Renal Ischemia and Function After Partial Nephrectomy: A Collaborative Review of the Literature

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Renal Ischemia and Function After Partial Nephrectomy: A Collaborative Review of the Literature

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Abstract

Context

Partial nephrectomy (PN) is the current gold standard treatment for small localized renal tumors.; however, the impact of duration and type of intraoperative ischemia on renal function (RF) after PN is a subject of significant debate.

Objective

To review the current evidence on the relationship of intraoperative ischemia and RF after PN.

Evidence acquisition

A review of English-language publications on renal ischemia and RF after PN was performed from 2005 to 2014 using the Medline, Embase, and Web of Science databases. Ninety-one articles were selected with the consensus of all authors and analyzed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria.

Evidence synthesis

The vast majority of reviewed studies were retrospective, nonrandomized observations. Based on the current literature, RF recovery after PN is strongly associated with preoperative RF and the amount of healthy kidney parenchyma preserved. Warm ischemia time (WIT) is modifiable and prolonged warm ischemia is significantly associated with adverse postoperative RF. Available data suggest a 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. Surgical techniques that minimize or avoid global ischemia may be associated with improved RF outcomes.

Conclusions

Although RF recovery after PN is strongly associated with quality and quantity of preserved kidney, efforts should be made to limit prolonged WIT. Cold ischemia should be preferred when longer ischemia is expected, especially in presence of imperative indications for PN. Additional research with higher levels of evidence is needed to clarify the optimal use of renal ischemia during PN.

Patient summary

In this review of the literature, we looked at predictors of renal function after surgical resection of renal tumors. There is a strong association between the quality and quantity of renal tissue that is

preserved after surgery and long-term renal function. The time of interruption of renal blood flow during surgery is an important, modifiable predictor of postoperative renal function.

Keywords

- Ischemia;
- Nephron-sparing surgery;
- Partial nephrectomy;
- Renal cell carcinoma;
- Renal function

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1. Introduction

Partial nephrectomy (PN) is currently the gold standard treatment for localized renal tumors [1] and [2]. The interruption of renal blood flow with clamping of the renal artery or arteries is often performed during nephron-sparing surgery (NSS), especially for large and anatomically complex masses with deep parenchymal invasion. Vascular clamping allows the surgeon to work in a relatively bloodless field, facilitating tumor resection and closure of the parenchymal defect; however, the temporary interruption of arterial flow may lead to ischemic injury of the healthy renal parenchyma. Nevertheless, the significance of the effect of ischemia type and duration on long-term renal function (RF) has been questioned. In fact, some investigators suggest that the human kidney is extremely tolerant to ischemic insults [3], whereas others report that the amount of preserved healthy renal parenchyma may supersede ischemia as the primary predictor of RF after NSS [4] and [5].

Consequently, the impact of renal ischemia on RF outcomes after PN remains a debated issue. In this review, we analyzed the available evidence on the relationship between intraoperative renal ischemia and RF after PN to provide an overview of the current knowledge in this controversial field.

