Referral patterns, prognostic models and treatment in soft tissue sarcomas

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Chapter 4

Prognostic models and the role of biomarkers

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Prognosis means 'foreseeing' and is used in medicine to predict the probable course and outcome of a disease. Especially in the oncology field, prognosis is an important topic and a continuous subject of investigation. Although most studies analyze groups of patients, and the observed outcome cannot be translated directly to the individual patient, these outcomes can be used as a tool to define groups of patients with a low or high risk profile regarding recurrent disease and survival. This distinction between patients with a good and poor outcome is clinically relevant because it supports the decision for treatment, in particular for (neo-) adjuvant treatment. Additional information is needed to generate a better risk profile for the individual patient. Therefore, researchers are looking for new prognostic factors that can estimate the risk on a particular event – e.g. local or distant recurrence and disease specific mortality – over a specific time. Usually a combination of prognostic factors predicts the outcome more precisely and several prognostic factors are therefore used in a prognostic model.

Predicting the prognosis of soft tissue sarcoma patients is complicated due to the heterogeneity of these malignancies, both at the histological and genetic level. Over the last decades, the discovery of novel immunohistochemical markers led to a better distinction between histological subtypes and even the recognition of new subtypes. Today, pathologists can recognize more than fifty different subtypes using immunohistochemical staining. Furthermore, scientific advancements have provided insight into molecular pathways and mechanisms, and showed that histological different soft tissue sarcomas may share the same genetic aberration, thereby introducing another classification based on these genetic alterations. Furthermore, the clinical behavior of the tumors can be related to the histological and genetic specificity, yet similar tumors may have very different clinical behavior.

This chapter describes the classification systems, the different staging and grading systems used in soft tissue sarcomas, prognostic models and new biomarkers.

Classification systems

Histological classification

Soft tissue sarcomas are mesenchymal tumors, predominantly arising from the embryonic mesoderm, but in some cases they arise from the ectoderm, e.g. peripheral nervous sheath tumors. Mesodermal cells give rise to the connective tissues, including pericardium, pleura, blood vessels endothelium, smooth and striated muscle, bone, cartilage, and synovium. Soft tissue sarcomas have been traditionally classified according to the adult mesenchymal tissue they most resemble, though no firm link exists between this tissue and sarcoma origin. For example, there is no evidence that liposarcomas either originate from mature fat, or represent malignant transformation of lipomas. Since 2013 the World Health Organization recognizes since 8 types of soft tissue sarcomas, namely; adipocytic, fibroblastic/myofibroblastic, so-called fibrohistiocytic, smooth muscle, skeletal-muscle, nerve sheat, tumours of uncertain differentiation, as well as a final group of undifferentiated/unclassified sarcomas. [1] At present, the most frequent histological subtypes of the extremities and trunk are leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma. [2] Of the abdominal tract, the gastrointestinal stromal tumor (GIST) is the most common sarcoma subtype. [3]

Although most soft tissue sarcomas form only one type of tissue, some of these tumors appear to have the ability to dedifferentiate. Dedifferentiation can be of prognostic value, e.g. myogenic differentiation in pleomorphic sarcomas is reported as an adverse prognostic factor, being associated with more aggressive behaviour and higher metastatic rate. [4] Dedifferentiation and heterogeneity in sarcomas result in a variety of overlapping patterns, making a uniform diagnosis difficult. As a consequence, even experienced sarcoma pathologists frequently disagree as to the cell of origin of an individual tumor, in as many as 28% to 47% of cases. [5-7] Reliable immunohistochemical markers and reproducible genetic changes are therefore greatly contributing to the accurate diagnosis of soft tissue sarcomas.

Genetic classification

Remarkable gains in the understanding of sarcoma genesis have been attained in the past two decades. First of all, methodologies and laboratory techniques, e.g. reverse transcriptase-polymerase chain reaction (RT-PCR) and fluorescence in-

situ hybridization (FISH), have allowed unraveling of the deregulation pathways and the involved regulating oncoproteins. Hirota and colleagues started the revolution for sarcomas in 1998, when they found that gastrointestinal stromal tumors contain a mutation in a gene called 'c-kit'. [8] This gene encodes for the protein 'KIT' that functions as a receptor, allowing transmission of survival and proliferation signals to cells. Hirota found that this receptor was continuously turned on and in turn caused continuous growth of gastrointestinal stromal tumors.

