

# Clinical Outcomes of Atypical Lipomatous Tumor/Well-Differentiated Liposarcoma of the Extremities: Analysis of Recurrence Factors

**Toshiki Zeniya**

Sapporo Medical University: Sapporo Ika Daigaku

**Makoto Emori** (✉ [emrmkt@yahoo.co.jp](mailto:emrmkt@yahoo.co.jp))

Sapporo Medical University: Sapporo Ika Daigaku <https://orcid.org/0000-0003-2512-2795>

**Hiroyuki Tsuchie**

Akita Daigaku Igakubu Fuzoku Byoin

**Hiroyuki Nagasawa**

Akita Daigaku Igakubu Fuzoku Byoin

**Kousuke Iba**

Sapporo Medical University: Sapporo Ika Daigaku

**Emi Mizushima**

Hakodate goryokaku Hospital

**Yoshiko Keira**

Hakodate Goryokaku Hospital

**Junya Shimizu**

Sapporo Medical University: Sapporo Ika Daigaku

**Yasutaka Murahashi**

Sapporo Medical University: Sapporo Ika Daigaku

**Atsushi Teramoto**

Sapporo Medical University: Sapporo Ika Daigaku

**Naohisa Miyakoshi**

Akita Daigaku Igakubu Fuzoku Byoin

**Shintaro Sugita**

Sapporo Medical University: Sapporo Ika Daigaku

**Tadashi Hasegawa**

Sapporo Medical University: Sapporo Ika Daigaku

**Yoichi Shimada**

Akita Daigaku Igakubu Fuzoku Byoin

**Toshihiko Yamashita**

Sapporo Medical University: Sapporo Ika Daigaku

## Research

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# Abstract

**Background:** Atypical lipomatous tumors/well-differentiated liposarcomas (ALT/WDLPS) are low-grade, slow-growing, and locally aggressive tumors. We investigated clinical outcomes and recurrence factors for ALT/WDLPS of the extremities.

**Patients and Methods:** The variables were evaluated as potential recurrence factor using Fisher's exact test. The 5-year recurrence-free survival (RFS) rate was calculated using the Kaplan-Meier method, and differences in survival were assessed using a log-rank test in univariate analyses.

**Results:** Sixty-two patients were identified, including 29 men and 33 women. The median age was 63.7 years (range, 34–82 years). The average maximum tumor diameter was 15.9 cm (range, 5–28 cm). The maximum tumor diameter ( $\geq 20$  cm) was significantly associated with local recurrence ( $p=0.049$ ). Ten patients (16.1%) developed local recurrence, and the mean time to recurrence was 48.4 months (range, 5–161 months).

## Conclusions:

Tumor diameter  $\geq 20$  cm was identified as a risk factor for recurrence.

# Introduction

Liposarcomas are the most common type of soft tissue sarcomas, accounting for approximately 20% of all soft tissue sarcomas[1, 2]. These are commonly classified into several subtypes, and among them, atypical lipomatous tumor/well-differentiated liposarcomas (ALT/WDLPS) are the most common adipocytic tumors accounting for 40–45% of all liposarcomas[3]. ALT/WDLPS most frequently occur in the deep soft tissue of the proximal extremity and trunk. The retroperitoneum is also commonly involved. ALT/WDLPS are low-grade, slow-growing, and locally aggressive tumors that have a risk of local recurrence and often dedifferentiate but do not metastasize. Therefore, in the clinical setting, it is important to identify recurrence factors for ALT/WDLPS of the extremities. Several factors including the length of the follow-up period, history of prior recurrence, incomplete or non-extensive resection, and tumor location have been reported as risk factors for recurrence of this disease[4–6].

ALT/WDLPS shares amplifications in the chromosomal region 12q13-15; these amplifications consistently affect murine double minute (MDM) 2 and, sometimes, cyclin-dependent kinase (CDK) 4 gene sequences. These amplifications can be detected using fluorescence in situ hybridization (FISH), which is currently the standard method; however, FISH requires specific equipment that is only available at specialized medical centers[7, 8]. Alternatively, immunohistochemistry (IHC) may serve as a convenient method for diagnosis. Antibodies against MDM2 and CDK4 are reliable for detecting protein overexpression that results from amplification of the corresponding genes[9]. The combination of IHC results for these two markers has not been described as a predictor of recurrence of ALT/WDLPS in the extremities.

In this study, we investigated: (1) the clinical outcomes of extremity ALT/WDLPS cases; (2) recurrence factors; (3) the role of IHC markers (MDM2, CDK4) as the correlation of their expression with recurrence.

