Ewing's Sarcoma
Adjuvant Indications
Role of Radiation – unresectable tumors

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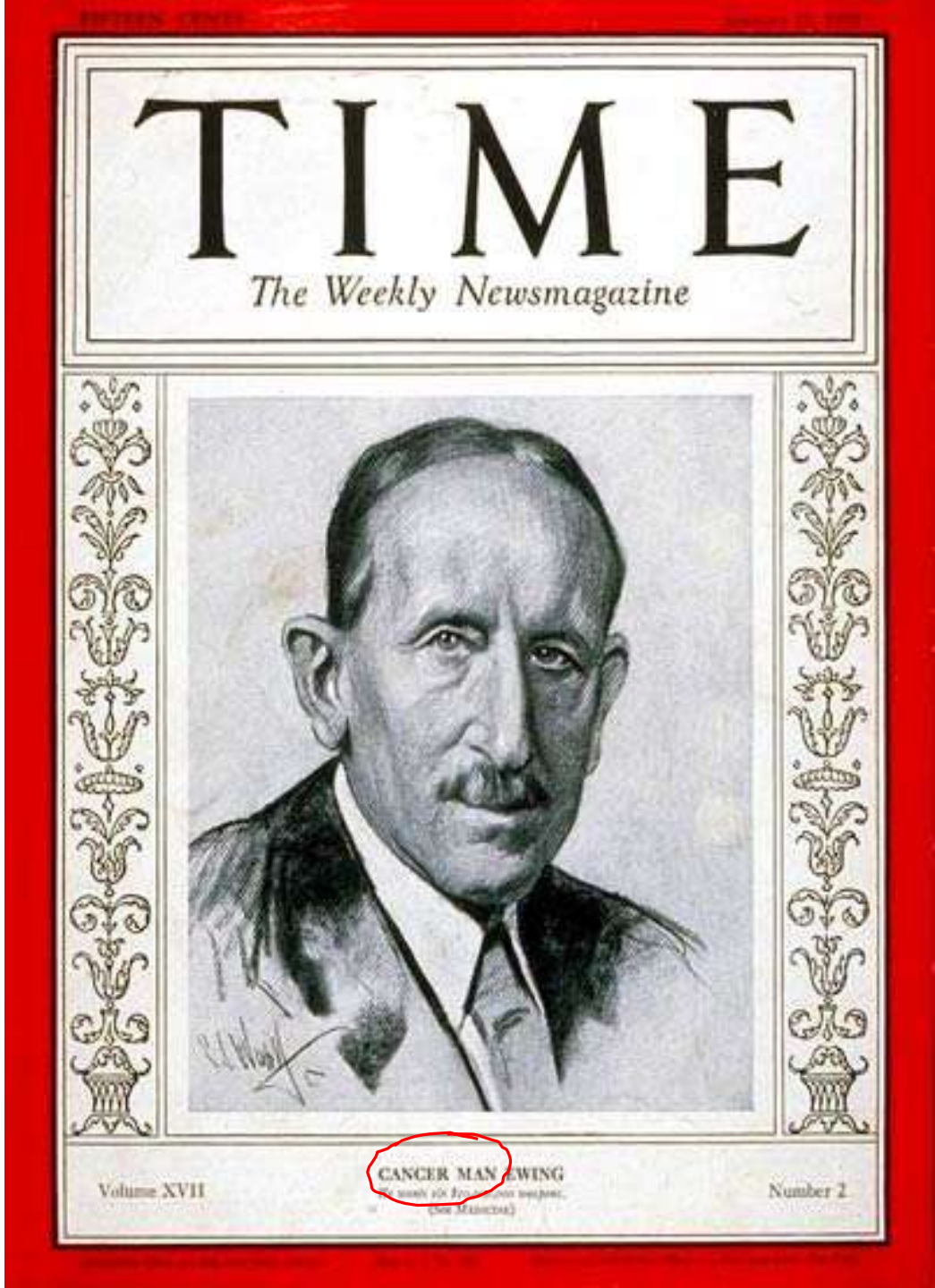
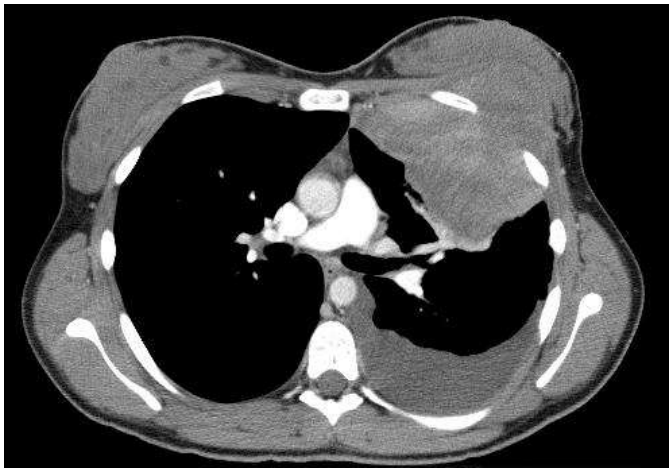


Ewing’s sarcoma family of tumors (ESFT)

- Classical Ewing’s sarcoma of the bone
- Extra skeletal Ewing’s sarcoma
- Askin tumor of the thoracic wall
- Peripheral neuro-ectodermal tumor (pPNET)



WHO classification : ES/PNET

ES/PNET – Genetic abnormality

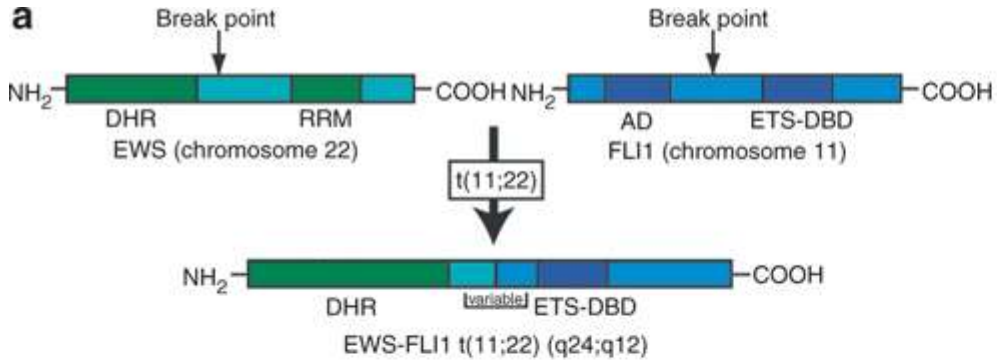
- Rearrangements of ***EWSR1*** with ***FLI1*** or ***FLI-1* related gene**.
  - Seen in 98%.
    - t(11;22)(q24;q12) → *EWS-FLI* gene seen in 85%
    - t(21;22)(q22;12) → *EWS-ERG* gene seen in 10%

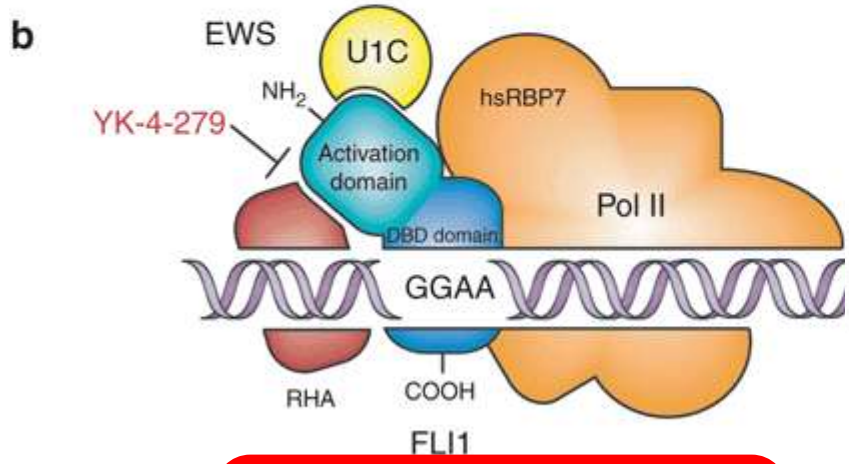
Summary of the different fusions and their frequency in Ewing sarcoma

Ewing's sarcoma translocation		
EWS member	ETS member	Frequency (%)
EWS	FLI1	85
EWS	ERG	10
EWS	ETV1	<1
EWS	ETV4	<1
EWS	FEV	<1
TLS	ERG	<1

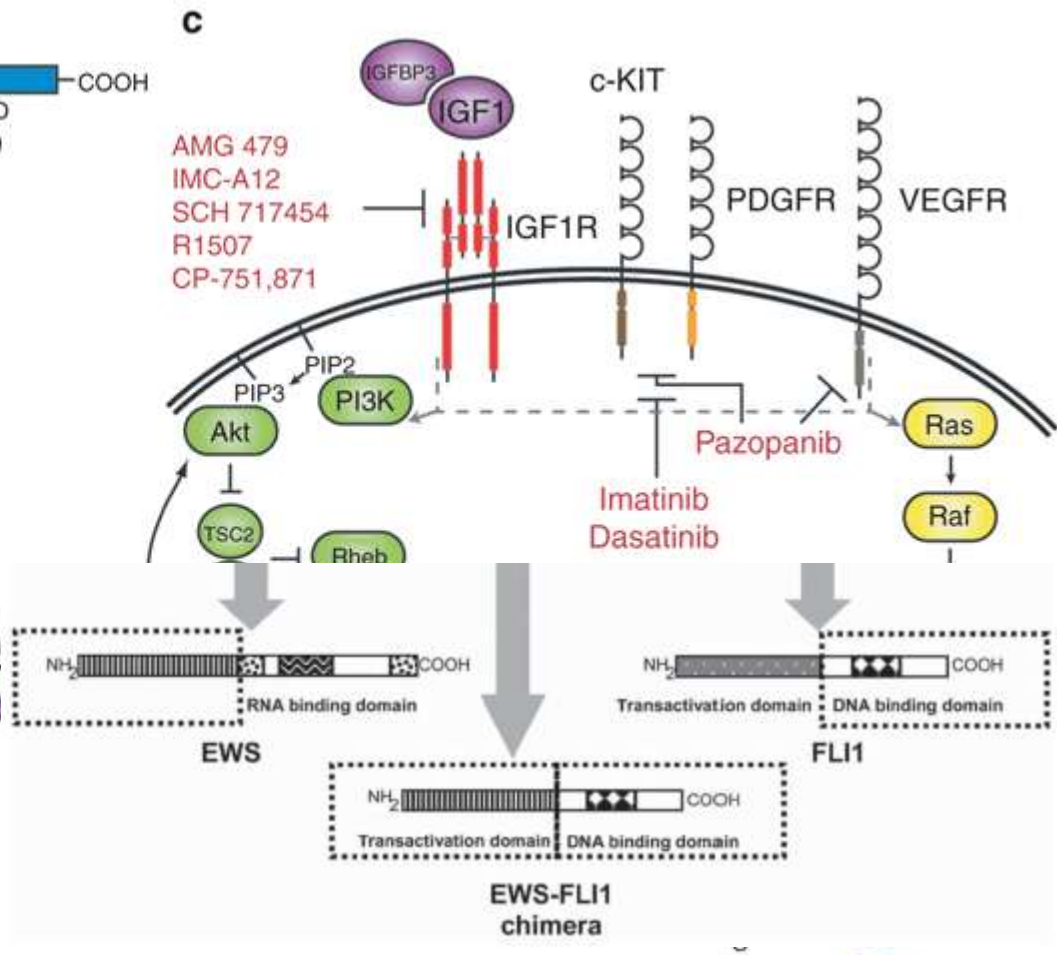
  - Ewings like sarcomas
    - BCOR re-arranged sarcoma
    - CIC re-arranged sarcoma (older age, mean ~30yrs, mostly soft tissue)

ES/PNET – Molecular pathogenesis





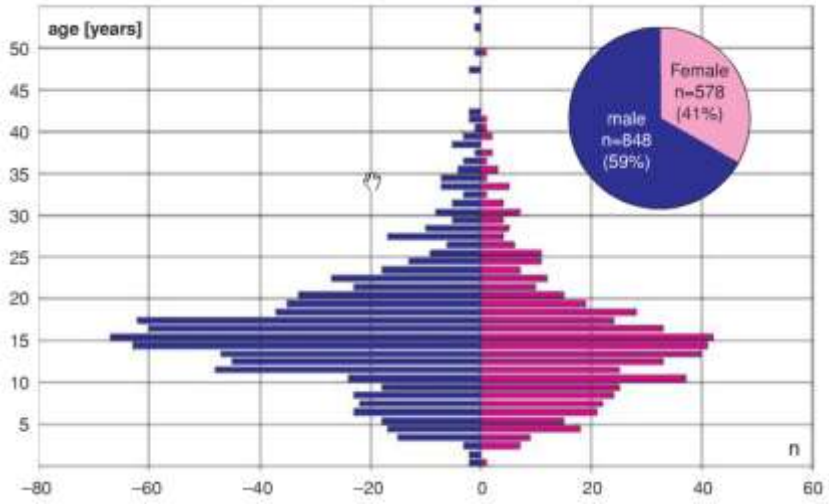
Transcriptional activation and repression
Alteration of splice site selection
Modulation of RNA half-life

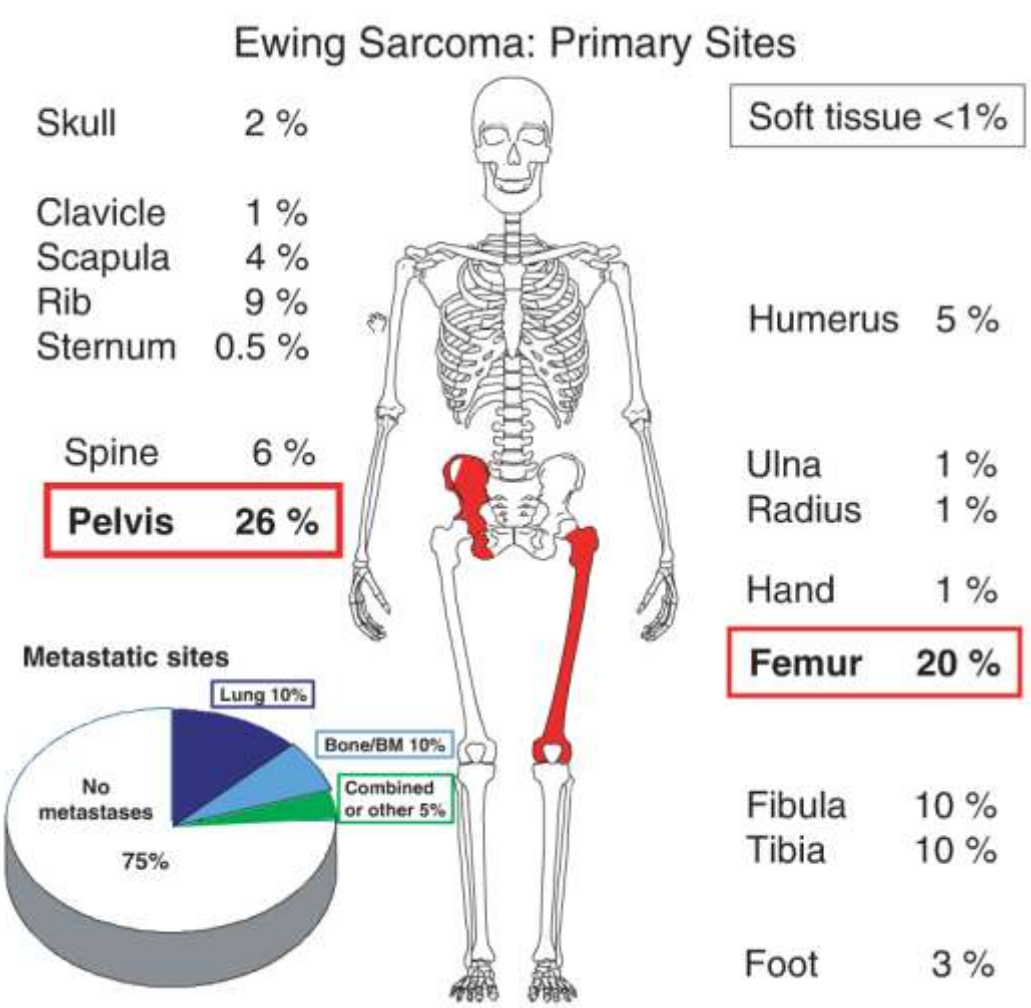


Pediatr Res. 2012 Aug;72(2):112-21.
DOI:10.1038/pr.2012.54

Clinical Presentation

- Pain 90%
- Swelling 80%
- Impaired limb movt 25%
- Neurological 10%
- Fever 5%
- Mets symptoms





- Axial skeleton
- Diaphyseal
- Mets to LNs, liver, CNS – v. rare

FIGURE 33.3 Primary tumor and metastatic sites in Ewing sarcoma. Data based on 1,426 patients from European Intergroup Cooperative Ewing Sarcoma Studies (EI-CESS) trials.

- Prognostic factors
  - Metastasis
    - Pulmonary vs Others
  - Site
    - Axial vs Extremity
  - Location, distal better than proximal : failures
    - 5% distal
    - 25% proximal
    - 35% central
  - Size ≤ 8cm better than > 8cm (failure rate 10% vs. 30%)
  - Volume >200ml
  - Response to chemotherapy
  - Elevated LDH
  - Age > 17 yrs

Workup

- Imaging of primary
  - X-ray
  - CT
  - MRI – preferred
    - superior definition of tumor size, local intraosseous and extraosseous extent, and the relationship of the tumor to fascial planes, vessels, nerves, and organs.
    - Image the entire bone to detect any skip lesions

TV = a x b x c x F,

where a, b, and c represent the maximum tumour dimensions in three planes,

with $F = \pi / 6 = 0.52$ for spherical tumours,

or $F = \pi / 4 = 0.785$ for cylindrical tumours

Workup

- Biopsy
  - Multiple core Bx or
  - Open, Longitudinal
    - In accordance with planned resection
    - From soft tissue component
    - Drain if needed (avoid hematoma)

IHC

Optimal panels of various IHC antibody markers for individual malignant RCTs are as follows:

- **Ewing sarcoma: MIC2/CD99 (invariably diffuse, cytoplasmic membranous immunoexpression), NKX2.2, Fli1, Caveolin, coupled with negative expression of LCA.**

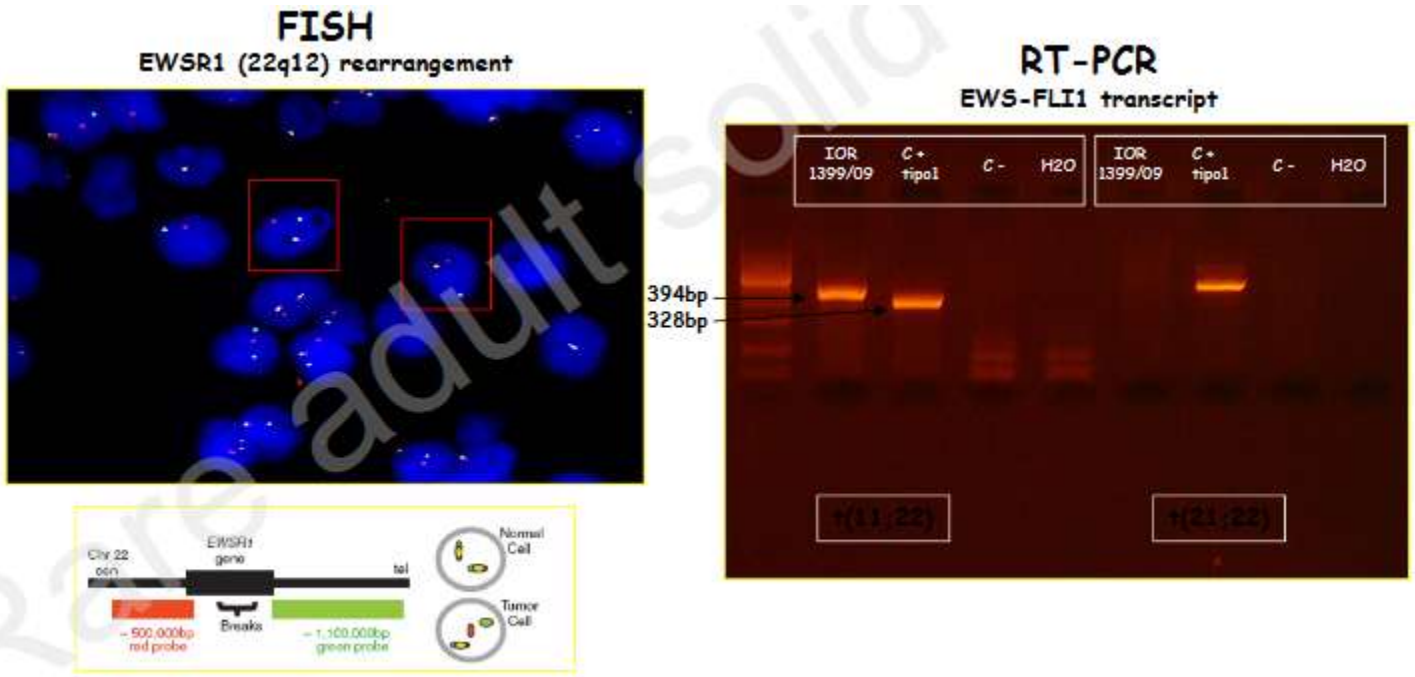
- **Neuroblastoma**: Synaptophysin, chromogra
  and CD56.
- **Non-Hodgkin's lymphomas**: LCA, CD20, an
  as CD30 for ALCL (ALK+ or ALK-), Tdt for ly
- **Small cell osteosarcoma**: SATB2. Considerin
  positive for MIC2, similar to Ewing sarcom
  recommended as Ewing sarcoma is charac
  translocations t (11; 22) (*EWS-FLI1), in mo*
- **Plasma cell dyscrasia/myeloma**: CD138 (Sy
  evaluating light chain restriction
- **Rhabdomyosarcoma**: Desmin, MyoD1, Myogenin
- **Mesenchymal chondrosarcoma**: MIC2/CD99 and Leu7. S100 protein highlights the chondroid component.

CD99/MIC2 is also positive in cases of

lymphoblastic lymphoma,
poorly differentiated synovial sarcoma,
Small cell osteosarcoma
mesenchymal chondrosarcoma, and
melanoma,
to name but a few tumors

Rekhi et al. **DOI: 10.4103/IJPM.IJPM_675_18**

FISH/RT-PCR



- If neg : EWSR1 breakapart probe → ?NGS

Workup

- CT chest

Definite	Questionable
1 nodule > 1cm	1 nodule > 0.5-1cm
>1 nodule >0.5cm	>1 nodule >0.3-0.5cm
	Suggest Biopsy

- Bone scan

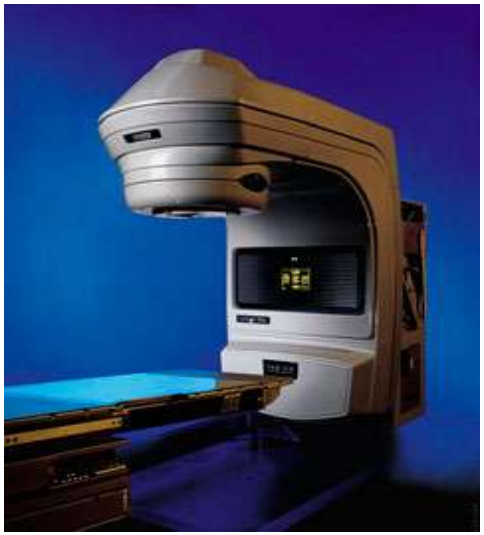
EURO EWING 99/2008, COG AEWS0031 Protocols

- Bone marrow biopsy
  - As of now : Mandatory
  - Incidence of isolated marrow involvement is rare !!

- Role of PET-CT in replacing Bone marrow biopsy and bone scan, and CT chest ?
  - Entire body needs to be covered (not upto just mid-thigh)
  - May be inferior to dedicated CT-chest

ES/PNET - Treatment

- Local therapy



- Systemic therapy

Multi-disciplinary treatment

Induction Chemotherapy

- Early metastasis prophylaxis
- Facilitate conservative surgery and/or radiotherapy

Local Control

- Surgery and/or
- Radiotherapy

Maintenance Chemotherapy

- Metastasis prophylaxis

ES/PNET – Evolution of treatment

- Initial documentation of response to Radium
- MGH (1930-1952)
  - 68% local control
  - 18% 6 yr survival
- Univ of California (1935-70)
  - 72% local control
  - 24% 5yr survival

No chemotherapy
Whole bone RT
Low voltage X-rays
Tumor dose above 5000 rads.

1970s……multiagent chemotherapy

1968 – Hustu: Combination – V+C & RT- sustained resp-5 pt

1976 – Jaffee: Improved survival – VAC vs. Single agent

- IESS -1 (1973-78)
  - 89% local control with 55-65 Gy WB RT
  - 60% 5yr EFS

Longer survival – c/c toxicities of RT – apparent & less acceptable.

