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REVIEW ARTICLE

Important surgical considerations in the management of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus

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Accepted for publication 8 February 2012

What's known on the subject? and What does the study add?
Historically, the surgical management of renal tumours with intravascular tumour thrombus has been associated with high morbidity and mortality. In addition, few cases are treated, and typically at tertiary care referral centres, hence little is known and published about the ideal surgical management of such complex cases.

The present comprehensive review details how a multidisciplinary surgical approach to renal tumours with intravascular tumour thrombus can optimise patient outcomes. Similarly, we have developed a treatment algorithm in this review that can be used in the surgical planning of such cases.

OBJECTIVES

- To detail the perioperative and technical considerations essential to the surgical management of renal cell carcinoma (RCC) with inferior vena cava (IVC) tumour thrombus, as historically patients with RCC and IVC tumour thrombus have had an adverse clinical outcome.
- Recent surgical and perioperative advances have for the most part optimized the clinical outcome of such patients.

MATERIALS AND METHODS

- A comprehensive review of the scientific literature was conducted using MEDLINE from 1990 to present using as the keywords 'renal cell carcinoma' and 'IVC tumor thrombus'.
- In all, 62 manuscripts were reviewed, 58 of which were in English. Of these, 25 peer-reviewed articles were deemed of scientific merit and were assessed in detail as part of this comprehensive review.
- These articles consist of medium to large (≥25 patients) peer-reviewed studies containing contemporary data pertaining to the surgical management of RCC and IVC tumour thrombus.
- Many of these studies highlight important surgical techniques and considerations in the management of such patients and report on their respective clinical outcomes.

RESULTS

- Careful preoperative planning is essential to optimising the outcomes within this patient cohort. High quality and detailed preoperative imaging studies help delineate the proximal extension of the IVC tumour thrombus and possible caval wall direct invasion while determining the potential necessity for intraoperative vascular bypass.
- The surgical management of RCC and IVC tumour thrombus (particularly for level III or IV) often requires the commitment of a multidisciplinary surgical team to optimise patient surgical outcomes.
- Despite significant improvements in surgical techniques and perioperative care, the 5-year overall survival remains only between 32% and 69%, highlighting the adverse prognosis of such locally advanced tumours.
- Important prognostic factors within this patient cohort include pathological stage, nuclear grade, tumour histology, lymph node and distant metastatic status, preoperative performance status, Charlson comorbidity index, and nutritional status.

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CONCLUSIONS

- The multidisciplinary surgical care of RCC and IVC tumour thrombus (particularly high level thrombi) is pivotal to optimising the surgical outcome of such patients.
- Similarly, important preoperative, perioperative, and postoperative considerations can improve the surgical outcome of patients.

KEYWORDS renal cell carcinoma (RCC), inferior vena cava (IVC), tumour thrombus, surgery

INTRODUCTION

In 2011, there will be an estimated 56 000 new cases and 12 000 deaths from RCC [1,2]. RCC with inferior vena cava (IVC) tumour thrombus extension occurs in 4–10% of cases [3–5]. Reported mortality rates for radical nephrectomy with concomitant IVC thrombectomy range between 5% and 12.5% for higher level thrombus depending on patient comorbidities and tumour characteristics [3,6–11]. Selection for nephrectomy and IVC thrombectomy with or without caval reconstruction should be limited to patients with an anticipated good performance status, as this patient cohort has a significantly shorter cancer-specific survival than do patients with RCC without IVC involvement [3,12,13].

In a report from the Mayo Clinic, 659 patients were reviewed from 1970–2000 [12]. Complications occurred in 15% of nephrectomies undergoing concomitant IVC thrombectomy. This study reported an increased rate of both major and minor complications proportional to the level of the tumour thrombus. For IVC tumour thrombus levels I to IV, adverse event rates were noted as 18%, 20%, 26% and 47%, respectively. Among the most frequent complications were haemorrhage (3.0%), pulmonary embolism (2.7%), wound infection (2.6%), acute renal failure (1.8%), ileus (5.3%), and the need for additional surgery (3.6%). These technical challenges of surgical resection therefore lend themselves to a multidisciplinary approach to optimise surgical outcomes.

Preoperative management of RCC with IVC thrombus requires high-quality imaging for determining the additional tumour thrombus extension. This step is crucial, as the surgical approach is tailored to offer the best exposure based on thrombus level [14–16]. There are several different imaging methods that can be used, with MRI being the current standard [15]. Surgically, there are multiple approaches that offer adequate exposure. However, there is evidence that a chevron incision combined with sternotomy provide the best exposure, particularly for higher level IVC tumour thrombus [17,18]. During the operation, there are several surgical techniques that may improve exposure including complete IVC mobilisation with lumbar and hepatic veins control and isolation of major venous tributaries (i.e. contralateral renal vein as well as supra- and infra-renal IVC) [19–23]. IVC reconstruction is indicated if >50% of the caval wall is resected, although in some cases there are ample collaterals that would obviate the need for major vascular reconstruction [22,24,25]. Radical nephrectomy with IVC thrombectomy is a detailed and potentially complicated procedure with significant risk of morbidity and mortality requiring the need for good communication between urology, anaesthesiology, and other ancillary surgical disciplines if required [11,26,27]. The aim of the present manuscript is to provide a comprehensive review of the important perioperative and technical considerations in the surgical management of RCC with IVC thrombus.

