

Leiomyosarcoma of the renal vein: analysis of outcome and prognostic factors in the world case series of 67 patients

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Background. Leiomyosarcoma is a rare malignant mesenchymal tumour. Some cases of leiomyosarcoma of the renal vein (LRV) have been reported in the literature, but no analysis of data and search for prognostic factors have been done so far. The aim of this review was to describe the LRV, to analyse overall survival (OS), local recurrence free survival (LRFS) and distant metastases free survival (DMFS) in LRV world case series and to identify significant predictors of OS, LRFS and DMFS.

Methods. Cases from the literature based on PubMed search and a case from our institution were included.

Results. Sixty-seven patients with a mean age of 56.6 years were identified; 76.1% were women. Mean tumour size was 8.9 cm; in 68.7% located on the left side. Tumour thrombus extended into the inferior vena cava lumen in 13.4%. All patients but one underwent surgery (98.5%). After a median follow up of 24 months, the OS was 79.5%. LRFS was 83.5% after a median follow up of 21.5 months and DMFS was 76.1% after a median follow up of 22 months. Factors predictive of OS in univariate analysis were surgical margins, while factors predictive of LRFS were inferior vena cava luminal extension and grade. No factors predictive of DMFS were identified. In multivariate analysis none of the factors were predictive of OS, LRFS and DMFS.

Conclusions. Based on the literature review and presented case some conclusions can be made. LRV is usually located in the hilum of the kidney. It should be considered in differential diagnosis of renal and retroperitoneal masses, particularly in women over the age 40, on the left side and in the absence of haematuria. Core needle biopsy should be performed. Patients should be managed by sarcoma multidisciplinary team. LRV should be surgically removed, with negative margins.

Key words: leiomyosarcoma; renal vein; surgery, outcome

Introduction

Leiomyosarcoma (LMS) is a rare malignant mesenchymal tumour of smooth muscle origin. It represents only 5–7% of soft tissue sarcomas.¹ Approximately 2.0% of LMS originate from the smooth muscle of vessel walls, predominantly

veins and 60.0% of these originate from inferior vena cava (IVC).¹ According to Gage *et al.*¹, the most common location of extracaval venous LMS is the renal vein, followed by the great saphenous, pulmonary and femoral vein. Leiomyosarcoma of the renal vein (LRV) is extremely rare. There have been some cases reported in the literature, but no

analysis of data and search for prognostic factors have been done so far. The first case was reported by Lopez Varela and Pereira Garro in 1967.² We present an additional case, world literature overview and the outcome of these patients.

Patients and methods

Literature overview and data collection

The search criteria in PubMed were “leiomyosarcoma” and “renal vein”. In the literature 62 articles were identified describing cases of LRV. Fourteen of the articles were in Japanese, 7 in French, 4 in Spanish, 1 in Polish and 36 in English. Data from 49 articles only²⁻⁵⁰ were merged into a database, because out of 18 Japanese cases only 4 were reported in English articles^{23,37,40,44} and the rest in Japanese articles, not accessible to us (Figure 1). The last review of Japanese cases by Kato *et al.*⁴² was translated and these data included in the study. Three times the patient was discussed as different case report by two different authors.^{3-4,13-14,20-26} That lowered the total number of reported cases in the last review by three.⁵⁰ In some articles more than one case was reported.^{14,19,26,42,46} The authors were from the fields of urology (18/49; 36.7%), surgery (15/49; 30.6%), radiology (8/49; 16.3%), pathology (5/49; 10.2%) and internal medicine (3/49; 6.1%). A retrospective review was performed to evaluate patient demographics, tumour site, clinical presentation, operative details, tumour thrombus IVC extension, neoadjuvant and adjuvant treatment, tumour size, tumour grade, surgical margin status, time to local recurrence, time to dissemination, time to death and status at last follow up. To the authors or coauthors 18 emails were sent around the world to update the data and follow up, we received 4 replies.

Illustrative case

A 46-years old female presented in January 2014 to University Hospital Ljubljana with upper abdominal pain of 6 months duration and weight loss. Her past medical history was unremarkable. On physical examination there was a palpable mass in the left upper abdomen. Gastroscopy was not diagnostic, but computed tomography (CT) revealed a left retroperitoneal mass, 11 x 10 x 9 cm in size, interposed between the aorta and hilum of the left kidney (Figure 2). The tumour surrounded the left renal artery and the vein was not identified. Ultrasound guided fine needle aspiration biopsy

(FNAB) was performed. The sample was suspicious for LMS. She was referred to the Institute of Oncology Ljubljana in February 2014 for management and treatment. A dynamic renal scintigraphy was performed for evaluation of kidney function.

