Management of Bone Sarcomas

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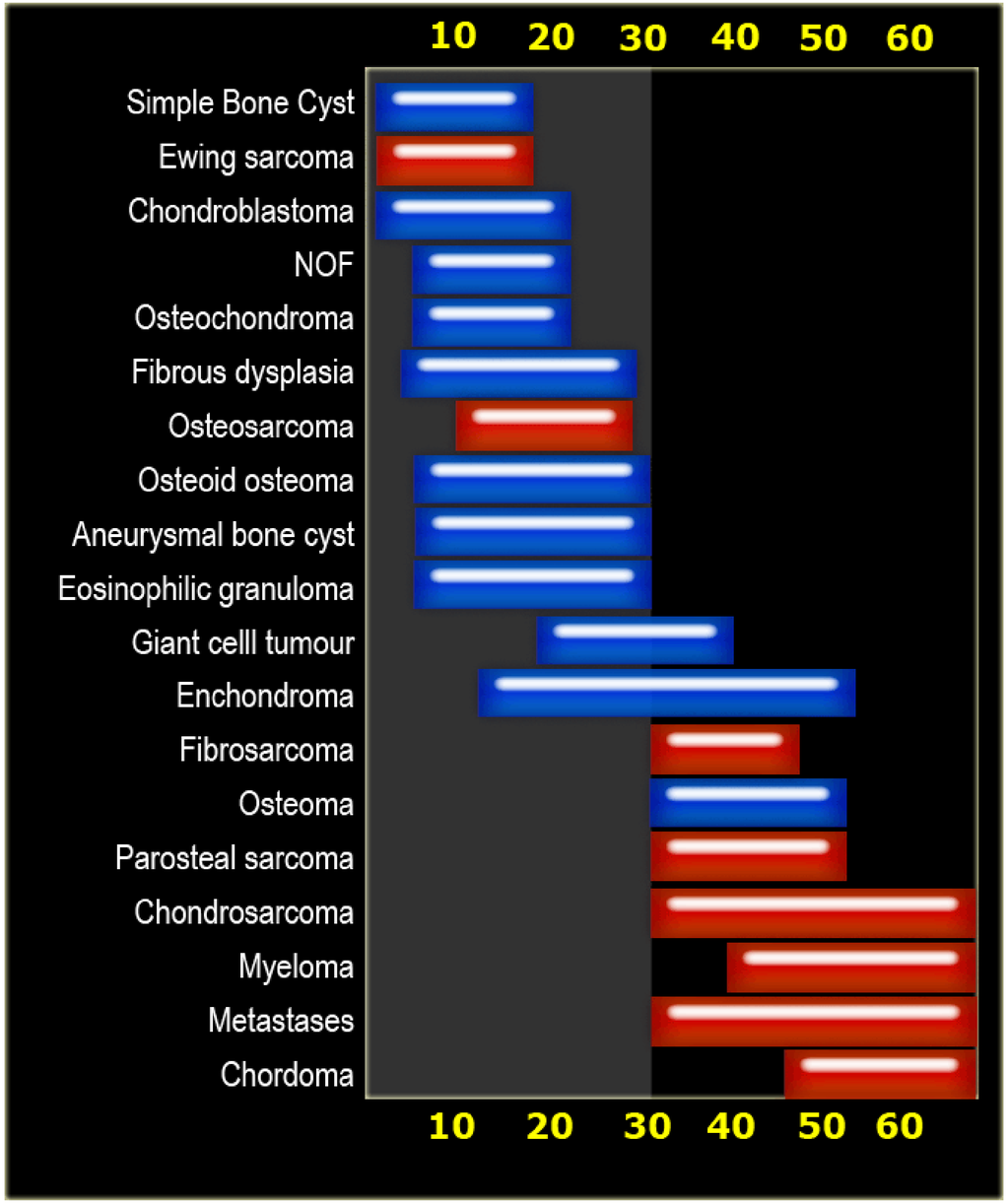
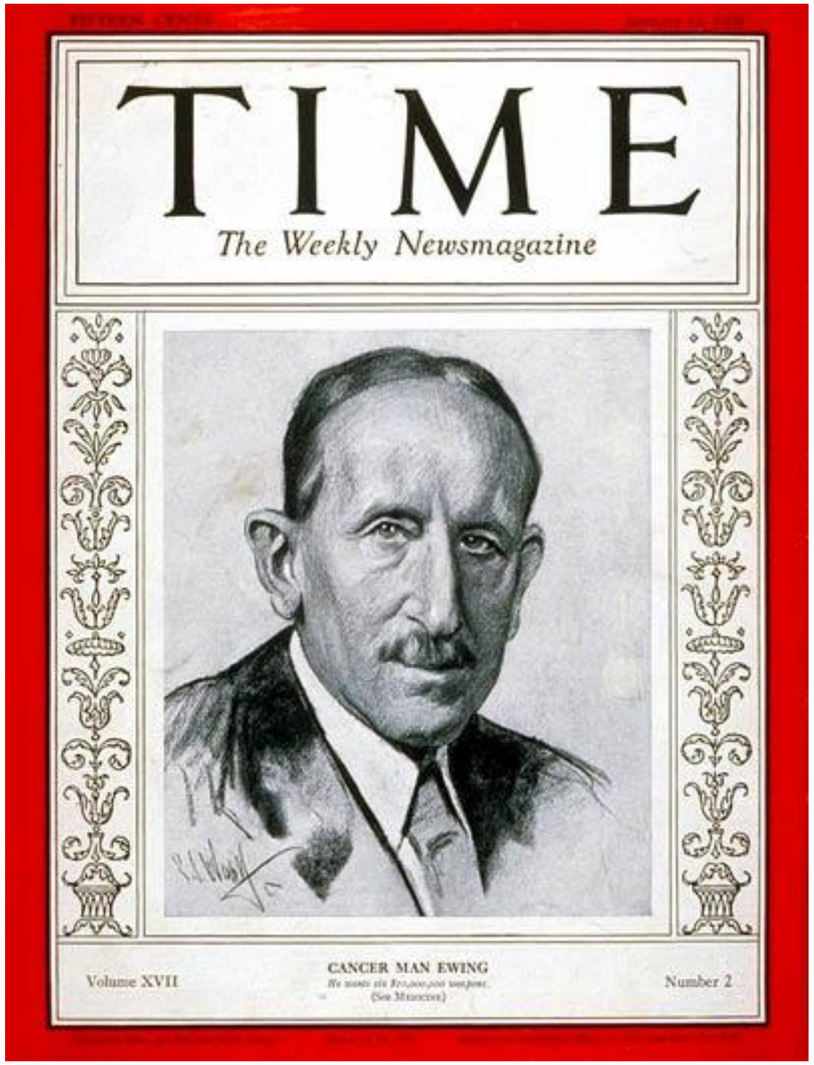
Bone Tumors Basics

- Primary malignant bone tumors are rare- **0.2% of all cancers**
- **In age <15 yrs- incidence – 5%**
- Common- **Osteosarcoma-** 30 %, Chondrosarcoma- 30% , **Ewing-** 16%
- Other rare entities- malignant fibrous histiocytoma, fibrosarcoma, GCT, chordoma etc.



Ewing Sarcoma



HISTORY

- **1918:** 14-year-old girl with arm swelling post-spontaneous fracture; initially misdiagnosed as osteogenic sarcoma.
- **X-ray:** Diffuse fading of bone shaft, no periosteal reaction, no bone formation—unlike osteogenic sarcoma
- **HPR**: Sheets of small, round, polyhedral cells; no osteoid, stroma, or plasma cells. Some lined blood-filled channels
  - **→ ENDOTHELIAL ORIGIN SUSPECTED**

- Coleys toxin given→ No response
- Radiotherapy (using radium) → DRAMATIC RESPONSE
  - Not typical of osteosarcoma

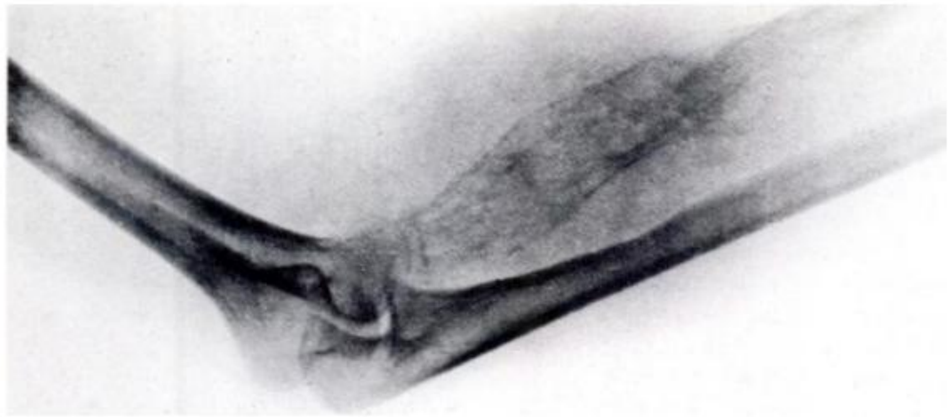


Fig. 1. Diffuse endothelioma of radius. Diffuse absorption of shaft; spontaneous fracture; invasion of soft parts.

Fig. 2. Diffuse endothelioma of radius. After radium treatment.

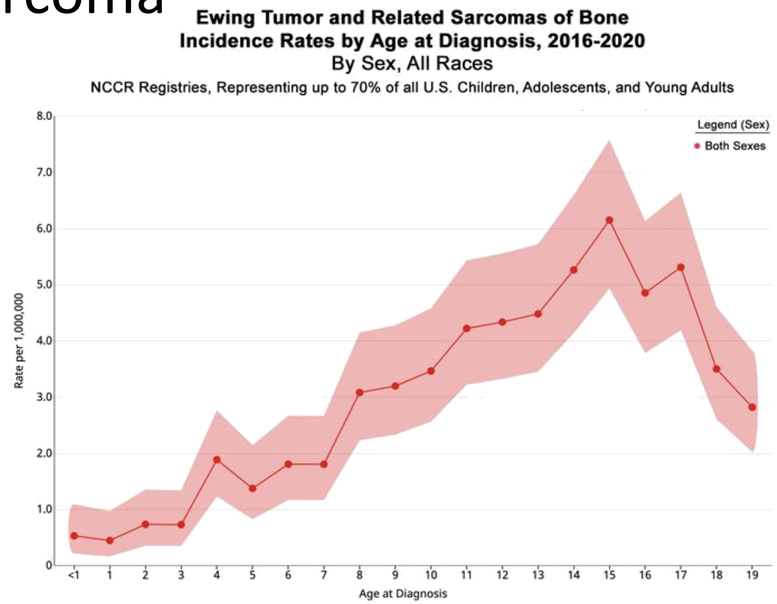
Multiple similar cases were noted- which were mainly in the age group of 14-19

Differential Diagnosis

	Ewing's Sarcoma (Diffuse endothelioma of bone)	Osteogenic Sarcoma	Myeloma
Age group	Young (14–19 yrs)	Young adults	Older adults
Radiographic pattern	**Diffuse bone fading**, no periosteal rxn	**Bone destruction with new bone**	Punched-out lytic lesions
Histology	Round polyhedral cells, vascular-like	Malignant osteoblasts, osteoid	Plasma cells
Bence-Jones protein	Absent	Not applicable	Often present
Response to radiation	Excellent	Poor	Variable

EWING'S SARCOMA

- **2nd most common** malignant bone tumor after osteosarcoma
- **Aggressive tumor**
- **Predominantly affects adolescents**
  - Median age at diagnosis: **15 years**
  - Most cases occur in the **second and third decades of life**
- **Slight male predominance** (1.6:1)
- **Incidence** (<20 yr) : **2.9 per million**
- More common in Caucasians than Asians
- **Sites**: long bones (45 %), pelvis (26 %), axial skeleton, extraskeletal (15 %)



- 5 yr OS: localized disease ≈ 70% vs Metastatic disease ≈ 10–30%

CLINICAL PRESENTATION

- **Pain-** *mc presenting complaint* (**90**%)
- Swelling (usually it is followed weeks to months after onset of pain)
- **Pathological fracture** in 10-15% of cases
- Reduced range of motion, stiffness (if near joint)
- Limp, pain on weight-bearing (commonly in pelvic and femur)
- Back pain, radicular symptoms, neurologic deficits (Pelvic and spinal lesions) – **Constitutional symptoms-** fever, weight loss, fatigue.
- *Extra-skeletal lesions present as soft-tissue masses (e.g., thoracic wall 'Askin tumour')*

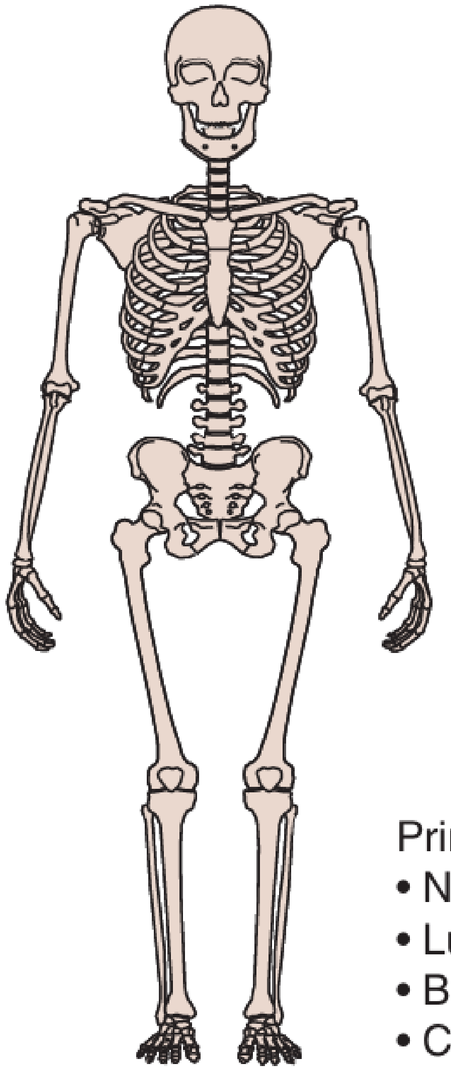


Fig. 80.1 Distribution of Primary Sites and Sites of Metastases in Ewing Sarcoma.

Primary Localization

Bone (~80%)
Axial skeleton (45%)
- Pelvis (20%)
- Ribs (10%)
- Other axial bones (15%)

Distal skeleton (35%)
- Femur (12%)
- Humerus (4%)
- Other distal bones (19%)

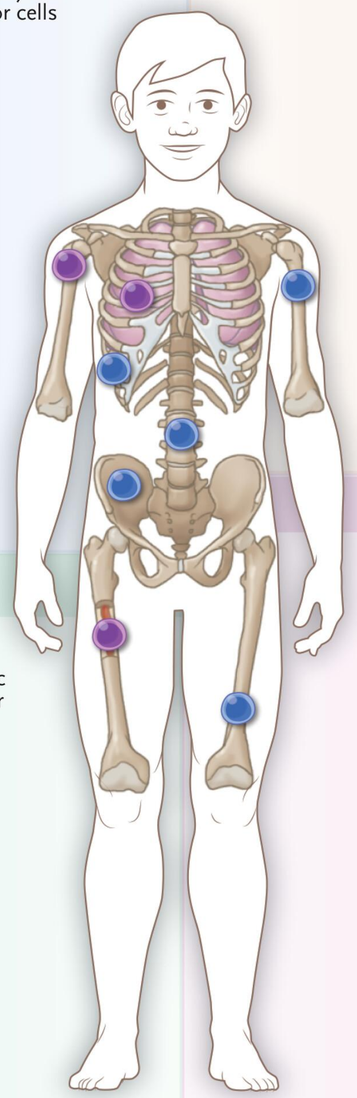
Extraosseous location (~20%)
Mostly paravertebral and thoracic soft tissues. Nonskeletal primary cancers have been documented in the retroperitoneum, esophagus, pancreas, ileum, kidney, bladder, vagina, uterus, penis, adrenal gland, lung, breast, spinal cord, orbit, and intracranial tissue.

