Cumulative Sum Analysis of the Operator Learning Curve for Robot-Assisted Mayo Clinic Level I–IV Inferior Vena Cava Thrombectomy Associated with Renal Carcinoma: A Study of 120 Cases at a Single Center

Background: This study aimed to use cumulative sum analysis of the operator learning curve for robot-assisted Mayo Clinic level I–IV inferior vena cava (IVC) thrombectomy associated with renal carcinoma, and describes the development of an optimized operative procedure at a single center.

Material/Methods: A retrospective study included 120 patients with Mayo Clinic level I–IV IVC thrombus who underwent robotic surgery between 2013 and 2018. Points in the learning curve were identified using cumulative sum analysis, and their impact was assessed by multiple regression analysis. Perioperative indicators analyzed included operative time, estimated blood loss, early complications, and the 90-day progression rate.

Results: Cumulative sum analysis identified three phases in the learning curve of robot-assisted IVC thrombectomy. The median operative time decreased from 265 min (range, 212–401 min) to 207 min (range, 146–276 min) (p=0.003), the median estimated blood loss decreased from 775 ml (range, 413–1500 ml) to 300 ml (range, 163–813 ml) (p=0.006), and the early complication rate decreased from 52.5% to 15.0% (p<0.001). Multivariate analysis showed that for an initial 40 cases and a further 80 cases, the learning phase, the affected side, the Mayo Clinic level, and the surgical method were independent factors that affected operative time, estimated blood loss, and the rate of early complications.

Conclusions: Experience from an initial 40 cases and a further 80 cases of Mayo Clinic level I–IV IVC thrombectomy associated with renal carcinoma were found to provide acceptable surgical and clinical outcomes.

MeSH Keywords: Carcinoma, Renal Cell • Learning Curve • Robotics • Thrombectomy • Vena Cava, Inferior

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/922987
Background

Primary renal cell carcinoma can invade the renal vein, resulting in inferior vena cava (IVC) thrombosis that requires thrombectomy. Locally advanced renal tumors can spread from the primary focus into the inferior vena cava (IVC) in 4–10% of patients [1]. IVC thrombectomy remains the standard treatment for renal tumors with IVC tumor thrombosis. However, IVC thrombectomy is technically difficult and is one of the most challenging types of surgery. Robot-assisted IVC thrombectomy is a relatively recent advance for the surgical treatment of Mayo Clinic level I–II IVC thrombus and was first reported in 2011 [2]. The initial reports for Mayo Clinic level III robot-assisted IVC thrombectomy were reported in 2015 [3,4]. In 2019, we described the use of robotic surgery for the management of Mayo Clinic level IV thrombus [5]. Since these early publications, additional centers have recently reported their experiences and proved the safety and feasibility of robot-assisted IVC thrombectomy for selected patients [6-8]. Currently, there have been no published studies on the learning curve of robot-assisted IVC thrombectomy.

Therefore, this study aimed to use cumulative sum analysis of the operator learning curve for robot-assisted Mayo Clinic level I–IV inferior vena cava (IVC) thrombectomy associated with renal carcinoma and describes the development of an optimized operative procedure at a single center.

Material and Methods

Patients studied

From June 2013 to December 2018, 120 patients with renal carcinoma and inferior vena cava (IVC) tumor thrombosis were enrolled in this study, who had undergone a complete endoscopic robotic tumor thrombectomy. All patients underwent color Doppler ultrasound, computed tomography (CT) and/or magnetic resonance imaging (MRI) to identify the tumor location and vascular extension. IVC venography was performed in some patients to evaluate the collateral circulation. Other investigations were performed, including a complete blood cell count (CBC), liver function tests, renal function tests, tests of coagulation function, and serum electrolytes. This retrospective study was approved by the Ethics Committee of the Chinese PLA General Hospital (No. S2013-065-01). All patients provided written informed consent for the robotic surgery procedure and the use of perioperative data.

Patient exclusion criteria

The study exclusion criteria included: Mayo Clinic level 0 renal vein thrombosis, which could be treated by radical nephrectomy; supradiaphragmatic thrombus, which could be treated with combined thoracoscopic and laparoscopic thrombectomy with or without cardiopulmonary bypass; thrombi with a fragile texture, filling the vena cava lumen, or diffusely invading the IVC wall, without well collateral circulation, which required inferior vena cavectomy with IVC reconstruction using an open approach; patients with distant metastasis; patients with a history of upper abdominal surgery; and patients with an unacceptable anesthetic risk and cardiopulmonary insufficiency.

Baseline characteristics

Baseline characteristics that were recorded and analyzed included clinicopathological data and surgical indicators of the operative time, IVC occlusion time, estimated blood loss, and surgical complications, and postoperative outcomes, including the surgical margin, early complications, length of hospital stay, and the 90-day progression, including recurrence, metastasis, and patient mortality. The renal tumors were classified according to the 2017 TNM staging system from the American Joint Committee on Cancer (AJCC) [9], the tumor thrombi were graded according to the Mayo Clinic classification [10], and the postoperative complications were assessed according to the Clavien-Dindo classification system [11].

