



The outcome of primary retroperitoneal sarcoma patients treated at sarcoma referral centre: the Institute of Oncology Ljubljana experience

Primarni retroperitonealni sarkomi: preživetje bolnikov, zdravljenih na Onkološkem inštitutu Ljubljana, referenčnem centru za sarkome

Marko Novak,¹ Naja Bohanec,² Andraž Perhavec,^{1,3} Sonja Kramer,¹ Darja Eržen¹

Abstract

Background: Retroperitoneal sarcomas are extremely rare, therefore, patients should be treated at sarcoma referral centre. Surgery is the mainstay of treatment. Compartmental resection is proposed as the best surgical approach.

Methods: The Institute of Oncology Ljubljana is the only referral centre for these patients in Slovenia. Data for all consecutive patients surgically treated from January 1999 to June 2020 for primary localized retroperitoneal sarcoma were extracted from a prospective surgical database. The patient outcome, quality of surgery, and postoperative adverse events were analysed.

Results: A hundred patients were eligible for the study. Their median age was 62 years. The median tumor size was 21.5 cm. Dedifferentiated liposarcoma was the most common histology (39%). Compartmental resection was performed in 24% and multivisceral resection in 25%. 29% of patients had postoperative complication grade 3a or higher according to Clavien-Dindo classification and 58.6% (17/29) of them required reoperation. The 30-day and 90-day mortality rate was 3% and 5%, respectively. The median follow-up was 55.1 months. The 5-year overall survival was 67.8%. The 5-year crude cumulative incidence of local recurrence and distant metastases were 16.9% and 21.4%, respectively. ASA score and blood loss during surgery were significant prognostic factors of overall survival.

Conclusion: Retroperitoneal sarcomas belong to the group of rare cancers. We achieve very good results in the treatment of retroperitoneal sarcoma patients and outcomes are comparable to other referral centres. Our results also confirm the crucial role of sarcoma referral centre in the management and treatment of these patients.

¹ Department of Surgical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia

² Statistics and modeling, Novartis, Mengeš, Slovenia

³ Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Correspondence / Korespondenca: Marko Novak, e: mnovak@onko-i.si

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Izvleček

Izhodišča: Retroperitonealni sarkomi so izredno redki, zato naj zdravljenje bolnikov z retroperitonealnimi sarkomi poteka v referenčnem centru. Temeljno zdravljenje je kirurško. Priporočen tip operacije je kompartment resekcija.

Metode: Onkološki inštitut Ljubljana je edini referenčni center za sarkome v Sloveniji. V raziskavo so bili vključeni bolniki s primarnim lokaliziranim retroperitonealnim sarkomom, zdravljeni pri nas v obdobju od januarja 1999 do junija 2020. Opredelili smo preživetje, kakovost kirurškega zdravljenja in zaplete.

Rezultati: Vključenih je bilo 100 bolnikov. Srednja starost je bila 62 let. Srednja velikost tumorja je bila 21,5 cm. Najpogostejši histološki podtip je bil dediferenciran liposarkom (39 %). Kompartment resekcija je bila opravljena v 24 %, multivisceralna resekcija pa v 25 %. Zaplete po posegu je imelo po klasifikaciji Clavien-Dindo stopnje 3a ali višje 29 % bolnikov, pri 58,6 % (17/29) je bila potrebna ponovna operacija. Zgodnja in pozna smrtnost po operaciji sta bili 3 % in 5 %. Srednji čas sledenja je bil 55,1 mesecev. 5-letno celokupno preživetje je bilo 67,8 %. Kumulativna verjetnost za lokalno ponovitev bolezni po 5 letih je bila 16,9 %, za oddaljene zasevke pa 21,4 %. Ocena ASA in izguba krvi med operacijo sta bila neodvisna napovedna dejavnika celokupnega preživetja.

Zaključek: Retroperitonealni sarkomi sodijo med redke vrste raka. Naši rezultati zdravljenja bolnikov z retroperitonealnimi sarkomi so zelo dobri in primerljivi z rezultati drugih referenčnih centrov iz tujine. Potrjujejo tudi ključno vlogo referenčnega centra pri obravnavi in zdravljenju teh bolnikov.

