Sarcoma of soft tissue

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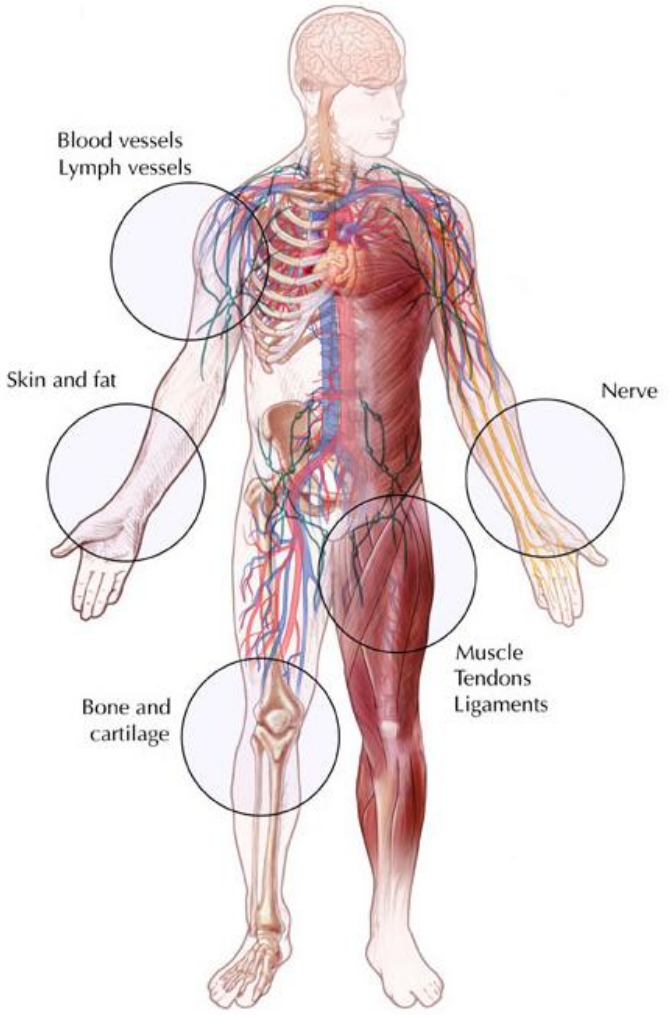
Soft Tissue Sarcomas:Definition

- Sarcomas are malignant tumors that arise from skeletal and extraskeletal connective tissues (mesenchymal cells).
- Including:
- Adipose tissue
- Bone
- Cartilage
- Smooth muscle
- Skeletal muscle



Soft Tissue Sarcomas: Statistic

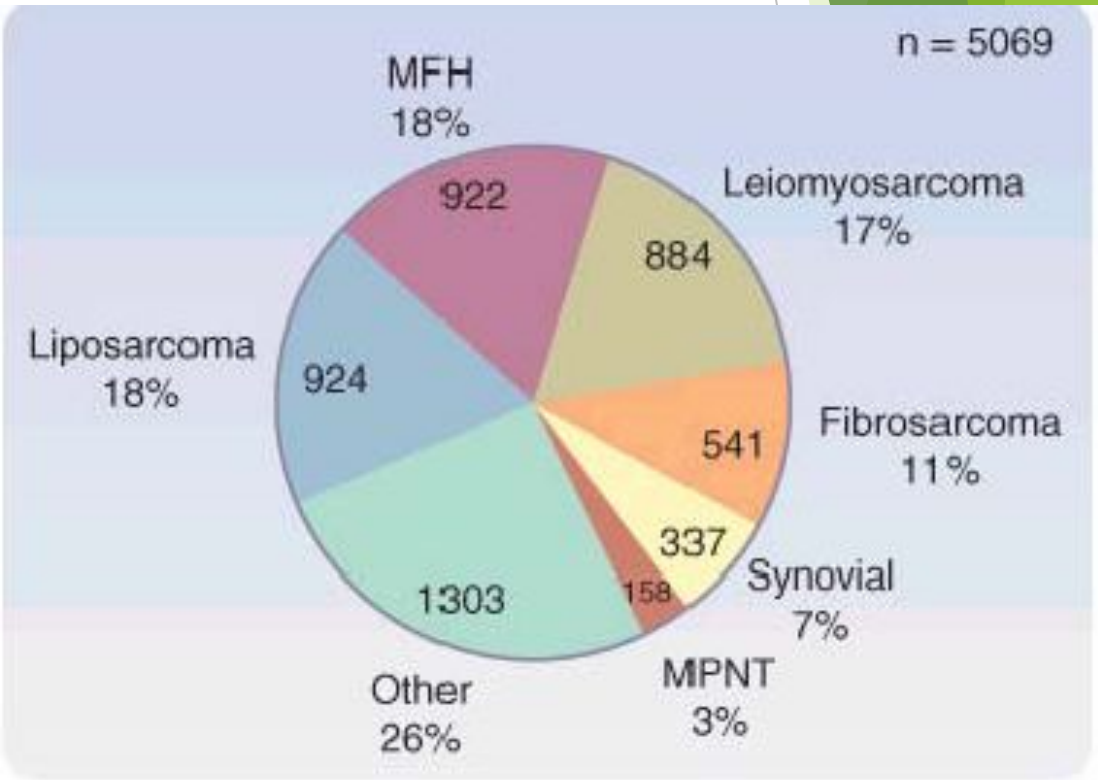
- Rare and unusual cancer.
- About 1% of adults human cancers
- 15% of pediatric malignancies
- Most commonly occur in the extremities (50%)
- Other sites: Abdominal cavity/ retroperitoneum, Trunk/ thoracic region and head and neck.

Soft Tissue Sarcomas: Histology

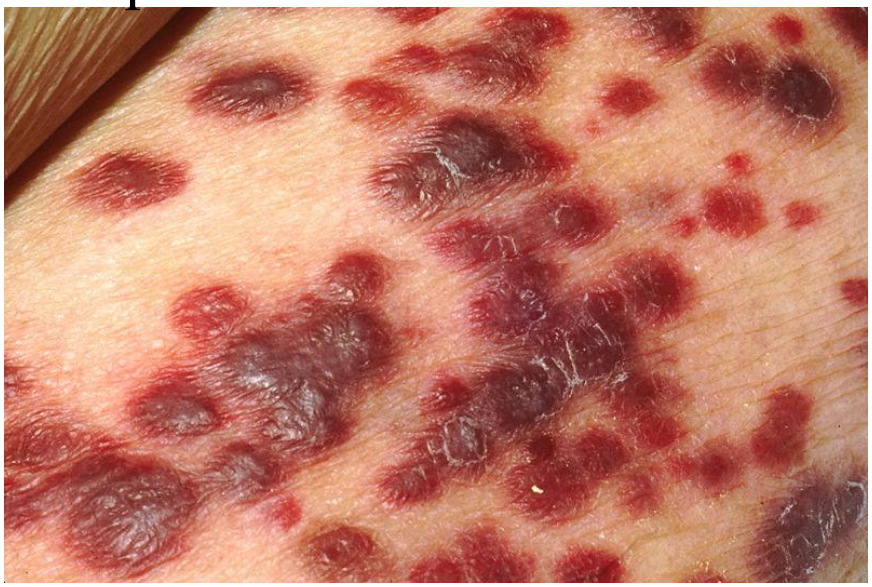
Cell of origin	*Sarcoma type*
Adipocyte	Liposarcoma
Fibrohistiocyte	Malignant fibrous histiocytoma
Fibroblast	Fibrosarcoma
Smooth muscle	Leiomyosarcoma
Skeletal muscle	Rhabdomyosarcoma
Vascular	Angiosarcoma, Kaposi's
Synovial	Synovial sarcoma
Melanocyte	Malignant melanoma
Unknown	Ewing's sarcoma, Epithelioid sarcoma

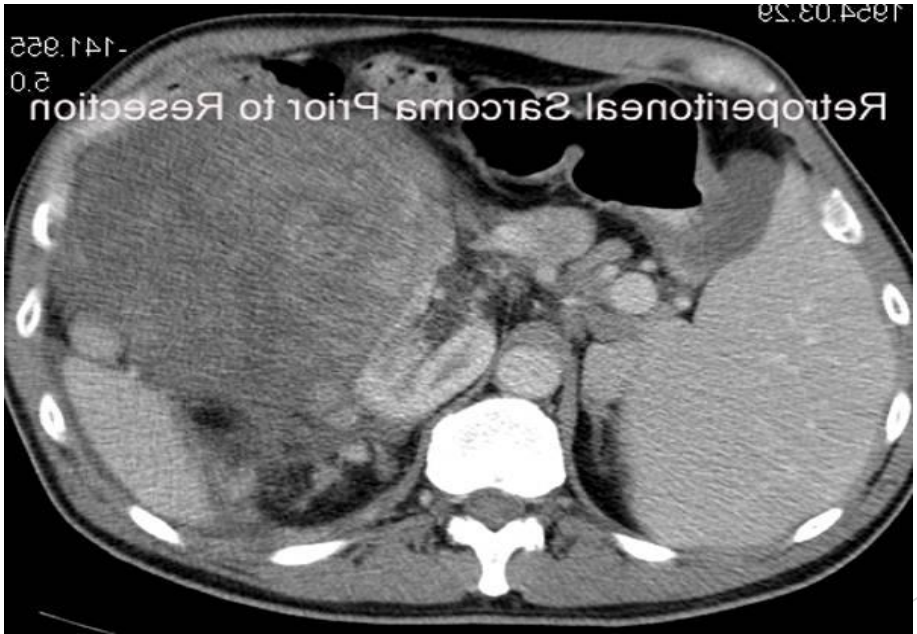
Soft Tissue Sarcomas: Histology

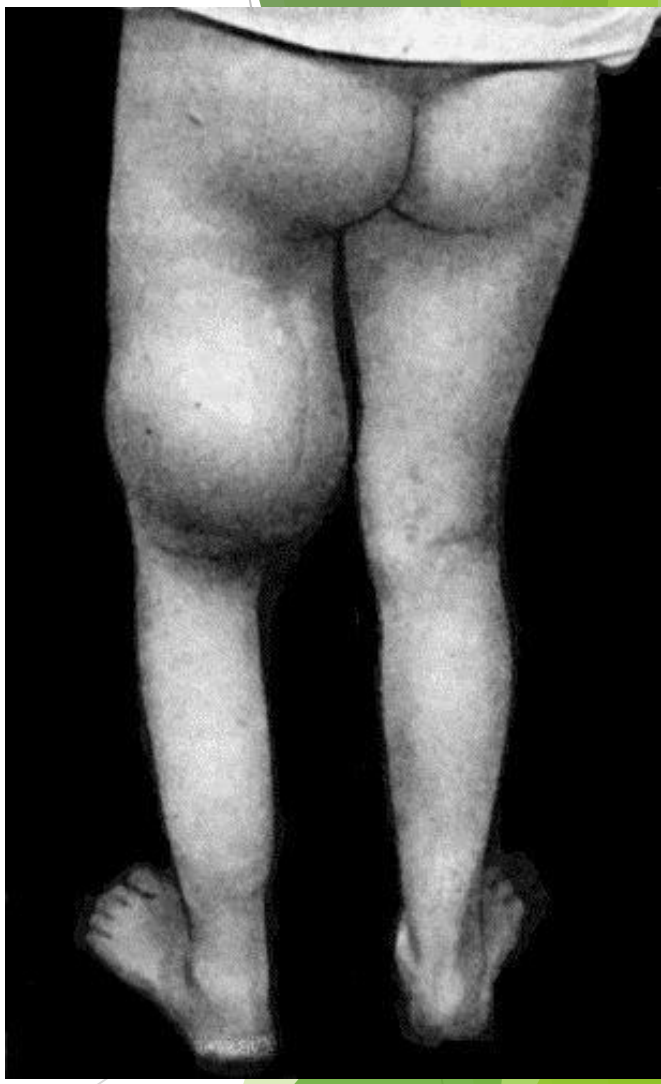
- Histopathology is determined by anatomic site. Common:
- Extremity: Malignant fibrous histocytoma
  liposarcoma
- Retroperitoneal:
- liposarcoma
  leiomyosarcoma
- Visceral: GIST



Kaposi’s sarcoma







PNST

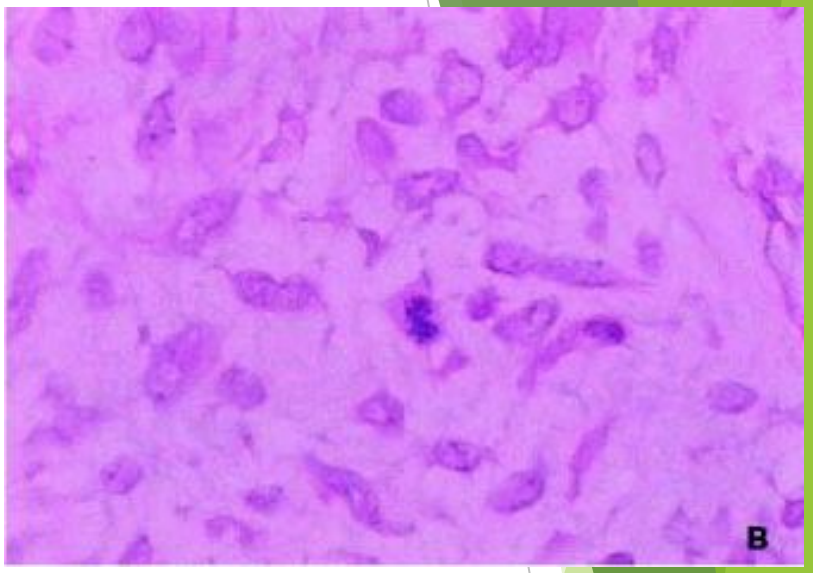
Sarcomas: Age as factor in Histology

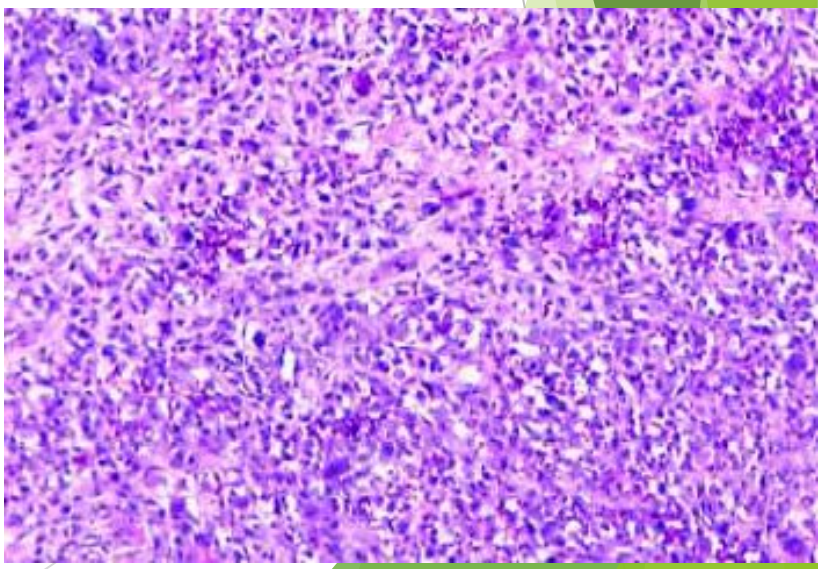
- Childhood: embryonal rhabdomyosarcoma
- Bone: Ewing's sarcoma, osteosarcoma
- Synovial sarcoma is more likely to be seen in young adults (<35 years old)
- Liposarcoma, MFH are the predominant types in the oldest population

