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

Cajal cells. This marker is the best to define GISTs, as almost all of these tumors (leiomyomas and schwannomas excluded) are positive. In our experience, other CD34-positive tumors, such as solitary fibrous tumor, hemangiopericytoma and Kaposi's sarcoma, are negative but some primitive sarcomas have been positive. CD117-positive GISTs, especially the malignant ones, may also have c-kit gene mutations.

MyoDi is a transcriptional regulator present in developing skeletal muscle. It has been proven to be a sensitive and specific marker for rhabdomyosarcomas of children and adults, including poorly differentiated variants. This antigen is localized in the nucleus but cytoplasmic staining may be seen in non muscular tumors.

Cytoskeletal proteins of muscle cells, such as actin and myosin isoforms, have been shown to be useful in the evaluation of myofibroblastic, smooth muscle, pericytic and skeletal muscle differentiation; antibodies specific to smooth muscle, skeletal muscle, and cardiac isoforms of actin and myosin are available. Other cytoskeleton-associated proteins are also of interest and they include calmodulin, tropomyosin and isoforms of caldesmon and calponin.

Tyrosinase and melan-A (MART = melanoma antigen recognized by T-cells) are new markers for melanocytes. Both have been reported to be approximately equally sensitive as HMB-45 (80-90%) to detect amelanotic melanomas. Reactivity for both antigens is also seen in clear cell sarcoma of tendons and aponeuroses and melan-A is expressed in angiomyolipomas, lymphangiomyomas and related tumors. Melan-A may also react with adrenal cortical carcinomas.

Osteocalcin is a bone matrix protein, which appears specific for osteoid matrix, It has been employed in the analysis of skeletal and extraskeletal osteosarcomas, and found positive in both, while other tumor shave been negative. Osteonectin, another bone matrix protein, appears not specific and is present in many cell types including subsets of fibroblasts.

Fine needle aspiration in the diagnosis of soft tissue tumors in Sweden. A little goes a long way

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Fine needle aspiration (FNA) cytology has a long history and a strong tradition in Sweden. Pioneering work was done by well-known names such as S~derstr~m, Franzen, Zajicek, Esposti and Lowhagen.

In our hospital, FNA started in the beginning of the 1960s. Today, we analyze 6-7,000 FNA per year; about 70% of these are taken by the cytopathologist and the remainder is taken by clinicians and radiologists. Our files contain more than 150,000 cases and 4-5,000 of these are soft tissue lesions. All slides and reports are archived and since 1983, patient data and diagnosis have been registered in computer files. Currently, at the G6teborg Musculoskeletal Center at Sahlgrenska University Hospital in G6teborg, Sweden, FNA is considered to be a routine preoperative diagnostic procedure in the investigation of bone and soft tissue lesions. Biopsies for ENA are easily taken from almost any organ or lesion. The procedure causes little discomfort for the patient and can be performed without anesthesia on an outpatient basis. Complications are rare and, if any, almost always of minor significance. Soft tissue lesions in subcutaneous tissue are biopsied through the vertex of the lump. The aspiration site of more deeply located soft tissue and bone lesions, as well as the maximum depth of biopsy, are decided with the orthopedic surgeon. The FNA site is tattooed by the cytopathologist after biopsy. All biopsies are performed with needles with an 0.6-0.7 mm outer diameter. The number of passes varies according to the macroscopic yield but is usually 3-5 passes. After smearing, most slides are air-dried and stained according to May-GrQnewald-Giemsa. Slides are also fixed in alcohol and stained according to Papanicolaou or with hematoxilyn and eosin. Material is also usually collected in PBS for Cytospin preparation and immunocytochemistry.

In our hospital, the orthopedic tumor surgeons became interested early on in the development of FNA as a preoperative diagnostic procedure. Open surgical biopsy may be technically difficult to perform on bone and soft tissue tumors; it may also increase the risk of local recurrence after definitive surgery. In certain instances, surgical removal can be performed without a prior morphological diagnosis, provided clinical and radiographic findings indicate that the lesion is a primary tumor best treated by surgery and that the operative procedure does not lead to a significant functional loss. Usually, however, a preoperative diagnosis is mandatory to determine whether the lesion is reactive or neoplastic, benign or malignant, primary or metastatic, and to exclude lymphomas and other hematopoietic malignancies as well as those sarcomas that require therapy other than primary surgery. If the planned surgical procedure could lead to functional loss, a preoperative morphological diagnosis is mandatory. Based on our experiences with FNA in the preoperative diagnosis of soft tissue and bone tumors, we believe that:

i) FNA must always be interpreted in the context of the clinical findings and imaging studies. Accurate interpretation of FNA of bone and soft tissue lesions requires a high level of morphological expertise since these are relatively rare tumors with a wide cytologic-histologic spectrum, replete with diagnostic pitfalls. Therefore, FNA of primary bone and soft tissue lesions should be performed only at medical centers with expertise in the diagnosis and treatment of such tumors.

ii) With FNA, sufficient material is obtained in 85-90% of cases to ascertain whether a lesion is primary or metastatic, benign or malignant and low- or high-grade malignant. In many cases, a specific diagnosis can be rendered or suggested. FNA of bone and soft tissue tumors also provides useful information about which tumors should be targeted for further investigation (such as morphological, cytogenetic, molecular biological studies) at the time of surgical resection.

iii) FNA is an easy, fast and cost-effective method for morphologic diagnosis that does not, with the exception of small children, require any anesthesia.

iv) FNA entails many of the same diagnostic problems and pitfalls that open biopsies of bone and soft tissue lesions have. However, FNA allows more extensive, representative sampling than an open biopsy and can be guided by imaging procedures such as CT and ultrasound.

v) When FNA is used as the primary diagnostic procedure, a less