Primary site tumor cells

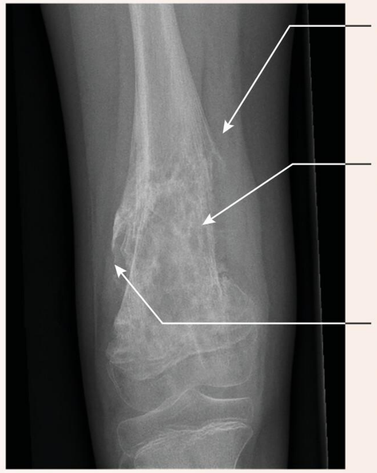
Main Metastatic Sites

- Lungs
- Bone
- Bone marrow

Metastatic site tumor cells



Radiologic Findings



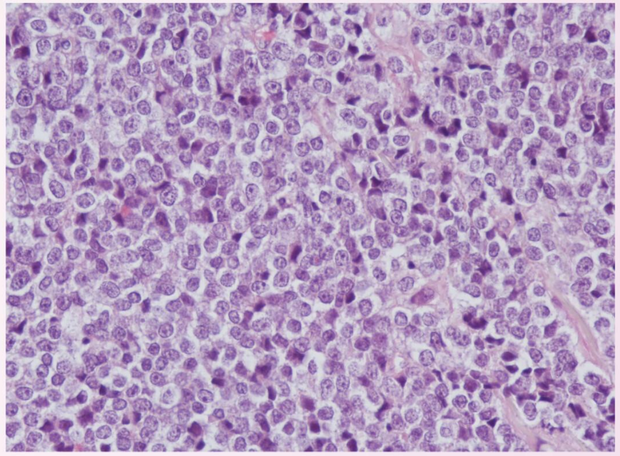
Codman triangle
New subperiostal bone growing on the tumor

"Moth eaten" pattern
Permeative destruction of bone due to multiple lytic lesions

"Onion peel" appearance
Delicate laminations constituting the periosteal layers

Histology

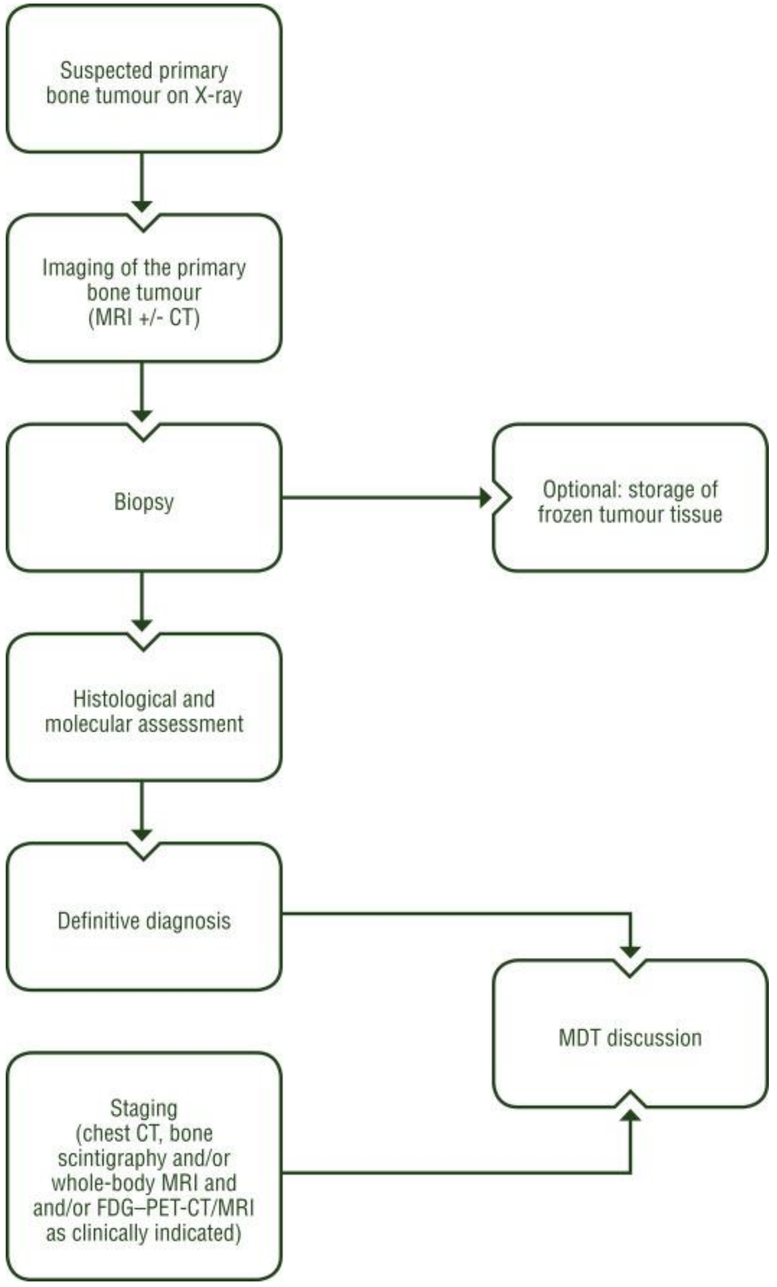
Poorly differentiated tissue consisting of small, round, blue cells with prominent nuclei and minimal cytoplasm



DIAGNOSTIC WORKUP

Imaging, Histopathology, Blood labs

Molecular testing



Laboratory Studies

- Blood: CBC, KFT, Sr Calcium, LDH, CRP, SIEP
- Urine Analysis

TABLE 61.5

Diagnostic Studies for Sarcomas of the Bone

Laboratory studies
- Serum
  - Creatinine, calcium, alkaline phosphatase, lactate dehydrogenase
  - Complete blood count, erythrocyte sedimentation rate, C-reactive protein
  - Immunofixation electrophoresis
- Urine
  - Urinalysis
  - Immunofixation electrophoresis

IMAGING

For Local Extent

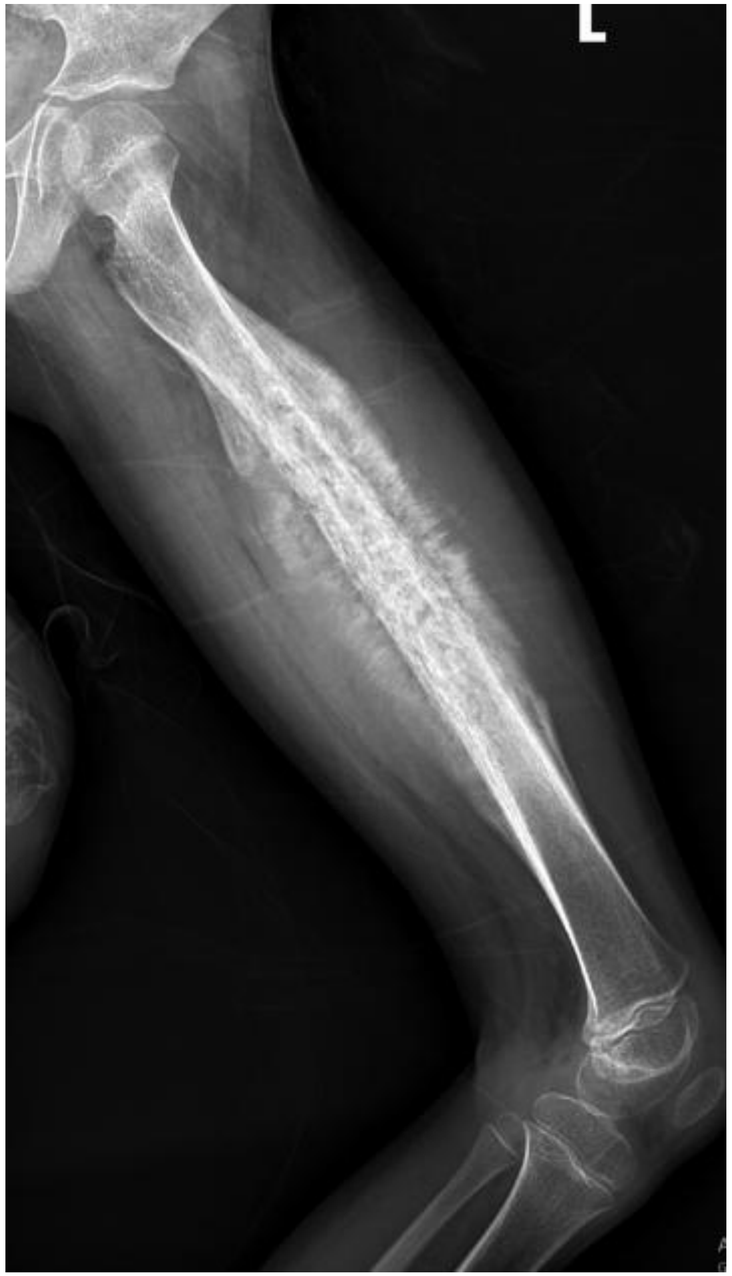
- Plain regional radiograph
- MRI
- CT

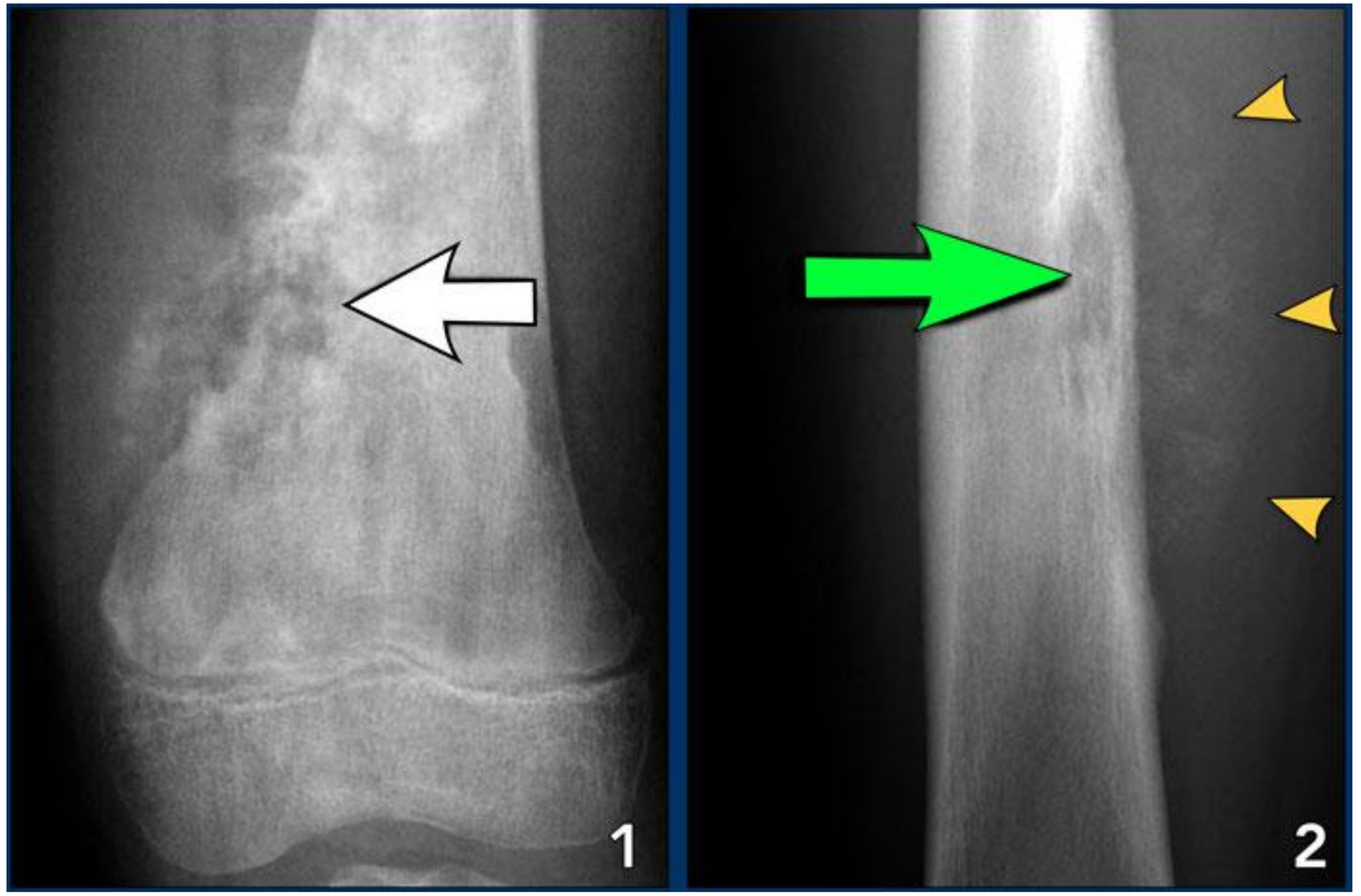
For Distant Mets

- CXR
- PET CECT
- HRCT Chest

Plain Radiograph

- First-line Imaging
- **Permeative “moth-eaten” pattern** of bone destruction.
- **Onion-skin periosteal reaction**: multiple concentric layers of new bone.
- **Codman’s triangle**: elevation of the periosteum creating a triangular area.
- This raise **high suspicion** for Ewing sarcoma
  - Similar appearances may also be seen in **osteomyelitis** or other **malignant bone tumors**.

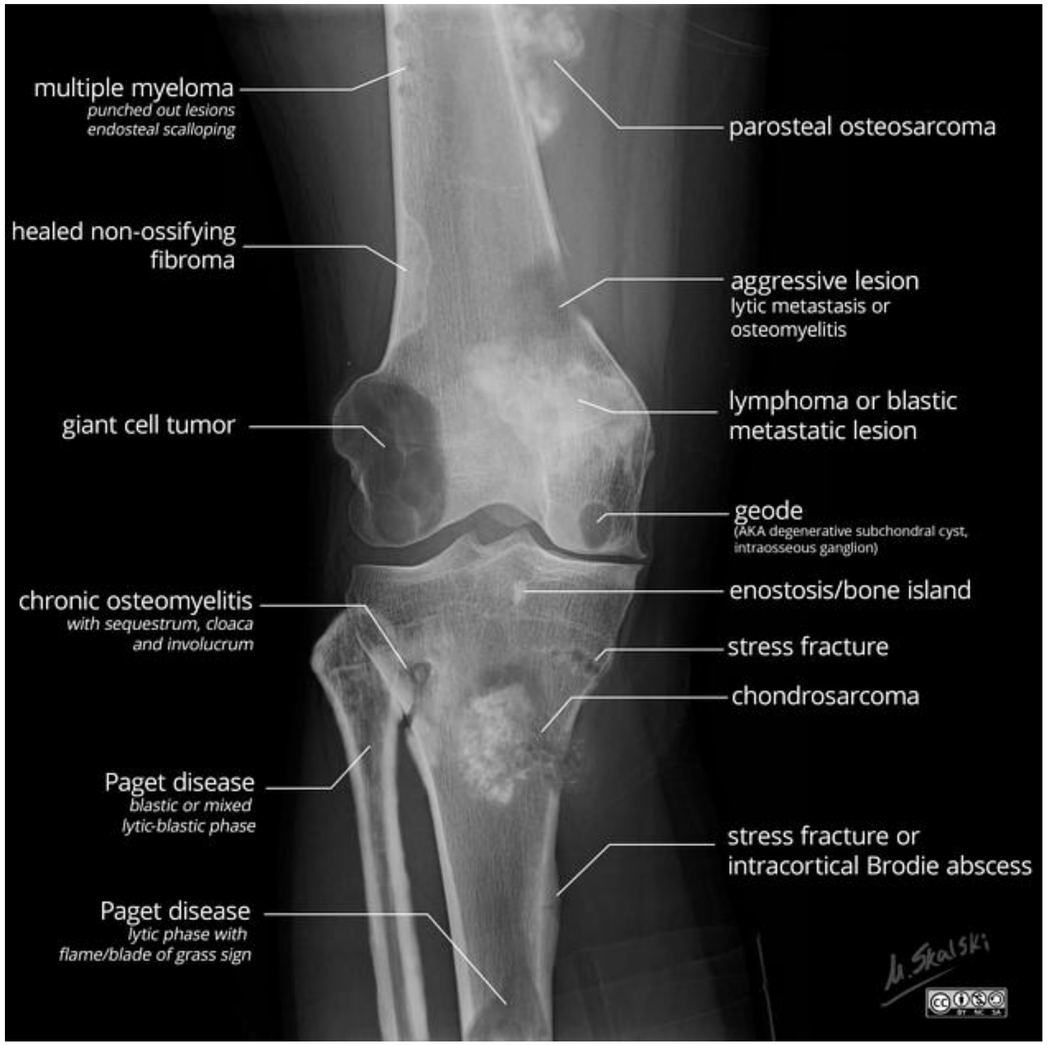




1- Osteosarcoma- Irregular cortical destruction
2- Ewing's sarcoma- Cortical destruction (green arrow) and aggressive periosteal reaction (arrow heads).

