PROGNOSTICATION OF SOFT TISSUE SARCOMAS

Saji Francis[1], Ramakrishnan Jayalekshmi[2], Krishna Govindan Balachandran Nair[3], Jayaprakash Madhavan[4]

[1]Associate Professor of Pathology, Government Medical College, Kozhikode, Kerala.
[2]Professor, Department of Pathology, PMS Dental College, Vattappara, Trivandrum, Kerala.
[3]Professor, Department of Pathology, Government Medical College, Trivandrum.
[4]Senior Consultant and HOD, Department of Oncology, KIMS Cancer Center, Trivandrum, Kerala.

ABSTRACT

BACKGROUND

Soft tissue sarcomas (STS) account for less than 1% of all malignant tumours but present a significant diagnostic and therapeutic challenge since there are more than 50 histological subtypes.[1] The clinical course of a sarcoma cannot be predicted by histologic typing alone but must be accompanied by grading and staging. Sarcomas with high metastatic potential can be picked out by histologic grading which is a cheap and simple method. One widely used and most reproducible grading system is French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) based on a score obtained by evaluating tumour differentiation, mitotic rate and amount of tumour necrosis.[2] Histologic grading is the mainstay in predicting prognosis of STS especially in centres where facilities for more sophisticated methods are not available. Hence this study was undertaken to assess the effectiveness of the FNCLCC grading system in the prognostication of STS in our patient population.

Aims and Objectives

1. To grade soft tissue sarcomas according to the FNCLCC system.
2. To study the association between grade and survival of soft tissue sarcomas in the patient population.

MATERIALS AND METHODS

The cases selected were adult patients with soft tissue sarcomas whose excision specimens were received in the Department of Pathology, Medical College, Thiruvananthapuram during a 3-year period for diagnosis. Histopathology slides of these tumours were retrieved and graded according to the FNCLCC system. The patients were followed up for 5 years. Overall and disease-free survival rates were estimated. The data was analysed with the help of computer software SPSS.

RESULTS

Of the 110 cases of soft tissue sarcoma reviewed, 27.3% were low grade, 49% intermediate grade and 23.7% high grade. Follow up was available only for 70 patients with STS. The prognostic factors found significant in univariate analysis were histologic grade, necrosis and mitosis. But by multivariate analysis only histologic grade and necrosis were found to be independent prognostic factors.

CONCLUSION

Histologic grading of soft tissue sarcomas definitely influences the survival of patients and it should be routinely mentioned while reporting soft tissue sarcomas. FNCLCC grading system may be modified giving more importance to necrosis.

KEYWORDS

Soft tissue Sarcomas; Prognosis; Necrosis; Mitosis.

HOW TO CITE THIS ARTICLE: Francis S, Jayalekshmi R, Nair KGB, et al. Prognostication of soft tissue sarcomas. J. Evid. Based Med. Healthc. 2018; 5(7), 593-599. DOI: 10.18410/jebmh/2018/122

BACKGROUND

Soft tissue sarcomas (STS) are rare malignant tumours with a wide spectrum in terms of histologic type and prognosis. Correct treatment decisions and improved patient outcome depend greatly on better histologic diagnosis and grading. It was Russell et al. in 1977 who first properly introduced concept of grading in STS which represented the TNM system with grade of tumor (G) added.[3] During the last few decades pathologists have been testing the accuracy and reproducibility of various grading systems. The two important grading systems reported in 1980s were the National Cancer Institute (NCI) & the FNCLCC systems. The NCI system was based on assessment of six histologic parameters and Costa et al found out by multivariate analysis that tumor necrosis had the greatest impact on prognosis.[4] The French Sarcoma group, shortly afterwards established by multivariate analysis, three independent prognostic factors- tumor differentiation, mitotic index and extent of necrosis.[3] Here we tested the value of FNCLCC system in predicting prognosis in our setting.

Aims and Objectives

1. To grade soft tissue sarcomas according to the FNCLCC System.
2. To study the association between grade and survival of soft tissue sarcomas in the patient population.

