Minimally Invasive Surgery for Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma

Ezequiel Becher, MD*, Dora Jericevic, MD, William C. Huang, MD

KEYWORDS

• Minimally invasive surgery • Renal cell carcinoma • Metastatic renal cell carcinoma
• Advanced renal cell carcinoma • Robotic surgery • Nephrectomy

KEY POINTS

- Surgery continues to have a vital role in the management of advanced renal cell carcinoma.
- Minimally invasive surgery for localized renal cell carcinoma has been shown to provide comparable oncologic outcomes as open surgery, while decreasing treatment-related morbidity.
- With advances in technology and refinements in surgical technique, a minimally invasive surgical approach is feasible in select cases.
- Several high-volume centers have reported favorable interim oncologic and nononcologic outcomes using minimally invasive surgery, including cases with inferior vena cava involvement and regional adenopathy.
- Patient selection and surgeon experience are critical, as proper oncologic principles should never be compromised when utilizing a minimally invasive surgical approach.

INTRODUCTION

Radical nephrectomy (RN) is considered the preferred treatment of surgically resectable advanced renal cell carcinoma (aRCC) by most guidelines.[1–3] Open RN (ORN) can be a considerably morbid surgery, because it often entails a large incision, extensive bowel mobilization and elevated estimated blood loss (EBL), factors that translate into significant postoperative pain and a longer recovery. Minimally invasive surgery (MIS), whether performed laparoscopically or robotically, is well-established for localized tumors. MIS for localized tumors is associated with improved perioperative outcomes, while maintaining oncologic outcomes.[4–6] There is increasing evidence that MIS may be similarly beneficial in cases of aRCC.

This article discusses the role of MIS in the management of aRCC, highlighting the potential benefits and drawbacks. MIS approaches for inferior vena cava (IVC) thrombectomy and lymph node dissection (LND) are also covered. Additionally, we address the role of minimally invasive cytoreductive nephrectomy (CN) in the context of metastatic RCC (mRCC). For the purposes of this article, we define aRCC as stage cT2 disease or higher, given that large organ-confined disease may be technically challenging to extirpate and potentially difficult to distinguish from locally aRCC at diagnosis. Locally advanced disease encompasses patients with cT3 and cT4 disease with venous thrombi, extracapsular extension, adjacent organ involvement, and/or nodal disease.

Department of Urology, NYU Langone Health, 222 East 41st, 12th Floor, New York, NY 10017, USA
* Corresponding author.
E-mail address: Ezequiel.becher@nyulangone.org

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HISTORY OF MINIMALLY INVASIVE SURGERY FOR RENAL MASSES

The first report of a laparoscopic kidney surgery dates to 1990 at Washington University by Dr Ralph Clayman's group.[7] The procedure was performed successfully in 6 hours and 45 minutes with a 300 mL EBL on an 85-year-old woman with a 3-cm midpole renal mass. She had an uncomplicated course and a 6-day length of stay. This successful procedure pioneered the way for significant advances in laparoscopic retroperitoneal surgery, with subsequent reports of laparoscopic partial nephrectomy and laparoscopic retroperitoneal LND (RPLND).[8]

Over the last decade, the increasing use of the robotic surgical platform has stimulated the adoption of MIS, thus contributing to the rising trend of nephron sparing surgery over RN.[9] With a flatter learning curve compared with laparoscopic surgery, along with other advantages such as the wristed instruments, 3-dimensional vision, and tremor suppression, surgeons have been emboldened to incorporate the minimally invasive approach for more complex scenarios, such as IVC invasion and local lymph node involvement.[10,11]

EVIDENCE AND POTENTIAL BENEFITS

When introducing any new technique in oncologic surgery, a primary concern is does the new method achieve at least the same oncologic efficacy as the established one? In this regard, several studies[4,6,12–14] support that for properly selected cases of aRCC, MIS can obtain equivalent overall survival, cancer-specific survival, and progression-free survival as open surgery. These studies also suggest that MIS for aRCC has similar benefits as those achieved with MIS for localized tumors, namely, equivalent oncologic control, with lower morbidity and shorter convalescence time.[4,6,12,13]

Using the Surveillance Epidemiology and End Results database and propensity score matching, Golombos and colleagues[13] compared the outcomes of MIS versus ORN. After a median follow-up of 57.1 months, they demonstrated comparable oncologic efficacy and superior perioperative outcomes in the MIS group. However, this article included all renal masses undergoing RN, 17% of which had tumors 7 cm or larger and 21% of which were stage III after matching.