STS-Grade

The biologic behavior of sarcomas is extremely variable

Histologic grade is a major prognostic factor
Based on degree of mitosis, cellularity, presence of necrosis,
Differentiation, stromal content

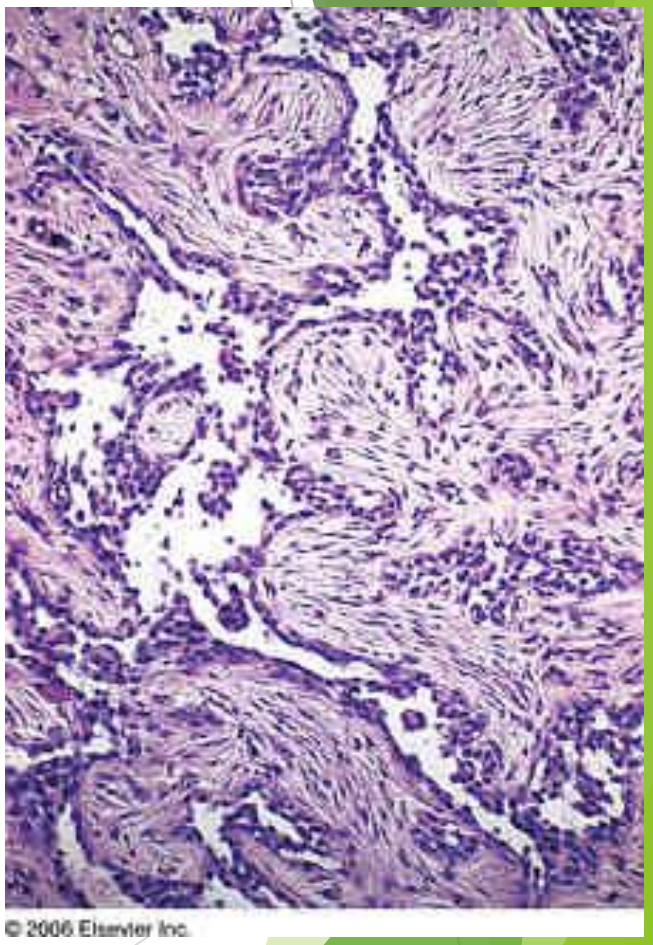




Low-grade sarcomas

Better differentiated, less cellular, tend to resemble the tissue of origin in some extent, mitotic rate is low

Grow slower, low risk of metastasis, a high risk of local recurrence after surgical removal

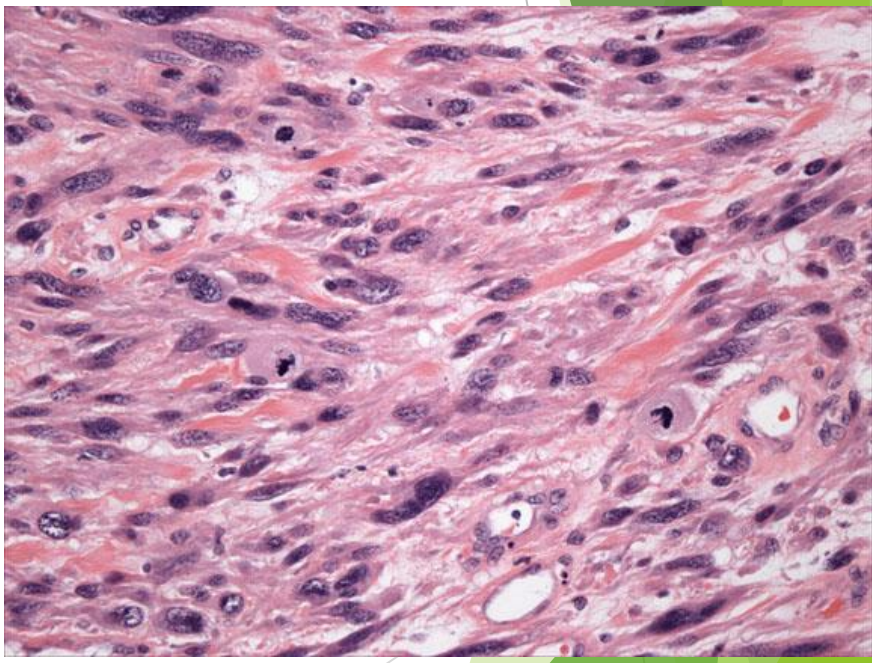


Fibromyxoid sarcoma

High grade-sarcoma

Highly cellular, poorly differentiated, mesenchymal cells with marked nuclear abnormality, high mitotic rate, anaplasia

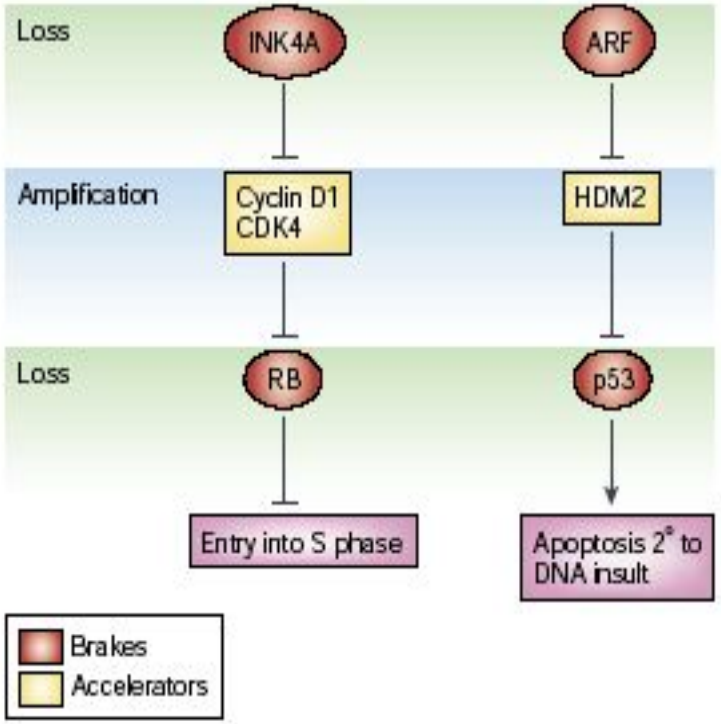
Grow rapidly, show extensive local invasion, metastasize early through bloodstream



Leiomyosarcoma

STS-Genetic risk factors

- Neurofibromatosis-Von Recklinghausen's disease
- Li-Fraumeni syndrome
- Retinoblastoma
- Gardner's syndrome

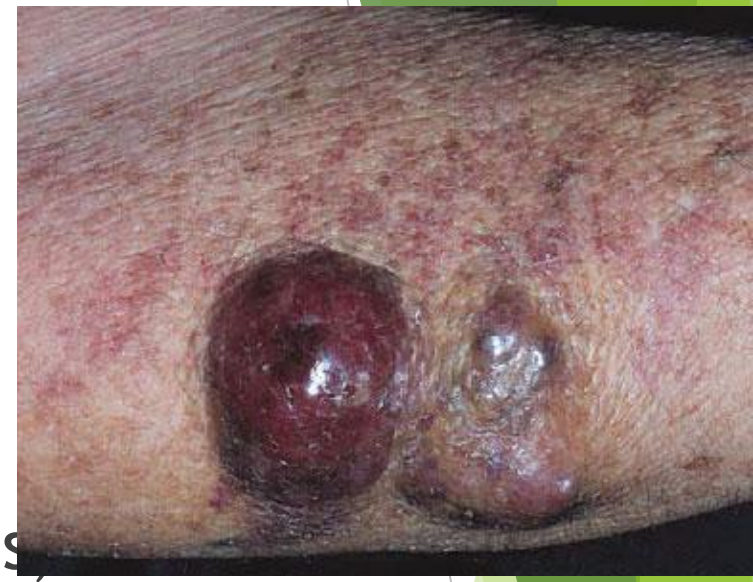


Phosphorylation of RB
50% of sarcomas

Inhibition of p53
60% of sarcomas

STS- risk factors

- Radiation Exposure
- Lymphedema
- Post-surgical
- Post-irradiation
- Parasitic infection (filariasis)
- Trauma
- Chemical:
- 2,3,7,8-Tetrachlorodibenzodioxin
- Polyvinyl chloride
- Hemachromatosis
- Arsenic



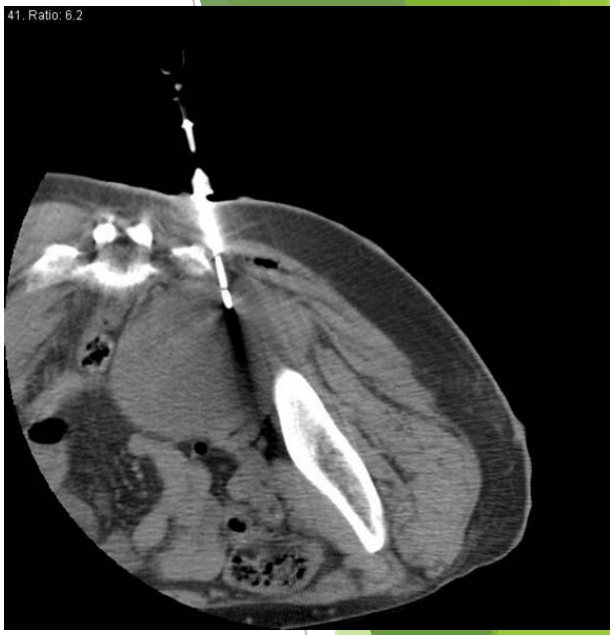
Angiosarcoma

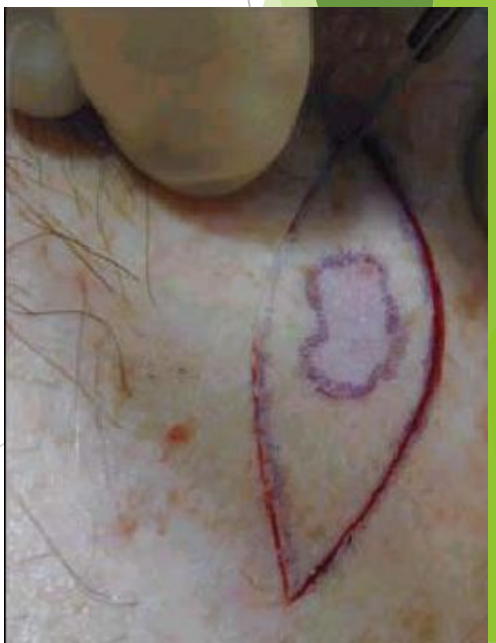
STS-Diagnosis

- Physical examination: assessment of the size of the mass and its relationship to neurovascular and bony structures
- Extremity sarcomas usually present as painless mass.
- Biopsy: any soft tissue mass that is symptomatic or enlarging or any new mass that persists beyond 4 weeks should be sampled.

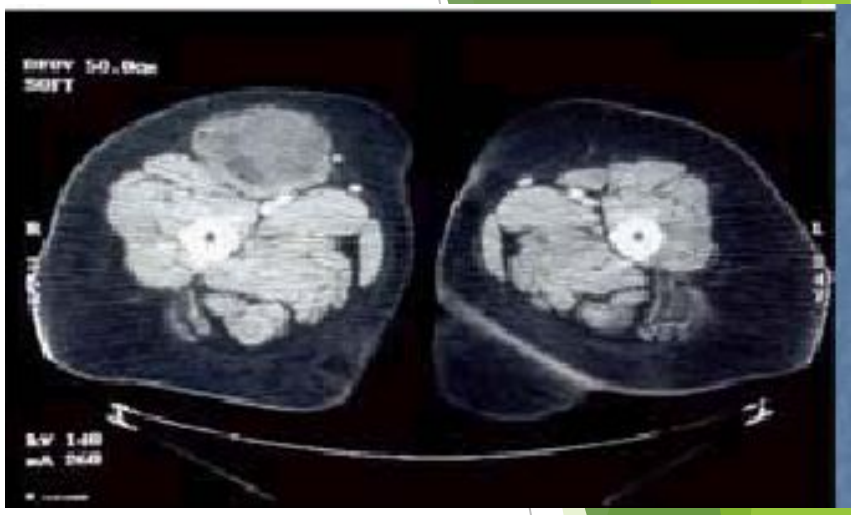
STS-Diagnosis

- Usually incisional or core biopsy preferred
- The incision should be centered over the mass in its most superficial location.





STS-Diagnosis



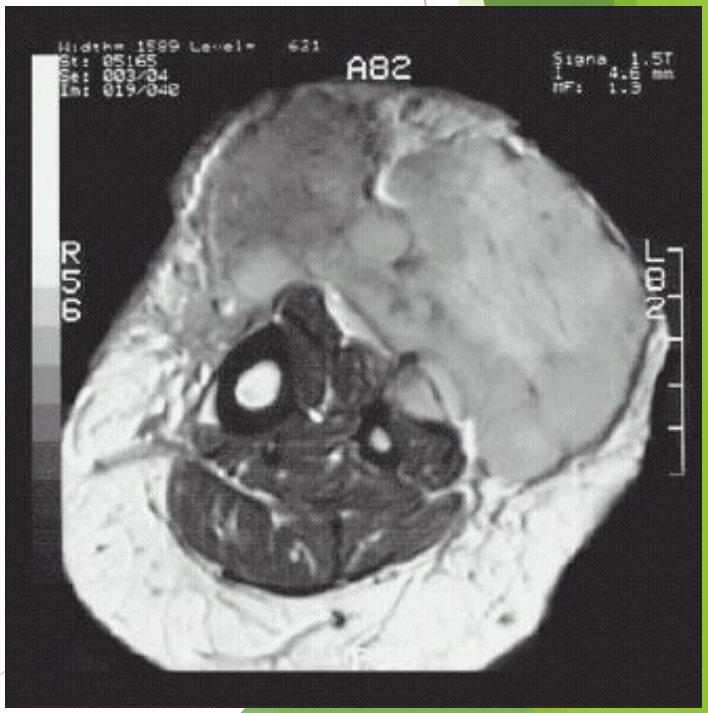
Imaging

MRI preferred

Enhances the contrast between tumor and adjacent structures

Provides excellent 3-dimensional definition of fascial plans

Combination of CT and MR images did not significantly improve accuracy

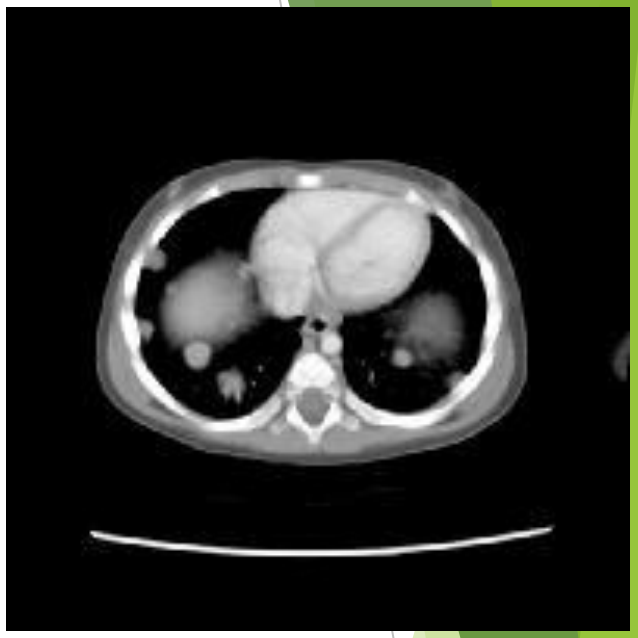


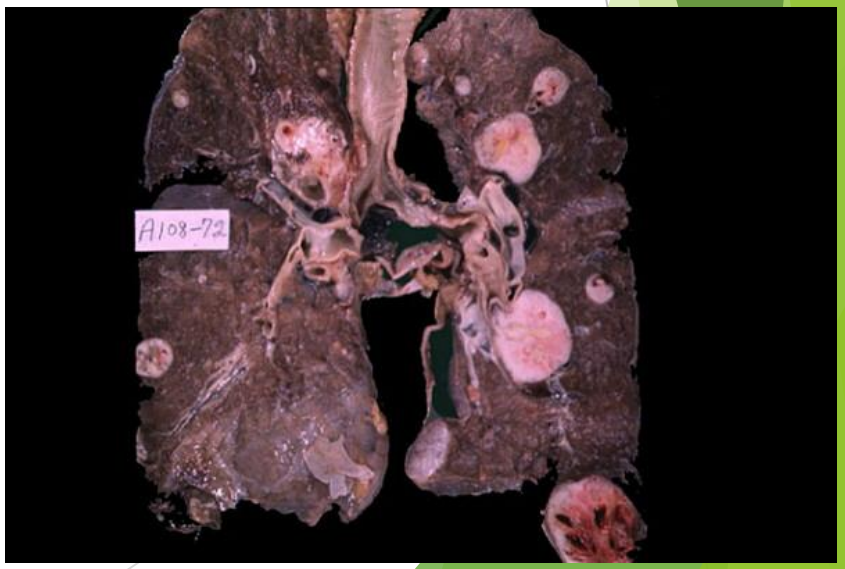
STS-Workup

- Evaluation for sites of potential metastasis:
- LN mets. Occur in less than 3% of adults STS.
- For extremity lesions, lungs is the principal site for mets.
- For visceral lesions the liver is the principal site.
- Low grade STS, the risk for mets.<15%
- High grade STS the risk for mets. >50%

STS-Workup

Extremity-STS:
MRI of the lesion
CT chest,bone scan
Visceral-STS:
MRI if needed
CT chest and abdomen
Childhood sarcomas:
PET-CT
MRI of the primary site
Bone scan if needed
BMB





STS staging

AJCC Staging - Soft Tissue Sarcoma

Histopathologic Grade

GX	Grade cannot be assessed.
G1	Well differentiated.
G2	Moderately differentiated.
G3	Poorly differentiated.
G4	Undifferentiated.

