



# Retroperitoneal Liposarcoma: Rational Extent of Surgery Tailored to Grade of Malignancy

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## Abstract

This study was aimed at determining the indications for combined and organ-preserving operations. The study included 190 patients with retroperitoneal liposarcoma (RLPS). The influence of the following factors on the overall survival (OS) and recurrence-free survival (RFS) were studied: involvement of adjacent organs in the tumor, volume of surgical intervention. OS and RFS were worse in pathologically confirmed visceral invasion in the both RLPS low grade and high grade ( $p=0.000$ ). In RLPS low grade, there was no significant difference in OS and RFS between the group of patients who underwent combined surgery without confirmed visceral invasion and the group of patients who underwent organ-preserving surgery ( $p>0.080$ ). In RLPS high grade, OS and RFS were higher in the group of patients who underwent combined surgery without confirmed visceral invasion than in the group of patients who underwent organ-preserving surgery ( $p<0.050$ ). In RLPS low grade, it is advisable to perform organ-preserving operations, including nephrosaving operations. In RLPS high grade, the organ-preserving operations worsen long-term results and prognosis. Combined operations including nephrectomy are justified in RLPS high grade.

**Keywords** Liposarcoma · Sarcoma · Surgery

## Introduction

Soft tissue sarcomas (STS) are an extensive group of relatively rare mesenchymal neoplasms with variable malignancy potential. Retroperitoneal localization of STS is observed in 10–15% of cases [1]. The most common

retroperitoneal mesenchymal tumor is liposarcoma, the proportion of which exceeds 50% of the total number of sarcomas [2]. Retroperitoneal liposarcoma (RLPS) are divided into 4 histological types (well-differentiated liposarcoma, dedifferentiated liposarcoma, myxoid liposarcoma, pleomorphic liposarcoma), each of which has features in the clinical course and a different prognosis [3]. As a rule, RLPS reach large sizes due to the long-term asymptomatic course associated with the localization and biological characteristics of the tumor. Thus, according to a number of authors, the average size of RLPS is 15–25 cm (at the time of initial detection) [1, 3–11]. In addition, in some cases, RLPS demonstrates the invasion into adjacent organs and structures. Surgery is still the only potentially radical method of treatment of patients with RLPS. Performing a wide excision of the tumor is difficult or impossible due to the anatomical features, and as a result, the frequency of local recurrence is the highest [1, 3–11]. The issue of the required volume of surgical intervention in RLPS has not yet been finally resolved and it is of particular interest. The literature data is contradictory. Some studies demonstrate the need for combined operations with the removal of adjacent organs in order to achieve maximum radicalism and improve long-term results

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[8, 12–15]. Other studies show that combined operations against the background of a possible increase in postoperative complications do not improve survival [9, 16, 17]. A number of researchers in determining the surgical strategy focus on the biology of the tumor, linking the effectiveness of combined interventions with the degree of malignancy or histological type of STS. So, Gronchi A. et al. reported about improved overall survival after extended surgical treatment in patients with STS low and middle malignancy [18]. At the same time, many studies have shown that with less aggressive histological types of STS, with technical capabilities, it is advisable to perform radical organ-preserving operations [2, 4, 19–27]. The purpose of this work is to determine the indications for combined and organ-preserving operations in retroperitoneal liposarcomas, taking into account the grade of malignancy of the tumor.

## Methods

### Case Series

Retrospectively analyzed data of prospectively maintained database. The study included 190 patients who underwent radical surgery (R0-negative margins) for primary RLPS in FSBI «National Medical Research Center of Oncology named after N.N. Blokhin» of the Ministry of Health of Russia in the period from 2004 to 2018 years. 162 patients followed up for 2 years; 110 patients followed up for 5 years; 41 patients followed up for 10 years. Patients with primary multiple malignant tumors were not included in the study. All patients had no distant metastases (M0). After reviewing the histological preparations of the surgical material, the pathologist determined the histological types of liposarcoma in accordance with the requirements of the WHO classification of bone and soft tissue tumors [3]. The histological grade of malignancy was determined in accordance with the FNCLCC/WHO criteria [3]. The stage of the disease is established according to the TNM classification of malignant tumors of the 8th edition [28]. The influence of the following factors on the long-term results of surgical treatment was studied: the grade of malignancy of the tumor; the combined method of treatment; involvement of adjacent organs in the tumor, resection/removal of adjacent organs. Separately, the question of the feasibility of nephrosaving operations and nephrectomy in RLPS is considered.