Surgical procedures

All robot-assisted IVC thrombectomy procedures were performed by a single surgical team with experience in open surgery and laparoscopic surgery. The Intuitive da Vinci Si Robotic Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) was used in all cases. Transesophageal echocardiography (TEE) and intraoperative ultrasound were used to monitor the extent and stability of the thrombus and to ensure that the tumor thrombus was removed completely during surgical manipulation.

Patient position, trocar placement, and liver mobilization

In cases of infrahepatic IVC tumor thrombus, the liver was mobilized with the patient in a left lateral decubitus position with a 70° elevation (the thrombectomy position), and a seven-port method was used, as previously described [12]. The hepatocolic ligament was incised, and the feeding veins were ligated, including the right adrenal vein, the gonadal vein, the lumbar veins, and between one and three short hepatic veins. In cases of retrohepatic IVC tumor thrombus, patients were positioned in a 30–45° dorsal elevated lithotomy position (the liver mobilization position), and a five-port method was used, as previously described [13]. The hepatocolic, coronary, and right triangular ligaments were incised, and the right lobe of the liver was mobilized from the IVC by clipping and dividing between three and five short hepatic veins. In cases of suprahepatic
IVC tumor thrombus, the liver was mobilized and a five-port method was used. Both the right and left lobes of the liver were mobilized by ligating the hepatocolic, coronary, right and left triangular, falciform and round ligaments.

**Vascular circumferential dissection and control**

For left renal tumors, left renal artery embolization was performed between 1–2 hours preoperatively. After liver mobilization, patients were returned to the thrombectomy position, apart from patients with infrahepatic thrombus. The tumor-bearing left renal vein was stapled, and the caudal IVC, right renal artery, right renal vein, and proximal IVC were sequentially clamped. For right renal tumors, the left renal vein was clamped, but the left renal artery was not. The right renal artery was not embolized preoperatively, and we did not staple the tumor-bearing right renal vein. For supra-hepatic IVC tumor thrombus, the porta hepatitis was clamped simultaneously.

**IVC thrombectomy or tumor-bearing inferior vena cavaectomy**

After occlusion of the above vessels, the IVC wall was incised. To avoid tumor dissemination, the thrombus was placed in a specimen bag after the thrombus was removed, and the IVC lumen was irrigated with heparinized saline. Then, the IVC was repaired with a continuous suture. Before the IVC was closed, the caudal IVC tourniquet was released to remove any clot in the IVC. In cases where the thrombus was friable, filled the inferior vena caval lumen, or densely adhered to the IVC wall, and the collateral circulation was reconstructed well, an en bloc dissection was performed of the tumor-bearing IVC. For retro-hepatic and suprahepatic IVC thrombus, the proximal part of the thrombus was removed, and the infrahepatic IVC was stapled. To protect the major hepatic veins, an incision was made on the right side of the IVC wall by rotating the right lobe of the liver to the left side, and the retrohepatic IVC was reconstructed using a continuous suture before stapling.

**Radical nephrectomy**

For right renal tumors, robot-assisted radical nephrectomy and IVC thrombectomy were performed. For left renal tumors, a right lateral decubitus position was used after robot-assisted IVC thrombectomy, and radical nephrectomy was performed [12].

**Statistical analysis**

Continuous data with a normal distribution were recorded as the mean and interquartile range (IQR). The mean and standard deviation (SD) were used when the data were normally distributed. The Students t-test, one-way analysis of variance (ANOVA), or the Wilcoxon rank-sum test were used to compare continuous variables between the study groups.

The chi-squared ($\chi^2$) test or Fisher’s exact test were used to compare the categorical variables between the groups. The association between the continuous variables was assessed by Pearson’s or Spearman’s correlation test. Cumulative sum analysis was performed for the quantitative assessment of the learning curve using the following equation:

$$\text{cumulative sum } n = \text{cumulative sum } n-1 + (\text{value } n - \text{value } \text{mean}).$$

The associations between the learning curve and the clinicopathological or surgical factors were calculated using multiple linear regression analysis or logistic regression analysis to identify the variables with $p<0.1$ on univariate analysis. SPSS version 18.0 (IBM, Chicago, IL, USA) and GraphPad Prism version 7.0 software (GraphPad, San Diego, CA, USA) were used to analyze the data and to plot the data graphically. Hypothesis testing was two-sided, and $p<0.05$ was considered statistically significant.

