Chapter 13
The Impact of Renal Tumor Surgery on Kidney Function

Sudhir Isharwal, Chalairat Suk-Ouichai, Joseph Zabell, Jitao Wu, Wen Dong, Elvis Radhames Caraballo Antonio, and Steven C. Campbell

Introduction

The American Cancer Society estimated that more than 63,000 new cases of kidney cancer would be diagnosed in the United States in 2017, representing the ninth most common malignancy [1]. Surgical excision is the most frequently used treatment for

S. Isharwal · J. Zabell · E. R. Caraballo Antonio
Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

C. Suk-Ouichai
Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

Division of Urology, Department of Surgery, Siriraj Hospital, Mahidol University, Bangkok, Thailand

J. Wu
Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

Department of Urology, Yantai Yuhuangding Hospital, Yantai, Shandong, China

W. Dong
Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

S. C. Campbell (✉)
Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

Center for Urologic Oncology, Glickman Urologic and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: campbes3@ccf.org

M. A. Gorin, M. E. Allaf (eds.), *Diagnosis and Surgical Management of Renal Tumors*, https://doi.org/10.1007/978-3-319-92309-3_13

localized disease [2–4]. Historically, radical nephrectomy (RN) was the treatment of choice in such patients, and partial nephrectomy (PN) was reserved for imperative indications such as solitary kidney or bilateral renal tumors. Once the potential association of chronic kidney disease (CKD) with increased cardiovascular events and reduced survival was understood [5], the role of PN was expanded for small renal masses even in patients with bilateral kidneys to preserve maximum renal function [4].

In addition to oncologic outcomes, renal function preservation has become an important objective in renal cancer survivors [6–9]. Accordingly, most treatment guidelines recommend PN as the standard of care for small renal masses, while RN is favored for large or anatomically complex masses not amenable to PN [3, 4]. However, these advances in the field of renal surgery have been controversial. The validity of the hypothesis that improved functional outcomes after PN translates into better survival has been questioned [10, 11]. Additionally, the notion that CKD primarily due to surgery has similar implications as CKD due to medical comorbidities has been challenged [12–14]. Moreover, there is ongoing debate about the important predictors of functional outcomes after PN [6, 7]. These issues are of great importance as they can affect surgical approach and intraoperative management and can have important implications for cancer survivorship. In this chapter, we review the evidence that addresses these issues and provide an update on recent advances in the field.

Chronic Kidney Disease

The Kidney Disease: Improving Global Outcomes (KDIGO) foundation defines CKD as glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 or presence of markers of kidney damage, such as proteinuria, for greater than 3 months [15]. The overall prevalence of CKD in the general population in the United States is approximately 14% [16]. Although the association of end stage renal disease with higher mortality rates has long been appreciated, the importance of even mild to moderate CKD was not well understood until the landmark study published in 2006 by Go and colleagues [5]. In a large population-based study including more than a million subjects, Go reported that increasing degrees of CKD were associated with increased cardiovascular events, hospitalization, and mortality, even after adjusting for medical comorbidities. The hazard ratio (HR) of mortality increased in a dose-dependent fashion from 1.2 in subjects with GFR 45–59 ml/min/1.73 m^2 to 5.9 in subjects with GFR <15 ml/min/1.73 m^2.

After the significance of CKD was highlighted in terms of increased all-cause mortality, Huang and colleagues studied the prevalence of CKD in patients with renal masses presenting for surgical resection and the impact of surgical removal of nephrons on the development or progression of CKD [17, 18]. In their cohort, 25–30% of patients with a localized renal mass had CKD, and after surgery the 3-year probability of freedom from new-onset CKD (GFR < 60 ml/min/1.73 m^2)

was 80% after PN but only 35% after RN. Studies from other centers have confirmed these findings with similar prevalence of CKD noted in patients undergoing surgery for renal tumors (Reviewed in [9]).

With increased recognition of CKD prevalence and its potential long-term deleterious effects, renal function preservation has become an important objective in the management of patients with kidney cancer. For patients with small renal masses, RN represents gross overtreatment, and the trend has shifted toward nephron-sparing approaches. Recognizing that there are many ongoing controversies in this field, the American Urologic Association (AUA) recently updated their evidence-based guidelines for the management of patients with localized kidney cancer, with particular focus on the roles of PN and RN and functional preservation related to renal surgery [4].

PN Versus RN

Historically, nephron-sparing surgery using PN was reserved for imperative indications such as a renal tumor in a solitary kidney or bilateral renal tumors. Long-term studies from Cleveland Clinic and Memorial Sloan Kettering confirmed overall survival of greater than 90% after PN for early-stage kidney cancer [19, 20]. However, adoption of PN was slow in the urologic community due to higher risk of bleeding and urinary fistula formation and uncertainty about the management of such complications [8].

PN gained greater acceptance after several studies demonstrated strong local control and metastasis-free survival in appropriately selected patients with localized kidney cancer [9, 21, 22]. With further understanding of association of CKD with future cardiovascular events and increased mortality in the general population, application of PN beyond the conventional indications was explored. Eventually, it was recognized that RN represents therapeutic overkill for many patients with localized kidney cancer, particularly those with small renal masses [9]. Based on developments in the field as of 2009, the AUA guidelines recommended PN as the standard of care for the clinical T1a renal tumor [3]. Upon further understanding of the functional advantages of PN and increased comfort level with the surgical techniques and management of complications, PN has been widely adopted in academic centers and to some degree in community settings as well. Various groups have expanded the role of PN to larger renal masses and tumors with increased complexity [23, 24]. However, a fundamental question persists, particularly when a normal contralateral kidney is present, does PN provide a survival advantage over RN?

Data from several observational studies confirm a functional advantage for PN even in the most challenging of circumstances and many also suggest an overall survival advantage (Table 13.1a) [25–27]. However, these studies are potentially contaminated by both measured and unmeasured biases. A large meta-analysis by Kim and colleagues of 36 retrospective studies comprising more than 40,000 patients showed a 61% risk reduction in the development of CKD ($p < 0.001$) and a 19% risk reduction in all-cause mortality ($p < 0.001$) for PN when compared to RN [25]. However, a 29% risk reduction for cancer-specific mortality in favor of PN was also reported ($p = 0.002$). This finding can only be explained by the selection biases that may reside within the included studies – it is difficult to understand how PN can provide an oncologic advantage over RN based on the basic tenets of surgical oncology.

Subsequent studies have used advanced statistical methods such as propensity scores and instrumental variables to control for the selection bias in these studies and to facilitate a more sophisticated comparison of the PN and RN cohorts (Table 13.1a) [26, 27]. Using a propensity score-based model, Weight et al. reported that patients undergoing RN for T1b renal tumors with a normal contralateral kidney were at higher risk of postoperative CKD and reduced survival [27]. Similarly, Tan et al., studying a cohort of Medicare beneficiaries with early-stage kidney cancer with an instrumental variable approach, reported increased survival with PN when compared with RN [26]. However, propensity score methods only account for measured biases and imbalance from unrecognized confounders may still persist.

Table 13.1 Selective studies comparing the outcomes of partial and radical nephrectomy

Study	Design	Main outcomes	Findings	Limitations/perspective
(a) Retrospective studies comparing PN vs. RN outcomes				
Kim SP, et al., 2012 [25]	Meta-analysis: 36 studies	ACM CSM CKD	PN correlated with 19% risk reduction for ACM, 29% risk reduction in CSM, and 61% risk reduction for CKD	Potential selection and publication biases *Perspective*: Lower CSM in PN cohort likely due to selection bias, as PN is not a stronger oncologic intervention
Tan HJ, et al., 2012 [26]	Study of Medicare beneficiaries with cT1a renal tumors, instrumental variable approach	OS CSS	Improved OS with PN No significant difference in CSS between PN and RN	Only cT1a included, instrument variable assumptions cannot be verified, and cannot control for unrecognized confounders *Perspective*: Selection bias remains a concern
Weight CJ, et al., 2010 [27]	Retrospective series using propensity score method for cT1b renal masses	OS,CSS, and cardiac-specific survival	PN associated with increased 5-year OS (85% vs. 78%, $p = 0.01$) and equivalent CSS (94% vs. 89%). Postoperative renal insufficiency independent predictor of OS and cardiac-specific survival	Single center, retrospective with concern about potential selection bias, hidden bias not tested, and cannot control for unrecognized confounders *Perspective*: Selection bias remains a concern

