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ORIGINAL ARTICLE

Prognostic factors and nomogram construction for primary retroperitoneal myxoid/round cell liposarcoma: an analysis of population-based data

Aobo Zhuang[1,2†], Yingxue Cheng[1,2†], Zhe Xi[1,2†], Guangting Yan[1,2], Yue Wang[1,2], Geng Zhang[1,2], Jialiang Zheng[1,2], Kun Chen[1,3], Qing Wang[1,3], Lanlan Lian[4], Xi Li[5,6], Tao Yu[1,2*], Fuan Xie[1,2*], Ting Wu[1,2*], Wengang Li[1,2,3*]

[1]Cancer Research Center, School of Medicine, Xiamen University, Xiamen, Fujian 361102, China, [2]Xiamen University Research Center of Retroperitoneal Tumor Committee of Oncology Society of Chinese Medical Association, Xiamen University, Xiamen, Fujian 361102, P China, [3]Department of Hepatobiliary Surgery, Xiang'an Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, Fujian 361102, China, [4]Department of Laboratory Medicine, Xiang'an Hospital of Xiamen University, Xiamen University, Xiamen, Fujian 361102, China, [5]Department of Biostatistics, School of Public Health, Harvard University, Cambridge, MA 02138 , USA, [6]College of Arts and Science, Boston University, Boston, MA, USA
[†]These authors contributed equally to this work.

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**Corresponding authors:*
Wengang Li
Cancer Research Center, School of Medicine, Xiamen University, Xiamen, Fujian 361102, China.
Email: lwgang@xmu.edu.cn
Ting Wu
Cancer Research Center, School of Medicine, Xiamen University, Xiamen, Fujian 361102, China.
Email: wuting78@189.cn
Fuan Xie
Cancer Research Center, School of Medicine, Xiamen University, Xiamen, Fujian 361102, China.
Email: 406205761@qq.com

ABSTRACT

Background: It has been reported that the prognosis for myxoid/round cell liposarcoma (MLPS/RCLPS) is inconsistent across different sites. However, there are neither prognostic studies nor predictive models that focused on MLPS/RCLPS of retroperitoneal origin.

Methods: Utilizing the Surveillance, Epidemiology, and End Results database, we selected 171 primary retroperitoneal MLPS/RCLPS cases from the period between 2000 and 2019. Prognostic factors influencing disease-specific survival were identified through Cox regression analysis. These independent prognostic factors were then used to construct a DSS nomogram prediction model. The accuracy and reliability of this nomogram were evaluated using the concordance index (C-index) and calibration plots. Furthermore, we categorized patient prognosis using an X-tile based on the nomogram score.

Results: The observed 5-year and 10-year DSS rates for all patients were 64.0% (95% CI: 56.2% – 71.8%) and 47.1% (95% CI: 38.1% – 56.1%), respectively. The patient cohort had a median age of 64 years, ranging from 24 to 92 years, with a slight male predominance (n = 92, 53.8%) over females (n = 79, 46.2%). Distant metastases were diagnosed in 24 patients (14%). The distribution of MLPS and RCLPS was 89.5% and 10.5%, respectively. In terms of treatment, adjuvant radiotherapy was administered to 33 patients (19.3%), neoadjuvant radiotherapy to 9 patients (5.3%), and chemotherapy to 20 patients (11.7%), while a significant majority (83.6%) underwent surgical procedures. Independent prognostic factors for DSS included age (HR = 1.039, P < 0.001), marital status (P = 0.029), history of previous tumors (HR = 0.257, P = 0.007), presence of metastatic disease (HR = 2.206, P = 0.027), and surgical treatment (HR = 0.490, P = 0.036). A nomogram prediction model was constructed to forecast 1-, 5-, and 10-year DSS rates, with a C-index of 0.739. Calibration plots demonstrated a strong correlation between the nomogram's predictions and actual observations. Based on the prediction model, patients were stratified into three groups, and significant differences in prognosis were observed between these groups.

Conclusion: A poorer prognosis is associated with retroperitoneal-derived MLPS/RCLPS than with other sites. The nomogram prediction model we built can be used to assist patients in consulting with their doctors and selecting patients for clinical trials.

Relevance for Patients: Our study highlights the unique challenges and prognosis variations in retroperitoneal myxoid/RCLPS. The developed nomogram serves as a valuable tool for patients, aiding informed discussions with doctors and guiding decisions on treatment and clinical trial participation.

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1. Introduction

Retroperitoneal soft-tissue sarcoma (RPS) accounts for approximately 15% of all soft-tissue malignancies, whereas myxoid/round cell liposarcoma (MLPS/RCLPS) represents less than 5% of all RPS [1-4]. MLPS/RCLPS is the most prevalent lipomatous malignancy in children and adolescents [5,6]. The onset of MLPS/RCLPS occurs earlier than that of other subtypes of liposarcoma and reaches its incidence peak in middle age.

