Soft Tissue Sarcoma

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Understanding Soft Tissue Sarcoma Is Not Easy !!

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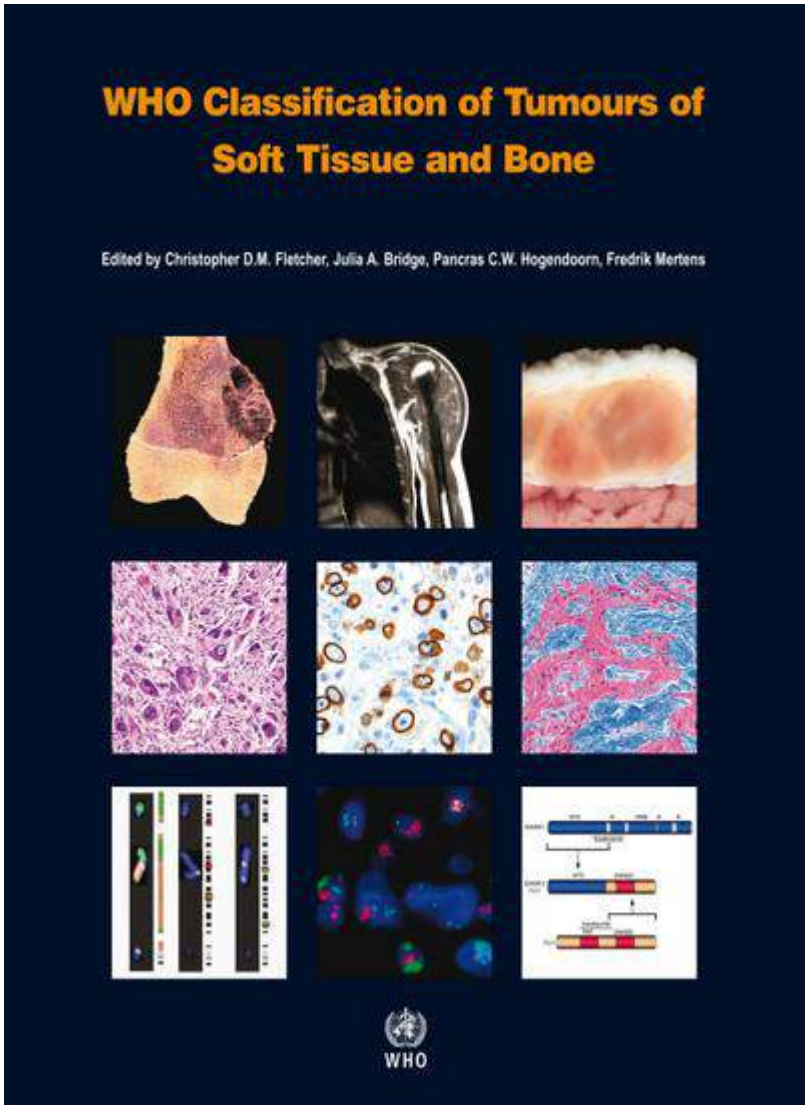

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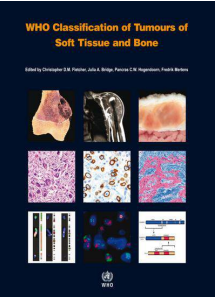


- multiple, distinct histologies

WHO classification of tumours of soft tissue[a,b]

ADIPOCYTIC TUMOURS

Benign

Lipoma	8850/0
Lipomatosis	8850/0
Lipomatosis of nerve	8850/0
Lipoblastoma/lipoblastomatosis	8881/0
Angiolipoma	8861/0
Myolipoma	8890/0
Chondroid lipoma	8862/0
Extra-renal angiomyolipoma	8860/0
Extra-adrenal myelolipoma	8870/0
Spindle cell/pleomorphic lipoma	8857/0
Hibernoma	8880/0

Intermediate (locally aggressive)

Atypical lipomatous tumour/ well differentiated liposarcoma	8850/1 8850/3

Malignant

Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Pleomorphic liposarcoma	8854/3
Liposarcoma, not otherwise specified	8850/3

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign

Nodular fasciitis	8828/0*
Proliferative fasciitis	8828/0*
Proliferative myositis	8828/0*
Myositis ossificans	
Fibro-osseous pseudotumour of digits	
Ischaemic fasciitis	
Elastofibroma	8820/0
Fibrous hamartoma of infancy	
Fibromatosis colli	
Juvenile hyaline fibromatosis	
Inclusion body fibromatosis	
Fibroma of tendon sheath	8813/0
Desmoplastic fibroblastoma	8810/0
Mammary-type myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	8816/0*
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Nuchal-type fibroma	8810/0
Gardner fibroma	8810/0
Calcifying fibrous tumour	8817/0*

Intermediate (locally aggressive)

Palmar/plantar fibromatosis	8813/1*
Desmoid-type fibromatosis	8821/1
Lipofibromatosis	8851/1*
Giant cell fibroblastoma	8834/1

Intermediate (rarely metastasizing)

Dermatofibrosarcoma protuberans	8832/1*
Fibrosarcomatous dermatofibrosarcoma protuberans	8832/3*
Pigmented dermatofibrosarcoma protuberans	8833/1*
Solitary fibrous tumour	8815/1*
Solitary fibrous tumour, malignant	8815/3
Inflammatory myofibroblastic tumour	8825/1
Low-grade myofibroblastic sarcoma	8825/3*
Myxoinflammatory fibroblastic sarcoma/ Atypical myxoinflammatory fibroblastic tumour	8811/1*
Infantile fibrosarcoma	8814/3

Malignant

Adult fibrosarcoma	8810/3
Myxofibrosarcoma	8811/3
Low-grade fibromyxoid sarcoma	8840/3*
Sclerosing epithelioid fibrosarcoma	8840/3*

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Tenosynovial giant cell tumour	
localized type	9252/0
diffuse type	9252/1*
malignant	9252/3
Deep benign fibrous histiocytoma	8831/0

Intermediate (rarely metastasizing)

Plexiform fibrohistiocytic tumour	8835/1
Giant cell tumour of soft tissues	9251/1

SMOOTH MUSCLE TUMOURS

Benign

Deep leiomyoma	8890/0

Malignant

Leiomyosarcoma (excluding skin)	8890/3

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)	8711/0
Glomangiomatosis	8711/1*
Malignant glomus tumour	8711/3
Myopericytoma	8824/0
Myofibroma	8824/0
Myofibromatosis	8824/1
Angioleiomyoma	8894/0

SKELETAL MUSCLE TUMOURS

Benign

Rhabdomyoma	8900/0
Adult type	8904/0
Fetal type	8903/0
Genital type	8905/0

Malignant

Embryonal rhabdomyosarcoma (including botryoid, anaplastic)	8910/3
Alveolar rhabdomyosarcoma (including solid, anaplastic)	8920/3
Pleomorphic rhabdomyosarcoma	8901/3
Spindle cell/sclerosing rhabdomyosarcoma	8912/3

VASCULAR TUMOURS OF SOFT TISSUE

Benign

Haemangioma	9120/0
Synovial	
Venous	9122/0
Arteriovenous haemangioma/malformation	9123/0
Intramuscular	9132/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma	9130/1

Intermediate (rarely metastasizing)

Retiform haemangioendothelioma	9136/1*
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9136/1
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9136/1
Kaposi sarcoma	9140/3

Malignant

Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma	9220/0
Extraskeletal mesenchymal chondrosarcoma	9240/3
Extraskeletal osteosarcoma	9180/3

GASTROINTESTINAL STROMAL TUMOURS

Benign gastrointestinal stromal tumour	8936/0
Gastrointestinal stromal tumour, uncertain malignant potential	8936/1
Gastrointestinal stromal tumour, malignant	8936/3

NERVE SHEATH TUMOURS

Benign

Schwannoma (including variants)	9560/0
Melanotic schwannoma	9560/1*
Neurofibroma (incl. variants)	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Malignant perineurioma	9571/3
Granular cell tumour	9580/0
Dermal nerve sheath myxoma	9562/0
Solitary circumscribed neuroma	9570/0
Ectopic meningioma	9530/0
Nasal glial heterotopia	
Benign Triton tumour	
Hybrid nerve sheath tumours	9563/0*

Malignant

Malignant peripheral nerve sheath tumour	9540/3
Epithelioid malignant peripheral nerve sheath tumour	9542/3*
Malignant Triton tumour	9561/3
Malignant granular cell tumour	9580/3
Ectomesenchymoma	8921/3

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Acral fibromyxoma	8811/0
Intramuscular myxoma (including cellular variant)	8840/0
Juxta-articular myxoma	8840/0
Deep ("aggressive") angiomyxoma	8841/0*
Pleomorphic hyalinizing angiectatic tumour	8802/1*
Ectopic hamartomatous thymoma	8587/0

Intermediate (locally aggressive)

Haemosiderotic fibrolipomatous tumour	8811/1*

Intermediate (rarely metastasizing)

Atypical fibroxanthoma	8830/1
Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	8842/0
Ossifying fibromyxoid tumour, malignant	8842/3*
Mixed tumour NOS	8940/0
Mixed tumour NOS, malignant	8940/3
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Phosphaturic mesenchymal tumour, benign	8990/0
Phosphaturic mesenchymal tumour, malignant	8990/3

Malignant

Synovial sarcoma NOS	9040/3
Synovial sarcoma, spindle cell	9041/3
Synovial sarcoma, biphasic	9043/3
Epithelioid sarcoma	8804/3
Alveolar soft-part sarcoma	9581/3
Clear cell sarcoma of soft tissue	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
Extraskeletal Ewing sarcoma	9364/3
Desmoplastic small round cell tumour	8806/3
Extra-renal rhabdoid tumour	8963/3
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	
PEComa NOS, benign	8714/0*
PEComa NOS, malignant	8714/3*
Intimal sarcoma	9137/3*

UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

Undifferentiated spindle cell sarcoma	8801/3
Undifferentiated pleomorphic sarcoma	8802/3
Undifferentiated round cell sarcoma	8803/3
Undifferentiated epithelioid sarcoma	8804/3
Undifferentiated sarcoma NOS	8805/3

STS in AYA

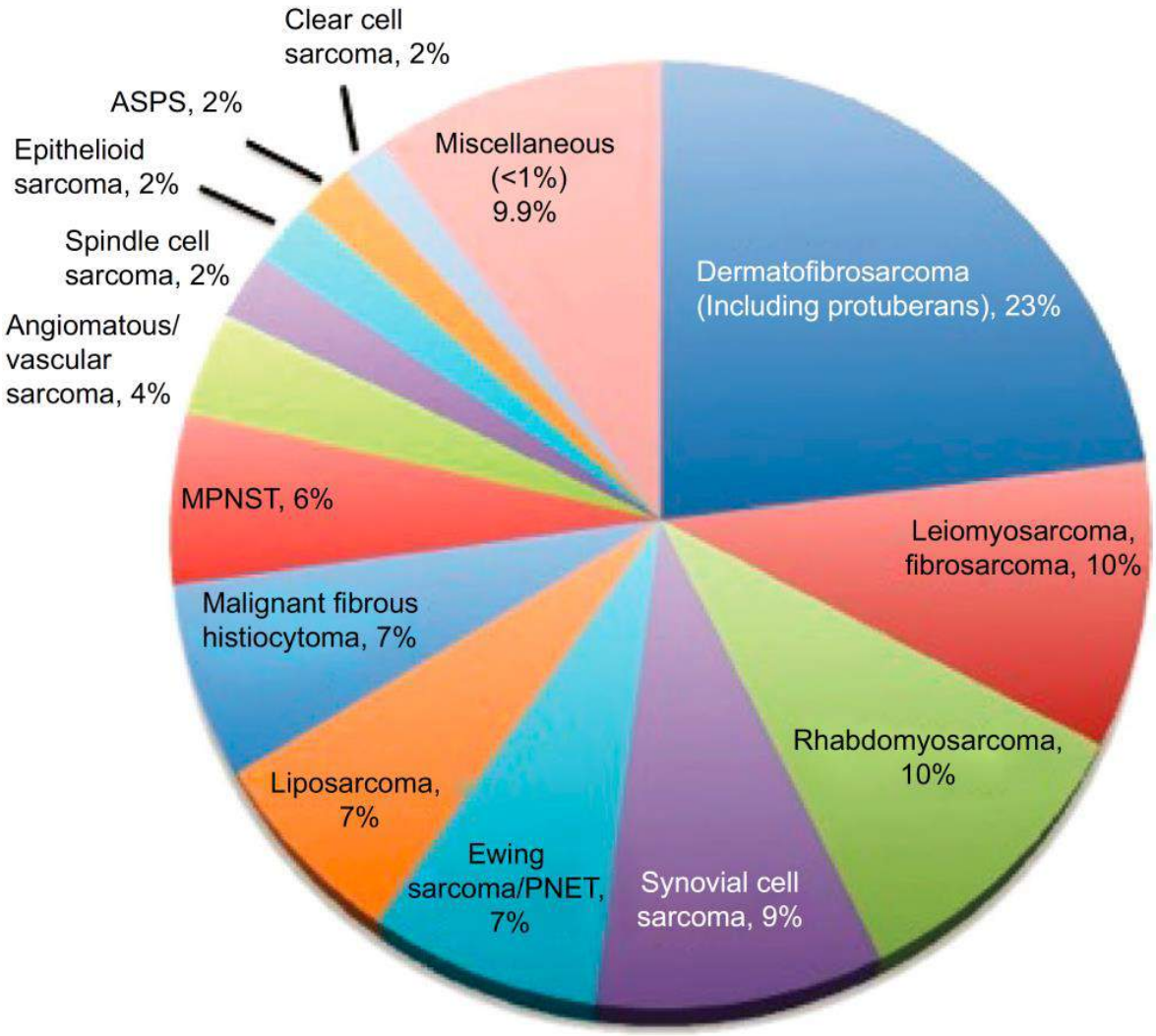
Adolescent Health, Medicine and Therapeutics Dovepress

REVIEW

Targeted therapy for soft tissue sarcomas in adolescents and young adults

Diana A Steppan
Christine A Pratilas
David M Loeb

Abstract: Soft tissue sarcomas (STSs) are a heterogeneous group of tumors originating from the mesenchyme. Even though they affect individuals in all age groups, the prevalence of subtypes of STSs changes significantly from childhood through adolescence into adulthood. The mainstay



