The Scandinavian Sarcoma Group

Background, organization and the Central Registry—the first 17 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 (Rydholm 1983) as illustrated in 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 initiated, each with regional responsibility for centralized treatment of sarcoma patients. Together, Denmark, Finland, Iceland, Norway and Sweden have a population of 24 million. The countries have similar social structures with modern medical services covering all inhabitants and an effective registration of all cancer patients. The similar medical care systems in the Scandinavian countries also make multicenter studies possible. The activities, reported at the annual Scandinavian meetings (Rydholm et al. 1994a, Rydholm et al. 1994b, Rydholm et al. 1995), stimulated sarcoma research, which is reflected by increasing number of reports in the scientific literature.

Organization

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

All subcommittees have a meeting once a year, separately and a joint meeting of all groups, to develop new strategies regarding research and treatment modalities for musculoskeletal tumors. At our annual meeting (130 active SSG members), new developments and strategies are submitted and discussed. Guest lectures are held by international and Scandinavian experts in the different fields.

The National Cancer Societies, several pharmaceutical companies and private donators have supported our Scandinavian research and development of treatment strategies for musculoskeletal tumors. The sala-

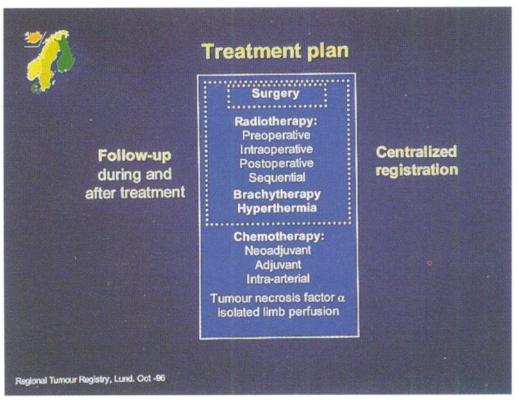

Figure 1A. Sarcoma tumor board defining the diagnosis.

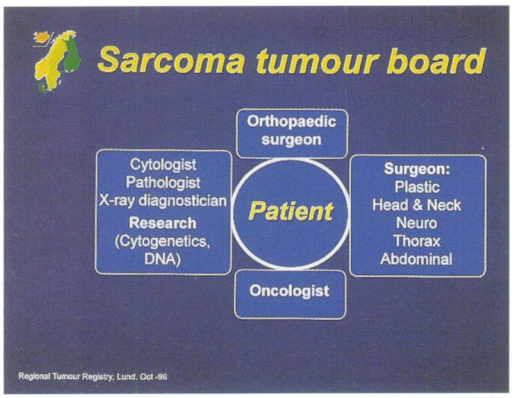

Figure 1B. The sarcoma tumor board determinate the treatment plan and centralized registration. Its important that all sarcoma experts meets jointly to define diagnosis, treatment and follow-up.

