ARROCase: Ewing Sarcoma

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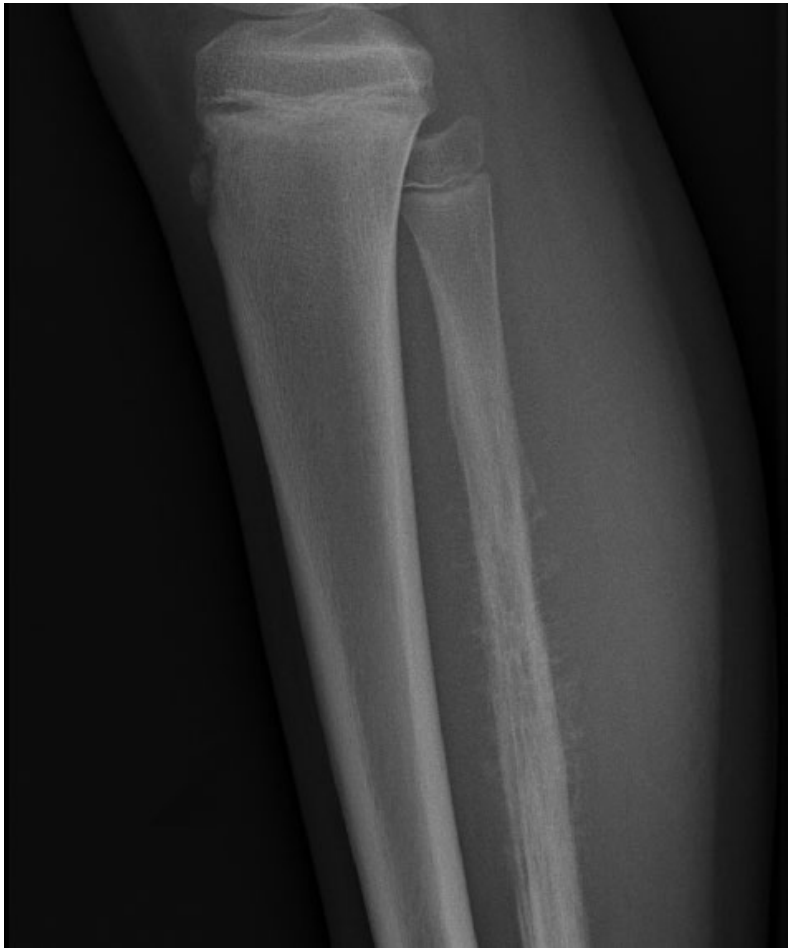
Case Presentation

- **13 year old** boy
- Localized, waxing & waning right leg pain
- **3 weeks** duration
    - Gradual onset
    - Increasing in intensity

- ROS
    - Otherwise negative
    - No fever, night sweats, fatigue, weight loss

Case Presentation

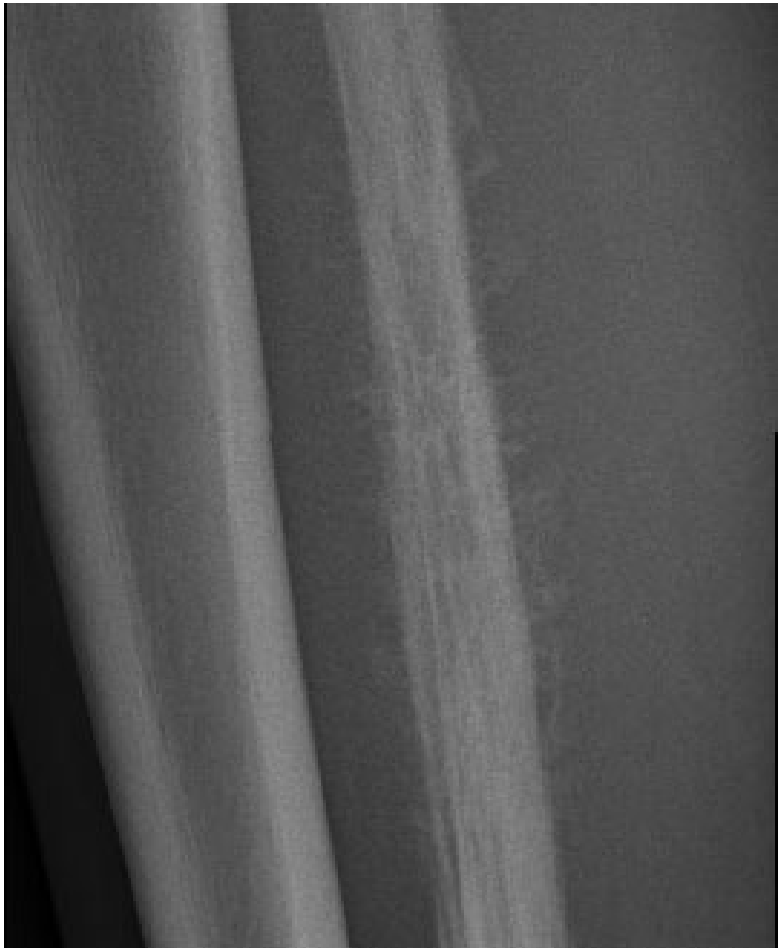
- History unrevealing
  - No history of trauma
  - Negative past medical/surgical history
  - Family history non-contributory
  - No medications or known allergies
- Physical examination
  - Afebrile, vital signs within normal range
  - Point tenderness on palpation of mid-lateral side of right leg with mild overlying swelling
  - Normal gait and range of motion; Neuro exam non-focal



