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ORIGINAL ARTICLE

Role of intraoperative ultrasound in robotic-assisted radical nephrectomy with inferior vena cava thrombectomy in renal cell carcinoma

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Abstract

Purpose To determine the impact of intraoperative ultrasound on robotic-assisted radical nephrectomy with inferior vena cava (IVC) tumor thrombectomy in renal cell carcinoma (RCC).

Methods We retrospectively analyzed intraoperative records of 27 patients with RCC and invasion of the IVC who underwent robotic-assisted nephrectomy with tumor thrombectomy at our center between December 2017 and July 2018. Diagnostic utility and impact of intraoperative transesophageal echocardiography (TEE), intraoperative robotic-assisted ultrasonography, and intraoperative contrast-enhanced ultrasound (CEUS) on surgical management were extracted from the surgical notes and intraoperative ultrasound reports.

Results Twenty-seven patients with thrombus had intraoperative ultrasound. Complete tumor removal was achieved in 22 patients, IVC transection in 5 patients, and no residual tumor was observed in all patients. Intraoperative TEE changed the robotic surgical strategy in three patients by monitoring thrombus-level regression. Downstaging of the thrombus level occurred in three patients: Levels IV to III in one and Levels III to II in two. Intraoperative robotic-assisted ultrasonography has facilitated safe VC clamp placement and identification and protection of collateral vessels during IVC transection in five patients. Intraoperative CEUS helped to differentiate the boundary between tumor thrombus (enhancement and small vessel pulsation) and bland thrombus (hypoechoic or no enhancement) in eight (29.6%) patients with bland thrombus.

Conclusions Intraoperative ultrasound is a safe, minimally invasive technique that can provide accurate real-time information regarding the presence and extent of IVC involvement and guidance for placement of a vena cava clamp, confirming the character of the thrombus to plan an optimal surgical approach.

Keywords Ultrasound · Robotics · Thrombectomy · Renal cell carcinoma · Inferior vena cava

Abbreviations

RCC	Renal cell carcinoma
IVC	Inferior vena cava
CEUS	Contrast-enhanced ultrasound
TT	Tumor thrombus
BT	Bland thrombus
RA	Right atrium
RHV	Right hepatic vein
MHV	Middle hepatic vein
LHV	Left hepatic vein

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Introduction

Renal cell carcinoma (RCC) has a tendency to extend from the kidney to its route of venous drainage, with 4%–10% of these extending into the inferior vena cava (IVC) [1]. With the development of laparoscopy and robotic technology in recent years, several centers have reported successful laparoscopic radical nephrectomy with IVC thrombectomy [2–6]. Our hospital took the lead in robot-assisted tumor thrombectomy in China and has proved the safety and effectiveness of this technique [7–9]. It is important to precisely identify the cranial extent of a thrombus prior to surgery i to plan the best surgical approach [10]. The most commonly used imaging investigations include magnetic resonance imaging (MRI), multidetector helical computerized tomography, and transabdominal ultrasound scanning. Each of these techniques has its own advantages [11–13]; however, these imaging scans are performed before surgery and the patients are in a state of high blood coagulation. In some cases, the tumor thrombus may progress or new bland thrombus may form after imaging and before surgery [14]. The greatest drawback of traditional laparoscopic and robotic-assisted surgery is the lack of tactile feedback compared to open surgery. Intraoperative real-time ultrasound can compensate for this weakness through precise positioning and real-time imaging of the target tissue. Intraoperative ultrasound is a multimodal medical technique that allows visualization of tissues beyond the two-dimensional laparoscopic image, enhancing the amount and quality of information available to the surgeon [15]. However, data to show its utility and impact on surgical decision-making are lacking. In the present study, we undertook a retrospective review of patients with RCC and IVC invasion to determine the utility and impact of intraoperative ultrasound on the robot-assisted radical nephrectomy with IVC thrombectomy.

