# In The Name of God

# Evaluation of Prognostic Factors and Treatment Result in Rhabdomyosarcoma Cases in Amirkola Children Hospital

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# Soft-Tissue Sarcomas

- Soft-tissue sarcomas (STS) are a heterogeneous group of malignant tumors derived from primitive mesenchymal cells.
- These tumors arise from muscle, connective tissue, supportive tissue, and vascular tissue.
- They are locally highly invasive and have a high propensity for local recurrence.
- They usually metastasize via the bloodstream and, less commonly, via the lymphatics.

**The STS can be divided into two groups:**

1) Rhabdomyosarcoma (RMS).
2) Nonrhabdomyosarcoma soft-tissue sarcomas (NRSTS).

# Incidence And Epidemiology

- RMS is the third most common solid extracranial tumor, following neuroblastoma and Wilms' tumor.
- RMS accounts for 3% of all malignant neoplasms in children, with approximately 400 new cases diagnosed in the United States each year in children under 19 years of age.
- Approximately one-third of cases of RMS are in children less than 5 years of age and 60% of cases are diagnosed in children less than 10 of age.
- In RMS there is a slight male predominance with a male: female ratio of 1.4:1; however adolescent patients are disproportionately males.
- RMS incidence in African-American females is half that of Caucasian females. The incidence is lower in Asian populations residing in Asia or the West.

# Incidence And Epidemiology …

- Most cases of STS occur sporadically but up to 30% of cases may have an underlying risk factor, which may include:
- Germline mutations of the p53 suppressor gene, as in Li Fraumeni familial cancer syndrome. There is an association between early-onset breast cancer, sarcomas, brain tumors, and adrenocortical tumors in family members.
- Ionizing radiation.
- Neurofibromatosis (NF1)—patients with NF1 have up to a 15% lifetime risk of developing an malignant peripheral nerve sheath tumors (MPNST) associated with chromosome 17 deletions.

# Incidence And Epidemiology …

- Syndromes such as Beck with Weidemann syndrome and Costello syndrome (a genetic disorder characterized by delayed development and mental retardation, unusually flexible joints, hypertrophic cardiomyopathy, short stature, and an increased risk of developing tumors, with the most frequent being RMS).
- DICER1 mutations familial pleuropulmonary blastoma predisposition syndrome increases the risk of developing tumors including embryonal RMS (ERMS).
- Maternal and paternal use of marijuana and cocaine and first-trimester prenatal X-ray exposure, possibly as an environmental interaction with a genetic trigger.

# Genetics of RMS

1. Alveolar rhabdomyosarcoma (ARMS) has a characteristic translocation of the FOXO1 gene (previously known as Forkhead, or FKHR) at 13q14 with PAX3 at 2q35 or less commonly PAX7 at 1p36. The fusion protein functions as a transcription factor that activates transcription from PAX binding sites that are 10- 100 times more active than wild-type PAX7 and PAX3. This alteration in growth, differentiation, and apoptosis results in tumorigenic behavior. Approximately 75% of ARMS contain the FOXO1-PAX 3 translocation; the remaining 25% contain the FOXO1-PAX7 translocation. There are conflicting data with regard to whether translocation subtype is prognostically significant for any group of patients.
2. ERMS has a loss of heterozygosity (LOH) at the 11p15.5 locus. This LOH involves loss of the imprinted maternal genetic information and all that remains is expression of the paternal genetic material. This LOH includes loss of tumor suppressor genes that have been implicated in oncogenesis which results in the overproduction of insulin-related growth factor-II (IGF-II). IGF-II stimulates the growth of RMS and blockade of the IGF-II receptor inhibits RMS growth in vivo.

# Genetics of RMS …

3. “Translocation-negative” ARMS (i.e., tumors that have an alveolar pattern on routine light microscopy but lack the defining FOXO1-PAX translocation) represent approximately 25% of cases of ARMS and have been demonstrated conclusively to cluster genomically and clinically with ERMS. These cases will be considered ERMS in future Children’s Oncology Group (COG) clinical trials. 4. Spindle cell RMS, a less common subtype of ERMS, may be seen in children and adults and appears to have distinctive genetic features and clinical behavior in each group: children typically have a favorable prognosis and cases of recurrent NCOA2 translocation have been described; conversely, adults typically have more aggressively behaving disease and there is growing evidence that many of these tumors contain mutations in the MYOD1 gene.

