Ewing's Sarcoma

RESIDENT LECTURE 6/2014

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Epidemiology

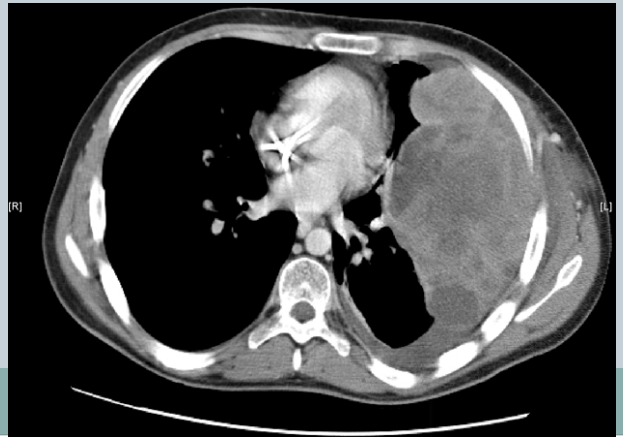
- Neuroectodermal origin
- Adolescents (40%), but 30% in <10 year olds
- 2nd most common bone tumor in children, after osteosarcoma
- ~225 cases/yr
- M:F 1.5-2:1
- white>>black /asian

Ewing Sarcoma Family of Tumors (ESFT)

- ES of bone
- Extra-skeletal ES
- Askin's tumor
- PNET

So Special They Named It

- Askin's tumor
  - Primary lesion of rib
  - Associated w/ direct pleural extension
  - significant extraosseous soft tissue mass
  - Female predominance
  - Poor prognosis (median survival: 8 mos)
  - RT delivered to hemithorax, 15-18 Gy



Presentation

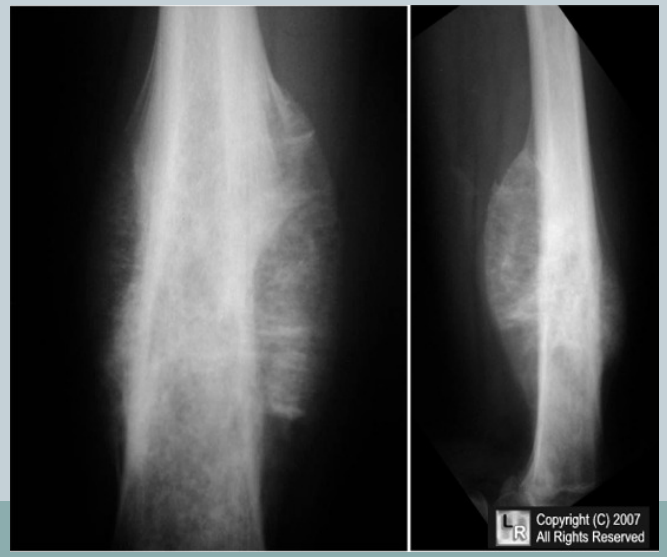
- Localized pain and swelling
- Constitutional symptoms 30%
  - fever, low appetite, weight loss
- Distribution
  - Axial skeleton 50%
    - Skull 2%
    - Chest wall 16%
    - Spine 6%
    - Pelvis 26%
  - Extremities
    - Upper 9%
    - Lower 41% (Femur 20%)
- Metastatic disease (20-25%)
  - Primary spread is hematogenous
  - Most commonly to lungs, bones, BM, soft tissue, brain, spine
  - Bilateral bone marrow biopsy part of staging, regardless of tumor size

