Keung *et al*. *J Transl Genet Genom* 2019;3:8
DOI: 10.20517/jtgg.2019.03

Journal of Translational Genetics and Genomics

Review

Open Access

Overview of liposarcomas and their genomic landscape

Emily Z. Keung[1], Neeta Somaiah[2]

[1]Department of Surgical Oncology, the University of Texas MD Anderson Cancer Center, Houston 77030, USA.
[2]Department of Sarcoma Medical Oncology, the University of Texas MD Anderson Cancer Center, Houston 77030, USA.

Correspondence to: Dr. Neeta Somaiah, Department of Sarcoma Medical Oncology, the University of Texas MD Anderson Cancer Center, Houston 77030, USA. E-mail: nsomaiah@mdanderson.org

How to cite this article: Keung EZ, Somaiah N. Overview of liposarcomas and their genomic landscape. *J Transl Genet Genom* 2019;3:8. https://doi.org/10.20517/jtgg.2019.03

Received: 15 Feb 2019 **First Decision:** 5 Mar 2019 **Revised:** 11 Mar 2019 **Accepted:** 13 Mar 2019 **Published:** 22 May 2019

Science Editor: David Cooper **Copy Editor:** Cai-Hong Wang **Production Editor**: Huan-Liang Wu

Abstract

Liposarcoma (LPS) is among the most common soft tissue sarcoma affecting adults. LPS is divided into three biologic subtypes characterized by specific genetic alterations. The most common LPS subtypes, well-differentiated and dedifferentiated LPS, are nearly uniformly characterized by ring chromosomes and giant markers with chromosomal amplification of 12q13-15 and resulting amplification of oncogenes *MDM2*, *CDK4*, and *HMGA2*. Myxoid/round cell LPS commonly exhibits a distinctive (12; 16) translocation resulting in the *FUS-DDIT3* fusion gene. Finally, pleomorphic LPS harbors diverse complex genomic changes and chromosomal rearrangements and frequent mutations in *TP53*, *RB1*, and *NF1* leading to dysregulation of tumor suppressor pathways. In this review, we summarize the currently available knowledge on the genomics and genetics of LPS subtypes as well as recent advances in the multimodality management of LPS.

Keywords: Dedifferentiated liposarcoma, liposarcoma, genetics, genomics, myxoid liposarcoma, pleomorphic liposarcoma, round cell liposarcoma, well-differentiated liposarcoma

INTRODUCTION

Soft tissue sarcomas (STS) encompass over 50 recognized entities according to the World Health Organization (WHO) classification. Liposarcomas (LPS) are among the most common STS histologies, representing 50% of retroperitoneal and 25% of extremity STS[1] LPS consist of 3 biologic subgroups encompassing 5 histologic subtypes characterized by specific genetic alterations [Table 1]. These three STS subgroups, their characteristic genetic alterations, and treatment will be reviewed herein.

WELL-DIFFERENTIATED AND DEDIFFERENTIATED LPS

Well-differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS) are the most common histologic subtypes of LPS [Table 1]. Together they represent 60% of all LPS and often coexist, occurring in the retroperitoneum and extremities. WDLPS is a typically indolent histologic subtype that presents as slowly growing masses but can be locally aggressive with minimal to no distant metastatic potential while DDLPS is a higher grade histology with a potential for faster growth and distant metastatic potential[1,2].

Chromosomal translocations and copy number alterations

Although genetic alterations are more complex in DDLPS than WDLPS, both commonly exhibit ring chromosomes and giant markers with chromosomal amplification of 12q13-15. This segment of chromosome 12q13-15 contains a number of cancer-related genes implicated in tumorigenesis. Included in these are the genes *CDK4*, *MDM2*, and *HMGA2* which are consistently amplified and in the recent TCGA genomic characterization of adult STS they were reported in 100%, 92%, and 76% of LPS cases, respectively[3], as well as *CPM* and *YEATS2*[4,5]. MDM2 is an E3 ubiquitin protein ligase which promotes degradation of p53 to prevent apoptosis and/or cell-cycle arrest and may also have effects independent of p53 (such as through other tumor suppressors such as p21)[6-10]. *CDK4* encodes a key regulator of the G1/S cell cycle checkpoint and is coamplified with *MDM2* in over 90% of patients[4]. *YEATS4* and *CPM* are genes implicated in dedifferentiation[11,12]; the former encodes a putative transcription factor required for physiologic suppression of p53 function while the later encodes a proteolytic enzymes that activates growth factors such as epidermal growth factor.