# Histologic Subtypes of Rhabdomyosarcoma (RMS)

| Pathologic subtype | Morphology | Usual site of origin | Usual age (years) distribution |
|---|---|---|---|
| Embryonal (ERMS) solid | Resembles skeletal muscle in 7- to 10-week fetus. Moderately cellular with loose myxoid stroma. Actin and desmin positive; myogenin scattered positivity <50% | Head and neck, orbit, genitourinary tract | 3–12 |
| Botryoid variant | Only one microscopic field of cambium layer necessary to diagnose as botryoid. Grossly presents with grape-like configuration | Bladder, vagina, nasopharynx, bile duct | 0–8 |
| Spindle cell variant[a] | Spindle-shaped cells with elongated nuclei and prominent nucleoli. Low cellularity. Collagen-rich and -poor variants | Paratesticular | 2–12 |
| Alveolar (ARMS) | Resembles skeletal muscle in 10- to 21-week fetus. Basic cell is round with scanty eosinophilic cytoplasm; alveolar pattern may be lost if densely packed; cross striations more common than embryonal variety. Up to one-third of ARMS-negative tumors are actually dense pattern ERMS. Diffuse myogenin positivity. ARMS requires confirmation of *PAX3/7-FKHR* (*FOXO1*) translocation | Extremities, trunk, perineum (adolescents) | 6–21 |
| RMS, NOS | Heterogeneous, unable to subtype due to paucity of tissue | Extremities, trunk | 6–21 |

[a]*Spindle cell RMS in adults is a distinct clinical entity with more aggressive behavior than in the pediatric population.*
NOS, not otherwise specified.

# Frequency of Primary Sites, Sites of Regional Spread, and Distant Metastatic Sites in Rhabdomyosarcoma

| Primary site | Relative frequency (%) | Regional spread and distant metastatic sites |
|---|---|---|
| **Head and neck** | **40** | |
| Orbit | 8 | Nodes rarely involved; rare lung metastasis |
| Parameningeal[a] | 25 | Regional spread to bone, meninges, brain; lung and bone metastases |
| Other[b] | 7 | Nodes rarely involved; lung metastases |
| **Genitourinary tract** | **29** | |
| Bladder, prostate | 10 | Nodes rarely involved; metastases to lung, bone, and bone marrow (primarily prostate primaries) |
| Vagina, uterus | 5 | Nodes rarely involved; metastases to retroperitoneal nodes (mainly from uterus) |
| Paratesticular | 14 | Retroperitoneal nodes in up to 50% of boys 10 or older; metastases to lung and bone |
| **Extremities** | **14** | Nodes involved in up to 50% of cases; metastases to lung, bone marrow, bone, central nervous system |
| **Trunk** | **12** | Nodes rarely involved; metastases to lung and bone |
| **Other** | **5** | Nodal involvement site-dependent (increased in perineal/perianal primaries); metastases to lung, bone, and liver |

[a] *Parameningeal sites are adjacent to the meninges at the base of the skull; they consist of nasopharynx, middle ear, paranasal sinuses, and infratemporal and pterygopalatine fossae.*

[b] *Nonorbital, nonparameningeal sites consist of larynx, oropharynx, oral cavity, parotid, cheek, and scalp.*

# Clinical Manifestations of Rhabdomyosarcoma in Various Anatomic Locations

| Location | Signs and symptoms |
|---|---|
| *HEAD AND NECK*[a] | |
| Neck | Soft-tissue mass |
| | Hoarseness |
| | Dysphagia |
| Nasopharynx | Sinusitis |
| | Local pain and swelling |
| | Epistaxis |
| Paranasal sinus | Sinus obstruction/sinusitis |
| | Unilateral nasal discharge |
| | Local pain and swelling |
| | Epistaxis |
| Middle ear/mastoid | Chronic otitis media—purulent blood stained discharge |
| | Polypoid mass in external canal |
| | Peripheral facial nerve palsy |
| Orbit | Proptosis |
| | Ocular palsies |
| | Conjunctival mass |

# Clinical Manifestations of Rhabdomyosarcoma in Various Anatomic Locations …

| | |
|---|---|
| ***GENITOURINARY*** | |
| Vagina and uterus | Vaginal bleeding |
| | Grapelike clustered mass protruding through vaginal or cervical opening (i.e., sarcoma botryoides) |
| Prostate | Hematuria |
| | Constipation |
| | Urinary obstruction |
| Bladder | Urinary obstruction |
| | Hematuria |
| | Tumor extrusion |
| | Recurrent urinary tract infections |
| Paratesticular | Painless scrotal or inguinal mass |
| Retroperitoneum | Abdominal pain |
| | Abdominal mass |
| | Intestinal obstruction |
| Biliary tract | Obstructive jaundice |
| Pelvic | Constipation |
| | Genitourinary obstruction |
| Extremity/trunk | Asymptomatic or painful mass |

*[a]All can extend through multiple foramina and fissures into the epidural space and infiltrate the central nervous system with cranial nerve palsies, meningeal symptoms, and brain stem signs.*

# Staging

**The prognosis, selection of systemic therapy, and the design of optimal local therapy depend on the following:**

- Primary site.
- Histologic type.
- Tumor size.
- Degree of regional spread.
- Nodal involvement.
- Distant metastatic disease.
- Extent of prechemotherapy tumor resection.