## **Materials And Methods**

### **Ethics**

This study was approved by our institutional review board (No. 285 – 65), and the requirement for informed consent was waived.

### **Patient Selection**

This retrospective study across three institutions (Sapporo Medical University, Akita University, and Hakodate Goryoukaku Hospital) included patients who had undergone surgery for ALT/WDLPS from 2001 to 2019. We identified 89 such patients. Eleven patients were excluded because they had tumors in their neck, back, or retroperitoneum. Sixteen patients were excluded due to lack of data, such as surgical margins, duration of follow-up, or IHC results. The patient selection procedure is shown in the flow chart (Fig. 1). Following these exclusions, 62 patients were included in the final analysis.

### **Data collection**

We collected the data such as the patient demographics, anatomical locations of the tumors (subcutaneous, intramuscular, intermuscular, upper extreme/lower extremity), immunohistochemical data, and the resected margin status.

### **Surgical margins**

The margin was defined as R0 if microscopically complete (wide resection), R1 if the margins were microscopically positive (marginal resection), and R2 if the resection was macroscopically positive (intralesional resection).

### **Immunohistochemical analysis**

IHC was performed on 4- $\mu$ m-thick formalin-fixed paraffin-embedded tissue sections using the following antibodies: MDM2 (clone IF2, dilution 1:100, Sigma-Aldrich, USA) and CDK4 (clone DCS-31, dilution 1:100, Thermo Fischer, USA). The results were independently evaluated by a pathologist (S.S.) who was blinded to the final diagnosis. A tumor was considered positive for MDM2 or CDK4 when at least one tumor cell nucleus was stained per high-power field, as previously described[9].

### **Statistical analyses**

Patients were evaluated for local recurrence and dedifferentiation. The following variables were evaluated as potential recurrence factors: age, sex, tumor diameter, anatomical location of the tumor, immunohistochemical results, and resected margins using Fisher's exact test for categorical and dichotomous variables. The 5-year local recurrence-free survival rate (RFS) was calculated using the

Kaplan-Meier method, and differences in survival were assessed using the log-rank test in univariate analyses. Statistical significance was defined as  $p < 0.05$ . Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA).

## Results

### *Patient Characteristics*

The characteristics of the 62 patients included in this series are listed in Table 1. The records of 62 patients (29 men and 33 women) who were admitted to three institutions from 2001 to 2019 were reviewed. The median patient age was 63.7 years (range, 34–82 years), and the mean follow-up period was 56.1 months (range, 3–201 months). The tumor sites included the lower extremities ( $n = 55$ ; thigh, 45; buttocks, 7; lower leg, 3) and upper extremities ( $n = 7$ ; shoulder, 4; upper arms, 3), and the median tumor diameter was 15.9 cm (range, 5–28 cm). Tumors developed intramuscularly or between muscles in 58 (93.5%) cases and subcutaneously in 4 (6.5%) cases. Twelve patients (19.4%) underwent R0 resection, 48 (77.4%) underwent R1 resection, and two (3.2%) underwent R2 resection. In one case of R0 resection, in 8 cases of R1 resection, and in one case of R2 resection, the patients developed local recurrences.

Table 1  
Demographic and clinicopathologic characteristics of the 62 patients

	No. of patients (n = 62)	%
<b>Age, years (mean age; 64.2)</b>		
<50	5	8.1
≥50	57	91.9
<b>Gender</b>		
Male	29	46.8
Female	33	52.2
<b>Tumor size, mm (median 150)</b>		
<200	42	67.7
≥200	20	32.2
<b>Tumor site</b>		
<b>Upper limbs</b>	7	11.3
upper arm	3	4.8
shoulder	4	6.5
<b>Lower limbs</b>	55	88.7
thigh	45	72.6
buttock	7	11.3
lower leg	3	4.8
<b>Margin status</b>		
R0	12	19.4
R1/2	50	80.6
<b>Local recurrence</b>		
Present	10	16.1
Absent	52	83.9
<b>Distant metastasis</b>		
Present	0	0
Absent	62	100

### Local recurrence and dedifferentiation

Ten patients (16.1%) developed local recurrences. However, we observed no cases of dedifferentiation and no metastatic disease during their follow-up. Details of these 10 patients are presented in Table 2. These patients included 6 men and 4 women with a mean age of 62.7 years (range, 34–82 years); the mean time to local recurrence was 48.4 months (range, 5–161 months), and the average maximum tumor diameter was 18.7 cm (range, 13–26 cm).

