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Research Article

A CORRELATIVE STUDY ON SPINDLE CELL SARCOMA WITH CYTO-HISTOLOGICAL GRADING BY CONVENTIONAL METHODS IN AN INDIAN TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Objective: Spindle cell sarcomas constitute an important component of soft tissue sarcomas, where accurate grading is more important than histologic subtypes to plan treatment strategies and determine prognosis. To assess whether histologic criteria for grading sarcomas could be applied to fine needle aspiration biopsy (FNAB) specimens of adult spindle cell sarcomas without knowledge of sarcoma subtypes. Furthermore, correlate this grading with histologic Federation Nationale Des Centres de lutte contre le cancer (FNCLCC) grading system and find out the percentage of accuracy of FNAB grading.

Methods: Hundred cases were studied by fine needle aspiration cytology (FNAC), among them 50 cases found to be spindle cell sarcoma; in only 42 cases surgical specimens were available. Each aspiration being spread into two or more slides. Subsequently, biopsy was done and studied. Technique used - grading of FNAB specimens and corresponding surgical specimens.

Result: Grading of FNAB specimens done taking into account four parameters - nuclear atypia, nuclear variation (nuclear contour, chromatin, nucleoli, and nuclear overlap), mitotic figure, and necrosis. Grading of surgical specimens done by FNCLCC system. The overall results were correlated for both FNAC and biopsy concordance and statistically analyzed. From there the sensitivity and specificity were calculated as 95.23% and 80.76%, respectively.

Conclusion: Histologic criteria for grading sarcomas in adults could be applied to FNAC specimens of spindle cell sarcomas with 88% accuracy. While comparing the diagnosis given by FNAC and biopsy, it revealed the true positive were 40 cases, true negative 42 cases, false positive 10 cases, and false negative (FN) 2 cases.

Key words: Spindle cell sarcoma, Fine needle aspiration biopsy (Fine needle aspiration cytology), Biopsy, Sensitivity, Specificity.

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INTRODUCTION

Spindle cell sarcoma constitutes an important component of soft tissue sarcomas, which are not very uncommon [1-3]. The incidence of new soft tissue sarcoma (Annual) - 9500 cases in the USA, 2006 [4]. Soft tissue tumor presents a challenge to the pathologist because of their extremely varied morphologic and biologic behavior. Several studies report that in spindle cell sarcomas and sarcomas, in general, a most important prognostic factor which influences survival and recurrence rate is the grade of sarcoma rather than the histologic subtype [5-7]. Fine needle aspiration biopsy (FNAB) is an effective tool for the diagnosis of soft tissue tumor both primary and metastatic, with high sensitivity and specificity [8-13]**.** It is a rapid outpatient procedure that provides an immediate diagnosis as compared to other techniques [13,14]. It permits the surgeons to discuss potential additional diagnostic procedure and therapy of the patient during the initial visit and facilitate for the processing or triaging of patient by the surgeon [13,14]. The procedure includes minimal trauma, no cost and no need for hospitalization. It can offer confirmation of local recurrence and metastasis [13,14]. Fine needle aspiration cytology (FNAC) can be performed on any subcutaneous lesion, any palpable mass/radiographically detectable mass, whenever incisional biopsy is contraindicated. Various authors have discussed about the role and efficacy of FNAC in the pre-operative diagnosis of soft tissue tumor. Pack, 1954 stated, the critics of aspiration biopsy are too specific in their demand of the method [15]. Chatura *et al*., 2015, is of the opinion that cytoarchitectural findings in conjunction with clinical correlation and ancillary methods have broadened the diagnostic spectrum [16]. Ricardo Gonzalez – Campora establish six basic categories, e.g., round cell tumor, myxoid tumor, pleomorphic tumor, spindle cell tumor, epithelial-like cell tumor, mature like cell tumor basing on stromal characteristic, cell shape and resemblance to normal tissue.

Miralles *et al*., 1986, basing on above criteria grouped soft tissue sarcoma into five categories, e.g., Group I - Low-grade sarcoma, Group II - Myxoid sarcoma, Group III - Monomorphic sarcoma, Group IV - Round cell sarcoma, and Group V - Pleomorphic sarcoma [17,19].

