Invited Review Article

Parenchymal volume analysis and functional recovery after partial and radical nephrectomy for renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) accounts for 2-3% of adult malignancies and has the highest mortality among genitourinary cancers. With the increasing use of cross-sectional imaging, RCC is now frequently diagnosed incidentally and at earlier stages, and partial nephrectomy (PN) has become the standard treatment for small renal masses. In appropriately selected patients, PN can significantly reduce the risk of chronic kidney disease (CKD), CKD-related mortality, and cardiovascular events. In cases where PN is high-risk or not feasible, radical nephrectomy (RN) remains a valid alternative, particularly when the new baseline glomerular filtration rate (NBGFR) is anticipated to be greater than 45 ml/min/1.73 m^2.

Functional recovery after surgery depends on multiple factors. Among these, parenchymal volume loss has been identified as the primary determinant, accounting for 70–80% of the decline in function associated with PN. Ischemia, particularly warm ischemia exceeding 30 minutes, can also contribute to renal impairment albeit to a lesser extent. Cold ischemia has a comparatively minor effect and is generally protective. Vascularized parenchymal loss results from both tumor resection and devascularization during reconstruction, with the latter playing the predominant role. Preserving well-perfused renal parenchyma is thus crucial for optimal recovery.

To analyze functional recovery after PN, accurate estimates of split renal function (SRF) are required to evaluate outcomes specific to the kidney exposed to ischemia. Our recent studies have used parenchymal volume analysis (PVA) rather than nuclear renal scans to estimate SRF, and this has allowed us to provide a more discerning analysis. PVA presumes that the amount of parenchyma on each side is proportionate to its function and this approach has proven to be more accurate than nuclear renal scans

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for estimating SRF. PVA also provides more accurate and objective measurements of the percent of parenchymal volume preserved (PPVP). Finally, PVA only requires availability of preoperative and postoperative imaging studies for analysis, allowing more robust cohorts of patients to be studied.

This article reviews and summarizes the modern perspectives regarding the preoperative, intraoperative, and postoperative factors influencing renal functional recovery after renal cancer surgery, aiming to guide surgical planning and improve patient outcomes.

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Introduction

Historically, most patients with renal cell carcinoma (RCC) presented with large, palpable renal masses, abdominal pain, and gross hematuria. However, with the widespread use of advanced imaging, more than 50.0% of renal tumors are now detected incidentally, often at a smaller size than seen in previous decades.[1]

As a result, partial nephrectomy (PN) has become the standard of care for most patients with RCC. PN improves functional outcomes, and in appropriately selected patients the associated morbidity remains low, with an overall complication rate of approximately 3.0-5.0%.[2,3] In cases where PN is not feasible or high risk, radical nephrectomy (RN) remains a viable treatment option. Prior studies have shown that patients who maintain a NBGFR >45 ml/min/1.73m² following RN have strong overall survival comparable to patients without CKD after surgery.[2,4,5] Therefore, RN may be considered in patients with high tumor complexity or aggressive tumor biology, provided the postoperative NBGFR exceeds this threshold.

Given the kidney's highly vascular nature, vascular occlusion is often required during PN to ensure a bloodless surgical field and facilitate tumor resection. However, this introduces ischemia, which may adversely affect postoperative renal function. Previous studies, particularly one titled "Every minute counts" suggested that ischemia was rather important, reporting that each additional minute of warm ischemia time associated with a 5.0% increased risk of acute kidney injury (AKI) and a 6.0% increased risk of stage 4 CKD.[6]

However, this data was misleading, because the analysis did not include parenchymal volume loss. When parenchymal volume loss was incorporated into the analysis, it proved to be the most significant determinant of functional recovery following PN, with ischemia playing a less critical role. Ischemia was essentially found to be a confounder.[7,8]

Further studies using more advanced methodologies and robust study populations have recently shown that warm ischemia actually can deleteriously impact functional recovery after PN to a modest degree, while hypothermia is protective. To drill down on the outcomes in the kidney exposed to ischemia, accurate estimates of split renal function (SRF) are required. Since 2022 we have used parenchymal volume analysis (PVA) rather than nuclear renal scans to estimate SRF and this has revolutionized the field. PVA has facilitated a more robust and intensive analysis of the impact of ischemia and other secondary factors on functional recovery after PN.[9-12]