Primary Tumor

TX		Primary Tumor cannot be assessed.
T0		No evidence of primary tumor.
T1		Tumor 5 cm or less in greatest dimension.
	T1a	Superficial tumor.
	T1b	Deep tumor.
T2		Tumor more than 5 cm in greatest dimension.
	T2a	Superficial tumor.
	T2b	Deep tumor.

Note: Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia or superfacial and beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

STS staging

The above four components are combined into the following staging criteria.

Stage Grouping

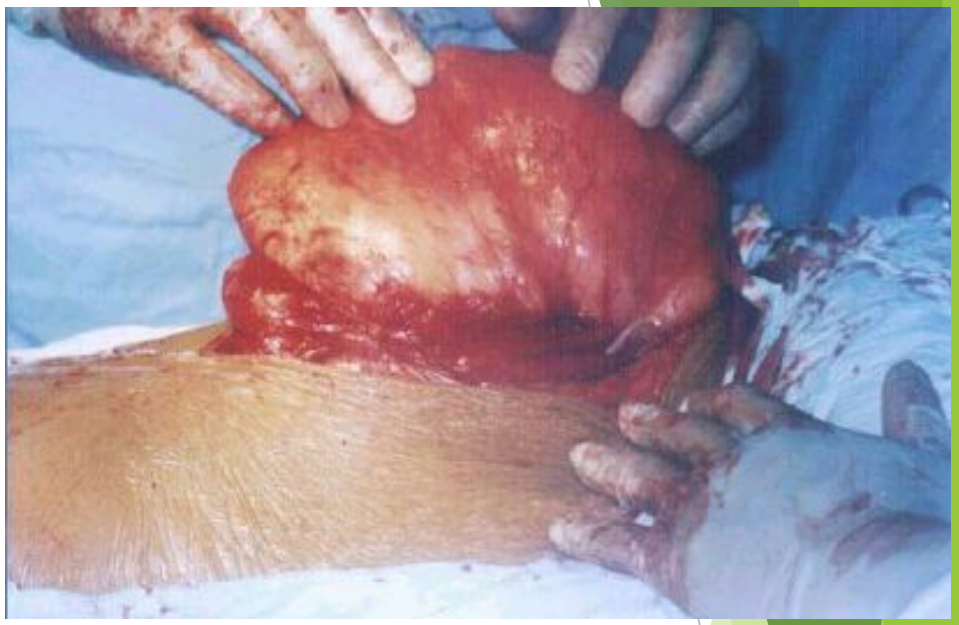
Stage I					
	A (Low grade, small, superficial and deep)	G1-2	T1a-1b	N0	M0
	B (Low grade, large, superficial)	G1-2	T2a	N0	M0
Stage II					
	A (Low grade, large, deep)	G1-2	T2b	N0	M0
	B (High grade, small, superficial, deep)	G3-4	T1a-1b	N0	M0
	C (High grade, large, superficial)	G3-4	T2a	N0	M0
Stage III					
	(High grade, large, deep)	G3-4	T2b	N0	M0
Stage IV					
	(any metastasis)	Any G	Any T	N1	M0
		Any G	Any T	N0	M1

STS-treatment: Surgical excision

- The only hope for cure
- The goal is complete removal of the tumor with negative margins and maximal preservation of function.
- Limb sparing procedures should be preformed, when possible.
- Less radical procedure do not adversely affect local control or outcome

STS-treatment

The best excision with 2-3cm margins.
The centrifugal growth creates pseudo-capsule, malignant cells penetrate this capsule.

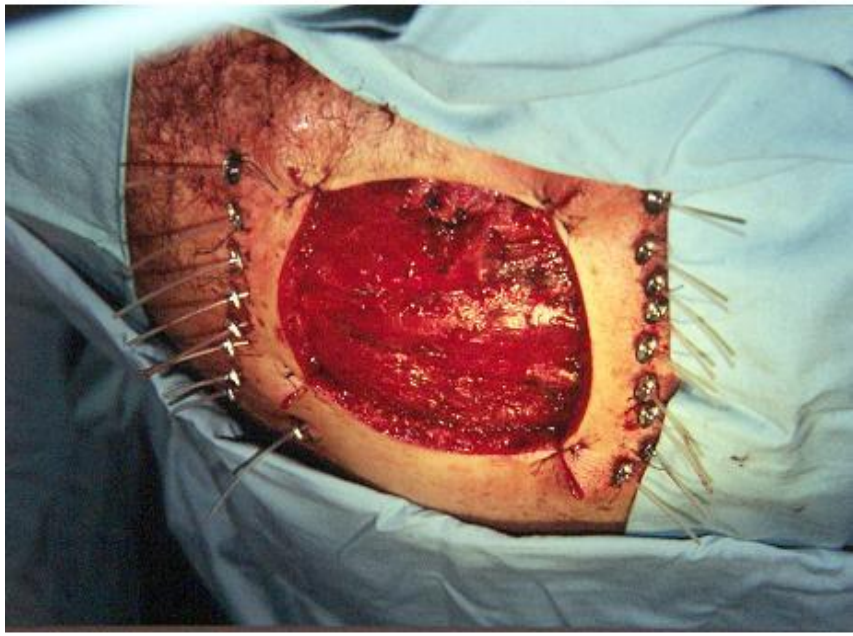


90% recur with only removal of visible tumor.

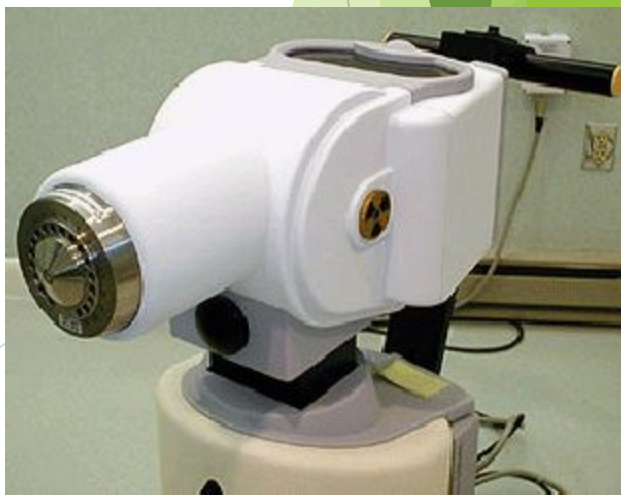
30% recur after excision of tumor bed, without radiotherapy

STS- Radiotherapy

External-beam therapy
Standardized fields



Brachytherapy “seeds of iridium-192



STS- Radiotherapy

- Indications:
- high grade of the limbs
- intermediate grade of the limbs with close or positive margins
- Little role in low grade, should be considered for a recurrence

STS- Radiotherapy

- For survival: Limb conserving+ adj. Radiotherapy= amputation
- Preoperative 50Gy dose.
- Postoperative 60-70Gy dose.
- Pre. Vs. Post: doubling the wound complications, slightly better functional outcome

STS-chemotherapy

- Adjuvant chemotherapy-controversial
- Meta-analysis: improved PFS (15%) but not overall survival (4% n.s.) Doxorubicin base.
- ESFT (childhood-round cell tumors)
- Initial chemo. Improved survival from 10% to 60%.
- Necrosis of 90% confers better outcome
- High dose chemo. With salvage autologous PBPC for recurrence.

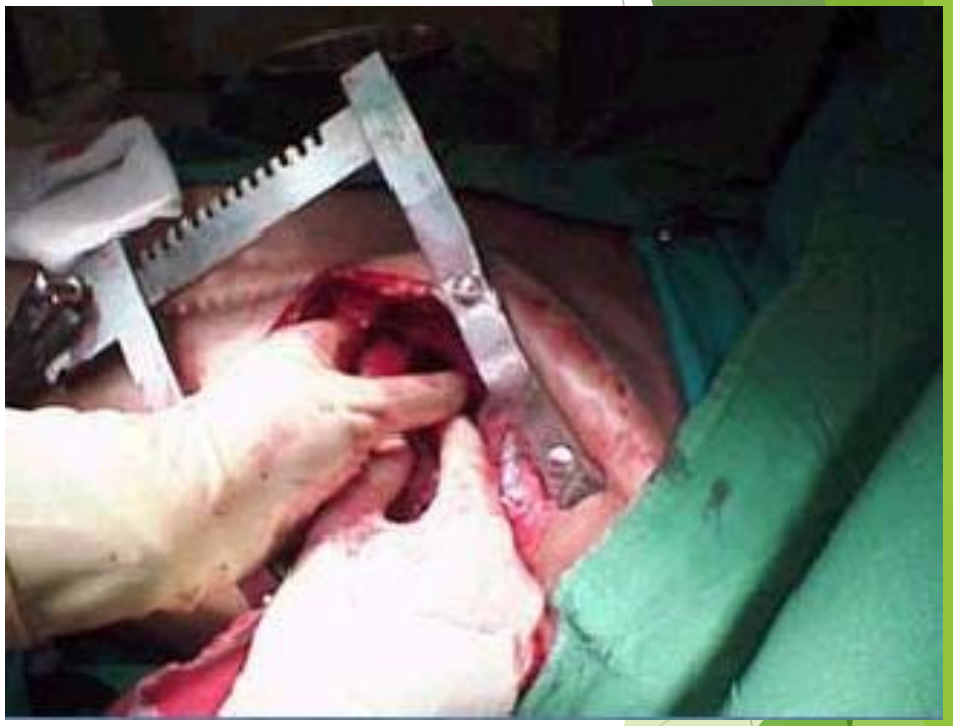
STS- Recurrent disease

- Local extremity rec.: if isolated should undergo resection and adj. Radiotherapy if feasible- 2/3 long term survival

- Distant metastasis:Lungs are the first metastatic site in 73% of rec.
- If possible- metastectomy is the best option

STS- Resection of pulmonary metastasis

Conditions:
primary tumor controlled
No extrathoracic disease
Complete resection of all lung disease appears possible



20%-30% 3 years survival after complete resection

STS-chemotherapy for metastatic disease

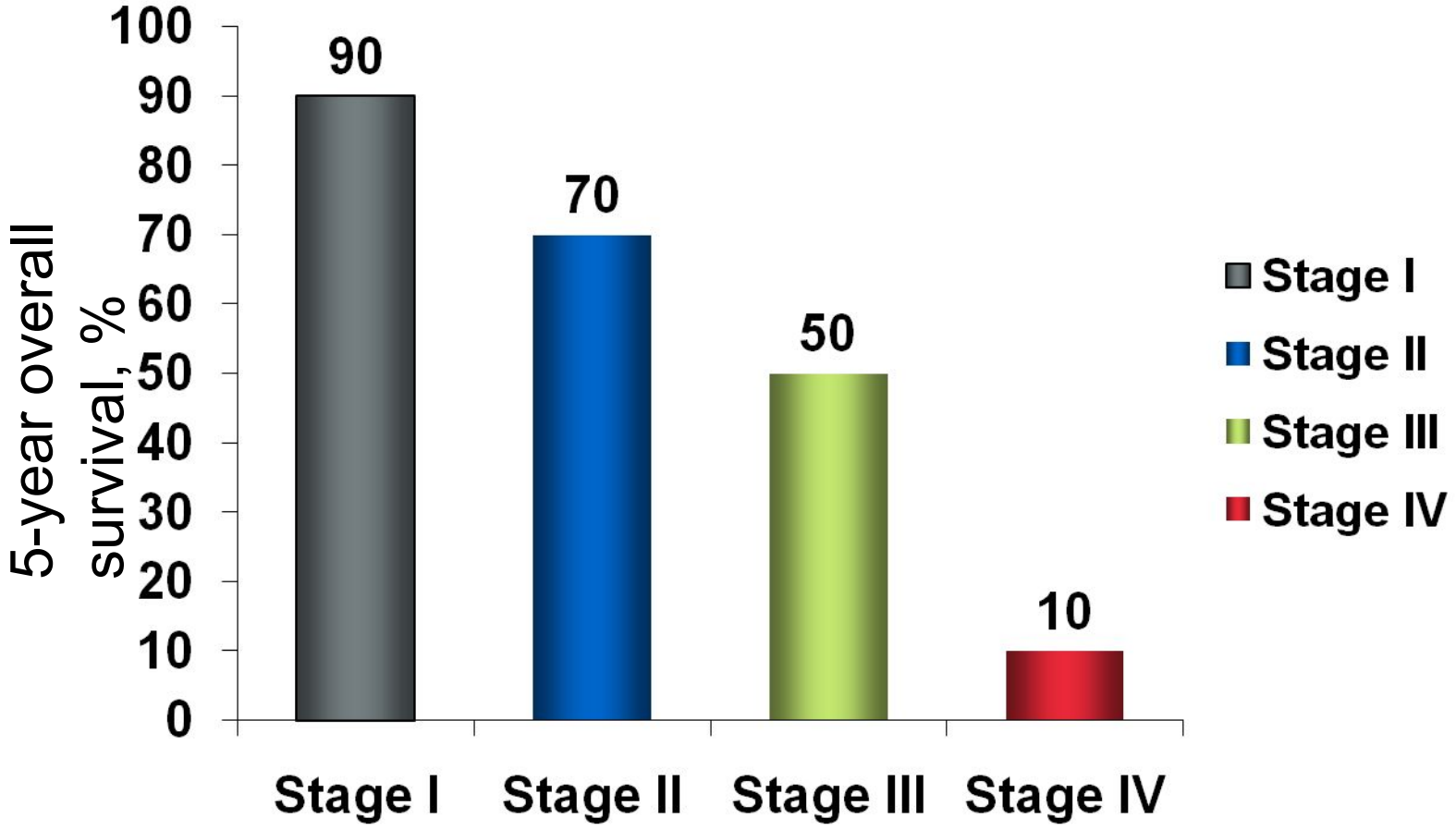
Palliative, not curative therapy
For unresectable pulmonary mets.
Extrapulmonary mets. In more than one site.

