

Prognostic factors in soft tissue sarcoma

A review and the Scandinavian Sarcoma Group experience

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Prognostic factors and staging systems

Prognostic factors correlate statistically with outcome. The factors commonly studied in cancer include patient and tumor characteristics such as age, gender, tumor size, specific histopathologic features, proliferation markers, as well as local and distant tumor extension. Prognostication or staging systems use combinations of prognostic factors to group patients, where patients in the same group or stage have similar expected survival rates. After surgery, such staging is sometimes supplemented by the histopathologic findings in the tumor or regional lymph nodes. Staging systems have been devised for most carcinomas, the commonest being the TNM system (Tumor – Nodes – Metastases). This system describes the progression of the disease in terms of increasing tumor size and infiltration of surrounding anatomic structures, followed by locoregional lymph node spread and, finally, distant metastases. Soft tissue sarcoma (STS) rarely shows this multi-step evolution of the tumor. Instead, progression is commonly detected only by increasing tumor size and the development of metastases, usually in the lungs first. Therefore, the TNM system is of little value in STS.

Specific problems in STS

The scarcity and heterogeneity of STS make it important but difficult to design a useful and reproducible prognostication system. The lack of an accurate prognostication system for STS was less a problem two or three decades ago, when treatment focused mainly on the primary tumor. However, the successful use of neo-adjuvant chemotherapy for osteosarcoma and Ewing's sarcoma has spurred several adjuvant chemotherapy studies of STS. In such studies, a subset of patients with a poor prognosis should be selected. In general, the prognosis of STS is too good - since two thirds of the patients with extremity or trunk wall sarcoma survive after removal of the primary tumor

(Gustafson 1994) - and the patients are too few to detect a moderate benefit from adjuvant chemotherapy if a number of "general STS" patients from one institution are included within a reasonable time-span. It was not until 1997, in a meta-analysis of more than 1,500 patients, that a small albeit indisputable benefit from adjuvant chemotherapy was shown (SMAC 1997). Although the benefit of this therapy was as much as in other solid tumors, e.g., breast cancer and colorectal cancer, it had not been detected in previous trials, due to insufficient statistical power. It has also become clear that very few, if any, centers around the world can do an adjuvant chemotherapy trial in STS patients alone; multi-center studies are necessary. Hence a reproducible prognostication system is required.

When it became evident that adjuvant radiotherapy was of value for local control, limb-sparing surgery routinely combined with radiotherapy, became the standard treatment. A local recurrence rate of around 10–15 % with this therapy has not stimulated further research on tumor factors of importance for local recurrence. Scandinavia, where adjuvant radiotherapy is given only to selected patients, is an exception to this policy (Alho et al. 1989, Wiklund et al. 1996).

Research on prognostic factors in STS is impeded by considerable heterogeneity in terms of morphology and clinical behavior. The clinical outcome of STS varies from cure after simple shelling out of the tumor to metastatic spread and death, despite radical amputation.

More than 50 histologic types—several of them with subtypes—have been described, which often show only a weak correlation between histologic type and behavior. Recently, a large subgroup of patients with synovial sarcoma, a tumor type usually described as highly malignant, has been found to have a good prognosis (Choong et al. 1995a, Bergh et al. 1996). Another problem in relating the prognosis to the histologic tumor type concerns tumor classifica-

tion. For example, the existence of malignant fibrous histiocytoma (MFH), the commonest diagnosis in the past 15 years, has been questioned (Fletcher 1992).

Prognostic factors

Survival

Death because of STS of the extremity and trunk wall is usually caused by metastatic disease. Few deaths are due to the primary tumor except when STS involves the head and neck or the retroperitoneum. In this case, death because of uncontrollable growth of the primary tumor is not uncommon. The following review of prognostic factors refers to the risk of metastasis in patients with STS of the extremity or trunk wall.

Patient characteristics, tumor localization and size

Advanced age and male sex have been reported as unfavorable prognostic factors by some authors, although not confirmed by others. If these factors are of prognostic importance, they are weak. Tumor localization and tumor depth have repeatedly been shown to have prognostic importance; proximal and deep-seated tumors have a worse prognosis. However, there is a close correlation between tumor size, localization 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); together with histologic malignancy grade, size seems to be the strongest prognosticator. Nevertheless, Coindre et al. (1996) and Pisters et al. (1996) in a large series reported that both tumor size and tumor depth were of independent prognostic importance.

