# MORTALITY AND MORBIDITY CONFERENCE

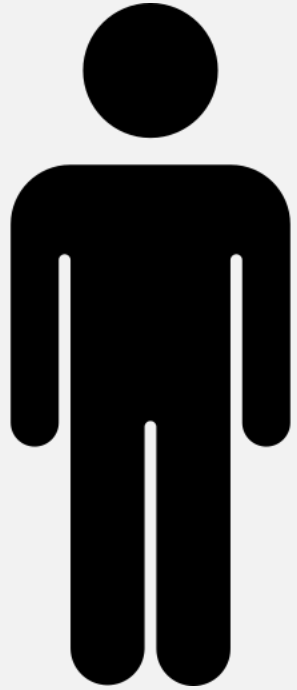
Presenter：PGY2 高樹賢

# PART I

- Case information

# PATIENT PROFILE

- Patient ID:
- Gender: 12 y/o boy
- Hospitalization: 2025/8/23-2025/8/26
- No previous disease
- Allergy: None
- TOCC: denied
- Height/weight : 145cm/ 32kg



# CHIEF COMPLAINT

Left eye proptosis and pain for 1 week

# OPHT. CONSULTATION

- 8/13 OS itchiness, slight pain noticed
- 8/16 OS proptosis and blurred vision started.
  Periorbital pain increased. Went to LMD. Chalazion was told.
  Cephalexin QID + Gentamicin oint TID, Delone eye drop TID.
- 8/20 symptoms progressed. Went to another LMD. Suggested referral.
- 8/23. Came to Dr. Su's OPD

# PHYSICAL EXAM AT ER

## Vital Signs

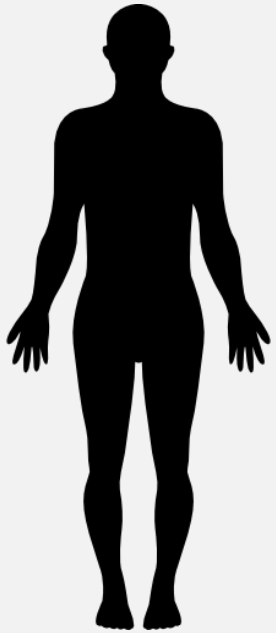
- PR:82 bpm, RR:18/min, BT:36.1°C
- BP: 124/80mmHg, SpO2:
- GCS: E4V5M6

## HEENT

- Conjunctiva: pink
- Sclera: not icteric
- Thyroid: no goiter
- Injected throat

## Chest

- bilateral coarse breathing sound
- No rales no wheezing
- Chest wall: symmetric expansion



## Heart

- regular heart beat without murmur

## Abdomen

- soft, normoactive bowel sound
- Non tenderness

## Others

- No limb edema

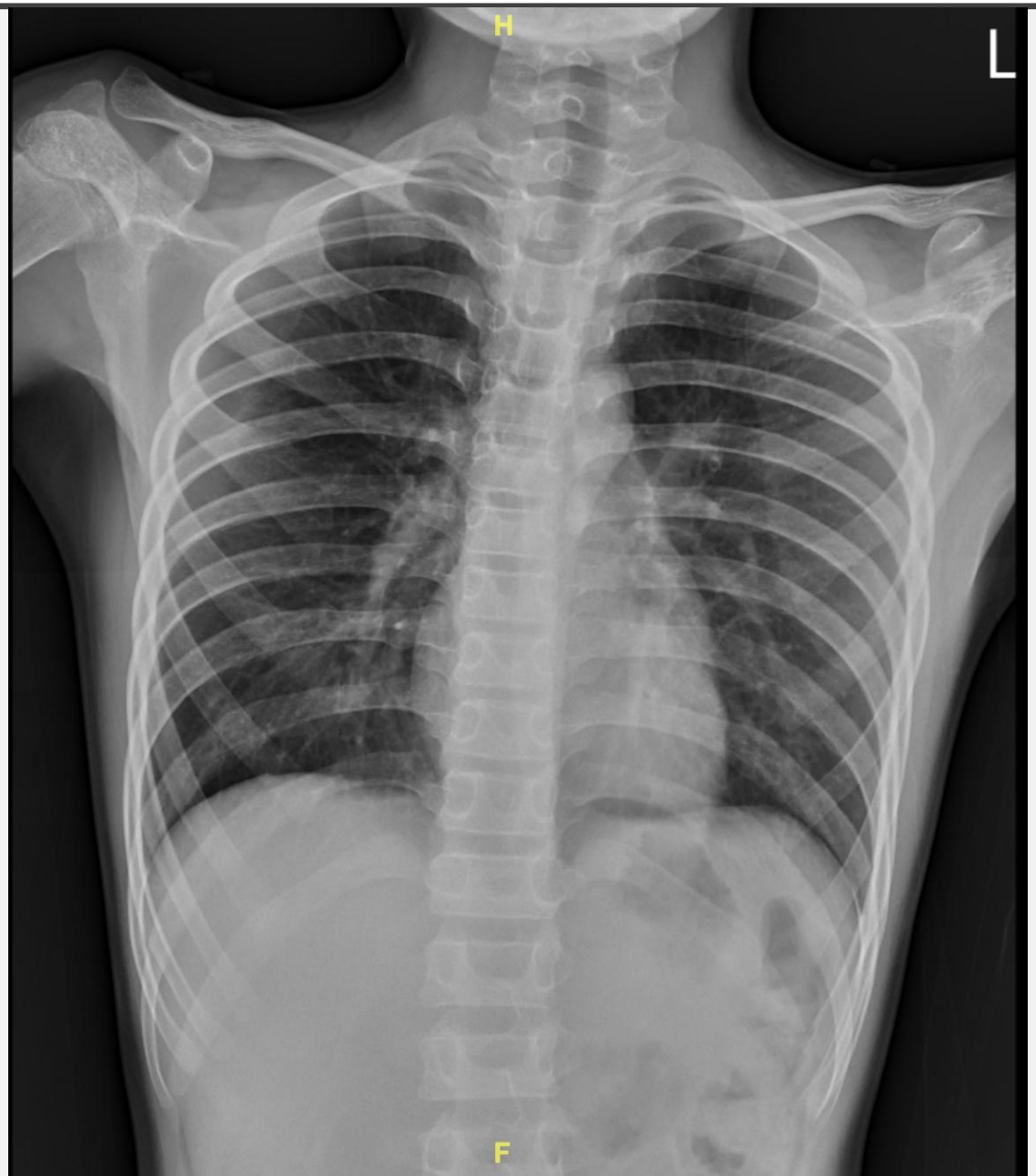
# 7/13 LAB DATA AT ER

| CBC-I | | | | |
|---|---|---|---|---|
| WBC | 6.63 | 10^3/μL | 3.80 – 10.40 | |
| RBC | 5.25 | 10^6/μL | 4.10 – 5.90 | |
| HGB | 15.8 | g/dL | 12.5 – 16.1 | |
| HCT | 46.1 | % | 36.0 – 47.0 | |
| MCV | 87.8 | fL | 78.0 – 95.0 | |
| MCH | 30.1 | pg | 27.0 – 33.0 | |
| MCHC | 34.3 | g/dL | 31.0 – 36.0 | |
| Platelet | 386 | 10^3/μL | 140 – 400 | |
| RDW-CV | 11.8 | % | 11.5 – 14.5 | |
| PDW | 8.8 | fL | 9.0 – 17.0 | |
| MPV | 8.60 | fL | 9.30 – 12.10 | |
| Plateletcrit | 0.33 | % | 0.17 – 0.32 | |
| **WBC DC** | | | | |
| Neutrophil | 61.3 | % | 40.0 – 75.0 | |
| Lymphocyte | 30.0 | % | 20.0 – 50.0 | |
| Monocyte | 6.9 | % | 3.0 – 10.0 | |
| Eosinophil | 0.6 | % | 0.0 – 7.0 | |
| Basophil | 1.2 | % | 0.0 – 2.0 | |

