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KIDNEY DISEASES (G CIANCIO, SECTION EDITOR)

Current Trends in Management of Renal Cell Carcinoma with Venous Thrombus Extension

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Abstract

Purpose of Review To review the evidence regarding the current trends in surgical management of renal cell carcinoma (RCC) with inferior vena cava (IVC) thrombosis. Recent published series have shown the role of minimally invasive surgery in IVC thrombectomy. This review article evaluates the present RCC with venous extent literature to assess the role of open and minimally invasive surgery in this scenario.

Recent Findings Robotic urological surgery has shown to have known benefits in radical prostatectomy, partial nephrectomy, and pyeloplasty. Recent published series showed feasibility of robotic IVC thrombectomy even for level IV cases.

Summary With growing number of robot-assisted and laparoscopic surgeries worldwide, there is a current tendency to treat this complex and challenging pathology with a minimally invasive approach, without compromising oncological outcomes.

Keywords Vena cava thrombosis · Laparoscopy · Radical nephrectomy · Renal cell carcinoma · Robotic surgery

Introduction

During the last 20 years, we have witnessed enormous changes in the presentation and the way of approaching and treating patients with localized and metastatic renal cell carcinoma (RCC) [1].

Nearly half of the renal tumors currently managed in urologic departments worldwide are small renal masses. When considering a surgical intervention, nowadays, there is a tendency to perform nephron-sparing surgery, through minimally invasive procedures [2].

A hallmark of RCC is its biological characteristic of invading the renal vein and/or inferior vena cava (IVC), which occurs in nearly 6% of patients. In this subgroup, 44% of patients present with renal vein extension and fortunately only 1–4% may have a thrombus extending into the right atrium [2, 3].

Since the first report of a laparoscopic kidney surgery in 1990 at Washington University by Dr. Ralph Clayman et al., laparoscopic nephrectomy has become a standard approach in the management of most renal tumors [4, 5].

Minimally invasive surgery (MIS), whether performed laparoscopically or robotically, is well established for localized tumors. MIS for localized RCC is associated with improved perioperative outcomes while preserving oncologic outcomes. There is increasing evidence that with MIS similar benefits and outcomes can be achieved for properly selected cases of locally advanced RCC (aRCC), with the advantage of lower morbidity and shorter convalescence time when compared with open surgery [6–8].

For many years, open surgery remained as the only and preferred approach for RCC with IVC extension, but with the development of MIS as well as with known technological innovations in surgery, a redefinition of the traditional approach in this challenging scenario emerged [5, 9–11].

In this article, we decided to carry out a critical analysis of different classification systems used in RCC with thrombus extension to IVC in order to recognize which classification best suits when planning surgery. We describe the critical points to take into consideration when choosing the approach as well as those specific maneuvers described for the minimally invasive approach. We also summarize the oncological and perioperative results of minimally invasive radical nephrectomy plus IVC thrombectomy for aRCC. Finally, we present the

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improvements in the management of this complex pathology in a Latin American high-volume university hospital over the last 10 years.

IVC Level Classifications

Many classifications have been proposed since Berg described the first radical nephrectomy with IVC thrombectomy in 1913 [12]. Despite the differences between the level classification models presented by different authors (Table 1), all of them were described for open surgical approach. While some follow more anatomical concepts and endorse changes in the TNM staging system [13], other models are more suitable for the surgical challenge proposed.

Determining the extent of the tumor thrombus (TT) is essential to define the surgical strategy.

Wilkinson et al. classified tumor extension in three levels, depending on whether it affects the renal vein or if it involves the IVC, below or above the diaphragm [14]. Libertino divided the TT into 2 groups, infradiaphragmatic which is subdivided according to its relationship with the hepatic veins and supradiaphragmatic, also subdivided into 2, intracardiac and intrapericardial [15]. Other authors classified the extension depending on the need for cardiopulmonary bypass; examples of such models are the one proposed by Belis et al. and the system described by Stief et al. in 1988 and 1995 respectively [16, 17].

