

## LIPOSARCOMA: A CLINICOPATHOLOGICAL STUDY OF 73 CASES DIAGNOSED AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

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**Background:** Liposarcoma is one of the most common adult soft tissue sarcomas, being second only to malignant fibrous histiocytoma. It ranges from the well-differentiated lipoma-like and myxoid tumors, to extremely cellular or pleomorphic malignant neoplasms. The clinical behavior is variable and reflects the variable microscopic picture.

**Patients and Methods:** Clinicopathological studies of liposarcoma in Saudi Arabia are lacking. In this study, we reviewed all liposarcoma cases reported at KFSH&RC from 1981 to 1996. Seventy-three cases of liposarcoma were studied morphologically. The cases were classified using the WHO International Classification of Diseases (ICD). Data regarding follow-up, mode of therapy, recurrence and survival status were available for 37 cases (50.68%). Survival analysis was performed. The patients' ages ranged from 15-94 years, with peak incidence between the ages 40 and 60 years. There was a male predominance of 1.3:1.

**Results:** The most common location was the thigh (36 cases), accounting for 49.3% of cases, followed by the retroperitoneum (16 cases), accounting for 21.9%. The most common histologic type was myxoid liposarcoma (41 cases; 56.2%), followed by well-differentiated liposarcoma (16 cases; 21.9%), including dedifferentiated liposarcoma (5 cases; 6.8%), pleomorphic liposarcoma (13 cases; 17.8%) and round-cell liposarcoma (3 cases; 4.1%). Twenty-two patients (59.45%) were treated by surgery only, and 13 patients (35.13%) were treated by a combination of surgery and postoperative radiotherapy. One patient was treated by surgery, radiotherapy and chemotherapy, and died one month after diagnosis. Another patient was treated by radiotherapy alone and is still alive after a four-year follow-up period. The correlation between survival and recurrence with tumor type, location in regard to surgical accessibility, and mode of therapy, was not statistically significant.

**Conclusion:** Site, histologic type and completeness of surgical excision were the most important factors in predicting prognosis and planning therapy for patients with liposarcoma. The overall prognosis depends on many variable factors. Complete surgical excision reduces the recurrence rate. The role of chemotherapy and radiotherapy is not well established.

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**Key Words:** Liposarcoma, therapy, survival.

Liposarcoma is one of the most common soft tissue sarcomas of adult life, and ranks second only to malignant fibrous histiocytoma.<sup>1-3</sup> It usually presents with large tumors and has variable histological features. It ranges from the well-differentiated lipoma-like and myxoid tumors, to extremely cellular or pleomorphic malignant neoplasms. The clinical behavior closely reflects the variable microscopic appearance.<sup>2</sup> The vast majority of

liposarcomas are found in the extremities and retroperitoneum.<sup>3</sup> Histopathologic subtype, tumor grade, size and completeness of resection are important prognostic indicators in multivariate analysis.<sup>4-6</sup>

The histologic classification of liposarcoma is controversial. The World Health Organization (WHO) subclassifies these tumors into well-differentiated, myxoid, round cell, and pleomorphic types.<sup>3,7</sup> The Armed Forces Institute of Pathology (AFIP) classifies them into five basic histological categories: myxoid, round cell, well-differentiated, dedifferentiated and pleomorphic. There are mixed forms in 5%-10% of the cases.<sup>2</sup> Liposarcoma can be conceptually divided into two basic groups: myxoid/round cell liposarcoma and well-differentiated/dedifferentiated liposarcoma. The myxoid/round cell group occurs in middle-aged adults, primarily as an extremity lesion, and

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TABLE 1. Anatomical locations of liposarcoma (KFSH&amp;RC, 1981-1996).

Anatomical location	Number of cases (%)
Upper limb	7 (9.6)
Hand	1 (1.4)
Chest	5 (6.9)
Retroperitoneum	16 (21.9)
Spermatic cord	2 (2.7)
Buttock	3 (4.1)
Thigh	36 (49.3)
Lower leg	2 (2.7)
Unknown	1 (1.4)
Total	73 (100)

ranges from the pure myxoid (low-grade) to pure round cell (high-grade lesion), with some cases exhibiting transitional features. Behavior can be related to the proportion of round cell areas. Well-differentiated/dedifferentiated liposarcomas occur in late adult life as extremity or retroperitoneal lesions. They consist of mature fat interlaced with atypical hyperchromatic cells and rare lipoblasts. They recur locally but do not metastasize. Their behavior is strongly influenced by location, with retroperitoneal lesion having the worst prognosis.<sup>1,8,9</sup> As a long-term complication of the disease, these lesions may progress histologically (dedifferentiate), increasing their metastatic potential. Dedifferentiated liposarcomas can arise *de novo*, and occur most commonly in the retroperitoneum.<sup>1,10</sup>

