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REVIEW

Techniques and outcomes of minimally-invasive surgery for nonmetastatic renal cell carcinoma with inferior vena cava thrombosis: a systematic review of the literature

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ABSTRACT

INTRODUCTION: Current guidelines recommend considering surgical excision of non-metastatic renal cell carcinoma (RCC) with inferior vena cava (IVC) thrombosis in patients with acceptable performance status. Of note, several authors have pioneered specific techniques for laparoscopic and robotic management of renal cancer with level I-IV IVC thrombosis.
EVIDENCE ACQUISITION: A systematic review of the English-language literature on surgical techniques and perioperative outcomes of minimally-invasive radical nephrectomy (RN) and IVC thrombectomy for nonmetastatic RCC was performed without time filters using the MEDLINE (*via* PubMed), Cochrane Central Register of Controlled Trials and Web of Science (WoS) databases in September 2018 according to the PRISMA statement recommendations.
EVIDENCE SYNTHESIS: Overall, 28 studies were selected for qualitative analysis (N.=13 on laparoscopic surgery, N.=15 on robotic surgery). The quality of evidence according to GRADE was low. Laparoscopic techniques included hand-assisted, hybrid and pure laparoscopic approaches. Most of these series included right-sided tumors with predominantly level I or II IVC thrombi. Similarly, most robotic series reported right-sided RCC with level I-II IVC thrombosis; yet, few authors extended the indication to level III thrombi and to left-sided RCC. Surgical techniques for minimally-invasive IVC thrombectomy evolved over the years, with specific technical nuances aiming to tailor surgical strategy according to both tumor side and thrombus extent. Among the included studies, perioperative outcomes were promising.
CONCLUSIONS: Minimally-invasive surgery is technically feasible and has been shown to achieve acceptable perioperative outcomes in selected patients with renal cancer and IVC thrombosis. The evidence is premature to draw conclusions on intermediate-long term oncologic outcomes. Robotic surgery allowed to extend surgical indications to more challenging cases with more extensive tumor thrombosis. Nonetheless, global experience on minimally-invasive IVC thrombectomy is limited to high-volume surgeons at high-volume Centers. Future research is needed to prove its non-inferiority as compared to open surgery and to define its benefits and limits.

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KEY WORDS: Vena cava, inferior; Laparoscopy; Nephrectomy; Kidney neoplasms; Robotics; Thrombosis.

Introduction

Renal cell carcinoma (RCC) with inferior vena cava (IVC) thrombosis accounts for 4-10% of renal cancer cases.[1] A recent study using the National Cancer Database reported a rate of stage III RCC of 8.3% over the period 2004-2015, with a trend toward improved survival in recent years.[2]

Current guidelines from the European Association of Urology (EAU) recommend considering surgical excision of non-metastatic RCC with IVC thrombosis in patients with acceptable performance status.[3] This concept is also endorsed by the latest National Comprehensive Cancer Network (NCCN) clinical guidelines.[4] Notably, the surgical technique and approach for each individual case should be selected based on the extent of tumor thrombus.[3, 4]

However, the evidence supporting these recommendations is still suboptimal and rather heterogeneous,[5] mainly due to the paucity of comparative data. In particular, uncertainties remain over the relative benefits and harms of different approaches, including preoperative renal artery embolization, use of cardiopulmonary bypass, IVC filters and liver mobilization techniques, as well as strategies for access to the IVC and excision of the venous thrombus.[3, 5]

Specific surgical principles have been advocated to face this challenging surgery.[5] While minimal modifications of the standard surgical approach for radical nephrectomy (RN) are usually required for level I thrombi,[6] specific technical steps should be followed to manage renal masses with level II-IV thrombi.[5]

The use of minimally-invasive approaches for "frontier surgery" in urology, including cystectomy and intracorporeal urinary diversion,[7] kidney transplantation,[8, 9] retroperitoneal lymph node dissection,[10] nephron-sparing surgery for T2 renal masses,[11] and augmented-reality-guided surgery,[12, 13] has dramatically increased over the last decade. In this scenario, several Authors have pioneered specific techniques for laparoscopic and robotic management of renal cancer with level I-IV IVC thrombosis.[14, 15]

Herein we provide a comprehensive overview of available series of laparoscopic and robotic radical nephrectomy and IVC thrombectomy for nonmetastatic RCC, focusing on surgical techniques and perioperative outcomes.

Evidence acquisition

Search strategy

A systematic review of the English-language literature was performed without time filters using the MEDLINE (*via* PubMed), Cochrane Central Register of Controlled Trials and Web of Science (WoS) databases in September 2018 combining the keywords "renal cell carcinoma," "inferior vena cava," "thrombosis" or "thrombus," "minimally-invasive surgery" (including laparoscopic and robotics), "thrombectomy" or "nephrectomy" (Supplementary Digital Material 1: Supplementary Text File 1).

The systematic review process was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations.[16]

A specific search strategy was designed combining free text and Mesh Terms.

Additionally, hand-search of bibliographies of included studies and previous reviews was also performed to include additional relevant studies. Two reviewers (R.T. and F.S.) carried out the literature search independently.

Inclusion criteria and objectives

A specific population (P), intervention (I), comparator (C), outcome (O) and study design (S)

(PICOS) framework was prespecified to assess study eligibility.[17]

Studies with insufficient reporting of the PICOS criteria were excluded from the review.

The primary objective of this review was to provide a critical assessment of the available surgical techniques of minimally-invasive (laparoscopic or robotic) surgery for RCC with IVC thrombosis, with special emphasis on technical nuances, perioperative results and oncologic outcomes.

Systematic review process

After all records were identified from the literature search, Mendeley software (Mendeley Ltd, London, UK) was used to identify and remove duplicates among included records.

Overall, 3373 articles were preliminarily identified by the literature search. After exclusion of duplicates and articles unrelated to the topic of this review (N.=584), two independent reviewers (R.T., F.S.) screened titles and abstracts of 2789 records. To guide the selection process, an *a priori* developed screening form was used. Disagreement was solved by a third party (R.C.), who supervised the systematic review process. After exclusion of book chapters, editorials, conference abstracts, preclinical studies, studies on cadaveric models, previous reviews and articles not related to the primary endpoints of this review, 84 articles were assessed for eligibility. Finally, 28 studies fulfilling all PICOS criteria were selected for qualitative analysis.

The flow-chart depicting the systematic review process according to PRISMA is shown in Figure 1.

Data extraction

Data were extracted independently by two Authors (R.T., A.M.) in a-priori developed data extraction form, including information on all elements of the PICOS framework (Table I, II, III, IV).[18-45]

Risk of bias (RoB) assessment in case-series and observational studies was performed independently by two Authors [F.S., R.T.] according to the Newcastle-Ottawa-Scale (NOS)[46] (Supplementary Digital Material 2: Supplementary

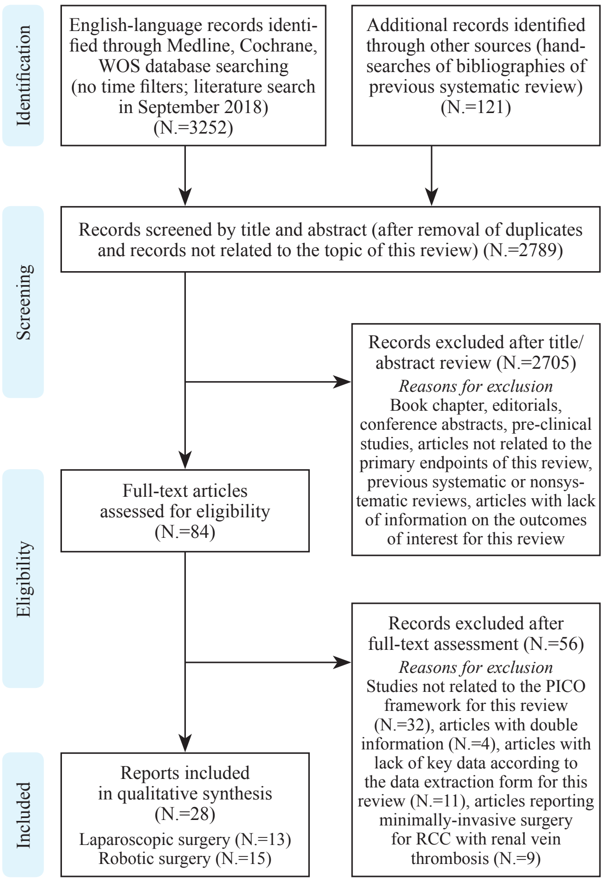

Figure 1.—Flow-chart showing the literature search and systematic review process according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement recommendations.