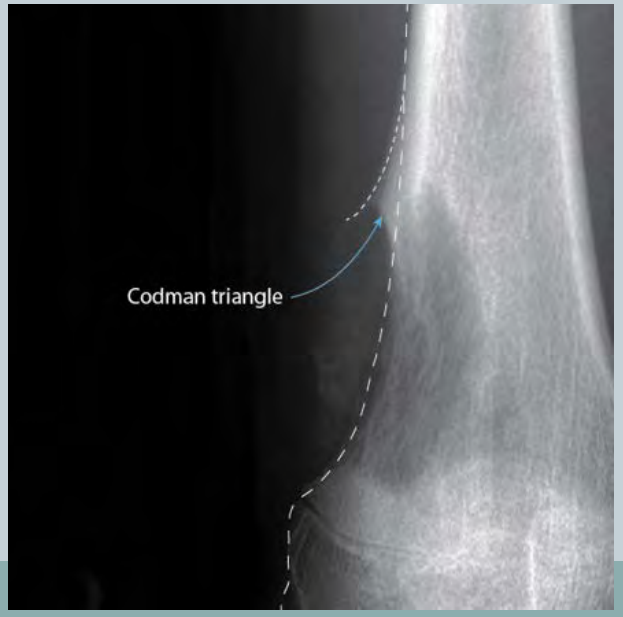
Workup

- H/P
- Lab: Nonspecific (increased ESR, LDH, WBC)
- Imaging studies: x-ray, CT (chest and primary site), MRI, bone scan
- PET highly sensitive for detecting bone met (96% sens, 92% spec)
- Ongoing study comparing whole body MRI and conventional imaging for detecting distant mets
- Biopsy of mass (open preferred) and bone marrow

Imaging Studies

- Bone scan, CXR, CT or MRI of primary, CT of chest
- Plain films show "onion skinning"
  - soft tissue mass growing out from the bone giving rise to multilamellated periosteal reaction vs "sunburst" pattern seen in osteosarcoma.
  - Diaphysis rather than metaphysis (osteosarcoma)
  - Periosteum displaced by underlying tumor
    - Codman triangle
  - New bone formation beyond periosteal margin rare
  - Associated soft tissue mass common





AJCC Staging (Bone Staging)

Primary Tumor:

- T1 - 8 cm or less in greatest dimension
- T2 - >8 cm
- T3 - discontinuous tumors in the primary bone site

Regional Lymph Nodes:

- N0 - no
- N1 – yes

Distant Metastases:

- M0 - no
- M1a - lung
- M1b - other distant sites

Stage Grouping:

~~IA - T1 N0, Low grade~~
~~IB - T2 N0, Low grade; or T3 N0, Low grade~~
IIA - T1 N0, High grade
IIB - T2 N0, High grade
III - T3 N0, High grade
IVA - M1a
IVB - N1, M1b

Note: Ewing's sarcoma is classified as grade 4

Simplified Staging

Stage	Grade	Size	Node	Metastasis	5y OS
IA	Low Grade	< 8cm	None	None	
IB	Low Grade	> 8cm	None	None	
	Low Grade	discontinuous (skip) lesion	None	None	
IIA	High Grade	< 8cm	none	none	70%
IIB	High Grade	> 8cm	none	none	70%
III	High Grade	discontinuous (skip) lesion	none	none	70%
IVA	Any	Any	none	lung	30%
IVB	Any	Any	present	other than lung	15%

Pathology

- Small round blue cell tumor
  - likely arising in the bone marrow
    - Other small round blue cell tumors of childhood inclu
      - Neuroblastoma
      - Wilm's Tumor
      - Rhabdomyosarcoma
      - PNET
      - Small cell lymphoma
      - Desmoplastic small round cell tumor
- Fusion between EWS gene and a partner gene which dysregulates cell growth
  - t(11;22) EWS-FLI1 (85%) → correlates with IHC expression of CD99
  - t(21;22) EWS-ERF (10-15%)

Prognostic Features

- *Disease site*
  - Favorable: non-pelvic
    - distal, ribs and other having the best prognosis
  - Unfavorable: Pelvic
  - Intermediate: Proximal
- *Age:* younger is favorable
- *Size:* >8cm is unfavorable
- *Labs*
  - Unfavorable: anemia, elevated ESR, leukocytosis, and elevated LDH

Table 9.2

Prognostic Factors in Ewing Sarcoma

Negative	
	Metastases at diagnosis
	Large tumor volume (>200 mL)
	Pelvic/central location of primary
	Age over 17 years
Positive	
	Good response to chemotherapy