Imaging

X-ray of the Right Leg

Case courtesy of Dr Samir Benoudina, Radiopaedia.org, rID: 75437



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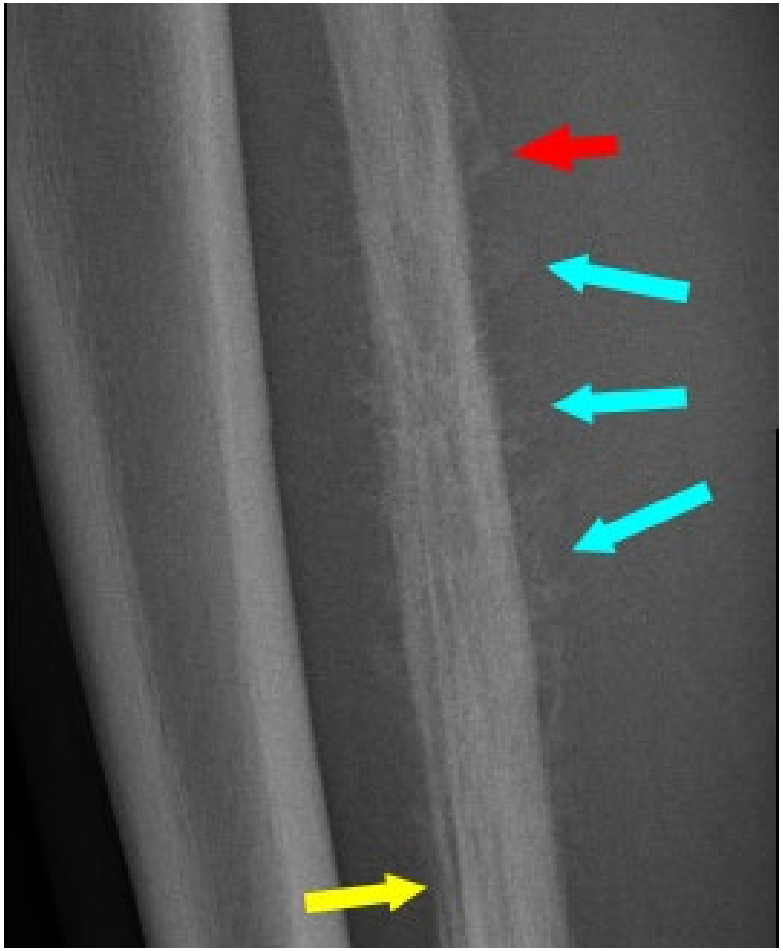
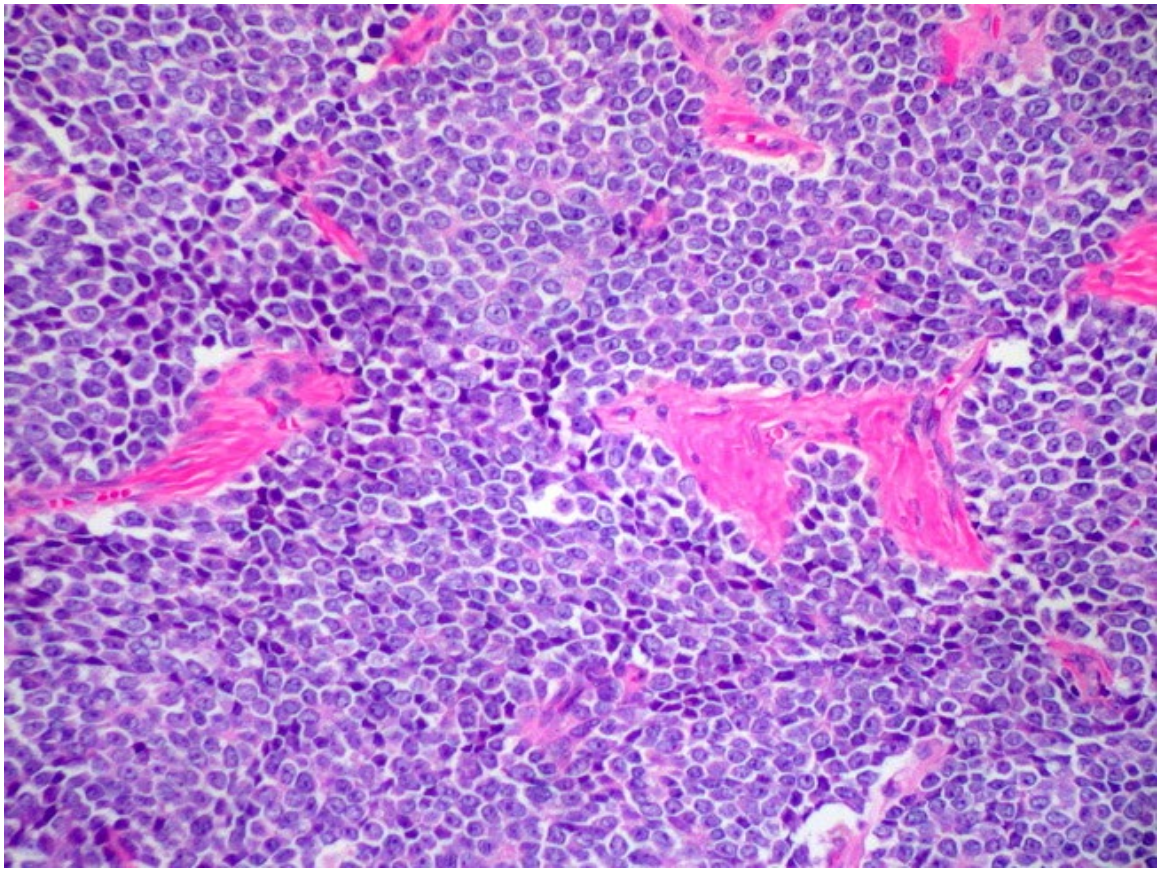


