Chapter 9
Approach to the Management of Large and Advanced Renal Tumors

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Introduction

Since the 1990s, the increasing use of abdominal imaging has led to a stage migration, with a marked rise in the incidental detection of small renal masses [1–6]. However, approximately 30% of renal cell carcinomas (RCCs) are still diagnosed as stage II (organ confined larger than 7 cm in size) or stage III (tumor extends into major veins or perinephric tissues and/or regional lymph node involvement), and approximately 10% are still diagnosed at stage IV (adjacent organ invasion or distant metastatic disease) [6].

The oncologic outcomes for large and advanced RCC are very different from pT1a tumors, where the 10-year cancer-specific survival is 90–96% [7, 8]. The 10-year cancer-specific survival for large organ-confined tumors decreases gradually with increasing tumor size and ranges from 85% for 4–5 cm tumors to 49% for >15 cm tumors [9]. Meanwhile, the 10-year cancer-specific survival among those treated for pT3a, pT3b, pT3c, and pT4 RCC is 36%, 26%, 25%, and 12% at 5 years, respectively.

There are many facets that warrant attention in the surgical management of large and advanced renal tumors. In this chapter, we describe the anatomic considerations, preoperative evaluation and preparation, perioperative considerations, surgical principles, and outcomes of the surgical management of large and advanced renal tumors.

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Anatomic Considerations

Surgeons who operate on large and advanced renal tumors must be well-versed in retroperitoneal anatomy. While this is not meant to be a comprehensive description of surgical anatomy, several key points are highlighted.

Anatomic Relationships

The kidneys are retroperitoneal structures with their hila at the level of the L1 vertebral body and are surrounded by Gerota's fascia. They are related posteriorly to the diaphragm, quadratus lumborum, and psoas muscles. The left kidney is typically positioned slightly more cranially and is bordered by the spleen superolaterally, the adrenal gland superomedially, and the tail of the pancreas anteriorly. The left colonic flexure, descending colon, and the colonic mesentery are in turn anterior to the lower pole of the left kidney and the tail of the pancreas. The right kidney is usually slightly more inferior compared to the left and is bordered superiorly by the liver, superomedially by the adrenal gland, and medially by the duodenum. The ascending colon, right colonic flexure, and the colonic mesentery are in turn anterior to the lower pole of the right kidney and duodenum. These anatomic relationships must be considered, especially when normal anatomy is distorted by large renal tumors.

Vascular Anatomy and Variants

The renal artery is normally positioned posterior to the vein and is anterior to the renal pelvis. The right renal artery courses posterior to the inferior vena cava (IVC). Understanding the path of the right renal artery can be valuable when a locally advanced right renal tumor renders the approach to the right renal hilum difficult. An often preferable and easier option is identification and ligation at its origin in the interaortocaval space. The left renal vein crosses anterior to the aorta, inferior to the superior mesenteric artery, and posterior to the small bowel mesentery. On the left, the adrenal and gonadal veins drain into the left renal vein, while on the right, these veins each drain directly into the IVC. The other branches of the abdominal aorta include the paired inferior phrenic branches, the celiac trunk, the paired adrenal arteries, the superior mesenteric artery, the paired gonadal arteries, the inferior mesenteric artery, the paired common iliac arteries, and the paired lumbar arteries. Additional arterial supply to the adrenal can be provided via the inferior phrenic and renal arteries. The second, third, and fourth paired lumbar arteries are infrarenal and somewhat variable in position. The additional tributaries of the abdominal IVC include the hepatic veins, the minor hepatic veins, the right inferior phrenic vein, the right adrenal vein, the right gonadal vein, the paired common iliac veins, and the

lumbar veins. In the setting of an IVC thrombus, the azygos and hemiazygos venous systems may provide collateral drainage. The identification of relevant venous branches is essential to ensure a bloodless field at the time of cavotomy during IVC tumor thrombectomy (Fig. 9.1).

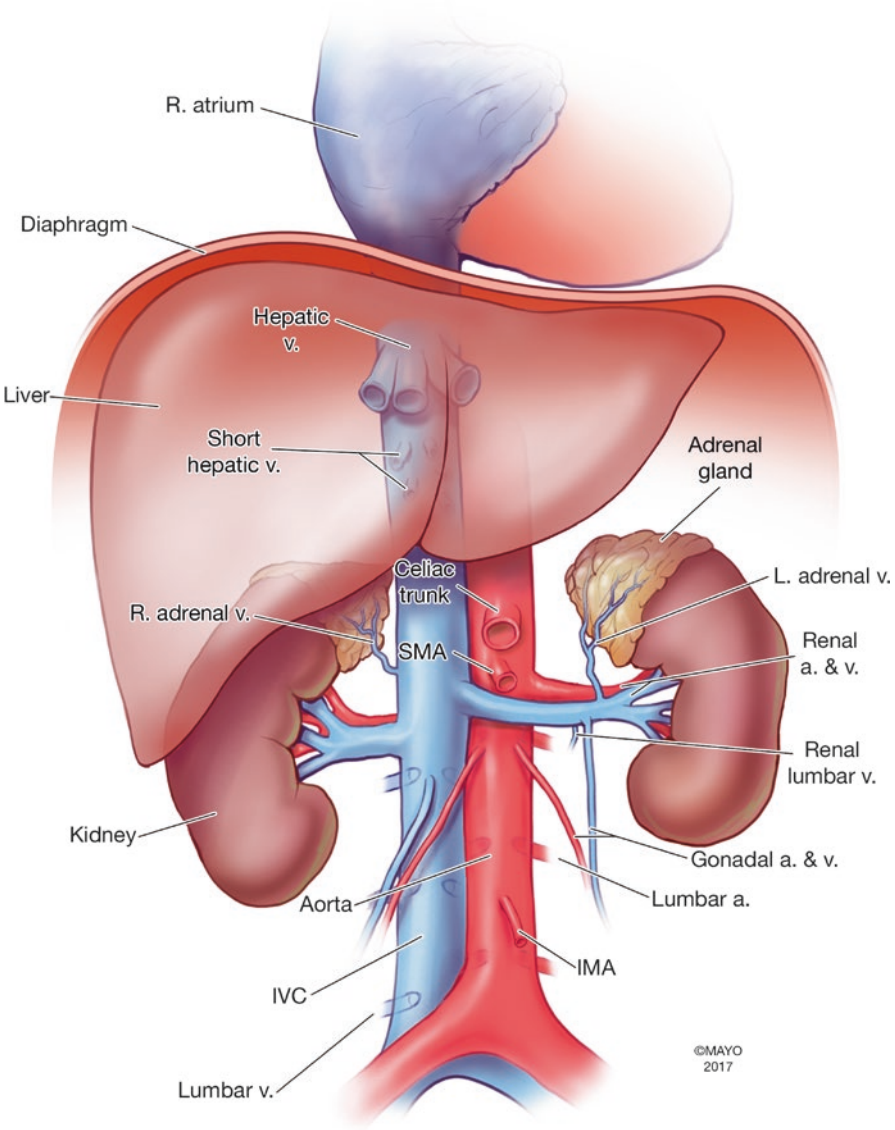

Fig. 9.1 Relevant vascular anatomy of the retroperitoneum. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

Arterial anatomic variants are not uncommon. In cadaver studies, approximately 80% of kidneys have a single artery [10]. In contrast, the reported probabilities of a single renal artery are higher in studies relying solely on imaging (88–95%). This suggests that preoperative imaging may not detect all clinically relevant accessory vessels and intraoperative vigilance is necessary. Accessory upper or lower pole renal arteries can arise from the aorta or branch early off the main renal artery.