Nonetheless, FNA is not without pitfalls, some of which are derived from the nature of the tumor such as - scarcity of cells in the aspirate, tumor heterogeneity, focal nature of certain sarcomatous overgrowth, absence of strict criteria, for diagnosis of some sarcomas and last but not the least - limited experience of pathologist owing to low incidence of sarcomas [16,19].

In the hands of the expert; cytopathologist, it can afford a diagnostic specificity >90% [16,19] so it is considered valuable tools in the management of soft tissue tumor. For practical purposes, pattern analysis is always recommended. All smears fall in one or more of the

six categories, i.e., round cell/spindle cell tumor. Certain diagnostic signs are specific to a lesion, i.e., atypical lipoblast in liposarcoma, atypical rhabdomyoblast in rhabdomyosarcoma, cytoplasmic glycogen in Ewing's sarcoma, and neuroblastoma.

In 1999, Weir *et al*. stated that accurate grading may be more important than histologic subtyping to plan treatment strategies and determine prognosis [6,18]. In subsequent years many histologic and cytologic grades were developed. Among them, important is Federation National Des Centres de lutte contre le cancer (FNCLCC) histologic grading system. Weir *et al.* in 1999 stated that establishing an effective grading system is more important than histologic subtyping and is very helpful for the management and survival of the patient and assessing the recurrence rate [18]. This treatment protocol for adults include pre-operative radiotherapy and chemotherapy for intermediate and high-grade sarcoma, regardless of histologic subtype. FNA from a wide variety of soft tissue tumor was carried out, and cytomorphologic study and grading are done according to the specific criteria, of Weir *et al*., 1999 [6,18].

A careful histopathological examination and grading of the tissue obtained from either incisional/excisional biopsy were done and a comparison between cytologic and histologic grading was attempted to establish the percentage of accurate cytologic grading of adult spindle cell sarcoma. The purpose of the study is to assess whether histologic criteria for grading sarcomas could be applied to FNAB specimens of adult spindle cell sarcomas without knowledge of sarcoma subtypes, to correlate this grading with histologic FNCLCC grading system and to find out the percentage of accuracy of FNAB grading.

METHODS

This study "Cyto-histologic grading of spindle cell sarcoma - a correlative study" was conducted from December 2013 to December 2015 in the Department of Pathology, IMS and SUM Hospital, Odisha, India. A total of 50 cases of spindle cell sarcomas were studied in FNAB. 162 number of aspirations were done and each aspiration being spread onto two or more slides. Hence, 346 number of cytosmear slides were studied with an average of 7 slides per case and a range of 1-11 slides. Subsequently, in 42 cases, we were able to get the surgical specimen. Hence, finally, 42 cases were evaluated with reference to cytological and histological grading and correlated.

For cytological study, under low power, looked for cellularity, nuclear overlap, architectural arrangement, cell type, and background. Under high power looked for the type, the degree of cellular differentiation, nuclear atypia, mitosis, and necrosis. Cytological grading was done basing on modified histological grading (modified by Weir *et al*.) [18]. It took into account four parameters - nuclear atypia, nuclear overlap, mitosis, and necrosis. Nuclear atypia was designated as mild, moderate and marked basing on - nuclear variations, nuclear contour, chromatin, and nucleoli (Table 1). Surgical biopsy examined for gross, low power, high power microscopic picture and given histological diagnosis. Histological grading is done basing on FNCLCC [18] by French Federation of Cancer Centre Sarcoma Group. It considered three parameters, i.e., cellular differentiation, mitosis, and necrosis (Table 2). Then, the cytological and histological correlations were carried out.

Table 1: Cytologic grading

Grade - 1					Grade - 2						Grade - 3						Final grade
Nuclear atypia mild				Necrosis	Nuclear atypia moderate					Necrosis	Nuclear atypia marked						
Nuclear variation	Nuclear contour	Chromatin	Nucleoli	Nuclear overlap	Mitotic figure		Nuclear variation	Nuclear contour	Chromatin	Nucleoli	Nuclear overlap	Mitotic figure		Nuclear variation	Nuclear contour	Chromatin	Nucleoli	Nuclear overlap	Mitotic figure	
Minimal	Smooth or Min Irrg	Bland	Absent or tiny	Minimal <20 g/Sl. Each Gr>3 cells	Minimal <2/10 Hpf	Absent	Mod	Slight Irr.	Clumped	Variable macro nucleoli	>Mod (20-50) groups/Sld	Numerous (>3/10 Hpf)	Present	Marked	Irregular	Coarse	Macro nucleoli	>Mod	Numerous	Present	

Cytological procedure

FNAC study of soft tissue tumor was performed preoperatively. The technique of aspiration employed was to obtain a sample from a lump with a 21-23 gauge needle [12,31] attached to a disposable plastic syringe of 10 ml capacity mounted on a aspirator. Larger diameter needles were used for obtaining samples from dense fibrous lesions. The patient briefed about the procedure, the skin over the soft tissue lump was cleaned properly by rectified spirit. Smears were prepared, fixed and stained for H and E, Giemsa/Leishman stain (Figs. 1-4).