Including only pT3a or higher tumors, Laird and colleagues[4] retrospectively analyzed matched cohorts of 25 laparoscopic RN (LRN) and 25 ORN cases with a median follow-up of 54.6 months. They observed that the MIS cohort had a statistically significant lower EBL (LRN 100 mL vs ORN 650 mL; $P<.01$) and length of stay (LRN 4 days vs ORN 9 days; $P<.01$), while maintaining cancer-specific survival and progression-free survival.[4] A critique of this article is that the matched paired analysis may have underpowered the sample size, but its findings were replicated by a larger, nonmatched study from Bragayrac and colleagues.[6] Although there is substantial concordance among the studies,[6,12,14–16] the results remain limited to primarily level 3 and level 4 evidence.

In terms of perioperative outcomes, the benefit of lower EBL associated with the MIS approach is multifactorial, but is largely attributed to the pneumoperitoneum's homogeneous positive pressure applied to tissues during surgery. In vascular tumors such as clear cell RCC, this pneumoperitoneum is particularly beneficial in controlling bleeding from frail parasitic vessels, which often feed the tumor.

Perioperative outcomes are also important to note because a shorter convalescence may allow for potential improvements in survival. We know that surgery alone is not curative in many patients with aRCC. Subsequently those undergoing cytoreductive nephrectomy may have a delay in receipt of systemtic therapy. Additionally in patients with locally aRCC, a prolonged recovery may result in adjvuant therapy, particularly in clinical trials.[17] This particular aspect was highlighted by Gershman and colleagues[18] in their retrospective study evaluating factors contributing to the postoperative complications of 294 patients undergoing CN for M1 disease. On multivariate analysis, they found that undergoing MIS was independently associated with earlier administration of systemic therapy.[18]

Currently, several studies support the notion that minimally invasive RN can be safely performed even in more complex and clinically advanced cases. Depending on the study, the rates of Clavien grade IIIa or higher complications range from 3% to 10% for MIS, generally less than what is reported for ORN[12,19–22] (8%–25%).

ROBOTIC VERSUS LAPAROSCOPIC SURGERY

There are only a few studies comparing robotic RN (RRN) with LRN. In a multi-institutional retrospective study by Anele and colleagues,[23] the authors did not appreciate any significant differences in the perioperative outcomes of RRN versus LRN. Although, this study included patients undergoing RN for all tumor sizes, the proportion of patients with cT3 or higher disease, or undergoing CN, was higher in the robotic cohort, suggesting that surgeons may have tended to favor RRN over LRN when facing more complex cases. Despite its fairly large sample

size (n = 941), further prospective randomized studies are warranted however, to draw stronger conclusions.

CASES OF RENAL VEIN AND/OR INFERIOR VENA CAVA INVOLVEMENT

The role of MIS in the management of patients with venous tumor thrombi (VTT) has significantly evolved since it was first described in 2003.[24] The latest reports demonstrate that indications for MIS have expanded to include level 3 and 4 tumor thrombi, extensive adenopathy along with disease in the chest resulting in a combined thoracic MIS approach.[10,25–27]

It is commonly accepted that Robot-assisted surgery is especially useful in cases with short tumor thrombi that either do not extend into the IVC (level 0) or do not extend far from the ostium such that they can be milked back (level 1). The robotic platform provides the surgeon with an enhanced ability to control these thrombi without the need for a cavotomy. However, most extensive level I thrombi require an incision into IVC. Techniques that replicate the use of the Satinsky clamp as a tangential clamp, allowing for a subsequent oversewing of the removed vein ostium site without significantly interrupting IVC flow, as done in the open surgery approach, have been described.[28]

