

A Scoring System Combining Clinical, Radiological, And Histopathological Examinations For Differential Diagnosis Between Lipoma And Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma

Yohei Asano

Kanazawa University Graduate School of Medical Science

Shinji Miwa

Kanazawa University Graduate School of Medical Science

Norio Yamamoto (✉ norinori@med.kanazawa-u.ac.jp)

Kanazawa University Graduate School of Medical Science

Katsuhiko Hayashi

Kanazawa University Graduate School of Medical Science

Akihiko Takeuchi

Kanazawa University Graduate School of Medical Science

Kentaro Igarashi

Kanazawa University Graduate School of Medical Science

Hiroataka Yonezawa

Kanazawa University Graduate School of Medical Science

Yoshihiro Araki

Kanazawa University Graduate School of Medical Science

Sei Morinaga

Kanazawa University Graduate School of Medical Science

Takayuki Nojima

Kanazawa University Graduate School of Medical Science

Hiroko Ikeda

Kanazawa University Hospital

Hiroyuki Tsuchiya

Kanazawa University Graduate School of Medical Science

Research Article

Keywords: radiological, histopathological, atypical lipomatous tumor, magnetic resonance imaging

Posted Date: July 7th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-279121/v2>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Scientific Reports on January 7th, 2022.

See the published version at <https://doi.org/10.1038/s41598-021-04004-1>.

Abstract

This study evaluated the diagnostic accuracy of clinical, radiological, and histopathological examinations for differential diagnosis between atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLS) and lipoma, and aimed to develop a new combined scoring system for the preoperative diagnosis of ALT/WDLS. Eighty-nine ALT/WDLS and 56 lipomas were included and their clinical characteristics, magnetic resonance imaging (MRI) findings, histological findings by hematoxylin and eosin (HE) staining were investigated. Then, univariate and multivariate logistic regression analyses were performed for the findings, and a combined scoring system consisted of predictive factors of ALT/WDLS was developed. The univariate and multivariate logistic regression analyses revealed that tumor location (lower extremity), deep site, size (>11 cm), thick septa (>2mm), enhancement of septa or nodular lesions, and lipoblasts were significantly different for the diagnosis of ALT/WDLS. We developed a combined scoring system based on the six predictive factors (total 0–16 points, the cutoff was 9 points). The area under the curve was 0.945, and sensitivity was 87.6% and specificity was 91.1% by the receiver operating characteristics curve. This combined scoring system does not require special equipment and reagents such as fluorescence in situ hybridization (FISH), and anyone can use it easily in many medical institutions with high diagnostic accuracy.

Introduction

Adipocytic tumors are the most common soft tissue tumors, and the frequency of lipoma and atypical lipomatous tumor (ALT)/well-differentiated liposarcoma (WDLS) is high in clinical practice¹. Most of the adipocytic tumors are either lipomas or ALTs, accounting for 40–45% of all tumors of the adipose tissue^{2,3}. On the other hand, liposarcomas are the most common soft tissue sarcoma⁴. ALT/WDLS is the most common subtype of liposarcoma, accounting for 40–45% of all liposarcomas^{5,6}. It has been reported that ALT and WDLS are essentially synonymous, as the lesions are morphologically and karyotypically identical distinguished only by the tumor site. Adipocytic tumors located in the retroperitoneal or regions in which the tumor cannot be resected with a sufficient margin are termed WDLS², whereas those located in the extremities and superficial sites are classified as ALT¹.

It has been difficult to differentiate between ALT/WDLS and lipoma preoperatively because their magnetic resonance imaging (MRI) findings are similar¹, and small biopsy samples are insufficient for histopathological diagnosis⁷. The selection of surgical resection margins in these tumors remains controversial. ALT and WDLS are classified as intermediate (locally aggressive) and malignant tumors, respectively, and they have a high risk of local recurrence than lipoma⁷. Additionally, as they may undergo dedifferentiation and become malignant tumors⁸, some patients need wider resection margins while still avoiding dysfunction. Therefore, the preoperative differential diagnosis between ALT/WDLS and lipoma is critical for the determination of the resection margin.

Although there have been some reports regarding the usefulness and high accuracy of the assessment, such as fluorescence in situ hybridization (FISH) for murine double-minute 2 (*MDM2*) and cyclin-dependent kinase 4 (*CDK4*) for the diagnosis of ALT/WDLS⁹⁻¹⁶, these technologies require special equipment and reagents, so not all medical institutions can perform this examination⁷. The assessment with MRI and hematoxylin and eosin (HE) staining remains the standard method of diagnosis for adipocytic tumors, so it is crucial to determine the diagnosis by a comprehensive assessment of clinical, radiological, and histopathological examinations. Here, we evaluated the diagnostic accuracy of various findings in some examinations and aimed to develop a combined scoring system based on the accuracy of each finding for the preoperative differential diagnosis between ALT/WDLS and lipoma.