Poor prognosis
Median survival less than 1 year

STS-chemotherapy for metastatic disease

- Every STS : adriamycin, ifosfamide, decarbazin as single or combination 20-40% response rate
- Leiomyosarcoma (maybe MFH): docotaxel with gemcitabine
- Angiosarcoma: paclitaxel, doxil
- New chemotherapy: trabectidin (yondelis) product from marine tunicate Ecteinascidia tubinata (4% response but high stable dis.)

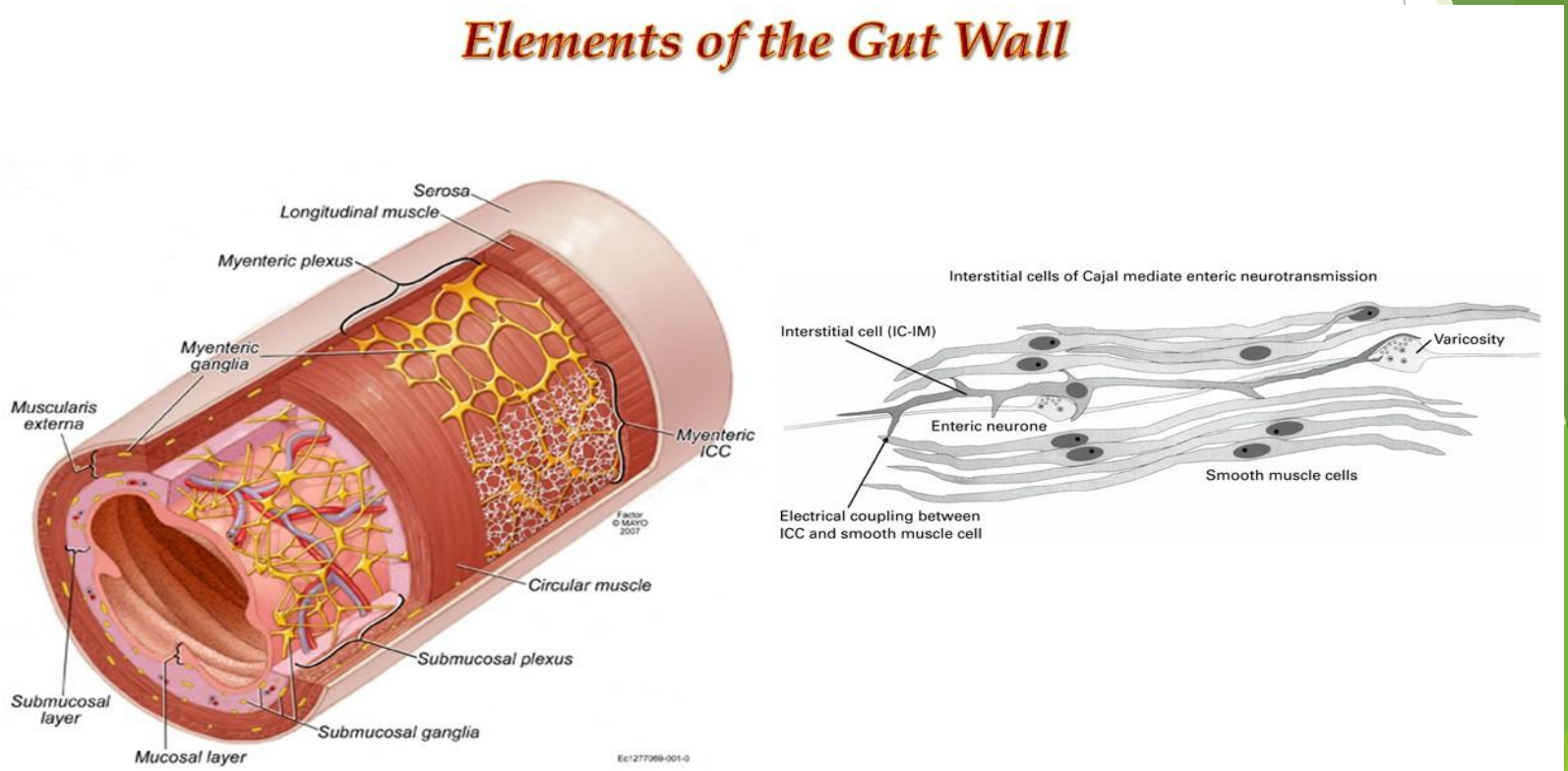
STS: 5-year Survival Rates



Stojadinovic et al. J Clin Oncol 2002; 20: 4344–52

GastroIntestinal Stromal Tumors (GIST): A Brief Overview

- Definition
  - Rare soft tissue tumor of the GI tract, mesentery, and omentum
  - Histologic subtypes include spindle, epitheliod, mixed
  - Originate from Cajal cells.



GIST facts

- 10-20 cases per million.
- Similar incidence in males and females.
- Only 0.2% of all GI tumors, 80% of GI sarcomas.
- >90% positive for C-KIT.
- Origin:
  - stomach 40-70%
  - Small intestine 20-40%
  - Colon and rectum 5-15%
  - Esophagus <5%

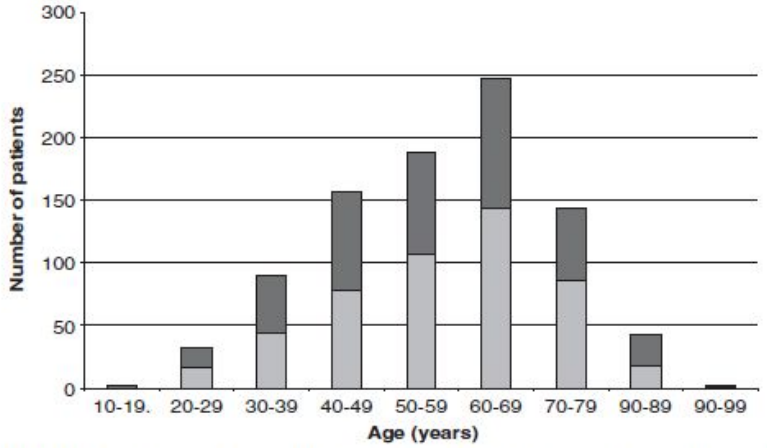


FIGURE 1. Age and sex distribution of 906 patients with small intestinal GISTs. Pale, males; dark, females.

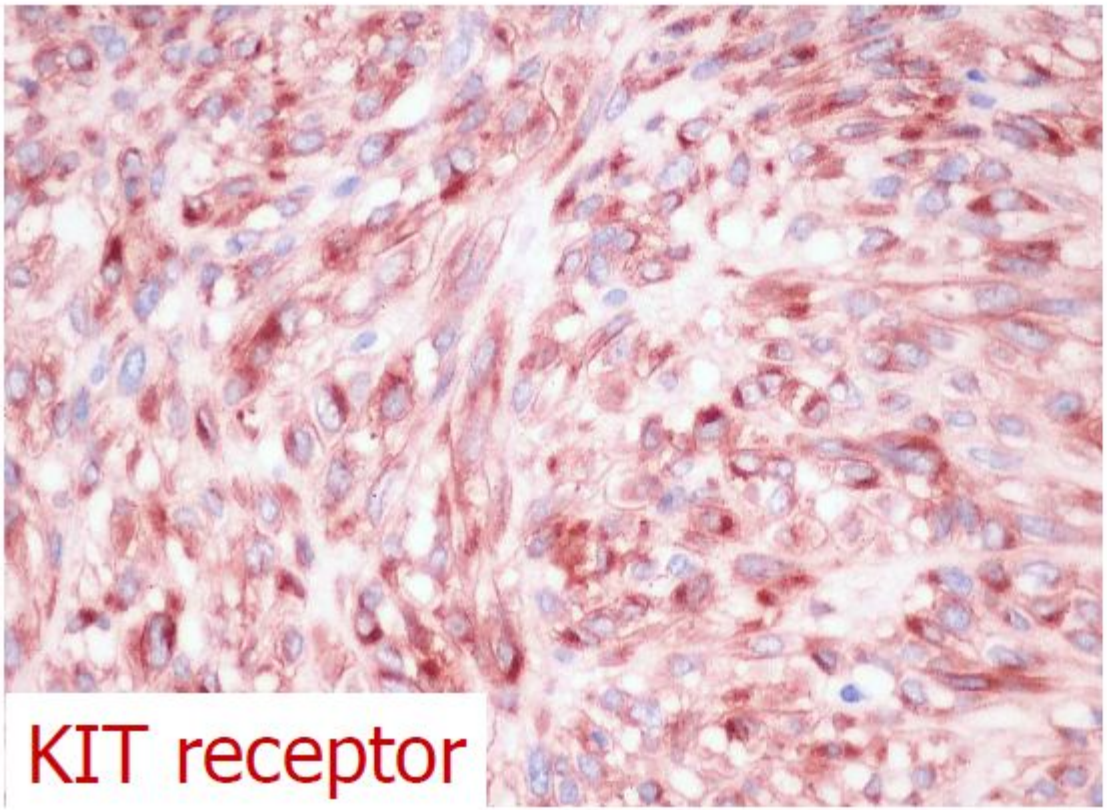
GIST: A Brief Overview

- Clinical Presentation
  - Abdominal Pain, GI Bleeding, Mass, Obstruction
  - Primary tumor only (46%), Metastatic disease (47%)
- Prognostic Factors
  - No uniform prognostic guidelines, poor Px associated with
    - increasing tumor size
    - metastatic disease at presentation
    - high grade (high mitotic index)
- Primary Treatment = Surgery
  - ~67% primary tumors resectable,
  - However, 40-90% recur (most often: intra-abdominal, liver)

Differential diagnoses of GIST

- leiomyoma/leiomyosarcoma
- schwannoma/malignant peripheral nerve sheath tumor (MPNST)
- lipoma/liposarcoma
- angiosarcoma
- sarcomatoid carcinoma
- solitary fibrous tumor
- abdominal fibromatosis (of desmoid type)
- endometrial stromal sarcoma
- histiocytic sarcoma
- inflammatory fibroid polyp
- desmoplastic small round cell sarcoma
- clear cell sarcoma
- PEComa (neoplasm with perivascular epithelioid cell differentiation)
- melanoma
- pleomorphic high grade sarcoma/malignant fibrous histiocytoma

Important differential diagnoses of GIST with possible KIT receptor expression



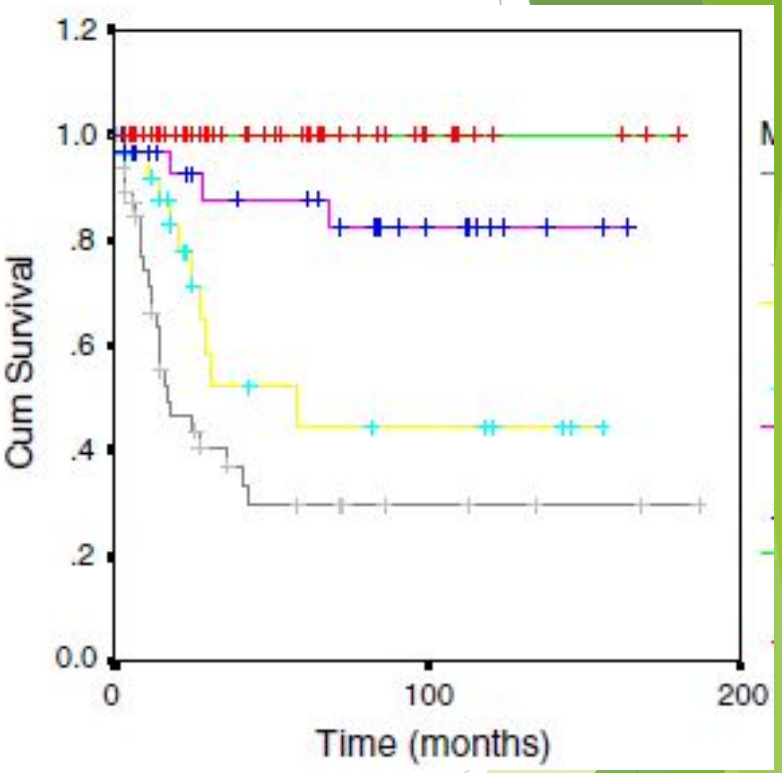
Desmoid

Modified Risk Stratifications for post-operative recurrence

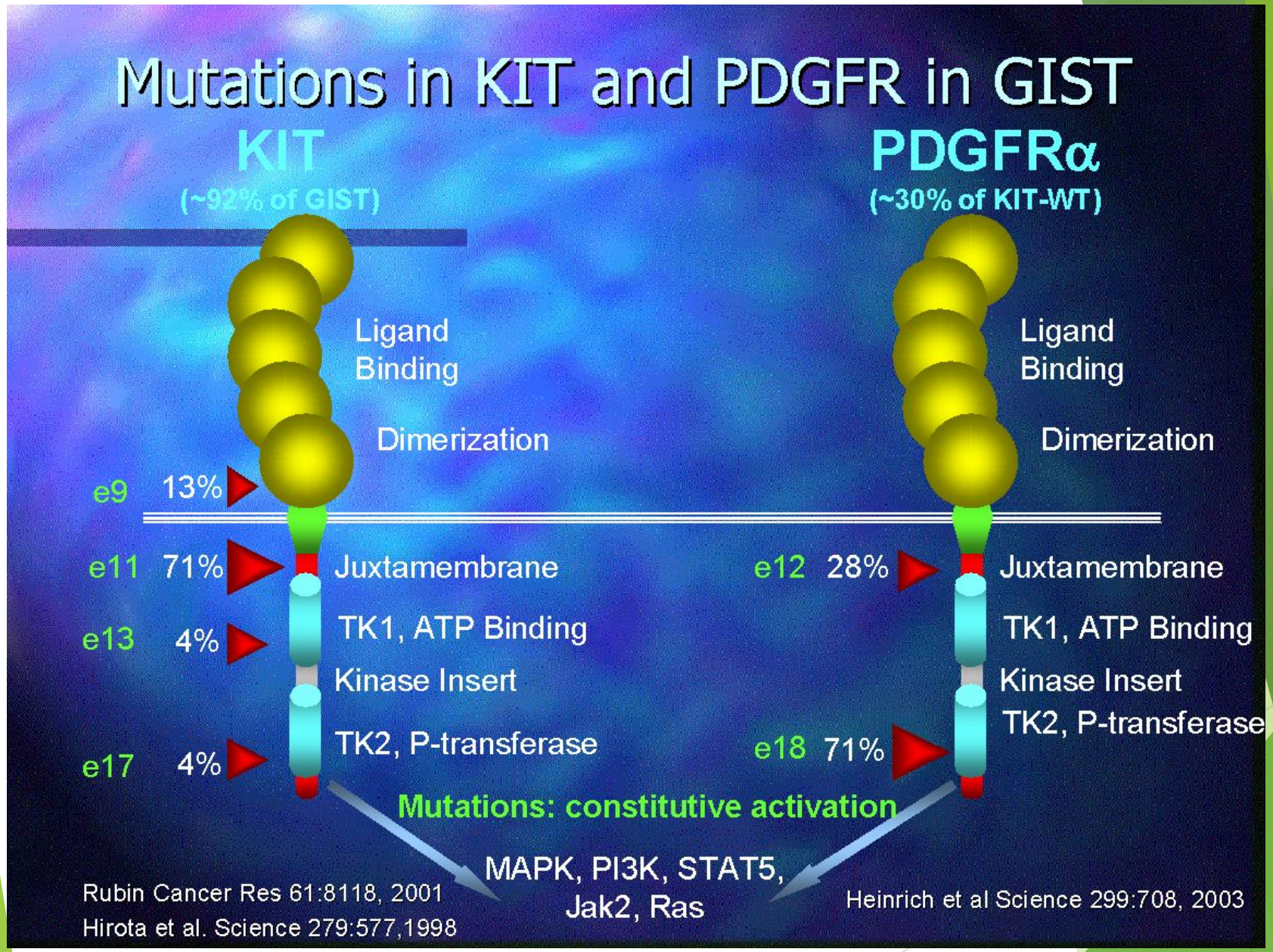
Table 4 Proposed modification of consensus classification for selecting patients with GIST for adjuvant therapy