BONE TUMORS
Based on Location of Lesion

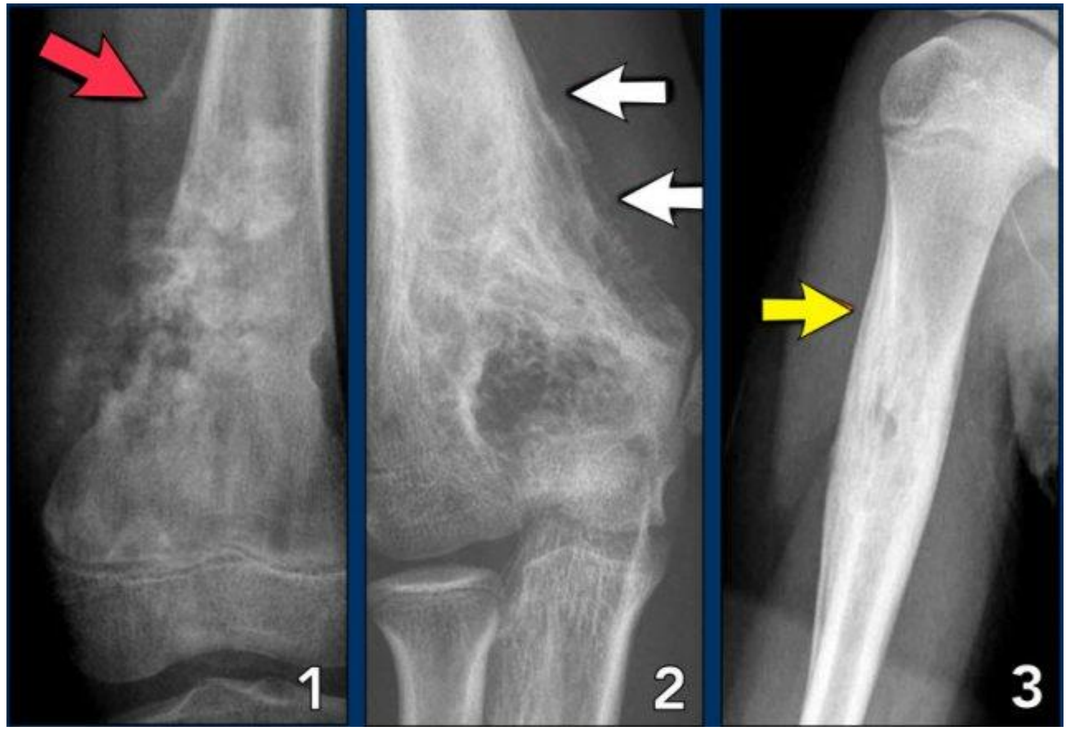
Part of Bone	Associated Tumors
Epiphysis	**Chondroblastoma** **Giant Cell Tumor** Clear Cell Chondrosarcoma
Metaphysis	**Osteosarcoma** Chondrosarcoma Enchondroma ABC / SBC
Diaphysis	**Ewing Sarcoma** Adamantinoma Osteoid Osteoma Osteoblastoma

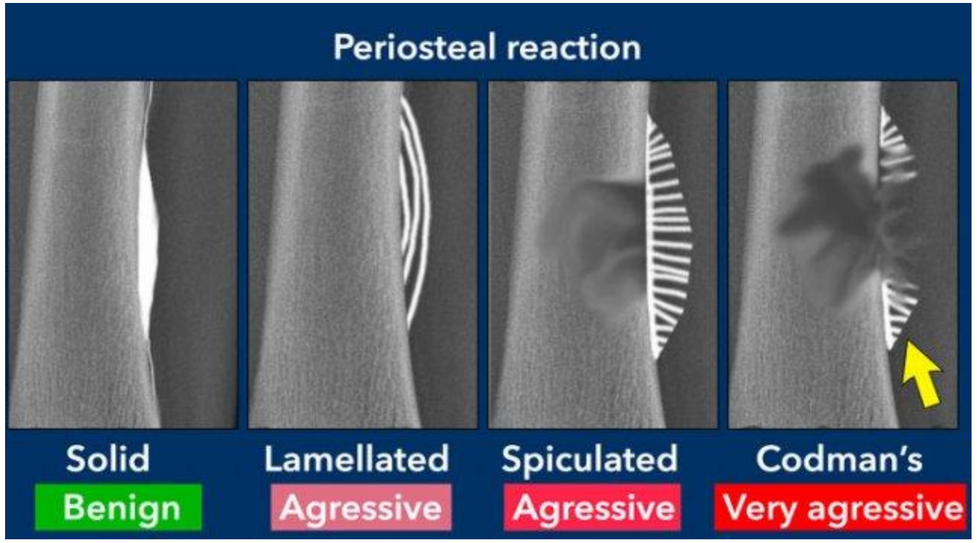


Periosteal Reaction

Periosteal new bone formation is a nonspecific response of the periosteum to underlying bone inflammation.

1. **Ewing sarcoma** – Lamellated, focally interrupted periosteal reaction
2. **Osteosarcoma** – Interrupted periosteal reaction with Codman's triangle, perpendicular periosteal bone formation, and extensive tumor matrix.
3. **Infection** – Multilayered





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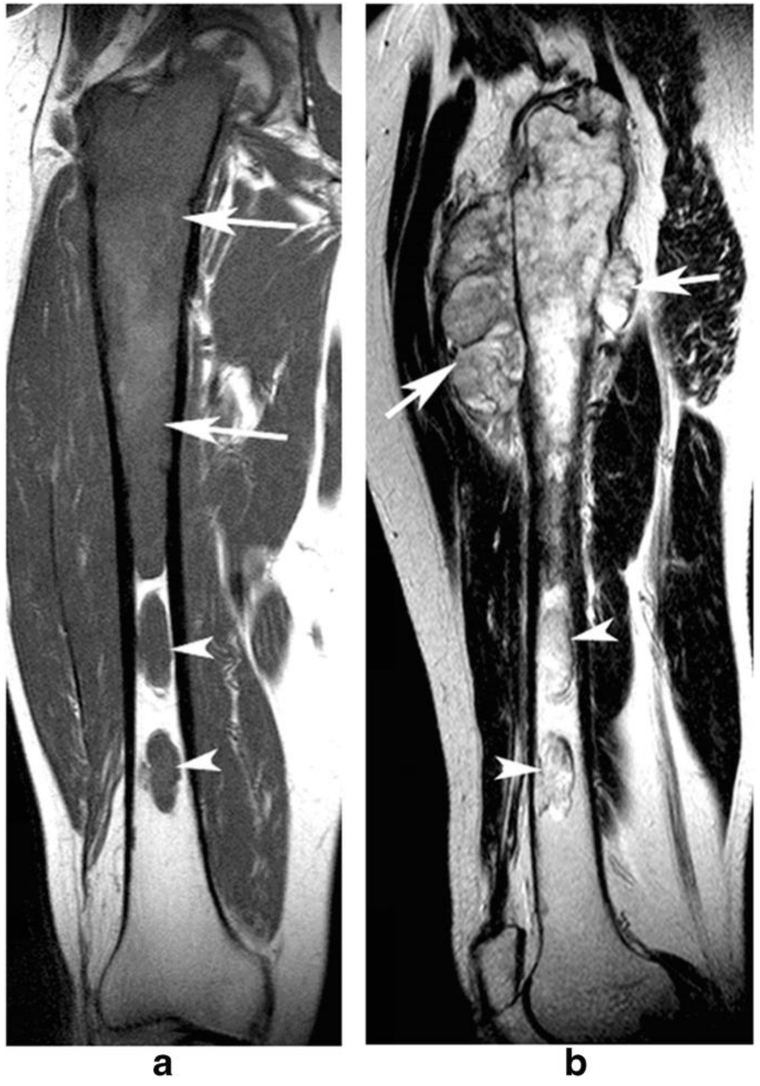
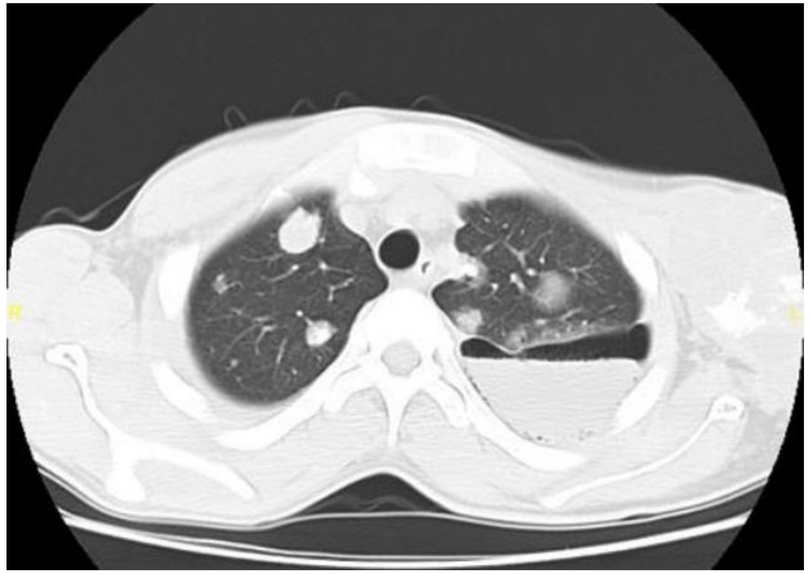
MRI

- **Modality of choice** for assessing **local extent of disease** due to superior soft tissue contrast.
- It shows
  - Intramedullary tumor spread
  - Soft tissue extension
  - Involvement of adjacent joints
  - Relationship to muscles, neurovascular bundles
- **Performed *before biopsy*** to avoid post-biopsy changes
- Entire involved bone including Adjacent joints
  - Detect possible **skip metastasis** within the same bone



CT Scan

- **Local Tumor Anatomy**- Defines cortical involvement and soft tissue extension beyond bone
- **Supplement to MRI/PET/CT-**Provides clearer bony detail where MRI or PET lacks sensitivity or specificity
- **Staging (Lungs)-** Detects lung mets (mc site- distant mets)

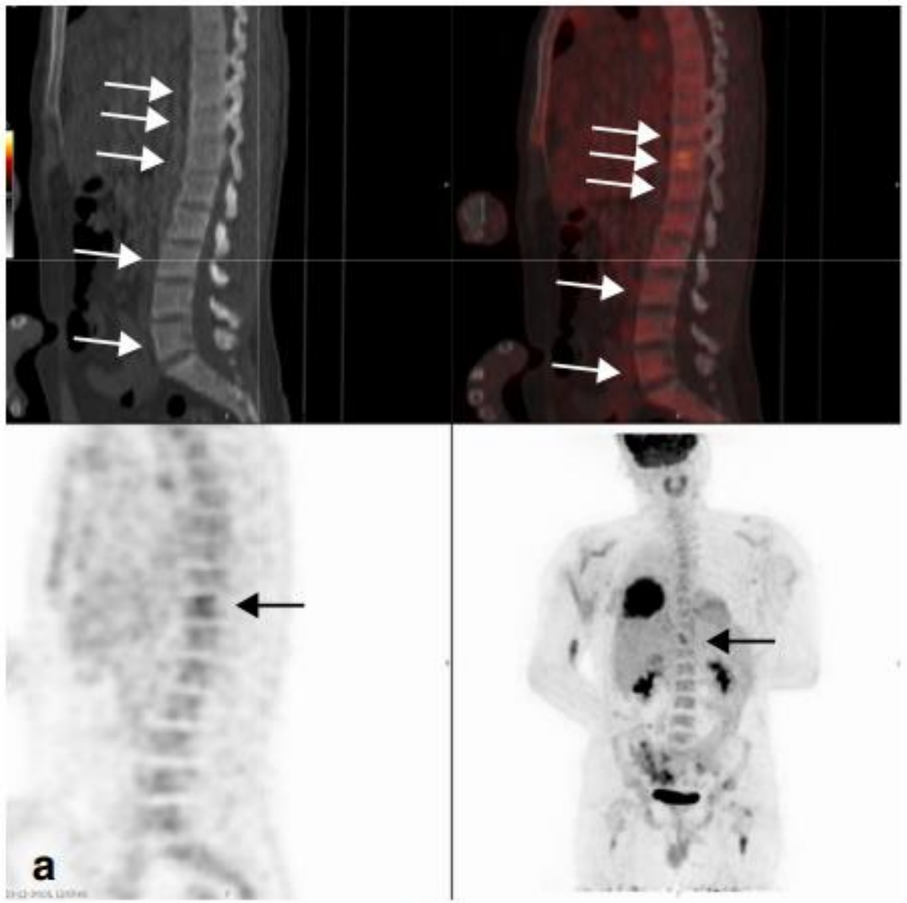


PET

- **41/1**
- Fals
  - Act
  - On
  - Les

^{18}F-FDG PET-CT versus MRI for detection of skeletal metastasis

Dijkstra [1] · J. L. Bloem [3]



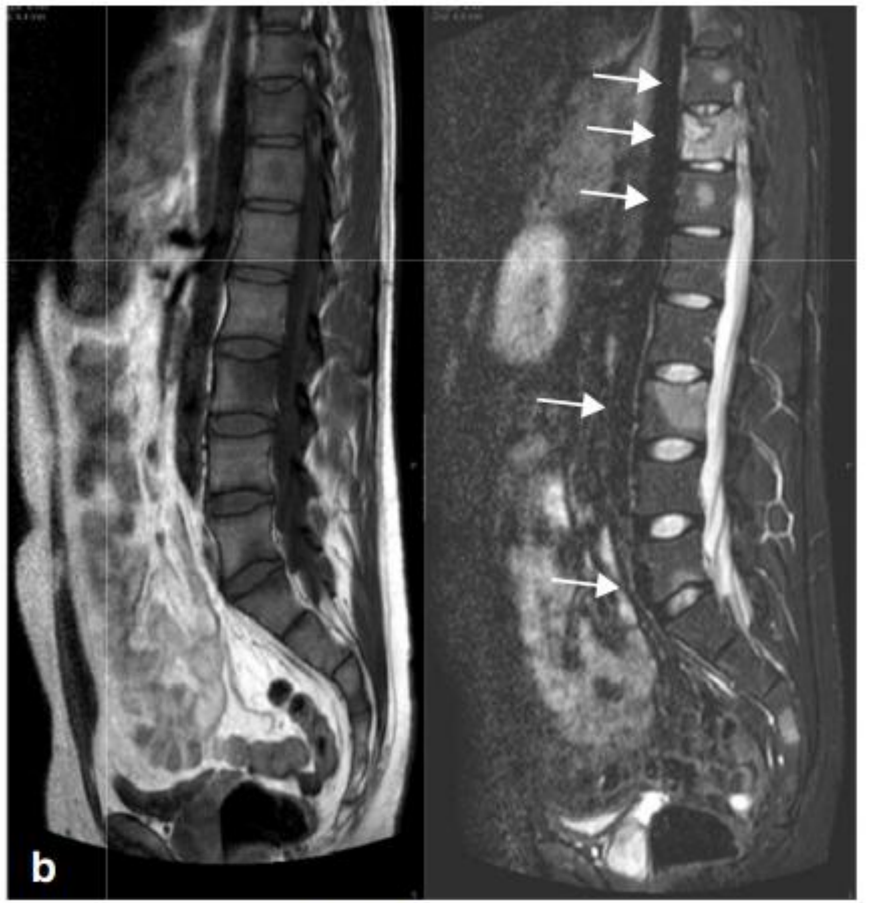


Fig. 5 False-negative lesions on ^{18}F-FDG PET-CT (*arrows*). A 23-year-old man presenting with metastatic Ewing sarcoma of the right seventh rib. Images obtained at diagnosis, before the start of treatment. **a** ^{18}F-FDG PET-CT showing increased ^{18}F-FDG-uptake at the eleventh thoracic vertebrae only. **b** T1-weighted (*left*) and STIR (*right*) images showing nodules with a high degree of suspicion for metastasis at the tenth, eleventh, and twelfth thoracic vertebrae and the third and fifth lumbar vertebrae

ns

	Total
1	106
2	6
3	112

MRI more sensitive for detecting skeletal metastases.

