

# Bone Sarcomas

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# Outline

- Ewing Sarcoma
  - Diagnosis & workup
  - Treatment approach
  - Local control considerations
  - Metastatic disease
  - Target volume examples
- Osteosarcoma
  - Diagnosis & workup
  - Treatment approach
  - Radiation indications

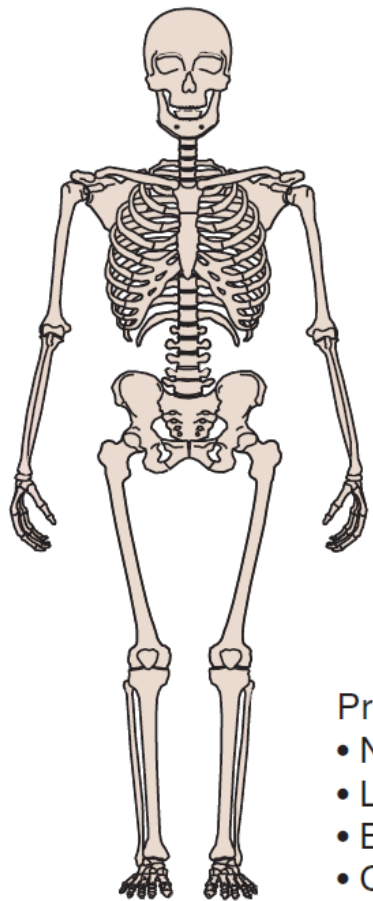
# Ewing Sarcoma

# Diagnosis

- 2<sup>nd</sup> most common primary malignant bone tumor
- *EWS-FLI1*, 85% of cases



Humerus	6%
Ulna	1%
Radius	1%
Hand	1%
Femur	20%
Fibula	8%
Tibia	10%
Foot	3%



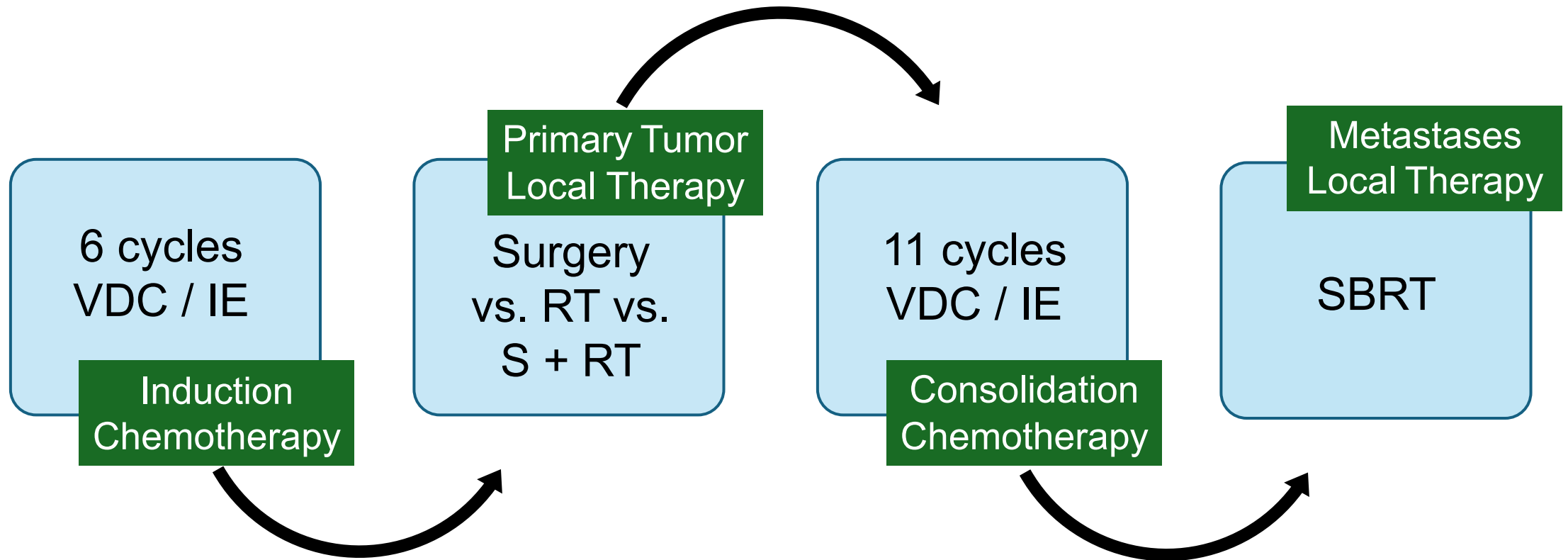
Skull	2.0%
Clavicle	1.5%
Scapula	4.0%
Sternum	0.5%
Ribs	10.0%
Spine	6.0%
Pelvis	26.0%

Primary metastases	
• None	74%
• Lung	10%
• Bone/BM	10%
• Combined/other	6%

# Workup

- Physical exam and history
- Labs
- Xray of primary site
- MRI of primary site
  - Image entire extremity for skip lesions
- CT chest
- PET-CT (vertex to toes)
- Bone marrow biopsy
- Image guided biopsy
  - *EWS-FLI1*
  - *EWS-ERG*
- Referrals:
  - Pediatric/medical oncology
  - Orthopedic oncology
  - Radiation Oncology
  - Reproductive endocrinology/fertility preservation

# Current US Treatment Paradigm



VDC/ IE: vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide

# Modern COG Trials

## INT0091:

VDC/IE

1988-1992

OS: 72%; EFS: 69%

Improved outcomes

## AEWS0031:

q2 weeks VDC/IE

2001-2005

OS: 83%; EFS: 73%

Improved EFS

## INT0154:

Dose-intensified

VDC/IE

1993-1995

OS: 81%; EFS: 72%

No difference in  
outcomes

## AEWS1031:

q2 weeks VDC/IE/VTC

2010-2017

OS: 87%; EFS: 78%

No difference in  
outcomes

# Local Therapy Modalities

Surgery Only

Definitive  
Radiation  
(RT)

Surgery +  
Radiation  
(S+RT)

- No randomized local therapy studies to guide decision making
- Choice of local therapy made on a case-by-case basis with multi-disciplinary input