Financial or Other, Competing Interest: None.
Submission 12-01-2018, Peer Review 23-01-2018,
Acceptance 05-02-2018, Published 08-02-2018.
Corresponding Author:
Dr. Saji Francis,
Kozhimannil House, Kottamparamba P. O.,
Calicut- 8. Kerala, India.
E-mail: drsajijose@gmail.com
DOI: 10.18410/jebmh/2018/122

Setting and Design-
The setting of the study involves two hospitals; Medical College, Thiruvananthapuram and the Regional Cancer Centre, Thiruvananthapuram. Both are tertiary care referral hospitals. This is a retrospective cohort study.

MATERIALS AND METHODS

The study subjects were adult patients (>15 years) with soft tissue sarcomas who underwent excision or amputation. These specimens were received in the Department of Pathology, Medical College, Thiruvananthapuram during a three-year period for diagnosis. Histopathology request forms and paraffin tissue blocks were retrospectively retrieved, from the archives of pathology department. New sections were taken and stained by haematoxylin and eosin. Slides were reviewed and graded by FNCLCC system (Table 1) without knowledge of patient evolution. The three criteria in the FNCLCC grading system were analysed and for each a numerical score was assigned. The scores for each parameter were then added to determine the histologic grade. After locating the active area, 10 consecutive high power fields were counted. Four separate sets of high power fields were counted and the average taken. In the microscope used, 10 high power fields (HPF 450x) corresponds to 1.1334 mm^2. Field area was measured using the micrometer scale.

Postoperative treatment and follow up details were obtained from the Regional Cancer Centre case sheets. The patients were followed up with respect to disease free and overall survival. The follow up period was assessed in months from the time of initial surgery to the last follow up. Reminders were sent to patients who did not turn up for their regular follow-up which was done every 3 months. The patients who were alive but free from any recurrences or other disabilities were included under Group I. Those who were alive but with evidence of local recurrence, lymph node involvement or distant metastases were included under Group II. Patients who died but not due to the disease were categorized as Group III and those who died as a result of the disease as Group 1V.

Parameter	Score
Degree of Tumor Differentiation	
Close resemblance to normal adult tissue	1
Tumor type clearly recognizable	2
Tumor type uncertain	3
Necrosis	
No tumor necrosis on any slide	0
Less than 50% tumor necrosis	1
More than 50% tumor necrosis	2
Mitotic Count	
0-9/10 HPF	1
10-19/10 HPF	2
20+/10 HPF	3
Histological Grade	**Total Score**
Grade I	2, 3
Grade II	4, 5
Grade III	6,7,8

Table 1. French Federation of Cancer Centres (FNCLCC) Grading System.[5]

Inclusion Criteria
All consecutive adult patients with soft tissue sarcoma diagnosed after tumour excision at the department of pathology, Govt. Medical College Thiruvananthapuram during a 3-year period was taken for the study.

Exclusion Criteria
1. Patients with metastasis at the time of initial admission.
2. Treated cases.

Ethics- Ethical clearance was obtained before commencement of this study.

Statistical Analysis- The statistical analysis was done using SPSS software. Qualitative variables were presented as frequencies and percentages. Overall and disease-free survival rates were estimated using Kaplan/Meier Method. For overall survival and disease-free survival, death and relapse were taken as end points respectively. Survival according to grade, the individual histological parameters constituting grade and the clinical parameters such as site and tumour size were estimated, and the statistical significance computed using log rank test. To identify the prognostic factors, initially a univariate Cox proportional Hazards model was employed. A multivariate analysis was done according to the factors significant in the univariate analysis.

RESULTS

The age of the patients at time of definitive surgery for the primary tumor ranged from 15-84 years. The maximum number of patients was seen in the 40-44 year age group (Figure 1). The male to female ratio was 1.8:1. (Figure 2).

