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## The Scandinavian Sarcoma Group 30 years' experience

Edited by Thor Alvegård, Kirsten Sundby Hall, Henrik Bauer,  
and Anders Rydholm



THE SCANDINAVIAN SARCOMA GROUP: 30 years' experience

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# **The Scandinavian Sarcoma Group**

## **30 years' experience**

**Edited by Thor Alvegård, Kirsten Sundby Hall, Henrik Bauer,  
and Anders Rydholm**

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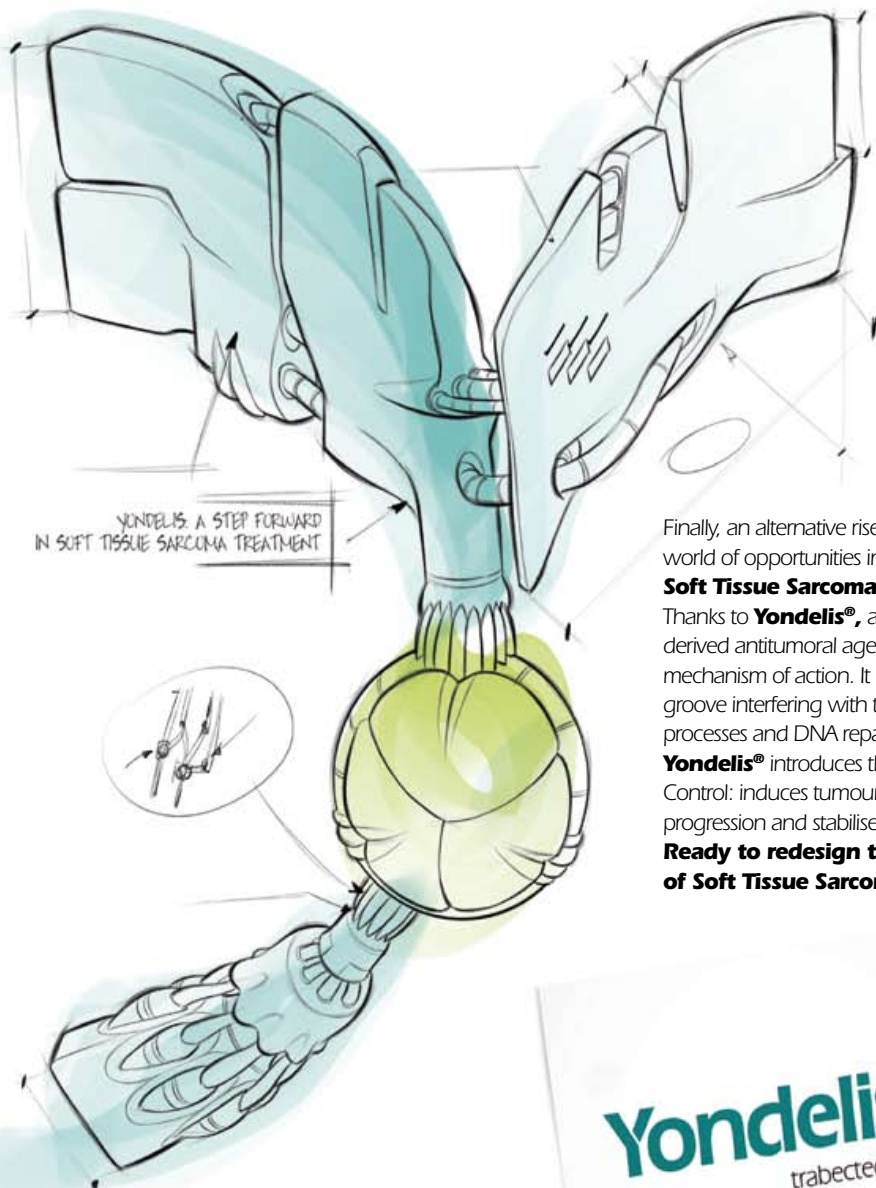
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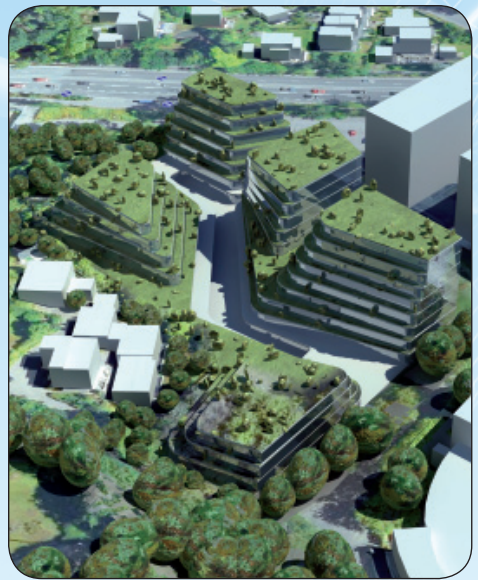
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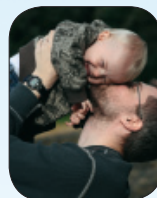
Oslo Cancer Cluster is a natural regional cluster, and was established in 2006 as a result of more than 80 years of excellent cancer-related activities in the region. The cluster comprises over 45 members – all with their main focus on cancer. Oslo Cancer Cluster has an impressive 44 projects in pipeline, and the members represent more than 70% of the human resources in cancer research in Norway.

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## Introduction

This Supplement marks 30 years of cooperation in sarcoma treatment in Scandinavia. The focus of sarcoma management has changed dramatically since the SSG was founded in 1979. Then referral of patients to a sarcoma center before surgery was the most important treatment associated factor that could be changed.

Today, approximately 90% of bone and soft tissue sarcoma patients in orthopedic sites are referred untouched to Scandinavian sarcoma centers. The improvement of referral practices of patients with intraabdominal and retroperitoneal sarcomas has been much slower. With the advent of more pre-operative imaging in undiagnosed abdominal conditions and with the focus on GIST, the referral of these patients is improving dramatically. In gynecological sarcoma patients the need for centralized management is the same as for retroperitoneal tumors. The SSG Registry was primarily designed for orthopedic tumors and the recording of sarcomas in other sites has been haphazard at best. In the last edition of the SSG Registry ([www.ssg-org.net](http://www.ssg-org.net)) specific forms to register abdominal, retroperitoneal and uterine sarcomas have been designed. We expect that knowledge of diagnostic practices and treatment results for this large patient group, mostly treated outside of clinical trials, will increase as more patients are reported to the SSG Registry.

The population-based series of all chondrosarcomas in Sweden 1980–2002 of the chest wall shows that correct diagnostics at a sarcoma center are at least as important as the treatment. Almost half of the chondrosarcoma patients were treated outside of sarcoma centers and there was often a long doctor's delay. Interestingly, doctor's delay was often associated with a needle biopsy performed outside of a sarcoma center, providing incorrect assurance that the swelling of the chest wall was benign. This type of clinical series is important to show what happens when sarcoma care is not centralized and shows that the cost and inconvenience

of traveling to a sarcoma center are far outweighed by the benefits.

The first clinical trial run by the SSG was the SSG I protocol of doxorubicin treatment in high-grade soft tissue sarcoma. 30-years later the benefits of adjuvant chemotherapy remains unclear. However, we know much more about prognostic factors in soft tissue sarcoma and can now select patients who are at high risk of metastatic disease. Many trials of adjuvant treatment for soft tissue sarcoma are flawed by the inclusion of patients with a good prognosis. By applying the clinical risk factors that have been proven relevant we can select a cohort of high-risk patients where it will be easier to assess the effect of adjuvant treatment.

In 1979, adjuvant and neo-adjuvant chemotherapy in osteosarcoma and Ewing sarcoma still remained to be explored and proven. Today we know the benefits but also the limitations of chemotherapy as still about 30% of the patients will eventually die of their sarcoma. The first SSG trial of osteosarcoma was initiated in 1982. We now realize that to improve survival we need randomized multi-group trials of new approaches to osteosarcoma treatment. Here EURAMOS constitutes a unique collaboration between sarcoma groups in Europe and the USA. Although we are moving towards more international collaboration, regional sarcoma groups such as the SSG will remain necessary to ensure compliance and quality of data.

One pillar of quality control within the SSG is the pathology board. This group now has a vast experience in reviewing common and uncommon sarcoma entities, and also in assessing chemotherapy response in different SSG protocols. All treatment protocols rest upon assurance that the diagnosis is correct, and that histological malignancy grade and risk factors are correctly assessed. When the Central Registry is used for in-depth studies of specific entities, such as liposarcoma in the present volume, uniform diagnostic criteria and grading are a prerequisite to assess treatment results. The

SSG pathology group has always maintained close collaboration with cytogenetics primarily for diagnosis, for example in Ewing and synovial sarcoma, but the paper on genetic profiling shows that cytogenetics also has a role in prognostication.

We thank you for taking the time to read this volume dedicated to the SSG experience

*Kirsten Sundby Hall*

*Thor Alvegård*

*Henrik Bauer*

Chairpersons of the SSG

# The Scandinavian Sarcoma Group

## Summary of the first 30 years

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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 27 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, tumor biologists, nurses and physiotherapists from the Nordic countries (Figure 2). The aim of the SSG is to 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 (Bauer et al. 2004, Hansen et al. 2004). The SSG is open to all specialists in the Nordic countries interested in sarcoma and has no membership fee. The Swedish Cancer Society, Nordic Cancer Union (NCU), several



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.

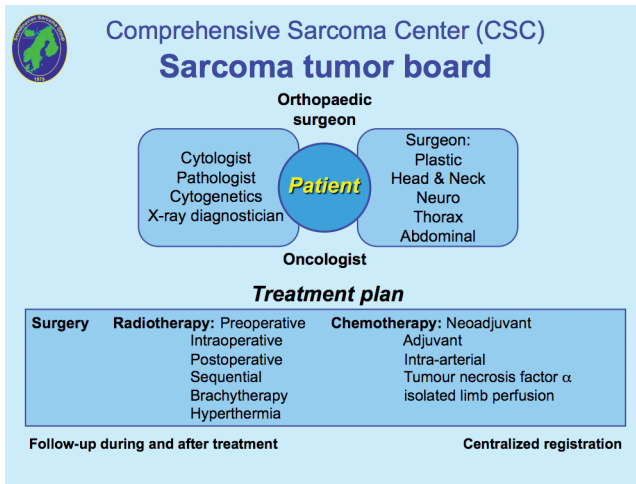


Figure 2. Organization of the Scandinavian Sarcoma Group. The morphology group meets 2–3 times a year for peer-review of all registered sarcomas.

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 Southern Swedish Oncologic Center, University Hospital of Lund, Sweden.

The SSG holds meetings yearly, Subcommittee Meetings in December yearly and the General Assembly in the spring every other year. Notes of the meetings are kept by the SSG secretary and chairmen of the subcommittees. The SSG Board consists of two Chairmen, two Vice-Chairmen, one Secretary, one Vice-Secretary and the respective chairmen of the 10 subcommittees (SSG Sarcoma Register, Epidemiology, Imaging, Morphology, Tumor Biology, Orthopedic Surgery, Visceral and Retroperitoneal Surgery, Oncology (pediatric and adult), SSG Metastasis Register and SSG Nurses and Physiotherapists). The Chairmen and Secretaries are elected by the General Assembly for 5 years. The Subcommittees elect their own chairmen.

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. All subcommittees have a joint meeting once a year, to develop new strategies regarding research and treatments for musculoskeletal tumors. At our general meeting every other year (with about 130 active SSG members), new developments and strategies are submit-

ted 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 outcome 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 translational sarcoma research easier to perform (Figure 3).

### 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

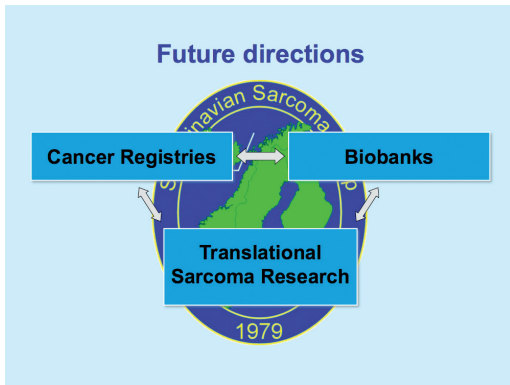


Figure 3. SSG – Central register, cancer registries and biobank registries makes translational sarcoma research easier in the future.

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 advanced tumors, local 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 biopsy, 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 4 countries representing 9 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, Bauer et al. 2004).

### Clinical investigations

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

**SSG I:** Soft tissue sarcoma. Malignancy grades III and IV. Wide  $\pm$  adj. doxorubicin. Marginal surgery + radiotherapy  $\pm$  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; >10 000 patients.

**SSG VIII:** Osteosarcoma. Combined primary treatment with high doses of methotrexate, cisplatin and adriamycin preoperatively. Nonrandomized. Started 1990, ended December 1997; 113 patients (Saeter 1996a, Saeter 1996b, Smeland 2003).

**SSG IX:** Ewing's sarcoma. Combined modality treatment with cisplatin, vincristin, adriamycin, ifosfamide, surgery  $\pm$  hyperfractionated irra-

- diation. 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:** Metastectomy 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 1998, ended 2007; 143 patients.
- SSG XIV:** A Scandinavian treatment research protocol for extremity localized high-grade osteosarcoma. Started 2001, ended 2005; 73 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; 1 000 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, ended 2008; 400 patients.
- SSG XX:** Phase II non-randomized treatment protocol for adult patients with non-metastatic high-risk soft tissue sarcoma of the extremities and trunk wall. Started 2007, ongoing; 25 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, ended September 2000; 187 patients (Ferrari et al. 2005, Serra et al. 2006).
- ISG/SSG II:** An Italian - Scandinavian treatment protocol for metastatic and pelvic osteosarcoma. Started March 1998, ended December 2003; 55 patients (Del Prever et al 2005).
- ISG/SSG III:** An Italian - Scandinavian treatment protocol for standard-risk Ewing's sarcoma. Started June 1999, ongoing; 106 patients (Ferrari et al. 2007).
- ISG/SSG IV:** An Italian - Scandinavian treatment protocol for high-risk Ewing's sarcoma. Started June 1999, ongoing; 70 patients.
- Euroboss I:** A European treatment protocol for bone sarcoma in patients older than 40 years. Started February 2003, ongoing; 220 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. Started spring 2004, ongoing; 60 patients.

### *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. 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 (Bauer et al. 2004).

## **Results and strategies**

### *Soft tissue sarcoma*

In our first randomized study (SSG I, 1981–1986), we reported that adjuvant chemotherapy with doxo-

rubicin 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 preliminary good results of this analysis (SSG XIII). A phase II non-randomized treatment protocol for adult patients with non-metastatic high-risk soft tissue sarcoma of the extremities and trunk wall started in October 2007 (SSG XX).

#### ***Intraabdominal, retroperitoneal, pelvic and uterine sarcoma working group***

All patients should at suspicion or diagnosis of a sarcoma be referred to a specialized centre for further evaluation and treatment. The management of intraabdominal retroperitoneal and pelvic soft tissue tumors is complex and prognosis of patients with such tumours can be affected from the earliest stages of work-up. All patients should therefore be treated by a multidisciplinary group with interest and experience in sarcoma. That includes all categories involved in the evaluation and treatment as surgeon, oncologist, cytologist, pathologist and radiologist. The only way to achieve this is by gather these rare patients to only a few units; centralization is the only way to be able to collect patients enough to get and maintain skill and experience, to develop and improve treatment, to collect patients and biological material enough for e.g. tissue bank and scientific studies and to be able to report outcome and follow-up.

Our SSG recommendations are based on proposals made by the Scandinavian Sarcoma Group (SSG) members, mainly from the recently established group responsible for intraabdominal, retroperitoneal, pelvic and uterine soft tissue sarcoma. The guidelines are aimed to give a general overview for the most important and initial decisions to be made and will provide recommendations that are based on the best available evidence. They will be updated periodically in accordance to the current knowledge of these disease entities.

Soft tissue sarcomas arising in the retroperitoneal space or in the intraabdominal cavity traditionally carry a poor prognosis. Many factors contribute to the fact that both the disease free and overall survival figures are poor among patients with sarcomas within these areas. However, the introduction of tyrosine kinase inhibitors has dramatically changed the treatment and course of GIST. Even in metastatic disease the maximum duration of response to Imatinib and other tyrosine kinase inhibitors is not yet known, and some patients may respond for longer than 5 years.

With the goal of increasing the survival of this group of sarcoma patients, the subsequent recommendations will focus on the:

- anatomical evaluation
- pathological diagnosis
- surgical management
- adjuvant and palliative therapy
- clinical trials
- follow-up

#### ***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 SSG VIII protocol the good tumor response rate is 60% after preoperative chemotherapy with high doses of methotrexate, cisplatin 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, cisplatin and doxorubicin did not show increase of the

metastasis-free or overall survival rates (Bacci et al. 2002). The SSG XIV protocol started in 2001 and ended in 2005 with 73 patients. A publication is under preparation. Since spring 2004 SSG is joining the European and American Osteosarcoma Study Group (EURAMOS I).

### **Ewing's sarcoma**

The first report on our first study (SSG IV) was made by Nilbert et al. (1998) with a long-time follow-up time by Smeland et al. (2004). 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. 1994, 1996, 1999). 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) and started June 1999.

### **Surgical sarcoma network**

In the Nordic countries surgical sarcoma treatment is centralized to larger university clinics. Many studies show that the most important prognostic factor for local control is centralization of untouched sarcomas to centres where treatment is supervised by formally organized multidisciplinary sarcoma teams. To ensure compliance with centralization guidelines for such rare tumours as sarcomas, the guidelines and procedures of centralization must be well known at local hospitals. This is best achieved when the geographical distance between local hospital and centre is not too large. The organisational guidelines was pioneered in the Southern Swedish Health region 30 years ago, and the University Hospital in Lund now has more than 90% of sarcomas referred as virgin tumours. The guidelines are implemented throughout Scandinavia and the organization has served as a model to other regions in Europe.

As the Nordic countries are a relatively sparsely populated large geographical area, the organizational arrangements imply that no sarcoma centre has more than 3–4 million inhabitants in their

uptake area. This is less than many European centres and necessitates closer cooperation among surgeons in Scandinavia. To facilitate this, the SSG has since 2005 organised an internet based discussion forum called the surgical sarcoma network. It is e-mail based communication with attached radiological material, chosen by the surgeon initiating discussion, and distributed to all sarcoma surgeons in Scandinavia. This normally results in several suggestions of treatment within hours after a problem is posted. The suggestions are informal opinions "among equals", much like the discussion among senior sarcoma surgeons at in-house meetings at the larger sarcoma centres in Europe and USA. The discussion has on occasions concluded that an unusual operation are best performed by a multi-institutional team of surgeons, and details have been arranged using the net-work facility. The legal responsibility for all actions based on the discussions remains with the treating surgeon.

The current treatment protocol for high grade soft tissue sarcomas has an optional arm for preoperative radiation treatment when there is "an obvious risk of intralesional surgery". The surgical sarcoma network is used to establish a uniform interpretation of this inclusion criterion.

Annually about 20 new cases are presented from 13 institutions in Sweden, Finland, Denmark, Norway and Iceland, resulting in 115 e-mailed contributions to the discussion.

### **Centralized registration of patients with surgically treated skeletal metastases**

Current surgical treatment for pathologic fractures is based on retrospective analyses of single institution experience. The reported series comprise heterogeneous patient populations regarding types of primary cancer, extent of the metastatic disease and location of the lesions. Areas of uncertainty include operative methods, indications for prophylactic surgical treatment and need for postoperative radiotherapy as radiation decreases the risk of local tumor progression but increases bone-healing complications.

The Scandinavian Sarcoma Group started the Skeletal Metastasis Registry in 1999 to improve the surgical treatment of skeletal metastases. Criteria for inclusion are patients surgically treated for either impending or complete non-spinal fractures

due to skeletal metastase. 9 orthopedic oncology centres from Sweden, Denmark, Norway and Finland participate and data regarding more than 900 surgically treated patients have so far been registered. Additional aims of the registry are to provide a tool for quality assessment as measured in terms of reoperation date, operation morbidity and operation frequency for impending fractures.

### **SSG Nurses and physiotherapists group**

At the annual SSG meeting 2007, May, 8–11, in Bergen, Norway, this group was officially established. Increased cooperation between nurses, physiotherapists and doctors is necessary for the outcome of the Scandinavian sarcoma patients. The main goal of this group is to: increase cooperation, knowledge and motivation. See also page 91 in this issue

### **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 and Rydholm 1994), 1993–1998 (Rydholm and Alvegård 1998), 1998–2003 (Alvegård and Rydholm 2004). For publications 2004–2008 see 92–104 in this issue. These publications represent research from the various Scandinavian Tumor Centers and the Scandinavian Sarcoma Group Research program. 31 members wrote their Ph.D. theses on issues relevant to sarcoma in this period (Table).

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Del Prever AB, Smeland S, Tienghi A et al. High-risk osteosarcoma (OS): Preliminary results of the ISG-SSG II protocol. *ASCO meeting abstract* 2005;23(26):9002.

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Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. *Acta Orthop Scand* 1994 (Suppl 259); 65: 131.

Table. Overview of Ph.D. theses by SSG members on issues relevant to sarcoma, 1979–2007

Title	Author	Year	Place
Soft tissue sarcoma patterns: Multiplicity, heterogeneity and growth characteristics	J. Fernebro	2007	Dept. of Oncology, Lund University, Sweden
Genetic profiling in soft tissue sarcoma	P. Francis	2007	Dept. of Oncology, Lund University, Sweden
Clinical and molecular studies of liposarcoma	K. Engström	2007	Dept. of Oncology, Gothenburg University, Sweden
Desmoid tumors: New aspects on diagnostic procedures, treatment and outcome	M. Dalén	2006	Dept. of Oncology, Gothenburg University, Sweden
Fine needle aspiration diagnosis of spindle cell tumors of soft tissue, including the use of ancillary methods, and correlation with clinical data	H. A. Domanski	2005	Dept. of Pathology and Cytology Lund University, Sweden
Molecular cytogenetic characterization of chromosome aberrations in soft tissue and bone tumors	M. Nilsson	2005	Dept. of Clinical Genetics, Lund University, Sweden
Genetic characterization of bone and soft tissue tumors	A. Dahlén	2005	Dept. of Clinical Genetics, Lund University, Sweden
Prognostic factors in soft tissue sarcoma: Tissue microarray for immunostaining, the importance of whole-tumor sections and time-dependence	J. Engellau	2004	Dept. of Oncology, Lund University, Sweden
Imaging of soft tissue tumors	H. Einarsdóttir	2003	Dept. of Surg. Sciences, Karolinska Institute, Stockholm, Sweden
Combined radiology and cytology in the diagnosis of bone lesions	V. Söderlund	2002	Dept. of Surg. Sciences, Karolinska Institute, Stockholm, Sweden
Local recurrence of soft tissues sarcoma: A Scandinavian Sarcoma Group project	C. Trovik	2001	Dept. of Orthopedics, Haukeland University Hospital, Bergen, Norway
The complexity of prognostication in musculo-skeletal sarcomas: An analysis of four illustrative entities	P. Bergh	2000	Dept. of Surg. Sciences, Karolinska Institute, Stockholm, Sweden
Chromosomal instability and genomic amplification in bone and soft tissue sarcomas	D. Gisselsson	2000	Dept. of Clinical Genetics, Lund University, Sweden
Synovial sarcoma: A Scandinavian Sarcoma Group project	B. Skytting	1999	Dept. of Orthopedics and Dept. of Cellular and Molecular Tumor Pathology, Karolinska Institute, Stockholm, Sweden
A study of chromosome breakage in patients with mesenchymal tumors	F. Mertens	1998	Dept. of Clinical Genetics, Lund University, Sweden
Electron microscopy in diagnostic pathology	B. Carlén	1996	Dept. of Pathology, Lund University, Sweden
Soft tissue sarcoma: Epidemiology and prognosis in 508 patients	P. Gustafson	1994	Dept. of Orthopedics, Lund University, Sweden
Cytogenetic heterogeneity and clonal evolution in bone and soft tissue tumors	C. Örndal	1994	Dept. of Clinical Genetics, Lund University, Sweden
Commentationes physico-mathematicae et chemico-medicae	T. A. Wiklund	1992	Dept. of Radiotherapy and Oncology, University of Helsinki, Finland
Uterine leiomyoma cytogenetics	M. Nilbert	1991	Dept. of Pathology, Lund University, Sweden
Kaposi's sarcoma: Pathogenesis, ultrastructure and epidemiology	M. Dictor	1990	Dept. of Pathology, Lund University, Sweden
Management and prognosis of patients with high-grade soft tissue sarcoma	T. A. Alvegård	1989	Dept. of Oncology, Lund University, Sweden
Uterine sarcoma: An epidemiological and clinicopathological study	B. Larsson	1989	Dept. of Obstetrics and Gynecology, and Dept. of Gynecologic Oncology, Karolinska Institute, Stockholm, Sweden
Fine needle aspiration in the diagnosis of soft tissue tumors: The 15 years experience from an Orthopedic Oncology Center	M. Åkerman	1988	Dept. of Pathology, Lund University, Sweden

Table continued.

Title	Author	Year	Place
On leiomyosarcomas of bone and venous origin and the surgical treatment and prognosis for extremity soft tissue sarcomas	Ö. Berlin	1988	Dept. of Orthopedics and Pathology, Gothenburg University, Sweden
Osteosarcoma and interferon: Studies of human xenografts in the nude mouse	O. Brosjö	1988	Karolinska Institute, Stockholm, Sweden
Prognosis in soft tissue sarcoma	B. Rööser	1987	Orthopedic Oncology Group, Lund University, Sweden
Management of patients with soft tissue tumors	A. Rydholm	1983	Dept. of Orthopedics, Lund University, Sweden
Function-preserving surgery for extirpation of	G. Markhede	1980	Depts. of Orthopedics II, Pathology II, Rehabilitation Medicin II, Gothenburg University, Sweden
On the natural history of osteosarcoma:	L-Å. Broström	1979	Dept. of Orthopedics, Karolinska Institute, Stockholm, Sweden

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# The Scandinavian Sarcoma Group Register 1986–2008

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The Scandinavian Sarcoma Group Register (SSG Register) was initiated in 1986 with the aim of collecting prospective sarcoma data from all Scandinavian countries. There was a consensus that we needed population based data on all sarcoma patients, not only the few who qualified for clinical treatment trials. The SSG Register was based on the experience from the Southern Sweden Sarcoma Register founded in 1975 (Rydholm 1983). The SSG Register was designed to acquire data on referral, tumor characteristics, treatment and outcome with a minimum follow-up of 5 years. All centers in Sweden and Norway participated from the conception whereas no centers from Denmark and only Helsinki in Finland chose to participate. In the early 1990ies Helsinki advised that they did not have the resources to continue so the SSG Register has essentially become a Norwegian and Swedish affair. With a population base of approximately 14 million people and all centers participating we accomplished our goal of creating a population based sarcoma Register. Comparisons with patients entered in the National Cancer Registries show that more than 90% of sarcomas of extremities and the trunk wall are reported to the SSG Register.

9 052 sarcoma patients have been prospectively recorded in the SSG Register until September 2008. There are 4 583 soft tissue sarcomas of extremity and trunk wall and 1 852 soft tissue sarcomas of “non-orthopedic” sites, *i.e.* visceral, retroperitoneal, gynecological, and head-neck. There are 2 671 bone sarcomas including also benign giant cell tumors.

The SSG Register serves two purposes: to monitor referral pattern, treatment, and outcome over

time, and to identify subsets of patients for in-depth studies. Regarding monitoring we have shown that referral of extremity sarcoma patients has continuously improved and since several years almost all these patients are referred to sarcoma centers, four fifths of them with primary tumors before biopsy or surgery (Bauer et al. 2001).

We have also shown that we have been too restrictive in our indications for adjuvant radiotherapy in soft tissue sarcoma. Wide surgical margins (including myectomy) for deep-seated high-grade sarcomas were associated with a 25% risk of local recurrence (Trovik et al. 2000). Hence, since 1998 we advise radiotherapy for all high-grade deep seated soft tissue sarcomas, irrespective of surgical margin and SSG Register data shows that the 5-year local recurrence rate has decreased to 15% (Jebsen et al. 2008).

In-depth studies based on SSG Register data are of importance to maintain interest in the Register. There have been 4 doctoral theses based on patients from the SSG Register and there are 3 ongoing projects (Table). Since these in-depth studies involves going back to the original patient charts they lead to control and improvement of data quality. They also lead to improved follow-up. Most importantly all patients included in these projects have had their diagnosis reviewed by the SSG Pathology Board. This ensures consistency in applying diagnostic criteria across Scandinavian Sarcoma Centers.

The question arises whether collecting data to the SSG Register and assuring follow-up and data quality is worth the effort. There has been a slowing of reporting both new patients and of follow-up. This may be related to generation changes, the

## Thesis projects based on the SSG Register

Title	Author	Year
Completed thesis projects		
Synovial sarcoma	Björn Skytting	1999
Local recurrence in soft tissue sarcoma	Clement Trovik	2001
Prognostic factors in soft tissue sarcoma	Jacob Engellau	2004
Clinical and molecular studies of liposarcoma	Katarina Engström	2007
Ongoing projects		
Leiomyosarcoma	Catarina Svarvar	
Radiotherapy in soft tissue sarcoma	Nina Jebsen	
Sarcoma of the thoracic wall	Björn Widhe	

individuals who started registration at the different sarcoma centers in Norway and Sweden are being replaced by a younger generation. But steps are now taken to revitalize to local coordinators. We firmly believe that the type of quality control that is maybe the most important feature of the SSG Register is paramount for maintaining excellent sarcoma care. We do not need the Register to monitor osteosarcoma care in the young, but we need it as a means of defining and defending our treatment recommendations in the 90-year-old with a soft tissue sarcoma.

