Prognostic factors in soft tissue sarcoma

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A prognostic factor is one that statistically correlates with outcome. Prognostic factors usually refer to patient and tumor characteristics (for example, age, sex, tumor size, specific histologic features, proliferation markers in tumor cells, local and distant tumor extension). Staging systems use combinations of prognostic factors to group patients in stages. Patients in the same stage have about the same prognosis and with higher stages the prognosis worsens. Prognosis usually refers to survival chance. Patients are classified into different stages before treatment to decide on optimal treatment and to compare different treatment regimens. Pretreatment studies mainly include physical examination, radiologic imaging studies, and often microscopic examination of a biopsy obtained by needle or surgery. In some neoplasms the correct stage is not decided upon until after surgery and microscopic examination of the surgical specimen—various intratumoral features may define the stage as also may microscopic tumor extension into contiguous tissue (in, for example, colon and bladder carcinoma). In breast carcinoma, the presence of microscopic tumor growth in axillary lymph nodes is of prognostic importance; lymph nodes are sampled at surgery of the breast tumor more for staging than for therapy. In tumors that are treated by surgery, the postsurgical stage determines whether adjuvant treatment (for example, irradiation and cytostatic agents) should be given.

Staging systems have been devised for most carcinomas, usually as a TNM system (Tumor, Nodes, Metastases). The TNM system, however, is not applicable for soft tissue sarcomas; tumor spread via regional lymph nodes is rare as also is the diagnosis of metastases concomitantly with the primary tumor. This leaves only T for determination of the stage in most soft tissue sarcoma patients. Other staging systems have been proposed for soft tissue sarcomas, but none has been universally approved. Staging systems for carcinoma usually describe the progression of the tumor. For example, in ordinary colon cancer the tumor starts as a benign polyp in the mucosa. The polyp gradually grows into a malignant tumor. With continuous growth the tumor penetrates the bowel wall and eventually metastasizes to regional lymph nodes and finally generalized metastases occur. Molecular changes in specific oncogenes and tumor suppressor genes are gradually acquired and parallel histological and clinical tumor progression. The surgical curability of colon cancer is clearly related to the stage of tumor progression.

This type of progression is rare in sarcoma—i.e, a liposarcoma does not develop from a lipoma, a leiomyosarcoma does not arise from a leiomyoma. With the exception of malignant transformation of a primarily benign nerve tumor in patients with neurofibromatosis, all soft tissue sarcomas seem to develop de novo. Furthermore, the microscopic features of a sarcoma in most cases do not seem to progress into a more malignant appearence with time. An increasing malignancy-grade has been described in local recurrences as compared to the primary tumor but this does not seem to occur often. So-called dedifferentiation is apparently rare in soft tissue sarcomas of the extremities and trunk wall, but it may be commoner in locally recurrent retroperitoneal lipomatous sarcomas.

High-grade malignant soft tissue sarcomas infiltrating surrounding tissue is common but this may also be observed in low malignant tumors, for example low-grade malignant fibrous histiocytoma of the myxoid type (myxofibrosarcoma). Infiltration of major nerves, vessels and bone is rare. However, the position of a tumor in relation to muscles, vessels, nerves and bone, and its microscopic invasion of surrounding structures is of importance for surgery. Such macro- and microanatomy has been used to construct *surgical staging systems* (Enneking et al. 1982). With increasing surgical stage, the local recurrence risk increases, unless more extensive surgery and/or adjuvant therapy is given.

In summary, staging systems for carcinomas describe the progression of the tumor disease in terms of histologic features of increasing malignancy, increasing tumor size and infiltration of surrounding anatomic structures, followed by locoregional lymph node spread and finally distant metastases. This multistep evolution of the tumor disease is rarely seen in sarcomas with a progression that can be detected only by

increasing tumor size and the appearance of metastases, in most cases first in the lungs. Therefore, it is difficult to devise meaningful *staging systems* for sarcomas. Systems combining the occurrence of different prognostic factors in sarcomas to predict the outcome, should, perhaps, be called *prognostication systems*.