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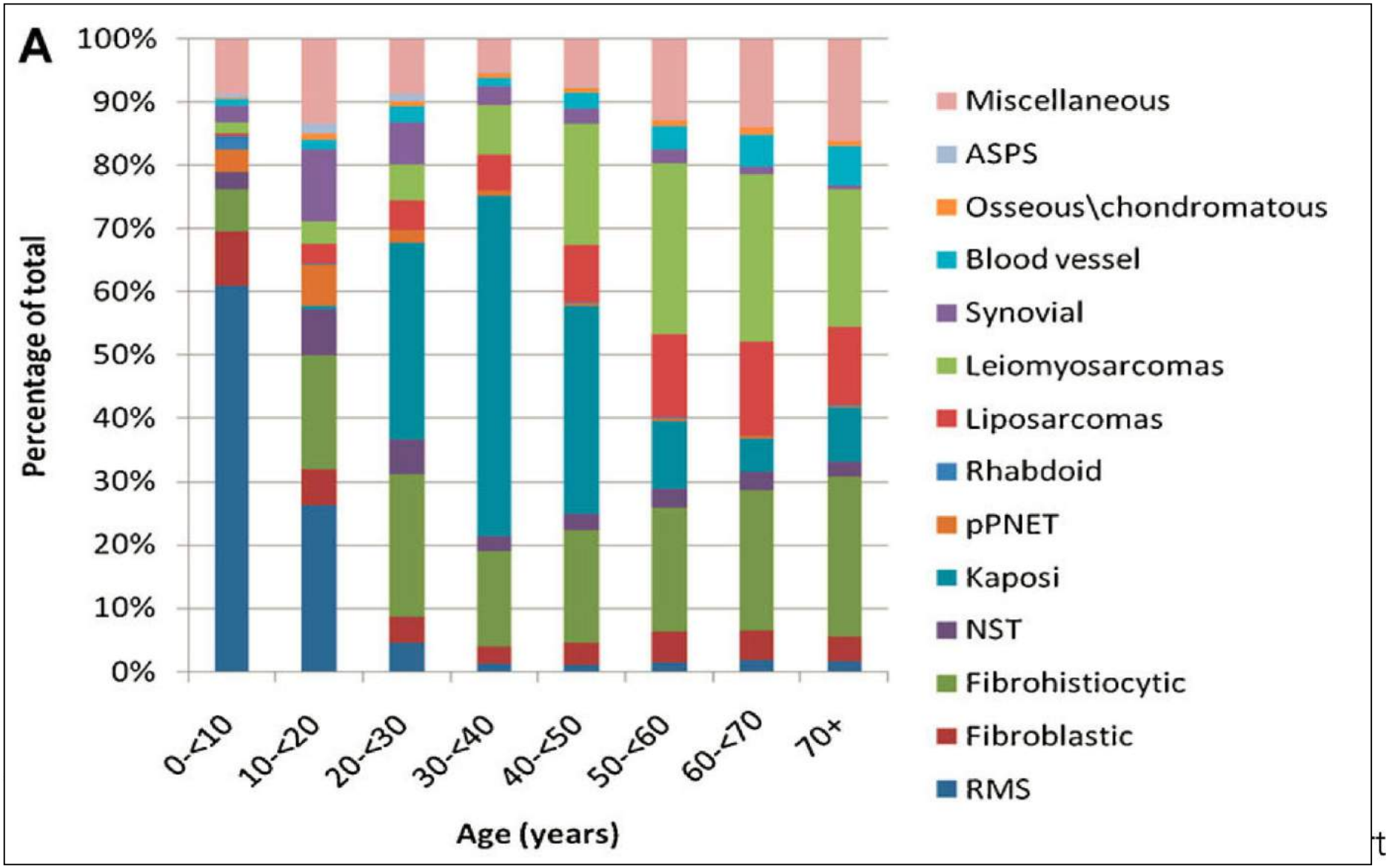
Andrea Ferrari, MD,[1] Iyad Sultan, MD,[2]* Tseng Tien Huang, PhD,[3] Carlos Rodriguez-Galindo, MD,[4] Ahmad Shehadeh, MD,[5] Cristina Meazza, MD,[1] Kirsten K. Ness, PhD,[3] Michela Casanova, MD,[1] and Sheri L. Spunt, MD[6,7]



FNCLCC grading system: definition of parameters

Tumour differentiation	
Score 1: sarcomas closely resembling normal adult mesenchymal tissue (e.g., low grade leiomyosarcoma).	
Score 2: sarcomas for which histological typing is certain (e.g., myxoid liposarcoma).	
Score 3: embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, osteosarcomas, PNET.	
Mitotic count	
Score 1:	0-9 mitoses per 10 HPF*
Score 2:	10-19 mitoses per 10 HPF
Score 3:	≥20 mitoses per 10 HPF
Tumour necrosis	
Score 0:	no necrosis
Score 1:	<50% tumour necrosis
Score 2:	≥50% tumour necrosis
Histological grade	
Grade 1:	total score 2,3
Grade 2:	total score 4,5
Grade 3:	total score 6, 7, 8

Modified from Trojani et al. {2131}.
PNET: primitive neuroectodermal tumour
*A high power field (HPF) measures 0.1734 mm^2

Soft Tissue Sarcoma

Grading

according to FNCLCC

(French Federation of Cancer Centers Sarcoma Group)

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World Health Organization Classification of Tumours

WHO OMS

International Agency for Research on Cancer (IARC)

Pathology and Genetics of Tumours of Soft Tissue and Bone

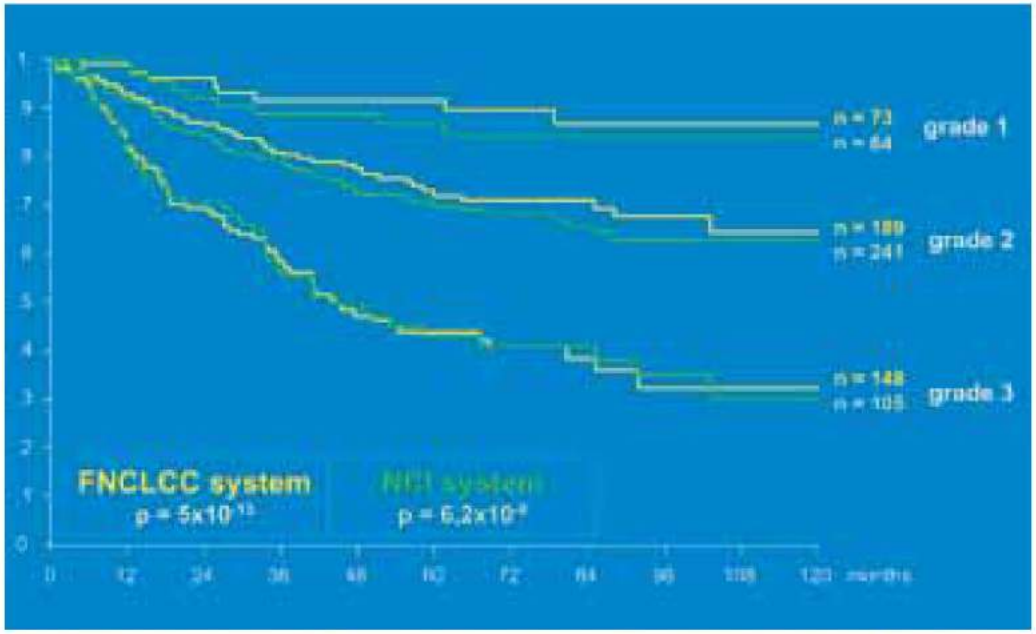


Fig. A.1 Comparison of overall survival curves for a cohort of 410 patients with soft tissue sarcomas graded according to the NCI and FNCLCC systems. Reproduced from Guillou et al {851}.

•various molecular peculiarities

Tab. 1 Chromosomale Translokationen bei Weichteilsarkomen. (Mod. nach [1])

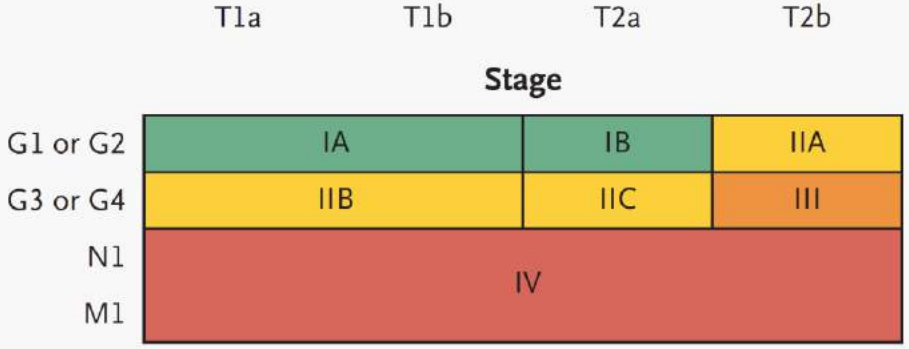
Histologischer Phänotyp	Translokation	Involvierte Gene
Synovialsarkom	t(X;18)(p11.2;q11.2)	*SSX1 oder SSX2; SYT*
Myxoides/rundzelliges Liposarkom	t(12;16)(q13;p11) t(12;22)(q13;q11-q12)	*CHOP;TLS* *CHOP;EWS*
Ewing-Sarkom oder PNET	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(2;22)(q33;q12) t(17;22)(q12;q12)	*FLI1;EWS* *ERG;EWS* *ETV1;EWS* *FEV;EWS* *E1AF;EWS*
Desmoplastischer Tumor	t(11;22)(p13;q12)	*WT1;EWS*
Alveoläres Rhabdomyosarkom	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3;FKHR* *PAX7;FKHR*
Extraskelettales myxoides Chondrosarkom	t(9;22)(q21-31;q12.2) t(9;17)(q22;q11)	*CHN;EWS* *CHN;RBP56*
Klarzellsarkom	t(12;22)(q13;q12)	*ATF1;EWS*
Alveoläres Weichteilsarkom	t(X;17)(p11;q25)	*TFE3;ASPL*
Dermatofibrosarkom, Riesenzellfibroblastom	t(17;22)(q22;q13)	*COL1A1;PDGFB1*
Infantiles Fibrosarkom	t(12;15)(p13;q25)	*ETV6;NTRK3*
Fibromyxoidsarkom	t(7;16)(q34;p11)	*FUS;BBF2H7*

TNM classification of soft tissue sarcomas

Primary tumour (T)	TX:	primary tumour cannot be assessed
	T0:	no evidence of primary tumour
	T1:	tumour ≤ 5cm in greatest dimension
		T1a: superficial tumour*
		T1b: deep tumour
	T2:	tumour > 5cm in greatest dimension
		T2a: superficial tumour
		T2b: deep tumour
Regional lymph nodes (N)	NX:	regional lymph nodes cannot be assessed
	N0:	no regional lymph node metastasis
	N1:	regional lymph node metastasis
Distant metastasis (M)	M0:	no distant metastasis
	M1:	distant metastasis

Note: Regional node involvement is rare and cases in which nodal status is not assessed either clinically or pathologically could be considered N0 instead of NX or pNX.

Grade and TNM	Description
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated
T1	Tumor ≤5 cm in largest dimension
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]

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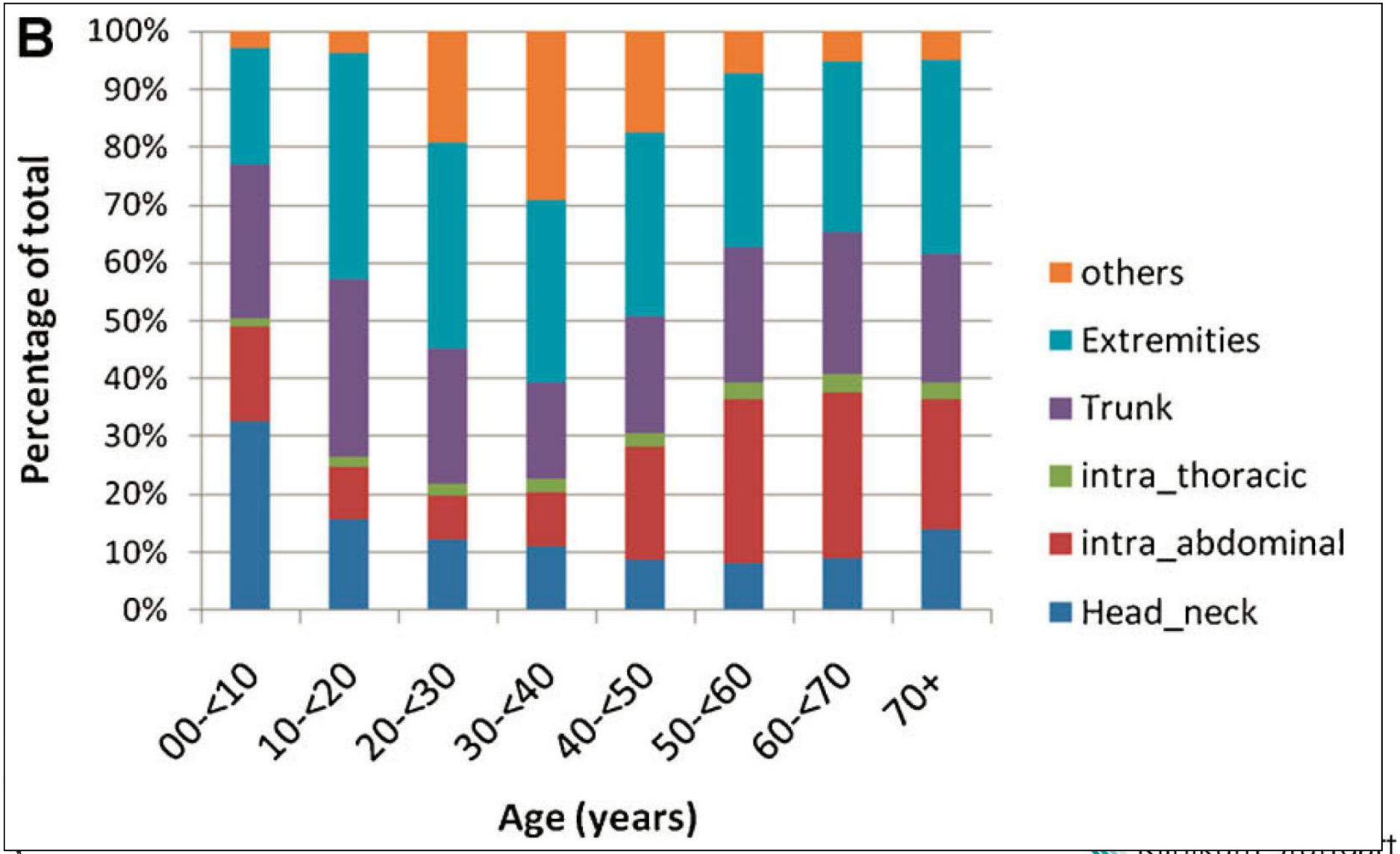

