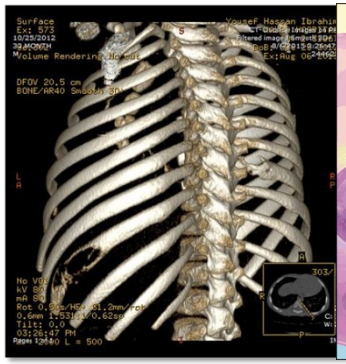
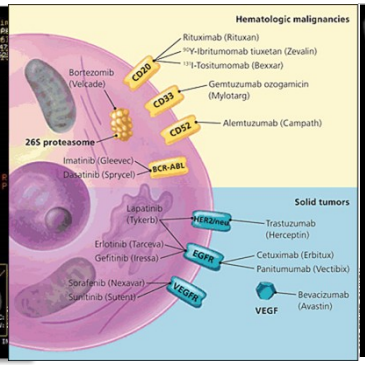
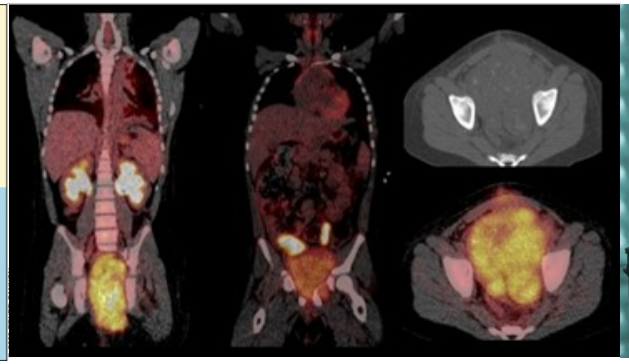
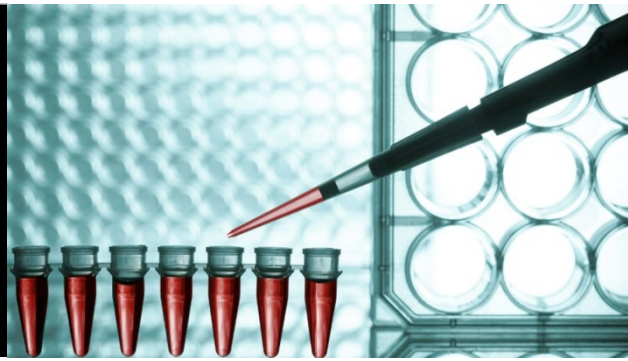
Sarcomas in Children

Langerhans Cell Histiocytosis

3rd Intensive Review in Pediatric Hematology/Oncology 2018

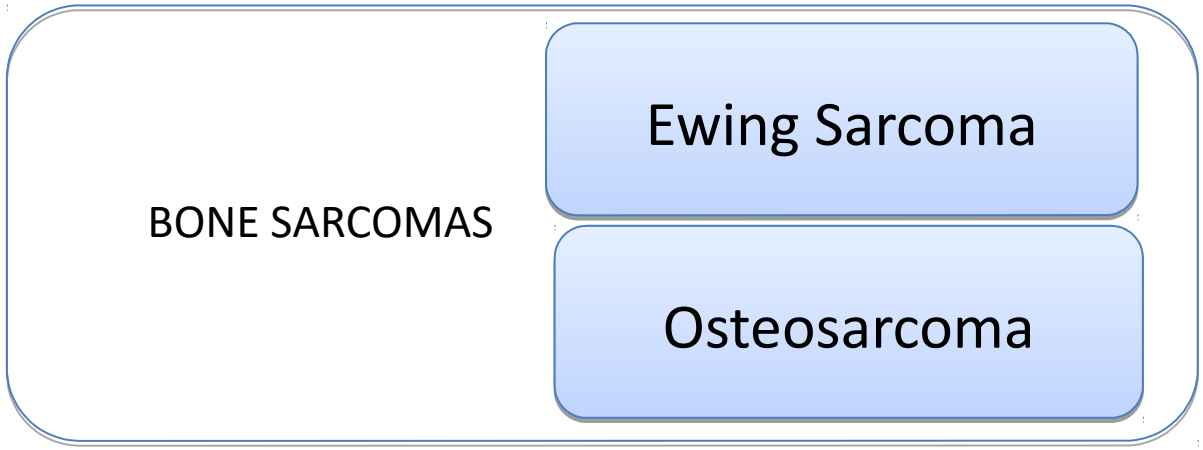
7-8 September, 2018

Chalinee Monsereenusorn, M.D.

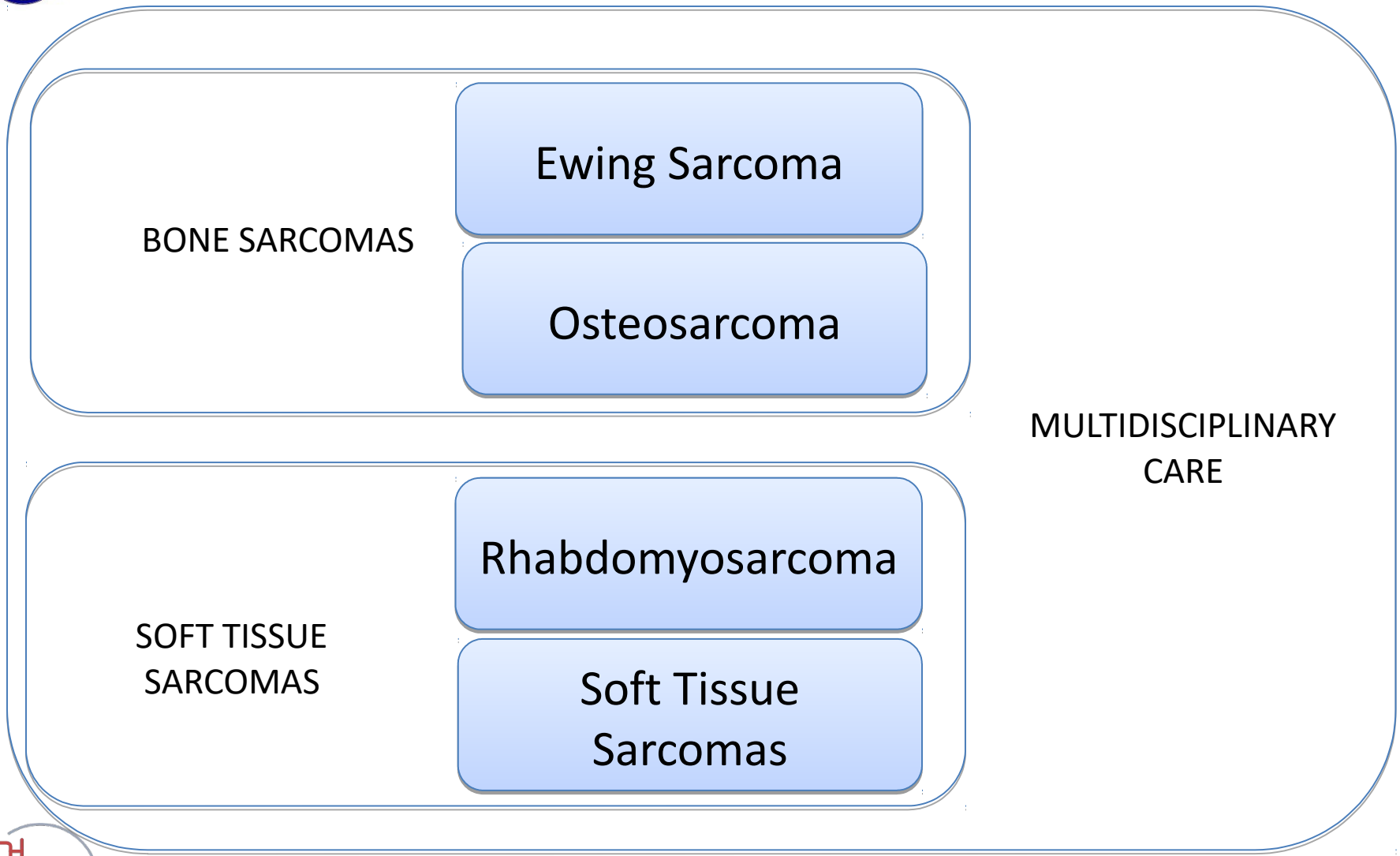
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Division of Hematology-Oncology,
Department of Pediatrics, Phramongkutklao Hospital

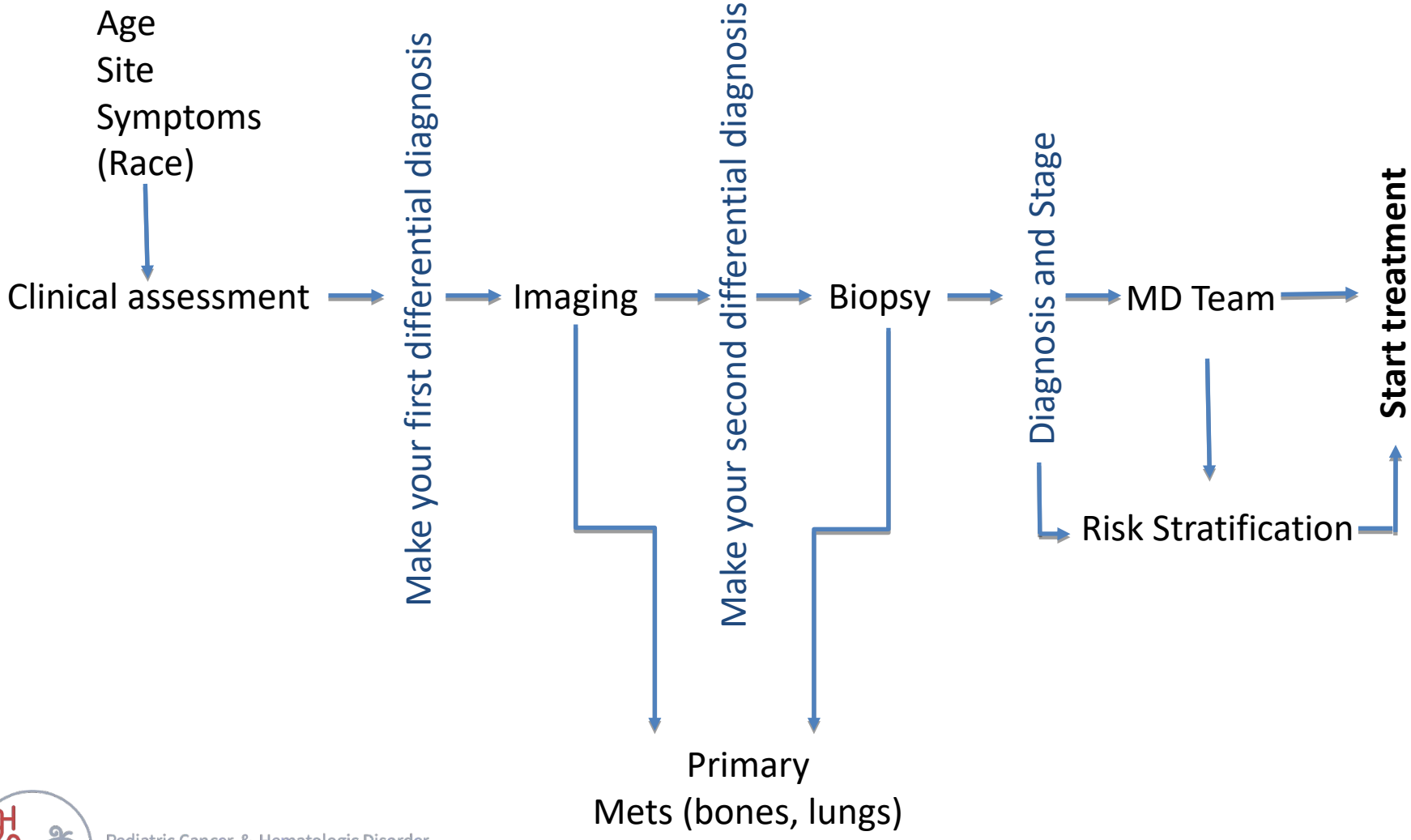
Management of Sarcomas



Management of Sarcomas



Principles of Management



Pediatric Cancer & Hematologic Disorder
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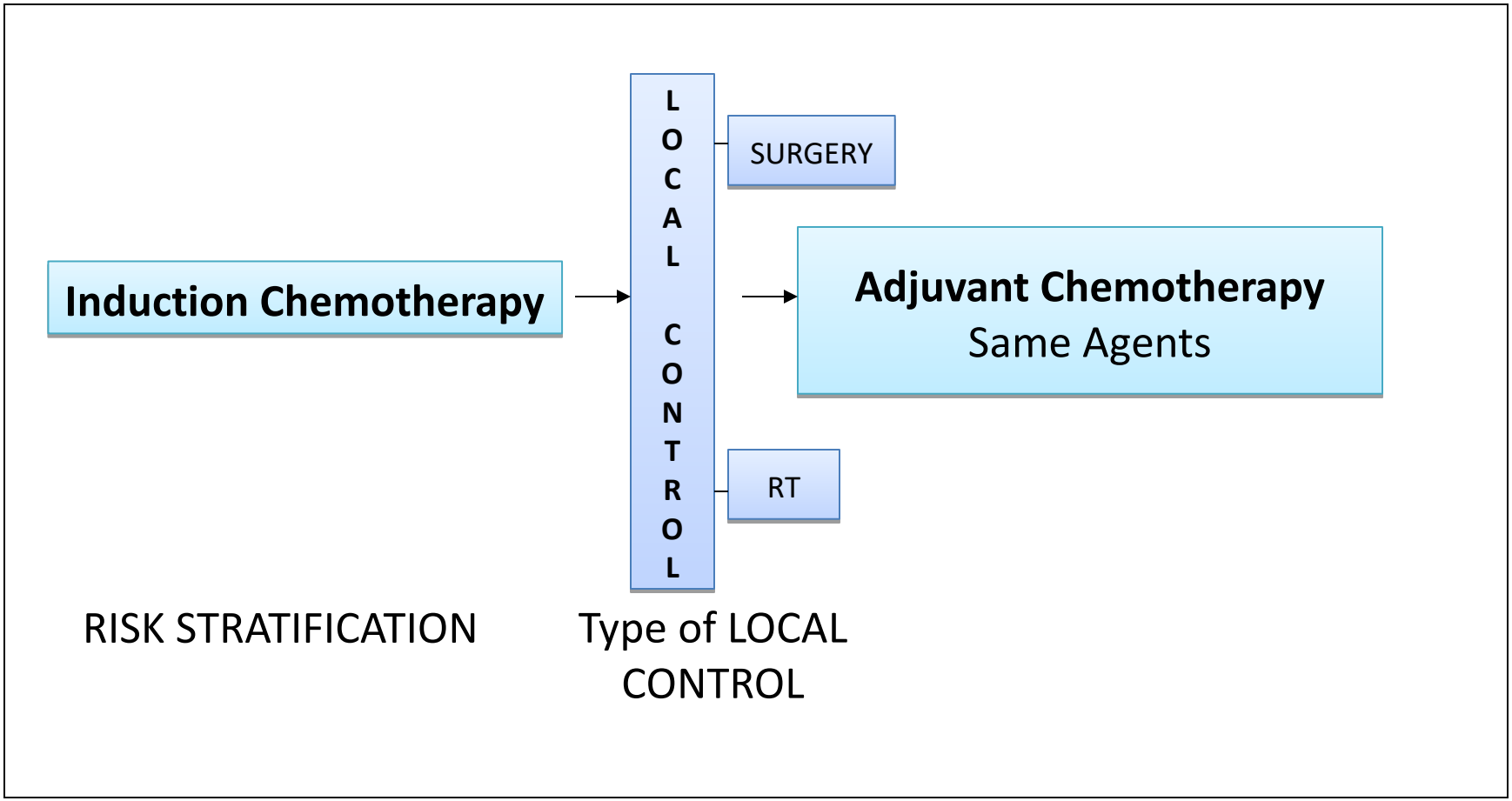
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Principles of Management



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

Management of Sarcomas

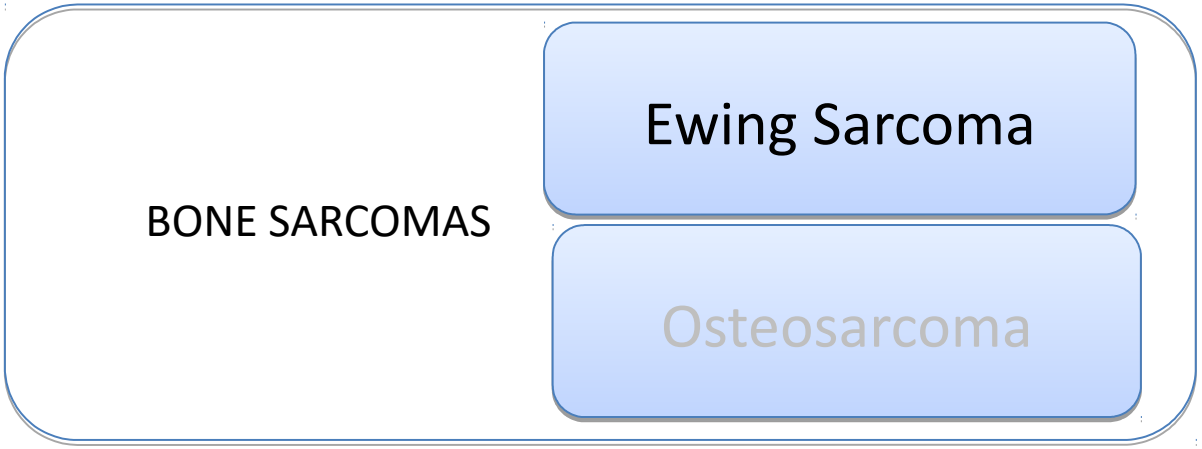
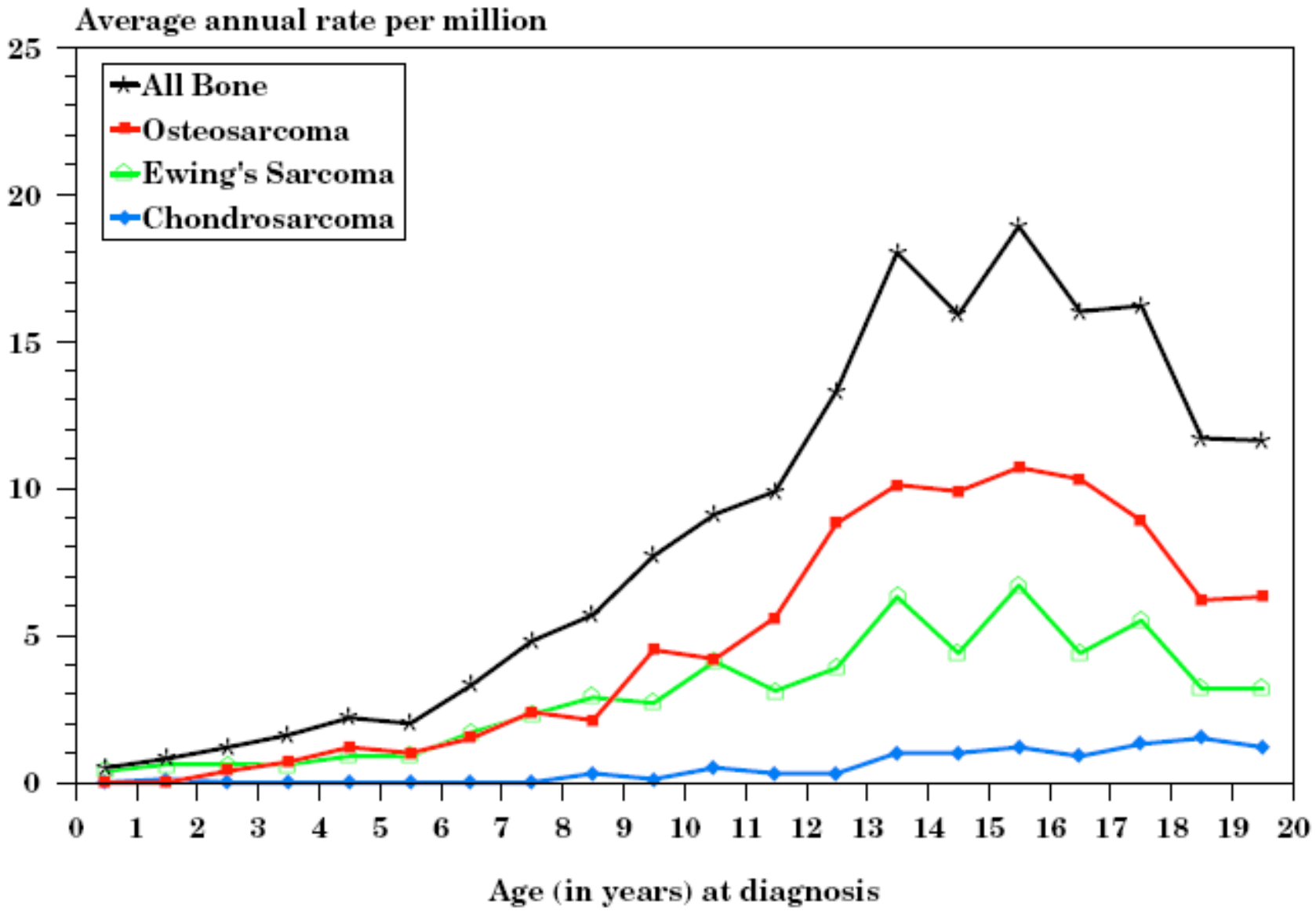


Figure VIII.2: Bone cancer age-specific incidence rates by histology all races, both sexes, SEER, 1976-84 and 1986-94 combined