Table I). Disagreement was solved by a third party [R.C.].

The overall quality of evidence was assessed according to Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations.[47]

A narrative form was used for qualitative data synthesis.

Evidence synthesis

Characteristics of included studies

The key characteristics of the studies included in the review are shown in Table I, II.

In the laparoscopic group (Table I), 13 studies including 66 patients between 2002 and 2018 were included, either as retrospective case series (N.=9) or case reports (N.=4). The number of patients included in the studies ranged from 1 to 17.

TABLE I.—*Key characteristics of studies on laparoscopic radical nephrectomy with inferior vena cava thrombectomy.*

Author/year	Study type	Number of patients	Age (median or mean)	BMI (median or mean)	Gender (M/F)	Study period (years)	Tumor size cm) (median or mean)	RCC Histology	pTNM
Hand-assisted or hybrid laparoscopy									
Sundaram, 2002[18]	Case report	1	76	NR	M	2002	12.5	ccRCC	T3bNx
Varkarakis, 2004[19]	Case series	4	56	32.8	M	NR	9.0	ccRCC	T3bNx
Disanto, 2004[20]	Case report	1	87	NR	F	2004	7	ccRCC	T3bNx
Martin, 2008[21]	Case series	4	65	NR	NR	2000-2007	6.8	ccRCC	T3bNx
Hoang, 2010[22]	Case series	9	66	30.5	NR	2004-2009	9.1	ccRCC	T3bNx
Pure laparoscopy									
Romero, 2006[23]	Case report	1	58	NR	F	2006	7.5	Other	T3bNx
Xu, 2014[24]	Case series	17	50	23	M: 9; F: 8	2009-2013	7.9	NR	NR
Wang, 2014[25]	Case series	2	56/73	25/27	M	2008-2012	8.1/9.5	RCC	T3bN0M0
Shao, 2014[26]	Case series	11	52	21.9	M: 9; F: 2	2010-2013	8.2	ccRCC; pRCC	T3bN0: 5 pts; T3bN1: 1pt; T3cN0: 4pts; T3cN1: 1pt
Wang, 2015[27]	Case series	2	55/71	17.6/20.0	F/M	2011-2012	14/8.5	ccRCC	T3bN0M0
Wang, 2016[28]	Case series	5	57	22.4	NR	2012-2014	6.9 (3.5-9)	ccRCC	T3bN0M0
Cinar, 2018[29]	Case series	8	61.6	27	NR	2005-2017	9.5	ccRCC/pRCC	T3bN0M0: 6; T3bN1M0: 2;
Giannubilo, 2018[30]	Case report	1	56	NR	M	2018	12.5	NR	NR

BMI: Body Mass Index; RCC: renal cell carcinoma; M: male; F: female; NR: not reported; ccRCC: clear-cell renal cell carcinoma; pRCC: papillary renal cell carcinoma.

TABLE II.—*Key characteristics of studies on robotic radical nephrectomy with inferior vena cava thrombectomy.*

Author/year	Study type	Number of patients	Age (median [IQR] or mean [SD])	BMI (median [IQR] or mean [SD])
Abaza, 2011[31]	Case series	5	64 (53-70)	36.6 (22-43)
Lee, 2012[32]	Case report	1	61	43.5
Bratslavsky, 2014[33]	Case report	1	52	45
Hui, 2014[34]	Case report	1	73	NR
Gill, 2015[35]	Case series	7 (level II trombus)	69	31.6
		9 (level III trombus)	61	27.5
Ball, 2015[36]	Case series	2	NR	NR
Wang, 2015[37]	Case series	17	61	24.7
Abaza, 2015[38]	Multicenter prospective series	32 (9 institutions)	63	30
Ramirez, 2016[39]	Case report	1	75	28.4
Kundavaram, 2016[40]	Case series	6	64.5	24.4
Chopra, 2016[41]	Two-center series	24 (one patient of the series was electively converted to open surgery within 30-45minutes of starting because of failure to progress due to insurmountable bowel loops)	64	28
Wang, 2017[42]	Case series	22	58.5 (46.8-64.0)	24.7 (18.1-29.8)
Aghazadeh, 2017[43]	Case report	1	79	38.8
Gu, 2017[44]	Retrospective study (matched-pair analysis of robot-assisted *versus* open radical nephrectomy and IVC thrombectomy)	31	55.7	24.8
Nelson, 2017[45]	Case report	1	53	NR

BMI: Body Mass Index; IQR: inter-quartile range; SD: standard deviation; RCC: renal cell carcinoma; M: male; F: female; NR: not reported; ccRCC: clear-cell renal cell carcinoma; pRCC: papillary renal cell carcinoma.

Histology was clear cell RCC (ccRCC) in most cases. Tumor pathological stage was T3b in 11 studies while one series included both pT3b and pT3c tumors.[26] In two studies, pathological stage was not reported.[30]

In the robotic group (Table II), 15 studies including 161 patients from 2008 to 2017 were included. Similar to the laparoscopic group, most were retrospective case-series (N.=9) or case reports (N.=6). Two multicenter studies were reported, of which one retrospective[41] and one prospective.[31] At histopathological analysis, most cases were ccRCC. Pathological stage was pT3b in all studies while three series reported also more advanced stages (pT3c,[35] or pT4a,[35, 38, 41]).

A detailed overview of perioperative outcomes from available series on laparoscopic and robotic RN and IVC thrombectomy is shown in Table III, IV, respectively.

Overall, a hand-assisted or hybrid laparoscopic approach was used in 5 series. Most surgeons employed a transperitoneal approach while a retroperitoneal approach was reported in 5 series;[20, 24, 25, 27, 28] one report described a combined approach.[30]

All series on robotic RN and IVC thrombectomy reported a transperitoneal approach (Table IV).

Figure 2 depicts the number of studies on minimally-invasive treatment of RCC with IVC thrombosis according to tumor side and the level of IVC thrombus.

