Research article

Exploring the biological behavior differences between retroperitoneal and non-retroperitoneal liposarcomas

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ABSTRACT

Background: Liposarcoma is a malignant tumor that originates from adipose tissue and can occur in any part of the body. There is currently no clear conclusion on whether there are significant differences in prognosis between liposarcoma at different anatomical locations, especially retroperitoneal liposarcoma (RLPS) and non retroperitoneal liposarcoma (NRLPS). The aim of this study is to reveal whether there are differences in prognosis between these two locations of liposarcoma, and further explore the fundamental reasons behind these differences.
Methods: We conducted an in-depth investigation into the factors affecting the prognosis of patients with liposarcoma by analyzing the data from the Surveillance, Epidemiology, and End Results Program (SEER) database. Then, we used propensity score matching (PSM) to balance these prognostic factors for comparative analysis of survival between RLPS and NRLPS. In addition, by analyzing transcriptome and whole exome data from TCGA and the Japan Genotypic Phenotype Archive (JGA), we identified genes with significant expression differences and explored changes in the immune microenvironment.
Result: Through analysis of RLPS and NRLPS patients in the SEER database, we observed significant prognostic differences between the two groups, with RLPS exhibiting worse prognosis (p < 0.001). Even after adjusting for confounding factors through PSM, these survival rate differences remained significant, with RLPS still showing worse prognosis (p = 0.017). Furthermore, our analysis of transcriptomic data led to the identification of 467 differentially expressed genes.

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Additionally, we noted significant differences in the immune microenvironment and whole exome sequencing data between the two groups.

Conclusion: There are significant differences between patients with RLPS and NRLPS. Therefore, from clinical research to treatment strategies, RLPS and NRLPS should be considered as two distinct types of tumors, necessitating differentiated approaches for their study and treatment.

1. Introduction

Soft tissue sarcomas (STS) are a rare group of heterogeneous tumors, accounting for 1 % of all adult malignancies [1]. Liposarcoma is a malignant tumor derived from adipocytes, they are one of the most common subtypes of STS, accounting for approximately 15 %– 20 % of all STS [2,3]. Liposarcoma is classified by morphological and genetic characteristics into four principal subtypes: well-differentiated liposarcoma (WDLPS; also known as atypical lipomatous tumor), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), and pleomorphic liposarcoma (PLPS) [2,4,5]. In the United States, the most prevalent subtypes of liposarcoma are WDLPS and DDLPS, which together constitute more than 60 % of all liposarcoma cases [6], with WDLPS making up about 33 % and DDLPS around 20 % [7,8].

Liposarcoma can be found anywhere in the body, with the retroperitoneum being a common area [8]. RLPS accounts for about 45 % of retroperitoneal STS [9]. RLPS usually has a poor prognosis and is highly prone to recurrence [10,11], surgery remains the primary and most effective way to treat RLPS [12,13]. Although NRLPS has a more optimistic prognosis compared to RLPS [14], but there is

Table 1
Patient and tumor characteristics of 4590 liposarcoma patients.

Characteristics	Tumor location				
	Retroperitoneal (N = 1178)	% of Total	Non-Retroperitoneal (N = 3412)	% of Total	p-value
Gender					<0.001
Male	655	55.6	2182	64.0	
Female	523	44.4	1230	36.0	
Age, years median (range)	19-92(64)		14-100(64)		<0.001
Race					0.229
White	978	83.0	2800	82.1	
Black	64	5.4	242	7.1	
Asian	119	10.1	318	9.3	
Other	17	1.4	52	1.5	
Histologic subtypes					<0.001
Well-differentiated (WDLPS)	563	47.8	2308	67.7	
Dedifferentiated (DDLPS)	615	52.2	1104	32.4	
Grade					<0.001
Well differentiated; Grade I	563	47.8	2288	67.1	
Moderately differentiated; Grade II	84	7.1	207	6.1	
Poorly differentiated; Grade III	254	21.6	452	13.2	
Undifferentiated; anaplastic; Grade IV	277	23.5	465	13.6	
Marital status at diagnosis					0.245
Married (including common law)	783	66.5	2184	64.0	
Single (never married)	145	12.3	436	12.8	
Divorced	96	8.1	279	8.2	
Widowed	100	8.5	298	8.7	
Other	54	4.6	215	6.3	
Tumor metastasis					
Localized only	588	49.9	2445	71.7	<0.001
Regional	472	40.1	828	24.3	
Distant	118	10.0	139	4.1	
Tumor burden, mm median (range)	1-989(200)		1-989(132)		<0.001
Cause of death					<0.001
Alive	596	50.6	2328	68.2	<0.001
Death of disease	360	30.6	427	12.5	
Other Cause of Death	222	18.8	657	19.3	
Operation			0		
Yes	1103	93.6	3243	95.0	0.062
No	75	6.4	169	5.0	
Chemotherapy					
Yes	129	11.0	215	6.3	<0.001
No	1049	89.0	3197	93.7	
Radiation					
Yes	286	24.3	851	24.9	0.650
No	892	75.7	2561	75.1	
Survival months median (range)	0-190(48)		0-191(62)		0.006

still no research exploring the mechanisms of differences. The aim of this study is to compare the prognostic differences between RLPS and NRLPS, and to explore the possible causes of this biological difference.

2. Method

2.1. Patient source

We queried the SEER Research Plus Data, 17 Registries, Nov 2022 Sub (2000–2020), for patients diagnosed with Liposarcoma (variable: AYA site recode 2020 Revision coded as "Liposarcoma").

