Grading of Spindle Cell Sarcomas in Fine-Needle Aspiration Biopsy Specimens

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Abstract

We studied whether histologic criteria for grading sarcomas could be applied to fine-needle aspiration biopsy (FNAB) specimens of adult spindle cell sarcomas, without knowledge of the sarcoma subtype, by reviewing 36 specimens. Grade 1 was assigned for minimal nuclear atypia and overlap, no necrosis, and rare mitotic figures, and grade 2 for moderate nuclear atypia, at least moderate nuclear overlap, appreciable mitotic figures, and necrosis. Severe nuclear atypia distinguished grade 3 from grade 2. A major noncorrelation between FNAB and histologic grades was defined as a misclassification of grade 1 vs *grade 2 or 3. FNAB grades assigned were grade 1, 1; grade 2, 25; and grade 3, 10. There was 1 major noncorrelation due to a probable FNAB interpretation error. In 15 of 16 FNAB specimens of grade 2 or 3 sarcomas lacking mitotic figures, necrosis, or both, the nuclear atypia reflected the grade. In the remaining case, the degree of nuclear overlap and necrosis determined the grade. The histologic grading of sarcomas can be applied accurately to most FNAB specimens of spindle cell sarcomas without knowledge of the sarcoma subtype.*

Fine-needle aspiration biopsy (FNAB) is an effective tool for the diagnosis of primary and metastatic soft tissue tumors with reported high sensitivity and specificity rates.[1–5] Exact subclassification of sarcomas, especially spindle cell sarcomas, can be difficult on FNAB and histologic examination without the use of ancillary studies, such as immunohistochemistry and electron microscopy.[6–8] However, several studies report that among spindle cell sarcomas and sarcomas in general, the most important prognostic factor, which influences survival and recurrence rates, is the grade of the sarcoma, rather than the histologic subtype.[6,9,10] In addition, some current treatment protocols for adults include preoperative radiation, chemotherapy, or both, for intermediate- and high-grade sarcomas regardless of the histologic subtype. The grading schemes of sarcomas reported in the literature, however, were developed from histologic specimens and not FNAB specimens.[6,11–16] We studied whether the criteria used in histologic grading can be applied to FNAB specimens of spindle cell sarcomas in adults, without knowledge of the sarcoma subtype.

Materials and Methods

The FNAB specimens of 36 consecutive spindle cell sarcomas from adults, which had a corresponding histologic specimen, were reviewed without knowledge of the grade or histologic subtype. The grading scheme was adapted to FNAB material from a modification of the grading scheme applied to histologic specimens of sarcomas at our institution **Table 1**. FNAB cell groups and single cells were assessed for nuclear atypia (mild, moderate, or marked), presence of necrosis, and number of mitotic figures per 10 high-power fields (HPFs). Cell groups also were evaluated for nuclear overlap (minimal, moderate, or marked). The number of cell groups on each FNAB slide was classified as low (<20 groups per slide,

with at least 3 cells per group); moderate (20–50 groups per slide); or high (>50 groups per slide).

Grade 1 was assigned to FNAB specimens showing minimal nuclear overlap, mild nuclear atypia, no necrosis, and rare mitotic figures (≤2 per 10 HPFs). *Mild nuclear atypia* was defined as nuclei with minimal variation in size and shape, smooth to minimally irregular nuclear contours, bland chromatin, and absent to tiny nucleoli **Table 2**. Grade 2 was selected when FNAB material showed at least moderate nuclear overlap, moderate nuclear atypia, appreciable mitotic figures (≥3 per 10 HPFs) and necrosis. Moderate nuclear atypia included nuclei with moderate variation in size and shape, slightly irregular nuclear contours, chromatin clumping, and variable macronucleoli (Table 2). Necrosis was identified as background necrotic debris, individual cell necrosis, and/or necrosis within groups. Grade 3 was distinguished from grade 2 by marked nuclear atypia, which included irregular nuclear contours, coarse chromatin, macronucleoli, and marked variation in nuclear size and shape (Table 2). When the FNAB smears showed areas of grade 1 and 2, or grade 2 and 3, the highest grade was assigned. The corresponding histologic specimens also were reviewed without knowledge of the FNAB grade and assigned a grade based on the grading scheme for histologic specimens of sarcomas at our institution, which resembles the FNAB grading scheme, except it has no requirement for a detailed mitotic figure count (Table 1). The slides from 4 histologic specimens were unavailable for review (3 needle core biopsies and 1 excision), and the grade was obtained from the histologic report from our institution. All of these specimens had concurrent or subsequent histologic specimens, which were available for review (2 with cell block material, 1 with cell block and excision, and 1 with excision alone).

