Pediatric Oncology

Rhabdomyosarcoma

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Introduction

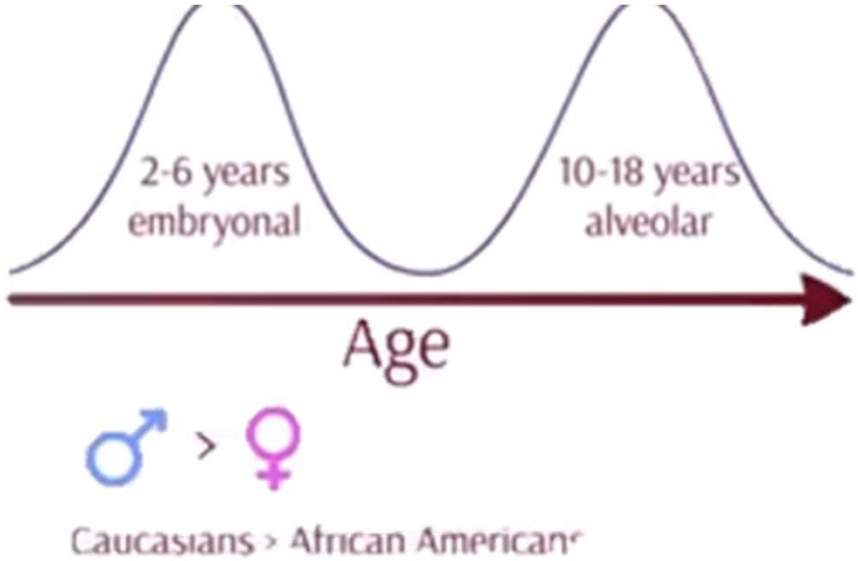
- Most common soft tissue sarcoma (5% pediatric tumors)
- 3rd most common extracranial tumor (after neuroblastoma & Wilms)
- In the 1960s survival was 25%
- 1970s: Combination chemo (VAC regimen) improved survival (55%)
- 1990s: Cooperative studies (IRS I-IV) improved survival (71%)

OUTLINE

1. Basics
2. Approach
3. Site specific principles
4. Summary

Basics

Epidemiology



Bimodal age distribution: peaks b/n 2-6 yr and 10-18 yr. This also corresponds to 2 major histologic subtypes. Predilection for white males.

Etiology

Pediatric Blood & Cancer

Research Article

The Role of Childhood Infections and Immunizations on Childhood Rhabdomyosarcoma: A Report From the Children's Oncology Group

Hari Sankaran MD, Heather E. Danysh PhD, MHS, Michael E. Scheurer PhD, MPH, M. Fatih Okcu MD, MPH, Stephen X. Skapek MD, Douglas S. Hawkins MD, Logan G. Spector PhD ... See all authors

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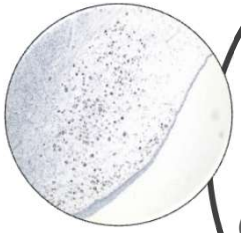
- **Most occur sporadically**: Also associated with Li Fraumeni, neurofibromatosis type I, BWS. Linked with maternal exposure to marijuana and cocaine. Incomplete or lack of immunization (MMR, OPV) was reported to be associated with RMS

Histology

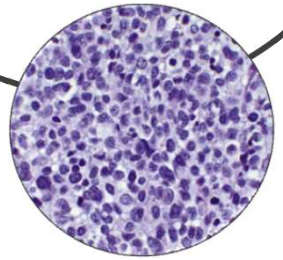


Embryonal (70%)
Favorable
Rhabdomyoblast
(myogenic differentiation)
LOH 11p15 in 80%

Botryoid (6%)
Hollow viscus
(vagina, bladder, biliary)
Grape like appearance

Spindle cell (3%)
paratesticular
RMS with Spindle pattern

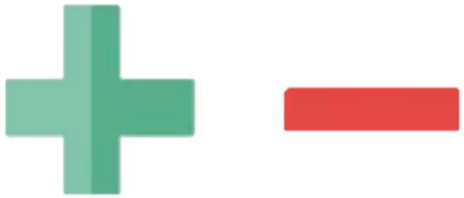
Alveolar (25%)
Unfavorable
Hyperchromatic nuclei (resemble pulmonary)
Gene translocations



**embryonal subtypes have the best prognosis*

Biology

Fusion



Expression of fusion proteins: arise from fusion of FOXO gene with PAX3 (55%) or PAX7.(23%). PAX7-FOXO fusion has worst prognosis. **Fusion status has now become more important than histology** (2nd predictor after stage). All ERMS are fusion negative. 25% of alveolar are fusion negative and have similar prognosis to embryonal.