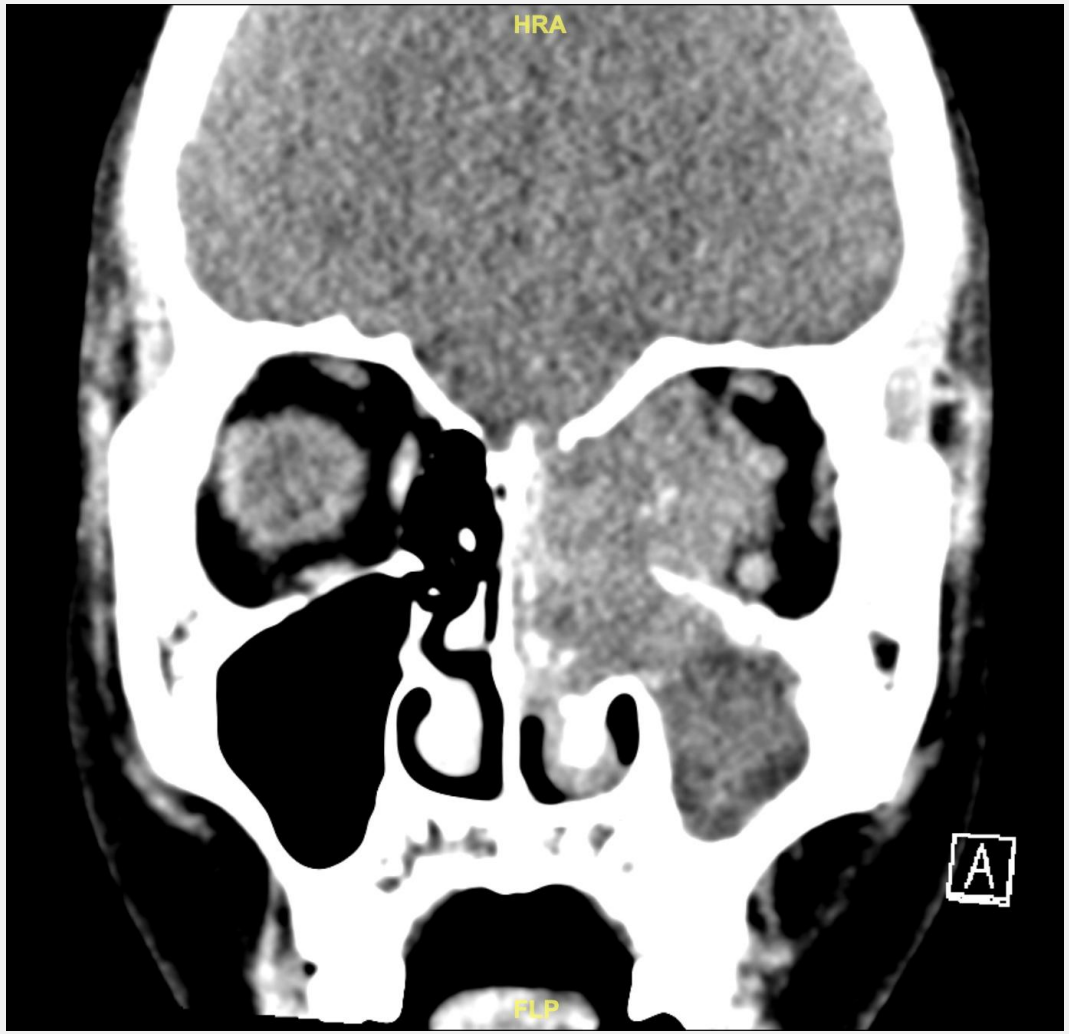
| [ Blood ] | | | | |
|---|---|---|---|---|
| C-ANCA (Anti-PR3) | <0.20 | IU/mL | – 2.00 | |
| **Antinuclear Ab (ANA)** | | | | |
| ANA | Negative (<1:80) | | – | |
| P-ANCA (Anti-MPO) | <0.20 | IU/mL | – 3.50 | |
| IgG | 902.9 | mg/dL | 635.0 – 1741.0 | |
| IgG 4 level | 22.000 | mg/dL | 3.000 – 201.000 | |
| **[ Blood ]** | | | | |
| **PT** | | | | |
| PT | 11.5 | sec | 8.0 – 12.0 | |
| INR | 1.15 | | 0.80 – 1.20 | |
| **APTT** | | | | |
| APTT | 28.1 | sec | 23.3 – 35.8 | |
| ESR | 4 | mm/hr | 0 – 10 | |

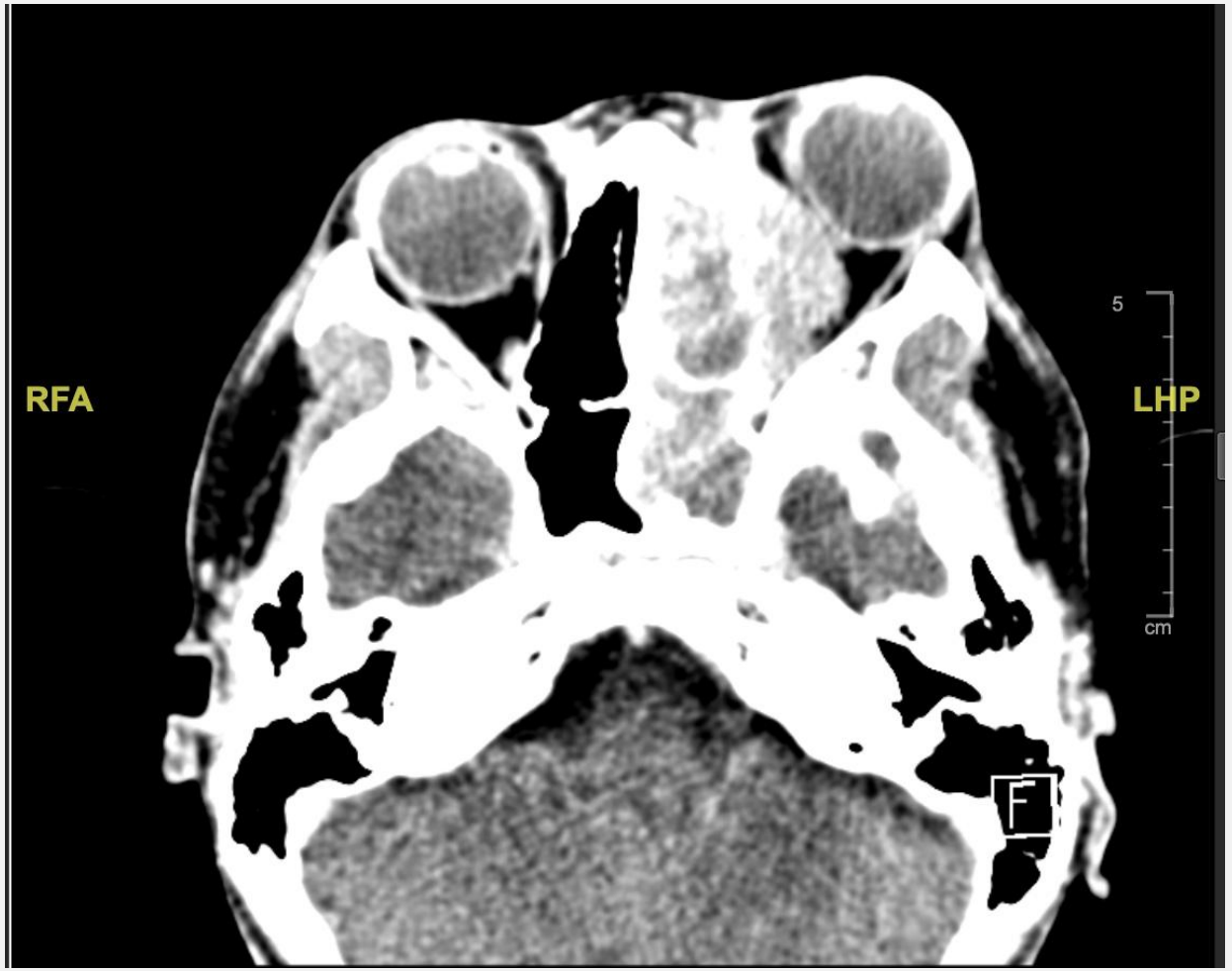
| [ Blood ] | | | | |
|---|---|---|---|---|
| Na | 134 | mmol/L | 134 – 143 | |
| K | 4.1 | mmol/L | 3.3 – 4.6 | |
| **Creatinine & eGFR** | | | | |
| Creatinine | 0.40 | mg/dL | 0.57 – 0.80 | |
| ALT | 6 | U/L | 5 – 45 | |
| CRP | <0.030 | mg/dL | 0.000 – 1.000 | |

# CXR AT ER



# ORBITAL CT



# CT REPORT

- Presence of proptosis. The distance from anterior margin of globe to interzygomatic line: Right: 1.8 cm; Left : 2.7 cm
- No obvious enhancing space occupying lesion in visible part of the brain parenchyma.

