Scandinavian Sarcoma Group

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Scandinavian sarcoma group—centralized registration

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Centralized registration of Scandinavian sarcoma patients started in 1986, and until February 1992, 1176 patients have been included. This multi-national database, which is used for epidemiologic and prognostic studies, contains detailed clinico-pathologic, treatment, and follow-up data.

Soft tissue tumors (N 927): The ratio men to women is 1.3:1. The median age is 64 (1–96) years. 27% of the tumors are superficial (median size 4 cm) and 73% are deep (median size 10 cm). The most common location is the thigh (25%). MFH, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant schwannoma constitute together two thirds of the tumors. The most common malignancy-grade is IV (40%).

93% of the patients were referred to a tumor center for the primary tumor. 35% of all patients had untouched tumors when referred, and 15% were referred after fine-needle aspiration. 12% of the patients had metastases at presentation.

A marginal margin was obtained in 33% of the patients, a wide margin in 43%, and a radical margin in 10%. 8% of patients with extremity tumors were amputated.

Bone tumors (N 249): The ratio men to women is 1.5:1. The median age is 37 (6–84) years. 18% of the tumors are intraosseous, 11% have cortical breakthrough, and 71% have extraosseous extension. Femur is the most frequent location (39%). The most common malignancy-grade is IV (33%), and chondrosarcoma is the most frequent histotype (33%). 3 of 4 bone tumors were untouched at referral. 5% of osteosarcomas and Ewing's sarcomas were diagnosed by fine and/or coarse needle biopsy. 11% of the patients had metastases at presentation.

Surgical margins in soft tissue sarcoma

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In soft tissue sarcoma the quality of the surgical margin obtained is the strongest predictor of the local recurrence risk. Therefore, correct classification of the margin is important to assess the local recurrence risk, which in turn determines whether surgery should be combined with radiotherapy. We analyzed the reproducibility of the Scandinavian Sarcoma Group (SSG) classification of margins (1) by comparing the local recurrence rate in two studies, neither of which included radiotherapy. Both had a follow-up of median 4 years. Patients treated with marginal excision or amputation were not analyzed.

The first (SSG I multicenter trial on adjuvant chemotherapy) included 185 patients (2). The surgical margins reported were reviewed by a panel of surgeons who had no knowledge of the clinical course. Compartmental or wide margins were in 19 patients reclassified to marginal margins based on the information in the operation reports (14 cases) or histology reports (5 cases); local recurrence was diagnosed in 12 of these patients. Local recurrence occurred in 1/24 patients with compartmental excision and in 7/84 (8 %) with wide excision.

The second (SSG Central Registry, Abstract 3) included 189 patients. No review of the margins was performed. Local recurrence occurred in 3/33 patients with compartmental excision and in 14/76 (18 %) with wide excision.

These findings may indicate different requirements for the classification of a wide and compartmental margin. Margins should be classified by the surgeon and be based on the combined surgical, macro- and microscopic findings.

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Table 1. Risk factors associated with local recurrence for subcutaneous tumors

	Relative risk	p
Female sex	1.6	.6
Patient age (years)[1]	1.02	.4
Tumor size (cm)[1]	1.1	.04
High malignancy grade	3.0	.3
Lower extremity	–	.8
Upper extremity	3.2	.3
Marginal surgery	2	.5

[1]continuous variables

Table 2. Risk factors associated with local recurrence for deep tumors

	Relative risk	p
Male sex	–	.9
Patient age (years)[1]	–	.5
Tumor size (cm)[1]	1.08	.1
High malignancy grade	3.1	.1
Intracompartmental	–	.7
Trunk	5.1	.002
Upper extremity	2.5	.2
Marginal	4.6	.03
Marginal + Radiotherapy	–	.7
Wide	2.0	.3

[1]continuous variables

Local recurrence in soft tissue sarcoma: Analysis based on the Scandinavian Sarcoma Group Central Registry

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Local recurrence after surgery was analyzed in a multicenter study of soft tissue sarcoma patients reported to the Scandinavian Sarcoma Group Central Registry 1986 through 1988.

189 patients (102 men, 87 women) without metastasis at time of diagnosis were included. The median age was 64 (16–91) years. Subcutaneous tumors (n 58, median size 4 cm) were smaller than deep (n 131, median size 9 cm). Local surgery was performed in 94% of cases, only patients with deep tumors were amputated (8%). The final surgical margin achieved was marginal in 29% of superficial lesions and in 40% of deep. Radiotherapy was only given after marginal surgery, and in only half of those patients.

The median follow-up was 3.6 years. The overall local recurrence rate at 4 years was .22. The rate was .18 for patients with subcutaneous tumors (.25 after marginal surgery, .15 after wide) and .24 for those with deep tumors (.38 after marginal surgery, .26 after marginal with radiotherapy, .26 after wide, .15 after myectomi and 0 after compartmental surgery). Large tumor size was prognostic for local recurrence in subcutaneous tumors (Table 1). For patients with deep tumors, truncal localization and marginal surgery were prognostic for local recurrence (Table 2).

Local control can be achieved in the vast majority of subcutaneous soft tissue sarcomas by surgery solely. For patients with deep tumors, only myectomy and compartmental procedures gave acceptable local recurrence rates without radiotherapy.

Indications for radiotherapy in soft tissue sarcoma (STS)—a review

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In 20 studies of non-radical surgery combined with post- or pre-operative irradiation published between 1981 and 1991 a mean local control rate of 17% was reported, comparable to the results from most series on radical surgery alone. The effect of radiotherapy on local control has also been documented in a randomised trial [1].

Most experience is derived from postoperative radiotherapy. Postoperative irradiation is usually indicated after intralesional or marginal surgery, at least if a radical reoperation is not feasible. The indication for irradiation after wide excision remains unclear, and at least two series have reported an acceptable rate of local control in patiens with STS treated with wide excision alone [2, 3]. After radical surgery of STS postoperative radiation is not indicated.

Some recent studies of preoperative irradiation have documented a promising local control rate, however, the risk of complications seems to be increased. Although theoretically preoperative radiation would be preferable to postoperative no firm evidence exists favouring pre- or postoperative irradiation; however, in large inoperable sarcomas, where even marginal surgery is impossible or associated with excessive morbidity pre-operative irradiation may be preferable.

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MRI of soft tissue sarcomas in Stockholm

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34 preoperative MRI examinations were made on the 100 patients with soft tissue tumors seen at the Karolinska Hospital in 1991. 48 of the patients had malignant lesions; 19 were examined by MRI (metastases excluded). Only half of the malignant soft tissue tumors were referred before surgery or surgical diagnostic procedures which explains the low number of preoperative MRI examinations in this group.