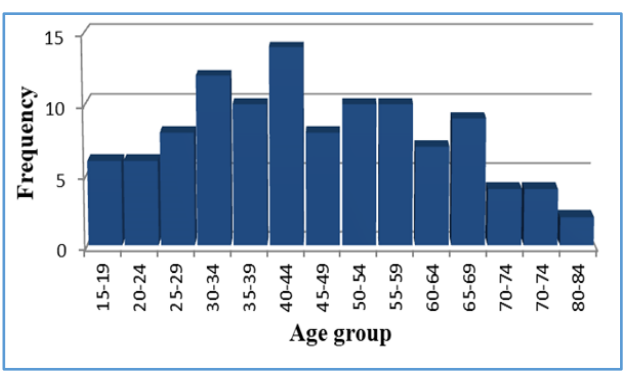

Figure 1. Age Distribution of Soft Tissue Sarcoma Patients (n=110)

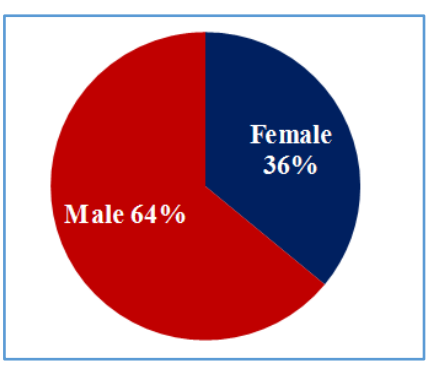

Figure 2. Sex Distribution of Soft Tissue Sarcomas (n=110)

The lower extremity was the commonest site involved (44%) followed by the upper extremity (28%), and retroperitoneum (16%). The greatest diameter of the tumor was considered as the tumour size. The majority of cases (87%) had tumour size greater than 5 cm with the maximum number of cases (40.9%) in the group with tumor size 6-10 cm (Table 2).

Size	Number of Tumours	Percentage
<5	14	12.7
6-10	45	40.9
11-15	38	34.6
16-20	8	7.3
> 20	5	4.5
Total	**110**	**100**

Table 2. Size of 110 Cases of Soft Tissue Sarcomas

The most common type of STS was malignant peripheral nerve sheath tumor (23.6%) followed by liposarcoma (17.3%) and malignant fibrous histiocytoma (14.5%). 27.3% of the sarcomas were low grade, 49% were of intermediate grade and 23.7% were of high grade.

Majority of the tumours were in the cell type certain category. Regarding necrosis, most of the cases had necrosis less than 50% (See Figure 3). Table 3 shows that most cases had mitosis in the range 10-19/10 HPF. Figure 4 shows a case with mitosis greater than 20 /10 HPF.

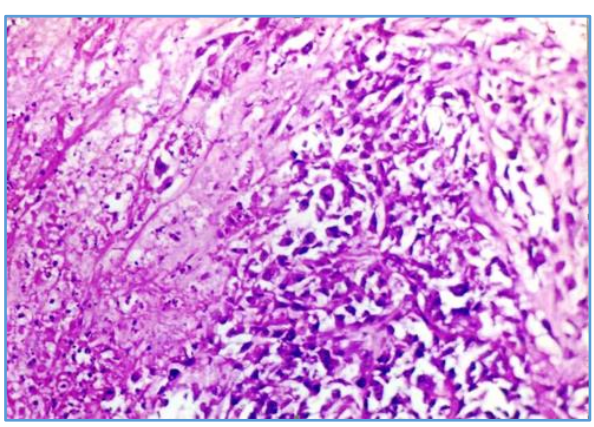

Figure 3. Necrosis Score 1

Variable	Scores	Number of Patients	%
Degree of Differentiation			
Close resemblance to normal adult issue	1	19	17.3
Cell type certain	2	65	59.1
Type Uncertain	3	26	23.6
Necrosis			
No Necrosis	0	31	28.2
< 50% Necrosis	1	77	70.0
> 50% Necrosis	2	2	1.8
Mitosis			
0-9/10 HPF	1	47	42.7
10-19/10 HPF	2	50	45.5
20+/10 HPF	3	13	11.8

