EWINGS SARCOMA

S Laskar ICRO July 2015

JAMES EWING, 1921

Endothelial origin

14 yr Girl

SPECTRUM OF ESFT

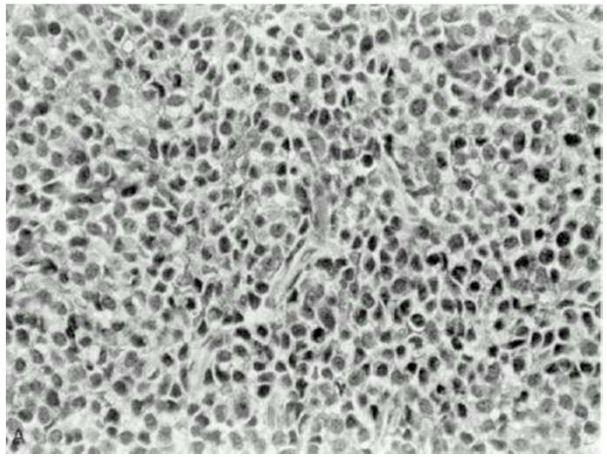
NEURAL DIFFERENTIATION

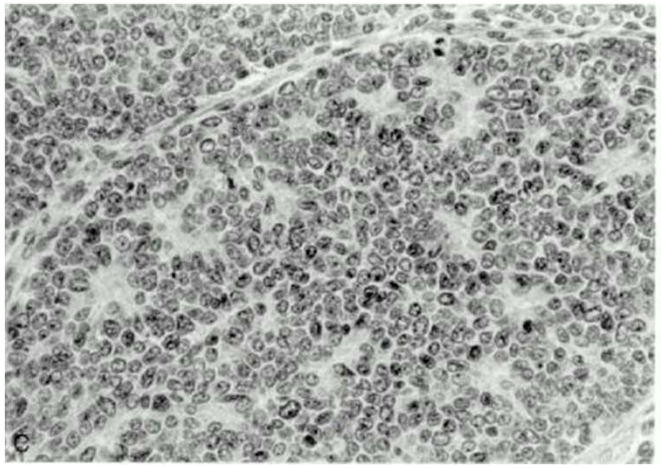
Least → **Well**

EWING'S SARCOMA

ATYPICAL EWING'S SARCOMA

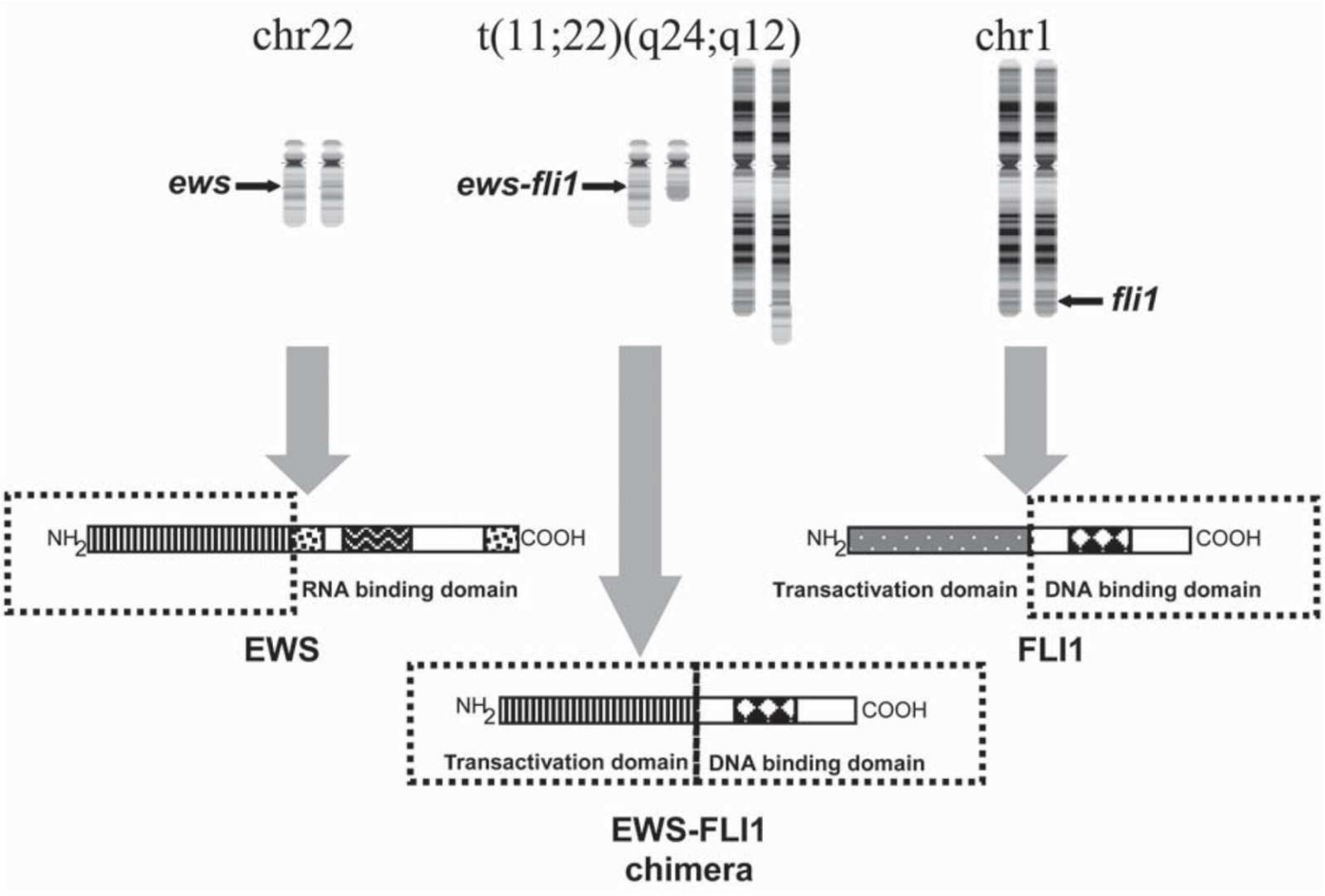
- PNET
- Peripheral Neuroepithelioma
- ASKIN TUMOR (thoraco-pulmonary)





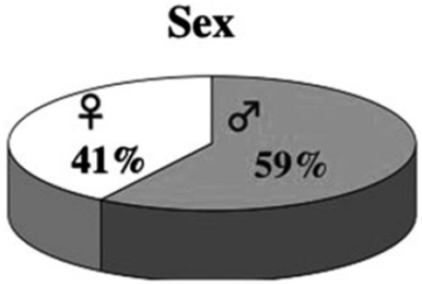
GENETICS

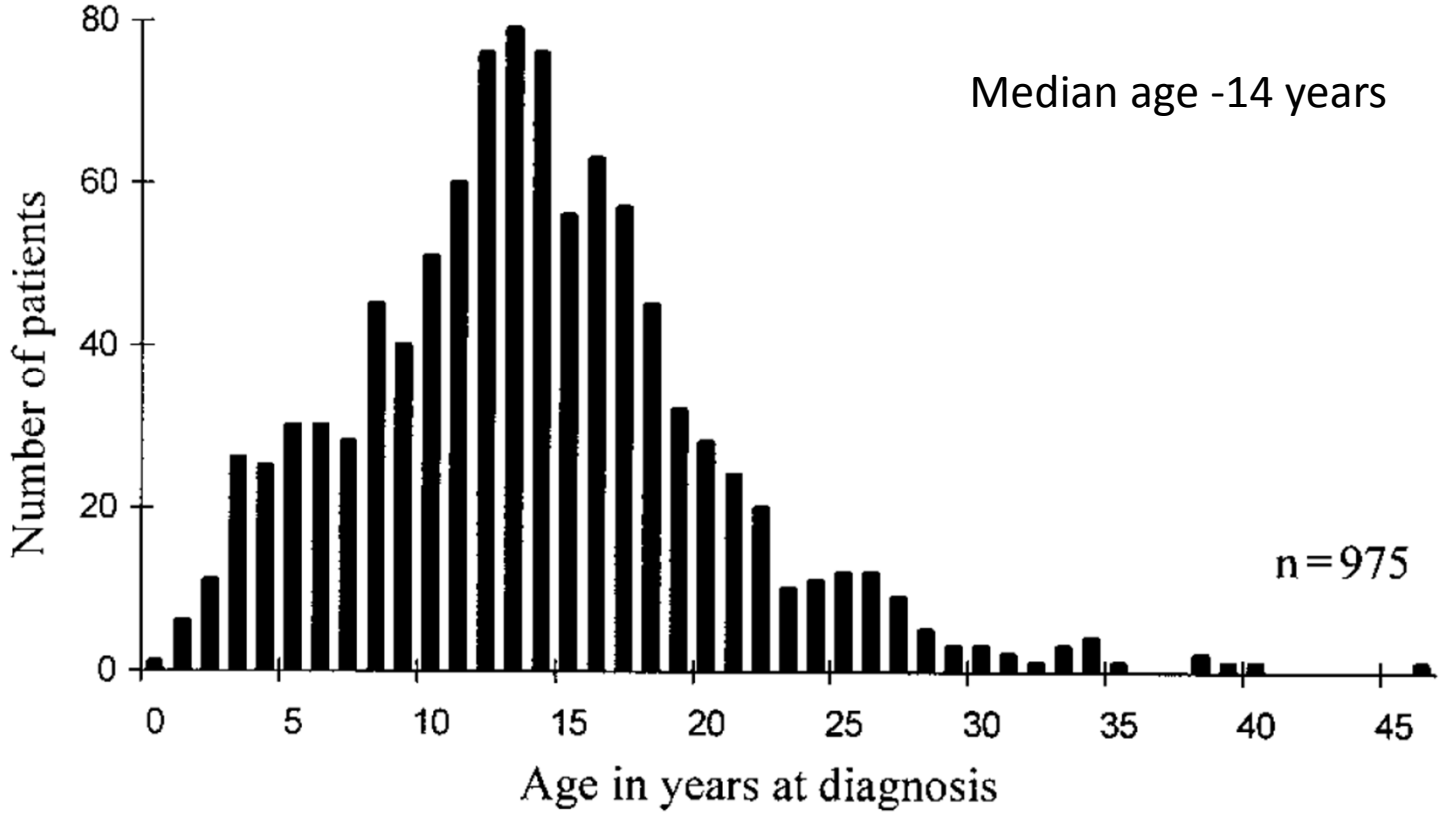
- Most Consistent : Pathognomic of EFT
- 85 % : Reciprocal Translocation t(11;22) (q24;q12)
- Results EWS-FLI1 gene
- 5-10 % : Translocation t(21;22)(q21;q12)
- Results EWS-ERG gene


chr22
t(11;22)(q24;q12)
chr1
ews
ews-fli1
fli1
NH2
COOH
RNA binding domain
EWS
NH2
COOH
Transactivation domain
DNA binding domain
FLI1
NH2
COOH
Transactivation domain
DNA binding domain
EWS-FLI1
chimera

