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Current Controversies in Cancer

Is Histological Grading of Value for the Prognosis of Soft Tissue Sarcomas?

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THE VARIOUS types of tumour currently included under the heading of soft tissue sarcomas (STS) vary widely in their clinical behaviour, from slowly growing lesions with a tendency to local, but rarely distant recurrence, to highly aggressive, fast growing tumours which metastasise early. Although a few histological types are fairly constant in their behaviour—a typical example of an indolent type being the well-differentiated liposarcoma, while rhabdomyosrcoma is representative of a highly malignant tumour—the majority cover more or less the whole clinical spectrum [1].

Histological grading was developed as a tool for predicting the relative malignancy of a given tumour. It soon proved to be a very useful prognostic parameter for defining subgroups with different prognoses for overall survival and, to a certain degree, also recurrence-free and metastasis-free survivals [2–5]. It helps clinicians determine the most appropriate therapy, especially when tumours are located extracompartmentally or in other difficult sites. Grading is not only a statistically significant prognostic factor in univariate analyses, it often surpasses other parameters, including histological type, in multivariate analyses [7–9].

Although histological grade does not appear to predict response to chemotherapy [10], unpublished data from the EORTC show that it retains its prognostic significance for patients in advanced stage both in uni- and multivariate analyses. There are also data indicating that radiation treatment is most beneficial in tumours of high grade [11].

Unfortunately, several grading systems are currently in use. Some are based on the subjective impression of a tumour's overall differentation, while others evaluate individual histological parameters—but the parameters vary, and they are weighed differently. Most systems utilise three grades [1, 3–5, 12], but there are also two- [13] and four-grade systems [14, 15]. Thus, the grades are not immediately comparable, nor have there been any major studies comparing different grading systems with regard to both prognostic information and reproducibility (although data from Scandinavia show that subdivision of grade III sarcomas into two prognostically distinct subgroups is possible [15, 16]).

Examples of histological parameters utilised in grading include degree of differentiation, cellularity, necrosis/pyknosis, mitotic activity and myxoid degeneration. When these are tested in multivariate analyses, mitotic activity and the presence of necrosis are consistently among the most important [4, 5, 17, 18]. The French (Trojani) grading system is based on degree of differentiation, necrosis and mitotic count [5]; this system has the advantage of having an acceptable interobserver variation [19]. It is currently used by the EORTC, where both the grade and the scores of the individual parameters are registered at the EORTC Data Centre. The histological type influences the grade through the parameter of differentiation, but both type and differentiation are subject to a considerable interobserver disagreement, a deplorable situation which is not improved by the increasing number of recognised pathological entities [20]. However, a recent paper by van Unnik and associates [21] proposes a simplified grading which ignores the histological type and is based solely on the mitotic count and the presence or absence of necrosis. They found these two parameters, together with tumour size, to be the only significant factors in a multivariate analysis of 282 patients entered into the EORTC adjuvant trial. As pointed out by the authors themselves, the behaviour of rare sarcoma types may differ from the main group, without this becoming evident in the statistical analyses due to their small numbers. Further analyses, for example on the collected EORTC data, will reveal whether this system is superior to the Trojani grade.

The ideal grading system carries a maximum of prognostic information, is simple and easy to use and has a minimum of interobserver variation. As in the study by van Unnik and associates, individual histological parameters should be tested for their prognostic importance by multi-

variate analyses on sufficiently large samples. The rarer histological subtypes should be studied in order to ascertain whether they should be included in the grading procedure or possibly given an *a priori* grade, as is the case in some grading systems [3, 4]. Interobserver variation may be reduced by improved definition of parameters, or by the use of morphometry.

Other techniques have been suggested as adjuncts to grading, e.g. DNA measurement, immunohistochemical staining for p53/MDM2, or proliferation markers such as PCNA or Ki67 (for review, see [22]); these may even lend themselves to automated image analysis, thereby reducing interobserver variation [23]. Tomita and associates [24] suggested a grading system based on cellularity and extent of necrosis, with the mitotic index replaced by the AgNOR count (silver staining of nucleolar organiser regions). However, with these methods, the problem of interlaboratory variation arises: AgNOR staining is notoriously tricky and immunohistochemical staining results vary with the techniques used. For a multi-institutional organisation such as the EORTC, where a central review is performed on limited material (the standard requirement being eight unstained slides or the loan of one paraffin block), it is necessary to be realistic and keep grading procedures as simple as possible.

In conclusion, grading of STS is indispensable because of the prognostic information it provides. Stratification according to grade is necessary if treatment results are to be evaluated reliably. At present, there are no other parameters or procedures that can replace grading. However, the grading systems should be adjusted and improved in order to enhance prognostic information and reduce interobserver variation. Such an improved grading system (a candidate being the one proposed by van Unnik and associates [21]) might hopefully gain wider acceptance and thereby facilitate comparison of patient materials and treatment results between different sarcoma groups.

