Provisional chapter

Surgical Strategy for the Management of Renal Cell Carcinoma with Inferior Vena Cava Tumor Thrombus

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Abstract

The hallmark of renal cell carcinoma is its biological characteristic of invading the renal vein and/or inferior vena cava (IVC), which occurs in 4–10% of patients. Radical nephrectomy (RN) with tumor thrombectomy is the standard approach for treating such challenging cases. Except tumor thrombus height, several factors can determine the surgical strategy, including the effect of targeted molecular therapy (TMT), invasion of the IVC wall, venous occlusion, establishment of collateral circulation, IVC thromboembolism, and primary tumor location. The surgical strategy for patients with retrohepatic vena cava tumor thrombi depends on the upper extent of the tumor thrombus. In addition, the first porta hepatis and hepatic veins are important anatomical boundaries. Based on previous studies, the effect of pre-surgical TMT is limited. The safety of IVC venography, an imaging modality that can observe congestion of the tumor thrombus and show the collateral circulation, has considerably improved. IVC interruption plays an important role in tumor thrombectomy for patients with invasion of the venous walls, complete occlusion of the vena cava, and the presence of distal thrombus. A series of retrospective and prospective studies are needed to be conducted, which will provide our clinical work with more powerful reference and basis.

Keywords: renal cell carcinoma, tumor thrombus, targeted molecular therapy, inferior vena cava venography, vascular resection, surgical strategy

1. Introduction

The Chinese Cancer Registry Annual Report of 2015 indicates that renal cell carcinoma (RCC) represents approximately 2–3% of new cases of malignant tumor in China annually and the trend in the morbidity of RCC has been increasing [1]. The hallmark of RCC is its biological characteristic of invading the renal vein and/or inferior vena cava (IVC), which occurs in 4–10% of patients [2]. Past clinical decision making mostly adopts conservative treatment, in terms of high morbidity and mortality rates during this kind of procedures. Radical nephrectomy (RN) with tumor thrombectomy is the standard approach for treating such challenging cases [3]. These patients were able to obtain, as literature reported, better long-term survival, and the tumor-specific survival rate is in up to 50% [4–7].

With the development of laparoscopy and robotic technology and the accumulation of practical experience in surgery, we noted that the height of IVC thrombus could not sufficiently guide the choice of surgical strategy, considering that only the thrombus height was assessed. Several factors, such as the effect of neoadjuvant targeted molecular therapy (TMT), invasion of the IVC wall, venous occlusion, establishment of collateral circulation, IVC thromboembolism, and primary tumor location, can determine the surgical strategy. The present comprehensive review describes how those factors influence surgical strategy and patient outcomes.

2. Technological innovations and classifications

RCC tends to invade the renal venous system, forming a thrombus that invades the IVC and even involving the right atrium [2]. RN with tumor thrombectomy is the standard approach for treating such challenging cases. The grading system based on tumor thrombus height was created to determine surgical strategies. As early as 1987, the Mayo Clinic had adopted the "NEVES grading." Level I is defined as a tumor thrombus that is <2 cm apart from the orificium of the renal vein. Level II is defined as a tumor thrombus extending to the IVC >2 cm above the renal vein but below the hepatic veins. Level III is defined as a tumor thrombus that extends above the hepatic veins but below the diaphragm. Level IV is defined as a tumor thrombus located above the diaphragm. Surgical strategies are varied in corresponding levels. Traction of the liver is required in levels I to II. Turning-up the liver, blocking-up vessels located below the diaphragm, and clamping the portal vein are required in levels II to III. The establishment of an extracorporeal circulation is necessary in levels III and IV [8]. In 2002, the University of Miami divided level III tumor thrombus into four categories ulteriorly, which corresponded to diverse surgical strategies [9]. However, the most classic guideline is the "5-level classification" of a tumor thrombus, which was proposed by the Mayo Clinic in 2004 [10]. Idiographic grading standards and surgical strategies are shown in **Table 1**.