2. Evidence acquisition

A literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [6] (Fig. 1). The literature search was carried out on the Medline, Embase, and Web of Science databases using the terms *ischemia* or *renal function* in combination with *partial nephrectomy* or *nephron-sparing surgery*. We limited our search to English-language articles published between January 2005 and June 2014. In addition, cited references from the selected articles and from previous review articles on this topic were assessed to identify significant manuscripts that were not included previously. This process also led to the inclusion in this review of some significant articles that were published outside of the time window of our original search. After exclusion of duplicates and papers with topics that were not specific for this review, we identified a list of 197 papers. The full text of these articles was assessed by two independent reviewers. Level of evidence, sample size, study design, and relevance of each study with regard to the topics of the review were assessed. Based on these criteria, 91 articles were selected with the consensus of all authors and were critically analyzed. The review is the result of an interactive peer-reviewing process by the expert panel.
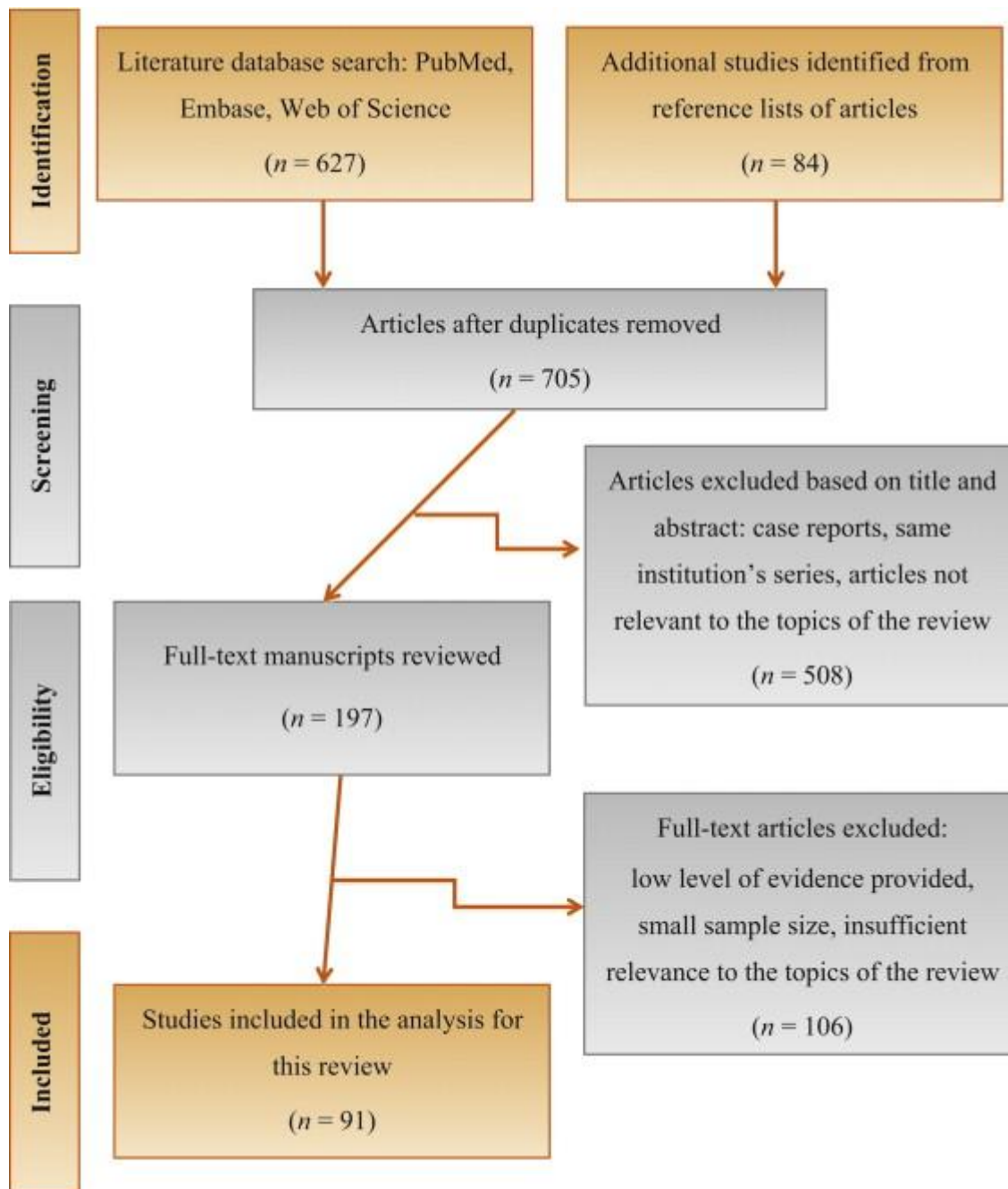
Fig. 1.

Flow diagram: search and study selection process for this systematic review.

Figure options

3. Evidence synthesis

3.1. Partial nephrectomy and renal function

The current major urologic guidelines indicate that patients with clinically T1 renal tumors should undergo NSS whenever technically feasible [1], [2] and [7]. The oncologic equivalence of PN and radical nephrectomy (RN) for small renal tumors was shown in retrospective series and more recently in the European Organization for Research and Treatment of Cancer randomized phase 3

trial 30904 [8], [9] and [10]. Other studies have also shown acceptable oncologic outcomes of NSS for larger localized renal tumors [9], [11] and [12].

The main trigger to the expansion of elective indications for PN was the growing evidence that RF is significantly better preserved with NSS compared to RN [13] and [14]. PN for a renal tumor <7 cm rarely results in temporary or permanent loss of RF. Lane et al reviewed the functional outcomes of a large series of 1169 open PN (OPN) and laparoscopic PN (LPN) and observed that the incidence of acute renal failure (ARF) after surgery was 3.6% for the entire cohort and 0.8%, 6.2%, and 34% for patients with preoperative normal RF, stage 3 chronic kidney disease (CKD), and stage 4 CKD, respectively [15]. The incidence of end-stage renal disease (ESRD) after PN was 2.5% for the entire cohort and 0.1%, 3.7%, and 36% for patients with preoperative normal RF, stage 3 chronic kidney disease (CKD), and stage 4 CKD, respectively, indicating a significantly more relevant risk of severe functional impairment for patients with preexisting CKD. The same study showed that RF remained stable after surgery in most patients, with an 8.8% average loss over time [15].

3.1.1. Assessment of renal function after partial nephrectomy

Serum creatinine (sCr) is the easiest and most commonly used tool to assess RF after PN; however, its concentrations are significantly affected by age, sex, and muscle mass, and it is not a reliable indicator of RF, especially in the presence of a healthy contralateral kidney. Studies indicate that approximately 25% of patients with a renal mass, normal sCr, and a normal contralateral kidney have at least moderate CKD (glomerular filtration rate [GFR] <60 ml/min per 1.73 m^2) preoperatively [13] and [15]. Determination of GFR by 24-h urine creatinine clearance or the simple estimation of GFR with dedicated formulas has been shown to reflect RF more accurately than sCr, and the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are used with this purpose [16], [17] and [18]. Although all formulas are inferior to the gold standard direct GFR measurement using iodine 125 (^{125}I) iothalamate and are less accurate in patients without CKD [19], the CKD-EPI and the MDRD equations were observed to give the best estimation of GFR [17].

