high-grade behavior. Liposarcomas are graded according to subtype, with well-differentiated and myxoid liposarcomas being grade 1 and 2, respectively, while round cell, dedifferentiated and pleomorphic liposarcomas are, by definition, high-grade sarcomas. Angiosarcomas are graded according to differentiation, with highly vascular neoplasms representing the low-grade end of the spectrum and solid tumors considered as high grade. However, in soft tissues, angiosarcomas have a tendency to behave aggressively, no matter what their histology looks like.

Finally, it should be emphasized that in grading of soft tissue sarcomas, sampling is the greatest pitfall. Benign neurofibromas and grade 4 malignant peripheral nerve sheath tumors can share space in the same tumor and retroperitoneal liposarcomas can display areas of dedifferentiation side by side with grade 1 well-differentiated liposarcoma. This phenomenon casts some doubts in the usefulness of fine needle aspiration biopsies in the grading process of soft tissue sarcomas.

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# On the comparison of apples, oranges and sundry fruits: Problems with grading and prognostication in soft tissue tumors


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Grading of tumors began in the early part of this century with Broder, who used a four-tiered grading scheme for carcinomas and eventually for sarcomas. Since then, various types of grading schemes have been used – some of these continue to use four grades (as we do in Goteborg) while others use three and others use two. Grades III-IV in the four-tiered system and grades II-III in the three-tiered system correspond roughly to high-grade tumors.

In most sarcoma grading schemes, the degree of histological differentiation, cellularity, pleomorphism, mitotic activity, necrosis and vascular invasion are taken into account. In addition, some grading schemes take the pathological diagnosis into consideration, recognizing that certain sarcomas have a specific biological behavior *(i.e.,* the grade is inherent in the diagnosis). Most grading schemes separate low-grade from high-grade tumors, allowing treatment decisions to be made. However, they have not been completely satisfactory in terms of predicting prognosis. Therefore, attempts to refine grading schemes have been made: i) using flow cytometry to separate diploid from aneuploid tumors and to identify the S-phase fraction; ii) using markers such as Ki67 (MIB 1) to more accurately assess proliferative activity; and iii) looking for p53 expression, MDM2 expression and RB gene product expression among others to identify potentially more aggressive sarcomas.

There are several underlying assumptions in most grading schemes. Some of these assumptions are not valid, in our opinion, and account, in part, for the failure of most grading schemes to consistently function well. There are over 250 soft tissue diagnoses; approximately 50 of these represent sarcomas. The same histological grading criteria have been applied to 50 different types of sarcoma, despite the fact that some behave as borderline or low-grade malignant tumors (e.g., dermatofibrosarcoma protuberans) and others are uniformly high grade.

Another problem with grading is that the concept of low and high grade is ambiguous and simplistic from a biological perspective. What is meant by a low-grade tumor? Does it mean only a long survival despite repeated local recurrences, a long disease-free survival or a long survival despite the presence of metastasis with an ultimate tumor-related death (as in some cases of extraskeletal myxoid chondrosarcoma)? The problems in defining a high-grade tumor are even more complex. Does a high-grade tumor mean only that survival is short or that the tumor metastasizes early, whether or not it leads to the patient's demise? Does it include locally aggressive, nonmetastasizing tumors that frequently cause an early death?

Another problem with grading schemes is the accurate assessment of necrosis. Ideally, this should be done macroscopically and verified with histological sections, since all areas that may appear to be necrotic to the naked eye may not be so. The extent of necrosis may be prognostically significant in some sarcomas but not in others *(i.e.,* in some sarcomas, the presence of any necrosis, even if only microscopic, may be a bad prognostic feature). Moreover, necrosis is often an intrinsic part of some tumors (as in epithelloid sarcoma). It may be influenced by location where tumor expansion is limited, such as in the finger or foot and the prognostic significance of necrosis in such cases is questionable. Similar arguments can be made with regard to differentiation, cellularity, pleomorphism, mitotic activity and vascular invasion with specific sarcomas.

Most sarcomas are graded as high grade in current grading schemes regardless of which system is used. Since the overwhelming majority of adult soft tissue sarcomas are liposarcoma and so-called malignant fibrous histiocytoma, the current grading schemes have (by default) functioned reasonably well. However, the discriminating ability of current grading schemes is significantly less for rarer tumors. We have found that specific sarcomas, such as synovial sarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma, angiosarcoma of deep soft tissue, malignant granular cell tumor, intravascular lelomyosarcoma and malignant peripheral nerve sheath tumor have specific prognostic criteria. In some of these entities (e.g., intravascular lelomyosarcoma, malignant granular cell tumor and deep soft tissue angiosarcoma, which are nearly always uniformly high-grade lesions), the diagnosis dictates the tumor grade and predicts clinical behavior. In others, such as synovial sarcoma, histological grading using specific criteria is the single most important prognosticator, whereas in extraskeletal myxoid chondrosarcoma, the clinical features of age and tumor size are

predictive, regardless of histological features (provided the correct histological diagnosis has been madel).

