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"…diagnosis and prognosis need to be taken to a higher level if any impact is to be made on the modest survival of high-risk patients."

Historical background

John Abernethy (1764–1831) first introduced the term 'sarcoma', which in Greek means a fleshy excrescence, to describe a circumscribed neoplasm consisting of malignant fat cells occurring principally in the trunk [1]. Almost 200 years later, over 30 types of soft-tissue sarcoma have been described, and many of these are accompanied by innumerable subtypes [2]. Despite the wide range of entities, sarcomas today only represent less than 1% of all cancers, but still represent one of the more scientifically and therapeutically challenging groups of tumors.

"Following the introduction of strict criteria of surgical margins, the control of local recurrence with surgery improved…"

The aggressive nature of sarcoma, including that of bone, was alluded to by the surgical pathologist Samuel Gross, when he said, "Next to carcinomata of the soft parts, the sarcomata are the most malignant of all neoplasms, as is evinced by the local infection of the adjacent tissues. They show a great disposition to recur locally after extirpation, so that in the performance of an operation for their removal, the rule should be to amputate as far as possible from the seat of disease" [3]. Indeed, 75 years later, the sentiment was no different, with some suggesting that "the worse thing that could happen was local recurrence" [4]. It has taken almost 100 years from the time of Gross to recognize that local recurrence following tumor excision is less a reflection of the tumor than that of the quality of surgery to remove it. The indifferent manner in which soft-tissue tumors were excised was due to a lack of clear guidelines for the treatment that sarcomas mandated. Enneking proposed a classification of surgical margins, including intralesional, marginal, wide and radical margins, which correlated with decreasing incidences of local recurrence [5]. Following the introduction of strict criteria of surgical margins, the control of local recurrence with surgery improved, and this was significantly enhanced by the addition of radiotherapy, giving local recurrence rates of less than 10% [6–8].

Today's challenges

While the challenge of local recurrence seemed to have been addressed, the dilemma of distant metastasis remains even today. Despite improvements in local control of disease, little advance has been made on the overall survival of patients, with up to 50% of patients succumbing to their disease [9]. This suggests that metastasis has already occurred by the time of initial diagnosis, and the impact of surgery is limited to local disease. Indeed, 10% of patients have metastatic disease at diagnosis [10–12], while a further 25% of patients with localized disease subsequently develop distant spread [13,14]. The most common site for metastatic spread is the lungs. Thus, systemic chemotherapy would seem the obvious choice in dealing with disseminated disease, and doxorubicin was one of the first drugs that tumor centers focused on [15,16].

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An early meta-analysis had suggested that the addition of adjuvant chemotherapy had a beneficial effect on overall survival [17]; but it was not till a quantitative meta-analysis of updated data from individual patients from all available randomized trials was performed that evidence was put forward which showed a statistically significant improvement in local and distant recurrence-free survival and overall recurrence-free survival [18]. Disappointingly, despite the inclusion of 14 trials with 1568 patients, this meta-analysis was unable to demonstrate more than a trend for improved overall survival. The failure of chemotherapy to produce the desired effect may be a consequence of a number of factors, including the poor selection of candidates for chemotherapy, the admix of low-risk patients and heterogeneity of tumors within treatment groups, the assumption that all sarcomas behave similarly or respond to chemotherapy in the same manner, and the lack of an ideal cytotoxic agent. The challenge then was to find a prognostic factor, or series of prognostic factors, that would identify patients at most risk of metastasis to form the basis of controlled trials of chemotherapy. It was a reasonable assumption that tumors with the most malignant features would have cellular machinery most susceptible to the effects of chemotherapy.

Prognostic factors

As would be anticipated, the search for characteristics of tumors that manifest a predictive value for the development of metastases revealed a wide range of independent factors. Many of these related to the histomorphology of the tumor, while others related to its local behavior.

Size

Tumor size is an independent prognostic indicator [10,11]. Size greater than 5 cm is associated with a poorer metastasis-free survival. Some have shown that the risk of metastasis may extend beyond the intermediate term (5 years) for small yet high-grade tumors, and these should be followed beyond 5 years to exclude the possibility of late presentation of metastasis [19,20].