The most reliable way to assess differential RF loss in patients with bilateral kidneys is to evaluate estimated split RF by renal scintigraphy. The clearance of technetium Tc 99m mercaptoacetyltriglycine (^{99m}Tc-MAG-3) is reported to correlate more closely to the clearance of ^{125}I-orthoiodohippurate than the clearance of chromium 51 ethylenediaminetetraacetic acid (^{51}Cr-EDTA) and is widely used for gamma camera renography and for measurement of RF [20]. However, the use of functional nuclear imaging is time consuming and costly and is not devoid of limitations, including test variability and reproducibility [21].

Several biomarkers of subclinical renal cellular injury and clinical ARF have been investigated [3] and [22]. Although some of these markers, such as neutrophil gelatinase-associated lipocalin, have been shown to have potential diagnostic and prognostic value, further research in this field is warranted before they can be introduced into routine clinical practice.

3.2. Studies of renal ischemia after partial nephrectomy

3.2.1. Studies of pathologic mechanisms of ischemic renal injury

In studies on the pathophysiology of acute ischemic RF, ischemia was found to lead to acute kidney damage through three interrelated main mechanisms. The first mechanism is vascular, caused by persistent vasoconstriction and an abnormal response of endothelial cells to compensatory means.

The second mechanism is obstructive, in which sloughed tubular epithelial cells and membrane debris form casts that obstruct tubules, and glomerular filtrate leaks from the tubular lumen into capillaries and the circulation, causing a reduction in the *effective* GFR. Finally, the third mechanism is caused by reperfusion injury after blood flow is restored. Reperfusion injury can be mediated by several mechanisms, including the generation of reactive oxygen species, cellular derangement, hypercoagulation, and microvessel congestion and compression, which can significantly reduce renal blood flow [23] and [24].

3.2.2. Studies of renal ischemia in animal models

Several studies have been published on the effects of renal ischemia on porcine, canine, and rabbit models. Although some of these studies suggest that kidneys can tolerate a warm ischemic injury >30 min, the results are contradictory [24]. This could be due to the different designs of the available studies or to a variable physiologic response to ischemia in different animal species. For the same reason, the findings of animal studies cannot be easily extrapolated to humans because animal physiology does not necessarily approximate human physiology.

3.2.3. Early studies of renal ischemia in human kidneys

The clinical research on surgically induced renal ischemia dates back to the late 1970s, when studies were carried out to develop optimal techniques to minimize RF loss during renal transplantation and surgical removal of upper urinary tract stones with nephrolitotomy or extended pyelolithotomy [25] and [26]. During warm ischemia, histologic changes were observed mainly in the proximal tubules after 20 min, with rapidly increasing signs of cellular degeneration at ≥30 min, and complete cellular degeneration at all levels of the nephron at ≥60 min. In predamaged kidneys, such as those affected by pyelonephritis or chronic obstruction, tolerance to ischemia was even lower [26]. Based on these historical experiences, a maximum normothermic ischemia without specific protective measures of 30 min has been traditionally recommended. When a longer ischemic time was expected, protective measures such as surface cooling to achieve medullary temperatures of 15–20 °C was found to allow 60–70 min of safe renal ischemia [25] and [27]. In further studies, Novick reported that the RF recovery from ischemic damage occurs within a few hours after 20 min, a few days after 30 min, and may require several weeks after 60 min of clamping in hypothermia [25]. Early studies also showed the role of the infusion of diuretics such as mannitol and furosemide before vessels are clamped, to decrease intracellular swelling, and before renal hilum is unclamped, to promote diuresis and minimize the sequelae of revascularization injury, cell swelling, and release of free radicals [28] and [29]. Finally, other studies demonstrated that intermittent renal arterial occlusion should be avoided, since it potentiates arterial vasospasm and hence renal damage [30].

3.2.4. Recent studies of renal ischemia in the setting of solitary kidneys

Solitary kidneys have been considered an ideal model to assess RF after PN because postoperative renal damage cannot be masked by compensatory hypertrophy of the healthy contralateral organ. However, some studies have suggested that a solitary kidney is more resistant to ischemic damage compared with paired kidneys, making the results not necessarily applicable to patients with bilateral kidneys [31] and [32]. In fact, studies on solitary kidneys may overestimate the maximal renal tolerance to ischemia of patients with a normal contralateral renal unit.

In 2007, the groups from Mayo Clinic and Cleveland Clinic assessed the renal effects of vascular clamping in a large series of 537 patients who underwent OPN in a solitary kidney setting. Renal complications and function assessed by sCr were compared among patients who did not require

vascular clamping ($n = 85$), and those who had warm ischemia ($n = 174$) and cold ischemia ($n = 278$). Although the populations were not fully comparable (similar age and preoperative sCr but significantly smaller tumors in the unclamped group), the authors observed that both warm and cold ischemia were associated with a significantly increased risk of acute ($p < 0.001$) and chronic ($p = 0.027$) renal failure and temporary dialysis ($p = 0.028$) compared with patients with no ischemia. A WIT >20 min and a cold ischemia time (CIT) >35 min were associated with a higher incidence of ARF ($p = 0.002$ and $p = 0.003$, respectively). In addition, WIT >20 min was associated with an increased risk of CKD (41% vs. 19%; $p = 0.008$), increase in sCr >0.5 mg/dl (42% vs 15%; $p < 0.001$), and permanent dialysis (10% vs 4%; $p = 0.145$) [33].

