Outcome of iliocaval resection and reconstruction for retroperitoneal sarcoma

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ABSTRACT

Objective: The aim of this study was to investigate the oncologic and surgical outcomes of patients treated with inferior vena cava (IVC) or iliac vein (IV) resection for retroperitoneal sarcoma (RPS). Surgery is the only curative option for patients with primary RPS. The IVC or IV can be directly invaded by RPS or can be the organ of origin of retroperitoneal leiomyosarcoma. In both cases, resection of the IVC or IV is required to achieve a complete resection.

Methods: Patients who underwent IVC or IV resection for primary or recurrent RPS between 2000 and 2016 at a single referral institution were included in this retrospective study. The oncologic outcome was explored in terms of overall survival and crude cumulative incidence (CCI) of local recurrence and distant metastasis. Surgical outcomes were explored in terms of complications, renal function, lower limb edema, and vascular graft patency.

Results: Sixty-seven patients were included: 24 IV resections (IV group), 39 IVC resections, and 4 IVC and IV resections (IVC group). The most frequent histologic types were leiomyosarcoma (63%) and liposarcoma (27%). Five-year overall survival, CCI of local recurrence, and CCI of distant metastasis (95% confidence interval) were 56.2% (43.6-72.4), 12.4% (5.2-29.5), and 51.5% (39.3-67.5). IVC was circumferentially resected in 38 of 43 patients; 32 were treated with graft reconstruction (22 with interposition of banked venous homograft [BVH] and 10 with polytetrafluoroethylene [PTFE] graft) and 6 with ligation only, mostly dependent on the presence of an adequate collateral vessel network. Patients with preoperative IVC obstruction treated with ligation only (n = 6) did not develop severe postoperative lower limb edema. IVC graft primary patency at 5 years was 100% in IVC PTFE grafts and 76.7% in IVC BVHs. Fifteen patients (22.4%) suffered a Clavien-Dindo grade ≥3 complication within 60 days of surgery.

Conclusions: IVC or IV resection in the context of RPS surgery is of value in achieving long-term survival. A policy of vascular grafting in case of circumferential resection of a patent IVC or IV is rewarding. For IVC reconstruction, both BVHs and PTFE grafts offer good results in terms of high patency rate and low risk of infection. (J Vasc Surg: Venous and Lym Dis 2019;7:547-56.)

Keywords: Retroperitoneal sarcoma; Inferior vena cava; Surgical resection; Vascular reconstruction; Banked venous homograft; Leiomyosarcoma

Complete surgical resection is the only curative option for retroperitoneal sarcoma (RPS) patients, and quality of surgical margins is critical in determining the oncologic outcome.[1-4] In particular, the adoption of an extended surgical approach encompassing the resection of adherent organs has been shown in retrospective series to be associated with a reduction of local recurrence (LR) and an improvement in survival.[5] This approach has been endorsed in major guidelines and consensus papers.[6-8]

In about 8% to 15% of primary RPS, tumor arises from or invades major abdominal vessels such as the inferior vena cava (IVC) and iliac veins (IVs).[9-11] The invasion of these structures does not contraindicate surgery as long as a macroscopically complete resection can be achieved.[9-19] The optimal management of the IVC or IV after partial or complete resection is controversial; some authors advocate ligation only,[20] whereas others propose selective or routine reconstruction.[10,11,18] The aim of this study was to explore the surgical outcome of a single-institution cohort of RPS patients treated with multivisceral resections involving the IVC or IV.

METHODS

All consecutive adult patients operated on for primary or recurrent RPS and requiring IVC or IV resection at Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, between January 2000 and December 2016 were included in the study. Clinical-pathologic data were

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Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X

https://doi.org/10.1016/j.jvsv.2018.10.023

retrieved from a prospectively maintained electronic institutional sarcoma database.

Before surgery, patients underwent a contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis and electrocardiographic and anesthetic evaluation. Further tests, such as cardiac ultrasound or pulmonary function tests, were tailored to the individual risk.

The IVC was anatomically divided into three segments according to Mingoli et al[21]: segment I (infrarenal), between the confluence of the common IVs and the renal veins; segment II (suprarenal), between the renal veins and the suprahepatic veins; and segment III (suprahepatic), between the suprahepatic veins and right atrium. Similarly, the IV was divided into two segments: segment I, between the origin of the external IV and the hypogastric vein; and segment II, between the hypogastric vein and the origin of the IVC.

After partial IVC or IV resection, primary repair was performed when >50% of the vessel diameter could be maintained; otherwise, a patch repair was applied. After circumferential IVC or IV resection, vessel ligation was performed in case of intraoperative confirmation of complete vessel occlusion associated with an adequate collateral vessel network. The surgical team deemed a collateral venous network adequate if enlarged collateral veins were detected on preoperative CT scan and confirmed intraoperatively after specimen removal and in the absence of tension on the distal vein stump. Collateral veins had to be present in at least one of four pathways: deep (azygos-hemiazygos), intermediate (gonadal), superficial (epigastric-mammarian), or portal.[22]

In case of IVC or IV reconstruction, banked venous homograft (BVH) was the conduit of choice to restore caval continuity.[10,23,24] If BVH was not available, a nonringed polytetrafluoroethylene (PTFE) graft was used. On the contrary, nonringed PTFE and ringed PTFE grafts were the conduits of choice for IV reconstruction and arterial reconstruction, respectively. Left renal vein (LRV) reimplantation was considered in a segment II tumor location unless there was evidence of adequate vein drainage before or during surgery. Concomitant right nephrectomy did not constitute an absolute indication for LRV reimplantation.