# Local Therapy Modality Considerations

## Surgery Only

- Gross total resection achievable with acceptable morbidity
- Patient is a medical candidate and agreeable

## Definitive Radiation (RT)

- Anatomically unresectable tumor and/or unacceptable surgical morbidity
- Patient cannot undergo or does not want surgery

## Surgery + radiation (S+RT)

- R1 or R2 resections
- Traditionally postoperative RT

# Surgery + RT: AEWS1031 Guidelines

## R0 Resection

- No viable tumor at cut surface

*No Postop RT*

## R1 Resection

- Microscopically positive cells at cut surface
- Cells with treatment effect at cut surface

*Postop RT required:  
50.4 Gy / 28 fx*

## R2 Resection

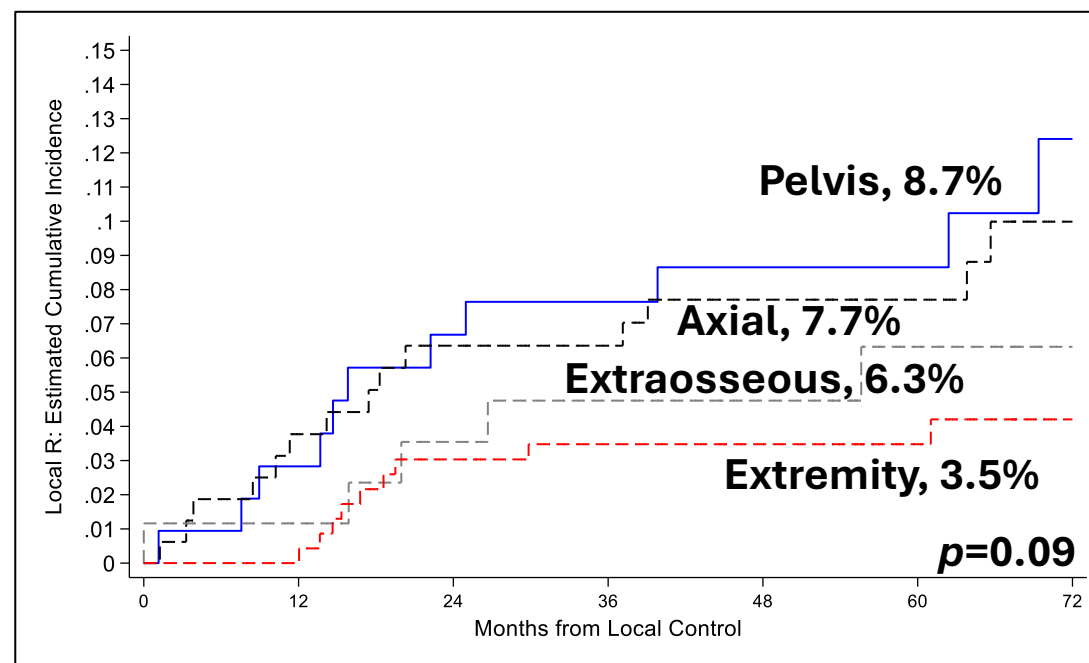
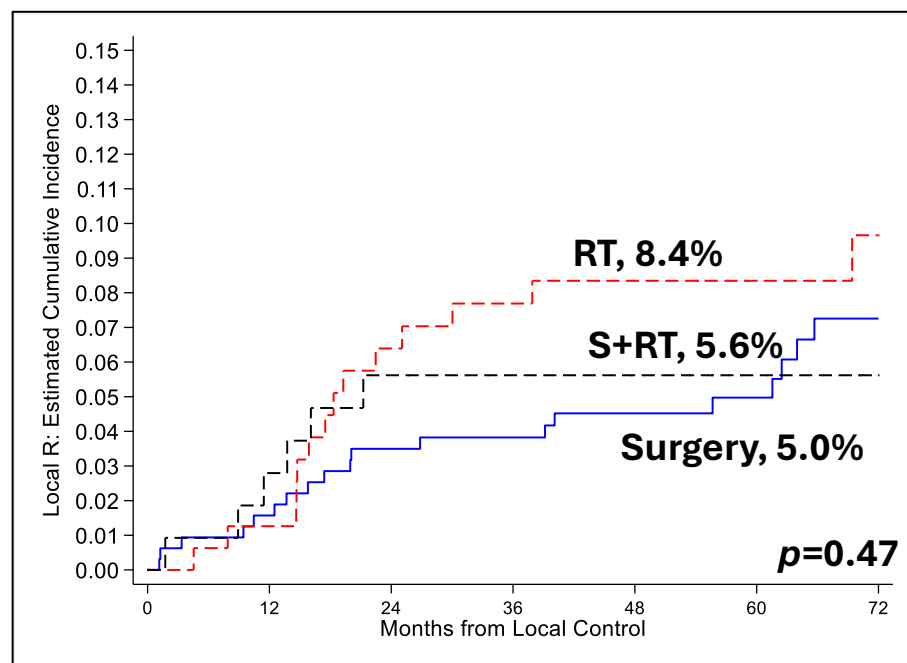
- Intralesional / debulking surgeries

*Postop RT required:  
Definitive RT dosing*

\*Preoperative RT: 36 Gy / 20 fx may be considered. Objective is not to make an inoperable tumor operable. Applicable in select sites where there is a higher risk of microscopic positive margin for resectable tumors (e.g., pelvis, chestwall, etc.)

