

Treatment strategies for well-differentiated liposarcomas and therapeutic outcomes

著者	Yamamoto Norio, Hayashi Katsuhiro, Tanzawa Yoshikazu, Kimura Hiroaki, Takeuchi Akihiko, Igarashi Kentaro, Inatani Hiroyuki, Shimozaki Shingo, Kitamura Seiko, Tsuchiya Hiroyuki
journal or publication title	Anticancer Research
volume	32
number	5
page range	1821-1826
year	2012-05-01
URL	http://hdl.handle.net/2297/31969

Submit to *Anticancer Research*

Treatment Strategies for Well-differentiated Liposarcomas and Therapeutic Outcomes

NORIO YAMAMOTO¹, KATSUHIRO HAYASHI¹, YOSHIKAZU TANZAWA¹,
HIROAKI KIMURA¹, AKIHIKO TAKEUCHI¹, KENTARO IGARASHI¹,
HIROYUKI INATANI¹, SHINGO SHIMOZAKI¹, SEIKO KITAMURA² and
HIROYUKI TSUCHIYA¹

¹Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Ishikawa, Japan;

²Department of Pathology, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan

Key Words: Well-differentiated liposarcoma, surgical resection, prognosis

Running title: Clinical Outcomes of Well-differentiated Liposarcoma

Clinical study

Date of submission: February 29, 2012

Correspondence to: Norio Yamamoto, MD, Ph.D., Department of Orthopedic Surgery, Graduate School of Medical Sciences, Kanazawa University, 13-1 Takaramachi, Kanazawa, Ishikawa, 920-8641 Japan. Tel: +81 762652374, Fax: +81 762243763, e-mail: norinori@med.kanazawa-u.ac.jp

Abstract. This study examined 45 patients with well-differentiated liposarcoma who were surgically treated at our hospital (initial surgery in 41 patients and reoperation in four). Only one patient had recurrence among patients who underwent initial surgery, and the recurrence was in the retroperitoneal space. For patients who underwent reoperation, the mean time between the initial surgery and recurrence was 16.5 years. None of the 45 patients developed distant metastasis. It is important to preserve not only neurovascular bundles but also lower limb muscles to maintain ambulatory ability in the elderly. For well-differentiated liposarcomas of the limbs, it is important to establish a surgical margin beyond the marginal resection border and to perform muscle resection to the extent that would not greatly reduce the muscle strength.

Well-differentiated liposarcoma is a relatively slow-growing tumor that usually occurs in elderly patients. It is difficult to differentiate from a benign lipoma and other lipomatous tumors; Magnetic resonance imaging (MRI) (1-4) and murine double minute 2 (*MDM2*) gene amplification (5, 6) in tissue samples have been reported to be useful in their differentiation. However, definitive differentiation is often difficult before resection. In many cases, the entire resected specimen is evaluated histopathologically and diagnosis can subsequently be made for the first time. The resection margin of well-differentiated liposarcoma tends to be less than that in conventional extensive resection (7, 8). However, operative procedures from marginal resection to extensive resection vary with institution. In this study, we examine the outcomes of well-differentiated liposarcomas treated at our hospital and discuss future treatment strategies.

Patients and Methods

The subjects of this study were 45 patients with well-differentiated liposarcomas who were surgically treated at our hospital between January 1989 and July 2010 and who were followed up for at least 6 months. There were 17 men and 28 women. The procedure was their initial surgery in 41 patients and reoperation in four patients who were referred to our hospital due to recurrence. After the surgeries, these patients revisited our outer patient clinic every four to six months and local recurrences were checked by magnetic resonance imaging (MRI) and lung metastases were checked by chest computed tomography (CT).

Results

The mean age was 63.4 years (range: 35-80 years) in 41 patients who received the initial surgery at our hospital. Liposarcoma occurred in the lower limbs in 29 patients, the trunks in 8 patients (including in the retroperitoneal space in 1 patient), and the upper limbs in 4 patients, indicating a predilection for the lower limbs. The mean tumor size was relatively large at 14.4 cm X 11.5 cm. The mean time between when the patient first noticed the tumor and when the patient presented at the hospital was 38.2 months (range: 2 days-30 years). In many cases, the tumor was left untreated for a long period of time. Six patients underwent extensive resection, thirty-two patients underwent marginal resection, and three patients underwent intralesional resection of the microfocal lesion. The mean postoperative follow-up period was 62 months (range: 5-247 months). Recurrence was observed in only one patient. This patient had undergone marginal resection and had retroperitoneal recurrence (1/41 patients). The recurrence occurred two years after surgery.