The SSG Register has been extensively revised during the last year (SSG VII: 4 [www.ssg-org.net](http://www.ssg-org.net)). Dr. Clement Trovik in Bergen ([clement.trovik@helse-bergen.no](mailto:clement.trovik@helse-bergen.no)) has taken over the Chairmanship of the SSG Register Subcommittee. He has worked closely with the SSG secretariat and data manager to revise the entry and follow-up forms and to insert checkpoints to identify incongruent or missing data. The forms for visceral and retroperitoneal sarcomas have been better adapted to treatment and classification applied in these regions. Trials of online registration are under way.

The viability of the SSG Register will be ensured if it is used for quality control and as a

research tool. All SSG members are invited to submit plans for in-depth studies of Scandinavian sarcoma care.

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Trovik CS, Bauer HCF. Local recurrence of soft tissue sarcoma a risk factor for late metastases: 379 patients followed for 0.5-20 years. *Acta Orthop Scand* 2000; 65: 553-8.

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# Genetic profiling – implications for refined diagnosis and treatment of soft tissue sarcomas

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**Summary** Soft tissue sarcomas (STS) are challenging as they represent a morphologically and genetically heterogeneous groups of tumors. A multitude of genetic changes, often in the form of fusion genes, were recognized during the 1980's and now constitute a diagnostic lexicon in several STS subtypes, whereas many of the more common subtypes are genetically complex without distinct alterations. Refined STS management requires improved diagnostic reproducibility, novel prognosticators, and introduction of targeted therapies. In recent years, a number of genetic profiling studies – analyzing copy-number alterations as well as gene expression changes – have deepened our understanding of STS development through demonstration of recurrently deregulated tumorigenic pathways. The challenge is now to bring the genetic profiles into clinical decision-making. This review, in conjunction with the Scandinavian Sarcoma Group's (SSG) 30 years jubilee, discusses how the information from genetic profiling studies may be translated into clinical practice for refined diagnostics, prognostics, and treatment of STS.

In the past 3 decades cytogenetics and molecular genetics have revealed specific chromosomal translocations and fusion genes in a large number of soft tissue sarcoma (STS) subtypes, but have also demonstrated extensive genetic complexity in other subtypes. Within the last decade, high-throughput techniques have enabled simultaneous analysis of multiple genes and thereby provided a deeper insight into the genomic aberrations and their interrelations with tumor associated pathways in STS (Figure 1).

## Simple and complex karyotypes

The identification of chromosomal abnormalities in STS has added a new dimension to diagnostics by complementing traditional microscopic examination. Detection of tumor specific chromosomal aberrations by conventional cytogenetics is nowadays especially useful in confirming the diagnosis of poorly differentiated sarcomas, in particular those arising in unusual locations or age groups, or tumors exhibiting atypical histopathologic features. From a genetic perspective, sarcomas fall into two major categories; one characterized by relatively simple, near-diploid karyotypes and another characterized by highly complex, severely deranged chromosomes and aneuploidy. Sarcomas with relatively simple karyotypes harbor reciprocal chromosome translocations resulting in the formation of fusion genes. Although these translocations are probably crucial in tumorigenesis, they are typically associated with additional genetic alterations, the roles of which remain to be defined (Deneen et al. 2001).

The genetically complex subtypes continue to puzzle clinicians and pathologists due to extensive heterogeneity, frequent pleomorphism, and lack of discriminative genetic alterations. STS with complex karyotypes can be exemplified by leiomyosarcoma, pleomorphic liposarcoma, and undifferentiated pleomorphic sarcoma (UPS, formally referred to as malignant fibrous histiocytoma – MFH). Cell-cycle gene disturbances are commonly present with a high prevalence of p53 checkpoint alterations, including inactivating mutations of TP53 and homozygous deletion of

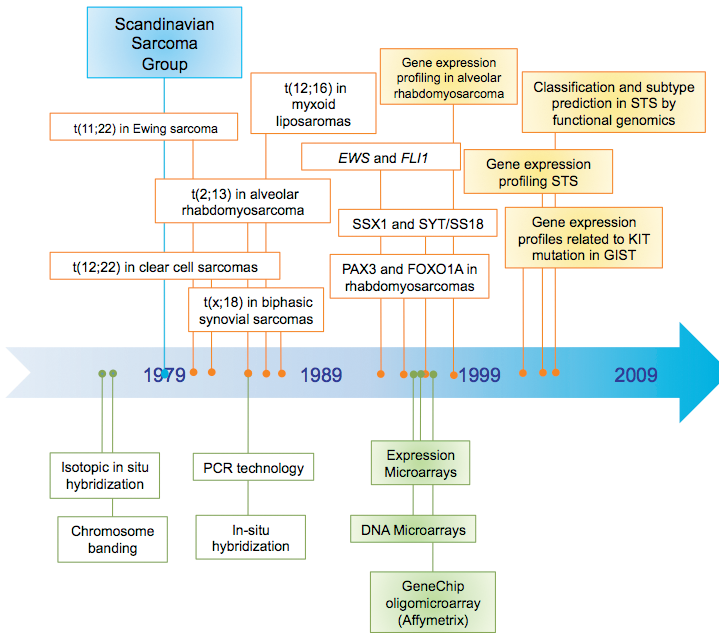


Figure 1. Timeline with the most important genetic and expression findings in soft tissue sarcomas and the techniques used for cytogenetic, genomic and expression studies in the past 30 years. Studies that first used a given approach are highlighted in yellow: Khan et al. published the first expression profiling study in sarcomas (alveolar rhabdomyosarcoma) in 1998, while the first study profiling different STS histotypes was published in 2002 by Nielsen et al.; Segal et al. (2003) first applied genomic profiling for classification and subtype prediction in STS; correlation of genomic and expression profiles with given tumor characteristics was first performed in GIST with KIT mutation by Allander et al. (2001).

*CDKN2A* (Stratton et al. 1990, Latres et al. 1994, Dei Tos et al. 1996, Orlov et al. 1999, Creager et al. 2001). Frequent amplification of *CDK4* and *MDM2* have also been reported in sarcomas with complex karyotypes, although the exact roles and interactions of these two genes in sarcoma development and progression remains unknown. Amplification of *CDK4* and *MDM2* occur both in well differentiated lesions and in pleomorphic tumors, suggesting that these events may occur early in tumorigenesis. Genetically complex STS frequently show dramatically lengthened and heterogeneous telomeres (Montgomery et al. 2004). The large brightly stained telomeric regions are reminiscent of those observed in immortalized cells that maintain telomeres in a telomerase-independent manner, consistent with deregulation of the alternative lengthening of telomeres (ALT) pathway. The discovery of heterogeneous telomere lengths and ALT pathway involvement in most sarcomas with complex karyotypes supports the existence of a telomere maintenance pathway that is incapable of karyotypic stabilization. In addition, both ALT activation and telomerase expression have been correlated to poor prognosis (Avigad et al. 2007, Cairney et al. 2008).

## Methodological considerations in genetic profiling

In STS, most diagnostically applied alterations are apparent using low-resolution techniques such as cytogenetics, but detailed mapping of the resultant fusion genes and high-throughput genetic profiling provides detailed insights into the various signalling pathways involved. Moreover, high-resolution mapping of copy-number alterations and expression changes represent powerful techniques to identify novel markers for diagnostic, prognostic, and predictive applications. High-density gene arrays simultaneously allow characterization of the expression of more than 30,000 genes (or more in oligonucleotide arrays) in a single experiment.

Pre-processing and gene filtering are essential steps before data analysis, the latter aiming at eliminating genes that are poorly measured or that lack variation across the samples. By eliminating genes from further analysis, this step irreversibly influences the number of informative genes and thereby the final results. Depending on the aims of the study, data can be analyzed for class discovery, class prediction, and class comparison. Class discovery refers to analyses aimed at discovering clusters within a sample set, and is generally achieved by unsupervised clustering algorithms. Such analy-

ses are performed without use of information about the expected samples class. Supervised data analyses are generally applied for class prediction studies (in which the objective is to predict a given feature, e.g. treatment response) and class comparison studies (in which the objective is to identify biological differences between groups of samples). The latter analyses use data in which samples show a given asset e.g. development of metastasis, and herein aim to identify genes that are differentially expressed. In order to not introduce bias, the findings should be validated in an independent sample set. In this type of analysis, the number of false discoveries is crucial. The conventional level of significance,  $p=0.05$ , is not applicable since it would imply 500 false positive genes per 10.000 genes analyzed and frequently re-sampling methods are therefore preferred for the identification of consistently deregulated genes linked to the variable studied. Limited sample size represents a weakness of many microarray studies. The required number of samples depends on the fold-difference in mean expression as well as on the variation in expression within each class, but formulas for calculation of appropriate sample sizes are available. Data management and statistical methods differ between studies and the many steps in the analysis, subject to variable handling, influence the top-ranked gene lists in different studies. However, if interacting genes and pathways, rather than single genes, are considered, the currently available genetic profiling data in STS demonstrate considerable reproducibility with deregulated pathways recurrently demonstrated.

### Genetic profiling for refined STS diagnosis

Gene expression profiling has suggested novel classification patterns in several malignancies, including STS, breast cancer, lymphoma, malignant melanoma, and leukemia (Golub et al. 1999, Alizadeh et al. 2000, Bittner et al. 2000, Perou et al. 2000, Sorlie et al. 2001). In STS, array-based copy-number alterations and gene expression profiling have broadly supported the division into the genetically simple and complex subtypes, but have also provided promising insights into sarcoma biology for application in refined diagnostics.

Nielsen et al. (2002) analyzed 41 STS, including GIST, synovial sarcomas, liposarcomas, leiomyosarcomas, MFH and malignant peripheral nerve sheath tumors (MPNST), by cDNA microarray (Nielsen, Lancet 2002). Hierarchical clustering yielded 5 major clusters with synovial sarcomas, GIST, and MPNST forming distinct groups. Among the leiomyosarcomas, 6/11 samples formed a separate cluster, distinguished by e.g. calponin expression, whereas the remaining leiomyosarcomas clustered with MFH/UPS and liposarcomas. Class prediction for GIST involved 125 genes, including *KIT*. Synovial sarcomas were recognized by a 104-gene cluster containing e.g. *SSX*, *EGFR*, and retinoic acid receptor pathway genes, leiomyosarcomas were associated with muscle-related genes, and MPNST showed expression of nerve sheath-related genes.

Segal et al. (2003) used Affymetrix GeneChip arrays to analyze 51 STS of 9 subtypes. Distinct clustering was observed among STS with specific translocations, but not among subtypes with genetic complexity and pleomorphism. The discriminating genes within this study included *SCF* and *KIT* for GIST, *WNT5A*, and *FZD1* in synovial sarcoma, melanocytic genes in clear-cell sarcomas, and *CDK4* and *MDM2* in dedifferentiated liposarcoma.

Baird et al. (2005) used oligonucleotides-arrays to obtain gene expression profiles of 181 tumors representing 16 histotypes of STS and osteosarcomas. 2766 genes showed differential expression among the sarcoma subgroups and separated the tumors into two distinct clusters: one harboring cytogenetically simple STS and the other composed STS with cytogenetic complexity. Up-regulation of tyrosine kinases and tyrosine kinase receptors was identified in half of the samples. Altered expression of genes in the WNT signaling pathway, e.g. *WNT5A* and *FZD1*, was observed in all synovial sarcomas, whereas homeobox genes were overexpressed in several sarcoma subtypes.

Francis et al. (2007) applied cDNA expression profiling to 177 STS. Unsupervised analysis resulted in two major clusters – one mainly containing STS characterized by type-specific genetic alterations and the other predominantly genetically complex and pleomorphic STS. Synovial sarcomas, myxoid/round-cell liposarcomas, and GIST clustered tightly within the former cluster and dis-

crimatory signatures for these were characterized by developmental genes from the EGFR, FGFR, WNT, Notch, Hedgehog, RAR, and KIT signaling pathways. The more pleomorphic STS subtypes, e.g. leiomyosarcoma, MFH/UPS, and dedifferentiated/pleomorphic liposarcoma, were part of the latter cluster and were characterized by relatively heterogeneous profiles, although subclusters herein were identified.

Heidenblad et al. (2006) applied tiling resolution microarrays to sarcomas with ring chromosomes. The DNA copy number profiles revealed multiple amplification targets, with a large number of small amplicons. More than 40% of all amplicons, in STS as well as bone tumors, mapped to chromosome 12 with recurrent amplifications in 12q13.3-14.1 and 12q15.1, encompassing *SAS* and *CDK4*, and *MDM2*, respectively. This study also showed amplification of genes involved in the c-JUN pathway in most of the tumors with 12q amplification.

Meza-Zepeda et al. (2006) used aCGH to create a detailed map of DNA copy number changes in GIST and leiomyosarcomas and herein demonstrated multiple gains and losses in both tumor types. Leiomyosarcomas showed more frequent losses of 10q21.3 and 13q14.2-q14.3 and recurrent high-level amplification of the 17p13.1-p11.2 region. Hierarchical clustering analysis separated GIST from leiomyosarcomas and herein identified 6 discriminating regions, suggesting that aCGH could provide independent and distinct information in histologically similar tumors.

Price et al. (2007) used whole-genome gene expression to study 68 GIST and leiomyosarcomas in order to identify distinct genetic classifiers. *Obscurin* and *Prune2* were found to accurately distinguish most GIST from leiomyosarcoma, and this classifier was validated in 19 independent samples.

Segal et al. (2003) studied 21 cell lines and 60 primary STS, melanoma, and clear-cell sarcoma. Unsupervised cluster analysis of the gene expression profiles clearly distinguished between STS and melanoma and identified the clear-cell sarcoma cluster as a distinct group with genes involved in melanocyte differentiation as discriminators.

Fritz et al. (2002) performed expression profiling and aCGH in pleomorphic, dedifferentiated liposarcomas. The highest amplification peaks contained

the genes *MDM2*, *GLI* and *CDK4*, which served as class predictors for this tumor type. Involvement of 12q13-15 indicated a close relationship between dedifferentiated and well-differentiated liposarcomas. Clustering based on the expression levels of 1600 genes allowed most of the tumors to be separated into pleomorphic or dedifferentiated liposarcomas, with the heat shock protein HSP90 and the adaptor protein gene *SCAP* showing high expression in pleomorphic liposarcomas.

Fernebro et al. (2006) applied 27k spotted cDNA microarray slides to assess gene expression profiles in synovial sarcomas with various fusion genes e.g. *SS18-SSX1/SSX2* types and with correlations to clinicopathological data. Oncogenes (*TCF7* and *NOTCH*), G-protein coupled receptors, histones, and metallothioneins were more frequently upregulated in tumors with the *SSX1* fusion, suggesting different downstream effects for synovial sarcomas with the *SSX1* and *SSX2* gene fusion types.

Carneiro et al. (2009) applied aCGH and gene expression profiling to 18 leiomyosarcomas and 31 UPS with the aim to identify molecular subtype signatures. Both the gains/losses and the gene expression signatures revealed striking similarities between these STS subtypes. Leiomyosarcomas and UPS were indistinguishable using unsupervised hierarchical cluster analysis and significance analysis for microarrays, which suggests a shared lineage.

### Genetic profiling of for refined STS prognostics

Genetic signatures have been recognized to serve not only as diagnostic adjuncts, but also as prognostic markers. Francis et al. (2007) reported a potential metastatic signature in high grade pleomorphic sarcomas characterized by expression of hypoxia-related genes, e.g. HIF-1 alpha (HIF-1a), which independently predicted risk of metastasis. Lee et al. (Lee et al. 2004) identified a gene signature related to cell-cycle signal transduction genes that predicted metastasis in leiomyosarcomas. Fernebro et al. (2006) reported a set of 30 genes (among them *TOP2A*) related to metastatic potential in synovial sarcomas, albeit in a small sample set. Carneiro et al. (2009) used aCGH and identi-

fied loss of 4q31 and loss of 18q22 as markers of metastasis.

Despite the limited data, these studies suggest that the use of microarrays may provide novel information, which may be particularly relevant in high-grade, pleomorphic, and genetically complex STS, 50% of which metastasize and in which conventional prognostic markers have reached their limit. Moreover, these studies point to specific pathways/aberrations that could be further pursued to unravel mechanisms of metastasis.

### Towards targeted therapies in STS

Surgery remains the mainstay treatment for STS. Treatment options in metastatic STS are limited since highly effective chemotherapy regimens are lacking. The two most commonly used drugs are doxorubicin, which yields a response rate of about 20%, and ifosfamide, the added value of which is debated. Subtype-specific treatment and most likely the introduction of targeted therapies are therefore needed in STS. Most clinical trials have considered STS as a single pathological entity, although more than 50 different subtypes exist, many of which develop through specific tumorigenic mechanisms as outlined. Not surprisingly, these subtypes differ in drug sensitivity and a major undertaking in STS is to translate better knowledge of sarcoma biology into application of targeted therapies. GIST with c-kit mutations and the successful introduction of imatinib represent the prime example of a targeted therapy. Although several ongoing trials evaluate targeted therapies in STS, these therapeutic options have not yet reached clinical application.

For STS containing fusion genes, strategies specifically inhibiting the fusion genes or their products are attractive as reviewed by Tomescu et al. (2001). Such approaches could include antisense therapies, direct targeting of deregulated transcription factors or their pathways, and applications related to immune response mechanisms. For STS with complex karyotypes identification of deregulated pathways through genomic profiling studies constitutes a **valuable source to identify biologically relevant tumor subsets and pathways that can be therapeutically targeted**. Deregulation of multiple targets within the **mammalian target of rapa-**

**mycin (mTOR)** pathway and of factors involved in hypoxia and angiogenesis have repeatedly been observed in STS. Among the more specific targets are e.g. the insulin growth factor receptor (IGFR), members of the WNT pathway in synovial sarcoma, and MDM2 and CDK4 in pleomorphic liposarcoma.

### *AKT and Mammalian target of rapamycin (mTOR)*

Using high-density microarrays, Hernando et al. (2007) identified upstream modulators or intrinsic components of the PI3K-AKT pathway overexpressed at the mRNA level in different STS types. The functional relevance of AKT upregulation was confirmed by the concomitant activation of upstream regulators, suggesting a potential involvement of deregulated AKT-mTOR activity, which was particularly common in MFH/UPS and leiomyosarcomas. mTOR is a key part of AKT activation and therefore a potential drug target for tumors with deregulated AKT. Unlike other kinases, mTOR seems to be a stable target and has not been shown to be mutated in human cancers. mTOR acts as a master modulator of cellular catabolism and anabolism, thereby compromising cell growth and proliferation. Rapamycin and derivatives that specifically block mTOR have recently been developed. Rapamycin, also known as sirolimus, is a lipophilic macrolide demonstrated to have anti-proliferative properties attributed to the modulation of the synthesis of proteins required for ribosome biosynthesis, protein translation, and cell cycle progression, resulting in G1 cell cycle arrest through mTOR inhibition (Figure 2). Three rapamycin analogs are currently being evaluated i.e. the cell-cycle inhibitor-779 (CCI-779, temsirolimus), RAD-001 (everolimus), and AP23573 (deforolimus). No other proteins have been identified as rapamycin targets, thus making mTOR-rapamycin interaction specific. Results from phase I studies with mTOR inhibitors have shown favorable tolerability and have suggested antitumor activity in several tumor types, including sarcomas. Several phase II trials have been performed with promising clinical efficacy of AP23573, which is currently being evaluated in a phase III trial (ClinicalTrials.gov identifier: NCT00538239).

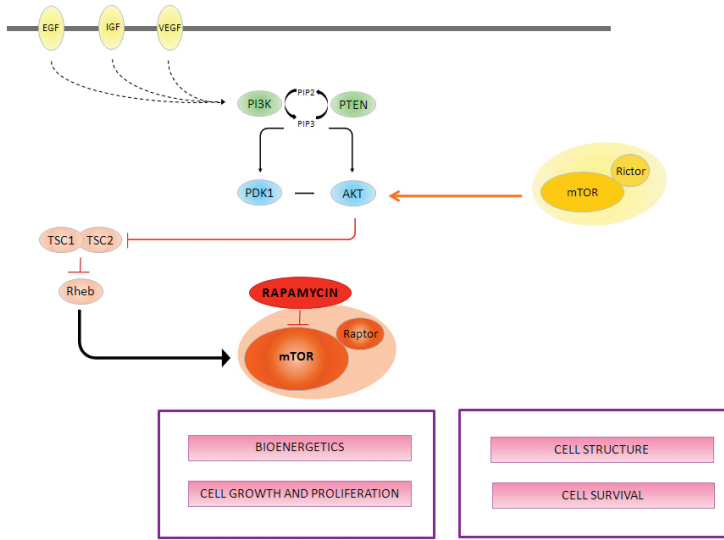


Figure 2. mTOR is a large protein kinase that nucleates at least two distinct multi-protein complexes: the rapamycin-sensitive complex, also called mTOR complex 1 (mTORC1) and the rapamycin-insensitive complex (also called mTOR complex 2, mTORC2), which is defined by its interaction with RICTOR (rapamycin-insensitive companion of mTOR). In response to growth factors and nutrients mTORC1 regulates cell growth by modulating translation of eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) and ribosomal S6 kinase 1 (S6K1). mTORC2 is considered part of the PI3K–AKT pathway as it directly phosphorylates AKT in response to growth-factor signaling mediated by tyrosine kinases receptors (EGF, VEGF, IGF). After being recruited to the membrane, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) and thereby converts PIP<sub>2</sub> to PIP<sub>3</sub>. Subsequently, PIP<sub>3</sub> recruits AKT and 3-phosphoinositide-dependent protein kinase 1 (PDK1) to the plasma membrane resulting in partial activation of AKT. Phosphatase and tensin homologue deleted on chromosome ten (PTEN) dephosphorylates PIP<sub>3</sub> back to PIP<sub>2</sub> and thus shuts off PI3K signaling. Activated AKT leads to the inhibition of the tumor suppressors tuberous sclerosis complex (TSC1 and TSC2), thus promoting the activation of mTOR through Rheb.

### Insulin growth factor (IGF)

Elevated expression of IGF2 has been demonstrated in several STS histotypes as well as in osteosarcomas. In synovial sarcomas, IGF2 overexpression is induced by the SYT/SSX oncoprotein (de Bruijn et al. 2006, Sun et al. 2006). High levels of IGF2 have also been reported in rhabdomyosarcomas (Zhan et al. 1994, Zhan et al. 1998). In desmoplastic small-cell tumors, high expression of IGF-1 receptor (IGF-1R) is related to an effect from the fusion protein EWS-WT1 on the IGF-1R promoter. These findings have also been confirmed in gene expression studies. Baird et al. (2005) identified IGF2 among the top expressed genes in synovial sarcomas, which was confirmed by immunostaining. Binding of the IGF1 and IGF2 ligands to IGF-R activates its intrinsic tyrosine kinase activity resulting in signaling through cellular pathways that modulate proliferation and inhibit apoptosis. The key downstream signaling pathways include PI3K-AKT-mTOR and RAF-MEK-ERK (Figure

3). Antibodies as well as tyrosine kinase inhibitors are clinically evaluated as IGF-1R targets. Several monoclonal antibodies that block ligand binding have been developed and are now in phase I-II clinical trials. One of these, R1507, has shown activity against Ewing sarcoma, but gene expression studies suggest that such agents may be of value also in other sarcoma types, including synovial sarcoma and rhabdomyosarcoma. Another monoclonal antibody against IGF-1R, IMC-A12 (cixutumumab), is being evaluated in a phase I/II trial in STS (ClinicalTrials.gov identifier: NCT00720174). Tyrosine kinase inhibitors have also been designed against IGF1R, but because the insulin receptor and the IGF-1R are 95% homologous at the tyrosine kinase ATP-binding site, small molecules will to some degree also inhibit the insulin receptor (Rodon et al. 2008). Currently, one tyrosine kinase inhibitor (OSI906) is being evaluated in phase I trials (ClinicalTrials.gov identifier: NCT00514306 and NCT00514007).

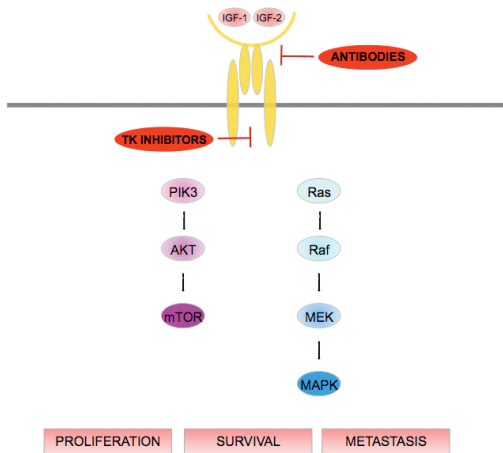


Figure 3. Binding of IGF-1 to its receptor triggers the auto-phosphorylation of the latter and leads to activation of different signaling cascades through the phosphatidylinositol 3-kinase/AKT and *ras/raf/mitogen-activated protein/extracellular signal-regulated kinase* pathways. The IGF pathway thus modulates cell proliferation, survival and metastasis.

### Anti-angiogenesis and hypoxia

Angiogenesis is a key factor in cancer progression (Folkman et al. 1989). Most tumors develop their own blood vessels already at 1-2 mm in size. Using gene expression profiling several angiogenic genes have been found to be upregulated in STS, including the PDGF receptor (PDGFR), MMP-2, and Notch-1 and Notch-4 (Yoon et al. 2006). Overexpression of PDGF-B has been associated with increased cell growth and high-grade tumors (Wang et al. 1994). Anti-angiogenic agents have proven effective in several cancer types and various types of angiogenesis inhibitors, e.g. monoclonal antibodies and tyrosine kinase inhibitors of VEGF and other angiogenic factors, thalidomide, and retinoic acids are being investigated, also in metastatic sarcoma (Gasparini et al. 2005). Initial investigation of the monoclonal anti-VEGF antibody bevacizumab in combination with doxorubicin in metastatic STS demonstrated stable disease, but no objective response (D'Adamo et al. 2005). Small-molecule inhibitors of VEGF signaling, e.g. sorafenib, sunitinib, and pazopanib are being examined in phase II studies in patients with metastatic STS and recently, pazopanib showed activity against STS in a phase II multicentre EORTC study. A phase III study is currently recruiting (ClinicalTrials.gov identifier:NCT00794521).

The extent of hypoxia within the tumor micro-environment has been linked to metastatic spread and radiotherapy resistance. Detwiller et al. (2005) demonstrated upregulation of hypoxia-related genes. Francis et al. (2007) identified a gene expression signature in metastizing tumors and among the top ranked genes were HIF-1 $\alpha$  and its targets, which suggests that the HIF-1 $\alpha$  related pathway may represent a potential target. Preclinical data indicate that local control can be improved using tirapazamine before surgery and radiotherapy in STS (Lunt et al. 2005).

### CDK4 and MDM2 as potential therapeutic targets

Well-differentiated and dedifferentiated liposarcoma harbour a characteristic 12q13-15 amplicon encompassing both *CDK4* and *MDM2* (Wunder et al. 1999). Heidenblad et al. (2006) and Carneiro et al. (2009) have reported recurrent amplification of *CDK4* (and *MDM2*) in a subset of pleomorphic STS. On the basis of *CDK4* amplification and overexpression, cyclin-dependent kinase inhibitors (CDKI) are a compelling group of agents to pursue as new therapeutics in STS (Schwartz et al. 2005). Flavopiridol is the best studied of these agents and phase I studies are currently under way. Nutlins are a family of MDM2-specific agents with proven activity against sarcoma cell lines (Ambrosini et al. 2007) and also represent promising targets for clinical evaluation.

### Frizzled pathway/WNT

The WNT pathway has demonstrated consistent upregulation in synovial sarcoma. Nagayama et al. first reported to have identified 26 genes upregulated in synovial sarcomas (Nagayama et al. 2002), including the Frizzled homologue 10 (FZD10), whose product belongs to the Frizzled family of seven-pass transmembrane receptors in the WNT signaling pathway. Pre-clinical studies in mice with synovial sarcomas, have shown that treatment with monoclonal antibody against native FZD10, increases time to tumor progression. Despite being a promising therapeutic target, no clinical application directed to FZD10 is yet available.

## Conclusions

STS elegantly demonstrate how conventional histopathology and molecular genetics can complement each other (Helman et al. 2003, Oliveira et al. 2004, Antonescu 2006, Antonescu 2008, Bridge 2008). Molecular pathology is increasingly applied as a diagnostic adjunct to morphology and molecular characterization has in several STS types identified recurrent derangement of central signaling pathways. Examples include KIT in GIST, EGFR, WNT, frizzled, and retinoic acid receptor pathways in synovial sarcoma, CDK4 and MDM2 in dedifferentiated liposarcoma, muscle-related genes in leiomyosarcoma, and nerve-sheath related genes in MPNST. A major undertaking in STS is to translate this knowledge into targeted therapies with inhibitors of mTOR, IGF-1, angiogenesis, CDK4, and MDM2 as potential targets. The detailed mapping of fusion genes, amplified regions, altered expression, and deranged signaling pathways leads to an increasingly diversified diagnosis and treatment of STS, and the integration of genetic profiles into the successes and failures of targeted therapies is likely to improve outcome for future STS patients.

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# Clinical and molecular studies of liposarcoma

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## Liposarcoma in the Scandinavian Sarcoma Group Register

Liposarcoma (LS) represents a uniform nomenclature for several subtypes with different morphological and cytogenetic characteristics and clinical behavior. In 2002, the World Health Organization (WHO) published the third edition of its classification of soft tissue tumors. The 5 LS subtypes are well differentiated LS (WDLS), dedifferentiated LS (DDLS), pleomorphic LS (PLS), myxoid/round cell LS (MLS/RCLS) and mixed-type LS. The term WDLS should be used for tumors in deep locations, difficult to surgically access with risk for local recurrence (e.g. the retroperitoneum and mediastinum) and the preferred term for tumors in the extremities and trunk wall is atypical lipomatous tumor (1).