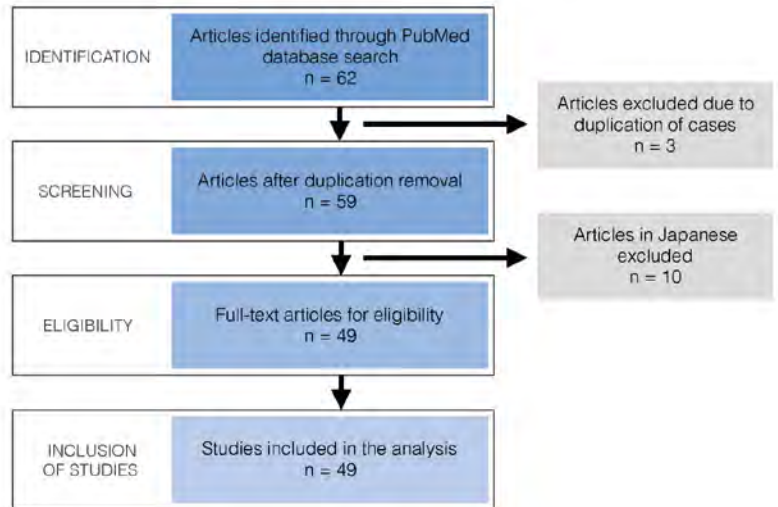


FIGURE 1. Flow chart of identification, screening, eligibility and inclusion of studies.

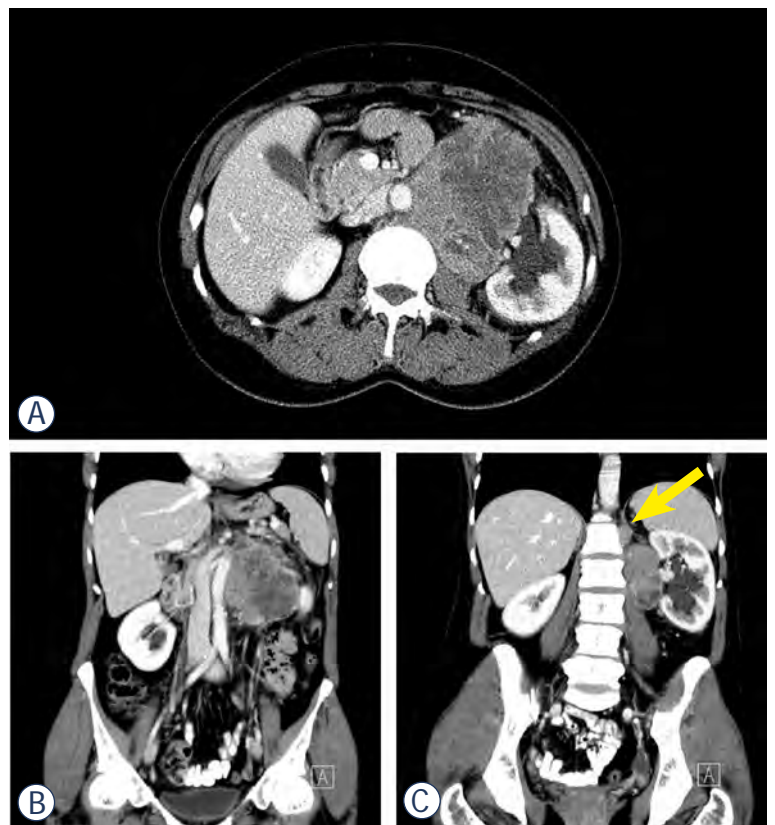


FIGURE 2. Enhanced computed tomography showing retroperitoneal tumour, interposed between the aorta and the left kidney, axial (A) and coronal plane (B). Separately removed satellite node in coronal plane, arrow (C).