Cytogenetic abnormalities are common in liposarcomas. They correlate reliably with the morphological subtype in most cases, and can be of diagnostic value in histologically borderline or difficult cases.<sup>13</sup>

### Patients and Methods

All the cases of liposarcoma diagnosed at King Faisal Specialist Hospital and Research Centre between 1981 and 1996 were reviewed. Cases representing undifferentiated sarcoma, probably liposarcoma, were excluded. Recurrent cases with more than one specimen were considered as one case. A total of 73 cases of liposarcoma were retrieved from our files and reviewed histologically. Data regarding age, sex, site, method of therapy and survival status were collected. The WHO classification was used to classify the cases into myxoid, pleomorphic, well-differentiated and round cell types.<sup>1,2</sup> In addition, cases of well-differentiated liposarcoma with dedifferentiation were studied. Electron microscopic studies were performed in 20 cases and immunohistochemical studies were performed in 14 cases. Identification of lipoblasts was used as an essential mean for establishing the diagnosis of liposarcoma. Lipoblasts ranging from undifferentiated mesenchymal cells, univacuolated or multivacuolated cells were considered in the diagnosis, along with the sharply defined lipid droplets

which push and scallop the nuclei.<sup>1</sup> Data regarding follow-up, mode of therapy, recurrence and survival status were available for 37 cases (50.68%). The treatment modalities used for such patients included surgery alone, surgery and radiotherapy, radiotherapy only, and a combination of radiotherapy, chemotherapy and surgery.

Statistical analysis has been performed using log rank statistics, Wilcoxon statistics and chi-square test, as well as survival data in relation to site.

### Results

The patients' ages ranged from 15-100 years, with a mean age of 57 years. A peak incidence was seen between the ages of 40 and 60 years (Figure 1). Data about the age of patients were not available in five cases. There were 38 males and 35 females, with a M:F ratio of 1.3:1.

The two major sites of liposarcoma were the extremities, particularly the thigh (n=36 cases; 49.3%) and the retroperitoneum (16 cases; 21.9%). Seven cases were found at the upper limb (9.6%), five from the chest wall (6.9%), three from the buttock (4.1%), two from the spermatic cord (2.7%), two from the lower leg (2.7%), one from the hand (1.4%), and one case of unknown site (1.4%). Table 1 illustrates the distribution of the liposarcomas.

The 73 cases included 41 cases of myxoid liposarcoma (56.2%) (Figure 2), 16 cases of well-differentiated liposarcoma (21.9%) (Figure 3), including five cases with dedifferentiation (6.8%) (Figure 4), 13 cases of pleomorphic liposarcoma (17.8%) (Figure 5) and three cases of round cell liposarcoma (4.1%).

Electron microscopy was performed in 20 cases and showed primitive mesenchymal cells, lipoblasts with non-membrane-bound lipid inclusions and capillaries in association with the cells. It also showed variability in cellular differentiation. Fourteen cases had immunohistochemical stains performed. These stains were S100 protein, vimentin, desmin and CD34. The neoplastic cells were S100 and vimentin positive. Desmin was negative and CD34 highlighted the complex capillary architecture along with occasional positive cytoplasmic staining in mesenchymal cells scattered in the tumor (Figure 6).

Thirty-seven patients (50.68%) had variable follow-up periods, which ranged from 1 to 179 months after the initial surgery (median 22 months). Thirty-four of these patients (87.2%) are alive, but five (12.8%) died with disease after follow-up periods ranging from 1 to 85 months (median 22 months). Nineteen (51%) of the 37 patients had no evidence of disease or recurrence in the follow-up period, while 18 patients (49%) had evidence of the disease during the follow-up period, 11 of which were recurrences and seven of which resulted from residual disease.

Information regarding the mode of therapy was available in 37 cases (50.7%), from which 22 patients

(59.5%) were treated by surgery only. Of these, 21 patients (86.4%) are alive with no evidence of disease. The follow-up period ranged from 1 to 179 months, with a median of 39 months. One patient died after 22 months of the initial diagnosis. Thirteen patients (55.1%) underwent surgery and received chemotherapy. Of those, 10 patients (77%) are alive, but three (23%) died of the disease within 1 to 6 years of the initial diagnosis. Four out of the surviving 10 patients (31.1%) had recurrences which were treated surgically. One patient (2.7%) received radiotherapy alone, and is still alive after 48 months' follow-up. One patient (2.7%) was treated by surgery, radiotherapy and chemotherapy together, and died within one month of the initial surgery.

Fourteen out of 16 cases of well-differentiated liposarcoma (87.5%) are well and alive, while the remaining two had recurrence after six and seven years of initial diagnosis, respectively.

Statistical analysis using log rank statistics and chi-square test revealed no significant difference in survival or recurrence rates and duration between surgically accessible and non-accessible tumors (Figure 7).