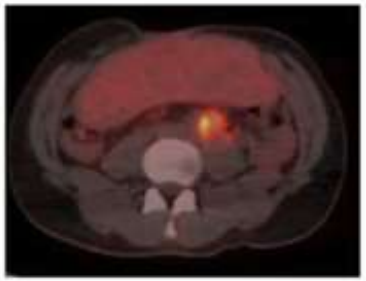
Sites

Favorable sites : **orbit**, **head & neck** and **genitourinary**
Unfavorable sites: **trunk & extremity,** bladder/prostate, parameningeal

Other factors

age > 10 y

size > 5 cm



retroperitoneal nodal involvement

Other poor prognostic factors: LN involvement, large size & age. Adolescent (>10yr) have worse prognosis (fusion positive) and Infants (<1yr) also have poor prognosis b/c less aggressive treatment.

Approach

Presentation

- **Asymptomatic mass**
- Symptoms depending on the site
  - **Head & neck (35%):** proptosis, opthalmoplagia, CN palsy
  - **Genitourinary (20%)**: constipation, urinary symptoms, vaginal bleeding
  - **Extremity (15%)**
  - **Metastasis** : bone, BM, lung
- Neonatal presentation is rare and most are botryoid

Workup

- **Lab –** CBC, urinalysis, electrolyte, RFT, LFT, coagulation panel
- **Imaging of primary tumor**
  - CT – Better for bone involvement and LAP
  - MRI – better definition of primary tumor
- **Metastatic workup:** whole body CT (if locally invasive), LP, BMA
- **Biopsy**
  - Incisional / core needle
  - Primary excision – if superficial & small (minority)

Staging (preop) & **Grouping** (postop)

Stage	Site	T	N	M
1	Favorable			No mets
2	Unfavorable		No LN	No mets
3		<5cm	LN	No mets
		>5cm		No mets
4				Mets

Clinical Group	Definition
I	Complete resection
II	LN disease / microscopic margin/ Removed piecemeal
III	Incomplete resection/ biopsy only
IV	Metastatic

Chemotherapy

Risk group	Stage	Clinical Group	Fusion	Age
Low (35%)	1	1-3	-	
(VAC 24 wk 90% survival	**2**	1-2	-	
Intermediate (50%)	1	3 (non orbit)	-	
	2-3	3	-	
(+ irrenotecan ± tamsirolimus 42 wk) 60% - 85% survival	3	1-3	-	
	1-3	1-3	+	
	4	4	-	<10
High (15%) (+ irrenotecan…?) 40% survival	4	4	-	>10
			+	

Surgery

Primary excision	Pre-treatment re-excision (PRE)	Delayed primary excision (DPE)
Prior to establishing diagnosis	Prior to chemo to remove positive margins	Residual after 12 weeks induction chemotherapy
If possible without significant functional/ cosmetic sequalae	- Determines clinical group	Doesn't change clinical group but may allow RT reduction

Resection must be attempted only if it can be achieved without significant morbidity

- ***No role of debulking in RMS*** *(require wide complete resection with 5mm margin)*
- ***In some patients RT is definitive*** *(no surgery needed)*
- ***No role of excising residual after definitive RT*** *(inc morbidity, no benefit)*

Radiation

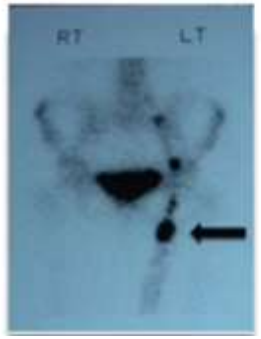
- **Essential for all except Embryonal, Group I** (complete resection)
  - 50% operative bed recurrence occur in those who didn't receive RT
- Initiation 6-12 wk after beginning chemo (earlier for intracrainal)
- **DPE Allows reduction of definitive radiotherapy** (50Gy)
  - 36 Gy if negative margin
  - 41 Gy if microscopic margin
- Size >5cm is biggest contributor to local failure

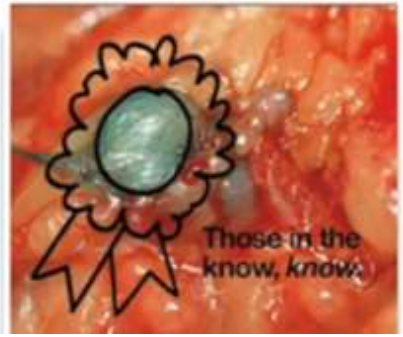
Lymph node disease

- **Regional LN determines need for RT**
- **alters prognosis for alveolar (fusion positive)** but not embryonal
- LN involvement in 25% of RMS but Imaging can fail to detect 50% of LN
- nodal evaluation is recommended for
  - any palpable node
  - Site specific (extremity, trunk and paratesticular RMS)
  - Any fusion positive RMS