Table 13.1 (continued)

Study	Design	Main outcomes	Findings	Limitations/perspective
Shuch B, et al., 2013 [28]	Matched cohort study using SEER Medicare dataset	OS	OS was similar between RN and controls (low-grade bladder cancer and noncancer controls) However, PN had improved survival compared to controls (HR; 1.25, $p < 0.001$)	Retrospective design, dataset has limitations *Perspective*: RN had similar survival to age and comorbidity matched controls with no cancer or nonlife-threatening cancer suggesting that reduced renal function did not impact survival. PN patients fared better suggesting selection bias
(b) Randomized trial comparing PN vs. RN				
Poppel HV, et al., 2011, Scosyrev E, et al., 2013 (EORTC 30904) [11, 29]	Randomized trial of PN vs. RN for renal mass < 5 cm and normal contralateral kidney	OS Incidence CKD	10-year OS for RN vs. PN (81% vs. 75%, HR 1.5, $p = 0.03$) At median follow-up of 6.7 years RN vs. PN, eGFR<60: 86% vs. 64% RN vs. PN, eGFR <30: 10% vs. 6.3% RN vs. PN, eGFR <15: 1.5% vs.1.6%	Suboptimal accrual, underpowered, crossover between treatment arms, normal function defined by serum creatinine level, not GFR *Perspective*: Despite flaws, results are provocative, suggesting that survival advantage related to PN may not be as large as previously thought
(c) Impact of CKD primarily due to surgical nephron loss (CKD-S)				
Lane BR, et al., 2013 [12]	Large cohort study of patients undergoing RCS	Progression of renal function decline	Annual renal function decline was 4.7% for CKD-M and 0.7% for CKD-S Annual renal function decline >4% associated with 43% increase in mortality ($p < 0.0001$).	Single tertiary center retrospective study *Perspective*: CKD-M had decreased survival and less stable renal function. Decline of function for CKD-S approximates normal aging process
Zabell J, et al., 2017 [30]	Analysis of >4000 patients undergoing RCS	Predictors of 5-year CKD and 10-year nonrenal cancer mortality	Preoperative GFR and GFR loss related to surgery correlate with 5-year risk of CKD. Preoperative GFR, new baseline GFR, and age correlated with 10-year nonrenal cancer mortality GFR loss with typical PN vs. RN only changed absolute mortality risk by 1–3%	Validation of the predictors needed *Perspective*: Age and preoperative GFR strongly associated with nonrenal cancer mortality. Although choice of PN versus RN influences risk of developing CKD, it has less impact on survival

(continued)

Table 13.1 (continued)

Study	Design	Main outcomes	Findings	Limitations/perspective
Gor R, et al., 2015 [14]	Analysis of >1400 patients from renal tumor registry to study impact of CKD subtypes	Impact of CKD-M and CKD-S on risk of mortality	CKD-M associated with higher risk of mortality compared to CKD-S. CKD-S had similar mortality as no CKD cohort	Tertiary center retrospective study *Perspective*: Validated the findings that CKD-S has mortality risk similar to no CKD patients
Capitanio U, et al., 2015 [31]	Multicenter analysis of 1189 patients: RN or PN for ≤cT1b renal mass and preoperative GFR≥60	CKD and other-cause mortality	On multivariable analysis, PN associated with lower risk of CKD, but there was no significant difference in other-cause mortality (HR 0.8, CI 0.67–1.40)	Retrospective study *Perspective*: PN associated with better preservation of renal function compared to RN, but this did not translate into a survival benefit
Lane BR; et al., 2015 [13]	Large cohort study of patients undergoing RCS with long follow-up	Impact of new baseline eGFR	CKD-M/S had higher rates of GFR decline, all-cause mortality, and nonrenal cancer mortality CKD-S survival and stability of renal function approximated the no CKD cohort	Tertiary center retrospective study *Perspective*: CKD-S has good prognosis as long as new baseline GFR is >45 ml/min/1.73 m^2
(d) Collaborative review of literature comparing PN and RN				
Kim SP, et al., 2016 [9]	Critical review of available literature comparing outcomes of PN and RN for anatomically complex tumors	Risks and benefits of PN over RN	For anatomically complex tumors, PN preserves renal parenchyma, although PN has increased perioperative risk Prospective randomized trial is needed to provide better data about the merits of PN versus RN	Comparison of retrospective studies with selection bias and one imperfect randomized clinical trial *Perspective*: Available literature unable to establish the superiority of PN over RN in complex renal tumors and a randomized trial is needed

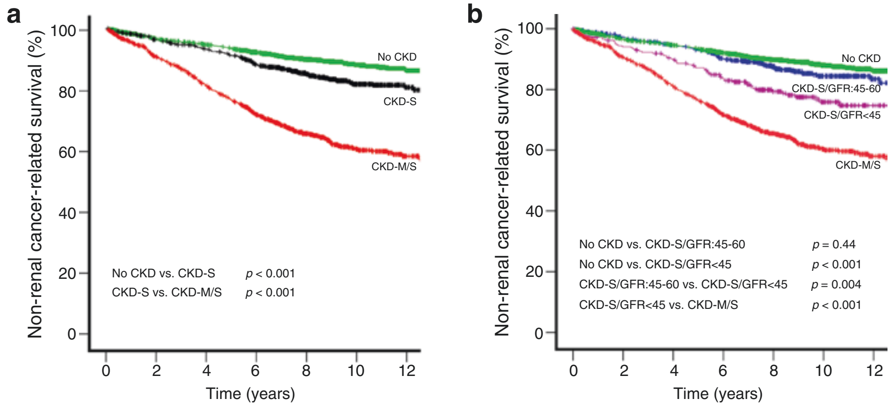
ACM all-cause mortality, *CKD* chronic kidney disease, *CKD-M* chronic kidney disease due to medical diseases, *CKD-S* chronic kidney disease primarily due to surgical removal of nephrons, *CSM* cancer-specific mortality, *CSS* cancer-specific survival, *eGFR* estimated glomerular filtration rate, *GFR* glomerular filtration rate, *HR* hazard ratio, *OS* overall survival, *PN* partial nephrectomy, *RN* radical nephrectomy, *RCS* renal cancer surgery, *SEER* surveillance, epidemiology, and end results

Furthermore, Shuch et al. demonstrated potential selection bias in this literature using the Surveillance, Epidemiology, and End Results Medicare dataset [28]. In their matched cohort study, subjects with PN had better overall survival even when compared to noncancer controls, suggesting that the PN population had advantages with respect to unrecognized confounders. Patients selected for PN may just be healthier on average than patients in other cohorts and manipulation of the identified covariates may not be able to control for this reality. Conclusions drawn from these retrospective studies showing an overall survival advantage associated with PN may therefore be unreliable [10, 28].

The best study design to avoid selection bias and thus allow for more reliable conclusions is, of course, a randomized controlled trial. There is, however, only one such trial in this domain, namely, EORTC 30904 (Table 13.1b) [11, 29]. Patients with a single, clinically localized tumor up to 5 cm with a normal contralateral kidney were randomized to either PN ($n = 268$) or RN ($n = 273$). As expected PN provided better functional outcomes, while surgical morbidity was less with RN. Surprisingly, PN was not associated with better overall survival. At a median follow-up of 9.3 years, the intention to treat analysis showed 10-year overall survival of 81% for RN compared to 76% for PN ($p = 0.03$). A follow-up analysis of functional outcomes confirmed the advantage of PN over RN in terms of preservation of renal function; however, this did not translate into a survival advantage in subjects with a normal contralateral kidney [29].

