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Bone and Soft Tissue Cancer

Prognosis of Liposarcoma Patients in Modern ERA: Single-Center Experience

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Abstract

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Objective Liposarcomas are relatively rare tumors. Prognostic and predictive factors and treatment options are limited. We herein presented our 10-year experience with liposarcomas.

Materials and Methods Adult patients with liposarcoma treated between 2005 and 2015 in our center were included. Demographic and clinicopathologic features of patients were retrieved from patient files.

Statistical Analyses Outcomes in terms of disease-free survival (DFS) and overall survival (OS) were assessed along with potential prognostic factors using Kaplan–Meier analyses.

Results A total of 88 patients were included. The median age was 52. Rates of well-differentiated (WDLS), dedifferentiated (DDLS), myxoid (MLS), and pleomorphic liposarcomas (PLS) were 42, 9.1, 37.5, and 4.5%, respectively. Only 10% of patients had high-grade tumors and 93% had localized disease. Ninety-six percent of patients ($n = 84$) underwent surgery. Adjuvant chemotherapy was delivered to 16 patients. The most common regimen was ifosfamide–doxorubicin. Recurrences were observed in 30 patients, 21 had local, and 9 had distant metastasis. Five-year DFS of patients with the localized disease was 68%. All patients with PLS had relapses and those had the highest distant relapse rates among all subtypes. Multivariate analysis showed T stage and grade were associated with DFS. Five-year OS of the entire population was 68%. Five-year OS was 79, 76, 50, and 0% in WDLS, MLS, DDLS, and PLS, respectively ($p = 0.002$).

Conclusion Management of liposarcomas is still challenging. Surgery is the mainstay of treatment. Novel effective therapies are needed, particularly in advanced disease settings.

Keywords

- liposarcoma
- histologic subtypes
- prognosis
- surgery
- Sarculator

Introduction

Liposarcomas constitute approximately 20% of all soft tissue sarcomas (STS).[1] The estimated age-adjusted incidence rate was reported as 1.08 per 100.000 person-years.[2] Four major subtypes are well-differentiated/atypical lipomatous tumor (WDLS), dedifferentiated (DDLS), myxoid (MLS), and pleomorphic liposarcomas (PLS). The frequency of histological subtypes was 33% for WDLS, 20% for DDLS, 19% for MLS, 7%

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for PLS, and 21% for other histologies, respectively.[2] Surgery is the treatment of choice.[3] MLS is more chemosensitive and radiosensitive.[4–7] PLS is more aggressive and highly resistant to conventional cytotoxic therapy.[8,9]

Liposarcomas are rare tumors, with even more rare histological subtypes with diverse responses to chemotherapy (CT) and radiotherapy (RT). Limited data are available for the treatment options. In this study, we aimed to review our 10-year experience regarding clinicopathologic features, treatment modalities, and survival data of liposarcoma patients in a tertiary oncology center.

Methods

Histologically confirmed adult liposarcoma patients diagnosed and treated between 2005 and 2015 in Hacettepe University Cancer Institute were included in this study. Demographic characteristics, pathologic features, tumor locations, surgical approaches, CT, and RT data were retrieved from patient files. Outcomes were analyzed in terms of recurrence rates, disease-free survival (DFS), or overall survival (OS). Written informed consent was obtained from all participants for this study. Approval for the study was obtained from the independent ethics committee.

Categorical variables were compared with the chi-squared or Fisher's exact test, as appropriate. Survival estimates were calculated by Kaplan–Meier analysis and median survival times were compared by log-rank test. A p-value of less than 0.05 was considered to denote statistical significance.

The possible factors detected in univariate analyses were further entered into multivariate Cox regression analysis with enter selection to determine independent risk factors for patients. Variables with a p-value of up to 0.20 in univariate analysis or with clinical significance regardless of p-value were included in multivariate analyses. SPSS Software Version 26 (IBM, Chicago, Illinois, United States) was used for the analysis.

