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Leiomyosarcoma

An Overview of Etiology, Prognosis, and Treatment Options

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Contents

Abstract

Approximately 2400 people were diagnosed with leiomyosarcoma in 2004 in the US. This rare tumor of connective tissue is clinically subdivided into uterine and nonuterine leiomyosarcoma. No predisposing factors are known, and presentation is usually related to mass involvement and intrusion of adjacent structures.

Tissue obtained for the initial diagnosis should be of sufficient quantity to evaluate the grade of the tumor, and a full work-up for the extent of disease must include chest, abdomen, and pelvic imaging.

For localized disease, the standard of care remains limited to surgical excision. Radiation therapy can be considered for larger tumors and/or positive margins if anatomically feasible. Adjuvant chemotherapy has not been proven to be effective and remains investigational. Treatment for metastatic disease is palliative. Active agents include doxorubicin, ifosfamide, gemcitabine, and docetaxel. The last two agents in combination have recently been shown to be highly active in uterine leiomyosarcoma in the metastatic setting and are now being further pursued at the Memorial Sloan-Kettering Cancer Center (New York, NY, USA) in both the adjuvant uterine leiomyosarcoma setting and in the nonuterine leiomyosarcoma metastatic setting.

Patients diagnosed with leiomyosarcoma should be referred to specialty sarcoma centers and encouraged to participate in clinical trials.

Leiomyosarcoma is a malignant tumor of smooth muscle cells that may arise anywhere smooth muscle cells exist. Common sites include the smooth muscle component of the uterus and the muscularis layers of the gastrointestinal tract and large blood vessels. Traditionally, leiomyosarcoma has been divided into uterine and nonuterine (soft-tissue) leiomyosarcoma.

Uterine sarcomas represent approximately 1% of gynecologic malignancies and <5% of all uterine corpus cancers.[1] The incidence of leiomyosarcoma amongst all uterine sarcomas is estimated to be between 30%[2] and 50%.[3] Based on US annual incidence data for 2006,[4] which included 321 000 cases of all gynecologic malignancies and 40 000 cases of uterine malignancies, there were approximately 1000 cases of uterine leiomyosarcoma. Similarly, leiomyosarcoma accounted for 15% of the approximately 6000 cases of soft-tissue sarcoma recorded in the Memorial Sloan-Kettering Cancer Center (MSKCC) sarcoma pathology database between 1982 and 2003. Based on an annual incidence of 9500 cases of soft-tissue sarcoma (according to the American Cancer Society 2006 statistics),[4] 1400 cases of soft-tissue leiomyosarcoma occurred in the US in 2004. The relatively small number of cases and the diversity in the anatomic site and biologic behavior of leiomyosarcoma makes a comprehensive understanding of this condition challenging. This article provides on overview of the etiology, prognosis, and management options for leiomyosarcoma.

1. Etiology and Risk Factors

Unlike several other subtypes of sarcoma, leiomyosarcoma does *not* involve specific genetic alterations such as fusion genes due to reciprocal translocations and/or specific point mutations. Instead, leiomyosarcoma displays complex unbalanced karyotypes representing numerous genetic losses and gains.[5] Either causatively or consequently, alterations in the tumor suppressor genes *RB1*[6] and *TP53*[7] are detected in a substantial proportion of leiomyosarcomas. A genetic or familial predisposition to leiomyosarcoma has not been identified.

Radiation has been identified as a risk factor for the development of soft-tissue and bone sarcomas;[8] however, most patients with leiomyosarcoma have no prior history of radiation exposure. Despite multiple reports linking chemical carcinogens (e.g. dioxins and pesticides) and sarcomas,[9,10] a causal relationship remains to be proven. There is sufficient evidence to link sarcomas to exposure to vinyl chlorides and arsenic; however, this relationship is limited almost exclusively to hepatic angiosarcomas.[11]

Uterine leiomyosarcoma has been diagnosed in women treated with tamoxifen for breast cancer.[12] Uterine sarcoma is extremely rare in tamoxifen recipients, being estimated to occur in 0.17 per 1000 users per year. However, this represents a 10-fold increase in risk compared with women who have never been exposed to tamoxifen. One study estimated that since 1978, <200 cases of uterine sarcoma have developed worldwide in women taking tamoxifen.[13] Although women should be cautioned about the increased risk of uterine cancers (including sarcomas) with tamoxifen use, the benefits of tamoxifen in terms of breast cancer treatment greatly outweigh the risk of uterine cancer.[14,15]

2. Diagnosis and Staging

2.1 Presentation

Soft-tissue tumors may be benign or malignant; a variety of lesions of borderline malignant potential are also recognized. The ratio of benign to malignant tumors is >100 : 1,[16] and benign tumors are not believed to evolve into malignant tumors.[17] An excellent clinical example of this observation is uterine fibroids. Although uterine fibroids are very common, there is little or no risk that this histologically benign lesion will progress and/or develop into a leiomyosarcoma. However, leiomyosarcoma may co-exist in a uterus that also contains benign fibroids.[18] Imaging studies may be helpful in assessing the characteristics of uterine masses that suggest malignancy.[19]

Although leiomyosarcomas may arise in any site containing smooth muscle, more than half are located in retroperitoneal or intra-abdominal sites. In these locations they often present as fairly large masses with vague, nonspecific symptoms.

