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Research Article

Evaluation of performance of various histological grading systems of soft tissue sarcomas and the prognosis (metastatic risk and survival rate)

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ABSTRACT

Background: Histologic grade represents the most important prognostic factor for all soft tissue sarcomas and it is strongly associated with the advent of metastasis and patients survival. The main objective of this study is to test individual grading system with metastatic risk and patients survival rate (prognosis).
Methods: Soft tissue sarcomas (250) were graded by FNCLCC, NCI & Mhyre Jensens grading system. Special stains & immunohistochemistry were employed whenever necessary.
Results: FNCLCC system shows Grade 1 = 50 (20%), Grade 2 = 75 (30%) & Grade 3 = 125 (50%). NCI (Costa et al.) showed Grade 1 = 70 (28%) Grade 2 = 85 (34%) & Grade 3 = 95 (38%). Myhre Jensen showed Grade 1 = 84 (33%), Grade 98 (39%) & Grade 3 = 68 (27%). Undoubtedly, FNCLCC system is the best of all grading systems which is very well supported by statistical analysis in this study.
Conclusions: FNCLCC grading system of soft tissue sarcomas is the best documented and tested system. This present study strongly recommends FNCLCC grading system of soft tissue sarcomas to be internationally accepted because the grading system has well defined criteria & so least possible chances of interobserver variability. The present study & few other previous studies highly recommend the mandatory use of FNCLCC grading system in histopathology report format.

Keywords: Soft tissue tumors, Benign tumors, Malignant tumors, Enzinger & Weiss, FNCLCC, AFIP, MPNST, PNET, MFH, Grading, Staging

INTRODUCTION

Soft tissue tumors are defined as mesenchymal proliferations which occur in the extraskeletal non-epithelial tissues of the body, excluding the viscera, coverings of brain and lymphoreticular system.[1] The annual incidence of soft tissue tumor is 1.4 per 100000 population.[1]

Soft tissue tumors are the fourth most common malignancy in children, after hematopoietic neoplasm, neural tumor and Wilms tumor. Soft tissue sarcomas account for 15% of all childhood cancers. Benign tumors outnumber malignant ones by margin of 100:1.[1]

Virchow proposed connective tissue as the origin of all soft tissue tumors in 1858.[1]

Stout was the first investigator to provide a detailed description of tumors of soft tissues.

Systemic clinical study of soft tissue tumors were primarily initiated by Pack and his colleagues.[2]

The annual incidence of benign soft tissue tumors is 300 per 100000 and that of sarcoma is 1.4 per 100000 population.[1] Incidence of soft tissue tumors varies depending on age and sex of patient. Soft tissue Sarcoma is more common in men.

Classification of soft tissue tumors: The first classification of soft tissue tumors was given by Rokitansky in 1842.[1] Wilkis in 1859, proposed a classification based on cellular and fibrous components of tumors.[1] Brost in 1902 classified soft tissue tumors based on histogenesis and structure. Stout in 1953 proposed classification of tumors based on histogenesis, morphology and behavior.[2] Classification of soft tissue tumors by Armed Forces Institute of Pathology (AFIP) in 1957, 1967 and 1983. WHO in 1969 proposed classification of soft tissue tumors based on review of more than 500 soft tissue tumors, which was later on revised in 1994.[2]

The classification followed in this study is "Histologic classification of soft tissue tumors" given in Enzinger and Weiss's soft tissue tumor, 4th Edition, Chapter-1, page No. 7. This classification is similar but not identical to the 1994 WHO classification.[1]

Histologic grade represents the most important prognostic factor for all soft tissue sarcomas, strongly associated with the advent of metastasis and patients survival.[3]

Multiple studies have confirmed its effectiveness for predicting distant metastases and overall survival, and histologic grade has even shown some value in predicting local recurrence.[4] Grading forms a central and necessary element of the major clinical staging systems for sarcoma and is regarded by most contemporary oncologists as an absolute necessity for clinical decision making.[5]

Grading: Determines the degree of malignancy and is based on evaluation of several histologic parameters. Broders et al. in 1939 graded soft tissue sarcoma by a combined assessment of several histologic features.

