Treatment of Soft Tissue Sarcomas

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Cancer Treatment and Research

Foreword

Where do you begin to look for a recent, authoritative article on the diagnosis or management of a particular malignancy? The few general oncology textbooks are generally out of date. Single papers in specialized journals are informative but seldom comprehensive; these are more often preliminary reports on a very limited number of patients. Certain general journals frequently publish good in-depth reviews of cancer topics, and published symposium lectures are often the best overviews available. Unfortunately, these reviews and supplements appear sporadically, and the reader can never be sure when a topic of special interest will be covered.

Cancer Treatment and Research is a series of authoritative volumes that aim to meet this need. It is an attempt to establish a critical mass of oncology literature covering virtually all oncology topics, revised frequently to keep the coverage up to date, easily available on a single library shelf or by a single personal subscription.

We have approached the problem in the following fashion: first, by dividing the oncology literature into specific subdivisions such as lung cancer, genitourinary cancer, and pediatric oncology; second, by asking eminent authorities in each of these areas to edit a volume on the specific topic on an annual or biannual basis. Each topic and tumor type is covered in a volume appearing frequently and predictably, discussing current diagnosis, staging, markers, all forms of treatment modalities, basic biology, and more.

In *Cancer Treatment and Research*, we have an outstanding group of editors, each having made a major commitment to bring to this new series the very best literature in his or her field. Kluwer Academic Publishers has made an equally major commitment to the rapid publication of high-quality books and worldwide distribution.

Where can you go to find quickly a recent authoritative article on any major oncology problem? We hope that Cancer Treatment and Research provides an answer.

William L. McGuire
Series Editor

Preface

One of the major advances of the last decade concerning the treatment of patients with soft tissue sarcomas is that an increased number of patients are being discussed in multidisciplinary teams prior to the initial treatment. The present volume on soft tissue sarcomas in the series *Cancer Treatment and Research* reflects the multidisciplinary approach with a focus on recent developments.

The availability of new histopathologic techniques has reduced the number of unclassified sarcomas and has further increased the importance of the histopathologist in providing estimates of the prognosis of the patient as well as data for the planning of treatment strategy. Further data for this strategy will be provided by diagnostic imaging. In this field, the role of magnetic resonance imaging has been further defined. Of utmost importance is the recent trend toward consensus in staging. The modification of the staging system of the American Joint Commission for Cancer Staging and End Results Reporting brings the possibility of a single staging system within reach in the next decade.

As surgery still provides the only chance for cure, the importance of being the most sparing as possible is obvious. For this reason, radiotherapy has been applied with success. The introduction of relatively new radiation techniques is therefore being observed with interest.

As for staging, there is also growing consensus about the role of chemotherapy in advanced disease. More and more trials have addressed the activity of the few truly active drugs, the most important being doxorubicin, ifosfamide and dacarbazine (DTIC). The answer to the question of whether single-agent chemotherapy is as effective as combination chemotherapy may be answered in the next few years. The lack of efficacy of adjuvant chemotherapy with the drugs presently available has definitively been demonstrated. Chemotherapy, however, may have an important role in the preoperative treatment of soft tissue sarcomas, although the optimal method of administration has yet to be defined.

A new topic in the present volume is thermochemotherapy, a combined-modality treatment with interesting preliminary results. Although the present volume focuses on new developments, previously obtained data are also briefly

reviewed. With this in mind, we have invited a number of new authors to contribute to the present volume in order to extend its scope with regard to the present state of the art. We would like to thank all authors for their contributions.

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Abbreviations

ADIC	=	Adriamycin (doxorubicin)–DTIC
AIDS	=	acquired immune deficiency syndrome
AJC	=	American Joint Commission for Cancer Staging and En. Results Reporting
CAP	=	Cytoxan (cyclophosphamide), Adriamycin (doxorubicin) CDDP (Platinol)
CDDP	=	cisplatin (*cis*-diammine dichloroplatin)
CR	=	complete remission
CT	=	computer tomography
CTX	=	Cytoxan (cyclophosphamide)
CYVADIC	=	cyclophosphamide/vincristine/Adriamycin (doxorubicin)/ DTIC
DACT	=	dactinomycin (actinomycin D)
DSA	=	digital subtraction angiography
DTIC	=	dacarbazine
DX	=	doxorubicin
ECOG	=	Eastern Cooperative Oncology Group
EORTC	=	European Organisation on Treatment and Research of Cancer
G	=	grade
GOG	=	Gynaecologic Oncology Group
HAP	=	hyperthermic antiblastic perfusion
i.a.	=	intra-arterial
IFOS	=	ifosfamide
i.v.	=	intravenous
LPAM	=	L-phenylalanine mustard (melphalan)
M	=	metastasis
MDR	=	multidrug resistance phenotype
MFH	=	malignant fibrous histiocytoma
MPNST	=	malignant peripheral nerve sheath tumor
MMS	=	mixed mesodermal sarcoma
MR	=	magnetic resonance
MTS	=	Musculoskeletal Tumor Society
NCI	=	National Cancer Institute