Development of DDLPS is associated with accumulation of additional chromosomal abnormalities[4]. Copy number alterations are common in DDLPS with deletions reported in chromosome 1p, 11q, 13q, 15q and 17p and focal amplifications at chromosomes 1q, 5p, 6q, 8q, 11p, 12q, 14q, and 15q[3,11,13]. Recurrent amplifications of 1p32 and 6q23 with resulting overexpression of *JUN* and *ASK1*, respectively, have been implicated in adipocyte dedifferentiation, have been reported only in DDLPS, and are associated with worse prognosis[3,14-16]. Chromosomal deletions of tumor suppressor genes including RUNX3 and ARID1A (1p36), ATM and CHEK1 (11q22-24), and RB1 (13q14.2) have been associated with reduced adipocytic differentiation, genomic instability, and worse patient outcomes[11,12].

Mutations

Mutation rates are modest in WDLPS and DDLPS, with few consistently and recurrently mutated genes across case series[3,11,13,17-19]. No significant differences have been reported in the mutations between WDLPS and DDLPS to explain the differences in behavior.

Epigenetics

DNA methylation and histone modifications

Studies have reported alterations in LPS methylomes leading to changes in expression of differentiation pathway genes. Epigenetic silencing via methylation of CEBP - gene was identified in 10 or 42 DDLPS samples (24%) and treatment with demethylating agents induced cellular apoptosis and increased CEBP - expression[18]. More recently, The Cancer Genome Atlas (TCGA) reported that among DDLPS cases included in the sarcoma analysis, patients whose tumors were hypermethylated compared to hypomethylated had shorter disease-specific survival[3].

Additionally, a small number of other studies describe other epigenetic mechanisms of gene silencing, including altered histone modifications, that are associated with dedifferentiation and/or tumor growth[20,21].

MicroRNAs

MicroRNAs (miRNAs) are small non-protein coding RNA molecules that exert regulatory functions on gene expression. In the context of the RNA-induced silencing complex (RISC), these 21-25 nucleotide long RNA

Table 1. Clinical characteristics of liposarcoma histologic subtypes

Subtype	Genomic alterations	Affected oncogenes	Local recurrence rate	Distant recurrence rate	Chemosensitivity	Radiosensitivity
Well differentiated	12q13-15 amplification	*MDM2, CDK4*	Moderate	Low/-	None	Moderate
Dedifferentiated	12q13-15 amplification 3p14-21 loss 11q23-24 loss 19q13 loss	*MDM2, CDK4* Unknown Unknown Unknown	High	Low	Low	Moderate
Myxoid	FUS-DDIT3 translocation	Unknown	Low	Moderate	High	High
Round cell	FUS-DDIT3 translocation	Unknown	Moderate	High	High	High
Pleomorphic	Rb/p53 loss	Rb, p53	Moderate	High	High	Moderate

Adapted from Crago and Dickson[1]

molecules bind to the 3'-untranslated region of target mRNA and induce the degradation of target mRNA. Dysregulation of miRNAs has been reported in many malignancies and altered miRNA expression can result from deficiencies in their processing pathways, epigenetic modifications, or miRNA gene mutations[22].

There have been a number of miRNA alterations described in LPS. MiR-26a-2 is located near the *MDM2* gene region and is overexpressed in both well-differentiated and dedifferentiated LPS, associated with enhanced cellular proliferation, survival, and invasion[23,24]. MiR-155 is a strong oncogene that has been shown to be overexpressed in myxoid/round cell, dedifferentiated, and pleomorphic LPS compared to normal adipose tissue. It promotes cellular growth by targeting casein kinase 1α that in turn enhances β-catenin signaling and cyclin D1 expression[25,26]. MiR-143, miR-193b, and miR-133a exhibit inhibitory effects on cellular proliferation; miR-143 and miR193b are downregulated in well-differentiated and dedifferentiated LPS compared to normal adipose tissue[27,28] while miR-133a is downregulated in dedifferentiated LPS[29].

MYXOID/ROUND CELL LPS

Myxoid/round cell LPS represents ~30% of LPS [Table 1][30]. Myxoid/round cell LPS typically develop in the proximal extremities. Other sites such as bone, retroperitoneum, serosal surfaces, and contralateral limbs are commonly affected at time of recurrence. Increasing aggressiveness is associated with increasing round cell component with tumors containing > 5% round cell component carrying an unfavorable prognosis[31-33] as well as higher histologic grade, multifocality, and p53 overexpression[4]. Compared to WDLPS and DDLPS, myxoid/round cell LPS are significantly more sensitive to chemotherapy and radiation therapy[34].