Materials and methods

Study participants

After receiving Institutional Review Board approval, we retrospectively analyzed data from 27 patients with RCC and Levels I–IV IVC invasion who underwent robotic-assisted radical nephrectomy with IVC thrombectomy between December 2017 and July 2018 (Table 1). Exclusion criteria for this study included: (1) patients with more than one metastatic site; (2) patients with poor heart and lung function, who could not tolerate surgery; and (3) patients who did not want to risk the surgery, or refused surgery. For each patient, hospital records and all of the preoperative radiographic studies were reviewed. All patients were preoperatively evaluated with routine blood analysis, chest X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and contrast venacavography; all of these examinations were performed within 7 days prior to the operation. We reviewed all cases to identify the level of tumor thrombus based on the classification system originally described by Blute et al. [1]. Patients were then divided into four levels (I–IV) based on the cranial extent of the thrombus. All procedures were performed by two surgeons (Xu Zhang and Xin Ma) with advanced robot-assisted laparoscopic skills.

Table 1 Descriptive clinicopathologic characteristics of 27 patients with clear-cell renal cell carcinoma and inferior vena cava tumor thrombus

Characteristics	Results
Patients, *n*	27
Median age, year (interquartile range)	59.5 (47.8–65.0)
Male/female (*n*)	17/10
Mean body mass index, kg/m^2 (range)	24.9 (17.9–30.8)
Affected kidney (*n*)	
Left	9
Right	18
Mean tumor size, cm (range)	7.9 (3.0–15.5)
Clinical stage (*n*)	
T3bN0M0	19
T3bN0M1	4
T3cN0M0	2
T3cN0M1	2
IVC thrombus classification (*n*)	
Level I	7
Level II	14
Level III	3
Level IV	3
Mean IVC thrombus length cm (range)	7.8 (4.6–13.4)
Presence of bland thrombus (*n*)	8
Cephalic bland thrombus (*n*)	3
Caudal bland thrombus (*n*)	5
Surgical strategy during IVC thrombectomy	
Incision of the IVC for thrombectomy (*n*)	22
IVC Segmental transection (*n*)	5

Intraoperative transesophageal echocardiography (TEE)

Intraoperative TEE was performed in 20 patients with Level II–IV thrombus. Patients with tumor involvement of the renal vein only or within the IVC but ≤ 2 cm from the renal vein ostium were not investigated. Under general anesthesia, a multiplane TEE probe was placed in the esophagus to observe the location and movement of the tumor thrombus during surgery. After excision of the thrombus, the repaired VC was assessed by TEE for residual thrombus. No complication was caused by TEE. Information obtained by TEE examination was reviewed, and diagnostic utility and impact on surgical management were extracted from the surgical notes and TEE report. The diagnostic utility of intraoperative TEE was defined by its capacity to: (1) supplement preoperative radiological findings; (2) monitor and diagnose pulmonary embolism or emboli; (3) confirm complete tumor removal; and (4) identify residual tumor. This information impacts: (1)

decisions to initiate cardiopulmonary bypass (CPB); (2) decisions to avoid CPB; (3) decisions to avoid controlling the suprahepatic IVC and mobilization of both lobes of the liver; and (4) guiding IVC clamp placement.

Intraoperative robotic-assisted ultrasonography (IOU)

Twenty-seven patients with IVC thrombus underwent IOU. An ultrasound doctor who was a board-certified radiologist was present in each case to perform ultrasound and help provide interpretation of the scan. There were no physicians involved in the ultrasound procedure. A ProART robotic transducer 8826 (BK Medical) was used for intraoperative ultrasonography. The TilePro was selected to observe the images on the robotic console, which allowed simultaneous vision of both the operative field and ultrasound images. After entry into the peritoneal cavity, sterile saline warmed to body temperature was poured into the operative field to create an acoustic interface between the ultrasound probe and whatever organ structure had to be examined. A diagnostic ultrasound unit with 10-MHz linear array transducer was placed in a sterile plastic sheath filled with sterile gel. Generally, the transducer was handled by the surgeon under the guidance of an ultrasonographer. The results obtained with IOU were then compared to the real extension of the thrombus after incision of the wall of the VC and before removal of the tumor thrombus. The diagnostic utility of IOU was defined by its capacity to: (1) supplement preoperative radiological findings; (2) monitor and diagnose bland thrombus; (3) confirm complete tumor removal; (4) identify residual tumor; and (5) identify collateral circulation. This information impacts: (1) guiding IVC clamp placement, and (2) decisions to protect the collateral circulation.

