OPEN ACCESS
Saudi Journal of Pathology and Microbiology
Abbreviated Key Title: Saudi J Pathol Microbiol
ISSN 2518-3362 (Print) |ISSN 2518-3370 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://scholarsmepub.com/sjpm/

Review Article

The Histopathological Grading Of Soft Tissue Sarcomas: A Review

Fahd Refai*

Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

DOI:10.21276/sjpm.2019.4.8.2 | **Received:** 28.06.2019 | **Accepted:** 25.07.2019 | **Published:** 10.08.2019

***Corresponding author:** Dr. Fahd Refai

Abstract

Soft tissue sarcomas (STS) are a rare a highly heterogeneous set of malignant mesenchymal neoplasms. Histological grading plays a central role in the assessment and management of patients with STS, since histological gradeis prognostic, contributes to clinical staging, and is also predictive of chemotherapy responses so drives clinical decision-making on the use of adjuvant chemotherapy. Here we review the main histopathological grading systems andthe main considerations for the practising pathologist when grading STS. We highlight that histological STS gradingis not without its limitations, not least in classifying 50% of tumours as of uncertain behaviour (grade 2). However, recent developments in molecular risk stratification hold promise for molecular grading of STS with the ultimate goal of personalising therapy based on molecular profiles.

Key points / clinical take-home messages

- Histological grade is important for prognostication, as a guide to management, and as a major determinant of stage Both the NCI and FNCLCC grading systems provide reasonable prognostic information, although the FNCLCC system classifies more STS as grade 3
- Replacing mitosis counting with Ki67 scoring as part of histological grading may improve reproducibility but is not widespread clinical practice
- Care must be taken when grading STS using diagnostic core biopsies, which may not be representative of the tumour as a whole; clinicopathological correlation is required
- Molecular grading might better identify high-risk patients across all histological grade groups, paving the way for personalised medicine approaches.

Copyright @ 2019: This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and sources are credited.

INTRODUCTION

Soft tissue sarcomas (STS) are a heterogeneous group of malignant neoplasms of mesenchymal origin. STS account for less than 1% of all malignant neoplasms and are diverse in presentation, morphology, and behaviour, occurring at any anatomical site [1]. STS reflect the large number and types of human mesenchymal cells, with >110 histotypes described [1]. However, liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma (UPS), rhabdomyosarcoma, synovial sarcoma, myxofibrosarcoma, and malignant peripheral nerve sheath tumours (MPNST) account for about two thirds of STS, with about 8% defying classification and regarded as unclassified sarcomas [2].

As with epithelial tumours, staging and grading remain the cornerstone of prognostication in patients with STS. The tumour grade represents a morphological surrogate of the intrinsic tumour biology, with low-grade tumours having a very good prognosis (approximately 90% five-year metastasis-free survival rate) and high-grade tumours having a poor prognosis (approximately 40% five-year metastasis-free survival rate) [3]. As such, grade features in every well-established nomogram for STS prognosis after primary treatment along with staging parameters (depth, size), histological subtype, and patient age [4], and STS grade is included as a parameter in clinical stage grouping in the Union for International Cancer Control (TNM) system [5].

The histopathological diagnosis and clinical management of STS are specialist endeavours best approached through multidisciplinary engagement in tertiary centres [6]. Nevertheless, in addition to securing an accurate histological diagnosis, both specialist and non-specialist pathologists reporting STS must know how to grade STS according to a recognised system, since this is essential for treatment planning and to provide appropriate information regarding prognosis. For healthcare systems without centralised STS

services, knowledge of grading STS according to a recognised system might encourage consistent reporting and terminology across centres to provide information for health service planning, clinical audit, and patient selection for clinical trials.