MRI (1.0 Tesla) was performed with T1- and T2-weighted images with maximal field of view using the bodycoil to begin with in order to define tumor localisation. Therafter in most cases a surface coil was applied to increase resolution of the lesion and its boundaries. Images were then acquired in planes perpendicular to important boundary surfaces between the lesion and surrounding tissue/organs with thin slices to minimize partiell volume effects. Standard spin echo sequences with T1, proton density and T2-weighted images were used. In most cases intravenous contrast media (Magnevist_) was given as a bolus dose immediatly followed by T1-weighted images making the time consuming T2-weighted images not always necessary.

Signal characteristics and contrast enhancement patterns were correlated to histological diagnosis and in available cases to CT and/or to slices of deep frozen growth specimens.

Differentiation between different types of sarcomas was in most cases not possible. Discrimination between sarcomas and non-sarcomatous lesions was on the other hand often possible due to the specific features of the MRI images, including growth pattern. Most soft tissue sarcomas presented with a clear margin against healthy tissue without an oedematous reactive zone, which often made staging easy. Staging difficulties were seen in cases with large tumor masses distorting the local anatomy or when subcutaneous tumors exerted pressure on the deep fascia or in cases with tumors located in the distal parts of the extremities.

Radiology of chondrosarcomas

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To nevaluae the need for diagnostic examinations in patients with chondrosarcomas, 49 patients seen during the last 11 years were re-evaluated. Plain films of the tumor and chest radiography had been performed in all patients; CT of the tumor in 31 and MRI in 7 patients; skeletal survey in 45 and CT of the lungs in 13 patients.

42 patients had been radically operated on, in 29 by local resection and in 13 by amputation. Local recurrence occurred in 6 of these patients after mean 1.4 (0.3–4) years, 5 of whom had grade II–III tumors. Lung metastases were seen at chest radiography in 12 patients after mean 0.9 (0.1–1.8) years, 10 of whom had grade II–III tumors.

We proposethat the initial evaluation always includes plain films and MRI or CT of the tumor region, in patients with grade II–III tumors also CT of the lungs. All patients should be observed for 10 years with regard to local recurrence and metastases: Grade II–III tumors at intervals of 3–4 months during the first 2 years including CT of the lungs, then half-yearly/yearly; Grade I tumors after 3 months; then half-yearly/yearly.

Cytogenetic heterogeneity in soft tissue sarcomas

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It is well established that a tumor cell population may be phenotypically heterogeneous. However, little is known about cytogenetic intratumor heterogeneity. Tumor progression is generally associated with increasing karyotypic complexity and progression models suggest the coexistence of cytogenetically related subclones with different evolutionary fitness. Investigation of cytogenetic heterogeneity, by analysis of multiple separate samples from each tumor gives a momentaneous picture of the clonal evolution, and also increases the possibility to distinguish primary cytogenetic changes from cytogenetic "noise", in tumor types that tend to have complex karyotypic changes.

We have investigated multiple (2–7) samples from different parts of the same tumor in 43 soft tissue sarcomas. Thirty-one tumors were non-informative: only normal karyotypes (18 cases), abnormal karyotype in only one sample (3 cases), or extensive karyotypic variation both within and between samples (10 cases). Of the 12 informative tumors 2 (1 liposarcoma and 1 extraskeletal myxoid chondrosarcoma) were homogeneous, i.e., only one clone were found in all samples. Ten tumors were heterogeneous (3 malignant fibrous histiocytomas (MFH), 2 liposarcomas, 2 synovial sarcoma, 1 fibrosarcoma, 1 neurofibrosarcoma, and 1 spindle cell sarcoma). In all tumors except one MFH the detected clones were related. In 6 tumors there were differences in structural aberrations, in 3 only numerical differences were found. In a liposarcoma clones with different ploidy levels were found.

In conclusion, cytogenetic tumor heterogeneity is common in soft tissue sarcomas. Thus the analysis of different pieces of a tumor gives a more complete momentaneous picture of the clonal evolution than single sampling.

Ewing's sarcoma of the pelvis—to operate or not to operate?

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Introduction: The combination of chemotherapy and surgery has been reported to be the best treatment for Ewing's sarcoma. Radiotherapy substitutes or complements surgery when the tumor cannot be completely removed. Tumors of the truncal skeleton are seldom operated on. However, pelvic tumors may be amenable to surgical treatment, although this can be technically demanding and in some cases lead to severe disability. We tried to assess the benefit of surgical treatment instead of radiotherapy in Ewing's sarcoma of the pelvis.

Patients: 47 consecutive cases were reviewed. Nineteen tumors were located in the pelvis. The mean age in the whole series was 18 years (pelvis 19). The mean largest tumor diameter was 9 cm (pelvis 9,6 cm). 5 of the primary pelvic tumors were operated on, 14 were not. The chemotherapy did not differ significantly between these groups.

Results: Out of the 5 operated patients 2 are alive NED 4 and 6 years after diagnosis. Out of the 14 patients with non-operated primary tumors 1 is alive NED, 2 years after diagnosis and 1 died of other causes 11 years after diagnosis. The patients with other tumor location than the pelvis had the same tendency for better prognosis after surgery.

Conclusion: It appears worthwhile to attempt surgical removal of Ewing's sarcoma of the pelvis.

Desmoid tumors—is radiation effective when surgery fails?

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Introduction: Desmoid tumors are fibrous, infiltrating, non-metastasizing and notorious for recurrences. Trauma may contribute to initiate desmoid growth, which seems to be regulated by several factors, including steroid sex hormones. The recommended treatment is wide surgical excision. Some authors advice radiation therapy when wide margins cannot be achieved. We reviewed our cases with special emphasis on those who received radiotherapy after failed surgery.

Patients: 40 consecutive patients were studied. 9 tumors were located in the abdominal wall, the rest were distributed over the body. The mean age was 49 years. Male/female ratio was 18/22. The mean tumor size was 5x9 cm. All except 3 were operated on, 17 with wide margins, 20 with marginal margins.

Results: 14 tumors recurred after surgical treatment 12 of which were reoperated on. 2 primary and 8 recurrent or not completely removed tumors received radiotherapy. 7 of these have a follow-up exceeding 2 years. One tumor disappeared, 4 tumors decreased in size and 1 stopped to grow (information missing on one patient).

Conclusion: Although radiation is a potential danger for malignant change it presently appears to be the only treatment alternative to surgery in uncontrollable desmoid tumor. Further trials with antiestrogenic substances might change this.

