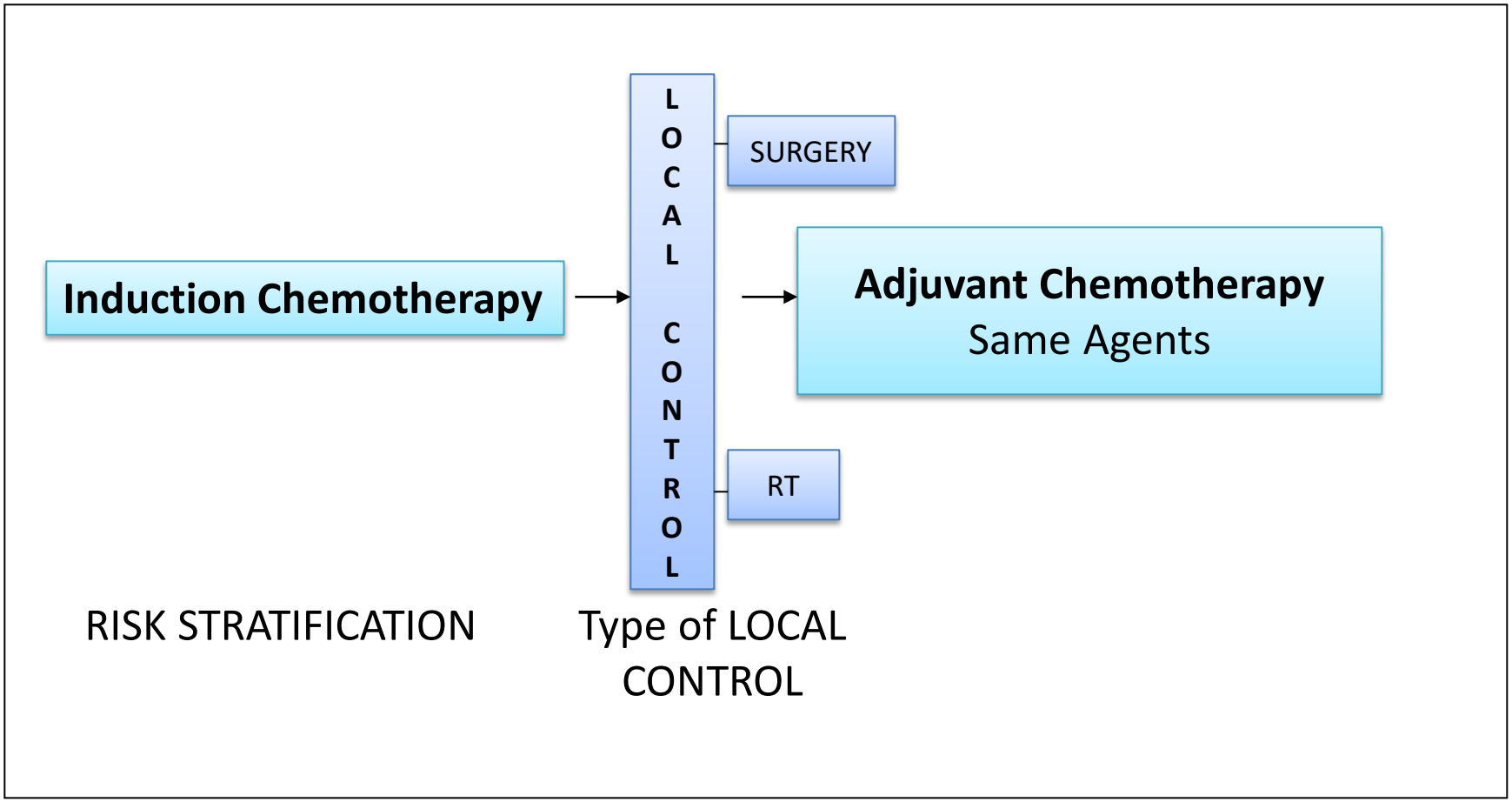
Principles of Management



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

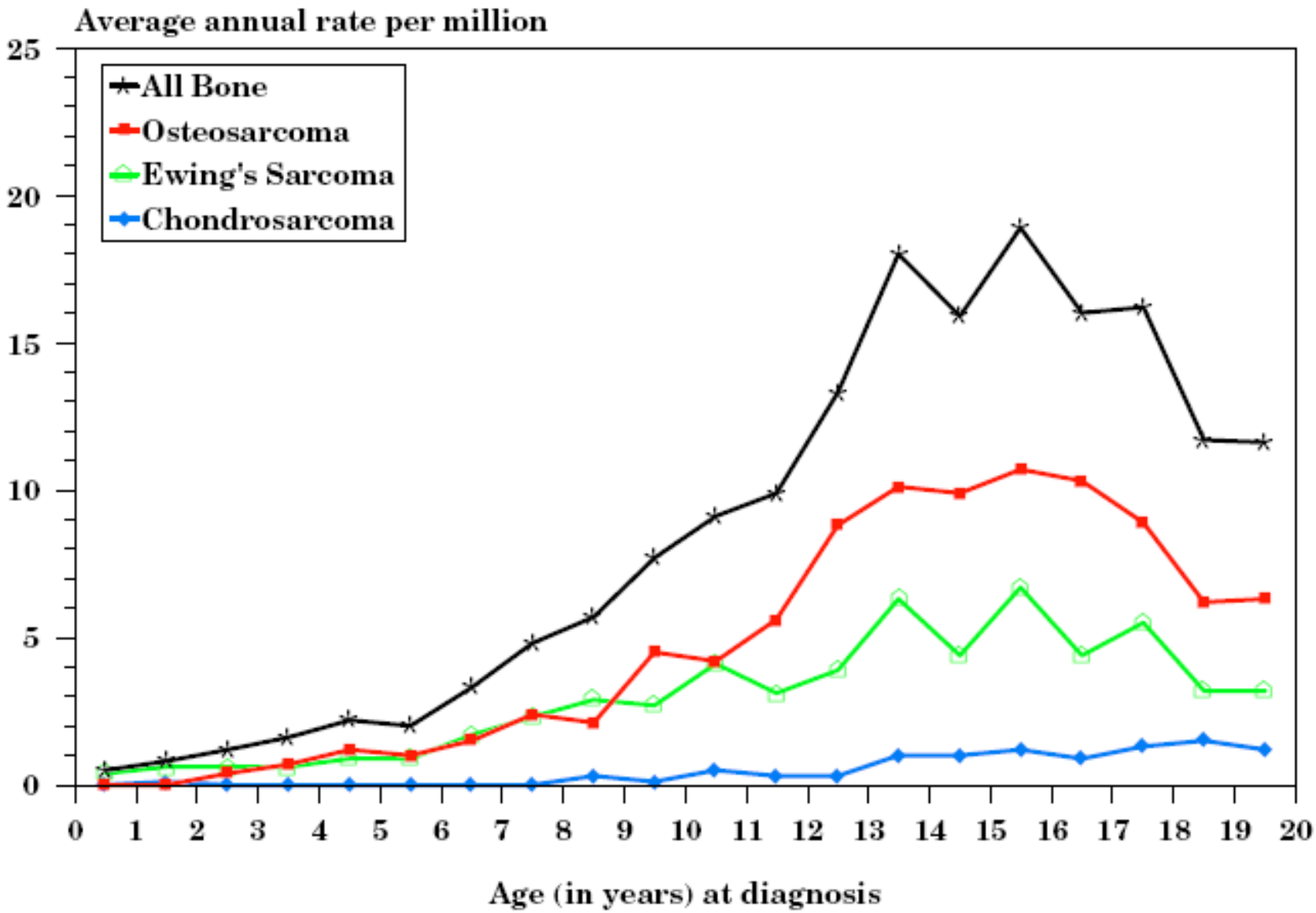
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Principles of Management



Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Figure VIII.2: Bone cancer age-specific incidence rates by histology all races, both sexes, SEER, 1976-84 and 1986-94 combined



Lanzkowsky 5th edition, 2011

Malignant Bone Tumors

	Osteosarcoma	Ewing's Sarcoma
Age (yrs) Adult > 40 yr	12-18 Yes	5-25 Very rare
Race	Asian> Caucasian	Caucasian>>>>>>> Asian
History Previous RT Family Hx	 Ye LFS, RB1	 No No
Constitutional symptoms	No	Yes
Location	Bone	Bone, soft tissue, renal
Skip lesion	Uncommon	Common
Metastasis	Lung	Lung, bone, BM