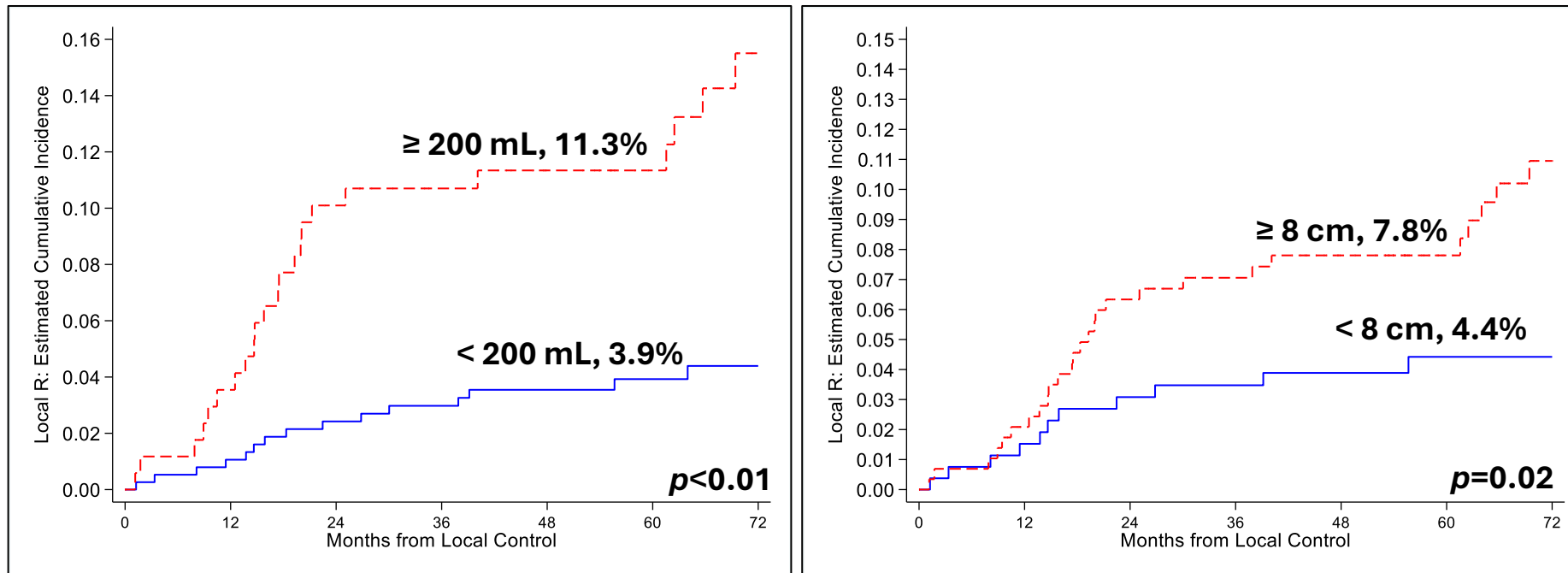
# Current Local Control Outcomes: AEWS1031

- N=588 patients, 5-yr cumulative incidence of local failure (LF): 6.0%



No difference in outcomes by modality, tumor site, or patient age (data not shown)

# Current Local Control Outcomes: AEWS1031



Larger tumor at diagnosis associated with worse local control outcomes

# Unknowns- Further Investigation Needed

- Role of postoperative RT in surgical cases with negative margins and suboptimal percent necrosis
  - “Suboptimal” percent necrosis needs to be defined
  - AEWS1031 data suggests 5% LF incidence for surgery only patients with negative margins, regardless of percent necrosis status
  - Analysis of percent necrosis and LF incidence upcoming
- Possible associations of imaging response prior to local control and LF incidence (e.g., PET response)

# Unknowns- Further Investigation Needed

- Possible associations of chemotherapy administration (i.e., q2 weeks vs. q3 weeks; chemotherapy breaks) with local control outcomes
- Local therapy nuances by primary tumor site (e.g., optimal surgical margins for extraosseous tumors, outcomes by pelvic subsite)