Results

The 145 participants comprised 77 men and 68 women, with a mean age of 58.8 ± 14.7 years (range 18–87 years). Based on the diagnoses established by the pathologists, the numbers of patients in the ALT/WDLS and lipoma groups were 56 and 89, respectively (Table 1). Of the 56 cases of ALT/WDLS, 46 cases underwent FISH for *MDM2* and 37 cases (80.4%) were positive and diagnosed definitively. The other 10 cases were diagnosed based on histological features^{2,17} or positive of FISH for *CDK4*. All ALT/WDLS cases were followed up after surgery and recurrence was observed in 2 cases. Clinical findings showed that the mean age of patients in the ALT/WDLS group was significantly higher than that in the lipoma group (64.0 ± 13.3 vs. 55.7 ± 14.6 , $p < 0.001$). All tumors in the ALT/WDLS group were located deep (100% vs. 67.4%, $p < 0.0001$) and significantly larger than those in the lipoma group (17.2 ± 6.7 cm vs. 9.7 ± 4.2 cm, $p < 0.0001$) (Table 1). On MRI, every criterion showed a significant difference between the ALT/WDLS and lipoma groups (thick septa (> 2 mm); $p < 0.0001$; enhancement; $p < 0.0001$; and neurovascular involvement, $p = 0.0225$). The histological findings by HE staining, such as nuclear atypia and enlargement, difference in size of adipocytes and lipoblasts, and FISH examination for *MDM2* and/or *CDK4* showed a significant differences between them ($p < 0.0001$). Only the proliferation of fibrous septa has a non-significant p-value of 0.949 (Table 1).

The tumor size was analyzed using the receiver operating characteristic (ROC) curve, with the cutoff value was set to 11 cm. In previous studies, cutoff values of tumor size for differential diagnosis between lipoma and ALT/WDLS were 10–13 cm^{1,18}, and our result was consistent with those studies. Univariate analyses revealed that age, tumor location, depth and size, thick septa (> 2 mm), enhancement of septa or nodular lesions, histological findings excluding the proliferation of fibrous septa, and FISH examination for *MDM2* and/or *CDK4* were significantly different (Table 2). Among these factors, the odds ratio of tumor depth, nuclear atypia, and FISH examination were extremely higher than other factors. Particularly, nuclear atypia and FISH examination were not positive in the lipoma group in this study, and the specificity of these parameters for the diagnosis of ALT/WDLS was 100%. If nuclear atypia is found in the specimens of the adipocytic tumor, the diagnosis of lipoma is excluded. *MDM2* and *CDK4* gene amplification by FISH examination is considered the gold standard for the differential diagnosis between ALT/WDLS and lipoma¹⁵, and these gene amplifications are not observed in lipoma. From these results,

nuclear atypia and FISH examination, which are used for the definitive diagnosis of ALT/WDLS, were excluded in this study. We aimed to develop a scoring system in which these factors were negative.

Subsequently, multivariate analysis incorporating the variables with $p < 0.05$ in the univariate analysis was performed. In the analysis, tumor location (lower extremity), depth (deep site), and size (> 11 cm), thick septa (> 2 mm), enhancement of septa or nodular lesions, and lipoblasts were significantly different, and they had a high accuracy in the diagnosis of ALT/WDLS (Table 2).

Based on these results, a combined scoring system for the preoperative differential diagnosis of ALT/WDLS was developed according to the predictive factors (Table 3). With reference to the odds ratio, the points of this score were set as follows: < 5 , 1 point; 5–10, 2 points; and > 10 , 3 points. The odds ratio of the tumor depth was extremely high, so the point was set to 5 points. The total points ranged from 0 to 16, and the mean number of points of the ALT/WDLS group was significantly higher than that of the lipoma group (mean points of ALT/WDLS and lipoma groups were 11.9 vs. 5.6, $p < 0.0001$). The cutoff value was 9 points based on the ROC curve analysis. The increased points suggested that the possibility of ALT/WDLS was higher, with a sensitivity of 87.6% and a specificity of 91.1% (Fig. 1). The analysis of the ROC curve also showed an area under the curve (AUC) of 0.945, which indicated that the accuracy of this combined scoring system for the differential diagnosis of ALT/WDLS was very high. If needle biopsy could not be performed, the total points were ranged from 0 to 13, excluding lipoblast, and the ROC curve analysis showed the cutoff value was 10 points and AUC was 0.943 with a sensitivity of 94.4% and a specificity of 80.4%.

Discussion

A lipoma is a benign tumor that can usually be treated conservatively^{1,7}. Even if the tumor size is large, surgical treatment is not necessary as long as it remains asymptomatic. On the other hand, ALT/WDLS is the most common subtype of liposarcoma, and the treatment for these tumors is controversial¹ because it is reported that 1–4% of them undergo dedifferentiation^{19–21} and may become malignant tumors^{2,8,19,22}. If preoperative differential diagnosis between ALT/WDLS and lipoma is easy in ALT/WDLS patients, surgical resection is recommended before dedifferentiation¹. The decision of the resection margin of ALT/WDLS is difficult because the local recurrence rate is high⁷. It has been reported that there was no significant difference in the recurrence rate between the wide and marginal resection in ALT²³, and "conservative" surgery, aiming to preserve major vessels or nerves, may be recommended for deep-seated ALT/WDLS^{24–27}. However, insufficient resection may increase the risk of recurrence and dedifferentiation and resulting in the need for more surgery to perform additional tissue resection. On the other hand, in recent years, Vos et al. reported that observation could be a reasonable option for selected patients with extremity WDLS²⁸. For these reasons, it is crucial to make an accurate differential diagnosis between ALT/WDLS and lipoma for the preoperative plan of the appropriate resection margin and the appropriate selection of patients who can be observed.