- **Impression**:
  - Enhanced mass with hypoenhanced foci in left maxillary and ethmoid sinus with bony erosion and intraorbital extension, lacrimal duct invasion, favor sinusitis,
  - DDx: orbital cellulitis.

# 8/23 ENT. CONSULTATION

- Impression
  - left nasal cavity tumor with bony erosion and intraorbital extension, suspect left sinonasal tumor with orbital involvement such as rhabdomycosarcoma, olfactory neuroblastoma or lymphoma
  - left sinusitis
- Plan:
  - adequate pain control
  - IV antibiotics usage and hydration
  - other symptomatic treatment agents
  - well explained current condition and treatment plan to patient and her family, arrange emergent navigator left FESS+/- left
  - pre op survey

# SYMPTOM PROGRESSION

8/23

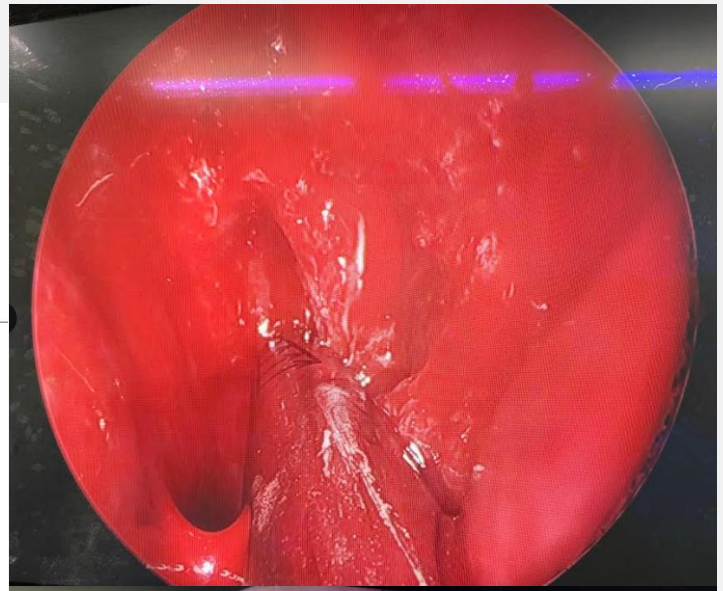
- BCVA: (OD) 0.8 (-7.0/-2.5x5) (OS) 0.5 (-6.5/-2.75x155)
- IOP: (OD) 19.3 (OS) 19.4
- Appearance: left proptosis, left upper and lower eyelid erythema, no palpable nodule, no pus, no heat
- Conj: (OD) clear (OS) mild injection, no corkscrew vessel
- Cornea: (OU) clear
- AC: (OU) D/Cl
- Lens: (OU) clear

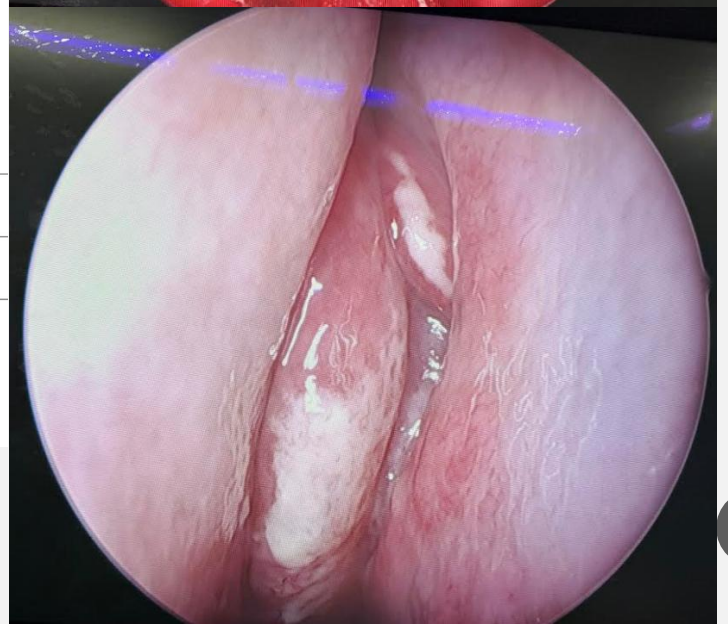
8/25

- BCVA(od)0.7 (os)ND/15 cm
- IOP(od)20.9 (os)23.1
- cornea(ou)claer
- AC(ou)deep/clear
- lens(ou) clear conj(os) mild injected , no obvisou cheomosis
- EOM(od) f&f (os) nearly frozen