Complications in soft tissue sarcoma surgery

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The overall incidence of wound complication was 36% in 132 consecutive patients treated with local surgery for soft tissue sarcoma 1987–1991. There were 19 infections, 15 haematomas and 13 necroses. Furthermore, infection complicated 3 hematomas and 5 necroses. The complication rate was lower in the upper extremity (14%) as compared to the trunk and lower extremity (40%) (P 0.05).

Subcutaneous and deep tumors had an approximately equal incidence of wound complications. The median hospitalization time for patients with deep tumors who developed complications was 23 days as compared to 11 days for those without (P 0.002). Complications in patients with superficial tumors did not lead to a lengthened hospital stay.

The incidence of wound complications decreased from 59% 1987 to 27% 1991 (P 0.05). For subcutaneous tumors, this was probably due to a more liberal use of split skin grafts instead of primary closure. For deep tumors, the better results could be ascribed to several factors, i. e., prophylactic antibiotics, better perioperative hemostasis, and the use of suction drains for a longer period postoperatively.

This study showed a considerable complication rate in limb sparing surgery for soft tissue sarcomas. This incidence can probably be reduced by taking into account risk factors associated with wound complications and better preoperative planning in close cooperation with plastic surgeons for adequate wound coverage.

Improved metastasis-free survival in soft tissue sarcoma with recurrent local recurrences

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We determined the metastasis-free survival rates after one or more local recurrences without simultaneous metastases in a population-based series (minimum follow-up 2 years) of

patients with soft tissue sarcoma.

Patients: We analyzed those 432 patients who were metastasis-free at presentation and were treated with surgery with a marginal or better margin.

Observations: The MFS (metastasis-free survival, crude rates) was 290/432 [67%] for the whole group, compared to 55/124 [44%] in patients with local recurrence, and 235/308 [76%] in patients without.

110 patients had 1 or 2 local recurrences, 63 of whom had no metastases when the last local recurrence was diagnosed, and the MFS was 45/63 (71%) with a median follow-up after the last local recurrence of 58 (1–295) months. One of the 45 patients died from the local recurrence.

14 patients had 3 or more local recurrences, 10 of whom had no metastases when the last local recurrence was diagnosed, and the MFS was 10/10 with a median follow-up after the last local recurrence of 20 (5-80) months. 3 of the 10 patients died from the local recurrence.

Conclusions: Patients with local recurrence but without simultaneous metastases constitute subgroups with increasingly lesser risk for metastatic disease the higher the number of local recurrences. These subgroups should be separately analyzed in prognostic studies.

Limb salvage after infected allograft

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It is difficult to treat infected allografts; amputation ios often necessary. We have developed a method which can salvage the extremity.

Patients: 4 patients with infected allografts were operated on. The primary diagnoses were 2 osteosarcomas, 1 chondrosarcoma, and 1 giant cell tumor.

Method: We removed the infected allograft and debrided the wound thoroughly. A model of the allograft was molded during surgery using a plastic mold and gentamycin loaded metylmetacrylate bone cement (Palacos cum gentamicin). This dummy was inserted into the defect. The concentration of gentamycin was measured in the serum and in the drainage. After 2–3 months the dummy was removed and replaced by a tumor prosthesis (Kotz) of appropriate size.

Results: All clinical and biochemical signs of infection disappeared after implantation of the dummy. The mean gentamycin-concentration in the drainage was 5.6 microg/mL, and in serum 0.02 microg/mL. There was no infection after implanting the tumor prosthesis and there is good function of the joints in the reconstructed limb in three patients. In one case the observation time is too short.

Conclusions: The local effect of gentamycin contributes to eradicate the infection, and the spacer prohibits shortening of the limb, and gives ample room fo insertion of a permanent tumor prosthesis. The method can solve the problem of an infected allograft, and conserve the limb.

Chemotherapy in soft tissue sarcoma with etoposide and ifosfamide

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27 patients (pts) with advanced high-grade soft tissue sarcoma were treated with etoposide 600 mg/m^2 in 72h continous infusion and ifosfamide 1500 mg/m^2/day for 3 days every 3 weeks. There were 17 male and 10 female pts of median age 43 (15–73) years. Of 23 pts with distant metastases, 17 had lung and 5 had liver metastases. The most common histological types were MFH (6 pts), synovial sarcoma (5 pts) and leiomyosarcoma (4 pts). The median number of courses was 6 (range 2–9). 11 pts showed partial remission, including 5/10 pts previously treated with doxorubicin-containing chemotherapy. 11 pts achieved stable disease, and progressive disease was observed in 5 pts. 9/11 responders had lung metastases. 6 pts had macroscopically complete surgery after 3–7 preoperative chemotherapy courses (3 lung resections, 2 liver resections and 1 chest wall resection), and 4 pts in addition received 2–5 postoperative courses. Of the operated on patients, one has relapsed 8 months after surgery, the others remain free of disease after 1, 1, 4, 6, and 15 months.

Apart from mild gastrointestinal discomfort, the only significant toxicity seen was bone marrow depression. WBC nadir <1.0 x 10^6/l was seen after 27% of all courses, and was seen at least once in two thirds of the patients. Neutropenic infections requiring hospitalization and parenteral antibiotics were seen in half of the patients, complicating 14% of all courses. One fatal septicemia occurred. Leucopenia led to dose reduction in 39% of the courses and to prolongation of the treatment-free interval to > 4 weeks in 32%. Thrombocytopenia was not problematic.

The results represent an update on the pilot study which has prompted a large SSG phase II study of the effect of etoposide/ifosfamide in advanced soft tissue sarcoma, with the addition of G-CSF to reduce leucopenia and its associated infectious complications and reduced treatment intensity. This study (SSG X/91) was activated in September 1991, and preliminary data indicate that G-CSF significantly reduces the degree of leucopenia associated with this regimen.

IVADIC in adult patients with advanced soft tissue sarcoma

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Adult patients with locally advanced or metastatic soft tissue sarcoma, were treated with combination chemotherapy based on the CYVADIC regimen, in which cyclophosphamide was replaced by ifosfamide and mesna.

Chemotherapy schedule: Ifosfamide 1g/m^2 daily on days 1 to 5 (2-hours infusions), mesna 0.2g/m2x3 daily on days 1 to 5

(short infusion), vincristine 1.5 mg/m^2 on day 1 (injection), doxorubicin 50 mg/m^2 on day 1 (5-minute infusion), and dacarbazine 250 mg/m^2 daily on days 1 to 5 (30-minute infusions).

Patients: 24 patients were evaluable for response, 31 for toxicity.