Secondly, more recent techniques called 'next generation DNA sequencing' allow for more rapid and inexpensive sequencing of both DNA and RNA. Because the costs of sequencing is now less than 1% of the costs ten years ago [9], whole genome analysis has become widely available. The more prevalent identified gene mutations in sarcomas are: p53, retinoblastoma (RB), P13K and isocitrate dehydrogenase (IDH). [10] P53 mutation is found in 15% of all soft tissue sarcomas, but frequently altered in several other malignant tumors, and therefore greatly exploited for targeted therapy. At this moment, most studies analyzing targeted therapy for these four gene mutations mainly preclude pre-clinical studies, although some have advanced to phase II clinical trials, e.g. ridaforolimus targeting P13K and Palbociclib targeting RB. [10]

Based on genetic alterations soft tissue sarcomas can now be broadly divided into two main categories: 1) genetically simple subtypes with specific genetic alterations most often involving formation of a fusion gene, including the SYT-SS18 fusion in synovial sarcoma, the TLS-CHOP fusion in myxoid liposarcoma and PAX3-FKHR in alveolar rhabdomyosarcoma [11,12], and 2) genetically complex subtypes with multiple numerical and structural aberrations, including e.g. undifferentiated pleomorphic sarcomas, leiomyosarcomas and pleomorphic liposarcomas [13].

Prognostic models

There are several prognostic models for soft tissue sarcoma. Similar to other types of malignancies, a staging system is used to provide information about the extension of the disease, based on both clinical and histological parameters. In addition, a grading system is used to describe the level of malignancy of the

sarcoma, based on solely histological parameters. Other prognostic models have been proposed to aid in predicting patient outcome, combining clinical and histological parameters. An example of such a prognostic model is the SIN (Size, vascular Invasion, Necrosis) model, proposed by the Scandinavia Sarcoma Group (SSG), and used throughout Scandinavia. [14]

Staging

There are three staging systems employed for soft tissue sarcomas, including the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) system [15], the Musculoskeletal Tumor Society System [16], and the Memorial Sloan-Kettering system [17]. The most widely used means for classifying the extent of sarcoma is the TNM system of the AJCC /UICC. This TNM based system is based on the size and extent of the primary Tumour (T), the involvement of regional lymph Nodes (N) and the presence of distant Metastasis (M). In 1977, the TNM classification was extended by adding the histological malignancy grade. [18] Later also tumor depth was included, with a distinction between superficial and deep tumors in relation to the fascia. Nowadays the staging of soft tissue sarcomas is based on the size (T1 ≤5cm or T2 >5cm), depth (Ta superficial and Tb deep), the presence or absence of regional lymph node or distant metastasis. These factors are combined with grade. Large series have confirmed size, depth and grade as important prognostic markers. [19,20]

In the 7th edition of the AJCC/UICC staging system, a specific TNM classification for gastrointestinal stromal tumors was introduced [15], which was validated in a prospective study in 2011 [21]. The use of the TNM classification for retroperitoneal sarcomas is less accurate prognostically, since nearly all retroperitoneal sarcomas are larger than 5cm and deep to the superficial fascia, leading to a minimal classification of stage IIB (low grade) or stage III (high grade). In the most recent 8th edition anatomic location is specifically addressed.

Soft tissue sarcomas mainly metastasize through the hematogenous route, and lymph node metastasis is therefore rare. Nevertheless, when present lymph node metastases represent a group of patients with an adverse prognosis with a 5-year overall survival rate of 35% and, therefore, accordingly classified as stage III in the TNM staging system. [22]