PR	=	partial remission
OS	=	overall survival
RFS	=	relapse-free survival
SWOG	=	Southwest Oncology Group
T	=	tumor
VCR	=	vincristine
VP-16	=	etoposide
VRN	=	von Recklinghausen's neurofibromatosis

Contents

1. Pathology of soft tissue sarcomas

Cyril Fisher

comprising <1% of all malignant tumors. They are a heterogeneous group of tumors with a wide range of biological behavior. They are grouped together on an anatomical basis and present common clinical problems that, together with the rarity of many of the subtypes, dictate a uniform clinicopathological approach. Nonetheless, accurate histopathological diagnosis is essential for management because the grading of soft tissue sarcomas is an integral part of most current staging systems and may be the most important single prognostic factor. Several studies [1–3] have emphasized that, for many sarcomas, prognosis is related directly to the diagnosis, i.e., the precise histological subtype. Thus, synovial sarcoma, epithelioid sarcoma, and rhabdomyosarcoma generally have a poor outlook. Other sarcomas, including many liposarcomas, leiomyosarcomas, nerve sheath tumors, and malignant fibrous histiocytomas have a wider spectrum of behavior and, in grading each case, microscopic details such as cellularity, pleomorphism, amount of necrosis, and mitotic count must be considered.

The basic histological patterns [4] of soft tissue sarcomas are familiar, but this group of tumors still retains considerable diagnostic difficulties for the pathologist. Some sarcomas, such as liposarcoma or rhabdomyosarcoma, resemble embryonic or adult mesenchymal-derived tissues and are readily identified. Others, for example, malignant fibrous histiocytoma and synovial sarcoma, do not have normal counterparts and often manifest a variety of histological patterns. Conversely, different sarcoma subtypes can share common microscopic appearances; a spindle cell morphology can be displayed by synovial sarcoma, leiomyosarcoma, malignant tumors of nerve sheath, rhabdomyosarcoma, malignant fibrous histiocytoma, and the (now rare) true fibrosarcoma. Round cell tumors include Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma and epithelioid sarcoma, and on occasion these require distinction from lymphoma, melanoma, and carcinoma.

Diagnosis depends on the detection of specific features of cellular differentiation, which may not be apparent in ordinary histological sections. The supplementary techniques of immunohistochemistry, electron microscopy, and cytogenetics can often reveal such differentiation in soft tissue sarcomas;

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this not only results in increased accuracy of diagnosis, but has suggested new concepts of histogenesis and challenged established nomenclature. This chapter reviews recent pathological observations for the main sarcoma subtypes, and considers current concepts of grading soft tissue sarcomas.

Classification and frequency

Using standard nomenclature [4], the distribution of diagnoses in a consecutive series of 200 soft tissue sarcomas studied at the Royal Marsden Hospital, London, is shown in Table 1. Malignant fibrous histiocytoma is the commonest category, and fibrosarcoma, if strictly defined (see below), is extremely uncommon. There was no evidence of differentiation by light or electron microscopy or by immunohistochemistry in 3.5% of tumors, and these remain uncategorized.

Malignant fibrous histiocytoma

Malignant fibrous histiocytoma (MFH) is the adult soft tissue sarcoma diagnosed most frequently today. The category now includes many tumors previously considered as fibrosarcoma, pleomorphic rhabdomyosarcoma, or

Table 1. Distribution of 200 sarcomas diagnosed by light and electron microscopy and immunohistochemistry