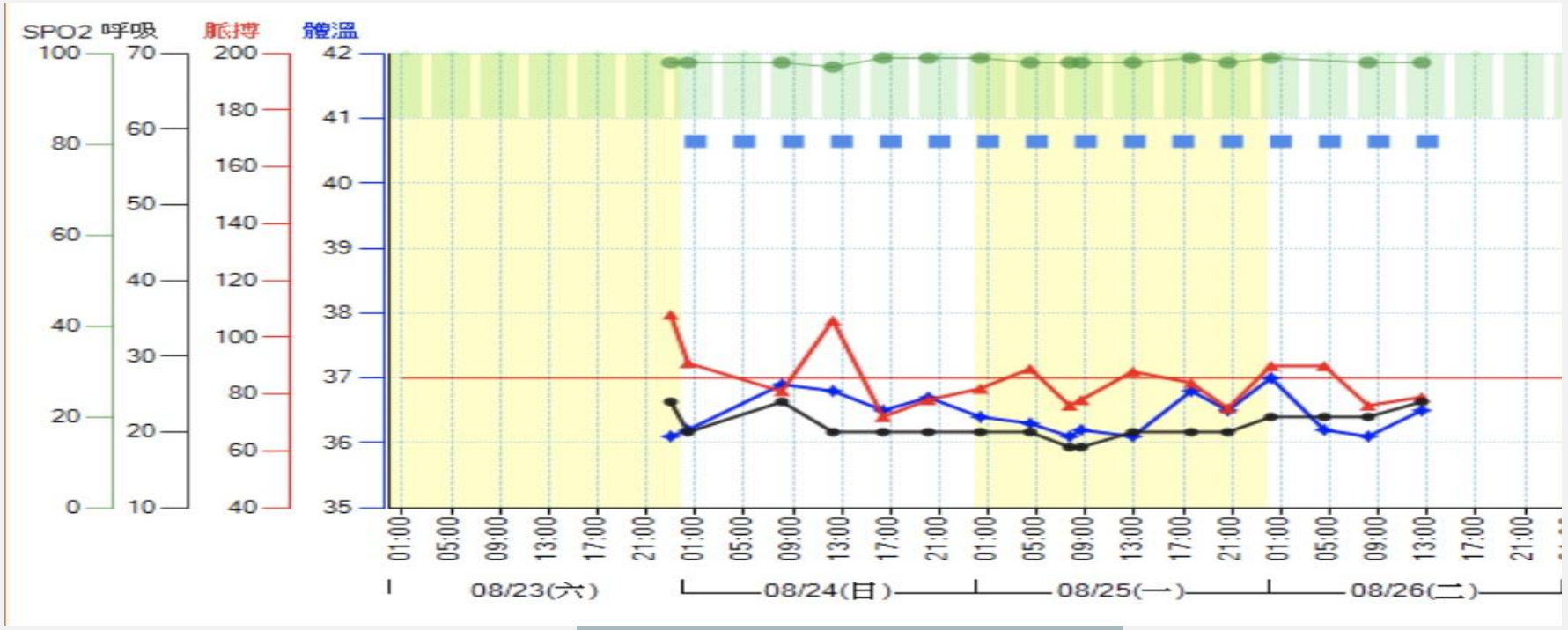
# OPERATION

| | |
|---|---|
| 手術內容 | 1.Stereotaxic procedure– for biopsy<br>2.導航手術微創刀片<br>3.Sinoscopy<br>4.SMT–unilateral<br>5.Multiple sinusectomy |
| 手術發現 | 1. bilateral hypertrophic inferior turbinates<br><br>Left side<br>ok edematous mucopus polypoid polyps tumor<br>Inf _____V_____<br>AE _____V_____<br>PE _____V_____<br>Max _____V_____<br>Fro _____<br>Sph _____ |
| 手術時間 | 2 小時 0 分鐘 |
| 病理檢體 | 有，送檢1件。 |
| 手術程序 | 1.Left inferior turbinectomy was performed with scissors<br>2.The left nasal cavity packing done.<br>3.Bleeding was checked and hemostasis was confirmed. |





# CLINICAL COURSE. 8/23-8/26




Cefazolin

Tazocin

ER admission

OP

Blurry vision
couldn't identify number
of fingers above 15cm

AAD

# PATHOLOGIC REPORT

## Finding:

The specimen submitted consists of multiple tissue fragments, measuring up to 0.9 x 0.7 x 0.2 cm in size, fixed in formalin.
Grossly, they are brown and firm.
All for section.

Microscopically, section shows respiratory mucosa with subepithelial sheets of small primitive round cells having scant cytoplasm. By immunohistochemistry, the tumor cells are Desmin (+, diffuse), Myogenin (+, partial), MyoD1 (+, partial), Synaptophysin (+, partial), Calretinin (-), S100 (-), CK(-), CD99 (-), CD34 (-), and CD45 (-).

Taken together, rhabdomyosarcoma is diagnosed, and embryonal rhabdomyosarcoma is firstly considered.
Anaplasia is not identified in this specimen.

## Impression:

Paranasal sinus, left, FESS, rhabdomyosarcoma

帶入報告

*Immunostain for PAX5 is negative.*

# FINAL DIAGNOSIS

- Left sinonasal rhabdomyosarcoma with orbital invasion
  s/p left FESS + left SMT with Navigation on 2025-08-23

# PART 2

- Discussion:
Overview of Rhabdomyosarcoma

Published in final edited form as:

*Nat Rev Dis Primers*. ; 5(1): 1. doi:10.1038/s41572-018-0051-2.

# Rhabdomyosarcoma

**Stephen X. Skapek**[1,2], **Andrea Ferrari**[3], **Abha Gupta**[4], **Philip J. Lupo**[5], **Erin Butler**[1], **Janet Shipley**[6], **Frederic G. Barr**[7], **Douglas S. Hawkins**[8]

[1]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2]Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

[3]Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

[4]Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, ON, CA

[5]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX, USA

[6]Divisions of Molecular Pathology and Cancer Therapeutics, The Institute of Cancer Research, Belmont, UK

[7]Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

[8]Seattle Children's Hospital, University of Washington, and Fred Hutchinson Cancer Research Center, Seattle, WA

# OUTLINE

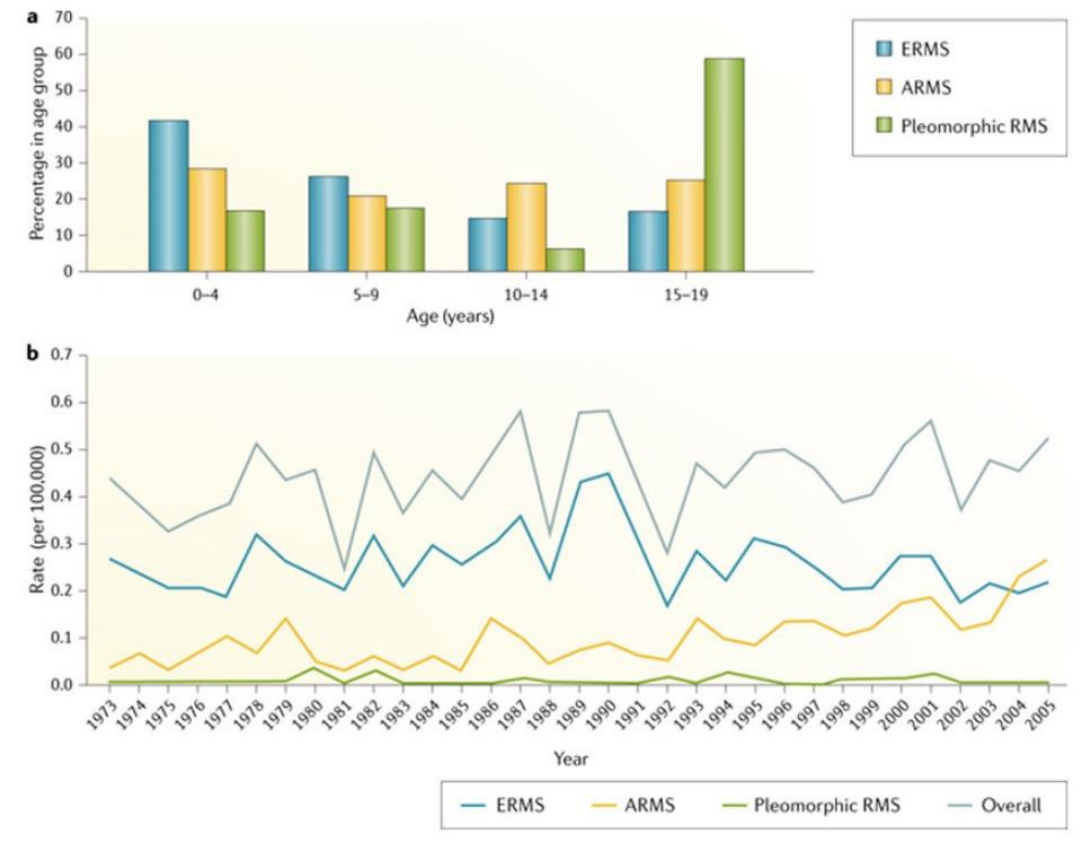
- Epidemiology
- Risk factors
- Classifications
- Treatment

# INTRODUCTION

- 50% of pediatric soft tissue sarcomas.
- Two main histologic subtypes:
  - **Embryonal (ERMS)** and **Alveolar (ARMS)**
- Biologically now categorized as
  - **Fusion-Positive (FP; PAX3/7–FOXO1)** and **Fusion-Negative (FN)** RMS.
- Major groups:
  - COG (US/Canada), EpSSG (Europe), CWS (German).

# EPIDEMIOLOGY AND RISK

- Incidence: **~4.5/million <20 years** in US & Europe (~350 new US cases/year).
- Asia: lower incidence (~2/million).
- Sweden: 4.9/million <15 yrs.
- Peak ages:
  - ERMS: bimodal (infancy & adolescence).
  - ARMS: constant across childhood/adolescence



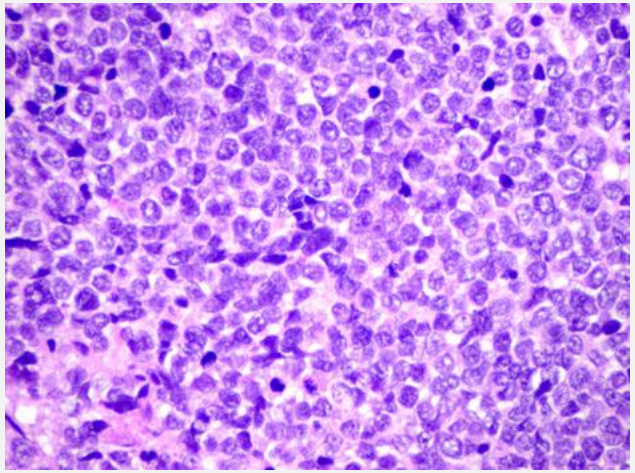

Nat Rev Dis Primers . Author manuscript; 2020 August 30.