Histopathologic features

Together with tumor size, the histologic malignancy grade is of unquestionable importance (Hashimoto et al. 1986, Collin et al. 1987, Orson et al. 1987, Mandard et al. 1989, Bauer et al. 1991, Gaynor et al. 1992, Pisters et al. 1996). However, they are not equally reproducible. Size can be measured with good precision and reproducibility by the radiologist or pathologist, while histopathologic malignancy grading is largely subjective. There is no consensus as to whether a two-, three-, or four-tiered system should be used. Histopathologic malignancy grading is normally based on cellularity, cell atypia, degree of anaplasia, mitotic activity, cell and tissue differentiation, as well as necrosis. It is unclear which of these histopathologic variables should be included, how they should be defined, and whether they should be given different weights. Furthermore, the importance of various histopathologic prognostic factors may not be the same

in different subtypes of STS. Another problem is to determine the cut-off points between the various grades. Thus the survival rates of patients with the highest malignancy grade when determined by various systems may differ. This is an important drawback when prognostication systems are used to select high-risk patients for chemotherapy studies. It also obstructs comparisons between outcomes in different studies concerning the effect of treatment. If a malignancy grading system is to be clinically useful, the classification of the histologic variables must be reproducible, their prognostic weight should be determined with multivariate analysis, and the different subtypes of STS ought to be analyzed separately.

Tumor necrosis has often been found to be of great prognostic importance (Costa et al. 1984, Lack et al. 1989, Mandard et al. 1989, Becker et al. 1991, Oda et al. 1993, van Unnik et al. 1993, Gustafson 1994). The occurrence of tumor necrosis is often included in the histopathologic malignancy-grading systems, although the definition of tumor necrosis may vary—i.e., microscopic, macroscopic or diagnosed with CT (Gustafson et al. 1992).

Vascular invasion—invasion of intratumoral vessels by the tumor—is another strong prognostic factor (Trojani et al. 1984, Rösser et al. 1987, Ruka et al. 1988, Mandard et al. 1989, Alvegård et al. 1990, Gustafson 1994).

Angiogenesis is necessary for growth of solid tumors and metastatic capacity. Little is known about angiogenesis in STS, but a high intratumoral microvessel density has been associated with poorer survival (Dirix et al. 1997). Serum levels of vascular endothelial growth factor and basic fibroblast growth factor have been reported to correlate with the grade of differentiation of the tumor (Dirix et al. 1996).

Proliferation markers

S-phase fraction (SPF) has been found to be a prognostic factor in several malignancies (for review, see Merckel and McGuire, 1990) as well as in STS (Alho et al. 1993, Huuhtanen et al. 1996). Gustafson et al. (1997), in an analysis of SPF with multivariate analysis in 160 patients with STS, found that it was of independent prognostic importance.

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 recognized by 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 STS. Dreinhöfer et al. (1994) and Choong et al. (1994, 1995b)

showed that PCNA and Ki-67 were of independent prognostic importance. However, they found a poor correlation between the two markers when analyzed in the same tumors. Furthermore, the prognostic strength differed between various types of tumors. Recently, Heslin et al. (1998) and Jensen et al. (1998) reported that the Ki-67 (MIB-1) score was of independent prognostic value in STS. In a recent study Huuhtanen et al. (1999) found that Ki-67 was a somewhat stronger prognostic factor for metastasis-free and overall survival than SPF.

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 STS (Kuratso et al. 1995).

DNA analysis

DNA ploidy status has repeatedly proved to be a prognostic factor in STS (Keen et al. 1985, Alvegård et al. 1990, El-Naggar et al. 1990, Bauer et al. 1991), but not a strong one; few authors have assigned it an independent prognostic value. Kuratso et al. (1995) found no independent prognostic importance of DNA ploidy status in 111 patients with STS. In a series of 315 patients with STS, the 5-year metastasis-free survival rate (MFSR) was 0.8 in patients with diploid tumors and 0.6 in patients with aneuploid tumors (Gustafson 1994). The poor discrimination can in part be explained by cytogenetic findings; highly malignant tumors may harbor chromosomal aberrations which cannot be detected by DNA analysis—e.g., the balanced translocation (X;18) in synovial sarcoma.

Chromosome and gene abnormalities

In MFH, 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). However, this aberration was not found to be of prognostic importance in a later study of pleomorphic sarcomas (Mertens et al. 1998).

Synovial sarcomas are characterized by a balanced translocation (X;18). This translocation fuses the *SYT* gene from chromosome 18 to either of two homologous genes at the X chromosome, *SSX1* or *SSX2*. Kawai et al. (1998) reported that patients with the *SYT-SSX2* translocation had a better prognosis than those with the *SYT-SSX1* translocation.

Reduced expression of the RB1 protein (retinoblastoma tumor suppressor gene) is associated with a poor prognosis, as also is increased expression of the TP53 and MDM2 proteins (Hieken et al. 1996, Taubert et al. 1996, Würl et al. 1998 a,b).