Antithrombotic prophylaxis was administered as follows: low-molecular-weight heparin (LMWH) the day before surgery (at a dose of 38 IU/kg of anti-Xa before 2012 and 54 IU/kg of anti-Xa after 2012), intraoperative systemic heparin infusion before vascular clamping (0.6-0.7 unit/kg) for both arterial and venous reconstruction, and postoperative LMWH for 30 to 90 days at the same dose used preoperatively. Patients were treated with intraoperative and postoperative compression stockings until discharge. In patients with an IVC or IV PTFE graft, the LMWH dose was doubled in the postoperative period once the hemorrhagic risk was deemed to be low enough. Continuation of anticoagulation therapy was re-evaluated on a single basis during follow-up.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** Iliocaval resection in 67 retroperitoneal sarcoma (RPS) patients resulted in a 56.2% overall survival, 12.4% local recurrence, and 51.5% distant metastases at 5 years. The 5-year patency of the inferior vena cava polytetrafluoroethylene grafts and banked venous homografts was not significantly different (100% vs 76.7%). Fifteen patients (22.4%) suffered severe postoperative adverse events.
- **Take Home Message:** Iliocaval resection during RPS surgery aids in long-term survival and has complication rates comparable to multivisceral RPS surgery. For inferior vena cava reconstruction, both banked venous homografts and polytetrafluoroethylene grafts had good patency rates and low risk of infection.

Surgical resection was classified as macroscopically complete (R0-R1) or incomplete (R2). Postoperative complications were classified according to the Clavien-Dindo classification.[25] Complications requiring surgical, endoscopic, or radiologic intervention (grade 3) and life-threatening complications (grade 4) as well as death (grade 5) within 60 days of surgery were recorded. Postoperative lower limb edema (LLE) was evaluated at hospital discharge and at first follow-up (4 months after surgery). LLE was classified as minimal, transient severe, or persistent severe according to Hollenbeck et al.[13]

Histologic subtypes were defined according to the 2013 World Health Organization classification system.[26] The French Federation of Cancer Centers grading system was applied for tumor grading.[27]

Adjuvant or neoadjuvant radiotherapy and chemotherapy were administered after discussion of the individual patient's case at the multidisciplinary tumor board or as part of ongoing clinical trials. As a general principle, chemotherapy was considered for patients at higher risk of disease recurrence (ie, high-grade leiomyosarcoma [LMS] and high-grade liposarcoma [LPS]). Anthracycline-based regimens were administered as first choice. Radiotherapy was considered for patients at higher risk of local failure or with an anticipated critical margin (ie, LPS with a critical margin on the spine). Radiotherapy was always delivered in the preoperative setting, through an external beam modality, at a median dose of 50 Gy.

After surgery, patients were followed up with clinical examination and CT scan of the chest, abdomen, and pelvis every 4 months for the first 2 years, then every 6 months until the fifth year and annually thereafter.

Renal function was classified as increased in patients with 1.5 times or more the upper reference limit (URL) of serum creatinine concentration, as already referred to in a previous study from our institution.[28] Institutional Review Board approval was obtained for the study protocol.

Statistical methods. Continuous variables were displayed as medians with interquartile range extreme (IQRE) values, categorical variables as absolute and relative frequency.

Overall survival (OS) was defined as the time elapsing from diagnosis to death from any cause. Time was censored as at the last follow-up for patients still alive. IVC patency probabilities were defined as the time elapsing from surgery to occlusion. Time was censored as at the last follow-up for patients whose reconstruction was still patent. The OS and patency curves were estimated using the Kaplan-Meier method[29] and compared using the log-rank test. The median follow-up was estimated with the reverse Kaplan-Meier method, using the OS data.[30]

Crude cumulative incidence (CCI) curves of LR and distant metastasis (DM) were calculated in a competing risk framework. Concomitant LR and DM were included in the estimation of the CCI curves for DM.[31]

Adverse events and worsening of creatinine levels after surgery were analyzed as a dichotomous variable.

Univariable logistic regression analyses were performed to investigate associations between adverse events and clinicopathologic characteristics including age at diagnosis (linear or categorized in age groups of ≤64 years or ≥65 years), tumor size, resected organ number, chemoradiation therapy (yes or no), and type of vascular resection (IVC or IV). Univariable and multivariable linear regression analyses were performed to investigate associations between postsurgery creatinine levels and surgery procedures including IVC ligation, IVC segment II surgery, perioperative chemotherapy, and nephrectomy. Tumor size and resected organ number (in logistic models) and age at diagnosis and preoperative creatinine level (in multivariable linear models) were modeled as continuous variables by using three-knot restricted cubic splines to obtain flexible fit.[32] All other variables were modeled as categorical by using dummy variables.

Statistical analyses were performed with SAS (SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From January 2000 to December 2016 at our institution, 741 patients affected by primary or recurrent localized RPS were operated on with curative intent. Among them, 67 (9.0%) underwent resection of the IVC or IV and were included in the analysis. Forty patients (59.7%) had a sarcoma originating from the IVC or IV (39 LMS cases and 1 solitary fibrous tumor); in 27 patients (40.3%), a sarcoma originating from the retroperitoneum determined a secondary invasion of the IVC or IV (mainly LPS). Median follow-up was 58 months (20-85 months). Patients who had IV resection only (n = 24) were included in the IV group, whereas patients who had IVC resection only (n = 39) or concomitant IVC and IV resection (n = 4) were included in the IVC group. Baseline demographic and clinical-pathologic characteristics of the study population are detailed in Table I.

Surgical technique and patency. Details of tumor location are reported in Table I. In the IVC group, the IVC was partially and circumferentially resected in 5 (11.6%) and 38 (88.4%) patients, respectively. After IVC circumferential resection, 32 patients were treated with IVC reconstruction, whereas 6 were managed with ligation only. Of 32 IVC reconstructions, 22 (68.8%) were performed with the interposition of a BVH and 10 (31.2%) with a PTFE graft. A total of 17 renal vein reimplantations were performed among 21 renal vein resections. In 14 cases, the renal vein was directly reimplanted on the IVC graft; in 3 cases after IVC ligation, the LRV was reimplanted on the retrohepatic IVC through the interposition of a BVH.[23] No patient needed venovenous bypass shunting during IVC clamping.