The management of more extensive tumor thrombi (level II–III) can also be done through a MIS approach. Chopra and colleagues[26] have described a reproducible step-by-step technique for the management of right and left sided level II to III IVC robotic thrombectomy and RRN. The authors suggest addressing the IVC first and mobilizing the kidney later, reportedly decreasing the risk of tumor embolization. After the IVC has been dissected and all lumbar veins have been identified, clipped, and divided, they proceed with the placement of Rummel tourniquets on the contralateral renal vein, as well as the IVC proximal and distal to the tumor borders. Next, they proceed with ligation of the renal artery and sequential cinching of the tourniquets. The unique step the authors describe is the transection of the thrombus-containing vein with a laparoscopic stapler. The authors state that this maneuver allows for a complete evaluation of the IVC's circumference and an early bagging of the thrombus once it is dissected, thus avoiding spillage. Even though the article suggests the technique can be used on level II and III thrombi, it does not address the concern of extensive liver mobilization required for some level III thrombi.

Wang and colleagues[25] have described their management of complex level III and IV tumor thrombi with a purely robotic approach, achieving acceptable short- and medium-term oncologic outcomes. Even though there is substantial heterogeneity in complexity among their series of 13 patients, as well as concerns about the reproducibility of their technique, the authors should be congratulated on their pioneering efforts.

RETROPERITONEAL LYMPH NODE DISSECTION AND ADENOPATHY

The role of LND in aRCC is controversial. There is no high-level evidence that demonstrates a survival benefit of LND in aRCC.[29,30] However, LND seems to have an important role in staging patients with aRCC at the time of nephrectomy.[31] Even though these concepts are more thoroughly analyzed in another article in this issue (please see Pooja Unadkat and colleagues' artcile, "The Role of Lymphadenectomy in Patients with Advanced Renal Cell Carcinoma (RCC)," in this issue), we focus on the role of MIS in LND for aRCC.

Some studies suggest that MIS is associated with a less extensive or absent LND.[32–34] Although there is no clear oncologic benefit of LND in patients with aRCC (including those with clinically visible nodes), we do not advocate for the omission of a proper lymphadenectomy particularly in patients with suspicious nodes. The introduction and widespread use of robotic-assisted surgery has facilitated the performance of higher yield lymphadenectomies, achieving similar node counts as those seen with the open approach.[35]

There is no standardized lymphadenectomy template for RCC, given the lack of data supporting therapeutic benefit. This is not the case with nonseminomatous germ cell tumors (NSGCT) of the testis, where there are clear indications and quality metrics for RPLND. In this regard, Pearce and colleagues[36] have examined the clinical outcomes of robotic RPLND performed for NSGCT using a large multi-institutional series, concluding that robotic RPLND can achieve adequate oncologic metrics with an acceptable morbidity profile. Given that the most cephalad part of the RPLND template for NSGCT reaches the renal hilum, one could argue that part of the LND done for NSGCT mimics the LND done for aRCC. We cannot extrapolate the conclusions reached by Pearce and colleagues[36] to the RCC paradigm. The authors demonstrate that a meticulous and proper retroperitoenal lymph node dissection can be performed with low morbidity regardless of the primary site.

CRITIQUES AND POTENTIAL DRAWBACKS

One of the major concerns in oncologic MIS is the risk of tumor dissemination owing to the use of

pneumoperitoneum in the setting of potentially aggressive tumor biology. There are reports of worsened oncologic outcomes and unusual sites of disease recurrence after MIS for various malignancies including cervical,[37] NSGCT,[38] and adrenocortical carcinoma.[39] In their prospective trial, Ramirez and colleagues[37] randomized women with early stage cervical carcinoma to open and MIS radical hysterectomy, observing that the MIS approach provided a lower cancer-specific survival and overall survival.

Incisional and local recurrences secondary to tumor spillage are rare phenomena in RCC,[40] accounting for less than 0.1% of cases (mostly described in case reports or series).[40–42] A metaanalysis comparing oncologic and perioperative outcomes of ORN and LRN was not able to find significant differences in overall local recurrence rates between these 2 approaches.[43] Even though this metanalysis included tumors of all sizes and stages, the recurrence rates were also comparable in the subgroup analysis of T3 and T4 tumors.[43] Song and colleagues[44] conducted a review of this subject, concluding that even though port site recurrence is rare, it entails a poor prognosis, with only 31% survival at 1 year in this small cohort (n = 16). However, no technical aspect was found to be a risk factor for occurrence of port site metastasis, suggesting that the tumor biology might play a greater role in the development of these unusual sites of recurrence.