Liposarcoma comprises 10–16% of all soft tissue sarcomas (2). In the last 20 years, several large studies dealing with LS have been published by different sarcoma centers (3-7). The Scandinavian Sarcoma Group (SSG) Register started in March 1986. In Norway and Sweden, approximately 90% of all soft tissue sarcomas of extremities and chest wall are reported to the SSG Register, and so the Register is considered population-based for these two countries (8). The SSG Pathology Board has previously reviewed liposarcomas and malignant fibrous histiocytomas in the Register (9). We recently performed an analysis of 237 patients diagnosed with LS of extremities and chest wall between 1986 and 1998 (10), with a focus on the clinicopathological characteristics, treatment, and outcome. Since only 2 patients in this material received adjuvant chemotherapy, the results, that is, the rate of first local recurrence or

distant metastasis, represent the outcome of surgery and radiotherapy. The analysis revealed a high proportion of low-grade LS (histopathological grade I and II on a IV-grade scale), in particular WDLS, which accounted for 53% of low-grade LS and 36% of all subtypes. In the subcutaneous location, there was a 1:1 ratio between the low-grade and high-grade (histopathological grade III and IV) group, but the corresponding ratio in the deep location was 2.6:1.

Well-differentiated liposarcomas may recur locally, but they do not metastasize unless they undergo dedifferentiation, which occurs in only a few percent on extremities and chest wall (2, 11). The local recurrence rate of WDLS on extremities and trunk is reported in the literature as ranging from 8% to 52% (12-18). In our study, the local recurrence rate was 13% with surgically treatable recurrences. Well-differentiated liposarcomas with non-wide surgery and without postoperative radiotherapy (45 patients) showed no local recurrence in 82% of cases, and so the routine use of radiotherapy cannot be recommended. No patient developed metastases. Our results support the use of the term “atypical lipomatous tumor” for these lesions when they arise in the extremities or trunk wall.

During the investigation period, SSG recommended that soft tissue sarcomas operated on with intralesional and marginal surgical margins should be treated with postoperative radiotherapy. In the low-grade group (WDLS and MLS), radiotherapy was applied in 17% of cases; the local recurrence rate was 13% with radiotherapy and 18% without. In the high-grade group (MLS/RCLS, RCLS, DDLS, and PLS), radiotherapy was applied in 58% of tumors with non-wide surgery; the local recurrence rate was 19% with radiotherapy and 47%

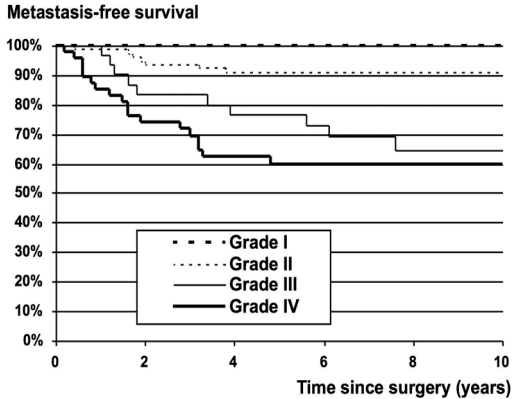


Figure 1. Metastasis-free survival for liposarcoma grade I-IV.

without. Univariate analysis of radiotherapy as a prognostic factor for local recurrence revealed no statistical significance in the low-grade group, the high-grade group, or the total group. However, this factor became significant in the multivariate analysis, when radiotherapy was analyzed together with final surgical margins and grade, a result which was interpreted as an effect of radiotherapy for the same grade and margin. This result is supported by Jebsen et al., who, in a Scandinavian Sarcoma Group study, showed that adjuvant radiation therapy effectively prevents local recurrence in soft tissue sarcoma of the extremities and trunk wall irrespective of the tumor depth, malignancy grade, and surgical margin status (19). In multivariate analysis, surgery outside a sarcoma centre and the subtype DDLs were adverse prognostic factors for local recurrence, while old age, large tumor size, high grade, and histological type RCLS were prognostic for metastatic disease. The estimated 10-year metastasis-free survival rate was 95% for low-grade LS and 61% for high-grade LS. Local recurrence-free survival rates were 87% for low-grade LS and 75% for high-grade LS (Figures 1 and 2).

The study revealed high rates of metastases in the different high-grade subtypes. Dedifferentiated liposarcoma patients developed metastases in 57% of cases, followed by MLS/RCLS (46%), PLS (36%), and RCLS (33%). There are several reports of sensitivity in myxoid liposarcoma to cytotoxic drugs such as doxorubicine, ifosfamide, and trabectedin (Yondelis®) (20-22). The ongoing Scandinavian Sarcoma Group study, SSG XX, on adjuvant chemotherapy in high-grade soft tissue

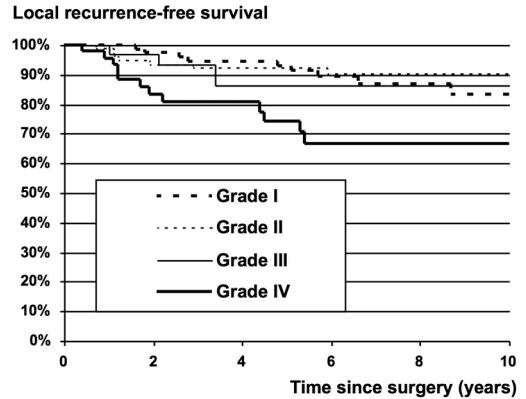


Figure 2. Local recurrence-free survival for grade I-IV.

sarcomas used as inclusion criteria either vascular invasion or 2 of the following 3 criteria: tumor size > 8 cm, necrosis, and infiltrative growth pattern. Our study showed no vascular invasion in MLS/RCLS, and necrosis and infiltrative growth pattern was seldom present; applying the SSG XX protocol on this tumor group would result in exclusion of 50% of patients that later metastasize. Conversely, the prognostic factors of tumor size > 10 cm and a diagnosis of MLR/RCLS or RCLS identified 90% of the high-grade MLS/RCLS that later developed metastases. Considering the reported chemosensitivity in this subtype of LS, it is important that future prognostic studies are able to better identify high-risk MLS/RCLS patients.

Well-differentiated liposarcomas show the presence of extra ring and/or giant marker chromosomes derived from the chromosome 12q(13-15). Amplification of mouse double minute (*MDM2*) and cyclin-dependent kinase (*CDK4*) genes from this region is frequently seen in WDLS, but *TP53* is very rarely mutated (23-25). Dedifferentiated liposarcomas display the same chromosomal abnormality associated with WDLS, but the amplification levels of *MDM2* and *CDK4* are frequently higher (25). The *MDM2* gene is a proto-oncogene, and the phosphoprotein MDM2 negatively regulates P53. MDM2 binds to the transactivation domain of P53, inhibits the P53-mediated transcriptional activity, and promotes P53 degradation through ubiquitination. It even degrades pRB, and thereby supports the transcription activity of the E2F family and cell cycle progress (26-29). Nutlin-3a, a recently-developed small-molecule antagonist of MDM2 (30-32), has been shown to

work as a P53 inducer in DDLs-derived cell lines (33) and WDLs-derived cell lines (34), leading to apoptosis. This is a promising therapeutic agent, especially needed for treatment of WDLs in abdominal and thoracic cavity and for DDLs.

### **Clinical and molecular studies of myxoid/round cell liposarcoma**

The myxoid/round cell liposarcoma subgroup constitutes approximately 40% of all LS (2, 35). Round cell liposarcoma is a morphologic continuum of MLS which carries the same unique cytogenetic features as MLS. Presence of round cell differentiation > 5%, presence of necrosis, and over-expression of P53 are associated with poorer disease-specific survival (36).

More than 95% of MLS cases carry the translocation t(12; 16)(q13; p11), which results in the *FUS-DDIT3* (also known as '*TLS-CHOP*') fusion oncogene. A few percent carry a variant translocation, t(12; 22), and an *EWS-DDIT3* fusion oncogene (37, 38).

Until 1990, a few reports on MLS showed post-radiotherapy reduction in tumor size with radiation doses as low as 30 and even 10 Gy (39, 40). At the Department of Oncology, Sahlgrenska University Hospital, Gothenburg, 15 patients with 33 MLS tumors were treated with radiotherapy between 1994 and 2004 (41). 30 tumors were evaluated with radiology before and after radiation therapy; 17 responded with more than 30% tumor volume reduction (4 with complete response and 8 with more than 50% response). This response was achieved with a radiation dose of 40-46 Gy. In recent years, several larger studies of radiation response in MLS have shown both excellent reduction of tumor size (42) and high local control rate (43, 44). The SSG study also demonstrated excellent local control in MLS, MLS/RCLS, or RCLS treated with radiation therapy. No patient developed local recurrence after postoperative radiation therapy (24 out of 99 patients), but 15% of the non-irradiated patients had local recurrences. In the Gothenburg study (41), all tumors surgically removed after preoperative radiation (27 tumors) showed a dramatic morphologic response, with paucicellularity, hyalinization, and in most lesions a lipomatous appearance with mostly univacuolated adipocyte-like cells that varied in size (Figure 3). Minimal microscopic foci of characteris-

tic MLS were also occasionally seen. The presence of round cells did not correlate to either radiological response or the post-irradiation morphology.

The Scandinavian Sarcoma Group does not recommend preoperative radiation therapy, but the tumor volume reduction and the elimination of tumor cells seen in this study support the use of preoperative radiotherapy whenever a non-wide surgery is overhanging.

The mechanism behind the morphologic response to radiation therapy is unclear. The immature spindle cells were to a large extent eradicated in our tumors. According to Kuroda et al. (45), *FUS*-deficient mice exhibited increased radiosensitivity, and it may be that it is the translocated *FUS* gene that contributes to the high radio-responsiveness in MLS. The lipoma-like appearance after radiotherapy could be due to the more differentiated lipoblasts having been left unaffected, or it could be due to radiation-induced cell cycle arrest leading to maturation of the lipoblasts. In the literature, it is suggested that a mixed MLS with WDL is rare (46, 47), but in our material 21 out of 27 lesions had areas with lipoma-like appearance.

Demetri et al. reported in 1999 that treatment with troglitazone, a PPAR- $\gamma$  synthetic ligand, induced adipocytic differentiation in 2 patients with MLS and MLS/RCLS (48). In addition, in 2007, Grosso et al. reported paucicellularity, hyalinization, and adipocyte-like maturation in patients treated with preoperative trabectedin (Yondelis<sup>®</sup>) (22). The possible mechanism behind the lipoma-like appearance after radiation therapy could be an induction of P53, which is seldom mutated in MLS (49-52). Wild-type P53 activates transcription of *P21*, and the P21 protein in turn inactivates the cyclin E/CDKs - pRB pathway and arrests the cell at the G1-S checkpoint. Unpublished data from our group showed an induction of P21 expression after irradiation of cultured MLS cells.

Further support for our hypothesis can be found in the work of Ventura et al. (53), who showed that mice carrying a reactivable *TP53* knockout allele developed lymphomas and sarcomas, and that the lymphomas underwent apoptosis when the *TP53* gene was reactivated. However, regression of sarcomas was delayed, and no extensive apoptosis was evident. Instead, restoration of P53 expression suppressed proliferation and induced cell

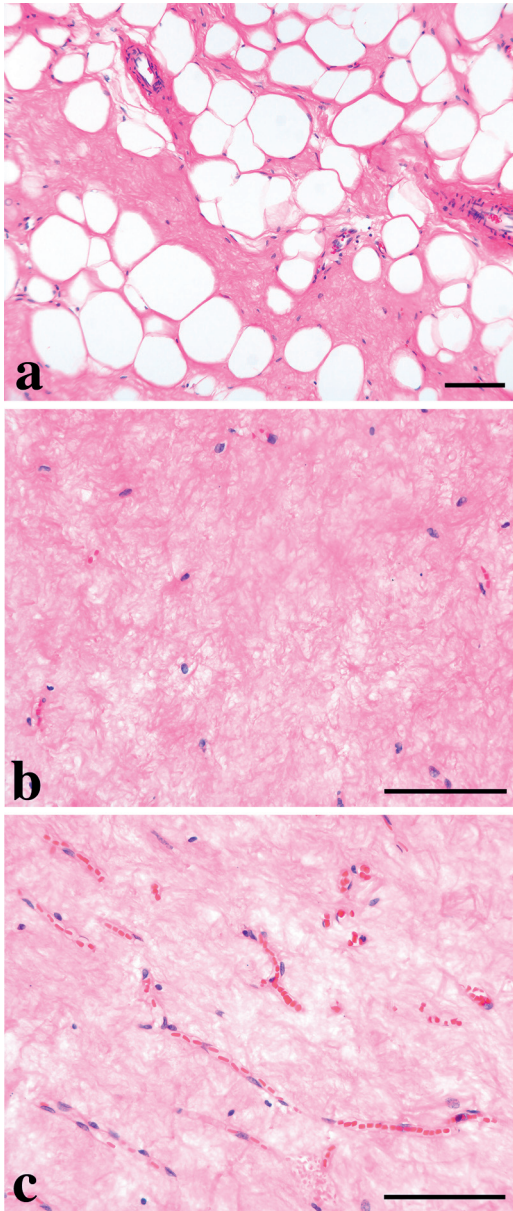


Figure 3. Irradiated MLS/RCLS with lipogenic maturation with mostly univacuolated adipocyte-like cells, (10x) (a), hyalinisation and paucicellularity, (20x) (b) and preserved delicate capillary network, (20x) (c). Bar denote 100 micrometres.

cycle arrest, and the cells changed morphology and expressed senescence-associated  $\beta$ -galactosidase, P15 and P16. This report supports our hypothesis that radiation-induced expression of P53 may lead to cell cycle arrest in MLS and terminal differentiation of lipoblasts.

The question remains of whether the gene fusion in MLS arises in normal mesenchymal stem cells or whether it occurs at a later differentiation stage; and it may also be asked whether the fusion gene is sufficient for neoplastic transformation. It has been shown that the fusion gene can block terminal differentiation of pre-adipocytes in vivo and in vitro. Also, transgenic mice that expressed FUS-DDIT3 in all tissues developed MLS/RCLS-like tumors arising in adipose tissue. These reports led to the hypothesis that MLS/RCLS develops from pre-adipocytes carrying *FUS-DDIT3* which are incapable of terminal differentiation. However, since myxoid liposarcomas in humans preferentially develop in or between the large muscles of the thigh, and rarely in adipose tissue, this hypothesis has been called into question. At the Lundberg Laboratory for Cancer Research in Gothenburg, we observed that the *pFUS-DDIT3*-EGFP and *pDDIT3*-EGFP-transfected, xenografted HT1080 cell line induced a switch from a poorly differentiated sarcoma to an MLS/RCLS-like morphology (Figure 4) (54). Microarray expression profiling supported the switch in morphology by showing a changed expression pattern of transfected HT1080 cells toward an MLS/RCLS-like profile. These findings support the idea that *FUS-DDIT3* can drive a primitive mesenchymal tumor cell toward an MLS/RCLS phenotype. Further support comes from Riggi et al., who reported that mesenchymal progenitor cells isolated from mouse bone marrow transformed and grew as MLS-like tumors in SCID mice when transfected with the *FUS-DDIT3* fusion gene (55). Pérez-Losada et al. showed that transgenic mice expressing high levels of DDIT3 did not develop liposarcoma tumors (56). In our experiments, DDIT3, when expressed in a primitive fibrosarcoma cell, induced a switch in morphology and expression pattern toward an MLS/RCLS type. This supports the hypothesis that it is the *DDIT3* gene that determines the tumor entity when fused with the *FUS* gene.

The above results show that forced expression of *FUS-DDIT3* and *DDIT3* induces a switch in HT1080 cells toward MLS/RCLS-like morphology and gene expression. The results also indicate that the transcription factor partner *DDIT3* of *FUS-DDIT3* is the tumor type-determining part of this EWS-group fusion oncogene.

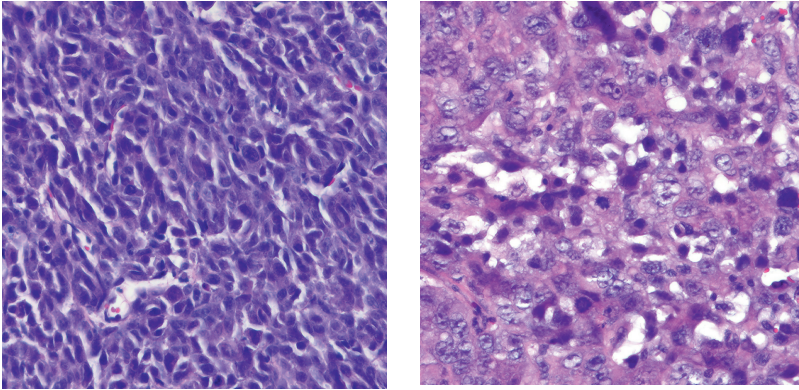


Figure 4. Microphotographs of section from SCID mouse tumors of HT1080 cells (left column) and the pFUS-DDIT3EGFP-transfected variant (right column).

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# SSG pathology review experiences and histological grading of malignancy in sarcomas

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The rarity of sarcomas, the histological variation with often complex diagnostic work-up and overlap with benign mesenchymal tumors emphasize the importance to have dedicated pathologists working in the field. Sarcoma pathology is in continuous development with new histological entities and changes of diagnostic criteria. One example of refinement in diagnostics in mesenchymal tumors was the identification of the gastrointestinal stromal tumors (GISTs) in the late 1990ths with the use of the antibody CD117 and identification of activating mutations in *KIT* or *PDGFA* (Joensuu and Kindblom 2004). Previously most of these tumors were diagnosed as benign or malignant epithelioid leiomyomatous tumors or other spindle cell tumors. This means that projects including abdominal sarcomas diagnosed before 2000 have to be reviewed.

The Scandinavian Group (SSG) was established in 1979 and from the beginning pathologists took part in the organization. In the first years the morphology group was lead by Lennart Angervall. The aim for the pathology group has been to standardize and improve the quality of diagnostics in sarcoma. They have contributed to treatment protocols and recommendations for diagnosis and research. For study cases the pathologists have reviewed the diagnosis, malignancy grade and evaluated the histological response after preoperative chemotherapy in bone sarcomas.

Lars-Gunnar Kindblom established in 1995 a panel of pathologists from Scandinavia in a peer-

review committee with the aim to review all cases in the SSG Central database. Since 1995 the panel has reviewed 2304 cases.

## Review process

The morphology group in SSG consists of trained sarcoma pathologists from tumor centers in the Nordic countries (Table 1). The SSG Central Register contains data on 9384 sarcoma cases (October 2008) treated at sarcoma centres in Scandinavia from 1986. (<http://www.ssg-org.net/>). Histopathological data of the tumors is included in the database. The pathology group has met 2-4 times annually reviewing histopathological diagnosis of sarcomas from different institutions in SSG. Many of the cases are from patients included in clinical trials, but cases in specific research projects are also included.

The review is usually performed with a multi-headed microscope (Figure 1). The SSG secretary participates in the meeting. From the pathology report the following parameters are extracted: sex, age at diagnosis, site, localization, depth of infiltration, size, and the contributor's diagnosis. If ancillary methods like immunohistochemistry, ultrastructural pathology, FISH, RT-PCR or cytogenetic studies were used, it is noted. From the review process the histopathological diagnosis, diagnostic alternatives, grade of malignancy, tumor necrosis, vascular invasion, mitotic rate, and pushing or dif-

Table 1. Participants of the review group 1995–2008

Country	Member
Denmark	Olaf Myhre-Jensen
Finland	Tom Böhling Jyrki Parkkinen Martti Virolainen
Norway	Bodil Bjerkehagen Per Johannes Bøhler Johan Eide Tore B. Halvorsen Hans-Kristian Haugland Peer Lilleng Wenche Reed Elisabeth Stenwig Trond Viset Lisa Walaas
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Figure 1. The multiheaded microscope.

fuse infiltrative growth pattern are evaluated. The status of the surgical margins has not been re-evaluated; information about the status of the margins is based on the original reports. In special cases new immunohistochemical analyses as well as genetic analyses were performed to aid classification. Most cases diagnosed with only cytology

were excluded. Furthermore sarcomas pretreated with radiotherapy and/or chemotherapy were difficult to review because the treatment can induce necrosis and morphological changes. All cases are classified according to the WHO recommendations (Fletcher et al. 2002). A special protocol was used for registration of data (Figure 2).

### Histological grading of malignancy

The grading of soft tissue and bone sarcomas is important because of the prognostic impact. The clinical course of sarcomas varies within a particular histopathological entity. There is no generally accepted grading system for sarcomas (Deyrup and Weiss, 2006) and there is an ongoing discussion which grading system to prefer. The French Federation of Cancer Centers system has been tested in several studies and is probably the best documented system, see Table 2 (Guillou et al. 1997, Coindre et al. 1996, Miettinen 2006). Because there are so many types of sarcomas and subgroups therein it is difficult to validate grading systems for sarcomas. The different morphologic variables are of varying importance for the different types of sarcomas (Angervall and Kindblom 1993). Ideally there should be one specific grading system for every subtype of sarcoma, but that is not clinically meaningful.

In the SSG, the histological grading of sarcomas has been based on a four tiered grading system primarily based on Broders grading model (Broders 1920, Broders et al. 1939). Generally only untreated primary sarcomas using good quality slides and representative tissue should be used for grading. Grade 1 and 2 means low grade malignancy and grade 3 and 4 tumors are regarded as high-grade malignant sarcomas. This system considers the degree of cellularity, cell and nuclear polymorphism, differentiation, the presence and amount of necrosis, hemorrhage, mitotic activity and growth pattern, but does not score the different parameters (Angervall and Kindblom 1993).

For many soft tissue sarcomas the grade is given by the diagnosis. For instance atypical fibroxanthoma of skin, dermatofibrosarcoma protuberans and well differentiated abdominal or retroperitoneal liposarcoma are all grade 1 sarcomas. Typi-

SSG Review Protocol Date: \_\_\_\_\_

SSG-no: \_\_\_\_\_

Name: \_\_\_\_\_

Patient identification: \_\_\_\_\_

Hospital and surgical number: \_\_\_\_\_

Number of slides: \_\_\_\_\_

Sex:  Male  Female Age: \_\_\_\_\_ Site: \_\_\_\_\_

Location:  
 Cutaneous  Subcutaneous  Intermuscular  Intramuscular  Bone

Size: \_\_\_\_\_

Contributors diagnosis: \_\_\_\_\_

Review diagnosis: \_\_\_\_\_

Diagnostic alternatives: \_\_\_\_\_

Grades:  1  2  3  4  Can't assess

Necrosis: Macro:  Yes  No  Can't assess  
Micro:  Yes  No  Can't assess

Growth pattern:  Pushing margins  Diffuse infiltration  Can't assess

Vascular invasion:  Yes  No  Can't assess

Mitotic rate:  
 Low (0-2/10 hpf)  Moderate (3-9/10 hpf)  High (10 and more/10 hpf)  Can't assess

Ancillary methods:  
Immunohistochemistry:  Yes  No  
EM:  Yes  No  
Cytogenetics:  Yes  No  
Frozen material:  Yes  No

Other: \_\_\_\_\_

Excluded  
Reason: \_\_\_\_\_

Supplementary investigation needed:  
Which: \_\_\_\_\_

Figure 2 . The SSG review protocol

cal examples of grade 2 sarcomas include myxoid liposarcoma and many subcutaneous myxofibrosarcomas. For high grade sarcomas (grades 3 and 4)

the grade is partly based upon histogenetic diagnosis and partly upon the morphologic features. Examples of grade 4 sarcomas include round cell

liposarcoma and pleomorphic liposarcoma. Immunostains for evaluating proliferative activity with Ki-67 (MIB1) is also helpful (Hasegawa 2007, Engellau et al. 2004).

Grading specific for myxofibrosarcoma has been described by Angervall et al. (1977). A good association between grade as defined by this system and outcome (metastatic disease) has been reported in many studies by the SSG, for review see Gustafson (1994) and recently in liposarcoma (Engstrom et al. 2008, see also pp 24–30 in this issue) and in nonvisceral soft tissue leiomyosarcoma (Svarvar et al. 2007).

A widely used system is the French grading system (FNCLCC). This is based on tumor differentiation, mitotic count and the amount of tumor necrosis (Guillou et al. 1997, Deyrup and Weiss 2006). The total score of each of these parameters gives the grade. Grade 2 and grade 3 are considered high-grade malignant tumors.

In SSG the so called SIN system also has been applied for prognostication of soft tissue sarcoma. Here one use information about the size of the tumor, necrosis, and tumoral vascular invasion instead or as a complement to the histological grade of the tumor (Gustafson et al. 2003). More recently also the peripheral tumor growth pattern, defined as infiltrative or pushing border, has been included in the prognostic work-up (Engellau et al. 2005, 2007, see also pp 44–50 in this issue).

## Reviews of soft tissue sarcoma

The pathology group started to review malignant fibrous histiocytoma/pleomorphic and spindle cell sarcoma, followed by synovial sarcoma and liposarcoma. Several doctoral theses and projects based on the sarcoma database has included the revised pathology data (Engellau et al. 2004, Svarvar et al. 2007, Engstrom et al. 2008,). For details about the reviews and methods for the first 1000 soft tissue sarcoma see Meis-Kindblom et al. (1999).

The SSG XIII protocol includes patients with high risk soft tissue sarcoma and required pathology review not only to confirm the diagnosis and the malignancy grade but also to evaluate defined risk factors according to the SIN system. Likewise pathology required in the SSG XX protocol opened

in 2007 which replace SSG XIII and adds growth pattern to the risk factors. SSG XVIII is a closed protocol for adjuvant treatment of patients with a high risk GIST. According to the protocol all cases had to be reviewed by a reference pathologist.

Currently an ongoing project initiated by the pathologists in SSG includes the review of angiosarcomas and solitary fibrous tumors.

## Reviews of bone tumors

Within SSG the pathologists have been involved in 7 osteosarcoma and 4 Ewing sarcoma treatment protocols. The diagnosis has to be verified by review in each case. Another important role for the pathologist is the evaluation of the histological response to the preoperative chemotherapy. The response grade is an important prognostic marker, and in most protocols decides the postoperative treatment. The response has to be evaluated shortly after surgery, and cannot wait until the pathologists have a review meeting. The response is therefore usually evaluated by the local pathologist, but in some protocols by a specifically named single pathologist within the SSG. However, both the diagnosis and treatment response have later been evaluated by the review group for several protocols (Bohling et al. 2004).

### Osteosarcoma

In osteosarcoma SSG has been involved in 5 closed protocols; SSG II, SSG VIII, ISG/SSG I, ISG/SSG II and SSG XIV. In these protocols three different ways of evaluating the response grade has been used. In SSG II and SSG VIII the criteria defined by Huvos was used, which uses a four-grade scale, where grades III and IV were considered as good response (Huvos 1991). In the collaborative protocols with the Italian sarcoma group ISG/SSG I and II a new evaluation system was developed in collaboration with the Italian pathologists. In these protocols the criteria for good response was rather tight, and therefore less than 20% of the cases were classified as such (Ferrari et al. 2005). In the SSG XIV protocol (Smeland et al. 2009) the criteria for good response were not as tight as in the ISG/SSG protocols, and the response was defined as a good in tumors where < 10% of examined tumor area

revealed unquestionable viable tumor and no single area of unaffected viable tumor exceeded 2,5 mm in largest diameter.

At the moment SSG participates in a multinational osteosarcoma treatment protocol together with many European and American centres, called EURAMOS-1 (<http://www.ctu.mrc.ac.uk/euramos/>). This protocol requires that only named reference pathologists are allowed to give the final response grade. In the Nordic countries all cases are sent to Helsinki for evaluation. So far approximately 60 cases have been evaluated by the reference pathologist (TB). The response is considered good if less than 10% of the tumor is viable.

### **Ewing sarcoma**

SSG has used two closed treatment protocols, SSG IV and SSG IX, in Ewing sarcoma. In these, the effect of the induction chemotherapy was evaluated using a modified Huvos grading system (Bohling et al. 2004). However, in 1999 SSG entered together with the Italian sarcoma group two protocols, one for localized and one for metastatic tumors. In these protocols the diagnosis requires molecular pathology, either a wide range of immunohistochemistry, but preferably genetic analysis to demonstrate the typical 11;22 translocation. The chemotherapy response is evaluated by the Picci-method (Picci et al. 1997), where the response is graded into 3 categories. This system has shown to be very accurate, and the results are reliable also in review settings.

### **Chondrosarcoma and other bone tumors**

So far, there is only one SSG project on chondrosarcomas. This is an ongoing project and includes primary chondrosarcomas of the thoracic wall. The main aspect for the review group has been to verify the diagnosis and to grade the chondrosarcomas.

### **Conclusion**

The pathology group contributes on several aspects in SSG. Histopathology data in the central SSG register is updated. The work in the peer-review committee standardizes diagnostic practice among SSG centres. The group gives mandatory support to research projects and clinical trials. In addition the review process offers an optimal opportunity to train young pathologists in sarcoma diagnostics.

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# Adjuvant systemic therapy of gastrointestinal stromal tumors

## The Scandinavian Sarcoma Group perspective

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**ABSTRACT** – Gastrointestinal stromal tumors (GISTs) have a malignant potential varying from virtually no risk of recurrence (microscopic GISTs) to a high risk. Acquired secondary mutations that interfere with imatinib binding have been identified as a common mechanism for drug resistance and tumor progression in advanced GIST. Patients with advanced GIST but with a small tumor mass have the longest time to disease progression suggesting that the rate of secondary mutations that confer drug resistance may be low when the number of cancer cells is small. Thus, early administration of imatinib in the adjuvant setting might result in a low rate of secondary mutations and might improve survival. The results of the ACOSOG Z9001 trial demonstrated a significantly longer recurrence-free survival among patients treated with adjuvant imatinib as compared to placebo. Although data on influence of adjuvant imatinib on overall survival is lacking, its administration may be warranted to patients who have a high risk of recurrence and death from GIST that likely exceeds the risks related to adjuvant administration of imatinib. Many aspects of adjuvant treatment remain unknown including the overall benefits and harms of adjuvant treatment, optimal selection of patients for treatment, and the duration of adjuvant treatment, which is currently being investigated in the ongoing Scandinavian Sarcoma Group/AIO trial (SSG/AIO XVIII).

in the Western populations (Nilsson et al. 2005, Tryggvason et al. 2005, Steigen et al. 2006). Small GISTs, a few mm in diameter, occur in a large proportion of the normal population and have no to minimal malignant potential (Kawanowa et al. 2006, Agaimy et al. 2007, Abraham et al. 2007). The larger GISTs are often highly malignant and commonly give rise to intraabdominal implants and liver metastases. GISTs generally do not respond to conventional chemotherapy agents, but they are excellent targets for small molecule tyrosine kinase inhibitors that selectively inhibit the KIT and PDGFRA receptor tyrosine kinases, which have an important role in the molecular pathogenesis of GIST. *KIT* and *PDGFRA* are frequently mutated in GISTs leading to genesis of constitutively active mutant proteins.