# Soft-Tissue Sarcoma—Children's Oncology Group Pretreatment Tumor Node Metastasis Staging of Rhabdomyosarcoma

| Stage | Sites | T Invasiveness | T Size | N | M |
|---|---|---|---|---|---|
| I | **Favorable sites** Orbit, head, and neck (excluding parameningeal), genitourinary (nonbladder/nonprostate) | T1 or T2 | a or b | N0 or N1 or NX | M0 |
| II | **Unfavorable sites** Bladder/prostate, extremity Cranial parameningeal Other (includes trunk, retroperitoneum, etc.) | T1 or T2 | a | N0 or NX | M0 |
| III | **Unfavorable sites** Bladder/prostate, extremity Cranial parameningeal Other (includes trunk retroperitoneum, etc.) | T1 or T2 | a b | N1 N0 or N1 or NX | M0 |
| IV | **Any sites** | T1 or T2 | a or b | N0 or N1 | M1 |

| T = Tumor | N = Regional nodes | M = Metastasis[a] |
|---|---|---|
| T1 = Confined to anatomic site of origin | N0 = Not clinically involved | M0 = No distant metastasis |
| T2 = Extension and/or fixation to surrounding tissue | N1 = Clinically involved | M1 = Distant metastasis present |
| a ≤ 5 cm in diameter | NX = Clinical status unknown | M1 includes positive CSF cytology, pleural and/or peritoneal fluid and distant nodes |
| b > 5 cm in diameter | | |

[a]*Distant metastatic disease consists of lung, liver, bones, bone marrow, brain, and distant muscle and nodes. The presence of positive cytology in CSF, pleural, or abdominal fluids, as well as implants on pleural or peritoneal surfaces, also constitutes stage IV disease.*
*Modified from Mandell (1993) with permission.*

# Postoperative Clinical Grouping System (Intergroup Rhabdomyosarcoma Study)

| Group | Definition (Incidence) |
|---|---|
| I. | No residual disease (16%) |
| | A. Localized, completely resected, confined to site of origin |
| | B. Localized, completely resected, infiltrated beyond site of origin |
| II. | Microscopic residual disease (20%) |
| | A. Margins positive, lymph nodes negative |
| | B. Margins negative, lymph nodes positive |
| | C. Margins positive, lymph nodes positive |
| III. | Gross residual disease (48%) |
| | A. Biopsy only |
| | B. Grossly visible disease after 50% resection of primary tumor |
| IV. | Distant metastasis present at diagnosis (16%) |

# Pretreatment …

- The intermediate-risk group includes all nonmetastatic alveolar tumors, and embryonal tumors in unfavorable primary sites (stage 2 or 3) that have been incompletely resected (group III).
- Girls with nonbladder genitourinary tract ERMS treated without local radiation therapy have inferior outcomes, and should be considered to have intermediate risk disease. Their prognosis improves when treated with either intensified systemic therapy (cyclophosphamide at a dose of 2.2 g/m2/cycle) or “standard-intensity” systemic therapy (cyclophosphamide at 1.2 g/m2/cycle) combined with appropriate local therapy consisting of some combination of conservative surgery with either vaginal brachytherapy or external beam radiation therapy.
- Children under the age of 10 years with ERMS and isolated lung metastases have been included in the high-risk group, but are better categorized as intermediate-risk as they have a more favorable prognosis than other patients with metastatic disease, and can be considered to have intermediate-risk disease.

# Rhabdomyosarcoma Risk Group Classification and Outcome for Rhabdomyosarcoma (RMS) from Soft Tissue Sarcoma—Children's Oncology Group

| Risk group | Histology | Pretreatment stage | Postoperative clinical group | EFS (%) |
|---|---|---|---|---|
| Low | Embryonal | 1 (all favorable sites) | I or II | 85–95 |
| Subset 1 | | 1 (orbit only) | III | |
| | | 2 (unfavorable sites ≤ 5 cm) | I or II | |
| Low | Embryonal | 1 (nonorbit only) | III | 70–85 |
| Subset 2 | | 3 (unfavorable sites <5 cm, or unfavorable site, any size, with regional nodal involvement)[a] | I or II | |
| Intermediate | Embryonal | 2, 3 | III | 65–75 |
| Intermediate | Alveolar | 1, 2, 3[b] | I, II, III | 50–60 |
| High | Embryonal | 4[c] | IV | 20–40 |
| High | Alveolar | 4 | IV | 5–20 |