Treatment Overview

- Assume occult metastatic disease with chemotherapy as the backbone of treatment
  - Radiation alone had cure rate ~10%, with majority failing distally
- Chemotherapy is typically given for 12-15 weeks prior to local therapy
- Local control is imperative (surgery or radiation therapy or both)
  - No randomized studies comparing the two treatment approaches
  - Surgery favored if complete resection is feasible without significant morbidity and functional loss
  - Radiation favored for central lesions

Surgical Technique

- Limb-salvage preferred, if feasible
- Margins: >1cm bone, >0.5cm STS, >0.2cm fascia
- Preferred for accessible sites
- PORT offered to + margins, gross residual disease
- “Expendable sites”
  - Proximal fibula, lateral 4/5th of clavicle, scapular body, ileum, ischium, pubis, small bones of arms/feet – good functional results with surgery alone with no reconstruction (RT may be avoided in 75% of cases)

Local control: RT

- Definitive RT: large tumors, location – vertebra, sacrum, periacetabular pelvis, soft tissue ESFTs
- Post-op RT: + margins, poor histological responders, microscopic residual or tumor spill
  - European data (EICSS) – local failure after WIDE RESECTION
    - <1% in good histologic responders (only 10% viable tumor in specimen)
    - 12% for poor responders (>10% viable tumor) → post-op RT brings down to 6%
- Pre-op RT: used to downstage large tumors, increasingly used in European protocols
- Radiation dose
  - Doses >60 Gy result in unacceptable risk of secondary bone malignancies
  - Doses <40 Gy have unacceptable local failures
  - Currently, ~45 Gy are given for microscopic disease and ~55.8 Gy for gross disease
  - Whole lung radiation used for consolidation after chemotherapy (12-15 Gy)

Local control rates

- Extremity lesions: 90-95% after RT, 70-80% for pelvic tumors
- Tumors > 8cm diameter (80%) vs. 90% in < 8cm

CESS 86, Paulussen et al. *JCO* 2001

- Does VAIA improve outcomes in high-risk (>100ml and/or central-sites) compared to VACA?
- n=177, Nonrandomized, Chemo-sandwich
- Induction chemo x 3c:
  - Standard risk: VACA
  - High risk: VAIA
- Surgery alone (23%), Surgery + RT (49%), RT alone (28%)
  - RT alone: 60 Gy
    - QD vs BID
  - Adj RT: 44.8 Gy
    - Proximal/distal margin: 5 cm
    - Deep/lateral margin: 2 cm
- Chemo x 9c (12 total)

CESS 86

- 5 yr OS: 69%
- No differences in OS/RFS for local tx
- LC:
  - Surgery: 100%
  - Surgery + RT: 95%
  - RT alone: 86%
    - No difference for QD vs BID
- DM: 24-52%
- Prognostic factors:
  - Size (200 mL)
  - Response to chemo
  - VACA vs VAIA