In terms of local recurrence after RN, it is rare, accounting for 1% to 2% of open and MIS cases.[45] Resection of these isolated local recurrences has been shown to improve oncologic outcomes.[46,47] Some case series suggest that MIS is more advantageous than an open approach for the recurrence resection, achieving equivalent oncologic quality with lower morbidity.[45] However, the low prevalence of local recurrence makes it challenging to produce strong evidence to support the potential benefit of MIS in this setting.

The pneumoperitoneum system and inefficient bagging of the specimen are often considered putative causes of unusual site recurrence, including port sites.[44,48] However, there is no clear evidence that these are the causes of port site recurrences, and the rarity of this event makes it close to impossible to run any study to objectify this finding. Another potential risk factor for port site recurrence is specimen morcellation.[44] However, this procedure is now rarely used for RCC, mainly because it precludes standard pathologic examination of the specimen, thus limiting tumor staging.[49]

Regardless of the approach, adherence to strict oncologic principles is critical to minimize local recurrences. It is our belief, particularly for patients with aRCC, that careful manipulation of the mass without violation of tumor boundaries and an early bagging of the specimen are the key factors for mitigating unusual patterns of recurrence.

CYTOREDUCTIVE NEPHRECTOMY IN METASTATIC RENAL CELL CARCINOMA: A ROLE FOR MINIMALLY INVASIVE SURGERY?

In light of seminal clinical trials such as CARMENA and SURTIME, the role of CN in the context of mRCC is constantly being redefined.[50,51] Nevertheless, most guidelines agree that surgery plays an important role for the management of patients with mRCC who have a good performance status and do not present with poor risk features.[52]

A challenge yet to be fully explored is the impact of MIS for CN in the era of targeted therapy and immunotherapy. Several retrospective series report that the preoperative use of targeted molecular therapies (such as tyrosine kinase inhibitors) before CN does not increase the rate of perioperative complications.[53–55] Even though the study by Harshman and colleagues[55] did show the benefit of reduced EBL with MIS, only a minority of cases in this study were performed through a MIS approach. The SURTIME trial[51] randomized patients with mRCC and resectable primary tumors to either CN followed by systemic targeted therapy or CN preceded by systemic targeted therapy with progression as the primary endpoint. The safety of deferred CN was among the secondary end points. This trial did not find significant differences in perioperative morbidity of CN with prior targeted therapy, though it did not comment on surgical difficulty or approach (open vs MIS). Neither the retrospective series[55] nor the findings of SURTIME reported increased perioperative morbidity with the preoperative use of targeted therapy. However, the majority of these cases were performed through an open approach, which raises the concern of whether MIS is the right approach for these theoretically more difficult cases.

Regarding surgery after the use of immunotherapy, a series was recently published that describes the difficulty surgeons encountered when performing a CN in cases of complete distant response to immune checkpoint inhibitor therapy.[56] In their series of 11 patients (7 open and 4 MIS), they encountered serious intraoperative difficulties that resulted in longer median operative time procedures with an elevated average EBL (243 minutes and 903 mL, respectively). A history of immunotherapy should caution the surgeon that the case might be more difficult than expected and perhaps warrant an open approach. Until

larger studies on these cases shine a brighter light on the matter, the approach chosen will have to be left to the discretion of the surgeon.

PROPER PATIENT SELECTION FOR MINIMALLY INVASIVE SURGERY IN ADVANCED RENAL CELL CARCINOMA

As previously mentioned, although MIS can achieve oncological results comparable to ORN, it does not imply that MIS is applicable to every patient scenario. It is important for surgeons to acknowledge their own level of expertise and comfort when selecting a surgical approach, keeping in mind that the proper approach will be one that derives the most benefit for the patient.