In the IV group, the IV was partially and circumferentially resected in 3 and 21 patients, respectively. Among patients who underwent IV circumferential resection, 12 were treated with ligation only and 9 with graft reconstruction. Seven reconstructions were performed with PTFE graft, one with BVH, and one with autologous vein graft (contralateral superficial femoral vein). In segment II resections (13 patients), hypogastric vein was never reimplanted. Two iliac grafts crossed the inguinal ligament. Characteristics of vascular resection and reconstruction are listed in Table II.

Overall, in the IVC group, 5 of 32 patients who underwent graft reconstruction experienced graft thrombosis during the study period at a median time of 1 month after surgery. All of them had an IVC BVH. Two of five patients had postoperative complications: one retroperitoneal collection treated with percutaneous drainage and one postoperative bleeding treated with reoperation. Five-year IVC graft primary patency probability was 100% for PTFE graft and 76.7% for BVH ($P = .106$; Fig 1). Overall, in the IV group, five of nine patients treated with graft reconstruction (one IV BVH, three IV PTFE grafts, and one IV autologous graft) experienced graft occlusion at a median time of 3 months after surgery. Among the two grafts that crossed the inguinal ligament, one autologous graft underwent thrombosis 2 months after surgery, whereas one PTFE graft was patent 13 months after surgery. During the study period, IV PTFE graft and IV BVH primary patency was conserved in five of seven

Table I. Baseline demographic, clinical, and pathologic characteristics of the study population

	No.	%
No. of patients	67	100
Age at surgery, years, median (IQRE)	61 (51-69)	
Sex		
Male	38	56.7
Female	29	43.3
Tumor presentation		
Primary	62	92.5
Recurrent	5	7.5
IVC or IV involvement		
IVC or IV origin	40	59.7
IVC or IV secondary invasion	27	40.3
Tumor size, cm, median (IQRE)	10.5 (7.0-15.0)	
FNCLCC grade		
I	7	10.4
II	29	43.3
III	31	46.3
Histologic subtype of primary/ recurrent tumor		
LMS	39/3	58.2/4.5
LPS	17/1	25.3/1.5
Dedifferentiated LPS	13/1	19.3/1.5
Well differentiated LPS	4/0	6.0/0.0
MPNST	3/1	4.5/1.5
SFT	1	1.5
Other	2	3
Extent of resection		
R0-R1	65	97
R2[a]	2	3
No. of resected organs, median (IQRE)	4 (3-5)	
Primary	4 (3-5)	
Recurrent	4 (2-4)	
LMS	3 (3-4.75)	
LPS	5 (4-6.75)	
Presenting symptoms or signs[b]		
Asymptomatic mass	27	41.5[b]
Abdominal or flank pain	24	36.9[b]
LLE[c]	11	16.9[b]
Other	3	4.6[b]
Pattern of vascular resection		
IVC	39	58.2
IV	24	35.8
IVC and IV	4	6
Concomitant aorta and iliac artery resection	17	25.4
Tumor location		
IVC		
Segment I	21	
Segment II	22	
Segment III	—	
IV		
Segment I	15	
Segment II	13	
Preoperative vessel occlusion at tumor site		
IVC	13	19.4
IV	19	28.4
LRV management in segment II tumors		
Ligation	4	
Reimplantation	17	
LRV uninvolved	1	
Radiation therapy (neoadjuvant or adjuvant)	19	28.4
Chemotherapy (neoadjuvant or adjuvant)	34	50.7
Follow-up, months, median (IQRE)	58 (20-85)	

FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; *IQRE,* interquartile range extreme values; *IV,* iliac vein; *IVC,* inferior vena cava; *LLE,* lower limb edema; *LMS,* leiomyosarcoma; *LPS,* liposarcoma; *LRV,* left renal vein; *MPNST,* malignant peripheral nerve sheath tumor; *R0-R1,* macroscopically complete resection; *R2,* incomplete resection; *SFT,* solitary fibrous tumor.
[a]Both patients suffered from locally advanced malignant peripheral nerve sheath tumor with extensive infiltration of lumbar and presacral nerve roots.
[b]Data available in 65 patients, percentages calculated out of 65 patients.
[c]Three of 11 patients presented with deep venous thrombosis.

patients and zero of one patient, respectively. The low number of patients hampered the chance to estimate an actuarial 5-year IV graft primary patency probability. All IVC and IV graft occlusions were treated conservatively. No cases of pulmonary embolism were recorded.

Intraoperative and postoperative morbidity. Postoperative complications are listed in Table III. Fifteen patients (22.4%) developed a grade ≥3 Clavien-Dindo complication.

Seven (10.4%) patients were reoperated on for a postoperative complication, five (11.6%) in the IVC group and two (8.3%) in the IV group. Hematoma/bleeding was the most frequent cause of surgical reintervention (six patients). In one case, the bleeding originated from the vascular anastomosis. One patient experienced acute vein graft thrombosis (IVC BVH) on postoperative day 9 and was treated with systemic fibrinolytic therapy without recovery of graft patency. Two patients (3%) died of multiorgan failure (MOF) after postoperative complications. The first was an American Society of

Table II. Characteristics of vascular resections and reconstructions

	PTFE graft	BVH graft	Autologous graft	PTFE patch	Primary closure	Ligation only
IVC resection	10	22	–	3	2	6
IV resection						
CIV (SII)	1	1	–	–	1	1
EIV (SI)	2	1	1	–	2	9
CIV + EIV (SII + SI)	4	–	–	–	–	5
Arterial resection						
AO	3	–	–	1	–	–
CIA	–	–	–	–	–	–
EIA	8	–	–	–	–	–
CIA + EIA	5	–	–	–	–	–

AO, Aorta; *BVH,* banked venous homograft; *CIA,* common iliac artery; *CIV,* common iliac vein; *EIA,* external iliac artery; *EIV,* external iliac vein; *IV,* iliac vein; *IVC,* inferior vena cava; *PTFE,* polytetrafluoroethylene; *SI,* segment I; *SII,* segment II.
Four IVC + IV patients are represented in both IVC and IV distributions.