Histological procedure

The resected mass or the biopsy specimen was obtained from the operation theater in containers using 10% formal saline as the fixative

and processed as per culling, 1963, via steps of section cutting and staining - (H and E stain) and Mount with DPX**.** Then, microscopic study and interpretation were done (Figs. 1-4).

A comparative study between all the available FNAB and histologic specimens were done in reference to grading. Finally, the percentage accuracy of the grading of FNAB specimens of spindle cell sarcomas was assessed.

RESULT

This study was conducted in the Department of Pathology, IMS and SUM Hospital, Bhubaneswar during the period of December 2013-December 2015. A total of 50 cases of spindle cell sarcomas, diagnosed in FNAB were studied. Grading was done basing on a histological grading system, modified by Weir *et al*., 1999. Subsequently, only in 42 cases, surgical specimens were available. They were studied in reference to age, sex, site of distribution, subtypes, and histological grading. Hence, a cytological and histological correlative study was based on 42 cases. Table 3 shows the frequency of spindle cell sarcomas diagnosed histologically. After analyzing all the data, of age and gender distribution it was revealed that 5th and 6th decades are the most common age of occurrence of spindle cell sarcomas in both males and females. The percentage in males is 74% in females 26%. Males outnumber females in most age groups. Also seen that all the subtype are commoner in 5th and 6th decade, except synovial sarcoma which is commoner in younger age groups. In all cases males outnumber females, except in leiomyosarcoma (LMS), where females are more affected.

Coming to the site distribution extremities are the most common site of distribution (47.62%) followed by central trunk (26.20%). Least common parenchyma (4.76%). The most ommon site of malignant fibrous histiocytoma (MFH) is lower extremities, F.S is lower extremity and trunk, LMS. is retroperitoneum, F.S and A.S can be found in parenchymatous organs.

Parameters of FNAB grading according to the grade of sarcoma is given in Table 4. This table showed that Grade - 1 constitutes 15 numbers of cases, Grade - 2 constitutes 20 numbers of cases, and Grade - 3 constitutes 7 numbers of cases. In Table 5, parameters of grading surgical specimens according to the grade of sarcoma are shown, where Grade - 1 constitutes 17 cases, Grade - 2 constitutes 15 cases, and Grade - 3 constitutes 10 cases. In Grade - 3 lesions usually bony erosions were noted (Fig. 5).

Correlations between cytologic and histologic gradings are shown in Table 6. Out of 42 cases of FNAB, cytologic and histologic concordance were found in 37 numbers of cases, accounting for 88% of correlation. The overall results were correlated for both FNAC and Biopsy concordance and statistically analyzed. From there the sensitivity and specificity were calculated as 95.23% and 80.76%, respectively (Table 6).

DISCUSSION

FNAB have become an established method in the diagnostic armamentarium of many clinical practices. It is preferred by many authors due to its rapidity, simplicity, and safety of the procedure. It is cost effective and does not have any complication usually. These similar observations have been noted by various authors like Akerman *et al*., 1985 [8,19].

In this study, the adequate material was obtained using a 22 gauge needle, thus a needle core biopsy was not required. The cytosmears prepared from the aspirates were subjected to routine Giemsa staining, hematoxylin and eosin and at times Papanicolaou staining. Giemsa is

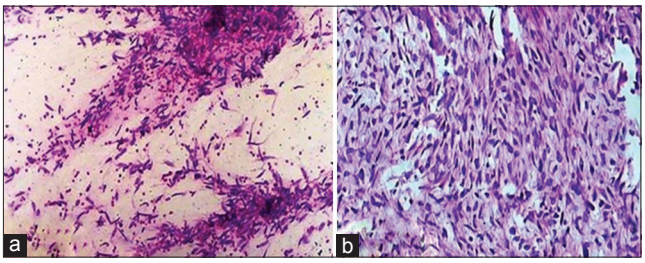

Fig. 1: (a) Fine needle aspiration cytology Grade - 1 fibrosarcoma (H and E ×100) (b) BIOPSY Grade - 1 fibrosarcoma (H and E ×100)

