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OPTIMAL USE OF TREATMENT MODALITIES AND TREATMENT RESULTS OF OSTEOSARCOMA AND SOFT TISSUE SARCOMAS

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ACADEMIC DISSERTATION

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ABSTRACT

SOFT TISSUE SARCOMA

Soft tissue sarcomas are rare malignant tumours of mesenchymal origin. Because of infiltrative growth pattern simple enucleation of the tumour with the pseudocapsule causes a high rate of local recurrence. Instead, these tumours should be resected with a rim of normal tissue around the tumour. At Helsinki University Central Hospital a specialized multidisciplinary treatment group started in 1987. Surgical resection with a wide margin (2.5 cm) is the primary aim. In case of narrower margin radiation therapy is necessary. The role of adjuvant chemotherapy remains unclear. This thesis deals with soft tissue sarcomas of the extremities and the trunk wall. Our aims were to study local control by the smallest surgical margin (Study I) and to develop a new prognostic tool to aid decision-making on which soft tissue sarcoma patients should receive adjuvant chemotherapy (Study II). Soft tissue sarcoma patients referred to the Soft Tissue Sarcoma Group at Helsinki University Central Hospital during 1987–2002 form material in Studies I and II. External validation material for Study II comes from the Lund university soft tissue sarcoma registry.

The smallest surgical margin of at least 2.5 centimetres yielded local control of 89 per cent at five years. Amputation rate was 9 per cent. The smallest margin in centimetres retained its independent significance for local recurrence. The proposed prognostic model with necrosis, vascular incasion, size on a continuous scale, depth, location and grade worked well both in Helsinki material and in the validation material. The proposed model also showed good calibration.

Based on the present study we recommend the smallest surgical margin of 2–3 centimetres in soft tissue sarcoma irrespective of grade. Improvement in local control was present but modest in margins wider than 1 centimeter, and in cases where gaining a wider margin would lead to a considerable loss of function smaller margin is to be considered combined to radiation therapy. Patients treated with inadequate margins should be offered radiation therapy irrespective of grade. Our new prognostic model to estimate 10-year survival probability in patients with soft tissue sarcoma of the extremities or trunk wall showed good dicscrimination and calibration. For time being the prognostic model is available for scientific use and further validations at www.prognomics.org/sam. In the future, the model may aid in clinical decision-making.

OSTEOSARCOMA

For operable osteosarcoma, neoadjuvant multidrug chemotherapy and delayed surgery followed by multidrug adjuvant chemotherapy is the treatment of choice. Overall survival rates at five

years are approximately 75 per cent in modern trials with classic osteosarcoma which is a local, high-grade extremity osteosarcoma in patients less than 40 years. Prognosis among patients older than 40 years with an axial or metastatic tumour is significantly worse. All patients diagnosed with osteosarcoma in Finland during 1971–2005 form the material in Studies III and IV. Data on patients were retrieved from the Finnish Cancer Registry.

Among patients with an extremity osteosarcoma limb-salvage rate increased from 23 per cent to 78 per cent during 1971–2005. The 10-year osteosarcoma-specific survival for the whole study population improved from 32 per cent to 62 per cent. It was 75 per cent for patients with a local high-grade osteosarcoma of the extremity diagnosed during 1991–2005.

This study outlines the improved prognosis of osteosarcoma patients in Finland with modern chemotherapy, and the 10-year survival of 75 per cent for patients with a local high-grade osteosarcoma of the extremity is good also in an international scale. Nonetheless, their limb-salvage rate remains inferior to those seen for highly selected patient series. Overall, the centralisation of osteosarcoma treatment would most likely improve both survival and limb-salvage rates even further.

CONTENTS

INTRODUCTION

Soft tissue sarcomas are malignant tumours of mesenchymal origin. They constitute approximately one per cent of cancers. They can occur in all locations but most tumours arise in the extremities and the trunk wall. Soft tissue sarcomas of the extremities and the trunk wall are usually considered one entity because of their treatment similarities and they are the tumour locations this thesis deals with.

There were approximately 100 soft tissue sarcomas of the extremities and the trunk wall registered annually in the Finnish Cancer Registry in 2007–2009. Based on histology, these tumours are further divided into 56 intermediate or malignant subtypes according to the classification of World Health Organisation (Fletcher *et al*, 2002). Excluding certain histologic subtypes, diagnostics and local treatment of extremity and trunk wall tumours are more or less similar despite the vast number of histologic entities. The most common histologic types of the soft tissue sarcomas are liposarcoma, malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma, synovial sarcoma, fibrosarcoma, and leiomyosarcoma.

Due to the rarity of soft tissue sarcomas, specialized multimodality treatment centres have been established, and the importance of centralisation of diagnostics and treatment of this rare neoplasm is well established. This progress is evident also in Finland: local-recurrence rate has reduced to 13 per cent from 48 per cent and disease-free survival at three years has improved from 36 per cent to 69 per cent (Table 1).

Table 1. Published soft tissue sarcoma series from Finland

Authors	Study target	Period	Location	LRR (%)	DFS (%)
Rantakokko et al. 1979	population-based	1960–1960	limb and limb girdles	48	nd
Gröhn et al. 1979	HUCH prior to STS Group	1965–1975	limb and limb girdles	nd	36 (3-year)
Wiklund et al. 1996	HUCH STS Group	1987–1993	extremities and trunk wall	13	69 (3-year)

HUCH, Helsinki University Central Hospital. STS, soft tissue sarcoma. LRR, local recurrence rate. Nd, no data. DFS, disease-free survival.

A prospective treatment protocol was set up in 1987 based on recommendations by the Scandinavian Sarcoma Group. Later, we have updated our protocol and made more detailed. Surgical resection is the primary treatment for soft tissue sarcoma. The margin is defined as wide if the tumour is excised with a smallest microscopic margin of at least 2.5 cm. A smaller margin is accepted, however, if it includes an uninvolved fascia, periosteum or joint capsule. The definition of the wide margin is controlversial. Many authorities

recommend 10 mm (Borden *et al*, 2003; Grimer *et al*, 2010). Adequate local treatment is defined as wide surgery alone or a marginal surgical margin combined with radiation therapy.

At present, patients less than 70 years and with adequate performance status are offered adjuvant chemotherapy if the tumour malignancy grade is high and the tumour fulfills at least two of the following criteria: more than 8 cm in size (in synovial sarcomas 5 cm), necrosis, or vascular invasion. In patients over 70 years of age, the decision is made on a case-by-case basis. The limited effect of adjuvant chemotherapy should be weighed against its potential toxicity and adjuvant chemotherapy should be directed to patients who benefit from it most.

Whilst soft tissue sarcoma is generally a disease of adulthood, the peak incidence of osteosarcoma is during the second and third decades of life. According to data from the Finnish Cancer Registry, the mean annual incidence of osteosarcoma was eight during 2002–2009. Up to 73 per cent of patients were amputated in the 1970s and 1980s (Fuchs *et al*, 1998; Winkler *et al*, 1988) and up to one half of patients developed metastatic disease at some point in the course of the disease in the 1980s (Bramwell *et al*, 1992; Ferrari *et al*, 1997). Treatment was revolutionized in the 1970s when doxorubicin, methotrexate, and cisplatinum were shown to have an effect on osteosarcoma. Rosen and colleagues introduced the concept of preoperative multidrug chemotherapy and delayed surgery. Modern trials demonstrate overall survival rates of approximately 75 per cent at five years for local high-grade extremity tumour in patients less than 40 years. In non-selected series also including patients over 40 years of age, patients with axial tumours and with metastatic disease at diagnosis survival rates are considerably lower. Nowadays over 90 per cent of patients can be treated with limb-salvage surgery with a local recurrence rate of 5 per cent to 10 per cent at five years (Bramwell *et al*, 1992; Ferrari *et al*, 1997).

The Soft Tissue Sarcoma Group at Helsinki University Central Hospital has been running for over 20 years and has treated patients with the same protocol with minor modifications. The first aim of this thesis was to assess the local control by the smallest surgical margin. More precise prognostic tools are needed for both the selection of patients to receive adjuvant chemotherapy and patient counselling in soft tissue sarcoma, the development of which was a second aim of this thesis.

The overall aims of these osteosarcoma studies were that they would act as quality-control studies: good treatment results are accomplished only by concentrating on a few patients. We also studied prognostic factors for survival together with survival rates in a nationwide, population-based series spanning 35 years.

REVIEW OF THE LITERATURE

SOFT TISSUE SARCOMA

1. GENERAL CONSIDERATIONS

Soft tissue sarcomas are malignant nonepithelial extraskeletal neoplasms that are principally derived from the mesoderm with some contribution from the neuroectoderm (Weiss *et al*, 2001). They constitute a highly heterogeneous group of tumours with a broad spectrum of biological potential. The classification of histologic subtypes is done on the basis of tumour differentiation according to their resemblance to various mature tissue types. The current soft tissue tumour classification of the World Health Organization dates back to the year 2002 and includes 56 intermediate and malignant histologic entities (Fletcher *et al*, 2002).

The classification of soft tissue sarcoma is based on histology. In addition to immunohistochemical staining, genetic methods have revealed specific translocations with fusion genes in several soft tissue sarcoma types, for example t(X;18)(p11.2;q11.2) (SSX1&2;SYT) in synovial sarcoma (Clark *et al*, 1994), and t(11;22)(q24;q12) (FLI1;EWS) in Ewing tumour/peripheral primitive neuroectodermal tumour (Delattre *et al*, 1992) which now serve to aid diagnosis.

Soft tissue sarcomas are locally invasive. Pseudoencapsulation, because of the tumour's eccentric growth, by surrounding mesenchymal proliferation and peripheral tumour cells compressed in parallel layers, is common (Broders *et al*, 1939; Enneking *et al*, 1981). Plain removal of the tumour with this pseudocapsule results in a high rate of local recurrence because of the frequent presence of microscopic invasive extensions of the tumour through the pseudocapsule into the surrounding normal tissue.

The most common histologic subtypes of soft tissue sarcoma of the extremities in adults, according to the largest series published (1,041 patients), are liposarcoma, malignant fibrous histiocytoma or undifferentiated high-grade pleomorphic sarcoma, synovial sarcoma, fibrosarcoma, and leiomyosarcoma constituting approximately 80 per cent of cases (Pisters *et al*, 1996b). Seventy-two per cent of soft tissue sarcomas were located in the extremities or in the superficial trunk in a large series with all locations (Stojadinovic *et al*, 2002). Eleven per cent of tumours were confined to the retroperitoneum and 10 per cent were visceral tumours. The mean annual number of new soft tissue sarcomas was 178 for all locations and 100 for the extremities and the trunk wall in the Finnish Cancer Registry in 2007–2009. Diagnostics and local treatment are more or less similar despite the vast number of histologic entities in adult patients with extremity or trunk wall soft tissue sarcoma. Surgery is the mainstay that, in cases of inadequate margin, radiation therapy compliments. The

role of adjuvant chemotherapy is still somewhat controversial.

En bloc resection is the primary treatment also for retroperitoneal and visceral soft tissue sarcomas. However, obtaining adequate margin is in many cases more difficult because of the close relation to vital structures. Further, because of the extent of the tumour bed and non-acceptably high radiation doses to vital structures such as kidneys, liver, bowel and medulla, radiation therapy is less often a feasible treatment option (Willett *et al*, 1991). Because of these differences in the treatment, this thesis is based on soft tissue sarcomas arising in the extremities and the trunk wall.

Radiation therapy is a known predisposing factor for soft tissue sarcoma. Because the latent period from potential exposure to the detection of the tumour is usually long (the median latent period from radiation to the detection of sarcoma was reported to be 13 years (Amendola *et al*, 1989; Wiklund *et al*, 1991), mean 10 years (Laskin *et al*, 1988)), evaluation of the causal factors and their impact on pathogenesis remains difficult. The risk of developing a post-irradiation sarcoma after radiation therapy with long-term follow-up is increased among patients receiving radiation therapy under the age of 55 years in particular (Virtanen *et al*, 2006). Patients with invasive breast carcinoma and receiving radiation therapy had a cumulative 15-year incidence of 3.2 per 1000 for soft tissue sarcoma (Yap *et al*, 2002). In a single tertiary referral centre cohort, 2.5 per cent of patients had a radiation-induced soft tissue sarcoma (Cha *et al*, 2004). It is likely that post-irradiation sarcomas are overrepresented in tertiary referral centres because of the challenges in the treatment. Numbers are considerably small but it's worth noting that these cancers are iatrogenically incurred, in most cases, in patients who have achieved cure from their primary malignancy.

Angiosarcoma arising from chronic lymphoedema after mastectomy and radiation therapy is known as Stewart-Treves syndrome (Stewart *et al*, 1948). Exposure to certain chemicals such as vinyl chloride, phenoxyacetic herbicides, and dioxin has been proposed to increase the risk of developing soft tissue sarcoma (Evans *et al*, 1983; Kogevinas *et al*, 1995), however the role of low exposure to dioxin via food in increasing the risk of soft tissue sarcoma was questioned in a population-based Finnish series (Tuomisto *et al*, 2004). Some hereditary syndromes predispose individuals to soft tissue sarcomas: in type I neurofibromatosis, patients develop numerous benign neurofibromas and the risk of developing malignant peripheral nerve sheath tumour is increased (Bien *et al*, 2007; Ferrari *et al*, 2007), whilst patients with Li-Fraumeni syndrome with a *TP53* gene mutation suffer an increased risk of developing rhabdomyosarcomas, osteosarcomas, and other neoplasms (Birch, 1990).