> ‘technical challenges of surgical resection lend themselves to a multidisciplinary approach to optimise surgical outcomes’

STAGING

As shown in Table 1 pertaining to the 2010 American Joint Committee on Cancer (AJCC) clinical staging system for RCC, an RCC tumour of >7 cm and no >10 cm in diameter confined within Gerota's fascia is staged as a clinical stage T2a tumour. A tumour of >10 cm is staged as T2b. A tumour extending into the renal vein or its segmental branches is staged as T3a. A tumour extending into the IVC, below the level of the diaphragm, is staged as T3b. A supradiaphragmatic tumour or tumour with vena cava wall invasion is staged as T3c. A tumour extending beyond Gerota's fascia including into the ipsilateral adrenal gland is staged as T4 [28].

TABLE 1 2010 AJCC TNM clinical staging system for renal cell carcinoma

Tumor status.
- **TX:** The primary tumor cannot be evaluated.
- **T0:** There is no evidence of a primary tumor in the kidney(s).
- **T1:** The tumor is found only in the kidney and is 7 centimeters (cm) or smaller in size at its largest area. There has been much discussion among doctors whether this classification should only include a tumor 5 cm and under.
  - **T1a:** The tumor is found only in the kidney and is 4 cm or smaller in size at its largest area.
  - **T1b:** The tumor is found only in the kidney and is between 4 cm and 7 cm at its largest area.
- **T2:** The tumor is found only in the kidney and is larger than 7 cm in size at its largest area.
  - **T2a:** The tumor is only in the kidney and is more than 7 cm but 10 cm or less at its largest area.
  - **T2b:** The tumor is only in the kidney and is more than 10 cm at its largest area.
- **T3:** The tumor has grown into major veins or perinephric tissue (connective, fatty tissue around the kidneys). It has not grown into the adrenal gland (gland on top of each kidney that produces hormones and adrenaline to help control heart rate, blood pressure, and other body functions) on the same side of the body as the tumor, and it has not spread beyond Gerota's fascia (an envelope of tissue that surrounds the kidney).
  - **T3a:** The tumor has spread to the large vein leading out of the kidney, called the renal vein, or the muscles of the vein, or it has spread to the fat surrounding the kidney and/or the fat inside the kidney. The tumor has not grown beyond Gerota's fascia.
  - **T3b:** The tumor has grown into the large vein leading out of the heart, called the vena cava, below the muscle known as the diaphragm under the lungs that helps breathing.
  - **T3c:** The tumor has spread to the vena cava above the diaphragm or the walls of the vena cava.
- **T4:** The tumor has spread to areas beyond Gerota's fascia and extends into the adrenal gland on the same side of the body as the tumor.

Nodal status. The 'N' in the TNM staging system stands for lymph nodes. Lymph nodes near the kidneys are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes.
- **NX:** The regional lymph nodes cannot be evaluated.
- **N0:** The cancer has not spread to the regional lymph nodes.
- **N1:** The cancer has spread to regional lymph nodes.

Distant metastasis. The 'M' in the TNM system indicates whether the cancer has spread to other parts of the body. Common areas where kidney cancer may spread include the bones, liver, lungs, brain, and distant lymph nodes.
- **M0:** The disease has not metastasized.
- **M1:** The cancer has spread to other parts of the body beyond the kidney area.

Assessing the cephalad extension of a tumour thrombus is important in determining the preferred surgical approach. Therefore, accurate clinical staging is critical in this respect. Various surgical staging systems have been proposed including the Neves system, Novick system, and the Hinman system. A tumour thrombus found in the renal vein extending <2 cm within the IVC is staged as a level I thrombus in the Neves and Novick systems. Infrahepatic thrombus is staged as a level II thrombus.

An intrahepatic IVC thrombus below the diaphragm is staged as level III and an IVC tumour thrombus extending above the diaphragm is staged as level IV [29,30] as shown in Fig. 1. The Hinman staging system includes three respective levels of IVC tumour thrombus. Infrahepatic thrombus is staged as a level I. Thrombus above the hepatic veins but below the diaphragm is staged as a level II. Thrombus at or above the level of the diaphragm is staged as level III [31]. The Novick staging system will be

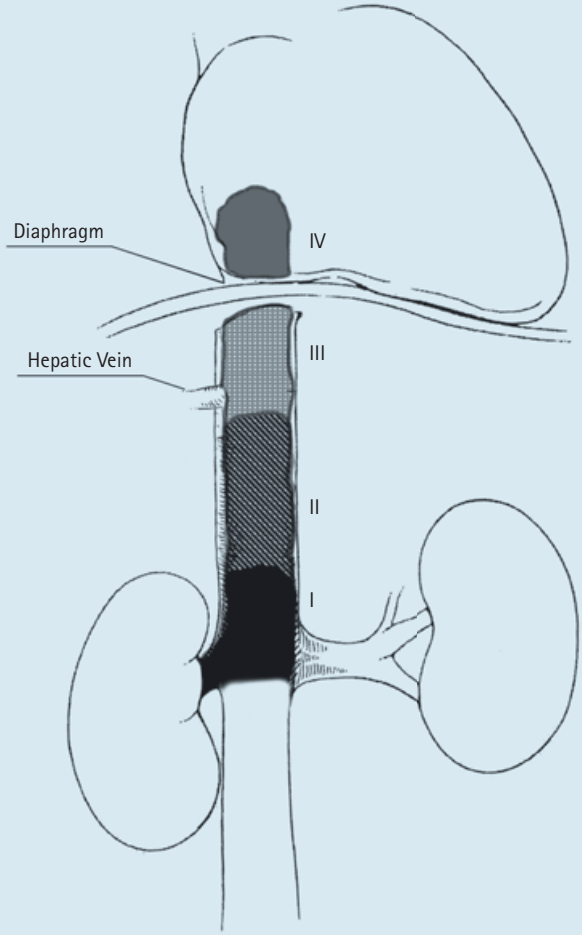


FIG. 1.
Classification of IVC tumour thrombus levels according to the Novick staging system.

used in this review when describing the level of IVC tumour thrombus.