Depth

Tumors that arise deep within the deep fascia have been implicated in a higher metastatic rate [14]. There is, however, a division of opinion regarding the validity of this [21]. One multivariate analysis showed no major prognostic effect of tumor depth when grade and size were taken into account [21]. In this population-based study, the mean size of small tumors was the same whether superficial or deep, but the mean size of large and deep-seated tumors was a third larger than that of large but superficial tumors. Tumor depth was shown to influence the prognosis in the subset of high-grade and large tumors, but the poorer survival rate of deep-seated tumors in comparison with superficial tumors could be explained by the larger mean size of the deep-seated tumors.

Site

Extracompartmental tumors have twice the metastatic rate of intramuscular tumors, and almost five-times the metastatic rate of subcutaneous tumors [11]. Retroperitoneal tumors had a worse prognosis than limb or truncal tumors [22,23], although this is likely to be related to the inability of the surgeon to resect the tumor totally than to the biology of the tumor itself. Retroperitoneal tumors also occupy a larger space cavity and, in comparison with extremity sarcoma, often reach a very large size prior to diagnosis. Thus, the rate of metastasis is related less to the site of the retroperitoneal sarcoma and more to the size of the tumor.

Growth pattern

soft-tissue sarcomas with a microscopically 'infiltrative' growth pattern, as determined on whole tumor sections, have a significantly higher risk for local and systemic recurrence compared with lesions with a 'pushing' growth pattern [24].

> "...10% of patients have metastatic disease at diagnosis, while a further 25% of patients with localized disease subsequently develop distant spread."

Histotype

The heterogeneity of soft-tissue sarcomas is likely to be an important factor behind the differences in metastatic behavior of the group. For example, liposarcoma is recognized by a number of different subtypes, namely, lipoma-like liposarcoma, myxoid liposarcoma, round cell liposarcoma and pleomorphic liposarcoma. Although these are united as a genus by the demonstration of lipoblasts, the propensity to metastasize differs widely, with lipoma-like liposarcoma having a minimal incidence of metastasis, while pleomorphic liposarcoma or the round cell variant of liposarcoma have a high risk of metastasis [25–28]. Similarly, the risk of metastasis differs between myxoid malignant fibrous histiocytoma (MFH) and pleomorphic MFH [28]. Tumors such as synovial sarcoma, rhabdomyosarcoma and Ewing's sarcoma are considered high-risk tumors, while dermatofibrosarcoma protuberans, a dermal sarcoma with aggressive local features, is regarded as having low risk for metastasis [29,30].

Patterns of metastatic spread

The manner in which soft-tissue sarcoma metastasize may have bearing on the manner in which these metastases are treated and, therefore, the subsequent outcomes. Specifically, most soft-tissue sarcomas demonstrate a predilection for the lungs. Some histotypes, however, target other sites for metastasis, and these sites may impede our ability to treat them effectively. For example, synovial sarcoma, rhabdomyosarcoma and epithelioid sarcoma are known for their increased incidence of lymphatic spread [31,32]. Alveolar soft-part sarcoma has a predilection for the brain [33–35]. It has

been found that gastrointestinal stromal tumors (GISTs) have a predilection for the liver [36], while true leiomyosarcomas of the intestinal tract metastasize to the lungs [37]. Pulmonary resection of sarcoma is an established means of prolonging disease-free survival [38,39], while management of intracranial and hepatic metastases is more problematic.

Responsiveness to chemotherapy

Despite the heterogeneity of soft-tissue sarcomas, the standard of care has long grouped these neoplasms as if they were a single entity. It is becoming more apparent that the response to chemotherapy may be stratified by the histologic type, and that successful chemotherapy regimes will require acknowledgement of this [40]. For example, rhabdomyosarcomas are relatively sensitive to conventional chemotherapy, especially the embryonal subtypes that occur in the pediatric age group [41,42]. Myxoid liposarcoma is another group that appears to be responsive to chemotherapy despite being low grade, while the dedifferentiated form of liposarcoma is not. GISTs are not responsive to standard doxorubicin-based therapy, yet respond to specific targeted molecular therapy in a most impressive way [43]. Synovial sarcoma may be a histotype that is responsive to ifosfamide-based therapy [44].