The histological parameters taken into consideration are degree of cellularity, cellular pleomorphism, mitotic activity (frequency and abnormality), degree of necrosis, expansive or infiltrative and invasive growth. Other factors are matrix formation, hemorrhage, calcification and inflammatory infiltrate.[5]

In 1982, Markhede et al.[6,7] suggested a grading system that used four grades based on cellularity, cellular pleomorphism, mitotic activity. Grade-1 and 2 tumors had similar clinical course. 5 and 10 years survival rates with grade 3 tumors were 68% and 55% respectively and with grade 4-tumors they were 47% and 26% respectively.

In 1983, Myhre Jensen et al.[7,8] graded 261 soft tissue tumors. They employed 3-grades with 5 years survival rates of 97% for grade-1 tumors, 67% for grade-2 and 38% for grade-3 tumors. The histologic parameters used were cellularity, pleomorphism, mitotic rates.

Costa et al.[9] described a grading system based on review of 163 sarcomas from National Cancer Institute (NCI). The histologic parameters used were cellularity, cellular pleomorphism, mitotic rate and necrosis. They employed a 3-grade system, 5 years survival rates were 100%, 73% and 46% respectively.

Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) System: In 1984 Trojani et al.,[10,11] presented FNCLCC system of grading soft tissue sarcoma based on analysis of 155 adult patients. So far FNCLCC system is the best documented and tested system.[1]

Table 1: Various grading systems.[1]

Parameter	Markhede	Myhre Jensen	Costa	Coindre
Cellularity	+	+	+	--
Differentiation	--	--	--	+
Pleomorphism	+	+	+	--
Mitotic rate	+	+	+	+
Necrosis	--	--	+	+

Table 2: Definitions of grading parameters for FNCLCC system.[10,11]

Parameter	Criterion
Tumor differentiation	
Score-1	Sarcoma closely resembling normal adult mesenchymal tissue (e.g., well differentiated liposarcoma)
Score-2	Sarcoma for which the histologic typing is certain (e.g., alveolar soft part sarcoma)
Score-3	Embryonal & undifferentiated sarcomas
Mitosis count	
Score-1	0-9/10 HPF
Score-2	10-19/10 HPF
Score-3	≥20/10 HPF
Tumor necrosis (microscopic)	
Score-0	No necrosis
Score-1	≤50% tumor necrosis
Score-2	>50% tumor necrosis
Histologic grade	
Grade-1	Total score 2, 3
Grade-2	Total score 4, 5
Grade-3	Total score 6, 7, 8

Table 3: The National Cancer Institute grading system for soft tissue sarcomas.

Grade 1	Grade 2	Grade 3
Liposarcoma (well diff. & myxoid)	Pleomorphic liposarcoma	ASPS
DFSP	MFH	PNET
Fibrosarcoma	Synovial sarcoma	Alveolar rhabdomyosarcoma
Hemangio-endothelioma	Malignant hemangiopericytoma	

Table 4: Tumor differentiation score according to histologic type in the updated version of the FNCLCC system.[1,10,11]

Histologic type	Tumor differentiation score
Well differentiated liposarcoma	1
Myxoid liposarcoma	2
Round cell liposarcoma	3
Pleomorphic liposarcoma	3
De-differentiated liposarcoma	3
Well differentiated fibrosarcoma	1
Conventional fibrosarcoma	2
Poorly differentiated fibrosarcoma	3
Well differentiated MPNST	1
Conventional MPNST	2
Poorly differentiated MPNST	3
Epitheloid MPNST	3
Malignant triton tumor	3
Well differentiated malignant hemangio pericytoma	2
Conventional malignant hemangiopericytoma	3
Myxoid MFH	2
Typical storiform/ pleomorphic MFH	2
Giant cell and inflammatory MFH	3
Well differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated / pleomorphic / epitheloid leiomyosarcoma	3
Biphasic/ monophasic synovial sarcoma	3
Embryonal / alveolar/ pleomorphic rhabdomyosarcoma	3
Well differentiated chondrosarcoma	1
Myxoid chondrosarcoma	2
Mesenchymal chondrosarcoma	3
Conventional angiosarcoma	2
Poorly differentiated/ epithelial angiosarcoma	3
Extraskeletal osteosarcoma	3
Ewings sarcoma/ PNET	3
Alveolar soft part sarcoma	3
Epitheloid sarcoma	3
Malignant rhabdoid tumor	3
Clear cell sarcoma	3
Undifferentiated sarcoma	3