EPIDEMIOLOGY

- 2 nd most common primary osseous malignancy in children
- Incidence is 2.1 / million (U.S.)
- Males > Females
- 65% in the 2nd decade of life
- Rare in blacks and Asians





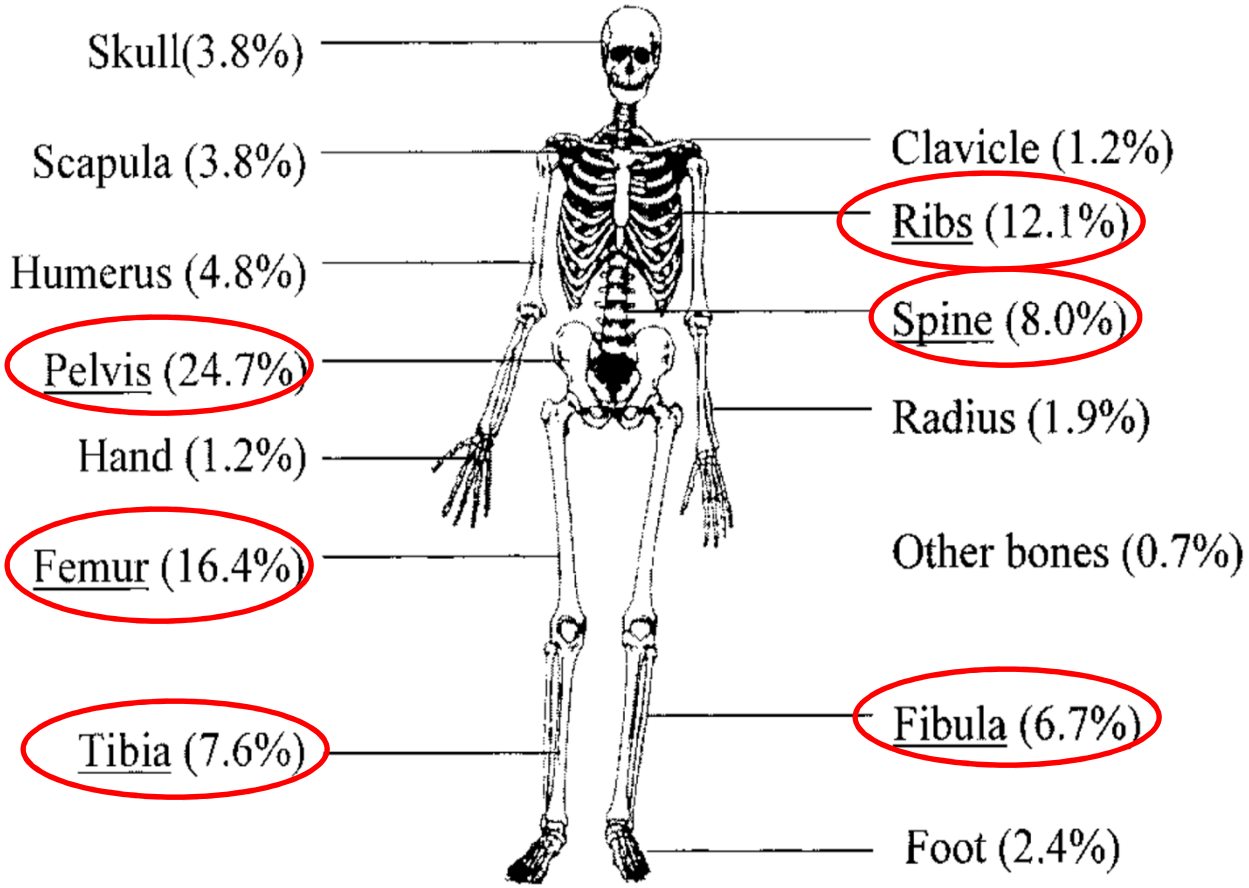
Age distribution of Ewing's sarcoma patients registered with CESS and UKCCSG/MRC

S.J. Cotterill et al, JCO: 18;2000, 3108-3114

CLINICAL PRESENTATION

o Pain	90%
o Swelling	80%
o Impaired limb movement	25%
o Neurological symptoms	10%
o Fever	5%
o Symptoms of metastatic disease	

SITES OF INVOLVEMENT



S.J. Cotterill et al, JCO: 18;2000, 3108-3114

INVESTIGATIONS

Pathology

Biopsy with routine histology
Immunohistochemistry
Cytogenetics

Laboratory

Routine chemistries, LDH

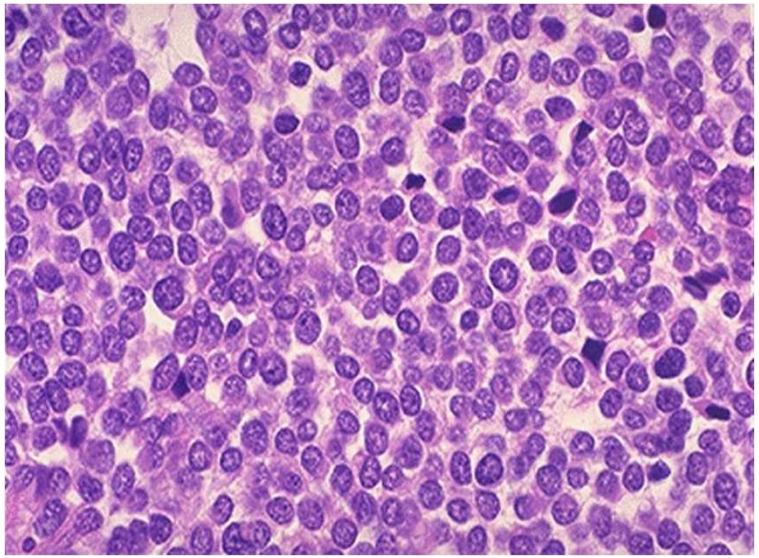
Radiography

X Ray of the primary
CT Scan & MRI of the primary
Chest CT Scan
Bone scan
PET-CT Scan

Bone marrow aspirate and biopsy

BIOPSY

- Multiple core
- Open Inx biopsy Longitudinal
- Soft tissue extension



Tissue Processing

- Cytogenetics (Karyotyping)
- Molecular RT-PCR & Immuno-cytochemical studies
- Flow Cytometry – DNA ploidy

IMMUNOHISTOCHEMISTRY

- **Ewing's sarcomas**
  MIC2 positive
  PAS-positive
  Reticulin negative

- **Lymphomas**
  PAS-negative and Reticulin-positive
  Positive for leukocyte common antigen and other T and B cell markers

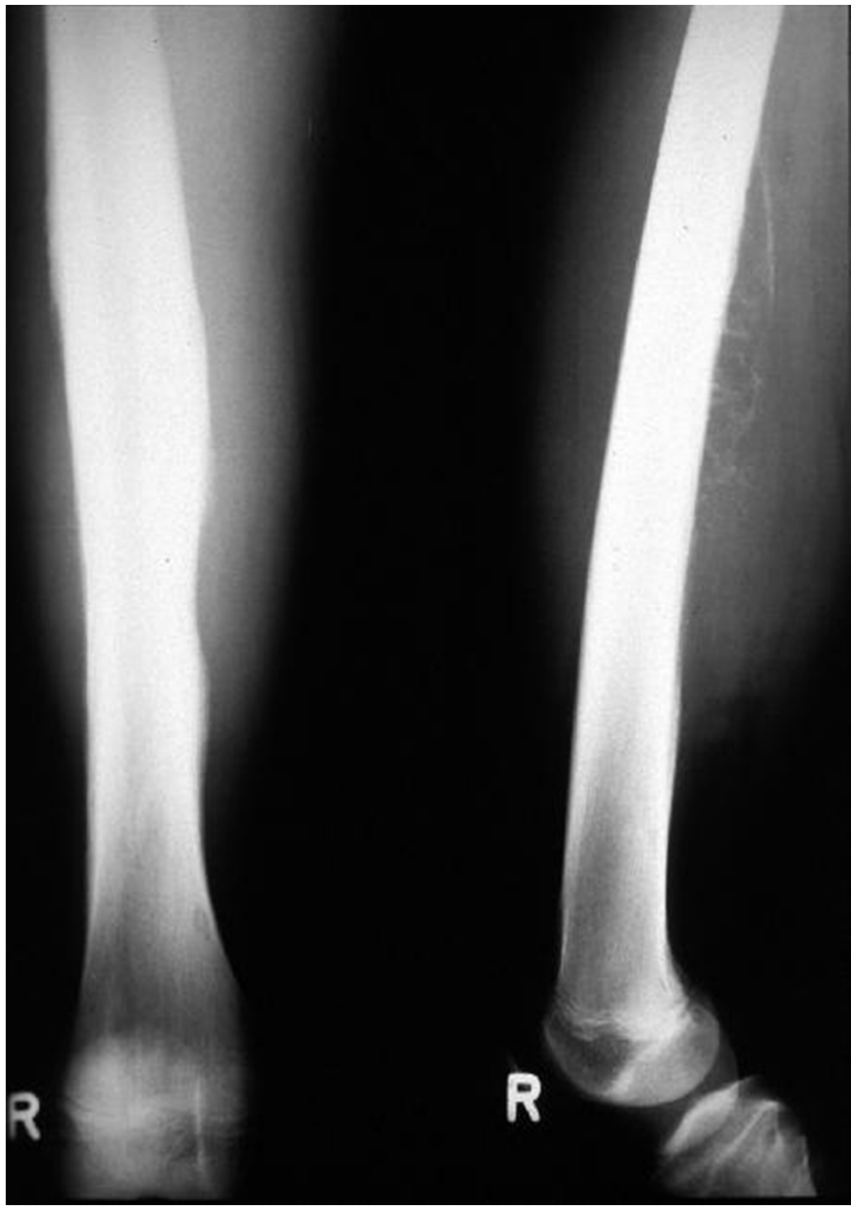
- **Embryonal Rhabdomyosarcoma**
  Positive for Desmin, myoglobin and muscle-specific actins.

- **Small-cell metastatic carcinomas & Melanomas**
  Express detectable Cytokeratin.