STS GRADING SYSTEMS

Although earlier studies had recognised an association between histological grade and prognosis in fibrosarcoma, liposarcoma, and other "general" soft tissue sarcomas, Russell et al. [7] were the first to describe a coherent clinicopathological staging system in their 1977 study of 1215 cases of STS, in which grade was a core parameter. However, they noted that grade was essentially subjective, reliant on an experienced pathologist assessing cellularity, cellular pleomorphism, mitotic activity, and more general features such as the presence of extracellular matrix or collagen as a marker of differentiation [7]. Nevertheless, this study provided the foundation for further, more objective multiparametric studies of clearly defined histological parameters such as differentiation, tumour necrosis, mitotic index, and vascular invasion. After refinement in the 1980s [8], two grading systems emerged and are mainly used clinically today: the National Cancer Institute (NCI) grading system [9] and the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system [10], with the latter scheme recommended by the College of American Pathologists, the AJCC, and the European Organization for Research and Treatment of Cancer (EORTC) [11]. Indeed, head-to-head comparisons of the two grading systems in the same population of patients showed discrepancies in about a third of cases but that the FNCLCC system defined more patients as grade 3, which has clearer management implications in terms of benefit from chemotherapy [12]. Therefore, while both systems are prognostic for metastasis and survival [12], the FNCLCC system probably has some benefits and is the most widely used system worldwide [11].

The NCI grading system, first described by Costa et al. [9] in 1984, was based on a multidisciplinary study of 163 patients and correlated histologic type, mitosis, necrosis, pleomorphism, cellularity, and matrix of the primary lesion to time to recurrence and overall survival. Necrosis best predicted both outcomes and was independent of age, sex, location, and size of the tumour. Based on this key finding, the authors proposed a grading system based on histologic typing to define minimal metastatic potential (Grade 1), with necrosis (15% cut-off) used to distinguish between aggressive lesions with good outcomes (Grade 2) and aggressive lesions with poor outcomes (Grade 3).

In a bid to further refine and determine independent prognostic histopathological features, Trojani et al. [10] and the French Sarcoma Group analysed seven histological parameters (tumour differentiation, cellularity, nuclear atypia, presence of malignant giant cells, mitotic count, extent of tumour necrosis, and presence of vascular emboli) in 155 patients. Multivariate analysis revealed that tumour differentiation, mitotic index, and extent of necrosis were independent prognostic factors, which formed the basis for their three-step scoring system. The full grading scheme is shown in Table 1.

Table-1: The French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system [10].

Parameter	Score	Description
Tumour differentiation	1	Sarcoma histologically very similar to normal adult mesenchymal tissue
	2	Sarcoma of defined histological subtype (e.g., myxofibrosarcoma)
	3	Sarcoma of uncertain type, embryonal and undifferentiated sarcomas
Mitosis count	1	0-9 / 10 HPF
	2	10-19 / HPF
	3	>20 / 10 HPF
Microscopic tumour necrosis	0	No necrosis
	1	<50% tumour necrosis
	2	>50% tumour necrosis
Final histological grade	1	Total score 2 or 3
	2	Total score 4 or 5
	3	Total score 6, 7, or 8

In practice, the assessment of differentiation encompasses both the histological features and the histotype, recognising that the intrinsic subtype is also of prognostic significance; the scores assigned to the common STS are shown in Table 2.

© 2019 |Published by Scholars Middle East Publishers, Dubai, United Arab Emirates

Table-2: Individual tumour differentiation scores according to the FNCLCC system.

Well-differentiated liposarcoma	1
Well-differentiated leiomyosarcoma	1
Malignant neurofibroma	1
Well-differentiated fibrosarcoma	1
Myxoid liposarcoma	2
Conventional fibrosarcoma	2
Conventional MPNST*	2
Myxofibrosarcoma	2
Myxoid chondrosarcoma	2
Conventional leiomyosarcoma	2
Conventional angiosarcoma**	2
High-grade myxoid (round cell) liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Poorly differentiated/epithelioid angiosarcoma	3
Poorly differentiated MPNST*	3
Malignant Triton Tumour	3
Poorly differentiated/pleomorphic leiomyosarcoma	3
Synovial sarcoma	3
Rhabdomyosarcoma**	3
Mesenchymal chondrosarcoma	3
Poorly differentiated/epithelioid angiosarcoma	3
Extraskeletal osteosarcoma**	3
Extraskeletal Ewing sarcoma**	3
Alveolar soft part sarcoma**	3
Malignant rhabdoid tumour	3
Clear cell sarcoma**	3
Undifferentiated (spindle cell and pleomorphic) sarcoma	3

* Grading of malignant peripheral nerve sheath tumour is of no prognostic value.