2.2. Patients selection

Select all patients with complete oncological information. We excluded patients with missing tumor locations, patients with tumor pathological types other than WDLPS and DDLPS, patients with missing tumor size data, patients with unclear tumor grading, and patients with unclear tumor metastasis status. Finally, a total of 1178 patients with RLPS and 3412 patients with NRLPS met the inclusion criteria.

3. Data elements

We evaluated the following clinical and demographic characteristics: gender, age, race, histologic subtypes, grade, marital status at diagnosis, tumor metastasis, tumor burden(mm), cause of death, survival months, operation, chemotherapy and radiation. (Table 1).

3.1. Statistical methods

The three continuous variables of survival data, age, and tumor size were compared with the baseline of RLPS and NRLPS using independent sample t-tests. All other data were converted into categorical variables and compared with Pearson's chi square test. Calculate the overall survival (OS) rate using Kaplan-Meier and compare it using logarithmic rank test. Perform univariate Cox proportional risk analysis to evaluate the impact of various clinical and pathological factors on prognosis, and variables with a p-value<0.05 are further included in the multivariate Cox model. The PSM method is used to reduce selection bias and potential baseline differences between patients with RLPS and NRLPS.

3.2. Transcriptomics and exonomics

The data files for transcriptomics and exonomics are sourced from the Cancer Genome Atlas (TCGA) database and the Japan

Table 2
Univariable and multivariable analyses to determine independent predictors of overall survival of liposarcoma.

Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	P value	Hazard Ratio (95%CI)	P value
Gender female vs. male	0.759(0.686–0.841)	<0.001	0.802(0.722–0.890)	<0.001
Age (continuous)	1.050(1.045–1.054)	<0.001	1.045(1.041–1.050)	<0.001
Race		0.179		
White vs. Black	0.905(0.742–1.103)	0.323		
White vs. Asian	0.868(0.728–1.036)	0.116		
White vs. Other	0.734(0.472–1.141)	0.169		
Histologic subtypes DDLPS vs. WDLPS	3.773(3.417–4.166)	<0.001	1.586(1.319–1.907)	<0.001
Grade		<0.001	1.296(1.209–1.390)	<0.001
Grade II vs. Grade I	2.179(1.783–2.662)	<0.001		
Grade III vs. Grade I	3.952(3.488–4.478)	<0.001		
Grade IV vs. Grade I	4.453(3.957–5.011)	<0.001		
Marital status at diagnosis		<0.001	0.937(0.907–0.969)	0.889
Married vs. Single (never married)	0.939(0.803–1.099)	0.434		
Married vs. Divorced	1.991(1.726–2.296)	<0.001		
Married vs. Widowed	1.062(0.888–1.270)	0.508		
Married vs. Other	0.915(0.733–1.143)	0.435		
Tumor metastasis		<0.001	1.567(1.449–1.694)	<0.001
Localized only vs. Distant	0.159(0.137–0.185)	<0.001		
Regional vs. Distant	0.324(0.276–0.379)	<0.001		
Tumor burden (continuous)	1.001(1.001–1.002)	<0.001	1.001(1.001–1.001)	<0.001
Operation Yes vs. No	0.177(0.152–0.206)	<0.001	0.276(0.234–0.325)	<0.001
Radiation Yes vs. No	1.102(0.990–1.228)	0.077		
Chemotherapy Yes vs. No	2.925(2.541–3.367)	<0.001	1.572(1.346–1.836)	<0.001
Location		<0.001	0.760(0.683–0.846)	<0.001
Retroperitoneum vs. Non-Retroperitoneum	1.792(1.620–1.982)	<0.001		

Genotypic-Phenotype Archive (JGA) [15], which is hosted by DDBJ with login numbers JGAS000000177 and JGAS000000182. The baseline information is placed in Table 4. Initially, we performed Principal Component Analysis (PCA) on the transcriptome data from TCGA as well as on two sets of transcriptome data obtained from the JGA (Supplementary Fig. 1). After removing outliers (N = 6), we obtained a total of 103 transcriptome data samples, which included 75 samples of RLPS and 28 samples of NRLPS. Subsequently, batch effects were eliminated using the combat function [16,17]. To visualize the consistency of the data before and after the removal of batch effects, we produced corresponding box plots (Supplementary Figure 2-3). After the removal of batch effects, PCA was conducted again (Supplementary Figure 4), demonstrating good consistency among the three sets of data following the elimination of batch effects. By first applying PCA to identify and remove outliers, then using the combat function to eliminate batch effects, data normalization is achieved, and genes with expression levels exceeding 25 % are selected [18]. Finally, transcriptome and whole exome data were obtained from 75 patients with RLPS and 28 patients with NRLPS. Differential gene expression (DEG) among liposarcomas situated in distinct locations was ascertained utilizing the "limma" R package, with an adjusted p-value <0.1 designated as the threshold criterion. Volcano plots, crafted via the "ggplot2" package, facilitated the visualization of DEGs. Gene Ontology (GO) analysis was performed using the "ClusterProfiler" package, utilizing the org.Hs.eg.db gene set. Leveraging transcriptomic markers, the quantification of ten immune and stromal cell populations within liposarcomas from various locations was conducted using the Microenvironment Cell Populations-counter (MCP-counter) approach [16,19], with visualizations rendered through the ggplot2 packages. We utilized the MCP-counter tool to assess the composition of the immune microenvironment (TIME) in RLPS and NRLPS. This tool enables the evaluation of the detailed constitution, including eight types of immune cells (T cells, CD8^{+} T cells, cytotoxic lymphocytes, natural killer cells, B cell lineage, monocyte lineage, myeloid dendritic cells, and neutrophils) and two types of stromal cells (endothelial cells and fibroblasts). These scores are derived from the analysis of transcriptomic markers, i.e., transcriptomic features that are highly expressed, specific, and stable in distinct cell populations. Similarly, we also used two other methods to compare the differences in the immune microenvironment between RLPS and NRLPS, namely ssGSEA (Single sample Gene Set Enrichment Analysis) and Cibersort (Cell type Identification By Estimating Relative Subsets of RNA Transcripts)

4. Result

4.1. Patient and tumor characteristics

A total of 1178 patients with RLPS and 3412 patients with NRLPS met the inclusion criteria, and the Kaplan-Meier survival curves is

Table 3
Patient and tumor characteristics of 556 patients with retroperitoneal liposarcoma and 556 patients with non-retroperitoneal liposarcoma after propensity matching.