1 Introduction

Retroperitoneal sarcomas (RPS) are extremely rare. According to the literature, the incidence is 0.3–0.4/100,000 inhabitants (1), which means 6–8 patients per year for Slovenia. Surgery is the mainstay of treatment of RPS patients. Compartmental resection offers the best option for local control and the potential cure to the patients (2). This surgical procedure involves removing the tumour along with the colon, kidney, and psoas fascia or muscle. If during surgery the tumour is estimated to involve other organs, the compartmental resection is extended to multivisceral resection. In this case, the tumour is removed together with the colon, kidney, psoas fascia or muscle and all the organs involved. We speak of primary localized RPS if the patient has not yet been operated on and the disease has not spread.

Local recurrence of the disease is possible as a recurrence at the site of the primary tumour in the retroperitoneum and/or in other areas of the abdomen and/or as peritoneal sarcomatosis. In the case of liver metastases, which are classified as distant, the disease is defined as metastatic.

The benefit of preoperative radiotherapy for local recurrence in patients with primary localized RPS is still in the research phase and is therefore not routinely recommended in treatment guidelines. EORTC 62092 (STRASS 1) was the only prospective phase III randomized study comparing the impact of preoperative radiotherapy and surgery versus surgery alone on local recurrence (3). The benefit of preoperative radiotherapy in various histological subtypes of RPS was not confirmed, it was indicated

only in well-differentiated liposarcoma. The effect of chemotherapy on local recurrence or distant metastases in these patients has not been explored in the research.

The purpose of our study was to determine the parameters of survival, quality of surgical treatment and complications after surgical treatment of patients with RPS who underwent surgery at the Institute of Oncology Ljubljana (IOL). We wanted to compare our results with the results of some reference centres with a similar number of cases.

2 Methods

We analyzed data from patients treated at the IOL for primary localized RPS between January 1999 and June 2020. The primary objective of the study was to determine overall survival (OS) and the five-year cumulative incidence of local disease recurrence and distant metastases. Secondary objectives were to define the quality of surgical treatment, complications after surgical treatment, and prognostic factors of OS by multivariate analysis. The Institutional Review Board (KSOPKR-0020-2020) and the IOL Ethical Commission (ERID 0023-2020) approved the study.

The quality of surgical treatment was assessed by analyzing the status of surgical margins, duration of surgery, blood loss during surgery, complications, duration of hospitalization, and mortality after surgery. To identify possible independent prognostic factors for OS, the analysis included the ASA classification and blood loss during the surgical procedure. The ASA classification summarizes

the American Society of Anaesthesiologists' scale for categorizing the patient's physiological status prior to surgery (4). Tumour grade was based on the FNCLCC grading system (*fr.* Fédération Nationale des Centers de Lutte Contre le Cancer) (5,6).

2.1 Statistical Methods

The main objective of the study was to identify OS, local recurrence of the disease, and the occurrence of distant metastases. OS was defined as the time from surgery to the time of death or truncation, regardless of the cause of death. The survival curve was constructed using the Kaplan-Meier method. Local recurrence of the disease and the occurrence of distant metastases were defined by competing risk analysis and status analysis with the assessment of cumulative incidence.

In the competing risk analysis, the cumulative incidence of local recurrence of the disease, the occurrence of distant metastases, and death without recurrence of the disease or metastases were assessed. The first of these events was analyzed; however, the events did not coincide. In the status analysis, the probability of individual statuses over time was estimated. The analysis included local recurrence status, occurrence of distant metastases, local recurrences and distant metastases together (LR + DM), and deaths. Cox proportional hazards model was used to identify possible independent prognostic factors for OS. Results were defined as statistically significant if the *p* value was less than 0.05.

3 Results

During the period covered by the study, 134 patients underwent surgery for RPS at IOL. Patients who had undergone operations with primary metastatic disease (*n*=6), patients with residual sarcoma after being operated on in another hospital (*n*=14), and those who came for treatment due to recurrent RPS (*n*=14) were excluded from the study. The study thus included 100 patients who underwent surgery for primary localized RPS (Figure 1). The median age of patients at diagnosis was 62 years. Half of the patients were diagnosed due to a palpable tumour in the abdomen (*n*=49), 23% (*n*=23) due to other health problems, and in 28% (*n*=28) of cases the tumour was detected by chance during imaging tests. Weight loss was reported by 41% (*n*=41) of patients. Prior to surgery, fine needle aspiration biopsy was performed in 60% of patients (*n*=60), core needle biopsy in 23% (*n*=23), and both (*n*=11) were performed in 11% of patients. Only 6% (*n*=6) of patients underwent surgery without tumour