A *major* noncorrelation between the FNAB and the histologic grades was defined as a misclassification of a low-grade (grade 1) specimen *vs* intermediate (grade 2) or high-grade (grade 3) specimen, which in some treatment protocols could have resulted in a change in preoperative therapy. A *minor* noncorrelation between the FNAB and the histologic grades was grade 2 *vs* grade 3.

For the 36 specimens, a total of 281 slides were reviewed, with an average of 8 slides per case and a range of 1 to 19 slides. Alcohol-fixed, Papanicolaou-stained or H&E-stained, directly smeared material was reviewed. In the rare case with extra air-dried Diff-Quik–stained material, the slides were examined only for necrosis and mitotic figures. The degrees of nuclear atypia and overlap were not assessed on these few slides to avoid overcalling the exaggerated nuclear changes as a result of the air-drying artifact. The material was obtained after multiple passes by a radiologist using image guidance (ultrasonography or computed tomography) in 21 cases, and by a cytopathologist in 15 cases. Material was stained for immediate interpretation by a cytopathologist in 34 of 36 cases, with no documentation available for the remaining 2 cases, which predated computerization. A single pass usually was spread onto 2 or more slides, with multiple passes obtained to provide additional material for diagnostic purposes or for special marker studies.

Results

Valid statistical analysis could not be performed owing to too few specimens. The 36 FNAB specimens from 33 patients were obtained from 14 primary, 15 metastatic, and 7 recurrent

Table 1
Grading Scheme for Fine-Needle Aspiration Biopsy Specimens of Spindle Cell Sarcomas

	Grade		
	1	2	3
Nuclear atypia	Mild	Moderate	Marked
Nuclear overlap	Minimal	≥ Moderate	≥ Moderate
Mitotic figures	Rare	Numerous	Numerous
Necrosis	Absent	Present	Present

Table 2
Nuclear Atypia Criteria

	Parameters			
	Nuclear Variation	Nuclear Contour	Chromatin	Nucleoli
Nuclear atypia				
Mild	Minimal	Smooth or minimally irregular	Bland	Absent or tiny
Moderate	Moderate	Slightly irregular	Clumped	Variable macronucleoli
Marked	Marked	Irregular	Coarse	Macronucleoli

spindle cell sarcomas. One patient had 3 FNAB specimens from different sites, and 1 patient had 2 FNAB specimens. The histologic subtypes were as follows: malignant fibrous histiocytoma, 16; leiomyosarcoma, 5; synovial sarcoma, 4; gastrointestinal stromal sarcoma, 4; malignant schwannoma, 2; malignant hemangiopericytoma, 2; classic fibrosarcoma, 1; myxoid fibrosarcoma, 1; and fibromyxoid sarcoma, 1. The sites of the sarcomas were the extremities in 12 cases; the retroperitoneum, pelvis, or abdomen in 6; central areas in 5 (buttock, scalp, chest wall, paraspinal); and parenchyma in 13 cases (lung, 7; liver, 4; lymph node, 1; thyroid, 1). The corresponding histologic specimens included 21 excisions (10 had cell block, needle core biopsy, or both, as well), and 15 cell blocks (2 had needle core biopsies as well). All FNAB, cell block, and needle core biopsy specimens were obtained before radiation or chemotherapy. Among the 21 patients for whom excision specimens were available, 13 received preexcision radiation, chemotherapy, or both.

