Bone and Soft Tissue Sarcomas

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Cancer Cases in the USA by Organ Site 2002

	New Cases	Deaths
Digestive System	250,600	132,3000
Breast	205,000	40,000
Respiratory System	183,200	161,400
Lymphoma	60,6900	25,800
Multiple Myeloma	14,600	10,800
Soft Tissue	8,300	3,900
Bone	2,400	1,300

- From the Greek "sarkos" = "fleshy"
  - Fleshy tumors rather than "crab-like"
- Tumors of mesodermal origin
  - Ectodermal: Ewing's/PNET, neurosarcoma
- Tumors of connective tissue
  - Muscle, bone, fat, fascia, cartilage, etc.

Risk Factors

- Hereditary
  - Retinoblastoma (RB1)
  - Neurofibromatosis (17q del)
  - Li Fraumeni (17p del)
  - Gardner's syndrome (5q del)
- Radiation
  - 4-40 years later
- Occupational exposure
  - dioxin, pesticides, arsenic, PVC, Thoratrast

Biology

- Hematogenous spread
  - Lungs are predominant site of metastases
- Rare lymph node involvement
  - Poor prognosis
- Evolution from benign tumors
  - Neurofibrosarcoma (neurofibromas)
  - Chondrosarcoma (enchondromas)
  - Osteosarcoma (Pagetoid bone, osteochondromas)

Sarcomas

Primed for "Targeted Therapies"

• GIST	c-Kit
• Dermatofibrosarcoma protuberans	COL1A1-PDGFB
• Ewing's sarcoma	EWS-FLI1
• Synovial sarcoma	SYT-SSX1
• Myxoid liposarcoma	FUS-CHOP
• Extraskeletal myxoid chondrosarcoma	EWS-CHN
• Alveolar soft parts sarcoma	TFE3-ASPL

Soft Tissue Sarcoma

Histologic Subtypes	n	%
Malignant Fibrous Histiocytoma	349	28
Liposarcoma	188	15
Leiomyosarcoma	148	12
Unclassified Sarcoma	140	11
Synovial Sarcoma	125	10
Malignant Peripheral Nerve Sheath Tumor	72	6
Rhabdomyosarcoma	60	5
Fibrosarcoma	38	3
Ewing's Sarcoma	25	2
Angiosarcoma	25	2
Osteosarcoma	14	1
Epithelioid Sarcoma	14	1
Chondrosarcoma	13	1
Clear cell Sarcoma	12	1
Alveolar Soft Part Sarcoma	7	1
Malignant Hemangiopericytoma	5	0.4

Coindre JM et al. *Cancer* 2001;91:1914–1926.

STS - Identification

Alveolar soft parts sarcoma	desmin, MyoD1, sarcomeric actin
Angiosarcoma	CD31, CD34, Factor VIII
Clear cell sarcoma	S-100, HMB-45
Epitheliod sarcoma	Keratin proteins, epithelial membrane Ag
Ewings/PNET	NSE, Leu-7, HBA-71/013
GI stromal tumor (GIST)	CD 117 (c-kit), CD 34, vimentin
Hemangioendothelioma	CD 34, F VIII
Hemangiopericytoma	HLA-DR, F XIIIa
Leiomyosarcoma	desmin, muscle specific (HHF-35) and sm muscle actin
Malignant schwannoma	S-100, Leu-7
Paraganglioma	Chromogranin, NSE, S-100
Rhabdomyosarcoma	desmin, HHF-35, myoglobin, skeletal muscle myosin
Synovial sarcoma	EMA, keratin proteins

Table 1. **Distribution of Soft-Tissue Sarcoma.***

Site	Incidence
	%
Lower limb and girdle	40
Upper limb and girdle	20
Retroperitoneal and intraperitoneal sites†	20
Trunk	10
Head and neck	10

* Percentages are approximate.
† These sites include gastrointestinal stromal tumors.