While it has been interesting to learn more about such secondary factors, these studies have also confirmed that PPVP during PN is of paramount importance. PPVP is the king, and ischemia and other secondary factors are the jesters. Achieving a bloodless surgical field introduces ischemia, but more importantly it facilitates maximal preservation of functioning renal tissue and thus optimizes functional outcomes.[13]

Interestingly, analysis of long-term follow-up after PN demonstrates that the functional trajectory of the kidney exposed to ischemia, after initial recovery, is comparable to that of the contralateral kidney. Both kidneys exhibit similar rates of age-related decline, even though the ipsilateral kidney has been exposed to ischemia.[14,15]

The objective of this article is to comprehensively review the factors influencing renal functional recovery following PN, in contrast to RN, based on current literature and evidence (KEY POINTS).

KEY POINTS

- Software based parenchymal volume analysis (PVA) has revolutionized the analysis of functional outcomes after renal cancer surgery. PVA allows more patients to be analyzed and provides more accurate estimates of split renal function and percent parenchymal volume preserved.
- Preserving parenchymal volume is the most important factor in determining functional recovery after PN. Loss of parenchymal volume accounts for approximately 70–80% of the decline in function associated with the procedure.
- Ischemia can also contribute to the decline of function following PN as a secondary factor, but this typically is only seen with prolonged warm ischemia (> 30 minutes).
- Limiting warm ischemia time to less than 30 minutes and using cold ischemia are associated with negligible functional decline related to ischemia.
- Zero ischemia PN can provide a benefit for functional recovery; however, the difference is marginal and may be associated with an increased risk of perioperative complications.
- The reconstructive phase of PN is the most critical in terms of parenchymal volume preservation and functional recovery.
- For tumors with increased oncologic risk or for those with increased tumor complexity, radical nephrectomy may be a reasonable consideration, particularly if the NBGFR is anticipated to be >45 ml/min/1.73 m^2.
- NBGFR after radical nephrectomy can be estimated as: 1.25 × (Preoperative GFR_{Global}) × (Split Renal $Function_{Contralateral}$).

Prediction of New Baseline GFR after Radical Nephrectomy (RN)

According to current consensus, the new baseline GFR (NBGFR) measured 1-12 months after PN or RN serves as a reliable indicator of functional recovery.[7,8] Using GFR values measured earlier than this may lead to inaccurate assessments, because some patients may develop AKI following PN, requiring time for the nephrons to recover. After RN, the contralateral kidney will undergo renal functional compensation and typically requires several weeks to establish its NBGFR. GFR values beyond 12 months may reflect the impact of other medical comorbidities and the aging process and are not preferred for analysis of recovery from surgery. Between 1-12 months postoperatively, the GFR tends to remain stable and is defined as the NBGFR.[7,8,16]

For patients undergoing RN, a predictive formula for estimating NBGFR has been established as follows:

$$\text{NBGFR after RN} = 1.25 \times (\text{Preoperative } GFR_{Global}) \times (\text{Split Renal } Function_{Contralateral})$$

This SRF-based formula has outperformed all other algorithms for predicting NBGFR after RN. The coefficient 1.25 represents the average amount of renal functional compensation observed in adults after loss of a kidney.[17,18]

The SRF used in this formula has traditionally been derived from nuclear renal scans but recent studies have demonstrated that PVA is more accurate for this purpose (Fig. 1). Such measurements are now facilitated by readily accessible software platforms capable of producing precise estimates of both tumor and parenchymal volumes. The incorporation of direct measurements of vascularized parenchymal volume represents a significant advance in predicting postoperative renal function, enabling more individualized surgical planning and improved prediction of functional outcomes.