Imatinib mesylate was the first effective systemic treatment for advanced GIST, and it has a generally favorable adverse effect profile (Joensuu et al. 2001, Demetri et al. 2002). A few other tyrosine kinase inhibitors, such as sunitinib, nilotinib, sorafenib and vatalanib (PTK787/ZK222584) have also been found to be active in the treatment of advanced GIST. Most (up to 85%) patients achieve a durable response or a long-lasting disease stabilization with imatinib therapy, and the median survival time of patients diagnosed with inoperable/metastatic GIST has now increased to approximately 5 years as calculated from the date of treatment initiation (Blanke et al. 2008).

These results represent a giant leap forward as compared to the era that preceded the times of

Gastrointestinal stromal tumor (GIST), the most common sarcoma of the gastrointestinal tract, has an annual incidence of 10 to 15 cases per million

targeted therapies. Unfortunately, secondary drug resistance was soon found to develop in most patients, although a few patients diagnosed with advanced GIST have now responded to imatinib for up to 8 years, and it is currently not known whether secondary drug resistance will develop in all GIST patients with advanced disease. The median time to GIST progression was approximately 2 years in the B2222 trial that was the first randomized trial to address efficacy of imatinib in the treatment of inoperable/advanced GIST (Blanke et al. 2008).

Delay or prevention of development of secondary resistance to tyrosine kinase inhibitors and other targeted agents is a key for a major improvement in the outcome of GIST patients who present with advanced disease, since responses to subsequently administered agents tend to be short-lived once resistance to the first-line tyrosine kinase inhibitor has emerged. Administration of a targeted agent early in the course of the disease in the adjuvant setting is potentially one of the most promising strategies to avoid early emergence of secondary drug resistance. Here we discuss the rationale for adjuvant systemic therapy for GIST and the ongoing clinical trials.

### Tumor mutation rate and secondary resistance to tyrosine kinase inhibitors

Although responses to targeted agents are usually durable, most responses remain partial. When metastatic deposits are removed at surgery while the patient is still responding to imatinib or sunitinib, almost all responding tumors contain at least some cells that immunostain for KIT and that are likely persisting GIST cells (Rutkowski et al. 2006, Ruka et al. 2008). GIST cells thus have a variable responsiveness to tyrosine kinase inhibition, which often allows a few GIST cells to survive despite persistent treatment.

Only one mutation in *KIT* or *PDGFRA* has invariably been found in mutation analyses of GISTs that have never been exposed to tyrosine kinase inhibitors, whereas secondary *KIT* mutations occur in most GISTs that grow under tyrosine kinase treatment. Interestingly, the secondary mutations are commonly found in *KIT* exons 13, 14 or 17, which exons are rarely mutated in primary GISTs (Hein-

rich et al. 2006, Wardelmann et al. 2006). These mutations are often located adjacent to the binding site of imatinib likely interfering with its binding, are often associated with a decreased responsiveness to imatinib (Heinrich et al. 2006), and confer a growth advantage to the mutated cell population. Apparently, GIST cells that survive under imatinib administration continue to mutate at multiple sites of the genome. When a mutation that interferes with imatinib binding is generated, the cell harboring the mutation will gain a substantial growth advantage relative to other surviving GIST cells, and will eventually progress to a clinically detectable drug-resistant tumor.

Recent evidence suggests that several *KIT* mutations may coexist in a GIST lesion that grows under imatinib treatment, and that the number of mutations detected in a mutation analysis of such tumors may depend on the number of biopsies analyzed (Wardelmann et al. 2006). It is not known why multiple coexistent mutations cannot be found in GISTs that have not been treated with imatinib or other tyrosine kinase inhibitors. Hypothetically, such cell clones fail in competition with cells with only one mutation in the absence of imatinib, and escape detection in a conventional mutation analysis.

These findings lend support to presence of clinically significant mutational activity in most GISTs. In one study, nuclear and mitochondrial microsatellite instability were detected in 3 and 10 of the 62 GISTs examined, respectively, suggesting that mitochondrial microsatellite instability may play a role in the development of some GISTs, whereas nuclear microsatellite instability may have little importance (Kose et al. 2006). Yet, aberrant methylation of CpG islands of DNA repair genes may be common in GISTs. One recent study found aberrant methylation of human mutL homolog 1 (*hMLH1*) in 60% of the GISTs examined (Saito et al. 2008).

### Clinical consequences of mutational activity

Large GISTs are likely to generate mutations that lead to drug-resistance earlier than small GISTs. This hypothesis is supported by the data from the

B2222 trial, where GIST patients diagnosed with overtly metastatic disease were treated with imatinib administered either 400 mg or 600 mg per day. In this study the time to GIST progression was the longest (median 6 years) among the quartile of patients who had the smallest tumor volume at the time of imatinib initiation and the shortest (median 1.5 years) among the quartile of patients who had the largest tumor volume (Blanke et al. 2008, supplement Figure 2). However, the more favorable outcome of GISTs with a small tumor volume may also be due to either lead bias (tumors with a small volume are at an earlier stage of the course of the disease) or length bias (the tumors with a small volume may be biologically less aggressive). There was no apparent plateau in the proportions of tumors that eventually progressed within the first 5 years of imatinib treatment in this study.

The potential propensity of large GISTs to develop drug-resistant mutations sooner than smaller GISTs may be an argument for administering targeted therapy early during the course of the disease when the number of cancer cells is still small. If the rate of mutations remains the same irrespective of cancer volume, emergence of imatinib resistance may take a considerably longer time when imatinib is administered in the adjuvant setting than in advanced disease, because the number of GIST cells that may potentially develop a mutation leading to drug resistance is much smaller. Little is known about the mutation rates of GISTs during the natural course of the disease vs. during tyrosine kinase administration, but cancers in general tend to become less differentiated with time due to tumor progression, which might lead to a greater genomic instability and higher spontaneous mutation rates as the tumor bulk increases with time.

### Other factors associated with drug resistance

Besides the inherent mutation rate and the overall number of GIST cells, many other cancer biological and pharmacokinetics related factors may influence emergence of drug resistance. In one cohort study, GIST patients who had imatinib plasma trough concentration below 1110 ng/mL

(the lowest quartile of plasma concentrations) had a significantly shorter median time to disease progression as compared to those who had a higher imatinib plasma trough concentration (11 months vs. over 30 months, respectively), and they also had a lower response rate to imatinib (44% vs. 67%) (von Mehren et al. 2008). Low imatinib plasma concentrations might allow more GIST cells to survive and to maintain a relatively high cancer cell proliferation rate, which might favor emergence of drug-resistant mutations. Administration of adequate drug doses and good compliance to treatment may be important strategies to delay emergence of drug resistance.

### Adjuvant trials in GIST

Two prospective, single-arm, multicenter trials have evaluated imatinib administered 400 mg/day for 12 months as adjuvant systemic treatment of GIST patients considered to have a high risk for disease recurrence (DeMatteo et al. 2005, Zhan et al. 2007). Both trials found imatinib to be well tolerated by most patients and GIST recurrence to be infrequent (<10%) during imatinib administration.

Patients with KIT-positive GIST, no prior adjuvant therapy, and with a tumor 3 cm or larger in diameter were randomly allocated after macroscopically complete surgery to receive either adjuvant imatinib 400 mg/day or placebo in the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial. The primary endpoint was recurrence-free survival in this Phase III trial with planned cross-over between the study arms, and secondary endpoints included overall survival and safety. The trial was interrupted early when 732 patients had entered the study due to markedly improved recurrence-free survival in the imatinib arm as compared with placebo (97% vs 83% at 1-year of follow-up;  $P < 0.001$ ) (DeMatteo et al. 2008).

Two other large randomized trials that address imatinib as adjuvant treatment of operable GIST have recently completed accrual. EORTC 62024 (NCT00103168) compares 2 years administration of adjuvant imatinib (400 mg/day) to observation following macroscopically complete surgery. The study population consists of patients diagnosed with a GIST of either intermediate or high risk of

recurrence as defined by the NIH Consensus Classification criteria. 900 patients have entered this prospective Phase III trial that has overall survival as the primary endpoint.

The Scandinavian Sarcoma Group/AIO trial (SSGXVIII/AIO) (NCT00116935) compares 12 to 36 months of adjuvant imatinib administered 400 mg/day following macroscopically complete surgery. The study population consists of GIST patients considered to have a high risk of recurrence based on the National Institute of Health (NIH) of the United States Consensus Classification, but includes also patients with tumor rupture (either spontaneously or during surgery). The primary endpoint in this prospective Phase III trial is recurrence-free survival. The accrual of the trial (400 patients) was completed in September 2008, and the first efficacy results are anticipated in 2010.

The main focus of the SSG/AIO trial is whether a prolonged adjuvant treatment, as compared to a potential standard of 12 months as used in the ACOSOG Z9001, is beneficial or harmful to patients with a high risk of GIST recurrence. The recurrence rate during the first year off treatment will be compared as one of the secondary endpoints between the two arms. A smaller relapse rate during the first year after stopping adjuvant imatinib in the 3-year arm might reflect curative potential of adjuvant treatment. The efficacy of imatinib rechallenge among patients who relapse after adjuvant treatment will also be studied within the frame of the SSG/AIO trial, a topic that is discussed further below.

### Response to imatinib rechallenge after adjuvant imatinib

The ACOSOG Z9001 trial found that adjuvant imatinib prolongs the time to GIST recurrence (DeMatteo et al. 2008). There has been a concern of whether patients treated with adjuvant imatinib will respond to imatinib in cases where GIST recurs during the follow-up. The prospective, randomized BR-14 trial carried out in advanced GIST found that interruption of imatinib treatment among the subset of patients who continued to respond to imatinib usually resulted in rapid disease progression after imatinib withdrawal, but the most patients

responded again after imatinib rechallenge (Blay et al. 2007). This scenario resembles the one where adjuvant imatinib administration is discontinued as planned without detectable macroscopic GIST, and is radically different from the one where GIST progresses during imatinib treatment.

No data have been published regarding sensitivity of GISTs that recur after completion of adjuvant therapy to imatinib. One of the authors (H.J.) treated 7 consecutive GIST patients who were estimated to have a high risk of recurrence with adjuvant imatinib for 6 to 12 months between May 2002 and April 2004, and whose GIST subsequently recurred during the follow-up. 5 of these 7 patients responded to imatinib rechallenge, and one further patient had stabilized disease. One patient with a high risk GIST treated by the other author (M.E.) had GIST recurrence 18 months after a 2-year adjuvant treatment period, and rechallenge with imatinib resulted in a partial remission that has now continued for longer than 2.5 years. Although based on small numbers of patients treated, these findings suggest that most patients who have been treated with adjuvant imatinib will respond to imatinib rechallenge when the disease recurs (unpublished data).

### Effect of adjuvant treatment on survival

Due to the short follow-up time at the time of the ACOSOG Z9001 trial interruption, only a few deaths had occurred, which prevented carrying out a meaningful analysis of overall survival. It is currently not known whether adjuvant imatinib influences overall survival.

It has been speculated that administration of adjuvant imatinib might decrease frequency or the duration of response to imatinib if GIST recurs after adjuvant therapy. There are currently no data to support this hypothesis. The overall rate of a secondary drug-resistant mutation is likely the slower the fewer GIST cells are exposed to imatinib. This may be reflected as a longer time to emergence of a drug-resistant cell clone when imatinib is administered in the adjuvant setting when the tumor burden is small as compared to the overtly metastatic stage of the disease. Importantly, most tumors that recur after adjuvant imatinib will respond to imatinib

rechallenge, although the median duration of the response is still unknown. Thus, even if adjuvant imatinib might not cure any patient, which is not known, early administration of imatinib and other targeted agents in the adjuvant setting could be beneficial in terms of overall survival provided that systemic adjuvant treatments do not shorten survival by toxicity, especially of those patients who might be cured by surgery alone.

### The target group for adjuvant therapy

Patients who are likely to be cured by surgery alone should preferably not be exposed to adjuvant therapies. To address the question of patient selection for adjuvant therapy, many prognostic factors have been studied in GIST. The generally accepted most important adverse prognostic features are a large tumor size, a high mitotic count, and tumor origin in the intestine. The NIH Consensus Classification uses 2 of these 3 features, the tumor size and the mitotic count (Fletcher et al. 2002). The Consensus Classification has now been shown to predict survival of GIST patients in several large population-based series (reviewed in Joensuu 2008). Of note, patients with GIST with a low or intermediate risk of recurrence by the Consensus Classification have in most studies favorable survival not markedly inferior of that of the general population suggesting that many patients with either a low or an intermediate risk GIST may not be ideal candidates for adjuvant therapies.

The NIH Consensus Classification does not take into account the tumor site. Evidence from 2 large series from the Armed Forces Institute of Pathology (AFIP) of the United States suggests that fairly small GISTs of intestinal origin are frequently associated with metastases and death (Miettinen et al. 2005, 2006, Miettinen and Lasota 2006) and, therefore, the Consensus Classification probably needs to be modified accordingly. The AFIP risk classification, in turn, does not include ruptured GISTs, which have a high risk of recurrence (Takahashi et al. 2007). A suggested modification of risk classification to define the group with a high risk of GIST recurrence after macroscopically complete surgery is presented in Table 1. Limiting of systemic adjuvant treatment to the modified high

**Table 1. Proposed modification of consensus classification for selecting GIST patients for adjuvant therapy (with permission from Joensuu H. Hum Pathol 2008)**

Risk category	Tumor size (cm)	Mitotic index (per 50 HPF)	Primary tumor site
Very low risk	< 2.0	≤ 5	Any
Low risk	2.1–5.0	≤ 5	Any
Intermediate risk	2.1–5.0	> 5	Gastric
	< 5.0	6–10	Any
High risk	5.1–10.0	≤ 5	Gastric
	Any	Any	Tumor rupture
	> 10	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	2.1–5.0	> 5	Nongastric
	5.1–10.0	≤ 5	Nongastric

risk group would result in administration of adjuvant treatment to approximately 50% of all patients diagnosed with GIST (Joensuu 2008).

### Adjuvant systemic therapy: current practise

Adjuvant administration of imatinib to GIST patients who present with localized disease has been considered investigational (Casali et al. 2008). Yet, imatinib has now been found to increase considerably progression-free survival in a large randomized study (DeMatteo et al. 2008), and the time to appearance of a mutation leading to drug resistance is likely often relatively long when imatinib is administered in the adjuvant setting to patients who have a minimal tumor burden. These factors make administration of adjuvant imatinib appealing especially to patients who have a high (≥50%) risk for GIST recurrence and thus a high risk of death from GIST, since risk of fatal toxicity related to imatinib appears to be rare.

At present, there are different opinions regarding adjuvant administration of imatinib. The views of experts range from abstaining from treatment even in cases with close to 100% risk of recurrence (such as patients with a spontaneously ruptured tumor) to administration of adjuvant imatinib to GIST patients diagnosed with a relatively small single tumor (3 cm or larger in diameter). Use of the 3 cm cut-off as the sole criterion for patient

selection results in administration of adjuvant imatinib to some patients with an intermediate or even a low risk of recurrence and who often have a favorable outcome with surgery alone, whereas some patients with GIST with a high mitotic count and thus with a relative unfavorable prognosis might be deprived from adjuvant therapy. A more rational choice may be to use the high risk group of the modified Consensus Classification in selection of patients for adjuvant treatment.

The optimal duration of adjuvant therapy is currently not known. If adjuvant imatinib therapy is chosen to be administered, a feasible choice is imatinib administration at the dose of 400 mg/day for a total of 12 months. Patients with the imatinib-resistant *PDGFRA* mutation D842V may not benefit from adjuvant imatinib therapy, and adjuvant imatinib might not be effective for neurofibromatosis-1 associated GIST (Mussi et al. 2008). It is not known whether patients with *KIT* exon 9 mutation or with no mutation (wild type GIST) will benefit less from adjuvant imatinib than those with GIST with *KIT* exon 11 mutation, which could be anticipated from data generated in the metastatic setting (Heinrich et al. 2003).

### Future directions

The effect of adjuvant systemic administration of tyrosine kinase inhibitors on overall survival will not be known for several years, although survival data are being collected in the ongoing adjuvant trials. Prevention of secondary drug resistance will remain an important research target, as well as methods to identify patients who are at a clinically significant risk for GIST recurrence.

Combinations of drugs and sequential treatments of novel targeted agents deserve to be investigated not only in advanced GIST but in the adjuvant setting as well. These approaches might lead to improved eradication of GIST cells, and to a reduced risk of drug resistance. Studies addressing individualized dosing of targeted agents based on patient metabolic properties and tumor biological features are also warranted.

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# Prognostic systems for soft tissue sarcoma of the extremities and trunk wall in adults

## A review and the Scandinavian Sarcoma Group experience

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In soft tissue sarcoma (STS) of the extremities and trunk wall population-based patient series have demonstrated that more than one-third of patients will develop metastases, most commonly to the lungs, and most of these patients will die from their sarcoma (Gustafson 1994, Möller-Nielsen 2001). For a long time the value of chemotherapy for patients with STS was unclear. The scarcity of the tumors and the many histological subtypes, sometimes difficult to delineate even for experienced pathologists, have hampered adequate recruitment and analysis of studies investigating the effects of chemotherapy. Meta-analyses of several randomized controlled trials (RCT) have, however, demonstrated a marginal efficacy of chemotherapy in STS (Sarcoma Meta-analysis Collaboration 1997, Meta-analysis Group 2000, Pervaiz et al. 2008). Despite this, the use of adjuvant chemotherapy for STS patients has become more and more common. Most STS patients are elderly, the median age at diagnosis for the commonest histotypes is 60-70 years. The chemotherapy regimens used in neoadjuvant and adjuvant settings usually contain doxorubicin and ifosfamide, sometimes together with other cytotoxic drugs. Thus, these regimens portend considerable toxicity. Therefore, identification of true high-risk patients for developing metastases is of obvious clinical importance in order to avoid over-treatment in actual low-risk patients as the modest improvement in outcome may well be outweighed by treatment induced toxicity and mortality. For this purpose, there has been a strong interest in designing clinically applicable prognostic systems for STS patients. For practical clinical use,

an ideal prognostic system should clearly identify high-risk and low-risk patients for metastasis, be unambiguous in applicability and based on strong and reproducible prognostic factors for metastasis. Due to the pattern of dissemination in STS, with uncommon involvement of regional lymph nodes, the TNM-system is not applicable in prognosticating STS without overt metastasis at diagnosis. Local recurrence as a marker of an aggressive phenotype, or as a causative risk factor in itself for metastasis, has been the subject for extensive debate in STS. A review of this, still ongoing, issue is beyond the scope of this review, but suffice to say is that the development of a local recurrence after surgery with negative margins is associated with a high risk for metastatic disease in high-grade STS. This risk is particularly high if the local recurrence develops a short time (< 2 years) after the primary surgery.

### Malignancy grading

Determining histotype does for most STS not provide adequate information on which to base treatment decisions of neoadjuvant or adjuvant chemotherapy. Histologic classification is also subject to periodic variations due to changes in diagnostic methods and concepts of classification. Therefore, combinations of histopathologically determined specific factors have been combined into malignancy grading systems to improve prognostication. Over the years there have been many such systems in use, most based on assessment of histological

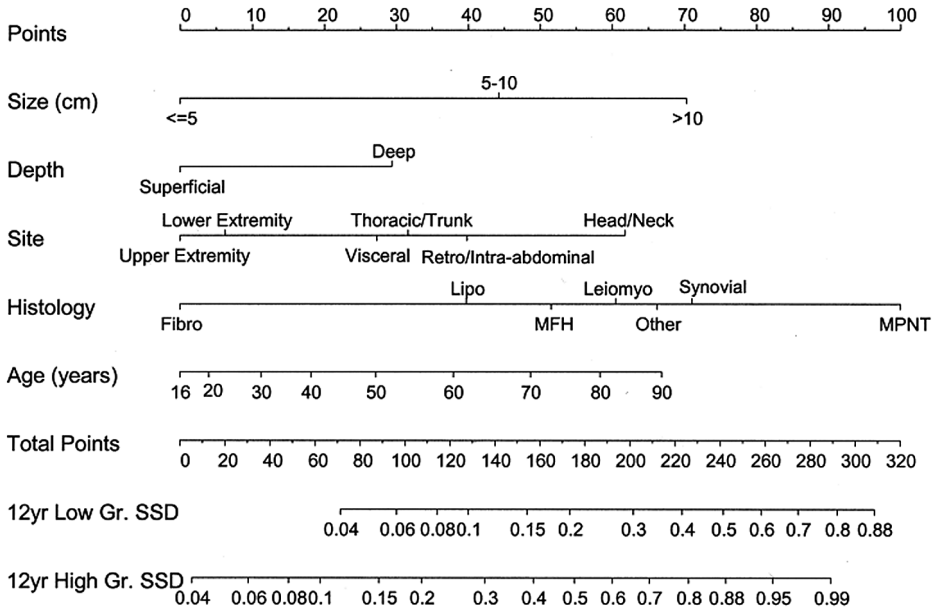
subtype, degree of differentiation, cellularity, cellular pleomorphism, mitotic count, and presence of tumor necrosis (Kilpatrick 1999). Subsequently, two systems have come to prevail internationally. These are the III-tiered malignancy grading systems devised by the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) (Coindre 2006) and the National Cancer Institute (NCI) system (Costa 1990). However, in the Scandinavian countries Sweden, Norway and Finland a IV-tiered system is used (Markhede et al. 1982, Angervall et al. 1986, Meis-Kindblom et al. 1999), and Denmark uses a separate III-tiered system (Myhre-Jensen et al. 1983). This lack of agreement on a uniform malignancy grading system is, of course, a problem when comparing different tumor series. There is also no consensus as to the weights that should be attributed to the various components included in the grading systems. Furthermore, none of the common systems for malignancy grading includes presence of vascular invasion, which repeatedly has been shown to be one of the strongest prognostic factors for metastasis in STS (Trojani et al. 1984, Gustafson 1994, Mandard et al. 1989, Coindre et al. 2001, Gustafson et al. 2003, Engellau et al. 2005, 2007). The different systems of malignancy grading all identify about 10% of the tumors as of low-grade with low risk of metastasis (< 10%), and a large proportion of high-grade tumors which metastasize in about 60%, but almost half of the patients are classified in an intermediate group with a risk of metastasis of about 30%. The low-grade tumors are virtually never considered for systemic adjuvant therapy whereas the histologic intermediate-grade and high-grade tumors, comprising the large majority of STS, need to be considered for chemotherapy. For clinical purposes, these patients need to be classified further in categories of low-risk and high-risk tumors to avoid both over-treatment and omitting treatment of patients at true high risk of metastasis.

Although determining malignancy grade clearly improves prognostication compared to histologic classification, malignancy grade does not provide enough prognostic information for clinical treatment decisions.

## Current common prognostic systems in STS of the extremities and trunk wall

### *The nomogram*

A model for addressing the problem of clinical prognostication in STS has been developed at Memorial Sloan Kettering Cancer Center (MSKCC). Based on patients treated at their institution, a series of 2 327 patients for which clinicopathological factors, treatment related factors and follow-up had been prospectively entered into a database were used to construct a nomogram (Kattan et al. 2002). The nomogram included all sites of a STS, also head and neck, intra-thoracic, visceral, and retroperitoneal localizations and has henceforth been in use at MSKCC. It provides an estimate of projected risk of sarcoma-specific death, combining both the risk of death as a result of metastasis and the risk of treatment-related mortality. The nomogram can be used for patient counseling and determining whether adjuvant chemotherapy should be advocated, or argued against. The original nomogram has subsequently been validated and adapted for extremity STS in an independent series of 642 patients treated at the Instituto Nazionale per lo Studio e la Cura dei Tumori in Milano, Italy (Mariani et al. 2005, Figure 1). In this validation and adaptation, the III-tiered FNCLCC system for malignancy grading was used, instead of the II-tiered system proposed by Hajdu which was used in the original nomogram. Although providing a useful tool for assessment of sarcoma-related survival, the nomogram includes prognostic factors that could be questioned, and lacks other, strong prognostic factors. In population-based series age has not been found to be a prognostic factor (Gustafson 1994). Also tumor depth may be questioned as there is a strong correlation between tumor size and depth, and when tumor size and malignancy grade are accounted for, tumor depth loses its prognostic value (Rydholm and Gustafson 2003). One of the strongest prognostic factors, the abovementioned factor vascular invasion is not included in the set of parameters on which the nomogram is based. The nomogram does not categorize patients, and may therefore paradoxically be difficult to employ clinically. At what level of risk of metastasis is cytotoxic treatment warranted? A large proportion



**Instructions for Physician:** Locate the patient's tumor size on the Size axis. Draw a line straight upwards to the Points axis to determine how many points towards sarcoma-specific death the patient receives for his tumor size. Repeat this process for the other axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to either the Low Grade or High Grade axis to find the patient's probability of dying from sarcoma within 12 years assuming he or she does not die of another cause first.

**Instruction to Patient:** "If we had 100 patients exactly like you, we would expect between <predicted percentage from nomogram - 8%> and <predicted percentage + 8%> to die of sarcoma within 12 years if they did not die of another cause first, and death from sarcoma after 12 years is still possible."

Figure 1. Modified MSKCC Nomogram for postoperative prediction of sarcoma-specific survival in adult (>16 years) patients with localized soft tissue sarcoma of the extremities. From Mariani et al. 2005 (Reprint with permission from Wiley-Blackwell).

of patients with localized STS will be attributed an intermediate risk of metastasis, and given the modest gain of the chemotherapy used, patient counseling may thus still be difficult using the nomogram.

### The American AJCC/UICC system

The system, originally presented in 1977, classifies tumors based on the TNM concept. In soft tissue sarcoma, the classification takes into account histopathological malignancy grade dichotomized as low-grade or high-grade. If a III-tiered grading system is used grade 1 is low-grade and, grades 2–3 are denoted as high-grade, whereas in a IV-tiered grading system grades 1–2 are considered low-grade, and 3–4 high grade. The staging system also incorporates tumor size, tumor depth, and presence of positive regional lymph node(-s) or

distant metastasis. In the current 6<sup>th</sup> edition staging manual, this translates into 4 stages (Table 1) (Greene et al. 2002).

The patients that are commonly considered for adjuvant treatment are patients with stage II and stage III tumors. These comprise almost 88% in the series of 1097 patients from MSKCC on which the basis for staging of STS was based (Greene et al. 2002). In subsequently reported series the patients with the highest risk of metastasis (excluding stage IV tumors with overt metastases and dismal prognosis), stage III with histological high-grade, large (> 5 cm), and deep-seated tumors constitute almost 50% (Wunder et al. 2000). However, almost 50% of tumors are classified as stage II, with a risk of metastasis of about 30% and whether these patients should be candidates for adjuvant chemotherapy is unclear. Although in widespread use, there are obvi-

Table 1. Stage grouping in the AJCC/UICC staging system (6<sup>th</sup> ed.) for soft tissue sarcomas

Stage	Histologic grade	Primary tumor	Distant metastasis
Stage I. Localized low-grade tumors of any size or depth	G1–2	T1a, T1b, T2a, T2b	N0, M0
Stage II. Localized high-grade small or large superficial tumors, or small deep-seated tumors	G3–4	T1a, T1b, T2a	N0, M0
Stage III. Localized high-grade, large and deep-seated tumors	G3–4	T2b	N0, M0
Stage IV. Any metastasis	Any G Any G	Any T Any T	N1, M0 N0, M1

Histologic grade: G1 well differentiated, G2 moderately differentiated, G3 poorly differentiated and, G4 undifferentiated. Primary tumor: T1 5 cm or less in greatest dimension, T2 more than 5 cm. Tumor depth is denoted a for a superficial lesion that does not involve the superficial fascia or b for a tumor that is deep to, or involves, the superficial fascia.

ous shortcomings in the AJCC system for staging STS due to the fact that several known strong prognostic factors for a highly malignant phenotype are not incorporated into the system. The inclusion of nodal involvement has also been questioned as it is a vary rare manifestation in most STS, reported to occur in less than 5% of patients during their course of disease (Behranwala et al. 2004, Fong et al. 1993). Although nodal involvement at diagnosis carries a considerable risk of also developing distant metastasis, the prognosis is better than overt distant metastasis at the time of diagnosis (Behranwala et al. 2004).

An assessment of possible improvements to the current 6<sup>th</sup> edition of the AJCC staging system has recently been demonstrated in a large series from University of Texas MD Anderson Cancer Center. In this series of 1091 patients, clear improvements to the AJCC staging system could be demonstrated if further known prognostic factors were incorporated. These included age, primary site, histologic subtype, and surgical margin status (Lahat et al. 2008). It remains to be seen to what extent the AJCC staging system will be modified in the forthcoming 7<sup>th</sup> edition expected to be introduced during 2009.

### *Prognostic systems—the Scandinavian experience*

In the realm of the Scandinavian Sarcoma Group (SSG), composed of centers where most of Scandinavian sarcoma patients are treated, there have been a longstanding interest in prognostic factors

for metastasis in STS. Much of the understanding thus acquired has come from collaborative studies on population-based tumor series. Already in 1983 the benefits of a centralized management of soft-tissue tumors and soft tissue sarcomas was demonstrated (Rydholm 1983). In this work, the importance of adequate surgical margins was also shown and an algorithm for management of soft-tissue lesions suggested. This has henceforth been adopted by virtually all sarcoma centers in the SSG. Also prediction of survival was assessed; in a series of STS of extremity and trunk wall the following risk factors and their weights (coefficient of the survival function) were identified: grade IV (weight 1.78), grade III (1.0), tumor pain (0.94), male sex (0.86), age > 50 years (0.86), size < 6 cm (0.84), marginal surgery (0.77) extracompartmental site (0.66). The sum of the weights for a specific patient determined the survival probability which could be easily found in a diagram: a sum > 6 implied almost 100% mortality, 3 or lower was associated with 80% survival. This system for prognostication is similar to the Nomogram used by the MSKCC.