The diagnosis of MLPS/RCLPS is definitive due to its distinctive morphology, which is rarely mistaken for other monomorphic soft tissue tumors with myxoid stromal and lipomatous differentiation [7]. In addition, specific chromosomal translocations were identified, including *FUS* and *CHOP* gene fusions [(t12;16)(q13;p11)] and *EWS* and *CHOP* gene fusions [(t12;22)(q13;q12)] in 90% of tumors in >5% of tumors. The detection of these translocations with polymerase chain reaction (PCR) techniques enables pathologists to make precise diagnoses in difficult cases [8,9]. RCLPS refers to MLPS with round cells, accounting for more than 5% of all cases [7]. In terms of aggressiveness, RCLPS has a worse prognosis than MLPS [10].

MLPS/RCLPS is distinguished from other soft-tissue sarcomas by a number of characteristics. First, it is more susceptible to extrapulmonary metastases than other sarcomas [11,12]; second, it is more sensitive to radiotherapy and chemotherapy than other liposarcomas [13]; third, the prognosis is favorable, with the 5-year disease-specific survival (DSS) rate for local diseases exceeding 90% [13].

Several crucial prognostic factors impact patient survival, including both distant and local recurrence. Key factors include the completeness and negative margins of surgical resection, histological grade reflecting differentiation in myxoid/round cell liposarcoma patients [14], patient age, and the role of tumor biomarkers for treatment monitoring, prognosis assessment, early diagnosis, and treatment prediction.

Furthermore, analysis suggests that high FGF-21 expression improves prognosis [15]. Multivariate analysis considers clinicopathological factors, such as tumor site, round cell (RC) components, high MIB-1 labeling index, and p53 missense mutation as unfavorable indicators. In cases of MLS/RCLS, reduced p14 protein expression and p53 mutations associate with poor prognosis. In addition, the RC component is identified as a negative prognostic factor, potentially involving the p14ARF/p53 pathway in its development [16].

Commonly mutated genes such as *TP53*, *NF1*, and *PIK3CA* are identified in STS through genome studies. *PIK3CA* mutations, more frequent in myxoid/round cell and pleomorphic tumors compared to well-differentiated/dedifferentiated tumors, suggest *PIK3CA* as a potential driver gene and therapeutic target. Survival analysis reveals that patients with increased *PIK3CA* copy numbers have worse prognosis, highlighting its significance [17]. NY-ESO-1's association with higher tumor grade and shorter survival establishes it as a valuable prognostic marker for myxoid liposarcoma. In addition, PRAME's high expression is correlated with unfavorable prognosis and elevated levels in myxoid liposarcoma, indicating its role as a prognostic factor [18]. Elevated levels of SIRT1 and VEGF are linked to unfavorable clinical characteristics and prognosis, suggesting SIRT1 as a potential therapeutic target [19]. Finally, modulation of FGFR signaling and its inhibitors show promise in high-grade liposarcoma treatment, which highlights the potential of developing targeted therapies [20]. Moreover, CXCR4 and AXL are emerging as promising therapeutic targets in the management of aggressive MLPS behavior.

Although it has been known for some time that the prognosis of MLPS/RCLPS of different primary sites varies [21,22], there is currently no prognostic study on MLPS/RCLPS of retroperitoneal origin and no prognostic tool. Therefore, we analyzed the surveillance, epidemiology, and end results (SEER) database, which provides data from 17 geographically variable cancer registries representing approximately 26% of the U.S. population [21,22], to investigate the DSS-related prognostic factors in MLPS and to attempt to develop a prognosis nomogram prediction model.

2. Materials and Methods

Using SEER*Stat 8.4.0.1, patients diagnosed with MLPS/RCLPS between 2000 and 2019 were identified from the SEER database, in which all cases were reported from the United States. The following were the criteria for inclusion: (1) the International Classification of Diseases (ICD) code O-3 morphology 8852 or 8853; (2) the primary site recodes of ICD-O-3 was the retroperitoneum; and (3) active patient monitoring to ensure a reliable patient status. The following were the criteria for exclusion: (1) patients with non-primary tumor and (2) patients younger than 18 years old. Myxoid/Round cell liposarcoma is diagnosed through a combination of histological, immunohistochemical, and genetic examinations. Pathologically, it is characterized by abundant myxoid stroma and a round cell component, with varying degrees of lipogenic differentiation. Immunohistochemically, these tumors typically express S-100 protein, CDK4, and MDM2. A critical aspect of the diagnosis is the identification of hallmark genetic alterations, particularly the *FUS-CHOP* or *EWS-CHOP* fusion genes, often detected through molecular tests like reverse-transcription PCR or fluorescence *in situ* hybridization.