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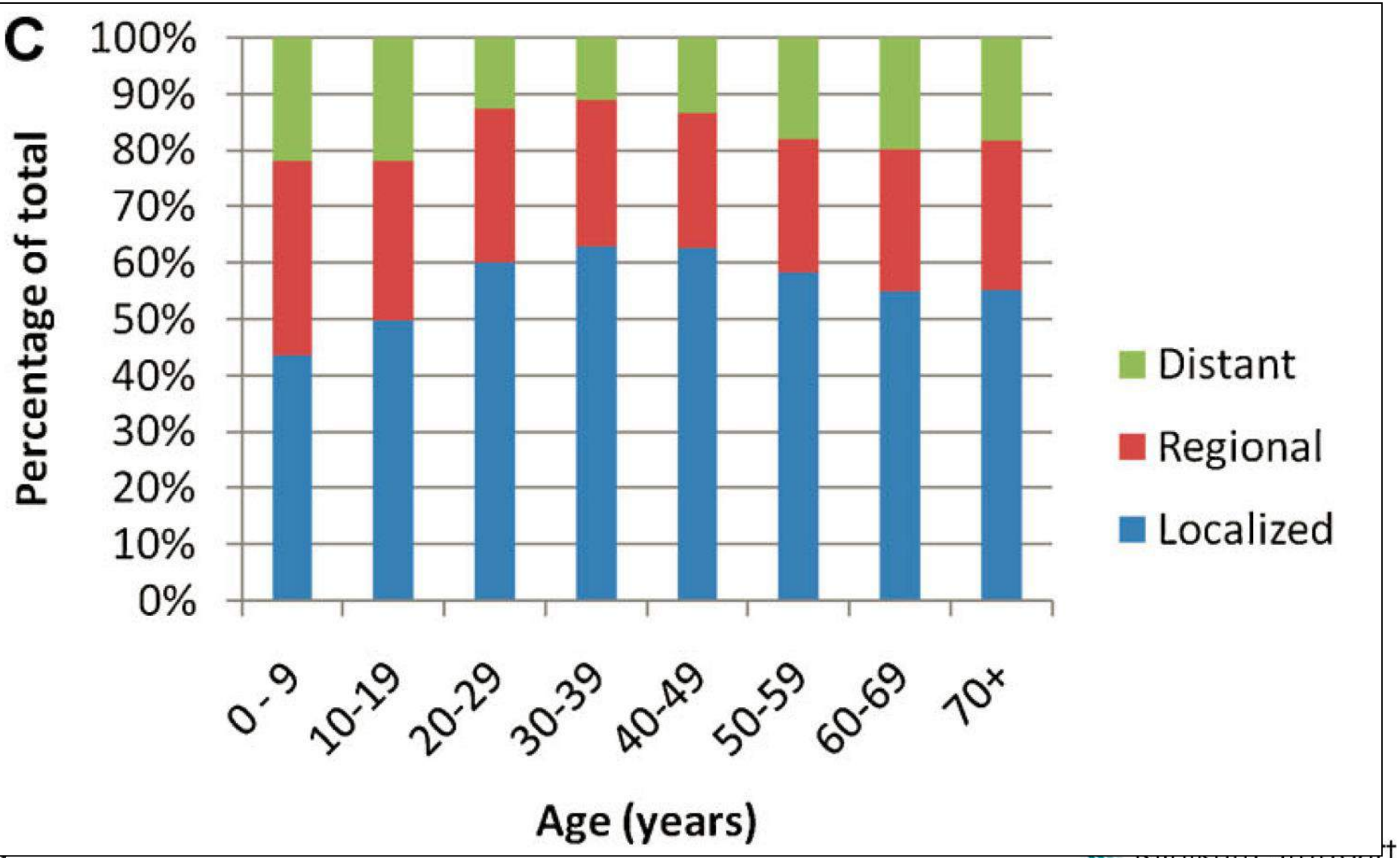

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TABLE III. Five-Year Relative Survival Rates for the Soft Tissue Sarcomas by Histology and Age Groups

Age (years)	Interval (years)	Overall	RMS	Fibrobl	Fibrohis	MPNST	Ka	EW	RH	Lipo	Leio	Syn	BV	Osse	ASPS	Mis
0–9	5	75 (0.3)	70 (1.6)	89 (2.8)	97 (1.6)	64 (7.9)	50 (35.5)	74 (6.0)	45 (8.6)	89 (10.5)	82 (7.5)	92 (4.3)	43 (13.2)	[a]	100	57 (4.3)
10–19	5	75 (0.3)	50 (2.1)	89 (2.8)	95 (1.2)	51 (4.1)	55 (15.1)	63 (4.2)	[a]	81 (4.8)	87 (3.9)	77 (2.8)	71 (7.5)	64 (11.0)	91 (5.5)	59 (3.0)
20–29	5	79 (0.2)	38 (3.4)	84 (2.6)	97 (0.6)	50 (3.1)	20 (1.0)	43 (5.4)	67 (27.2)	88 (2.2)	74 (2.7)	68 (2.7)	50 (4.6)	71 (7.6)	56 (6.6)	58 (2.4)
30–39	5	74 (0.1)	32 (4.1)	78 (2.5)	94 (0.6)	49 (3.1)	23 (0.6)	38 (5.9)	43 (18.7)	85 (1.5)	69 (1.6)	63 (3.0)	53 (3.8)	76 (5.1)	54 (11.2)	52 (2.2)
40–49	5	69 (0.1)	42 (4.9)	78 (2.3)	88 (0.8)	57 (3.0)	27 (0.8)	38 (7.8)	36 (12.9)	84 (1.3)	63 (1.1)	58 (3.5)	51 (3.1)	82 (4.2)	24 (19.2)	48 (1.8)
50–59	5	64 (0.1)	32 (4.2)	73 (2.3)	78 (1.1)	57 (3.3)	37 (1.6)	27 (8.4)	55 (15.1)	82 (1.3)	47 (1.1)	55 (3.9)	41 (2.7)	74 (5.1)	26 (15.9)	42 (1.5)
60–69	5	60 (0.1)	28 (4.0)	59 (2.7)	70 (1.2)	54 (3.6)	64 (2.6)	41 (9.5)	43 (22.9)	78 (1.4)	44 (1.1)	52 (5.2)	31 (2.4)	67 (5.4)	0	33 (1.5)
70+	5	56 (0.1)	18 (3.0)	56 (3.0)	63 (1.2)	47 (3.6)	79 (2.2)	30 (10.6)	[a]	71 (1.7)	41 (1.1)	38 (6.0)	30 (2.0)	57 (6.3)	0	29 (1.2)

RMS, rhabdomyosarcomas; fibrobl, fibroblastic and myofibroblastic tumors; fibrohis, fibrohistiocytic tumors; MPNST, malignant peripheral nerve sheath tumors; Ka, Kaposi sarcoma; EW, Ewing family tumors; RH, extraneral rhabdoid tumor; Lipo, liposarcomas; Leio, leoimyosarcomas; Syn, synovial sarcomas; BV, blood vessel tumors; Osse, osseous and chondromatous neoplasm of soft tissue; ASPS, alveolar soft parts sarcoma; Mis, miscellaneous/unspecified soft tissue sarcomas including other fibromatous neoplasms; STS, overall survival rate for the soft tissue sarcomas. [a]The Kaplan–Meier method could not be calculated because of not enough intervals to produce rate. The data show 5, 10, and 15 years estimated relative survival rate including standrad error denoted with brackets.

Can we make sense of this?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL ARTICLE

Improved survival using specialized multidisciplinary board in sarcoma patients

J.-Y. Blay[1,2*], P. Soibinet[3], N. Penel[4], E. Bompas[5], F. Duffaud[6], E. Stoeckle[7], O. Mir[8], J. Adam[8], C. Chevreau[9], S. Bonvalot[8,10], M. Rios[11], P. Kerbrat[12], D. Cupissol[13], P. Anract[14], F. Gouin[15], J.-E. Kurtz[16], C. Lebbe[17], N. Isambert[18], F. Bertucci[19], M. Toumonde[7], A. Thyss[20], S. Piperno-Neumann[10], P. Dubray-Longeras[21], P. Meeus[1,2], F. Ducimetière[1,2], A. Giraud[7], J.-M. Coindre[7], I. Ray-Coquard[1,2], A. Italiano[7†] & A. Le Cesne[8†], on behalf of the NETSARC/RREPS and French Sarcoma Group–Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) networks[‡]

Background: Sarcomas are rare but aggressive diseases. Specialized multidisciplinary management is not implemented for all patients in most countries. We investigated the impact of a multidisciplinary tumor board (MDTB) presentation before treatment in a nationwide study over 5 years.

Patients and methods: NETSARC (netsarc.org) is a network of 26 reference sarcoma centers with specialized MDTB, funded by the French National Cancer Institute to improve the outcome of sarcoma patients. Since 2010, presentation to an MDTB and second pathological review are mandatory for sarcoma patients in France. Patients' characteristics and follow-up are collected in a database regularly monitored and updated. The management and survival of patients presented to these MDTB before versus after initial treatment were analyzed.

Results: Out of the 12 528 patients aged ≥15 years, with a first diagnosis of soft tissue and visceral sarcoma obtained between 1 January 2010 and 31 December 2014, 5281 (42.2%) and 7247 (57.8%) were presented to the MDTB before and after the initiation of treatment, respectively. The former group had generally worse prognostic characteristics. Presentation to a MDTB before treatment was associated with a better compliance to clinical practice guidelines, for example, biopsy before surgery, imaging, quality of initial surgery, and less reoperations (all $P < 0.001$). Local relapse-free survival and relapse-free survival were significantly better in patients presented to a MDTB before initiation of treatment, both in univariate and multivariate analysis.

Conclusion: The compliance to clinical practice guidelines and relapse-free survival of sarcoma patients are significantly better when the initial treatment is guided by a pre-therapeutic specialized MDTB.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 2852–2859, 2017
doi:10.1093/annonc/mdx484
Published online 28 August 2017

ORIGINAL ARTICLE

Improved survival using specialized multidisciplinary board in sarcoma patients

J.-Y. Blay[1,2*], P. Soibinet[3], N. Penel[4], E. Bompas[5], F. Duffaud[6], E. Stoeckle[7], O. Mir[8], J. Adam[8], C. Chevreau[9], S. Bonvalot[8,10], M. Rios[11], P. Kerbrat[12], D. Cupissol[13], P. Anract[14], F. Gouin[15], J.-E. Kurtz[16], C. Lebbe[17], N. Isambert[18], F. Bertucci[19], M. Toumonde[7], A. Thyss[20], S. Piperno-Neumann[16], P. Dubray-Longeras[21], P. Meeus[1,2], F. Ducimetière[1,2], A. Giraud[7], J.-M. Coindre[7], I. Ray-Coquard[1,2], A. Italiano[7†] & A. Le Cesne[81], on behalf of the NETSARC/RREPS and French Sarcoma Group–Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) networks[‡]

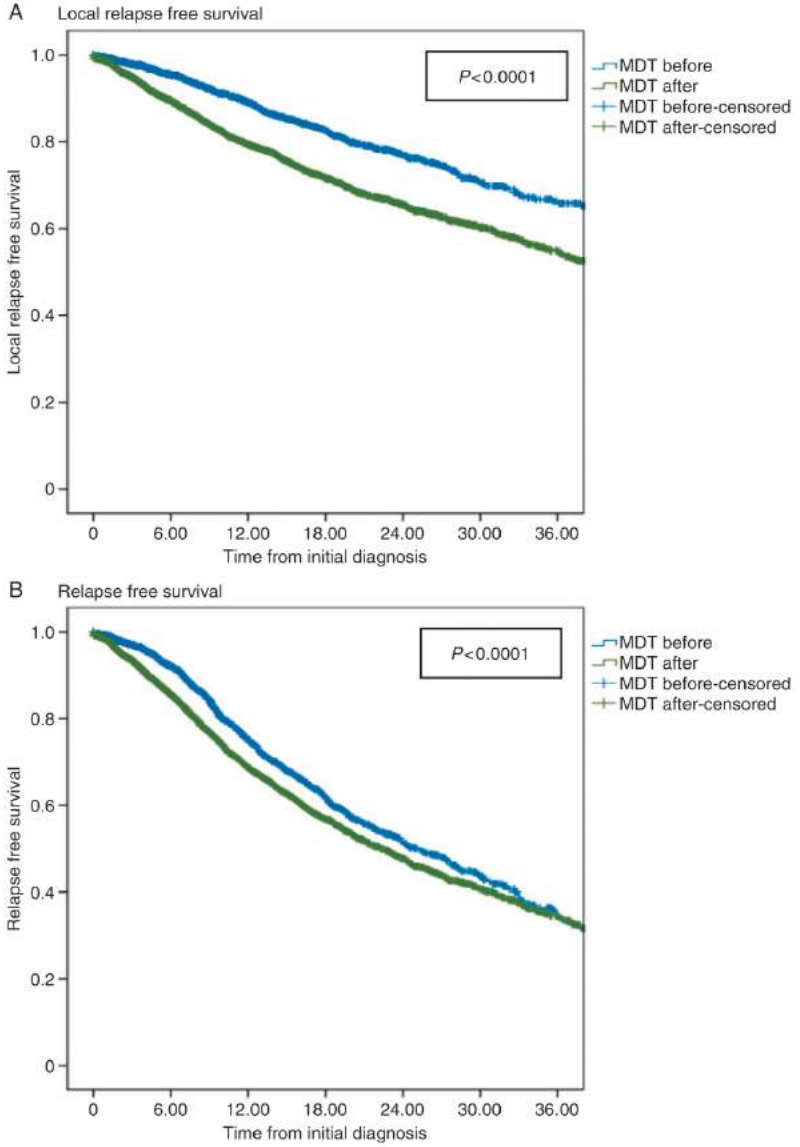

Figure 1. Local relapse-free survival and relapse-free survival in non-metastatic sarcoma patients according to the date of MDTB presentation. (A) Local relapse-free survival in patients presented to a MDTB before, versus after initiation of treatment. (B) Relapse-free survival in patients presented to a MDTB before, versus after initiation of treatment.

Understanding Soft Tissue Sarcoma Is Not Easy

various treatment options

- surgery
- radiotherapy
- chemotherapy
- surgery & radiotherapy
- surgery & chemotherapy
- radiotherapy & chemotherapy
- surgery & radiotherapy & chemotherapy

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ESMO / GUIDELINES & PRACTICE / CLINICAL PRACTICE GUIDELINES / SARCOMA AND GIST / Soft Tissue and Visceral Sarcomas

Soft Tissue and Visceral Sarcomas: ESMO Clinical Practice Guidelines

Published in 2012 – Ann Oncol 2012; 23 (Suppl 7): vii92-vii99.