Results

After the exclusion of patients with incomplete follow-up data ($n = 31$), a total of 88 patients were included in the study. ►Table 1 shows the demographic and clinical features of patients. The median age at diagnosis was 52 years (min: 21, max: 81). Thirty-nine (44%) patients were female. WDLS was the most common histology with 37 patients (42%), followed by MLS, DDLS, and PLS. Median tumor size was 13 cm (min: 2, max: 65 cm). Fifty-five (63%) patients had low-grade tumors, and 9 patients (10%) had intermediate-high-grade tumors. The majority of the patients had localized (93%) disease, while six patients had node-positive and/or metastatic disease.

Upfront resection was performed in 84 patients (96%), 14 of whom had R1 and 2 patients had R2 resection. Disease recurrence rates were 28.3% ($n = 15$) and 50% ($n = 7$) in R0 and R1 resection groups. Adjuvant CT was performed in 16 patients (8 with MLS, 2 with PLS, 2 with DDLS, 4 with WDLS).

Table 1 Demographic and clinical features (all patients)

	n	%
Gender		
Male	49	55.7
Female	39	44.3
Histologic subtype		
Well-differentiated	37	42
Dedifferentiated	8	9.1
Myxoid	33	37.5
Pleomorphic	4	4.5
Unknown	6	6.8
Tumor grade		
Low	55	62.5
High	9	10.2
Unknown	24	27.3
Stage		
Localized	82	93.2
Node positive	2	2.3
Metastatic	4	4.5
Tumor location		
Retroperitoneal/intra-abdominal/ deep localization	16	18.2
Head neck/superficial body/extremity	30	34.1
Unknown	42	47.7
Perioperative chemotherapy[a]	26	23.4
Perioperative radiotherapy[a]	16	18.2
Relapse[a]	30	34.1
Relapse sites[a]		
Local	21	70
Distant	9	30

[a]Among patients with early-stage disease.

Ifosfamide–doxorubicin was the most commonly used regimen (12 of 16 patients). Clinical characteristics of patients treated with perioperative CT were shown in ►Table 2. Adjuvant RT was utilized in 19 patients (22%).

On follow-up, 30 patients had disease recurrence, 21 had local, and 9 had a distant recurrence. Five-year DFS was 68%. Recurrence rates and patterns varied significantly according to histology; 30% in WDLS (91% local), 30% in MLS (60% local), 50% in DDLS (100% local), and 100% in PLS (25% local). Fifteen recurrences (50%) were observed within the first 2 years of diagnosis, 10 (33%) within 2 to 5 years, and 5 recurrences (17%) were seen more than 5 years after diagnosis. Five-year DFS rates were 71 and 51% for patients younger and older than 60 years, respectively ($p = 0.06$). DFS curves among different histological subtypes were shown in ►Fig. 1. Five-year DFS was 85% for T1-T2, 62% for T3, and 53% for T4 disease ($p = 0.032$). Five-year DFS according to histological grade was 71% for grade 1 disease, 44% for grade 2 to 3

Table 2 Clinicopathological characteristics of patients who received and did not receive perioperative chemotherapy

	Perioperative chemotherapy (%)	No perioperative chemotherapy (%)
Age (years)(median)	58	52
Grade		
1	6 (60)	46 (90.2)
2–3	4 (40)	5 (9.8)
Tumor size (cm) (median)	10	13.5
Histologic subtypes		
Well-differentiated	4 (25)	30 (44.1)
Dedifferentiated	2 (12.5)	6 (8.8)
Myxoid	8 (50)	25 (36.8)
Pleomorphic	2 (12.5)	2 (2.9)
Unknown	0 (0)	5 (7.4)
Tumor location		
Retroperitoneal/ intra-abdominal/ deep location	3 (18.8)	13 (19.1)
Head neck/ superficial body/ extremity	8 (50)	20 (29.4)
Unknown	5(31.3)	35 (51.5)

disease ($p = 0.003$). In the multivariate analysis, T stage and histological grade were the only independent prognostic factors (►Table 3).

Adjuvant CT and RT were not associated with 5-year DFS ($p = 0.96$ and $p = 0.69$; respectively) (►Fig. 2). Only 2 of the 19 patients who had received RT had local recurrence, while 19 of the remaining patients had local recurrence (11 vs. 29%, $p = 0.14$).