Results: The overall response rate was 46% (25–67%), and for chemotherapy naive patients 50% (27–73%). Four achieved a complete response, two are still in remission. 3 additional were surgically rendered disease-free after a partial response. Toxicity was mainly hematological; in 3 patients the nadir WBC was below 0.5x10^9/L, and in two the nadir platelet count was below 50x10^9/L. Infections during neutropenia requiring intravenous antibiotics appeared in 8 patients , and in 14 of 190 cycles (8%), one was fatal.

Conclusion: This is a promising new regimen for advanced STS with acceptable toxicity.

Table. Statistical power for different combinations of 3-year (5-year) survival probabilities. Logrank-test, a=0.05, two-sided. N=75 patients per group, 2 years of continuous accrual + 3 years of follow-up

		Treatment group, 3-year (5-year) survival					
		0.35 (0.17)	0.40 (0.22)	0.45 (0.26)	0.50 (0.32)	0.55 (0.37)	0.60 (0.43)
Control group 3-year (5-year) survival	0.30 (0.13)	0.11	0.30	0.56	0.80	0.93	0.98
	0.35 (0.17)	0.05	0.11	0.29	0.55	0.78	0.93
	0.40 (0.22)		0.05	0.10	0.28	0.54	0.78
	0.45 (0.26)			0.05	0.11	0.28	0.54
	0.50 (0.32)				0.05	0.11	0.28
	0.55 (0.37)					0.05	0.11

Adjuvant chemotherapy in soft tissue sarcoma—is a randomized study possible?

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In the Scandinavian Sarcoma Group trial—SSG I (1), a randomized study of 240 patients with and without Doxorubicin in high-grade soft tissue sarcoma (STS), we concluded that Doxorubicin has no effect on metastases-free and overall survival (2). We found that intratumoral vascular invasion, malignancy grade IV, tumor size over 10 cm, aneuploidy, and male sex were independent risk factors for developing distant metastases. The five-year survival for the 19 patients with all these factors was zero (3).

The use of combination chemotherapy with Ifosfamide and VP-16 in metastatic STS has resulted in an objective tumor response of 50% (4). The subjective tolerability of the regimen was excellent. However, bone marrow toxicity was pronounced with severe leucopenia in two thirds of the patients, leading to prolongation of treatment-free intervals in one third of the courses and infection requiring antibiotics in 11% of courses. The results of this pilot study indicate that VP-16 - Ifosfamide regim may be more active in STS than previous regimens.

The Scandinavian Sarcoma Group (SSG trial X) decided to investigate this drug combination in addition with G-CSF to evaluate effects in a larger series of patients (5). The outcome of this phase II trial will determine whether this drug combination should be used for a randomized trial in high risk STS patients. To perform such an investigation it is necessary to randomize 75 patients in each treatment arm in a two years period (Table)

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Treatment of metastatic osteosarcoma in Norway 1975–1991

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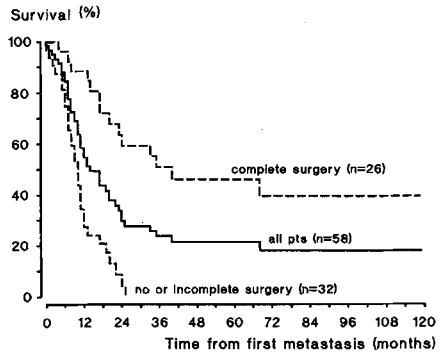
From 1975 to 1980, primary treatment for extremity-localized, high-grade osteosarcoma included adjuvant chemotherapy (CT) with methotrexate 2g/m^2, adriamycin and actinomycin D (period 1; 36 patients). From 1981 (period 2), high-dose methotrexate (8–12g/m^2) and cisplatin was introduced (T-10 and SSG VIII protocols, 47 patients). 6 patients (pts) were primarily treated with surgery alone. Results were significantly improved in period 2, with 5-year relapse-free survival increasing from 22% to 45%. 58 pts (65%) have relapsed, 88% with lung metastases (met). The time to met was longer for period 2 pts (median 19 months) than for period 1 (10 months, $p < 0.05$), but the number of metastases was not significantly different. At first met, 58% were treated by surgery, and 45%

had complete resections of all macroscopic tumour. 43% of surgically treated pts also received pre- and/or postoperative second line CT. Two-thirds of pts who had "complete" surgery at first met developed a second relapse after median 9.5 months.

The median number of operations was 2 (range 1–5), and one third of all pts had more than one thoracotomy.

Five-year overall survival from first met was 22%. For the 26 pts with "complete" surgery at first met, the 5-year survival was 46%, while none of the pts with no or non- radical surgery survived beyond 30 months (p 0.001) (Fig. 1). There was a trend for better survival from first met for patients primarily treated by the T-10 or SSG VIII protocols (28% 5-year survival vs. 12% for period 1, p 0.10). Apart from the advent of macroscopically complete surgery, no treatment at first met was found to significantly influence long-term results. Nevertheless, 10/23 pts (43%) treated with preoperative CT showed clinical and/or histological response, and CT-treated pts had a longer time interval before the next metastatic event. Whether second line CT can further improve survival in patients undergoing surgery for metastatic disease should be addressed in a prospective, randomized, multicenter trial.

Figure 1: Survival from first metastatic event by treatment.



Liposarcoma—a population-based epidemiologic and prognostic study of 43 patients

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We analyzed a population-based 25-year-series of 43 patients with reviewed liposarcoma of the extremities and trunk wall. Follow-up was complete, median 6 (3–27) years.

Epidemiology: Liposarcoma constituted 10% of all soft tissue sarcoma. The median age was 58 (29 – 90) years. 29 of the tumors were located in the hip girdle, thigh and knee. 7 tumors were superficial (median size 7 cm) and 36 were deep-seated (median size 12 cm). Malignancy-grade II (four-grade scale) was the most common (n 20). 4 tumors were well-differentiated, 25 myxoid, 10 pleomorphic, and 4 tumors were of round-cell type.

Clinical course: All patients but one were operated on. 9 patients developed local recurrence, and 16 patients developed metastases.

Prognosis: Univariate analysis showed that increasing malignancy-grade, ≥ 6 mitoses/10 HPF, tumor necrosis > 4 mm, vascular invasion, pleomorphic type, and high cellularity impaired metastasis-free survival. Multivariate analysis revealed only tumor necrosis > 4 mm to have independent prognostic value. 12 of 14 patients with necrosis developed metastases, compared to 4 of 29 patients without necrosis. Flow cytometric DNA-ploidy analysis of tumors from 35 patients gave no prognostic information.

Comments: Histopathologic classification systems for liposarcoma intended also for prognostication should include tumor necrosis.