Clark et al. NEJM 2005:353: 701

Presentation

- Painless mass
- Delay in diagnosis common

STS – Diagnosis & Staging

- Core Tru-Cut
  - Much more sensitive and specific than FNA
  - FNA may be used to assess for recurrence
- Incisional biopsy
  - Plane should be longitudinal to muscle

STS – Diagnosis & Staging

- Define local extent
  - MRI – extremity, trunk, head & neck
  - CT – retroperitoneal, intraabdominal
- Evaluate for distant metastases
  - Chest CT

STS – Prognostic Features

- Histologic grade
  - Differentiation, mitotic activity, necrosis
- Tumor size (<5, >5, >10 cm)
- Tumor depth: subcutaneous vs. deep
- Primary site
  - Extremities>Head&neck>retroperitoneum
- Histopathology
- Age

AJCC Staging STS

Grade and TNM	Description	T1a	T1b	T2a	T2b
		Stage			
G1	Well differentiated				
G2	Moderately differentiated	G1 or G2	IA	IB	IIA
G3	Poorly differentiated	G3 or G4	IIB	IIC	III
G4	Undifferentiated	N1	IV		
T1	Tumor ≤5 cm in largest dimension	M1			
T1a	Superficial to deep fascia				
T1b	Deep to deep fascia (includes retroperitoneal, intrathoracic, and most head and neck tumors)				
T2	Tumor >5 cm in largest dimension				
T2a	Superficial to deep fascia				
T2b	Deep to deep fascia (includes retroperitoneal, intrathoracic, and most head and neck tumors)				
N1	Regional nodal metastasis				
M1	Distant metastasis				

5-Yr Survival	
Stage	%
I	86
II	72
III	52
IV	10–20

Figure 3. **Descriptions of Stages, Grades, and the Tumor–Node–Metastasis (TNM) System of the American Joint Committee on Cancer for Soft-Tissue Sarcoma and the International Union against Cancer.**
Data have been modified from Greene et al.[30]

Clark et al. NEJM 2005:353: 701

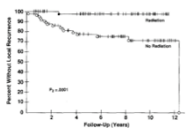
Soft Tissue Sarcoma Treatment: "Save Life and Limb"

- Stage I-II (low grade or superficial)
  - Surgery +/- XRT
- **Stage III (high grade, large, deep)**
  - **Surgery + XRT**
  - **Chemotherapy (Neoadjuvant or adjuvant)**
- **Stage IV (metastatic)**
  - **Chemotherapy**
  - **Metastectomy**

Surgery

Procedure	Plane	Local Recurrence
Marginal	Shell-out	90%
Wide	Intracompartmental en bloc	50%
Radical	Extracompartmental en bloc	<15%

Adjuvant Radiation



Yang et al. J Clin Oncol 1998 16;197-203

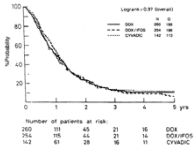
Chemotherapy

Active Chemotherapy Agents

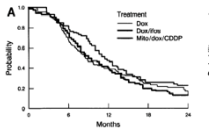
- Doxorubicin
  - 15-35% RR
  - Dose-response
- Ifosfamide
  - ~25% RR
  - Dose-response
- DTIC
  - ~18% RR

Doxorubicin vs. Doxorubicin + Ifosfamide

Overall Survival



Santoro *JCO* 1995

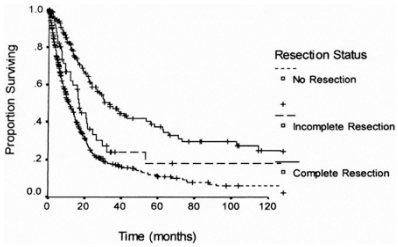


Edmonson *JCO* 1993

Other Chemotherapy

- Gemcitabine/Docetaxel
  - Leiomyosarcoma
- Paclitaxel
  - Angiosarcoma
- Trabectedin
  - Leiomyosarcoma
  - Liposarcoma

