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# Clinicopathological and immunohistochemical analysis of the risk factors of recurrence of atypical lipomatous tumor/well-differentiated liposarcoma of the extremities

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**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. This is retrospective study across three institutions which included patients who underwent surgery for ALT/WDLPS from 2001 to 2019. 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. The following variables were evaluated as potential recurrence factors: age, sex, tumor diameter, anatomical location of the tumor, immunohistochemical results, and resected margins. The 5- year local recurrence-free survival rate (RFS) was calculated and differences in survival were assessed. Sixty-two patients were identified, including 29 men and 33 women. The mean 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 (≥20 cm) was significantly associated with local recurrence (p=0.042). Ten patients (16.1%) developed local recurrence, and the mean time to recurrence was 48.4 months (range, 5–161 months). In our series of 62 patients, the differences in local recurrences were not statistically significant for age, sex, tumor site, surgical margin (R0 or not) and immunohistochemical results. Tumor diameter ≥20 cm, which was the only identified factor for recurrence.**

**Keywords:** Atypical lipomatous tumor/well-differentiated liposarcoma, recurrence, surgery, immunohistochemistry.

## INTRODUCTION

Liposarcomas are the most common type of soft tissue sarcomas, accounting for approximately 20% of all soft tissue sarcomas[1]. 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[2]. ALT/WDLPS can occur at any age, but its peak incidence is observed during the fifth to seventh decades of life with no sex predilection[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[2]. Surgery is the standard treatment for ALTs/WDLPSs of the extremities. However, there is no consensus on the most appropriate surgical resection approach for ALTs/WDLPSs in the extremities[4]. Some groups have recommended wide resection as a curative treatment to reduce the risk of local recurrence[5]. In contrast, a recent systematic review reported that the local recurrence rate was not significantly higher for the marginal resection group[6]. 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[7-9].

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[10]. Alternatively, immunohistochemistry (IHC) may serve as a convenient method for diagnosis. As a surrogate, immunohistochemistry for MDM2 and CDK4 is now commonly used, with most cases showing nuclear positivity[11]. 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 aimed to investigate the clinical outcomes and risk factors of the recurrence of ALT/WDLPS of the extremities and the roles of the immunohistochemical markers MDM2 and CDK4 and the correlation between their expression and recurrence.

## PATIENTS AND METHODS

*Ethics*

The study procedure was conducted in accordance with guidelines approved by the Institutional Review Board of Sapporo Medical University (reference number 285-65) and the Declaration of Helsinki. The need for informed consent was waived because of the retrospective nature of this study.

*Patient Selection*

This retrospective study across three institutions included patients who had undergone surgery for ALT/WDLPS from 2001 to 2019. We identified 89 such patient and inclusion in this study. 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 (Figure 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.

*Treatments*

All patients underwent limb-sparing surgical resection. The margin was defined as R0 if a rim of soft tissue around the lesion was present (wide resection), R1 if the margins were contaminated but the tumor capsule with the latter remaining closed (marginal resection), and in few selected patients, part of the tumor was left as part of the surgical strategy and there were classified as a R2 (intralesional resection)[12]. Patient follow-up and MRI were basically performed at 6-month intervals until 5 years after the primary tumor diagnosis, then at 12-month intervals until 10 years after the primary tumor diagnosis. We usually recommend surgery with wide resection for recurrence.

*Immunohistochemical analysis*

IHC was performed on 4-μm-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

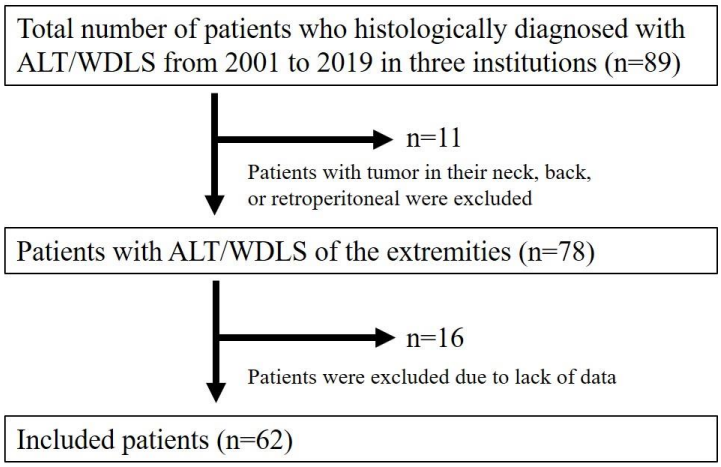


*Fig. 1 — A detailed flowchart of the study selection process.*

least one tumor cell nucleus was stained per high-power field, as previously described[12].

*Follow-up management and Assessment of the dedifferentiation*

All patients were followed up for evidence of local recurrence or dedifferentiation using MRI. MRI was performed every 6 months during the third year after tumor resection and every year thereafter. We suspected dedifferentiation if there was a nodule in the surgical area showing a central area without adipose tissue on T1-weighted images.