Nevertheless, these grading systems are completely based on the experience of open surgery. Since Skinner first reported the open surgery of IVC tumor thrombectomy in 1972 [11], the technique of IVC tumor thrombectomy has been improving continuously. Some scholars had attempted to accomplish these surgeries with laparoscope in 2002 [12, 13]. In 2011, Abaza first reported on robot-assisted IVC tumor thrombus extraction [14]. In recent years, several medical centers have investigated the safety and feasibility of robot-assisted laparoscopic IVC thrombectomy (RAL-IVCTE) [15–18]. Based on the anatomic characteristics of RCC, we

Tumor thrombus level	Definition	Surgical strategy
0	Tumor thrombus is limited to the renal vein	Radical nephrectomy of renal cell carcinoma
I	Tumor thrombus extend into IVC with <2 cm above the renal vein	Tumor thrombus could be extruded to renal vein and then radical nephrectomy
II	Tumor thrombus extends in to IVC >2 cm above the renal vein but below the hepatic veins	The traction of liver is required; blocking-up the section of IVC underneath hepatic vein
III	Tumor thrombus which extends above the hepatic veins but below diaphragm	The mobilization of the liver; vena-venous bypass is required
IV	Tumor thrombus is above diaphragm	Intraoperative extracorporeal circulation is requisite

IVC = inferior vena cava.

Table 1. The grading standards and surgical strategies tumor thrombus.

reported the particular steps of robot-assisted surgery and concluded that RAL-IVCTE is safe, and different sides require different techniques [18]. Gu and colleagues performed a retrospective comparison between open and robotic surgeries in IVC thrombus. The study indicated that level I–II IVC tumor thrombectomy performed with robot-assisted surgery resulted in better perioperative periodical outcomes and analogous oncological outcomes compared with open surgery, marking that such surgery has entered the era of mini-traumatic surgery [19].

3. Surgical procedure

3.1. Anesthesia and patient position

After general anesthesia induction and Foley catheter placement, the patients were positioned in a left lateral decubitus position with a 60–70° bump (**Figure 1A** and **B**). For right RCC, R-IVCTE and RN can be both completed with this position. For left RCC, R-IVCTE can be completed with this position. After R-IVCTE, the placement of patients was converted to a right lateral decubitus position with a 60–70° bump, and left RN was performed.

3.2. Right RN and IVC thrombectomy

The hepatocolic, hepatorenal, and chain ligaments were incised. The liver required to be up-retracted. The anterior layer of the perirenal fascia was opened, the duodenum was dissected and retracted inside, and the IVC was exposed. Full dissection of the IVC, left renal vein, and part of the lumbar vein were required at the location of the tumor thrombus (**Figure 1C**). For level II IVC thrombus, the hepatic short vein, and even right central vein of the adrenal gland, was also clipped and divided (**Figure 1D**). Sequential clamping of the caudal IVC, left renal vein, and cephalic IVC were performed using vessel loops (**Figure 1E**). After the vessels were clamped, the IVC wall was cut, and the thrombus was removed (**Figure 1F**). After the IVC