In 1987 Rösser et al. explored the prognostic factors for metastasis in a population-based series of 237 patients with STS of the extremities and trunk wall. For high-grade tumors the strongest independent prognostic factors were found to be malignancy grade IV, tumor size > 10 cm, presence of tumor necrosis, and vascular invasion. Vascular invasion was defined as intratumoral invasion of vascular elements with tumor cells adherent to the

vessel wall or associated with fibrin, red or white blood cells. This definition has henceforth been employed. A prognostic system based on presence of these factors was shown to identify almost 50% of high-grade tumors with 3–4 factors present and a long-term tumor-related survival of < 0.25. Tumors with 0–1 factors present had a survival comparable to histological low-grade tumors (Rööser 1987).

In 1989 it was again demonstrated that metastasis correlated with a high malignancy grade, presence of vascular invasion, large tumor size (> 10 cm), and male sex. The results were based on one of the first RCT's of adjuvant doxorubicin in STS, the SSG I trial which recruited 240 patients from 1981–1986 (Alvegård et al. 1989).

These findings were further explored in a population-based series of 508 histologically mixed soft tissue sarcomas of the extremities and trunk wall. In this series the prognostic factors vascular invasion, presence of tumor necrosis, and tumor size > 10 cm were identified as the strongest factors predicting metastasis (Gustafson 1994). Malignancy grade lost its prognostic value in multivariate analysis when presence of vascular invasion and tumor necrosis were adjusted for, which accounts for the considerable importance these factors have been attributed in subsequent prognostic systems implemented by the SSG. Based on the results in the latter series a prognostic system was suggested that included tumor Size, vascular Invasion, and presence of tumor Necrosis, the SIN-system (Gustafson 1994). In this system patients were categorized as low-risk if 0–1 of the abovementioned factors were present, and high-risk with 2–3 factors. In the original series, low-risk tumors constituted two-thirds of the patients and had a 5-year metastasis-free survival rate of 0.8. The one-third of the patients which were classified as high-risk tumors had a corresponding 5-year metastasis-free survival of 0.3. The system has been prospectively implemented in a prospective non-randomized adjuvant treatment protocol, the SSG XIII protocol, in which in adjunction to local treatment recommendations high-risk patients were treated with doxorubicin and ifosfamide. The results in the SSG XIII compare favorably with previous trials which support the selection of prognostic factors on which patient accrual was based.

The reproducibility of the SIN-system was demonstrated in a bi-institutional study of 200 STS analyzed in Lund and Institut Bergonié. In this study, the strong importance of vascular invasion, size, and necrosis was again shown, and also that the extent of necrosis had no bearing on the impact of necrosis as a prognostic factor. The SIN-system also favorably compared with the AJCC/UICC 5<sup>th</sup> edition staging system (Gustafson et al. 2003).

Clinically applied there were, however, drawbacks with the SIN-system. Vascular invasion is not included into any of the systems of malignancy grading. This, and the fact that vascular invasion may be difficult to detect if not specifically sought for, probably explains the low rate of detection of vascular invasion which in turn led to a pivotal importance of tumor size when applying the SIN-system. Based on pathology peer-review data in the SSG tumor registry, a retrospective analysis of the probability of being classified as high-risk and thus be a candidate for adjuvant chemotherapy was calculated. This demonstrated that for tumors < 8 cm, the risk, or opportunity, to be classified as high-risk was 1%, whereas for tumors > 8 cm the corresponding likelihood for adjuvant treatment was 46% (unpublished data). It should be added, though, that vascular invasion was not a principal aim of the pathology peer-review, which focused on histological classification and attribution of malignancy grade.

In a study of 140 histologically mixed STS of the extremities or trunk wall on which whole-tumor sections had been established clinically useful prognostic factors were explored (Engellau et al. 2005). The whole-tumor section facilitates detection of necrosis and vascular invasion, and the peripheral tumor growth pattern (pushing or infiltrative) is also readily discernable. This series clearly supported the importance of the established prognostic factors tumor size and necrosis, and also vascular invasion which was demonstrated in one-third of the cases, of which more than two-thirds metastasized. The tumor growth pattern was also an independent strong prognostic factor for both local recurrence and metastasis. These findings were further explored in a retrospective study including two independent series of 434 patients with high-grade STS of the extremities or trunk wall treated in Sweden and Norway, and 175 patients treated

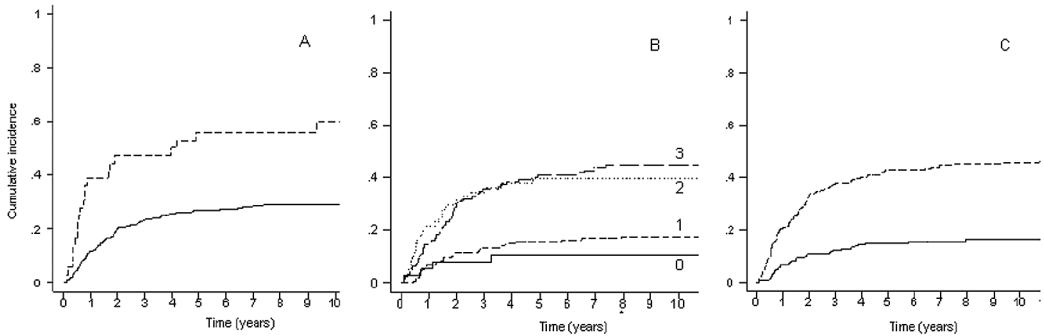


Figure 2. Cumulative incidence of metastasis in a series of 434 histological high-grade STS: (A) tumors with vascular invasion ( $n=36$ , dashed line) versus tumors without vascular invasion ( $n=398$ , solid line). (B) Cumulative incidence of metastasis in tumors without vascular invasion ( $n=398$ ) with presence of 0–3 risk factors (size  $>8$  cm, tumor necrosis, infiltrative peripheral tumor growth pattern), 3 factors ( $n=61$ ), 2 risk factors ( $n=130$ ), 1 risk factor ( $n=169$ ) and 0 risk factors ( $n=38$ ). (C) Cumulative incidence of metastasis in the 227 high-risk tumors with vascular invasion ( $n=36$ ) or presence of 2–3 risk factors ( $n=191$ ) versus the 207 low-risk tumors without vascular invasion and presence of 0–1 risk factors.

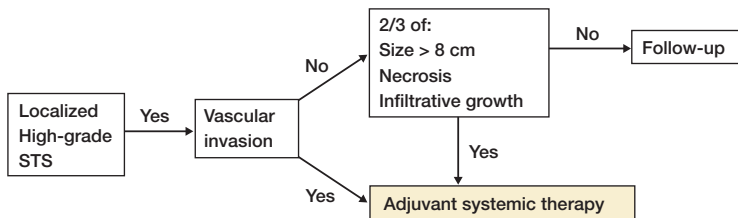


Figure 3. The SSG decision tree for classification of risk for metastasis in high-grade STS of the extremities or trunk wall based on the factors vascular invasion, tumor size, tumor necrosis and, peripheral tumor growth pattern.

at the sarcoma center in Lund and at the Norwegian Radium Hospital in Oslo, Norway (Engellau et al. 2007). In the larger series, the importance of the prognostic factors tumor size  $> 8$  cm, presence of tumor necrosis, vascular invasion, and infiltrative growth pattern was again demonstrated, and formed the basis for a novel prognostic system. This system of recursive partitioning, or a decision tree, was based on a step-wise attribution of risk where the strongest prognostic factor, presence of vascular invasion provided the primary fork (Figures 2 and 3). The prognostic system was independently validated in the series of 175 tumors, and its prognostic usefulness confirmed. A comparison was also made with the SIN-system and the American AJCC/UICC staging system 6<sup>th</sup> edition. Compared to the SIN-system, half of the tumors were discordantly classified and all of these were classified as low-risk in the SIN-system and high-risk in the decision tree and one-third of these

patients developed metastasis. In comparison with the AJCC/UICC staging system, there were one-third discordantly classified tumors. 11 tumors classified as high-risk in the AJCC/UICC system were attributed low-risk in the decision tree, and 1 metastasized, and 43 tumors were discordantly classified as low-risk in the AJCC/UICC system, and 23 metastasized. Of particular interest was the capacity of the decision tree to identify patients with high-grade malignant STS, but at low-risk for metastasis. These patients comprised almost half of the series, also including large and deep-seated tumors, and only 15% metastasized making them phenotypically comparable to histological low-grade STS (Engellau et al. 2007).

The decision tree thus validated is now implemented in Scandinavia in the SSG XX trial.

In summary, there has been a continuous interest of the SSG to improve patient selection for adjuvant chemotherapy. For this purpose the popula-

tion-based series made possible by the high degree of centralization of diagnosis and treatment of STS in Scandinavia provide excellent conditions. In repeated series the importance of tumor vascular invasion, presence of tumor necrosis, and tumor size has been demonstrated and recently also tumor growth pattern, forming the basis of prognostic systems for patients with STS of the extremities and trunk wall. Future work in this setting will undoubtedly enable histotype-specific prognostication with incorporation of important prognostic factors identified by molecular genetics of STS.

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# Treatment of soft tissue sarcoma of the extremity and trunk wall

## The Scandinavian Sarcoma Group perspective

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Since the founding of the Scandinavian Sarcoma Group (SSG) 30 years ago, development of an optimal management of soft tissue sarcomas (STS) has been an important task based on clinical studies, review based treatment recommendations and biological research. Surgery remains the mainstay of STS treatment and has been used as the sole treatment in most patients in Scandinavia. However, the use of adjuvant radiotherapy and chemotherapy has steadily increased. In this overview, we briefly describe our experiences with no ambitions of reviewing the entire field as such.

### Epidemiology and centralization

Soft tissue sarcomas account for less than 1% of all malignant tumors (Jemal et al. 2004, Olsson 2004). Physicians outside tumor treatment centers, who most often are first to see the patients, must know when to suspect a sarcoma and refer the patient to specialized centers with multidisciplinary sarcoma teams (Rydholm 1998). Evidence points to significant improvements in outcome for patients treated in specialist centers (Bauer et al. 2001)

A recent paper from SSG demonstrated that the referral pattern has shown a gradual increase of virgin STS referred to and treated at sarcoma centers; from 62% in the late 1980s to 77% in the last time period of 1998–2005 (Jebsen et al. 2008).

### Surgical treatment

During the early years of SSG, compartmental excisions according to Enneking et al. (1980) were attempted. However, improved referral patterns with more patients referred to tumor centers before surgery (biopsy or excision), now most often makes it possible to avoid the loss of function seen with compartmental excisions. Also, the routine use of CT/MRI in the preoperative planning facilitates safe resection margins with less loss of normal tissue. At present, the surgical goal is to obtain a wide margin; i.e. a cuff of healthy tissue surrounding the tumor. For strictly intramuscular tumors such a margin is often obtained by a myectomy.

The quality of the surgical margin obtained is still classified according to Enneking (1980) with some modifications. It is done in cooperation between the surgeon and the pathologist. An intralesional margin is recorded when the plane of excision, in any part of the tumor, passes through the tumor, leaving microscopic or macroscopic tumor tissue behind. The intralesional margin is categorized into two types depending on whether macroscopic tumor tissue remains or not. A marginal margin is recorded when the plane of excision passes outside the tumor, but in any part too close to the tumor to merit for a wide margin. With another terminology an intralesional margin (both types) reflects a positive margin, whereas a marginal margin corresponds to a negative margin.

Table 1. Local recurrence rates, wide surgical margin and use of radiotherapy in three treatment time periods

Diagnose year	1986–1991	1992–1997	1998–2005	P-value
Local recurrence rate (%)	27	16	15	< 0.001
Wide or compartmental surgical margin (%)	57	61	52	0.02
Adjuvant radiotherapy (%)	28	36	53	< 0.001

A wide margin is recorded when the excised tumor is surrounded all around by a cuff of healthy tissue or uninvolved fascia. The necessary thickness of this cuff to merit for a wide margin has been discussed during the years. In the latest soft tissue sarcoma protocol (SSG XX – activated 2007, see [www.ssg-org.net](http://www.ssg-org.net)) a cuff of fatty or muscular or loose areolar tissue must be minimum 10 mm in a formalin fixed specimen to qualify for a wide margin. Unengaged fascia, even if close to the tumor, is also sufficient for a wide margin. The margin obtained by myectomy is regarded as a subtype of the wide margin and has been applied for strictly intramuscular lesions (not subjected to open biopsy) when the involved muscle, from origin to insertion, is completely removed (Rydholm & Rösser 1987).

To examine whether classification of the surgical margin obtained at different institutions adhered to SSG guidelines, a random sample, comprising one quarter of patients included in a recent study of radiotherapy effects, were evaluated (Jebsen et al. 2008). A panel of Scandinavian sarcoma surgeons independently scrutinized the surgical and pathology reports. The few discrepancies in the individual classifications of surgeons in this panel were solved by consensus. The panel disagreed with the original margin assessment in 6% of cases. In 4% of all cases this reclassification changed from wide to marginal /intralesional or vice versa. Considering the element of judgment inherent in all margin assessment, we find this validity and reliability acceptable for using the Scandinavian Sarcoma Group Register for studies of local tumor control.

Compiled since 1986, this Register contains data on more than 9000 sarcoma patients who had their definitive treatment of the primary tumor at a sarcoma center in Scandinavia. The surgical margins were wide in 76% of subcutaneous lesions, and wide in 58% of deep-seated lesions. The amputation rate was 7% and has been declining. The rate

of wide margins obtained is lower than sometimes reported in international sarcoma series, but the risk of local recurrence (Table 1) is, however, similar (Jebsen et al. 2008). This may imply that our definition/classification of surgical margins could be somewhat more rigorous than that applied by other sarcoma centers.

When SSG was established in 1979, surgery with a wide margin was considered sufficient treatment of STS, and radiotherapy was used only for tumors which had been resected with an intralesional or marginal margin. In a series of STS of the extremities and trunk wall from the SSG register it was found that a wide surgical margin in high-grade deep STS was associated with a 25% risk of local relapse (Trovik et al. 2001a). This has influenced the radiotherapy practice in SSG, as described below.

## Radiotherapy

A high malignancy grade and the quality of the surgical margins are the two most important risk factors for a local recurrence (Gustafson et al. 1994, Eilber et al. 2003, Zagars et al. 2003, Pisters et al. 2007). The impact of radiotherapy on improved local control of STS in conjunction with surgery has been demonstrated in several prospective randomized trials (Harrison et al. 1993, Pisters et al. 1994, 1996, Yang et al. 1998), as well as in retrospective reviews (Lindberg et al. 1981, Suit and Spiro 1994, Wilson et al. 1994, Trovik et al. 2001a). This effect is mainly demonstrated after intralesional or marginal surgery, but improvement in local control after wide margin surgery has also been reported (Stotter et al. 1990, Pisters et al. 1996, Trovik et al. 2001b).

After wide and marginal surgery for deep-sited tumors a dose of 50–60 Gy in conventional 2 Gy daily fractions is generally recommended as

well as following marginal surgery of superficial tumors. If macroscopic tumor tissue is left behind, doses above 60 Gy should be attempted (Zagars et al. 2003a, Pisters et al. 2007). The benefit of radiotherapy on low grade malignant sarcomas is still controversial (Pisters et al. 1996, Mollabashy et al. 2002, Strander et al. 2003, Jebsen et al. 2008).

The timing of radiotherapy varies between studies. In a prospective trial involving 94 patients randomized to preoperative radiotherapy with 50 Gy in 25 fractions versus 96 patients postoperatively given 66 Gy in 33 fractions a slightly better overall survival was demonstrated in the preoperative arm (O'Sullivan et al. 2002). A higher rate of wound complications was demonstrated in the preoperative arm after a median follow up of 3.3 years. However, no significant difference was demonstrated at 5 years follow up with recurrence free survival rates of 58 % and 59 % respectively, albeit with a slightly higher incidence of late radiation related complications in the latter arm (Davis et al. 2005).

With increasing use of adjuvant radiotherapy within SSG, the local 5-year local recurrence rates have decreased, despite similar distributions of surgical margins among patients receiving primary treatment at a sarcoma center (Jebsen et al. 2008). 1093 adult patients with extremity and trunk wall STS with a median follow up of 5 years, treated at 4 Scandinavian sarcoma centers during 1986–2005, were stratified according to the treatment period. The use of radiotherapy, with 77% of the patients given postoperative radiotherapy, increased from 28% to 53%. The 5-year local recurrence rate decreased from 27% to 15%, without any obvious change in the rate of wide surgical margins (Table 1). The positive impact of radiotherapy on local recurrence was also significant after a surgery with wide margin and also in low grade STS (Jebsen et al. 2008).

At present, SSG recommends that postoperative radiotherapy starts as soon as the wound has healed. To our knowledge, only one study has specifically studied this aspect and demonstrated an improved local recurrence-free survival rate in patients starting less than 4 months after surgery compared to those who started radiotherapy later (Schwartz et al. 2002). In the SSG study mentioned above (Jebsen et al. 2008) the median interval from surgery to start of radiotherapy was 7 weeks with

as many as 98 % starting within 4 months. However, no difference between the two groups in local recurrence rate was demonstrated.

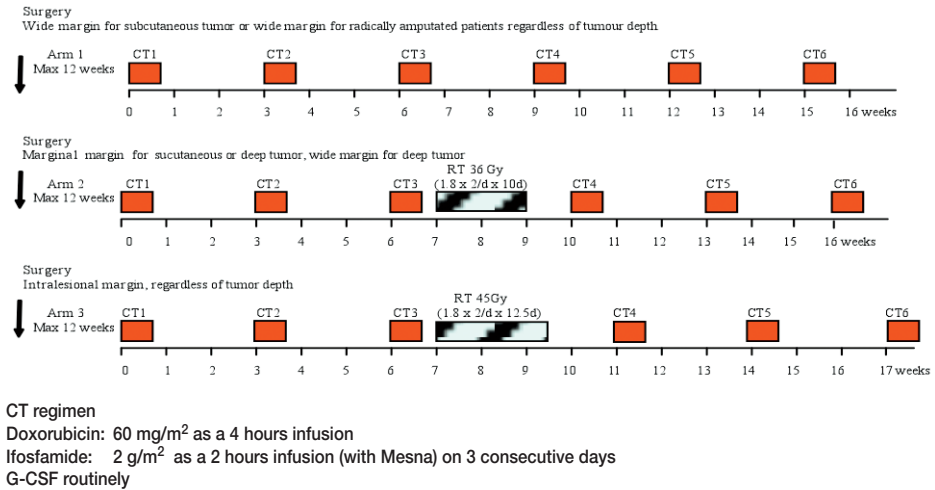
Both experimental and clinical evidence in several tumor types indicate that accelerated tumor cell proliferation occurs during prolonged radiotherapy regimens, or in treatment schedules containing breaks/split course regimes (Bese et al. 2007). There is clinically no clear evidence for this in sarcomas. However, the high expression of proliferation markers such as mitotic index and MIB-1 expression in STS indicate that prolonged radiotherapy treatment time, low doses per fraction or split-course treatment is less effective for local control also in STS (Møller Nilsen 2001). Within the two latest adjuvant studies in STS performed by SSG; SSG XIII (completed, but unpublished) and the ongoing SSG XX, hyperfractionated/accelerated radiotherapy (1.8 Gy twice 2 daily, 5 days a week) is given in between chemotherapy cycles in order to shorten the overall treatment period. The interval between the 2 daily fractions should be at least 6 hours to allow for repair of sub-lethal radiation damage in normal tissues. The preliminary survival data from SSG XIII are promising and with a low, acceptable rate of late radiation tissue sequelae. This has encouraged us to explore a modification of this multimodal treatment algorithm, within the framework of the current SSG XX. Both acute and late radiation toxicity will be prospectively studied based on the RTOG/EORTC scoring schemes. In this protocol, most patients will be treated postoperatively (Figure 1, group A). The protocol also includes a treatment group with preoperative chemo- and radiotherapy, aimed for patients in whom resection of the tumor carries an obvious risk for an intralesional surgical margin (Figure 1, group B). The radiotherapy schedule and doses are similar to SSG XIII. For further details see: [www.ssg-org.net](http://www.ssg-org.net) where the SSG XX protocol may be downloaded.

## Chemotherapy

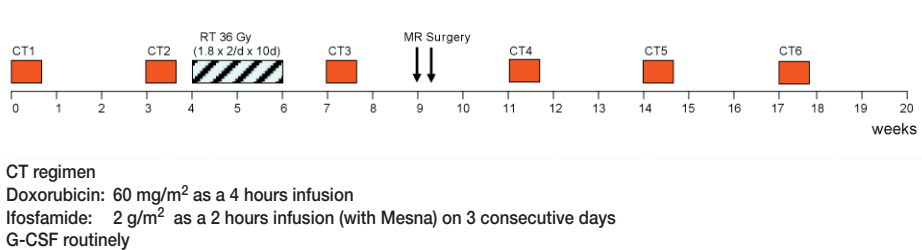
### *Adjuvant chemotherapy*

A considerable fraction of all STS patients will, however, develop metastatic disease, most commonly in the lungs, and with the highest risk within

Figure 1. The SSG XX protocol.



Group A: Adjuvant therapy arm for high-risk STS in extremities and trunk wall with primary surgery.



Group B: Preoperative and adjuvant treatment for STS when primary resection carries an obvious risk of an intralesional margin.

the first 2 years after surgery. STSs are in general considered to be moderately responsive to chemotherapy (Clark et al. 2005). The role of adjuvant chemotherapy has been an area of great interest for SSG since its inception and has been tested prospectively in two earlier adjuvant protocols, and with a third one on-going (SSG XX), activated in October 2007.

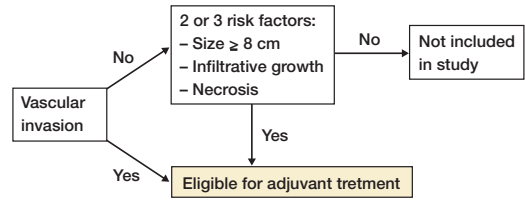
The first Scandinavian adjuvant chemotherapy study, carried out 1981–1986 (SSG I), was a randomized trial (Alvegård 1989). The study could not demonstrate any effect of adjuvant doxorubicin on metastasis-free- or overall survival in patients with high-grade malignant soft tissue sarcomas of the extremities and trunk wall. This study was included in a meta-analysis of results from 14 published randomized clinical trials in STS. Here, however, the use of adjuvant chemotherapy improved metastasis-free survival and local tumor

control, with a trend toward better overall survival (Tierney et al. 1995). A recent update of this meta-analysis, which included the addition of 4 new eligible trials, showed a statistical significance for overall survival ascribed to the use of adjuvant chemotherapy (Pervaiz et al. 2008). This new finding may be attributed to either the larger sample size resulting in narrower confidence interval, or to the evolution in the chemotherapeutic regimens used, involving dose intensification and the addition of ifosfamide to doxorubicin-based protocols. The EORTC-STBSG 62931 adjuvant trial, which was recently closed, was not included in this meta-analysis. Results from this trial failed to demonstrate a benefit in overall or relapse-free survival among 351 STS patients included (Woll et al. 2007).

The second adjuvant STS protocol by SSG (SSG XIII) was a phase II non-randomized trial for a subgroup of patients operated for soft tissue sar-

coma of the extremity and trunk wall with high risk to develop metastases. It was opened in 1998, and the prognostic SIN-system was used for selection of high risk patients (Gustafson 1994, Gustafson et al. 2003). The study included patients operated for STS grade III and IV, in a four-graded scale, and in addition displaying at least two of the following factors: tumor size  $\geq 8$  cm, microscopic and/or macroscopic necrosis, and vascular invasion. Patients above 70 years of age were not included. Chemotherapy consisted of 6 cycles of doxorubicin and ifosfamide with hyperfractionated/accelerated radiotherapy as described above interpolated between chemotherapy cycles 2 and 3. The preliminary survival data of SSG XIII is promising and also toxicity seems moderate. The protocol had recruited 114 eligible patients when it was replaced by the present SSG XX trial October 1th., 2007. The results of SSG XIII will be published when all analyses are finalized.

Based on the experience from SSG XIII, and improved knowledge of prognostic factors in STS, the SSG decided to initiate a new protocol for high-risk STS (SSG XX) with a modification of the current system of prognostication. During the period 1998-2005 1074 primary, high-grade STS of the extremities and the trunk wall have been registered in the SSG Central Register. In SSG XIII only 114 patients have been included since the protocol was launched in 1998. The identification of high risk patients eligible for adjuvant treatment may have been hampered by the difficulties of identifying vascular invasion in the tumor, one of the adverse prognostic factors in the SIN-system. Consistent with other investigators, SSG found in retrospective reviews a considerable variation in the frequency of which this prognostic factor was identified. When present it is a strong risk factor for metastases, but a non-finding may not be informative. Data from Engellau et al. (2007) supported the prognostic importance of the peripheral tumor growth pattern, infiltrating worse than pushing, which provided independent prognostic information in addition to tumor size, necrosis, and vascular invasion (Engellau et al. 2005). Based on the relative importance of the prognostic factors vascular invasion, size  $\geq 8$  cm, necrosis, and infiltrative growth pattern, a novel prognostic system for histologically high-grade malignant tumor was designed (Engellau et



- Vascular invasion alone is a powerful high-risk identifier
- Without vascular invasion still high risk if 2 or 3 risk factors

Figure 2. Decision algorithm for adjuvant treatment.

al. 2007). Tumors with vascular invasion were thus shown to entail a high risk. Following this algorithm, a further selection into the high risk-group is based on the presence of two of the 3 factors tumor size  $\geq 8$  cm, necrosis, and infiltrative tumor growth pattern (Figure 2).

This new prognostic algorithm is the basis for selection of eligible patients in the on-going adjuvant SSG XX protocol (Figure 2). There are biological research studies linked to the protocol with focus on genetic profiling, and also pharmacogenetic studies attempting to study the relationship between genetic variants and side-effects of treatment.

#### Treatment of metastatic disease

Most patients (80–90%) with STS have clinically localized disease at diagnosis. Nevertheless, STS has a propensity for early distant metastases despite local treatment with a curative intent (Clark et al. 2005). A subset of patients with operable distant metastases and chemosensitive disease may have a long disease-free interval, or might even be cured. The role of chemotherapy combined with metastasectomy has been uncertain in metastatic STS. In 1996 EORTC and SSG started a prospective trial (SSG XII) randomizing operable patients to excisions of lung metastases with or without aggressive chemotherapy, but this study was closed in 2001 due to low inclusion rate. However, promising results have been reported when effective chemotherapy was combined with complete surgical removal of all metastatic lesions. Good histopathological response to chemotherapy was associated with good prognosis and more relevant for outcome than a good radiological response (Sæter et al. 1995, Wiklund et al. 1997).

SSG X was a prospective phase II study designed to evaluate response and toxicity to ifosfamide in combination with continuous infusions of etoposide (VIG). In 26 patients treated with VIG + complete surgery of metastases the relapse free and overall survival at 2 years postsurgery were 39% and 74%, respectively (Sæter et al. 1997).

In 2004, SSG presented treatment recommendations that may guide therapy for metastatic STS patients (SSG XIX, see [www.ssg-org.net](http://www.ssg-org.net)). Because there are relatively few studies of sufficient standard (small studies, retrospective studies, limited randomized data, diversity of histological diagnosis etc) on treatment for these patients, it is difficult to draw conclusions from the literature on the role of various treatment regimens. Therefore definitions like "Levels of evidence" and "Grade of Recommendations" were used in order to show the degree of uncertainty of the current recommendations.

Proposals for decision of chemotherapy should be based on the consideration of curative or palliative treatment intent. In principle, curative intention implies that surgery of the metastases is possible. Further, choice of treatment should be planned individually according to age, performance status, symptoms, and co-morbidity that may influence tolerability. Tumor-related factors like size, histological type and grade, location of metastases, rate of tumor growth, and current status at the primary tumor site also have to be taken into account.

So far, doxorubicin and ifosfamide are the most effective combination regimen against STS with regard to response rates, but no clear advantage has been demonstrated in survival. For the anthracyclines and ifosfamide, a dose response has been documented in phase II studies (Reichardt et al. 1998, Patel et al. 2000). Since there are no randomized trials showing that dose-intensified chemotherapy regimens will result in a survival benefit, standard dose chemotherapy should be the preferred treatment in metastatic or unresectable STS. The combination of doxorubicin and ifosfamide (doxorubicin: 50 mg/m<sup>2</sup> + ifosfamide: 5 g/m<sup>2</sup>) with or without dacarbazine (250 mg/m<sup>2</sup>) are two options.

### **Isolated limb perfusion**

Hyperthermic isolated limb perfusion (ILP) with

tumor necrosis factor alpha (TNF-alpha) and melphalan has been adopted at 3 Scandinavian centers, Sahlgrenska sjukhuset (Gothenburg), Rigshospitalet (Copenhagen) and Radiumhospitalet (Oslo). TNF-alpha-ILP is an established treatment in large, bulky tumors in the limbs to avoid amputations (Eggermont et al. 2003). Further indications for this treatment modality in extremity located STS may be: attainment of primary tumor control in metastatic disease, recurrent tumor in an irradiated field, multiple tumors in the extremity, aggressive fibromatosis, and elderly patients where surgery is not feasible (Verhoef et al. 2007).

### **Regional hyperthermia**

Regional hyperthermia in combination with chemotherapy and radiotherapy (Issels 2008) has shown improved clinical outcome (both regarding local control and disease-free survival) in high-risk soft tissue sarcomas in an EORTC study (Issels et al. 2007). Haukeland University Hospital in Bergen contributed to this study and is so far the only center in Scandinavia with facilities and experience with this treatment modality in bone and soft tissue sarcoma. A phase II protocol is currently running.