The numbers of cell groups per slide was low in 13 specimens, moderate in 15, and high in 8. The assigned grades for the FNAB specimens and the histologic specimens from the 36 spindle cell sarcomas are given in **Table 3**. The grade 1 assigned by FNAB correlated with the excision grade (a fibromyxoid sarcoma) **Image 1**. Among the 25 sarcomas assigned grade 2 from the FNAB specimen **Image 2** and **Image 3**, there was 1 major noncorrelation (grade 1 by cell block) and 2 minor noncorrelations (grade 3 by needle core biopsy). The major noncorrelation could have been attributable to a FNAB interpretation error, since the previous gastrointestinal stromal sarcoma was grade 1. However, the possibility of a higher grade in the metastasis cannot be excluded either. The FNAB grading was difficult owing to low numbers of cell groups in the FNAB specimen, with sarcoma cells showing spindled and epithelioid features from Schwannian differentiation, which may have resulted in overcalling of the nuclear atypia and, therefore, the grade. The 2 minor noncorrelations were from FNAB sampling errors because the marked nuclear atypia present in the needle core biopsy specimens and/or excision specimens were not identified in the FNAB.

Among the 3 sarcomas assigned grade 1 by histologic examination, one correlated, the second was the case described in the previous paragraph, and in the third case, the FNAB specimen was graded as grade 2, but the cell block as grade 1. This was believed to be due to a cell block sampling error because the original sarcoma was graded as grade 2 on previous sampling, and the FNAB specimen had a morphologic appearance similar to the original tumor.

For the 21 sarcomas assigned grade 2 by histologic examination, there were 2 minor noncorrelations (grade 3 by

Table 3
Grading Categories Assigned on FNAB and All Histologic Specimens of 36 Spindle Cell Sarcomas

	Grade		
	1	2	3
Specimen			
FNAB	1	25*	10
Histology	3†	21‡	12§

FNAB = fine-needle aspiration biopsy.
* Includes 1 FNAB interpretation error and 2 FNAB sampling errors.
† Includes 1 cell block sampling error.
‡ Includes 2 cell block sampling errors.
§ One excision specimen was overgraded owing to radiation effects.

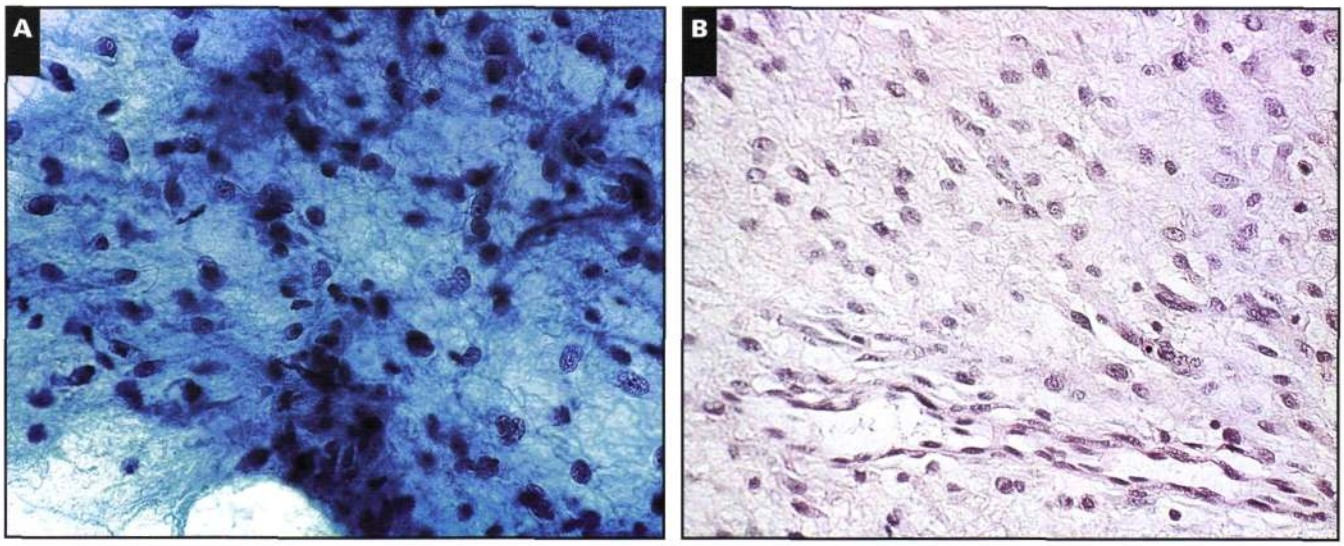

Image 1 A, Grade 1 fibromyxoid sarcoma showing minimal nuclear atypia and overlap, no necrosis, and no mitotic activity in fine-needle aspiration biopsy specimen (Papanicolaou, ×500). B, Similar features in excision of grade 1 fibromyxoid sarcoma (H&E, ×250).