Imaging

X-ray of the Right Leg: Codman triangle (Red Arrow)
Sunburst Appearance (Blue Arrow)
Onion-Skin Periosteal reaction (Yellow Arrow)

Case courtesy of Dr Samir Benoudina, Radiopaedia.org, rID: 75437



Biopsy*

Sheets of small, uniform cells with scant cytoplasm, round nuclei, and small punctate nucleoli

**Open incisional biopsy is preferred so that the biopsy tract can be removed with definitive surgery.*

https://www.webpathology.com/image.asp?n=5&Case=340

Diagnosis and Workup

EWING SARCOMA

Epidemiology

- **Aggressive** bone and soft-tissue cancer
- Predominant in **children** and **adolescents**
    - Peak incidence at **15 years** of age
    - About **2%** of all cancers in children
    - Around **200 new cases**/year
    - **Second** most common bone cancer
    - **Male** > Female
    - About **25%** present with metastatic disease

Presentation

- Localized pain and swelling
    - Most commonly in pelvis and proximal long bones
- Possible palpation of a firm mass
- Pathological fracture in 10-15% of cases
- Constitutional symptoms
    - Fever, night sweats, fatigue, and weight loss

Diagnosis

TEST	RESULT
Plain radiograph	• Multiple confluent lytic lesions, like “Moth eaten” bone • Periosteal reaction, giving rise to “onion peel” or Codman’s triangle
Biopsy	• Sheets of small, round, blue cells with a prominent nucleus and scant cytoplasm
Blood tests	• May show elevated levels of nonspecific markers of inflammation and bone remodeling (ESR, Alk Phos) • Elevated serum LDH

