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SCIENTIFIC REVIEW

Inferior Vena Cava Leiomyosarcoma: What Method of Reconstruction for Which Type of Resection?

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Abstract Inferior vena cava leiomyosarcoma (IVCL) is a rare tumor with a poor prognosis, and its surgical resection remains a challenge. To date, surgery is the only potentially curative treatment for IVCL with a 5-year survival rate of 55%. The main challenge is to combine oncological surgery with clear margins and vascular reconstruction of the inferior vena cava (IVC). In this review, we discuss the different approaches to vascular reconstruction after IVCL resection, using a prosthetic or autologous patch, direct suture or simple ligation without IVC reconstruction. The reconstruction of IVC depends of tumor location and its extension. We recommend no reconstruction if venous collaterality is well-established. When vascular reconstruction is required, we prefer prosthetic PTFE graft. These patients should be referred to high-volume centers with a multidisciplinary team of sarcoma surgeons with cardio-thoracic, vascular and hepatic specialties.

Abbreviations

LMS	Leiomyosarcoma
STS	Soft tissue sarcoma
IVC	Inferior vena cava
IVCL	Inferior vena cava leiomyosarcoma
ESMO	European Society of Medical Oncology
MRI	Magnetic resonance imaging
CT scan	Computed tomography scan
RPS	Retroperitoneal sarcoma
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
RA	Right atrium
PTFE	Polytetrafluoroethylene

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Introduction

Leiomyosarcoma (LMS) is a rare tumor arising from mesenchymal smooth cells. It accounts for 5–7% of all soft-tissue sarcomas (STSs) [1]. In 2% of cases, LMS develops in large vessels, with 60% in the IVC [2]. Some rare cases have been reported in the literature, including portal [3, 4], renal [5], splenic [6] or mesenteric [7] vein LMS. To date, no vascular LMS risk factors have been identified. Usually, IVCL has no specific symptoms that could explain the delayed diagnosis, sometimes occurring even at an advanced stage. Surgical resection with clear margins remains the only curative treatment and should be performed in a sarcoma referral center [8]. The management of STS, including LMS of the inferior vena cava, is currently being outlined by sarcoma working groups, especially the European Society of Medical Oncology (ESMO) [8]. Following appropriate imagery assessments, such as magnetic resonance imaging (MRI) or computed

tomography scan (CT scan), the ESMO recommends a histopathological diagnosis confirmed by a sarcoma pathologist for all suspected sarcoma diagnoses. Most often, multiple percutaneous biopsies are performed using a 14G or 16G needle, and guided by CT scan or ultrasonography. Unlike the procedure for other STSs, percutaneous biopsy for vascular sarcoma is associated with an increased risk of massive hemorrhage, ranging from 0.1 to 8.3% [9]. A new minimally invasive vascular biopsy technique using catheter-based aspiration of an intravascular tumor is an alternative, with lower risk of vascular injury [10]. The diagnosis of LMS is confirmed by immunohistochemistry with positive staining of α-smooth muscle actin, desmin and heavy-caldesmon on the samples [11]. The gold standard for IVCL treatment is surgery which consists on "en bloc" complete excision with clear margins. For patients achieving complete resection with clear margins, the 5-year survival rate is 55% [12]. Incomplete resection is strongly correlated with poor prognosis and an increased risk of metastases. Indeed, while retroperitoneal sarcomas (RPS) are subject to a high risk of local recurrence, recurrences of IVC LMS are mostly metastatic (50%) in the lung and/or liver [13]. Unlike RPS involving the IVC, which requires compartmental resection with systematic resection of the right kidney, the right colon and a portion of the IVC [14], complete surgery for IVCL consists in removing the IVC and adjacent organs, but only if there is tumor involvement. The surgical challenge for sarcoma surgeons is the location of the IVC and its venous drainage of the liver, kidneys and lower limbs. Obviously, renal, hepatic or cardiac involvement, the risk of major bleeding and especially the need for local tumor control greatly complicate surgery. However, the most important issue is surgical management after IVCL removal. The need for IVC reconstruction, depending on the LMS location and hepatic or renal vein involvement, is still debated, and different strategies have been described in the literature. In the present study, the different options for vascular reconstruction after IVCL resection are discussed and therapeutic guidelines are proposed, based on a review of the literature and our own experience as a referral center.