IMAGING

Imaging is a crucial step in the management of RCC with IVC thrombus by evaluating the proximal extent, volume of tumour thrombus, and potential of caval wall invasion thus providing the information necessary to determine the best surgical approach for a given patient. This is readily apparent particularly for larger tumours and higher levels of IVC tumour thrombus. Several studies have shown that a larger IVC diameter seen on MRI or CT is associated with wall invasion [32,33]. Likewise, a clear preoperative understanding of the tumour and burden of tumour thrombus may direct the need for a multidisciplinary surgical approach. Historically, vena cavography was used for the detection and evaluation of a tumour thrombus within the IVC [15]. However, this procedure was limited by its invasive nature and risks of complications imposed upon patients.

Ultrasonography (US) is another imaging method commonly used to evaluate patients with RCC [15]. Although non-invasive, this method is largely dependent on the ultrasonographer and the position of the thrombus [15]. It has been shown that the use of US in detecting tumour thrombus below the level of the insertion of the hepatic vein has a sensitivity of 68% [15,16]. In addition, prior studies would suggest that in >40% of cases, the IVC is not fully visualised by US [16].

While both CT and MRI can be used to evaluate the retroperitoneum, currently MRI is the 'gold standard' [15]. MRI has proven to be the most effective in detecting IVC tumour thrombus, with a sensitivity level of 100% [15]. MRI has thus replaced vena cavography as the imaging method of choice for elucidating the presence of IVC tumour thrombus. The advantage of MRI is that it offers multiplanar anatomical views with detailed images clearly showing the relationship of the thrombus to the liver, heart, and other vital structures, while delivering no radiation to the patient [14,16,34]. Transoesophageal echocardiography (TOE) can also provide accurate information about the presence and extent of the IVC thrombus [35]. Nevertheless, TOE is an invasive procedure but does not provide any diagnostic advantage over MRI. However, the use of TOE has been studied as a safe and accurate technique used to monitor thrombus position in 'real-time' throughout an operation [36].

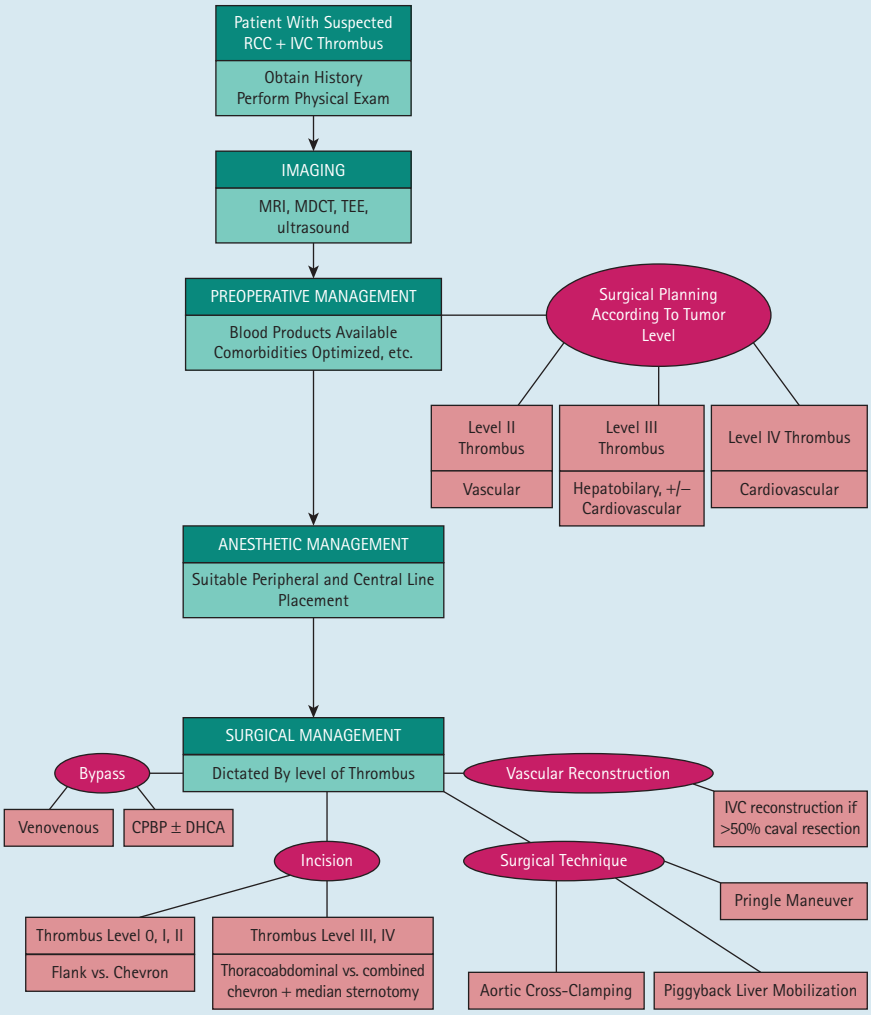
Conventional CT has been somewhat ineffective as a primary imaging tool, as it is associated with a diagnostic accuracy of 65% in determining the extent of tumour thrombus within the IVC [34]. However, with the advent of the multidetector CT (MDCT), it may soon replace MRI as the imaging method of choice. Recent studies have shown that MDCT has a sensitivity of 93% and a specificity of 80% in delineating the extent of tumour thrombus [15,36,37]. Another recent study by Nazim *et al.* [38] concluded that MDCT has 97% specificity for detecting tumour thrombus in the renal vein and IVC.