For the differential diagnosis, previous studies reported critical factors such as clinical findings (older age^{13,29,30}, tumor size [$> 10\text{cm}$]^{1,12,29,31}, tumor site [lower extremity]^{12,29,31}, and deep-seated location¹) and MRI findings (thick septa [$> 2\text{mm}$]^{32,33}, fat content less than 75%³⁰, and contrast enhancement¹). In this study, a multivariate analysis was performed to evaluate the predictive factors for ALT/WDLS, and there was a significant difference in tumor site (lower extremity), depth, size ($> 11\text{cm}$), thick septa, and enhancement of septa or nodular lesions. All of these were consistent with the previously mentioned factors, demonstrating high accuracy for the differential diagnosis of ALT/WDLS. MRI findings have high sensitivity but low specificity for the diagnosis of ALT/WDLS, and it has been reported that it may be difficult to decide the diagnosis of them by only MRI findings^{7,29}. On the other hand, Brisson et al. reported that histopathological examination could be used to distinguish ALT/WDLS from lipomas²⁹, so for adipocytic tumors, needle biopsies have been generally performed preoperatively to obtain the diagnosis².

Histopathological findings in the multivariate analysis showed that lipoblasts were statistically significant for the diagnosis of ALT/WDLS. Traditionally, lipoblasts have been emphasized as a histopathological finding in the diagnosis of liposarcoma³⁴. However, lipoblasts are also observed in benign lipogenic tumors such as spindle cell/pleomorphic lipoma. Furthermore, it has been reported that they are not always observed in ALT/WDLS³⁵. Although the diagnostic accuracy of lipoblasts in the diagnosis of ALT/WDLS has not been clarified, our study revealed that their sensitivity was low (19.6%), but the specificity was very high (98.9%). Although only lipoblasts cannot make a definitive diagnosis of ALT/WDLS, they may be important factors in the diagnosis by comprehensive evaluations together with clinical and radiological examinations.

In this study, nuclear atypia had a significant difference in the differential diagnosis of ALT/WDLS by univariate analysis. ALT/WDLS features a mature adipocytic tumor showing atypical hyperchromatic nuclei², which is consistent with our results. No nuclear atypia is found in lipoma, which is a benign tumor, so this characteristic is used for the rule out of the diagnosis of these tumors. The specificity of nuclear atypia was 100% in the diagnosis of ALT/WDLS in this study. However, needle biopsies may not provide enough sample for the identification of unequivocal atypical cells^{7,36}, and the atypical stromal cells sometimes scatter throughout the lesion; therefore, in some cases, the difference between ALT/WDLS and lipoma may be subtle challenging the differential diagnosis process³⁶. In addition, FISH examination for *MDM2* and *CDK4* gene amplification has provided the most accuracy for the diagnosis of ALT/WDLS^{9-13,15,16}, and it is considered the gold standard for the differential diagnosis between ALT/WDLS and lipoma¹⁵. In this study, as well as previous studies, *MDM2* and/or *CDK4* amplification by FISH examination showed a significant difference as a predictive factor for ALT/WDLS. Furthermore, the specificity was 100%. *MDM2* gene amplification in FISH examination has high sensitivity and specificity¹⁵, and this finding has been used for the definitive diagnosis of ALT/WDLS. However, similar to nuclear atypia, an insufficient sample and the selection of an inappropriate needle biopsy site might complicate the accurate exclusion of a diagnosis of ALT/WDLS due to the absence of *MDM2* gene

amplification. Furthermore, HE staining in the histopathological examination can be generally performed in many institutions, but FISH examination requires special equipment and reagents, which not all institutions are equipped to perform⁷. For these reasons, this study excluded the nuclear atypia and FISH examination used for the definitive diagnosis of ALT/WDLS.

Based on these results, in adipocytic tumors, the differential diagnosis should be evaluated based on a comprehensive assessment of clinical, radiological, and histopathological examinations. Although a few scoring systems for the differential diagnosis of ALT/WDLS based on radiological findings have been reported^{1,7}, there is no diagnostic scoring system that includes histopathological findings. In the previous studies of similar scoring systems, Nagano et al. reported a sensitivity of 100% and specificity of 77%¹, and Cheng et al. reported a sensitivity of 90% and specificity of 92.5%⁷. The diagnostic accuracy for ALT/WDLS of this scoring system is almost the same as in these studies. However, Nagano et al. study examined 48 lipomas and 12 ALTs, without including WDLS, and the case number was lower compared with our study¹. In addition, this study investigated adipocytic tumors in all locations, but Cheng et al. investigated only deep-seated adipocytic tumors⁷. These limitations may have affected the difference in accuracy between our scoring system and those studies. Although the diagnostic accuracy of our combined scoring system for ALT/WDLS was slightly lower than that of FISH for MDM2, our scoring system will help to distinguish between ALT/WDLS and lipoma in general orthopedic surgeons at clinics where cannot perform FISH examination.

This study had a limitation that the evaluation of specimens of needle biopsy may be affected by the biopsy site and the amount of sample. If a preoperative needle biopsy can be performed with an accurate procedure, the diagnostic accuracy for ALT/WDLS of this scoring system may be higher, which makes it a very useful diagnostic tool for the preoperative differential diagnosis of adipocytic tumors.

In conclusion, we developed a new combined scoring system based on a comprehensive assessment of clinical, radiological, and histopathological examinations for the preoperative differential diagnosis between ALT/WDLS and lipoma. This scoring system had high diagnostic accuracy for differential diagnosis of ALT/WDLS and was a useful preoperative diagnostic tool that anyone can use easily in many medical institutions.