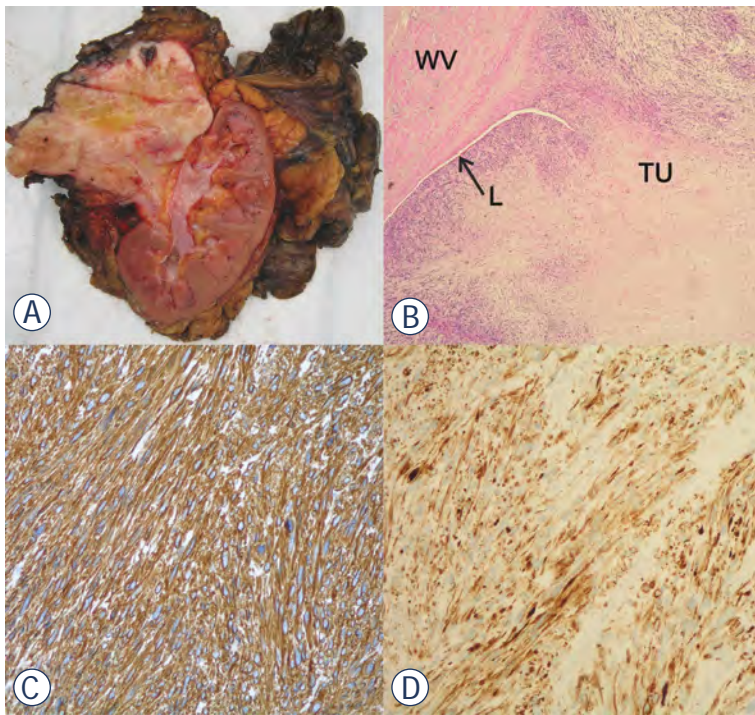


FIGURE 3. (A) A gross specimen of renal vein leiomyosarcoma. The tumour is well-circumscribed, is lying in the renal hilum, without infiltration of the renal parenchyma. (B) Hematoxylin & Eosin stain section. Showing the vascular lumen (L) and the tumour (TU) growing from the wall of the renal vein (WV). Immunohistochemical stains for SMA (C) and desmin (D) showing strong positivity.

Excretory function of the left kidney was 47% and of the right kidney 53%. Thoracic CT revealed no metastases. After discussing the case at the multidisciplinary team (MDT) we decided to perform surgery, without preoperative core needle biopsy (CNB). Tumour was removed *en bloc* with left colon, left kidney, adrenal gland and psoas fascia. A suspicious node 3 cm in size was found intraoperative in psoas muscle close to the vertebra. It was removed separately. The main specimen weighed 1152 g. Histology confirmed a LMS, according to Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system grade 3, 12 cm in largest diameter, originating from the left renal vein, not infiltrating the surrounding organs. Surgical margins were negative. The spindle tumour cells stained positive for smooth muscle actin, desmin and focally for CD34. The separately removed node was an LMS satellite, margins were positive (Figure 3). She received adjuvant radiotherapy (RT), 59 Gy. There were no surgical or radiotherapy-related complications. In December 2014, 10 months postoperatively, liver metastases were detected on CT. After subsequent magnetic resonance imaging treatment was planned at the

MDT. All 4 liver metastases, 4 to 17 mm in size were removed surgically with clear margins. She received no adjuvant treatment. In October 2015 lung metastases were detected on both sides, the largest 17 mm. She is receiving chemotherapy (ChT) with adriamycin, ifosfamide and mesna at the time of this report.

Written informed consent for all diagnostic and therapeutic procedures was obtained from the patient.

Statistical analysis

On the basis of limited data, univariate analysis was used to evaluate the following potential prognostic factors for overall survival (OS), local recurrence free survival (LRFS) and distant metastases free survival (DMFS): age, gender, tumour site, dissemination, weight loss, palpable mass, operation type, tumour thrombus IVC luminal extension, tumour size, grade, margin status, number of mitoses and neoadjuvant or adjuvant treatment. OS and LRFS were compared using log-rank test. All comparisons were two sided. P-value of 0.05 was considered statistically significant. Survival curves were calculated and plotted using Kaplan-Meier method. Cox's multivariate regression was used to identify independent prognostic variables of OS, LRFS and DMFS. The statistical program SPSS® version 22 was used for analysis.