When comparing MRI and MDCT, Boorjian *et al.* [39,40] reported that the timing of imaging may be more important than the diagnostic method itself. Woodruff *et al.* [4] recommend imaging ≤14 days before resection for ideal surgical planning and recommend that the longest interval from CT and/or MRI imaging of the renal tumour and IVC thrombus until the day of surgery should be no longer than 30 days.

'Imaging is a crucial step in the management of RCC with IVC thrombus'

If the surgery warrants the use of cardiopulmonary bypass (CPBP) in cases of a higher level thrombus (III or IV), a cardiology consult should be requested preoperatively, in order to perform coronary angiography.

FIG. 2. Flow diagram showing appropriate surgical planning and considerations in the management of RCC and IVC tumour thrombus.



The cardiovascular team would then have the information needed to perform a simultaneous coronary artery bypass at that time if necessary [14].

PREOPERATIVE MANAGEMENT

The importance of surgical planning must never be understated. It is vital to have significant amounts of readily available blood products (packed red blood cells [RBC], platelets, cryoprecipitate, fresh frozen plasma, and clotting factors) based on the expected complexity of the surgery. In addition, addressing the patient's preoperative comorbidities is critical, with surgical clearance from the respective medical/surgical specialists essential. As with any complex retroperitoneal surgery, standard cardiopulmonary optimisation should be undertaken preoperatively. Development of an experienced surgical team with excellent communication between urology, anaesthesia, and vascular/cardiothoracic surgery (if involved) will favour optimal perioperative outcomes. In this context, a vascular surgery team may need to be involved with level II IVC tumour thrombus or beyond, hepatobiliary involvement with level III, and a cardiovascular team for any level IV thrombus. Important surgical considerations in the management of RCC and IVC thrombus are depicted in the flow diagram shown in Fig. 2.

> 'The importance of surgical planning must never be understated'

Some clinicians have advocated routine preoperative arterial embolization of the kidney to decrease the tumour size, thereby potentially facilitating the surgical procedure [14]. Embolization is typically associated with an angioinfarction syndrome and an overall complication rate of 5% [14,41], leading some centres to only recommend renal embolization in specific clinical settings if at all. A recent study by Subramanian *et al.* [42] showed that there is no significant advantage to preoperative embolization in the treatment of an IVC thrombus with RCC and in fact may increase the risk of complications and mortality probably by inducing significant reaction around the kidney and surgical field. Preoperative placement of an IVC Greenfield Filter has also been shown to be ineffective, with an end result of the thrombus being incorporated into the filter, thus necessitating total resection and IVC reconstruction [14,43]. A recently developed protocol for management of RCC with IVC thrombus recommends avoidance of preoperative IVC filter provided this is not in the setting of a patient with active tumour embolus who is not deemed to be a surgical candidate or solely as a means of symptomatic control or palliation. If an IVC filter is required, it is recommended to place the filter <48 h before surgery to reduce the incidence of thrombus infiltration within the filter [4].

Tyrosine kinase inhibitors have been shown to be an effective treatment for metastatic RCC [44]. In a prior study, sunitinib was shown to have the ability to decrease tumour size in ≈36% of cases [45]. Further small studies have corroborated these findings [46–51]. However, the potential merit of tyrosine kinase inhibitors in the management of IVC tumour thrombus secondary to RCC cannot be endorsed at this time until we can conclusively show an IVC tumour thrombi can consistently regress or at the very least stabilise with such a systemic approach.

ANAESTHESIA MANAGEMENT

The anaesthesiology team is of critical importance in the preoperative and postoperative planning of such cases. In addition, modern perioperative care has three strategic goals [52]:

(a) modulate inflammation
(b) minimise pain
(c) avoid iatrogenic harm

Although inflammation can be harmful, it is absolutely necessary to enable effective healing. Lees *et al.* [53] and Banz *et al.* [54] detailed that goal directed approaches to patient care focusing on the invasive nature of the surgery and optimisation of oxygen delivery and tissue perfusion are strongly predictive of perioperative surgical outcome.

Concise and effective communication between surgeon(s) and anaesthesiologist is of paramount importance. Each case is discussed and the surgeon(s) and anaesthesiologist decide on the appropriate types of invasive vascular access lines to be placed. Routine resection of tumours involving the IVC and potentially other major vascular structures mandate at a minimum an arterial line, pulmonary artery catheter, and a large bore central line. A pulmonary artery catheter is placed, as patients may have been exposed to cardiotoxic drugs and massive blood transfusion may ensue. The same invasive vascular access lines are placed when it is anticipated a median sternotomy maybe necessitated for intra-atrial tumour removal, which are usually performed on CPBP with or without deep hypothermic circulatory arrest (DHCA).