Malignant Bone Tumors

	Osteosarcoma	Ewing's Sarcoma
Bone	Long bones	Long and Flat bones (Pelvis, skull, ribs)
Site	Metaphysis	Diaphysis
Genetic	Rb, p53 TS genes	t(11;22)EWS-FLI Oncogene activation
Radiologic findings	• Sunburst pattern • Calcification	• Moth-eaten lytic lesion • Onion skin
	• Periosteal reaction • Codman's triangle	
LAB	↑ALP CBC-normal	Normal ALP CBC-abnormal (if BM+)
PATH	Osteoblast Malignant osteoid +	Small round blue cell, primitive neuroectodermal cell ***No*** malignant osteoid
RT	Resistance	Responsive

Bone Tumors in Children

Site	Osteosarcoma	Ewing's sarcoma
Distal Femur	32%	5%
Proximal Tibia	16%	4%
Proximal Humerus	10%	6%
Pelvis	8%	20%
Spine	2%	10%
Ribs	1%	9%

Management of Sarcomas

BONE SARCOMAS

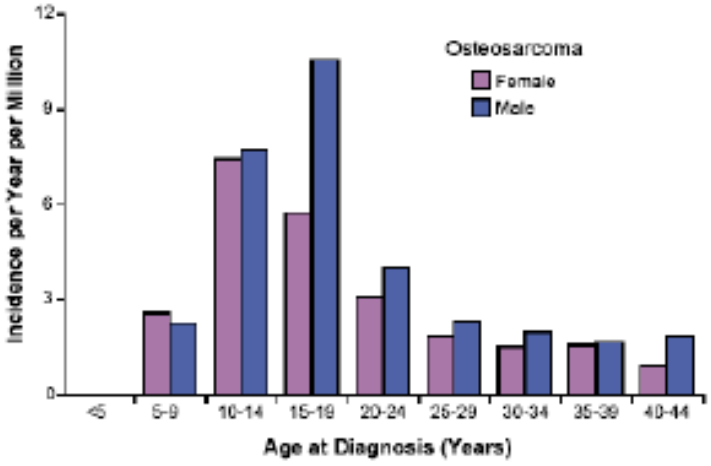
- Ewing Sarcoma
- Osteosarcoma

SOFT TISSUE SARCOMAS

- Rhabdomyosarcoma
- Soft Tissue Sarcomas

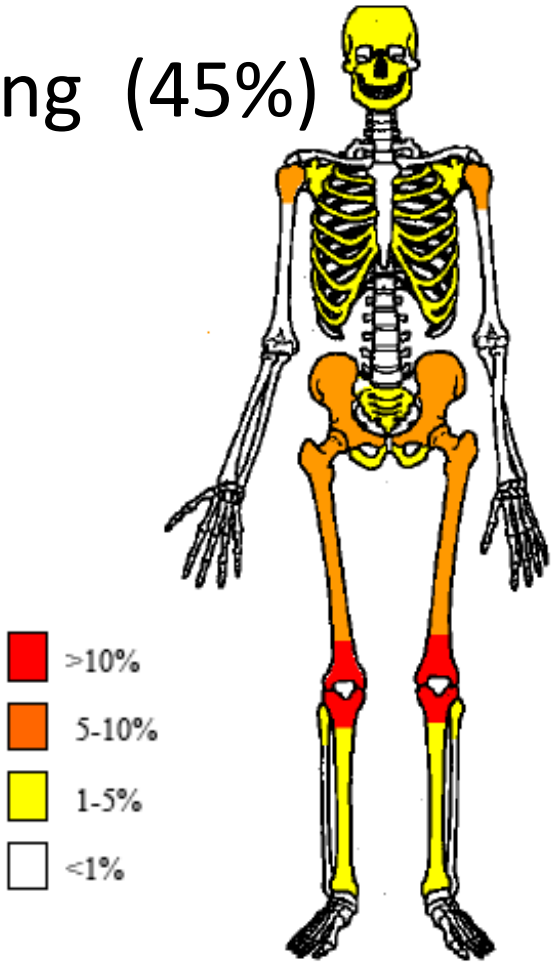
Osteosarcoma

- MCM primary malignant bone tumor in children
- Rare : < 10 years of age
- Genetic predisposing syndrome
  - Li-Fraumeni syndrome (p53)
  - Hereditary RB (RB1)
- Radiation therapy
  - 3% of all osteosarcoma
  - Long latency > 10 years
  - Potentiated by prior chemotherapy (alkylators, anthracyclines)



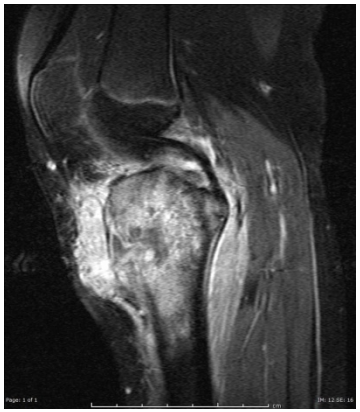
Clinical presentation

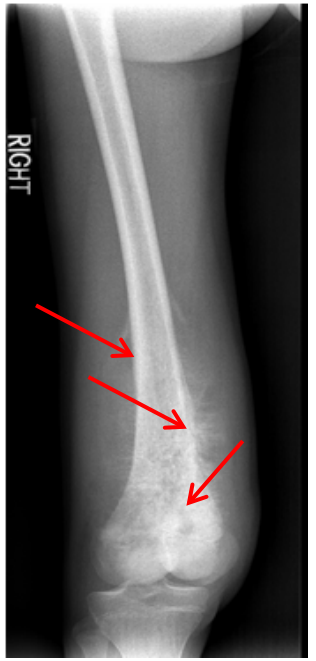
- Local pain (90%)
- Local swelling (50%)
- Decreased range of motion, limping (45%)
- Pathologic fracture (8%)
- Lab
  - Elevated LDH 30%
  - Elevated ALP 40%



Investigations

- Plain film at primary and bone met site(s)
- CXR
- MRI of primary tumor
- CT chest
- Bone scan
- PET scan: (recommend) evaluation for metastatic disease (bone, lung)
  - PET/CT more sensitive and accurate than bone scan*
  - Combined use improves sensitivity*
- Biopsy
  - Requires planning for later resection of biopsy tract

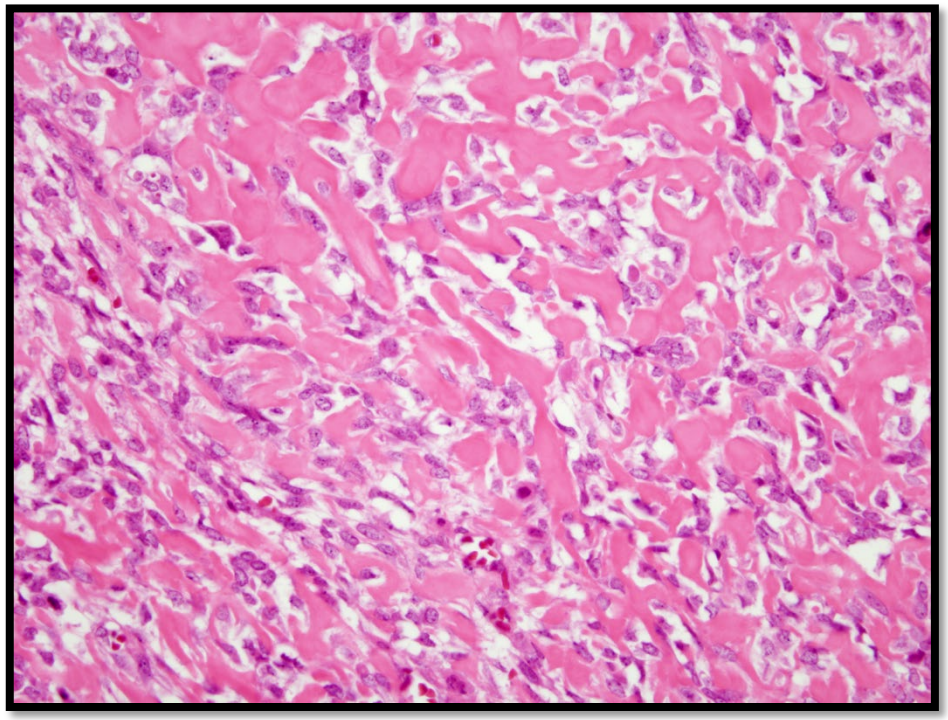




*Byun BH et al, Skeletal Radiol 2013
Meyer et al., Pediatr Blood Cancer 2008;51:163–170

