7 Management of Renal Cell Carcinoma with IVC Thrombus, Nodal Involvement, and T4 Disease

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Introduction

Background

Renal cell carcinoma (RCC) is one of the ten most common malignancies worldwide, with over 400,000 new global cases diagnosed annually and 74,000 new cases in the USA [1]. RCC comprises several different histologic subtypes, each varying in clinical presentation, features, and prognosis. The most common is clear cell type, comprising of 75% of new cases; the remaining dominant subtypes include papillary, chromophore, medullary, and collecting duct, comprising of 10%, 5%, 1%, and 1% of remaining cases, respectively [2].

The historic presentation of the "classic triad" of signs and symptoms—hematuria, flank pain, palpable masses—is identified in less than 10%, with most cases in

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the developed world found incidentally on magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasound in asymptomatic patients [3]. As such, it is postulated that contemporary ubiquitous use of abdominal imaging contributes to recently observed increasing incidence rates of RCC worldwide with the highest rates in North America, Northern and Eastern Europe [3]. Other hypothesized explanations for the high incidence in developed nations include prevalence of modifiable risk factors for RCC such as smoking, obesity, physical inactivity, and hypertension [3].

RCC is twice as common among men as women. Additionally, female sex is associated with a higher likelihood of presenting with localized disease and improved cancer-specific survival [4]. By gender, RCC accounts for 5% in men and 3% women of all oncological diagnoses in the USA [1, 2]. RCC commonly presents in older individuals (median age at diagnosis: 64 years) with approximately 53% of patients diagnosed between the ages of 55 and 74, while less than 10% are diagnosed before the age of 45 years [4]. Patients with RCC commonly present with a high burden of comorbidities. On average, a newly diagnosed RCC patient has eight chronic comorbid conditions compared to only four in age-matched controls [5]. Within the United States, SEER data demonstrates a higher incidence rate of RCC amongst Black patients compared to other minority ethnicities [1, 4]. RCC tumor subtypes vary across racial groups with clear cell histology more commonly identified in Caucasians while medullary and papillary RCC are seen more often in Black patients [2, 3].

Incidence

With the increasing ubiquity of abdominal imaging, the incidence of incidental RCC detection in the USA has increased at 2.4%/year from 1992 to 2008 (incidence rate of 14.1/100,000) with a plateau from 2008 to present (incidence rate of 16.0/100,000) [6]. Clinically localized RCC accounts for 65% of cases, while 16% of patients present with regional spread and 16% have distant metastatic disease [6]. A large series of nearly 3000 patients found that 14% of patients undergoing cross-sectional imaging harbor an incidental renal mass larger than 1 cm in size while another review reported 15% of patients undergoing surgical management of renal masses were “incidentalomas” [3, 5].

Indeed, most renal masses are clinically localized, measuring less than 4 cm in size at time of diagnosis, accounting for 48–66% of new RCC cases [1]. Thompson et al. reported 25% increased odds of metastasis for every centimeter increase in tumor diameter [7]. Thus, in patients with tumor diameter <3 cm, the risk of metastasis is remote with several active surveillance cohorts reporting 0–1.1% metastatic events [7]. While we have noted an increased incidence of small renal masses, rates of locally advanced, node positive, and metastatic RCC at presentation have been stable with approximately 25% of contemporary patients present with nodal or distant metastasis (N1 or M1) while an additional 20–30% of patients presenting with organ-confined disease will ultimately develop systemic recurrence [5].

Mortality

Despite improvements in diagnosis and management over the last two decades, RCC remains one of the most lethal urological malignancies. The 5-year relative survival rates for patients with RCC in the USA improved from less than 50% in 1977 to over 75% (from 2009–2015) [8]. Similarly, incidence-based mortality rates peaked in the early 2000s and declined dramatically over the last decade with rates equilibrating around 30% [8]. It is estimated that 175,000 patients worldwide and 14,830 in the USA will die from RCC annually, accounting for 1.8% and 2.4% of all cancer deaths, respectively [4]. Increased access to care, lead-time bias from earlier diagnosis to treatment of small renal masses, and advancement in availability of local and systemic therapeutics may account for this decreased mortality-to-incidence ratio. However, survival rates vary and are contingent on cancer stage, with 5-year relative survival in patients with localized (cT1-2), regional (cN+), and distant (cM+) RCC being 93%, 70%, and 12%, respectively [8]. Beyond clinical stage, a patient's age, performance status (Karnofsky performance score <80), nodal involvement, fat invasion, tumor necrosis, and tumor size (>7 cm) have all been associated with increased risks of mortality [7].

Clinical Staging of Locally Advanced and Node Positive RCC

Accurate clinical staging of RCC is critical to selecting appropriate treatment approach and optimizing prognostication in a uniform and standardized manner. The tumor-node-metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) remains the predominant means to risk-stratify RCC patients. Since inception in 1974, it has undergone major revisions with the primary goal to best approximate outcomes on a stage-for-stage basis [9, 10].

Based on the TNM system, locally advanced RCC (cT3-T4N0M0) is defined as having any of the following characteristics: extension into major veins, invasion the adrenal gland, extension into the peri-renal or peri-pelvic fat, or invasion beyond the Gerota's fascia. Updated TMN editions revised the definition of factors constituting locally advanced disease, specifically adjusting the definition of clinical stage 3 disease which is observed in 5–10% of patients [11]. One major change included reclassification of direct ipsilateral adrenal gland invasion to T4 from T3a to better reflect the worse prognosis associated with this pathologic feature. Direct adrenal gland invasion is rare, occurring in approximately 2.5% of cases and has been found to have worse cancer-specific survival than other high-risk features. Tumors involving the renal vein but without extension into the IVC were downgraded from stage T3b to T3a [10].

Table 7.1 describes the commonly utilized Mayo Clinic classification system for venous tumor thrombus according to the associated anatomic landmarks [12].

Table 7.1 Tumor thrombus level and definition

Level	Anatomic landmark
0	Thrombus limited to renal vein, detected clinically or during pathologic evaluation
I	Thrombus extending into IVC, <2 cm above renal vein
II	Thrombus extending into IVC, >2 cm above renal vein but below hepatic veins
III	Thrombus at/above the level of hepatic veins but below the diaphragm
IV	Thrombus extending above the diaphragm

Nodal Involvement

Clinically node positive disease in RCC is denoted cN1 vs. cN0, which represents a radiographic classification while pathologically node positive disease is denoted pN1 vs. pN0/pNx (a histologic classification). Of note, previously, in the 2002 TNM system stratified node positive disease by both the size and number of lymph nodes involved, but this was subsequently converted to a binary system as there is no historic consensus regarding oncologic outcome differences associated with involvement of one or more than one lymph node by RCC [11].

The most recent iteration of AJCC staging system for RCC patients published in 2018 categorizes node positive (cT1-3N1M0) malignancies as stage III. While the incidence of lymph node involvement has reportedly decreased overtime, historic series documented pN1 disease in 23–35% of surgical patients undergoing RN and LND [3]. Current pN1 rates in localized, low risk populations (cTxN0N0) range from 1 to 5% [4] and increase to 5.2–13.2% in pT1-2 disease and 23.4–36.1% in pT3-4 [1].

Determining candidacy for lymphadenectomy (LND) at the time of nephrectomy currently relies heavily on preoperative imaging; however, CT and MRI only have a 77% and 73% sensitivity for identifying nodal metastases with limited reliability in detecting nodal micrometastases [13]. For example, when LND is performed for lymphadenopathy over 1 cm in maximal diameter, final nodal pathology demonstrates benign or inflammatory changes in 58% of cases [13]. Radadia et al. similarly observed that the sensitivity of conventional imaging for detecting nodal metastases was only 67% while the NPV was 94% [14]. As a result, clinical nomograms and predictive tools have been proposed in the perioperative, intraoperative, and postoperative settings in an effort to identify lymph node involvement and those patients who would benefit most from LND at time of surgical intervention. Multiple variables have been proposed to be predictive of risk of nodal involvement including maximal LN diameter and presence of radiographic fat invasion, ECOG status, cN stage, LDH, and local symptoms and tumor grade, size, stage, necrosis, and sarcomatoid differentiation [15–17] with generally modest accuracy and generalizability of the published models. This will be further addressed in the section entitled "The Role of Lymphadenectomy in the Management of RCC".

Surgical Approach to Locally Advanced RCC

Preoperative Evaluation

For patients with large and locally advanced renal tumors, a focused history and physical exam is the first step in the evaluation. In addition, basic laboratory evaluation should include, at minimum, a complete blood count, serum electrolytes, coagulation profile, serum calcium, liver enzymes, and urinalysis [18]. Laboratory evaluation should furthermore be tailored to individual history and presenting symptoms, such as bilateral leg swelling, concern for paraneoplastic syndromes, weight loss, neurological deficits, bone pain or respiratory distress. Patients presenting with cachexia, weight loss, and anorexia warrant additional nutritional work up including liver function testing, albumin, prealbumin, BMI and nutritional assessment and rehabilitation. Furthermore, patients with neurologic symptoms (lethargy, neurologic deficits, mental status change, and new onset headaches) in setting of advanced renal tumors, warrant additional CT head imaging to rule out leptomeningeal carcinomatosis.

Cross-sectional imaging is a crucial next step in characterizing RCC with IVC tumor thrombus by evaluating (1) tumor thrombus presence and invasion into IVC wall, (2) volume of tumor and bland thrombus, and (3) surgical planning for resection, and reconstruction [19]. Historically, venography (venogram) was used for detection and evaluation of IVC tumor thrombus, however, this modality is limited by its invasive nature and moderate risk of complications. (Fig. 7.1) [20]. However, venography can be useful in establishing collateral blood supply if IVC resection is anticipated intraoperatively due to bulky venous tumor thrombus (VTT) with chronic IVC occlusion.