Five-year OS was 68% among all patients, 71% among patients with localized disease, and 25% among those with metastatic disease at the time of diagnosis. Only one patient with upfront multiple lung metastases survived more than 10 years with slowly growing metastases and without response to any CT. Five-year OS according to T stage was 82% for T1 to T2, 67% for T3, and 57% for T4 disease ($p = 0.046$). Patients who had recurrence had a significantly lower rate of 5-year OS compared with those without recurrence (88 vs. 48%, respectively, $p < 0.001$). Patients with distant recurrence had significantly lower 5-year OS compared with those with local recurrence (13 vs. 63%, respectively, $p < 0.001$). Five-year OS according to histology was 79% in WDLS, 76% in MLS, 50% in DDLS, and 0% in PLS ($p = 0.002$). Five-year OS according to histological grade was 83% for grade 1 disease, 34% for grade 2 to 3 disease ($p = 0.009$).

Among patients treated with salvage CT at relapse, seven patients (50%) received ifosfamide–doxorubicin (IMA) and five patients (35.7%) received ifosfamide–etoposide (IMET) regimens. Only one patient (14.3%) in IMA and two patients (40%) in the IMET group achieved partial response (PR). One patient with PR had PLS and two had WDLS (►Table 4). In the relapsed setting, 20 patients underwent surgery and 6

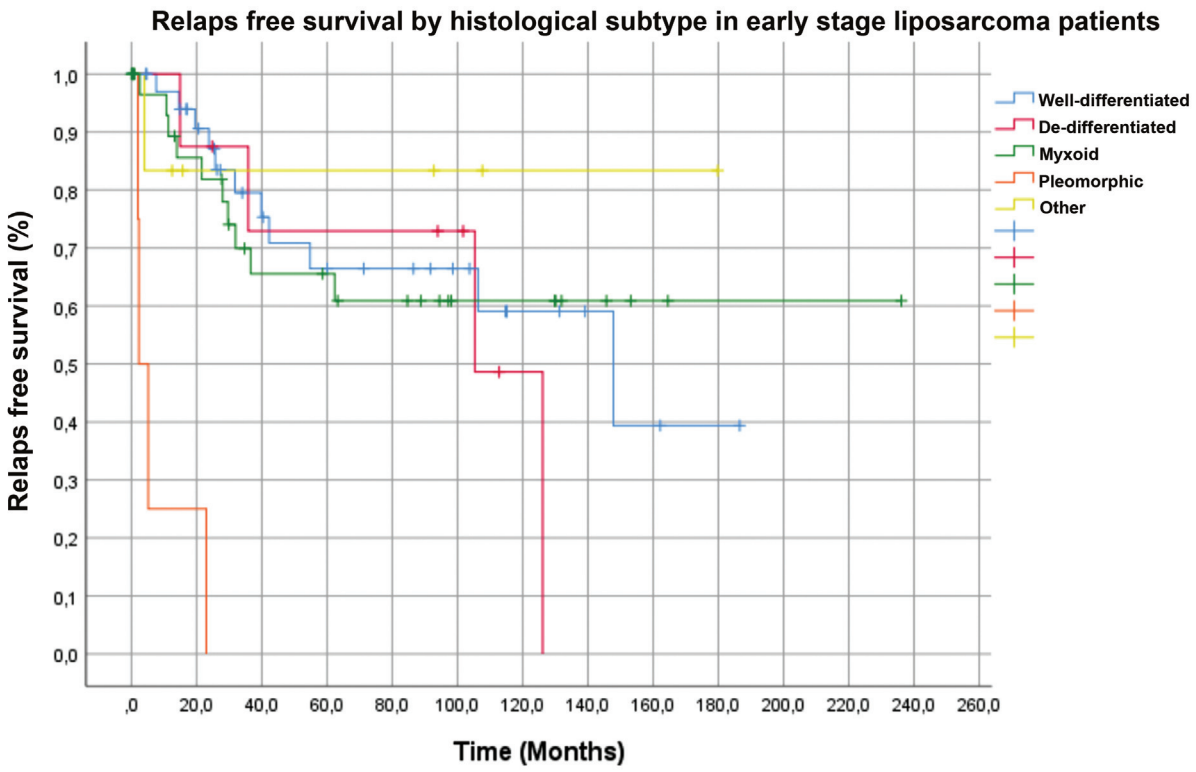

Fig. 1 Relapse-free survival for early stage liposarcoma patients ($p < 0.001$, log-rank test).