# Metastatic Disease: Modern COG Trials

## INT0091:

VDC/IE

1988-1992

OS: 35%; EFS: 22%

## AEWS0031:

q2 weeks VDC/IE  
2001-2005

*Local treatment for  
metastatic sites*

## INT0154:

Dose-intensified  
VDC/IE  
1993-1995

## AEWS1031:

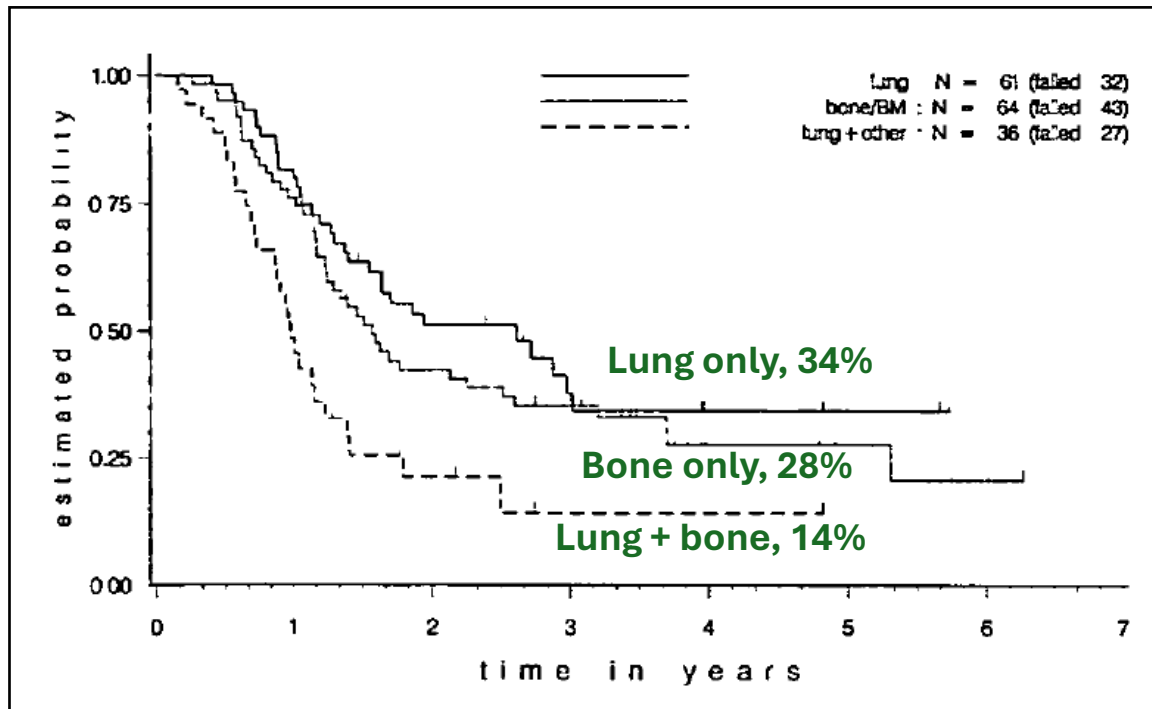
VDC/IE/VTC  
2010-2017

## AEWS1221:

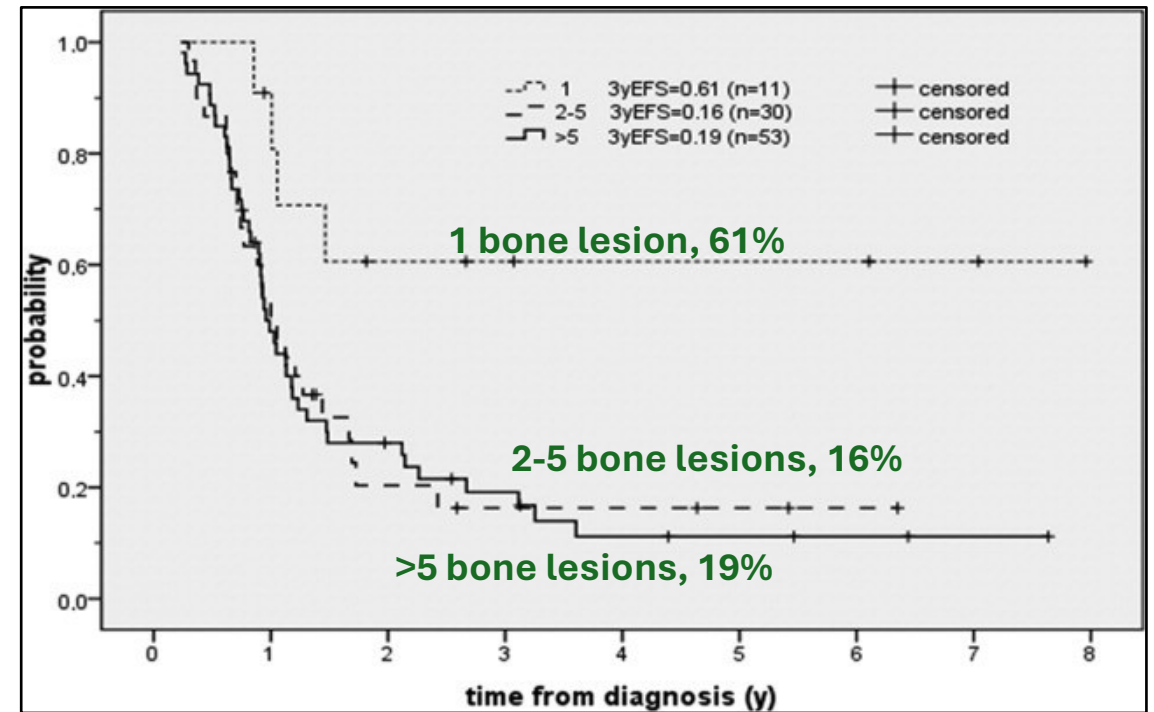
VDC/IE/Ganitumab  
2014-2019  
EFS: 25%  
No improvement

# Metastatic Disease

- EICESS Studies



- EURO-EWING 99 Trial





# Local Therapy for Metastatic Sites

- In the absence of effective systemic therapy, can we improve oncologic outcomes by administering local therapy to all metastatic sites?

Series	Treatment	EFS
Methodist Hospital, Texas	Absence of local therapy to primary site	Median OS: 9 mo.
Euro-EWING99	Absence of local therapy to metastases	17%
	Local therapy to metastases	39%
Mayo Clinic	Absence of local therapy to all metastases	0%
	Local therapy to all metastases	11%

- Local therapy for metastatic sites administered at the end of all chemotherapy given concern for volume of bone marrow irradiated and effect on chemotherapy completion

# Local Therapy for Metastatic Sites

- AEW1221: Evaluated treatment of metastatic sites
  - Attempt to treat all metastases present at diagnosis
  - SBRT for bone metastases  $\leq 5$  cm

Target Volumes	Dose / Fx
PTV2 = GTV2	40 Gy / 5 fx
PTV1 = GTV1 + 2mm	35 Gy / 5 fx
<b><u>After 15 Gy whole lung radiation</u></b>	
PTV2 = GTV2	35 Gy / 5 fx
PTV1 = GTV1 + 2mm	30 Gy / 5 fx

- Conventionally fractionated RT for metastases not amenable to SBRT
- Analysis of outcomes pending

# Whole Lung Irradiation (WLI)

- Standard of care since 1970s
- EICESS: 40% EFS with WLI vs. 19% without
- CESS: WLI associated with improved survival
- Memorial Sloan Kettering: 55% 3-year pulmonary relapse incidence in adults with WLI
- COG Guidelines:
  - 15 Gy in 10 fractions if complete clinical response
  - Excise persistent disease or treat with RT boost

# Upcoming Trial Concepts: AEWS2431

- Study aim: To describe the feasibility and toxicity of augmented dose RT as local control for patients with large primary tumors
- Previously published studies:

Study	N	RT Dose	Outcomes
St. Jude (Kacar et. al., Cancer, 2023)	32, all tumors $\geq 8$ cm	64.8 Gy	6.6% 5-year LF incidence One grade 4 toxicity (SM)
Tata Memorial (Laskar et. al., IJROBP, 2022)	95, 63% pelvic tumors	55.8 Gy vs. 70.2 Gy	5-year LC: 49.4% vs. 76.4%

# Upcoming Trial Concepts: AEWS2431

- Volume at diagnosis:  $0.5 * a * b * c$ 
  - Dose escalation for tumors  $\geq 200$  mL
- GTV1/CTV/PTV1 defined as standard and treated to 45 Gy / 25 fx\*
- GTV2/CTV2/PTV2 defined as standard and treated to 55.8 Gy / 31 fx\*