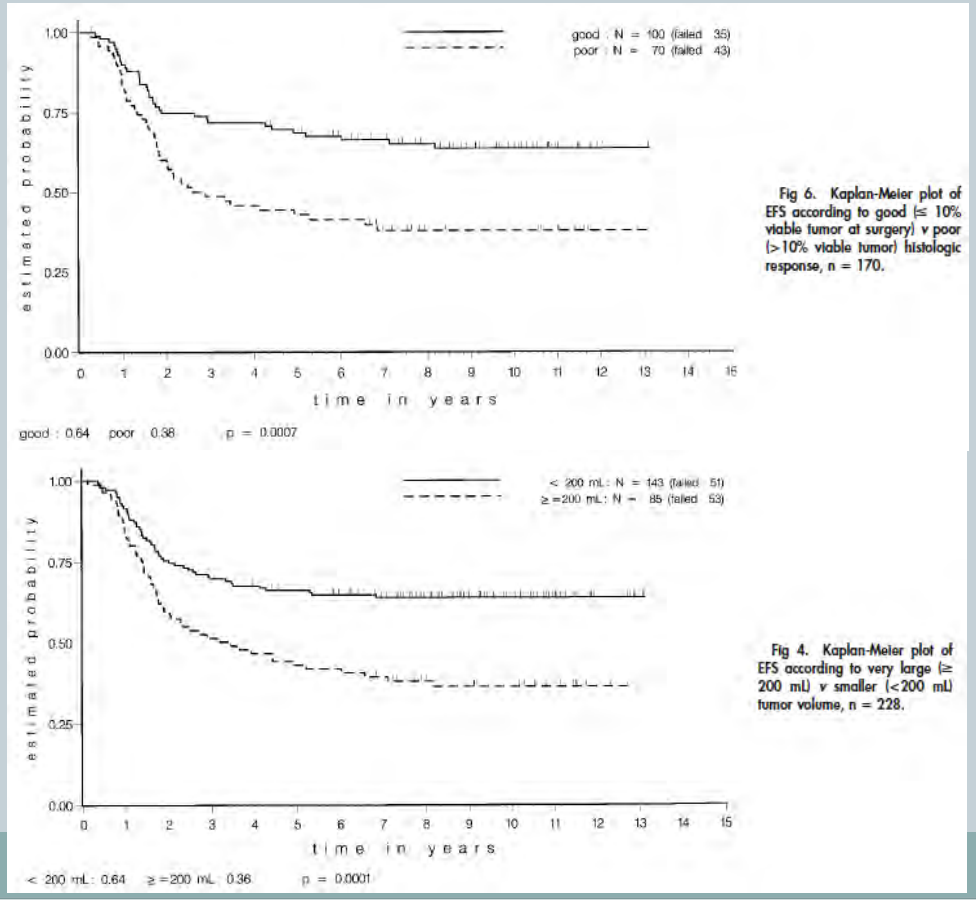


Fig 6. Kaplan-Meier plot of EFS according to good (≤ 10% viable tumor at surgery) v poor (>10% viable tumor) histologic response, n = 170.

Fig 4. Kaplan-Meier plot of EFS according to very large (≥ 200 mL) v smaller (<200 mL) tumor volume, n = 228.

INT 0091, Yock, JCO, 2006

- 75pts with pelvic tumors
- VACA vs. VACA-IE
- Local control modality chosen by physician
  - Surgery alone – 16%
  - RT alone – 56%
  - Surgery +RT – 28%
- 5yr EFS : 49%
- No significant effect of local control modality

Combined results of CESS81, CESS86 and EICESS92 (Schuck, IJROBP, 2003)

- 1058 pts analyzed
- Again, local treatment modality up to physician preference “wherever feasible, a surgical local therapy approach was used”
  - EICESS 92 – pre-op RT introduced for pts with expected close margins
- Local failure significantly lower after surgery (with or without postop RT) than after definitive RT (7.5% vs 26.3%)
- Local control rate with preop RT comparable to that of surgery (7.5% vs 5.3%)

RT for Ewing's of Vertebrae (Ahrens, IJROBP, 2005)

- Again, combined results of CESS 86, CESS 81 and EICESS 92
- 116 pts with primary tumors of C/T/L spine
- 65% had RT alone, 28% had RT + surgery, 3% had surgery alone
- Definitive RT local control rate = 22.6% (comparable to those of other tumor sites treated with definitive RT)
- EFS and OS at 5 yrs, 47% and 58%

Local therapy for metastatic disease? EURO-EWING 99

- Retrospective. 120 patients.
- Primary: Surgery 22%, Surgery + RT 17%, or definitive RT 33%
- Local treatment of mets: Surgery 5%, Surgery + RT 7%, RT 27%. No local therapy in 27%
- 3-year EFS 24%
  - Surgery 25%
  - surgery + RT 47%
  - RT 23%
  - no local therapy 13%
- 3-year EFS if treatment of primary and met 39% vs either primary or met 17% vs no local therapy 14% (SS)
- Conclusion: Local therapy important for patients with disseminated Ewing sarcoma and should complement systemic treatment whenever possible