*Statistical analyses*

Patients were evaluated for local recurrence and dedifferentiation. The following variables were evaluated as potential recurrence factors using Mann-Whitney U test: age, sex, tumor diameter, anatomical location of the tumor, immunohistochemical results, and resected margins. 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. Hazard ratio was evaluated using proportional hazards regression model. Statistical significance was defined as $p<0.05$. Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA) and JMP Pro 17 (SAS Institute, Cary, NC, USA).

## RESULTS

*Patient Characteristics*

The records of 62 patients (29 men and 33 women) who were admitted to three institutions from 2001 to 2019 were reviewed. The characteristics of the 62 patients included in this series are listed in Table I. The mean 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 mean tumor diameter was 15.9 cm (range, 5-28cm).

*Local recurrence and dedifferentiation*

Ten patients (16.1%) developed local recurrences. In one case of R0 resection, in 8 cases of R1 resection, and in one case of R2 resection, the patients developed local recurrences. Details of these 10 patients are presented in Table II. 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). A comparison of the non-recurrence and recurrence groups is presented in Table II. However, there was a statistically significant difference in the maximum tumor diameter over 20 cm (p=0.042). As for recurrent cases, some were resected, while others were observed because they had no symptoms. The immunohistochemical results for ALT/WDLPS cases are shown in Table II. However, we observed no cases of dedifferentiation during their follow-up.

*Recurrence-free survival and the recurrence factors*

The 5-year RFS rate was 85.4%. The univariate analyses of RFS are presented in Table III. The 5-year RFS rates of patients with CDK4neg and CDK4pos tumors were 72.6% and 27.4%, respectively (p=0.15). The 5-year RFS rates of patients with MDM2neg and MDM2pos tumors were 75.8% and 24.2%, respectively (p=0.57). No difference was observed in RFS between patients with MDM2neg and CDK4neg tumors and those with other tumors (p=0.64).

**Table I.** — Demographic and clinicopathologic characteristics of the 62 patients.

| | No. of patients (n=62) | % |
|---|---|---|
| Age, years (median age; 66.5) | | |
| < 50 | 6 | 9.7 |
| ≥50 | 56 | 90.3 |
| Gender | | |
| Male | 29 | 46.8 |
| Female | 33 | 52.2 |
| Tumor size, cm (median; 15) | | |
| <20 | 42 | 67.7 |
| ≥20 | 20 | 32.2 |
| Tumor depth | | |
| intramuscularly or between muscles | 58 | 93.5 |
| subcutaneously | 4 | 6.5 |
| Tumor site | | |
| Upper limbs | 7 | 11.3 |
| upper arm | 3 | 4.8 |
| shoulder | 4 | 6.5 |
| Lower limbs | 55 | 88.7 |
| thigh | 45 | 72.6 |
| buttock | 7 | 11.3 |
| lower leg | 3 | 4.8 |
| Margin status | | |
| R0 | 12 | 19.4 |
| R1 | 48 | 77.4 |
| R2 | 2 | 3.2 |
| Local recurrence | | |
| Present | 10 | 16.1 |
| Absent | 52 | 83.9 |

**Table II.** — Factor analysis between patients with no recurrence and patients with recurrence.

| | No. of patients with no recurrence (n=52) | No. of patients with recurrence (n=10) | p-value |
|---|---|---|---|
| Age, years | | | 0.13 |
| <50 | 3 | 2 | |
| > 50 | 49 | 8 | |
| Gender | | | 0.36 |
| Male | 23 | 6 | |
| Female | 29 | 4 | |
| Tumor size, cm | | | 0.042 |
| <20 | 38 | 4 | |
| ≥ 20 | 14 | 6 | |
| Tumor depth | | | 0.37 |
| intramuscularly or between muscles | 4 | 10 | |
| subcutaneously | 48 | 0 | |
| Tumor site | | | 0.89 |
| Upper limbs | 6 | 1 | |
| Lower limbs | 46 | 9 | |
| Margin status | | | 0.24 |
| R0 | 11 | 1 | |
| R1 | 40 | 8 | |
| R2 | 1 | 1 | |
| Immunohistochemistry | | | |
| $CDK4^{neg}MDM2^{neg}$ | 35 | 6 | 0.52 |
| $CDK4^{pos}MDM2^{neg}$ | 6 | 1 | |
| $CDK4^{neg}MDM2^{pos}$ | 4 | 0 | |
| $CDK4^{pos}MDM2^{pos}$ | 7 | 3 | |

## DISCUSSION

In this study, we evaluated the clinical outcomes and recurrence factors of ATL/WDLPS of the extremities. In our series of 62 patients, the differences in local recurrences were not statistically significant for age, sex, tumor site, surgical margin (R0 or not) and CDK4 and/or MDM2 immunohistochemical results. Tumor diameter ≥20 cm was identified as a recurrence factor.

*Recurrence factor including CDK4 and MDM2 expression*

Tumor diameter ≥20 cm was only identified as a recurrence factor. Rozantal et al. reviewed the clinical outcomes of ATL/WDLPS of the extremities and suggested that the tumor size at presentation was not a statistically significant predictor of recurrence[13]. However, only twenty-three of thirty-one patients underwent an MRI before surgery. The tumor size was accurately evaluated for only a few cases, and the results were not reliable.