Uterine leiomyosarcomas may present with pelvic pain or pressure, or abnormal vaginal bleeding.[20,21] Extremity leiomyosarcoma most frequently arises in the thigh and may be associated with medium or large veins.[22] Rarely, leiomyosarcoma may arise in large vascular structures and present with symptoms of obstruction to the normal flow of blood.[23] The most common arterial site is the pulmonary artery; patients may present with symptoms of decreased pulmonary outflow. Leiomyosarcoma of the inferior vena cava may present with Budd-Chiari syndrome, with obstruction of hepatic veins. Involvement of the middle portion of the inferior vena cava may result in blockage of renal veins and renal dysfunction, whereas involvement of the lower portion may cause leg edema.[24] Cutaneous leiomyosarcomas usually appear as small, solitary, extremity nodules.[25] Accurate diagnosis requires an adequate and representative biopsy or excision of the tumor with careful histologic review for correct subtyping of soft-tissue sarcoma (see section 2.2).

2.2 Tissue Diagnosis and Pathology

The objective of a biopsy in the management of soft-tissue sarcomas is to obtain adequate tissue for definitive histopathologic confirmation of the diagnosis, to evaluate the tumor grade, and to identify prognostic factors that may alter the approach to definitive treatment. For lesions that are <5cm in size and superficial, an excisional biopsy is generally preferred.

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Uterine leiomyosarcomas are often found at the time of hysterectomy performed for what may have been thought to be benign disease prior to surgery. If leiomyosarcoma is suspected intraoperatively or suggested by frozen section, an attempt should be made to excise all visible tumor; however, routine lymph node dissection is not required if the lymph nodes appear normal.

There is no single standard approach for nonuterine, nonsuperficial soft-tissue sarcomas, whether the tumor is a leiomyosarcoma or of a different sarcoma histology. The utility of a Tru-Cut biopsy versus a fine needle aspiration as a first-line diagnostic option has been studied extensively. Some studies have shown that, upon independent review, a Tru-Cut biopsy improves both diagnostic accuracy and tumor grading.[26] Fine needle aspiration is usually favored for confirmation of recurrence rather than for primary diagnosis.[27] Others have argued that no open biopsy is indicated, fearing local tumor spread which would increase both the extent of the definitive operation and the need for adjuvant radiation therapy.[28] Nevertheless, because the tumor grade influences treatment options and cannot currently be determined by fine needle aspiration, adequate tissue from a Tru-Cut, excisional or incisional biopsy is generally favored over fine needle aspiration and is the preferred approach at MSKCC.

Histologically, the typical leiomyosarcoma cell is elongated and spindle-shaped and has an abundant cytoplasm. Multinucleated giant cells are common. Epithelioid changes, in which the cells become rounded, with concomitant clear cell changes in the neoplasm are commonly noted. Identification of muscle antigens by means of immunohistochemistry supports the diagnosis of leiomyosarcoma. Desmin and smooth muscle actin are the most common immunohistochemical stains. Mitotic activity has been demonstrated in multivariate analysis to be the best indicator of prognosis, along with the tumor location and size (see also section 3).[29]

The grading of sarcoma, as determined by cellularity, differentiation, pleomorphism, necrosis, and number of mitoses, is an important prognostic factor (see also section 3). However, disagreement exists as to which is the best grading system. The American Joint Committee on Cancer (AJCC)[30] recommends a three-tier system (low, intermediate, and high), whereas a two-tier system (low and high) is used at MSKCC for all soft-tissue sarcomas.[31] The clinical implications of this discordance are obvious since it makes comparisons of clinical trials, and attempts at combining the results of multiple trials, difficult.

In an attempt to define a practical grading system for soft-tissue sarcoma, the European Organisation for Research and Treatment of Cancer (EORTC) studied the histologic features of tumors from 282 patients who participated in an adjuvant chemotherapy trial, and correlated the pathologic findings with outcome. Although no feature was found to correlate independently with survival, in a multivariate analysis, the combination of the mitotic count, presence or absence of necrosis, and tumor size did correlate with survival.[32] Mutation of *TP53*, nuclear overexpression of *TP53*, and a high Ki-67 proliferation index have been associated with high grade and poor survival in other studies.[33] However, because biologic markers have not been consistently shown to be independent prognostic factors, they cannot at present be used to grade sarcomas.