Pathology

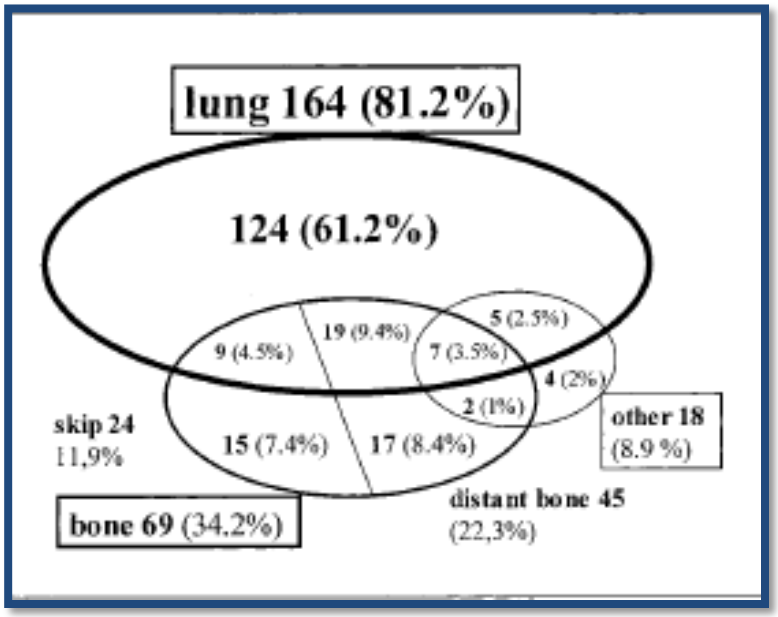
- Proliferation of malignant cells
- Osteoid formation
- Subtypes
  - Osteoblastic
  - Chondroblastic
  - Fibroblastic
  - Telangiectatic
  - Small Cell
- Periostial Osteosarcoma
- Parosteal Osteosarcoma



Staging

- Localized
- Metastatic
  - 15-20% metas at presentation
  - Lungs
  - Bone:

    distant and skip lesions
  - Combined

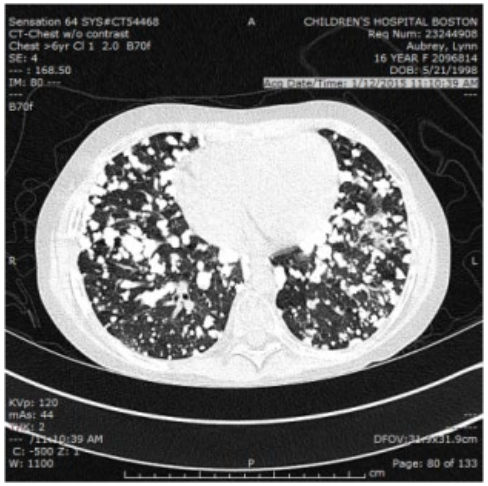


Kager L et al. J Clin Oncol 2003

Pulmonary metastatic disease criteria

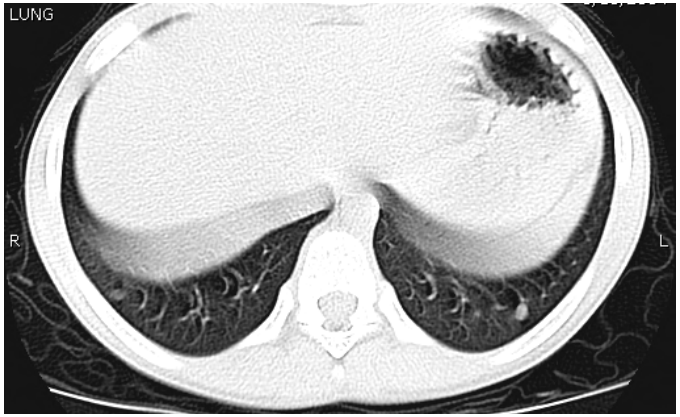
Certain

- ≥ 3 lesions with ≥ 0.5 cm max diameter
- ≥ 1 lesion(s) with ≥ 1 cm



Possible

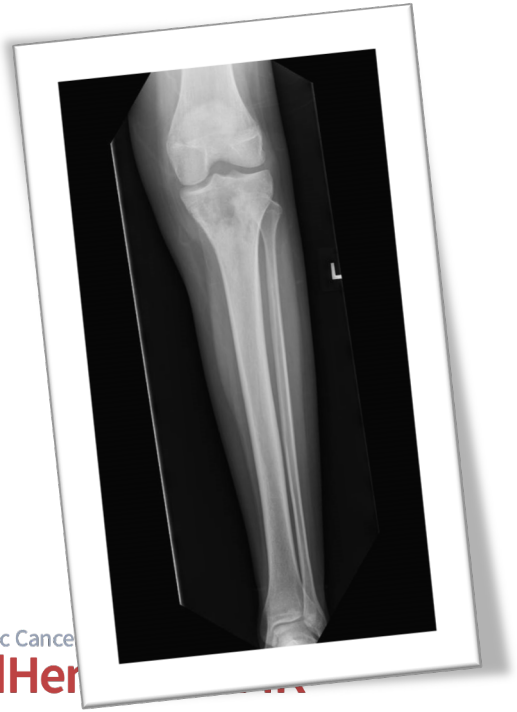
- Fewer or smaller lesion(s) that not met "certain criteria"

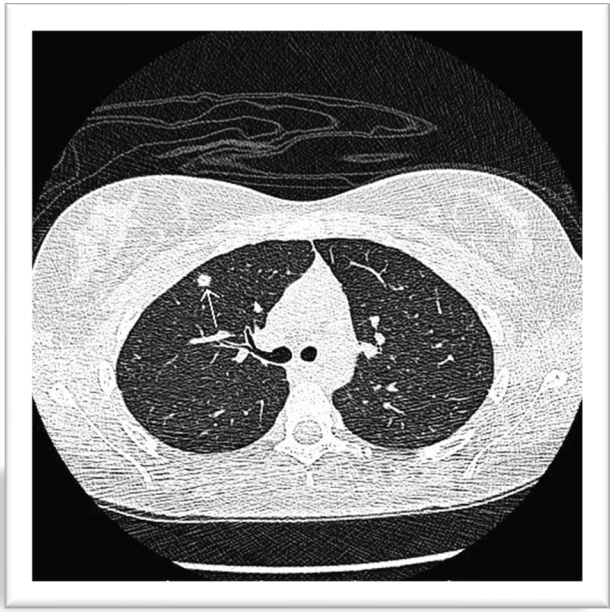


EURAMOS I Trial
TPOG protocol 2015
Meyer et al., Pediatr Blood Cancer 2008;51:163–170

5y OS in osteosarcoma

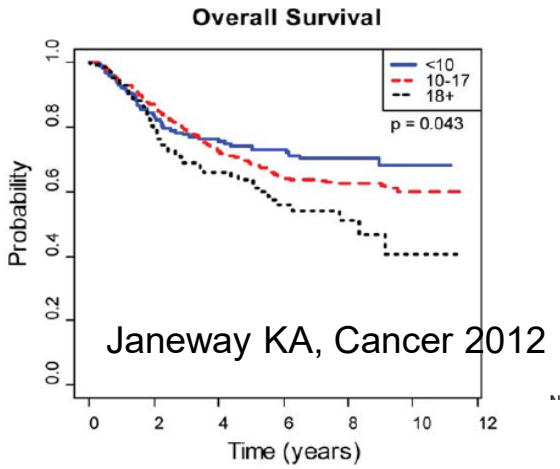
- Localized osteosarcoma ~ 70%
  - If CMT response ≥90% TN → increased to 80%
- Metastatic osteosarcoma ~ 25%

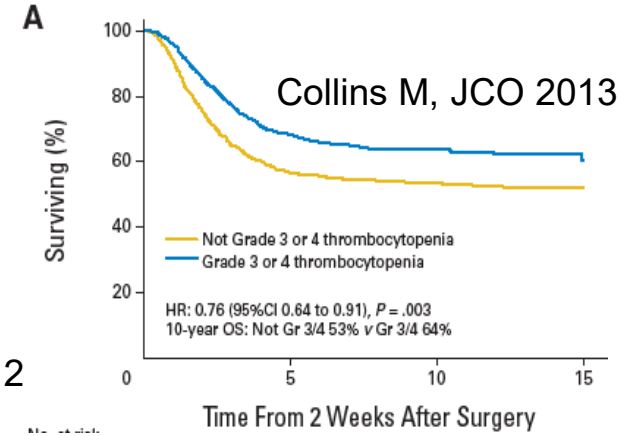


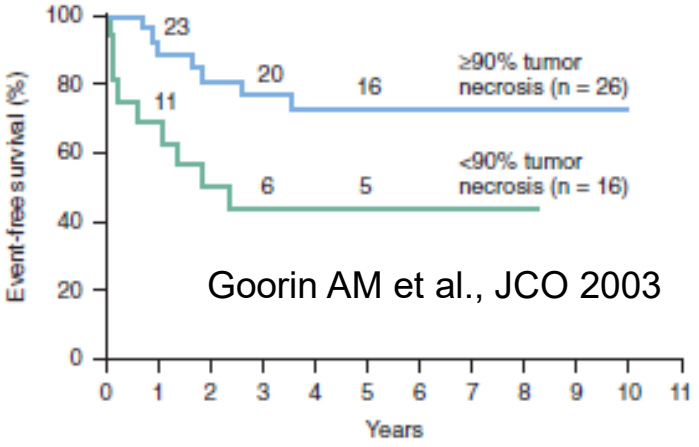


Osteosarcoma: Updated Prognostic Factors

- Metastatic
- Pelvic site
  - HR 3.08 [1.92-4.92]
- Older age
  - HR 1.42 [1.05-1.92]
- Male gender
  - Female: HR 0.85 [0.76-0.95]
- Lack of chemotherapy toxicity
- *Histologic response to chemotherapy*