- **Primitive Neuroectodermal Tumors (PNET)**
  Neural differentiation by light microscopy (Homer Wright rosettes in more than 20% of tumor tissue) and immunohistochemical staining for neuron-specific enolase (NSE), S-100, Leu-7

X-RAY

Diaphyseal Tumour



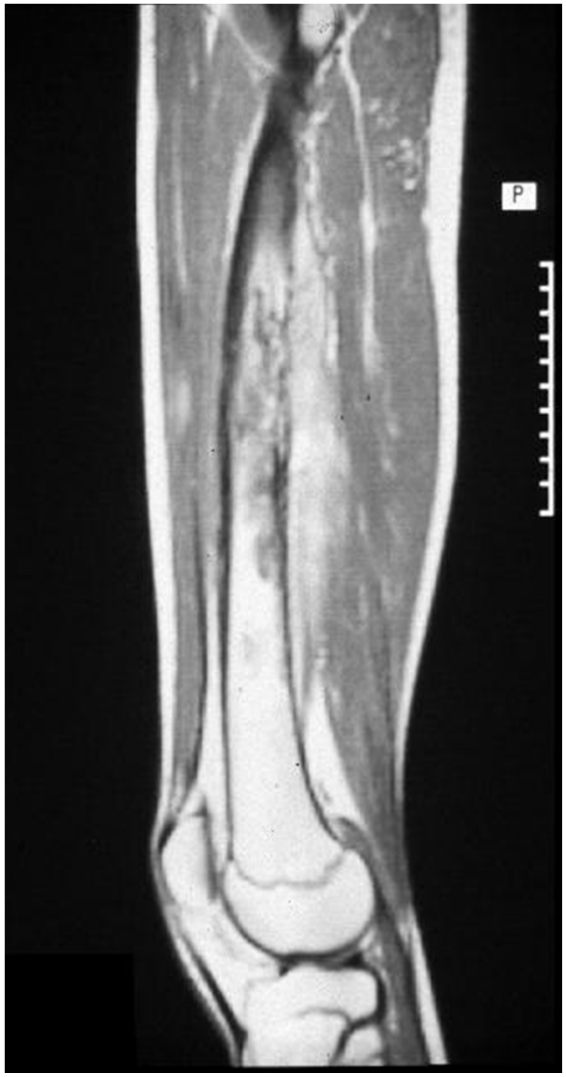
Periosteal Lamellation

(circular)

Soft Tissue

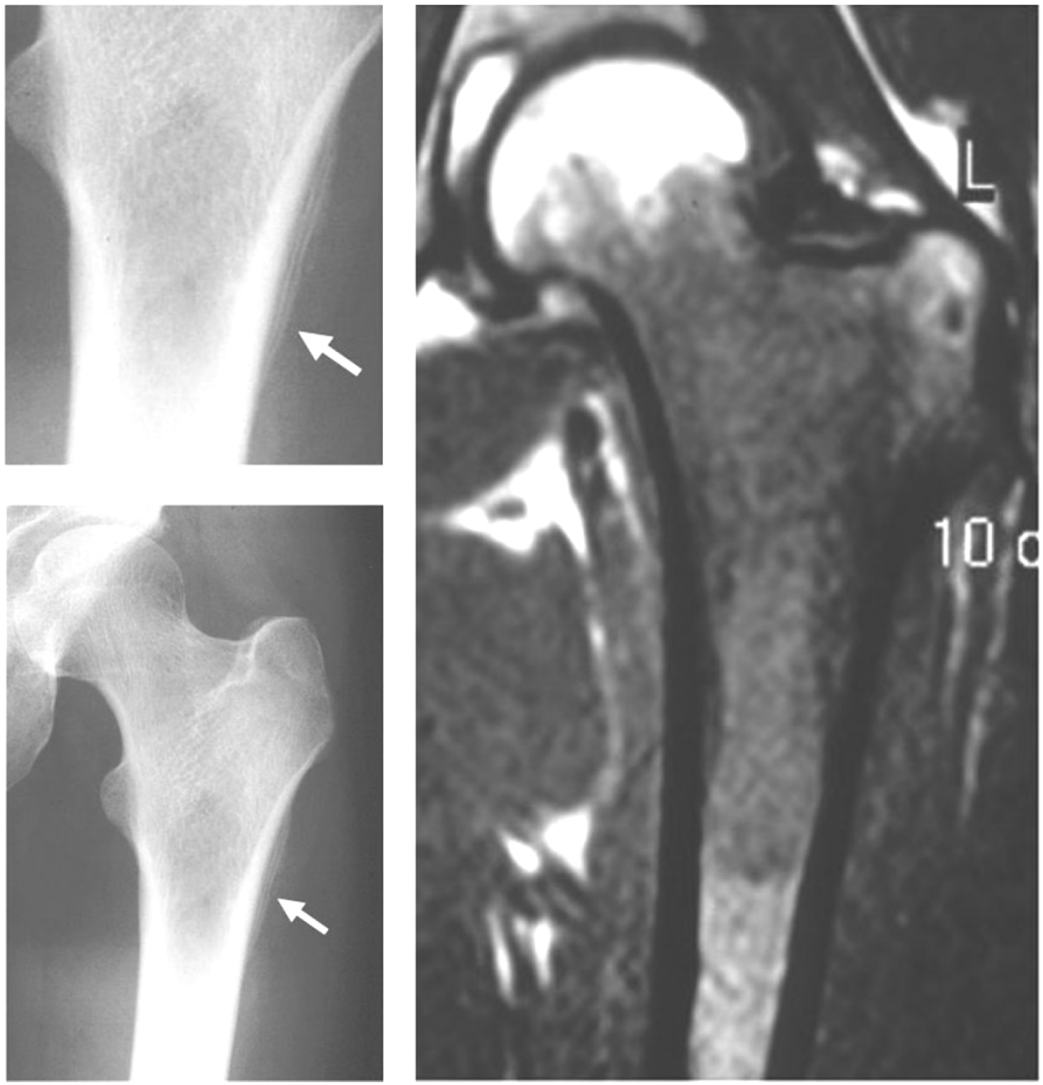
Component

MRI

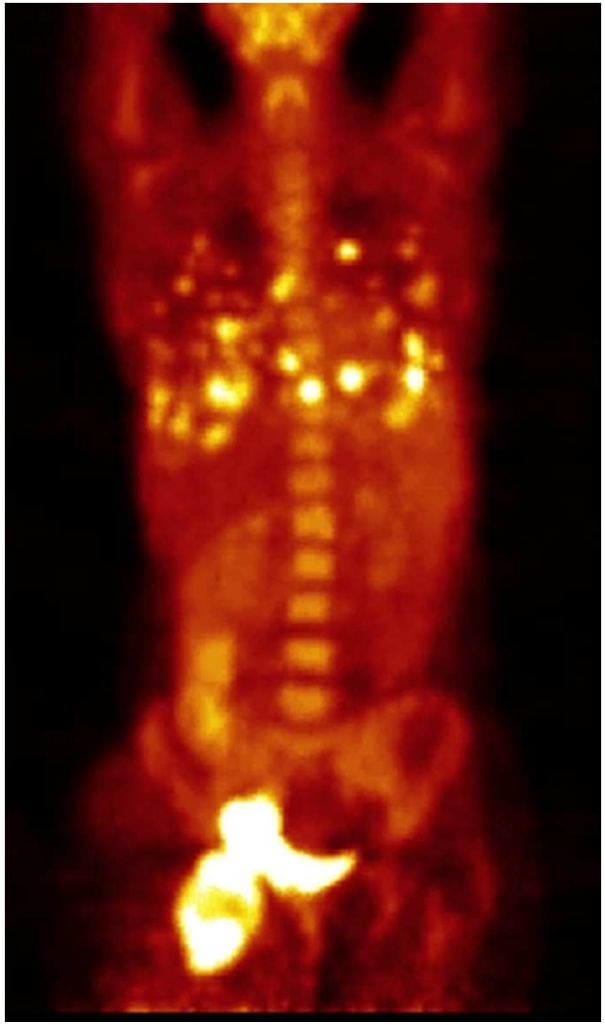


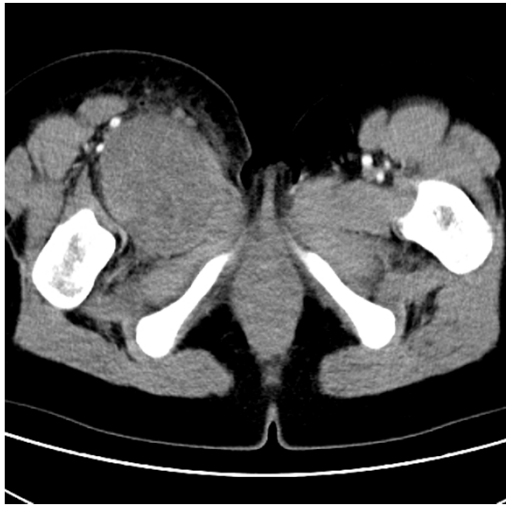
- Intraossous extension
- Soft tissue extension
- Skip lesions
- Relation to adjacent structures, vessels , nerves
- Intra-medullary extent
- Multi-planar reconstruction