Materials And Methods

Study design and patients

This retrospective study included patients diagnosed with ALT/WDLS or lipoma from 2005 to 2019 collected from the database at Kanazawa University Hospital. A total of 297 patient charts were extracted, and 145 patients who underwent surgical resection after evaluation by MRI and needle biopsy were included in this study. The diagnoses were established by pathologists based on the resected specimens. Histologically, ALT/WDLS has been reported that the proliferation of mature and variably pleomorphic adipocytes containing single, enlarged, hyperchromatic nuclei, and intersection by fibrous

septa are observed and distinguished from lipoma^{2,17}. Of the 145 resected specimens, 82 cases were diagnosed with ALT/WDLS based on these histological features, but in the other 63 cases that differential diagnosis was histologically difficult were performed FISH of *MDM2* and/or *CDK4* and diagnosed. Spindle cell lipoma and pleomorphic lipoma which have relatively typical pathological findings, and tumor recurrences were excluded from this study. This study was approved by the ethics committee of Kanazawa University Hospital, and Informed consent was obtained from all the participants. In addition, all methods were carried out in accordance with relevant guidelines and regulations.

Data analyses

We collected the patients' clinical characteristics, including age, sex, symptoms (pain and numbness), and tumor site and depth from the medical records. The tumor depth was defined as a superficial or deep site with the fascia as the boundary by MRI (Philips Ingenia Elition 3.0T, Amsterdam, Netherlands). Based on the previous studies regarding MRI findings used to distinguish ALT/WDLS and lipoma, radiologists evaluated three criteria: thick septa (>2mm), enhancement of septa or nodular lesions, and neurovascular involvement in the tumor^{1,32,33} (Fig. 2). The enhancement of septa or nodular lesions was evaluated on fat-suppressed T1 or T2-weighted images after the administration of contrast medium. All images were evaluated by 2 specialists of radiology, and in cases that their evaluations were equivocal, evaluated by another specialist and diagnosed with an agreement of inter-observer. Furthermore, based on histological findings by HE staining from needle biopsies specimens, the pathologists evaluated characteristics such as nuclear atypia and enlargement, proliferation of fibrous septa, differences in the size of adipocytes, and lipoblasts^{2,8,33} (Fig. 3). Lipoblasts were defined as the cells having hyperchromatic indented or sharply scalloped nuclei and lipid-rich mono- or multivacuolated cytoplasm^{8,37}. In most patients diagnosed after 2013, the needle biopsy specimens were evaluated by FISH for *MDM2* and/or *CDK4* based on the recommended criteria for the test; deep lesions that are >10 cm and in cases with equivocal atypia¹¹.

Statistical analyses

These characteristics and findings were compared between the ALT/WDLS and lipoma groups by Student's t-test or the chi-square test. A p-value of less than 0.05 was considered statistically significant. Univariate logistic regression analysis was performed to determine the predictive factors for the diagnosis of ALT/WDLS and variables with p<0.05 from univariate analysis were used for multivariate logistic regression analysis. A combined scoring system for the diagnosis of ALT/WDLS was developed according to the predictive factors that showed statistical significance by multivariate analyses. The accuracy of the diagnoses of the scoring system was evaluated using a ROC curve. All data analyses were performed using EZR³⁸.

Declarations

Acknowledgments

We would like to thank Editage (www.editage.jp) for English language editing.

Authors' contributions

All authors were involved in the preparation of this study. YA and SM collected the data and performed the operation, and YA wrote the manuscript. NY, KH, AT, KI, HY, YA, and SM performed the operation and designed the study. TN and HI performed a histopathological evaluation of the specimens. HT revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

References

1. Nagano, S. et al. Differentiation of lipoma and atypical lipomatous tumor by a scoring system: implication of increased vascularity on pathogenesis of liposarcoma. *BMC. Musculoskelet. Disord.* **16**, 36 (2015).
2. The World Health Organization classification of Tumor Editorial Board. WHO Classification of Tumors Soft Tissue and Bone Tumors. 5th ed. Lyon. (IARC Press, 2020).
3. Dalal, K. M., Antonescu, C. R. & Singer, S. Diagnosis and management of lipomatous tumors. *J. Surg. Oncol.* **97**, 298–313 (2008).
4. Coindre, J. M. New WHO classification of tumors of soft tissue and bone. *Ann. Pathol.* **32 Suppl 5**, 115–116 (2012).
5. Wang, J. & Zhu, X. Z. Introduction of WHO classification of tumours of soft tissue, the fourth edition. *Zhonghua. Bing. Li. Xue. Za. Zhi.* **42**, 363–365 (2013).
6. Conyers, R., Young, S. & Thomas, D. M. Liposarcoma: Molecular Genetics and Therapeutics. *Sarcoma.* 483154; 10.1155/2011/483154 (2011).
7. Cheng, Y. et al. Developing a clinical scoring system to differentiated deep-seated atypical lipomatous tumor from lipoma of soft tissue. *Asian. J. Surg.* **42**, 832–838 (2019).
8. Laurino, L., Furlanetto, A., Orvieto, E. & Dei Tos, A. P. Well-differentiated liposarcoma (atypical lipomatous tumors). *Semin. Diagn. Pathol.* **18**, 258–262 (2001).
9. Binh, M. B. et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. *Am. J. Surg. Pathol.* **29**, 1340–1347 (2005).
10. Kimura, H. et al. Utility of fluorescence in situ hybridization to detect MDM2 amplification in liposarcomas and their morphological mimics. *Int. J. Clin. Exp. Pathol.* **6**, 1306–1316 (2013).

