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What is current practice in soft tissue sarcoma grading?

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Purpose. *Most published grading systems of soft tissue sarcomas (STS) are somewhat subjective and it seems that there is no definite consensus among experts which of them is the most effective. The aim of this study was to collect data from practicing pathologists and to get some insight in the practice of STS grading.*
Subjects. *A questionnaire was sent to 135 pathologists chosen randomly.*
Results. *There were 88 responders from 30 countries from 5 continents. Most responders (85%) grade STS, more frequently in Europe than in non-European countries. Three-grade system is preferred by both European and non-European pathologists, who use it in almost 77% and 67%, respectively. They apply the criteria set by FNCLCC in 37.3%, by NCI in 24%, by Broders in 12% and by Markhede in 1.4%. In Europe, FNCLCC system is the most widely used. Beside classical histological criteria, other modern methods are applied by more than one half of the responders. Immunohistochemical evaluation of proliferation markers is the method most widely used, followed by molecular markers and DNA flow cytometry.*
Conclusion. *The results of our study indicate that most pathologists consider histologic grade of STS as a valuable, however not completely satisfactory predictor of a patient's survival.*

Key words: soft tissue neoplasms; sarcoma pathology; neoplasms staging; prognosis

Introduction

No other variable seems to work better in the prediction of the behavior of soft tissue sarcomas (STS) than histological grade, but at the same time, no other prognostic factor has been responsible for so much controversy and debate. Soft tissue sarcomas are a large group of approximately 50 different nosologic entities that, despite sharing common clinical features such as blood-borne metastatic spread, also present significant clinical differences. The value of histopathological grading should, therefore, be balanced against the predictive significance of other morphologic and clinical parameters that vary according to the specific type of sarcoma.

In most sarcoma grading systems, the degree of histological differentiation, cellularity, pleomorphism, mitotic activity, necrosis and vascular invasion are taken into account. In addition, some schemes take the pathological diagnosis of the tumor as a dominant component for grading as it is well known that certain sarcomas have a specific biological be-

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havior that is defined mostly by their line of differentiation.

However, many grading systems applied to STS have not been completely satisfactory in terms of predicting prognosis. Therefore, attempts to identify potentially more aggressive sarcomas have been made using additional quantitative methods such as flow cytometry, markers for assessment of proliferative activity as well as molecular techniques looking for oncogenes, suppressor genes and gene product expression.

Although most published grading systems may provide valuable prognostic information, an international consensus on STS grading has not been reached. One may, therefore, suppose that grading of STS varies considerably among different places and even among experts in the field.

The historical and practical aspects of histologic grading of STS have recently been extensively reviewed.[1] In addition, some guidelines regarding STS grading have been proposed in the recently published recommendations for the reporting of soft tissue sarcoma.[2] The aim of the present study was to collect data from practicing pathologists and to get some insight in the current practice of STS grading in different institutions of different countries.

Material and methods

To obtain first-hand information, a questionnaire was sent to 135 pathologists who were chosen at random from the list of participants of the 15th European Congress of Pathology. They were asked to answer to four specific questions, as follows:

1. Do you grade STS (yes, no)?
2. How many grades do you use (two, three, four)?
3. Which grading system do you use (Broders, NCI, Jensen, FNCLCC, other-specify)?
4. Do you use other methods to assess STS prognosis (no, yes - DNA ploidy, S-phase fraction, proliferation markers, molecular markers, other - specify)?

Finally, all potential responders were asked for their comments.

Results

All the data were processed anonymously. In total, there were 88 responders from 30 countries of 5 continents (Table 1). Most of them (74%) were from Europe. Their answers are shown in Table 2.

Table 1. Geographical distribution of the responding pathologists

Australia	2	Iceland	1
Austria	2	Italy	6
Brasil	1	Japan	5
Canada	1	Macedonia	2
Croatia	1	Norway	5
Czech Republic	2	Poland	1
Denmark	3	Portugal	2
Finland	3	Slovenia	1
France	5	Spain	7
Germany	5	Sweden	2
Great Britain	4	Switzerland	3
Greece	2	Turkey	2
The Netherlands	3	Ukraine	1
Hong Kong	2	USA	12
Hungary	1	Yugoslavia	1

Most responders (85%) grade STS. Among them, however, certain geographical differences became evident. Pathologist in Europe use gradation of STS more frequently (in nearly 88%), compared to the pathologists in non-European countries, who grade STS in 78%.

Similarly, number of grades used, namely 2, 3 or 4, also varies considerably - 11%, 74%, and 15%, respectively. Three-grade system is preferred by both European and non-European pathologists, who use it in almost 77% and 67%, respectively.