Anesthesiologists class 2 patient who developed postoperative acute pulmonary and kidney failure after multivisceral resection encompassing six organs and IVC partial resection and reconstruction with PTFE patch. The patient eventually died of MOF on postoperative day 49. The second was an American Society of Anesthesiologists class 3 patient who underwent resection of a right malignant peripheral nerve sheath tumor en bloc with part of the duodenum and IVC segment I circumferential resection and reconstruction with BVH. The patient had postoperative bleeding and bile leak and eventually died of MOF on postoperative day 58 after multiple reoperations. At univariable analysis, older patients (≤64 years vs ≥65 years) were at higher risk for development of postoperative Clavien-Dindo grade ≥3 complications (odds ratio, 4.07; 95% confidence interval [CI], 1.22-13.53; $P = .022$). Tumor size, resected organ number, chemoradiation therapy, and type of vascular resection (IVC vs IV) were not significantly associated with postoperative complications.

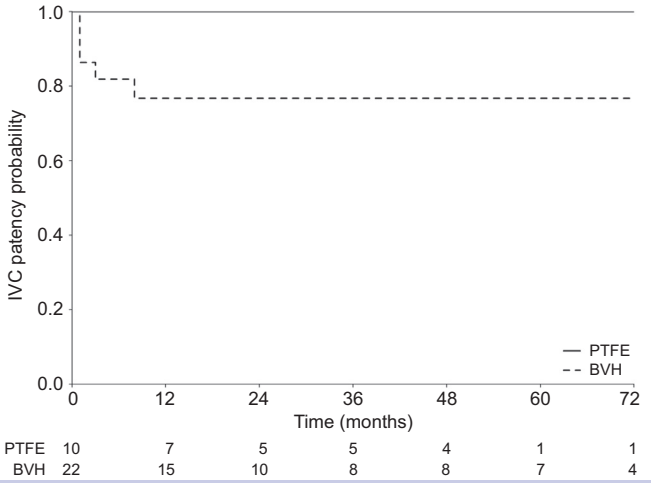

Fig 1. Patency probability in the inferior vena cava (*IVC*) group according to banked venous homograft (*BVH*) and polytetrafluoroethylene (*PTFE*) graft reconstruction.

Sixteen patients in the IVC group had concomitant bowel resection and were treated with IVC ligation (n = 2), patch (n = 2), PTFE graft (n = 8), and BVH (n = 4). In the IV group, 13 patients had concomitant bowel resection and were treated with IV ligation (n = 5), PTFE graft (n = 6), and primary repair (n = 2). Overall, no IVC or IV BVH and no IVC or IV PTFE graft infections were seen during follow-up. Conversely, one patient treated with resection of a left iliac LMS en bloc with psoas muscle, adnexa, inguinal ligament, and iliac artery and vein had an infection of the arterial PTFE graft 5 months after surgery with concomitant pseudoaneurysm of the distal arterial anastomosis site. The patient was treated with PTFE graft removal and in situ reconstruction with a biologic graft.

Renal function. Preoperative and postoperative serum creatinine levels were available for 66 patients. Creatinine concentration was within 1.5 times the URL both preoperatively and postoperatively in 55 patients (83.3%). One patient (1.5%) had baseline altered creatinine concentration. Ten patients (15.2%) with a normal baseline value had an increased creatinine level after surgery. Among the last group, all patients had undergone nephrectomy.

At univariable analysis, IVC ligation ($P = .079$), IVC segment II resection ($P = .534$), and perioperative chemotherapy ($P = .478$) were not associated with worsening of creatinine levels after surgery, whereas nephrectomy was ($P = .027$). At multivariable analysis adjusting for the patient's age and preoperative creatinine level, nephrectomy was associated with a mean increase of 0.46 mg/dL in baseline creatinine value ($P = .024$). Among 18 patients with segment II tumors undergoing IVC resection and right nephrectomy, the LRV was reimplanted in 14 and ligated in 4. The median (IQRE) postoperative creatinine concentration of patients treated with ligation and

Table III. Postoperative complications grade ≥3 according to Clavien-Dindo classification

	All (N = 67)		IVC group (n = 43)		IV group (n = 24)		
	No.	%	No.	%	No.	%	*P*
Hematoma/bleeding	7	10.4	6	14.0	1	4.2	
Acute renal failure	3	4.5	2	4.7	1	4.2	
Sepsis	2	3	1	2.3	1	4.2	
Lymphatic fistula	2	3	2	4.7	–	–	
DVT	2	3	1	2.3	1	4.2	
Wound infection	2	3	1	2.3	1	4.2	
Incisional hernia	2	3	1	2.3	1	4.2	
Bowel anastomosis leakage	1	1.5	1	2.3	–	–	
Bile leakage	1	1.5	1	2.3	–	–	
Urinary leakage	1	1.5	–	–	1	4.2	
Acute respiratory failure	1	1.5	1	2.3	–	–	
Retroperitoneal collection	1	1.5	1	2.3	–	–	
Patients with postoperative complications grade ≥3	15	22.4	11	25.6	4	16.7	0.545

DVT, Deep venous thrombosis; *IV,* iliac vein; *IVC,* inferior vena cava.

reimplantation was 1.92 mg/dL (1.47-2.20 mg/dL) and 1.09 mg/dL (0.84-1.27 mg/dL), respectively.