Skeletal Radiol. 2019

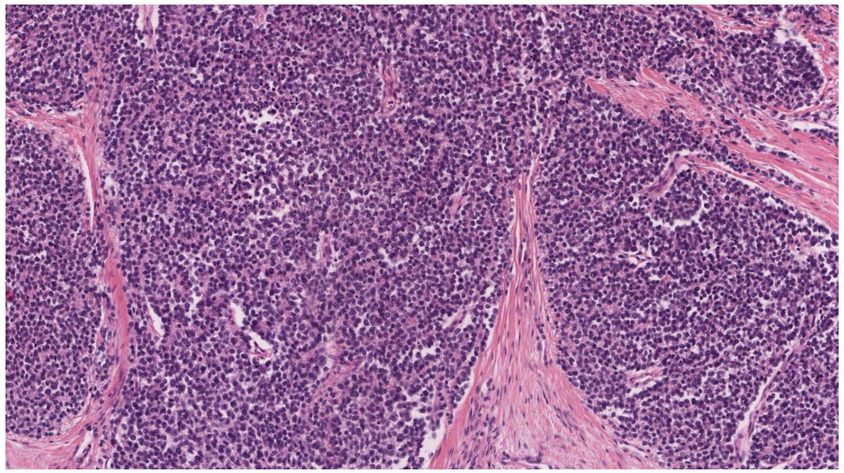
BIOPSY

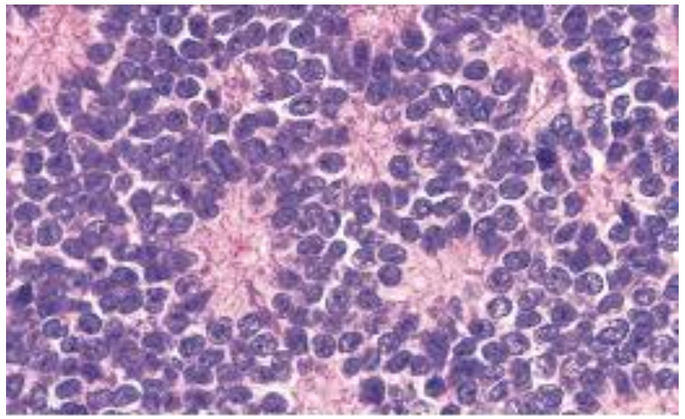
- Core (tru-cut / needle) biopsy is preferred
- Avoid contamination of future surgical planes
- Advisable to be done by the operating surgeon
- To be done after local MRI
- Biopsy should come from the **enhancing / viable region**, avoid necrotic / cystic zones
- In bone lesions with extraosseous component, use soft tissue route

Open / incisional biopsy reserved when needle biopsy is non-diagnostic or difficult location.
Excisional biopsy only in small lesions (< ~ 3 cm), superficial, benign-appearing.

HISTOPATHOLOGY

- **Sheets/lobules of uniform small round blue cells** (10-20 µm)
- Scant clear cytoplasm with glycogen (**PAS-positive, diastase-sensitive**)
- Round nuclei, finely stippled chromatin, inconspicuous nucleoli
- Delicate fibrovascular septa; patchy necrosis
- **Homer-Wright rosettes (pseudo-rosettes)** in ~20 %



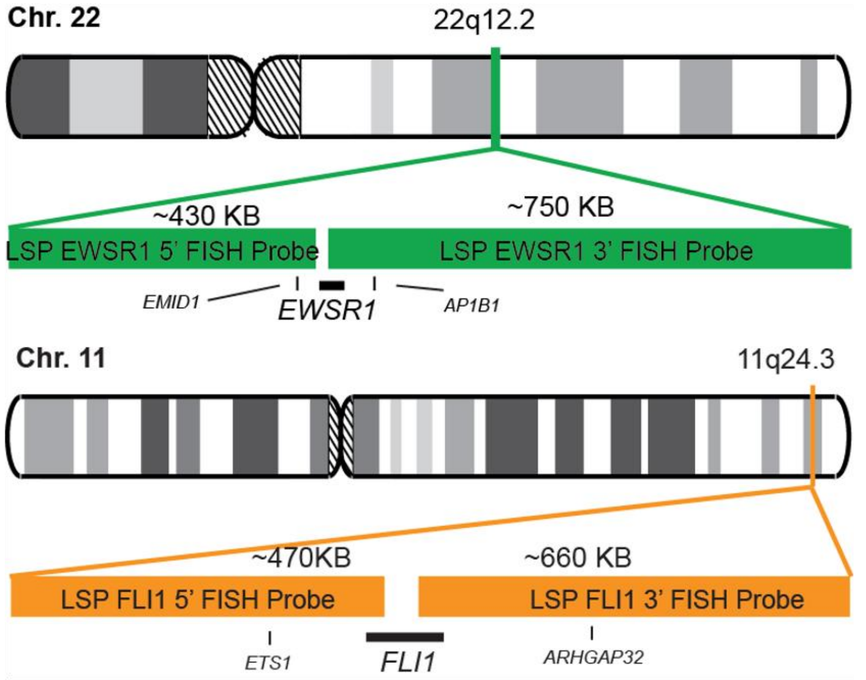


IMMUNOHISTOCHEMISTRY

CD99 (MIC2)	**Strong, diffuse membranous positivity** in >90% of cases
FLI-1	Nuclear positivity in ~85–90%
NKX2.2	Nuclear positivity**; ~90% sensitive and more specific than CD99**
Vimentin	Positive
Cytokeratin (low-molecular-weight)	Focal positivity in ~20–30%
Desmin, Myogenin, MyoD1	Negative (Helps exclude rhabdomyosarcoma.)
LCA (CD45)	Negative (Excludes Lymphoma)
Synaptophysin, Chromogranin, NSE	Often negative; NSE may be weakly positive
EMA	Focal positivity in some cases- non specific marker

Molecular Pathology

- **EWSR1–FLI1 Fusion Protein→** Pathognomonic fusion in ~85% of Ewing sarcoma family tumors (ESFT)
- Results from **t(11;22)(q24;q12) translocation →** Fusion **of EWSR1 gene (22q12) with FLI1 gene (11q24)**
  - **EWSR1: RNA-binding protein** → transcriptional activation
  - **FLI1: ETS family transcription factor** → DNA-binding domain
- **Fusion Protein**: Abnormal transcription factor → **activates oncogenic pathways**
- *Biological Effects*
  - Upregulation of **IGF-1, NKX2.2**, and other oncogenes
  - Promotes **proliferation, invasion, and survival of tumor cells**
  - Alters epigenetic landscape and blocks normal differentiation



EWS Like Tumors

Small RBCT similar to ES but lack the classic EWSR1-ETS fusion.

- Round cell sarcomas with **EWSR1 (or FUS)** fused to *non-ETS* partners
- **CIC-rearranged sarcomas** (e.g. CIC-DUX4) – MORE AGGRESSIVE
  - focal pleomorphism and epithelioid morphology
- **BCOR-rearranged sarcomas** (e.g. BCOR-CCNB3)
  - spindled neoplastic cell population
- Other rarer fusions like NFATC2, PATZ1 etc

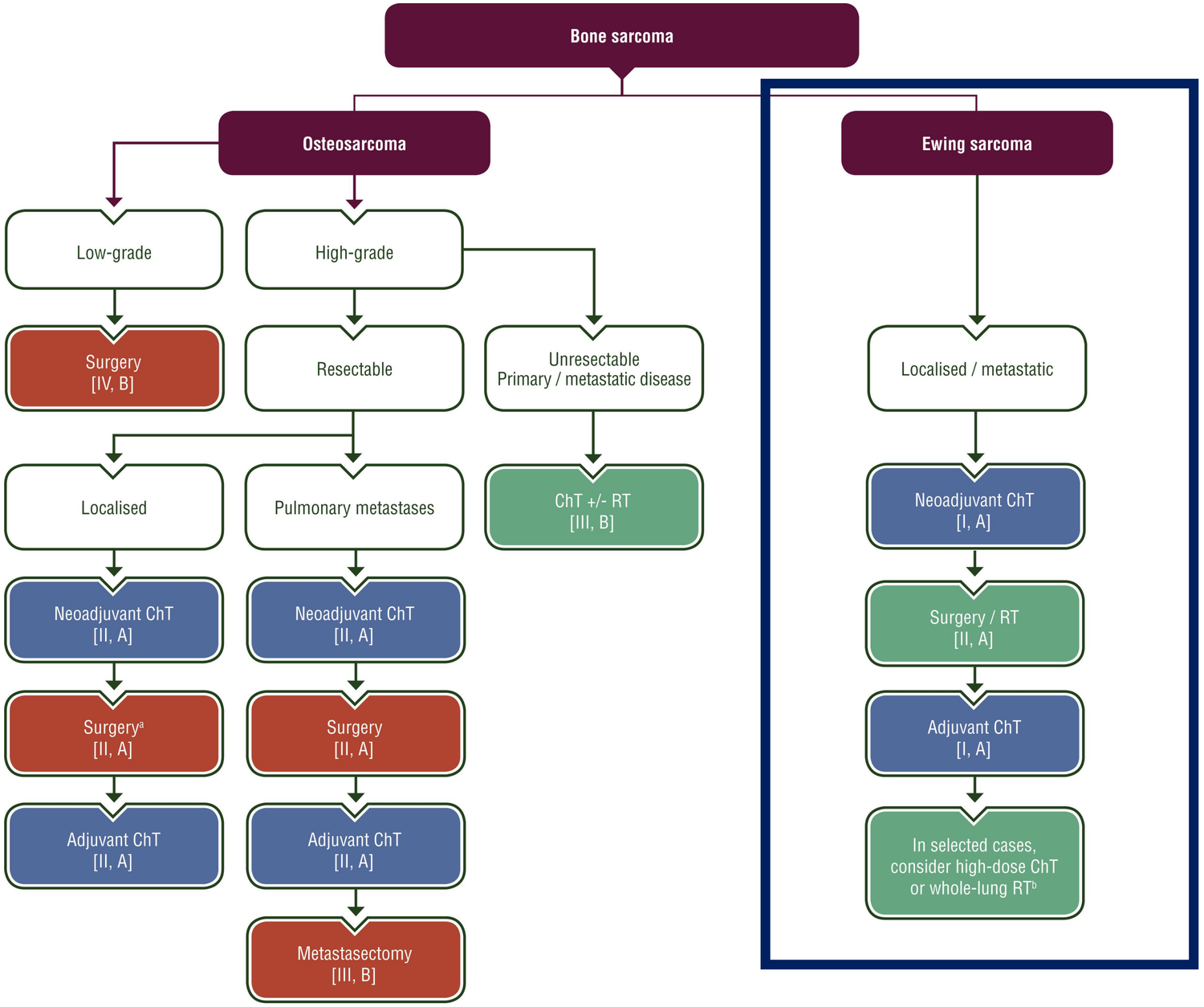
Histotype	Molecular alteration	Gene fusion
Ewing sarcoma	t(11;22)(q24;q12)	EWSR1-FLI1 (85%)
	t(21;22)(q22;q12)	EWSR1-ERG (10%)
		EWSR1-ETS gene family
		FUS-ETS gene family
EWSR1 RCS-non-ETS partners	t(20;22)(q13.2;q12)	EWSR1-NFATC2
	t(20;16)(q13.2;p11.2)	FUS-NFATC2
	inv(22)(q12; q12)	EWSR1-PATZ1
CIC sarcomas	t(4;19)(q35;q13)	CIC-DUX4
	t(10;19)(q26;q13)	CIC-DUX4
	t(x;19)(q13;q13.3)	CIC-FOXO4
	t(;19)()	CIC-LEUTX
	t(15;19)(q14;q13.2)	CIC-NUTM1
	t(10;19)(q23.3;q13)	CIC-NUTM2B
BCOR sarcomas	inv(x)(p11;p11)	BCOR-CCNB3
	BCOR-ITD	BCOR-ITD
	T(10;17)(q23.3;p13.3)	YWHAE1-NUTM2B
	t(4;x)(p11;q31)	BCOR-MAML3
	t(x;22;)(p11;q13.2)	ZC3H7B-BCOR

Prognostic Factors

Favorable Factors	Unfavorable Factors
Localized disease	Metastatic disease at diagnosis
Lung-only metastasis	Bone or bone marrow metastasis
Peripheral (limb) location	**Axial / pelvic location**
Small tumor size (< 8 cm)	**Large tumor size (≥ 8 cm)**
Younger age (< 15 years)	Older age (> 15–25 years)
Normal LDH levels	Elevated LDH levels
Good response to chemotherapy	**Poor response to chemotherapy**

Historical Treatment

- Surgery / RT was mainstay of treatment
- **5 yr OS <10 %**
- Major failure- DISTANT METS


Bone sarcoma
Osteosarcoma
Ewing sarcoma
Low-grade
High-grade
Surgery
[IV, B]
Resectable
Unresectable
Primary / metastatic disease
Localised
Pulmonary metastases
ChT +/- RT
[III, B]
Neoadjuvant ChT
[II, A]
Neoadjuvant ChT
[II, A]
Surgery[a]
[II, A]
Surgery
[II, A]
Adjuvant ChT
[II, A]
Adjuvant ChT
[II, A]
Metastasectomy
[III, B]
Localised / metastatic
Neoadjuvant ChT
[I, A]
Surgery / RT
[II, A]
Adjuvant ChT
[I, A]
In selected cases,
consider high-dose ChT
or whole-lung RT[b]

Current Treatment Practice

Important Drugs

Drug	Mechanism	Dose	Common Toxicities
Vincristine (V)	Microtubule inhibitor → mitotic arrest	1.5 mg/m² IV (max 2 mg)	Peripheral neuropathy, constipation/ileus, SIADH, alopecia
Doxorubicin (D)	Topoisomerase II inhibitor, free radical generation	75 mg/m² IV (single or divided)	Cardiotoxicity (cumulative), myelosuppression, mucositis, alopecia
Cyclophosphamide (C)	Alkylating agent (DNA crosslink)	1,200 mg/m² IV	Myelosuppression, hemorrhagic cystitis, nausea/vomiting
Ifosfamide (I)	Alkylating agent (non–cross-resistant)	1,800 mg/m²/day × 5 days (total 9 g/m²)	Hemorrhagic cystitis, renal tubular injury, encephalopathy, myelosuppression
Etoposide (E)	Topoisomerase II inhibitor	100 mg/m²/day × 5 days	Myelosuppression, alopecia, mucositis, secondary AML

TMH I

Drug Name	Drug Description	Cycle 1 [14 Days]	Cycle 2 [14 Days]	Cycle 3 [21 Days]	Cycle 4 [21 Days]
FILGRASTIM PEG	6.00 mg, 6.00 mg(Total Dose), Subcutaneous Once	D:3	D:3	D:7	D:7
CYCLOPHOSPHAMIDE	600.00 mg/m2, Intravenous Peripheral Line, in 100 ml Onceof Normal Saline, over 30	D:1	D:1	X	X

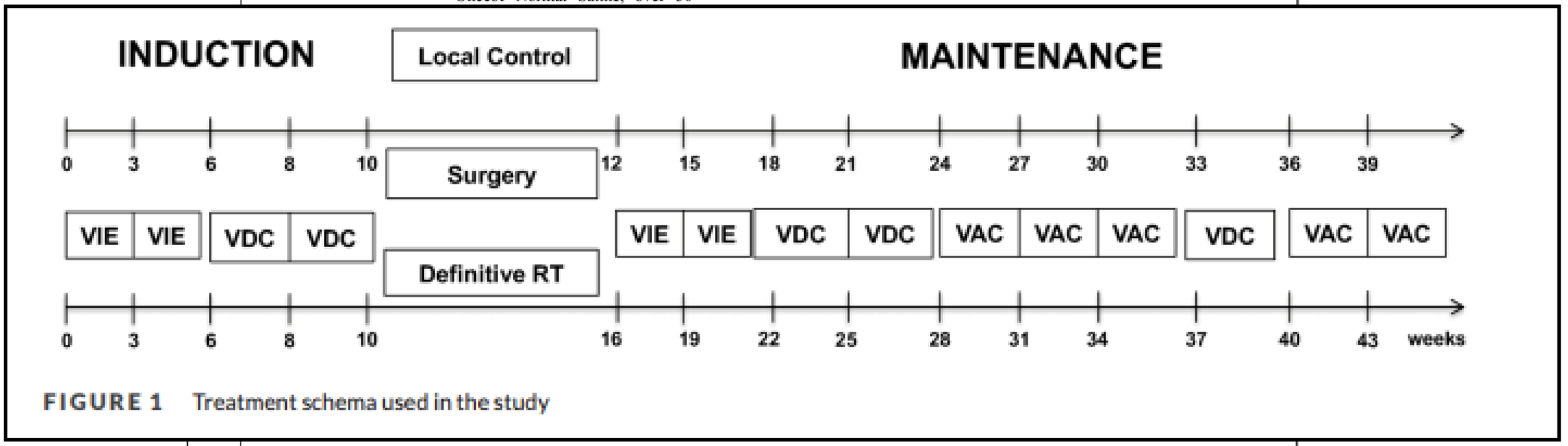


FIGURE 1 Treatment schema used in the study

OLANAZIPINE	10.00 mg, 10.00 mg(Total Dose), Per Oral Once, after dinner	D:1, D:2, D:3, D:4	D:1, D:2, D:3, D:4	X	X
ETOPOSIDE	100.00 mg/m2, Intravenous Peripheral Line, in 500 ml Onceof Normal Saline, over 2 Hours as Infusion	X	X	D:1, D:2, D:3, D:4, D:5	D:1, D:2, D:3, D:4, D:5
APREPITANT	80.00 mg, 80.00 mg(Total Dose), Per Oral Once	D:2, D:3	D:2, D:3	D:2, D:3	D:2, D:3