The primary endpoint of this study was DSS. We collected and analyzed data on gender, age, marital status, race, history of previous tumors, the interval between diagnosis and treatment, presence of metastatic disease, histologic subtypes, tumor differentiation, tumor size, and treatment methods including radiotherapy, chemotherapy, and surgery. Information regarding the interval between diagnosis and treatment and tumor size was missing for 20 (11.7%) and 21 (12.3%) patients, respectively. Given the rarity of retroperitoneal MLPS/RCLPS, we chose not to exclude these patients, instead substituting the missing values with their respective medians (1 month, 20 cm). All the aforementioned variables were included in the univariate Cox model analysis. Variables with $P < 0.1$ were further included in the multivariate analysis. Variables with $P < 0.05$ in the Cox multivariate regression model were selected for the nomogram prediction model. The accuracy of the nomogram was subsequently validated using the

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C-index and calibration curve. Based on the nomogram score, patients were stratified into low-, intermediate-, and high-risk groups. Survival differences between these groups were compared using the Kaplan–Meier curve and the log-rank test. The risk stratification cutoff point was determined using X-tile, a novel bioinformatics tool for biomarker assessment and outcome-based cut-point optimization.

All tests were conducted with two-tailed statistics, and $P < 0.05$ was considered statistically significant. Data were analyzed using R statistical software (version 4.1.2, http://www.r-project.org).

3. Results

3.1. Patient and tumor characteristics

A total of 171 patients fulfilled the inclusion criteria, with 77 succumbing to their disease by the time of the last follow-up. The median follow-up duration for all surviving patients was 87 months (IQR: 25 – 156 months). Patient characteristics are detailed in Table 1. The patient cohort had a median age of 64 years, ranging from 24 to 92 years, with a slight male predominance (n = 92, 53.8%) over females (n = 79, 46.2%). Marital status was distributed as follows: married (53.8%, n = 92), single (18.1%, n= 31), widowed (14.0%, n = 24), and divorced or separated (8.8%, n = 15). The majority of patients were white (n = 138, 80.7%), and 83.0% had no history of other tumors. Distant metastases were diagnosed in 24 patients (14%). The distribution of MLPS and RCLPS was 89.5% and 10.5%, respectively. In terms of treatment, adjuvant radiotherapy was administered to 33 patients (19.3%), neoadjuvant radiotherapy to 9 patients (5.3%), and chemotherapy to 20 patients (11.7%), while a significant majority (83.6%) underwent surgical procedures.

Table 1. Patient and tumor characteristics in 171 patients with primary retroperitoneal myxoid/round cell liposarcoma

Characteristics	N=171	% of total
Gender		
Male	92	53.8
Female	79	46.2
Age, years median (range)	64 (24 – 92)	
Marital status		
Married	92	53.8
Single	31	18.1
Widowed	24	14.0
Divorced	15	8.8
Separated	2	1.2
Unknown	7	4.1
Race		
White	138	80.7
Asian or Pacific Islander	17	9.9
Black	15	8.8
Unknown	1	0.6
Past tumor history		
No	142	83.0
Yes	29	17.0
Months from diagnosis to treatment	1 (0 – 6)	
Metastasis disease		
Yes	24	14
No	147	86
Histologic subtypes		
Myxoid liposarcoma	153	89.5
Round cell liposarcoma	18	10.5
Tumor size, cm median (range)	200 (15 – 750)	
Tumor differentiation		
Well-differentiated	60	35.1
Moderate-differentiated	30	17.5
Poor-differentiated	16	9.4
Undifferentiated	14	8.2
Unknown	51	29.8
Radiation		
Adjuvant	33	19.3
Neoadjuvant	9	5.3
No/Unknown	129	75.4
Chemotherapy		
Yes	20	11.7
No/Unknown	151	88.3
Surgery		
Performed	143	83.6
Not performed	28	16.4
Dead because of disease		
Yes	77	45.0
No	94	55.0

3.2. Survival analysis

The 1-year, 5-year, and 10-year DSS rates (Figure 1) and overall survival (OS) rates (Figure 2) for all patients were 86.7% (95% CI, 81.6 – 81.8), 64.0% (95% CI, 56.2 – 71.8), 47.1% (95% CI, 38.1 – 56.1) and 83.1% (95% CI, 77.4 – 88.8), 55.2% (95% CI, 47.4 – 63.0), 35.5% (95% CI, 27.5 – 43.5), respectively.

In the univariate analysis, factors such as patient age ($P < 0.001$), marital status ($P = 0.002$), history of previous tumors ($P = 0.044$), presence of metastatic disease (P = 0.001), tumor differentiation (P = 0.009), radiotherapy (P = 0.030), and surgery (P = 0.003) were found to be associated with DSS (Table 2). Variables with $P < 0.1$ in the univariate analysis were subsequently included in the multivariate analysis of the Cox model. The multivariate analysis revealed that patient age (HR = 1.039, $P < 0.001$), marital status ($P = 0.029$), history of previous tumors (HR = 0.257, $P = 0.007$), presence of metastatic disease (HR = 2.206, P = 0.027), and surgical treatment (HR = 0.456, P = 0.036) were independent prognostic factors for DSS (Table 2).

