Title: Clinical Outcome of Deep-seated Atypical Lipomatous Tumor of the Extremities with Median-term Follow-up Study

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Abstract

Aims: There is no consensus on the best surgical treatment for deep-seated atypical lipomatous tumor (ALT) of the extremities; furthermore, the appropriate duration for follow-up observation remains unclear. We investigated clinical and functional median-term outcomes in the primary operations for ALT of the extremities in order to find its best treatment methods and observation periods.

Methods: From 1996 to 2009, we diagnosed 41 patients with deep-seated ALT of the extremities. Wide resection was performed on 11 patients and marginal resection was performed on 30 patients. The minimum follow-up was 5 years (median, 8.5; range, 5-17.4). Patients were evaluated for their local recurrence, dedifferentiation, and post-operative function using the ISOLS/MSTS scoring system.

Results: Recurrence and dedifferentiation rates were both 0% for the wide resection group, while the rates were 23 % (7/30) and 3 % (1/30) for the marginal resection group, respectively. Median duration before recurrence was 7.2 years (range, 4.0-14.2). Local recurrence-free survival rate was significantly higher in the wide resection group (P=0.013). In the marginal resection group, 10% (3/30) of the cases showed residual tumor. The localization of these tumors was all intermuscular. The ISOLS/MSTS scores were 98% (range, 90-100) for wide resection and 99% (range, 93-100) for marginal resection, with no statistical difference (P=0.694). No ALT-related deaths occurred during the observation period.

Conclusions: In addition to long-term (at least 8 years) of continuous observation, a wide resection is necessary in order to prevent recurrence, dedifferentiation, and residual tumor.

Key words: atypical lipomatous tumor, extremities, surgical method

Introduction

Atypical lipomatous tumor (ALT) is a locally aggressive tumor with low malignant potential that constitutes 40-45% [1] of liposarcoma. Middle-aged patients are most susceptible to ALT, and the tumors do not metastasize without dedifferentiation. However, because ALT usually develops slowly and occurs in deep soft tissue, the tumors can be relatively large by the time they are discovered. Depending on its site of involvement, the prognostic implication of ALT can differ; for example, a total removal in the retroperitoneum and mediastinum is difficult, often resulting in a poor prognosis with multiple relapses that ultimately implicate important internal organs or dedifferentiation [2-5]. Nevertheless, the mortality rate for tumors originating in the extremities is near 0%.

There is no consensus on the best surgical treatment for deep-seated ALT of the extremities, as some recommend a wide resection to place emphasis on definitive therapy [3, 5, 6], while others believe marginal resection is sufficient for low-potential malignancy [7-9]. The purpose of this research is to evaluate the median-term results of patients with deep-seated ALT of the extremities, provide a comparative study of wide resection and marginal resection, and investigate (1) the best surgical method; and (2) the appropriate duration of follow up observation for deep-seated ALT of the extremities.

Patients and Methods

From 1996 to 2009, we diagnosed and treated 59 patients with ALT. The diagnosis included patients with atypical lipoma, well-differentiated liposarcoma (WDLS), and WDLS/ALT using previous classifications. The inclusion criteria were as follows: 1) the site of involvement for the tumor is the extremities and deep-seated; 2) the initial tumor resection was conducted at our institution; and 3) the follow-up period is more than 5 years. For patients with discontinuous observation periods, we contacted patients via phone to ask them for a return visit and consultation. Excluded from this study were six patients with tumors that had originated subcutaneously, seven patients that recurred after resection conducted at other hospitals, and five patients that we were unable to follow-up more than five years. The remaining 41 patients were included in our research. Patients included in our study were examined for their local recurrence rate, dedifferentiation rate, and post-operative functional evaluation, according to the different surgical treatment they received. All patients were examined using magnetic resonance imaging (MRI), and we confirmed the tumor size, site of involvement, and localization. In terms of the final diagnosis of ALT, resected specimens were diagnosed by an experienced pathologist (K.S.). Pathological findings of ALT are derived from mature adipocytes, but difference in size can be conspicuous compared to benign lipomas, in addition to atypia and hyperchromatic nuclei. Furthermore, hyperchromatic nuclei and polynuclear stromal cells are often found in the fibrous septa. A varying number (from many to none) of monovacuolated or multivacuolated lipoblasts can be found [2]. In this study, prepared specimens diagnosed as atypical lipoma, WDLS, and WDLS/ALT were reevaluated to confirm ALT under our criteria.

