WHAT IS MALIGNANT FIBROUS HISTIOCYTOMA?
Malignant fibrous histiocytoma (MFH), a type of sarcoma, is a malignant neoplasm of uncertain origin that arises both in soft tissue and bone. It was first introduced in 1961 by Kauffman and Stout (Ref. 22) and controversy has plagued it since. They described MFH as a tumor rich in histiocytes with a storiform growth pattern. By 1977, MFH was considered the most common soft tissue sarcoma of adult life. Despite the frequency of diagnosis, MFH has remained an enigma. No true cell of origin has ever been identified. In 2002, the World Health Organization (WHO) declassified MFH as a formal diagnostic entity and renamed it as an undifferentiated pleomorphic sarcoma not otherwise specified, NOS (Ref. 4). This new terminology has been supported by a compelling body of evidence over the last decade to suggest that MFH represents a final common pathway in tumors that undergo progression towards undifferentiation (Refs. 5, 12, 15, and 19). While it remains unclear how to most accurately organize these tumors, the term malignant fibrous histiocytoma represents the diagnosis for thousands of patients and is still commonly used by both patients and physicians. This review will describe soft tissue tumors once diagnosed as MFH.

MFH manifests a broad range of histologic appearances with four sub-types described (Ref. 3):
1. Storiform-pleomorphic
2. Myxoid
3. Giant cell
4. Inflammatory

Of these, the storiform-pleomorphic is the most common type, accounting for up to 70% of most cases (see Figure 1).

**Figure 1 (left):** A histologic specimen showing a classic storiform-pleomorphic malignant fibrous histiocytoma. Microscopically, the storiform pattern shows short fascicles of spindle cells radiating from a central point which is intermixed with neoplastic giant cells in the pleomorphic portion. **Figure 2 (right):** A histologic example of myxoid type MFH. In order for a tumor to be characterized as a myxoid variant, myxoid tissue must account for at least half of the tumor.
The myxoid variant is the second most common accounting for approximately 20% of cases (Figure 2).

Unlike the other sub-types of MFH, the myxoid form tends to be less aggressive and as a result is associated with a better prognosis. Giant cell and inflammatory types are rare. Inflammatory MFH tends to occur in the retroperitoneum.

**The myxoid subtype** must contain at least 50% myxoid areas by definition. Occasionally an entire nodule of tumor can have a myxoid appearance causing diagnostic confusion including less aggressive entities such as myxoma or nodular fasciitis. Most myxoid variants of MFH behave as low grade neoplasms and thus pursue a less aggressive course.

**HOW DOES MALIGNANT FIBROUS HISTIOCYTOMA PRESENT?**
As with all sarcomas of soft tissue and bone, MFH is rare, with just a few thousand cases diagnosed each year.

MFH of soft tissue typically presents in a patient that is approximately 50 to 70 years of age though it can appear at any age. MFH is very rare in persons less than 20 years old.

There is a slight male predominance. Soft tissue MFH can arise in any part of the body but most commonly in the lower extremity, especially the thigh. Other common locations include the upper extremity and retroperitoneum. Patients often complain of a mass or lump that has arisen over a short period of time ranging from weeks to months. It is not uncommon for patients to report trauma to the affected area. For example, patients will state that they “ran into the corner of a table” and have had a thigh lump since. Trauma as far as we know does not cause MFH but rather the incident draws attention to the extremity. The mass does not usually cause any pain unless it is compressing a nearby nerve. Symptoms such as weight loss and fatigue are not typical but can present in patients with advanced disease. Retroperitoneal tumors can become quite large before they are detected as patients do not feel a mass per se but rather associated constitutional symptoms such as anorexia or increased abdominal pressure.

Because MFH is extremely rare in children, other diagnostic possibilities must be exhausted before accepting it as a diagnosis in the pediatric population.

"I FEEL A LUMP. NOW WHAT?"
Not all lumps and bumps are cancerous and in fact, most are not. Nonetheless, all masses should be brought to the attention of a physician. Your doctor will likely ask a series of questions regarding the mass such as “How long has the mass been present?” and “Is it enlarging? If so, over what period of time?” She or he will then perform a thorough physical examination assessing the size and firmness of the mass, examining other parts of the affected extremity, and searching for enlarged lymph nodes.

Often an x-ray is obtained as the first imaging test. Usually this is followed with an MRI. MRI is the most useful test to image soft tissue tumors as it provides very valuable information about the mass such as the size, location, and proximity to neurovascular structures. It is important to note that the diagnosis of a cancerous tumor cannot be made by MRI alone. For patients that are unable to undergo MRI because of metallic implants such as pacemakers, a CT scan may be obtained.
After analyzing all of the information that has been gathered, if the mass remains suspicious for sarcoma the patient will likely be referred to a physician who specializes in sarcoma. The specialist, usually an orthopaedic oncologist or general surgical oncologist, will then likely perform additional tests and arrange for a biopsy.