### **Future prospects**

The new ESMO recommendations for diagnosis, treatment and follow-up of STS to which SSG has participated, define the current best standard of care (Casali et al 2008).

With the improvements of imaging, surgical techniques and increased use of adjuvant radiation therapy most patients with localized disease can be cured. However, a proportion of patients will develop metastatic disease, and there is need for new therapies to improve the long-term prognosis for such patients.

Trabectedin is a novel chemotherapeutic agent which has been shown to slow the growth and stabilize the tumor, especially in lipo- and leiomyosarcoma, as recently reviewed by Cassier (2008). It has been registered in Europe for use as second line treatment in metastatic soft tissue sarcomas. The combination of gemcitabine and docetaxel is also effective as second-line treatment in some

patients (Maki et al. 2007). Taxanes seems to be an option in angiosarcoma, at least as second line treatment. Presently, some SSG centers are participating in clinical trials of other drugs for STS such as tyrosine kinase inhibitors and monoclonal antibodies targeting the insulin-like growth factor-1 receptor (IGF-1R).

There seems to be a shift in the strategy from broad-spectrum cytotoxic chemotherapy to more molecular molecular-targeted therapies. Microarrays have been used to profile gene expression in several subtypes (Nilbert et al. 2004). This information might be used to develop new targeted therapies that later may be integrated into standard treatment such as has been the case for gastrointestinal stromal cell sarcoma. Moreover, there is need for broad international collaboration in accruing sufficient numbers of patients into clinical studies given the rarity of sarcoma. SSG has on several occasions shown a positive attitude to join relevant intergroup studies.

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# Scandinavian experience in classical osteosarcoma

## Results of the SSG XIV protocol

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**Background and purpose** The Scandinavian Sarcoma Group (SSG) XIV protocol was based upon the organisations experience from 3 previous osteosarcoma trials and was considered best standard of care for patients with extremity localised, non-metastatic osteosarcoma. We report the outcome of this protocol.

**Patients and methods** From March 2001 to April 2005, 63 patients recruited from 10 centres in Finland, Sweden and Norway were included in this analysis. Patients received pre-operative chemotherapy consisting of 2 cycles of paired methotrexate (12 g/m<sup>2</sup>), cisplatin (90 mg/m<sup>2</sup>) and doxorubicin (75 mg/m<sup>2</sup>). Good histological responders continued with 3 cycles postoperatively whilst poor responders were salvaged with the addition of 3 cycles of ifosfamide (10–12 g/m<sup>2</sup>). Outcome data was compared to previous SSG osteosarcoma trials.

**Results** With a median follow-up of 64 months for survivors, the projected metastasis-free and sarcoma-related survivals at 5 years were 69% and 77%, respectively. 84% of the patients were treated with limb salvage surgery (49 patients) or rotationplasty (4 patients). 3 toxic deaths (5%) were recorded, all related to acute chemotherapy toxicity. The 5-year metastasis-free survival of patients receiving salvage therapy was 47% compared to 89% for good histological responders that only received the 3 drug combination postoperatively.

**Interpretation** Outcome in the SSG XIV protocol compares favourably to previous SSG osteosarcoma

trials and other published trials. The addition of ifosfamide to poor responders as an add on treatment did not improve outcome for poor responders to a similar level as for good responders. In a multi-institutional setting limb salvage surgery can safely be used in more than 80% of the patients. ■

Current management of high-grade osteosarcoma comprises pre- and postoperative chemotherapy in combination with complete surgical removal of all tumour sites (Link et al. 1986, Fuchs et al. 1998, Bacci et al. 2000). With this strategy, long-term overall survival rates of 70% are reported for patients with non-metastatic, extremity localized (classical) osteosarcoma and more than 80% of the patients are managed by limb-salvage surgery (Bielack et al. 2002, Smeland et al. 2003, Ferrari et al. 2005). Preoperative chemotherapy offers an opportunity to modify postoperative chemotherapy according to histological response. Although never proven effective in a randomized trial, this principle has been used in several osteosarcoma trials (Rosen et al. 1979, Rosen et al. 1982, Winkler et al. 1988).

The active drugs in osteosarcoma are doxorubicin, methotrexate, cisplatin, and ifosfamide, but

there is no general agreement on their optimal combination (Fuchs et al. 1998, Ferrari et al. 2005, Meyers et al. 2005, Lewis et al. 2007). In the SSG VIII study all patients received a preoperative combination of methotrexate, doxorubicin, and cisplatin (Smeland et al. 2003). Poor responders were salvaged with an exchange to a combination of ifosfamide/etoposide postoperatively. The overall results were good with 5-year metastasis-free and sarcoma-related survival of 63% and 74%, respectively. However, the ifosfamide/etoposide replacement combination resulted in a poor outcome of poor responders. In the recent Italian/Scandinavian ISG/SSG 1 protocol dose intensification by addition of high-dose ifosfamide up-front to all patients failed to improve outcome (Ferrari et al. 2005). In a previous trial from the Rizzoli institute addition of ifosfamide (9 g/m<sup>2</sup>) to poor responders resulted in a similar outcome for poor as for good responders and, this together with the COSS-86 study also using all 4 active drugs, represent the best survival data published (Bacci et al. 1993, Fuchs et al. 1998). Thus, based on SSG's own experience and that of other intergroups, the SSG XIV protocol was considered best standard therapy in classical osteosarcoma. All patients received a 3-drug combination of methotrexate, doxorubicin and cisplatin both pre- and postoperatively and poor histological responders were salvaged with the addition of high-dose ifosfamide.

## Patients and methods

### Patients

From March 2001 to April 2005, 71 patients with high-grade extremity localized osteosarcoma from 6 centres in Sweden, 3 centres in Norway and 2 centres in Finland, were treated according to the SSG XIV protocol. Eligibility criteria were age ≤ 40 years and no evident metastases by mandatory use of chest CT and whole body bone scan at presentation. The primary tumor was assessed by plain radiographs, technetium 99-MDP bone scan, CT scan and MRI of the entire bone involved. 8 patients were excluded due to metastatic disease (n=6), a revised diagnosis of clear cell sarcoma (n=1) or malignant fibrous histiocytoma (n=1) rendering 63 patients eligible for this analysis. The diagnosis of

osteosarcoma was confirmed by open biopsy in all cases. The SSG pathology panel reviewed all slides and agreed on diagnosis, subtype, and malignancy grade. The median age at diagnosis was 15 (8-39) years. 40 (64%) patients were male. Tumor localizations were femur (n=34), tibia (n=15), humerus (n=6), fibula (n=4), radius (n=2) and other (n=2).

### Chemotherapy

Chemotherapy consisted of 2 cycles of paired methotrexate (MTX), 12 g/m<sup>2</sup>, doxorubicin (ADM), 75 mg/m<sup>2</sup> and cisplatin (CDP), 90 mg/m<sup>2</sup> pre-operatively and 3 cycles post-operatively (Figure 1). Poor histological responders continued to receive 3 courses of ifosfamide (IFO), 10 g/m<sup>2</sup> as an add on treatment.

With good bone marrow tolerance the protocol allowed escalation of the IFO dose with 20% for the next course. MTX was administered in a 4-hour infusion with 11 doses of leucovorin (folinic acid) as rescue (8 mg/m<sup>2</sup>) every 6th hour, beginning 24 hours after starting the MTX infusion (Ferrari et al. 2005). CDP was delivered as a 48-hour continuous infusion intravenously and was followed by ADM given as a 4-hour continuous infusion. IFO, in combination with an equal amount of mesna, was delivered as continuous infusion at a dose of 2 g/m<sup>2</sup>/day for 5 consecutive days. Postoperative chemotherapy was scheduled to begin 7 days after surgery. All drugs were given as single agents per course.

Complete blood counts and renal and liver function were monitored before each chemotherapy administration. No dose reduction was allowed, and if the absolute granulocyte count was equal to or less than 1000/μL (500 for MTX cycles), and/or the platelet count was equal to or less than 100.000/μL (60.000 for MTX cycles), chemotherapy was delayed until recovery. After each cycle, the blood count was monitored twice weekly starting on day 7 from the beginning of the chemotherapy infusion. G-CSF support was given according to the ASCO guidelines (1994).

### Surgery and histological response assessment

The type of surgery was chosen depending on the size and the location of the tumor, neurovascular involvement and skeletal maturity. For limb salvage surgery, it was mandatory that the preoperative staging showed the possibility of achieving

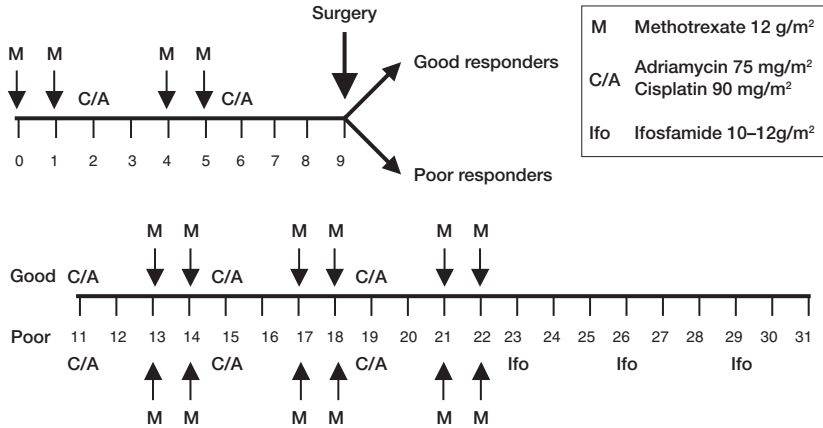


Figure 1. Treatment outline in SSG XIV protocol.

adequate surgical margins. In resected patients, the type of reconstruction was chosen according to tumor location and extension, patient age and preferences. After surgery, the surgical margins were assessed according to Enneking et al. (1980) as radical, wide, marginal or intralesional. The grading of histological response analysis was done with a two-grade scale. Good response was defined as < 10% of the examined tumor area revealing unquestionably viable tumor and no single area of unaffected viable tumor exceeding 2.5 mm in largest diameter. Poor response was defined as any of the two above criteria unfulfilled. Unaffected was defined as a morphologic appearance closely resembling that of the pretreatment biopsy and unquestionably viable tumor as various degrees of response, including decreased cellularity, and signs of maturation with bone and cartilage matrix production, but with remaining clearly viable tumor cells. The initial pathologic evaluation at each institution determined the postoperative chemotherapy. Sections from each patient were reviewed for histological response by the SSG reference pathology panel.

#### Response criteria and statistical analyses

Projected metastasis-free survival was calculated from the date of diagnosis until the date of distant metastases or last follow-up. Event-free survival was calculated from the date of diagnosis until the date of distant metastases, local recurrence, treatment-related death or last follow-up. Sarcoma-related survival was calculated from the

date of diagnosis until death from osteosarcoma, treatment-related causes or last follow-up. For statistical analyses SPSS for Windows (Release 15.0, SPSS Inc., Chicago, IL, USA) was used. The Kaplan Meier method was used for survival analysis and curves were compared by the log-rank test.

## Results

### Compliance

2 patients did not receive neoadjuvant chemotherapy. 1 was in need of prompt surgical treatment and the other had a preoperative diagnosis of chondrosarcoma, later revised to high-grade osteosarcoma. 1 patient was postoperatively treated according to a different chemotherapy protocol as a decision of the treating physician. 3 treatment-related deaths were recorded, 1 shortly after completion of preoperative chemotherapy, 1 during postoperative therapy and 1 during completion of chemotherapy. The median time from start of chemotherapy to surgery was 80 days which represents a median delay of 17 days to protocol. The median treatment duration was 219 days in good responders and 275 days in poor responders, representing median delays of 65 days for good responders and 67 days for poor responders. Data on chemotherapy compliance was available for 57 patients. 88% of the patients received all 5 courses of CDP/ADM of whom 75% were given with no dose reduction. 2 patients received only 2 courses, one due to early death and the other due to change in postoperative therapy. 5

patients received only 4 courses due to toxicity. 47 of the 63 patients received all 10 courses of MTX. No dose reduction was observed for MTX. Regarding IFO courses, 23 of the 26 patients received all 3 courses with a dose reduction for 12% of the patients. Except the 3 treatment-related deaths and 1 case of change in postoperative chemotherapy, 91% of the patients received 4 or more courses of CDP/ADM and 8 or more courses of MTX.

### **Toxicity**

Detailed toxicity data was available for 48 (75%) of the patients. 36% of CDP/ADM courses and 26% of the IFO courses were followed by grade IV leucopenia. 21% of the patients did not experience any episode of grade IV leucopenia. Regarding platelet toxicity, 28% of the CDP/ADM courses were followed by grade IV thrombocytopenia and 31% by platelet transfusion. For the IFO courses, only 1 of 81 recorded courses were followed by grade IV toxicity and no platelet transfusion was given. 9 patients (14%) experienced a mild to moderate renal impairment mainly after MTX administration. This caused changes in planned schedule for 1 patient. None of these patients required dialysis. We recorded 3 treatment related deaths all related to acute chemotherapy toxicity. 1 patient (boy, 8 years) developed neutropenic fever and septic shock after completion of preoperative therapy. 1 patient (good responder) developed typhlitis and septicemia after the first postoperative cycle of chemotherapy and 1 patient (poor responder) developed septic shock in relation to the last cycle of postoperative chemotherapy. In addition, 2 cases of life-threatening toxicity were observed. A male patient (age 21) stayed 10 days at the intensity care unit after completion of preoperative chemotherapy due to development of severe enterocolitis in combination with grade IV neutropenia and thrombocytopenia. The second case was a girl (age 15) that developed grade IV cardiotoxicity before the third course of IFO and was in need of prompt medical treatment. The cardiac function is not fully normalized more than 3 years from end of therapy and the patient is in need of permanent medical treatment.

### **Surgery and local control**

53 (84%) of the patients were treated with limb salvage surgery (n=49) or rotationplasty (n=4).

8 patients (13%) were amputated and 2 patients were not operated upon due to early progression or toxic death. 63% of the operated patients obtained wide or radical margins. 2 patients, both poor responders, developed local recurrence at 18 and 29 months from diagnosis. One had a primary wide and the other a marginal margin at surgery. 1 of these patients later developed distant metastases and died 30 months from diagnosis. The other is alive in second complete remission 64 months from diagnosis and 35 months from local recurrence. The 5-year projected local-recurrence free survival is 96% (95% CI, 91–100%).

### **Histological response and postoperative chemotherapy**

Histological response was documented in 59 patients. 2 patients were treated up-front with amputation. 1 patient died a toxic death before surgery and 1 patient was never operated upon due to early dissemination of disease. According to the assessment by the review pathologists, 27 (46%) obtained a good response. The review process changed the response assessment in 4 patients, in 3 from good to poor response and in 1 from poor to good response. Regarding postoperative chemotherapy for the 59 patients that received preoperative chemotherapy, information on postoperative chemotherapy is lost for 1 patient (poor responder). For the remaining 58, 1 good responder received postoperative chemotherapy according to another protocol as decided by the treating physician, and in 1 patient with poor response alpha-interferon was exchanged for IFO as salvage therapy. Thus, 4 patients with a definite evaluation of poor response did not receive IFO. 30 patients received unchanged MTX-CDP-DOX postoperatively and 26 patients received salvage therapy with addition of IFO according to protocol. In 5 of 26 patients the IFO dose was escalated 20% for the second and/or third cycle. No patient had a second escalation of the IFO dose.

### **Survival and postrelapse outcome**

With a median follow-up of 64 (16–85) months for survivors, 49 patients are alive and 46 patients are in complete remission (Figure 2). The projected sarcoma-related survival at 5 years is 77% (95% CI 65–89%). 40 patients (64%) are alive in first

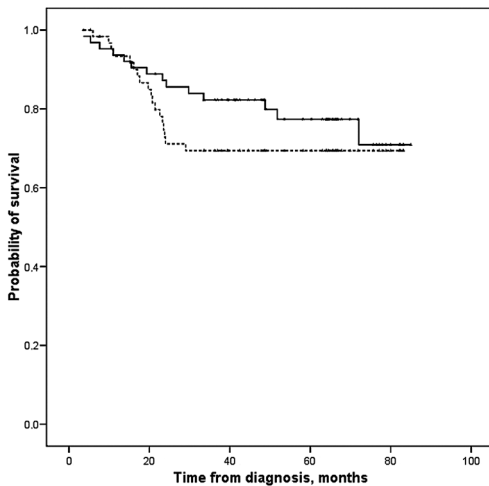


Figure 2. SSG XIV: Sarcoma-related (—) and metastasis-free (····) survival (n = 63).

complete remission. The projected metastasis-free survival at 5 years is 69% (95% CI 57–81%). The projected event-free survival at 5 years is 65% (95% CI 53–77%), including 1 local recurrence and 3 treatment related deaths in addition to 18 metastatic relapses (Table 1). 5-year metastasis-free survival by response (n=59) was 89% for good responders (n=27) and 53% (n=32) for poor responders (Log Rank p= 0.004). 5-year metastasis-free survival by postoperative chemotherapy (n= 56) was 89% (n=30) for patients receiving unchanged MTX-CDP-DOX and 47% (n=26) for patients receiving addition of IFO (Log Rank p=0.001). Metastasis-free survival by sex revealed no differences with 5-year survival of 68% for men and 73% for women (Log Rank p=0.7). Of the 18 patients that developed distant metastases, 14 had lung metastases, 2 bone metastases and

no information is available for 2 patients. Relapse treatment was not defined by protocol and varied between centres according to previous therapy; 14 patients were treated by second line surgery and surgery only was offered to 7 patients. Second line chemotherapy was given to 7 patients and 1 patient received interferon adjuvant to surgery. 13 patients obtained a second complete remission and 7 of those are alive, 12–65 months from relapse. All 5 patients that did not obtain a second complete remission are dead of osteosarcoma.

## Discussion

The survival data in the present analysis compares favorably with previous SSG studies and other osteosarcoma trials reported (Saeter et al. 1991, Fuchs et al. 1998, Smeland et al. 2003, Ferrari et al. 2005, Meyers et al. 2005). The 5-year sarcoma-related survival was 77% and metastasis-free survival 69% compared to 64% and 55% in the SSG II study, 74% and 63% in the SSG VIII study and 72% and 60% in the ISG/SSG 1 study, respectively (Table 1). Metastasis-free survival probably best reflects the efficacy of the chemotherapy regimen. Interestingly the metastasis-free survival is higher in SSG XIV using a 3-drug regimen for all patients with addition of IFO only for poor responders, compared to the recent ISG/SSG 1 trial using all 4 drugs up-front for all patients. This may reflect that not only cumulative doses but also dose-intensity of individual drugs are important for the effect (Bruland and Pihl 1997).

The percentage of patients that received limb salvage surgery or rotationplasty was at the same level as for the ISG/SSG 1 trial (Table 2). Thus, it seems

Table 1. Outcome in SSG osteosarcoma protocols

Study	No of patients	Time period	5-year survival (%)		
			sarcoma-related	metastasis-free	event-free
SSG II	97	1982–1989	64	55	54
SSG VIII	113	1989–1997	74	63	61
ISG/SSG 1	57	1997–2000	72	60	59
SSG XIV	63	2001–2005	77	69	65

Table 2. Surgery and local recurrence (LR) rate in SSG osteosarcoma protocols

Study	No of patients	Time period	Percentage of limb salvage surgery and rotationplasty	Percentage of LR
SSG II	97	1982–1989	23	5
SSG VIII	113	1989–1997	59	7
ISG/SSG 1	57	1997–2000	89	5
SSG XIV	63	2001–2005	84	3

appropriate to conclude that in a multi-institutional setting more than 80% of the patients can safely receive limb-salvage surgery or rotationplasty without compromising the risk of local recurrence when compared to previous trials in which amputation rate were much higher, as in SSG II (Table 2). The low number of local recurrences in SSG XIV may also have contributed to the favorable sarcoma-related survival rate since local recurrences are often followed by distant metastases and death from disease (Bacci et al. 2007). In SSG XIV, 2/63 patients had a local recurrence in contrast to 8/113 in SSG VIII. Another issue that may influence overall results is stage migration due to more consistent use of high-resolution CT chest scans. Patients with metastases at presentation have a worse prognosis and for the 6 patients not included in this analysis due to metastatic disease, but treated according to the protocol, 4 are dead of disease. Postrelapse therapy was not defined by the protocol, but the data reveals a substantial practise of metastasectomy. 13 of 18 relapsed patients obtained a second complete remission and of these 7 are alive. This is comparable to published results from other intergroups and SSG's own experience (Saeter et al. 1995, Ferrari et al. 2003, Kempf-Bielack et al. 2005). In SSG VIII, three quarters of the relapsed patients received second line surgery and the overall survival at 5 years from relapse was 21%, all in the group that obtained a second complete remission (Smeland et al. 2003)

The preoperative chemotherapy in this protocol was similar to SSG VIII. However, the percentage of good responders differs from 46% in SSG XIV to 58% in SSG VIII. This probably reflects the modification of the assessment criteria that was defined for this protocol. The median delay to surgery was similar in SSG XIV and SSG VIII with

17 and 20 days, respectively. Hence a difference in preoperative drug intensity cannot explain the difference in histological response. The difference in outcome between good and poor histological responders in the current report was 42%. Thus, the strategy to add IFO failed to improve prognosis for poor responders to the level of good responders. This emphasizes the importance to address the salvage question in a randomized trial, such as in the ongoing EURAMOS-1. The result from SSG XIV may reflect an underlying chemoresistance, including to IFO, but may also be influenced by the late introduction of IFO in this protocol. The reason for the chosen design was not to interfere with the dose intensity of the other drugs.

SSG has previously reported a sex dependent outcome in both the SSG II and the SSG VIII trials. In SSG XIV, however, there was no such difference in outcome between men and women. This is in accordance with the data in ISG/SSG 1 and published results from other groups. It probably reflects that data from the previous protocols are not due to a major underlying difference in tumor aggressiveness and/or chemosensitivity by sex (Saeter et al. 1991, Bielack et al. 2002, Smeland et al. 2003, Ferrari et al. 2005).

3 treatment related deaths occurred. In general, the reported percentage of treatment related death in SSG osteosarcoma trials is 1–3%; 3/113 in SSG VIII and 1/57 in ISG/SSG. The relatively high number of treatment related deaths in this trial, and all due to acute chemotherapy induced toxicity, emphasizes the importance of organizing a safe osteosarcoma care. One may speculate that the more frequent use of growth factor support does not reduce but rather shift the pattern of serious life-threatening toxicity. However, by Aug 2008, SSG has recruited 57 patients to the EURA-

MOS-1 study with a slightly more intensive chemotherapy regimen than SSG XIV and a similar use of growth factor support. So far no toxic death has been reported among SSG patients.

In conclusion, the outcome in the SSG XIV protocol compares favorably with both previous SSG and other reported osteosarcoma trials. However, the use of high-dose IFO as an add on treatment did not improve the outcome for poor responders to a similar level as for good responders. The salvage question has to be addressed in a randomized trial in order to demonstrate whether the addition of IFO to the 3-drug regimen of MTX, ADM, and CDP improves the prognosis or not. Current data shows that more than 80% of the patients in a multi-institutional setting can expect to be operated upon with limb salvage surgery with no increased risk of local recurrence.

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# The European postmarketing adult Osteosarcoma Surveillance Study: characteristics of patients

## A preliminary report

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**SUMMARY** The Scandinavian Sarcoma Group (SSG) registry participates in a multinational postmarketing drug surveillance study evaluating potential medication exposures (including teriparatide) in a population-based series of adult osteosarcoma cases. We present preliminary data from this study.

The SSG registry systematically identifies eligible cases in collaboration with regional and national cancer registries in Sweden, Norway, Denmark, Finland, and Iceland. All cases aged  $\geq 40$  years initially diagnosed in January 2004 or later with histologically confirmed osteosarcoma or 5 other prespecified types of bone sarcomas are eligible. Data were collected from the medical records.

This review includes all information abstracted to date from patient records of 49 of 85 cases diagnosed between January 2004 and September 2008 (estimated to be all reported adult cases). All patients were Caucasian, mean age 59 (41-88 years), the majority were men. The most prevalent morphology subtypes were osteosarcoma NOS and chondroblastic osteosarcoma. Leg bones were the most frequent tumor site. Potential risk factors for osteosarcoma included prior history of cancer (27%), radiation treatment (24%), or prior injury or infection at the site of the tumor (14%). Site of prior radiation treatment and osteosarcoma tumor matched for 7/9 cases. One prior history of Paget's disease was reported. Treatment with teriparatide before diagnosis had not been reported.

Data collected in this study present population based demographic and risk-factor data and are consistent

with prior research reporting a link between radiation site and tumor site, and a possible association between osteosarcoma and prior history of cancer, and prior injury or infection at the site of the tumor. ■

As an element of the post-approval surveillance program for teriparatide (Forsteo™), the European Agency for the Evaluation of Medicinal Products (EMA) requested a 10-year safety surveillance study to monitor for a trend signaling a possible association between teriparatide and adult osteosarcoma. Teriparatide is a biosynthetic human parathyroid hormone (PTH [1-34]) used for treatment of osteoporosis. In clinical studies, osteoporosis treated for up to 2 years with teriparatide demonstrated significantly increased bone mineral density with a decreased incidence of fractures, compared with the placebo group in clinical studies (Neer et al. 2001). As a part of the routine preclinical testing program, teriparatide was administered to rats in varying doses. In rats, teriparatide caused increases in bone mass and a dose-dependent increase in the incidence of osteosarcoma (Vahle et al. 2002). Subsequent rat studies targeted for the detection of osteosarcoma documented a "no-effect" dose (Vahle et al. 2004). In a long-term study in cynomolgus monkeys (spanning 18 months of treatment plus 3 years of follow up observation), no bone tumors were detected by radiographic or histologi-

cal evaluation in any monkey in the study (Vahle et al. 2008). Studies have shown that the rat skeleton is more sensitive to the pharmacological effects of PTH in formation of new bone and osteosarcoma than monkey or human skeletons (Miller 2008).

Due to the rare incidence of adult osteosarcoma and of the drug exposure (daily injections of teriparatide), traditional case control or cohort study designs were not feasible to address the potential association between osteosarcoma in humans and teriparatide exposure. A surveillance study design was chosen to monitor cases; if exposure rates exceeded the expected exposure level, a traditional study design could be implemented to measure statistical association between the rare exposure and the rare outcome.

Bone sarcomas are rare (0.2% of all tumors), and the United States (US) Surveillance, Epidemiology and End Results (SEER) program reports that osteosarcoma accounts for one third of all sarcomas of the bone (Dorfman and Czerniak 1995). The incidence of osteosarcoma in patients aged 40 years and older is estimated to be approximately 3 per million per year in Sweden (Socialstyrelsen 2007, Stark et al. 1990). The incidence of osteosarcoma has a bimodal distribution, with the first peak between ages 10 and 25 years and the second peak starts at 50 and rises up to 80 years of age (Dorfman and Czerniak 1995, Socialstyrelsen 2007, Stark et al. 1990, Unni and Dahlin 1996). Most data reveal a higher incidence of osteosarcoma among males, with a male-to-female ratio ranging from 1.3:1 to 1.6:1 (Stark et al. 1990, Dorfman and Czerniak 1995, Unni and Dahlin 1996).

Little is known about the etiology of osteosarcoma among adults (Unni and Dahlin 1996, International Agency for Research on Cancer [IARC] 2002). Potential risk factors for osteosarcoma include family history of osteosarcoma or retinoblastoma, Li-Fraumeni syndrome, or a prior history of radiation treatment, Paget's disease, injury or infection at the tumor site or metallic implant at tumor site (IARC 2002, Unni and Dahlin 1996). Among adults, Paget's disease and prior radiation treatment are more common among those aged over 40 years than among younger patients (Unni and Dahlin 1996). The male-to-female ratio changes to a predominance of females among those with prior exposure to radiation. Radiation therapy

accounts for 5 % of all osteosarcomas (Unni and Dahlin 1996) and 8% of the osteosarcoma cases aged of 40 years and above (Grimer et al. 2003). The postirradiation interval to osteosarcoma diagnosis among the Mayo cohort reported on by Unni and Dahlin (1996) ranged from 1 to 55 years with a median interval of 5 to 9 years. Nearly half of osteosarcomas occur in the knee region (Unni and Dahlin 1996). In the Mayo cohort (Unni and Dahlin 1996), among those aged 40 years and older, half of the cases occurred in long bones. Atypical sites are more common among older patients and include pelvis, sternum, clavicle, scapula, and spine, in descending order of frequency. Although nonclassical osteosarcoma represents 40% of the high-grade osteosarcoma population (Smeland et al. 2004), few of the osteosarcomas are extraskel-etal osteosarcomas (Unni and Dahlin 1996). Stark and colleagues (1990) reported that 6% of their Swedish cohort were diagnosed with soft tissue osteosarcomas. The Mayo cohort also reported that atypical sites were more common among those exposed to radiation therapy, sites such as clavicle, scapula, ribs, innominate bone, and sacrum being more common (Unni and Dahlin 1996).

This 10-year case-series surveillance study is a multinational study (comprised of the US and a European component) that includes data from 5 Nordic countries. The European Osteosarcoma Surveillance study identifies cases through the Scandinavian Sarcoma Group (SSG) registry—primarily reported to them from the population-based regional and national cancer registries in Sweden, Norway, Denmark, Finland, and Iceland—and collects data through review of medical records. Primarily, the study aims to identify newly diagnosed cases of osteosarcoma in men and women aged 40 years and older and to identify incident cases of adult osteosarcoma with a history of treatment with teriparatide, if any occur. The study also aims to systematically collect, for descriptive epidemiologic purposes, additional patient information including demographics, other drug exposures, relevant risk factors, and comorbid conditions in this large series of adults with osteosarcoma.

Nordic countries were selected for participation in the European Osteosarcoma Surveillance study because of their high incidence of osteoporosis and, therefore, the potential for higher teriparatide expo-

sure rates than other European countries. These countries also have high quality, population-based, national cancer registries with mandatory reporting of new tumor cases. In addition, the well-established SSG registry has the capability to coordinate the identification and data collection of cases.

