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AMERICAN ONCOLOGY INSTITUTE
PRECISION CANCER CARE

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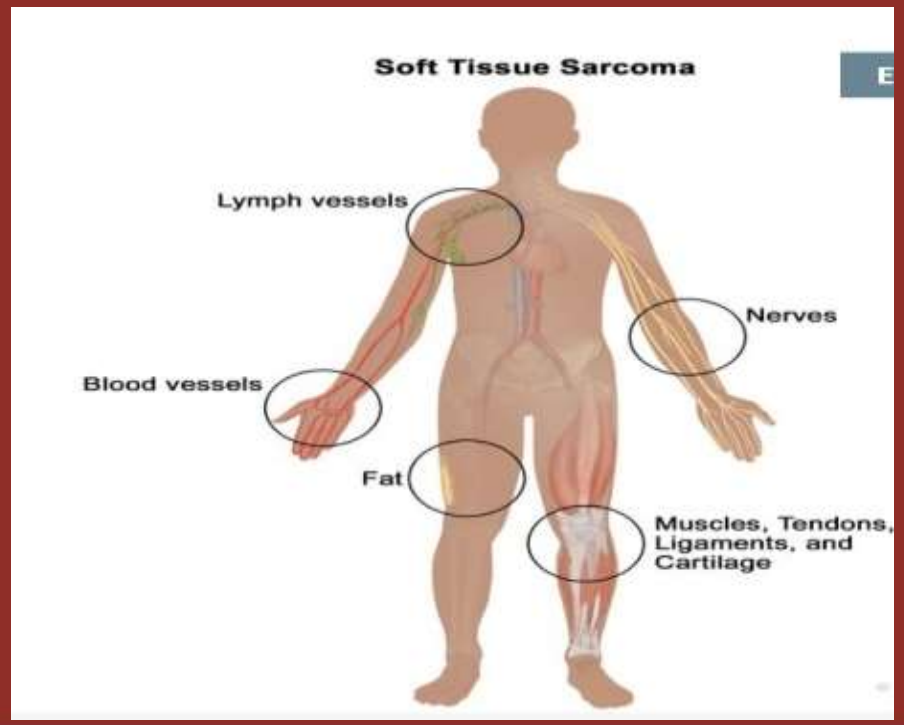
44th ICRO PG TEACHING COURSE

TOPIC: OVERVIEW OF SOFT TISSUE SARCOMAS IN PEDIATRIC POPULATION ? :