Characteristics	Tumor location				
	Retroperitoneal (N = 556)	% of Total	Non-Retroperitoneal (N = 556)	% of Total	p-value
Gender					0.103
Male	300	54.0	327	58.8	
Female	256	46.0	229	41.2	
Age, years median (range)	19-92(64)		16-95(63)		0.786
Race					0.742
White	463	83.3	458	82.4	
Black	34	6.1	40	7.2	
Asian	51	9.2	53	9.5	
Other	8	1.4	5	0.9	
Histologic subtypes					0.120
Well-differentiated (WDLPS)	340	61.2	365	65.6	
Dedifferentiated (DDLPS)	216	38.8	191	34.4	
Grade					0.417
Well differentiated; Grade I	325	58.5	351	63.1	
Moderately differentiated; Grade II	46	8.3	45	8.1	
Poorly differentiated; Grade III	88	15.8	75	13.5	
Undifferentiated; anaplastic; Grade IV	97	17.4	85	15.3	
Marital status at diagnosis					0.614
Married (including common law)	358	64.4	339	61.0	
Single (never married)	72	12.9	80	14.4	
Divorced	51	9.2	47	8.5	
Widowed	41	7.4	46	8.3	
Other	34	6.1	44	7.9	
Tumor burden, mm median (range)	1-989(190)		1-989(170)		0.106
Chemotherapy					0.529
Yes	36	6.5	31	5.6	
No	520	93.5	525	94.4	
Radiation					0.943
Yes	130	23.4	129	23.2	
No	426	76.6	427	76.8	
Survival months median (range)	0-188(56)		0-189(63.5)		0.147

Table 4
Patient and tumor characteristics of 103 patients with transcriptomic liposarcoma.

Characteristics	Tumor location				p-value
	Retroperitoneal (N = 75)	% of Total	Non-Retroperitoneal (N = 28)	% of Total	p-value
Gender					0.039
Male	50	66.7	25	89.3	
Female	25	33.3	3	10.7	
Age, years median (range)	34-82(60)		37-86(65)		0.061
Radiation					0.051
Yes	6	8.0	2	7.1	
No	69	92.0	26	92.9	
Survival of patient					0.060
Alive	46	61.3	24	85.7	
Dead	28	37.3	4	14.3	
NA	1	1.3	0	0	
Survival months median (range)	0.57–170.1(67.8)		1.7–161.2(85.8)		0.801

shown in Fig. 1. The median OS time for RLPS and NRLPS was 48 months (95 % CI 75.646–96.354) and 62 months (95 % CI 163.060–186.940), respectively. In the population of patients with RLPS, the proportion of DDLPS is significantly higher (52.2 % vs 32.4 %, p < 0.001), and the risk of tumor metastasis is also higher, with localized metastasis accounting for only 49.9 % compared to 71.7 % (p < 0.001). The proportion of patients receiving surgical treatment is relatively low (93.6 % vs 95.0 %) (p = 0.062), which may reflect that in this group, there are more cases that are not suitable for surgery due to advanced tumors or other factors, resulting in a higher chemotherapy rate (11.0 % vs 6.3 %) (p < 0.001). For patients with NRLPS, the proportion of males is higher (64 % vs 55.6 %) (p < 0.001), with higher tumor differentiation and relatively better prognosis. Patients with RLPS and NRLPS have similar age and marital status distribution, with a large proportion of patients in marital status (66.5 % vs 64.0 %) (p = 0.245). The proportion of patients receiving radiotherapy is close (24.3 % vs 24.9 %) (p = 0.650).

4.2. Univariable survival analyses

Table 2 shows the univariate Cox proportional risk analysis results of important prognostic factors affecting OS. As shown in the table, we conducted a univariate Cox proportional hazard analysis on 13 potential factors and identified 11 related variables that affect the survival of patients with liposarcoma, including age (p < 0.001), gender (p < 0.001), histological subtype (p < 0.001), pathological subtype (p < 0.001), marital status (p < 0.001), tumor burden (p < 0.001), tumor metastasis (p < 0.001), chemotherapy (p < 0.001), surgery (p < 0.001) and location (p < 0.001).