Intraoperative contrast-enhanced ultrasound (CEUS)

Twenty-seven patients with IVC thrombus underwent intraoperative CEUS. CEUS is an advanced technique that utilizes ultrasound contrast agents to improve thrombus visualization. Microbubbles vibrate under the pressure changes induced by the probe transmitter. This oscillation produces energy that is detected by the transducer and converted into an image [16, 17]. As an effective diagnostic modality, this method leads to better, enhanced scanning of the microvasculature of the thrombus. The ultrasound contrast agent acts as a blood pool tracer and there is enhancement of echogenicity with areas of high blood flow, as seen with RCC lesions [18]. The contrast microbubble agent used in the CEUS procedure is nonallergenic and does not interfere with renal function, as it is not excreted by the kidneys. In this study, we used the contrast agent SonoVue (Bracco, Milan, Italy); a second-generation ultrasound contrast agent composed of sulfur hexafluoride gas and phospholipid monolayer shell. Before the examination, a 5-mL dose of SonoVue was bolus injected via a forearm vein through a 20-gauge cannula, followed by 5-mL normal saline flush using a three-way stopcock to ensure that no residual contrast agent remained in the intravenous catheter. The injection of contrast material into a peripheral vein allowed detection of thrombus microcirculation.

Evaluation of the CEUS finding was conducted as follows. Tumor thrombus: enhancement and small vessel pulsation of the thrombus, witnessed in real time. Bland thrombus: hypoechoic thrombus with no enhancement. The diagnostic utility of intraoperative CEUS was defined by its capacity to monitor and diagnose bland thrombus. This information impacts: (1) guiding IVC clamp placement in cases with cephalic bland thrombus; and (2) guiding IVC ligate placement in cases with caudal bland thrombus. If the presence of bland thrombus was confirmed by CEUS, cephalic bland thrombus and short caudal bland thrombus were treated as tumor thrombus. For patients with long caudal bland thrombus associated with tumor thrombus, in which the thrombus filled the IVC lumen and where there was excellent collateral circulation, we simply ligated the IVC above and below the thrombus using an Endo GIA stapler.

Results

Clinicopathological characteristics and surgical robotic techniques

We enrolled 27 patients with histologically confirmed RCC with thrombus, and the clinicopathological characteristics are described in Table 1. These tumors were classified according to the thrombus cephalad extension into the venous system [1], and the thrombus Level was I in seven patients (25.9%), II in 14 patients (51.9%), III in three patients (11.1%), and IV in three patients (11.1%). Robotic technology was utilized for all of the 27 patients with IVC thrombectomy.

We adopted the robotic techniques that depend on the level of venous thrombus, which were earlier described and summarized by our department [7–9]. For the thrombus inferior to the first porta hepatis (Level I and part of Level II), we ligated some short hepatic veins; for a thrombus between the first porta hepatis and second porta hepatis (Level II), we mobilized the right lobe of the liver from the IVC by ligating additional short hepatic veins; for a thrombus near or above the second porta hepatis but below the diaphragm (Level III), we mobilized both the right and left lobes of the liver to obtain high proximal control of the suprahepatic and infradiaphragmatic IVC, and simultaneously clamped the first porta hepatis. For a thrombus above the diaphragm and in the right atrium (Level IV), we established cardiopulmonary bypass (CPB), and thoracoscopy-assisted thrombectomy was performed for the intra-atrial part of the thrombus under CPB; the infradiaphragmatic part was completed in a manner similar to that for Level III. All nine patients with left-sided tumors and seven of 18 patients with right-sided tumors received preoperative artery embolization on the day of surgery that aimed to reduce intraoperative blood loss and technical difficulty. In five cases in which the thrombus filled the VC lumen and where there was excellent collateral circulation, we simply ligated the IVC above and below the thrombus-bearing IVC and renal vein using an Endo GIA stapler (Medtronic, Minneapolis, MN, USA) with a 45-mm vascular load. There were six patients with preoperative therapy with tyrosine kinase inhibitors.