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1-5.0	≤5	Any
Intermediate risk	2.1-5.0	>5	Gastric
	<5.0	6-10	Any
	5.1-10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10 cm	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1-5.0	>5	Nongastric
	5.1-10.0	≤5	Nongastric

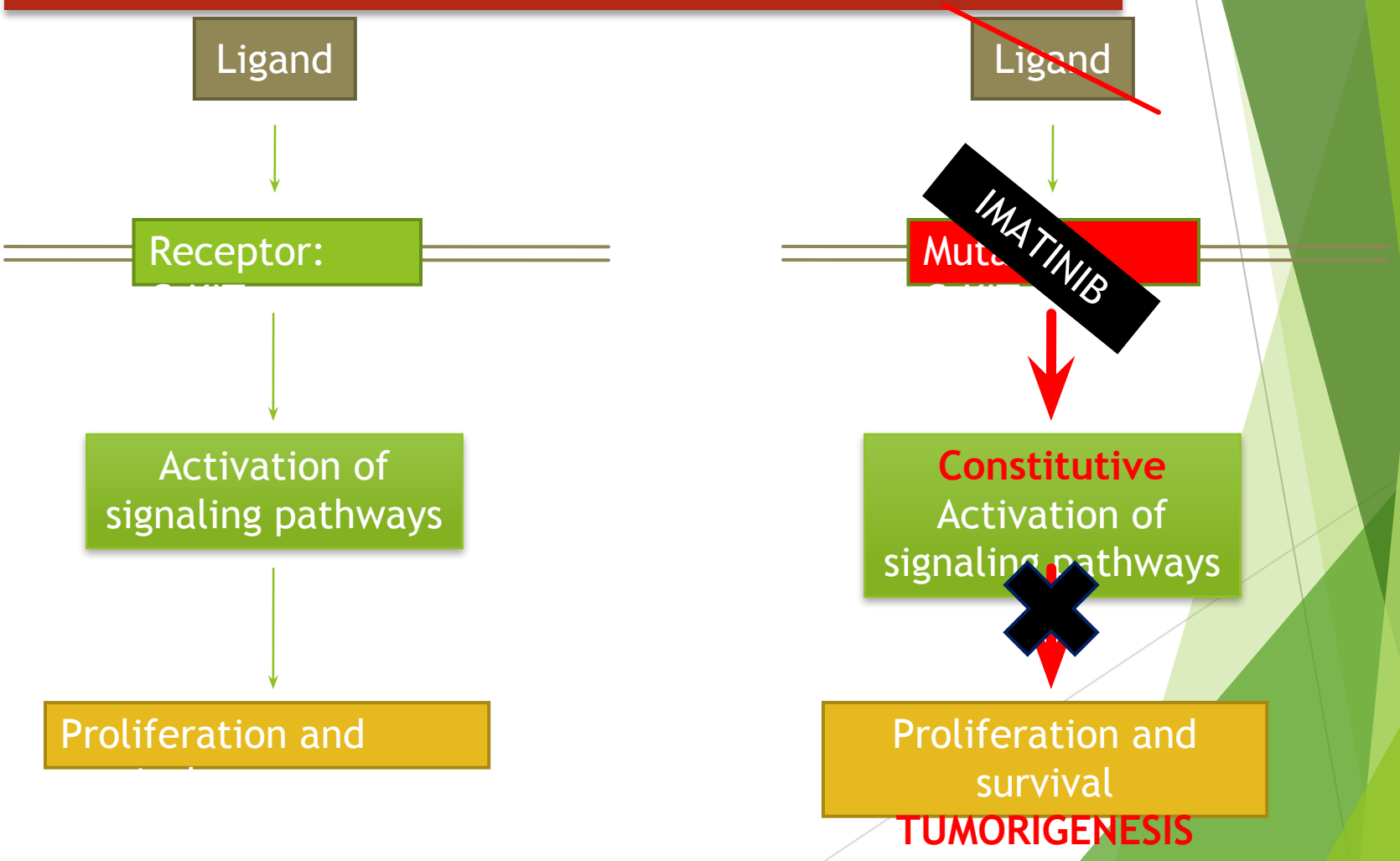
Human Pathology (2008) **39**, 1411–1419



Can we prevent recurrence of high risk GIST?

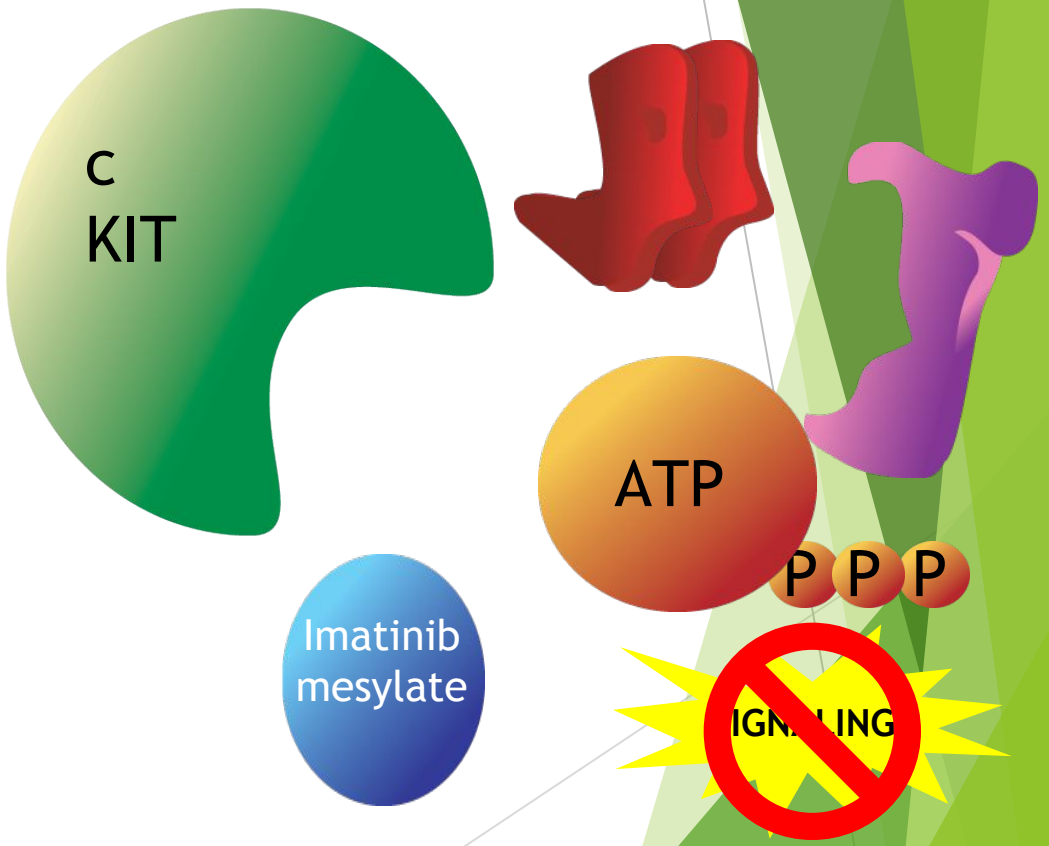

Mutations in KIT and PDGFR in GIST
KIT
(~92% of GIST)
PDGFRα
(~30% of KIT-WT)
Ligand Binding
Dimerization
Ligand Binding
Dimerization
e9 13%
e11 71%
e13 4%
e17 4%
Juxtamembrane
TK1, ATP Binding
Kinase Insert
TK2, P-transferase
e12 28%
e18 71%
Juxtamembrane
TK1, ATP Binding
Kinase Insert
TK2, P-transferase
Mutations: constitutive activation
MAPK, PI3K, STAT5, Jak2, Ras
Rubin Cancer Res 61:8118, 2001
Hirota et al. Science 279:577,1998
Heinrich et al Science 299:708, 2003

From Molecular Biology to novel therapies



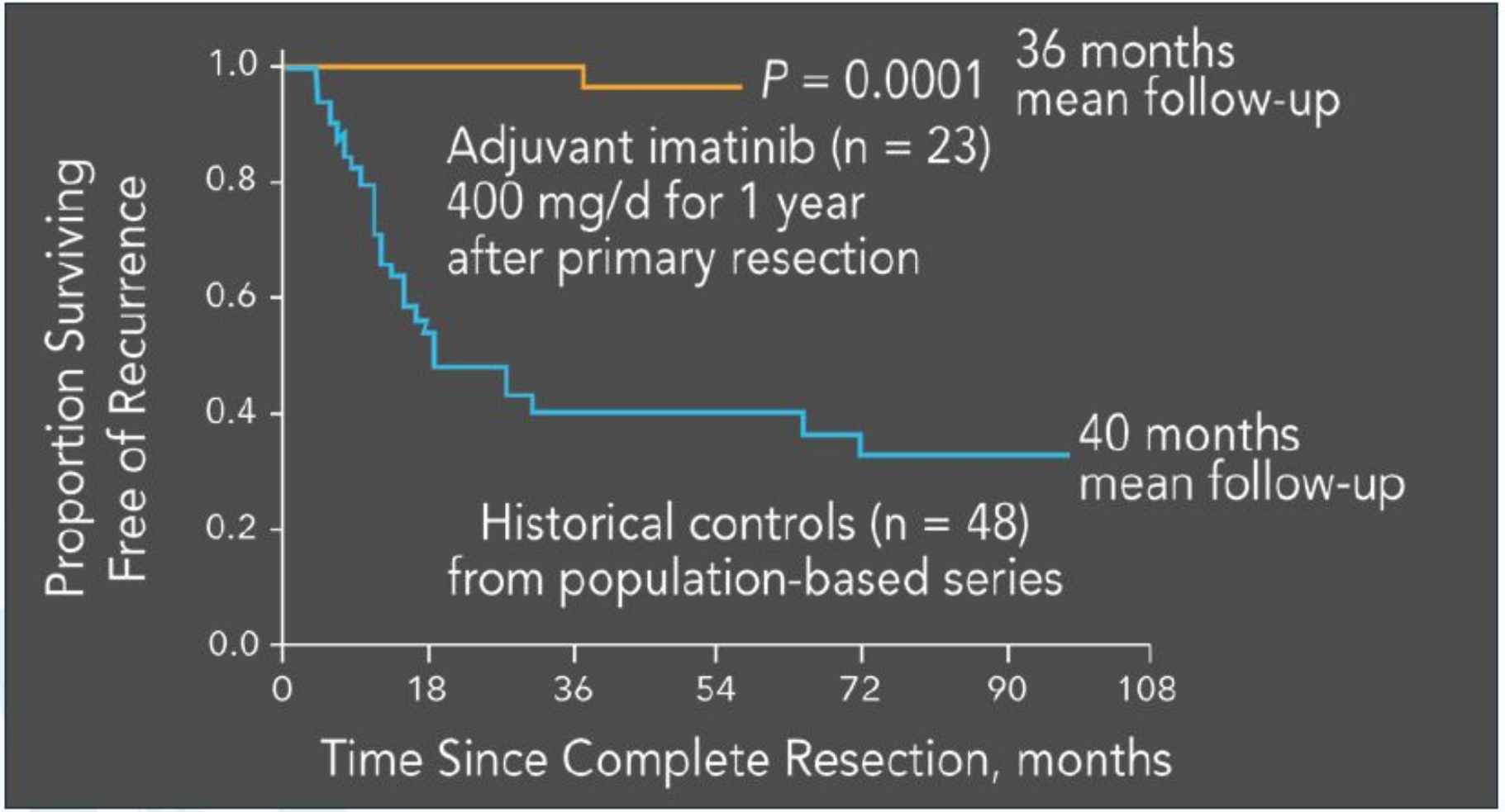
Imatinib Mesylate: Mechanism of Action

- Imatinib mesylate occupies the ATP binding pocket of the kit kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



RFS in Patients With High-Risk GIST Receiving Adjuvant Imatinib

Kaplan-Meier estimates of RFS after adjuvant imatinib vs historical control

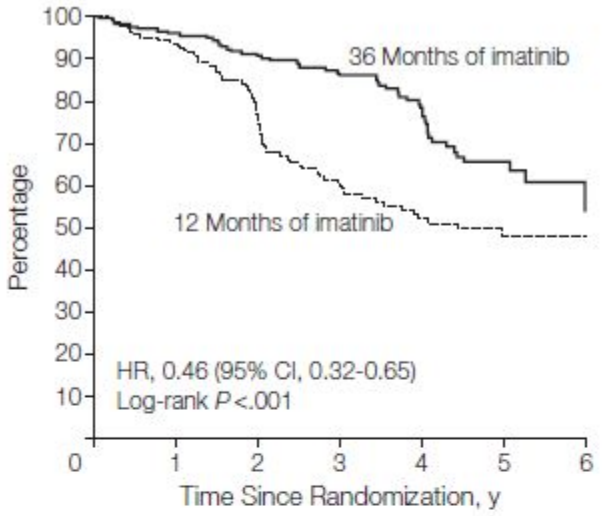


Adapted with permission from Nilsson B et al., Br J Cancer. 2007;96:1656-1658.