The incidence of soft tissue sarcoma accounts for 0.63 per cent to 0.9 per cent of all diagnosed malignant tumours and this incidence is increasing (Clark *et al*, 2005; Jemal *et al*, 2008; Ross *et al*, 1993). In a published Finnish study,

three quarters of patients were diagnosed after the age of 40 and both sexes were affected similarly (Rantakokko *et al*, 1979). Of the tumours located in the extremities and the trunk wall 60 per cent are deep-seated (Trovik *et al*, 2001). Approximately 10 per cent of patients have detectable metastases at diagnosis, lungs being the most frequent location. Lymph node metastases are rare and usually associate with clear cell sarcoma, malignant fibrous histiosytoma and synovial sarcoma (Al-Refaie *et al*, 2008; Atalay *et al*, 2007; Rantakokko *et al*, 1979; Rydholm *et al*, 1984).

In a grading system by Broders and colleagues from 1939, the tumour grade of fibrosarcoma was assigned based on cellularity, pleomorphism or anaplasia, mitotic activity, degree of necrosis, and invasive growth seen under light microscopy (Broders *et al*, 1939). Many variations and simplifications of this grading method have followed since, the mitotic count being common to all (Coindre *et al*, 1986; Costa *et al*, 1984; Guillou *et al*, 1997; Jensen *et al*, 1991; Markhede *et al*, 1982; Tomita *et al*, 1993; Trojani *et al*, 1984). The original grading scale by Broders and colleagues had four grades as does the system used by the Scandinavian Sarcoma Group, where grades I and II denote low-grade and grades III and IV high-grade tumours (Angervall *et al*, 1986; Markhede *et al*, 1982; Meis-Kindblom *et al*, 1999). In the latest Cancer Staging manual by the American Joint Committee on Cancer, a four-tiered grading system was changed to a three-tiered system as recommended by the College of American Pathologists (Edge *et al*, 2009). Both the French Federation of Cancer Centers and the National Cancer Institute grading systems are three-tiered systems (I low-grade, II and III high-grade) (Costa *et al*, 1984; Trojani *et al*, 1984). Soft tissue sarcomas may also be segregated into two groups, namely low-grade and high-grade tumours, but compared with a three-tier grading system, the three-grade system may predict systemic relapse more precisely (Kandel *et al*, 1999). Further, a four-grade system produces more prognostic information than a three-tiered system does (Alvegard *et al*, 1989; Broders *et al*, 1939).

2. DIAGNOSTICS

Soft tissue sarcomas most often present as an enlarging, painless mass, and local symptoms develop late (Stefanovski *et al*, 2002). Compression of the nearby structures, such as nerves (pain), vessels (venous stasis, lymphoedema) or joint (disability), by the enlarging tumour causes first local symptoms to arise. Tumour necrosis may cause subfebrile fever, and rapid growth of the tumour may lead to necrosis of the overlying skin causing ulceration.

In soft tissue sarcoma treatment, exact preoperative diagnosis and staging are essential for definite treatment planning. According to the Scandinavian Sarcoma Group's referring policy, subcutaneous lesions larger than 5 centimetres in size and all deep lesions should be referred to a specialized soft

tissue sarcoma treating group before any biopsy or surgery (Rydholm, 1983; Stener, 1978). Biopsy technique should be planned to avoid any complication or contamination that might complicate or jeopardize limb-sparing surgery. Biopsy can be a traditional open biopsy or a percutaneous core needle biopsy. Fine needle aspiration may be used to compliment diagnostics. Both core needle biopsy and fine needle aspiration are frequently performed. Less invasive percutaneous techniques have replaced open biopsy to large extent, as adverse evidence concerning open biopsy has accumulated. In a 597-patient series, open biopsy carried a complication rate as high as 16 per cent in addition to a diagnostic error rate of 18 per cent (Mankin *et al*, 1996). To ensure representative samples in deep tumours in particular and in large tumours with radiologically divergent areas, needle biopsies are frequently taken under ultrasound, computed tomography or magnetic resonance imaging (MRI) guidance.

Proper staging is paramount for the decision of treatment strategy. MRI is the standard method to show possible tumour necrosis and cystic component, size of the tumour and relation to nearby structures, such as nerves and vessels (Clarkson *et al*, 2004). Evaluation of bone involvement is also most reliably assessed with MRI. Computed tomography scan may provide aid in evaluation of bone involvement (Fenstermacher, 2003; Misra *et al*, 2009), and it is also the imaging modality of choice for patients not suitable for MRI (Tzeng *et al*, 2007). A computed tomography scan is also used in large scale as it reliably detects pulmonary metastases. There is, however, controversy over which patients should have a primary computed tomography scan of the chest. Some recommend it for all patients diagnosed with soft tissue sarcoma (Misra *et al*, 2009). Another group recommends a primary computed tomography scan of the chest for patients with a high-grade tumour exceeding five centimetres (Robinson *et al*, 2008). At Helsinki, patients with high-grade sarcomas have preoperative computed tomography scan of the chest based on high metastasizing potential. Preoperative plain chest radiography is currently recommended for patients with diagnosed low-grade sarcomas as some of the subtypes metastasize more readily than others.

3. SURGERY

In the treatment of local soft tissue sarcoma, surgery plays a central role which other treatment modalities compliment. Bowden and colleagues introduced the principles and techniques for resection of soft parts for sarcoma in 1958 (Bowden *et al*, 1958). Their hypothesis was that soft tissue sarcoma should be treated with a wide ablation of surrounding grossly normal soft tissues *en bloc* whenever anatomically possible to minimize the use of mutilating amputations. In a classic paper by Enneking and colleagues from 1981, surgical margins were divided into four categories based on studies on fascial

boundaries and local recurrence rates in soft tissue sarcoma (Enneking *et al*, 1981). In the intralesional margin, tumour forms the periphery of part, or all of the resection specimen. In the marginal margin a pseudocapsule forms the periphery of the specimen. In the wide margin a cuff of normal tissue forms the periphery of the specimen, and in the radical margin, all normal tissue of the compartment involved is resected *en bloc* together with the tumour. Enneking's classification is widely used to describe surgical margins but there remains controversy on how wide a normal tissue rim around the tumour is wide enough to yield sufficient local control without causing excessive functional impairment. Enneking gives no answer. To clinical practise, several more precise margin width evaluation systems have been described. Question of sufficient margin is closely related to the decision on adjuvant radiation therapy.

Surgery also plays a central role in locally recurrent disease, and isolated local recurrence can in many cases be treated with a curative intention and aggressive surgical treatment of isolated local recurrences seems justified (Midis *et al*, 1998). Radiation therapy is generally combined to surgical treatment unless been part of the primary treatment. Twenty per cent to 40 per cent of patients with local disease at presentation develop systemic disease at a later course of disease (Billingsley *et al*, 1999; Gadd *et al*, 1993; Potter *et al*, 1985). A patient-series with 994 patients with local extremity tumour at presentation showed a two-year postmetastases survival of 28 per cent (Billingsley *et al*, 1999). Only eight per cent of patients developing metastatic disease survived more than three years. The most important factor was a complete resection of metastases. This was also shown in another series: patients who had pulmonary metastases completely resected had a three-year survival of 23 per cent compared to two per cent among patients with non-surgical treatment (Gadd *et al*, 1993). Yet another series showed a five-year survival of 26 per cent among patients with a complete resection of pulmonary metastases (Casson *et al*, 1992).

4. RADIATION THERAPY

Adequate local control and good functional outcome, together with improved overall survival, are the main outcome measures in soft tissue sarcoma treatment today. Radiation therapy improves local control but the effect on overall survival remains unclear (Yang *et al*, 1998). External radiation therapy can be applied either preoperatively or postoperatively; in some centres, internal radiation therapy (brachytherapy) is used, most commonly combined to external radiation therapy (Alektiar *et al*, 2002). In soft tissue sarcoma, radiation therapy is most widely studied combined to complete resection of tumours of the extremity and the trunk wall. Radiation therapy is now a widely used modality and in most cases limb-sparing surgery can be performed combined with radiation therapy to yield equally high local control rates as

seen for amputation alone. This is shown in three prospective randomized trials (Pisters *et al*, 1996a; Rosenberg *et al*, 1982; Yang *et al*, 1998). Pisters and colleagues found the improvement in local control to be limited to high-grade tumours (Pisters *et al*, 1996a) but in the trial by Yang and colleagues, local control was significantly improved for both low-grade and high-grade sarcoma (Yang *et al*, 1998).

There remains controversy over timing of radiation therapy. Postoperative radiation therapy is preferred in many centres. In a randomized study comparing oncological outcome, function and health status of patients receiving limb-salvage surgery and radiation therapy either preoperatively or postoperatively, patients treated with preoperative radiation therapy had significantly more wound complications whereas patients receiving postoperative radiation therapy had more frequently lymphoedema and fibrosis; local control was similar in the both arms (Davis *et al*, 2002; O'Sullivan *et al*, 2002). Patients receiving radiation therapy postoperatively had larger target fields and higher doses. Timing of radiation therapy had only a minimal effect on the function during follow-up. Instead, tumour characteristics and wound complications had an adverse effect on function. Possible advantages in administering postoperative radiation therapy instead of preoperative radiation therapy are that it can be omitted in cases wide margins are achieved at definite surgery, histology can be classified and surgical margins assessed more precisely both macroscopically and microscopically and surgery can be performed without delay.

Preoperative radiation therapy challenges tumour pathologists because the structure of the tumour is disturbed and viable cells are scarce after radiation. In some cases, however, preoperative radiation therapy can be used to render an inoperable tumour operable or to permit limb-salvage surgery in a situation otherwise requiring amputation. Another advantage of preoperative radiation therapy is that it engages a multimodality soft tissue sarcoma team early diminishing the number of inappropriate biopsies and surgeries and improves outcome (Bauer *et al*, 2001; Eilber *et al*, 1985; Gustafson *et al*, 1994).

Radiation therapy is recommended after inadequate surgery (intralesional and marginal surgery) and in addition for patients with inoperable tumours or with tumour contamination of the surgical bed. Although radiation therapy serves as an effective modality to destroy possible viable microscopic tumour tissue after surgery, it cannot wholly abrogate the adverse effect of positive margins on local control (Alektiar *et al*, 2002; Herbert *et al*, 1993; Sadoski *et al*, 1993), and the importance of re-resection is emphasized, even if radiation therapy is routinely used (Fiore *et al*, 2006; Lewis *et al*, 2000; Zagars *et al*, 2003b).

Several definitions for adequate local treatment exist. Adequate treatment has been defined as either surgery with

surgical margins of at least 2 cm alone, or surgery with smaller margins combined with postoperative radiation therapy (Karakousis *et al*, 1991). Amputation rate in the above study was six per cent and five-year local recurrence-free rate was 94 per cent in both groups at five years. In a review of 111 patients with an amputation rate of three per cent, smallest margin of at least 1 cm (38 per cent received radiation therapy) yielded a five-year local recurrence-free survival of 84 per cent and smaller margin (38 per cent received radiation therapy) 58 per cent (McKee *et al*, 2004). As a conclusion, McKee and colleagues recommend radiation therapy for all patients having their surgery performed with narrower than a 1-cm margin. Khanfir and colleagues recommended radiation therapy after surgery with a margin of less than 1 cm and also after intralesional definite surgery based on a patient review with limb-salvage surgery (Khanfir *et al*, 2003). In case of optimal surgical treatment, there was no benefit from radiation therapy. Adjuvant radiation therapy improved local control significantly in case of suboptimal surgery. In a retrospective study from Boston, surgical margins of at least 10 mm and less than 10 mm yielded local control rates of 100 per cent and 87 per cent, respectively, at 10 years in patients treated with function-saving surgery alone (Baldini *et al*, 1999). Consensus treatment guidelines also recommend a 1-cm margin as an optimal surgical treatment (Borden *et al*, 2003; Grimer *et al*, 2010).

Dickinson and colleagues concluded in their study on 279 patients with local soft tissue sarcoma that even with margins measuring approximately 1 mm satisfactory local control can be achieved as long as margins are not contaminated (Dickinson *et al*, 2006). The principal weakness of the above study was that adjuvant therapy was not reported, and local control was not stratified for radiation therapy. In a comprehensive Japanese evaluation system for adequate margin, surgical margin is defined as the distance from tumour's reactive zone (Kawaguchi *et al*, 2004). This classification also takes into account the role of natural barriers (*e.g*. fascia, joint capsule) and includes both soft tissue and bone sarcomas and response to non-uniform preoperative treatment was also considered.

In a 1,093-patient study in Scandinavia, local control was most improved in deep-seated, high-grade tumours even if a wide margin was achieved, and adjuvant radiation was strongly recommended for these tumours (Jebsen *et al*, 2008; Trovik *et al*, 2001). On the contrary, many subcutaneous soft tissue sarcomas can be safely treated by wide surgery alone (Al-Refaie *et al*, 2010; Pisters *et al*, 2007; Rydholm *et al*, 1991). Decisions regarding adjuvant radiation therapy are at many centres based on margin and grade (Alektiar *et al*, 2000; Chandrasekar *et al*, 2008; Stefanovski *et al*, 2002), in some centres on size (Demetri *et al*, 1998; Pisters, 1998), and in some centres the use of radiation therapy is very liberal, and nearly all patients receive radiation therapy (Zagars *et al*, 2003b).