4.3. Multivariable survival analyses

After removing the outcome variable of cause of death, we included variables with p < 0.05 in the univariate Cox proportional hazards regression analysis into the multivariate Cox hazards regression analysis to determine independent factors affecting the prognosis of liposarcoma. The research results indicate that among the 11 influencing variables, 10 independent factors have statistical significance, with a p-value of<0.05. These factors include age (p < 0.001), gender (p < 0.0010), histological subtypes (p < 0.001),
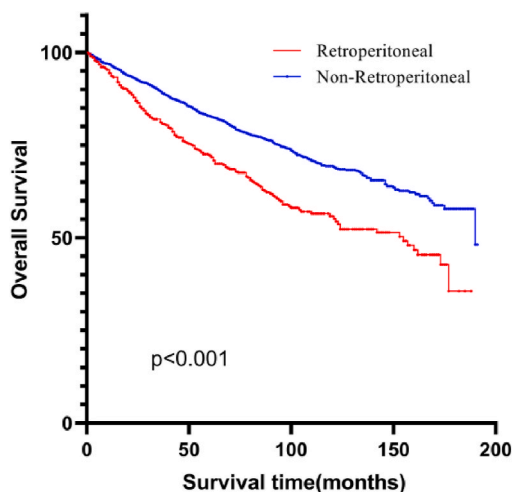
Fig. 1. The overall survival rate of patients with retroperitoneal liposarcoma and non-retroperitoneal liposarcoma.

pathological subtypes (p < 0.001), tumor burden (p < 0.001), tumor metastasis (p < 0.001), chemotherapy (p < 0.001), surgery (p < 0.001) and location (p < 0.001).

4.4. Propensity matching analysis

After analyzing the baseline characteristics of RLPS and NRLPS patients in Table 1, we used factors with differences in baseline (age, gender, histological grade, pathological type, tumor metastasis, tumor burden, and chemotherapy) as propensity matching variables. Given the potential significant impact of tumor metastasis and surgical intervention on patient prognosis, we specifically selected a patient group with localized only disease who had undergone surgical treatment, and performed PSM on the remaining six variables, setting a matching tolerance threshold of 0.04. After PSM, we successfully matched 556 pairs of patients with RLPS and NRLPS (Table 3). The previously observed baseline differences in variables such as age (p = 0.786), gender (p = 0.103), histologic grade (p = 0.417), pathological type (p = 0.120), tumor burden (p = 0.106), and chemotherapy (p = 0.529) were no longer significant. After the PSM, we divided the 556 matched pairs of patients based on the location of the tumor and plotted Kaplan-Meier survival curves (Fig. 2). The analysis indicated that, with identical baseline characteristics, there was a significant difference in survival between patients with RLPS and those with NRLPS (p = 0.017).

4.5. Transcriptomic analysis

To further investigate the transcriptomic characteristics of liposarcomas located in different regions, we conducted a DEG analysis between patients with RLPS and those with NRLPS. Considering the smaller sample size of NRLPS in the transcriptome data, we relaxed the p-value threshold to 0.1. Ultimately, we identified 467 differentially expressed genes, with 238 genes downregulated and 229 upregulated in RLPS compared to NRLPS. Based on the analysis of differentially expressed genes, we plotted a volcano plot with Log2 fold change on the x-axis and -Log10 adj.P-value on the y-axis (Fig. 3). Among them, PRKCE, SOAT1, and RGS3 genes not only showed extremely significant differential expression (with adjusted P values and LogFC ranking in the top 20), but they were also closely related to immune function. This indicates that these genes may play important roles in the biological processes we are studying. Furthermore, we conducted a GO pathway analysis based on these differentially expressed genes and created the corresponding GO pathway chart (Fig. 4). The GO analysis results indicate that upregulated genes are primarily associated with the metabolism of unsaturated fatty acids, development of the skin and epidermis, as well as the metabolic processes of sterols and glycosides. Conversely, downregulated genes are mainly related to the organization of the extracellular matrix, organization and metabolic processes of collagen fibers, adhesion between cells and the matrix, and the positive regulation of cellular responses to growth factor stimulation. This finding is consistent with the conclusions of a study analyzing retroperitoneal and non-retroperitoneal leiomyosarcomas [20].

Numerous studies have established a close relationship between the progression of sarcomas and TIME [16,21,22]. We analyzed the differences in immune cells between RLPS and NRLPS patients using three methods: MCP counter, ssGSEA, and Cibersort, and obtained scores for each type of immune cell. These scores reflect the relative abundance of various cell populations within the tumor, allowing for sample and analysis comparisons in large-scale cohorts (Fig. 5), the differences between RLPS and NRLPS were determined using t-tests. By visualizing the abundance of immune cells through box plots, we found significant differences in immune cell infiltration between RLPS and NRLPS. Due to the small number of patients, we have relaxed the p-value threshold to 0.1. In the mononuclear phagocytic cell system, Macrophages M0 and Monocytes, which can develop into various types of macrophages and dendritic cells, exhibit significant differences. In addition, there are significant differences between RLPS and NRLPS in T cells, including T cells CD4 memory resting, Activated CD4 T cells, Effector memory CD8 T cells, Regulatory T cells (Treg), and T follicular
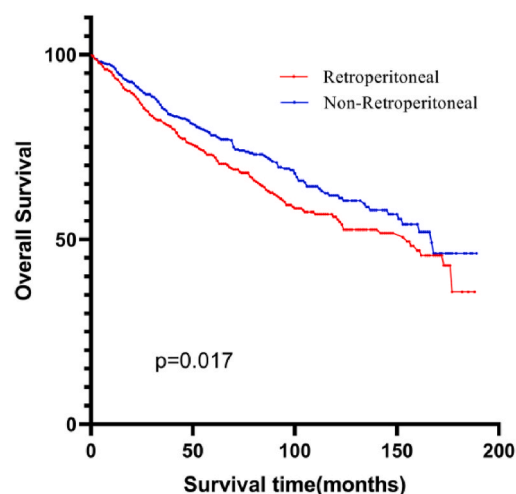

Fig. 2. The overall survival rate of propensity matched retroperitoneal liposarcoma and non-retroperitoneal liposarcoma patients.