2.3 Imaging for the Extent of Disease

The imaging studies performed for soft-tissue sarcomas in general depend on the primary lesion site, the histology, and the potential sites of metastases.

CT is the modality used most often. Several small studies have suggested that magnetic resonance imaging (MRI) may provide better anatomic detail for determining resectability.[34] However, a Radiology Diagnostic Oncology Group (RDOG) study comparing these modalities showed no clear benefit of MRI over CT.[35] Positron emission tomography (PET) is a metabolic scan that can detect areas of enhanced metabolism (e.g. cancer cells) but, in the absence of an anatomical mass (as visualized by CT), the significance of enhanced metabolism is currently unclear. As yet, there is no clear role for the routine use of PET in leiomyosarcoma. Although some studies support PET as a useful modality,[36] sites of known metastases may not be PET-avid. PET may, however, be useful in assessing early responses[37] in areas known to be PET-avid prior to treatment, but has not yet been shown to have a clear advantage over CT. Additional imaging studies should be driven by patient symptomatology.

Metastatic spread in leiomyosarcoma is mostly hematogenous, with lymph node involvement being unusual.[38,39] For patients with extremity leiomyosarcoma, 70% of distant metastases will be in the lung,[40,41] whereas patients with retroperitoneal leiomyosarcoma or uterine leiomyosarcoma seem as likely to develop intra-abdominal (including parenchymal liver metastases) and pulmonary metastases.[42,43]

Thus CT with contrast of the chest, abdomen, and pelvis is the standard imaging procedure for leiomyosarcoma.

2.4 Staging

There have recently been significant changes in the staging of soft-tissue sarcoma. The original 1992 staging system was based on a review published in 1977,[44] which incorporated tumor size into the determination of the grade. The newest staging system, defined by the AJCC in 2002,[30] includes both the tumor size and the depth of invasion (table I). Lymph node involvement is rare in sarcoma but when it does occur the disease is considered to be

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Table I. American Joint Committee on Cancer classification system for soft-tissue sarcomas (including leiomyosarcoma), based on tumor grade (G),[a] primary tumor (T),[b] regional lymph nodes (N),[c] and distant metastasis (M)[d] [30]

Stage I	Stage II	Stage III	Stage IV
Low grade	High grade	High grade	Metastasis to lymph nodes
Superficial and deep[e]	Superficial and deep[e]	Large and deep[e]	Metastasis to distant sites
G1, T1a, N0, M0	G3, T1a, N0, M0	G3, T2b, N0, M0	Any G, any T, N1,[f] M0
G1, T1b, N0, M0	G3, T1b, N0, M0	G4, T2b, N0, M0	Any G, any T, N0, M1
G1, T2a, N0, M0	G3, T2a, N0, M0		
G1, T2b, N0, M0	G4, T1a, N0, M0		
G2, T1a, N0, M0	G4, T1b, N0, M0		
G2, T1b, N0, M0	G4, T2a, N0, M0		
G2, T2a, N0, M0			
G2, T2b, N0, M0			

a GX: grade cannot be assessed; G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated; G4: poorly differentiated or undifferentiated.

b TX: primary tumor cannot be assessed; T0: no evidence of primary tumor; T1: tumor ≤5cm in greatest dimension; T1a: superficial tumor; T1b: deep tumor; T2: tumor >5cm in greatest dimension; T2a: superficial tumor; T2b: deep tumor.

c NX: regional lymph nodes cannot be assessed; N0: no regional lymph node metastasis; N1: regional lymph node metastasis.

d MX: distant metastasis cannot be assessed; M0: no distant metastasis; M1: distant metastasis.

e Superficial tumors are located exclusively above the superficial fascia without invasion of the fascia. Deep tumors are located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

f The presence of positive nodes (N1) is considered stage IV.

stage IV metastatic, as disease-free survival is identical to that for patients with metastases to other sites.[30] Uterine leiomyosarcoma is still frequently staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification system (table II).[45] An important research question is whether staging uterine leiomyosarcoma according to soft-tissue sarcoma staging systems might improve estimations of the prognosis.