Table 3. Distribution of Histological Features Constituting the Grade

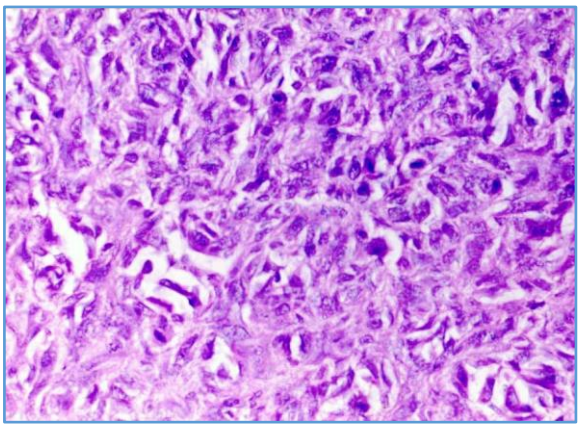

Figure 4. Mitosis Score 3

Survival- Survival rates were estimated for 70 cases as complete follow up data were available only for those cases. The minimum followup time was 5 years. The overall five-year survival rate was 52%. However, the disease free five-year survival rate was only 22% (Figure 5). The survival was least for retroperitoneum. The survival rate decreased when the tumor size increased. The five-year survival rate for patients aged greater than 50 years was 53% compared to 50% for those less than 50 years of age. Female patients had a greater survival rate (61%) compared to male patients (47%).

The survival was comparatively low for the patients who had incomplete excision (41%) as compared to the patients with complete excision (57%). The type of treatment differed based on the post-operative status. The most common mode of treatment was radiotherapy. The survival rate with radiotherapy as the mode of treatment was the greatest (75%).

The survival rate decreased when the degree of differentiation was poor (p=0.468) as shown in Figure 6. Cases with necrosis less than 50% showed a lower survival compared to cases with no necrosis (p<0.001) (Figure 7). The five-year survival rate for patients with necrosis greater than 50% was 0%. However, there were only two cases in this group. Cases with higher mitosis scores showed lesser survival (p<0.001) (Figure 8). Higher grades showed lesser survival (p<0.001) (Figure 9). Considering all these variables, the factors that were statistically significant were grade, necrosis and mitosis scores. All others were statistically insignificant.

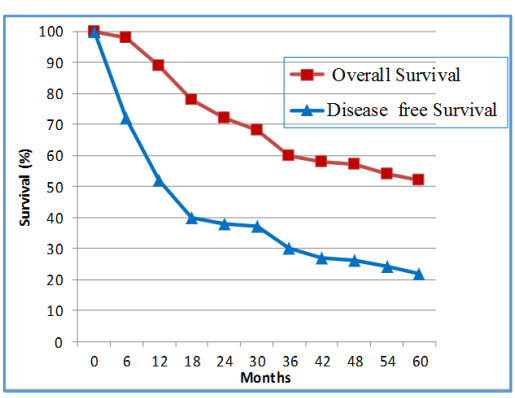

Figure 5. Overall and Disease Free Survival of Soft Tissue Sarcoma (n=70)

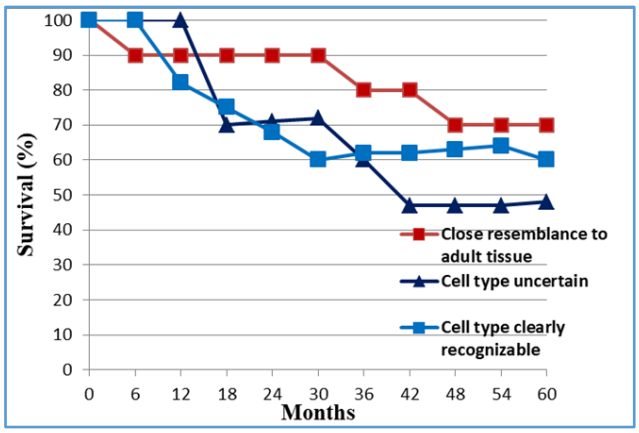

Figure 6. Overall Survival of Soft Tissue Sarcomas by Degree of Differentiation (n=70)