Venous anatomic variants also warrant attention. For example, a lumbar vein drains into the left renal vein in approximately 40% of individuals [11]. Persistence of the left supracardinal vein can lead to a left-sided IVC, which crosses at the level of the renal vein and returns to the right side once suprarenal. Persistence of both supracardinal veins can lead to a duplicated IVC. It is possible to have multiple renal veins, most commonly on the right. A retroaortic left renal vein is present in 3% of individuals [12]. A circumaortic left renal vein is also possible. Persistence of the posterior cardinal vein can lead to a retrocaval right ureter [12]. These must be recognized in order to avoid intraoperative vascular disasters.

Preoperative Evaluation and Preparation

Basic Evaluation

For patients presenting with a renal mass, a focused history and physical exam should routinely be performed regardless of the presentation and radiographic findings. While most small renal masses are asymptomatic, large and locally advanced renal tumors may present with gross hematuria, flank pain, or palpable mass or may even present with a spontaneous retroperitoneal bleed [13–15]. Signs and symptoms indicating the presence of a paraneoplastic syndrome should be noted. Resting blood pressure should be measured. Symptoms and signs of distant disease, such as pulmonary symptoms, bone pain, constitutional symptoms, weight loss, and cervical adenopathy, should be fully evaluated. Potential symptoms and signs of IVC obstruction from thrombus, such as bilateral leg swelling, weight gain, caput medusa, and nonreducing or right-sided varicocele, should not be missed. Although rare, symptoms and signs of hepatic vein obstruction (Budd-Chiari syndrome) may also be present [16]. Finally, a family history of renal tumor syndromes and personal history of associated findings of these syndromes should be considered, as these may warrant referral for genetic counselling [17–19].

Laboratory evaluation should be tailored to the history and physical exam and should generally include, at a minimum, a complete blood count, serum electrolytes, serum creatinine, coagulation profile, serum calcium (with correction for hypoalbuminemia as needed), liver enzymes, and urinalysis [20].

Cross-sectional imaging is central in the evaluation of a renal mass [21]. As it pertains to large and advanced renal tumors, the images should be personally reviewed by the surgeon to anticipate intraoperative challenges. The number and position of renal vessels should be confirmed. The relationship of the tumor to adja-

cent structures should be assessed and potential for local invasion considered. Neovascularity and aberrant parasitic vessels should be noted. The renal vein and IVC should be inspected for the presence of tumor thrombus, and attempts should be made to differentiate tumor and bland thrombus. Retroperitoneal lymphadenopathy should be noted, and other intra-abdominal organs should be assessed for potential metastases. The contralateral kidney and adrenal gland should be inspected.

For staging, a chest X-ray should be performed at minimum. A CT scan of the chest may be worth considering in patients with high-risk tumors. For example, in a large study of patients undergoing nephrectomy who had a CT scan of the chest, a strategy of performing a CT scan of the chest for ≥cT1b, cN1, systemic symptoms, or anemia and thrombocytopenia would spare 37% of patients from this test while missing only 0.2% of intrathoracic metastases [22]. A bone scan or brain imaging should be performed as indicated based on symptoms, signs, and extent of disease on other imaging studies. Additionally, brain imaging may be worth considering if perioperative systemic anticoagulation is being considered in the setting of venous tumor thrombus (VTT) to avert potentially catastrophic intracranial bleeding related to an occult metastasis. If present, hematuria should be evaluated via cystourethroscopy and urine cytology, along with upper tract imaging to rule out a concurrent urothelial tumor.

Renal Mass Biopsy

In contrast to small renal masses, the role of renal mass biopsy is limited in the setting of a large or locally advanced nonmetastatic renal tumor and should only be performed if it will alter clinical management [23]. For example, renal mass biopsy may be considered if the tumor is central in location or if other features lead to the suspicion of urothelial carcinoma, as this will alter operative approach. Biopsy may also be helpful in establishing a tissue diagnosis for unresectable tumors prior to initiation of systemic therapy. Otherwise, for patients with large and locally advanced tumors destined for surgery, the risk of malignant histology [24] and cancer-specific mortality [9] is sufficiently high that biopsy will not alter management and will only delay definitive therapy.

Imaging for Venous Tumor Thrombus

Multiple VTT classification systems have been described (Table 9.1) [30]. In this chapter we use the Neves and Zincke classification [26], since it offers the greatest degree of granularity, which in turn directly relates to management.

VTT can present with a wide array of symptoms, while approximately 19% are found incidentally on imaging [31]. Cephalad extension of the tumor thrombus between the time of imaging and operative date can radically change the operative

Table 9.1 VTT classification systems

Landmark	Staging classification				
	AJCC-TNM [25]	Neves and Zincke 1987 [26]	Novick et al. 1989 [27]	Hinman 1998 [28]	Robson 1982 [29]
Renal vein	T3a	0	I	I	IIIa
IVC <2 cm from renal vein ostium	T3b	I	II		
IVC >2 cm from renal vein ostium		II			
IVC at/above major hepatic veins		III	III	II	
Above diaphragm	T3c	IV	IV	III	

Summary of surgical and prognostic VTT classifications for renal cell carcinoma. Adapted from Pouliot et al. [30]

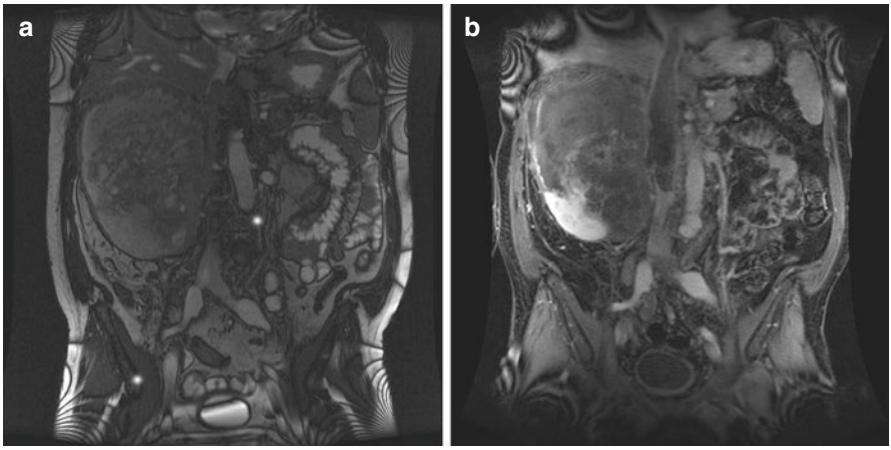

Fig. 9.2 Potential for rapid venous tumor thrombus progression. Images (**a**) and (**b**) were taken 20 days apart in a patient with a right renal mass and venous tumor thrombus prior to surgery. A contrast-enhanced MRI is recommended within 7–10 days of surgery. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