Diagnosis	No. of cases	(%)
Malignant fibrous histiocytoma	57	(28.5)
Liposarcoma	38	(19)
Rhabdomyosarcoma	26	(13)
Synovial sarcoma	21	(10.5)
Malignant nerve sheath tumor	12	(6)
Extraskeletal osseous tumors	11	(5.5)
Ewing's sarcoma	5	
Chondrosarcoma	3	
Osteosarcoma	3	
Epithelioid sarcoma	7	(3.5)
Leiomyosarcoma	7	(3.5)
Myofibrosarcoma and fibrosarcoma	4	(2)
Fibrosarcoma	1	
Angiosarcoma	4	(2)
Malignant hemangiopericytoma	1	(0.5)
Alveolar soft part sarcoma	3	(1.5)
Clear cell sarcoma	2	(1)
Unclassified	7	(3.5)
Total	200	(100)

indifferentiated pleomorphic sarcoma. While occurring most frequently in he extremities and retroperitoneum, MFH can involve any part of the body [5]. The wide range of histological patterns within this entity includes storiform-pleomorphic, myxoid [6], inflammatory [7], and angiomatoid [8] variants as well as malignant giant cell tumor of soft parts [9]. In general, the tumors are of intermediate or high grade with size and depth from sur face being important additional prognostic factors [10]; the relatively few cases arising superficial to the deep fascia have a good prognosis [5]. Some regard dermatofibrosarcoma protuberans as a superficial MFH, and atypical fibroxanthoma has also been included in this category [4].

MFH was originally designated malignant fibroxanthoma [11]. Tissue culture studies [12] had suggested origin from histiocytes that, it was thought, could behave as facultative fibroblasts. Ultrastructurally, cells with characteristics of histiocytes, of fibroblasts, of both, and of their supposed derivatives (giant cells, myofibroblasts) have been observed [13–16] as well as primitive (supposedly stem) cells. Although of diagnostic use, the lack of specificity of these morphological observations limits their contribution to determining the nature of the tumor. The immunohistochemical detection of alpha-1-antitrypsin and alpha-1-antichymotrypsin supported the hypothesis of histiocytic differentiation [17, 18]. These enzymes were regarded initially as markers for histiocytes, but are now known to be detectable in a variety of other tumors [19], although they remain of use in diagnosing MFH in the appropriate histological context. However, the concept of the histiocytic nature of MFH has been challenged by recent studies with cell type-specific antibodies which showed [20–23] that most markers for cells of monocyte/macrophage lineage were absent from the tumor cells. These immunohistochemical [22, 23] studies, together with enzyme histochemical [22] data, have demonstrated a fibroblastic phenotype, suggesting that this tumor originates from primitive mesenchymal cells rather than histiocytes. The monoclonal antibodies to monocytes/macrophages used in these studies recognize marrow-derived cells, and the histiocyte-like cells in MFH may be of a different lineage. Some cases of MFH have in fact demonstrated monocyte/macrophage markers [20, 24], but this is not necessarily inconsistent with the concept of origin from locally derived pluripotential primitive cells.

Support for this concept has come from the demonstration in MFH of coexpression of intermediate filament subtypes. All MFHs, in common with other mesenchymal tumors, display vimentin and, in some, desmin has been demonstrated, perhaps correlating with myofibroblastic differentiation. The additional expression of neurofilament and cytokeratin [25] in ultrastructurally confirmed cases of these tumors suggests multidirectional differentiation in mesenchymal cells. MFH can arise in, or be associated with, other types of sarcoma and it has been postulated [26] that MFH, representing a dedifferentiated stage, is a final common pathway for other soft tissue sarcomas.

Diagnosis of MFH is usually possible by routine light microscopy. Distinction of pleomorphic tumors from rhabdomyosarcoma can be made utilizing

myoglobin immunohistochemistry, and from liposarcoma occasionally by electron microscopy [27, 28].

Liposarcoma

Liposarcomas are classified by histological appearance into well-differentiated, myxoid, round cell, and pleomorphic types, the first two having a good prognosis and the last two being of high grade [29–32]. It has been suggested [33, 34] that well-differentiated liposarcoma of the extremities (but not of the retroperitoneum) should, because of its excellent prognosis, be reclassified as an atypical lipoma.

The relatively distinctive morphology of liposarcoma, which includes the presence of lipoblasts, means that special diagnostic techniques are rarely required. Pleomorphic liposarcoma can be difficult to distinguish from pleomorphic malignant fibrous histiocytoma, especially as some lipid may be found in cells of the latter, and electron microscopy is sometimes useful here [27]. Electron microscopy can also help in the diagnosis of those myxoid liposarcomas from which typical lipoblasts are absent; primitive lipoblasts often have an external lamina that is absent from the cells of MFH [35, 36]. Some liposarcomas demonstrate S100 protein [37]; this is unlikely to be a source of diagnostic confusion with nerve sheath tumors, and may assist in distinguishing myoxid liposarcoma from myxoid malignant fibrous histiocytoma [38].