Overall, most laparoscopic series included right-sided tumors, with predominantly level I or II IVC thrombi (Table III). Of note, only two laparoscopic series reported IVC thrombectomy for right-sided RCC with level III[22] or level IV[26] IVC thrombosis. Moreover, only two studies included left-sided tumors with IVC thrombosis.[25, 29]

Similarly, most robotic series reported right-sided RCC with level I-II IVC thrombosis,[31, 32, 35-38, 40-42, 44] while few extended the indication to level III thrombi.[33-35, 38-42] Notably,

Gender (M/F)	Study period (years)	Tumor size (cm) (median [IQR] or mean [SD])	RCC histology	Pathological stage
NR	NR	10.4 (7.8-15.5)	RCC (not specified)	T3bN0M0
M	2012	12.0	ccRCC with rhabdoid differentiation	T3bNx
F	2013	8.5	ccRCC	T3bN0M0
F	2014	4.8	ccRCC	T3N0M0
M: 6; F: 1	2013-2015	8.5	ccRCC	T3aN0Mx: 2; T3aN1Mx: 1; T3bN0Mx: 3; T4aN0Mx: 1
M: 7; F: 2				T3bN0Mx: 7; T3cN0Mx: 1; T3bN0M1: 1
NR	2015	NR	ccRCC	T3bNx
M: 12; F: 5	May 2013 - July 2014	5.8	NR	T3b
NR	2008 - 2014	9.6	ccRCC (six with sarcomatoid features).	T3bN0 in all patients except one (pT4)
M	2015	9.8	Collecting duct RCC	T3bN1
M	2016	8.5	ccRCC; pRCC; Collectind Duct RCC	T3cN0: 3; T3cN1: 1; T34N2: 1
M: 21; F: 3	July 2013 - March 2015	8.5	ccRCC in all cases except one (pRCC)	T3a: 5 (20.9%) pts; T3b: 14 (58.3%); T3c: 2 (8.3%); T4a: 3 (12.5%). Positive lymph nodes were found in 3 (12.5%).
M: 15; F: 7	May 2013- July 2016	7.8 (2.5-15.0)	ccRCC; pRCC; Xp11.2-RCC; unclassified carcinosarcoma	T3aN0M0: 1; T3bN0M0: 16; T3bN0M1: 3; T3cN0M1: 1; T3bN0M1: 1
M	2017	7.0	ccRCC	T3bN0M0
M: 26; F: 5	2006 - 2015	7.3	ccRCC; pRCC; Other RCC	T3bN0: 29; T3bN1: 2
M	2017	11	ccRCC	T3bN0 M1 (adrenal gland)

Table III.—*Perioperative and oncologic outcomes in studies on laparoscopic radical nephrectomy with inferior vena cava thrombectomy. Some studies included patients undergoing cytoreductive robotic radical nephrectomy and inferior vena cava thrombectomy. However, data from these patients could not be selectively excluded from the analysis of perioperative and oncologic outcomes; as such, data are provided for the overall cohort of patients.*

Author/ year	Approach	Level of IVC thrombus (maximal thrombus length in cm)	Tumor Side	LND (yes/no)	Operative time (min) (mean/ median)
Hand-assisted or hybrid laparoscopy					
Sundaram, 2002[18]	Transperitoneal	I (1.0)	Right	No	NR
Varkarakis, 2004[19]	Transperitoneal	I (2.0)	Right	No	248
Disanto, 2004[20]	Retroperitoneal	II (7.0)	Right	No	105
Martin, 2008[21]	Transperitoneal	I-II (NR)	Right	No	129
Hoang, 2010[22]	Transperitoneal	II (N.=8) III (N.=1) (NR)	Right	No	240
Pure laparoscopy					
Romero, 2006[23]	Transperitoneal	II (3.0)	Right	No	143
Xu, 2014[24]	Retroperitoneal	I (N.=5) II (N.=12)	Right N.=11 Left N.=6	No	209
Wang, 2014[25]	Retroperitoneal	II (3.7)	Right	Yes	130/140
Shao, 2014[26]	Retroperitoneal + Transperitoneal	II (NR)	Right	Yes	155 (135-210)
		IV (NR)	Right	Yes	275 (260-310)
Wang, 2015[27]	Transperitoneal (left-sided tumor); Retroperitoneal (right-sided tumor)	II	Left (N.=1); Right (N.=1)	Unclear	400/180
Wang, 2016[28]	Retroperitoneal	II [5.5 (4-10)]	Right	Yes (3 cases)	241 (180-300)
Cinar, 2018[29]	Transperitoneal	I; II; (NR)	Right/Left	Yes (2 cases)	137
Giannubilo, 2018[30]	Combined transperitoneal and retroperitoneal	II (5.5)	Right	Yes	320

9 series reported left-sided RCC (with predominantly level I-II IVC thrombosis) managed with robotic thrombectomy.[35, 37, 38, 40-45]

Lymph node dissection (LND) was reported in 6 studies in the laparoscopic group,[25-30] while in 10 in the robotic group;[31, 33, 35, 37-39, 41-43, 45] yet, the anatomic template was not standardized (Table III, IV).

The length of median follow-up was highly heterogeneous among included studies, ranging between 4[20] and 32[26] in the laparoscopic group (Table III) while between 3[40] and 27[44] in the robotic group.

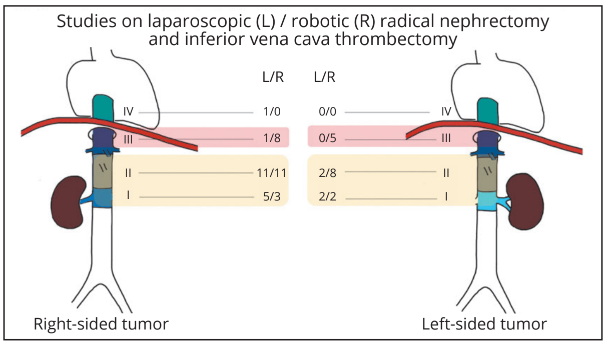

Figure 2.—Number of studies on laparoscopic and robotic treatment of Renal Cell Carcinoma with Inferior Vena Cava thrombosis according to tumor side and the level of IVC thrombus.

EBL (cc) (median or mean)	Transfusion rate (%)	Intraoperative and/or major postoperative complications (n, %, Clavien-Dindo grade >2)	LOS (days) (median [IQR] or mean [SD])	Follow-up (months) (mean/ median)	Oncologic outcomes at last follow-up
500	0%	1 (Clavien-Dindo grade V - death on POD 3 due to a large myocardial infarction).	NR	-	-
517 (250-900)	50%	0 (0)	6 (4-11)	6	Alive, disease-free
300	100%	0 (0)	6	4	Alive, disease-free
120	0%	0 (0)	3	32	Alive, disease-free (N.=3) Alive, with disease (N.=1; pulmonary metastasis)
600	0%	0 (0) [elective conversion to open surgery in one patient]	5	16	Alive, disease-free (N.=8) Dead due to the disease (N.=1)
200	0%	0 (0)	2	NR	NR
147	12%	0 (0)	6	18	Alive, disease free (N.=13)
200/ 240	0%	0 (0)	5 (4 -6)	35	Alive, disease-free
275 (150-510)	0%	0 (0)	9	32.5 (16-52)	Alive, disease-free (N.=6)
850 (600-1100)	80%	0 (0)		28 (18-36)	Alive, disease-free (N.=5) Dead due to the disease (N.=1; brain metastasis; patient with level IV IVC thrombus)
1600/200	50%	1 (intraoperative major bleeding)	15/7	18/15	Alive, disease-free
290 (50-1000)	20%	0 (0)	9 (5-18)	11.5	Alive, disease-free (N.=4) Alive, with disease (N.=1; pulmonary metastasis)
105	23%	Spleen injury (N.=1) IVC injury (N.=1)	4	25	Alive, disease-free (N.=4) Alive, with disease (N.=4) • pulmonary metastasis (N.=1) • liver metastasis (N.=1) • bone metastases (N.=2)
470	0%	0 (0)	5	NR	NR

Reported oncologic outcomes after laparoscopic and robotic RN and IVC thrombectomy are shown in Table III, IV.

Overall, the quality of evidence according to GRADE was low.