approach (Fig. 9.2). Contrast-enhanced magnetic resonance imaging (MRI) is the preferred modality to characterize an IVC tumor thrombus, and this should ideally be performed within 7–10 days of the surgical date [32–34]. Although multidetector CT scan will identify 79–100% of venous tumor thrombi, MRI appears to be superior in delineating the cephalad extent of the thrombus, in identifying whether there is flow around the thrombus, and in differentiating bland (non-enhancing) and tumor thrombus (enhancing) [32, 35–37] (Fig. 9.3).

The possibility of IVC wall invasion and the potential need for vascular resection must be considered preoperatively. One study considered several clinical and radiologic variables and developed a parsimonious multivariable model to predict

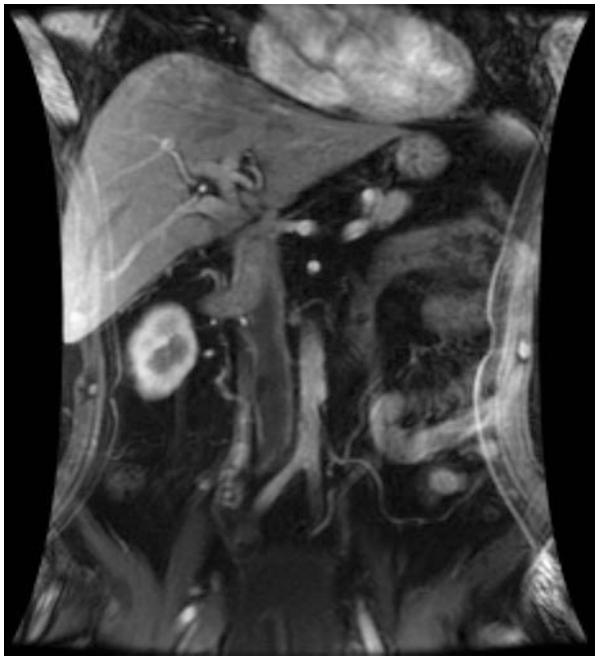

Fig. 9.3 MRI differentiation of bland and tumor thrombus. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

the need for vascular resection in patients with an IVC tumor thrombus [14]. The authors found that right-sided tumor location (OR = 3.30; 95%CI 1.24–8.81), anterior-posterior diameter of the IVC ≥24 mm at the renal vein ostium (OR = 4.35; 95%CI 1.31–14.53), and radiographic identification of complete occlusion of the IVC at the level of the renal vein ostium (defined by the absence of contrast passing around the thrombus within the IVC on preoperative MRI; OR = 4.90; 95%CI 1.96–12.26) were the most important predictors of needing vascular reconstruction at the time of tumor thrombectomy (*c*-index = 0.81).

Assessment of Retroperitoneal Lymph Nodes

In patients with advanced renal tumors, it is important to consider the potential for retroperitoneal lymph node metastasis. Several predictors of lymph node involvement have been described [38–42]. One study found that the two most important radiographic predictors of pN1 disease are the maximum short axis diameter and perinephric/sinus fat invasion [38]. The probabilities of pN1 disease are 28.9%, 66.1%, and 90.4%, for lymph nodes measuring 10, 20, and 30 mm on short axis, respectively. Pathologic features associated with nodal involvement include high nucleolar grade (grades 3 and 4), pT3–4 tumor stage, tumor size ≥10 cm, histologic tumor necrosis, and sarcomatoid component [39]. There is a progressive increase in the risk of pathologic nodal involvement with increasing number of these features.

With 0–1, 2–4, and 5 of these features, the risk of pathologic node positivity was 0.6%, 10%, and 53%, respectively. However, it should be noted that in order to apply this risk stratification scheme, intraoperative pathologic assessment is required [40]. One group reported a preoperative nomogram to predict the probability of nodal metastasis using age, presence of symptoms, and tumor size (AUC = 0.784) [41]. Similarly, Capitanio et al. reported a prediction model for pathologic nodal involvement with an AUC of 0.869, using clinical T-stage, clinical node status (cN1 versus cN0), metastases at diagnosis, and tumor size [42].

Preoperative Consultations

Preoperative cardiology evaluation may be warranted if considering cardiopulmonary bypass for a level III–IV IVC tumor thrombus in order to assess coronary risk and the need for coronary angiography. If significant coronary artery disease is present, performance of concurrent coronary artery bypass grafting at the time of radical nephrectomy may be considered [30].

Preoperative cardiothoracic surgery consultation should be considered if cardiopulmonary bypass is potentially necessary. Hepatobiliary surgeon involvement may be helpful if liver mobilization is needed, particularly in patients with liver congestion secondary to IVC obstruction. Additionally, involvement by a vascular surgeon may be helpful if IVC graft reconstruction is necessary. All efforts should be made to ensure the appropriate personnel are available for the critical stages of the procedure.

Perioperative Considerations

Preoperative Angioembolization

There is insufficient evidence to support the routine use of preoperative arterial embolization (PAE). PAE using absolute ethanol, polyvinyl alcohol particles, acrylic microspheres, or water-insoluble gelatin is considered by some surgeons for patients with large renal tumors and/or VTT [43]. PAE can provide arterial control in instances when intraoperative arterial identification is anticipated to be challenging, such as a bulky hilum, and may allow for the vein to be addressed directly. It may also be associated with reduced blood loss and transfusion requirement [44, 45]. Following PAE, a postinfarction syndrome is anticipated, which includes flank pain, nausea, and fever [46].

The utility of PAE, however, has been contested. In most cases, early arterial control can be achieved intraoperatively, which will reduce the size and turgor of the primary tumor, and even of the tumor thrombus, if present, in the same way as PAE. Second, a survival benefit of PAE has not been demonstrated in the literature

[45, 47]. In fact, one large institutional series evaluating PAE in patients with IVC tumor thrombi found no associated benefit in complication risk or length of hospital stay and even found an associated increased risk of perioperative mortality on multivariable analysis (OR = 5.5, 95%CI 1.2–25.6; $p = 0.029$) [47]. While unmeasured selection bias and confounding cannot be ruled out, these data certainly urge for caution in the liberal use of PAE.