The portal venous phase of CT imaging is utilized to evaluate the endoluminal VTT level as well as to differentiate VTT from bland thrombus, and to detect VTT continuity with adjacent organs [20, 21]. While both CT and MRI are both considered high quality diagnostic imaging, MR is generally the preferred imaging modality for the detection of VTT, characterization of the extent of wall invasion, and evaluation of level of VTT extension [22]. For the detection of VTT, the sensitivity of MR approaches 100% while the diagnostic accuracy of conventional CT and multidetector CT lags behind (MDCT are 65% and 93%), respectively [22]. When comparing the two imaging modalities, timing of the imaging is considered more important than the imaging modality itself due to the potential for rapid VTT growth. Therefore, obtaining cross-sectional imaging to evaluate the VTT level within 14 days of surgery is generally recommended [23]. Images should be reviewed by the surgeon in conjunction with a radiologist to anticipate intraoperative challenges and facilitate operative planning. Aberrant anatomy, and relationship of the tumor to adjacent structures should be assessed. The contralateral kidney, adrenal gland, and regional lymph nodes should also be carefully evaluated to assess the risk of local invasion (Fig. 7.1).

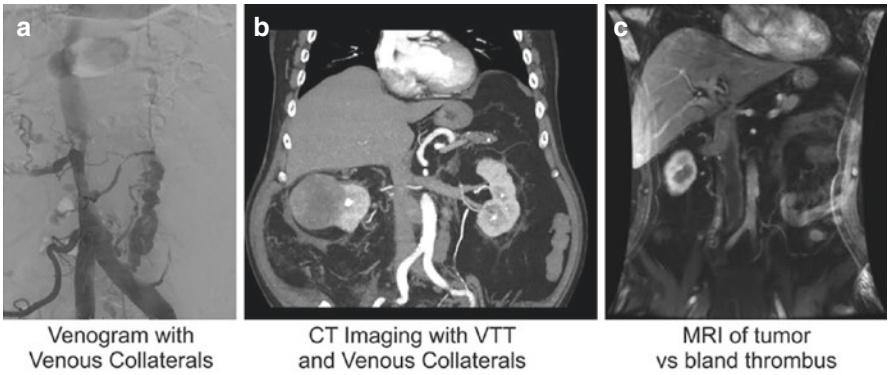

Fig. 7.1 (**a**) Venogram showing inferior vena cava filling defect with collaterals into the ascending lumbar vein and gonadal veins. (**b**) CT and (**c**) MRI imaging of the IVC thrombus. MRI imaging is used in conjunction to differentiate tumor from bland thrombus

Preoperative Management of Venous Thromboembolic Risk in Patients with RCC and Associated VTT

Patients with RCC and associated VTT represent a challenging group of patients, due to the nature of the disease and high risk for perioperative complications. Approximately 6% of patients with VTT are diagnosed with concurrent pulmonary embolism (PE), which carries a high mortality rate of up to 72% [21]. Furthermore, the presence of lower extremity thrombus alone increases risk of minor and major complications twofold [24].

Although there is no society-based consensus regarding anticoagulation, recent guidelines put forth by multidisciplinary group of experts recommended the use of anticoagulation (low molecular weight heparin) in all patients with VTT without contraindications such as active bleeding [21]. Similarly, others have proposed that symptomatic PE is an absolute indication for anticoagulation, while asymptomatic PE, bland IVC thrombus, complete or near complete IVC occlusion, and atrial tumor are considered relative indications [21]. Therapeutic anticoagulation is administered preoperatively, and is held 24 h prior to planned surgery. Placement of IVC filters is typically not recommended due to the risk of incorporation of tumor thrombus into the IVC filter (Fig. 7.2), which may complicate surgical thrombectomy and necessitate total IVC resection and reconstruction [25]. However, IVC filters may be placed at the discretion of the treating physician for continued PE despite anticoagulation or in patients with a contraindication to anticoagulation in setting of recurrent PE. 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 [21].

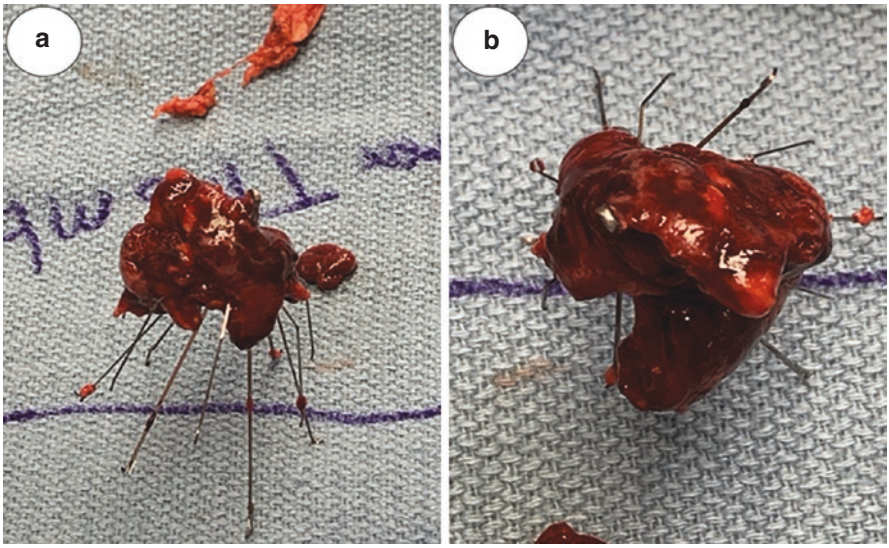

Fig. 7.2 Depiction of IVC filter placed preoperatively, with incorporation of tumor thrombus into the IVC filter (**a**, **b**) at the time of IVC thrombectomy, requiring IVC resection and reconstruction

Surgical Management of VTT

Surgical Preparation

For higher levels VTT (e.g., Level III, IV) cardiac anesthesia support is recommended, especially, for instances, with cardiopulmonary bypass or venovenous bypass is anticipated. Following induction of anesthesia and endotracheal intubation, adequate vascular access should be secured. Central access may be preferred in the setting of higher level VTT. Arterial lines are generally used for continuous blood pressure monitoring. Transesophageal echocardiography (TEE) is helpful to evaluate for involvement of the intra- and suprahepatic IVC, hepatic veins, and left atrium. It may also be utilized throughout the case to evaluate for embolization and cardiac function in real time [26]. After TEE is completed, orogastric tube or nasogastric tube placement may be considered and is especially helpful in the setting of a left-sided tumor. Given the high risk of intraoperative blood loss, the patient's blood type should be established and we recommend holding 2–4 units of packed red blood cells and fresh frozen plasma on standby.

Incisions

The surgical approach should be individualized according to the level of thrombus, surrounding organ involvement, regional lymphadenopathy, and variations in vascular anatomy. Regardless of the level of the VTT, surgical approach

requires excellent exposure and visualization of the IVC and retroperitoneum. While flank incisions are commonly utilized for open partial, simple, or radical nephrectomy, this incision is unlikely to provide adequate exposure of the IVC and therefore should be sparingly for patients with level 0 or 1 VTT where the thrombus is anticipated to be able to be easily milked back into the renal vein [18].

A midline incision provides excellent exposure to the entire abdomen including the lateral aspects of the tumor with adequate retraction. Similarly, a subcostal incision allows for versatility in exposure as well as the ability to extend the incision to the contralateral side or cephalad in setting of need for cardiopulmonary bypass (CPB) or liver mobilization. While there are no differences in postoperative pain, pulmonary complications, or incisional hernia risk at 1 year, chevron incisions have been found to be associated with an increased risk of rectus abdominus atrophy as compared to midline incisions [27, 28]. Large upper pole tumors can benefit from a thoracoabdominal incision, however, this approach is associated with a higher rate of complications including pneumothorax, phrenic nerve injury, increased postoperative pain, and need for chest tube placement [29] (Fig. 7.3). The Makuuchi incision is very helpful in large renal tumors with VTT, where IVC reconstruction and adjacent organ involvement in suspected. This incision is helpful for liver mobilization and IVC reconstruction, allowing for perfect surgical exposure while preserving the intercostal muscles, reducing muscle atrophy and postoperative pain [30]. The transverse portion of the incision can be extended to the contralateral side to improve visualization, analogous to a liver transplant incision. For patients with level 4 VTT necessitating sternotomy, the midline and Makuuchi incisions can be extended vertically to the sternal notch.

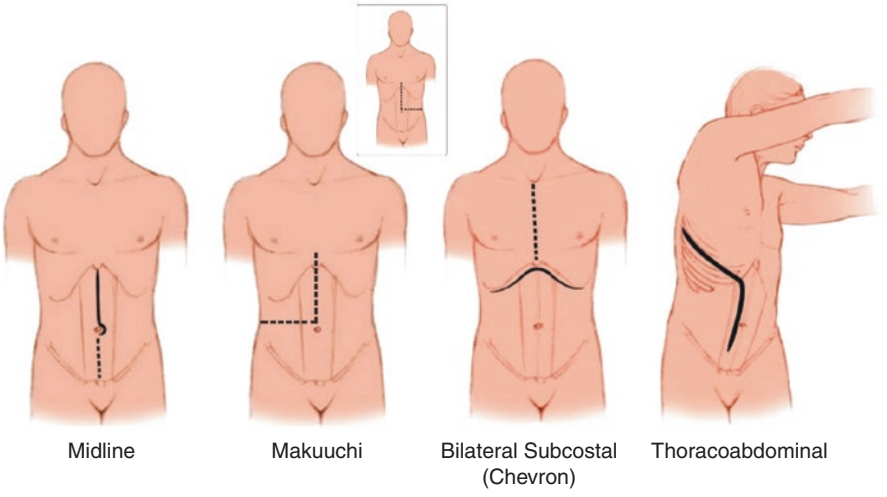

Fig. 7.3 Schematic representation of open surgical incisions utilized for radical nephrectomy with concomitant IVC thrombectomy. Source: Original

Approach to Level 0-I VTT

Following intraperitoneal access, the retroperitoneum is visualized via mobilization along the peritoneal reflection of the ascending/descending colon ipsilateral to the primary tumor. After mobilization of this avascular plane, the colon is reflected off of Gerota's fascia to expose the anterior surface of the kidney, the IVC, and the aorta. Any adhesions between the gall bladder and the omentum or visceral adhesions are lysed. Mesenteric lymphatics should be identified and ligated with either suture or surgical clips to reduce the risk of postoperative chyle leak.