Three years later, further observations from the same institutions focused the analysis on 362 patients who underwent OPN or LPN using warm ischemia with hilar clamping (median: 21 min) in solitary kidneys. A strength of this study is that RF was assessed not only by sCr values but also with eGFR using the MDRD equation. Longer WIT as a continuous variable was associated with ARF (odds ratio [OR]: 1.05 for each 1-min increase; $p < 0.001$), eGFR <15 ml/min per 1.73 m^2 (OR, 1.06; $p < 0.001$) in the postoperative period, and new-onset stage 4 CKD (hazard ratio [HR]: 1.06; $p < 0.001$) during follow-up. Similar results were obtained at multivariable analysis after adjustment for preoperative eGFR, tumor size, and surgical approach. The authors also assessed cut-off values of WIT and observed that 25 min of WIT was the best cut-off to separate patients who did and did not develop short- and long-term RF decline [34].

Subsequently, Lane et al [5] reviewed a multi-institutional series of 660 PNs performed in solitary kidneys from 1980 to 2009 in which cold ischemia was used in 300 cases and warm ischemia was used in 360 cases. Although median CIT was much longer than WIT (45 vs 22 min; $p < 0.001$), 3 mo after PN no significant difference in the decrease of median eGFR (CKD equation) was observed according to the type of ischemia performed (21% vs 22%, respectively; $p = 0.7$). On multivariable analyses, increasing age, larger tumor size, lower preoperative eGFR, and longer ischemia time were all associated with decreased postoperative eGFR ($p < 0.05$). When percentage of parenchyma spared was incorporated into the analysis, this factor and preoperative eGFR proved to be the primary determinants of ultimate RF, and duration of ischemia lost statistical significance [5].

To validate these results, the previously mentioned combined cohort of Mayo Clinic and Cleveland Clinic was reassessed incorporating in the analysis the percentage of kidney preserved [35]. On multivariate analysis, WIT ($p = 0.021$), percentage of kidney preserved ($p = 0.009$), and preoperative eGFR ($p < 0.001$) were significantly associated with ARF, and only the percentage of kidney preserved ($p < 0.001$) and preoperative eGFR ($p < 0.0001$) were significantly associated with new-onset stage 4 CKD during follow-up, whereas WIT >25 min remained significantly associated with new-onset stage 4 CKD in a multivariate analysis adjusting for the parenchymal quantity and quality factors (HR: 2.27; $p = 0.049$). Collectively, these results, presented in Table 1, suggest that preoperative RF, amount of healthy parenchyma after PN, and WIT (continuous variable) are each associated with short-term RF following hilar clamping. In addition, long-term RF is dependent on preoperative RF, amount of healthy parenchyma preserved, and minimizing WIT to <25 min.

Table 1.

Recent studies on renal ischemia during partial nephrectomy in solitary kidneys

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Main outcomes	Level of evidence
Thompson et al [33]	537	OPN	To compare renal complications among patients who underwent no ischemia (n = 85), WI (n = 174), and CI (n = 278)	0 vs 22 vs 45	2.5 vs 3.5 vs 4	WI and CI were associated with a significantly increased risk of acute and chronic renal failure and temporary dialysis compared to no ischemia. WIT >20 min and CIT >35 min were associated with a higher incidence of acute renal failure. WIT >20 min was associated with an increased risk of chronic renal failure and permanent dialysis.	3
Thompson et al [34]*	362	OPN (n = 319) LPN (n = 43)	To assess the association of WIT with postoperative and long-term RF	Median: 21 (range: 4–55)	Median: 3.4 (range: 0.7–18)	Longer WIT was associated with acute renal failure, a GFR <15 in the postoperative period, and with new-onset stage 4 CKD during follow-up. A WIT cut point of 25 min provided the best distinction between patients with and without these end points.	4
Lane et al [5]*§	660	OPN	To compare the impact of WI (n = 360)	WI median: 22 (IQR:	WI median: 4 (IQR:	Median GFR decreased similarly 3 mo	3

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Main outcomes	Level of evidence
			and CI (n = 300) on RF	17–29) CI median: 45 (IQR: 35–60)	2.8–5.2) CI median: 4 (IQR: 2.9–5.4)	after surgery with CI or WI. Percentage of parenchyma spared and preoperative GFR were the only primary determinants of ultimate RF at multivariable analysis.	
Thompson et al [35][*§]	362	OPN (n = 319) LPN (n = 43)	To evaluate the effects of WIT and quantity and quality of kidney preserved on recovery of RF after surgery	Median: 21 (range: 4–55)	Median: 3.4 (range: 0.7–18)	WIT, percentage of kidney preserved, and preoperative GFR were independent predictors of ARF, and only the percentage of kidney preserved and preoperative GFR were independent predictors of new-onset stage 4 CKD during follow-up.	4
Lane et al [15][*]	199	OPN (n = 169) LPN (n = 30)	To compare RF outcomes of OPN and LPN and assess predictors of postoperative RF	OPN median: 21 (IQR: 17–27) LPN median: 29 (IQR: 19–35)	OPN median: 3.8 (IQR: 2.8–4.8) LPN median: 2.8 (IQR: 2.5–3.9)	WIT was significantly longer with LPN. WIT, age, preoperative eGFR, but not surgical approach, were independently associated with poorer postoperative eGFR at multivariate analysis.	3

CI = cold ischemia; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IQR = interquartile range; LPN = laparoscopic partial nephrectomy; OPN = open partial nephrectomy; RF = renal function; WI = warm ischemia; WIT = warm ischemia time.