Perioperative Management of Venous Thromboembolic Risk

Although there is no consensus [30, 48], we feel that symptomatic pulmonary embolism should be considered an absolute indication for anticoagulation, while asymptomatic pulmonary embolism, presence of bland IVC thrombus, complete or near complete IVC occlusion, and atrial tumor thrombus (level 4) should be considered relative indications. Anticoagulation can be administered preoperatively, held the day before the procedure, and resumed postoperatively when the bleeding risk is felt to be sufficiently low relative to the thromboembolic risk, usually by postoperative days 2–3. Conventional venous thromboembolism (VTE) prophylaxis should be considered while the patient is not on therapeutic-dose anticoagulation.

Although intraoperative placement of an IVC filter may have a role in some patients presenting with a large or locally advanced renal mass, preoperative percutaneous placement of an IVC filter should be avoided in patients with VTT. One reason to avoid preoperative filter placement in patients with VTT is that insertion of the device can dislodge clot or tumor thrombus leading to pulmonary embolus. Additionally, the presence of a filter can make dissection of the IVC more complicated due to reactive fibrosis. Finally, tumor incorporation into the filter has been described, which complicates the ensuing operation [49].

Neoadjuvant and Adjuvant Systemic Therapy

Neoadjuvant tyrosine kinase inhibitor (TKI) use may facilitate the resection of a locally advanced renal tumor or may facilitate nephron-sparing surgery for large tumors in a solitary kidney that would have otherwise required radical nephrectomy [50–52]. There are also reports where neoadjuvant TKI use reduced the level of a VTT to the extent that it altered the operative approach [53–55]. However, for the majority of patients, the impact of preoperative TKI use is limited. In a study of patients with clinical stage II or higher renal masses who received preoperative sorafenib, the median decrease in tumor size was only 9.6% [50]. Meanwhile, in another study of patients with VTT, a change in thrombus level was observed in 3 of 25 patients (12%) [56]. Therefore, the data are insufficient to support the routine use of neoadjuvant TKIs. Trials evaluating neoadjuvant immunotherapy are ongoing at this time.

TKI use in the adjuvant setting is controversial. The ASSURE randomized trial found no survival benefit with adjuvant sunitinib or sorafenib compared to placebo in 1943 patients with high-grade T1b or greater, completely resected, nonmetastatic renal cell carcinoma (RCC) [57]. Similar results were observed when looking at a high-risk subset of this trial [58]. In contrast, the S-TRAC trial found that adjuvant sunitinib resulted in improved disease-free survival compared to placebo (median 6.8 vs. 5.6 years, HR = 0.76, $p = 0.03$) in patients with higher-risk clear cell RCC, defined as tumor stage 3 or higher, regional nodal metastasis, or both [59]. At this time, S-TRAC is not sufficiently mature to assess differences in overall survival. Finally, the PROTECT trial comparing pazopanib to placebo in the adjuvant setting found no disease-free survival benefit [60]. Based on the S-TRAC trial, the United States Food and Drug Administration granted approval for sunitinib in the adjuvant setting, although in the absence of an overall survival benefit, its use in this setting remains controversial for now.

Perioperative Medical Management

Appropriate physician consultations should be made for medical optimization prior to major surgery. In all patients, diuretics and angiotensin-converting enzyme inhibitors should be held the day of surgery. In diabetic patients, perioperative glucose management should be directed by the severity of diabetes.

Following anesthetic induction, placement of an arterial line for continuous blood pressure monitoring and a central venous line for central venous pressure monitoring are helpful. The urethral catheter drainage bag should be accessible to the anesthesiologist to allow for monitoring of urine output. Efforts should be made to ensure ample hydration, particularly in anticipation of IVC clamping. In patients with a patent IVC despite tumor thrombus, IVC clamping may meaningfully reduce venous return and cardiac output. Active communication between the surgeons and anesthesiologists is crucial.

Operative Management

Surgical Approach

Large renal tumors including those with IVC tumor thrombi have traditionally been managed using an open approach. However, there is increasing experience at certain centers with minimally invasive approaches. The surgeon should use whichever approach allows for a safe and oncologically sound operation.

Although technically challenging, laparoscopic radical nephrectomy can be performed for large and locally advanced renal masses [61, 62]. Hand-assisted laparoscopy may also be an option, given that these tumors will require a large incision for

extraction [63]. Robotic-assisted laparoscopic radical nephrectomy is also increasingly being utilized, although it is unclear whether this offers a meaningful advantage over conventional laparoscopy [64]. One study of the Nationwide Inpatient Sample found that 32% of radical nephrectomies were done robotically between 2009 and 2011 [65]. In this study there were no differences in perioperative complications or mortality between robotic-assisted and conventional laparoscopic approaches, yet the robotic cases were associated with a $4565 more in-hospital costs and $11,267 more in-hospital charges.

Recently, cases of pure laparoscopic [66] and robotic IVC tumor thrombectomy [67] have been reported. These procedures are currently only being performed in highly selected patients at experienced centers. A full description of the nuances of these procedures is beyond the scope of this chapter.

Positioning, Incision, and Retroperitoneal Exposure

Regardless of approach, these procedures require excellent exposure and visualization. Therefore, the choice of incision for an open procedure is crucial (Fig. 9.4). The decision can be influenced by the location and size of the tumor, the presence and level of VTT, body habitus, costal flare, any anatomic abnormalities, and surgeon preference.

We have found that a midline incision can be used to approach virtually any renal tumor, and this is currently our preferred incision for open renal surgery. Adequate access to the entire abdomen including the lateral aspects of the tumor can be

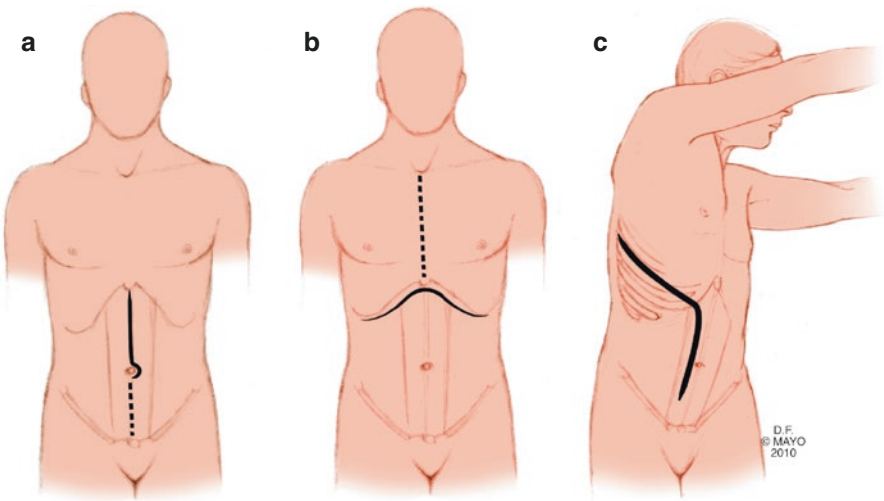

Fig. 9.4 Common surgical incisions used during radical nephrectomy. (**a**) Midline, (**b**) bilateral subcostal (chevron), and (**c**) thoracoabdominal. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

obtained with appropriate use of a self-retaining retractor. The incision can be continued cranially into a sternotomy when cardiopulmonary bypass (CPB) is needed.