Histologic grade

Histologic grading is considered an independent prognostic factor for soft-tissue sarcomas [45]. Grading is a method of categorizing soft-tissue sarcomas into groups that range from low to high risk of metastasis, and is based on a number of cytomorphologic features including, but not limited to, cellularity, necrosis, vascular invasion, nuclear atypia, presence of malignant giant cells, tumor differentiation, pleomorphism, histotype, presence and nature of matrix, and mitotic activity [45]. The use of grading systems for soft-tissue sarcoma followed from the initial work of Broders on squamous carcinoma of the lip [46], and a subsequent report on fibrosarcoma [47].

While appearing logical in approach, the numbers of grading systems attest to the lack of consensus as to which features should be included into a grading system, as well as a recognition that there are a number of confounding factors that may influence the accuracy of all grading systems, including: patient selection bias, incomplete clinicopathologic information, the influence of variable and uncontrolled treatment within groups, uneven representation of histotypes, sampling errors, variation in preparation of specimens, and statistical methodology. Added to this is the subjective nature in which many objective criteria are measured. Authors who have employed the 4-grade Broders criteria for grading have alluded to the subjective nature of this system for assessing differentiation [48], and this sentiment is expressed further in another 3-grade system where the authors stated that "the final evaluation of the degree of malignancy was based on subjective evaluation and an assessment of all factors, and was not necessarily contingent on the number of mitotic figures or any single characteristic" [49].

A good grading system should easily delineate between low- and high-risk metastatic groups, and be reproducible amongst pathologists. In this regard, it is interesting how variable the emphasis is on different prognostic factors in the many modern grading systems that exist [50–54]. The common thread throughout these grading systems, however, is the reliance on mitotic activity and necrosis to define the final grade. One of the more well-known systems was developed at the National Cancer Institute (USA) and is frequently known as the NCI system [50]. Unlike the more rudimentary systems that predated it, the hallmark of the NCI grading system was the strict codification of criteria. Following this benchmark, the French system (French Federation of Cancer Centers [FNCLCC]) developed a three-tiered grading system that relied on the identification, from multivariate analysis, of three independent prognostic factors, namely necrosis, mitotic activity and degree of differentiation [55].

> "Size greater than 5 cm is associated with a poorer metastasis-free survival."

The NCI and French grading systems dominate in North America and Continental Europe, respectively, and are similar not only in their reliance on tumor necrosis, but also the recognition that histotype was important. Ironically, the weakness of the NCI system is the risk of error when trying to identify and procure representative samples of necrotic tumor. This is particularly relevant where needle biopsies are used. Similarly, a major weakness of the French system is the fact that the assignment of a differentiation score relies on the presence of tissue resembling normal tissue. This is not always applicable with tumors such as MFH where the histologic characteristics, such as the storiform pattern of MFH, have no normal counterpart against which to estimate differentiation. Although both systems have well-defined criteria, the application of these criteria to formulate a grade does fall victim to a significant degree of subjectivity.

It is also clear that not all grading systems apply similarly to each known histotype of sarcoma. Indeed, certain sarcomas define their behavior by histotype rather than grade. For example, lipoma-like liposarcoma do not generally recur or metastasize, while round cell liposarcoma are well known for their systemic aggressiveness if more than 15% of the cellular population consists of round cells [27]. Other sarcomas, such as epithelioid sarcoma, clear cell sarcoma and alveolar soft-part sarcoma, are so rare that their known histologic and non-histologic characteristics are not of accurate or reliable prognostic value. Still others, such as synovial sarcoma, are notoriously difficult to assign a behavior based on histologic features and, yet, have been regarded as high grade. More recently, Bergh *et al.* have been able to combine clinicopathologic features to develop a grading system for synovial sarcoma based on size, age of patient and the degree of poorly differentiated areas [56].

Although mitotic activity and necrosis are two important factors to be included in most grading systems, their use is not without caution. For example, different microscope specifications, variations in thickness of tissue specimens, tissue fixation times, number of visual fields scanned, number of cells within visual fields, intratumoral variability and sampling errors may confound the reliability of these two factors. Concerns have also been raised regarding the value of necrosis, because of the strong relationship that this parameter has with size [57]. However, other studies have also assessed necrosis as being an independent prognostic factor after adjustment for tumor size [51,54]. Differences in these results may be attributed to the nonlinear association between tumor necrosis and tumor size [58], the balance between tumor proliferation and apoptosis [59], angiogenesis [60] and tumor–host interactions [61].