Leiomyosarcomas arising from different anatomical primary sites may behave differently even when matched for stage and grade. Whether this is simply a function of the anatomy or an inherent difference in leiomyosarcomas of various anatomical primary sites remains to be elucidated. However, what is currently clear is that there are factors that impact on our ability to treat tumors at specific sites, such as the difficulty of radical resections for head and neck tumors, and the limitations of radiation therapy in intra-abdominal sites. Moreover, it is difficult to separate the site from the adequacy of treatment. Patients with retroperitoneal sarcomas commonly die due to complications caused by local recurrence[42,43] – an uncommon event in extremity lesions. Distant metastatic disease is often the cause of death from intra-abdominal and pelvic visceral leiomyosarcomas.[40,41]

3. Prognosis

The stage and grade are the most important prognostic factors in soft-tissue sarcoma, including leiomyosarcoma. For small, superficial, extremity soft-tissue sarcomas, whether high- or low-grade, there is a relatively low chance of recurrence. For large (>5cm), high-grade lesions, the risk of metastasis is significant. The primary location may impact on the prognosis, perhaps because of issues of resectability. A computer program (nomogram) that calculates the prognosis for overall survival in soft-tissue sarcomas has been developed and is available on the MSKCC website.[46] The median survival from the time metastases are recognized is 8–12 months, although 20–25% of patients with metastatic sarcoma are alive 2 years after diagnosis.

Table II. International Federation of Gynecology and Obstetrics classification of uterine leiomyosarcoma[45]

Stage	Description of extent of uterine cancer
IA	Tumor limited to lining of uterus
IB	Invasion to <½ thickness of lining
IC	Invasion to ≥½ thickness of lining
IIA	Invasion into cervical nodes
IIB	Invasion of cervical stroma
IIIA	Invasion of ovaries; positive peritoneal cytology
IIIB	Vaginal metastases
IIIC	Involvement of pelvic lymph nodes
IVA	Invasion of bladder or rectum
IVB	Distant or abdominal metastases; or inguinal lymph node involvement

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Although disease stage is an important prognostic factor for recurrence and survival, recent data suggest that the relative importance of certain prognostic factors may vary with time. For early recurrence, it would appear that the grade is a more powerful prognostic indicator, whereas for late recurrence, tumor size assumes a progressively more important role.[47,48]

4. Management Approaches

Treatment of soft-tissue sarcomas depends on the location of the primary tumor, the stage, and the grade. A multimodality approach including surgical resection, radiation therapy, and chemotherapy may be required (figure 1). The relative rarity of soft-tissue sarcomas has meant that many clinical trials have enrolled all, or most, sarcoma histologic subtypes. Although this approach improves patient accrual, it makes parsing out specific recommendations for one histologic subtype difficult. As understanding of the molecular variabilities among soft-tissue sarcoma subtypes improves, it is hoped that treatment recommendations will become more histologic-type specific. Success in conducting subtype-specific clinical trials will require a strong commitment to multi-institution cooperative efforts.

4.1 Uterine Leiomyosarcoma

Uterine sarcomas are rare, accounting for approximately 1% of gynecologic malignancies, and <5% of all uterine corpus cancers.[1] The uterus is the only organ that can give rise to three different types of sarcomas: leiomyosarcoma, endometrial stromal sarcoma, and carcinosarcoma (also known as malignant mixed Müllerian tumor, or MMMT). Approximately 60% of women present with disease that is limited to the uterus or to the uterus and cervix (FIGO stages I and II), and undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy, resulting in cure rates of 20–60%.[49-51] Women who present with advanced disease (FIGO stages III and IV) and women whose disease recurs after total abdominal hysterectomy and bilateral salpingo-oophorectomy have a poor prognosis and, with few exceptions, their disease is not considered curable.

4.1.1 Local Control

For disease confined to the uterus, surgical resection is the appropriate treatment. Adjuvant radiation remains controversial. Most retrospective studies have suggested a decrease in local recurrence rates with adjuvant pelvic radiation but no improvement in overall survival because of the high risk of distant metastatic disease.[52] However, a study from Spain[53] did show a survival advantage with the use of radiation therapy. This trial accrued 103 patients, 41.5% of whom had a diagnosis of leiomyosarcoma. Postoperative external beam radiotherapy was administered to 55 patients (24 of whom received brachytherapy as well); 33 patients received postoperative chemotherapy and 15 patients were observed without further treatment. When compared with no postoperative radiotherapy, treatment with postoperative radiotherapy increased the 5-year locoregional disease-free interval from 36% to 76%; the 5-year disease-free interval from 53% to 68%; and overall survival from 37% to 73%. Although these numbers are impressive, it is believed that distant metastases are the main reason for disease recurrence in uterine leiomyosarcoma. Interestingly, 84% of relapses occurred locally in this study. It is hoped that the ongoing, randomized EORTC-55874 trial will determine the exact impact of adjuvant radiation in this malignancy.

