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# Myogenic dedifferentiation is associated with poor outcomes in retroperitoneal dedifferentiated liposarcomas

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## Abstract

Sarcomas are a heterogenous group of malignant tumors with origin or mesenchymal differentiation, they comprise 1–2% of all solid tumors. Retroperitoneum is the second most frequent site affected. Prognosis is worse compared to the limbs, with a 5y OS of 36–58%, and 50–60% patients will relapse. Dedifferentiated liposarcomas (ddLPS) are more aggressive, it is known that presence of a de-differentiated component increases the probability of distant recurrence and lowers OS. There is little information about the specific impact of each type of de-differentiation. To determine if the presence of myogenic differentiation markers in DDLPS is an adverse prognostic factor. A retrospective, observational, analytic cohort study was performed. Cases identified from the electronic clinical files from the National Cancer Institute in Mexico City, we included cases from January 1st 2005 to December 31st 2016. We correlated the presence of expression of myogenic markers (Smooth muscle actin, Calponin, H-caldesmon, Desmin and Myogenin) in the dedifferentiated component of DDLPS with overall survival and surgical outcomes. One hundred and forty-three cases were analyzed. Eighty-two were liposarcomas, and 38 had a dedifferentiated component. Of these 38 cases, 21(55.3%) were males and, 17(44.7%) were females. Median age was 54.1(27–79) years, median tumor size was 28 cm (13–56). Most patients had locally advanced disease: 32(84.2%) were in stage IIIB. 2.6% had metastatic disease and 5(13.2%) had stage Ib at diagnosis. Myogenic marker expression was found in 18.4% of cases; these patients had a worse median survival than cases with no myogenic expression: 18 months (95% CI 15.4–20.5) vs 32 months (95% CI 21.8–42.1) $p = 0.01$, we also found a relation with higher postoperative morbidity in these cases ($p = 0.045$). The presence of myogenic differentiation markers might be associated with a worse prognosis, in our series it corelated with worse OS, however it is not a common event. Relation with surgical morbidity is to be analyzed in further studies.

## Keywords

Retroperitoneal sarcoma, liposarcoma, myogenic dedifferentiation

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## Background

Soft tissue sarcomas (STS) are an uncommon and diverse group of malignant tumors characterized by mesodermal differentiation and constitute 1–2% of all solid malignant tumors, incidence is estimated at 1.8–5/100,000 cases every year.[1,2] The Globocan initiative estimates 12,750 new cases for 2019 in the US, and 5270 deaths due to STS.[1] These tumors may arise in any anatomical location, only 15% develop in the retroperitoneum (rtpSTS), so, the estimated annual incidence is 0.3/100,000.[2] Disease is usually advanced at presentation, so overall survival (OS) and disease free survival (DFS) are worse than sarcomas arising in other sites: 5y OS 60% versus 80% for extremity STS.[1–4]

Surgery is the main treatment for rtpSTS. Multimodal treatment can improve outcomes in properly selected cases. Goal is to achieve a negative margin resection (R0/R1 resections), but still when this goal is achieved, recurrence is common, as it occurs in 50% cases, being the primary cause of death.

Dedifferentiated liposarcomas (ddLPS), opposite from their well differentiated counterpart, can recur in distant sites and are also locally aggressive. Local recurrence rate is as high as 40–80% and distant metastasis (DM) is 15–20%, most common site of DM is the lung. 5y OS varies between 44–53%.[5]

Heterologous coexisting components within the same tumor were first described in the formerly called malignant fibrous histiocytoma (currently named undifferentiated pleomorphic sarcoma) by Evans in 1979, who described them similar to the classification used for dedifferentiated chondrosarcomas.[6]

Dedifferentiation is found in 10% of wdLPS, this can be identified at initial diagnosis or in the event of a recurrence from a wdLPS. Genetic mutations of the 12q14–15 chromosome and amplification of the oncogenes MDM2 and CDK4, are commonly found.[7]

Myogenic dedifferentiation in other sarcomas such as UPS and malignant peripheral nerve sheath tumors (MPNST) have shown a worse prognosis: lower OS and lower DFS. Gronchi et al.[8] identified myogenic differentiation in 15% of wdLPS, 48% of ddLPS and rhabdomyoblastic differentiation in 8% of ddLPS, with a 5y-OS of 42% in cases with myogenic differentiation and only 29% in rhabdomyoblastic, compared to 75% in cases of ddLPS without any of these characteristics.

Our objective was to retrospectively evaluate prognosis in dedifferentiated retroperitoneal liposarcoma cases with myogenic differentiation. We have hypothesized that this event entails a worse prognosis. Cases treated at the Sarcoma Unit in the National Cancer Institute in Mexico City from January 1st 2005 to December 31st 2016 are included.