In intravascular tumour thrombus cases where there is intrahepatic IVC involvement, invasive lines will be set-up similar to patients undergoing liver transplantation with:

(1) pulmonary artery catheter
(2) a large bore central venous catheter
(3) a 15 F catheter in the right internal jugular vein
(4) right radial arterial catheter
(5) left femoral venous catheter lines

Percutaneous right internal jugular or subclavian vascular approaches for veno-venous bypass (VVBP) and left femoral vein access are usually carried out under real-time fluoroscopy after anaesthesia induction and before the start of the surgical procedure. The patient can then be placed on femoral-portal to right atria bypass percutaneously in order to totally isolate the intrahepatic venous circulation while minimising intraoperative blood loss and hypotension. The surgeon and anaesthesiologist should be particularly attentive to specific portions of the procedure during which there is a potential for an air embolism which typically are:

(1) during liver mobilisation and ligation of the small hepatic veins
(2) during vascular bypass (VVBP and CPBP with or without DHCA)
(3) after IVC closure and re-establishing venous reperfusion.

In a case where massive blood loss is anticipated, blood product requirements may include >10 units of packed RBC, 10 units of fresh frozen plasma, 20 units of platelets and 20 units of cryoprecipitate. If blood loss is >5000 mL, then our massive blood transfusion protocol is initiated intraoperatively emphasising the excellent communication between the surgical team, anaesthesia, and blood bank. The intraoperative goal is to replace blood loss with blood products, although a series of trials have shown that postoperative patients could be managed successfully with quantities of fluids that previously would be considered inadequate [55–57]. In these trials, fluid-restricted groups had fewer complications, less oedema, and earlier return of bowel function. Similarly, renal failure was a rare event in fluid-restricted patients. However, we must emphasise that there remains a fine line between fluid restriction and inadequate end organ perfusion with its inherent sequelae (i.e. severe hypotension, renal hypoxia and ensuing acute tubular necrosis). A recent study showed that TOE can be used to assess preoperative left ventricular end-diastolic volume and cardiac output during colorectal surgery hence facilitating resuscitation efforts [58]. In our experience, we routinely use Swan Ganz haemodynamic parameters to tailor our resuscitative efforts and transfusion requirements, albeit TOE is quite possibly a better alternative. A widely held dogma in oncology is that blood transfusion is avoided whenever possible in patients with cancer due to the immunosuppressive potential of the transfused leukocytes. To minimise this risk, a perfusionist can use the cell saver to wash all packed RBC to be transfused from the blood bank in a 3 : 1 ratio (3000 mL of normal saline for every unit of packed RBC).

Regional epidural anaesthesia is typically avoided in patients with RCC and IVC tumour thrombus, as these patients, especially those with extensive tumour thrombus burdens, may have significant blood losses and may become coagulopathic, hence making epidural haematomas a legitimate concern. In patients with lower level IVC tumour thrombus (level I or II according to the Novick staging system) and a normal coagulation profile (prothrombin, partial thromboplastin time, and platelet count), a single intrathecal injection of morphine (duramorph) may provide improved perioperative pain control. However, in most cases inhalation anaesthetic agents combined with i.v. narcotics provide the most satisfactory anaesthesia management scheme.

If surgery was uneventful at the conclusion of the case, most patients are extubated after careful weaning off the ventilator and careful assessment of their ventilatory parameters, tissue oxygenation, and return to suitable level of alertness. Removal of invasive catheters soon thereafter follows. Uncomplicated cases typically recover routinely and patients are transferred to a surgical ward. In complex cases in which large perioperative transfusion requirements occurred (i.e. two times or more the patient's blood volume), patients are typically kept intubated and ventilated overnight. Consultation with a critical care physician is recommended to ensure safe perioperative resuscitation and extubation, with an overall goal of extubation within the ensuing 12–24 h provided there are no active medical or surgical concerns.

SURGICAL MANAGEMENT

The surgical approach to a specific patient with RCC and IVC tumour thrombus should be individualised according to the level of the tumour thrombus and the characteristics of the primary renal tumour, i.e. size, location, regional lymphadenopathy, aberrant vascular anatomy. Therefore, it is imperative that accurate preoperative imaging be obtained as highlighted earlier [17]. One of the most pivotal surgical considerations is determining whether the tumour thrombus is infrahepatic, intrahepatic, or suprahepatic, as this will ultimately determine which surgical approach, technique of IVC control, and necessity of vascular bypass that maybe needed [17,59,60]. We have tailored our surgical recommendations to such cases based on the proximal level of the IVC tumour thrombus.

> 'The surgical approach should be individualised according to the level of the tumour thrombus and the characteristics of the primary renal tumour'

Level I and Level II thrombus

Although flank incisions are commonly used for open partial, simple, or radical nephrectomies, they provide limited access to the IVC and thus should only be considered for a renal vein or low volume level I IVC tumour thrombus that can be easily 'milked' back distal to the renal vein ostium [14]. Subcostal incisions offer excellent exposure, which allows the extension of the incision to the contralateral side or cephalad in the midline [61]. Unfortunately, this type of approach can result in considerable postoperative pain [14]. A thoracoabdominal incision may afford better exposure for large tumours of the upper renal pole. Albeit, thoracic complications plague this approach, e.g. risk of a pneumothorax, phrenic nerve injury, severe postoperative pain, increased risk of atelectasis and pneumonia, and necessity for a postoperative chest tube [14,62].