Chromosomal translocations and copy number alterations

Myxoid LPS is almost always associated with a chromosomal translocation, most commonly t(12;16)(q13;p11) in over 90% of cases and which leads to the fusion of the *DDIT3* (also known as *CHOP*) and *FUS* (also known as *TLS*) genes resulting in the FUS-DDIT3 fusion protein[32,33,35,36]. The *DDIT3* gene encodes for a nuclear protein belonging to the CCAAT/enhancer binding protein (C/EBP) family of transcription factors and is implicated in adipocyte differentiation. The *FUS-DDIT3* fusion protein is implicated to confer tumorigenicity through dysregulated adipocyte differentiation. Although different variants of the FUS-DDIT3 transcript have been reported, no prognostic difference has been described between the variants. Myxoid LPS are also less commonly associated with other translocations, including the t(12;22)(q13;q22) translocation resulting in expression of EWSR1-DDIT3 fusion protein. These resulting fusion proteins are thought to result in malignant transformation by functioning as aberrant transcriptional regulators that interfere with adipocyte terminal differentiation and favor proliferation[32,37,38].

Myxoid LPS have relatively normal karyotypes compared to other STS histologic subtype, including DDLPS and pleomorphic LPS[12].

Mutations

In addition to the nearly ubiquitous presence of a chromosomal translocation, a subset of myxoid LPS (15%) are also characterized by mutations or amplifications of *PIK3CA*, which encodes the catalytic subunit of phosphatidylinositol 3-kinase (PI3K)[12]. Patients with tumors harboring *PIK3CA* mutations have shorter disease-specific survival compared to those with wild-type *PIK3CA*. Thus, the *PI3K* pathway in patients with myxoid LPS with *PIK3CA* mutations is an attractive therapeutic target. *PTEN* deletion has also been described[12,39]. Additionally, myxoid LPS are also characterized by expression of the cancer-testis antigen, NY-ESO-1[35], and patients with myxoid LPS are candidates for various immunotherapy trials targeting NY-ESO-1[40,41].

Epigenetic alterations

There have been limited studies investigating the epigenetics of myxoid LPS[11,42-44]. Epigenetic silencing of *p14ARF*, a p53 target, by promoter methylation has been reported as a common event in both myxoid and pleomorphic LPS.

MicroRNAs

As in the case for well-differentiated and dedifferentiated LPS, miRs dysregulation has also been demonstrated in myxoid/round cell LPS. miR-155 is a strong oncogene that has been shown to be overexpressed in myxoid/round cell LPS[26]. miR-486, which interacts with plasminogen activator inhibitor 1 (PAI-1), a promoter of cellular proliferation and invasion, is downregulated in myxoid LPS[45,46].

PLEOMORPHIC LPS

Pleomorphic LPS are the rarest histologic subtype of LPS, representing ~5% of cases, and associated with the worst prognosis [Table 1][1,47-50]. Pleomorphic LPs typically arise in the extremities, although less commonly can occur in the trunk or retroperitoneum[4]. Up to 50% of patients develop metastatic disease and disease-specific survival is poor[51].

Chromosomal translocations and copy number alterations

Our current understanding of the molecular pathology of pleomorphic LPS is poor. They characteristically harbor diverse complex genomic changes and chromosomal rearrangements without unifying molecular alterations nor targetable aberrations. Deletion of 13q14.2-5, which contains *RB1*, has been described in up to half of pleomorphic LPS[12,52].

Mutations

Mutations or loss of *TP53* is frequently seen in pleomorphic LPS, unlike in LPS subtypes where TP53 loss is uncommon. Loss of NF1 is also seen in some patients[12,47].

Epigenetic alterations

There is not much known about the epigenetics of pleomorphic LPS[11,42]. As noted before, promoter methylation resulting in epigenetic silencing of p14ARF has been reported as a common event in both myxoid and pleomorphic LPS.

MicroRNAs

As in the case for well-differentiated and dedifferentiated LPS, miRs dysregulation has also been demonstrated in pleomorphic LPS. miR-155 is a strong oncogene that has been shown to be overexpressed in pleomorphic LPS[26].

THERAPEUTIC OPPORTUNITIES AND CONSIDERATIONS

Despite our increasing understanding of the genomic alterations across LPS subtypes, their implications for LPS management and translation into novel therapeutics in the clinic has, to date, remained limited.

Here we review the current state of multimodality treatment of LPS and highlight opportunities for future advancements in LPS management.

Local therapies - surgical resection and radiation therapy

For patients with primary localized LPS, surgery with complete gross tumor resection (R0/R1 margins) remains the definitive management and only potential curative treatment. However, local recurrence rates are high (> 80%)[53,54]. Radiation therapy (RT) and/or chemotherapy can be used as adjuncts to reduce local and distant recurrence risk for those with dedifferentiated, myxoid/round cell, or pleomorphic LPS.