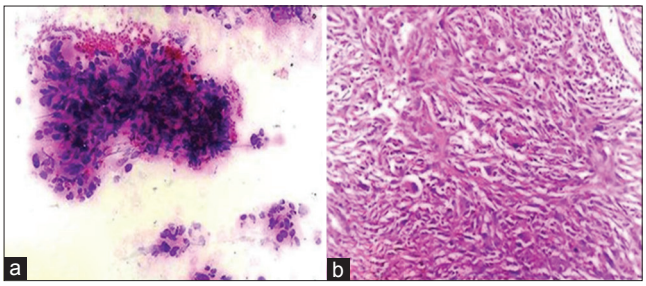

Fig. 2: (a) Fine needle aspiration cytology Grade - 2 malignant fibrous histiocytoma (H and E ×100), (b) BIOPSY Grade - 2 malignant fibrous histiocytoma (H and E ×100)

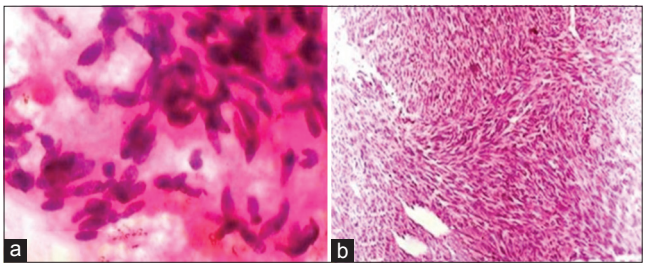

Fig. 3: (a) Fine needle aspiration cytology Grade - 2 fibrosarcoma (H and E ×100), (b) BIOPSY Grade - 1 fibrosarcoma (H and E ×100)

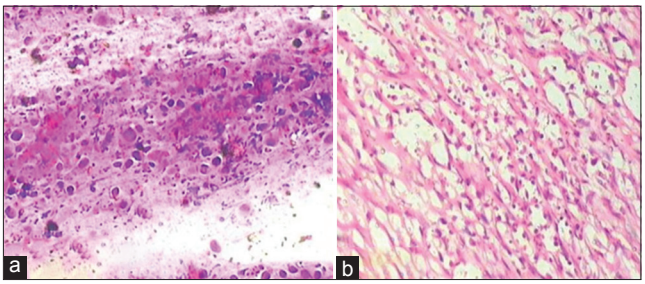

Fig. 4: (a) Fine needle aspiration cytology Grade - 3 angiosarcoma (H and E ×100), (b) BIOPSY Grade - 3 angiosarcoma (H and E ×100)

Table 2: Histopathologic grading

Score											
Tumor differentiation			**Mitosis count**			**Tumor necrosis**			**Histologic grade**		
1	2	3	1	2	3	0	1	2	1	2	3
Well differentiated	Histologic typing	Un differ	0-9/10 Hpf	10-19/10 Hpf	>20/10 Hpf	No	<50%	>50%	2,3	4,5	6,7,8

Table 3: Frequency of spindle cell sarcomas subsequently diagnosed histologically (n=42)

Histological diagnosis	n (%)
MFH	18 (42.86)
FS	13 (30.96)
LMS	5 (11.90)
DFSP	3 (7.14)
AS	1 (2.38)
MPNST	1 (2.38)

MFH: Malignant fibrous histiocytoma, FS: Fibro sarcoma, LMS: Leiomyosarcoma, DFSP: Dermatofibrosarcoma protuberance, AS: Angiosarcoma, MPNST: Malignant peripheral nerve sheath tumor

Table 4: Parameters of FNAC grading according to grade of sarcoma

Parameters	Grade		
	1 (n=15)	2 (n=20)	3 (n=7)
Nuclear atypia			
Mild	13	1	0
Moderate	2	19	1
Marked	0	0	6
Nuclear overlap			
Minimal	14	1	0
Moderate	1	18	1
Marked	0	1	6
Mitotic figure			
None/unable to count	14	2	1
Rare (1-2/10 HPF)	1	14	2
Many (≥3/10 HPF)	0	4	4
Necrosis			
Present	0	14	6
Absent	15	6	1

FNAC: Fine needle aspiration cytology

a romanosky type of stain, and the staining procedure is quick and simple. In this method, the smear is air-dried. Thus, the dried cells appear larger than wet fixed cells, which are shrunken. It gives a better detail of cytoplasmic features. Many worker such as Akhtar *et al*., 1985 [20] and Rajwanshi *et al*., 2009 **[**21] used Giemsa for assessment of soft tissue tumor.