EORTC 30904 thus raised the possibility that CKD due to surgical loss of nephrons (CKD-S) may not have same adverse implications as CKD due to medical diseases (CKD-M). Lane and colleagues explored this hypothesis in over 4000 patients managed with PN or RN [12]. Their population included over 1000 patients with preexisting CKD-M who required surgery for a renal mass (thus designated CKD-M/S) compared to a similar number of patients with CKD primarily due to surgical removal of nephrons (CKD-S). The control group comprised almost 2000 patients with no CKD even after renal surgery. The prevalence of CKD-M/S and CKD-S in this series were 28% and 22% of all patients, respectively (Table 13.1c, Fig. 13.1). Several important observations were gleaned from this study. First, GFR decline per year was substantially increased in the CKD-M/S cohort compared to CKD-S (4.7% vs. 0.7%, $p < 0.05$). Furthermore, an annual decline of renal function of >4% was associated with a substantial increase (43%) in mortality ($p < 0.0001$). In a follow-up study, patients with CKD-M/S had the highest rate of GFR decline, nonrenal cancer-related mortality, and all-cause mortality on multivariable analysis [13]. In contrast, the CKD-S cohort had GFR stability and nonrenal cancer mortality rates that were similar to the no CKD group. Gor et al. validated these findings, reporting that CKD-S has similar mortality rates as patients with no CKD even after surgery for a renal mass [14]. Thus etiology of CKD appears to play an important role in the outcomes of patients undergoing surgery. Patients with CKD due to medical etiology by definition have comorbidities that are impactful, and most, such as diabetes, are longstanding. Thus their renal function will typically continue to decline and eventually this leads to increased mortality rates. Patients with CKD primarily due to surgical removal of nephrons typically do not require further surgery, and their renal function can thus stabilize, leaving them in a better position for long-term survival.

Although PN is associated with better preservation of renal function compared to RN, this functional advantage may not always translate into a substantial survival benefit, at least for patients with a normal contralateral kidney. This hypothesis was recently explored by developing predictive models from our population of



No. of events

No CKD	78	46	49	32	17	6
CKD-S	42	26	42	22	9	4
CKD-M/S	122	99	82	38	21	5

No. of events

No CKD	78	46	49	32	17	6
CKD-S/GFR:45-60	23	13	26	13	6	2
CKD-S/GFR<45	19	13	16	9	3	2
CKD-M/S	122	99	82	38	21	5

Fig. 13.1 Nonrenal cancer-related survival stratified by etiology of chronic kidney disease (CKD) in patients requiring renal cancer surgery. **a**) Patients with preexisting CKD due to medical comorbidities who then required surgery (CKD-M/S, $n = 1113$) experienced significantly reduced survival when compared to patients with CKD primarily due to surgical removal of nephrons (CKD-S, $n = 931$). Patients with CKD-S by definition only developed GFR < 60 ml/min/1.73 m^2 after surgical intervention. The survival of patients with CKD-S approximates that of patients with no CKD even after surgery ($n = 2202$). **b**) Patients with CKD-S are heterogenous to some degree as those with new baseline GFR < 45 ml/min/1.73m^2 have reduced survival when compared to those with new baseline GFR > 45 ml/min/1.73 m^2. (From Wu et al. [32], Fig. 1, with permission oF John Wiley and Sons)

over 4000 patients who underwent surgical removal of a renal tumor with almost 10 years of median follow-up [30]. In these models, age, demographic factors, and important comorbidities were incorporated, in addition to relevant functional parameters, including preoperative GFR, GFR loss with surgery, and new baseline GFR. However, PN versus RN status was not utilized, because it carries too much potential bias related to selection processes, and there is often substantial overlap in the amount of function lost with these procedures. More specifically, challenging PNs can occasionally lead to considerable loss of GFR, while some RN for poorly functioning kidneys can be associated with minimal loss of function. Predictive algorithms were then developed for 5-year incidence of CKD or 10-year nonrenal cancer-related survival. As expected, the models confirm that a surgical intervention associated with about 10% loss of global function (as seen with a prototypical PN) correlated with substantially lower incidence of CKD when compared to an intervention associated with about 40% loss of global renal function (i.e., prototypical RN). However, the predictive models suggest that absolute differences in 10-year survival for these two interventions should be relatively small, in the range of 1–3%. For instance, for a 54-year-old with a preoperative GFR of 80 ml/min/1.73 m^2, 10-year survival was predicted to be 90% if prototypical PN was performed (loss of 10% of global function) versus 88% if a prototypical RN was performed. In contrast, age and preoperative GFR were much stronger predictors of 10-year survival in this patient population. Preoperative GFR is a strong indicator of health status, as it reflects important comorbidities and their physiologic impact. This study suggests that interventions that on average save 90% versus 60% of the global renal function (i.e., PN versus RN) may not impact survival in a substantially divergent manner, at least in patients with relatively good preoperative renal function.

Similarly, Capitanio et al. in a large multicenter analysis of patients without preexisting CKD noted that even though PN is associated with lower risk of developing CKD (HR = 0.65, 95% CI 0.47–0.92), there was no significant difference in other-cause mortality on multivariable analysis (HR 0.8, 95% CI 0.67–1.40) during extended follow-up of 10–15 years [31]. These findings raise the possibility that optimal preservation of GFR may not be critically important in all patients. Stated another way, the more robust survival advantages of PN may be primarily limited to patients with preexisting CKD.

It is important to emphasize that while most patients with CKD-S have a good prognosis, there may be heterogeneity in this patient population that could affect management decisions. In particular, a recent study suggests that CKD-S patients with new baseline GFR < 45 ml/min/1.73 m^2 have significantly worse survival compared to those with GFR of 45–60 ml/min/1.73 m^2 [32]. In addition, survival of the latter group appeared to be very similar to patients who did not have CKD even after surgery. This suggests that if renal mass surgery is going to lead to new-onset CKD, it is best to avoid dropping the GFR below this critical threshold, and PN should thus be considered in some such patients.

In summary, the decision to perform PN versus RN in patients with a normal contralateral kidney remains complex and challenging [8]. A functional advantage for PN is clear and not subject to debate. However, the evidence suggesting a potential survival benefit of PN over RN in this setting is primarily driven by retrospective studies plagued with inherent selection biases. The single prospective randomized trial in this space failed to confirm a survival benefit of elective PN over RN [33]. A recent collaborative review of PN versus RN demonstrated increased perioperative morbidity and better renal function with PN, but a survival advantage again proved elusive when strict principles were applied, at least in the elective setting (Table 13.1d) [9].

Recent AUA guidelines address this issue in detail, recognizing ongoing overutilization of RN in the community setting and substantial controversies regarding the issue of PN versus RN [4]. The guidelines recommend consideration for RN whenever increased oncologic potential is suggested by increased tumor size, high tumor grade or unfavorable histology (if renal mass biopsy has been performed), or infiltrative or locally invasive appearance on imaging. Beyond this, the guidelines suggest that RN is then *preferred* if the following three criteria are *all* also satisfied: (1) high tumor complexity, such that PN would be challenging even in experienced hands, (2) there is no preexisting CKD or proteinuria, and (3) presence of a normal contralateral kidney that is likely to provide GFR > 45 ml/min/1.73 m^2 after intervention. If these specific criteria are *not* met, then PN should be considered if feasible [4]. It is hoped that these guidelines will prove useful for the practicing urologist and will stimulate further research in this field.

Determinants of Functional Recovery After PN

In addition to the choice of PN versus RN, there are several factors that may affect the recovery of renal function after surgery for a renal tumor (Fig. 13.2). Preoperative factors are often related to patient or tumor characteristics and are usually non-modifiable. As already discussed, PN is preferred in imperative indications such as patients with preexisting CKD or a solitary kidney, and in these settings optimal functional recovery is of paramount importance. However, recovery of function after PN can be variable, and much work has been done to understand the determinants of functional recovery after this procedure. In this section we will focus on the roles of parenchymal mass preservation and ischemia type and duration as well as recent advances in this field.