Pulmonary Metastectomy



Billingsley et al. Ann Surg 1999

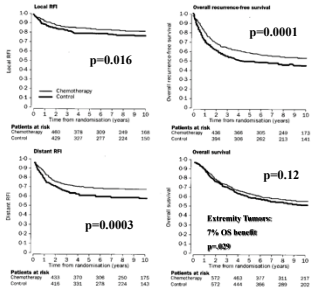
"First Generation" Adjuvant Studies

Institution, years of accrual	Stages	Patients	Scheme	Median FU months	DFS, %			OS, %			Last analysis
					FU	CT	p	FU	CT	p	
DFC/MGH, 1978/83 ECOG, ISSG, 1985/87	IIB–IVA	168	ADM	52	53	66	NS	65	68	NS	Antman 1990
Rizzoli, 1981–1986	III–IVA	77	ADM	106	29	56	0.1	49	63	0.06	Gherlinzoni 1993
UCLA, 1981–1984	III	119	ADM	28	54	58	NS	80	85	NS	Eilber 1987
SSG, 1981–1986	III–IVA	240	ADM	40	56	62	NS	70	75	NS	Alvegard 1989
GOG, 1973–1982	FIGO I/II	136	ADM	24	47	59	NS	42	45	NS	Omura 1985
MDAH, 1973–1976	IIB–IIIB	43	ACVAd	120	83	76	NS	n.d.	n.d.		Benjamin 1987
Extremities		47		120	35	54	0.05	36	65	0.06	
Mayo, 1975–1981	I–IVB	61	AVDAd	64	68	65	n.s.	70	70	NS	Edmonson 1984
NCI											
Extremities		67		85	54	75	0.04	82	60	NS	Chang, 1988
Other sites		72		69	51	57	NS	58	60	NS	Glenn, 1985
EORTC, 1977–1988	IA–IIIB	468	ACVD q 4w	80	43	56	NS	55	63	NS	Bramwell 1994
F. Bergonie, 1980–1988	IIB–IVA	59	ACVD q 3w	52	16	57	0.0003	53	87	0.002	Ravaud 1990

ADM/A = Doxorubicin; C = cyclophosphamide; V = vincristine; Ad = actinomycin-c; D = dacarbazine.

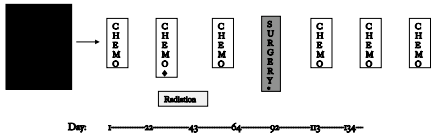
Frustaci *Oncology* 2003;65(suppl 2):80–84

Adjuvant chemotherapy meta-analysis: 1568 patients, 14 trials



Tierney et al, *Lancet* Dec 1997;350:1647

OHSU Treatment Schema



Chemotherapy (q21 days)

Epirubicin 30 mg/m^2/day I.V. D1-4

(♦ omit epirubicin cycle 2)

Ifosfamide: 2.5 g/m^2/day I.V. D1-4

Mesna

Filgrastim/Pegfilgrastim

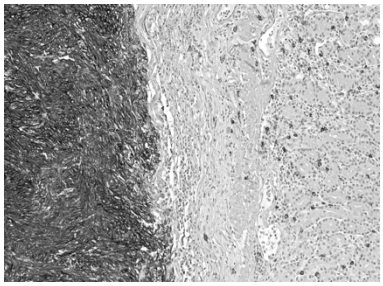
Radiation

350 cGy x 8 fractions D22-31

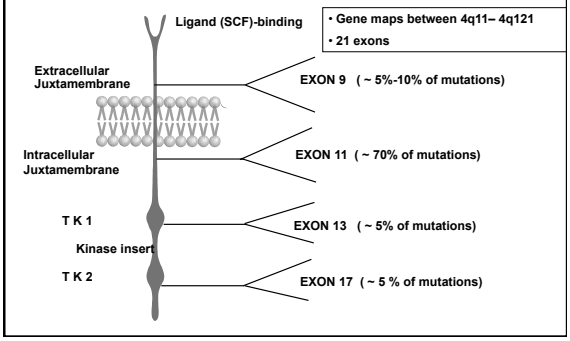
* For patients with positive margins, 200 cGy x 6 fractions boost D78-85

GIST

CD117+ (KIT)



c-*kit* Gene Mutations in GISTs



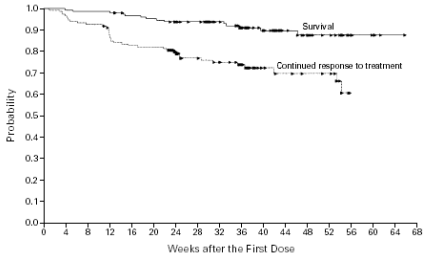
Imatinib Mesylate

(STI-571, Gleevec, Glivec)

- Orally bioavailable, small-molecule
- Highly selective tyrosine kinase inhibitor
  - Abl and BCR-Abl fusion protein
  - PDGF receptor
  - KIT
- Durable, complete remissions in chronic phase CML
- Inhibits auto-phosphorylation of mutant and wild-type KIT