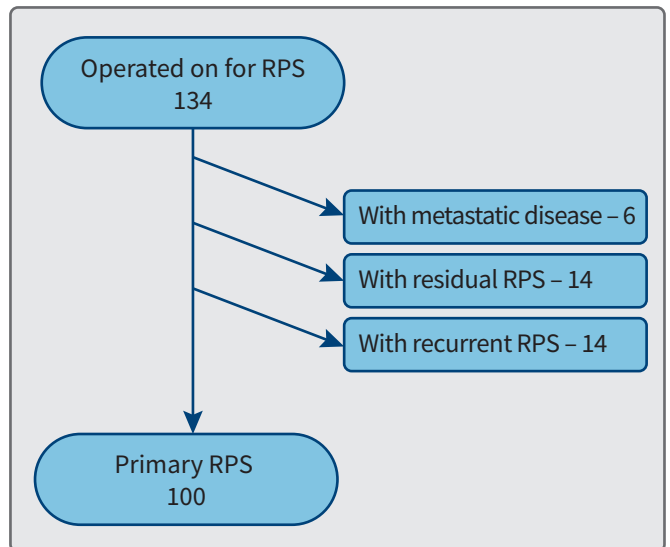


Figure 1: Selection of patients with primary localized retroperitoneal sarcoma included in the study.

Legend: RPS – retroperitoneal sarcoma.

biopsy before surgery.

The most common histological subtype was dedifferentiated liposarcoma (39%). The median tumour size was 21.5 cm. In all operations, we managed to achieve macroscopic complete resection, in 74% (*n*=74) with negative margins. Compartmental resection was performed in 24% (*n*=24) and multivisceral resection in 25% (*n*=25) of patients. Only in two patients (2%) the tumour was removed without a simultaneous resection of a larger organ. Organ removal by frequency: kidney 56%, colon 55%, adrenal gland 40%, psoas fascia 31%, psoas muscle 26%, diaphragm 19%, small intestine 12%, spleen and distal part of the pancreas 10%, inferior vena cava 8% and liver resection 5%. The median number of resected organs in surgery was four. On average, surgery lasted 7.5 hours, median time was seven hours (range 1.3–19.0). The mean blood loss during surgery was 3260 ml and the median value was 1330 ml (range 100–32000).

The median time of hospitalization after surgery was 20.5 days (range 5–102) and in the intensive care unit it was eight days (range 0–55). According to the Clavien-Dindo classification, complications after surgery, grade 3a or higher, were experienced by 29% (*n*=29) of patients and 17 patients (17/29; 58.6%) required reoperation. The most common complications were: ileus (*n*=7), sepsis (*n*=6), retroperitoneal abscess (*n*=5), bleeding (*n*=4), abdominal abscess (*n*=3), anastomotic dehiscence (*n*=2), and intestinal gangrene (*n*=1). Within 30 days after surgery, three patients died (3%), and within 90 days after surgery, five patients died (5%). Most of the data are shown in Table 1.

Table 1: Demographic, pathological and clinical data.

Characteristics	Number (% as well)
Gender	
Male	55
Female	45
Median age at diagnosis (age, range)	62 (24 – 84)
<50 years	23
≥50 years	77
Mean BMI (kg/m²)	26.9
Weight loss before treatment	41
ASA score	
ASA 1	21
ASA 2	49
ASA 3	26
ASA 4	4
Histological subtype	
Dedifferentiated liposarcoma	39
Well-differentiated liposarcoma	22
Leiomyosarcoma	16
Solitary fibrous tumour	9
Other tumours	14
Average tumour size (cm)	23.4
Median tumour size (cm, range)	21.5 (3–80)
Tumour grade (FNCLCC system)	
G1	35
G2	18
G3	35
No data	12
AJCC staging (8th edition)	
IA	1
IB	47
IIIA	7
IIIB	45

Characteristics	Number (% as well)
Postoperative complications (Clavien-Dindo classification)	
3a	7
3b	9
4	8
5	5
Preoperative treatment	
No	94
Chemotherapy	1
Radiotherapy	3
Chemotherapy and radiotherapy	2
Postoperative treatment	
No	90
Chemotherapy	1
Radiotherapy	7
Chemotherapy and radiotherapy	2
Status at the last documentation review	
Alive	61
Dead	39
Local recurrence	
No	75
Yes	25
Distant metastasis	
No	71
Yes	29

Legend: BMI – body mass index; ASA – American Society of Anesthesiologists classification; FNCLCC – *fr.* Fédération Nationale des Centres de Lutte Contre Le Cancer; G – tumour grade; AJCC – American Joint Committee on Cancer.