Differential Diagnosis for **Small Round Blue Cell Tumors**

- Histologic findings shared with:
  - Neuroblastoma
  - Desmoplastic small round-cell tumor
  - Alveolar rhabdomyosarcoma
  - Peripheral neuroectodermal tumor
  - Non-Hodgkin's lymphoma
  - Acute lymphoblastic leukemia
  - Poorly differentiated synovial sarcoma
  - Other rare "Ewing-like" tumors

Molecular Studies

- **Fusion of:**
  - EWS gene (chr. 22)
  - Gene of the ETS family
- Most common (85%):
  - EWS & FLI-1 fusion; t(11;22)(q24;q12)
  - Associated with a **better prognosis**
- Identification of signature chromosomal translocation —> Definitive diagnosis
  - Consider fusion panels if initial studies -ve

Prognostic Factors

- **Favorable**
  - Distal lesion
  - Tumor volume < 100 mL
  - Normal LDH level
- **Adverse**
  - Metastatic disease at presentation
  - Poor response to initial chemotherapy

Staging

- **MRI** with or without CT of 1^{o} lesion (with contrast)
- Head-to-toe **PET CT** scan and/or **bone scan**
- In case of high risk disease or concerning symptoms, consider:
    - CT Chest with contrast
    - Bone marrow biopsy
    - Scanning MRI of spine and pelvis

Staging System

- **Localized** v.s. **Metastatic**
  - Metastases can be
    - Regional (nearby structures/lymph nodes)
    - Distant (distant organs; eg, lung)

- **TNM** staging
  - Less commonly used

TNM Staging

Appendicular skeleton, trunk, skull, and facial bones	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

Spine	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one vertebral segment or two adjacent vertebral segments
T2	Tumor confined to three adjacent vertebral segments
T3	Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments
T4	Extension into the spinal canal or great vessels
T4a	Extension into the spinal canal
T4b	Evidence of gross vascular invasion or tumor thrombus in the great vessels

TNM Staging

Pelvis	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor confined to one pelvic segment with no extraosseous extension
T1a	Tumor ≤8 cm in greatest dimension
T1b	Tumor >8 cm in greatest dimension
T2	Tumor confined to one pelvic segment with extraosseous extension or two segments without extraosseous extension
T2a	Tumor ≤8 cm in greatest dimension
T2b	Tumor >8 cm in greatest dimension
T3	Tumor spanning two pelvic segments with extraosseous extension
T3a	Tumor ≤8 cm in greatest dimension
T3b	Tumor >8 cm in greatest dimension
T4	Tumor spanning three pelvic segments or crossing the sacroiliac joint
T4a	Tumor involves sacroiliac joint and extends medial to the sacral neuroforamen
T4b	Tumor encasement of external iliac vessels or presence of gross tumor thrombus in major pelvic vessels

TNM Staging

Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed. Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate, and cases should be considered N0 unless clinical node involvement clearly is evident.
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
M1a	Lung
M1b	Bone or other distant sites

Outcomes

- 5-year relative survival rates
  - Localized: **82%**
  - Regional: **70%**
  - Distant: **39%**

  - All stages combined: **62%**

American Cancer Society statistics: 2010-2016.

Outcomes

- Cure rate in case of metastases in:
  - Lung: **30%**
  - Bone/bone marrow: **20%**

- Local control rates:
  - Surgery for extremity tumor: **>90%**
  - Surgery for central tumor: **75%**
  - Radiation therapy: **75-90%**

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GUIDELINES ON MANAGEMENT

LOCALIZED EWING SARCOMA

Treatment of **Localized** Ewing Sarcoma

- In brief:

Treatment of **Localized** Ewing Sarcoma

- **Induction Chemotherapy**
  - Alternating VDC & IE
    - Vincristine, Doxorubicin, Cyclophosphamide
    - Ifosfamide, Etoposide
  - Six Cycles
- **Re-staging**
  - Repeat imaging of initial workup
    - Stable/improved v.s. progressive

Treatment of **Localized** Ewing Sarcoma

- **If stable or improved —> Local therapy at ~ 15 wks**
- **Surgery**
  - Wide local excision or amputation
  - Followed by
    - Chemo (regardless of surgical margins)
    - + RT (if close or positive margins, consider for pelvic tumors)
- **OR Definitive chemoradiation**

