# Ewing Sarcoma

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PEDIATRIC HEMATOLOGY-ONCOLOGY

UPR-RCM CCUPR-HOPU

# Outline

- Epidemiology
- Presentation
- Diagnosis
- Treatment

# Epidemiology

# Ewings Sarcoma

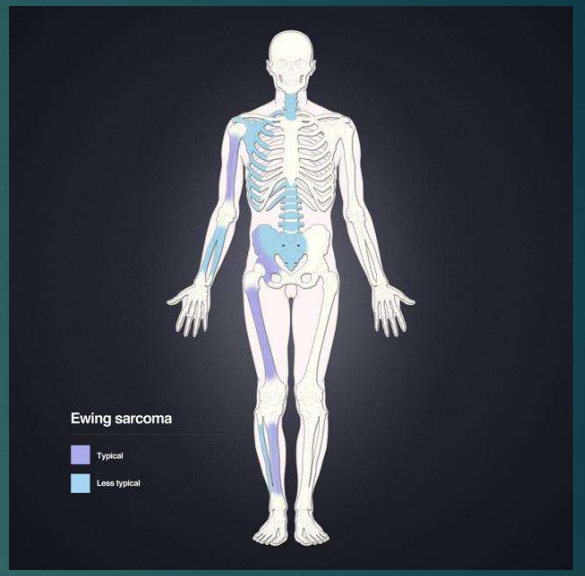
- Rare primary bone tumor and less often soft tissue (extraosseous)
- Second most common primary bone cancer
- Incidence: 200 case/yr
  - 10-14 yrs of age: 3.5%
  - 15-19 yrs of age: 2.3%
  - Whites > Blacks +Asian
- Inherited cancer: not typical but has been associated with the following genetic mutations:
  - TP53 (Li-Fraumeni)
  - RET gene (MEN2)
  - PMS2 (DNA mismatch repair)

https://seer.cancer.gov/archive/csr/1975_2018/

# Presentation

# Clinical presentation

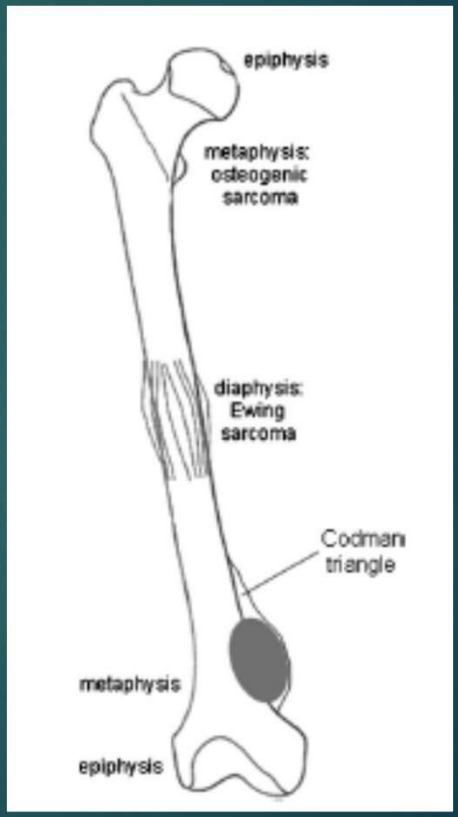
- Localized Painful expanding mass often associated with swelling
- Common locations:
  - 54% axial skeleton
  - 42% appendicular skeleton
  - 0.7% other bones
- 20-30% metastatic at presentation
  - Common Metastatic sites:
    - lung, bone marrow, bone
- Other non-specific symptoms:
  - Fatigue, Weight Loss, Fever
  - Petechiae, Anemia or other symptoms in the setting of bone marrow involvement




http://radiopaedia.org/articles/ewing-sarcoma

# Clinical presentation

- Often arises in diaphysis (shaft of bone)
- "Onion skinning" is common




Maki, Journal of Surgical Oncology, 2008

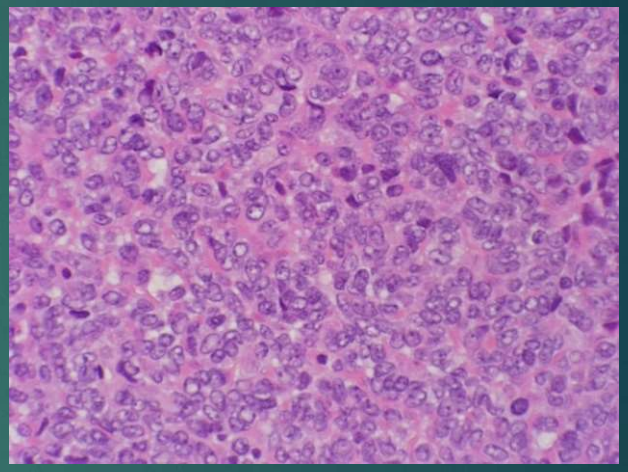
# Diagnosis

# Initial Evaluation

- Imaging
  - Xray
  - CT/MRI of affected area
  - CT chest/abdomen/pelvis
  - PET/CT
- Biopsy
  - Of primary lesion
  - Bilateral Bone marrow
- Labwork
  - CBC+diff
  - CMP
  - Urinalysis
  - LDH