Proper patient selection cannot be driven solely on size or clinical stage. The current AJCC staging for RCC[57] describes cT2 tumors as confined to the kidney and 7 cm or larger, regardless of the maximum diameter. Tumors become cT3 if there is evidence of invasion either to the perirenal/sinus fat or to the segmental branches of the renal vein. Obviously, small cT3 tumors (vein thrombus or sinus fat involvement) may not be as technically challenging as a 7-cm left upper pole cT2 renal mass with large parasitic vessels and extensive regional adenopathy.

Even though clinical stage should not be the only driving factor in patient selection for MIS, it is still an important factor to consider, especially for more advanced stages. RN for tumors with invasion into neighboring organs can be extremely challenging. The largest retrospective series from experienced tertiary level institutions exploring surgical outcomes of nephrectomy in T4 disease report that the majority (if not all) of the cases were done through an open approach.[58–60] The series published by Oake and colleagues[60] does include cases performed laparoscopically (16%), which did not seem to be an indicator of adverse outcomes in the univariate analysis. However, it is important to add that invasion into neighboring organs (with concomitant organ resection) only accounted for 7.3% of the study population with the remaining categorized as T4 because of soft tissue invasion outside Gerota's fascia.

We have described the role and some technical aspects of MIS for IVC thrombectomy cases and LND. There are no clear patient selection criteria for a minimally invasive approach. The literature is filled with outcomes of complex cases performed minimally invasively that are certainly stimulating and a sign of progress. However, the enthusiasm should be met with caution and surgeons must always be aware of their limitations particularly as they pertain to novel treatment approaches.

NEW YORK UNIVERSITY EXPERIENCE ON MINIMALLY INVASIVE SURGERY FOR ADVANCED RENAL CELL CARCINOMA

At the department of Urology of New York University Langone Health, we began prospectively collecting the data on patients undergoing radical or partial nephrectomy for aRCC in 2004 as part of a prospectively maintained database including patients undergoing surgery for renal masses. This dataset captures our experience as we developed a formal program for robotic surgery.

During this period, from a total of 1668 patients, 302 (18%) had stage cT2 or higher disease. When examining all oncologic kidney surgery, the proportion performed for aRCC has been stable at approximately 20% over the last 16 years at our institution. However, we have observed an increasing percentage of our RNs being performed for aRCC (from 25% in 2006 to 70% in 2019; Fig. 1). This can be explained by an increasing

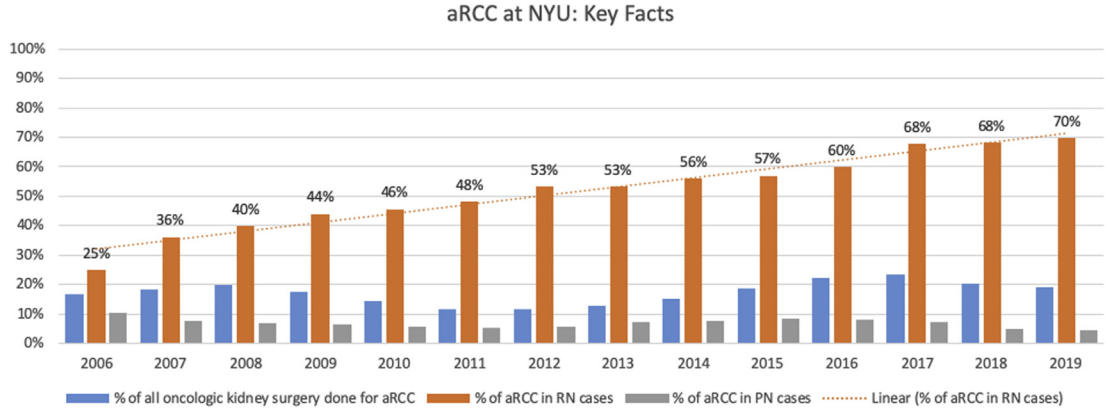

Fig. 1. Historic rate of patients with aRCC (stage ≥cT2) at New York University Langone Health.