4.1.2 Adjuvant Chemotherapy

Similarly, there is currently a lack of robust data to support the use of adjuvant chemotherapy. The Gynecologic Oncology Group (GOG) performed a prospective randomized trial which compared adjuvant chemotherapy with doxorubicin versus no further therapy in patients with stage I–II uterine leiomyosarcoma or MMMT. No significant improvement was noted in the progression-free interval or overall survival for the group as a whole. There was a small improvement in progression-free survival in the subset of patients with leiomyosarcoma, but the study was neither designed nor powered to assess the impact of adjuvant doxorubicin by histologic type.[54] Since that study was designed, it has become clear that uterine leiomyosarcoma and MMMT have different chemotherapy sensitivities. Doxorubicin is not a highly active agent in MMMT but remains one of the most active agents in advanced uterine leiomyosarcoma. Appropriately designed, histology-specific trials of adjuvant therapy for completely resected uterine leiomyosarcoma are needed. Encouraging results demonstrating the activity of docetaxel plus gemcitabine in patients with measurable disease who have failed prior therapy[55] make the investigation of this regimen in the adjuvant setting attractive. A pilot study of adjuvant docetaxel plus gemcitabine in patients with completely resected leiomyosarcoma of the uterus is currently in progress at MSKCC and a multi-institution study of adjuvant therapy has recently opened.

4.1.3 Advanced/Recurrent Disease

Current treatment options for advanced and/or recurrent leiomyosarcoma are somewhat limited. Phase II trials have demonstrated minimal activity with cisplatin,[56] mitoxantrone,[57] aminothiadiazole,[58] and oral etoposide.[59] Moderate activity was observed with ifosfamide (response rate 17%),[60] intravenous etoposide (response rate 10.7%),[61] and doxorubicin (response rate 25%).[62]

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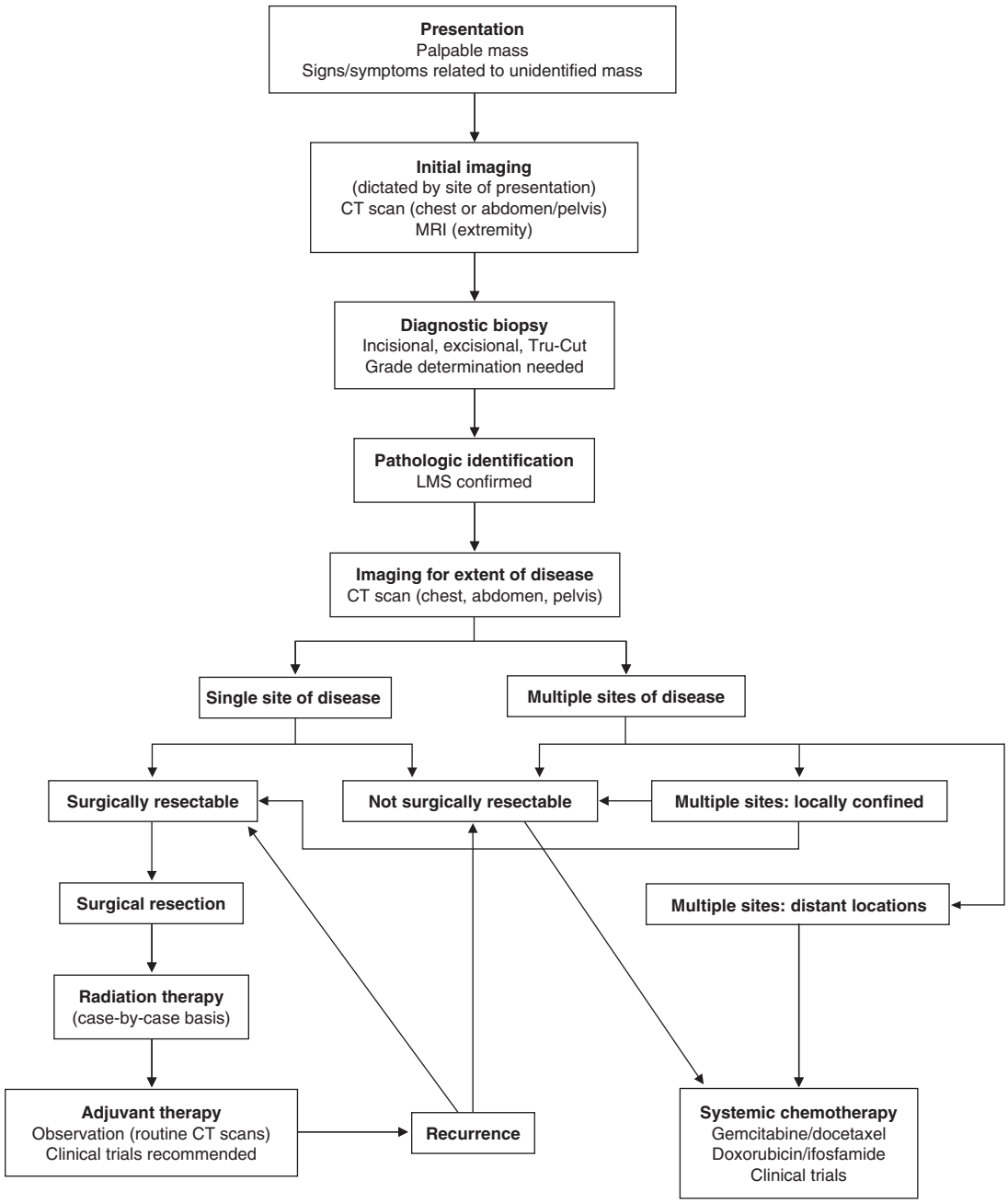