Due to the highly vascular nature of the kidney, PN has traditionally required clamping of the renal vasculature to prevent blood loss and maintain a clear field of visualization during tumor resection. Several investigators have considered the potential impact that renal ischemia may have on the recovery of renal function, both short and long-term. Ischemia may impact the recovery process through

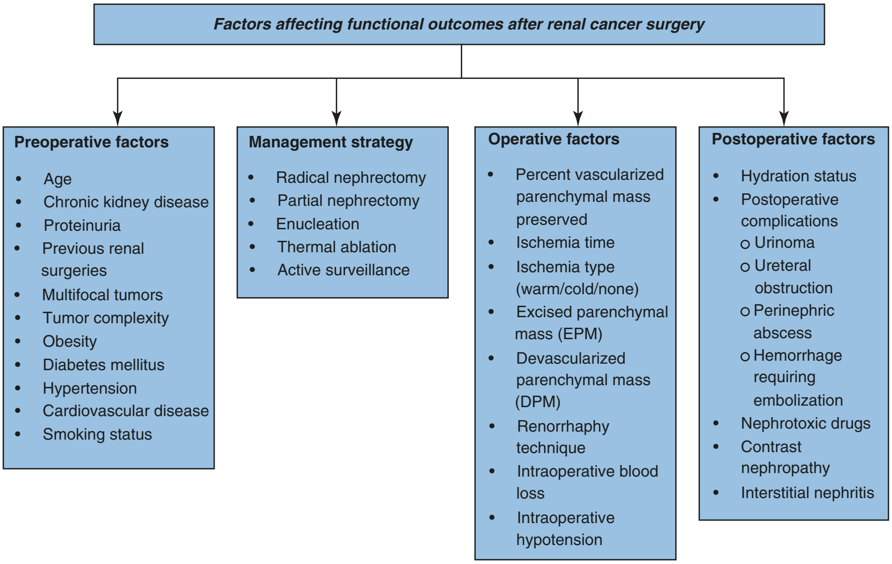


Fig. 13.2 Factors affecting functional outcomes after renal cancer surgery

several hypothesized mechanisms such as ischemia-reperfusion injury, constriction of renal arterioles, and renal tubular injury [6–8].

Cold Ischemia vs. Warm Ischemia

Hypothermia, typically through the use of ice slush, decreases cellular metabolism and has been proven to have a strongly protective effect with respect to ischemic renal injury. Previous experience with renal transplantation established that most kidneys recovery strongly and durably even after several hours of ischemia as long as hypothermia is utilized [6]. Hypothermia has traditionally been used for most cases of open PN and is now also being applied for minimally invasive cases at many centers. In a cohort of 662 patients, Yossepowitch and colleagues evaluated the impact of cold ischemia time on the percent change in GFR after surgery [34]. Longer duration of hypothermia was associated with increased risk of acute kidney injury (AKI) in the early postoperative period; however it was not a significant predictor of functional outcomes 1 year after surgery. Zhang and colleagues evaluated the impact of hypothermia in a more refined manner, including normalizing for parenchymal mass loss [35]. In a series of 277 PNs, a median recovery of 99% was noted when cold ischemia was used, suggesting that most nephrons make a complete recovery from the ischemic insult. Several other studies have confirmed these findings [6–8]. The general consensus is that the duration of hypothermia can be extended out 1–2 h if necessary, although in the short-term postoperative care can be complicated by AKI, as discussed below [6, 8].

Recovery from warm ischemia, while somewhat more variable, also appears to be relatively strong as long as prolonged durations of ischemia are avoided. In the series by Zhang [35], median functional recovery to level predicted by nephron mass loss was 91% for cases managed with warm ischemia, although limited durations of ischemia (<25–30 min) predominated in this series. Recovery from extended durations of warm ischemia has not been well studied and the threshold at which irreversible ischemic injury begins to occur remains controversial [6–8].

Impact of Parenchymal Mass Preservation and Ischemia Duration

One important early study in this domain evaluated a retrospective cohort of 362 patients undergoing PN in a solitary kidney with warm ischemia and reported that longer ischemia duration is associated with increased risk of AKI, need for dialysis, and new-onset CKD (Table 13.2a) [36]. Every minute increase in ischemia duration was associated with a 5% increased risk of AKI and a 6% increased risk of new-onset CKD. These findings popularized the concept that "every minute counts when

Table 13.2 Selective studies on determinants of renal function after partial nephrectomy

Study	Design	Main outcomes	Findings	Limitations/ perspective
(a) Studies without consideration of parenchymal mass preserved				
Yossepowitch O, et al., 2006 [34]	Retrospective review of patients undergoing PN with solitary kidney (*n* = 70) or bilateral functioning kidneys (*n* = 592)	Percentage change of GFR related to surgery	Longer hypothermia time associated with poor GFR recovery in early postoperative period but was not a significant predictor 1 year after PN	Parenchymal mass preserved not considered in multivariable analysis *Perspective*: Ischemia can lead to AKI, but ischemia duration did not impact ultimate GFR recovery in setting of hypothermia
Thompson RH, et al., 2010 [36]	Retrospective review of patients with solitary kidney (*n* = 362) undergoing PN with warm ischemia	ARF, acute-onset GFR <15, or new-onset GFR <30	Risk of new-onset CKD increased 6% with each minute of WIT, and risk of AKI increased 5% with each minute. Hence, "every minute counts"	Parenchymal mass preserved not incorporated into the analysis. *Perspective*: Findings about WIT potentially misleading because primary confounder (nephron mass loss) not incorporated
(b) Studies with subjective estimation of parenchymal mass preserved				
Lane BR, et al., 2011 [37]	Multicenter comparative study of PN in solitary kidney (*n* = 660) with warm or cold ischemia	AKI CKD	Preoperative GFR (quality) and % parenchyma preserved (quantity) associated with functional outcomes. Ischemia time did not correlate	Retrospective studies with subjective estimation of parenchymal mass preserved *Perspective*: Quantity and quality of parenchyma preserved are strong predictors of the functional outcomes after PN. Suggests that most nephrons recover from ischemia as long as hypothermia or limited warm is applied
Thompson RH, et al., 2012 [38]	Retrospective: solitary kidney (*n* = 362) undergoing PN with WIT. Repeat analysis: now incorporating subjective estimate of "quantity" factor	CKD	Percentage nephron mass preserved and preoperative GFR significantly associated with new-onset stage IV CKD. WIT lost statistical significance unless >25 min	

Table 13.2 (continued)

Study	Design	Main outcomes	Findings	Limitations/perspective
(c) Studies with direct measurement of parenchymal mass preserved				
Song C, et al., 2011 [39]	Prospective:116 patients with 2 kidneys undergoing PN Ipsilateral renal function determined by DTPA scan	Determine course and factors affecting ipsilateral GFR recovery	Preoperative GFR, parenchymal mass loss, and collecting system repair associated with functional outcomes	Retrospective studies limited to only patients with data available for detailed functional analysis *Perspective*: Preoperative renal function (quality) and percent parenchyma preserved (quantity) are the primary predictors of ultimate renal function. Recovery from cold ischemia is very reliable and remains near complete even with prolonged cold ischemia. Recovery from warm ischemia is also relatively strong even out to 35 min (>90% when normalized by nephron mass preserved). The impact of more prolonged warm ischemia is not well studied
Mir C, et al., 2014 [40]	155 patients undergoing PN Renal volume determination by CT scan, MAG3 scan to estimated ipsilateral function	Recovery from ischemia: percent function saved/percent parenchyma saved	Parenchymal mass preserved is key factor for functional recovery. Recovery from ischemia most reliable with hypothermia	
Ginzburg S, et al., 2015 [42]	179 patients with bilateral kidneys underwent PN. CT estimated parenchymal volume preservation	Percent GFR preserved after surgery	Preoperative GFR and parenchymal mass preserved associated with functional outcomes 6 months after surgery	
Zhang Z., et al., 2016 [35]	Bilateral (194) and solitary (83) kidneys. Renal mass determination by CT, MAG3 for split renal function	Evaluate impact of type and duration of ischemia on functional recovery after PN	Recovery from hypothermia is near complete and remains strong (>96%) with prolonged hypothermia. Recovery from warm ischemia is also relatively strong to 35 min (>90%)	

(continued)

Table 13.2 (continued)