Lymph node disease

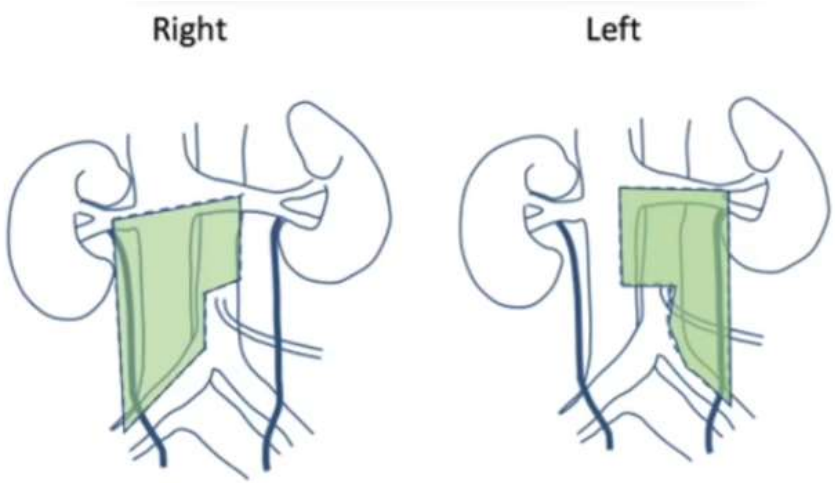
2-3 hrs pre-op inject ^{99}Tc ➤ lymphoscintigraphy ➤ OR blue dye ➤ use gamma probe / blue dye to identify SLN





Sentinel LN biopsy, should be preformed in the absence of palpable nodes (especially in **extremity/trunk RMS**). Use of both technetium and blue dye improves success. Complete LN dissection is not necessary.

Lymph node disease



Ipsilateral RPLN sampling (8-12 LN upto renal hilum): for **paratesticular RM** if age >10yr, >5 cm or enlarged LN on imaging. A nerve sparing ipsilateral template modification to the standard bilateral RPLND is recommended.. Positive suprarenal node is considered metastasis. Children <10 years without LAP can be followed with CT every 3 mo

Metastatic & recurrent disease

- Metastasis confers a 5-year survival under 20%.
- **Attempt resection of primary tumor in metastatic disease** (most recurrence is from tumor bed)
- **Primary resection of metastasis doesn't improve survival** (may consider pul. Metastatectomy after chemo radio if cure possible)
- **Resection of recurrent RMS improves survival** from 8–37%

Late effects

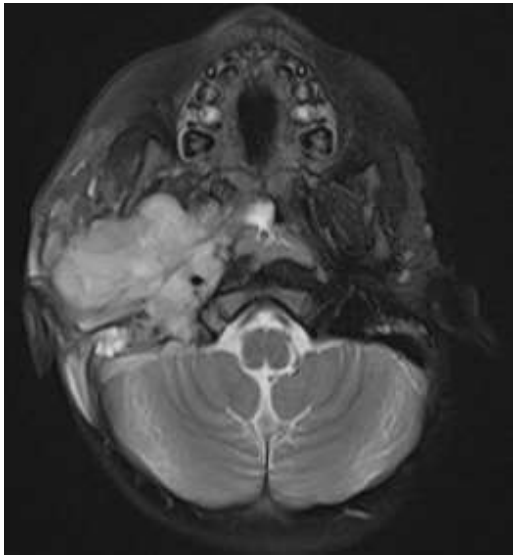
- increased risk of
  - secondary malignancies
  - thyroid/PTH dysfunction, hearing loss
  - fracture, impaired growth & fertility
  - increased mortality compared to the general population
- monitor regularly with **physical examination and imaging every 3–6 months for the first 2 years** after completing treatment

Site specific principles

Head & Neck

75% in the orbit : others include buccal, oropharynx, larynx, parotid. Difficult to achieve margin except in parotid. Most undergo chemoradiotherapy after biopsy.

Head & Neck: Parameningeal



Can arise from middle ear/mastoid, nasal cavity, parapharyngeal space, paranasal sinus. Often present late with bony erosion, CN palsy. Poor prognosis