### 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. It was significant when the  $p$  value  $< 0.05$ .

## Results

190 patients who underwent radical surgery (R0) for primary RLPS were included in the analysis. There were 126 women and 64 men with a median age at diagnosis of 54 years (range, 17–80). RLPS are represented by the following histological types: well-differentiated liposarcoma low grade (G1) in 111 cases (58.5%); dedifferentiated liposarcoma high grade (G2-3) in 74 cases (39%), while in 49 (66%) cases corresponded to grade 2, in 25 (34%) cases—grade 3; myxoid liposarcoma high grade (G2-3) in 4 cases (2%); pleomorphic liposarcoma grade 3 was detected in one case (0.5%). The frequency of occurrence of each histological type of RLPS was comparable to the world statistical data [3, 5, 10, 29–31]. The size of the primary RLPS G1 in the largest dimension varied from 5 to 65 cm, the median—27 cm. The size of the primary RLPS G2-3 varied from 15 to 60 cm, the median – 28 cm. The "T" status of the primary tumor was as follows: T1 in 1 case (0.5%), T2 in 5 (2.5%), T3 in 8 (4%), T4 in 176 cases (93%). Metastatic involvement of the lymph nodes was not detected in any case. According to the grade of malignancy, RLPS low grade (G1) were 111 cases (58%), and RLPS high grade (G2-3) were noted in 79 cases (42%). The disease was staged according to the TNM classification of the 8th edition: stage IA was detected in 1 case (0.5%), stage IB in 110 (57.5%), stage IIIB in 79 cases (42%). The severity of concomitant pathology and the functional state of patients according to the ASA – classification (American Society of Anesthesiologists), as well as the size of the tumor in the compared groups did not differ.

The analysis of overall (OS) and recurrence-free (RFS) survival was carried out, taking into account the grade of RLPS. OS and RFS were statistically significantly worse in RLPS high grade vs RLPS low grade ( $p = 0.000$ ). The median OS in the low grade group was 136 (95% CI, 120, 152) months; in the high grade group—50 (95% CI, 41, 59) months, the 5-year OS rates were 73% and 28%, respectively. The median RFS in the low grade group was 52 (95% CI, 39, 65) months; in the high grade group—18 (95% CI, 13, 23) months, the 2-year RFS rates were 73% and 23%, respectively.

Then, an intragroup analysis was performed 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 were no significant difference between G2 and G3 ( $p > 0.067$ ).

Due to the undeniable influence of the grade of RLPS on the long-term results, further studies were conducted separately in RLPS low grade and RLPS high grade.

The fact of ingrowth into adjacent organs was established taking into account the volume of surgical intervention performed and the results of morphological examination. In RLPS low grade in 86 (77%) cases, according to the histological conclusion, visceral invasion was absent; in 25 (23%) cases, the morphologist confirmed the ingrowth of RLPS into adjacent organs. In high grade, there was no visceral invasion in 37 (47%) cases; in 42 (53%) cases, the ingrowth of RLPS into the adjacent organs was confirmed. The tumor was significantly more likely to grow into adjacent organs in RLPS high grade than in RLPS low grade (53% vs. 23%,  $p=0.000$ ).