** Grading of embryonal and alveolar rhabdomyosarcoma, angiosarcoma, extraskeletal myxoid chondrosarcoma, alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma is not recommended. In practice, the following tumours are graded by definition as follows: (1) Atypical lipomatous tumour/well-differentiated liposarcoma, dermatofibrosarcoma protuberans, infantile fibrosarcoma and angiomatoid fibrous histiocytoma are Grade 1. (2) Ewing sarcoma/PNET, rhabdomyosarcoma (except spindle cell and botryoid variants), angiosarcoma, pleomorphic liposarcoma, soft tissue osteosarcoma, mesenchymal chondrosarcoma, desmoplastic small round cell tumour, and extra-renal malignant rhabdoid tumour are Grade 3. (3) Alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma are not graded but are usually considered as high grade for management purposes.

Mitoses should be counted in the most mitotically active areas in ten successive fields using a x40 objective lens with a standard x10 eyepiece. The mitotic index is expressed as number of mitoses in 10 high-power fields (HPFs), where one HPF (x 400) = 0.1734 mm^2 (the number of HPFs might need to be varied according to the field area of individual microscopes). For low-grade smooth muscle tumours where the mitotic index is critical for assessing malignancy or metastatic potential, 15–17 mitoses should be counted in 50 high power fields. Important practice points include assessment in high-quality, adequately fixed tissue; good quality sections; taking time to assess mitoses to preserve reproducibility; and repeating borderline scores (i.e., 8 / 10 HPF or 18 / 10 HPF).

The percentage necrosis should be assessed both microscopically and macroscopically, with confirmation of macroscopic necrosis confirmed in tissue sections and necrosis related to previous surgery or ulceration excluded and hyalinisation and haemorrhage ignored.

LIMITATIONS OF HISTOLOGICAL GRADING

The weakest component of FNCLCC grading system is the differentiation component, which is relatively subjective and can be difficult to assess if there is no normal tissue counterpart for comparison, such as in the case of undifferentiated pleomorphic sarcoma. Furthermore, STS grading systems have been developed based on the entire heterogeneous STS population and may not be generalizable to every histological subtype; indeed, some histotypes define the dominant clinical behaviour and therefore histotyping is more important than grading in these cases. For example, atypical lipomatous tumour/well-differentiated liposarcoma, dermatofibrosarcoma protuberans, infantile fibrosarcoma and angiomatoid fibrous histiocytoma are Grade 1; Ewing sarcoma/PNET, rhabdomyosarcoma (except spindle cell

© 2019 |Published by Scholars Middle East Publishers, Dubai, United Arab Emirates

and botryoid variants), angiosarcoma, pleomorphic liposarcoma, soft tissue osteosarcoma, mesenchymal chondrosarcoma, desmoplastic small round cell tumour, and extra-renal malignant rhabdoid tumour are Grade 3; and alveolar soft part sarcoma, clear cell sarcoma, and epithelioid sarcoma are not graded but are usually considered high-grade for management purposes [13].

In practice, care should be taken when grading using small diagnostic core needle biopsies, which may not be representative of the entire lesion especially with regard to mitotic counting and assessment of necrosis, although accuracy is still reported to be in the region of 60-80% and especially accurate for high-grade lesions [14, 15]. This highlights that histopathological reporting of STS should not be performed in isolation, instead as a multidisciplinary effort with close clinicopathological correlation with clinical and radiological data.