Table 2

Details of 62 patients with atypical lipomatous tumor/well-differentiated liposarcoma of the extremities

	No. of patients with no recurrence (n = 52)	No. of patients with recurrence (n = 10)	p-value
<b>Age, years</b>			0.18
≤50	3	2	
> 50	49	8	
<b>Gender</b>			0.28
Male	23	6	
Female	29	4	
<b>Tumor size, mm</b>			0.049
<200	38	4	
≥200	14	6	
<b>Tumor site</b>			0.69
Upper limbs	6	1	
Lower limbs	46	9	
<b>Margin status</b>			0.38
R0	11	1	
R1/2	41	9	
<b>Immunohistochemistry</b>			
CDK4 <sup>neg</sup> MDM2 <sup>neg</sup>	35	6	0.49
CDK4 <sup>pos</sup> MDM2 <sup>neg</sup>	6	1	
CDK4 <sup>neg</sup> MDM2 <sup>pos</sup>	4	0	
CDK4 <sup>pos</sup> MDM2 <sup>pos</sup>	7	3	

A comparison of the non-recurrence and recurrence groups is presented in Table 2. The differences in local recurrences were not statistically significant for age ( $p = 0.18$ ), sex ( $p = 0.28$ ), tumor site ( $p = 0.69$ ), and surgical margin (R0 or not) ( $p = 0.38$ ). However, there was a statistically significant difference in the maximum tumor diameter over 20 cm ( $p = 0.049$ ).

#### *Recurrence-free survival and the recurrence factors*

The 5-year RFS rate was 85.4%. The univariate analyses of RFS are presented in Table 3. The differences in RFS were not statistically significant for age ( $p = 0.58$ ), sex ( $p = 0.19$ ), tumor site ( $p = 0.67$ ), surgical margin (wide resection or not) ( $p = 0.68$ ), and maximum tumor diameter over 20 cm or not ( $p = 0.09$ ).



Table 3  
Outcome in Univariate Analysis of Prognostic Factors

	5-y Local recurrence-free survival (%)	P value
Age, years		
≤ 50	82.50%	0.58
>50	100%	
Gender		
Male	79.20%	0.20
Female	89.90%	
Size		
<200	85.20%	0.09
≥200	83.90%	
Tumor site		
Upper limbs	100%	0.67
Lower limbs	83.60%	
Margin status		
R0	90%	0.9
R1/2	84.30%	
Immunohistochemistry		
CDK4 <sup>neg</sup> MDM2 <sup>neg</sup>	86.40%	0.6
CDK4 <sup>pos</sup> MDM2 <sup>neg</sup>	100%	
CDK4 <sup>neg</sup> MDM2 <sup>pos</sup>	100%	
CDK4 <sup>pos</sup> MDM2 <sup>pos</sup>	60%	

*CDK4 and MDM2 expression status*

The immunohistochemical results for ALT/WDLPS cases are shown in Table 2. Ten patients were CDK4<sup>pos</sup> and MDM2<sup>pos</sup>, 41 patients were CDK4<sup>neg</sup> and MDM2<sup>neg</sup>, 7 patients were CDK4<sup>pos</sup> and MDM2<sup>neg</sup>, and 4 patients were CDK4<sup>neg</sup> and MDM2<sup>pos</sup>. The 5-year RFS rates of patients with CDK4<sup>neg</sup> and CDK4<sup>pos</sup> tumors were 72.6% and 27.4%, respectively (p = 0.15). The 5-year RFS rates of patients with MDM2<sup>neg</sup> and MDM2<sup>pos</sup> tumors were 75.8% and 24.2%, respectively (p = 0.57). No difference was observed in RFS between patients with MDM2<sup>neg</sup> and CDK4<sup>neg</sup> tumors and those with other tumors (p = 0.64).

## Discussion

In this study, we evaluated the clinical outcomes and recurrence factors of ALT/WDLPS of the extremities. In our series of 62 patients, tumor diameter  $\geq 20$  cm was identified as a recurrence factor.