Table 3 Univariate and multivariate Cox regression analyses for DFS

		Univariate				Multivariate			
		HR	95.0% CI for HR		*p*-Value	HR	95.0% CI for HR		*p*-Value
T Stage	T1 and T2 (ref.)								
	T3	4.75	1.19	18.91	0.03	9.56	1.02	89.71	0.05
	T4	4.58	1.21	17.41	0.03	14.71	1.62	133.90	0.02
Age	65> (ref.)								
	65≤	1.55	0.53	4.52	0.42	1.90	0.41	8.73	0.41
Grade	Grade 1 (ref.)								
	Grade 2 and 3	3.60	1.44	8.96	0.01	4.49	1.16	17.43	0.03

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio

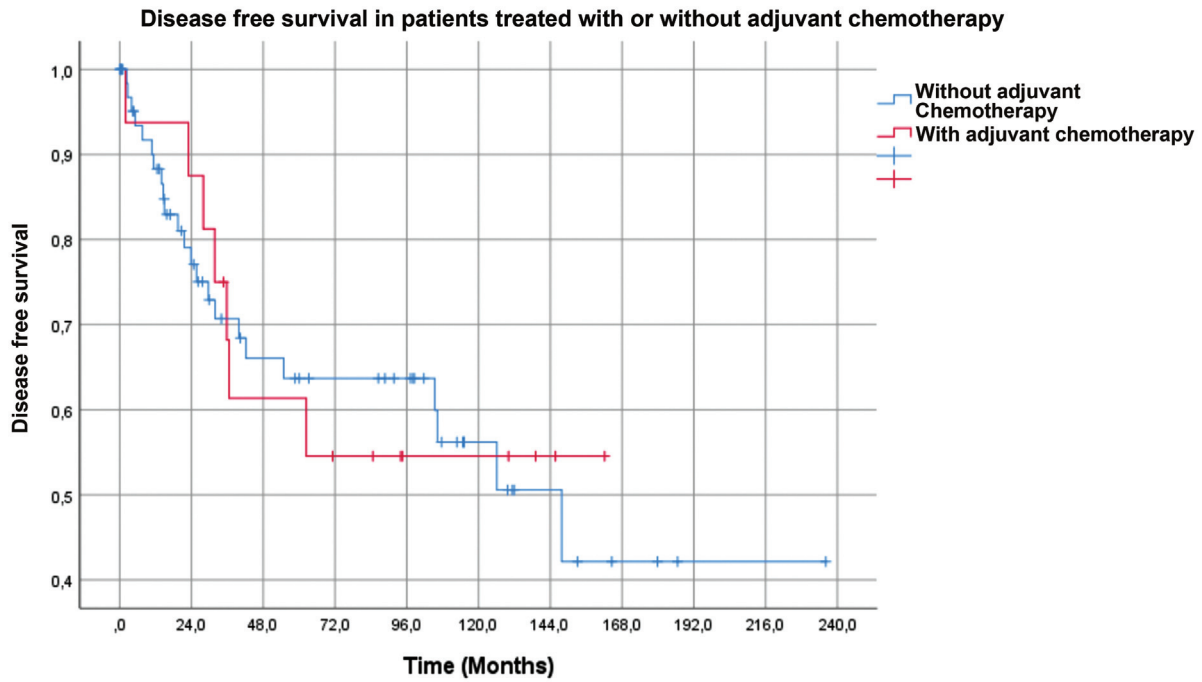

Fig. 2 Disease-free survival in patients treated with or without adjuvant chemotherapy ($p = 0.96$, log-rank test).

patients did not. Three of 20 patients underwent metastasectomy due to pulmonary involvement. Median OS was 64.4 and 23.7 months in relapsed patients who underwent metastasectomy and those who did not, respectively ($p = 0.94$).

