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ORIGINAL ARTICLE

Prediction of Recurrence-Free and Overall Survival in Retroperitoneal Well-Differentiated and Dedifferentiated Liposarcoma After Surgery

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Abstract

This study was aimed at creating an effective model for predicting the course of the disease in retroperitoneal well-differentiated (WDLPS) and dedifferentiated (DDLPS) liposarcomas after surgery. The study included 111 patients with WDLPS and 74 patients with DDLPS. We developed a methodology for stratification of patients into prognostic groups. Overall survival (OS) and recurrence-free survival (RFS) were analyzed in accordance with it. The highest OS was achieved in the group "favorable prognosis," while the shortest OS was in the group "extremely poor prognosis" ($p < 0.001$). The median OS in the "favorable prognosis" group was 225 (95% *CI*, 174, 276) months; "intermediate prognosis" — 130 (95% *CI*, 115, 145) months; "poor prognosis" — 90 (95% *CI*, 79, 101) months; and "extremely poor prognosis" — 22 (95% *CI*, 15, 29) months. The highest RFS was achieved in the group "favorable prognosis," while the shortest RFS was achieved in the group "extremely poor prognosis" ($p < 0.001$). The median RFS in the "favorable prognosis" group was 80 (95% *CI*, 65, 95) months; "intermediate prognosis" — 47 (95% *CI*, 33, 61) months; "poor prognosis" — 26 (95% *CI*, 24, 28) months; "extremely poor prognosis" — 10 (95% *CI*, 6, 14) months. The method of predicting recurrence-free and overall survival demonstrates an adequate distribution of patients and the reliability of intergroup differences in the survival rate.

Keywords Liposarcoma · Sarcoma · Prediction

Introduction

Liposarcoma is the most common retroperitoneal sarcoma. In the vast majority of cases retroperitoneal liposarcoma (RLPS) are represented by well-differentiated (WDLPS) (58.5%) and dedifferentiated (DDLPS) (39%). Extremely rarely, LPS is represented by myxoid (MLPS) (2%) and pleomorphic (PLPS) (0.5%) [1–7]. Classification and staging of LPS is carried out according to "TNM: Classification of malignant tumors" (TNM). For the first time, a special section for retroperitoneal sarcoma was included in the eighth edition of TNM [8]. At the same time, the conducted study on the evaluation of the prognostic significance of the 8th edition of TNM in RLPS demonstrates its inefficiency. As previous editions, the 8th edition of TNM does not fully reflect the prevalence of the tumor and the prognosis of the disease in RLPS [2]. Also, this study proposed a modified TNM classification with new values of the T-category, which demonstrated a more adequate distribution of patients by stages and the reliability of intergroup differences in the survival rate. [2]. According to the literature, the most significant prognostic factors for RLPS are: tumor size, radical surgery, histological type of liposarcoma, grade of malignancy, and age of the patient [4, 6, 9–15]. In addition, recent studies have identified new factors influencing prognosis in RLPS. Along with the grade of malignancy, the impact of visceral invasion on overall (OS) and recurrence-free (RFS)

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survival has been demonstrated in both low-grade and high-grade RLPS [2]. A more aggressive course of the disease was shown in DDLPS with a shortening of the OS and RFS with an increase in the proportion of the dedifferentiated component in the tumor. At the same time, a direct dependence of the frequency of visceral invasion on the proportion of the dedifferentiated component in the tumor was revealed [16]. It has also been shown that an increase in the proportion of the sclerosing component in WDLPS is an unfavorable prognostic factor, as evidenced by an increase in the frequency of tumor ingrowth into adjacent organs and a decrease in OS and RFS [17–19]. Similar results are presented for studying the effect of myxoid matrix in the tumor on survival. OS and RFS in patients with WDLPS without myxoid matrix are significantly higher than in patients with WDLPS with the presence of myxoid matrix in the tumor [20]. Given the above, it should be noted that to date, in clinical practice, no effective method has been developed for stratifying patients with RLPS into prognostic groups to determine the tactics of managing the disease. The purpose of this study is to develop a method for stratifying patients into prognostic groups with the most common histological types of RLPS — WDLPS and DDLPS, taking into account new prognostic factors.