Fig. 1. Outline of recommended diagnostic and treatment strategy for leiomyosarcoma (LMS). **MRI** = magnetic resonance imaging.

In combination chemotherapy trials, the combination of hydroxycarbamide, dacarbazine, and etoposide showed a response rate of 18.4%,[63] while the combination of doxorubicin and ifosfamide showed a response rate of 30.3%.[64] No randomized clinical trials have evaluated the combination of doxorubicin and ifosfamide versus doxorubicin alone. Either approach may be reasonable as first-line therapy for advanced and/or recurrent uterine leiomyosarcoma. A phase II study of docetaxel plus dose-rate-based gemcitabine for patients with recurrent/persistent leiomyosarcoma who had had treatment failure with 0–2 prior chemotherapy regimens, conducted at MSKCC, resulted in a 53% objective response rate.[55] Seven patients had stable disease. Approximately half of these patients had failed prior doxorubicin-based therapy. Fourteen patients had received prior radiation therapy. Toxicity was moderate, with a 21% incidence rate of grade 3 or 4 neutropenia. There were only two episodes of neutropenic fever and no treatment-related deaths. Thus, the results of this phase II study make dose-rate-based gemcitabine plus docetaxel a reasona-

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ble first-line option for uterine leiomyosarcoma. Two multi-institution GOG trials of this regimen are currently under way in patients with advanced uterine leiomyosarcoma who have either had treatment failure after one cytotoxic regimen or no prior cytotoxic chemotherapy.

4.2 Nonuterine Leiomyosarcoma

Approximately 1400 patients are diagnosed with soft-tissue leiomyosarcoma annually in the US; according to the MSKCC sarcoma database it is the third most common sarcoma. Very few histology-specific clinical trials have been performed. Current treatment options are derived from larger clinical trials that have encompassed many subtypes of sarcomas.

The mainstay of treatment for soft-tissue sarcoma remains wide surgical excision. Adjuvant radiation therapy, using either external beam radiation or brachytherapy, has been shown to be beneficial for local control in situations where (i) negative margins were clearly obtained but the primary tumor was large (>5cm); or (ii) the edge of the resection was close to the negative margin.[65-67] However, the utility of radiation therapy in improving disease-free survival and overall survival remains unproven in both the preoperative[67] and postoperative settings.[66]

4.2.1 Adjuvant Chemotherapy

The use of adjuvant chemotherapy remains unclear although it has been evaluated in >20 clinical studies. All of these studies enrolled patients with all types of soft-tissue sarcoma, not specifically leiomyosarcoma. Most of the studies were small and lacked sufficient statistical power to detect small changes in overall survival. The most rigorous meta-analysis was performed in 1997[68] and updated in 2000;[69] 23 potential studies were initially considered but only 14 were ultimately included, giving a study cohort of 1568 patients. The trials all used doxorubicin either alone (in six trials) or in combination with various other chemotherapeutic agents. Leiomyosarcoma represented 12% of all diagnoses. On the whole, disease-free survival at 10 years was found to be significantly improved with adjuvant chemotherapy compared with surgery alone (55% vs 45%; p = 0.0001). Local disease-free survival at 10 years also favored chemotherapy, improving from 75% to 81%. However, although overall survival improved from 50% to 54% at 10 years with combination therapy, the difference was not statistically significant (p = 0.12). In the Kaplan-Meier subset analysis of patients with leiomyosarcoma (n = 188; 12% of all patients), recurrence-free survival and overall survival did not differ between those who received adjuvant chemotherapy and those who did not. Specifically, events per patient (i.e. overall risk of death or recurrence) occurred in 43 of 91 (47.3%) patients in the adjuvant chemotherapy versus 42 of 88 (47.7%) patients in the control group.