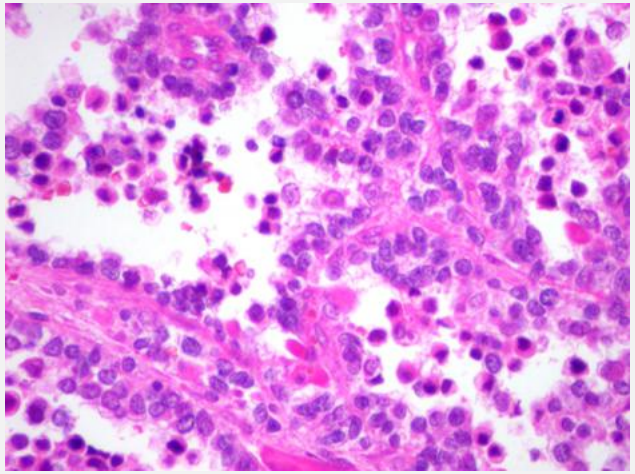
# RISK FACTORS

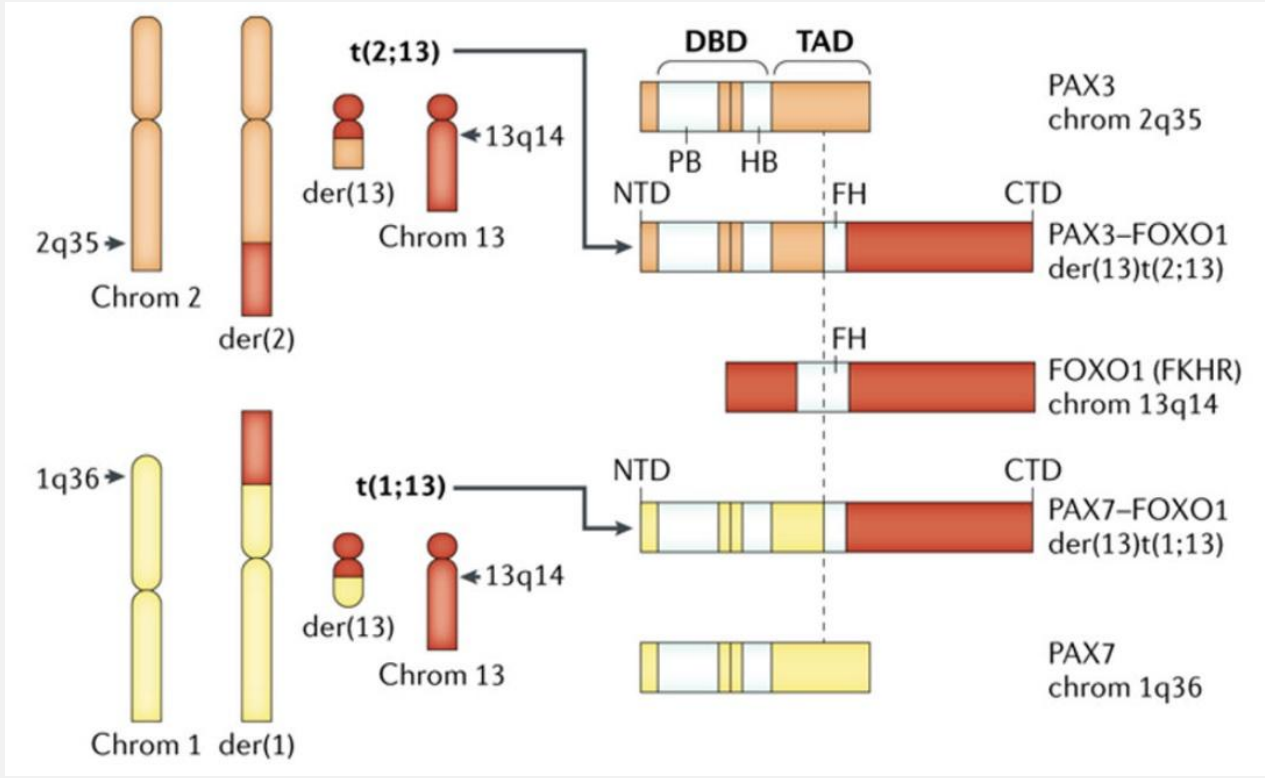
- **Genetic predisposition syndromes (~5% cases):**
  - Li-Fraumeni (TP53), NF1, Costello (HRAS), Noonan (RAS-MAPK), Beckwith-Wiedemann, DICER1.
- **Environmental exposures (case–control studies):**
  - Prenatal X-ray, parental drug use, maternal age extremes.
- Males > females for ERMS (M:F ~1.5:1)