The surgical methodology was categorized under a wide resection group and marginal resection group. We used the resection margin as defined by Enneking, et al [10]. Wide resection was defined as resection able to obtain a wide margin, and marginal resection was defined as resection able to obtain a marginal margin. Surgical methodology differed according to the time period to which the resection took place; wide resection was chosen for a large number of cases

from 1996-2004, whereas marginal resection was performed for most cases after 2005. Because ALT is an intermediate tumor, reports recommending a more conservative approach began to surface in the literature during the 2000s [8, 9]. As a result, after 2005, our institution began to increasingly perform marginal resections. Evaluation of the surgical margin was conducted using resected specimens by two or more experienced orthopedic oncologists and pathologists at the time of surgery. The least margin of the resected specimen was defined as the margin that was obtained by the surgery. Furthermore, in cases that were able to attain a wide resection, we measured the degree to which the normal tissue was attached to the periphery of the tumor.

MRI or CT imaging was conducted 3 months post-operatively. When tumors were confirmed at this point, patients were diagnosed with residual tumor. As a general rule, MRI or CT imaging was conducted once a year after initial imaging examination. Patients were diagnosed with recurrence when a recurrent tumor was confirmed by routine imaging, conducted once a year. In cases that had interruptions during the follow-up period, the period of recurrence was defined as the time patients became self-aware of their tumor before the follow-up examination. We calculated the time to recurrence from the date of operation. Post-operative functional evaluation was performed during the final observation period using the ISOLS/MSTS scoring system described by Enneking [11]. Preoperative scores were used for cases that underwent surgery for recurrence. This score is based on six parameters: pain, function, and emotional acceptance in upper and lower extremities; supports, walking and gait in the lower extremity; and hand position, dexterity and lifting ability in the upper extremity. Each parameter is rated from 0 to 5. All scores were added to obtain the overall function score and expressed as a percentage of a maximum total score of 30. There were no patients who perioperatively received chemotherapy or radiation therapy. This study had ethical approval and all patients gave written informed consent.

For statistical analysis, the correlation between clinical characteristics and surgical methodology were analyzed by Mann-Whitney's U test that evaluated the difference in median and Fisher's exact test that evaluated the difference in ratio. Local recurrence-free survival probabilities

were estimated using the Kaplan-Meier method, comparing their results with a log-rank test. The difference in the mean ISOLS/MSTS scores were analyzed using Welch's t-test. Statistical significance was defined as $P<0.05$. The data analysis software used was IBM SPSS Statistics version 21.

Results

The median age of the 41 patients included in our study was 65 years (range, 32-79), consisting of 20 male patients and 21 female patients. The site of involvement consisted of 36 cases in the lower extremities (thigh, 29; buttock, 5; lower leg, 2) and 5 cases in the upper extremities (upper arm, 2; shoulder, 2; forearm, 1). Localization was intramuscular in 20 cases and intermuscular in 21 cases. The median size of the tumors, measured by their maximum diameter, was 15cm (range, 6.5-25). Median intraoperative blood loss was 100cc (range, 10-400), and the median operating time was 103 minutes (range, 27-306). The follow-up period was at minimum 5 years, and the median duration was 8.5 years (range, 5.0-17.4). Out of 41 patients, wide resection was performed on 11 patients, and marginal resection was performed on 30 patients. For the evaluation of surgical margin width in patients who had a wide resection, nine cases had margins less than 1cm and two cases had margins more than 2cm. The comparison of the wide resection and marginal resection groups are presented in Table 1. Although the follow-up observation period for the wide resection group was significantly longer (P=0.023), the results reflected the larger number of wide resections performed during the first half of this study. Local recurrence did not occur in the wide resection group, but 23% of the marginal resection group had developed local recurrence. Details on the 7 cases showing recurrence are presented in Table 2.

Median duration before recurrence was 7.2 years (range, 4.0-14.2). One of the 7 cases showing recurrence was confirmed to be dedifferentiated on its first recurrence. Two cases were operated by marginal resection for recurrent tumors. One patient relapsed 3 times, while the other patient relapsed 4 times.

One of the recurrent tumors that underwent reoperation had been found with dedifferentiation. Although the observation period had ended 3.5 years after the initial operation, we contacted the patient via phone 14.6 years post-operatively for a follow-up examination. The patient was self-aware of the tumor 5 months prior to the follow-up examination. The tumor had recurred with dedifferentiation. The recurred tumor was large, and the wide resection resulted in the total

resection of the quadriceps (Figure 1). There are 4 cases under observation that have not undergone reoperation after recurrence, and they are growing albeit slowly. However, those cases have only shown indications of a tumor under imaging with no signs of dedifferentiation. In the marginal resection group, there were no cases of tumor morcellation or intratumoral resection under gross observation, but 10% of cases (3/30) had confirmed residual tumor during the 3-month post-operative imaging. The localization of these tumors was all intermuscular. One case underwent an additional wide resection, and has developed no indications of recurrence. The remaining 2 cases have demonstrated gradual tumor growth under our observation. The local recurrence-free survival rate of both wide and marginal resection groups are presented in Figure 2. Cases with residual tumor in the marginal resection group were excluded from the local recurrence-free survival rate in order to differentiate residual tumors from recurred tumors. The local recurrence-free survival rate was significantly lower in the marginal resection group (P=0.013). There were no ALT-related deaths or metastasis that occurred during our observation period.