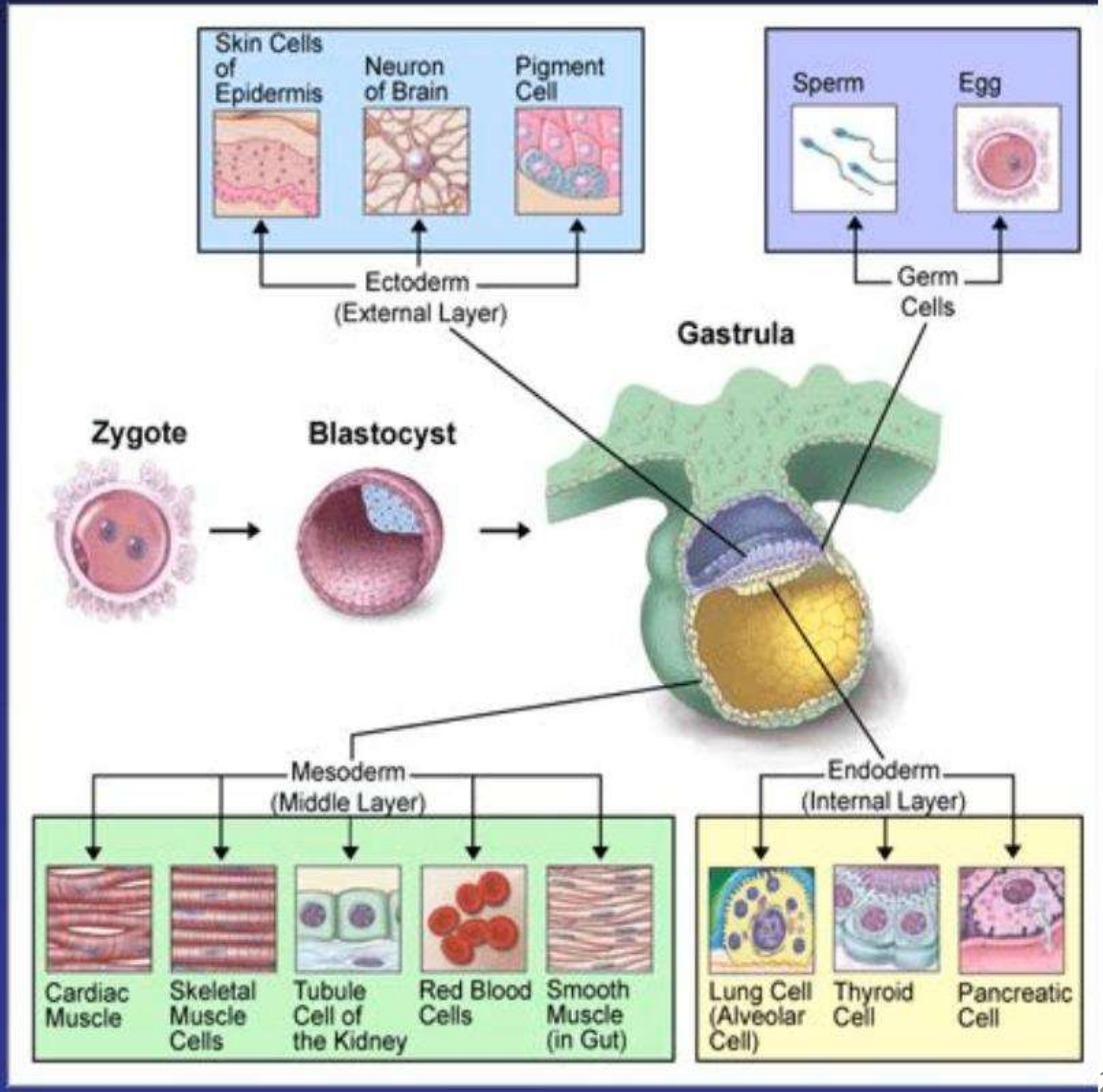


DR DEEPAK ABROL
SENIOR CONSULTANT
RADIATION ONCOLOGY
AMERICAN ONCOLOGYINSTITUTE
ASCOMS JAMMU

Tumors are named after their cell of origin and the embryonal layer that cell arose from

The middle embryonal layer – the mesoderm- gives rise to **mesenchymal tissues**- bone, muscle, cartilage, adipose tissue, blood vessels and more

Mesenchymal tumors are called **sarcomas**



Mesenchymal tumors

- Tumors of bone (Osteosarcoma, Ewing sarcoma)

- Tumors of soft tissues (Soft tissue sarcomas=STS)

  - Tumors of skeletal muscle (Rhabdomyosarcoma)

  - Tumors of smooth muscle (Leiomyosarcoma)
  - Tumors of adipose tissue (Liposarcoma)
  - Tumors of fibroblasts (Fibrosarcoma)
  - Tumors of cartilage (Chondrosarcoma, synovial sarcoma)
  - Tumors of blood vessels (Angiosarcoma)
  - MPNST, clear cell sarcoma, inflammatory myofibroblastic tumor, desmoid (fibromatosis), DSRCT, MFH

Cytogenetic abnormalities in soft tissue sarcomas

Diagnosis	Cytogenetic abnormality	Genes involved
Alveolar RMS	t(2;13) or t(1;13)	FKHR on chromosome 13 and PAX3 (chromosome 2) or PAX7 (chromosome 1)
Infantile fibrosarcoma	t(12;15)	TEL (ETV6) on chromosome 12 and NTRK3 (TRKC) on chromosome 15
Dermatofibrosarcoma Protuberans	t(17;22)	PDGF β-chain on chromosome 17 and collagen type Ia on chromosome 22
Synovial sarcoma	t(X;18)	SYT on chromosome 18 and SSX-1 or SSX-2 on the X chromosome
Liposarcoma	t(12;16)	FUS gene on chromosome 16 and CHOP gene on chromosome 12
Myxoid chondrosarcoma	t(9;22)	EWS on chromosome 22 and TEC gene on chromosome 9
Alveolar soft part sarcoma	t(X;17)	Unidentified genes, esp. at chromosome band 17q25

