Liposarcoma
LIPOSARCOMA

An ESUN Article

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INTRODUCTION
The term "liposarcoma" refers to a spectrum of neoplastic processes ranging from lesions that are essentially benign to those that are malignant, more aggressive, and likely to recur and/or metastasize (spread). Decisions regarding the treatment and aftercare of liposarcomas are guided by the known characteristics and behavior patterns of the various subtypes. While many of the principles governing the evaluation and management of other soft tissue sarcomas certainly apply to liposarcoma, there are many features unique to it that deserve special consideration. Management of these tumors requires a multidisciplinary team approach, and should be rendered in centers experienced in the many facets of care of sarcoma patients.

BACKGROUND
In relation to other types of cancer, soft tissue sarcomas are relatively rare. Approximately 5000 new cases of soft tissue sarcoma are diagnosed each year (Sim 1994) representing about 1% of all newly diagnosed human neoplasms (Lewis 1996). Liposarcoma itself constitutes about 9.8% to 18% of soft tissue sarcomas, its incidence second only to that of Malignant Fibrous Histiocytoma (MFH), (Peterson 2003, Enzinger 1995).

Liposarcoma is a tumor derived from primitive cells that undergo adipose differentiation. It is largely a disease of adults, its incidence peaking between the ages of 40 and 60 years, and it shows a slight predominance toward men (Enzinger 1995). When liposarcomas do occur in the pediatric population, they tend to present in the second decade of life (Coffin 1997). In either event, the deep soft tissues of the extremities, particularly those of the thigh, are the most common location, accounting for more than 50% of liposarcomas (Coffin 1997, Pisters 1996). Its presentation in this location is most commonly that of a slow growing, painless mass. Often these tumors are first noticed after the patient has sustained a minor trauma to the area. Having noted a hard lump that doesn’t go away with time often is what prompts the patient with a sarcoma to first seek medical attention. Unfortunately, since patients with sarcomas don’t initially feel "sick", their diagnosis, and thus their treatment, is often delayed.

Liposarcoma was originally described by R. Virchow in 1857. In 1944, Arthur Purdy Stout wrote "surely, one of the most bizarre and fantastic chapters in the story of oncology is furnished by the tumors of fat-forming cells. The strange way in which they grow, their astounding size…and many other peculiar features … make them of great interest." See R. Virchow, "Ein Fall von Bosartigen zum Theil in der Form des Neurons auftretenden Fettgeschwulsten," Arch A Pathol Anat Phys, 1857, 11: pp 281-288 and "Liposarcoma—the malignant tumor of lipoblasts", A. P. Stout, Annals of Surgery, 1944; 119(1): pp 86-107.
One unique feature of liposarcoma is its tendency to occur in visceral spaces, particularly that of the retroperitoneum. Up to 1/3 may occur in this location (Peterson 2003). The presentation of liposarcoma in this scenario may be quite different. While a mass may be appreciated, it tends to be found much later, since the retroperitoneal space can accommodate a much larger change in volume than can the thigh, for instance. Also, obstructive urinary and bowel symptoms may predominate as the mass impinges on these structures. The management of liposarcoma in this location can be particularly difficult.

It is worth mentioning that, in addition to the previously described locations, liposarcoma may occur in many other locations. Those occurring in the head and neck represent about 5%, while the upper extremity accounts for 10%. Other unusual locations may include the spermatic cord, peritoneal cavity, axilla, vulva and even the breast. While most liposarcomas are believed to arise de novo, those in the breast may arise from a preexisting cystosarcoma phyllodes (Donegan 1979, Austin 1986). Liposarcomas are not known to arise from benign lipomas.

**HISTORY AND PHYSICAL EXAM**

Most patients with liposarcomas will present to a clinician with complaint of a mass. Often they are painless unless some sort of trauma has occurred. As stated previously, liposarcomas can become quite large, depending on the site of involvement. Their character can be soft and fleshy or notably firm to palpation. This largely depends on how much the tumor resembles mature fat, or how well-differentiated the lesion is. It is important early on to distinguish large benign lipomas from liposarcoma. Factors that tend to suggest malignancy are masses > 5 cm (about 2 inches) in size and lesions that are deep-seated, firm and fixed to underlying structures (Sim 1994). As with the evaluation of any mass, a thorough physical examination is a must, and careful attention should be directed toward the chest, abdomen and pelvis in addition to the extremity of interest.