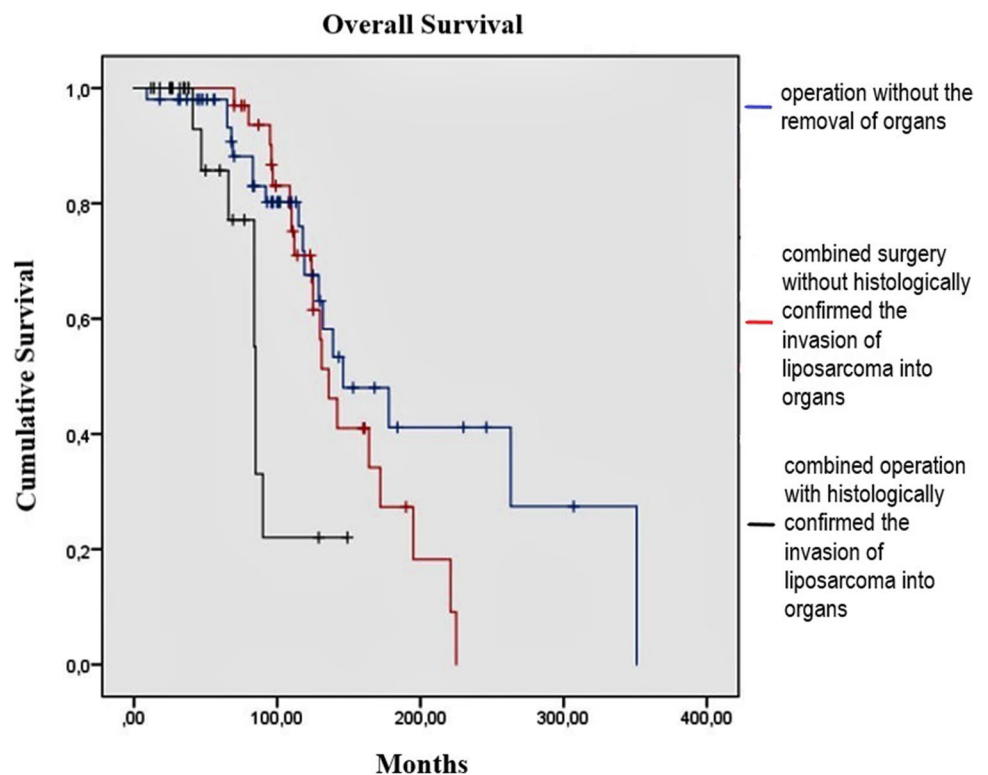
Following that, we have studied the effect on the long-term results of tumor ingrowth into adjacent organs and the volume of surgery separately in RLPS low grade and RLPS high grade. The most frequently removed organ in primary RLPS was the kidney (in 52% of cases), other organs and structures (small or large intestine, pancreas, liver, diaphragm, stomach, lung, aorta, inferior vena cava, iliac vessels, etc.) were less frequently removed/resected.) There was no postoperative mortality.

111 patients with RLPS low grade were divided into comparison groups. The first group "operation without removal of organs" included 52 (47%) patients; the second group "combined operation without histologically confirmed