Systemic therapies

Cytotoxic therapies

WDLPS and DDLPS are relatively chemoresistent[1,2,55], with response rates in the literature reported as low as ≤ 12%[56] and as high as 21%[53] [Table 1]. Thus, in the primary or recurrent resectable setting, systemic therapy has not been frequently used and there is no consensus regarding their use in the neoadjuvant or adjuvant setting. For those with unresectable or metastatic LPS, cytotoxic chemotherapy is the standard of care[4,57]. Myxoid/round cell LPS is considered to be relatively chemosensitive and thus chemotherapy may be considered for those patients with resectable disease in the neoadjuvant or adjuvant as well as in the unresectable or metastatic settings[58]. The role of systemic therapy for pleomorphic LPS is less well defined although a number of retrospective studies suggest a degree of chemosensitivity in the metastatic setting[58].

Despite the differences in chemosensitivity, in the first line, anthracycline (typically doxorubicin), often in combination with ifosfamide, is the standard systemic therapy. Second-line systemic therapy options that are used frequently include trabectedin[59-61], eribulin[60,62-64] and gemcitabine/docetaxel[65]. Other regimens with activity in soft tissue sarcomas are used infrequently, include gemcitabine, and dacarbazine monotherapies as well as combination of gemcitabine/dacarbazine[58]. Though trabectedin and eribulin are both approved for the treatment of all liposarcomas, trabectedin has much higher response in MRCLS and eribulin leads to longer progression free survival benefit in pleomorphic LPS.

Investigational therapies - targeted therapies

For patients who have failed standard of care systemic therapies, there are a number of investigational therapies that may be considered including targeted agents[66] and immunotherapies alone or in combination with other therapies[41,67,68]. Amplification of the *CDK4* oncogene as well as *MDM2* are seen in > 90% of WDLPS/DDLPS. Small molecule inhibitors targeting CDK4/6 (palbociclib) and MDM2, are being evaluated in ongoing studies, either alone or in combination with chemotherapy. These trials are enrolling patients with WDLPS/DDLPS[58,69].

Pazopanib, a tyrosine kinase inhibitor approved for use in second/third-line and beyond in non-adipocytic soft tissue sarcoma, has limited activity in LPS subtypes[68,69]. Olaratumab is a recombinant human immunoglobulin G (IgG) monoclonal antibody that binds PDGFRa and blocks receptor activation and has shown improved overall survival in a randomized phase Ib/II study for all soft tissue sarcoma subtypes, when given in combination with doxorubicin compared to doxorubicin alone[58], but the recently released phase III data did not validate these results. Selenixor (XPO-1 inhibitor) and PPARγ agonists are also under investigation for advanced LPS.

Investigational therapies - immunotherapy

In recent decades, major advances have been made in cancer therapy through the use of immune checkpoint blockade - with the FDA approval of therapies targeting the CTLA-4 and PD-1 across multiple cancer types and cancer care continuum in the metastatic and adjuvant settings[70]. Current FDA approvals for immune checkpoint blockade therapies are limited to cancer types characterized by high mutational burden such

as melanoma, non-small cell lung carcinomas, urothelial cancers, and microsatellite instability-high or mismatch repair-deficient solid tumors. Interestingly, immunotherapy was first reported as a potential therapeutic strategy for sarcomas by William Coley[71] in 1891, when he noted spontaneous regression of a recurrent malignant sarcoma in a patient after a serious bout of infection.

Recent evidence suggests that immune checkpoint inhibitors may have activity in particular subtypes of soft tissue sarcomas[72,73] and in histologic subtypes such as undifferentiated pleomorphic sarcoma (UPS) and DDLPS that have mutational and copy number heterogeneity[11]. Two multicenter phase II clinical trials examining the efficacy of anti-PD-1 therapy in advanced metastatic sarcoma included patients with DDLPS have been reported in recent years[72,73]. The first study, SARC028, enrolled 86 patients with advanced STS and bone sarcomas to receive pembrolizumab (anti-PD-1)[72]. Of the 80 patients evaluable for response, 10 had DDLPS with 2 of these patients (20%) achieving disease control (stable disease or partial response) after only 8 weeks of treatment with pembrolizumab. The second study, Alliance A091401, enrolled and randomized 85 patients with locally advanced, unresectable, or metastatic sarcoma to receive nivolumab (anti-PD-1) monotherapy or nivolumab plus ipilimumab (anti-CTLA-4)[73]. No responses were observed in the 5 patients with LPS, although patients with both WDLPS and DDLPS were enrolled in this study. Both SARC028 and A091401 have been expanded to include additional patients with UPS and LPS; results from these expansion cohorts are eagerly anticipated.