Techniques for laparoscopic radical nephrectomy and inferior vena cava thrombectomy

In 2002, Sundaram *et al.* described the first report of transperitoneal hand-assisted laparoscopic surgery for a right-sided RCC with level I IVC thrombosis using the Gelport hand-assisted device.[18] After proximal and distal control of the IVC, a Satinsky vascular clamp was inserted through a 12 mm flexible port. The thrombus was dislodged proximal into the renal vein and the renal vein was divided with a laparoscopic scalpel. The IVC was closed with a running suture with a hand-assisted intracorporal knotting technique.[18]

In the case-series by Varkarakis *et al.* including 4 patients with right-sided RCCs and level I IVC thrombosis,[19] a hybrid strategy combining a 4-ports laparoscopic approach and a subsequent open incision was described. In particular, an 8-12 cm open incision was made to allow posi-

TABLE IV.—*Perioperative and oncologic outcomes in studies on robotic radical nephrectomy with inferior vena cava thrombectomy. Some studies included patients undergoing cytoreductive robotic radical nephrectomy and inferior vena cava thrombectomy. However, data from these patients could not be selectively excluded from the analysis of perioperative and oncologic outcomes; as such, data are provided for the overall cohort of patients.*

Author/ year	Approach	Level of IVC thrombus (thrombus length in cm)	Tumor Side	LND (yes/no)	Operative time (min) (mean/median)	EBL
Abaza, 2010[31]	Transperitoneal	I (2); II (3) (5.0)	Right	Yes (4/5 patients) LN yield: 12.5 (7-24)	327 (240-411)	170 (50-400)
Lee, 2012[32]	Transperitoneal	II NR	Right	No	527	750
Bratslavsky, 2014[33]	Transperitoneal	III (11)	Right	Yes LN yield: 44	366	1200
Hui, 2014[34]	Transperitoneal	III	Right	NR	NR	NR
Gill, 2015[35]	Transperitoneal	II (3.4)	Right: 5; Left: 2	Yes	270	280
		III (5.8)	Right: 6; Left: 3 (5.7)		294	375
Ball, 2015[36]	Transperitoneal	II (NR)	Right	NR	243	150
Wang, 2015[37]	Transperitoneal	I (4) II (13) (4.2)	Right: 13 Left: 4	Yes (2/17 patients)	131 250	240
Abaza, 2015[38]	Transperitoneal	II: 30; III: 2 (4.2)	Right: 27; Left: 5	Yes (75% of patients) LN yield: 11	292	399
Ramirez, 2016[39]	Transperitoneal	III (NR)	Right	Yes	353	150
Kundavaram, 2016[40]	Transperitoneal	II (2); III (4) (8.5)	Right: 5; Left: 1	NR	330	350
Chopra, 2016[41]	Transperitoneal	II (13); III (11) (4)	Right: 17; Left: 7	Yes LN yield: 7	270	240
Wang, 2017[42]	Transperitoneal	II (20); III (2) (7.6)	Left: 6; Right: 16	Yes (in 12/22 cases)	285 (191-390)	1350 (1000-2075)
Aghazadeh, 2017[43]	Transperitoneal	II (3.75)	Left	Yes	420	500
Gu, 2017[44]	Transperitoneal	I (10); II (21) (4.7)	Right: 25; Left: 6	NR	150	250
Nelson, 2017[45]	Transperitoneal	III (NR)	Left	Yes	530	NR

IVC: inferior vena cava; LND: lymphadenectomy; EBL: estimated blood loss; LOS: length of stay; IQR: inter-quartile range; SD: standard deviation; POD: postoperative day; NR: not reported.

Transfusion rate (%)	Intraoperative and/or major postoperative complications (N. (%), Clavien-Dindo grade >2)	LOS (mean or median)	Follow-up (months) (mean/ median)	Oncologic outcomes at last follow-up
0%	0 (0)	1.2	15	Alive, disease-free
100%	• Liver laceration (N.=1) (treated with haemostatic agents). • 1 Clavien-Dindo III (Postoperative pneumothorax treated with a right-sided chest tube).	4	NR	NR
100%	0 (0)	3	24	Alive, disease-free
NR	0(0) [Conversion to open surgery due to densely adherent caval thrombus]	NR	NR	NR
14%	0 (0)	4	21	Alive, disease-free (N.=5) Alive, with disease (N.=2)
33%	• 1 (11.1%) Clavien-Dindo IIIb (1 patient with sub-phrenic abscess drained percutaneously)	4.5	7	Alive, disease-free (N.=8) Alive, with disease (N.=1 patient with spinal cord metastasis undergoing surgery)
0%	0 (0)	4.5	NR	NR
0%	• 1 (5.8%) Clavien-Dindo IV (Venous bleeding treated with endoscopic suture)	5	14	Alive, disease-free
9%	• Bowel injury (treated with suture) (N.=1)	3	15	Alive, disease-free (N.=25) Dead due to the disease (N.=3) Alive, with disease (N.=4)
0%	0 (0)	3	NR	NR
33%	• 1 (16.6%) Clavien-Dindo IIIa (Chylous ascites treated with paracentesis) • 1 (16.6%) Clavien-Dindo V (stroke on POD 12)	3	3	NR
20.8%	• 1 (4.2%) Clavien-Dindo IIIa (Chylous ascites treated with paracentesis) • 1 (4.2%) Clavien-Dindo IIIb (Subphrenic abscess treated with percutaneous drainage)	4	16	Alive, disease-free (N.=13) Alive, with disease (N.=11)
63.6%	• 5 (22.7%) Clavien IV (4 cases of vascular injuries treated with endoscopic sutures and 1 case of bowel fistula treated with gastrointestinal decompression)	18 (7-40)	17	Dead due to the disease (N.=1) Alive, with disease (N.=4) Alive, disease-free (N.=17)
0%	0 (0)	5	12	Alive, disease-free
6.5%	• 1 (3.2%) Clavien-Dindo IV (Venous bleeding treated with endoscopic suture)	5	27	Alive, with disease (N.=11; 45.5%)
0%	0 (0)	4	NR	NR

tioning of a Satinsky vascular clamp on the IVC and tumor thrombectomy *en bloc* with the kidney.

Disanto *et al.* reported the first retroperitoneal laparoscopic RN and IVC thrombectomy for RCC with level II IVC thrombosis using a hybrid strategy.[20]

In 2010 Hoang *et al.* described for the first time in literature a hybrid approach for laparoscopic transperitoneal RN and IVC thrombectomy for RCC with level III thrombus. Intraoperative ultrasound was used to confirm the extent of the IVC thrombus. Duplicating the principles of open surgical,[5, 48, 49] the authors achieved entire mobilization of the liver to allow suprahepatic and subdiaphragmatic control of the IVC. If necessary, a Pringle maneuver was performed. In one case, partial IVC wall excision was required with the need of a patch graft.

The first case of pure laparoscopic RN and IVC thrombectomy for RCC was reported by Romero *et al.* in 2006.[23]

In the report by Wang *et al*, two cases of RCC with level II IVC thrombosis treated with pure laparoscopic RN and IVC thrombectomy were described.[25] Surgical technique followed the previously described steps;[23] however, in this case a laparoscopic Satinsky clamp was used to block only the distal IVC. Then, the left renal vein was incised circumferentially, the tumor thrombus immediately extracted and another laparoscopic Satinsky clamp introduced to clamp the proximal IVC, before closing it with a running suture. Estimated blood loss in this case was 1600 cc, requiring intraoperative blood transfusions.

Another series by Wang *et al.* in 2014 reported two patients undergoing retroperineoscopic RN and IVC thrombectomy for right-sided RCC with level II IVC thrombosis.[27] In this case, a laparoscopic vascular clamp was applied to tangentially occlude the partial IVC with the flow preserved through the remaining lumen.

In their series reporting a pure conventional laparoscopic RN with level II IVC thrombectomy in 5 patients with right-sided RCC,[28] Wang *et al.* used a modified Rummel tourniquet technique to occlude the proximal and distal IVC.