Authors: *The ESMO / European Sarcoma Network Working Group*

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- Adjuvant chemotherapy is not used in histological subtypes known to be insensitive to chemotherapy.
- If the decision is made to use chemotherapy as upfront treatment, it may well be used preoperatively, at least in part [III, B]. A local benefit may be gained, facilitating surgery.
- If used, adjuvant chemotherapy should consist of the combination chemotherapy regimens proven to be most active in advanced disease.
- Radiation therapy should not delay the start of chemotherapy.
- In one large randomized phase III study (in patients with G2–3, deep, >5 cm STSs), regional hyperthermia in addition to systemic chemotherapy was associated with a local progression-free survival (PFS) and disease-free survival advantage [I, B].

Data have been provided that **adjuvant chemotherapy might improve, or at least delay, distant and local recurrence in high-risk patients**. A meta-analysis found a statistically significant, limited benefit in terms of both survival- and relapse-free survival [5]. However, study results are conflicting. It is also unknown whether adjuvant chemotherapy may be particularly beneficial in specific subgroups. Therefore, adjuvant chemotherapy is not standard treatment in **adult-type** STS and can be proposed as an option to the high-risk individual patient (high-grade, deep, >5 cm tumor) for shared decision-making with the patient [II, C]. **A randomized trial showed no differences between 3 (pre-operative) and 5 (pre- and postoperative) courses of full-dose chemotherapy [6].**

VOLUME 30 · NUMBER 8 · MARCH 10 2012
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Short, Full-Dose Adjuvant Chemotherapy in High-Risk Adult Soft Tissue Sarcomas: A Randomized Clinical Trial From the Italian Sarcoma Group and the Spanish Sarcoma Group

Alessandro Gronchi, Sergio Frustaci, Mario Mercuri, Javier Martin, Antonio Lopez-Pousa, Paolo Verderio, Lidia Mariani, Pinuccia Valagussa, Rosalba Miceli, Silvia Stacchiotti, Angelo Paolo Dei Tos, Antonino De Paoli, Alessandra Longhi, Andres Poveda, Vittorio Quaglhuolo, Alessandro Comandone, Paolo Giovanni Casali, and Piero Picci

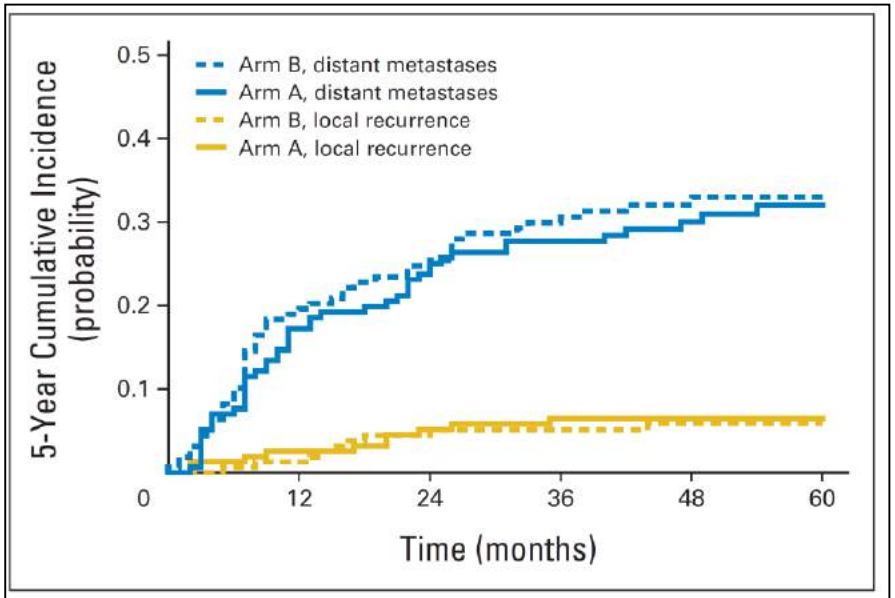
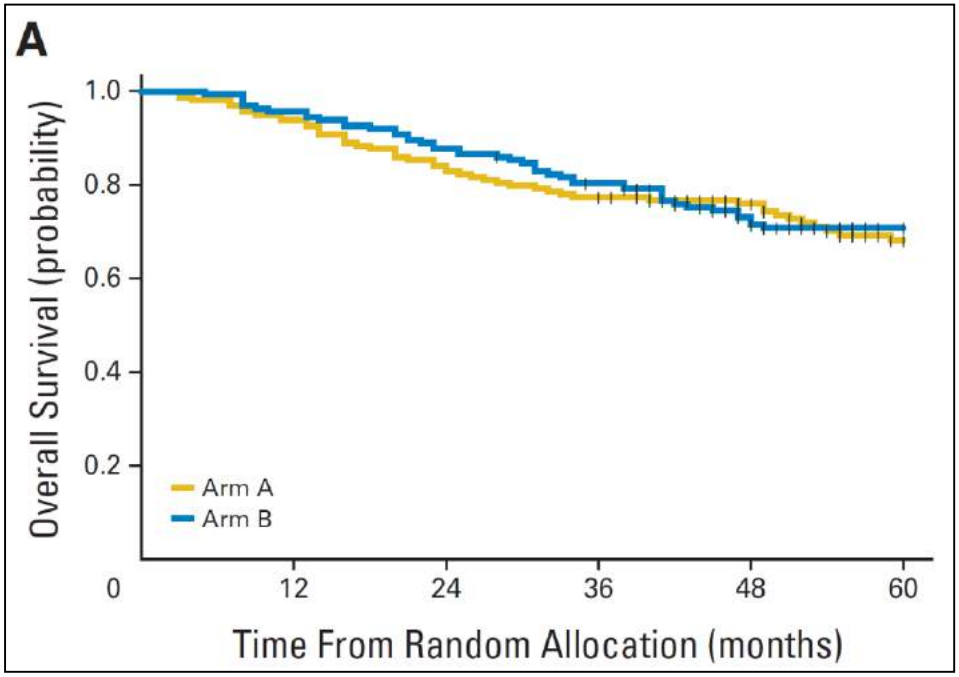
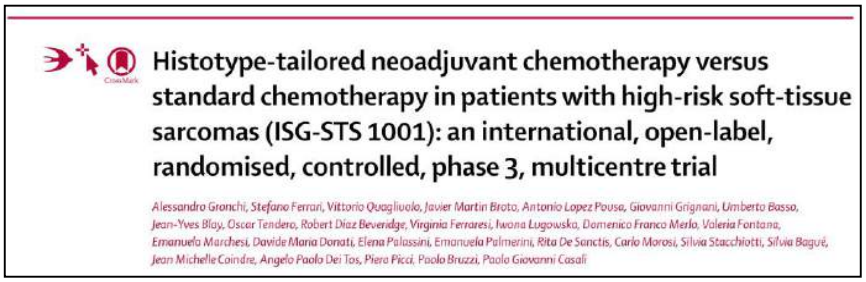


Fig 3. Five-year cumulative incidence of local recurrence and distant metastases according to study arm.





Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero Picci, Paolo Bruzzi, Paolo Giovanni Casali

undifferentiated pleomorphic sarcoma

high-grade myxoid liposarcoma

synovial sarcoma

malignant peripheral nerve sheath tumor

leiomyosarcoma

	n (%)
Standard chemotherapy (n=125)	
Ifosfamide-epirubicin	
Ifosfamide	125 (100%)
Epirubicin	125 (100%)
Histotype-tailored chemotherapy (n=114)	
Gemcitabine-docetaxel	
Gemcitabine	39 (34%)
Docetaxel	39 (34%)
Trabectedin*	18 (16%)
Ifosfamide*	27 (24%)
Ifosfamide-etoposide*	
Ifosfamide	9 (8%)
Etoposide	9 (8%)
Gemcitabine-dacarbazine	
Gemcitabine	15 (13%)
Dacarbazine	15 (13%)

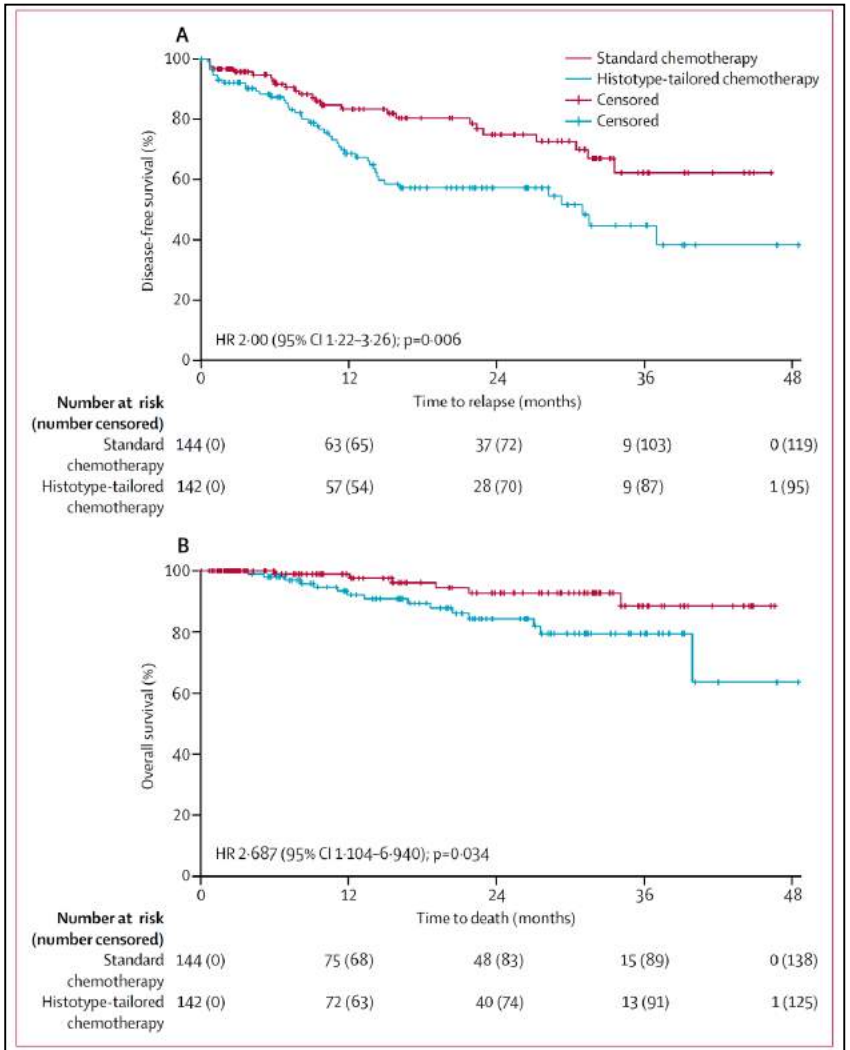


Figure 2: **Disease-free survival and overall survival at 46 months from randomisation**
(A) Disease-free survival. (B) Overall survival. HR=hazard ratio.

Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial

Alessandro Gronchi, Stefano Ferrari, Vittorio Quagliuolo, Javier Martin Broto, Antonio Lopez Pousa, Giovanni Grignani, Umberto Basso, Jean-Yves Blay, Oscar Tendero, Robert Diaz Beveridge, Virginia Ferraresi, Iwona Lugowska, Domenico Franco Merlo, Valeria Fontana, Emanuela Marchesi, Davide Maria Donati, Elena Palassini, Emanuela Palmerini, Rita De Sanctis, Carlo Morosi, Silvia Stacchiotti, Silvia Bagué, Jean Michelle Coindre, Angelo Paolo Dei Tos, Piero Picci, Paolo Bruzzi, Paolo Giovanni Casali

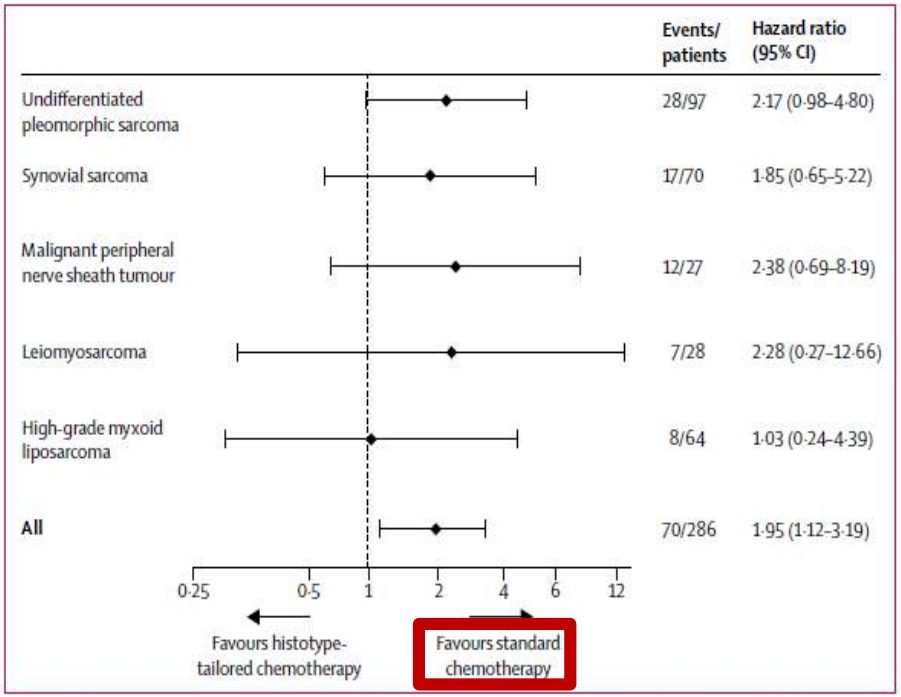


Figure 4: **Standard versus histotype-tailored chemotherapy in the five different histology subtypes**
Hazard ratios of disease-free survival were estimated with binary logistic models.

Advanced Disease

Standard chemotherapy is based on **anthracyclines** as first-line treatment [8] [I, A]. At the time of writing these Guidelines, there is no formal demonstration that multiagent chemotherapy is superior to single-agent chemotherapy with doxorubicin alone in terms of OS. However, a higher response rate may be expected, in particular in a number of sensitive histological types, according to several, although not all, randomized clinical trials. Therefore, multiagent chemotherapy with adequate-dose anthracyclines plus ifosfamide may be the treatment of choice, particularly when a tumor response is felt to be able to give an advantage and patient performance status is good.