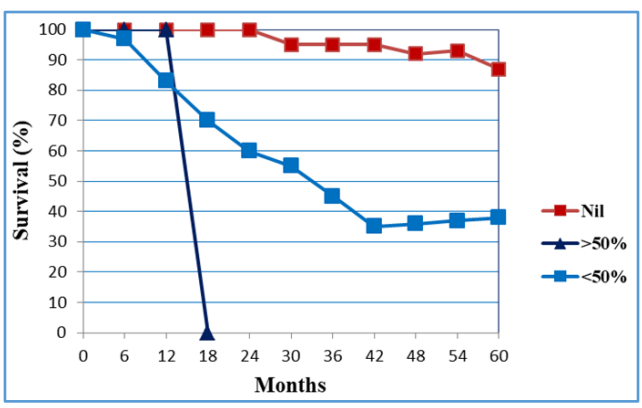

Figure 7. Overall Survival of Soft Tissue Sarcoma by Necrosis Scores

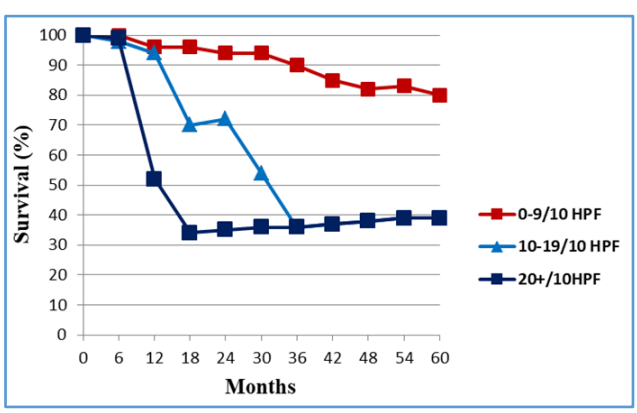

Figure 8. Overall Survival of Soft Tissue Sarcomas by Mitosis Scores (n=70)

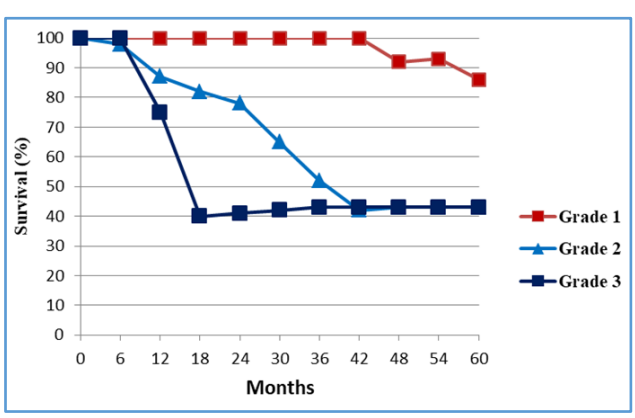

Figure 9. Overall Survival of Soft Tissue Sarcomas by Grade (n=70)

Complete resection could be done only for 41 cases among which local recurrence occurred in 11 cases and metastases in 14 cases (34%). The most common site of metastases was lungs. The occurrence of local recurrence was found to be higher with the lower grades compared to grade III. The development of metastases was proportionately higher with grade of tumor (Table 4).

Grade	Number of Cases	Local Recurrence	Metastases
I	14	5	1
II	19	5	5
III	8	1	8

Table 4. Grade Versus Local Recurrence and Metastases (n=41)

Prognostic Factors

Prognostic factors identified using Cox proportional hazards model (Table 5 & 6). Hazard ratio for grade 3 was 61 as compared to 1 for grade I. In the case of degree of differentiation, the hazard ratio was twofold higher for the groups- cell type certain and uncertain as compared to the group with cells having close resemblance to adult tissue. Cases with necrosis less than 50% had a 7-fold more risk of dying than those with no necrosis.