For right RCC of Levels I and II, patients were placed in a modified left lateral decubitus position with a 70° bump; in this position, IVC thrombectomy and radical nephrectomy could both be completed. For left RCC of Levels I and II, the position for IVC thrombectomy was the same as for right RCC. The placement of patients was converted to a modified right lateral decubitus position, and left radical nephrectomy was performed. For RCC of Levels III and IV, at first, the patient was placed in a 30°–45° dorsal elevated lithotomy position for liver mobilization.

In the presented cases, the involved kidney and tumor thrombus were removed by robot-assisted approach without significant operative morbidity or mortality, and without any massive pulmonary embolic episode due to migration of the thrombus. The median operation duration was 165 min (range 58–720 min), and the median estimated blood loss was 500 mL (range 20–15,000 mL). The intraoperative blood transfusion increased from Levels I to IV. However, the duration of hospitalization (range 4–29 days) showed no significant difference according to different level of thrombus. During a median follow-up of 12 months (range 10–20 months), there was no tumor embolus infringement of the IVC wall, positive lymph nodes, or distant metastasis.

Intraoperative TEE changes in robotic surgical strategy by monitoring thrombus-level regression

Of the 27 patients, 20 (except for Level I patients) underwent intraoperative TEE. Downstaging of the thrombus level occurred in three patients: Level IV to III in one (Fig. 1) and Level III to II in two (Fig. 2). The thrombus levels in the other patients remained stable; none of the 20 patients experienced upstaging. The surgical strategy was re-evaluated in three patients who underwent robot-assisted laparoscopic radical nephrectomy with IVC thrombectomy. For one patient (downstaged from Level IV to III), a thoracoscope-assisted open atriotomy and CPB were avoided owing to intraoperative TEE. Two patients (downstaged from Level III to II) avoided height-proximal control of the suprahepatic IVC and mobilization of both lobes of the liver during robotic surgery; thus reducing surgical risk. Three patients