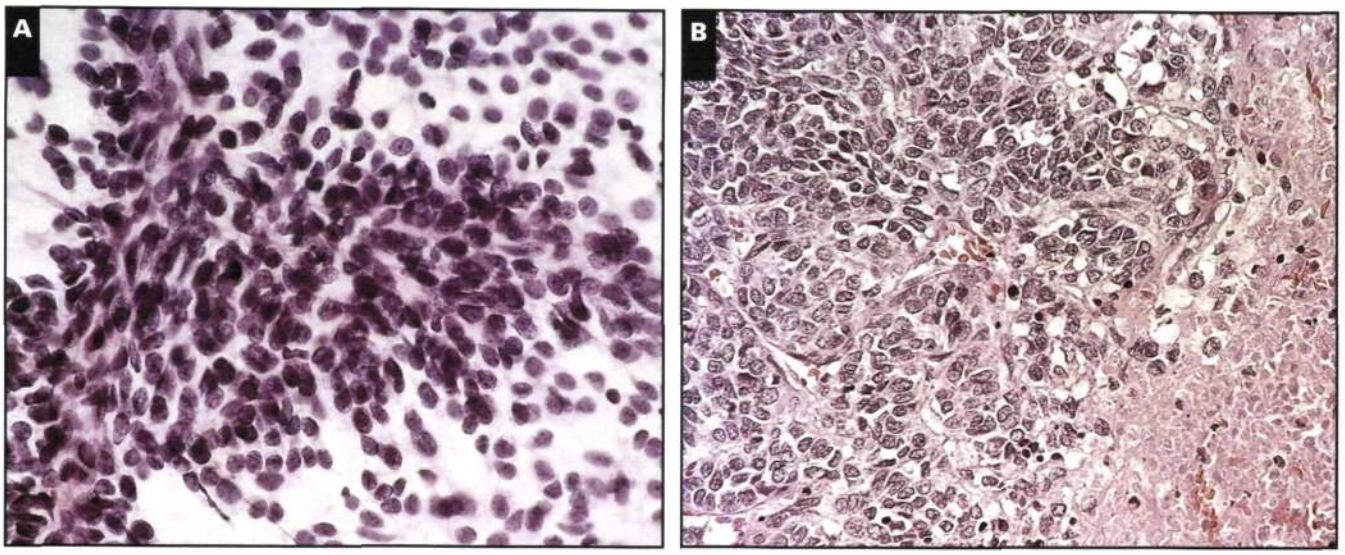

Image 2 A, Fine-needle aspiration biopsy specimen of a synovial sarcoma, assigned grade 2, that shows moderate nuclear overlap and atypia (H&E, ×650). B, Corresponding excision specimen showing grade 2 synovial sarcoma with moderate nuclear atypia, abundant necrosis, and scattered mitotic figures (H&E, ×320).

