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Alvegård, Thor; Bauer, H.; Blomqvist, C.; Rydholm, Anders; Smeland, S.

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The Scandinavian Sarcoma Group—background, organization and the SSG Register—the first 25 years

T. A. Alvegård[1], H. Bauer[2], C. Blomqvist[3], A. Rydholm[4] and S. Smeland[5]

[1]Dept of Cancer Epidemiology and Regional Southern Swedish Tumour Registry, Lund University Hospital, Lund, [2]Orthopedic Oncology Service, Karolinska Hospital, Stockholm, Sweden, [3]Dept of Oncology, University Hospital, Helsinki, Finland, [4]Dept of Orthopedic Surgery, Lund, Sweden, [5]Dept of Oncology, The Norwegian Radium Hospital, Oslo, Norway
evy.nilsson@cancerepid.lu.se

Musculoskeletal sarcomas call for multidisciplinary management by a "tumor team" of specialized orthopedic surgeons, radiologists, pathologists, tumor biologists (e.g. molecular and cytogenetics, DNA cytometry), cytologists, radiotherapists, and oncologists (Figure 1). Only a few such teams existed in Scandinavia during the 1970s. With the inception of the Scandinavian Sarcoma Group (SSG) in 1979, several new teams were started, each with regional responsibility for centralized treatment of sarcoma patients. Together, Denmark, Finland, Iceland, Norway and Sweden have a population of 25 million. These countries have similar social structures, with modern medical services covering all inhabitants and an effective registration of all cancer patients. The similarity of the medical care systems in the Scandinavian countries makes multicenter studies easier to perform. The activities reported at the annual Scandinavian meetings (SSG) (Rydholm and Alvegård 1994a, 1994b, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003) stimulated Scandinavian sarcoma research, which is reflected in an increasing number of reports in the scientific literature.

Organization of the Scandinavian Sarcoma Group

The Scandinavian Sarcoma Group (SSG) was constituted in 1979 and is composed of oncologists (pediatric and adult), surgeons, radiologists, pathologists and tumor biologists from the Nordic countries (Figure 2). The aim of the SSG is to

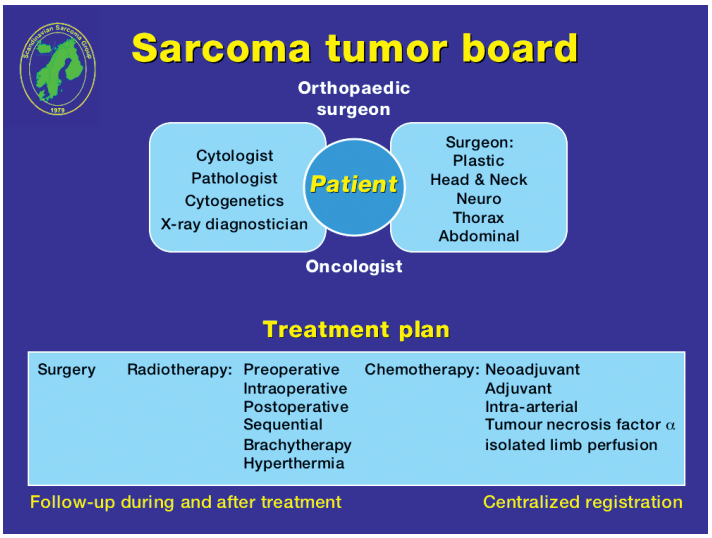

Figure 1. The sarcoma tumor board defines the diagnosis and determines the treatment and centralized registration. It is important that all sarcoma experts jointly to define diagnosis, treatment and follow-up.

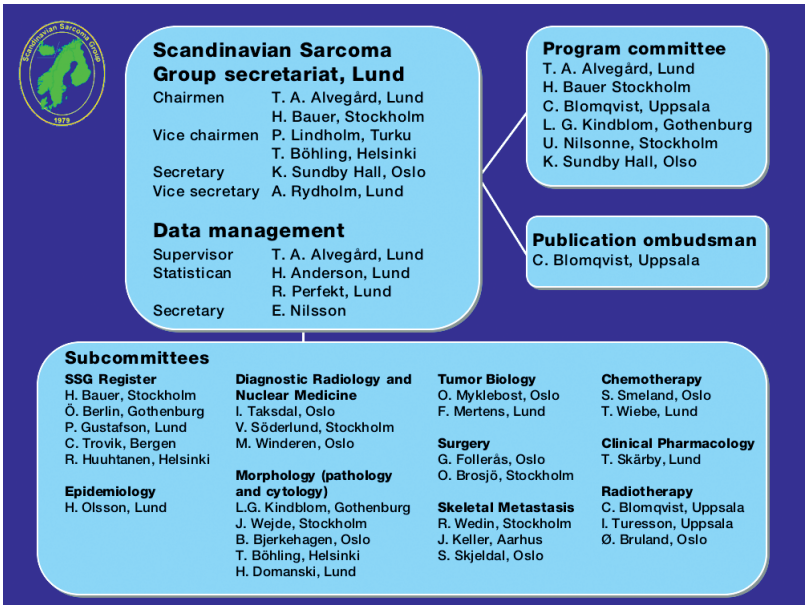

Figure 2. Organization of the Scandinavian Sarcoma Group. The morphology group meets 2–3 times a year for peer-review of all registrated sarcomas.