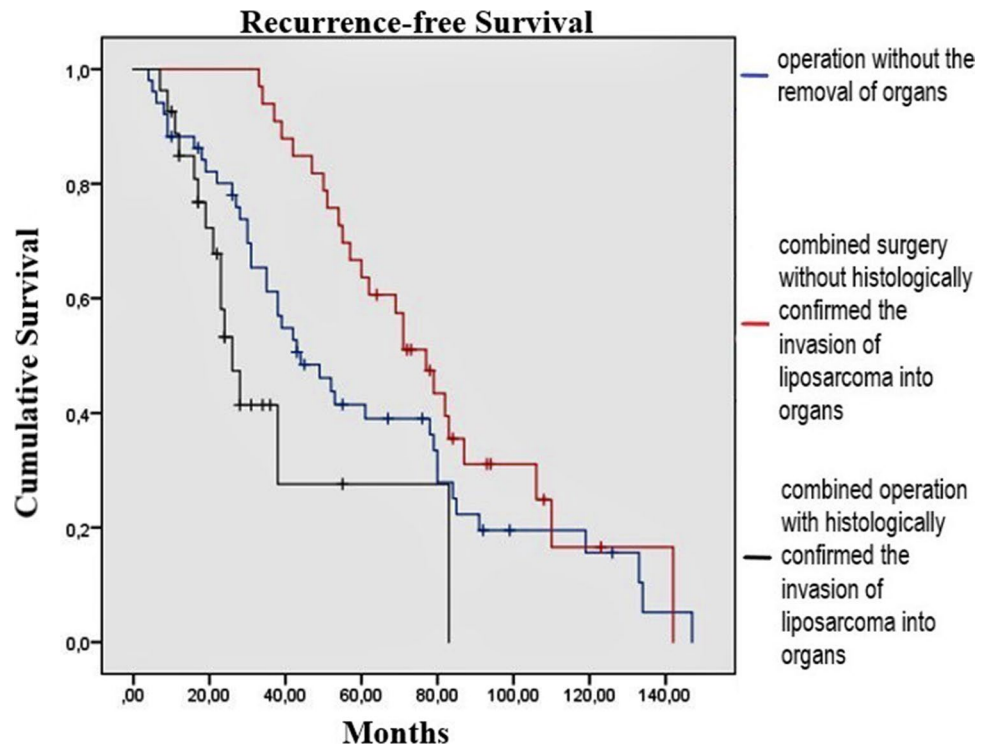
ingrowth of liposarcoma into organs"—34 (31%) patients; the third subgroup "combined operation with histologically proven ingrowth of liposarcoma into organs"—25 (22%) patients. The results of the comparative inter-group analysis of OS and RFS are presented in Fig. 1, 2. OS was significantly worse in the group of patients whose morphological examination revealed the ingrowth of RLPS into adjacent organs than in the groups without ingrowth. ( $p=0,000$ ). A significant difference was achieved between 1 and 3 groups ( $p=0.010$ ), 2 and 3 ( $p=0.002$ ). A significant difference between the 1 and 2 groups was not achieved ( $p=0.222$ ). The medians OS in the 1, 2 and 3 groups were 146 (95% CI, 92, 200), 136 (95%CI, 120, 152) and 85 (95% CI, 84, 86) months, respectively; the 10-year OS rates were 32%, 47% and 4%, accordingly. RFS was significantly worse in the group of patients whose morphological examination revealed the ingrowth of RLPS into adjacent organs than in the groups without ingrowth. ( $p=0,000$ ). A significant difference was achieved between the 1 and 3 groups ( $p=0.047$ ), 2 and 3 ( $p=0.000$ ). A significant difference between the 1 and 2 groups was not achieved ( $p=0.080$ ; log-rank test). The medians RFS in the 1, 2 and 3 groups were 44 (95% CI, 29, 59), 77 (95% CI, 65, 89) and 26 (95% CI, 20, 32) months, respectively; the 5-year RFS rates were 31%, 66% and 4%, accordingly.

Then, 79 patients with RLPS high grade were divided into comparison groups. The first group "operation without removal of organs "included 22 (28%) patients; the second

**Fig. 1** OS of patients depending on the type of operation and the presence or absence of visceral invasion in RLPS low-grade. The Kaplan–Meier method