11. Clay, M. R., Martinez, A. P., Weiss, S. W. & Edgar, M. A. MDM2 Amplification in Problematic Lipomatous Tumors: Analysis of FISH Testing Criteria. *Am. J. Surg. Pathol.* **39**, 1433–1439 (2015).
12. Fisher, S. B. et al. The General surgeon's quandary: atypical lipomatous tumor vs lipoma, who needs a surgical oncologist? *J. Am. Coll. Surg.* **217**, 881–888 (2013).
13. Weaver, J. et al. Can MDM2 analytic tests performed on core needle biopsy be relied upon to diagnose well-differentiated liposarcoma? *Mod. Pathol.* **23**, 1301–1306 (2010).
14. Kulkarni, A. S. et al. MDM2 RNA In Situ Hybridization for the Diagnosis of Atypical Lipomatous Tumor: A Study Evaluating DNA, RNA, and Protein Expression. *Am. J. Surg. Pathol.* **43**, 446–454 (2019).
15. Kashima, T. et al. Sensitivity of MDM2 amplification and unexpected multiple faint aliphoid 12 (alpha 12 satellite sequences) signals in atypical lipomatous tumor. *Mod. Pathol.* **25**, 1384–1396 (2012).
16. Dei Tos, A. P. et al. Coordinated expression and amplification of the MDM2, CDK4, and HMGI-C genes in atypical lipomatous tumours. *J. Pathol.* **190**, 531–536 (2000).
17. Lee, A. T. J., Thway, K., Huang, P. H. & Jones, R. L. Clinical and Molecular Spectrum of Liposarcoma. *J. Clin. Oncol.* **36**, 151–159 (2018).
18. Knebel, C. et al. Differentiating atypical lipomatous tumors from lipomas with magnetic resonance imaging: a comparison with MDM2 gene amplification status. *BMC. Cancer.* **19**, 309 (2019).
19. Sommerville, S. M., Patton, J. T., Luscombe, J. C., Mangham, D. C. & Grimer, R. J. Clinical outcomes of deep atypical lipomas (well-differentiated lipoma-like liposarcomas) of the extremities. *ANZ. J. Surg.* **75**, 803–806 (2005).
20. Bassett, M. D. et al. Deep-seated, well differentiated lipomatous tumors of the chest wall and extremities: the role of cytogenetics in classification and prognostication. *Cancer.* **103**, 409–416 (2005).
21. Kooby, D. A., Antonescu, C. R., Brennan, M. F. & Singer, S. Atypical lipomatous tumor/well-differentiated liposarcoma of the extremity and trunk wall: importance of histological subtype with treatment recommendations. *Ann. Surg. Oncol.* **11**, 78–84 (2004).
22. Lucas, D. R., Nascimento, A. G., Sanjay, B. K. & Rock, M. G. Well-differentiated liposarcoma. The Mayo Clinic experience with 58 cases. *Am. J. Clin. Pathol.* **102**, 677–683 (1994).
23. Mussi, C. E. et al. Atypical lipomatous tumors: should they be treated like other sarcoma or not? Surgical consideration from a bi-institutional experience. *Ann. Surg. Oncol.* **21**, 4090–4097 (2014).
24. Chang, D. H., Ma, H., Liao, W. C., Huang, M. H. & Wu, P. S. Atypical lipomatous tumors of the extremities and trunk wall-the first case series of Chinese population with 45 cases. *Ann. Plast. Surg.* **76 Suppl 1**, 8–12 (2016).
25. Yamamoto, N. et al. Treatment strategies for well-differentiated liposarcomas and therapeutic outcomes. *Anticancer. Res.* **32**, 1821–1825 (2012).
26. Gronchi, A. et al. Extremity soft tissue sarcoma in a series of patients treated at a single institution: local control directly impacts survival. *Ann. Surg.* **251**, 506–511 (2010).