Upon entry into the abdomen, medial mobilisation of the colon is necessary to expose retroperitoneal structures. The kidney is mobilised outside of Gerota's fascia and the ureter is ligated. After the renal hilum has been exposed, the renal artery is ligated to leave the kidney attached by only the renal vein [60,63]. With a level I thrombus, a Satinsky vascular clamp is generally sufficient to gain control of the IVC and allow completion of the thrombectomy by manually 'milking' the thrombus toward the renal vein ostium. If the IVC tumour thrombus cannot be brought back distally to the renal vein ostium, a Satinsky clamp can be put parallel to the wall of the IVC and medial to the proximal extent of the IVC tumour thrombus. The side wall of the IVC can thereafter be re-approximated using a running 3-0 or 4-0 polypropylene suture. It is always prudent in such cases to have suprarenal, infrarenal, and contralateral renal vein control. In addition, meticulous

control and ligation of all surrounding venous lumbar vessels cannot be overemphasised and failure to do so may result in significant intraoperative blood loss and hypotension. Balloon occlusion can be used in specific cases to aide in thrombectomy and ileo-caval control but is usually reserved to the infrequent situations of poor distal IVC control or major intraoperative haemorrhage resulting from distal IVC, iliac, femoral, or lumbar venous bleeding [64].

Patients with RCC and IVC thrombus level II require without exception mobilisation of the entire IVC and contralateral renal vein. Control of the IVC above and below the tumour thrombus is imperative for safe vascular control. Similarly, meticulous identification and ligation of all surrounding lumbar veins is critical and should never be obviated. Before performing the cavotomy, we encourage the surgical team to communicate with the anaesthesia team and other members of the surgical team that this critical portion of the procedure is about to commence. We as well encourage the anaesthetist to have blood products readily available at this point, as rapid resuscitative measures may ensue. In addition, we frequently perform what we term a 'test clamping' before the cavotomy, which is to clamp the IVC for a brief period of time (typically a ≈1 min) and monitor for results in terms of the patient's haemodynamic parameters, with significant resulting hypotension indicative that additional resuscitative and/or transfusion measures may be necessitated before conducting the cavotomy and thrombectomy. Once these technical points and considerations have been addressed, complete occlusion of the supra- and infrarenal IVC and contralateral renal vein ensues using vascular clamps or umbilical tapes with Rammels, an incision is circumscribed around the ostium of the renal vein allowing entry into the IVC [59]. Commonly, the tumour thrombus is not invading into the wall of the IVC and can be removed without difficulty. We typically use a Penfield dissector, if the thrombus is slightly adherent to the wall of the IVC. Nevertheless, potential caval wall resection may be required if there is direct wall invasion by the thrombus. After complete removal of the tumour thrombus, the cavotomy incision is closed with a 3-0 or 4-0 polypropylene suture(s).

It has been shown that a laparoscopic approach is possible in very select cases of RCC and IVC tumour thrombus (typically level I). However, these reports have for the most part noted a higher intraoperative complication rate with limited studies pertaining to its oncological efficacy and safety [65,66]. Robotic radical nephrectomy for patients with RCC extension into the IVC has also been successfully reported [67], again in very select cases. Although feasible for low level thrombi, these minimally invasive procedures have not been studied in detail, hence they cannot be recommended as a suitable surgical approach for most patients.

Level III and Level IV thrombus

Level III thrombi may be approached via a bilateral subcostal incision to provide an excellent approach to the kidney and great vessels while avoiding the inherent morbidity of entry into the thoracic cavity, i.e. necessity for a chest tube, increased risk of atelectasis and pneumonia, and increased postoperative pain. Nevertheless, the thoracoabdominal incision provides ideal exposure for large renal tumours, particularly if originating from the upper pole and/or exposure to the retrohepatic IVC [60]. A midline incision can also be considered and provides the benefit of good IVC and contralateral kidney exposure, while enabling an extensive metastatic survey to be performed intraoperatively and minimising postoperative pain [62]. On the other hand, this approach does not provide adequate exposure for hepatic mobilisation or retrohepatic IVC access [14]. Similarly, the midline approach can be challenging when faced with a large renal tumour, especially of the upper pole. For patients with an IVC level IV thrombus, Ayati *et al.* [17] have been proponents that a combined bilateral subcostal (i.e. chevron) incision with concomitant median sternotomy is the preferred surgical approach for such cases, providing direct contiguous access to the kidneys, IVC, and heart. Other surgical reports have supported this finding and indicate the drawbacks of both thoracoabdominal and flank incisions in such complex cases where simultaneous exposure to a host of vital organs is required [18]. In such cases, adequate retroperitoneal exposure is essential and the kidney is mobilised extensively, such that it is solely attached by the renal vein, with the renal artery(ies) ligated and divided whereby potentially decreasing intraoperative blood loss [60,63]. Complete IVC mobilisation with rigorous ligation and division of all lumbar veins is critical. For a supra- or intrahepatic IVC tumour thrombus, extensive liver mobilisation is pivotal, with ligation of the short hepatic veins and incision of the peritoneal reflection at the edge of the right hepatic triangular ligaments, exposure of the bare area of the liver, as well as division of the falciform ligament, ligamentum teres, and left triangular ligaments, allowing full rotation of the liver toward the left and subsequent control of the suprahepatic IVC [68]. The short hepatic veins draining the right and caudate lobe are suture ligated on the IVC side. Control of the suprahepatic IVC with umbilical tapes or vascular clamps and of the right hepatic vein and main trunk of the middle and left hepatic veins is advantageous during suprahepatic clamping and the Pringle manoeuvre, as it may reduce back-bleeding during the cavotomy. Importantly, if suprarenal IVC vascular control above the proximal extent of the tumour thrombus cannot be gained with retrohepatic IVC mobilisation, then a midline sternotomy will be required to control the supra-diaphragmatic IVC. Similarly, a sternotomy with consideration of CPBP and DHCA should be considered the standard for IVC tumour thrombus extending into the right atrium [59].