Although immune checkpoint therapy offered significant and durable responses for some patients with DDLPS in the SARC028 study, most failed to respond to immunotherapy or had short-lived responses. At baseline, both the tumor immune microenvironment and the poor antigenicity of these tumors may facilitate escape of immune recognition. There are considerable ongoing efforts in other malignancies to identify predictors of response to immune checkpoint blockade and elucidate mechanisms of resistance to immunotherapy. In STS, ongoing studies include those combining immunotherapies with other systemic therapies (cytotoxic) or local treatment modalities (RT, injectables) in advanced disease or applying immunotherapy for earlier stage sarcoma, such as in the neoadjuvant setting[65,66,72].

Patients with myxoid LPS often overexpress the cancer testis antigen, NY-ESO-1, which is being targeted by investigational immunotherapies including adoptive cell therapies and peptide vaccines[4]. The adoptive transfer of T-cells genetically modified to express a T-cell receptor recognizing NY-ESO-1, has shown promising responses in a heavily pre-treated MRCLS patients in a pilot study[74].

CONCLUSION

LPS is classified into 3 biologic groups encompassing 5 histologic subtypes characterized by specific genomic and genetic alterations and variable clinical behavior and prognosis. Both WDLPS and DDLPS are characterized by the presence of chromosomal amplification of 12q13-15 with associated amplification of oncogenes MDM2, CDK4, and HMGA2. DDLPS is notable for having additional and more complete genetic alterations compared to WDLPS. Myxoid/round cell LPS are nearly uniformly characterized by the presence of a chromosomal translocation, most commonly t(12;16)(q13;p11) resulting in the fusion protein FUS-DDIT3, with mutations in *PIK3CA* more common in high grade tumors. Lastly, pleomorphic LPS is notable for diverse complex genomic changes and chromosomal rearrangements without unifying molecular alterations nor targetable aberrations. To date, achieving a comprehensive understanding of LPS biology has been challenging, in part due to the rarity of these tumors and relative dearth of *in vitro* and *in vivo* experimental model systems. Many of the ongoing clinical trials are testing novel therapeutic targets, with correlative analyses of associated biospecimens, which should help shed light on molecular mechanisms behind response and resistance to these novel therapies, and lead to future advancements in the multimodality treatment for patients with LPS.

DECLARATIONS

Authors' contributions

Design: Keung EZ, Somaiah N
Literature research: Keung EZ, Somaiah N
Manuscript writing: Keung EZ, Somaiah N
Manuscript editing: Keung EZ, Somaiah N
Manuscript revision: Keung EZ, Somaiah N

Availability of data and materials

Not applicable.

Financial support and sponsorship

Dr. Keung is supported by National Institutes of Health (NIH) (T32 CA009599).

Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Crago AM, Dickson MA. Liposarcoma: multimodality management and future targeted therapies. Surg Oncol Clin N Am 2016;25:761-73.
2. Crago AM, Singer S. Clinical and molecular approaches to well differentiated and dedifferentiated liposarcoma. Curr Opin Oncol 2011;23:373-8.
3. Abeshouse A, Adebamowo C, Adebamowo SN, Akbani R, Akeredolu T, et al. Comprehensive and integrated genomic characterization of adult soft tissue sarcomas. Cell 2017;171:950-65.e28.
4. Jones RL, Lee ATJ, Thway K, Huang PH. Clinical and molecular spectrum of liposarcoma. J Clin Oncol 2018;36:151-9.
5. Somaiah N, Beird HC, Barbo A, Mills Shaw KR, Wang WL, et al. Targeted next generation sequencing of well-differentiated/dedifferentiated liposarcoma reveals novel gene amplifications and mutations. Oncotarget 2018;9:19891-9.
6. Haupt Y, Maya R, Kazaz A, Oren M. Mdm2 promotes the rapid degradation of p53. Nature 1997;387:296-9.
7. Kubbutat MH, Jones SN, Vousden KH. Regulation of p53 stability by Mdm2. Nature 1997;387:299-303.
8. Zhang Z, Wang H, Li M, Rayburn ER, Agrawal S, et al. Stabilization of E2F1 protein by MDM2 through the E2F1 ubiquitination pathway. Oncogene 2005;24:7238-47.
9. Jin Y, Lee H, Zeng SX, Dai MS, Lu H. MDM2 promotes p21waf1/cip1 proteasomal turnover independently of ubiquitylation. EMBO J 2003;22:6365-77.
10. Wang SP, Wang WL, Chang YL, Wu CT, Chao YC, et al. p53 controls cancer cell invasion by inducing the MDM2-mediated degradation of Slug. Nat Cell Biol 2009;11:694-704.
11. Kanojia D, Nagata Y, Garg M, Lee DH, Sato A, et al. Genomic landscape of liposarcoma. Oncotarget 2015;6:42429-44.
12. Barretina J, Taylor BS, Banerji S, Ramos AH, Lagos-Quintana M, et al. Subtype-specific genomic alterations define new targets for soft-tissue sarcoma therapy. Nat Genet 2010;42:715-21.
13. Beird HC, Wu CC, Ingram DR, Wang WL, Alimohamed A, et al. Genomic profiling of dedifferentiated liposarcoma compared to matched well-differentiated liposarcoma reveals higher genomic complexity and a common origin. Cold Spring Harb Mol case Stud 2018;4. pli:a002386.
14. Chibon F, Mariani O, Derré J, Malinge S, Coindre JM, et al. A subgroup of malignant fibrous histiocytomas is associated with genetic changes similar to those of well-differentiated liposarcomas. Cancer Genet Cytogenet 2002;139:24-9.
15. Chibon F, Mariani O, Derré J, Mairal A, Coindre J-M, et al. ASK1 (MAP3K5) as a potential therapeutic target in malignant fibrous histiocytomas with 12q14-q15 and 6q23 amplifications. Genes Chromosomes Cancer 2004;40:32-7.
16. Mariani O, Brennetot C, Coindre JM, Gruel N, Ganem C, et al. JUN oncogene amplification and overexpression block adipocytic