Predicting New Baseline GFR after Partial Nephrectomy (PN)

For patients who undergo PN, the preferred formula for predicting NBGFR is even more simple:[12]

$$\text{NBGFR} = 0.9 \times (\text{Preoperative Global GFR})$$

This formula has proven to be equivalent to or superior to all other algorithms that have been published, most of which are rather complex. The average PN is associated with only a minimal loss of parenchyma, and thus function, so the NBGFR is strongly anchored by the preoperative global GFR. While this estimate tends to be very accurate, it can be influenced by the complexity of the surgery. In cases involving high tumor complexity, one can assume that approximately 80.0-85.0% of renal function may be preserved, whereas in cases of low to intermediate tumor complexity, 95.0% of renal function may be retained.[19,20]

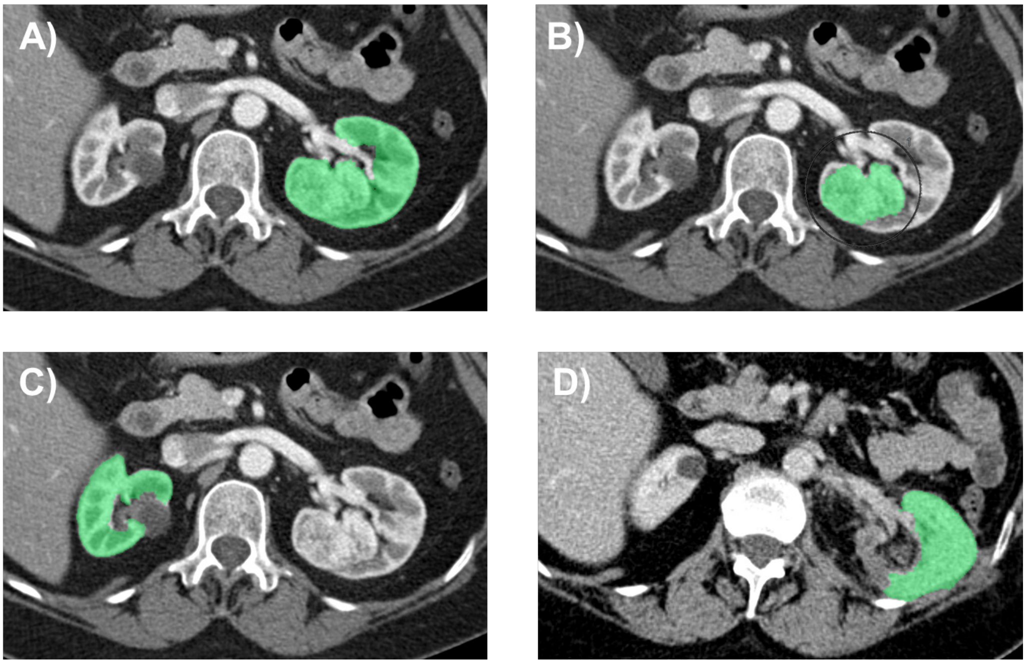

Figure 1. Parenchymal volume analysis (PVA) using three-dimensional volumetric software. Methodology for PVA using three-dimensional volume-calculating software (Fujifilm Medical Systems Inc., Tokyo, Japan). A) Measurement of the left (ipsilateral) kidney and tumor combined, with a total volume of 260 ml. B) Measurement of the tumor alone, calculated at 30 ml, resulting in an ipsilateral parenchymal volume of 230 ml (260 ml – 30 ml). C) Measurement of the right (contralateral) kidney, excluding a renal cyst, with a volume of 140 mL, consistent with a modest degree of atrophy. D) Measurement of the ipsilateral kidney following PN, excluding devascularized/atrophic parenchyma identified by reduced contrast enhancement, which was 180 ml. Using these measurements, the preoperative ipsilateral SRF could be calculated as the ipsilateral parenchymal volume normalized by the total parenchymal volume, which in this case was (230 ml ÷ (230 ml + 140 ml)) x 100% = 62%. This confirms that the ipsilateral kidney was the predominant functioning kidney despite the presence of the tumor. The ipsilateral percent parenchymal volume preserved (PPVP) could also be calculated as follows, PPVP = postoperative ipsilateral parenchymal volume normalized by preoperative parenchymal volume. In this case the PPVP was (180 ml ÷ 230 ml) x 100% = 78%.