Surgical advocates – Pritchard
Observational studies – better time to relapse and OS in IESS-1

			5yr EFS	
IESS-I (1973-78)	VAC		24%	Value of Doxorubicin. Benefit of WLI ?
	VAC+WLI		44%	
	VACD		60%	
IESS-II (1978-82)	VACD-MD		48%	Value of aggressive cytoreduction
	VACD-HD		68%	
UKCCSG/MRC (1978-86)	VACD		41% Axial: 38% Extre: 52%	Tumor site as prognostic factor
CESS-81 (1981-85)	VACD	Local failure Sx : 6% Sx+RT: 17% RT : 50%	Sx (54%) Sx+RT (68%) RT (43%)	Poor quality RT Tumor volume & Histologic response as prognostic factors
		Tmr vol <100ml : 80% >100ml : 31%	Viable tmr <10% : 79% >10% : 31%	
CESS-86 (1986-91)	<100ml VACD	Local Failure Relapse Sx : 4% 26% Sx+RT : 3% 34% RT : 13% 30%	52%	RT randomised to Conventional (1.8 Gy) Hyper# split course (1.6 Gy BD) - No difference
	>100ml VAID		51%	

			5yr EFS	
POG 8346 (1983-88)	SFRT IFRT (tailored)	WBRT (39.6Gy)+Bst(16.2) Only to Boost field (55.8) No difference in EFS or LC	Distal extr : 65% Central : 63% Prox extre : 46% Pelvi-sacral:24%	5yr local control Appropriate RT : 80% Minor deviation: 48% Major deviation: 16%
1st POG-CCG (INT-0091) (1988-93)	VACD		54%	Localised : IE beneficial Metastatic: IE no benefit
	VACD+IE		69%	
EICESS-92 (1992-99)	SR: VAID vs. VACD HR: VAID vs. EVAID		68% vs. 67% 44% vs. 52%	Prognostic factors -Stage, Histologic response, type of local treatment. C more toxic than I, E beneficial in HR
2nd POG-CCG (INT-0154) (1995-98)	VCD+IE		72%	No benefit of high-dose alkylating agent
	VCD+ IE(HD)		70%	
1st COG (AEWS0031) (2001-05)	VCD+IE (Q3w) vs. (Q2w)		65% (4yr) 76%	Dose compression better
Euro-Ewing 99				

Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group

Womer, JCO 2012

VOLUME 30 · NUMBER 33 · NOVEMBER 20 2012

Richard B. Womer, Daniel C. West, Mark D. Krailo, Paul S. Dickman, Bruce R. Pawel, Holcombe E. Grier,

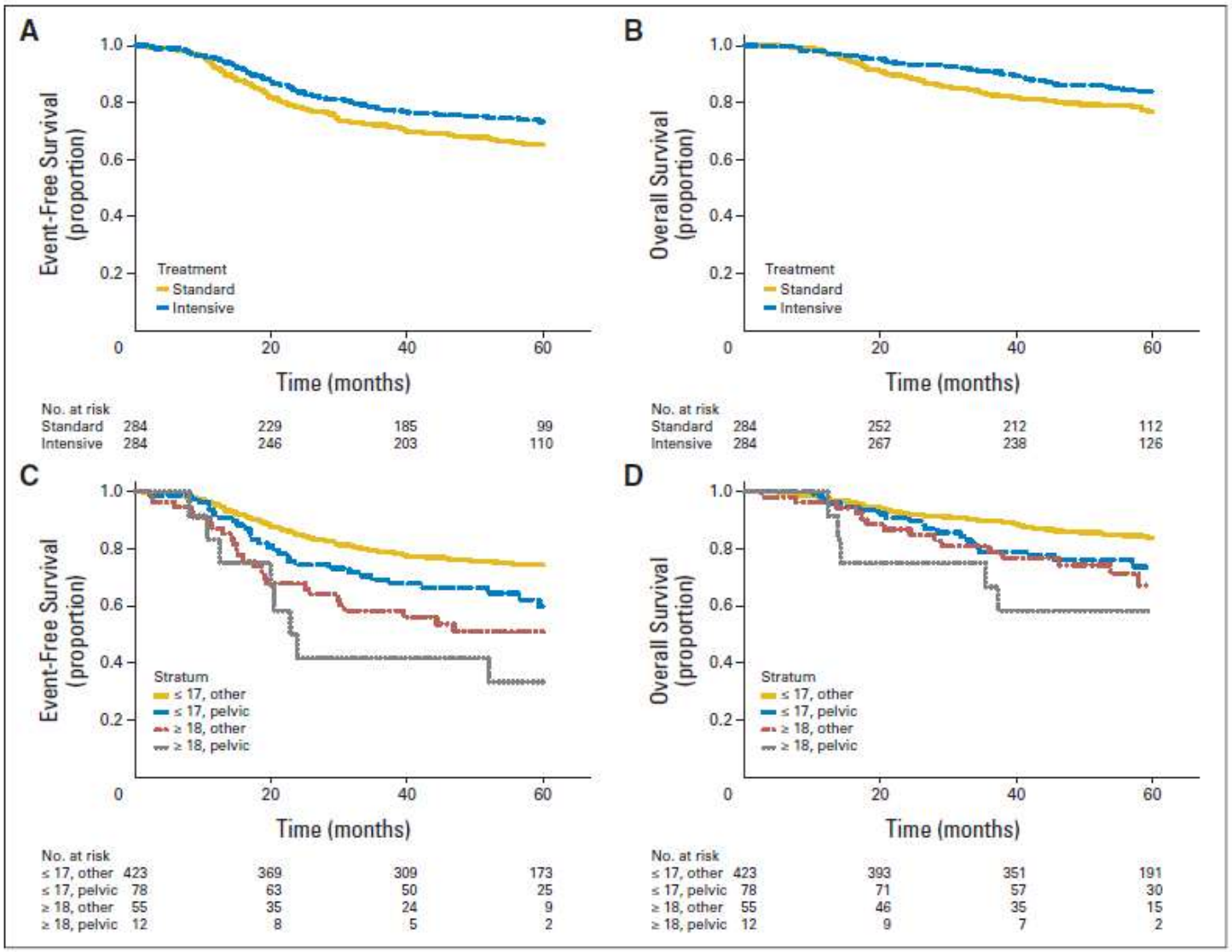
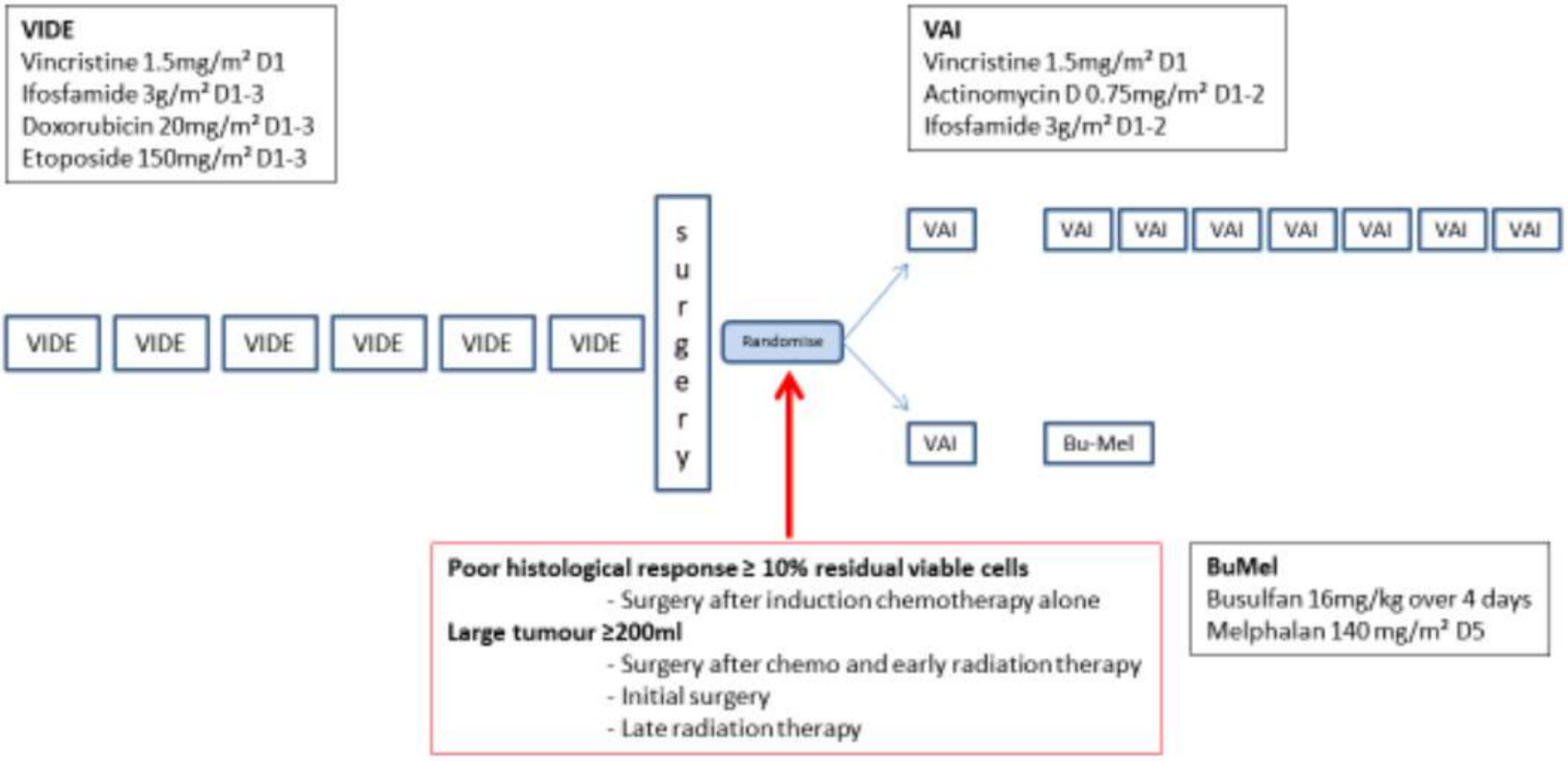


Fig 3. Kaplan-Meier plots of treatment outcome. (A) Event-free survival (EFS) according to the assigned treatment regimen. (B) Overall survival (OS) by regimen. (C) EFS and (D) OS, respectively, for the four strata, pooling the treatment regimens.

HD Chemo, SC support
EURO EWING 99,2008

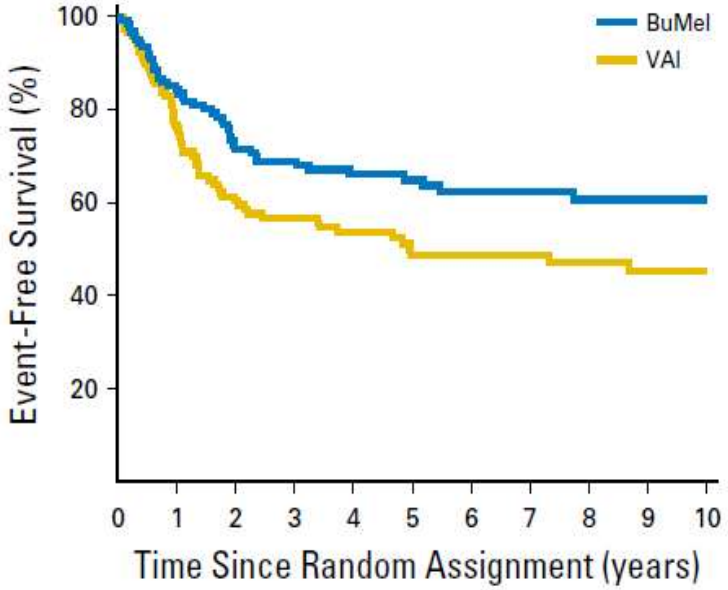


High-Dose Chemotherapy and Blood Autologous Stem-Cell Rescue Compared With Standard Chemotherapy in Localized High-Risk Ewing Sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008

Jeremy Whelan, Marie-Cecile Le Deley, Uta Dirksen, Gwénaël Le Teuff, Bernadette Brennan, Nathalie Gaspar,

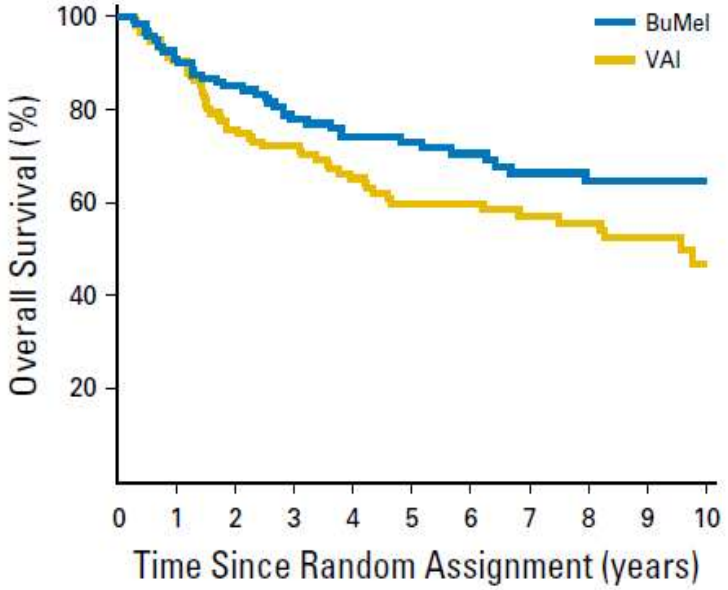
Whelan
JCO,2018 Sep

Intralesional surgery	54.4 Gy
Marginal surgery with poor histological response (≥ 10% residual tumour cells)	54.4 Gy
Marginal surgery with good histological response (< 10% residual tumour cells)	44.8 Gy
Wide resection with poor histological response (≥ 10% residual tumour cells)	44.8 Gy



No. at risk:

BuMel	122	84	62	48	33	16
VAI	118	67	49	36	27	12



No. at risk:

BuMel	122	100	72	55	35	18
VAI	118	85	63	48	35	14

Local treatment

- Attain complete tumor eradication
- Maximising function and cosmesis
- Minimising long term morbidity

RT vs. Sx

No randomised trials – no direct comparison
Many retrospective series – local control improves when surgery is possible.

Radiotherapy

- Site : Unfavourable
- Volume: Bulky
- Inoperable

Surgery

- Site : Favourable
- Volume: Less bulky
- Operable - expendable

Table 5.15 Results of radiotherapy for Ewing's sarcoma

Institution	*Years*	*No. of patients*	*Chemotherapy agents*	*Radiation dose*	*Volume*	*Local control*	*5-year EFS/DFS*	*Reference*
MGH	1930–1952	22	None	2000–6000 r	WB	68%	18%	Wang *et al.*[1]
UCSF	1945–1965	20	None	16–65 Gy	WB	72%	25%	Phillips and Sheline[2]
IESS-I	1973–1978	148*	VACA	55–65 GY	WB	89%	60%*	Nesbit and Rosen[71]
IESS-II	1978–1982	108†	VACA	55 GY	WB	93%	73%†	Burgert *et al.*[175]
CESS-I	1981–1985	32	VACA	45–60 GY	WB	54%[a]	44%	Sauer *et al.*[158]
CESS-II	1986–1991	44	VACA/VAIA	60 Gy	PB	86%	70%	Dunest *et al.*[177]
St Jude	1978–1988	43	VA/CA/BCNU	30–60 Gy	PB	58%[b]	53%	Arai *et al.*[155]
NCI	1968–1980	107	VC/VAC/VADRIAC	50 Gy	WB	80%	29%	Kinsella *et al.*[163]
NCI	1986–1992	46	VADRIAC/IE	26–63 Gy	N/A	80%	42%	Wexler *et al.*[165]
Chile	1986–1991	11	VACA	45–63 Gy	PB	73%	36%	Villareall *et al.*[161]
Scandinavia	1984–1990	17	VACAMB	40–60 Gy	N/A	76%	35%	Nilbert *et al.*[181]
UK	1978–1986	108	VACA	32–55 Gy	WB	69%	35%	Craft *et al.*[184]
Bologna	1972–1987	62	VA/VACA	35–60 Gy	WB/PB	66%	N/A	Toni *et al.*[154]
University of Florida	1971–1990	31	VADRIAC	50–68 Gy	WB/PB	77–81%	N/A	Bolek *et al.*[166]
POG 8346	1983–1988	94	AC/VAC/VACA	55.8 Gy	WB/PB	65%	41%	Donaldson *et al.*[157]

Table 5.14 Local control following resection ± radiation for extremity Ewing's sarcoma

Reference	*Institution*	*No. of patients*	*Local control*	*5-year survival, DFS, RFS*	*Preoperative/postoperative radiotherapy*	*Amputation*
Wilkins	Mayo	27	96% (26/27)	74%	27/27 (100%)	5/27 (18.5%)
Sauer	CESS-I	60	90% (54/60)	64%	29/60 (48%)	ND
Sailer	MGH	12	100%	92%	92%	1/12 (8%)
Hayes	St Jude	11	100%	80%*	0	ND
Arai	St Jude	17	100%	75%	7/17 (18%)	ND
Toni	Bologna	69	96%	59%	31/56 (55)	13/69 (19%)
Dunst	CESS-II	132	96%	70%	63/91 (69%)	(9%)
Tereki	Brown University	22	95%	41%	13/22 (59%)	4/22 (18%)
Villoreal	Chile	16	100%	50% (7-year)	50%	ND

*This survival estimate is for all treated patients. Only two relapses occurred among the 11 patients treated with surgery alone as the local treatment. ND = Not described; DFS = disease-free survival; RFS = relapse-free survival.

Comparative Evaluation of Local Control Strategies in Localized Ewing Sarcoma of Bone

A Report From the Children's Oncology Group

Cancer 2015;121:467-75.

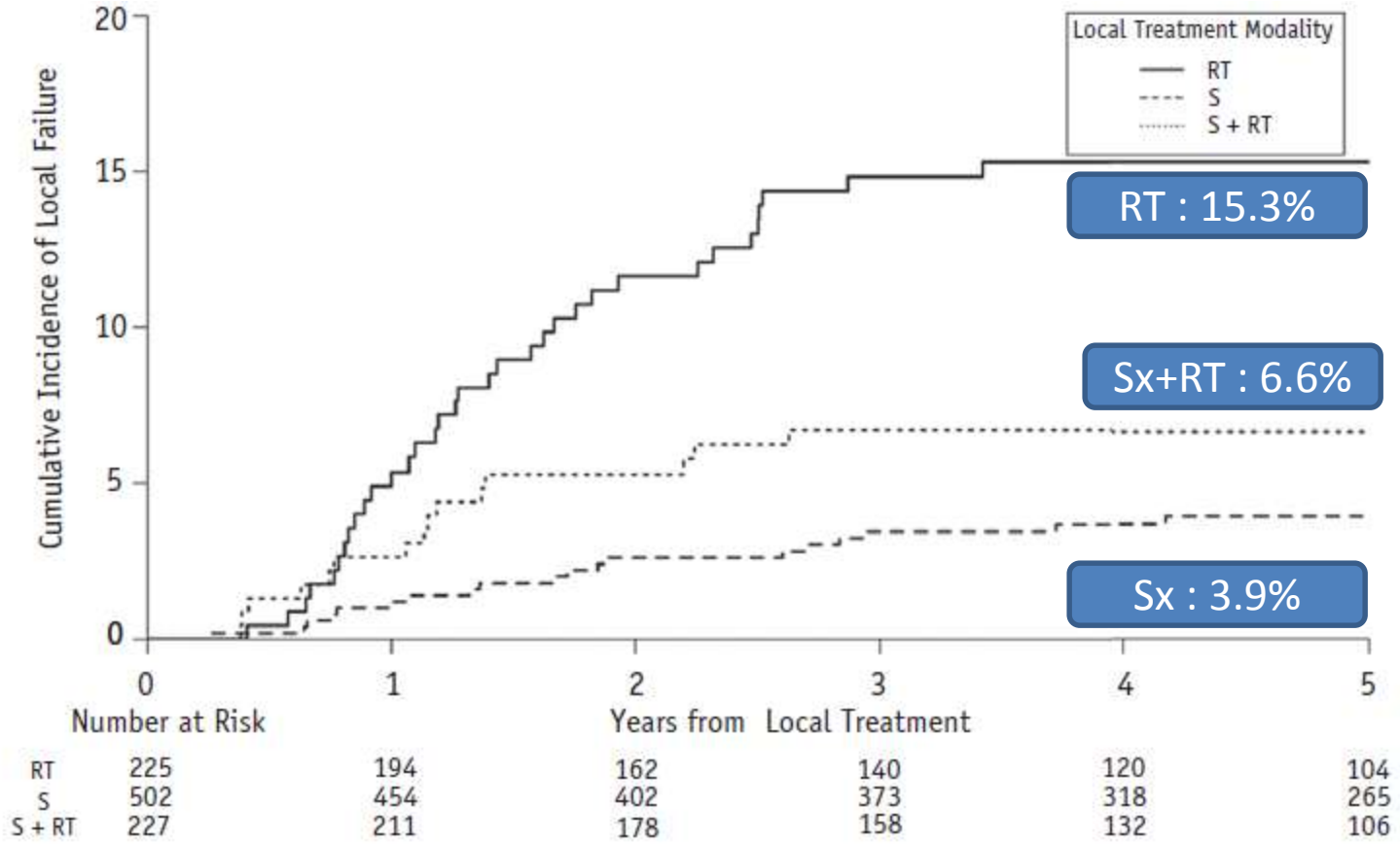
- Patients who underwent surgery were
  - younger (P5.02) and had
  - more appendicular tumors (P<.001).
- Compared with surgery, radiation had higher unadjusted risks of
  - any event (HR, 1.70; 95%CI, 1.18-2.44),
  - death (HR, 1.84; 95% CI, 1.18-2.85), and
  - local failure (HR, 2.57; 95% CI, 1.37-4.83).
- On multivariate analysis, compared with surgery, radiation had a
  - higher risk of local failure (HR, 2.41; 95% CI, 1.24-4.68), although there
  - no significant differences in
    - EFS (HR, 1.42; 95% CI, 0.94-2.14),
    - overall survival (HR, 1.37; 95% CI, 0.83-2.26), or
    - distant failure (HR, 1.13; 95% CI, 0.70-1.84)

These data support surgical resection when appropriate, whereas radiotherapy remains a reasonable alternative in selected patients.

Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group

Safia K. Ahmed, MD*

Int J Radiat Oncol Biol Phys. 2017 December 01; 99(5): 1286–1294.



Identification of Patients With Localized Ewing Sarcoma at Higher Risk for Local Failure: A Report From the Children's Oncology Group

Safia K. Ahmed, MD*

Int J Radiat Oncol Biol Phys. 2017 December 01; 99(5): 1286–1294.

	All	Sx (502) (52%)	RT (226) (24%)	Sx+RT (228) (24%)
INT-0091	164(17.2)	65(40)	64(39)	35(21)
INT-0154	333(34.8)	208(62)	69(21)	56(17)
AEWS0031	459(48)	229(50)	93(20)	137(30)
Extremity		310(74)	54(13)	55(13)
Pelvis		51(29)	86(49)	39(22)

Local failure rate : Overall : 7.3%
Significantly higher in

1. Age ≥ 18 yrs : 11.9%
2. Pelvic subsite : 13.2%
3. Radiation : 15.3%

		Local failure (%)
Extremity	Sx	3.7
	RT	14.8
	Sx+RT	5.4
Pelvis	Sx	3.9
	RT	22.4
	Sx+RT	5.1

- Surgery
  - Resectable lesions arising from dispensable bones, or reconstruction / prosthesis feasible.
    - Better local control (?) Doubtful benefit in EFS
    - Avoid RT induced 2nd malignancy
    - In skeletally immature child – prevent long term morbidity, disfigurement
    - Analyze degree of necrosis – prognosis estimation.

    - Site: Dispensable - Fibula, ribs, distal extremities, ileum, body of scapula. Reconstruction – Proximal extremities (long bones, tibia, ulna)
- Radiotherapy
  - Lack function preserving surgery. (Better function preservation)
  - Inoperable
    - Site : Scapula, pelvis around acetabulum, vertebra, skull, facial bones

Eradication vs. function vs. morbidity

- Local treatment individualised based on
  - Site
  - Size
  - Operability
  - Age
  - Individual preference

No benefit of intra-lesional excision+ post-op RT vs. Radical RT

Surgery

- Would it be possible to perform a wide excision with adequate margins ?
  - If No, how to proceed
    - GO ahead with surgery ?
    - RT and then surgery ?
    - Radical RT ?
- What structures need to be excised ?
  - Only residual disease – soft tissue component, involved bone?
  - Previously involved muscles also ?
- Is PORT anticipated ?
- What would be the expected morbidity ?
  - Immediate
  - Long term

Assessing Margins of Resection

- What is considered adequate margin ?
  - Bone margin
    - Bone margin: 2 to 5 cm
      - 1cm may be adequate
  - Soft tissue Margin
    - Fat, muscle: 5 mm
    - Fascia, periosteum and intermuscular septa: 2 mm

Pathological response assessment

- What method do you use ?
  - Huvos or modified Huvos
  - CCG / POG grading scheme
  - Salzer-Kuntschik

HUVOS grading scheme		
No necrosis	I	No Rx effect
<50% necrosis	IIA	Partial/Low
50-95% necrosis	IIB	Partial/high
96-99% necrosis	III	Scattered viable foci
100% necrosis	IV	No viable tissue

CCG / POG grading scheme		3yr survival
No chemo effect	I	30%
1-10% necrosis	IIA	30%
11-90% necrosis	IIB	49%
91-99% necrosis	III	73%
100% necrosis	IV	100%

Any issues in assessing tumor response for Ewing ??

Ref: Protocol for the Examination of Specimens From Patients With Primitive Neuroectodermal Tumor (PNET)/Ewing Sarcoma (ES)

- Issues in assessing tumor response
  - the evaluation of percentage necrosis in ES can be difficult, because unlike osteosarcoma, there is no residual acellular osteoid framework left to demarcate the original tumor bed.
  - Ewing cells disappear completely, dramatic volume reduction – necrosis % maybe erroneous.
  - Furthermore, data regarding correlation of necrosis with outcome in extraosseous ES is not available.
  - Currently, histologic assessment of percentage necrosis is not used formally to guide therapy in ES

Histologic Response

Series	Histologic Response	EFS	Local Failure Rate
CESS 86	≤10% viable tumor cells >10% viable tumor cells	64% 38%	
AEWS0031	<90% necrosis ≥90% necrosis No viable tumor cells	~65% ~70% ~80%	
Mayo Clinic	≤5% viable tumor cells >5% viable tumor cells	76% 59%	
MD Anderson	≤95% necrosis >95% necrosis	36% 74%	44% 9%

MAYO CLINIC

Chihak, Ahmed et. al., Manuscript in preparation
Pan et. al., *Int J Rad Onc Bio Phys*, 2015
Paulussen et. al., *J Clin Oncol*, 2001
Womer et. al., CTOS Annual Meeting, 2016

Slide courtesy: Ahmed S, Mayo Clinic 2017

Radiological response assessment Investigational

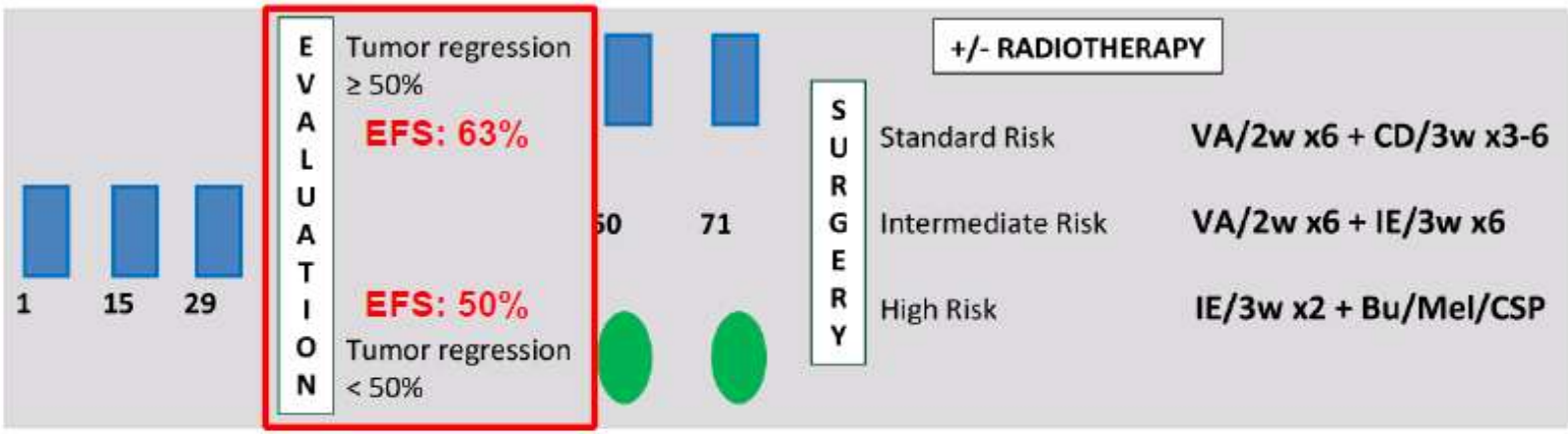
- MRI
  - Is soft tissue response assessment sufficient ?