PEDIATRIC STS

- The most common form of soft-tissue sarcoma in childhood is rhabdomyosarcoma (50% of all STS)
- For convenience – all other soft-tissue sarcomas of childhood are called non-rhabdo soft tissue sarcomas (NRSTS) – and account for the remaining 50% of STS

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Cancer Types by Age Group

Tumor Type	Ages 0-14	Ages 15-19
Leukemia	28%	10%
CNS	22%	10%
Neuroblastoma	8%	0.2%
NHL	6%	8%
Hodgkin's	3.6%	16.8%
Wilm's tumor	6%	0.3%
Rhabdomyosarcoma	3.6%	1.7%
NRSTS	3.5%	5.1%
Osteosarcoma	2.6%	4.2%
Ewing sarcoma	1.5%	2.4%
Germ cell/gonadal	3.5%	12.4%
Retinoblastoma	3.2%	0%
Hepatoblastoma	1.3%	0%

RHABDOMYOSARCOMA

- 3 percent of childhood cancer.
- Most are Sporadic, Li Fraumeni , Neurofibromatosis 1 and Beckwith Wideman associated., Costello.
- Classic Histological Types are
- 1.Embryonal, 70 %
- 2.Alveolar, 20 to 40 %
- 3.Botryoid, 10 %
- 4.Undifferentiated and 5 %
- 5.Spindle cell 5 %

- Embryonal tumors typically arise in the orbit, head and neck, or genitourinary tract (OS 66%).
- Botryoid tumors often arise in the vagina, bladder, nasopharynx, and biliary tract (OS 95%).
- Spindle cell tumors most frequently occur in paratesticular sites (OS 88%).
- Alveolar tumors most commonly arise in the extremity, trunk, or retroperitoneum of adolescents (OS 54%).

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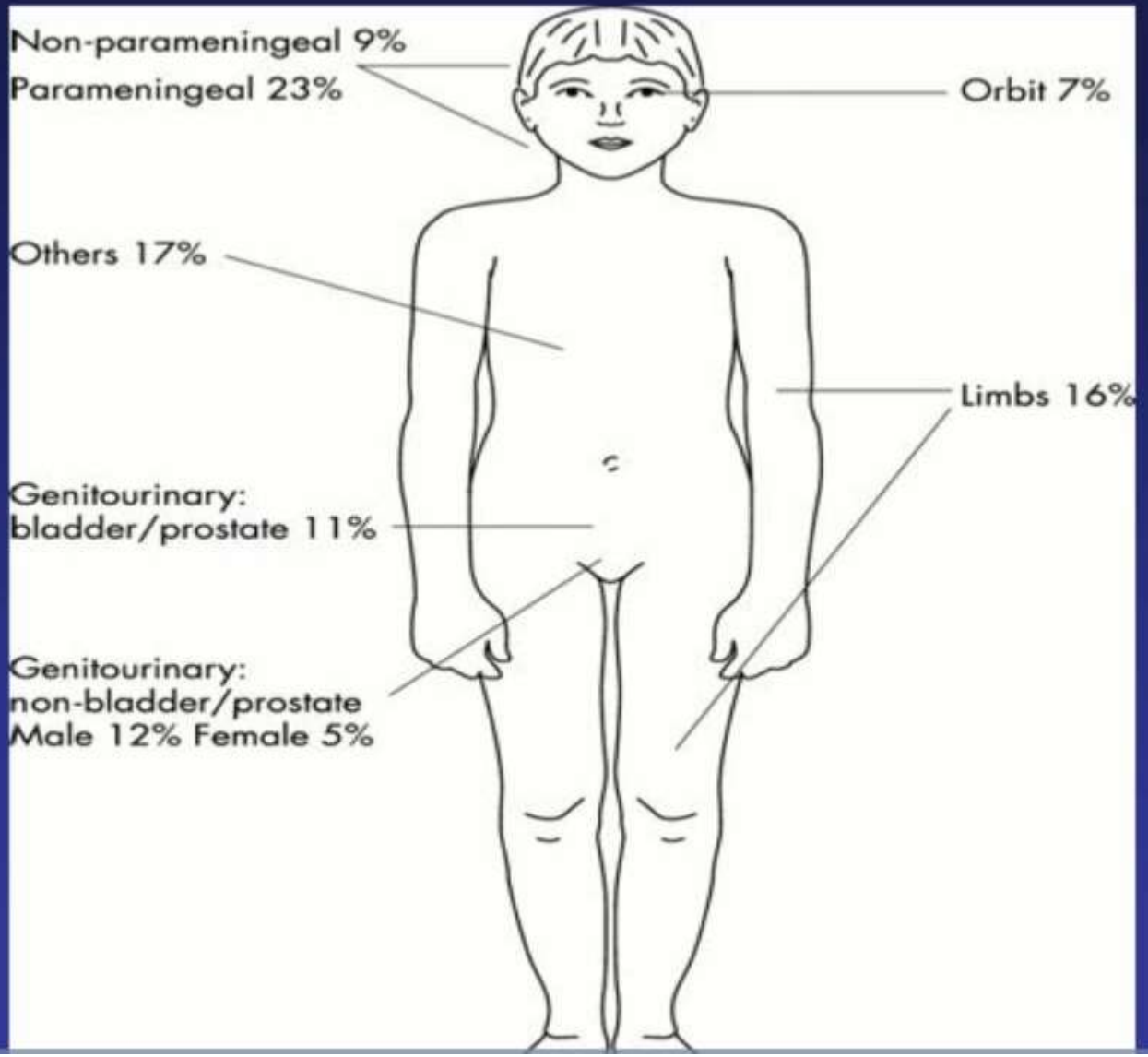
Rhabdomyosarcoma Sites of disease

