Kidney Cancer

Recent Advances in Surgical and Molecular Pathology

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Preface

Conceptual knowledge regarding kidney cancer has been undergoing a paradigm shift over the past few years. Significant advancements have been made in the development of molecular targeted therapies with implications for the role of precise tumor subtyping by the pathologists, progress in molecular diagnostics with cytogenetic analysis, revisions of kidney tumor classification with incorporation of newly recognized and evolving entities, updates in cancer staging systems, and advances in imaging with applied theranostics.

This textbook provides a comprehensive overview of pathology of kidney tumors along with radiological features and up-to-date treatment strategies that enable the readers to avail this information in day-to-day pathology sign-out as well as interaction with clinical colleagues of different disciplines. It also serves as a referral resource for the current medical or surgical practice while preparing for examinations or maintenance of certification. The chapters contain an updated review of important pathologic parameters mandated for diagnosis and reporting with emphasis on updated information regarding new developments in this interesting field. Numerous high-resolution color images aptly illustrate the various pathologic entities and their features as outlined in the text section along with tables that highlight the differential diagnoses and salient ancillary features.

Each chapter is authored by experts with significant experience in the diagnosis and management of kidney cancers. The editors wish to acknowledge their contributions to this book as well as to the ongoing developments in the field of kidney cancers. The goal of this text is to provide up-to-date information on renal tumor pathology, radiology, and management that are required in daily practice. We hope that this book serves as a quick reference for all categories of readers alike.

We are indebted to our colleagues and friends who contributed slides and images to this volume and to clinical colleagues who contribute interesting and challenging cases to our pathology service. As lifelong learners, we continue to be amazed with all the new developments in kidney cancer that prompt us to revisit old concepts and establish newer parameters, allowing our vast field to progress.

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Part I
Clinical Aspects

Chapter 1
Surgical Consideration in Renal Tumors

Dalsan You, Se Young Choi, Jeman Ryu, and Choung-Soo Kim

Renal cell carcinomas (RCCs) account for approximately 2–3% of adult malignancies and 90–95% of kidney tumors [1, 2]. In 2012, there were approximately 338,000 new cases of RCC, and 143,000 deaths occurred from kidney cancer worldwide [3]. In 2017, there were approximately 64,000 new cases and 14,000 deaths in the United States [4]. As a result of increased utilization and availability of ultrasonography and cross-sectional imaging, more renal masses have been identified and stage migration has occurred; namely, renal masses are detected at much earlier stages. Of 236,975 RCC patients registered in the National Cancer Data Base, the percentage of patients with stage I disease significantly increased from 43.0% in 1993 to 57.1% in 2004, and the proportion of stage IV disease decreased from 27.4% to 18.7% over the 12-year period [5]. Traditionally, partial and radical nephrectomies are therapeutic surgical options for long-term cure in localized RCC. Globally, 25% of patients with RCC have metastatic disease at diagnosis, and 20–40% of patients develop metastatic disease after nephrectomy. The prognosis for patients with metastatic RCC was poor, with a median survival of 1 year and a 2-year survival rate of 10–20% [6]. Since the inception of new systemic agents, the survival of patients with metastatic RCC has been prolonged [7]. However, these new agents rarely provide complete (less than 1%) or long-term responses [8–10]. Therefore, surgical resection of the primary tumor and metastases is considered

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important for cure or long-term survival. In this chapter, we summarize the contemporary surgical management of localized, locally advanced, and metastatic RCC.

Surgical Treatment of Localized Renal Cell Carcinoma

The incidence of localized renal mass detection has increased due to the widespread use of cross-sectional imaging [11]. Clinical T1 renal masses are heterogeneous; 20% of them are benign and only about 20% exhibit potentially aggressive carcinoma at diagnosis [12]. Multiple management options, including surgery, thermal ablation, and active surveillance, are now available [1, 13, 14]. Urologic/non-urologic morbidities of each option, the patient's coexisting conditions, life expectancy, and the treatment provider's experience should be taken into consideration in tumor management [14, 15].

Renal mass biopsy can be used to assess tumor grade and histology, given that clinical and radiographic factors have very limited accuracy in predicting tumor aggressiveness [16, 17].