Methods

Case Series

The retrospective study included 111 patients with primary WDLPS and 74 patients with primary DDLPS who underwent radical surgery treatment in FSBI "N.N. Blokhin National Medical Center of Oncology" in the period from 2004 to 2018. Patients with multiple primary malignant neoplasms are not included in the study. All patients had no distant metastases (M0). The excision of the sarcoma was performed, according to the recommendations of the experts of the College of American Pathologists (CAP) [21]. After revision, the histological types of liposarcoma were determined in accordance with the requirements of the WHO classification [3]. The histological grade of malignancy was determined in accordance with the criteria FNCLCC/WHO [3]. During the revision of the histological preparations a semi-quantitative method was used to calculate the proportion of well-differentiated, sclerosing, myxoid, inflammatory and dedifferentiated components of the tumor, as well as necrosis foci, expressed as a percentage. The percentage composition of each component was determined by light microscopy for each clinical case in all sections of tumor tissue, rounded to the nearest side with 5% steps (for example, 0%, 5%, and 10%,). The obtained values of the proportion (%) were summed up, and the resulting sum was divided by the number of examined sections in each case. The final proportion (%) of each tumor component was expressed as the arithmetic mean and rounded to the nearest side with a 5% step [16–18]. The stage of the disease was established according to the modified TNM classification presented in Table 1 [2].

Statistical Methods

Statistical analysis was performed using the program IBM SPSS Statistics v23. OS and RFS curves were constructed using the Kaplan–Meier method. The significance of differences between groups was determined using the log-rank test with a significant p value < 0.05.

Results

The age of patients ranged from 17 to 80 years: 30 (16%) patients under 40 years old, 123 (67%) patients from 41 to 60 years old, and 32 (17%) patients over 61 years old. There were 64 (35%) men and 121 (65%) women. Lymph node metastases were not detected in any case. In accordance

Table 1 The modified TNM classification of retroperitoneal liposarcoma [2]

Stages	T[†]	G	N	M	The median OS, months	The median RFS, months
IA	T1	G1	N0	M0	225	80
IB	T2	G1	N0	M0	130	53
II	T3	G1	N0	M0	84–90	24–26
	T1	G2-3				
IIIA	T2	G2-3	N0	M0	52	24
IIIB	T3	G2-3	N0	M0	26	11
	T — any	G — any	N1	M0	no data	No data
IV	T — any	G — any	N — any	M1	no data	No data

[†]Category "T": T1 — the size of the tumor < 20 cm; T2 > 20 cm; T3 — the invasion of the tumor into adjacent organs (cT3 — according to CT or MRI, pT3 — histologically confirmed) [2]

with the WHO criteria [3], all WDLPS had a low-grade of malignancy — grade 1. Of these, 102 (92%) patients with WDLPS without myxoid matrix and 9 (8%) patients with WDLPS with myxoid matrix (the proportion of the myxoid component in the tumor was not less than 5%). With regard to the sclerosing component in WDLPS, the distribution of patients is as follows: 41 (37%) patients with the lipoma-like subtype of WDLPS, with a minimal proportion of sclerosis in the tumor (< 15%) and 70 (63%) patients with the sclerosing subtype of WDLPS — the proportion of sclerosis in the tumor was > 15%. DDLPS in 50 (68%) cases corresponded — grade 2, and in 24 (32%) cases — grade 3. Of these, 28 (38%) patients had a proportion of the dedifferentiated component in the tumor of 15% or less, and 46 (62%) patients had a proportion of the dedifferentiated component of more than 15%. The disease was staged according to the modified TNM classification [2]: stage IA in 23 (12%) cases; IB — 60 (33%); II — 39 (21%); IIIA — 25 (14%); and IIIB—38 (20%). There were no patients with N1 and M1 (IV) stages of the disease.

The first stage was the analysis of survival depending on the histological type of RLPS. OS and RFS were significantly worse in DDLPS in comparison with the WDLPS ($p < 0.001$). Median OS in the WDLPS — 136 (95% *CI*, 120, 152) months; DDLPS — 50 (95% *CI*, 43, 57) months; and the 5-year OS rates were 73% and 28%, respectively. The median RFS in the WDLPS — 52 (95% *CI*, 39, 65) months; DDLPS — 19 (95% *CI*, 14, 24) months; and the 2-year RFS rates were 73% and 25%, accordingly.

In continuation, an intragroup analysis was performed in DDLPS in order to find differences between G2 and G3 in survival. The G2-group included 49 (66%) patients and the G3 — 25 (34%). The analysis of OS and RFS was performed; there was no significant difference between G2 and G3 ($p = 0.069$; $p = 0.102$).

To assess the effect of age on OS, a comparative intergroup analysis was performed separately for WDLPS and DDLPS.