Variable	Hazard Ratio	95% Confidence Limits
Age ≤ 50 yrs.	1	-
>50 yrs.	0.9	0.4-2.4
Sex Male	1	-
Female	0.6	0.2-1.6
Size ≤ 5	1	-
6-10	1.5	0.4-5.7
11-15	1.2	0.3-4.9
16-20	0.9	0.9-8.6
>20	2.3	0.4-14.1
Edge of Resection-Infiltration		
No	1	-
Yes	1.6	0.7-3.9
Site		
Upper extremity	1	-
Lower extremity	1.1	0.4-3.0
Trunk	1.6	0.3-7.7
Retroperitoneum	1.5	0.3-7.4
Type of Treatment		
Follow up only	1	-
External radiation	0.47	0.1-1.7
Chemotherapy	2.3	0.5-10.2

Table 5. Results of Univariate Cox Regression Analysis- Age, Sex & Clinical Variables

Variable	Hazard Ratio	95% Confidence Limits
Grade		
I	1	-
II	9.1	1.9-42.6
III	61.6	9.4-403.7
Degree of differentiation		
Close resemblance to adult issue	1	-
Cell type certain	2.0	0.6-7.3
Cell type uncertain	2.1	0.5-8.7
Necrosis		
No necrosis	1	-
<50% necrosis	7.4	2.1-26.3
>50% necrosis	31	2.8-340.7
Mitosis		
0-9/10 HPF	1	-
10-19/10 HPF	5.2	1.7-15.5
20+/10 HPF	25.8	6.1-109

Table 6. Results of Univariate Cox Regression Analysis by Histologic Variables

When the mitosis scores were considered, the risk of dying in cases with mitosis greater than 20/10 HPF was 25 times more than those with mitosis less than 10/10 HPF. The statistically significant factors in the univariate analysis were grade, necrosis and mitosis scores.

To identify the independent prognostic factors, statistically significant factors in the univariate analysis were subjected to multivariate analysis. (Table 7)

Variable	Hazard Ratio	95% Confidence Limits
Grade		
I	1	-
II	7.3	1.2-44.7
III	15.5	1.2-200.4
Necrosis		
No necrosis	1	-
< 50 % necrosis	6.2	1.3-29.3
>50% necrosis	19.0	1.1-332.4

Table 7. Results of Multi Variate Cox Regression Analysis

In this analysis it was found that for grade III the hazard ratio was 15.5 compared to 1 for grade I. In case of necrosis, the risk of dying in cases with greater than 50% necrosis was 19 times more than those with no necrosis. This was statistically significant (p value <0.001). So, in the present study, the variables that emerged as independent prognostic factors were histologic grade and necrosis.

DISCUSSION

Majority of the patients in this study were males constituting 64% and the male to female ratio was 1.8:1. The National Cancer Data Base (USA) in 2014 reported a male-to-female ratio of about 1.23:1.[6] The maximum number of patients were seen in the 40-44-year age group. This was similar to the study conducted by Shukla et al in India which showed that the mean age of patients at presentation was 40.6 years.[7] STS were more common in the lower extremity (Figure 10). Table 8 shows the common histologic types of soft tissue sarcomas compared to other studies.

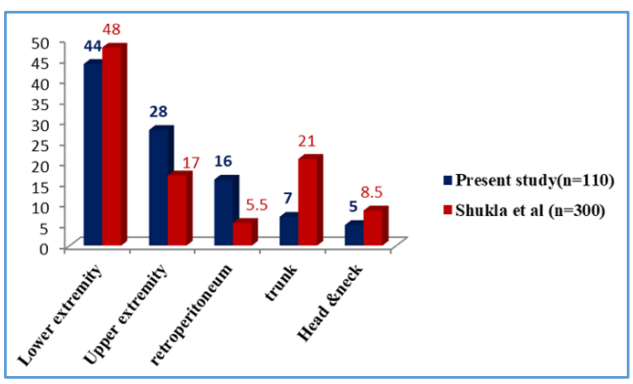

Figure 10. Anatomic Locations of Soft Tissue Sarcomas (%)