Discussion

Liposarcomas are relatively rare tumors and treatment modalities beyond surgery are limited. In our study, 5-year DFS and OS was 68%. Surgery was the mainstay of treatment, RT reduced local recurrence rate but no effect was observed on DFS. CT in the perioperative setting was utilized in less than 20% of the patients. The benefit of CT in advanced the setting was marginal at best. PLS portended the worst prognosis with no long-term survivors in our series. A recent large database analysis from United States and Canada also showed similar results; WDLS was the most common histology, with a high 5-year OS rate of 82%, followed by 76% for MLS, 63% for mixed tumors, 55% for round cell, 51% for PLS, and 49% for DDLS.[10] Our findings are consistent with these data, except for the extremely poor prognosis of PLS in our series but there were only four patients with PLS.

The principal treatment modality for STS is still surgery. Resection of the tumor with negative surgical margins confers a low risk of local relapse and better long-term survival advantage.[11] The vast majority of our patients (96%) had undergone surgery in our study. R0 resection was achieved in 77% and R1 in 21% of the patients. Our resection rates were similar to the literature. In a clinical trial including 911 STS patients (31% of those were liposarcoma), R0 and R1 resection rates were 82 and 18%, respectively.[12] Several trials revealed that neoadjuvant RT enables to achieve negative

Table 4 Responses to salvage chemotherapy regimens for histologic subtypes

	N (%)		
	PR	**SD**	**PD**
Well-differentiated	2 (50)	0 (0)	2 (50)
Dedifferentiated	0 (0)	1 (100)	0 (0)
Myxoid	0 (0)	2 (40)	3 (60)
Pleomorphic	1 (33.3)	0 (0)	2 (66.7)
Others	0 (0)	1 (100)	0 (0)

Abbreviations: PD, progressive disease; PR, partial response; SD, stable disease.

margins, prevent local relapse, reduce tumor diameter, and is associated with increased OS.[12–14] Neoadjuvant RT might be beneficial in whom R0 resection seems unlikely.

Adjuvant CT is still a controversial issue in the treatment of STS. In SMAC meta-Analysis, doxorubicin-based adjuvant CT improved local, distant, and overall relapse-free interval, particularly in extremity sarcomas. There was a trend toward improved OS but did not reach statistical significance.[15] The more recent 2008 meta-analysis showed significant benefit in OS (odds ratio: 0.56; 95% confidence interval [CI]: 0.36–0.85) with doxorubicin–ifosfamide combination.[16] Tumor location was not specifically assessed in this meta-analysis. In a phase 3 randomized controlled trial investigating histotype-driven therapy, standard anthracycline-based therapy was not inferior compared with histology-specific antineoplastic agents in the neo-adjuvant setting.[17,18] Five-year DFS was 47 versus 55% (hazard ratio [HR]: 1.23, 95% CI: 0.88–1.73) and 5-year OS was 66 versus 76%, (HR: 1.77, 95% CI: 1.10–2.83), for anthracycline-based and histotype-tailored therapy, respectively. This study also included patients with high-grade MLS and the results were also similar in this subgroup with trabectedin compared with doxorubicin. We use perioperative CT in patients with large high-grade sarcomas in fit and relatively younger patients regardless of tumor location. The most common CT regimen in our study was ifosfamide and doxorubicin (75%). A low number of patients and selection according to risk factors preclude assessment of the efficacy of CT in this retrospective study.

RT is recommended in the treatment of patients with intermediate- or high-grade tumors either of the extremities or the superficial trunk and was shown to reduce the risk of local recurrence. The role of RT in the treatment of retroperitoneal sarcomas is debatable. Neoadjuvant RT did not improve abdominal RFS in the EORTC-62092 STRASS trial in patients with primary retroperitoneal sarcoma.[19] In the liposarcoma subgroup, which consisted 75% of the trial cohort, a 10% absolute abdominal RFS benefit was observed. Given most of the recurrences are local in retroperitoneal LPS, RT may be considered in selected cases in this disease with a poor prognosis. Patients who received RT had a lower local recurrence rate (26 vs. 11%) in our study, consistent with the previous studies.