**Results**

**Baseline characteristics, technical indicators, and clinical outcomes**

The baseline characteristics, technical indicators, and clinical outcomes of all patients who underwent robot-assisted inferior vena cava (IVC) thrombectomy are summarized in Table 1. There were 36 (30%) patients with a left renal tumor and 84 (70%) patients with a right renal tumor. The TNM stage was T3b in 93 (77.5%) cases, T3c in 23 (19.2%) cases, and T4 in 4 (3.3%) cases. The Mayo Clinic thrombus classification was level I–II in 104 (86.6%) patients and level III–IV in 16 (13.4%) patients. Thrombectomy was performed for 86 (71.7%) cases, and inferior vena cavaectomy was performed for 34 (28.3%) cases. There were 81 (67.5%) patients with clear cell renal cell carcinoma and 39 (32.5%) patients with other pathology results, including papillary renal cell carcinoma, mixed renal cell carcinoma, urothelial carcinoma, and angiomyolipoma. The Fuhrman grade was level 1–2 in 53 (44.2%) cases and level 3–4 in 50 (41.7%) cases. There were 15 (12.5%) patients and 13 (10.8%) patients with preoperative lymph node metastasis and distant metastasis, respectively.

The median operative time was 245 min (range, 190–355 min). The median IVC occlusion time was 19 min (range, 13–28 min). The median estimated blood loss was 600 ml (range, 250–1200 ml). Sixty-one (50.8%) patients received a blood transfusion during or after the operation. There were three cases of conversion to open surgery for severe adhesions (2 cases) and massive bleeding (1 case). R0 resection was achieved in 118 (98.3%) patients. The median postoperative length of hospital stay was 7 days (range, 5–10 days). There was no perioperative...
mortality, but fourteen (11.6%) patients suffered 90-day progression, including recurrence, metastasis, and mortality.

The major intraoperative complications included vascular injury (3 cases) and duodenal injury (1 case), which were treated with endoscopic sutures. A total of 40 (33.3%) patients developed complications, which were severe (Clavien-Dindo classification system III–IV) in 11 (9.2%) patients. The main early postoperative complications were hepatorenal dysfunction, neuropsychiatric symptoms, coagulation disorders that included disseminated intravascular coagulation and lower limb venous thrombosis, and duodenal ulcer that was treated with endoscopic sutures. A total of 40 (33.3%) patients developed complications, which were severe (Clavien-Dindo classification system III–IV) in 11 (9.2%) patients. The main early postoperative complications were hepatorenal dysfunction, neuropsychiatric symptoms, coagulation disorders that included disseminated intravascular coagulation and lower limb venous thrombosis, and duodenal ulcer that was treated with endoscopic sutures. A total of 40 (33.3%) patients developed complications, which were severe (Clavien-Dindo classification system III–IV) in 11 (9.2%) patients. The main early postoperative complications were hepatorenal dysfunction, neuropsychiatric symptoms, coagulation disorders that included disseminated intravascular coagulation and lower limb venous thrombosis, and duodenal ulcer that was treated with endoscopic sutures. A total of 40 (33.3%) patients
There were no cases of Budd-Chiari syndrome in patients with suprahepatic thrombus, possibly because the IVC was gradually obstructed by tumor thrombus, and the majority of the patients had established good collateral circulation. Also, the major hepatic veins were protected during surgery.

**Improvements in intraoperative and postoperative outcomes**

As shown in Figure 1, the operative time and estimated blood loss were negatively correlated with the number of cases treated. The cumulative sum curve of operative time and estimated blood loss was divided into three phases. The inflection points were between cases 40 and 80.

**Factors associated with the operative time, estimated blood loss, and early complications**

The potential factors that influenced the operative time and estimated blood loss were shown in Table 2. Increased operative time and estimated blood loss were significantly correlated with increased tumor size ($p<0.001$ and $p=0.043$), the clinical stage ($p=0.014$ and $p=0.005$), thrombus length ($p<0.001$ and $p<0.001$), Mayo Clinic level ($p<0.001$ and $p<0.001$), and early learning phase ($p=0.003$ and $p=0.006$). The operative time and estimated blood loss were significantly associated with medically. There were no cases of Budd-Chiari syndrome in patients with suprahepatic thrombus, possibly because the IVC was gradually obstructed by tumor thrombus, and the majority of the patients had established good collateral circulation. Also, the major hepatic veins were protected during surgery.

**Improvements in intraoperative and postoperative outcomes**

As shown in Figure 1, the operative time and estimated blood loss were negatively correlated with the case number, and there were three phases of the learning curve for the operative time and estimated blood loss, according to the cumulative sum analysis. Phase I (cases 1–40) was the rapid increase period, phase II (cases 41–80) was the plateau period, and phase III (cases 81–100) was the steady improvement period. The operative time decreased from 265 min (range, 212–401 min) to 207 min (range, 146–276 min) ($p=0.003$), the estimated blood loss decreased from 775 ml (range, 413–1500 ml) to 300 ml (range, 163–813 ml) ($p=0.006$) (Table 2). The IVC occlusion time decreased from 29 min (range, 20–33 min) to 12 min (range, 10–15 min) ($p<0.001$), and the postoperative length of hospital stay decreased from 9 days (range, 6–11 days) to 5 days (range, 4–7 days) ($p<0.001$) (Figure 2A, 2B). The rate of blood transfusion ($p=0.044$) and postoperative complications ($p<0.001$) decreased from 55% and 52.5% to 32.5% and 15%, respectively. Also, the rate of intraoperative injury ($p=0.062$), conversion to open surgery ($p=0.152$), and 90-day progression ($p=0.082$) also showed a downward trend, although there was no statistical difference between the learning phases (Figure 2C).
The surgical method ($p=0.001$ and $p<0.001$). Also, the operative time was influenced by the body mass index (BMI) and the affected side ($p=0.027$ and $p<0.001$), and estimated blood loss was also affected by the Fuhrman grade ($p=0.037$). For the rate of early postoperative complications, the potential impact factors included thrombus length ($p<0.001$), Mayo Clinic level ($p<0.001$), surgical method ($p<0.001$), and learning phase ($p<0.001$).