### Discussion

In this study of liposarcoma, the effect of histopathologic typing, location, treatment modality, and completeness of surgical excision on prognosis and predicting survival and recurrences were studied. Our data correlates well with comparable studies performed elsewhere. The M:F ratio in the literature is 1.5:1, which correlates with our study.<sup>2,3</sup> Liposarcoma is rare in young patients and children, but many cases of liposarcoma in children are on record. The peak incidence is in the fifth and sixth decade, with an age range from less than three years to over 80 years. Similar age distribution was noted in our population.<sup>2,3,11,12</sup>

The histologic subclassification used by the WHO was proposed by Enzinger and Winslow in 1962. This classification is correlated clinically with the outcome of therapy. The five-year survival rate for well-differentiated and myxoid types has been reported as 75%-100%. In their study, two patients with well-differentiated liposarcoma and one patient with myxoid liposarcoma died after a period of follow-up ranging from 2-6 years. Well-differentiated liposarcoma almost never metastasizes unless dedifferentiation occurs.<sup>2,4,7,8</sup> In our study, only two out of 16 cases (12.5%) with well-differentiated liposarcoma recurred after six and seven years of initial diagnosis, respectively. The survival for pleomorphic and round cell types is 20%, with a higher rate of local recurrence (80%) than well-differentiated liposarcoma (50%).<sup>6,7</sup> In our study, one patient treated for pleomorphic liposarcoma presented with liver metastases which were treated surgically, and he died within 16 months of the initial diagnosis. Metastases are related to the histologic

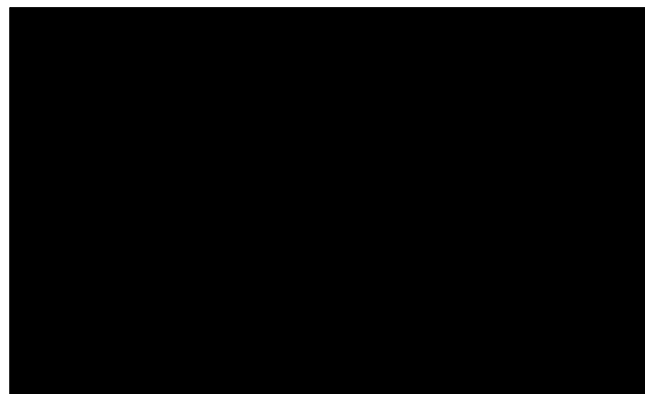


FIGURE 1. Age distribution of 68 liposarcomas.

type, in the sense that round cell and pleomorphic types of liposarcoma are more likely to give rise to distant metastases than the well-differentiated and myxoid subtypes.<sup>2,4,7,8</sup>

Patients with a complete surgical excision and superficial location have a better survival rate and less incidence of recurrence than those with incompletely excised or unresectable deep-seated tumors.<sup>1,2</sup> In the current study, the correlation between superficial location and complete surgical excision with survival rate and rate of recurrence was not statistically significant. This could be attributed to the small number of cases, which were not enough to draw conclusions from or apply survival analysis. Enzinger and Weiss have noted that tumor location may be more significant than histologic type in predicting local recurrence. Accessible tumors in the extremities are more likely to have complete excision than retroperitoneal neoplasms that have higher risk of recurrence and metastasis.<sup>2</sup> Tumor location in terms of surgical accessibility and the risk of recurrence was not statistically significant in our study, but in the previously mentioned case of pleomorphic liposarcoma which metastasized to the liver, the tumor was in the retroperitoneum, which is a surgically challenging site for complete excision. Patients may die of unresectable disease.<sup>3</sup> In our study, all 11 recurrences were secondary to incomplete excision, especially in deep-seated or inoperable locations, mostly the retroperitoneum.

The presence of lipoblasts and their identification is an important feature in diagnosing liposarcoma with confidence. It has been always been a problem for the pathologist, since the distinction between true lipoblast from other vacuolated cells that can be seen in a variety of mesenchymal, epithelial or degenerating tumors is difficult. Lipoblasts of liposarcomas can range from primitive mesenchymal cells containing tiny lipid droplets to large "signet-ring" cells in which most of the cytoplasm is occupied by a single droplet of fat. Additionally, some types of liposarcoma, such as dedifferentiated or pleomorphic liposarcomas lack definitive lipoblasts, and in those cases, the differentiation from malignant-fibrous



FIGURE 2. A case of myxoid liposarcoma, showing myxoid background, vascular pattern and lipoblasts.



FIGURE 3. A case of well-differentiated liposarcoma showing adipose tissue with scattered lipoblasts.



FIGURE 4. A case of dedifferentiated liposarcoma showing malignant fibrous histiocytoma pattern with mitosis.