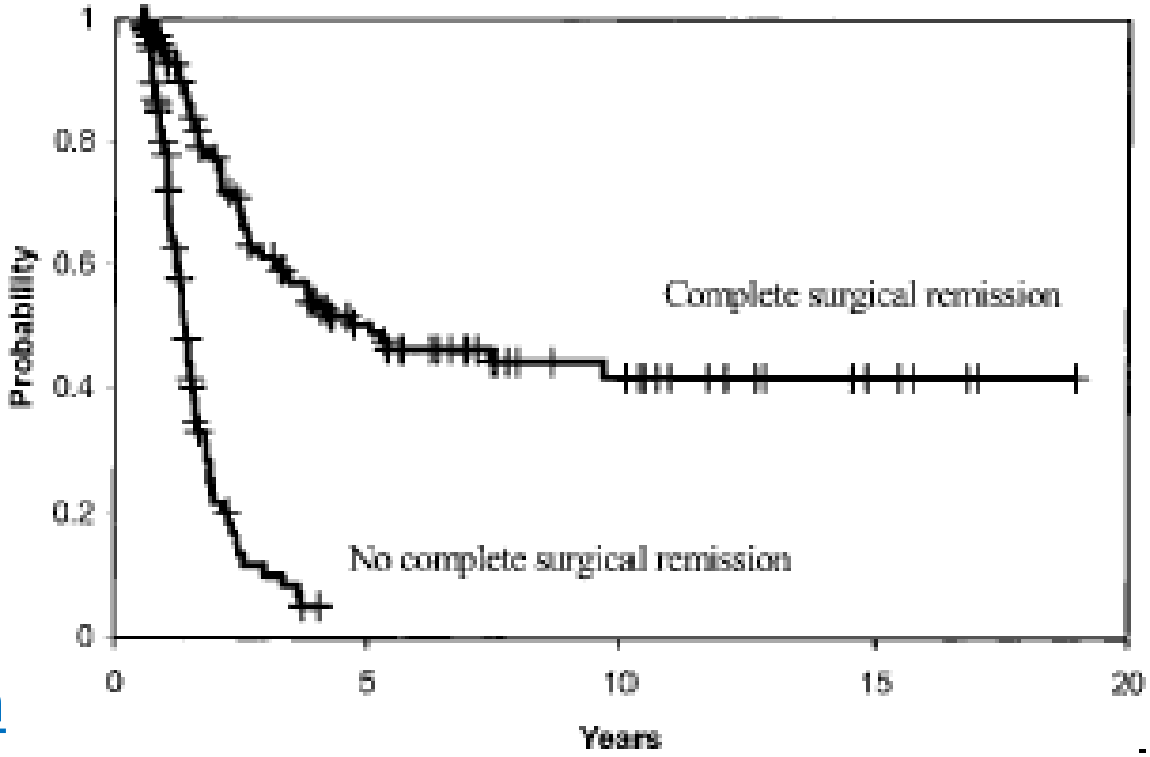


Metastatic Osteosarcoma at Dx: Prognostic factors

Table 3. Multivariate Cox Regression Model on Prognostic Factors

Variable	RHR	95% CI	P
Age, > 20 v < 20 years	1.0	0.66 to 1.6	.840
Trunk v extremities	1.5	0.87 to 2.7	.136
Multiple organ system v one	0.9	0.53 to 1.4	.581
Other v lung/skip	1.5	0.93 to 2.4	.096
Multiple v solitary	2.3	1.2 to 4.3	.012
Incomplete surgical remission	2.4	1.4 to 4.3	.003

Abbreviations: RHR, relative hazard rate; CI, confidence interval.



- Achieve surgical remission
- No. of mets

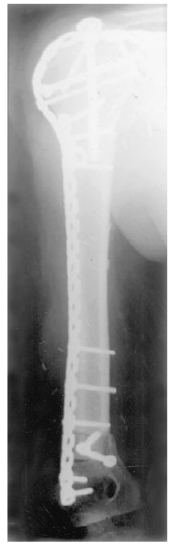
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

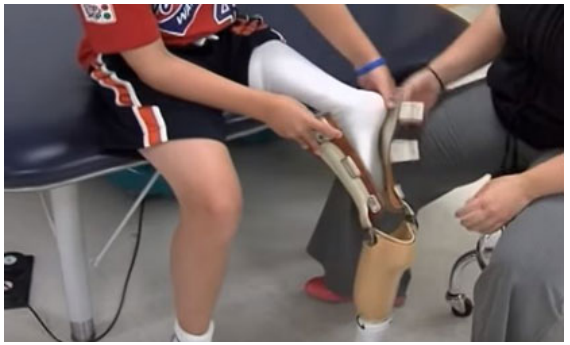
Kager L et al, 2003 JCO 21: 2011-2018

Treatment

- Chemotherapy :
  - Neoadjuvant
  - Adjuvant: MAP
    - Cisplatin
    - Doxorubicin
    - HDMTX
- Surgery: complete surgical resection necessary for survival at wk 10th
  - Limb-sparing (limb savage) surgery
    - Rotationplasty
  - Amputation

Do not adjust adjuvant CMT dose according to amputation





AOST0331

TN indicated prognosis but not changing the treatment

Induction
"MAP"

Surgery
Access histologic response

Good responder
≥ 90% TN

Poor responder
< 90% TN

Not significant Bielack SS, et al. JCO 2015

MAP
3y EFS 74%

MAPInf
77%

MAP
54%

MAPIE
52%

Not significant but higher toxicity in MAPIE arm
Marina N, et al. Lancet Oncol 2016

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Treatment schema for osteosarcoma protocol

(Update March 2018)

Osteosarcoma[#]

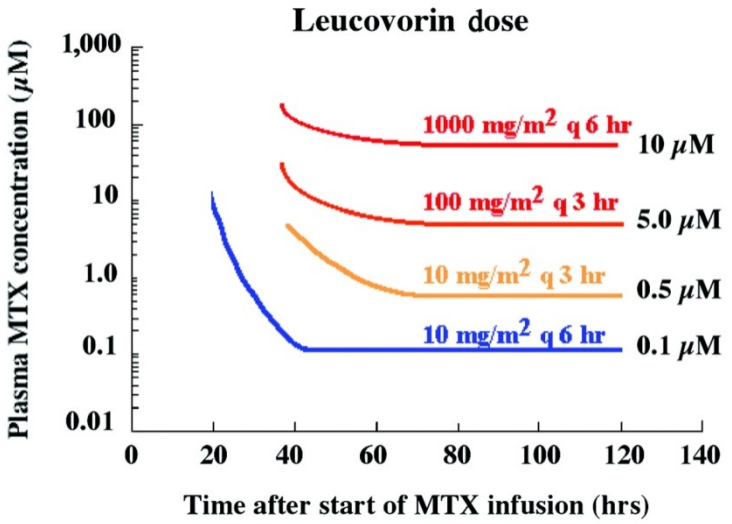
Metastasis

- **No** → Feasiblity for HD-MTX administration
  - **No** → ThaiPOG-OS-13-CD-rev 2018
  - **Yes** → ThaiPOG-OS-18-MTX
- **Yes** → ThaiPOG-OS-18-MTX