27. Kubo, T., Sugita, T., Shimose, S., Arihiro, K. & Ochi, M. Conservative surgery for well-differentiated liposarcomas of the extremities adjacent to major neurovascular structures. *Surg. Oncol.* **15**, 167–171 (2006).
28. Vos, M., Grünhagen, D. J., Koseła-Paterczyk, H., Rutkowski, P., Sleijfer, S. & Verhoef, C. Natural history of well-differentiated liposarcoma of the extremity compared to patients treated with surgery. *Surg. Oncol.* **29**, 84–89 (2019).
29. Brisson, M. et al. MRI characteristics of lipoma and atypical lipomatous tumor/well-differentiated liposarcoma: retrospective comparison with histology and MDM2 gene amplification. *Skeletal Radiol.* **42**, 635–647 (2013).
30. Kransdorf, M. J., Bancroft, L. W., Peterson, J. J., Murphey, M. D., Foster, W. C. & Temple, H. T. Imaging of fatty tumors: distinction of lipoma and well-differentiated liposarcoma. *Radiology.* **224**, 99–104 (2002).
31. Bird, J. E. et al. Non-radiographic risk factors differentiating atypical lipomatous tumors from lipomas. *Front. Oncol.* **6**, 197 (2016).
32. Ohguri, T. et al. Differential diagnosis of benign peripheral lipoma from well-differentiated liposarcoma on MR imaging: is comparison of margins and internal characteristics useful? *AJR. Am. J. Roentgenol.* **180**, 1689–1694 (2003).
33. Arkun, R., Memis, A., Akalin, T., Ustun, E. E., Sabah, D. & Kandiloglu, G. Liposarcoma of soft tissue: MRI findings with pathologic correlation. *Skeletal Radiol.* **26**, 167–172 (1997).
34. Hisaoka, M. Lipoblast: morphological features and diagnostic value. *J. UOEH.* **36**, 115–121 (2014).
35. Dei Tos, A. P. Liposarcomas: diagnostic pitfalls and new insights. *Histopathology.* **64**, 38–52 (2014).
36. Coindre, J. M., Pedetour, F. & Aurias, A. Well-differentiated and dedifferentiated liposarcomas. *Virchows. Arch.* **456**, 167–179 (2010).
37. Goldblum, J. R., Folpe, A. L. & Weiss, S. W. Enzinger & Weiss's Soft Tissue Tumors. 6th ed. 484–523 (Elsevier; 2013).
38. Kanda, Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow. Transplant.* **48**, 452–458 (2013).

Tables

Table 1. Characteristics of patients, MRI, and histopathological findings

	ALT/WDLs (N=56)	Lipoma (N=89)	p-value
Clinical findings			
Age			<0.001
Median (range)			
Sex: n (%)	64.0±13.29 (30–87)	55.7±14.60 (18–83)	0.547
Male			
Female	32 (57.1%)	45 (50.6%)	
Symptoms: n (%)	24 (42.9%)	44 (49.4%)	0.150
6 (10.7%)		4 (4.5%)	
Tumor site: n (%)			<0.0001
Upper limb	5 (8.9%)	29 (32.6%)	
Lower limb	39 (69.7%)	24 (27.0%)	
Other	12 (21.4%) ^a	36 (40.4%) ^b	
Tumor depth: n (%)			<0.0001
Superficial	0 (0%)	29 (32.6%)	
Deep	56 (100%)	60 (67.4%)	
Tumor size (cm)			<0.0001
Median	17.2±6.7	9.7±4.2	
MRI findings: n (%)			
Thick septa (>2mm)	52 (92.9%)	52 (58.4%)	<0.0001
Enhancement (septal and/or nodular lesions) (n=20)	20 (100%)	4 (20.0%)	<0.0001
Neurovascular involvement	5 (8.9%)	1 (1.1%)	0.023
Histopathological findings: n (%)			
Nuclear atypia	10 (17.9%)	0 (0%)	<0.0001
Nuclear enlargement	26 (46.4%)	8 (9.0%)	<0.0001
Difference in size of adipocytes	26 (46.4%)	24 (27.0%)	0.016
Proliferation of fibrous septa	2 (3.6%)	3 (3.4%)	0.949
Lipoblasts	11 (19.6%)	1 (1.1%)	<0.0001
FISH: positive number / n=total number (%)			
MDM2	37 / n=46 (80.4%)	0 / n=73 (0%)	<0.0001
CDK4	18 / n=33 (54.5%)	0 / n=49 (0%)	<0.0001

^a neck (n=4), chest (n=2), retroperitoneum (n=2), and back (n=2)

^b neck (n=15), chest (n=13), back (n=6), and abdomen (n=2)

Abbreviations: *MRI* magnetic resonance imaging, *ALT* atypical lipomatous tumor, *WDLs* well-differentiated liposarcoma, *FISH* Fluorescence in Situ Hybridization, *MDM2* murine double-minute 2, *CDK4* cyclin-dependent kinase 4

Table 2. Univariate and multivariate logistic regression analysis of predictive factors for ALT/WDLS

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Clinical findings				
Age	4.26 (1.87-9.74)	<0.001	4.16 (0.93-18.60)	0.062
Sex	1.30 (0.67-2.56)	0.440		
Symptoms	2.55 (0.69-9.47)	0.162		
Tumor site				
Lower limb vs Upper limb or Other	6.21 (2.97-13.00)	<0.0001	5.51 (1.51-20.10)	0.001
Depth	>1000 (0.00-Inf)	<0.0001	>1000 (0.00-Inf)	<0.0001
Tumor size (>11cm)	12.40 (5.20-29.60)	<0.0001	4.83 (1.37-17.00)	0.014
MRI findings				
Thick septa (>2mm)	9.25 (3.08-27.80)	<0.0001	5.56 (1.09-28.30)	0.039
Enhancement (septata or nodular lesion)	24.50 (7.90-76.10)	<0.0001	15.10 (2.91-77.90)	0.001
Neurovascular involvement	8.63 (0.98-75.90)	0.052		
Histopathological findings				
Nuclear atypia	>1000 (0.00-Inf)	<0.0001		
Nuclear enlargement	8.77 (3.58-21.50)	<0.0001	1.69 (0.40-7.17)	0.480
Difference in size of adipocytes	2.35 (1.16-4.74)	0.018	0.91 (0.26-3.20)	0.888
Proliferation of fibrous septa	1.06 (0.17-6.56)	0.949		
Lipoblasts	21.5 (2.69-172.00)	0.004	17.60 (1.08-286.00)	0.043
FISH				
MDM2 and/or CDK4	>1000 (0.00-Inf)	<0.0001		

Abbreviations: *MRI* magnetic resonance imaging, *CI* confidence interval, *Inf* infinity, *ALT* atypical lipomatous tumor, *WDLS* well-differentiated liposarcoma, *FISH* Fluorescence in Situ Hybridization, *MDM2* murine double-minute 2, *CDK4* cyclin-dependent kinase 4

Table 3. A combined scoring system for the preoperative differential diagnosing of ALT/WDLS

The total points ranged from 0 to 16, and the cutoff value was 9 points.