Diagnostic implications of cytogenetics in musculoskeletal tumors

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Cytogenetic analysis has revealed a variety of chromosome aberrations in bone and soft tissue tumors. Some aberrations are specific for certain tumor types, some are shared by a few types, whereas other aberrations seem not to be associated with any particular type.

Specific aberrations include t(X; 18) in synovial sarcoma, t(12; 16) in myxoid liposarcoma, t(2; 13) in rhabdomyosarcoma, t(9; 22) in extraskeletal myxoid chondrosarcoma, t(12; 22) in clear cell sarcoma, and t(3; 12) in lipoma. Loss of one chromosome 22 is a common finding in benign Schwannoma, and infantile fibrosarcomas have gain of in particular chromosomes 8, 11, 17, and 20. Aberrations shared by several types are t (11; 22) in Ewing's sarcoma and primitive neuroectodermal tumors and supernumerary, unidentified ring chromosomes as the sole structural anomaly in atypical lipoma/well differentiated liposarcoma, parosteal osteosarcoma, dermatofibrosarcoma protuberans, and malignant fibrous histiocytoma (MFH) of low malignancy grade. Recombination between 12q 13-15 and varios chromosome segments other than 3q 27-29, 16 pll, and 22q 12-13 are found in subgroups of lipoma, chondroma, and hemangiopericytoma. Most pleomorphic sarcomas have complex, seemingly unspecific aberrations. However, a 19p + marker in MFH seems to indicate a highly malignant tumor.

In conclusion, in some cases cytogenetic analysis may be diagnostically useful, independently of histopathologic findings. In other cases it may complement histopathology and clinical observations, and in still other cases it has yet little to add to diagnosis by histopathology.

Pre/per/postoperative localization of scintigraphically positive bone lesions by fiberoptic scintillation detector and gammacamera

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This prospective study was started to explore the possible benefit of using techniques in nuclear medicine as an aid in peroperative localization of bone tumors.

Method: Bone lesions not easily localized by x-ray were included. We localized the lesion preoperatively by CT scan and scintigraphy, marking the position on the skin. Peroperatively an image intensifier and a sterile fiberoptic scintillation detector were used to localize the tumor. The specimen and the patient were examined by gammacamera to determine whethhistology of the specimen.

Results: 7 patients were operated on, mean age 20 (1.5–52) years. Diagnoses: 5 osteoid osteoma, 1 enchondroma and 1 undetermined. The results are shown in the table:

Modality	Useful	Not useful	Not used
CT-localization	5	1	1
Peroperative scint.	6	1	0
Specimen scint.	6	1	0
Postoperative scint	6	1	0
Peroperative x-ray imaging	1	6	0

Conclusions: Scintigraphic techniques are useful adjuncts to localize small positive bone tumors during operation, and corresponds well with the CT-scan. They are effective in determining whether the correct specimen has been removed or not. Nevertheless, one must be aware that false results does occur.

Soft tissue sarcomas in Iceland 1955–1988. Prognostic factors including nuclear DNA content

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From 1955 to 1988 a total of 129 cases (69 men and 60 women) of soft tissue sarcoma were diagnosed in Iceland. The median age was 55 (0–91) years. All the cases have been reviewed clinically and histopathologically and graded on both a three- and four point scale. The average age-standardized incidence was 1.8/100.000 for men and 1.6 for women, similar as in the other Nordic countries. The tumor was most often localized in the thigh and retroperitoneal space. The most common histologic subtypes were malignant fibrous histiocytoma (23%), liposarcoma (19%) and leiomyosarcoma (16%). Most were high-grade (69% grades III and IV and 31% grades I and II). The 5- and 10 year survival rates were 38% and 29%, respectively. The nuclear DNA content was determined in 124 cases by flow cytometry using tumor material from paraffin embedded tissue. 57 (48%) were aneuploid and 63 (53%) were diploid. The 10-year survival for the patients with diploid tumors was 35 % compared to 26% for patients with aneuploid tumors (p 0.6). The Cox's proportional hazard model was used with respect to different survival end-points and include the following covariates: age, period of diagnosis, sex, tumor localisation, histopathology, subtype, tumor size, malignancy grade and DNA ploidy. The strongest prognostic factor was malignancy grade (IV vs. I; p 0.001 and RR 5 and III vs I; p 0.02 and RR 2) followed by tumor size (pT2 vs pT1; p 0.001 and RR 3 and pT3 vs. pT1; p 0.002 and RR 3) and year of diagnosis (p 0.003 and RR 0,9); corresponding to a 54% reduction in mortality risk during a 20-year-period. DNA ploidy was not found to be an independent prognostic factor.

Prognostic importance of DNA-ploidy in soft tissue sarcoma

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We analyzed whether the prognostic strength (metastasis-free survival) of DNA-ploidy and other clinicopathologic factors varied between different histotypes in 213 patients with soft tissue sarcoma of the extremities and trunk wall, who were followed for median 5 (3–27) years.

Descriptive data: The median age was 64 (21–87) years. Half of the tumors were located in the hip girdle, thigh and knee. 64 tumors were superficial with a median size of 5 cm and 149 were deep-seated with a median size of 8 cm. 107 tumors were MFH, 43 tumors were leiomyosarcoma, 33 tumors were liposarcoma, 17 tumors were synovial sarcoma, and 13 tumors were of another type. 113 tumors were designated grade IV. 166 tumors were aneuploid. All patients were operated on. 60 patients developed local recurrence and 74 developed metastases.

Prognostic factors: Tumor size, malignancy grade, tumor necrosis, vascular invasion, and DNA-aneuploidy were prognostic in univariate analysis. Multivariately analyzed, the three latter factors were most important (Table 1). The prog-

Table 1. All histotypes, N 213

Factor	Univariate RR (95% CI)	Multivariate RR (95% CI)
Tumor size > 8cm	3 (1.6–4.1)	1 (0.9–2.4)
Malignancy-grade III	3 (1.8–9.7)	1 (0.3–3.8)
Malignancy-grade IV	6 (2.1–17)	1 (0.3–3.6)
Tumor necrosis	6 (3.3–11)	4 (1.8–7.5)
Vascular invasion	4 (2.5–6.2)	3 (1.6–4.4)
DNA-aneuploidy	3 (1.2–5.0)	2 (1.2–5.0)

Table 2. DNA-aneuploidy

Histotype	Univariate RR (95% CI)
MFH	6 (0.8–45)
Leiomyosarcoma	2 (0.6–11)
Liposarcoma	1 (0.3–4.0)
Synovial sarcoma	7 (1.2–38)
Other	3 (0.3–23)

nostic strength of DNA-aneuploidy varied considerably between each histotype (Table 2).