The Mayo Clinic classification introduced by Neves and Zincke established 4 levels; if the thrombus involves <2 cm above the renal vein, it is classified as level 1; level 2 or infrahepatic which is for thrombus with extent more than 2 cm but below intrahepatic vena cava; level 3 for thrombus that reached intrahepatic portion of vena cava; and level 4 above diaphragm [18].

Table 1 Most relevant models proposed for thrombus level classification

Thrombus level classification	Neves	Blute	Ciancio
Renal vein		0	
< 2 cm above renal vein	I	I	
> 2 cm below intrahepatic IVC	II	II	
Intrahepatic IVC	III	III	
Intrahepatic IVC below MHV			IIIa
Intrahepatic IVC above MHV			IIIb
Suprahepatic below diaphragm			IIIc
Supradiaphragmatic below atrium			IIId
Atrium	IV	IV	

IVC, inferior vena cava; *MHV*, major hepatic veins

Although there is no consensus on which is the classification that best defines the surgical strategy to adopt, the one described by Neves and Zincke and later modified by Blute [19] is currently the most frequently used in many centers.

Xiao et al. postulate some drawbacks with thrombus level 2 which would be broadly defined as extent >2 cm above the renal vein to the level below major hepatic veins (MHV), placing in the same category infra and retrohepatic thrombus. The authors found that this could be the reason why many different surgical maneuvers have been proposed to approach level II thrombectomy, such as liver mobilization, veno-venous bypass, and cardiopulmonary bypass with cardiac arrest [12].

The cephalic extension reached by tumor thrombus, especially in the intrahepatic portion of the vena cava, implies different surgical situations; for this reason, Ciancio et al. proposed in 2002 a model that divides level 3 into 4 subgroups, according to the surgical maneuver required in the intrahepatic portion of the vena cava [20].

In this regard, level IIIa corresponds to thrombus extending into the retrohepatic inferior vena cava but below MHV, IIIb or hepatic corresponds to thrombus reaching MHV, IIIc thrombus extending above MHV but below the diaphragm, and finally, IIId—thrombus extending into the supradiaphragmatic intrapericardial IVC.

Despite the fact that this model defines more precisely the surgical challenge and therefore the complexity of the procedure, it is remarkable that this classification has not been considered in later series reported.

In our experience, an adequate classification must be adjusted to the surgical maneuvers required by the level of the thrombus; thus, changes introduced by Ciancio et al. are more appropriate and more suitable for this requirement.

Approach Selection

Radical nephrectomy with IVC thrombectomy remains a challenging procedure that requires a multi specialized well-trained surgical team.

Open surgery remains the standard approach to address RCC involving IVC due to the need for wide exposure and safe control of the vena cava, especially in those cases that require dissection of the suprahepatic portion of the IVC or combined intrathoracic access.

In the last decade, there has been a cautious movement towards performing minimally invasive treatments. Although laparoscopic and robot-assisted approaches have been described even for supradiaphragmatic thrombectomy, such situations seem to be more a description of initial experiences than an established procedure [21–23].

A tumor thrombus inside the renal vein (level 0) does not represent more challenge than a standard radical nephrectomy and could be resolved using a pure laparoscopic approach.

When the thrombus extends into the inferior vena cava and requires a cavotomy for extraction, the choice to use laparoscopic or robotic assistance will be given by the ability and preference of the surgeon to solve such situations [22].

Despite having a robotic surgery program at our institution since 2008, we prefer to approach these cases in a purely laparoscopic manner for two main reasons; first, the proximity with the patient in case of conversion and second, the advantage of choosing the site and the number of ports that each case requires. For level IIIa, the procedure can also be safely approached with minimally invasive techniques as dissection and clipping of short hepatic veins allow a direct access to the retrohepatic IVC as seen in Image 1.

Conversely, for level IIIb or higher, surgery requires control of the hepatic pedicle through a Pringle's maneuver and a dissection of the suprahepatic inferior vena cava; thus, we do not recommend to do this procedure through minimally invasive access if the entire multidisciplinary team is not well trained in such approaches.