The lack of an accurate prognostic system for soft tissue sarcoma was less a problem 20 years ago, when treatment focused on the primary tumor. However, after the dramatic results of chemotherapy for osteosarcoma and Ewing sarcoma, several chemotherapy studies for soft tissue sarcoma were started and the number of trials has grown exponentially because no effective regimens have been found. (One exception is soft tissue sarcoma in children, notably rhabdomyosarcoma, for which effective chemotherapy now exists. This article concerns soft tissue sarcomas in adults). For these studies it became important to select a subset of patients with a poor prognosis; in an unselected series of patients with soft tissue sarcoma of the extremities and trunk wall the 5-year survival was close to 70% (Gustafson 1994). Obviously, not all patients with soft tissue sarcoma should be included in chemotherapy studies.

During the same time period it became evident that adjuvant radiotherapy was of value for local control; previously radiotherapy was considered useless for sarcoma. This stimulated research on prognostic factors that also included *local recurrence*. However, radiotherapy has fewer serious side-effects than chemotherapy and soon limb-sparing surgery routinely combined with radiotherapy became the standard treatment. A local recurrence rate of less than 10% with this therapy has not stimulated research on tumor factors of importance for local recurrence! Scandinavia is an exception to this policy. Here adjuvant radiotherapy, which does not have negligible side-effects, is given only in selected cases (see also pages 117–119).

Research on prognostic factors in soft tissue sarcoma is hampered by the enormous heterogeneity of tumors in terms of morphology and clinical behavior. More than 50 different histologic types—several of them with subtypes—have been described and the outcome varies between cure after simple shelling out and metastatic spread, despite radical amputation. There is only a weak correlation between histologic type and clinical behavior. As knowledge has accumulated, new clinicopathologic subgroups have been defined. Recent reports show that even in synovial sarcomas, a tumor type conventionally described as highly malignant, one subgroup of patients have a good prognosis (Bergh et al. 1996, Choong et al. 1995a). The same holds true for malignant fibrous histiocytoma. Another problem, in relating the prognosis to the histologic tumor type, concerns tumor classification. Thus, the existence of malignant fibrous histiocytoma, the commonest diagnosis in the past 15 years, was recently questioned (Fletcher 1992)! Different prognostication systems should probably be constructed for different tumor types. However, this is not easy because of the rarity of the tumors and the difficulties with histologic classification.

Treatment failure in a patient with a soft tissue sarcoma without detectable metastases at the time of diagnosis of the primary tumor occurs as local recurrence and/or metastases. The prognosis for patients who present with metatastic disease is bad and in the past it was the same for those who developed metastases after treatment of the primary tumor. In outcome studies, the endpoint chosen was either the occurrence of metastases or death due to tumor; the median survival time after the diagnosis of metastases was less than 6 months. However, during the last 10 years, surgery for pulmonary metastases has increased considerably thanks to promising results. Therefore, prognostic systems for soft tissue sarcoma can be used to predict 3 different treatment failures: metastatic spread, local recurrence, and survival after metastatectomy. The cause of death in soft tissue sarcoma of the extremity or trunk wall is, with very few exceptions, metastatic disease; few patients die because of a local recurrence. This is not always the case for retroperitoneal, visceral, and head and neck sarcomas; especially retroperitoneal sarcomas may kill the patient because of uncontrollable local growth. In such cases, the use of prognostic factors for metastatic disease, such as histologic malignancy-grade is irrelevant; a low-grade retroperitoneal liposarcoma may kill a patient without metatastatic spread. In the following presentations, I refer to soft tissue sarcomas of the extremities and trunk wall in adults.