differentiation in highly aggressive sarcomas. Cancer Cell 2007;11:361-74.
17. Asano N, Yoshida A, Mitani S, Kobayashi E, Shiotani B, et al. Frequent amplification of receptor tyrosine kinase genes in welldifferentiated/ dedifferentiated liposarcoma. Oncotarget 2017;8:12941-52.
18. Taylor BS, DeCarolis PL, Angeles CV., Brenet F, Schultz N, et al. Frequent alterations and epigenetic silencing of differentiation pathway genes in structurally rearranged liposarcomas. Cancer Discov 2011;1:587-97.
19. Li C, Shen Y, Ren Y, Liu W, Li M, et al. Oncogene mutation profiling reveals poor prognosis associated with FGFR1/3 mutation in liposarcoma. Hum Pathol 2016;55:143-50.
20. Nakazawa MS, Eisinger-Mathason TSK, Sadri N, Ochocki JD, Gade TPF, et al. Epigenetic re-expression of HIF-2α suppresses soft tissue sarcoma growth. Nat Commun 2016;7:10539.
21. Keung EZ, Akdemir KC, Al Sannaa GA, Garnett J, Lev D, et al. Increased H3K9me3 drives dedifferentiated phenotype via KLF6 repression in liposarcoma. J Clin Invest 2015;125:2965-78.
22. Smolle MA, Leithner A, Posch F, Szkandera J, Liegl-Atzwanger B, et al. MicroRNAs in different histologies of soft tissue sarcoma: a comprehensive review. Int J Mol Sci 2017;18. pli:E1960.
23. Lee DH, Forscher C, Di Vizio D, Koeffler HP. Induction of p53-independent apoptosis by ectopic expression of HOXA5 in human liposarcomas. Sci Rep 2015;5:12580.
24. Lee DH, Amanat S, Goff C, Weiss LM, Said JW, et al. Overexpression of miR-26a-2 in human liposarcoma is correlated with poor patient survival. Oncogenesis 2013;2:e47.
25. Boro A, Bauer D, Born W, Fuchs B. Plasma levels of miRNA-155 as a powerful diagnostic marker for dedifferentiated liposarcoma. Am J Cancer Res 2016;6:544-52.
26. Zhang P, Bill K, Liu J, Young E, Peng T, et al. MiR-155 is a liposarcoma oncogene that targets casein kinase-1α and enhances β-catenin signaling. Cancer Res. 2012;72:1751-62.
27. Ugras S, Brill E, Jacobsen A, Hafner M, Socci ND, et al. Small RNA sequencing and functional characterization reveals MicroRNA-143 tumor suppressor activity in liposarcoma. Cancer Res 2011;71:5659-69.
28. Mazzu YZ, Hu Y, Soni RK, Mojica KM, Qin L-X, Agius P, et al. miR-193b-regulated signaling networks serve as tumor suppressors in liposarcoma and promote adipogenesis in adipose-derived stem cells. Cancer Res 2017;77:5728-40.
29. Yu PY, Lopez G, Braggio D, Koller D, Bill KLJ, et al. miR-133a function in the pathogenesis of dedifferentiated liposarcoma. Cancer Cell Int 2018;18:89.
30. Manji GA, Schwartz GK. Managing liposarcomas: cutting through the fat. J Oncol Pract 2016;12:221-7.
31. Kilpatrick SE, Doyon J, Choong PFM, Sim FH, Nascimento AG. The clinicopathologic spectrum of myxoid and round cell liposarcoma: a study of 95 cases. Cancer 1996;77:1450-8.