Table 2. Univariate analysis of the correlation of operative time, estimated blood loss and early complication rate with clinical, pathological and surgical characteristics of patients treated with robot-assisted Mayo Clinic level I–IV inferior vena cava (IVC) thrombectomy associated with renal carcinoma.

| Characteristic                  | Operative time median (IQR), min | p-Value | Estimated blood loss median (IQR), ml | p-Value | Complication N (%) | p-Value |
|--------------------------------|----------------------------------|---------|--------------------------------------|---------|--------------------|---------|
| BMI (kg/m²)                    |                                  |         |                                      |         |                    |         |
| <20                            | 193 (151–210)                    | 0.027   | 225 (163–550)                        | 0.083   | 1 (8.3)            | 0.139   |
| 20–25                          | 250 (189–330)                    |         | 600 (238–1225)                      |         | 19 (35.2)          |         |
| ≥25                            | 260 (199–374)                    |         | 650 (300–1238)                      |         | 20 (37.1)          |         |
| Affected side                  | <0.001                           |         | 0.089                                |         | 0.678              |         |
| Left                           | 360 (286–431)                    |         | 725 (413–1413)                      |         | 13 (36.1)          |         |
| Right                          | 210 (165–265)                    |         | 550 (200–1200)                      |         | 27 (32.1)          |         |
| Tumor size                     | <0.001                           |         | 0.043                                |         | 0.587              |         |
| Clinical stage                 | 0.014                            |         | 0.005                                |         | 0.208              |         |
| T3b                             | 225 (183–324)                    |         | 500 (200–1000)                      |         | 27 (29.3)          |         |
| T3c                             | 340 (235–410)                    |         | 1000 (400–2300)                     |         | 12 (50)            |         |
| T4                              | 299 (245–385)                    |         | 1500 (825–1763)                     |         | 1 (25)             |         |
| IVC thrombus length            | <0.001                           | <0.001  | <0.001                               |         |                    |         |
| I                              | 195 (151–274)                    | <0.001  | 225 (100–500)                        | <0.001  | 5 (16.7)           | <0.001  |
| II                             | 245 (194–322)                    | <0.001  | 625 (300–1200)                      | <0.001  | 23 (31.1)          | <0.001  |
| III–IV                         | 408 (310–483)                    | <0.001  | 1850 (913–3113)                     | <0.001  | 12 (75)            | <0.001  |
| Fuhrman grade                  | 0.678                            | 0.037   | 0.419                                |         |                    |         |
| 1–2                            | 230 (190–368)                    |         | 500 (200–1025)                      |         | 17 (32.1)          |         |
| 3–4                            | 253 (190–340)                    |         | 850 (300–550)                       |         | 20 (40)            |         |
| Surgical method                | <0.001                           | <0.001  | <0.001                               |         |                    |         |
| Thrombectomy                   | 225 (184–313)                    |         | 475 (200–850)                       |         | 18 (20.9)          |         |
| Inferior vena cavaectomy       | 320 (228–410)                    |         | 1425 (650–2075)                     |         | 22 (64.7)          |         |
| Learning phase                 | 0.003                            | 0.006   | <0.001                               |         |                    |         |
| I (1–40)                       | 265 (212–401)                    |         | 775 (413–1500)                      |         | 21 (52.5)          |         |
| II (41–80)                     | 260 (193–364)                    |         | 750 (400–1275)                      |         | 13 (32.5)          |         |
| III (81–120)                   | 207 (146–276)                    |         | 300 (163–813)                       |         | 6 (15)             |         |

IQR – interquartile range; BMI – body mass index; IVC – inferior vena cava; OT – operative time; EBL – estimated blood loss.

* The proximal IVC in some of the level IV cases was confirmed to be clamped under the diaphragm by intraoperative ultrasound.
These variables were used for multiple linear regression or logistic regression analysis. Table 3 shows the independent factors that influenced the operative time. These factors included a left-sided renal tumor (change in operative time, 132.1 min, \( p < 0.001 \)); thrombus length (change in operative time, 7.8 min per each cm, \( p = 0.011 \)); Mayo Clinic level III–IV thrombus (change in operative time, 107.1 min, \( p < 0.001 \)); and the learning phase (change in operative time, –23.3 min from phase I to phase II, and –53.3 min from phase II to phase III, \( p < 0.001 \)).