Results

Patient and tumour characteristics

In total 67 cases were identified. The tumour predominantly occurred in women (76.1%; 51/67) and on the left side (68.7%; 46/67). The mean age at diagnosis was 56.6 years (range 27–93 years). Detailed patient and clinicopathologic characteristics are presented in Table 1, Figure 4 and 5. Histological biopsy before treatment was performed in 9 patients (13.4%; 9/67); 1 patient had biopsy during exploration⁹, 4 patients had CT guided CNB^{19,20,27,50}, the biopsy type for 2 patients was not specified in the article^{33,41} and 2 patients had biopsy through femoral approach during cavography.^{36,43} FNAB before operation was performed in 1 patient³⁴ and in our case (3.0%; 2/67). The mean tumour size was 8.9 cm, described in 54 cases (80.6%; 54/67). System used for sarcoma grading was defined in single article.¹⁰ Tumour grade was described in 28 cases (41.8%; 28/67), surgical margin status in 18 cases

(26.9%; 18/67) and number of mitoses in 18 cases (26.9%; 18/67). Tumour cells stained positive for smooth muscle actin in 23 cases (34.3%; 23/67), for desmin in 22 cases (32.8%; 22/67) and for vimentin in 6 cases (9.0%; 6/67). Intraluminal caval tumour thrombus was reported in 9 cases (13.4%; 9/67), IVC mural invasion in 3 cases (4.5%; 3/67), the renal parenchyma invasion in 8 cases (11.9%; 8/67) and the adrenal gland invasion in a single case (1.5%; 1/67). The data about IVC mural invasion were taken as stated in the articles.^{11,15,16}

Surgery

All patients but one underwent surgery (98.5%; 66/67). Four patients had tumorectomy (6.0%; 4/67) and 60 had nephrectomy (89.6%; 60/67). One patient had attempt of laparoscopic tumorectomy, two had laparoscopic nephrectomy and one had robotic laparoscopic nephrectomy. Two patients (3.0%; 2/67) had compartment resection, tumour removed *en bloc* with (at least) adjacent segment of colon, kidney and psoas. Adrenalectomy was performed in 11 patients (16.4%; 11/67) and lymph node dissection in 6 patients (9.0%; 6/67). Tumour thrombus extended into the lumen of IVC in 9 patients (13.4%; 9/67), in 4 cases tumour was on the left side and in 5 cases on the right. In two of these patients there was also invasion of the caval wall. IVC was resected in 5 patients (7.5%; 5/67), once ligated and without reconstruction, once oversewn, once reconstructed with venous patch and once with allograft. There are no data about the type of operation on IVC for the fifth patient. Cavotomy and extraction of the tumour thrombus was performed in 3 patients (4.5%; 3/67). One patient had locally advanced tumour, with tumour extension into the right atrium and received palliative ChT only. In a patient with tumour caval wall invasion

TABLE 1. Patients data and histologic variables, treatment modalities and disease progression

Characteristic	Subgroup	Value (n = 67)	%
Age at diagnosis (year)	Mean	56.6	
	Range	27-93	
Gender	Female	51	76.1
	Male	16	23.9
Side	Left	46	68.7
	Right	21	31.3
Size (cm)	Mean	8.9	
	Range	3.5-25	
Tumour thrombus extension	IVC	9	13.4
Preoperative biopsy	Histology	9	13.4
	Fine needle aspiration	2	3.0
	No biopsy	56	83.6
Tumour grade	G1	6	9.0
	G2	8	11.9
	G3	14	20.9
	Unknown	39	58.2
	Surgical margins	Negative	15
Operation	Positive	3	4.5
	Unknown	49	73.1
	Nephrectomy	60	89.6
	Tumorectomy	4	6.0
Preoperative treatment	Compartment resection	2	3.0
	No operation	1	1.5
	Embolization	3	4.5
	ChT	1	1.5
Intraoperative treatment	RT + ChT	2	3.0
	RT	1	1.5
Postoperative treatment	RT	7	10.4
	ChT	9	13.4
	ChT + RT	1	1.5
	Immunotherapy	1	1.5
	Disease progression	LR	3
Site of dissemination	M	20	29.9
	LR + M	10	14.9
	Total	33	49.3
	Liver	17	25.4
Site of dissemination	Lungs	16	23.9
	Bone	8	11.9
	Soft tissue	4	6.0

ChT = chemotherapy; G = grade; IVC = inferior vena cava; LR = local recurrence; M = metastases; RT = radiotherapy