Level IV represents a major challenge that includes cardiopulmonary bypass (CBP), deep hypothermia, and cardiac arrest. Although some reports endorse the feasibility and reproducibility of minimally invasive access for this level, the widespread applicability of this procedure is yet to be determined and therefore may only be appropriate for well-selected patients, extremely skilled surgeons, and high-volume centers [23].

Minimally Invasive Surgical Techniques

Main Surgical Principles

Gaining adequate exposure in the upper abdomen and retroperitoneum may be a major task for many urologists, especially in cases of a large renal tumor or vena caval involvement. When performing IVC thrombectomy through a minimally invasive approach, most surgeons try to reproduce the same surgical maneuvers as in open surgery. According to thrombus level, surgical complexity will variate. For level I/II, patients require infrahepatic IVC dissection and mobilization to perform cross-clamping and cavotomy. Contrarily, adequate exposure of the retrohepatic inferior vena cava is the key to successful removal of the thrombus in patients with level III/IV [19]. For liver mobilization, "piggy-back" technique described for liver transplantation and "Pringle's" technique for hepatic hilum clamping are usually employed. Piggy-back liver transplantation is so called because the recipient vena cava remains in situ and the liver is mobilized off of the vessel. Small hepatic veins passing from the caudate lobe are ligated and divided. The only remaining structural attachments of the liver are the hepatic veins and porta hepatis, which enable the 3 major hepatic veins to be clamped and the liver removed without clamping the vena cava. Pringle maneuver consists of a temporary occlusion of the portal venous and arterial inflow to the liver [24].

Preoperative Renal Artery Embolization

Preoperative renal artery embolization preoperative renal artery embolization (PRAE) is not routinely used in RN with IVC thrombectomy. Chan et al. compared PRAE with no PRAE in patients with T3 RCC and found that PRAE was associated with increases in operating time, blood loss, and hospital stay (all statistically significant) and higher perioperative mortality (8.4% vs. 3.4% for PRAE vs. no PRAE, respectively, p value not stated) [25]. Tang et al. found that PRAE may be more appropriate for patients with advanced tumor thrombus because of its benefit in reducing intraoperative blood loss and blood transfusion ($p = 0.043$ and $p = 0.028$, respectively), but otherwise, the authors did not find a measurable advantage in terms of long-term prognosis for patients in the PRAE group [26]. Conversely, prophylactic embolization also had some merits in minimal invasive surgery. Chopra et al. performed the preoperative embolization in 80% (20/24) of patients undergoing robot-assisted level II–III IVC thrombectomy. They concluded that RAE decompressed the venous collaterals, decreased blood loss, and enhanced robotic efficacy. Wang et al. reported that the preoperative artery embolization could reduce intraoperative oozing, which was helpful for mobilizing the kidney and manipulating the vessels in robot-assisted IVC thrombectomy. Embolization was necessary and critical for left renal cancer, as the thrombectomy was performed in the left decubitus position. It was very difficult to expose the left renal artery. The embolization allowed the left renal vein to be disconnected well before the left renal artery can be robotically secured, intraoperatively.

Minimally Invasive Approach Aspects

The first case of pure laparoscopic RN and IVC thrombectomy for RCC was reported by Romero et al. in 2006, using a laparoscopic Satinsky clamp to occlude the proximal IVC [27].

In 2011, Abaza [5] reported the first series of transperitoneal robotic RN with level I–II IVC tumor thrombectomy for right-sided RCC, including the first cases of minimally invasive cross-clamping of the IVC.