For right-sided tumors, additional mobilization of duodenum medially (Kocher maneuver) is necessary to expose the IVC and right renal hilum. On the left, the splenorenal attachments are divided to expose the upper pole of the kidney and prevent a traction injury of splenic capsule during mobilization. Further mobilization of the tail of the pancreas along with splenic hilum off of Gerota's fascia is undertaken to expose the left renal vein. The mobilization of the spleen and the pancreas off Gerota's fascia is performed en bloc toward the midline, allowing for exposure of the entire upper retroperitoneal space from the diaphragm to the inferior border of the kidney. In certain circumstances, IVC exposure also can be obtained by mobilizing the root of the mesentery off the great vessels (Fig. 7.4) The bowel is

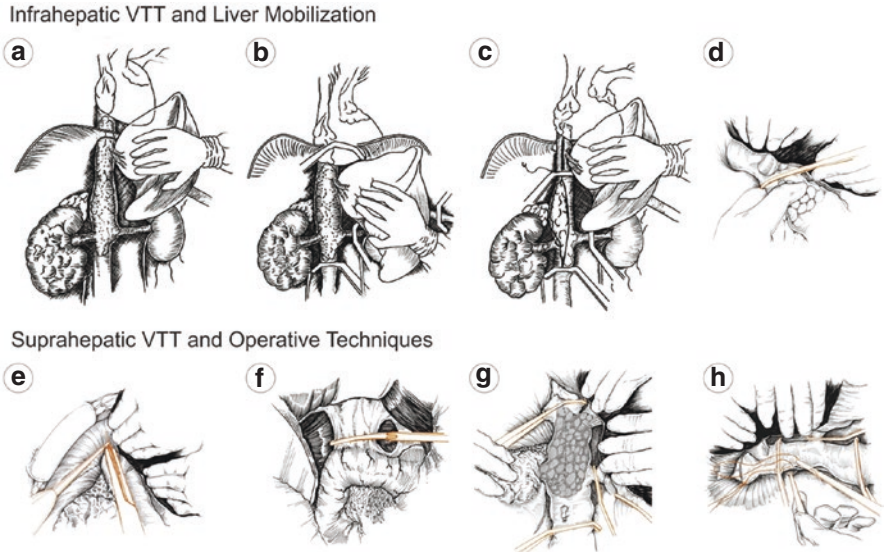

Fig. 7.4 (**a**–**c**) Depiction of liver mobilization with division of the ligamentum teres, the falciform ligament, then the right coronary ligament, and the left triangular ligament. (**d**) If the thrombus reaches a level above the major hepatic veins, surgeon can attempt to milk the thrombus downwards to the level below. (**e**) If control of suprahepatic portion of vena cava is necessary, the central tendon of the diaphragm can be opened to achieve proximal control. (**f**) The pringle maneuver allows of the vascular control of the liver, within the lesser omentum, to allow decompression of the liver in the setting of suprahepatic IVC clamping. (**g**) Once the hepatic hilum is secured, a new clamp above the hepatic veins is placed, and the inferior vena cava is incised to permit VTT extraction (**h**) Source: Reproduced with permission © Elsevier

then packed beneath a self-retaining (i.e., Thompson, Bookwalter, Omni) retractor. Early renal artery ligation should be performed next to reduce collateral circulation, decrease blood loss and potentially to facilitate VTT retraction. For large right-sided tumors, the renal artery may be more easily approached in the interaortocaval space. This minimizes kidney and IVC manipulation, theoretically reducing the risk of VTT embolization [16, 31]. For many of the level 0 VTT and some level I, "milking" of the thrombus gently into the renal vein can be attempted, with rein vein ligation or vascular clamp placement at the level of the renal vein ostium. The goal is removal of the VTT en bloc with the nephrectomy specimen without tumor spillage. If vascular clamps are used, venotomy is repaired with continuous 4-0 polypropylene suture in running fashion.

Approach to Level II–III VTT

Level II VTT necessitate control of the proximal and distal IVC control, as well as the contralateral renal vein exposure. Once the lumbar veins have been ligated and divided, the cranial extent of the VTT can be gently assessed either by manual palpation or intraoperative ultrasound. The short hepatic veins draining into the anterior surface of the IVC beneath the caudate lobe are ligated to permit exposure of the IVC superior to the thrombus. IVC control can be achieved either by Rummel tourniquets or vascular clamps. Rummel tourniquets are often favored due to the bulkiness of the vascular clamps in surgical field. In the absence of bland thrombus inferior to VTT, a trial of IVC clamping should be performed to confirm that the patient can tolerate a reduction in cardiac preload, thereby maintaining hemodynamically stability during the clamp maneuver. Following IVC clamp trial, venous flow is reestablished followed by sequential clamping of the infrarenal IVC, contralateral vein, then the suprarenal IVC.

In most cases of level II and III VTTs, where clamps are applied below the hepatic confluence and therefore, the Pringle maneuver (clamping of the portal venous triad/the hepatoduodenal ligament) is not required, bypass can be avoided due to the collateral venous return via the lumbar and portal system. For level III VTT, the thrombus may be able to be milked below the major hepatic veins [16], a technique that is facilitated by early renal arterial ligation. By retracting the VTT below the hepatic veins, hepatic drainage can be maintained, avoiding hypotension from decreased venous return, and minimizing liver congestion and postoperative hepatic dysfunction [32].

Depending on the cranial extent of the VTT, additional liver mobilization might be necessary. Liver mobilization begins with division of the ligamentum teres, the falciform ligament, then the right coronary ligament, and the left triangular ligament (Fig. 7.4a–c). The visceral peritoneum on the right of the hepatic hilum and the infrahepatic vena cava are incised in conjunction with right inferior coronary and hepato-renal ligaments, as the liver is rolled to the left [32]. We recommend involvement of a hepatobiliary or transplant surgeon to assist for this portion of the procedure, due to variety of additional liver transplant maneuvers which may be required to expose the retrohepatic IVC [33]. For a level III thrombus, vascular clamps are sequentially applied, starting with infrarenal IVC, the contralateral vein,

and hepatoduodenal ligament containing the portal vein and hepatic vein (Pringle Maneuver), and suprahepatic IVC. (Fig. 7.4d, e). It is important to clamp the hepatic hilum first when employing the Pringle maneuver, before applying the suprahepatic IVC clamp, as doing so allows the liver to decompress. It is often useful for some level III and level IV VTT to dissect the central tendon of the diaphragm until the supradiaphragmatic IVC is identified to assist with mobilization of suprahepatic IVC [32, 34, 35] (Fig. 7.4e).

Once vascular control is secured, an "L"-shaped cavotomy is performed longitudinally along the IVC starting along the anterior surface of the renal vein. The VTT and kidney are removed en bloc, and lumen of IVC is inspected for residual thrombus (bland or tumor), tumor invasion into the wall of the IVC, or small venule invasion. If vascular wall invasion is suspected or confirmed via frozen section, additional IVC resection might be necessary. As a general rule of thumb, narrowing of IVC lumen more than 30% necessitates reconstruction with biological, autologous, or synthetic graft [36]. Closure of the IVC is performed in similar fashion to level I after aspiration of air. This may be completed in Trendelenberg position, with the release of infrarenal clamp to allow for back bleeding prior to completion of cavorraphy [33]. A final renal vein margin can be excised prior to vascular repair to confirm negative vascular margins. In the event that vascular reconstruction with either patch graft or tube interposition graft is anticipated, preoperative collaboration with vascular surgery is recommended.

An additional maneuver that can be beneficial in the management of free-floating left-sided level II–III thrombi to limit hepatic ischemia and rapidly return venous drainage to the right kidney is to perform the cavotomy, reduce the thrombus into the cavotomy then replace a diagonal vascular clamp from beneath the right renal vein ostium to superior to the left renal vein ostium, then removing the suprahilar IVC clamp and Pringle's clamp. The cavotomy can then be repaired in a controlled fashion with limited blood loss while maintaining perfusion and drainage of both the right kidney and liver.

Approach to Level IV VTT

Level IV VTT resection may require sternotomy, cardiopulmonary bypass (CPB), and hypothermic circulatory arrest (HCA), which is performed in collaboration with experienced cardiothoracic surgical and cardiac anesthesia teams. As with level III VTT, some authors recommend dissection of central tendon of the diaphragm until the intrapericardial IVC is identified, where the IVC can be encircled at its confluence with the right atrium. The atrium at this point is gently pulled beneath the diaphragm, avoiding the need for sternotomy [35]. There is significant morbidity associated with higher level III and IV thrombi, including risk of myocardial infarction, brain ischemia, and shock liver, which can be minimized by circulatory bypass [19, 37]. Critics of CPB argue that it is associated with the release of inflammatory mediators, leading to coagulopathy, platelet dysfunction, and increased bleeding risk. As such, care must be taken to cauterize or ligate any bleeding vessels before CPB is initiated [38]. In addition, this maneuver is associated with risk of hepatic and renal dysfunction, with and increased risk of renal failure of

approximately 12%. Despite the associated risks of CPB and HCA, the operative mortality is significantly lower (8.3% vs. 37.5%, $p = 0.006$), than those resected using CPB alone [39].