- **Head & Neck**
  - Orbit
  - Parameningeal
  - Non-Parameningeal
- **Genitourinary**
  - Bladder
  - Prostate
  - Para-testicular
  - Vagina/uterus
- **Extremity**
- **Others**



RMS – Clinical Presentation is Site Dependent

- Orbit - Proptosis, ophthalmoplegia
- Other head and neck/parameningeal – nasal or aural obstruction, cranial nerve palsies
- Genitourinary tract – Bladder: Hematuria, urinary obstruction
  Paratesticular – painless scrotal mass
  Vaginal – Vaginal mass, discharge
- Extremities – Swelling, pain, lymph node involvement

WORKUP

- H&P: EUA may be required for pelvic tumors; cystoscopy should be performed for GU sites.
- Labs include CBC, LFTs, BUN/Cr, and LDH.
- Imaging includes CT/MRI of primary, CT of the chest and abdomen, and bone scan.
- If parameningeal site → lumbar puncture; obtain neuraxis MRI for positive CSF cytology.
- Bone marrow biopsy.

IRS PREOPERATIVE STAGING SYSTEM

Stage 1: Favorable site, any T, N0–1, M0
Stage 2: Unfavorable site, T1a/T2a, N0 M0
Stage 3: Unfavorable site, T1b/T2b, N0 M0, or any T, N1 M0
Stage 4: Any M1

Favorable sites: Orbit, nonparameningeal H&N (scalp, parotid, OPX, oral cavity, larynx), GU nonbladder-prostate (paratestes, vagina, vulva, uterus), and biliary tract

Unfavorable sites: Parameningeal (NPX, nasal cavity, paranasal sinuses, middle ear, mastoid, pterygopalatine fossa, infratemporal fossa), bladder, prostate, extremity, and others (trunk, retroperitoneum, etc.)

T1: Tumor is confined to site/organ of origin (a ≤5 cm, b >5 cm)
T2: Tumor extends beyond site/organ of origin (a ≤5 cm, b >5 cm)
N1: Regional lymph node involvement
M1: Distant metastases at diagnosis

Rhabdomyosarcoma clinical group definitions

Group	Definition
Group I	Localized disease completely resected
Group IIa	Gross total resection with microscopic residual disease
Group IIb	Regionally involved lymph nodes, completely resected with the primary
Group IIc	Regional disease with involved nodes, totally resected with microscopic residual disease or histologic evidence of involvement of the most distant lymph node in the dissection
Group III	Incomplete resection
Group IV	Distant metastases

