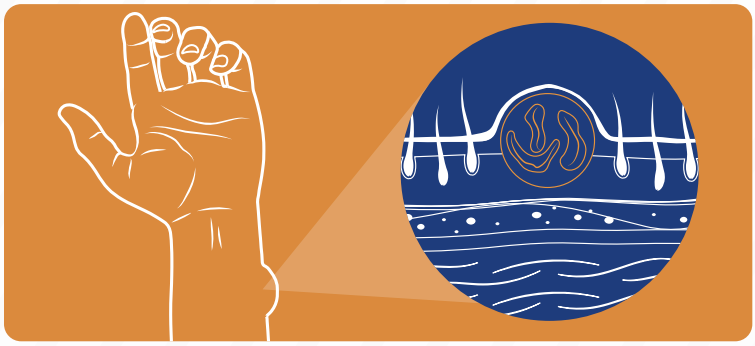
WILEY

Understanding the Pathophysiology, Diagnosis, and Treatment of Dedifferentiated Liposarcomas

An update on recent advances



Liposarcomas are a diverse and heterogenous group of soft tissue sarcomas arising from lipoblasts or fat cells in the extremities, retroperitoneum, and oesophagus[1,2]

Four main subtypes[1,2,3,4]

- Atypical lipomatous tumours/well-differentiated liposarcomas (ALT/WDLS)
- Myxoid/round cell liposarcomas (MLS)
- Pleomorphic liposarcomas (PLS)
- Dedifferentiated liposarcomas (DDLS)

	ALT/WDLS	MLS	PLS	DDLS
Histology	Mature adipocytes, atypical stromal cells, and few lipoblasts	Hypercellular round cell component Categorised based on areas (%) having round cells/hypercellularity: Myxoid cell liposarcoma (MCL) >25% Round cell liposarcoma (RCL) >75%	Irregular cell groups and abundant isolated, non-adherent, pleomorphic cells	• Well-differentiated tissue with a transitioned region of non-adipose tissue sarcoma • 90% DDLs arise *de novo* and 10% arise from previous WDLS
Genetic markers	Amplification within chromosome 12q13-15 region which includes *CDK4, MDM2,* and *HMGA2*	95% MLS have a characteristic t (12; 16) (q13; p11) chromosomal translocation, which produces FUS-DDIT3 (TLS-CHOP) fusion protein	• Complex genetic and molecular profile • Commonly mutated genes - *TP53, NF1, RB1, PIK3CA, SYK*	Co-amplification in the 12q13-15, 1p32, and 6q23 chromosome regions, including *CDK4* and *MDM2, JUN,* and *ASK1/MAP3K5*
Predominant tumour site	Extremities, retroperitoneum, abdomen, paratesticular region, mediastinum, or head and neck region	Extremities, retroperitoneum, and abdomen	• Extremities (65%) • Retroperitoneum and abdomen (15%)	• Retroperitoneum (most common; 80% of cases) • Can also occur in the extremities, spermatic cord, trunk, head and neck regions • Rare in superficial soft tissue
Patient group	Common in adults aged >50 years	Common in children, adolescents, and young adults	>80% of cases seen in patients aged >50 years	Common in middle-aged and older adults
Metastatic potential	• Weakly invasive • Distant metastasis is rare • 10% DDLS undergo dedifferentiation and become invasive	• Metastasise to extrapulmonary sites including abdominal wall, retroperitoneum, skeletal sites such as the spine • RCL is more invasive than MCL	High rate of local recurrence and metastasis	Aggressive with high metastatic potential
Prognosis	Excellent	A higher proportion of round cells is associated with a poorer prognosis	Poor	Poor
Chemosensitivity	Surgical resection is usually curative for localised tumours Unclear	High in some high-grade MCLs	Low-moderate response	Poor
Radiosensitivity	Unclear	High	Low-moderate response	Unclear

Visit https://ddl.knowledgehub.wiley.com for additional resources

Retroperitoneal sarcomas[4,5]

70–80% of retroperitoneal tumours are malignant and extremely rare, accounting for only 0.1–0.2% of all malignancies

Over 50% are DDLS

Retroperitoneal DDLS are usually challenging to treat

May warrant combined resection of the tumour and surrounding tissues/organs

High rate of recurrence may lead to multiple surgeries

Treatments should focus on preventing locoregional recurrence and improving survival

Multi-disciplinary care can improve patient outcomes

Diagnosis, staging, and clinical evaluation[4]

- DDLS of the retroperitoneum and extremities are categorised into four stages depending on their aggressiveness and metastatic potential
- Symptoms often emerge after the tumour has grown significantly, underscoring the need for early diagnosis
- The tumour grade, stage, and metastatic status govern the optimal treatment course