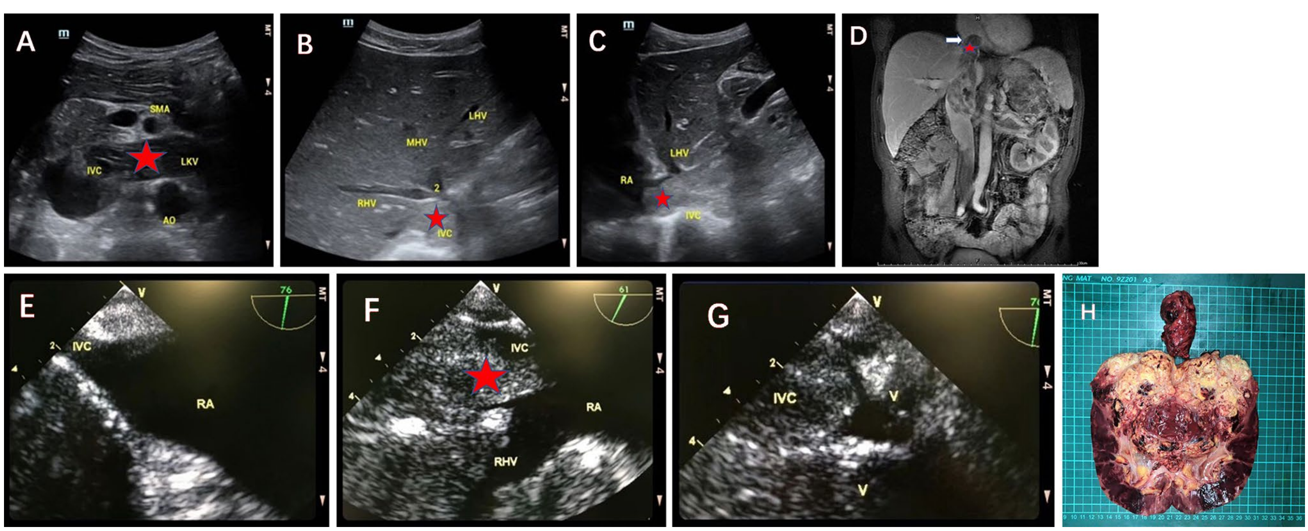

Fig. 1 Preoperative images of thrombus Level IV (**a**–**d**): ultrasound image of tumor thrombus (asterisk) in LKV (**a**); ultrasound image of tumor thrombus (asterisk) in IVC at the level of second porta hepatis (**b**); ultrasound image of tumor thrombus (asterisk) in RA (**c**); magnetic resonance imaging of tumor thrombus (asterisk) (**d**). Intraoperative transesophageal echocardiography images of thrombus Level III (**e**–**g**): no tumor thrombus in RA was observed (**e**); the superior extent of the tumor thrombus above the hepatic vein but below the diaphragm (**f**); cross-clamp (v) application cranial to the level of the tumor thrombus (asterisk) (**g**); nephrectomy specimen with tumor thrombus (**h**). *LKV* Left renal vein, *AO* aorta, *SMA* superior mesenteric artery, *IVC* inferior vena cava, 2 second porta hepatis, *RA* right atrium; *RHV* right hepatic vein, *MHV* middle hepatic vein, *LHV* left hepatic vein, *V* cross-clamp location

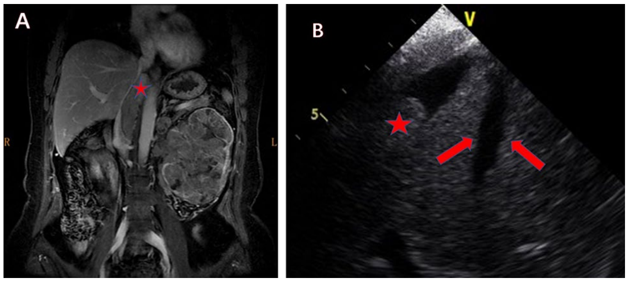

Fig. 2 Tumor thrombus above the hepatic vein in an infradiaphragmatic location as shown on preoperative magnetic resonance imaging (Level III) (**a**); two-dimensional transesophageal echocardiogram long-axis view of the intrahepatic inferior vena cava demonstrating a tumor thrombus (asterisk) caudad to the ostium of the hepatic vein (arrow) (Level II) (**b**)

with Level IV underwent CPB after TEE aided in the monitoring of intraoperative pulmonary embolism. Three patients with Level III had the IVC clamp placed with TEE guidance so as to avoid residual tumor thrombus. TEE showed complete resection in three patients with Level IV and CPB was not restarted for complete removal. All probes were placed according to plan at the onset of the case.

Intraoperative robotic-assisted ultrasonography is essential for identification of collateral vessels during IVC transection

Intraoperative laparoscopic ultrasound probes were used in all 27 patients to identify and demarcate the extent of the IVC thrombus. The longitudinal view of the IVC demonstrated the cranial site of the thrombus, which was necessary to evaluate the distance between the thrombus and the site of the temporary IVC clamp for thrombectomy. The VC was dissected to allow a 1–2-cm margin distal to the thrombus to ensure complete removal of the thrombus. Five patients (18.5%) in whom the thrombus filled the VC lumen, and with excellent collateral circulation, underwent IVC resection during robot-assisted laparoscopic radical nephrectomy. Flexible intraoperative ultrasonography identified the extent of the thrombus before stapling the IVC, and protected the established collateral circulation as much as possible. In the event of IVC interruption (Fig. 3), collateral venous flow was maintained by minimizing ligation of the venous tributaries.