The analysis of OS included 111 patients with WDLPS. The "under 40 years" group included 16 (14%) patients; "from 41 to 60 years" — 81 (73%); and "61 years and older" — 14 (13%). Tumor sizes in the compared groups did not differ significantly. OS was significantly worse in the 61 years and older group than in the comparison groups. A statistical difference was achieved between groups 1 and 3 ($p = 0.008$), 2 and 3 ($p = 0.009$). A statistical difference between the 1 and 2 groups was not achieved ($p = 0.101$). The median OS in the 1 group was 140 (95% *CI*, 116,164) months; 2 — 131 (95% *CI*, 122,139) months; 3 — 95 (95% *CI*, 76,114) months; and the 10-year OS rates were 35%, 31%, and 7%, respectively.

The analysis of OS included 74 patients with DDLPS. The group "under 40" included 13 (18%) patients; "from 41 to 60 years" — 43 (58%); "61 years and older" — 18 (24%). Tumor sizes in the compared groups did not differ significantly. OS was significantly worse in the 61 years and older group than in the comparison groups. A statistical difference was achieved between groups 1 and 3 ($p = 0.026$) and 2 and 3 ($p < 0.001$). A statistical difference between the 1 and 2 groups was not achieved ($p = 0.779$). The median OS in the 1 group was 51 (95% *CI*, 7.95) months; 2 — 59 (95% *CI*, 44, 74) months; 3 — 21 (95% *CI*, 14, 28) months; and the 5-year OS rates were 31%, 35% and 11%, accordingly.

Then, multivariate Cox regression analyses were performed to assess independent factors that affect the prognosis. The results of the analyses are presented in Table 2. It should be noted that the significance of the new prognostic factors studied in the multivariate analysis (criterion "T" (with the values recommended by us [2]), the proportion of sclerosing, myxoid, and dedifferentiated components in RLPS) was described in the introduction of this article and previous publications [2, 16–18, 20].

Adjuvant Therapy

Twenty-three patients received postoperative chemotherapy; of these, 13 patients are with high grade RLPS and 10 patients with low grade RLPS; the number of courses was from 3 to 8, the median — 6. Therapy regimens were mainly in two variants: (1) iphosphomide and doxorubicin and (2) doxorubicin monotherapy.

When evaluating the effectiveness of additional chemotherapy, we were primarily interested in the RFS, since in the event of a relapse, patients were most often reoperated, which undoubtedly affected OS. The analysis of RFS included 108 patients with low grade. There were 98 (91%) patients in the "only operation" group, 10 (9%) patients in the "operation + chemotherapy" group. There was no statistically significant difference between patient groups ($p = 0.072$; log-rank test). The median RFS in the surgery-only group was 54 (95% *CI*, 40, 68) months; in the "surgery + chemotherapy" group — 38 (95% *CI*, 32, 43) months, the 2-year RFS were 72% and 70%, respectively.

The analysis of RFS included 70 patients with high grade. There were 57 (11%) patients in the "only operation" group, 13 (19%) patients in the "operation + chemotherapy" group. There was no statistically significant difference between patient groups ($p = 0.589$; log-rank test). Median RFS in the surgery-only group was 18 (95% *CI*, 13, 23) months; in the "surgery + chemotherapy" group — 22 (95% *CI*, 7, 42) months, the indicators of the 2-year RFS were 23% and 30%, respectively.

Then, we developed a methodology for stratifying patients into prognosis groups. The predictive group is determined by the sum obtained by adding the scores corresponding to each of the following criteria:

Table 2 The results of multivariate Cox regression analysis to assess the factors affecting OS and RFS in well-differentiated and dedifferentiated retroperitoneal liposarcoma

Indicator	Cox multivariate analysis WDLPS					
	Overall survival			Recurrence-free survival		
	HR	95% *CI*	*p*	*HR*	95% *CI*	*p*
The proportion of the sclerosing component and/or myxoid*	0.262	0.112–0.611	0.002	0.497	0.293–0.843	0.009
pT ** criterion (created by us)	0.186	0.055–0.631	0.026	0.189	0.078–0.457	0.001
Patient's age***	0.409	0.172–0.971	0.043	—	—	—
Indicator	Cox multivariate analysis DDLPS					
	Overall survival			Recurrence- free survival		
	HR	*95% CI*	*p*	*HR*	*95% CI*	*p*
The proportion of the dedifferentiated component†	0.151	0.067–0.343	< 0.001	0.341	0.176–0.663	0.001
pT†† criterion (created by us)	0.199	0.059–0.667	0.009	0.278	0.143–0.538	0.001
Patient's age†††	0.376	0.197–0.716	0.003	—	—	—

* The proportion of the sclerosing component and/or myxoid up to 15% inclusive and more than 15%