The independent factors that affected the estimated blood loss included thrombus length (change in estimated blood loss, 110.2 ml per each cm, \( p = 0.004 \)); Mayo Clinic level III–IV thrombus (change in estimated blood loss, 745.6 ml, \( p = 0.028 \)); and the learning phase (change in estimated blood loss, –189.6 ml from phase I to phase II, and –275.9 ml from phase II to phase III, \( p = 0.015 \)).

The independent factors that affected the rate of early postoperative complications included Mayo Clinic level III–IV thrombus (OR, 35.928; 95% CI, 1.52–849.41; \( p = 0.026 \)); inferior vena cavaectomy (OR, 16.463; 95% CI, 2.939–92.203; \( p = 0.001 \)); learning phase II (OR, 0.179; 95% CI, 0.039–0.812; \( p = 0.026 \)); and learning phase III (OR, 0.022; 95% CI, 0.00–0.24; \( p = 0.002 \)). There was no significant difference in the affected side, thrombus length, Mayo Clinic level, or surgical method between the phases after stratifying the patient clinicopathological characteristics according to the learning curve (Table 4).

**Discussion**

Robotic surgical systems are a relatively recent advance for use in technically demanding surgical procedures [14]. Radical nephrectomy and inferior vena cava (IVC) tumor thrombectomy are among the most challenging surgical procedures in urology and are traditionally performed using an open approach. However, open surgery requires a large abdominal or thoracoabdominal incision for vascular control, thrombectomy, and radical nephrectomy, which results in a relatively high rate of
early complications, which have been reported in 24.4–78% of cases [15,16]. Compared with the open method, the robotic surgical system offers a three-dimensional view of the surgical field, the use of flexible robotic arms with compensation for tremor, all of which may reduce the challenges of the complicated manipulation required in IVC thrombectomy and shorten the learning period for surgical operators [17].

With the development of robot-assisted surgical techniques in urological surgery, the safety and feasibility of robot-assisted IVC thrombectomy for selected patients have previously been demonstrated. For level I–II IVC tumor thrombus, the Mayo Clinic experience showed that [18], compared with open surgery, robotic surgery had a longer operative time (284 minutes compared with 242 minutes), lower estimated blood loss (450 ml compared with 1800 ml), shorter length of stay

| Characteristic             | Change in OT (min) | p-Value | Change in EBL (ml) | p-Value | Complication rate OR (95% CI) | p-Value |
|---------------------------|--------------------|---------|--------------------|---------|------------------------------|---------|
| BMI                       | 1.1                | 0.545   | −7.8               | 0.731   | 0.985 (0.818–1.186)          | 0.873   |
| Affected side             |                    |         |                    |         |                              |         |
| Left                      | 132.1              | <0.001  | 19.1               | 0.918   | 2.553 (0.594–10.965)         | 0.208   |
| Right                     | Reference          | Reference| Reference          | Reference|                              |         |
| Tumor size                | 2.4                | 0.274   | −2.1               | 0.938   | 0.934 (0.749–1.165)          | 0.545   |
| Clinical stage            | 0.165              |         | 0.244              |         | 0.089                        |         |
| T3b                       | Reference          | Reference| Reference          | Reference|                              |         |
| T3c                       | −9.4               |         | 236.8              | 0.797   | 0.169–5.679                  |         |
| T4                        | −47.5              |         | 358.7              | 0.065   | 0.003–1.514                  |         |
| IVC thrombus length       | 7.8                | 0.011   | 110.2              | 0.004   | 1.177 (0.883–1.569)          | 0.266   |
| IVC thrombus level        | <0.001             |         | 0.028              |         | 0.026                        |         |
| 1                         | Reference          | Reference| Reference          | Reference|                              |         |
| 2                         | 4.9                |         | 148.7              | 0.28    | 0.05–1.583                   |         |
| I–IV*                     | 107.1              |         | 745.6              | 35.928  | 1.52–849.41                  |         |
| Fuhrman grade             | 0.756              |         | 0.228              |         | 0.349                        |         |
| 1–2                       | Reference          | Reference| Reference          | Reference|                              |         |
| 3–4                       | −3.9               |         | 189.1              | 1.877   | 0.502–7.018                  |         |
| Surgical method           | 0.096              |         | 0.076              |         | 0.001                        |         |
| Thrombectomy              | Reference          | Reference| Reference          | Reference|                              |         |
| Inferior vena cavectomy   | 26.7               |         | 353.6              | 16.463  | 2.939–92.203                 |         |
| Learning phase            | <0.001             |         | 0.015              |         | 0.002                        |         |
| I (1–40)                  | Reference          | Reference| Reference          | Reference|                              |         |
| II (41–80)                | −23.3              |         | −189.6             | 0.179   | 0.039–0.812                  |         |
| III (81–120)              | −76.6              |         | −465.5             | 0.022   | 0.002–0.24                   |         |

BMI = body mass index; IVC = inferior vena cava; OT = operative time; EBL = estimated blood loss; OR = odds ratio; CI = confidence interval. * The proximal IVC in some of the level IV cases were confirmed to be clamped under the diaphragm by intraoperative ultrasound.
in hospital (3 days compared with 7 days), and a lower complication rate (17% compared with 43%) [8]. In a previously reported preliminary study, we showed that robot-assisted IVC thrombectomy had a shorter operative time (150 minutes compared with 230 minutes), a lower estimated blood loss (250 ml compared with 1000 ml), a shorter length of stay in hospital (5 days compared with 9 days), and lower complication rate (9.7% compared with 29%) when compared with the open approach [19].