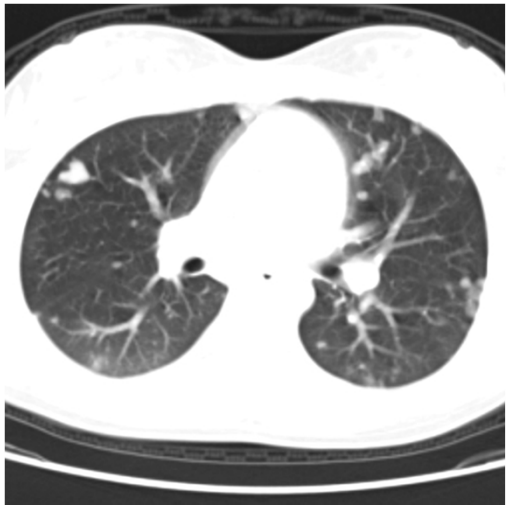
EXTENT OF LESION

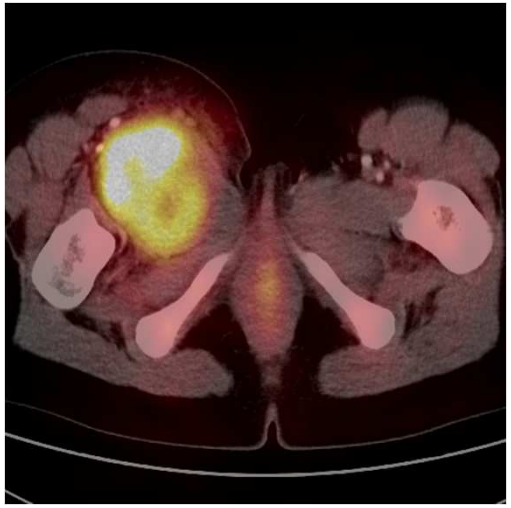


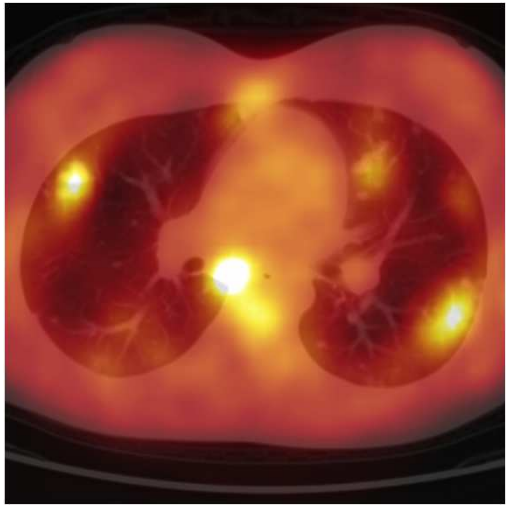
PET SCAN







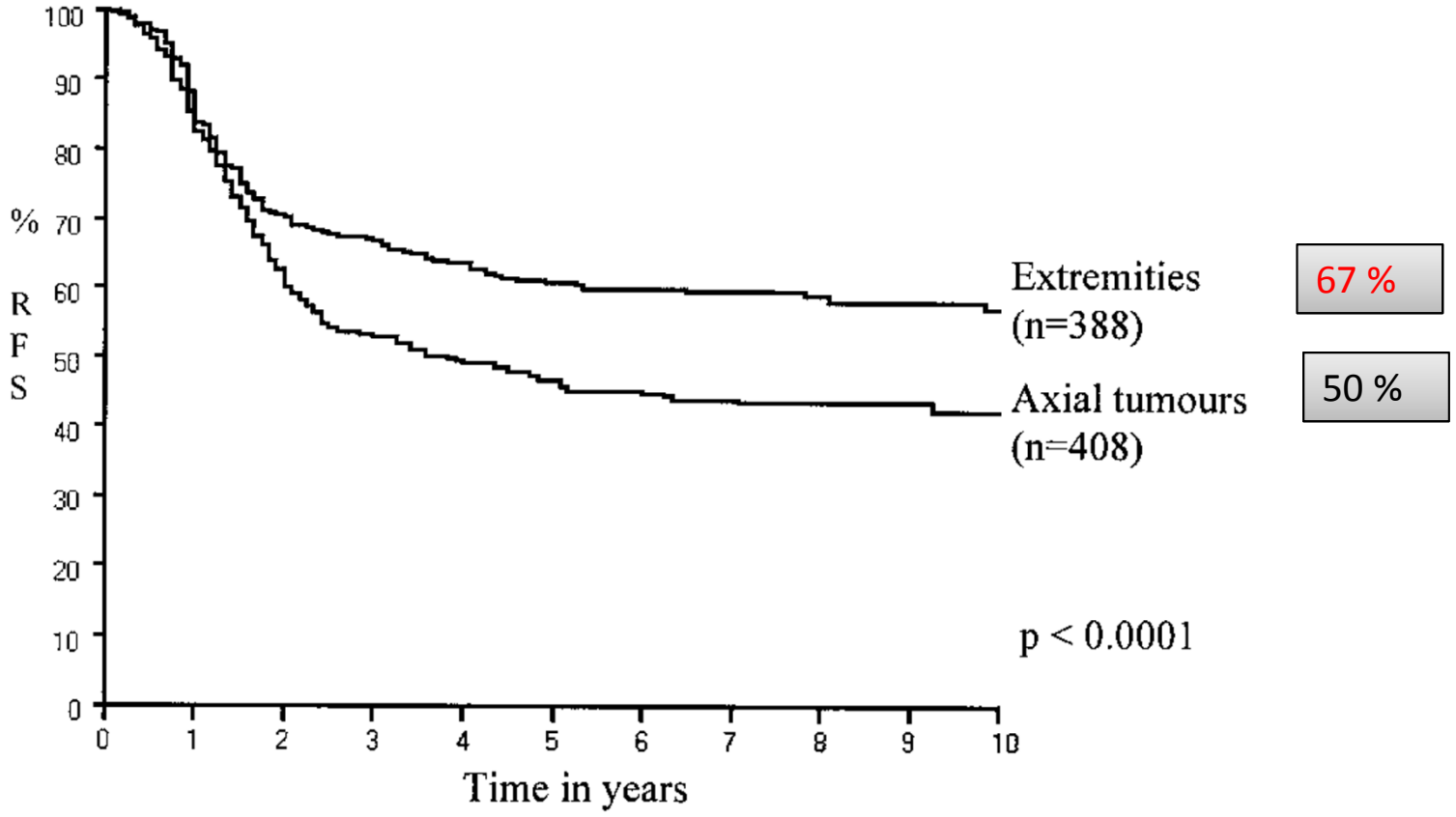




PROGNOSTIC FACTORS

- Site
- Stage: localised / metastatic
- Size
- Age
- Molecular prognostic factors
- Response to chemotherapy (Necrosis)
- Minimal residual disease

SITE



67 %

50 %

RFS by primary site for patients free of metastases at diagnosis.

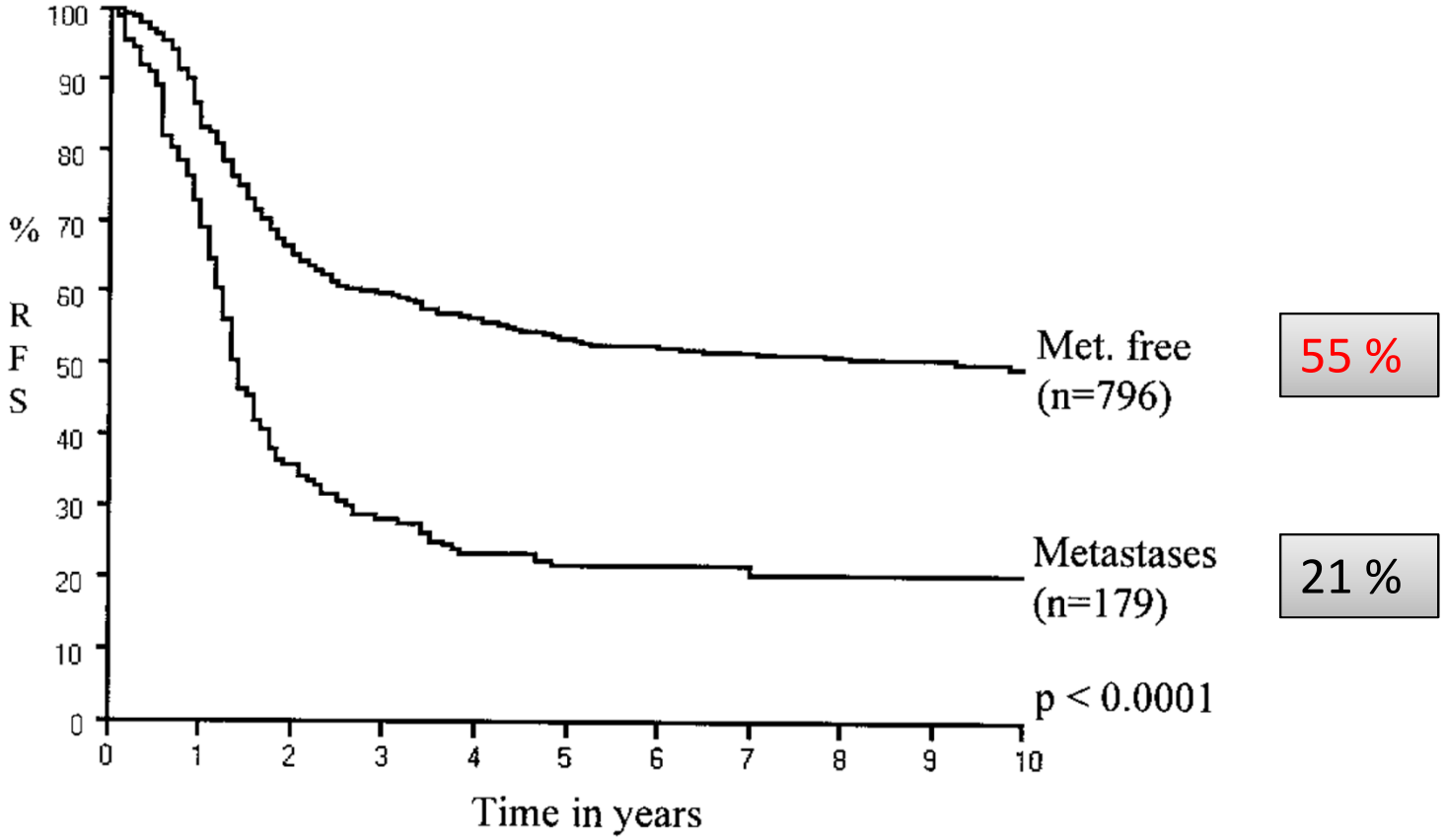
S.J. Cotterill et al, JCO: 18;2000, 3108-3114

Table 3. RFS by Primary Site in Patients Without Metastases at Diagnosis

Site	No. of Patients	5-Year RFS (%)	95% CI (%)
Axial sites			
Pelvis	179	46	38-54
Rib	97	53	42-63
Spine	58	58	45-72
Scapula	38	41	25-56
Skull	20	68	43-93
Clavicle	14	32	4-61
Sternum	2	50*	–
Total	408	40	31-51
Extremities			
Femur	139	58	49-66
Humerus	49	78	66-90
Tibia	82	63	52-74
Fibula	78	55	44-67
Foot	24	51	29-72
Ulna	7	71*	–
Radius	7	86*	–
Hand	2	100*	–
Total	388	61	56-66
All sites combined	796	56	52-59

S.J. Cotterill et al, JCO: 18;2000, 3108-3114

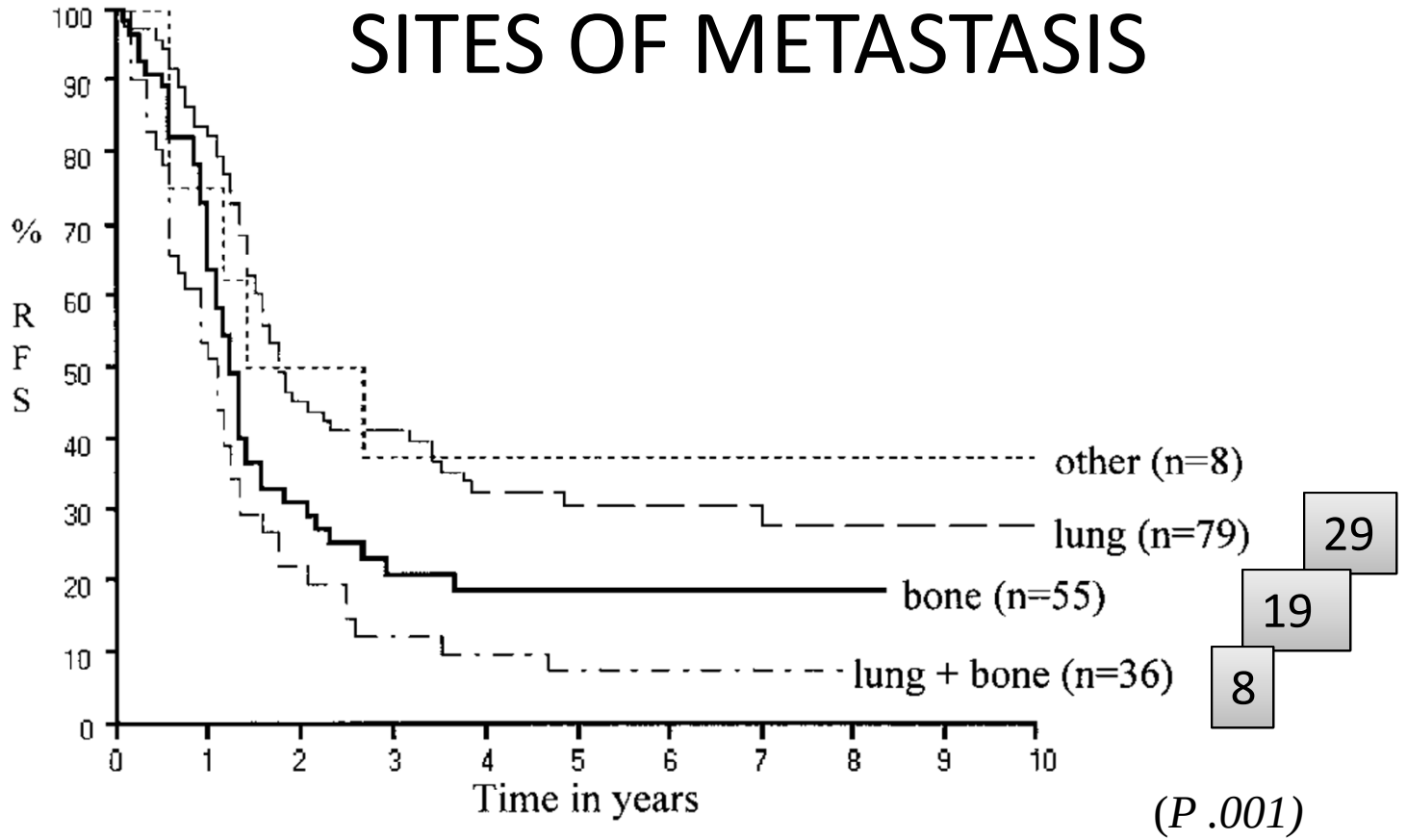
LOCALISED VS. METASTATIC



RFS according to detectable metastases at diagnosis.