Cinar *et al.* reported a case-series of 8 patients undergoing laparoscopic transperitoneal RN and IVC thrombectomy for level I-II thrombi.[29]

Giannubilo *et al.* recently described a combined trans-retroperitoneal approach for pure laparoscopic RN and IVC thrombectomy in one patient with right-sided RCC and level II IVC thrombus in a 7-arm configuration.[30]

Xu *et al.* reported a series of 17 patients with RCC and level I-II IVC thrombosis.[24]

In all cases, a retroperitoneal approach was used. For short level I thrombi, a pure retroperitoneal technique was performed without occlusion of IVC and contralateral RV. On the contrary, for level II thrombi, especially if extending at the intrahepatic level, a hybrid technique was employed combining laparoscopic surgery and transperitoneal open thrombectomy through a 5-10 cm subcostal incision.

Of note, Shao *et al.* reported for the first time five cases of right-sided RCC with level IV IVC thrombi.[26] For this procedure, cardiopulmonary bypass was employed. Two 2-cm incisions were made in the intercostal spaces and another 6-cm incision was made in the right fifth intercostal space to allow entry into the pleural cavity. Atriotomy was performed and a thoracoscope (and the relevant instruments) were inserted through the ports for assistance.

After incising the pericardium, the superior vena cava (SVC) was mobilized and prepared for cardiopulmonary bypass. Following systemic heparinization, cardiopulmonary bypass was initiated without cardiac arrest. Hypothermia (33-35° C) was achieved. The right atrium was incised to monitor the status of the thrombus and to prevent its dislodgment. The IVC was laparoscopically incised at the right renal vein ostium and the thrombus was exposed. Complete thrombus evacuation was confirmed by endoscopic examination or transesophageal ultrasonography. The IVC and atrium were then closed and all vessel occlusions were unclamped to restore the blood flow.[26]

Techniques for robotic radical nephrectomy and inferior vena cava thrombectomy

In 2011 Abaza 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.[31] No patient underwent preoperative angioembolization.

For more extensive tumor thrombi, the robotic fourth arm instrument was used for lateral kidney retraction to shorten the tumor in the IVC lumen after complete mobilization of the kidney excluding only the lateral attachments.

This surgical technique was replicated in 2012 by Lee *et al.*[32] The procedure was performed by two surgeons in learning curve (<25 robotic cases performed).

In 2015 Wang *et al.* reported an initial series of 17 patients undergoing pure robotic RN and IVC thrombectomy for right- and left-sided RCC with level I-II IVC thrombi.[37] The exclusion criterion was suspect IVC wall infiltration. For right RCC, 7/13 patients underwent preoperative right renal artery embolization. Surgical principles followed previously described steps.[31]

In cases where renal artery embolization was not performed, the right renal artery was dissected and ligated in the interaortocaval space before clamping of the IVC.

For left-sided RCCs, all patients underwent renal artery embolization. The left renal vein was ligated and divided with Endo-GIA. While for right-sided RCC the left renal artery blood flow can return to the venous system through the left gonadal vein even if the left renal vein is clamped, on the contrary, the right renal artery blood flow cannot return to the venous system if the right renal vein is clamped in case of left-sided RCC, owing to the inherent anatomical difference in venous drainage. Thus, the right renal artery was dissected in the interaortocaval space, and complete IVC cross-clamping was achieved. The IVC tumor thrombus was removed and a right renal warm ischemia time (WIT) was recorded. After robotic IVC thrombectomy, the patient was positioned in a modified right lateral decubitus position to complete left robotic RN.

Recently, Aghazadeh *et al.* reported a novel single-dock supine approach for pure robotic RN and IVC thrombectomy for left-sided RCC with level II IVC thrombosis,[43] without the need for preoperative left renal artery embolization and patient repositioning.

In 2014, Bratslavsky *et al.* published the first report of transperitoneal robotic RN with retrohepatic (level III) IVC thrombectomy combined with extended retroperitoneal LND for a right-sided RCC.[33] The short hepatic veins (SHV) to the posterior right and caudate lobes of the liver were clipped and divided, allowing for an excellent exposure of the retrohepatic IVC. Intraoperative US and transesophageal echocardiography were performed simultaneously to evaluate the tumor thrombus and its relationship with the right atrium. Then, cross-clamping of the IVC was achieved, a cavotomy was performed and the tumor was extracted.

In the same year, Hui *et al.* reported a case of a right-sided RCC with level III IVC thrombosis beyond the level of the hepatic veins managed with robotic RN and IVC thrombectomy with a thoracoscopic technique for control of the IVC.[34] This approach combined video-assisted thoracoscopic isolation of the supradiaphragmatic IVC, laparoscopic control of the porta hepatis with the Pringle maneuver, and a robotic right RN and resection of IVC tumor thrombus. Specific nuances of this technique included: 1) selective ventilation; 2) intraoperative transesophageal echocardiography (TEE) to confirm absence of tumor thrombus in the supradiaphragmatic IVC; and 3) intermittent apnea to optimize exposure. The pericardium was incised and a laparoscopic finger retractor was used to improve exposure by depressing the diaphragm. The IVC was bluntly dissected circumferentially from the pericardium. Thoracoscopic IVC control was accomplished to proximally occlude the IVC with a Rummel tourniquet. Right RN with IVC thrombectomy and excision of IVC was attempted robotically; however, the densely adherent caval thrombus necessitated open conversion for complete thrombus extraction and caval closure.

In 2015 Gill *et al.* reported a prospective single-surgeon experience of 16 patients undergoing completely intracorporeal robotic RN and IVC thrombectomy for RCC with level II-III IVC thrombi, including both right- and left-sided tumors.[35] To minimize chances of intra-operative IVC thrombus embolization, an “IVC-first, kidney-last” robotic technique was developed. Moreover, to minimize chances of major hemorrhage, the technique evolved towards a “midline-first, lateral-last” robotic operative strategy, wherein the inter-aorto-caval region is dissected first, and dissection of the laterally-located renal hilar region is deferred towards the end of the case. Preoperative angioembolization was performed in all but one patient with level III IVC thrombi while in 4/7 patients with level II IVC thrombi.

Technique for robotic RN and IVC thrombectomy differed according to tumor side.[35]

In particular, for right-sided tumors, complete caval exclusion with cross-clamping was performed routinely. High proximal control of intrahepatic IVC required transection of short hepatic (SH) veins.[50] The caudate lobe was retracted anteriorly. Right adrenalectomy was completed and supra-renal IVC was mobilized. Intra-hepatic IVC was circumferentially mobilized to allow safe passage of a Rummel tourniquet. Complete IVC cross-clamping was achieved, the thrombus-bearing right renal vein was transected with endo-GIA stapler and a longitudinal cavotomy was made to excise the thrombus en-bloc with stapled right renal vein stump/ostium and any involved caval wall. After IVC thrombectomy, RN with ipsilateral retroperitoneal LND is completed.

For left-sided tumors, reliable preoperative angio-embolization is critical, as the left renal vein is disconnected well before the left renal artery can be robotically secured.

During surgery, the patient was placed in the right side-up position to perform IVC thrombectomy. Important surgical aspects include preservation of right adrenal gland, transient bull-dog clamping of right renal artery and Rummel control of right renal vein. Patient was then re-positioned left side-up and robot re-docked to complete left RN and LND.

In case of tumors with completely occlusive IVC thrombus, complete robotic IVC transection with Endo-GIA stapler was performed given the non-functional, no-flow IVC, to prevent embolism of any distal bland thrombus.