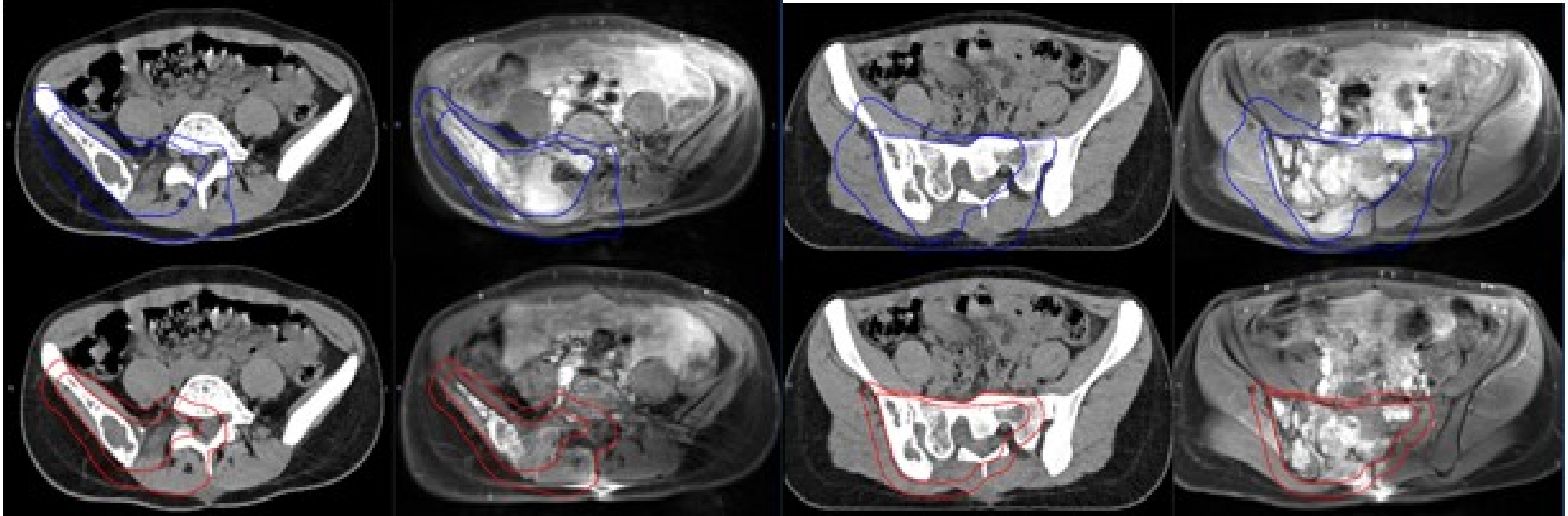
\*See target volume example on upcoming slides

# Upcoming Trial Concepts: AEW2431

- CTV3=GTV3=GTV2
  - 64.8 Gy / 36 fx
- PTV3: 0-0.5cm to meet dose constraints for OARs. Image guidance strongly recommended
- SIB option for patients  $\geq 15$  years (skeletally mature):
  - PTV1: 45 Gy / 30 fx
  - PTV2: 55.8 Gy / 30 fx
  - PTV3: 63 Gy / 30 fx

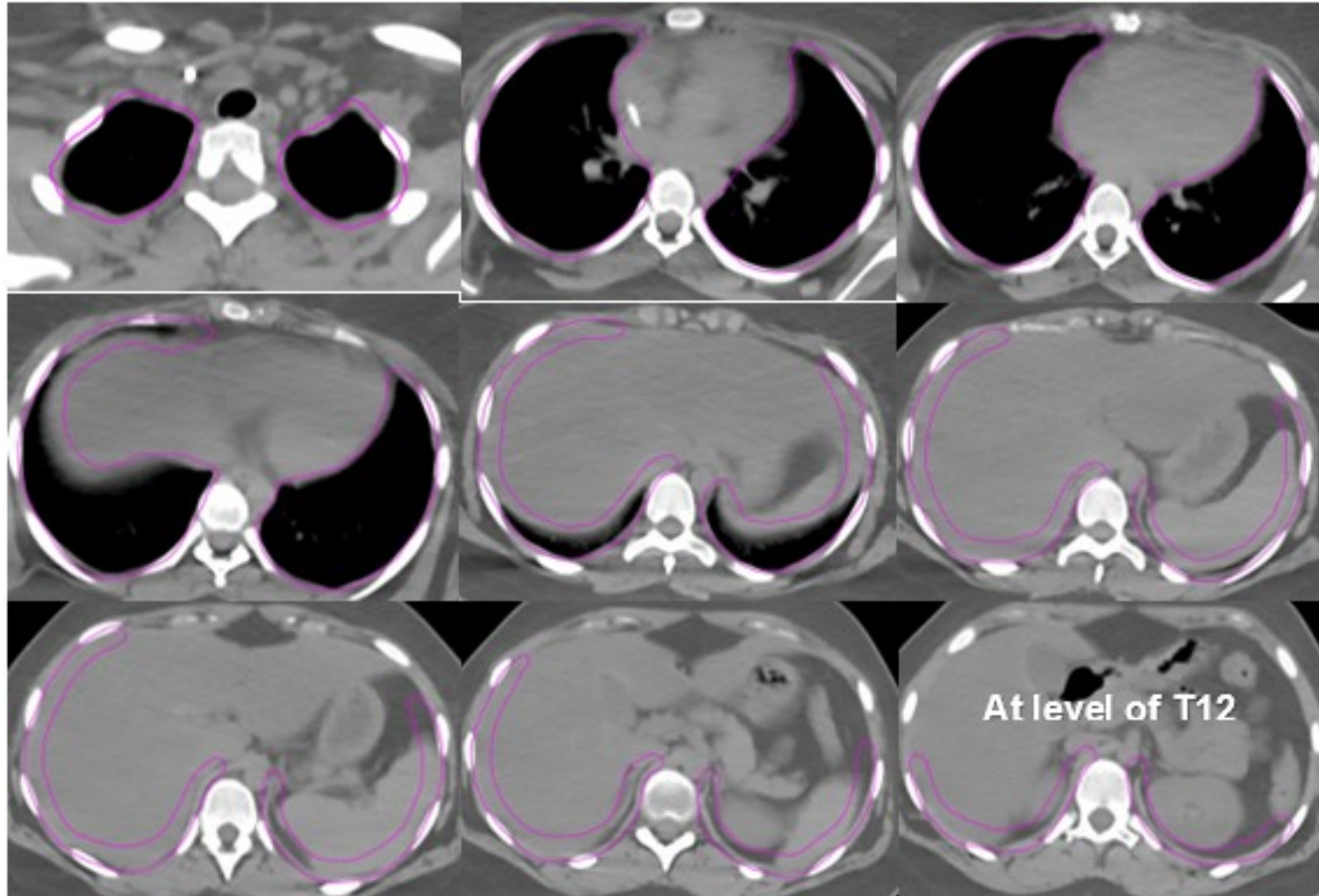
*\*Priority is given to normal tissue dose constraints\**