Partial Nephrectomy

In 1890, Czerny described nephron-sparing surgery for RCC. However, high complication rates were reported in the early years. Partial nephrectomy techniques were developed after taking into consideration detailed renal imaging, various techniques preventing ischemic renal damage, renal vascular surgery expertise, deleterious effects of chronic kidney disease, a large number of incidentally detected low-stage RCCs during medical checkups, and good survival rates after this treatment (Fig. 1.1) [18]. Table 1.1 summarizes the indications of partial nephrectomy (nephron-sparing surgery).

Traditionally, partial nephrectomy is considered in cases where radical nephrectomy can be associated with high risk of chronic kidney disease or dialysis [18]. Patients with bilateral RCC or RCC in a solitary functioning kidney are relevant. Another indication

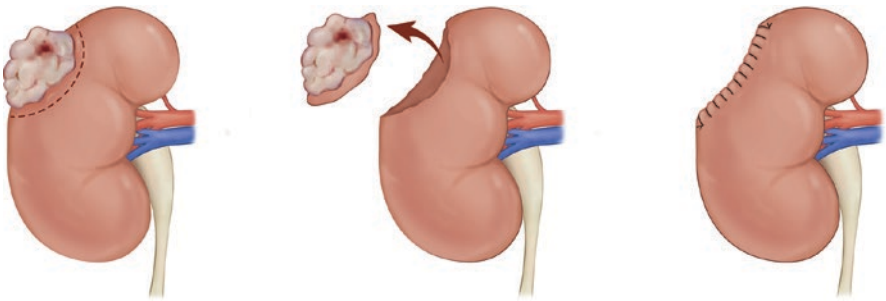

Fig. 1.1 The concept of partial nephrectomy

Table 1.1 Indications for partial nephrectomy (nephron-sparing surgery)

Absolute
Bilateral tumors
Tumor in single kidney
Poorly functioning or nonfunctioning contralateral kidney
Relative
Renal dysfunction
Hereditary renal cell carcinoma
Genetic predisposition to metachronous renal cell carcinoma
Systemic threats to future renal function (e.g., diabetes mellitus, hypertension)
Local threats to either kidney (e.g., obstructive uropathy, stone disease, renovascular disease)
Elective
Small renal mass and normal contralateral kidney

of partial nephrectomy is unilateral carcinoma when the opposite kidney can potentially have decreased function due to another cause, such as renal artery stenosis [19]. Partial nephrectomy can also preserve functioning renal tissue in patients with bilateral synchronous RCC. If the tumors are large, staged procedures can be performed. However, patients with RCC involving an anatomically or functionally solitary kidney should be warned about the risk of postoperative dialysis. In a previous study, 4.5% of patients were followed up for 3.6 years after surgery [20]. Renal function was preserved in the majority of patients who underwent partial nephrectomy, in accordance with the aforementioned indications [1, 18]. Local recurrence rates of 3–5% were reported after partial nephrectomy, due to many challenges such as hilar tumors, minimized excision of functional parenchyma, or multifocal tumors [1, 18].

Partial nephrectomy presently is the treatment of choice for the management of clinical T1 RCC in patients with a normal contralateral kidney [13, 21]. Several reports comparing partial with radical nephrectomy have showed comparable results in terms of oncologic and renal functional outcomes [1, 22–25]. Previous reports of partial nephrectomy for T1a RCC showed 1–2% local recurrence rates and over 90% cancer-free survival [18]. In addition, similar promising results were reported in clinical T1b tumors [26–28].

To determine the possibility of partial nephrectomy in RCC, the exclusion of locally extensive or metastatic disease with preoperative testing and additional specific renal imaging, identifying the relationship of the tumor with the intrarenal vascular supply and collecting system, is necessary. Renal imaging methods include computed tomography (CT) and renal arteriography/venography, and presently, three-dimensional volume-rendered CT is considered an accurate imaging modality [29].

The performance of partial nephrectomy by minimally invasive methods has recently evolved. Minimally invasive partial nephrectomy is a challenging procedure because poor visualization due to suboptimal hemostasis and the absence of tactile sensation could result in positive resection margins at surgery. However, various techniques, including the occlusion of renal vasculature and intracorporeal suture closing the collecting system and repairing the capsular defect, have been developed to resolve these problems [30, 31]. The oncological outcomes of laparo-

scopic and open partial nephrectomies were excellent for clinical T1 renal cortical tumors in the previous 10-year follow-up reports of carefully selected patients with limited risk of recurrence [32]. Early unclamping maneuver immediately after running sutures in deep parenchyma across the defect reduced warm ischemic times and postoperative bleeding rates [33, 34].