Currently, there have been no previously reported studies to compare open and robotic surgery for Mayo Clinic level III–IV IVC tumor thrombus. Mukul et al. [20] reported that for Mayo Clinic level III–IV thrombi, the mean operative time was 325 min, and the complication rate was 54% for open surgery without cardiopulmonary bypass. Gill et al. [3] and Chopra et al. [8] reported similar results for the operative time (270–294 min), the estimated blood loss (240–375 ml), and the complication rate (11.1–16.7%) using intracorporeal robotic surgery for level III thrombi. Also, during a previous study [5], the operative time, estimated blood loss, and complication rate for Mayo Clinic level III–IV robot-assisted IVC thrombectomy without cardiopulmonary bypass was 430 min, 1,100 ml, and 37.5%, respectively. However, these results were reported in studies with a relatively small sample size, ranging from 8–31 cases, which are not large enough to determine efficacy and safety.

Table 4. Baseline characteristics, operative indicators, and clinical outcomes stratified according to the learning phase for patients treated with robot-assisted Mayo Clinic level I–IV inferior vena cava (IVC) thrombectomy associated with renal carcinoma.

| Characteristic                        | Phase I (cases 1–40) | Phase II (cases 41–80) | Phase III (cases 81–120) | p-Value |
|--------------------------------------|----------------------|------------------------|--------------------------|---------|
| Affected side, n (%)                 |                      |                        |                          | 0.155   |
| Left                                 | 11 (27.5)            | 15 (37.5)              | 10 (25)                  |         |
| Right                                | 29 (72.5)            | 25 (62.5)              | 30 (75)                  |         |
| IVC thrombus length, median (IQR), cm| 6.7 (4.4–10.5)       | 6.6 (5.2–9.1)          | 6.4 (5–8)                | 0.639   |
| IVC thrombus level, n (%)            |                      |                        |                          | 0.894   |
| I                                  | 11 (27.5)            | 10 (25)                | 9 (22.5)                 |         |
| II                                  | 25 (62.5)            | 25 (62.5)              | 24 (60)                  |         |
| III–IV                              | 4 (10)               | 5 (12.5)               | 7 (17.5)                 |         |
| Surgical method, n (%)               |                      |                        |                          | 0.750   |
| Thrombectomy                         | 30 (75)              | 27 (67.5)              | 29 (72.5)                |         |
| Inferior vena cavectomy              | 10 (25)              | 13 (32.5)              | 11 (27.5)                |         |
| IVC occlusion time, median (IQR), min| 29 (20–33)           | 20 (14–26)             | 12 (10–15)               | <0.001  |
| Blood transfusion, n (%)             | 22 (55)              | 26 (65)                | 13 (32.5)                | 0.044   |
| Intraoperative injury, n (%)         | 3 (7.5)              | 1 (2.5)                | 0 (0)                    | 0.062   |
| Conversion, n (%)                    | 2 (5)                | 1 (2.5)                | 0 (0)                    | 0.152   |
| Postoperative complication, n (%)    |                      |                        |                          | <0.001  |
| Clavien-Dindo classification system  |                      |                        |                          |         |
| I–II                                 | 15 (37.5)            | 9 (22.5)               | 5 (12.5)                 | 0.009   |
| III–IV                               | 6 (15)               | 4 (10)                 | 1 (2.5)                  | 0.048   |
| Positive surgical margin, n (%)      | 1 (2.5)              | 1 (2.5)                | 0 (0)                    | 0.383   |
| Postoperative hospital stay, median (IQR), days | 7 (6–9) | 9 (6–11) | 5 (4–7) | <0.001 |
| 90-day progression, n (%)            | 7 (17.5)             | 5 (12.5)               | 2 (5)                    | 0.082   |

IQR – interquartile range; IVC – inferior vena cava. * The proximal IVC in some of the level IV cases were confirmed to be clamped under the diaphragm by intraoperative ultrasound.

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The learning curve refers to the time required to master a new technique, which can include three phases. The performance of the first two phases varies with different procedures, different surgeons, and how many and how often a surgeon has performed the technique. Only the final phase is stable, and may objectively reflect the advantages and disadvantages of a novel technique. Studies on learning curves for new surgical procedures may be useful for surgeons preparing to develop a new technique. However, to our knowledge, there have been no previously reported studies on the development of a learning curve for robot-assisted IVC thrombectomy.