Among 10 patients with altered postoperative creatinine level, median baseline creatinine concentration was 1.23 mg/dL (IQRE, 0.88-1.42 mg/dL) and median postoperative creatinine level was 2.11 mg/dL (IQRE, 1.86-2.36 mg/dL). None of them required dialysis.

LLE. The occurrence of LLE after surgery and after graft occlusion is described in Table IV.

In the IVC group, 42 of 43 patients experienced postoperative bilateral minimal LLE. One patient had persistent monolateral severe LLE. This patient had preoperative monolateral LLE due to deep venous thrombosis (DVT) of the left femoroiliac axis and was treated with PTFE graft implantation with associated ligation of the left common IV to minimize thrombus mobilization. Five patients experienced BVH occlusion. Among them, two patients developed transient severe LLE, one patient had persistent severe LLE, and two patients were asymptomatic.

In the IV group, 12 of 24 patients underwent IV ligation. Among them, eight (66.7%) had minimal LLE and four (26.7%) had persistent severe LLE. Among the latter four patients, LLE was present in the preoperative setting (concomitant DVT of the iliac axis) in two patients (50%). All patients who underwent primary repair, BVH, PTFE graft, and autologous graft reconstruction experienced minimal LLE. During follow-up, five patients had graft thrombosis. Among them, three patients developed transient severe LLE, one had persistent severe LLE, and one patient had no symptoms.

All patients who experienced graft thrombosis were treated with oral anticoagulant therapy. As a general rule, long-term anticoagulation therapy was recommended after PTFE graft thrombosis; after BVH

Table IV. Postoperative and postgraft occlusion lower limb edema (*LLE*) according to type of surgery

	Postoperative LLE						Postgraft occlusion LLE					
	IVC group (43 patients)			IV group (24 patients)			IVC group (5 patients)			IV group (5 patients)		
	m-LLE	ts-LLE	ps-LLE	m-LLE	ts-LLE	ps-LLE	m-LLE	ts-LLE	ps-LLE	m-LLE	ts-LLE	ps-LLE
Ligation	6	–	–	8	–	4[b]	–	–	–	–	–	–
Primary repair or patch repair	5	–	–	3	–	–	–	–	–	–	–	–
BVH graft	22	–	–	1	–	–	2	2	1	–	1	–
PTFE graft	9	–	1[a]	7	–	–	–	–	–	1	2	–
Autologous graft	–	–	–	1	–	–	–	–	–	–	–	1

BVH, Banked venous homograft; *IV,* iliac vein; *IVC,* inferior vena cava; *m-LLE,* minimal lower limb edema; *ps-LLE,* persistent severe lower limb edema; *ts-LLE,* transient severe lower limb edema; *PTFE,* polytetrafluoroethylene.
[a]Patient with preoperative monolateral lower limb edema due to deep venous thrombosis of the left femoroiliac axis.
[b]Two patients of four with preoperative deep venous thrombosis of the iliac axis.

thrombosis, it was not, as the BVH appeared to have been resorbed at the follow-up CT scan. Each case was discussed in the coagulation clinic, and pros and cons were singularly considered before a final recommendation was made.

Long-term oncologic outcomes. Overall, 27 (40.3%) patients died. Six (9.0%) patients developed LR, 30 (44.8%) patients developed DM, and 4 (6.0%) died as a first event from surgery (two patients died of postoperative complications, two patients died of other causes 12 months and 25 months after surgery). OS, CCI of LR, and CCI of DM at 5 years were 56.2% (95% CI, 43.6-72.4), 12.4% (95% CI, 5.2-29.5), and 51.5% (95% CI, 39.3-67.5), respectively (Fig 2). OS was not significantly different between IVC and IV resection groups (59.7% vs 49.5%; log-rank test, $P = .119$).

DISCUSSION

In this retrospective single-center cohort study of 67 patients surgically treated with IVC or IV resection for primary or recurrent RPS, we showed that IVC or IV invasion did not hamper the chance of achieving a complete resection and prolonged survival. Vascular grafting in the context of multivisceral resection was safe, and postoperative complications were comparable to what is observed for multivisceral RPS surgery without major vascular involvement. In IVC patients, the patency rate of PTFE graft and BVH was not significantly different, although a trend toward lower patency of the BVH was observed. In the IV district, there was a higher risk of graft occlusion. Indeed, this series is large and homogeneous, and our vascular reconstruction policy did not change during the study period; the IVC and IV were repaired by primary closure when >50% of the vessel diameter could be maintained, by patch repair in case of partial resection involving >50% of the vessel diameter, by graft reconstruction in case of circumferential resection of a patent IVC or IV, and by ligation only in case of complete segment I or segment II IVC or IV occlusion in the context of an adequate collateral venous network present at the end of the resection. Moreover, this study benefits from a long median follow-up and from the approaches adopted to estimate the vascular outcome, namely, patency rate, LLE, and renal function.

Major limitations of this study are related to the retrospective design. In particular, we were not able to reliably analyze the anticoagulation regimen administered to each patient in the long term. The standard practice in our center is to use a more aggressive anticoagulation regimen in PTFE graft patients compared with BVH patients, as described in the Methods section. In IVC patients, this may have contributed to a higher patency rate in the first group or, on the contrary, to the observed lower patency rate in the second group, although not significant. Because the patency rates are high and consistent with previous studies, we think that this possible bias did not exert a major influence.