Lanzkowsky 5th edition, 2011

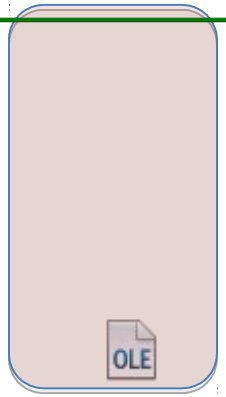
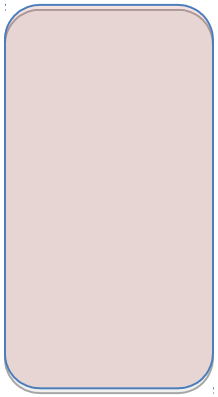
Malignant Bone Tumors

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

Malignant Bone Tumors

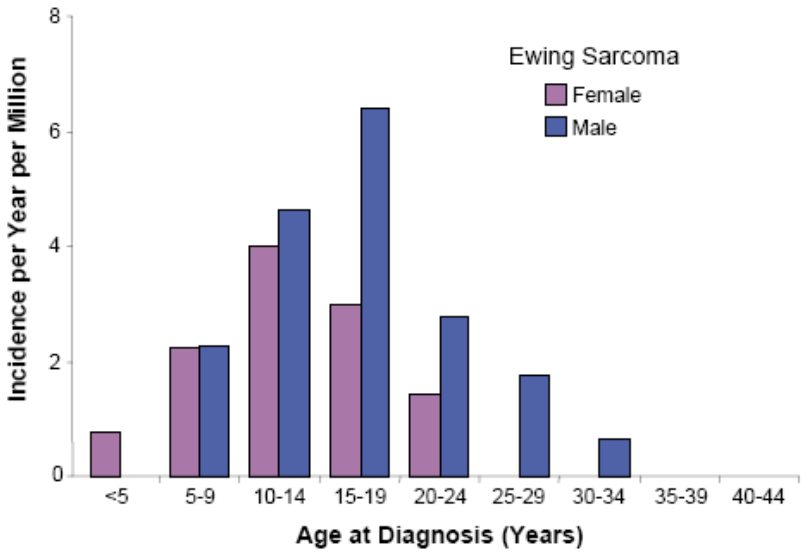
	Osteosarcoma	Ewing's Sarcoma
Bone	Long bones	Long and Flat bones (Pelvis, skull, ribs)
Site	Metaphysis	Diaphysis
Genetic	Rb, p53 TS genes	t(11;22)EWS-FLI Oncogene activation
Radiologic findings	• Sunburst pattern • Calcification	• Moth-eaten lytic lesion • Onion skin • Periosteal reaction • Codman's 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	
Distal Femur	 

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



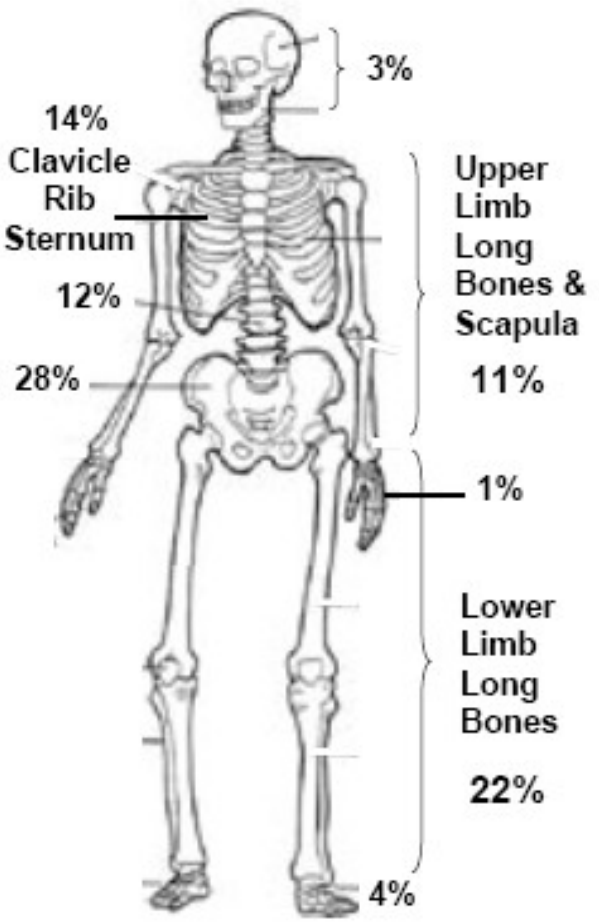
Mascarenhas et al., 2006
SEER Data 1975-1999

Site of Origin

- Bone primaries (75%)

  Axial=extremities

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



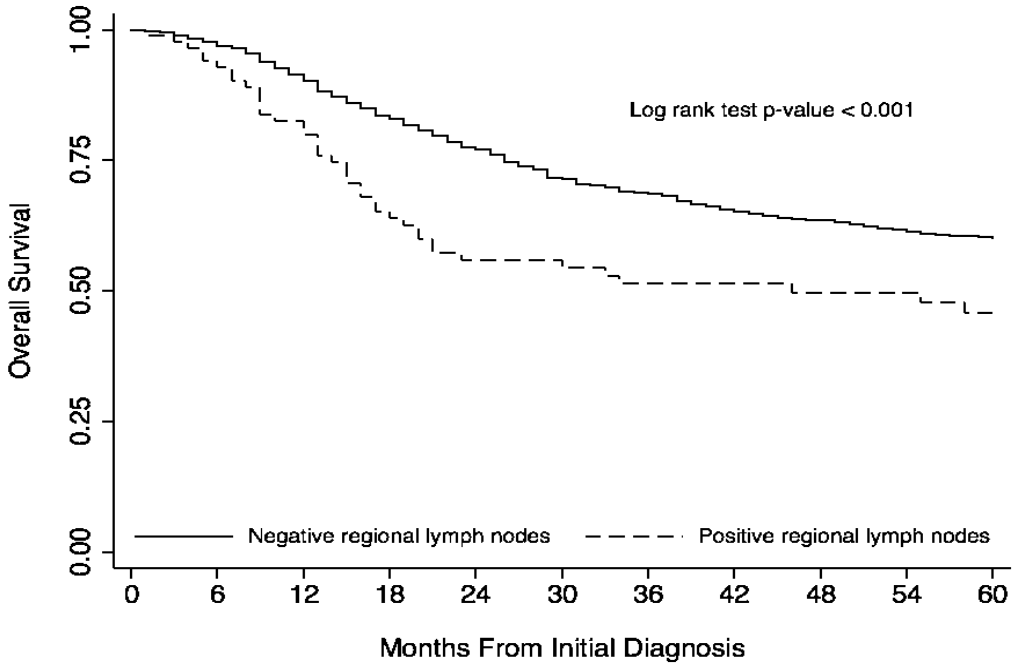
Mascarenhas et al., 2006
SEER Data 1975-1999

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.

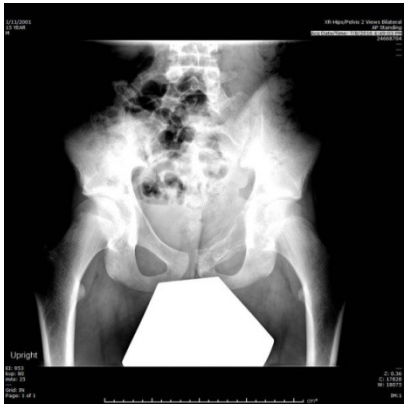
Biology

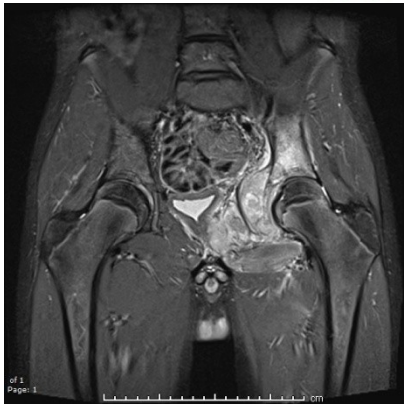
Tumor Type	Translocation	Fusion Gene	
Ewing sarcoma	t(11;22)(q24;q12)	*EWSR1/FLI1*	80-95%
	t(21;22)(q22;q12)	*EWSR1/ERG*	5-10%
	t(7;22)(p22;q12)	*EWSR1/ETV1*	
	t(17;22)(q12;q12)	*EWSR1/ETV4*	
	t(2;22)(q35;q12)	*EWSR1/FEV*	
	t(16;21)(p11;q22)	*TLS/ERG*	
	t(2;16)(q35;p11)	*TLS/FEV*	
Ewing-like sarcoma	t(20;22)(q13;q12) (NB: can occur in ring chromosome and may be amplified)	*EWSR1/NFATC2* *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

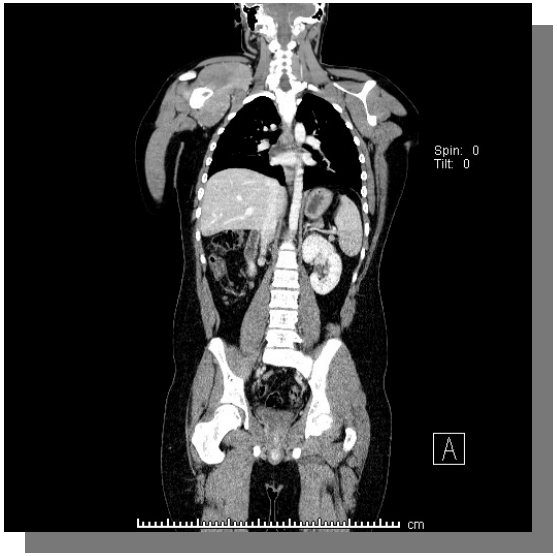
- Plain film
- MRI of affected region

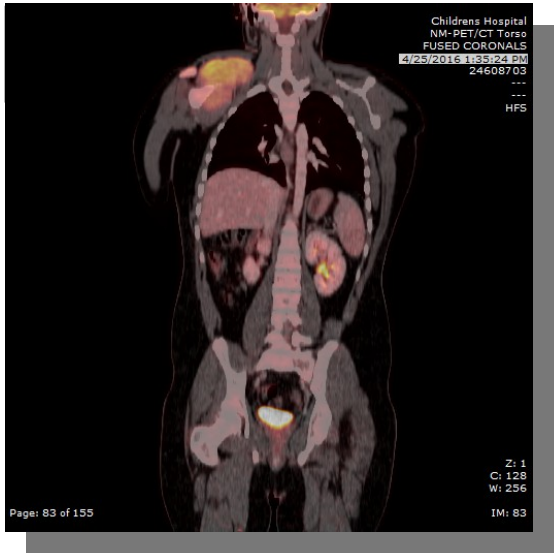




Metastasis detection and staging

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





Tissue biopsy

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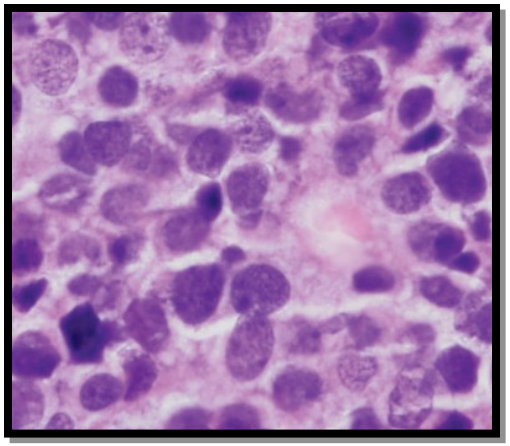
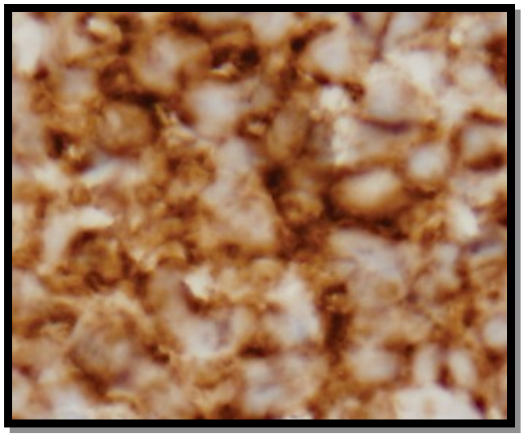
Diagnosis-Pathology

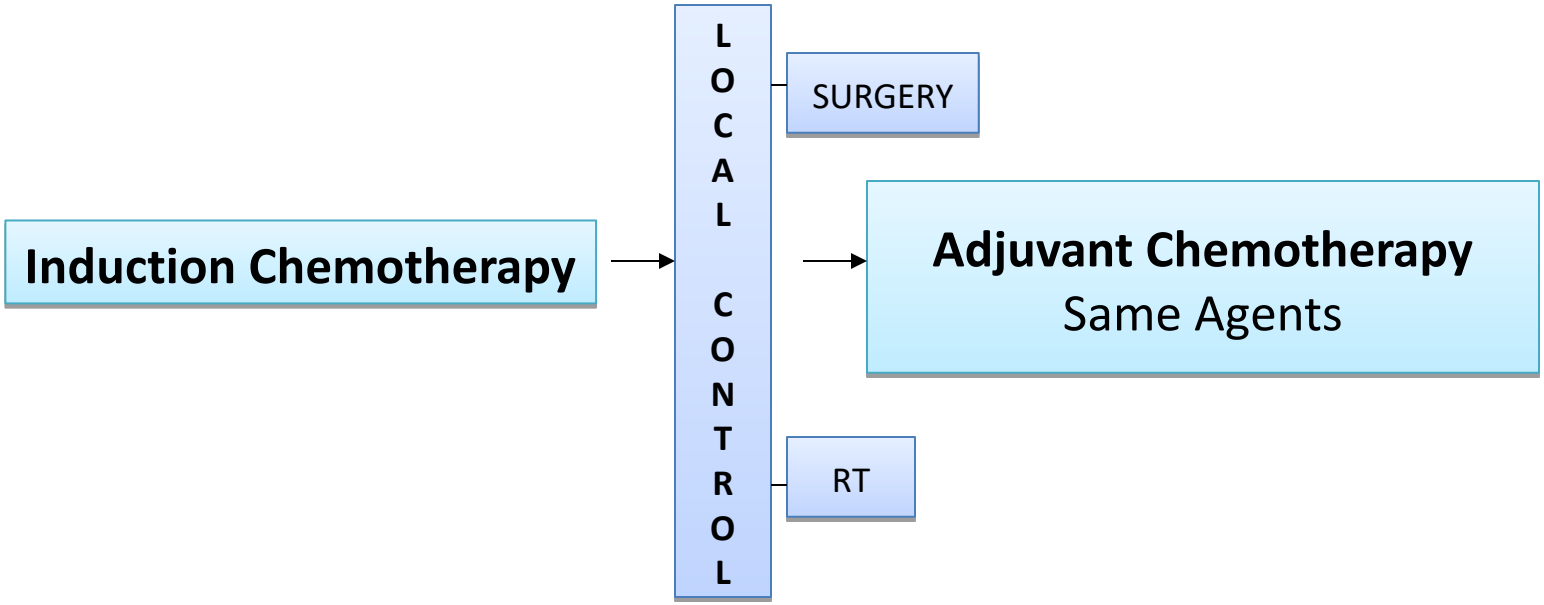


- Small round blue cell tumor
- Neural differentiation with PNET
- Nearly universal membranous CD99 expression
- Molecular diagnostics
  - Cytogenetics
  - FISH
  - PCR



CD 99

Principles of Management



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

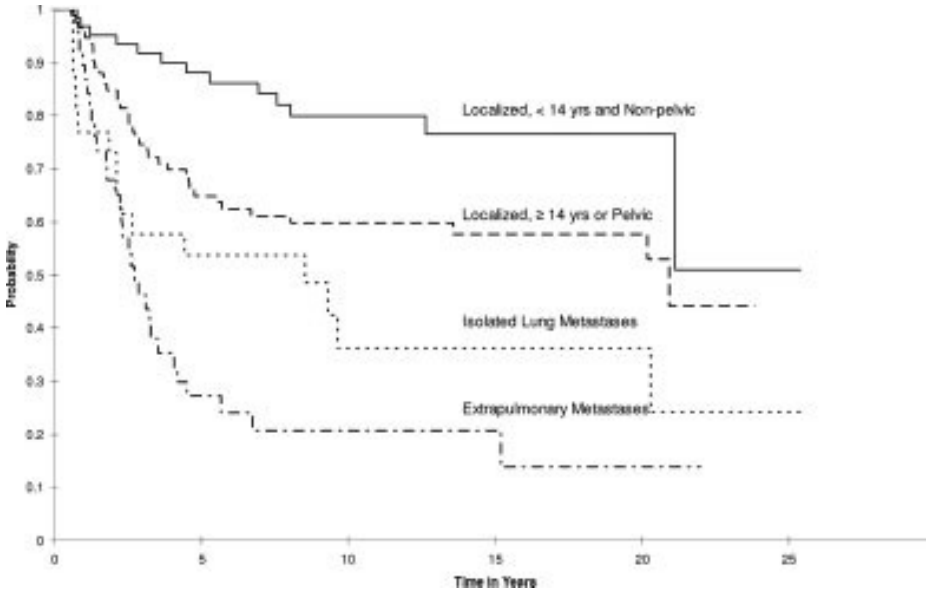
Local Control

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

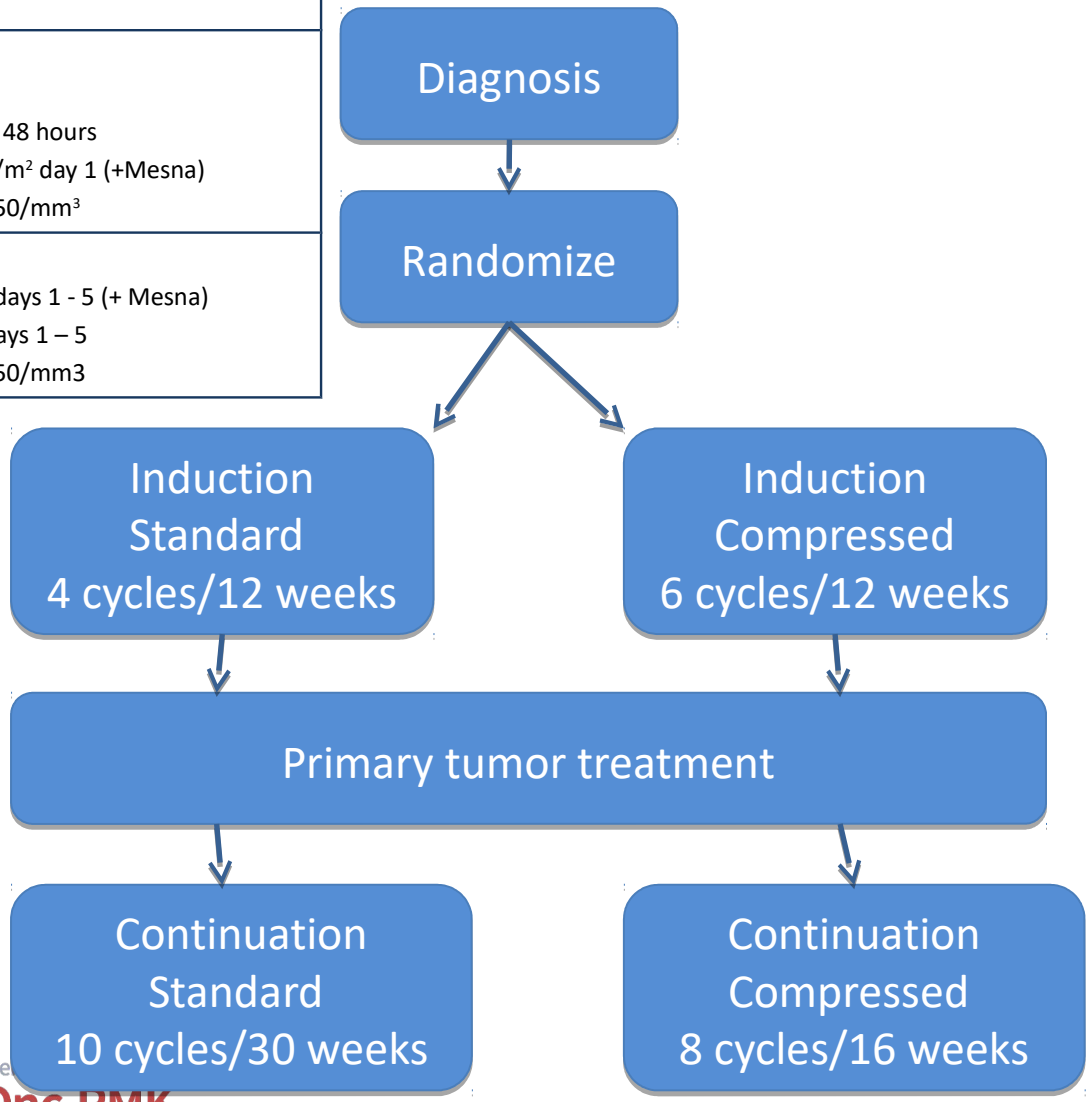
- Age at presentation: ≥ 14 yrs
- Site of disease: pelvic
- Size of tumor: > 200 ml or > 8 cm
- CMT without IE
- Stage
  - Localized: 5 year EFS ~ 70%
  - Metastatic: 5 year EFS < 30%
    - Isolated lung metastases do slightly better
    - High dose chemotherapy: modest benefit with significant toxicity