Intraoperative CEUS helped to differentiate the boundary between tumor and bland thrombi

Technical success for intraoperative CEUS was achieved in all 27 patients. No adverse events occurred during administration of the contrast agent. Early enhancement of a mass within the IVC lumen on CEUS was an indicator of tumor thrombus, and bland thrombus showed no intraluminal flow

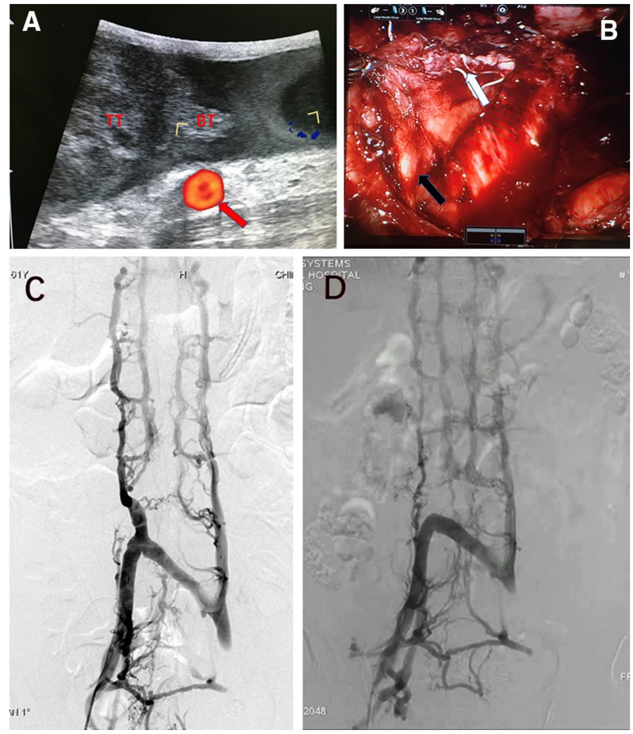

Fig. 3 Intraoperative laparoscopic ultrasound showing TT, BT, and collateral circulation vessel (**a**); robotic view of the IVC with transection (white arrow) above the bland and tumor thrombus-bearing IVC and the collateral circulation vessel was retained (black arrow) (**b**); preoperative inferior cavography (**c**); and postoperative inferior cavography (**d**). *IVC* inferior vena cava, *TT* tumor thrombus, *BT* bland thrombus

on CEUS (Fig. 4). There were eight (29.6%) patients with bland thrombus, including three Level II, two Level III, and three Level IV. There were three cases with cephalic bland thrombus and five with caudal bland thrombus. Three caudal bland thrombi extended to the iliac vein and underwent surgical IVC segmental transection during IVC thrombectomy. The intraoperative CEUS guided IVC clamp placement in five cases with bland thrombus to ensure the site of the clamp, and guided IVC ligate placement of three cases with caudal bland thrombus to ensure the Endo GIA stapler was below the caudal tumor thrombus.

Discussion

The emergence of intraoperative ultrasonography has helped to resolve the problem of laparoscopy not being able to touch organs directly, thus lacking any tactile feedback that can assist in the detection of tumor boundaries, as well as the extent of tumor thrombi [15, 19]. Intraoperative ultrasonography has become an important tool that has improved the rates of successful surgery, and has been applied to early and