** The pT criterion is our created stratification of patients with RLPS, where T1 is a tumor up to 20 cm in the largest dimension; T2 — more than 20 cm; T3 — histologically confirmed ingrowth of liposarcoma in adjacent organs

*** The patient's age is up to 60 years old inclusive and older

†The proportion of the dedifferentiated component is up to 15% inclusive and more than 15%

††The pT criterion is our created stratification of patients with RLPS, where T1 is a tumor up to 20 cm in the largest dimension; T2 — more than 20 cm; and T3 — histologically confirmed ingrowth of liposarcoma in adjacent organs

†††The patient's age is up to 60 years old inclusive and older

1. Independent statistically significant predictor

– for WDLPS

Proportion of sclerosing component and/or myxoid ≤ 15% – 1 point

Proportion of sclerosing component and/or myxoid > 15% – 2 points

– for DDLPS

Proportion of dedifferentiated component ≤ 15% – 3 points

Proportion of dedifferentiated component > 15% – 4 points

2. Independent statistically significant prognostic factor for WDLPS/DDLPS

– Age ≤ 60 years – 1 point
– Age > 60 years – 2 points

3. TNM classification (modified) [2]

– Stage IA 1 point
– Stage IB 2 points
– Stage II 3 points
– Stage III A 4 points
– Stage IIIB 5 points
– Stage IV 6 points

Prognostic groups for retroperitoneal WDLPS and DDLPS.

1. Favorable prognosis group — 3 points
2. Intermediate forecast group — 4–6 points
3. Group of unfavorable prognosis — 7–9 points
4. Extremely unfavorable prognosis group — ≥ 10 points

In order to confirm the correctness of the proposed distribution of patients with WDLPS/DDLPS into prognostic groups, a comparative intergroup analysis of OS and RFS was performed, the results of which are presented in Figs. 1 and 2.

The patients were divided into comparison groups in accordance with the described stratification method. The first group of "favorable prognosis" included 16 (9%) patients; 2 — "interim prognosis" 92 (50%); 3 — "unfavorable prognosis" — 39 (21%); and 4 — "extremely unfavorable prognosis" — 38 (20%).

OS differed significantly between all groups ($p < 0.001$). The highest OS was achieved in the "favorable prognosis"

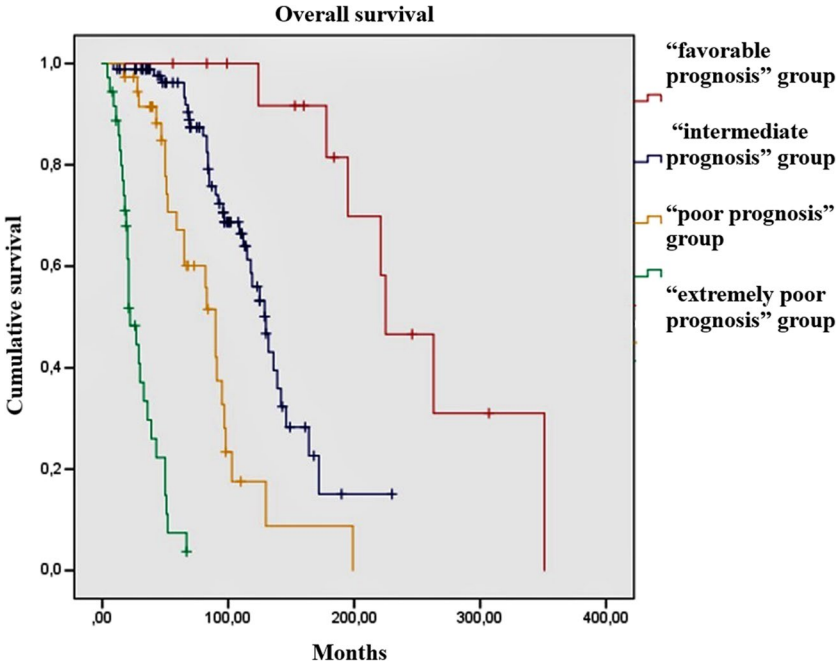

Fig. 1 Overall survival of patients with WDLPS/DDLPS in accordance with the proposed stratification of patients into prognostic groups. Kaplan–Meier method