5. CHEMOTHERAPY

Effect of adjuvant chemotherapy in soft tissue sarcoma is still somewhat controversial. The largest randomized study failed to show a survival advantage for adjuvant chemotherapy (doxorubicin-ifosfamide) among patients with a high-grade soft tissue sarcoma (Woll *et al*, 2007). So far, only a meeting abstract has been published. Of patients allocated chemotherapy, only 73 per cent completed planned five courses, of these 38 per cent had dose reductions or delays, mostly for haematologic toxicity or infection despite lenograstim. Adjuvant chemotherapy is generally considered for patients with large high-grade tumours in highest risk for metastatic relapse and sarcoma-specific death. Requirements for administration of chemotherapy include age less than 70 years and adequate performance status. Wide margins in the resection of large high-grade tumours are seldom achieved and patients frequently also need postoperative radiation therapy. There is no generally accepted schedule for combining these two treatment modalities.

In an 18-randomized controlled trial meta-analysis, adjuvant anthracycline-based combination chemotherapy significantly improved both relapse-free and overall survival in soft tissue sarcoma (Pervaiz *et al*, 2008). The meta-analysis has been criticized for including many small patient series, the oldest ones dating back to the year 1981. The overall risk ratio for local recurrence was 0.73, which translated into an absolute risk reduction of 5 per cent in studies with ifosfamide combination chemotherapy. Doxorubicin alone showed no significant risk reduction. For distant recurrence the overall risk ratio was 0.61 with an absolute risk reduction of 10 per cent in studies with ifosfamide combination chemotherapy. Ifosfamide and doxorubicin-based regimens also showed significant risk reduction, respectively. In terms of survival, the combination of anthracyclines and ifosfamide seemed to be most efficacious combination yielding a relative risk reduction of 0.56 and an absolute risk reduction of 11 per cent for mortality. Doxorubicin alone showed no significant risk reduction in overall survival. The moderate risk reduction has to be weighed against toxicity.

In an adjuvant randomised phase II study the combination of doxorubicin and ifosfamide was associated with a 29 per cent incidence of grade 3–4 nausea and vomiting, and an 8 per cent incidence of grade 3–4 haematological toxicity with one death related to neutropenic treatment-associated infection (Gortzak *et al*, 2001). Addition of ifosfamide to the regimen significantly improved the tumour response rate but didn't produce a significant difference for one-year survival in a meta-analysis (Verma *et al*, 2008). Adverse events, particularly grades 3–4 myelosuppression, were observed more frequently in patients who received regimens that contained ifosfamide. Ifosfamide was recommended for advanced soft tissue sarcomas. Renal and cardiac toxicity also increase when using combination chemotherapy. Ensuring that a selection

of patients receive (neo)adjuvant chemotherapy is therefore critical.

6. PROGNOSIS AND PROGNOSTIC FACTORS

Improved survival and limb-sparing surgery with a good functional outcome and good local control are the indicators of the quality of treatment in soft tissue sarcoma. The local recurrence rate in single-institution patient series over 200 patients with extremity or trunk wall tumour is 6 to 25 per cent and amputation rates are 0 to 45 per cent (Table 2). Patient series usually extend over decades because of the rarity of the disease. It is therefore difficult to draw any profound conclusions because patients in the series seldom are uniformly treated. Five-year metastases-free survival was 74 per cent to 79 per cent (Table 2). Many soft tissue sarcoma patients die unrelatedly during follow-up because of advanced age and therefore sarcoma-specific survival offers more precise approximation. Five-year sarcoma-specific survival at five years was 55 per cent to 82 per cent.

Table 2. Characteristics and survival rates in single-institution soft tissue sarcoma patient series of more than 200 patients

Authors	Period	N	Site(s)	% High grade	% Deep	% XRT	% CT	% LR included	AMP	LR %	MFS	SSS	DFS
Shiu et al. 1975	1949–1968	297	lower extremity	40†	nd	no	no	46	47	18	74	55	40
Lindberg et al. 1981	1963–1977	253	extremity, trunk*	75	nd	yes	nd	nd	15	21	77‡		64
Collin et al. 1987	1968–1978	453	exrtemity	62	48	20	16	34	33	12			
Huth et al. 1988	1973–1986	255	extremity	100	nd	98	98	0	4	7			54
Potter et al. 1986	1975–1982	211	extremity	100	nd	58	59	0	39	6			69
Eilber et al. 2003	1975–1997	753	extremity	100	nd	66	66	19	6.5	12		70#	
Vraa et al. 1998	1979–1993	316	extremity, trunk	84	59	16	4	15	30	18	71‡	75	
Gronchi et al. 2005	1980–2000	911	extremity	72	82	37	20	30	8	25		76	
Lewis et al. 1997	1982–1995	911	extremity	67	77	nd	nd	0	9	15			
Pisters et al. 1996	1982–1994	1,041	extremity	65	76	40	23	20	10	17	78	76	
Gronchi et al. 2010	1985–2005	997	extremity	70	76	45	20	0	4	12	79	82	
Stoeckle et al. 2006	1996–2002	205	extremity, trunk	77	85	80	50	0	0	13			

*patients with abdominal and head and neck tumours excluded. † of tumours possible to grade in review. ‡ approximated from survival curves. # overall survival. nd, no data. XRT, radiation therapy. CT, chemotherapy. LR, local recurrence. AMP, amputation rate. MFS, metastases-free survival. SSS, sarcoma-specific survival. DFS, disease-free survival.

Prognostic factors for survival can be divided into at least three groups: tumour-related, patient-related and treatment-related. For local recurrence, prognostic factors are not as uniformly defined as for distant recurrence. The most frequently cited independent adverse prognostic factors for local control are positive surgical margin, high grade, advanced age, prior local recurrence, and certain histologic subtypes (malignant peripheral nerve sheath tumour, leiomyosarcoma) (Table 3). High-class surgery is still the first line treatment in soft tissue sarcoma and surgical margin is the only prognostic factor the surgeon can affect. Positive surgical margin has an adverse effect on local control, distant recurrence and overall survival (Table 3). Of the prognostic factors, tumour-related and patient-related factors are the ones that cannot be altered by treatment but provide information about the biological aggressiveness of the disease and provide help to decide upon a proper treatment strategy and follow-up.

Tumour malignancy grade is the best measure of a tumour's biological aggressiveness. A high malignancy grade is widely accepted as an independent prognostic factor for local recurrence. Some, however, disagree (Gibbs *et al*, 1997; Pisters *et al*, 1996b). A possible explanation is that differences in radiation therapy administration and the extent of surgical margins between low-grade tumours and high-grade tumours confound multivariate analysis in addition to the interpretation of histological grades. Advanced age also contributes to an adverse prognosis for local recurrence, with cut-off values of 50 and 60 years respectively (Eilber *et al*, 2003; Lewis *et al*, 1997; Pisters *et al*, 1996b). One explanation for this, although not wholly satisfactory, might be that older patients have not been operated on as radically and with such wide margins as in younger patients, but data on this is lacking. In the SEER material, older patients were more likely not to receive adjuvant therapy and had more sarcoma-related morbidity and mortality (Horton *et al,* 2011). Prior local recurrence was of adverse prognostic value for subsequent local recurrence in two large published series (Gronchi *et al*, 2005; Pisters *et al*, 1996b). The adverse impact of local recurrence on the development of metastases and overall survival is widely discussed and questioned (Barr *et al*, 1991; Evans, 1993). Development of local recurrence (Eilber *et al*, 2003; Lewis *et al*, 1997; Novais *et al*, 2010) and recurrent disease at presentation (Eilber *et al*, 2003; Pisters *et al*, 1996b) were independent adverse prognostic factors for survival. There is, however, some evidence that further local control and survival can be improved in a growing number of patients with isolated local recurrence with aggressive approach (Midis *et al*, 1998; Moureau-Zabotto *et al*, 2004; Ramanathan *et al*, 2001; Zagars *et al*, 2003a).

Large tumour size, high malignancy grade and deep location are well defined adverse prognostic factors for metastasis-free survival (Table 3).

Table 3. Independent prognostic factors for local recurrence, distant recurrence and overall survival/sarcoma-specific survival in patients with extremity or trunk wall soft tissue sarcoma

Authors	Years	N	Site(s)	LR	DR	OS/SSS
Gaynor et al. 1992	1968–1978	423	extremity	nd	Grade, Size, Depth	Grade, Size, Depth
Collin et al. 1987	1968–1978	453	extremity	nd	nd	Grade, Size, Age, Surgical margin, Extension of surgery, Local symptoms, Site, Positive regional nodes
Potter et al. 1986	1975–1982	211	extremity	nd	nd	Size
Eilber et al. 2003	1975–1997	753	extremity	Grade, Age, Histology	nd	Grade, Size, Age, Histology, Site, Local recurrence, Grade, Size, Local recurrence, Male gender
Vraa et al. 1998	1979–1993	316	extremity, trunk wall	Grade, Surgical margin, Compartment, Extension of surgery, Radiation therapy	nd	Grade, Size, Age, Compartment, Site, Local recurrence
Gronchi et al. 2005	1980–2000	911	extremity	Surgical margin, Recurrent disease, Radiation therapy	Grade, Size, Histology, Depth	Grade, Size, Local recurrence, Depth, Histology, Radiation therapy
Lewis et al. 1997	1982–1995	911	extremity	Age, Positive margin, Histology	Local recurrence	Local recurrence
Pisters et al. 1996	1982–1994	1,041	extremity	Age, Surgical margin, Recurrent disease, Histology	Grade, Size, Recurrent disease, Histology, Depth	Grade, Size, Surgical margin, Recurrent disease, Histology, Depth, Site
Gronchi et al. 2010	1985–2005	997	extremity	Surgical margin, Histology, Radiation therapy	Grade, Size, Histology	Grade, Size, Histology, Depth
Trovik et al. 2000	1986–1991	559	extremity, trunk wall	Surgical margin, Grade	Grade, Size	nd
Novais et al 2010	1995–2008	248	extremity	nd	nd	Gender, Age, Distant relapse, Local relapse, AJCC stage
Stoeckle et al. 2006	1996–2002	205	extremity, trunk wall	Grade, Surgical margin	nd	nd

LR, local recurrence. nd, no data. DR, distant relapse. OS, overall survival. SSS, sarcoma-specific survival.

Although prognostic factors for survival of soft tissue sarcoma are published widely (Collin *et al*, 1987; Gaynor *et al*, 1992; Heise *et al*, 1986; Huuhtanen *et al*, 1999; Markhede *et al*, 1982; Pisters *et al*, 1996b; Rooser *et al*, 1988; Rydholm *et al*, 1984; Singer *et al*, 1994; Stotter *et al*, 1990; Trojani *et al*, 1984; Ueda *et al*, 1988), high grade, large tumour size, advanced age, locally recurrent disease and certain histologic subtypes (malignant peripheral nerve sheath tumour, leiomyosarcoma) are the most cited adverse prognostic factors when extremity and trunk wall soft tissue sarcomas are concerned (Table 3). Regional nodal involvement was included in the multivariate analysis in one series where it lost its adverse effect on survival (Collin *et al*, 1987). However, only 39 per cent of patients underwent lymphadenectomy. There is growing evidence that sentinel node biopsy should be included in the treatment of sarcoma subtypes known to metastasize more frequently to lymph nodes (Andreou *et al*, 2009). In a series with interest on the survival of the patients with metastatic disease at presentation when primary tumour is resected simultaneously with the metastases, patients with lymph node metastases removed had better survival than patients with pulmonary metastases removed (Ferguson *et al*, 2011).

7. PROGNOSTIC TOOLS

Practical prognostic tools for patient counselling, follow-up scheduling and more precisely directing adjuvant chemotherapy for patients are scarce. The seventh edition of the Cancer Staging Manual, of the American Joint Committee on Cancer, divides soft tissue sarcomas into four prognostic groups based on tumour malignancy grade, tumour size and depth, and nodal and distant involvement (Edge *et al*, 2009).

A new prognostic system, the SIN system with three adverse factors (size, vascular invasion, necrosis), was constructed based on experience in a population-based study (Gustafson, 1994). In the reproducibility study of the SIN staging system involving 200 patients, the three adverse factors became tumour size larger than 8 cm, presence of vascular invasion, and tumour necrosis of any size (Gustafson *et al*, 2003). This model divided patients into only two groups, namely high-risk patients and low-risk patients, which was found inadequate for clinical practise. From the same source, the Lund University, also comes a more recent prognostic system designed to discriminate low-risk and high-risk patients among patients with a high-grade tumour (Carneiro *et al,* 2011): the system uses vascular invasion, tumour necrosis, size (≥5 cm) and infiltrative growth pattern. This prognostic instrument also divides patients into only two groups and provides insufficient data for clinical decision-making.

A database of 2,136 patients was used as base to construct a prognostic nomogram for 12-year sarcoma-specific death on the basis of a Cox regression

model with a concordance index of 0.77 (Kattan *et al*, 2002). Probability estimations for any given patient to die of sarcoma within 12 years are based on size, depth, site, histology, age at diagnosis, and grade: the nomogram included all locations. Two validation studies of the nomogram have been performed (Eilber *et al*, 2004; Mariani *et al*, 2005). There are differences in biological behaviour of soft tissue sarcomas of different locations and also treatment differs. Many elderly patients have poor physical condition which frequently prevents the use of adjuvant therapy. The model also included rare histological subtypes with different biological potential and some with targeted therapy.

8. TREATMENT GUIDELINES AT THE HELSINKI UNIVERSITY CENTRAL HOSPITAL SOFT TISSUE SARCOMA GROUP

All patients referred to the multidisciplinary group are discussed at weekly interdisciplinary meetings. Scandinavian Sarcoma Group introduced the treatment program for soft tissue sarcoma (SSG V) in 1986, and our group has updated the protocol and made it more detailed. Our prospective treatment protocol, which has been followed from 1987 with minor changes, included recommendations for adequate local treatment, that is, wide surgery alone (≥2.5 cm) or marginal surgery combined with radiation therapy. The treatment protocol includes all adult soft tissue sarcomas excluding visceral sarcomas, dermatofibrosarcoma protuberans and Kaposi sarcoma. The principles of treatment are surgery selectively combined with postoperative radiation therapy. Preoperatively patients undergo an MRI, computed tomography or both of the primary tumour area. Histological core biopsies and fine needle aspiration are taken under the guidance of ultrasound and in deep locations computed tomography and, to avoid contamination with tumour cells, the biopsy track is placed so that it could be excised with the tumour at the time of definite surgery. Patients with a high-grade tumour also undergo preoperative computed tomography of the chest. Currently, patients with diagnosed low-grade tumour undergo preoperative plain chest radiography.