In the present study, the cumulative sum analysis was used to assess the learning curve. The use of cumulative sum analysis confirmed the three learning phases for robot-assisted IVC thrombectomy. Multivariate analysis showed that an initial 40 cases and a further 80 cases of Mayo Clinic level I–IV IVC thrombectomy associated with renal carcinoma were required to improve outcomes and reduce complications significantly. Phase I (cases 1–40) was the period of a rapid increase in learning in which the operative time and estimated blood loss were significantly more than the average level of the entire cohort. However, in the early stage of phase I (cases 1–10), the cumulative sum of the operative time and estimated blood loss showed a small decrease as all the cases were right-sided tumors with infra-hepatic IVC tumor thrombus. With the inclusion of patients with a left-sided renal tumor or renal tumor with retrohepatic or suprarehepatic thrombus (cases 11–40), the cumulative sum increased rapidly. Because patients with left renal tumors need to be repositioned before radical nephrectomy, patients with retrohepatic thrombus require the mobilization of the right lobe of the liver. Patients with suprarehepatic thrombus require additional mobilization of the left lobe of the liver and the simultaneous control of the porta hepatis. Phase II (cases 41–80) was the plateau period, in which the operative time and the estimated blood loss were almost the same as the average level, indicating that the surgical procedure had become more stable. In this phase, we identified different robotic surgical strategies for right and left renal tumors with IVC tumor thrombus and found that the porta hepatis and the major hepatic veins were important boundary landmarks for level II–III IVC tumor thrombus [12,13]. Then, we established a set of standardized procedures for robot-assisted IVC thrombectomy. Phase III (cases 81–120) was the steady improvement period, in which the operative time and the estimated blood loss decreased below the average level, which indicated that further modification of the procedure contributed to better outcomes. In this phase, we also made some minor improvements for the standardized procedures, based on our clinical practice. For example, we applied the sequential vascular control strategy which duplicated open surgery to reduce the warm ischemic time, and determined whether should receive thrombectomy or inferior vena cavaectomy. Preoperative IVC venography and three-dimensional computed tomography (CT) reconstruction were used, instead of temporary conversion to inferior vena cavaectomy when it was found that the tumor thrombus could not be removed completely during the surgery.

Although three phases of the learning curve were identified in this study, it remains unknown whether the first 40 cases were included in the learning curve, or whether the first 33% of the cohort might be included, regardless of the sample size. The standardization of the surgical procedure and the modification of the surgical technique with increasing numbers of cases may further reduce the mean operative time and estimated blood loss, and the inflection points may change accordingly. Compared with some recent studies involving cumulative sum analysis for other types of robotic surgery [21–25], the present study identified a similar boundary case number ranging from 25 to 50, or between 20% and 50%. However, as far as we know, there has been no previously reported study on the learning curve of robot-assisted IVC thrombectomy for reference. Therefore, further validation by large-scale multicenter studies if required in the future.

The most important indicators to measure the learning curve for surgical procedures and patient outcomes have been previously reported [26–30]. The most commonly used indicators for the evaluation of the learning curve include the operative time, and the estimated blood loss [31]. Although it is easier to measure and compare the operative time and the estimated blood loss, the learning curve based on these indicators alone does not present a valid index of surgical proficiency. Therefore, functional and clinical results must be considered, and the confounders should be minimized to draw reliable conclusions [27,32–34]. In the present study, we also summarized other technical indicators, including IVC occlusion time, intraoperative injury rate, conversion rate, blood transfusion rate, and clinical outcomes, including the rate of early complication, the perioperative mobility rate, the rate of positive margins, postoperative length of hospital stay, and 90-day progression rate. These indicators were used to evaluate the learning curve of robot-assisted IVC thrombectomy more accurately. Although the majority of these factors were not significantly different between the three learning phases, they showed a downward trend. Also, multiple regression analysis identified independent factors that affected the operative time, the estimated blood loss, and the early complication rate, which included the affected side, thrombus length, the Mayo Clinic level, and the surgical method. These factors were stratified according to the learning phase to minimize the confounding factors.

Univariate and multivariate analysis showed that the surgical method played an important role in patient outcomes.
The thrombi that were friable filled the IVC lumen or densely adhered to the IVC wall, usually brought great difficulties to the surgery. For cases with good collateral circulation, complete endoscopic inferior vena cavectomy with a partial IVC reconstruction was performed to protect the hepatic veins and preserve the collateral circulation on the premise of the tumor-free principle. Through comparing the baseline characteristics of the patients stratified by surgical method (Table 5), we found that patients who underwent inferior vena cavectomy had a larger tumor size, longer thrombus length, more distant metastasis, and higher clinical stage, Fuhrman grade, and Mayo Clinic level. Therefore, there was a significant difference in the