The relatively small size of remnant renal parenchyma after partial nephrectomy can lead to long-term deterioration of renal function with hyperfiltration renal injury [35]. The occurrence of proteinuria is linearly correlated with the duration of follow-up and depends inversely on the size of remnant renal tissue. Proteinuria should be evaluated annually in patients with a solitary remnant kidney to detect hyperfiltration nephropathy. Angiotensin-converting enzyme inhibitors and protein-restricted diet can improve long-term renal function in patients who underwent partial nephrectomy [36].

There are various partial nephrectomy techniques because it is technically challenging as compared to radical nephrectomy. The selection of the incision site is crucial to expose the tumor, kidney, and renal vasculature. Incision above the 11th rib and the retroperitoneal approach have been predominantly used. The incision level can be adjusted depending on kidney location and the position/size of tumor on preoperative CT. The thoracoabdominal approach is advantageous in upper pole tumors, whereas the subcostal incision is useful in lower pole tumors. After incision, the kidney should be dissected to allow tumor excision. The ureter is encircled with a vessel loop to prevent injury; subsequently, the ureter is dissected superiorly to renal pelvis, and renal pedicles are identified, dissected, and controlled with vessel loops. Perirenal fat is dissected except when overlying the tumor.

Clamping of the renal artery and/or vein is essential to control bleeding during tumor excision. However, the procedure may induce decreased long-term renal function postoperatively [37]. Ischemic time is the most important surgical risk factor affecting decreased renal function after partial nephrectomy, and measures to limit ischemic time and injury should be taken [38]. The non-clamping method can preserve long-term renal function. In non-clamping method, enucleation of tumor can be associated with reduced blood loss and parenchymal damage compared to conventional tumor excision. If abrupt bleeding occurs during tumor excision with non-clamping method, compression of the renal parenchyma near the cut surface with Monocryl sutures into the transected vessels facilitates easy hemostasis.

The conventional process of partial nephrectomy includes the occlusion of the renal artery during tumor excision. The clamping method is advantageous in bleeding control, improved visualization, and decreased expansion of renal tissue [39]. Hypothermia of the kidney with ice slush is often used to prevent ischemic renal injury [40]. Cooling of the entire kidney should begin immediately after the occlusion of the renal artery and before tumor excision. Warm ischemia for $\geq$25 min caused long-lasting diffuse damage throughout the kidney, whereas cold ischemia for up to 58 min prevented ischemic injury to the kidney [41].

Tumor excision with negative resection margin is crucial for oncological outcomes. However, adjacent parenchyma should be maximally preserved for long-term renal function; the width of tumor-free resection margin is not associated with

prognosis [42]. Various techniques of proper resection, such as enucleation, wedge resection, and polar segmental nephrectomy, have been developed. After tumor excision, 4-0 monocryl suture is performed for hemostasis of transected blood vessels, and the argon beam coagulator can also be used. If the collecting system is opened, interrupted or running 4-0 monocryl suture is useful for closure. When leakage of urine is suspected despite suturing collecting system, retrograde ureteral stent insertion should be considered. After closure of the blood vessels and collecting system, hemostatic bolster, composed of Surgicel and Floseal hemostatic matrix, is applied to the defect of the renal tissue. The approximation of cortical edges with a bolster and interrupted 2-0 polyglactin sutures in a tension-free manner is performed. Nephropexy to the posterior muscle can be useful in preventing kidney migration. Jackson-Pratt drain is retroperitoneally placed to drain blood and identify urine leakage by checking creatinine levels.

Thermal Ablative Therapies

Alternative nephron-sparing procedures for patients with localized RCC, thermal ablative therapies, such as radiofrequency ablation and renal cryosurgery, have also emerged (Fig. 1.2) [43–46]. Thermal ablative therapies are useful in old patients or patients with life-threatening comorbidities who are not candidates for partial nephrectomy, patients with local recurrence after prior partial nephrectomy, and multifocal hereditary RCC, where it is not possible to perform multiple partial nephrectomies [12]. Thermal ablative therapies have been associated with decreased