Treatment of **Localized** Ewing Sarcoma

- **If progressive** —> Consider **local therapy**
  - RT **or**
  - Surgery
- For local control or palliation

Treatment of **Localized** Ewing Sarcoma

- More on **local therapy**
- Prefer **surgery** for:
  - Younger children (to avoid 2nd malignancy)
  - Tumors in proximal fibula, lateral clavicle, ribs, scapular body, iliac wings, small bones of the hands/feet (i.e. “expendable” bones)
- Prefer **definitive chemoRT** for:
  - Prevention of limb amputation
  - Tumors in pelvis/spine (surgery would be debilitating)

Treatment of **Localized** Ewing Sarcoma

- **Consolidation chemotherapy**
  - To be given after local therapy
  - Alternating **VDC & IE**
  - For 11 cycles

METASTATIC EWING SARCOMA

Treatment of **Metastatic** Ewing Sarcoma

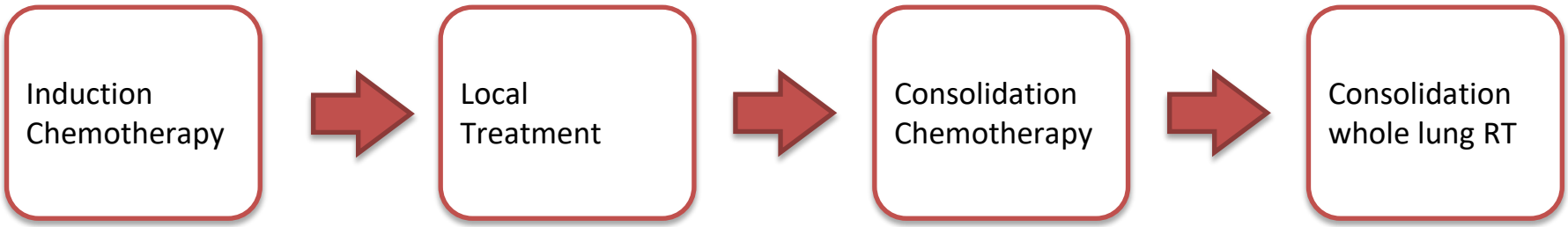
- **Primary Treatment: Chemotherapy**
- **Then**:
    - Consider **local therapy**, especially if:
        - Oligometastatic
        - Good response to chemotherapy
    - Otherwise, **if widely metastatic**, consider:
        - Chemo with palliative surgery
        - Palliative RT to symptomatic areas

Treatment of **Metastatic** Ewing Sarcoma

- **Special case:**

  Ewing sarcoma metastatic to **lung** only

- Treat definitively:



More on

RADIATION THERAPY

Radiation Therapy

- **Definitive** RT
  - **GTV1:** pretreatment bone + soft tissue (45 Gy at 1.8 Gy/fx)
    - **CTV1:** 1-1.5 cm
    - **PTV1:** 0.5-1 cm
  - **GTV2:** post-chemotherapy soft tissue (55.8 Gy at 1.8 Gy/fx)
    - **CTV2:** 1-1.5 cm
    - **PTV2:** 0.5-1 cm

- **N.B.**
  - Anatomically modified **CTV** so as not to cross nearby borders
  - No need to expand into structures which the tumor abutted (but did not invade)
  - **PTV2** of **vertebral body** tumors receives 50.4 Gy instead

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Donaldson. *Pediatr Blood Cancer*. 2004.

Radiation Therapy

- **Preoperative** RT
  - For **marginally resectable** tumors to improve margin status
    - Eg, R1 —> potential R0
    - Goal is not to downstage an un-resectable tumor (Eg, R2 —> potential R1/R0)
  - Initial **GTV** + **2** cm
  - Dose: 36-45 Gy (1.8 Gy/fx)

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Radiation Therapy

- **Postoperative** RT (Within 60 days) all at (1.8 Gy/fx)
  - **GTV2** (45 Gy) + **CTV1** + **PTV1**
    - **R0 resection** (No microscopic residual)
      - Esp. if unfavorable histology
    - **R1 resection** (Microscopic residual)
    - **R2 resection** (Gross residual)
      - With cone down to residual
      - Total dose: 55.8 Gy to GTV2 + CTV2 + PTV2
  - **LN +ve** areas
    - **Resected**: 50.4 Gy
    - **Un-resected**: 55.8 Gy