## Material and methods

Retrospective review of the internal database at the Sarcoma Unit in the National Cancer Institute. Patients with histology proven retroperitoneal ddLPS treated from January 1st 2005 to December 31st 2016 are included. Institutional approval was obtained. Paraffin embebbed tissue was retrieved from the pathology archive. These cases were analyzed independently by two sarcoma pathologists, who reported myogenic dedifferentiation as "present" or "absent" based on an immunohistochemistry panel consisting of: smooth muscle actin, calponin, h-caldesmon, desmin, and myogenin. In case of discrepancy between report, a third pathologist reviewed the case.

Central tendency and dispersion measures were obtained. Qualitative variables with a normal distribution were analyzed using a Chi-square test, and for non-parametric distribution variables, a Fisher test was used. We compared the presence of myogenic dedifferentiation in the dedifferentiated component of retroperitonea ddLPS with OS and DFS. The SPSS Ver 25 program IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp. was used for analysis and data processing.

## Results

One hundred forty-three rtpSTS were identified, 82 were liposarcomas; 38 were ddLPS and the remaining 44 were classified as other subtypes. The 38 ddLPS were tested for the expression of myogenic differentiation markers as described previously (Figure 1).

Gender distribution was 21 (55.3%) males and 17 (44.7%) females. Median age was 54.1 (27–79), and median tumor size 28cm (13–56), most common symptom was palpable abdominal tumor and 20 (84.2%) patients presented at stage IIIb (AJCC 8$^{a}$ ed). Cohort characteristics are summarized in Table 1

Complete stage distribution was as follows: 13.2% ($n=5$) cases were diagnosed at stage IB; 84.2% ($n=32$) at stage IIIB, and 31.6% ($n=12$) at stage IV. Multifocality was found in 12 cases at primary treatment and in three recurrent cases.

A simple resection was performed in 44.7% ($n=17$), wide resection in 15.8% ($n=6$) and in 39.5% ($n=15$) a compartment resection. Median operating time was 3.25 h (1–9). A complete resection (R0, R1) was achieved in 92.1% ($n=35$), and a macroscopic positive (R2) resection occurred in 7.89% ($n=3$). Treatment is summarized in Table 2.

A multivisceral resection was performed in 34.2% cases, most common organs resected were the kidney (36.8%), colon (28.9%) and spleen (10.5%). All type morbidity rate was 34.2% ($n=13$) and postoperative mortality was 5.3% ($n=2$). Adjuvant treatment was given to only 14 patients.

Myogenic immune expression was found in seven (18.42%) of the 38 cases of ddLPS. The relation between prognosis (OS and DFS) and presence of immune myogenic markers was analyzed using a Fisher test. We found a significant correlation between myogenic dedifferentiation and postoperative morbidity, although we cannot establish yet a cause for this relation, these cases also had a higher