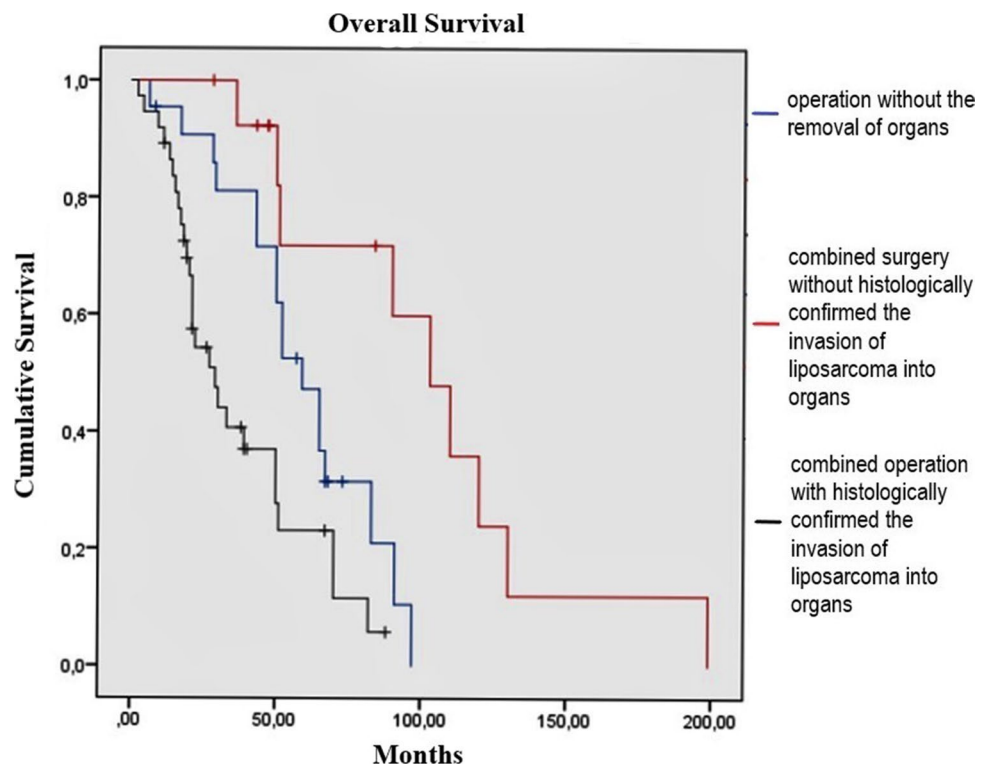
**Fig. 2** RFS of patients depending on the type of operation and the presence or absence of visceral invasion in RLPS low-grade. The Kaplan–Meier method



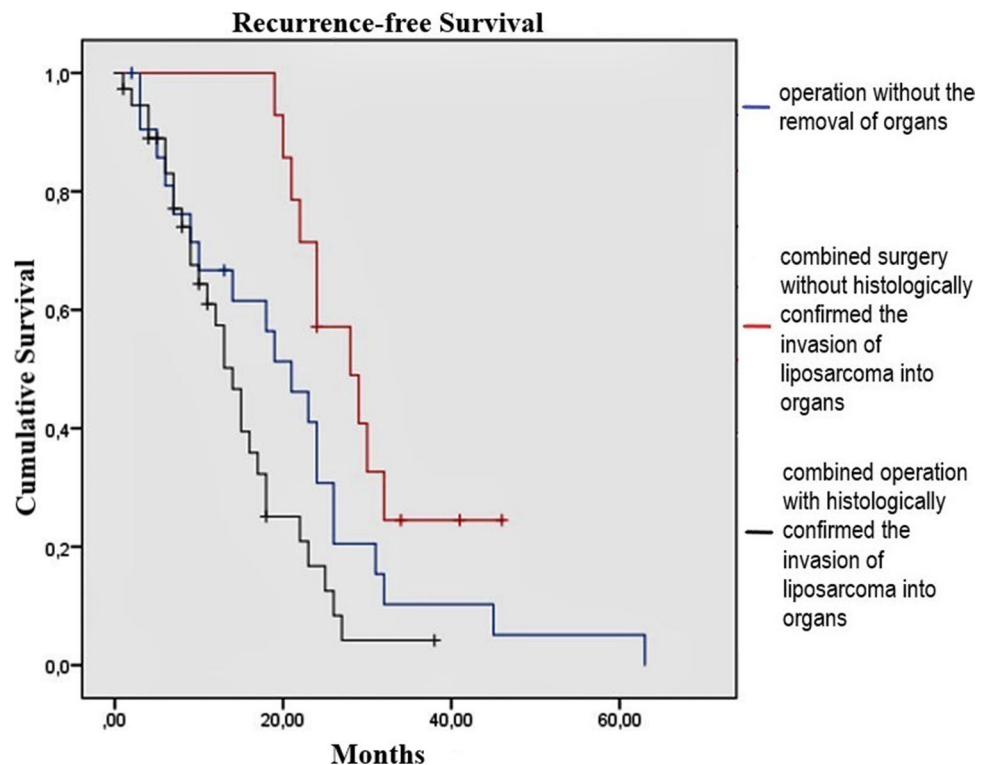
group" combined operation without histologically confirmed ingrowth of liposarcoma into organs" - 15 (19%) patients; the third group" combined operation with histologically proven ingrowth of liposarcoma into organs"—42