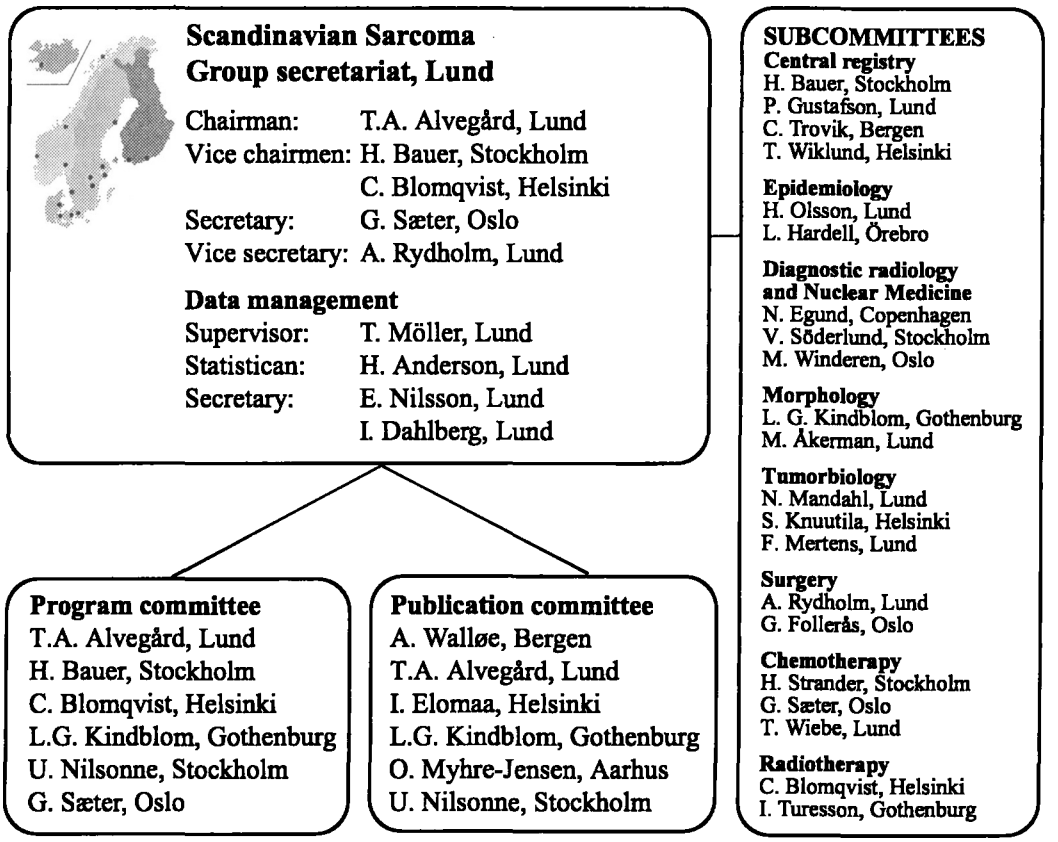

Figure 2. Organization of the Scandinavian Sarcoma Group. The morphology group meets 4 times a year to have a peer-review of all centralized registrated sarcoma tumors.

ry of the secretary, a full-time position, is paid by the Swedish Cancer Society.

Goal

The main goal of the group is to improve the treatment of sarcoma patients in the Scandinavian countries. Their survival depends upon a number of factors, some of which may be influenced. This include patient's and doctor's delay, referral to a highly specialized tumor centres, the capabilities of the diagnostic and therapeutic teams, the principles of treatment, the available equipment, and the details of the treatment schedules.

Communication lines

The local groups are represented in the Scandinavian Sarcoma Group by one or several members securing a direct line of communication 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 from the meetings of Societe Internationale de Oncologie Pediatrique (SIOP), European Organization for Research and Treatment of Cancer (EORTC), Connective Tissue Oncology Society (CTOS), Chromosomes 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

At the time of the inception of the SSG, many sarcoma patients throughout the Scandinavian countries were treated after considerable delay in local hospitals and often with inadequate surgery. Many patients arrived at the tumor centres with locally advanced tumors, recurrences or metastases.

In order to improve the prognosis for these patients, the following recommendations were made:

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

This recommendation was signed by all active SSG members in Helsinki in 1982 from four countries representing nine specialities and 21 tumor centres. The recommendation has been published in each country in the national medical journals, in books, and has been communicated at meetings. Copies have been sent to local hospitals and to individual doctors. In southern Sweden, 9 out of 10 patients with soft tissue sarcomas are referred to the regional tumor centre. Of patients with deep sarcomas, 80% are referred before biopsy., see also page 7. During the past years all centres in the Scandinavian Sarcoma Group have improved their centralization of patients.

Clinical investigations

The following investigations have been initiated by the SSG since 1979:

SSG I: Soft tissue sarcoma. Malignancy grade III and IV. Radical surgery ± adj. doxorubicin. Marginal surgery + radiotherapy ±adj. doxorubicin. A randomized study. Opened 1981, closed 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).

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

SSG III: Soft tissue sarcoma. Planned in 1983 as a randomized study on the effects of different irradiation schedules for inoperable tumors. However, very few patients were entered, and the study was cancelled.