In case of level III thrombi extending above the hepatic veins, control of supra-hepatic IVC and porta hepatis was obtained by the authors with specific technical modifications, as previously reported.[34]

In 2016 Abaza *et al.* reported a multi-institutional experience including 32 patients undergoing robotic RN with level II-III IVC tumor thrombectomy at 9 Institutions from 2008 to 2014.[38]

All procedures were performed transperitoneally as previously described with minor variations among surgeons.[38]

Ramirez *et al.* reported a case of a right-sided RCC with level III IVC thrombosis treated with robotic transperitoneal RN and level III IVC thrombectomy in a 6-arm configuration.[39]

Real-time intraoperative esophageal ultrasound and a drop-in ultrasound probe were used to monitor the tumor thrombus. The laparoscopic locking Allis clamp was dynamically held in place by the bedside assistant to maximize exposure of the IVC beneath the level of the liver.

In a series of 6 patients with RCC and level II-III IVC thrombi, Kundavaram *et al.* described ongoing technological innovations and advances in surgical techniques of robotic RN and IVC thrombectomy, such as intracaval balloon occlusion, patch grafting, and vena cavoscopy.[40]

First, the authors presented four cases of proximal intra- or retro- hepatic IVC control solely with an intracaval Fogarty balloon catheter (for 2 patients with level II and 2 patients with level III thrombi). This technique is grounded in the previously described “mid-line first, kidney-last” approach for robotic RN and IVC thrombectomy.[35]

After control of the infrarenal IVC and left renal vein with Rummel tourniquets, a 9F Fogarty balloon catheter was inserted through a 5-mm laparoscopic port. The infrarenal IVC and left renal vein Rummel tourniquets were cinched. At the proposed infrarenal site of balloon catheter entry into the IVC, a purse-string stitch was preplaced in the caval wall just caudal to the right renal vein and a small cavotomy was created on the caval wall contralateral to the thrombus to allow smooth atraumatic catheter insertion without rubbing against the thrombus.

Afterwards, the Fogarty catheter was carefully inserted over a soft-tip guidewire and easily advanced past the thrombus into an intrahepatic location. Laparoscopic ultrasonography and/or transesophageal echocardiography were used to confirm adequate inflation of the intracaval balloon. The length of catheter insertion into the IVC and the volume of water injected to inflate the balloon are predetermined, based on the individual patient’s computed tomography (CT) scan data.

Once the thrombus, along with the stapled right renal vein ostium, was excised, the Fogarty balloon was deflated, removed, and the catheter-site purse- string suture tied after evacuating any intraluminal carbon dioxide bubbles. No case required liver mobilization or short hepatic vein control.

Other technical advances proposed by Kundavaram *et al.* included robot-guided flexible cystoscopy of the IVC lumen to rule out any residual or secondary skip thrombi (for a patient with level III IVC thrombus) and one case of robotic reconstruction of caval wall defect after thrombus excision using a bovine pericardial patch (in a patient with level III thrombus).

Wang *et al.* reported a series of 22 patients undergoing robotic retrohepatic IVC thrombectomy for both left- and right-sided RCC.[42] The Authors focused on the relationship of a proximal thrombus with either the first porta hepatis (FPH, a H-shaped sulcus of the visceral surface of the liver including the portal vein, common hepatic duct, and hepatic artery) or second porta hepatis (SPH, the position of the left, middle, and right hepatic veins entering the IVC).

For tumors with proximal thrombus inferior to the FPH (not reaching the portal vein), the patient was positioned in a modified left lateral decubitus position with a 70° bump (thrombectomy position) with a seven-port configuration. Surgical technique for robotic thrombectomy followed the previously discussed principles[37] without need of liver mobilization.

For tumors with proximal thrombus between the FPH and SPH *(*exceeding the portal vein but not reaching the hepatic veins), the patient was placed in a 30-45° dorsal elevated lithotomy position (liver mobilization position) and a five-port configuration was used. To achieve liver mobilization, additional SHVs, often three to five, were ligated; yet, the FPH was not clamped. After liver mobilization, the patient was re-secured in the thrombectomy position.

For tumors with proximal thrombus close to or above the liver vein but below the diaphragm, the patient was placed in the liver mobilization position. Then, as robotic transabdominal control of the suprahepatic and infradiaphragmatic IVC requires mobilization of both the right and left lobes of the liver, the right and left triangular, round, falciform, and coronary ligaments were disconnected. Then, with the patient in the thrombectomy position, cross-clamping of the IVC was achieved, and a vessel tourniquet was placed suprahepatically above the proximal IVC thrombus under ultrasound guidance. The FPH was clamped simultaneously.

In cases of IVC thrombi filling the caval lumen and/or of excellent collateral circulation, the IVC was ligated above and below the thrombus-bearing IVC using an Endo GIA stapler.

For left-sided tumors, the patient was shifted to a modified right lateral decubitus position after IVC thrombectomy and left robotic RN, as previously reported.[42]

Postoperative outcomes after minimally-invasive surgery for RCC with IVC thrombosis

In the laparoscopic group (Table III), median/mean operative time ranged between 105 minutes (for a right-sided RCC with level II IVC thrombus[20] and 400 minutes (for a left-sided RCC with level II IVC thrombus.[27] In the robotic group (Table IV), the minimal operative time was 131 minutes[37] while the maximum 530 minutes (for a left-sided RCC with level III IVC thrombus.[45]

Median/mean estimated blood loss (EBL) was variable across both laparoscopic and robotic series, ranging between 120 cc[21] and 1600 cc[27] in the laparoscopic group while between 120 cc[33] and 750 cc.[32] Accordingly, transfusion rate significantly varied among included series (Table III, IV).

Intraoperative complications were reported in two laparoscopic series,[27, 29] including a major intraoperative bleeding, a spleen injury and IVC injury, and in two robotic series,[32, 38] including liver laceration treated with hemostatic agents and bowel injury treated with robotic suture.

Of note, conversion to open surgery was reported only in one patient in the laparoscopic group[22] and in one patient in the robotic group.[34]

Major (Clavien-Dindo grade >2) postoperative complications were recorded in one laparoscopic series[40] while in 7 robotic series.[32, 35, 37, 40-42, 44]

Median/mean length of stay ranged between 2 [23] and 15[27] days in the laparoscopic group, while between 1.2[31] and 18[42] days in the robotic group.

In their matched group comparative analysis, Gu *et al.* reported the first head-to-head comparison of robotic *versus* open RN and IVC thrombectomy for RCC with level I-II IVC thrombosis.[44] Robotic surgery had distinct intra- and postoperative benefits as compared to open surgery, including significantly shorter median operative time (150 *vs.* 230 minutes, P<0.001), lower median estimated blood loss (250 *vs.* 1,000 mL, P<0.001), a lower rate of blood transfusion (6.5% *vs.* 54.8%, P<0.001), a lower median transfusion requirement (420 *vs.* 790 mL, P=0.012) and a shorter median postoperative hospital stay (5 *vs.* 9 days, P<0.001).

Minimally-invasive surgery for RCC with IVC thrombosis: duplicating open surgical principles

In 1972, Skinner *et al.* first reported RN with IVC thrombectomy.[51]

This is still nowadays one of the most challenging procedures in urologic oncology.

While current Guidelines recommend RN and IVC thrombectomy for patients with RCC and IVC involvement with acceptable performance status,[3, 4] the role of minimally-invasive surgery in this setting is still debated.[15, 52]

Open surgery remains the gold standard for RN and IVC thrombectomy. In this systematic review we provided a comprehensive evaluation of current evidence on laparoscopic and robotic RN and IVC thrombectomy for nonmetastatic RCC with level I-IV thrombosis, with special emphasis on surgical techniques and perioperative outcomes.