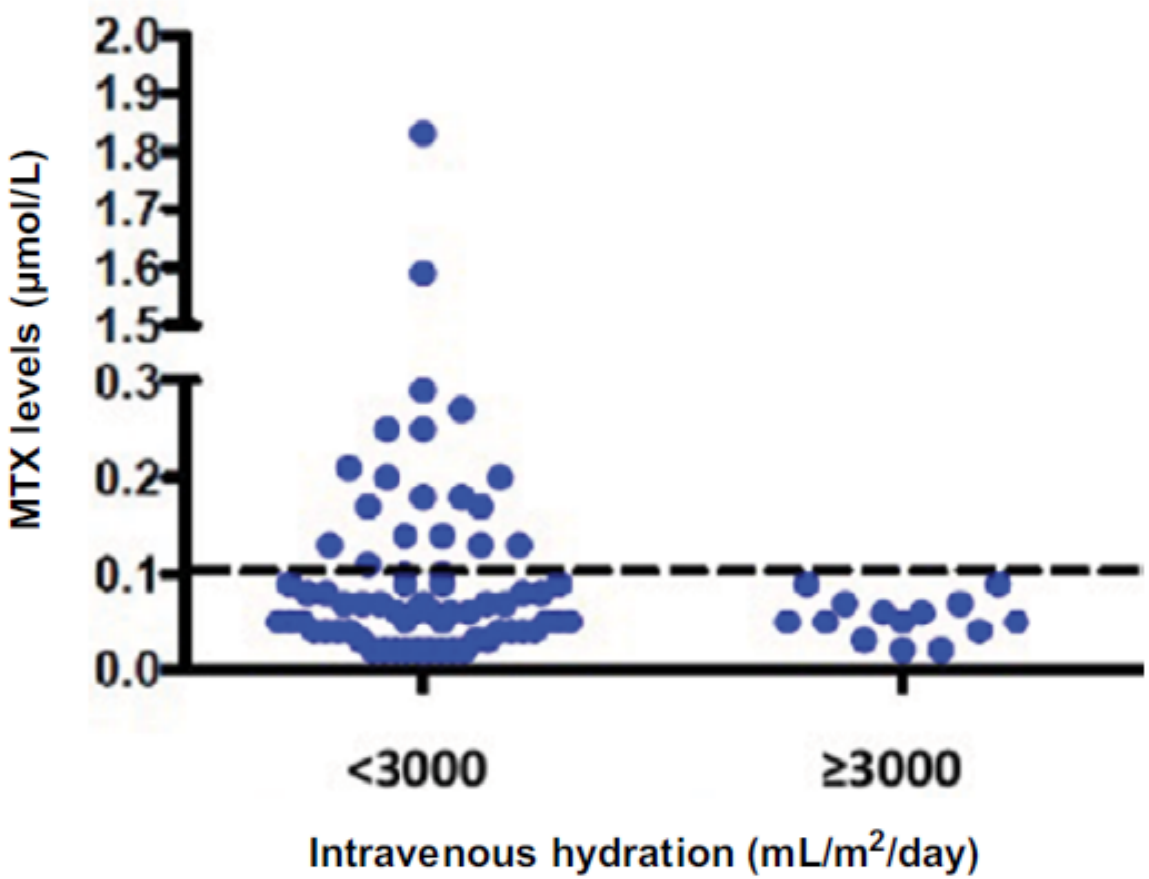
[#]Histological diagnosis of osteosarcoma (including chrondrosarcoma, fibrosarcoma) is required before starting treatment.

Methotrexate elimination

- 90% renal excretion
- <10% hepatic
- Precipitates in kidney at pH <6.3
- Elimination maximized at alkaline pH
- Medications interfering with elimination
  - Vancomycin
  - Bactrim
  - H_2 blockers
  - NSAIDS
  - Penicillins
- Reminder: fluid collections → delayed MTX clearance
- Variability is common even in the same patient



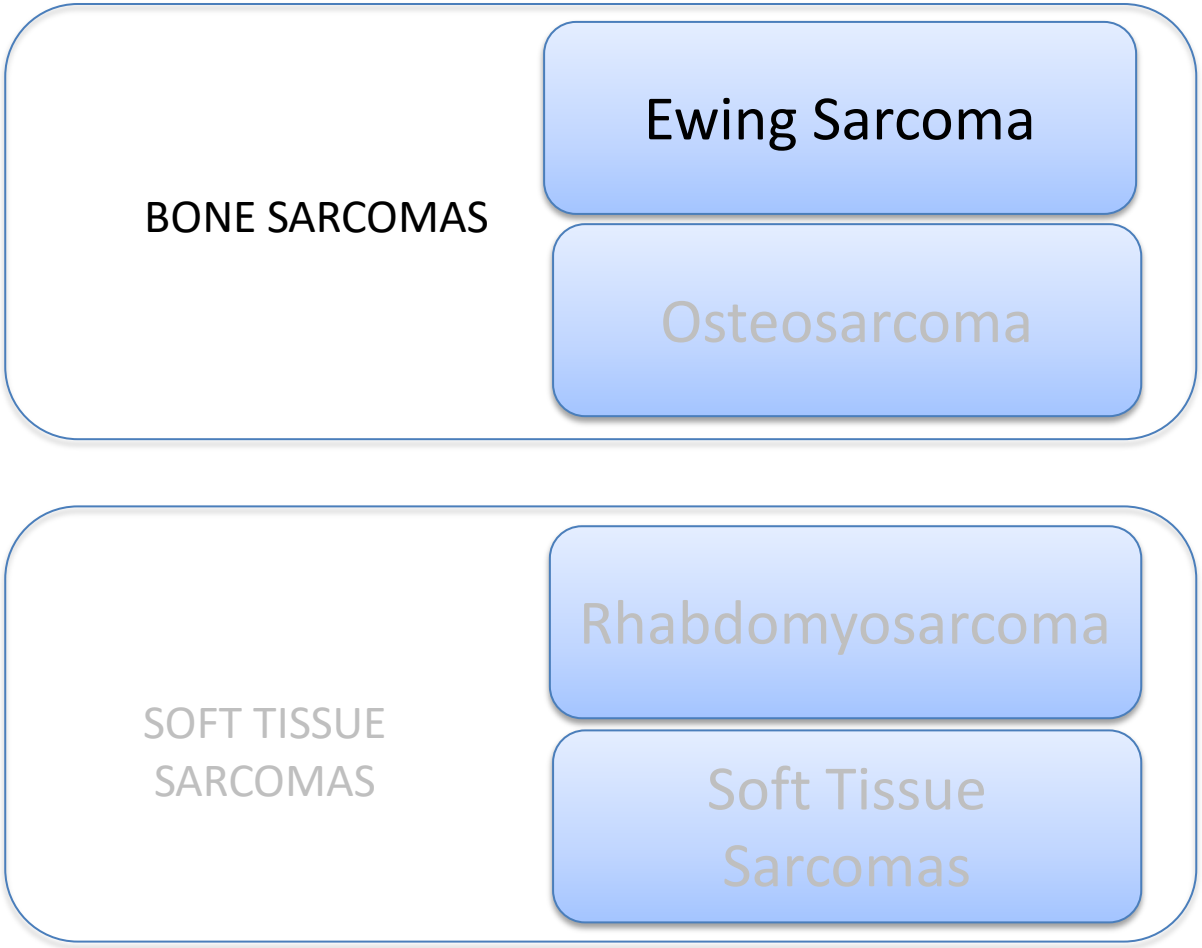
The Effect of IV fluid on 72 hr MTX Levels in Osteosarcoma Patients



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

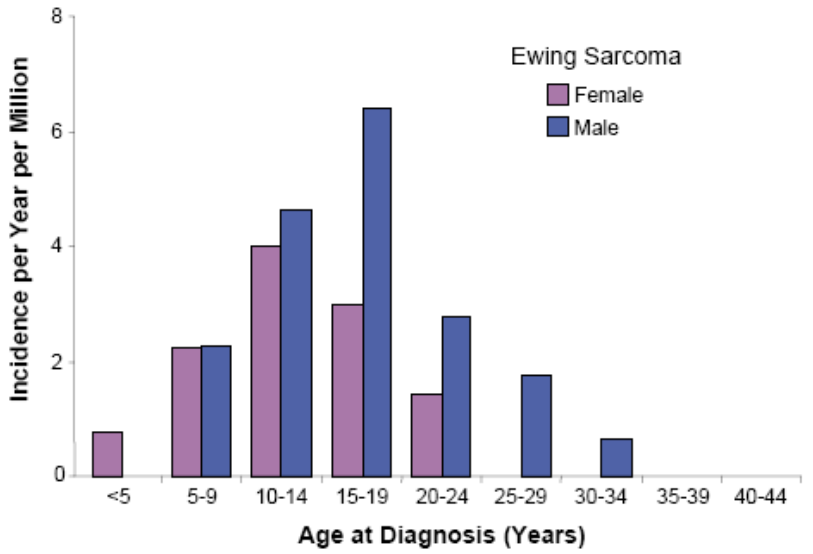
Traivaree C, et al. Cancer management and research. 2018

Management of Sarcomas



Ewing Sarcoma Family of Tumors (ESFT)

- Majority present in the 2nd decade of life
- 2nd MCM bone malignancy in children
- Bone, soft tissue, Askin's tumor or PNET
- Metastasis: 25% of patients present with metastases
  - Lung 38%
  - Bone 31%
  - BM 11%
  - Other unusual sites



