ORIGINAL ARTICLE

WILEY

TNM classification of malignant tumors: Eighth edition for retroperitoneal liposarcoma. Ways to improve

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Abstract

Aim: This study was aimed at assessing the prognostic significance of the "TNM: Classification of Malignant Tumors" eighth edition (TNM8) in the most common retroperitoneal tumors - liposarcoma.

Methods: The study included 192 patients with retroperitoneal liposarcoma (RLPS). The distribution of patients by stages and survival in accordance with the TNM8 were studied.

Results: In the TNM8, only the degree of malignancy of the tumor has a prognostic value. The T-category does not reflect the actual size of the RLPS and is considered as T4 in 93%, which leads to inadequate staging. During the 15-year period, there were no cases with stages II and IIIA, and the survival rate was estimated only in patients with stages I and IIIB. The tumor node metastasis (TNM) classification with new values of the T-category was proposed by us, which demonstrated a more adequate distribution of patients by stages and the reliability of intergroup differences in the survival rate. **Conclusion:** It is advisable to create a special TNM classification for RLPS, which makes up more than half of all retroperitoneal sarcomas. The TNM8 does not accurately reflect the prevalence of the tumor and the prognosis in RLPS. Revision of the T-staging is necessary to improve the accuracy of the prognosis in RLPS. The modified by us TNM classification demonstrated a more adequate distribution of patients by stages.

KEYWORDS

liposarcoma, sarcoma, TNM classification

1 | INTRODUCTION

Soft tissue sarcomas are rare tumors. About 3500 new cases of these neoplasms are registered in Russia annually, which is less than 1% of all oncological diseases.¹ Retroperitoneal sarcomas account for 10%-15% of all types of soft tissue sarcomas.² The most common retroperitoneal tumor is liposarcoma: more than 50% cases.³ Retroperitoneal liposarcomas (RLPS) are divided into four histological types, which have a different prognosis.⁴ Until 2017, the tumor node metastasis

(TNM) classification of malignant tumors did not have a special section for staging non-organ retroperitoneal tumors (NRT). Determination of the non-organ retroperitoneal tumors (NRT) stage was carried out in accordance with the TNM classification intended for all soft tissue sarcomas. Size of the neoplasm is the one of the main prognostic factors, which has only two meanings—more or less 5 cm in this classifications (6, 7 editions).^{5,6} Since in most cases, the size of the neoplasm is more than 15 cm, and tumors less than 5 cm were observed only in 1.5%–6% of patients,^{7,8,10–13} the effect of the actual size of the neoplasm is practically not taken into account on the stage and prognosis. Another criterion defining the symbol T (a-deep, b-superficial tumor) does

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overwhelming majority of NRTs classified as T2b. The state of regional lymph nodes and the presence of distant metastases have prognostic value in an extremely limited group of patients because it is very rare event in NRT. Consequently, only the tumor grade (G1-low; G2, G3-high) plays the main prognostic role in this classification and makes it possible to distinguish the majority of NRTs between stages IB and III. The prognostic value of the TNM classification 7th edition in RNTs has been criticized by researchers from different countries.^{14–16} "TNM: Classification of Malignant Tumors" eighth edition (TNM8) was published in 2017,¹⁷ in which NRS were first identified as a separate group. The division into superficial and deep tumors has been canceled in this classification; a new gradation of primary tumor sizes has been introduced. Categories "N," "M," and "G" remained unchanged. American Joint Committee on Cancer (AJCC) proposes to use the Gronchi nomogram¹⁵ in the TNM8 as an additional prognostic tool, which makes it possible to make a 7-year prognosis of overall (OS) and recurrence-free (RFS) survival in patients with NRTs, but this does not solve the problem of staging. According to TNM8, when staging NRTs, the size of the sarcoma is more prognostically significant in high grade tumors than in low.¹⁷ It is assumed that the innovations in the TNM8 will make it possible to more accurately predict the course of the disease.

not work, since all NRTs are deep located tumors. As a result, the

2 | METHODS

2.1 | Case series

The retrospective study included 192 patients with primary RLPS who underwent radical surgical 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 (MO). After revision, the histological types of liposarcoma were determined in accordance with the requirements of the WHO classification.⁴ The histological grade of malignancy was determined in accordance with the criteria FNCLCC/WHO.⁴ We studied the frequency of occurrence of different values of the criteria T, N, and G, the stage of the disease in accordance with TNM8. A comparative assessment of OS and RFS was carried out depending on the status of "T," "G," and the stage of the disease. Also, in order to consider new criteria for improving the predictive accuracy of TNM classification, the OS and RFS were analyzed depending on the invasion of liposarcoma into adjacent organs; gradation according to the new "T" criterion and stages which were modified by us.