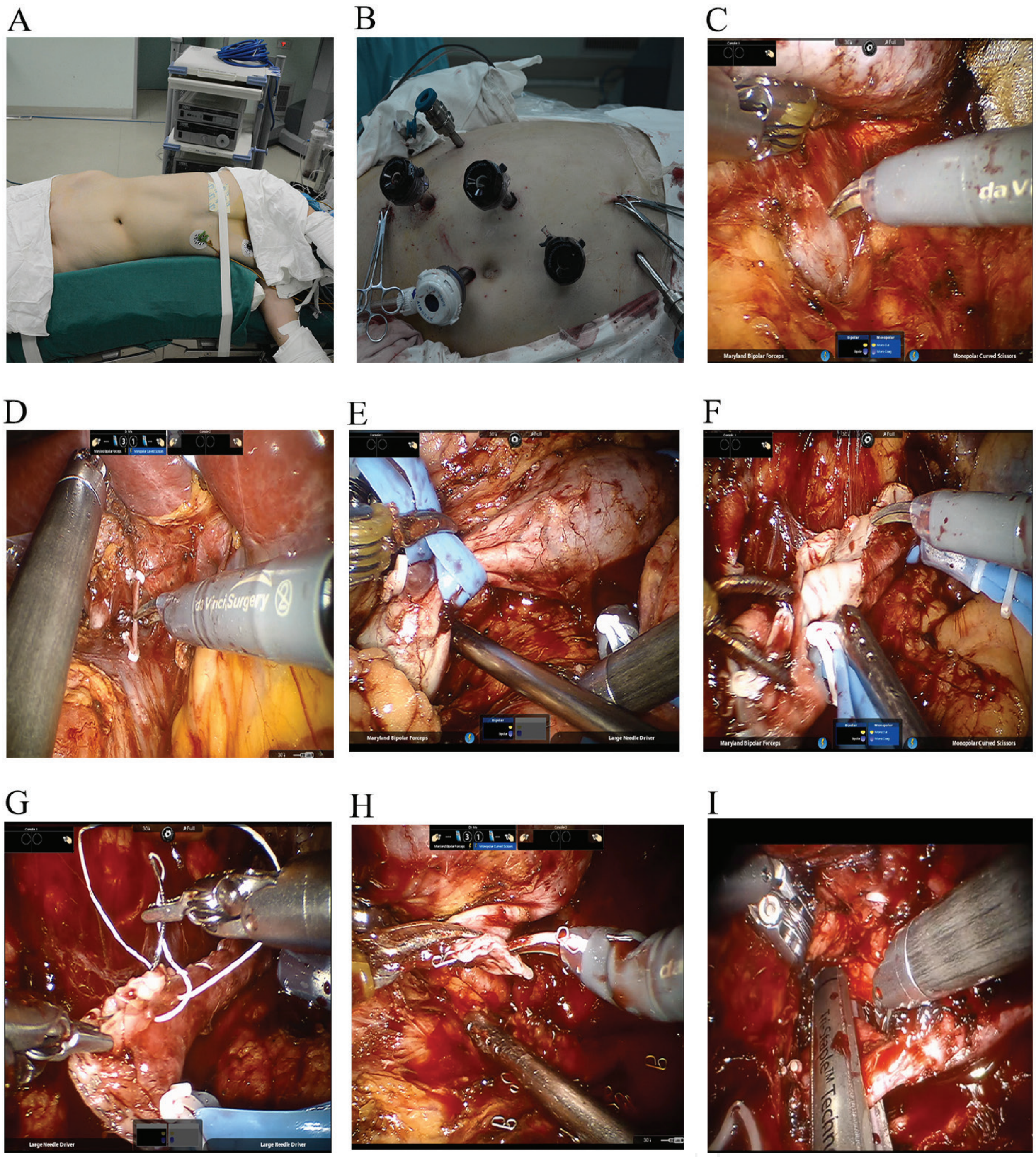

Figure 1. Surgical procedure for robot-assisted laparoscopic inferior vena cava thrombectomy. Patient position and port placement is shown, with three assistant ports used. (A and B). The inferior vena cava and left renal vein was exposed (C). The hepatic short vein was clipped and divided (D). Sequential clamping caudal IVC, left renal vein, and cephalic IVC were performed by vessel loops (E). The thrombus was removed (F). The IVC was closed with 5-0 polypropylene suture (G). Ligation and division of the left renal vein for the left RCC (H). Intraoperative IVC interruption in selected cases (I). IVC = inferior vena cava; RCC = renal cell carcinoma.

lumen was irrigated with heparinized saline, 5-0 polypropylene suture was used to close the IVC (**Figure 1G**). The tourniquets of the caudal IVC, left renal vein, and cephalic IVC were sequentially loosened. In the same position, right RN was completed.

3.3. Left RN and IVC thrombectomy

The patient position and port placement were the same as those for the right RCC. However, we suggest that left renal artery embolization must be performed 1–2 h preoperatively. The steps were similar in dissecting the IVC. Subsequently, we ligated and divided the left renal vein, which included the thrombus, with Endo-GIA (**Figure 1H**). The clamping sequence was the caudal IVC first, followed by the right renal artery, right renal vein, and cephalic IVC. After thrombus removal, the placement of the patients was converted to a right lateral decubitus position, with a 60–70°bump, and left RN was performed.