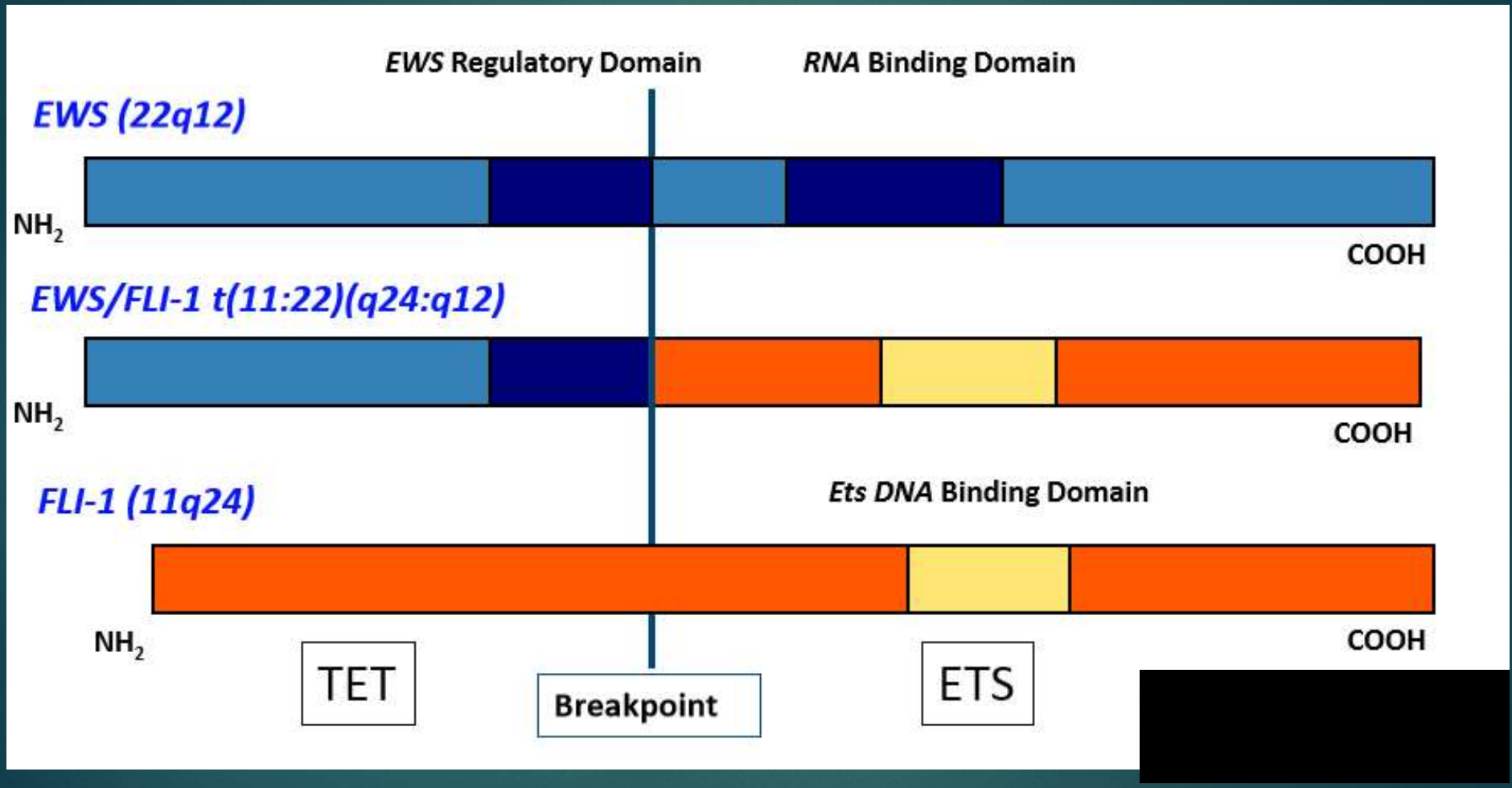
# Pathology

- Proposed Origin
  - Neuroectodermal cells
    - Variable neuronal immunohistochemical markers
    - Primitive Neuroectodermal Tumor
    - Askin Tumor (PNET of the chest wall)
  - Mesenchymal progenitor cells
    - Ewing Sarcoma of Bone
    - Extraosseous Ewing Sarcoma