1. Enzinger FM, Weiss SW. *Soft Tissue Tumors*, 3rd edn. St. Louis, MO, Mosby-Year Book Inc, 1995.
2. Suit HD, Russell WO, Martin RG. Sarcoma of the soft tissue. Clinical and histopathological parameters and response to treatment. *Cancer* 1975, **35**, 1478–1483.
3. Myhre-Jensen O, Kaae S, Hjøllund Madsen E, Sneppen O. Histopathological grading in soft-tissue tumours. Relation to survival in 261 surgically treated patients. *Acta Path Microbiol Immunol Scand A* 1983, **91**, 145–150.
4. Costa J, Wesley RA, Glatstein E, Rosenberg SA. The grading of soft tissue sarcomas. Results of a clinicohistopathologic correlation in a series of 163 cases. *Cancer* 1984, **53**, 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**, 37–42.
6. Gaynor JJ, Tan CC, Casper ES, *et al.* Refinement of clinicopathologic staging for localized soft tissue sarcoma of the extremity: a study of 423 adults. *J Clin Oncol* 1992, **10**, 1317–1329.
7. Ravaud A, Bui NB, Coindre JM, *et al.* Prognostic variables for the selection of patients with operable soft tissue sarcomas to be considered in adjuvant chemotherapy trials. *Br J Cancer* 1992, **66**, 961–969.
8. Keus RB, Rutgers EJT, Ho GH, Gortzak E, Albus-Lutter CE, Hart AAM. Limb-sparing therapy of extremity soft tissue sarcomas: treatment outcome and long-term functional results. *Eur J Cancer* 1994, **30A**, 1459–1463.
9. Drobnjak M, Latres E, Pollack D, *et al.* Prognostic implications of p53 overexpression and high proliferation index of Ki-67 in adult soft-tissue sarcomas. *J Natl Cancer Inst* 1994, **86**, 549–554.
10. Daugaard S, van Glabbeke M, Schiødt T, Mouridsen HT. Histopathological grade and response to chemotherapy in advanced soft tissue sarcomas. *Eur J Cancer* 1993, **29A**, 811–813.
11. Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in the management of completely resected soft tissue sarcomas of the extremity and superficial trunk. *Int J Radiat Oncol Biol Phys* 1993, **27**, 259–265.
12. Shiraki M, Enterline HT, Brooks JJ, *et al.* Pathologic analysis of advanced adult soft tissue sarcomas, bone sarcomas, and mesotheliomas. *Cancer* 1989, **64**, 484–490.
13. Hajdu SI. *Pathology of Soft Tissue Tumors*. Philadelphia, PA, Lea & Febiger, 1979.
14. Markhede G, Angervall L, Stener B. A multivariate anaylsis of the prognosis after surgical treatment of malignant soft-tissue tumors. *Cancer* 1982, **49**, 1721–1733.
15. Myhre Jensen O, Høgh J, Østgaard SE, Nordentoft AM, Sneppen O. Histopathological grading of soft tissue tumours. Prognostic significance in a prospective study of 278 consecutive cases. *J Pathol* 1991, **163**, 19–24.
16. Alvegård TA, Berg NO. Histopathology peer review of high-grade soft tissue sarcoma: the Scandinavian Sarcoma Group experience. *J Clin Oncol* 1989, **7**, 1845–1851.
17. Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients (Thesis). *Acta Orthop Scand* 1994, **65**(Suppl. 259), 65.
18. Stéfani ED, Deneo-Pellegrini H, Carzolgio J, *et al.* Sarcomes des tissus mous: facteurs histologiques de pronostic. *Bull Cancer (Paris)* 1982, **69**, 443–450.
19. Coindre JM, Trojani M, Contesso C, *et al.* Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. *Cancer* 1986, **58**, 306–309.
20. van Unnik JAM. Classification and grading of soft-tissue sarcomas. *Hematol Oncol Clin North Am* 1995, **9**, 677–700.
21. van Unnik JAM, 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**, 2089–2093.
22. Dirix LY, van Oosterom AT. Diagnosis and treatment of soft tissue sarcomas in adults. *Curr Opin Oncol* 1995, **7**, 340–348.
23. Michie BA, Black C, Reid RP, Barrett A, Hamblen DL. Image analysis derived ploidy and proliferation indices in soft tissue sarcomas: comparison with clinical outcome. *J Clin Pathol* 1994, **47**, 443–447.
24. Tomita Y, Aozasa K, Myoui A, *et al.* Histologic grading in soft-tissue sarcomas. An analysis of 194 cases including AgNOR count and mast-cell count. *Int J Cancer* 1993, **54**, 194–199.