Risk stratification in rhabdomyosarcoma

Histology	Clinical group	Stage	Risk group
Embryonal	I, II, III	1	Low
Embryonal	I, II	2, 3	Low
Embryonal	III	2, 3	Intermediate
Embryonal	IV	4	High
Alveolar	I, II, III	1, 2, 3	Intermediate
Alveolar	IV	4	High

~3-year OS by risk group
Low >90–95%
Intermediate 55–70%
High 30–50%

~5-year OS by histology
Botryoid 95%
Spindle cell 88%
Embryonal 66%
Alveolar 54%
Undifferentiated 40%

~5-year OS by site
Orbit >90%
Parameningeal 75%
H&N nonparameningeal: 80%
Genitourinary sites 82%
Paratesticular 69–96%
Gynecologic sites 90–98%
Extremity 70%

IRS TREATMENT

- All patients require multimodality therapy consisting of surgery (if possible) followed by chemo ±RT. Treatment is based on stage, group, and primary site.
- Chemotherapy agents include VCR, AMD, CY, topotecan, and irinotecan.
- VA = VCR/AMD; VAC = VCR/AMD/CY; VTC = VCR/topotecan/CY; VCPT = VCR/irinotecan.

IRS-V TREATMENT SCHEME

Stage/group	IRS-V treatment
Low risk	
Stage 1–3 Group I	Surgery → chemotherapy (VA or VAC). No RT
Stage 1 Group II	Surgery → chemotherapy (VA) + RT at week 3 (36 Gy for N0 or 41.4 Gy for N1)
Stage 1 Group III	Surgery (biopsy only for orbit) → chemotherapy (VA) + RT (50.4 Gy except for orbit which is 45 Gy). Most get RT at week 3, but primary sites at vulva, uterus, biliary tract, and certain nonparameningeal H&N get RT at week 12 to allow for possible second-look surgery; vaginal primaries get RT at week 12 (N1) or 28 (N0)
Stage 2 Group II	Surgery → chemotherapy (VAC) + RT at week 3 (36 Gy)
Stage 3 Group II	Surgery → chemotherapy (VAC) + RT at week 3 (36 Gy for N0 or 41.4 Gy for N1)
Intermediate risk	
Embryonal stages 2–3, Group III; embryonal stage 4, age 2–10 years; alveolar/undifferentiated stages 1–3	Surgery → chemotherapy (VAC or VAC alternating with VTC) At week 12, perform second-look surgery or definitive RT if unresectable RT doses depend on extent of resection and site, but, in general, 0–36 Gy for complete resection, 36 Gy for microscopic residual and N0, 41.4 Gy for microscopic residual and N1, and 50.4 Gy for gross residual
High risk	Chemotherapy (VCPT → VAC or VAC alternating with VCPT depending on response) RT at week 15 to primary and metastatic sites, except for patients with intracranial extension, spinal cord compression, or other indications for emergent RT (day 0). Definitive RT dose is 50.4 Gy except for the orbit which is 45 Gy. If second-look surgery is performed, postoperative RT doses are the same as for intermediate-risk disease
Site-specific recommendations	
Orbit	Biopsy to establish diagnosis → chemotherapy → RT. RT target is tumor +2 cm margin. Dose depends on stage and group as above (45 Gy for stage 1, Group III). Orbital exenteration is reserved for salvage
Head and neck (nonparameningeal sites)	Follow stage/group guidelines above. For Group III, perform second-look surgery or definitive RT if unresectable at week 12 with RT doses as above