Prognostication of metastatic spread

Size and histologic malignancy-grade are of unquestionable importance (Table 1). Curiously, the reproducibility of these factors is diametrically opposed. Size can easily be measured with good precision and reproducibility by the ruler of the diagnostic radiologist or the pathologist. Conversely, histologic malignancy-grading is subjective with poor reproducibility and no consensus between pathologists as to whether a 2, 3 or 4 grade system should be used. Such grading is mainly based on cellularity, cell atypia, the degree of anaplasia, mitotic activity, cell and tissue differentiation and necrosis. There is no consensus as to which histologic variables should be included, how

Table 1 Prognosis related to tumor size and malignacy-grade. 471 surgically treated adult patients with soft tissue sarcoma of the extremities and trunk wall (from Gustafson 1994)

		5-year MFSR
Size (cm)	1-5	0.8
	6-10	0.6
	11-15	0.5
	>15	0.4
Grade	I	1.0
	II	0.9
	III	0.7
	IV	0.5

MFSR metastasis free survival rate.

Table 2. Prognosis related to tumor necrosis and vascular invasion. 471 surgically treated adult patients with soft tissue sarcoma of the extremities and trunk wall (from Gustafson 1994)

		5-year MFSR
Necrosis	no	0.8
	yes	0.5
Vascular invasion	no	0.8
	yes	0.4

MFSR metastasis free survival rate.

they should be defined and whether they should be given different weights. To complicate the problem further, various histologic prognostic factors may be variously importanct in different tumor types.

Another problem is to determine the cut-off points between the various grades; all specialized pathologists can distinguish between a grade 1 and a grade 3 or 4 tumor in a three- or four-grade system. However, distinguishing between a grade 1 and grade 2, or between a grade 3 and grade 4 tumor, may be less easy. This also means that the survival rates of patients with, for example, the highest malignancy-grade in different systems may vary considerably. This is an important drawback when prognostication systems are to be used to select high-risk patients for chemotherapy studies. It also hinders comparisons between outcomes in different studies concerning the effect of treatment.

The construction of a reliable malignancy grading system requires that the classification of the histologic variables be reproducible, their prognostic weight be determined by multivariate analysis, and different tumor types should be separately analyzed, a formidable task! The only studies which have analyzed the reproducibility of prognostic factors among pathologists are those by Coindre and coworkers (Trojani et al. 1984, Coindre et al. 1988). In the system they used, they found acceptable reproducibility for the assessment of tumor differentiation, mitotic count and necrosis.

High *age* and male *sex* have been reported to be unfavorable prognostic factors by some authors, but not confirmed by others. If they are of prognostic importance, they are weak factors.

Tumor *localization* and tumor *depth* have repeatedly been shown to have prognostic importance, proximal and deep-seated tumors having a worse prognosis. However, there is a close correlation between tumor size and location and depth; proximal and deep-seated tumors are larger. In most studies, size seems to be the relevant factor. (Gustafson 1994, Peabody et al. 1994). However, Coindre et al. (1996) and Pisters et al. (1996) in larger series reported an independent prognostic importance of both tumor size and tumor depth.

Tumor necrosis has often been reported to be of strong prognostic importance (Costa et al. 1984, Mandard et al. 1989, Lack et al. 1989, Becker et al. 1991, van Unnik et al. 1993, Oda et al. 1993, Gustafson 1994). The occurrence of tumor necrosis is often included in the histologic malignancy-grading systems. The amount of necrosis is assessed in different ways by researchers; there is no consensus as how to classify it.

Vascular invasion—invasion of tumor into intratumoral vessels—is another strong prognostic factor (Mandard et al. 1981, Gustafson 1994). Tumor necrosis and vascular invasion seem to have such great prognostic strength that they should be included in a prognostic system (see below and Table 2).

Urokinase plasminogen activator (uPA) is a proteolytic enzyme which regulates extracellular matrix proteolysis and therefore it may be of importance for metastatic tumor spread. uPA has been found to have prognostic value in several tumor types; its value for prognosticating breast carcinoma is well established. In a pilot study of 69 patients with soft tissue sarcomas, high tumor tissue uPA levels correlated with poor survival (Choong et al. 1996).