Study	Design	Main outcomes	Findings	Limitations/perspective
(d) Studies with limited or zero ischemia during PN				
Thompson RH, et al., 2010 [44]	Retrospective: solitary kidneys having PN with no ischemia or warm ischemia	New-onset stage IV CKD	Warm ischemia associated with significantly increased risk of developing stage IV CKD	Potential selection bias, parenchymal mass preservation not taken into account *Perspective*: Reduced ischemia associated with better functional outcomes. However, minimal or zero ischemia cases may have been easier and thus associated with less parenchymal mass loss
Smith GL, et al., 2011 [45]	Single-center retrospective study comparing renal vascular clamping group with non-clamped group	Percent change in GFR at 1 year Complication rates	Non-clamped group had lower decrease in eGFR compared to vascular clamping group but had higher transfusion rates	
Desai MM, et al., 2014 [46]	Retrospective comparison (n = 121) of superselective PN versus main artery clamping	Perioperative complications Percent decrease in GFR	Superselective clamping had less decrease in percent GFR after PN and similar parenchymal volume preservation but had longer operative time and more need for transfusion	Potential selection bias, measurement of function early in the postoperative period when new baseline GFR not well defined *Perspective*: zero ischemia PN can be associated with higher blood loss although generally appears to be feasible. Current data suggests that zero ischemia PN may not provide significantly improved functional outcomes compared to clamped PN
Satkunasivam R, et al., 2015 [47]	Comparison of superselective clamping to non-clamped PN	Percent reduction in GFR and new-onset CKD stage >3 at 1 month	Percent GFR reduction was similar, however, new-onset CKD stage >3 occurred less frequently in non-clamped group	

Table 13.2 (continued)

Study	Design	Main outcomes	Findings	Limitations/ perspective
(e) Study evaluating histology and markers of renal tubular damage during renal ischemia				
Parekh D, et al., 2013 [48]	Prospective evaluation: renal histology and biomarkers before/during/ after renal ischemia. Included cases with prolonged ischemia	Renal histological changes, AKI biomarkers, and functional changes	Histologic changes less severe than animal models of renal ischemia Functional changes did not correlate with ischemia duration. Biomarkers did not suggest substantial ischemic damage	Biomarkers chosen may not have been optimal for this purpose. The implications of acute structural findings are not clear *Perspective*: Extended warm ischemia may not be as deleterious as previously thought although further studies are needed
(f) Review articles about factors associated with decline in renal function after PN				
Mir MC, et al., 2015 [6]	Review of evidence from 71 studies evaluating renal function after PN	Factors associated with loss of renal function after PN	Renal function decline after PN averages about 20% in the operated kidney. Preservation of nephron mass appears to be the main factor affecting functional recovery	Evidence synthesized primarily from retrospective studies *Perspective*: Amount of parenchymal mass preserved is primary determinant of renal function recovery after PN
Volpe A, et al., 2015 [7]	Collaborative review of 91 studies about the impact of renal ischemia on functional recovery after PN	Impact of renal ischemia on functional recovery after PN	Functional recovery after PN strongly correlates with nephron mass preserved. WIT is modifiable. Prolonged WIT can lead to reduced functional recovery	Available data suggest a potential benefit of keeping WIT<25 min, although the level of evidence to support this threshold is limited. Cold ischemia safely facilitates longer durations of ischemia

AKI acute kidney injury, *ARF* acute renal failure, *CKD* chronic kidney disease, *CT* computed tomography, *DPM* devascularized parenchymal mass, *DTPA* diethylenetriaminepentacetate, *EPM* excised parenchymal mass, *GFR* glomerular filtration rate, *MAG3* mercaptoacetyltriglycine, *PN* partial nephrectomy, *WIT* warm ischemia time

the renal hilum is clamped." However, this study did not incorporate the amount of parenchymal mass preserved into the analyses, thus potentially compromising the conclusions that could be drawn from this data.

Subsequently, in a nonrandomized comparative study, Lane and colleagues evaluated 660 PN performed in solitary kidneys where cold ischemia and warm ischemia were used in 300 and 360 cases, respectively [37]. At 3 months after PN, no significant difference in percent GFR decline was noted between the groups despite longer ischemia times in the cold ischemia cohort. On initial multivariable analysis, preoperative GFR, increasing age, larger tumor size, and longer ischemia time were all significantly associated with functional recovery. However, when subjectively estimated amount of parenchyma preserved was incorporated into the analysis, it proved to be a very strong predictor of functional outcomes, and ischemia duration lost statistical significance. In the final analysis, only preoperative GFR (i.e., quality) and amount of parenchymal mass preserved (i.e., quantity) were significantly associated with the ultimate functional recovery after PN (Table 13.2b). This prompted a repeat analysis of the previous study of 362 solitary kidneys managed exclusively with warm ischemia, which suggested that "every minute counts" [38]. With updated analysis, percent of nephron mass preserved and preoperative GFR were significantly associated with functional outcomes, while ischemia duration proved to be insignificant, unless it was extended beyond 25 min [38]. In the process, nephron mass preservation was identified as the strongest predictor of functional outcomes after PN.

The findings of the above mentioned studies were further augmented with more accurate and direct estimation of parenchymal mass preserved using imaging studies (Table 13.2c) [35, 39–42]. In these studies the amount of vascularized parenchyma within the operated kidney was estimated from preoperative and postoperative CT scans using software or free-hand scripting with summation, and the percent of parenchyma preserved by the procedure was thus directly measured. Functional correlates were also obtained based on preoperative and postoperative serum creatinine-based estimates of global GFR complimented by split renal function from nuclear renal scans, when necessary [40]. As summarized in Table 13.2c, all such studies confirm a strong relationship between parenchymal mass saved and function saved in the operated kidney, confirming the primary importance of nephron mass preservation. Furthermore, these studies also support the importance of preoperative GFR for functional outcomes, because it defines the ceiling for recovery.

A more refined analysis of functional recovery after PN was recently reported by Dong and colleagues in a robust cohort of 401 patients, all of whom had detailed analysis of parenchymal mass and function saved specifically in the kidney exposed to ischemia [43]. Consistent with previous studies, function saved correlated strongly with parenchymal mass preservation. On multivariable analysis, ischemia type (warm) and duration both correlated significantly with functional recovery after controlling for nephron mass loss, while in many previous studies ischemia characteristics had not correlated in this manner. This study included substantially more patients with warm ischemia, and also more with prolonged duration of ischemia (>25–35 min), and thus facilitated a more refined perspective about the potential impact of ischemia. However, it is important to note that while ischemia correlated significantly with functional outcomes, the effects were rather marginal. On average, choice of warm rather than cold ischemia reduced the functional recovery only 7%, and each additional 10-min interval of warm ischemia reduced the functional recovery by only an additional 2.5%. Hence, a 40-min interval of warm ischemia would, on average, reduce the functional recovery in the ipsilateral kidney by only 17% [43]. By placing this field on a more scientific basis, these recent studies further support the importance of both quality and quantity with respect to functional recovery after PN, and they also demonstrate real effects of ischemia, albeit marginal in impact.

Limited or Zero Ischemia PN: Real-world Test of Importance of Ischemia

Despite evidence showing that ischemia plays a limited role in the recovery of function after PN, several technical modifications have been made to reduce or eliminate exposure to ischemia. These modifications include early unclamping, selective vascular clamping, and zero ischemia approaches, and their feasibility and impact on functional recovery has been evaluated in several retrospective studies (Table 13.2d) [44–47]. In a cohort of patients with solitary kidneys, Thompson et al. compared the outcomes of off-clamp PN with clamped PN with warm ischemia [44]. Warm ischemia (median = 21 min) was associated with increased risk of developing new-onset stage IV CKD compared to off-clamp PN (HR 2.3, 95% CI 1.3–5.8). Other retrospective studies have reported similar findings; however, selection bias may be a contributing factor [6, 8]. Patients undergoing off-clamp PN are more likely to have small, peripheral tumors, and parenchymal mass loss is typically less in this setting. However, nephron mass preservation was not incorporated into these analyses, so definitive conclusions are difficult to draw.

Gill and colleagues have pushed forward with a variety of innovative approaches to reduce or eliminate ischemia [46, 47]. These techniques are feasible in hands of experienced surgeons and may provide benefit in the setting of severe preexisting CKD, where a patient may be on the verge of dialysis. However, zero or superselective clamping can be associated with increased blood loss and transfusion rates. Furthermore, these modifications are technically challenging and diffusion can be limited due to a steep learning curve [6, 7]. Beyond this, the logical question arises as to whether these technically complex modifications provide a significant functional advantage over the traditional clamped PN? Comparison of functional outcomes has failed to establish superiority of reduced ischemia approaches over traditional clamped PN. Global GFR preservation noted with zero/selective clamping has been in range of 86–92% (Table 13.2d), which is not substantially improved when compared to clamped PN [6–8, 43, 46].