3.4. Surgical technique for retro- or superohepatic IVC thrombus

Recently, the latest research completed by our team investigated the surgical method of robot-assisted retro- or superohepatic vena caval tumor thrombectomy and its influence factor. We found that the surgical strategy for patients with retrohepatic vena caval tumor thrombi depends on the upper extent of the tumor thrombus [20]. In addition, the first porta hepatis and hepatic veins are important anatomical boundaries. The surgical technique was described as follows. If the retrohepatic thrombus was located inferior to the first porta hepatis (**Figure 2A**), some short hepatic veins should be ligated, but the liver should not be mobilized. If the retrohepatic thrombus was located between the first porta hepatis and hepatic veins (**Figure 2B**), mobilization of the right lobe of the liver is an important step. For retrohepatic thrombus located closer or above the second porta hepatis (liver vein) but below the infra-diaphragm (**Figure 2C**), mobilization both the right and left lobes of the liver can facilitate high proximal control of the superohepatic IVC. In addition, the first porta hepatis should be clamped. For superohepatic (level IV) thrombus, thoracoscope-assisted open atriotomy was performed to cut the atrial part of the thrombus, and vena caval tumor thrombectomy was subsequently performed by clamping the superodiaphragm IVC after cardiopulmonary bypass was established (**Table 2**).

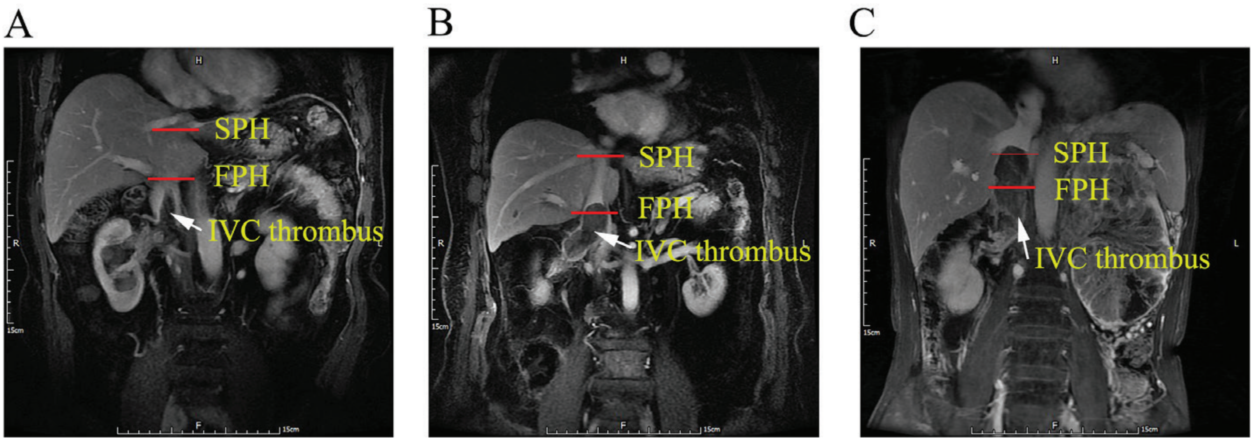

Figure 2. The first porta hepatis and hepatic veins are important anatomical boundaries on representative images of radiography. The retrohepatic thrombus inferior to the first porta hepatis (A). The retrohepatic thrombus inferior to the first porta hepatis (B). The retrohepatic thrombus closer or above the second porta hepatis (liver vein) but blew infra-diaphragm (C). FPH = first porta hepatis; SPH = second porta hepatis; IVC = inferior vena cava tumor.

Location of IVC thrombus	Surgical strategy
Retrohepatic but inferior to the FPH	1. Ligating some SHV 2. Retracting but not liver mobilization
Retrohepatic and between the FPH and hepatic veins	1. Ligating more SHV 2. Mobilizing the right lobe of the liver. 3. Not clamping FPH
Retrohepatic and closer (level II) or above (level III) the second porta hepatis (liver vein) yet infra-diaphragm	1. Mobilizing both the right and left lobes of the liver 2. High proximal control of superohepatic IVC 3. Clamping of the FPH Simultaneously
Superohepatic (level IV)	1. Thoracoscopic atriotomy for cutting atrial part of the thrombus 2. Establishing cardiopulmonary bypass 3. Performing IVC tumor thrombectomy after Clamping the superodiaphragm IVC

IVC = inferior vena cava; SHV = short hepatic vein; FPH = first porta hepatis.

Table 2. Changes of techniques for robot-assisted retro- or supero-hepatic vena caval tumor thrombectomy in our method.