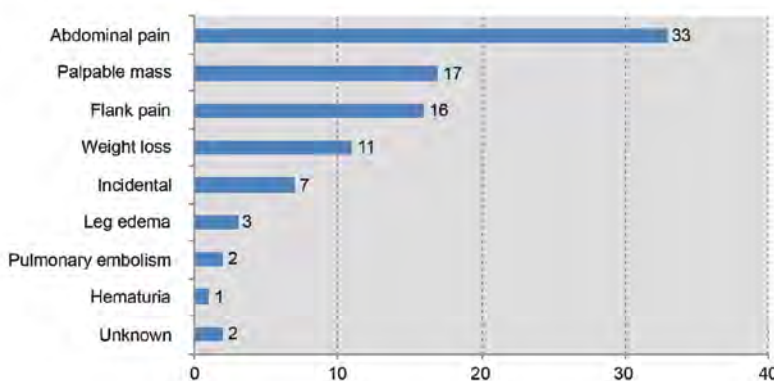


FIGURE 4. Clinical presentation of leiomyosarcoma of the renal vein cases.

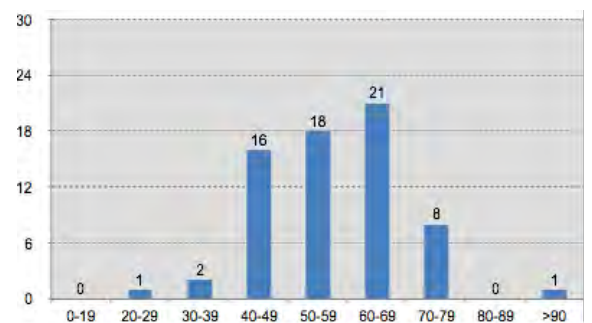


FIGURE 5. Age distribution of leiomyosarcoma of the renal vein patients.

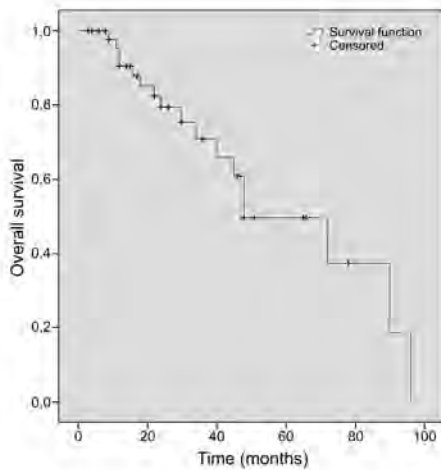


FIGURE 6. Kaplan-Meier curve of overall free survival.

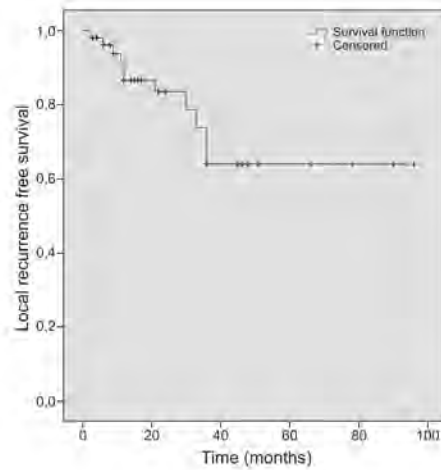


FIGURE 7. Kaplan-Meier curve of local recurrence free survival.

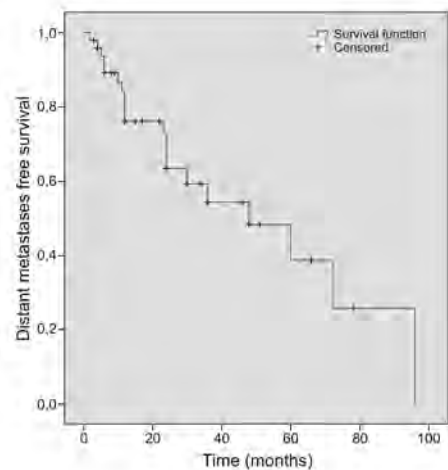


FIGURE 8. Kaplan-Meier curve of distant metastases free survival.

the IVC was reconstructed with venous patch after resection. Splenectomy was performed in 2 patients, in 1 jejunal resection and in 1 synchronous liver metastatectomy.

