Lipomatous tumors represent the most common soft tissue tumors. The biological spectrum ranges from benign lipomas to high-grade liposarcomas of variable histology. The fact that well-differentiated liposarcomas (WDL) show no potential for metastasis unless they undergo dedifferentiation led to the introduction of terms such as atypical lipoma or atypical lipomatous tumor (ALT), particularly for lesions arising at surgically amenable locations in the limbs and on the trunk because at these sites, wide excision usually is curative and hence the designation “sarcoma” is not warranted.

Currently, ALT/WDL are considered intermediate, low-grade, locally aggressive malignant lipomatous tumors. However, their differential diagnosis from lipomas can be problematic if based on morphology and imaging alone. Lipomas usually present as solitary, slow-growing, and painless tumors in the trunk or extremities in adults. Lipomas usually are well-circumscribed, lobulated lesions composed of adipose tissue, often separated from surrounding adipose tissue by a thin fibrous capsule. However, when presenting as intramuscular tumors, they can be poorly circumscribed and infiltrative, similar to ALT/WDL. The most common locations for ALT/WDL are the...
extremities and the retroperitoneum.\textsuperscript{4,7} Despite identical histologic features among all ALT/WDL, those outside the retroperitoneum typically follow a more benign course.\textsuperscript{8}

Most of the studies reporting on lipomas and ALT/WDL are based only on histologic analysis.\textsuperscript{1-8} Consequently, due to the histologic similarity, accurate diagnosis often is challenging because of subjective histologic interpretation and subtle differences between the 2 entities. Without a correct diagnosis, the literature can create confusion about the diagnosis of these lipomatous tumors, with a tendency to overdiagnose lipomas and underdiagnose ALT/WDL.\textsuperscript{9} In this setting, a molecular cytogenetic analysis is useful for the distinction between the 2 entities;\textsuperscript{2,4} a molecular mutation characterized by amplification of the MDM2 gene on chromosome 12 (12q13-15) is typical for ALT/WDL, whereas this molecular mutation has not been reported for lipomas.\textsuperscript{4}

In addition, it is unclear whether the differential diagnosis between lipomas and ALT/WDL of the extremities is of clinical interest regarding the optimal surgical treatment and outcome for patients;\textsuperscript{6} the published risks of local recurrence and dedifferentiation of ALT/WDL vary, and no unified treatment and follow-up plan has been accepted.\textsuperscript{1,4-8,10} Some authors have suggested that ALT/WDL should be resected by a wide margin to reduce the risk of local recurrence,\textsuperscript{1,8,10} whereas other authors recommend conservative surgery with marginal excision.\textsuperscript{5,7} Therefore, to address these conflicting reports, this study was performed on patients with histologically diagnosed and cytogenetically confirmed lipomas and ALT/WDL to evaluate clinical outcome after marginal excision of the tumors and to determine whether local recurrence had any correlation with patient age and sex, or tumor size and location.

**Materials and Methods**

This retrospective study examined the medical files of 90 patients with lipomas (47 patients) and ALT/WDL (43 patients) of the extremities treated at the authors’ institution from 2006 to 2012. There were 52 men and 38 women with a mean age of 56 years (range, 33-78 years). Mean follow-up was 52 months (range, 14-96 months); none of the patients were lost to follow-up. All of the patients gave written informed consent for their data to be included in the study, and the study was approved by the institutional review board/ethics committee of the authors’ institution.

Preoperative magnetic resonance imaging (MRI) studies were available for all patients. All patients had deep-seated tumors, and in all patients, an ultrasonography-guided biopsy was performed preoperatively. A purely fatty stroma without altered fat signal or nonfatty mass, with either thin or no septa, was observed in both lipomas and ALT/WDL (Figure 1).

Histologic sections of the tissue blocks from the excised specimens were available for re-review for all patients; a consensus with postoperative histologic analysis was confirmed (Figure 2). Molecular chromosome analysis was performed on fluorescence in situ hybridization (FISH) in all cases for the purpose of this study. Representative tissue sections from the tissue blocks were examined by FISH using ZytoLight SPEC MDM2/CEN12 Dual Colour Probe kit (Zyto-Vision GmbH, Bremerhaven, Germany), according to the protocol provided by the manufacturer. This probe cocktail highlighted the chromosomal region of the human MDM2 gene. Evaluation of the sampled tissue sections was performed with fluorescence microscopy (OLYMPUS BX 41 fluorescence microscope; Olympus, Hamburg, Germany). A ratio of greater than 2 was considered to represent MDM2 amplification consistent with a diagnosis of ALT/WDL. A ratio of 2 or less was considered to be nonamplified consistent with a diagnosis of lipoma (Figure 3).