DNA aneuploidy has repeatedly proved to be a prognostic factor in soft tissue sarcoma (Alvegård et al. 1990, Bauer et al. 1991, Keen et al. 1985, El-Naggar et al. 1990), but not a strong factor; few authors have assigned it independent prognostic value. Kuratso et al. (1995) found no independent prognostic importance of DNA ploidy in 111 soft tissue sarcomas. In a large series of soft tissue sarcomas, the 5-year metastasis free survival rate (MFSR) was 0.8 for 94

patients with diploid tumors and 0.6 for 221 patients with aneuploid tumors (Gustafson 1994). The poor discrimination can be explained in part by cytogenetic findings; highly malignant tumors may harbor chromosomal aberrations which cannot be detected by DNA analysis—for example, the balanced (X;18) translocation in synovial sarcoma.

Nuclear organizer regions (NOR) are segments of DNA with ribosomal genes, which are of importance for proliferation. They can be stained (Ag) and counted; their number seems to correlate with the prognosis of soft tissue sarcoma (Kuratsu et al. 1995)

S-phase fraction has been identified as a prognostic factor in several malignancies (for review, see Merckel and McGuire, 1990). Alho et al. (1993) and Huuhtanen et al. (1995) have reported a prognostic value of S-phase fraction in also soft tissue sarcomas. Gustafson et al. (1996) analyzed S-phase fraction by multivariate analysis in 160 soft tissue sarcomas and found it to have an independent prognostic importance.

Proliferation markers. Proliferating cell nuclear antigen (PCNA) and Ki-67 are two proteins associated with the proliferative phase of the growth cycle. An overexpression of these proteins in tumor cells can be recognizedby an increased proportion of cells stained by monoclonal antibodies to the proteins. Several studies, most of them small, have found a correlation between overexpression of these markers and prognosis in soft tissue sarcoma. The largest studies. comprising 48–182 patients, are those published by Dreinhöfer et al. (1994) and Choong et al. (1994, 1995b), whose findings indicated an independent prognostic importance of PCNA and Ki-67. However, they found a poor correlation between the two markers when analyzed in the same tumors. Furthermore, the prognostic strength differed between different tumor types. In all types, best prognostication was achieved by combining PCNA and Ki-67 indices; the 5-year MFSR for patients with tumors where both indices were low was 0.8. The corresponding figure for patients with tumors where both indices were high was 0.5.

Cytogenetics and molecular genetics. In malignant fibrous histiocytomas, abnormalities of the short arm of chromosome 19 have been associated with an increased risk of local recurrence and metastasis while the presence of ring chromosomes indicated a low risk of relapse (Choong et al. 1996).

Reduced expression of the RB1 protein (*RB* is the retinoblastoma tumor suppressor gene) is associated with a poor prognosis as is increased expression of the TP53 and MDM2 proteins (see pages 64 and 68–73).

Local treatment. Few authors have been able to show a correlation between type of treatment of the primary tumor and prognosis as regards survival. In univariate analyses, inadequate treatment is often associated with poor prognosis. However, when prognostic factors are multivariately analyzed, treatment loses its significance (Gustafson 1994). One explanation may be that there is a correlation between other prognostic factors and the treatment; large and high-grade malignant tumors more often may have inadequate surgical margins (those with a high risk of local recurrence) (Gustafson and Rydholm 1992).

Local recurrence is a well-known prognostic factor; patients with local recurrence more frequently develop metastases (or, patients with metastases more often develop a local recurrence), see below.

Prognostication of local recurrence

The strongest predictor of local recurrence is the adequacy of surgical margin achieved at (see pages 81–85). Adjuvant therapy reduces the local recurrence rate which is the rationale for surgery combined with radiotherapy. All other things being equal, high-grade malignant tumors recur locally more often than low-grade malignant tumors (Gustafson et al. 1991). Thus, local recurrence reflects the type of treatment *and* the local tumor characteristics (invasion, local metastases); surgical and biological features determine the local recurrence risk.

Prognosis after local recurrence. It is well known that the prognosis for patients with local recurrence is worse than for patients without. In a large series (124 patients had one or more local recurrences), the 5-year MFSR for patients with local recurrence was 0.5 compared to 0.8 for patients without (Gustafson et al. 1993). However, for patients without metastases when the last local recurrence was diagnosed, the 5-year MFSR (after the last local recurrence) was 0.7. The selection of patients with local recurrence but no concurrent metastases, creates a subset of the population with a good prognosis. These patients should not be combined with patients with primary tumors in chemotherapy trials. In studies of prognosis, this group should be analyzed separately.