Comments: DNA-aneuploidy has been shown to be a prognostic factor in mixed series of soft tissue sarcoma; however, the strength seems to vary between different histotypes.

Subcutaneous sarcoma—SSG central registry

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Patients and methods: 860 patients with soft tissue sarcoma are included in the SSG central registry since 1986. 551 surgically treated patients were chosen from the registry and divided into 164 patients (30%) with subcutaneous and 387 (70%) with deep-seated tumors. Excluded were all patients who received preoperative chemotherapy or radiation therapy, had metastasis at time of diagnosis or had no follow-up data. Differences in the frequencies of the descriptive variables between the two groups were studied using t-tests or frequency-tables statistics. The influence of prognostic variables on local recurrence rate after resection of subcutaneous sarcoma were explored in a proportional hazard model.

Results: The subcutaneous sarcomas were more often MFH, of smaller size and there was a tendency towards a better surgical margin after resection. The cumulative three-year survival rate was 0.9 in the subcutaneous group and 0.75 in the deep-seated group. The multivariate analysis identified only surgical margin as an independent prognostic factor when the rate of local recurrence after resection of a subcutaneous sarcoma was studied.

Conclusions: In accordance with other studies our analysis indicates a good prognosis, and a low local recurrence rate after surgical resection with adequate margin of a subcutaneous sarcoma.

Malignant bone tumors with fracture at diagnosis—preliminary report from the SSG central registry

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21 (*m:f=15:6, mean age 45 (9–77) years*) of 300 registered patients presented a pathologic fracture at diagnosis. These included 8 osteosarcomas, 7 MFH, 4 chondrosarcomas and 2 Ewing sarcomas. The most common location was femur (13), followed by humerus (3) and tibia (2). The average follow up is 103 (30–172) weeks.

3 of 4 patients with pulmonary metastasis at diagnosis died after 2, 8 and 10 weeks. In 4 patients chemo- (2) or radiotherapy (2) was the only treatment applied, one in each group died.

In the other 13 patients amputation was the primary surgical treatment in 4 and limb-sparing was performed in 9 cases. 11 of these operated on patients received adjuvant radio- or chemotherapy. All amputated patients survived; two following additional operation for pulmonary metastases. 4 cases treated by limb-sparing intralesional or marginal surgery either developed local recurrence (3) requiring amputation or died (1). In the 5 other patients with limb-sparing surgery wide margins were obtained. No local recurrence appeared in these patients, one died from metastasis.

This series is small and the follow-up is still short. However, the findings do not seem to indicate that a pathologic fracture in a bone sarcoma is a contraindication for limb-sparing surgery, provided a wide margin can be obtained.

Characteristics of patients with recurrent disease in soft tissue sarcoma; SSG central registry

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There are several reports indicating a causal relationship between local recurrence, metastasis and survival after surgical treatment of soft tissue sarcoma. Some studies, however, suggest a stronger connection between metastasis and survival than between local recurrence and survival. The answer to this question is of importance when planning future studies of adjuvant therapy.

Patients and methods: 860 patients with soft tissue sarcoma are included in the SSG central registry since 1986. 551 surgically treated patients were chosen for analyses. Patients who received chemotherapy or radiation therapy preoperatively, had metastasis at time of diagnosis or had no follow-up data were excluded. The following prognostic factors influence on survival, metastasis and local recurrence were explored in three separate sets of survival analyses; age at diagnosis, sex, histotype, malignancy-grade, tumor localization, size and surgical margin. Using Cox regression techniques the combined

effect of these variables were studied. Histotype was included as a stratification variable.

Results: The variables that had the strongest effect on metastasis and survival were tumor size (p 0.0001) and malignancy-grade (p 0.0001). Surgical margin was significant only when intralesional surgery was compared with marginal or better (p 0.002) and (p 0.0001). The variable with best effect on the rate of local recurrence was surgical margin (p 0.0001). There was a difference between wide/radical and marginal surgery (p 0.002). The univariate analysis did not show any effect of tumor size or malignancy-grade on the rate of local recurrence. Multivariate analysis supported these trends.

Conclusion: It is probable that local control and metastasis/survival are influenced by a different pattern of prognostic factors.

Accuracy of computed tomography in diagnosing pulmonary metastases in sarcoma patients

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The resection of pulmonary metastases of sarcomas seems to prolong the survival of some patients. The problem is how to diagnose the metastases early enough and how to find those patients who will benefit from surgery. The diagnostic accuracy of preoperative CT-scanning was assessed retrospectively in a series of 30 consecutive thoracotomies, of which 26 could be analyzed.

Patients and methods: During 1986–1990 the multidisciplinary sarcoma group of our hospital recommended thoracotomy to 18 patients with suspected pulmonary metastases. 6 osteosarcoma patients and 12 soft tissue sarcoma patients. Thoracotomy was performed when the metastases appeared to be operable, were confined to the lungs only, and the patient was healthy enough and willing to undergo the operation. If metastases were suspected only in one lung, only unilateral thoracotomy was performed. 4 patients with bilateral metastases underwent only unilateral thoracotomy because of disease progression.

Results and conclusions: The average time from the primary sarcoma operation to diagnosed metastases was 2 (0–12) years. Unilateral thoracotomy was performed on 11 patients, bilateral on 3 patients and consecutive operations on 4 patients. CT-scanning was preoperatively performed in 17 patients. CT detected on the average 2,5 metastases in the lung to be operated. However the fortcoming operation revealed on the average 5.7 nodules of which 5.0 were metastases. In one case both the CT results and surgical diagnosis suggested 4 metastases, but the pathological diagnosis proved them all benign. In most cases, however, the excised tumours were metastases. When one or two metastases were found at operation the CT-scanning was accurate in 10 cases of 11. If more than two metastases were found at operation, CT was accurate only in 1 of 15 cases.

Table. Number of metastases in CT-scanning and operation

Diagnosed metastases in one lung	≤3	>3
CT-scanning	20	7
Operation	11	16

Risk factors for soft tissue sarcoma in southern Sweden—a case-control study

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Within the scope of SSG-1 a non-population based case-control study previously performed suggested an increased odds ratio for patients with soft tissue sarcoma after herbicide exposure (OR 2). A population based case-control study was therefore initiated in May 1990 to try to confirm this finding in a strictly population-based setting and to investigate the role of some possible new risk factors such as constitutional factors and trauma.

New cases of sarcomas are identified monthly in the regional cancer registry and the diagnoses are reviewed by one pathologist (HW).