POG 8346: Donaldson et al. *IJROBP* 1998

- IFRT equivalent to whole bone (SF) RT for LC?
- n=178, 1983-1988
- Induction chemo: cyclophosphamide/doxorubicin x 12wks (5c)
- Local Tx based on response:
  - PD → RT + salvage chemo
  - If CR/PR → surgery (if feasible) + PORT if + margins/gross dz
  - RT alone: randomized to IFRT vs SFRT
    - IF 55.8Gy
    - SF 39.6 Gy + 16.2 Gy boost (GTV + 4cm)
- VACA x 50 wks

POG 8346

EBM – POG 8346

No benefit to whole bone RT

- 5yr EFS: SF 37% vs. IF 39%
- 5yr LC: SF 53% vs IF 53%

- Limitations: low accrual, high rate DM

Extracorporeal Irradiation

- Pelvic tumors: poor prognosis
- Primary resection difficult, chemoRT mainstay
- Wide en-block resection → ECI 50Gy @ 2Gy/min → debulking of tumor from bone → re-implantation
- 13 patients, median age 16 yrs, no mets
- OS 69%, 9/13 NED at last followup, 4 died of metastatic disease, no local relapse
- 7/13 with good/excellent functional outcomes

Krieg AH, J Bone Joint Surg 2009

RT Target Volume (AEWS1031)

- RT to entire bone not necessary (POG 8346)
- GTV: pre-chemo bony disease and post-chemo soft tissue disease
- CTV margin of 1-1.5cm
- Make sure scars and drain sites are wired and apply bolus to ensure adequate coverage
- 45 Gy + 10.8 Gy (definitive RT or gross residual)
- 36 Gy (pre-op RT)
- 45-50.4 Gy (post-op RT)

RT Complications

- Bone growth abnormalities
  - > 20 Gy can prematurely close epiphysis
  - > 20-30 Gy can cause permanent lymphedema
  - Limb length discrepancy – 2-6 cm
  - Permanent weakening of bone
    - High risk of fracture within 18 mos of RT
- Dermatitis: recall-reaction w/ ADR and dactinomycin
- Decreased ROM 2/2 joint fibrosis
- Skin hyperpigmentation
- Cystitis (worse w/ cyclophosphamide/ifos)
- Second malignancies (5-10% @ 20yrs →osteosarcoma)

Chemotherapy Regimens

- For non-metastatic disease, standard 5-drug U.S. regimen (VAC + IE)
  - Vincristine
  - Doxorubicin
  - Cyclophosphamide
  - Alternating with ifosfamide and etoposide x 48 weeks
  - Actinomycin sometimes thrown in (VACA+IE)
- For metastatic disease (VAC)
  - Vincristine
  - Doxorubicin
  - Cyclophosphamide

IESS-I

- 342 pts. Localized Ewing's sarcoma of bone, previously untreated
  - Group I Institutions: Randomized 3:2 to 1) RT to primary plus VAC + Adriamycin or 2) RT plus VAC
  - Group II Institutions: Randomized 3:2 to 3) RT to primary plus VAC and bilateral pulmonary RT (BRP) or 2) RT plus VAC (same as above)
- *Chemotherapy* given x 6 weeks
  - Vincristine and cyclophosphamide q weekly and adriamycin given with the last dose.
  - After 6 weeks rest, pts had a 7 week course of continuation therapy that consisted of dactinomycin IV x 5 days followed 9 days later by VCR and cyclophosphamide weekly x 5 weeks. For treatment 1, adriamycin given with the last course in the 7th week of each course.
- *RT* : entire involved bone to 45-55 Gy (based on age), followed by 10 Gy boost to gross radiographic tumor + soft tissue mass with margin.
  - Lung RT: 15-18 Gy given at 150-180 cGy/day.

IESS-1

- 5-yr RFS treatment 1 - 60%, 2 - 24%, 3 - 44%. Similar trend for OS.
  - Worse survival for pelvic sites.
  - 15% LR overall.
  - DM in 1-30%, 2-72%, and 3-42%.
  - BPR was not effective in preventing lung mets.
- Conclusion: improved survival with addition of Adriamycin to VAC.