The Osteosarcoma Surveillance Study is being conducted by RTI International (RTI), acting as the Coordinating Epidemiology Unit, and is sponsored by Eli Lilly and Company (a pharmaceutical company) with advice from the Osteosarcoma Surveillance Study Advisory Board, composed of members independent of RTI and Lilly.

### Objective

This paper provides a descriptive review of data from the ongoing surveillance study to characterize the environmental and treatment exposures in adult osteosarcoma patients according to tumor type. This review also examines demographic information, morphologic distribution of tumors by anatomical site, and the distribution of potential risk factors among adult osteosarcoma patients from the ongoing European Osteosarcoma Surveillance Study in the 5 Nordic countries.

## Methods

### Design

This case-series surveillance study collects information on demographics, cancer descriptors, brief medical history, and environmental and drug exposures in adult patients diagnosed with osteosarcoma and other prespecified tumors where site equals bone (i.e. “other bone sarcomas”).

The definition of a case is histologically confirmed disease based on International Classification of Diseases for Oncology, Third Edition, (ICD-O-3) codes. All types of osteosarcoma are eligible (ICD-O-3 codes 9180, 9181, 9182, 9183, 9184, 9185, 9186, 9187, 9192, 9193, 9194, 9195). To ensure a broad-based review and to capture potentially misclassified cases of true osteosarcoma, data are also collected from patients diagnosed with five other prespecified tumors—sarcoma NOS (ICD-O-3 code 8800), spindle cell sarcoma (8801), fibrosarcoma NOS (8810), malignant fibrous histiocytoma (8830), and dedifferentiated chondrosarcoma

(9243)—where the primary site is bone. Descriptive analyses characterize the demographic profile, tumor cell morphology, and topography among all reported cases and quantify the prevalence of potential risk factors among cases.

### Setting

The SSG registry acts as the European coordinator to identify and collect data from population-based regional and national cancer registries in Sweden, Norway, Denmark, Finland, and Iceland. These 5 Nordic countries comprise a total population of approximately 25 million. Cancer has been a reportable disease for 50 years in Scandinavia, and the national cancer registries have a long history of producing high quality cancer surveillance data.

### Data collection

Study cases are identified by the SSG registry. Once an incident case of osteosarcoma is diagnosed in the Nordic countries, the treating physician routinely reports it directly by case report to the regional or national cancer registry and also to the SSG registry. Upon notification of an eligible case, the SSG registry contacts the local investigator to obtain consent from the treating physician to contact the patient and then to obtain patient consent (when applicable). The local investigator abstracts data from the patient’s medical record and returns a completed data collection form to the SSG. Patient identifiers are removed, and a limited data form without any patient identifiers is sent to RTI for data entry and analysis. A summary of the study progress in Europe and the US is regularly reported to the EMEA and the US Food and Drug Administration.

In parallel with the US study, the European study collects data on the following dimensions: personal cancer information; demographics including race, age, country of residence and vital status; a brief medical history including cancer, osteoporosis, Paget’s disease, bone fracture, infection at tumor site, and history of medication use and treatments such as use of osteoporosis medications, and radiation and chemotherapy treatment; family medical history of osteosarcoma, selected cancers, and Paget’s disease; lifestyle habits such as smoking and alcohol use; and occupational and environmental exposures.

### **Ethics committee**

The Osteosarcoma Surveillance Study has been approved by the RTI Institutional Review Board (IRB) under a Federalwide Assurance in the US and applicable ethics committees' approvals in each Nordic country. Data collection was initiated on cases diagnosed January 1, 2004, and is currently planned to include incident cases diagnosed until December 31, 2013.

### **Analysis**

Descriptive analyses were conducted to summarize the main outcomes including demographic profile (age and age range, gender, race, and ethnicity), tumor topography and morphology distribution, prevalence of potential risk factors (lifestyle exposures, treatment, injury, and infection exposures, environmental exposures, and personal and family health history), and matching of prior radiation treatment site and tumor site.

### **Results**

Between January 1, 2004, and September 30, 2008, 85 cases (61 osteosarcoma and 24 other bone sarcomas) were identified by the SSG. Sweden reported most of the cases, as expected, due to larger population size and the use of rapid case reporting by the Swedish cancer registries. Iceland has reported no cases to date, well within statistical projections for Iceland due to the small population size of that country (Figure). At present, out of 85 identified cases, 49 abstraction forms have been completed and returned, 6 cases are pending abstraction, and 25 cases are pending patient consent. Only 5 patients or physicians (6% of reported cases) have denied consent to access the medical records. Table 1 summarizes the current status of the data collection process.

### **Demographic profile**

All cases with abstracted medical records were Caucasian, and the majority were men (59% of the osteosarcomas and 75% of the other bone sarcomas). The mean age at diagnosis of osteosarcoma was 59 (41–88) years. The other bone sarcoma cases had a mean age of 60 (42–86) years. Nearly half of the cases were deceased (21/49) when reported to the SSG registry.

### **Tumor morphology and topography**

Of the 49 abstracted cases, 31 patients were diagnosed with osteosarcoma NOS, 5 patients with chondroblastic osteosarcoma, and 1 with parosteal osteosarcoma (Table 2). In addition, data were collected on cases with the other bone sarcomas (sarcoma NOS, spindle cell sarcoma, fibrosarcoma NOS, malignant fibrous histiocytoma and dedifferentiated chondrosarcoma). Nearly one quarter (12/49) of all the abstracted cases were other bone sarcomas, with spindle cell sarcoma and malignant fibrous histiocytoma being most common.

The primary tumor site demonstrated great variability between cases, but was most prevalent in the lower part of the body, with more than half of the cases occurring in the legs and pelvic region.

### **Personal and family medical history**

One fourth of the cases (10/37) had a history of any other cancer prior to the osteosarcoma diagnosis. Prior to the diagnosis, 5 cases had a history of some kind of injury or infection at the site of the osteosarcoma (Table 3). Among the osteosarcoma patients, 1 case had a family history of breast cancer and 1 case had a family history of leukemia. Among cases of the other bone sarcomas, 1 case had a family history of breast cancer. None of the cases had any family history of osteosarcoma, retinoblastoma, brain cancer, or Paget's disease.

### **Drug exposure**

History of osteoporosis and medication use was recorded, primarily to detect use of teriparatide. There were no reports of teriparatide use in any of the cases abstracted. Overall, the cases had a history of no or little use of medications related to osteoporosis before diagnosis of the tumor. Although 3 cases reported a history of osteoporosis, only one of these cases was actively treated with calcium and alendronate. Four out of a total of 18 women were treated with estrogens. Four of 49 cases have been continuously treated for at least 1 month with corticosteroids.

### **Treatment exposure**

9 of the 37 osteosarcoma cases and 1 case of the 12 other bone sarcomas had a history of radiation treatment before the osteosarcoma diagnosis. Six of the osteosarcoma cases and none of the other

## Sarcoma Registries Countries

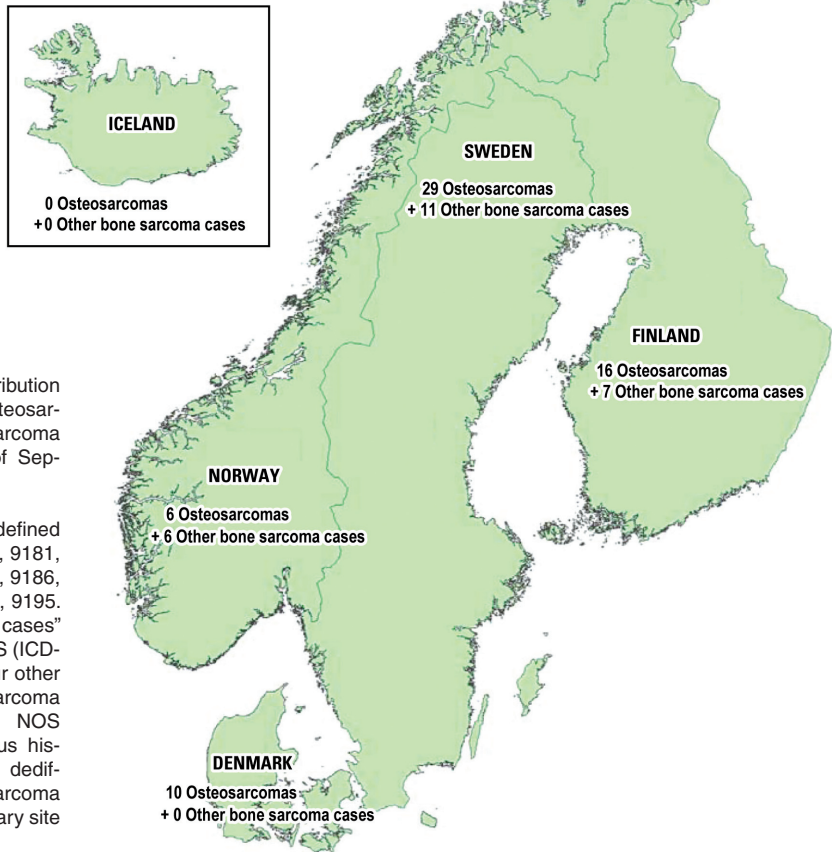


Figure. Geographic distribution of identified cases of osteosarcoma and other bone sarcoma cases by country as of September 2008.

Note: Osteosarcomas defined as ICD-O-3 codes 9180, 9181, 9182, 9183, 9184, 9185, 9186, 9187, 9192, 9193, 9194, 9195. "Other bone sarcoma cases" defined as sarcoma NOS (ICD-O-3 code 8800) and four other tumors—spindle cell sarcoma (8801), fibrosarcoma NOS (8810), malignant fibrous histiocytoma (8830), and dedifferentiated chondrosarcoma (9243)—where the primary site is bone.

Table 1. Case status summary for osteosarcoma and other bone sarcomas by patient consent and records abstracted

Data collection stage	Osteosarcoma	Other bone sarcomas <sup>a</sup>	Total
Reported cases	61	24	85 (100%)
Consented or consent waived (deceased)	39	16	55 (65%)
Cases pending consent	18	7	25 (29%)
Physician or patient refused consent	4	1	5 (6%)
Records pending abstraction	2	4	6 (7%)
Records abstracted	37	12	49 (58%)

<sup>a</sup> Other bone sarcomas were sarcoma NOS (ICD code 8800), spindle cell sarcoma (8801), fibrosarcoma NOS (8810), malignant fibrous histiocytoma (8830), and dedifferentiated chondrosarcoma (9243) where the primary site is bone.

bone sarcomas were treated with chemotherapy. None of the cases received any radioactive iodine treatment.

Table 4 displays the individual characteristics of the cases that had been exposed to radiation. The site of prior radiation treatment and site of tumor matched for 7/9 osteosarcoma cases. Among the site-matched cases, the mean interval between radiation treatment and tumor diagnosis was 20 (7–36) years.

**Table 2. Tumor morphology by ICD-O-3 Code and tumor topography**

OCD-O-3 Code	Primary tumor site	n
<b>Osteosarcoma (n = 37)</b>		
9180/3 osteosarcoma NOS	all sites	31
	femur	6
	tibia	5
	pelvis	5
	mandible	3
	skull/facial bones	3
	lung	2
	abdomen	1
	breast	1
	humerus	1
	knee	1
	rib	1
	scapula	1
	vertebra	1
9181/3 chondroblastic osteosarcoma	all sites	5
	scapula	2
	clavicle	1
	foot	1
	pelvis	1
9192/3 parosteal osteosarcoma	femur	1
<b>Other bone sarcomas (n = 12)</b>		
8800/3 sarcoma NOS	sacrum	1
8801/3 spindle cell sarcoma	all sites	4
	pelvis	2
	humerus	1
8810/3 fibrosarcoma NOS	sacrum	1
	all sites	2
	foot	1
8830/3 malignant fibrous histiocytoma	pelvis	1
	all sites	4
	femur	2
9243/3 dedifferentiated chondrosarcoma	scapula	1
	skull/facial bones	1
	femur	1

Almost half of the cases were current or former smokers and/or consumed alcohol. Eight osteosarcoma cases (n=37) were current cigarette smoker and 11 additional cases had stopped smoking. 2 osteosarcoma cases (n=37) and 1 case with other bone sarcoma (n=12) had been exposed to petrochemicals in their occupation. 1 case had been exposed to pesticides, and no case had been exposed to nuclear power or nuclear waste.

**Table 3. Selected medical history among osteosarcoma cases and cases with other bone sarcomas**

Selected medical history	Osteosarcoma (n = 37)	Other bone sarcomas (n = 12)
Paget's disease	1	0
Any bone fracture	4	4
Injury/trauma/fracture to the bone; or infection of the bone at site of tumor prior to diagnosis	5	2
Knee/hip replacement, or other orthopedic implant	4	0
Ewing sarcoma	0	0
Li-Fraumeni syndrome	0	0
Prior history of cancer	10	2
Primary or secondary hyperparathyroidism	0	0

## Discussion and conclusion

Data collected in this ongoing surveillance study from a population-based case series provides information regarding characteristics of adult patients with osteosarcoma and other tumors where the primary site is bone. In addition to demographic information, the study examines morphology distribution by site and the distribution of potential risk factors among adult osteosarcoma patients. While the numbers are expected to be small, they do present a population-based view of these rare tumors in adults in the Nordic countries.

The average age of this cohort is younger than others in the literature, especially among the osteosarcoma patients, where 43% were aged 50 to 59 years. The majority of the cases were reported in long bones, but approximately a third were reported in the pelvic and craniofacial bones. Among the osteosarcoma cases, a positive history was reported for bone fractures, Paget's disease of bone, joint replacement, and infection or trauma at the site of the tumor prior to diagnosis, as well as a history of cancer resulting in prior radiation therapy. The results are consistent with those of Unni and Dahlin (1996) and Grimer and colleagues (2003), who reported an association between radiation site and tumor site, and an possible association between osteosarcoma and prior history of cancer, Paget's disease, and possibly of infection or injury at the site. The study has yet not identified any case with a history (or family

Table 4. Patients with history of radiation treatment (n = 10), by tumor type

Country and patient number	Number of individual treatments	Radiation site(s)	Tumor site <sup>a</sup>	Match of radiation and tumor site	Interval between radiation and tumor diagnosis in years
Osteosarcoma (n = 37)					
Finland 21050	30	Rib/breast/chest	9180/3 OS NOS - breast	Yes	8
Finland 21023	10	Rib/breast/chest	9181/3 chondroblastic OS - scapula	Yes	30
Norway 51016	25	Rib/breast/chest	9181/3 chondroblastic OS - scapula	Yes	22
Norway 51008	30	Skull/ facial bones	9180/3 OS NOS - skull/facial bones	Yes	7
Finland 21049	20	Skull/facial bones	9180/3 OS NOS - skull/facial bones	Yes	13
Sweden 11044	33	Head-neck	9180/3 OS NOS - mandible	Yes	36
Finland 21024	24	Pelvis/ abdomen	9180/3 OS NOS - pelvis	Yes	18
Sweden 11015	1	Arteriovenous malformation	9181/3 chondroblastic OS - foot	No	3
Finland 21052	6	Left orbit	9180/3 OS NOS - lung	No	52
Other bone sarcomas (n = 12)					
Sweden 11002	26	Skull/facial bones	8830/3 MFH - skull/facial bones	Yes	25

<sup>a</sup>OS – osteosarcoma; MFH – malignant fibrous histiocytoma

Note: All patients received external beam radiation; patient 21024 received additional implant radiation.

#### Participating investigators

Country	Investigator	Hospital
Denmark	Dr. Ole Steen Nielsen	Århus University hospital, Århus, Denmark
Finland	Dr. Carl Blomqvist	Helsinki University Central Hospital, Helsinki, Finland
Iceland	Dr. Oskar Johannsson	AMS Landspítali, Reykjavik, Iceland
Norway	Dr. Sigbjørn Smeland	Norska Radium Hospitalet, Oslo, Norway
Norway	Dr. Clement Trovik	Haukeland Hospital, Bergen Norway
Sweden	Dr. Thor Alvegård	Lund University Hospital, Lund, Sweden

history of) retinoblastoma or Li-Fraumeni syndrome, which are often referred to as risk factors for osteosarcoma.

Very little medication exposure was reported among this cohort. There were no reports of teriparatide exposure. This 10-year population-based surveillance study of adult osteosarcoma patients will continue to add to our body of knowledge concerning the epidemiology of adult osteosarcoma.

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# Treatment of localized Ewing sarcoma family of tumors

## The Scandinavian Sarcoma Group experience

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The Ewing sarcoma family of tumors (ESFT) consists of Ewing sarcoma, peripheral primitive neuroectodermal tumor (PNET) and malignant small cell tumor of the thoracopulmonary region (Askin tumor) (Khoury, 2008). SSG has conducted two trials in ESFT, SSG IV, SSG IX and in cooperation with the Italian Sarcoma Group ISG/SSG III (localized disease) and IV (metastatic disease).

### SSG IV

The SSG IV protocol for Ewing's sarcoma of bone, eligible for patients with localized and metastatic disease, recruited 52 patients in the period 1984 to 1990. Patients received five blocks of 12 week cycles of vincristine, methotrexate, doxorubicin, cyclofosfamide, bleomycin and dactinomycin. After two induction cycles, local treatment was performed (week 24), surgery and/or radiotherapy as daily fractions of 2 Gy to a total dose of 40 Gy or 60 Gy. Sixty Gy was delivered to patients receiving radiotherapy alone or after incomplete surgery (Alvegård et al. 1989, Nilbert et al. 1998). Local recurrence developed in 10 patients. Of the 47 patients with localized disease at presentation, 27 later developed metastases. With 10 year median follow-up time, the metastasis-free and sarcoma-related survival at 5 years was 43% and 46%, respectively (Nilbert et al. 1998).

### SSG IX

The high local recurrence rate in SSG IV (19%) compared to other studies (Jürgens et al. 1988, Burgert et al. 1990) lead to a changed strategy for local treatment in the following SSG IX protocol. That included earlier timing (week 9) and introduction of hyperfractionated and accelerated radiotherapy, 1.5 Gy twice daily. Based on the CESS 86 study, cyclofosfamide was replaced by ifosfamide (Jürgens et al. 1988) and cisplatin was introduced based on reported effects (Castello et al. 1988, Tursz et al. 1989). Thus, the chemotherapy regimen in SSG IX consisted of four cycles of a VAI (vincristine, adriamycin, ifosfamide) and PAI (cisplatin, adriamycin, ifosfamide) in combination. The treatment duration was scheduled to 35 weeks. SSG IX was open for all patients with Ewing's sarcoma, also extraosseous tumors. The aims of the study were to improve the sarcoma-related survival and local control rate at 5 years to 70% and 90%, respectively. In the period 1990–1999, 88 patients were recruited. The sarcoma-related and metastasis-free survival rates at 5 years for patients with localized disease were 70% and 58%, respectively. 9 patients (10%) developed local recurrence. Thus, the aims of the study were achieved (Table 1, Figure) (Elomaa et al. 2000). The improved local control probably reflects a combined effect of more and better surgery, earlier timing of local treat-

Table 1. Outcome in SSG's ESFT trials for localized disease

Study	No of patients with localized disease	Time period	5-year metastasis-free survival	5-year sarcoma-related survival
SSG IV	47	1984–1990	45	49
SSG IX	73	1990–1999	58	70
ISG/SSG III	56	1999–2006	91	87

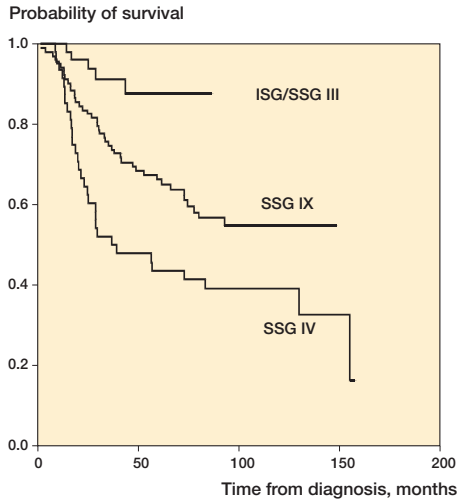


Figure. SSG's EFST trials. Sarcoma-related survival in localized disease.

ment and the use of hyper fractionated/accelerated radiotherapy. Multivariate analyses of prognostic factors for outcome revealed weight loss, presence of metastasis at presentation, inadequate surgical margins and poor histologic response to chemotherapy as independent adverse factors.

#### *The Italian/Scandinavian ISG/SSG III protocol*

The chemotherapy regimen in the ISG/SSG III protocol for non-metastatic disease was based upon the Rizzoli Institute REN-1 protocol utilizing a 4-drug regimen containing vincristine, doxorubicin, dactinomycin and cyclofosfamide (Bacci et al. 1998) and a later study demonstrating a benefit of adding etoposide, ifosfamide and dactinomycin to the VACA regimen (Bacci et al. 2002). Response to induction chemotherapy is a strong prognostic factor in ESFT (Picci et al. 1993, Picci et al. 1997, Elomaa et al. 2000, Paulussen et al. 2001). Accordingly, in the protocol, patients with poor response (histological or radiological) were salvaged by

high-dose chemotherapy (HDCT), busulfan 4mg/kg x 4 days and melfalan 140 mg/m<sup>2</sup>, with autologous stem cell support in an attempt to improve their prognosis.

The ISG/SSG III study was closed by Dec 2006 and 296 Scandinavian and Italian patients were enrolled. Preliminary data was reported at the 2007 ASCO meeting (Ferrari et al. 2007). 52% of the patients were poor responders and 86% of those received HDCT. With a median follow-up of 37 months the 5-year overall and event-free survival were 74% and 66%, respectively and importantly the event-free survival for poor responders who received HDCT (68%) and for the good responders (71%) were in the same range. No toxic deaths were recorded. The key conclusion was that HDCT was feasible and in a large non-randomized study seems to improve outcome for poor responders. An updated analysis of the Scandinavian patients (n=56), at a median follow-up time of 40 months, revealed a 5 year sarcoma-related survival of 88%, event-free survival of 87% and metastasis-free survival of 91% (Table 1). The sarcoma-related survival for good responders and poor responders receiving HDCT was 86% and 88%, respectively. Only one patient experienced local recurrence (after radiotherapy alone as local therapy). 23 patients (44%) received surgery, 20 (39%) combined therapy and 9 patients (17%) radiotherapy alone (Table 2). Two treatment-related deaths were observed among the Scandinavian patients, one patient died of septic emboli 17 months from diagnosis and one patient died of secondary leukemia 29 months from diagnosis.

The survival data for the Scandinavian patients in ISG/SSG III represents a substantial improvement compared to SSG IV and SSG IX (Figure 1) and also compares favorably with published results from other intergroups (Oberlin et al. 2001, Pau-

Table 2. Local treatment and local control rate in SSG's ESFT trials for localized disease

Study	No of patients	RT dose, Gy		Daily dose	Local treatment, %			Local recurrence rate
		RT alone	Postop RT		Surgery	Surgery & RT	RT alone	
SSG IV	47	60	40	2 Gy x 1	40	32	28	19%
SSG IX	73	60	42	1.5 Gy x 2	49 <sup>a</sup>	19 <sup>a</sup>	32 <sup>a</sup>	10%
ISG/SSG III	56	54	42	1.5 Gy x 2	44	39	17	1.8%

<sup>a</sup>including primary metastatic patients (n=88)

lussen et al. 2001, Grier et al. 2003). The outcome for poor responders was much better than reported from previous Scandinavian and Italian studies (Elomaa et al. 2000, Bacci et al. 2002). Thus, the data suggest a substantial benefit of adding HDCT to the group of poor responders in a setting in which about 50% of the patients were assessed as poor responders. Another factor that may have contributed to the good result in ISG/SSG III was the improved local therapy with a more combined approach of surgery and radiotherapy (Table 2). Only one patient has experienced local recurrence in ISG/SSG III in contrast to 10% in SSG IX and 19% in SSG IV. Regarding long-term effects after treatment for Ewing's sarcoma cautions should be addressed to the risk of developing secondary malignancies due to the high doses of alkylating agents and topoisomerase inhibitors, radiotherapy and in ISG/SSG III also high-dose therapy (Paulussen et al. 2001). Among SSG's study patients (n=176) four patients have so far developed secondary malignancies, acute myelogenous leukemia or radiation-induced osteosarcoma (one patient in ISG/SSG III, two patients in SSG IX and one in SSG IV).

### Future aspects and concluding remarks

No new drugs have been included in first line treatment for ESFT the last decades and currently none are tested out in randomized trials. In the ongoing studies, strategic questions are addressed including intensity of induction therapy and HDCT or not to poor responders or patients with metastatic disease. Recently, an improved effect of more condensed (every 2-weeks) chemotherapy compared to standard every 3-week has been reported (Womer et al.

2008). Currently the most promising new agent is the insulin-like growth factor antibody, anti-IGFR. IGFR signaling is important in the oncogene pathway in ESFT and mechanistic data is supported by clinical results from a phase I study (Le Roith et al. 2004, Olmos et al. 2008). The drug is currently tested out in several phase II studies including relapsed and/or refractory ESFT and a randomized trial for ESFT patients in first relapse is underway.

To conclude, conventional poly-agent chemotherapy including the six active drugs (doxorubicin, ifosfamide, cyclophosphamide, etoposide, dactinomycin and vincristine) in combination with surgery and/or radiotherapy is highly successful in standard-risk patients and long-term survival rates of more than 70 % are reported. The results from ISG/SSG III offering salvage therapy with HDCT suggests a benefit in poor responders but is not proven in a randomized trial or in a context with more intensified induction therapy as in EuroE. W.I.N.G.99. Novel drugs targeting the oncogene pathway are currently tested out with promising early results. In addition to optimize therapy with new drugs and compare treatment strategies the international community should aim to have a common language in ESFT as in osteosarcoma established by the EURAMOS-1 protocol. This will optimize the care and better standardize relapse treatment, but also facilitate ancillary biology projects.

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# Giant cell tumor of bone

## The Scandinavian Sarcoma Group experience

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The method of filling bone defects with cement after curettage of giant cell tumor (GCT) was introduced simultaneously in Sweden and in the Netherlands (Persson and Wouters 1976) (Figure 1).

Although curettage and cementation of GCTs has become widely accepted there remain several controversies as regards indications and long-term complications. Does the cement – especially the heat generated when setting – kill remaining tumor cells leading to lower recurrence rates? Should a fracture through the tumor lead to resection and endoprosthetic replacement instead of curettage and cementation? What are the results for treatment of recurrences after curettage and cementation? GCTs are almost always located juxtaarticularly in the epiphyseal bone causing destruction of the subchondral bone. Does the cement induce osteoarthritis due to heat or disturbed nutrition to the cartilage?

These issues have been addressed in a number of studies based on all GCT patients reported to the SSG Registry (Vult von Steyern et al. 2006, Kivioja et al. 2008) or on those treated in Lund and Stockholm (Dreinhöfer 1995, Vult von Steyern et al. 2007).

294 GCT patients from 13 Scandinavian hospitals were prospectively collected in the SSG Registry 1986–2003 (Kivioja et al. 2008). The overall local recurrence rate was 0.22. A resection with marginal or wide margin was performed in 92 patients leading to a recurrence rate of 0.12. 200 patients underwent intralesional curettage and these had a recurrence rate of 0.27. In this group, filling with cement was associated with a 0.20 recurrence,

compared to 0.56 after filling with bone graft or no filling at all.

We concluded that our recurrence rate was not as low as the best reported, i. e. around 10% from single institutions, but acceptable taking into account that 13 hospitals were involved and patients were accrued since 1986. We did not use high-speed burring during most of the time period that the operations were performed. The large difference in recurrence rates between cementation of the defect after curettage compared to bone grafting implies that the cement does indeed kill remaining tumor cells. This remains controversial since in other series even better results have been obtained without cement. We don't consider leaving the cavity without filling since we don't recognize any adverse effects of the cement. In addition, cement with contrast enables early detection of a local recurrence, as pointed out already by Persson and Wouters (1976).

In our series better local control rates were obtained by marginal or wide excision as opposed to curettage. Nevertheless we consider that excision is only indicated for expendable bones like the head of the fibula. For femur, tibia and humerus, resection and endoprosthetic replacement will indeed give low recurrence rates but involves the risk of considerably higher morbidity through implant wear and loosening. Such procedures should be reserved for recurrent cases and when the joint is destroyed (Figure 2).

In a further study based on the same patients, we analyzed 19 patients treated for local recurrence with a follow-up time of 4 years after the last recur-



Figure 1. 17-year-old girl with a large destruction of the tibial condyle. Cytology proved GCT.



After curettage and cementation reinforced with a metal plate. Immediate full weightbearing after surgery. Painless, normal function at latest follow-up, 1.5 years after surgery, no local recurrence.

rence (Vult von Steyern et al. 2006). 6 patients had resection but in 13 further curettage and cementation was performed, in 2 patients twice as they had another local recurrence. Hence the local recurrence rate was 0.15 after the repeat curettage. This means that if the recurrence rate is 0.15 after both primary and secondary curettage. Hence, 98% of GCT patients will have local control with 2 operations involving curettage and cementation.

Fracture at presentation may be considered an indication to opt for resection rather than curettage in GCT (Figure 2). We reviewed 15 patients with a pathological fracture at presentation of the primary GCT (Dreinhöfer et al. 1995). In 10 cases curettage and cementation was performed leading to good or excellent function and only 2 local recurrences were seen. We concluded that fracture does not preempt curettage and cementation but sometimes the reconstruction must be reinforced by plates or pins.

Finally we reviewed 9 patients 6 to 16 years after curettage and cementation for GCT around the

knee (Vult von Steyern et al. 2007). To assess the condition of the cartilage plain radiography, gadolinium-enhanced MRI and measurement of the cartilage oligomeric matrix protein was performed. Only 1 patient had signs of degenerative changes to the knee joint and had both intraarticular fracture and local recurrence in the medical history. All were physically active and the Lysholm knee score was excellent to good in all patients. We conclude that there is no evidence that the cement placed directly under the cartilage in GCT is harmful to the joint. There is no reason to replace cement for newer bone-filling agents, which are more expensive and not evaluated for long-term outcome and do not produce the heat which may prevent local recurrence.

