

A single institutional experience treating adipocytic tumors: incidence, disease-related outcomes, and the clinical significance of MDM2 analysis

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Abstract

Adipocytic tumors exist either as a benign or malignant form. The benign variant, lipoma, is composed of normal fat tissue. Lipomas typically develop from superficial fat cells beneath the skin or mucous membranes. Liposarcoma, the malignant counterpart, often develops in deeper tissues and is the most commonly diagnosed Soft Tissue Sarcoma (STS), comprising at least 20% of adult STS. However, malignant tumors of fatty origin exist as a spectrum of diagnoses, each carrying a unique risk of recurrence, metastasis, and long-term survival. The World Health Organization classifies liposarcomas into five categories: i) Atypical Lipomatous Tumors/Well Differentiated (ALT/WD); ii) Dedifferentiated (ALT/DD); iii) Myxoid; iv) Round cell; and v) Pleomorphic. Lipomatous tumors often exhibit different immunohistochemical patterns. Benign lipomas are distinguished by the absence of Murine Double-Minute 2 (MDM2) amplification. Similarly, ALT/WD, classically defined as a low-grade and locally aggressive tumor, demonstrates consistent patterns of MDM2 amplification. Some studies suggest 10% of ALT/WD progress to the high-grade DD form, with others report a dedifferentiation rate of as high as 20% for primary ALT/WD based on location. The ALT/DD subtype is aggressive and has a high capacity to metastasize. While the mechanism of pathogenesis of ALT/DD metastasis is unknown, previous studies suggest that increased MDM2 amplification may play a role. This study sought to evaluate a single institutional experience treating the entire spectrum of lipomatous tumors and describe utilization patterns of

MDM2 testing. The group hypothesized: i) Atypical Lipomatous Tumors (ALT), which include ALT/DD and ALT/WD, would exhibit a higher rate of local recurrence than lipomas with no significantly increased incidence of metastases; and ii) at least 50% of our MDM2 testing of ALT would prove positive for the MDM2 overamplification. This study retrospectively reviewed 105 cases (66 lipomas, 27 ALTs, 12 liposarcomas) of patients who underwent lipomatous tumor excision at our institution from 2013 to 2017. Twenty-five tumors (6 lipomas, 18 ALT, 1 liposarcoma) were tested for MDM2 amplification. Three of the tested tumors recurred (2 ALT, 1 liposarcoma), and each exhibited MDM2 overamplification. Five tumors (5 liposarcoma) developed late metastases. These data suggest that although ALT is associated with a higher rate of local recurrence, metastases are quite rare. Additionally, the data demonstrate a high rate of positive MDM2 testing (76%) based on clinical and imaging characteristics of the tumors.

Introduction

Adipocytic tumors exist as benign or malignant variants. Lipomas are the benign form, while liposarcoma, the malignant counterpart, is more invasive and comprises at least 20% of adult Soft Tissue Sarcoma (STS) diagnoses.¹ The transformation of a pre-existing lipoma to malignant liposarcoma is rare, and most documented cases arise *de novo*.^{2,3} The World Health Organization classifies liposarcoma into five categories: i) atypical lipomatous tumors/well differentiated (ALT/WD); ii) dedifferentiated (ALT/DD); iii) myxoid; iv) round cell; and v) pleomorphic.⁴ Each of these liposarcoma subtypes is diagnosed primarily on histology, though also by patterns of Murine Double-Minute 2 (MDM2) amplification or overexpression. MDM2, a proto-oncogene that encodes a nuclear-localized E3 ubiquitin ligase, promotes tumor formation by targeting tumor suppressor proteins, such as p53, for proteasomal degradation.⁵ MDM2 overexpression has been previously identified as a promoter of oncogenesis in different cancer types and has therefore begun to be used as a diagnostic marker for distinguishing lipomas from liposarcomas.^{6,7}

Lipomas are distinguished by the absence of MDM2 overamplification, while ALT/WD, the intermediate-grade and locally aggressive tumor subtype of liposarcoma, has been reported to exhibit increased MDM2 overamplification.^{8,9} One review of the immunohistochemical properties of 92