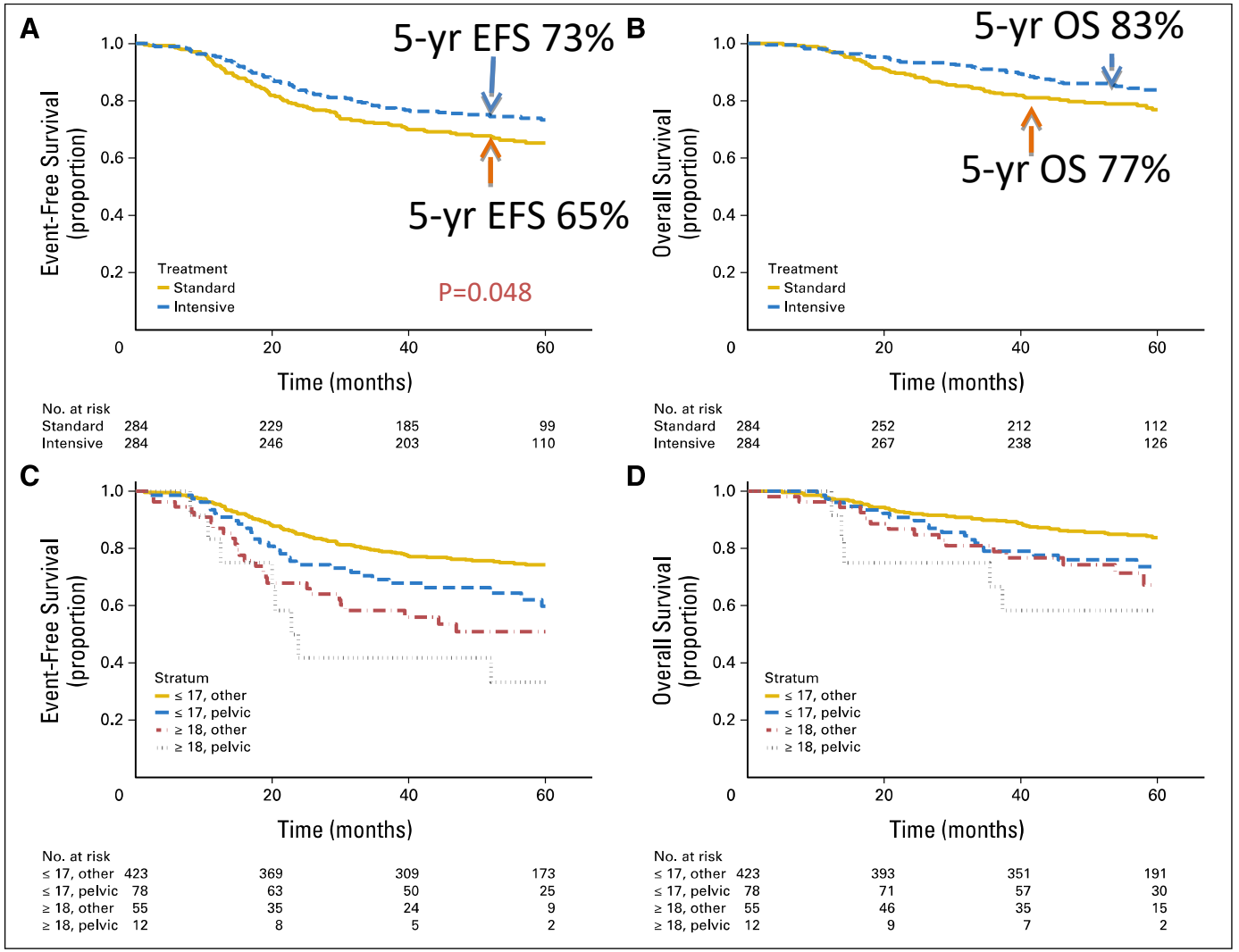
Cotterill et al., 2000
Rodriguez-Galindo C, Cancer 2007
Marina et al., Sarcoma 2015

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



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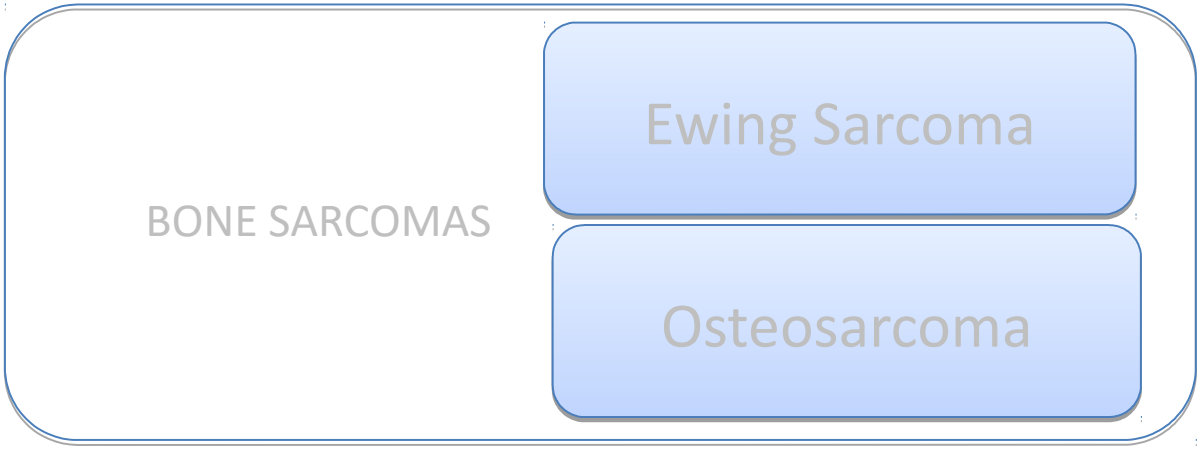
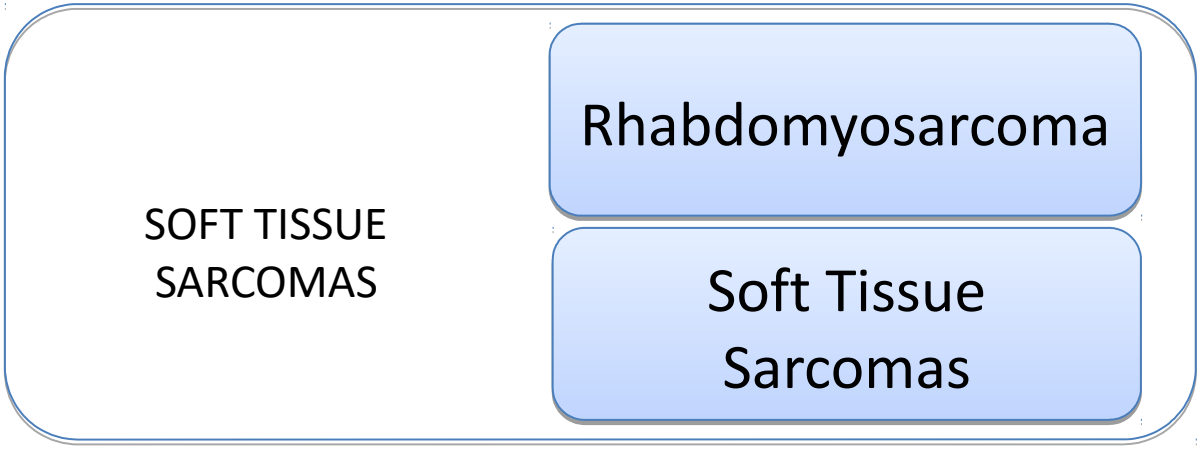
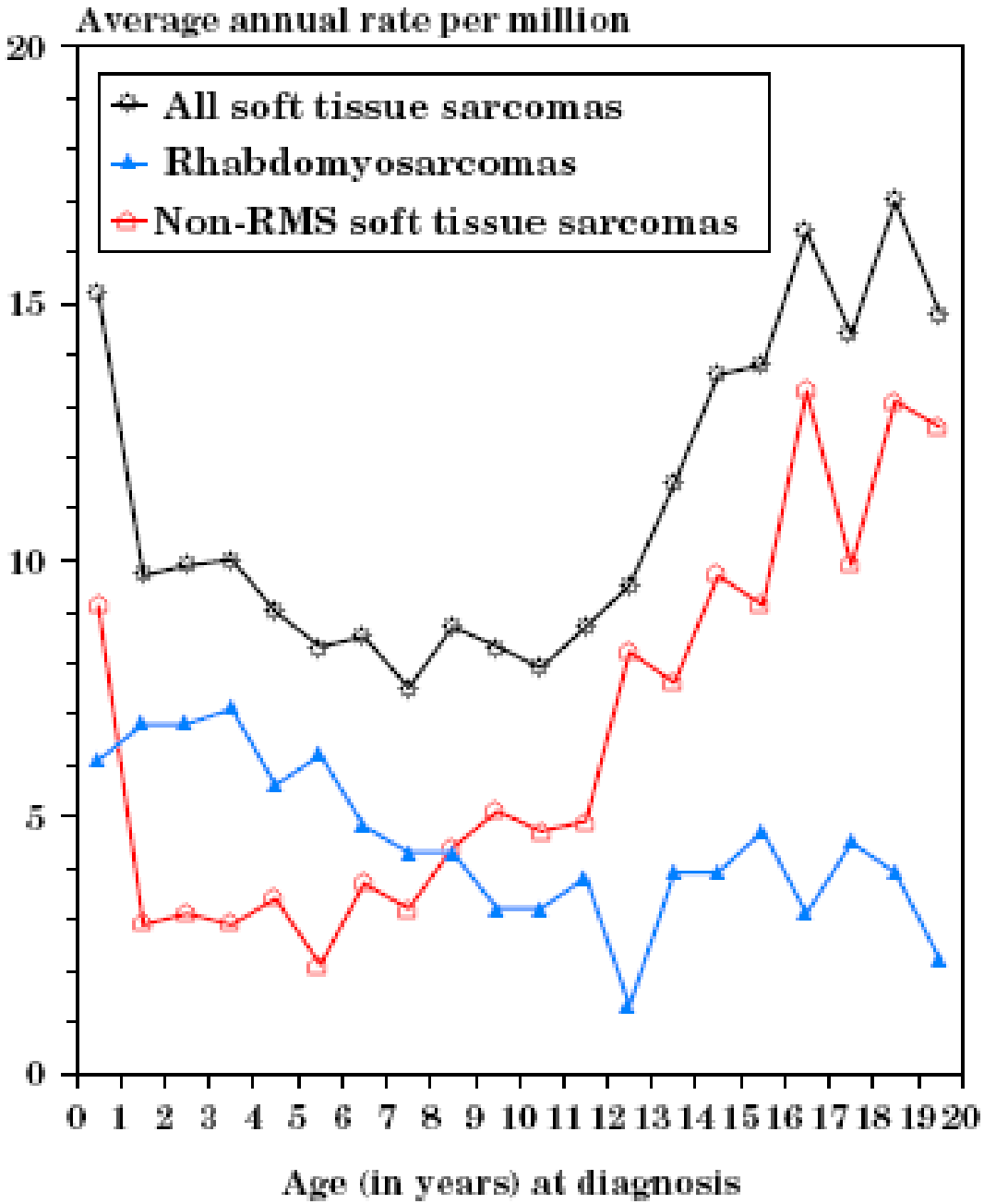
Womer et al. J Clin Oncol 30:4148-4154

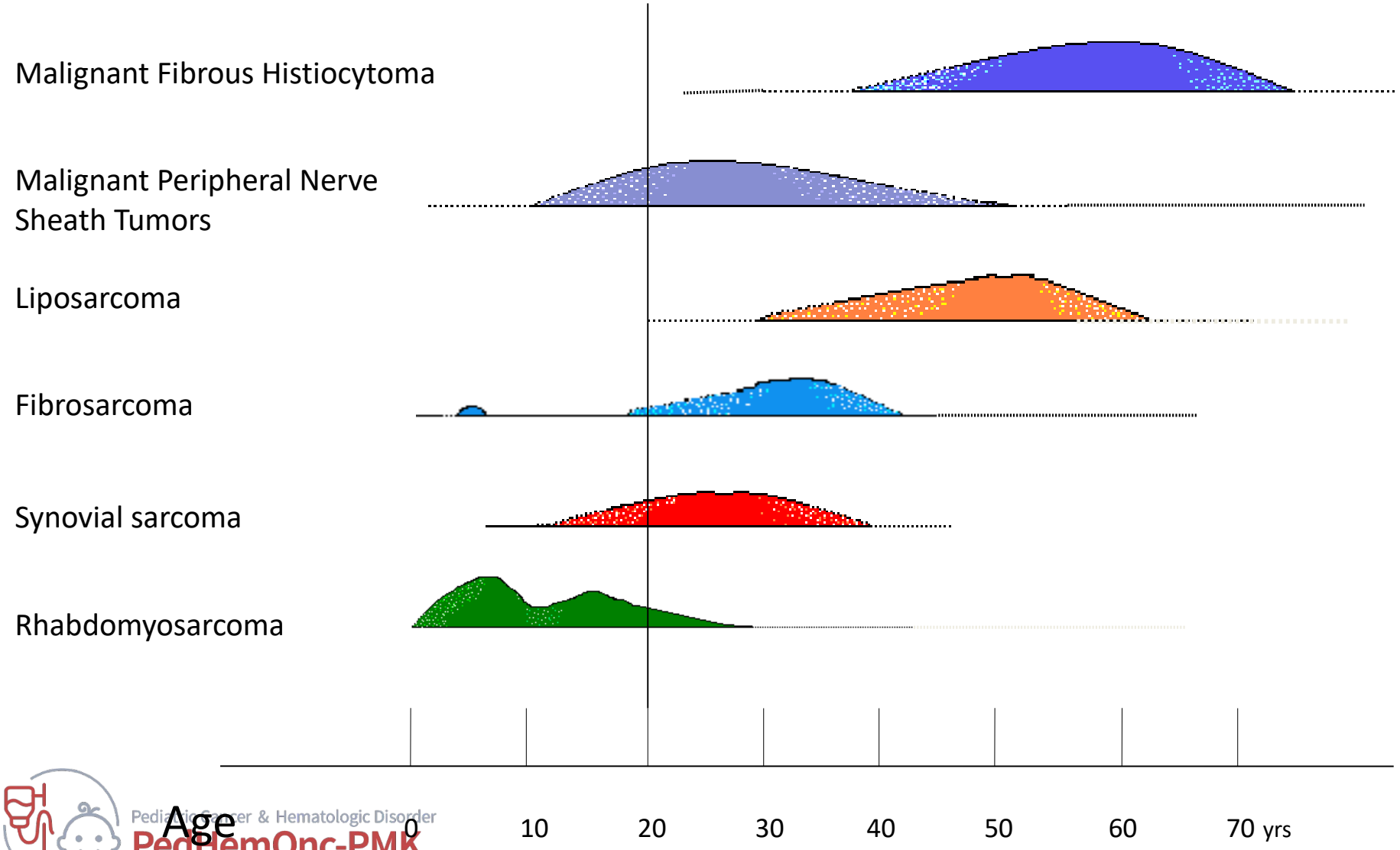
Management of Sarcomas







Incidence of Soft Tissue Sarcomas According to Age



A. Ferrari, MD

RMS vs NRSTS

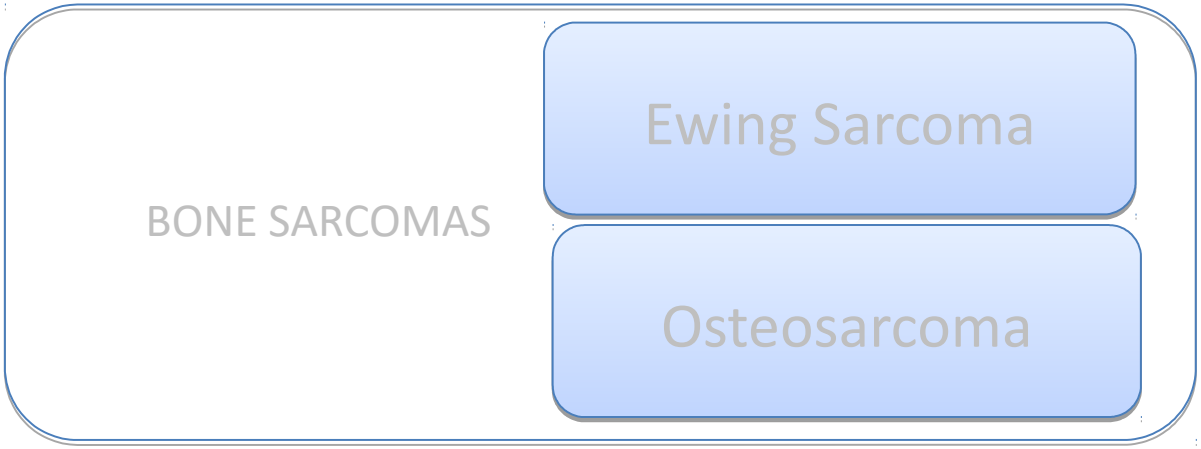
RMS

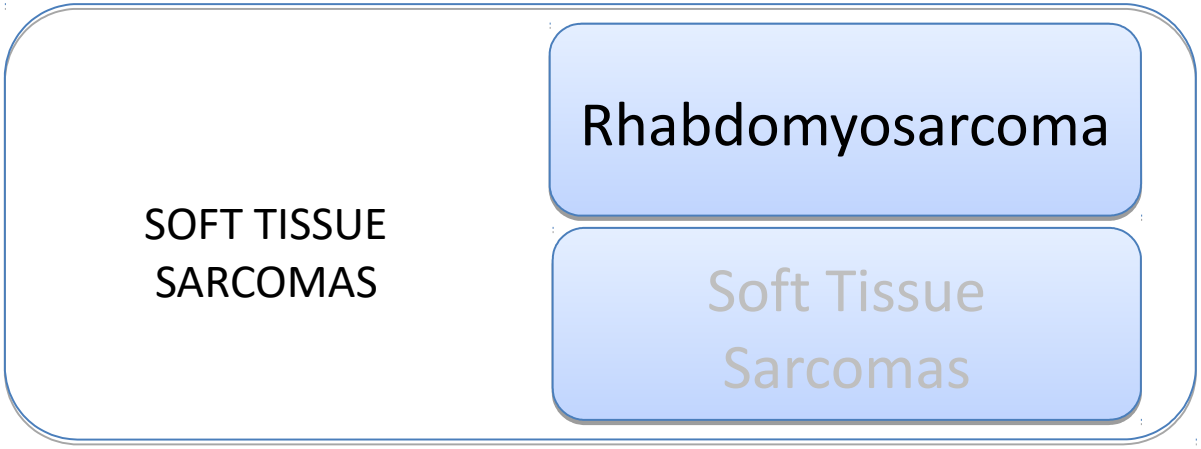
- Age < 10
- H&N
- Unresected (50%)
- Two histologic types
- Chemosensitive
- Adjuvant therapy is effective
- Metastases: lung, bone, bone marrow
- Rx: Risk based-VAC

NRSTS

- Age > 10
- Extremities
- Resected (70%)
- Many histologic types
- Chemoresistant
- Unproven benefit of adjuvant therapy
- Metastases: lung; other sites are rare
- Rx: Ifos/Dox

Management of Sarcomas





Disease characteristics

Primary site	Frequency (%)	Symptoms and signs	Predominant pathologic subtype
Head and neck	**35**		Embryonal
Orbit	9	Proptosis	
Parameningeal	16	Cranial nerve palsies; aural or sinus obstruction +/- drainage	
Other	10	Painless, progressively enlarging mass	
Genitourinary	**22**		Embryonal (botryoid variant in bladder and vagina)
Bladder and prostate	13	Hematuria, urinary obstruction	
Vagina and uterus	2	Pelvic mass, grape liked mass, vaginal discharge	
Paratesticular	7	Painless mass	
Extremities	**18**	Affects adolescents; swelling of affected body part	Alveolar (50%)
Perineal and perianal (PRMS)	**2**	Mass	Alveolar (60-80%)
Other	**23**	Mass	Embryonal, alveolar

Rhabdomyosarcoma

HISTOLOGY

- Embryonal 55-60%
- Botryoid 6%
- Alveolar 15-20%
- Undiff 20%

Prognostic Factors

- TNM
  - Diameter ≤ 5cm with improved survival (correlation between size and BSA*)
  - Metastasis and regional LN involvement
- Resectability
- Age: 1-9 yo have best prognosis
- Sites of primary tumor
- Histopathology

* Ferrari et al., JCO, 2009

Prognostic Factors : Sites of primary tumor

Favorable

- Orbit
- GU non bladder, non prostate
- H&N non parameningeal
- Biliary tract

Unfavorable

- Bladder
- Prostate
- Parameningeal
- Extremities
- (Perineal and perianal)*

*Casey at al., Int J Radiation Oncol Biol, 2014
Fuchs et al., Annals of Surgery, 2014

Prognostic Factors : Histopathology

Favorable

- Embryonal
- Botryoid (under mucosa of the vagina, bladder, nasopharynx and biliart tract)
- Spindle cell (mostly at paratesticular site)