Prognostic Factors and Patterns of Relapse in Ewing Sarcoma Patients Treated With Chemotherapy and R0 Resection

CONCLUSIONS—Histologic and radiologic response to chemotherapy were independent predictors of outcome. Additional study is needed to determine the role of adjuvant RT for patients who have poor histologic response after R0 resection.

-Pan, Mahajan, IJROBP 2015 June.

Radiologic Response



EURO-EWING99 :Tumor regression >90% associated with lower local failure rate

MAYO CLINIC

Andreou et. al., CTOS Annual Meeting, 2016
Gaspar et. al., *Eur J Cancer*, 2012

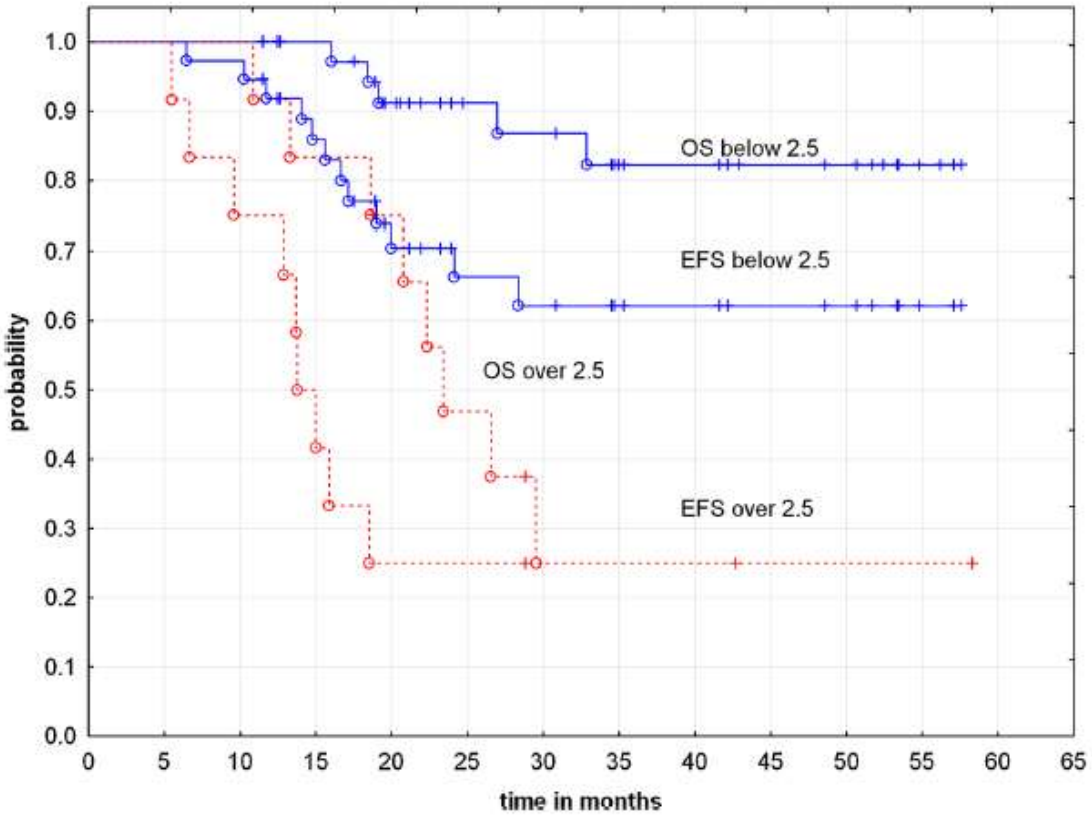
Slide courtesy: Ahmed S, Mayo Clinic 2017

Investigational

- PET-CT ?

SUV at diagnosis was significantly lower in patients with good histological response than in patients with poor histological response.

the positive predictive value of an SUV II ≤ 2.5 for favorable response was 84.21 %, and the median SUV II was significantly higher in patients with disease progression (2.3 vs. 1.6, p = 0.04)



Raciborska 2016 Feb, Clin Trans Oncol

Radiotherapy

- Indications
  - Definitive Radiotherapy
  - Post-op adjuvant RT
  - ? Pre-op RT
  - Metastatic

Radical Radiotherapy

- Indication
  - Surgery not feasible
    - Axial site : Spine, Pelvis around the acetabulum, skull/facial bones
    - Extremity: Limb preservation not feasible.
  - Margin negative resection not feasible.

Post-op RT

- Indication
  - Gross or microscopic positive margin
  - Poor histologic response to chemo (European)
  - Pre treatment fracture, hematoma, tissue violation (S Laskar, ICRO 2015)

ENNEKING CLASSIFICATION OF SURGICAL INTERVENTION

Intralesional resection	Tumor opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease
Marginal resection	Tumor removed *en bloc*; however, resection through the pseudocapsule of the tumor; microscopic residual disease likely
Wide resection	Tumor and its pseudocapsule removed *en bloc*, surrounded by healthy tissue, within the tumor-bearing compartment
Radical resection	The whole tumor-bearing compartment is removed *en bloc*, for example, above-knee amputation in lower leg tumor

From Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980;153:106–120.

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

- Inadequate surgical margins.

Role of Surgical Margins, in 512 pts (Italy) - Bacci et al, IJROBP 2006

Conclusions: Surgery is better than radiotherapy in cases of extremity ESFT with achievable adequate surgical margins, and in cases of inadequate surgical margins, adjuvant reduced-dose radiotherapy is ineffective. Therefore, when inadequate margins are expected, patients are better treated with full-dose radiotherapy from the start.

Implication: Inadequate margin requires more than 45 Gy.
When inadequate margin expected – radical RT is a good option, also pre-op RT.

Local therapy in Ewings, 1058 pts, CESS 81,86, EICESS 92 – Schuck et al, IJROBP 2003

Results: The rate of local failure was 7.5% after surgery with or without postoperative RT, and was 5.3% after preoperative and 26.3% after definitive RT ($p = 0.001$). Event-free survival was reduced after definitive RT ($p = 0.0001$). Irradiated patients represented a negatively selected population with unfavorable tumor sites. Definitive RT showed comparable local control to that of postoperative RT after intralesional resections. Patients with postoperative RT had improved local control after intralesional resections and in tumors with wide resection and poor histologic response compared with patients receiving surgery alone. Patients with marginal resections with or without postoperative radiotherapy showed comparable local control, yet the number of patients with good histologic response was higher in the latter treatment group (72.2% vs. 38.5%).

Conclusion: Patients with resectable tumors after initial chemotherapy had a low local failure rate. With preoperative RT, local control was comparable. RT is indicated to avoid intralesional resections. After intralesional or marginal resections and after a poor histologic response and wide resection, postoperative RT may improve local control.

- Adjuvant PORT in poor responder ?

Table 4. Local and combined local and systemic relapses according to combined tumor or treatment characteristics

	Definitive RT	Preoperative RT	Surgery with or without postoperative RT	Surgery without postoperative RT	Surgery with postoperative RT
Extremity tumor (cm^3)					
<100	10/36 (27.7)	1/56 (1.7)	3/110 (2.7)	3/64 (4.6)	0/46 (0)
≥100	11/31 (35.4)	2/67 (2.9)	1/159 (0.6)	0/88 (0)	1/71 (1.4)
Central tumor (cm^3)					
<100	7/57 (12.3)	1/29 (3.4)	9/62 (14.5)	2/18 (11.1)	7/44 (15.9)
≥100	28/106 (26.4)	8/83 (9.6)	20/155 (12.9)	3/45 (6.6)	17/110 (15.4)
Wide resection and good histologic response	—	—	6/190 (3.1)	1/101 (1)	5/89 (5.6)
Wide resection and poor histologic response	—	—	6/84 (7.1)	3/25 (12)	3/59 (5.0)

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.,†

Int. J. Radiation Oncology Biol. Phys., Vol. 55, No. 1, pp. 168–177, 2003

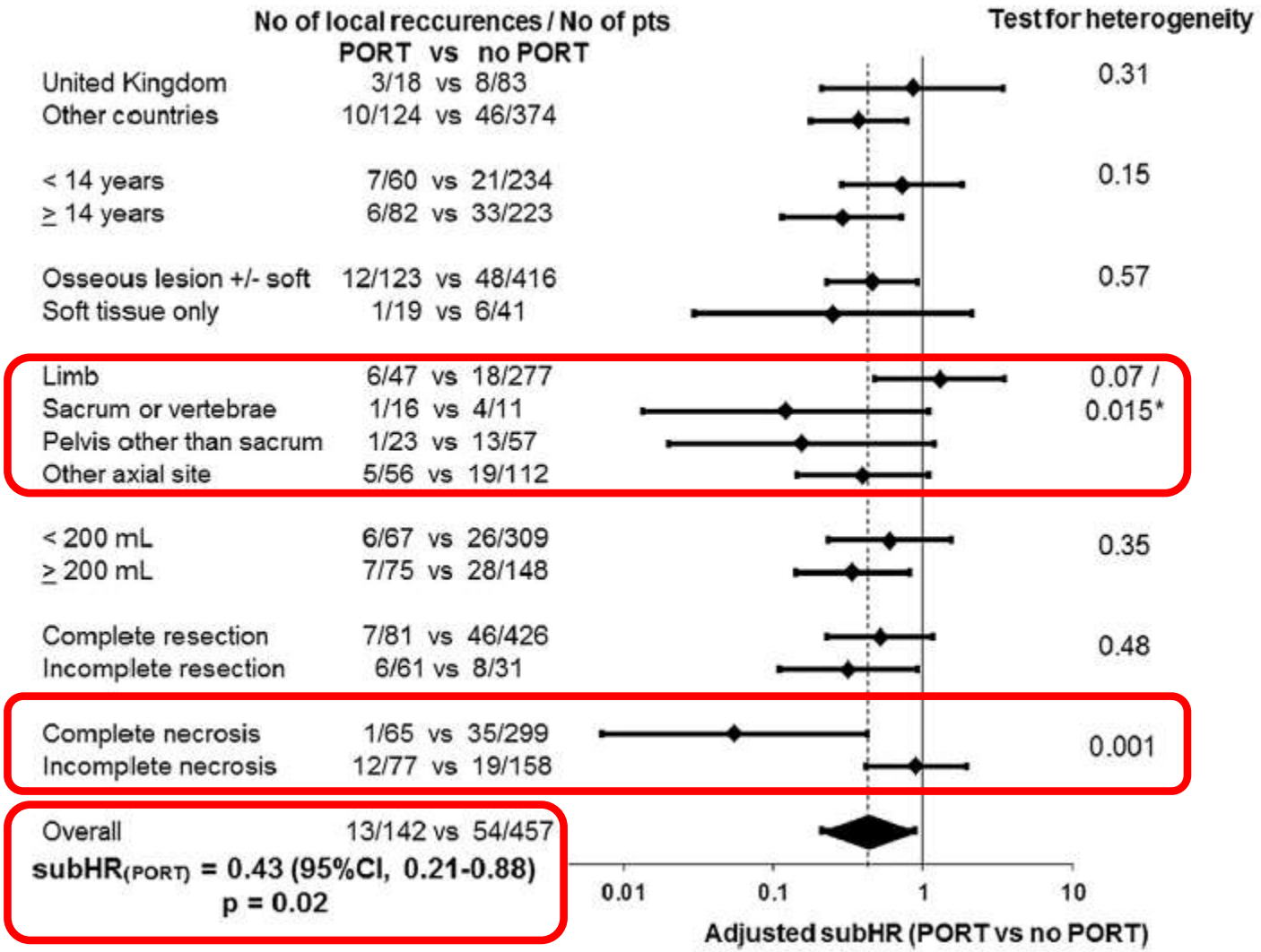
- Adjuvant radiation
  - Role in complete pathological response ?

Can postoperative radiotherapy be omitted in localised standard-risk Ewing sarcoma? An observational study of the Euro-E.W.I.N.G group

Results: One hundred forty-two (24%) of the 599 patients included from 1999 to 2009 received PORT (median dose: 45 Grays). With median follow-up of 6.2 years, 67 patients had an LR (with concomitant metastases in 28), leading to an 8-year LR-incidence = 11.9% (standard error [se] = 1.4%). Overall survival (OS) = 21% (se = 5%) 3 years after LR (31% in isolated LR). Controlling for possible confounders, we observed a statistically significant reduction of LR in patients treated by surgery + PORT compared to surgery alone (subdistribution-hazard ratio = 0.43, 95% confidence interval: 0.21–0.88, p = 0.02). The benefit of PORT was particularly marked for tumours larger than 200 ml at diagnosis and 100% necrosis. We observed a non-significant trend for benefit associated with PORT for disease-free, event-free and OS.
Conclusion: Radiotherapy appears to improve local control. We now recommend PORT in case of incomplete removal of the tissues involved by the pre-chemotherapy tumour volume. Further studies are required to assess the balance between benefit and risks.

the initial tumour bed. We now recommend PORT in the situation of incomplete removal of tissues originally involved by the pre-chemotherapy tumour volume, provided that anticipated adverse side-effects of PORT do not outweigh the expected benefit for local control.

European Journal of Cancer 61 (2016) 128–136


No of local reccurences / No of pts
PORT vs no PORT
Test for heterogeneity
United Kingdom 3/18 vs 8/83
Other countries 10/124 vs 46/374
0.31
< 14 years 7/60 vs 21/234
≥ 14 years 6/82 vs 33/223
0.15
Osseous lesion +/- soft 12/123 vs 48/416
Soft tissue only 1/19 vs 6/41
0.57
Limb 6/47 vs 18/277
Sacrum or vertebrae 1/16 vs 4/11
Pelvis other than sacrum 1/23 vs 13/57
Other axial site 5/56 vs 19/112
0.07 /
0.015*
< 200 mL 6/67 vs 26/309
≥ 200 mL 7/75 vs 28/148
0.35
Complete resection 7/81 vs 46/426
Incomplete resection 6/61 vs 8/31
0.48
Complete necrosis 1/65 vs 35/299
Incomplete necrosis 12/77 vs 19/158
0.001
Overall 13/142 vs 54/457
subHR(PORT) = 0.43 (95%CI, 0.21-0.88)
p = 0.02
0.01
0.1
1
10
Adjusted subHR (PORT vs no PORT)

PORT – RT Dose

		Dose
Margin negative	Poor response	
	Bulky disease, good response	
	Bulky disease, poor response	
R1 resection	Good response	
	Poor response	
R2 resection	Good response	
	Poor response	

European

Surg .margins	Necrosis 100 %	Necrosis <100 %	Boost
Negative	NO RT	45 Gy	----
Close (< 1cm)	45 Gy	50 Gy	5.4 Gy
Micro R1	45 Gy	50 Gy	5.4 Gy
Gross R2	50 Gy	55 Gy	5.4-10-8

Definitely PORT

Positive margin/Gross
Poor responder

Definitely No RT

Limb tumor < 200ml
Clear surgical margins
Complete necrosis

??

Pelvis subsite
Bulky, >200ml
Incomplete removal of involved soft tissue

Pre-op RT

- Would it be possible to perform a wide excision with adequate margins ?
  - If No, how to proceed
    - GO ahead with surgery ?
    - RT and then surgery ?
    - Radical RT ?

tumors. Low-dose (36.0 Gy) preoperative RT was encouraged on AEWS1031 as a method to improve local tumor control for large pelvis tumors. The results of this study are still pending.

AEWS1031
-Ahmed et al, IJROBP Dec 2017.

undertaken whenever possible. Preoperative radiotherapy (44.8 Gy) was recommended when there was < 50% reduction of a soft tissue component, evident on repeat imaging after 2 chemotherapy courses. Radiotherapy

EURO EWING99
-Whelan etal, Clin Sarcoma Res 2018

No benefit of intra-lesional excision+ post-op RT vs. Radical RT

Target Volume

Int. J. Radiation Oncology Biol. Phys., Vol. 42, No. 1, pp. 125–135, 1998

0360-3016/98 $19.00 + .00

PII S0360-3016(98)00191-6

● *Clinical Investigation*

A MULTIDISCIPLINARY STUDY INVESTIGATING RADIOTHERAPY IN EWING'S SARCOMA: END RESULTS OF POG #8346

- 94 pts received radical RT
  - 40 pts randomized to Whole bone (standard field) vs. Involved field (Tailored field RT)
  - Standard field: Whole bone (39.6 Gy) + Boost to initial tumor with 2cm margin (upto 55.8 Gy)
  - Tailored field: Initial tumor with 2cm margin
  - 5yr EFS
    - Whole bone : 37%
    - Involved field: 39%

- Subsequently adopted in the next POG-CCG trial (INT 0091)

Target Volume

- Phase I (45 Gy / 25# / 5 wks)
  - Pre-chemotherapy tumor volume on MRI + 1.5-3cm longitudinal margin
  - Appropriate modifications into cavities / lung
  - Include scar if post-op

- Phase II (10.8 Gy / 6# / 2 wks)
  - Post-operative / Post – Chemo residual disease + 1.5-2cm margin

EURO EWING99

Axial

GTV: Pretreatment extent

Safety margin: 2cm margin all around

Extremity

GTV: Pretreatment extent

Safety margin: 3-5cm proximal&distal and 2cm other directions

<u>Boost volume</u>

2cm proximal&distal, 1-2cm other directions

Donaldson etal (2004)

GTV1: Pretreatment tumor

CTV1+PTV1: 2-2.5cm margin

GTV2: Postchemo volume

CTV2+PTV2: 1.5-2cm margin

AEWS1031

GTV: Prechemo bony disease and Post chemo soft tissue

CTV: Margin of 1-1.5cm (covering biopsy site/drain site)

Ongoing…Not sure if it is safe !!

Modifications around cavities ?

AEWS slide courtesy: Nima Nabavizadeh

RT Dose

- Radical intent
  - 55-60 Gy
- Post-op
  - Close or R1 : 50.4 Gy
  - R2 : 55.8 Gy
- Pre-op
  - 36-45 Gy to Pre-chemo volume
- Vertebral lesions
  - 45 Gy

European

Surg .margins	Necrosis 100 %	Necrosis <100 %	Boost
Negative	NO RT	45 Gy	----
Close (< 1cm)	45 Gy	50 Gy	5.4 Gy
Micro R1	45 Gy	50 Gy	5.4 Gy
Gross R2	50 Gy	55 Gy	5.4-10-8

Data from the University of Florida suggest that hyperfractionated RT (1.2 Gy twice daily with a six hour interfraction interval) may be associated with less long-term toxicity .

RT dose escalation

FP019 SIOP19-0483 Radiotherapy Dose Escalation in Unresectable Ewing's Sarcoma/PNET: Final Results of a Single Institute Phase III Randomized Controlled Trial (SIOP -19 abstract)

Dr Laskar, et al TMH

- Following induction Chemotherapy patients were randomised between
  - standard dose RT (SDRT: 55.8Gy/31 fractions) vs.
  - escalated dose RT (EDRT: 70.2Gy/39 fractions delivered in two phases:
  - Phase I - 55.8Gy/31 fractions followed by Phase II - 14.4Gy/8 fractions boost to the post-induction chemotherapy (CTh) volume
  - **LC was significantly superior** in EDRT as compared to SDRT (79.2% vs 55.3%, p=0.02).
  - Difference in EFS (29.8% vs 43.8%, p=0.20) and OS (40.4% vs 62.5%, p=0.08) were not significant

https://doi.org/10.1002/pbc.27989
ASTRO 2019

RT dose escalation

Pelvis Ewing sarcoma: Local control and survival in themodern era
Safia K. Ahmed, Mayo Clinic **2017,** DOI: 10.1002/pbc.26504

- The 5-year cumulative incidence of local recurrence was 19%, with a
  - 26% incidence for radiation,
  - 13% for surgery, and
  - 0% for surgery + radiation (*P = 0.54).*

- **Patients treated with definitive radiation doses ≥5,600 cGy had a lower incidence of local recurrence (17% vs. 28%,** *P = 0.61).*
- Though statistically not significant, surgery + radiation and definitive radiation dose ≥5,600 cGy were associated with the lowest incidence of local failure, suggesting treatment intensification may improve local control for pelvis ES.

Higher dose – may be beneficial. However it Needs validation

Timing of Local treatment

- Ideally @ 12 weeks.

- Is delay detrimental ?
  - For every increase of 4 weeks, the risk of an event increased by
    - 27% for pre-op RT (HR 1.27, 95% CI 1.05–1.53)
    - 14% for Sx+-RT (HR 1.14, 95% CI 1.02–1.27)
    - 7% for RT (HR 1.07, 95% CI 0.96–1.19)
      - Analysis of EICESS 92

Whelan *et al. Clin Sarcoma Res (2018) 8:6*
https://doi.org/10.1186/s13569-018-0093-y

  - Patients initiating local therapy at
    - 6 to 15 weeks versus 5yr OS of 78.7% 10-year OS 70.3%
    - ≥16 weeks 5yr OS of70.4% 57.1%, (P < .001).
    - The difference in OS according to time to local therapy was particularly more important in patients receiving radiation therapy alone
      - NCD analysis

Lin TA, Int J Radiat Oncol Biol Phys.
2019 May 1;104(1):127-136

Ewings – chest wall

- Indications for hemithorax RT
  - Initial pleural effusion
  - Pleural infiltration
  - Intraoperative contamination ?
- Dose:15 Gy/10#

Survival is influenced by approaches to local treatment of Ewing sarcoma within an international randomised controlled trial: analysis of EICESS-92

Jeremy Whelan[1]
Department of Oncology, University College Hospitals London NHS

- UK -More extremity, fewer central
- Most UK pts had single modality
  - Single (72%)
    - Central → RT
    - Extremity → Sx

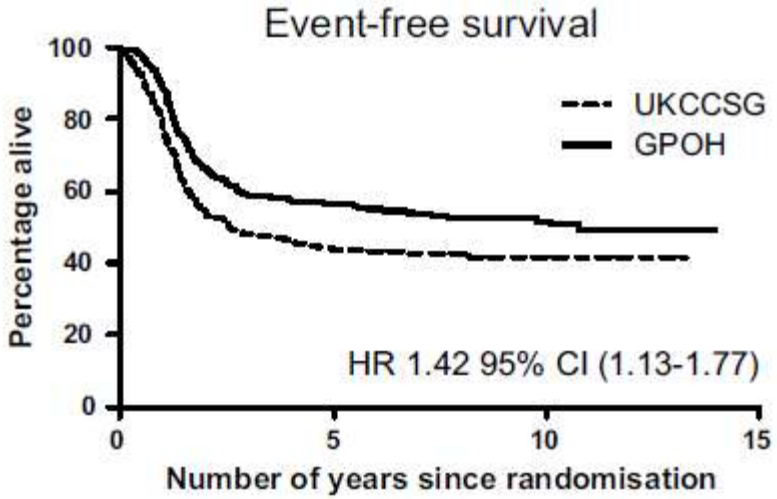
		CCLG	GPOH
Central	RT	62%	32%
	Sx	17%	10%
	Sx+RT	11%	56%
Extremity	RT	24%	6%
	Sx	47%	25%
	Sx+RT	23%	67%

- Most German had multimodality
  - Single (40%)

Surgery alone	59 (39)	63 (19)
Radiotherapy alone	53 (35)	55 (17)
Radiotherapy then surgery	5 (3)	147 (45)
Surgery then radiotherapy	24 (16)	47 (14)
None (progressive disease)	9 (6)	3 (1)
Unknown	0	14 (4)

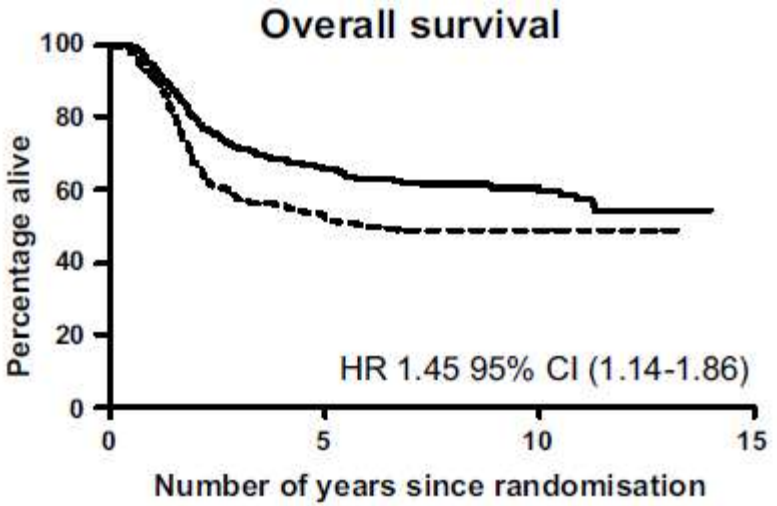
Whelan *et al. Clin Sarcoma Res (2018) 8:6*
https://doi.org/10.1186/s13569-018-0093-y

- Surgery whenever feasible
- Pre-op RT (44.8Gy) if <50% reduction in soft tissue on imaging after 2 cycles.
- Postop RT
  - Intralesional surgery – 54.4Gy
  - Marginal surgery with poor response (<90% necrosis) – 54.4Gy
  - Marginal surgery with good response – 44.8Gy
  - Wide resection with POOR response – 44.8Gy
- Radical RT if inoperable



No. at risk:

UKCCSG	210	87	26
GPOH	437	222	64



No. at risk:

UKCCSG	210	106	38
GPOH	437	261	81

Survival is influenced by approaches to local treatment of Ewing sarcoma within an international randomised controlled trial: analysis of EICESS-92

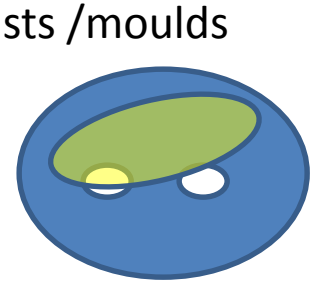
- Conclusions

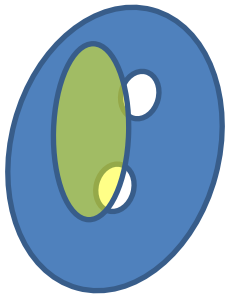
How would you apply these to your pediatric patients….?

underwent surgical resection and received radiotherapy, indicates that clinicians should always consider this option. Nevertheless, this must be balanced against the additional late effects, including second malignancies, which are associated with the use of radiotherapy in ES.