One vs Three Years of Adjuvant Imatinib for Operable Gastrointestinal Stromal Tumor

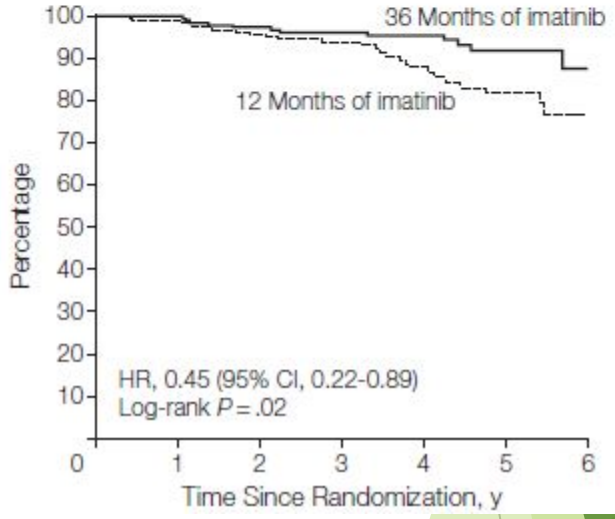
A Randomized Trial

A Recurrence-free survival: intention-to-treat population

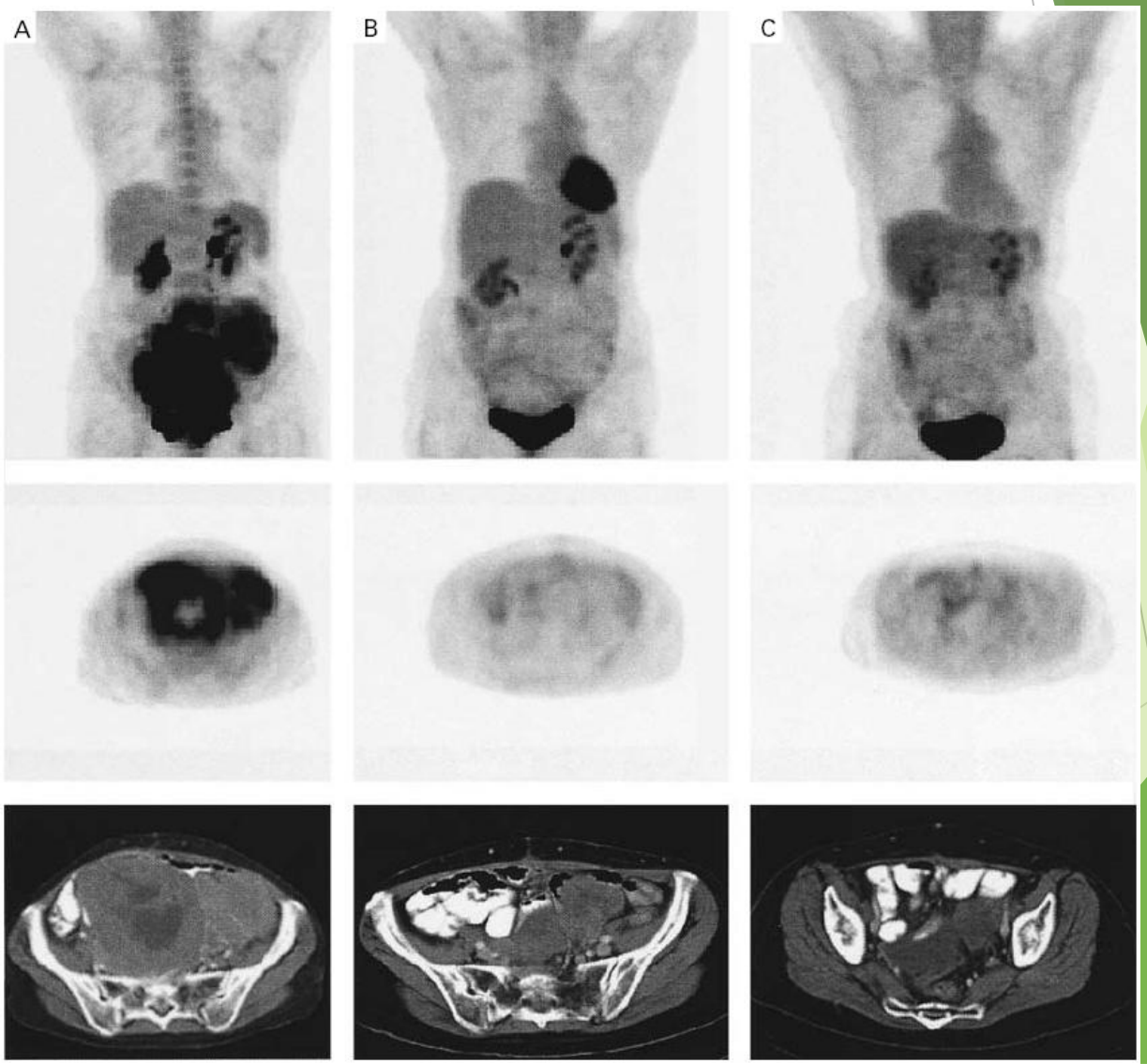


No. of patients							
36 Months of imatinib	198	184	173	133	82	39	8
12 Months of imatinib	199	177	137	88	49	27	10

C Overall survival: intention-to-treat population



Imatinib Mesylate in metastatic GIST



Overall survival of EORTC trial

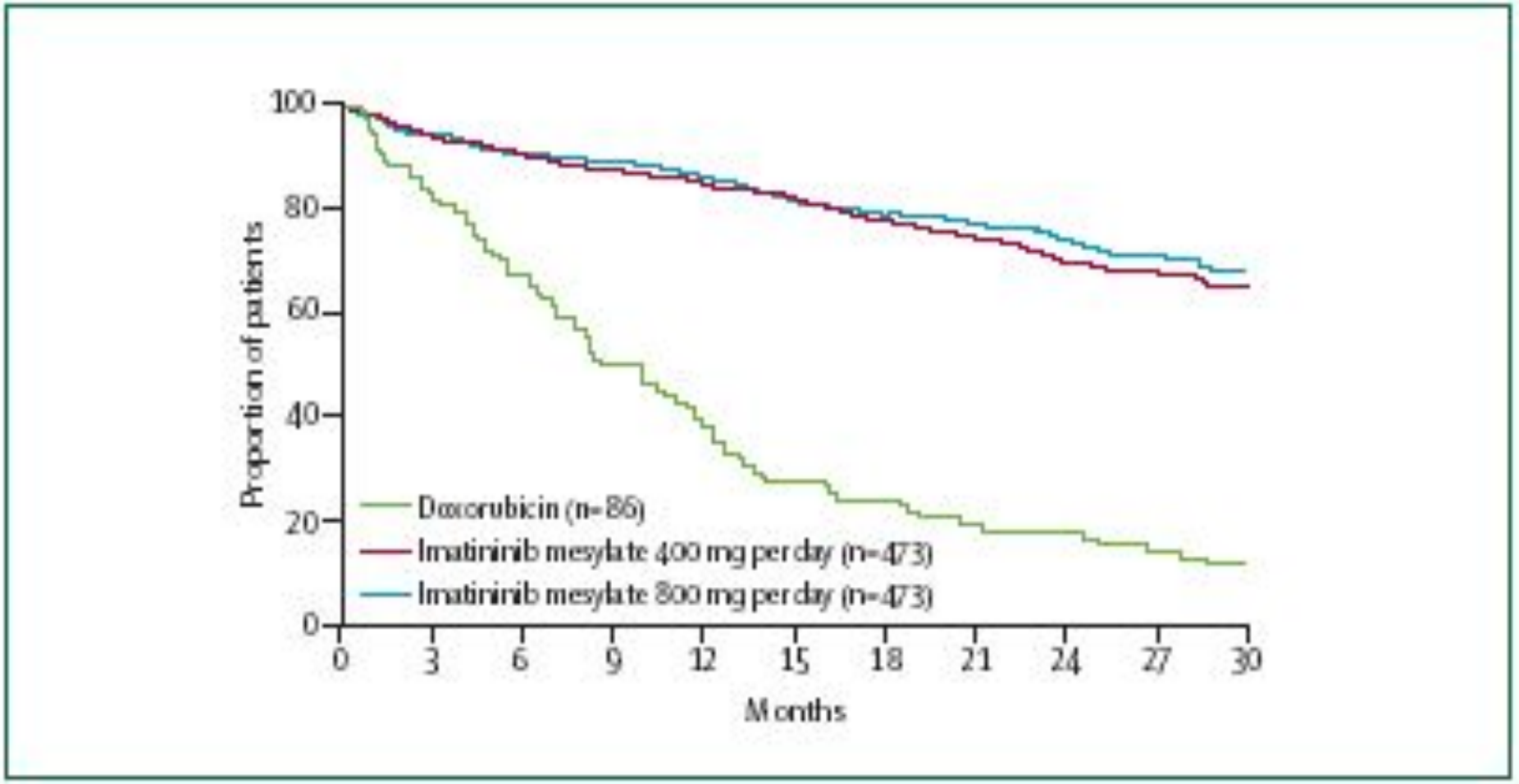


Figure 6: Overall survival for study population of EORTC 62005
The study data are compared with historical gastrointestinal stromal tumour controls from the EORTC database.
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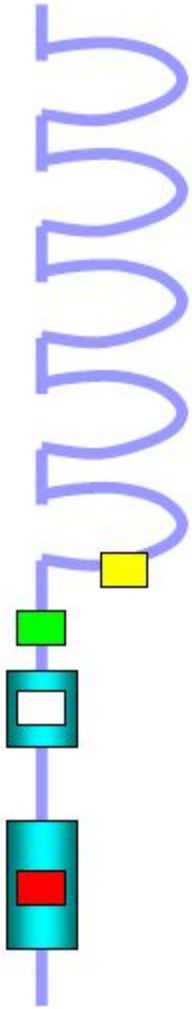
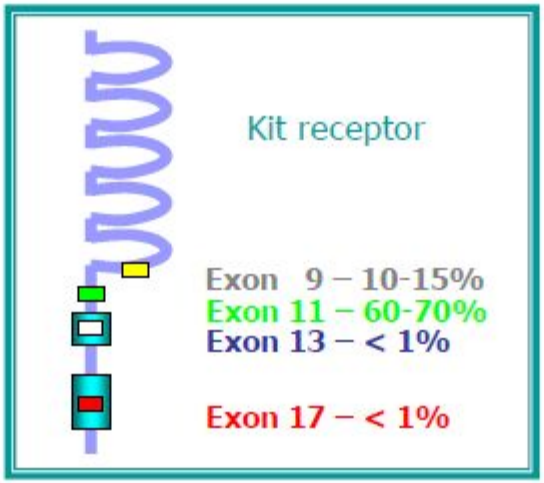
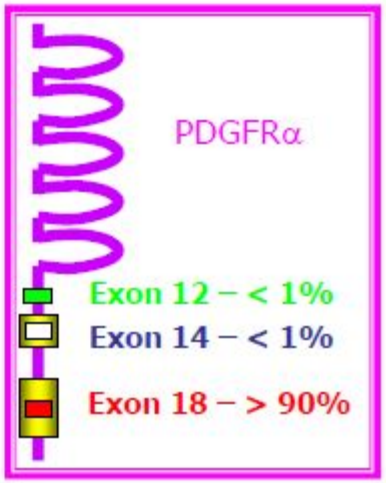
Response to treatment with imatinib in correlation with the mutational status







Exon 9 – response rate 45 %

Exon 11 – response rate 80 %

Exon 13 – response rate unknown

Exon 17 – primary resistance

no *c-kit* mutation – response rate 10%

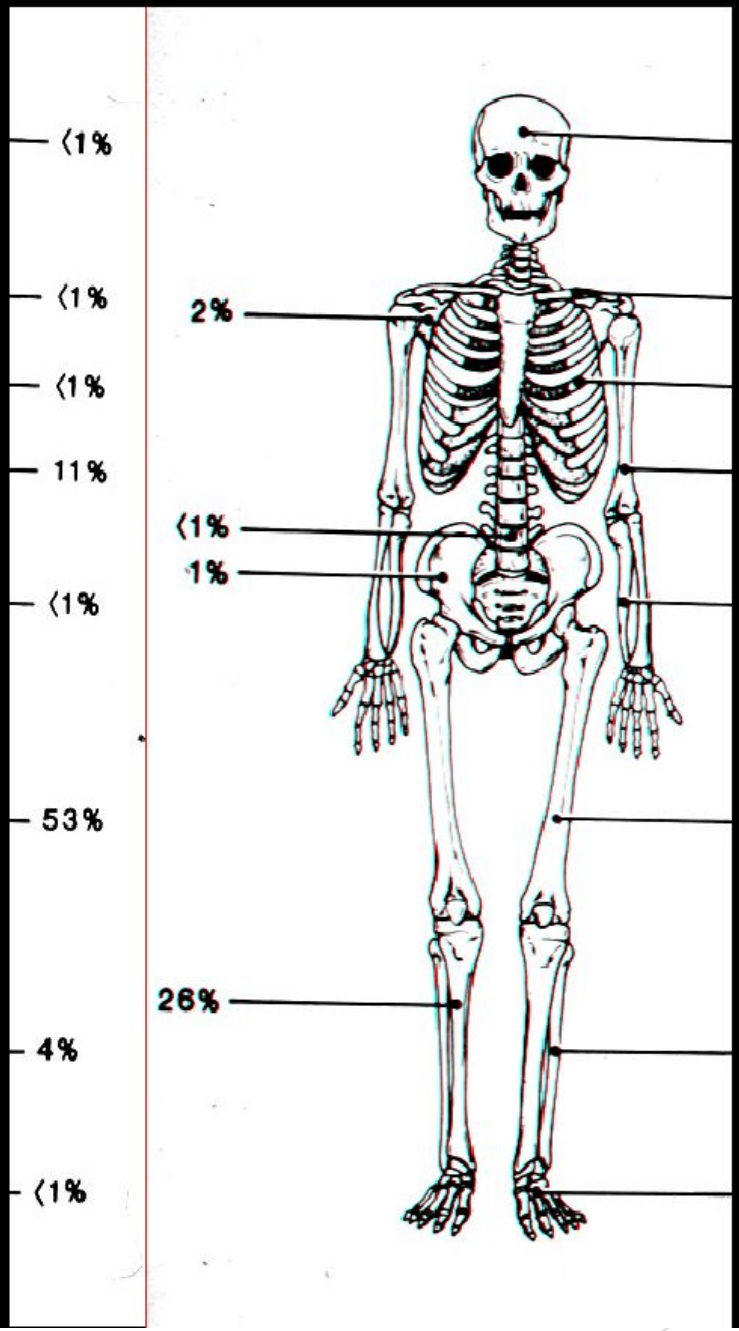
Pediatric Sarcomas

- Ewing's Sarcoma Rhabdomyosarcoma
- Osteosarcoma

- Multimodality approach: Chemotherapy, Radiation and Surgery
- Curative Therapy for majority of patients with localized disease

Osteogenic Sarcoma

- The most common bone tumor
- Peak incidence: second decade of life
- Females earlier than males
- May be primary or secondary (radiation-induced and as a part of Li-Fraumeni syndrome)
- Most commonly located in methaphyses of long bones, especially around the knee
- The most common sites of mets: lungs, bones (20% of all children with OS have macroscopic lung mets in lungs at the time of initial diagnosis)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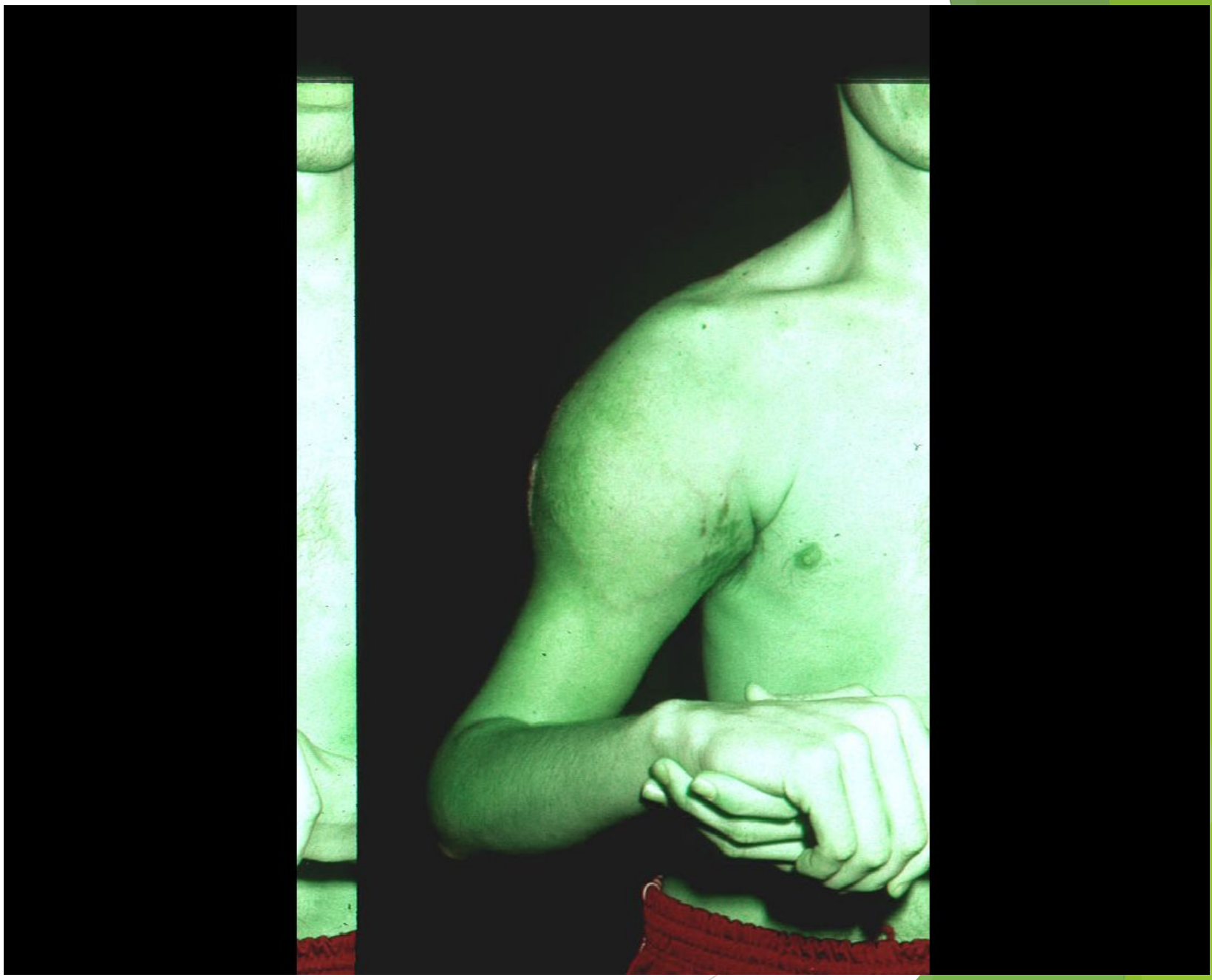