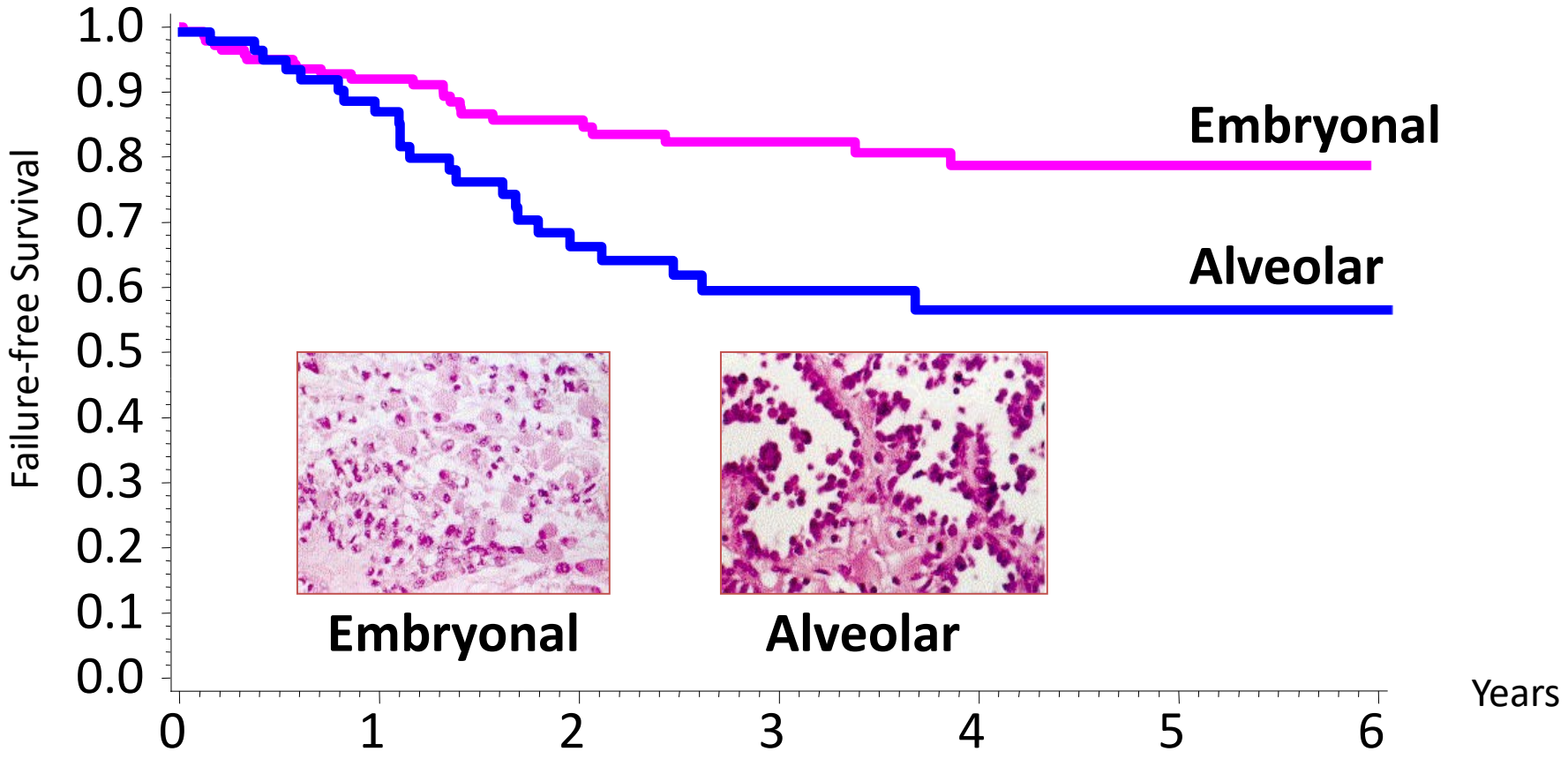
Unfavorable

- Alveolar
- Anaplastic* (not influence treatment)

Prognostic Factors

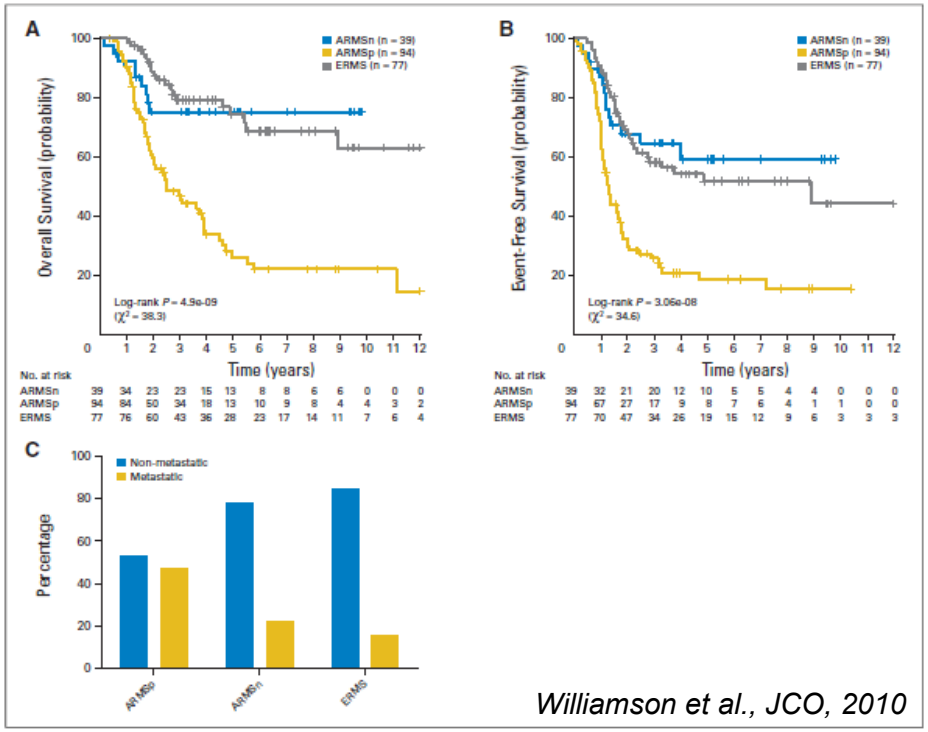
Histologic Subtypes of RMS

Failure-free Survival, IRS-IV Patients

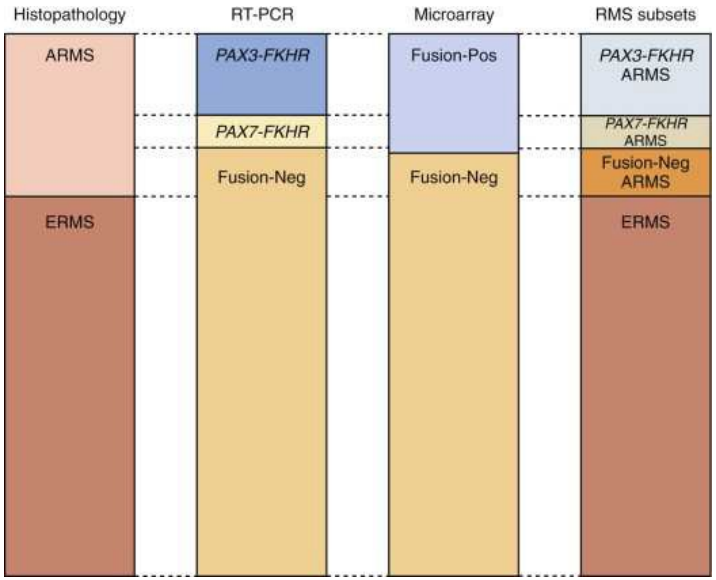


Molecular Biologic Characteristics

- Alveolar: 70-80% fusion gene positive FOXO1
  - PAX3/FOXO1, PAX7/FOXO1
  - Outcome ARMSn = ERMS



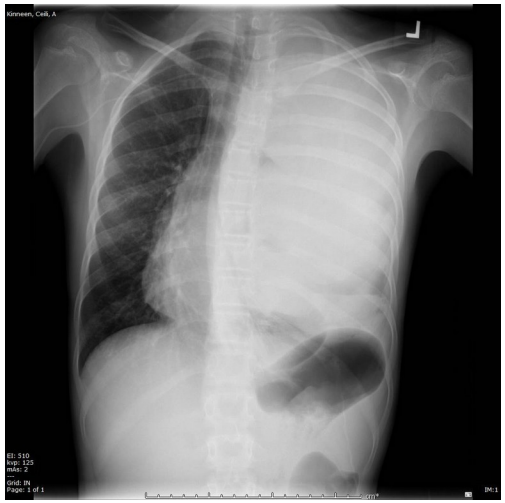
Williamson et al., JCO, 2010

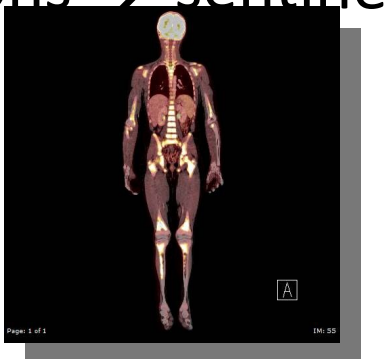


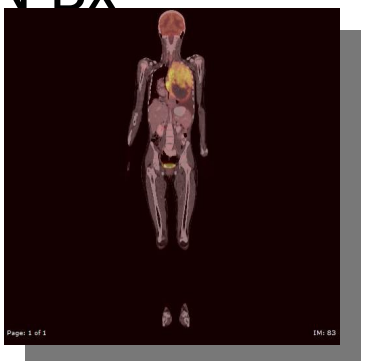
Nathan and Oski's Hematology and Oncology of Infancy and Childhood 7th ed, 2009

Investigations

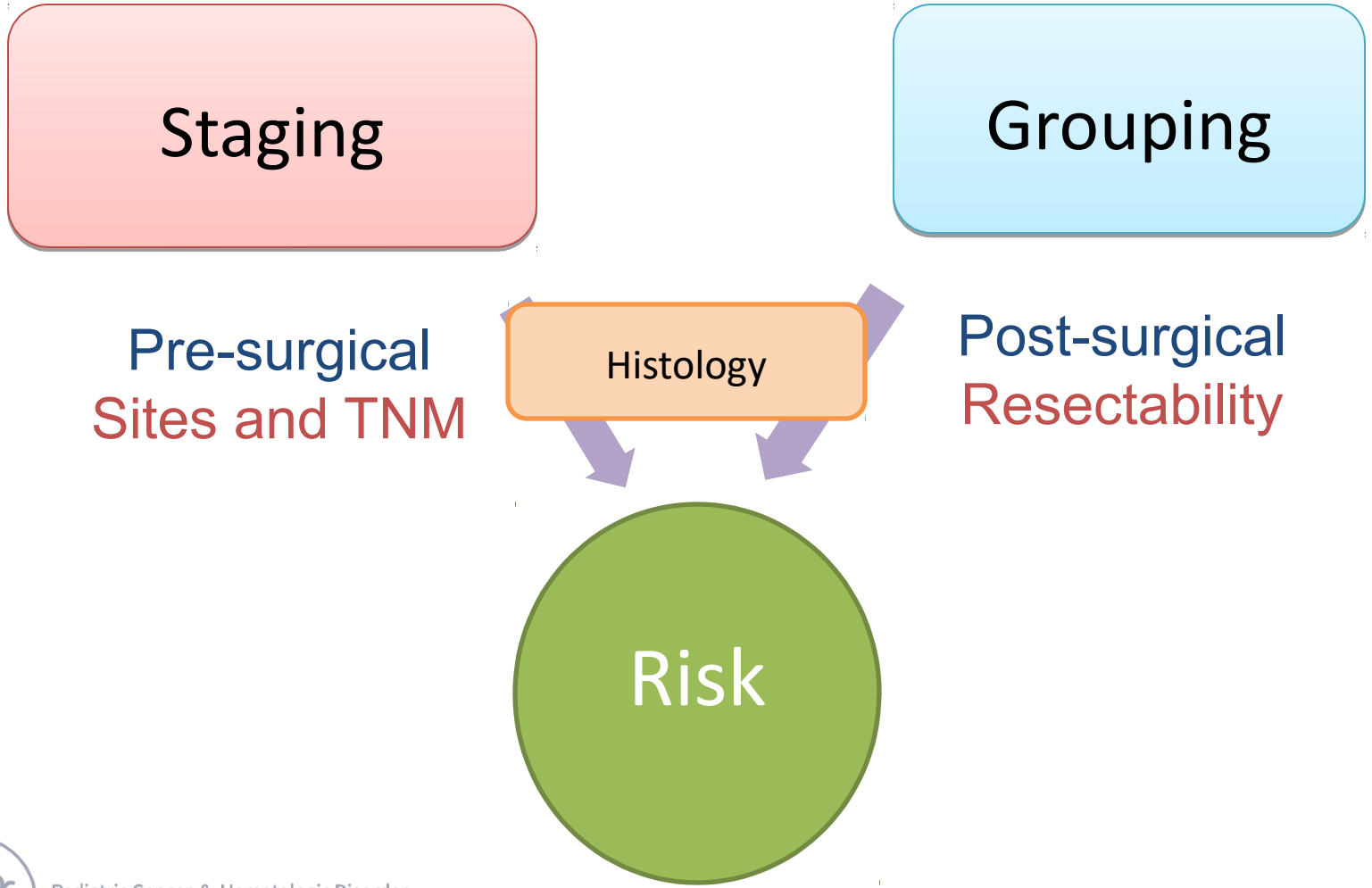
- CT/ MRI primary lesion
- CT chest, CXR
- CT abdomen include pelvis
- Bone scan
- PET scan
- BMA & BM biopsy
- Biopsy
  - ARMS with extremities lesions → sentinel LN Bx







Risk Stratification



IRSG staging system 1972

Stage	Site	Tumor size (T)	LN (N)	Metastasis (M)
1	Favorable	Any	Any	No
2	Unfavorable	≤ 5 cm	Negative	No
3	Unfavorable	≤ 5 cm	Positive	No
		>5 cm	Any	
4	Any	Any	Any	Yes

Favorable: Orbit, GU non bladder, non prostate, H&N non parameningeal, Biliary tract

PM: Middle ear, nasal cavity and paranasal sinuses, nasopharynx and infratemporal fossa/pterygopalatine and parapharyngeal area

LN staging

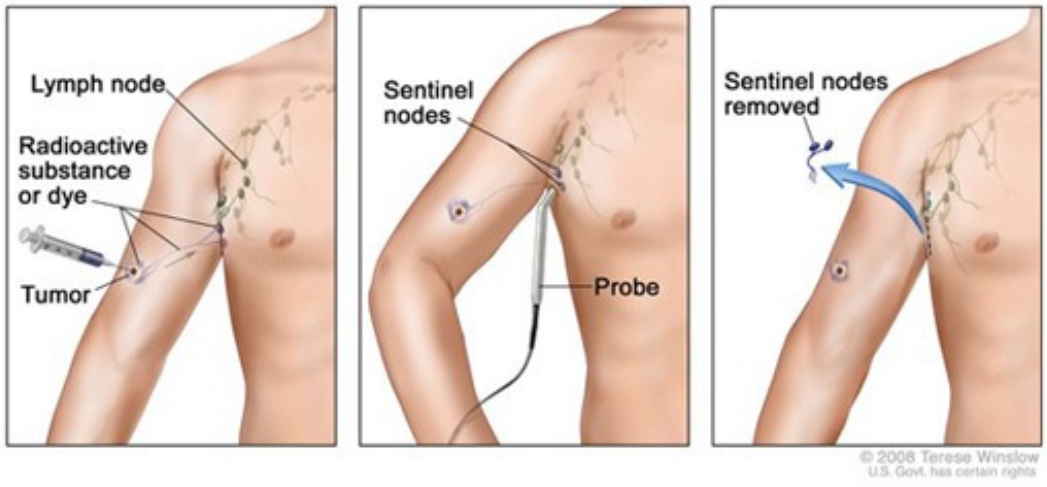
- Clinical/radiological staging → By PE, imaging
- Surgical staging → LN resection/biopsy

How's important??

- LN + → CMT +RT
- Clinical/CT → Surgical LN Bx → + → CMT +RT
  - → - → no RT

LN staging

- Extremity site -> sentinel LN biopsy
- Indication for LN Bx
  1. Clinical/radiologinal warranted
  2. Extremity site -> sentinel LN biopsy
  3. Boy ≥ 10 yo w paratesticular RMS

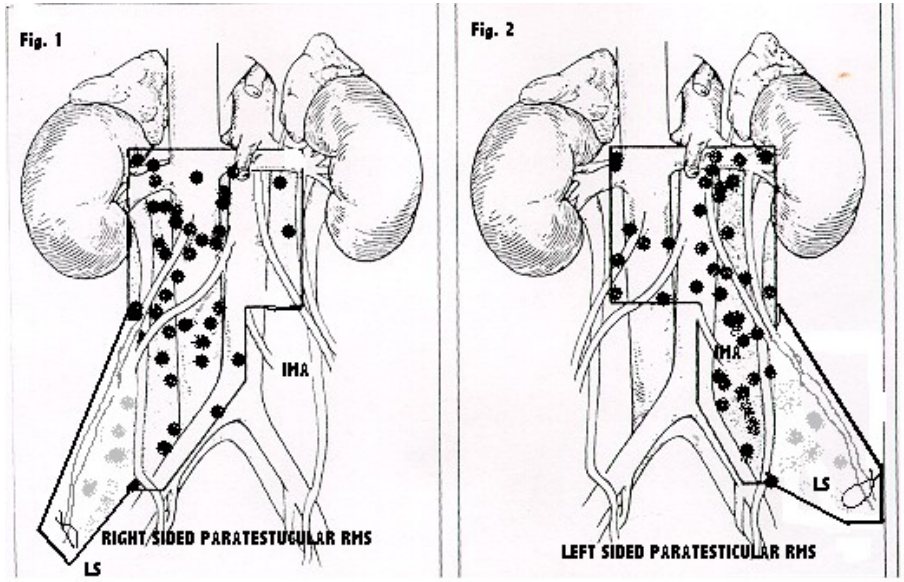


LN staging

- Ipsilateral Retroperitoneal LN dissection (RPLND)

  Indications

  - ≥ 10 yo with paratesticular tumor and abd/pelvis imaging negative
  - < 10y w LN positive in CT
  - ➢ Result will distinguish the treatment (esp. RT)

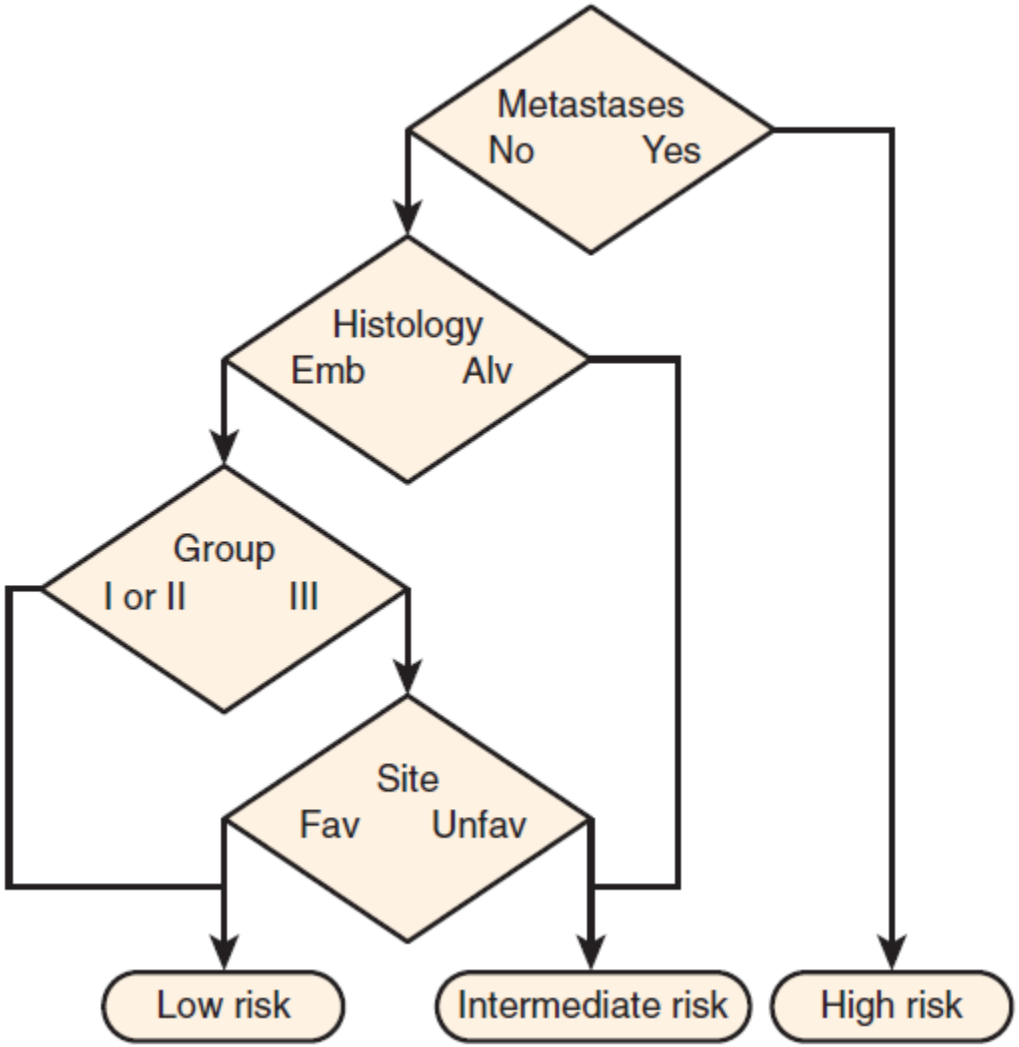


Dang et al., Cancer 2013; 119: 3228-33
COG AOST 0531

IRSG clinical group

Group	Incidence (%)	Extent of disease
I	13	Localized disease, *completely* resected, no residual tumor, no LN
II	20	Total gross resection with A. microscopic residual disease B. LN positive, without microscopic residual disease C. LN positive, with evidence of microscopic residual disease
III	49	• Biopsy only • *Incomplete* resection with gross residual disease
IV	18	Distant metastatic disease

Risk group assignment algorithm



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Nathan and Oski's Hematology and Oncology of Infancy and Childhood 8th ed, 2015
ARST0331, ARST0431, ARST0531