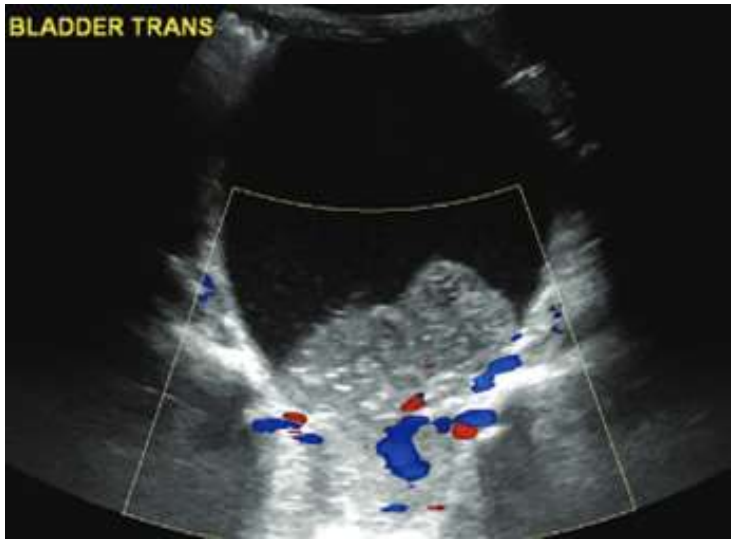
Genitourinary: Vulva/vaginal/uterine

Good response to chemo : **87% survival.** vaginectomy/hysterectomy only if persistent/recurrent disease (poor outcome)

Genitourinary: Paratesticular

Ultrasound to differentiate testicular from paratesticular mass.Account 10% of GU RMS. Require Inguinal orchiectomy with high ligation of spermatic cord. Scrotal violation (biopsy) mandates hemiscrocectomy *only if fusion + or scrotal invasion*. **96% survival**

Genitourinary: Bladder/prostate



- **Bladder**: usually require neoadjuvant to preserve function. (bladder salvage possible in 50-60%). Sometimes may primarily resect tumor confined to dome. **Prostate:** require prostatectomy ± bladder. LN in 20% (sample iliac, paraortic and other involved)

Extremity

Amputation is rarely necessary complete excision with 5mm margin for tumor <5 cm. Larger tumors can undergo biopsy and neoadjuvant before resection. **80% survival for LN negative. 46% if LN positive**

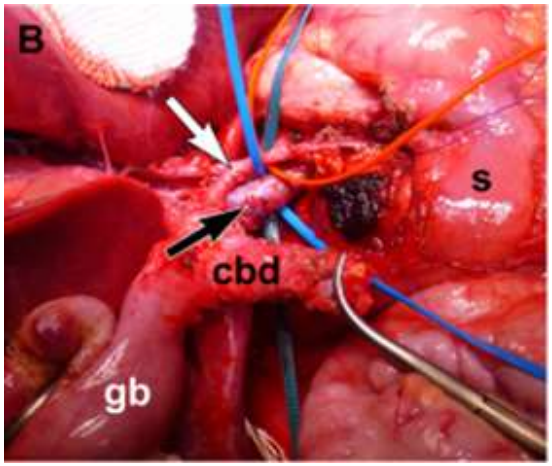
Trunk

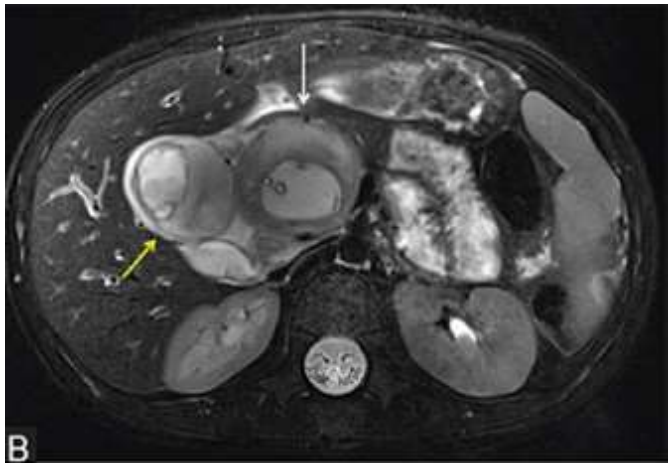
Chest wall RMS require biopsy and excision entails removal of muscles, rib and any involved lung. **Abdominal wall** makes up 7% and resection entails wide excision (full thickness) with prosthetic reconstruction.

Retroperitoneum

Retroperitoneal RMS presents advanced (most cant be resected) poor prognosis

Biliary tract





Biliary RMS presents at young age. It can mimic choledochal cyst. Diagnosis usually made postop after excision. Difficult to achieve gross resection but favorable outcome with chemo radiotherapy. **80% survival** despite residual disease .

Perianal/perineal

Rare : misdiagnosed (as condyloma) and presents with advanced stage and clinical group. Usually alveolar. Resection is challenging b/c urethra/rectum. Colostomy may be done for obstruction. Evaluation of ilioinguinal LN is recommended. **45% survival**

Summary

- RMS is **staged** preop and **grouped** postop
- **Fusion status** is important for risk stratification
- **LN evaluation** is essential for trunk, extremity & paratesticular RMS
- All patients require **chemotherapy** (VAC)
- The eye, vagina and bladder can usually be saved (**surgery omitted**)
- **RT can be omitted** for localized, completely excised embryonal RMS

THANK YOU!