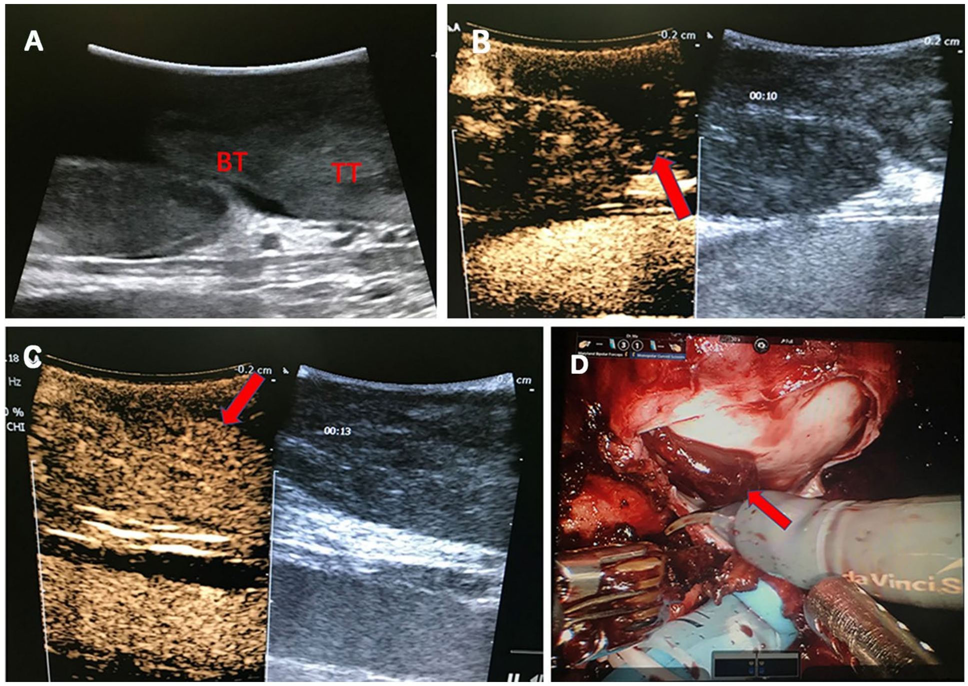

Fig. 4 Intraoperative laparoscopic ultrasound showing TT and BT (**a**); Intraoperative laparoscopic CEUS showing nonenhancement of the BT (arrow), in situ mapping of blood flow using B mode ultrasound image of the thrombus (right) with CEUS mode (left) (**b**); and enhancement of the TT (arrow), in situ mapping of blood flow using B mode ultrasound image of the thrombus (right) with CEUS mode (left) (**c**); robotic view of the BT (arrow) (**d**). *IVC* inferior vena cava, *TT* tumor thrombus, *BT* bland thrombus, *CEUS* contrast-enhanced ultrasonography

locally advanced RCC, monitoring ablation therapy, testing renal blood perfusion, and exposing renal pedicles [20–24]. Sonographic techniques used intraoperatively include TEE, robotic-assisted ultrasonography, and CEUS.

Surgery was performed for metastatic disease in six patients in our study. Some retrospective studies have confirmed that cytoreductive nephrectomy is associated with significantly improved overall survival in de novo metastatic RCC. The incremental survival benefit associated with cytoreductive nephrectomy was seen irrespective of neutrophil–lymphocyte ratio [25]. Treatment with molecular-targeted agents following cytoreductive nephrectomy may improve survival of patients with metastatic RCC compared with immunotherapy alone, and it may be important to use aggressive systemic treatment for patients with increased preoperative C-reactive protein [26]. According to the 2018 European Association of Urology guidelines, cytoreductive nephrectomy has been an option in low-risk patients with metastatic clear-cell renal cancer who present with the tumor in place [27].

Intraoperative TEE provides real-time accurate delineation of thrombus and, thus, has the potential to alter surgical decision-making and management. This benefit has been previously described in smaller case series and case reports [28, 29], but a review in robotic-assisted radical nephrectomy with IVC thrombectomy for RCC has been lacking. In the present study, the use of TEE changed robotic-assisted surgical management in three patients. CPB was avoided in one patient who had preoperative documentation of Level IV thrombus. The ability to avoid CPB is important because it prevents exposure of the patient to the inherent physiological and mechanical risks of CPB. Two patients (downstaged from Level III to II) avoided height-proximal control of the suprahepatic IVC and mobilization of both lobes of the liver during robotic surgery, thus reducing surgical risk. We focused on the possible causes of intraoperative degradation: (1) preoperative renal artery embolism, decreased blood supply and volume of thrombus; (2) change from supine to lateral position increased the distance between the renal vein and atrium; (3) pneumoperitoneal pressure elevated the diaphragm and increased the length of the subphrenic IVC; (4) squeezed atrium, increased pressure in the right atrium, blocked venous reflux, increased pressure in the IVC and increased volume; (5) influence of anesthesia on circulation, decrease in returned blood volume, and decrease in the pushing force of the thrombus; and (6) the thrombus did not invade the IVC wall, and the above factors may lead to relative displacement of the thrombus. As illustrated by our recent study, since the information obtained from intraoperative TEE frequently influenced the surgical decision-making, particularly in patients with intracardiac tumor extension, we recommend that intraoperative TEE should be considered in all patients with Level II–IV tumor thrombi.