The median postoperative follow-up time was 55.1 months (range 1–223). 39 patients died. The corresponding five-year OS was 67.8% (Figure 2). 25 patients had local recurrence and 29 patients had distant metastases.

14 patients had local recurrence alone, six patients had local recurrence and then distant metastases, three patients had distant metastases and then local recurrence, two patients had local recurrence and concurrent distant

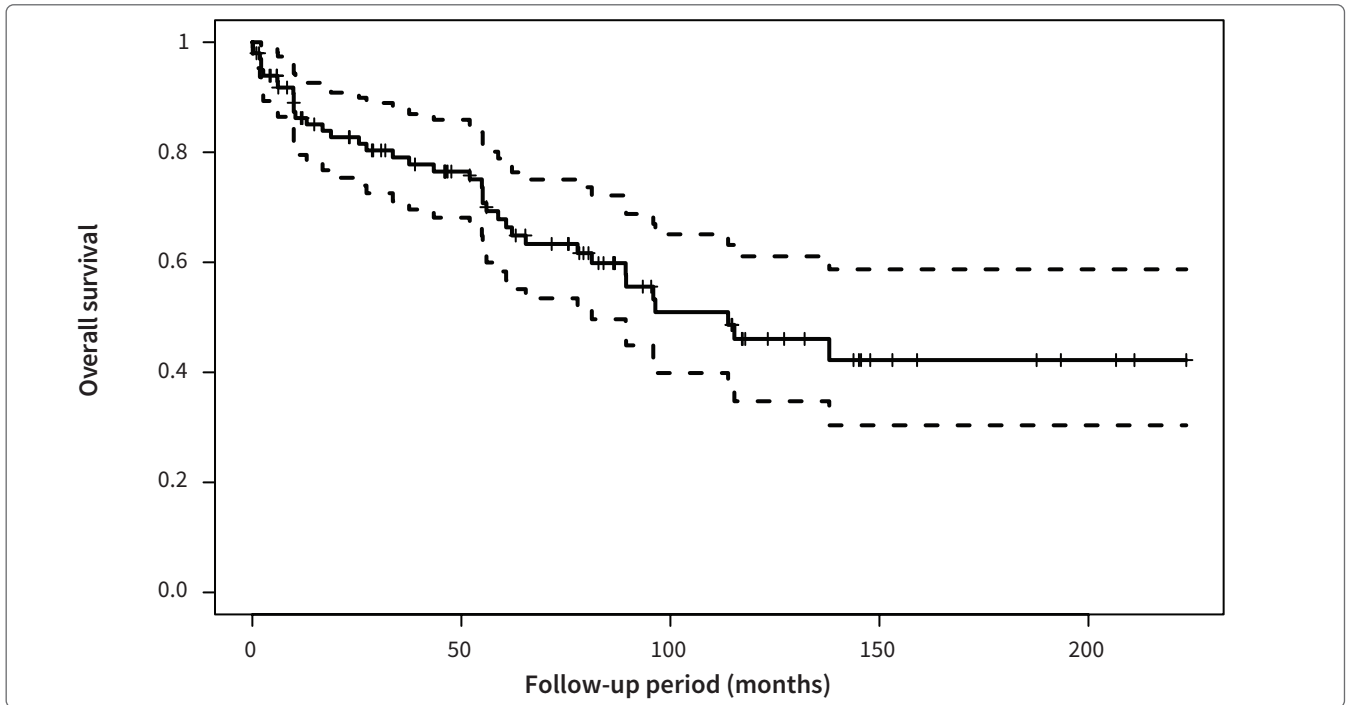


Figure 2: Overall survival curve.

metastases and 18 patients had distant metastases alone. In the competing risk analysis, the five-year cumulative incidence of local recurrence was 16.9%, for distant metastases 21.4%, and for death without local recurrence and distant metastases 9.12% (Figure 3). In the status

analysis, the cumulative incidence of death after five years was 32.1% and the probability of the patient remaining disease-free after five years was 52.6% (Figure 4).