The ultimate aim of laparoscopic and robotic approaches is to duplicate the principles of open surgery, while adding the advantages of minimally-invasive surgery, including a smaller incision, decreased postoperative pain, perioperative blood loss, length of hospitalization and faster recovery time, as well as potentially reduced perioperative complications.

In this scenario, one of the major challenges of minimally-invasive surgery is to translate the cornerstones of open RN and IVC thrombectomy in the laparoscopic and robotic environment. As such, successful robotic IVC thrombectomy surgery requires extensive knowledge of surgical anatomy, detailed preoperative planning and meticulous robotic technique,[35] as well as non-technical skills.[53]

Pivotal principles of open RN and IVC thrombectomy according to the thrombus level are summarized in Table V.[14, 15, 22, 26, 34, 35, 37, 40-43, 48, 49, 54, 55]

Overall, hand-assisted/hybrid and subsequently pure laparoscopic approaches have been shown to accurately translate these principles into minimally-invasive surgery in the setting of RCC with level I-II IVC thrombosis (Figure 2, Table V). Of note, the current evidence on laparoscopic management of level III-IV IVC thrombi is limited to few series[22, 26] and required a hand/assisted or hybrid approach.

Thanks to the advantages of the robotic technology, robotic RN and IVC thrombectomy was first performed for the management of level I-II IVC thrombi but proved to be technically feasible also in case of level III thrombi, accurately replicating the fundamentals of open surgery. In addition, robotic surgery allowed surgeons to pioneer further technical advances for more extensive IVC thrombi, such as intracaval Fogarty balloon catheter, robotic flexible cavoscopy and thoracoscopic isolation of the IVC (Table V).

Despite no studies reporting performance of robotic IVC thrombectomy for level IV thrombi were included in final qualitative analysis, this procedure has been recently described.[15, 55] Indeed, Ahmadi *et al.* reported the initial case of robotic level IV IVC tumor thrombectomy for a right-sided 8 cm non-metastatic renal tumor with a 16 cm long level IV thrombus extending 5.2 cm into the right atrium.[55] A 7-port trans-abdominal approach was used. A 6 cm, minimally-invasive thoracotomy incision was used to perform aortic cross-clamping and cardiopulmonary bypass with cardiac arrest. Using a simultaneous trans-abdominal and trans-thoracic, the thrombus was extracted after opening the right atrium and infra-hepatic IVC. No postoperative blood transfusions were required and no intra-operative or postoperative complications were recorded.

Zhang *et al.* also described a technique for robotic level IV IVC thrombectomy[15] involving thoracoscope-assisted thrombectomy for the intra-atrial part of the thrombus with establishment of cardiopulmonary bypass.

TABLE V.—*Pivotal principles and technical nuances for open and minimally-invasive radical nephrectomy with inferior vena cava thrombectomy according to the current evidence.*

	Radical nephrectomy and inferior cava thrombectomy	
	Open	Minimally-invasive surgery

General principles[49]	• Comprehensive preoperative patient evaluation, including Performance Status, anesthesiologic risk and comorbidity profile, is critical for surgical planning
	• High-quality imaging within few weeks is crucial to assess tumor thrombus extension
	• Surgical approach must be individualized according to thrombus level and extension
	• Transesophageal echocardiography and intraoperative ultrasound can provide reliable real-time thrombus monitoring
	• Exposure and complete mobilization of the IVC with control of major venous tributaries (*e.g.* lumbar veins) is essential
	• For thrombi invading the caval wall, IVC resection and reconstruction is needed. Reconstruction is indicated if >50% of the caval wall is resected
	• A multidisciplinary, experienced surgical team is often required, including cardiac, vascular and general surgeons
	• The choice to perform preoperative arterial embolization should be carefully considered according to tumor side and tumor/thrombus characteristics
	• The adrenal gland is removed en bloc with the specimen
	• Ipsilateral LND is performed, if indicated
	• Careful monitoring of hemodynamic status and vital parameters is mandatory, especially if IVC cross-clamping is performed
	• Vena cavoscopy has been reported to assess under direct vision the completeness of caval thrombus extraction
	• Level IV tumors have generally required cardiopulmonary bypass with or without deep hypothermic circulatory arrest However, advances in surgical techniques have allowed avoidance of sternotomy in level III tumors and selected cases with level IV tumors
		Specific aspects of minimally-invasive surgery
		• A program of minimally-invasive RN and IVC thrombectomy should be developed in a stepwise manner
		• Suspect infiltration of the IVC wall at preoperative MRI may represent an exclusion criteria; yet, caval wall resection may be potentially performed in selected cases
		• The threshold for conversion to open surgery should be low, especially in case of extended thrombi[14]
		• Both trans- and retroperitoneal approaches are technically feasible
		
		Technical nuances of laparoscopic IVC thrombectomy
		Intraluminal thrombus should be free-floating without extensive involvement of the peripheral tissue or vascular wall[26]
		
		Technical nuances of robotic IVC thrombectomy
		• Renal angioembolization before surgery is recommended for left-sided RCCs while is optional for right-sided RCCs[14, 37]
		• Specific technical considerations include:
		  • choice of daVinci robotic platform (Si *vs.* Xi)[43]
		  • patient positioning and trocar placement (according to surgeon's preference, thrombus extension and tumor side)
		  • pneumoperitoneum pressure
		• Initial preservation of lateral renal attachments to improve exposure of the IVC for thrombectomy and reconstruction
		• Use of third robotic arm to assist in lateral retraction of the kidney
		• minimal-touch technique for caval mobilization to minimize chances of inadvertent thrombus manipulation and embolization (peri-caval tissues are retracted principally, rather than the IVC itself)[35]
		• "IVC first, kidney last" approach to minimize chances of major pulmonary embolism due to intraoperative tumor thrombus dislodgment[41]
		• "midline-first, lateral-last" strategy to minimize chances of major hemorrhage[35]
		• Transection of the thrombus-bearing renal vein to: 1) eliminate back-bleeding from the tumor-bearing kidney; 2) reduce chances of thrombus embolization; 3) allow full mobilization of the excluded IVC segment; 4) eliminate the risk of local tumor spillage
		• Different sides require different techniques[14, 35, 42]
		For left-sided RCCs, IVC thrombectomy is performed in the right-side-up position (preserving the right adrenal gland); then, the patient is repositioned to complete RN. As such, the specimen (RCC and IVC thrombus) is separate. Moreover, stapling the left renal vein is necessary and the right renal artery is temporarily clamped. Consequently, a right renal warm ischemia time is recorded

(To be continued)

Table V.—*Pivotal principles and technical nuances for open and minimally-invasive radical nephrectomy with inferior vena cava thrombectomy according to the current evidence (continues).*