2.2 | 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.

3 | RESULTS

One hundred ninety patients underwent radical surgical treatment. Exploratory laparotomy was performed in two cases; cases were recognized as inoperable (one case with RLPS G1, the second - RLPS G3). There were 127 women and 65 men with a median age at diagnosis of 54 years (range, 17-80). RLPS were represented by the following histological types: well-differentiated liposarcoma low grade (G1) in 112 cases (58.5%): dedifferentiated liposarcoma high grade (G2-3) in 75 cases (39%); myxoid liposarcoma high grade (G2-3) in four cases (2%); high grade pleomorphic liposarcoma (G3) was detected in one case (.5%). The frequency of occurrence of each histological type of RLPS was comparable with the world statistics.^{4,9,10,18,19} The T- status of the primary tumor was as follows: T1 in one case (.5%), T2 in five (2.5%), T3 in eight (4%), T4 in 178 cases (93%). Lymph node metastases were not detected in any case. RLPS low grade (G1) accounted in 112 cases (58%), and RLPS high grade (G2-3) were noted in 80 cases (42%). The disease was determined by the TNM8 stage: stage IA was detected in one case (.5%), IB in 111 (58%), IIIB in 80 cases (41.5%).

According to the TNM8, the effect of category "T" on OS and RFS was justified to study separately in the groups of patients with RLPS (G1) and the RLPS (G2-3). The first group included 112 patients with RLPS (G1). The T-status was as follows: T1 in one case (1%), T2 in five (4.5%), T3 in six (5.5%), T4 in 100 cases (89%). In the analysis of survival, T1 and T2 subgroups were combined due to the insufficient number of cases. A significant difference in OS was achieved between T1-2 and T4 (p = .005); T3 and T4 (p = .008). Differences between groups T1-2 and T3 were statistically insignificant (p = .695). The 10-year OS rates in the T1-2, T3 and T4 groups were 67%, 67%, and 25%, respectively. When comparing RFS, a significant difference was achieved between T1-2 and T4 (p = .007); T3 and T4 (p = .002). Differences between groups T1-2 and T3 were statistically insignificant (p = .478). The 5-year RFS rates in groups with T1-2, T3, and T4 were 67%, 67%, and 30%, respectively.

The second study included 80 patients with RLPS (G2-3). The Tstatus was as follows: there were no tumors with T1 and T2, T3 in two cases (2.5%), T4 in 78 cases (97.5%). Thus, it was not possible to conduct a comparative assessment of survival depending on the "T" criterion by TNM8.

Following that, the analysis of OS and RFS was carried out, taking into account the grade of the RLPS.

OS and RFS were significantly worse in RLPS (G2-3) in comparison with the RLPS (G1) (p = .000). Median OS in the G1 - group was 136 (95% CI, 120, 152) months; G2-3 - 50 (95% CI, 41, 59) months, the 5-year OS rates were 73% and 28%, respectively. The median RFS in the G1 - 52 (95% CI, 39, 65) months; in the G2-3 - 18 (95% CI, 13, 23) months, the 2-year RFS rates were 73% and 23%, accordingly.

In addition, the analysis of OS and RFS of patients was carried out depending on the stage of the disease according to TNM8. In the analysis of survival, patients with stage IA and IB were combined due to the insufficient number of cases. OS and RFS were significantly worse in RLPS stage IIIB compared to stages IA-IB (p = .000). Median OS in

group IA-IB was 136 (95% CI, 120, 152) months; in group IIIB - 50 (95% CI, 41, 59) months, the 5-year OS rates - 73% and 28%, accordingly. Median RFS in group IA-IB was 52 (95% CI, 39, 65) months; in group IIIB - 18 (95% CI, 13, 23) months, the 2-year RFS rates - 73% and 23%, respectively.

In continuation, an intragroup analysis was performed in RLPS high grade in order to find differences between G2 and G3 in survival. The G2-group included 52 (66%) patients and the G3 - 27 (34%). The analysis of OS and RFS was performed; there was no significant difference between G2 and G3 (p > .067).

We then looked for new criteria to improve the predictive accuracy of the TNM classification.

One hundred ninety patients were included in the analysis in accordance with the criterion "ingrowth of liposarcoma into organs and volume of surgery." Two patients were excluded due to nonradical operations.