Stage/group	IRS-V treatment
Parameningeal sites	If intracranial extension or cranial neuropathy present, RT is given first. Otherwise, RT is given at week 12 or week 15 if a second-look surgery is performed. For focal intracranial extension, include a 2 cm margin. If extensive intracranial involvement, treat the whole brain
Biliary tract	Follow stage/group guidelines above. For Group III, perform second-look surgery or definitive RT if unresectable at week 12. Postoperative dose is 36 Gy for complete resection and microscopic residual and 50.4 Gy for gross residual
Extremity	Wide local excision with *en bloc* removal of a cuff of normal tissue and nodal sampling → chemotherapy → local treatment as described in stage/group guidelines above
Trunk, retroperitoneum, perineum, GI	Follow stage/group guidelines above
Bladder/prostate	Follow stage/group guidelines above. Because one goal is bladder preservation, an initial biopsy is often performed followed by chemotherapy + RT, with surgery reserved for residual disease
Paratesticular	Inguinal orchiectomy with resection of entire spermatic cord and ipsilateral lymph node dissection including high and low infrarenal and bilateral iliac nodes for all patients ≥10 and for those <10 with radiographic involvement (except Group I and III biopsy-only patients) If scrotal violation, give RT to hemiscrotum. Contralateral testicle can be transposed into thigh prior to RT and later reimplanted. RT dose depends on stage and group as above (50.4 Gy for stage 1, Group III)
Uterus, cervix	Follow stage/group guidelines above. For Group III, perform second-look surgery or definitive RT if unresectable at week 12 with doses as above
Vulva	Follow stage/group guidelines above. For Group III, perform second-look surgery or definitive RT if unresectable at week 12 with doses as above
Vagina	Follow stage/group guidelines above, but local treatment is at week 12 (N1) or week 28 (N0) followed by reassessment with biopsy. If biopsy is negative, no further local treatment. If biopsy is positive, resect or initiate RT if unresectable with doses as above

IRS 6 TREATMENT

Stage/group	IRS-VI treatment
All patients require multimodality therapy consisting of surgery (if possible) followed by chemo ± RT. Chemotherapy agents include VCR, AMD, CY, irinotecan, Doxo, etoposide	
Overall IRS-VI summary	*Chemo* Low risk: VAC × 22–46 weeks (46 weeks for stage III or Group III nonorbit) Intermediate risk (all alveolar, Group III unfavorable embryonal): VAC vs. VAC/VI × 42 weeks High risk (met): Alternating between V/Irinotecan, VDC, IE, and VAC *Timing of RT* Direct extension into brain or cord compression or loss of vision: day 0 Intermediate risk (Group III unfavorable sites and all alveolar): week 4 Low risk: week 13 Base of skull invasion or CN palsy: week 15 High risk (metastatic): week 20 Vagina Group II–III: week 25 AMD is given just before, but not during RT. No doxo during RT *RT volumes* GTV = prechemo, presurgical tumor, and mets at diagnosis CTV = GTV + 1 cm. If planning 50.4 Gy, cone down to GTV + 0.5 cm after 36–41.4 Gy If LN+, include entire LN chain For orbit, CTV does not extend beyond bony orbit If pushing border, do not need to cover displaced normal tissues that return to normal position after chemo. Do include entire pretreatment extent of disease PTV = CTV + 0.5 cm *RT dose* Stage 1–3 Group I = No RT, except alveolar = 36 Gy Stage 1–3 Group II = 36 Gy N0, 41.4 Gy N+ Stage 1 Group III = 45 Gy (orbit only). Otherwise, 50.4 Gy IV = 50.4 Gy unless resected initially, as above. If second-look surgery margin, 36 Gy If >1 lung met = whole lung RT 1.5/15 Gy *RT dose limitations* Optic nerve/chiasm: 46.8 Gy Lacrimal gland: 41.4 Gy Small bowel, spinal cord: 45 Gy Lung: <50% >18 Gy Kidney: <14.4 Gy Liver: whole <23.4 Gy Heart: whole <30.6

Stage/group	IRS-VI treatment
Low risk Stage 1 Group I–III Stage 2 Group I–II Stage 3 Group I–II	All patients get surgery first (except orbit and vagina biopsy only) → VAC chemo × 22–46 weeks; 46-week chemo is given for stage III or Group III nonorbit *Timing of RT* RT at week 13 for most patients, except Group I disease or node-negative Group III uterine/cervix primaries that are completely resected at week 13 (who do not receive RT), and patients with node-negative vaginal primaries (who begin RT following surgery at week 24) Patients with Group III disease may undergo second-look surgery at week 13, followed by response-adjusted RT dosing (see Appendix VI of ARST 0331 protocol) *Volumes* GTV = prechemo, presurgical tumor at diagnosis CTV = GTV + 1 cm. If Group III and CR to chemo, give 36 Gy to 1 cm margin, and then cone down to 0.5 cm margin to complete 50.4 Gy. If LN+, include entire LN chain. There are special modifications of GTV and CTV for certain sites (see protocol) PTV = CTV + 0.5 cm *Dose* Stage 1–3 Group I = No RT Stage 1–3 Group II = 36 Gy N0, 41.4 Gy N+ Stage 1 Group III = 45 Gy (orbit only). Otherwise, 50.4 Gy
Intermediate risk Stage 2–3, Group III embryonal unfavorable site; Nonmetastatic, Group I–III alveolar	Surgery → chemo × 42 weeks (randomized to VAC vs. VAC alternating with VI for total of 14 cycles) *Timing of RT* Simulation before week 4, RT begins at week 4 Symptomatic spinal cord compression RT may begin during week 1 No second-look surgery for unfavorable site Group III or alveolar *Volumes* Same as low risk *Dose* Stage 1–3 Group I alveolar = 36 Gy Stage 2–3 Group II = 36 Gy N0, 41.4 Gy N+ Group III = 45 Gy (orbit only). Otherwise, 50.4 Gy. For patients receiving total dose of 50.4 Gy, cone down is permitted after 36 Gy. Volume reduction not recommended for invasive tumors