RT planning – special points

- Extremity lesions : Sparing a strip of linear soft tissue
  - Reduce late fibrosis and edema
    - Oblique opposed fields / angled pairs / rotate the limb
    - Adeq immobilisation – casts /moulds





- Extremity lesions near a joint
    - May reduce margin near growth plate
    - Avoid irradiating both epiphyses of a joint (esp. knee)
    - Avoid irradiating joint surface if feasible

RT planning – special points

- Pelvis
  - Avoid full dose irradiation of bladder (C & I in chemo)
  - Testicular shielding / Ovarian transposition
- Vertebral lesions
  - Uniform irradiation of adjacent vertebra
    - Weighted AP II PA or wedged pair technique
- Rib (Askin's), pushing into cavities - abdomen
  - Use post chemo volume for Phase I also
    - (be careful about the extension into adjacent cavity wall)
  - Treatment of entire pleural cavity - controversial

Metastatic disease - Lung

- Low dose irradiation beneficial in controlling lung micromets
  - From IESS-I study (VAC+WLI)

- Dose of 12 – 21 Gy
  - 12 Gy / 10#
  - 15 Gy / 10# or 18 Gy / 12#

Group/Instituion	Primary author	Patient with lung metastasis - Whole lung irradiation	Lung metastasis treatment arms	Type of study	Event free survival	Overall survival
Euro Ewing 99	Haeusler *et al.*[5]	120	Metastatectomy	Retrospective	25% (3 years)	Not reported
			Metastatectomy + WLI		47% (3 years)	
			WLI alone		23%(3 years)	
			none		13%3 years)	
EICESS 92	Bolling T *et al.*[44]	70/99	WLI (12-21 Gy)	retrospective	NR	61% (5 years)
		19/99	No WLI			49%(5 years)
Intergroup sarcoma study	Cangir A *et al.*[17]	53(I) and 69(II)	WLI (12-20Gy)	Retrospective	30% (3 years)	30%(5 years)
SFMC	Margolis *et al.*[45]	7	5.5-30Gy	Retrospective	NR	28%(3 years)
MSKCC	Rosen *et al.*[46]	2/12	20 Gy/10fr	retrospective	NR	100%(2 years)
CESS	Dunst *et al.*[47]	22/30	12-21 Gy	Retrospective	NR	30%(3 years)
CESS 81,86	Paulussen M *et al.*[6]	27	Metastatectomy + WLI (12-20Gy)	Retrospective	30% (10 years)	44% (10 years)
CESS	Paulussen M *et al.*[7]	75/114	WLI (15-18 Gy)	retrospective	36%(5 years)	NR
					30%(10 years)	
St Judes	Spunt S *et al.*[9]	8/28	16.5 Gy	Retrospective	22.5% (5 years)	37.3%(5 years)
Houston	Paulino *et al.*[21]	9/19	WLI (15 Gy)	Retrospective	66% control (2 years)	22% (5 years)
			No WLI		0%	
EICESS	Paulussen *et al.*[20]	57/171	WLI (15-18Gy)	Retrospective	EFS 34% (4 years)	NR
MSKCC	Casey *et al.*[8]	26	WLI (12-15Gy)	Retrospective	40% (3 years)	NR
Italian Sarcoma Group	Luksch *et al.*[18]	57/65	WLI (15Gy)	Retrospective	48% (3 years)	49% (3 years)

NR – Not reported

Impact of Whole Lung Irradiation on Survival Outcome in Patients With Lung Relapsed Ewing Sarcoma

Sergiu Scobioala, MD,* Andreas Ranft, MD,† Heidi Wolters, PhD,*

IJROBP 2018

Results: The survival outcome was significantly improved after WLI when analyzing the entire group of pulmonary relapsed patients: 3-year PFS 36% (+WLI) versus 14% (−WLI) (P = .001); 3- year OS 47% (+WLI) versus 33% (−WLI) (P = .007). The 3-year PFS in patients with complete remission of lung relapse receiving WLI (n = 48) compared with those without WLI (n = 40), was 37% (+WLI) versus 21% (−WLI) (P = .18). The site of the primary tumor and the response of pulmonary lesions to Ctx were significant prognostic indicators for survival in patients treated with WLI. No severe pulmonary function disorders or lung toxicities were observed after WLI treatment in both pediatric and adult patients.

Conclusions: The WLI does not correlate with improved OS in patients with pulmonary relapsed EwS. However, a marginal trend toward superior PFS and improved local control of pulmonary disease suggests the application of WLI in patients with EwS with isolated lung relapse and second clinical remission.

Late effects

- Younger, prepubertal children : radiation-induced arrest of bone growth.
  - Sparing of uninvolved epiphyseal plates
- RT doses above 60 Gy - markedly increased rates of soft tissue induration and fibrosis
- High-dose circumferential irradiation of an extremity - edema, fibrosis, and compromised limb function
  - sparing of an adequate strip of tissue.

- Weight-bearing bones are at risk for pathologic fractures. The highest risk is within the first 18 months of RT completion

Late effects

- 2nd malignancy
  - RT induced Osteosarcomas
  - Chemo induced leukemias

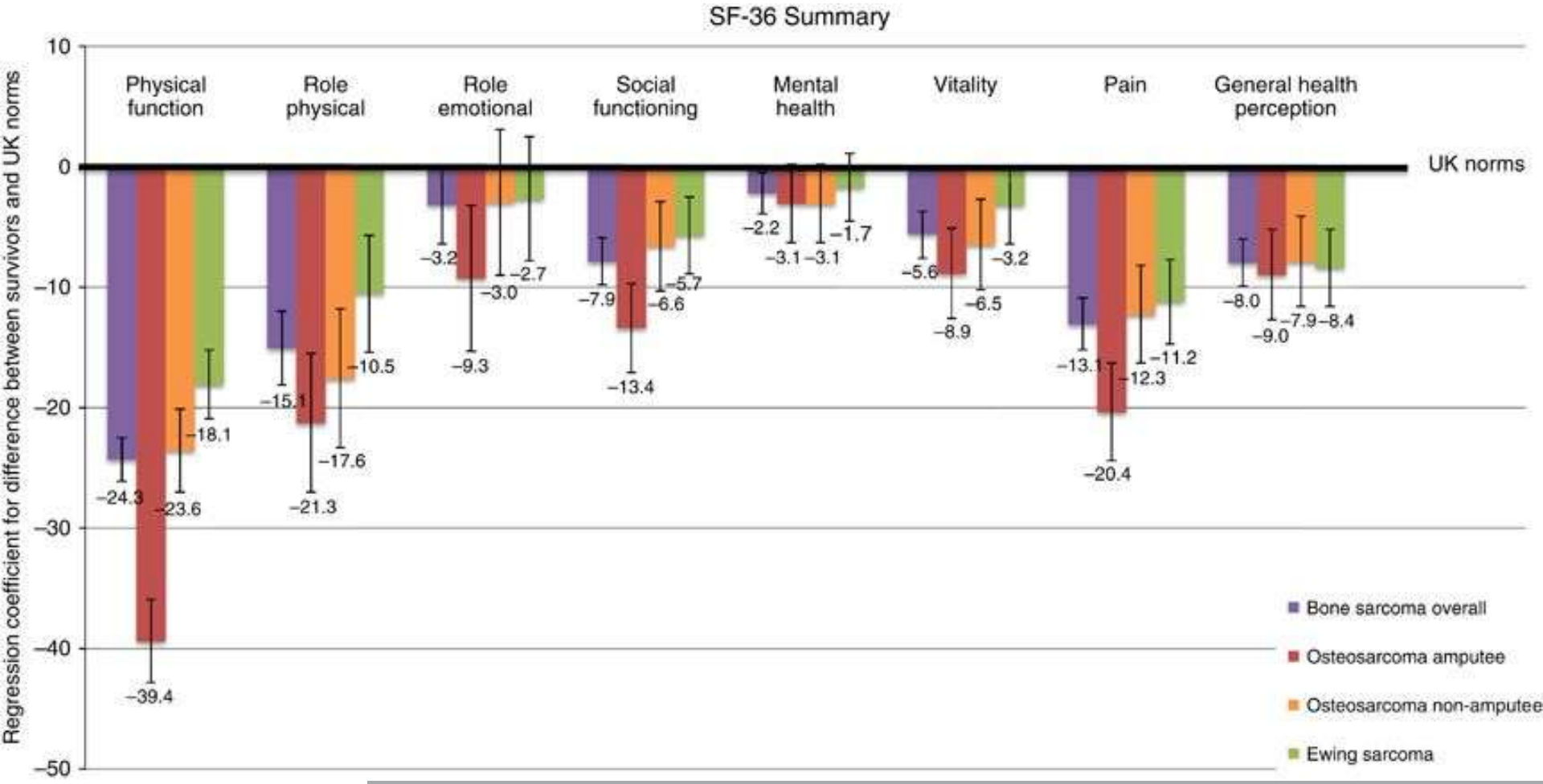
  - Late effects study group : Secondary sarcomas ~ 22% at 20 yrs
    - Related to RT dose. Esp if > 60 Gy

  - With lower doses of RT & Tailored field, lower risk
    - St Jude, NCI, Univ of Florida : 6.5% at 20 yrs for sarcoma
      - Median time : 7.6 yrs
    - Italian group : 4.7% at 20 yrs
    - CESS 81,86 : 4.7% at 15 yrs

  - MSKCC (Friedman et al. Ped Blood Can 2017 Nov)
    - SMN at 25 years (15%)
    - 9% - MDS/AML
    - 6% - Solid tumors (one was Ca breast –chest wall not irradiated, other was Ca Lung with 30 Pack year smoking and scapula RT)

Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study

664 survivors



British Journal of Cancer (2015) 112, 1857–1865 | doi: 10.1038/bjc.2015.159

Changes in Health Status Among Aging Survivors of Pediatric Upper and Lower Extremity Sarcoma: A Report From the Childhood Cancer Survivor Study

Results

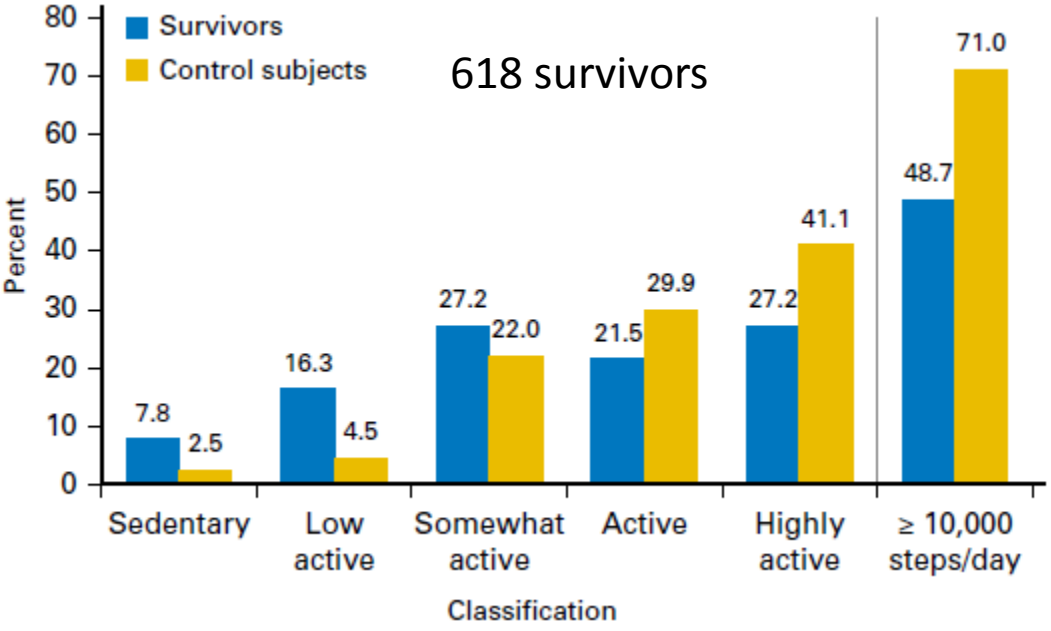
- In adjusted models, when compared with upper extremity survivors, **lower extremity survivors had an increased risk of activity limitations** but a lower risk of not completing college.
- Compared with those who did not have surgery, those **with limb-sparing (LS) and upper extremity amputations (UEAs) were 1.6** times more likely to report **functional impairment**, while those with an **above-the-knee amputation (AKA) were 1.9 times** more likely to report **functional impairment.**
- Survivors treated with LS were 1.5 times more likely to report activity limitations. Survivors undergoing LS were more likely to report **inactivity, incomes <$20,000, unemployment, and no college degree**.
- Those with UEAs more likely reported inactivity, unmarried status, and no college degree. Those with AKA more likely reported no college degree.

Archives of Physical Medicine and Rehabilitation 2013;94:1062-73

Quality of Survivorship in a Rare Disease: Clinicofunctional Outcome and Physical Activity in an Observational Cohort Study of 618 Long-Term Survivors of Ewing Sarcoma

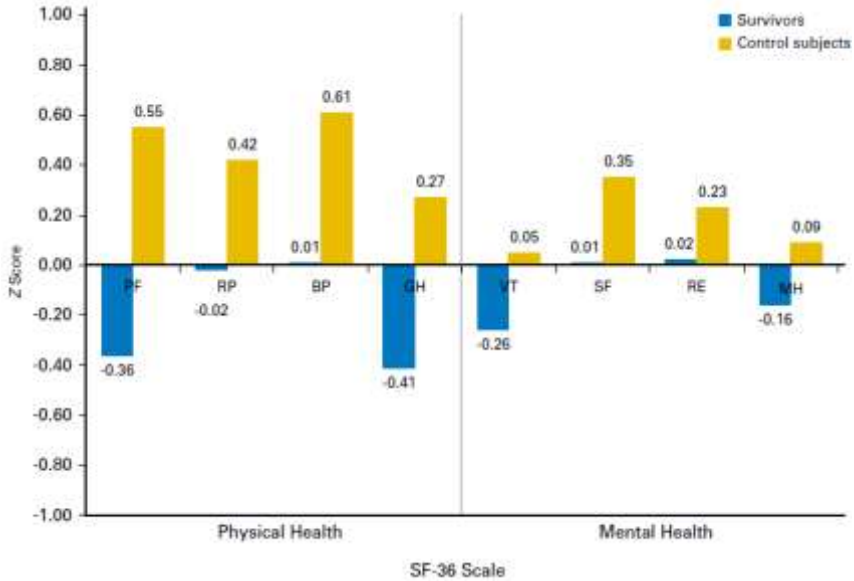
Germany

J Clin Oncol 35:1704-1712.



Site	
Pelvis	125 (20.2)
Axial	206 (33.3)
Lower extremity	224 (36.3)
Upper extremity	63 (10.2)
Local treatment	
None	2 (0.3)
S	174 (28.2)
RT	96 (15.5)
S + RT	346 (56.0)

Survivors of Ewings sarcoma apparently returned to normal life with minor limitations




CYTOXAN
ADRIAMYCIN
DTIC-Dome

Summarising

- Ewings – radio responsive tumor

- Indications
  - Radical 55 Gy – 60 Gy (55.8 Gy) Surgery generally preferred !!
  - Postop
    - R1/R2 resection (55.8 Gy)
    - Poor responder (45 Gy)
    - Pelvis / Bulky / All tissues involved by tumor initially – not removed ??
  - Pre-op
    - Inadequate response (36-45 Gy)
  - Metastatic
    - Radical intent Rx if lung mets – WLRT
    - Palliative RT

Thankyou

Case scenario 1

- 11yr old girl
  - Pain Rt lowerlimb – 3m duration
  - Swelling Rt lower back – 1wk
  - No other symptoms
  - Evaluated at nearby hospital
    - MRI – s/o mass lesion
    - Underwent open biopsy (had torrential bleed)
    - s/o – Possibly Ewings → referred

- Examination
  - Alert & Cooperative child, no dysmorphic features/NC markers
  - General examination , systems – unremarkable
  - Unable to walk due to pain
  - Suture marks of biopsy – Rt lower lumbar region (5-6cm long)
  - Diffuse swelling, mild tenderness
  - No neurological deficits

- Biopsy review – compatible with Ewings/PNET

MIC-2: Strong membrane +

<u>Negative for</u>
Chromo/Synapto
Desmin/Myogenin
LCA/Tdt

- Blood investigations
  - LDH: 204 U/L
  - Ca : 9.8mg/dL

Hb	:11.4gm%
TC	:5400/cmm
Pltlt	:3.71 L/cmm

B. Urea	:16mg/dL
S. Creat	:0.5mg/dL
SGOT	:27U/L
SGPT	:39U/L
S.Bil	:0.3mg/dL

- CT chest : No evidence of mets
- Bone scan: uptake at primary site only
- Bone marrow biopsy: No evidence of BM infiltration
- Cardiac consult : ECHO – Normal LVEF

- CT chest --- what is defined as lung mets ?

Definite	
1 nodule	> 1cm
>1 nodule	>0.5cm

Questionable	
1 nodule	> 0.5-1cm
>1 nodule	>0.3-0.5cm

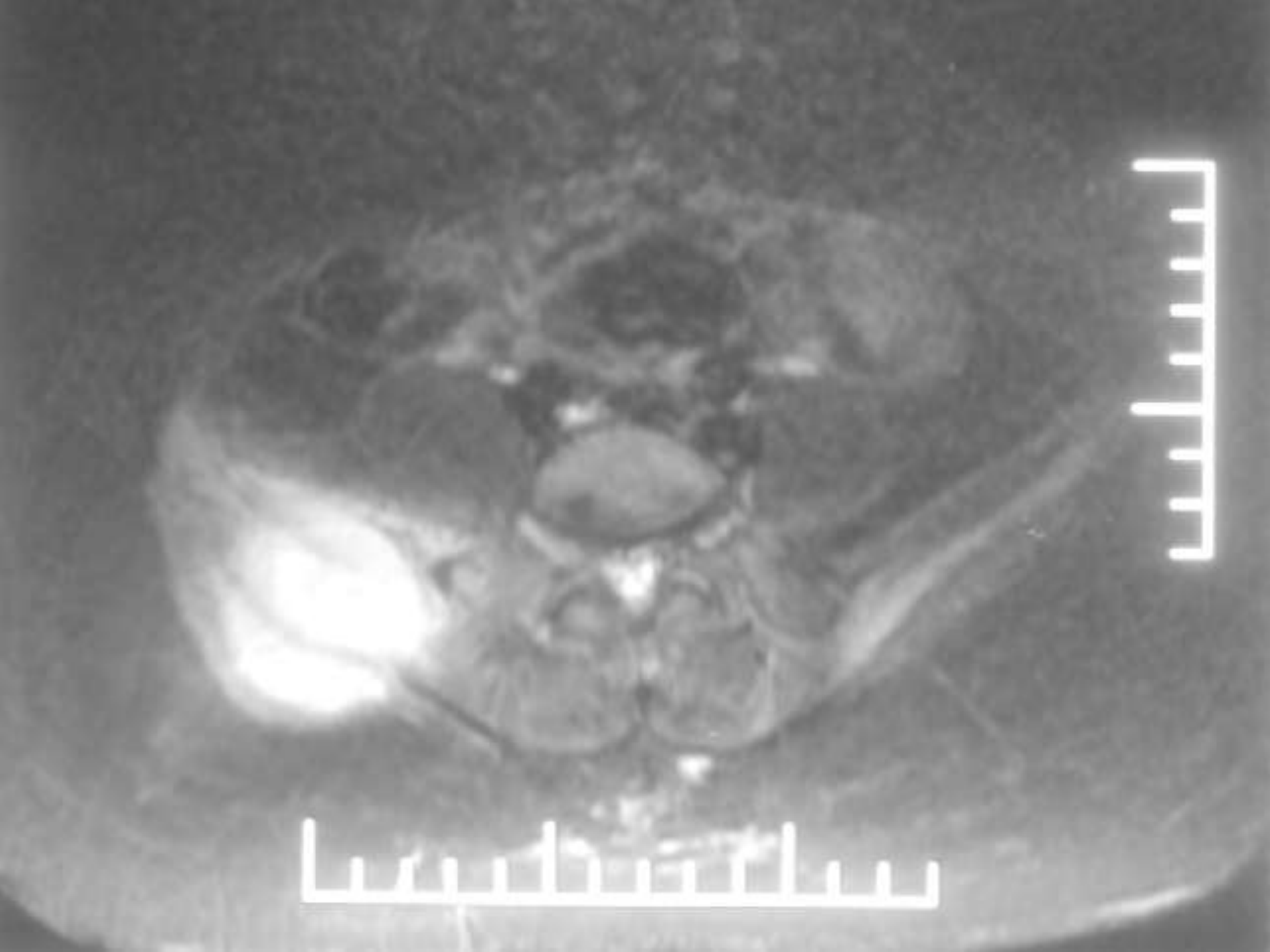
Suggest Biopsy

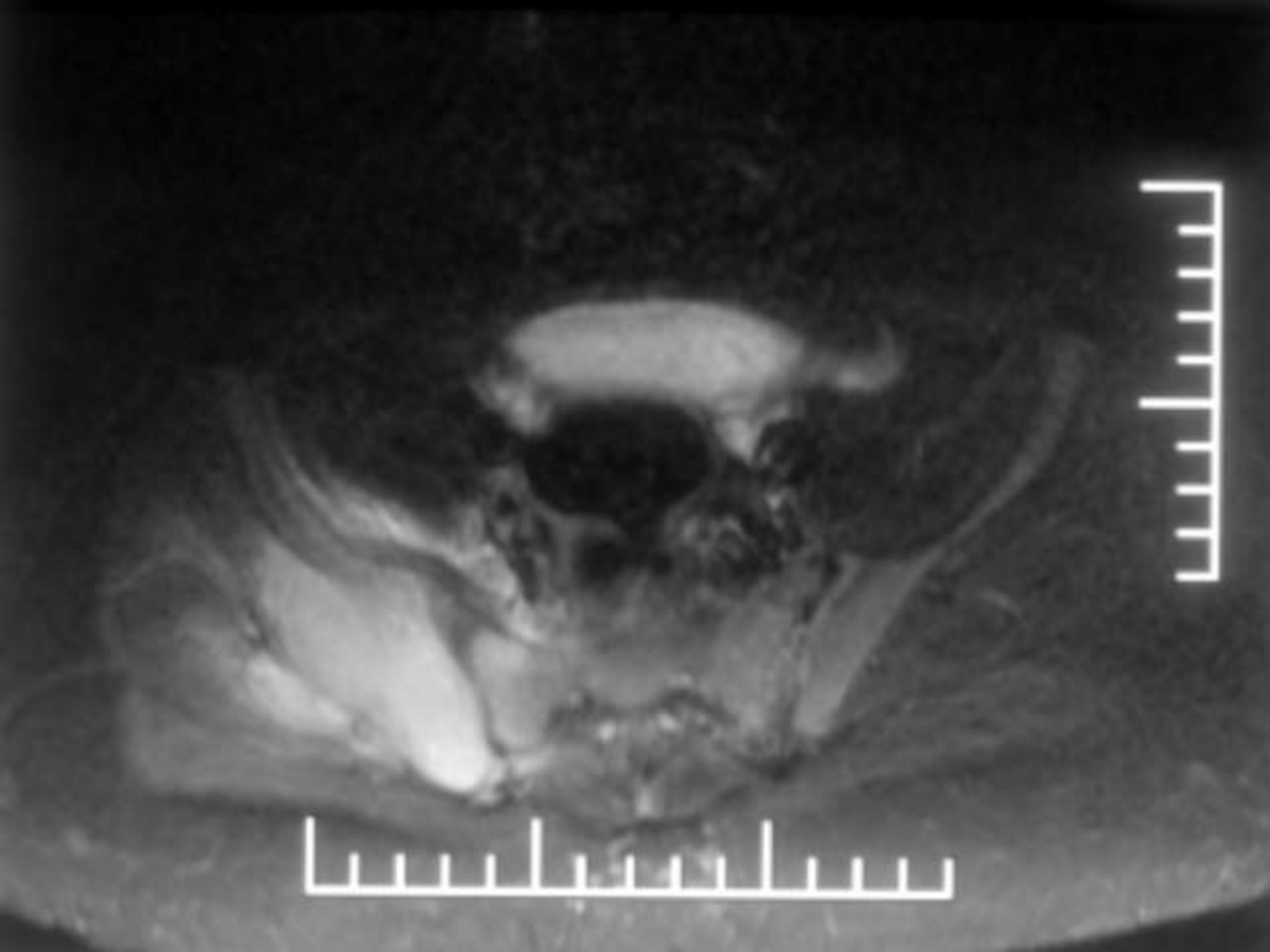
EURO EWING 99/2008, COG AEWS0031 Protocols

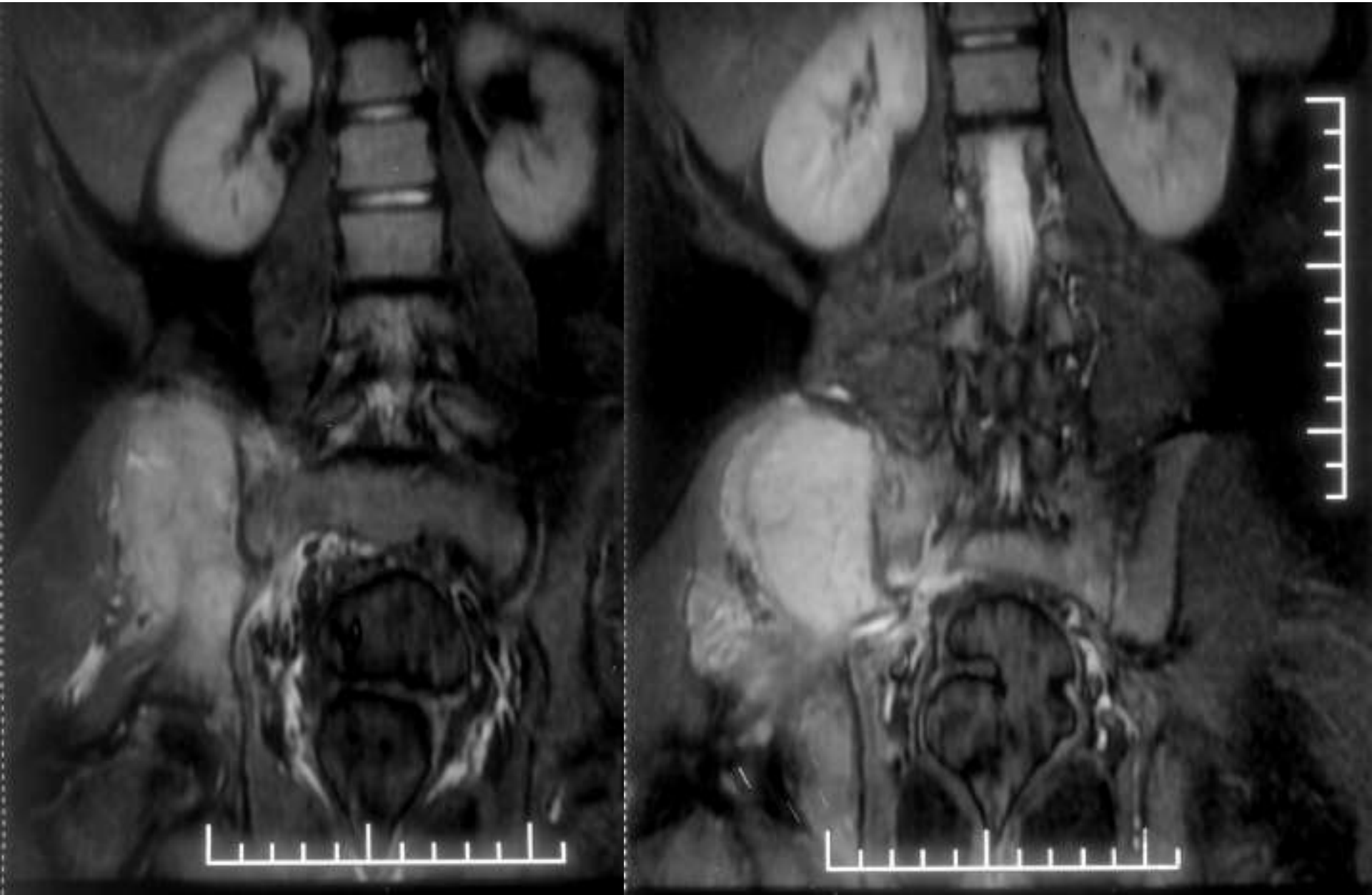
- Role of PET-CT in replacing Bone marrow biopsy and bone scan, and CT chest ?