Fang et al[8]	Brennan et al[9]	Present Study
Malignant fibrous histiocytoma (MFH) (35.2%)	Liposarcoma (20%)	Malignant peripheral nerve sheath tumor (23.6%)
Synovial sarcoma (17%)	Leiomyosarcoma (14%)	Liposarcoma (17.3%)
Liposarcoma (16.3%)	Undifferentiated pleomorphic sarcoma (14%) (Formerly MFH)	Malignant fibrous histiocytoma (14.5%)

Table 8. Comparison of Common Histologic Types of STS

The distribution of patients in the different grade groups of soft tissue sarcomas in this study appeared similar to the studies by Trojani et al and Mandard et al in that the maximum percentage of cases was in grade II.[5,10] Moreover the percentage of tumours in grade I in the three studies was more or less the same (see table 9).

Studies	Grade I	Grade II	Grade III
Trojani et al	25.2 %	42.6%	32.3%
Mandard et al	26.6%	39.4%	24.8%
Present study	27.3%	49%	23.6%

Table 9. Comparison of Distribution of cases in Various Grades

The overall five year survival rate of soft tissue sarcomas in the present study was found to be similar to other studies, but the disease free survival was different (Table 10).

Studies	Overall Five Year Survival Rate	Disease Free Survival Rate
Ueda et al[11]	56.7%	51.5%
Markhede et al[12]	59.3%	50.1%
Present study	52%	22%

Table 10. Comparison of Five Year Survival Rates

Many workers including Trojani et al in 1984 and van Unnik et al in 1993 have observed by multivariate analysis that mitotic count and necrosis are important factors in predicting prognosis.[13] However in this study, mitosis lost its significance after multivariate analysis (Table 11). The objections against the use of mitotic figures are twofold. 1) Instability due to prefixation factors and 2) Lack of reproducibility of the assessment. Brearley et al has shown that with increasing length of delay in fixation, the microscopic identifiability of mitosis becomes more difficult.[14] Lin et al in 2016 graded 53 STSs on needle core biopsies using a modified FNCLCC grading system that substituted Ki-67 immuno expression for mitotic count and radiological assessment of necrosis. They compared the results with those obtained by conventional FNCLCC grading of the corresponding untreated, surgically resected specimen. The concordance rate of Ki-67 score with the FNCLCC mitotic score was 55%.[15]

	Grade	Degree of Differentiation	Necrosis	Mitosis
Trojani et al	☑	☑	☑	☑
Van Unnik et al	☑	☒	☑	☑
Hashimoto et al	☑	☒	☑	☒
Present study	☑	☒	☑	☒

Table 11. Histologic Parameters Significant by Multivariate Analysis

We found that the amount of necrosis to be the most important prognostic factor among the histological parameters that constituted the grade of STS. Hashimoto et al and Rööser et al also found by similar studies that extensive tumor necrosis to be an independent risk factor for a worse prognosis.[16,17] Coindre et al observed that grading should be established only on untreated tumours because radiotherapy or chemotherapy can increase necrosis.[18] We did not consider treated cases for grading. Finally, the variables that emerged as independent prognostic factors were histologic grade and necrosis. However, the confidence intervals corresponding to grade III and necrosis above 50% were wide.

Many questions remain to be resolved and a larger series of patients with prolonged follow up (over 10 years) will be needed to refine histologic grading. Among the most crucial issues to be addressed is to determine if certain histologic types of tumours have poorer prognosis even in the absence of necrosis. Newer sophisticated methods in diagnosis and prognosis like immunohistochemistry, cytogenetics and molecular techniques can be used to complement grading. In addition, there is need for validation of our findings in an unselected population-based series which is homogeneous with respect to patient characteristics and treatment with uniform determination of the histologic grade.