Referents are matched to the cases on geography, sex and age. Both cases (after the permission of the treating doctor) and referents are interviewed through a standardized written questionnaire including questions on occupation, certain exposures, family history, constitutional factors, medical history, and some life style habits. 7 of 120 cases were at the reexamination found to have other diagnoses (benign tumours 4 cases and other malignancies 3 cases). 6 patients were dead at the time of contact with the responsible doctor. 5 patients were considered too ill to be interviewed and in one case the doctor had not informed the patient about the diagnosis.

Up to February 1992, approximately 100 cases and 400 controls have been interviewed giving an overall 80% response rate. 4% of the cases and 4.5 % of the referents claim that they have been exposed to herbicides occupationally. In a preliminary interim analysis no increased risk for soft tissue sarcoma can be seen after herbicide exposure. Cases show significant odds ratios for a family history of soft tissue sarcoma among first or second degree relatives. It is the objective to continue the study for another 3 years, to be able to analyse also subtypes of soft tissue sarcoma.

Pesticides and soft tissue sarcoma

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We have described an association between exposure to chlorinated phenols and soft tissue sarcoma (STS) in three case-control studies. A fourth investigation was performed to further evaluate the influence of various chemicals, i.e. different types of phenoxyacetic acids, chlorophenols and their contaminants in relation to STS.

Materials and methods: The study subjects were residents in central Sweden where use of phenoxyacetic acids other than 2,4,5-T has been more prevalent than in northern Sweden, where two of our earlier studies were performed. 237 male cases were included in this investigation with one matched control to each case. Exposure was assessed by a questionnare. Incomplete information was completed by telephone by an interviewer. All intestigators were blinded regarding the status of the study subjects as being cases or controls.

Results: A completed questionnaire was obtained from 218 cases and 212 controls. Exposure to phenoxyacetic acids or chlorophenols gave a rate ratio (RR) of 1.8 (95% CI=1.0–3.2). For exposure to phenoxyacetic acids a RR of 1.3 (0.7–2.6) and regarding chlorophenols (high grade) a RR of 5 (1.7–16) was obtained. No increased risk was found for exposure to phenoxyacetic acids other than 2,4,5-T, whereas exposure to 2,4,5-T during the 1950s gave a significantly increased RR of 3 (1.1–8). If only those phenoxyacetic acids and chlorophenols (high grade) that are known to be contaminated by dioxins were regarded, a RR of 2 (1.3–5) was obtained. Exposure to various other agents was assessed whereby no other risk factors for STS were identified. In clonclusion this study indicated that exposure to dioxins, not only 2,3,7,8-TCDD but also higher chlorinated isomers, might be a risk factor for STS.

Conclusion: Some cohort studies of workers exposed to dioxins, especially 2,3,7,8-TCDD, have verified an increased risk for STS. In one recent investigation a significantly increased risk for all cancer combined was noted. Also an effekt of exposure time and latency period was described. In a metaanalysis of our four studies on STS we found a dose-response effect for duration of exposure to dioxins. Exposure for < 1 year gave a RR for all dioxins of 2 and for 2,3,7,8-TCDD only of 3 whereas exposure for > 1 year gave RRs of 6 and 7 respectively.

Adjuvant chemotherapy with Doxorubicin in high-grade soft tissue sarcoma—Scandinavian sarcoma trial SSG I—a follow-up report

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From 1981 to 1986, a total of 240 patients with primary, malignancy-grade III or IV soft tissue sarcoma were entered into an adjuvant chemotherapy multicenter trial. 181 patients were evaluable. After radical surgery (wide and compartmental) the patients were randomized to treatment with single-agent doxorubicin 60 mg/m^2 administered as an intravenous bolus once a month for 9 months (group 1, n 77) or to control (group 2, n 77). If the surgical procedure was marginal, the patients initially received postoperative radiotherapy, followed by doxorubicin (group 3, n 16) or control (group 4, n 11). With a median follow-up of 83 (2–97) months, and for 105 survivors 62 (35–97) months, there was no significant difference between the four groups in overall survival, disease-free survival or local tumor control. The findings were the same whether the total group or evaluable patients only were included in the analysis.Intratumoral vascular invasion (RR: 2.8), histologic malignancy-grade IV (RR 3), tumor size over 10 cm (RR 3), DNA aneuploidy (RR 2), and male sex (RR 2) were found to be independent prognostic risk factors in 148 high-grade soft tissue sarcomas of the extremities and trunk. It is recommended that all SSG I-patients should be followed for a total of 10 years from the randomization date and reported to the SSG-secretariat. So far there is follow-up in 97% of the patients.

Surgical margin in osteosarcoma

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Limbsparing surgery has become increasingly applied in the treatment of osteosarcoma. The rate of local recurrence ranges from 10 to 30%. It has been claimed that recurrence is more strongly related to surgical margin than type of procedure, i.e. local or ablative. The increasing use of CT and MRT in preoperative planning has facilitated the achievement of an adequate margin by local excision. Moreover, preoperative chemotherapy has been reported to produce a tumor pseudocapsule, increasing the feasibility of obtaining an adequate margin by local excision. A multicenter, pre- and postoperative chemotherapy protocol in high-grade osteosarcoma was decided by the Scandinavian Sarcoma Group in 1981 (SSG II trial). We analyzed retrospectively local recurrence in relation to surgical procedure and margin in the SSG II-series.

Patients and methods: The study included 105 patients treated 1981 to 1989 according to the SSG II protocol. Type of surgery was recorded as ablative or local. Surgical margin was assessed as adequate, i.e. radical or wide or inadequate, i.e. marginal and intralesional.

Results: According to the Surgical Staging System there were 102 IIB and 3 IIA lesions. Local excision was performed in 27 cases. The rate of local excision varied according to tumor location. Femoral tumors were treated by local excisions in 14 of 60 cases. The corresponding rate for tibial tumors was 4/26, fibular 1/3, humeral 7/14, and radial 2/2. An adequate margin was obtained in 67% of the cases as compared to 97% after ablative surgery. After a mean of 6 years follow-up there were five local recurrences (5%). All five

patients had undergone surgery by a wide margin; three by local and two by ablative procedure. Discussion.: The rate of ablative procedures in the present series was high. This may explain the high rate of adequate margin obtained and the low rate of local recurrence. Notably, none of 12 cases treated by inadequate margin developed local recurrence. Whether this should be attributed to erroneous assessment of margin or the effect of adjuvant chemotherapy remains unsettled.