	Radical nephrectomy and inferior cava thrombectomy	
	Open	Minimally-invasive surgery
Level I-II IVC thrombi	• Mobilization of the IVC and its control above and below the tumor thrombus and contralateral renal vein • Liver mobilization, if required by thrombus extent • After safe vascular control is obtained, cavotomy and thrombectomy are performed	*Laparoscopic surgery* -Cavotomy and IVC thrombectomy can be performed with both hand-assisted/hybrid and pure laparoscopic approaches following the open principles *Robotic surgery* • For thrombi inferior to FPH, few (1-3) SHVs are usually ligated to retract the liver and gain access to the retrohepatic IVC • For level II thrombi between FPH and SPH, mobilization of the right lobe of the liver is achieved by ligating additional SHVs, without need to clamp the FPH[42]
Level III IVC thrombi	• Extensive liver mobilization is critical, with ligation of the short hepatic veins and division of hepatic ligaments allowing full rotation of the liver toward the left (applying liver transplant mobilization techniques[48]) to control and clamp the suprahepatic IVC • Complete ‘piggyback’ liver mobilization may facilitate addressing a level III IVC thrombus, as the cavotomy can be extended cranially • Pringle maneuver with temporary clamping of hepatic artery and portal vein may be required • If suprarenal IVC control above the proximal extent of the thrombus cannot be achieved with retrohepatic IVC mobilization, then midline sternotomy is required to control the supra-diaphragmatic IVC • Balloon occlusion techniques have been described for control of retro/suprahepatic IVC[54]	*Laparoscopic surgery (hybrid approach)* • After laparoscopic mobilization of the kidney and ligation of the renal artery, a subcostal incision is performed to obtain a direct access to sub-diaphragmatic IVC and perform the cavotomy, thrombectomy and caval reconstruction in an open fashion[22] *Robotic surgery* • Preoperative IVC angiography may be considered to determine the adequacy of the collateral circulation[42] • Mobilization of both the right and left lobes of the liver are required to obtain high proximal control of the suprahepatic and infradiaphragmatic IVC • When the IVC is clamped above the SPH infradiaphragmatically, the FPH should be clamped simultaneously to avoid liver congestion • Proximal intra-/retro- hepatic IVC control with intracaval Fogarty balloon catheter was technically feasible (a contraindication is complete IVC occlusion with minimal caval flow)[40] • Robot-guided flexible cystoscopy of the IVC lumen (cavoscopy) to rule out any residual or secondary skip thrombi and robotic reconstruction of caval wall defect after thrombus excision using a bovine pericardial patch have been reported[40] • Total thoracoscopic isolation of the IVC is technically feasible[34]
Level IV IVC thrombi	-Midline sternotomy is required to control the supra-diaphragmatic IVC -In case of IVC thrombi extending into the right atrium, cardio-pulmonary bypass and deep hypothermic circulatory arrest should be performed	*Laparoscopic surgery* In well-selected RCC patients, laparoscopic IVC thrombectomy combined with thoracoscope-assisted open atriotomy is technically feasible[26] *Robotic surgery* • Thoracoscope-assisted thrombectomy is performed for the intra-atrial part of the thrombus with establishment of cardiopulmonary bypass; the infradiaphragmatic IVC thrombus is excised in a similar way as for level III thrombi[15] • A 6 cm thoracotomy incision is used to perform aortic cross-clamping and cardio-pulmonary bypass with cardiac arrest. Using a simultaneous antegrade-retrograde approach, the thrombus is extracted after opening the right atrium and infra-hepatic IVC. A Fogarty intracaval balloon and endoluminal cavoscopy are used to check for complete thrombus clearance[55]

IVC: inferior vena cava; MRI: magnetic resonance imaging; LND: lymphadenectomy; RCC: renal cell carcinoma; FPH: first porta hepatis; SPH: second porta hepatis; SHV: short hepatic veins.

Table VI.—*Potential limitations and future perspectives of minimally-invasive surgery for the treatment of renal cancer with inferior vena cava thrombosis.*

Minimally-invasive surgery for RCC with IVC thrombosis	
Potential limitations	Future perspectives
Lack of tactile feedback during robotic surgery	Integration of multiple imaging modalities (intraoperative ultrasound, transesophageal echocardiography, flexible cavoscopy) and potentially augmented reality to guide robotic IVC thrombectomy
Need of extensive previous experience in robotic renal surgery, robotic pelvic and retroperitoneal lymph node dissection, as well as in open urologic vascular surgery	Development of modular surgical training, stepwise development of structured robotic IVC thrombectomy programs
Most cases were performed by highly experienced surgeons at tertiary referral centers in the setting of a multidisciplinary surgical team	Centralization of care
Pneumoperitoneum pressure should be adapted carefully to balance the need for optimal exposure and reduce bleeding and the potential increased risk of embolism, cardiovascular instability and tumor spillage	The Airseal device may contribute to stabilize the pressure during the most critical phases of IVC thrombectomy
Potential selection bias in current series potentially confounds meaningful outcome comparison with open surgery	Prospective multicenter comparative studies are needed to evaluate the benefits and harms of laparoscopic and robotic surgery for RCC with IVC thrombosis
Lack of randomized studies (open *versus* minimally-invasive surgery or laparoscopic *vs.* robotic)	
Patient positioning and trocar placement need to be set according to the extension of the tumor thrombus and tumor side	Reclassification of the level of IVC thrombosis may be based critical anatomic landmarks (such as the first or second porta hepatis) rather than the length of the thrombus within the IVC
Non-inferiority of minimally-invasive surgery as compared to open surgery regarding long-term oncologic outcomes is yet to be proven	Assessing the impact of neoadjuvant systemic therapy to improve feasibility of minimally-invasive surgery
Distance of the robotic surgeon from the bedside, increasing the complexity of emergency open conversion in case of major intraoperative adverse events	
If needed, intraoperative assistance from cardiac, vascular, and hepatobiliary surgeons may be complex, depending on their expertise in minimally-invasive surgery	
The impact of minimally-invasive (especially robotic) surgery on health care costs	

IVC: inferior vena cava; RCC: renal cell carcinoma.

Finally, endovascular extraction of an IVC tumor thrombus using a percutaneous endovascular suction thrombectomy device via an extracorporeal venous bypass circuit was recently proposed to facilitate subsequent minimally invasive cytoreductive nephrectomy.[56] Future improvements of this technique may potentially extend indications to patients with nonmetastatic disease.

An overview of potential limitations and future perspectives of minimally-invasive (especially robotic) surgery for the treatment of RCC with IVC thrombosis according to our systematic review is shown in Table VI.[52]

Limitations of the study

Our systematic review has few limitations at both a review- and study-level.

Despite the assessment of oncologic outcomes was part of the review endpoints, we were unable to achieve meaningful conclusions on the oncologic benefits of minimally-invasive IVC thrombectomy due to several limitations of included studies, such as limited sample size, heterogeneous and limited follow-up and lack of detailed reporting of key outcomes (*i.e.* cancer-specific survival and overall survival) in most series. Second, the review strategy was limited to English-language publications, potentially reducing the number of eligible studies. Third, our review might not have been able to identify all relevant studies on the topic of interest. Fourth, the generalizability of surgical techniques described in our review might be limited, as most studies included in the review were retrospective single-Institution noncomparative case-series (often case reports). Moreover, the vast majority of surgeries were performed by high-volume surgeons at high-volume centers.

Acknowledged these limitations, this is the first systematic review on techniques and outcomes of minimally-invasive radical nephrectomy and inferior vena cava thrombectomy for RCC.

We found low quality evidence supporting technical feasibility and favorable short-term perioperative outcomes of minimally-invasive RN and IVC thrombectomy for RCC extending into the IVC. Nonetheless, evidence is premature to draw reliable conclusions on the oncologic safety of this technique.

While minimally-invasive surgery has the potential to move this field forward, future research is needed to define its benefits and limits.

Conclusions

Minimally-invasive surgery has been shown to be technically feasible and to achieve acceptable perioperative outcomes in selected patients with renal cancer and inferior vena cava thrombosis.

Several techniques have been proposed to achieve safe and reproducible IVC thrombectomy with specific technical nuances aiming to tailor surgical strategy according to both tumor side and thrombus extent. In particular, robotic surgery allowed to overcome the current limitations of laparoscopic techniques and to extend surgical indications to more challenging cases with more extensive tumor thrombosis. Nonetheless, the current global experience on minimally-invasive IVC thrombectomy is limited to selected series from high-volume surgeons.

Evidence is premature to draw reliable conclusions on intermediate-long term oncologic outcomes of this technique.

Future research is needed to prove the non-inferiority of this strategy compared to open surgery and to define reliable selection criteria as a first step to evaluate the reproducibility of minimally-invasive surgery beyond expert surgical teams.

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