Pediatr Blood Cancer. 2020

EVOLUTION OF CHEMOTHERAPY

IESS1

Multimodal Therapy for the Management of Primary, Nonmetastatic Ewing's Sarcoma of Bone: A Long-Term Follow-Up of the First Intergroup Study

By Mark E. Nesbit, Jr, Edmund A. Gehan, E. Omer Burgert, Jr, Teresa J. Vietti, Ayten Cangir, Melvin Tefft, Richard Evans, Patrick Thomas, Frederic B. Askin, J.M. Kissane, Douglas J. Pritchard, Janice Herrmann, James Neff, John T. Makley, and Louis Gilula

- 1st RCT in ES
- Compared 3 arms
  - VAC + ADR + RT primary
  - VAC + RT primary
  - VAC + Lung RT + RT primary

Arm	RFS at 5y	OS at 5y	Mets
T1 (VAC+ADR)	**60%**	**65%**	**30%**
T2 (VAC)	24%	28%	72%
T3 (VAC+BPR)	44%	53%	42%

- **Pelvic primaries → poor OS** (34%) vs non-pelvic (57%)
- **Failure pattern**
  - Distant Mets- 44% (lung/bone ~50% each)
  - Local recurrence 15%
  - Lung mets not prevented by B/L lung RT- 20% pt had lung mets vs 15% in VAC + ADR

Established **chemo (VAC+ADR) + RT** as **standard of care**

JCO, 1990

IESS-2

- IESS-II designed to test **intensive chemotherapy regimens** for **nonpelvic, localized ES**.
- Treatment Arms

  High-dose intermittent VAC + ADR
  - ADR 75 mg/m², Cyclophosphamide 1400 mg/m², Vincristine 1.5 mg/m², Dactinomycin 0.45 mg/m²
  - 6-week cycles × 13 (78 weeks)

  Moderate-dose continuous VAC + ADR
  - ADR 60 mg/m², Cyclophosphamide 500 mg/m², Vincristine 1.5 mg/m², Dactinomycin 0.45 mg/m²
  - Alternating 6-week and 10-week cycles (76 weeks)
- **Local Treatment-** Surgery / RT (if unresected or incomplete resection).

JCO, 1990

- **High-dose intermittent VAC+ADR** superior to moderate-dose continuous regimen.
- Improved **DFS, RFS, and OS**.
- Main failure- distant metastases, esp. lung.
- Toxicity comparable, but higher cardiac risk (ADR).

INT-0091

NEJM, 2003

- Patients ≤30 years, bone primary, untreated Ewing's/PNET.
- **Standard arm:** VACD × 17 cycles.
- **Experimental arm:** VACD alternating with IE.

- Duration: 49 weeks.
- Local control (week 12): surgery, RT, or both

Non-Metastatic Group
5-yr EFS: **69%** vs 54%, *P=0.005*.
5-yr OS: 72% vs 61%, *P=0.01*

Metastatic Group
5-yr EFS: 22% (both arms)
5-yr OS: 34% vs 35%
No statistical difference

ORIGINAL ARTICLE

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

Authors: 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., +7 , and James S. Miser, M.D. Author Info & Affiliations

Published February 20, 2003 | N Engl J Med 2003;348:694-701 | DOI: 10.1056/NEJMoa020890 | VOL. 348 NO. 8

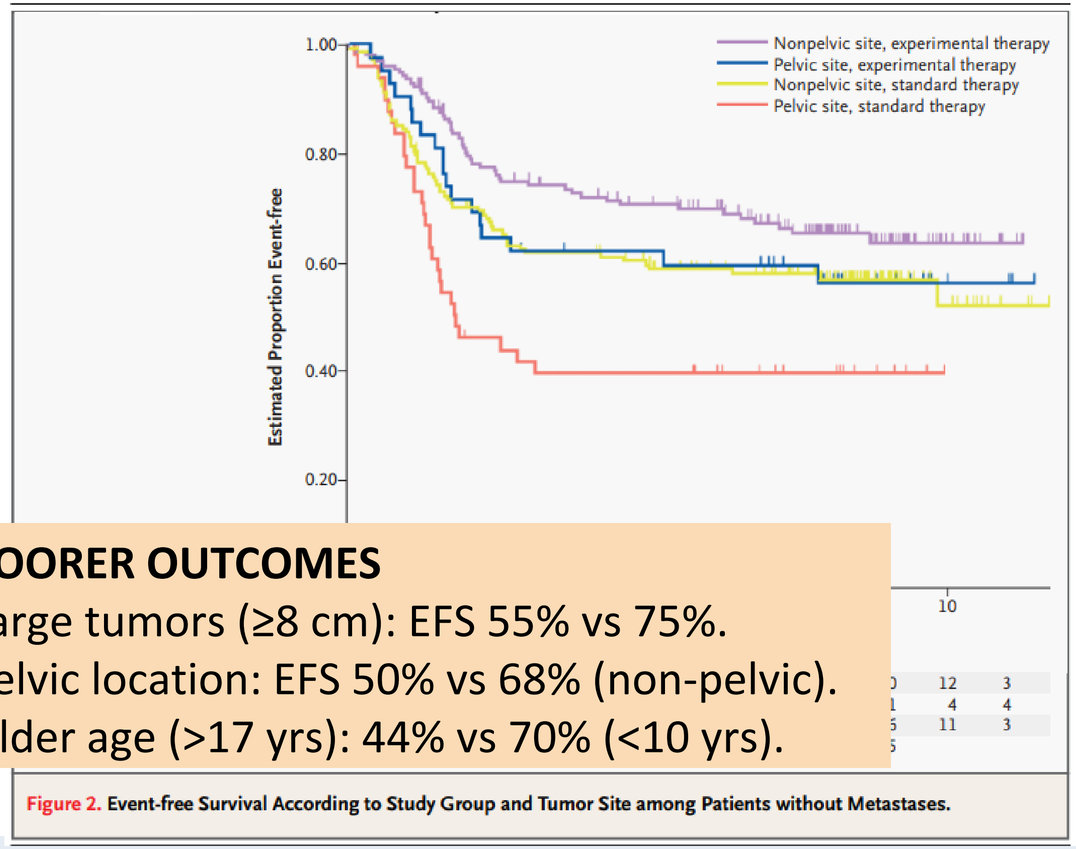


Figure 2. Event-free Survival According to Study Group and Tumor Site among Patients without Metastases.

POORER OUTCOMES
Large tumors (≥8 cm): EFS 55% vs 75%.
Pelvic location: EFS 50% vs 68% (non-pelvic).
Older age (>17 yrs): 44% vs 70% (<10 yrs).

NEJM, 2003

INT 0154

- Study on dose intensification
- **Standard arm:** VDC/IE every 3 weeks × 17 cycles (48 weeks).
- **Intensified arm:** VDC/IE every 3 weeks × 11 cycles (30 weeks)
- Same cumulative dose

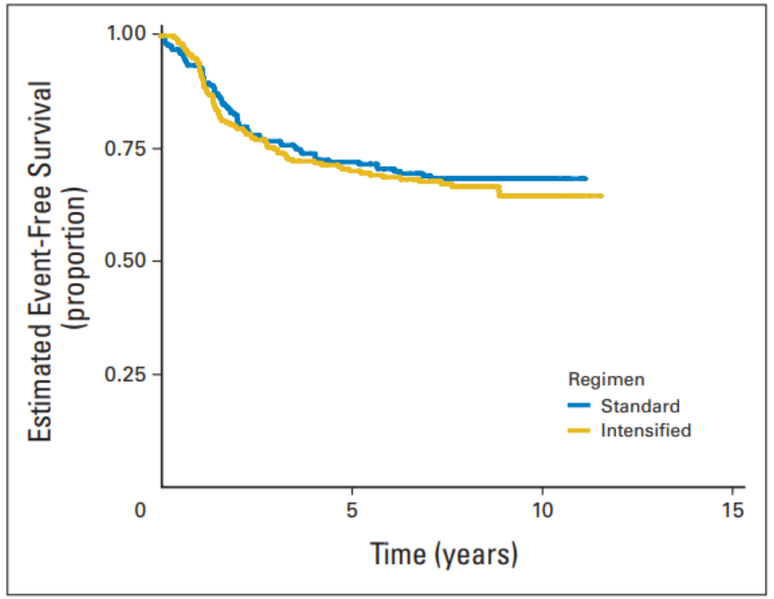


Fig 2. Event-free survival for all eligible patients by regimen.

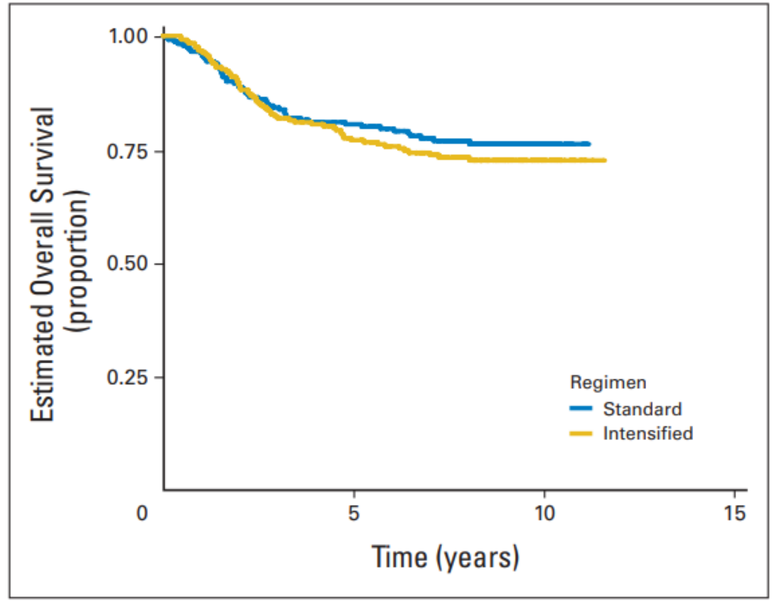


Fig 3. Overall survival for all eligible patients by primary bone site.

Dose-intensification of alkylating agents did not improve survival in localized ESFT of bone or soft tissue.

JCO, 2009

AEWSC

- Hypothesis
  drug doses
  outcomes
- Treatment

5 yr EFS: 65
5 yr OS: 77%

- Similar tox
- <17 yr and

Randomized Controlled Trial of Interval-Compressed
alized Ewing
Oncology Group

ce R. Pawel, Holcombe E. Grier,
R. Weiss

keeping
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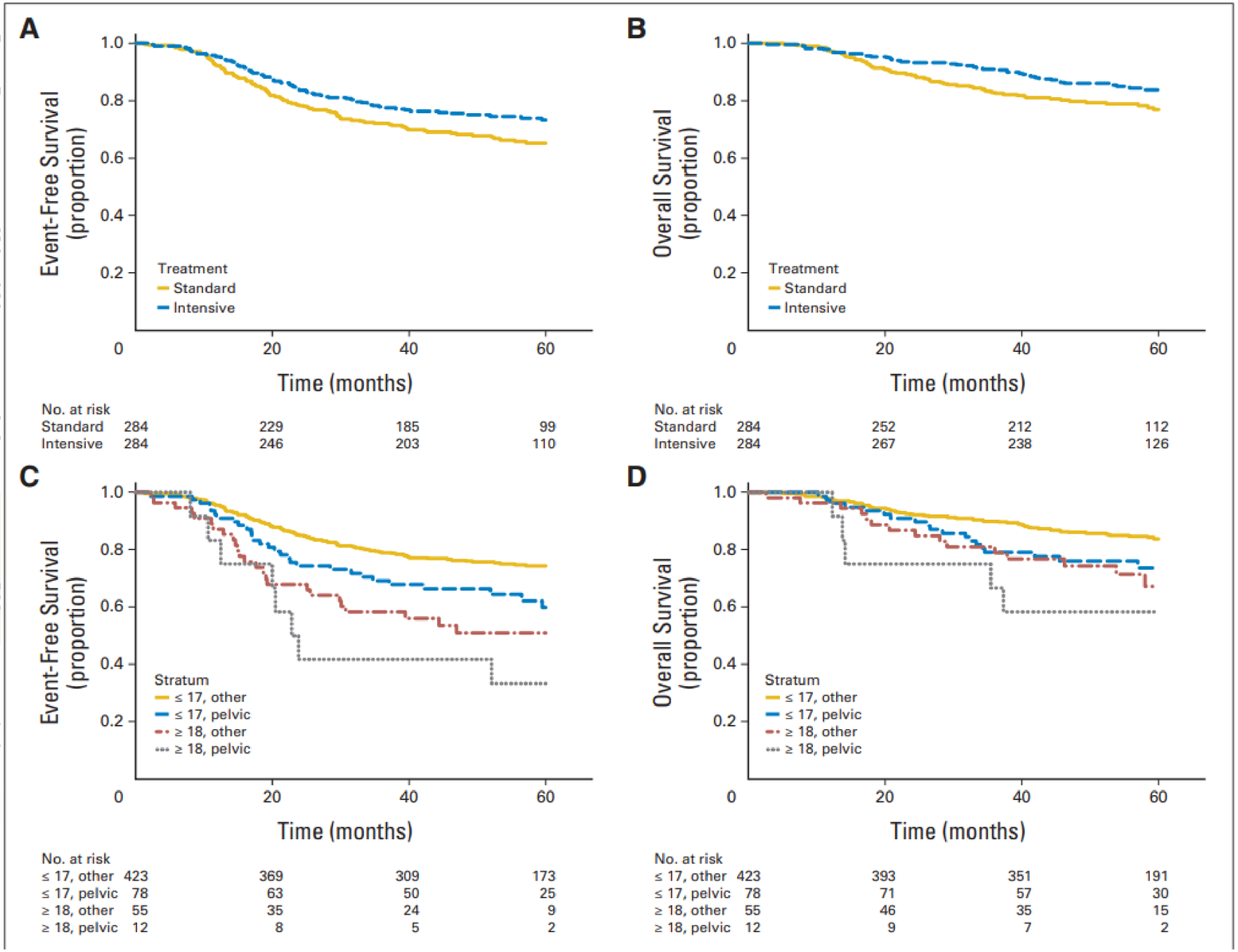


JCO, 2012

EURO EWING 2012 (EE2012)