The Cox model of multivariate analysis included two variables: ASA score and blood loss during surgery.

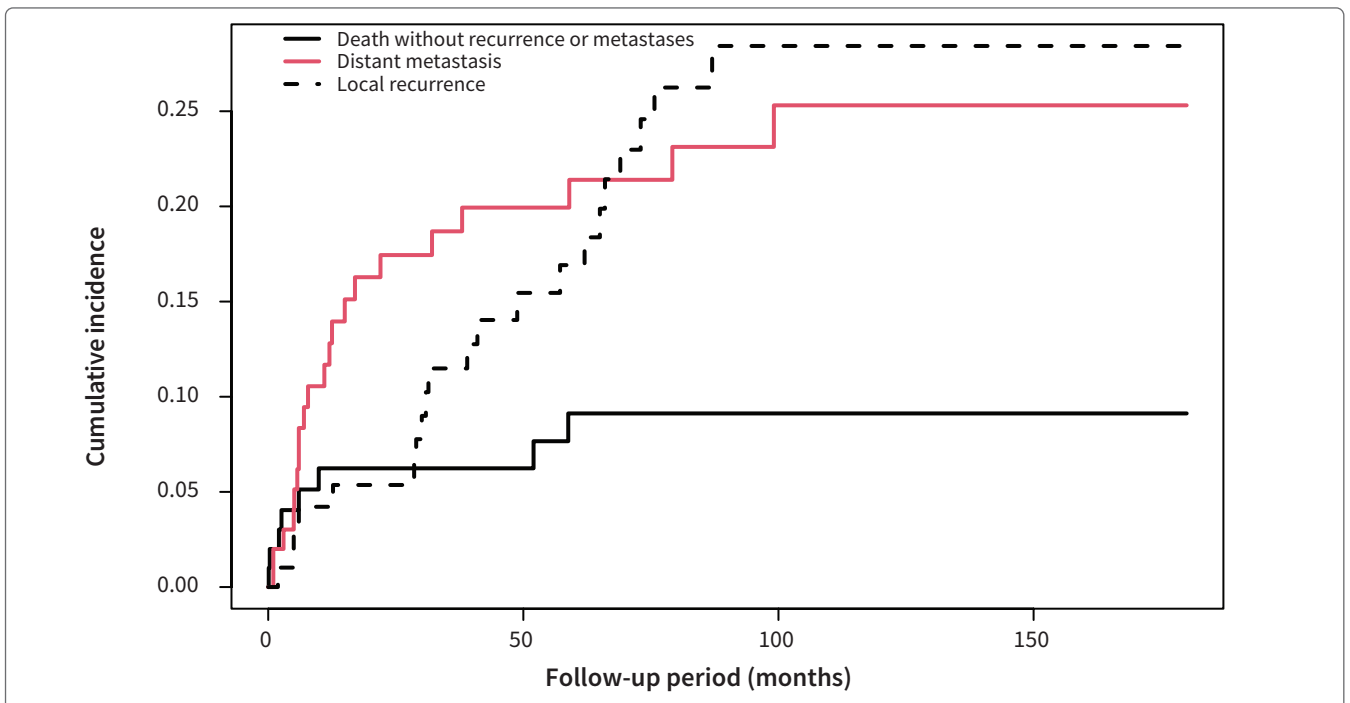


Figure 3: Graphical representation of competing risk analysis.