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ALT/WD subtypes noted that 79 (86%) demonstrated MDM2 overamplification.¹⁰ Similarly, ALT/DD, the aggressive, high-grade and dedifferentiated variant of ALT/WD, demonstrated MDM2 overamplification in 90% of cases.¹⁰ ALT/WD and DD comprise the largest subgroup of liposarcomas, collectively referred to herein as ALT. 40% of lipomatous tumors are ALT/WD, and while these tumors generally lack the capacity to metastasize, they can dedifferentiate to DD, a high-grade malignant tumor with a much greater propensity to metastasize.^{11,12} More specifically, reports from the literature suggest that 10% of ALT/WD progress to the DD form depending on location and clearance. While the pathogenesis of this progression is unclear, MDM2 overamplification may play a role.¹³ Tumor location, size, and histologic subtype are well-described prognostic factors in patients with liposarcoma. Extremity liposarcoma carries a better prognosis than retroperitoneal liposarcoma, and tumors less than 10-15cm in size portend a better

prognosis than larger tumors.^{13,14} Additionally, histologic grade may impact the clinical course and management of liposarcomas. Patients with a low-grade, well-differentiated subtype portend a relatively favorable 5-year overall survival of 85%, while high-grade tumors have a sub-optimal prognosis, with reports suggesting a 5-year survival range of 18% to 21%.^{15,16}

Purpose

The aim of this study was to evaluate a single institutional experience treating the entire spectrum of lipomatous tumors. The research group hypothesized that ALT (collectively ALT/WD and ALT/DD) carry a higher risk of local recurrence than lipoma, though exhibit no increased incidence of metastases. Additionally, the group hypothesized that within our institution there would exist a high positive rate of MDM2 testing due to selective testing based on clinical and imaging characteristics of these tumors.

Materials and Methods

This study was approved by the Institutional Review Board. In a retrospective analysis from the year 2013 to 2017, 105 lipomatous tumor cases and corresponding electronic medical records were reviewed. Descriptive characteristics, including surgical pathology reports for patients who underwent lipomatous tumor excision were recorded. Samples were read by an experienced musculoskeletal pathologist following excision, and slides were not

re-reviewed for this study. Lipomatous tumor subtypes were histologically classified, and patient data including age, sex, and tumor size, anatomic location, and depth were collected. Twenty-five total cases (6 lipomas, 18 ALT, 1 liposarcoma) were tested for MDM2 overamplification based on a combination of characteristics including rapid growth, deep location, size greater than 10cm, heterogeneity on imaging, or findings clinically inconsistent with benign fat on surgical resection. Perioperative complications were recorded and defined by Clavien-Dindo classification.¹⁷ Continuous variables of interest are reported as mean with range, and categorical variables of interest are represented as percentages in terms of frequency. All other data were analyzed using descriptive statistics through SPSS version 26.0 (IBM Corp, New York, USA).

Results

A total of 105 lipomatous tumors (66 lipomas, 27 ALT, 12 liposarcomas) in 105 consecutive patients were recorded. Patient demographics and tumor characteristics are summarized in Table 1 below. The median age for all patients was 57 years (range of 11 to 83) and there was female predominance (61.9%). The body mass index of the included patients ranged from 16.5 to 53.6 kg/m². Tumor location was characterized as involving either the anatomic extremities, the trunk, or the head and neck. Lipomas (N=40, 60.6%) were predominantly found

in the extremities, though were also found in the trunk (N=25, 37.9%). Twenty-six ALT (96.3%) were found in the extremities and only 1 (3.7%) was found in the trunk. Ten liposarcomas (83.3%) occurred in the extremities, while 2 (16.7%) occurred in the trunk. Tumors across all three subtypes ranged in size from 1.0 to 55cm: lipomas from 1.0 to 29cm; ALT from 3.5 to 55cm; and liposarcomas from 6 to 28cm. The median lipoma size was 8.1cm, while the median size for ALT and liposarcomas was 19 and 14.75cm, respectively. For lipomas with recorded characteristics, 13 of 64 (20.3%) were superficial or subcutaneous and 51 (79.7%) were deep/intramuscular. Similarly, 2 of 27 (7.4%) ATL were superficial or subcutaneous, while 25 (92.6%) were deep/intramuscular. All (12) liposarcomas were found within the deep intramuscular tissue. Of the total tumors, 30 (28.6%) were tested for MDM2 expression based on mixed or incongruent imaging or clinical and histological findings. No lipomas demonstrated MDM2 amplification. However, 19 ALT and 2 liposarcomas tested showed immunohistologic evidence of MDM2 amplification.