# Target Volume Example: Pelvic Ewing Sarcoma



Pelvic Ewing sarcoma involving the right ilium and sacrum, with extension into sacral canal and right gluteus and paraspinal muscles. Top row illustrates the simulation CT co-registered to the MRI at presentation. The GTV1 (inner blue line) includes all gross disease prior to induction chemotherapy, and the CTV1 (outer blue line) includes the GTV1 with a 1cm anatomically confined margin, including the entire sacrum, sacral canal, soft tissue edema and biopsy tract to the skin. The bottom row illustrates the same CT slices co-registered to the MRI after induction chemotherapy. The GTV2 (inner red line) includes all remaining gross disease and all originally involved bone. The CTV2 (outer red line) includes the GTV2 plus 1 cm margin in bone and 5 mm in soft tissue, anatomically confined.

# Target Volume Example: Whole Lung Irradiation



The clinical target volume (CTV; pink) includes the bilateral lungs and pleural space, making sure to include the inferior pleural extent at the costophrenic angles. Full inspiration diagnostic CT should be used to define the inferior pleural extent and the lower border of the lung field as this may not be visualized on 4DCT. ITV encompasses respiratory motion either with free-breathing based on all the phases of a 4D scan or with breath hold using 2-3 breath hold scans. PTV is a 0.5-1 cm geometric expansion from ITV to account for day-to-day set-up uncertainty.



# Osteosarcoma

# Diagnosis

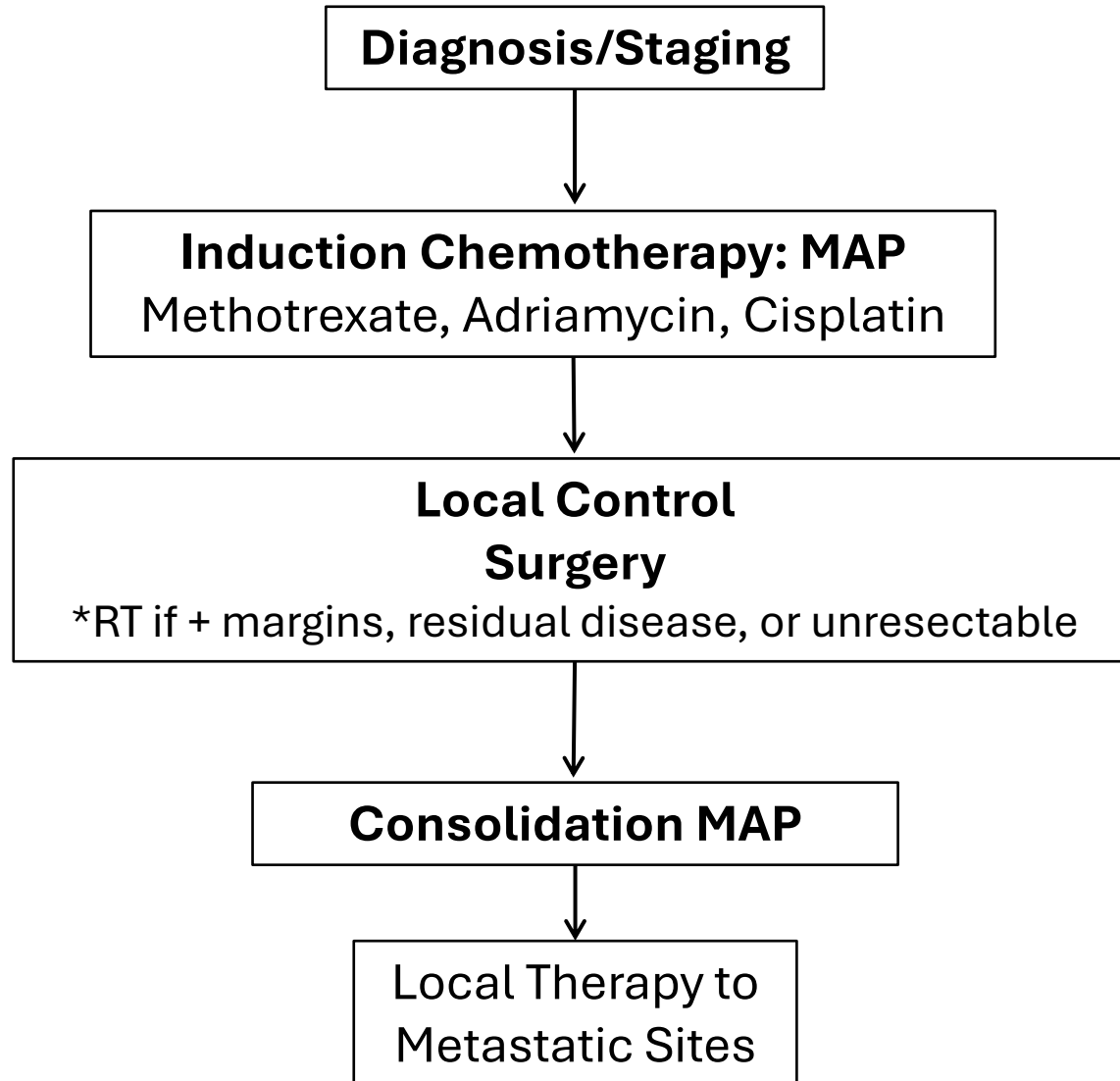
- Most common bone tumor in children and adolescents
- Commonly located in the metaphysis of long bones such as distal femur or proximal tibia
  - “sunburst” pattern on x-ray
- 25% metastatic at diagnosis (lungs most often)
- Genomic alterations
  - TP54 inactivation
  - RB inactivation