Chopra and Gill described in 2015 the primary concept of "IVC-first, kidney-last" approach in a minimal IVC touch manner, to minimize chances of tumor embolism and major hemorrhage. The right colon and duodenum are reflected medially to expose the vena cava. Retroperitoneal dissection begins infra-renally in the midline to expose the

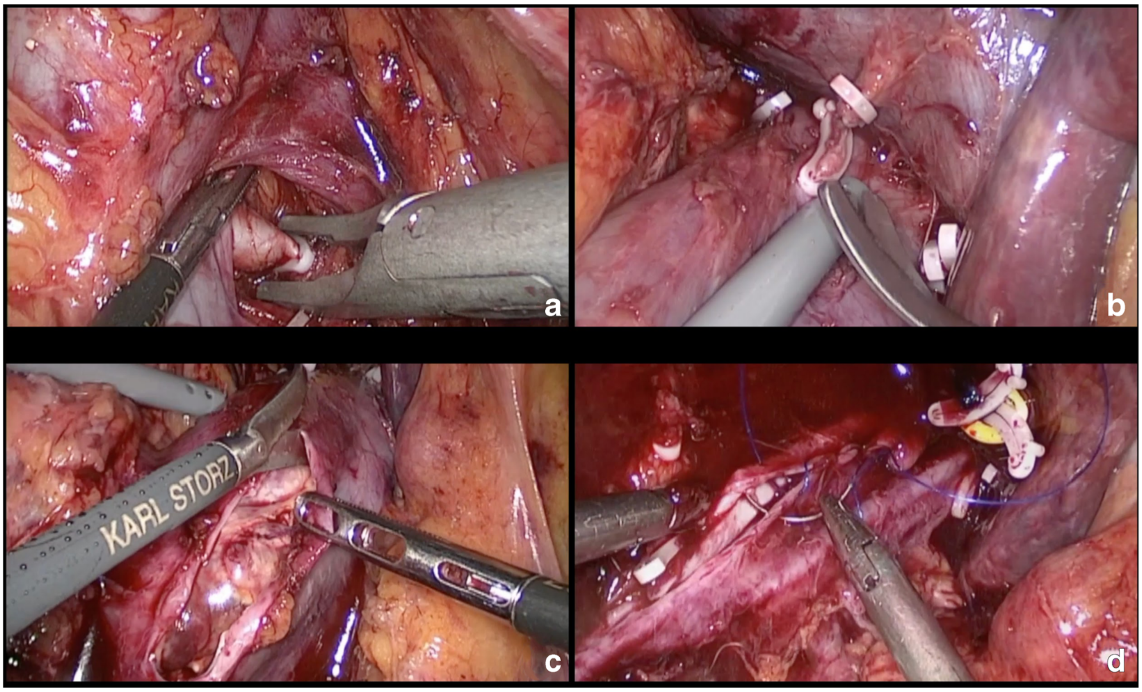

Image 1 Pure laparoscopic dissection for thrombus level IIIa. **a** Right renal artery in interaortocaval space. **b** Short hepatic vein dissection and clipping. **c** Cavotomy and thrombectomy. **d** Vena cava closure (cavorraphy)

interaortocaval region. Dissection of the infrarenal IVC involves control of all relevant lumbar veins and the gonadal vein, which are taken with Hem-o-lok clips. The infrarenal IVC is encircled with a double-loop tourniquet (Rummel) using a vessel loop passed through a piece of 20-F red rubber urethral catheter and secured in place with a Hem-o-lok clip. Dissection is carried out cephalad within the interaortocaval region. The left renal vein is mobilized and encircled with another Rummel tourniquet.

For proximal IVC control, careful interaortocaval dissection is performed towards the liver. For level III thrombus, the relevant number of short hepatic veins is controlled with Hem-o-lok clips and/or suture-ligation. Releasing the short hepatic veins is essential to retract the caudate lobe; this maneuver exposes an additional 3–4 cm of the IVC allowing high intrahepatic access to the retrohepatic IVC. The right main adrenal vein is controlled with Hem-o-lok clips, and the right lateral border of the suprarenal IVC is dissected. Retrocaval dissection of the intrahepatic IVC is performed. A double-fenestrated grasper is used to encircle the IVC with a Rummel tourniquet in this high retrohepatic location. The right renal hilum is dissected and the right renal vein is exposed. In case of right-sided tumors, the right renal artery is dissected and clipped in the interaortocaval region.