**IMAGING**

After a careful history and physical exam has been performed, imaging studies are obtained. For extremity lesions, this begins with standard X-Rays (Sim 1994). These will help elucidate whether or not the bone is involved. Next, an MRI is usually obtained, both with and without contrast enhancement. The MRI findings in liposarcoma can be quite distinct, and suggest the diagnosis even before biopsy is performed. This largely depends on how closely the tumor resembles normal fat (i.e. how “well-differentiated” it is); see Figure 1.

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![Figure 1](image.png)

*Figure 1:* Axial and coronal MR images showing a large but relatively homogeneous, well-defined lesion in the left groin/thigh of a 20 year old male. This lobular appearance is characteristic of large benign lipomas and well-differentiated liposarcomas.
Liposarcomas tend to appear well-circumscribed and lobulated on MRI (Arkun 1997). Contrast enhancement depends on the level of differentiation. Little enhancement is noted in well-differentiated liposarcomas, and more is seen with the more aggressive round cell, pleomorphic and dedifferentiated subtypes. Myxoid liposarcoma, an intermediate variant, shows corresponding heterogeneity with regards to contrast enhancement (Arkun 1997). Other findings characteristic of liposarcoma are thick fibrous septae, nodularity and contrast enhancement on fat-suppressed sequences (Peterson 2003). Additionally, foci of hemorrhage and necrosis may be seen; see Figure 2.

**Figure 2:** Axial T1 weighted and STIR images of a myxoid liposarcoma in the posterior compartment of the thigh of a 41 year old woman. This lesion appears heterogeneous and does not resemble the intensity of the surrounding subcutaneous fat. Also notable is the significant amount of associated edema. These findings are highly suggestive of malignancy.

**STAGING AND BIOPSY**

Once a sarcoma is suspected by exam and imaging, staging and biopsy must be performed. This basically helps determine the nature of the lesion and to what extent, if any, the tumor has spread. Imaging of the tumor as described above is a critical part of the staging process. Additionally, since the lungs are the most common site of metastasis, radiography and CT scanning of the chest is routinely undertaken. With liposarcoma, CT of the abdomen is also recommended due to the relatively common involvement of retroperitoneal and visceral spaces. Laboratory studies including CBC, sedimentation rate and chemistries should be obtained. These tests provide insight into the systemic response elicited by the tumor, and provide a baseline by which therapy may be monitored.

Biopsy is critical, as it is the means by which tissue is acquired in order to make a definitive diagnosis. The histology (or the way it looks under the microscope) of the tumor gives the first clues to its behavior. The requisite tissue can be obtained via needle aspiration or through open incisional or excisional biopsy methods. Open techniques constitute surgery and are performed in the operating room. These provide the most tissue for review by the pathologist, however are often not necessary, or even appropriate. Because many soft tissue sarcomas are readily palpable, needle biopsy is often all that is necessary. This is frequently performed by a radiologist under CT guidance. Incisional biopsy sometimes is necessary to attain an adequate sample of tissue. This involves making an incision in the skin, and obtaining some pieces of the tumor for evaluation. Except for the rarest of instances, excisional biopsy (removing the entire tumor as a biopsy) should be avoided with suspected sarcomas as a well-planned, definitive resection after appropriate staging and tissue diagnosis is preferred.
PATHOLOGY
Once tissue from a biopsy or resection is obtained, it is examined under the microscope to determine its histology. There are many special kinds of tests that may be run to aid the pathologist in making a diagnosis from the provided specimen. For this reason, biopsy results may take several days or sometimes even weeks to be finalized.

The World Health Organization currently recognizes four subtypes of liposarcoma: well-differentiated (or atypical lipoma), myxoid, pleomorphic and dedifferentiated (Christopher 2002). While these categories represent various points on a spectrum of disease, each of these entities displays its own unique character. Table I provides a simplified description of each of the aforementioned subtypes. Also, see Figure 3 and Figure 4.