# Workup

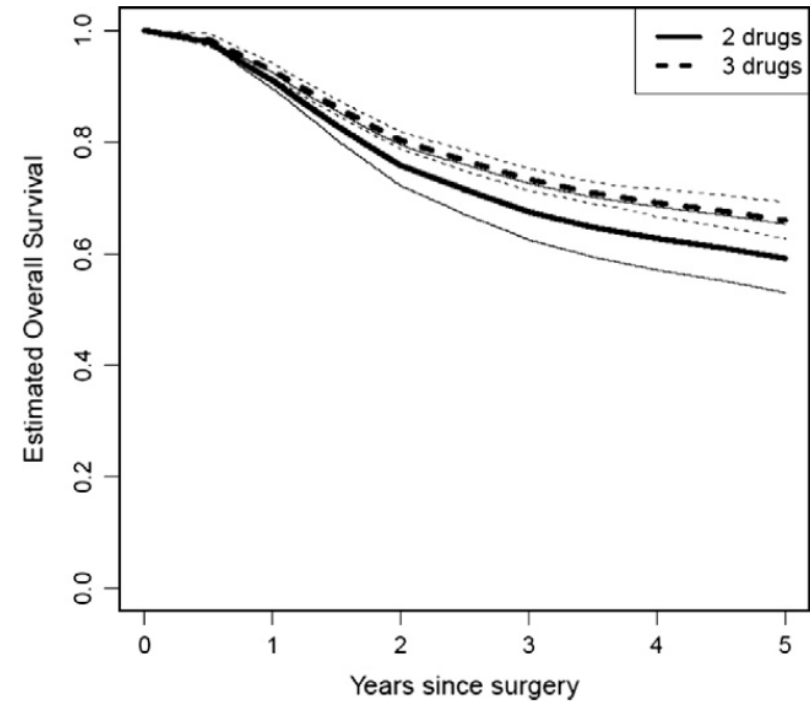
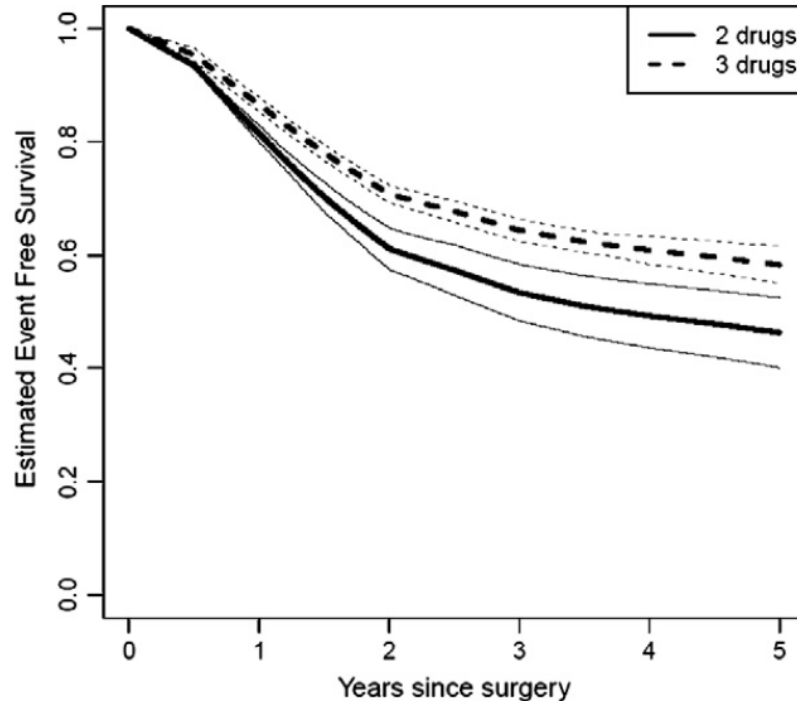
- Physical exam and history
- Labs (LDH, ALP)
- Xray of primary site
- MRI +/- CT of primary site
  - Image entire extremity for skip lesions
- CT chest
- PET-CT (vertex to toes)
- MRI or CT with contrast of metastatic sites
- Image guided biopsy
- Referrals:
  - Pediatric/medical oncology
  - Orthopedic oncology
  - Rehabilitation Medicine
  - Reproductive endocrinology/fertility preservation

# Osteosarcoma Treatment Paradigm



Surgical Resection  
is the preferred  
local control method  
for OS

# Osteosarcoma Chemotherapy



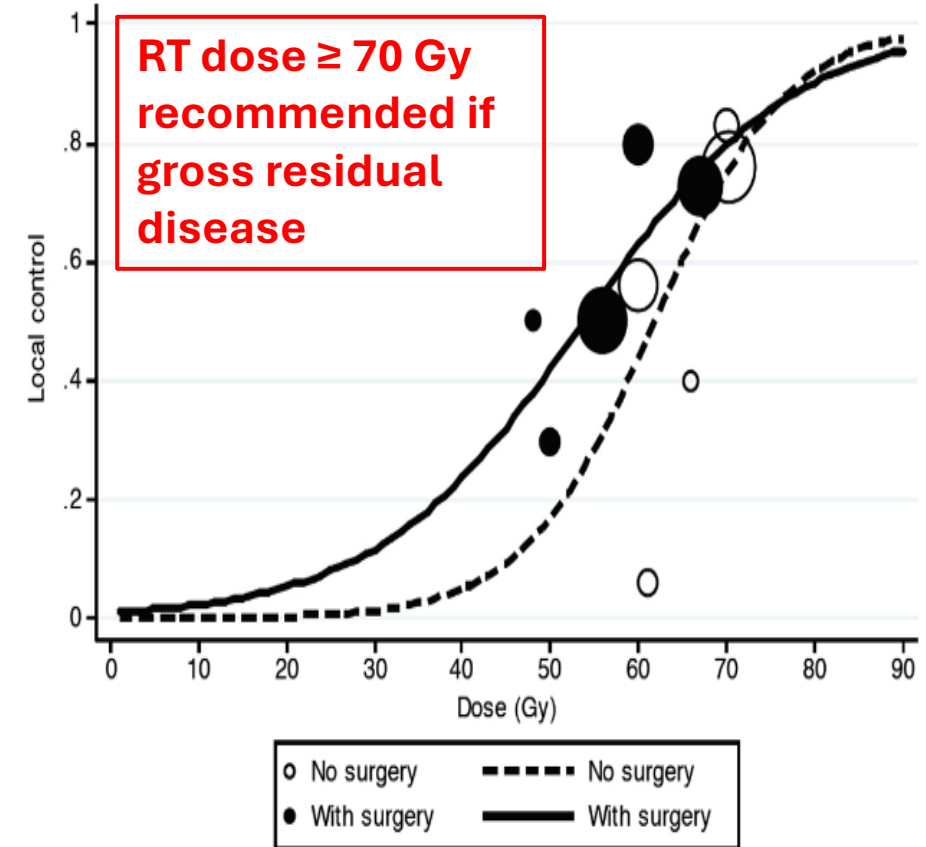
- Meta-analysis of multiple chemotherapy trial demonstrated significantly improved EFS and OS with the use of 3-drug combinations as opposed to 2 drug combinations, and the importance of high-dose methotrexate.
- Methotrexate, Adriamycin and Cisplatin is the general standard approach in both US and European clinical trials. The addition of additional chemotherapy agents to the MAP backbone has not improved results.
- AOST2032 is testing the addition of Cabozantinib to MAP