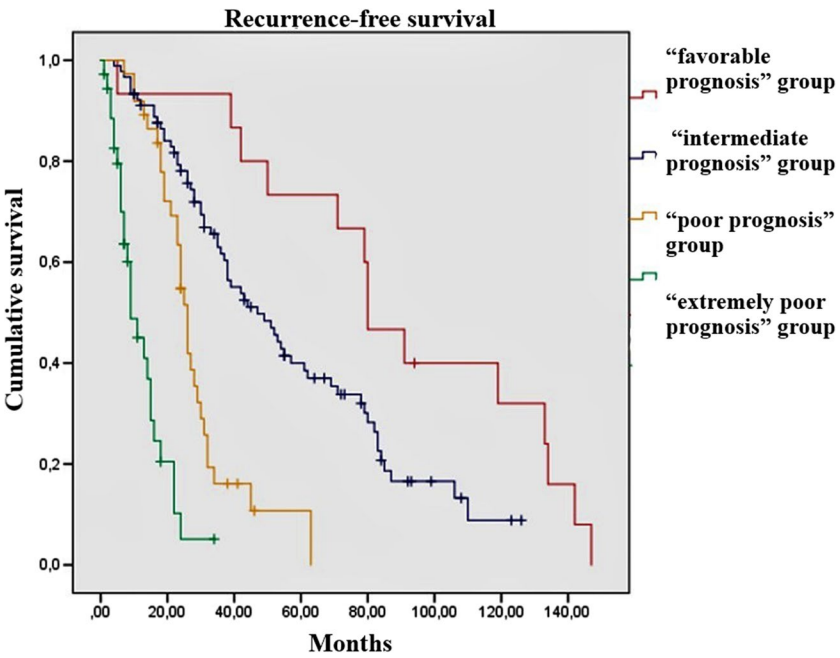

Fig. 2 Recurrence-free survival of patients with WDLPS/DDLPS in accordance with the proposed stratification of patients into prognostic groups. Kaplan–Meier method

group, while the shortest OS was achieved in the "extremely unfavorable prognosis" group ($p < 0.001$). The median OS in the "good prognosis" group was 225 (95% *CI*, 174, 276) months; "interim prognosis" group — 130 (95% *CI*, 115, 145) months; "poor prognosis" group — 90 (95% *CI*, 79, 101) months; and "extremely unfavorable prognosis" group — 22 (95% *CI*, 15, 29) months. The 5-year OS rates were 100%, 73%, 51%, and 6%, respectively. The 10-year OS rates were 80%, 23%, 5%, and 0%, accordingly. RFS differed significantly between all groups ($p < 0.001$). The highest RFS was achieved in the "favorable prognosis" group, while the shortest RFS was achieved in the "extremely poor prognosis" group ($p < 0.001$). The median RFS in the "favorable prognosis" group was 80 (95% *CI*, 65, 95) months; "interim prognosis" group — 47 (95% *CI*, 33, 61) months; "poor prognosis" group — 26 (95% *CI*, 24, 28) months; and "extremely unfavorable prognosis" group — 10 (95% *CI*, 6, 14) months. The 2-year RFS rates were 100%, 71%, 46%, and 3%, respectively. The 5-year RFS rates were 73%, 29%, 3%, and 0%, accordingly.

Discussion

According to the present study, OS and RFS were significantly worse in DDLPS than in WDLPS ($p < 0.001$). Herewith, there was no significant difference between DDLPS G2 and G3 in OS and RFS. This fact is consistent with the TNM8, which combines G2 and G3 sarcomas into a single group of high grade tumors [3]. When assessing the effect of the patient's age (at the time of the initial detection of RLPS) on OS, a borderline value of 60 years was determined. Thus, with WDLPS and DDLPS, significant differences in OS were achieved only between groups of patients whose age was up to 60 years and older ($p = 0.008$; $p = 0.026$). The survival graphs demonstrate the effectiveness of the developed technique for stratifying patients into prognostic groups. Reliably significant differences in both OS and RFS were achieved between each prognostic group of patients.

Conclusion

It is recommended to conduct a semi-quantitative assessment of the proportion of the sclerosing and myxoid components in WDLPS, as well as the proportion of the dedifferentiated component in DDLPS for a more accurate prediction of the course of the disease in RLPS during the morphological study. In clinical practice, more accurate staging of the disease according to the modified TNM classification can be additionally used [2]. The proposed method for stratification of patients with RLPS into the prognostic groups developed by us demonstrates an adequate distribution of patients and the reliability of intergroup differences in the survival rate. Based on the study data, it can be concluded that this model clinically applied in order to select patients for combined treatment and optimize follow-up after treatment.

Author Contribution All the authors have contributed significantly.

Data Availability All the data generated or analyzed during this study are included in this published article. Additional information about the datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent for Publication All the authors are in agreement with the content of the manuscript.

Conflict of Interest The authors declare no competing interests.

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