While the FNCLCC system makes efforts to standardise the assessment criteria, there is still a subjective component to each of the three elements. Therefore, inter-observer reproducibility can be a problem, with reported concordances between pathologists of 75% for tumour grade, 73% for mitotic index, 74% for differentiation, and 81% for tumour necrosis [16]. In an effort to improve reproducibility, a Japanese group assessed the value of assessing proliferation with antibodies targeting Ki67 (MIB-1 antibody), a proliferative marker, and showed that agreement was higher using the Ki67 grade compared to the mitotic index (79% vs. 69%) [17]. This finding was borne out in a recent assessment of the Ki67 grading system in a prospective clinical trial of perioperative chemotherapy for STS, with the Ki67 system not only showing better reproducibility than mitosis counting but also better associations with survival outcomes [18]. However, Ki67 grading has yet to be routinely adopted in clinical practice.

Finally, as with other three-grade systems in histopathology, the grade 2 lesions are of uncertain prognosis and therefore less useful for clinical decision-making. Although as noted above the FNCLCC system categorises more lesion as grade 3 than the NCI system (46 vs. 58%, respectively), grading becomes less useful for about half of all STS patients [12]. As well as providing prognostic information, STS grading is important since it guides the use of adjuvant chemotherapy, with grade 3 STS patients with the worst prognosis more likely to respond to chemotherapy than grade 2 patients [13].

The future of grading: molecular grading

Molecular profiling has already become routine clinical practice for prognostication in a number of epithelial cancers, not least with the FDA-approved Oncotype DX and MammaPrint breast cancer gene expression tests, which are used to risk stratify early-stage breast cancer patients and guide adjuvant therapy planning [19]. Similar efforts are underway in STS which, given the limitations of histological grading, the overlap between histotype and grade, and the large grade 2 group, would benefit from a similar diagnostic assay to better risk stratify patients and guide therapy. Furthermore, as in other solid organ epithelial malignancies, molecular characterisation efforts also reveal information about the underlying tumour biology independent of grade and histotype, so might be useful for targeted therapies in individual patients, the so-called "personalised medicine" approach.

To this end, there have been several efforts to apply gene expression and molecular profiling approaches to STS to produce prognostic signatures [13]. Of these, the 67-gene CICSARC transcriptomic signature developed by the French Sarcoma Group is probably the most developed, having now been tested in over 600 STS samples and optimised for formalin-fixed, paraffin-embedded routine diagnostic tissue. Furthermore, a recent meta-analysis showed that CINSARC perfectly splits STSSTS patients into two separate prognostic groups more accurately than FNCLCC grade and, importantly, identifies a subgroup of high-risk patients in each FNCLCC grade – not only in grade 2 patients, but also a subgroup of grade 1 patients likely to have poor outcomes [20]. These high-risk patients are likely to respond better to perioperative chemotherapy, and future prospective trials with patient stratification based on molecular testing are warranted.

CONCLUSIONS

Histological grading is a well-established and integral component of the pathological assessment of STS that provides information about prognosis, is required for staging, and influences patient management. Given their rarity and complex management, pathological assessment is best performed in specialist centres, by experienced specialised soft tissue pathologists, and in a highly multidisciplinary environment with access to clinicopathological information for correlation. Progress is being made in applying modern molecular techniques to STS grading, which requires further validation in prospective clinical trials.

REFERENCES

1. Jo, V. Y., & Doyle, L. A. (2016). Refinements in sarcoma classification in the current 2013 World Health Organization classification of tumours of soft tissue and bone. *Surgical Oncology Clinics*, *25*(4), 621-643.
2. Oda, Y., Yamamoto, H., Kohashi, K., Yamada, Y., Iura, K., Ishii, T., ... & Bekki, H. (2017). Soft tissue sarcomas: From a morphological to a molecular biological approach. *Pathology international*, *67*(9), 435-446.
3. Coindre, J. M., Terrier, P., Guillou, L., Le Doussal, V., Collin, F., Ranchère, D., ... & N'Guyen Bui, B. (2001). Predictive value of grade for metastasis

development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *91*(10), 1914-1926.