Objectives

1. To study soft tissue sarcomas based on degree of cellularity, cellular pleomorphism, mitotic activity, degree of necrosis, invasive growth, hemorrhage, inflammatory infiltrate (Broder et al., 1939).

2. To grade soft tissue sarcomas by various grading system.

3. To test individual grading system with metastatic risk (Prognosis).

METHODS

This is a 2 years study from April 2005 to March 2007 & includes 250 cases of soft tissue sarcomas. The present study is done by examining surgically removed soft tissue specimens submitted in the Department of Pathology, M.R. Medical College, Gulbarga from Basaveshwar Teaching & General Hospital, Government General Hospital, Gulbarga and from referred cases of private hospitals.

Inclusion criteria: The malignant soft tissue tumors were histologically graded by FNCLCC system (Trojani et al., 1984), Markhede et al.,[6,7] NCI by Costa et al. & Myhre Jensen et al.[7,8]

Exclusion criteria: Benign soft tissue tumours & tumour like lesions were excluded from the study.

Special stains like PAS, Masson's trichrome, PTAH, iron hematoxylin, reticulin were employed whenever necessary for diagnosis.

RESULTS

Total number of malignant soft tissue tumours = 250.

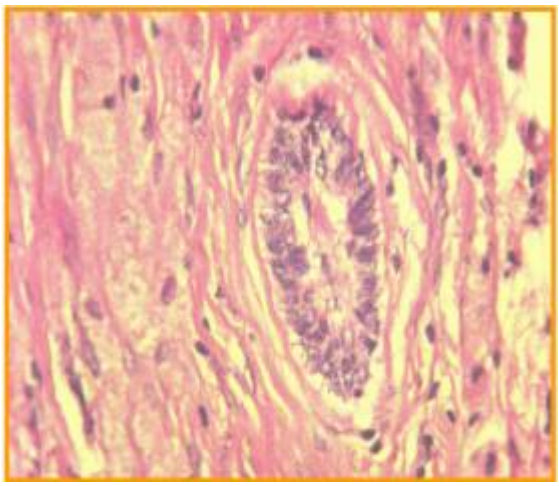

Figure 1: Rare case: granular cell tumor showing odontogenic epithelium (H&E x400).

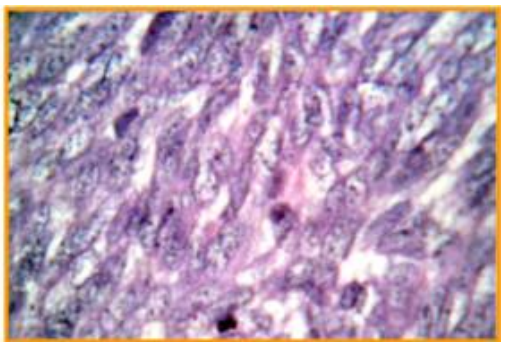

Figure 2: Fibrosarcoma showing pleomorphic spindle shaped cells with nuclear atypia (H&E x400).

Figure 3: Myxoid liposarcoma. The tumour is globular C/s shows capsule and smooth gelatinous grey white areas.