The initial maneuver is to cinch the distal IVC tourniquet. Once assured that the patient is able to tolerate caval cross-clamping with no hemodynamic impact, the left renal vein and proximal IVC Rummel tourniquets are cinched sequentially, thus excluding the thrombus-bearing caval segment. The thrombus-bearing right renal vein is transected with stapler. The excluded caval segment is now rotated and circumferentially inspected to reconfirm visually that all feeding lumbar veins have been secured. An appropriately situated cavotomy is created towards the right edge of the IVC, adjacent to the right renal vein ostium; the cavotomy should be well planned so that subsequent caval reconstruction does not overly narrow its lumen. The thrombus is carefully dissected free from the IVC lumen without local spillage. The right renal vein ostium, along with its staple line, is excised en bloc with the thrombus. Caval reconstruction is performed with a 5–0 Gore-Tex or prolene suture with a single-layer running stitch. Tourniquets are released sequentially (left renal vein, suprarenal IVC, infrarenal IVC) and caval flow restored. Then, right RN is completed.

In case of left-sided renal tumors, maneuvers are different. Temporary cessation of blood flow to the right kidney is necessary to properly exclude the caval segment for controlled thrombectomy. The right renal artery and vein are controlled with individual bulldog clamps, prior to cinching the infra and suprarenal IVC tourniquets. The thrombus-bearing left renal vein is transected with a stapler as left-sided tumors routinely undergo preoperative angioembolization. After caval thrombectomy and reconstruction, caval flow is restored and the right kidney revascularized. Then, the patient is repositioned left side up for left RN [28].

Inferior Vena Cava Thrombus Removal: En Bloc Versus Transected Techniques

Klink et al. compared patients in whom the thrombus was purposely transected (n:92) with those in whom the IVC thrombus was removed en bloc (n:60) with the kidney. The overall rate of complications was not statistically significant when comparing both groups, although in the transected group, 3 patients had intraoperative tumor thrombus embolization to the pulmonary artery requiring surgical embolectomy, but all 3 survived [29]. While this technique was assessed in open surgery, it can be applied in MIS. Transected technique is being widely used in left side tumors for robotic or laparoscopic approach, as renal artery is often embolized prior to surgery, and this allows an early stapling of the left renal vein to eliminate back-bleeding from the tumor-bearing kidney, reduces chances of thrombus embolization, allows full mobilization of the excluded IVC segment, and eliminates the risk of local tumor spillage.

Technique Innovations in Minimally Invasive Surgery

In 2016, Kundavaram et al. [30] published an initial report of four cases of RCC and level II–III IVC thrombus, where proximal IVC vascular control during robotic thrombectomy was achieved introducing a 9-French intracaval Fogarty balloon catheter in a retrograde fashion.

Another technological innovation introduced in this report was the vena cava endoscopy (cavoscopy). After excluding the caval segment and performing thrombectomy, a flexible cystoscope was introduced into the abdomen through a 10-mm accessory trocar and then was guided robotically into the IVC through the cavotomy incision, and the caval lumen was inspected to rule out IVC wall invasion or secondary skip lesions [30].

Recently, Alahmari et al. [31] described another endoluminal method using a stent graft balloon catheter inserted through endovascular access through the right internal jugular vein under fluoroscopy and placed above the tumor thrombus.

These innovations allow us to perform a fully minimally invasive surgical procedure.

Perioperative Results

In the pure laparoscopic IVC thrombectomy published series, median operative time (OT) ranged between 105 min for a right-sided and 400 min for a left-sided RCC with level II IVC thrombus. In the robot-assisted published series, OT ranged between 250 and 465 min. These major OT were seen in the last published series of 6 patients who underwent level IV robotic thrombectomy.

Median/mean estimated blood loss (EBL) was variable across both laparoscopic and robotic series. In level IV series published by Wang, 5 patients who underwent cardiopulmonary bypass (CPB) had a median estimated intraoperative blood loss of 2800 (IQR: 1500–6500) ml. The perioperative mortality rate was 7.7%, with one perioperative death. Although no intraoperative deaths were noted, one patient with level IV thrombus died on the 1st postoperative day in the intensive care unit ward due to extensive blood loss (12,000 ml) and coagulation dysfunction [21]. This reveals the complexity of IVC thrombectomy when level is III/IV.