3.3. Development and validation of nomograms

Subsequently, a DSS nomogram prediction model was developed using a Cox regression model, based on the results of the aforementioned multivariate analysis (Figure 3). This model accurately predicts 1-year, 5-year, and 10-year DSS. Calibration plots (Figure 4) demonstrate a strong correlation between the nomogram's predictions and the actual outcomes. The concordance

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Table 2. Univariable and multivariable analyses to determine independent predictors of disease-specific survival in primary retroperitoneal myxoid/round cell liposarcoma

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender female versus male	0.950 (0.607 – 1.487)	0.823		
Age (continuous)	1.033 (1.015 – 1.051)	<0.001	1.039 (1.017 – 1.061)	<0.001
Marital status		0.002		0.029
Single vs. married	0.448 (0.209 – 0.960)		0.408 (0.181 – 0.921)	
Widowed vs. married	1.288 (0.701 – 2.369)		0.722 (0.363 – 1.436)	
Divorced vs. married	2.053 (1.018 – 4.143)		1.916 (0.931 – 3.940)	
Separated vs. married	4.972 (1.184 – 20.887)		4.701 (0.818 – 27.029)	
Unknown vs. married	3.792 (1.132 – 12.699)		0.734 (0.155 – 3.483)	
Race		1.000		
Asian Pacific Islander vs. White	0.971 (0.465 – 2.030)			
Black vs. White	0.982 (0.449 – 2.148)			
Unknown vs. White	NA			
Past tumor history yes vs. no	0.628 (0.399 – 0.988)	0.044	0.257 (0.096 – 0.688)	0.007
Months from diagnosis to treatment (continuous)	0.907 (0.707 – 1.163)	0.907		
Metastatic disease yes vs. no	2.666 (1.510 – 4.707)	0.001	2.206 (1.096 – 4.438)	0.027
Histologic subtypes round cell vs. myxoid	1.759 (0.902 – 3.433)	0.098	1.936 (0.776 – 4.825)	0.156
Tumor size (continuous)	1.001 (1.000 – 1.003)	0.120		
Tumor differentiation		0.009		0.471
Moderate vs. well	0.961 (0.513 – 1.801)		0.961 (0.478 – 1.929)	
Poor vs. well	3.123 (1.545 – 6.315)		1.993 (0.754 – 5.273)	
Undifferentiated vs. well	0.585 (0.205 – 1.671)		0631 (0.178 – 2.233)	
Unknown vs. well	1.220 (0.680 – 2.189)		0.939 (0.498 – 1.771)	
Radiotherapy yes vs. no		0.030		0.170
Adjuvant vs. no/unknown	0.432 (0.227 – 0.823)		0.567 (0.262 – 1.228)	
Neoadjuvant vs. no/unknown	0.539 (.0132 – 2.204)		0.385 (0.086 – 1.722)	
Chemotherapy yes vs. no/unknown	1.695 (0.867 – 3.314)	0.123		
Surgery performed vs. not performed	0.423 (0.240 – 0.747)	0.003	0.490 (0.251 – 0.954)	0.036

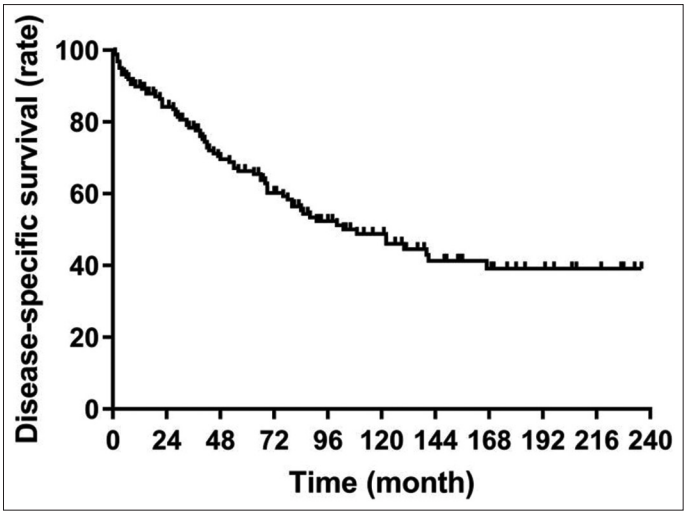

Figure 1. Disease-specific survival in patients with primary retroperitoneal myxoid/round cell liposarcoma.