SSG IV: Ewing's sarcoma. Combined modality treatment ad modum Rosen T 11 protocol. Nonrandomized. Opened 1984, closed 1989; 53 patients included (Alvegård et al. 1989).

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

SSG VI: Osteosarcoma metastases. Combined modality. Nonrandomized. Opened in the summer of 1987, closed 1989; 15 patients included.

SSG VII: Centralized registration of sarcoma patients in Scandinavia. Opened 1986, 4 000 patients included.

SSG VIII: Osteosarcoma. Combined primary treatment with preoperative high dose methotrexate, cisplatinum and adriamycin. Nonrandomized. Opened 1990, closed December 1996; 125 patients included (Sæter 1996A, Sæter 1996B).

SSG IX: Ewing's sarcoma. Combined modality treatment with cisplatinum, vincristin, adriamycin, ifosfamide, surgery, ±irradiation hyper fractionated. Nonrandomized. Opened 1990 still ongoing trial; 80 patients included (Elomaa et al. 1996).

SSG X: Treatment of metastatic soft tissue sarcoma with ectoposide, ifosfamide and G-CSF. Opened 1991, closed 1995; 114 patients included (Sæter et al. 1995, Sæter et al. 1996, Sæter et al. 1994).

SSG XI: Treatment of metastatic soft tissue sarcoma trofosfamid. Opened 1994, closed 1996; 40 patients included.

SSG XII: Metastasectomy and chemotherapy for lung metastasis from soft tissue sarcoma. A EORTC/SSG randomized phase III study. Opened July 1996.

SSG XIII: (IOR/SSG I) A comprehensive protocol for the treatment of extremity osteosarcoma - A joint Istituti Ortopedico Rizzoli/Scandinavian Sarcoma Group study I. Preoperatively high dose methotrexate, cisplatinum, adriamycin and high dose ifosfamide. The trial will open spring 1997. The centres are free to decide whether to join a particular program. For instance, Denmark does not participate in the osteo- and Ewing's sarcoma studies.

Centralized registration of sarcoma patients in Scandinavia

The common registration of data allows for multicenter studies addressing treatment results and prognostic factors for local recurrence and survival in patient with soft tissue and bone sarcomas. Such studies are necessary to further define the treatment for these patients. The 100% follow-up that is possible in Scandinavian countries makes our position unique.

The SSG Central Registry of soft tissue and bone tumors was initiated on March 1, 1986. All centres in Finland, Norway, Sweden and one centre in Denmark participate in the Registry. The yearly accrual rate is approximately 250 soft tissue and 100 bone tumor patients. The Registry is now being used for detailed studies on treatment and prognosis. The Registry

gives important information on how treatment of patients with musculoskeletal tumors is evolving in the Scandinavian countries. For example, important changes in referral pattern, preoperative diagnostic techniques, and surgical margin, have been observed.

Results and strategies

Soft tissue sarcoma

In our first randomized study (SSG I) we reported that adjuvant chemotherapy doxorubicin had no effect on metastasis-free - and overall survival. SSG participated in a review and meta-analysis of the published results of all 15 randomized clinical trials (Tierney et al. 1995). A re-analysis of individual person data is just concluded and will be published in spring of 1997.

In a multivariate analysis of the SSG I material, the following factors were commonly identified as independent variables for predicting the development of distant metastases: malignancy grade IV, tumor size >10 cm, intratumoral vascular invasion and necrosis, and male sex. Recently, the Lund group constructed a system based on three factors: tumor size >10 cm; the presence of necrotic areas >4 mm in diameter and the identification of vascular invasion. In a population-based study of data from the Southern Health Region of Sweden, two prognostic groups were identified: a good prognostic group with one or no factors present and a five-year metastasis-free survival of 81%, and a poor prognostic group with two or three factors present in a metastasis-free survival of 32%. The good and poor prognostic group contained approximately 70% and 30% of the patients, respectively (Gustafson 1994). In a comparative analysis between the Lund, AJC and SSS systems, the Lund system gave the best separation as regards metastasis-free survival. The Lund system will subsequently be tested on the entire patient data contained in the Central Registry of the SSG which houses details of approximately 3 000 STS patients from Sweden, Norway and Finland. Adjuvant treatment strategies will be developed based on the outcome of this analysis.