Venovenous bypass (VVB) can be utilized for some level IV and most level III VTT, entailing the cannulation of the infrarenal IVC or femoral veins in addition to venous cannulation above the IVC (e.g., axillary, subclavian, superior vena cava, internal jugular veins) or the right atrium. VVB provides many of similar advantages of CPB in allowing for continuous venous return to the heart during clamping, without systemic heparinization [18].

Minimally Invasive Approaches in VTT Management

Advances in minimally invasive surgical (MIS) techniques have allowed surgeons to perform radical nephrectomy with venous tumor thrombectomy using laparoscopic and robotic-assisted laparoscopic techniques. Purported benefits of robotic-assisted MIS approaches include shorter postoperative stay, lower estimated blood loss, and lower transfusion rates. Single institution retrospective studies and case reports evaluating use of MIS in level I-III VTT, and hybrid approaches to the management of level IV VTT have been published, demonstrating the feasibility and safety of this approach when applied by an experienced robotic surgeon applying open surgical principles via robotic platform [40]. A recently published review of 24 robotic-assisted radical nephrectomies with venous tumor thrombectomy (92% Level I) reported non-transfusion-related complications in 26% of patients with a median LOS of 1 day [40]. Gill et al. reported their initial experience with level III venous tumor thrombectomy in 16 patients. Their study highlighted a total blood loss of 379 cc, median operative time of 4.9 h, and hospital stay of 4.5 days, and no conversions to an open approach [41]. Recent meta-analysis comparing robotic vs. open VTT perioperative outcomes reported a 39% reduction in blood transfusion rate and 22.2% reduction in complications [42]. The results, however, have to be interpreted with caution, as nearly 75% of the patients were level I and II VTT. Although these early results are encouraging, careful oncologic comparison with open surgical IVC thrombectomy is lacking and warranted to determine the proper place of robotic surgery in this arena. Additionally, the available series highlight the importance of a very experienced high volume robotic surgeon and surgical team, with the availability to rapidly convert to an open approach, if necessary, as well as prudent patient selection.

Surgical Team and Preoperative Management

Preoperative Care Coordination: (i.e., hepatobiliary, transplant, cardiothoracic, vascular surgical team and cardiac anesthesiology) consultations should be made, as appropriate for the anticipated VTT level. If the primary surgeon does not have expertise in IVC reconstruction, vascular surgery should be involved in planning and conduct of the operation in patients with higher level VTT [33]. Cardiac anesthesia should be consulted for the care of patients older than 50, as well as those with level III and IV VTT in anticipation of possible need for VVBP or CPB. Patients

with two or more risk factors for coronary artery disease as identified by American Heart Association, might require a cardiac catheterization in anticipation of CPB [43].

Hemodynamic Monitoring and Access: In all VTT patients, the anesthesiology team is of critical importance in the pre- and intraoperative planning. In addition to American Society of Anesthesiology (ASA) standard monitors, resection of tumors involving the IVC and right atrium mandates an arterial line at minimum. For intravenous access, large bore peripheral intravenous lines should be placed *above* the diaphragm due to potential IVC interruption during the case [44]. In the case of intrahepatic IVC VTT, invasive lines should mirror a liver transplantation set-up, generally including a pulmonary artery catheter, two large bore venous catheters, arterial line, and femoral line.

Massive Blood Transfusion and Coagulopathy: In conjunction with hemorrhage, acidosis, and dilution, CPB activates fibrinolysis and impairs platelet function further worsening intraoperative coagulopathy. As such, in addition to conventional coagulation assays such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, it has been suggested that assays such as thromboelastographic (TEG) and rotational thromboeleastometry (ROTEM) might be considered, to inform blood component transfusion requirements [45]. Viscoelastic monitoring assays (VEM) are routinely used in cardiac surgery and liver transplantation with the benefits of rapid turnaround and providing a personalized hemostatic profile. The turnaround time for ROTEM and TEG have been shown to be significantly shorter, with a time saving of 30–60 min in detection coagulation abnormalities [46].

In cases with large volume blood loss (>5000 ml), a massive transfusion protocol (MTP) should be initiated intraoperatively. This requires clear and concise communication between the surgical and anesthesia teams and the blood bank to achieve appropriate resuscitation. Principles of MTP include speed of transfusion, which should occur at a rate greater than exsanguination, augmented by optimal vascular access and pressurized tubing. Blood and fluid warming is important as to not to exacerbate hypothermia (<35 °C), which is exceedingly dangerous in patients undergoing MTP [47]. Generally, MTPs entail a predefined ratio of RBCs, FFP/cryoprecipitate and platelets units (random donor platelets) in each pack (e.g., 1:1:1 or 2:1:1 ratio) for transfusion, with administration of 1 unit cryoprecipitate if level for fibrinogen <100 mg/dL [48].

As noted, transesophageal electrocardiography (TEE) can provide supplemental information during surgery, including defining the cranial extent of the VTT, as well as consistency, fragility, adherence, and mobility of the thrombus. Furthermore, should the need arise for CPB, TEE provides additional benefit in its ability to guide cannula placement, and assess systolic ventricular dysfunction. Furthermore, any invasive central line placement in patient with level IV thrombus, should be performed with TEE, due to the presence of VTT in atrium, and potential risk for inadvertent dislodgment with placement [49]. With its relative ease of use, TEE is a valuable adjunct in surgical management of VTT.

Surgical Management of Locally Advanced RCC

Metastatic or locally invasive RCC remains a significant surgical challenge. While resection of localized cancer can be curative for some solid tumors, the evidence for extensive consolidative surgery for renal cell carcinoma with local invasion or metastatic disease is conflicting [50, 51]. However, despite advances in the developments and approvals of newer targeted systemic agents, a body of observational evidence supports a survival benefit in patients with locally invasive RCC who undergo complete surgical resection of all visible disease [52]. As such, careful preoperative preparation is mandatory to determine the resectability of a tumor and to anticipate what additional adjunctive procedures may be necessary in the case of locally advanced RCC to render a patient without evidence of disease.

Management of RCC with Hepatic Involvement

In the contemporary care of patients with locally advanced RCC involving the liver, surgical resection of hepatic disease in the form of partial hepatectomy or wedge resection remains an underutilized therapeutic option [53]. Overall, across all locally advanced or metastatic RCC, liver involvement is estimated to occur in about 20% of cases. Although there is substantial technical difficulty and perioperative morbidity of surgical hepatectomy, improved survival has been observed following complete resection of hepatic lesions. In a multicenter study from the Netherlands, ablation or surgical resection of liver metastases was associated with overall survival at 1, 3, and 5 years of 79%, 47%, and 43%, respectively [54]. Similarly, Joyce et al. performed a matched cohort analysis comparing outcomes between patients undergoing nephrectomy with hepatic resection to those undergoing nonhepatic, adjacent locally advanced or metastatic disease, demonstrating no significant increase in the risk of cancer-specific mortality (HR 0.63, $p = 0.53$) or all-cause mortality (HR 0.67, $p = 0.13$) between the cohorts [53]. Although this difference did not reach statistical significance, the median survival was modestly longer at 1.5 years in patients who underwent hepatic resection compared to 0.9 years in those who did not [53]. Surgical hepatectomy confers an inherent high risk with in-hospital mortality of up to 5% and a prevalence of postoperative morbidity of up to 41% [55]. Therefore, careful patient selection is key and surgical expertise in the necessary maneuvers is critical. Optimal candidates for concurrent hepatic resection include those with low metastatic burden that is anticipated to be completely surgically resectable, excellent preoperative performance status, robust nutritional status, and limited burden of comorbidities.

Management of RCC with Adrenal Involvement

The ipsilateral adrenal need not to be removed with the kidney in the absence of gross tumor invasion/ipsilateral metastatic involvement. Contrary to previously accepted clinical dogma, Lane and colleagues presented evidence that there is no "penalty" for adrenal preservation, as patients in their series who underwent delayed adrenal metastases resection ($n = 11$) fared no worse than those who had the adrenal resected at the time of renal surgery [56, 57]. Routine resection of healthy adrenal

glands exposes the patient to generally minor but unnecessary intraoperative risks. Furthermore, adrenalectomy may give rise to challenging clinical circumstances where patients may be subject to life-long adrenal insufficiency—a condition that significantly impacts quality of life and possibly life-expectancy [58, 59].

However, certain tumor characteristics have traditionally been associated with an increased risk of adrenal involvement such as tumor size (>7 cm), tumor location (upper pole), venous thrombus status, and radiographic appearance [60]. In the presence of these risk factors, concurrent adrenalectomy at the time of nephrectomy should be considered to optimize the likelihood of an R0 resection, and adrenalectomy/partial adrenalectomy should be undertaken as necessary to excise all evidence of gross disease.

Preoperative cross-sectional imaging (e.g., CT and MRI) are highly accurate at detection of adrenal gland involvement, with sensitivity and negative predictive value approaching 100% [57, 60–63]. Of note, if the adrenal gland cannot be appropriately visualized on preoperative imaging, the gland should be presumed infiltrated by the renal mass and adrenalectomy should be undertaken at the time of surgery [63]. Lane et al. suggested that intraoperative assessment of adrenal adherence/invasion by the renal tumor is reliable and could be used to guide final decisions regarding adrenal resection in cases where preoperative imaging suspicious for adrenal involvement [56].

Overall, when assessing the risk of adrenal involvement at the time of nephrectomy, the estimated risk is around 2.2%, while the risk of subsequent adrenal metastasis is 3.7% [60]. In other words, the practice of routine adrenalectomy in the average patient today would necessitate removal of nearly 199 normal adrenal glands for one involved with the RCC [64].