- Undifferentiated small round blue cell tumor; must exclude lymphoma, NBL, RMS, other sarcomas
- CD99 antibody is positive but not specific for EWS

# Molecular Pathology



# Molecular pathology

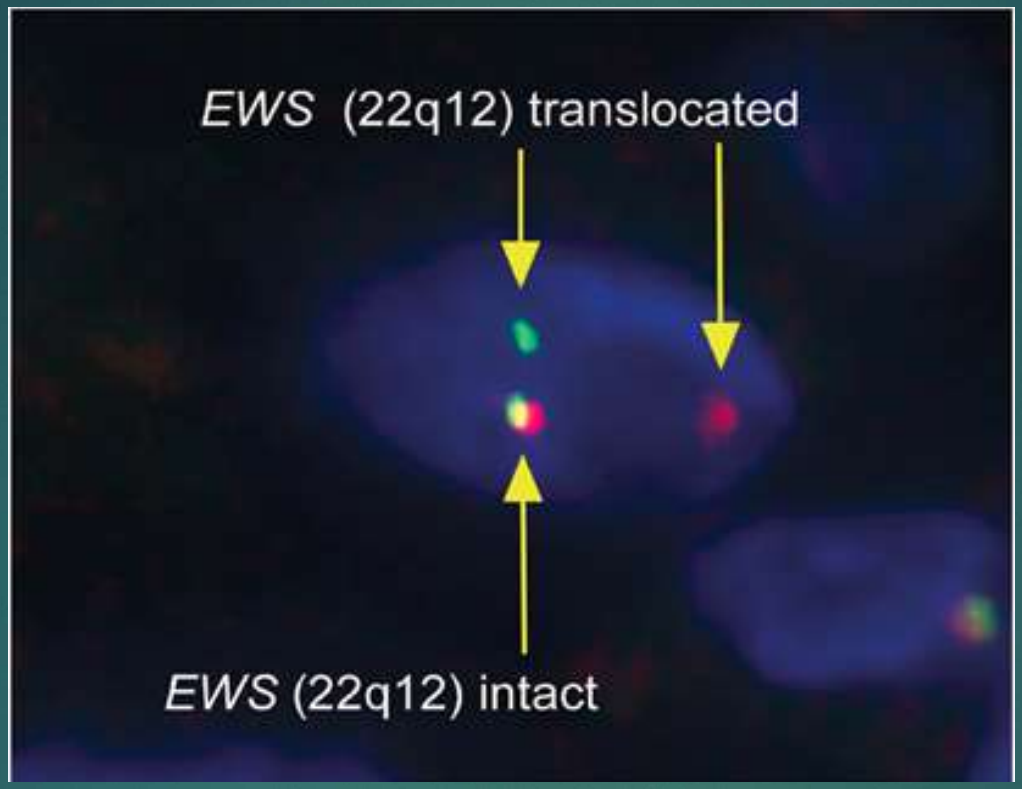
**1-Ewing sarcoma family of tumor (ESFT) with *EWSR1/FUS* rearrangement**

| | | |
|---|---|---|
| t(11;22)(q24;q12) | *EWSR1-FLI1* | ESFT |
| t(21;22)(q22;q12) | *EWSR1-ERG* | ESFT |
| t(7;22)(p22;q12) | *EWSR1-ETV1* | ESFT |
| t(17;22)(q21;q12) | *EWSR1-ETV4* | ESFT |
| t(2;22)(q35;q12) | *EWSR1-FEV* | ESFT |
| t(20;22)(q13;q12) | *EWSR1-NFATC2* | ESFT |
| t(2;22)(q31;q12) | *EWSR1-SP3* | ESFT |
| inv (22) | *EWSR1-PATZ1* | ESFT |
| t(4;22)(q31;q12) | *EWSR1-SMARCA5* | ESFT |
| t(16;21)(p11;q22) | *FUS-ERG* | ESFT |
| t(2;16)(q35;p11) | *FUS-FEV* | ESFT |