Table 2. Answers provided by the participating pathologists

	All (n=88)	European (n=65)	non-European (n=23)
grading used	75 (85.2%)	57 (87.7%)	18 (78.3%)
number of grades			
2	8 (9.1%)	5 (8.9%)	3 (16.7%)
3	55 (62.5%)	43 (76.8%)	12 (66.7%)
4	11 (12.5%)	8 (14.3%)	3 (16.7%)
grading system			
Broders	9 (12.0%)	6 (10.5%)	3 (16.7%)
NCI	18 (24.0%)	13 (22.8%)	5 (27.8%)
FNCLCC	28 (37.3%)	26 (45.6%)	2 (11.1%)
other/not specified	20 (26.7%)	12 (21.1%)	8 (44.4%)
other methods used	47 (53.4%)	38 (58.5%)	9 (39.1%)
proliferation markers	38 (43.2%)	31 (47.7%)	7 (30.4%)
SPF and/or DNA ploidy	12 (13.6%)	11 (16.9%)	1 (4.3%)
molecular	15 (17.0%)	12 (18.5%)	3 (13.0%)
other/not specified	10 (11.4%)	8 (12.3%)	2 (8.7%)

Of the 75 individuals who systematically grade STS, only 56 specified the system used. Pathologists apply the criteria set by FNCLCC in 37.3%, by NCI in 24%, by Broders in 12%, and by Markhede in 1.3%; the remaining 25.3% did not specify the system they use. Again the analysis disclosed some differences between the regions studied. While FNCLCC system is the most widely used in Europe (46%), non-European pathologists seem to prefer other systems.

Rather surprisingly, of the 56 pathologists who specified the grading system they use, 11 (19.6%) stated that they use a number of grades different to that applied in the original published grading scheme.

Beside classical histological criteria to assess soft tissue sarcoma prognosis, other modern methods are applied by more than one half of the responders. In Europe, these are used in 59%, compared to 30% in non-European countries. Immunohistochemical evaluation of proliferation markers is the method most widely used, followed by molecular methods and flow-cytometric determination of DNA ploidy and/or S-phase fraction.

Discussion

The results of our study show that the large majority of pathologists apply grading to the diagnosis of soft tissue sarcoma. On the other hand, they also indicate that, in practice, this is done rather inconsistently, that various grading schemes are in use, and that the guidelines set forth by the published grading systems are often only loosely applied. One of the reasons for this, as well as for the fact that as many as 15% of pathologists do not use STS grading, might be the lack of international consensus.

Despite the validation of many histologic grading systems for STS, none have been universally accepted. Because of the overall rarity of specific sarcoma subtypes, the evaluation of grading systems and their prognostic significance have tended to be based on sarcomas as a general group, diminishing the value and significance of histologic subtyping. The same histological criteria have been applied to 50 different types of sarcomas, despite the fact that some behave as borderline or low-grade malignant tumors (dermatofibrosarcoma protuberans, retiform heman-

gioendothelioma) and others are uniformly high grade (clear cell sarcoma, desmoplastic small cell tumor). It has been pointed out that histologic grading may overestimate or underestimate the biological potential of some STS. Therefore, it has been suggested that the grading criteria should be revised for each type of soft tissue tumor. Moreover, the study of each specific type of STS should be subjected to multivariate statistical analysis with simultaneous consideration of histological, clinical and treatment factors.[3]

If histologic grading is to be applied to certain types of STS, which grading should be used and what is the current grading practice?

Most grading systems incorporate similar histologic parameters, namely histologic type, cellularity, tumor necrosis, and mitotic activity. The parameters by which these criteria are applied tend to be less defined in systems of Broders[4] and Markhede[5] both of which use a four-grade scale. The more recent systems, preferred by our responders, the National Cancer Institute (NCI) system as proposed by Costa[6] and the system of Federation Nationale des Centres de la Lutte Contre le Cancer (FNCLCC),[7,8] appear far less subjective than its predecessors and provide specific guidelines for applying tumor grade. They both are 3-tiered. The NCI largely incorporates histologic subtype and extent of necrosis, whereas FNCLCC uses tumor differentiation, mitotic count and volume of tumor necrosis. Although both systems have predictive value for metastatic development and tumor mortality, the FNCLCC system appears to be slightly superior to the NCI system, both in the ability to predict a patient's survival and in the reproducibility of the scoring system among pathologists.[7,9]

In contrast to most previous attempts that tried to evaluate STS as an entire group, predictive value for metastatic disease has recently been specifically assessed for the main histologic types of adult STS.[10] The results of a study of 1240 patients, assessed by FNCLCC system, confirmed the impression that histologic grade is the most important predictor of metastasis development in several malignant soft tissue tumors. In order of importance, the following parameters were reported to have independent predictive value: (1) grade, neurovascular or bone involvement (NBI), tumor size and depth for the whole group; (2) grade and tumor size for liposarcoma (n=188); (3) NBI, grade and tumor size for leiomyosarcoma (n=148); (4) grade and NBI for synovial sarcoma (n=125); (5) grade for unclassified sarcomas (n=140) and sarcomas of other types (n=158). Interestingly, the authors could not identify any prognostic parameter for malignant schwannoma (n=72) and for rhabdomyosarcoma (n=60).