Osteosarcoma

In our first neo-adjuvant chemotherapy protocol for osteosarcoma (SSG II) we had a good tumor response in 18% with four high-dose methotrexate treatments. Five-year overall and (metastasis-free survival) is 62% and 58%, respectively (Solheim et al. 1989, Sæter et al. 1991, Solheim et al. 1992). In our ongoing protocol (SSG VIII) the tumor response rate is now 60% after pre-operative chemotherapy with high-dose methotrexate, cisplatinum and adriamycin. A new protocol is under preparation in collaboration with the Rizzoli Institute, Bologna. By intensification of the preoperative chemotherapy including high-dose methotrexate, ifosfamide, cisplatinum and doxorubicin there is the potential to increase the tumor response and subsequently metastasis-free- and overall survival.

Ewing's sarcoma

The final report of our first study (SSG IV) is under preparation and we will have a long follow-up time for this study (Alvegård et al. 1989). Our recent study (SSG IX) using intensive combination chemotherapy, surgery and accelerated fractionated radiation therapy has so far resulted in good tumor response following pre-operative chemotherapy, and preliminary results shows a five-years overall survival of approximately 70% (Elomaa et al. 1994, 1996). Collaboration with the Rizzoli Institute has been initiated to develop a dose intensity treatment modality for poor responders following pre-operative chemotherapy.

Central Registry

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

SSG's publications

A list of publications from the Scandinavian Sarcoma Centers in the period of 1979–1989 (Solheim et al. 1989) and the period from 1989–1993 (Alvegård 1989–1994) have been published comprising altogether 500 publications. The publications represent research from the different Scandinavian Tumor Centers and also from the Scandinavian Sarcoma Group Research program. 10 members have published their Ph.D. theses on issues relevant to sarcoma during this period.

References

Alho A, Alvegård T A, Berlin Ö, et al. (1989) for the Scandinavian Sarcoma Group. Surgical margin in soft tissue sarcoma. The Scandinavian Sarcoma Group experience. Acta Orthop Scand 60(6): 687-692.

Alvegård T A, Solheim Ø, Elomaa I (1989). Ewing's sarcoma – a preliminary report from the Scandinavian Sarcoma Group. Acta Oncol (Suppl 2) 28: 59-64.

Alvegård T A, Solheim Ø, Åkerman M, Berg N O (1989). Ewing's sarcoma. A preliminary report from the Scandinavian Sarcoma Group. Acta Orthop Scand (Suppl 2) 28: 59-64.

Alvegård T A (1989). Management and prognosis of patients with high-grade soft tissue sarcomas. An evaluation of a Scandinavian joint care program. University of Lund (thesis), Lund.

Alvegård T A, Sigurdsson H, Mouridsen H, et al. (1989). Adjuvant chemotherapy with Doxorubicin in high-grade soft tissue sarcoma: A randomized trial of the Scandinavian Sarcoma Group. J Clin Oncol 7: 1504-1513.

Alvegård T A, Berg N O (1989). Histopathology peer review of high-grade soft tissue sarcoma. The Scandinavian Sarcoma Group experience. J Clin Oncol 7: 1845-1851.

Alvegård T A, Berg N O, Ranstam J, et al. (1989). Prognosis in high-grade soft tissue sarcomas. The Scandinavian Sarcoma Group experience in a randomized adjuvant chemotherapy trial. Acta Orthop Scand 60(5): 517-521.

Alvegård T A, Berg N O, Baldetorp B, et al. (1990). Cellular DNA content and prognosis of high grade soft tissue sarcoma. The Scandinavian Sarcoma Group experience. J Clin Oncol 8: 538-547.