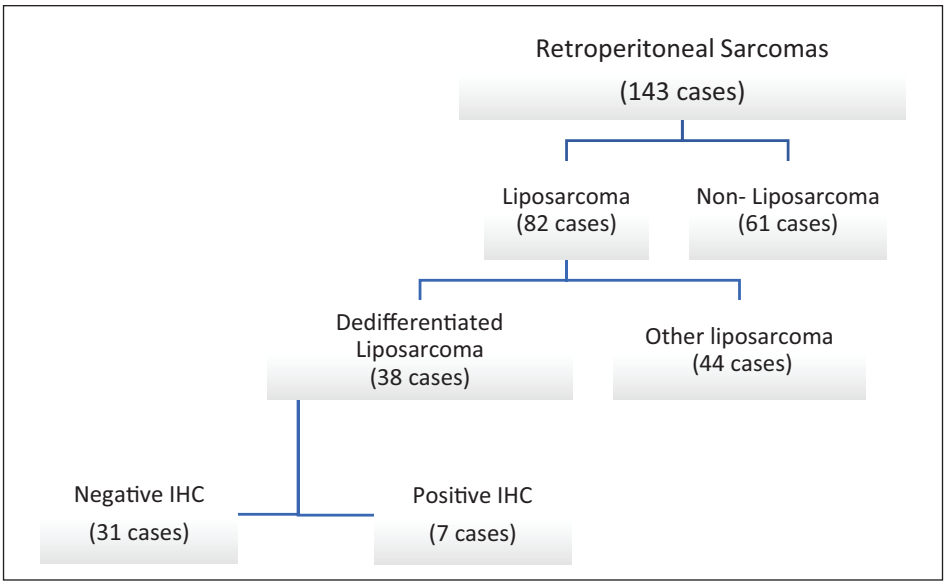


**Figure 1.** Retroperitoneal sarcoma cases identified.

**Table 1.** Clinical and demographic characteristics.

| Variable | *n* (%) |
|---|---|
| Male | 21 (55.3 %) |
| Female | 17 (44.7%) |
| Symptoms | |
| Abdominal tumor | 20 (52.6%) |
| Unspecified malaise | 6 (15.8%) |
| Pain | 4 (10.5%) |
| Incidental finding | 3 (7.9%) |
| Vascular involvement | |
| Yes | 3 (7.9%) |
| No | 35 (92.1%) |
| Number of recurrences | |
| 0 | 14 (36.8%) |
| 1 | 14 (36.8%) |
| 2 | 6 (15.8%) |
| >3 | 4 (10.5%) |
| Stage (AJCC 8th ed) | |
| IB | 5 (13.2%) |
| IIIB | 32 (84.2%) |
| IV | 1 (2.6%) |
| Multifocality | |
| Yes | 12 (31.6%) |
| No | 26 (68.4%) |
| Peritoneal sarcomatosis | |
| No | 35 (92.1%) |
| Yes | 3 (7.9%) |

probability of requiring reoperation ($p=0.04$). Myogenic dedifferentiation was not associated with age ($p=0.21$), postoperative death ($p=0.26$) nor peritoneal sarcomatosis ($p=0.46$). We also found other types of dedifferentiation: UPS in 76.3%, MPNST in 5.3%, fibrosarcoma in (5.3%) and liposarcoma con bone metaplasia in (5.3%). Types of dedifferentiation found are detailed in Table 3.

Median OS in the cohort of ddLPS was 40.8 (2–129 months), median DSF was 26.6 (0–127 months). Myogenic dedifferentiation was associated with worse OS ($p=0.01$) (Figure 2)

During follow up, recurrence occurred in 63.15% ($n=24$): 14 presented one recurrence, 6 two and 4 three or more. Only 8.3% ($n=2$) had distant recurrences. Recurrences were treated with surgery in 29.1% ($n=7$), chemotherapy in 8.3% ($n=2$), surgery plus chemotherapy in 4.1% ($n=1$) and 25% ($n=6$) received medical palliative treatment.

## Discussion

Variability in clinical behavior among sarcomas should be considered when selecting treatment. Small differences in clinical and pathologic characteristics influence prognosis.[1]

Prognostic factors in retroperitoneal ddLPS are size, grade, clinical stage, treatment facility, and resection margins.[1,9,10] Average tumor size reported is 18 cm, our series has larger tumors with a median size of 23.7. Our rate of incomplete macroscopic resections is similar to other series.[11,12]

Wide margins and compartment resections have shown to benefit only Grade 1 or Grade 2 sarcomas, in correspondence, most of our cases were treated with a simple resection, according to current recommendations.[13,14]

Our cohort found less cases of myogenic expression than other reports. Gronchi et al.[8] reported 37.5% of myogenic expression, our series found only 18.4% of cases, however their sample was larger, they included 144 cases. Despite the percent of cases identified, our findings are similar regarding the impact in OS, this paper confirms the finding that myogenic expression is related to worse

**Table 2.** Treatment and surgery performed.

| | |
|---|---|
| Simple resection | 17 (44.7%) |
| Wide resection | 6 (15.8%) |
| Compartment resection | 15 (39.5%) |
| Number of resected organs | |
| 0 | 14 (36.8%) |
| 1 | 11 (28.9%) |
| 2 | 9 (23.7%) |
| 3 | 3 (7.9%) |
| >4 | 1 (2.6%) |
| Resection type | |
| R0/R1 | 35 (92.1%) |
| R2 | 3 (7.9%) |
| Nephrectomy | 14 (36.8%) |
| Spleen resection | 4 (10.5%) |
| Colectomy | 11 (28.9%) |
| Pancreatectomy (any type) | 2 (5.3%) |
| Mayor vascular resection | 1 (2.6%) |
| Orchiectomy | 3 (7.9%) |
| Adjuvant treatment | |
| Radiation therapy (RT) | 9 (23.7%) |
| Chemotherapy (CT) | 2 (5.3%) |
| CT/RT | 3 (7.9%) |
| None | 24 (63.2%) |
| Multivisceral resection | |
| No | 25 (65.8%) |
| Yes | 13 (34.2%) |
| Postoperative morbidity | |
| Yes | 13 (34.2%) |
| No | 25 (65.8%) |
| Postoperative mortality (30d) | |
| Yes | 2 (5.3%) |
| No | 36 (94.7%) |