Intraoperative complications were reported in two laparoscopic series including a major intraoperative bleeding, a spleen injury, and IVC injury, and in two robotic series, including liver laceration treated with hemostatic agents and bowel injury treated with robotic suture. Conversion to open surgery was reported only in one patient in the laparoscopic group and in one patient in the robotic group [22].

All major robotic series perioperative results are summarized in Table 2.

Oncologic Outcomes

The most relevant minimally invasive IVC thrombectomy published series is recent, heterogeneous, and with short follow-up time (range 3–27 months vs. 4–32 months in robotic vs. laparoscopic, respectively) [22]. Thus, the non-inferiority of minimally invasive surgery compared to open surgery regarding long-term oncologic outcomes is yet to be addressed.

Several studies included in a review by the International Renal Cell Carcinoma–Venous Thrombus Consortium in 2010 demonstrated that the extent of venous involvement (renal vein vs. IVC) impacts on survival rate [33]. In this review (n:1215), the overall median survival time by tumor thrombus level was 44.6 months (renal vein), 27.9 months (level 1), 21.4 months (level 2), and 12 months (level 3). There was a difference in 5- and 10-year CSS between patients with thrombus in the renal vein only, the IVC, or above the diaphragm. Patients with only renal vein involvement show improved 5-year CSS compared to those with IVC extension below the diaphragm ($p < 0.002$).

At 10-year follow-up, the survival differences are less marked but still persist ($p = 0.037$).

According to this, further prospective studies comparing open vs. minimally invasive approach and considering thrombus level are needed to draw reliable conclusions on intermediate long-term oncologic outcomes of each technique.

Table 2 Perioperative results of major robotic IVC thrombectomy published series

Author/year	Approach	Thrombus level	OR (min)	EBL (ml)	HS (days)	Conversion (*n*)	Complication rate (*n*)
Abaza, 2011 [5]	Transperitoneal	I–II n:5	327	170	1.2	0	0
Gill, 2015 [31]	Transperitoneal	I–II n:7 III: n:9	294	375	5.8	0	1
Abaza, 2016 [22]	Transperitoneal	I–II n:30 III: n:2	292	399	3	0	8
Wang, 2016 [32]	Transperitoneal	I–II n:17	250	240	5.2	0	2
Kundavaram, 2016 [33]	Transperitoneal	I–II n:2 III: n:4	387	668	5.5	0	4
Chopra, 2016 [26]	Transperitoneal	I–II n:13 III: n:11	270	240	4	1	4
Wang, 2018 [34]	Transperitoneal	I–II n:20 III: n:2	285	1350	18	0	13
Wang, 2019 [29, 35]	Transperitoneal	III: n:7 IV: n:6	465	2000	13.2	0	9

OR, operative time; *EBL*, estimated blood loss; *HS*, hospital stay

Hospital Italiano de Buenos Aires Experience on RCC with Venous Thrombus Extension

In 2010, we prospectively began registering patients treated for RCC at the Urology Department of Hospital Italiano de Buenos Aires, as part of a multi-institutional registry database on Renal Masses designed by the Clinical Research Office of the Endourological Society (CROES) [36]. This registry captures our approach for RCC with venous extension over the last 10 years.

From January 2010 to December 2019, 119 out of 1958 patients (6%) were surgically treated for RCC with venous thrombus extension (including renal vein thrombus).