### TABLE I: LIPOSARCOMA SUBTYPES

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Well-differentiated</td>
<td>Includes atypical lipoma</td>
</tr>
<tr>
<td></td>
<td>Most common subtype (50% of liposarcomas)</td>
</tr>
<tr>
<td></td>
<td>Low grade (doesn’t metastasize, but may recur locally)</td>
</tr>
<tr>
<td></td>
<td>Risk of dedifferentiation</td>
</tr>
<tr>
<td>Myxoid</td>
<td>Intermediate grade</td>
</tr>
<tr>
<td></td>
<td>Includes round-cell variant as its high-grade counterpart</td>
</tr>
<tr>
<td></td>
<td>Most common type in pediatric age group</td>
</tr>
<tr>
<td></td>
<td>Metastatic risk especially in round-cell variant</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>Rarest type (5-10% of liposarcomas)</td>
</tr>
<tr>
<td></td>
<td>High grade</td>
</tr>
<tr>
<td></td>
<td>May mimic MFH or even carcinoma or melanoma</td>
</tr>
<tr>
<td></td>
<td>High risk of local recurrence and metastasis</td>
</tr>
<tr>
<td>Dedifferentiated</td>
<td>High grade sarcoma arising in association with well-differentiated liposarcoma</td>
</tr>
<tr>
<td></td>
<td>(MFH, fibrosarcoma)</td>
</tr>
<tr>
<td></td>
<td>Most common with retroperitoneal lesions</td>
</tr>
<tr>
<td></td>
<td>Risk of metastasis</td>
</tr>
</tbody>
</table>

Table 1 compiled from Peterson 2003, Dei Tos 2000, Coffin 1997, Enzinger 1995 and Weiss 1992

A number of cytogenetic correlations also have been made with liposarcoma. Well-differentiated liposarcomas have been found to be associated with abnormalities derived from the q13-15 region of chromosome 12 (Rubin 1997). Such abnormalities also are found in dedifferentiated liposarcoma. Perhaps the best characterized genetic association is that found with myxoid liposarcoma. This represents a translocation, or sharing of genetic material between two chromosomes. In myxoid liposarcoma, the translocation is between chromosome 12 and 16. The result is a gene called TLS-CHOP which is an oncogene, or gene that when expressed can lead to the formation of cancer. This particular translocation and its products are found only in myxoid liposarcoma and therefore are diagnostic of this tumor (Rubin 1997).
Figure 3a: Surgical specimen of a well-differentiated liposarcoma (images shown in Figure 1). The appearance is similar to that of mature fat.

Figures 3b and 3c: Microscopically, ‘signet-ring’ type cells resembling normal adipose tissue are seen. Lipoblasts closely associated with spindle cells (typical of sarcomas) are appreciated at higher power.

Figure 4a: Cut gross specimen of a myxoid liposarcoma. While there are areas resembling fat, thick fibrous septae and heterogeneous tissue suggest a more aggressive process than that seen in Figure 3.

Figure 4b: Histologically, areas of high-grade tumor are noted by a high degree of cellularity, nuclear atypia and mitotic figures. Compared to well-differentiated liposarcoma, few ‘signet-ring’ type cells are seen.
Once the tumor has been characterized, the staging is complete and an appropriate course of treatment can be planned. Table II demonstrates the commonly used staging system for bone and soft tissue sarcomas used by Musculoskeletal Oncologists (adapted from Enneking 1980).

**TABLE II: SURGICAL STAGING OF SARCOMAS**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>Site</th>
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<tbody>
<tr>
<td>IA</td>
<td>Low</td>
<td>Intracompartmental (in bone or muscle compartment of origin)</td>
</tr>
<tr>
<td>IB</td>
<td>Low</td>
<td>Extracompartmental</td>
</tr>
<tr>
<td>IIA</td>
<td>High</td>
<td>Intracompartmental</td>
</tr>
<tr>
<td>IIB</td>
<td>High</td>
<td>Extracompartmental</td>
</tr>
<tr>
<td>III</td>
<td>Any + Mets</td>
<td>Any + Mets</td>
</tr>
</tbody>
</table>

*Table II adapted from Enneking, 1980.*

**TREATMENT**

Liposarcoma is, like other soft tissue sarcomas, primarily a surgical disease. The main goal of surgery is to remove the tumor entirely and prevent recurrence. This is most reliably achieved with a wide or radical resection; see Table III.

**TABLE III: SURGICAL RESECTION**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| Intralesional | Curettage  
              | Partial tumor removal |
| Marginal | May leave microscopic tumor behind |
| Wide    | Remove tumor and surrounding cuff of normal tissue |
| Radical | Remove entire compartment  
          | Includes amputation         |

*Table III adapted from Enneking 1980.*

Although amputation historically was the surgical option of choice for these tumors, today most are amenable to limb-sparing surgery. This is due in large part to advances in the understanding of sarcoma behavior, and in principles of radiation therapy. Such advances have led to a decrease in the frequency of amputations for primary soft tissue sarcomas from more than 50% to about 5% (Spiro 1997). If a limb-sparing procedure is performed however, it must not compromise the main oncologic goal of tumor removal, and should preserve an extremity that serves the patient better than could a post-amputation prosthesis. It is important to note that even
with limb-sparing procedures, functional deficits may be encountered. These may vary significantly depending on the size and location of the individual tumor, and are due to the removal of tissues associated with the tumor (i.e. muscles, tendons, nerves, etc). Reconstruction of post resection deficits can in some instances be performed to minimize these effects; see Figure 5.