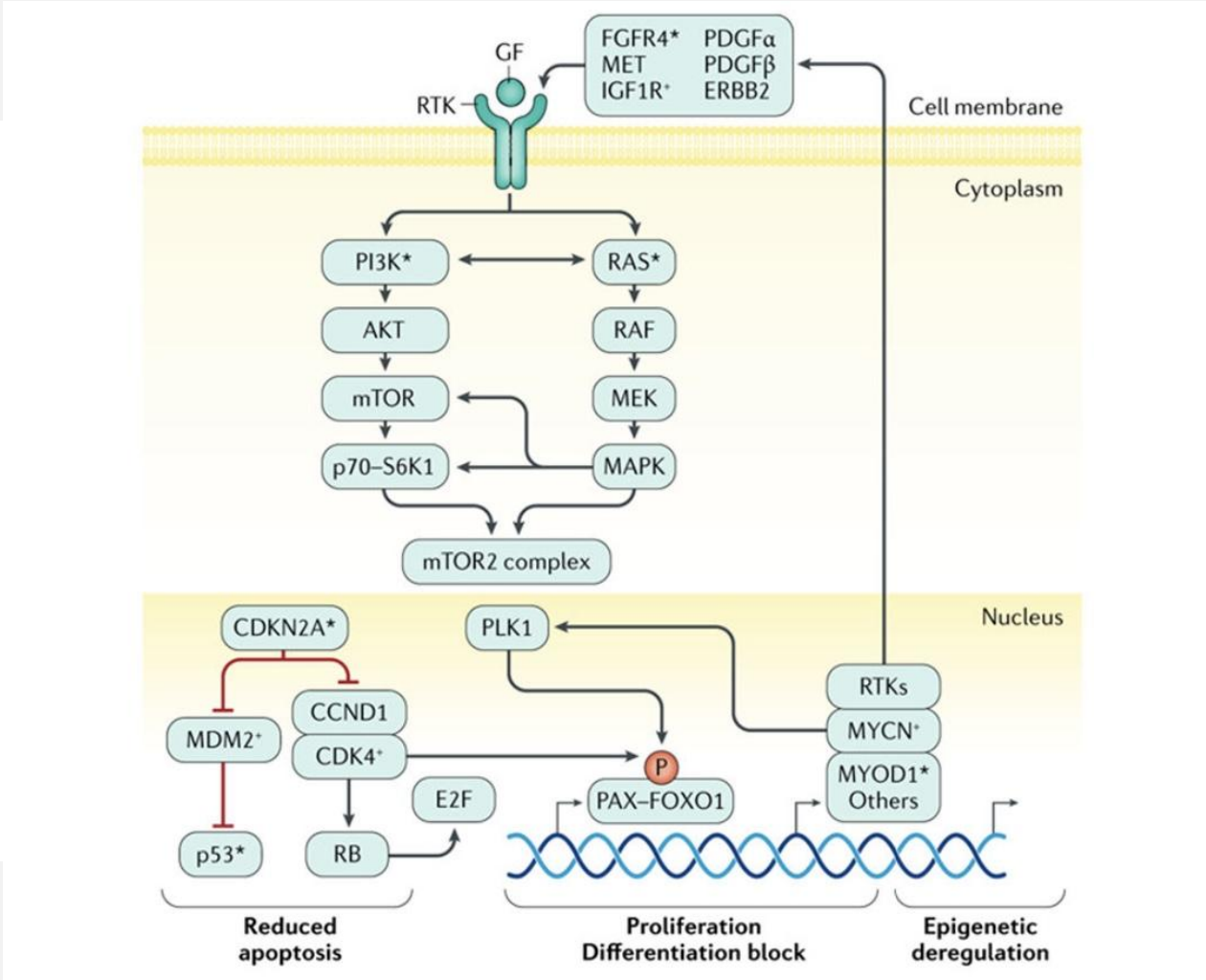
# PATHOGENESIS AND BIOLOGY

- **FP RMS**: Translocations t(2;13) or t(1;13) → PAX3/7–FOXO1 fusion proteins.
  - Act as potent transcription factors, creating super-enhancers regulating MYCN, FGFR4, ALK, MET, IGF1R.
  - Collaborate with epigenetic regulators (BRD4, CHD4, PRC2).
- **FN RMS**: Characterized by RAS/PI3K/MAPK mutations, 11p15.5 abnormalities, MYOD1 mutations (aggressive subtype).
- Tumor biology involves disrupted differentiation, oncogenic signaling, immune evasion, and metastatic capacity.





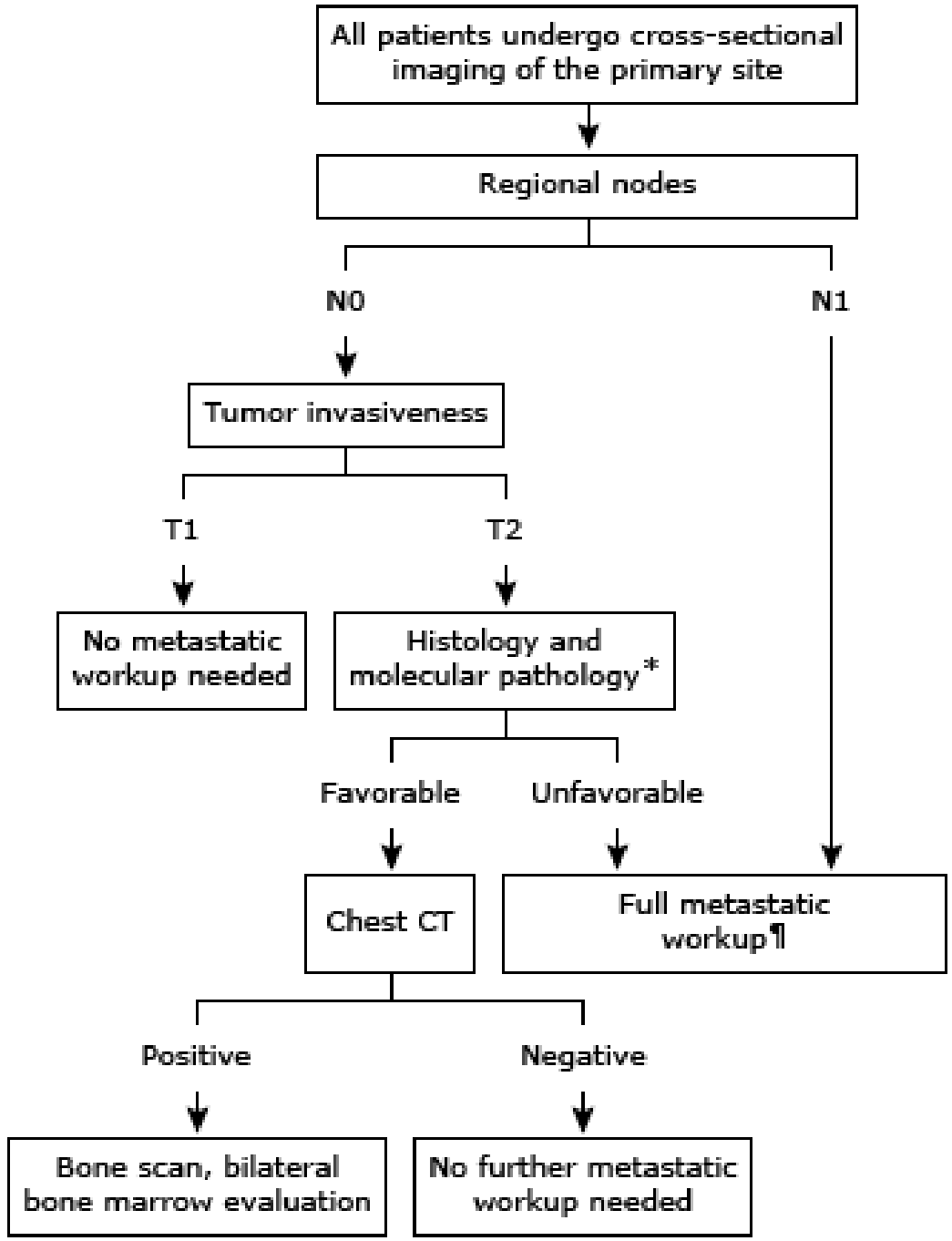



Nat Rev Dis Primers . Author manuscript; 2020 August 30.

# CLINICAL PRESENTATION

- Primary sites:
  - ERMS → head/neck (orbit), genitourinary tract.
  - ARMS → extremities, trunk.
- 20% metastatic at diagnosis (lung, bone, marrow).
- Typical sign: painless mass; unique features:
  - Orbital: unilateral proptosis.
  - Vaginal: "grape-like" botryoid mass.




**Prognosis of nonmetastatic rhabdomyosarcoma according to site of primary tumor from two different clinical trials**

| Site of primary tumor | Five year rates, percent | | | |
|---|---|---|---|---|
| | MMT-89 | | IRS-IV | |
| | OS | EFS | OS | EFS |
| Orbit | 85 | 53 | 100 | 93 |
| Genitourinary (not bladder or prostate) | 94 | 82 | 90 | 83 |
| Genitourinary (bladder or prostate) | 80 | 64 | 86 | 79 |
| Head and neck (nonparameningeal) | 64 | 35 | 89 | 83 |
| Head and neck (parameningeal) <3 years of age | 59 | 33 | 64 | 60 |
| Head and neck (parameningeal) ≥3 years of age | 65 | 62 | 78 | 73 |
| Limbs | 46 | 35 | 71 | 64 |
| Other | 63 | 54 | 81 | 77 |

MMT-89: International Society of Pediatric Oncology Malignant Mesenchymal Tumor Study-89; IRS-IV: Intergroup Rhabdomyosarcoma Study Group IV protocol; OS: overall survival; EFS: event-free survival.

*Data from: Donaldson SS, Anderson JR. Rhabdomyosarcoma: many similarities, a few philosophical differences. J Clin Oncol 2005; 23:2586.*

# THREE WAYS TO DESCRIBE THE CANCER

- TNM staging
- Clinical grouping by IRSG
- Risk stratification by COG

## TNM staging system for rhabdomyosarcoma

| Stage | Sites | Tumor stage invasiveness | T stage size | N | M |
|---|---|---|---|---|---|
| 1 | Orbit<br>Head and neck*<br>Genitourinary¶ | $T_1$ or $T_2$ | a or b | Any N | $M_0$ |
| 2 | Bladder/prostate<br>Extremity<br>Cranial parameningeal<br>Other$^{\Delta}$ | $T_1$ or $T_2$ | a | $N_0$ or $N_X$ | $M_0$ |
| 3 | Bladder/prostate<br>Extremity<br>Cranial parameningeal<br>Other$^{\Delta}$ | $T_1$ or $T_2$ | a | N1 | $M_0$ |
| | | | b | Any N | |
| 4 | All | $T_1$ or $T_2$ | a or b | $N_0$ or $N_1$ | $M_1$ |

| T: Tumor stage | N: Regional nodes | M: Metastases |
|---|---|---|
| $T_1$: Confined to anatomic site of origin<br>$T_2$: Extension<br>a: ≤5 cm in diameter<br>b: >5 cm in diameter | $N_0$: Not clinically involved<br>$N_1$: Clinically involved<br>$N_X$: Clinical status unknown | $M_0$: No distant metastases<br>$M_1$: Distant metastases present (lung, bone, bone marrow, or presence of cells in cerebrospinal, pleural, or peritoneal fluid cytology) |

* Excluding parameningeal.