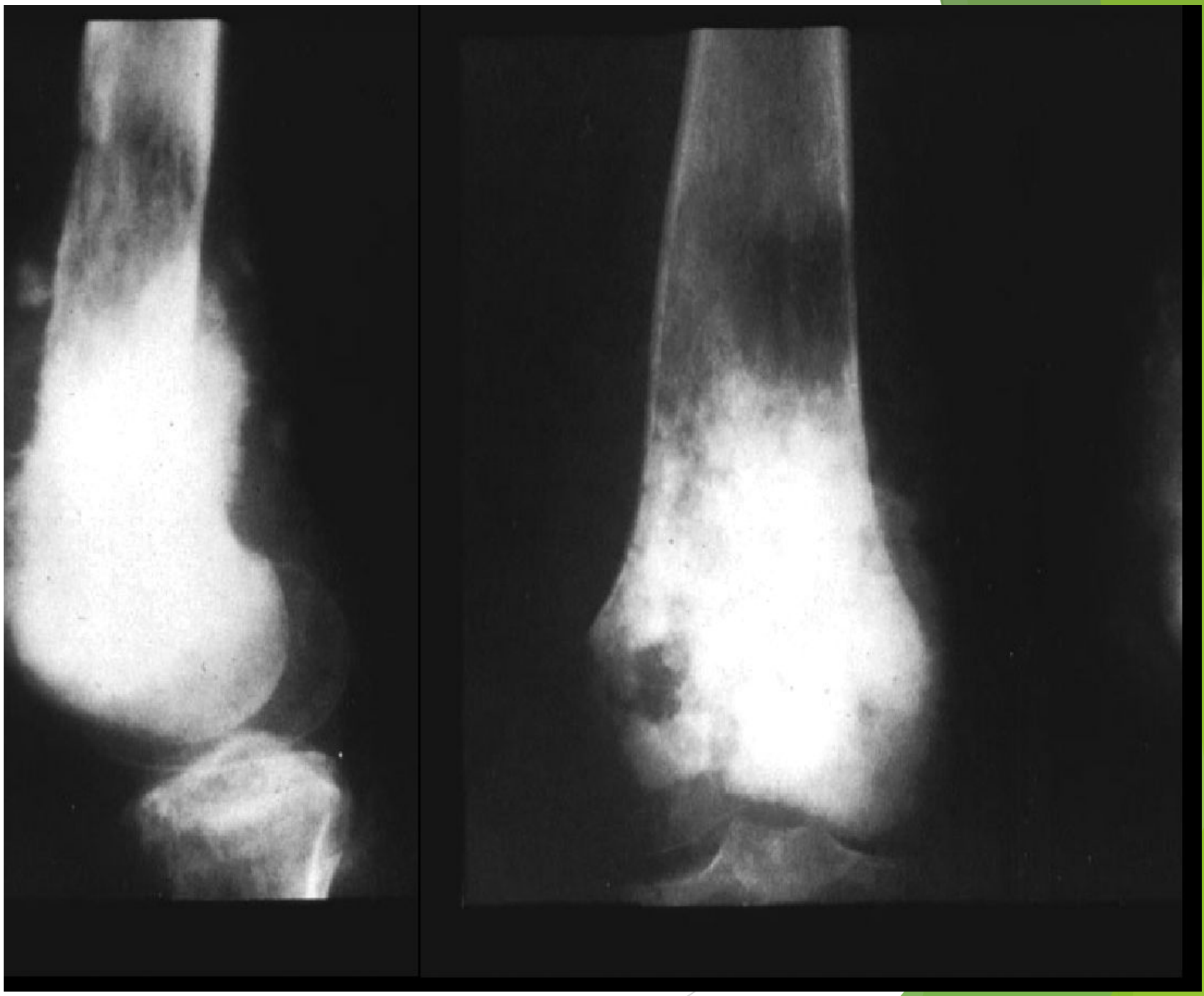

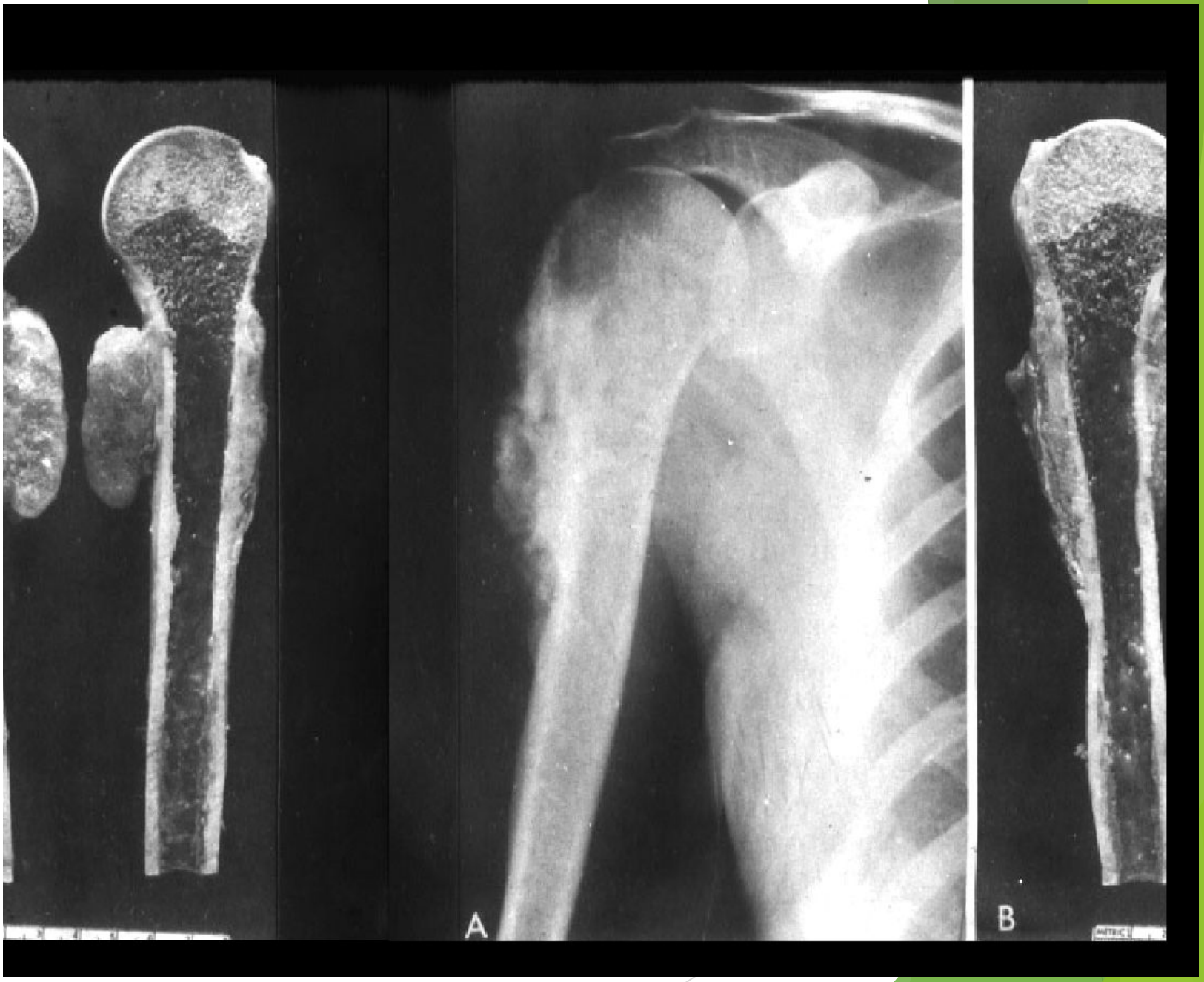
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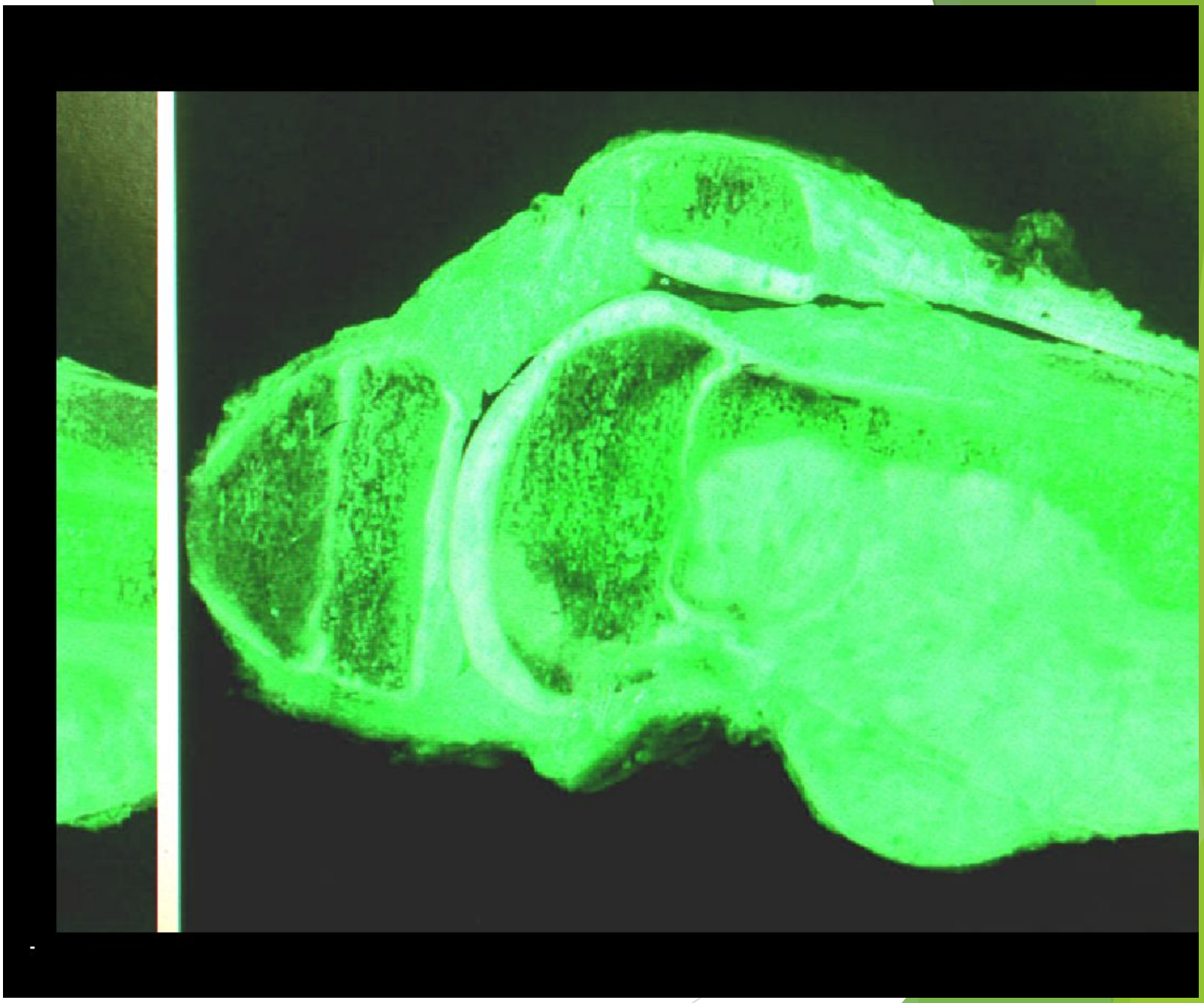
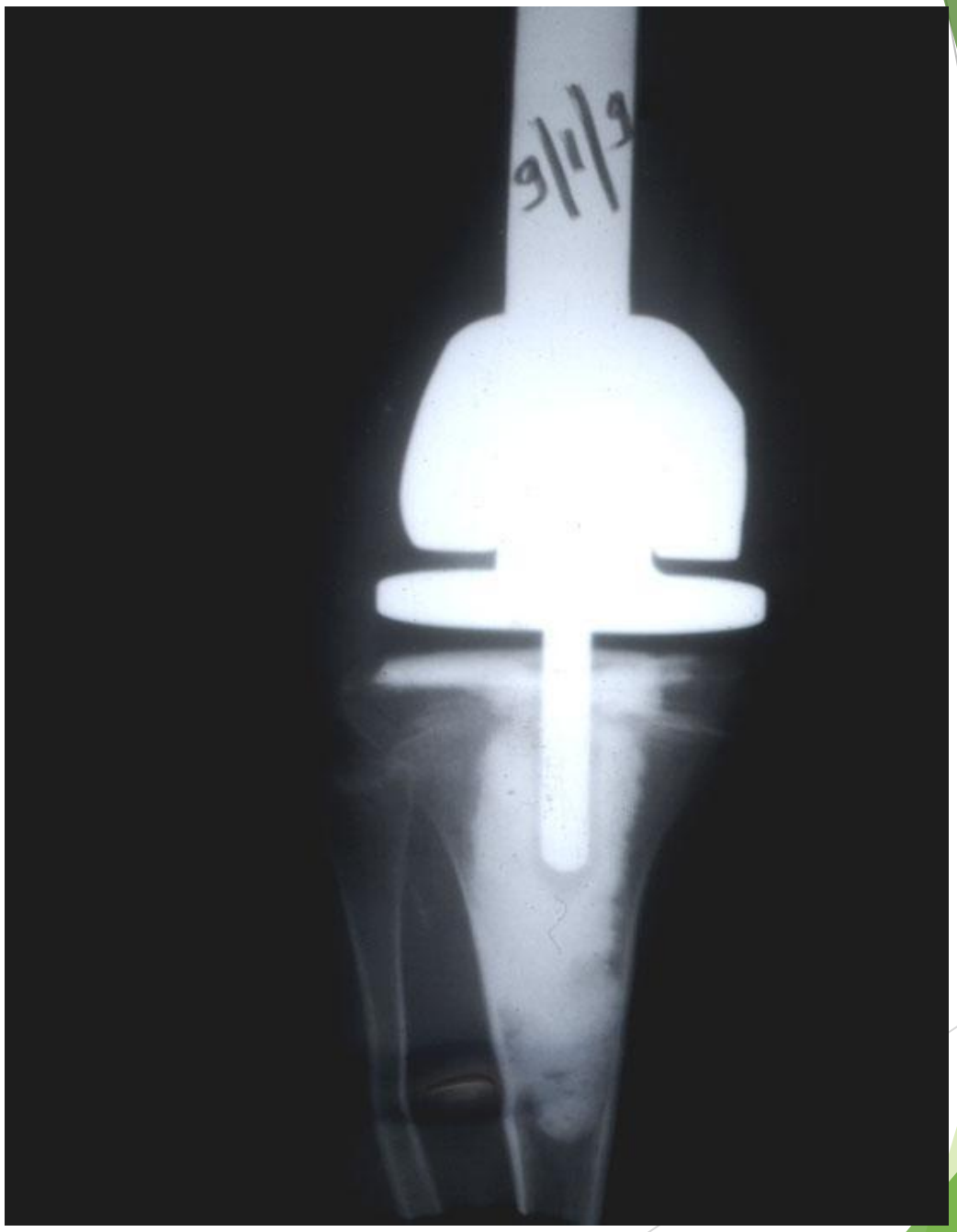