The first group "surgery without organ removal" due to their intactness included 75 (40%) patients; in the second group "combined operation without histologically confirmed visceral invasion" - 48 (25%) patients; in the third group "combined operation with histologically confirmed visceral invasion" - 67 (35%) patients. The highest OS was achieved in the group "surgery without organ removal," while the shortest OS was observed in the group "combined operation with histologically confirmed visceral invasion" (p = .000). A significant difference was achieved between groups 1 and 3, groups 2 and 3 (p = .000). There was no significant difference in OS between groups 1 and 2 (p = .789). The medians OS in the 1st, 2nd and 3rd groups were 119 (95% CI, 87, 151), 130 (95% CI, 118, 142) and 51 (95% CI, 13, 89) months, respectively. The 5-year OS rates were 65%, 82%, and 23%, respectively; the 10-year rates OS - 21%, 38%, and 2%, accordingly. The RFS was better in group "combined operation without histologically confirmed visceral invasion" than in group "surgery without organ removal." The shortest RFS was noted in the group "combined operation with histologically confirmed visceral invasion" (p = .000). A statistically significant difference was achieved between each group (p < .011). The medians RFS in the 1st, 2nd, and 3rd groups were 32 (95% CI, 24, 40), 69 (95% CI, 52, 85), and 18 (95% CI, 12, 24) months. The 2-year RFS rates in the 1st, 2nd, and 3rd groups were 61%, 89% and 20%, accordingly; the 5-year RFS rates - 22%, 47%, and 2%, respectively.

Further, we have proposed a new grading system for the "T" criterion based on the following provisions:

- The incidence of tumors less than 15 cm among all primary RLPS tracked by us for 15 years was only 7%, and among RLPS G2-3

 2.5%. Therefore, it is advisable to subdivide T1 and T2 tumors relative to the larger size of the neoplasm -20 cm.
- 2. The influence of histologically confirmed tumor invasion into adjacent organs on the prognosis revealed in our study indicates the need to take this factor into account in the stratification of patients according to the T criterion.

The patients were divided into comparison groups, which included the following gradation of RLPS according to the "T" criterion: T1 < 20 cm; T2 > 20 cm; T3-histologically confirmed ingrowth of the tumor into adjacent organs. The OS and RFS were analyzed (Figure 1A,B)

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The RLPS G1 group included 112 patients. T1 in 23 (20%) cases, T2 in 60 (54%), T3 in 29 (26%). The OS differs significantly between the groups with the "T" grading we proposed. The highest OS was achieved in T1, while the shortest in T3 (p = .000). A statistically significant difference was also achieved between T1 and T2 (p = .001); T2 and T3 (p = .002). The medians OS in the groups with T1, T2, and T3 were 225 (95% CI, 159, 290), 130 (95% CI, 117, 143) and 84 (95% CI, 67, 101) months, respectively. The 5-year OS rates in the groups with T1, T2, and T3 were 96%, 83%, and 32%, respectively; the 10-year OS rates were 61%, 28% and 3%, accordingly. RFS also differs between groups. The highest RFS was achieved in T1, while the shortest in T3 (p = .001). A statistically significant difference was also achieved between T1 and T2 (p = .029); T2 and T3 (p = .000). The medians RFS in the T1, T2, and T3 were 80 (95% CI, 67, 93),53 (95% CI, 39, 67), and 26 (95% CI, 20, 32) months, respectively; the 2-year RFS rates were 88%, 80%, and 31%; the 5-year RFS rates - 64%, 40%, and 0%, accordingly.

The RLPS G2-3 group included 80 patients. Tumors with T1 in 11 (14%) cases, T2 in 28 (35%), T3 in 41 (51%). The highest OS was achieved in T1, while the shortest in T3 (p = .001). A significant difference was also achieved between T1 and T2 (p = .016); T2 and T3 (p = .006). The medians OS in the T1, T2 and T3 were 90 (95% CI, 73, 107), 52 (95% CI, 39, 65), and 26 (95% CI, 20, 32) months, respectively; the 5-year OS rates were 80%, 33%, and 14%, respectively. RFS also differs between groups. The highest RFS was achieved in T1, while the shortest in T3 (p = .002). A significant difference was also achieved between T2 and T3 (p = .000). The medians RFS in the T1, T2, and T3 were 24 (95% CI, 19, 29), 24 (95% CI, 21, 27), and 11 (95% CI, 4, 18) months, respectively; the 2-year RFS rates were 45%, 42% and 5%, respectively.

The project of new TNM classification for RLPS was developed taking into account the survival rates with new criteria «T» received in this study and degree of malignancy (Table 1). According to it, patients were grouped by disease stages; then curves of survival were constructed (Figures 2A,B).