There is an established role of resection of pulmonary metastases of STS. In a trial with 3149 adult STS patients, median OS was 33 and 11 months for patients who underwent surgery and those who did not, respectively.[20] A more recent study showed consistent results with a median OS of 33.2 months for STS patients who underwent surgery for pulmonary metastases.[21] The benefit of hepatic resection of STS metastases is controversial. A systematic literature review that screened available studies between 2000 and 2018 showed that in 62.5% of case reports and in 20.8 to 100% of original articles, STS hepatic metastases were resected. This trial showed OS of up to 44 months after diagnosis of metastases.[22] In our trial, OS of three patients who underwent pulmonary metastasectomy were 7, 13, and 28 months.

In advanced disease setting, doxorubicin with or without ifosfamide is the standard of care for liposarcomas. Among subtypes, MLS is more chemosensitive compared with others.[23] In a phase 3 trial, trabectedin improved PFS in advanced liposarcoma and leiomyosarcoma (median PFS for trabectedin vs. dacarbazine, 4.2 vs. 1.5 months; HR: 0.55; $p < 0.001$).[24] The only agent that improves OS in liposarcoma is eribulin. In 2016, Schöffski et al randomized more than 450 patients and patients assigned to eribulin arm achieved a median OS of 13.5 months (95% CI: 10.9–15.6) compared with those assigned to the dacarbazine arm (median OS was 11.5 months [95% CI: 9.6–13.0]) (HR: 0.77 [95% CI: 0.62–0.95], $p = 0.0169$).[25] In a trial in which WDL was excluded, the best responses to first-line systemic treatment were as follows: 17% PR/complete response (CR), 25% stable disease, and 46% progressive disease. Anthracycline-based regimens provided the objective responses most frequently and patients who did not progress with CT had significantly higher OS than those who progressed (HR: 0.34 [95% CI: 0.15–0.77], $p = 0.009$).[26] We did not have any CR in our population. Patients treated with combined chemoregimens IMA and IMET had PR ratios of 14.3 and 40%, respectively. Our data belongs to the time period in which novel agents such as trabectedin and eribulin were not frequently used in our country. These findings were similar to the literature and supported that liposarcomas are highly chemoresistant. With the paucity of available therapeutic options, new anticancer agents are investigated. Studies on murine double minute (MDM-2) inhibitors,[27] murine double minute (MDM-2) inhibitors combined with mitogen-activated protein kinase (MEK) inhibitors,[28] CDK4/6 inhibitors,[29] and immunotherapeutics[30] have promising results in liposarcoma. Unlike other subgroups, pazopanib did not show efficacy in adipocytic STS in a phase 2 trial.[31]

Our retrospective trial has some limitations. Retrospective design and the limited number of patients preclude effective comparison of treatment regimens. Toxicity data was lacking.

In conclusion, being a chemoresistant tumor, diagnosis in early-stage and appropriate surgery with or without perioperative treatment is very important. New nomograms such as Sarculator are promising for predicting survival on an

individual basis and enabling clinicians to make adjuvant therapy decisions.

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Conflict of Interest
The authors declare that they have no conflict of interest.