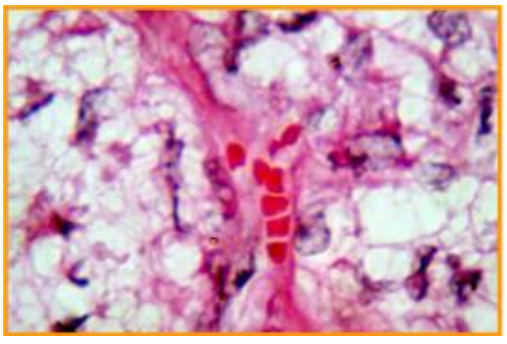

Figure 4: Myxoid liposarcoma showing differentiating lipoblasts, blood vessel & myxoid tissue (H&E x400).

Figure 5: Hemangiopericytoma. The tumor is well circumscribed C/s shows grey white areas.

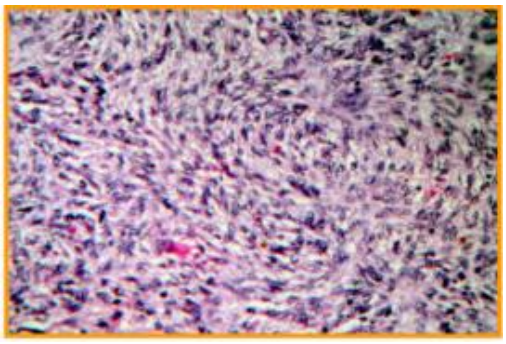

Figure 6: Hemangiopericytoma displaying thin walled branching vessels (H&E x100).

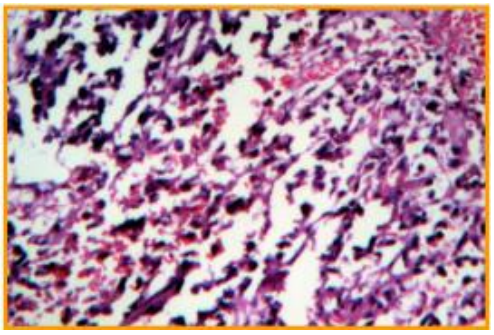

Figure 7: Angiosarcoma showing branching anastamosing vascular channels lined by atypical cells (H&E x100).

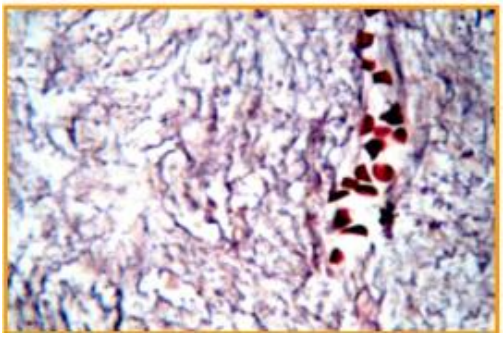

Figure 8: Angiosarcoma. Reticulin stain illustrates dense reticulin meshwork surrounding the tumor cells and blood vessels.

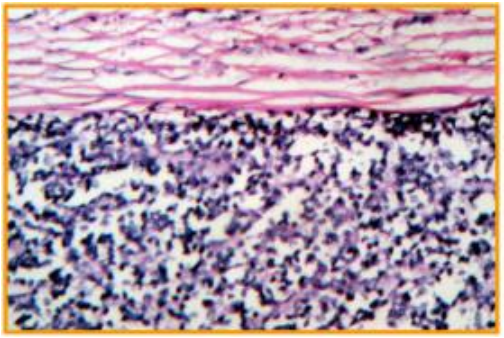

Figure 9: PNET shows well defined capsule along with cells arranged in peritheliomatous pattern (H&E x40).

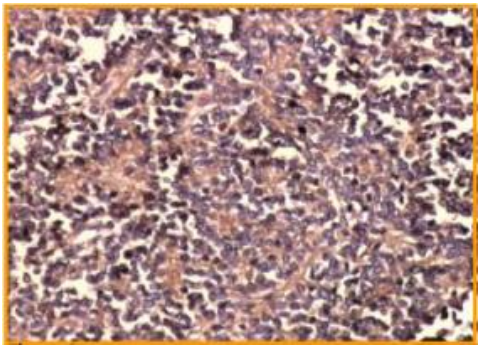

Figure 10: PNET showing immunoreactivity for CD99 (x100).