Figure 5: Intra-operative photo after limb-sparing surgery for a large liposarcoma. Proximity to major nerves (center of picture) can make wide margins difficult to achieve. Often, preoperative radiation and/or chemotherapy is given in hopes that the tumor will shrink away from major nerves and blood vessels to make limb-sparing surgery more feasible without compromising the ultimate oncologic goal.

Although local control rates of 85-90% have been achieved with combination therapy consisting of surgery and radiation (Spiro 1997), discussion is ongoing as to the timing of radiation, whether it should be given before or after surgery. Preoperative radiation has the advantage of allowing for smaller doses of radiation applied to a smaller field. Additionally, the tumor may actually shrink in size, making the surgery technically more feasible. The downside is that surgical complications, particularly those related to the wound, are increased. Pollack et al (1998) reported wound healing complications in 25% in patients radiated preoperatively versus 6% in those receiving postoperative treatment. It has been suggested that the improved oncologic outcomes and decreased incidence of more permanent late complications justify the use of preoperative radiation despite the increased complication rate (Virkus 2002). The role of chemotherapy in the treatment of liposarcoma also remains controversial, and is best addressed on a case-by-case basis.

What is commonly accepted regarding liposarcoma is that the behavior of a specific tumor is ultimately dependent on its histological subtype (see above). When treated with surgery and perioperative radiation therapy, well-differentiated liposarcomas exhibit a <10% local recurrence rate and a virtually 0% rate of metastasis (Zagars 1996). In contrast, pleomorphic liposarcomas recur in about 1/3 of cases and spread in about 40%. Five and ten year survival rates for patients with liposarcomas have been reported as 100% and 87% for well-differentiated, 88% and 76% for myxoid variants and 56% and 39% in the pleomorphic subtype (Zagars 1996, Chang 1989).
Local recurrence largely depends on margin status at the time of surgery, with margins positive for the presence of tumor conferring a higher recurrence rate (Sadoski 1993) and thus, less satisfactory outcomes (Spiro 1997). In some scenarios, amputation may still be the procedure of choice for a given patient with a sarcoma. While the goal of amputation is removal of the sarcoma, it does not address metastatic disease and is not fully protective against local recurrence. If amputation is required, the patient often will elect to use a post-amputation prosthesis. This depends largely on the level of the amputation. In short, the more native joints the patient is able to safely retain, the better his/her function tends to be. Essential elements of a successful transition to use of a prosthetic limb are the involvement of a knowledgeable prosthetist, a diligent program of physical therapy including appropriate post-operative stump care and gait training, and most-importantly, a patient that is truly committed to the process.

SURVEILLANCE
Once the tumor has been excised and adjuvant therapy completed, continued surveillance is required to promptly detect any evidence of local recurrence or distant metastasis. This typically involves careful physical examination, x-rays of the afflicted limb and serial imaging of the chest and abdomen (usually CT) and pelvis if indicated. Such follow-up is continued in some fashion for the remainder of the patient’s life. If such disease is detected, treatment is rendered accordingly.

An entity which can sometimes occur after radiation therapy is radiation-induced sarcoma. By definition this arises in previously irradiated tissues that were documented to be "normal" prior to radiation (Arlen 1971). They tend to occur at least 2-3 years after treatment, and may appear up to 30 years later. The most common histology is that of malignant fibrous histiocytoma (70%), and is typically high grade (Enzinger 1995). Survival rates of 5-26% have been reported with regards to these tumors (Robinson 1988, Laskin 1988).

CONCLUSION
The term "liposarcoma" refers to an array of cancerous tumors. The behavior of any liposarcoma is dependent on its histological subtype. The treatment principles, however, are essentially identical to those of other soft tissue sarcomas. Largely, this includes some combination of radiation therapy and surgery, with or without chemotherapy. It is important for the patient to be serially evaluated for any signs of recurrence or metastasis, and any new complaints should be addressed promptly. This is particularly true in the setting of liposarcoma, which may exhibit unusual patterns of spread and recurrence (Vassilopoulos 2001, Linehan 2000, Pearlstone 1999).

BIBLIOGRAPHY AND RELATED WORKS


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