An anterior bilateral subcostal (chevron) incision can be performed two fingerbreadths below the costal margin. It offers improved access to the lateral aspect of the tumor and allows for easier liver mobilization. This incision can also be joined with a sternotomy when required. In a randomized trial of midline versus transverse abdominal incisions, there were no differences in analgesic requirement, length of stay, pulmonary complications, median time to tolerance of solid food, or incision hernia risk at 1 year, although there were more wound infections in the transverse incision group [68]. Interestingly, one study found that Chevron incisions are associated with seven times more rectus abdominis atrophy than midline incisions [69].

A flank incision may also be used, which is typically made above the 11th or 12th rib. While this approach avoids anterior adiposity, hilar access can sometimes be difficult. For larger upper pole tumors, a thoracoabdominal approach using a higher rib level with the patient in a modified flank position may be useful; however, a postoperative chest drain will be necessary. The thoracoabdominal incision can also transition anteriorly to a midline incision, resulting in a hockey stick incision.

Following obtaining intraperitoneal access, a thorough exploration of the abdomen and retroperitoneum should be performed. Subsequently, the retroperitoneum should be accessed upon incision along the peritoneal reflection lateral to the ascending or descending colon for right and left renal masses, respectively. Following the avascular plane, the ipsilateral colon and its mesentery should be mobilized off from Gerota's fascia to expose the retroperitoneum. If IVC exposure for tumor thrombectomy is needed, the root of the small bowel mesentery can also be mobilized. For a right renal mass with tumor thrombus, the small and large bowel can all be displaced to the left to allow all relevant structures to be visualized in a single operative field. In contrast, for a left renal mass with IVC tumor thrombus, the IVC tumor thrombectomy is performed in the right hemi-abdomen, while the radical nephrectomy is performed in the left hemi-abdomen. Finally, for level III–IV tumor thrombi, the liver may need to be mobilized medially to gain exposure to the retrohepatic and suprahepatic IVC (Fig. 9.5). This is achieved by dividing the triangular and coronary ligaments, as well as ligating the short hepatic veins draining the caudate lobe of the liver.

Principles Radical Nephrectomy

Adjacent organ injury can be avoided by careful identification of structures and mobilization using the appropriate surgical planes. For a right-sided renal tumor, the duodenum should be reflected medially (Kocher maneuver), which will expose the IVC and renal hilum. On the left, the lateral peritoneal attachments of the spleen may require division to facilitate exposure of the upper pole. The tail of the pancreas, along with the splenic hilum, can be mobilized off from Gerota's fascia following an avascular plane. With this maneuver, the left renal vein should be apparent. If there is any difficulty in identifying the renal vein, the gonadal vein can be identified and traced upward.

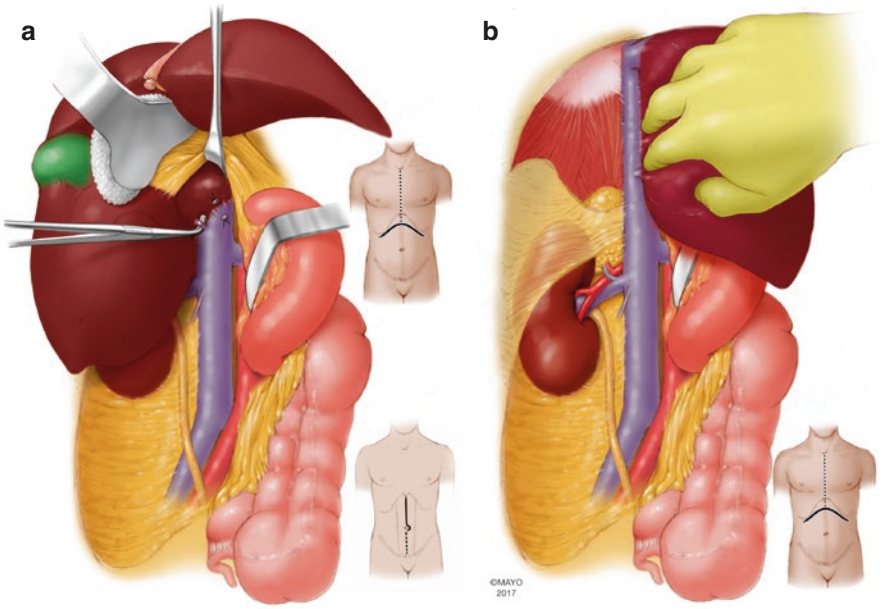

Fig. 9.5 Liver mobilization to gain access to retrohepatic and suprahepatic inferior vena cava. (**a**) The liver is retracted cranially, and the short hepatic veins draining the caudate lobe are divided in order to gain greater access to the infrahepatic IVC. (**b**) The right triangular and coronary ligaments of the liver have been divided, allowing for the liver to be rotated toward the patient's left in order to access the retrohepatic IVC. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

The ureter can be divided where convenient, as long as there is no concern for urothelial carcinoma. For both right- and left-sided renal tumors, we typically ligate the gonadal veins during the dissection.

Although surgeon preference and anatomic considerations vary significantly, our preferred approach is to dissect the hilar structures first and mobilize the kidney after ligation and division of the artery and vein. Early arterial control may be especially beneficial for large tumors, for those with parasitic vessels, and in the setting of an IVC thrombus. For bulky hilar tumors, consideration can be given to identifying the renal artery at its origin. For right-sided tumors, this can include identification of the renal artery in the interaortocaval space [34, 70]. Supernumerary veins can be divided prior to addressing arterial control in order to facilitate exposure, but all arteries should be controlled prior to dividing the main renal vein.

Adrenalectomy

The ipsilateral adrenal need not be routinely removed with the kidney if it is not involved by tumor. The preoperative CT scan is highly accurate in detecting ipsilateral adrenal gland involvement by kidney cancer, with a sensitivity of 100%, a

specificity of 95.2%, and a negative predictive value of 100% [71]. Thus, adrenal involvement can be accurately ruled out preoperatively, and upon intraoperative confirmation, adrenal sparing is usually feasible.

The risk of synchronous ipsilateral adrenal involvement is 2.2%, while the risk of developing a subsequent adrenal metastasis is 3.7% [72]. Moreover, this risk is similar in the ipsilateral and contralateral adrenal glands. As such, there is potential for harm with routine removal of the ipsilateral adrenal gland upon nephrectomy for a renal tumor if contralateral adrenal metastasis occurs. Meanwhile, no survival advantage has been demonstrated with adrenalectomy at the time of nephrectomy [72, 73], and in fact one study suggested worse survival with ipsilateral adrenalectomy [74].

Inferior Vena Cava Tumor Thrombectomy

The surgical management of a VTT is among the most technically challenging operative procedures in urologic surgery. The experience of the surgeon and the team is paramount. Involvement of vascular, hepatobiliary, and cardiac surgeons, as indicated, can be beneficial [15].