Short- and Long-term Effects of Renal Parenchymal Reduction on Renal Function

Following RN, a decline in renal function typically occurs in the short term. However, compensatory mechanisms in the contralateral kidney are initiated to offset the loss.[21,22] Despite the reduction in nephron complement, the intake of nutrients, salts, and fluids remains constant. Therefore, the remaining nephrons must increase their workload to maintain fluid and electrolyte homeostasis. While this adaptive mechanism is beneficial, over time, chronic hyperfiltration may develop, primarily due to elevated glomerular pressure, potentially leading to progressive renal damage or contributing to further functional decline.[23] However, this is only seen when the NBGFR falls below critical levels, such as <30 ml/min/1.73m^2 [24,25]

Studies have shown that in patients with a healthy contralateral kidney managed with PN, renal function tends to remain stable for several years, with only modest age-related changes. However, in elderly patients or those with risk factors such as smoking, hypertension, and diabetes, postoperative decline in renal function may exceed the rate of decline expected from the normal aging process.[8,13,25-27]

Preoperative Factors Affecting Functional Recovery after PN

Recent studies suggest that nonmodifiable preoperative factors can influence functional recovery after PN, including patient age and significant renal comorbidities, such as:[8,14,27]

- Hypertension (HTN) that requires more than three medications for control,
- Insulin-dependent diabetes mellitus (DM) or diabetes with end-organ damage, and
- Preexisting chronic kidney disease (CKD) stage 4-5.

Recent reports suggest that patients with CKD stage 4 and an GFR of less than 25-30 ml/

min/1.73m² may be a special consideration. Tumors in this population are often less aggressive, and these patients are generally not very healthy. As such, they can experience increased morbidity and unfavorable perioperative outcomes following PN. Therefore, in this high-risk population, PN should be approached with caution.[28,29] In selected cases, alternative strategies such as active surveillance with delayed RN may be more appropriate, depending on the patient's overall condition and oncologic risk. With this, RN is delayed until the patient has developed end stage renal failure.

Age-related decline in renal function is well documented. In the general population, GFR declines by approximately 0.8 mL/min/1.73m² per year (0.4 ml/min/1.73m² per kidney per year) after age 40.[30,31] Patients with medical comorbidities may experience a more rapid decline of 1.6–2.0 mL/min/1.73m² annually.[15,32] Similarly, individuals with hypertension tend to show faster deterioration compared to healthy peers. For patients with and without pre-existing CKD, the annual decline differs significantly—about 0.7% in non-CKD patients versus 4.7% in patients with preexisting CKD.[33]

Another important factor affecting PN outcomes is surgical experience. High-volume centers (performing more than 42 PN cases/year) show better oncologic and functional outcomes and fewer complications than low-volume centers.[34]

Intraoperative Factors Affecting Functional Recovery after PN

Among intraoperative variables, parenchymal volume preservation is the most critical determinant of functional recovery. During PN, meticulous surgical technique is essential. While the primary goal remains oncological efficacy, maximizing preservation of vascularized parenchymal volume is crucial for functional outcomes.[2,8,19]

Vascularized parenchymal volume loss occurs in two ways: 1) excised parenchymal volume—parenchyma removed along with the tumor to ensure negative margins; and 2) devascularized parenchymal volume—preserved tissue that becomes non-functional due to loss of blood supply during reconstruction.[35,36]

On average, about 20.0% of the vascularized parenchyma volume in the ipsilateral kidney is lost with PN, with about one-third due to excision and two-thirds due to devascularization. Hence, precision in renal reconstruction is crucial to optimizing functional outcomes.[8,37,38]

Intraoperative mannitol administration during PN was thought to help preserve renal function; however, more recent studies have shown that intraoperative mannitol administration in patients with normal preoperative renal function does not improve functional outcomes at 6 months postoperatively.[39-41]