The margins of soft tissue resections of the tumor specimens were defined as (1) intralesional (when the tumor was entered or cut into at any point during surgery; microscopically positive), (2) mar-
Based on this cytogenetic analysis (when a cuff <2 to 3 cm of normal tissue was left on all sides of the tumor or the surgical dissection extended into or through the abnormal, reactive tissues that surrounded the tumor but were not actually a part of the tumor, the so-called “reactive zone”; possibly microscopically positive), and (3) wide (when the reactive zone was not entered, but instead the dissection was through entirely normal tissues, and a cuff of 2 to 3 cm of normal tissue was left on all sides of the tumor; microscopically negative).11,12 The margins were marginal in all cases (lipomas and ALT/WDL); none of the patients had any treatment other than surgery.

Patient outcome was evaluated with regard to the occurrence of local recurrence and metastasis, and whether there was any relationship with the age and sex of the patients and the size (maximum tumor diameter) and location (upper and lower extremities) of the tumors. Statistical analysis was performed using t test and chi-square test. The t test was used to evaluate the relationship of the type of tumor (lipoma or ALT/WDL) with patient age and tumor size, and the relationship of local recurrence with patient age and tumor size. The chi-square test was used to evaluate the relationship of the type of tumor (lipoma or ALT/WDL) with patient sex, tumor location, and local recurrence, and the relationship of local recurrence with patient sex and tumor location. Analyses were performed using SPSS software for Windows version 22.0 (IBM Corp, Armonk, New York).

RESULTS

None of the patients with lipomas experienced local recurrence compared with 6 patients (13.9%) with ALT/WDL who experienced local recurrence within a mean interval of 48 months (range, 33-96 months) between surgical treatment and local recurrence; the difference was statistically significant (chi-square test, \( P=0.005 \)). Five of the 6 patients with ALT/WDL who experienced local recurrence were treated with re-excision with marginal margins without any evidence of local re-recurrence until the latest follow-up. One of the 6 patients with ALT/WDL who experienced local recurrence was treated with surgical excision of the recurrent tumor. No patient in either group had experienced metastasis at the time of this study. Local recurrence did not correlate with patient age (t test, \( P=0.155 \)) or sex (chi-square test, \( P=0.380 \)) for patients with lipomas or ALT/WDL, neither with size (t test, \( P=0.920 \)) or location (chi-square test, \( P=0.630 \)) of the tumors.

Lipomas were diagnosed in 25 men and 22 women compared with ALT/WDL in 27 men and 16 women; this difference was not statistically significant (chi-square test, \( P=0.327 \)). Mean age of patients with lipomas was 56 years (range, 34-74 years), and mean age of patients with ALT/WDL was 58 years (range, 33-78 years); this difference was not statistically significant (t test, \( P=0.630 \)).

In general, lipomas were smaller than ALT/WDL. The mean maximum diameter of lipomas was 13.5 cm (range, 6-24 cm) compared with 16.5 cm (range, 5-35 cm) for ALT/WDL; this difference was statistically significant (t test, \( P=0.000 \)). Lipomas had an equal predilection for upper and lower extremities, whereas most of ALT/WDL occurred in lower extremities; this difference was statistically significant (chi-square test, \( P=0.001 \)).

DISCUSSION

The differential diagnosis of lipomas and ALT/WDL in the extremities often is difficult with imaging alone and can also be problematic histologically.4,7 In addition, controversy exists regarding the rate of local recurrence, optimal treatment, and adequate length of follow-up for patients with lipomas and ALT/WDL.13 Therefore, accurate classification is necessary for an optimal treatment strategy.1,2

Currently, molecular cytogenetic analysis has enhanced the ability to differentiate between lipomas and ALT/WDL4; amplification of MDM2 gene on chromosome 12 (12q13-15) is typical for ALT/WDL, whereas it has never been reported for lipomas.4 Based on this cytogenetic analysis, this study was performed to classify patients with lipomas and ALT/WDL of the extremities, aiming to evaluate their outcome after marginal excision of their tumors. The results showed statistically significantly higher local recurrence rates for patients with ALT/WDL compared with patients with lipomas of the extremities, without any relationship with patient age and sex or size and location of the tumors.
There are 2 limitations with this study. First, the study design is retrospective with its inherent limitations. However, well-controlled retrospective studies are useful to evaluate a treatment approach. In this study, all of the patients had preoperative biopsy followed by marginal surgical resection and postoperative histologic analysis of their tumors. For the purpose of the study, the histology of the tissue specimens was reviewed again and evaluated for MDMA amplification in all of the patients; a consensus with postoperative histologic analysis was confirmed, and the diagnosis of ALT/WDL was documented. Therefore, in this setting, the current authors believe the analysis and results are valid.