**2-Ewing-like sarcoma/ round cell sarcoma (*CIC-DUX4, CIC-FOX04, BCOR-CCNB3, CIC or BCOR rearrangement*)**

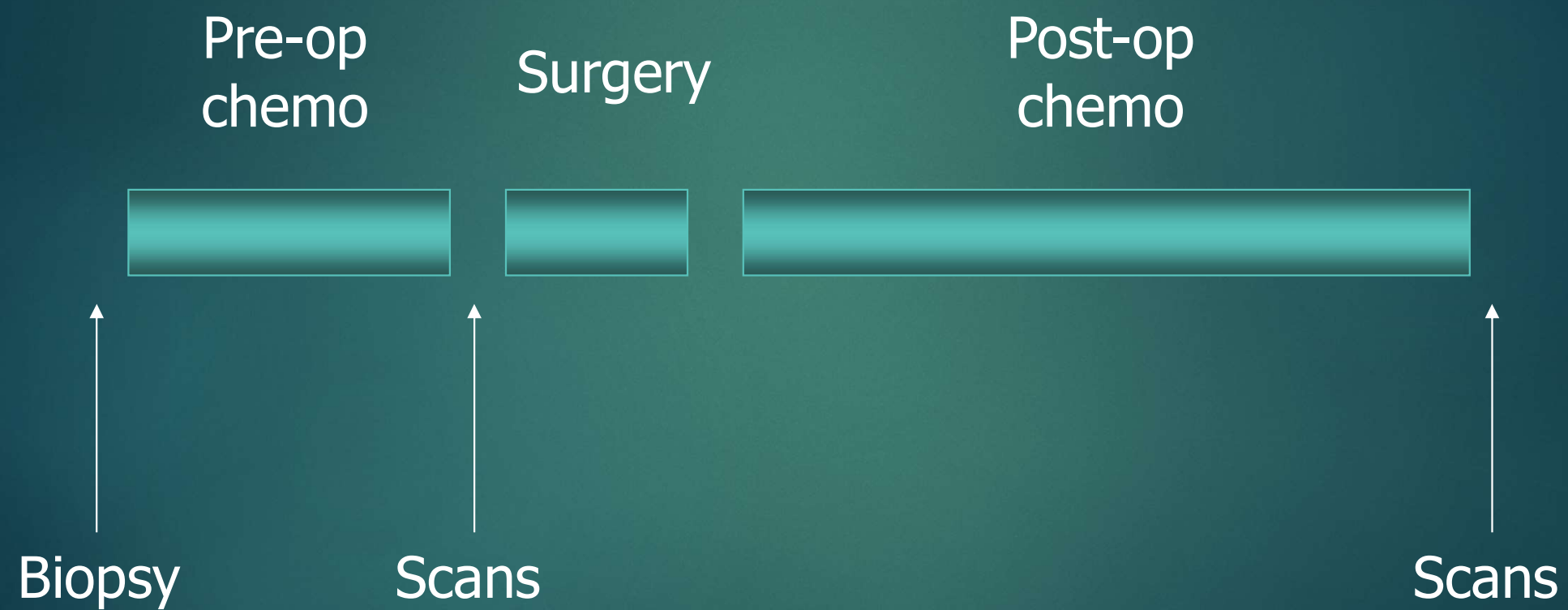
- **RT-PCR**: primers detect specific translocation
- **FISH**: EWS break-apart probes detect translocations involving EWS

# FISH: Break apart probe




# Treatment

# Treatment Overview



# Principles of treatment

- Local Control
  - Surgery
    - Preferred modality whenever a marginal or wide resection is possible
  - Radiation
    - Utilized when a gross total resection is not possible (55Gy)
    - May be used as adjuvant therapy in the case of an incomplete resection or (in Europe) if there is a poor histologic response to neoadjuvant chemotherapy
    - May (rarely) be indicated as neoadjuvant therapy if there is concern for residual tumor in the case of a planned complete resection – neoadjuvant radiation should NOT be given with intent of making an inoperable tumor operable
- Metastatic disease
  - Chemotherapy

# Evolution of chemotherapy

| Study | Observed Results | Ref | Conclusions |
|---|---|---|---|
| US intergroup IESSI 1972–78 (n = 342) Localized ES | 5-Year RFS<br>VAC 24%<br>VACD 60%<br>VAC + Lung RT 44% | 56 | VAC + doxorubicin better than VAC + lung irradiation, better than VAC for metastases prevention |

- VAC = Vincristine + Actinomycin D + Cyclophosphamide
- Doxorubicin offered a clear improvement in 5-year recurrence free survival

# Evolution of chemotherapy

| | | | |
|---|---|---|---|
| US intergroup IESSII 1978–82 (n = 214) Nonpelvic localized ES | VAC+ Dox ⇕ High-dose intermittent CT (every 3 weeks) 5-Year RFS 73%; Moderate-dose continuous CT (every week) 56%; $P = .04$ | 57 | Intensive intermittent chemotherapy regimen better than moderate-dose, continuous chemotherapy |

- VAC + Doxorubicin standard of care in next study
- High dose, intermittent chemotherapy preferable to lower dose, continuous chemotherapy