*

Assessment of preoperative renal function was included in the analysis of predictors of postoperative renal functional outcomes.

§

Assessment of the amount of preserved/resected renal parenchyma was included in the analysis of predictors of postoperative renal functional outcomes.

Table options

Data evaluating the impact of ischemia on solitary kidneys are drawn from a limited number of institutions, and further validation of these findings is needed.

3.2.5. Recent studies of renal ischemia in the setting of bilateral kidneys

The assessment of postoperative RF after NSS in the presence of two functioning renal units is influenced by the compensatory hypertrophy of the nonaffected kidney, which can mask the functional loss of the affected organ. In fact, in elective cases, a significant increase in sCr levels may not be apparent until the GFR drops to approximately 30% of the normal values. Consequently, eGFR in combination with renal scintigraphy is more ideal for RF assessment after PN in this clinical setting.

Lane et al [36] assessed the RF outcomes of 2402 consecutive patients with sCr ≤1.4 mg/dl and two functioning kidneys treated with PN or RN for cT1 renal cancer. Patients who underwent PN with a limited ischemia (<30 min) were less likely to have an ultimate eGFR (CKD-EPI) <45 ml/min per 1.73 m^2 compared with patients who had longer ischemia intervals (11% vs 19%). However, patients who had extended ischemia were far less likely to reach such eGFR thresholds compared to those who underwent RN (35%) [36].

In 2007, Porpiglia et al prospectively assessed the functional outcomes of 18 LPNs with WIT >30 min by serial ^{99m}Tc-MAG-3 renal scintigraphy. They observed that although total RF was not significantly decreased 3 mo after surgery (eGFR: 91.6 vs 79.1 ml/min per 1.73 m^2; $p \geq 0.05$), the differential function of the operated kidney was 48.3% before surgery and 36.9% 5 d postoperatively, and only partially recovered to 40.6% and 42.8% at 3 mo and 1 yr after surgery, respectively. At further analysis, the loss of function of the operated kidney was found to depend on the maximum thickness of resected healthy parenchyma and more significantly on WIT, with worsening outcomes with WIT >32 min [37]. In several other studies using renal scans to assess differential RF before and after LPN or OPN, WIT was found to be associated with a statistically significant loss of function of the operated kidney mainly in patients who experienced ischemia for >25–30 min [38], [39] and [40]. Preoperative RF and amount of preserved renal parenchyma were factored in the analysis in some but not all of these studies (Table 2).

Table 2.

Recent studies on renal ischemia during partial nephrectomy in the setting of bilateral kidneys

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Main outcomes	Level of evidence
Porpiglia et al [37]§	18	LPN with WIT >30 min	To evaluate the impairment of RF of the operated kidney 12 mo after surgery by using renal scans (preoperative; 5 d, 3 mo, and 6 mo postoperative)	Mean: 39 ± 8.1	Mean: 3.4 ± 1.8	Kidney damage occurs during LPN when WIT >30 min and is only partially reversible. The functional impairment of the operated kidney is significantly worse with WIT >32 min.	4
Simmons et al [4]*§	39	OPN/LPN	To assess a novel method to estimate the percent of functional volume preservation and to assess its effect on postoperative functional outcomes	Median CIT: 38.5 Median WIT: 24.5	Median: 3.5	Preoperative RF and percent of functional volume preservation are the primary determinants of long-term functional outcomes in patients with normal preoperative RF who have ischemia time within acceptable limits.	4
Parekh et al [3]	40	OPN	To prospectively assess the renal response to clamp	Mean CIT: 48 Mean WIT: 32.3	Median: 4.1	RF changes did not correlate with ischemia duration.	2

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Main outcomes	Level of evidence
			ischemia and reperfusion after PN, including histologic changes on biopsies performed before, during, and after clamping, and changes in biomarkers of acute kidney injury			Renal structural changes were much less severe than observed in animal models that used similar duration of ischemia. Acute kidney injury biomarkers were only mildly elevated and did not correlate with RF or ischemia duration.	
Shikanov et al [87]	401	LPN	To assess the influence of renal ischemia on long-term global RF assessed with eGFR	Median WIT: 29	Median: 2.5	WIT did not have a clinically significant impact on global RF after LPN	4
Pouliot et al [38]*	56	LPN	To evaluate the effect of WIT and other factors on differential RF of the operated kidney assessed by using renal scans (preoperative, 10 d postoperative)	Mean: 30 ± 9	Mean: 3.2 ± 1.6	WIT and endophytic tumor location are associated with a statistically significant loss of differential RF, but only in the group who experienced a WIT >30 min.	4
Funahash	32	OPN	To evaluate	OPN:	OPN:	While total	4