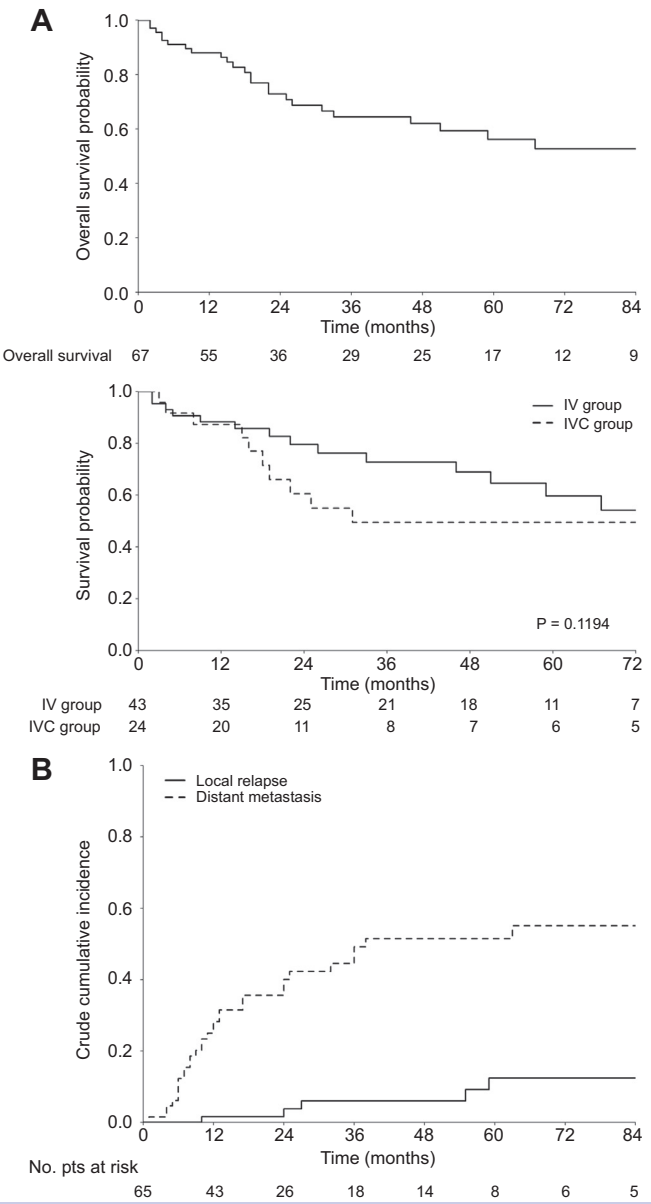

Fig 2. A, Overall survival (OS) curve in the study population and according to inferior vena cava (*IVC*) or iliac vein (*IV*) group. **B,** Crude cumulative incidence (CCI) of local relapse and distant metastasis (DM) in the study population.

This series accounts for 9% of patients surgically treated for primary or recurrent localized RPS in the study period, meaning that IVC or IV resection during RPS surgery is uncommon but not exceedingly rare. Surgeons dealing with RPS need to be trained to face this situation and to consider involvement of a vascular surgeon.

Overall, in this study, 5-year OS and CCI of LR and DM were 56.2%, 12.4%, and 51.5%, respectively. These results compare favorably with what has been observed in other multicenter series of primary RPS treated with a frontline extended resection policy[31,33-35] and should be

interpreted in light of the peculiarity of the series. The need to perform an IVC or IV resection should not be considered a contraindication to surgery as long-term survival is possible in a significant proportion of patients.

As previously reported by our group,[10,23] a cryopreserved BVH was the conduit of choice to restore caval continuity in case of vascular grafting because of its theoretical superiority in terms of resistance to graft infection and fewer long-term side effects due to the slowly progressing obstruction, which gives time for the collateral vein circles to develop. Overall, in IVC patients, the primary patency rate at 5 years for PTFE grafts (100%) and BVHs (76.7%) was not significantly different. These data compare favorably with previous studies in which graft occlusion rate ranged between 7% and 28% of PTFE grafts[9,12,13,36] and up to 40% of BVHs.[10] Interestingly, in this study, all IVC graft occlusions occurred within 1 year from surgery. The observation that venous occlusion occurs early after surgery is in agreement with what was shown in a previous study from our group[10] and should prompt maximization of medical therapy to reduce the chances of venous graft occlusions during the first year. In particular, the BVH may require a more aggressive anticoagulation regimen as was already adopted in the PTFE graft. In addition, we are now exploring the value of aortic banked grafts as an alternative to BVH, as aortic grafts may theoretically combine the resistance to infection and a higher patency rate.

In IV patients, the need for vascular reconstruction is lower. Indeed, in this cohort, 50% of IV patients had a pre-existing DVT of the iliac axis with a well-developed collateral venous network. In IV patients, the conduit of choice for vascular reconstruction was nonringed PTFE graft. After reconstruction, the probability of postgraft occlusion was higher, with five of nine patients experiencing graft occlusion during the study period. These results are in line with what was observed in a series of patients treated with IV resection during pelvic exenteration.[37] The higher incidence of graft thrombosis in the IV compared with the IVC is related to the smaller diameter, the existence of iliocaval anatomic collateral networks, and of course the length of the graft. In particular, when the graft crosses the inguinal ligament, this may become a critical point for graft compression. The use of a ringed PTFE graft in IV patients, especially when the graft crosses the inguinal ligament, might be of value in consideration of its resistance to kinking effect.

No venous graft infection was seen during follow-up regardless of the type of graft. Previous studies raised concerns about the association of bowel resection and IV or IVC synthetic grafting.[18,31,38] In our series, 14 patients had a concomitant bowel resection and IV or IVC PTFE grafting, and we did not observe any venous graft infections. These data are too limited to drive a change in our policy of using a homograft as a conduit of choice in the context of multivisceral surgery. However, when homografts are not available for IVC or IV grafting, PTFE grafts are a valid alternative, with a comparable if not superior patency rate and a safe profile in terms of risk of infection. Most important, the surgical and reconstructive plan should not change according to the type of graft.