# Evolution of Chemotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing's Sarcoma and Primitive Neuroectodermal Tumor of Bone

Holcombe E. Grier, M.D., Mark D. Krailo, Ph.D., Nancy J. Tarbell, M.D., Michael P. Link, M.D., Christopher J.H. Fryer, M.D., Douglas J. Pritchard, M.D., Mark C. Gebhardt, M.D., Paul S. Dickman, M.D., Elizabeth J. Perlman, M.D., Paul A. Meyers, M.D., Sarah S. Donaldson, M.D., Sheila Moore, M.D., Aaron R. Rausen, M.D., Teresa J. Vietti, M.D., and James S. Miser, M.D.

N ENGL J MED 348;8 WWW.NEJM.ORG FEBRUARY 20, 2003

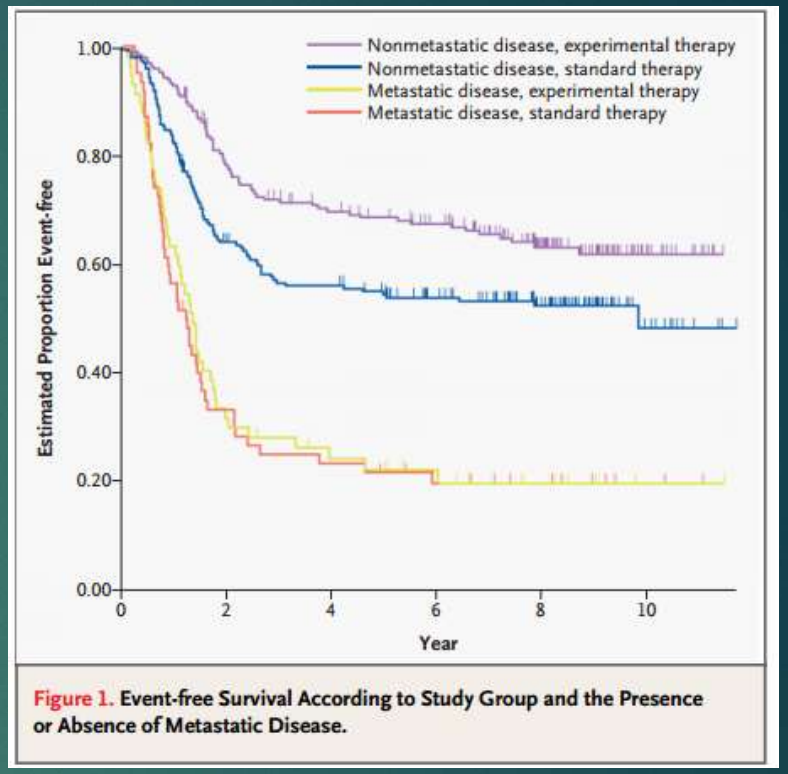



**Figure 1.** Event-free Survival According to Study Group and the Presence or Absence of Metastatic Disease.

- Addition of IE (Ifosfamide + Etoposide) to backbone of VAC + Doxorubicin improves event-free survival in nonmetastatic EWS
- Addition of IE does not improve event-free survival in metastatic EWS
- Growing sense that Actinomycin-D less efficacious than Doxorubicin (Actinomycin-D only administered when Doxorubicin dose reached 375 mg/m2)

# Evolution of chemotherapy

| | | | |
|---|---|---|---|
| COG<br>AEWS0031 2001–05<br>Localized ES<br>(n = 568) | 5-Year EFS<br>↗ VDC + IE (once every 3 weeks) 65%<br>↘ VDC + IE (once every 2 weeks) 73% ($P = .05$) | 61 | Chemotherapy administered every 2 weeks is more effective than chemotherapy administered every 3 weeks, with no increase in toxicity |