Review Article

Systemic Therapy for Advanced Soft Tissue Sarcomas

Highlighting Novel Therapies and Treatment Approaches

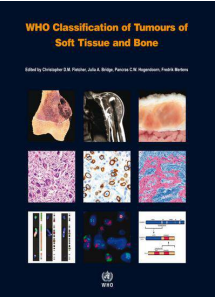
Richard F. Riedel, MD

Table 1. Options for First-Line Chemotherapy in Patients With Advanced STS

Treatment	Response Rate	Median OS, Months	Study
Single-agent regimen			
Doxorubicin (60-75 mg/m^2 every 3 wk)	16%-27%	7.7-12.0	Bramwell 2000[16] Lorigan 2007[21]
Epirubicin (75 mg/m^2)	18%	4.0	Mouridsen 1987[18]
Ifosfamide (5 g/m^2 over 24 h every 3 wk)	10%-25%	12.0	van Oosterom 2002[19]
High-dose ifosfamide[a]	25%-38%	10.2-18.5	van Oosterom 2002[19] Buesa 1998[20]
Temozolomide			
(Oral bid × 5 d every 4 wk)[b]	8%	13.2	Talbot 2003[15]
(Oral every d × 6 wk; then 3 wk off treatment)[b]	16%	8.1	Garcia del Muro 2005[22]
Dacarbazine (1.2 g/m^2 every 3 wk)	18%	NR	Buesa 1991[29]
Combination regimens			
Doxorubicin (50 mg/m^2) + ifosfamide (5 g/m^2) every 3 wk	21%-28%	13.8-14.0	Santoro 1995[24] Le Cesne 2000[28]
Doxorubicin (60 mg/m^2) + ifosfamide (7.5 g/m^2 over 2 d) every 3 wk	34%	~11.5	Edmonson 1993[23]
Doxorubicin (60 mg/m^2) + dacarbazine[c]	17%-30%	8.0-12.0	Borden 1987[17] Antman 1993[25]
Mesna, doxorubicin, ifosfamide, and dacarbazine (MAID)[d]	32%	13.0	Antman 1993[25]
Gemcitabine (900 mg/m^2 on d 1 and 8) + docetaxel (100 mg/m^2) on d 8 every 3 wk	16%	17.9	Maki 2007[26]
Gemcitabine (800 mg/m^2) + vinorelbine (25 mg/m^2) on d 1 and 15 every 4 wk	13%	75% (12-mo OS)	Dileo 2007[27]

Caution:

All of this only applies to „adult“, „non-RMS-like“ STS!



- multiple, distinct histologies

WHO classification of tumours of soft tissue[a,b]

ADIPOCYTIC TUMOURS

Benign

Lipoma	8850/0
Lipomatosis	8850/0
Lipomatosis of nerve	8850/0
Lipoblastoma/lipoblastomatosis	8881/0
Angiolipoma	8861/0
Myolipoma	8890/0
Chondroid lipoma	8862/0
Extra-renal angiomyolipoma	8860/0
Extra-adrenal myelolipoma	8870/0
Spindle cell/pleomorphic lipoma	8857/0
Hibernoma	8880/0

Intermediate (locally aggressive)

Atypical lipomatous tumour/ well differentiated liposarcoma	8850/1 8850/3

Malignant

Dedifferentiated liposarcoma	8858/3
Myxoid liposarcoma	8852/3
Pleomorphic liposarcoma	8854/3
Liposarcoma, not otherwise specified	8850/3

FIBROBLASTIC / MYOFIBROBLASTIC TUMOURS

Benign

Nodular fasciitis	8828/0*
Proliferative fasciitis	8828/0*
Proliferative myositis	8828/0*
Myositis ossificans	
Fibro-osseous pseudotumour of digits	
Ischaemic fasciitis	
Elastofibroma	8820/0
Fibrous hamartoma of infancy	
Fibromatosis colli	
Juvenile hyaline fibromatosis	
Inclusion body fibromatosis	
Fibroma of tendon sheath	8813/0
Desmoplastic fibroblastoma	8810/0
Mammary-type myofibroblastoma	8825/0
Calcifying aponeurotic fibroma	8816/0*
Angiomyofibroblastoma	8826/0
Cellular angiofibroma	9160/0
Nuchal-type fibroma	8810/0
Gardner fibroma	8810/0
Calcifying fibrous tumour	8817/0*

Intermediate (locally aggressive)

Palmar/plantar fibromatosis	8813/1*
Desmoid-type fibromatosis	8821/1
Lipofibromatosis	8851/1*
Giant cell fibroblastoma	8834/1

Intermediate (rarely metastasizing)

Dermatofibrosarcoma protuberans	8832/1*
Fibrosarcomatous dermatofibrosarcoma protuberans	8832/3*
Pigmented dermatofibrosarcoma protuberans	8833/1*
Solitary fibrous tumour	8815/1*
Solitary fibrous tumour, malignant	8815/3
Inflammatory myofibroblastic tumour	8825/1
Low-grade myofibroblastic sarcoma	8825/3*
Myxoinflammatory fibroblastic sarcoma/ Atypical myxoinflammatory fibroblastic tumour	8811/1*
Infantile fibrosarcoma	8814/3

Malignant

Adult fibrosarcoma	8810/3
Myxofibrosarcoma	8811/3
Low-grade fibromyxoid sarcoma	8840/3*
Sclerosing epithelioid fibrosarcoma	8840/3*

SO-CALLED FIBROHISTIOCYTIC TUMOURS

Benign

Tenosynovial giant cell tumour	
localized type	9252/0
diffuse type	9252/1*
malignant	9252/3
Deep benign fibrous histiocytoma	8831/0

Intermediate (rarely metastasizing)

Plexiform fibrohistiocytic tumour	8835/1
Giant cell tumour of soft tissues	9251/1

SMOOTH MUSCLE TUMOURS

Benign

Deep leiomyoma	8890/0

Malignant

Leiomyosarcoma (excluding skin)	8890/3

PERICYTIC (PERIVASCULAR) TUMOURS

Glomus tumour (and variants)	8711/0
Glomangiomatosis	8711/1*
Malignant glomus tumour	8711/3
Myopericytoma	8824/0
Myofibroma	8824/0
Myofibromatosis	8824/1
Angioleiomyoma	8894/0

SKELETAL MUSCLE TUMOURS

Benign

Rhabdomyoma	8900/0
Adult type	8904/0
Fetal type	8903/0
Genital type	8905/0

Malignant

Embryonal rhabdomyosarcoma (including botryoid, anaplastic)	8910/3
Alveolar rhabdomyosarcoma (including solid, anaplastic)	8920/3
Pleomorphic rhabdomyosarcoma	8901/3
Spindle cell/sclerosing rhabdomyosarcoma	8912/3

VASCULAR TUMOURS OF SOFT TISSUE

Benign

Haemangioma	9120/0
Synovial	
Venous	9122/0
Arteriovenous haemangioma/malformation	9123/0
Intramuscular	9132/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0

Intermediate (locally aggressive)

Kaposiform haemangioendothelioma	9130/1

Intermediate (rarely metastasizing)

Retiform haemangioendothelioma	9136/1*
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9136/1
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9136/1
Kaposi sarcoma	9140/3

Malignant

Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

CHONDRO-OSSEOUS TUMOURS

Soft tissue chondroma	9220/0
Extraskeletal mesenchymal chondrosarcoma	9240/3
Extraskeletal osteosarcoma	9180/3

GASTROINTESTINAL STROMAL TUMOURS

Benign gastrointestinal stromal tumour	8936/0
Gastrointestinal stromal tumour, uncertain malignant potential	8936/1
Gastrointestinal stromal tumour, malignant	8936/3

NERVE SHEATH TUMOURS

Benign

Schwannoma (including variants)	9560/0
Melanotic schwannoma	9560/1*
Neurofibroma (incl. variants)	9540/0
Plexiform neurofibroma	9550/0
Perineurioma	9571/0
Malignant perineurioma	9571/3
Granular cell tumour	9580/0
Dermal nerve sheath myxoma	9562/0
Solitary circumscribed neuroma	9570/0
Ectopic meningioma	9530/0
Nasal glial heterotopia	
Benign Triton tumour	
Hybrid nerve sheath tumours	9563/0*

Malignant

Malignant peripheral nerve sheath tumour	9540/3
Epithelioid malignant peripheral nerve sheath tumour	9542/3*
Malignant Triton tumour	9561/3
Malignant granular cell tumour	9580/3
Ectomesenchymoma	8921/3

TUMOURS OF UNCERTAIN DIFFERENTIATION

Benign

Acral fibromyxoma	8811/0
Intramuscular myxoma (including cellular variant)	8840/0
Juxta-articular myxoma	8840/0
Deep ("aggressive") angiomyxoma	8841/0*
Pleomorphic hyalinizing angiectatic tumour	8802/1*
Ectopic hamartomatous thymoma	8587/0

Intermediate (locally aggressive)

Haemosiderotic fibrolipomatous tumour	8811/1*

Intermediate (rarely metastasizing)

Atypical fibroxanthoma	8830/1
Angiomatoid fibrous histiocytoma	8836/1
Ossifying fibromyxoid tumour	8842/0
Ossifying fibromyxoid tumour, malignant	8842/3*
Mixed tumour NOS	8940/0
Mixed tumour NOS, malignant	8940/3
Myoepithelioma	8982/0
Myoepithelial carcinoma	8982/3
Phosphaturic mesenchymal tumour, benign	8990/0
Phosphaturic mesenchymal tumour, malignant	8990/3

Malignant

Synovial sarcoma NOS	9040/3
Synovial sarcoma, spindle cell	9041/3
Synovial sarcoma, biphasic	9043/3
Epithelioid sarcoma	8804/3
Alveolar soft-part sarcoma	9581/3
Clear cell sarcoma of soft tissue	9044/3
Extraskeletal myxoid chondrosarcoma	9231/3
Extraskeletal Ewing sarcoma	9364/3
Desmoplastic small round cell tumour	8806/3
Extra-renal rhabdoid tumour	8963/3
Neoplasms with perivascular epithelioid cell differentiation (PEComa)	
PEComa NOS, benign	8714/0*
PEComa NOS, malignant	8714/3*
Intimal sarcoma	9137/3*

UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS

Undifferentiated spindle cell sarcoma	8801/3
Undifferentiated pleomorphic sarcoma	8802/3
Undifferentiated round cell sarcoma	8803/3
Undifferentiated epithelioid sarcoma	8804/3
Undifferentiated sarcoma NOS	8805/3

Possible simplification

Rhabdomyosarcoma

-embryonal (2/3)

-alveolar (1/3)

Pediatric type STS (RMS-like)

(EOES, UDS, DSRCT, *SySa**)

(infantile fibrosarcoma, pleuropulm. blastoma, …)

Adult type STS (non-RMS-like)

RMS-like Soft Tissue Sarcoma

Chemotherapy

- **Indication** always*
- **Begin** primary

if surgery could only be mutilating otherwise

postoperatively

* synovial??

RMS-like Soft Tissue Sarcoma

Chemotherapy

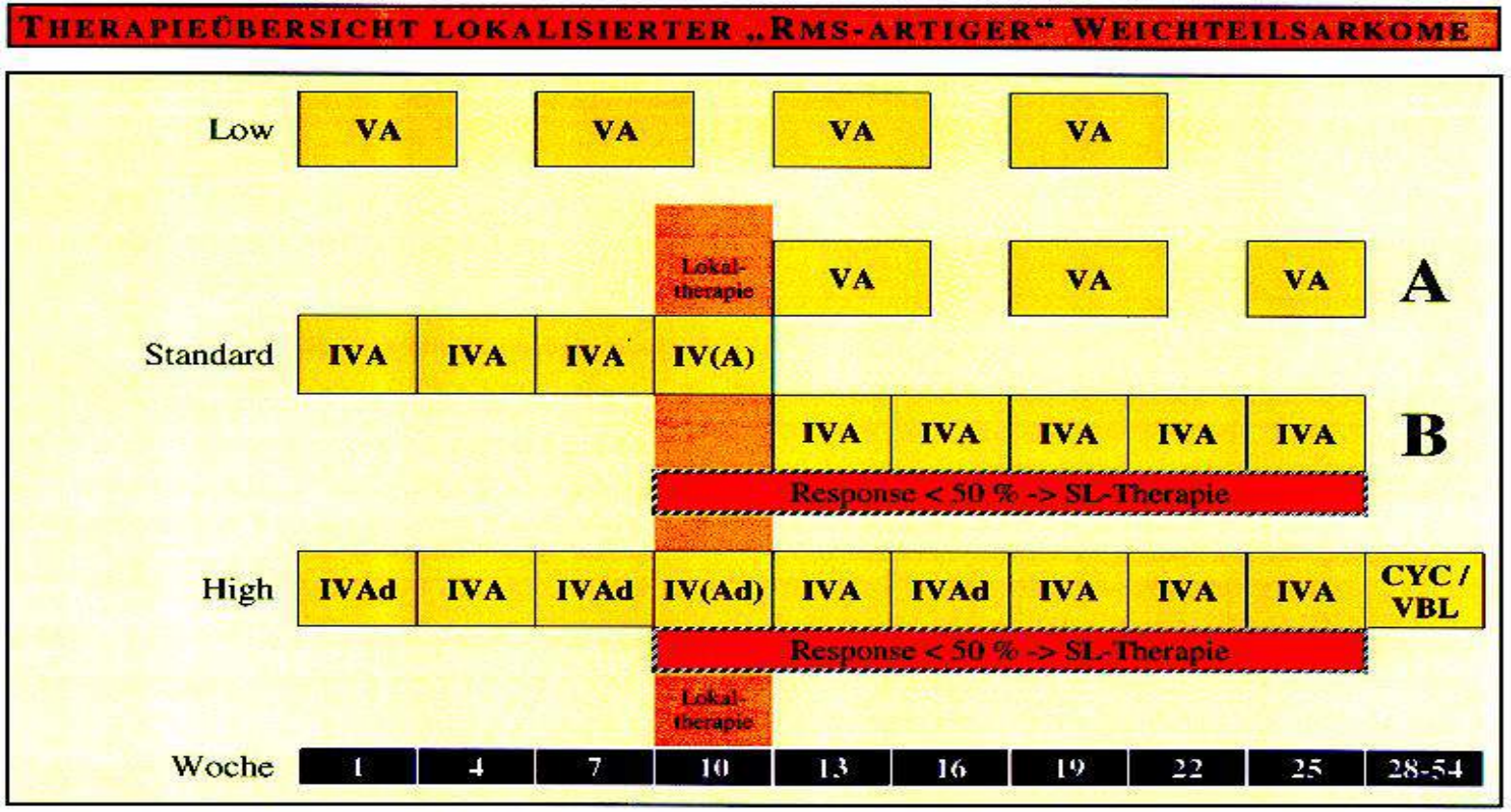
- Actinomycin D *(Pinkel 1959, Tan 1959)*
- Cyclophosphamide *(Pinkel 1962)*
- Vincristine *(Selawry 1963)*
- Daunomycin *(Sutow 1972)*
- Doxorubicin *(Evans 1974)*
- CCNU *(Chang 1976)*
- Etoposide *(Nissen 1980)*
- IFOS *(Pappo 1994)*
- Topotecan *(Vietti 1997)*
- HD-MTX *(Pappo 1997)*