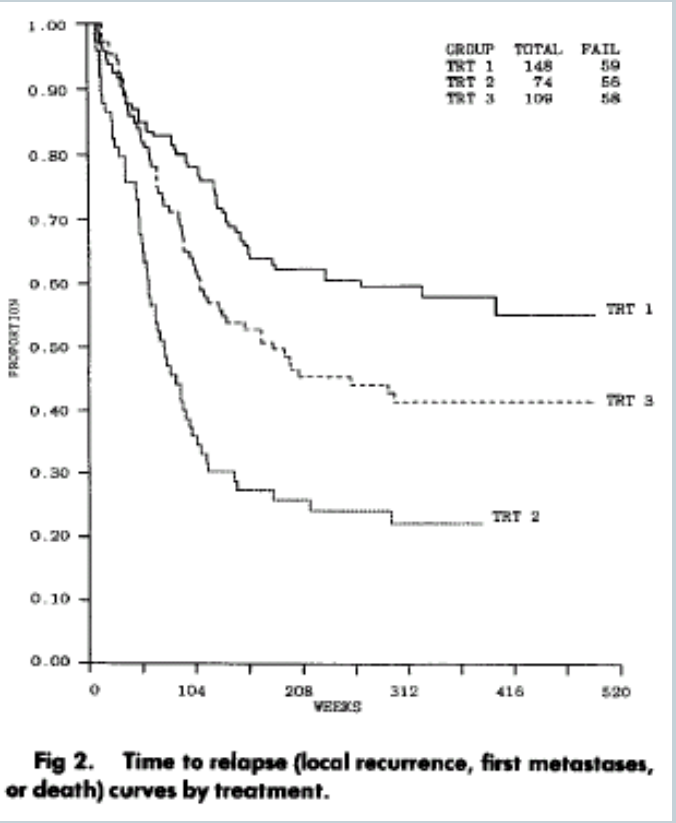


Fig 2. Time to relapse (local recurrence, first metastases, or death) curves by treatment.

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

IESS-3

- Non-metastatic pts
  - 5-yr EFS 69% vs 54% for VAC+ADR+IE vs VAC+ADR (RR=1.6)
  - 5-yr OS 72% vs 61% (RR=1.6)
  - Greater reduction in LR than in distant mets. Greater benefit for large primary tumors or pelvic tumors.
- For pts with mets, no difference between regimens:
  - 5yr EFS 22%
  - 5yr OS 34%
- <u>Conclusion:</u> improved survival with addition of ifosfamide and etoposide (in non-metastatic pts)