Stage IA included 23 (12%) patients; stage IB - 60 (31%); stage II - 40 (21%); stage IIIA - 28 (15%); stage IIIB - 41 (21%).

OS differs significantly between all groups. The highest OS was achieved in the stage IA, while the shortest OS was achieved in IIIB (p = .000). A statistically significant difference was achieved between stages IA and IB (p = .001); IA and II,IIIA,IIIB (p = .000); IB and II (p = .000); IB and IIIA, IIIB (p = .000); II and IIIA (p = .000); II and IIIB (p = .000); III and IIIB (p = .000); III and IIIB (p = .000). The medians OS in the stages IA, IB, II, IIIA, and IIIB were **225** (95% CI, 159, 291), **130** (95% CI, 117, 143), **85** (95% CI, 82, 88), **52** (95% CI, 39, 65), and **26** (95% CI, 19, 32) months, respectively; the 5-year OS rates were 100%, 84%, 44%, 32% and 11%, respectively; the 10-year OS rates - 61%, 28%, 5%, 4%, and 0%, accordingly. The highest RFS was achieved in the stage IA, while the shortest RFS was achieved in the stage IIIB (p = .000). A significant difference was also achieved between stages IA and IB (p = .029); IA and II, IIIA, IIIB (p = .000); IB and II, IIIA, IIIB (p = .000). II and IIIB (p = .000); II and III IIIA, IIIB (p = .000); II and III IIIA, IIIA, IIIB (p = .000); II and III III (p = .000); II and III, IIIA, IIIA, IIIB (p = .000); II and IIIB (p = .000); II and III IIIA, IIIA, IIIB (p = .000); II and III III (p = .000); II and II, IIIA, IIIA, IIIB (p = .000); II and IIII (p = .000); III and III (p = .000); III and IIII (p = .000); III and III (p = .000); III and III (p = .000); III and III (p = .000); III and IIII (p = .000); III and IIII (p = .000); III (p = .000); III and IIII (p = .000); III (p = .00

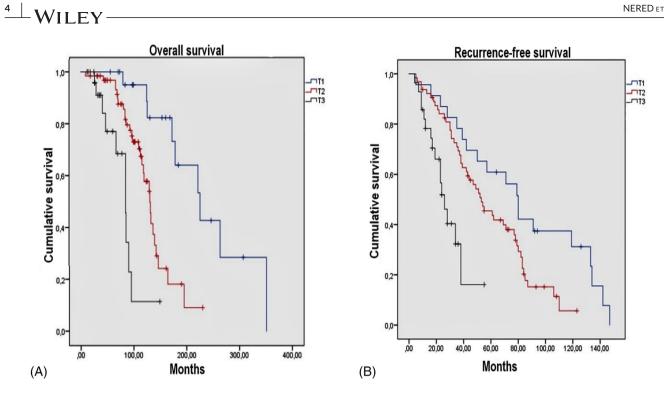


FIGURE 1 (A and B) Overall (A) and recurrence-free (B) survival, depending on gradation "T" criterion proposed by us [Colour figure can be viewed at wileyonlinelibrary.com]

Stages	\mathbf{T}^{\dagger}	G	N	М	The median OS, months	The median RFS, months
IA	Т1	G1	NO	MO	225	80
IB	Т2	G1	NO	MO	130	53
II	Т3	G1	NO	MO	84-90	24-26
	Т1	G2-3				
IIIA	T2	G2-3	NO	MO	52	24
IIIB	Т3	G2-3	NO	MO	26	11
	T - any	G - any	N1	MO	No data	No data
IV	T - any	G - any	N - any	M1	No data	No data

TABLE 1 Our project of the TNM classification of retroperitoneal liposarcoma

Abbreviations: OS, overall survival; RFS, recurrence-free survival.

[†]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).

and IIIB (p = .000). The medians RFS in the stages IA, IB, II, IIIA, and IIIB were 80 (95% CI,67, 93), 53 (95% CI, 39, 67), 24 (95% CI, 20.28), 24 (95% CI, 21, 27), 11 (95% CI, 5.18) months, respectively; the 2-year RFS rates were 87%, 81%, 36%, 35%, and 5%, accordingly; the 5-year RFS rates - 57%, 38%, 4%, 0%, and 0%, respectively.