Choong et al. (1995c) studied the growth rate of a local recurrence defined as the quotient (growth rate index, GRI) between the size (cm) of the local recurrence and the number of months between surgery for the primary tumor and detection of the recurrence. Patients with a GRI exceeding 0.4 had a 2-year MFSR of 0.8 compared to 0.3 for patients with a lower GRI. A staging system for patients with local recurrence were suggested based on these observations. By combining primary tumor characteristics (necrosis) and

GRI, 4 prognostic groups could be identified. Almost all patients who had had a primary tumor with necrosis and a local recurrence with high GRI died. The 5-year MFSR for patients without necrosis and with low GRI was 0.9 (Choong et al. 1995d).

The association between local recurrence and metastatic disease. There is a well known statistical association between metastases and local recurrence in soft tissue sarcoma; patients who develop metastases more often have a local recurrence than those who do not develop metastases. This association has been interpreted as causal; metastases emanate from the local recurrence and not from the primary tumor. However, in many cases the metastases are diagnosed concomitantly with the local recurrence, in some cases, even before. In one study, using our population-based databank, we analyzed a group of 128 patients with unquestionably highly malignant tumors; all of them had developed metastases which was the inclusion criteria (Gustafson et al. 1991). This population-based databank includes all patients in our region, whether or not they have been treated at our center, which means that the series includes many patients with a local recurrence because of inadequate treatment outside our center; an advantage when analyzing of thé association between locarl recurrence and metastases. Half of the 128 patients had also developed a local recurrence. However, when we compared the groups with or without a local recurrence, we found that the timing for the occurrence of metastatic disease was the same in both groups. Furthermore, there were no differences between the groups as regards tumor size and distribution of malignancy-grade. These observations suggest an alternative explanation of the association between metastases and local recurrence—namely, that highly malignant tumors combine local and distant aggressiveness; a highly malignant tumor recurs locally more often than a low malignant tumor. Highly malignant soft tissue sarcomas probably behave in the same manner as highly malignant bone tumors. Before the introduction of chemotherapy, 80–90% of children with osteosarcoma and Ewing sarcoma died of metastatic disease, despite radical amputation; metastatic spread had occurred long before diagnosis of the primary tumor. That a local recurrence in rare cases is responsible for metastatic spread cannot, of course, be excluded, dedifferentation into a highly malignant tumor may occur, especially after repeated local recurrences of a tumor that primarily was not of high grade. For a detailed discussion of the association between local recurrence and metastases, see Gustafson (1994).

Prognostication of survival after pulmonary metastatectomy

Several authors report good results after pulmonary metastatecomy in soft tissue sarcomas (for review, see pages 145–147). Common prognostic factors include the number of metastases and the length of time between treatment of the primary tumor and diagnosis of the metastases: the fewer metastases and the longer the time, the better is the prognosis.

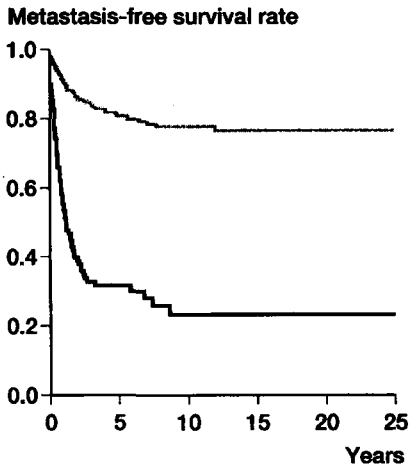
Prognostic systems

Two prognostic systems for soft tissue sarcomas are in common use: the AJC (American Joint Committee on Cancer, revised by Bears et al. 1988) and SSS (Surgical Staging System, Enneking et al. 1980). The AJC system is based on malignancy-grade (3 grades) and tumor size (cut-off 5 cm); three groups based on grade are subdivided into two, depending on size. SSS is based on malignancy-grade (2 grades) and tumor compartmentalization (intra/extra) which means 4 groups. Both systems group patients with metastases separately. Rööser et al. (1987) applied these systems to the Lund database and found that prognostication with these systems was mainly dependent on malignancy-grade; a 5 cm cut-off for size may not be optimal and compartmentalization—which is of importance for surgical planning—is not an independent prognostic factor. In a later study by Gustafson (1994), the systems were applied to 338 patients (patients with metastases at diagnosis were excluded).