Tumor resection was performed in each of the 105 included cases. Of the 12 patients with liposarcoma, 8 received radiation therapy (neoadjuvant or adjuvant), and 4 received chemotherapy (neoadjuvant or adjuvant) for tumor treatment. No patients within either the ALT or lipoma group received any radiation or chemotherapy treatment. The outcome variables of interest are summarized in Table 2. One of 66 lipoma

Table 1. Patient demographics and tumor characteristics of 105 patients who were included in the study.

Parameter	Lipoma (n=66)	ALT (n=27)	Liposarcoma (n=12)
Sex			
Male	26/66 (39.4%)	11/27 (40.7%)	3/12 (25%)
Female	40/66 (60.6%)	16/27 (59.3%)	9/12 (75%)
Age			
Median	55	67	48.5
Range	11.0-79	27-82	18-83
Body Mass Index (kg/m ²)			
Median	30.6	26.9	26.3
Range	16.53-53.6	19.31-43.12	20.47-43.46
Site of tumor			
Extremity	40/66 (60.6%)	26/27 (96.3%)	10/12 (83.3%)
Trunk	25/66 (37.9%)	1/27 (3.70%)	2/12 (16.7%)
Head/neck	1/66 (1.52%)	0/27 (0%)	0/12 (0%)
Size (cm)			
Median	8.1	19	14.75
Range	1.0-29	3.5-55	6.0-28.0
Depth			
Superficial/subcutaneous	13/64 (20.3%)	2/27 (7.41%)	0/12 (0%)
Deep/intramuscular	51/64 (79.7%)	25/27 (92.6%)	12/12 (100%)

mas (1.52%) demonstrated local recurrence, and none were noted to have metastasized. One patient (1.2%) who underwent lipoma excision developed post-operative urinary retention. Similar to the lipoma group, none of the patients who underwent excision for ALT received any neoadjuvant or adjuvant chemotherapy or radiotherapy. For the ALT group as a whole, follow-up data were retrieved from the medical record or by contacting patients inquiring about disease status. Of the 27 diagnoses with ALT, 19 had follow-up data. Of these 19 patients, 16 (84.2%) were alive without disease, while 3 (15.8%) had evidence of recurrent disease. One patient who had surgery for ALT developed post-operative urinary retention. Two liposarcomas developed local recurrence after excision, and 1 patient who underwent surgical excision of liposarcoma died from progression of the cancer. The remaining 9 patients were alive without disease or had died from other causes at the conclusion of the study.

Discussion

Liposarcoma is the most common soft tissue sarcoma and comprises at least 20% of all STS diagnoses.¹⁻³ Additionally, liposarcoma, the malignant counterpart of a benign lipoma (Figure 1), exists on a spectrum of histologic heterogeneity that includes atypical well-differentiated (ALT/WD) and atypical de-differentiated liposarcoma (ALT/DD) (Figure 2), myxoid (Figure 3), round cell, and pleomorphic liposarcoma.⁴ While each subtype is reported to share a common genetic component of highly amplified chromosomal sequences, they are primarily distinguished by histology. Secondly, they are often differentiated by rates of local recurrence, metastasis, and proclivity to de-differentiate. Therefore,

the primary histologic diagnosis, given that it accurately predicts these patient outcomes, may serve as a useful prognostic marker for one or more of the well-classified subtypes.^{18,19} Some studies suggest ALT/DD, round cell, and pleomorphic liposarcoma exhibit the highest metastatic potential, while myxoid and ALT/WD liposarcoma are amenable to wide excision and do not metastasize.^{20,21} Furthermore, examination of margins of ALT/WD and ALT/DD after surgical resection with curative intent found a near two-times greater frequency of negative margins with ALT/WD compared to ALT/DD (35.5% versus 17.6%, respectively), which may explain the observed propensity for worse

oncologic outcomes in ALT/DD.²¹ In the aforementioned study, the recurrent ALT/WD cases were limited to regional recurrence, while 66% of the recurrent ALT/DD cases recurred as distant metastasis. These rates are notably higher than their benign counterpart, the lipoma, which according to the literature has a long term (10-years) local recurrence rate of only 1-2%.²² Similarly, the patterns of dedifferentiation of ALT/WD and myxoid liposarcoma into ALT/DD have been reported to vary by primary tumor location and macroscopic clearance.^{23,24} According to studies that classify location, ALT/WD liposarcoma that occurs in the retroperitoneum demonstrates a rate of dedifferentiation of nearly 20% for