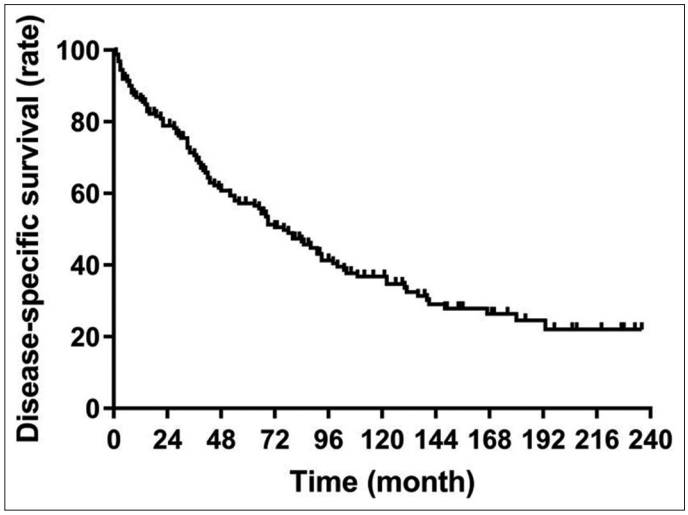

Figure 2. Overall survival in patients with primary retroperitoneal myxoid/round cell liposarcoma.

indices and bootstrapped 95% confidence intervals (95% CI) for the nomogram were 0.739 (0.616 – 0.862).

Utilizing X-tile software, patients were stratified into high-risk (>165), intermediate-risk (141 – 165), and low-risk (<141)

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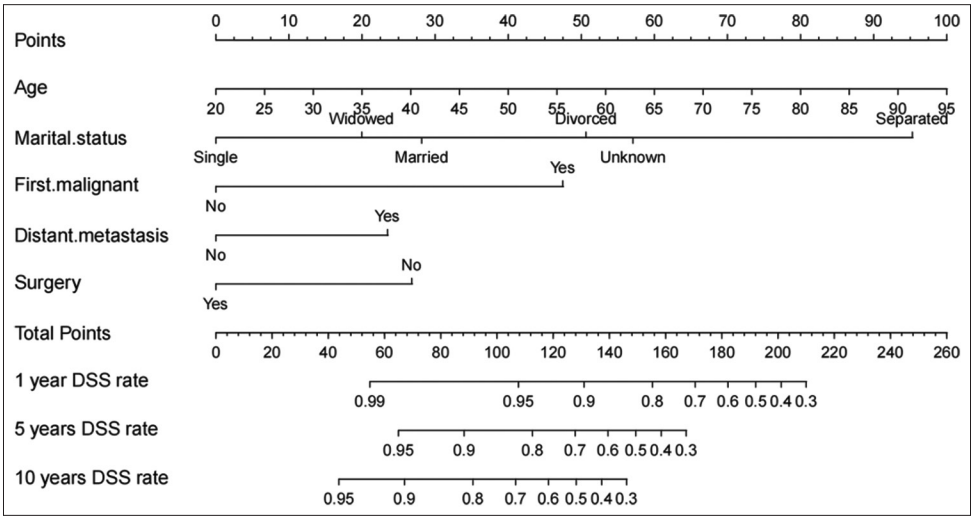

Figure 3. Nomogram for 1-year, 5-year, and 10-year disease-specific survival (DSS) in patients with primary retroperitoneal myxoid/round cell liposarcoma.

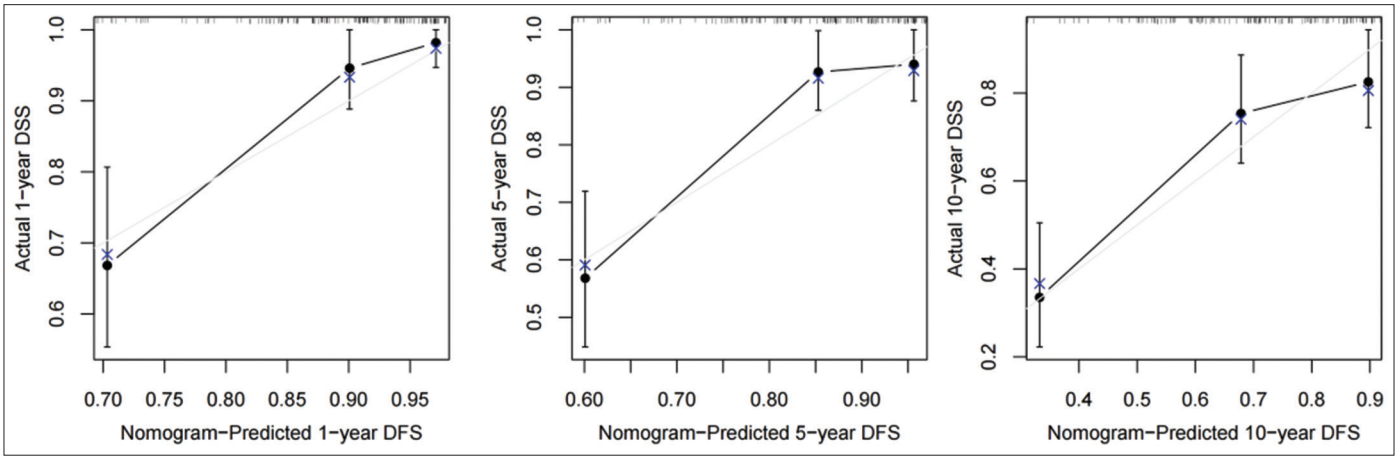

Figure 4. Calibration plots for internal validation of 1-year, 5-year, and 10-year disease-specific survival nomogram.