Stage/group	IRS-VI treatment
High risk (metastatic patients, patients with parameningeal paraspinal, or intracranial extension)	Chemo for 51 weeks (alternating between V/Irinotecan, VDC, IE, and VAC) *Timing of RT* RT begins at week 20 to the primary and metastatic sites Exceptions Intracranial extension consisting of direct extension into the brain, or emergent RT for spinal cord compression or loss of vision, begins week 1, day 0, with RT to other metastatic sites at week 20 *Volumes* Same as low risk, include all sites of metastases Patients with >1 lung met or pleural effusion receive bilateral whole lung RT *Dose* All patients 50.4 Gy to primary and met sites Orbit limited to 45 Gy Whole lung RT for >1 met = 1.5/15 Gy. Boost residual if possible to 50.4 Gy If initial surgery, resected margins negative, embryonal = 0 Gy, alveolar = 36 Gy. Microscopic residual LN– 36 Gy, microscopic residual LN + 41.4 Gy If second-look surgery, same except all patients with negative margins get 36 Gy

Group/stage	Treatment	3-year OS	Findings
I paratesticular	VA	90%	No difference from IRS III
I orbit	VA	100%	No difference from IRS III
II orbit	VA + RT	100%	No difference from IRS III
I, stage 1–2	VAC vs. VAI vs. VIE; no RT	84–88%	No difference between chemo regimens
I, stage 3; all II	VAC vs. VAI vs. VIE + RT	84–88%	No difference between chemo regimens
III	VAC vs. VAI vs. VIE, + RT (qd vs. b.i.d.)	72–83% (3-year FFS)	No difference between chemo regimens. b.i.d. RT did not improve LC (~87%) or OS vs. qd RT
IV	VM vs. IE → VAC, + RT	27 vs. 55%	IE improved FFS, OS vs. VM chemo

RADIATION TECHNIQUES

Simulation and Field Design

- Many patients may require pediatric anesthesia.
- Excellent immobilization is required, and 3DCRT or IMRT is encouraged to limit doses to normal structures.
- In IRS-V RT, volumes were to the prechemotherapy, presurgical tumor plus a 2 cm margin with inclusion of involved lymph nodes (prophylactic nodal RT not used). For Group III patients requiring 50.4 Gy, the volume is reduced to the prechemotherapy, presurgical tumor plus a 0.5 cm margin at 36 Gy for N0 patients or at 41.4 Gy for N1 patients.

- The timing of RT is described in the IRS-V treatment summary table above and always given at 1.8 Gy/day.
- Dose limitations are as follows: kidney <14.4 Gy, whole liver <23.4 Gy, bilateral lungs <15 Gy in 1.5 Gy fractions, optic nerve and chiasm <46.8 Gy, spinal cord <45 Gy, GI tract <45 Gy, whole abdomen 24 Gy in 1.5 Gy fractions, heart <30.6 Gy, lens <14.4 Gy, and lacrimal gland and cornea <41.4 Gy.
- Uninvolved ovaries or testicles should be shielded or moved in patients with pelvic or paratesticular primaries.

FOLLOW-UP

- H&P and CXR every 2 months for first year with repeat imaging studies that were positive at diagnosis every 3 months, then H&P and CXR every 4 months for second and third years, then H&P annually for years 5–10, and annual visit or phone contact after 10 years.