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[12]. Amplification of MDM2 and CDK4 is almost always present[2]. CDK4 is a protein serine kinase involved in the cell cycle. MDM2 is a protein that suppressively regulates the activity of the tumor suppressor p53. 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[14]. 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

**Table III.** — Outcome in Univariate Analysis of Prognostic Factors.

| | 5-y Local recurrence-free survival (%) | P value | Hazard Ratio |
|---|---|---|---|
| Age, years | | 0.79 | 0.8 |
| <50 | 100 | | |
| 50 | 82.5 | | |
| Gender | | 0.15 | 0.38 |
| Male | 79.2 | | |
| Female | 89.9 | | |
| Tumor size, cm | | 0.17 | 2.45 |
| <200 | 85.2 | | |
| ≥200 | 83.9 | | |
| Tumor depth | | 0.6 | 1.371E-08 |
| Intramuscularly or between muscles | 100 | | |
| Subcutaneously | 84.7 | | |
| Tumor site | | 0.95 | 0.93 |
| Upper limbs | 100 | | |
| Lower limbs | 83.6 | | |
| Margin status | | 0.85 | 1.38 |
| R0 | 90.0 | | |
| R1 | 83.5 | | |
| R2 | 100.0 | | |
| Immunohistochemistry | | 0.35 | 1.35 |
| $CDK4^{neg}MDM2^{neg}$ | 86.2 | | |
| $CDK4^{pos}MDM2^{neg}$ | 100 | | |
| $CDK4^{neg}MDM2^{pos}$ | 100 | | |
| $CDK4^{pos}MDM2^{pos}$ | 60.0 | | |

ALT/WDLPS of the extremities. FISH is currently the standard method[10,15-17], but IHC might serve as an easier method to detect protein overexpression that results from amplification of MDM2 and CDK4 expression. However, the sensitivities ranged from 45%-100% and 41%-100% for MDM2 and CDK4 immunostaining, respectively[18]. The most plausible explanation for these differences relates to case selection. Previous reports found unsatisfactory correlation between IHC for the MDM2 protein and MDM2 gene amplification status, particularly in poorly differentiated cases or in cases with MDM2 overexpression not related to gene amplification[19-21]. 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[18]. MDM2 and CDK4 immunostaining was observed in only 23% and 27% of our cases, respectively. We hypothesized that positive immunohistochemical results for MDM2 and/or CDK4, as proteins with levels of overexpression below the threshold for antigenic detection, could be predictors of the recurrence of ALT/WDLPS in the extremities. However, no difference in the RFS was observed between the patients with MDM2-negative and CDK4-negative tumors and those with other tumors (p=0.64). It is difficult to predict local recurrence using immunohistochemical results alone. The key costs are attributed to the purchase of antibodies for immunohistochemistry and probes for FISH and personnel costs for laboratory staff, including technicians, histotechnologist, and pathologists. The immunohistochemistry-only strategy yielded the quickest turnaround time (one to two working days), whereas a sequential approach of prescreening with immunohistochemistry followed by FISH had a turnaround time of up to seven working days. The specificities were 59–100% and 71–100%

for MDM2 and CDK4 immunohistochemistry[18]. When MDM2 amplification detected by FISH was considered the gold standard, the sensitivity and specificity of histopathological assessment alone were 81.5% and 96.6%, respectively[16]. The current consensus on the use of immunostaining for MDM2 and CDK4 in differentiated lipomatous tumors is to use it as a screening procedure, with reflex testing by FISH if negative[18]. he problem with this approach is that a proportion of cases would require both immunohistochemistry and FISH because both sensitivity and specificity are not very high. Therefore, there was no cost-comparison analysis for MDM2 and CDK4; however, it may be cheaper to perform FISH for all cases than negative immunohistochemistry plus FISH and positive immunohistochemistry.

*Surgical management*

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[8]. 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[8,22]. 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(9). 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.

*Follow-up management*

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%)[7,9,23] 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[7-9,13,23]. 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[7,23]. Mavrogenis et al. reported that a local re-recurrence rate of total recurrent ALT/WDLPS of 52%[7]. 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.

*Limitations*

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. We were not able to adequately assess that given that only 14/62 patients had expression of MDM2, which is typically found in most WDLPS tumors because in this study, patients were selected based on histopathological diagnosis in past medical records, and therefore many cases with negative immunostaining are included. This is one of the uncertainties in our research.

## CONCLUSIONS

This study identified tumor size as the only risk factor for the recurrence of ALT/WDLPS of the extremities in this study. Age, sex, tumor depth, tumor site, surgical margin, and immunohistochemical results for CDK4 and MDM2 did not demonstrate significant risk relationships. There were also no significant differences in the 5-year local recurrence-free survival. It is difficult to predict local recurrence using the CDK4 and MDM2 immunohistochemical results. We recommend R1 (marginal) resection for ALTs/WDLSs of the extremities in older patients based on functional problems or complications after surgery.

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