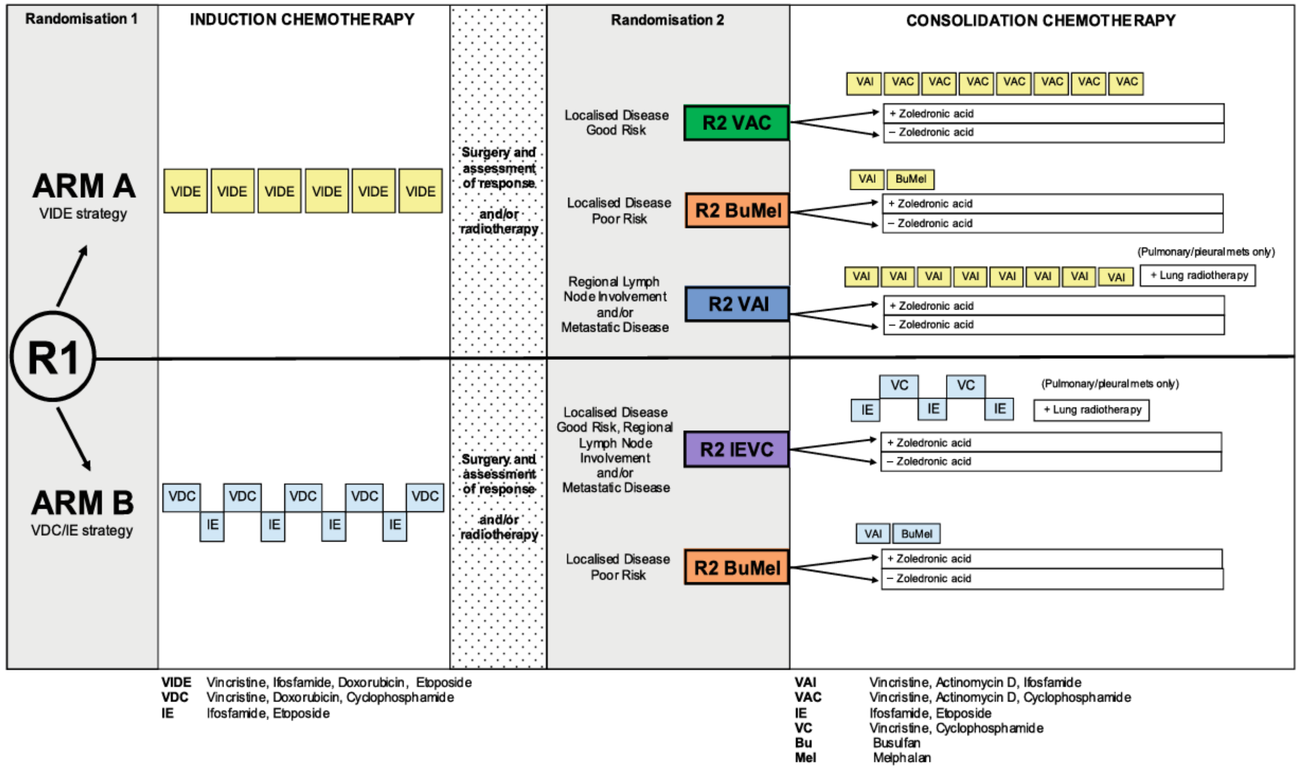
- **Arm A (Europe strategy – VIDE)**
- **Induction:** 6× VIDE
- **Consolidation (risk-adapted):**
  - Good-risk localized → VAI → VAC ×7
  - Poor-risk localized (no BuMel CI) → VAI → BuMel (HDCT + PBSC)
  - Poor-risk / LN / metastatic (BuMel CI) → VAI ×8

- **Arm B (US strategy – VDC/IE)**
- **Induction:** 9 alternating VDC + IE
- **Consolidation:**
  - Good-risk / LN / metastatic / poor-risk (BuMel CI) → 5× (IE ↔ VC)
  - Poor-risk localized (no BuMel CI) → VAI → BuMel

Lung RT given in pulmonary/pleural mets

POOR RISK FEATURES

- **Large tumor volume ≥200 mL**
- **Poor histologic response** (≥10% viable tumor)
- **Unresectable primary** treated with RT alone
- Tumor **<200 mL but poor radiological response** (<50% regression on induction)
- Need for **pre-operative RT**



Lancet, 2020

Comparison of two chemotherapy regimens in patients with newly diagnosed Ewing sarcoma (EE2012): an open-label, randomised, phase 3 trial

Bernadette Brennan, Laura Kirton, Perrine Marec-Bérard, Nathalie Gaspar, Valerie Laurence, Javier Martín-Broto, Ana Sastre, Hans Gelderblom, Cormac Owens, Nicola Fenwick, Sandra Strauss, Veronica Moroz, Jeremy Whelan, Keith Wheatley

- Showed that- VDC/IE improves EFS & OS
- less hemat toxicities
- shorter & more deliverable
- New International standard

	VIDE (n=320)	VDC/IE (n=320)	HR (95% CI)
3-yr EFS	61%	**67%**	0.71 (0.55–0.92)
3-yr OS	74%	**82%**	0.62 (0.46–0.85)

- **Grade 3–5 AEs:** ~90% both groups
- **Febrile neutropenia:** 74% (VIDE) vs **58% (VDC/IE)**
- **Platelet transfusion:** 64% (VIDE) vs 43% (VDC/IE)
- **Blood transfusion:** 87% vs 89%

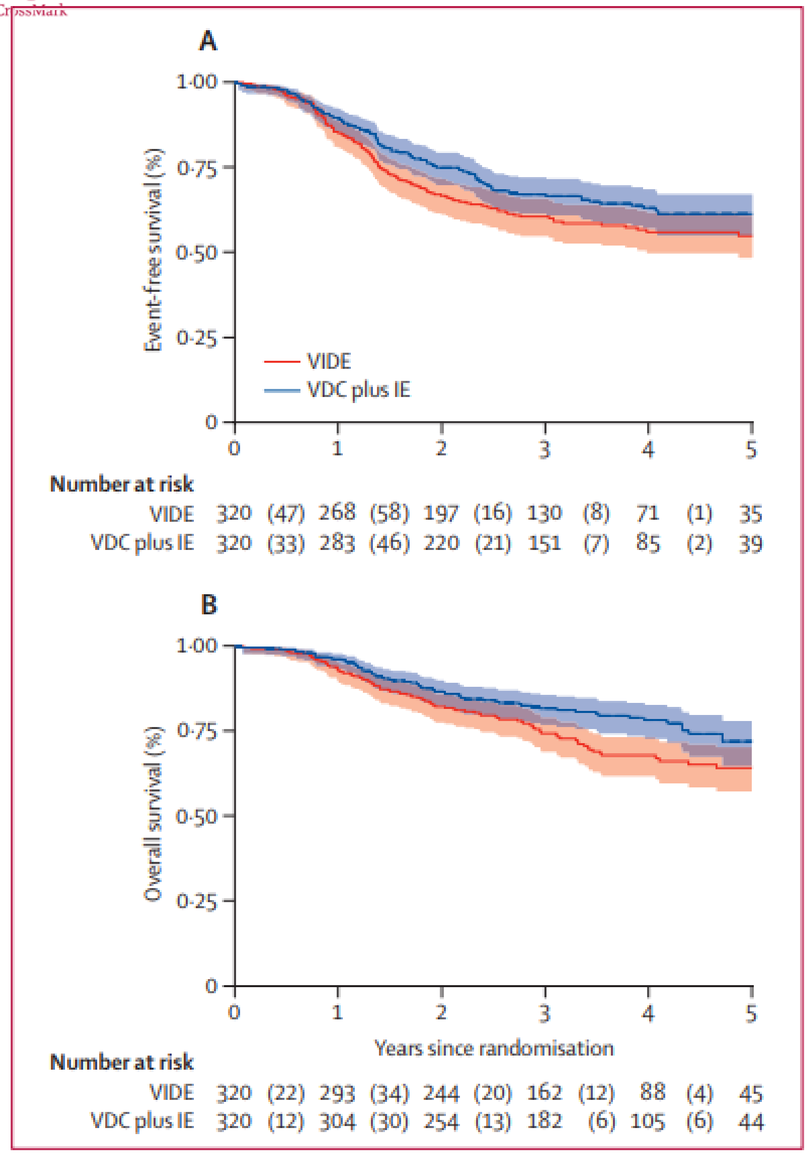


Figure 2: **Kaplan-Meier estimates**
(A) Event-free survival. (B) Overall survival. IE=ifosfamide and etoposide. VDC=vincristine, doxorubicin, and cyclophosphamide. VIDE=vincristine, ifosfamide, doxorubicin, and etoposide.

Lancer, 2020

Study	N	Intervention	Results	
IESS I 1973	143	VAC + ADR + RT vs VAC + RT vs VAC + ADR + Lung RT	5-yr OS: Pelvic 34% vs Non-pelvic 57%; Lung RT didn't prevent mets	Established chemo (VAC+ADR) + RT as standard
IESS II 1981	214	High-dose intermittent VAC+ADR vs Moderate-dose continuous	High-dose better DFS/OS; lung mets main failure	Intensive chemo superior
INT-0091 (NEJM 2003)	518	VACD vs VACD/IE (alternating)	Localized ES: 5-yr OS 72% vs 61% (p=0.01); No benefit in metastatic	VACD/IE new standard
INT-0154 1990s	478	Standard VDC/IE vs Dose-intensified VDC/IE	No OS benefit	Dose-intensification not useful
AEWS0031 2009	587	q3w vs q2w interval-compressed VDC/IE	5-yr OS 83% vs 77%; EFS 73% vs 65%	Interval compression improves outcomes
EURO EWING 2012	640	VIDE (Europe) vs VDC/IE (US)	VDC/IE less toxic, more deliverable, similar efficacy	VDC/IE international standard

Local Treatment

Surgery

Radiotherapy

- Local therapy is essential for cure.
- ES is radiosensitive → RT was standard for decades
- Advances in orthopedic surgery → function preservation + improved survival.
- **No RCTs** directly comparing Surgery vs RT.
- Reasons: inherent biases, ethical dilemmas.

Goal of Surgery: Complete **en-bloc resection with adequate margins**.
Functional limb-sparing resections preferred when feasible.

Timing of Local Treatment

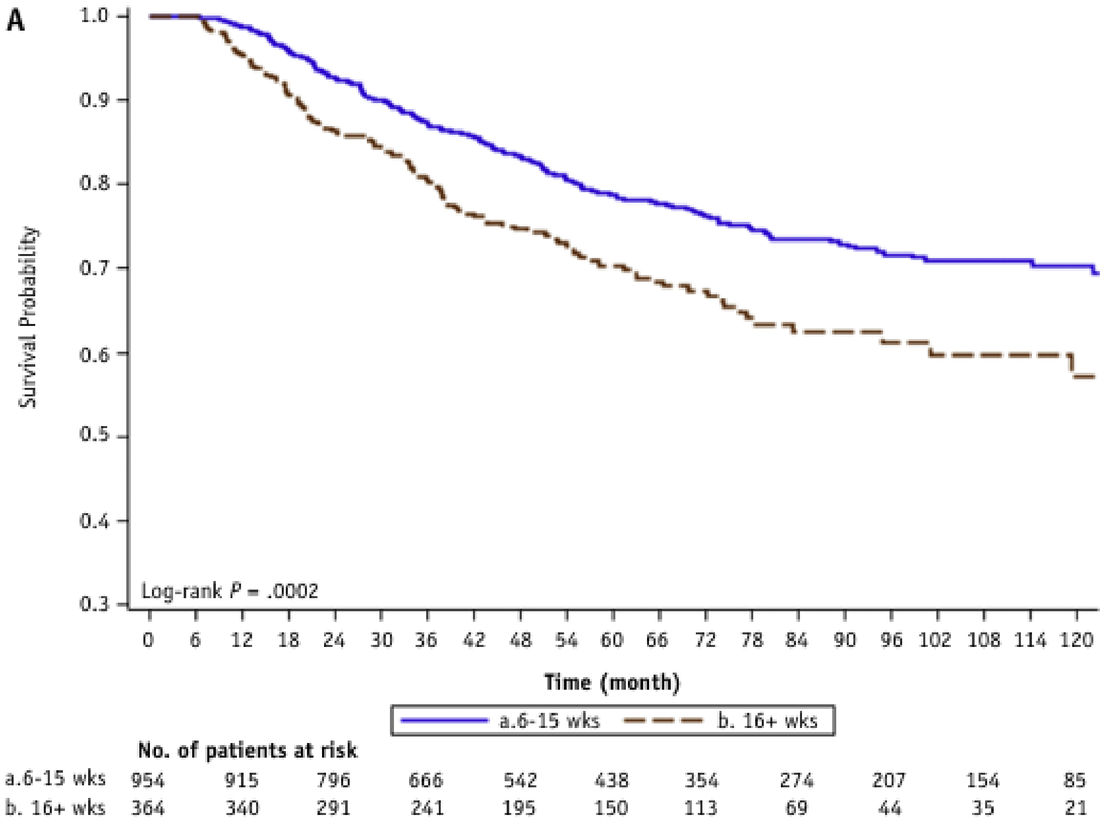
Timing of Local Therapy Affects Survival in Ewing Sarcoma

Timothy A Lin [1], Ethan B Ludmir [2], Kai-Ping Liao [3], Mary Frances McAleer [2], David R Grosshans [2], Susan L McGovern [2], Andrew J Bishop [2], Kristina D Woodhouse [2], Arnold C Paulino [4], Debra Nana Yeboa [5]

- Local therap
- 5-yr OS: **78.7**
- 10-yr OS: **70.**

- Effect strong

Other adverse fa



p=.003)

vs neg. margins.

Conclusion: Local th ndependently predict inferior OS, esp. with RT-alone.

IJROBP, 2019

SURGERY

Margins

Type	Definition
Intralesional	Tumor violated during surgery, positive margins
Marginal	Through reactive zone, close margin
Wide	Margin of normal tissue around the tumor
Radical	Removal of entire compartment containing the tumor

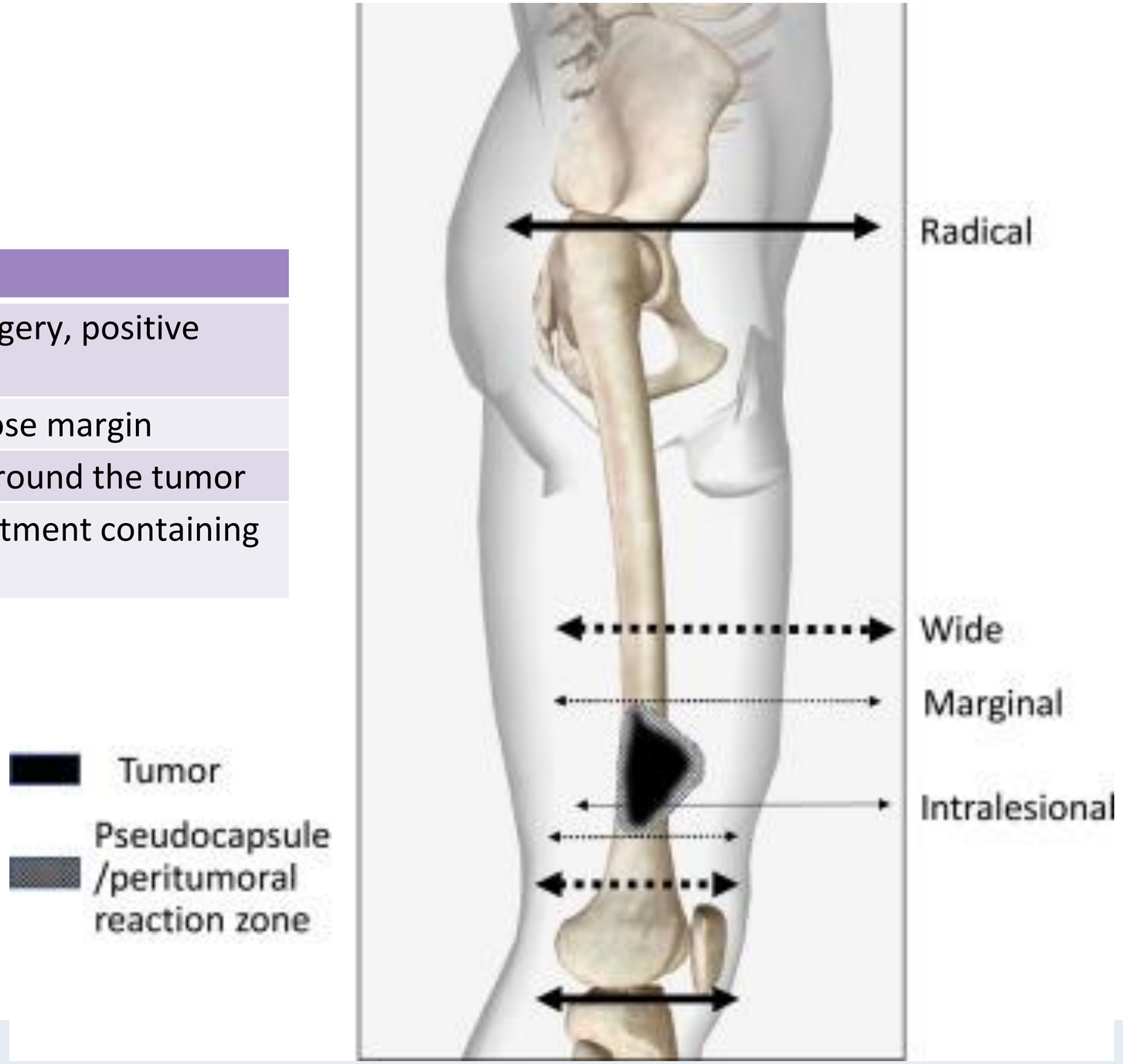


TABLE II. A Comparison of Outcomes Based on Surgical Margins

References	Margins	Local control	Event-free survival	Overall survival
Ozaki et al. [4]	Adequate	96%		
	Inadequate	88%		
		($P = 0.045$)		
Bacci et al. [5]	Adequate	93%	69.5%	
	Inadequate	81%	50% ($P < 0.001$)	
		($P = 0.001$)		
Sluga et al. [6]	Adequate			60.2%
	Inadequate			40.1% ($P < 0.05$)
Lin et al. [7]	$\geq$10 mm	93%		
	3–9 mm	83%		
	$\leq$2 mm	78%		
		($P = 0.23$)		

Principles of Surgery

Achieve R0 resection while preserving function wherever feasible

- **Wide en bloc resection** of primary with margins including biopsy tract.
- **Compartmental resection** preferred.
- **Limb-salvage surgery** (LSS)
  - Feasible in majority (~85–90% cases at major centers).
  - Requires endoprosthesis, allograft, or vascularized fibula reconstruction.
- **Amputation** is considered
  - Tumor encases **neurovascular bundle**
  - **Extensive contamination** from biopsy/previous surgery
  - Poor reconstruction options.
- **Chest wall primaries**: en bloc resection of involved ribs ± lung wedge resection.