S.J. Cotterill et al, JCO: 18;2000, 3108-3114

SITES OF METASTASIS



(*P .001*)

Survival by site of metastases (figure excludes 1 patient for whom site of metastasis was not specified).

S.J. Cotterill et al, JCO: 18;2000, 3108-3114

RESPONSE TO CHEMOTHERAPY

Huvos Grading System

Grade	Necrosis %	5 yr EFS %	Responders %
I	<50	0	19
II	50 -90	37	22
III	90-99	84	18
IV	100	84	42

POG-CCG (Modified Huvos System)

Grade	Necrosis (%)	OS – 3 yrs (%)
I	0	30
II	A – 1 to 10 B – 11 to 90	30
III	91-99	49
IV	100	73

S Laskar ICRO July 2015

TREATMENT

- Multi-disciplinary treatment
- Current standard treatment
  - Primary induction chemotherapy
  - Local therapy (Surgery / radiotherapy)
  - Maintenance chemotherapy

CHEMOTHERAPY

1960 – Sutow & Pinkel: Cyclophosphamide 3/4 response

1966 – Jenkin: N2 mustard – 3/3 response

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

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

1976 – Rosen MSKCC: RT + VACD Long term survival

1990 – Nesbitt: VACD vs. VAC – Improved EFS & LC

Treatment results in selected clinical studies of localized Ewing's sarcoma

Study	Reference	Schedule	Patients	5-year EFS	*p* value[a]	Comments
IESS studies						
IESS-I (1973–1978)	Nesbit et al. [68]	VAC	342	24%	VAC vs. VAC + WLI, .001	Value of D
		VAC + WLI		44%	VAC vs. VACD, .001	Benefit of WLI?
		VACD		60%	VAC + WLI vs. VACD, .05	
IESS-II (1978–1982)	Burgert et al. [69]	VACD-HD	214	68%	.03	Value of aggressive cytoreduction
		VACD-MD		48%		
First POG–CCG, INT-0091 (1988–1993)	Grier et al. [75]	VACD	200	54%	.005	Value of combination IE in localized disease, no benefit in metastatic disease
		VACD + IE	198	69%		
Second POG–CCG (1995–1998)	Granowetter et al. [98]	VCD + IE 48 weeks	492	75% (3 yrs)	.57	No benefit of dose-time compression
		VCD + IE 30		76% (3 yrs)		

Paulussen et al. The Oncologist 2006;11:503–519

Study	Reference	Schedule	Patients	5-year EFS	*p* value[a]	Comments
CESS studies						
CESS-81 (1981–1985)	Jürgens et al. [67]	VACD	93	<100 ml, 80%; ≥100 ml 31% (both 3 yrs) Viable tumor <10%, 79%; >10%, 31% (both 3 yrs)		Tumor volume (< or ≥100 ml) and histological response are prognostic factors
CESS-86 (1986–1991)	Paulussen et al. [73]	<100 ml (SR): VACD	301	52% (10 yrs)		Intensive treatment with I for high-risk patients. Tumor volume (< or ≥200 ml) and histologic response as prognostic factor
		≥100 ml (HR): VAID		51% (10 yrs)		.

Paulussen et al. The Oncologist 2006;11:503–519

COMPARISION OF VACD vs. VACD + IE

Non metastatic (398)

Randomise

200 –standard therapy VACD
198 – experimental therapy VACD alt I+E

Metastatic (120)

Randomise

62 – standard arm
58 – experimental arm

Primary End-point: Event free survival

Holcombe E. et al N Engl J Med 2003;348:694-701

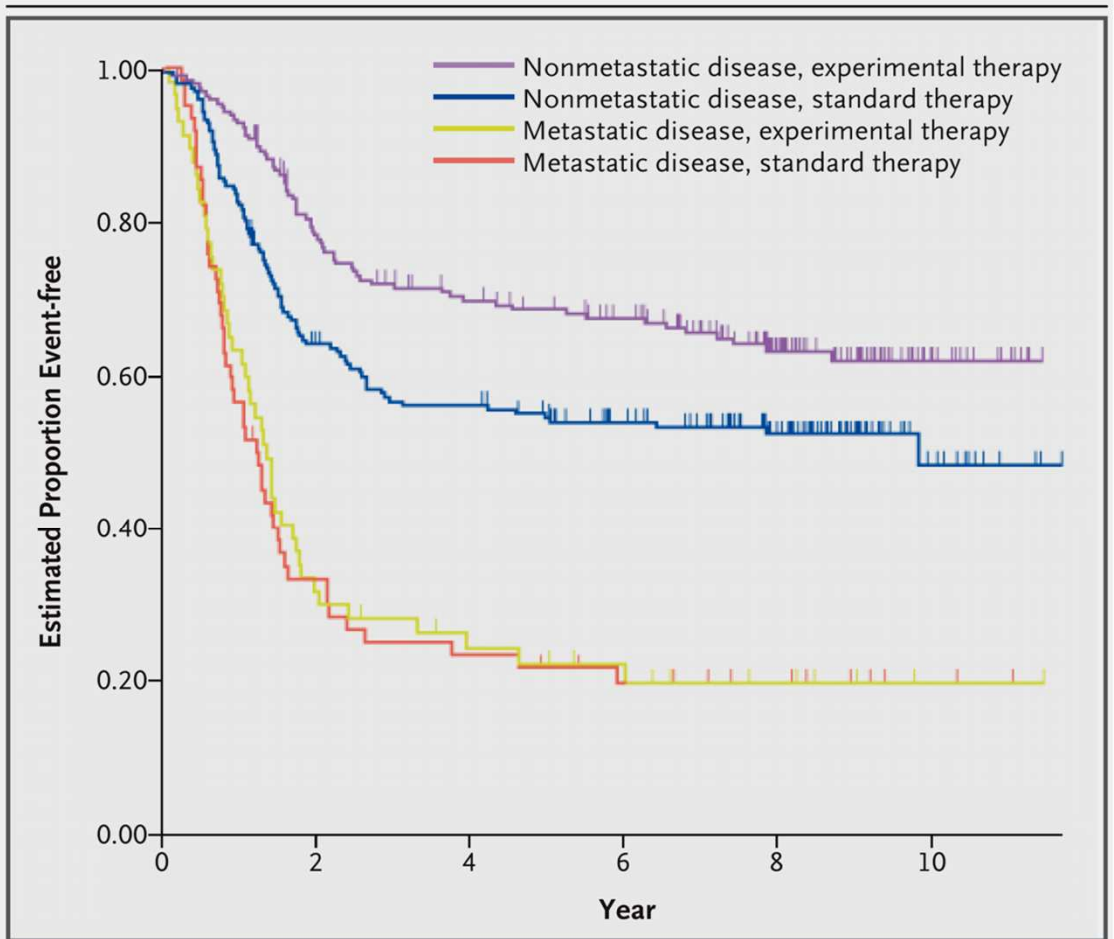


Figure 1. Event-free Survival According to Study Group and the Presence or Absence of Metastatic Disease.

Without Mets

The 5 year EFS

Exper group - 69 %

Standard - 54 %

With Mets

The 5 year EFS

Exper - 22 ± 5 %

Standard - 22 ± 6 %

Holcombe E. et al N Engl J Med 2003;348:694-701

RESULTS

- Addition of I+E to VACD improved outcomes in patients with Non-metastatic Ewing's sarcoma BUT not with Metastatic disease

- Improvement was greatest with large primary tumors or primary tumors of the pelvis

LOCAL THERAPY FOR ESFT: EVOLUTION

- 1970s: limited imaging
  - Most patients received radiation therapy
  - Field encompassed the entire medullary cavity of the bone and all soft tissue extensions
  - Dose: 5500-6500Gy

- 1980s: Neoadjuvant chemotherapy/ improved imaging
  - Smaller field size: 3 cm margin in current trials
  - Improved technique/better machinery
  - Dose: 4500-6500Gy
  - New surgical options available
    - Prosthesis

Sx vs. XRT: RETROSPECTIVE REVIEWS

- Patients who undergo primary surgery have a better prognosis than patients who receive XRT

  (Pritchard et al. Mayo 1912-1968, 1975 and Wilkins Mayo 1969-1982, 1986)

  Selection bias: patients with smaller tumors and better prognostic sites are more likely to have surgery

- Patients who receive surgery/XRT have better prognosis than XRT alone (Sailer, MGH 1988)

  - 92% survival with surgery vs. 37% survival without surgery, significant on univariate analysis