In this series, nephrectomy was the only factor associated with an increased risk of altered postoperative creatinine level. In a previous study from our group,[8] this association was not retained at multivariable analysis adjusting for the patient's age and preoperative creatinine value. Nonetheless, in both studies, renal function remained within 1.5 URL after surgery in most patients, and in this series, the observed median increase of creatinine level after nephrectomy in multivariable analysis (0.46 mg/dL) did not have a clinical implication. This finding reinforces the policy of including en bloc nephrectomy in the treatment of RPS when this would translate into a better surgical margin. Interestingly, in patients treated with segment II resections and right nephrectomy, reimplantation of the LRV was associated with a lower median postoperative creatinine level (1.10 mg/dL vs 1.92 mg/dL). Although these results should be interpreted with caution because of the low number of patients, in patients undergoing segment II resection and right nephrectomy, LRV reimplantation should be preferred to LRV ligation whenever possible.

In a series of six patients with LMS treated with ligation only, there was a high probability of postoperative acute kidney failure (50%) and LLE (18%-50%).[20] Other studies highlighted how LLE after IVC ligation could impair the patient's quality of life, especially if the vessel was patent at preoperative imaging.[39,40] In this series, patients treated with IVC ligation did not develop severe postoperative LLE. This suggests that IVC or IV ligation performed in case of preoperative vessel obstruction is not directly related to the development of persistent severe LLE and emphasizes the importance of selection of patients. Moreover, as shown in a previous study,[23] we confirm that the occlusion of a BVH is most of the time associated with transient LLE.

The rates of postoperative complication (22%), reintervention (10%), and mortality (3%) reported here compare favorably with previous studies. In other series of major vascular resections for RPS, postoperative morbidity ranged between 36% and 41%.[9,18] In other studies of patients treated with multivisceral resection for primary RPS regardless of vascular involvement, morbidity was between 9% and 18%, and the reoperation rate was between 7.5% and 12%.[34,41] The results reported here are noteworthy, bearing in mind that major vascular resections were found to be associated with a higher risk of postoperative morbidity in two previous studies with a hazard ratio >1.5 and odds ratio of 2.63.[34,41]

CONCLUSIONS

IVC or IV resection in the context of RPS surgery is of value in achieving long-term survival and does not significantly worsen the complication rate. Preoperative and intraoperative assessment of vessel patency and collateral networks is key to guide the surgical strategy after IV or IVC resection. A policy of vascular grafting in case of circumferential resection of a patent IV or IVC is rewarding in terms of LLE and, for segment II resection, in terms of renal function. For IVC reconstruction, both BVH and PTFE grafts offer good results in terms of patency rate and low risk of infection. In case of IVC segment II resection and concomitant right nephrectomy, the LRV should be reimplanted whenever possible. Reconstruction of the IV is burdened by a higher risk of postoperative occlusion, and a PTFE graft might be preferred.

AUTHOR CONTRIBUTIONS

Conception and design: MatF, DC, FB, RM, AG
Analysis and interpretation: MatF, DC, FB, MarF, SR, SS, RM, AS, PL, AG
Data collection: MatF, DC, AG
Writing the article: MatF, DC, AG
Critical revision of the article: MatF, DC, FB, MarF, SR, SS, RM, AS, PL, AG
Final approval of the article: MatF, DC, FB, MarF, SR, SS, RM, AS, PL, AG
Statistical analysis: FB, RM
Obtained funding: Not applicable
Overall responsibility: MatF