A consistent chromosomal translocation, t(12;16), has been reported in myxoid liposarcoma [39].

Rhabdomyosarcoma

The three major histological subtypes of rhabdomyosarcoma characterized by skeletal muscle differentiation are embryonal, alveolar, and pleomorphic [4].

Most interest has centered on the recognition of childhood embryonal rhabdomyosarcomas. Those composed of small cells are likely to be confused with other similar tumors (Ewing's sarcoma, neuroblastoma, and lymphoma); these are myoglobin negative. Alveolar rhabdomyosarcoma is not difficult to diagnose histologically, and pleomorphic rhabdomyosarcoma, occurring in adults, has become a rare tumor since the recognition that many cases previously so identified are in fact liposarcomas or malignant fibrous histiocytomas.

The immunohistochemical demonstration of specific or semispecific markers for muscle differentiation has made the diagnosis of rhabdomyosarcoma much easier. Myoglobin, which is specific for skeletal (and cardiac) muscle, is demonstrable in 60%–90% of embryonal rhabdomyosarcomas [40–43] and in all alveolar and pleomorphic rhabdomyosarcomas [41]. In embryonal tumors, however, myoglobin is detectable only in cells with a sufficient amount of cytoplasm. Desmin is demonstrable in many embryonal rhabdomyosarcomas [44], although the reported sensitivity of its detection varies between 50% [45]

and 100% [46]. This intermediate filament is also present in smooth muscle, but the morphological and clinical differences from rhabdomyosarcoma should prevent confusion. Furthermore, the other histologically similar tumors of childhood lack desmin. Other markers advocated for diagnosis of rhabdomyosarcoma include myosin, which appears to be less sensitive than desmin [47], creatine kinase [48], beta-enolase [49], and Z protein [50], but none of these has been sufficiently assessed for specificity in routine diagnostic use.

Skeletal muscle differentiation is characterized ultrastructurally by the presence of thick and thin intermediate filaments with or without Z-band formation [51]. Unfortunately, such features can be detected in only about half of all embryonal rhabdomyosarcomas [52], and therefore electron microscopy has less to offer than immunohistochemistry in this area. Kahn et al. [48] compared electron microscopy with immunohistochemistry and found that only 37% of childhood embryonal rhabdomyosarcomas were myoglobin positive, whereas 54% of the cases examined showed the characteristic ultrastructure. In a study at the Royal Marsden Hospital, London, 13 (76%) of 17 embryonal rhabdomyosarcomas displayed myoglobin positivity, whereas only 8 (47%) could be diagnosed by electron microscopy.

A consistent chromosomal translocation, t(2;13), has been demonstrated in examples of alveolar rhabdomyosarcoma [53].

Malignant peripheral nerve sheath tumors

About 12% of soft tissue sarcomas show nerve sheath differentiation; they may arise in recognizable nerve trunks, in neurofibromas, or without any discernible nervous connection. Since they are not always composed of Schwann cells or of fibroblasts, and since they may be considered to be of neuroectodermal origin, the term malignant peripheral nerve sheath tumor (MPNST) [54] is preferable to malignant schwannoma or neurofibrosarcoma, unless the cellular composition has been demonstrated by immunohistochemistry and electron microscopy. About half of these tumors are associated with von Recklinghausen's neurofibromatosis (VRN) [55], in which there is at least a 5% chance of malignant change. The rest are sporadic, although the incidence of these may be somewhat higher than generally reported, as a number of cases without obvious neural origin are, without electron microscopy, incorrectly diagnosed as fibrosarcoma or MFH [56]. Histological patterns include a spindle cell type with characteristic nuclear morphology, a rare epithelioid variant resembling melanoma or carcinoma [57], and a pleomorphic MFH-like tumor seen more frequently complicating VRN. Heterotopic epithelial or cartilaginous metaplasia is occasionally seen [58, 59] and a skeletal muscle component is present in the high-grade triton tumor [60–63].

Ultrastructurally, nerve sheath tumors may be shown to be composed of two major cell types, the Schwann cell (Fig. 1) and the perineurial cell (Fig. 2) [54, 64, 65] although most authors [66–70] have sought or recognized only Schwann cells. Both types are present in some neurofibromas, but in a per-