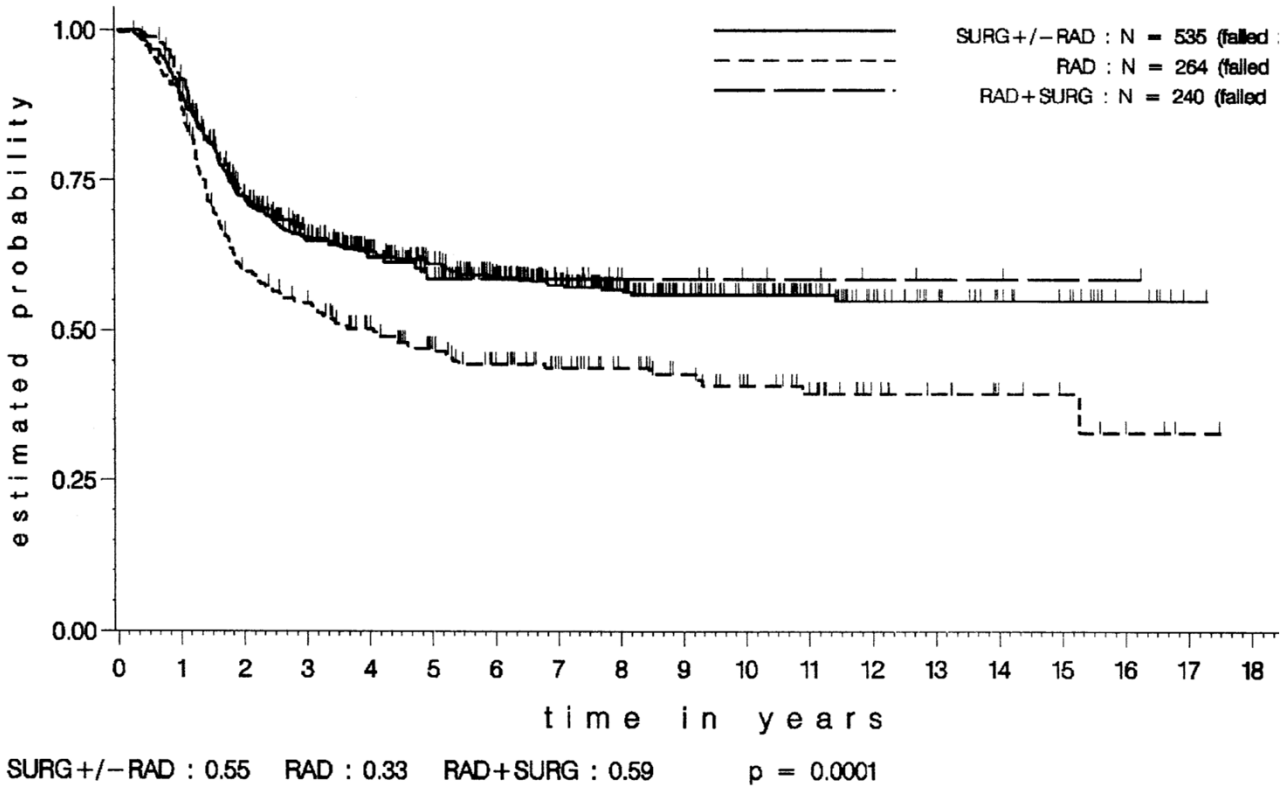
Local and combined local and systemic relapses according to local therapy modality

	Definitive RT	Preoperative RT	Surgery with or without postoperative RT	Surgery without postoperative RT	Surgery with postoperative RT
CESS 81, CESS 86, EICESS 92	70/266 (26.3)	13/246 (5.3)	41/546 (7.5)	10/242 (4.1)	31/304 (10.2)
CESS 86, EICESS 92	50/222 (22.5)	11/239 (4.6)	29/452 (6.4)	5/192 (2.6)	24/260 (9.2)
Central	44/188 (23.4)	10/118 (8.5)	36/251 (14.3)	6/71 (8.5)	30/180 (16.7)
Proximal	14/46 (30.4)	0/59 (0)	2/138 (1.4)	1/77 (1.3)	1/61 (1.6)
Distal	12/32 (37.5)	3/69 (4.3)	3/157 (1.9)	3/94 (3.1)	0/63 (0)
Tumor volume (cm^3)					
<100	17/93 (18.3)	2/85 (2.4)	12/172 (6.9)	5/82 (6.1)	7/90 (7.8)
≥ 100	39/137 (28.5)	10/150 (6.7)	21/314 (6.6)	3/133 (2.3)	18/181 (9.9)
Radical resection	—	0/4 (0)	1/68 (1.4)	1/63 (1.6)	0/5 (0)
Wide resection	—	8/165 (4.8)	19/318 (5.9)	6/145 (4.1)	13/173 (7.5)
Marginal resection	—	0/30 (0)	4/70 (5.7)	1/18 (5.6)	3/52 (5.8)
Intralesional resection	—	1/14 (7.1)	11/51 (21.5)	2/7 (28.6)	9/44 (20.5)
Good histologic response after initial chemotherapy	—	—	14/282 (4.9)	3/154 (2)	11/128 (8.6)
Poor histologic response	—	—	11/150 (7.3)	3/46 (6.5)	8/104 (7.7)

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



. EFS according to local therapy in CESS 81, CESS 86, and EICESS 92.

Definitive RT : reduced EFS

ANDREAS SCHUCK, et al ; IJROBP, 55(1),168–177, 2003

LOCAL THERAPY & EFS

Study	% 5yr EFS				local therapy in %		
	all	Sx	Sx+RT	RT	Sx	Sx+RT	RT
CESS 81	54 ± 10%	55 ± 18%	67 ± 17%	44 ± 17%	34	32	34
CESS 86	61 ± 7%	62 ± 15%	63 ± 10%	58 ± 15%	22	53	25
EICESS 92	64 ± 6%	72 ± 13%	66 ± 7%	46 ± 13%	15	65	20

RADIOTHERAPY - INDICATIONS

Definitive Radiotherapy

Location (Unfavourable): Axial, Pelvic with involvement of adjacent joints

Intralesional resection expected

Post-op adjuvant Radiotherapy

Gross or microscopic positive margin

Poor histological response to chemo

Pre Treatment Fracture/ Hematoma/ Tissue Violation

TARGET VOLUME

Phase I (Large volume) (45Gy/ 25#/ 5wks):

Pre-chemotherapy tumor volume on MRI + 1.5-3 cm longitudinal margin

Appropriate modifications into cavities or the lung

Phase II (Boost) (10.8Gy/ 6#/ 2wks):

Post-operative/ Post - CTh gross residual disease + 1.5–2 cm margins

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

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PII S0360-3016(98)00191-6

● *Clinical Investigation*

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

SARAH S. DONALDSON, M.D.,* MARGARET TORREY, M.D.,* MICHAEL P. LINK, M.D.,*
ARVIN GLICKSMAN, M.D.,† LOUIS GILULA, M.D.,‡ FRAN LAURIE, B.S.,† JOHN MANNING, M.D.,§
JAMES NEFF, M.D.,‖ WILLIAM REINUS, M.D.,‡ ELIZABETH THOMPSON, M.D.,#
JONATHAN J. SHUSTER, PH.D.¶

- 178 eligible patients
- 141 (79%) had localized disease and 37 (21%) had metastatic disease
- 37 of the localized patients underwent resection
  of whom 16 (43%) required postoperative radiotherapy
- Remaining 104 localized patients were
  eligible for randomization to receive radiotherapy

- 94 patients received radiotherapy.
- Forty patients were randomized to receive
- either Whole bone (n = 20) vs. Involved field (n = 20) RT

- Outcome by treatment field

- 5-year EFS: Whole bone 37%
  Involved Field 39%

- Conclusion: Tailored Portals for Radiotherapy in Ewing's Sarcoma

POST-OP ADJUVANT RADIOTHERAPY

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

TIMING OF POST-OPERATIVE RADIATION

In an analysis of patients receiving PORT in the CESS 86 and EICESS trials,

Schuck et al
No significant difference in the local control and survival who received RT within 60 days of surgery or later.

Dunst J et al
Improved local control in CESS 86 over CESS 81
timing of RT was brought forward from the 18th week to the 10th week

Schuck A,. Strahlenther Onkol 2002;178:25–31.

Dunst J, Results of CESS 81 and CESS 86. Cancer 1991;67:2818–2825

DOES PORT ACTUALLY BENEFIT PATIENTS WITH POOR RESPONSE TO CHEMOTHERAPY?

The EICESS 92 – first cooperative group include poor histologic response (<90% necrosis) as an indication for PORT even with clear surgical margins.

Reduction in local failures (5% vs. 12%) in the poor responders if they received PORT

Schuck A: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. IJROBP 2003;55:168–177.

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

MANAGEMENT OF PULMONARY METASTASES

- Whole Lung Irradiation
  - Biologic effect observed in randomized trials following 1500-1800 rads in non-metastatic patients in IESS-1
    - 5 yr. RFS
      - VACA 60%>
      - VAC + Pulm XRT 44%
      - VAC 24%

      (Nesbit 1990)

  - Dose response effect reported between 12-21Gy (Dunst, 1993) using historical, non-randomized analyses

  - Retrospective Analysis of CESS 81,CESS 86,CESS 92 (Paulssen, JCO 1998)
    - Improved survival in patients with metastatic disease who receive whole lung irradiation
    - Independent prognostic factor in Cox analysis but not logistic regression analysis
  - Long term morbidity not well defined
  - Standard treatment arm on current EuroEwing's Trial for patients with pulmonary metastases

WHOLE LUNG RT (LUNG BATH) FOR LUNG METS

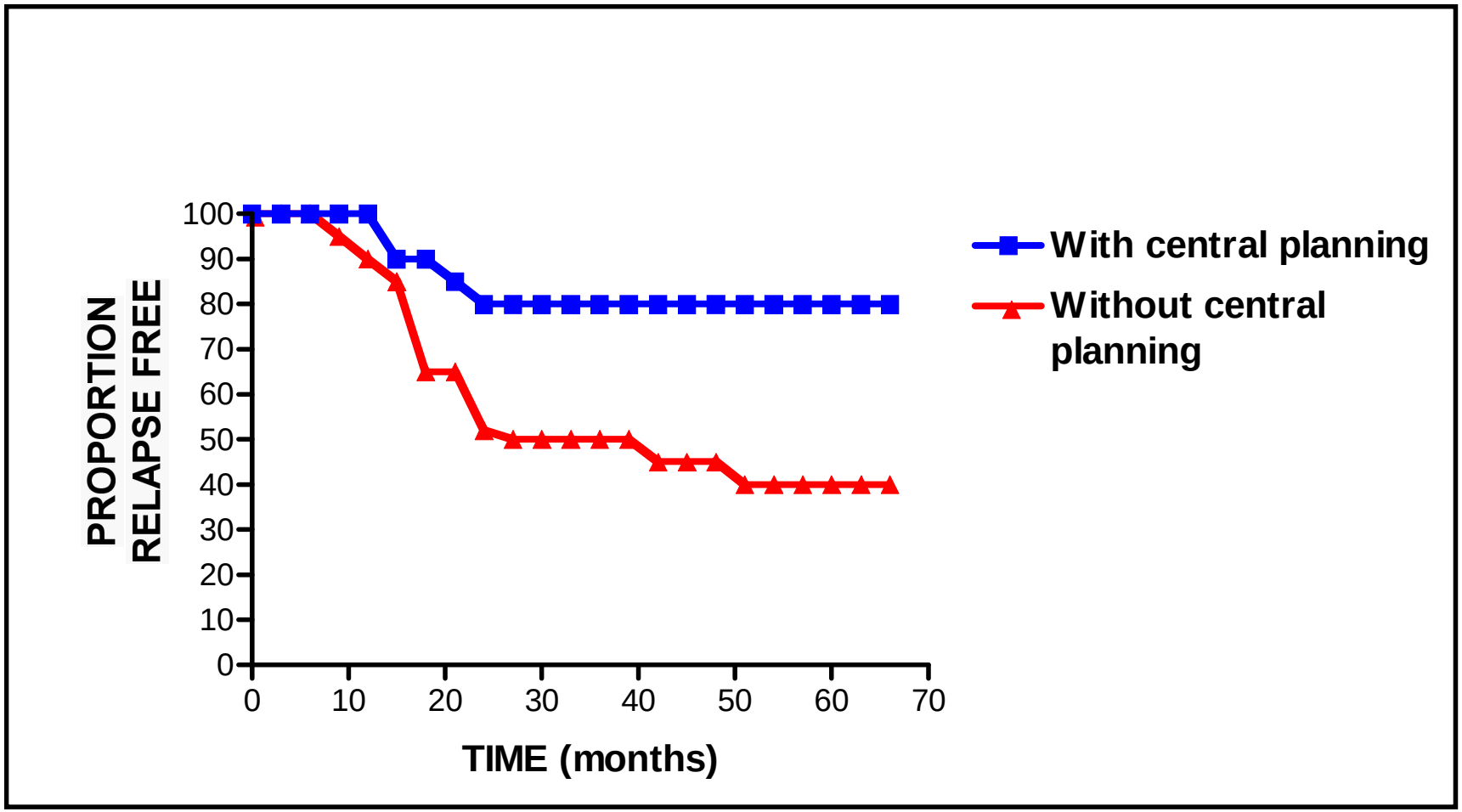
- Analysis EI-CESS 92 trial

- Lung Mets (5 year EFS):