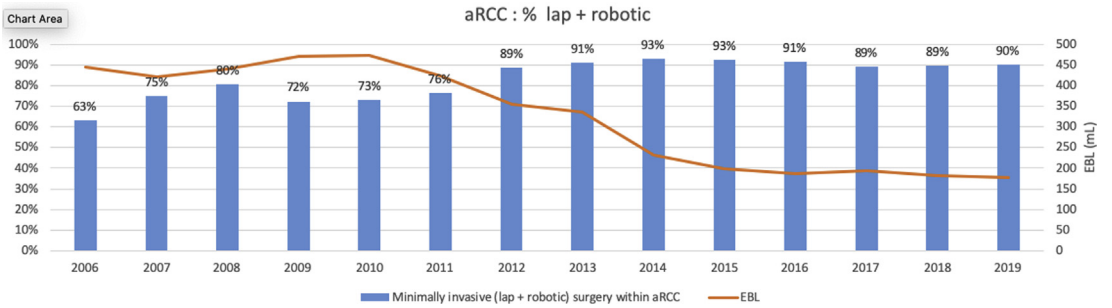

Fig. 2. Historic rate of patients undergoing MIS for aRCC (stage ≥cT2) at New York University Langone Health.

percentage of localized RCC being managed through partial nephrectomy instead of radical nephrectomy. Since 2012, MIS has constituted 90% of all oncologic kidney surgery, which has been associated with improvements in perioperative outcomes, such as EBL (from 450 mL in 2006–175 mL in 2019; Fig. 2).

With a thoughtful and stepwise application of MIS to our practice, we now incorporate a MIS approach in more complex cases of aRCC, such as those with IVC level I-II thrombi or regional adenopathy. At New York University, we routinely consider RRN with IVC thrombectomy for level I and II tumor thrombi. Our approach differs from what has been described elsewhere in this article in that we have not adopted the use of a stapler across the renal vein for level II thrombi. Our technique for level II thrombi consists of a venotomy either around the ostium of the renal vein (for short level II thrombi) or a cavotomy (for longer thrombi) with an intact extraction followed by an immediate bagging of the specimen (Figs. 3 and 4). With our