COG Risk Group

Risk group	Incidence (%)	Histology	Pre-Treatment Staging	Post Treatment Clinical Group	5 years FFS
Low-subset A	35	Embryonal	1	I, II, III (orbit)	90%
			2	I, II	
Low-subset B		Embryonal	1	III (non-orbit)	87%
			3	I, II	
Intermediate	50	Alveolar	1-3	I, II, III	65-73%
		Embryonal	2,3	III	
High	15	Any	4	IV	<30%

LR *Embryonal* *Fav*
Unfav – complete resect
IR *Alv*
Embryonal *Unfav- not complete resect*
HR *Metas*

RMS – COG Studies

LOW-RISK

Localized ERMS:

Subset 1:
Stage 1, 2 Group I, II Stage 1, Group III (orbit)

Subset 2:

Stage 1, group III Stage 3, Group I, II

D9802

ARST0331
A. VAC x 4 → VA (24 wk)
B. VAC x 4 → VA (48 wk)

INTERMEDIATE-RISK

Localized ARMS/UDS:
Stages 1-3,

Localized ERMS:
Stages 2-3,
Group III

D9803

ARST0531
VAC vs. VAC/VIRN

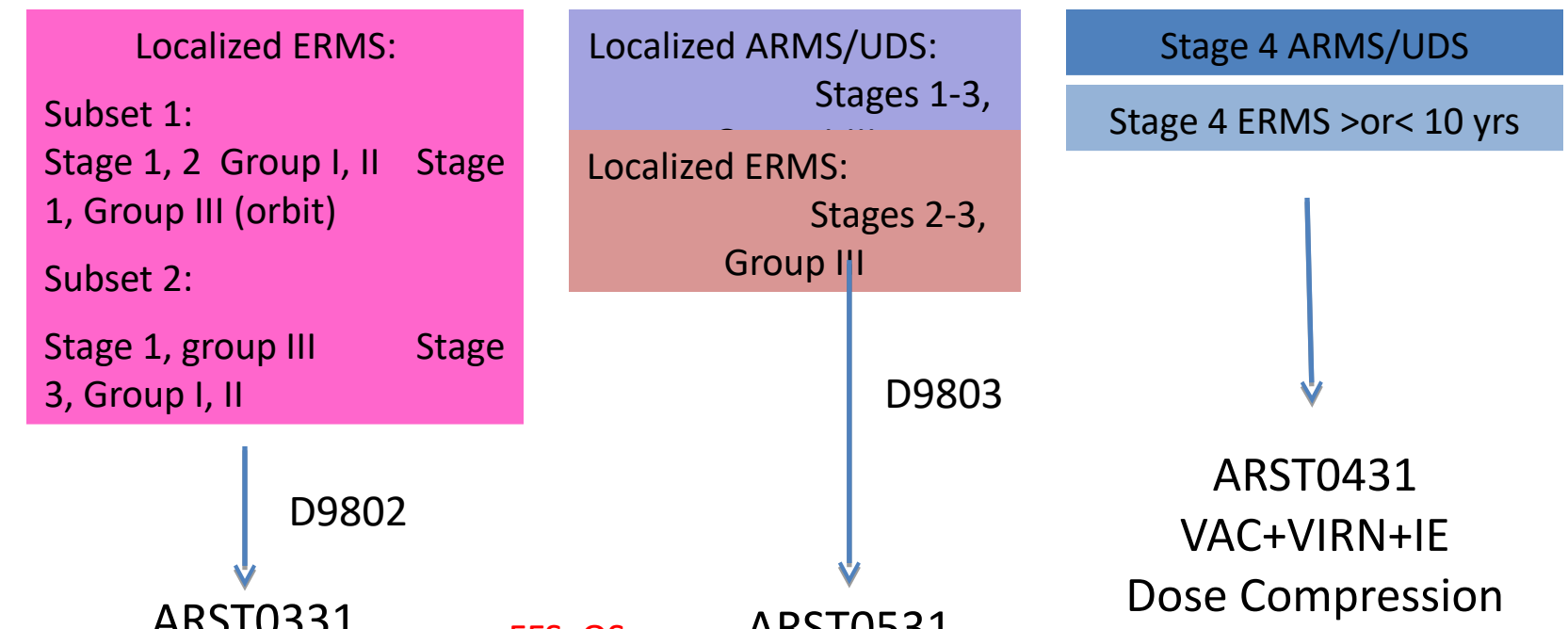
HIGH-RISK

Stage 4 ARMS/UDS

Stage 4 ERMS >or< 10 yrs

ARST0431
VAC+VIRN+IE
Dose Compression

RMS – COG Studies



Low Risk RMS ARST0331

- Lessons learned:
  - Results for subset 1 (A) were at least as good as predicted with low dose cyclophosphamide +/- reduced dose XRT
  - FFS for subset 2 (B) is lower than expected with lower dose cyclophosphamide
    - Particularly for Female GU patients who did not receive XRT

↓

Low risk-Subset 2 (B)- recommend VAC

RMS – COG Studies

LOW-RISK

Localized ERMS:

Subset 1:
Stage 1, 2 Group I, II Stage 1, Group III (orbit)

Subset 2:

Stage 1, group III Stage 3, Group I, II

D9802

ARST0331
A. VAC x 4 → VA (24 wk)
B. VAC x 4 → VA (48 wk)

INTERMEDIATE-RISK

Localized ARMS/UDS:
Stages 1-3,

Localized ERMS:
Stages 2-3,
Group III

D9803

ARST0531
VAC vs. VAC/VIRN

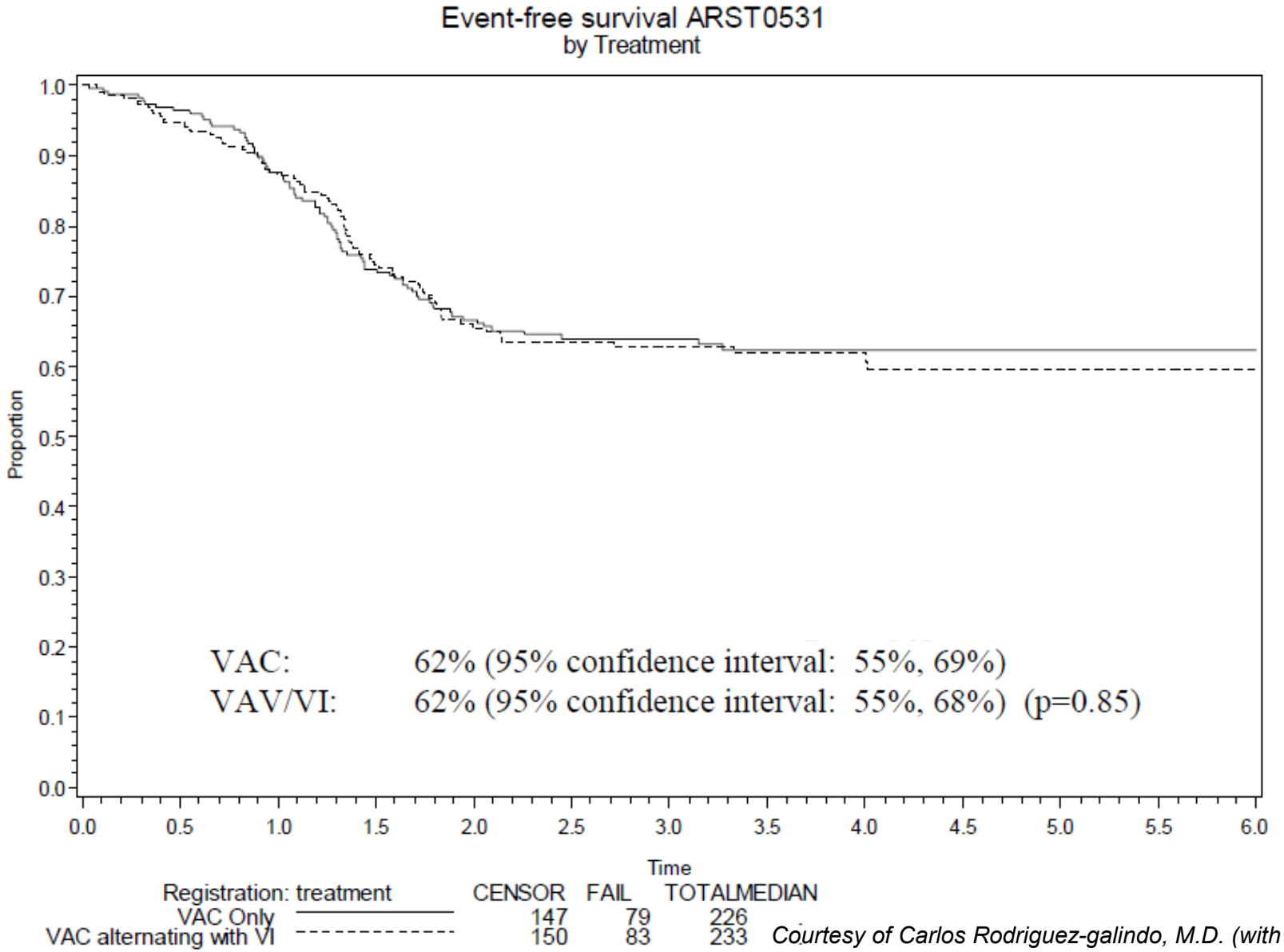
HIGH-RISK

Stage 4 ARMS/UDS

Stage 4 ERMS >or< 10 yrs

ARST0431
VAC+VIRN+IE
Dose Compression

IR RMS ARST0531: Overall Survival



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

IR RMS ARST0531:

- Lessons learned:
  - Patients treated with VI had no improvement in EFS compared to VAC
  - Nevertheless, VAC/VI treatment resulted in less hospitalization, less use of growth factor, and somewhat similar adverse event experience
  - No evidence to suggest that lower RT dose negatively impacted outcomes

VAC/VI = NEW STANDARD FOR IR RMS IN COG

RMS – COG Studies

LOW-RISK

Localized ERMS:

Subset 1:
Stage 1, 2 Group I, II Stage 1, Group III (orbit)

Subset 2:

Stage 1, group III Stage 3, Group I, II

D9802

ARST0331
A. VAC x 4 → VA (24 wk)
B. VAC x 4 → VA (48 wk)

INTERMEDIATE-RISK

Localized ARMS/UDS:
Stages 1-3,

Localized ERMS:
Stages 2-3, Group III

D9803

ARST0531
VAC vs. VAC/VIRN

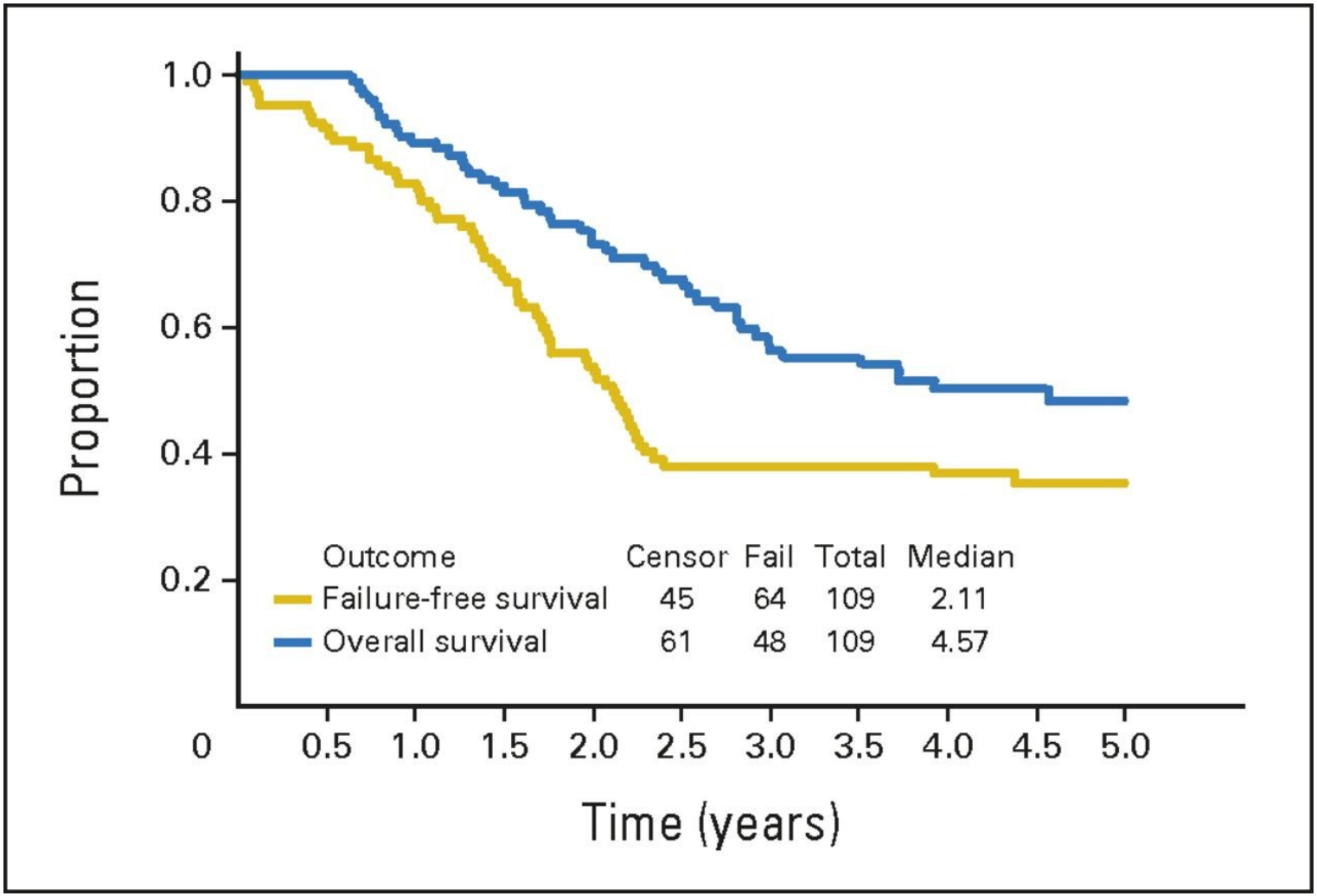
HIGH-RISK

Stage 4 ARMS/UDS

Stage 4 ERMS >or< 10 yrs

ARST0431
VAC+VIRN+IE
Dose Compression

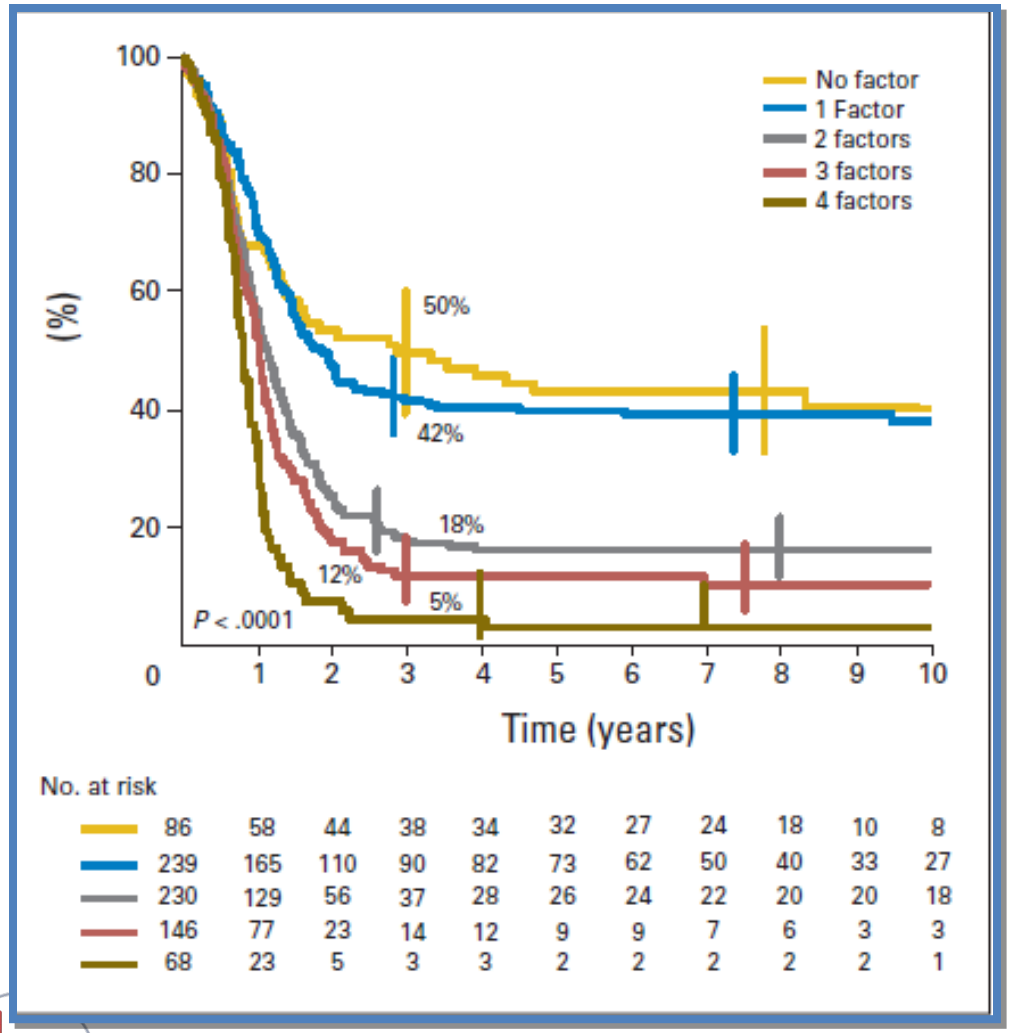
Outcome for all patients in ARST0431



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Brenda J. Weigel et al. JCO 2016;34:117-122

EFS of metastatic RMS

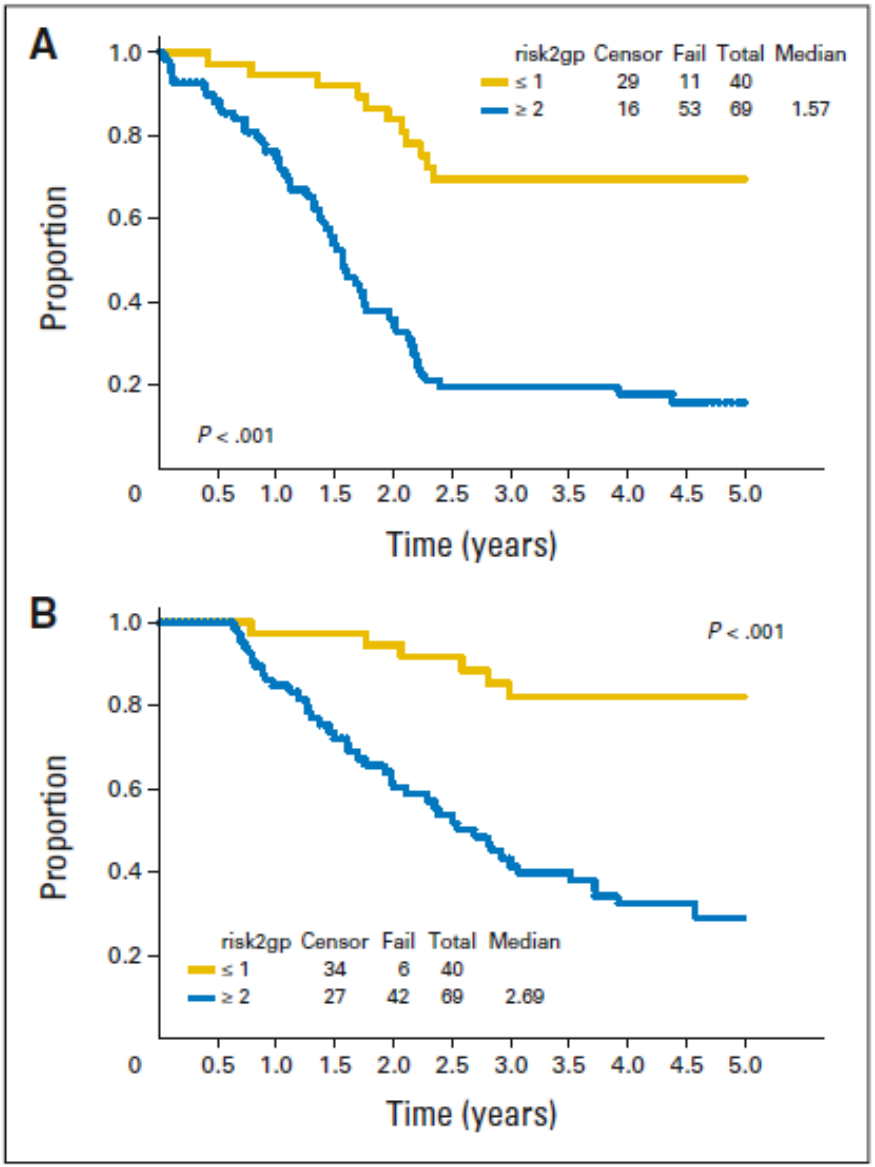


Oberlin RF

- Age ≤ 10 or ≥1 yo
- Unfavorable sites
- Bone or BM involvement
- ≥3 metastatic sites

Oberlin et al., JCO, 2008

EFS of metastatic RMS



Oberlin RF

- Age ≤ 10 or ≥1 yo
- Unfavorable sites
- Bone or BM involvement
- ≥3 metastatic sites