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Main outcomes	Level of evidence
i et al [40]**		(n = 20) LPN (n = 2012)	the differential RF of the operated kidney by using renal scans (preoperative; 1 wk and 6 mo postoperative)	24.2 ± 6.2 LPN: 24.5 ± 7.2	2.5 ± 0.6 LPN: 2.9 ± 1.1	RF is almost unaffected after surgery, a WIT >25 min leads to a significant decrease in effective renal plasma flow on the operated side.	
Porpiglia et al [39]*§	53	LPN	To assess the effects of WIT on RF after LPN in patients with a normal contralateral kidney by using renal scans (preoperative; 3 and 6 mo postoperative)	Mean: 21.9	Mean: 3.0	WIT as a continuous variable is associated with greater loss of RF. ROC analysis identifies 25 min as a *safe* WIT cut off. Loss of RF occurs within 3 mo and remains stable until 12 mo after LPN.	4
Chan et al [41]*§	65	OPN (n = 35) LPN (n = 30)	To retrospectively evaluate predictors of postoperative unilateral RF by using renal scans (preoperative, 1 mo postoperative)	OPN: 29.8 ± 9.9 LPN: 28.7 ± 11.2	OPN: 3.8 ± 1.9 LPN: 2.6 ± 1.1	Intraoperative, visually estimated preserved parenchyma volume, radiologic tumor size, and procedure type significantly correlate with postoperative unilateral RF	4

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Main outcomes	Level of evidence
						at univariable analysis. No factor is an independent predictor at multivariable analysis.	
Song et al [42][§]	117	OPN (*n* = 52) LPN (*n* = 65)	To investigate factors determining RF decrease. (preoperative; 6 mo postoperative)	OPN: 20.5 (range: 8–35) LPN: 33.5 (range: 13–75)	OPN: 3.72 (range: 0.9–11) LPN: 2.14 (range: 0.8–4)	Renal volume reduction, tumor location, and patient age are independent predictors of postoperative RF at multivariable analysis.	4
Porpiglia et al [44][§]	54	LPN	To evaluate the long-term effects of WI on RF by using renal scans (preoperative; 3 and 6 mo postoperative; yearly)	Mean: 27.98 ± 11.12	Mean: 3.69 ± 1.39	Split RF of the operated kidney decreases significantly at 3 mo from surgery and subsequently remains stable during follow-up up to 4 yr. WIT is the only independent predictor of split RF at 4 yr from surgery.	4

CIT = cold ischemia time; eGFR = estimated glomerular filtration rate; LPN = laparoscopic partial nephrectomy; OPN = open partial nephrectomy; RF = renal function; WIT = warm ischemia time.

§

Assessment of the amount of preserved/resected renal parenchyma was included in the analysis of predictors of postoperative renal functional outcomes.

Chan et al [41] included the intraoperative visually estimated functioning residual renal volume after PN in the analysis of postoperative RF of the operated kidney, using ^{99m}Tc-MAG-3 scintigraphy. The authors observed that this variable was the most accurate predictor of unilateral RF 1 mo after surgery at univariable analysis [41]. Song et al also observed that the percent of residual renal parenchyma evaluated by postoperative computed tomography (CT) scan was an independent predictor of eGFR at a median of 6.5 mo from surgery in elective cases of PN with bilateral kidneys [42].

Finally, Porpiglia et al [43] recently reported the long-term outcomes of a series of 54 LPNs in patients with bilateral renal units. The split function of the affected kidneys at ^{99m}Tc-MAG-3 scintigraphy decreased significantly at 3 mo after surgery and subsequently remained stable after a minimum follow-up of 4 yr. Age and WIT were significant predictors of loss of function of the operated kidney at 3 mo, whereas only WIT was a significant predictor at 48 mo [43].

3.2.6. Human studies evaluating techniques of early unclamping, no ischemia, or selective ischemia

Several technical modifications have been proposed to reduce or minimize WIT [44] and [45]. These concepts can be applied to all surgical approaches but have been more intensively pursued by laparoscopic surgeons due to the average longer WIT reported with this approach for its intrinsic technical challenges [46].

The early unclamping technique implies clamping of the renal hilum only for the duration of tumor excision and placement of the initial central running suture on the renal medulla. All subsequent suturing in the PN bed to ensure parenchymal hemostasis and pelvicaliceal repair is done in the perfused revascularized kidney. Gill et al reported that this technical modification allowed a significantly shorter WIT (14.4 vs 31.9 and 31.6 min in previous periods of experience; $p < 0.0001$), which resulted in significantly superior RF outcomes (decrease in eGFR within 90 postoperative days: 11% vs 18% and 20%, respectively; $p < 0.0001$) [47].

The attempt to decrease intraoperative WIT has also led to the introduction of the concept of off-clamp PN and of PN with selective clamping, which aims to avoid or minimize the ischemic injury on the healthy parenchyma of the operated kidneys (Table 3).

Table 3.