Anatomical classification and clinical features

IVC leiomyosarcomas are classified according to the level of involvement of the IVC (Fig. 1). The lower segment of the IVC extends from the infra-renal veins to the iliac bifurcation of the IVC; the middle segment is the portion of the vena cava between the renal and hepatic veins, corresponding to the retro-hepatic vena cava; the upper segment extends from the hepatic vein to the right atrium (RA), corresponding to the supra-hepatic vena cava. IVC leiomyosarcomas can be classified as type I for infra-renal vena cava (36% of cases), type II for retro-hepatic vena cava (44% of cases) and type III for supra-hepatic vena cava (20% of cases) [15, 16].

In the early stage of the disease, IVCLs are asymptomatic or only cause abdominal pain and asthenia. The clinical expression of an IVCL depends on its location and extent. For type I, patients often present only lower-limb edema, which can be transitory because of collateral venous development. Leiomyosarcomas located in the middle segment of the IVC, type II, usually only cause right hypochondrium pain unless there is renal vessel involvement causing renal failure. Supra-hepatic leiomyosarcomas, type III, generally lead to Budd-Chiari syndrome with hepatomegaly, jaundice and ascites [12].

Technical considerations

First, surgical excision of an IVCL requires expertise in sarcoma surgery and vascular skills to avoid venous injury and major intraoperative bleeding. Before any dissection, ligation or opening of the IVC, clamping of the IVC above and below the tumor is strongly recommended. It can be performed between the iliac bifurcation or above and the supra-renal vena cava for type I, below or above the renal veins and above the hepatic vein confluence for type II. For type III, a cardio-vascular surgical approach is essential. In addition, a veno-venous bypass to maintain the venous return to the heart during IVC clamping should be performed to prevent significant hemodynamic instability. IVCL surgery requires complete resection with the adjacent organs if they are involved (especially the liver, kidney or ostium of supra-hepatic IVC in the right atrium) and clear margins [14]. Numerous surgical strategies, depending both on the proximal extent of the tumor and the thrombus, have been described. They include ligation of the IVC in 20% of cases, primary repair by pericardium or other patch cavoplasty in 22% of cases and prosthetic repair in 49% of cases [12]. However, partial IVC resection followed by direct suture, and saphenous vein or prosthetic patch angioplasty is rarely an optimal oncological resection. In fact, selective partial resection of the IVC increases the risk of involved margins. Consequently, broad, complete resection of the IVC should be recommended. Complete circumferential IVC resection is essential in most cases.

Type-I IVCL

For type I, IVC reconstruction is not systematic and its simple ligation is preferred when feasible [17]. IVC

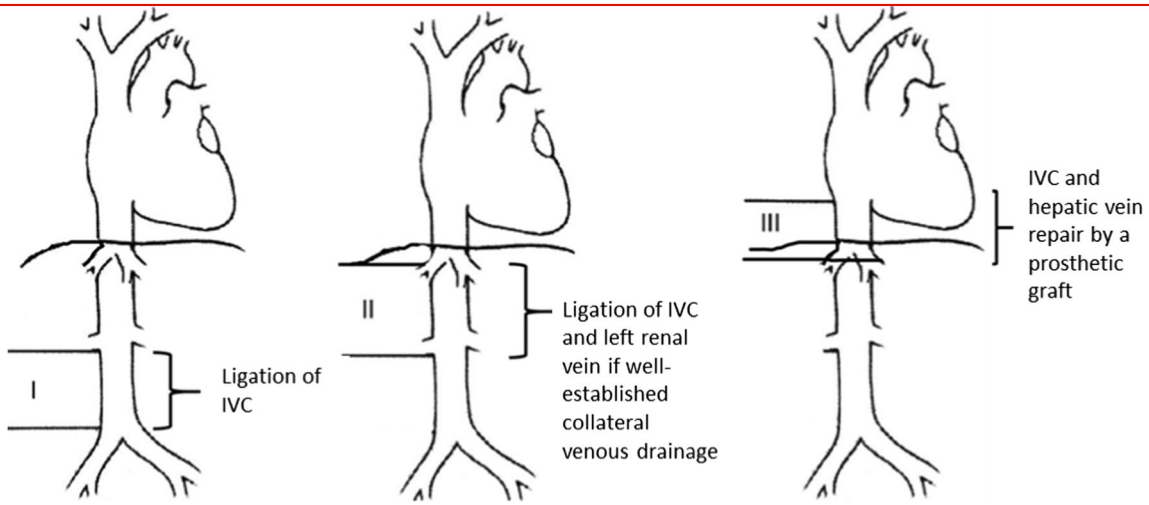

Fig. 1 Classification of IVC leiomyosarcomas and the different surgical management strategies