32. Antonescu CR, Elahi A, Healey JH, Brennan MF, Lui MY, et al. Monoclonality of multifocal myxoid liposarcoma: confirmation by analysis of TLS-CHOP or EWS-CHOP rearrangements. Clin Cancer Res 2000;6:2788-93.
33. Antonescu CR, Tschernyavsky SJ, Decuseara R, Leung DH, Woodruff JM, et al. Prognostic impact of P53 status, TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma. Clin Cancer Res 2001;7:3977-87.
34. Jones RL, Fisher C, Al-Muderis O, Judson IR.. Differential sensitivity of liposarcoma subtypes to chemotherapy. Eur J Cancer 2005;41:2853-60.
35. Pollack SM, Jungbluth AA, Hoch BL, Farrar EA, Bleakley M, et al. NY-ESO-1 is a ubiquitous immunotherapeutic target antigen for patients with myxoid/round cell liposarcoma. Cancer 2012;118:4564-70.
36. Panagopoulos I, Mertens F, Isaksson M, Mandahl N. A novel FUS/CHOP chimera in myxoid liposarcoma. Biochem Biophys Res Commun 2000;279:838-45.
37. Kuroda M, Ishida T, Takanashi M, Satoh M, Machinami R, et al. Oncogenic transformation and inhibition of adipocytic conversion of preadipocytes by TLS/FUS-CHOP type II chimeric protein. Am J Pathol 1997;151:735-44.
38. Adelmant G, Gilbert JD, Freytag SO. Human translocation liposarcoma-CCAAT/enhancer binding protein (C/EBP) homologous protein (TLS-CHOP) oncoprotein prevents adipocyte differentiation by directly interfering with C/EBPbeta function. J Biol Chem 1998;273:15574-81.
39. Demicco EG, Torres KE, Ghadimi MP, Colombo C, Bolshakov S, et al. Involvement of the PI3K/Akt pathway in myxoid/round cell liposarcoma. Mod Pathol 2012;25:212-21.
40. Lim J, Poulin NM, Nielsen TO. New strategies in sarcoma: linking genomic and immunotherapy approaches to molecular subtype. Clin Cancer Res 2015;21:4753-9.
41. Pollack SM. The potential of the CMB305 vaccine regimen to target NY-ESO-1 and improve outcomes for synovial sarcoma and myxoid/ round cell liposarcoma patients. Expert Rev Vaccines 2018;17:107-14.
42. Davidović R, Sopta J, Mandušić V, Krajnović M, Stanojević M, Tulić G, et al. p14(ARF) methylation is a common event in the pathogenesis and progression of myxoid and pleomorphic liposarcoma. Med Oncol 2013;30:682.
43. Oda Y, Yamamoto H, Takahira T, Kobayashi C, Kawaguchi K, et al. Frequent alteration of p16(INK4a)/p14(ARF) and p53 pathways in the round cell component of myxoid/round cell liposarcoma: p53 gene alterations and reduced p14(ARF) expression both correlate with poor prognosis. J Pathol 2005;207:410-21.
44. De Cecco L, Negri T, Brich S, Mauro V, Bozzi F, et al. Identification of a gene expression driven progression pathway in myxoid liposarcoma. Oncotarget 2014;5:5965-77.
45. Borjigin N, Ohno S, Wu W, Tanaka M, Suzuki R, et al. TLS-CHOP represses miR-486 expression, inducing upregulation of a metastasis regulator PAI-1 in human myxoid liposarcoma. Biochem Biophys Res Commun 2012;427:355-60.