Intraoperative ultrasound probes are recommended in patients undergoing robotic-assisted radical nephrectomy with IVC thrombectomy. The robotic ultrasound probe angle can be adjusted with the robotic instrument [30]. The robotic ultrasound probe also eliminates the issue of instrument clashing in the operating field [28]. RCC tumor progression may be rapid, and from the time of initial imaging to the time of surgery, the tumor extent can change significantly [31]. Intraoperative ultrasound not only provides the tumor extent on the day of surgery but also enables simultaneous re-evaluation of tumor mobility or immobility. In cases in which the thrombus fills the VC lumen and when there is excellent collateral circulation, the surgeon simply ligates the IVC above and below the thrombus-bearing IVC and renal vein using an Endo GIA stapler. As soon as adequate hemostasis is achieved, the thrombus is transected at the level of the renal vein, which we reported in 2018 [8, 9]. In the present study, five cases were in this situation, and flexible intraoperative ultrasonography identified the thrombus extent before stapling the IVC, and protected the established collateral circulation as much as possible. The venous drainage of the remaining kidney was restored, which was confirmed by pre- and postoperative IVC cavography.

Embolization of bland and tumor thrombi to the pulmonary circulation is potentially a fatal complication in patients undergoing radical nephrectomy with IVC thrombectomy for the surgical management of RCC [32]. Pulmonary embolism is a rare complication, but it has been described [33] and mortality is high. Tumor thrombus behaves differently from bland thrombus because it contains organized tumor cells and is more stable. Bland thrombus and extension into the VC may increase the likelihood of thrombus embolization. According to a new report, the presence of bland thrombus is associated with adverse survival outcomes in patients treated surgically for renal tumors with venous tumor thrombi [34]. Therefore, it is essential to judge the coexistence of bland thrombus; however, the echogenicity between these thrombi is poorly discriminated. The superior performance of CEUS in the present study is a result of its ability to detect and demonstrate tiny vessels in tumor thrombi and no enhancement in bland thrombi. In contrast to CT and MRI contrast agents, microbubbles used in CEUS remain in the intravascular space, thus displaying thrombus vascularization rather than extravascular diffusion of the contrast agent. The greatest advantage of CEUS is that it allows for real-time observation. This is a limitation of CT and MRI; enhancement of tumor thrombus can be missed when phase scans are not optimally timed or when patient respiration is poorly controlled. To our knowledge, we present the first report to evaluate the utility and impact of intraoperative CEUS on robotic-assisted surgical management on this unique patient population.

Conclusions

Intraoperative TEE, robotic-assisted ultrasound, and CEUS are useful tools that can accurately assess the precise extent and characteristics of thrombi to plan an optimal surgical approach. Real-time monitoring of IVC thrombus and the cardiopulmonary system during robotic-assisted radical nephrectomy with IVC thrombectomy for RCC is an area in need of further investigation. Larger randomized studies are required to determine the true benefits of intraoperative ultrasound monitoring in this patient population.

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Authors' Contributions LQY and LYK conceived of the present study. TJ and ZX supervised the project. LN and YHK acquired, analyzed and interpreted the patient data regarding ultrasound imaging and surgical findings. LQY was a major contributor in writing the manuscript. MX gave technical support and conceptual advice. All author read and revised the manuscript critically, approving the final manuscript.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Informed consent Written informed consent was obtained from the patients for publication of this study and any accompanying images.

Ethical approval This retrospective study was approved by the Institutional Review Board of the Chinese PLA General Hospital (No. S2017-100-01).

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