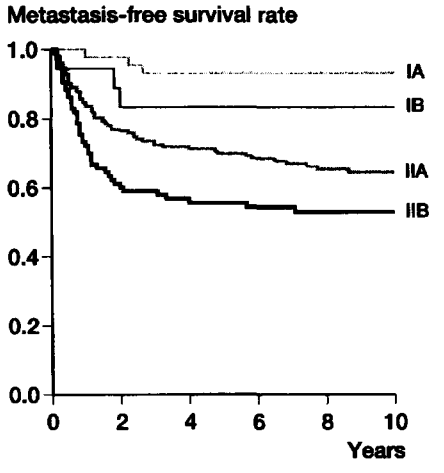
With both systems, the 5-year survival for the worst groups was over 50 % (Figure). This means that none of these systems has sufficient strength to identify the high-risk group of patients who should be included in trials with adjuvant chemotherapy.

Coindre et al. (1996) have introduced a prognostication system based on grade (3-grade scale), tumor depth and tumor size. By combining these factors, they defined 4 prognostic groups which were tested on 537 patients. The 5-year MFSR was 0.9 in group I (139 patients), and 0.4–0.3 in groups III–IV (187 patients).

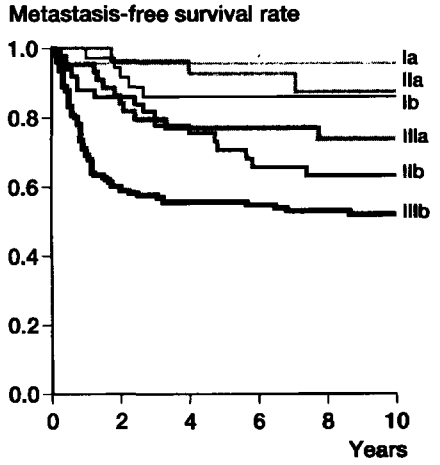
Gustafson (1994) introduced a new system based on tumor size (cut-off 10 cm), tumor necrosis and intratumoral vascular invasion by tumor. Patients were divided into two groups: those with 0 or 1 factor and those with 2 or 3 factors. Two thirds of the patients belonged to the good prognosis group with a 5-year MFSR of 0.8, the corresponding rate for the remaining third of the patients was 0.3 (Figure). Thus, this system separated patients into only two groups, with a good or a poor prognosis; patients in the poor prognosis group are clearly candidates for chemotherapy tri-



Metastasis-free survival in subsetsof 354 patients with soft tissue sarcoma of the extremity and trunk wall, using tumor size > 10 cm, tumor necrosis, and vascular invasion. 245 with 0 or 1 factor (grey line). 109 patients with 2 or 3 factors (black line).



Metastasis-free survival in subsetsof 338 patients with soft tissue sarcoma of the extremity and trunk wall, staged according to the Surgical Staging System.



Metastasis-free survival in subsetsof 338 patients with soft tissue sarcoma of the extremity and trunk wall, staged according to the AJC system.

als after surgery alone. We are now testing this system for reproducibility among pathologists as regards classification of necrosis and vascular invasion and reproducibility of prognostic strength when tested in other series of patients.