Lastly, a point mentioned earlier that we want to re-emphasise is that meticulous review of preoperative imaging studies is imperative by all members of surgical team, such that a methodical approach to the individual patient can be devised. The necessity for vascular bypass must be anticipated for a higher level IVC tumour thrombus (level III or IV) and this must be readily available on the day of surgery together with a perfusionist familiar with such cases [20,59,60].

Vascular bypass

The potential for major blood loss and significant intraoperative hypotension with its sequelae (i.e. acute myocardial infection, ischaemic brain injury, shocked liver) are a major concern when surgically addressing higher level IVC thrombus (level III or IV) cases, which can be circumvented for the

most part by circulatory bypass. VVBP can be used to manage level III and select level IV tumour thrombi [14]. It has been shown that the use of VVBP is associated with decreased intraoperative blood loss and operative times when compared with cases performed on CPBP, although a host of additional surgical parameters and considerations are critical in selecting VVBP vs CPBP for a specific case [69]. Patients with level III or IV tumour thrombi can be managed with CPBP to provide continuous cardiac venous return and preserve cardiovascular output [14,59,70,71]. Although this approach provides optimal cardiac protection, it imparts serious risks, e.g. cerebrovascular thrombotic and air emboli [14,72–74]. In a recent small study, the authors were able to show that DHCA combined with CPBP may limit perioperative mortality [19]. Novick *et al.* [75] reported successful outcomes using CPBP and DHCA for level III and IV IVC tumour thrombus cases, citing the benefits of visualising the entire caval wall lumen simultaneously from both the supradiaphragmatic and infradiaphragmatic sites while operating in a relatively bloodless surgical field. However, several previous studies would suggest that CPBP with or without DHCA may in fact increase the likelihood of perioperative renal dysfunction and multi-organ failure [20,21].

Technical considerations

As most level I and level II IVC tumour thrombi do not require extensive hepatic mobilisation, most cases can be individualised for vascular approach and planned reconstruction [22]. Patients in which the tumour thrombus cannot be 'milked' back into the ostium of the renal vein, one cannot deviate from the underlying surgical principle of obtaining suprarenal and infrarenal IVC as well as contralateral renal vein control while meticulously identifying and ligating all lumbar veins within the surgical field. Higher levels of IVC tumour thrombus (level III or IV) may require the hepatoduodenal and hepatogastric ligaments to be divided after the falciform and round ligaments are divided, thereby optimising surgical exposure while avoiding iatrogenic gastrointestinal and hepatic tears or lacerations [14,23]. The application of liver transplant mobilisation techniques as proposed by Facciuto *et al.* [76] are very useful, particularly when managing an intrahepatic level III IVC tumour thrombus not extending above the diaphragm [68]. Complete 'piggyback' liver mobilisation may facilitate addressing a level III IVC tumour thrombus, as the cavotomy can be extended cranially [68,76]. Hepatic congestion can occur with suprahepatic clamping of the IVC, therefore use of the Pringle manoeuvre [77], with temporary clamping of the hepatic artery and portal vein, maybe beneficial to reduce intraoperative bleeding and optimise vision within the surgical field [14,22,76]. Several reports have described aortic cross-clamping during IVC occlusion in an attempt to prevent intraoperative hypotension and maintain haemodynamic stability [22,24]; although in our experience, we have not routinely clamped the aorta as this manoeuvre carries with it potential deleterious homeostatic effects, i.e. ischaemia to bowel, lower extremities, and spine. Posterior lumbar and hepatic vein branches can result in nuisance intraoperative bleeding and hence are often ligated and clipped; however, in the setting of a complete IVC occlusion, collaterals from the gonadal and lumbar veins are often recruited as a form of collateral venous drainage. If IVC resection without vascular grafting is elected, then these vessels should be preserved to allow for suitable venous drainage [14,43].

In general, IVC reconstruction with grafting is indicated if >50% of the caval wall must be resected, although primary infrarenal IVC resection and ligation should be considered particularly if collateral venous circulation is suspected based on the chronicity of the venous occlusion after review of the patient's history, preoperative imaging, and/or intraoperative findings [24]. Primary venorrhaphy (without resection) of the IVC has been shown to have a high patency rate (>90%) due to its large venous wall diameter [25]. IVC tumour thrombus caval wall invasion necessitating resection of a portion of the vessel wall via a medial venotomy, has a higher risk of narrowing with turbulent venous outflow and thus may require caval wall reconstruction [22]. Vein or synthetic patch angioplasty can also be performed if caval stenosis is of concern. In cases were caval replacement is required; our preference has been to use a ringed PTFE interposition vascular graft. There is currently a lack of data about the patency and efficacy of the different types of IVC resection and reconstruction techniques and

TABLE 2 Reported outcomes in surgical series of patients undergoing nephrectomy and IVC thrombectomy for RCC