When the diagnosis of sarcoma is suspected, it is important to determine if a tumor is isolated (localized) or has spread (metastatic). When soft tissue sarcomas spread, they most commonly metastasize to the lungs. As such, a CT scan of the chest is routinely obtained to determine the presence or absence of metastatic disease. While sarcomas including MFH can spread to other sites such as lymph nodes and bones, it is fairly uncommon. The role of tests such as bone scan and PET scan is not totally clear (Refs. 20, 23, and 30). There is considerable variability among physicians as to whether these additional studies are useful.

The vast majority of metastatic disease from sarcomas including MFH present as pulmonary disease (90%). Involvement of extra-pulmonary sites is uncommon: lymph nodes (10%), bone (8%), liver (1%).
PET scans exploit the high metabolic activity of cancer cells. The technique utilizes the radiolabeled glucose analog (Ref. 18) fluoro-2-deoxy-D-glucose which is metabolized at higher rates by the tumor cells. The uptake of the FDG is expressed as maximum standard uptake value (SUV). While it is a very sensitive test, it is not specific for sarcoma. Several investigations have attempted to define the role of PET scanning in soft tissue sarcomas (refs. 13, 33, and 34). As our understanding of this new technology develops, its diagnostic and staging capabilities will become more refined. For now, the role and cost-effectiveness of PET scanning have yet to be clearly defined.

**BIOPSY OF MALIGNANT FIBROUS HISTIOCYTOMA**

A biopsy is a procedure in which diagnostic tissue is obtained. Biopsies can be performed by different methods. A needle biopsy involves inserting a small needle into the tumor to obtain a specimen (Refs. 17 and 45). Needle biopsies can often be performed in the physician’s office (see Figure 6). If the tumor is in a location that is difficult to feel or there are structures near the tumor that could be damaged, then a CT-guided needle biopsy might be arranged.

An open biopsy is a surgical procedure that is usually performed in the operating room under sedation or anesthesia. With incisional biopsies, just a small part of the tumor is removed for analysis. With excisional biopsies, the entire mass is removed. Excisional biopsies are usually reserved for small tumors (less than 3 cm).

The decision to remove part of the mass or the entire mass at the time of biopsy is extremely critical. The importance of having a sarcoma specialist either perform the actual biopsy or guide the treating surgeon in planning a biopsy cannot be overstated.

The biopsy is often the first step to a successful limb-sparing procedure. The location of the biopsy incision and technical aspects of obtaining tissue can have a major impact on subsequent operations (Ref. 28).

**Figure 6:** Needle biopsy of an MFH in the thigh. Needle biopsies such as this one can often be performed in the clinic. It is important to draw out the incision which will be utilized to remove the tumor. The biopsy should then be obtained along that incision. **Figure 7:** Limb sparing incision in the upper extremity for a sarcoma of the forearm. Biopsies must be performed along or directly parallel to an incision that allows for a limb sparing operation to remove the tumor. Note that an ellipse has been drawn around the previous biopsy incision. The biopsy tract should be excised at the time of definitive surgery to prevent local recurrence.

The tissue obtained from the biopsy is evaluated by a pathologist. The pathologist uses a number of diagnostic tools including light microscopy, immunohistochemistry, electron microscopy, and
molecular studies to make the diagnosis. In addition to making a diagnosis, the pathologist also provides an important piece of information called the grade. The grade refers to a tumor’s appearance under the microscope and is a reflection of a tumor’s aggressiveness. High grade tumors behave more aggressively meaning they have a higher tendency to recur and spread. Low grade tumors are less aggressive and have a lower tendency to recur and spread. The grade is not a guarantee of a tumor’s behavior but rather is one of the factors that helps the treatment team make recommendations.

Several cytogenetic abnormalities have been described for STS including MFH. More than 80% of MFH tumors display mutations affecting 1q31, 9q31,5p14, and 7q32. Abnormalities at 3p12, 11p11, and 19p13 have also been described. In a multivariate analysis of tumor grade and size, gains at 7q32 predicted a worse survival (Ref. 24).