Studies Evaluating Biomarkers and Histologic Changes During PN

A study by Parekh and colleagues also suggests that ischemia may not be as deleterious as previously thought [48]. This group studied a limited cohort of 40 patients and prospectively evaluated the renal histological and functional changes associated with ischemia with duration up to 60 min during minimally invasive PN (Table 13.2e). Renal histological changes were less pronounced than previously noted in analogous animal studies and renal functional changes did not correlate with duration of ischemia. Furthermore, biomarkers of renal tubular injury also failed to correlate with functional outcomes [48]. This study suggests that the human kidney may tolerate prolonged ischemia better than previously thought; however, given the limitations of the analysis, further studies will be needed in this area.

Functional Recovery in Poorly Functioning Kidneys

Patients with poorly functioning kidneys pose a major challenge in the management of renal masses. Some have proposed that such kidneys may be more frail and thus less likely to recover from the ischemic insult. Mir and colleagues addressed this by evaluating four tiers of functional status within the operated kidney, namely, ipsilateral kidneys with GFR > 60 ml/min/1.73 m^2, GFR 45–60 ml/min/1.73 m^2, GFR 30–45 ml/min/1.73 m^2, or GFR < 30 ml/min/1.73 m^2 [41]. Recovery from ischemia was defined as percentage of GFR saved in the operated kidney normalized by percentage of parenchymal mass saved and would be 100% if all nephrons recovered completely from the ischemic insult. In a cohort of 155 patients, preoperative GFR status was not associated with recovery from ischemia, as it remained high (90–100%) in all of the cohorts. Kidneys with preoperative GFR < 30 ml/min/1.73 m^2 had median recovery from ischemia of 99% suggesting that even poorly functioning kidneys recover well from the ischemic insult, i.e., proportional to nephron mass preserved, as long as cold ischemia or limited warm ischemia is utilized [41].

Acute Kidney Injury After PN

Most studies in the literature have predominantly focused on new baseline GFR that is defined a few to several months after PN. However, acute changes in renal function within the immediate postoperative period could also be important and may play a role in establishing the new baseline GFR. In the general population, AKI due to medical etiologies, such as congestive heart failure, can predispose to CKD, but it is unknown if AKI due to surgical exposure to ischemia also predispose to CKD [8].

Zhang and colleagues addressed this by evaluating a cohort of patients with a solitary kidney undergoing PN to assess the incidence of AKI, risk factors for AKI, and impact of AKI on subsequent functional recovery [49]. One of the fundamental findings was that AKI as defined by conventional criteria (peak serum creatinine level (SCr) normalized by preoperative SCr) typically overestimated the incidence and degree of AKI, because it does not take into account nephron mass loss, which is the other major source of increased SCr in the early postoperative period. In this study the authors proposed a novel criteria for AKI after PN, whereby the peak SCr is normalized by the projected peak SCr taking into account loss of nephron mass. In this manner the degree of AKI more accurately reflects the true impact of ischemia. On multivariable analysis, ischemia time correlated with increased degree of AKI. While increased degree of AKI by the proposed criteria correlated with reduced functional recovery, even patients with grade 3 AKI ultimately reached functional recovery levels of 88–90% [49].

Further work by Zhang and colleagues focused on studying AKI in patients with two kidneys, which is more complex because the contralateral kidney can mask functional events within the operated kidney [50]. To address this they developed a novel "spectrum score" whereby the peak postoperative SCr level is placed on a spectrum between two extreme scenarios. In the worst-case scenario, the operated kidney completely shuts down temporarily due to ischemic injury and renal function is entirely dependent on the contralateral kidney. Based on preoperative renal scans with split renal function, the projected worst-case peak SCr can be estimated. In the best-case scenario, the operated kidney does not experience or exhibit any ischemic injury, and changes in postoperative SCr levels are only influenced by nephron mass loss related to the surgery. Again, a projected peak SCr related to this best-case scenario can be estimated. The observed peak SCr level can then be placed on the spectrum between these two extreme values, on a scale from 0 to 100%, with the latter corresponding to the worst-case scenario. Four quartiles of spectrum score were defined as 0–25%, 26–50%, 51–75%, and 76–100%, and increased spectrum score correlated with ischemia type (warm worse than cold) and duration of ischemia. While increased spectrum score, analogous to increased degree of AKI, correlated significantly with reduced functional recovery, even patients with high spectrum score still ultimately demonstrated relative strong functional recovery (median = 83%) [50]. Further work is needed to understand the implications of AKI with respect to stability of renal function on a longitudinal basis.

Vascularized Nephron Mass: The Key to Functional Outcomes with PN

As outlined above, the quantity of vascularized parenchymal mass preserved has been established as the most important determinant of functional outcomes after PN, presuming that extended warm ischemia has been avoided [6–8]. Loss of vascularized nephron mass can be due to two primary sources (Fig. 13.3): (1) healthy parenchyma that is excised along with the mass (excised parenchymal mass, EPM) and (2) parenchyma that is devascularized during the reconstructive phase of the procedure (devascularized parenchymal mass, DPM).

Several studies have focused on technical modifications, such as "minimal-margin" PN or tumor enucleation (TE), to limit EPM [47, 51]. During TE blunt dissection is performed within the hypovascular plane along the pseudocapsule, potentially preserving more vascularized nephron mass. Current perspective about the role of TE in the management of localized kidney cancer is provided in

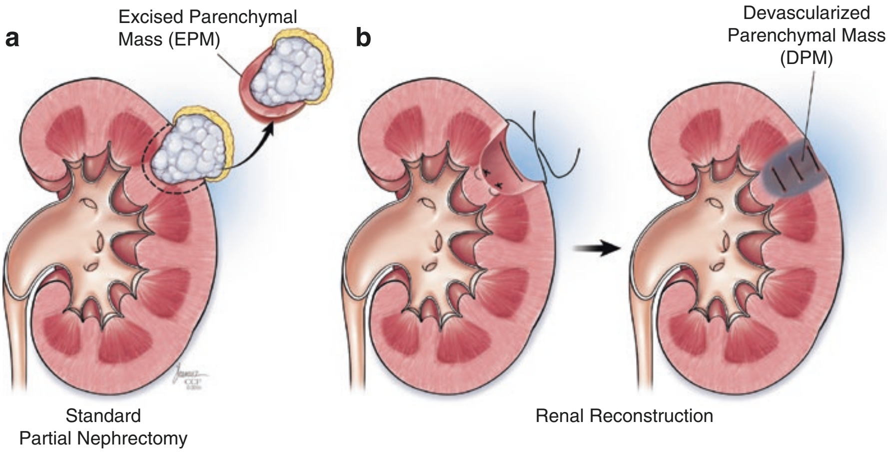


Fig. 13.3 Loss of nephron mass during partial nephrectomy (PN) is primarily due to excised parenchymal mass (EPM) or devascularized parenchymal mass (DPM), as illustrated in **a** and **b**, respectively. Renal reconstruction typically includes sutures placed into the base of the defect to address transected vessels and capsular re-approximation to reduce the risk of postoperative hemorrhage and urine leak. In the process a modest amount of parenchyma is devascularized. (From Dong et al. [52], with permission of Elsevier)

the recent AUA guidelines (see section on principles related to PN). In a recent study, median ipsilateral vascularized parenchymal mass preserved was 95% for TE and 84% for standard PN ($p < 0.001$), and median estimated global GFR preserved was 101% and 89% for TE and standard PN, respectively ($p < 0.001$). This study suggests that TE may provide marginally better functional outcomes than standard PN [51].

Another concept to minimize EPM is a minimal-margin approach to PN whereby wedge resection is prioritized rather than heminephrectomy, and this has been adopted at many centers. Dong and colleagues recently studied the impact of EPM and DPM in a cohort of 168 patients resected with a minimal-margin approach to PN [52]. Median EPM was 9 cm^3, representing only 5% of the preoperative ipsilateral parenchymal mass. In contrast, median DPM was 16 cm^3, representing 9% of the preoperative ipsilateral parenchymal mass. As expected, total loss of vascularized parenchymal mass correlated strongly with functional outcomes ($r = 0.64$, $p < 0.001$). DPM also correlated strongly with functional outcomes ($r = 0.55$, $p < 0.001$), while EPM failed to correlate. This suggests that loss of vascularized parenchymal mass predominantly occurs during the reconstructive phase of PN, and in this era of minimal-margin PN, the amount of nephron mass excised along with the tumor is of secondary importance. This emphasizes the need for precise ligation of transected vessels within the parenchymal defect, taking care to avoid inadvertent occlusion of adjacent branch arteries. Capsular closure should also be performed carefully to minimize devascularization, or this step can be omitted in some circumstances. TE may facilitate reduced DPM by precluding the need for capsular closure and reducing the need for parenchymal suturing [51].