Fig. 3. shows the volcano plot of DEG in patients with retroperitoneal liposarcoma compared to non retroperitoneal liposarcoma. Red represents upregulated genes, while blue represents downregulated genes.

helper cells (Tfh). In addition, the two also show differences in dendritic cells, NK cells, neutrophils, and immature B cells.

4.6. Whole exome omics analysis

To delve deeper into the specific exomic differences of liposarcomas located in various sites, we quantified the mutational frequencies within the exonic regions of two patient groups and visualized the data as a bar chart (Fig. 6). Our comparative analysis revealed significant differences between the groups in non-synonymous single nucleotide variants (SNVs)(p < 0.001), frameshift deletions (p < 0.001), and stop-gain SNVs (p < 0.001). Subsequently, we delved deeper into the differences in mutation genes between the RLPS and NRLPS groups. Through comprehensive Fisher's exact tests conducted on the mutations present in each gene, we ultimately identified a significant disparity in the mutations of several genes between the two groups. These genes include *CD1E*, *CPEB2*, *HSD17B6*, *OTOP1*, *PISD*, *RYR1*, *SOGA3*, *TCHP*, and *ZDHHC17*. The aforementioned analysis reveals substantial differences at the whole-exome level between patients with RLPS and those with NRLPS.

5. Discussion

Until now, the scientific community has not extensively explored the potential differences in biological behavior between RLPS and NRLPS patients, nor the underlying reasons for such variations. Our investigation stands as the inaugural comprehensive and systematic study aimed at elucidating the prognostic divergences between RLPS and NRLPS. Leveraging transcriptomic and whole-exome

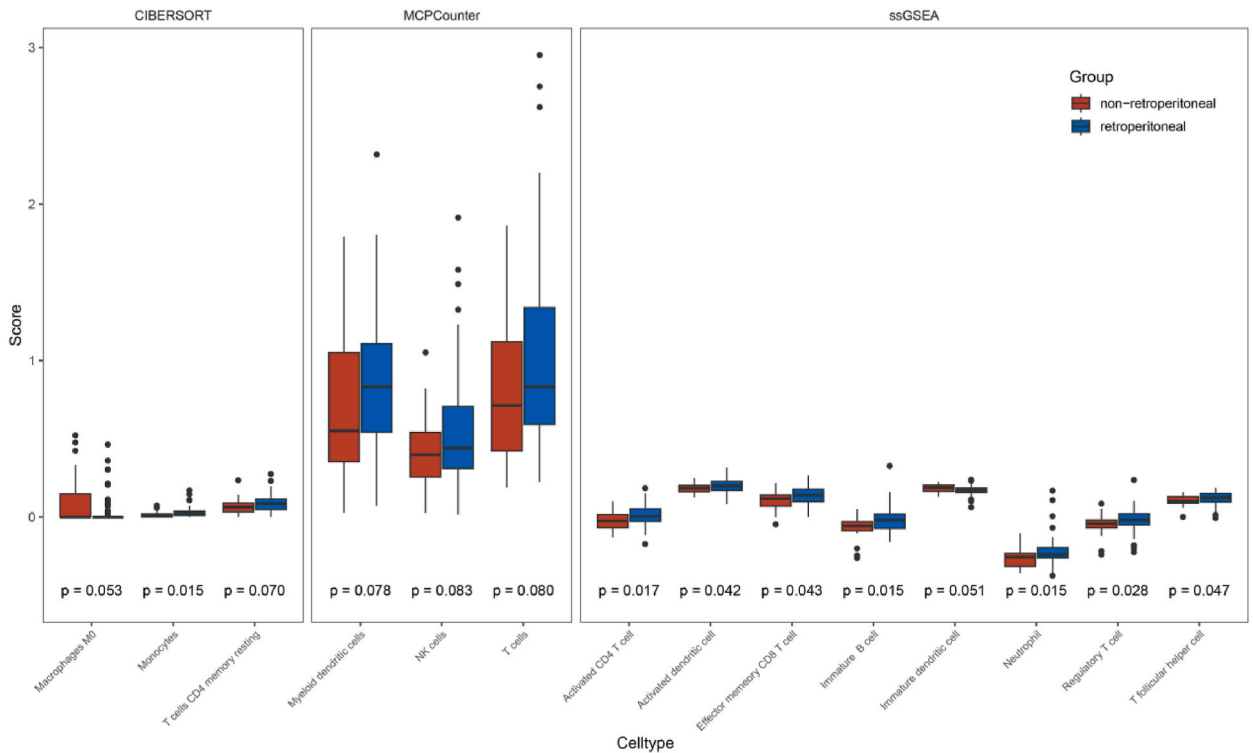**Fig. 4.** Up-regulated and down-regulated DEG enriched GO pathways.

Fig. 5. Immunocyte box plots of retroperitoneal and non-retroperitoneal liposarcoma.

Fig. 6. Histogram of the frequency of whole exome mutations in retroperitoneal and non retroperitoneal liposarcoma.

sequencing data from liposarcomas, this study meticulously delineates the variances between RLPS and NRLPS patients, encompassing aspects from gene expression profiles to immune microenvironmental interactions.

In our study, through the analysis of the SEER database, we found significant differences in the biological behavior of RLPS and

NRLPS patients, which is consistent with the conclusion in previous studies that the biological behavior of different anatomical liposarcoma sites is different [23–25].