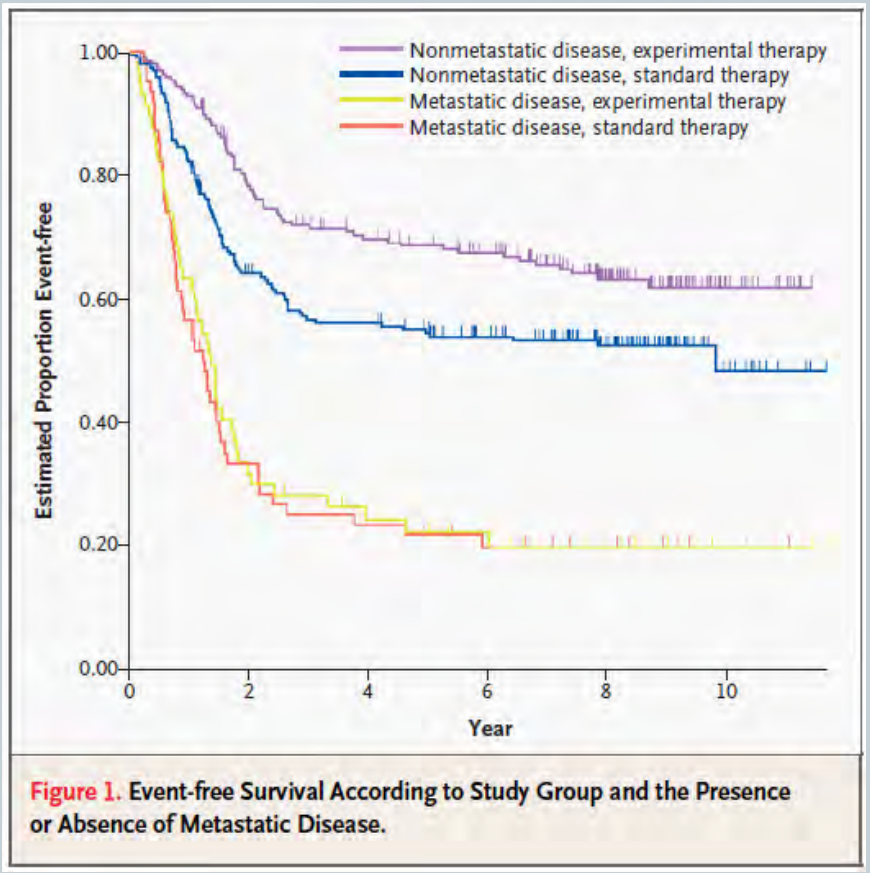


Figure 1. Event-free Survival According to Study Group and the Presence or Absence of Metastatic Disease.

WLI- EICESS 92
Bolling et al., *Strahlenther Onkol*, 2008

- Any benefit to WLI? Toxicity?
- 99 with pulmonary mets, 70 received WLI,
- Local: VAIA +/- etop x14c
  - WLI: wk 31, 12-21 Gy +/- boost to thoracic tumor to 54Gy
    - 1.5 Gy QD vs 1.25 Gy BID
    - AP/PA fields
- 5yr OS:
  - 61% (WLI) vs 49% (none) p=0.36
- 5yr EFS
  - 39% (WLI) vs 37% (none)

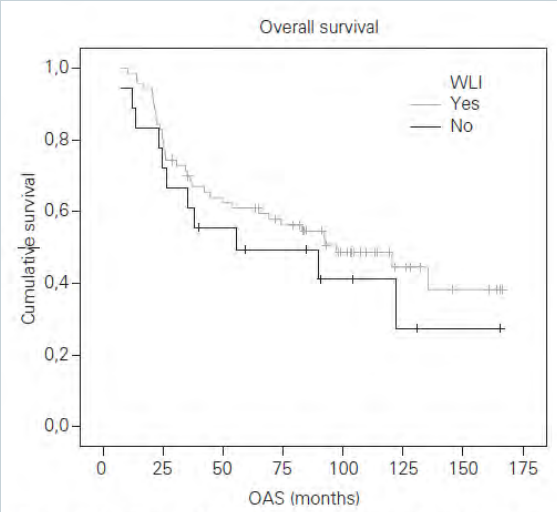


Figure 1. Overall survival (OAS) of patients who were treated with (upper line, n = 70) and without (lower line, n = 18) whole lung irradiation (WLI). Patients without WLI who had progressive disease before scheduled start of radiotherapy were excluded from this analysis (n = 9). The difference between both groups is not significant (p = 0.363).

WLI- EICESS 92: Toxicity

	Late lung toxicity, grade					
	n	0	1	2	3	mean grade
WLI, no thoracic surgery	16	8	6	2	0	0.6
WLI plus thoracic surgery	12	4	2	4	2	1.3
All	28	12	8	6	2	0.9

PFT complications	None	Mild	Moderate	Severe
	43	29	21	7

Group	n	Age median (range)	≤ 15 Gy	> 15 Gy	Median follow-up (range)	Surgery	EVAIA/ VAIA	2nd CTX	3rd CTX
Without side effects	12	14.7 years (5.6-25.8)	6	6	11.6 months (0.1–151)	4 (33%)	8/4	5 (42%)	3 (25%)
With pulmonary function abnormality	16	16.1 years (4.3–34.8)	6	10	32.6 months	8 (50%)	6/10	11 (69%)	6 (40%)
All	28	15.0 years (4.3–34.8)	12	16	25.2 months (0.1–151)	12 (43%)	14/14	16 (57%)	9 (34%)