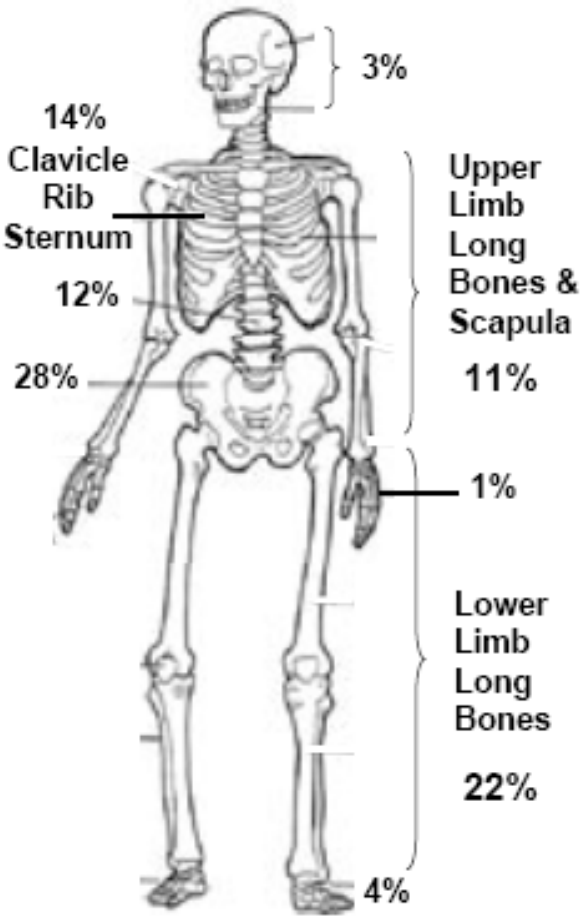
Mascarenhas et al., 2006
SEER Data 1975-1999

Site of Origin

- Bone primaries (75%)

  Axial=extremities

  - Pelvis
  - Long bones
  - Other axial sites
- Soft tissue primaries (25%)
  - Paraspinal
  - Chest wall
  - Various other sites



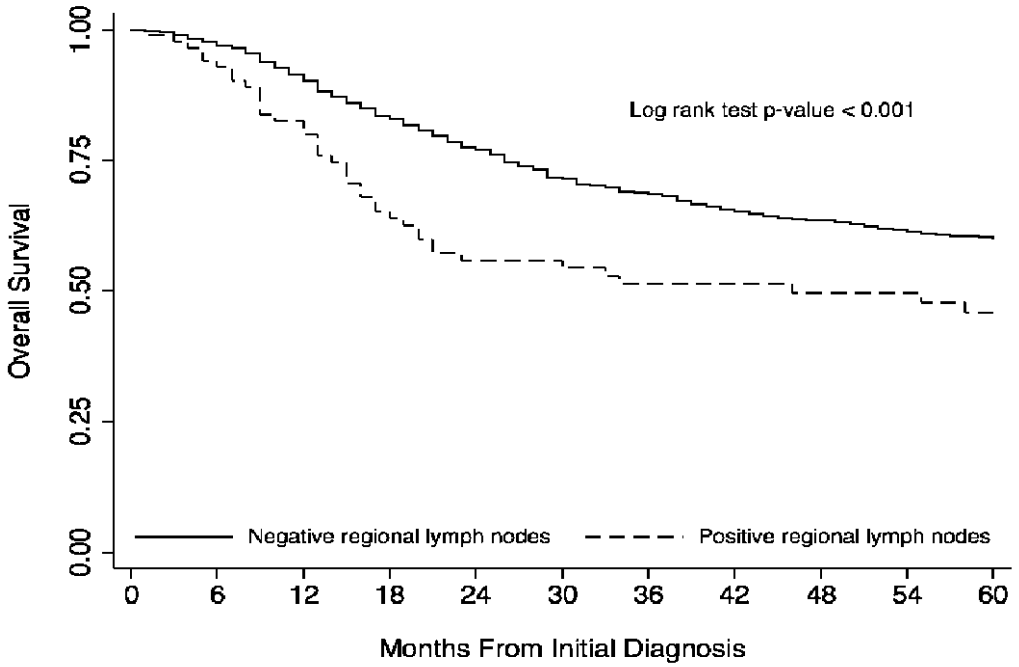
Mascarenhas et al., 2006
SEER Data 1975-1999

Primary Sites of ESFT of Bone

Site	Frequency
Central Axis	***52-55%***
Skull	2-6%
Clavicle/Scapula	4-6%
Ribs	12-13%
Spine	6-8%
Pelvis	23-27%
Extremities	***41-47%***
Humerus	5-7%
Radius/Ulna	1-3%
Hand	<1%
Femur	16-19%
Tibia	7-10%
Fibula	6-9%
Foot	2-3%

Regional Node Involvement

- Overall low incidence (6%)
- Higher incidence in soft tissue tumors (12% vs. 3%)
- Higher incidence in axial tumors



Applebaum et al.

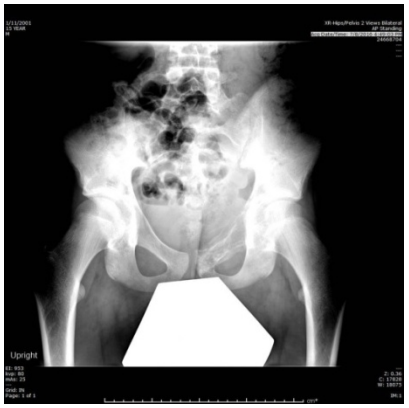
Biology

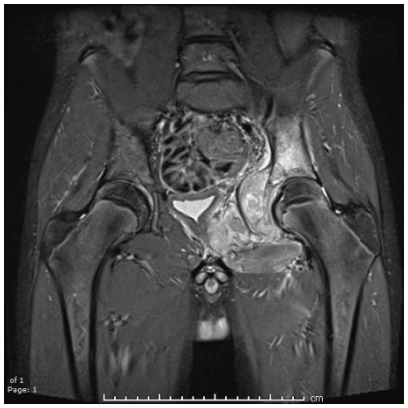
Tumor Type	Translocation	Fusion Gene
Ewing sarcoma	t(11;22)(q24;q12)	*EWSR1/FLI1* 80-95%
	t(21;22)(q22;q12)	*EWSR1/ERG* 5-10%
	t(7;22)(p22;q12)	*EWSR1/ETV1*
	t(17;22)(q12;q12)	*EWSR1/ETV4*
	t(2;22)(q35;q12)	*EWSR1/FEV*
	t(16;21)(p11;q22)	*TLS/ERG*
	t(2;16)(q35;p11)	*TLS/FEV*
Ewing-like sarcoma	t(20;22)(q13;q12)	*EWSR1/NFATC2*
	(NB: can occur in ring chromosome and may be amplified)	*EWSR1/POU5F1*
	t(6;22)(p21;q12)	*EWSR1/SMARCA5*
	t(4;22)(q31;q12)	*EWSR1/ZSG*
	Submicroscopic inv(22) in t(1;22)(p36.1;q12)	
	t(2;22)(q31;q12)	*EWSR1/SP3*
	t(4;19)(q35;q13)	*CIC/DUX4*
	inv(X)(p11.4;p11.22)	*BCOR/CCNB3*