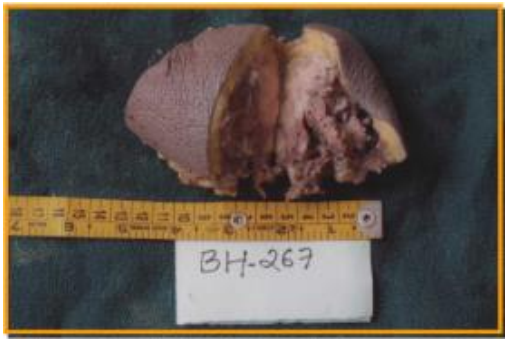

Figure 11: Pleomorphic sarcoma. The tumor is large, lobulated C/S shows grey white to yellowish areas with foci of hemorrhages and necrosis.

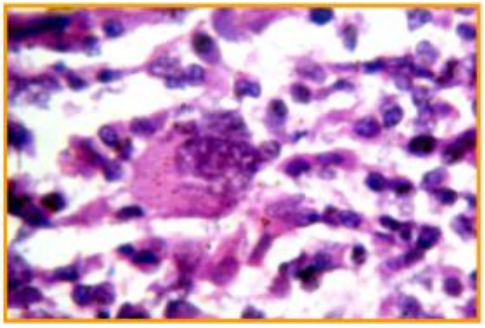

Figure 12: Pleomorphic sarcoma show anaplastic cells with a multinucleate tumor giant cell (H&E x400).

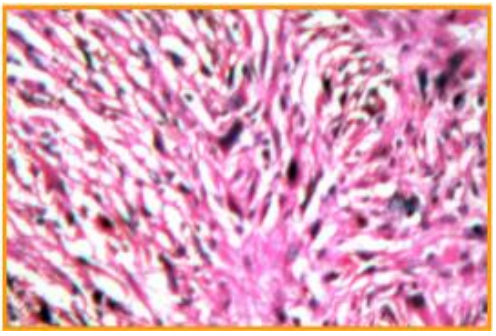

Figure 13: MFH showing short fascicles of spindle shaped cells arranged in storiform pattern (H&E x100).

Table 5: Sex wise distribution of soft tissue sarcomas.

	Male	Female	Total
Soft tissue sarcomas	145 (58%)	105 (42%)	250

There are 145 (58%) males and 105 (42%) females in the present study. The male:female ratio = 1.38:1.

Table 6: Age distribution of malignant soft tissue tumors.

Age group (years)	Soft tissue sarcomas	
	No. of patients	% of total patients
0-10	04	1.6
11-20	09	3.6
21-30	16	6.4
31-40	**61**	**24.4**
41-50	**90**	**36**
51-60	39	15.6
61-70	31	12.4

Majority of soft tissue sarcomas belonged to 4th & 5th decade comprising 60% of total number of cases.

Table 7: Anatomical location of malignant soft tissue tumors.

Anatomical location	Malignant 250	
	Number	Percent
Head and neck	02	0.8
Trunk	24	9.6
Chest axilla and upper back	19	7.6
Extremities - upper	08	3.2
Extremities - lower	**192**	**76.8**
Retroperitoneum	05	02

The most common location of soft tissue sarcomas is lower extremity (77%). It was evenly distributed over trunk, chest, upper axilla.

Table 8: Histological types of soft tissue sarcomas.

Tumor type	Number	Percent %
Fibrous tumors	11	4.40
Fibrohistiocytic tumor	111	44.4
Lipomatous tumor	72	28.8
Smooth muscle tumors	00	00
Blood vessel tumors	14	5.60
Perivascular tumor	08	3.20
Tumors of lymph vessels	00	00
Synovial tumors	06	2.40
Peripheral nerve sheath tumors	06	2.40

Primitive neuroectodermal tumors	11	4.40
Miscellaneous tumors (rare)	11	4.40
Total	250	100

The most common histological types of sarcomas were MFH (44.4%) & liposarcomas (28.8%). Storiform Pleomorphic MFH is the most common type in this study.