Alvegård T A (1994). List of publications from the Scandinavian Sarcoma Centers. Scandinavian Sarcoma secretariat. 1989-1993: 1-25.

Elomaa I, Blomqvist C, Sæter G, et al. (1994). Three-year results of the SSG IX protocol in Ewing's sarcoma. Acta Orthop Scand (Suppl 262) 65: 77-78.

Elomaa I, Blomqvist C, Sæter G, et al. (1996) for the Scandinavian Sarcoma Group. Five-year results of the SSG IX protocol in Ewing's sarcoma. Med Ped Oncol 27(4): 225.

Gustafson P (1994). Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand (Suppl 259) 65: 1-31.

Rydholm A (1983). Management of patients with soft-tissue tumors. Strategy developed at a regional oncology center. Acta Orthop Scand (Suppl 203) 54.

Rydholm A, Alvegård T A (1994a). Scandinavian Sarcoma Group, Göteborg, Sweden, May 5-7, 1993. Acta Orthop Scand (Suppl 265) 65: 55-72.

Rydholm A, Alvegård T A (1994b). Scandinavian Sarcoma Group, Helsinki, April 10-22, 1994. Acta Orthop Scand (Suppl 262) 65: 63-80.

Rydholm A, Alvegård T A (1995). Scandinavian Sarcoma Group, Stockholm, April 26-28, 1995. Acta Orthop Scand (Suppl 265) 66: 89-100.

Solheim Ø, Alvegård T A, Elomaa I (1989). Adjuvant chemotherapy for osteosarcoma - a preliminary report from the Scandinavian Sarcoma Group. Acta Oncol (Suppl 2) 28: 53-57.

Solheim Ø, Alvegård T A (1989). The Scandinavian Sarcoma Group. 10 Years' experience. Acta Oncol (Suppl 2) 28: 1-75.

Solheim Ø, Sæter G, Elomaa I, Alvegård T A (1992). The treatment of osteosarcoma: Present trends. The Scandinavian Sarcoma Group experience. Annals of Oncology (Suppl 2) 3: 7-11.

Sæter G, Alvegård T A, Elomaa I, et al. (1991). Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of pre-operative chemotherapy with single agent high-dose methotrexate. A Scandinavian Sarcoma Group study. J Clin Oncol 9: 1766-1775.

Sæter G, Strander H, Monge O R, Alvegård T A (1994). Dose escalating etoposide (E), ifosfamide (I) and granulocyte-colony stimulating factor (G-CSF) (VIG-regimen) in advanced adult soft tissue sarcoma. A Scandinavian Sarcoma Group study. Ann Oncol (5 suppl) 8: 171.

Sæter G, Talle K, Solheim Ø (1995). Treatment of advanced, high-grade soft-tissue sarcoma with ifosfamide and continuos-infusion etoposide. Cancer Chemotherapy and Pharmacology 36: 172-175.

Sæter G, Alvegård T A, Monge O et al. (1996). VIG chemotherapy in advanced soft tissue sarcoma - results of the Scandinavian Sarcoma Group SSG X trial. Acta Orthop Scand (in press).

Sæter G (1996a) for the Scandinavian Sarcoma Group. Treatment of osteosarcoma with high-dose methotrexate-containing neoadjuvant chemotherapy. Scandinavian Sarcoma Group data. Med Ped Oncol 27(4): 263.

Sæter G (1996b) for the Scandinavian Sarcoma Group. Treatment strategies and outcome in metastatic (relapsed) osteogenic sarcoma. The Scandinavian Sarcoma Group (SSG) experience. Med Ped Oncol 27(4): 264.

Tierney J F, Mosseri V, Stewart L A, et al. (1995). Adjuvant chemotherapy for soft-tissue sarcoma: review and meta-analysis of the published results of randomized clinical trials. Br J Cancer 72: 469-475.

Wiklund T A, Alvegård T A, Mouridsen H T, et al. (1993). Marginal surgery and postoperative radiotherapy in soft tissue sarcomas. Eur J Cancer 29A: 306-9.