Upon analyzing the transcriptomic data of patients with RLPS and NRLPS, significant differences in the expression levels of genes such as *PRKCE*, *SOAT1*, and *RGS3* were observed. In comparison, patients with RLPS exhibited upregulation in the expression of *PRKCE* and *SOAT1*, whereas *RGS3* showed a downregulated trend. This highlights the distinct gene expression patterns in different types of liposarcomas, providing critical insights into their biological characteristics suitable for a high-impact scientific publication. Research by Zhang Xiaoping demonstrated that *PRKCE* can promote cancer progression by inhibiting apoptosis in thyroid papillary carcinoma cells [26]. Similarly, the work of Kumar S also emphasized the role of *PRKCE* as an anti-apoptotic gene [27]. *SOAT1* is recognized as an oncogene [28], promoting hepatocellular carcinoma (HCC) development through the enhancement of cholesterol esterification [29]. Additionally, in adrenal cortical carcinoma (ACC), *SOAT1* expression is notably elevated, closely associated with the tumor microenvironment, adaptive immune responses, interferon signaling, and cytokine signal transduction [30]. Furthermore, inhibiting the *SOAT1* gene has emerged as a therapeutic strategy for treating gliomas, underscoring its significant role across various cancer contexts and highlighting potential intervention points for targeted therapy [31].*RGS3* is considered a potential inhibitor of the *MEK-ERK1/2* signaling axis [32], and it also has the ability to inactivate *KRAS* [33], playing a crucial role in inhibiting cancer progression. In our study, we observed significant upregulation of *PRKCE* and *SOAT1* in patients with RLPS, a change that could potentially enhance the apoptosis resistance of liposarcoma cells. Concurrently, the notable downregulation of *RGS3* might impair its tumor-suppressive function. Together, these phenomena may synergistically contribute to the poorer prognosis observed in RLPS patients.

By analyzing TIME of two groups of patients, we observed that in patients with RLPS, the levels of T cells, natural killer (NK) cells, and myeloid dendritic cells were higher than those in patients with NRLPS. For those "hot tumors" with a higher infiltration of immune cells, they typically indicate a stronger recognition and response capability of the immune system to these tumors, which usually translates to a better response to immunotherapy [34,35]. Therefore, we speculate that patients with RLPS may have a higher sensitivity to immunotherapy compared to patients with NRLPS.

However, this study also has its limitations. Due to the rarity of liposarcoma, our analysis was conducted on a limited dataset. Furthermore, considering that the transcriptomic data were derived from sequencing batches at two different times, different methods of batch effect removal might have varying impacts on the outcomes. Additionally, as the transcriptomic data for NRLPS patients were relatively scarce, we only selected genes with an adjusted p-value of less than 0.1 for differential expression analysis. Lastly, it is imperative to further clarify the specific differences in treatment approaches between retroperitoneal and non-retroperitoneal liposarcomas.

6. Conclusion

Compared to NRLPS, the biological behavior of RLPS is worse and the prognosis is also worse. When studying liposarcoma, we need to distinguish them. In addition, we also found that RLPS may be more sensitive to immunotherapy.

Data availability statement

All data in this article are from public databases.

Funding

CRediT authorship contribution statement

Zhe Xi: Writing – original draft, Visualization, Methodology, Investigation, Data curation. **Aobo Zhuang:** Writing – review & editing, Visualization, Supervision. **Xi Li:** Project administration, Data curation. **Turhong Maimaiti Ming:** Resources, Investigation. **Yingxue Cheng:** Formal analysis, Conceptualization. **Chenhe Zhang:** Software. **Fuan Xie:** Software. **Yue Wang:** Data curation. **Guangting Yan:** Methodology. **Jialiang Zheng:** Software, Methodology. **Zhenhang Lin:** Project administration. **Geng Zhang:** Formal analysis. **Huichen Li:** Software, Funding acquisition. **Ting Wu:** Writing – review & editing, Visualization. **Qi He:** Writing – review & editing, Resources, Project administration. **Wengang Li:** Writing – review & editing, Supervision, Data curation.

Declaration of competing interest

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34878.

List of abbreviations

RLPS   Retroperitoneal Liposarcoma
NRLPS   Non-retroperitoneal Liposarcoma
SEER   Surveillance, Epidemiology, and End Results Program
PSM   Propensity Score Matching
STS   Soft Tissue Sarcomas
WDLPS   Well-differentiated Liposarcoma
DDLPS   Dedifferentiated Liposarcoma
MLPS   Myxoid Liposarcoma
PLPS   Pleomorphic Liposarcoma
OS   Overall Survival
JGA   Japan Genotypic-Phenotype Archive;
PCA   Principal Component Analysis
DEG   Differential Gene Expression
GO   Gene Ontology
MCP-counter   Microenvironment Cell Populations-counter
ssGSEA   Single Sample Gene Set Enrichment Analysis
Cibersort Cell type Identification By Estimating Relative Subsets of RNA Transcripts
TCGA   The Cancer Genome Atlas
TIME   The Immune Microenvironment
SNVs   Single Nucleotide Variants
HCC   Hepatocellular Carcinoma
ACC   Adrenal Cortical Carcinoma