In the wide resection group, there were no cases that underwent combined resection for significant nerves and vessels, and complication from combined resections was limited to that of the muscles. Post-operative functional evaluation using ISOLS/MSTS scoring was in mean 98% (range, 90-100) for the wide resection group and 99% (range, 93-100) for the marginal resection group, with no significant difference between the two groups (P=0.694). The relationship between combined resection of the muscle and ISOLS/MSTS scores are presented in Table 3. Furthermore, three patients who underwent re-operation for recurrence had a pre-operative ISOLS/MSTS score of 100%; however, all post-operative ISOLS/MSTS scores after re-operation demonstrated lower scores, with one patient at 66.7% after performing a wide resection for dedifferentiation, 83% for a patient that relapsed 3 times, and 86.7% for a patient that relapsed 4 times.

Discussion

The prognosis of ALT differs according to its site of involvement and as a result, establishing its nomenclature has suffered from a history of ambiguities. When involved in the extremities, the tumor cannot metastasize unless it dedifferentiates, and the mortality rate is near 0%; thus, the term "sarcoma" was found unsuitable to describe the tumor, which led to the decision to change the WHO classification of ALT/WDLS to ALT [1]. However, because the tumor has locally aggressive qualities, the problem lies in its possibility of recurrence and the dedifferentiation that may follow after recurrence. Recurrence rates of ALT in the extremities and trunk have been reported to be between 0-51% [3, 5-9, 12-19]. Although a "total or wide resection" of ALT was previously recommended in order to attain a high local control factor [3, 5, 6], some recent reports have also recommended a "marginal resection" due to the low recurrence rate and low malignancy of ALT [7-9]. In our study, the recurrence rate of the wide resection group was 0%, while the marginal resection group had a higher rate at 23%. Therefore, the local recurrence-free survival rate was significantly lower in the marginal resection group ($p=0.013$), and wide resection showed significance in terms of local control.

Cases with a less 1 cm margin width occupied most of the details regarding wide resections, but we believe recurrence can be prevented if there is a barrier of at least 1cm when wide resection for ALT is performed, since there were no cases of recurrence. In reports recommending a "total or wide resection," there are no thorough accounts on its surgical methodology, and there are also no objective analyses on the functional disorders associated with wide resections. In this study, cases that underwent a wide resection have also undergone a combined resection involving the muscles in addition to the tumor. In elderly patients, an extensive removal of muscles may lower the ADL. However, despite the advanced median age of 69 in our wide resection group, the ISOLS/MSTS score was in average 98% (range, 90-100), a score comparable to that of the marginal resection group. Although we cannot assert a significance difference due to the low statistical power as a result of a small sample size, we believe these results support the validity of performing wide

resections for ALT that can attain a wide margin through a combined resection of muscles. However, for cases in which important nerves and vessels are in contact with the tumor, there is a high probability of major functional disorders. Kubo et al. [17] and Kemp et al. [15] report good results without recurrence when marginal resection was performed for ALT in contact with nerves, although the described results are short-term. Unless the ALT dedifferentiates, the tumor will not metastasize even in cases of recurrence, and mortality rates are reportedly near 0%. Therefore, because combined resections can cause major functional disorders in the treatment of ALT that are in contact with important nerves and vessels, marginal resection may be considered only for regions that are in contact with nerves and vessels, despite its risk of recurrence.