4. Preoperative targeted therapy

Although mini-traumatic surgery has been applied in patients with RCC and tumor thrombus, level III and IV tumor thrombus might have lethal complications, including hemorrhage, thrombotic shedding, etc. The operative mortality and overall morbidity rates of postoperative complication of patients with tumor thrombus patients have been reported up to 5–10% and 38%, respectively [21]. Moreover, as tumor thrombus level advanced, the morbidity of perioperative periodical complications is higher accordingly. With regard to patients with level III and IV tumor thrombus, surgical strategies usually involve thoracotomy, dealing with retro- or superohepatic IVC, and establishing extracorporeal circulation, which can be achieved with the assistance of hepatobiliary and cardiovascular surgeons.

With the targeted molecular therapy (TMT) of rising, TMT has been widely acknowledged as the most effective treatment for advanced RCC, particularly for patients with metastatic RCC. In recent years, targeted drugs have been reported to be applied in preoperative adjunctive therapy for tumor thrombus because of its high success rate in the treatment of advanced RCC [22, 23]. The purpose of administering target drugs was to lessen the height of tumor thrombus or shrink the primary lesions or metastases, which may enhance the safety and feasibility of surgical intervention. The results of some retrospective observations with a small sample present diversities [24–26]. After preoperative TMT, 44–76% of the patients' IVC tumor thrombus had shrinkage in different degrees, with tumor thrombus degradation averaging approximately 20%. Cost and colleagues reported a retrospective outcome from a sample of 25 patients, wherein three patients (12%) had a reduction in the thrombus degradation, and one patient (4%) had an increase [25]. As a result of first-class evidence deficiency, this therapeutic regimen has not been recommended by the guidelines. Thus, further prospective investigations with a larger number of patients are needed to overcome the limitations.

5. Postoperative targeted therapy in patients without metastasis

For patients with non-metastatic RCC and tumor thrombus, the recurrence rate of the tumor is approximately 50% at 3 years preoperatively, despite performing RN [27]. Thus, for these patients, only operative treatment may not be sufficient. Adjuvant IL-2/IFN applied in prophase postoperatively, chemotherapy, and hormone therapy are all negative for high-recurrence risk RCC [28]. Small molecules targeting the vascular endothelial growth factor pathway prolong the progression-free survival of patients with advanced RCC [29, 30]. Based on these, the postoperative application of antiangiogenic medicine for patients with high-relapse risk RCC will play a positive role. Three randomized controlled trials, currently, have reported the outcomes of adopting targeted therapy for high-recurrence risk RCC. Although a study found that sunitinib treatment 1-year postoperatively prolonged relapse-free survival for 1–2 years. Two other studies did not find a survival benefit [31–33]. Therefore, the European Association of Urological Surgeons does not recommend targeted drugs for postoperative RCC with high risk of relapse [34].

For patients with non-metastatic RCC and tumor thrombus, a cohort study designed by the Chinese PLA General Hospital analyzed the efficacy and safety of the postoperative administration of sorafenib or sunitinib. The results showed that no survival benefit was observed for patients with tumor thrombus or IVC tumor thrombus who were administered postoperative adjuvant sorafenib or sunitinib [19].

6. Strategies and indications of IVC venography

Sufficient preoperative imaging data is requisite for successful thrombectomy. However, several problems in the imaging diagnosis of IVC tumor thrombus still exist: Type-B ultrasound has difficulty in accurately diagnosing abnormal changes owing to numerous interferences. Magnetic resonance imaging (MRI) and computed tomography cannot effectively reflect the collateral circulation, and cannot define the degree of occlusion [35]. Therefore, more effective means are required to supplement these three routine examinations. IVC venography can observe the thrombus occlusion through the lateral position, which enables to maximize a rich data of tumor thrombus preoperatively and to make a more accurate surgical plan.

IVC venography has been widely used in the diagnosis of Budd-Chiari syndrome and other diseases [36]. There are still more applications in renal cancer with IVC tumor thrombus yet. Some studies reported that <15% of cases of patients with cancer thrombus would use IVC venography, and some researchers previously thought that the inspection might have false-positive or false-negative results. Meanwhile, there is a risk of emboli-induced pulmonary embolism or tumor embolus exfoliate diffusion. Therefore, performing IVC venography routinely is not recommended [37, 38].