References

[1] A. Dangoor, B. Seddon, C. Gerrand, R. Grimer, J. Whelan, I. Judson, UK guidelines for the management of soft tissue sarcomas, Clin. Sarcoma Res. 6 (2016) 20.
[2] A. Lee, K. Thway, P.H. Huang, R.L. Jones, Clinical and molecular spectrum of liposarcoma, J. Clin. Oncol. 36 (2018) 151–159.
[3] F. Ducimetiere, A. Lurkin, D. Ranchere-Vince, A.V. Decouvelaere, H.M. Peoc, L. Istier, Diez Chalabreysse, C. Muller, L. Alberti, P.P. Bringuier, J.Y. Scoazec, A. M. Schott, C. Bergeron, D. Cellier, J.Y. Blay, I. Ray-Coquard, Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing, PLoS One 6 (2011) e20294.
[4] M. Sbaraglia, E. Bellan, T.A. Dei, The 2020 WHO classification of soft tissue tumours: news and perspectives, Pathologica 113 (2021) 70–84.
[5] C. Xu, L. Yan, X. Guan, Z. Wang, J. Wu, A. Lv, D. Liu, F. Liu, B. Dong, M. Zhao, L. Jia, X. Tian, C. Hao, Tsp2 facilitates tumor-associated fibroblasts formation and promotes tumor progression in retroperitoneal liposarcoma, Int. J. Biol. Sci. 18 (2022) 5038–5055.
[6] M.Y. Zhou, N.Q. Bui, G.W. Charville, K.N. Ganjoo, M. Pan, Treatment of de-differentiated liposarcoma in the era of immunotherapy, Int. J. Mol. Sci. 24 (2023).
[7] N. Somaiah, W. Tap, MDM2-p53 in liposarcoma: the need for targeted therapies with novel mechanisms of action, Cancer Treat Rev. 122 (2024) 102668.
[8] S. Bock, D.G. Hoffmann, Y. Jiang, H. Chen, D. Il'Yasova, Increasing incidence of liposarcoma: a population-based study of national surveillance databases, 2001-2016, Int. J. Environ. Res. Publ. Health 17 (2020).
[9] A. Caizzone, E. Saladino, F. Fleres, C. Paviglianiti, F. Iaropoli, C. Mazzeo, E. Cucinotta, A. Macri, Giant retroperitoneal liposarcoma: case report and review of the literature, Int J Surg Case Rep 9 (2015) 23–26.
[10] F. Xie, Y. Niu, L. Lian, Y. Wang, A. Zhuang, G. Yan, Y. Ren, X. Chen, M. Xiao, X. Li, Z. Xi, G. Zhang, D. Qin, K. Yang, Z. Zheng, Q. Zhang, X. Xia, P. Li, L. Gu, T. Wu, C. Luo, S.H. Lin, W. Li, Multi-omics joint analysis revealed the metabolic profile of retroperitoneal liposarcoma, Front. Med. (2023) 375–393.
[11] A. Lawless, D.D. Zhou, J. McDonough, H. Lo, J. Mar, S. Lazarakis, I. Ward, J. Connor, S.R. Thompson, D. Coker, A. Johnston, D.E. Gyorki, A.M. Hong, The role of radiation therapy in the management of primary retroperitoneal sarcoma: a systematic review and clinical practice guidelines from the Australia and New Zealand Sarcoma Association, Cancer Treat Rev. 120 (2023) 102620.
[12] A. Zhuang, Q. Wu, H. Tong, Y. Zhang, W. Lu, Development and validation of a nomogram for predicting recurrence-free survival of surgical resected retroperitoneal liposarcoma, Cancer Manag. Res. 13 (2021) 6633–6639.
[13] A. De Vita, L. Mercatali, F. Recine, F. Pieri, N. Riva, A. Bongiovanni, C. Liverani, C. Spadazzi, G. Miserocchi, D. Amadori, T. Ibrahim, Current classification, treatment options, and new perspectives in the management of adipocytic sarcomas, OncoTargets Ther. 9 (2016) 6233–6246.
[14] F. Mendoza-Moreno, B. Matias-Garcia, A. Quiroga-Valcarcel, N.F. Garcia-Moreno, C. Diez-Corral, A. Blazquez-Martin, C. Vera-Mansilla, E. Ovejero-Merino, M. Diez-Alonso, L. Diego-Garcia, M. Alvarez-Mon, M.A. Ortega, A. Gutierrez-Calvo, Malignant adipocytic tumours: a 20-year single-centre retrospective study, Oncol. Lett. 25 (2023) 247.
[15] M. Hirata, N. Asano, K. Katayama, A. Yoshida, Y. Tsuda, M. Sekimizu, E. Kobayashi, M. Komiyama, H. Fujimoto, T. Goto, Y. Iwamoto, N. Naka, S. Iwata, Y. Nishida, T. Hiruma, H. Hiraga, H. Kawano, T. Motoi, Y. Oda, D. Matsubara, M. Fujita, T. Shibata, H. Nakagawa, R. Nakayama, T. Kondo, S. Imoto,

S. Miyano, A. Kawai, R. Yamaguchi, H. Ichikawa, K. Matsuda, Integrated exome and RNA sequencing of dedifferentiated liposarcoma, Nat. Commun. 10 (2019) 5683.

[16] F. Petitprez, A. de Reynies, E.Z. Keung, T.W. Chen, C.M. Sun, J. Calderaro, Y.M. Jeng, L.P. Hsiao, L. Lacroix, A. Bougouin, M. Moreira, G. Lacroix, I. Natario, J. Adam, C. Lucchesi, Y.H. Laizet, M. Toulmonde, M.A. Burgess, V. Bolejack, D. Reinke, K.M. Wani, W.L. Wang, A.J. Lazar, C.L. Roland, J.A. Wargo, A. Italiano, C. Sautes-Fridman, H.A. Tawbi, W.H. Fridman, B cells are associated with survival and immunotherapy response in sarcoma, Nature 577 (2020) 556–560.

[17] W.E. Johnson, C. Li, A. Rabinovic, Adjusting batch effects in microarray expression data using empirical Bayes methods, Biostatistics 8 (2007) 118–127.