For differential diagnosis between ALT/WDLPS and lipoma, core needle biopsy with subsequent CDK4 and MDM2 expression analysis may help in diagnosis prior to surgery[9]. Amplification of *MDM2* and *CDK4* is almost always present[3]. CDK4 is a protein serine kinase involved in the cell cycle. It is essential for the transition from G1 to S phase during the cell cycle, and its expression is mainly regulated at the transcriptional level. MDM2 is a protein that suppressively regulates the activity of the tumor suppressor p53. A previous study suggested that the absence of *CDK4* amplification in ALT/WDLPS is associated with a lower rate of recurrence and favorable prognosis, and *CDK4* amplification predicts recurrence of ALT/WDLPS[10]. However, this study included tumors that occurred in the upper or lower extremities and the trunk and retroperitoneum. Lee et al. suggested that the level of *CDK4* amplification determined by qPCR was associated with recurrence of ALT/WDLPS of the retroperitoneum and peritoneal cavity after surgical resection[11]. However, there is a paucity of data regarding ALT/WDLPS of the extremities with no study evaluating *CDK4* and *MDM2* amplification as predictor of recurrence in ALT/WDLPS of the extremities. FISH is currently the standard method[7, 8], but IHC might serve as an easier method to detect protein overexpression that results from amplification of *MDM2* and *CDK4* expression. MDM2 and CDK4 immunostaining was observed in only 45% and 41% of our cases, respectively. However, the sensitivities ranged from 45%-100% and 41%-100% for MDM2 and CDK4 immunostaining, respectively[12]. The most plausible explanation for these differences relates to case selection. Moreover, it is possible that gene dosage and protein expression correlate with large nuclear size, implying that adipocytes express proteins below the threshold for antigenic detection. Therefore, MDM2 and CDK4 immunostaining is a relatively insensitive method for diagnosing ALT/WDLPS[12]. We evaluated IHC results for these two markers as recurrence factors of ALT/WDLPS in the extremities. However, IHC results of these two markers could not adequately predict recurrence.

In our case series, ten patients (16.1%) developed local recurrences, and the mean time to local recurrence was 48.4 months (range, 5–161 months). This incidence of local recurrence is similar to that reported in several other studies (8–17.8%)[4, 6, 13, 14]. Rozantal et al. suggested that tumor size and age at presentation were not statistically significant predictors of recurrence, but occurrence of a deep lesion and positive margins at the time of initial excision were risk factors for recurrence[15]. We observed a higher local recurrence rate with large tumors ( $\geq 20$  cm). However, Smith et al. did not find a correlation between tumor size and local recurrence[16].

There is controversy regarding optimal surgical margins for ALT/WDLPS. Although wide resection is recommended to decrease local recurrence, marginal resection is recommended to ensure good functional outcome as it is associated with a relatively low recurrence rate and lower risk of malignancy[5]. There were no significant differences in recurrence between the different types of resection in our study. Several previous studies have suggested that local RFS rate is significantly higher

in the wide resection group compared to those in other groups[5, 17]. This discrepancy in results could be attributed to the time of follow-up in our study (about 5 years), which was shorter than that in the previous studies. However, Chang et al. found in their study that patients undergoing wide resection had more postoperative complications, such as nerve injury (drop foot), hematomas, and wound infections, than patients undergoing other resections did[6]. Further, a wide resection may result in a significant sacrifice of the tissue surrounding the muscle, which could reduce muscle strength in elderly patients. Considering that ALT/WDLPS have a risk of local recurrence and are often dedifferentiated but do not metastasize, we suggest that patients undergo marginal resection.

The mean time to local recurrence in our cohort was 48.4 months (range, 5–161 months), as well as what has been shown in other studies[4–6, 13, 15]. There is a controversy regarding the appropriate length of follow-up. In most previous studies, local recurrence developed more than 60 months after surgery, and there is data indicating that the risk of local recurrence is correlated with the time of follow-up; therefore, they suggest that patients should be followed up for at least 5 years after surgery[4, 13]. Mavrogenis et al. reported that a local re-recurrence rate of total recurrent ALT/WDLPS of 52%[4]. Therefore, it is important to remember that recurrent tumors have a high risk of local recurrence, even if wide re-resection is performed, and long-term follow-up is required for such cases. In our study, two of 10 (20 %) patients presented with re-recurrence. One patient had 2 recurrences and the other had three.

The present study has several limitations. This study was limited by the small number of patients and its retrospective design. The follow-up time was relatively short.

## Declarations

### Authors' contributions;

Toshiki Zeniya Data collection, Analysis of data , Writing the manuscript.

Makoto Emori Data collection, Analysis of data, Writing the manuscript.

Hiroyuki Tsuchie: Data collection, Analysis of data.

Hiroyuki Nagasawa: Data collection, Analysis of data.

Kousuke Iba: Drafting of the manuscript.

Emi Mizushima: Data collection, Analysis of data.

Toshiko Keira: Data collection, Analysis of data.

Junya Shimizu: Drafting of the manuscript.