Second, the length of follow-up of the study is relatively short. To obtain useful results, all patients with deep-seated lipomas and ALT/WDL of the extremities with a minimum follow-up of 12 months and complete imaging and histologic data were included in the study. However, given the relatively short follow-up, the results should be regarded with caution as it is possible that the results of this series underestimates the true rate of local recurrence of ALT/WDL, which likely will increase over time.

The differential diagnosis of lipomas and ALT/WDL can be problematic because of overlapping demographic, imaging, and histologic features. Increased patient age, tumor size, and deep location have been suggested as indicators of ALT/WDL instead of lipomas. Other studies have evaluated the sensitivity and specificity of MRI for the differential diagnosis of lipomas and ALT/WDL. On MRI, ALT/WDL have a homogenous signal and are differentiated from lipomas by their size, increased number of fibrous septations, nodules, and contrast medium uptake. Lipomas often show thin areas of linear enhancement, whereas thicker septae are more typical for ALT/WDL.

Only 2 previous studies evaluated the outcome of patients with cytogenetically confirmed ALT/WDL. Using immunohistochemistry, reverse transcriptase polymerase chain reaction, or FISH, lipomas are characterized by rearrangements of the chromatin remodeling gene HMGA2 on chromosome 12q15. In contrast, ALT/WDL have been shown to contain a supernumerary ring or giant marker chromosomes in the 12q13-15 region. FISH has been shown to provide the best correlation between the presence of the amplified MDMA gene and the morphologic features of ALT/WDL.

Bidault et al compared imaging criteria of malignancy with combined cytogenetic and molecular genetic analyses, and concluded that the main pitfall for a false-positive radiologic diagnosis of ALT/WDL was a large-sized tumor. Brisson et al reviewed 102 cases of molecularly confirmed lipomas and ALT/WDL and concluded that the most reliable imaging discriminators of ALT/WDL were the size of the lesion and lipomatous content, but due to the overlap in the MRI appearances of lipoma and ALT/WDL, discrimination should be based on molecular pathology rather than imaging. Both studies reported that ALT/WDL and lipoma had overlapping MRI characteristics, and that MRI overdiagnosed ALT/WDL.

The current authors concur with these reports and recommend molecular cytogenetic analysis for the differential diagnosis of lipomas and ALT/WDL to obtain a tissue diagnosis before surgical intervention. Molecular analysis using MDMA amplification contributes to the correct diagnosis of ALT/WDL. This can be performed on the tissue sample obtained with the preoperative needle biopsy.

The reported rates for local recurrence and dedifferentiation of ALT/WDL vary widely. The local recurrence rate for ALT/WDL ranges from 5% to 52%, and the recurrence rate of lipoma is similar, ranging from 3% to 62.5%. However, it is possible that the true recurrence rate of lipoma may be lower and that these studies likely misclassified many patients with ALT/WDL as having lipomas. Therefore, local recurrence rates for molecular-confirmed lipomas and ALT/WDL have not been established until the present study.

The optimal treatment and follow-up protocol for lipomas and ALT/WDL has been unclear. Although marginal excision has been a standard practice for lipomas, current treatment for ALT/WDL is controversial. Some surgeons suggest a marginal excision, whereas others recommend a wide resection. Lucas et al reported that ALT/WDL resected with wide margins locally recurred in 11% of cases, whereas those resected by marginal margins recurred in 60% of cases. Similarly, Kooby et al reported a higher risk of local recurrence after marginal excision of ALT/WDL. In contrast, Sommerville et al reported a local recurrence rate of 8% after marginal excision of 61 ALT/WDL, and Bassett et al also recommended a marginal excision for ALT/WDL because of a low risk for local recurrence. However, these studies are limited by the lack of molecular analysis for accurate diagnosis of lipomatous tumors.

In the current study, the authors acknowledge that obtaining a tissue diagnosis before surgical intervention is ideal. Although histology remains the cornerstone for the diagnosis of lipomatous tumors, complementary molecular cytogenetic analysis enhances the results obtained with histologic analysis, aiming to diagnose a lipoma or ALT/WDL correctly before surgery to predict the outcome and risk of local recurrence of deep-seated lipomatous tumors.