Molecular assessment[4]

Fluorescent *in situ* hybridisation to assess *MDM2* and *CDK4* overexpression may be used to differentiate between WDL or DDLS and other lipomas

Biopsy[5,6]

- Tissue examination following a needle biopsy or surgical resection is often necessary for a definitive diagnosis
- Contributes to tumour dissemination through seeding of cancer cells; biopsy tract may be resected or irradiated to avoid dissemination
- Imaging guided biopsy can enable safe and accurate diagnosis of retroperitoneal tumours

Imaging[4,6]

- Magnetic resonance imaging to visualise soft tissue tumours and demarcate the fatty cell
- Undifferentiated tumour
- Positron emission tomography for the differential diagnosis of undifferentiated tumours

Visit https://ddl.knowledgehub.wiley.com for additional resources

Treatment

Surgery

- **R0** – complete resection with negative margins (preferrable)
- **R1** – resection with microscopic margins
- **R2** – resection with gross residual disease (not recommended)

- Complete tumour resection of tumours in the extremities is effective[1]
- Adjuvant radiotherapy may be used for shrinkage of such tumours[4]
- Adjacent visceral organs around tumours makes complete resection challenging[4,5]

Radiation[1]

Adjuvant radiation in treating DDLS is currently being investigated in the STRASS clinical trial

Chemotherapy[5]

Systemic therapy may benefit patients with high-grade and unresectable DDLS with local recurrence

Considerations while selecting the optimal treatment[4]

Individual patient features

Tumour location

Size and stage

Relationship with surrounding neurovascular and bone elements

Functional and cosmetic requirements

Visit https://ddl.knowledgehub.wiley.com for additional resources

Management of DDLS[4]

Localised disease

Complete surgical resection of tumours in extremities is associated with excellent outcomes

The use of preoperative or postoperative adjuvant radiotherapy is still evolving with limited data on its potential benefits

Results from the STRASS Phase 3 trial are expected to guide clinicians on the use of adjuvant radiation in patients

Advanced disease: Systemic therapies

First-line standard treatment

- Anthracycline-based therapy
- Doxorubicin + ifosfamide

Second-line treatments

- Eribulin
- Trabectedin
- Gemcitabine
- Vinorelbine
- Dacarbazine
- Pazopanib

Therapies under investigation

- MDM2 inhibitors
- CDK4 inhibitors: Palbociclib, ribociclib, and abemaciclib
- XPO1 inhibitor: Selinexor
- PD-1 inhibitors: Pembrolizumab and nivolumab

Treatment trajectories for DDLS[4]

- Surgery: Complete tumour resection
- Neoadjuvant radiation for tumour shrinkage → Surgical resection
- Surgical resection → Postoperative adjuvant radiation
- Postoperative adjuvant radiation → Surgical resection → Postoperative adjuvant radiation
- Neoadjuvant chemotherapy → Surgery
- Surgery → Adjuvant chemotherapy

- Surgical resection with negative margins continues to remain the mainstay treatment for DDLS
- Radiotherapy and chemotherapy may be used in combination with surgery for selected patients with high-grade and widespread tumours
- The risk versus benefit of adjuvant radiotherapy and chemotherapy must be assessed while devising a treatment regime
- Judicious palliative tumour resection can help prolong the life of patients with high-grade tumours

References

1. Haddox, C. L., & Riedel, R. F. (2021). Recent advances in the understanding and management of liposarcoma. *Faculty Reviews, 10*.
2. Yang, L., Chen, S., Luo, P., Yan, W., & Wang, C. (2020). Liposarcoma: Advances in cellular and molecular genetics alterations and corresponding clinical treatment. *Journal of Cancer, 11*(1), 100–107.
3. Nassif, N. A., Tseng, W. W., Borges, C. C., Chen, P., & Eisenberg, B. L. (2016). Recent advances in the management of liposarcoma. *F1000Research, 5*.
4. Nishio, J., Nakayama, S., Nabeshima, K., & Yamamoto, T. (2021). Biology and management of dedifferentiated liposarcoma: state of the art and perspectives. *Journal of Clinical Medicine, 10*(15), 3230.
5. Sassa, N. (2020). Retroperitoneal tumors: Review of diagnosis and management. *International Journal of Urology, 27*(12), 1058–1070.
6. Zafar, R. (2023, March 20). Liposarcoma. StatPearls - NCBI Bookshelf.

Published by WILEY

Visit https://ddl.knowledgehub.wiley.com for additional resources