Management of RCC with Bowel and Pancreas Involvement

Involvement of bowel, especially duodenum at the time of surgery is rare, while involvement of pancreas via direct extension is more commonly observed [65]. In fact, the involvement of isolated adjacent organs without clinically evident metastatic disease in RCC is exceeding uncommon, occurring in <1% of patients undergoing nephrectomy [66]. The kidney's retroperitoneal location coupled with the isolation offered by Gerota's fascia, provides theoretical protection against direct tumor invasion into surrounding organs. More commonly, renal masses are observed to "indent" or compress adjacent organs than to directly invade them [65]. With that said, direct pancreatic, duodenal, and colon involvement have been reported. Ciancio et al. evaluated 11 patients with pancreatico-duodenal involvement in their study, observing isolated duodenal involvement in two cases [67]. Similarly, Karellas et al. reported no isolated duodenal involvement, while 3/40 patients had pancreatic involvement. Isolated pancreatic-duodenal resection at the time of nephrectomy may be managed with a Whipple procedure if partial duodenal resection in conjunction with distal pancreatotomy and splenectomy is unable to be safely performed [51]. Median recurrence-free survival in the setting of pancreatic or duodenal invasion can be relatively short, at approximately 2.3 months [51]. However, other authors have reported an actuarial 15% improved 5-year OS with

combined pancreatic-duodenal resection group [67].The variation in survival is most pronounced in patients with exclusive pancreatico-duodenal involvement compared to resection of other adjacent organs, which may reflect the oncologic potential related to direct invasion (as more commonly occurs in the setting of pancreatico-duodenal involvement), while involvement of the liver and other sites may reflect coexisting direct invasion and hematogenous dissemination [65].

Despite the significant improvement in OS, pancreatectomy is associated with substantial postoperative morbidity (34.8%), with 21.7% developing fistulae and 7.2% developing delayed gastric emptying [66]. Again, while there are no concise guidelines regarding patient selection to determine who will most benefit from consolidative surgery and R0 resection, a careful risk–benefit calculus incorporating performance status and tumor biology should drive decision-making regarding the resection.

The Role of Lymphadenectomy in the Management of RCC

Patients with nodal disease have poor prognosis and N stage is independently associated with reduced CSS and DFS. Conversely, as reported by Srivastava et al., lymph node positive stage III disease patients experienced similar 5-year survival to stage IV RCC as compared to LN negative stage III disease (22.7% vs. 15.6% vs. 61.9%) [68]. Overall, CSS in patients with RCC with lymph node involvement (LNI) is limited, ranging from 22% to 39% at 5 years and 11–29% at 10 years (Table 7.2) [75, 76]. LNI has shown significantly worse 5-year CSS

Table 7.2 Survival outcomes in pN10M0 RCC stratified by LND

Study	Median follow-up (months)	MFS At median follow-up	CSS At median follow-up	OS At median follow-up
1° LND for pN1Mo				
Chen (2011) [69]	15.5	29%	38% 22% at 5 years	–
Delacroix (2011) [70]	43.5	22%	– 39% at 5 years	– 37% at 5 years
Gershman (2017) [71]	102	– 16% @ 5y 15%@ 10y	– 26% at 5 years 21% at 10 years	– 25% at 5 years 15% at 10 years
Sun (2013) [72]	NR	–	– 38% at 5 years	–
Terrone (2006) [11]	14	–	– 25% at 5 years	–
Trinh (2012) [73]	17	–	– 38% at 5 years 26% at 10 years	–
Zhang (2010) [74]	42	–	– 32% at 5 years	–

MFS metastasis-free survival, *CSS* cancer-specific survival, *OS* overall survival

for node positive patients compared to node-negative stage to stage and numerous series identified LNI as one of the most important prognostic factors for survival [77, 78]. Yu et al. examined oncologic outcomes of stage III RCC (pT3N0M0 and pT1-3N1M0) patients and noted survival patterns of node positive patients resemble that of stage IV patients [79]. Others have proposed reclassification of the TNM scale to better reflect the impact of nodal involvement on survival [11, 73].

A challenge in the management of high-risk RCC is the unpredictable anatomic localization of metastases due to the heterogeneous spread by both hematogenous and variable lymphatic routes [75]. The most common lymphatic loco-regional retroperitoneal landing sites for nodal disease include paracaval and retrocaval nodes (right kidney), paraaortic and preaortic nodes (left kidney), and interaortocaval nodes (both right and left kidneys). However, lymphatic drainage may extend beyond these predicted retroperitoneal landing sites in over a third of cases [76]. At the same time, a significant number of patients present with metastatic RCC due to early hematogenous dissemination without lymph node involvement [77]. For example, Nini et al. examined dissemination patterns for node positive RCC patients and observed positive LN in right-sided tumors in the paracaval (44%), interaortocaval (40%), and renal hilar regions (16%), compared to the pre/paraaortic (67%), renal hilar region (24%), and interaortocaval (9%) regions for left-sided tumors [80]. A meta-analysis of 25 studies reviewing the role of lymph node dissection (LND) in RCC highlights the heterogeneity in reporting LND extent and the ambiguity surrounding RCC drainage patterns and LND templates [75]. Due to this variability in lymph node involvement, the role of regional LND at the time of RCC extirpation remains controversial.

Surgical Technique: Retroperitonal Lymphadenectomy for Locally Advanced Renal Cell Carcinoma

A traditional template recommended for right-sided tumors, includes hilar, paracaval (lateral side of IVC), and precaval (anterior side of IVC) with the extended right-sided templating retrocaval, interaortocaval, common iliac with or without the pre/paraaortic nodes. The analogous templates for left-sided tumors include the hilar, para/preaortic (anterior and lateral side of aorta) lymph nodes with extended templates incorporating retroaortic, interaortocaval, common iliac, and paracaval lymph nodes. Lymphadenectomy is accomplished with a standard "split and roll" maneuver along the renal vessels, aorta, and IVC, and common iliac arteries, according to the laterality of the tumor. Meticulous placement of surgical clips or suture ligatures is employed to optimize lymphostasis. Care is taken to identify the cistern chyli anterior to the first and second lumbar vertebral bodies, medial to right diaphragmatic crus and appropriately ligate lymphatics in this area to prevent a high-volume chylous leak/chylous ascites. Following synchronous LND and RN, drainage of the retroperitoneum is variably performed [81].

The optimal lymph node yield has not been defined for LND in the setting of locally advanced or cN1 RCC. Joslyn et al. observed a positive correlation between the increasing number of nodes resected and number of positive LN identified, reporting when ≥13 lymph nodes were removed, the rate of pN+ increased from 10.2% to 20.8% ($P < 0.001$) [82]. Conversely, in subgroup analysis of patients with higher risk for LN involvement, Kokorovic et al. found no association between LND and improved outcomes with higher LN yield [83].

Overall, postoperative complications following retroperitoneal LND and RN for RCC are observed in 17–26% of patients [84, 85]. One perioperative complication that may occur after RPLND is persistent lymphatic drainage with development of chylous ascites, occurring in 0.6–5.9% of cases with an average time to presentation of 17 days after surgery [86]. Risk factors include preoperative protein deficiency and electrolyte imbalances [86]. This complication can be mitigated by meticulous lymphatic control with titanium clip placement and/or suture ligasure of the lymphatic channels that are disrupted by the dissection. If detected, first line treatment includes conservative management such as bed rest, salt restriction, and a medium chain triglyceride (MCT) diet with high protein (2 g/kg body weight/day) and low fat (<20–40 g/day). Persistently high output drainage, defined as more than 1000 mL per 24 h is unlikely to resolve to conservative therapy alone, and may require subcutaneous octreotide, avoidance of oral intake with total parenteral nutrition (TPN), lymphangiogram with embolization, or surgical reintervention with ligation of perihilar lymphatic tissue if resolution or improvement is not identified in the first 2–6 weeks following treatment initiation [87].

Oncologic Outcomes Following LND

Proponents of LND advocate for the practice citing both staging (diagnostic) and therapeutic benefits citing the potential to resect micrometastatic disease, in patients who otherwise appear to have clinically organ-confined tumors [88–91]. Canfield et al. argued that extended lymph node dissection (eLND) is a critical staging tool to avoid under-staging, reporting that 17.5% patients with clinically node-negative and localized RCC had pathological node positive disease on eLND [92]. In a contemporary series of high-risk patients with RCC and tumor thrombus (cT3b-cM0), nodal involvement in cN0 patients was observed in nearly 10% of patients [93].

Several historic studies argue for the therapeutic efficacy of systemic LND at time of RN. Early work suggested that LND at the time of RN for patients with cN1 disease was associated with improved 5-year survival of 43.5% vs. 25.8% [94]. Pantuck et al. compared 129 patients with node positive disease who underwent RN and concluded those who underwent LND had an approximately 5-month survival advantage over the patients who did not undergo LND ($p = 0.0002$). In patients with pT1-3N0-3, M0 disease with an associated increase in 5- and 10-year OS of 58% vs. 55% and 56% vs. 41%, respectively

[84]. Capitanio et al. reported a statistically significant decrease in CSM in pT4M0 RCC patients treated with eLND (CSM at 1, 2, and 3 years were 65.0, 36.1, and 90% vs. 13.3, 13.0, and 6.7%, for pN0 vs. pN+ cases, $p = 0.004$) [95], with similar findings echoed by others [96, 97]. Whitson et al. performed a population-based analysis in N+M0 RCC patients and showed an association between increased LN yield and improved disease-specific survival in individuals with pN+ disease (HR 0.8, 95% CL 0.7–1.0, $p = 0.04$); however, separate analysis by Sun et al. utilizing a similar cohort with different statistical techniques found no prevailing association [72, 98].

In recent years, however, the oncologic benefit associated with LND at the time of nephrectomy for RCC has been called into question [71, 99, 100]. Most notably, EORTC 30881 was a randomized controlled trial evaluating LND in patients with cN0M0 RCC with a primary endpoint of overall survival. This trial demonstrated a prevalence of nodal involvement of 4% with no significant difference in postoperative complication, time to progression, progression-free or overall survival between patients who did and did not undergo LND at the time of RN [85]. Criticisms of the study include the high proportion of low risk patients enrolled.