uphold and improve the quality of diagnostics, treatment and care of sarcoma patients by sharing information and education, and stimulate and coordinate basic and clinical research. The SSG maintains two patient registers, i. e., the SSG Register of Bone and Soft Tissue Sarcoma Patients and the SSG Skeletal Metastasis Register, both financed by grants (see Bauer et al. 2004 pp 8–10, and Hansen et al. 2004 pp 11–15 in this issue). The SSG is open to all specialists in the Nordic countries interested in sarcoma and has no membership fee. The national cancer societies, several pharmaceutical companies and private donors have supported our Scandinavian research and development of treatment strategies for musculoskeletal tumors. The salary of the full–time secretary, is paid by the Swedish Cancer Society.

The SSG holds meetings twice yearly, Subcommittee Meetings in December and the General Assembly in the spring. The SSG Board consists of 2 Chairmen, 2 Vice-Chairmen, 1 Secretary, 1 Vice-Secretary, the publication ombudsman, and the respective chairmen of the 8 subcommittees (SSG Sarcoma Register, Epidemiology, Diagnostic Radiology and Nuclear Medicine, Morphology, Tumor Biology, Surgery, Oncology, and SSG Metastasis Register). The Chairmen and Secretaries are elected by the General Assembly for 5 years. The Subcommittees elect their own chairmen and coordinators.

The SSG office is located in Lund and is responsible for the preparation of meetings, keeping the Register of SSG members, and for the applications and details concerning grants. The SSG must be mentioned in the title of all publications based on the SSG Registers and SSG treatment protocols. Before manuscripts are submitted they should be forwarded to the publication ombudsman.

All subcommittees have a joint meeting once a year, to develop new strategies regarding research and treatments for musculoskeletal tumors. At our annual general meeting (with about 130 active SSG members), new developments and strategies are submitted and discussed. Guest lectures are given by Scandinavian and international experts in various fields.

Goal

The main goal of the group is to improve the treatment of sarcoma patients in Scandinavian countries. Their survival depends on a number of factors, some of which can be influenced. These include patient's and doctor's delay, referral to a highly specialized tumor center, the abilities of the diagnostic and therapeutic teams, the principles of treatment, the available equipment and details of the treatment schedules. Better treatment requires clinical and basic research. Our SSG register in connection with the national cancer registries and new biobank registry will in the future make trans-

lational sarcoma research easier to perform.

Communication lines

The local groups are represented in the Scandinavian Sarcoma Group by one or several members. This permits direct contact between the SSG and the doctors treating the patients. The chairmen, the vice–chairmen, the secretary, the vice–secretary and most subcommittee chairmen are members of the European Musculoskeletal Oncology Society (EMSOS). Other members participate in and report about meetings of the Société Internationale d' Oncologie Pédiatrique (SIOP), European Organization for Research and Treatment of Cancer (EORTC), Connective Tissue Oncology Society (CTOS) and International Society of Limb Salvage (ISOLS). The SSG is thus part of the international sarcoma society network.

Centralization

Physicians outside the tumor treatment centers, who are the first to see the patient, must know when to suspect a sarcoma. This is a simple matter in most cases of skeletal sarcomas: pain and/or a palpable tumor lead to a conventional radiographic examination, which almost always arouses suspicion of a sarcoma. Therefore most patients with skeletal sarcomas were referred to tumor treatment centers before the Scandinavian Sarcoma Group was founded. However, at the time of inception of the SSG, many patients who had soft tissue sarcomas were treated after considerable delay in local hospitals and often with inadequate surgery. They therefore arrived at the tumor centers with locally advanced tumors, recurrences or metastases. To improve the prognosis for these patients, the following recommendations were made:

- All patients with soft tissue lesions suspected of malignancy should be referred to a tumor center, without prior biopsy.
- Indications for referral to a tumor center before surgery:
- deep tumor of any size
- subcutaneous tumors larger than 5 cm and
- all other tumors, suspected of being malignant.
- If a soft tissue sarcoma has been diagnosed by fine needle aspiration, incisional biopsy or excision, the patient should be referred to a tumor center, without further surgery.