Surgical resection is the primary treatment in all cases where the tumour can be removed without major sacrifice of function. If the preoperative investigations indicate that adequate surgical margins are not achievable, surgery is aimed at marginal surgical margins followed by radiation therapy. Reoperation is recommended after intralesional surgery whenever feasible. Amputation is recommended in cases of extensive infiltration of a major nerve or vascular structures, or of a joint or bone so that even marginal resection is not feasible.

Radiation therapy is recommended after intralesional and marginal surgery and postoperative radiation therapy is preferred. Other indications include inoperable tumour and tumour contamination of the surgical bed.

Preoperative radiation therapy is administered to large tumours in difficult locations where even marginal surgery does not seem feasible and conservative surgery is attempted. After preoperative radiation therapy, patient is operated in four weeks.

As with surgery, radiation therapy is individually planned. Computer tomography-based treatment planning is used although MRI-based treatment planning is increasingly used. Patients are individually fixated. The target volume in the transversal direction is the surgical bed with a margin of at least 5 centimetres longitudinally and 2–3 centimetres axially. The radiation dose is 50 Gy in 5 weeks (2 Gy/day) with a boost of 10 Gy to 20 Gy to a smaller target volume in 1–2 weeks when adjuvant chemotherapy is not planned. In some patients receiving chemotherapy, 50 Gy is however exceeded. The decision is made case-by-case and depends on the timing of radiation therapy among other things. If radiation therapy is combined with chemotherapy, hyperfractioned radiation therapy is used, 1.5 Gy twice daily. Nowadays intensity-modulated radiation therapy is used (Alektiar *et al*, 2008).

Amendment to protocol was added in 1998 concerning adjuvant chemotherapy: patients less than 70 years with adequate performance status are offered adjuvant chemotherapy if the tumour malignancy grade is high (III-IV in a four-tiered scale) and the tumour fulfills at least two of the following criteria: size larger than 8 cm (in synovial sarcomas 5 cm), necrosis or vascular invasion. Adjuvant chemotherapy consists of a doxorubicin-ifosfamide combination that is administered six times with three-week breaks between treatments. Our protocol for interdigitating chemotherapy courses and hyperfractioned radiation therapy derives from the Scandinavian Sarcoma Group protocol IX for Ewing's sarcoma (Elomaa *et al*, 2000). Combined chemotherapy and radiation therapy treatment starts with two cycles of chemotherapy followed by hyperfractioned radiation therapy of 30 Gy/1.5 Gy twice a day for ten days. After first cycle of radiation therapy patients receive one cycle of chemotherapy followed by hyperfractioned radiation therapy 12 Gy/1.5 Gy twice a day for four days and therafter three cycles of chemotherapy. In case of neoadjuvant treatment, limb-sparing surgery is planned after the fourth cycle of chemotherapy whenever feasible. Postoperatively patients receive two cycles of chemotherapy if a good histological response is detected in the resection specimen. Patients with positive margins have a reoperation and when this is not feasible, further radiation if possible.

The resected specimens are sent to the pathologist fresh, whole, without making any cuts on the surface, the ideal being a situation where the surgeon never sees the tumour itself. After taking necessary samples for molecular analysis, the specimens are fixated in formalin. After fixation the surfaces are painted and thereafter the specimens are dissected. The narrowest margins

are measured in millimetres from the tumour sections. Samples for histological examination are also selected from those areas, where the margin is smallest on macroscopic examination. The final margin is evaluated on histological slides, and the smallest margins as well as their location are reported.

The surgical margins are defined as compartmental if an intracompartmental tumour and the whole muscle compartment are excised *en bloc* including the natural barriers of the compartment. The margin is defined as wide if the tumour was excised with smallest microscopic margin of at least 2.5 cm. A smaller margin is accepted, however, if it consists of an uninvolved anatomical barrier (*e.g.* fascia or periosteum). If the requirements for a wide margin are not fulfilled, the margin is classified as marginal (margins less than wide) or intralesional (microscopic or macroscopic tumour left). Adequate local treatment is defined as wide surgery alone or marginal surgical margin combined with radiation therapy.

Currently, all patients with solitary pulmonary metastases undergo metastasectomy if feasible. After surgery, chemotherapy is administered to patients less than 70 years if the number of metastases exceeds five or the disease-free survival was less than six months. Inoperable metastases are treated with chemotherapy, radiation therapy or with best supportive care.

Patients undergo a regular follow-up. For high-grade sarcomas, the interval is 2 months during the first 2 years, thereafter 3 times annually up to 5 years. Follow-up is extended in patients with synovial sarcomas to 10 years with annual visits up to 7 years and thereafter every 18 months. Patients undergo a chest X-ray at each visit. An MRI or computed tomography scan of the operative area is taken 6 months postoperatively and every 6 months up to 2 years and thereafter once annually up to five years, and for patients with synovial sarcomas annually up to 7 years after 5 years and thereafter once in every 18 months up to 10 years.

For low-grade tumours, the interval is 3 times annually up to 2 years and thereafter 2 times a year up to 5 years, annually up to 7 years and thereafter once in every 18 months up to 10 years. Patients undergo a chest X-ray at each visit. An MRI or computed tomography scan of the operative area is taken annually up to 7 years and thereafter once in every 18 months up to 10 years.

OSTEOSARCOMA

1. GENERAL CONSIDERATIONS

Osteosarcoma is characterized as a malignant tumour of bone in which malignant proliferating mesenchymal cells produce osteoid or immature bone. Fibroblastic, chondroblastic and osteoblastic osteosarcoma are the three histologic subtypes that constitute the conventional osteosarcoma group in the World Health Organization's classification (Fletcher *et al*, 2002). Telangiectatic, small-cell,

intramedullary well-differentiated, parosteal (or juxtacortical), and periosteal osteosarcoma are rare variants of osteosarcoma, some of which have a different prognosis from conventional osteosarcoma. Osteosarcomas are graded histologically, according to the system described by Huvos, based on the degree of cellularity, mitotic count, tumour cell polymorphism and the amount of matrix formation (Huvos, 1991).

Osteosarcoma is the most frequent primary malignant bone tumour with a mean annual incidence of eight during 2002–2009 in Finland according to the Finnish Cancer Registry. It is the tumour of adolescense, approximately 60 per cent of tumours occurring in patients during their two first decades (Arndt *et al*, 1999); patients older than 60 years form only about 10 per cent of the patient population (Huvos, 1991). Osteosarcoma most commonly arises in the metaphyses of long bones (femur, tibia, humerus) rapidly growing in length. Axial bones, foot, hand and skull are rather rare locations for primary tumours in adolescent patients but represent more frequent sites among older patients. In approximately 15 per cent to 20 per cent of patients metastases are present at the time of diagnoses lungs being the most frequent site (Bacci *et al*, 1997; Meyers *et al*, 1993).

Little is known about the causes of osteosarcoma and a predisposing factor can be found in only a small number of new cases. In animal tests, methylcholanthrene (Brunschwig, 1938), beryllium oxide (Dutra *et al*, 1950), and zinc beryllium silicate (Cloudman *et al*, 1949) are shown to induce osteosarcoma. Ionizing radiation is a known predisposing factor for osteosarcoma and in a minimal portion of new cases patients have been exposed to radiation usually as a part of treatment of former cancer (Huvos *et al*, 1985; Wiklund *et al*, 1991). Post-irradiation osteosarcomas usually arise several years later after initial exposure to radiation. Osteosarcoma is frequent among patients with hereditary retinoblastoma, characterized by a mutated *RB1* gene (Hawkins *et al*, 1987). Osteosarcoma is also one of the most frequent tumours among patients with Li-Fraumeni syndrome, which is characterized by germ line mutations of tumour suppressor gene *TP53* leading to multiple primary tumours and a unusually early age of developing tumours (Malkin *et al*, 1990). In a population-based study, 0.4 per cent of patients with Paget's disease developed osteosarcoma (Wermers *et al*, 2008). Multiple hereditary exostoses is an autosomal dominant skeletal disorder characterized by the development of multiple osteochondromas. Malignant transformation is the most serious, but fortunately rare, complication and only a few case reports have been published on osteosarcomas developing in patients with multiple hereditary exostoses (Bovee *et al*, 2002; Lamovec *et al*, 1999). Finland has the highest prevalence of RAPADILINO syndrome, an autosomal recessive disease with special features: RAdial hypoplasia/aplasia, PAtellar hypoplasia/aplasia, and cleft or highly

arched PAlate, DIarrhea, and DIslocated joints, LIttle size and LImb formation, NOse slender and NOrmal Intelligence, known to predispose to osteosarcoma (Siitonen *et al*, 2009).

2. DIAGNOSTICS

Tumour growth rate and clinical symptoms vary a lot. First symptoms usually to arise are pain that grows worse and swelling over the area of bone affected and nearby joint may be partly disabled (Huvos, 1991). In many cases the start of symptoms is linked to a trauma, but trauma is most likely the reason patient draws attention to the body area affected by osteosarcoma, not the cause of the tumour (Sneppen *et al*, 1984; Widhe *et al*, 2000). X-ray usually awakens the suspicion of osteogenic sarcoma and the radiographic appearance of osteogenic sarcoma is characterized by the interrelationship of three aspects: destruction of pre-existent cortical or medullary bone, calcification and bone production, and periosteal new bone formation (Huvos, 1991). Soft tissue extension is frequently seen. MRI is superior compared to the computed tomography scan in delineating bone tumours from adjacent muscle (Hudson *et al*, 1985) and in assessing the local extent of osteosarcoma and planning of limb-sparing procedures (Sundaram *et al*, 1986; Zimmer *et al*, 1986). MRI is a valuable imaging modality to monitor response to neoadjuvant chemotherapy. A computed tomography scan of the chest is widely used for staging. ^{99m}Tc-bone scan is an important part of staging because it allows the detection of other bone sites of involvement: metastases and skip lesions. To date, data on the usefulness of the whole-body positron emission tomography (PET) in staging of osteosarcoma are scarce. In a prospective study of 11 osteosarcoma patients, the sensitivity of PET to find bone metastases was equal to other modalities including bone scan (Volker *et al*, 2007). However, it was inferior to computed tomography scan of the chest in detecting pulmonary metastases. The Children's Oncology Group Bone Tumor Committee recommends wholebody PET for monitoring response to chemotherapy and for surveillance (Meyer *et al*, 2008).

Incisional biopsy or core needle biopsy should be performed preoperatively (Mankin *et al*, 1982). Biopsies are normally taken in the most peripheral part of the lesion in which osteoid production is scarce or even absent and this makes histologic evaluation of biopsy specimens challenging. Biopsies are taken under computed tomography or MRI guidance. As misplaced biopsy, or one that causes hematoma or infection may preclude the subsequent limb-sparing surgery, biopsies should only be performed by those fully aware of planned subsequent surgical procedures (Boriani *et al*, 1984; Mankin *et al*, 1982) and the biopsy tract should be thoroughly excised at the time of definite surgery to avoid local recurrence (Campanacci *et al*, 1980).

3. SURGERY

With improved survival rates, quality of life among patients with osteosarcoma has become an important issue. Amputation or exarticulation was once considered the only acceptable method for eradication of osteosarcoma in the lower extremity. A study of 227 patients with osteosarcoma of the distal end of the femur showed that when divided into three groups, limb-salvage surgery, above-knee amputation or exarticulation of the hip, patient groups had similar survival rates (Simon *et al*, 1986). In a later analysis of the same patients, limb-salvage surgery was associated with a higher rate of reoperations and better functional outcome (Rougraff *et al*, 1994). With improved chemotherapeutic regimens limb-salvage techniques are nowadays possible in a majority of patients with amputation rates of less than 10 per cent (Table 4).

Amputation, however, remains a good option for a small portion of patients: those with poor histological response to neoadjuvant treatment and no opportunity of limb-salvage surgery with negative margins, infiltration of tumour to neurovascular structures, or significant soft tissue involvement. Rotationplasty is a surgical technique for patients with tumour in the distal femur or the proximal tibia (Kotz, 1997). Quality of life 10 years after surgery was similar to the general population among patients that underwent rotationplasty, and rotationplasty was recommended if preoperative investigations indicated that the patient would require an above-knee amputation (Rodl *et al*, 2002). Rotationplasty can also be performed in the hip to avoid exarticulation to resect tumour of the proximal femur (Winkelmann, 1986). In the era of no expandable prosthesis, indications for hip rotationplasty were very young, skeletally immature children with intact neurovascular structures in the thigh and proximal tibia. For skeletally immature patients, advanced expandable and adjustable endoprosthesis are available making hip rotationplasty nowadays a rare procedure (Lewis, 1986). Effect of chemotherapy (Glasser *et al*, 1991) and radiation therapy (Goldwein, 1991) on growth plate should also be considered when choosing optimal reconstruction method after resection. Reconstruction options are allograft, metallic endoprosthesis or the combination of the two (Cannon, 1997). Development in the hardware is increasing durability and reliability in prosthetic reconstructions, and at the same time the need for revisions has decreased (Campanacci *et al*, 2010; Gosheger *et al*, 2006).