RMS-like Soft Tissue Sarcoma

Chemotherapy

- ACT + VCR *(James 1966)*
- ACT + VCR + CYC *(Pratt 1968, Wilbur 1971)*
- ACT + VCR + CYC + DOX *(Ghavimi 1981, Treuner 1989)*
- ACT + VCR + IFO *(Otten 1989)*
- ACT + VCR + DOX *(Crist 1995)*
- VADRC-VAC + ETO+ CDDP *(Crist 1995)*
- CARBO + EPI + VCR *(Frascella 1996)*
- ACT + VCR + IFO + DOX *(Treuner 1989, Pratt 1998)*
- DOX + IFO *(Sandler 2001)*
- IFO + ETO *(Breitfeld 2001)*
- VCR + MEL *(Breitfeld 2001)*
- TOPO + CYC *(Saylors 2001)*

Therapy concept of CWS-2002-P for RMS-like tumours:



Standard A) günstige Lokalisation in Vollremission oder initial Stadium I **Standard B)** ungünstige Lokalisation alle oder günstige Lokalisation nicht in Vollremission

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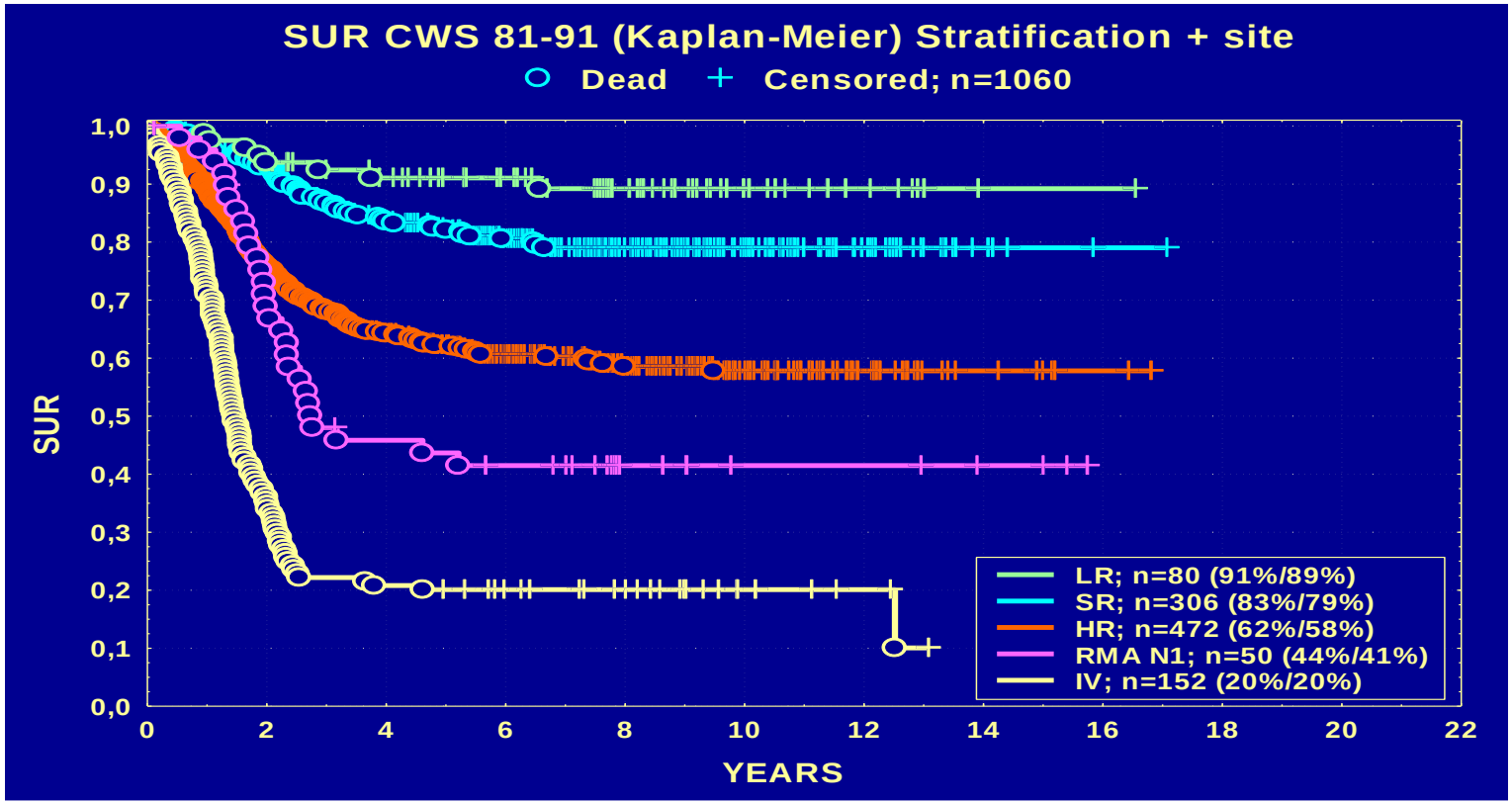
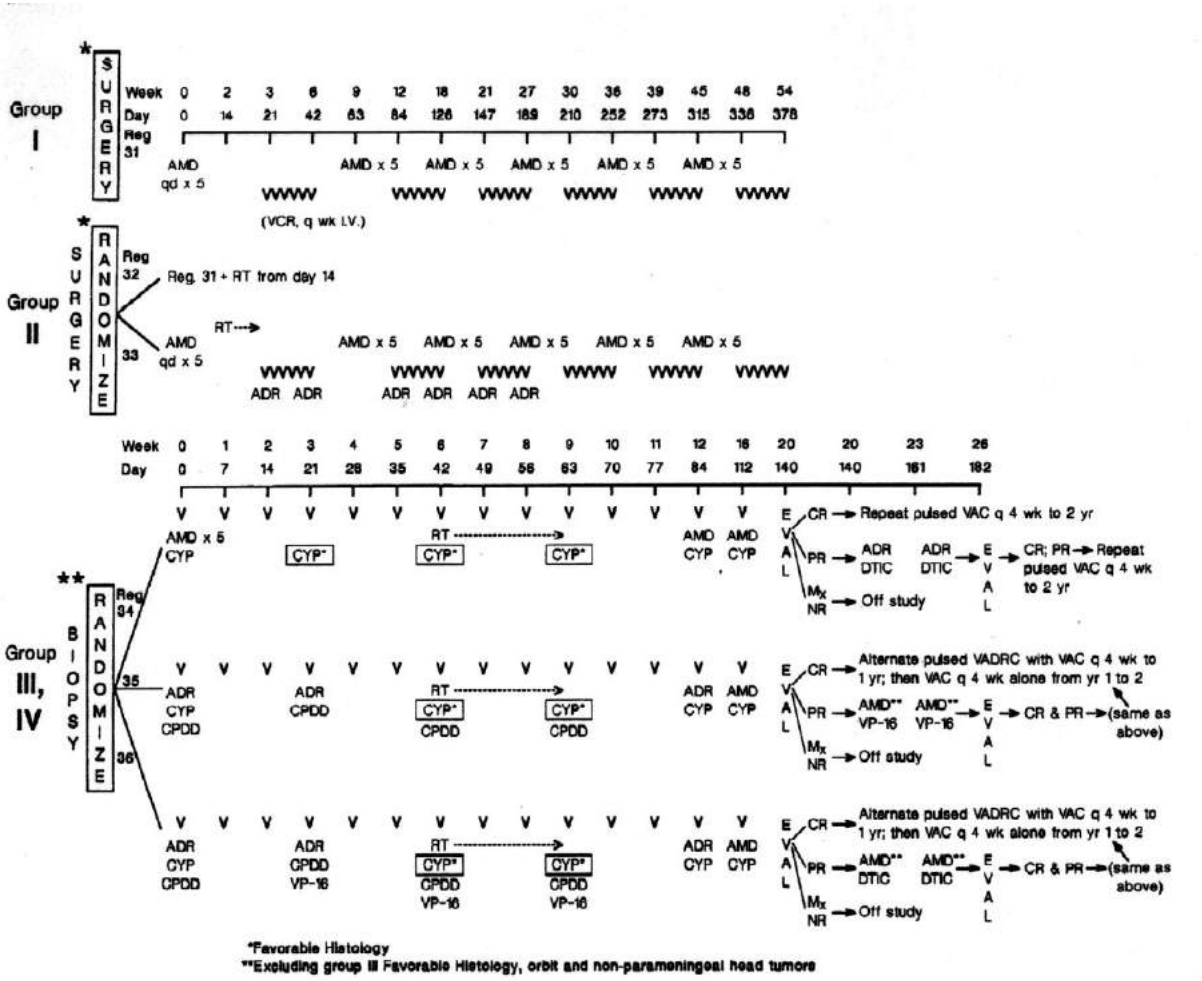
Overall survival in the studies CWS -81, -86, and -91:



Therapy concept of IRS III for RMS-like tumours:



*Favorable Histology
**Excluding group III Favorable Histology, orbit and non-parameningeal head tumors

Crist 1995

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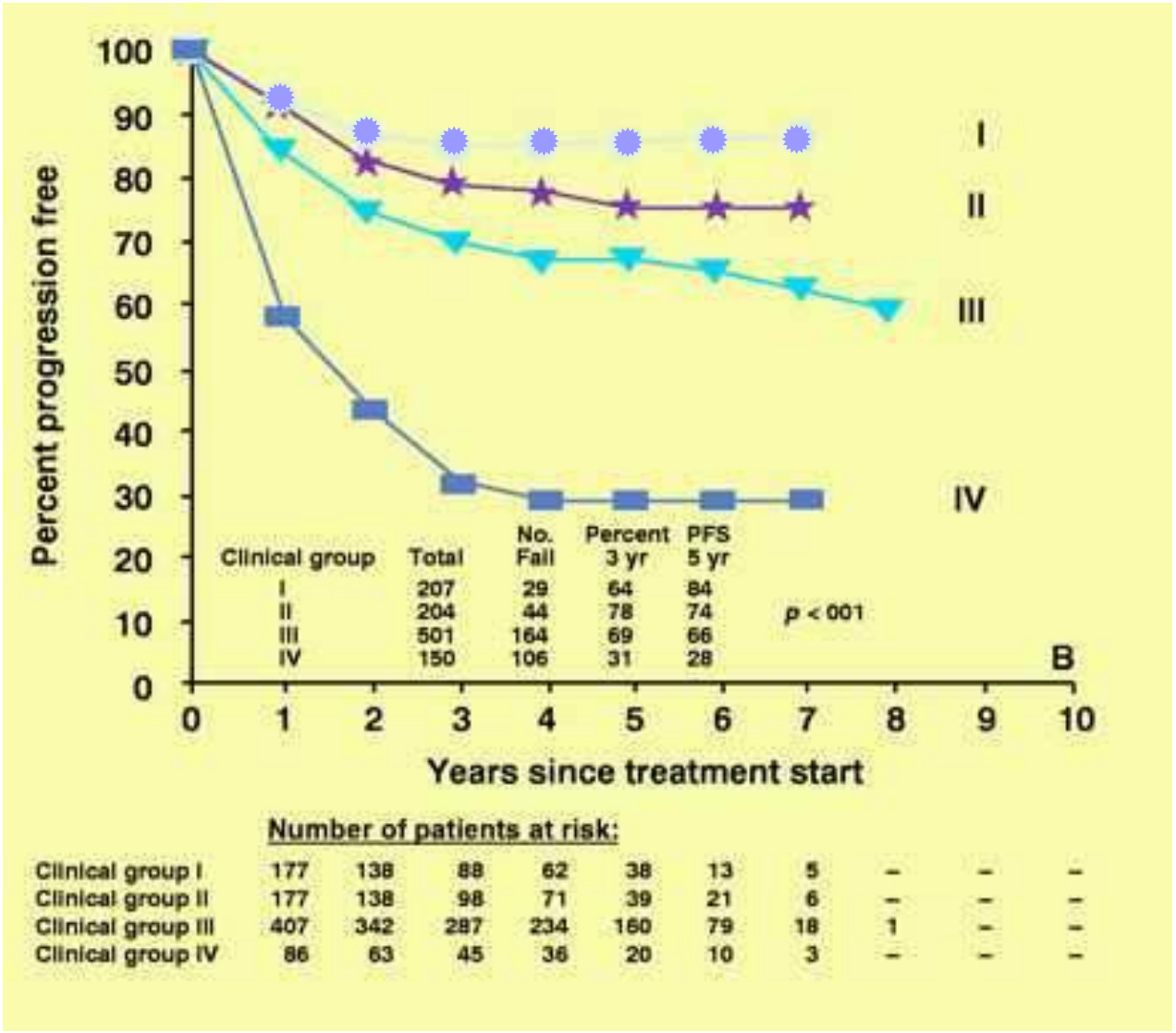

VA, VAC

VA, VAD

VAC, VACD

VAC, VACD, VACDE, VACDEPDtic

IRS-III, *Crist 1995*

Review

Lancet Oncol 2017; 18: e166–75

Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts

Winette T A van der Graaf, Daniel Orbach, Ian R Judson, Andrea Ferrari

SySa

	Stage	Outcome	p value
Sultan et al (2009);[50] n=1268			
Age ≤18 years (n=213)	Localised and metastatic disease	5-year cancer-specific survival 83% 10-year cancer-specific survival 75%	<0·001
Age >19 years (n=1055)	Localised and metastatic disease	5-year cancer-specific survival 62% 10-year cancer-specific survival 52%	..
Vlenterie et al (2015);[19] n=461			
Age <18 years (n=54)	Localised disease	5-year overall survival 89%; 10-year overall survival 77%	<0·001*
Age 18–34 years (n=148)	Localised disease	5-year overall survival 73%; 10-year overall survival 64%	<0·001*
Age 35–64 years (n=204)	Localised disease	5-year overall survival 55%; 10-year overall survival 48%	<0·001*
Age ≥65 years (n=55)	Localised disease	5-year overall survival 43%; 10-year overall survival 28%	<0·001*
Palmerini et al (2009);[51] n=204 (localised only)			
Age <18 years (n=21)	Localised disease	5-year overall survival 89%	0·09*
Age 18–65 years (n=170)	Localised disease	5-year overall survival 71%	0·09*
Age >65 years (n=13)	Localised disease	5-year overall survival 73%	0·09*
Italiano et al (2009);[52] n=237			
Age 0–35 years (n=119)	Localised disease	Overall survival, multivariate test HR 2·16 (95% CI 1·28–3·64)	0·004
Age >35 years (n=118)	Localised disease	..	..
Ferrari et al (2004);[53] n=215			
Age ≤16 years (n=41)	Localised disease, with macroscopic resection	5-year metastasis-free survival 69%	NR
Age 17–30 years (n=66)	Localised disease, with macroscopic resection	5-year metastasis-free survival 53%	NR
Age >30 years (n=108)	Localised disease, with macroscopic resection	5-year metastasis-free survival 43%	NR

HR=hazard ratio. NR=not reported. *p value based on the multivariate analysis.