Hematoxylin and eosin stained preparation were found to be of greatest aid in diagnosing mesenchymal tumor aspirate according to Layfield *et al*., 1986 [11]. It recapitulated the histologic appearance of the lesions more closely than Giemsa or PAP. Akhtar *et al*., 1985, [20] used hematoxylin and eosin stain in their cytological studies of soft tissue tumors. Like others, we have also used hematoxylin and eosin stain for our study.

Papanicolaou is a popular staining method in cytology. Nuclear chromatin and nucleolus are better appreciated. An immediate alcohol fixation allows cells to retain their natural configuration. Workers like, González-Cámpora, 1999 have successfully used this method for staining cytosmears from different soft tissue tumors [19]. We have utilized this staining method wherever necessary.

To correctly interpret the aspirates, the pathologist must be familiar with the normal pictures of various components, as well as with the clinical and cytological appearance of benign and malignant mesenchymal tumors along with pseudosarcomas [22].

In this study of 42 cases, of spindle cell sarcoma, Table 3 showed that the most frequent sarcoma was MFH, followed by fibrosarcoma and LMS. Our observation coincided with that of Markhede *et al*. 1982 [23**]** and Weiss, and Goldblum, 2001 [24] who analyzed 200 cases of MFH [25].

Table 5: Parameters of grading surgical specimens according to grade of sarcoma - FNCLCC system

Parameter	Grade		
	1 (score 2, 3) (n=17)	2 (score 4,5) (n=15)	3 (score 6, 7, 8) (n=10)
Tumor differentiation			
Well differentiated	7	0	0
Histo typing possible	10	14	9
Undifferentiated	0	1	1
Mitotic count			
0-9/10 HPF	15	6	0
10-19/10 HPF	2	8	6
≥20/10 HPF	0	1	4
Tumor necrosis			
Absent	16	0	0
<50%	1	9	3
>50%	0	6	7

FNCLCC: Federation National Des Centres de lutte contre le cancer

Table 6: Correlations between cytologic and histologic grading

Specimen	Grade		
	1	2	3
FNAB	15	20	7
Histology	17	15	10

FNAB: Fine needle aspiration biopsy

It was noted showed that spindle well sarcomas were more common in 5th and 6th decade. Males outnumbered females in most age groups. The percentage in males - 74% and in females - 26%. Weiss and Goldblum, 2001, also had similar observations [24].

In each subtype, it was found that MFH had a male predominance and peak incidence was between 5th and 6th decade considering age and gender distribution. Our observation coincided to that of Weiss and Goldblum, 2001 [24,25]. F.S was found to be common in a 4th decade with a range from 3rd to 5th decade, with a male predominance. This coincided with the study by Scott *et al*., 1989, who studied 132 cases, (male predominance and age range of 3rd and 5th decade) LMS was found in 5th and 6th decades, with a female predominance [26]. Thus, observation coincided with Weiss and Goldblum, 2001 [22,24]. We got very few cases of angiosarcoma (AS), synovial sarcoma, and malignant peripheral nerve sheath tumor.

Site of occurrence revealed that sarcomas had a greater predilection for extremities, specifically lower extremity, followed by the central trunk. This observation was similar to that made by Weiss and Goldblum, 2001 [24] who found lower extremity to be the most common site, however they noted that upper extremity was the 2nd most common site. This discrepancy could be due to fewer no of cases we studied.

Found that most common site of MFH was lower extremities; F.S was lower extremities and central trunk. LMS and dermatofibrosarcoma protuberance were commonly found in retro peritoneum and central trunk, respectively. Similar observations were noted by Weiss and Goldblum, 2001 [24,25]. Fibrosarcoma and AS can be found in parenchymal organs; as noted by Weir *et al*., 1999 [18]; Weiss and Goldblum, 2001 [24,25].