ligation can be safely performed when the IVC has been occluded by the tumor because of extensive collateral venous development. If the internal and external iliac bifurcation is not involved, the venous return from the lower limbs is ensured by the internal iliac vein and pelvic venous anastomosis. Some series with no IVC reconstruction after IVCL excision have been described with no postoperative complications. None of the patients presented IVC ligation symptoms after surgery, in particular no lower limb edema [18]. Following their experience, Jiang et al. [19] proposed guidelines for simple IVC ligation: (1) the duration of the disease is longer than 1 year, so that collateral venous circulation could be sufficient; (2) at least 75% of the IVC is obstructed; and (3) a preoperative intravenous injection of 20 mg furosemide leading to more than 100 ml urine within 30 min after the IVC is temporarily blocked. When the tumor is located on the iliac vein and involves both the origins of the external and internal iliac veins, iliac vein bifurcation resection is mandatory. In this case, reconstruction is required because simple ligation cannot ensure the venous return from the lower limbs. Indeed, the venous return is then impossible by the iliac vein, and venous anastomosis in the lower limbs and the pelvic area is no longer efficient to ensure adequate venous return. In this case, to facilitate reconstruction, we perform an end-to-side anastomosis between the extern iliac vein and the internal iliac vein. But IVC or iliac vein reconstruction is also possible with a prosthetic graft, autologous vein or cryovein.

In our center, simple ligation of the IVC is preferred since collateral venous circulation is well-developed. This strategy avoids vascular reconstruction complications such as preoperative and postoperative thrombosis, hemorrhage, and in the case of prosthetic graft, infection and anticoagulation therapy complications. In addition, the simple ligation of the IVC avoids vascular reconstruction, which could be complex, and enables operative time to be reduced.

The existence of a well-established collateral venous system is assessed from clinical examination and radiological imagery. The clinical examination looks in particular for lower limb edemas which indicate a poor collateral venous system, or for lower limb edemas at the beginning of the disease that later disappear, indicating considerable collateral venous development. We systematically complete the clinical examination by a radiological imagery. Intraoperative veno(cavo)graphy can therefore provide important information for the evaluation of collateral venous circulation and can facilitate planning in relation to the feasibility and safety of not performing IVC reconstruction [20]. Frequently, the development of a collateral venous system is assessed on CT scan with contrast enhancement, coupled with 3D reconstruction. A specific protocol enables the inferior vena cava venous system and its collateral venous system to be visualized. An autonomous workstation collects data in which multiplanar and 3D images are generated [21]. It thus appears to be a useful and easily available tool to define collateral venous systems and to decide on the surgical strategy.

Type-II IVCL

Several options can be proposed for the management of type II IVCL, but surgical treatment should include complete tumor resection and the preservation of the venous return. In this case, the surgical challenge is related to renal vein reconstruction. The distal part of the IVC should be ligated and excluded. If excision of the right renal vein is

required because of its involvement, the best strategy is to sacrifice the right kidney because of its poor residual venous drainage and a short right renal vein which would greatly complicate reconstruction. Prosthetic graft repair or auto-transplantation of the right kidney remains possible but is less often used. Simple ligation of the right renal vein is not safe because of the risk of renal failure and congestion of the right kidney. On the other hand, the left renal vein is longer and well-circulated collaterally, allowing the left kidney to be preserved, especially when the renal vein is chronically and totally occluded by the tumor. Indeed, the genital, adrenal and azygo-lumbar veins provide effective collateral drainage of the left kidney and safe ligation of the left renal vein without the occurrence of renal failure. Left renal vein reconstruction or left kidney auto-transplantation are required when the left renal vein has to be resected beyond the genital or lumbar collateral veins or when the renal vein is partially occluded without adequate collateral circulation. Several strategies have been described in the literature for left renal reconstruction. We recommend prosthetic graft reconstruction of the IVC and left renal vein. Reimplantation of the left renal vein in the IVC is performed by end-to-side anastomosis with a prosthetic graft. If the length of the left renal vein is sufficient, renal ostia venoplasty can be performed in order to avoid the use of a prosthetic graft [22]. Mann et al. [23] reported a series of 17 IVCL resections with left kidney salvage for all of their patients by preserving the native vein and performing reimplantation in the PTFE graft or by channeling outflow directly into the IVC. If renal auto-transplantation is required, the kidney is re-implanted by arterial and venous end-to-side anastomosis with common iliac vessels [24, 25].