STAGING
Once all of the imaging studies and biopsy have been performed, the stage of disease can be assigned. The most commonly used staging system is the AJCC (American Joint Commission on Cancer) system for soft tissue sarcoma, see Table 1 (Ref. 1). Patients often inquire about the stage of their disease. It must be kept in mind that stage is not a guarantee of a tumor’s behavior. Staging merely provides guidelines for the treatment team on how best to manage a given tumor to optimize clinical outcome.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Size</th>
<th>Depth</th>
<th>Grade</th>
<th>Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Any</td>
<td>Any</td>
<td>Low</td>
<td>No</td>
</tr>
<tr>
<td>II</td>
<td>&lt; 5cm, any depth OR &gt; 5cm</td>
<td>Superficial</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>III</td>
<td>&gt; 5cm</td>
<td>Deep</td>
<td>High</td>
<td>No</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Depth is termed superficial (above the deep fascia) or deep (deep to the deep fascia). Retroperitoneal tumors are considered deep.*

"I HAVE MFH. WHAT ARE THE NEXT STEPS?"
Once the diagnosis of MFH has been confirmed, an individual treatment plan is made for each patient. Sarcoma treatment requires a multimodality approach and hence a team of physicians will participate in a patient’s care. There are essentially three main types of treatment that will need to be coordinated to treat the MFH:

1. Surgery
2. Radiation
3. Chemotherapy

Surgery
Surgery is the cornerstone of treatment for all soft tissue sarcomas. The goal of surgery is to eradicate all disease in the affected area. For extremity sarcomas, surgical options fall into two categories: limb-sparing and amputation. Historically, soft tissue sarcomas were treated with
amputation. As our understanding of sarcoma has evolved, so has the treatment. Several studies have demonstrated no difference in patient survival with amputation versus limb-salvage (Refs. 46 and 47). In a randomized clinical trial run by the National Cancer Institute (ref. 40), there was no difference in overall survival for patients with soft tissue sarcoma that had amputation (70%) versus those that had amputation (71%). Currently at least 90% of tumors are now removed using limb-sparing surgery meaning that the tumor is removed while saving the extremity. Limb sparing surgery should only be performed if the surgeon is confident that the tumor can be completely removed and that the remaining extremity provides reasonable function. Obviously balancing oncologic and functional outcomes is a very complex and subjective undertaking. It is very important that the patient and treating surgeon discuss the expectations of all options preoperatively. Reconstruction following tumor resection is sometimes necessary depending on the size of the tumor and what structures need to be sacrificed. For example, a bone or joint may need to be reconstructed or soft tissue flaps may be needed for wound coverage.

Once a tumor has been removed, the pathologist analyzes the entire specimen to confirm the tumor’s grade and margins. The term margin refers to the outermost edges of a resection specimen. A negative margin indicates that there are no tumor cells on the periphery of the tumor implying that a complete resection was achieved. A positive margin means that tumor cells were found on the periphery of the resection specimen which implies there is likely residual microscopic disease. Obviously one hopes to achieve negative margins at the time of surgery. Unfortunately it is not always possible to accomplish this. Surgical procedures for sarcoma are classified as outlined in Table 2. When possible, wide and radical procedures are attempted in order to obtain negative margins.

<table>
<thead>
<tr>
<th>Table 2: Classification of surgical resections for the treatment of sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intralesional</strong></td>
</tr>
<tr>
<td><strong>Marginal</strong></td>
</tr>
<tr>
<td><strong>Wide</strong></td>
</tr>
<tr>
<td><strong>Radical</strong></td>
</tr>
</tbody>
</table>

Figure 8: Intra-operative photograph of an MFH of the scapula that was removed using limb salvage surgery. A cuff of normal tissue is kept with the mass so that the tumor is never actually exposed during the operation. Figure 9: Brachytherapy catheters traversing the operative field. Once the tumor has been completely excised, radiation oncologists place empty tubes (catheters) at the base of the wound and sew the tubes into place. The wound is then carefully closed.
**Radiation**

Radiation therapy is administered by a radiation oncologist. The purpose of radiation is to improve local tumor control by killing residual microscopic disease. Radiation has been clearly shown to improve the incidence of local recurrence and has become an integral part of the treatment for MFH (Refs. 6 and 27). Typical radiation doses vary from 45 Gy to 65 Gy.

In a prospective randomized trial from NCI, 91 patients with high grade tumors were randomized to surgery alone or surgery with post-operative external beam radiation therapy, XRT (Ref. 48). Patients in the surgery alone group experience 20% local recurrence rates compared to 0% for the surgery plus XRT group. For both groups, there was no difference in overall survival. In general, patients treated with adequate limb-sparing surgery supplemented with radiation have a likelihood of experiencing over 85% local control.