Aggressive treatment with even repeated metastatectomies is an accepted strategy for patients relapsed in the lungs only (Antunes *et al*, 1999; Bielack *et al*, 2009; Briccoli *et al*, 2010; Ferrari *et al*, 2003; Huth *et al*, 1989; Kempf-Bielack *et al*, 2005). The impact of surgery for other locations or multiple sites is not as well established (Goorin *et al*, 1991; Huth *et al*, 1989; Saeter *et al*, 1995; Ward *et al*, 1994) but the resection of solitary bone metastases may render patient longterm survivor (Kempf-Bielack *et al*, 2005). Bacci and colleagues presented a study on 162 patients with

extremity osteosarcoma and pulmonary metastases at presentation (Bacci *et al*, 2008). After neoadjuvant therapy primary tumour and metastases were resected simultaneously whenever feasible. Five-year event-free survival for the whole population was 19 per cent; 27 per cent for patients with a complete resection and zero for an incomplete resection.

4. RADIATION THERAPY

Conventional osteosarcoma is known to be relatively resistant to radiation therapy and delivery of an adequate dose is frequently difficult when using external beam irradiation (Beck *et al*, 1976; Berg *et al*, 1977). Neither lung irradiation (Rab *et al*, 1976; Zaharia *et al*, 1986) nor local radiation therapy (Beck *et al*, 1976; Berg *et al*, 1977) is proven to be effective in the absence of systemic therapy. Radiation therapy, administered to the lungs or locally, has not been shown to improve overall survival among patients treated with the appropriate surgery and chemotherapy (Ivins *et al*, 1987; Jenkin, 1977; Kuhl *et al*, 1986). In addition, radiation therapy is not without long-term toxicity and therefore its routine use cannot be recommended in the treatment of osteosarcoma (Anonymous, 1988; Ellis *et al*, 1992; Ivins *et al*, 1987). A possible exception is the small cell variant of osteosarcoma that may be more sensitive to radiation therapy (Martin *et al*, 1982; Stea *et al*, 1988). There is, however, a place for radiation therapy as part of the treatment of unresectable primary tumours or of cases with intralesional surgery (Hernberg *et al*, 2010; Hershey *et al*, 1996; Hug *et al*, 1995; Marsden *et al*, 1991). In the present EURAMOS-1 treatment protocol for osteosarcoma, radiation therapy is included in the treatment in case of positive or uncertain margin (Marina *et al*, 2009).

5. CHEMOTHERAPY

A new era in the treatment of osteosarcoma began in the 1970s, as high-dose methotrexate and doxorubicin were shown to improve survival (Cortes *et al*, 1974; Jaffe *et al*, 1974; Rosen *et al*, 1976). A randomized trial on postoperative chemotherapy versus no chemotherapy had six-year event-free survival rates of 11 per cent and 61 per cent, respectively (Link *et al*, 1991; Link *et al*, 1986). Rosen and colleagues introduced the use of preoperative multi-drug chemotherapy together with delayed surgery as a new treatment strategy (Rosen *et al*, 1979; Rosen *et al*, 1976). In protocol T-10, all patients received the same neoadjuvant chemotherapy but adjuvant chemotherapy was chosen of the two alternatives based on the histologic response of the primary tumour to neoadjuvant chemotherapy (Rosen *et al*, 1982). The histologic response to neoadjuvant chemotherapy is a strong prognostic factor for survival (Bielack *et al*, 2002; Ferrari *et al*, 2005; Meyers *et al*, 1992; Sluga *et al*, 1999). Methotrexate (Jaffe, 1972), cisplatinum (Ochs *et al*, 1978), doxorubicin (Cortes

et al, 1974) and ifosfamide (Pinkerton *et al*, 1985; Pratt *et al*, 1987) are the four generally accepted active drugs against osteosarcoma. Etoposide displays synergy with ifosfamide in the treatment of recurrent sarcomas (Miser *et al*, 1987), and the combination was used as salvage-therapy for poor responders in a Scandinavian Sarcoma Group study VIII (Smeland *et al*, 2003).

In a Scandinavian Sarcoma Group II study on neoadjuvant chemotherapy, only 17 per cent of patients achieved a good histologic response with high-dose methotrexate (Saeter *et al*, 1991). In the later Scandinavian Sarcoma Group study VIII on chemotherapy for classical osteosarcoma, the rate of good responders increased to 58 per cent with more intense preoperative chemotherapy but this did not translate to improved survival rate (Smeland *et al*, 2003).

The conclusions of the Italian Sarcoma Group / Scandinavian Sarcoma Group study I included that high-dose ifosfamide carries major renal and hematologic toxicities with no improvement to overall survival compared to protocols using standard doses (Bacci *et al*, 2002; Ferrari *et al*, 2005). In the Scandinavian Sarcoma Group study XIV, ifosfamide was omitted from preoperative chemotherapy and administered only to patients with a poor histologic response to primary chemotherapy (Smeland *et al*, 2011). Survival rates were comparable to other osteosarcoma series but ifosfamide as a salvage therapy failed to improve survival to equal that of good responders. The Italian Sarcoma Group / Scandinavian Sarcoma Group study II was for high-risk osteosarcoma patients with pelvic tumour or metastatic disease at presentation (Brach Del Prever *et al*, 2005). In addition to conventional chemotherapy, it contained two cycles of high-dose chemotherapy with peripheral blood stem cell rescue. High-dose chemotherapy was fairly well tolerated, but because of the projected overall survival of only 39 per cent at three years the authors concluded that there is no evidence for using high-dose chemotherapy in high-risk osteosarcoma patients. In EURAMOS-1, a randomized trial on adjuvant chemotherapy, all patients receive neoadjuvant combination regimen of methotrexate, cisplatinum and doxorubicin (Marina *et al*, 2009). Poor responders are then randomized to either receive methotrexate, doxorubicin and cisplatinum, with or without ifosfamide combined with etoposide. Good responders are randomized to either receive methotrexate, doxorubicin and cisplatinum, with or without interpheron-α.

6. PROGNOSIS AND PROGNOSTIC FACTORS

Improved survival and good local control with limb-sparing surgery with good functional outcome are the indicators of the quality of treatment in osteosarcoma of the extremity. With modern multi-drug chemotherapy, amputation rates as low as ten per cent

are achieved with treatment protocols for highly selected patients (Table 4). Local recurrence rates in the same series have also been less than ten per cent. Local recurrences are in many cases also curable but amputation rate is higher at this point. Development of metastatic disease still poses a real threat to survival as nearly all patients die of metastases. In the latest series reported, the rate of metastases varied from 20 per cent to 30 per cent (Table 4).

The prognosis of non-metastatic osteosarcoma has improved dramatically with modern chemotherapy, and nowadays the five-year overall survival rates are up to 77 per cent among patients with classical osteosarcoma, which is a high-grade, extremity, local osteosarcoma in patients less than 40 years (Table 4). In less selected national, population-based series the 4-year survival was 25 per cent during 1953–1974 and 47 per cent during 1975–1977 in Norway (Harvei *et al*, 1981), the 5-year survival rate was 53 per cent during 1990–1994 in Britain (Stiller *et al*, 2006), the 5-year survival was 44 per cent in New Zealand during 1994–1999 (Curry *et al*, 2006), and the 5-year survival rate was 42 per cent in England during 1998–2002 (Whelan *et al*, 2011). In a single-institution experience only 41 per cent of patients with osteosarcoma were eligible for modern chemotherapy trials, that is they had classical osteosarcoma (Saeter *et al*, 1996). Trials enrolling these "non-classical" high-risk osteosarcoma patients are therefore warranted. EUROBOSS 1 is one such trial enrolling patients aged 41–65 years (Anonymous, 2011). Protocol includes high-grade bone sarcomas of any stage and patients are administered cisplatinum, doxorubicin and ifosfamide. Only patients with poor histologic response to neoadjuvant chemotherapy receive methotrexate. Radiation therapy is recommended for patients with inoperable tumours and for positive margins. Patients less than 40 years with axial, secondary or metastatic osteosarcoma at presentation were eligible for EURAMOS-1 study as long as disease was considered resectable (Marina *et al,* 2009).

Although prognostic factors for osteosarcoma are published widely (Bielack *et al*, 2002; Ferrari *et al*, 1997; Meyers *et al*, 1992; Sluga *et al*, 1999; Smeland *et al*, 2003; Stiller *et al*, 2006; Tarkkanen *et al*, 1999), of these, poor histologic response to neoadjuvant treatment, high grade, axial site, high lactate dehydrogenase level and large size are the most cited adverse factors when non-metastatic osteosarcomas are concerned (Table 5). High malignancy grade is widely accepted as an independent prognostic factor for overall survival and metastases-free survival but because of the different disease course of low-grade osteosarcoma, these patients are excluded from treatment studies. Metastatic disease at presentation yields very poor prognosis despite aggressive treatment (Bacci *et al*, 2008; Meyers *et al*, 1993). Advanced age of the patient at diagnosis is shown to be of adverse prognostic value for overall survival but for most series, only patients less than 40 years are eligible. Pelvic site is

Table 4. Characteristics and survival rates in patients with osteosarcoma in large series

Authors	Period	Type of study	N	Site(s) and grade#	Age	AMP	LR%	MET%	MFS	DFS	EFS	OS
Dahlin et al. 1967	1909–1964	single-institution report	600	all except jaw	all ages	nd	nd	nd	nd	nd	nd	20.3§
Marcove et al. 1970	1949–1965	single-institution report	145	extremity	under 21	100	nd	83	nd	nd	nd	17.4§
Meyers et al. 1992	1975–1984	single-institution experience	279	extremity and axial	all ages	51	nd	nd	nd	65	nd	71
Krailo et al. 1987	1976–1981	randomised multicenter study	166	extremity	under 21	nd	nd	nd	nd	38¶	nd	20¶
Glasser et al. 1992	1976–1986	single-institution report	279	extremity	all ages	41	6	nd	nd	73 (10-year)	69 (10-year)	73 (10-year)
Sluga et al. 1999	1977–1990	single-institution report	130†	extremity	under 21	35	2	28	nd	67	nd	70
Stiller et al. 2006	1980–1994	national report	1349	all locations	under 40	nd	nd	nd	nd	nd	nd	42, 54, 53**
Bielack et al. 2002	1980–1998	multicenter study	1,702‡	all locations	all ages	45	12	nd	nd	nd	49 (10-year)	60 (10-year)
Eyre et al. 2010	1981–2002	population-based study	236	nd	under 40	nd	nd	nd	nd	nd	nd	58
Winkler et al. 1988	1982–1984	randomised multicenter study	125	extremity	under 40	73	2	38	48 (4-year)	nd	nd	nd
Bacci et al. 1990	1983–1986	single-institution study	127	extremity	under 50	26	5	48	nd	51	nd	nd
Ferrari et al. 1997*	1983–1986	single-institution study	127	extremity	under 50	26	8	50	nd	46 (12-year)	nd	53 (12-year)
Bramwell et al. 1992	1983–1986	randomised multicenter study	198	extremity	under 40	30	6	46	nd	57, 41	nd	64, 50
Provisor et al. 1997	1983–1986	multicenter study	231	extremity	under 22	57	2	44	nd	nd	53 (8-year)	60 (8-year)
Goorin et al. 2003	1986–1993	randomised multicenter study	100	extremity	under 30	51	nd	nd	nd	nd	65	78
Fuchs et al. 1998	1986–1988	multicenter study	171	extremity	under 40	58	4	25	nd	nd	66 (10-year)	72 (10-year)
Bacci et al. 1993	1986–1989	single-institution study	164	extremity	under 40	17	2	32	nd	63	nd	71
Souhami et al. 1997	1986–1991	randomised multicenter study	391	extremity	under 40	28	nd	nd	nd	nd	nd	55
Smeland et al. 2003	1990–1997	multicenter study	113	extremity	under 40	42	7	37	63	nd	nd	74
Lewis et al. 2007	1993–2002	randomised multicenter study	490	extremity	under 41	26	13	44	nd	nd	nd	55, 58
Meyers et al. 2005	1993–1997	randomised multicenter study	677	extremity and axial	under 30	23	nd	nd	nd	nd	63	nd
Bacci et al. 1998	1993–1995	single-institution study	121	extremity	under 40	5	6	21	nd	75 (3-year)	nd	91 (3-year)
Le Deley et al. 2007	1994–2001	randomised multicenter study	234	extremity	under 20	6	4	31	nd	nd	62	76
Ferrari et al. 2005	1997–2000	multicenter study	182	extremity	under 40	8	4	30	nd	nd	64	77

*follow-up study of Bacci et al. 1990 study. †includes 11 patients with M1 disease. ‡includes 211 patients with M1 disease. #89 % high-grade tumours in Dahlin et al. 1967, no data in Marcove et al. 1970. Others include only high-grade tumours. ¶estimated from survival curves. § percentage of deceased patients. **by five-year periods. AMP, amputation rate. nd, no data. LR, local recurrence. MET, metastases. MFS, 5-year metastases-free survival. DFS, 5-year disease-free survival. EFS, 5-year event-free survival. OS, 5-year overall survival.

more frequently seen in older patients and survival of these patients is worse than in patients with extremity tumours (Bielack *et al*, 2002; Kawai *et al*, 1998). Worse survival among patients over 40 years is also partly explained by the fact that these patients don't tolerate chemotherapy regimen for osteosarcoma (methotrexate in particular) as well as younger patients.