≥2 RF worse prognosis

Brenda J. Weigel et al. JCO 2016;34:117-122

Risk Tailored Treatment

Risk group	CMT		RT	EFS	OS	5 years FFS from RMS-IV
	COG	TPOG				
Low-subset A	ARST0331 (regimen A) VAC/VAx24wk	LR VAC/VAx24wk	Group I no RT Wk 1-6	89%	98%	90%
Low-subset B	ARST0531 VAC x 42 wk	SR VAC x42wk				87%
Intermediate	ARST0531 VAC/VI x42 wk	SR VAC x42wk	Wk 4	55%	68%	65-73%
High	ARST0431 VDC/IE alt VDC/IE/VI x54 wk	HR IVA/CbEV/ IVE/VAC x52 wk	Wk 20	38%	56%	<30%

Local Control in RMS

- Depends on size, nodal involvement, and site
  - Orbit, vagina, paratesticular → > 80%
  - Trunk, extremitie, > 10 cm → 60-70%
- Chemotherapy may help with local control

Local Control in RMS

Surgery

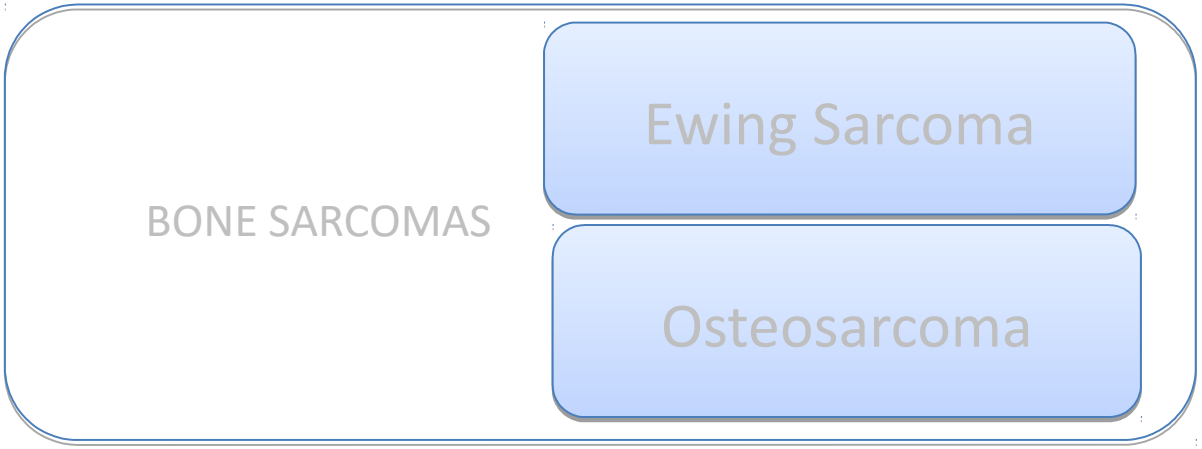
- Complete resection is preferable, but avoiding radical resections that would impact function
- Primary resection → wide excision > pseudocapsule
- Muscular tumors → complete compartmental resection is not necessary (margin > 0.5 cm)

Local Control in RMS

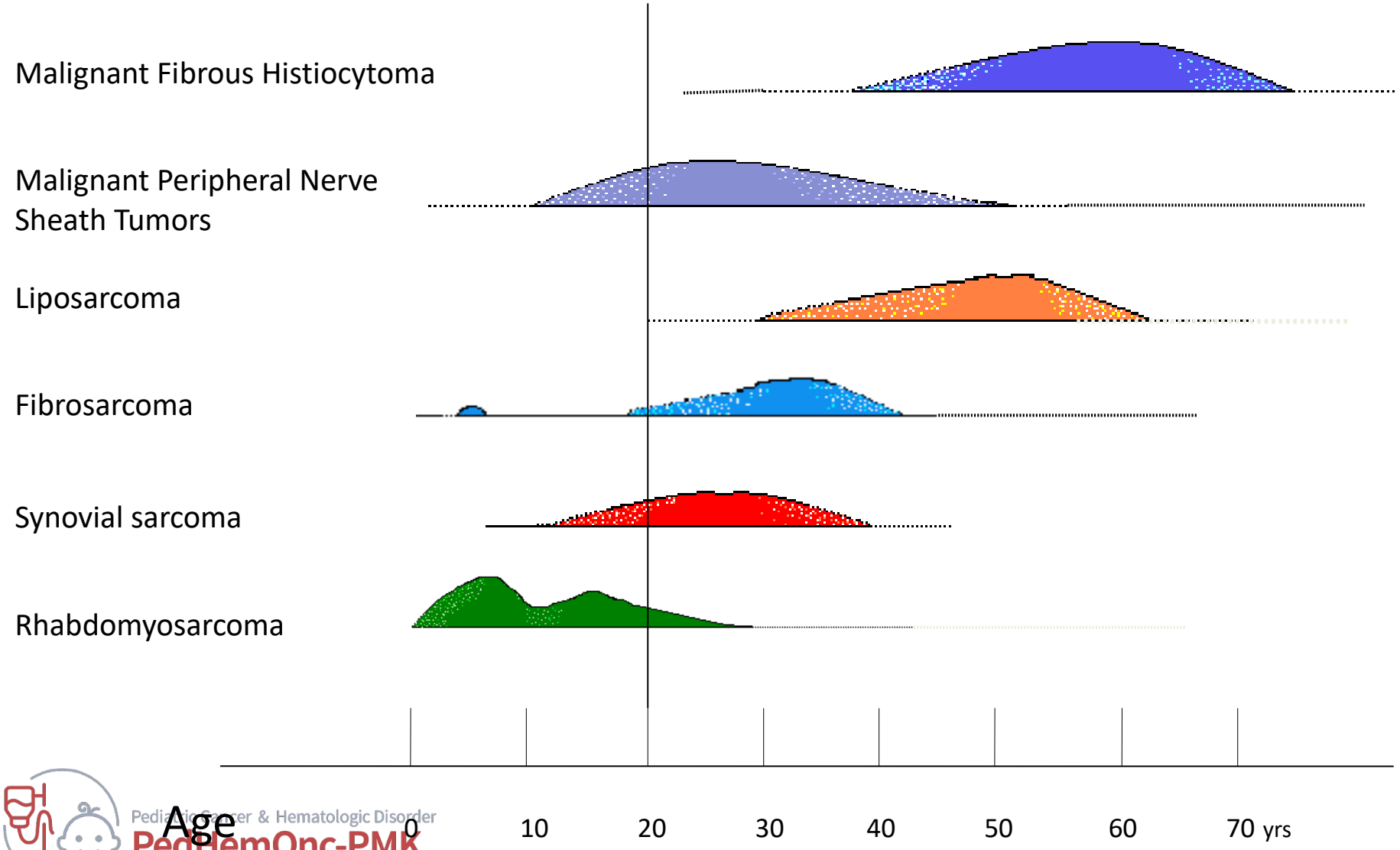
Radiotherapy

- XRT is an effective method to achieve local control for patients with microscopic/gross residual disease
- Dose:
  - 41.4 to 45 Gy for microscopic disease
  - 50.4 to 54 Gy for gross residual disease

Management of Sarcomas

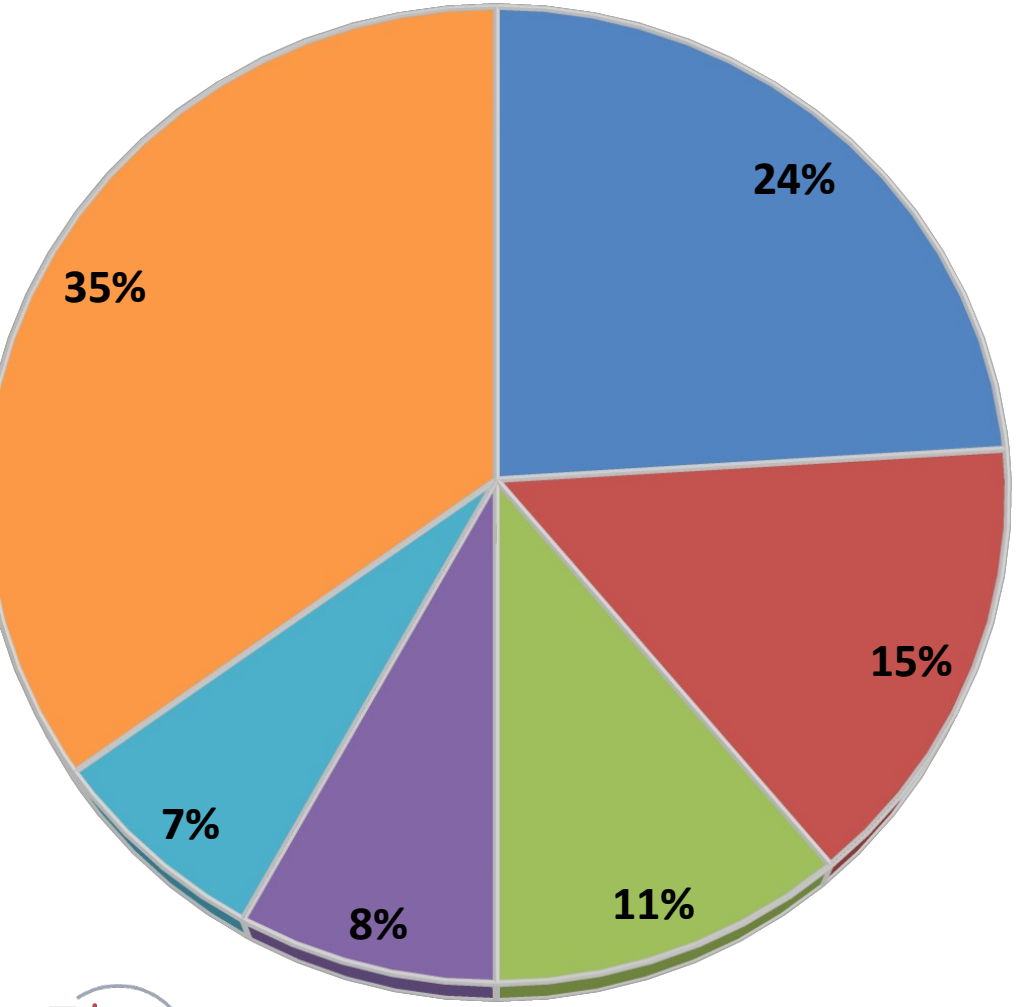


Incidence of Soft Tissue Sarcomas According to Age



A. Ferrari, MD

Pediatric NRSTS Histologic Subtypes



- Synovial Sarcoma
- Malignant Peripheral Nerve Sheath Tumor
- Malignant Fibrous Histio-cytoma
- Fibrosarcoma/Infantile Fibrosarcoma
- Alveolar Soft Part Sarcoma
- Other

Tumor Features

- **Site** (497 w/ pretreatment scans)
  - Extremity 262 (53%)
  - Visceral 106 (21%)
  - Body wall 65 (13%)
  - Head/neck 55 (11%)
  - Unknown 9 (2%)
- **Grade** (551 eligible/evaluable)
  - POG 1 (59; 11%)
  - POG 2 (93; 17%)
  - POG 3 (396; 72%)
  - Indeterminate (3; <1%)
- **Size** (431 eligible/evaluable)
  - ≤ 5 cm (102; 24%)
  - > 5 cm and ≤ 10 cm (166; 38%)
  - >10 cm (163; 38%)

- **Metastases** (14%)
  - Lung (57)
  - Regional nodes (17)
  - Bone (5)
  - Liver (6)
  - Distant nodes (3)
  - Peritoneum (3)
  - Pleura (3)
  - Brain (2)
  - Pancreas (1)
  - Mesentery (1)
  - Leptomeninges (1)
  - Omentum (1)

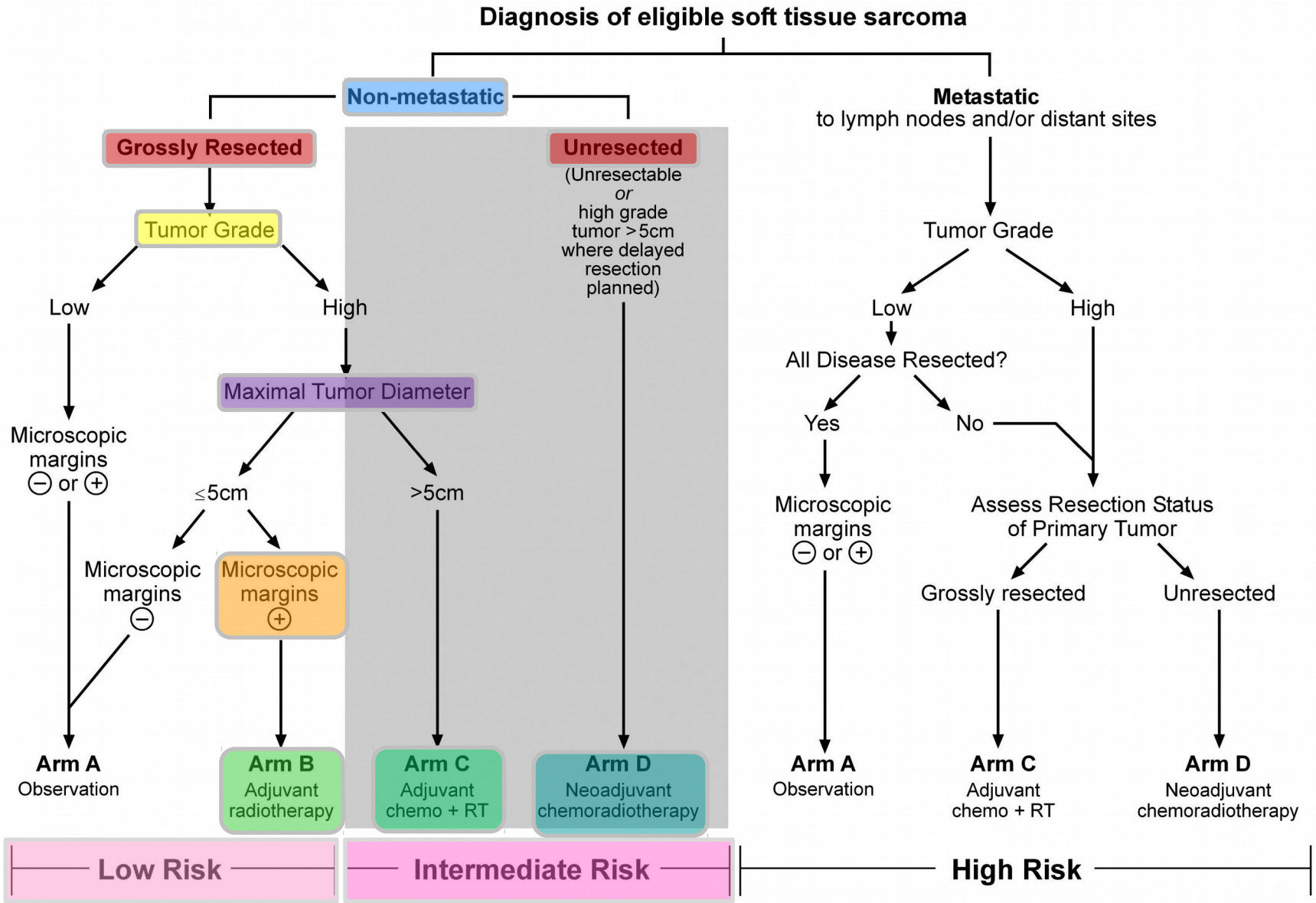
ARST 0332
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Prognostic Factors in Resected STS

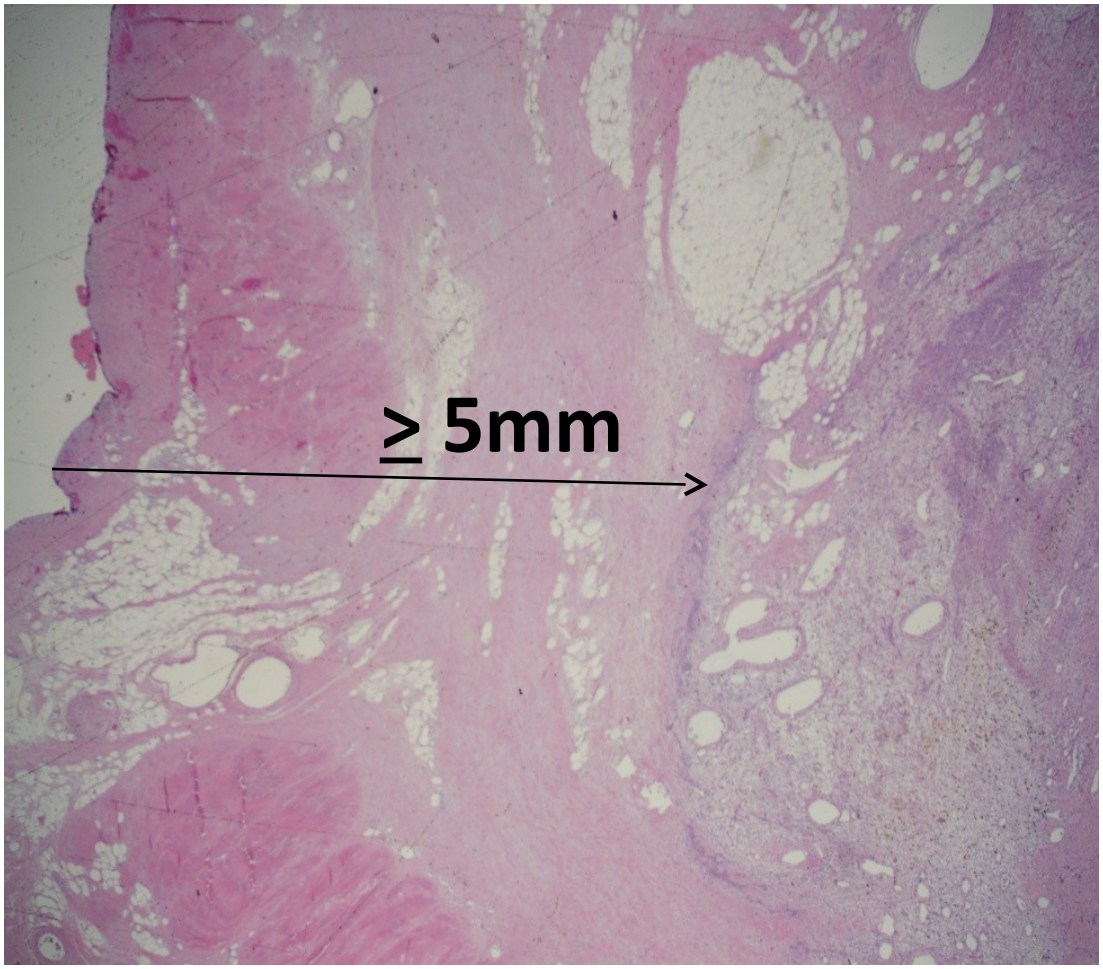
Local Recurrence	Microscopic Margin
Distant Recurrence	Grade, Size
EFS	Grade, Size,
OS	Microscopic Margin

Spunt et al. J Clin Oncol 1999; 17:3697
Ferrari et al. J Clin Oncol 2005; 23:4021-30

ARST 0332 (2007-2012)