groups according to their nomogram scores. Figure 5 illustrates the DSS of the three groups; the median DSS was 7.0 months (95% CI: 0.0 – 26.4), 25.4 months (95% CI: 2.2 – 101.8), and 167 months (95% CI: NA), respectively (p <0.001). The usage of the nomogram prediction model is as follows. Assume an MLPS patient comes for a consultation in the outpatient department, with the following basic information: a 65-year-old (60 points) divorced (50 points) woman with no history of malignant tumors (48 points). She is diagnosed without distant metastasis (0 points), but the lesion is inoperable (28 points). Therefore, the total score for this patient is 176 points, placing her in the high-risk group (>165 points), with a corresponding prediction of less than 30% for 5-year DSS. If existing medications are ineffective in controlling the condition, we recommend considering clinical trial enrollment for this patient.

4. Discussion

Retroperitoneal MLPS/RCLPS represents a rare subset of an already rare group of tumors. According to the only reported cohort focused on retroperitoneal MLPS/RCLPS to date, based on five cases from the National Cancer Center Hospital in Tokyo, MLPS/RCLPS accounted for a mere 2.3% of RPS and 3.2% of all sites [2]. In a large cohort study on retroperitoneal liposarcoma, the proportion of MLPS/RCLPS was less than 10% [3,23]. In this study, we retrospectively examined prognostic factors and reported long-term survival status based on the SEER database. For the first time, we identified age (HR = 1.039, P < 0.001), marital status (P = 0.029), previous tumor history (HR = 0.257, P = 0.007), and presence of distant metastasis (HR = 2.206, P = 0.04) as risk factors for DSS. Furthermore, we developed a DSS prediction model for retroperitoneal MLPS/RCLPS that accurately forecasts patients' prognoses. Patients were stratified into three groups based on the nomogram scores. Twenty patients (11.6%) in the high-risk group and thirty-four patients (19.8%) in the intermediate-risk group had a median DSS of only 7.0 (95% CI, 0.0 – 26.4) months and 25.4 months (95% CI, 2.2 – 101.8 months), respectively. In contrast, the median DSS for patients in the low-risk group was 167 (95% CI, NA) months. Based on these

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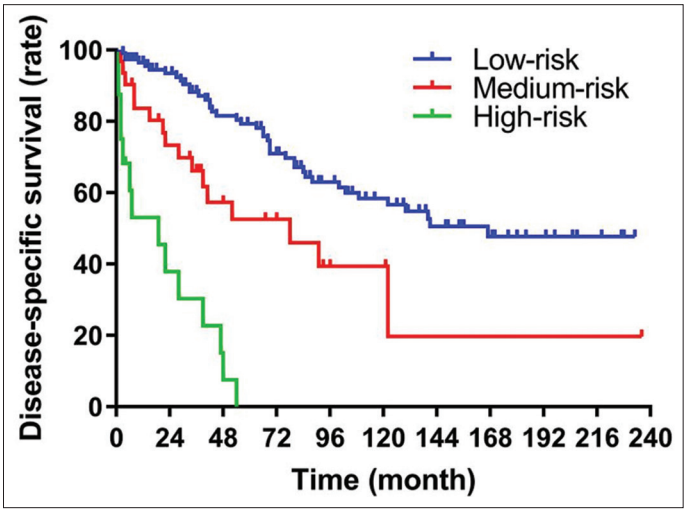

Figure 5. Disease-specific survival in patients with low-, medium-, and high-risk groups.

findings, we recommend more active follow-up for patients in the middle- and high-risk groups and consideration for clinical trials when permissible.

In a retrospective cohort study, we found that retroperitoneal MLPS/RCLPS differed from MLPS/RCLPS at other sites in several ways. Firstly, the prognosis was poorer. In a study conducted by Hans Roland Dürr in 2018 involving 43 cases of MLPS/RCLPS, the 5-year and 10-year OS rates were 81% and 72%, respectively [24]. In a study involving 174 cases of primary MLPS/RCLPS reported by Fiore *et al.*, the 5-year and 10-year DSS rates for the MLPS and RCLPS group were 93% and 92%, and 87% and 77%, respectively. However, only 7% of patients in the cohort were of retroperitoneal origin [10]. Based on 85 patients with MLPS, Chowdhry *et al.* found that tumor size was the only factor affecting OS, and the 5-year OS in this study was 87.5% [25]. In 2020, 89 patients with MLPS/RCLPS participated in a multicenter prospective cohort study, and their 3-year DSS was as high as 96%. Similarly, no retroperitoneal patients were included in this study [26]. The patients in this study cohort had a significantly worse prognosis than those in the preceding cohorts (5-year and 10-year DSS were only 64.0% and 47.1%, respectively). Second, the median age and tumor diameter of patients with retroperitoneal MLPS/RCLPS were also significantly different. As an example, the median age of patients in this study was 64 years, whereas in previous studies, it was less than 50 years; the median tumor size was 20 cm, as opposed to approximately 10 cm in previous studies. The Trans-Atlantic RPS Working Group reported that the 10-year OS of RPS was 46%, the median age of patients in this cohort of 1007 patients was 58 years, and the median tumor size was 20 cm [27]. Retroperitoneal MLPS/RCLPS appears to have a prognosis more comparable to that of an RPS than systemic MLPS/RCLPS. In other words, even in MLPS/RCLPS, the primary site may be as crucial to the patient's prognosis as the pathological subtype.