To account for concerns regarding unmeasured confounding and selection bias in the retrospective literature, recent retrospective studies have evaluated associations between LND and oncologic outcomes using propensity score modeling [71]. In a multi-institutional cohort of 2722 patients with M0 RCC treated between 1990 and 2010, 45% of patients underwent LND [71]. The rate of pN1 disease was 6.3%. LND was not significantly associated with a reduced risk of distant metastases, cancer-specific or overall survival overall or among patients with cN1 disease. Furthermore, the authors noted that neither extended LND nor the extent of LND was associated with an improvement in oncologic outcomes. Using similar methods, Kokorovic et al. performed a large, multi-institutional analysis of M0 RCC patients undergoing RN and demonstrated no association between LND and improved OS, CSS or RFS [83]. A systematic review on the topic including 51 studies similarly demonstrated that LND yields independent prognostic information, such that nodal involvement is independently associated with adverse prognosis in the M0 setting [pooled OS hazard ratio 1.02 (95% CI 0.92–1.12)] [101]. Among patients with high-risk M0 disease, the authors noted that a small proportion of patients with pN1 disease did demonstrate durable long-term oncologic control with 10-year cancer-specific survival of 21–31%, however, LND was not significantly associated with either cancer-specific or overall survival.

As such, the 2019 EUA guidelines have removed recommendation for the use of routine LND during surgery for RCC, while National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) Guidelines emphasized the use of LND to provide information primarily for staging and prognostic purposes but did not recommend routine LND in patients with clinically negative node [102–105].

Surgical Decision-Making in Locally Advanced RCC and Patient-Specific Risk Factors

Surgical intervention for advanced RCC is associated with substantial risk of morbidity and mortality. Therefore, careful patient selection weighing the risks and benefits of intervention is imperative. An in-depth evaluation of the patient-specific factors, such as comorbidities and performance status, and the tumor's oncologic potential, must be weighed carefully with patient preferences and priorities. What follows is a discussion of objective evaluations of patient and tumor-centric factors that can be employed to provide an evidence-based preoperative patient evaluation for prognostication and treatment election. This section will also discuss strategies for patient optimization related to preoperative evaluation findings ("prehabilitation" interventions), and will discuss indications for consideration of preoperative systemic therapy.

As previously discussed, the average age of diagnosis of RCC in the USA is 64 years old [106]. More importantly, patients with RCC have approximately twice the number of comorbid conditions as their age-matched peers [5]. Thus, assessment of perioperative and postoperative risk for morbidity is critical in RCC patients. Patient comorbidities are often quantified by the Charlson Comorbidity Index (CCI) or the ASA Physical Status Classification System (ASA) score. Both CCI and ASA have been correlated with higher complication rates in patients with advanced RCC [107].

Beyond comorbidities, specific and highly predictive patient-centric prognostic factors include functional status and frailty, which is defined as a state of increased vulnerability to developing complications or mortality after a stressor event [108]. The most widely utilized measure of patient performance status (PS) is the Eastern Cooperative Oncology Group (ECOG) criteria [109, 110] which evaluates a patient's physical abilities, ranging from with "fully active" (0) to "completely disabled" (4). ECOG PS, and the analogous scale of Karnofsky Performance Status (KPS) are strong predictors of OS and PFS in metastatic RCC [111]. However, it is important to remember this measure is an estimate made by physicians that is subject to bias and may not match the patient's assessment of their own functional status [112].

Similarly, frailty can be challenging to reproducibly quantify. A commonly employed assessment is the Fried Frailty criteria, which incorporates assessments of fatigue, weight loss, grip strength, walking speed, and low energy expenditure [113].The Fried criteria and other frailty metrics can aid in prediction of outcomes in cancer patients with advanced age. However, poor sensitivity and interobserver variability of many of these scales has been used to support the contention that all cancer patients of advanced age should undergo a complete geriatric assessments (CGA) [114].

A CGA is a multidimensional evaluation of a patient's health that may identify potentially modifiable risk factors to improve outcomes. The core domains assessed in a standard CGA include functional status, comorbidities, polypharmacy, cognition, psychological status/mental health, social support, and nutritional reserve, using validated assessments. GCAs are generally administered by trained medical professionals with expertise in geriatric medicine however recently validated

self-assessments have been developed and implemented successfully in patients with cancers such as the Cancer and Aging Resilience GA (CARE-GA) [115]. CGAs offer additive specificity over conventional assessments of performance status. For example, in patients with a normal ECOG PS or normal ASA score, actionable vulnerabilities will be detected in 61% and 65% of patients, respectively, if a CGA is utilized. As such, multiple current guideline bodies advocate for the use of a geriatric screening tool or CGA in older adults with cancer prior to treatment election [116–119].

Body composition, nutritional status, and the presence of systemic inflammation are important "host" factors that are associated with prognosis in RCC. Sarcopenia, a critical loss of muscle mass, is associated with increased risk of mortality and recurrence after nephrectomy in both localized and metastatic RCC [120, 121] and provides more nuanced measure of a person's body composition than the traditional body mass index (BMI) measurement. In addition, poor nutritional status, as measured by hypoalbuminemia, has been associated with a 10-fold increased risk of early mortality in advanced RCC with TT [122]. Pro-inflammatory states can also be assessed using accessible preoperative laboratory tests. Low albumin, elevated CRP and ESR, neutrophil-to-lymphocyte ratio (NLR) and IL-6 portend a worse prognosis in advanced RCC [123, 124]. A common prognostic model for metastatic RCC, the International Metastatic RCC Database Consortium (IMDC) score, relies on the combination of serum inflammation markers and patient performance status to predict oncologic outcomes [125].These patient-centric metrics are readily accessible to clinicians. Gathering these important data during the preoperative patient assessment can provide powerful insights into the patient's potential disease trajectory.

Surgical Management versus Neoadjuvant Systemic Therapy in Advanced RCC

Neoadjuvant therapy for RCC has been proposed with the goal of reducing metastatic burden prior to surgical resection. In the nonmetastatic setting, proposed benefits of neoadjuvant therapy include facilitating surgical resection with reductions in the morbidity and mortality associated with nephrectomy and resection of neighboring organs. With advent of novel targeted agents and immunotherapies, there is interest in the potential of presurgical therapy to shrink tumors, reducing the need for synchronous adjacent organ resection, facilitating partial nephrectomy when feasible, and downstaging of IVC thrombus [126]. Figure 7.5 depicts a representative patient's burden of disease following 3 months of neoadjuvant immunotherapy prior to surgical debulking in advanced non metastatic RCC.

Neoadjuvant therapy theoretically offers the advantage of potential tumor cytoreduction, improving prospects for subsequent surgical resection or feasibility of nephron-sparing surgery [127]. The utility of neoadjuvant tyrosine kinase inhibitors (sunitinib and sorafenib) has been investigated in advanced RCC patients with tumors deemed unsuitable for primary resection. One initial study demonstrated

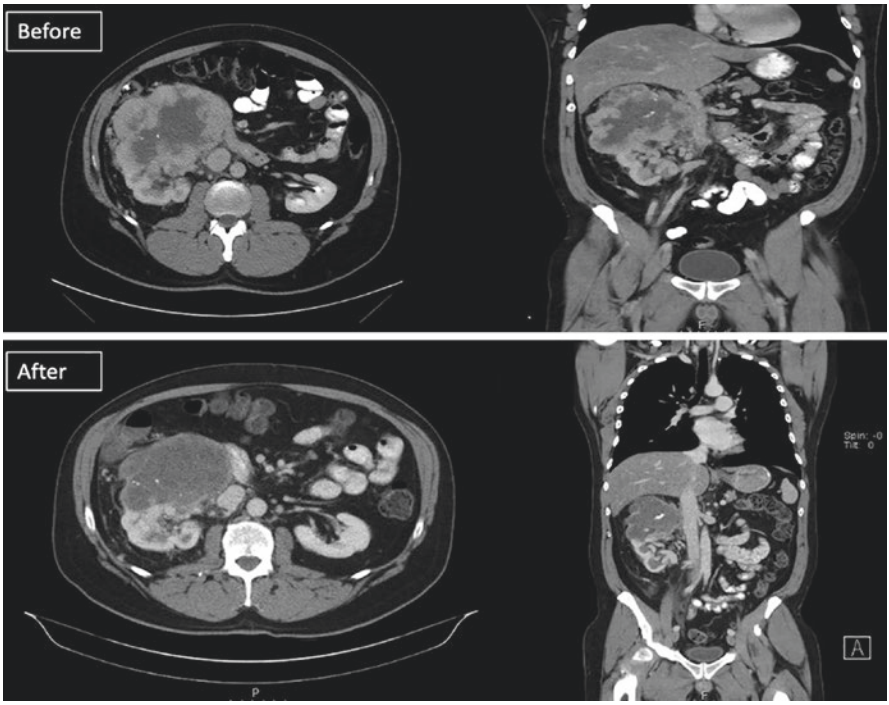

Fig. 7.5 Depiction of neoadjuvant immunotherapy (Axitinib 5 mg BID and Pembrolizumab 200 mg Q3weeks), with change in tumor volume and nearby organ infiltration over 3 months. Prior to neoadjuvant therapy, infiltration into the pancreas, duodenum and large bowel visualized on the scan. Post infusion reduction 22% in tumor volume with cystic degeneration as well as regression of disease from nearby organs, allowing for organ preservation during radical nephrectomy. Source: Original

tumor shrinkage in 42% of patients, with an average decrease in size of 24% and 21% of patients undergoing subsequent nephrectomy [128]. Additional small, early studies demonstrated reduction in tumor size in 77–85% of patients [129, 130]. Subsequently, a small prospective trial has demonstrated a reduction of tumor diameter of 28% with axitinib [131], while another retrospective study found a reduction of 32% with sunitinib with no additional morbidity after partial nephrectomy [132]. Overall, several smaller studies demonstrate modest reduction in tumor size with subsequent feasibility of surgical intervention. However, most studies are small retrospective or phase II prospective trials, thus are insufficient to inform broader guidelines. Larger prospective studies are lacking to further support the utility of TKIs in the neoadjuvant setting.