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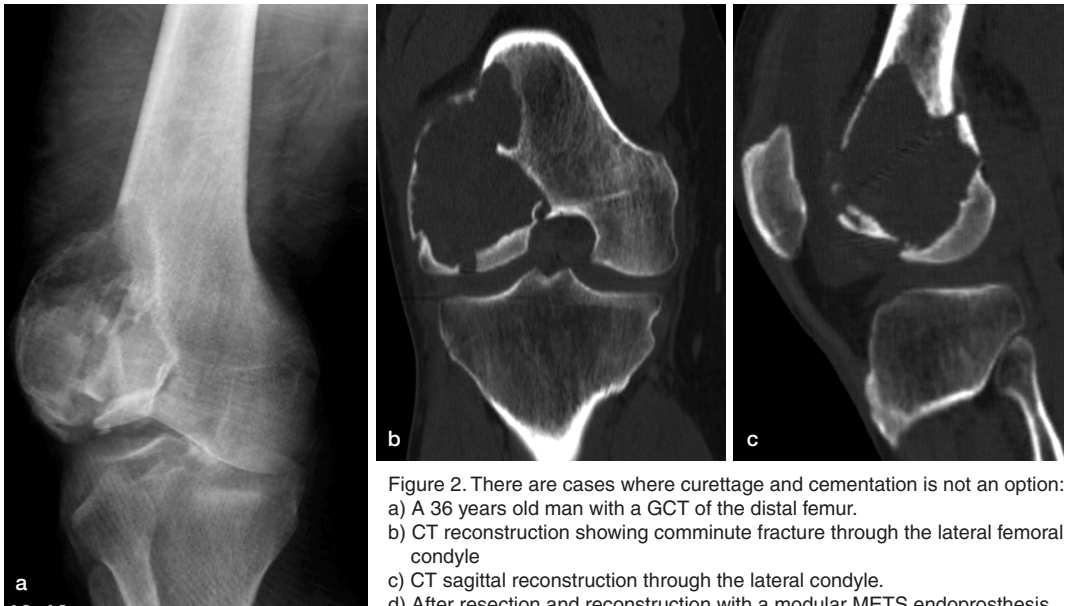


Figure 2. There are cases where curettage and cementation is not an option:  
 a) A 36 years old man with a GCT of the distal femur.  
 b) CT reconstruction showing comminute fracture through the lateral femoral condyle  
 c) CT sagittal reconstruction through the lateral condyle.  
 d) After resection and reconstruction with a modular METS endoprosthesis.



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# Chest wall chondrosarcoma

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Chondrosarcoma is the second most common primary bone malignancy after osteosarcoma. Chondrosarcoma has been reported in almost every bone in the body but the more common sites are pelvis, proximal and distal femur, proximal humerus and ribs. Approximately 10-15 % of the chondrosarcoma are located in the chest wall, which makes chondrosarcoma the most common primary malignant tumor of the chest wall (Burt et al. 1992).

There are limited number of studies of chondrosarcoma of the chest wall and most of them are case reports or single institutional experiences with small number of patients included (McAfee et al. 1985, Burt et al. 1992, Agrawal et al. 1995, Lioulis et al. 2003, Fong et al. 2004)

We have conducted a population based study on chest wall chondrosarcoma (Widhe and Bauer 2009. All 106 patients with chondrosarcoma of the chest wall in Sweden (1980-2002) were identified from the Scandinavian Sarcoma Group Register and the Swedish Cancer Register. The diagnoses were confirmed by a blinded review by the SSG pathology board. That study forms the basis for this presentation of chest wall chondrosarcoma in general.

## Symptoms and clinical picture

The most prominent symptom of chest wall chondrosarcoma is a bony-hard, palpable mass. Previous reports have shown that two thirds to three quarters of the patients had a palpable mass, often for a long period of time before diagnosis (McAfee et al. 1985, Burt et al. 1992). The mass slightly increased in size but remained often painless. In our patient series the duration of symptoms varied

from a couple of days to several years and occasionally even decades. 14% of the patients were diagnosed accidentally from a regular chest radiograph prescribed for other reasons. A minority of the patients, approximately 15%, related the onset of symptoms to a minor trauma.

## Diagnosis

Plain chest wall radiographs may detect a chest wall chondrosarcoma but other radiological examinations are more accurate. CT and/or MRI are now routine procedures before treatment of chest wall chondrosarcoma. With these two radiological modalities the tumor extension within the bone and soft tissues can be visualized for preoperative planning.

Several SSG reports have demonstrated the importance and accuracy of fine-needle aspiration cytology in the diagnosis of primary bone tumors (Kreicbergs et al. 1996, Willen 1997). Fine-needle analysis and/or core biopsies can be used to confirm the chondrosarcoma diagnosis before treatment. However, the pathological diagnosis is difficult and requires specialized pathologists with knowledge and experience of sarcoma. A false benign diagnosis by the pathologist might result in a long doctor's delay, in our series more than 1 year in several patients. A benign or inconclusive cytological analysis not only might prolong doctor's delay but also result in poor surgical margins; many patients at non-specialty centers were operated with shelling out for what was believed to be a benign lesion. This might be one reason why non-specialty centers obtained poor surgical margins (Figure).

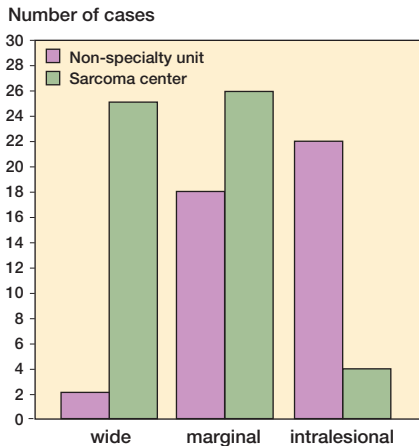


Figure. Surgical margins.

## Treatment

Radiotherapy and chemotherapy are of little help in chondrosarcomas (Bjornsson et al. 1998, Bruns et al. 2001). Surgery, with wide margins, still remains the only effective treatment. A wide excision not only reduces the risk of local recurrences but also results in better overall survival (Burt et al. 1992, Fong et al. 2004, Widhe and Bauer 2009). Postoperative radiotherapy have been used after narrow surgical margins, the benefit, however, remains unclear.

In Sweden there are specialized sarcoma centers diagnosing and treating sarcoma patients. This is strictly adhered to for patients with sarcomas of long bones. However, chest wall chondrosarcoma have also been treated by thoracic surgeons and general surgeons at non-specialty centers. In our study of chondrosarcoma of the chest wall, only half of the patients were operated at a sarcoma center.

In chest wall chondrosarcoma, a wide surgical margin requires intact pleura internally, and a transverse rib resection > 2 cm from the tumor at both sides. If the tumor penetrates into the subcutaneous tissue also the overlying subcutaneous tissue and often skin has to be removed. In Sweden, better surgical margins were achieved at SSG centers (Widhe and Bauer 2009) (Figure).

Most series show low or no perioperative mortality. A few patients in our series were not treated with a curative intent due to high age and poor

general condition. They experienced severe social distress as the tumor expanded to an enormous mass. A decision not to operate must be carefully considered given the poor outcome with nonoperative treatment.

## Local recurrence

Local recurrence after chondrosarcomas may develop after a long period of time - even more than 10 years after the primary operation. Surgical margin and histological grade are two independent factors related to development of local recurrence. In our study, the local recurrence rate after a wide surgical margin was 0.04 compared to 0.76 after an intralesional operation. The difference in surgical margin achieved between sarcoma centers and non-specialty centers explained why local recurrence rate was 57% (24/42) at non-specialty centers and 16% (9/55) at sarcoma centers. Previous studies of chest wall chondrosarcomas reported local recurrence rates of 0.3–0.5 (McAfee et al. 1985, Burt et al. 1992; Fong et al. 2004). Fiorenza et al. (2002) found that local recurrence in chondrosarcoma in general (all locations) does not influence survival. However, in our series of chest wall chondrosarcoma local recurrence *per se* was a risk factor for death even without metastasis. The progression of a local recurrence in the chest wall can result in an enormous mass leading to respiratory failure and death.

## Metastases

The metastasis rate in chest wall chondrosarcoma is reported to be 0.2–0.3 (McAfee et al. 1985, Burt et al. 1992). This is slightly less than in chondrosarcoma of the pelvis but more than in chondrosarcoma of the extremities. In our series, tumor size was one independent factor related to development of metastasis, others were histological grade and local recurrence. None of the patients with malignant grade 1 tumors developed metastasis, whereas 7/8 of grade 4 metastasized. Patients who developed metastases had a dismal prognosis. In selected cases surgical resections of metastases might be of benefit as a palliative treatment.

## Outcome

In a previous Scandinavian study by Soderstrom et al, the reported 10 year survival rate was 0.49 for patients with chest wall chondrosarcoma (Soderstrom et al. 2003). In our study, surgical margin was an independent factor in predicting outcome, where patients treated with a wide surgical margin had a 10-year survival rate of 0.92, with a marginal surgical margin 0.66 and with an intralesional margin 0.47. Patients treated at a sarcoma center had a 10-year survival rate of 0.75 compared to 0.59 for patients treated at non-specialty centers. The difference in outcome between sarcoma centers and non-specialty centers can be explained by the surgical margins obtained. At sarcoma centers 4/55 operations were intralesional compared to 22/42 at non-specialty centers.

In the previous Scandinavian study of chondrosarcoma no improvement in outcome over time was seen. In fact, the survival rates were higher in the first half of the study (1970–1980) compared to the last (1980–1990) (Soderstrom et al. 2003). Neither could we find any improvement of survival over time.

Patients with chest wall chondrosarcoma should be referred to sarcoma centers for diagnosis and treatment. Better referral practices would improve overall survival rates in chondrosarcoma.

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# The Scandinavian Sarcoma Group Skeletal Metastasis Registry

## Functional outcome and pain after surgery for bone metastases in the pelvis and extremities

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**Background** Few authors have investigated function and pain after surgical treatment of patients with bone metastases. In 1999 the Scandinavian Sarcoma Group (SSG) initiated the Skeletal Metastasis Registry as a multi-centric, prospective study to provide a scientific basis for recommendations of treatment.

**Patients and methods** We have analyzed function and pain in 530 patients (mean age 65 yr) operated on (599 operations) for non-spinal skeletal metastases at 9 SSG centres. 7 % were operated for more than 1 metastasis. Carcinoma of the breast, prostate, kidney, and lung were the dominating sites for primary tumors.

**Results** 25% of the patients died within 6 weeks after operation. 11 % of the patients had complications. 6 % had reoperation. In patients surviving more than 1 year the reoperation rate was 12 %. 92 % of the patients had no, light or moderate pain from metastasis at 6 weeks (first control) and 6 months follow-up. Patients using opioids were reduced from 40 % preoperative to 30 % at 6 months after surgery. In patients with metastases in pelvis or lower extremity 79 % were walking with or without crutches, 6 weeks and 88 %, 6 months after surgery. More patients with metastases in proximal femur were mobile at 6 weeks and 6 months when treated with prosthetic replacement compared to internal fixation.

**Interpretation** Palliative surgery for bone metastases improves function and reduce pain. Mobility is improved by surgery in patients with metastases in the

pelvis or lower extremity. Prosthetic replacement seems to do better than internal fixation for metastases in the proximal femur. We need to analyze function and pain earlier than 6 weeks postoperative to investigate the benefit of surgery in patients with short time survival. ■

Skeletal metastasis is a severe complication in malignant disease and often dramatically decrease quality of life by causing pain, pathologic fracture, hypercalcemia, anemia, and paraparesis. During recent years, more attention has been directed towards improved palliative care for cancer patients with skeletal metastases. Radiotherapy remains the mainstay for painful skeletal metastases (Sze et al. 2003), but hormone therapy, chemotherapy, and bisphosphonates (Diel et al. 2004, Pavlakis et al. 2005) are also important treatment modalities. The aim of surgical treatment is to restore function while alleviating pain. Immediate improvement in pain and functional status is particular important in patients with short life expectancy. Outcome after surgery for bone metastases have been reported (Yazawa et al. 1990, Allan et al. 1995, Vena et al. 1999, Kunisada et al. 2000, Wedin et al. 2001, Ward et al. 2003) but only few authors have reported prospective data (Clohisy et al. 2000, Marco et al. 2000, Cheng 2003, Talbot et al. 2005).

Most of the reported series have a small number of patients. SSG has since 1986 maintained a sarcoma registry and in 1999 the Skeletal Metastasis Registry was started with prospective registration of patients operated for skeletal metastases in the long bones and pelvis. In this paper we analyze function and pain in patients surgically treated in 9 SSG centres.

## Patients and methods

530 patients with bone metastases, myeloma or lymphoma in the extremities or pelvis were included (Table 1). They underwent a total of 599 operations and were followed prospectively. 7% of the patients were operated for more than 1 metastasis. There were 283 (53%) women and 247 (47%) men with a median age of 65 (19–96) years at the first operation. Carcinomas of the breast, prostate, kidney and lung were the most common sites of primary tumor. 71% of the patients had more than 1 known bone metastasis at the time of the first surgical procedure and 34% had known visceral metastases. The indication for surgery was a complete pathological fracture in 75%, impending fracture in 21%, and pain in 4%. Operations concerned femur in 66%, humerus in 19%, pelvis in 8%, tibia in 3%, and other locations in 4%. 226 (43%) patients were treated with prosthetic procedures and 274 (51%) with internal fixation. The rest were treated with other surgical procedures. 129 (24%) patients had received preoperative radiation of the operated bone metastasis.

The patients were registered at operation and followed at least 6 months or until death. Pain, use of analgesics, functional ability assessed with the Karnofsky score as good, moderate, or poor performance and mobility were registered preoperatively, at 6 weeks and at 6 months. In patients treated for more than 1 metastasis, survival was assessed from the time of the first operation. No outcome data concerning function and pain are available in patients who died before the 6 weeks follow-up. In case of a fracture the preoperative data were just before the fracture. Postoperative complications and reoperations were registered.

**Table 1. Clinical features of the 530 patients operated for bone metastases**

Factors	Number of patients	%
Sex		
Female	283	53
Male	247	47
Primary Tumor		
Breast	146	28
Prostate	83	16
Lung	63	12
Kidney	58	11
Myeloma	44	8
Lymphoma	17	3
Others	76	14
Unknown	43	8
Localization		
Femur	350	66
Humerus	101	19
Pelvis	44	8
Tibia	17	3
Others	18	4
Pathologic fracture		
Yes	399	75
No	131	25
Metastatic load		
Solitary skeletal	89	17
Multiple skeletal	374	71
Unknown skeletal	67	12
Visceral metastasis	181	34
No visceral metastasis	233	44
Unknown visceral	116	22
Operation method		
Internal fixation	274	51
Prosthesis	226	43
Other	30	6
Preoperative radiation		
Radiation	129	24
No radiation	384	73
Not known	17	3

## Results

25% of the patients died within the first 6 weeks after operation and 55% within the first 6 months. The 1-year survival rate, estimated with the Kaplan-Meier method, was 0.4.

Of the 411 patients treated for bone metastases in the pelvis or lower extremity, 61% were walking, with or without crutches, before surgery compared to 79% of the surviving patients at 6 weeks and 87% at 6 months after the operation (Table 2). 9% of the patients were confined to bed at 6 weeks and 5% at 6 months. In patients with a fracture, 75% were walking at 6 weeks and 84% at 6 months. In patients with metastases in the proximal femur 65% walked preoperatively. After treatment

**Table 2. Mobility in 411 patients operated for bone metastases in pelvis or lower extremity and the surviving patients at 6 weeks and 6 months**

Mobility	n	With or without crutches	Wheel-chair or confined to bed	Not known
Preoperative <sup>a</sup>	411	249 ( 61%)	84 ( 20%)	78 ( 19%)
6 weeks	307	242 ( 79%)	53 ( 17%)	12 ( 4%)
6 months	181	158 ( 87%)	19 ( 11%)	4 ( 2%)

<sup>a</sup> Preoperative mobility is just before fracture

**Table 3. Mobility in 189 patients operated for bone metastases in proximal femur with prosthesis or internal fixation**

Mobility	n	With or without crutches	Wheel-chair or confined to bed	Not known
Preoperative <sup>a</sup>	189	123 ( 65%)	34 ( 18%)	32 (17%)
6 weeks				
Internal fixation	35	24 ( 68%)	9 ( 26%)	2 ( 6%)
Prosthesis	107	89 ( 83%)	16 ( 15%)	2 ( 2%)
6 months				
Internal fixation	20	16 ( 80%)	3 ( 15%)	1 ( 5%)
Prosthesis	61	55 ( 90%)	4 ( 7%)	2 ( 3%)

<sup>a</sup> Preoperative mobility is just before fracture

**Table 4. Pain and use of analgesics in the 530 operated patients preoperative and in the surviving patients at 6 weeks and 6 months after operation**

	Preoperative <sup>a</sup> (n=530)	6 weeks (n=396)	6 months (n=237)
<b>Pain</b>			
No, light or moderate	236 (45%)	364 (92%)	218 (92%)
Strong, severe	196 (7%)	26 (7%)	17 (7%)
Not known	98 (18%)	6 (1%)	2 (1%)
<b>Analgesics</b>			
No, peripheral or light	217 (41%)	220 (56%)	160 (67%)
Opioids	213 (40%)	156 (39%)	70 (30%)
Not known	100 (19%)	20 (5%)	7 (3%)

<sup>a</sup> Preoperative mobility is just before fracture

with internal fixation (46/189) 68% of the surviving patients walked at 6 weeks compared to 83% having prosthetic treatment (142/189). 1 patient underwent a Girdlestone procedure and had no walking ability after operation. At 6 months 80% of the patients with internal fixation compared to 90% with prosthesis were walking with or without crutches (Table 3).

25% of the patients had pain from the metastasis for less than 1 month before the operation. 10% had pain for more than 6 months. Only 13% of the patients had no pain from the metastasis before operation. 92% of the surviving patients had no, light, or moderate pain from the metastasis at 6 weeks and 6 months after operation compared to 45% preoperatively. 36% and 38% had no pain at 6 weeks and 6 months. 28% and 35% of the patients used no analgesics at 6 weeks and 6 months after operation. 40% used opioids preoperatively compared to 39% at 6 weeks and 30% at 6 months (Table 4).

84 patients were treated with internal fixation for metastases in humerus and 14 had prosthetic treatment. In the proximal humerus 17 patients had internal fixation and 14/31 had a prosthesis. All of these patients had no, light or moderate pain 6 weeks and 6 months after operation with no difference in treatment. Half of the patients treated with internal fixation used no or only light analgesics compared to two thirds of the patient treated with prosthesis at 6 weeks follow-up. All patients treated with prosthesis used no or light analgesics at 6 months compared to three quarters treated with internal fixation.

Preoperative 81% of the operated patients had a good or moderate Karnofsky score. At 6 weeks postoperative 77% had the same score and 85% at 6 months after operation (Table 5).

56 of the 530 operated patients (11%) had complications, mainly infections (40%) and prosthetic dislocations (36%). 33/530 (6%) had reoperation related to the first operated metastasis. In patients surviving less than 6 weeks 6% had complications and 3% were reoperated. In patients surviving

**Table 5.** Karnofsky performance score in the 530 operated patients, and the surviving patients at 6 weeks and 6 months

Karnofsky score	Preoperative <sup>a</sup> (n=530)	6 weeks (n=396)	6 months (n=237)
Poor	95 (18%)	86 (22%)	34 (15%)
Good or moderate	431 (81%)	305 (77%)	202 (85%)
Not known	4 ( 1%)	5 ( 1%)	1 ( - )

<sup>a</sup> Preoperative mobility is just before fracture

more than 1 year the complication rate was 13 % and the reoperation rate 12%.

## Discussion

As shown in other studies (Talbot et al. 2005) evaluation of the impact of surgical treatment on quality of life in patients with skeletal metastases is complicated. There is always loss of follow-up data making it difficult to make conclusions.

Talbot et al. (2005) used SF36 in a series of 65 patients with non-spinal bone metastases and showed no improvement in quality of life postoperatively, but showed substantial improvements in functional scores (MSTS and TESS). In another prospective study on non-spinal bone metastases by Clohisy et al. (2001) pain was the only improvement among the 8 dimensions of SF36 at 6 weeks and 12 weeks postoperatively. Bauer (2005) stated that assessment of outcome after surgery for long bone or pelvic metastases should focus on failures instead of functional outcome; the surgeon can do no more than try to stabilize impending or manifest fractures. Reoperation because of failure is a severe complication for these often gravely ill patients. Mobility as well as pain treatment is important for quality of life, and operative treatment for a pathological fracture in the femur may give immediate reduction in pain, facilitate patient nursing and re-establish walking function. Functional ability in this series measured by Karnofsky performance score showed a small decrease in the group of good and moderate 6 weeks after operation, 77% compared to 81% preoperative and a small increase at 6 months to 85%. This is indicating that functional ability is maintained and not improved. This should be compared to the improvement in func-

tional scores found by Talbot et al. (2005) at both 6 and 12 weeks by measuring MSTS and TESS.

Mobility is particularly affected when the patients have bone metastases in the pelvis or lower extremity. Most of the operations in this series involved these localizations (77%). In patients with impending or manifest fracture we found that 79 % were walking with or without

crutches at 6 weeks and 87% at 6 months (Table 2). This strongly indicates that surgery improves mobility in patients with bone metastases in pelvis or lower extremity. In patients with metastases in the proximal femur 75 % where treated with prosthetic replacement and we found a tendency showing that more patients were mobile after 6 weeks and 6 months when treated by prosthesis compared to internal fixation (Table 3). Wedin et al. (2005 ) found that the failure rate leading to reoperation 2 years after operation with internal fixation was 0.35 compared to 0.18 after endoprosthetic reconstruction in patients with fracture in the proximal femur. Our and Wedins findings indicate that prosthetic replacement should be the choice of treatment in these patients.

Function was not specifically analyzed in patients having metastases in the proximal humerus. We found a tendency indicating that prosthetic treatment in these patients reduced the use of analgesics compared to internal fixation. This supports the findings of Frassica et al. (2003). In treatment of metastases in humerus there is no absolute indications for operative treatment because most patients can be treated effectively with analgesics and irradiation. Function is not affected in the same degree as in patients having metastases in pelvis and lower extremity.

92% of the patients had no, light or moderate pain from the operated bone metastasis at 6 weeks and 6 months postoperative (Table 4). At the same time 6% and 7% had strong or severe pain compared to at least 37% of the patients that had strong or severe pain preoperatively. This support the studies of Talbot et al. (2005) and Barwood et al. (2000) finding that surgery can improve pain control. We found that 39% of the patients were using opioids at 6 weeks compared to at least 40% preopera-

tively. Patients using opioids were reduced to 30% at 6 months, suggesting that surgery might reduce the use of strong analgesics at late follow-up (Table 4). In this study we do not know the exact number of patients treated with postoperative radiation as pain treatment. Talbot et al. (2005) was not able to show a decrease in the number of patients receiving pain medication, maybe because he stopped the follow-up 12 weeks postoperatively. The complication rate of 11% in our series is lower than reported in other series (Yazawa 1990, Allan et al. 1995, Kunisada et al. 2000, Wedin et al. 2001, Talbot et al. 2005). Despite our intention to have all reoperations reported we cannot exclude missing reports. Wedin et al. (1999) have shown, that the greatest risk factor for failure leading to reoperation after operative treated bone metastases is long survival. This is supported by a tendency in our study with an increase in reoperation rate in patients surviving more than 1 year after operation.

In patients with very limited life expectancy improvement from surgery must occur within short time. We have no good tools for prognostication of expected survival although different prognostic systems have been suggested (Tokuhashi et al. 1991, Bauer et al. 1995, Hansen et al. 2004, Nathan et al. 2005). In most studies of metastatic bone disease, including the present, the prognosis has been poor. In our series the 1-year survival was 0.4, which is similar to other series. (Bono et al. 1991, Bauer et al. 1995, Dürr et al. 1998, Bohm et al. 2002). One quarter of the patients died within the first 6 weeks postoperatively as also found in other studies (Clohisy et al. 2001, Talbot et al. 2005). We have no follow-up data on these patients, so we do not know if they had any benefit from surgery. Obviously we need to analyze pain and function even earlier than 6 weeks after operation to assess short-time benefit from surgery. In our series patients who died before 6 weeks had a higher frequency of fracture and higher percentage of known visceral and multiple bone metastases. They also more often had lung cancer and a higher frequency of poor Karnofsky performance score indicating that we might be able to identify this group of patients.

Our study shows that surgery for bone metastases in the pelvis and extremities can improve function and pain control in palliative care to help improving quality of life in these often gravely ill patients,

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# The Scandinavian Sarcoma Group for Nurses and Physiotherapists

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In August 2006 Reg. Nurses and Physiotherapists at The Norwegian Radiumhospital in Oslo invited health care professionals working with sarcoma patients to a presymposium to assess the need for cooperation within the Scandinavian countries. There were 46 participants attending this meeting. A working group was established to work towards SSG's next meeting. Denmark, Sweden, and Norway were all represented in this group. Hard work ended in our first official seminar in Bergen in May 2007.

The SSG for Nurses and Physiotherapists was formed at the annual SSG meeting in Bergen in May 2007 by health personnel from Scandinavia who primarily work with sarcoma patients.

A board consisting of nurses and physiotherapists from Denmark, Sweden, and Norway was elected for a period of 2 years. Our Chairman, Lotta Våde, is at The Norwegian Radiumhospital in Norway and the rest of the members are geographically divided between Sweden, Denmark, and Norway

SSG for Nurses and Physiotherapists participates in the SSGs meetings and has so far primarily worked with practical issues on how to establish the group. In the process there has been a lot of work and learning. The group is now established with it's own board, web-site, separate seminars/workshops and an independent economy, see [www.ssg-nurses-physiotherapists.org](http://www.ssg-nurses-physiotherapists.org).

In May 2008 the group arranged a Scandinavian day during EMSOS meeting in Warszawa with 25 participants.

In addition, each country has been working with different issues. Swedish nurses and physiotherapists have arranged national meetings once a year for health care professionals working with sarcoma patients This has been a great success, and health care professionals from several different professions have attended.

Our main goal for the future is to improve the cooperation between Scandinavian health care professionals. We think we can achieve this by:

- establishing research projects within the Scandinavian countries, with a multi disciplinary project involving nurses, physiotherapist, oncologists, orthopedists and other health care professionals;
- introducing mutual guidelines within the Scandinavian countries e.g. routines for administration of MTX and isolation routines;
- introducing mutual guidelines for physical therapy during all phases of the treatment;
- participating and arranging conferences/seminars/workshops.

It is also an important goal for us to give other professions working with sarcoma knowledge about sarcoma and the existence of our group. We look forward to continue our cooperation and develop our relationship with the SSG in the years to come.

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## TID ÄR EN GÅVA

### Hög andel GIST-patienter uppnår behandlingssvar

- Efter 31 månaders behandling med Glivec uppvisade 83 % av GIST-patienterna i studiegruppen klinisk nytta – 67 % partiella och kompletta behandlingssvar plus 16 % stabil sjukdom.<sup>1</sup>
- Medianöverlevnad i studiepopulationen var 58 månader.<sup>2</sup>

### Uthållighet är en dygd

- Var inte för snabb med att klassificera ett uteblivet *snabbt* behandlingssvar som resistens.
  - Mediantid till behandlingssvar var 13 veckor.<sup>1</sup>
  - Tiden till optimalt behandlingssvar varierar – det kan ta upp till ett år.<sup>3</sup>

Glivec® (imatinib) är en protein-tyrosinkinashämmare. Glivec är indicerat för behandling av: • vuxna och barn med nydiagnostiserad Philadelphia-kromosom- (bcr-abl)-positiv (Ph+) kronisk myeloisk leukemi (KML), för vilka benmärgstransplantation inte är en förstahandsbehandling • vuxna och barn med (Ph+) KML i kronisk fas efter terapivikt med interferon alfa-behandling, eller i accelererad fas eller blastkris • vuxna patienter med nyligen diagnostiserad Philadelphia-kromosom-positiv akut lymfoblastisk leukemi (Ph+ ALL) tillsammans med kemoterapi • vuxna patienter med recidiverande eller refraktär Ph+ ALL som monoterapi • vuxna patienter med myelodysplastiska/myeloproliferativa sjukdomar (MDS/MPD) förenat med rearrangemang av platelet-derived growth factor receptor (PDGFR)-genen • vuxna patienter med avancerat hypereosinofilt syndrom (HES) och/eller kronisk eosinofil leukemi (CEL) med FIP111-PDGFR-rearrangemang. Effekten av Glivec på utfallet av benmärgstransplantation har inte undersökts. Glivec är också indicerat för behandling av: • vuxna patienter med Kit (CD 117)-positiva, icke-resecerbara och/eller metastaserande, maligna gastrointestinala stromacellstumörer (GIST) • vuxna patienter med icke-resecerbara dermatofibrosarkoma protuberans (DFSP) • vuxna patienter med återkommande och/eller metastaserande DFSP som är olämpliga att operera. Hos vuxna och barn baseras effekten av Glivec på det sammantagna hematologiska och cytogenetiska svaret och progressionsfri överlevnad vid KML, på hematologiskt och cytogenetiskt respons vid Ph+ ALL, MDS/MPD, på hematologiskt respons vid HES/CEL och på objektiv tumörrespons hos vuxna patienter vid GIST och DFSP. Erfarenheten av Glivec hos patienter med MDS/MPD förenat med rearrangemang PDGFR-genen är mycket begränsat. Förutom vid nyligen diagnostiserad KML i kronisk fas finns det inga kontrollerade studier som visar på en klinisk nytta eller ökad överlevnad för dessa sjukdomar. Beredningsform, styrka och förpackning: Tablett 100 mg förpackas om 60 tabletter och 40 mg tabletter förpackas om 30 tabletter. Förmån och pris: Rx, F. Produktresumén uppdaterad 2007-11-20. ATC-kod L01XE01. För senaste prisuppgift och mer information se [www.fass.se](http://www.fass.se).

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