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Radiation Therapy

- **Hemithorax** Irradiation
  - **Indication:** Chest wall 1º tumor w/ extensive pleural involvement
  - Dose:
    - 15-20 Gy (1.5 Gy/fx) to ipsilateral whole lung and pleura; **THEN**
    - 21.6 Gy (1.8 Gy/fx) to PTV1; **AND**
    - 14.4 Gy boost to PTV2
    - Note: same PTV1 & PTV2 as definitive RT expansions
- **Whole Lung** Irradiation
  - **Indication:** pulmonary metastases after chemotherapy (even if complete response) or surgical resection
  - Dose: 15 Gy if <14 y.o. or 18 Gy if >14 y.o. (1.5 Gy/fx)

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Radiation Therapy - Some Constraints

- Keep **V40 < 66%**
    - To avoid pathological fracture
- Avoid **circumferential** RT & add **skin strip**
    - To avoid lymphedema
- Keep in mind:
    - Epiphyseal closure at **~ 20 Gy**
    - Ovarian failure at **~ 8 Gy**

        —> Lead shielding or ovarian transposition out of field
    - Testicular failure at **~ 2 Gy**

        —> Lead shielding

Radiation Therapy - Side Effects

- Secondary malignancy
- Growth abnormalities
- Fibrosis/edema
- Hypoplasia of muscles
- Femoral head necrosis
- Pathologic fractures
- Infertility

Chemotherapy - Side Effects

- Regimen: alternating VDC & IE

- **Secondary AML** (DC & IE)
- **Cardiomyopathy** (D)
- **Infertility** (I &C)
- **Renal toxicity** (I)
- **Cystitis** (C)

V: Vincristine, D: Doxorubicin, C: Cyclophosphamide, I: Ifosfamide, E: Etoposide

Evidence

STUDIES AND TRIALS

Induction Chemotherapy

- **IESS-I:** **(VACD)** v.s. (VAC) v.s. (VAC +BPR) (Nesbit et al. 1990)
  - Localized Ewing sarcoma; N=342
  - 5-year RFS: **60%** v.s. 24% v.s. 44% ($p < 0.001$)
  - 5-year OS: **65%** v.s. 28% v.s. 53% ($p < 0.001$)

- **IESS-II:** **High-dose intermittent** v.s. Moderate-dose continuous of VACD (Burgert et al. 1990)
  - 5-year RFS: **73%** v.s. 56% ($p=0.03$)
  - 5-year OS: **77%** v.s. 63% ($p=0.05$)

V: Vincristine; A: Actinomycin D; C: Cyclophosphamide; D: Doxorubicin; BPR: Bilateral pulmonary radiation

Induction Chemotherapy

- **INT-0091: (VACD + IE)** v.s. VACD (Grier et al. 2003)
  - Ewing, PNET or primitive sarcoma of bone; N=398 with non-metastatic dx
  - 5-year EFS: **69%** v.s. 54% (p=0.005)
  - 5-year OS: **72%** v.s. 61% (p=0.01)

V: Vincristine; A: Actinomycin D; C: Cyclophosphamide; D: Doxorubicin; I: Ifosfamide; E: Etoposide

Induction Chemotherapy

- **INT-0154:** VADC/IE in 30 w (dose intensified) v.s. 48 weeks (Granowetter et al. 2009)
    - Ewing sarcoma family of tumors; N=478
    - 5-year EFS: 70.1% v.s. 72.1% (p=0.57)

- **COG AEWS0031:** VDC-IE **q2w** v.s. q3w (Womer et al. 2012)
    - Localized, extradural Ewing sarcoma; N=568
    - 5-year EFS: **73%** v.s. 65% (p=0.048)
    - No increase in toxicity

V: Vincristine; A: Actinomycin D; C: Cyclophosphamide; D: Doxorubicin; I: Ifosfamide; E: Etoposide

Local Modality: Surgery v.s. RT

- **COG Meta Analysis** of INT-0091, INT-0154, and AEWS0031 (Ahmed et al. 2017)
  - Ewing sarcoma; N=956
  - Modality: **Surgery** v.s. RT v.s. (Surgery + RT)
  - 5-year LF: **3.9%** v.s. 15.3% (p<0.01) v.s. 6.6% (p=0.12)
  - Stratified by tumor location and age:

Location	5-year local failure Surgery	5-year local failure Definitive RT
Extremity	**3.7%**	14.8% (p≦0.01)
Pelvic	**3.9%**	22.4% (p≦0.01)
Axial non-spine	No difference	
Spine	No difference	
Extraskeletal	No difference	

Age	5-year Local Failure
≧18 years	**11.9%**
< 18 years	6.7% (p=0.02)

* A statistically greater number of patients who underwent surgery had tumors in more favorable locations (ie. Extremity).