Case 1 - MRI

- Expansile destructive lesion – posterior aspect of Rt Iliac bone 9x5x8cm
- Cortical break, and soft tissue component infiltrating gluteus medius and minimus, and ilacus muscles, with adjacent soft tissue edema.
- Involvement of Iliac sub-articular margin of Rt SI joint.
- Marrow edema of Rt Saccral Ala







- Tumor volume ?

TV = a x b x c x F,

where a, b, and c represent the maximum tumour dimensions in three planes,

with $F = \pi / 6 = 0.52$ for spherical tumours,

or $F = \pi / 4 = 0.785$ for cylindrical tumours

282cc

- Treatment outline
  a) Chemo → Surgery → Chemo
  b) Chemo → Surgery → PORT → Chemo
  c) Chemo → RT → Surgery → Chemo
  d) Chemo → RT → Chemo
  e) Others?

- Chemo regimen
  a) VDC
  b) VDC/IE q3w
  c) VDC/IE q2w (interval compressed)
  d) VIDE → VAC/VAI
  e) VIDE → Bu-Mel/VAI

- Interval compression

Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group

Womer, JCO 2012

VOLUME 30 · NUMBER 33 · NOVEMBER 20 2012

Richard B. Womer, Daniel C. West, Mark D. Krailo, Paul S. Dickman, Bruce R. Pawel, Holcombe E. Grier,

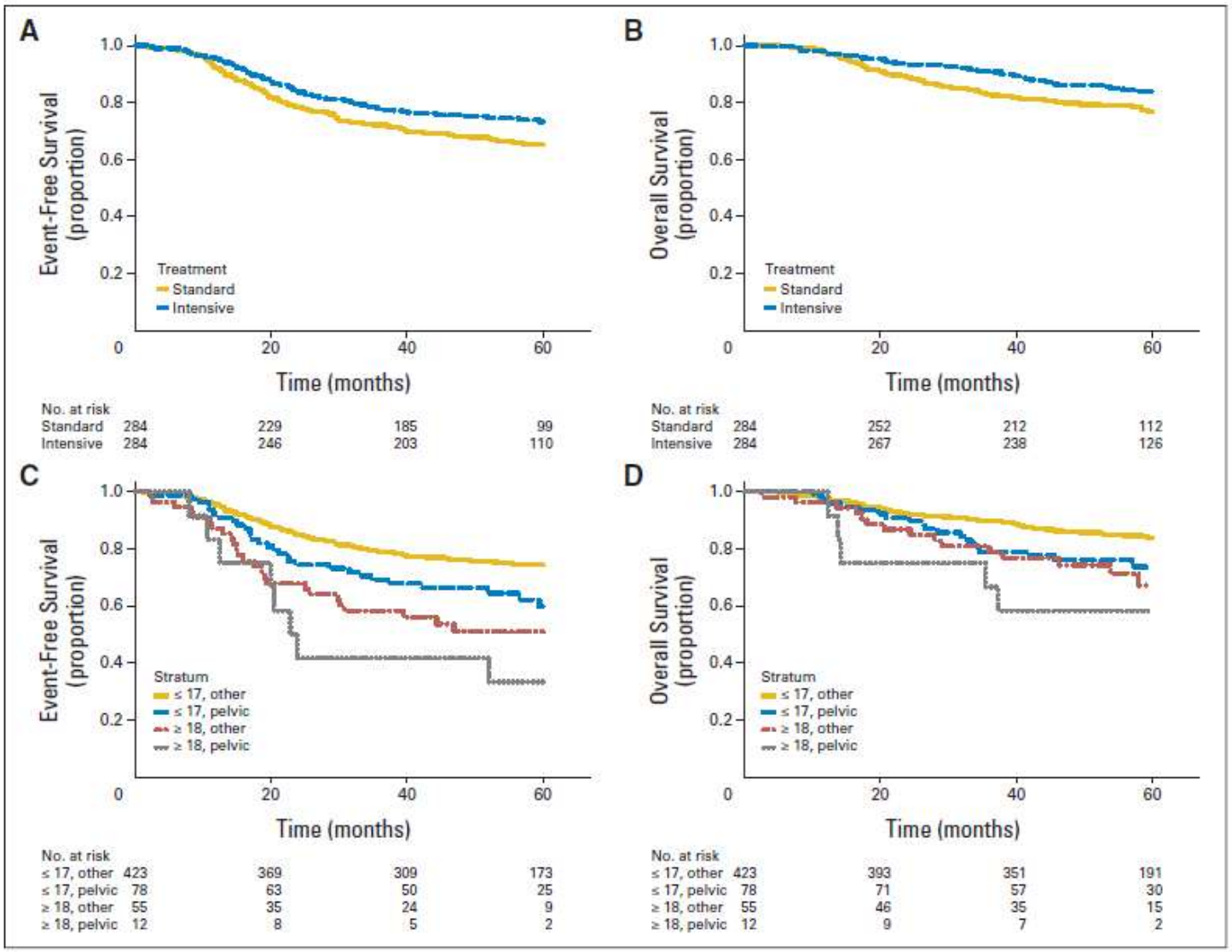
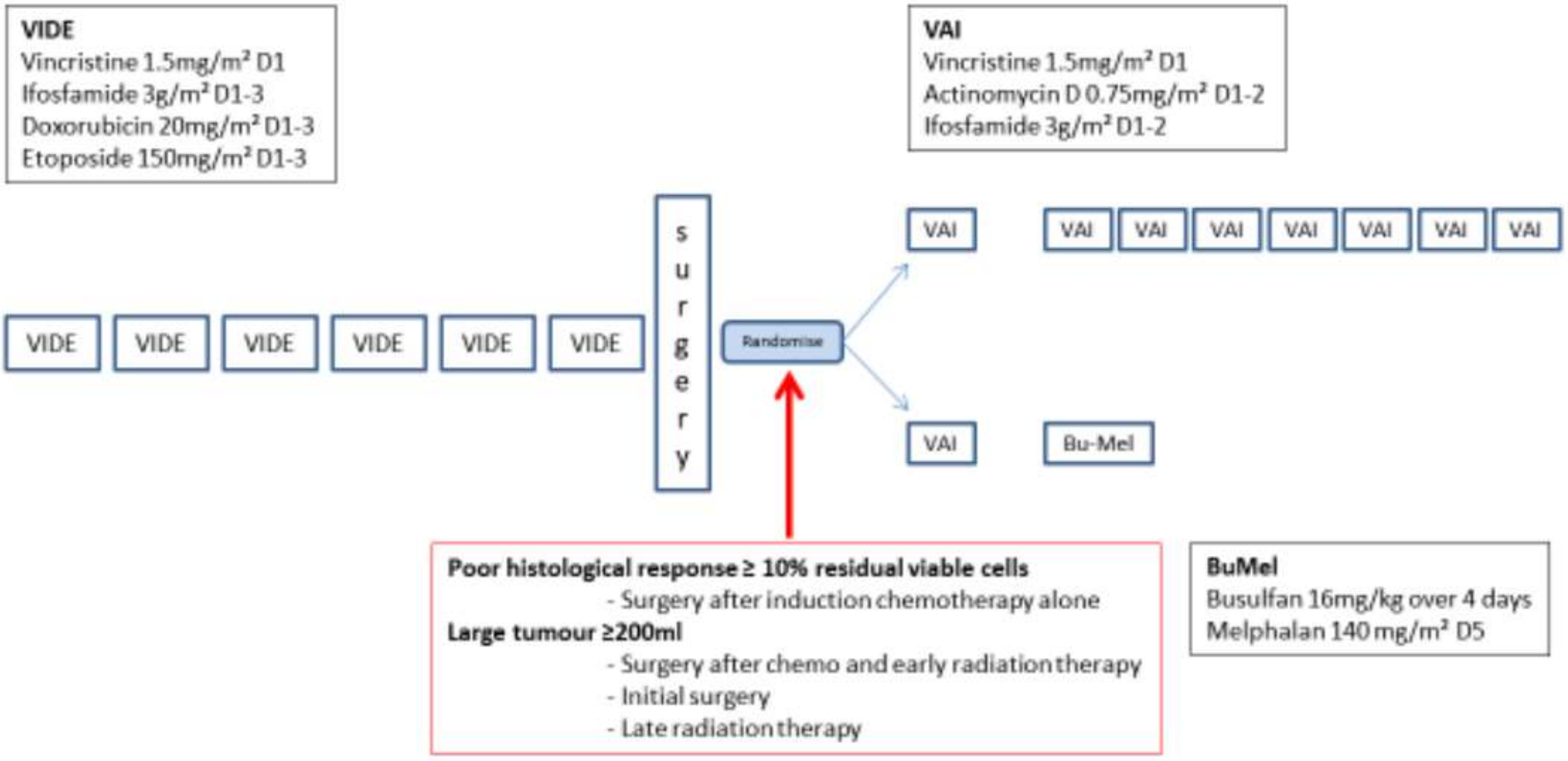


Fig 3. Kaplan-Meier plots of treatment outcome. (A) Event-free survival (EFS) according to the assigned treatment regimen. (B) Overall survival (OS) by regimen. (C) EFS and (D) OS, respectively, for the four strata, pooling the treatment regimens.

HD Chemo, SC support
EURO EWING 99,2008

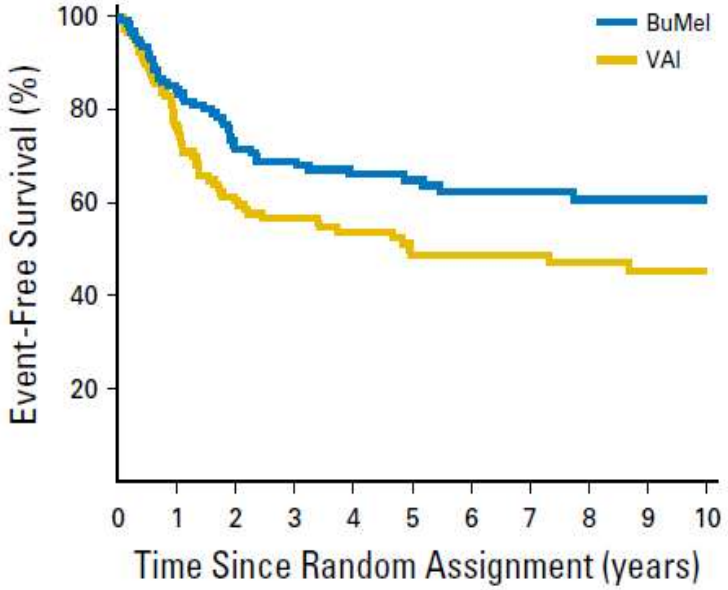


High-Dose Chemotherapy and Blood Autologous Stem-Cell Rescue Compared With Standard Chemotherapy in Localized High-Risk Ewing Sarcoma: Results of Euro-E.W.I.N.G.99 and Ewing-2008

Jeremy Whelan, Marie-Cecile Le Deley, Uta Dirksen, Gwénaël Le Teuff, Bernadette Brennan, Nathalie Gaspar,

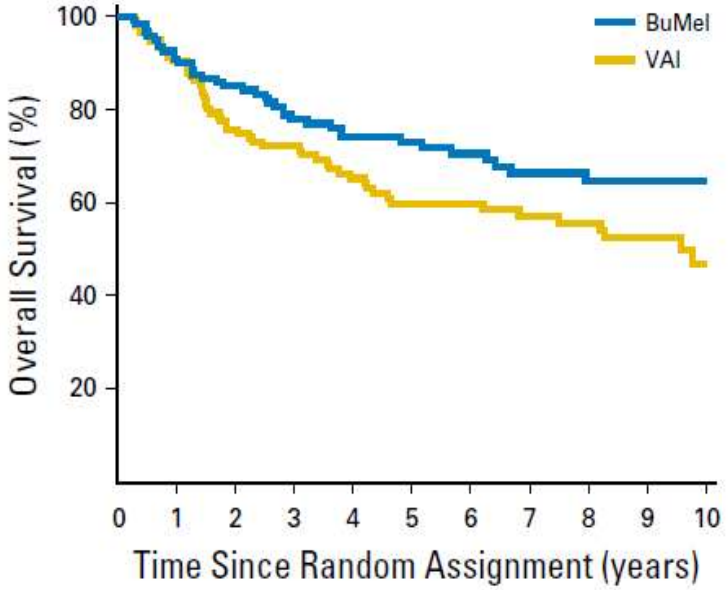
Whelan
JCO,2018 Sep

Intralesional surgery	54.4 Gy
Marginal surgery with poor histological response (≥ 10% residual tumour cells)	54.4 Gy
Marginal surgery with good histological response (< 10% residual tumour cells)	44.8 Gy
Wide resection with poor histological response (≥ 10% residual tumour cells)	44.8 Gy



No. at risk:

BuMel	122	84	62	48	33	16
VAI	118	67	49	36	27	12

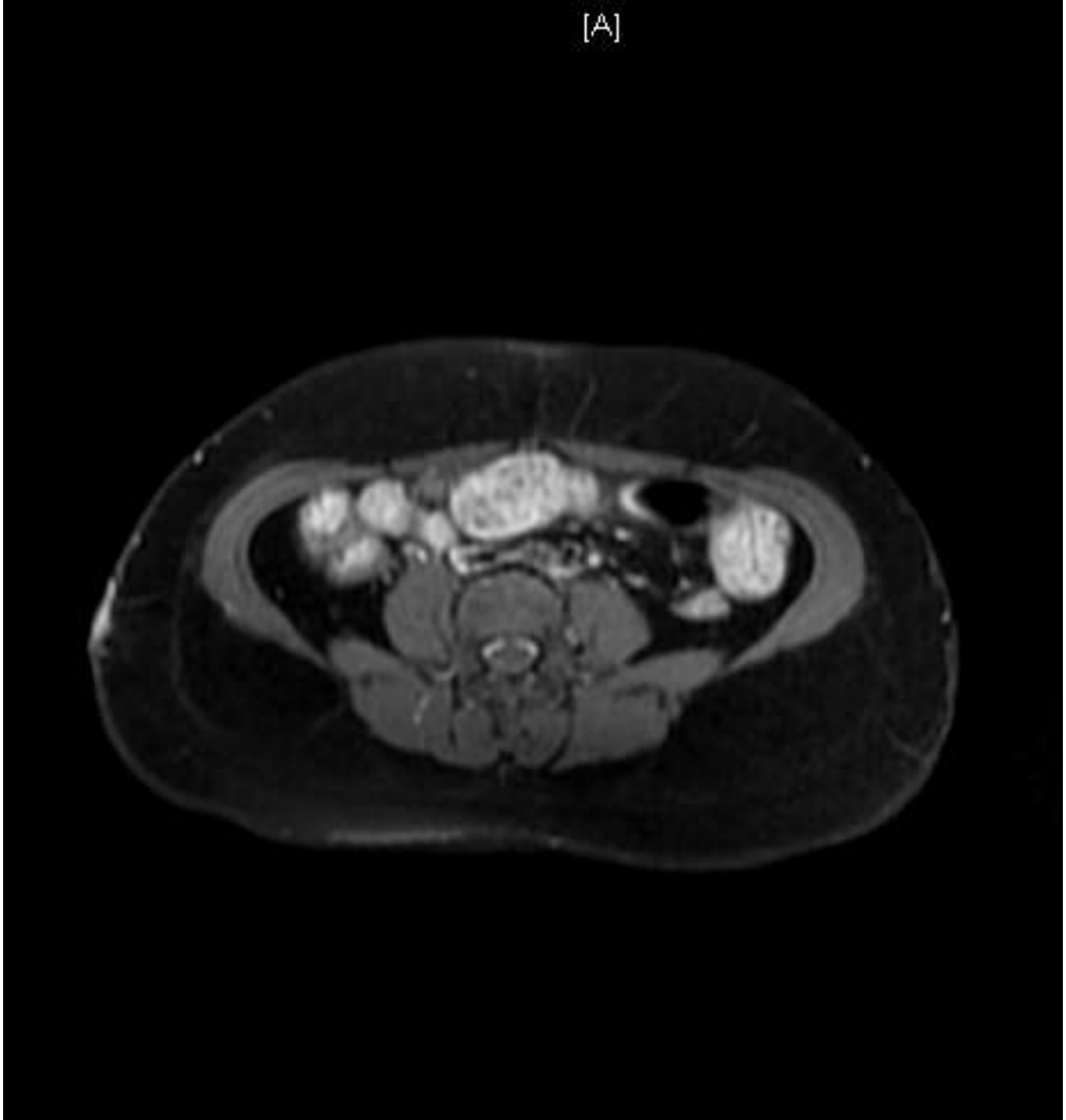


No. at risk:

BuMel	122	100	72	55	35	18
VAI	118	85	63	48	35	14

MRI – Post chemo

- Rt iliac bone lesion, involving articular surface of saccrum.
  - 8x4.5x8cm.
- No infiltration to sacrum, Acetabulum appears normal.
- Intra and extra pelvis soft tissue abutting iliacus and gluteal muscle, no obvious infiltration.
- Fat plane with vessels maintained.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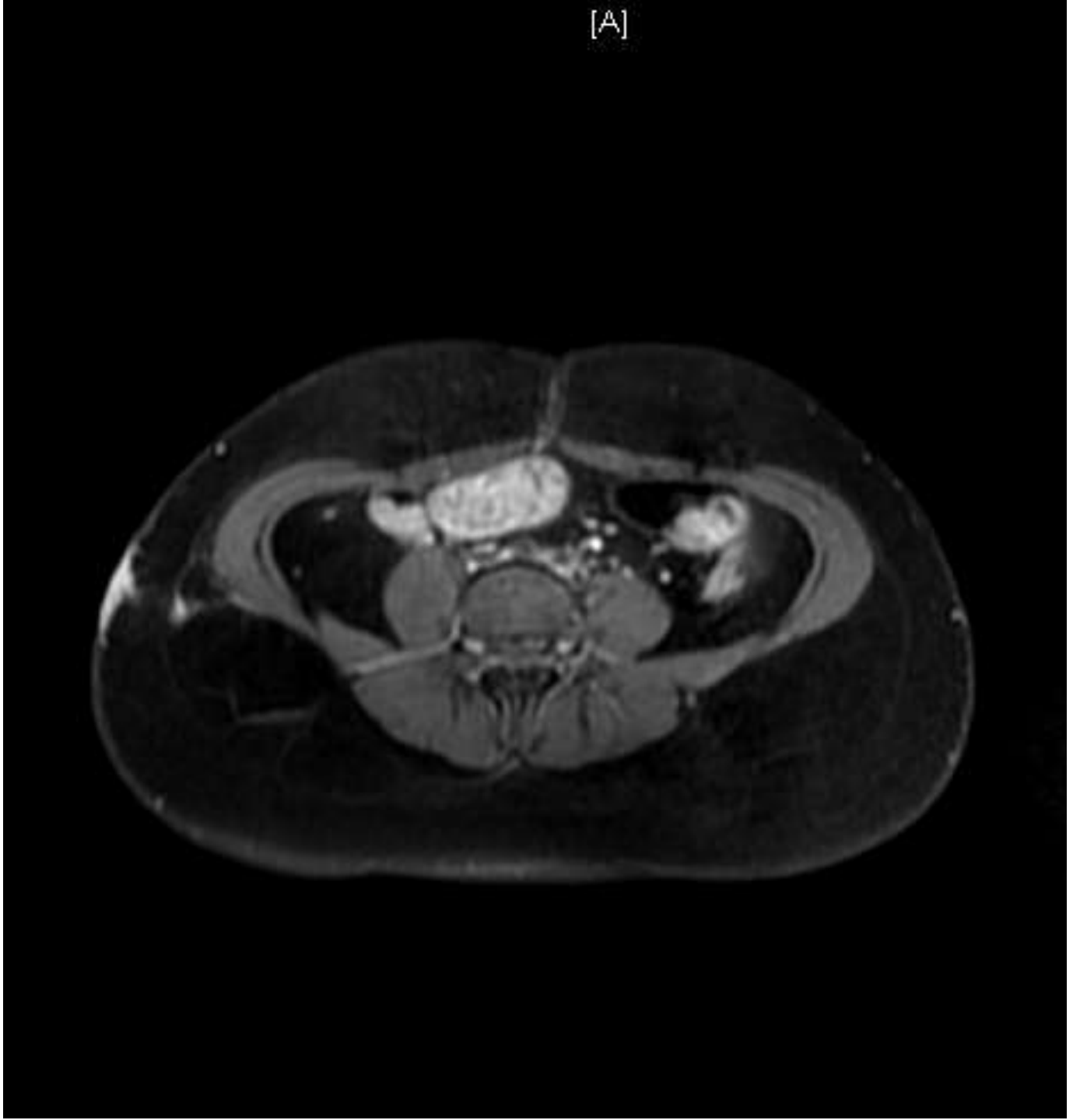
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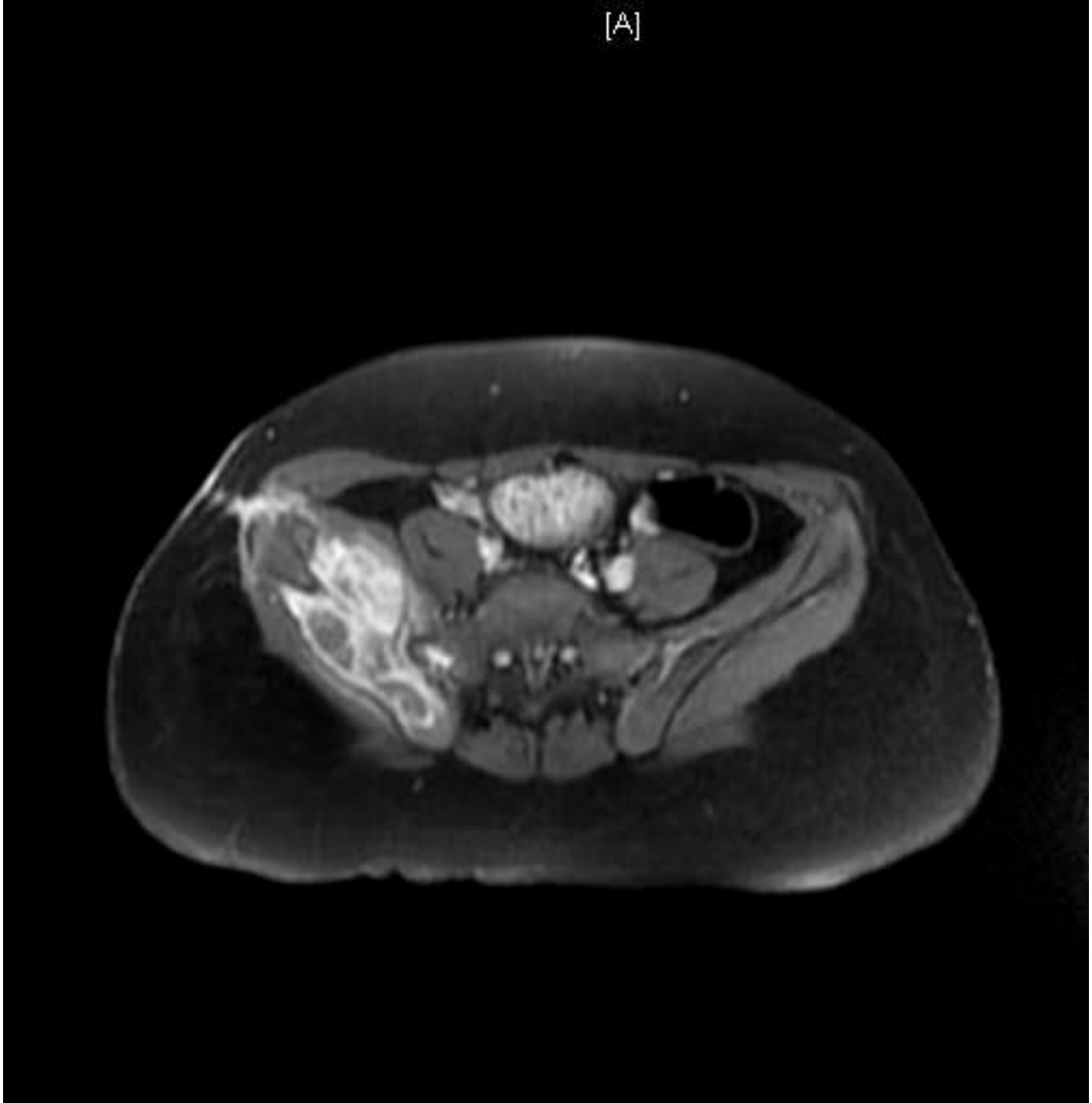
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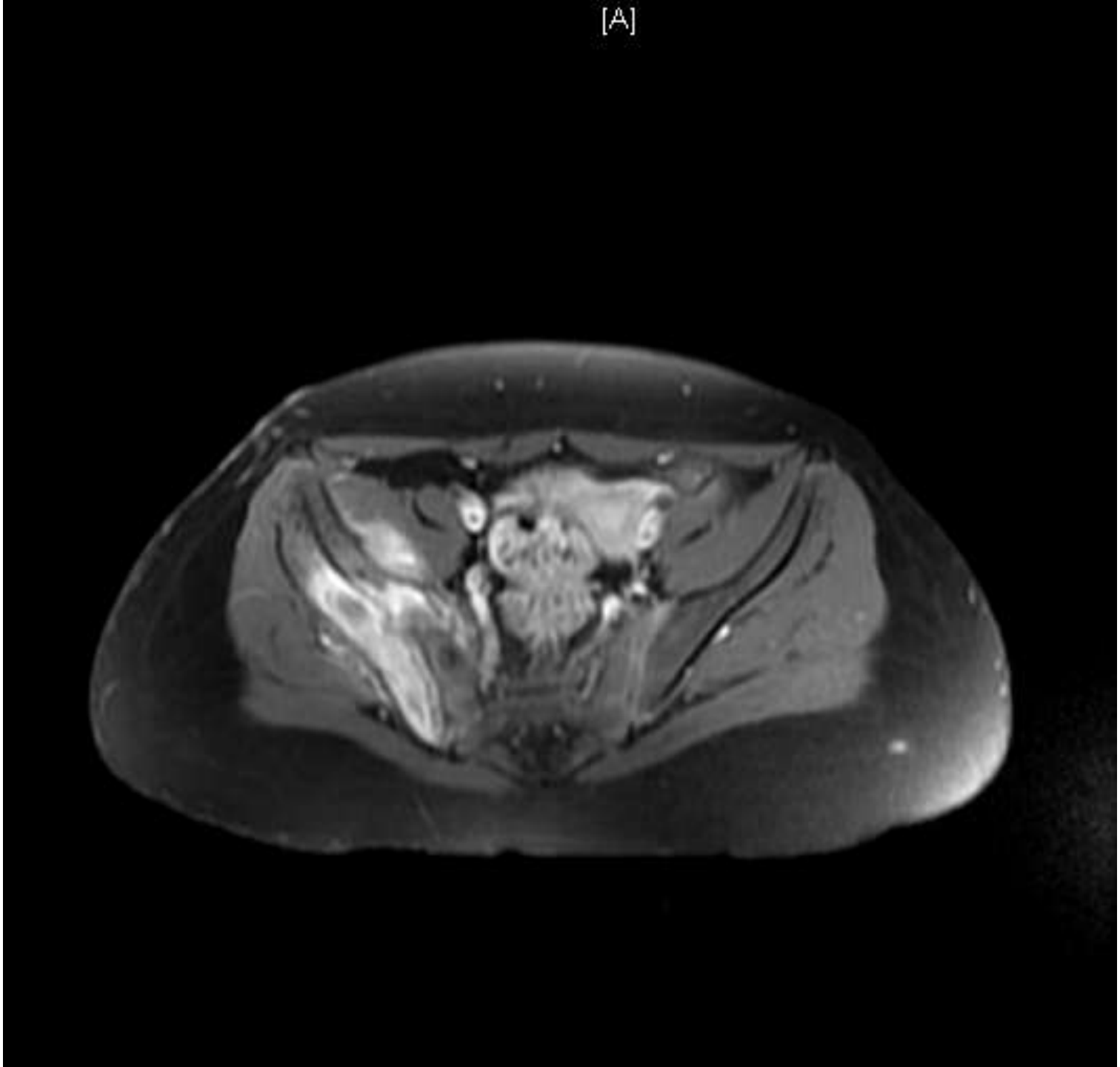
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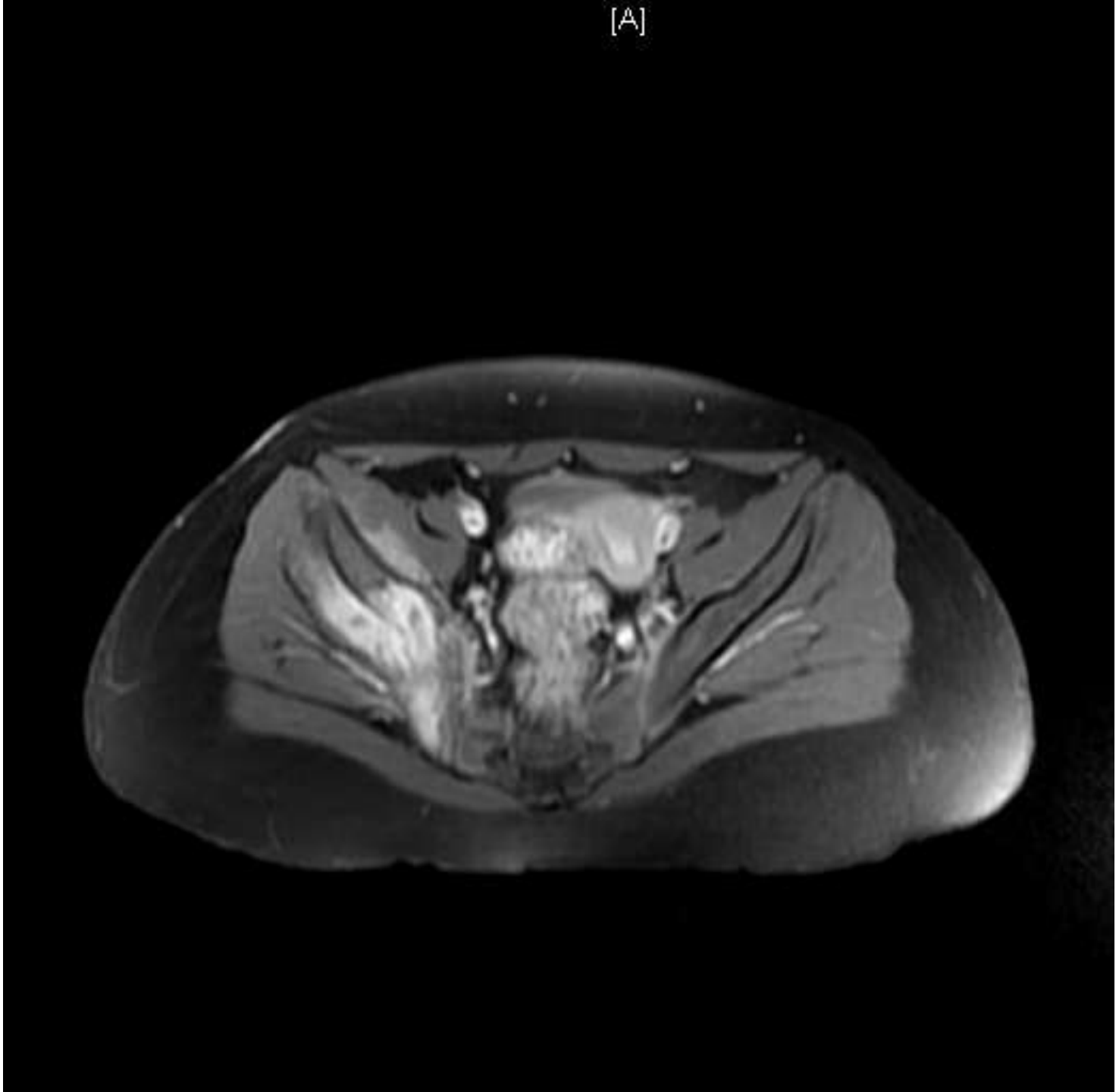
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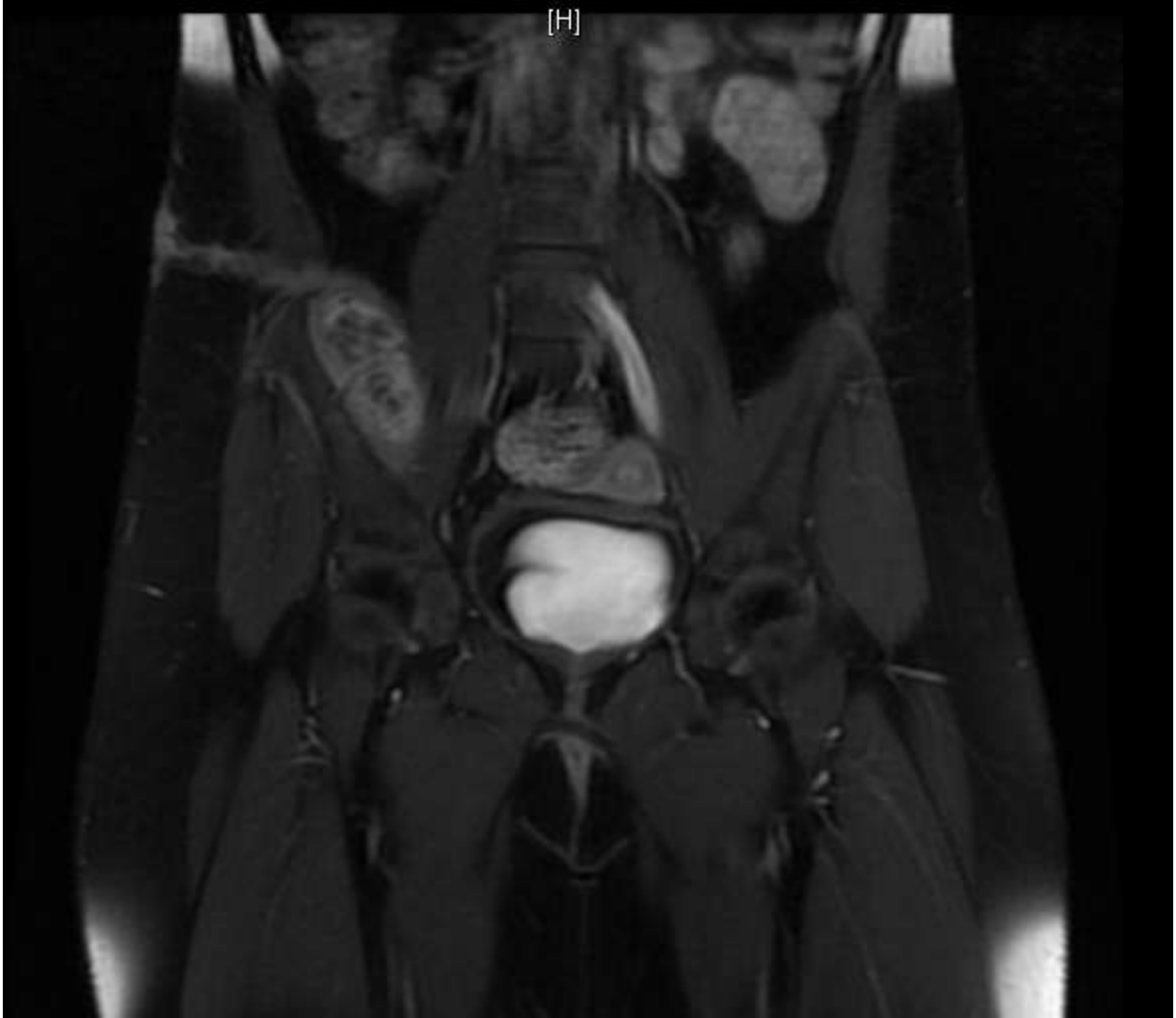
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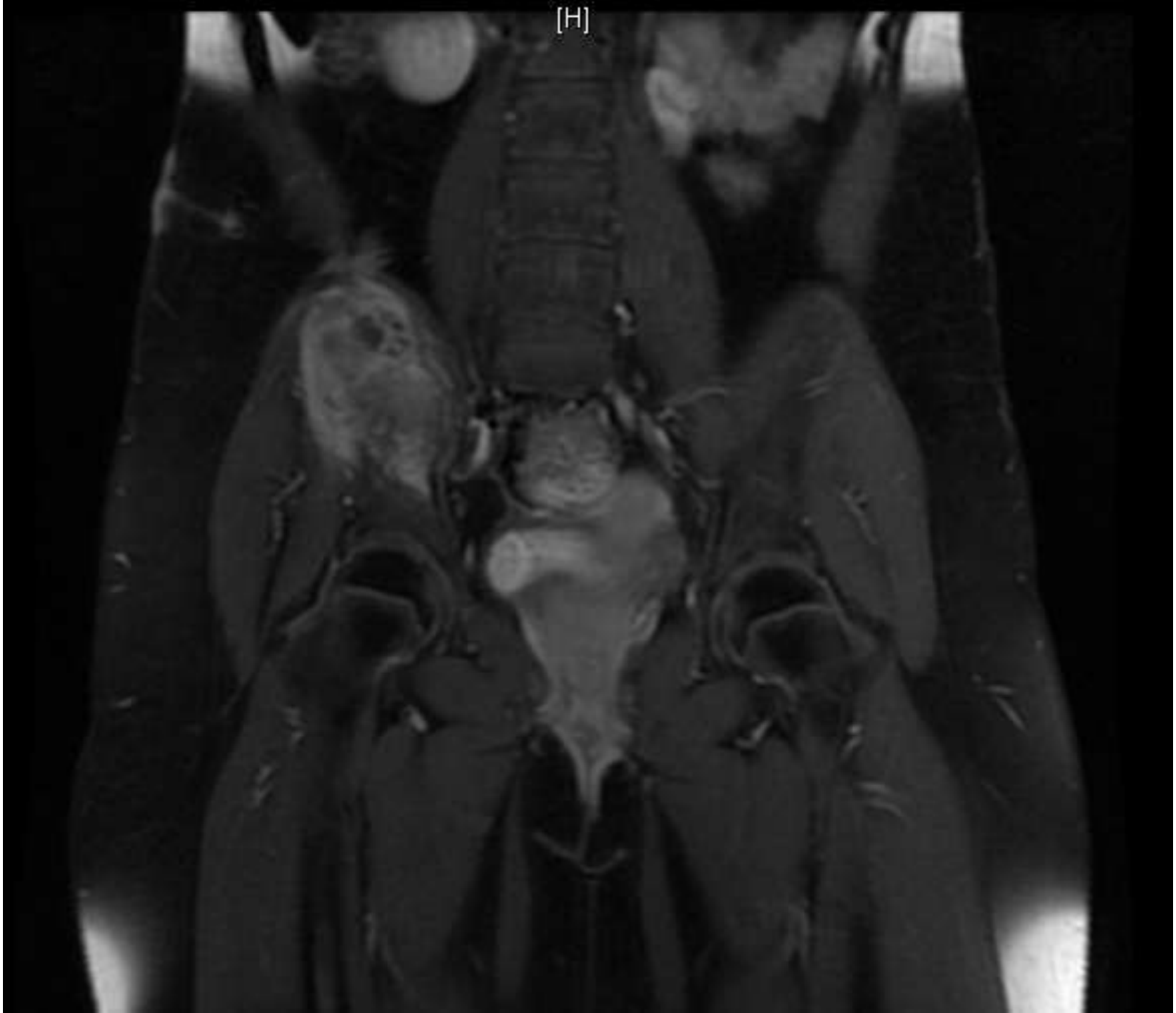

[H]

Local control modality

a) Surgery
b) Radiotherapy
c) Surgery + RT
d) RT+ Surgery

Surgery

- Would it be possible to perform a wide excision with adequate margins ?
  - If No, how to proceed
    - GO ahead with surgery ?
    - RT and then surgery ?
    - Radical RT ?
- What structures need to be excised ?
  - Only residual disease – soft tissue component, involved bone?
  - Previously involved muscles also ?
- Is PORT anticipated ?
- What would be the expected morbidity ?
  - Immediate
  - Long term

- Would it be possible to perform a wide excision with adequate margins ?
  - If No, how to proceed
    - GO ahead with surgery ?
    - RT and then surgery ?
    - Radical RT ?

No benefit of intra-lesional excision+ post-op RT vs. Radical RT

tumors. Low-dose (36.0 Gy) preoperative RT was encouraged on AEWS1031 as a method to improve local tumor control for large pelvis tumors. The results of this study are still pending.

AEWS1031
-Ahmed et al, IJROBP Dec 2017.

undertaken whenever possible. Preoperative radiotherapy (44.8 Gy) was recommended when there was < 50% reduction of a soft tissue component, evident on repeat imaging after 2 chemotherapy courses. Radiotherapy

EURO EWING99
-Whelan etal, Clin Sarcoma Res 2018

imaging after 2 chemotherapy courses. Radiotherapy (54.4 Gy) replaced surgery for tumours deemed inoperable. Post-operative radiotherapy (54.4 Gy) was recommended after intralesional surgery or marginal surgery with poor response (< 90% necrosis). Postoperative

- Subsites of pelvis
  - Surgery – Morbid
  - Surgery – Less morbid

Sacrum
Acetabulum
Extensive

Ilium
Pubic Ramus
Ischium

Surgery

- Would it be possible to perform a wide excision with adequate margins ?
  - If No, how to proceed
    - GO ahead with surgery ?
    - RT and then surgery ?
    - Radical RT ?
- What structures need to be excised ?
  - Only residual disease – soft tissue component, involved bone?
  - Previously involved muscles also ?
- Is PORT anticipated ?
- What would be the expected morbidity ?
  - Immediate
  - Long term

Assessing Margins of Resection

- What is considered adequate margin ?
  - Bone margin
  - Soft tissue Margin

- Bone margin: 2 to 5 cm
  - 1cm may be adequate
- Fat, muscle, and medullary bone: 5 mm
- Fascia, periosteum and intermuscular septa: 2 mm

Assessing response to chemotherapy

Pathological response assessment

- What method do you use ?
  - Huvos or modified Huvos
  - CCG / POG grading scheme
  - Salzer-Kuntschik

HUVOS grading scheme		
No necrosis	I	No Rx effect
<50% necrosis	IIA	Partial/Low
50-95% necrosis	IIB	Partial/high
96-99% necrosis	III	Scattered viable foci
100% necrosis	IV	No viable tissue

CCG / POG grading scheme		3yr survival
No chemo effect	I	30%
1-10% necrosis	IIA	30%
11-90% necrosis	IIB	49%
91-99% necrosis	III	73%
100% necrosis	IV	100%

Any issues in assessing tumor response for Ewing ??

Ref: Protocol for the Examination of Specimens From Patients With Primitive Neuroectodermal Tumor (PNET)/Ewing Sarcoma (ES)

Histologic Response

Series	Histologic Response	EFS	Local Failure Rate
CESS 86	≤10% viable tumor cells >10% viable tumor cells	64% 38%	
AEWS0031	<90% necrosis ≥90% necrosis No viable tumor cells	~65% ~70% ~80%	
Mayo Clinic	≤5% viable tumor cells >5% viable tumor cells	76% 59%	
MD Anderson	≤95% necrosis >95% necrosis	36% 74%	44% 9%

MAYO CLINIC

Chihak, Ahmed et. al., Manuscript in preparation
Pan et. al., *Int J Rad Onc Bio Phys*, 2015
Paulussen et. al., *J Clin Oncol*, 2001
Womer et. al., CTOS Annual Meeting, 2016

Slide courtesy: Ahmed S, Mayo Clinic 2017

Radiological response assessment

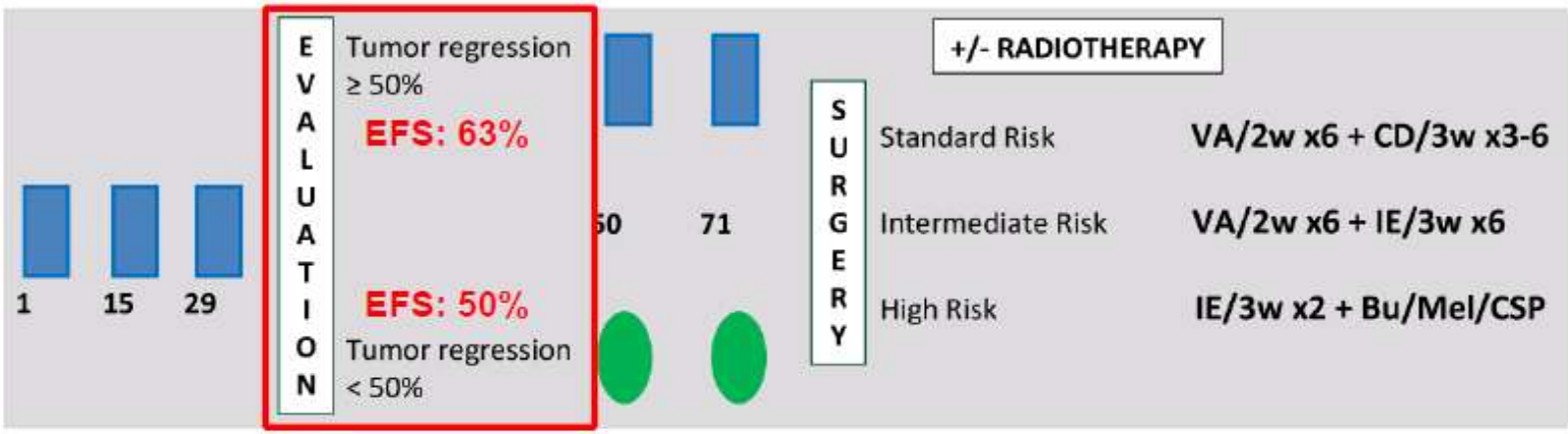
- MRI
  - Is soft tissue response assessment sufficient ?

Prognostic Factors and Patterns of Relapse in Ewing Sarcoma Patients Treated With Chemotherapy and R0 Resection

CONCLUSIONS—Histologic and radiologic response to chemotherapy were independent predictors of outcome. Additional study is needed to determine the role of adjuvant RT for patients who have poor histologic response after R0 resection.

-Pan, Mahajan, IJROBP 2015 June.

Radiologic Response



EURO-EWING99 :Tumor regression >90% associated with lower local failure rate

MAYO CLINIC

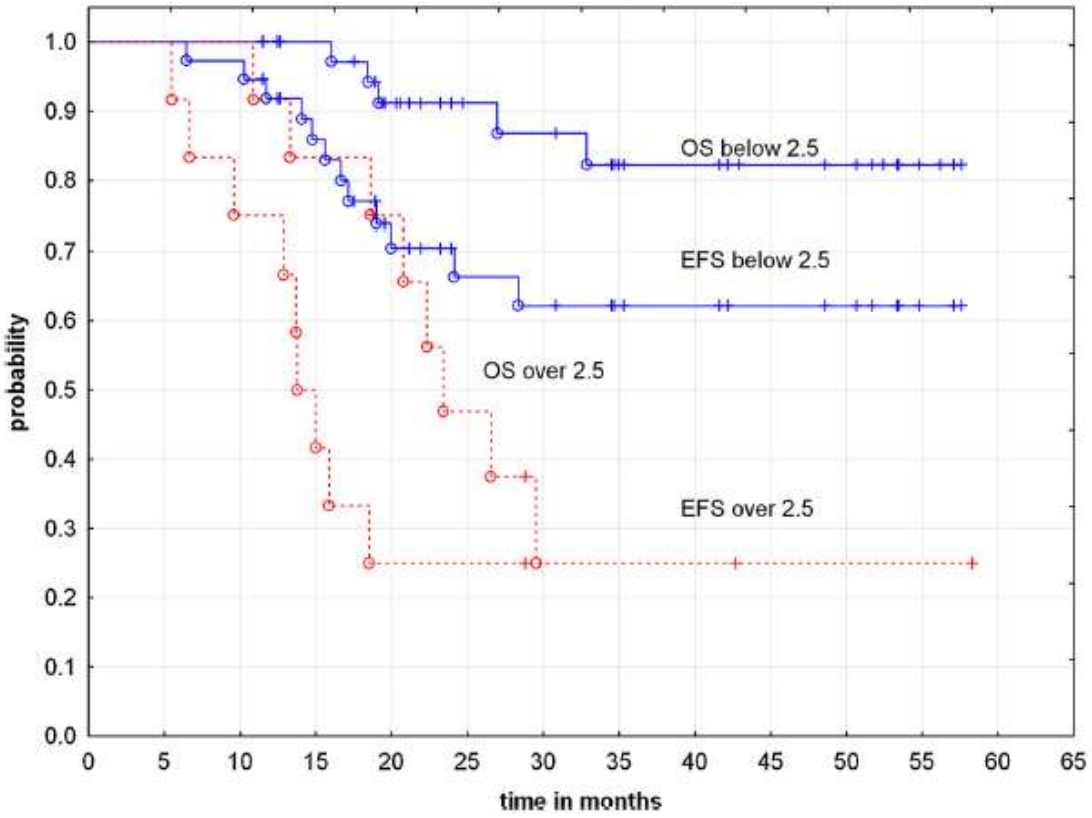
Andreou et. al., CTOS Annual Meeting, 2016
Gaspar et. al., *Eur J Cancer*, 2012

Slide courtesy: Ahmed S, Mayo Clinic 2017

- PET-CT ?

SUV at diagnosis was significantly lower in patients with good histological response than in patients with poor histological response.

the positive predictive value of an SUV II ≤ 2.5 for favorable response was 84.21 %, and the median SUV II was significantly higher in patients with disease progression (2.3 vs. 1.6, p = 0.04)



Raciborska 2016 Feb, Clin Trans Oncol

Adjuvant treatment

- Chemotherapy
  - Role for chemo intensification ?
  - Role of HD chemo with SC support ?

- Adjuvant radiation
  - Margin positive
    - Microscopic +ve
    - Gross residual
  - Inadequate margin / close margin ?
  - Margin negative ?
    - In poor responder ?
  - Size >8cm ?
  - Volume >200ml ?

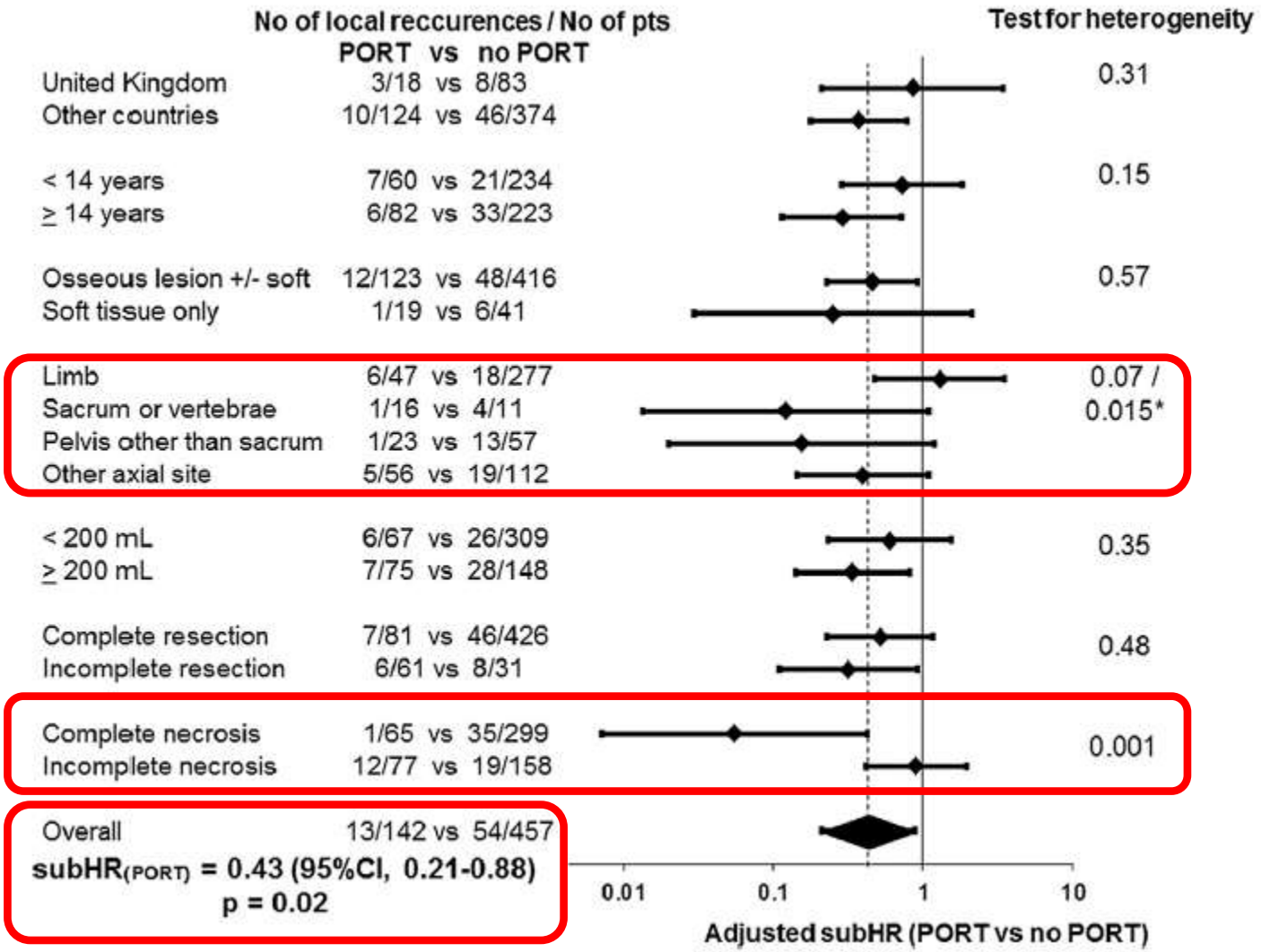
- Adjuvant radiation
  - Role in complete pathological response ?