  WLI EFS 47%

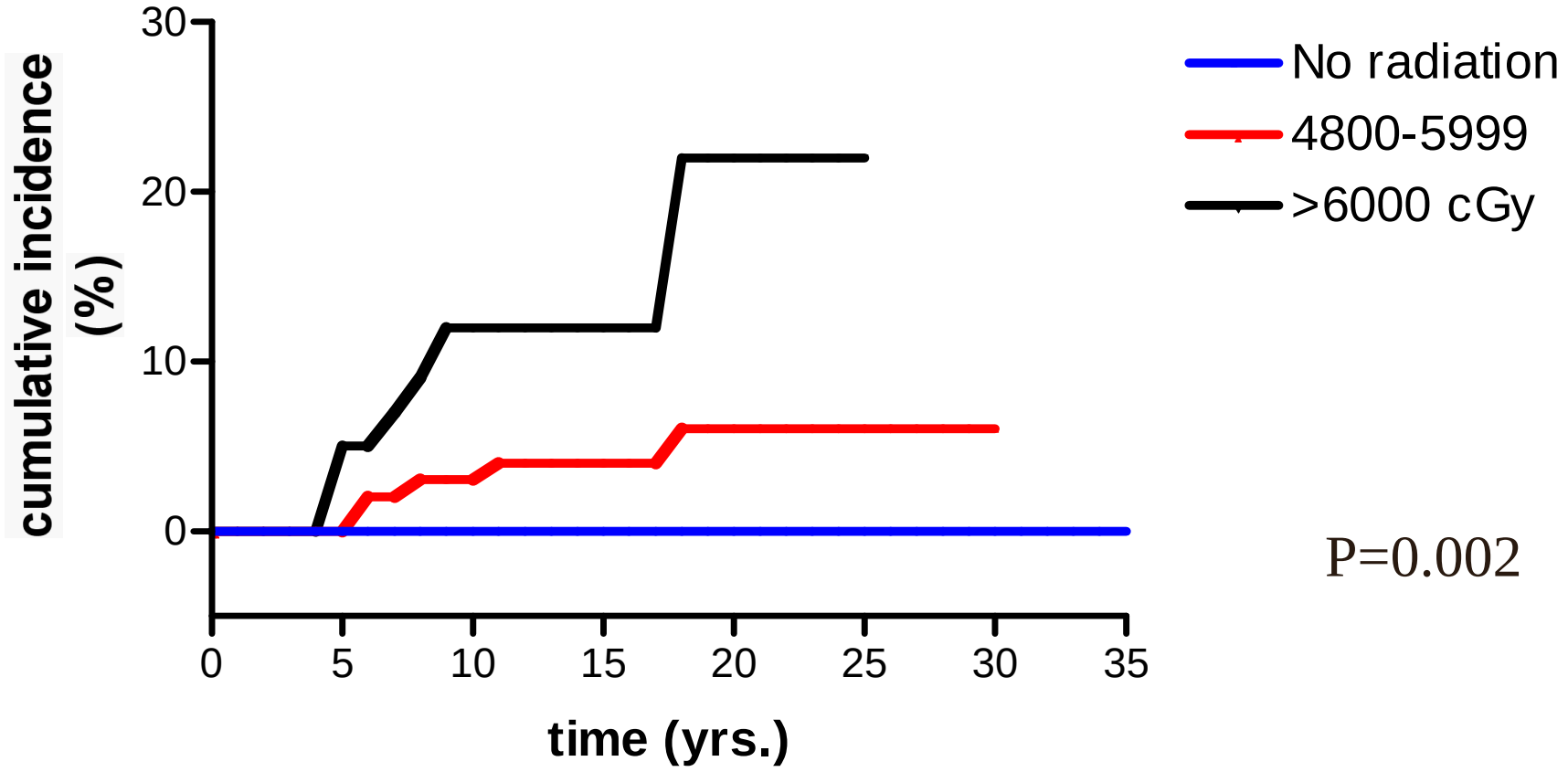
  Without WLI 24%

RADIATION PLANNING OF CRITICAL IMPORTANCE IN THE TREATMENT OF EWING'S SARCOMA (CESS-81)



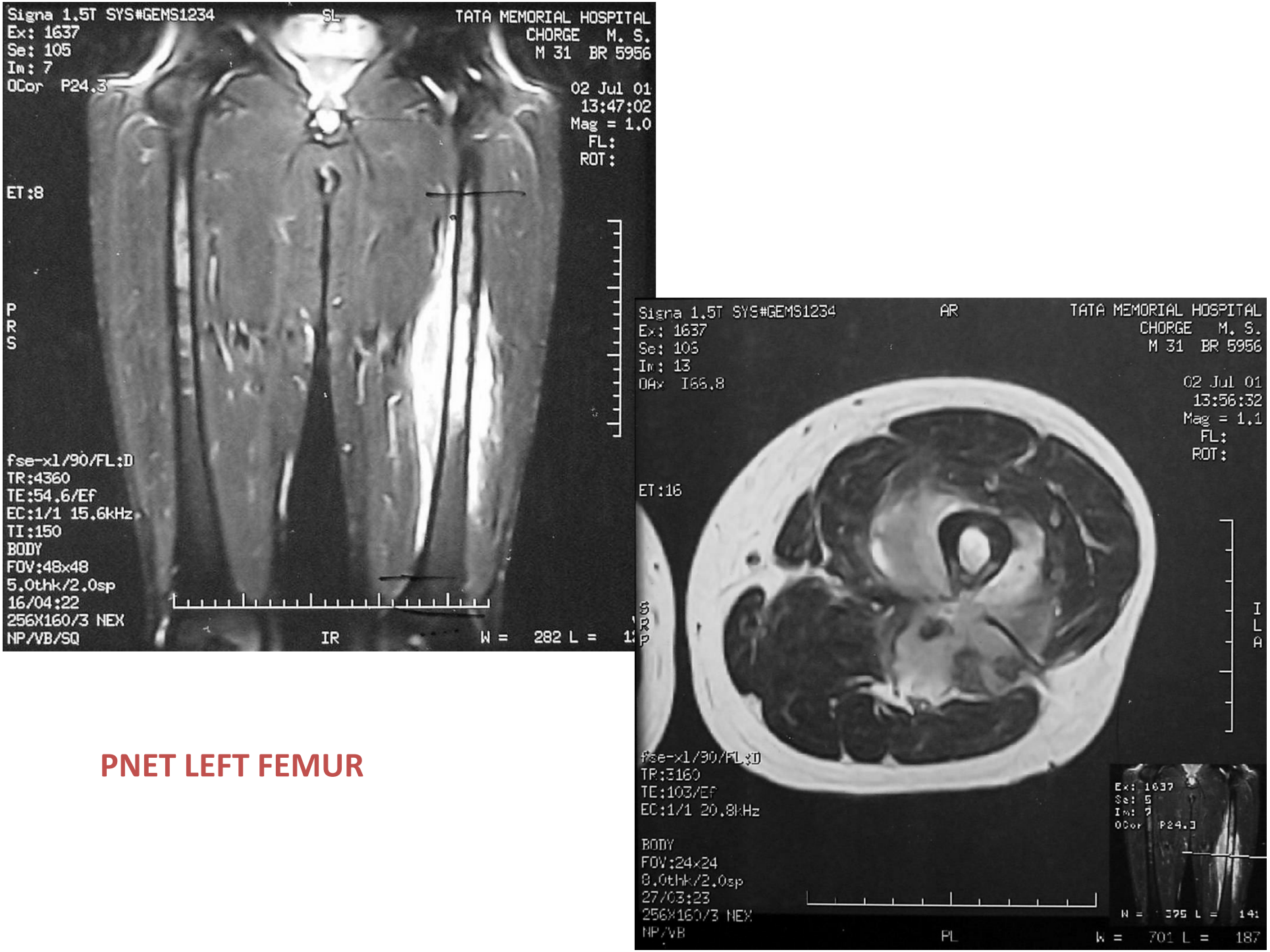
Sauer et al., Radiotherapy and oncology, 1987