It should be pointed out that both NCI and FNCLCC systems are best applied to adult soft tissue sarcomas. Recognizing the differences between children and adults, Parham *et al.* reported the criteria of Pediatric Oncology group (POG) for nonrhabdomyomatous sarcomas in children.[11] POG system is similar to NCI grading scheme, but takes into account more adequately the unique clinico-pathologic features of children and therefore better suits this age group. On the other hand, for childhood rhabdomyosarcoma the Intergroup Rhabdomyosarcoma Study Group have proposed a grading system which better correlates with prognosis of this specific group of STS.[12] The classification, specifically designated as the International Classification of Rhabdomyosarcoma (IRC), divides RMS in three groups - tumors with superior, intermediate and poor prognosis.

Arguably, the classification, histological subtyping, and grading systems of STS are mostly based on classical, morphologic features. Recent advances in our understanding of the cytogenetic and molecular features of STS have yielded significant insight into STS pathogenesis.[13] It is not surprising that, ac-

cording to our study, more than one half of pathologists apply additional methods, although their value in predicting behavior of STS is not entirely clear at present. Markers such as MIB1 to more accurately assess proliferative activity are most commonly used. They are followed by molecular methods to evaluate the expression of p53, MDM2, RB and other gene products, and flow cytometry to separate diploid from aneuploid tumors and to determine S-phase fraction. Again, it has to be stressed that additional studies of these and many other modern methods are needed to evaluate their specific prognostic significance for each type of STS.

Although the data gathered in this study suggest that certain differences exist in the practice of STS prognostication between European and non-European pathologists, none of this differences proved to be statistically significant. It should be noted, however, that the number of responders from non-European countries was far too small to draw any firm conclusion.

In conclusion, the results of our study indicate that most pathologists are aware of the fact that histologic grade of STS appears to be a valuable, however not completely satisfactory predictor of a patient's survival. Despite the impressive advances in our understanding of STS and high level of expertise in stating accurate diagnosis of common and many recently described entities, there are still many problems that account for the failure of most grading schemes to consistently function well.

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References

1. Kilpatrick SE. Histologic prognostication in soft tissue sarcomas: Grading versus subtyping or both? A comprehensive review of the literature with proposed practical guidelines. *Ann Diagn Pathol* 1999; **3:** 48-61.

2. Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of soft tissue sarcoma. *Virchows Arch* 1999; **434:** 187-91.

3. Meis-Kindblom JM. On the comparison of apples, oranges and sundry fruit: problems with grading and prognostication in soft tissue tumors. *Patologia* 1999; **32:** 426-7.

4. Pritchard DJ, Soule EH, Taylor WF, Ivins JC. Fibrosarcoma. A clinicopathologic and statistical study of 199 tumors of soft tissues of the extremities and trunk. *Cancer* 1974; **33:** 888-97.

5. Markhede G, Angervall L, Stener B. A multivariate analysis of the prognosis after surgical treatment of malignant soft-tissue tumors. *Cancer* 1984; **49:** 1721-33.

6. Costa J, Wesley RA, Glatstein E, Rosenberg SA. The grading of soft tissue sarcomas: Results of a clinicopahological correlation in a series of 163 cases. *Cancer* 1984; **53:** 530-41.

7. Guillou L, Coindre JM, Bonichon F, Nguyen BB, Terrier P, Collin F, et al. 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 sarcomas. *J Clin Oncol* 1997; **15:** 350-62.

8. Trojani M, Contesso G, Coindre JM, Rouesse J, Bui NB, de Mascarel A, et al. Soft tissue sarcomas of adults: Study of pathological prognostic variables and definition of a histopathologic grading system. *Int J Cancer* 1984; **33:** 37-42.

9. Coindre JM, Trojani M, Contesso G, David M, Rouesse J, Bui NB, et al. Reproducibility of histopathologic grading system for adult soft tissue sarcoma. *Cancer* 1986; **58:** 306-9.

10. Coindre JM, Terrier P, Collin F, le Doussal V, Guillou L, Ranchere D, et al. Predictive factors for metastasis development in main histologic types of adult soft tissue sarcomas. United States and Canadian Academy of Pathology. Annual Meeting, San Francisco, 1999. Abstract 9A.

11. Parham DM, Webber BL, Jenkins JJ 3rd, Cantor AB, Maurer HM. Nonrhabdomyosarcomatous soft tissue sarcomas of childhood: Formulation of a

simplified system for grading. *Mod Pathol* 1995; **8:** 705-10.

12. Newton WA Jr, Gehan EA, Webber BL, Marsden HB, van Unnik AJ, et al. Classification of rhabdomyomatous and related sarcomas; pathologic aspects and proposal for a new classification - an Intergroup Rhabdomyosarcoma Study. *Cancer* 1995; **76:** 1073-85.

13. Ladanyi M. The emerging molecular genetics of sarcoma translocation. *Diagn Mol Pathol* 1995; **4:** 162-73.