Radiotherapy in Ewing’ Sarcoma

Pre OP

Post OP

Definitive

Intra OP RT

Brachytherapy

ECRT

Lung Bath

Palliative RT

Indications for dRT/CTRT

Sites	• Surgery may be **morbid/not feasible** (spine/skull base)
Large tumor volumes	• Difficult to resect safely (also a poor prognostic factor).
Function preservation priority	• Pelvic Tumors → Pelvic instability, Loss of ambulatory function, Bowel or bladder dysfunction
Unresectable tumors	• Only intralesional or debulking surgery is otherwise feasible. (skull base tumor extending into brain, chest wall tumors infiltrating great vessels)
Preference	• **Patient refusal** of surgery in otherwise operable case

Post-operative RT (PORT)

- **Positive surgical margins** (R1/R2 resections).
- **Poor histologic response to chemotherapy** (>10% viable tumor).
- **Large soft tissue component** before surgery.
- **Pretreatment pathological fracture**.
- **Contamination of surrounding tissue** during Sx or inadequate surgical technique.
- **Close or marginal margins**, especially in high-risk anatomical sites.
- **Pelvic primaries**

Pediatr Blood Cancer 2008;51:575–580

REVIEW
Post-Operative Radiotherapy for Ewing Sarcoma: When, How and How Much?

S. Laskar, MD,* I. Mallick, MD, T. Gupta, MD, and M.A. Muckaden, MD

TABLE IV. Summary of Recommendations on Post-Operative RT

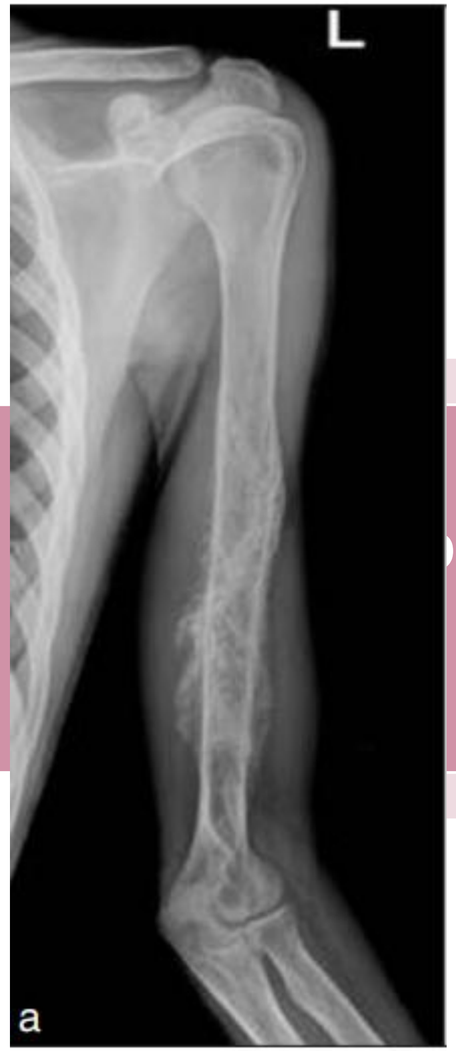
Indications	Gross or microscopic positive margins
	Clear margins but poor histopathological response to chemotherapy (necrosis <90% is the suggested minimum threshold, but <95–99% may be used based on institutional practice)
Timing	Within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)
Dose	45 Gy to the pre-chemotherapy volume
	10.8 Gy boost to areas of gross tumor residual
Fractionation	Standard daily fractionation of 1.8 Gy per fraction
	Hyperfractionated RT (with equivalent total dose) may be used to reduce long term side effects
Target volume	Initial phase (45 Gy): pre-chemotherapy tumor volume on MRI with 1.5–2 cm margins. Appropriate modifications should be made in tumors expanding into cavities or the lung
	Boost phase (10.8 Gy): post-operative gross residual disease with 1.5–2 cm margins

Pediatr Blood Cancer, 2008

ECRT

Extracorporeal irradiated tumor bone: A reconstruction option in diaphyseal Ewing's sarcomas

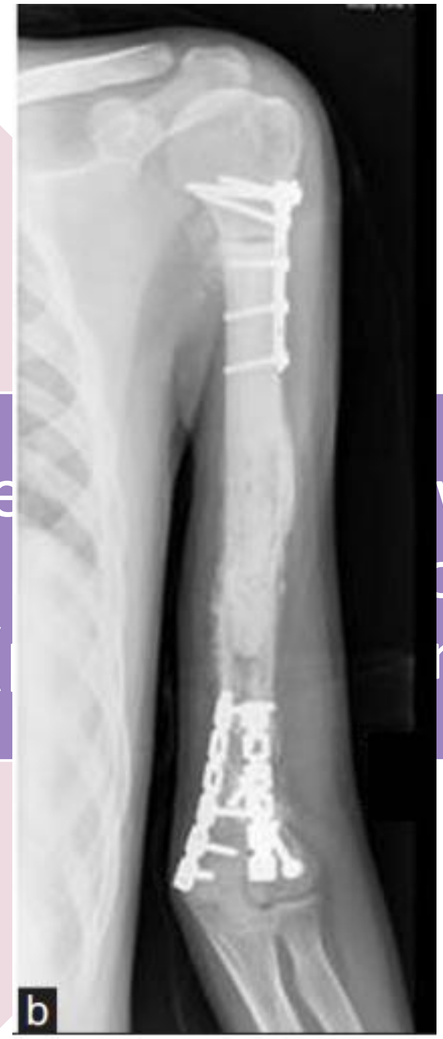
Ajay Puri [1,✉], Ashish Gulia [1], MG Agarwal [1], NA Jambhekar [1], S Laskar [2]



Advantages of re implanting sterilized bone:

- Biological reconstruction
- Inexpensive
- Obviates needs of bone bank
- Neglates risks associated with allograft implant: graft rejection, transmission of viral diseases

50 Gy extracorporeal irradiation

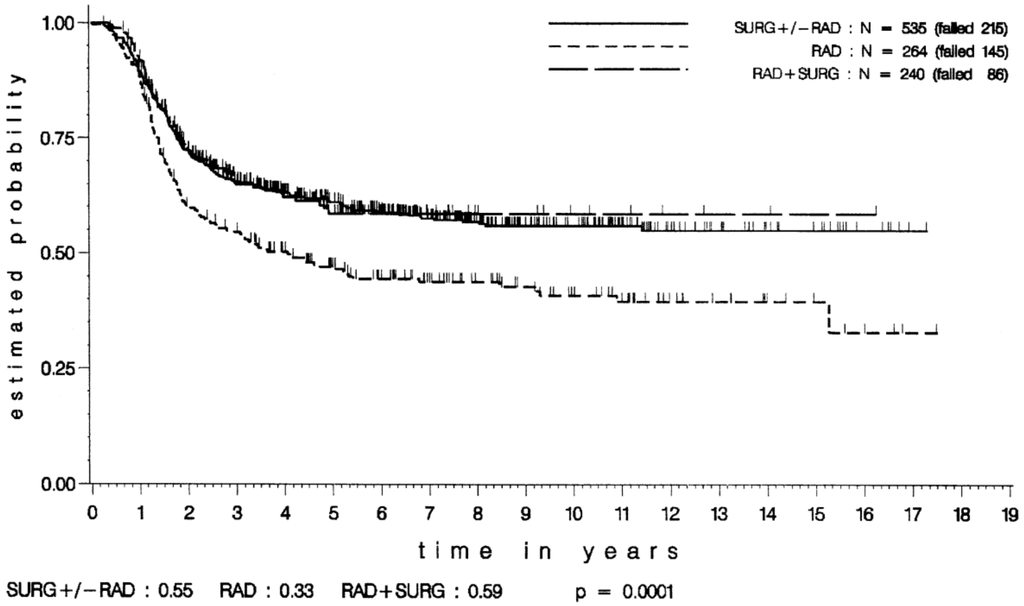


Indian J Orthop. 2010 Oct-Dec

LOCAL THERAPY IN LOCALIZED EWING TUMORS: RESULTS OF 1058 PATIENTS TREATED IN THE CESS 81, CESS 86, AND EICESS 92 TRIALS

ANDREAS SCHUCK, M.D.,* SUSANNE AHRENS, B.S.,† MICHAEL PAULUSSEN, M.D.,† MICHAELA KUHLEN, M.D.,† STEFAN KÖNEMANN, M.D.,* CHRISTIAN RÜBE, M.D.,‡ WINFRIED WINKELMANN, M.D.,§ RAINER KOTZ, M.D.,‖ JÜRGEN DUNST, M.D.,¶ NORMANN WILLICH, M.D.,* AND HERIBERT JÜRGENS, M.D.†

Study	Definitive RT	Post-op RT
CESS 81	46–60 Gy	36 Gy for incomplete resections
CESS 86	60 Gy	44 Gy (wide/marginal), 60 Gy (intralesional)
EICESS 92	54 Gy	44 or 54 Gy (based on margins & histology)



Local Therapy	Local Failure (LF)	
Surgery ± Post-op RT	**7.5%**	Standard approach. Post-op RT for marginal/intralesional resections or poor histologic response.
Pre-op RT + Surgery	**5.3%**	Good LC. Useful for function-preserving surgery.
Definitive RT (RT alone)	**26.3%** ($p<0.001$)	Negative selection (unresectable, central tumors). Comparable to post-op RT after intralesional resection.

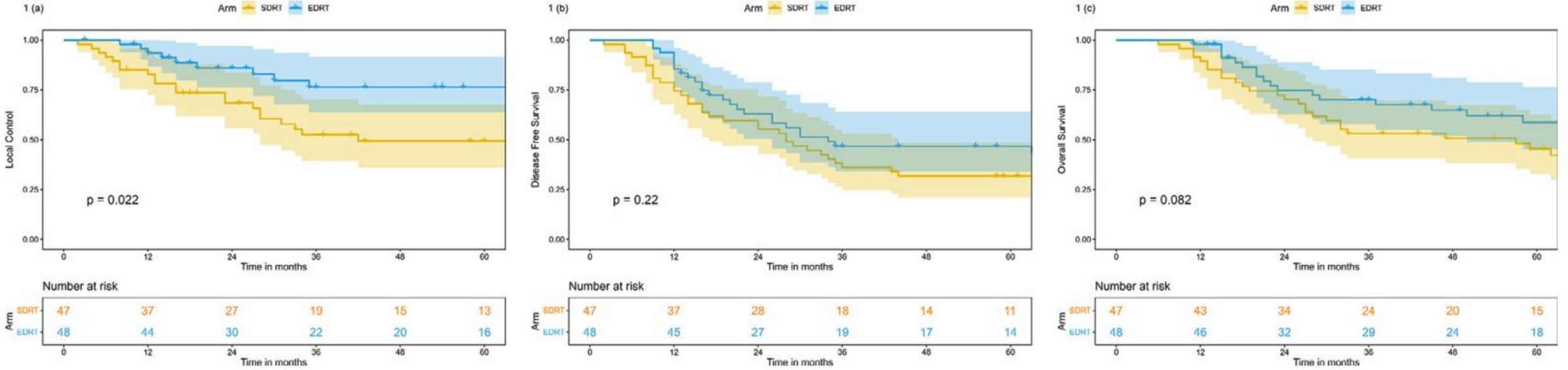
IJROBP, 2003

Dose Escalation

Radiation Therapy Dose Escalation in Unresectable Ewing Sarcoma: Final Results of a Phase 3 Randomized Controlled Trial

Siddhartha Laskar, MD,* Shwetabh Sinha, MD,* Abhishek Chatterjee, MD,* Nehal Khanna, MD,* Jifmi Jose Manjali, MD,* Ajay Puri, MS,† Ashish Gulia, MCh,† Prakash Nayak, MS,† Tushar Vora, MD,‡ Girish Chinnaswamy, MD,‡ Maya Prasad, MD,‡ Jyoti Bajpai, DM,§ Shashikant Juvekar, MD,‖ Subhash Desai, MD,‖ Amit Janu, DNB,‖ Venkatesh Rangarajan, MD,¶ Nilendu Purandare, MD,¶ Sneha Shah, MD,¶ Bharat Rekhi, MD,# Nirmala Jambhekar, MD,# Mary Ann Muckaden, MD,* and Purna Kurkure, MD‡

- Non-metastatic, **unresectable** extracranial Ewing sarcoma (PNET, role of dose



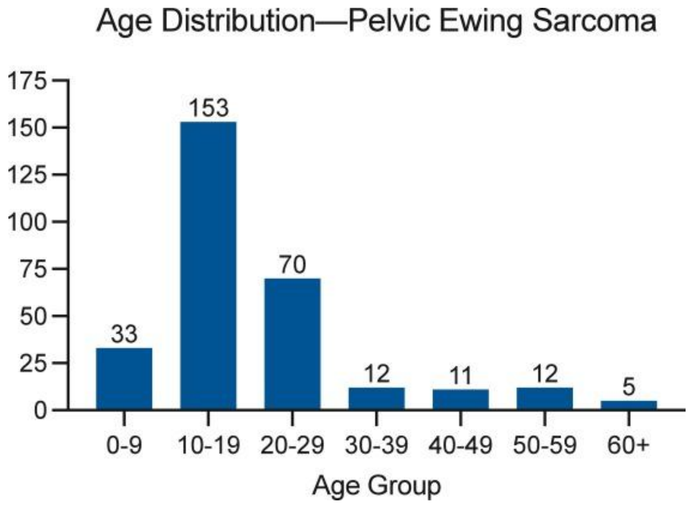
ig. 2. Local control (a), (b) disease-free survival (b), and overall survival (c) for standard dose radiation therapy (SDRT) ersus escalated dose radiation therapy (EDRT).

- Pelvic LC: **74.1% vs 42.7%**, *p=0.01*

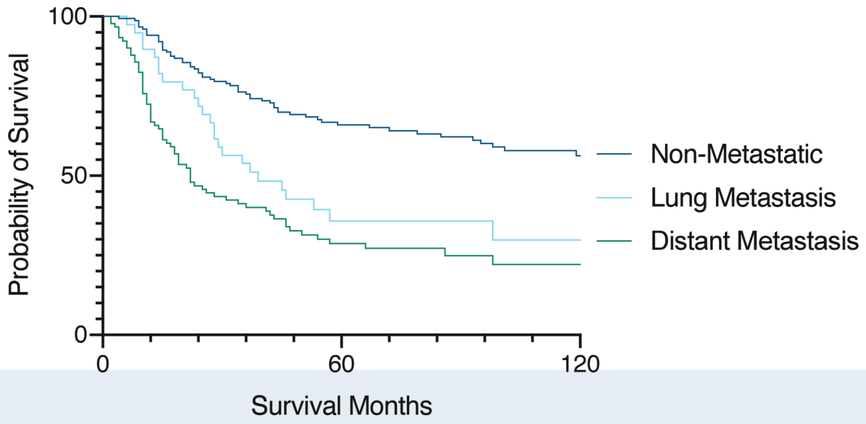
Dose escalation **significantly improves LC** with acceptable toxicity and function. Especially valuable for **pelvic, unresectable ES**

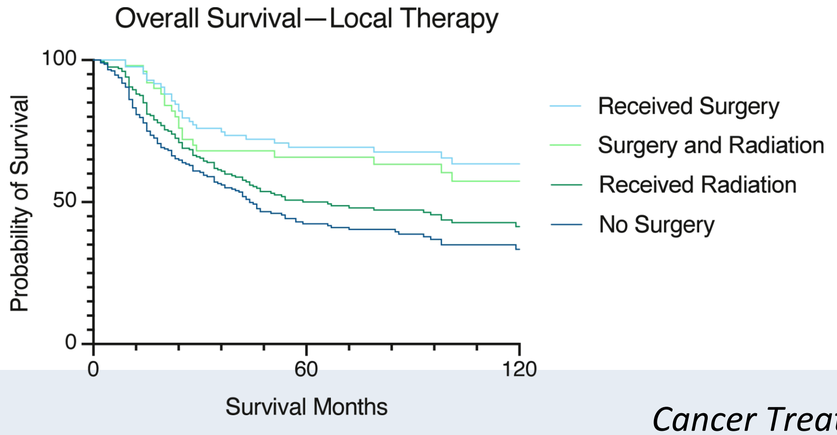
IJROBP, 2022

Pelvic ES



- Larger tumor size- mean size 9.7 cm
- More mets- 46% vs 25%
- **Surgery:** Only 28.6% underwent resection (vs higher rates in non-pelvic).
- **Radiation:** 67.6% received RT (substantially more than other sites).
- **OS:** 2-year: 70.3%, 5-year: 49.7%, 10-year: 41.9%
- Survival **significantly worse** than other anatomic sites across all time points.