Vascular Bypass

The use of vascular bypass should be considered and anticipated ahead of time so that the appropriate personnel and equipment are available. For patients with a supradiaphragmatic (level IV) VTT, CPB with or without hypothermic circulatory arrest (HCA) is commonly utilized and affords a brief period with a bloodless field for complex tumor thrombus extraction and potential reconstruction. Vascular bypass may also be required for certain patients with a subdiaphragmatic IVC tumor thrombus if they are dependent on venous return from the IVC (i.e., collateral venous return is limited) and if a prolonged clamp time is anticipated due to the complexity of the thrombectomy and/or venous reconstruction. For such patients, either CPB and HCA or veno-venous bypass (VVB; e.g., from the infrarenal IVC to the right brachial vein) can be used [70]. However, VVB may not be possible in some instances when there are no acceptable areas to place the IVC cannula, for example, due to bland infrarenal IVC thrombus.

General Principles

Following retroperitoneal exposure, the key steps of the operation include (1) control of the renal artery or arteries, (2) venous tumor thrombectomy, and (3) radical nephrectomy. These steps should be performed in order. Early renal artery ligation reduces blood loss from venous collaterals. In some cases, whereby the risk of disturbing the tumor thrombus is felt to be low and bleeding from collateral vessels is limited, the kidney can be mobilized early.

The approach to VTT is dependent on many factors, but general principles are similar based on the level of the thrombus and the presence or absence of clot in addition to tumor thrombus.

Level 0–I VTT

The approach to the management of a VTT depends on its level (Fig. 9.6). For a level 0 VTT and minimal level I thrombus that can be gently milked into the renal vein, control can be achieved by renal vein ligation or by placing a vascular clamp at the level of the renal vein ostium. If using renal vein ligation, then the procedure does not meaningfully deviate from a radical nephrectomy without tumor thrombus. If using a vascular clamp, a venotomy can be made on the specimen side of the vascular clamp (Fig. 9.6a). Upon confirming a satisfactory margin, the venotomy can then be continued circumferentially to complete the venous resection.

Level I–II VTT

For many level I tumor thrombi and essentially all level II tumor thrombi, no attempt should be made to milk the thrombus into the renal vein. In these instances, it is necessary to obtain exposure and circumferential control of the infrahepatic IVC. The cranial extent of the tumor thrombus should be assessed by gentle palpation and/or ultrasound to guide the extent of IVC dissection. Lumbar veins may require ligation, and in some cases, short hepatic veins from the caudate lobe of the liver inserting into the anterior IVC need to be sacrificed to allow exposure of the IVC superior to the thrombus.

In the absence of bland thrombus inferior to the thrombus, a trial of IVC clamping inferior to the thrombus to confirm hemodynamic tolerability is often worthwhile [34, 70]. If clamping cannot be tolerated despite satisfactory hydration, or if a complex vascular reconstruction is anticipated, then vascular bypass may be necessary prior to clamping [70]. Conversely, if a trial of vascular clamping is tolerated, then vascular clamps should be sequentially placed on the infrarenal IVC, contralateral renal vein, and infrahepatic IVC (Fig. 9.6b). This is followed by cavotomy starting from the renal venal vein ostium and proceeding along the anterolateral aspect of the IVC. Upon extraction of the tumor thrombus and excision of the ipsilateral renal vein, the caval lumen should be inspected to ensure removal of all tumors and clot prior to venous reconstruction.

Level III VTT

For a level III thrombus (at or above the level of the major hepatic veins), transesophageal ultrasound is helpful to assess the proximal extent of the thrombus both prior to incision and following renal artery control. Additionally transesophageal ultrasound can be used to assess for residual tumor following tumor thrombectomy

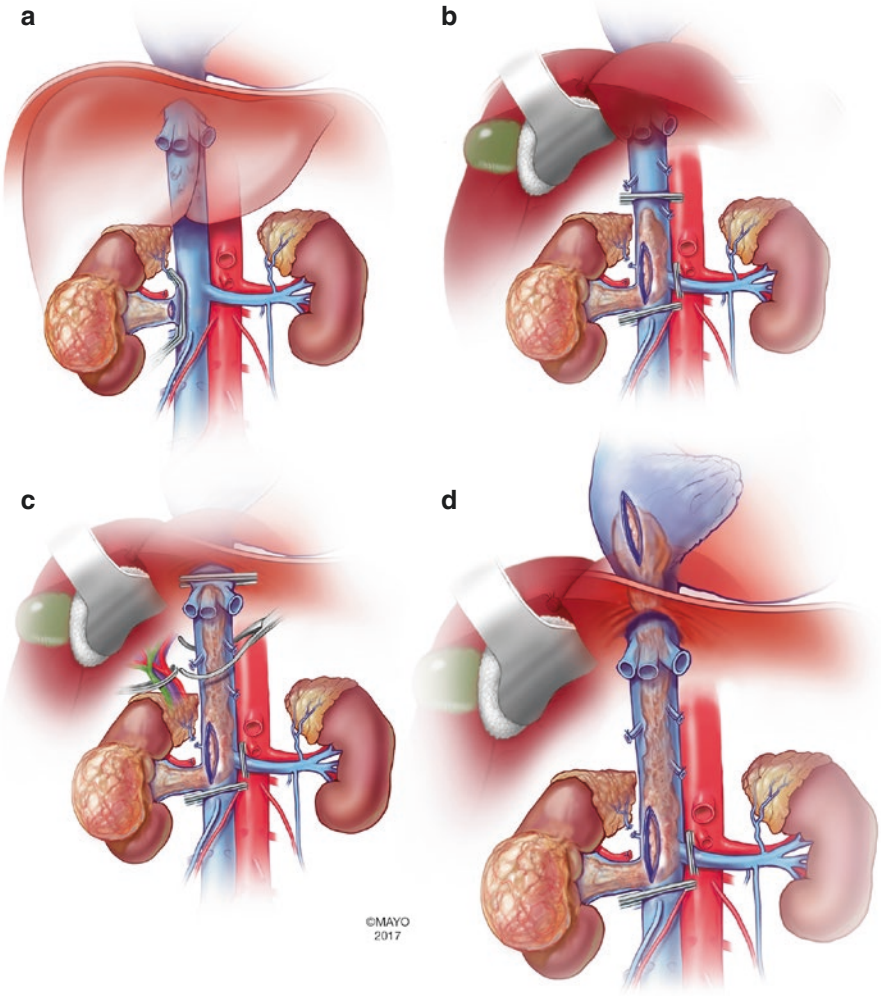

Fig. 9.6 Approach to the intraoperative management of a venous tumor thrombus according to its level. Shown are (**a**) level 0–I, (**b**) level II, (**c**) level III, and (**d**) level IV venous tumor thrombi with appropriate vascular clamps applied and cavotomies performed. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

and for flow around the tumor thrombus, which will aid in the decision of whether to perform IVC reconstruction or ligation following tumor thrombectomy.