Treatment modalities

Three patients (4.5%; 3/67) had preoperative tumour embolization. One patient received preoperative ChT and two preoperative ChT and RT (3.0%; 2/67). Seven patients (10.4%; 7/67) received postoperative RT and 9 patients postoperative ChT (13.4%; 9/67). One patient received postoperative ChT and RT and 1 patient had immunotherapy. The information about RT and ChT as neoadjuvant and adjuvant treatment is summarized in Table 1.

Outcome

Four patients were excluded for the survival analysis, because 3 were disseminated at the time of diagnosis^{19,20,26} and one was not treated surgically.³⁶ Two patients were alive with disease and on palliative care at the time of report.^{34,46} Three patients (4.5%; 3/67) had local recurrence, 10 patients (14.9%; 10/67) had local recurrence and dissemination and 20 patients (29.9%; 20/67) had dissemination of the disease after treatment. Spread was hematogenous to different organs. In this group of 67 patients to the liver in 25.4% (17/67), lungs in 23.9% (16/67), bones in 11.9% (8/67) and soft tissue in 6.0% (4/67) (Table 1).

After the median follow up of 24 months, the OS was 79.5%. LRFS was 83.5% after median follow up of 21.5 months and DMFS was 76.1% after median

follow up of 22 months. Factors predictive of OS in univariate analysis were surgical margins ($p = 0.014$), while factors predictive of LRFS in univariate analysis were IVC luminal extension ($p = 0.016$) and tumour grade ($p = 0.05$). No factors predictive of DMFS were identified in univariate analysis. Univariate analysis of OS, LRFS and DMFS are presented in Table 2. In multivariate analysis none of the factors were predictive of OS, LRFS or DMFS. Survival curves are presented in Figures 6, 7 and 8.

Discussion

Points to be discussed about the case from our institution are biopsy, surgery, adjuvant RT and treatment of liver metastases.

The patient presented to the Institute of Oncology Ljubljana because of retroperitoneal location of the tumour and cytological suspicion for LMS. Ultrasound guided FNAB was performed in another hospital. At the MDT it was not decided for CNB, because the mass was a spindle cell tumour, suspicious for LMS, with the renal vein not identified on CT, indeed suspicious for primary LRV, and because the tumour was deemed resectable and not disseminated, as such not planned for neoadjuvant treatment.

The tumour was removed with compartment resection with negative margins, in separately removed satellite margins were positive. Analysing the CT scans again after the histological report, the satellite was found on CT and it seems that the tumour was invading the psoas muscle in continuity. Surgery was planned as wide resection but was

TABLE 2. Univariate analysis of overall, local recurrence free and distant metastases free survival (log-rank)

Characteristic	Subgroup	OVERALL SURVIVAL			LOCAL RECURRENCE FREE SURVIVAL		
		Alive (n = 39)	Dead (n = 17)	p-value	No LR (n = 45)	LR (n = 11)	p-value
Age	≤ 50	13	5	0.285	15	3	0.519
	> 50	26	12		30	8	
Gender	F	32	15	0.812	38	9	0.993
	M	7	2		7	2	
Side	L	29	9	0.448	31	7	0.987
	R	10	8		14	4	
Weight loss	Y	5	6	0.414	9	2	0.734
	N	34	11		36	9	
Palpable mass	Y	9	6	0.581	12	4	0.562
	N	30	11		34	9	
Operation	Nephrectomy	35	15	0.543 (nephrectomy or tumorectomy vs. compartment)	41	9	0.562
	Tumorectomy	2	2		2	2	
	Compartment	2	0		2	0	
Intracaval luminal extension	Y	5	3	0.340	4	4	0.016
	N	34	14		41	7	
Tumour size	≤ 10 cm	23	10	0.485 (≤ 10 cm vs. > 10 cm)	28	5	0.219 (≤ 10 cm vs. > 10 cm)
	> 10 cm	11	3		11	3	
	Unknown	5	4		6	3	
Grade	1	4	2	0.265 (1 vs. 2 or 3)	6	0	0.05 (1 vs. 2 or 3)
	2 or 3	13	6		12	7	
	Unknown	22	9		27	4	
Margins	Negative	14	1	0.014 (neg. vs. pos.)	12	3	0.096 (neg. vs. pos.)
	Positive	1	1		0	2	
	Unknown	24	15		33	6	
Mitoses/10hpf	<10	8	2	0.782 (<10 vs. ≥10)	8	2	0.244 (<10 vs. ≥10)
	≥10	2	1		1	2	
	Unknown	29	14		36	7	
Neoadjuvant/ adjuvant chemotherapy	Y	8	3	0.987	7	4	0.337
	N	31	14		38	7	
Neoadjuvant/ adjuvant radiotherapy	Y	6	4	0.165	8	2	0.975
	N	33	13		37	9	