CONCLUSION

The survival of patients with soft tissue sarcomas are definitely influenced by histologic grading. So grade should be routinely mentioned while reporting soft tissue sarcomas. FNCLCC grading system may be modified giving more importance to necrosis, compared to other factors. However, there is a definite need to do a more controlled and possibly prospective study, incorporating newer proliferation markers to reinforce the merits of histological grading of soft tissue sarcomas, with standardization for the treatment given.

Acknowledgement

The support given by Dr. Eleyamma Mathew, Professor and Head, Tumour registry and epidemiology division, RCC, Thiruvanthapuram and Dr Rajasi, Assistant professor, Dept. of Community Medicine, Govt. Medical College Kozhikode for statistical analysis is acknowledged.

REFERENCES

[1] Fletcher CDM, Bridge JA, Hogendoorn PCW, et al. WHO: classification of tumours of soft tissue and bone. Lyon: IARC Press 2013.
[2] Neuville A, Chibon F, Coindre JM. Grading of soft tissue sarcomas: from histological to molecular assessment. Pathology 2014;46(2):113-120.
[3] Russell WO, Cohen J, Enzinger F, et al. A clinical and pathological staging system for soft tissue sarcomas. Cancer 1977;40(4):1562-1570.
[4] Costa J, Wesley RA, Glatstein E, et al. The grading of soft tissue sarcomas. Results of a clinicohistopathologic correlation in a series of 163 cases. Cancer 1984;53(3):530-541.
[5] Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984;33(1):37-42.
[6] Corey RM, Swett K, Ward WG. Epidemiology and survivorship of soft tissue sarcomas in adults: a national cancer database report. Cancer Med 2014;3(5):1404-1415.
[7] Shukla NK, Deo SV. Soft tissue sarcoma-review of experience at a tertiary care cancer centre. Indian J Surg Oncol 2011;2(4):309-312.

[8] Fang ZW, Chen J, Teng S, et al. Analysis of soft tissue sarcomas in 1118 cases. Chin Med J (Engl) 2009;122(1):51-53.
[9] Brennan MF, Antonescu CR, Moraco N, et al. Lessons learned from the study of 10,000 patients with soft tissue sarcoma. Ann Surg 2014;260(3):416-421.
[10] Mandard AM, Petiot JF, Marnay J, et al. Prognostic factors in soft tissue sarcomas. A multivariate analysis of 109 cases. Cancer 1989;63(7):1437-1451.
[11] Ueda T, Aozasa K, Tsujimoto M, et al. Multivariate analysis for clinical prognostic factors in 163 patients with soft tissue sarcoma. Cancer 1988;62(7):1444-1450.
[12] Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of malignant soft-tissue tumors. Cancer 1982;49(8):1721-1733.
[13] van Unnik JA, Coindre JM, Contesso C, et al. Grading of soft tissue sarcomas: experience of the EORTC Soft Tissue And Bone Sarcoma Group. Eur J Cancer 1993;29A(15):2089-2093.
[14] Brearley N, Kumah P, Bell JA, et al. Delay to fixation of invasive breast carcinoma: effect on mitotic count, MIB1, ER and P53 expression. Eur J Cancer 2001;37:10.
[15] Lin X, Davion S, Bertsch EC, et al. Federation Nationale des Centers de Lutte Contre le Cancer grading of soft tissue sarcomas on needle core biopsies using surrogate markers. Hum Pathol 2016;56:147-154.
[16] Hashimoto H, Daimaru Y, Takeshita S, et al. Prognostic significance of histologic parameters of soft tissue sarcomas. Cancer 1992;70(12):2816-2822.
[17] Rööser B, Attewell R, Berg NO, et al. Prognostication in soft tissue sarcoma. A model with four risk factors. Cancer 1988;61(4):817-823.
[18] Coindre JM. Grading of soft tissue sarcomas: review and update. Arch Pathol Lab Med 2006;130(10):1448-1453.