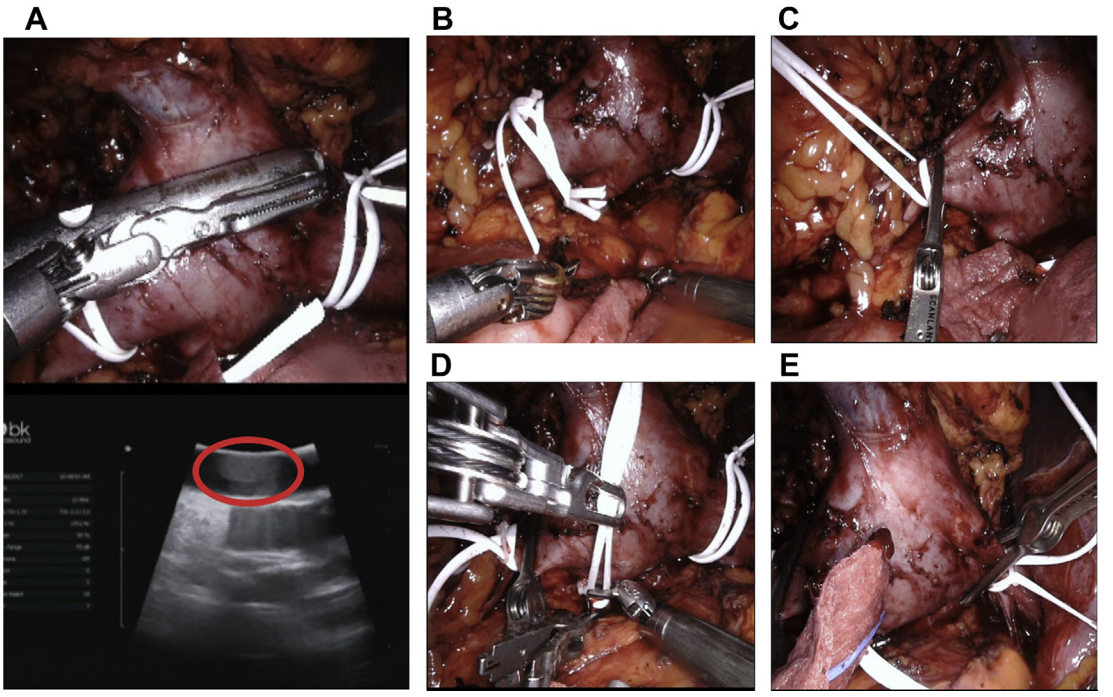

Fig. 3. Robotic approach to level II thrombi. Intraoperative ultrasound examination enables to define the limits of the thrombus (*red circle*), which in this case is extending outside the ostium of the right renal vein (*A*). Mobilization and control with a double-loop vessel loop secured by a Hem-o-Lok clip of the infrarenal and suprarenal IVC, as well as the left renal vein is paramount (*B*). We use bulldog clamps to clench the vessels. This is aided by the tightening of the tourniquet. The infrarenal IVC should be the first segment to be interrupted (*C*). These steps are repeated to close the circulation of the left renal vein (*D*) and suprarenal IVC (*E*), in that order.

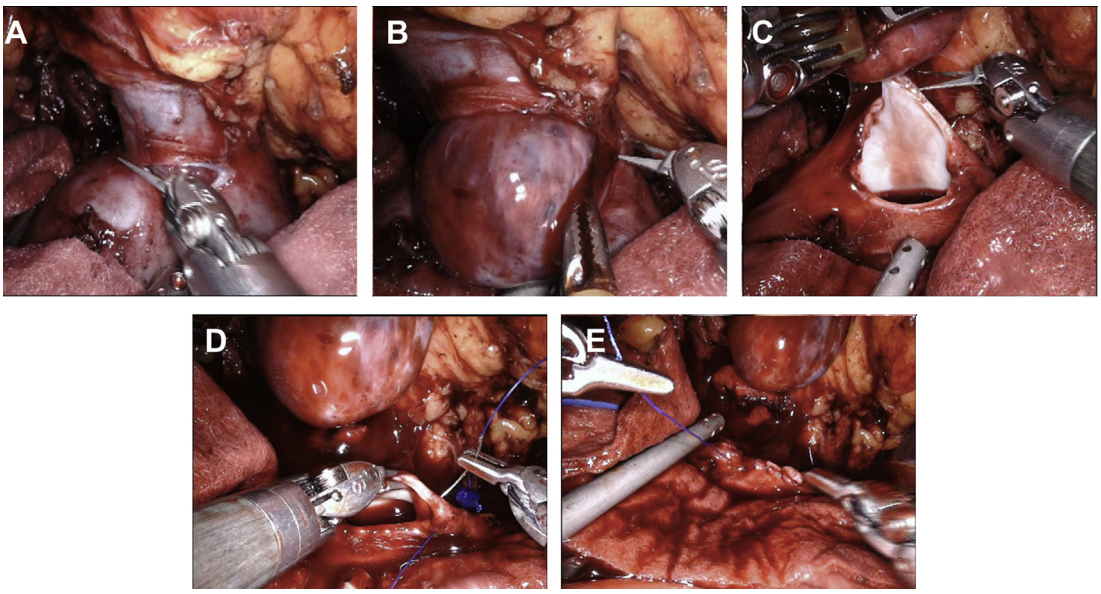

Fig. 4. IVC thrombectomy. After proper cinching of the tourniquets, a cavotomy on the anterior aspect of the IVC is made medial to the ostium of the right renal vein (*A*). The IVC is incised until a careful delivery of the tumor thrombus is done (*B*) (it is crucial to preserve the integrity of the tumor). The cavotomy is completed and the right renal vein containing the tumor is divided (*C*). A running 4-0 polypropylene suture is used to repair the IVC defect (*D*, *E*).

expanding experience of MIS RPLND in testis cancer, we are incorporating the same techniques for LND in patients with RCC.[61]

SUMMARY

In the era of targeted therapy and immunotherapy, surgery continues to have a role in the management of aRCC. Traditionally, cases of aRCC with IVC involvement or extensive adenopathy were performed through an open approach. However, advantages of the robotic platform have fostered the implementation of MIS in these more challenging scenarios. In properly selected patients, it seems that the MIS approach for aRCC provides comparable oncologic outcomes with decreased postoperative morbidity. Although MIS may not be applicable to all cases of aRCC, the role of MIS will continue to expand by adhering to proper oncologic principles and appropriate patient selection.

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