In addition to the steps in managing a level II thrombus, we would additionally recommend liver mobilization to allow for exposure and mobilization of the retrohepatic and suprahepatic IVC (Fig. 9.5). For a level III tumor thrombus, vascular clamps should be sequentially placed on the infrarenal IVC, the contralateral renal vein, the hepatoduodenal ligament containing the portal vein and hepatic artery

(Pringle maneuver), and the suprahepatic IVC (Fig. 9.6c). Occasionally, clamping of the hepatic veins is also necessary. This is followed by cavotomy and extraction of the tumor thrombus, as described above. If the cavotomy does not extend to the hepatic veins, then an infrahepatic IVC clamp can be placed following tumor thrombectomy, so that the suprahepatic and Pringle clamps can be released, allowing for liver perfusion during vascular reconstruction of the IVC.

Level IV VTT

For a level IV thrombus, the standard approach includes sternotomy, CPB and HCA. Deep HCA is essential, as its use is associated with reduced in-hospital mortality and improved survival [75]. A total intra-abdominal approach has been described, whereby the right atrium was approached upon dissection through the central tendon of the diaphragm [76]. The use of VVB instead of CPB and HCA has also been reported; however, these cases were performed at highly experienced centers in well-selected patients [70].

The cardiothoracic and intra-abdominal components of the operation can proceed concurrently. The intra-abdominal approach is similar to that of a subdiaphragmatic tumor thrombus. Transesophageal ultrasound is recommended. An appropriate length of vena cava should be exposed and controlled. Liver mobilization may be required depending on hepatic vein involvement of the thrombus. Infrarenal and contralateral renal vein clamps should be placed. The thrombectomy should then be approached from above and below (Fig. 9.6d), ensuring completing removal of all tumor.

Venous Reconstruction Versus Inferior Vena Cava Ligation

The key factors in guiding the management of the IVC after tumor thrombectomy are whether the IVC has been completely occluded and whether collateral venous drainage has developed.

If the patient is dependent on the IVC for venous return, then the IVC must be reconstructed following caval thrombectomy. This can be accomplished by primary closure if there was minimal caval wall resection and the luminal diameter is relatively preserved. If the luminal diameter has been narrowed significantly (most surgeons set the threshold at 50%), then biologic or synthetic patch graft (Fig. 9.7) or tube interposition graft placement should be performed [77]. If there is bland thrombus in the pelvic veins that has not yet propagated to the IVC, consideration can be given to deploying a filter in the infrarenal IVC prior to reconstruction, pending initiation of postoperative anticoagulation [49].

If the infrarenal IVC is occluded with bland thrombus, consideration should be given to IVC ligation using ties or a vascular stapler [49]. This should be performed immediately below the level of the contralateral renal vein, with care to avoid leaving a blind-ending stump where stasis may develop, leading to new bland thrombus

formation. Segmental IVC resection should be performed as necessary, for example, if there is infrarenal extension of the IVC thrombus. Importantly, if the IVC is ligated, every effort must be made to preserve collateral venous drainage, such as lumbar veins, gonadal veins, and aberrant collateral veins in the contralateral retroperitoneum, colonic mesentery, and pelvis.

Once the vascular reconstruction or caval ligation is complete, the radical nephrectomy should be completed, ideally yielding a single en bloc specimen with the tumor thrombus.

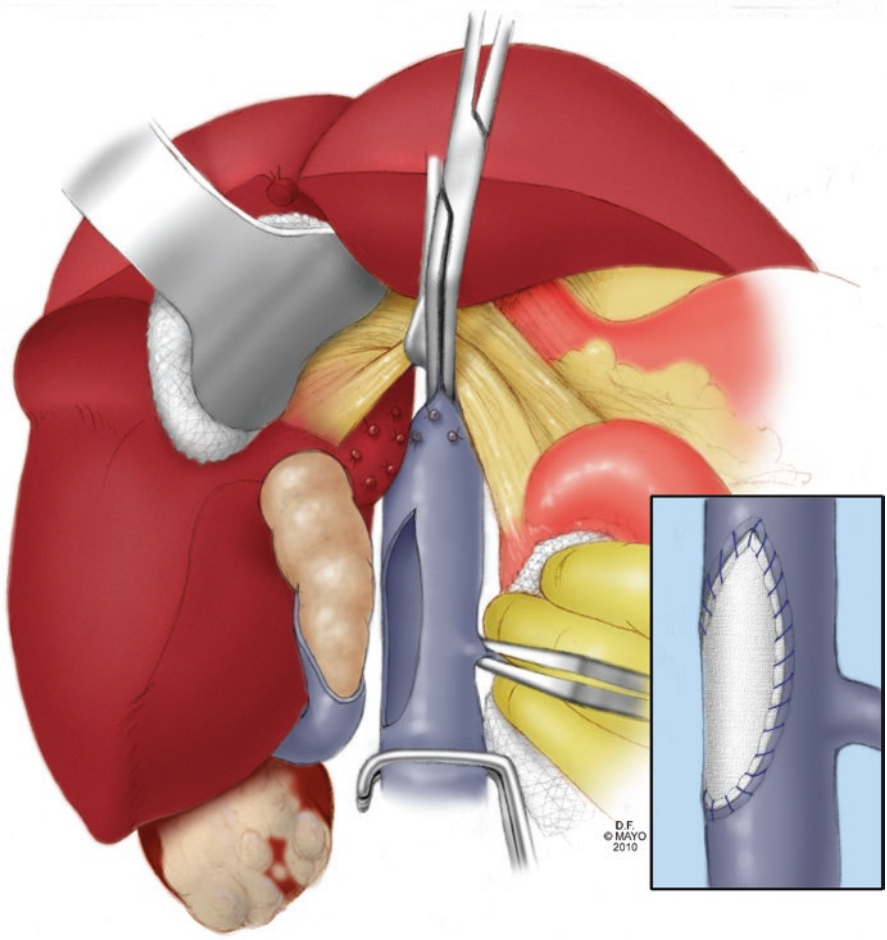

Fig. 9.7 Patch graft reconstruction of the inferior vena cava. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

Role of Lymphadenectomy

The relatively unpredictable nature of the lymphatic drainage of the kidney has made it difficult to define the appropriate template for lymphadenectomy for RCC. The primary lymphatic landing zone for RCC is the retroperitoneal lymph nodes between the first and fifth lumbar vertebrae. Lymph from the left kidney tends to drain into the paraaortic and preaortic nodes, while lymph from the right kidney tends to drain into the paracaval, precaval, retrocaval, and interaortocaval nodes. Lymph connections thereafter are unpredictable, with eventual drainage in the thoracic duct [78]. Moreover, direct drainage from the kidney into the thoracic duct is not uncommon [79].