Predictive factors	Odds ratio	Points
Tumor size (MRI)	4.83	
<11cm		0
≥11cm		1
Tumor location (MRI)	5.51	
Upper limb or Other*		0
Lower limb		2
Thick septa (>2mm) (MRI)	5.56	
No		0
Yes		2
Enhancement of septa or nodular lesion (Enhanced MRI)	15.10	
No		0
Yes		3
Lipoblast (HE staining)	17.60	
Negative		0
Positive		3
Depth (MRI)	>1000	
Superficial		0
Deeper than fascia		5
Cutoff value		9 / 16 points

*: neck, chest, abdomen, back, and retroperitoneum

Abbreviations: *MRI* magnetic resonance imaging, *HE* hematoxylin and eosin, *ALT* atypical lipomatous tumor, *WDLs* well-differentiated liposarcoma

Figures

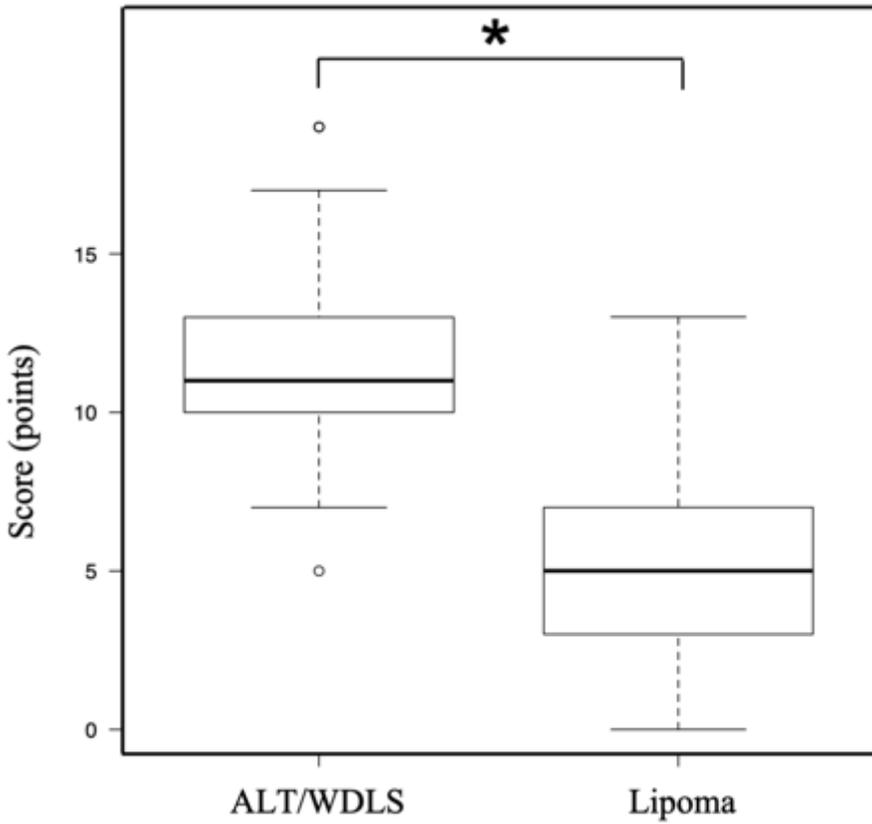


Figure 1

Comparison of the total score of the ALT/WDLS and lipoma groups (mean points were 11.9 vs. 5.6, * $p < 0.0001$)