Since the 1997 meta-analysis,[68] two studies have been performed in which ifosfamide was incorporated into the adjuvant therapy regimen. A small randomized trial from the Italian Sarcoma Group showed adjuvant therapy with epirubicin and ifosfamide to statistically significantly improve disease-free survival and overall survival compared with no adjuvant chemotherapy.[70] However, as only 8 of the 104 patients in the trial had leiomyosarcoma (3 in the chemotherapy arm and 5 in the control arm), the applicability of these data to leiomyosarcoma is not known; most patients in the trial were classified pathologically as having malignant fibrous histiocytoma and synovial sarcoma. More importantly, in a subsequent report after a median 7 years of follow-up in which an intention-to-treat analysis was performed, the overall survival benefit was seen to be only a trend and was no longer statistically significant (p = 0.07).[71] Another study by Brodowicz et al.[72] enrolled 59 patients who underwent primary surgery and then were randomized to receive either radiotherapy alone or radiotherapy followed by dacarbazine, ifosfamide, and doxorubicin. There were no statistically significant differences between the two treatment groups in terms of relapse-free survival, time to local failure, time to distant failure, or overall survival.

There are several reasons why these previous trials may have failed to detect a benefit with chemotherapy. Firstly, the studies, while large by sarcoma trial standards, were small in comparison with clinical trials of other cancer subtypes and therefore may not have had sufficient statistical power to detect smaller differences in outcome. Secondly, the studies did not limit enrollment to patients with high-grade, large tumors, who have the poorest prognosis and therefore the most to gain. Thus the benefit of chemotherapy may have been diluted by inclusion of patients with tumors associated with a better prognosis. Thirdly, we must accept the daunting possibility that, despite using the best study designs and inclusion criteria, current chemotherapy agents may not be 'effective' for sarcomas in the adjuvant setting. The difficulty is in defining effectiveness. While the 1997 Sarcoma Meta-analysis Collaboration did not show whether doxorubicin-based chemotherapy was associated with an overall survival advantage in the adjuvant setting, it did show a benefit in disease-free survival (p = 0.0001) and local-recurrence-free survival (p = 0.016).[68] A subset analysis showed that doxorubicin-based chemotherapy was associated with a statistically significant survival advantage in patients with large (>10cm), high-grade sarcomas of the extremities. However, the study was not designed to examine this subgroup *a priori*.[69]

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In summary, current data suggest that adjuvant chemotherapy with the agents studied to date is not beneficial for patients with localized soft-tissue sarcomas.

In response to these issues, and recognizing the inherent difficulties of performing clinical trials in patients with sarcomas, two recent editorials addressed the design of clinical trials assessing the efficacy of chemotherapy in soft-tissue sarcomas. Bramwell[73] maintains that it is ethically acceptable to perform a study with a control arm in which patients receive no chemotherapy and expressed hope that such a trial might provide a more definitive conclusion and clarify earlier results. Judson[74] points out that the true value of aggressive chemotherapy must be clearly defined through a prospective randomized trial of sufficient size and statistical power to provide meaningful results.

In an attempt to begin to address these points by using existing data, the clinical sarcoma databases of MSKCC and the M.D. Anderson Cancer Center (Houston, TX, USA) were combined to examine the efficacy of chemotherapy in the treatment of soft-tissue sarcomas. Of the 674 patients identified as having presented with primary, high-risk (AJCC stage III) extremity soft-tissue sarcoma from 1984 to 1999,[48] 338 patients received local therapy (surgery and/or adjuvant radiotherapy) only and 336 patients received local therapy plus chemotherapy. Surprisingly, the use of adjuvant chemotherapy was associated with shorter disease-free survival. One interpretation of these data may be that since this was a retrospective analysis, patients presenting with more aggressive primary lesions were predicted to fare worse and were therefore recommended to receive chemotherapy. Clearly, additional evidence is needed before subjecting all patients to the significant morbidity associated with chemotherapy in the adjuvant setting.

4.2.2 Advanced Disease

Approximately half of all patients with adequate local control of their disease will develop distant metastasis.[30] Accordingly, multiple agents have been tested alone and in combination. Although most clinical studies performed in this setting have included all pathological subtypes of soft-tissue sarcomas, we present here selected studies in which leiomyosarcoma represented ≥30% of cases. Doxorubicin has consistently demonstrated a response rate of 25%.[75,76] Other less active agents include dacarbazine (response rate 17%);[77] docetaxel (response rate 17%);[78] vinorelbine (response rate 11%);[79] and gemcitabine (response rate 11%).[80] Although ifosfamide has historically been considered not particularly effective in leiomyosarcoma,[81] recent reports have indicated a response rate of 25% with this agent.[82] One possible explanation for this inconsistency is over-representation in the earlier studies by gastrointestinal stromal tumors which, until very recently, were classified as leiomyosarcomas. To further complicate the issue, sarcoma classification has markedly changed with extensive advances in immunohistochemistry as well as nomenclature over the last several years;[83] in fact more than half of the previously classified sarcomas were reclassified upon recent review.[83] Although disconcerting, the overall percentage of patients with leiomyosarcoma increased from 10% to 20% (with a concurrent decrease in other sarcomas, mostly malignant fibrous histiocytoma), suggesting that the previously cited studies might have had an even greater preponderance of leiomyosarcoma than originally believed, thus adding somewhat to their validity in assessing the efficacy of certain treatments for leiomyosarcoma.