Table 4 demonstrated that, out of 42 cases of FNAB, Grade - 1, mostly with mild nuclear atypia, minimal nuclear overlapping, no mitotic figure, absence of necrosis, constituted 15 numbers of cases. Grade - 2, mostly with moderate nuclear atypia, moderate nuclear overlapping, rare mitotic figure, presence of necrosis, constitutes 20 numbers of cases. Grade - 3 mostly with marked nuclear atypia, marked nuclear

Fig. 5: (a) Synovial sarcoma, (b) malignant fibrous histiocytoma, (c) fibrosarcoma, and (d) rhabdomyosarcoma

overlapping, many mitotic figure, presence of neurosis, constituted 7 numbers of cases.

Grade - 1 was distinguished from Grades - 2 and 3 by both nuclear atypia, and nuclear overlapping. In Grade - 2 category out of 20 FNAB specimens we faced difficulty in grading 8 specimens, due to lack of mitotic figure in 2 cases, lack of necrosis in 6 cases. In Grade - 3 category, out of 7 FNAB specimens, we faced difficulty in 2 specimens, due to lack of mitotic figure in 1 cases and necrosis in 1 case.

In these (8+2) FNAB specimens, nuclear atypia predicted the grade. Moderate nuclear atypia-Grade - 2, marked nuclear atypia Grade - 3.

The corresponding surgical specimen (Table 5) showed that in Grade - 1 category, the tumor was either well differentiated/in which histologic typing was possible. Mitotic figures (M:F) was between 0 and 9/10 HPF, tumor necrosis was absent, this constituted 17 number of cases. In Grade - 2 category, the histologic typing of the tumor was possible. M.F was between 0 and 19/10 HPF, necrosis was present, constituted 15 number of cases. In Grade-III category, the tumor was either poorly differentiated/in which histologic typing was possible, M.F. was ≥20/10 HPF and necrosis was present, constituted 10 number of cases.

Table 6 is depicting the correlation between cytologic and histologic grading and it was found that out of 42 cases of FNAB, there was cytologic and histologic concordance of grading in 37 cases, accounting for 88%. All cases of Grade-I and Grade-III FNAB were correlated with the corresponding histologic grading. In Grade-II, out of 20 cases of FNAB only 15 cases correlated with corresponding histologic grade, and 2 major non-correlation and 3 minor non-correlations were found. Major non-correlations refers to misclassification of a low grade (Grade-1) specimen versus intermediate (Grade - 2) or high Grade (Grade - 3) specimen. (Cytologically given Grade-2/3 but histologically given Grade-1]. This was due to FNAB interpretation error. Those 2 cases were diagnosed as Grade-II cytologically, because in those cases along with spindle cells, other cells-rounded, epithelioid cells with high N.C ratio, angulated, irregular nuclei showing moderate degree of nuclear pleomorphism were found (poorly differentiated fibrosarcoma). But in histology grading, nuclear atypia was not taken into account, only the differentiation, M.F and necrosis were considered. Basing on these feature they were given Grade 1. This type of interpretation error was possible and had been observed by Weir *et al,* 1999 [6,18].

Minor non-correlation between the FNAB and the histologic grade was Grade - 2 versus Grade - 3. This was out of sampling error due to morphologic heterogeneity (cytologically given Grade - 2 but histologically given Grade - 3). Aspiration has been done from improper site showing low grade, but in histology grading is done according to the most malignant area, so given a high grade. Similar type of observation has been noted by Weir *et al*., 1999 [1,18].

Most of the subtypes given in cytology correlated with corresponding histologic subtypes excepting few, but this did not hamper our study as all subtypes were spindle cell sarcomas and grading was same for all spindle cell sarcomas. Percentage accuracy by Weir *et al*. (4 tier grading) in 1999 was 91%, followed by Mathur *et al*. (3 tier grading) in 2003 was 74% [1] and in this study with four tier grading, it was 88%, which is almost comparable to Weir *et al*. study [6,18].

CONCLUSION

Histologic criteria for grading sarcomas in adults could be applied to FNAC specimens of spindle cell sarcomas with 88% accuracy. While comparing the diagnosis given by FNAC and Biopsy, it was revealed that the true positive (TP) 40 cases, true negative 42 cases, false positive 10 cases, and false negative (FN) 2 cases.

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