¶ Nonbladder/nonprostate.

Δ Includes trunk, retroperitoneum, biliary tract, etc.

## Clinical grouping of rhabdomyosarcoma by the intergroup rhabdomyosarcoma study group (IRSG)

| Clinical group | Extent of disease/surgical result |
|---|---|
| I | **A** Localized tumor, confined to site of origin, completely resected |
| | **B** Localized tumor, infiltrating beyond site of origin, completely resected |
| II | **A** Localized tumor, gross total resection, but with microscopic residual disease |
| | **B** Locally extensive tumor (spread to regional lymph nodes), completely resected |
| | **C** Locally extensive tumor (spread to regional lymph nodes), gross total resection, but microscopic residual disease |
| III | **A** Localized or locally extensive tumor, gross residual disease after biopsy only |
| | **B** Localized or locally extensive tumor, gross residual disease after major resection (≥50% debulking) |
| IV | Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor |

## Rhabdomyosarcoma prognostic stratification

| Prognosis (EFS) | Stage | Clinical group | Site | Size | Age | FOXO1 fusion status* | Mets | Nodes |
|---|---|---|---|---|---|---|---|---|
| Excellent (>85%) Low risk subset A | 1 | I | Favorable | a or b | <21 | Negative | M0 | N0 |
| | 1 | II | Favorable | a or b | <21 | Negative | M0 | N0 |
| | 1 | III | Orbit only | a or b | <21 | Negative | M0 | N0 |
| | 2 | I | Unfavorable | a | <21 | Negative | M0 | N0 or NX |
| | 1 | II | Favorable | a or b | <21 | Negative | M0 | N1 |
| Very good (70 to 85%) Low risk subset B | 1 | III | Orbit only | a or b | <21 | Negative | M0 | N1 |
| | 1 | III | Favorable, excluding orbit | a or b | <21 | Negative | M0 | N0 or N1 or NX |
| | 2 | II | Unfavorable | a | <21 | Negative | M0 | N0 or NX |
| | 3 | I or II | Unfavorable | a | <21 | Negative | M0 | N1 |
| | 3 | I or II | Unfavorable | b | <21 | Negative | M0 | N0 or N1 or NX |
| Good (50 to 70%) Intermediate risk | 2 | III | Unfavorable | a | <21 | Negative | M0 | N0 or NX |
| | 3 | III | Unfavorable | a | <21 | Negative | M0 | N1 |
| | 3 | III | Unfavorable | b | <21 | Negative | M0 | N0 or N1 or NX |
| | 1, 2, 3 | I, II, III | Favorable or unfavorable | a or b | <21 | Positive | M0 | N0 or N1 or NX |
| | 4 | IV | Favorable or unfavorable | a or b | <10 | Negative | M1 | N0 or N1 or NX |
| Poor (<30%) High risk | 4 | IV | Favorable or unfavorable | a or b | ≥10 | Negative | M1 | N0 or N1 or NX |
| | 4 | IV | Favorable or unfavorable | a or b | <21 | Positive | M1 | N0 or N1 or NX |

- **Stage (1–4):** anatomic site, tumor size, node/metastasis status.
- **Clinical Group (I–IV):** surgical/pathological resection status.
- Fusion status & number of metastatic sites now incorporated.
- Prognostic metagene signature (MG5) validated in European & COG cohorts.

# GENERAL PRINCIPALS FOR TREATMENT

- Multimodal: Surgery + Radiation + Chemotherapy.

- 5-year OS improved to >70% with cooperative trials.

# RADIAL THERAPY

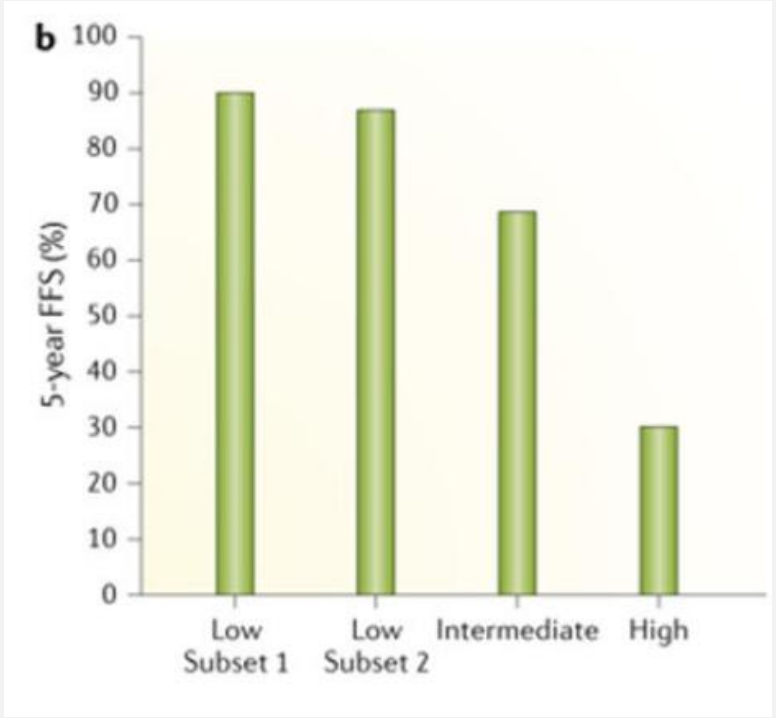
- **Primary goal:** Enhance local control after surgery/chemotherapy.
- **Indications:** All patients except **CG I, embryonal/ FN** tumors.
  - North American guidelines recommend RT for **all alveolar histology (fusion±)** even in CG I.
- **Timing**
  - **Standard:** RT begins **after 4 cycles of chemotherapy**.
  - **Emergency (Day 0):** Only for vision loss or spinal cord compression.
  - **Historic trials:** Earlier RT (week 4, lower cyclophosphamide) → worse local control than later RT (week 13, higher cyclophosphamide).
  - **Current trend:** Balance intensity of chemotherapy with RT timing.

# RADIAL THERAPY

- **Orbit**
  - Historically 50.4–59.4 Gy used.
  - Data suggest **45 Gy + alkylating chemotherapy** can achieve similar local control.
  - 13–16% local recurrence risk at 45 Gy without cyclophosphamide.
- **Parameningeal Sites**
  - Require ≥**50.4–55 Gy** to tumor, adjacent meninges, intracranial extension.
  - Proton therapy reduces late effects.
  - **CSF positive:** Craniospinal RT.
  - **Brain metastases without CSF involvement:** Whole-brain RT.
- **Metastatic Disease**
  - RT 50.4 Gy to primary and metastatic sites (orbit 45 Gy).
  - Whole-lung RT (14.4 Gy)

**Current standard chemotherapy regimens for newly diagnosed patients with rhabdomyosarcoma***

| Prognosis group¶ | Definition | Regimen | Dose△ | Schedule |
|---|---|---|---|---|
| **Low risk** | | | | |
| Subset A<br>Excellent prognosis<br>(>85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG I/II<br>▪ Stage 1 CG III orbital<br>▪ Stage 2 CG I/II | VA per subset A regimen of D9602 × 15 cycles (45 weeks)[1] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 0 to 8, 12 to 20, 24 to 32, and 36 to 44 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 0 through 45◇ |
| | | **or** | | |
| | | VAC/VA per subset A regimen of ARST0331 × 8 cycles (24 weeks)§[2] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 9 and 13 to 21 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 to 22◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and as-needed hematopoietic growth factor support | Every 3 weeks during weeks 1 to 10 for a total of 4 doses |
| Subset B<br>Very good prognosis<br>(70 to 85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG III non-orbit<br>▪ Stage 3 CG I/II | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **Intermediate risk** | | | | |
| Good prognosis<br>(50 to 70% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 2/3 CG III<br>▪ Metastatic disease, age <10 years<br>Alveolar fusion-positive tumors:<br>▪ CG I to III | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **High risk** | | | | |
| Poor prognosis<br>(<30% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Metastatic disease, age >10 years<br>Alveolar fusion-positive tumors:<br>▪ Metastatic disease, any age | VAC × 14 cycles (40 weeks)‡[4] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |




Nat Rev Dis Primers . Author manuscript; 2020 August 30.