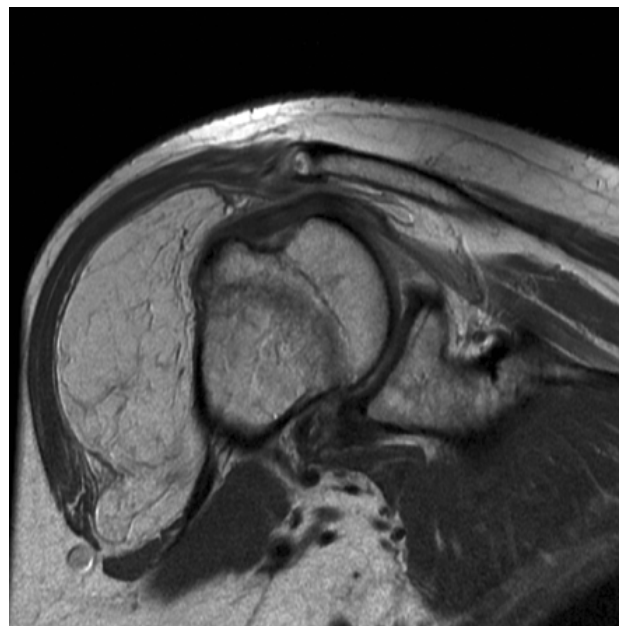


Figure 1. Benign lipoma. This figure of a lipoma within the subdeltoid region of the shoulder on MR imaging illustrates the morphology of these benign variants. Case courtesy of Associate Professor Frank Gaillard, Radiopaedia.org, rID: 7652.

Table 2. Treatment modalities and oncologic outcomes including complication profiles for patients who underwent surgical excision of lipomatous tumors.

Parameter	Lipoma (n=66)	ALT (n=27)	Liposarcoma (n=12)
Treatment			
Surgery	66/66 (100%)	27/27 (100%)	12/12 (100%)
Radiation	0/66 (0%)	0/27 (0%)	8/12 (66.7%)
Chemotherapy	0/66 (0%)	0/27 (0%)	4/12 (33.3%)
Local Recurrence	1/66 (1.52%)	5/27 (18.5%)	1/12 (8.3%)
Metastasis	0/66 (0%)	0/27 (0%)	5/12 (41.7%)
Complications			
Wound infection	0/66 (5%)	0/27 (0%)	2/12 (16.7%)
Urinary retention	1/66 (1.52%)	1/27 (3.70%)	0/12 (0%)
Outcome*			
Alive or dead from other cause	65/66 (98.5%)	16/19 (84.2%)	9/12 (75%)
Disease recurrence	1/66 (1.5%)	3/19 (15.8%)	2/12 (16.7%)
Death due to cancer	0 (0%)	0 (0%)	1/12 (8.3%)

*Outcomes for ALT only included data from patients from whom follow-up information was obtainable.

first-time tumors and up to 44% in locally recurrent tumors.²⁵ Thus, for lipomatous tumors the histology, rates of local recurrence, rates of metastasis, and patterns of dedifferentiation may predict oncologic outcomes, and represent an area ripe for further investigation.

In the present study, seven cases (1 lipoma, 5 ALTs, 1 liposarcoma) exhibited local

recurrence, while 5 total tumors (5 liposarcoma) had metastasized according to follow-up data obtained from the medical records. While a small series, these data suggest a rate of local recurrence rate nearing 19% for ALT, which is slightly above the range of 10-15% as described in the literature.^{26,27} ALT/WD and ALT/DD respond poorly to systemic chemotherapy and given