In addition, 3 cases (10%) in the marginal resection group had confirmed residual tumors during the 3 month post-operative imaging. These cases had no clear indication of residual tumors under gross observation. The localization of these tumors was all intermuscular. Because the boundary between normal adipose tissue and tumor is indistinct in deep-seated intermuscular tumors, marginal resection that seem successful to the naked eye may actually be an intratumoral resection. There is a need for cautious resection to prevent residual tumors when planning a marginal resection of intermuscular ALT. Once ALT recurs, the tumor often repeats multiple recurrences. In past literatures, these recurrences have been reported to be between 40-67% [3, 5, 6, 9, 13, 18]. In this current study, 2 out of 3 cases (67%) that underwent reoperation after recurrence demonstrated multiple recurrences, both of which were operated with marginal resection. Thus, preference for reoperation for recurrence is given to wide resection; however, because reoperation often reveals strong adhesion and makes contact with important nerves and vessels, the demerits of wide resection should also be considered. Therefore, we believe the most important factor to consider during the primary operation is to avoid recurrence through a complete resection. Although we recommend the wide resection of ALT whenever possible, preoperative diagnosis remains important for selecting an appropriate method of intervention. Differentiating ALT and benign lipomas is difficult at times. There are reports that suggest thickened or nodular septa (generally >

2mm), associated nonadipose masses, prominent foci of T2 weighted signal, and prominent areas of enhancement are useful to differentiate ALT and benign lipomas [20, 21]; however, there are also reports that suggest false-positive results are common in MRI scans [22]. In recent years, there have been reports that fluorescent in situ hybridization (FISH) of murine double-minute 2 (MDM2) is useful for biopsy [23, 24]. Thus, when the MRI reveals the possibility of an ALT, it is important to preoperatively perform a biopsy and definitive diagnosis.

The follow-up period is important when examining the recurrence of ALT. Many minimum follow-up periods described in the literature are short-term follow-ups that are less than or equal to 3 years (the majority of which are less than 2 years). Those who recommend marginal resections have suggested the limitations of their research in terms of their short follow-up periods, and also note that recurrence rates can increase as the follow-up period is increased in duration [8, 9].

Rozental et al. [6] and Macrogenesis et al. [18] both report the necessity of at least 5 or 6 years follow-up, and we set the general median-term follow-up of 5 or more years as a cutoff point of our observation period. Among studies describing the clinical outcome of ALT in the extremities, our study has the longest minimum follow-up period. Because our minimum follow-up period was extended for the purpose of our study, the recurrence in our marginal resection group was relatively high at 23%. In reports that describe a low recurrence rate [7-9, 14, 15, 17-19], the aforementioned extension in the follow-up period would be likely to increase recurrence rates. In our study, the median duration before recurrence was 7.2 years. However, upon reviewing the details of our study (Table 2), 2 cases showed a lengthy duration before recurrence at 11.8 and 14.2 years, respectively. Both cases were patients who had completed their final follow-up at 4.5 years and 3.5 years, respectively, and we contacted them via phone for reexamination. Although we defined the period of recurrence as the time when the patient became self-aware of the tumor, imaging during reexamination revealed their recurrent tumors had become massive. Considering the tendency of ALT to grow gradually, we can assume the period of recurrence was earlier than when the patient noticed the tumor. Moreover, the latter patient showed recurrence with dedifferentiation, resulting

in a wide resection with the total removal of the quadriceps. Although the patient can walk with the assistance of auxiliary equipment, the ADL of the patient showed a dramatic decrease. ISOLS/MSTS score decreased from 100% to 66.7%. ALT in the extremities and trunk are reported to have a dedifferentiation rate of 0-13% [3, 5-9, 12-15, 17-19]. Although our study also shows a low dedifferentiation rate at 2% (1/41), because wide resection is a standard procedure for high-grade sarcomas for dedifferentiation, we believe there was a possibility of limiting the extent of resection, provided that we had discovered the tumors at an earlier stage. Therefore, we believe there is a necessity for long-term continuous post-operative follow-up.

The limitation of this study includes a small sample size, the absence of randomization in selecting our surgical method, a significant difference in the duration of observation periods, and the inclusion of cases with discontinuous observation periods.

In conclusion, wide resection should be performed for deep-seated ALT in the extremities in order to prevent local recurrence, especially in cases that require no resection of important nerves and vessels, in addition to cases that can achieve wide resection with muscle resection. We believe a 1 cm margin should be sufficient. When the tumor is in contact with important nerves or vessels and their resection is believed to greatly reduce the ADL of the patient, because ALT will not metastasize without dedifferentiation, we believe marginal resection may only be considered for sections that are in contact with nerves and vessels, even if there is a greater risk of recurrence. In terms of a follow-up observation period, we believe long-term (a minimum 8-year) follow-up is necessary, in addition to a yearly imaging examination.

Conflict of interest

All authors declare to have no conflicts of interest.

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Figure Captions

Figure 1: A 58-year-old man with intramuscular ALT of the thigh

A. Axial T1-weighted image before initial surgery shows multinodular fatty mass.

B. Axial T1-weghted image at 14.6 years after initial surgery shows local recurrence and a central area of no adipose tissue suspicious for dedifferentiation (arrow).