Grading

Histological grade is the best prognostic factor in the majority of soft tissue sarcomas. Grade goes back till the late forties when Broder described as first the malignancy grade of soft tissue sarcomas in the subgroup of fibrosarcomas, by means of mitotic activity, number of tumor giant cells and percentage of fibrous stroma. [23] However, it was only until 1977 that Russel and colleagues proposed to integrate histological grade in a prognostic model with the clinical parameters of the TNM classification. [18] Since then, numerous grading systems have been suggested and today a variety of grading systems are used throughout the world with partly different parameters and number of grades. The two most widely applied grading systems are those of the National Cancer Institute (NCI) and of the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) [24]. The NCI system uses a combination of histological type, cellularity, pleomorphism and mitotic rate. The FNCLCC system is based on a score obtained by evaluating differentiation, mitotic rate and amount of tumor necrosis. Both are three-grade systems. For treatment purposes, the goal of the grade system is to separate patients into a group with a good prognosis (grade 1) and a group with a poor prognosis (grade 3). Therefore, the group with grade 2, corresponding to intermediate malignancy, should be minimized. In a comparative study between the NCI and FNCLCC system, it was demonstrated that both systems highly correlate with prognosis, however, the FNCLCC system had a higher discriminative power to identify patients with high risk. [24] Both staging systems are listed in the latest edition of the World Health Organization classification system of soft tissue tumors. [1]

The College of American Pathologists favors the FNCLCC system, because the NCI system uses parameters – quantification of cellularity and pleomorphism – that are difficult to determine objectively and the FNCLCC may be slightly better in predicting prognosis. [25]

There are limitations to the use of grading parameters. Most of these parameters are subjective and pathologists can disagree on for example the quantification of cellularity, pleomorphism and differentiation. [25] Moreover, a single parameter can not simply be applied to all subtypes, e.g. mitotic count is low in clear cell sarcoma, but this subtype has a high risk of metastasis. [26,27]

SIN prognostic model

The SIN prognostic model was introduced in 1994, and is the result of the collaboration between Scandinavian countries. The SIN system combines size (S), vascular invasion (I) and necrosis (N). In the original description of the system, size was dichotomized at 10 cm, and necrosis was microscopically evaluated and described as present if a focus larger than 4mm was observed. Vascular invasion was dichotomized as present or absent. In 2003, Gustafson et al. revised the SIN system and dichotomized size at 8 cm, which was closer to the median of a population based study. [14] In addition, they found that necrosis, however small, had significant prognostic relevance and re-dichotomized necrosis as present or absent irrespective of extent. [14]

The SIN system is a two-tiered system, dividing patients either into the group with low risk for metastasis (none or only one of the following three factors; tumor size >8 cm, vascular invasion, or microscopic tumor necrosis) or into the group with high risk for metastasis (two or three of these factors). Based on this score, the low and high risk groups differ highly significant.

The reproducibility of the revised SIN model has been assessed in collaboration with pathologists of Bordeaux and Boston. [14] A kappa of 0.77 (good agreement) for inter observer variation in the assessment of overall grading was found. Using the series of Bordeaux, consistent predictions of the five-year metastasis free survival were measured. They concluded that the SIN model offers a reproducible and favorable stratification for patients with low and high risk for metastasis.

Sarcoma biomarkers

Ideally, biomarkers distinguish between different prognostic subsets. Good prognosis groups that encompasses all tumors with very low metastatic potential that may be managed by surgery alone – from the poor prognosis group – which include all tumors with high potential for metastasis and for which (neo-)adjuvant therapy might reduce the risk of metastasis. Many biomarkers have been studied, and the quest to identify new biomarkers is continuously ongoing. This search is influenced by various bias. Sampling errors may cause bias and evaluation risks being performed in non-representative tumor areas. Tumor heterogeneity

has an impact on biomarker scoring. Whole-tumor evaluation may increase reproducibility, but is not an option if neo-adjuvant treatment is used. In addition, the rarity of soft tissue sarcomas and the variety of subtypes implies that study populations are typically restricted in size. Furthermore, to collect a significant number of patients, a long time span is often necessary and may include different treatment strategies that may not be directly comparable. From a statistical point of view, many studies limit their results to univariate analysis. This usual raise the expectation of valuable new biomarkers, but when they are analysed in multivariate analysis including other prognostic markers, their value loses statistical significance. Another important part of the process in evaluating new biomarkers is the reproducibility of the results. A good biomarker should be easy to score, show high reproducibility and should be interpreted according to strict rules.

The future for biomarkers depends not only on the use of prognostic or differential diagnostic marker, but also as predictive markers related to precision medicine. The unraveling of the genetic pathways has given us insight in the tumor growth and tumor sustainability. Elucidating the biology of gene fusions or mutations and their protein products may provide targets for novel therapeutic intervention.

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