This recommendation was signed by all active SSG members in Helsinki in 1982 from four countries representing nine specialties and 21 tumor centers. The recommendation has been published in each country in the national medical journals, in books and has been presented at meetings. Copies have been sent to local hospitals and individual doctors. Since many years 9 of 10 patients with soft tissue sarcomas in southern Sweden, are referred to the regional tumor center. Among patients with deep sarcomas, 80% are referred before biopsy. During recent years all centers in the Scandinavian Sarcoma Group have achieved this favourable referral pattern (Rydholm 1997, see also Bauer et al. 2004 pp 8–10 in this issue).

Clinical investigations

The following studies have been started by the SSG since 1979:

SSG I: Soft tissue sarcoma. Malignancy grades III and IV. Wide ± adj. doxorubicin. Marginal surgery + radiotherapy ± adj. doxorubicin. A randomized study. Started 1981, ended Feb. 1986; 240 patients (Alvegård et al. 1989, Alho et al. 1989, Alvegård et al. 1989, Alvegård et al. 1989, Alvegård et al. 1990, Alvegård 1989, Wiklund et al. 1993). This was the second largest study included in the individual data meta-analysis reported by Tierney et al. 1997.

SSG II: Osteosarcoma. Combined primary treatment, ad modum Rosen T 10 protocol. Nonrandomized. Started 1982, ended 1989; 114 patients (Solheim et al. 1989, Saeter et al. 1991, Solheim et al. 1992).

SSG III: Soft tissue sarcoma. Planned in 1983 as a randomized study on the effects of various irradiation schedules on inoperable tumors. However, too few patients were included, and the study was discontinued.

SSG IV: Ewing's sarcoma. Combined modality treatment ad modum Rosen T 11 protocol. Nonrandomized. Started 1984, ended 1990; 52 patients (Alvegård et al. 1989, Nilbert et al. 1998).

SSG V: Treatment program for soft tissue sarcoma (all malignancy grades). Nonrandomized.

SSG VI: Osteosarcoma metastases. Combined modality. Nonrandomized. Started summer of 1987, ended 1989; 15 patients.

SSG VII: Centralized register of patients with

sarcoma in Scandinavia. Started 1986, ongoing, 6 799 patients.

SSG VIII: Osteosarcoma. Combined primary treatment with high doses of methotrexate, cisplatinum and adriamycin preoperatively. Nonrandomized. Started 1990, ended December 1997; 113 patients (Saeter 1996a, Saeter 1996b).

SSG IX: Ewing's sarcoma. Combined modality treatment with cisplatinum, vincristin, adriamycin, ifosfamide, surgery ± hyperfractionated irradiation. Nonrandomized. Started 1990, ended April 1999; 133 patients (Elomaa et al. 1996, 1999, 2000).

SSG X: Treatment of metastatic soft tissue sarcoma with ectoposide, ifosfamide and GCSF. Started 1991, ended 1995; 114 patients (Saeter et al. 1995, Saeter et al. 1996, Saeter et al. 1994).

SSG XI: Treatment of metastatic soft tissue sarcoma with trofosfamide. Started 1994, ended 1996; 40 patients.

SSG XII: Metastasectomy and chemotherapy for lung metastasis from soft tissue sarcoma. EORTC/ SSG randomized phase III study. Started July 1996, ended 1998; 15 patients.

SSG XIII: A Scandinavian Sarcoma Group treatment protocol for adult patients with high-risk soft tissue sarcoma of the extremities and trunk wall. Started July 1998, ongoing; 75 patients.

SSG XIV: A Scandinavian treatment research protocol for extremity localized high-grade osteosarcoma. Started February 2001, ongoing; 48 patients.

SSG XV: Phase III randomized, intergroup, international trial assessing the clinical activity of STI-571 at two levels in patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) expressing the KIT receptor tyrosine (CD117). The Scandinavian Sarcoma Group was not accepted to participate in this trial by the EORTC because of patient health insurance problems.

SSG XVI: Registration of patients with surgically treated skeletal metastases. Started April 2000, ongoing; 554 patients.

SSG XVII: Recommendations for the diagnosis and treatment of abdominal, pelvic and retroperitoneal sarcomas. Started May 2002.

SSG XVIII: Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high-risk for recurrence: A randomized phase II study. Started January 2004, ongoing.

ISG/SSG I: An Italian–Scandinavian treatment and research protocol for high-grade osteosarcoma of the extremities. Localized disease and metastatic relapse. Started March 1997, ended September 2000; 187 patients.

ISG/SSG II: An Italian–Scandinavian treatment protocol for metastatic and pelvic osteosarcoma. Started March 1998, ended December 2003; 55 patients.

ISG/SSG III: An Italian–Scandinavian treatment protocol for standard-risk Ewing's sarcoma. Started June 1999, ongoing; 106 patients.

ISG/SSG IV: An Italian–Scandinavian treatment protocol for high-risk Ewing's sarcoma. Started June 1999, ongoing; 22 patients.