As mentioned previously, four patients were referred to our hospital for resection of the recurrence. The mean age at initial surgery was 53.5 years (range: 45-68 years), and the mean age at reoperation was 70.0 years (range: 67-72 years). The mean time between the initial surgery and recurrence was 16.5 years (range: 4-26 years). A long period of time had passed from the initial surgery to reoperation. Recurrence was seen in the lower limbs in three patients and the upper limb in one. All four patients underwent marginal resection. In all patients, details of the surgical margin at the initial surgery were unknown due to the long passage of time. The mean follow-up period after reoperation was 38.8 months (range: 33-47 months), and no patient had another recurrence.

In our study, there was no patient who had distant metastasis among 45 patients.

Discussion

The National Soft Tissue Tumor Registry is published annually in Japan (10). According to this registry, the number of liposarcoma cases registered in 2009 was approximately twice the number of malignant fibrous histiocytoma (MFH) cases due to revision of pathological criteria for MFH. Liposarcoma was the most prevalent tumor among the registered malignant soft tissue tumors. Well-differentiated liposarcoma accounts for approximately 50% of all liposarcomas, and it is a soft tissue tumor that is seen relatively often. Conventionally, well-differentiated liposarcoma is considered a soft tissue sarcoma with low malignancy. However, the new 2002 WHO classification categorized well-differentiated liposarcoma in the same group as atypical lipomatous tumor. Atypical lipomatous tumor has similar histopathological features to well-differentiated liposarcoma and occurs in superficial locations (10). In this WHO classification, well-differentiated liposarcoma was categorized as an intermediate, locally aggressive tumor and was excluded from the category of malignant tumor (Table I). The number of recent reports regarding minimizing the resection margin has increased. The basis of minimizing the resection margin is the WHO classification. However, there is still no consensus on the optimal surgical margin. In our study, we examined therapeutic outcomes for well-differentiated liposarcoma over 20 years and also examined future treatment strategies.

In our study, the mean time between when the patients first noticed the tumor and treatment was three years for patients who underwent the initial surgery. The tumor was left untreated for 30 years at the longest. The long length of time until treatment indicated that the tumor was slow growing, caused no subjective symptoms such as pain, and had predilection for areas such as the thigh, where it was less

noticeable by others. For patients who underwent reoperation, the mean time from the initial surgery to the final follow-up was 22 years. There was no distant metastasis in patients who underwent initial surgery or reoperation. This indicates that well-differentiated liposarcoma does not cause or only rarely causes distant metastasis. When past studies examined therapeutic outcomes of malignant soft tissue tumors in elderly patients, high-grade MFH was often included with the examination of well-differentiated liposarcoma. However, we believe that tumors such as high-grade MFH should be excluded from the examination of well-differentiated liposarcoma.

As in a previous reports (11), our study showed that well-differentiated liposarcoma has a predilection for the lower limbs in elderly patients. In many cases, the tumor size was large. If a simple extensive resection was performed including the surrounding muscle tissue, then muscle strength would have been greatly reduced after the surgery in many cases (Figure 1A and B). The results of our study revealed the following: (i) Well-differentiated liposarcoma usually occurred in relatively elderly patients. (ii) no distant metastasis occurred in any patient. (iii) the mean time to recurrence was approximately 16 years. Based on these results, we concluded that resection can be performed with reduced resection margins instead of a conventional, simple extensive resection for well-differentiated liposarcoma of the limbs. Specifically, marginal resection is considered appropriate for well-differentiated liposarcoma with a well defined border (such as in the muscle tissue) and for preservation of neurovascular bundles. If the tumor border with the surrounding normal tissue is ill-defined, extensive resection is considered appropriate. Such resection includes some normal tissues to prevent these being a large amount of residual tumor.

In recent years, the importance of locomotive syndrome has begun to be recognized (12, 13). From the standpoint of this syndrome, it is important to perform resection only to the extent necessary and to prevent dramatic decrease in the muscle strength. According to the 2010 Comprehensive Survey of Living Conditions of People on Health and Welfare, Japan, joint diseases and bone fractures/falls accounted for approximately 25% of the causes for the elderly aged 75 years or older to require primary nursing care (Table II) (14). This suggests that motor disorders of the limbs are the cause in approximately one quarter of the patients requiring primary nursing care. Such motor disorders are the most common cause of the elderly requiring primary nursing care in late old age. These elderly patients are often already enduring conditions such as dementia, cerebrovascular disease, and asthenia due to old age.