the generally high rates of local recurrence of ALT and liposarcoma subtypes, genetic targets have been under investigation as a novel treatment adjunct. Certain sarcoma oncogenes including HDM2, CDK4, HMGA2 and MDM2 have been identified as commonly amplified regions within lipomatous tumors. MDM2, a chromosome 12 gene product that when amplified inhibits p53 tumor suppressor activity, is a popular pharmacologic target.^{28,29} However, these genetic similarities among each of the liposarcoma subtypes are not ubiquitous. For example, some reports demonstrate a lower incidence of MDM2 genetic amplification in pleomorphic (high-grade, malignant potential) versus ALT/WD and ALT/DD subtypes.²⁹ Furthermore, the dedifferentiation of ALT/WD into ALT/DD exhibits strong immunohistologic evidence for MDM2 accumulation, and therefore, transcriptional profiling is often superior in discriminating liposarcoma subtype than relying on morphologic characteristics alone. For this reason, the current study sought to better characterize patterns of MDM2 and corroborate these findings with disease-related outcomes such as local recurrence and metastasis, as they might uniquely occur according to subtype.

Within our institution, MDM2 testing is obtained for predominantly normal appearing adipocytic tumors with rapid growth, histologic heterogeneity, atypical MRI appearance, large and deep-seated locations, abnormal clinical or histopathologic features after resection, or for recurring tumors. Twenty-five tumors in total were tested for MDM2 expression based on mixed or incongruent imaging or clinical and histological findings. Six negative tests confirmed the diagnosis of lipoma (24%) by default, while 15 positive tests led to the presumed of ALT (72%), inclusive of the WD and DD subtypes. Additionally, one positive test yielded the diagnosis of liposarcoma (4%). We therefore recommend utilization of MDM2 testing in this fashion to appropriately distinguish ALT/WD and ALT/DD subtypes. Proper identification can assist the multidisciplinary team with treatment, and follow-up based on reported rates of recurrence and metastasis. Future research with larger cohorts of patients is needed to assess the prognostic value of MDM2 as it varies by subtype, with higher-level statistical analyses. However, when combined with a well-defined testing regimen in an institutional setting, MDM2-targeted therapy may become the basis of future therapy for treatment of liposarcoma.



Figure 2. Liposarcoma. Subcutaneous liposarcoma of the shoulder region as seen on MR imaging. Case courtesy of Dr Roberto Schubert, Radiopaedia.org, rID: 18825.

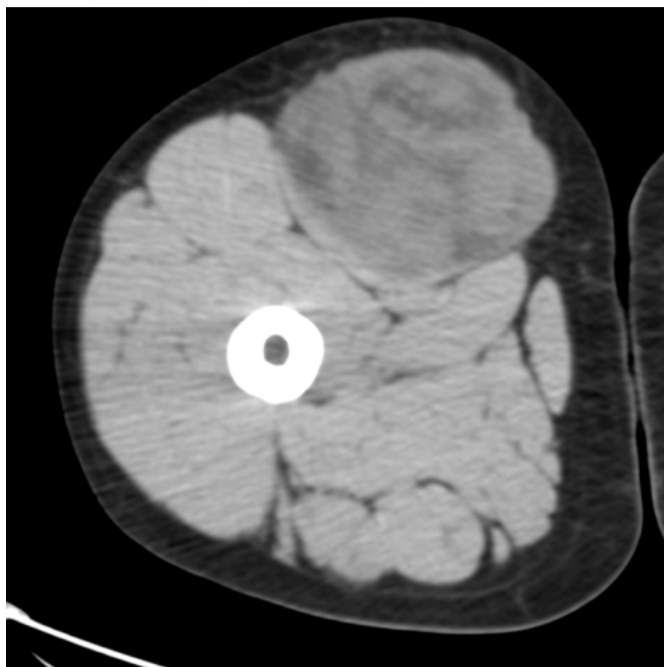


Figure 3. Myxoid liposarcoma. The myxoid variant is a liposarcoma subtype, here seen on MR imaging arising from the anterior compartment of the thigh. Case courtesy of Dr Bruno Di Muzio, Radiopaedia.org, rID: 62011.

Conclusions

While histology and morphology are often inaccurate in classifying liposarcoma subtype, MDM2 overamplification testing may prove a useful tool in distinguishing subtype. This study analyzed the utilization of MDM2 testing and its outcomes from a single institution's perspective, with the goal of contributing to an overall database on the classification and prognostic significance of lipomatous tumors as they may vary by subtype.

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