Euroboss I: A European treatment protocol for bone sarcoma in patients older than 40 years. Started February 2003, ongoing; 2 patients.

Euramos I: A randomized trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to preoperative chemotherapy (start: spring 2004).

The Scandinavian Sarcoma Group Register

A register for data makes possible multicenter studies concerning treatment results and prognostic factors for local recurrence and survival of patients with soft tissue and bone sarcomas. Such studies are needed to determine more exactly how these patients should be treated. Our position is unique because of the close to 100% follow-up that is possible in Scandinavian countries. The SSG Register of soft tissue and bone tumors was started on March 1, 1986. The Register is now used for detailed studies on treatment and prognosis. SSG – Central register and biobank registries makes translational sarcoma research easier in the future (Figure 3). It gives important information on how the treatment of patients with musculoskeletal tumors is evolving in Scandinavian countries. For example, important changes in referral patterns, preoperative diagnostic techniques and surgical margins have been found (see Bauer et al. 2004 pp 8–10 in this issue).

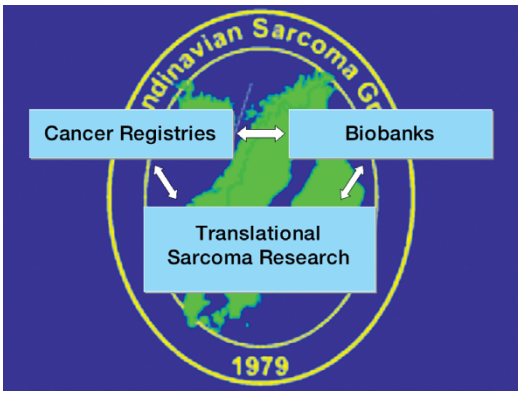

Figure 3. SSG – Central register, cancer registries and biobank registries makes translational sarcoma research easier in the future.

Results and strategies

Soft tissue sarcoma

In our first randomized study (SSG I, 1981–1986), we reported that adjuvant chemotherapy with doxorubicin had no effect on metastasis-free and overall survival rates (Alvegård et al. 1989). SSG participated in a review and meta-analysis of the published results of all 15 randomized clinical trials (Tierney et al. 1997). In a multivariate analysis of the SSG I material, the following factors were identified as independent variables for predicting the development of distant metastases: malignancy grade IV, tumor size >10 cm, intratumoral vascular invasion and necrosis, as well as male sex. Recently, the Lund group devised a system based on three factors: tumor size, necrosis and vascular invasion. In a population-based study from the southern health region of Sweden, two prognostic groups were identified: 1. a good prognosis group with one or no factors present with a 5-year metastasis-free survival of 81% and 2. a poor prognosis group with two or three factors present and a metastasis-free survival of 32%. The good and poor prognosis groups included approximately 70% and 30% of the patients (Gustafson 1993, 1994). Adjuvant treatment strategies have been developed, based on the outcome of this analysis (SSG XIII).

Osteosarcoma

In our first neo-adjuvant chemotherapy protocol for osteosarcoma (SSG II) we had a good tumor response in 19% using four treatment cycles with high doses of methotrexate. 5-year overall and metastasis-free survival rates were 62% and 58%, (Solheim et al. 1989, Saeter et al. 1991, Solheim et al. 1992). In our last protocol (SSG VIII) the good tumor response rate is 60% after preoperative chemotherapy with high doses of methotrexate, cisplatinum and adriamycin (Smeland et al. 2003). Two new protocols (ISG/SSG I, II) have been started in collaboration with the Rizzoli Institute, Bologna. Increasing preoperative chemotherapy, including high doses of methotrexate, ifosfamide, cisplatinum and doxorubicin did not show increase of the metastasis-free or overall survival rates (Bacci et al. 2002).

Ewing's sarcoma

The final report on our first study (SSG IV) was made by Nilbert et al. 1998 with a long follow-up time, see Smeland et al. 2004 pp 87–91 in this issue. Our second study (SSG IX), using a combination of high doses of chemotherapy, surgery and accelerated fractionated radiation therapy, has so far resulted in a good tumor response following preoperative chemotherapy and preliminary results show a 5–year overall survival of approximately 70% (Elomaa et al. 1999, 2000). Collaboration with the Rizzoli Institute has been started to develop a high dose treatment for poor responders, following preoperative chemotherapy (ISG/SSG III and IV).

SSG's publications

Since start 1986 more than 1000 articles have been published by members of the Scandinavian Sarcoma Centers i.e., 1979–1989 (Solheim et al. 1989), 1989-1993 (Alvegård 1989–1994) and 1993–1998 (Rydholm and Alvegård, 1998), for publications 1998–2003 see pp 99-114 in this issue. These publications represent research from the various Scandinavian Tumor Centers and the Scandinavian Sarcoma Group Research program. 15 members wrote their Ph.D. theses on issues relevant to sarcoma in this period.

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