Consolidation Treatment

- **Euro-E.W.I.N.G.99 and EWING-2008** (Whelan et al. 2018)
  - Localized Ewing sarcoma at high risk for relapse; N=240
  - VIDE induction (x6) then

    (VAI x1 and BuMel HDT) v.s. (VAI x 8)
  - 8-year EFS: **60.7%** v.s. 47.1% (HR of event: 0.64; p=0.026)
  - 8-year OS: **64.5%** v.s. 55.6% (HR of death: 0.63; p=0.028)

High risk for relapse:

- Poor histologic response (≧10% viable cells) after induction chemotherapy (VIDE)
- Large tumor volume at diagnosis (≧ 200 mL) for tumors that were unresected, initially resected, or resected after radiotherapy

V: Vincristine; A: Actinomycin D; D: Doxorubicin; I: Ifosfamide; E: Etoposide; BuMel HDT: High dose Busulfan and Mephalan with autologous SCT

Ewing sarcoma + **Pulmonary Mets**

- **Euro-E.W.I.N.G.99 and EWING-2008** (Dirksen et al. 2019)
  - Ewing sarcoma + pulmonary/pleural mets only; N=287
  - VIDE induction (x6) then

    (VAI x8 with WLI) v.s. (VAI x1 with BuMel HDT)
  - 8-year EFS: 43.1% v.s. 52.9% (HR=0.79, p=0.16)
  - No difference in OS (HR=1, p=0.99)
  - Toxicity-related death: No patients v.s. 4 patients

WLI: Whole lung irradiation

V: Vincristine; A: Actinomycin D; D: Doxorubicin; I: Ifosfamide; E: Etoposide; BuMel HDT: High dose Busulfan and Mephalan with autologous SCT

Proton therapy & Ewing Sarcoma

- Retrospective chart review (Rombi et al. 2012)
  - Pediatric Ewing's sarcoma at different sites; N=30
  - Proton + Chemotherapy
  - Median dose: 54 Gy RBE (range: 45-58 Gy)
  - 3-year LC, EFS, OS: 86%, 60%, 89% respectively
  - Adverse effects:
    - Scoliosis/kyphosis (x5)
    - Eye canalicular stenosis (x1) & corneal ulcer (x1)
    - Endocrine deficiency (x2)
    - High frequency hearing loss (x1)
    - Secondary hematologic malignancies (x4)

Risk of **Secondary Malignancy**

- Retrospective chart review (Fuchs et al. 2003)
  - Ewing's sarcoma s/p tx; N=397
  - Secondary malignancy **(29 tumors)** in 26 **(6.5%)** patients
    - Mean interval: 9.5 years (range: 1-32.5 years)
    - Distribution:
      - Hematologic (x8) - Chemo induced
      - Sarcoma (x12) - RT induced
      - Carcinoma (x9)
    - Worse prognosis in case of sarcoma/hematologic secondary malignancy

Prospective **Trial**

- **NCT00186992: Radiation Therapy to Treat Musculoskeletal Tumors**
  - Phase 2 trial, St. Jude Children's Research Hospital
  - Single group assignment, active & not recruiting
  - MSK tumors, including Ewing's; N=202
  - Intervention: **image-guided radiotherapy**
  - Outcomes:
    - **Local control** (1^{o})
    - RT-related changes in growth and muscle function

Beyond Treatment

SURVEILLANCE AND RELAPSE

Surveillance

- Physical exam
- CBC
- Imaging
- Intervals
    - Initially q2-3 months for at least 2 years
    - Annually after 5 years

Relapsed Disease

- **30-40%** recurrence
- Very poor prognosis (esp. if within 2 years)
- Management
    - Chemotherapy
    - +/- RT
    - +/- surgery

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