SECOND MALIGNANCIES AFTER RADIOTHERAPY

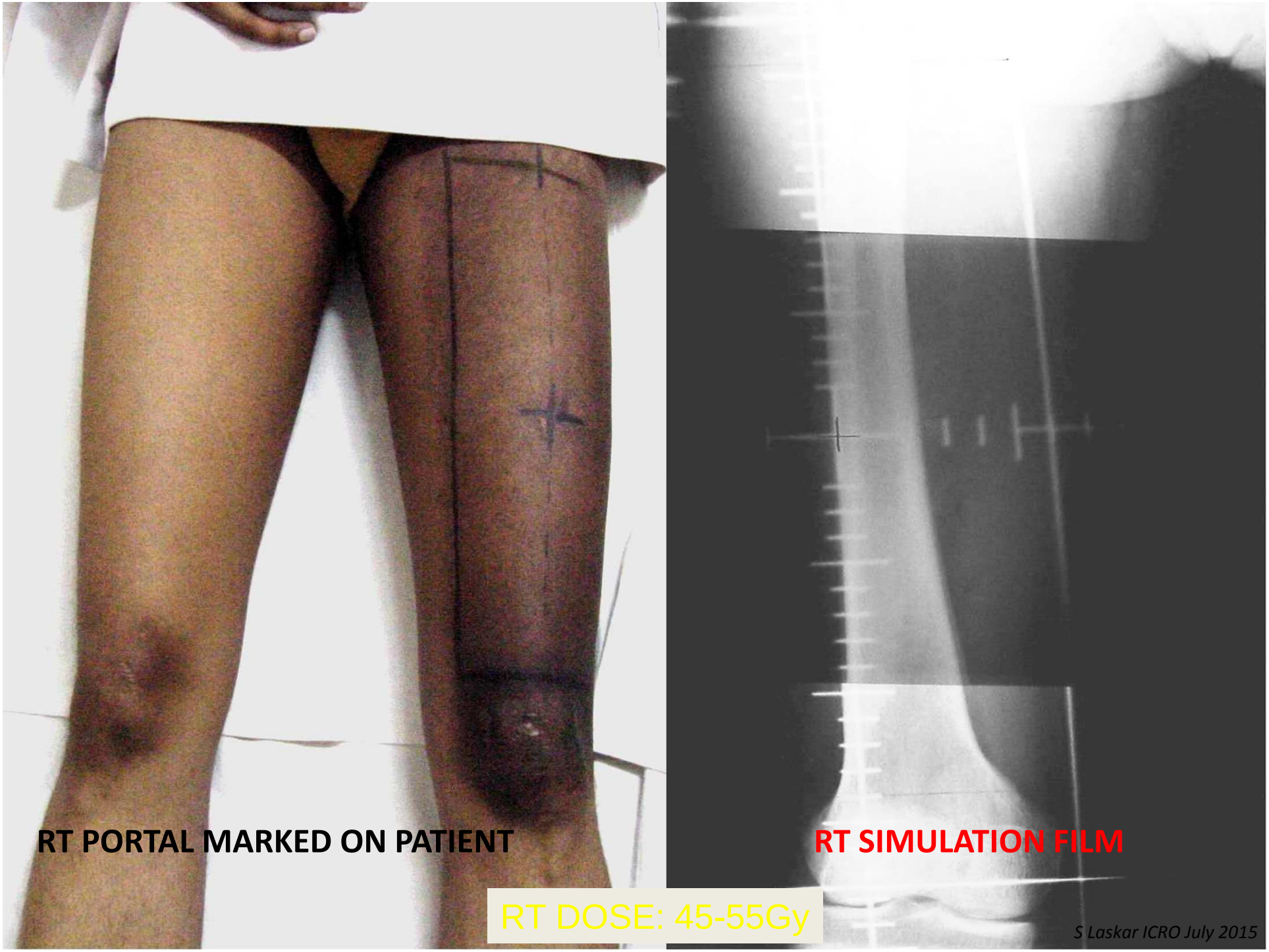


P=0.002

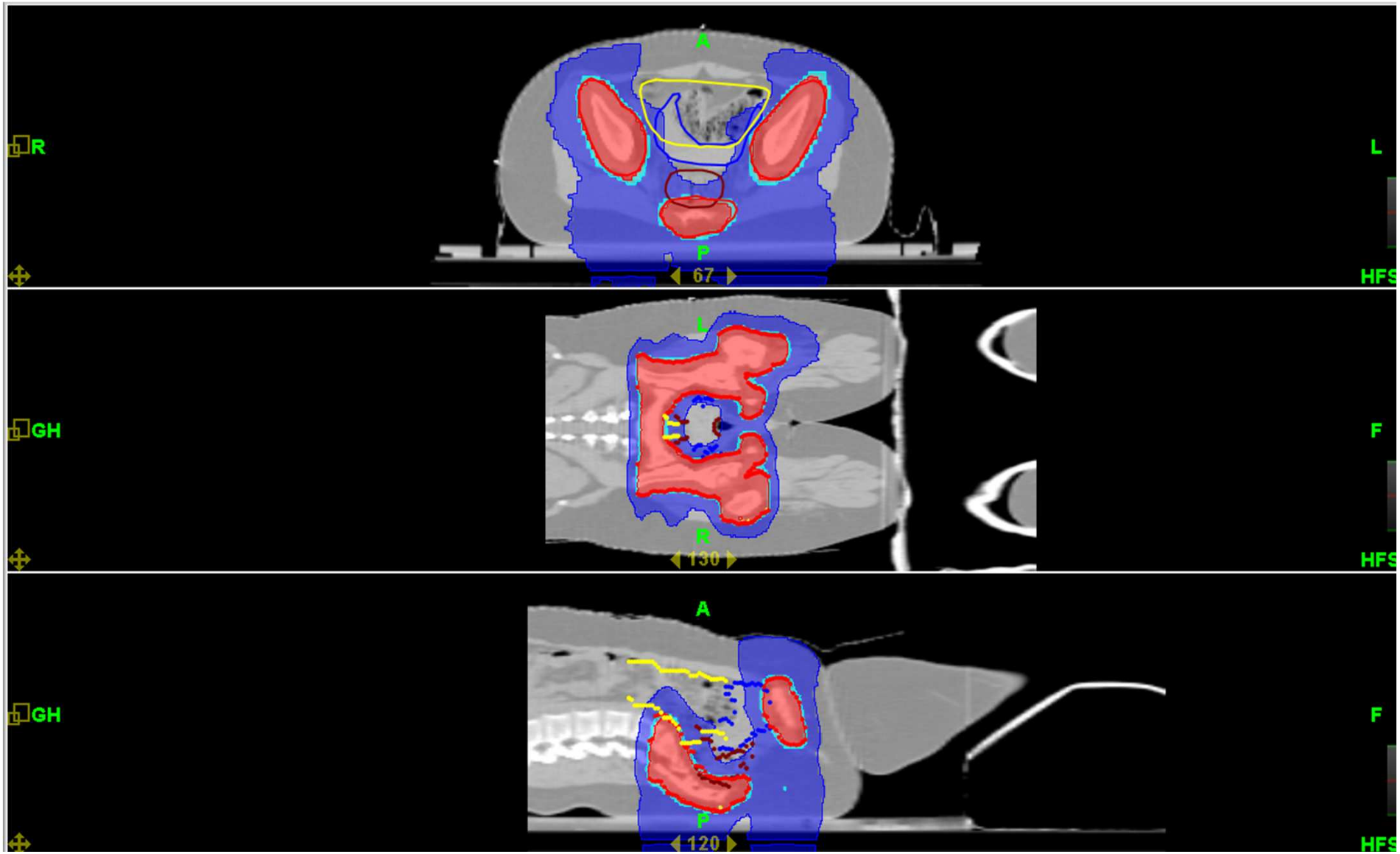
Adapted from Kuttesch, JCO, 1997



PNET LEFT FEMUR


RT PORTAL MARKED ON PATIENT
RT SIMULATION FILM
RT DOSE: 45-55Gy
S Laskar ICRO July 2015

NORMAL TISSUE SPARING USING ADVANCED TECHNIQUES



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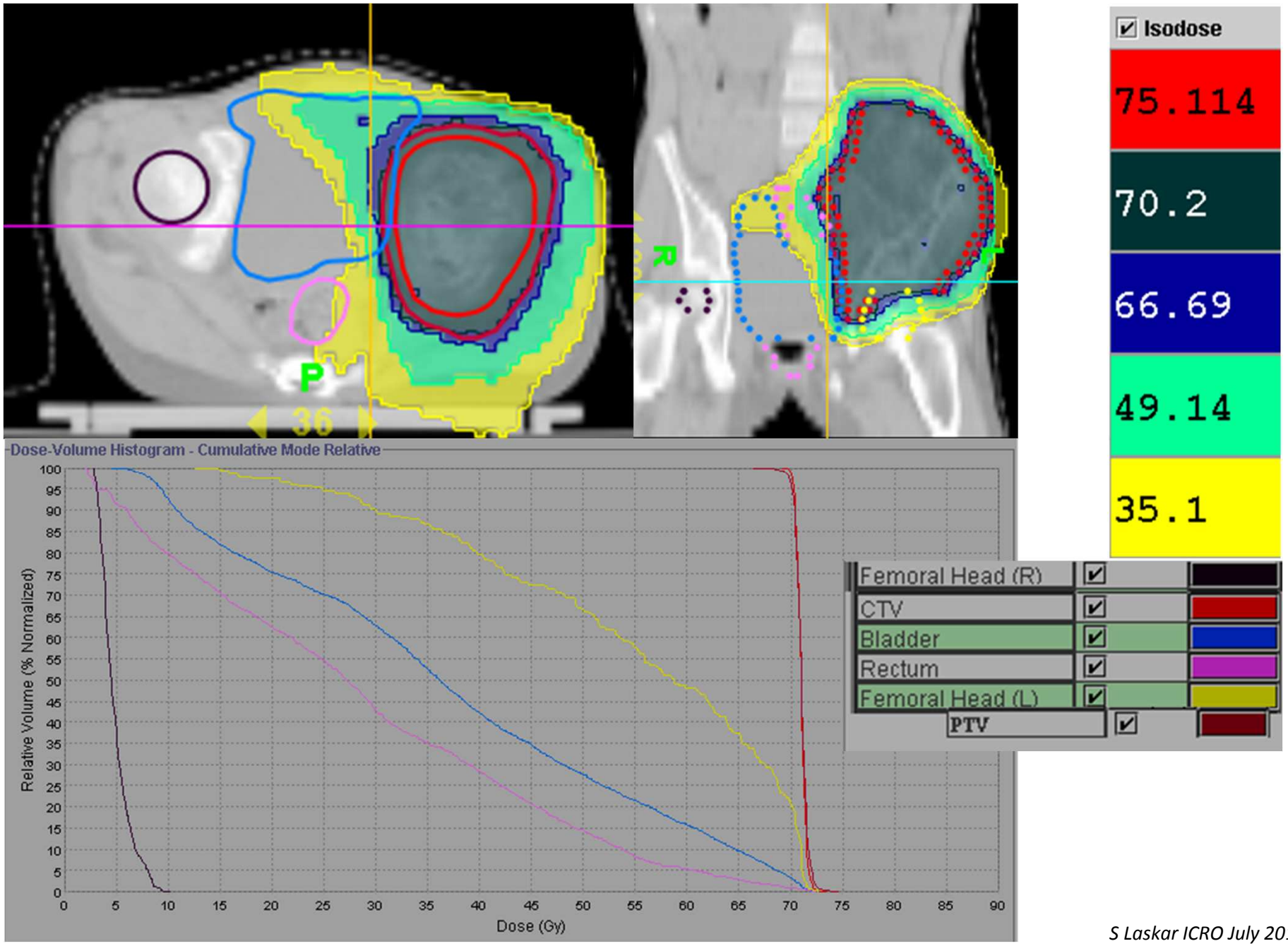
RT DOSE ESCALATION USING ADVANCED TECHNIQUES



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SUMMARY & CONCLUSIONS

- Ewing's sarcoma is best managed with multimodality approach comprising multiagent chemotherapy & local therapy (Surgery/ Radiotherapy).
- Organ & function preserving surgery remains the standard local therapy wherever feasible with negative surgical margins.
- Radiation therapy forms an important component of therapy for achieving optimal local control
- Definitive radiation therapy in patients with surgically inoperable disease can result in good local controls with the use of optimal dose & technique
- Adverse effects of radiation can be reduced significantly using modern radiotherapy techniques like 3D-CRT, IMRT, & Proton beam therapy.