However, with the improvement of radiographic technique in recent years, the safety of IVC venography has been observably improved, and this method may define the formation of collateral circulation of the vena cava and help develop a thrombectomy strategy, which has unique diagnostic advantages. Hence, conducting a new study for IVC venography is necessary. Based on our experience, we speculate that the following patients may be a candidate for IVC venography: (1) RCC with IVC tumor thrombus; (2) clearance of the tumor thrombus plane; (3) definition of the degree of occlusion; (4) existence of collateral circulation, which may affect intraoperative vascular resection; (5) detection of the variation of the communicating branches of vena cava, such as the variation communicating between IVC and vena azygos, which might interfere with the surgery.

7. Indications and strategies of intraoperative IVC interruption

With regard to dealing with the IVC intraoperatively is one of the difficulties of IVC thrombectomy. There necessity of reconstruction after IVC resection is still controversial.

Indications for vena caval interruption include invasion of the venous walls, severe adhesion of the tumor to the vascular endothelium, complete occlusion of the vena cava, and the presence of distal thrombus [21, 39, 40]. In addition, the texture of the cancer thrombus is one of the influencing factors. With regard to preoperative imaging, the IVC in line with the indications of interruption and accompanied by sufficient collateral circulation, meanwhile, without serious cardiac, hepatic, and renal insufficiencies can be completely cut off. IVC venography and intraoperative ultrasound can help determine the disjointed lumina, which enables protection of the established collateral circulation trunk. IVC interruptions include complete and partial vena caval resections with reconstruction. Based on our experience, for right tumors, the height of the tumor thrombus, which is below the secondary hepatic portal, linear cutters are used to successively cut off the proximal, distal, and left renal veins of the tumor thrombus (**Figure 1I**). With regard to right tumor thrombus above the secondary hepatic portal, or left tumor thrombus above the level of the right renal vein and combined with distal thrombus, the vena cava can be resected partially. Methods for right thrombectomy include cutting off the lumina of the IVC below the secondary hepatic portal and reconstructing the lumina of the IVC above the secondary hepatic portal. The left thrombectomy procedure is resecting the lumina of the IVC below the level of the right renal vein and reconstructing the lumina of the IVC above the level of the renal vein.

Meanwhile, IVC interruption is safe and feasible during vena caval thrombectomy [39, 40], and the establishment of collateral circulation can avoid severe hemodynamic disorders. Different strategies of interruption ought to be generated preoperatively based on the height of tumor thrombus, tumor side, degree of vena caval obstruction and invasion, and establishment of collateral circulation.

8. IVC tumor thrombus with thrombosis and treatment recommendations

Vena cava tumor thrombus with thrombosis is common. The prevalence of thrombosis gathered by the Urological Department of Chinese PLA General Hospital is 19.2%. Thrombosis, at the same time, is not found within the renal venous tumor thrombus; all thrombosis occurred in the vena cava tumor thrombus. Among them, vena caval thrombi were all located on the right, the thrombus was located in the distal end of the tumor thrombus, and the distal thrombus could reach the bifurcation of the iliac vessel. Preoperative MRI can help determine the location and length of the thrombus.

Preoperative anticoagulation therapy is recommended for patients with thrombosis, and medication should be administered from the diagnosis of tumor thrombus and thrombus. Low-molecular heparin is recommended for anticoagulation therapy, withdrawing drugs 24 h preoperatively, maintaining the international normalized ratio of 2–3, and anticoagulation therapy is continued for 48 h postoperatively and maintained for 6 months, except for the following: patients with tumor or tumor thrombus who did not undergo complete resection; those with metastasis; needs for systemic treatment; and patients with pulmonary embolism. Pre- and postoperative placement of the vena cava stent is not recommended only if the patient has pulmonary embolism and contraindications of anticoagulation therapy [41, 42]. Preoperative imaging examinations are required for patients with extensive thrombosis at the distal end of the tumor thrombus [43]. IVC interruption is recommended, which prevents embolization caused by thrombus shedding, for patients who meet the indications and possess sufficient collateral circulation.