(53%) patients. The results of the comparative inter-group analysis of OS and RFS are presented in Fig. 3, 4. OS was significantly worse in the group of patients whose morphological examination revealed the ingrowth of RLPS

**Fig. 3** OS of patients depending on the type of operation and the presence or absence of visceral invasion in RLPS high-grade. The Kaplan–Meier method



**Fig. 4** RFS of patients depending on the type of operation and the presence or absence of visceral invasion in RLPS high-grade. The Kaplan–Meier method



into adjacent organs than in the groups without ingrowth. ( $p=0,000$ ). It should be noted that the OS was significantly higher in the group of patients who underwent a combined operation without ingrowth of RLPS into the organs than in the group of patients who had only RLPS removed (organ-preserving operations) ( $p=0.006$ ). Also, a significant difference was achieved between the 1 and 3 groups ( $p=0.017$ ); 2 and 3 ( $p=0.000$ ). The medians OS in the 1, 2 and 3 groups were 59 (95% CI, 46, 72), 103 (95%CI, 76, 130) and 29 (95% CI, 6, 40) months, respectively; the 5-year OS rates were 43%, 54% and 11%, accordingly. RFS was significantly worse in the group of patients whose morphological examination revealed the ingrowth of RLPS into adjacent organs than in the groups without ingrowth. ( $p=0,000$ ). It should be noted that RFS was significantly higher in the group of patients who underwent a combined operation without ingrowth of RLPS into the organs than in the group of patients who had only RLPS removed (organ-preserving operations) ( $p=0.053$ ). Also, a significant difference was achieved between the 2 and 3 groups ( $p=0.000$ ). No significant difference was achieved between the 1 and 3 groups ( $p=0.108$ ). The medians RFS in the 1, 2 and 3 groups were 21 (95% CI, 14, 28), 28 (95% CI, 20, 36) and 14 (95% CI, 11, 17) months, respectively; the 2-year RFS rates were 29%, 54% and 8%, accordingly.

### Nephrectomy or nephrosaving surgery?

In order to consider the feasibility of nephrectomy in the technically possible performance of nephrosaving surgery, a comparative inter-group analysis of RFS was performed separately in RLPS low grade and RLPS high grade. This analysis included patients who, according to the preoperative assessment of the prevalence of the tumor process using spiral computed tomography with bolus amplification, direct angiography and magnetic resonance imaging, according to the indications, revealed a muff-like (the tumor covers the kidney from all sides) or zonal (only the pole(s) of the kidney with or without a renal pedicle) involvement of the kidney in the RLPS. The first group—"nephrosaving" surgery included patients who underwent radical surgery without removing adjacent organs, but with the removal of pararenalis adipose tissue with the removal or preservation of the fibrous capsule of the kidney. The comparison group—"removal of the tumor with nephrectomy" included patients who underwent radical surgery to remove the tumor with nephrectomy with or without adrenalectomy, but the histological examination of the surgical material did not confirm the organ invasion.