Additional Surgical Considerations to Optimize Renal Function Preservation

Mir [6] and Volpe [7] comprehensively reviewed the factors associated with functional recovery after PN (Table 13.2f) and outline a number of practical measures or intraoperative maneuvers to minimize loss of function associated with the procedure. The most important modifiable factors associated with the decline in function after PN are suboptimal preservation of vascularized nephron mass and incomplete recovery from renal ischemia (Fig. 13.4).

In Fig. 13.4a, preventive measures to avoid irreversible ischemic injury are detailed. Among these, the most substantial experience has been with cold ischemia and the clinical experience in favor of hypothermia as a protective factor is robust. Surgical modifications to reduce exposure to global ischemia within the operated kidney have also shown promise, although further research is needed. In particular, it will be important to define which cohorts of patients should be considered for these approaches. Patients with severe preexisting CKD might benefit most from a zero ischemia approach, because any form of ischemia, even hypothermia, can increase the risk of AKI and potential need for dialysis in the early postoperative period [35]. Also, even with hypothermia, there can be some variability in recovery from ischemia, and in this setting complete avoidance of ischemia may be worth the increased complexity and possible risks of the procedure [35]. Several pharmacological agents have been investigated in an effort to prophylactically ameliorate the effects of ischemia. Mannitol has been used for this purpose for the past three to four decades, but a recent randomized trial of mannitol versus placebo failed to show any significant differences in functional recovery,

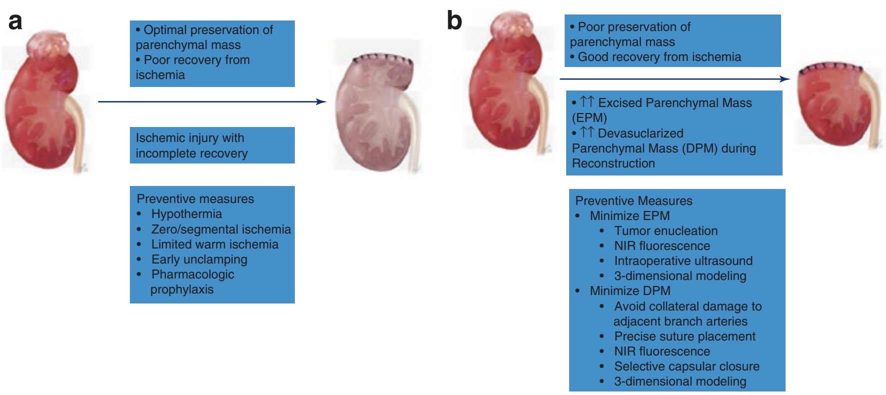


Fig. 13.4 Etiology of decline in renal function following partial nephrectomy and potential preventive measures. (**a**) Decline in function due to poor recovery from ischemia in the setting of optimal preservation of nephron mass. (**b**) Decline in function due to poor preservation of nephron mass in the setting of good recovery from ischemia. (From Mir et al. [6], Figs. 2, 3, with permission of Elsevier)

either short or long term [53]. Dopamine and fenoldopam have also been used in high-risk situations, such as solitary kidneys, to decrease the risk of AKI [54, 55]. However, randomized trials again failed to substantiate a benefit over placebo. Antioxidants including vitamins C and E have also been studied yet have not proven to be renoprotective [6]. In summary, the pharmacological agents investigated to date have not shown a protective effect against ischemic injury, and further research is needed [6].

As previously discussed, parenchymal mass preservation is of paramount importance for functional recovery from PN. Parenchymal mass preservation can be optimized by decreasing EPM and DPM and the practical measures to accomplish this are reviewed in Fig. 13.4b. The potential importance of TE or minimal-margin PN for reducing EPM was discussed above and such approaches may also minimize DPM by facilitating a more manageable reconstruction. Beyond this, advanced preoperative or intraoperative imaging, such as intraoperative ultrasound, near-infrared fluorescence, or three-dimensional modeling, may also be of use [56–58]. Information derived from such studies may help guide the resection allowing for more precise excision and strategic avoidance of branch arteries during reconstruction. For instance, adjacent branch arteries can be readily visualized with near-infrared fluorescence and by defining the edge of the tumor a more precise resection can be accomplished while still obtaining negative surgical margins. These imaging modalities are most useful for hilar or other endophytic tumors, but further research will be needed to explore their potential functional benefits.

Future Directions

Most studies on the implications of functional loss after renal mass surgery have follow-up that is limited to a decade or less. Studies with longer follow-up will be needed to determine the ultimate effect of functional loss on survival, which will be particularly important when managing younger patients. Also needed is a randomized trial of PN versus RN for larger renal masses, or other situations where oncologic potential is increased, such as infiltrative appearance on imaging or unfavorable histology on renal mass biopsy. In these settings optimal management is still controversial, in part related to concerns about selection biases [10]. Ideally such a trial would use overall survival as the primary endpoint and secondary outcomes could include functional stability, cardiovascular events, and cancer-related survival. The long-term implications of AKI after PN will also require further study, as some have hypothesized that nephrons that have been exposed to ischemic injury may be more frail during longitudinal follow-up [8]. Well-designed prospective studies will also be required to more fully understand the effects of EPM and DPM on functional outcomes after PN and to define procedural considerations to optimize outcomes with respect to both of these parameters [52].

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
2. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol. 2016;196(4):989–99.
3. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. J Urol. 2009;182(4):1271–9.
4. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198:520–9.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
6. Mir MC, Ercole C, Takagi T, Zhang Z, Velet L, Remer EM, et al. Decline in renal function after partial nephrectomy: etiology and prevention. J Urol. 2015;193(6):1889–98.
7. Volpe A, Blute ML, Ficarra V, Gill IS, Kutikov A, Porpiglia F, et al. Renal ischemia and function after partial nephrectomy: a collaborative review of the literature. Eur Urol. 2015;68(1):61–74.
8. Zabell JR, Wu J, Suk-Ouichai C, Campbell SC. Renal ischemia and functional outcomes following partial nephrectomy. Urol Clin North Am. 2017;44(2):243–55.
9. Kim SP, Campbell SC, Gill I, Lane BR, Van Poppel H, Smaldone MC, et al. Collaborative review of risk benefit trade-offs between partial and radical nephrectomy in the management of anatomically complex renal masses. Eur Urol. 2017;72(1):64–75.
10. Weight CJ, Miller DC, Campbell SC, Derweesh IH, Lane BR, Messing EM. The management of a clinical t1b renal tumor in the presence of a normal contralateral kidney. J Urol. 2013;189(4):1198–202.
11. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2011;59(4):543–52.
12. Lane BR, Campbell SC, Demirjian S, Fergany AF. Surgically induced chronic kidney disease may be associated with a lower risk of progression and mortality than medical chronic kidney disease. J Urol. 2013;189(5):1649–55.
13. Lane BR, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. Eur Urol. 2015;68(6):996–1003.
14. Gor R, Uzzo R, Li T, Haseebuddin M, Waingankar N, Ginzburg S, et al. Surgical chronic kidney disease appears to be a distinct subtype of chronic kidney disease based on mortality risks following renal surgery. J Urol. 2015;193:e975–6.
15. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837–46.
16. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Publ Gr. 2017;13:104–14.
17. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol. 2006;7(9):735–40.
18. Mashni JW, Assel M, Maschino A, Russo M, Masi B, Bernstein M, et al. New chronic kidney disease and overall survival after nephrectomy for small renal cortical tumors. Urology. 2015;86(6):1137–45.
19. Licht MR, Novick AC. Nephron sparing surgery for renal cell carcinoma. J Urol. 1993;149(1):1–7.