DISCUSSION 4

This investigation demonstrates the "T" criterion proposed by the TNM8 is irrelevant due to RLPS being regarded as T4 in 93% of cases. This is also evidenced by the majority of research papers on retroperitoneal tumors, in particular liposarcomas.^{7,8-13} Our study demonstrates no significant difference in the OS and RFS in RLPS G1 when comparing T1-2 and T3. A significant difference was achieved only between T1-3 and T4. In RLPS G2-3, it is not possible to conduct an intergroup survival analysis due to RLPS G2-3 being regarded as T4 in 97% of cases. Based on the above, the "T" criterion according to the TNM8 does not correlate with the prognosis in RLPS. The discrepancy between the category «T» and the actual size of the RLPS leads to inadequate staging of the disease. Among 192 patients who underwent surgical treatment, there were no cases with stages II, IIIA, so two

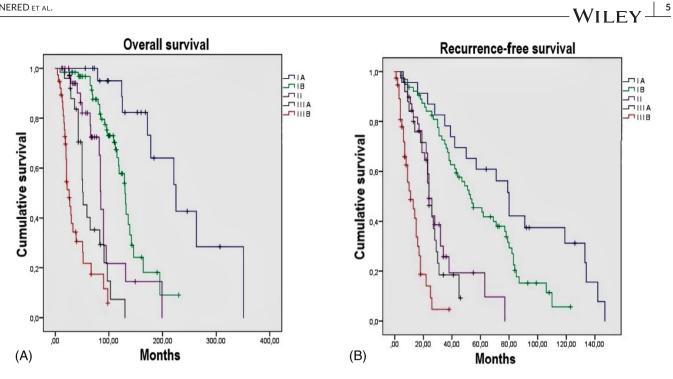


FIGURE 2 (A) Overall survival (OS) of patients in accordance with the proposed TNM classification of malignant tumors for retroperitoneal liposarcoma (LPS). (B) Recurrence-free survival (RFS) of patients in accordance with the proposed TNM classification of liposarcoma. The Kaplan-Meier Method [Colour figure can be viewed at wileyonlinelibrary.com]

of the six prognostic groups did not find their application during a 15year period. It should be noted, that there was no significant difference between RLPS grade 2 and RLPS grade 3 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.

In our study, there is no metastatic lesion of the lymph nodes in RLPS. The rare occurrence of lymphogenic metastases in RLPS is confirmed by the experience of foreign researchers. Since 1987, only 10 cases of metastatic lesions of the lymph nodes in liposarcomas with a predominant localization of primary tumors in the soft tissues of the trunk and extremities have been recorded in the press.²⁰⁻²³ Thus, the state of the lymph nodes has an extremely limited prognostic value in RLPS. However, we could not refuse to use the TNM abbreviation in the staging system, since according to the literature, lymphogenic metastases still occur in this tumor, and the frequency of distant metastases in dedifferentiated, pleomorphic, and myxoid liposarcoma is quite high. Not having our own data on the survival of patients with N+ or M1, we considered it possible to leave the N and M stages as they were in the TNM8, relying on the authoritative opinion of the AJCC/UICC. Our chosen strategy is that the cases with N+ and M1 in the proposed classification are assigned to the "terminal" stages by analogy with the TNM8. This study demonstrates only the degree of malignancy has a prognostic value in the TNM8. Looking for ways to improve TNM, we changed the threshold value of the tumor size from 15 to 20 cm. Another significant sign is the ingrowth into adjacent organs. The «T» category proposed by us (T1 < 20 cm; T2 > 20 cm; T3 -ingrowth into organs) showed significant differences in survival. Their use helps to achieve significant differences in survival between all groups of patients formed by the new TNM-stages.

CONCLUSION 5

The TNM8 does not accurately reflect the prevalence of the tumor and the prognosis of the disease in RLPS. In view of the fact that RLPS have certain features (the size is larger than in other non-organ retroperitoneal tumors, extremely rare lymphogenic metastasis) and account for more than 50% of the total number of retroperitoneal tumors, it is advisable to create a special TNM classification for RLPS in order to adequately stage and predict the disease. Revision of the T-staging is necessary to improve the accuracy of the prognosis in RLPS. The modified by us TNM classification with new category «T» demonstrated a more adequate distribution of patients by stages and the reliability of intergroup differences in the survival rate.

CONFLICT OF INTEREST

The authors declare the lack of the possible conflict of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

DATA AVAILABILITY STATEMENT

All 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 is available from the corresponding author upon reasonable request.

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How to cite this article: Nered SN, Volkov AY, Kozlov NA, Stilidi IS, Arhiri PP. TNM classification of malignant tumors: Eighth edition for retroperitoneal liposarcoma. Ways to improve. *Asia-Pac J Clin Oncol*. 2022;1-6. https://doi.org/10.1111/ajco.13898