Although lymphadenectomy can inform staging, there presently has no established role for lymph node resection in patients with nonmetastatic RCC [80]. This is primary driven by the findings of a randomized trial evaluating lymphadenectomy that failed to show a therapeutic benefit among patients with clinically localized RCC (EORTC 30881) [81]. Of note, most patients in this study were considered low risk, with approximately 70% of patients being clinical T1 as per modern staging [80]. With a pN0 rate of 96% among those who underwent lymphadenectomy, it is not surprising that no survival benefit was observed. There are, however, retrospective studies suggesting a benefit associated with lymphadenectomy for large and advanced tumors or those with high-risk pathologic features [82, 83]. Still other retrospective studies have found no difference [84, 85].

Isolated pN1M0 RCC carries a poor prognosis. In one study, median time to distant metastasis was 4.2 months, and estimated 5-year metastasis-free survival was only 16%, while cancer-specific and overall survival were 25% [86]. Although there is retrospective data to suggest that extent of lymphadenectomy, as evidenced by lymph node yield, is associated with better survival [82, 87], caution should be applied in using these fidnings to support extensive lymphadenectomy, as the robustness of these data has been questioned [88]. Moreover, it is possible that extent of lymphadenectomy and lymph node yield may merely be an indirect indicator of surgical quality and ability. Therefore, although resection of clinically positive nodes may be reasonable when technically feasible, these patients likely have micrometastatic disease elsewhere and extensive lymphadenectomy is unlikely to be curative. Finally, there is no evidence of survival benefit of added lymphadenectomy for patients undergoing cytoreductive nephrectomy for metastatic RCC [89].

Resection of Adjacent Organs with Tumor Invasion

Nonmetastatic locally advanced RCC with adjacent organ invasion is not a contraindication to surgery. Aggressive en bloc resection can be safely performed, including in the setting large bowel, small bowel, mesentery, adrenal, liver, pancreas, spleen, diaphragm, and/or retroperitoneal muscle invasion [90, 91]. Such cases should be performed at an experienced center in conjunction with the appropriate consulting services.

Outcomes of Nonmetastatic Advanced Renal Cell Carcinoma

Complications and Morbidity

Potential early complications of radical nephrectomy for large and locally advanced RCC can be classified as cardiac (myocardial infarction, postoperative cardiac arrest), respiratory (atelectasis, pneumonia, need for reintubation or prolonged ventilator support), neurologic (stroke, prolonged coma), thromboembolic (deep vein thrombosis, pulmonary embolism), renal/urinary (urinary tract infection, acute renal failure, need for renal replacement therapy), wound related (superficial or deep surgical site infection, wound dehiscence), hemorrhagic, and septic [92]. In addition, there is a risk of intraoperative injury to adjacent organs that may result in bowel leak, pancreatic leak, bile leak, or pneumothorax. Long-term effects can include chronic kidney disease, incisional hernia, and lower extremity edema in some cases if patent venous return is not restored and insufficient venous collaterals existed prior to surgery.

Based on data from the American College of Surgeons National Surgery Quality Improvement Program (ACS-NSQIP), the overall rate of complications following nephrectomy is 13% in-hospital and 17% overall [92]. The median length of hospital stay is 4 days, and the 30-day mortality rate is 0.7%. These complication and mortality rates, as well as this length of stay estimate, may be higher for patients undergoing surgical management of large and advanced renal tumors. Most major complications (88.1%) tend to occur in hospital, while the majority of minor complications (70.7%) tend to occur after hospital discharge.

Nephrectomy with IVC tumor thrombectomy is associated with significant perioperative risk. The risk of major complications is approximately 34%, in-hospital mortality rate is approximately 7%, and 90-day mortality rate is 10% [93, 94]. These risks depend heavily on surgeon experience. In one study, 75% of the deaths occurred in the first two cases of the surgeon's experience [94].

There is significant potential for VTE postoperatively following cavotomy and IVC reconstruction. The incidence of VTE in this setting is estimated to be 22%, diagnosed at a median of 6 days postoperatively [95]. Common presenting symptoms include lower extremity edema, hemodynamic compromise, and acute desaturation. There is an increased risk with tube interposition graft reconstruction versus primary repair and patch graft reconstruction [95]. Although uncommon, there is also potential for tube graft thrombosis [77, 95]. Nonetheless, while routine anticoagulation is not warranted beyond conventional postoperative prophylaxis, a high clinical suspicion and diagnostic vigilance is necessary.

The literature is mixed on whether CPB is associated with an increased risk of complications and inhospital mortality [93, 94]. However, if CPB is deemed necessary, it is essential to concurrently use deep HCA, as it is associated with reduced perioperative mortality (8.3% versus 37.5%) and longer median overall survival (15.8 months versus 7.7 months) [75].

Concurrent hepatic resection for locally advanced or metastatic disease is associated with acceptable morbidity. The estimated risk of Clavien grade 3–4 complications is 12%, and the estimated risk of perioperative mortality is 3% [90]. These risks are similar for patients undergoing non-hepatic resections for locally advanced RCC, although hepatic resections carry a slightly higher risk of VTE by comparison.

Oncologic Outcomes and Prognostic Factors

Various prognostic models have been developed for the preoperative and postoperative prediction of recurrence and survival [96, 97]. A comprehensive review of outcomes is beyond the scope of this chapter, but key points as they pertain to large and advanced RCC will be highlighted.

The oncologic outcomes for large and advanced RCC demonstrate a dramatic contrast to pT1a tumors, where the 10-year cancer-specific survival is 90–96% [7, 8]. In contrast, the 10-year cancer-specific survival for large organ-confined tumors decreases gradually with increasing tumor size and ranges from 85% for 4–5 cm tumors to 49% for >15 cm tumors [9]. Meanwhile, the 10-year cancer-specific survival among those treated for pT3a, pT3b, and pT3c RCC is 36%, 26%, and 25%, respectively. Oncologic outcomes for pT4 RCC are poor, with an estimated survival of 12% at 5 years [7].

Surgical treatment is particularly impactful in patients with a VTT. The median survival in those with RCC and VTT without treatment is 5–7 months [98, 99]. In contrast, if treated surgically, the 5-year survival is 40–65% [99–103]. Unfortunately, not all patients are good surgical candidates. Patients with poor performance status, acute or fulminant Budd-Chiari syndrome, or critical metastatic disease will likely have poor outcomes with upfront surgery and may be best managed with systemic therapy.

In addition to stage and tumor size, histologic subtype, grade, coagulative necrosis, and sarcomatoid differentiation are all important prognostic factors in RCC [9, 104–106]. Recent data also suggest that rhabdoid differentiation warrants classification as grade 4 but should not be grouped together with sarcomatoid differentiation, which is independently associated with worse cancer survival even among patients with grade 4 RCC [107].

Conclusion

The safe and efficacious surgical management of large and advanced renal tumors, particularly those with VTT, requires careful preoperative evaluation and preparation, a thoughtful surgical approach, and meticulous perioperative care. Appropriately managing all of these aspects of the patient's care is essential to maximize the chances of achieving satisfactory perioperative and oncologic outcomes.

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