F = female; L = left; LR = local recurrence; M = male; N = No; R = right; Y = Yes

Characteristic	Subgroup	DISTANT METASTASES FREE SURVIVAL		
		No DM (n = 31)	DM (n = 25)	p-value
Age	≤ 50	9	9	0.805
	> 50	22	16	
Gender	F	27	20	0.221
	M	4	5	
Side	L	19	19	0.138
	R	12	6	
Weight loss	Y	2	9	0.087
	N	29	16	
Palpable mass	Y	5	10	0.277
	N	26	15	
Operation	Nephrectomy	27	23	0.336 (nephrectomy or tumorectomy vs. compartment)
	Tumorectomy	3	1	
	Compartment	1	1	
Intracaval luminal extension	Y	4	4	0.284
	N	27	21	
Tumour size	≤ 10 cm	21	12	0.210 (≤ 10 cm vs. > 10 cm)
	> 10 cm	7	7	
	Unknown	3	6	
Grade	1	4	2	0.131 (1 vs. 2 or 3)
	2 or 3	9	10	
	Unknown	18	13	
Margins	Negative	10	5	0.815 (neg. vs. pos.)
	Positive	1	1	
	Unknown	20	19	
Mitoses/10hpf	<10	9	1	0.266 (<10 vs. ≥10)
	≥10	1	2	
	Unknown	21	22	
Neoadjuvant/ adjuvant chemotherapy	Y	5	6	0.683
	N	26	19	
Neoadjuvant/ adjuvant radiotherapy	Y	5	5	0.087
	N	26	20	

DM = distant metastases; F = female; L = left; M = male; N = No; R = right; Y = Yes

marginal and R1. The operation would be optimal if both specimens would be removed *en bloc*, but the margins on the vertebra would probably be positive anyway. Because reoperation with clear margins on vertebra in case of local recurrence would probably not be possible, we decided for adjuvant RT.

According to magnetic resonance imaging liver metastases were small and resectable and that was the reason at the MDT to decide for metastasectomy.

LRV is very rare. Cases from the last literature overview in 2010⁵⁰, cases from nonenglish literature, new reports from 2010–2015 and present case were summarised. From data gathered from these case reports, subsequent analysis and with respect to sarcoma guidelines, several observations can be made.

From the clinical point of view, LRV presents difficulties in making diagnosis, because it is uncommon, has no specific symptoms and no pathognomonic radiological features. It predominantly occurs in women (76.1%), on the left side (68.7%) and affects older population, with the peak occurring at age 60–69 years. Presenting symptoms are unspecific, abdominal pain was reported in 49.3%.

Hematuria was reported in a single case (1.5%) of LRV patients, but is present in more than one third of the cases (34.8%) of renal cell carcinoma (RCC) with venous extension.⁵¹ Genetic predisposition may play a role in development of primary LRV, with two patients being treated for retinoblastoma and one patient having Li Fraumeni syndrome.

From the point of imaging, location of LRV is more important than the size of the tumour. It can overlap with much more common RCC with venous extension. LRV is usually located in the hilum of the kidney. The bulk of the tumour lies predominantly or entirely outside the hilar parenchyma or the tumour is limited to the renal vessels [46]. The mean tumour size in this LRV group is 8.9 cm. In a study group of 1192 patients with RCC with extension into the renal vein (23.0%) and IVC (7.0%) the mean tumour size was 8.9 cm as well.⁵² It may not be possible to distinguish between these two entities by imaging. Other diagnoses considered in this location are metastatic lymph node in a patient with a history of malignancy, renal pelvis leiomyosarcoma, extremely rare as well, with around 10 cases reported in the literature⁵³, lymphoma, adrenal gland tumour, upper tract urothelial carcinoma, granulomatous disease and renal vein thrombus.⁴⁶