The microscopy showed plump spindle cells arranged in short fascicles in a storiform pattern around slit like vessels, plump round histiocytic cells, numerous typical and atypical mitotic figures noted. Myxoid & inflammatory MFH were also noted.

Liposarcomas were 2nd most common sarcomas noted. Well differentiated & myxoid variant were the common type in this study. Other sarcomas noted were fibrosarcomas (4.4%), angiosarcomas (5.6%), perivascular tumours (3.2%) & PNET (4.4%).

PNET shows uniform, small round to oval cells containing cytoplasmic glycogen and arranged in peritheliomatous pattern. Immunohistochemistry shows positivity for CD99.

Table 9: Grading of malignant soft tissue tumors (FNCLCC).

Tumors	Grade-1	Grade-2	Grade-3
Fibrous (11)	Others-03	Fibrosarcoma-04	Fibrosarcoma - 04
Fibrohistiocystic (111)	MFH (myxoid)- 20	MFH- 32	MFH (pleomorphic)-59
Lipomatous- (72)	Myxoid liposarcoma-17	Liposarcoma-24	Pleomorphic liposarcoma-31
Blood vessel-(14)	Epitheloid hemangio endothelioma-3	Angiosarcoma-04	Angiosarcoma-07
Perivascular-(08)	Hemangiopericytoma-2	Hemangio-pericytoma-3	Hemangiopericytoma-03
Peripheral nerve sheath tumor-(6)			MPNST-06
Primitive neuro-ectodermal tumor and related lesions-(11)		Extra-skeletal Ewing's sarcoma-07	Ganglioneuroblastoma-1, Extra-skeletal Ewing sarcoma-03
Miscellaneous-(11) Synovial sarcoma-(6)	05	Alveolar soft part sarcoma-1	Synovial Sa-06, Other -05
Total	50	75	125

Table 10: Comparative analysis of the 3 grading systems.

	Grade-1 (well differentiated)		Grade-2 (moderately differentiated)		Grade-3 (poorly differentiated)	
FNCLCC						
Number	50 (20%)		75 (30%)		125 (50%)	
5 year survival rate	48 (96%)	Mets - 00	71 (94%)	Mets-05%	05 (4%)	Mets- 45%
P value	P<0.05*		P<0.05*		P<0.05*	
NCI (Costa et al.)						
Number	70 (28%)		85 (34%)		95 (38%)	
5 year survival rate	60 (85%)	Mets- 15%	74 (87%)	Mets - 15%	07(7%)	Mets - 40%
P value	P>0.05		P>0.05		P<0.05*	
Myhre Jensen et al.						
Number	84 (33%)		98 (39%)		68 (27%)	
5 year Survival rate	50 (59%)	Mets- 35%	70 (71%)	Mets - 25%	13 (19%)	Mets - 25%
P value	P>0.05		P>0.05		P>0.05	

Grade 1 = 50 (20%), Grade 2 = 75 (30%) & Grade 3 = 125 (50%) (Table 9).

NCI (Costa et al.) showed Grade 1 = 70 (28%) Grade 2 = 85 (34%) & Grade 3 = 95 (38%); Myhre Jensen et al. showed Grade 1 = 84 (33%) Grade 2 = 98 (39%) & Grade 3 = 68 (27%) (Table 10).

DISCUSSION

In the present study, a total of 250 cases of soft tissue sarcomas received in the Department of Pathology, M.R. Medical College, Gulbarga, were studied during the three years period from April 2005 to March 2007.

In the present study there are 145 (58%) male patients and 105 (42%) female patients. Majority of Soft tissue sarcomas belonged to 4th & 5th Decade (60%) & the most common location of soft tissue sarcomas is lower extremity (77%). These results are comparable to studies conducted by Geeta Dev et al.[12,13] (1974), Kransdorf MJ[14,15] (1995), Abbas et al., Potter et al. and Lawrence et al.[1] The youngest patient was 5 months female (Ganglioneuroblastoma).