References
1 Brennan, MF, Antonescu CR, Maki RG. Management of soft tissue sarcoma. New York: Springer; 2013
2 Bock S, Hoffmann DG, Jiang Y, Chen H, Ilyasova D. Increasing incidence of liposarcoma: a population-based study of national surveillance databases, 2001-2016. Int J Environ Res Public Health 2020;17(08):E2710
3 Gronchi A, Strauss DC, Miceli R, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the multi-institutional collaborative RPS working group. Ann Surg 2016;263(05): 1002–1009
4 Chowdhry V, Goldberg S, DeLaney TF, et al. Myxoid liposarcoma: treatment outcomes from chemotherapy and radiation therapy. Sarcoma 2018;2018:8029157
5 Katz D, Boonsirikamchai P, Choi H, et al. Efficacy of first-line doxorubicin and ifosfamide in myxoid liposarcoma. Clin Sarcoma Res 2012;2(01):2
6 Peterson JJ, Kransdorf MJ, Bancroft LW, O'Connor MI. Malignant fatty tumors: classification, clinical course, imaging appearance and treatment. Skeletal Radiol 2003;32(09):493–503
7 Salduz A, Alpan B, Valiyev N, et al. Neoadjuvant radiotherapy for myxoid liposarcomas: oncologic outcomes and histopathologic correlations. Acta Orthop Traumatol Turc 2017;51(05):355–361
8 Ghadimi MP, Liu P, Peng T, et al. Pleomorphic liposarcoma: clinical observations and molecular variables. Cancer 2011;117(23): 5359–5369
9 Hornick JL, Bosenberg MW, Mentzel T, McMenamin ME, Oliveira AM, Fletcher CD. Pleomorphic liposarcoma: clinicopathologic analysis of 57 cases. Am J Surg Pathol 2004;28(10):1257–1267
10 Amer KM, Congiusta DV, Thomson JE, et al. Epidemiology and survival of liposarcoma and its subtypes: a dual database analysis. J Clin Orthop Trauma 2020;11(Suppl 4):S479–S484
11 Bonvalot S, Rivoire M, Castaing M, et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. J Clin Oncol 2009;27(01):31–37
12 Gronchi A, Casali PG, Mariani L, et al. Status of surgical margins and prognosis in adult soft tissue sarcomas of the extremities: a series of patients treated at a single institution. J Clin Oncol 2005; 23(01):96–104
13 Gingrich AA, Bateni SB, Monjazeb AM, et al. Neoadjuvant radiotherapy is associated with R0 resection and improved survival for patients with extremity soft tissue sarcoma undergoing surgery: a National Cancer Database Analysis. Ann Surg Oncol 2017;24 (11):3252–3263
14 Moreau LC, Turcotte R, Ferguson P, et al; Canadian Orthopaedic Oncology Society (CANOOS) Myxoid cell liposarcoma (MRCLS) revisited: an analysis of 418 primarily managed cases. Ann Surg Oncol 2012;19(04):1081–1088
15 Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997;350(9092):1647–1654
16 Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113(03):573–581
17 Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. Lancet Oncol 2017;18(06):812–822
18 Gronchi A, Palmerini E, Quagliuolo V, et al. Neoadjuvant chemotherapy in high-risk soft tissue sarcomas: final results of a randomized trial from Italian (ISG), Spanish (GEIS), French (FSG), and Polish (PSG) Sarcoma Groups. J Clin Oncol 2020;38 (19):2178–2186
19 Bonvalot S, Gronchi A, Le Péchoux C, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2020;21(10):1366–1377
20 Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229(05):602–610, discussion 610–612
21 Chudgar NP, Brennan MF, Munhoz RR, et al. Pulmonary metastasectomy with therapeutic intent for soft-tissue sarcoma. J Thorac Cardiovasc Surg 2017;154(01):319–330.e1
22 Smolle MA, Leithner A, Bernhardt GA. Abdominal metastases of primary extremity soft tissue sarcoma: a systematic review. World J Clin Oncol 2020;11(02):74–82
23 Jones RL, Fisher C, Al-Muderis O, Judson IR. Differential sensitivity of liposarcoma subtypes to chemotherapy. Eur J Cancer 2005;41 (18):2853–2860
24 Demetri GD, von Mehren M, Jones RL, 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(08):786–793
25 Schöffski P, Chawla S, Maki RG, 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(10028):1629–1637
26 Langmans C, Cornillie J, van Cann T, et al. Retrospective analysis of patients with advanced liposarcoma in a tertiary referral center. Oncol Res Treat 2019;42(7-8):396–404
27 Ray-Coquard I, Blay JY, Italiano A, et al. Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: an exploratory proof-of-mechanism study. Lancet Oncol 2012;13(11):1133–1140
28 Roy S, Laroche-Clary A, Verbeke S, Derieppe MA, Italiano A. MDM2 antagonists induce a paradoxical activation of Erk1/2 through a P53-dependent mechanism in dedifferentiated liposarcomas: implications for combinatorial strategies. Cancers (Basel) 2020; 12(08):E2253
29 Dickson MA, Schwartz GK, Keohan ML, et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with CDK4 inhibitor palbociclib: a phase 2 clinical trial. JAMA Oncol 2016;2(07):937–940
30 Tawbi HA, Burgess M, Bolejack V, 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(11):1493–1501
31 Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 2009;27 (19):3126–3132