Cancer Treatment and Research Communications, 2022

Chest Wall Ewing Sarcoma

- 10–20% of Ewing sarcoma arises from chest wall (ribs > sternum/scapula).
- High-risk features: large primary volume, **pleural effusion**/spread, incomplete resection (R1/R2), poor chemo response
- *Claren et al.* (French EE99 cohort, n=82; median age 13.6 y; median FU 8.4 y):
  - 5-year DFS 69%
  - **Pleural effusion and incomplete resection** (R1/R2) independently worsened DFS & OS
  - With initial pleural effusion: OS 27% without RT vs 68% with RT (P=0.01)

To consider hemithorax RT when pleural effusion is present.
Aim for complete surgical resection when feasible (avoid R1/R2).
Use conformal planning to keep lung/heart out of high-dose fields.

Pediatric Blood Cancer, 2012

Proton Rx in Pelvic ES

Clinical Trial > Int J Radiat Oncol Biol Phys. 2020 Aug 1;107(5):974-981.
doi: 10.1016/j.ijrobp.2020.04.043. Epub 2020 May 8.

Treatment Outcomes After Proton Therapy for Ewing Sarcoma of the Pelvis

- **35 patients**, age ≤21 y (median 14), pelvic primary; all received contemporary multi-agent chemo.
- intent: **definitive** (n=26), **pre-op** (n=7; 50.4 Gy[RBE]), **post-op** (n=2; 45–54 Gy[RBE]).
- **45 Gy** to initial volume, then boost; **definitive** cases got **54–64.8 Gy**.
- Later Tumors **≥8 cm** were **escalated up to 64.8 Gy**.

3-yr Local Control: 92%
3-yr Overall Survival: 83%
3-yr PFS: 64%

2 **in-field** local progressions (both large, unresectable tumors treated pre-escalation at 55.8–57.6 Gy[RBE]); **no marginal/out-of-field** failures. Distant relapse dominated (lungs/bone/lymph).

Definitive proton therapy is a strong local option for pelvic Ewing,
~90% LC at 3 y and potentially avoiding surgical morbidity in selected unresectable/complex cases.

IJROBP, 2020

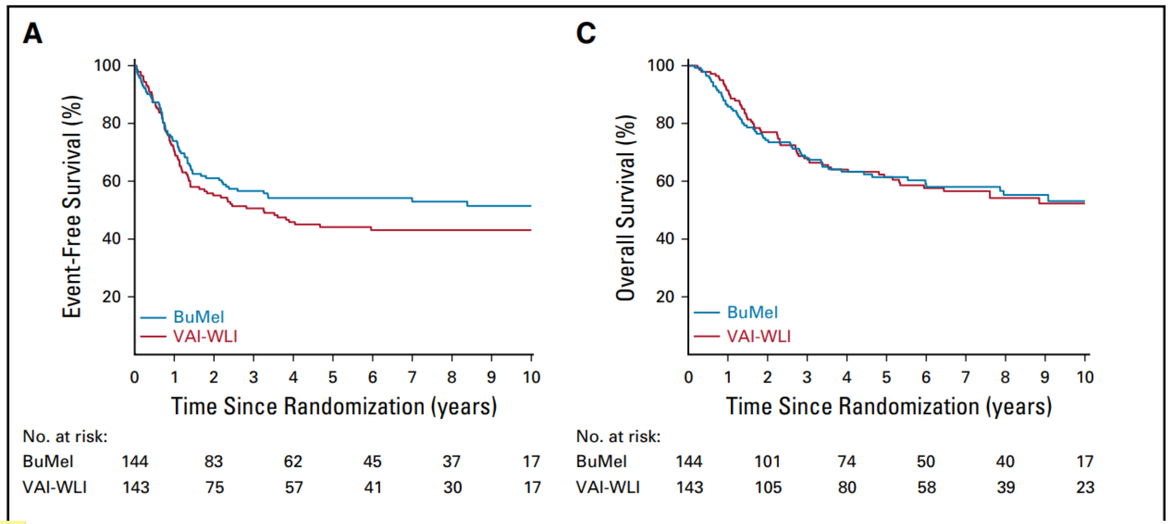
R2Pulm Trial

High-Dose Chemotherapy Compared With Standard Chemotherapy and Lung Radiation in Ewing Sarcoma With Pulmonary Metastases: Results o the European Ewing Tumour Working Initiative of National Groups, 99 Trial and EWING 2008

Uta Dirksen [1,✉], Bernadette Brennan [2], Marie-Cécile Le Deley [3], Nathalie Cozic [4], Henk van den Berg [5], Vivek

- ES with *isolated pulmonary/pleural metastases*, age < 50 yrs
- Trial Design- Induction: VIDE × 6 → VAI × 1
- Randomization:
  - Arm A: VAI × 7 + Whole-lung irradiation (WLI)
  - Arm B: High-dose Busulfan–Melphalan (BuMel) + ASCR

Outcome	VAI + WLI	BuMel
EFS – 3 yr	50.6%	56.6%
EFS – 8 yr	43.1%	52.9%
OS – 3 yr	68.0%	68.2%
OS – 8 yr	54.2%	55.3%



No OS/EFS advantage with BuMel
Higher toxicity → limits acceptability of BuMel
SOC: VAI + WLI for pulmonary-only ES

JCO 2019

Whole Lung Irradiation

- **Indication**: pulmonary metastases after chemotherapy
  - (even if complete response) or surgical resection
- **Dose**: 15Gy if <14 yr; 18 Gy if >14 yr (@ 1.5 Gy/#)
- In a retrospective series (Schuck et al.), hemithorax RT (15/20 Gy) in chest wall Ewing with pleural involvement showed **7-year EFS 63% vs 46%** in non-RT group (statistically NS)

Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial

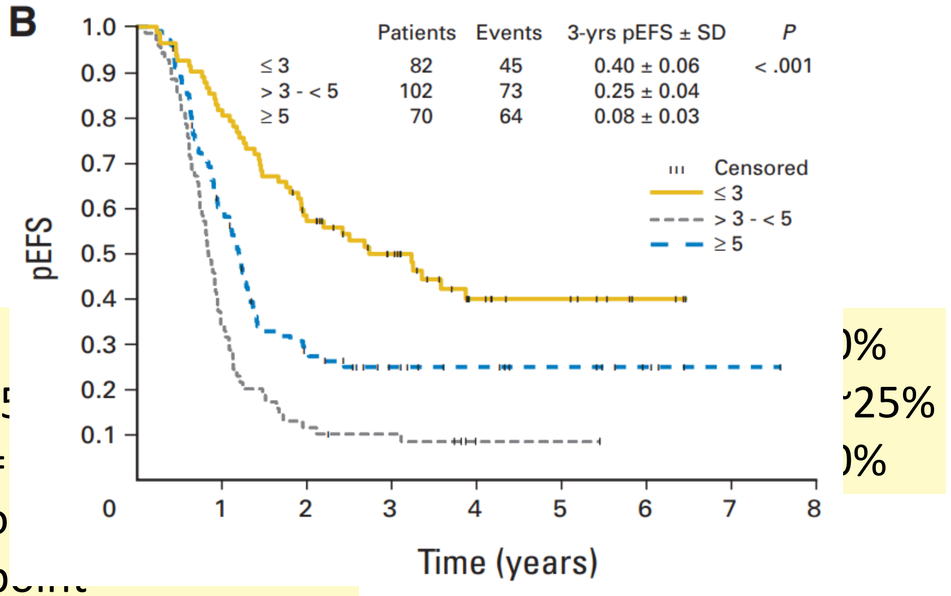
Ruth Ladenstein, Ulrike Pötschger, Marie Cécile Le Deley, Jeremy Whelan, Michael Paulussen, Odile Oberlin, Henk van den Berg, Uta Dirksen, Lars Hjorth, Jean Michon, Ian Lewis, Alan Craft, and Heribert Jürgens

- **Induction:** 6 cycles VIDE and 1 cycle VAI
- **Local therapy:** surgery and/or radiotherapy (post-VIDE or post-HDT)
- **Consolidation:** High-dose Busulfan + Melphalan (BU-MEL) followed by autologous SCT

- **3-year Event-Free Survival (EFS):** 27% ± 3%
- **3-year Overall Survival (OS):** 34% ± 4%

1. **Age > 14 years** (HR 1.6–1.7)
2. **Primary tumor volume ≥ 200 mL** (HR 1.8)
3. **>1 bone metastasis** (HR ~2.0)
4. **Bone marrow metastases** (HR 1.6)
5. **Additional lung metastases** (HR 1.5)

1. **Age >14 y** = 1 point
2. **Volume ≥200 mL** = 1.5
3. **Bone mets:** 1 lesion =
4. **BM metastasis** = 1 po
5. **Lung metastasis** = 1 p



JCO 2010

Relapse in EWS Treatment

- 25% relapse after localized ES
- 70% after metastatic
- 5-yr survival after relapse **<15%**; most progress within **6 months** of first relapse
- **Time to relapse** is strongest→ 2 yrs from initial Rx → better OS (30% vs 7%)

rEECur Trial

Phase III assessment of topotecan and cyclophosphamide and high-dose ifosfamide in rEECur: An international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES).

Authors: Martin McCabe, Laura Kirton, Maria Khan, Nicola Fenwick, Sandra J. Strauss, Claudia Valverde, Cristina Mata, ... SHOW ALL ... , and Keith Wheatley | AUTHORS INFO & AFFILIATIONS

- First randomized controlled trial comparing chemo in recurrent ES
- N = 451, age 4–50 yrs (median 19).
- Disease status: Refractory (18%), 1st relapse (66%), >1 relapse (17%).
- 4 regimens:
  - Topotecan + Cyclophosphamide (TC)
  - High-dose Ifosfamide (IFOS)
  - *Irinotecan + Temozolomide (IT); Gemcitabine + Docetaxel (GD) – closed early due to poor outcomes*
- Median EFS: TC 3.7 mo vs **IFOS 5.7 mo**
- Median OS: TC 10.4 mo vs **IFOS 16.8 mo**
- Bayesian probability favoring IFOS: 95% (EFS & OS)

High-dose Ifosfamide = most effective standard in RR-ES.

ASCO meeting 2022

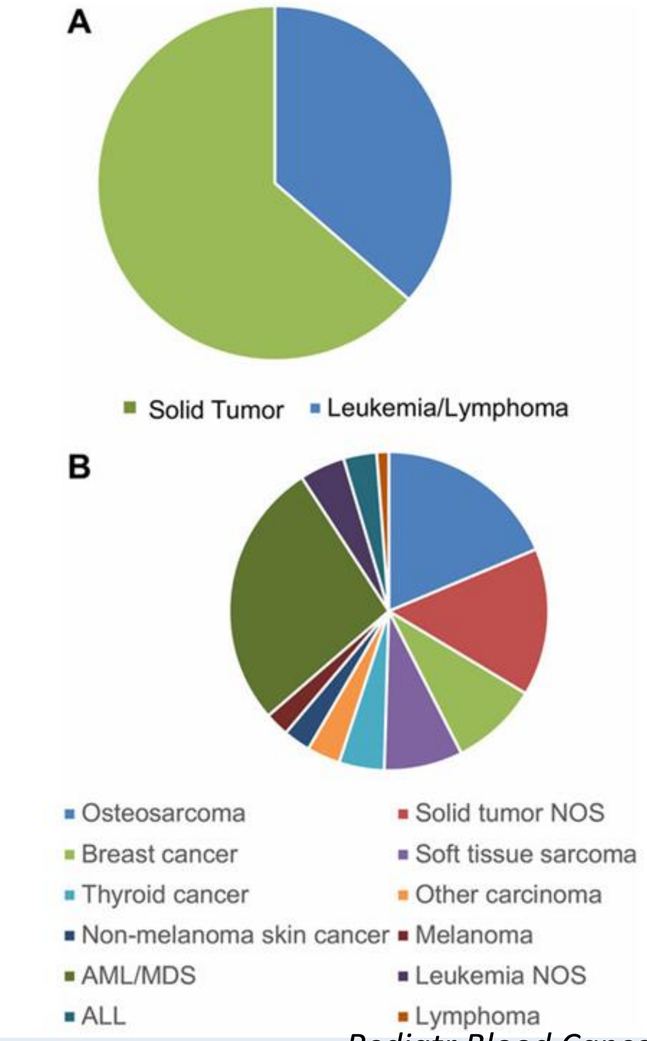
Secondary Malignancies

Second malignancies in patients treated for Ewing sarcoma: A systematic review

Jennifer Caruso[1] | David S. Shulman[2] | Steven G. DuBois[2]

- **Incidence:** 5 yrs: **0.9–8.4%**
  - 25–30 yrs: **10–20%** (risk rises steadily with time).
- **Types:**
  - **AML/MDS (~27%)** → most common, poor prognosis.
  - **Solid tumors (64%)** → most frequent = **osteosarcoma (~19%)**.
- **Latency:**
  - **Leukemia/MDS:** ~3 yrs (early).
  - **Solid tumors:** 8–20 yrs (late).
- **Outcomes:**
  - 5-yr OS after SMN: **~74% solid tumors** vs **~42% leukemia**.

Risk factors:
Younger age (<20), localized ES (survivorship bias).
Alkylators + etoposide, high-dose chemo → ↑ AML/MDS.
RT → dose-dependent secondary sarcoma.



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SOME OTHER POINTS TO CONSIDER

- Young age- chemotherapy and radiotherapy (pelvic) may lead to sterility – appropriate **fertility preservation** to be done prior to initiation of therapy
- Post-op **physiotherapy, gait training, prosthetic fitting** (if amputation), and psychosocial support.
- **Body image issues, schooling interruptions, long-term survivorship concerns** → need counseling.
- If chest wall radiotherapy or resection done- **pulmonary rehabilitation** warranted

Follow Up

- Risk of local recurrence (highest within 2–3 years).
- Risk of systemic relapse (lungs, bone, marrow).
- Monitor for late effects of chemo/RT (growth, fertility, cardiotoxicity, second malignancy).

First 2 yrs	q3 monthly	Physical examination, labs, local x-ray, chest imaging, PET-CT/Bone scan (if symptomatic)
2-5 yrs	q6 monthly	
>5 yrs	Annually	**Above + Monitor for late toxicities** Cardiac, Renal toxicities Fertility/endocrine issues Growth disturbances Second malignancies

SUMMARY

- Round blue cell tumor characterized by **EWSR1-FLI** fusion; **CD99 (MIC2)** strongly positive.
- Imaging: "**Onion-skin" periosteal** reaction on X-ray.
- Highly **Radiosensitive** and chemo-sensitive
- NACT (VAC/IE) → Local treatment (Surgery/RT) → Maintenance chemotherapy
- Localized tumor, size <8cm, long bones, low LDH better prognosis
- **Surgical** principle- negative margins, and limb sparing
- **Radiotherapy- PORT- 45 Gy** (to post op bed) **+ 10.8 Gy boost** (to residual)- (R1/R2 resection, poor response, pelvic tumors)
- **Definitive** RT to a dose of 55.8 Gy (dose escalation up to 70.2Gy) in unresectable tumors
- PORT dose- 45 Gy – 10.8 Gy Boost
- Regular surveillance with physical examination, lab, imaging (MRI/CT + chest imaging)