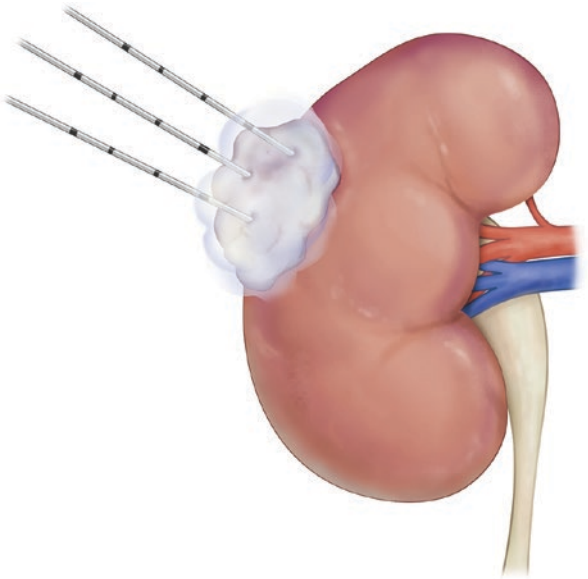

Fig. 1.2 The concept of thermal ablative therapy

Table 1.2 Indications for thermal ablation therapy

Small tumor (≤3 cm) in elderly, high-risk patients who opt against active surveillance and prefer intervention
Severe renal dysfunction
Previous abdominal surgery
Recurrent small renal mass in a postoperative renal remnant after prior partial nephrectomy

morbidity and faster recovery compared to partial nephrectomy, although long-term oncological outcomes have not been evaluated, and higher local recurrence rates were reported in preliminary studies [12, 45, 47]. Indications for thermal ablative therapy are listed in Table 1.2.

Active Surveillance

Active surveillance is acceptable for localized RCC and should be the first management option for small renal masses <4 cm in unfit patients or those with limited life expectancy [48]. Patients should be counseled in regard to slow and variable rates of tumor progression during observation period. Patients with active surveillance can lose the opportunity for partial nephrectomy and risk metastasis. Active surveillance is not usually recommended in patients with large renal tumors (>3 cm) and a young age or healthy patients with small tumors [12]. Due to lack of long-term data on surveillance, further research is required to define the preferred group of patients for active surveillance.

Surgical Treatment of Locally Advanced Renal Cell Carcinoma

Radical Nephrectomy

Simple nephrectomy was performed for several decades, but Robson et al. introduced radical nephrectomy as the golden standard to eradicate localized RCC [49]. The authors reported 66% and 64% overall survival for stage I and II tumors, respectively. Nowadays, radical nephrectomy is still the first choice for patients with localized RCC, such as large size (mostly T2 stage) or unsuitable location for nephron-sparing surgery. The major concern with radical nephrectomy is decreased renal function and the possibility of chronic kidney disease, which is correlated with increased mortality [50]. Go et al. reported increased rates of cardiovascular events and deaths in correlation with the progression of chronic kidney disease [51]. Proper selection of patients for radical nephrectomy is important, and radical nephrectomy should only be conducted when necessary.

Radical nephrectomy comprises early ligation of the renal artery and vein, removal of the kidney with Gerota's fascia, ipsilateral adrenalectomy, and regional lymph node dissection between the diaphragm and the aortic bifurcation [52]. The procedure of perifascial dissection is very important to prevent postoperative local recurrence because about 25% of clinical T2 renal RCCs displayed perinephric fat involvement [53]. The ipsilateral adrenalectomy is not always necessary if there is no radiologic adrenal involvement or upper pole tumor near the adrenal gland [52, 54]. There is a controversy with respect to complete regional lymphadenectomy in all patients. Randomized control trials, involving lymph node dissection in RCC, have not displayed significant improvement [55, 56]. RCC spreads through both blood and lymphatic system. Many patients with positive lymph nodes eventually show concealed metastases through the blood stream despite lymph node dissection. In addition, several patients with RCC have distant metastases without regional lymph node involvement, and the lymphatic course from the kidney is variable. Lymphadenectomy can be effective in a limited number of patients (about 2%) with micrometastases [52, 55, 57]. Thus, most urologists selectively conduct lymphadenectomy. Blute et al. reported that high-grade, sarcomatoid component, histologic necrosis, large tumors (>10 cm), and pathologic stages T3 or T4 were risk factors for lymph node involvement [57]. Patients with two or more risk factors showed about 10% lymph node involvement [57]. In a previous study, preoperative or intraoperative frozen sections were taken into consideration to decide dissection of hilar and regional lymph nodes [55].