In addition, conservative surgery is preferable for lipomas and ALT/WDL. Although a marginal surgical dissection extends into or through the reactive zone of the tumor that possibly is microscopically positive, the current authors perform marginal excision because of the benign and low-grade malignant behavior of the respective tumors, and the awareness that a wide resection is associated with...
increased morbidity compared with re-
excision of an eventual local recurrence. Although metastases have not been re-
ported, recurrent ALT/WDL may show
dedifferentiation in a rate ranging from
1% to 4%,7,13 as in one patient in the cur-
rent series.

**CONCLUSION**

This study showed that molecular cy-
togenetic analysis provides for accurate
differential diagnosis of lipomas and ALT/ WDL compared with histologic analysis
alone, and the local recurrence rate is higher for ALT/WDL compared with lipomas
of the extremities after marginal excision,
without any relationship of local recur-
rence with patient age and sex, or tumor
type, size and location. Late recurrences of ALT/ WDL may occur; therefore, long-term fol-
low-up is recommended for these patients.

**REFERENCES**

The general surgeon’s quandary: atypical
lipomatous tumor vs lipoma, who needs a

al. Molecular testing for lipomatous tumors:
critical analysis and test recommendations
based on the analysis of 405 extremity-based
tumors. Am J Surg Pathol. 2010; 34(9):1304-
1311.

3. O’Donnell PW, Griffin AM, Eward WC, et
al. Can experienced observers differentiate
between lipoma and well-differentiated li-
posarcoma using only MRI? Sarcoma. 2013;
2013:982784.

M. Conservative surgery for well-differen-
tiated liposarcomas of the extremities adjacent
to major neurovascular structures. Surg Oncol.

5. Dei Tos AP, Pedeutour F. Atypical lipoma-
tous tumour/well differentiated liposarcoma.
In: Fletcher CDM, Unni KK, Mertens F, eds.
World Health Organization Classification of
Tumours: Pathology and Genetics of Tu-
mours of Soft Tissue and Bone. Lyon, France:

6. Billing V, Mertens F, Domanski HA, Ryd-
holm A. Deep-seated ordinary and atypical
lipomas: histopathology, cytogenetics, clini-
cal features, and outcome in 215 tumours of
the extremity and trunk wall. J Bone Joint

Deep-seated, well differentiated lipomatous
tumors of the chest wall and extremities: the
role of cytogenetics in classification and prog-

8. Rozental TD, Khoury LD, Donthineni-Rao R,
Lackman RD. Atypical lipomatous masses of
the extremities: outcome of surgical treatment.
Clin Orthop Relat Res. 2002; 398:203-211.

of MDM2 amplification and unexpected
multiple faint alphoid 12 (alpha 12 satellite
sequences) signals in atypical lipomatous tu-

10. Lucas DR, Nascimento AG, Sanjay BK,
Rock MG. Well-differentiated liposarcoma:
the Mayo Clinic experience with 58 cases.

11. Campanacci M. Bone and Soft Tissue Tu-
mors: Clinical Features, Imaging, Pathol-
ogy and Treatment. 2nd ed. New York, NY:
Springer Verlag; 1999:983-1020.

12. Enneking WF. A system of staging musculo-

13. Mavrogenis AF, Lesensky J, Romagnoli C,
Alberghini M, Letson GD, Ruggieri P. Atypi-
cal lipomatous tumors/well-differentiated li-
posarcomas: clinical outcome of 67 patients.

MRI characteristics of lipoma and atypical
lipomatous tumor/well-differentiated liposar-
coma: retrospective comparison with histol-
ogy and MDM2 gene amplification. Skeletal

Septum-like structures in lipoma and liposar-
coma: MR imaging and pathologic correla-

coma or lipoma: does genetics change clas-
sic imaging criteria? Eur J Radiol. 2009;

17. Kooby DA, Antonescu CR, Brennan MF,
Singer S. Atypical lipomatous tumor/well-
differentiated liposarcoma of the extremity
and trunk wall: importance of histological
subtype with treatment recommendations.

18. Sommerville SM, Patton JT, Luscombe JC,
Mangham DC, Grimer RJ. Clinical outcomes
of deep atypical lipomas (well-differentiated
lipoma-like liposarcomas) of the extremities.

19. Mentzel T, Fletcher CD. Lipomatous tu-
mours of soft tissues: an update. Virchows