The Scandinavian Sarcoma Group

Background, organization and the Central Register—the first 20 years

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Musculoskeletal sarcomas call for multidisciplinary management by a "tumor team" of specialized orthopedists, 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 other 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 24 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 also makes multicenter studies possible. The activities reported at the annual Scandinavian meetings (SSG) (Rydholm and Alvegård 1994a, 1994b, 1995, 1996, 1997, 1998) stimulated Scandinavian sarcoma research, which is reflected in an increasing number of reports in the scientific literature.

Organization

The secretariat, located in Lund in Southern Sweden, consists of a chairman, 3 vice–chairmen, secretary, vice–secretary and the data management consists of a supervisor, statistician and secretary. We have our own program committee and publication committee. Subcommittees also exist for the central register, epidemiology, diagnostic radiology and nuclear medicine, morphology, tumor biology, surgery, chemotherapy and radiotherapy (Figure 2). 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 develop-

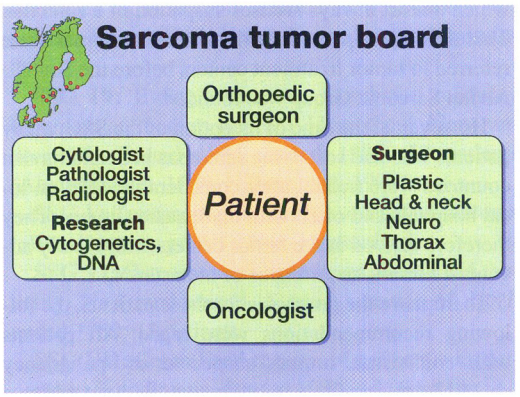

Figure 1A. Sarcoma tumor board defining the diagnosis.

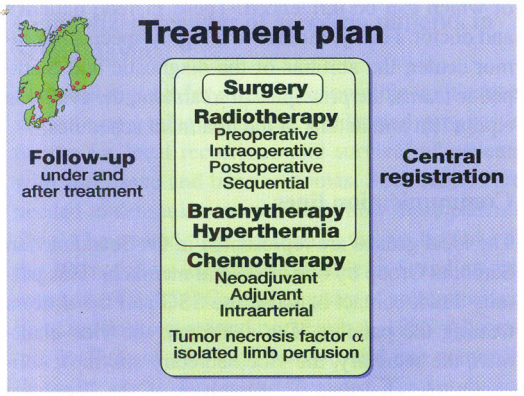

Figure 1B. The sarcoma tumor board determines the treatment and centralized registration. It is important that all sarcoma experts meets jointly to define diagnosis, treatment and follow-up.

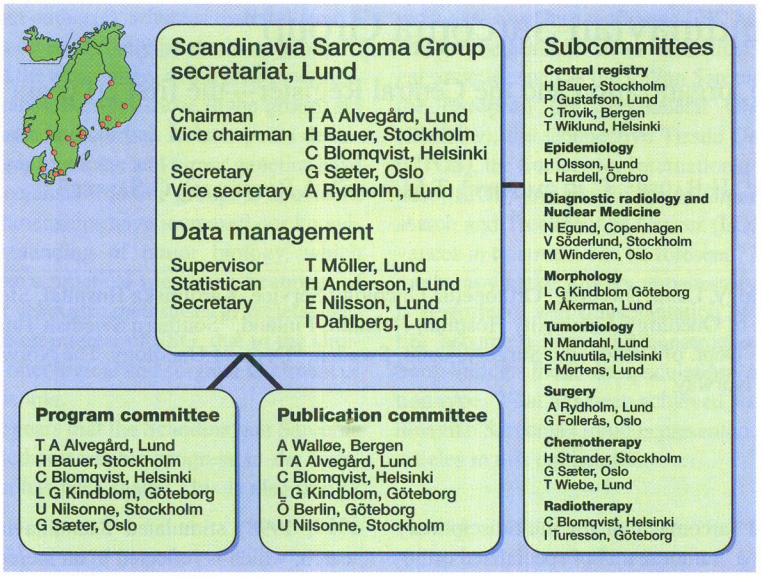

Figure 2. Organization of the Scandinavian Sarcoma Group. The morphology group meets 4 times a year for peer–review of all registrated sarcomas.

ments and strategies are submitted and discussed. Guest lectures are given by international and Scandinavian experts in various fields.

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.

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.