In terms of ischemia type, patients undergoing zero ischemia PN have the potential for optimal functional outcomes, followed by cold and then warm ischemia. However, zero ischemia cases have typically been less complex (e.g., lower RENAL scores, smaller tumor size) so direct comparisons are difficult to support.[8,42] Two randomized trials showed no functional advantage of zero ischemia PN over clamped PN, although the patients enrolled in these studies mostly had low complexity tumors, so the comparison was zero versus limited warm ischemia.[43-45] With prolonged warm ischemia, particularly beyond 30 minutes, functional outcomes worsen—ipsilateral recovery from ischemia decreases by approximately 9.0% for every 10 minutes beyond the 30-minute mark. In contrast, cold ischemia serves as a protective factor (Fig. 2).[46]

Furthermore, recent studies have reported that patients undergoing off-clamp PN may have a higher rate of conversion to RN and a greater incidence of perioperative blood transfusion. In the authors' opinion, the subgroup of patients most likely to benefit from off-clamp PN are those with severe CKD bordering on end stage renal failure for whom prolonged ischemia is anticipated, as this approach may help avoid dialysis both short and long term. Nonetheless, the precise indications for zero ischemia PN remain poorly defined, and further investigation is warranted to clarify its clinical utility.[47-49]

Pneumoperitoneum during laparoscopic or robotic PN may influence postoperative renal functional outcomes due to its impact on renal perfusion. The elevation of intra-abdominal pressure to levels typically ranging from 12 to 15 mmHg can reduce renal blood flow by compressing renal vasculature and increasing renal vascular resistance.[50] Prolonged duration of pneumoperitoneum and higher insufflation pressures have been associated with worsened

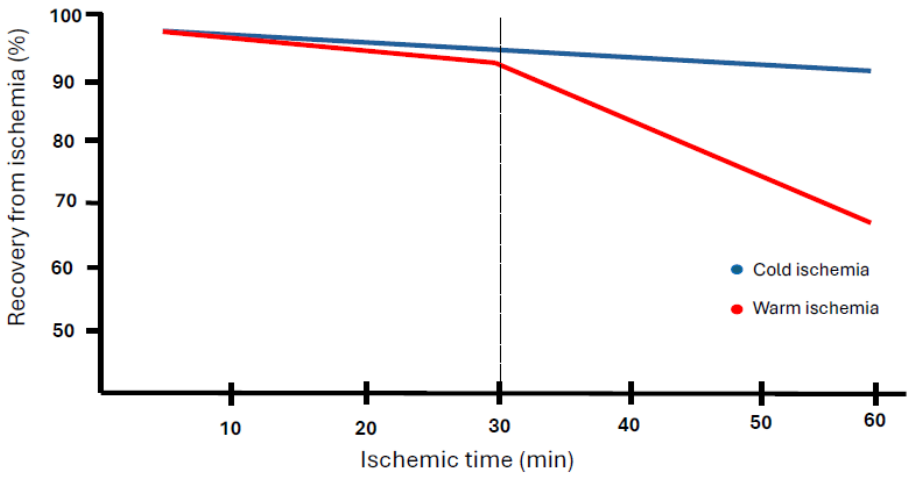

Figure 2. Functional recovery following clamped partial nephrectomy related to type and duration of ischemia. Recovery from ischemia is defined as percent GFR saved normalized by parenchymal volume saved, all specific to the operated kidney, and would be 100% if all of the preserved nephrons recovered completely from exposure to ischemia. Patients undergoing PN with limited warm ischemia (<30 minutes) or any duration of cold ischemia tend to experience minimal impact on postoperative functional recovery (recovery from ischemia ≈94.0%). In contrast, prolonged warm ischemia (>30 minutes) is associated with a significant decline in functional recovery. Recent studies have shown that recovery from ischemia in the ipsilateral kidney decreases by approximately 9% for every additional 10 minutes of warm ischemia beyond 30 minutes. Therefore, if the patient undergoes warm ischemia for 60 minutes, recovery from ischemia in the ipsilateral kidney will be approximately 68.0%. This is in addition to the baseline 20% loss of function in the ipsilateral kidney that typically occurs with PN related to parenchymal volume loss. In the final analysis then, the loss of function in the ipsilateral kidney associated with PN with 60 minutes of warm ischemia will be approximately 50.0%.