4. Grobmyer, S. R., & Brennan, M. F. (2003). Predictive variables detailing the recurrence rate of soft tissue sarcomas. *Current opinion in oncology*, *15*(4), 319-326.
5. Amin, M. B., & Edge, S. B. (Eds.). (2017). *AJCC cancer staging manual*. Springer.
6. Dangoor, A., Seddon, B., Gerrand, C., Grimer, R., Whelan, J., & Judson, I. (2016). UK guidelines for the management of soft tissue sarcomas. *Clinical sarcoma research*, *6*(1), 20.
7. Russell, W. O., Cohen, J., Enzinger, F., Hajdu, S. I., Heise, H., Martin, R. G., ... & Suit, H. D. (1977). A clinical and pathological staging system for soft tissue sarcomas. *Cancer*, *40*(4), 1562-1570.
8. Oliveira, A. M., & Nascimento, A. G. (2001). Grading in soft tissue tumors: principles and problems. *Skeletal radiology*, *30*(10), 543-559.
9. Costa, J., Wesley, R. A., Glatstein, E., & Rosenberg, S. A. (1984). The grading of soft tissue sarcomas results of a clinicohistopathologic correlation in a series of 163 cases. *Cancer*, *53*(3), 530-541.
10. Trojani, M., Contesso, G., Coindre, J. M., Rouesse, J., Bui, N. B., De Mascarel, A., ... & Lagarde, C. (1984). Soft- tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *International journal of cancer*, *33*(1), 37-42.
11. Golouh, R., & Bračko, M. (2001). What is current practice in soft tissue sarcoma grading?. *Radiology and Oncology*, *35*(1).
12. Guillou, L., Coindre, J. M., Bonichon, F., Nguyen, B. B., Terrier, P., Collin, F., ... & Jacquemier, J. (1997). Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *Journal of clinical oncology*, *15*(1), 350-362.
13. Neuville, A., Chibon, F., & Coindre, J. M. (2014). Grading of soft tissue sarcomas: from histological to molecular assessment. *Pathology*, *46*(2), 113-120.
14. Almond, L. M., Tirotta, F., Tattersall, H., Hodson, J., Cascella, T., Barisella, M., ... & Gronchi, A. (2019). Diagnostic accuracy of percutaneous biopsy in retroperitoneal sarcoma. *British Journal of Surgery*, *106*(4), 395-403.
15. Hoeber, I., Spillane, A. J., Fisher, C., & Thomas, J. M. (2001). Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors. *Annals of surgical oncology*, *8*(1), 80-87.
16. Coindre, J. M., Trojani, M., Contesso, G., David, M., Rouesse, J., Bui, N. B., ... & Goussot, J. F. (1986). Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. *Cancer*, *58*(2), 306-309.
17. Hasegawa, T., Yamamoto, S., Nojima, T., Hirose, T., Nikaido, T., Yamashiro, K., & Matsuno, Y. (2002). Validity and reproducibility of histologic diagnosis and grading for adult soft-tissue sarcomas. *Human pathology*, *33*(1), 111-115.
18. Tanaka, K., Hasegawa, T., Nojima, T., Oda, Y., Mizusawa, J., Fukuda, H., & Iwamoto, Y. (2016). Prospective evaluation of Ki-67 system in histological grading of soft tissue sarcomas in the Japan Clinical Oncology Group Study JCOG0304. *World journal of surgical oncology*, *14*(1), 110.
19. Kittaneh, M., Montero, A. J., & Glück, S. (2013). Molecular profiling for breast cancer: a comprehensive review. *Biomarkers in cancer*, *5*, BIC-S9455.
20. Valentin, T., Lesluyes, T., Le Guellec, S., & Chibon, F. (2019). Chemotherapy in localized soft tissue sarcoma: will we soon have to treat grade 1 tumors? Update on CINSARC performances. *Annals of Oncology*.

© 2019 |Published by Scholars Middle East Publishers, Dubai, United Arab Emirates