Muscle strength decreases approximately 2% each year due to aging. In particular, muscle mass decreases predominantly in the lower limbs. Some patients in their early old age might not have ambulatory problems in the early stages after surgery in which muscle strength is preserved. However, the muscle mass of the lower limbs can decrease with aging if excessive resection of muscles is performed. In such cases, there could be a great risk for gait disorder in the postoperative course. Thus, it is important to preserve as much muscle as possible to prevent future locomotive syndrome and to maintain a patient's activity of daily living (ADL).

Dedifferentiation occurs in 6% of well-differentiated liposarcomas of the limbs. Dedifferentiation has been reported to occur approximately three times more often for liposarcomas in the retroperitoneal space compared to those of the limbs (11). There has been a report of death after dedifferentiation of well-differentiated liposarcoma during follow-up. In a well-differentiated liposarcoma of the limb, the tumor can have an invasion-like growth pattern in parts of muscles and the tumor

border with the surrounding normal tissues can be ill-defined. In such a case, resection of muscle tissue might be unavoidable, for prevention of recurrence, to the extent that it does not greatly impair the function of the affected limb. Retroperitoneal well-differentiated liposarcomas have been reported to have poor therapeutic outcomes (15-17). When difficulty of reoperation is considered, it is important to perform resection as extensively as possible at the initial surgery.

It is important to note that our study retrospectively examined therapeutic outcomes of patients whose final pathological diagnosis was well-differentiated liposarcoma. As in patients with retroperitoneal well-differentiated liposarcoma, MRI can reveal septum or components other than fatty components in patients with well-differentiated liposarcoma of the limb. If a patient is suspected to have a high-grade tumor, extensive resection should be performed, as is conventionally done.

In conclusion, well-differentiated liposarcoma has a predilection for the lower limbs in relatively elderly patients. The mean time between when the patient first noticed the tumor and the initial examination was approximately three years. In patients with recurrence of well-differentiated liposarcoma, the mean time between the initial surgery and recurrence was long at approximately 16 years. There was no distant metastasis in patients with well-differentiated liposarcoma at our hospital. If the tumor border between the normal tissue and well-differentiated liposarcoma of the limb is ill-defined, sub-extensive resection is performed including the surrounding soft tissue, such as parts of muscle tissue. If the border is well-defined between such a tumor and its surroundings or areas adjacent to neurovascular bundles, marginal resection and sub-extensive resection are desirable.

Conflicts of Interest

The Authors have no conflicts of interest to disclosure.

References

- 1 El Ouni F, Jemni H, Trabelsi A, Ben Maitig M, Arifa N, Ben Rhouma K, Ben Ayech M and Tlili K: Liposarcoma of the extremities: MR imaging features and their correlation with pathologic data. *Orthop Traumatol Surg Res* 96: 876-883, 2010.
- 2 Craig WD, Fanburg-Smith JC, Henry LR, Guerrero R and Barton JH: Fat-containing lesions of the retroperitoneum: radiologic-pathologic correlation. *Radiographics* 29: 261-290, 2009.
- 3 Doyle AJ, Pang AK, Miller MV and French JG: Magnetic resonance imaging of lipoma and atypical lipomatous tumour/well-differentiated liposarcoma: observer performance using T1-weighted and fluid-sensitive MRI. *J Med Imaging Radiat Oncol* 52: 44-48, 2008.
- 4 Gaskin CM and Helms CA: Lipomas, lipoma variants, and well-differentiated liposarcomas (atypical lipomas): results of MRI evaluations of 126 consecutive fatty masses. *Am J Roentgenol* 182: 733-739, 2004.
- 5 Weaver J, Rao P, Goldblum JR, Joyce MJ, Turner SL, Lazar AJ, López-Terada D, Tubbs RR and Rubin BP: Can *MDM2* analytical tests performed on core needle biopsy be relied upon to diagnose well-differentiated liposarcoma? *Mod Pathol* 23: 1301-1306, 2010.
- 6 Weaver J, Downs-Kelly E, Goldblum JR, Turner S, Kulkarni S, Tubbs RR, Rubin BP and Skacel M: Fluorescence *in situ* hybridization for *MDM2* gene amplification as a diagnostic tool in lipomatous neoplasms. *Mod Pathol* 21: 943-949, 2008.
- 7 Kemp MA, Hinsley DE, Gwilym SE, Giele HP, Athanasou NA and Gibbons CL: Functional and oncological outcome following marginal excision of well-differentiated forearm liposarcoma with nerve involvement. *J Hand Surg Am* 36: 94-100, 2010.