> "Aneuploid DNA content has been correlated with a poorer prognosis..."

The logistics of tissue biopsy also pose a problem to the reliability of assessing many histologic variables, including mitotic activity and necrosis. The movement towards needle biopsy, while pursued in the interest of reducing patient morbidity [62–64], may result in procurement of tissue from nonrepresentative areas. This potential hazard, however, has not impeded the progression towards needle biopsy. For example, the use of needle biopsies increased from 10 to 80% between 1991 and 1995 at the Memorial Sloan Kettering Cancer Center [65]. In another institution where needle biopsy is the preferred technique, it discriminated benign from malignant soft-tissue tumors with a sensitivity greater than 98%, and pathologists were able to correctly identify histologic subtype in 80% and grade in 85% of sarcomas [66].

Staging systems

Staging systems combine the histologic grade with the extent of local and systemic disease to predict survival. Increasing stage is inversely correlated with survival. The American Joint Committee on Cancer (AJCC) staging system is based on histologic grade, primary tumor size, lymph node involvement and distant metastases [67]. Although grade in the AJCC system is divided into four categories, namely well-differentiated (grade 1), moderately differentiated (grade 2), poorly differentiated (grade 3) and undifferentiated (grade 4), the significance of the histomorphological differences between grades appear to be less important by the amalgamation of grades 1 and 2, and grades 3 and 4 in the staging system. In contrast, the Musculoskeletal Tumor Society (MSTS) surgical staging system stratifies tumors according to histologic grade, intra- or extracompartmental extent of the primary tumor, and the presence of distant metastases [5]. Unlike the AJCC staging system, size is not a variable in the MSTS system, which seems unusual since size has been shown to be a strong and independent prognostic factor for survival. Like the AJCC system, the MSTS staging system dichotomizes grades into low (grades 1 and 2) and high (grades 3 and 4) grade, according to Broder's criteria [47]. A comparison between the AJCC, MSTS and a third system (MSKCC) demonstrated the superiority of the AJCC system for predicting distant metastases [68]. It is noteworthy that the reproducibility of the AJCC system has not been tested.

Local recurrence as a predictor of metastasis

Despite improvements in local control of disease, the development of systemic metastases seems to depend largely on the biologic characteristics of the tumor. The earlier concept linking local recurrence causally to metastasis has largely been abandoned, and the current view is that, in the presence of adequate surgical margins, local and systemic recurrence results from an intrinsically aggressive biological behavior of the primary tumor. It is important, however, to consider the prognostic value of local recurrence, should it occur, in predicting subsequent metastasis. Surprisingly, there is a dearth of information in the literature regarding the prognostic value of local recurrence for systemic metastasis. One article that referred specifically to this relationship showed that the growth rate of local recurrence, from the time of primary tumor excision till diagnosis of the recurrence, was a potent independent predictor of metastasis [69].

Nonmorphologic prognostic factors

Subcellular characteristics have added to the wealth of information that may be predictive of biologic behavior of sarcomas. Aneuploid DNA content has been correlated with a poorer prognosis [70]; proliferative activity, as reflected by S-phase fraction, silver staining for nucleolar organizer regions, Ki-67 and PCNA, has also been correlated with survival [71–74]. The expression of oncogenic and tumor-suppressor proteins, such as Bcl-2, MDM2, retinoblastoma gene product and p53, are some of the more well-published molecules that have been associated with prognosis in soft-tissue sarcoma [24,75–78].

Molecular characterization of soft-tissue sarcoma

The limitations of light microscopy are giving way to the rapidly expanding field of molecular pathology. Genetic signatures are being recognized that serve not only as diagnostic, but also prognostic markers. soft-tissue sarcomas are characterized by a large number of chromosomal translocations, some of which are unique to the tumor type [79]. For example, the identification of t(x:18) in a tumor provides a high degree of certainty to the diagnosis of synovial sarcoma. Recently, the isolation of the SYT–SSX gene fusion product in synovial sarcoma has sharpened prognostication to a previously unknown level [80–82].