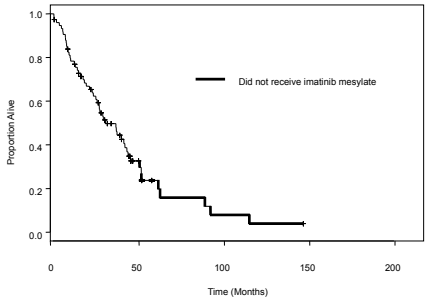
U.S./Finnish Phase II Study in Metastatic GIST

400 or 600 mg/day

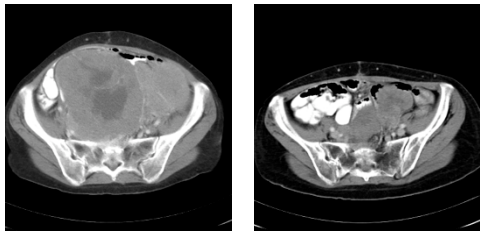


N Engl J Med, Vol. 347, No. 7 · August 15, 2002

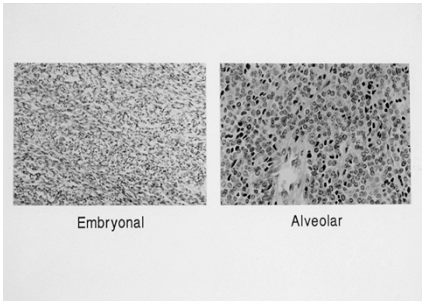
Historical Survival of Metastatic GIST Patients



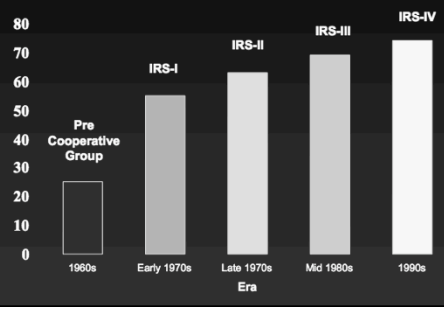
GIST
STI-571 Therapy



Common Histiotypes of Rhabdomyosarcoma

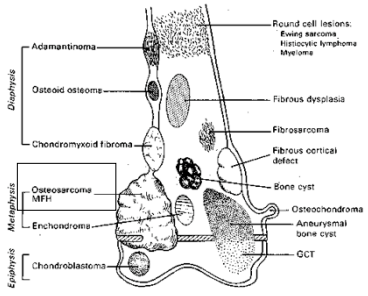


Survival in Rhabdomyosarcoma
Three Decades of Progress



Osteosarcoma
&
Ewing's Family of Tumors

Bone Tumors

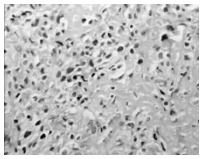


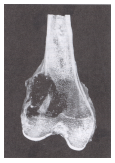
Osteosarcoma

- 1000 cases/year
- M:F = 1.6:1
- Biphasic occurrence
  - Adolescent
  - Elderly

Osteosarcoma

- Malignant sarcomatous stroma associated with *production of osteoid*
- Involves metaphyseal portion of long bone (most common)
- Metastasizes to lung, bone





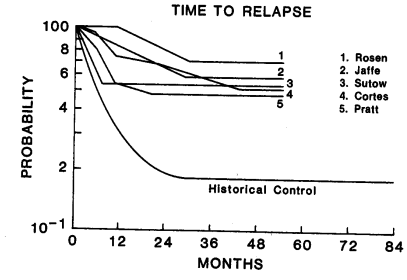
Osteosarcoma
Surgical Improvements

- Transition from amputation to >80% limb sparing
- Amputation
  - Neurovascular compromise
  - Pathologic fracture
  - Improper biopsy site
  - Infection
  - Lack of adequate residual extremity function

Osteosarcoma
5-Year Survival Improvement

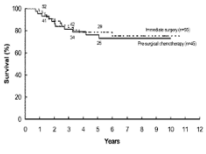
- 1940-1970 Surgery alone: 20%
- 1971 Adjuvant chemo phase II: 40-60%
- 1978 Mayo surgery alone: 40-50%
- 1984-1987 Randomized chemo studies: 50-60%
  - MIOS (36 randomized, 165 non-randomized)
    - RFS: 63% vs. 12% (P=.001) OS: 71% vs. 48% (P=.04)
  - UCLA (59 randomized)
    - RFS: 55% vs. 20% (P=.004) OS: 80% vs. 48% (P=.04)