Yasutaka Murahashi: Drafting of the manuscript.

Atsushi Teramoto: Drafting of the manuscript.

Naohisa Miyakoshi: Drafting of the manuscript.

Shintaro Sugita: Data collection, Analysis of data.

Tadashi Hasegawa; Data collection, Analysis of data.

Yoichi Shimada: Critically evaluated the manuscript.

Toshihiko Yamashita: Critically evaluated the manuscript, Gave final approval for the manuscript to be published.

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Not applicable

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### **Availability of data and materials**

All data obtained is available within the manuscript.

### **Authors' contributions**

All authors designed the study and drafted the manuscript. All authors read and approved the final manuscript.

### **Ethics approval and consent to participate**

Written informed consent was obtained from the patients prior to publication of this clinical research and all procedures performed were approved by the Institutional Review Board for Clinical Research at our university.

### **Patient consent for publication**

Written informed consent was obtained from the patients to publish the information, including their photographs. A copy of the written consent is available for review.

### **Conflict of interest**

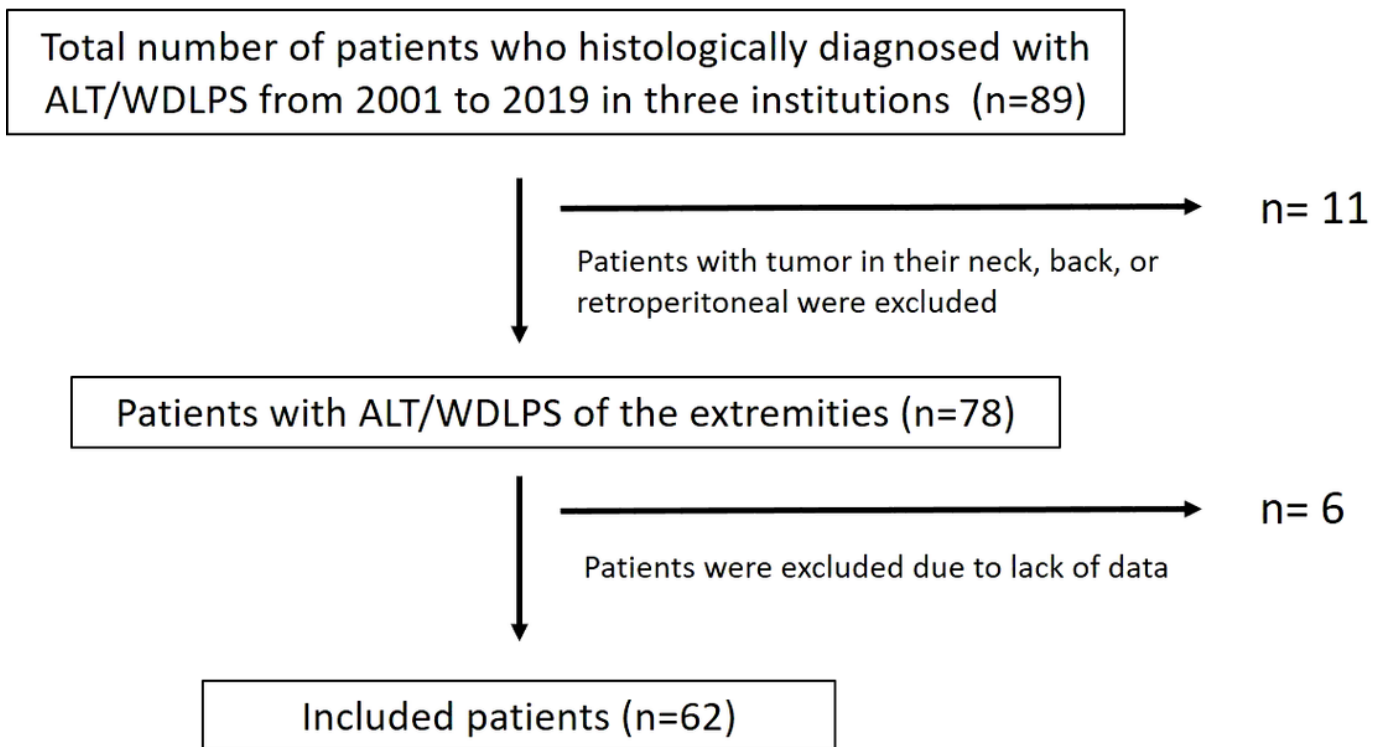
The authors declare that they have no conflict of interest.

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## Figures



**Figure 1**

A detailed flowchart of the study selection process