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 chairman, 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), Chromosome Morphology and Prognosis in Musculoskeletal Tumors (CHAMP), and the American Musculoskeletal Tumor Society (MSTS). 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 in Scandinavian countries 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 tumors suspected of malignancy should be referred to a tumor center, without taking a biopsy. Indications for referral:

1. deep tumors of any size,
2. subcutaneous tumors larger than 5 cm and,

3. all other tumors, suspected of being malignant.
4. 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 by 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. In southern Sweden, 9 of 10 patients with soft tissue sarcomas are referred to the regional tumor center. Of patients with deep sarcomas, 80% are referred before biopsy. During recent years all centers in the Scandinavian Sarcoma Group have improved their referral pattern.

Clinical investigations

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

SSG I: Soft tissue sarcoma. Malignancy grades III and IV. Radical surgery ± 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 is the second largest study included in an individual data meta–analysis reported by Tierney et al. 1997.

SSG II: Osteosarcoma. Combined primary treatment, ad modum Rosen T 10 protocol. Non–randomized. 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, very few patients were included, and the study was discontinued.

SSG IV: Ewing's sarcoma. Combined modality treatment ad modum Rosen T 11 protocol. Non–randomized. Started 1984, ended 1989; 53 patients (Alvegård et al. 1989, Nilbert et al. 1998).

SSG V: Treatment program for soft tissue sarcoma (all malignancy grades). Non–randomized.

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

SSG VII: Centralized register of patients with sarcoma in Scandinavia. Started 1986, 4 416 patients.

SSG VIII: Osteosarcoma. Combined primary treatment with high doses of methotrexate, cisplatinum and adriamycin preoperatively. Non–randomized. Started 1990, ended December 1996; 125 patients (Saeter 1996A, Saeter 1996B).

SSG IX: Ewing's sarcoma. Combined modality treatment with cisplatinum, vincristin, adriamycin, ifosfamide, surgery ± hyperfractionated irradiation. Non–randomized. Started 1990, still ongoing trial; 124 patients (Elomaa et al. 1996, 1999).

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

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, still ongoing trial; 11 patients.

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, still ongoing trial; 120 patients.

ISG/SSG II: An Italian—Scandinavian treatment protocol for metastatic and pelvic osteosarcoma. Started March 1998, still ongoing trial; 10 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, still ongoing trial; 20 patients.

ISG/SSG III: An Italian—Scandinavian treatment protocol for standard–risk Ewing's sarcoma. Will start April/May 1999.

ISG/SSG IV: An Italian—Scandinavian treatment protocol for high–risk Ewing's sarcoma. Will start April/May 1999.

Centralized register of sarcoma patients in Scandinavia

A central 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 100% follow–up that is possible in Scandinavian countries. The SSG Central Register of soft tissue and bone tumors was started on March 1, 1986. All centers in Finland, Norway, Sweden and one center in Denmark participate in the Register. The yearly accrual rate is approximately 250 soft tissue and 100 bone tumor patients. The Register is now used for detailed studies on treatment and prognosis. 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.

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. 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 >10 cm presence of necrotic areas >4 mm in diameter and the presence of vascular invasion. In a population–based study of data from the southern health region of Sweden, two prognostic groups were identified: 1) a good prognosis group with one or no factors present as well as a five–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 prognoses groups included approximately 70% and 30% of the patients, respectively (Gustafson 1994). In a comparative analysis of the Lund, AJC and SSS systems, the Lund system gave the best separation as regards metastasis–free survival. All patient data contained in the Central Register of the SSG will therefore me analyzed with the Lund system which houses details of approximately 4,700 STS patients from Sweden, Norway and Finland. 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 with high doses of methotrexate. Five–year overall and metastasis–free survival rates were 62% and 58%, respectively (Solheim et al. 1989, Saeter et al. 1991, Solheim et al. 1992). In our last protocol (SSG VIII) the good tumor response rate is now 60%, after preoperative chemotherapy with high doses of methotrexate, cisplatinum and adriamycin. Two new protocols (ISG/SSG I, II) have been started in collaboration with the Rizzoli Institute, Bologna. By increasing preoperative chemotherapy, including high doses of methotrexate, ifosfamide, cisplatinum and doxorubicin it may become possible to increase the tumor response as well as the metastasis–free and overall survival rates.

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. Our recent 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. 1994, 1996, and page 69 in this issue). Collaboration with the Rizzoli Institute has been started to develop a high dose treatment for poor responders, following preoperative chemotherapy.

Central Register

Several articles are under preparation regarding prognostic factors, referral pattern, and importance of surgical margins for musculoskeletal tumors.

SSG's publications

A total of 990 articles have been written 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). These publications represent research from the various Scandinavian Tumor Centers and the Scandinavian Sarcoma Group Research program. 10 members wrote their Ph.D. theses on issues relevant to sarcoma in this period.

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