Can postoperative radiotherapy be omitted in localised standard-risk Ewing sarcoma? An observational study of the Euro-E.W.I.N.G group

Results: One hundred forty-two (24%) of the 599 patients included from 1999 to 2009 received PORT (median dose: 45 Grays). With median follow-up of 6.2 years, 67 patients had an LR (with concomitant metastases in 28), leading to an 8-year LR-incidence = 11.9% (standard error [se] = 1.4%). Overall survival (OS) = 21% (se = 5%) 3 years after LR (31% in isolated LR). Controlling for possible confounders, we observed a statistically significant reduction of LR in patients treated by surgery + PORT compared to surgery alone (subdistribution-hazard ratio = 0.43, 95% confidence interval: 0.21–0.88, p = 0.02). The benefit of PORT was particularly marked for tumours larger than 200 ml at diagnosis and 100% necrosis. We observed a non-significant trend for benefit associated with PORT for disease-free, event-free and OS.
Conclusion: Radiotherapy appears to improve local control. We now recommend PORT in case of incomplete removal of the tissues involved by the pre-chemotherapy tumour volume. Further studies are required to assess the balance between benefit and risks.

the initial tumour bed. We now recommend PORT in the situation of incomplete removal of tissues originally involved by the pre-chemotherapy tumour volume, provided that anticipated adverse side-effects of PORT do not outweigh the expected benefit for local control.

European Journal of Cancer 61 (2016) 128–136


No of local reccurences / No of pts
PORT vs no PORT
Test for heterogeneity
United Kingdom 3/18 vs 8/83
Other countries 10/124 vs 46/374
0.31
< 14 years 7/60 vs 21/234
≥ 14 years 6/82 vs 33/223
0.15
Osseous lesion +/- soft 12/123 vs 48/416
Soft tissue only 1/19 vs 6/41
0.57
Limb 6/47 vs 18/277
Sacrum or vertebrae 1/16 vs 4/11
Pelvis other than sacrum 1/23 vs 13/57
Other axial site 5/56 vs 19/112
0.07 /
0.015*
< 200 mL 6/67 vs 26/309
≥ 200 mL 7/75 vs 28/148
0.35
Complete resection 7/81 vs 46/426
Incomplete resection 6/61 vs 8/31
0.48
Complete necrosis 1/65 vs 35/299
Incomplete necrosis 12/77 vs 19/158
0.001
Overall 13/142 vs 54/457
subHR(PORT) = 0.43 (95%CI, 0.21-0.88)
p = 0.02
0.01
0.1
1
10
Adjusted subHR (PORT vs no PORT)

PORT – RT Dose

		Dose
Margin negative	Poor response	
	Bulky disease, good response	
	Bulky disease, poor response	
R1 resection	Good response	
	Poor response	
R2 resection	Good response	
	Poor response	

European

Surg .margins	Necrosis 100 %	Necrosis <100 %	Boost
Negative	NO RT	45 Gy	----
Close (< 1cm)	45 Gy	50 Gy	5.4 Gy
Micro R1	45 Gy	50 Gy	5.4 Gy
Gross R2	50 Gy	55 Gy	5.4-10-8

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

Laskar S. Pediatr Blood Cancer 2008;51:575–580

Definitely PORT

Positive margin/Gross
Poor responder

Definitely No RT

Limb tumor < 200ml
Clear surgical margins
Complete necrosis

??

Pelvis subsite
Bulky, >200ml
Incomplete removal of involved soft tissue

Radical Radiotherapy

- Volume irradiated
  - GTV
  - CTV
  - Boost (higher dose) volume :

EURO EWING99

Axial

GTV: Pretreatment extent

Safety margin: 2cm margin all around

Extremity

GTV: Pretreatment extent

Safety margin: 3-5cm proximal&distal and 2cm other directions

Boost volume

2cm proximal&distal, 1-2cm other directions

Donaldson etal (2004)

GTV1: Pretreatment tumor

CTV1+PTV1: 2-2.5cm margin

GTV2: Postchemo volume

CTV2+PTV2: 1.5-2cm margin

AEWS1031

GTV: Prechemo bony disease and Post chemo soft tissue

CTV: Margin of 1-1.5cm (covering biopsy site/drain site)

Modifications around cavities ?

AEWS slide courtesy: Nima Nabavizadeh

Radical Radiotherapy

- Dose :

- Dose escalation ?

- Dose escalation studies
  - Patients treated with definitive radiation doses ≥5,600 cGy had a lower incidence of local recurrence (17% vs. 28%, *P = 0.61).*
    - Pelvis Ewing sarcoma: Local control and survival in the modern era (Ahmed *et al*. Ped Blood Can 2017) (Mayo)
      - » Anatomical localisation correlated with outcome
      - » Local control poorer with radical RT
      - » Sx+RT and Definitive RT with dose ≥ 56Gy – better LC

- Morbidity expected
  - Muscle / Soft tissue / Bone
  - Fertility
  - Bladder /bowel
  - 2nd Malignancy

Long term morbidity

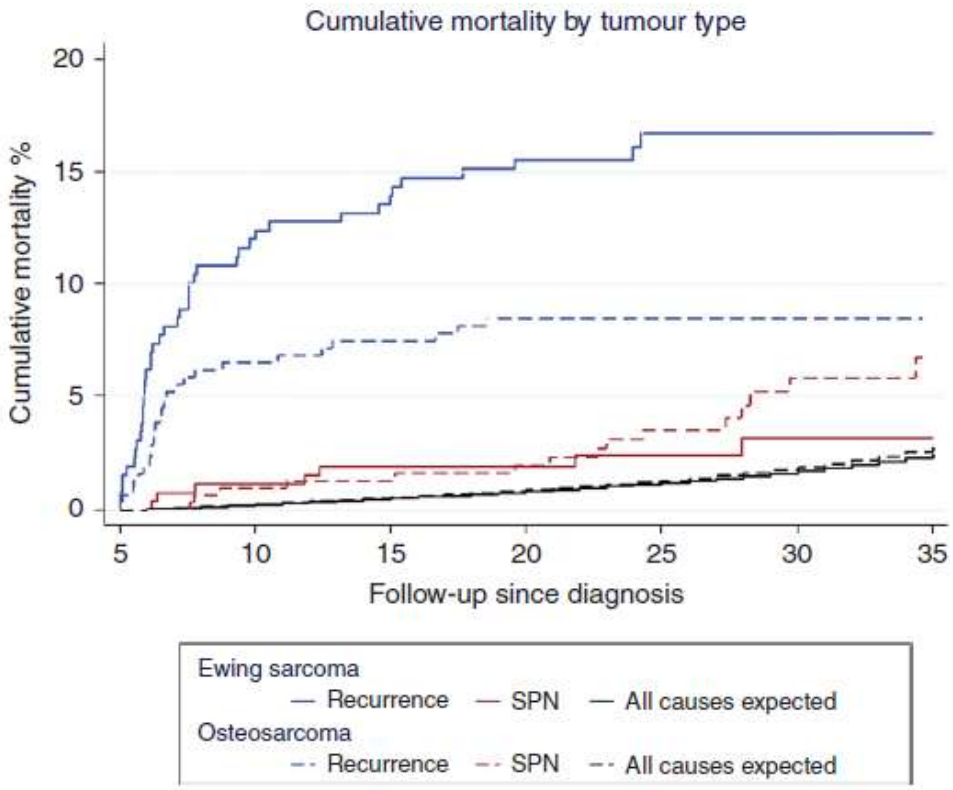
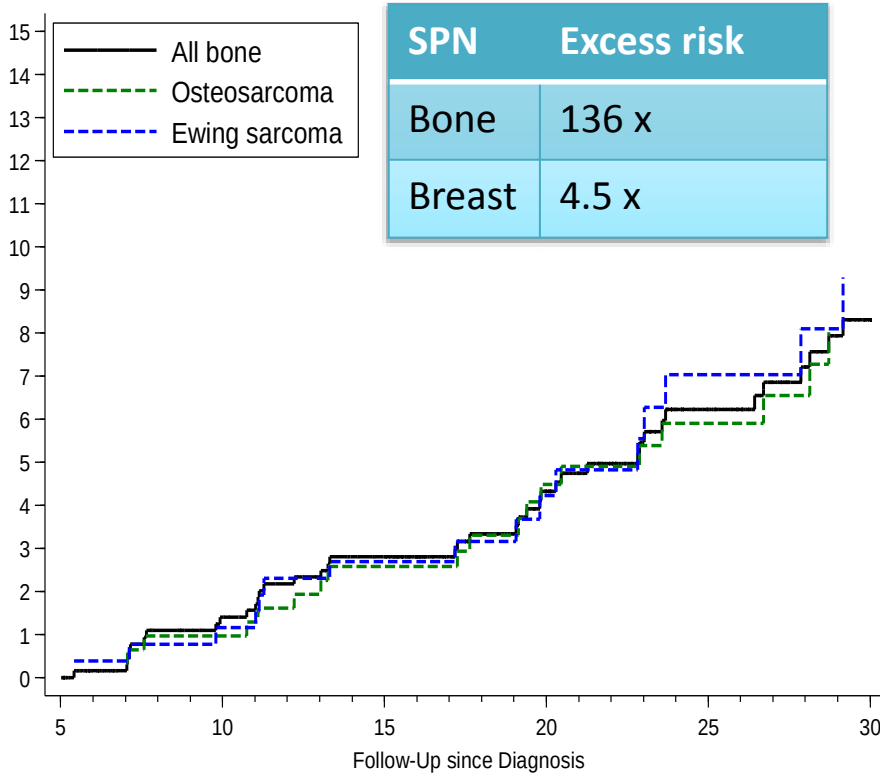


Figure 1. Cumulative mortality of recurrence and second primary n… British C…

mortality @35yrs	Osteo	Ewing
Recurrence	8.5%	16.7%
SPN	6.7%	3.2%



SPN	Excess risk
Bone	136 x
Breast	4.5 x

Up to 25 years after 5-year survival, bone sarcoma survivors are at substantial risk of death and SPNs, but this is greatly reduced thereafter

Sx vs. Sx+RT vs. RT

- Best oncological results ?

- Best functional results ?

- Sx vs. RT vs. Combination

Prognostic factors

- Metastatic disease vs Non metastasis
  - Metastatic : Non Pulmonary vs Pulmonary
- Site
  - Pelvic (central) vs Extremity
- Bulk
  - >8cm, >200ml
- Response to chemo
  - <90% (<95%) vs >90%necrosis
  - Radiological response
  - ?PET response
- Age

Case 2

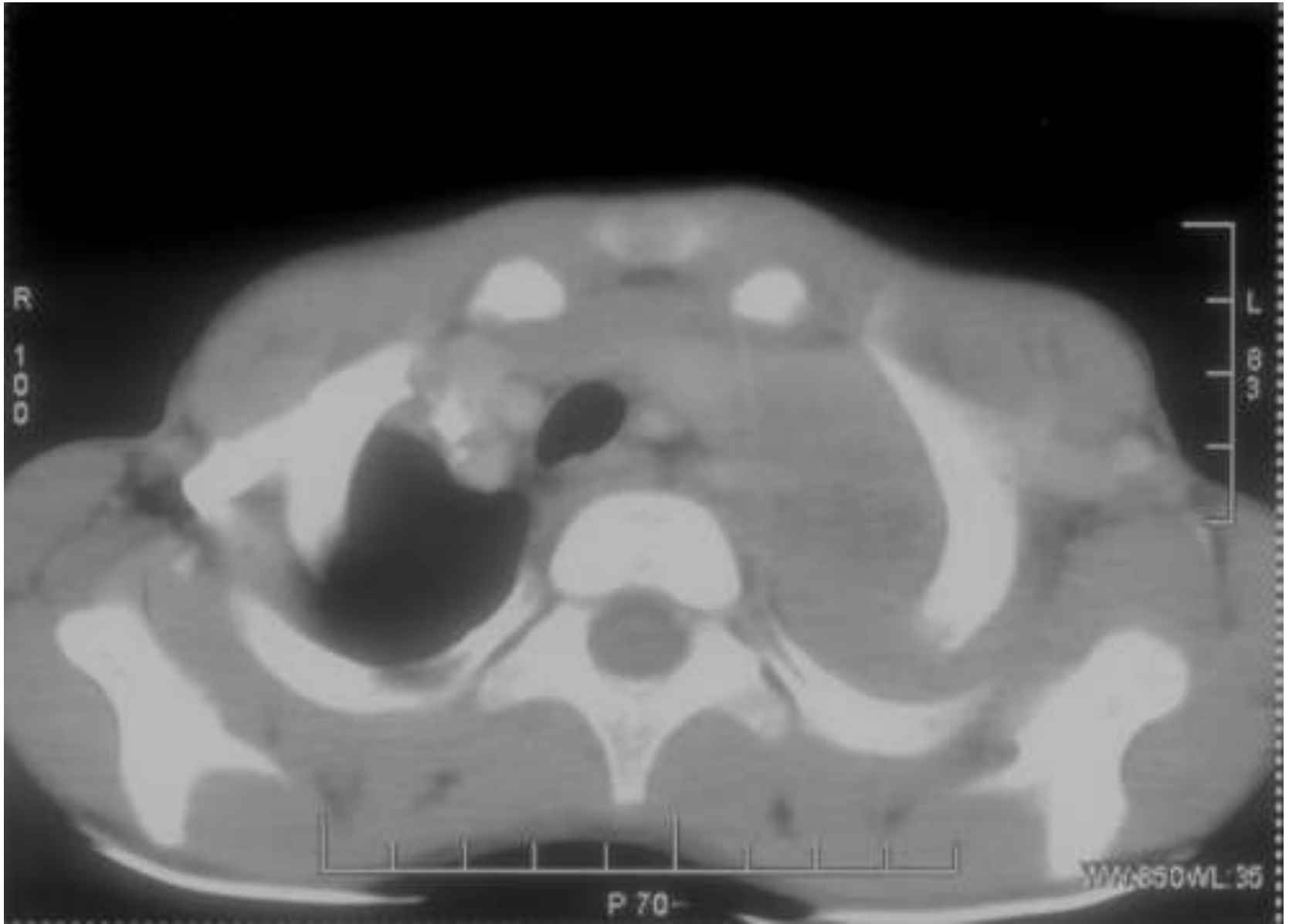
- 5yr old boy
  - Fever, cough , dyspnoea of <1wk duration.
  - CXR s/o ? Massive effusion Left chest

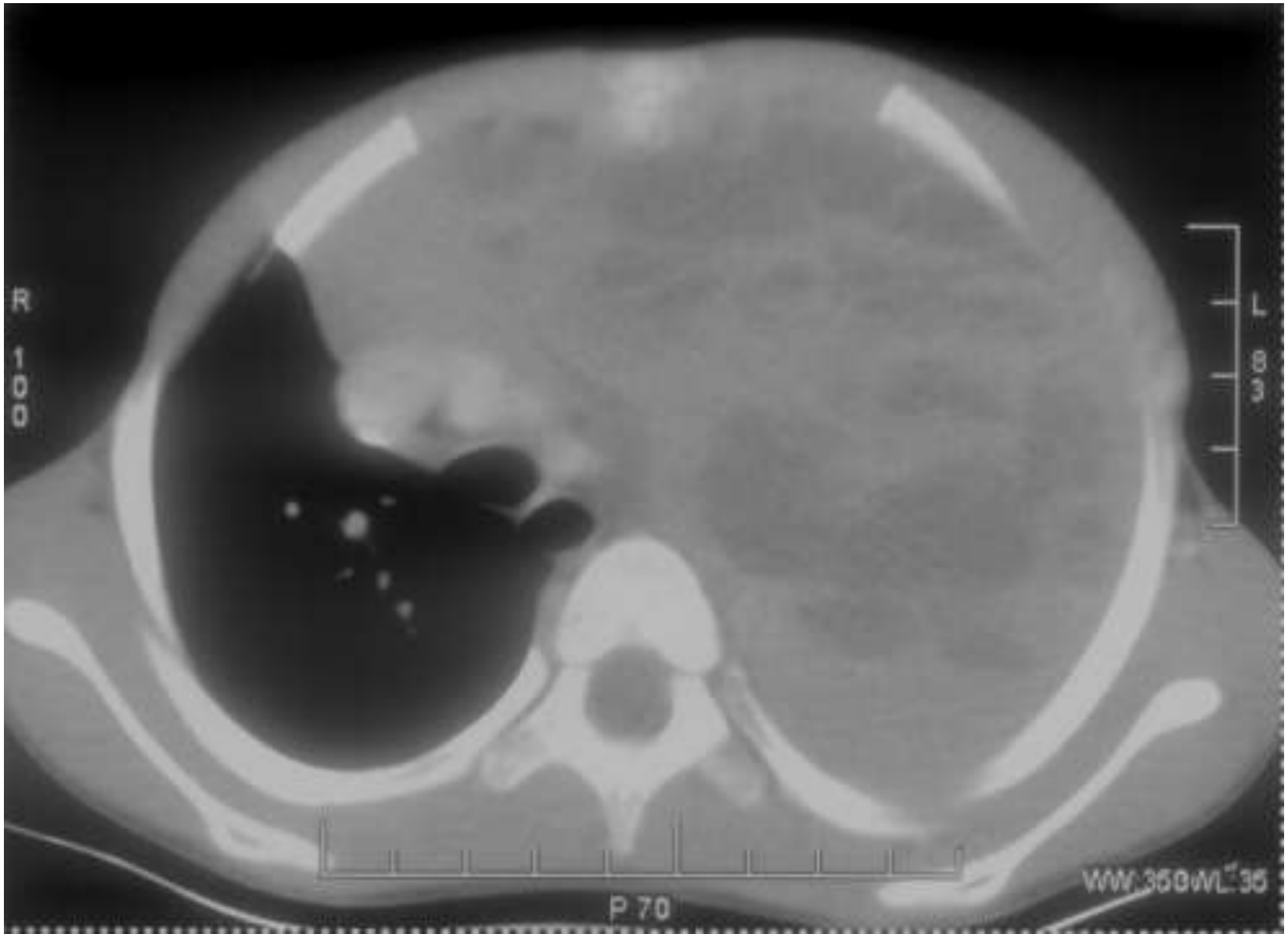
  - CT Thorax: Large solid cystic heterogenously enhancing mass entire left hemithorax
    - 12x10x16cm
    - Lung parenchyma compressed medially
    - Mediastinal shift +

- Trucut biopsy and ICD insertion was done by Pediatric surgeon.
- ICD drained hemorrhagic fluid
  - Cytology : negative, cell block preparation –not done.

- Biopsy: Small round cell tumor – IHC s/o Ewings
- Bone scan: Lytic sclerotic lesion left 5^{th} rib lateral $1/3^{rd}$
- BM biopsy: Normal

CT Images

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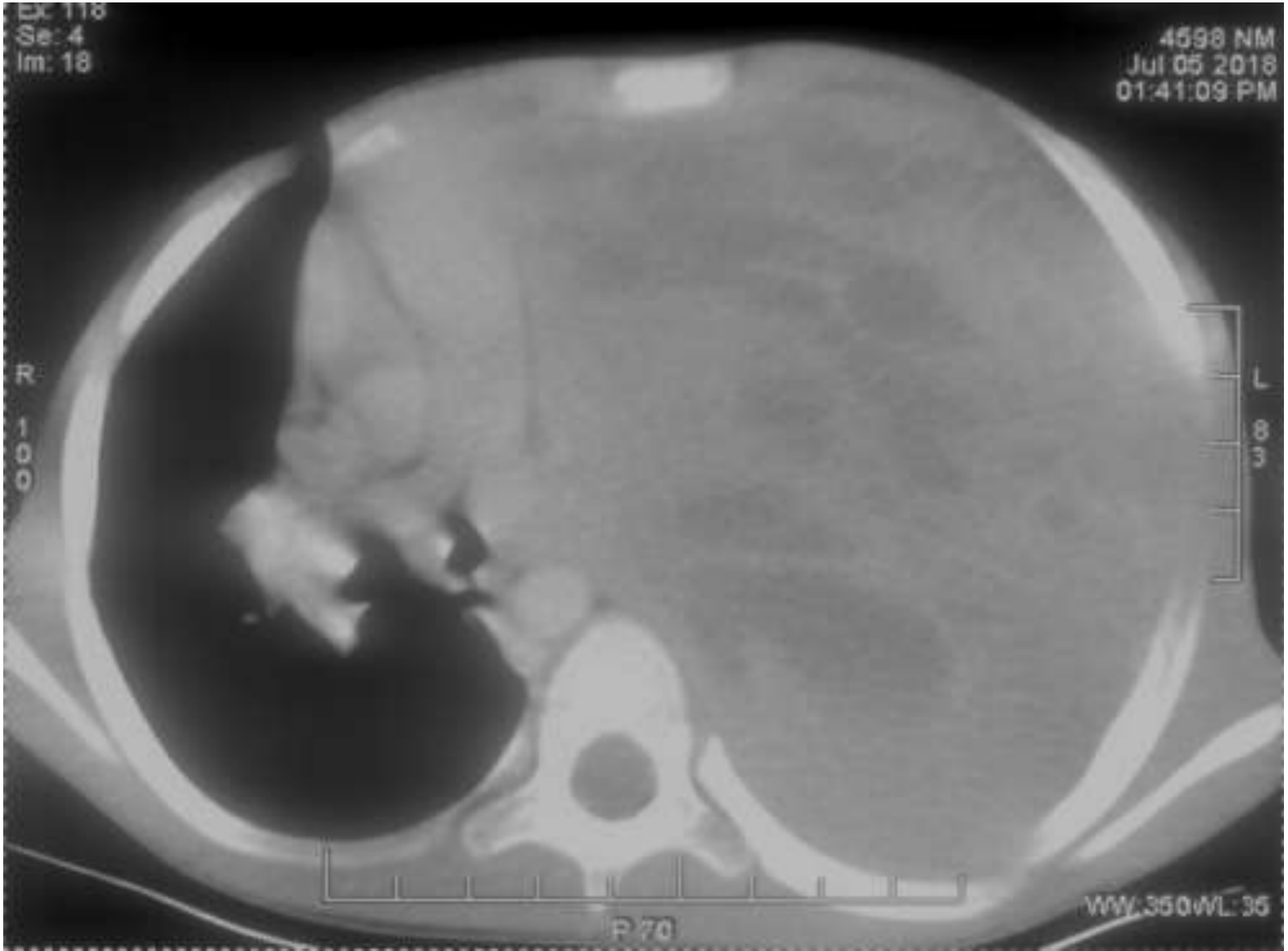
100
L
83
P 70
WW:360WL:36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Im: 18
4598 NM
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100
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3
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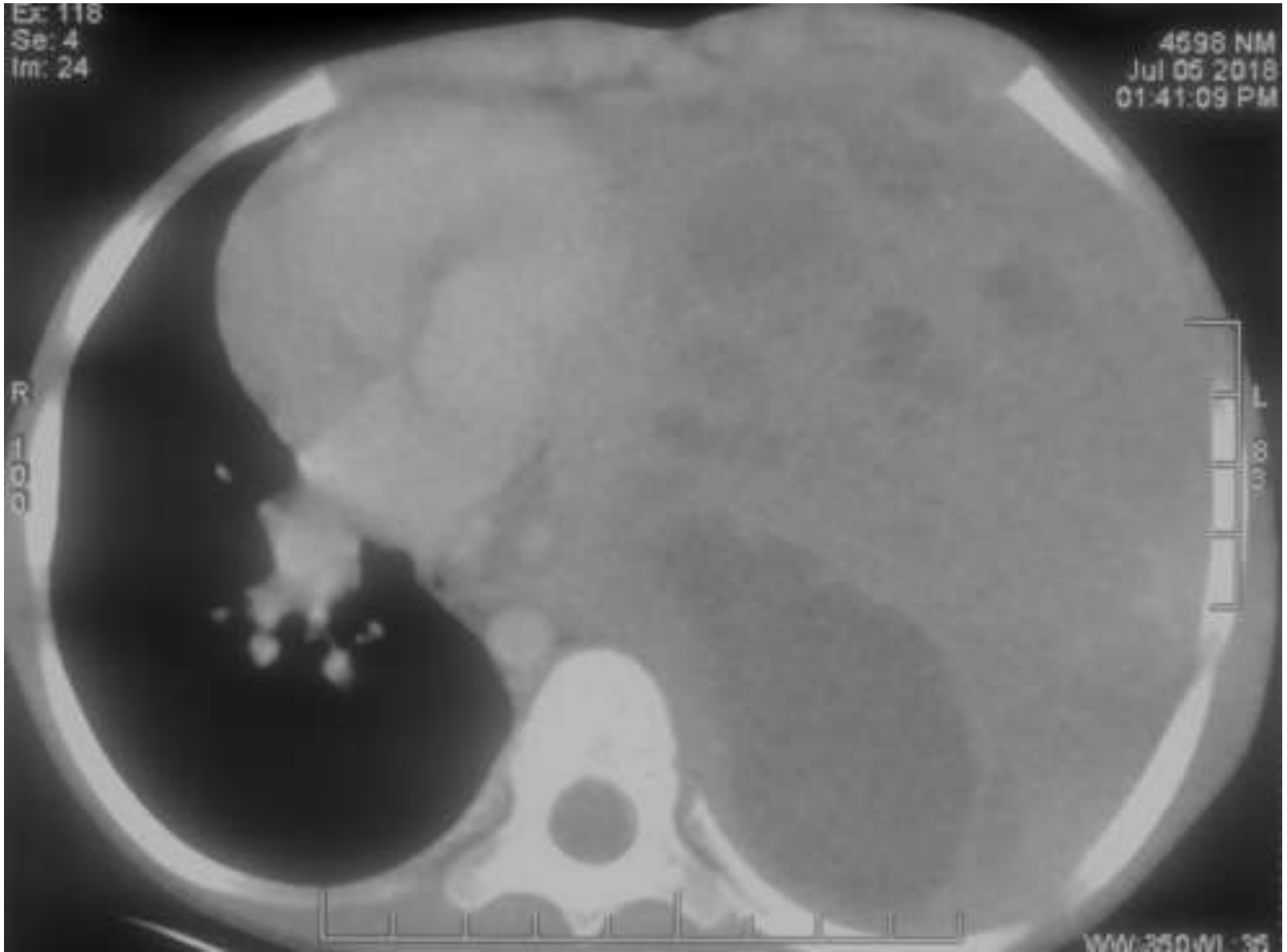
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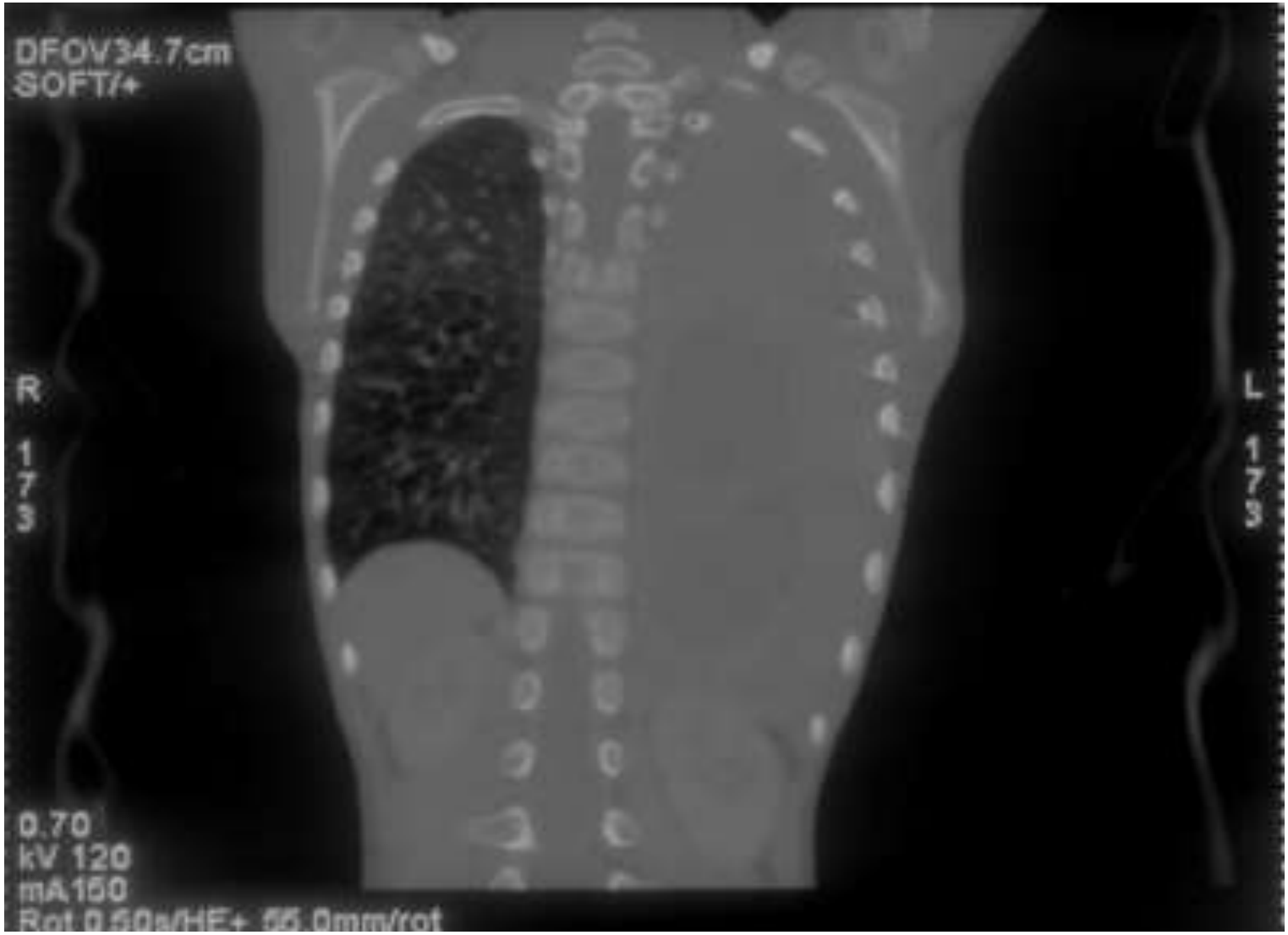
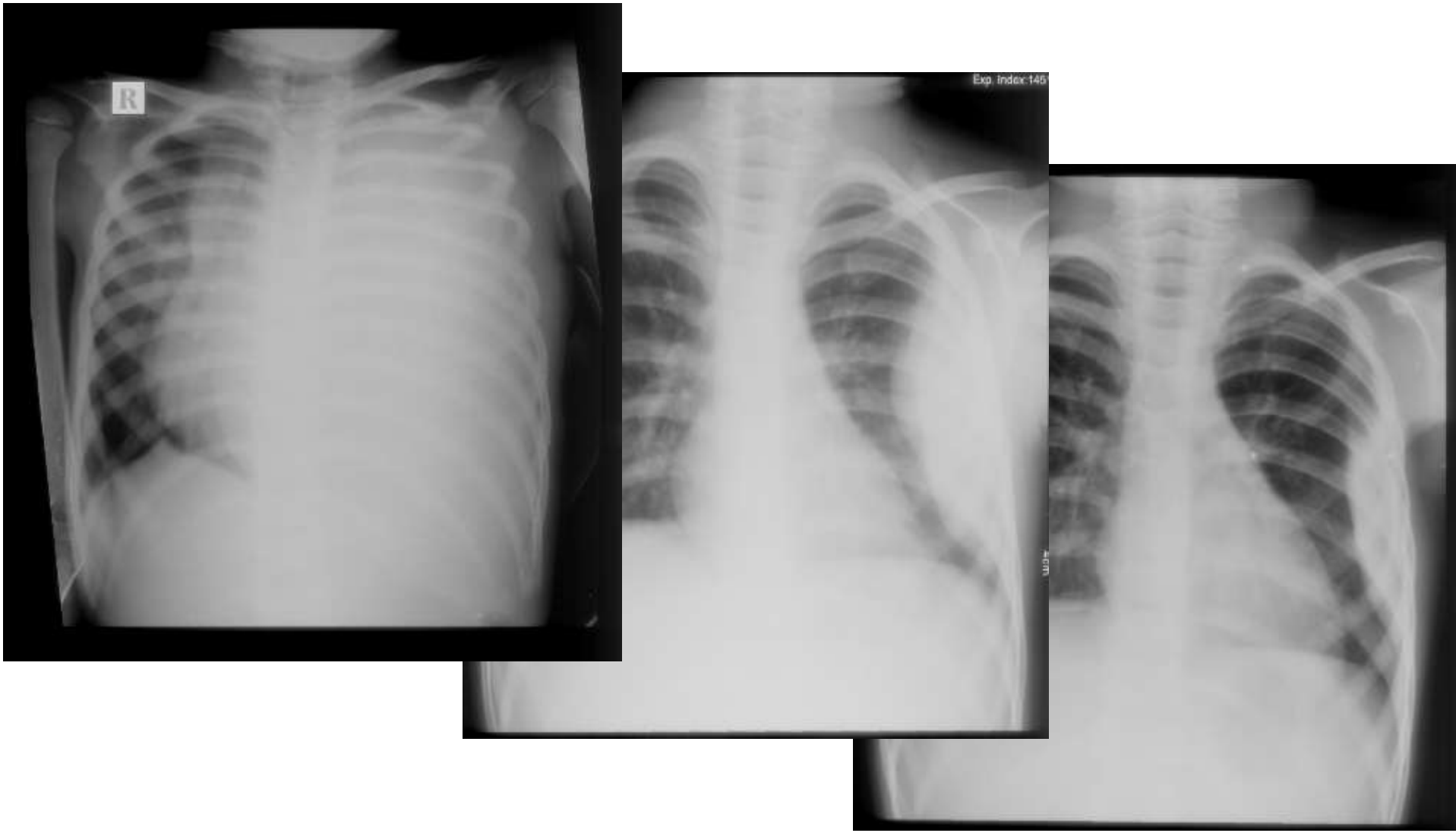
L
WW:350 WL:35