Building on the experience with single-agent chemotherapy, combination chemotherapy has been trialed. Once again, selective trials are discussed in which leiomyosarcoma represented ≥30% of cases. Although the combination of docetaxel and gemcitabine has been reported to yield a 53% response rate,[55] this occurred in a study in which 85% of the patients had uterine leiomyosarcoma, and thus its efficacy in nonuterine leiomyosarcoma and non-leiomyosarcoma soft-tissue sarcomas remains to be fully defined. Promising preliminary data on this combination in the treatment of soft-tissue sarcomas have come from the University of Michigan (Ann Arbor, MI, USA)[84] where 35 patients with various soft-tissue sarcomas were treated with docetaxel and dose-rate-based gemcitabine. Of the 12 patients with nonuterine leiomyosarcoma, two had a complete response and five had a partial response. An additional three patients had stable disease. Preliminary results of a randomized trial of gemcitabine versus gemcitabine plus docetaxel in soft-tissue sarcoma are due to be reported at the American Society of Clinical Oncology 2006 annual meeting by Maki et al. Doxorubicin with ifosfamide remains the most active combination, with reproducible response rates of 34–36%.[81,85] Three- and four-drug combination therapy regimens have been evaluated in the setting of advanced sarcoma, with no improvement beyond the response rates reported with the combination of doxorubicin and ifosfamide.[81,86] It should be pointed out that while an increase in the objective response rate can be achieved with combination chemotherapy, an increase in median survival has not been demonstrated in trials comparing combination chemotherapy with single agents.[62,75,86]

Although it might be argued that since historically nonuterine soft-tissue sarcomas have been grouped, the translational benefit from uterine leiomyosarcoma to nonuterine leiomyosarcoma may be obscured by the numerous other histological subtypes enrolled, a 1999 meta-analysis seems to indicate that this is not the case.[87] Overall, there were 2185 cases, of which 538 were classified as leiomyosarcoma. Statistical analysis showed that 1-year survival (overall 48% and leiomyosarcoma 49%), 2-year survival (overall 22% and leiomyosarcoma 20%), median survival time (overall 51

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weeks and leiomyosarcoma 52 weeks), and response rates (overall 26% and leiomyosarcoma 22%) were essentially identical when leiomyosarcoma-specific data were compared with the combined data on all soft-tissue sarcoma subtypes. This suggests that it is reasonable to extrapolate findings specifically to leiomyosarcoma from large clinical studies in which ≥25% of all cases were leiomyosarcoma.

5. Conclusion

The management strategy for leiomyosarcoma, as used at MSKCC, involves the judicious and appropriately timed use of surgery, radiation therapy, and chemotherapy. Of these three strategies, the initial approach in the treatment of soft-tissue sarcoma, including nonuterine leiomyosarcoma, is wide surgical excision. The surgical approach for uterine leiomyosarcoma is surgical excision by hysterectomy with or without oophorectomy. Radiation therapy is administered adjuvantly for high-grade lesions, positive margins, and nonuterine soft-tissue sarcoma lesions >5cm in size. Adjuvant radiation therapy is not generally recommended for completely resected, stage I and II uterine leiomyosarcoma for which surgical resection is complete. The efficacy of adjuvant chemotherapy for uterine or nonuterine leiomyosarcoma remains unproven as a means to improve overall survival. Currently, adjuvant chemotherapy for completely resected, high-grade leiomyosarcoma is offered to patients participating in an appropriate clinical trial.

Treatment for advanced, metastatic, and/or recurrent disease involves the use of chemotherapy in combination with radiotherapy and surgery. Active drugs in leiomyosarcoma include doxorubicin, ifosfamide, dose-rate-based gemcitabine plus docetaxel, and dacarbazine. Trials to assess whether single agents or combination therapy offer the best approach are in progress.

Finally, all patients diagnosed with sarcomas should be referred to cancer centers with expertise in the diagnosis and treatment of sarcomas for consideration of clinical trial participation to help establish a standard of care and improve treatment strategies.

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