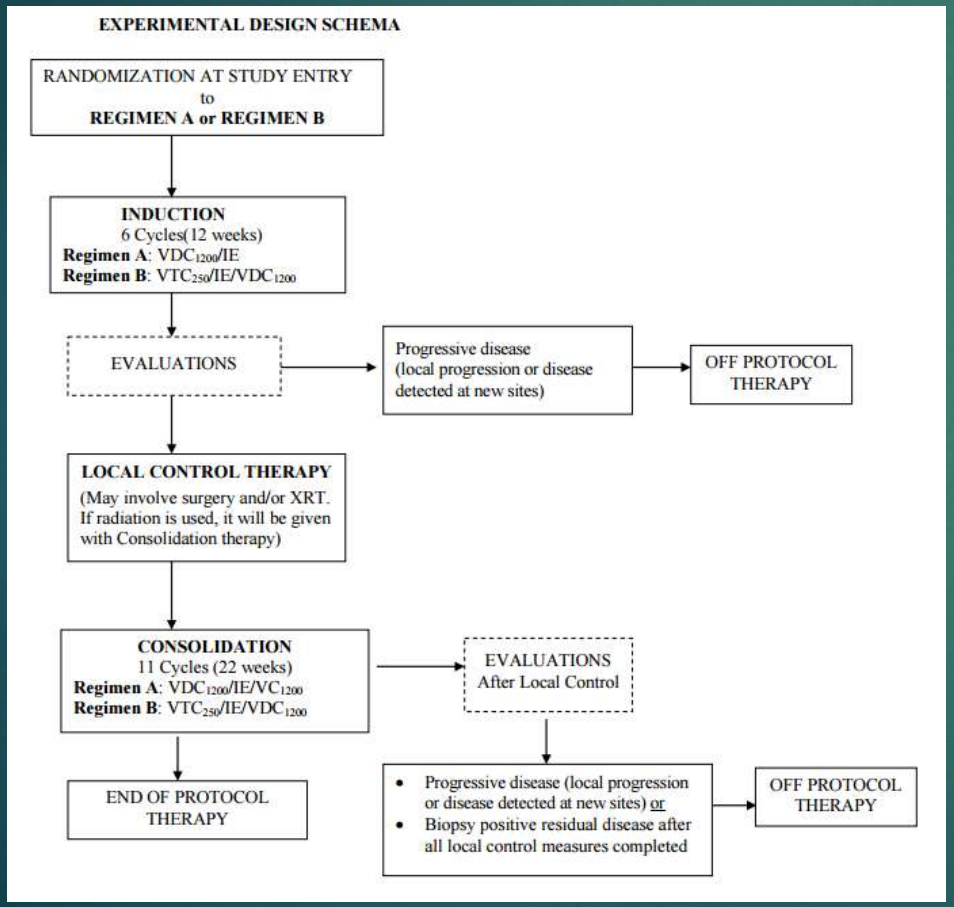
- Myelosuppression was dose limiting toxicity; introduction of G-CSF allows for interval compression and improved event-free survival
- Interval compression is now standard of care in North America for children
  - Somewhat less clear for patients >18yo (only 12% of total patient population in AEWS0031)

# Current Phase III protocols

| | | |
|---|---|---|
| COG AEWS1031 | Localized | VDC/IE<br>VDC/IE + cyclophosphamide/topotecan |
| Ewing 2008 | Localized | 6 VIDE → Standard risk: Good histologic response or < 200 mL, RT alone → 8 VAC/VAI; 8 VAC/VAI + zoledronate<br>6 VIDE → High risk: Poor histologic response or < 200 mL, RT alone → 8 VAC/VAI; 1 VAI + busulfan/melphalan |
| | Lung-only metastases | 6 VIDE + 1 VAI → 7 VAI + lung RT; Busulfan/melphalan |
| | Other metastases | 6 VIDE → 8 VAC; Treosulfan/melphalan + 8 VAC |
| Euro-Ewing 2012 | Localized or lung-only metastases | 6 VIDE → 8 VAC; 8 VAC + zoledronate<br>5 VDC + 4 IE → 3 VC + 4 IE; 3 VDC + 4 IE + zoledronate |
| Italy ISG/AIEOP EW-1 | Localized | Arm A: Conventional doses → Good response: conventional maintenance (37 weeks)<br>Arm B: Dose-intensification and shorter length of treatment → Poor response: busulfan/melphalan; Good response: intensive maintenance (25 weeks) |