With current therapy, less than 10 per cent of patients develop local recurrence (Bacci *et al*, 1998; Ferrari *et al*, 2005; Le Deley *et al*, 2007). For local recurrence, positive margin is a strong adverse factor. In two large series, isolated local recurrences comprised eight per cent to 12 per cent of all recurrences with a five-year postrelapse survival of 26 per cent to 39 per cent (Gelderblom *et al*, 2011; Kempf-Bielack *et al*, 2005). Many patients developing local recurrence also develop distant metastases at some point in the course of their disease (Bielack *et al*, 2009). In both series, early timing of relapse, within 18 months (Kempf-Bielack *et al*, 2005) or within 24 months (Gelderblom *et al*, 2011) was a strong adverse factor for overall survival after relapse.

Table 5. Prognostic factors for disease-free survival and overall survival in patients with osteosarcoma.

Author	Period	N	DFS	OS
Meyers et al. 1992	1975–1984	279	LDH, Histologic response, Site	nd
Sluga et al. 1999	1977–1990	130*	nd	Volume, Histologic response, Metastatic disease
Stiller et al. 2006	1980–1994	1,349	nd	Sex, Site, Treatment centre
Bielack et al. 2002	1980–1998	1,702†	nd	Macroscopic residual tumour, Histologic response, Metastatic disease, Site
Ferrari et al. 1997	1983–1986	127	LDH, Histologic response, MTX dose	nd
Smeland et al. 2003	1990–1997	113	Volume, Serum 24-h MTX, Sex	nd

* includes 11 patients with metastatic disease. †Includes 211 patients with metastatic disease. DFS, disease-free survival at 5 years. LDH, lactate dehydrogenase. nd, no data. MTX, methotrexare. OS, overall survival at 5 years.

7. GENERAL TREATMENT GUIDELINES FOR OSTEOSARCOMA

Treatment is conducted according to contemporary treatment protocol. Patients are either formally enrolled or treatment is modified from the treatment protocol according to the age of the patient, organ functions and wish. In general, diagnosis is confirmed with a histological biopsy, either with a core needle biopsy under the computed tomography or MRI guidance or an open biopsy in order to ensure sufficient

material for histologic evaluation. The primary site is assessed by X-ray and MRI scan of the entire bone involved, preferably including adjacent joints, and additional computed tomography scan if needed. ^{99m}Tc-bone scan allows the detection of other bone sites of involvement: metastases and skip lesions. The computed tomography of the chest is used to detect pulmonary metastases. Low-grade osteosarcoma can be treated with radical surgery alone (Campanacci *et al*, 1984). Complete blood count, renal function, and liver function are monitored for patients receiving chemotherapy. Cardiac function is tested with echocardiography or radionuclide ventriculography.

For operable high-grade osteosarcoma, neoadjuvant multidrug chemotherapy, (limb-salvage) surgery and adjuvant chemotherapy is the treatment of choice. Neoadjuvant chemotherapy is generally the combination of methotrexate, doxorubicin, and cisplatin. In some protocols ifosfamide is added. Surgery follows neoadjuvant therapy soon after (in a week). Surgery aims at achieving adequate surgical margins. In case preoperative staging gives no possibility of adequate margins with local excision, amputation is recommended. Radiation therapy can be used in case of inadequate margins and patient refusal of amputation. The type of reconstruction is chosen according to tumor location and extension, patient age, and preferences. The surgical margins are assessed according to Enneking and colleagues as radical, wide, marginal, or intralesional (Enneking *et al*, 1981). Histological response to neoadjuvant treatment is graded and postoperative chemotherapy planned according to response. Adjuvant chemotherapy is scheduled to begin after recovery from surgery. For inoperable osteosarcoma, chemotherapy combined to radical radiation therapy can produce long-term remission (Hernberg *et al*, 2010).

Patients are followed-up by chest x-ray and operated limb every 2 to 3 months for 3 years. Follow-up becomes less frequent thereafter with 3 visits annually during the fourth and fifth years, and subsequently every 6 months. Renal function with glomerular filtration rate and cardiac function with echocardiographic measurement of the left ventricular ejection fraction are performed at the end of chemotherapy treatment and every year for the first 3 years of follow-up to detect any renal or cardiac long-term side effect. An audiogram is recommended at the end of the treatment because of the use of cisplatinum (modified from EURAMOS-1 protocol).

CENTRALISATION OF SARCOMA TREATMENT

Due to the rarity of sarcomas, specialized multimodality treatment centres have been established. The importance of centralisation of diagnostics and treatment of this rare neoplasm is well established (Bauer *et al*, 2001; Clasby *et al*, 1997; Gustafson *et al*, 1994; Karakousis *et al*, 1995; Wiklund

et al, 1996). Shortages in all areas of diagnostics and treatment of soft tissue sarcoma have been published. In retrospective studies only 63 per cent of soft tissue sarcoma patients were referred to a specialized soft tissue sarcoma team before open biopsy or surgical excision (Bauer *et al*, 2001), and only 42 per cent of patients were biopsied before definite surgery (Ray-Coquard *et al*, 2004). In a single-institution review, 37 per cent of diagnoses were corrected (Randall *et al*, 2004).

Wide surgical margin was achieved in 44 per cent of patients, and of the patients not having a wide surgical margin, only 48 per cent received postoperative radiation therapy as recommended (Ray-Coquard *et al*, 2004). More than one half of patients with unsatisfactory surgical margins received no further therapy in another review (Clasby *et al*, 1997). The cumulative local recurrence rate was 20 per cent at five years among patients operated for primary soft tissue sarcoma at a specialized sarcoma centre and 70 per cent for patients treated by surgery outside a sarcoma centre (Bauer *et al*, 2001). In another review, treatment at a soft tissue sarcoma centre yielded a local recurrence rate of 19 per cent and treatment in district general hospitals 39 per cent (Bhangu *et al*, 2004). Hospital follow-up was not offered to 12 per cent of patients (Clasby *et al*, 1997). Gutierrez and colleagues concluded in their study on the Florida Cancer Data System that soft tissue sarcoma patients with tumours exceeding 10 cm, with high-grade tumours, and with truncal or retroperitoneal sarcomas, should be exclusively treated at a high-volume (more than four new patients annually) centre (Gutierrez *et al*, 2007).

Ferrari and colleagues reported a limb-salvage rate of 92 per cent and concluded that this was at least partly due to multidisciplinary treating teams with experienced surgeons (Ferrari *et al*, 2005). In a national retrospective review, the survival rate of osteosarcoma was lower in non-teaching hospitals (Stiller *et al*, 2006). Because of its rareness and challenges in the multimodality treatment of osteosarcoma, treatment is largely concentrated to university hospitals and other teaching hospitals. In research, intercontinental intergroup cooperation is necessary to yield sufficient patient accrual. The first such trial is the EURAMOS-1 trial which is currently underway (Marina *et al*, 2009).

AIMS OF THE STUDY

Study I: to evaluate local control by the smallest surgical margin in soft tissue sarcoma of the extremity and the trunk wall, to find prognostic factors for local recurrence and to study adherence to treatment protocol.

Study II: to construct a new prognostic tool to predict 10-year sarcoma-specific survival for soft tissue sarcoma of the extremity or the trunk wall, to validate the new tool in an external independent patient series, and to study if the tool has a role in decision-making on adjuvant chemotherapy.

Studies III-IV: to study survival rates in osteosarcoma in a nationwide, population-based series over the study period of 1971–2005, to describe the accuracy of histologic diagnostics with mandatory histology review, to describe the clinical features of osteosarcoma at presentation and their prognostic significance, to describe treatment, and to calculate the annual population-based incidence of osteosarcoma in Finland.

MATERIALS AND METHODS

Patients referred for primary or locally recurred local soft tissue sarcoma of the extremity or the trunk wall and treated by the Soft Tissue Sarcoma Group at HUCH during the 1987–2002 period are analyzed in Studies I and II. Patients not undergoing surgery and patients with tumours of uncertain biological potential were excluded. The southern Sweden soft tissue sarcoma database was used for external validation. It is a population-based database and includes adult patients with a soft tissue sarcoma in the extremity or the trunk wall.

Data on patients diagnosed with osteosarcoma in Finland during the 1971–2005 period were retrieved from the files of the nationwide population-based Finnish Cancer Registry for Studies III and IV. The re-evaluation of original specimens was performed by an experienced bone pathologist (T.B). Detailed data were gathered from patient files.

Local recurrence-free survival, metastases-free survival and sarcoma-specific survival rates were calculated according to the method of Kaplan and Meier (Kaplan *et al*, 1958) (Studies I-IV). Death occurring from an unrelated reason was regarded as lost in follow-up. Univariate analysis for clinical prognostic factors was performed by the log-rank test for discrete variables and by Cox regression analysis for continuous variables. The level of significance was set at $p<0.01$ in Studies I and II and at $p<0.05$ in Studies III and IV. If the univariate test showed a correlation between a descriptive variable and local recurrence this variable was included in a backwards stepwise Cox´s proportional hazards model for multivariate analysis. The $\chi 2$-test was used to assess differences in the distribution of tumour characteristics among margin width subgroups in Study I, and differences in groups by decades (1971–1980 vs. 1981–1990) in Study III.

In Study II, multivariate survival analyses were performed with the Cox proportional hazards model entering the following covariates: tumour size, necrosis, vascular invasion, tumour depth, location, and histologic grade. Based on the fitted Cox regression models, 10-year sarcoma-specific survival is estimated for each patient individually. With the β-coefficients of the Cox models, a prognostic index is calculated: the average prognostic index value is taken as a baseline reference and the relative risks of individual patients are calculated. The SIN model and the proposed model were statistically compared according to accuracy of 10-year sarcoma-specific survival prediction with regard to discrimination (the area under the ROC curve) in both the Helsinki series and the external Lund validation series. Calibration was analyzed by ranking the patients according to ascending predicted 10-year survival, dividing the cohort into ten equally sized groups and calculating

the observed 10-year sarcoma-specific survival in each group according Kaplan-Meier. In addition, the net reclassification improvement and the integrated discrimination improvement were used.

The study was approved by the Joint Ethics Committee of Helsinki University Central Hospital and by the Ministry of Health and Social Affairs.

RESULTS

1. LOCAL CONTROL BY MICROSCOPIC MARGIN, PROGNOSTIC FACTORS FOR LOCAL RECURRENCE, AND ADHERENCE TO TREATMENT PROTOCOL IN SOFT TISSUE SARCOMA OF THE EXTREMITY AND THE TRUNK WALL (STUDY I)

Two hundred and seventy patients are included in the analysis. Fifteen per cent of the patients were referred for locally recurrent disease: twenty-five patients for first local recurrence, seven patients for second local recurrence, and eight patients for third or later local recurrence; 230 patients had a primary tumour. Most tumours were located in the extremities (n=190, 70 per cent), 80 patients had a tumour of the trunk wall. Of the 270 tumours, 61 per cent were deep-seated and 71 per cent high-grade. In 12 (4 per cent) patients the tumour was a postirradiation sarcoma. Limb-sparing surgery was achieved in 173 (91 per cent) patients with tumors of the extremities. Local control rate at five years was 76 per cent for the whole study population with a median follow-up of 6.6 years.

Exclusion of patients with intralesional surgery (n=21) and patients with no reported smallest margin in centimetres (n=17) left 232 patients for the margin analysis: the smallest surgical margin of at least 1 centimetre, 2 centimetres and 2.5 centimetres yielded five-year local control rates of 83, 86 and 89 per cent, respectively. Seventy-eight per cent of patients with a margin of less than 1 centimeter received radiation therapy, 74 per cent of patients with a margin of less than 2 centimetres received radiation therapy and 67 per cent of patients with a margin of less than 2.5 centimetres received radiation therapy. Six per cent of patients with a margin of at least 2.5 centimetres received radiation therapy. The smallest margin in centimetres retained its statistical significance in multivariate analysis. Local control among patients with a post-irradiation sarcoma was significantly inferior, 29 per cent versus 79 per cent, at five years.

Of the 270 patients, 160 were treated with inadequate surgery (21 with intralesional surgery and 139 with marginal surgery), 119 (74 per cent) of them received radiation therapy. The reasons for not performing a reoperation after intralesional surgery included poor general condition and refusal of amputation. Of the 270 patients, 59 (22 per cent) received inadequate local treatment according to the treatment protocol (Table 6). Local control among patients with inadequate local treatment was significantly lower compared to patients with adequate local treatment ($p<0.0001$). For patients with a marginal surgical margin, without adjuvant radiation therapy, five-year local recurrence-free survival rate was 75 per cent for low-grade and 39 per cent for high-grade tumours. Reasons for not administering radiation therapy included poor general condition and low histologic

grade of the tumour with expected low probability of local recurrence. Recurrent disease at presentation was not of adverse prognostic value for further local recurrence in our series (p=0.45).

Table 6. Local control by treatment category in 270 patients with soft tissue sarcoma

	Inadequate treatment	Adequate treatment
Treatment category	No. of patients / (no. of local failures) / estimated 5-year local control	No. of patients / (no. of local failures) / estimated 5-year local control
Intralesional without RT	3 / (3) / 0%	
Intralesional and RT	18 / (9) / 38%	
Marginal without RT	38 / (15) / 54%	
Marginal and RT		101 / (24) / 79%
Wide*		107 / (12) / 89%
Compartmental†		3 / (1) / 67%
Total	59 / (27) / 46%	211 / (37) / 84%

RT, radiation therapy. *six cases with RT. †two cases with RT

2. NEW PROGNOSTIC MODEL FOR SOFT TISSUE SARCOMA OF THE EXTREMITY AND THE TRUNK WALL AND ITS EXTERNAL VALIDATION (STUDY II)

Original histological slides of 294 patients with tumours of the extremities or the trunk wall were available for histological re-examination. Exclusion criteria comprised: extraskeletal osteosarcoma, chondrosarcoma, Ewing/PNET family tumour, angiosarcoma, alveolar soft tissue sarcoma, epitheloid sarcoma, clear cell sarcoma, atypical lipoma/grade I liposarcoma, dermatofibrosarcoma protuberans, preoperative radiation therapy, and metastatic disease. Fifteen patients with chemotherapy were also excluded. Thirty-eight patients had a locally recurrent tumour. Amputation rate was eight per cent for patients with a tumour of the extremity. The median follow-up for the patients alive at the end of follow-up was 7.2 years. Hundred and thirty-four patients received postoperative radiation therapy (nine patients after wide surgery, 103 after marginal and 22 after intralesional surgery).