# Radiation Therapy for Osteosarcoma

- Surgical resection is generally the preferred local control modality for the primary tumor
- RT indications:
  - Unresectable tumor
  - Positive surgical margins
  - Consolidation of metastatic sites
  - Palliation
- Osteosarcoma is not a radiosensitive histology and high RT doses are required for durable local tumor control

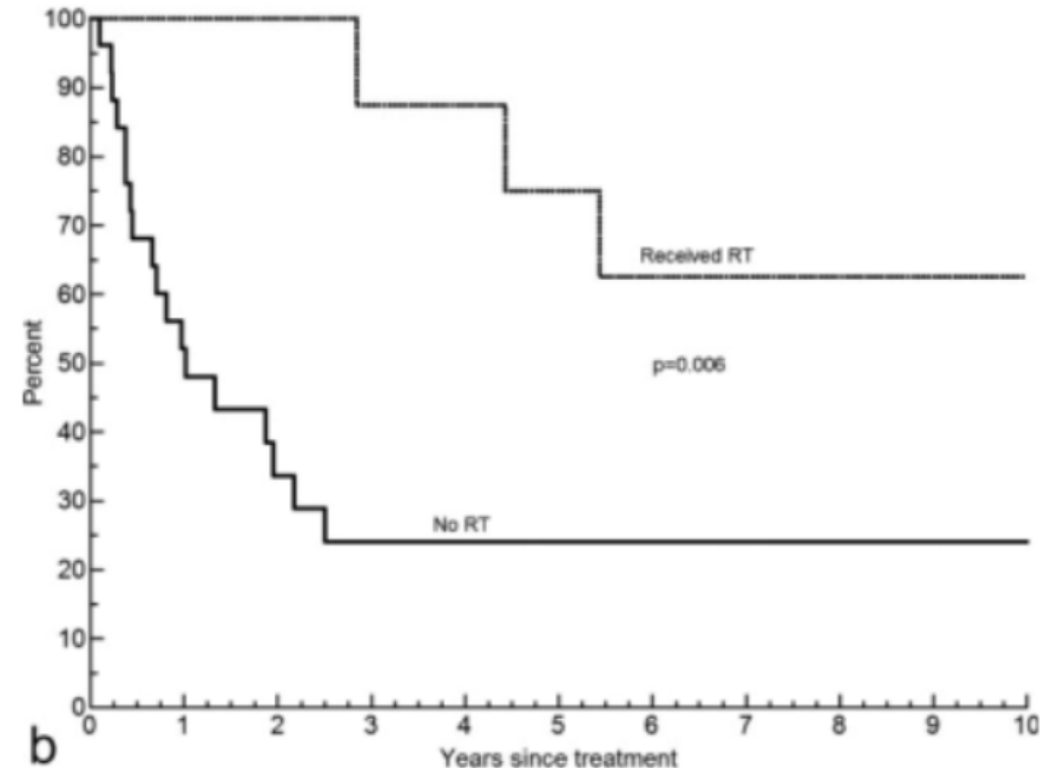
# Radiation Therapy for Osteosarcoma

- Massachusetts General Hospital Experience
  - 55 patients treated with proton (+/- photon) therapy , 1983-2009
  - 78% treated post-operatively
    - (R2 35%; R1 43%)
  - Median RT dose 64.8 Gy
    - 51% of patients >70 Gy
- Local control at 3 and 5 years 82% and 72%
- Higher local failure in H/N sites



# Head and Neck Osteosarcoma

- MD Anderson Experience
  - 119 patients with resected HN Osteosarcoma
  - Median RT dose 60 Gy (range 50-66 Gy)
  - Among patients with positive or uncertain surgical margins
    - Local Control: 75% RT vs 24% no RT ( $p=0.006$ )
    - Overall Survival: 80% RT vs. 31% no RT ( $p=0.02$ )





# RT Guidelines: Primary Tumor

sample guidelines as per AOST2032

GTV Target	≤ 5cm	Cumulative Dose
GTV1 = gross disease at presentation	CTV1 = GTV1 + 1.5-2 cm anatomically modified margin (3 cm longitudinally in an extremity)	50.4 Gy
GTV2 = gross disease after induction chemotherapy, preoperative if surgery if performed	CTV2 = GTV2 + 1cm anatomically modified margin	66.6 Gy
GTV3 = post-operative/unresected gross disease	CTV3 = GTV3	73.8 Gy

- PTV3/ 73.8 Gy dose level used only in the setting of gross residual disease after surgery or unresectable tumor/definitive RT
- Targets are treated sequentially in 1.8 Gy per fraction. Institutional and modality specific PTV recommended.
- Target coverage for PTV2/PTV3 may need to be compromised to respect high-priority OARs

# RT Guidelines: Metastatic Sites

sample guidelines as per AOST2032

- SBRT recommended for all metastases  $\leq 5\text{cm}$  in size
  - Bone/Non-Pulmonary
    - 40 Gy in 5 fractions to CTV (GTV + 1cm modified margin) + 2mm PTV margin
    - 50 Gy in 5 fractions to GTV as simultaneous integrated boost
  - Pulmonary Metastases
    - 50 Gy in 5 fractions to ITV + 5mm PTV margin
- GTV is defined as residual disease after chemotherapy
- Metastases larger than 5 cm treated with hypofractionated RT or conventional fractionation