Human Pathology (2016) **56**, 147–154

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Human PATHOLOGY

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Original contribution

Federation Nationale des Centers de Lutte Contre le Cancer grading of soft tissue sarcomas on needle core biopsies using surrogate markers☆

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Received 18 April 2016; revised 2 June 2016; accepted 11 June 2016

Keywords:
Needle core biopsy;
Soft tissue sarcoma;
Histologic grade;
FNCLCC grading system;
Ki-67;
Radiology

Summary Needle core biopsy (NCB) of soft tissue sarcomas (STSs) presents problems for French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) histological grading because small sample size hinders determination of necrosis and mitotic activity. We graded 53 STSs on NCB using a modified FNCLCC grading system that substitutes Ki-67 immunoexpression for mitotic count and uses a radiological assessment of necrosis, and compared the results with those obtained by conventional FNCLCC grading of the corresponding untreated, surgically resected specimen. Forty-eight of the 53 tumors were classified as malignant on NCB (concordance = 91%). The modified FNCLCC grade correctly separated high-grade (grades II and III) from low-grade sarcomas in 70% of cases and predicted the traditional FNCLCC grade given to the resected specimen in 49% of cases. Ki-67 scores of 2 or 3 were observed in 5 tumors classified as low-grade neoplasms on NCB but upgraded to a high-grade dedifferentiated liposarcoma on resection. Underestimated NCB grades were commonly encountered with lipomatous tumors due to sampling error, whereas Ki-67 or radiologic necrosis scores higher than the corresponding histological scores were responsible for the vast majority of overestimated NCB grades. Our FNCLCC grading scheme replacing conventional mitosis counting and histologic assessment of necrosis with surrogate markers is useful in separating high- and low-grade STSs on NCB for STS treatment planning. High Ki-67 rate should raise suspicion of a higher-grade component, particularly with fatty tumors.

1. Introduction

Most soft tissue pathology experts agree that the major risk factors for recurrence and death from a localized adult soft tissue sarcoma (STS) are tumor size, depth, and histological grade [1-3]—clinicopathologic elements integral to the commonly used American Joint Committee on Cancer (AJCC) staging system [4]. Studies have demonstrated that histologic grade is the best predictor of prognosis for localized adult

☆ Disclosures: All authors fully disclosed no financial conflicts of interest in the Support/Grant Information text box, as well as no ethical conflicts of interest.

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http://dx.doi.org/10.1016/j.humpath.2016.06.008
0046-8177/

STS [2,3,5-8], and clinicians rely heavily on it for STS treatment planning. For example, National Comprehensive Cancer Network guidelines for stage II and III sarcomas, which include high-grade tumors according to the AJCC guidelines, recommend preoperative chemotherapy or radiation therapy, whereas for AJCC stage I (and grade I) sarcomas, surgery is the mainstay of treatment [4,9,10].

The 2 most commonly used systems for STS grading in clinical practice are the 3-tiered National Cancer Institute [5] and the French Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) schemes [6,11]. Both systems evaluate mitotic activity and extent of necrosis, but the former also accesses histological subtype, tumor cellularity, and cellular pleomorphism, whereas differentiation (which is highly dependent upon histological subtype) is the third factor scored in the latter system. Accurate assessment of National Cancer Institute and FNCLCC grading requires enough representative tumor tissue to properly evaluate the aforementioned pathologic parameters. In the past, this was achieved by open biopsy. However, this once criterion standard for initial sarcoma diagnosis has been replaced in most institutions by the needle core biopsy (NCB), which is now accepted and even considered preferable for sampling deep-seated tumors. Studies examining STS histological grading (but not stipulating the grading system used) have demonstrated good concordance between the NCB and incisional biopsy [12-16]. To date, only 2 studies have evaluated the efficacy of traditional FNCLCC grading on NCB [16,17]. Strauss et al [16] effectively separated high-grade (FNCLCC grades II and III) from low-grade STS on NCB in 86% of cases. Khoja et al [17] concluded that FNCLCC grading of NCB samples was not predictive of patient outcome compared with grade obtained from conventional incisional biopsies but did not directly compare results from the 2 techniques.

Two main factors negatively impact the accuracy of FNCLCC grading of NCB specimens. These are the limited sample size provided by NCB and the inherent tumor heterogeneity typical of large STS. Both factors have the potential to result in an underestimation of tumoral necrosis and mitotic activity and subsequently an overall lower final tumor FNCLCC grade [16,17].

In this study, we attempt to improve FNCLCC grading of NCB by testing a modified FNCLCC grading system that supplants mitotic count with Ki-67 (MIB-1) immunoexpression and uses a radiologic assessment of necrosis. We examined the efficacy of this system by comparing the results with those derived from traditional FNCLCC grading performed on the corresponding, untreated surgically excised specimen.

2. Materials and methods

2.1. Case selection

After approval by our institutional review board (STU #5555 and #82702), we retrieved surgically resected STSs that have not had preoperative chemo- and/or radiation therapy and their corresponding NCB accessioned to the pathology department of Northwestern Memorial Hospital. Inherently high-grade sarcomas, such as primitive, "round cell" sarcomas and rhabdomyosarcomas, and sarcomas not amenable to conventional histologic grading (eg, angiosarcoma) were not included in the study. In keeping with this statement, we eliminated 2 cases (small cell sarcoma, not otherwise classified, and a rhabdomyosarcoma) and retabulated all pertinent calculations. Fifty-three tumors met the above criteria and were included in the study.

2.1.1. Fine needle aspiration and NCB

All NCBs were performed under ultrasonography or computed tomography (CT) guidance with 16-, 18-, or 20-gauge needle by a musculoskeletal-trained radiologist. When tumor size and conditions allowed, 2 to 4 NCB samples were obtained at different angles at the same time that the fine needle aspiration (FNA) was performed. An on-site cytopathologist determined adequacy of the specimen by evaluating Giemsa-stained FNA material and touch preparations of the NCB.

2.1.2. Histology and immunohistochemistry

The cores and resected tissues were fixed in 10% formalin, processed under standard procedures, and stained with hematoxylin and eosin (H&E) stain for histologic evaluation. Immunohistochemical (IHC) stain for Ki-67 (MIB-1, clone 30–9; Ventana, Tucson, AZ; prediluted antibody using high-pH antigen retrieval with mild CC1) and other selected antigens (data not shown) was performed in an automated immunostainer with appropriate positive and negative controls following manufacturers' instruction, which means that positive controls were stained positive and negative controls were stained negative. All H&E and IHC slides along with FNA and/or touch preparation slides were reviewed by a surgical pathologist (W. B. L.) and a cytopathologist (X. L.) with interest in soft tissue pathology.

2.1.3. Grading of STS

Soft tissue sarcomas on NCB specimens were graded using a modified FNCLCC grading system that summed the scores given to the percentage of necrosis determined by CT or magnetic resonance imaging (MRI), proliferative activity assessed by evaluating Ki-67 immunoexpression [18], and degree of differentiation using standard FNCLCC criteria [6,11].

Histological subtyping required IHC analysis in some cases (data not shown). The Ki-67 index was calculated by counting nuclear staining in 100 tumor cells in the area of highest immunoexpression and semiquantitatively scored in the manner described by Hasegawa et al [18] as follows: mitotic score of 1, between 1% and 9% tumor cells immunoreactive; 2, 10% to 29% tumor cells reactive; 3, 30% or more cells reactive.

The extent of necrosis was ascertained by a musculoskeletal radiologist (I. O.) blind to the final pathology diagnosis. By comparing pre- and postcontrast CT or MRI scans, areas of the tumor that failed to enhance postcontrast were