Recent studies evaluating no ischemia or zero ischemia techniques during partial nephrectomy

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Nephrometry score (mean)	Main outcomes	Level of evidence
Thompson et al [48]**	PN with WI (n = 362) PN with no ischemia (n = 96)	OPN (n = 411) LPN (n = 47)	To compare the short- and long-term renal effects of WI vs no ischemia in patients with a solitary kidney	Median: 21 (range: 4–55)	Mean: 3.4 Mean: 2.5	–	Patients who underwent WI were significantly more likely to develop acute renal failure, a GFR <15 ml/min per 1.73 m^2 in the postoperative period, and new-onset stage 4 CKD during follow-up.	3
Kopp et al [49]	Clamped PN (n = 164) Clampless PN (n = 64)	OPN	To analyze factors affecting postoperative RF using both the clampless and clamped warm ischemic technique	Mean: 24.50	Median: 3.5 Median: 4.0	6.9 ± 1.5 6.4 ± 1.5	De novo stage 3 CKD at last follow-up was more frequent after clamped vs clampless PN. Increasing WIT was an independent predictor of stage 3 CKD after clamped PN.	3
Smith et al [50]**	Clamped PN (n = 116) Clampless PN (n = 192)	OPN	To determine safety and impact on RF of clampless PN	Mean: 200	Median: 3.0 Median: 2.8	–	The % eGFR change at 1 yr was overall similar for the clamped and unclamped group (p = 0.037), but not in patients with	3

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Nephrometry score (mean)	Main outcomes	Level of evidence
							solitary kidneys (21% vs 4.4%; $p = 0.027$). The rate of complications was similar in the groups.	
Kaczmarek et al [52]**	Clamped PN ($n = 49$) Clampless PN ($n = 283$)	RAPN	To evaluate the functional outcomes of RAPN with and without hilar clamping in a propensity score matched analysis	Mean 18.50	–	5.3 ± 0.2 5.6 ± 0.2	Off-clamp RAPN had a significantly shorter operative time, higher EBL, and smaller decrease in eGFR compared to clamped RAPN.	3
Porpiglia et al [53]*	Clamped PN ($n = 44$) Clampless PN ($n = 42$)	LPN	To compare postoperative RF of clampless vs clamped LPN (WIT <25 min) by using renal scintigraphy	Mean: 18 0	Mean: 3.4 ± 1.1 Mean: 3.6 ± 1.4	6.9 ± 1.2 7 ± 1.5	RF loss assessed by renal scan was not significantly different 3 mo after clamped and clampless LPN. Patients with poor preoperative RF had the most benefit with a clampless approach.	3
Gill et al [54]**	Zero ischemia ($n = 58$)	LPN ($n = 43$) RAPN	To present the concept	0	Mean: 3.2 (range:	7 ± 1.9	In patients with available	4

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Nephrometry score (mean)	Main outcomes	Level of evidence
	(n = 15)		and assess the perioperative outcomes of zero ischemia PN		0.9–13)		preoperative and 6-mo postoperative MAG-3 scans, ipsilateral function decreased by a mean of 10%. This functional decrease correlated with the mean percent of kidney excised. High-grade complications were infrequent (3.5%).	
Ng et al [55]**	Zero ischemia with VMD (n = 22) Zero ischemia without VMD (n = 22)	LPN or RAPN	To evaluate whether VMD of renal artery branches allows zero ischemia PN to be performed even for challenging medial tumors	0	Mean: 4.3 ± 2.6 Mean: 2.6 ± 1.0	7.7 ± 1.8 6.2 ± 1.8	Perioperative outcomes were similar in the two groups. The median serum creatinine level was similar 2 mo postoperatively.	3
Shao et al [58]**	Segmental artery clamping (n = 44) Main artery clampin	LPN	To evaluate the feasibility and efficiency of LPN with	Mean: 22 ± 4.4 Mean: 27 ± 5.3	Mean: 3.5 ± 0.4 Mean: 3.4 ± 0.5	–	LPN with segmental artery clamping improves early postoperative RF compared	4

Study	Patients, no.	Surgical approach	Aim of the study	Ischemia time, min	Tumor size, cm	Nephrometry score (mean)	Main outcomes	Level of evidence
	g (n = 31)		segmental renal artery clamping in comparison with the conventional technique				with main renal artery clamping.	

CKD = chronic kidney disease; EBL = estimated blood loss; GFR = glomerular filtration rate; LPN = laparoscopic partial nephrectomy; MAG = mercaptoacetyltriglycine; OPN = open partial nephrectomy; PN = partial nephrectomy; RAPN = robot-assisted partial nephrectomy; RF = renal function; VMD = vascular microdissection; WI = warm ischemia; WIT = warm ischemia time.

*

Assessment of preoperative renal function was included in the analysis of predictors of postoperative renal functional outcomes.

**

Analysis of predictors of postoperative renal functional outcomes not performed.

§ Assessment of the amount of preserved/resected renal parenchyma was included in the analysis of predictors of postoperative renal functional outcomes.

Full-size table
Table options

Thompson et al [48] retrospectively compared the short- and long-term RF outcomes of 362 patients who underwent OPN or LPN in a solitary kidney with clamping of the renal artery (median: 21 min) with those of 96 patients who had no intraoperative renal ischemia. The authors observed that the warm ischemia group had significantly increased risk of acute kidney injury after surgery and increased risk of new-onset CKD during follow-up [48]. A similar analysis on a cohort of patients with bilateral kidneys showed a higher rate of long-term CKD in patients after PN performed with WIT versus no ischemia (24.4% vs 12.5%). Conversely, off-clamp cases had a higher estimated blood loss (EBL; median: 300 vs 200 ml) but similar complication rates [49]. It is important to note that a proportion of off-clamp cases in these and other reports were performed with simple manual compression of peritumoral parenchyma [48], [49] and [50]. The application of Kauffman clamps on the kidney was also proposed to achieve hemostasis during tumor resection [51].