With regard to biopsy, retroperitoneal mass is usually detected on abdominal CT scans. When imaging is not diagnostic of a retroperitoneal liposarcoma, image-guided CNB of retroperitoneal tumour is strongly recommended to obtain the sample for diagnosis. Correct diagnosis may significantly affect surgical decision and neo/adjuvant therapy.^{54,55} Wilkinson *et al.*⁵⁶ from Royal Marsden, London reported, that preoperative CNB for retroperitoneal sarcoma (RPS) is safe and does not affect oncological outcome. Patients with intermediate and high-grade RPS were included. There were no intra-abdominal complications requiring early operation. The group of 90 patients with preoperative CNB was compared to a group of 60 patients, who did not have preoperative CNB. There was no significant difference in local recurrence ($p = 0.101$) or OS ($p = 0.191$). FNAB in retroperitoneal tumours rarely yields diagnostic information and should be avoided⁵⁵, but it can be performed in RCC in spite of danger of haemorrhage. In the present review preoperative histological biopsy was performed in 13.4% of cases only and FNAB in 3.0%.

With regard to treatment, the only potentially curative treatment for RPS is surgery with macroscopically complete resection.^{54,55,57} The role of

ChT and RT in RPS is not proven and still under investigation. It is generally recommended, that in case of RT administration, it should be delivered in the preoperative setting and possibly within a clinical trial.⁵⁴ Postoperative RT should not be administered routinely in R0 and R1 resections.⁵⁴ ChT is an option in the preoperative setting of resectable disease, is an option after surgery in case of R2 resection and is an option in case of unresectable or metastatic disease.⁵⁴

Because of complex evaluation and treatment options patients with RPS should be managed by sarcoma MDT in a specialized reference center.^{54,55}

Histologic subtype is one of the major determinants of the oncologic outcome in RPS. The most common location of LMS is the retroperitoneum⁵⁸, where it represents the second most common histological subtype after liposarcoma, accounting for 14–36% of patients in major series.^{59,60} Retroperitoneal LMS has a high propensity for distant recurrence. The reported rate of distant metastases for retroperitoneal LMS at 5 years is around 40–50% and for local recurrence at 5 years around 5%.⁶¹ Similar results are present in the present review, with the rate of local recurrence of 4.5% (3/67), distal metastases of 29.9% (20/67) and both in 14.9% (10/67), but in much shorter period of follow up.

And finally, in the present review of the literature 79.5% of the LRV patients survived at 2 years. A 5-year OS, LRFS and DMFS was not performed because of the inadequate sample size at that length of follow up. Retrospective comparisons of series of RPS patients have demonstrated 5-years OS rates of 50–70% and 5-years local control rates of 40–80%.⁵⁷ In the IVC LMS series 5-year survival has been reported between 33.0% and 53.0%.²⁶ Data from different large series of RPS patients have demonstrated tumour grade and surgical margin status as independent prognostic factors of OS and LRFS.^{62,63} Cases from this review are dispersed world wide and through half of the century, lacking data for tumour grade (58.2%; 39/67), surgical margin status (73.1%; 49/67) and follow up (16.4%; 11/67). Because of insufficient histologic data and truncated follow up, we were not able to identify prognostic factors of OS, LRFS and DMFS in multivariate analysis.

As a retrospective analysis this study has limitations. Most of the information collected was from case reports, without significant follow up and lacking histological data. As a consequence, there was a limitation in the statistical analysis and the

conclusions that could be drawn from it, particularly in patients' outcome. However, to our knowledge, this is the largest study on this topic, and even this limited survey expands our understanding of the natural history of this rare sarcoma.

Conclusions

LRV is usually located in the hilum of the kidney. It should be considered in differential diagnosis of renal and retroperitoneal masses, particularly in women over the age of 40, on the left side and in the absence of hematuria. Core needle biopsy should be performed. Patients should be managed by sarcoma MDT. For optimal clinical outcomes, LRV should be surgically removed, with negative margins. After a median follow up of 24 months OS was 79.5%, LRFS was 83.5% after a median follow up of 21.5 months and DMFS was 76.1% after a median follow up of 22 months. Factors predictive of OS in univariate analysis were surgical margins, while factors predictive of LRFS were inferior vena cava luminal extension and grade. No factors predictive of DMFS were identified. Because of insufficient histologic data and follow up, we were not able to identify prognostic factors of OS, LRFS and DMFS in multivariate analysis.

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