Liposarcoma

Multimodality Management and Future Targeted Therapies

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KEYWORDS

• Sarcoma • Liposarcoma • Myxoid liposarcoma • Pleomorphic liposarcoma • CDK4 • MDM2 • FUS-CHOP • Trabectedin

KEY POINTS

- Common genomic events define 3 biological groups of liposarcoma (LPS) – amplification of 12q13–15 in well-differentiated LPS (WDLS) and dedifferentiated LPS (DDLS), FUS-DDIT3 translocation in myxoid LPS (MLS)/round cell LPS (RCLS), and complex genomic changes in pleomorphic LPS.
- Surgery is the gold standard for cure of LPS, but grade, histology, and tumor site (retroperitoneal vs extremity) determine prognosis and pattern of recurrence.
- Retroperitoneal LPSs are almost always well-differentiated and dedifferentiated tumors that recur locally even after complete surgical resection, so active research focuses on optimizing surgical protocols and defining the role of radiation in multimodality therapy.
- WDLS and DDLS are relatively chemoresistant; however, MLS/RCLS and pleomorphic LPSs respond well to cytotoxic therapies, and MLS/RCLS is particularly radiosensitive.
- Among targeted therapies, CDK4 inhibitors are effective in WDLS and DDLS, and trabectedin, which prevents FUS-DDIT3 binding to DNA, is effective in MLS/RCLS.

INTRODUCTION

LPS is one of the most common histologies of soft tissue sarcoma (STS), representing 50% of retroperitoneal and 25% of extremity STS.[1] There are 3 separate biologic groups of LPS encompassing 5 histologic subtypes. Each group is characterized by

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specific genetic alterations presumed to drive tumor initiation (Table 1). WDLS and DDLS represent more than 60% of all LPS and are almost universally associated with amplification of chromosome segment 12q13–15, which carries the oncogenes *MDM2*, *CDK4*, and *HMGA2*.[2–6] More than 95% of MLS and RCLS carry a translocation of *FUS* and *DDIT3* (*CHOP*) genes.[7–9] Pleomorphic LPS has a complex karyotype often causing loss of tumor suppressors p53 and Rb.[5] This subtype, which is associated with a poor prognosis, is the rarest subtype of LPS, comprising approximately 5% of cases.[6]

Surgery remains the mainstay of treatment of LPS, but the 3 subgroups have highly variable response to systemic therapies, affecting recommendations regarding adjuvant therapy (Table 2). The different genomic underpinnings that define the groups mean that research has identified variable means of targeting these diseases using novel therapies. This article examines the data supporting current treatment strategies, including multimodality paradigms that integrate radiation and chemotherapy. Ongoing genomic and molecular studies elucidating novel methods for treating the diseases and results of clinical trials aimed at translating these findings into clinical practice are also examined.

WELL-DIFFERENTIATED LIPOSARCOMA AND DEDIFFERENTIATED LIPOSARCOMA

WDLS and DDLS are the most common histologic variants of LPS. DDLS represents progression of WDLS from an indolent, sometimes locally aggressive lesion to more rapidly growing disease with metastatic potential.[6,10,11] Five-year disease-specific survival in patients with DDLS is 44% compared with 93% in patients diagnosed with pure WDLS.[6] Genomic alterations are more complex in DDLS than in WDLS. In addition to amplification of 12q13–15, copy number alterations affecting segments of chromosome 11, 19, and 3, among others, are common in retroperitoneal DDLS and may affect genomic stability as well as prognosis.[12]

Management of Primary Well-differentiated Liposarcoma and Dedifferentiated Liposarcoma in the Extremity

Treatment strategies for WDLS/DDLS diagnosed in the extremity parallel those of STS in general[1]; however, diagnosis can often be made radiographically and not based on core biopsy. DDLS appears as an enhancing nodule in association with a lipomatous tumor (WDLS); the adipogenic component appears similar to fat on CT or MRI (Fig. 1A). High-grade DDLS is managed primarily with surgical resection. The tumor

Table 1
Genomic alterations in liposarcoma

Histologic Subtypes	Genomic Alterations	Affected Oncogenes	Clinical Correlation
Well-differentiated and dedifferentiated	12q13–15 amplification	MDM2 and CDK4	N/A
	3p14–21 loss	Unknown	Dedifferentiation
	11q23–24 loss	Unknown	Dedifferentiation, genomic instability
	19q13 loss	Unknown	Dedifferentiation, poor prognosis
Myxoid/round cell	FUS-DDIT3 translocation	Unknown	N/A
Pleomorphic	Rb/p53 loss	Rb and p53	N/A