The expression of P-glycoprotein (P-gp), a product of the multi-drug resistance gene (MDR) is of prognostic importance in osteosarcoma (Baldini et al. 1995). Nakanishi et al. (1997) have recently shown that STS expressing P-gp has a less favorable prognosis than P-gp negative tumors.

Other factors

Tumors use enzyme systems to invade surrounding tissues. One such system is that of matrix metalloproteinases and their inhibitors (TIMP). Hurskainen et al. (1996) reported that STS produced more TIMPs than benign soft tissue tumors. The clinical value of this finding remains to be established.

Adhesion molecules—i.e., major extracellular matrix molecules and their specific receptors (integrins)—were studied immunohistochemically by Benassi et al. (1998), who noted a correlation between integrin expression and prognosis.

Urokinase plasminogen activator (uPA) is a proteolytic enzyme which regulates extracellular matrix proteolysis and may play a role in metastatic tumor spread. It is of prognostic value in several types of tumors—e.g., its use in breast carcinoma is now well established. In a pilot study of 69 patients with STS, high tumor tissue levels of uPA correlated with poor survival (Choong et al. 1996).

Tumor hypoxia has been associated with biologic aggressiveness. Brizel et al. (1996) showed that tumor hypoxia, unrelated to tumor volume, was associated with poorer survival in STS.

Local treatment

The aggressiveness of local treatment (surgical margin obtained, use of local radiotherapy) of the primary tumor, which is associated with the risk local of recurrence, has been difficult to correlate with survival rates. In univariate analyses, inadequate treatment is often associated with poor survival. However, when prognostic factors are multivariately analyzed, treatment loses its significance (Gustafson 1994). One explanation may be a correlation between other prognostic factors and the treatment; large and high-grade malignant tumors more often may have inadequate surgical margins and consequently higher local recurrence rates (Gustafson and Rydholm 1992).

This conclusion is supported by the findings of four randomized trials of less or more aggressive local treatment of STS. One of the trials compared amputation to limb-sparing surgery and irradiation and three of them surgery with or without irradiation. Although the local recurrence rate was reduced by the more aggressive approach, no difference was noted in metastasis-free or overall survival (Rosenberg et al.

1982, Harrison et al. 1993, Pisters et al. 1994, Yang et al. 1998).

Local recurrence

The strongest predictor of local recurrence is the adequacy of surgical margin achieved, followed by the grade of malignancy of the tumor. Adjuvant therapy reduces the local recurrence rate, which is the rationale for surgery combined with radiotherapy (Rosenberg et al. 1982, Harrison et al. 1993, Yang et al. 1998). All other factors being equal, high-grade malignant tumors recur locally more often than low-grade malignant tumors do (Enneking 1983, 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 risk of local recurrence.

It is well known that the prognosis of patients with a local recurrence is worse than that of those without. In a series of 432 patients with STS, the 5-year MFSR in 124 patients with local recurrence was 0.5, compared to 0.8 in patients without. However, in patients with multiple local recurrences but no metastases when the last local recurrence was diagnosed, the 5-year MFSR after the last local recurrence was 0.7 (Gustafson et al. 1993). Selection of patients with a local recurrence, but no concurrent metastases, creates a subset of the population having a good prognosis. In chemotherapy trials or in studies of prognosis, these patients should not be combined with those having primary tumors. Choong et al. (1995c) studied the growth rate of a local recurrence, defined as the quotient (growth rate index, GRI) between the size of the local recurrence and the time to detection of the recurrence. Patients with a low GRI had a 2-year MFSR of 0.8, compared to 0.3 in patients with a high GRI. These authors suggested a staging system for patients with a local recurrence which combines primary tumor characteristics (necrosis) and GRI. Almost all patients who had had a necrotic primary tumor and a high GRI local recurrence died unlike patients having non-necrotic primary tumors and low GRI local recurrences where the 5-year MFSR was 0.9 (Choong et al. 1995d).

Association between local recurrence and metastases

There is a well known statistical association between metastases and local recurrence in STS; patients who develop a local recurrence also develop metastases more often. This association has frequently been interpreted as causal; the metastases are supposed to emanate from the local recurrence. However, the metastases are in many cases detected at the same time as the local recurrence, in some cases even before. We

analyzed a group of patients with unquestionably highly malignant tumors; all of them had developed metastases, which was the inclusion criterion (Gustafson et al. 1991). Half of them had also developed a local recurrence. When we compared the groups with or without a local recurrence, we found that the metastases developed at the same time in both groups. Furthermore, there were no differences between the groups as regards tumor size and distribution of malignancy grades. These findings suggest an alternative explanation of the association between local recurrence and metastases; highly malignant tumors have both local and distant aggressiveness. Thus, given the same local treatment, a highly malignant tumor will recur locally more often than a low-malignant tumor. Highly malignant STS probably behave in the same manner as highly malignant bone tumors. Before the introduction of chemotherapy, 80–90% of children with osteosarcoma and Ewing's sarcoma died of metastatic disease, despite radical amputation; metastatic spread had occurred long before the primary tumor was diagnosed. That a local recurrence in rare cases is responsible for metastatic spread cannot, of course, be excluded; dedifferentiation of a low-grade tumor into a highly malignant tumor may occur, especially after repeated local recurrences (Trovik and Bauer 1994). This phenomenon is well known in retroperitoneal liposarcoma but seems to be rare in extremity sarcomas. For a detailed discussion of the association between local recurrence and metastases, see Gustafson (1994).