46. Bajou K, Maillard C, Jost M, Lijnen RH, Gils A, et al. Host-derived plasminogen activator inhibitor-1 (PAI-1) concentration is critical for in vivo tumoral angiogenesis and growth. Oncogene 2004;23:6986-90.
47. Ghadimi MP, Liu P, Peng T, Bolshakov S, Young ED, et al. Pleomorphic liposarcoma: Clinical observations and molecular variables. Cancer 2011;117:5359-69.
48. Hornick JL, Bosenberg MW, Mentzel T, McMenamin ME, Oliveira AM, et al. Pleomorphic liposarcoma: clinicopathologic analysis of 57 cases. Am J Surg Pathol 2004;28:1257-67.
49. Dalal KM, Kattan MW, Antonescu CR, Brennan MF, Singer S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann Surg 2006;24:381-91.
50. Gebhard S, Coindre JM, Michels JJ, Terrier P, Bertrand G, et al. Pleomorphic liposarcoma: clinicopathologic, immunohistochemical, and follow-up analysis of 63 cases: a study from the French Federation of Cancer Centers Sarcoma Group. Am J Surg Pathol. 2002;26:601-16.
51. Dei Tos AP. Liposarcomas: diagnostic pitfalls and new insights. Histopathology 2014;64:38-52.
52. Taylor BS, Barretina J, Socci ND, Decarolis P, Ladanyi M, et al. Functional copy-number alterations in cancer. PLoS One 2008;3:e3179.
53. Livingston JA, Bugano D, Barbo A, Lin H, Madewell JE, et al. Role of chemotherapy in dedifferentiated liposarcoma of the retroperitoneum: defining the benefit and challenges of the standard. Sci Rep 2017;7:1-8.
54. Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg 2003;238:358-70. discussion 370-1.
55. Dalal KM, Antonescu CR, Singer S. Diagnosis and management of lipomatous tumors. J Surg Oncol 2008;97:298-313.
56. Italiano A, Toulmonde M, Cioffi A, Penel N, Isambert N, et al. Advanced well-differentiated/dedifferentiated liposarcomas: role of chemotherapy and survival. Ann Oncol 2012;23:1601-7.
57. Ratan R, Patel SR. Chemotherapy for soft tissue sarcoma. Cancer 2016;18:604-10.
58. McGovern Y, Zhou CD, Jones RL. Systemic therapy in metastatic or unresectable well-differentiated/dedifferentiated liposarcoma. Front Oncol 2017;7:292.
59. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016;34:786-93.
60. Ratan R, Patel SR. Trabectedin and eribulin: where do they fit in the management of soft tissue sarcoma? Curr Treat Options Oncol 2017;18:1-9.
61. Jones RL, Demetri GD, Schuetze SM, Milhem M, Elias A, et al. Efficacy and tolerability of trabectedin in elderly patients with sarcoma: subgroup analysis from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Ann Oncol 2018;29:1995-2002.
62. Demetri GD, Schöffski P, Grignani G, Blay JY, Maki RG, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. J Clin Oncol 2017;35:3433-9.
63. Setola E, Noujaim J, Benson C, Chawla S, Palmerini E, et al. Eribulin in advanced liposarcoma and leiomyosarcoma. Expert Rev Anticancer Ther 2017;17:717-23.
64. Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: A randomised, open-label, multicentre, phase 3 trial. Lancet 2016;387:1629-37.
65. Maki RG. Gemcitabine and docetaxel in metastatic sarcoma: past, present, and future. Oncologist. 2007;12:999-1006.
66. Pollack SM, Ingham M, Spraker MB, Schwartz GK. Emerging targeted and immune-based therapies in sarcoma. J Clin Oncol 2018;36:125-35.
67. Wilky BA, Jones RL, Keedy VL. The current landscape of early drug development for patients with sarcoma. Am Soc Clin Oncol Educ B [Internet] 2017;37:807-10. Available from: http://meetinglibrary.asco.org/content/174701-199 [Last accessed on 25 Apr 2019]
68. Nathenson MJ, Conley AP, Sausville E. Immunotherapy: a new (and Old) approach to treatment of soft tissue and bone sarcomas. Oncologist 2018;23:71-83.
69. Samuels BL, Chawla SP, Somaiah N, Staddon AP, Skubitz KM, et al. Results of a prospective phase 2 study of pazopanib in patients with advanced intermediate-grade or high-grade liposarcoma. Cancer 2017;123:4640-7.
70. Keung EZ, Wargo JA. The Current Landscape of Immune Checkpoint Inhibition for Solid Malignancies. Surg Oncol Clin N Am. 2018;
71. Coley WB. II. Contribution to the knowledge of sarcoma. Ann Surg 1891;14:199-220.
72. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017;18:1493-501.
73. D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol 2018;19:416-26.
74. D'Angelo SP, Druta M, Liebner DA, Schuetze S, Somaiah N, et al. Pilot study of NY-ESO-1^{c259} T cells in advanced myxoid/round cell liposarcoma. J Clin Oncol 2018;36:3005. Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.3005. [Last accessed on 25 Apr 2019]