Figure 2: Kaplan-Meier survival analysis for local recurrence-free survival by surgical procedure

Table 1. Details of 41 patients with Atypical Lipomatous Tumor of the extremities

Characteristics		Surgical procedure		
	Total	Wide resection	Marginal resection	P-value
Number of patients	41	11	30	
Median age (range), y	65 (32-79)	69 (47-83)	64 (32-89)	P=0.385
Gender				P=0.484
Male	20	4	16	
Female	21	7	14	
Site				P=1.000
Lower extremity	36	10	26	
Upper extremity	5	1	4	
Localization				P=0.734
intramuscular	20	6	14	
intermuscular	21	5	16	
Median maximum diameter (range), cm	15 (6.5-25)	15 (6.5-25)	15 (9-25)	P=0.241
Median blood loss by operation (range), ml	100 (10-400)	70 (20-400)	140 (10-400)	P=0.848
Median operation time (range), min	103 (27-306)	134 (52-181)	97.5 (27-306)	P=0.458
Median follow-up duration (range), y	8.5 (5.0-17.4)	11.5 (5.0-17.4)	6.9 (5.0-16.4)	P=0.023*

* statistically significant difference

Table 2. Clinical details for 7 patients with local recurrence

Patients Number	Age (y)	Site	Localization	Surgical margin (Primary surgery)	Time to local recurrence (y)	Re-resection procedure	Number of recurrence	Dedifferentiation
1	45	Buttock	intermuscular	marginal	7.2	marginal	3	-
2	64	Thigh	intramuscular	marginal	11.8	-	1	-
3	57	Thigh	intramuscular	marginal	14.2	wide	1	+
4	47	Buttock	intramuscular	marginal	7.4	marginal	4	-
5	57	Thigh	intermuscular	marginal	5.8	-	1	-
6	73	Thigh	intramuscular	marginal	5	-	1	-
7	63	Thigh	intramuscular	marginal	4	-	1	-

Table 3. The relationship between combined resection of the muscles with wide resection and ISOLS/MSTS score

Patiens Number	Type of resected muscles	ISOLS/MSTS score (range), %
4	Adductor magnus + Gracilis	98 (90-100)
1	Gastrocnemius, medial head + Soleus	N/A
1	Rectus femoris + Vastus lateralis + Vastus medialis + Tensor fasciae latae	97
1	Gastrocnemius, medial head	100
1	Gluteus maximus	100
1	Adductor magnus + Gracilis + Semi-tendinosus + Semi-membranosus + Biceps femoris, long head	N/A
1	Deltoid	97
1	Semi-tendinosus	100

N/A: not available

Figure 1

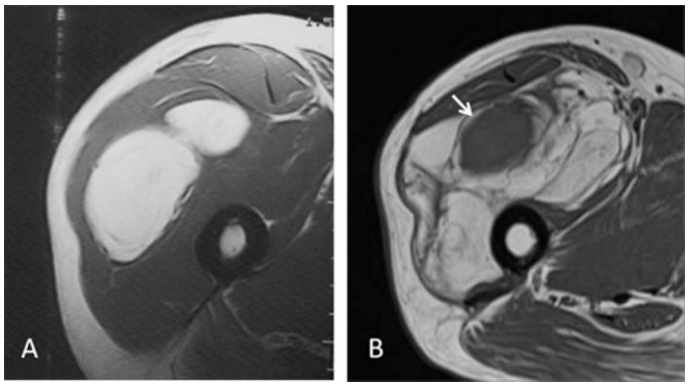
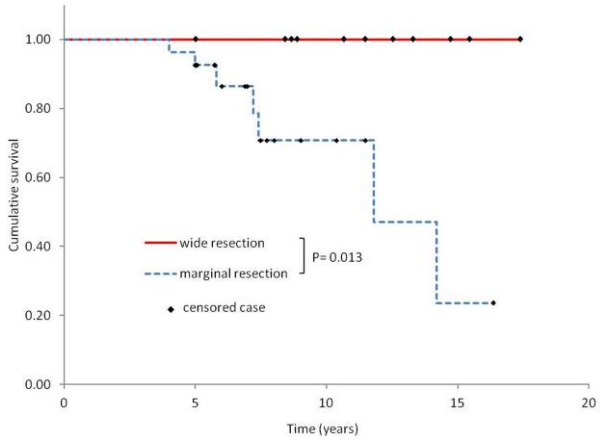


Figure 2


1.00
0.80
0.60
0.40
0.20
0.00
Cumulative survival
0
5
10
15
20
Time (years)
wide resection
marginal resection
censored case
P= 0.013