There are several different ways to administer radiation. The most commonly used form of radiation is external beam radiation which can be given pre-operatively, intra-operatively, post-operatively, or in some combination. Each has advantages and disadvantages, see Table 3. For tumors that are in contact with major nerves and blood vessels, pre-operative radiation can potentially shrink the tumor, making limb-sparing surgery possible or easier. The main disadvantage to pre-operative radiation is its association with post-operative wound complications (Ref. 10 and 35). Post-operative radiation is probably the most commonly used modality. Typically pre- and post-operative radiation is administered over a 5 week period. Intra-operative has the advantage of delivering a large dose of radiation directly to an area of concern while sparing nearby organs such as the bowel or bladder. It is particularly useful for treating large retroperitoneal sarcomas in which it is difficult to obtain local tumor control (Ref. 43).

### Table 3: The advantages and disadvantages of the timing of radiation therapy

<table>
<thead>
<tr>
<th>Delivery Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-operative</strong></td>
<td>1. potentially shrinks tumor 2. smaller volume required</td>
<td>1. increase in wound complications 2. delay in definitive surgery</td>
</tr>
<tr>
<td><strong>Intra-operative</strong></td>
<td>1. can concentrate very high doses to close margins 2. minimal injury to normal tissue</td>
<td>1. requires a special operating room with exposure to O.R. staff 2. wound complications</td>
</tr>
<tr>
<td><strong>Postoperative</strong></td>
<td>1. fewer wound complications 2. immediate surgery</td>
<td>1. larger volume required secondary to operative contamination</td>
</tr>
</tbody>
</table>

Another means of administering radiation is a technique called brachytherapy. After the surgeon has removed the tumor, a radiation oncologist then places empty catheters in the operative bed. Once the wound is starting to heal (approximately 5 days after surgery), the catheters are filled with radioactive material which sits in the surgical bed for 5 days. This allows for high doses of radiation over a short period of time obviating the need to travel daily for radiation treatments over several weeks.
In a prospective randomized trial from NCI, 91 patients with high grade tumors were randomized to surgery alone or surgery with post-operative external beam radiation therapy, XRT (Ref. 48). Patients in the surgery alone group experience 20% local recurrence rates compared to 0% for the surgery plus XRT group. For both groups, there was no difference in overall survival. In general, patients treated with adequate limb-sparing surgery supplemented with radiation have a likelihood of experiencing over 85% local control.

Unfortunately radiation does have well known side effects. Problems with wound healing have already been described above. Problems including scarring of the tissue resulting in firm stiff muscles, as well as skin discoloration, have also been well described. The most serious complication arising from radiation is the development of a second cancer within the radiated field (Refs. 8, 29, and 32). This is called a post-radiation or radiation-induced sarcoma. Radiation-induced sarcomas are rare and occur in less than 5% of long-term survivors.

**Chemotherapy**

The role of chemotherapy in the treatment of MFH is not entirely clear. Several clinical trials incorporating the chemotherapy drug doxorubicin have shown trends in improved event-free survival without a major impact on overall survival. The results of a large meta-analysis which included almost 1,600 soft tissue sarcoma patients concluded that the addition of chemotherapy improved overall survival by less than 10% (Ref. 2). Results were better in patients with extremity tumors than in patients with axial or retroperitoneal tumors. More recently, clinical trials incorporating ifosfamide and doxorubicin have demonstrated an improvement in disease-free survival (Refs. 26 and 36). One of the major limitations of chemotherapy is the associated toxicities with the doses necessary to have a significant impact on disease-specific survival. The addition of supportive drugs such as hematopoietic growth factors has allowed for higher doses and trends in improved survival are being observed.

Unfortunately, the interpretation of these and other chemotherapy trials results has varied so much that it has become difficult for patients to decipher the information in order to make decisions regarding chemotherapy as part of their treatment. The decision to incorporate chemotherapy in the treatment of MFH must be made with the guidance of a medical oncologist. Chemotherapy probably should be given to patients who already have metastatic disease or who are at the highest risk for developing metastatic disease. Most often, chemotherapy will likely be administered in the setting of a clinical trial.

**Prognosis and Outcome**

Prognostic factors that are known to correlate with survival in patients with MFH include tumor grade, depth, size, metastatic status, patient’s age, and histologic subtype (Refs. 11, 16, and 39). Favorable prognostic factors include age less than 60 years old, tumor size less than 5 cm, superficial location, low grade, the absence of metastatic disease, and a myxoid subtype. Older patients with large (> 5cm), deeply seated, high grade tumors do not have as favorable an outcome. For example, patients with a small low grade tumor are likely to achieve complete cure. For patients with large, deep, high grade tumors (Stage III), the 5 year survival estimates range from 34 to 70% (Refs. 25, 42, and 49).