**Table 3.** Type of dedifferentiation in retroperitoneal ddLPS.

| Type of dedifferentiation | *n* (%) |
|---|---|
| UPS | 29 (76.3%) |
| Fibrosarcoma | 2 (5.3%) |
| Liposarcoma con bone metaplasia | 2 (5.3%) |
| MPNST | 2 (5.3%) |
| Osteosarcoma | 1 (2.6%) |
| Myofibroblastic | 1 (2.6%) |
| UPS – myxofibrosarcoma | 1 (2.6%) |

outcomes compared to patients without it. An important difference between our paper and the one published by Gronchi et al. is that we did not find a relation with distant metastasis, this might be due to our small sample size, however we do identify a more aggressive behavior of these tumors. One of the main practical uses of identifying prognostic factors is to select cases that might benefit from chemotherapy or radiation therapy in future clinical trials.

The analysis of genetic events leading to the development of dedifferentiation might also help to understand the influence of tumor microenvironment and find potential treatment targets. Specific drug-gene interactions have been searched for using computational models to find potential treatments,[15] so knowledge of the genomics in sarcoma is of clinical relevance. Both well differentiated (WD) and dedifferentiated liposarcoma share basic genetic abnormalities: the formation of a ring MDM2 (12q15) chromosome leading to amplification and overexpression of the 12q amplicon. However, ddLPS has genetic differences: abnormalities of the c-Jun pathway characterized by co-amplifications of the 1p32 and 6q23 genes, this event is implicated in the progression from a WD to a DD liposarcoma.[16]

The PVT1 oncogene has shown to be an adverse prognostic factor in several tumors and in osteoblast differentiation, other genes like HMGA2 and CPM have also been found to influence the dedifferentiation of wdLPS, ddLPS have higher genomic complexity than their WD couterpart.[17] To elucidate the genomic changes that drive specific differentiation is quite harder. MicroRNAs have been found to be dysregulated in pediatric Rhabdomyosarcoma and in both wdLPS and ddLPS, but no certain relation with the type of differentiation has been established. The answer might be in mesenchymal stem cells and the regions amplified in them. Also, external factors like infection or chronic inflammation have shown to affect and possibly induce dedifferentiation in normal tissue and other cancers.[18,19] The specific type of dedifferentiation seems to be of clinical significance, cases of malignant phyllodes tumors of the breast with osteosarcoma or chondrosarcoma dedifferentiation seem to have a very aggressive course.

The importance of further analysis of specific risk factors is important in order to select patients who may benefit from systemic therapy, given the heterogeneity of STS it is highly likely that this decision will be based on a very individualized basis.

Adjuvant or neoadjuvant chemotherapy in extremity-STS, much more common than rtpSTS is conflicting. The phase III trial EORTC 62931 showed no survival benefit in patients given adjuvant chemotherapy in extremity STS,[20] however, further analysis has shown that selection of cases at high risk for distant metastasis improves the benefit of systemic therapy. This was confirmed in a large meta-analysis that found an OS benefit in high risk STS treated with adjuvant chemotherapy (HR 0.86 (CI 0.76–0.97) $p = 0.02$).[5] Regarding other agents, immunotherapy has not shown benefit in all STS types: Results of the phase II trial SARC028, although was a negative trial found a tendency toward better response in UPS and ddLPS.[21]The evidence in rtpSTS is even more complex to analyze. The benefit of extended surgery has been demonstrated[13,14] but even with this approach, recurrence is common. The pattern of recurrence varies according to the histology: well differentiated LPS recur only locally, while ddLPS may do so both locally and at distant sites.[22]