Because of the current problems in grading sarcomas, we believe that the grading criteria should be revised for each type of soft tissue tumor. This sounds like a formidable task, particularly in view of 50 different sarcoma diagnoses and the relative rarity of sarcomas. Moreover, the study of each specific type of sarcoma needs to be subjected to multivariate statistical analysis with simultaneous consideration of histological, clinical and treatment factors in order to elucidate which of these are independent prognostic factors. The literature is replete with studies in which only a few factors have been examined with regard to prognosis while completely ignoring others (i.e., the design of many studies has been flawed). Collecting a sufficient number of rare cases to allow statistical analysis could be overcome by interinstitutional collaboration and also through metaanalysis of appropriate cases.

One of the most important underlying assumptions in all grading schemes is that the histological diagnosis is correct. One should not take this for granted. Consistently accurate diagnosis of soft tissue tumors requires a high level of expertise. While there are several new ancillary diagnostic techniques available to improve diagnostic accuracy, morphology remains the basis for a firm diagnosis. In our consultation practice, we still see pseudosarcomas misdiagnosed as sarcomas (notably cellular fibrous histiocytoma and nodular fasciltis as well as recently described entities, such as benign epithelloid schwannoma and chondroid lipoma) in addition to melanomas, anaplastic lymphomas and sarcomatoid carcinomas. For this reason, those of us within the Scandinavian Sarcoma Group (SSG) recommend that a new sarcoma diagnosis be verified by sending the case to an expert for a second opinion. In a recent review of over 1,000 soft tissue sarcomas in the SSG Pathology Tumor Registry, we found a serious error rate of 8% (misdiagnosis of a benign tumor as a sarcoma in 5%, borderline tumor as a high-grade sarcoma in 1% and lymphoma, carcinoma or melanoma as sarcoma in 2%).

This figure is relatively low since many oases had initially been sent for a second opinion. Furthermore, the SSG recommends treatment of all malignant bone and soft tissue tumors at tumor referral centers in Scandinavia to avoid unnecessary morbidity and mortality.

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# Immunohistochemistry of soft tissue tumors. An update

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Numerous immunophenotypical markers are now applied in the diagnosis of soft tissue tumors. Some of the most important new markers and their application to specific tumor types and differential diagnosis will be summarized here. The vast, rapidly growing group of markers for prognostic and biological potential evaluation of tumors is not included.

CD34, the hematopoletic progenitor cell antigen is present in endothelial cells and subsets of fibroblasts and in fibroblastic, other spindle and endothelial cell tumors. Typically positive are dermatofibrosarcoma protuberans, solitary fibrous turiibr, Kaposi's sarcoma, 50% of angiosarcomas, hemangiopericytoma and fibroblastic populations in neurofibroma. This information is useful in differential diagnosis, since nodular fasciltis, fibrous histiocytoma, desmoid, synovial sarcoma, malignant peripheral nerve sheath tumor and low grade fibromyxoid sarcoma are almost always negative. Also 70% of gastrointestinal stromal tumors (GISTs) are positive, whereas typical smooth muscle tumors are negative.

CD31 is probably the best marker for endothelial cell differentiation. It is Consistently expressed in Kaposi's sarcoma and in 70-90% of angiosarcomas. Rare, usually weak reactivity with mesotheliomas and carcinomas has been encountered. In this respect, the potentially shared endothelial and mesothelial reactivity is similar to that observed with thrombomodulin, a less sensitive marker for angiosarcomas.

Vascular endothelial growth factor receptor 3 (VEGFR-3) is a tyrosine kinase receptor restricted to lymphatics in normal adult vessels, It is strongly expressed in lymphangiomas, lymphanglomatosis and some hemangiomas and its presence in Kaposi's sarcoma and Dabska tumor has been interpreted to support their lymphatic vascular differentiation. We have found VEGFR-3 in subsets of angiosarcomas and its expression in neovascularization has become apparent in diverse tumors including carcinomas, sarcomas, melanomas and lymphomas.

CD117 (c-kit protein) is a growth factor receptor tyrosine kinase expressed in hematopoletic stem cells, mast cells, germ cells, melanocytes and the interstitial cells of Cajal in the gastrointestinal tract. GISTs are usually strongly positive, in contrast to typical lelomyomas, which only show positive mast cells and residual