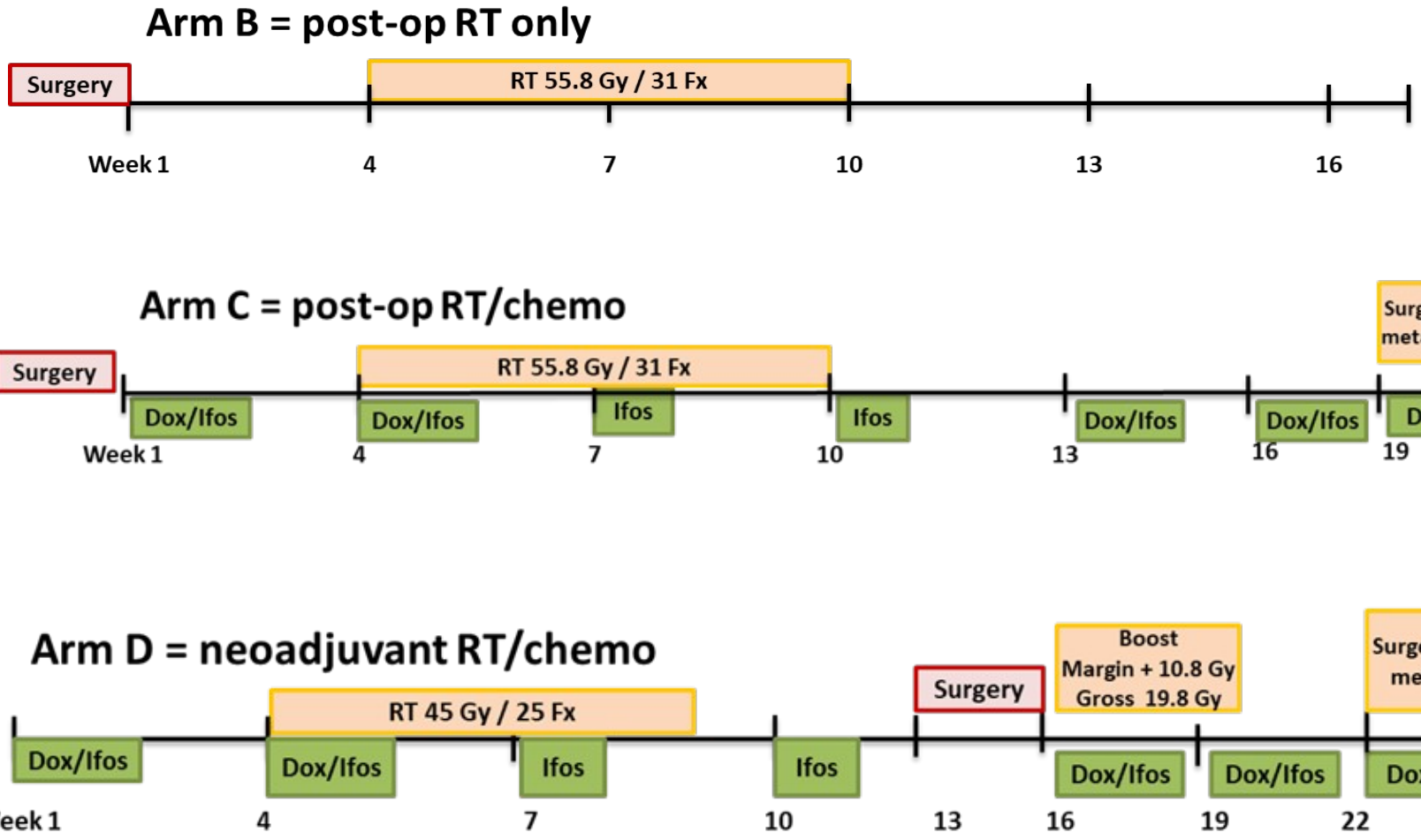


Definition of Negative Surgical Margin



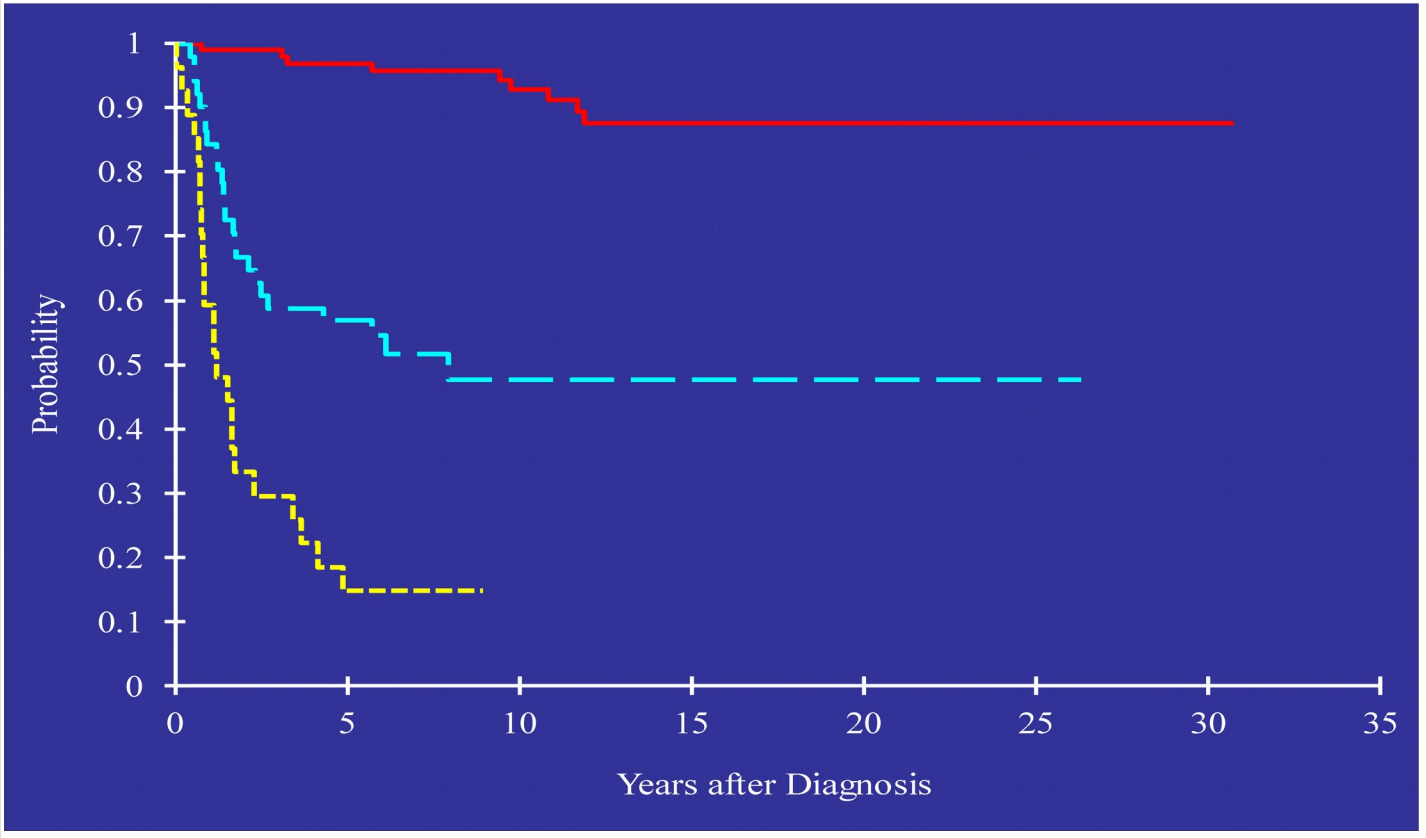
*or if tumor excised in continuity with periosteum/ fascia

ARST 0332 Treatment regimens



IFO 3 g/m^2 x 3
DOX 75 mg/m^2 CI 48 h

Survival by Risk Group



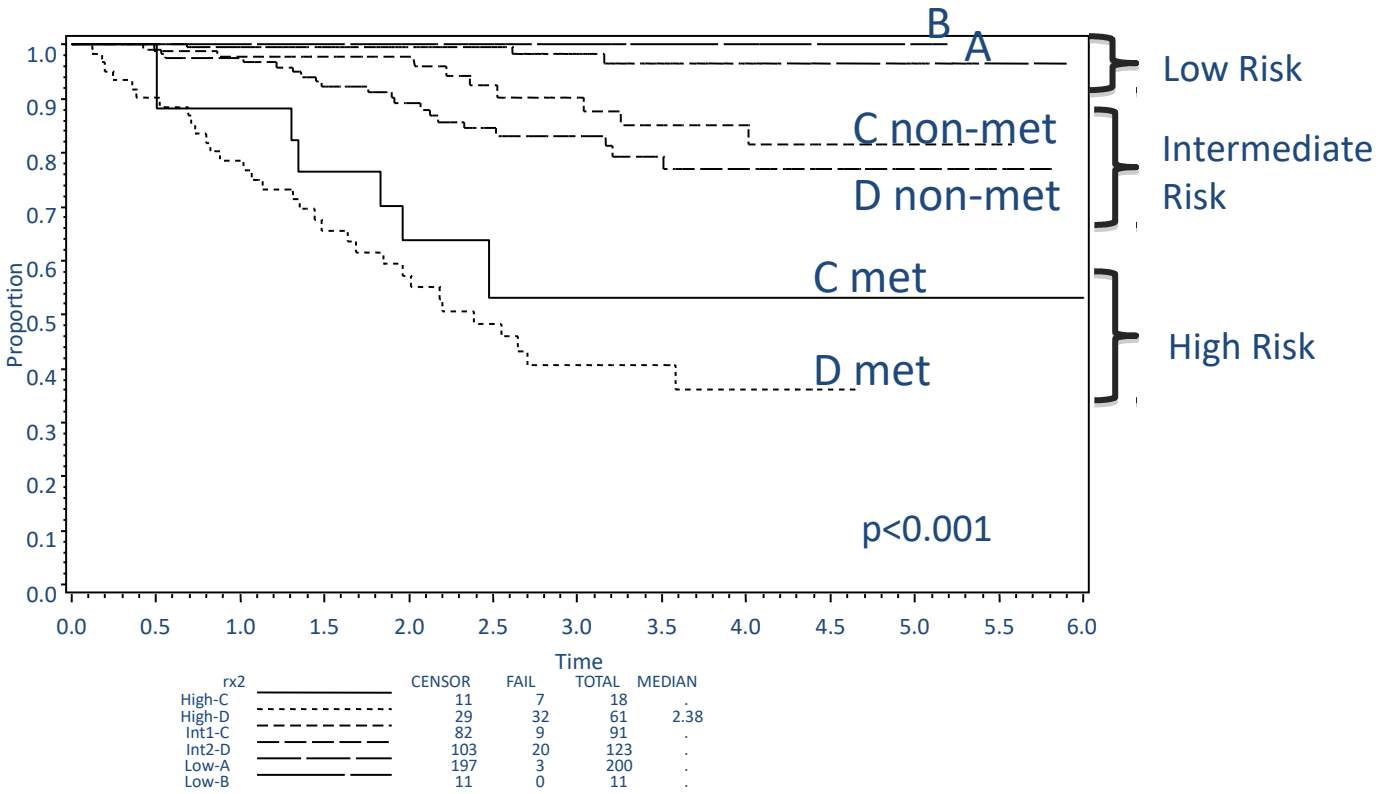
J Clin Oncol 20:3225-35, 2002

Event-Free and Overall Survival

Treatment Arm	# of Patients	4-year EFS (95% CI)	4-year OS (95% CI)
A (observation)	200	91% (85%, 94%)	97% (89%, 99%)
B (adjuvant RT)	11	73% (37%, 90%)	100%
C (adjuvant chemoRT)	109	64% (52%, 74%)	80% (68%, 88%)
D (neoadjuvant chemoRT)	184	49% (40%, 55%)	63% (54%, 71%)

ARST 0332
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Overall Survival

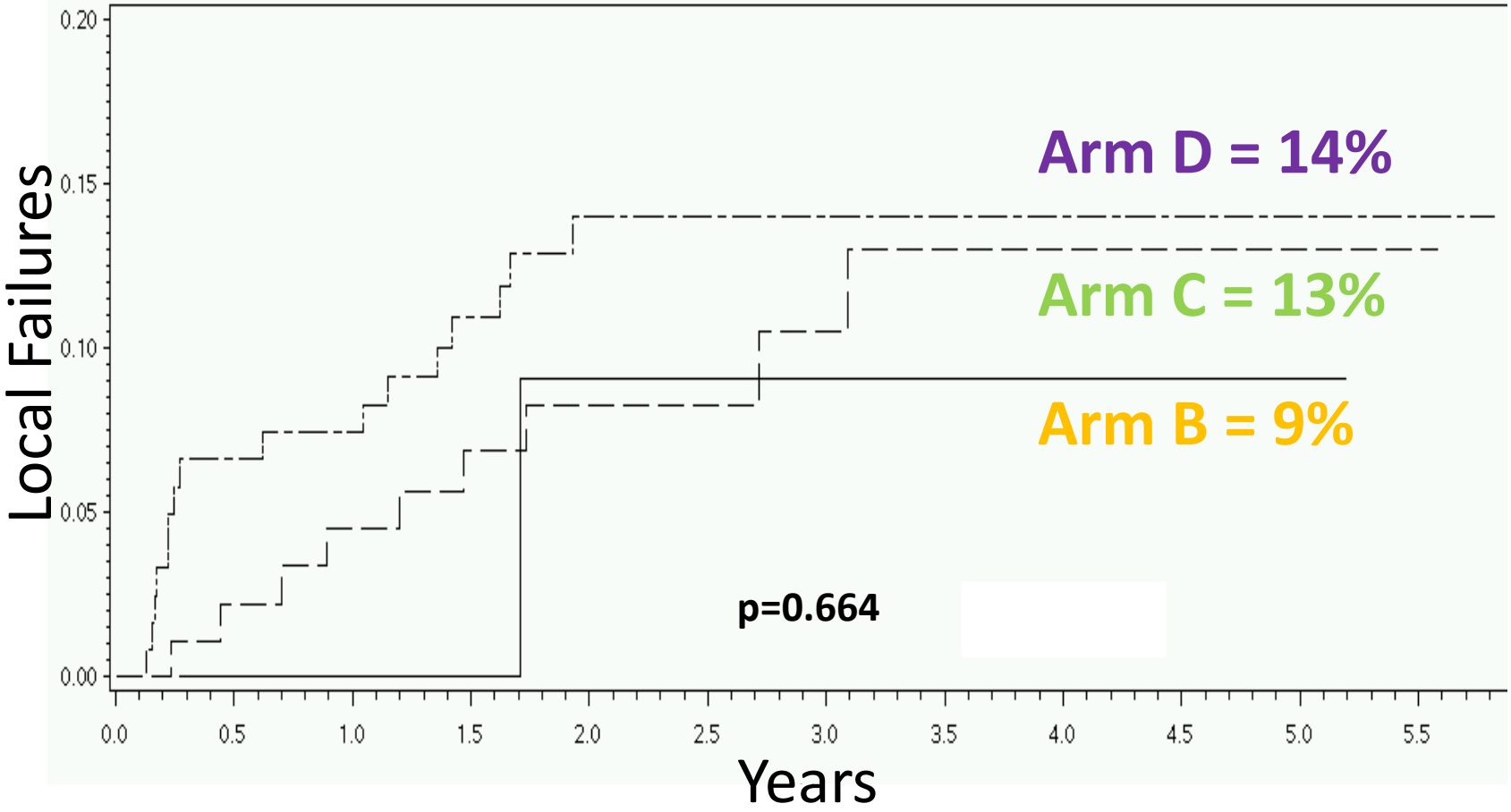


rx2	CENSOR	FAIL	TOTAL	MEDIAN
High-C	11	7	18	.
High-D	29	32	61	2.38
Int1-C	82	9	91	.
Int2-D	103	20	123	.
Low-A	197	3	200	.
Low-B	11	0	11	.

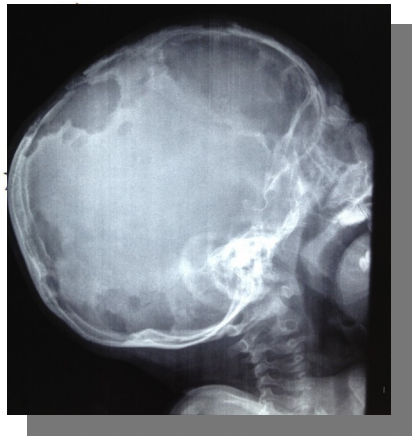
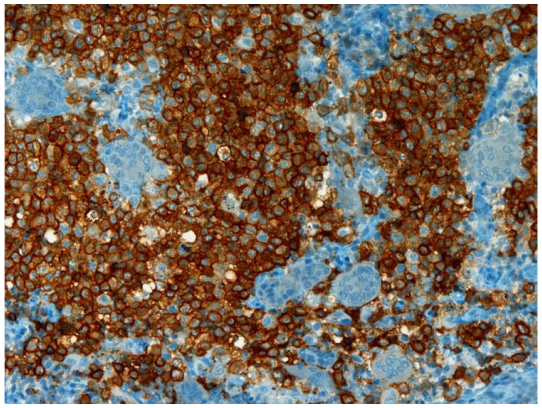
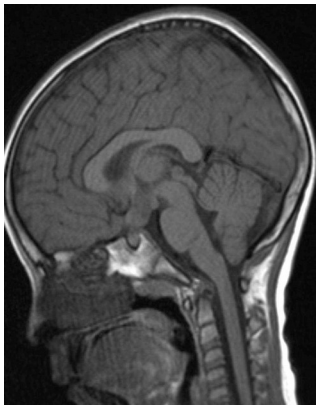
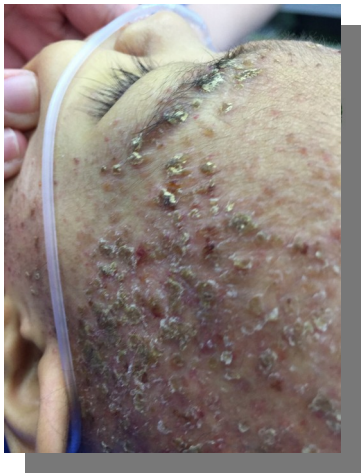
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

ARST 0332
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Results: 4 yr Cumulative Incidence of Local Failure



ARST 0332
Courtesy of Carlos Rodriguez-galindo, M.D. (with permission)

Langerhans Cell Histiocytosis

Classification of histiocytosis syndrome in children

Class	Syndrome

I
Dendritic/histiocytic disorder
	• Langerhans cell histiocytosis (LCH)
	• Non-LCH
	  ○ Erdheim-Chester Disease – primary in adult
	  ○ Juvenile xanthogranuloma (JXG) – occur in children and adult

II
Macrophage/monocytoid disorder
	• Rosai-Dorfman Disease
	• Hemophagocytic lymphohistiocytosis (HLH)
	  ○ Primary HLH – genetic disorder
	  ○ Secondary HLH- infectious associated hemophagocytic syndrome (IAHS)

III Malignant disorder	• Malignant histiocytosis (histiocytic sarcoma) • Monocytic/myelomonocytic leukemias

Adapted from http://www.cancer.gov/cancertopics/pdq/treatment/lchistio/HealthProfessional

Langerhans Cell Histiocytosis

- Clonal proliferation of “Langerhans Cells”
- Multiple organs and systems can be involved
- Clinical presentation and outcome very variable

Eosinophilic Granuloma

Skin Disease

Poliostotic Bone Disease

Hand-Schuler-Christian

Multi-systemic Disease

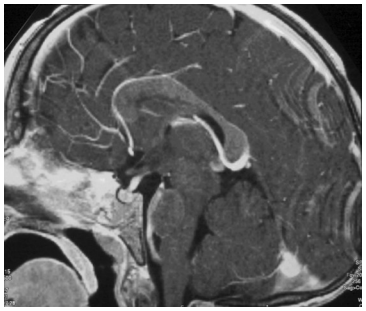
Letterer-Siwe

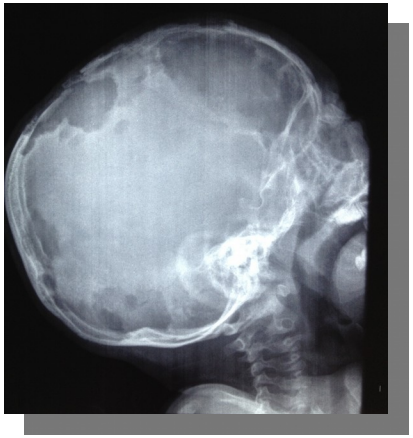
Biology

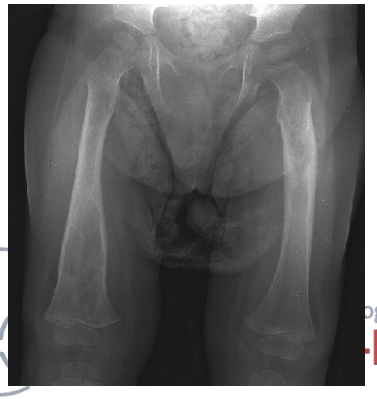
- Inflammatory response *vs.* Oncogenic event ???
- Originate from a myeloid-derived precursor
- Uncontrolled clonal periforation of CD1a+/CD207+ cells
- Activation of the MAPK/ERK signaling pathway
  - 60-70% somatic mutation in BRAF (BRAFV600E)
  - 10-25% Others
    - Mutation in MAP2K1
    - Mutation in ARAF
  - ¼ Unknown

Badalian-Very et al., Annu Rev Pathol 2013; 8: 1-20
Badalian-Very et al., Blood 2010; 116: 1919-23
Chakraborty et al., Blood 2014; 124: 3007-15

Organ system involvement in LCH







Brain	Neuroendocrine deficits Neurodegeneration
Skull and craniofacial bones	
Chest	Lung disease (infants, smokers) Thymus
Abdomen	Liver Spleen GI tract
Skeleton	Bones
Skin	Cradle cap, seborrhea
Hematopoietic system	pancytopenia, hypersplenism
Lymph nodes	

ogic Disorder
-PMK

Organ system involvement in LCH

Site
Bone

Criteria diagnosis

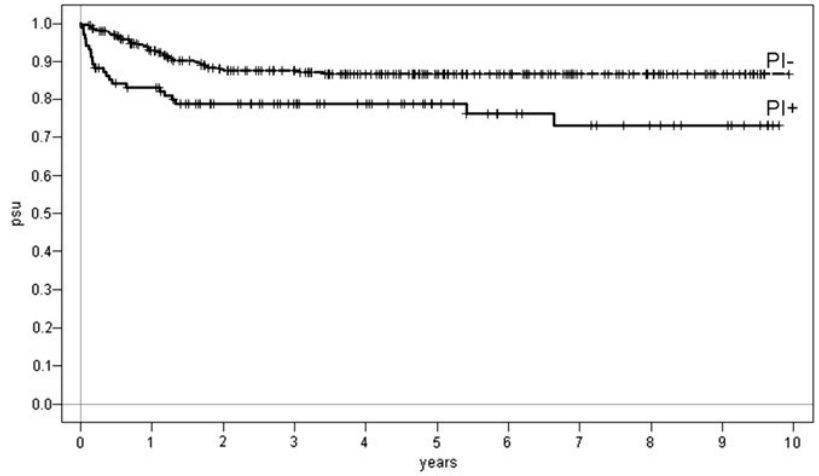
- Presumptive diagnosis:
  LM characteristics compatible
- Designated diagnosis
  - LM plus
  - ≥2 supplemental positive stains for
    - Adenosine triphosphatase
    - S-100 protein
    - α-D-Mannosidase
    - Peanut lectin

- Definitive diagnosis
  - LM plus
  - Birbeck granules in the lesional cell by EM

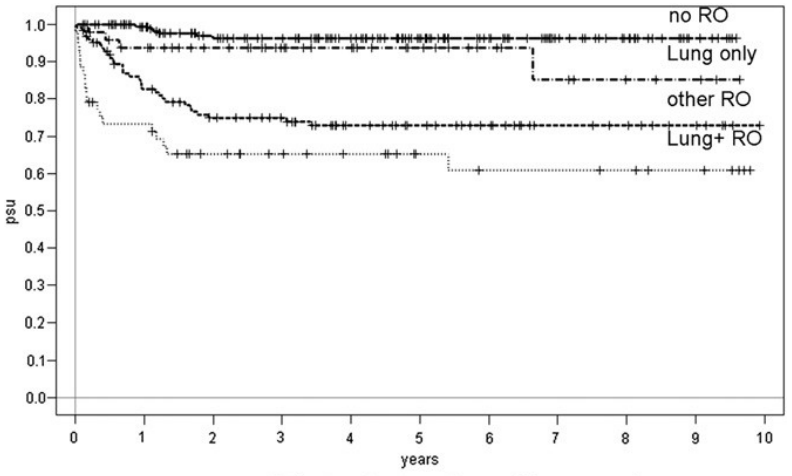
    and/or
  - Positive staining of CD1a antigen and/or CD207 (Langerin) staining on the lesional cell

Pulmonary involvement in MS LCH

- In multivariate analysis, pulmonary involvement was not an independent prognostic factor
- Therefore, it was excluded from the definition of risk organ involvement in MS-LCH.