As early as 2003, Memorial Sloan-Kettering Cancer Center (MSKCC) conducted a nomogram study on retroperitoneal liposarcoma. There were 177 patients in the study, and the 5-year DSS for all patients was 60%. There were only 13 (7%) patients with MLPS and RCLPS in the cohort, so the accuracy of prediction for these patients was limited even though pathological type was an independent prognostic factor for RLPS in multivariate analysis [23]. Subsequently, MSKCC developed a DSS nomogram prediction model using data from 801 liposarcoma patients (including 144 MLPS and 81 RCLPS). Despite the 12-year DSS of 72% for the entire cohort, the 12-year DSS for liposarcomas of retroperitoneal origin in subgroups by site was only 32%. This is consistent with our previous findings that the prognosis for retroperitoneal MLPS/RCLPS is worse than other sites. The researchers also developed a 5-year and 12-year DSS prediction model with good verification based on age, presentation status, primary site, histologic variant, tumor burden, and gross margin status (C-index = 0.776) [28]. Gronchi *et al.* developed a nomogram prediction model for RPS using data from 523 patients in 2013. The cohort's 5-year OS rate was 56.8%. Although this study did not differentiate the pathological subtype of myxoliposarcoma, it has been externally validated and can accurately predict the DFS and OS of patients, presenting significant implications for the diagnosis and treatment of RPS [29]. On the basis of pathological classification, MSKCC subsequently developed a DSS nomogram prediction model for RPS. This nomogram can predict DSS at 3, 5, and 10 years after surgery with high accuracy (C-index = 0.71). In addition, it is also a fly in the ointment that, due to the rarity of MLPS and RCLPS, MLPS is classified as WDLPS and RCLPS as DDLPS [30]. Compared to the aforementioned studies, the nomogram established in this research focuses on retroperitoneal MLPS/RCLPS, providing more precise diagnosis and treatment for this relatively rare disease.

In recent years, numerous studies have explored the impact of psychosocial factors on cancer outcomes, highlighting marital status as an independent predictor of survival across different cancer types. Research shows that unmarried individuals with cancer tend to experience more advanced disease stages than their married counterparts. Married patients typically enjoy higher socioeconomic status and better access to quality healthcare. They also benefit from emotional and financial support from their spouses, enhancing their focus on the healing process. Notably, partner-provided emotional support can alleviate the stress associated with cancer treatment. Social support within a marriage may influence cancer survival by affecting neuroendocrine, neurological, and immune interactions. For instance, higher social support levels are associated with increased activity of natural killer (NK) cells, which play a crucial role in recognizing and eliminating cancer cells. In addition, oxytocin hormone release during social interactions may indirectly inhibit cancer cell growth by suppressing stress responses [31-34].

Marital status was found to be a risk factor for DSS. In univariate analysis, the tumor-specific survival of married patients was greater than that of widowed, divorced, and separated patients [35-37]. However, contrary to previous research, we found that married patients had twice the risk of dying from cancer compared to single (never-married) patients, even after

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adjusting for other confounding variables (Table 2). To determine the reason, we compared baseline characteristics of single and married patients, but there was no difference between the two groups (data not shown). Intriguingly, when patients were divided into four groups consisting of married men, single men, married women, and single women, the DSS of single women was significantly higher than that of the other groups. In particular, the 10-year DSS for single women, married women, single men, and married women was 87.5 (95% CI, 75.6% – 100.0)%, 51.3 (95% CI, 32.5% – 70.1)%, 60.5 (95% CI, 35.8% – 85.2)%, and 44.8 (95% CI, 28.1% – 61.5)%. Most analyses indicate that women have better outcomes than men, but few studies indicate that single women have better outcomes than other demographic groups. Based on the current data, we cannot conclude the reasons for the above differences for the time being, and further in-depth research is needed.