Survival after pulmonary metastasectomy

Several authors report 10–40% long-term survival rates after pulmonary metastasectomy in selected patients with STS. 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 the metastases and the longer the time, the better the prognosis. Furthermore, the prognosis improves if the metastasectomy is complete and if a histological response to chemotherapy can be shown (for review, see Wiklund et al. 1997).

Prognostication systems

Several prognostication systems for STS are in use: the Surgical Staging System, based on histopathologic malignancy grade and compartmentalization (Enneking et al. 1980); the American Joint Committee system, based on histopathologic malignancy grade and tumor size (Bears et al. 1988); the NCI system, based on macroscopic histologic subtype and necrosis (Costa et al. 1984); the FNCLCC system, based on

differentiation, mitotic count, and microscopic tumor necrosis (Trojani et al. 1984); the Myhre-Jensen et al. (1991) system, based on cellularity, anaplasia, necrosis, histogenetic type and subtype of tumor; the EORTC system, based on mitotic count, macroscopic tumor necrosis and tumor size (van Unnik et al. 1993); and the Tomita et al. (1994) system, based on histologic grade and clinical factors in combination. All these systems have weaknesses; between three and seven prognostic groups are identified and most of them cannot select the group of patients without detectable metastases at the time of diagnosis, but who have a really poor prognosis justifying adjuvant chemotherapy. This has led some major centers to adopt their own two-grade histologic system (Pisters et al. 1996). The only study which have analyzed the reproducibility of histopathologic prognostic factors, identified by multivariate analysis, is that by Coindre et al. (1986). With their system they found good reproducibility for the assessment of tumor differentiation, mitotic count and necrosis.

The SIN system

We have recently proposed a system based on three negative prognostic factors: large tumor Size, vascular Invasion, and microscopic tumor Necrosis (the SIN system) (Gustafson 1994). With this system, tumors with 2 or 3 factors are categorized as high grade, the others as low grade. This system has now been modified slightly and tested for reproducibility both as regards classification of microscopic tumor necrosis and vascular invasion, as well as prognostic strength of the grading, in 100 STS patients from Lund and 100 STS patients from Institut Bergonie, Bordeaux, France. The tumors were graded according to the number of negative prognostic factors present and the prognostic strength was compared with the grades given by various pathologists.

Concordance in classification of vascular invasion, microscopic tumor necrosis, and grading was seen in around 80% of the 200 tumors. Based on the different observers' grading, the 5-year MFSR in the 200 patients varied between 0.85 and 0.80 in patients with low-grade tumors, and between 0.48 and 0.43 in patients with high-grade tumors. Thus, the system gave similar survival rates when used by different observers. It divided the patients into two clinically useful groups, i.e., a high- and a low-risk group for metastasis. It is now being used in a Scandinavian Sarcoma Group adjuvant chemotherapy study, the SSG XIII protocol.

Summary and future directions

Several prognostic markers have been identified for STS. However, their reproducibility as regards both classification by various examiners and prognostic strength, as evaluated in various tumor series of tumors is poorly documented. Relevant factors and their strengths differ in different subtypes of sarcoma. Thus, there is no generally accepted prognostication / staging system for STS. It seems possible that highly malignant STS behave like highly malignant bone tumors, such as osteosarcoma and Ewing's sarcoma—i.e., almost all patients have metastatic disease when the primary tumor is diagnosed, although in most cases it is not detectable with today's imaging techniques. In contrast, no STS histotype is per se associated with such a poor prognosis; more prognostic markers are needed. The ideal prognostication system should include only two groups of patients—i.e., after removal of the primary tumor, one group with 100% survival and the other 0% survival. In the latter group, the tumor has metastasized and adjuvant therapy is needed to improve the survival. Meaningful chemotherapy trials require reliable identification of high-risk patients; only these should be included. Inclusion also of low-risk patients—i.e., a group of patients most of whom have tumors that will not metastasize—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 such patients. Prognostication in STS has improved, but it may be a long time before STS histotypes as highly malignant as osteosarcoma and Ewing's sarcoma can be defined. Another approach would be to ignore efforts to characterize prognostic features of the primary tumor and instead improve the ability to diagnose micrometastases.

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