Validation material was from the southern Sweden soft tissue sarcoma database, a population-based database including adult patients with a soft tissue sarcoma of the extremity or trunk wall. Patients with metastatic disease at presentation, patients receiving adjuvant chemotherapy and patients with missing data on the assessed and reported parameters were excluded which left 354 patients diagnosed during 1973–1997 for this study. In the validation series, there were more

tumours larger than 5 cm. Fifty-seven patients received postoperative radiation therapy (11 patients after wide surgery, 39 after marginal surgery and seven after intralesional surgery).

In the multivariate Cox proportional hazards regression, tumour size per cm, histologic grade per grade, location, and tumour depth were significant predictors of sarcoma-specific survival. Necrosis and vascular invasion were included in the final prognostic model although they lost their statistical significance in multivariate analysis, because they showed relatively large hazard ratios in univariate analysis and have been validated in several studies.

The proposed model discriminated among patients in the Helsinki series better than the SIN model (area under the curve (AUC) of 0.81 versus 0.74, p=0.0007), in the prediction of sarcoma-specific survival. The same was also true for the validation series (AUCs of 0.77 vs. 0.73, p=0.035).

For concordance analysis, patients were divided into ten equally sized groups according to decreasing predicted 10-year sarcoma-specific survival, and the groups were plotted against observed survival (Kaplan-Meier estimates). A good concordance was seen in the groups with a predicted 10-year survival of over 50 per cent whereas a slight underestimation was observed in the groups predicted to have the lowest survival. That is, the observed sarcoma-specific survival was somewhat higher than predicted by the model in the groups with a predicted 10-year survival of less than 50 per cent. The model also showed good calibration in the reclassification method in the validation series.

3. INCIDENCE, TREATMENT RESULTS, AND PROGNOSIS OF OSTEOSARCOMA IN FINLAND DURING 1971–2005 (STUDIES III AND IV)

Of the 478 osteosarcomas, the original histologic slides of biopsy specimens of 361 patients (76 per cent) were available for re-evaluation. Patients not re-evaluated were significantly older at diagnosis and larger portion of tumours not available for re-evaluation were located axially compared to tumours available. By study periods, 1971–1980, 1981–1990, 1991–2005, showed false histologic diagnosis rates of 22 per cent, 13 per cent and 5 per cent, respectively.

The mean annual incidence of osteosarcoma per million was 1.8 during 1991–2005. The percentage of axial tumours and patients with metastatic disease at presentation increased during the study periods (Table 7). Of the patients with a high-grade tumour 36 per cent would have been ineligible for trials of classical osteosarcoma.

Table 7. Demographic data by study periods.

	1971–1980	1981–1990	1991–2005	p[a]
Sex (M/F)	1.54	1.58	1.22	0.57
Age, mean (percentage over 40 years)	22 (13)	21 (8)	26 (19)	0.04 (0.06)
Percentage of axial tumours	13.1	12.6	25.7	0.02
Percentage of metastatic disease at diagnosis	16.4	7.4	19.4	0.04
Percentage of low-grade tumours	1.6	4.2	12.5	0.01

[a]By $\chi 2$ test

Of the 255 patients with local disease, 246 (96 per cent) underwent surgery. During 1971–1990, patients were operated in 11 hospitals and treatment was centralized to five university hospitals during 1991–2005. Although the rate of limb-salvage surgery increased from 12 per cent to 78 per cent over the study periods, no changes were evident for local recurrence rates in patients that underwent surgery to treat extremity tumours during the study periods: 1971–1980 (84 per cent), 1981–1990 (88 per cent), 1991–2005 (84 per cent). Seventy-seven patients were formally enrolled to the trials. For patients not enrolled to the trials and receiving chemotherapy treatment, treatment was based on several regimens and modified for age and organ functions.

PROGNOSIS OF METASTATIC DISEASE AT PRESENTATION

Forty-five patients had metastatic disease at diagnosis (17 during 1971–1990 and 28 during 1991–2005), 33 (73 per cent) patients with isolated lung metastases. Of the 45 patients, six remain disease-free at 6–17 years: all of these patients had a peripheral tumour and isolated pulmonary metastases.

SURVIVAL

Ten-year osteosarcoma-specific survival improved from 31 per cent to 58 per cent in patients with high-grade osteosarcoma of any stage (Figure 1). The 10-year osteosarcoma-specific survival for local high-grade tumours improved from 37 per cent to 69 per cent (Figure 2). The 10-year osteosarcoma-specific survival for the whole study population improved from 32 per cent to 63 per cent (Figure 3). The 10-year osteosarcoma-specific survival for patients with a local high-grade extremity tumour improved from 37 per cent to 75 per cent during 1971–2005. Five deaths (four neutropenic febrile infections and one dilating cardiomyopathy) were recorded as therapy complications during 1971–1990, there were no treatment-related deaths during 1991–2005.

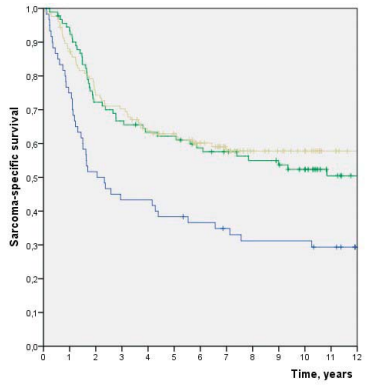

Figure 1. Sarcoma-specific survival during study periods in patients with a high-grade osteosarcoma of any stage. Blue 1971–1980, green 1981–1990 and brown 1991–2005.

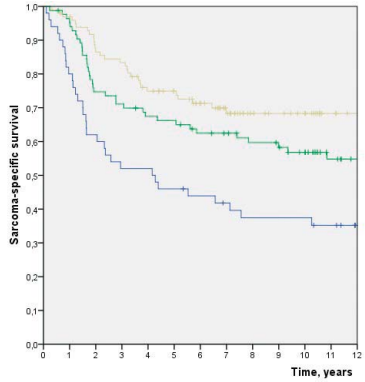

Figure 2. Sarcoma-specific survival during study periods in patients with a local high-grade osteosarcoma. Blue 1971–1980, green 1981–1990 and brown 1991–2005.

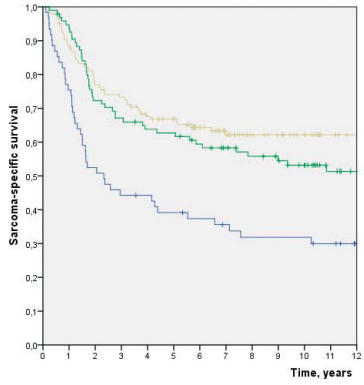

Figure 3. Sarcoma-specific survival during study periods in the whole study population with osteosarcoma. Blue 1971–1980, green 1981–1990 and brown 1991–2005.

DEVELOPMENT AND TREATMENT OF METASTATIC DISEASE

The 10-year metastasis-free survival rate for high-grade osteosarcoma improved during the study periods from 39 to 66 per cent. Of the 99 patients developing metastatic relapse, 11 patients (11 per cent) remain disease-free at follow-up (3–16 years after treatment). Isolated lung metastases was the most common pattern of first metastases seen in 71 patients.

MULTIVARIATE ANALYSIS ON PROGNOSTIC FACTORS

Multivariate analysis was performed only in the 1991–2005 study period: development of local recurrence and major deviation from the treatment protocol were significant factors for osteosarcoma-specific survival. For metastases-free survival, there were no significant prognostic factors in multivariate analysis.

DISCUSSION

1. LOCAL CONTROL BY SMALLEST SURGICAL MARGIN, PROGNOSTIC FACTORS FOR LOCAL RECURRENCE, AND ADHERENCE TO TREATMENT PROTOCOL IN SOFT TISSUE SARCOMA OF THE EXTREMITY AND THE TRUNK WALL (STUDY I)

We evaluated the effect of the smallest surgical margin in centimeters on local control: the smallest margin was reported by the pathologist measuring the narrowest margins from fixated tumour sections. The role of the team pathologist is therefore paramount. An adequate margin was defined as the smallest surgical margin of at least 2.5 cm. However, the choice of 2.5 cm was not evidence-based. The smallest margin of at least 1 centimeter yielded 5-year local control of 83 per cent, 2 centimeters 86 per cent and 2.5 cm 89 per cent. An amputation rate of 9 per cent in the present study is acceptable (Gronchi *et al*, 2005; Lewis *et al*, 1997). No functional scoring or systematic, quantified assessments of the functional results were performed, and therefore, we are unable to provide any data on functional status after resection. This, however, becomes more and more important issue as the prognosis of soft tissue sarcoma improves. Karakousis and colleagues reported local control of 94 per cent with surgery alone with the smallest margin of at least 2 centimeter with an amputation rate of 6 per cent (Karakousis *et al*, 1991). Data on the effect of the smallest margin in centimeters are scarce but the most frequently used cut-off point for an adequate margin is 1 centimeter (Baldini *et al*, 1999; Borden *et al*, 2003; Grimer *et al*, 2010; Khanfir *et al*, 2003; McKee *et al*, 2004).

With the smallest margin of at least 1 centimeter and an amputation rate of three per cent (38 per cent received radiation therapy) McKee and colleagues achieved a five-year local recurrence-free survival of 84 per cent (McKee *et al*, 2004), Baldini and colleagues reached 100 per cent (function-saving surgery alone) (Baldini *et al*, 1999). In addition to the studies above, also Khanfir and colleagues recommend radiation therapy after surgery with a margin of less than 1 centimeter and also intralesional surgery (Khanfir *et al*, 2003). Our results are similar to McKee's and colleagues' but show worse local control with the smallest margin of at least 1 centimeter than reported by Baldini and colleagues (Baldini *et al*, 1999; McKee *et al*, 2004). Based on this study we recommend a smallest surgical margin of 2–3 centimetres in soft tissue sarcoma surgery but a remark has to be made. Improvement in local control is present but moderate in margins more than 1 centimeter, and if a wider margin would lead to a considerable impairment of function, smaller margin is to be considered combined with radiation therapy.

Local control was inferior for patients with an inadequate margin

and not receiving radiation therapy compared to patients with inadequate margin combined to radiation therapy. This held true for both low-grade and high-grade tumours and, therefore, we recommend adjuvant radiation therapy for patients with an inadequate margin irrespective of grade. The smallest margin in centimetres was a strong prognostic factor for local recurrence indicating that surgical margin is more important than radiation therapy in achieving local control. McKee and colleagues found margin width, and size of the tumour, to have an independent prognostic effect for local control (McKee *et al*, 2004).

Recurrent disease at presentation had the same local recurrence-free rate as patients presented with a primary tumour. Local recurrence had independent adverse prognostic value for further local recurrence in two largest series published on extremity soft tissue sarcoma (Gronchi *et al*, 2010; Pisters *et al*, 1996b). We have treated locally recurrent disease according to the same principles as primary tumours which calls for surgeon's skills and experience. Our study states that with an aggressive local treatment approach for locally recurrent disease, local control rates can be achieved that are similar to patients treated for primary tumour.

The proportion of patients receiving inadequate local treatment according to treatment protocol (intralesional surgery with or without radiation therapy or marginal surgery without radiation therapy) in our previous report was 40 per cent (Wiklund *et al*, 1996). We learnt from our first report that postoperative radiation therapy, in cases of inadequate surgery, should not be lightly omitted. We have followed the protocol more firmly since the first report and managed to reduce the proportion of patients receiving inadequate treatment markedly: in the present study 22 per cent received inadequate local treatment. Adherence to treatment protocol should be emphasized because patients having inadequate local treatment had an inferior five-year local control. Possible explanations for suboptimal local treatment in the present study were low-grade tumour and expected low local recurrence rate. Many patients with advanced age have poor physical condition with many illnesses, thus large resection and possible reconstruction surgery would be with increased risk. Radiation therapy also is a challenging treatment modality for elderly and patients with poor general condition: radiation fields are generally large and doses high and treatment generally takes 5 weeks.

2. NEW PROGNOSTIC MODEL FOR SOFT TISSUE SARCOMA OF THE EXTREMITY AND THE TRUNK WALL AND ITS EXTERNAL VALIDATION (STUDY II)

The proposed prognostic model uses 294 patients treated according to the same prospective protocol since 1987 to predict the 10-year probability to die of soft tissue sarcoma. It is made online at www.prognomics.org/sam. By inserting parameters it calculates the 10-year sarcoma-specific survival probability instead of dividing patients into high-risk patients and low-risk patients. This

online tool serves as an aid in decision-making for adjuvant chemotherapy in the future. The user can draw his own cut-off value for probability of survival and when the estimate falls below the cut-off value the patient should receive adjuvant chemotherapy. Our model uses size on a continuous scale, grade, necrosis, invasion, location, and depth. None of the prognostic tools published are generally accepted. Some of them are insufficient for clinical use. Both meta-analyses on the role of adjuvant chemotherapy included the warning that benefit from chemotherapy should be carefully weighed against toxicity (Pervaiz *et al*, 2008; Verma *et al*, 2008), and prognostic tools are therefore valuable when considering patient selection to receive treatments with only limited potential.