**Current standard chemotherapy regimens for newly diagnosed patients with rhabdomyosarcoma***

| Prognosis group¶ | Definition | Regimen | Dose△ | Schedule |
|---|---|---|---|---|
| **Low risk** | | | | |
| Subset A<br>Excellent prognosis<br>(>85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG I/II<br>▪ Stage 1 CG III orbital<br>▪ Stage 2 CG I/II | VA per subset A regimen of D9602 × 15 cycles (45 weeks)[1] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 0 to 8, 12 to 20, 24 to 32, and 36 to 44 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 0 through 45◇ |
| | | **or** | | |
| | | VAC/VA per subset A regimen of ARST0331 × 8 cycles (24 weeks)§[2] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 9 and 13 to 21 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 to 22◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and as-needed hematopoietic growth factor support | Every 3 weeks during weeks 1 to 10 for a total of 4 doses |
| Subset B<br>Very good prognosis<br>(70 to 85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG III non-orbit<br>▪ Stage 3 CG I/II | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **Intermediate risk** | | | | |
| Good prognosis<br>(50 to 70% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 2/3 CG III<br>▪ Metastatic disease, age <10 years<br>Alveolar fusion-positive tumors:<br>▪ CG I to III | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **High risk** | | | | |
| Poor prognosis<br>(<30% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Metastatic disease, age >10 years<br>Alveolar fusion-positive tumors:<br>▪ Metastatic disease, any age | VAC × 14 cycles (40 weeks)ǂ[4] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |

## Low-Risk Disease (COG Subsets)

- Subset A (best prognosis): VA-only (D9602) **or** short VAC→VA (ARST0331).
  - ~3–5 yr FFS ≈ 85–90%, OS >90%.
- Subset B: needs higher cyclophosphamide (D9602).
- Very-low-risk (ARST2032): CG I Stage I without MYOD1/TP53 → VA x ~24 wks.

**Current standard chemotherapy regimens for newly diagnosed patients with rhabdomyosarcoma***

| Prognosis group¶ | Definition | Regimen | Dose△ | Schedule |
|---|---|---|---|---|
| **Low risk** | | | | |
| Subset A<br>Excellent prognosis<br>(>85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG I/II<br>▪ Stage 1 CG III orbital<br>▪ Stage 2 CG I/II | VA per subset A regimen of D9602 × 15 cycles (45 weeks)[1] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 0 to 8, 12 to 20, 24 to 32, and 36 to 44 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 0 through 45◇ |
| | | **or** | | |
| | | VAC/VA per subset A regimen of ARST0331 × 8 cycles (24 weeks)§[2] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 9 and 13 to 21 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 to 22◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and as-needed hematopoietic growth factor support | Every 3 weeks during weeks 1 to 10 for a total of 4 doses |
| Subset B<br>Very good prognosis<br>(70 to 85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG III non-orbit<br>▪ Stage 3 CG I/II | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **Intermediate risk** | | | | |
| Good prognosis<br>(50 to 70% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 2/3 CG III<br>▪ Metastatic disease, age <10 years<br>Alveolar fusion-positive tumors:<br>▪ CG I to III | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **High risk** | | | | |
| Poor prognosis<br>(<30% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Metastatic disease, age >10 years<br>Alveolar fusion-positive tumors:<br>▪ Metastatic disease, any age | VAC × 14 cycles (40 weeks)ǂ[4] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |

## INTERMEDIATE-Risk Disease (COG Subsets). OS=60-70%

- Definitions vary by protocol
  - Nonmetastatic alveolar rhabdomyosarcoma.
  - Stage 2 or 3, Clinical Group III embryonal rhabdomyosarcoma.
  - Some protocols also include children ≤10 years with Stage 4 embryonal disease.
- VAC/VI (irinotecan) vs VAC (ARST0531): similar OS/EFS, less heme tox with VAC/VI but higher local failures vs D9803 (lower cyclophosphamide dose, earlier RT).
- Off-protocol preference: use higher cumulative cyclophosphamide (D9803-like) if toxicity acceptable.

**Current standard chemotherapy regimens for newly diagnosed patients with rhabdomyosarcoma***

| Prognosis group¶ | Definition | Regimen | Dose△ | Schedule |
|---|---|---|---|---|
| **Low risk** | | | | |
| Subset A<br>Excellent prognosis<br>(>85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG I/II<br>▪ Stage 1 CG III orbital<br>▪ Stage 2 CG I/II | VA per subset A regimen of D9602 × 15 cycles (45 weeks)[1] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 0 to 8, 12 to 20, 24 to 32, and 36 to 44 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 0 through 45◇ |
| | | **or** | | |
| | | VAC/VA per subset A regimen of ARST0331 × 8 cycles (24 weeks)§[2] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 9 and 13 to 21 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 to 22◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and as-needed hematopoietic growth factor support | Every 3 weeks during weeks 1 to 10 for a total of 4 doses |
| Subset B<br>Very good prognosis<br>(70 to 85% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 1 CG III non-orbit<br>▪ Stage 3 CG I/II | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **Intermediate risk** | | | | |
| Good prognosis<br>(50 to 70% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Stage 2/3 CG III<br>▪ Metastatic disease, age <10 years<br>Alveolar fusion-positive tumors:<br>▪ CG I to III | VAC × 14 cycles (40 weeks)¥[3] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31, 34 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 2200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |
| **High risk** | | | | |
| Poor prognosis<br>(<30% EFS) | Embryonal and alveolar fusion-negative tumors:<br>▪ Metastatic disease, age >10 years<br>Alveolar fusion-positive tumors:<br>▪ Metastatic disease, any age | VAC × 14 cycles (40 weeks)‡[4] | | |
| | | Vincristine | 1.5 mg/m$^2$ (max 2 mg) | Weekly during weeks 1 to 13, 16, 19 to 25, 28, 31 to 37, and 40 |
| | | Dactinomycin | 0.045 mg/kg (max 2.5 mg) | Every 3 weeks during weeks 1 through 40◇ |
| | | Cyclophosphamide | 1200 mg/m$^2$ with mesna and hematopoietic growth factor support | Every 3 weeks during weeks 1 through 40 |

# High-Risk / Metastatic **(COG Subsets)**

- Five-year EFS often ~20–40% overall; heterogeneity by Oberlin factors (age <1/≥10, unfavorable site, bone/bone marrow, ≥3 mets).
- ARST0431 dose-dense multi-agent: better for <2 Oberlin factors; otherwise limited gains and high toxicity/cost.
- Intensive regimens (example: alternating vincristine/doxorubicin/cyclophosphamide with ifosfamide/etoposide) have not improved survival compared with standard VAC.
- Most effective approach remains enrollment in clinical trials testing novel agents or strategies.

# TAKE HOME MASSAGE

- Fusion status (PAX–FOXO1) is the most powerful prognostic biomarker in RMS
- Chemo for all; RT tailored by CG/site/fusion; surgery aims for negative margins without crippling function.; VAC/IVA are backbones
- Emerging targets: IGF1R, FGFR, MET, epigenetic regulators, MYOD1-mutant RMS
- Prognosis has improved via multimodal therapy and cooperative group trials, but outcomes for metastatic/relapsed disease remain poor.

# THANK YOU !