Summary

Several prognostic markers have been identified for soft tissue sarcomas. However, there reproducibility as regards both classification by different examiners and prognostic strength, as evaluated in different tumor series is poorly documented. Relevant factors and their strength differ in different subtypes of sarcoma. Thus, there is no generally accepted prognostic/staging system for soft tissue sarcoma. It seems possible that highly malignant soft tissue sarcomas behave like highly malignant bone tumors, such as osteosarcoma and Ewing sarcoma—i.e., almost all patients have metatastic disease when the primary tumor is diagnosed, although in most cases it is not detecable with today's imaging techniques. The highly malignant character of these tumors is defined by their histotype alone and the microscopic diagnosis is almost always easy. In contrast, no soft tissue sarcoma histotype is per se associated with such a poor prognosis; further prognostic markers are needed. The ideal prognostication system includes only two groups of patients; after removal of the primary tumor, one group has 100% survival and the other 0% survival. In the latter group, the tumor has metastasized and adjuvant therapy is necessary to improve survival. Meaningful chemotherapy trials requires reliable identification of high-risk patients; only these should be included. Inclusion of also low-risk patients is disadvantageous for two reasons: chemotherapy may have serious side-effects and positive effects may be difficult to detect when the trial is diluted by low-risk patients. Prognostication in soft tissue sarcoma has improved, but it may a long time before soft tissue sarcoma histotypes as highly malignant as osteosarcoma and Ewing sarcoma can be defined. Another approach would be to ignore efforts to characterize prognostic features of the primary tumor and instead,

with some type of tracer technique (see pp x-y in this issue), focus on whether it has metastasized or not.

References

Alho A, Skjeldal S, Melvik J E et al. (1993). The clinical importance of DNA synthesis and aneuploidy in bone and soft tissue tumors. Anticancer Research 13: 2383-8.

Alvegård A, Berg NO, Baldetorp B et al. (1990). Cellular DNA content and prognosis of high-grade soft tissue sarcoma: the Scandinavian sarcoma group experience. J Clin Oncol 8: 538-547.

Bauer H C F, Kreicbergs A Tribukait B (1991). DNA content prognostic in soft tissue sarcoam. 102 patients followed for 1-10 years Acta Orthop Scand 62: 187-94.

Bears O H, Henson D E, Hutter R V P, Myers M H (eds) (1988). American Joint Committee on Cancer: Soft tissues, Chapter 20. Manual for Staging of Cancer, 3rd ed. JB Lippincott, Philadelphia, pp 127-31.

Becker R L, Venzon D, Lack E E, et al (1991). Cytometry and morphometry of malignant fibrous histiocytoma of the extremities. Am J Surg Pathol 15(10): 957-64.

Bergh P, Berlin Ö, Gunterberg B, et al. (1996). The Gothenburg-Rizzoli joint study on synovial sarcoma. Acta Orthop Scand (Suppl 272): 55-56.

Choong P, Åkerman M, Willén H, et al. (1994). Prognostic value af Ki-67 expression in 182 soft tissue sarcomas. Proliferation - a marker of metastasis? APMIS 102: 915-24.

Choong P F M, Pritchard D J, Sim F H, et al. (1995a). Long-term survival in high grade soft tissue sarcoma. Prognostic factors in synovial sarcoma. Int J Oncol 7(1): 161-9.

Choong P, Åkerman M, Rydholm A, et al. (1995b). Proliferating cell nuclear antigen (PCNA) and Ki-67 expression in soft tissue sarcoma. Is prognostic importance histotype specific? APMIS 103: 797-805.

Choong P F M, Gustafson P, Rydholm A (1995c). Size and timing of local recurrence predicts metastases in soft tissue sarcoma. Growth rate index retrospectively analyzed in 134 cases. Acta Orthop Scand 66(2): 147-152.

Choong PFM, Gustafson P, Willén H et al. (1995d). Prognosis following locally recurrent soft-tissue sarcoma. A staging system based on primary and recurrent tumor characteristics. Int J Cancer 60: 33-37.

Choong PFM, Mertens F, Mandahl N et al. (1996). 19 p+ marker chromosome correlates with relapse in malignant fibrous histiocytoma. Genes Chromosom Cancer 16: 88-93.

Choong PFM, Fernö M, Åkerman M (1996). Urokinase plasminogen activator levels correlate with relapse in soft tissue sarcoma. Int J Cancer 69: 268-72.

Coindre J M, Terrier P, Bui N et al. (1996). Prognostic factors in adult patients with locally controlled soft tissue sarcoma: a study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol 14: 869-77.