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NRSTS

EPIDMIOLOGY AND ETIOLOGY

- INCIDENCE OF STS CHILDREN - 11/MILLION
- APPROXIMATELY 7.4%
- UPTO 60% ARE NRSTS
- MORE COMMON WITH INCREASING AGE AND OLDER ADOLESCENTS.
- NO SINGLE HISTOLOGY > 15%
- NO KNOWN CAUSES OR RISK FACTORS.

NRSTS ACCORDING TO INTERNATIONAL CLASSIFICATION OF CHILDHOOD CANCER

- FIBROSARCOMA CATEGORY
- KAPOSIS SARCOMA
- OTHER SPECIFIED STS
- UNSPECIFIED STS

Histologic subtypes of nonrhabdomyosarcoma soft tissue sarcomas in pediatric patients

Histology	Normal counterpart	Incidence
Fibrosarcoma	Fibroblast	0.6
Infantile fibrosarcoma	Fibroblast	0.2
Malignant fibrous histiocytoma	Fibroblast	0.8
Dermatofibrosarcoma protuberans	Fibroblast	1.0
Malignant peripheral nerve sheath tumor	Schwann cell	0.6
Kaposi's sarcoma	Blood vessels	0.1
Liposarcoma	Adipocyte	0.1
Leimyosarcoma	Smooth muscle	0.3
Synovial sarcoma	Synovial cells	0.7
Hemangiosarcoma	Blood vessels	0.2
Malignant hemangiopericytoma	Vessel pericytes	0.1
Alveolar soft part sarcoma		0.1
Chondrosarcoma	Chondrocytes	0.1

CHROMOSOMAL ALTERATIONS

- T(17;22) in Dermatofibrosarcoma Protuberans
- Inhibition of this receptor with Imatinib has been evaluated.

CLINICAL PRESENTATION

- PAINLESS MASS WHICH ARE SLOW GROWING
- SYMPTOMS DEPENDS ON LOCATION

EVALUATION AND MANAGEMENT

- CT SCAN
- MRI
- PET SCAN
- BIOPSY
- BIOPSY SITE TO BE CHOSEN TO INCLUDE TRACK LINES IN FIELD OF RESECTION.

SURGERY MAINSTAY

- A 1 cm MARGIN CONSIDERED APPROPRIATE
- LOCAL CONTROL RATES WITH ADJUVANT CT RT FOR LIMBSPARING IS APPROACHING 95%
- AMPUTATION IS BEING RESERVED FOR MAJOR ARTERY AND NERVE INVOLVEMENT

CHEMOTHERAPY

- For Patients Deemed at high risk of Metastasis
- Doxorubicin and Ifosfamide.

NOMOGRAMS FOR ADJUVANT TREATMENT

- Usefulness depends on risk of relapse and sarcoma specific death.
- Prognosis depends on Age, size of Tumor, histologic grade and subtype and location of tumor.
- In pediatric population TUMOR SIZE is most important.
- OTHER IMPORTANT THINGS ARE
    1. Localized versus metastatic disease
    2. Extent of Tumor resection
    3. Maximum Tumor Diameter
    4. Tumor Grade

ROLE OF RADIATION

- ALMOST ALWAYS USED IN COMBINATION WITH SURGERY.
- ADJUVANT OR NEOADJUVANT
- PREOPERATIVE 5000 cGY OR POSTOPERATIVE 6600cGY
- LOCAL CONTROL IDENTICAL , TOXICITIES DIFFERENT
- TREATMENT VOLUME ENCOMPASS PREOPERATIVE TUMOR VOLUME OR POST OPERATIVE TUMOR BED WITH 5CM LONGITUDINAL AND 2CM MEDIAL MARGINS.

TREATMENT COMPLICATIONS

- 1. Physical disabilities and Functional limitations.
- 2. Emotional and psychological challenges.
- 3. Cognitive and Learning disabilities.
- 4. Risk of Secondary cancers.
- 5. Cardiac and Pulmonary complications

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Thank You

American Oncology Institute

Dr. Deepak Abrol .
MBBS, MD (Radiation Oncology), Senior Consultant-Radiation Oncology