Preoperative renal scintigraphy is required in order to assess kidney anatomy and function. If nephrectomy is required, preoperative renal scintigraphy will confirm the proper functioning of the remaining kidney.

Type-III IVCL

Vascular LMS located in the upper segment of the IVC between the hepatic vein confluence and the RA requires a complex surgical approach with a well-coordinated contribution from numerous specialties for appropriate management. The surgical team should include oncological, hepatic, vascular and cardiothoracic surgeons, a cardiothoracic anesthesiologist and a perfusionist to manage the cardiopulmonary bypass (CPB).

Sternotomy or phrenotomy and subcostal laparotomy are usually performed with care because of the broad venous collaterality caused by IVC occlusion [26]. Preoperative transesophageal echocardiography (TEE) monitors the stability of the intraluminal mass. The anterior pericardium should be preserved for a potential pericardial patch during cavo-atrial reconstruction. A preoperative ultrasound is therefore performed to confirm the absence of hepatic parenchyma involvement. Depending on the extent of intraluminal thrombus and whether there is a need to open the RA, a CPB or veno-venous bypass after hepatic and IVC mobilization is performed. Leiomyosarcoma of the retro-hepatic IVC often requires complete resection of the IVC associated with a partial hepatectomy if the hepatic parenchyma is involved [27, 28]. In our experience, an ex vivo excision of the liver and retrohepatic IVC was performed with an in situ clamping of the hepatic pedicle, avoiding its section and reconstruction (Fig. 2). During total clamping of the IVC and hepatic pedicle, the liver is maintained in cold ischemia by a portal cannula to prevent ischemia reperfusion injury. In rare cases, hepatic auto-transplantation—ex vivo and ex situ—is necessary [29]. For type III, IVC reconstruction remains essential to ensure liver drainage. In our center, reconstruction is performed using a polytetrafluoroethylene (PTFE) graft with hepatic vein reimplantation when necessary.

Graft reconstruction

There have been no randomized studies in the literature comparing the efficacy of the different types of vascular grafts. However, most authors recommend a PTFE graft as a prosthesis for IVC reconstruction since it provides the best results in terms of the length of the missing segment and resistance to intra-abdominal compression [30]. In fact, collapse of the graft remains a major risk factor for thrombosis. Some authors use a 20 mm graft for best congruency with the native IVC while others prefer smaller grafts (14–16 mm) to increase blood velocity [16, 31, 32]. Despite prosthetic grafts for IVC replacement are the most widely options in the literature, it presents several disadvantages. Indeed, vascular reconstruction by prosthetic graft exposes the patient to a significant risk of thromboembolism, infection and anticoagulation therapy complications. In a series of 15 patients surgically treated for retroperitoneal sarcoma with IVC resection, 10 underwent IVC reconstruction with no postoperative mortality, and postoperative morbidity at 7%, mainly resulting from hemorrhage and graft infection. In this series, however, overall graft patency was only 60%, with graft thrombosis occurring after 4 postoperative months [18]. The main series of inferior vena cava leiomyosarcomas resections and their reconstruction are summarized in Table 1. The largest series reported by Wachtel et al. [12], was carried out in 2015 with 377 patients who underwent IVC resection. For 315 patients, the type of IVC reconstruction was reported, among which 20.3% were ligated, 21.9% repaired