Mayo Clinic classification was used to establish the level of thrombus extension [19]. Regarding level 0, 50 (42%) patients had thrombus limited to renal vein, while 69 patients presented with thrombus involving IVC. Level I was observed in 21 (17.6%) patients, level II in 19 (15.9%), level III in 15 (12.6%), and level IV in 14 (11.7%) patients. Although the majority of cases (74.7%) underwent open surgery, we

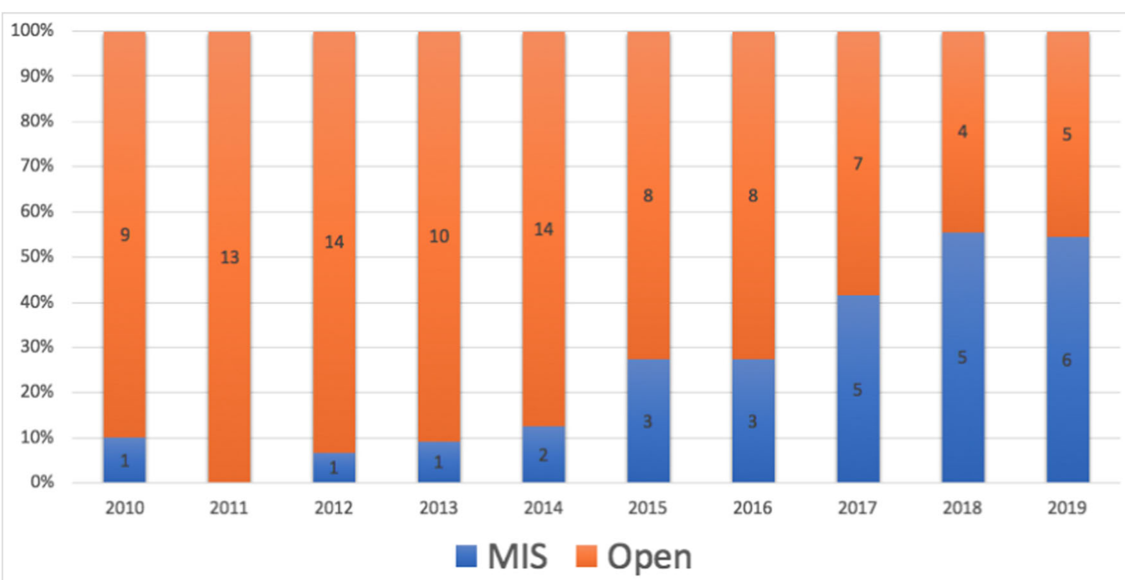

Fig. 1 Historic approach selection for RCC with venous extension at the Urology Department of Hospital Italiano de Buenos Aires

recently observed an increasing tendency of radical nephrectomies with venous thrombectomy performed by MIS (from 10% in 2010 to 54% in 2019, Fig. 1).

With a thoughtful and stepwise application of MIS to our practice, in 2016, we incorporated pure laparoscopic approach for RCC with thrombus levels I to III. Laparoscopic surgery was performed in 40%, 23%, 5%, 26%, and 0% of levels 0, I, II, III, and IV, respectively. Our case series in laparoscopic IVC thrombectomy ($n = 9$) is limited by the height of tumor thrombus, being the confluence of main hepatic veins the most relevant surgical limit. All 3 patients with retrohepatic level III IVC thrombus were limited to the short hepatic veins and did not extend proximally towards the main hepatic veins (IIIa according to Ciancio et al. level classification) [20]. No conversion to open surgery was observed in the MIS group.

We consider that appropriate approach selection is of paramount importance. Open surgery remains the predominant technique for treating RCC involving IVC. This is not surprising despite the known benefits of minimally invasive surgery. Open surgery still offers a reliable cancer control rate. Contrarily, if minimally invasive surgery can achieve these two goals of safety and long-term cancer control, short-term benefits as reduced pain, hospital stay, and less bleeding may justify a minimally invasive approach for such a complex pathology [5].

Conclusion

In conclusion, although different open approaches have been described for the treatment of RCC with thrombus extension, minimally invasive techniques are emerging as an alternative in experienced hands and selected patients. Validating a classification system is essential to be able to compare the results of published series.

Compliance with Ethical Standards

Conflict of Interest Alberto Jurado, Agustin Romeo, Guillermo Gueglio, and Patricio Garcia Marchiñena each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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