[18] F. Rapaport, R. Khanin, Y. Liang, M. Pirun, A. Krek, P. Zumbo, C.E. Mason, N.D. Socci, D. Betel, Comprehensive evaluation of differential gene expression analysis methods for RNA-seq data, Genome Biol. 14 (2013) R95.

[19] E. Becht, N.A. Giraldo, L. Lacroix, B. Buttard, N. Elarouci, F. Petitprez, J. Selves, P. Laurent-Puig, C. Sautes-Fridman, W.H. Fridman, A. de Reynies, Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression, Genome Biol. 17 (2016) 218.

[20] A. Italiano, P. Lagarde, C. Brulard, P. Terrier, M. Lae, B. Marques, D. Ranchere-Vince, J.J. Michels, M. Trassard, A. Cioffi, S. Piperno-Neumann, C. Chevreau, J. Y. Blay, C. Delcambre, N. Isambert, N. Penel, J.O. Bay, S. Bonvalot, A. Le Cesne, J.M. Coindre, F. Chibon, Genetic profiling identifies two classes of soft-tissue leiomyosarcomas with distinct clinical characteristics, Clin. Cancer Res. 19 (2013) 1190–1196.

[21] D.C. Hinshaw, L.A. Shevde, The tumor microenvironment innately modulates cancer progression, Cancer Res. 79 (2019) 4557–4566.

[22] M. Zhu, E. Shenasa, T.O. Nielsen, Sarcomas: immune biomarker expression and checkpoint inhibitor trials, Cancer Treat Rev. 91 (2020) 102115.

[23] M. Vos, H. Kosela-Paterczyk, P. Rutkowski, G. van Leenders, M. Normantowicz, A. Lecyk, S. Sleijfer, C. Verhoef, D.J. Grunhagen, Differences in recurrence and survival of extremity liposarcoma subtypes, Eur. J. Surg. Oncol. 44 (2018) 1391–1397.

[24] H.G. Lee, S. Aurit, P. Silberstein, J. Gootee, Primary anatomical site as a prognostic factor for pleomorphic liposarcoma, J. Cancer Res. Clin. Oncol. 146 (2020) 1501–1508.

[25] D.C. Linehan, J.J. Lewis, D. Leung, M.F. Brennan, Influence of biologic factors and anatomic site in completely resected liposarcoma, J. Clin. Oncol. 18 (2000) 1637–1643.

[26] X. Zhang, D. Li, M. Li, M. Ye, L. Ding, H. Cai, D. Fu, Z. Lv, MicroRNA-146a targets PRKCE to modulate papillary thyroid tumor development, Int. J. Cancer 134 (2014) 257–267.

[27] S. Kumar, H. Ingle, S. Mishra, R.S. Mahla, A. Kumar, T. Kawai, S. Akira, A. Takaoka, A.A. Raut, H. Kumar, IPS-1 differentially induces TRAIL, BCL2, BIRC3 and PRKCE in type I interferons-dependent and -independent anticancer activity, Cell Death Dis. 6 (2015) e1758.

[28] F. Geng, X. Cheng, X. Wu, J.Y. Yoo, C. Cheng, J.Y. Guo, X. Mo, P. Ru, B. Hurwitz, S.H. Kim, J. Otero, V. Puduvalli, E. Lefai, J. Ma, I. Nakano, C. Horbinski, B. Kaur, A. Chakravarti, D. Guo, Inhibition of SOAT1 suppresses glioblastoma growth via blocking SREBP-1-mediated lipogenesis, Clin. Cancer Res. 22 (2016) 5337–5348.

[29] Y. Zhu, L. Gu, X. Lin, X. Zhou, B. Lu, C. Liu, Y. Li, E.V. Prochownik, M. Karin, F. Wang, Y. Li, P53 deficiency affects cholesterol esterification to exacerbate hepatocarcinogenesis, Hepatology 77 (2023) 1499–1511.

[30] Y. Huang, X. Zhou, X. Li, D. Huang, Z. Fang, R. Ding, A pan-cancer analysis identifies SOAT1 as an immunological and prognostic biomarker, Oncol. Res. 31 (2023) 193–205.

[31] S. Sun, G. Qi, H. Chen, D. He, D. Ma, Y. Bie, L. Xu, B. Feng, Q. Pang, H. Guo, R. Zhang, Ferroptosis sensitization in glioma: exploring the regulatory mechanism of SOAT1 and its therapeutic implications, Cell Death Dis. 14 (2023) 754.

[32] S. Lu, J. Zhou, Y. Sun, N. Li, M. Miao, B. Jiao, H. Chen, The noncoding RNA HOXD-AS1 is a critical regulator of the metastasis and apoptosis phenotype in human hepatocellular carcinoma, Mol. Cancer 16 (2017) 125.

[33] C. Li, A. Vides, D. Kim, J.Y. Xue, Y. Zhao, P. Lito, The G protein signaling regulator RGS3 enhances the GTPase activity of KRAS, Science 374 (2021) 197–201.

[34] P.C. Tumeh, C.L. Harview, J.H. Yearley, I.P. Shintaku, E.J. Taylor, L. Robert, B. Chmielowski, M. Spasic, G. Henry, V. Ciobanu, A.N. West, M. Carmona, C. Kivork, E. Seja, G. Cherry, A.J. Gutierrez, T.R. Grogan, C. Mateus, G. Tomasic, J.A. Glaspy, R.O. Emerson, H. Robins, R.H. Pierce, D.A. Elashoff, C. Robert, A. Ribas, PD-1 blockade induces responses by inhibiting adaptive immune resistance, Nature 515 (2014) 568–571.

[35] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, Immunity 39 (2013) 1–10.