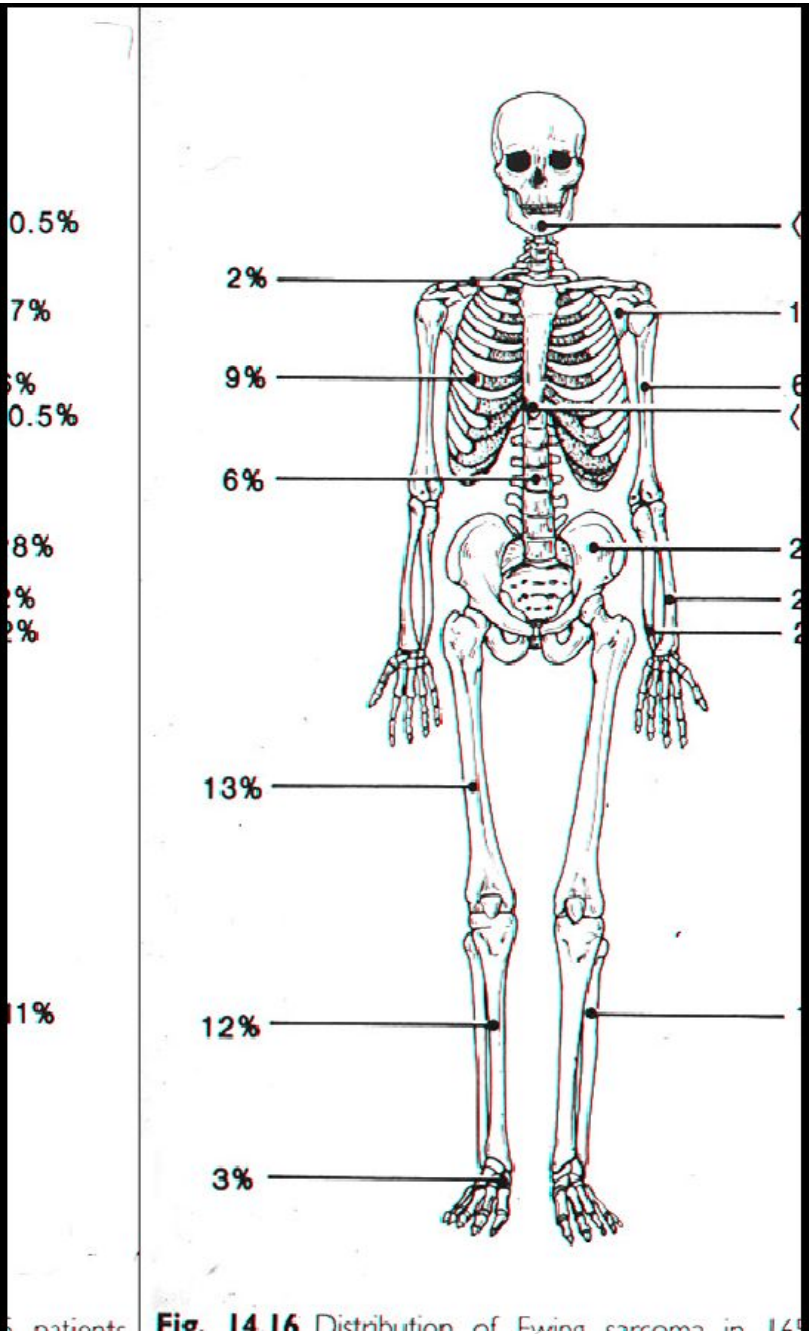
Treatment of Osteogenic Sarcoma

- Chemotherapy (every sarcoma in children is systemic disease – before era of chemotherapy 80% of pts developed distant metastases despite excellent local control)
- Surgery (limb-sparing with endoprothesis)
- Resection selected lung mets
- Chemotherapy
- OS is not sufficiently radiosensitive, at least 6000 cGy
- 5-y DFS in non-metastatic pts: 60-75%
- 5-y DFS in metastatic to lungs pts: 20-25%



Ewing Sarcoma

- The second most common bone tumor
- The peak incidence is appeared to be earlier than OS
- The most common location: diaphyses of long bones, frequently bones of pelvis
- The most common sites of mets: lungs and bones (20% of all pts have lung mets at the time of initial diagnosis), may be in bone marrow
- ES is one of small round blue cells tumors (others are neuroblastoma, rhabdomyosarcoma, and lymphoma)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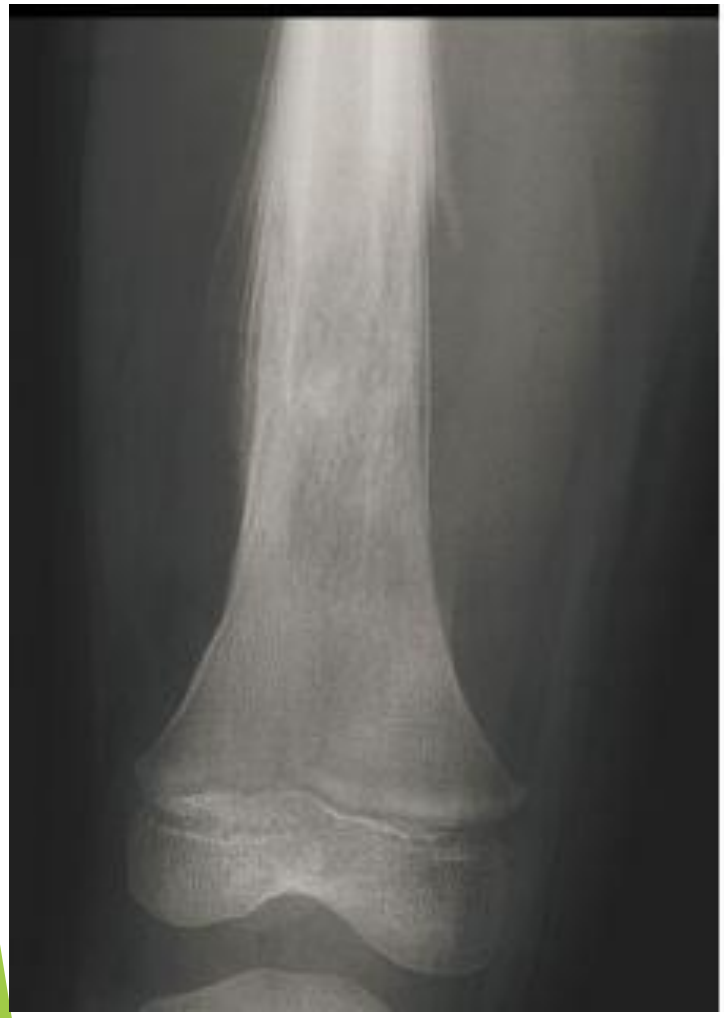
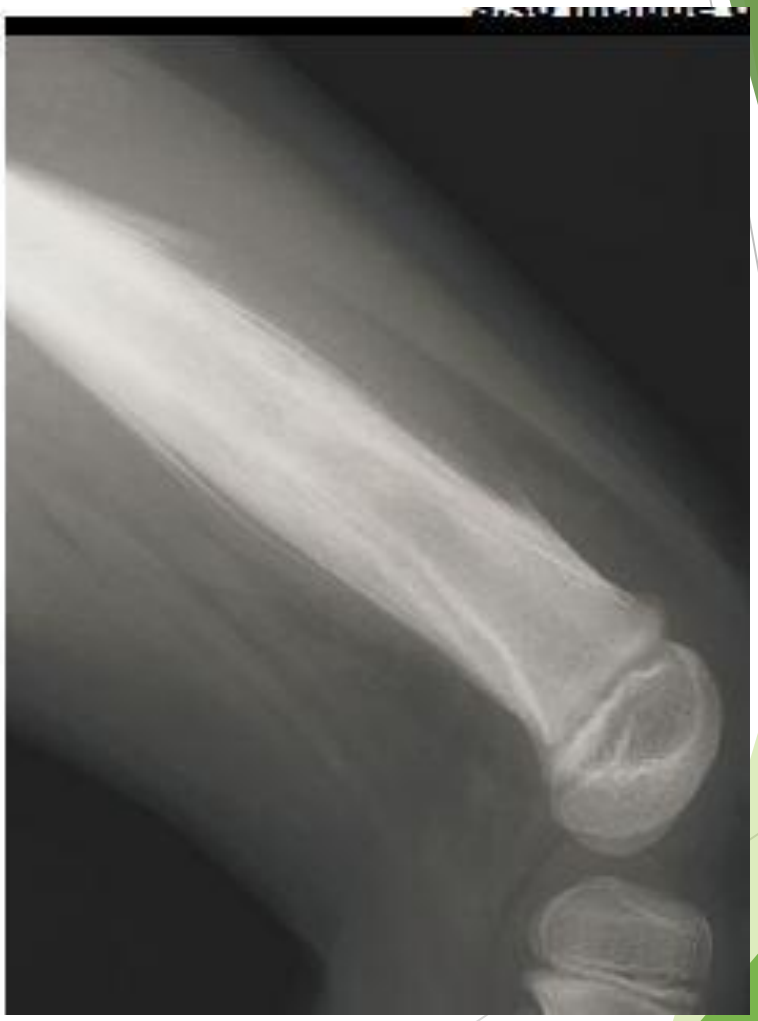
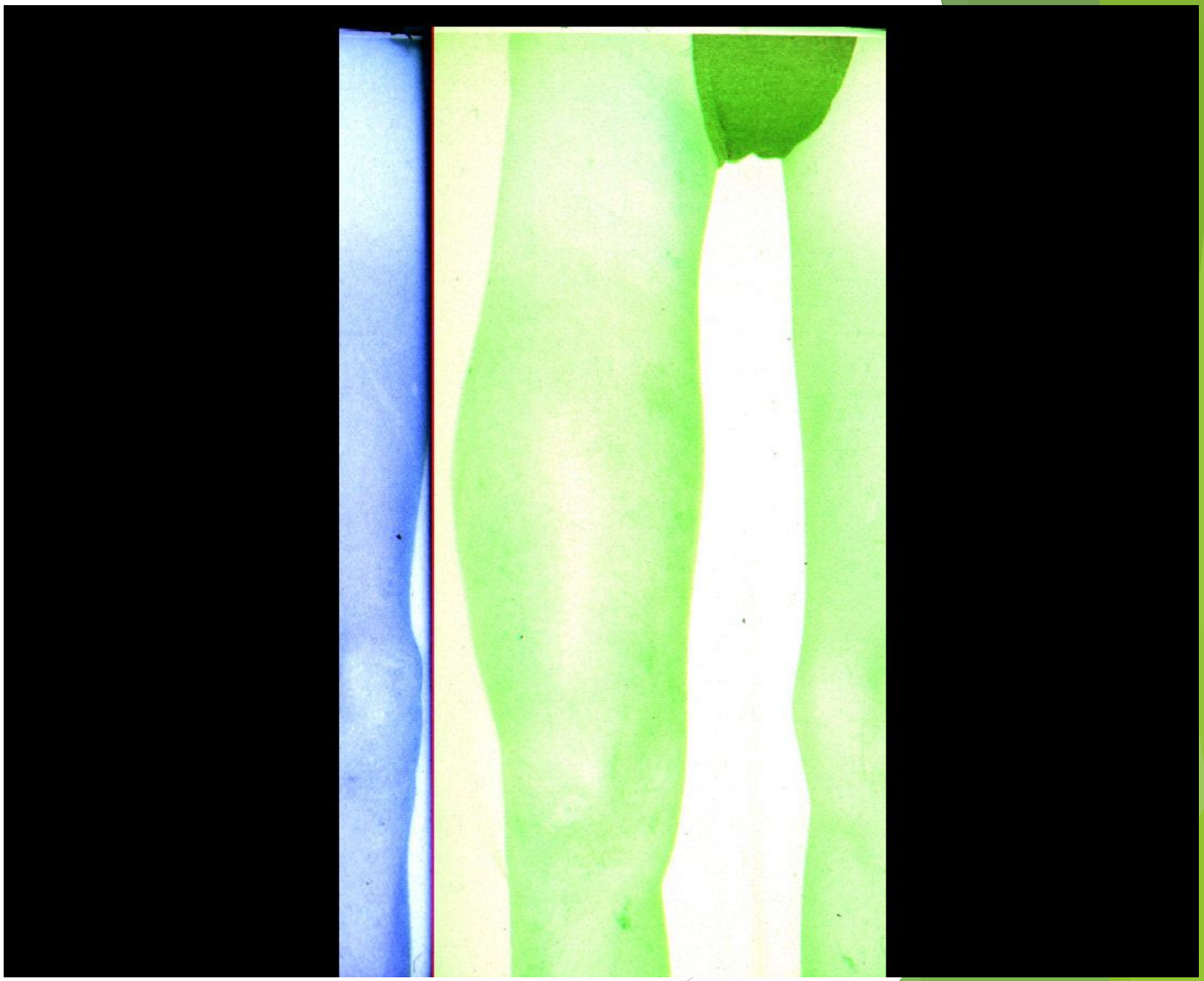
“Onion skin” sign («**луковая шелуха**»)







Ewing Sarcoma

- Molecular biology methods of diagnosis: t (11,22) and t (21,22) in approximately 95% of cases
- PCR for t (11,22) in tumorous tissue, peripheral blood, and bone marrow
- Prognosis of pts with PCR positive in peripheral blood and/or bone marrow approaches that of pts with overt metastatic disease

Ewing Sarcoma – Treatment considerations

- Biopsy and definitive diagnosis
- Neoadjuvant chemotherapy
- Surgery ± radiotherapy (5500 cGy)
- Continuation of chemotherapy

Percentage of necrosis (> or < 90%) have prognostic implications

5-y DFS in non-metastatic pts with more 90% necrosis after neoadjuvant chemotherapy is about 75%

Malignant bone tumors

Osteosarcoma

- During growth spurt (12-18 years)
- Metaphysis
- Distal femur>proximal tibia>proximal humerus
- No known chromosomal abberations
- No radiosensitive
- No really efficacious second-line chemotherapy

Ewing sarcoma

- Much younger patients (2y – 20 y)
- Diaphysis
- Pelvic bones>femur>chest wall
- EWS/FLI1; t(11;22)
- Radiosensitive
- There is second-line chemotherapy