[a] *See text on risk stratification for exceptions regarding girls with nonbladder genitourinary tract embryonal RMS treated without local radiation.*
[b] *See text on risk stratification for exceptions regarding children with alveolar RMS and regional lymph node involvement.*
[c] *See text on risk stratification for exceptions regarding children under 10 years of age with ERMS and isolated lung lesions.*

# Pretreatment …

- The high-risk group includes all metastatic tumors, both alveolar and embryonal. Children under the age of 10 years with ERMS and isolated lung metastases are discussed in the intermediate-risk group. Patients with ARMS with regional nodal involvement have been included in the intermediate-risk group, but they are better categorized as high-risk as their survival is less than 50%. Since prognosis is determined by the risk group, the risk group classification determines treatment.

# Staging for NRSTS

- Staging using the American Joint Committee on Cancer staging system incorporates tumor size (T), depth, nodal (N), and metastatic (M) involvement and histologic grade (G). Tumors with necrosis greater than 15% and mitotic rate greater than 5- 10 per high power field are consider high grade. Risk stratification is based on tumor size, tumor grade, margins, resectability, and metastatic disease. In pediatric NRSTS, risk stratification with an emphasis on tumor size and resectability predicts outcome.

**The low-risk group (~ 50% of patients) includes those whose primary tumor has been grossly resected, have nonmetastatic disease and whose pathology shows:**

Low-grade tumors regardless of margin status.

High-grade tumors ~5 cm in size.

- **The intermediate-risk group (~35% of patients) includes those with nonmetastatic disease and:**

High-grade tumors that are grossly resected and greater than 5 cm in size.

High-grade tumors that are unresectable and where a delayed resection is planned.

- **The high-risk group** (~15% of patients) includes those who have metastatic disease, irrespective of the pathological grade of the tumor.

# Prognosis

- Prognosis for RMS Overall, RMS is curable in the majority of children (70% survival 5 years after diagnosis).
- The type of treatment failure differs among different risk groups.

- **The failures are typically:**
- Local treatment failure for patients with nonmetastatic ERMS.
- Regional and distant treatment failure for patients with nonmetastatic ARMS.

# Prognosis …

- The high-risk group of patients have metastatic disease and represent approximately 20% of patients with RMS.
- Within this group there is significant diversity of outcome.
- Patients with ERMS aged 1- 9 years of age and lung- only metastases have 50% EFS and those with bone and bone marrow involvement at diagnosis having an overall survival less than 10%.
- The dominant risk of treatment failure is from the inability to control systemic disease, although local treatment failure also appears to be higher in patients with metastases at diagnosis.

# Evaluation of 27 Rhabdomyosarcoma cases

- **Age distribution:** 10 months- 16 Years
- **Gender:** 14 male- 13 female
- **Site of presentation:**
  - **Pelvic mass 6 cases**
  - **Cervical mass 5 cases**
  - **Abdominal mass 5 cases**
  - **Mandibular with parapharyngeal mass  3 cases**
  - **Orbital mass 2 cases**
  - **Upper chest wall and neck 2 cases**
  - **Parotid mass 1 case**
  - **Forearm muscel 1 case**
  - **Mediastinal mass + Pleurisy + BM Metastasis 1 case**
  - **Lumbar mass with extension to lung and abdomen 1 case**

# Histologic (Pathologic) subtype:

- Embryonal type 16 cases
- Alveolar type 7 cases
- Botyroid type 2 cases
- Mixed embryonal and Alveolar 1 case
- Spindle cell type 1 case

# Stage and group at presentation type:

- Stage II and group I Alveolar type  1 case
- Stage II or III group II or III 24 cases
- Stage IV group IV 2 cases

# Treatment plan:

- Radical surgery 5 cases, for the rest debunking or biopsy
- Irradiation therapy: for 17 cases
- No Irradiation therapy: 1 case
- Chemotherapy plan: for all cases depend on surgical result and extension of tumor and pathologic subtype (Low risk, intermediate risk, high risk group)

# Result of treatment:

- 10 cases died during treatment
- 5 cases relapsed,  1 case without irradiation (2-4 years post treatment)
- 12 cases cured (more than 5 years post treatment)
- Without complete surgical resection relapse happened in most of cases

# Some points:

- The role of radical surgery
- The role of irradiation (any modification irradiation dosage?)
- Radiation complications (needs to plastic surgery …)

# Thanks for your attention