***Table*: Age-related studies of patients with synovial sarcoma with localised disease at diagnosis**

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RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Access to clinical trials for adolescents with soft tissue sarcomas: Enrollment in European pediatric Soft tissue sarcoma Study Group (EpSSG) protocols

Andrea Ferrari[1] | Annalisa Trama[2] | Angela De Paoli[3] | Christophe Bergeron[4] | Johannes H. M. Merks[5] | Meriel Jenney[6] | Daniel Orbach[7] | Julia C. Chisholm[8] | Soledad Gallego[9] | Heidi Glosli[10] | Gian Luca De Salvo[3] | Laura Botta[2] | Gemma Gatta[2] | Gianni Bisogno[11] | RARECAREnet Working Group

TABLE 2 Observed and expected cases with O/E ratio and 95% CI

	Observed	Expected	O/E ratio	95% CI	
0–14 years old					
RMS	1,139	1,488	0.77	0.72	0.81
NRSTS	615	1,234	0.50	0.46	0.54
All STS	1,754	2,722	0.64	0.61	0.68
15–19 years old					
RMS	201	315	0.64	0.55	0.73
NRSTS	163	902	0.18	0.15	0.21
All STS	364	1,217	0.30	0.27	0.33

Review

Lancet Oncol 2017; 18: e166–75

Soft tissue sarcomas in adolescents and young adults: a comparison with their paediatric and adult counterparts

Winette T A van der Graaf, Daniel Orbach, Ian R Judson, Andrea Ferrari

SySa

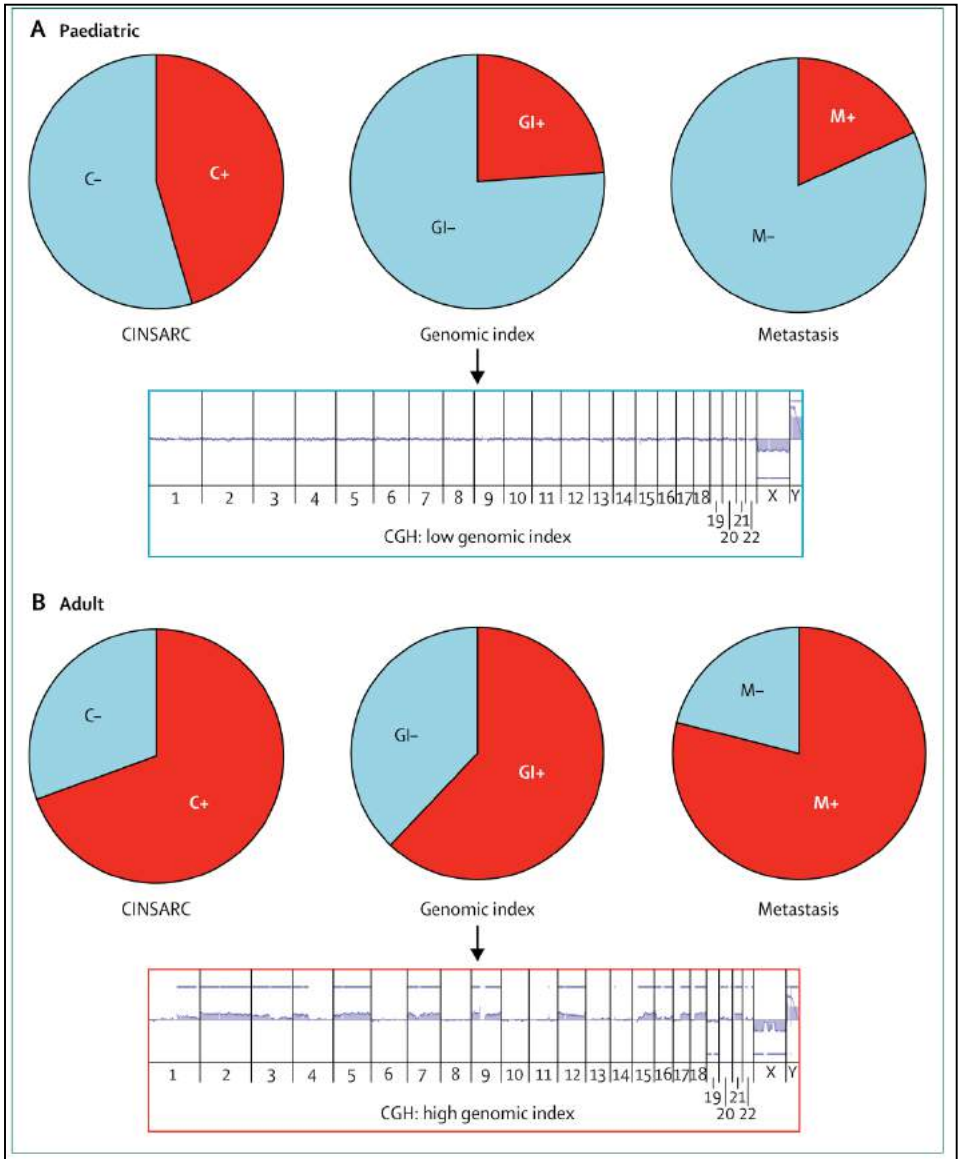

***Figure*: Distribution of the CINSARC, genomic index, and metastasis-free survival in paediatric and adult patients with synovial sarcoma**

An example of two CGH profiles in children and adults with synovial sarcoma. In this analysis, paediatric patients with synovial sarcoma have more favourable biological tumour features than do adults, a lower somatic tumour complexity index, lower genomic index signatures, and less metastatic tumour evolution. Data adapted from Lagarde and colleagues.[20] CGH=comparative genomic hybridisation. CINSARC=a somatic tumour complexity index in sarcoma signatures. C+=high CINSARC. C–=low CINSARC. GI+=high genomic index. GI–=low genomic index. M+=metastatic event. M–=absence of metastatic event.

European Journal of Cancer 78 (2017) 1–6

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journal homepage: www.ejcancer.com

Original Research

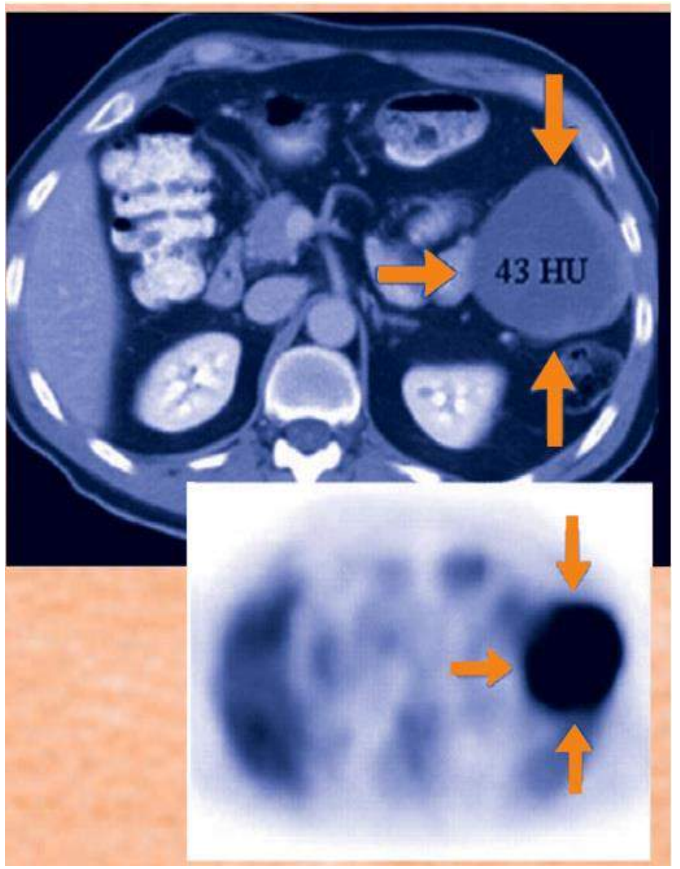
Surgery alone is sufficient therapy for children and adolescents with low-risk synovial sarcoma: A joint analysis from the European paediatric soft tissue sarcoma Study Group and the Children's Oncology Group

Andrea Ferrari [a,*], Yueh-Yun Chi [b], Gian Luca De Salvo [c], Daniel Orbach [d], Bernadette Brennan [e], R. Lor Randall [f], M. Beth McCarville [g], Jennifer O. Black [h], Rita Alaggio [i], Douglas S. Hawkins [j], Gianni Bisogno [k], Sheri L. Spunt [l]

But chemo is so boring, let‘s talk targeted therapies!

GIST: Definition

- Mesenchymal (connective tissue) neoplasms
- Located primarily in the GI tract, omentum and mesentery
- 0.2% of all GI tumors
- 80% of GI sarcomas
- 95% stain positive for KIT



Images adapted with permission from Choi H et al. Am J Roentgenol. 2004;183:1619-1628. Miettinen M et al. Arch Pathol Lab Med. 2006;130:1466-1478.

GIST: Molecular Genetics

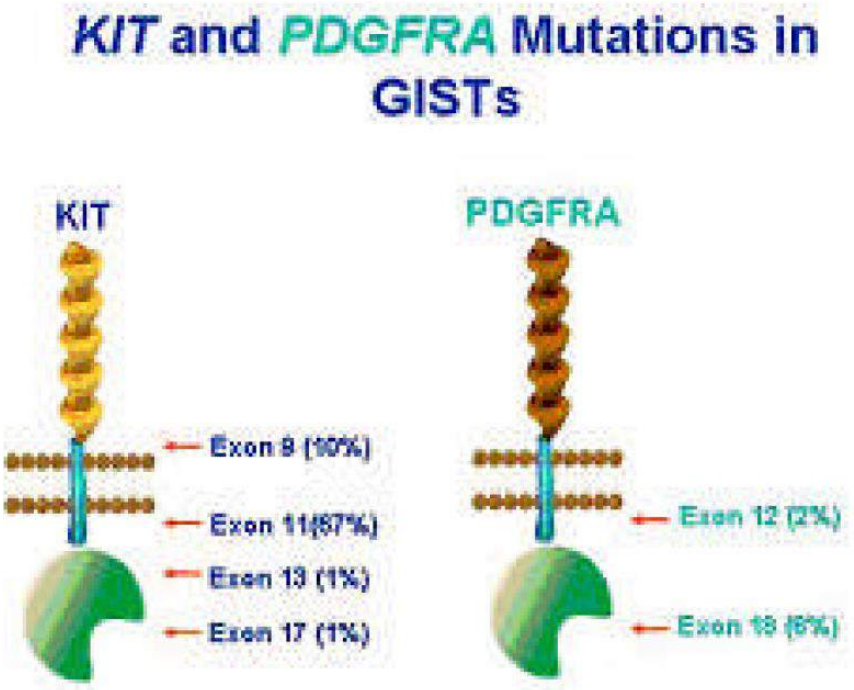


Figure 2
(From Heinrich M. ASCO 2005)

Brief Report

N Engl J Med, Vol. 344, No. 14 · April 5, 2001

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

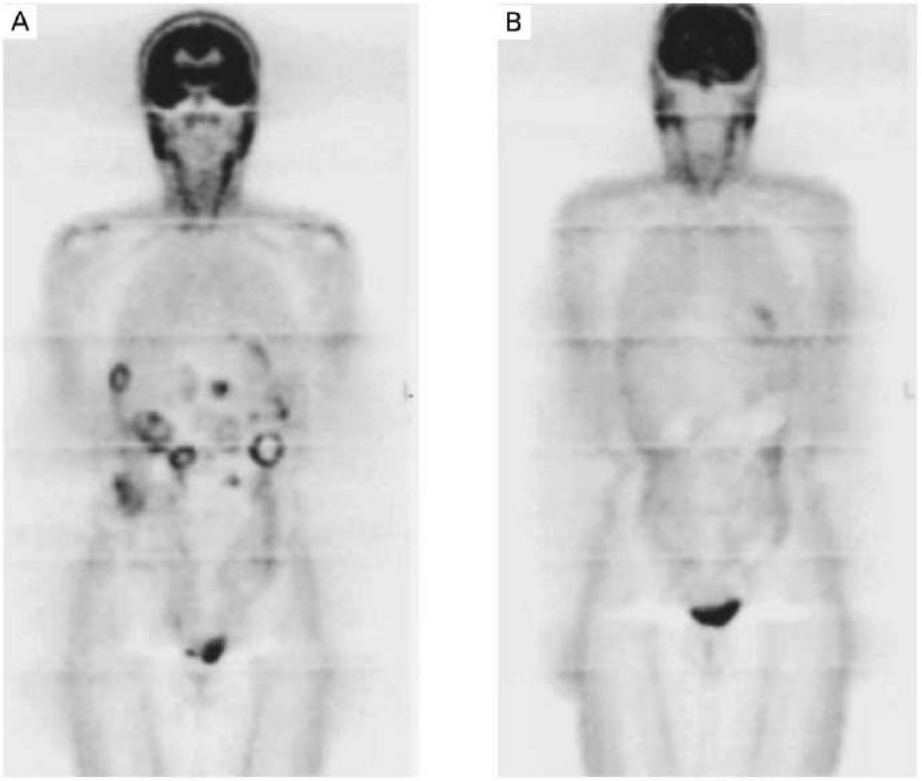


Figure 2. PET Studies with [18F]Fluorodeoxyglucose as the Tracer.

Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked retention of [18F]fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abnormal uptake of tracer in the liver or right kidney.

With reference to selected histological types, there is anecdotal evidence of activity of several **molecular targeted agents**, building on consistent preclinical data. Examples are:

- mammalian target of rapamycin (mTOR) inhibitors in malignant perivascular epithelioid cell tumors (PEComas), which are often associated with the loss of tuberous sclerosis complex 1 (TSC1)/TSC2 [18];

- crizotinib in inflammatory myofibroblastic tumor associated with anaplastic lymphoma kinase (ALK) translocations [19];

- sunitinib and cediranib in alveolar soft part sarcoma and solitary fibrous tumors, where molecular target is yet unclear [20, 21].