Osteosarcoma



Osteosarcoma
Neoadjuvant Chemotherapy

- Developed in 1970's
  - Time for custom prosthesis
- Test of in vivo chemosensitivity
- Randomized trial (POG):
  - adjuvant vs. neoadjuvant
  - No survival difference



Goorin et al, *J Clin Oncol 21:1574-1580*

Doxorubicin/Cisplatin vs. Multi-Drug

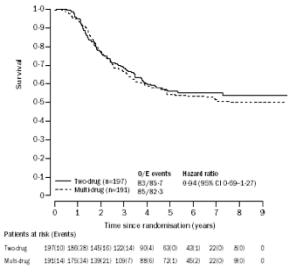
- Doxorubicin 25 mg/m2 D1-3
- Cisplatin 100 mg/m2 D1

Repeat q 21 days.

3 cycles pre-op, 3 cycles post-op

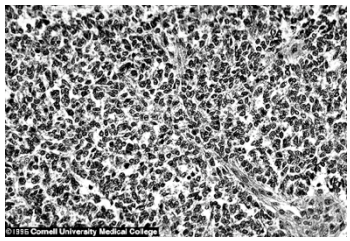
Vs.

- Vincristine
- High-dose Methotrexate
- Doxorubicin
- Bleomycin
- Cyclophosphamide
- Dactinomycin
- Cisplatin



Souhami et al, Lancet1997; 350: 911–17

Ewing's Family of Tumors



James Ewing
1866-1943

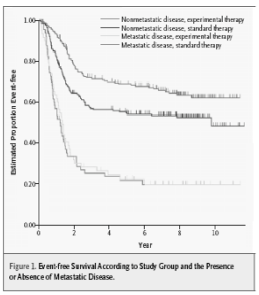
Ewing's Family of Tumors

- Ewing's – mostly bone
- PNET – soft tissue
- Age: 10-25
- T(11;22)(q24;q12) – EWS/FLI1
  - Chimeric transcription factor

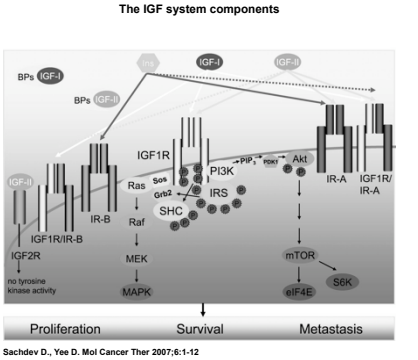
Ewing's Family of Tumors

- Chemo → XRT/Surgery → Chemo
- Cure 70% of children <10 year

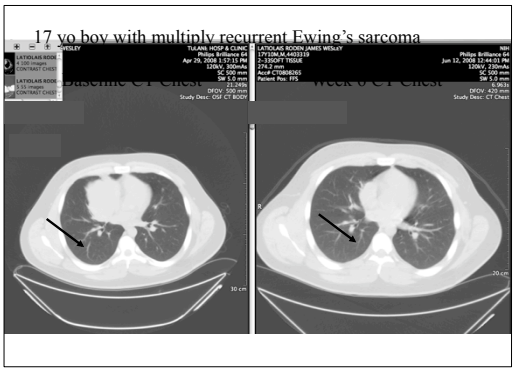
VAC vs. VAC/IE



Grier et al, N Engl J Med 2003;348:694-701.



17 yo boy with multiply recurrent Ewing's sarcoma



Baseline CT Chest Week 6 CT Chest

Conclusions

- Treatment of bone & soft tissue sarcomas is multdisciplinary
- Goals are to save life and limb
- Adjuvant chemotherapy
  - Essential for osteosarcoma, Ewing's/PNET
  - Not proven for soft-tissue sarcoma
- Metastatic disease
  - Potential cure in Ewing's/PNET

Musculoskeletal Oncology Group

- Orthopaedic Surgery
  - James Hayden, MD
  - Zachary Adler, MD
- Medical Oncology
  - Christopher Ryan, MD

- Radiation Oncology
  - Arthur Hung, MD
- Surgical Oncology
  - John Vetto, MD
  - Kevin Billingsley, MD
- Pathology
  - Atiya Mansoor, MD

- Multidisciplinary Bone & Soft Tissue Conference every Wednesday (x 4th) 12:30 p.m Hatfield 14th floor.