The most common histological types of sarcomas were MFH (44.4%) & liposarcomas (28.8%) which were in agreement with Enzinger & Weiss.[16,17]

Of the 250 sarcomas studied by FNCLCC grading system, Grade 1 - were 50 cases accounting for 20% of all sarcomas. These patients with well differentiated tumours (Grade 1) showed 96% 5 year survival rate and No metastasis was detected. The P value <0.05 which is statistically significant. Grade 2 - were 75 cases accounting for 30% of all sarcomas. These patients with moderately differentiated tumours (Grade 2) showed 94% 5 year survival rate and 05% cases showed metastatic deposits. The P value <0.05 which is statistically significant. Grade 3 - were 125 cases accounting for 50% of all sarcomas. These patients with poorly differentiated tumours (Grade 3) showed only 04% 5 year survival rate and 045% cases showed metastatic deposits. The P value <0.05 is statistically significant.

The results obtained from FNCLCC grading system of sarcoma were very well correlated with the studies conducted by Rosai & Ackerman & Anderson et al.[18,19]

By the NCI (Costa et al.) grading system Grade 1 - were 70 cases accounting for 28% of all sarcomas. These patients with well differentiated tumours (Grade 1) showed 85% 5 year survival rate and 15% cases showed metastatic deposits. The P value >0.05 which is statistically insignificant. Grade 2 - were 85 cases accounting for 34% of all sarcomas. These patients with moderately differentiated tumours (Grade 2) showed 87% 5 year survival rate and 15% cases showed metastatic deposits. The P value >0.05 which is statistically insignificant. Grade 3 - were 95 cases accounting for 38% of all sarcomas. These patients with poorly differentiated tumours (Grade 3) showed only 07 % 5 year survival rate and 40% cases showed metastatic deposits. The P value >0.05 which is statistically insignificant.

By Myhre Jensen et al. grading system Grade 1 - were 84 cases accounting for 33% of all sarcomas. This patients with well differentiated tumours (Grade 1) showed 59% 5 year survival rate and 35% cases showed metastatic deposits. The P value >0.05 which is statistically insignificant. Grade 2 - were 98 cases accounting for 39% of all sarcomas. These patients with moderately differentiated tumours (Grade 2) showed 75% 5 year survival rate and 25% cases showed metastatic deposits. The P value >0.05 which is statistically insignificant. Grade 3 - were 68 cases accounting for 27% of all sarcomas. These patients with poorly differentiated tumours (Grade 3) showed only 19 % 5 year survival rate and 25% cases showed metastatic deposits. The P value >0.05 which is statistically insignificant.

Guillou et al.[20] found that in univariate analysis, the FNCLCC system was slightly better at predicting tumor mortality and distant metastases. In multivariate analysis, it was more efficient than the NCI system in predicting metastasis in patients with grade 3 tumors and showed better correlation with overall survival. The FNCLCC system also was superior at selecting patients with grade 1 tumors relative to the NCI system. Of note, the necessary microscopic assessment of necrosis in the study by Guillou et al. might have underestimated the extent of necrosis compared with gross assessment and might, therefore, have hampered the performance of the NCI system, in which gross assessment is recommended. Notwithstanding, grading discrepancies were observed in 34.6% of the cases, and both systems had a similar percentage of grade 1 lesions that metastasized. Perhaps most important, the FNCLCC system allocated significantly fewer patients to the intermediate.

In absence of specialized techniques, the updated FNCLCC system for histologic grading seems to be the most effective and has mounting appeal internationally.[20]

CONCLUSION

Histologic grade represents the most important prognostic factor for all soft tissue sarcomas. It is the most important factor strongly associated with the advent of metastasis and patients survival. Among the Various Grading systems that were tested for prognostic outcome, FNCLCC grading system is the best documented and tested system.

The present study strongly recommends FNCLCC grading system of soft tissue sarcomas to be internationally accepted because the grading system has well defined criteria & so least possible chances of interobserver variability.

The present study & few other previous studies highly recommend the mandatory use of FNCLCC grading systems in histopathology report format.

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Ethical approval: The study was approved by the institutional ethics committee

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