56 patients with RLPS low grade were divided into comparison groups. The first group "nephrosaving" operation included 38 (68%) patients; the second group "removal of

a tumor with nephrectomy"—18 (32%) patients. A significant difference between the first and second groups was not achieved ( $p=0.456$ ). The median RFS in the first group was 49 (95% CI, 29, 69) months; in the second group was 57 (95% CI, 42, 71) months. The 5-year RFS rates in groups 1 and 2 were 32% and 44%, respectively.

Then, 24 patients with RLPS high grade were divided into comparison groups. The first group "nephrosaving" operation included 16 (67%) patients; the second group "removal of a tumor with nephrectomy"—8 (33%) patients. RFS was statistically significantly worse in the first group of patients—"nephrosaving" surgery, than in the group "removal of the tumor with nephrectomy" ( $p=0.039$ ). The median RFS in the first group was 21 (95% CI, 11, 31) months; in the second group, 24 (95% CI, 16, 32) months. The 2-year RFS in groups 1 and 2 were 19% and 50%, respectively.

## Discussion

We conducted a retrospective study to determine the indications for combined and organ-preserving operations in retroperitoneal liposarcomas. This work demonstrates that the long-term results of surgical treatment (OS and RFS) were significantly worse in RLPS high-grade compared to RLPS low-grade ( $p=0.000$ ). At the same time, it should be noted that there was no significant difference in OS and RFS, depending on the degree of malignancy in RLPS grade2 and grade3. This fact is consistent with the TNM classification of the eighth edition in the staging of retroperitoneal sarcomas, which combines G2 and G3 sarcomas into a single group of "high-grade" tumors [28].

Special attention should be paid to the fact of the frequency of histologically confirmed ingrowth of RLPS into adjacent organs in RLPS low grade—23% of cases, in RLPS high grade – 53% of cases. Analyzing the effect on long-term results of the degree of involvement adjacent organs in the tumor conglomerate and the volume of the operation, it was found that OS and RFS were significantly worse in histologically confirmed ingrowth of RLPS into adjacent organs in both RLPS low grade and RLPS high grade ( $p=0.000$ ). At the same time, special attention should be paid to the absence of a significant difference in OS and RFS when comparing groups of patients with RLPS low grade, who underwent a combined operation and organ-preserving. On the contrary, in RLPS high grade, OS and RFS were significantly higher in the group of patients who underwent combined surgery without ingrowing RLPS into organs (according to histological examination) than in the group of patients who had only RLPS removed (organ-preserving operations) ( $p<0.050$ ). Also, after conducting a comparative analysis of the feasibility of performing nephron-preserving operations

and nephrectomies in RLPS, excluding patients with histologically confirmed ingrowth of RLPS into the kidney, we obtained similar results. Thus, in RLPS low-grade, a significant difference in RFS between the groups "nephrosaving surgery" and "nephrectomy" was not achieved ( $p=0.456$ ). At the same time, in RLPS high grade, RFS was significantly worse in the group of patients with "nephrosaving" surgery than in the group of "tumor removal with nephrectomy" ( $p=0.039$ ). Taking into account the results obtained, it can be concluded that in RLPS low grade, it is advisable to perform organ-preserving operations, including nephrosaving (in technically possible cases), i.e., the involvement of the kidney and its capsule (fat, as well as fibrous) in the tumor process is not an absolute indication for nephrectomy. On the contrary, combined operations, including nephrectomy (when the adipose and fibrous capsule of the kidney is involved in the tumor) are justified in RLPS high-grade. However, small sample size and retrospective type of study remains a limitation of our study.

## Conclusion

Surgical intervention is the only potentially radical method of treating patients with RLPS. In RLPS low grade, it is advisable to perform organ-preserving operations, including nephrosaving operations. On the contrary, in RLPS high-grade, organ-preserving operations worsen the long-term results (OS and RFS) and the prognosis. Combined operations, including nephrectomy, are justified in RLPS high-grade.

**Author Contribution** All authors have contributed significantly.

All authors are in agreement with the content of the manuscript.

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

## Declarations

**Conflicts of Interests** Authors declare lack of the possible conflicts of interests.

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