		Thrombus level*						Median	5-year OS, %			Median survival, months	
Reference	Patients, *n*	I	II	III	II + III	IV	III + IV	follow-up, months	Without metastasis	With metastasis	Overall	Without metastasis	With metastasis
Fokin *et al.* [7]	82	53			40	11			54.1		54.1		
Kwon *et al.* [22]	35	10	17			12		28	50.6			54	
Haferkamp *et al.* [8]	111							16.4	45.8	6.5		51.7	10.7
Lambert *et al.* [82]	118	67			39	12		18	60.8		40.7		
Wagner *et al.* [9]	1192	933			196	63		61.4				Level I: 52 Level II+III: 25.8 Level IV: 18	
Staehler and Brkovic [10]	79	16	14	20	34	9	29		Level I+II: 38Level III: 30		34		13
Sweeney *et al.* [11]	96	39	28	7		14	21	25 (for patients alive)	40	28	35	35	
Klatte *et al.* [86]	321	166	110	19	129	26	45	25	65	19	36	116	16
Parra *et al.* [6]	32	8	9	6	15	9	15	64			47		
Kaag *et al.* [87]	78	24	44				10	51 (for patients alive)			48 (95% CI)		

**Several of the surgical series have reported their outcomes combining several levels of IVC tumour thrombus together (standardised using the Novick staging system).*

materials, which we hope future prospective multicentre randomised trials will address. Lastly, we want to remind surgeons embarking on such cases that a detailed knowledge of retroperitoneal anatomy, familiarity with vascular surgical techniques, and the commitment by a highly skilled core of surgeons and anaesthetists is critical to ensure favourable surgical outcomes.

PROGNOSTIC FACTORS

Preoperatively, nutritional status has been shown to be a significant predictor of surgical outcome among patients with RCC [78]. The 3-year overall survival (OS) and disease-specific survival have been reported to be 58.5% and 80.4%, respectively among nutritionally deficient patients vs 85.4% and 94.7% within a control group, respectively [78]. The presence of preoperative comorbidities also constitutes an important prognostic factor, with patients exhibiting a Charlson comorbidity index (CCI) of >3 having double the predicted mortality rate vs patients with no comorbidities. Those with a CCI of 1–2 had a 1.2-fold higher rate of mortality compared with those with a score of 0 [79]. The study also noted that the overall CCI score for the study population increased throughout the study duration. In addition, preoperative performance status and radiographic suspicion of retroperitoneal lymph node or distant sites of metastasis have also been shown to predict survival within this patient cohort [14,80].

Postoperatively, prognostic factors of OS within this patient cohort include pathological TNM stage, nuclear grade, histologic tumour subtype, regional lymph node status, and perinephric fat invasion [14,81]. Surprisingly, there has been little to no correlation for the level of the IVC tumour thrombus and OS [9,11,27,82]. A recent study by Al Otaibi *et al.* [26] suggests that the level of the IVC tumour thrombus may affect the recurrence rate but not OS. Recently, Bertini *et al.* [83] assessed the surgical outcome of 117 patients undergoing a nephrectomy and IVC thrombectomy for RCC and determined that the presence of friable venous tumour thrombus increased the likelihood of synchronous nodal or distant metastases. In this regard, the 5-year OS after surgical intervention has been reported to be between 32% and 69% among patients with IVC tumour thrombus wall invasion [29,72,84–87].

In the setting of metastatic disease, there may be a palliative benefit to nephrectomy and IVC thrombectomy, particularly if the patient has local symptoms (i.e. intractable haematuria, abdominal/flank pain, and/or shortness of breath) provided they are deemed a surgical candidate [85]. Nevertheless, it is the burden of metastatic disease and response to systemic therapy that are ultimately the best predictors of outcome among patients with metastatic RCC [8,14].

Overall, radical nephrectomy with concomitant IVC thrombectomy has been shown to have a reported perioperative

mortality rate of 5–10% [26,27]. Sweeney *et al.* [11] have reported that nephrectomy and IVC thrombectomy is associated with significant morbidity, with a 38% overall complication rate. Thus, such intricate and detailed surgeries should be performed at centres of excellence with adequate vascular, hepatobiliary, cardiothoracic, bypass capacity (CPBP with or without DHCA, VVBP), and anaesthesia support, particularly for higher level III or IV IVC tumour thrombi [26]. A summary of recent surgical series reporting on the outcomes of patients undergoing nephrectomy and IVC thrombectomy are shown in Table 2 [6–11,22,82,86,87].

CONCLUSIONS

The surgical management of RCC and IVC tumour thrombus requires the commitment of a multidisciplinary surgical team particularly for higher (level III and IV) tumour thrombus. Preoperative imaging is a vital component of the surgical planning and management of such cases. Although MRI with i.v. contrast is currently the imaging method of choice for assessing the presence and level of a tumour thrombus, MDCT remains an equally effective diagnostic method. Current recommendations do not support the preoperative placement of an IVC filter in patients with IVC tumour thrombus or for the use of neoadjuvant systemic therapy in an attempt to improve treatment outcomes. The surgical approach should be tailored to the individual patient case, as well as to the level of the IVC tumour thrombus. An extended chevron incision with or without a sternotomy provides excellent surgical exposure and has been our traditional approach for most cases. Patient education and counselling is essential before surgery recognising the complexity of such surgical procedures, particularly when dealing with higher level (III or IV) tumour thrombus. Lastly, the role of minimally invasive surgical approaches (including robotics) remains for the most part limited and should be considered only in highly selected cases, typically level I IVC tumour thrombus exhibiting favourable tumour and anatomical characteristics.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **IVC**, inferior vena cava; **AJCC**, American Joint Committee on Cancer; **US**, ultrasonography; **TOE**, transoesophageal echocardiography; **MDCT**, multidetector CT; **RBC**, red blood cells; **CPBP**, cardiopulmonary bypass; **DHCA**, deep hypothermic circulatory arrest; **VVBP**, veno-venous bypass; **CCI**, Charlson comorbidity index; **OS**, overall survival.

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