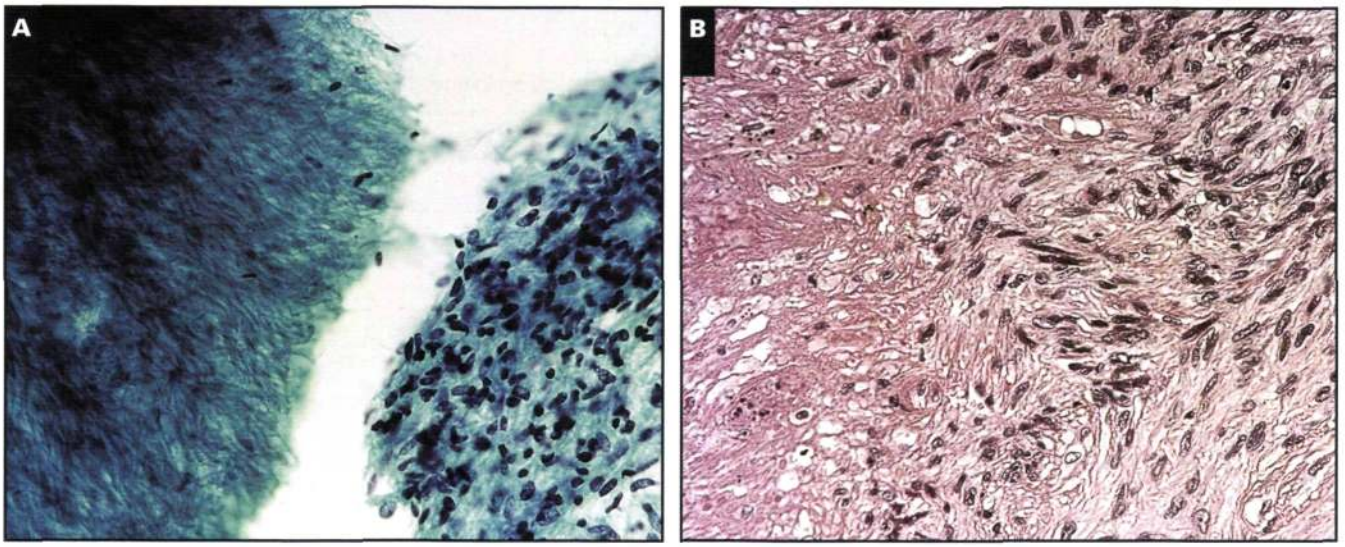

Image 3 A, Grade 2 leiomyosarcoma showing moderate nuclear atypia and overlap with associated background necrosis (Papanicolaou, ×650). B, Corresponding postradiation excision specimen showing moderate nuclear atypia and necrosis (H&E, ×320).

cytology) due to cell block sampling errors. One of the original sarcomas was grade 3, while the other had repeated FNAB and cell block specimens, which showed grade 3 as well.

For the sarcomas assigned grade 3 by histologic examination **Image 4**, there was 1 minor noncorrelation (grade 2 by FNAB) that likely was due to radiation effects that caused severe nuclear atypia in the excision specimen, which was not present in the preradiation FNAB and cell block specimens.

In total, we were able to correctly grade 33 FNAB specimens from the 36 spindle cell sarcomas, with 1 major noncorrelation due to a presumed FNAB interpretation error and 2 minor noncorrelations due to FNAB sampling errors (Table 3). For the histologic specimens, we correctly graded 32 of the 36 spindle cell sarcomas, with 1 major noncorrelation due to a cell block sampling error and 3 minor noncorrelations (2 cell block sampling errors and 1 radiation effect probably causing upgrading).

If only the FNAB and cell block grades (22 cases) were compared **Table 4**, the FNAB grades included no grade 1, 17 grade 2, and 5 grade 3. Of the 17 grade 2 FNAB cases, the cell block grades were 2 grade 1 and 15 grade 2. These 2 major noncorrelations, as previously discussed, included 1 cell block sampling error (previous tumor grade 2) and 1 presumed FNAB interpretation error. Among the 5 grade 3 FNAB cases, the cell block grades were 3 grade 3 and 2