	Patients	Events	5-yrs. pSU	*P*-value
PI-	318	38	0.87±0.02	.004
PI+	102	23	0.79±0.04	



	Patients	Events	5-yrs. pSU	*P*-value
no RO	192	6	0.96±0.01	
Lung only	49	4	0.94±0.03	.096
RO only	126	32	0.73±0.04	
Lung+RO	53	19	0.65±0.07	.070

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Ronceray et al., J Pediatr 2012; 161: 129-33 e1-3

Clinical Classification of LCH patients

- LCH-IV

Clinical Classification	Involved System	Involved Organs
Multisystem LCH (MS-LCH) (Group 1)	≥ 2	RO+/- (e.g. hemato, liver, and/or spleen)
Single System LCH (SS-LCH) (Group 2)	1 (UF/MF)	• Bone UF (single bone) or MF (>1 bone) • Skin • LN (excluding draining LN of another LCH lesion) • Lungs • Special site (eg. Vertebrae, spine) • "CNS-risk" • Central nervous system (CNS) • Other (e.g. thyroid, thymus)

Prognosis

- Rapid response to initial treatment within 6 weeks
- Involvement of “Risk organs”; hematopoietic system, liver, spleen and lungs
- Age at diagnosis: diagnosed before 2 years of age, mortality rate 66% (but not include in “Risk”)
- Number of organ involvement : mortality rate is increasing follow by numbers of organ involvement
- Bone involvement associated with favorable prognosis
- Organ dysfunction presented at diagnosis or during the course of disease
- Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%) and permanent consequences

Gadner et al., J Pediatr 2001; 138: 728-34
Gadner et al., Blood 2008; 111: 2556-62
Gadner et al., Klin Padiatr 1987; 199: 173-82
Gadner et al., Blood 2013; 121: 5006-14

HISTIOCYTE SOCIETY

Treatment

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Single system (SS)

Multisystem (MS)

Bone
or
Skin
or
LN
or
Lung

Unifocal (UF)

Multifocal (MF)
Or
UF-CNS risk/special site

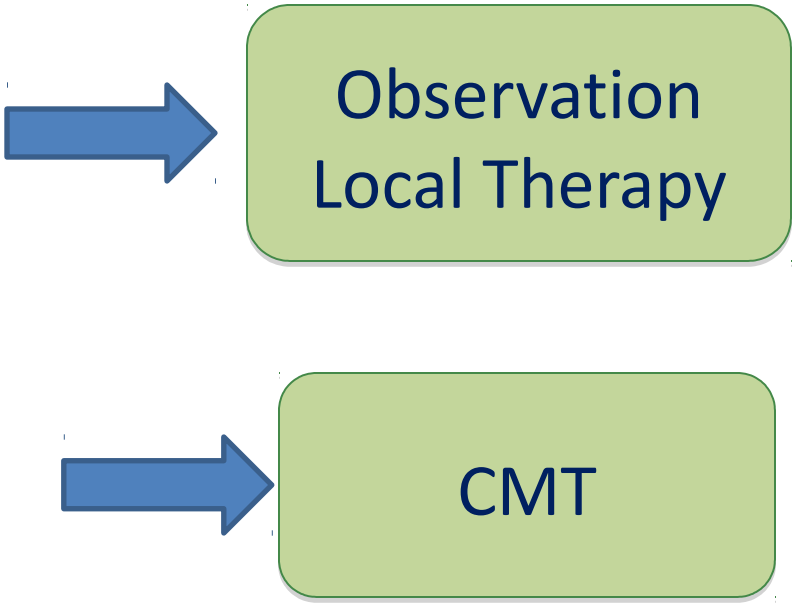
RO-

RO+

Liver
Spleen
Heme

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Bone
or
Skin
or
LN
or
Lung



Liver
Spleen
Heme

CMT

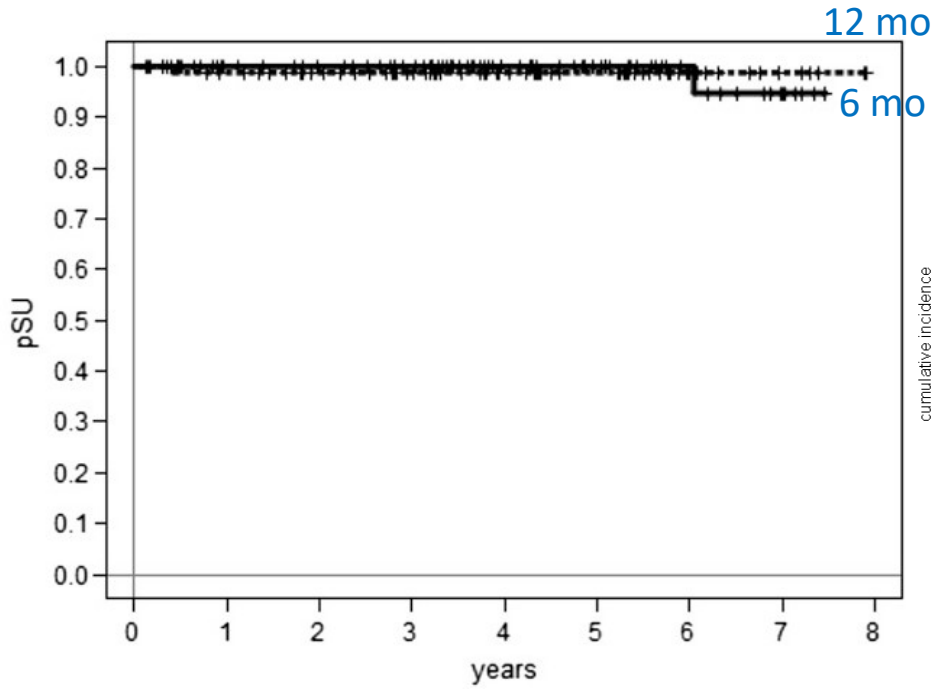
Intensive CMT

Indications for Systemic Therapy

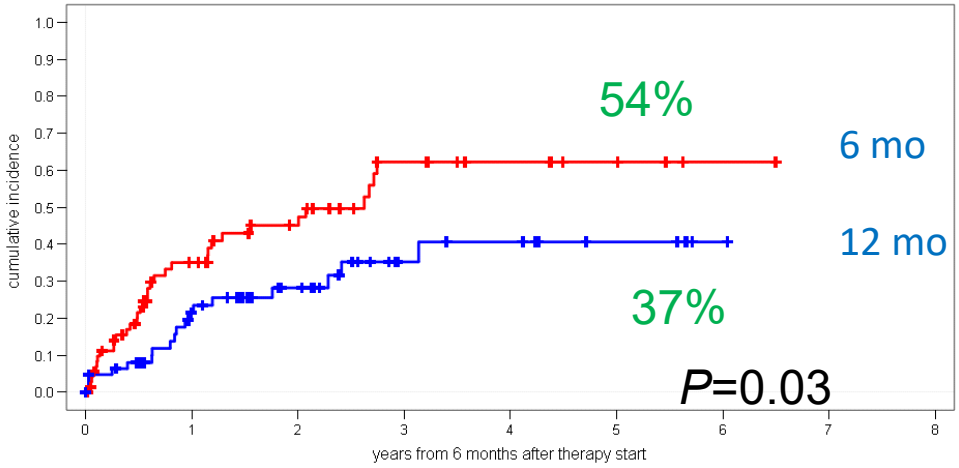
- SS-LCH with
  - CSN-risk lesions
  - Multifocal bone lesions
  - “Special Site” lesions
- MS-LCH with/without involvement of risk organs

Therapy prolongation improves outcome in RO- MS LCH

- Survival



- Reactivations



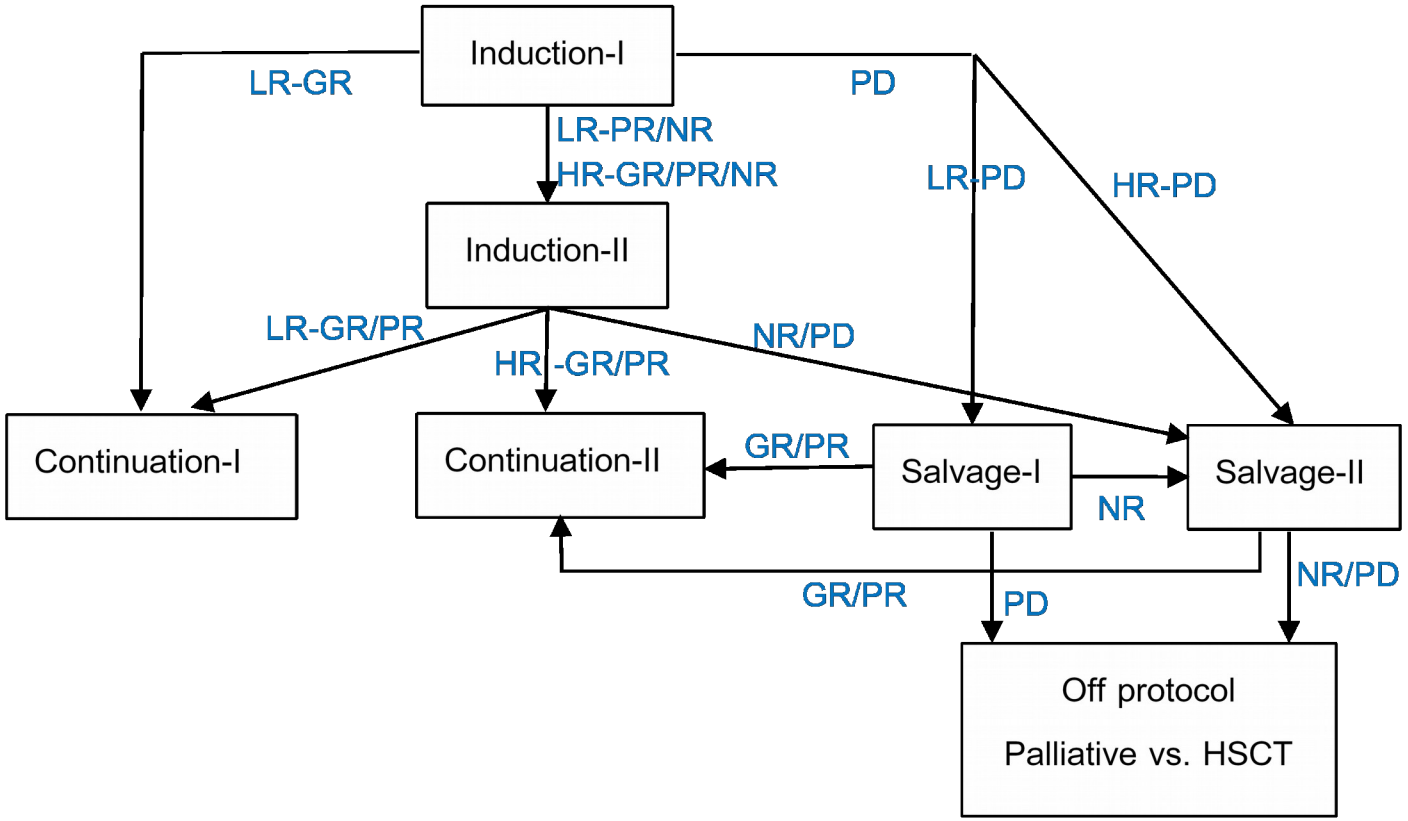
Benefit in decreased disease reactivation in prolongation of therapy

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Gadner et al., Blood 2013; 121: 5006-14

THAI POG
Thai Pediatric Oncology Group

LCH treatment Guideline



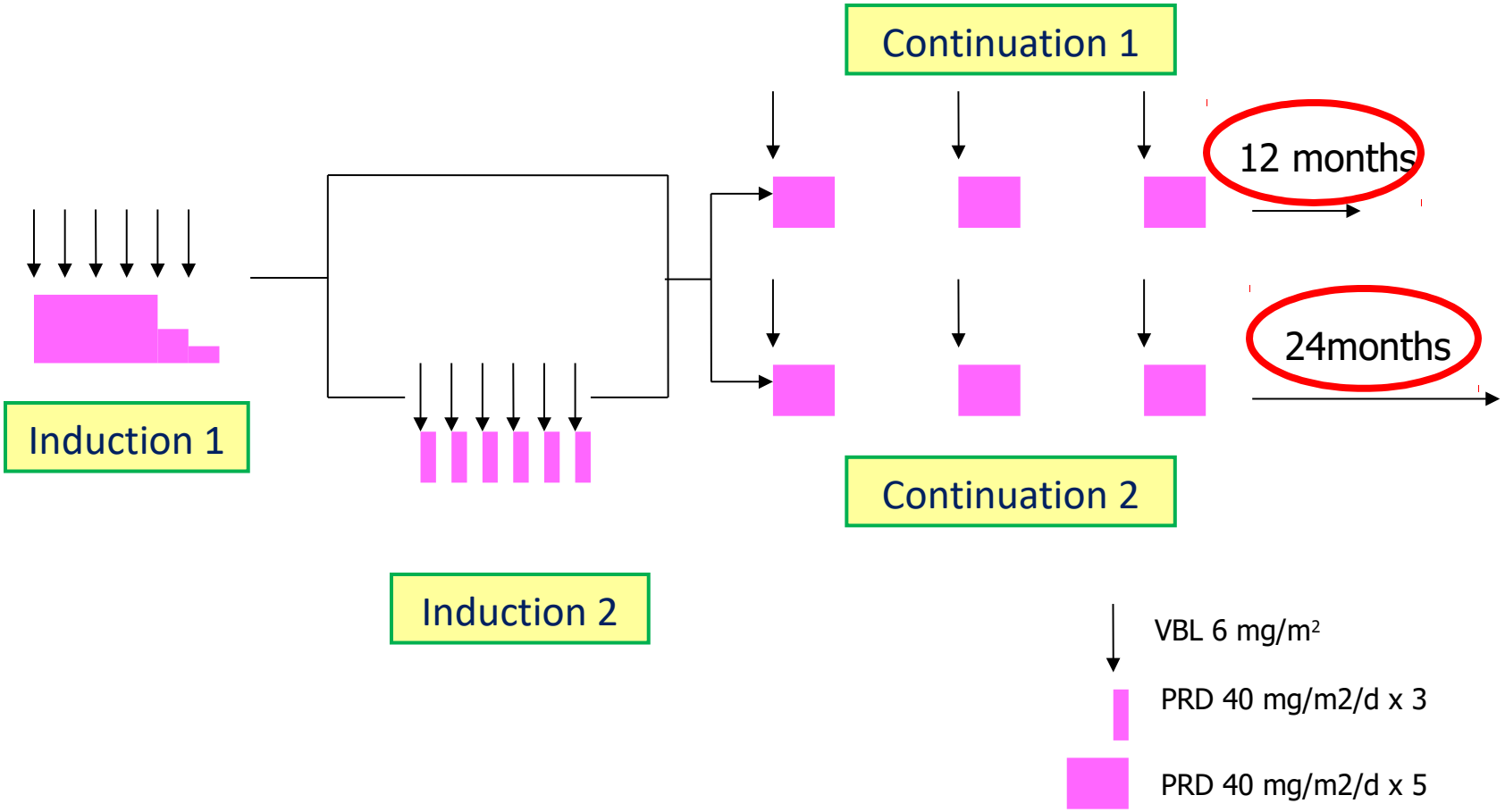
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

GR; good response, PR; partial response, NR; not response, PD; progressive disease

Indication for Treatment

- Low risk LCH (LR)
  - SS-LCH with
    - CSN-risk lesions
    - Multifocal bone lesions
    - “Special Site” lesions
  - MS-LCH without “risk organs”
- High risk LCH (HR)
  - MS-LCH with “risk organs”

LCH treatment Guideline



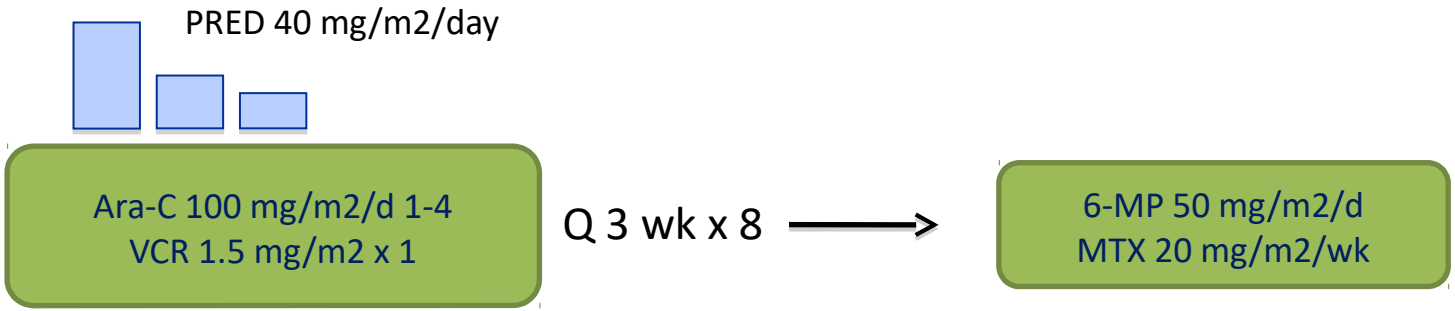
Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Gadner et al., Blood 2013; 121: 5006-14
LCH-IV Study Protocol

LCH treatment Guideline

Salvage I regimen

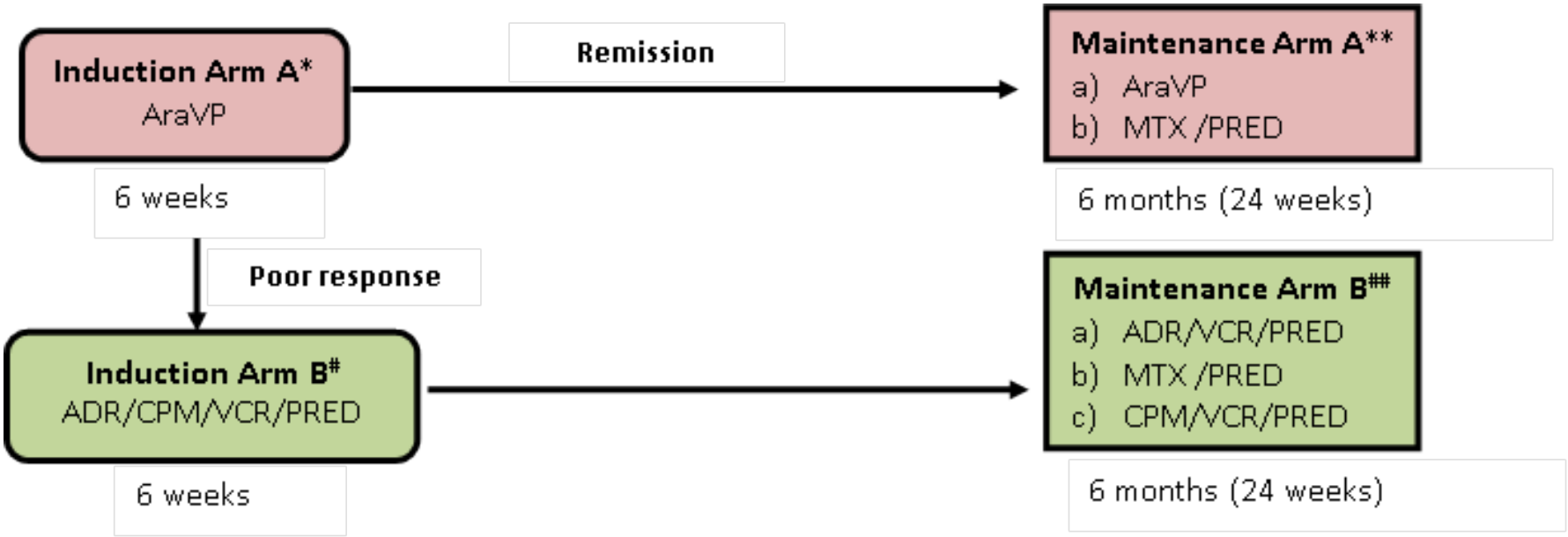
For LR with progressive disease



LCH treatment Guideline

Salvage II regimen

For HR with progressive disease*



Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

*or NR/PD for Induction-II or NR for Salvage-I protocol

JLSG-96 protocol for LCH patients
Morimoto et al., Cancer 2006; 107: 613-9

Conclusions

- LCH is a neoplastic proliferation of Langerin + myeloid dendritic cells → recruitment of activated lymphocytes
- Wide spectrum of clinical presentations that combine features of neoplastic proliferation with inflammation
- Challenges:
  - Patients with MFB have excellent prognosis but high tendency for disease reactivation (30-50%)
  - Treatment of patients with RO+ disease → Intensive upfront therapy
  - Reactivations → prolongation of therapy
  - Relapse in RO+

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