Advances in treating soft tissue sarcoma

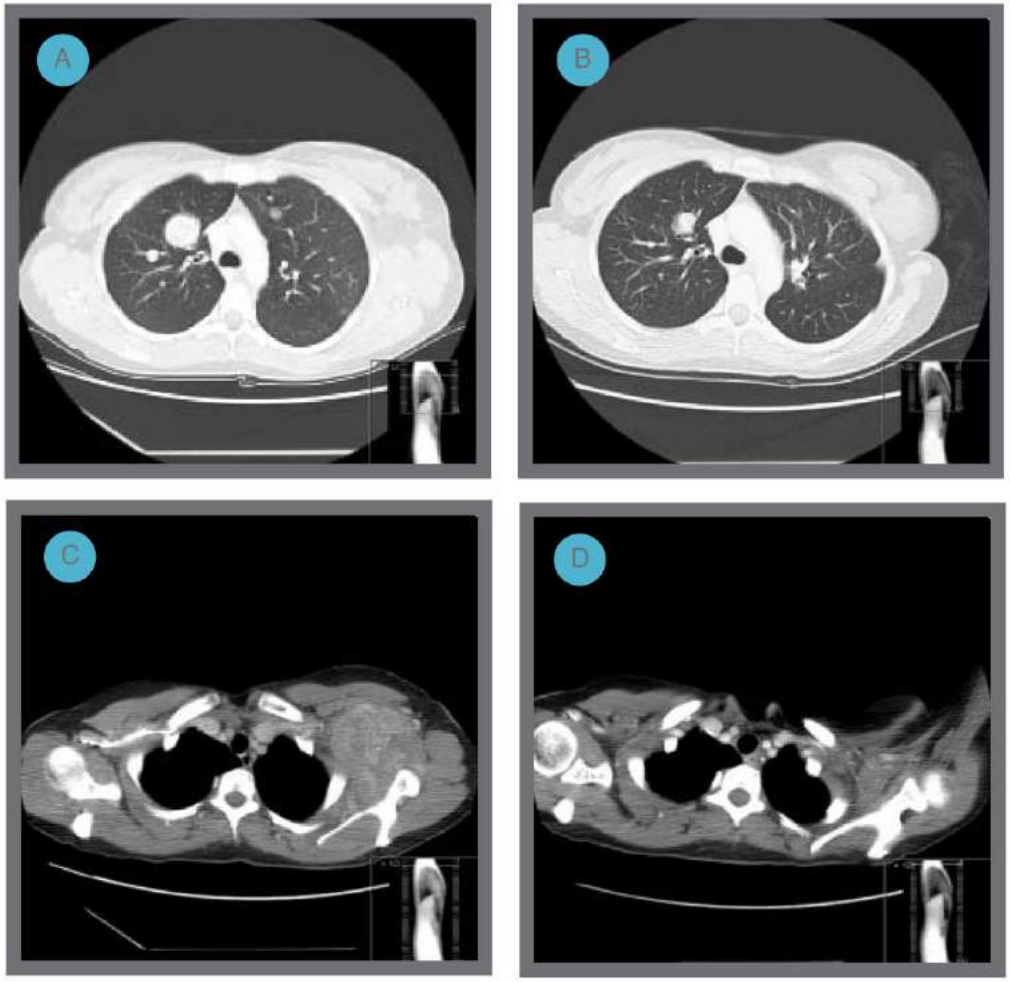


Figure 1: Response of alveolar soft part sarcoma (ASPS) to treatment with cediranib (AZD2171). (A) Lungs before treatment, (B) Lungs after 15 months of treatment with cediranib, (C) Left axilla mass before treatment and (D) Left axilla mass after 15 months of treatment with cediranib.

Advances in treating soft tissue sarcoma

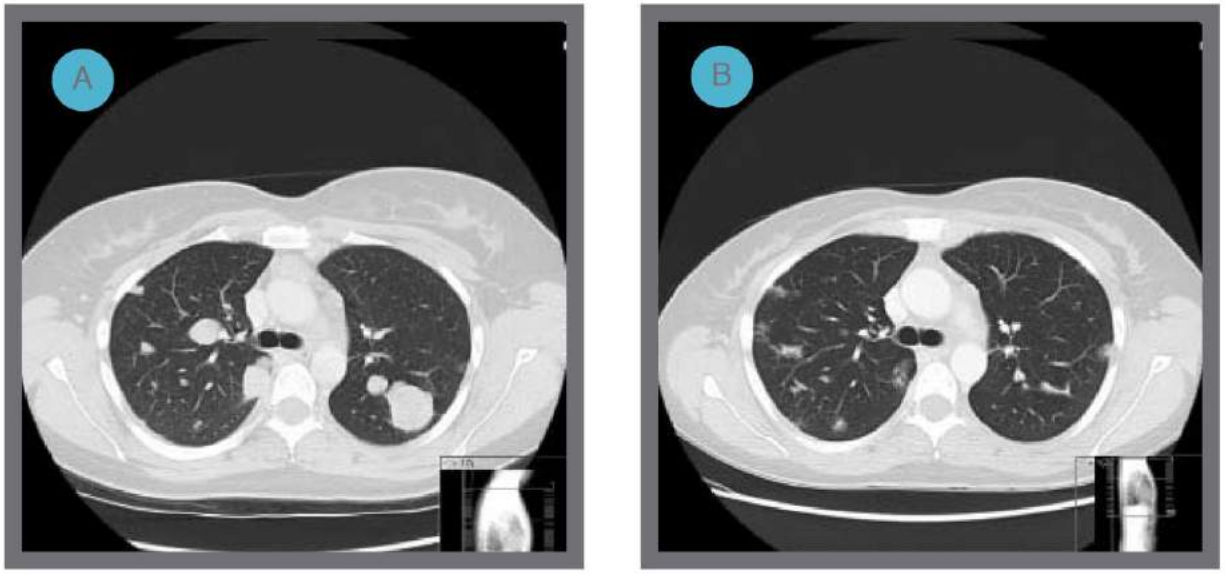


Figure 2: Patient with synovial sarcoma (A) before treatment and (B) following nearly a year of pazopanib treatment.

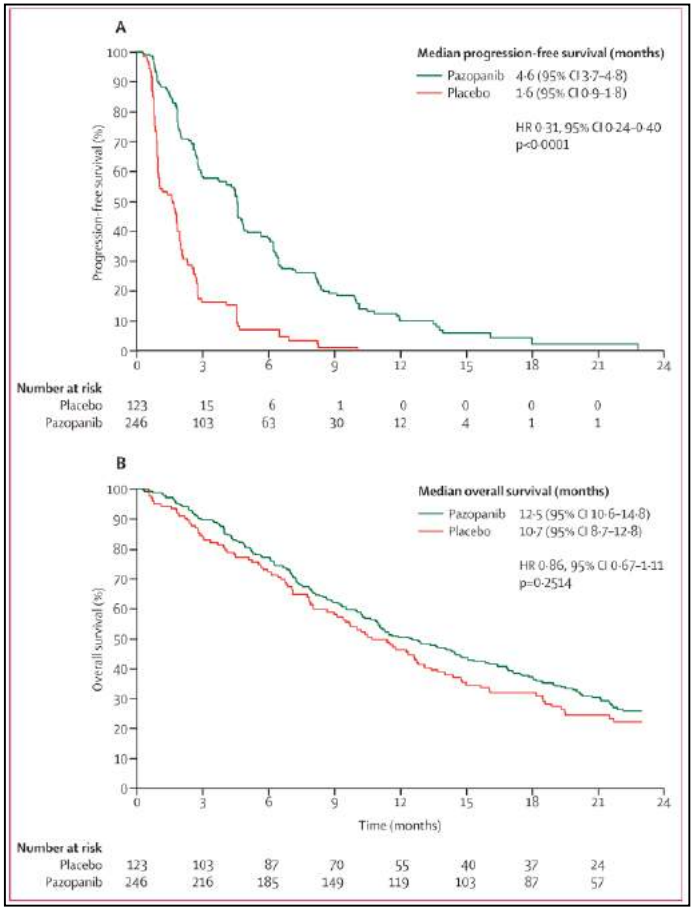
Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

Winette T A van der Graaf, Jean-Yves Blay, Sant P Chawla, Dong-Wan Kim, Binh Bui-Nguyen, Paolo G Casali, Patrick Schöffski, Massimo Aglietta, Arthur P Staddon, Yasuo Beppu, Axel Le Cesne, Hans Gelderblom, Ian R Judson, Nobuhito Araki, Monia Ouali, Sandrine Marreaud, Rachel Hodge, Mohammed R Dewji, Corneel Coens, George D Demetri, Christopher D Fletcher, Angelo Paolo Dei Tos, Peter Hohenberger, on behalf of the EORTC Soft Tissue and Bone Sarcoma Group and the PALETTE study group

Lancet 2012; 379: 1879–86
Published Online
May 16, 2012

Summary

Background Pazopanib, a multitargeted tyrosine kinase inhibitor, has single-agent activity in patients with advanced non-adipocytic soft-tissue sarcoma. We investigated the effect of pazopanib on progression-free survival in patients with metastatic non-adipocytic soft-tissue sarcoma after failure of standard chemotherapy.



Dosierung und Kosten

Votrient® (Pazopanib)		
Darreichungsform	**Dosis pro Tag[1]**	**Kosten pro Jahr [€][2]**
Filmtabletten	1 x 800 mg[3]	49.117,32

Adolescent Health, Medicine and Therapeutics

Dovepress

REVIEW

Targeted therapy for soft tissue sarcomas in adolescents and young adults

Diana A Steppan
Christine A Pratilas
David M Loeb

Abstract: Soft tissue sarcomas (STSs) are a heterogeneous group of tumors originating from the mesenchyme. Even though they affect individuals in all age groups, the prevalence of subtypes of STSs changes significantly from childhood through adolescence into adulthood. The mainstay

Table 1 Summary of results of targeted therapies in STS

Class of drugs	Drug studied	Phases	Main results	References
TKI	Imatinib	II	Response in GIST, not in other histologies	69,70
	Dasatinib	II	Response in undifferentiated pleomorphic sarcoma, currently being studied in more indolent types of STS	71
	Semaxinib	II	No significant anti-STS activity	75
	Pazopanib	II and III	Approved by the US FDA for the treatment of STS as second-line treatment. Pediatric and adult trials ongoing	76,77
	Regorafenib	II	Improved OS and PFS in LMS and improved PFS in other sarcomas	86
	Sunitinib	I and II	Activity in ASPS	92–94
	Cediranib	I/II	Activity in ASPS	97
	Vandetanib, gafetinib, and erlotinib	Preclinical and early clinical	Appeared promising in STS, but no conclusive studies yet	100–102
	Sorafenib	II	No objective responses	105
	Tivozanib	II	Response in metastatic and nonresectable STS (median follow-up 5.5 months)	106
mTOR inhibitors	Temsirolimus	I	Tolerable in combination with chemotherapy or other targeted agents. Phase II study results pending	108,109
	Sirolimus	II	In combination with cyclophosphamide or pazopanib some patients with PR or SD	110,118
	Everolimus	I and II	Investigated as monotherapy and in combination with figitumumab, or imatinib without RECIST response	115–117
Other pathways	Histone deacetylase inhibitors; multiple agents	I and II	SB939, abexinostat with or without doxorubicin, vorinostat with bortezomib: tolerable and indication of potential clinical benefit; panobinostat: 36% SDs and no CRs or PRs. Preclinical data encouraging	122–124, 126,128,129
	Heat-shock protein 90 inhibitors; multiple agents	I	Retaspimycin hydrochloride: SD (60% at 6 weeks and 18% at 12 weeks). AAG tolerable in children. Ganetespib with sirolimus under investigation	135,137
	SINE	I preclinical	Tolerable, preliminary evidence of activity	139,141
Immunotherapy	IGF-1R; multiple agents	I and II	Promising preclinically, but no consistent benefit in Phase II trials. Currently no further clinical studies	113,143–148
	Bevacizumab	I	Alone and in combination with several traditional chemotherapeutics tolerable but clinical benefit unclear	35,150,151
	Olaratumab	I/II	In combination with doxorubicin, improved PFS and OS, but mostly older adults	154
	Ipilimumab	Pilot	Stopped early due to low accrual	156
	Checkpoint inhibition		Anti-PD-1 therapy promising in several solid tumors. First clinical trial in STS currently ongoing. Additional molecules targeting LAG2, Tim3, and BTLA4 emerging	
	Tumor vaccines; multiple targets	I	Vaccine against SS18, GD2, GD3, and NY-ESO showed antibody induction. Phase II clinical data pending	170,171, 173,174
	Autologous T cell transfer (NY-ESO T cell receptor)	I	In synovial sarcoma promising (four out of six with response). Follow-up study currently ongoing	176
	CAR T cells		Mostly tested in hematologic malignancies and some bone sarcomas, but potentially promising modality especially in combination with immune-modulatory therapeutics	

Abbreviations: AAG, 17-N-allylamino-17-demethoxygeldanamycin; ASPS, alveolar soft part sarcoma; CAR, chimeric antigen receptor; CRs, complete remissions; FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; IGF-1R, insulin-like growth factor-1 receptor; LMS, leiomyosarcomas; mTOR, mechanistic target of rapamycin; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SINE, selective inhibitors of nuclear export; STS, soft tissue sarcoma; TKI, tyrosine kinase inhibitor.

Highlights

- Soft tissue sarcomas are relatively frequent in adolescents and young adults. For most histotypes, the survival decreases with advancing age.
- The clinical management of adolescents and young adults with soft tissue sarcoma is still a challenge due to tumor associated factors and lack of treatment standardization. Specific challenges are access to referral centers, inclusion in clinical trials, and centralization of care and research.
- The outcome of adults with rhabdomyosarcoma is decidedly worse than that generally seen in childhood. It is supposed that rhabdomyosarcoma patients, regardless of their age, would receive better treatment when following guidelines derived from the large pediatric experience.
- Different approaches have been historically adopted by pediatric and adult medical oncologists dealing with soft tissue sarcomas (i.e., synovial sarcoma), but in the last few years, the management has tended to converge towards a common strategy.
- The impact of new targeted agents in the pediatric population has not paralleled the progress seen in adult sarcoma patients. Increased international collaboration between pediatric and adult sarcoma groups is of critical importance to facilitate the transfer of potentially effective new agents from adults to children and adolescents, and to improve research programs dedicated to young patients.

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DOI: 10.1002/pbc.27013

REVIEW

WILEY Pediatric Blood & Cancer

The challenge of the management of adolescents and young adults with soft tissue sarcomas

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