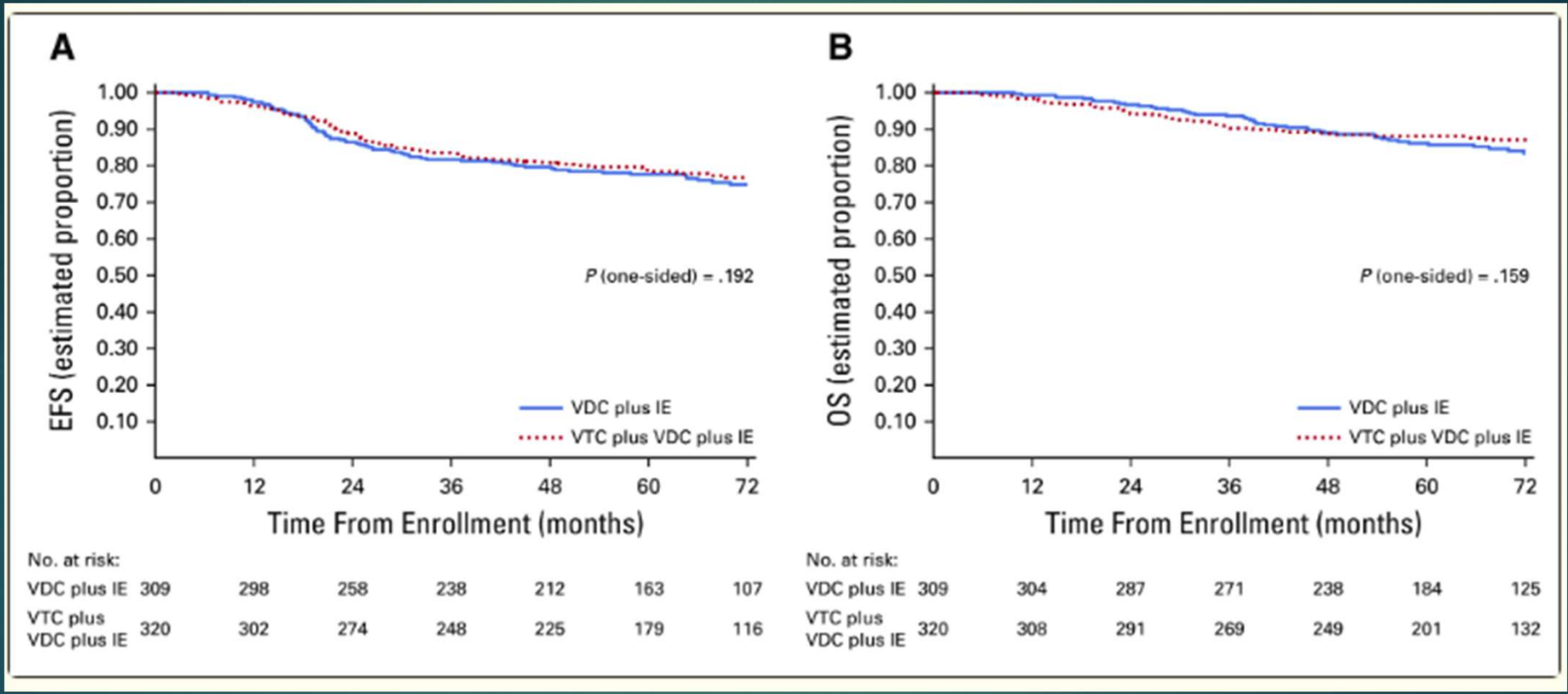
# COG AEWS1031

## A Phase III Randomized Trial of Adding Vincristine-Topotecan-Cyclophosphamide to Standard Chemotherapy in Initial Treatment of Non-metastatic Ewing Sarcoma