| Characteristic                        | Thrombectomy | Inferior vena cavectomy | p-Value |
|--------------------------------------|--------------|-------------------------|---------|
| Patients, n                          | 86           | 34                      |         |
| Sex, n (%)                           |              |                         | 0.276   |
| Male                                 | 57 (66.3)    | 26 (76.5)               |         |
| Female                               | 29 (33.7)    | 8 (23.5)                |         |
| Age, mean (±SD), years               | 54.3 (±14.0) | 53.6 (±11.8)            | 0.799   |
| BMI, mean (±SD), kg/m²               | 24 (±3.4)    | 24.7 (±3.3)             | 0.296   |
| Affected side, n (%)                 |              |                         | 0.331   |
| Left                                 | 28 (32.6)    | 8 (23.5)                |         |
| Right                                | 58 (67.4)    | 26 (76.5)               |         |
| Tumor size, mean (±SD), cm           | 7.5 (±3.2)   | 9 (±2.8)                | 0.022   |
| Clinical stage, n (%)                |              |                         | 0.013   |
| T3b                                  | 71 (82.5)    | 22 (64.7)               |         |
| T3c                                  | 14 (16.3)    | 9 (26.5)                |         |
| T4                                   | 1 (1.2)      | 3 (8.8)                 |         |
| Lymph node metastasis, n (%)         |              |                         | 0.746   |
| Nx                                   | 32 (37.7)    | 18 (52.9)               |         |
| N0                                   | 24 (27.9)    | 11 (32.4)               |         |
| N1                                   | 10 (11.6)    | 5 (14.7)                |         |
| Distant metastasis, n (%)            |              |                         | 0.031   |
| M0                                   | 80 (93)      | 27 (79.1)               |         |
| M1 (1 site)                          | 6 (7)        | 7 (20.9)                |         |
| IVC thrombus length, median (IQR), cm| 6 (4.6–8.0)  | 9.2 (7.5–12.1)          | <0.001  |
| IVC thrombus level, n (%)            |              |                         | <0.001  |
| I                                   | 30 (34.9)    | 0 (0)                   |         |
| II                                  | 30 (34.9)    | 0 (0)                   |         |
| III–IV*                              | 6 (7)        | 10 (29.4)               |         |
| Histologic subtype, n (%)**          |              |                         | 0.006   |
| Clear cell                           | 59 (68.6)    | 22 (64.7)               |         |
| Papillary                            | 9 (10.5)     | 5 (14.7)                |         |
| Others                               | 18 (20.9)    | 7 (20.6)                |         |
| Fuhrman grade, n (%)                 |              |                         | 0.005   |
| 1–2                                  | 44 (51.2)    | 9 (26.5)                |         |
| 3–4                                  | 29 (48.8)    | 21 (73.5)               |         |

SD – standard deviation; IQR – interquartile range; BMI – body mass index; IVC – inferior vena cava. * The proximal IVC in some of the level IV cases were confirmed to be clamped under the diaphragm by intraoperative ultrasound. ** There are eight cases with mixed renal cell carcinoma, three cases with urothelial carcinoma, seven cases with Angiomyolipoma and seven cases with other subtypes.
surgical outcomes between the two methods, and the oncological outcomes should be evaluated with further studies.

This study included cases with level I–III thrombus (infra-diaphragmatic thrombus), and some cases with level IV thrombus where the proximal IVC could be controlled under the diaphragm, which was confirmed by intraoperative ultrasound, to minimize the influence of interference factors on the results. Therefore, they could be treated with similar surgical procedures. However, Mayo Clinic level III–IV thrombus still had a significant impact on surgical and clinical outcomes. Therefore, it may be necessary to analyze the cases with Mayo Clinic level III–IV thrombus separately. The use of the Pringle maneuver to control bleeding from the liver, as an important indicator of surgery for suprahepatic thrombus, should also be included in the outcome assessment. We had previously reduced the time of the Pringle maneuver and improved the oncological outcomes using a modified vascular control strategy that was similar to the open surgical procedure. However, in the present study, the number of cases studied was relatively small, and the findings should be supported using a larger study sample size.

This study had several limitations. Firstly, this was a retrospective study at a single center and included selected patients, which might have resulted in study bias. Also, all the cases of robotic surgery for IVC tumor thrombus were performed by a single surgical team with experience in both open and laparoscopic surgery. Therefore, the learning curve might be different for a surgeon without establishing proficiency in conventional surgical approaches. The standardized steps in the robot-assisted IVC thrombectomy were gradually developed during clinical practice, which might have influenced the learning curve. Therefore, large-scale, multicenter studies, with a larger sample size and long-term follow-up should be performed to further investigate the learning curve for robot-assisted Mayo Clinic level I–IV IVC thrombectomy associated with renal cancer, to continue to develop an optimized operative procedure, which may lead to the development of surgical guidelines.

Conclusions

This study aimed to use cumulative sum analysis of the operator learning curve for robot-assisted Mayo Clinic level I–IV inferior vena cava (IVC) thrombectomy associated with renal carcinoma and described the development of an optimized operative procedure at a single center. Multiple regression analysis showed that the learning phase, affected side, thrombus length, Mayo Clinic level, and surgical method were independent factors that influenced operative time, estimated blood loss, and the complication rate of robot-assisted IVC thrombectomy. The experience from an initial 40 cases and a further 80 cases of Mayo Clinic level I–IV IVC thrombectomy associated with renal carcinoma were found to provide acceptable surgical and clinical outcomes.

Conflict of Interest

None.

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