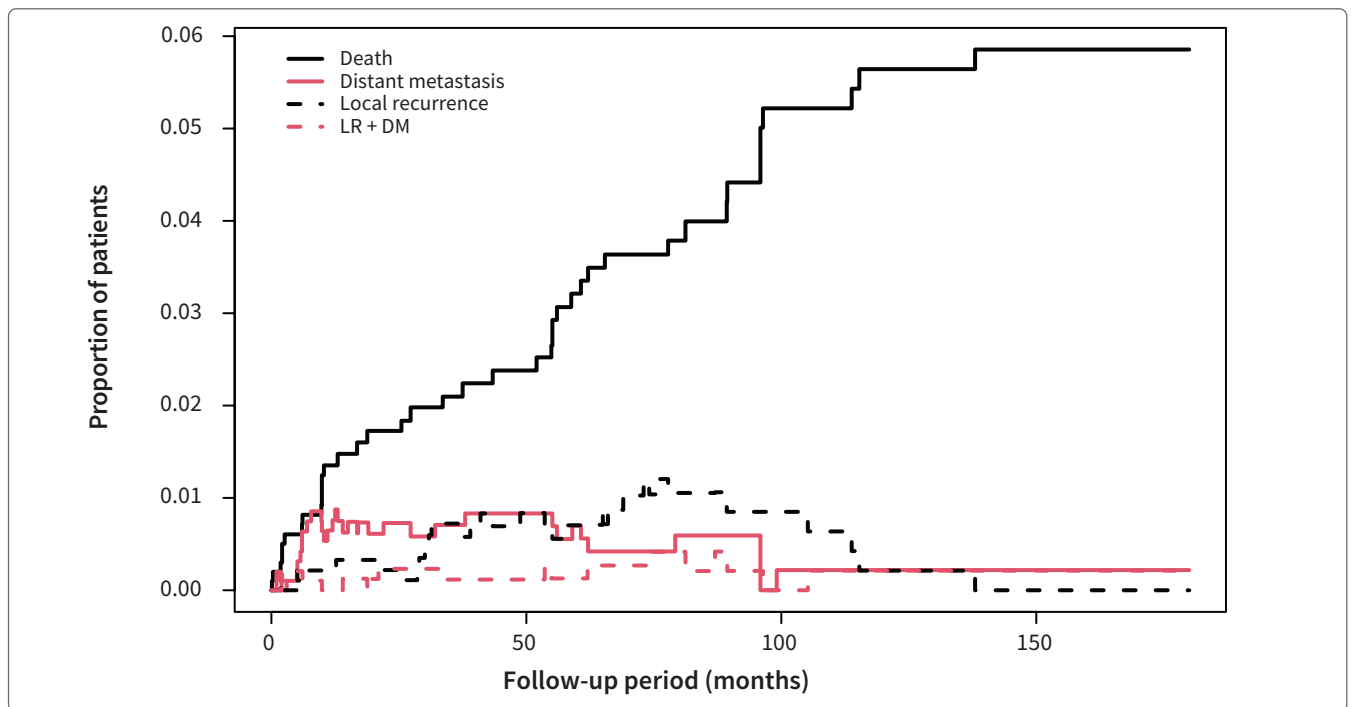


Figure 4: Graphic representation of status analysis.

Legend: LR + DM – local recurrence + distant metastasis.

Three coefficients were identified as statistically significant: ASA 3, ASA 4, and blood loss during surgery. The coefficient for patients with ASA 3 is statistically significant with $p=0.002$, hazard ratio 6.3 (95% CI: 1.9-20.7), which means that these patients are 6.3 times more at risk of death than patients from the ASA 1 group. The coefficient for patients with ASA 4 is statistically significant with $p=0.006$, hazard ratio 8.8 (95% CI: 1.9-41.8), which means that these patients are 8.8 times more at risk of death than patients from the ASA 1 group. Coefficient for blood loss during surgery is statistically significant with $p=0.040$, hazard ratio 1.05 (95% CI: 1.0-1.1), which means that each additional litre of blood lost during surgery increases the risk of death by 5% (Table 2).

During this period, 9 patients

with primary localized RPS were not surgically treated. In five, the risk of death during and after surgery was considered too high due to comorbidities, two were rejected due to old age, in one, the tumour was assessed as unresectable, and one patient refused surgery. Two were treated with palliative radiotherapy, and symptomatic and supportive treatment led by a chosen physician with the option of consulting with a palliative care team was suggested to the others.

4 Discussion

The care of sarcoma patients is differently organized around the world. Patients should be managed by a multidisciplinary team before starting treatment. Most

Table 2: Multivariate analysis of overall survival.