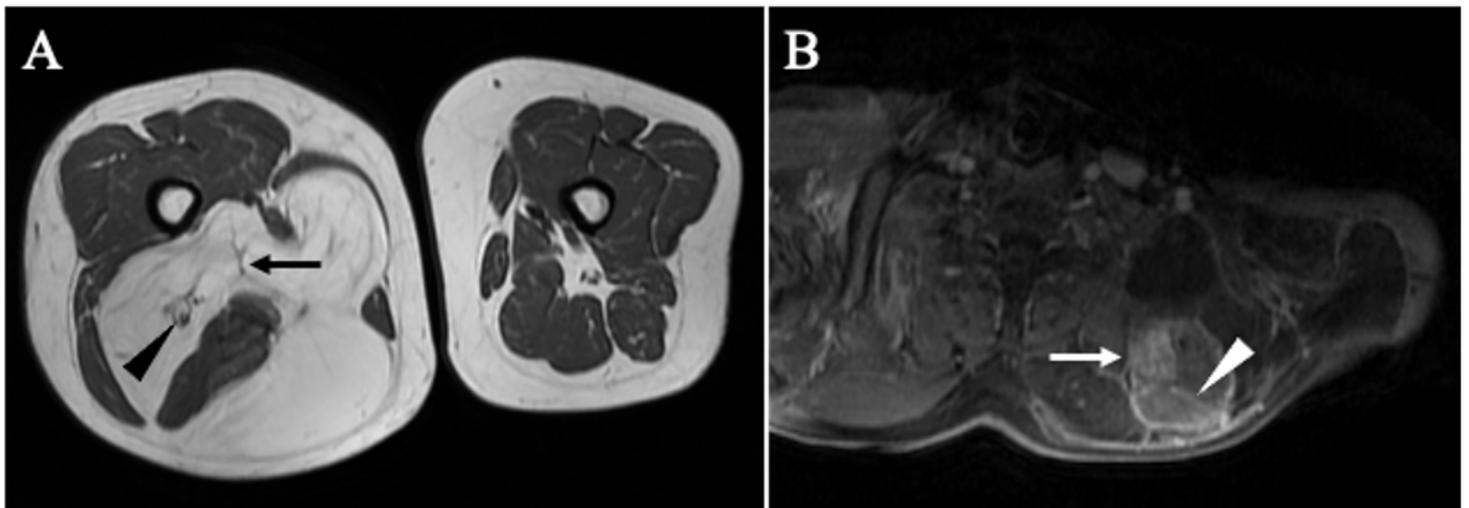


Figure 2

Radiological findings on MRI used in this study A. Thick septa (>2mm) (black arrow) and the sciatic nerve involved in the adipocytic tumor (black triangle) in T1-weighted image. B. Enhancement of septa (white triangle) and nodular lesion (white arrow) in contrast-enhanced fat-suppression T2 image.

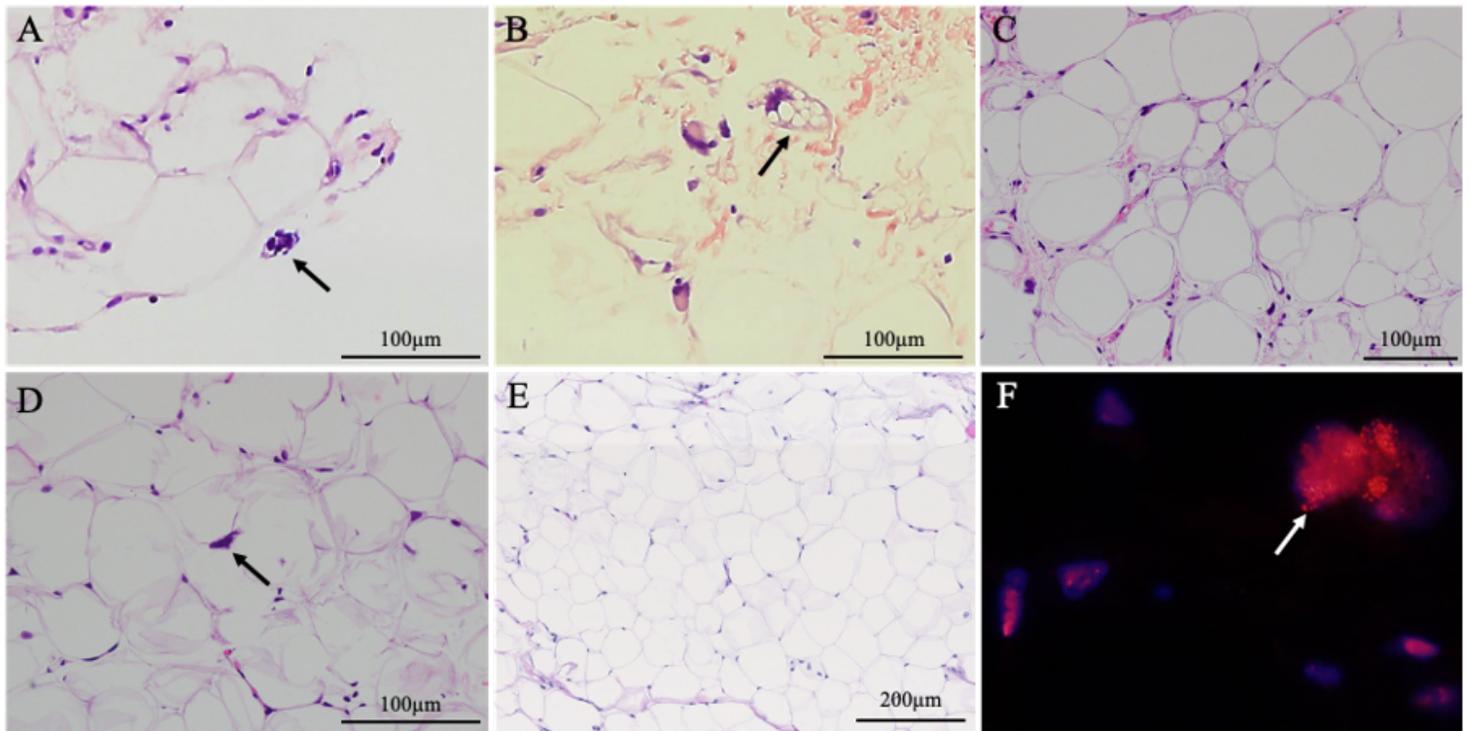


Figure 3

Histopathological findings by HE staining and FISH examination for MDM2 used in this study (A) Nuclear atypia, (B) lipoblast, (C) differences in size of adipocytes and proliferation of fibrous septa, (D) nuclear enlargement, and (E) lipoma specimen occupied by mature adipocytes without the differences in size in HE staining. (F) MDM2 gene amplification was detected by FISH.