Coindre J M, Bui N B, Bonichon F, et al. Histopathologic grading in spindle cell soft tissue sarcomas. Cancer 1988; 61: 2305-9.

Dreinhöfer K, Åkerman M, Willén H, et al. (1994). Proliferating cell nuclear antigen (PCNA) in high-grade malignant fibrous histiocytoma: prognostic value in 48 patients. Int J Cancer 59: 379-82.

El-Naggar A K, Ayala A G, Abdul-Karim F, W et al. (1990). Synovial sarcoma. A DNA flow cytometric study. Cancer 65: 2295-3000.

Enneking W F, Spanier S S, Goodman M A (1980). A system for the surgical grading of musculoskeletal sarcoma. Clin Orthop 153: 106-20.

Fletcher C D M (1992). Pleomorphic malignant fibrous histiocytoma: Fact or fiction?: A critical reappraisal based on 159 tumors diagnosed as pleomorphic sarcoma. Am J Surg Pathol 16(3): 213-28.

Gustafson P, Rööser B, Rydholm A (1991). Is local recurrence of minor importance for metastases in soft tissue sarcoma? Cancer 67: 2083-6

Gustafson P, Rydholm A (1992). Selection bias in treatment of soft-tissue sarcoma. J Bone Joint Surg (Br) 74: 501-503.

Gustafson P, Dreinhöfer K E, Rydholm A (1993). Metastasis-free survival after local recurrence in soft tissue sarcoma. J Bone Joint Surg (Br) 75; 658-60.

Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand 1994; (Suppl 259) 65: 2-31.

Gustafson P, Fernö M, Åkerman et al. (19??). Flow cytometric S-phase fraction in soft tissue sarcomas; prognostic importance analysed in 160 pateints. Br J Cancer, in press.

Huuthanen R, Blomqvist C, Wiklund T et al. (1996). A high S-phase fraction is a negative prognostic factor for diploid soft tissue sarcomas. Acta Orthop Scand 1996; (Suppl 265) (Abstract): 96.

Keen M E, Clevenger C V, Williams T J, et al. (1985). Correlation of two-color flow cytometric evaluatiuon of smooth muscle tumors with histopathological and clinical parameters. Am J Clin Pathol 83 :401-6.

Kuratso S, Tomita Y, Myoui A et al. (1995). DNA ploidy pattern and celll cycle stage of tumor sells in soft-tissue sarcomas: clinical implications. Oncology 52: 363-70.

Lack E E, Steinberg S M, White D et al. (1989). Extremity soft tissue sarcomas: analysis of prognostic variables in 300 cases and evaluation of tumor necrosis as a factor in stratifying higher-grade sarcomas. J Surg Oncol 41(4): 263-73

Mandard A M, Petiot J F , Marnay J, et al. (1989). Prognostic factors in soft tissue sarcomas. A multivariate analysis of 109 cases. Cancer 63(7): 1437-51.

Merkel DE, McGuire W L (1990). Ploidy, proliferative activity and prognosis. DNA flow cytometry of solid tumors. Cancer 65: 1194-1205.

Oda Y, Hashimoto H, Tsuneyoshi M, Takeshita S (1993). Survival in synovial sarcoma. A multivariate study of prognostic factors which special emphasis on the comparison between early death and long-term survival. Am J Surg Pathol 17(1): 35-44.

Peabody T D, Monson D, Montag A, et al. (1994). A comparison of the prognosis for deep and subcutaneous sarcomas of the extremities. J Bone Joint Surg (Am) 76: 1167-73.

Pisters P W, Leung D H, Woodruff J, et al. (1996). Analysis of prognostic factors in 1.041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 14: 1679-89.

Rööser B, Attewell R, Rydholm A (1987). The staging of soft-tissue sarcomas. Int Orthop 11: 339-44.

Trojani M, Contesso G, Coindre J M, et al. (1984). Soft tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 33: 37-42.

van Unnik J A M, Coindre J M, Contesso C, et al. (1993). Grading of soft tissue sarcomas: experience of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 29A(15): 2089-93.