Local recurrence (LR), recurrence of the tumor in the same location, will occur in approximately 20-30% of all patients with soft tissue sarcomas (Refs. 25, 42, and 49). LR is lowest in extremity sarcomas and highest in retroperitoneal and head and neck sarcomas. This distribution is directly related to the ability to completely resect a tumor at the time of surgery. Higher LR rates are observed in the setting of positive surgical margins, which are more difficult to achieve in anatomic locations outside of the extremity (Ref. 18). Whether local control has an impact on overall survival is unclear and remains controversial. Several well designed investigations have been reported that support both sides of the argument.
**Sarcoma Nomogram:** On the basis of a prospectively followed cohort of adult patients with primary soft tissue sarcoma (STS) who were treated at Memorial Sloan-Kettering Cancer Center, a nomogram for predicting sarcoma-specific mortality at 12 years was developed (Ref. 21). Nomogram predictor variables included age at diagnosis, tumor size (< or = 5, 5 to 10, or > 10 cm), histologic grade (high or low), histologic subtype (fibrosarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, malignant peripheral nerve tumor, synovial, or other), depth (superficial or deep), and site (upper extremity, lower extremity, visceral, thoracic or trunk, retrointraabdominal, or head or neck. The accuracy of the nomogram has been validated by both internal and external standards (Ref. 14). The tool is meant to be used in adult patients who are less than 6 months from their index surgical procedure and are without evidence of metastatic disease. The sarcoma nomogram may be useful for patient counseling, follow-up scheduling, and clinical trial eligibility determination.

It is very important for patients to understand that the data on outcomes and survival is derived from mostly heterogeneous, retrospective analyses that lack strict inclusion criteria. The survival statistics that are quoted are most useful to the treating physician to guide therapy and probably of limited value for an individual patient.

**Table 4: Clinical Outcome of Malignant Fibrous Histiocytoma from Large Cancer Centers**

<table>
<thead>
<tr>
<th>Center</th>
<th># of Patients</th>
<th>Local Recurrence (%)</th>
<th>Metastasis (%)</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>230</td>
<td>19</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td>271</td>
<td>21</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>French Federation of Cancer Centers</td>
<td>216</td>
<td>31</td>
<td>33</td>
<td>70</td>
</tr>
</tbody>
</table>

**FOLLOW-UP CARE AND SURVEILLANCE**

Probably about 1/3 of patients with extremity MFH and closer to ½ of patients with retroperitoneal MFH will experience recurrence either in the primary site (local recurrence) or at a distant site (distant recurrence or metastasis). Most recurrences usually develop in the first 2 years following treatment but may occur at any time during a patient’s lifetime. The frequency and length of follow-up vary according to the number of risk factors an individual has for developing a recurrence. On average patients are followed for approximately 10 years. Patients with large or high grade tumors will likely be evaluated every few months initially where as patients with low grade or small tumors will probably be seen annually. A follow-up exam consists of a physical examination and a chest evaluation in the form of an x-ray or CT-scan. Depending on the circumstances, an MRI of the primary site may be obtained.

If a recurrence is detected, the treatment team collaborates again to determine the roles of surgery, radiation, and chemotherapy. Most local recurrences can be effectively treated with additional surgery. For recurrent local disease that is resectable, approximately 2/3 of patients experience long term survival (Refs. 31 and 44). If no prior radiation was administered, the affected area should receive radiation for the recurrence. Metastatic disease represents the most serious type of recurrence and most commonly occurs in the lungs. Individual treatment plans vary significantly depending on a host of patient and disease factors as well as the limitations imposed by previous treatments. For patients that have isolated resectable pulmonary metastases, it is possible to achieve extended survival in approximately 20% to 50% of patients (Refs. 7, 9, and 41). Chemotherapy is often incorporated into the treatment of patients with
distant recurrence. Unfortunately, patients with unresectable recurrent disease have a uniformly poor prognosis.

**SUMMARY**

- MFH is a curable disease.
- The term "Malignant Fibrous Histiocytoma" has been changed by the WHO to undifferentiated pleomorphic sarcoma not otherwise specified.
- The mainstays of treatment for MFH are complete surgical excision most often supplemented with adjuvant radiation therapy.
- Chemotherapy is reserved for patients at the highest risk of disease recurrence or patients that already have recurrence.
- Patients with recurrent MFH can still be cured.
- Favorable prognostic factors that correspond to superior survival include small tumor size, low grade, extremity location, superficial location, and localized disease.

**REFERENCES**