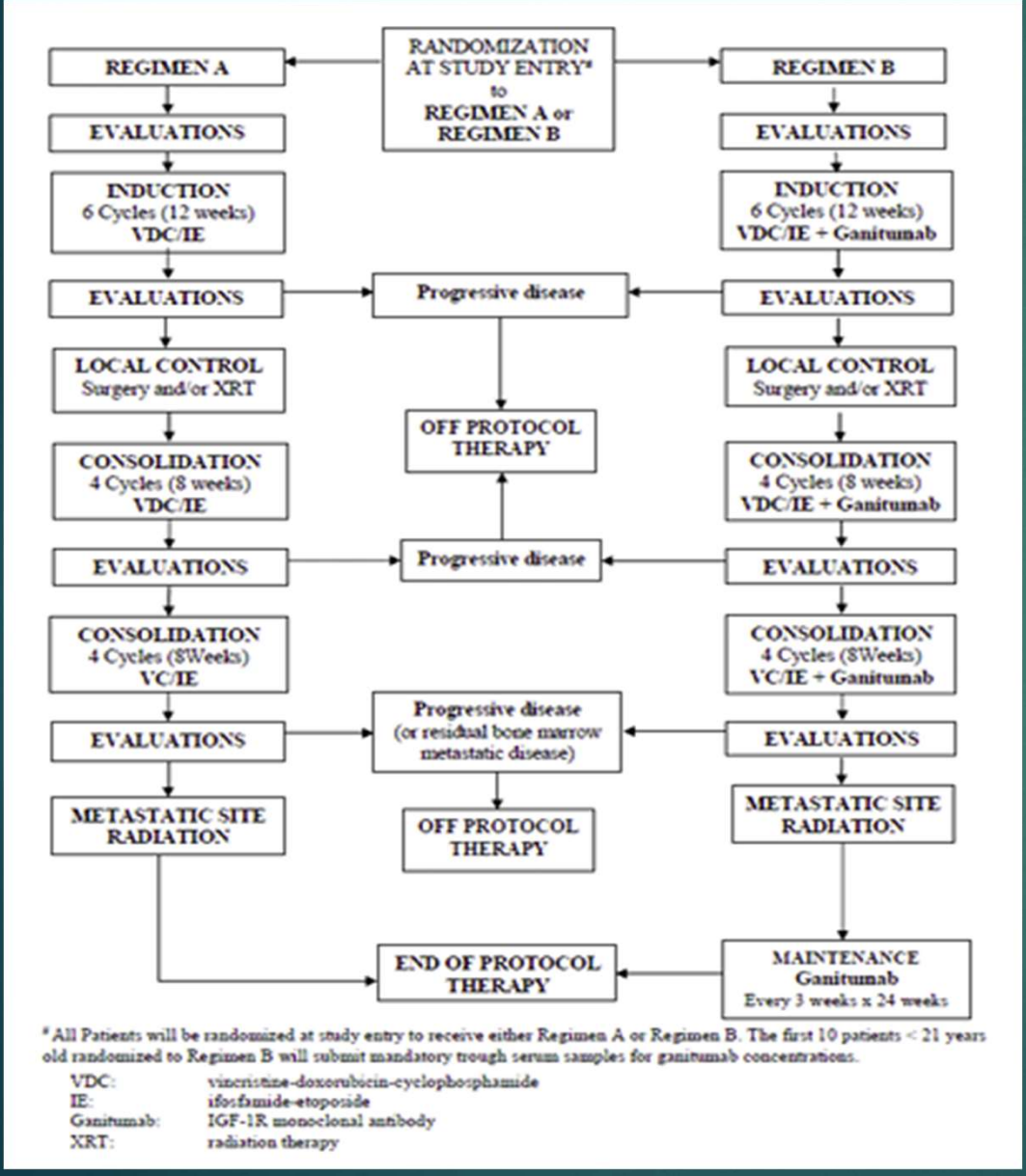

| | |
|---|---|
| $VDC_{1200}$: | vincristine-doxorubicin-cyclophosphamide$_{1200\ mg}$ |
| IE: | ifosfamide-etoposide |
| $VTC_{250}$: | vincristine-topotecan-cyclophosphamide$_{250\ mg}$ |
| $VC_{1200}$: | vincristine-cyclophosphamide$_{1200\ mg}$ |
| XRT: | radiation therapy |

# COG AEWS1031




- Addition of VTC did not improve OS or EFS

# COG AEWS1221




- Ganitumab showed no improvement in EFS or OS and increased toxicity observed when added to interval compressed chemotherapy

CURRENT STANDARD OF CARE CHEMOTHERAPY

# VCR/DOXO/CTX + IFOS/ETOP ADMINISTERED AS INTERVAL COMPRESSED

# Recurrent/Refractory Disease

- Cyclophosphamide/Topotecan
- Temozolomide/Irinotecan
- Gemcitabine/Docetaxel
- ICE
- Pazopanib

- Prognosis dismal for disease that does not respond to initial treatment

# Poor Prognostic Factors

- Metastasis at diagnosis (bone/marrow worse than pulmonary)
- Age >14yo
- Primary tumor volume >200ml (maximal diameter >8cm)

# Treatment Side Effects

# Treatment Effects

- Vincristine
  - SIADH
  - Myalgia
  - Neuropathy
  - Constipation
- Doxorobucin
  - Cardiomyopathy
  - BM suppression
  - Nausea/Emesis
  - Hyperpigmentation
  - Liver irritation
  - Neuropathy
- Cyclophosphamide
  - BM suppression
  - Nausea/Emesis
  - Hemorrhagic Cystitis


- Ifosfamide
  - BM suppression
  - Nausea/Emesis
  - CNS toxicity
    - Encephalopathy
    - Seizures
    - neuropathy
  - Arrythmia
- Etoposide
  - BM suppression
  - Nausea/Emesis
  - Hypotension
  - Neuropathy
  - Anaphylactoid reaction

# Supportive care

- Infection
  - Prompt broad-spectrum antibiotics for febrile neutropenia
  - Anti-fungal therapy for persistent or recurrent fever
- Transfusion support
- G-CSF
- PJP prophylaxis
- Cardiac Monitoring
  - EKG/ECHO

# Late effects

- Surgical intervention
  - Impair organ function, cause permanent disability or disfigurement
- Radiotherapy
  - Contribute to disability and disfigurement via effects on tissue growth and development
  - Secondary malignancy
- Chemotherapy
  - Cardiomyopathy, renal impairment, gonadal hormone failure/infertility
  - Secondary malignancy

# Questions?