Recent approval of immune checkpoint inhibition therapy for first line advanced RCC treatment has propelled further investigation of these agents in the neoadjuvant setting. Specifically, using PD-L1 inhibitors, which block tumor expression of the programmed death ligand (PDL) and allow for T-cell recognition and attack of cancer cells, preventing the cancer cells from avoiding immune response [133]. In a

trial of immunotherapy in previously untreated patients with advanced RCC, the combination of avelumab (a PD-L1 inhibitor) and axitinib resulted in a progression-free survival of 13.8 months, versus 8.4 months with sunitinib [134]. Several ongoing studies are aimed at evaluating the potential of PD-L1 inhibitors and other immunotherapies for neoadjuvant therapy in advanced RCC using the response evaluation criteria in solid tumors (RECIST) criteria [133]. It remains to be determined the full impact of these immunotherapies on RCC treatment, but they have exciting potential to expand the arsenal of treatments available for patients with advanced RCC not amenable to up-front surgical resection.

At this time, selection for presurgical therapy in the absence of clinical metastatic disease is not considered standard of care and should be considered only within the context of a clinical trial. Integration of this approach into routine practice is predicated upon expected benefit with respect to clinically significant downstaging balanced with a patient's willingness and ability to tolerate the potential toxicity profile of systemic therapy without substantial decline in functional status, and carries the risk of progression that may preclude surgical excision [131].

Adjuvant Therapy for Locally Advanced RCC

High-risk RCC is associated with high rates of recurrence despite definitive surgical resection. Due to the presence of micrometastases, up to 40% of patients will experience local or distal recurrence after surgery; this number approaches 75% for patients with high-risk features (≥T3 or node positive disease) [135]. Surgery followed by surveillance is the mainstay of care for patients with advanced RCC. While more than 80% of patients with locally advanced disease are considered at high risk of recurrence, limited adjuvant treatment recommendations have been available for these patients, until recently.

Due to the success of VEGF therapy in metastatic RCC, there have been a plethora of adjuvant anti-angiogenic drug trials. To date, six large randomized controlled trials have evaluated the efficacy of such agents in the postoperative setting. Most of these trials use drugs approved for the treatment of metastatic RCC under the assumption that moving these agents to the adjuvant setting could eliminate micrometastatic disease or prolong progression to radiographically detectable recurrence [136]. With the exception of the disease-free survival (DFS) advantage observed in S-TRAC, these trials have had limited success [137].

Several critical trial design differences (patient selection, study design, and drug exposure) could partially explain the observed disparate results. The first discrepancy centers around trial endpoints and outcome measures. Overall survival (OS) is the most intuitive outcome and has historically been considered the primary outcome of interest. However, the dogma of OS as "gold standard" has recently come into question. As the number of therapeutic options increases rapidly, surrogate endpoints (such as DFS) have increasing relevance. When death occurs longer after randomization, OS becomes more susceptible to confounding factors that may not

influence DFS, making DFS an appealing primary outcome [138]. Most importantly, DFS and OS are equally valued by RCC survivors [139].

Clinical trial enrollment for adjuvant treatment of high-risk RCC requires thoughtful risk stratification to select patients that are at highest risk of subsequent metastasis, thus most likely to benefit from treatment. Given that the risk–benefit ratio does not favor adjuvant therapy for all people, appropriate risk stratification helps avoid harm/treatment toxicity in patients with low risk of recurrence/metastasis. There are two validated prognostic methods assess relapse risk for RCC, the University of California Los Angeles Integrated Staging System (UISS) and the stage, size, grade, and necrosis (SSIGN) score [140, 141]. Unfortunately, there is no consensus on which prognostic model to use in clinical trial design, which adds heterogeneity to trial comparison. By standardizing clinical trials to the use of one prognostic model, there is potential to streamline clinical trial inclusion and homogenize outcomes. Finally, differences in drug exposure, including the starting dose, de-escalation protocols, and dose maintenance, may also influence outcomes.

Historical Trials

Historically, many adjuvant therapies have been evaluated for patients with high-risk RCC, including radiotherapy, hormone-based therapy, cytokine therapies, vaccine therapy, and chimeric monoclonal antibody studies, though these studies were largely unsuccessful. A meta-analysis showed that radiation therapy after resection of RCC with a high risk of relapse decreased the risk of local recurrence (OR 0.46, 95% CI 0.29–0.71; $p < 0.001$) but not the risk of DFS (HR 0.73, 95% CI 0.30–1.79; $p = 0.49$) or 10-year OS OR 0.77, 95% CI 0.25–2.39; $p = 0.65$) [142]. Given RCC's potentially hormone-responsiveness (reported estrogen and androgen receptor expression), a prospective randomized trial compared medroxyprogesterone acetate to observation after radical nephrectomy and found no significant difference in relapse rate (32.7% vs. 33.9%) [143].

Cytokine therapies (interferon-alpha and Interleukin-2) in the adjuvant setting ultimately failed to improve DFS or OS, and were associated with high levels of treatment toxicity [143–148]. There have been five vaccine therapy trials using autologous irradiated tumor mixed with bacillus Calmette-Guérin, tumor-derived heat-shock protein-peptide complex, and autologous renal tumor cells [149–152]. The only study of the five to demonstrate improvement in DFS (the autologous renal tumor cell study) had significant flaws (study was unblinded and baseline characteristics were unbalanced) limiting its impact and resulting in concerns regarding its external validity. As such, adjuvant vaccine therapy has not been implemented clinically. Finally, the chimeric monoclonal antibody gerituximab, which targets carbonic anhydrase IX, was studied for high-risk RCC without improvement in DFS (HR 0.97, 95% CI 0.79–1.19, $p = 0.74$) or OS (HR 0.99, 95% CI 0.74–1.32, $p = 0.94$) (Table 7.3) [153].

Table 7.3 Historical adjuvant therapy trials in RCC

Category	Author	Year	Study type	Therapy details	DFS At median follow-up	OS At median follow-up
Radiotherapy	Rodriguez-Fernandez et al. [142]	2019	Meta-analysis	High-dose IL-2 bolused postoperatively	HR 0.73, 95% CI 0.30–1.79; $p = 0.49$	*3 years*: OR 0.58 (95% CI 0.30–1.10); $p = 0.09$ *5 years*: OR 0.71 (95% CI 0.46–1.11); $p = 0.14$ 10 years: OR 0.77, 95% CI 0.25–2.39; $p = 0.65$
Cytokine	Clark et al. [144]	2003	Clinical trial	Interferon alpha-NL for 12 cycles	IL-2 32% (95% CI 16–66%) vs. OBS 45% (29–69%), $p = 0.431$	
	Messing et al. [145]	2003	Clinical trial	Low dose IL-2 and IFNa for one 4-week cycle	41% vs. 37%, $p = 0.33$	62% vs. 51%, $p = 0.09$
	Passalacqua et al. [146]	2014	Clinical trial	IL-2, IFNalpha, 5-FU	HR 84% (95% CI, 0.54–1.31); $P = 0.44$	*5 years:* HR 1.07 (95% CI, 0.64–1.79); $p = 0.79$
	Aitchison et al. [148]	2014	Clinical trial	Autologous, tumor-derived heat-shock protein (glycoprotein 96)–peptide complex	HR = 0.84 (95% CI 0.63–1.12); $p = 0.233$	
Vaccine	Wood et al. [150]	2008	Clinical trial	Autologous renal tumor cell vaccine	HR 0.923 (95% CI 0.73–1.17); $p = 0.506$	–
	Jocham et al. [151]	2004	Clinical trial	Gerituximab (targets carbonic anhydrase IX)	HR 1.58 (95% CI 1.05–2.37)	–
Chimeric monoclonal antibody	Chamie et al. [153]	2017	Clinical trial	High-dose IL-2 bolused postoperatively	HR 0.97 (95% CI 0.79–1.19), $p = 0.74$	3 years: HR 0.99 (95% CI 0.74–1.32), $p = 0.94$

DFS disease-free survival, *OS* overall survival

Current Approaches to Adjuvant Therapy

Anti-angiogenic Therapies (Anti-VEGF, TKI and mTOR Inhibitors)

Angiogenesis plays a known role in the pathogenesis of RCC; however, anti-angiogenic therapies targeting the VEGF pathway through tyrosine kinase (TKI) and mammalian target of rapamycin (mTOR) inhibition have shown mixed results for survival and progression when used in the adjuvant setting.

S-TRAC was a prospective, randomized, double-blind, phase 3 trial that randomized patients with ccRCC, ECOG ≤2, stage III or higher and/or regional lymph node positive disease using the UISS criteria to adjuvant sunitinib vs. placebo [140]. Among patients treated with sunitinib, median DFS was 6.8 years (95% CI 5.8-NR) versus 5.6 years (95% CI 3.8–6.6) in the placebo arm (HR 0.76, 95% CI 0.59–0.98, $p = 0.03$). At 3 years, 64.9% of the sunitinib group and 59.5% of the placebo group were disease free [137]. Similarly, at 5-year timepoint, the sunitinib-treated patients had 8.0% higher disease-free rate than placebo, which the authors argued confirmed the durability of benefit associated with adjuvant sunitinib over time. Serious adverse events occurred in 21.9% of the sunitinib group vs. 17.1% of the placebo group. In comparing QLQ-C30 and ED-5D scores for QOL, clinically significant declines in QOL were seen with diarrhea (mean difference, 12.0 points; 95% CI, 9.6–14.4; $p < 0.001$) and loss of appetite (mean difference, 10.0 points; 95% CI, 7.9–12.2; $p < 0.001$); no clinically meaningful difference in EQ-5D or EQ-VAS occurred in either group [137]. This publication led to the approval of sunitinib for adjuvant treatment of patients at high-risk of recurrence of RCC following nephrectomy in the USA [154].