Treatment Overview

- Chemotherapy is typically given for 12-15 weeks prior to local therapy
  - VAC(A)+/- IE (no IE if metastatic)
- Local Tx (surgery or radiation therapy or both)
  - Surgery favored if complete resection is feasible without significant morbidity and functional loss
  - Radiation favored for central lesions (55.8Gy)
- Radiation
  - PORT if + margins: 45Gy
  - Definitive RT or PORT w/ gross residual: 55.8Gy
  - Whole lung radiation used for consolidation after chemotherapy (15Gy/10fx), boost residual dz to 45Gy.
    - Can consider resection if <=4 mets

Late (>5yr) recurrences in Ewing's sarcoma)

- >12k childhood cancer survivors
- Overall late relapse 4% and 6% at 10 and 20 years
- Two tumors stood out
  - Ewing's and CNS tumors
    - 14% at 20 years
- Importance of monitoring 15-20years from therapy

Wassilewski-Master, JNCI, 2009

Questions

- What translocation is characteristic of Ewing's sarcoma?
  A. t(11;22)
  B. t(12;16)
  C. t(9;22)
  D. t(x;18)

A

- All of the following are true regarding Ewing's sarcoma, except
  A. There is a predilection for whites
  B. It is more common among males than females
  C. Cytokeratin and neuron-specific enolase can be positive
  D. Half of patients present with localized disease at diagnosis

D

- All of the following are true, except

A. Ewing's sarcoma exhibits chromosomal translocation t(11;22)

B. Codman's triangle can be observed on radiography

C. Presents more commonly with localized disease than osteosarcoma

D. Radiation plays a prominent role in therapy

C.
Ewing's presents with localized disease 75% of the time, osteosarcoma 90% of the time

- In a patient with Ewing's that has GRD after chemo and surgery, what is the correct RT dose and volume?

A. 45Gy to pre-chemo bone and post-chemo soft tissue tumor
B. 45 Gy to post-chemo bone and post-chemo soft tissue tumor
C. 55.8 Gy to the pre-chemo bone and pre-chemo soft tissue tumor
D. 55.8 Gy to the pre-chemo bone and post-chemo soft tissue tumor

D

- All of the following are true regarding IESS-1 in which adria was added to vincristine, actinomycin and cyclophosphamide, except:

A. The addition of adria improved OS
B. The addition of adria improved DFS
C. Pelvic disease sites fared no worse than nonpelvic disease sites
D. Local recurrence did not differ by treatment

C. IESS-1: randomized 335pts to receive adria to VAC + RT (45-55 Gy + 10 Gy boost). Addition of VAC improved both DFS and OS. Pelvic disease sites had poorer survival than nonpelvic (34 vs 57 %). Local recurrence did not differ by treatment

- All of the following are true regarding IESS-II in which intermittent high dose was compared to continuous moderate-dose chemo, except:

A. High dose chemo improved OS
B. High dose chemo improved DFS
C. High dose chemo arm had etoposide
D. Cardiac toxicity was worse in high-dose arm

C. IESS-II randomized 214pt to receive VAC + adria by either moderate-dose continuous or high-dose intermittent regimen. High dose improved OS (77 vs 63%) but with greater cardiotoxicity

- All of the following true regarding IESS-III in which ifosfamide and etoposide were added to VAC + adria, except:

A. The addition of IE improved OS in pts with both metastatic and non-metastatic disease
B. There was a greater reduction in local recurrence than in distant metastasis
C. A quarter of the enrolled patient had metastatic disease
D. There was a greater benefit seen in pelvic tumors

A. IESS-III randomized 518pts to receive IE or not in addition to VAC + adr. 23% of pts had metastatic disease. In non-metastatic pts, addition of IE improved EFS and OS. Greater reduction in local recurrence than distant mets and a greater benefit for large or pelvic tumors. Patients with metastatic disease did not benefit from IE in terms of EFS or OS.

THE END

QUESTIONS?