postoperative renal function.[51] However, these effects are generally transient, and the incidence of clinically significant AKI related solely to pneumoperitoneum is low. Overall, long-term renal functional outcomes appear to be primarily determined by the amount of preserved renal parenchymal volume rather than the effects of intraoperative pneumoperitoneum.[50]

Postoperative Factors Affecting Functional Recovery

AKI is a common short-term complication after PN, particularly in patients with a solitary kidney, where the incidence approaches 50.0%.[19,52] Causes include ischemia and parenchymal volume loss. The severity of AKI correlates with reduced functional recovery and is closely associated with ischemia duration, and can be seen with both cold and warm ischemia.[19,53] Overall, however, AKI is a minor contributor to reduced NBGFR after PN. Most kidneys recover well from AKI and parenchymal volume loss remains much more important, accounting for the lion's share (70.0-80.0%) of the loss of renal function after PN.[8,19,54]

Furthermore, AKI has minimal effect on long-term functional decline. Once NBGFR is reached, GFR gradually declines as the years go by, and atrophy generally follows the natural aging process (~1.0% per year).[14,30,31] Previous exposure to ischemia does not leave the kidney vulnerable to long-term atrophy or functional loss. In a subset of patients, however, GFR deterioration exceeds aging norms, particularly in those with significant renal comorbidities (severe HTN, insulin DM)—affecting both kidneys, not just the one previously exposed to ischemia.[14,15] Consultation and long-term follow-up by nephrology can help to maintain optimal renal function for such patients.[2]

Optimal postoperative renal perfusion and functional recovery are closely associated with appropriate fluid management and stable hemodynamic parameters, particularly blood pressure. Inadequate intravascular volume or hypotension may impair renal perfusion and exacerbate ischemic injury, especially in the context of a solitary kidney or reduced nephron volume following PN.[50]

Several studies have suggested that perioperative hypotension is a significant predictor of AKI and long-term renal dysfunction. De Backer et al. found that intraoperative episodes of mean arterial pressure below 55 mmHg for prolonged periods were independently associated with increased risk of postoperative AKI.[55,56] Furthermore, sustained postoperative hypovolemia or excessive diuresis may compound ischemic insults and delay functional recovery.[57]

Accordingly, perioperative protocols emphasizing euvolemia, the avoidance of nephrotoxic agents, and careful hemodynamic monitoring have been proposed to support renal recovery after nephron-sparing surgery.[58]

Conclusions

Renal functional recovery following PN and RN is a multifactorial process influenced by preoperative, intraoperative, and postoperative factors. The use of PVA has greatly improved our analysis of functional outcomes after PN, allowing us to more accurately determine the impact of ischemia during PN. Parenchymal volume preservation has emerged as the most critical determinant of long-term renal function after PN, whereas ischemia plays a secondary role unless warm ischemia time is prolonged. While zero ischemia techniques may offer theoretical benefits, current evidence suggests that their advantages over conventional approaches are marginal and can be offset by increased perioperative risks.

Preoperative risk stratification, including assessment of baseline renal function, comorbid conditions, and tumor complexity, is essential for selecting the most appropriate surgical strategy. Intraoperatively, techniques aimed at minimizing both excised and devascularized parenchymal volume are paramount. Though intraoperative mannitol use remains common practice, studies do not support its benefit in patients with normal preoperative renal function.

Postoperatively, maintaining adequate hydration and hemodynamic stability is crucial for supporting renal perfusion and minimizing ischemic injury. AKI remains a significant concern in the immediate postoperative period, especially in patients with solitary kidneys or compromised renal reserve. However, long-term functional decline typically follows the natural aging trajectory, unless compounded by underlying comorbidities that specifically affect the kidneys.

Taken together, a patient-centered approach that incorporates individualized surgical planning, careful intraoperative management, and vigilant postoperative care remains the cornerstone of optimizing functional recovery following nephron-sparing and radical renal surgery.

Conflict of Interest

The authors declare no conflict of interest.

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