However, due to the adverse-event profile and conflicting conclusions of S-TRAC vs. other similar trials (e.g., the ASSURE trial, discussed below) regarding overall benefit, adjuvant therapy with sunitinib is not approved in other parts of the world [155]. Real-world data has shown that even among high-risk cM0 patients, only 2.6–3.5% receive adjuvant targeted therapy [156]. Secondary analysis with mature data from S-TRAC confirmed DFS improvement with adjuvant sunitinib for groups at higher risk of recurrence (T3, no or undetermined nodal involvement, Fuhrman grade ≥2, and ECOG PS ≥1; or T4 and/or nodal involvement) and those with Fuhrman grade 3/4. Unfortunately, neither the original nor updated analysis for S-TRAC had mature data with overall survival; however, these updates suggest that there was no detrimental effect on OS for sunitinib treatment [157].

Additional trials are noteworthy in the study of adjuvant therapy for RCC with high risk of relapse, despite failure to meet primary outcomes.

The predecessor to S-TRAC was the **ASSURE** trial, which was the first trial to investigate VEGF inhibitors as adjuvant therapy for locally advanced, high-risk RCC [158, 159]. This phase III study enrolled pT1b (grade 3–4), pT2-4 or Tany, N+ M0 disease to sunitinib, sorafenib or placebo. Unfortunately, this study showed no difference between treatment and control arms in terms of DFS and OS. Median DFS was 70 months (5.8 years, IQR 1.6–8.2) for sunitinib, 73.4 months (6.1 years, IQR 1.7–NE) for sorafenib, and 79.6 months (6.6 years, IQR 1.5–NE) for placebo,

which did not differ between groups. Because ASSURE allowed enrollment of any histologic subtype of RCC, subgroup analysis was performed for ccRCC and no benefit was seen with sunitinib or sorafenib when compared to placebo (sunitinib vs. placebo, HR 1.02, 97.5% CI 0.85–1.22, stratified log-rank p=0.89; sorafenib vs. placebo, HR 0.99, 97.5% CI 0.83–1.19, stratified log-rank $p = 0.8734$).

In comparing the results of the ASSURE and S-TRAC trials, noteworthy differences may have impacted the trial outcomes. The two trials had distinctly different inclusion criteria, which created dissimilar patient populations (e.g., ASSURE allowed enrollment of non-ccRCC and stage 1 tumors). Although both trials started with 50 mg/day dosing of sunitinib, ASSURE amended the study protocol to 37.5 mg/day and allowed dose reduction to 25 mg/day, whereas S-TRAC remained consistent with 50 mg/day but allowed dose reductions to 37.5 mg/day [157, 160].

The **PROTECT** trial (pazopanib, a tyrosine kinase inhibitor (TKI)), failed to show improvement in DFS over placebo (HR 0.86; 95% CI, 0.70–1.06; $P = 0.165$) with 600 mg dosing; however, secondary analysis of 800 mg dosing did show significant improvement in DFS (HR of 0.69 (95% CI, 0.51–0.94)) [161]. Subsequent studies have suggested that it is not the dose of pazopanib itself that is predictive of clinical response, but alternatively the serum trough concentration of pazopanib that derives clinical benefit; this knowledge may be of use in the design of future trials [162].

In the **ATLAS** trial, axitinib (a selective inhibitor of VEGFR 1, 2, and 3) was evaluated for DFS and OS. Ultimately, the trial was stopped after interim analysis due to futility. Of note, ATLAS was designed to include patients at lower risk of recurrence, and subgroup analysis of patients at high risk of recurrence demonstrated a significant improvement in DFS associated with axitinib receipt (HR 0.641, 95% CI = 0.468–0.879); $P = 0.0051$). This led investigators to conclude that adjuvant therapy may have the most potential for individuals at highest risk of recurrence [163]. As such, future trials may choose to homogenize inclusion criteria and focus only on high risk of recurrence in order to have the greatest chance of trial success.

In the 3-armed **SORCE** trial, adjuvant sorafenib administration for 1-year and 3-year durations were compared with placebo. Restricted mean survival time (RMST) was equivalent for 3 years of sorafenib vs. placebo (6.81 vs. 6.82 years, respectively; RMST difference, 0.01 year; 95% CI, −0.49 to 0.48 year; $P = 0.99$) [164]. Given these findings, sorafenib was not recommended as adjuvant therapy after nephrectomy for RCC.

In a meta-analysis of the five major TKI trials (S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE), analysis suggested significantly longer DFS (pooled HR: 0.88, 95% CI: 0.81–0.96, $P = 0.004$), but not OS (pooled HR: 0.93, 95% CI: 0.83–1.04, $P = 0.23$) with adjuvant therapy compared with placebo. However, TKI therapy was associated with significantly higher rates of high-grade treatment-related adverse events (OR 5.20, 95% CI: 4.10–6.59, $p < 0.00001$). Based on this meta-analysis, authors conclude that the risk-to-benefit ratio of adjuvant TKI is insufficient, except for select patients with very poor prognosis [165].

Immune Checkpoint Inhibitors

The recent success of antibody-based immunotherapy and approval of both nivolumab monotherapy and combination of nivolumab with ipilimumab for mRCC have shifted adjuvant clinical trial evaluation to immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway.

Keynote-564 evaluated pembrolizumab monotherapy vs. placebo for patients with advanced clear cell RCC (ccRCC) (tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph node metastasis, or stage M1 with NED) in a phase III RCT [166]. At present, the first interim analysis has suggested that adjuvant pembrolizumab therapy improved its primary endpoint (DFS) when compared to placebo (HR 0.68 (0.53–0.87), $p = 0.002$), though the median DFS was not reached for either group. At 24 months, the estimated percentage of patients who were alive and recurrence-free was 9.2% higher for the adjuvant pembrolizumab group [77.3% (95% CI, 72.8–81.1) vs. 68.1% (95% CI, 63.5–72.2)]. Serious adverse events were observed in 20.5% of the pembrolizumab group vs. 11.3% of the placebo group; similarly, 34.6% of pembrolizumab and 5.8% of placebo group experienced immune-mediated adverse events. The difference in DFS was further analyzed in a subgroup analysis based on PD-L1 status, where having a PD-L1 combined score of ≥1 incurred a HR 0.67 (0.51–0.88). There was no clinically meaningful change in the pembrolizumab treated group in terms of symptoms or quality of life (as measured by FKSI-DRS and EORTC QLQ-C30 scores, respectively). The authors conclude that this trial supports the use of pembrolizumab as adjuvant immunotherapy in patients with renal cell carcinoma at intermediate- or high-risk of disease recurrence, and these results have led to recent FDA approval of pembrolizumab for this indication.

Ongoing Clinical Trials

Given the success of ICI in metastatic RCC and success of adjuvant pembrolizumab within Keynote-564, there is eager anticipation of the final results of several recently closed clinical trials, which unfortunately all demonstrated negative results. The **PROSPER RCC trial** (NCT03055013) was a phase III randomized trial evaluating perioperative (both neoadjuvant and adjuvant) nivolumab. In theory, the neoadjuvant treatment is designed to prime the immune system for enhanced efficacy of the subsequent adjuvant treatment; the neoadjuvant aspect of this study design distinguishes PROSPER from the other studies. **IMmotion010** (NCT03024996) was a phase III RCT of atezolizumab monotherapy versus placebo for patients with RCC at high risk of recurrence after nephrectomy. The **CheckMate-914** (NCT03138512) phase III RCT will evaluate nivolumab monotherapy, nivolumab combined with ipilimumab, and placebo for patients with localized RCC after radical or partial nephrectomy.

In addition to trials for ICIs, the EVEREST trial of mTOR inhibition using everolimus is being evaluated in patients with histologically confirmed RCC (all histologic subtypes) after surgical therapy [167].

Summary: Adjuvant Therapy for High Risk Localized RCC After Nephrectomy

After surgical intervention for high-risk RCC, many patients experience disease recurrence or metastasis, so advancements in adjuvant therapy are critically needed. Despite many clinical trials in this space, there has been a high rate of failed RCTs. Upon review, some clinical trial failures may be attributable to the heterogeneity of enrolled patients (although all were categorized as "high-risk" of recurrence, there is a stark contrast between not-so high risk and stage IV RCC). The major RCTs used different risk stratification methods (ATLAS and PROTECT use TNM and FG; ASSURE and S-TRACT used UISS). Similarly, histopathologic heterogeneity (ccRCC and non-ccRCC in the same study) may be responsible for differential outcomes and skewed results. As we move forward studying adjuvant therapy for RCC, standardizing inclusion criteria, risk stratification, and inclusion of molecular features has significant potential to help move these treatments into clinical practice. Urologic oncologists have a key role in this space and should consider referring patients with locally advanced, high-risk RCCs to medical oncology for a balanced discussion regarding the risks and benefits of adjuvant therapy.

Conclusions

In this chapter we reviewed the management of locally advanced, nonmetastatic renal cell carcinoma. While the prevalence of incidentally detected small renal masses increases, a considerable proportion of patients present with locally advanced disease. We highlighted the importance of careful diagnostic evaluation and risk stratification of patients, the critical need for meticulous preoperative preparation and the often-multidisciplinary care patients with these tumors to optimize patient outcomes. The field is moving forward as we further evaluate and define the role for perioperative systemic therapy in this space, with the goal of improving survival and reducing treatment-associated morbidity and mortality.

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