Investigations

Primary site

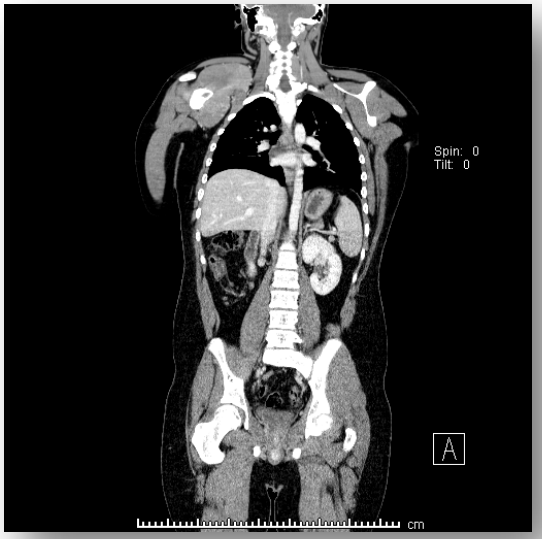
- Plain film
- MRI of affected region

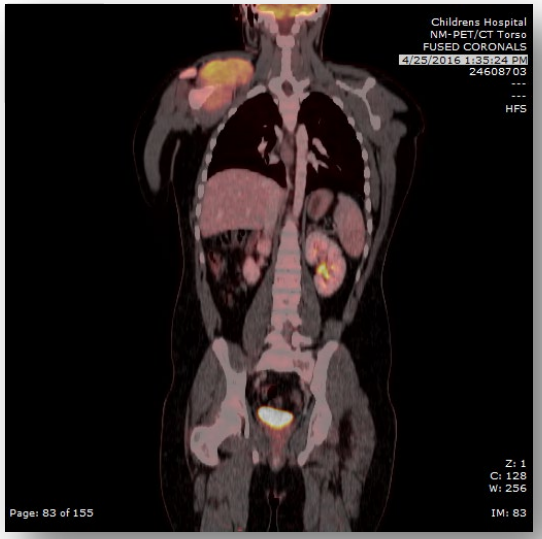




Metastasis detection and staging

- CT chest
- Bone scan
- Bilateral BM biopsy
- PET scan

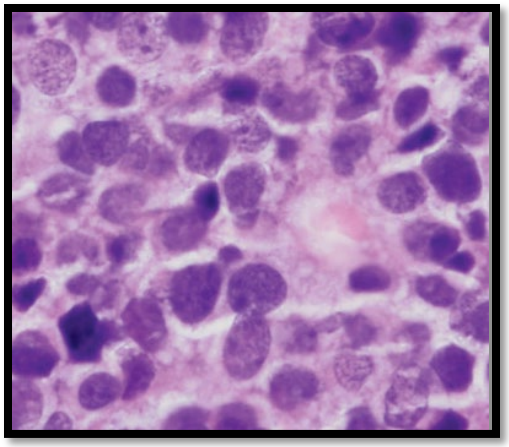




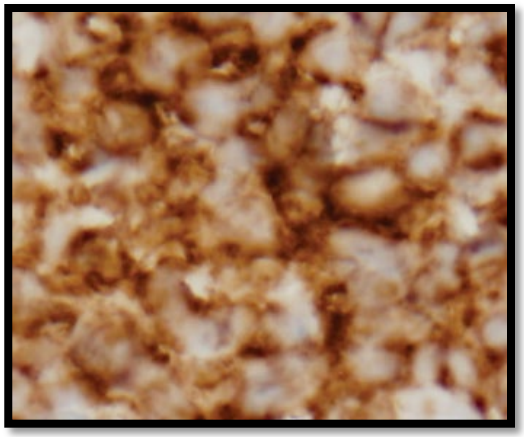
Tissue biopsy

Diagnosis-Pathology

- Small round blue cell tumor

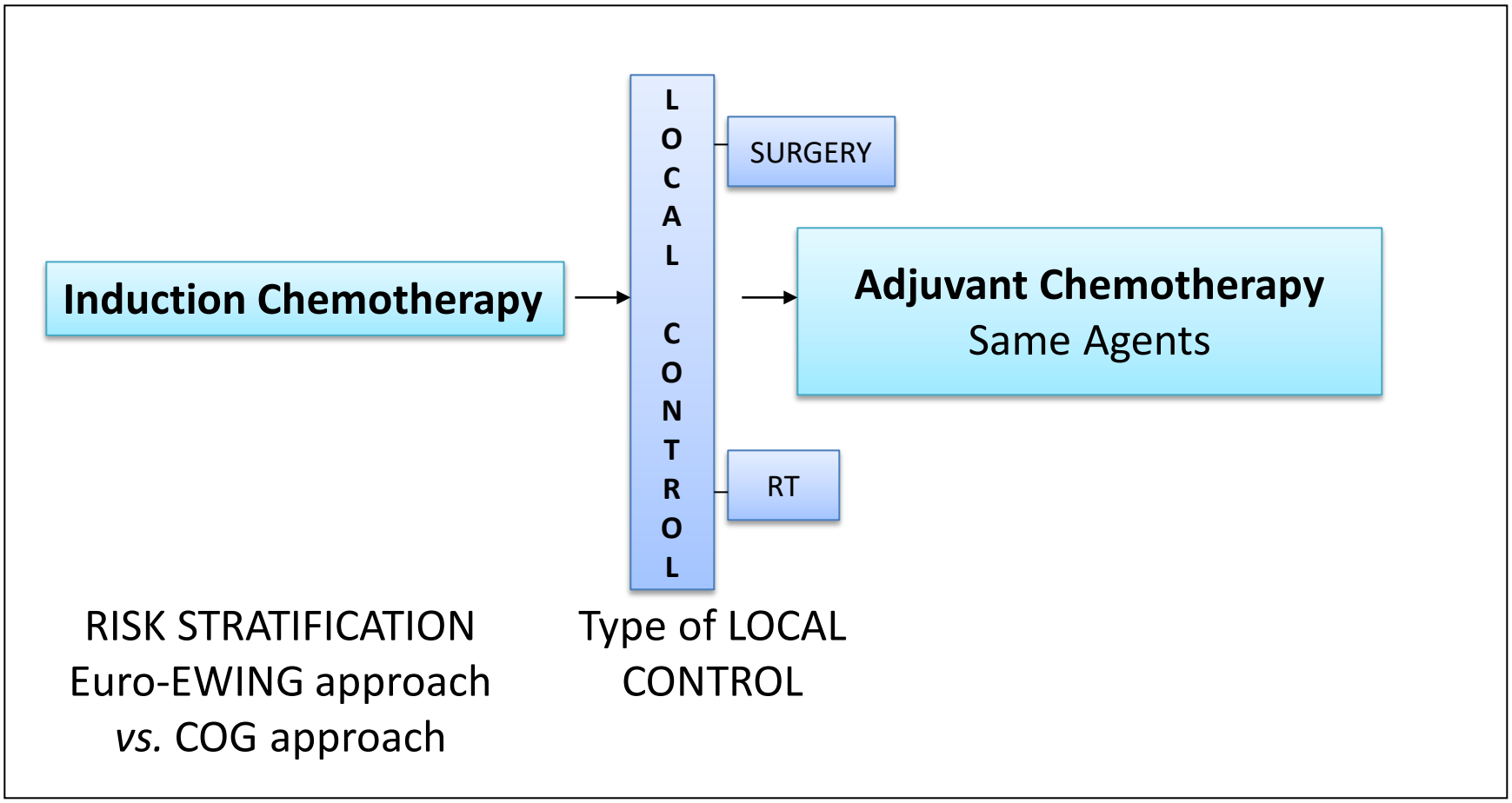


- Neural differentiation with PNET
- Nearly universal membranous CD99 expression
- Molecular diagnostics
  - Cytogenetics
  - FISH
  - PCR



CD 99

Principles of Management



Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

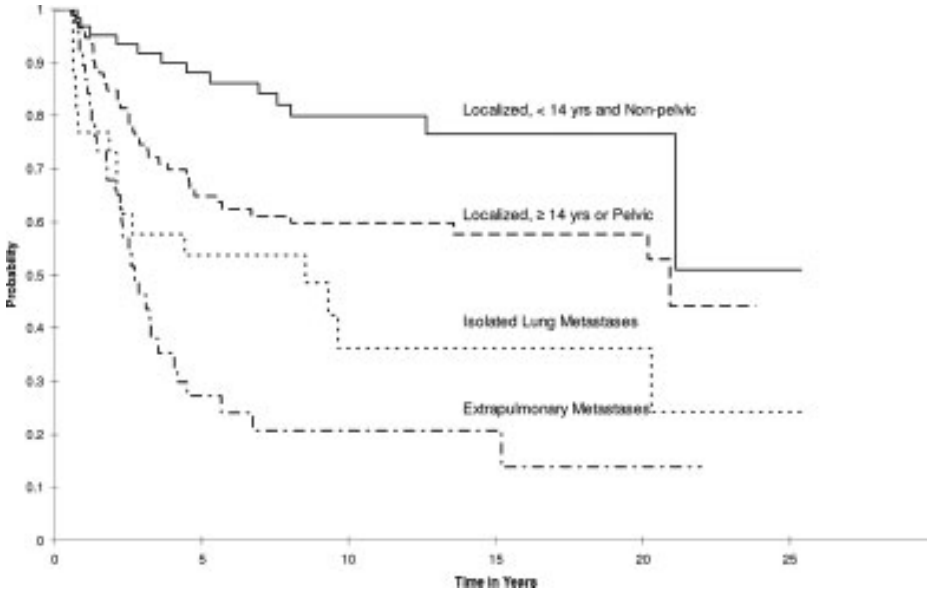
Local Control

Approach	Disadvantage
Complete surgical resection	Not an option for all tumors
Radiation	Late effects of therapy
Surgery plus radiation	• Late effects of therapy • Prolonged local control interferes with systemic therapy

- Patients treated with definitive radiation have higher risk of local failure
- Overall survival not different based upon mode of local control
- Favor surgical resection whenever feasible, with radiation reserved for selected cases

Prognostic factors

- Age at presentation: ≥ 14 yrs
- Site of disease: pelvic
- Size of tumor: > 200 ml or > 8 cm
- CMT without IE
- Stage
  - Localized: 5 year EFS ~ 70%
  - Metastatic: 5 year EFS < 30%
    - Isolated lung metastases do slightly better
    - High dose chemotherapy: modest benefit with significant toxicity