The surgical approach should be considered depending on the size and location of the tumor and body type of patient. The transperitoneal approach is applied to control metastatic lesions and access renal vessels. Thoracoabdominal incision is used for large tumors involving the upper pole. Extraperitoneal flank incision is applied in old patients, but it is difficult for large tumors. Radical nephrectomy using laparoscopy is in the limelight for tumors 10–12 cm or smaller, localized RCCs without local invasion or in the absence of renal hilum infiltration. Laparoscopic radical nephrectomy resulted in less discomfort and fast recovery [58]. In addition, cancer-specific survival periods of laparoscopic and open radical nephrectomies are similar [59]. Nowadays, laparoscopy is applied in patients who are old and obese, and have prior operation history and large tumors, although selection bias should also be considered in each case [60, 61]. However, laparoscopic radical nephrectomy has been excessively conducted even in the cases of small renal tumors [62].

The oncologic outcome of radical nephrectomy depends on the stage of the tumor. Levy et al. reported 7.1%, 26.5%, and 39.4% recurrences for stages T1, T2, and T3, respectively [63]. Stephenson et al. mentioned increased risk of recurrence in pathologic stage T3 compared to stages T1 and T2 [64]. After radical nephrectomy, bone scans and CT should be conducted only in cases with associated symptoms. This follow-up can be cost-effective and is useful to detect recurrence. Monitoring of chronic kidney disease is also important.

Inferior Vena Cava Involvement

A characteristic of RCC during progression is invasion into the renal veins, inducing venous thrombi. In a number of cases, the tumor thrombus grows into the inferior vena cava, and the thrombus can migrate in the brain or heart. Radical nephrectomy and inferior vena cava thrombectomy are possible solutions for RCC and inferior vena cava thrombus, with cure rates of about 45–70%. The invasion of perinephric fat and positive lymph node and direct wall invasion of the inferior vena cava are risk factors indicating poor prognosis [65]. The reported rates of tumor thrombus in the inferior vena cava were about 4–10%. Symptoms are leg edema, varicocele of the right scrotum, and varicose abdominal veins. The stages are divided in accord with the level of inferior vena cava thrombus: levels 1, 2, and 3 involve adjacent to the ostium of the renal vein (level 1), extending up to the lower aspect of the liver (level 2), and involving the intrahepatic portion of the inferior vena cava but below the diaphragm (level 3), respectively (Fig. 1.3) [66]. Level 4 is correlated with extending above the diaphragm [66]. The prognosis of thrombus levels is controversial. Many studies reported that levels 3–4 showed higher recurrence and progression and reduced survival [67, 68]. Other studies reported that node involvement, metastasis, or tumor grade were more important factors than overall survival rates [69, 70]. Surgical resection of the entire tumor, including inferior vena cava thrombus, is a plausible strategy to cure the disease [71].

Magnetic resonance imaging (MRI) is a useful diagnostic tool of inferior vena cava involvement [72]. Gadolinium helps differentiate tumor thrombus by enhancement. Recently, multiplanar CT was used to differentiate tumor thrombus [73]. MRI or CT preoperative images are very important, and shorter times between imaging and surgery are preferred, because tumor thrombus can rapidly progress [74]. Venacavography can provide accurate imaging of inferior vena cava thrombus, but it is generally conducted in patients who cannot be examined by MRI or CT.

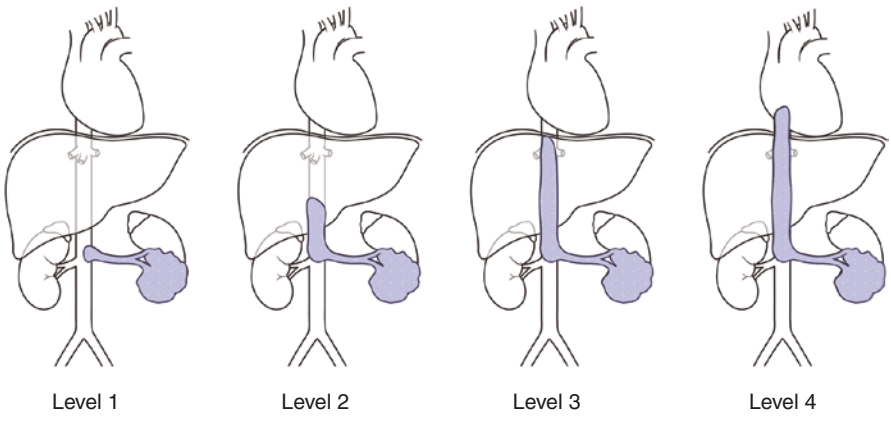

Fig. 1.3 Illustration of inferior vena cava thrombus level