Kattan and colleagues used age in a continuous scale in their Cox regression-based model, in addition to size in three categories, grade in two categories, histologic subtype, depth, and site (Kattan *et al*, 2002). Carneiro and colleagues used peripheral tumour growth pattern (infiltrating vs pushing growth), size in two categories, necrosis, and vascular invasion (Carneiro *et al*, 2011). Most soft tissue sarcoma patients are elderly and at considerable risk of developing life-threatening or fatal side-effects like neutropenic infections. Therefore, withholding adjuvant chemotherapy in those patients at low risk of dying of their disease is important. Our model does not use patient age at diagnosis as a parameter. We excluded age as many patients with advanced age have poor physical condition which prevents the use of chemotherapy. In addition, elderly patients benefit less from adjuvant chemotherapy if evaluated by the life-years saved. The proposed model only includes patients with extremity or trunk wall tumour, because biology and treatment of tumours in other locations is different in many cases. Our model uses a four-grade system that is widely used in Scandinavia instead of dichotomised histologic grade, namely low-grade and high-grade. Grade on a four-tier scale gave a higher hazard ratio than a two-tier scale. We used size on a continuous scale instead of three groups because of better prognostic value.

The new model more accurately discriminated among patients to predict 10-year sarcoma-specific survival. Also in an external independent validation material from the Lund University Central Hospital the new proposed model was better to discriminate among patients. Our prognostic model compares favourably with regard to prognostic accuracy and concordance index in the external validation, similar to the external validation studies of the Kattan model (Eilber *et al*, 2004; Kattan *et al*, 2002; Mariani *et al*, 2005). Calibration of the model showed a tendency towards underestimation in groups with lower predicted survival. A similar result was present also in one of the above-mentioned validation studies (Eilber *et al*, 2004).

Our future aim is to update the tool by expanding the patient series. At the moment our model is available for other external validations before it can be recommended for clinical decision-making.

3. OSTEOSARCOMA IN FINLAND 1971–2005 (STUDIES III AND IV)

To our knowledge only four studies have reported nationwide, population-based prognosis of osteosarcoma (Curry *et al*, 2006; Harvei *et al*, 1981; Stiller *et al*, 2006; Whelan *et al*, 2011) and all lacked histologic review. This is prone to cause selection bias as series usually span several decades. We retrospectively studied all patients diagnosed with osteosarcoma in Finland during 1971–2005 reported to the Finnish Cancer Registry. This study spans a long period of time and we performed a histologic re-evaluation on the original biopsy specimens to obtain homogenous material. This however causes selection bias itself as 24 per cent of samples were not available for re-examination.

No new effective drugs were introduced in the 1990s. However, 10-year sarcoma-specific survival for local high-grade extremity osteosarcomas improved from 58 per cent during the 1980s to 75 per cent during 1991–2005. One probable explanation is centralization of treatment to five university hospitals during 1991–2005 instead of patients treated during 1971–1990 in 11 hospitals and more aggressive chemotherapy for both local disease and metastatic disease at presentation. Improvement in radiological techniques enables precise staging and patients with metastatic disease at diagnosis can be excluded from survival analyses thus improving survival. In the largest series from a single-institution with 1,458 patients diagnosed during 1982–2002 with all locations, all ages and all stages but excluding low grade tumors, the five-year overall survival for the entire cohort was 57 per cent (Picci *et al*, 2010). When assessing the survival by year of recruitment the survival varied from 33 per cent to 52 per cent with annual improvement of 1.31 per cent. Survival improved most among patients with worst survival rates (metastatic disease at presentation, axial tumour, age over 40 years). In a critical evaluation, authors suggested that patients with classical osteosarcoma should receive neo-adjuvant therapy of only two active drugs, methotrexate and doxorubicin, to minimize acute toxicity and late morbidity (Bruland *et al*, 1997). More effective, and toxic, treatment should be reserved for high-risk patients and for relapsed patients.

Limb-salvage rate increased from 12 per cent to 78 per cent during the study period. The use of less radical surgery didn't increase the rate of local recurrences. However, amputation rate and local recurrence rates were high compared to other published osteosarcoma series. These are at least partly explained by the fact that the

approximately 10 annual osteosarcomas were treated in five university hospitals. Further centralization is probably needed to create only a few centres with experience of this rare disease.

During the study period 77 patients from Finland were formally enrolled to trials. Over one third of patients with a high grade tumour were ineligible to enroll. One subgroup in this category is patients with metastatic disease at presentation and dismal prognosis among these patients challenges researchers to find novel treatment strategies for these high-risk patients. All six long-term survivors in the present study with metastatic disease at presentation had a peripheral tumour and isolated pulmonary metastases. An aggressive approach to treat pulmonary metastases with even repeated metastasectomies and chemotherapy may be curative in some patients (Briccoli *et al*, 2010; Ward *et al*, 1994). In the present series, 11 out of 99 patients with metastatic relapse remain as long-term survivors.

CONCLUSIONS

1. We recommend surgery with a smallest surgical margin of 2–3 cm irrespective of grade for soft tissue sarcoma of the extremity and the trunk wall. In the case of a smaller margin and no uninvolved fascia, adjuvant radiation therapy is recommended (Study I).

2. Adherence to the treatment protocol should be firm and all deviations carefully discussed because local control is inferior in soft tissue sarcoma patients not receiving adequate local treatment (Study I).

3. Good local control can be reached with aggressive surgical treatment and possible radiation therapy also in locally recurrent soft tissue sarcoma of the extremity and the trunk wall (Study I).

4. An online tool for 10-year soft tissue sarcoma-specific survival is available at www.prognomics.org/sam for research purposes only for the time being. In the future, it may aid in clinical decision-making on which patients should receive adjuvant chemotherapy (Study II).

5. Treatment results of osteosarcoma have improved in Finland during 1971–2005, and 10-year osteosarcoma-specific survival of 75 per cent for local high-grade extremity osteosarcoma is good, but the limb-salvage rate and local control remain lower than in large centres. Further centralization is therefore warranted to treat this disease with an incidence of only 1.8 per million per year. Development of local recurrence and major deviation from the chemotherapy protocol independently predicted worse survival (Studies III and IV).

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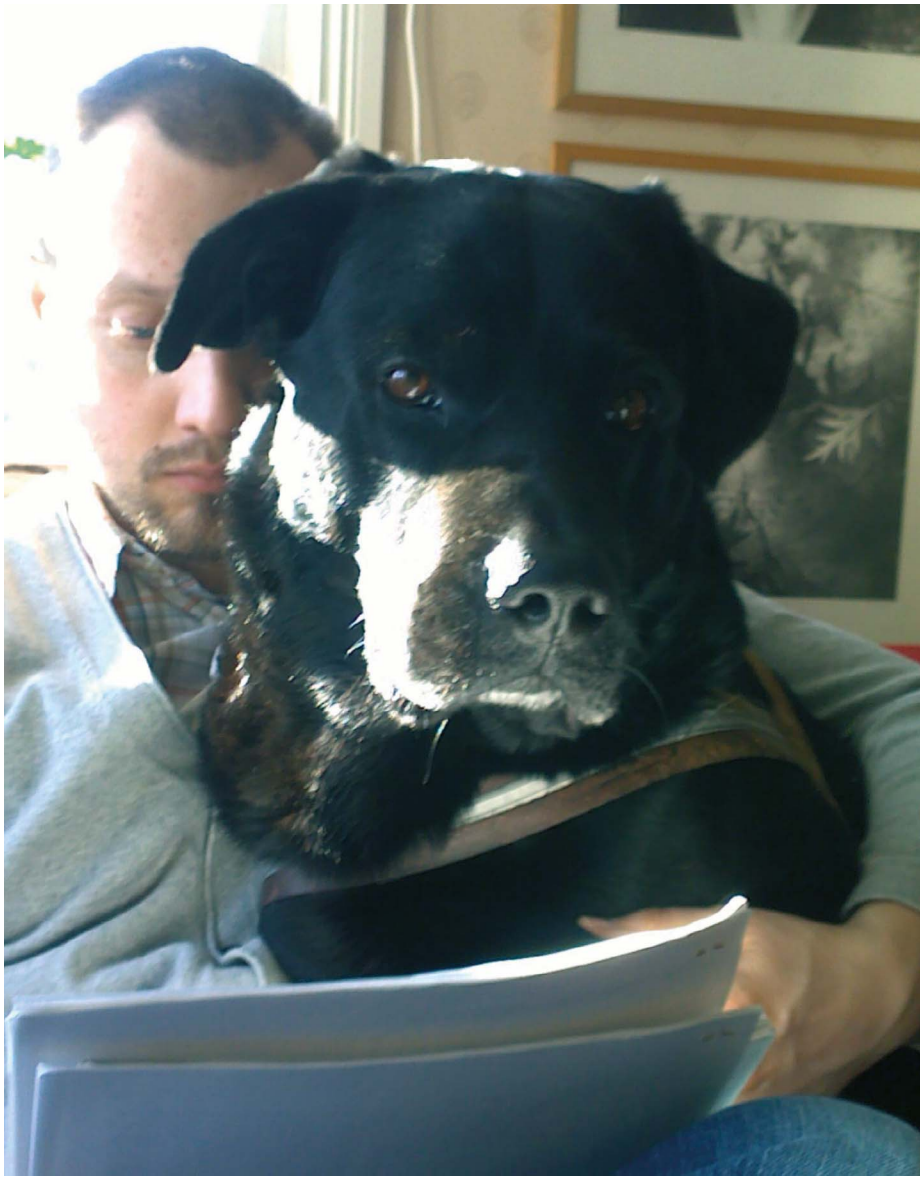
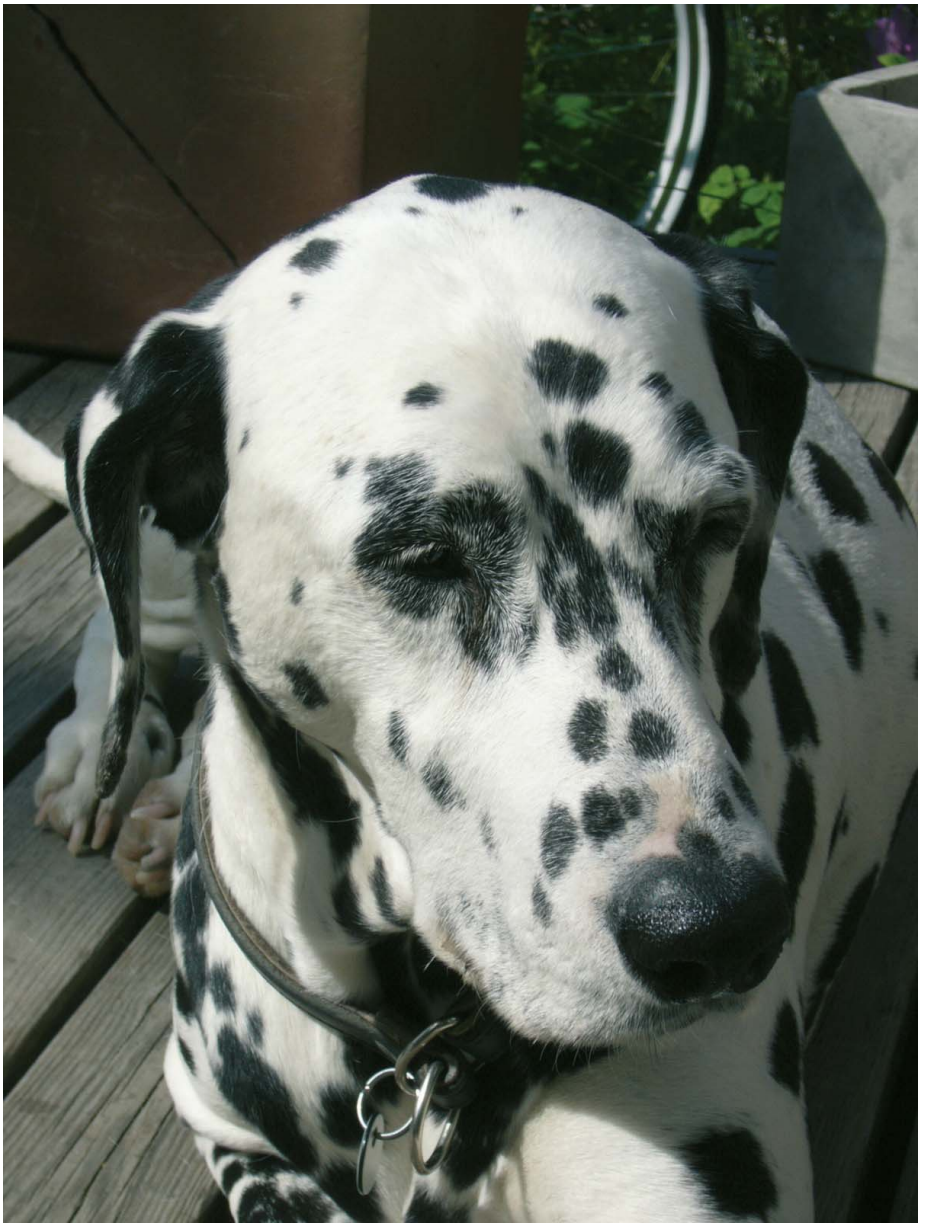


Rane who knows the true meaning of the word “loyalty”. I am not quite convinced if you are a proper watchdog but you most certainly make one hell of a lap dog!



My mother-in-law Marju and Essi are thanked for providing the fresh idea for the cover. And yes, Essi provided all the spots on the cover, but no dog was harmed during making this thesis as Pate Pesonius was so gentle.

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