20. Herr HW. Partial nephrectomy for unilateral renal carcinoma and a normal contralateral kidney: 10-year followup. J Urol. 1999;161(1):33–4. discussion 34–5
21. Russo P, Goetzl M, Simmons R, Katz J, Motzer R, Reuter V. Partial nephrectomy: the rationale for expanding the indications. Ann Surg Oncol. 2002;9(7):680–7.
22. BC L, ML B, JC C, CM L, AL W, H Z. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. J Urol. 2004;171(3):1066–70.
23. Karellas ME, O'Brien MF, Jang TL, Bernstein M, Russo P. Partial nephrectomy for selected renal cortical tumours of ≥7 cm. BJU Int. 2010;106(10):1484–7.
24. Breau RH, Crispen PL, Jimenez RE, Lohse CM, Blute ML, Leibovich BC. Outcome of stage T2 or greater renal cell cancer treated with partial nephrectomy. J Urol. 2010;183(3): 903–8.
25. Kim SP, Thompson RH, Boorjian SA, Weight CJ, Han LC, Murad MH, et al. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. J Urol. 2012;188(1):51–7.
26. Tan H-J, Norton EC, Ye Z, Hafez KS, Gore JL, Miller DC. Long-term survival following partial vs radical nephrectomy among older patients with early-stage kidney cancer. JAMA. 2012;307(15):1629–35.
27. Weight CJ, Larson BT, Fergany AF, Gao T, Lane BR, Campbell SC, et al. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. J Urol. 2010;183(4): 1317–23.
28. Shuch B, Hanley J, Lai J, Vourganti S, Kim SP, Setodji CM, et al. Overall survival advantage with partial nephrectomy: a bias of observational data? Cancer. 2013;119(16):2981–9.
29. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol. 2014;65(2):372–7.
30. Zabell J, Demirjian S, Campbell SC. MP59-15 long-term outcomes after renal cancer surgery: predictors of chronic kidney disease and non-renal cancer mortality. J Urol. 2017;197(4):e786–7.
31. Capitanio U, Terrone C, Antonelli A, Minervini A, Fiori C, Zegna L, et al. MP44-04 nephron-sparing surgery protects from chronic kidney disease relative to radical nephrectomy but does not impact on other-causes mortality: long-term (more than 10 years) survival and functional outcomes in patients with a T1A-T1B renal mass. J Urol. 2015;193(4):e527.
32. Wu J, Suk-Ouichai C, Dong W, Antonio EC, Derweesh IH, Lane BR, et al. Analysis of survival for patients with chronic kidney disease primarily related to renal cancer surgery. BJU Int. 2018;121(1):93–100.
33. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2007;51(6):1606–15.
34. Yossepowitch O, Eggener SE, Serio A, Huang WC, Snyder ME, Vickers AJ, et al. Temporary renal ischemia during nephron sparing surgery is associated with short-term but not long-term impairment in renal function. J Urol. 2006;176(4):1339–43.
35. Zhang Z, Zhao J, Velet L, Ercole CE, Remer EM, Mir CM, et al. Functional recovery from extended warm ischemia associated with partial nephrectomy. Urology. 2016;87:106–13.
36. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Every minute counts when the renal hilum is clamped during partial nephrectomy. Eur Urol. 2010;58(3):340–5.
37. Lane BR, Russo P, Uzzo RG, Hernandez AV, Boorjian SA, Thompson RH, et al. Comparison of cold and warm ischemia during partial nephrectomy in 660 solitary kidneys reveals predominant role of nonmodifiable factors in determining ultimate renal function. J Urol. 2011;185(2):421–7.

38. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Renal function after partial nephrectomy: effect of warm ischemia relative to quantity and quality of preserved kidney. Urology. 2012;79(2):356–60.
39. Song C, Park S, Jeong IG, Hong JH, Park HK, Kim C-S, et al. Followup of unilateral renal function after laparoscopic partial nephrectomy. J Urol. 2011;186(1):53–8.
40. Mir MC, Campbell RA, Sharma N, Remer EM, Li J, Demirjian S, et al. Parenchymal volume preservation and ischemia during partial nephrectomy: functional and volumetric analysis. Urology. 2013;82(2):263–9.
41. Mir MC, Takagi T, Campbell RA, Sharma N, Remer EM, Li J, et al. Poorly functioning kidneys recover from ischemia after partial nephrectomy as well as strongly functioning kidneys. J Urol. 2014;192(3):665–70.
42. Ginzburg S, Uzzo R, Walton J, Miller C, Kurz D, Li T, et al. Residual parenchymal volume, not warm ischemia time, predicts ultimate renal functional outcomes in patients undergoing partial nephrectomy. Urology. 2015;86(2):300–6.
43. Dong W, Wu J, Suk-Ouichai C, Caraballo Antonio E, Remer EM, Li J, et al. Ischemia and functional recovery from partial nephrectomy: refined perspectives. Eur Urol Focus. 2017; https://doi.org/10.1016/j.euf.2017.02.001.
44. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Comparison of warm ischemia versus no ischemia during partial nephrectomy on a solitary kidney. Eur Urol. 2010;58(3):331–6.
45. Smith GL, Kenney PA, Lee Y, Libertino JA. Non-clamped partial nephrectomy: techniques and surgical outcomes. BJU Int. 2011;107(7):1054–8.
46. Desai MM, de Castro Abreu AL, Leslie S, Cai J, Huang EY-H, Lewandowski P-M, et al. Robotic partial nephrectomy with superselective versus main artery clamping: a retrospective comparison. Eur Urol. 2014;66(4):713–9.
47. Satkunasivam R, Tsai S, Syan S, Bernhard J-C, de Castro Abreu AL, Chopra S, et al. Robotic unclamped "minimal-margin" partial nephrectomy: ongoing refinement of the anatomic zero-ischemia concept. Eur Urol. 2015;68(4):705–12.
48. Parekh DJ, Weinberg JM, Ercole B, Torkko KC, Hilton W, Bennett M, et al. Tolerance of the human kidney to isolated controlled ischemia. J Am Soc Nephrol. 2013;24(3):506–17.
49. Zhang Z, Zhao J, Dong W, Remer E, Li J, Demirjian S, et al. Acute kidney injury after partial nephrectomy: role of parenchymal mass reduction and ischemia and impact on subsequent functional recovery. Eur Urol. 2016;69(4):745–52.
50. Zhang Z, Zhao J, Dong W, Aguilar Palacios D, Remer EM, Li J, et al. Acute ipsilateral renal dysfunction after partial nephrectomy in patients with a contralateral kidney: Spectrum score to unmask ischemic injury. Eur Urol. 2016;70(4):692–8.
51. Dong W, Gupta GN, Blackwell RH, Wu J, Suk-Ouichai C, Shah A, et al. Functional comparison of renal tumor enucleation versus standard partial nephrectomy. Eur Urol Focus. 2017;3:437.
52. Dong W, Wu J, Suk-Ouichai C, Caraballo Antonio E, Remer E, Li J, et al. Devascularized parenchymal mass associated with partial nephrectomy: predictive factors and impact on functional recovery. J Urol. 2017;198(4):787–94.
53. Spaliviero M, Power NE, Murray KS, Sjoberg DD, Benfante NE, Bernstein ML, et al. Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: a double-blind, clinically-integrated, randomized trial. Eur Urol. 2017; 16:e369.
54. O'Hara JF, Mahboobi R, Novak SM, Bonilla AM, Mascha EJ, Fergany AF, et al. Fenoldopam and renal function after partial nephrectomy in a solitary kidney: a randomized, blinded trial. Urology. 2013;81(2):340–6.
55. O'Hara JF, Hsu THS, Sprung J, Cywinski JB, Rolin HA, Novick AC. The effect of dopamine on renal function in solitary partial nephrectomy surgery. J Urol. 2002;167(1):24–8.

56. Kaczmarek BF, Sukumar S, Petros F, Trinh Q-D, Mander N, Chen R, et al. Robotic ultrasound probe for tumor identification in robotic partial nephrectomy: initial series and outcomes. Int J Urol. 2013;20(2):172–6.
57. Bjurlin MA, Gan M, McClintock TR, Volpe A, Borofsky MS, Mottrie A, et al. Near-infrared fluorescence imaging: emerging applications in robotic upper urinary tract surgery. Eur Urol. 2014;65(4):793–801.
58. Ahmadi H, Liu J-J. 3-D imaging and simulation for nephron sparing surgical training. Curr Urol Rep. 2016;17(8):58.