DFOV34.7cm
SOFT/+
R
173
L
173
0.70
kV 120
mA150
Rot 0.50s/HE+ 55.0mm/rot

- Started on chemotherapy with VDC-IE

CXR During chemo



- Surgery
  - Chestwall resection with bone cement mesh reconstruction and LD flap cover
    - Epicenter located in the lateral portions of 4,5,6th ribs
    - Adherent to surface of the lung
    - No pleural nodules
    - Lesion excised with portion of adherent lung

- HPR: Sections from chest wall and lung shows chronic inflammation. No residual malignancy identified.

- Role of adjuvant RT ?

- Role of RT for pleural effusion?
  - Hemithorax RT ?
    - Timing ?
    - Dose ?
  - What if primary also requires RT ?

Chestwall Ewing – PORT ?

Local Control in Ewing Sarcoma of the Chest Wall: Results of the EURO-EWING 99 Trial

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOL

198 patients

- Sx 85(43%)
- PORT 106(53%)
- RT 7(4%)

Multivariate analysis – EFS
- Large volume (>200ml)
- Poor response to chemo

to achieve a complete resection. RT after surgery was frequently used in the presence of known risk factors for relapse, such as insufficient tumor resection or unfavorable histological response to induction chemotherapy.[17] RT was

Conclusions. Complete tumor resection is the best way to achieve local control of ES of the chest wall; additional RT is only useful in patients with incomplete resection. The main limitation of this study was its retrospective nature,

How much of rib to excise ?
- Whole rib / partial ??
- Adjacent ribs also ?? (Sabanathan et al. and Saenz et al.)

Ann Surg Oncol
DOI 10.1245/s10434-015-4630-0

PROGNOSTIC FACTORS AND OUTCOME IN ASKIN-ROSAI TUMOR: A REVIEW OF 104 PATIENTS

doi:10.1016/j.ijrobp.2009.10.039

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Age*
Pleural effusion*

Surg Margins
Chemo response*

when a nonmutilating wide resection could be achieved. In patients with positive surgical margins, large primary tumors with significant soft-tissue component at presentation, and in patients with a poor response to initial chemotherapy (as documented in the resected tumor specimen), postoperative irradiation was recommended. The vol-

Treatment	No:	Response to chemo		Local Control		DFS		OS	
CT + RT	21	57.1	$p = 0.39$	61.9	$p = 0.03$	28%	$p = 0.02$	48.1	$p = 0.11$
CT + Sx + RT	32	81.2		89.1		52.5		50.8	
CT + Sx	19	63.1		65.1		29.8		55.8	

A combination of neoadjuvant chemotherapy followed by surgery and radiotherapy resulted in optimal outcome in patients with this rare tumor

Summary

- Local control an important component of multimodality treatment of Ewings
- Choice of local treatment highly individualised
- Local failure rates higher with conventional dose radical radiotherapy

Summary

- Surgery + PORT to be considered when feasible.
- Take into consideration
  - Best oncological outcome
  - Best functional outcome
  - Late morbidity

Thank You

First COG trial – AEWS0031 (2001-05)

Week	Regimen A_1, Surgery only	Regimen A_2, Radiation only	Regimen A_3, Surgery then Radiation	Regimen B_1, Surgery only	Regimen B_2, Radiation only	Regimen B_3, Surgery then Radiation
1	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)	Cycle 1 (VDC)
2						
3				Cycle 2 (IE)	Cycle 2 (IE)	Cycle 2 (IE)
4	Cycle 2 (IE)	Cycle 2 (IE)	Cycle 2 (IE)			
5				Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 3 (VDC)
6						
7	Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 3 (VDC)	Cycle 4 (IE)	Cycle 4 (IE)	Cycle 4 (IE)
8						
9				Cycle 5 (VDC)	Cycle 5 (VDC)	Cycle 5 (VDC)
10	Cycle 4 (IE)	Cycle 4 (IE)	Cycle 4 (IE)			
11				Cycle 6 (IE)	Cycle 6 (IE)	Cycle 6 (IE)
12						
13	SURGERY	Cycle 5 (VDC) start RT	SURGERY	SURGERY	Cycle 7 (VDC) start RT	SURGERY
14						
15	Cycle 5 (VDC)		Cycle 5 (VDC) start RT	Cycle 7 (VDC)	Cycle 8 (IE)	Cycle 7 (VDC) start RT
16		Cycle 6 (IE)				
17				Cycle 8 (IE)	Cycle 9 (VC)	Cycle 8 (IE)
18	Cycle 6 (IE)		Cycle 6 (IE)			
19		Cycle 7 (VC)		Cycle 9 (VDC)	Cycle 10 (IE)	Cycle 9 (VC)
20						
21	Cycle 7 (VDC)		Cycle 7 (VC)	Cycle 10 (IE)	Cycle 11 (VC)	Cycle 10 (IE)
22		Cycle 8 (IE)				
23				Cycle 11 (VC)	Cycle 12 (IE)	Cycle 11 (VC)
24	Cycle 8 (IE)		Cycle 8 (IE)			
25		Cycle 9 (VDC)		Cycle 12 (IE)	Cycle 13 (VDC)	Cycle 12 (IE)
26						
27	Cycle 9 (VDC)		Cycle 9 (VDC)	Cycle 13 (VC)	Cycle 14 (IE)	Cycle 13 (VDC)
28		Cycle 10 (IE)				
29				Cycle 14 (IE)		Cycle 14 (IE)
30	Cycle 10 (IE)		Cycle 10 (IE)			
31		Cycle 11 (VDC)				
32						
33	Cycle 11 (VC)		Cycle 11 (VDC)			
34		Cycle 12 (IE)				
35						
36	Cycle 12 (IE)		Cycle 12 (IE)			
37		Cycle 13 (VC)				
38						
39	Cycle 13 (VC)		Cycle 13 (VC)			
40		Cycle 14 (IE)				
41						
42	Cycle 14 (IE)		Cycle 14 (IE)			
43						

IE = Ifosfamide – Etoposide - MESNA
VDC = Vincristine – Doxorubicin – Cyclophosphamide - MESNA
VC = Vincristine - Cyclophosphamide – MESNA

- VDC
  - Vincristine 2mg/m^2 (max 2mg) D1
  - Doxorubicin 37.5mg/m^2 D1,D2 (cumulative 375mg)
  - Cyclophosphamide 1.2gm/m^2 D1
- IE
  - Ifosphamide 1.8gm/m^2 D1-D5
  - Etoposide 100 mg/m^2 D1-D5

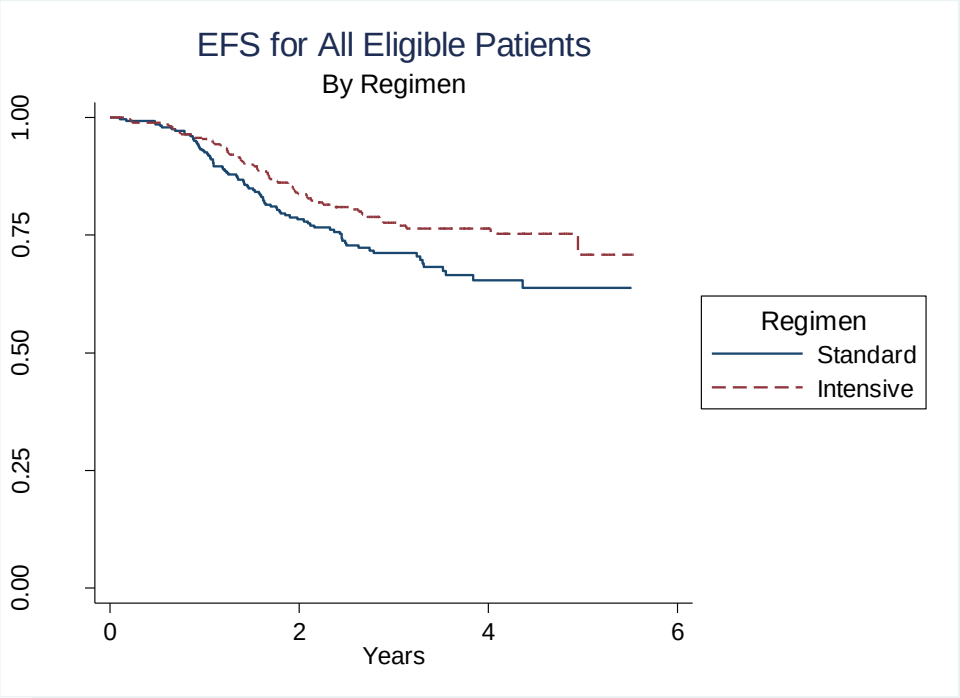
Candidates for radiotherapy alone will include patients with bulky lesions in surgically difficult sites such as the spine, skull and periacetabular pelvis, and those patients with a poor response to induction chemotherapy, in whom surgery would result in unacceptable functional results. Sites which if removed would result in significant impairment of function include: skull, facial bones, vertebrae and pelvic bones about the acetabulum. In some cases, resection even in these sites may be feasible in combination with radiation therapy, and decisions regarding a specific patient must be individualized.

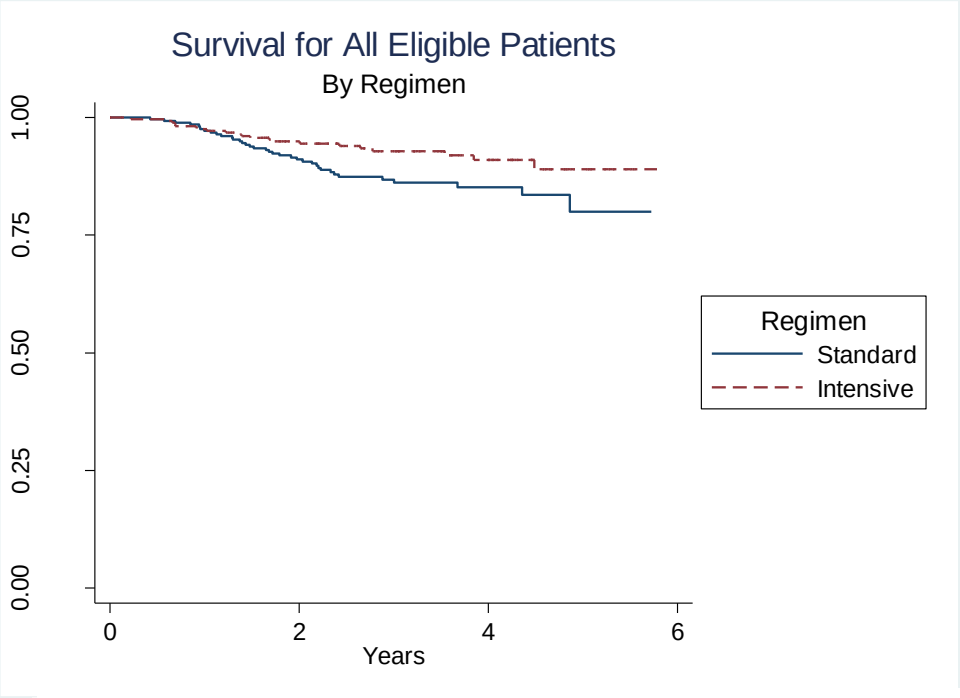
Surgery + RT

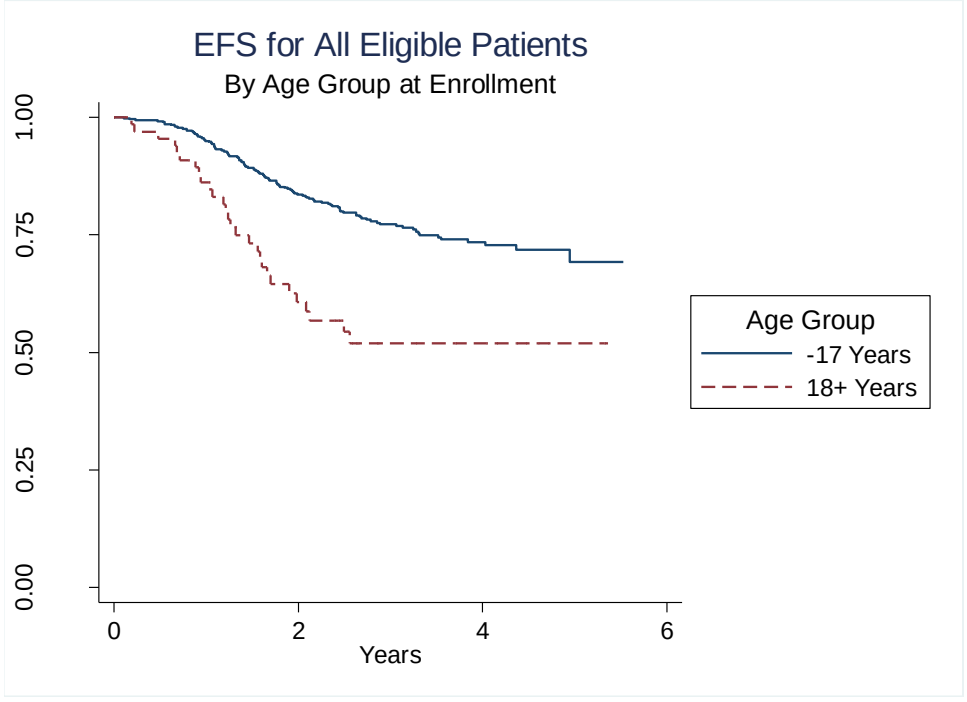
risk in each patient. This approach is most appropriate for large bulky primaries, greater than 10 cm. in maximal dimension, or when the lesion is unresectable after induction chemotherapy. The use of routine postoperative radiotherapy will permit use of a more limited surgical procedure, and will be administered in any patient who has residual disease, or inadequate surgical margins.

The decision regarding whether the radiation will precede or follow the resection will be left to the treating team. This should be planned in advance with the pediatric oncologist and the radiation oncologist. When surgery is done first, followed by radiation therapy, surgery should occur on week 13 (after 4 cycles of chemotherapy on Regimen A or 6 cycles of chemotherapy on Regimen B (see Section 5.1). Radiation therapy should begin as soon as feasible thereafter.

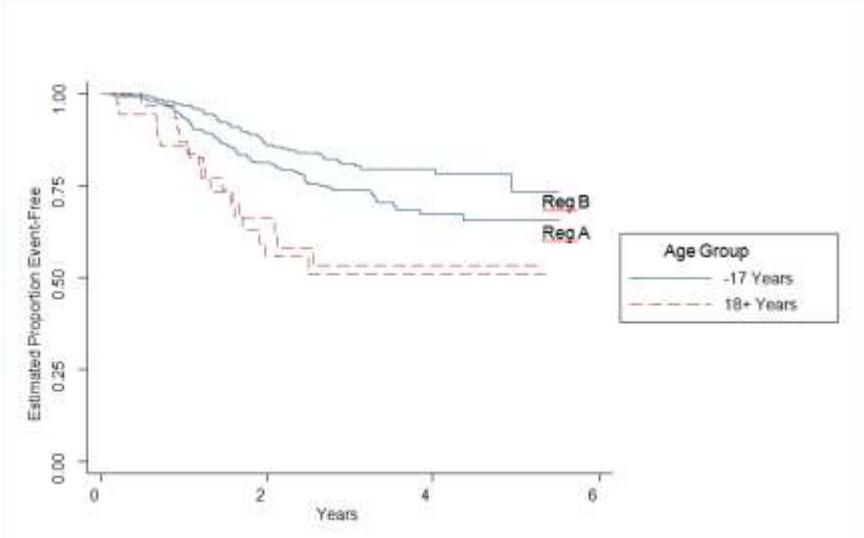
First COG trial – AEWS0031 (2001-05)



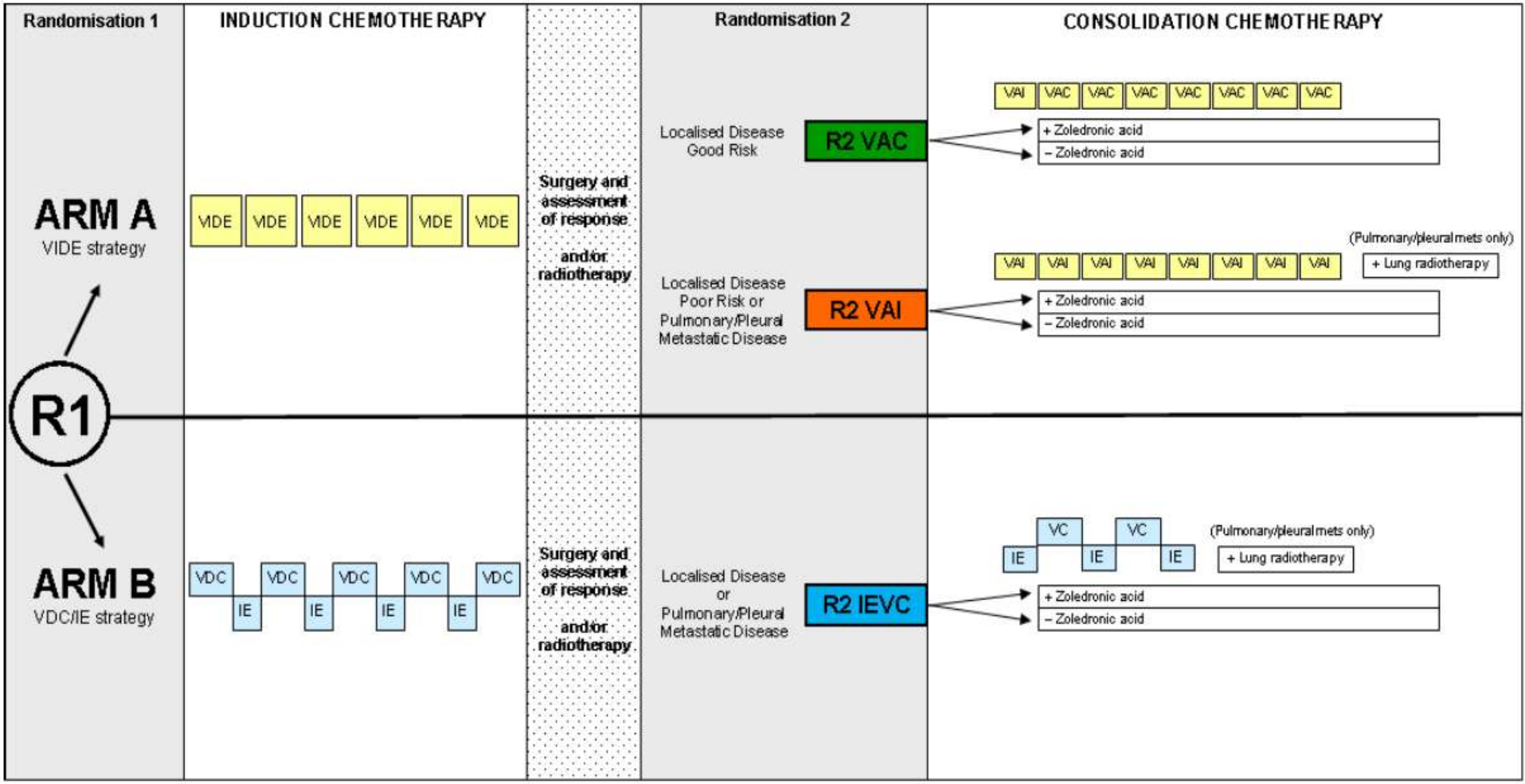




AEWS0031 Regimens and Age



Euro-Ewing's 2012 trial schema



VIDE Vincristine, Ifosfamide, Doxorubicin, Etoposide
VDC Vincristine, Doxorubicin, Cyclophosphamide
IE Ifosfamide, Etoposide

VAI Vincristine, Actinomycin D, Ifosfamide
VAC Vincristine, Actinomycin D, Cyclophosphamide
IE Ifosfamide, Etoposide
VC Vincristine, Cyclophosphamide