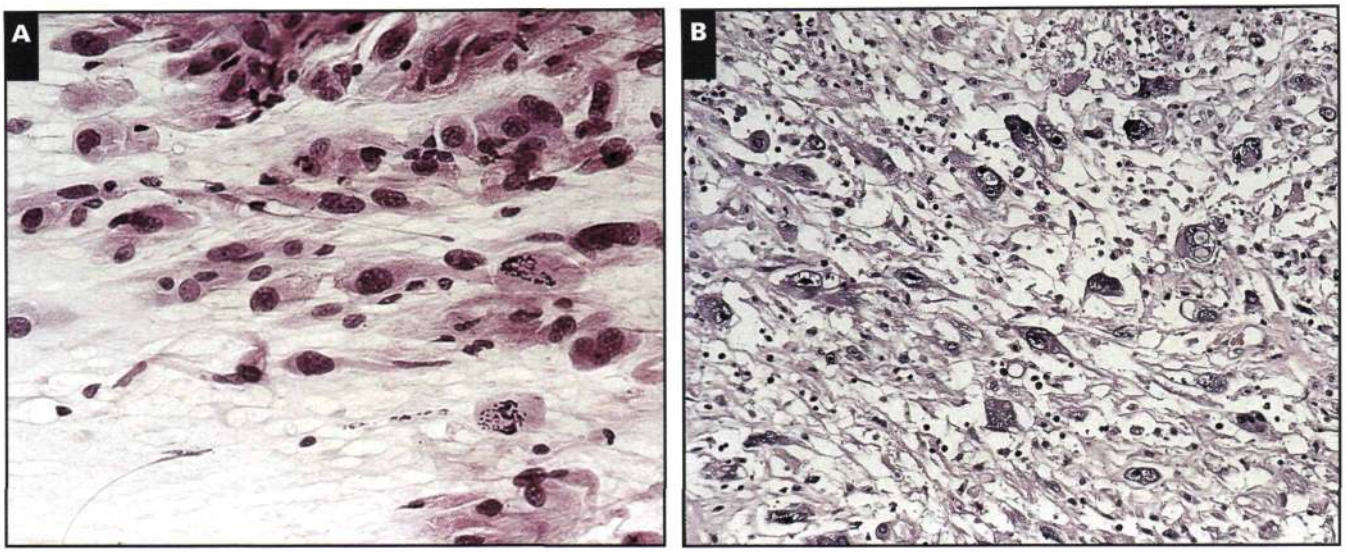

Image 4 A, Fine-needle aspiration biopsy specimen of a grade 3 malignant fibrous histiocytoma showing severe nuclear atypia and obvious mitotic figures with abnormal forms (H&E, ×320). B, Corresponding postradiation excision specimen showing grade 3 malignant fibrous histiocytoma with severe nuclear atypia. Necrosis was identified elsewhere in the specimen (H&E, ×160).

grade 2, both cell block sampling errors, as previously discussed. If only FNAB specimen grades were compared with the excision grades (21 cases), the FNAB grades included 1 grade 1, 14 grade 2, and 6 grade 3 **Table 5**. The excision grades included 1 grade 1, 12 grade 2, and 8 grade 3. The 2 minor noncorrelations (grade 2 by FNAB, grade 3 by excision) were probably due to radiation-induced atypia causing upgrading, as previously discussed.

Among the 22 grade 2 and 12 grade 3 spindle cell sarcomas, there were 16 FNAB specimens (12 grade 2 and 4 grade 3), which lacked necrosis in 5, mitotic figures in 7, or both in 4, and these parameters could not be used to assign a grade **Table 6**. Nine of these 16 FNAB specimens had fewer than 20 cell groups per slide. In these 16 cases, the degree of nuclear atypia accurately predicted the grade in 15. In the remaining case, the presence of necrosis and moderate nuclear overlap correctly predicted the grade as 2, when only minimal nuclear atypia was identified. The degree of nuclear overlap and atypia were especially useful for distinguishing grade 1 from grade 2 or 3 spindle cell sarcomas in most cases (Table 6).

Table 4
Grading Categories Assigned on 22 FNAB and Cell Block Specimens

	Grade		
	1	2	3
Specimen			
FNAB	0	17	5
Cell block	2*	17†	3

FNAB = fine-needle aspiration biopsy.
* Includes 1 cell block sampling error and 1 FNAB interpretation error.
† Includes 2 cell blocking sampling errors.

Table 5
Grading Categories Assigned on 21 FNAB and Excision Specimens

	Grade		
	1	2	3
Specimen			
FNAB	1	14	6
Excision	1	12*	8†

FNAB = fine-needle aspiration biopsy.
* Includes 7 postradiation or chemotherapy.
† Includes 6 postradiation or chemotherapy.

Discussion

Numerous studies have examined the prognostic factors that influence recurrence rates, survival, and treatment options for soft tissue sarcomas.[10,13–19] The most important prognostic variable for sarcomas in general seems to be the histologic grade, since the histologic subtype for most spindle cell sarcomas may not be as important according to some studies.[6,10–12,14–19] As well, the grade of the tumor is becoming more important in treatment strategies, because in some current protocols, patients with intermediate or high-grade sarcomas receive neoadjuvant radiation and chemotherapy. However, determination of the histologic grade is somewhat subjective and incorporates multiple factors, including cellularity, cytologic atypia, mitoses, necrosis, and degree of differentiation.[6,11,14–19] To date, grading schemes have been developed for application only to