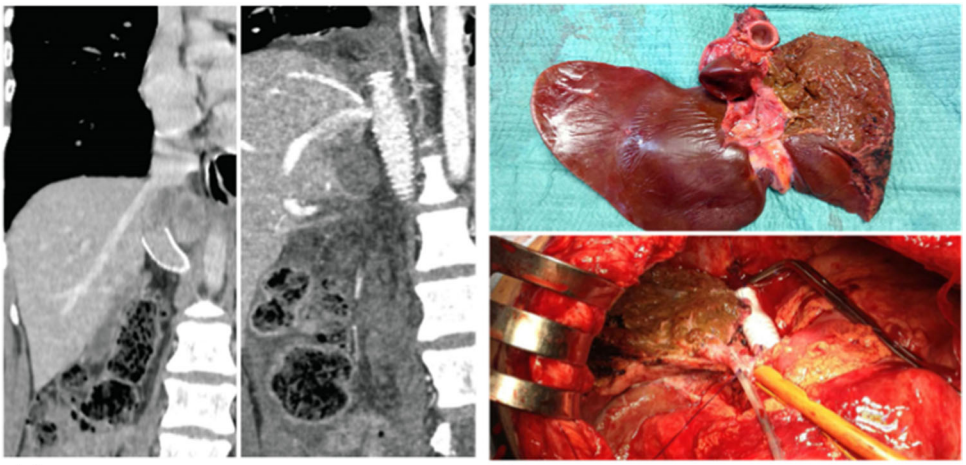

Fig. 2 Retro-hepatic vena cava leiomyosarcoma treated by ex vivo hepatectomy

primarily and 49.2% replaced by prosthetic graft. The 30-day mortality was low, at 1.9%, but 30-day morbidity was high with an overall complication rate of 24.7%. The most frequent postoperative complications were edemas with 10.1% and renal failure with 3.5%. Concerning graft patency, Cananzi et al. [33] reported 2 patients who underwent an interposition of PTFE graft following early postoperative graft thrombosis. In addition, Illuminati et al. performed 18 IVC resections followed by PTFE graft reconstruction. The diameters of the grafts ranged from 14 to 18 mm. In this series, 7 graft occlusions were observed, 4 of which had a diameter of 16 mm [2, 34, 35]. In 2016 however, Sulpice et al. [36] described 7 patients who underwent IVC reconstruction with a PTFE graft with no postoperative complication and satisfactory patency for all patients after a median follow-up of 56 months. They used a 16-mm diameter graft for one patient, an 18-mm diameter graft for 3 patients, and a 20-mm diameter graft for 3 patients. Overall, the results for graft patency and postoperative complications vary according to the series. It would seem that graft thrombosis does not occur as often with an 18 or 20 mm diameter graft. But these results require further comparative analyses to propose recommendations on the type of prosthesis graft. Regarding infectious complications, prosthetic graft infection remains a rare complication, but with severe morbidity. In a small series of patients treated with a prosthetic vascular graft, the authors reported a rate of prosthetic graft infection ranged from 1 to 6% but was associated with high morbidity and required prosthetic graft removal in 85% of the cases [37]. When the right colon, bowel, or duodenum has to be resected because of involvement, the risk of preoperative contamination by digestive bacteria and prosthetic graft infection is greatly increased. If vascular graft infection occurs, we recommend its complete removal followed by extensive debridement and systemic antibiotic therapy. If IVC reconstruction is necessary, an autologous vein is used with better results in terms of patency, resistance to infection and enlargement [38].

To avoid the use of a prosthetic graft after IVC removal, an autologous graft can be used, especially the saphenous vein, pericardium graft or bovine pericardium graft, which is effective but more expensive. In the literature, series and case reports using cryovein for IVC reconstructions are very rare and our experience is limited. Indeed, the accessibility of cadaveric veins is restricted because of grafts scarcity. Therefore, the main indication for cryovein use remains after removal of an infected prosthetic graft.

In order to reduce the risk of thrombosis and occlusion of the graft, an arteriovenous fistula between the aorta and the IVC or common iliac vein can be performed. This has been used for long prosthetic replacements of the supra-renal IVC to maintain high blood pressure through the graft. In addition, this technique avoids the use of long-term anticoagulants. For the infra-renal IVC, the creation of an arteriovenous fistula is not necessary because ligation remains preferable. Thus, for small or middle segment prosthetic replacement of the supra-renal IVC, the blood flow at this level is sufficient without an arteriovenous fistula.

IVC reconstruction requires special monitoring, especially for the patency of the IVC and anticoagulation therapy. During the postoperative period, we recommended IVC patency monitoring by Doppler-ultrasonography at least once before hospital discharge or in case of IVC thrombosis symptoms in clinical examination. If Doppler-ultrasonography is not available or unsuitable due to patient's morphology, a CT scan with contrast enhancement should be used. Concerning anticoagulation therapy, it is essential during the surgical procedure. Indeed,