FIGURE 5. A case of pleomorphic liposarcoma showing pleomorphism and bizarre lipoblasts with hyperchromatic nuclei.

histiocytoma or undifferentiated pleomorphic sarcoma is difficult.<sup>1,2</sup> In the present study, we excluded all cases where no definite lipoblasts or fat origin could be identified after examining numerous sections from the tumor.

Electron microscopy and immunohistochemistry can aid in establishing the diagnosis of liposarcoma. They still have limitations in undifferentiated tumors. Lipoblasts contain one or more non-membrane-bound lipid droplets of variable size and density, which are associated with a moderate to large number of mitochondria. In our study, electron microscopy was performed in only 20 cases and showed primitive mesenchymal cells, lipoblasts and lipid droplets. It confirmed the light microscopic diagnosis of liposarcoma, especially in two cases of dedifferentiated type.

Immunohistochemistry can be helpful in the differential diagnosis of liposarcoma, but its use is limited. S100 and vimentin positivity is seen in cases that are obvious by morphology, but is not helpful in difficult cases, where the origin of undifferentiated sarcoma toward

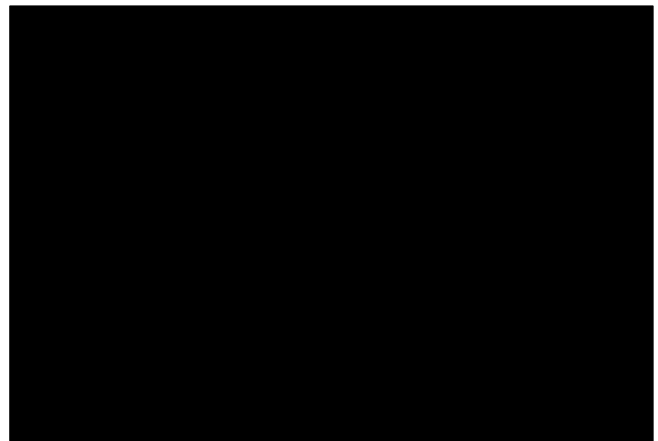


FIGURE 6. A case of myxoid liposarcoma showing branching blood vessels with positive staining for CD34 in the blood vessels and mesenchymal cells.

lipogenic differentiation is required. The use of other markers to rule out other sarcomas, such as desmin for leiomyosarcoma and CD68 for malignant fibrous

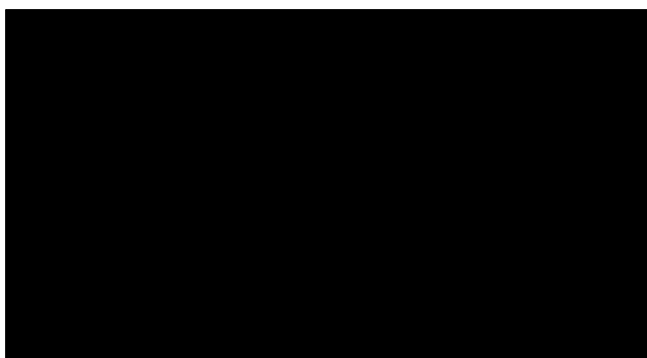


FIGURE 7. Survival curve of 37 cases of liposarcoma in relation to site.

histiocytoma, can be performed in undifferentiated cases. CD68 can be positive in some types of liposarcoma. CD34-positive undifferentiated mesenchymal cells and multinucleated cells have been reported in liposarcoma of different types, but the lipoblasts were negative for CD34.<sup>14</sup> Similar findings were found in our study, in which CD34 was performed on four cases and all showed positive mesenchymal cells, along with highlighting of the vascular pattern. It is thought that such positivity is related to the dendritic interstitial system rather than to lipoblasts.<sup>14</sup>

Special stains for fat, such as oil-red O, were not performed in our study, as they require fresh frozen tissue. Their use in identifying lipids in lipoblasts and excluding other intracellular substances such as mucin or glycogen is sometimes useful. The importance of such stains for the diagnosis of liposarcoma, however, should not be overemphasized, because lipids may be scarce in some liposarcomas and abundant in other unrelated mesenchymal or epithelial neoplasms.<sup>1,2</sup>

In Saudi Arabia, the relative frequencies of primary cancers are very different from those in the Western world. Soft tissue tumors account for 3.2% of all cancers, which is higher than in the USA, where they account for 0.5% of all cancers. In our experience, liposarcoma is one of the most common soft tissue tumors in adults, being second only to malignant fibrous histiocytoma, a rate similar to that in the USA. It accounts for 10.7% of all soft tissue tumors.<sup>2,15</sup>

In conclusion, liposarcoma in Saudi Arabia shows similar clinicopathologic features to other parts of the world. The overall survival from the disease shows rates similar to those seen in the West, indicating the need for similar management strategies in the Kingdom. The different disease outcome in our series compared to the world literature may be related to the relatively smaller number of patients.

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