REFERENCES

1. Strauss DC, Hayes AJ, Thway K, Moskovic EC, Fisher C, Thomas JM. Surgical management of primary retroperitoneal sarcoma. Br J Surg 2010;97:698-706.
2. Gronchi A, Pollock RE. Quality of local treatment or biology of the tumor: which are the trump cards for loco-regional control of retroperitoneal sarcoma? Ann Surg Oncol 2013;20:2111-3.
3. Nathan H, Raut CP, Thornton K, Herman JM, Ahuja N, Schulick RD, et al. Predictors of survival after resection of retroperitoneal sarcoma: a population-based analysis and critical appraisal of the AJCC staging system. Ann Surg 2009;250:970-6.
4. Gronchi A, Miceli R, Shurell E, Eilber FC, Eilber FR, Anaya DA, et al. Outcome prediction in primary resected retroperitoneal soft tissue sarcoma: histology-specific overall survival and disease-free survival nomograms built on major sarcoma center data sets. J Clin Oncol 2013;31:1649-55.
5. Gronchi A, Miceli R, Colombo C, Stacchiotti S, Collini P, Mariani L, et al. Frontline extended surgery is associated with improved survival in retroperitoneal low- to intermediate-grade soft tissue sarcomas. Ann Oncol 2012;23:1067-73.
6. Bonvalot S, Rivoire M, Castaing M, Stoeckle E, Le Cesne A, Blay JY, et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. J Clin Oncol 2009;27:31-7.
7. Gronchi A, Lo VS, Fiore M, Mussi C, Stacchiotti S, Collini P, et al. Aggressive surgical policies in a retrospectively reviewed single-institution case series of retroperitoneal soft tissue sarcoma patients. J Clin Oncol 2009;27:24-30.
8. Fiore M, Radaelli S, Gronchi A. Retroperitoneal sarcoma involving the vena cava. In: Azoulay D, Lim C, Salloum C, editors. Surgery of the inferior vena cava. Switzerland: Springer International Publishing; 2017. p. 61-74.
9. Schwarzbach MH, Hormann Y, Hinz U, Leowardi C, Böckler D, Mechtersheimer G, et al. Clinical results of surgery for retroperitoneal sarcoma with major blood vessel involvement. J Vasc Surg 2006;44:46-55.
10. Fiore M, Colombo C, Locati P, Berselli M, Radaelli S, Morosi C, et al. Surgical technique, morbidity, and outcome of primary retroperitoneal sarcoma involving inferior vena cava. Ann Surg Oncol 2012;19:511-8.
11. Quinones-Baldrich W, Alktai A, Eilber F, Eilber F. Inferior vena cava resection and reconstruction for retroperitoneal tumor excision. J Vasc Surg 2012;55:1386-93.
12. Dzsinich C, Gloviczki P, van Heerden JA, Nagorney DM, Pairolero PC, Johnson CM, et al. Primary venous leiomyosarcoma: a rare but lethal disease. J Vasc Surg 1992;15:595-603.
13. Hollenbeck ST, Grobmyer SR, Kent KC, Brennan MF. Surgical treatment and outcomes of patients with primary inferior vena cava leiomyosarcoma. Am Coll Surg 2003;197:575-9.
14. Kieffer E, Alaoui M, Piette JC, Cacoub P, Chiche L. Leiomyosarcoma of the inferior vena cava: experience in 22 cases. Ann Surg 2006;244:289-95.
15. Hines OJ, Nelson S, Quinones-Baldrich WJ, Eilber FR. Leiomyosarcoma of the inferior vena cava: prognosis and comparison with leiomyosarcoma of other anatomic sites. Cancer 1999;85:1077-83.
16. Mingoli A, Sapienza P, Cavallaro A, Di Marzo L, Burchi C, Giannarelli D, et al. The effect of extent of caval resection in the treatment of inferior vena cava leiomyosarcoma. Anticancer Res 1997;17:3877-81.
17. Dew J, Hansen K, Hammon J, McCoy T, Levine EA, Shen P. Leiomyosarcoma of the inferior vena cava: surgical management and clinical results. Am Surg 2005;71:497-501.
18. Bower TC, Nagorney DM, Cherry KJ Jr, Toomey BJ, Hallett JW, Panneton JM, et al. Replacement of the inferior vena cava for malignancy: an update. J Vasc Surg 2000;31:270-81.
19. Burke AP, Virmani R. Sarcomas of the great vessels: a clinicopathologic study. Cancer 1993;71:1761-73.
20. Daylami R, Amiri A, Goldsmith B, Troppmann C, Schneider PD, Khatri VP. Inferior vena cava leiomyosarcoma: is reconstruction necessary after resection? J Am Coll Surg 2010;210:185-90.
21. Mingoli A, Cavallaro A, Sapienza P, Di Marzo L, Feldhaus RJ, Cavallari N. International registry of inferior vena cava leiomyosarcoma: analysis of a world series on 218 patients. J Vasc Surg 1991;14:688-99.
22. Sonin AH, Mazer MJ, Powers TA. Obstruction of the inferior vena cava: a multiple modality demonstration of causes, manifestations, and collateral pathways. Radiographics 1992;12:309-22.
23. Fiore M, Locati P, Mussi C, Guarino A, Piva L, Santinami M, et al. Banked venous homograft replacement of the inferior vena cava for primary leiomyosarcoma. Eur J Surg Oncol 2008;34:720-4.
24. Faenza A, Ferraro A, Gigli M, De Paolis M, Errani C, Mercuri M. Vascular homografts for vessel substitution in skeletal and soft tissue sarcomas of the limbs. Transplant Proc 2005;37:2692-3.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of

6336 patients and results of a survey. Ann Surg 2004;240:205-13.
26. Fletcher CD, Jo VY. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. Pathology 2014;46:95-104.
27. Trojani M, Contesso G, Coindre JM, Rouesse J, Bui NB, de Mascarel A, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984;33:37-42.
28. Callegaro D, Miceli R, Brunelli C, Colombo C, Sanfilippo R, Radaelli S, et al. Long-term morbidity after multivisceral resection for retroperitoneal sarcoma. Br J Surg 2015;102:1079-87.
29. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457-81.
30. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-6.
31. Gronchi A, Strauss DC, Miceli R, Bonvalot S, Swallow CJ, Hohenberger P, et al. Variability in patterns of recurrence after resection of primary retroperitoneal sarcoma (RPS): a report on 1007 patients from the multi-institutional collaborative RPS working group. Ann Surg 2016;263:1002-9.
32. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551-61.
33. Radaelli S, Fiore M, Colombo C, Ford S, Palassini E, Sanfilippo R, et al. Vascular resection en-bloc with tumor removal and graft reconstruction is safe and effective in soft tissue sarcoma (STS) of the extremities and retroperitoneum. Surg Oncol 2016;25:125-31.
34. Bonvalot S, Miceli R, Berselli M, Causeret S, Colombo C, Mariani L, et al. Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. Ann Surg Oncol 2010;17:1507-14.
35. ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):102-12.
36. Hardwigsen J, Baqué P, Crespy B, Moutardier V, Delpero JR, Le Treut YP. Resection of the inferior vena cava for neoplasms with or without prosthetic replacement: a 14-patient series. Ann Surg 2001;233:242-9.
37. Brown KG, Koh CE, Solomon MJ, Qasabian R, Robinson D, Dubenec S. Outcomes after en bloc iliac vessel excision and reconstruction during pelvic exenteration. Dis Colon Rectum 2015;58:850-6.
38. Blair AB, Reames BN, Singh J, Gani F, Overton HN, Beaulieu RJ, et al. Resection of retroperitoneal sarcoma en-bloc with inferior vena cava: 20 year outcomes of a single institution. J Surg Oncol 2018;118:127-37.
39. Donaldson MC, Wirthlen LS, Donaldson GA. Thirty-year experience with surgical interruption of the inferior vena cava for prevention of pulmonary embolism. Ann Surg 1980;191:367-72.
40. Agrifoglio G, Edwards EA. Venous stasis after ligation of femoral or inferior vena cava. JAMA 1961;178:1-7.
41. MacNeill AJ, Gronchi A, Miceli R, Bonvalot S, Swallow CJ, Hohenberger P, et al. Postoperative morbidity after radical resection of primary retroperitoneal sarcoma: a report from the Transatlantic RPS Working Group. Ann Surg 2018;267:959-64.

Submitted Aug 28, 2018; accepted Oct 26, 2018.