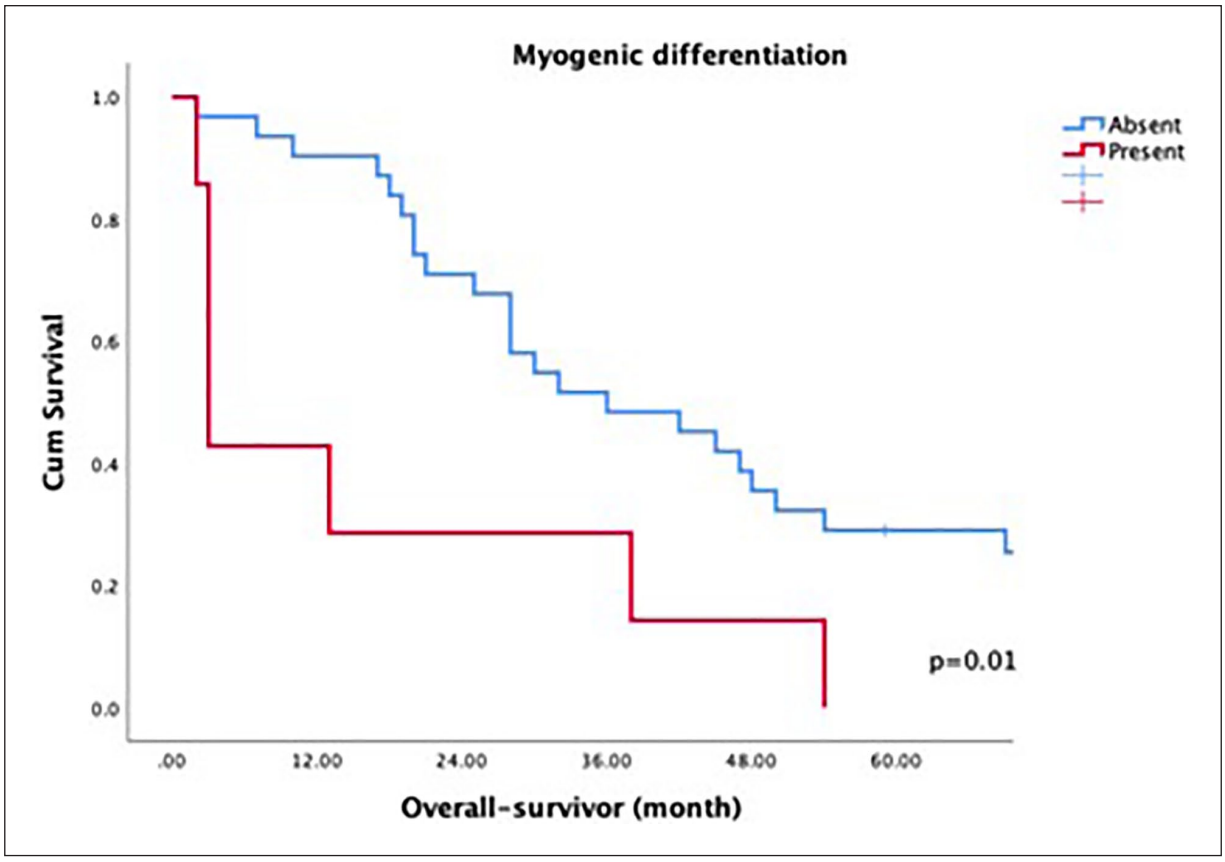


**Figure 2.** Overall survival of cases with and without myogenic differentiation (median OS 26.6 vs 40.8, $p = 0.01$).

A potential utility of this paper is to provide information about risk factors that may help elucidate patients who are more likely to benefit from systemic therapy, due to the clinical behavior. The results obtained in this work allow us to better understand how cell transformation (dedifferentiation) impacts on the oncological outcome and opens the possibility of carrying out studies that explain how the tumor microenvironment influences this transformation, which is associated with tumor progression as well as less understanding to design better management strategies.

The present study has limitations, first is a retrospective, single-center study, second, the small sample size included. The adjuvant or neoadjuvant chemotherapy use was low due to accessibility in our population. However, it opens the possibility of future studies in relation to the tumor microenvironment and its relation to the biological behavior of the neoplasms, the influence of the microenvironment and the tumor transformation.

## Conclusion

As sarcomas are better understood, treatment can be individualized to select specific treatment plans according to expected outcomes. In this paper we corroborated that the expression on myogenic differentiation markers in retroperitoneal dedifferentiated liposarcomas is associated with worse overall survival than the rest of ddLPS. The relation found with operative morbidity is to be further analyzed. Pathologist participating in sarcoma groups should consider routine testing for these markers. More intense follow up is to be considered in this group.

### Author contributions

Garcia-Ortega Dorian Yarih: Conceptualization, Methodology, Software, Writing- Reviewing and re-Editing. Alvarez-Bojorquez Mario and Rodríguez-Ayala Ernesto: Data curation, Writing-Original draft preparation. Alvarez-Cano Alethia: Visualization, Investigation, Reviewing.
Caro-Sánchez Claudia and Melgarejo-Estefan Emmanuel: Supervision.

### Declaration of conflicting interests

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## Ethical approval

Ethical approval to report this study was obtained from Institutional Review Board of Instituto Nacional de Cancerología (México) (INCAN/CI/0628/18).
This study was conducted according to the declaration of Helsinki (2008) principles and Mexican Health Guidelines.

## Informed consent

This is a retrospective study, in which intervention was not performed on the patients.

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## Data availability

The database used to support the findings of this study are available from the corresponding author upon request via e-mail. Personal patient information will not be shared in the interest of confidentiality.

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