Five-year results of T-10 chemotherapy for extremity-localized osteosarcoma

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From 1982 to 1989, 97 patients (pts) (median age 16 years) with high-grade, extremity-localized osteosarcoma were treated according to the T-10 regimen (protocol SSG II/82). Four weekly preoperative courses with high-dose methotrexate 8-12 g/m2 (HDMTX) were followed by postoperative adjuvant chemotherapy (CT) guided by the histological response grading in the primary tumour. Thus, good responders (grade III or IV) continued HDMTX-based CT, whereas intermediate (grade II) and poor (grade I) responders crossed over to receive a cisplatin/doxorubicin-based regimen. As previously reported (1), only 17% of pts attained a grade III/IV response, where as 62% had grade II and 21% had grade I response. Median follow-up for living pts is now 58 (23–108) months. 41 pts (42%) have relapsed with distant metastases after median 18 (2–49) months, and 5% of pts have developed local recurrence. Five-year relapse-free and overall survival is 56% and 63%, respectively. There are persistent, statistically significant differences in both relapse-free and overall survival between good and intermediate/poor histological responders (5-year relapse-free survival 78% vs. 54%, respectively, p 0.046). Also, there is a persisting trend for better relapse-free survival for patients with higher serum MTX levels during preoperative CT. We have previously demonstrated a significant correlation between histological response and serum MTX levels (1). Thus, both response to preoperative CT and serum MTX levels appear to be important parameters for long-term outcome.

Reference: Saeter G, Alvegård TA, Elomaa I, Stenwig AE, Holmström T, and Solheim OP. Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effect of preoperative chemotherapy with single agent high-dose methotrexate. A Scandinavian Sarcoma Group Study. J Clin Oncol 9, 1766-1775, 1991.

Treatment of osteosarcoma—Scandinavian Sarcoma trial SSG VIII—a follow-up report

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From protocol activation 01.06.90 to 01.04.92, 23 patients (pts) with extremity-localized, non-metastatic, high-grade osteosarcoma have been registered from 6 Scandinavian institutions. There are 14 male and 9 female pts of median age 15 (2–39) years, with tumor localization in the femur (13 pts), proximal tibia (6 pts) or proximal humerus (4 pts). 18 pts have been operated on, 11 with amputations and 7 with limb salvage procedures. Protocolled preoperative treatment consists of two chemotherapy (CT) cycles, each containing two high-dose methotrexate and one cisplatin/doxorubicin course. Histologic response has been reported in 14 pts, with grade III or IV response in 7 pts, grade II response in 4, and grade I response in 3 pts.

Post-operative CT has been completed (and reported) in 8 pts, of which 6 pts have received the methotrexate/doxorubicin arm (grade II–IV responders), and 2 have received etoposide/ifosfamide (grade I responders). Median follow-up for all pts is now 7.5 (1–21) months. 4r pts have relapsed after 1, 2, 12 and 13 months.

Treatment-related toxicity has been quite severe, with WHO grade 4 bone marrow toxicity and serious infections seen in more than half of patients. Dose reductions had to be performed in 6 of pts pre-operatively and 17 post-operatively. Other toxic events included severe reversible creatinine rise (1 pt), hemorrhagic proctitis (1 pt), symptomatic hypomagnesemia (1 pt) and exanthema/enanthema (4 pts). Two patients did not receive the last post-operative CT cycle due to toxicity.

These preliminary results strongly indicate that the preoperative CT in SSG VIII has improved histological response as compared to SSG II (50% vs. 17% grade III/IV responders). This is of considerable importance, as histological response has been proven to be strongly correlated to long-term outcome. However, the preliminary data indicate that SSG VIII toxicity is severe.

Treatment of Ewing's sarcoma—Scandinavian sarcoma trial SSG IV/84—a follow-up report

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From 1984 to 1989, 47 patients (30 men and 17 women) from 13 participating institutions from the Scandinavian countries were registrered at the SSG secretariat. The median age was 17 (7–49) years. 42 patients had non-metastatic and 5 metastatic disease. The tumour location was around the knee (15), pelvis (11), costa (7), upper extremity (6), lower extremity (4),

and in other locations (4). No exclusion was made as regard eligibility for the trial. Following diagnosis (fine-needle aspiration, open biopsy or both), all the patients, except one, received pre-local-treatment chemotherapy with two 12-week cycles of six drugs (actinomycin, adriamycin, bleomycin, cyclophosphamide, methotrexate, and vincristine) according to a modified T-11 protocol of Rosen. Thereafter 18 patients had surgery alone, 14 patients radiotherapy alone, 13 patients surgery and radiotherapy, and 2 patients did not receive any local treatment. 3 additional cycles of chemotherapy was given after local treatment. The patients were followed with chest radiographs, primary tumor-site radiographs, and a whole-body radionucleide bone scan every third month for 3 years. After this time, these examinations were performed less frequently. No patient was lost to follow-up. Out of 27 reviewed postoperative tissue samples, 10 patients had a grade I tumor response, 6 a grade II, 6 a grade III and finally 5 patients hade a grade IV response. The cumulative five-year overall survival was 52%, median follow-up 64 (5–84) months, and for 23 survivors 52 (21–84) months. Metastasis-free survival was 46% and the local tumor control was 60% for all 47 patients registered, including the 5 patients with disseminated disease. Differences in overall survival were observed with respect to different tumor locations, costa (85%), pelvis (60%), lower extremity and knee (50%), and upper extremity (20%).

Comments and conclusions: The overall metastasis-free survival in the SSG IV-trial compares favourably with the results of other cooperative studies. However, there is a distinctive difference of failures. In comparison with other studies, our is compromised by a relatively high local failure rate. Therefore the SSG introduced a new protocol in 1990 to improve the overall survival and local tumor control rate by using more potent combination chemotherapy (including ifosfamide, doxorubicin, vincristine, cisplatinum) and accelerated hyperfraction radiotherapy as local treatment (1). It is recommended that all SSG IV-patients should be followed for a total of ten years from the date of biopsy and reported to the SSG secretariat.

Reference: Combined modality therapy in Ewing's sarcoma, SSG-trial X, Lund 1990.

Is platelet-derived growth factor (PDGF) involved in the pathogenesis of human sarcoma ?

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PDGF stimulates the proliferation of mesenchymal cells in vitro, and PDGF-B can induce sarcomas in experimental animals. Little is however known about the role of PDGF in the development of human tumors. Using immuno-histochemistry and in situ hybridization we describe the presence of PDGF and PDGF receptors in a series of proliferative disorders of fibroblastic origin. High expression of PDGF B-receptor mRNA and protein is seen in malignant tumors, but also in the benign dermatofibroma. High expression of PDGF α-receptor mRNA was on the contrary seen only in the malignant lesions investigated, i.e. malignant fibrous histiocytoma. PDGF A- and B-chain mRNAs were coexpressed with the receptors. The results indicate that autocrine stimulation via PDGF receptors could occur both in benign and malignant mesenchymal tissue lesions.