Variable	Hazard ratio	Lower limit 95% CI	Upper limit 95% CI	P-value
ASA 2	1.50	0.42	5.23	0.527
ASA 3	6.30	1.91	20.70	0.002
ASA 4	8.81	1.86	41.81	0.006
Blood loss	1.05	1.00	1.09	0.040

Legend: IC – confidence interval for the risk relationship; ASA – American Society of Anesthesiologists classification.

patients with limb and trunk sarcomas are operated on by orthopaedists, while patients with RPS are operated on by abdominal surgeons, both focused on sarcoma surgery. Reference centres in which the same team operates on patients with tumours in all anatomic locations are rare. According to the recommendations of the European Cancer Organisation published in 2017, an institution is considered to be a reference centre if it treats at least 100 new cases of patients with soft tissue and bone sarcoma per year (7). A sarcoma surgeon should perform at least 2–3 sarcoma surgeries per month (7). Villano et al. published an article in 2019 in which the limit for optimal treatment of these patients was identified as at least 13 RPS surgeries per year in the reference centre (8). The centre that meets this condition was declared “a high-volume retroperitoneal sarcoma centre”.

IOL was founded in 1938, and the multidisciplinary team for sarcomas in 1975. It is the only reference centre for sarcoma patients in Slovenia. There are currently 23 doctors on the team. We treat patients with soft tissue and bone tumours/sarcomas in anatomic locations and propose a diagnostic and treatment plan. At IOL, patients with sarcomas of the soft tissues of the limbs, trunk, superficial part of the head and neck, and with visceral, retroperitoneal and pelvic sarcomas are operated on. Patients with sarcomas in the ORL area, central nervous system and the chest are operated on by appropriate specialists. According to the Cancer Registry, the incidence of patients with soft tissue sarcomas was highest in 2015, when 112 cases were recorded (9). At the IOL, about 90 new cases are dealt with per year and about 60–70 sarcoma surgeries are performed, of which (only) five are due to primary RPS. A sarcoma surgeon performs at least two surgeries a month.

In our series, the five-year OS rate is 67.8%, cumulative incidence of local recurrence after five years is 16.9%, and of distant metastases it is 21.4%. 29% of patients in our series had serious postoperative complications, early postoperative mortality was 3%, and late mortality was 5%. The data can be compared with the results of the largest retrospective study to date, which included 1,007 patients treated in centres with a high number of patients. The five-year OS rate was 67%, the five-year cumulative incidence of local recurrence was 25.9%, and of distant metastases it was 21.0% (10). In the same series, the complication rate was 16.4% and postoperative early mortality was 1.8% (11). Reports of reference centres similar to ours in the number of patients treated with primary RPS are rare. In an article, written in 2019, Malinka et al. from the Charité Clinic in Berlin reported the

results of the treatment of 61 patients (12). The five-year OS rate was 58% and the five-year local disease recurrence rate was 41%. The postoperative complication rate was 31% and the 90-day mortality rate was 3%. Similar results as reported by us were reported in an article published in 2018 by Snow et al. from the MacCallum Centre in Melbourne (13). 88 patients with primary RPS were operated on. The five-year OS rate was 66%, the five-year local disease recurrence rate was 35%, and the five-year distant metastases rate was 29%. In the future, we want to reduce the complication rate and shorten hospital stays. There are no recommendations in the form of guidelines for enhanced recovery of patients with RPS after surgery (ERAS) (14).

In a multivariate analysis, the ASA score and blood loss during surgery proved to be an independent predictor of OS. In addition to age, the ASA score is a key parameter for deciding whether a patient is fit for surgery. Patients with localized RPS from groups ASA 1 and 2 are operated without restraint if the tumour is removable (resectable). However, the final decision regarding surgery in the ASA 3 and 4 group of patients also takes into account the size, location and histological subtype of the tumour. The final decision regarding the operation is made at the anaesthesiology-surgical tumour board. In the analyzed period, five patients were rejected, although their tumour was resectable. Dealing with groups ASA 3 and 4 by means of the multivariate analysis is important, as patients in this group are expected to have poorer survival than in groups ASA 1 and 2.

Membership in the international Transatlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG), led by dr. Gronchi from Milan, gives us the opportunity for education, international cooperation and participation in research. Thus, we get to know this rare disease better in the desire to provide our patients with the best possible treatment.

5 Conclusion

Our results in the treatment of RPS patients are very good and comparable to the results of other reference centres. However, we would like patients with retroperitoneal tumours, where sarcoma is suspected, to be referred to us for diagnosis and treatment without prior surgery, because only then do they have the opportunity for optimal treatment.

Conflict of interest

None declared.

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