Comprehensive analysis of molecular characteristics of cells and tissue has recently become more widely available. Gene arrays are tools for profiling protein expression, allowing evaluation of expression levels of thousands of genes simultaneously. Microarray data sets are appealing in that they have a theoretical capacity to capture a picture shot of gene expression at a given point in time. This technique not only provides information about the expression of every single gene represented within the

microarray, but also provides a survey of gene interactions and pathways. Therefore, it is able to provide a snapshot of molecular interactions in a depth previously unheard of. In contrast to most other ancillary techniques available to surgical pathologists, including immunohistochemistry, *in situ* hybridization and PCR, which all look at usually only one marker at a time, gene arrays are capable of providing a vast amount of data.

> "...histologic groupings of today may make way for functional genetic groupings..."

However, this new technology also has problems and pitfalls. Analysis of microarrays is demanding and requires several steps, including normalization, and filtering for data quality and probable biologic interest. In addition, such huge data sets are prone to random correlations and false discoveries, which is a real problem if no specific hypothesis is tested and where data computing is adapted during the process of analysis rather than applied in a standardized fashion, defined up front. It is therefore critical to develop a careful study design and statistical approaches beforehand [83].

This technique, introduced in 1995 [84], was shown to be applicable to musculoskeletal soft-tissue tumors [85]. However, only a few groups are using this relatively new technology to further characterize soft-tissue sarcoma. Using array-based gene expression analysis, Francis *et al.* recently reported that genes related to hypoxia predict metastatic potential in pleomorphic high-grade sarcoma [86]. Others have reported that upregulated signal transduction genes of the cell cycle were a feature of a gene signature prognostic of metastasis in leiomyosarcoma [87]. Similarly, a genetic signature in synovial sarcoma has been related to the development of metastases, albeit with a high false-positive rate [88].

Targeted therapy

Advances in subcellular techniques have permitted researchers to probe and dissect out the molecular processes that are important for the survival and progression of soft-tissue sarcomas. This information will contribute valuable knowledge that may enhance our ability to successfully treat high-risk patients. Understanding important aspects of tumor biology will be fundamental to developing future strategies of targeted therapy [89]. Such mechanisms may include resistance to chemotherapy via several mechanisms, including drug transporting proteins [90], alternative pathways to cell death, such as death receptor ligands [91] and receptor tyrosine kinase inhibitors, and the tumor-initiated protection against apoptosis that is mediated by P-glycoprotein and the MDR-associated protein family (e.g., MRP1) [92]. One of the best examples of targeted therapy in soft-tissue sarcomas is in the modern management of GISTs. GISTs characteristically manifest c-kit activation, which has a physiologic role in regulating the proliferation and differentiation of the progenitors of GISTs [93]. The management of GISTS has been problematic in the past because of their strong resistance to conventional chemotherapy [94]. Exposure to STI-571, a small-molecule inhibitor of c-kit tyrosine kinase, leads to apoptosis in GIST cells [95]. This treatment has profoundly modified the manner in which this tumor is now treated. A similar effect of STI-571 has also been reported in dermatofibrosarcoma protuberans [96].

Conclusion

Histopathologists have made a tremendous contribution to the identification of prognostic factors in soft-tissue sarcoma and the subsequent development of grading and staging systems. It is clear, however, that diagnosis and prognosis need to be taken to a higher level if any impact is to be made on the modest survival of high-risk patients. The management of soft-tissue sarcomas in the future will be driven by a combination of high-tech molecular analyses to define as accurately as possible the specific identity of individual sarcomas. This will allow them to be allocated to tumor groups whose functional genetic profile have been accurately characterized by techniques such as microarray analysis. It is conceivable that the histologic groupings of today may make way for functional genetic groupings, especially if correlations between biologic behavior and treatment responsiveness can be identified. This will facilitate the introduction of cytotoxic and/or radiation therapy that is most efficacious for a particular tumor type. Identification of the tumor-specific regulators of the processes involved in the metastatic cascade will add a new arm of treatment that specifically targets pivotal steps in tumor progression and metastasis.

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