The current study considered that an anthracycline-based combination chemotherapy regimen is the first-line treatment option and trabectedin may be considered in first-line therapy when anthracyclines cannot be used. Although doxorubicin ± ifosfamide remains the first-line treatment for most STS subtypes, some STSs (alveolar soft part sarcoma, clear cell sarcoma, epithelioid sarcoma, and extraosseous myxoid chondrosarcoma) have been reported to show little response to these cytotoxic chemotherapies [38]. In addition to chemotherapy, new treatments are also being investigated, some of which have already shown considerable results. Trabectedin is a marine-derived antitumor drug that achieves anti-tumor cell activity by inhibiting transcription, anti-angiogenesis, and immune regulation. Related tests show that MRCL and other translocation-related sarcomas (liposarcoma and leiomyosarcoma) are the most sensitive types of sarcoma related to trabectedin [39]. The French Sarcoma Group conducted a randomized phase III study evaluating the efficacy of trabectedin versus best supportive care (BSC) in patients with advanced STS. Patients were randomized (1:1) to receive trabectedin (1.5 mg/m^2 24 h intravenous infusion every 3 weeks) or BSC. The median PFS was 3.1 months in the trabectedin group, and the median PFS was 1.5 months in the BSC group. It can be seen that trabectedin is better for disease control than BSC [40]. Eribulin is a non-taxane microtubule inhibitor, which is more sensitive to leiomyosarcomas and liposarcomas. Eribulin has now become an effective treatment for MRCL. Several recent trials of eribulin combined with other drugs for advanced liposarcoma have prolonged the median PFS in patients with considerable results [39]. In a phase II trial of eribulin-gemcitabine combination in patients with advanced liposarcoma, a 12-week PFS rate was 70.6% (n = 12/17) in the liposarcoma cohort, with a median PFS of 5.7 months [41].

Radiotherapy is often used in combination with surgery and allows for preoperative, intraoperative, or postoperative radiotherapy. Preoperative radiotherapy may enable surgery for unresectable tumors. Different liposarcoma subtypes differ in their sensitivity to radiotherapy, and MLPS is highly radiosensitive [42]. Neoadjuvant radiotherapy is mostly used in patients with mucoid LPS because of its great radiosensitivity. The effects of radiotherapy may be initiated by reducing the myxoid stroma produced by tumor cells as well as promoting adipocyte maturation [43]. Radiotherapy can also cause a change in tumor size. Studies have shown that pre-operative radiotherapy to patients can reduce tumor seeding during surgery, but the disadvantage of pre-operative radiotherapy is that it can affect wound healing [44]. Pre-operative radiotherapy may improve the prognosis of low-grade retroperitoneal sarcoma without much benefit for high-grade retroperitoneal sarcoma [45]. Post-operative radiotherapy can be effective in improving local control in patients with positive surgical margins, but the associated side effects of post-operative radiotherapy will also increase [44]. For soft-tissue sarcomas, tumor size is an important prognostic factor and is associated with both the local recurrence rate and overall survival. Magnetic resonance imaging (MRI) examination of tumor size before and after radiotherapy revealed a median maximum tumor size of 12.4 cm and a median tumor volume of 298.9 cm^3. After radiotherapy, the median maximum tumor size on MRI was 8.7 cm, and the median tumor volume was 106.9 cm^3 [46]. However, the role of radiotherapy in liposarcoma should be explored in a prospective trial.

Recently, significant advances have been made in an increasing number of targeted therapies, with some targeted agents showing promising results in patients with advanced or metastatic STS. Unlike other liposarcomas, the tumor microenvironment of MRCL is relatively "cold" immunologically, rendering MRCL less sensitive to immunotherapy. However, the cancer testicular antigens in these tumors are highly expressed, such as NY-ESO-1 and MAGEA4. Therefore, these two antigens have become ideal targets for the treatment of MRCL patients [39]. Others such as PPARγ agonists, PI3KCA inhibitors, and tyrosine kinase inhibitors have been shown to play a key role in the treatment of MRCL patients.

This research has the following limitations: First, because it is a retrospective study, there were unavoidable selection bias; second, data used in this study were derived from the SEER database, and some information was missing; third, although 171 cases of MLPS/RCLPS represent the largest cohort to date, the nomogram prediction model established in this study had only been internally validated, and additional external validation is required to increase the confidence of the prediction.

5. Conclusion

One hundred and seventy-one patients with primary retroperitoneal MLPS/RCLPS were retrospectively analyzed for prognostic factors using the SEER database, and the findings indicate that age, marital status, previous tumor history, metastatic disease, and whether surgery was performed are associated with DSS. In addition, we developed the first retroperitoneal MLPS/RCLPS prognostic prediction model. By dividing patients into three risk categories, it may useful for outpatient consultations and patient selection for clinical trials.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

Author Contributions

Aobo Zhuang, Yingxue Cheng, and Yue Wang contributed to the design of the study. Zhe Xi, Guangting Yan, and Gen Zhang contributed to recruiting patients. Jialiang Zheng, Lingwei Gu, and Peng Li contributed to collecting data. Wengang Li, Lanlan Lian, Xi Li, Fuan Xie, and Ting Wu approved the final version of this manuscript and were responsible for the decision to submit the manuscript.

Ethics Approval and Consent to Participate

This article does not contain any studies with human or animal subjects performed by any of the authors.

Consent for Publication

Not applicable.

Availability of Data

The data that support the findings of this study are available from SEER database. Data are available from the authors on reasonable request and with permission of SEER database.

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