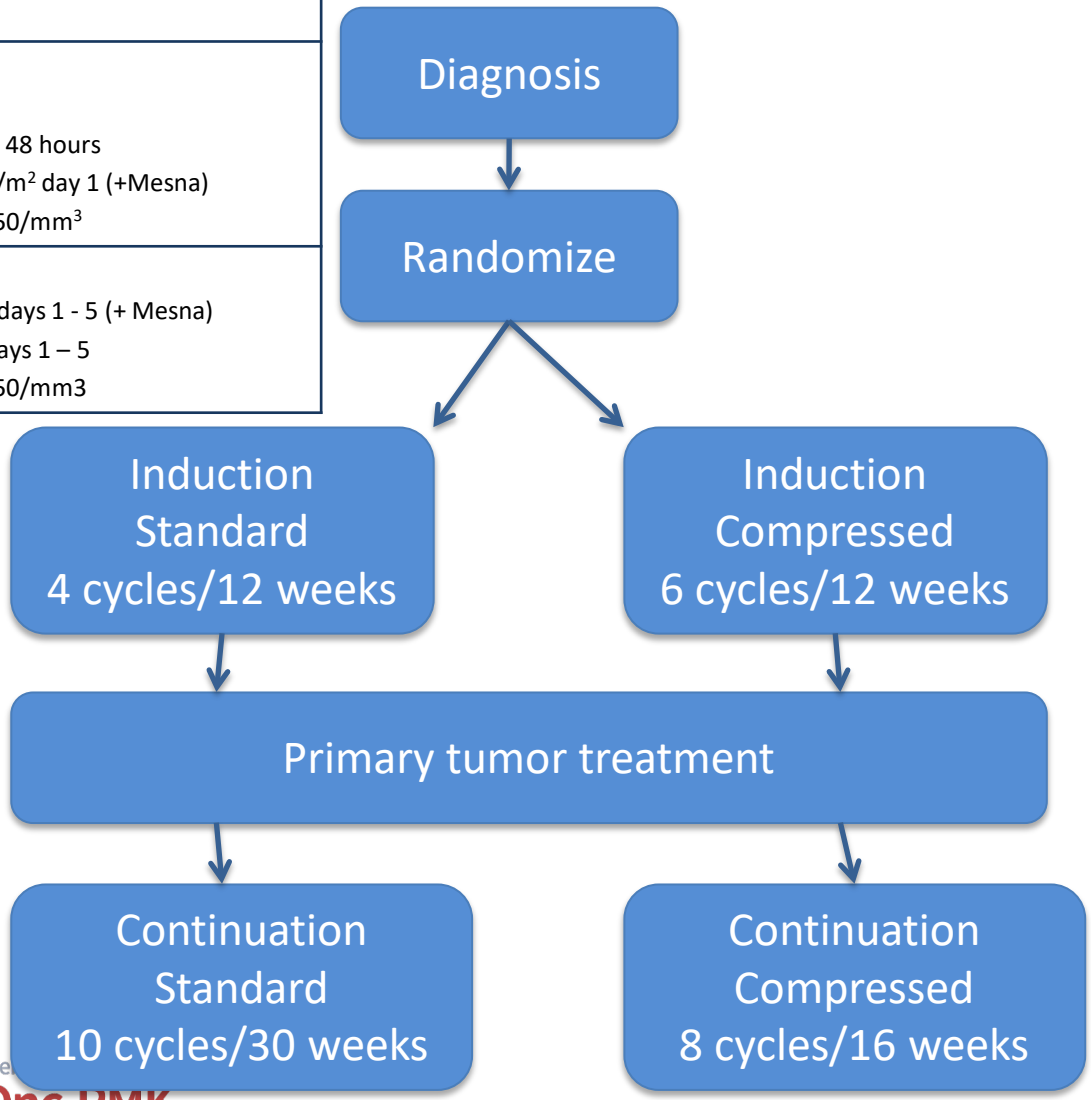


Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

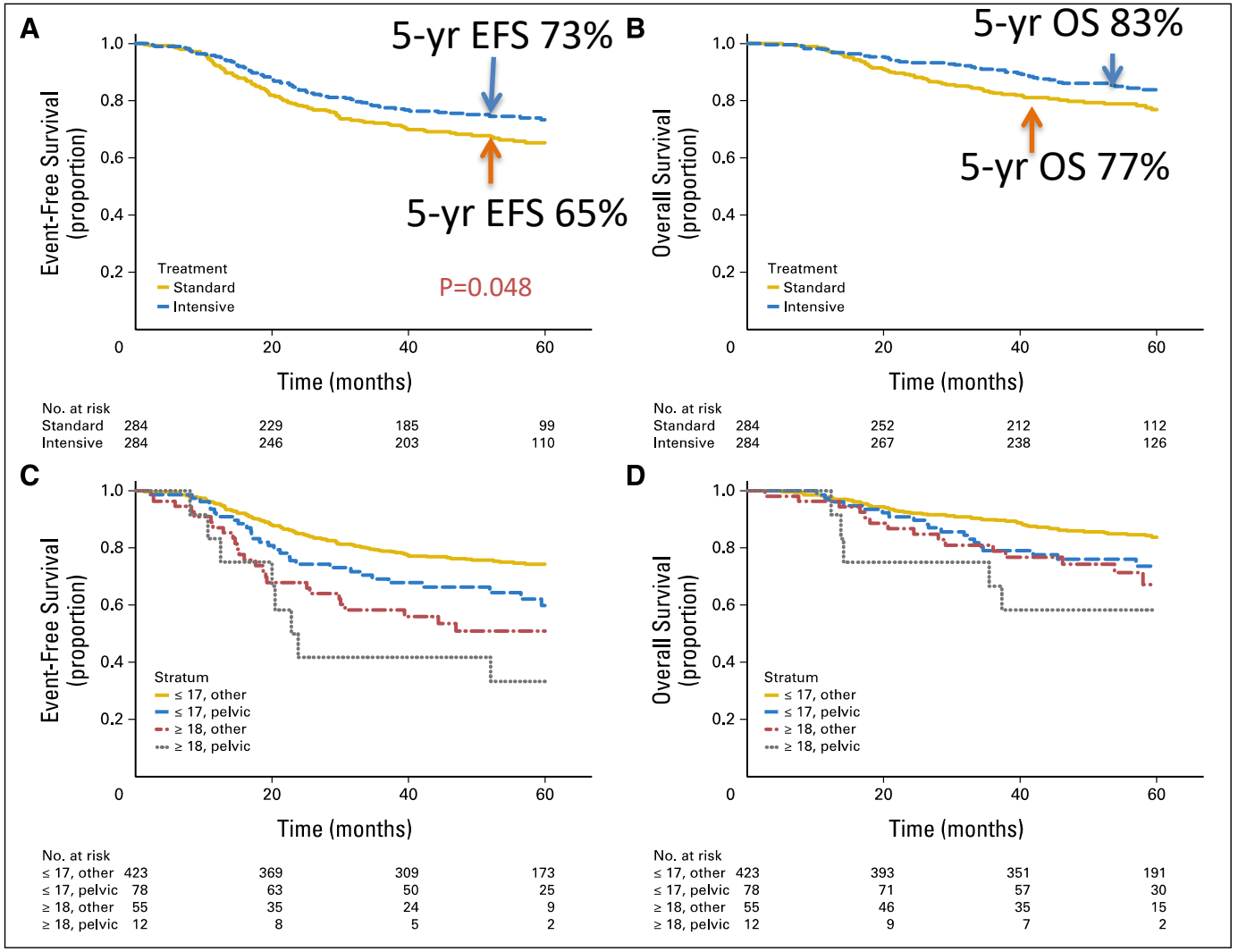
Cotterill et al., 2000
Rodriguez-Galindo C, Cancer 2007
Marina et al., Sarcoma 2015

AEWS-0031 – Chemotherapy Intensification through Interval Compression for Ewing Sarcoma

Drugs and Cycles
VDC x 7 cycles*   (V) Vincristine 2 mg/m^2 day 1   (D) Doxorubicin 75 mg/m^2 CI for 48 hours   (C) Cyclophosphamide 1200 mg/m^2 day 1 (+Mesna)   G-CSF 5 mcg/kg/d until ANC > 750/mm^3
IE x 7 cycles   (I) Ifosfamide 1800 mg/m2/day days 1 - 5 (+ Mesna)   (E) Etoposide 100 mg/m2/day days 1 – 5   G-CSF 5 mcg/kg/d until ANC > 750/mm3



AEWS-0031 – Chemotherapy Intensification through Interval Compression for Ewing Sarcoma



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Womer et al. J Clin Oncol 30:4148-4154

Conclusions

- Bone tumors: 50% benign: 50% malignant
- Treatment consisting neoadjuvant, local control and adjuvant CMT
- Staging: localized vs. metastasis
- MCM: Osteosarcoma and Ewing sarcoma
- Prognosis is vary
- Outcomes depend on staging, size of tumor, response to CMT

www.pedhemeoncpmk.com