9. Other developments and issues

Besides the previously mentioned issues, some problems need to be solved in the field of RCC with tumor thrombus. First, whether the tumor thrombus is invading the venous walls is an important issue in diagnosis and treatment process to decide on the preoperative surgical strategies. Furthermore, it may also relate to postoperative survival. However, because the diagnostic criteria of imaging and pathology are currently insufficient, further studies should be conducted.

Second, the survival of patients with RCC and venous thrombus postoperatively was significantly worse than those with localized RCC, particularly in patients with preoperative distant metastases. For IVC tumor thrombus, particularly patients with level III–IV tumor thrombus, the perioperative risk and mortality are higher. At the same time, although some patients completed the radical resection of tumor, survival after surgery is still less than 6 months. Therefore, for patients with high surgical risk or short life expectancy, the necessity for surgery deserves further discussions. The prognosis of patients with RCC and venous tumor thrombus, at present, lacks the preoperative predicting models particularly related to imaging features. The study of preoperative imaging characteristics of tumor thrombus and biological behavior of the tumor and the prognosis of patients may provide some guidance for preoperative choice of treatment.

Augmented reality (AR) is a real-time technology to calculate the location and angle of the camera images and add corresponding images. The goal of this technology is to set the virtual world in the real world and interact with it on screen [44]. Based on individual anatomy, the AR and computer system have been used in partial nephrectomy as a new technology *in vivo* and *in vitro* [45–47]. To overcome the problem of soft tissue and organ shift, Teber and colleagues reported a new navigation approach added to endoscope that was used in laparoscopic partial nephrectomy [47]. The study showed that the new AR tracking system proved to be effective, with a reasonable margin of error and a time to match each other. In addition, combining pre- or intraoperative imaging features with real-time endoscopy will simplify and increase the accuracy of laparoscopic surgery [47]. Thus, AR combined with three-dimensional vision has a great application value in robotic surgery in the future.

Finally, although RCC invades the venous system to form tumor thrombus, the tissue components between the primary tumor of the kidney and the tumor thrombus has a large difference. Meanwhile, heterogeneity exists in primary RCC and tumor thrombus, which may be the reason why primary tumor and tumor thrombus response to preoperative targeted therapy was asynchronous, and drugs among different patients respond differently. Therefore, the research of heterogeneity between primary RCC and venous tumor thrombus may find a more effective therapeutic target and drug for the reduction of tumor thrombus level, which can provide the basis for selecting appropriate patients for neoadjuvant targeted therapy preoperatively.

10. Future perspectives

Open IVCTE is still a standard surgery for RCC with IVC thrombus. With the development of laparoscopy and robotic technology in recent years, the safety and feasibility of robot-assisted laparoscopic IVC thrombectomy have been investigated at several centers. Those successful experiences mark that such surgery tends to enter the era of mini-traumatic surgery. Considering the complexity of the patient and the high complication rates, multidisciplinary cooperation and detailed preoperative assessment will play an important role in surgical decisions in future. Some new or mature techniques will also provide a basis for the surgical strategies, including artificial blood vessel, augmented reality, transesophageal echocardiography, IVC venography, and so on. From a safety perspective, IVCTE is still a challenging technology. Only a hospital with skilled laparoscopic and mature surgical team is recommended. Preoperative TMT is expected to shrink the IVC thrombus and reduce the complexity of the surgery. However, prospective investigations are required in the future.

11. Conclusions

RCC tends to invade the venous system and form venous tumor thrombus in 4–10% of patients. Surgical treatment is the standard therapy for these patients; however, postoperative complications include hemorrhage, thrombotic shedding, and other risks. Because of the huge population and relatively backward treatment concepts, the proportion and number of patients with advanced RCC in China are significantly higher than those in developed countries, such as Europe and the United States. With regard to patients with RCC and tumor thrombus, the strategies for diagnosis and treatment are mostly based on open surgery. Several clinic-related strategies are no longer suitable for current laparoscopic and robot-assisted mini-traumatic surgeries owing to the development of surgical techniques and improvement of auxiliary equipment. With regard to the tumor thrombus, a series of retrospective and prospective studies are needed to be conducted, which would enable to solve some difficulties and issues in the course of diagnosis and treatment, to improve the clinical strategies of diagnosis and treatment of patients with RCC and tumor thrombus ulteriorly, and to provide our clinical work with more powerful reference and basis.

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Conflict of interest

The authors have declared that they have no conflict of interest.

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