- 8 Kubo T, Sugita T, Shimose S, Arihiro K and Ochi M: Conservative surgery for well-differentiated liposarcomas of the extremities adjacent to major neurovascular structures. *Surg Oncol* 15: 167-171, 2006.
- 9 Japanese Orthopaedic Association Musculoskeletal Tumor Committee. National Soft Tissue Tumor Registry. Tokyo: Japanese National Cancer Center, pp22-25, 2009.
- 10 Fletcher CDM and Unni KK, eds. Pathology and Genetics: Tumours of Soft Tissue and Bone. World Health Organization Classification of Tumors. Lyon: IARC Press, pp 35-46, 2002.
- 11 Weiss SW and Goldblum JR: Enzinger and Weiss's Soft Tissue Tumors, 5th ed. St. Louis: Mosby, pp 477-493, 2008.
- 12 Nakamura K: The concept and treatment of locomotive syndrome: its acceptance and spread in Japan. *J Orthop Sci* 16: 489-491, 2011.
- 13 Yoshimura N, Oka H, Muraki S, Akune T, Hirabayashi N, Matsuda S, Nojiri T, Hatanaka K, Ishimoto Y, Nagata K, Yoshida M, Tokimura F, Kawaguchi H and Nakamura K: Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time as indices for locomotive syndrome and associated disability: the second survey of the ROAD study. *J Orthop Sci* 16: 768-777, 2011.
- 14 2010 Comprehensive Survey of Living Conditions of People on Health and Welfare. Japan Ministry of Health, Labour and Welfare (in Japanese). http://www.e-stat.go.jp/SG1/estat/GL08020103.do?_toGL08020103_&listID=000001083953&requestSender=dsearch (accessed in February 1st 2012).
- 15 Smith CA, Martinez SR, Tseng WH, Tamurian RM, Bold RJ, Borys D and Canter RJ: Predicting survival for well-differentiated liposarcoma: The importance of tumor location. *J Surg Res* 2011 Aug 10. (Epub ahead of print)

16 Lahat G, Anaya DA, Wang X, Tuvin D, Lev D and Pollock RE: Resectable well-differentiated *versus* de-differentiated liposarcomas: two different diseases possibly requiring different treatment approaches. *Ann Surg Oncol* 15: 1585-1593, 2008.

17 Mussi C, Collini P, Miceli R, Barisella M, Mariani L, Fiore M, Casali PG and Gronchi A: The prognostic impact of dedifferentiation in retroperitoneal liposarcoma: a series of surgically treated patients at a single institution. *Cancer* 113: 1657-1665, 2008.

Figure legends

Figure 1. A case of well-differentiated liposarcoma that originated at the posterior aspect of the right thigh. If a simple extensive resection had been performed, a marked decrease in muscle strength would have occurred postoperatively. A: T1-weighted axial magnetic resonance image. B: T2-weighted sagittal magnetic resonance image.

Table I. WHO classification of liposarcomas (revised 2002) (10).

Table II. Major causes of patients (75 years or older) requiring primary nursing care according to the 2010 Comprehensive Survey of Living Conditions of People on Health and Welfare, Japan.

Figure 1



Table I

Benign	Intermediate (locally aggressive)	Malignant
Lipoma	Atypical lipomatous tumor/well differentiated liposarcoma	Dedifferentiated liposarcoma
Lipomatosis		Myxoid liposarcoma
Lipomatosis of nerve		Round cell liposarcoma
Lipoblastoma/lipoblastomatosis		Pleomorphic liposarcoma
Angiolipoma		Mixed-type liposarcoma
Myolipoma		Liposarcoma, not otherwise specified
Chondroid lipoma		
External angiomyolipoma		
Extra-adrenal myelolipoma		
Spindle cell/pleomorphic lipoma		
Hibernoma		

Table II