Table 6
Parameters for Grading FNAB Specimens According to Grade of Sarcoma

	Grade		
	1 (n = 2)	2 (n = 22)	3 (n = 12)
Nuclear atypia			
Mild	1	1	0
Moderate	1	21	2
Marked	0	0	10
Nuclear overlap			
Minimal	2	1	0*
Moderate	0	19	5
Marked	0	2	5
Mitotic figures			
None or unable to count	1	7†	4‡
Rare (1–2/10 HPF)	1	5	2
Many (≥ 3/10 HPF)	0	10	6
Necrosis			
Present	0	14	11
Absent	2	8§	1¶

FNAB = fine-needle aspiration biopsy; HPF = high-power fields.
* Unable to assess in 2 cases (low cellularity).
† Low cellularity in 5 cases.
‡ Low cellularity in 2 cases.
§ Low cellularity in 4 cases.
¶ Low cellularity.

histologic specimens of sarcoma and not to cytologic samples obtained by FNAB.[6,11–16] With the increasing use of FNAB in the initial evaluation of primary and metastatic soft tissue tumors, a grading scheme would be very useful. Therefore, we designed a grading scheme for spindle cell sarcomas obtained by FNAB and tested its usefulness by applying it to 36 FNAB specimens from primary, metastatic, and recurrent spindle cell sarcomas without knowledge of the sarcoma subtype or grade.

In the present study, grading was accurately applied to 33 (92%) of 36 FNAB specimens obtained from spindle cell sarcomas, and there was 1 major noncorrelation between the FNAB and histologic grades, due to a probable FNAB interpretation error. This error was likely unavoidable, since the smears showed epithelioid cells (Schwannian differentiation) in addition to spindle cells, which posed problems for applying the grading scheme, and in retrospect should have been excluded from the study. However, this example illustrates that our criteria are best applied to pure spindle cell sarcomas, and modifications may be necessary to accurately grade non–spindle cell sarcomas.

Modification of the grading system was necessary to take into account FNAB specimens of grade 2 or grade 3 sarcomas, which lacked mitotic activity, necrosis, or both. Other grading criteria had to be used to assign a grade. The nuclear atypia on the FNAB specimen was an accurate reflection of the sarcoma grade in 15 of 16 FNAB specimens of intermediate (grade 2) and high-grade (grade 3) sarcomas that lacked mitotic figures, necrosis, or both, even in the scantly cellular FNAB specimens. Attention to the degree of nuclear overlap and necrosis helped to increase the FNAB grade from grade 1 to 2 when nuclei with mild atypia were identified, as occurred in 1 case. The degree of nuclear overlap and atypia were most useful overall for predicting the grade on FNAB.

A possible factor that may influence the correlation between the FNAB and excision grade is preoperative treatment. The present study included 13 patients who had pretreatment FNAB specimens and posttreatment tumor excisions. However, there was only 1 minor grade noncorrelation (grade 2 by FNAB, grade 3 by excision), which may have been attributable to radiation effects causing increased nuclear atypia in the excision specimen.

The present study does not address the sensitivity or specificity of FNAB in the diagnosis of specific sarcoma type or its usefulness for distinguishing benign from malignant soft tissue lesions. The sole purpose of this study was to examine the application of a grading scheme to FNAB specimens of spindle cell sarcomas, without knowledge of the sarcoma subtype. The problems in recognition of some soft tissue lesions as sarcoma by FNAB examination are well-known and have been discussed elsewhere in the literature.[5,7–9,20,21] The appearance of soft tissue sarcomas in FNAB smears can mimic melanoma, carcinoma, and some pseudoneoplastic lesions, such as nodular fasciitis, postsurgical scar, inflammatory pseudotumor, and fibromatosis.[5,7,20] This grading system can be applied only to FNAB specimens that unequivocally show spindle cell sarcoma.

One weakness of the present study was the low numbers of grade 1 spindle cell sarcomas. However, since

the grading of the FNAB specimens was done without knowledge of the true grade distribution, the study shows that most grade 2 and 3 spindle cell sarcomas can be graded accurately by using our criteria, even without knowledge of the histologic subtype.

Our results indicate that this grading scheme can accurately grade the majority of spindle cell sarcomas on FNAB specimens. However, careful attention must be exercised in these cases to exclude confounding factors that may lead to overgrading, such as epithelioid features. Further evaluation is necessary to determine whether this grading scheme can be applied to non–spindle cell sarcomas and whether these results can be confirmed in a larger series.

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