Table 1 Review of the recent reported series of IVC leiomyosarcomas

First author	Year	Nbr of patients	IVC management (%)	Median EBL (ml)	Median OR time (min)	IVC complication (%)	30-Day severe morbidity (%)	In-hospital mortality (%)	3- and 5-years overall survival (%)
Wachtel et al.	2015	377	Ligation: 64 (16.9) Primary repair: 69 (18.3) Graft: 155 (41.2) Cadaveric: 10 (2.6) Bovine pericardium: 5 (1.3) Autologous vein: 11 (2.9) Autologous peritoneum: 1 (0.3) NA: 62 (16.5)	NA	NA	NA	56 (24.7)	7 (1.9)	NA-55
Cananzi et al.	2016	11	Ligation: 3 (27.2) Primary repair: 4 (36.4) Graft: 4 (36.4)	NA	NA	0	4 (36.4)	0	77.8–77.8
Alkhalili et al.	2016	3	Ligation: 1 (33.3) Graft: 2 (66.7)	1300	320	0	1 (33.3)	0	NA-49.4
Sulpice et al.	2016	8	Primary repair: 1 (12.5) Graft: 7 (87.5)	NA	NA	0	2 (25)	0	87.5-NA
Illuminati et al.	2016	18	Graft: 18 (100)	NA	NA	Graft thrombosis: 7 (39)	5 (28)	0	NA
Teixeira et al.	2017	7	Ligation: 3 (43) Graft: 4 (57)	NA	NA	0	1 (14)	0	100–25
Ghose et al.	2018	6	Ligation: 1 (17) Primary repair: 2 (33) Graft: 3 (50)	1925	450	0	1 (17)	0	NA
Liu et al.	2018	10	Ligation: 1 (10) Primary repair: 1 (10) Graft: 8 (80)	1935	358	Graft thrombosis: 2 (25)	6 (60)	0	NA-68.6
Jeong et al.	2019	12	Ligation: 2 (17) Primary repair: 1 (8) Graft: 9 (75)	NA	NA	NA	NA	NA	87.5–75
Kalluri et al.	2019	4	Graft: 4 (100)	NA	NA	Graft thrombosis: 1 (25)	1 (25)	0	NA

Nbr number, *IVC* inferior vena cava, *EBL* estimated blood loss, *OR* operative room, *NA* no applicable

intraoperative venous control, which is obtained by distal and proximal IVC clamping, leads to venous stasis and increases the risk of thrombus formation. Intraoperative systemic heparinization could prevent this complication [39]. In contrast, the use of postoperative systemic anticoagulants after IVC resection and reconstruction is still debated. The risk of postoperative thromboembolic complication is significant, but there are no clear guidelines on this topic. Some centers advocate postoperative anticoagulation after IVC resection and reconstruction to decrease postoperative venous thromboembolism (VTE) event. For example, Bower et al. reported a series of 29 patients who underwent IVC reconstruction with PTFE prosthesis. They used warfarin in the postoperative period and reported a 7% rate of acute graft thrombosis and a 3% rate of deep vein thrombosis (DVT). Likewise, Fiore et al. reported the same rate of VTE in a series of 15 patients treated with prophylactic doses of low molecular-weight heparin [18, 39]. Conversely, Hicks et al. reported a series of 65 patients who underwent IVC reconstruction with no systematic postoperative anticoagulation therapy. All patients received prophylactic heparin therapy but antiplatelet therapy was indicated only for patients with a cardiovascular risk factor, and postoperative systemic anticoagulation was indicated in case of VTE. In their series, the overall rate of VTE was 22% with an incidence of DVT of 9% and pulmonary embolism of 12% [40]. Therefore, there is currently no recommendation concerning systemic postoperative anticoagulation therapy, and its indication remains at the discretion of the surgeon. In our center, however, we prefer to use bi-antiplatelet medication for prosthetic graft reconstruction associated with routine prophylactic heparin therapy. Concerning venous grafts, we only use routine prophylactic heparin therapy.

Conclusion

IVC leiomyosarcomas are rare tumors and their surgical management remains a major challenge for sarcoma surgeons [30]. Because of their rarity, most of the available data has been collected from individual case reports or relatively small case series, which explains the lack of consensus for the surgical management of IVCL resection and its reconstruction. On the basis of previous studies and our own experience, we propose clear guidelines. Finally, three major factors influence the need for, and the type of, IVC reconstruction: the site of the tumor (especially renal vein involvement); the extent of IVC resection needed; and the presence of well-established collateral venous drainage. We therefore strongly recommended no IVC repair for types I and II, if the collateral venous system is well-developed and allows sufficient venous return. When IVC reconstruction is required, a PTFE graft prosthesis should be recommended.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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