The perioperative and functional outcomes of off-clamp PN performed with robotic assistance were retrospectively assessed in a large multi-institutional series of 886 cases. In propensity score-

matched analyses, the off-clamp patients had a significantly shorter mean operative time, a higher EBL, and a smaller decrease in eGFR compared with those with intraoperative ischemia (2% vs −6%; $p = 0.008$) [52]. More recently, Porpiglia et al [53] used renal scans to compare the postoperative RF after LPN with clamping of the renal artery <25 min and no clamping of the renal artery. All postoperative functional parameters at 3 mo from surgery were not significantly different in the two groups. Interestingly, a lower preoperative RF significantly predicted a higher benefit in terms of reduced RF loss after PN in the clampless group [53].

The concept of laparoscopic or robotic "zero ischemia" PN was recently introduced by Gill et al. This technique involves anatomic microdissection to isolate and superselectively control tumor-specific tertiary or higher-order renal artery branches with neurosurgical micro–bulldog clamps [54]. In an interesting study from the same group comparing robotic or laparoscopic PN performed with microvascular dissection and selective clamping versus no clamping, Ng et al found similar comparative median EBL, complications, and postoperative sCr for the two groups [55]. Most recently, Desai et al [56] retrospectively compared the outcomes of superselective and main renal artery clamping during robotic PN in 121 patients. Despite having larger and more complex tumors in the superselective clamping group, these patients trended towards greater parenchymal preservation (95% vs 90%; $p = 0.07$) and lesser decrease of eGFR at discharge (0% vs 11%; $p = 0.01$) and at last follow-up (11% vs 17%; $p = 0.03$; median follow-up: 4 vs 6 mo) [56]. Finally, other authors proposed LPN with preoperative superselective embolization of the feeding arteries and subsequent off-clamp tumor resection, reporting a median decrease of split RF of 9% and 5% at 3 mo and 1 yr from surgery, respectively [57]. In general, when a selective clamping approach is planned, precise preoperative imaging such as dual-source CT angiography was shown to be helpful to assist the surgeon in the delineation of renal vasculature and in the selection of the arterial branches feeding the tumor [58].

The concept of selective clamping without hilar ischemia is interesting, and this approach has been associated with encouraging results; however, the series presented to date are relatively small, include selected patients treated by surgeons with significant experience, and have relatively short follow-up.

3.3. Summary of factors associated with renal function after partial nephrectomy

Several preoperative factors (preoperative RF, presence of a solitary kidney, age, sex, tumor size and complexity) and surgical factors (ischemia type, duration of ischemia, amount of healthy kidney parenchyma preserved, surgical approach) can have an impact on RF after PN [15]. The following section provides a summary of the current knowledge on the role and significance of the most important factors influencing RF after NSS.

3.3.1. Ischemia type and duration

The definition of the ideal ischemia time threshold during PN is still debated. Although the WIT historically thought to allow complete recovery of kidney function was ≤30 min, data from animal models and small, retrospective clinical studies in patients with bilateral functioning kidneys suggested that ischemia times >30 min can also allow full recovery of postoperative RF [59], [60], [61], [62] and [63]. More important, a 2013 paper provided the first detailed analysis of structural and functional responses of the human kidney to controlled clamp ischemia in 40 patients undergoing OPN with ischemia times >30 min in 82.5% of the cases [3]. The authors showed greater-than-expected resistance to ischemia time of human kidneys, with little or no acute RF loss in the early postoperative period. Progressive levels of ischemia up to 61 min had no effect on the injury produced, which was assessed functionally by sCr and cystatin C levels, structurally by light

and electron microscopy and immunofluorescence analysis, and by biomarkers excreted in the urine [3]. The strength of this prospective study is that pathologists who evaluated renal structure and biomarkers were blinded to the clinical results and the duration of ischemia. In contrast, the study is limited by the lack of follow-up beyond the hospital duration of a few days, by the presence of a mixed population of patients who underwent cold and warm ischemia, by the lack of information on tumor complexity and estimated volume of preserved parenchyma, and by the absence of RF scans to evaluate contributions from the contralateral kidney.

At present, efforts should be always made to minimize ischemia time when planning surgery, especially with imperative indications. Based on level 3–4 evidence from several studies, 20–25 min represents the most accurate cut-off to separate patients who do and do not develop short- and long-term RF decline after PN [15], [33], [34], [39], [40], [64] and [65] (Table 1 and Table 2).

The temporal trend of loss of RF has been diffusely investigated, especially in the setting of bilateral kidneys. RF appears to decrease immediately after PN and to partially recover to reach a new steady state, generally within 3 wk to 3 mo after PN [39]. It was suggested that the longer the period of RF decline after PN, the worse the nadir and the ultimate GFR. However, RF appears to remain stable after 3 mo from surgery up to 4 yr, according to recent data [43].

The use of cold ischemia is variable and depends on the institution and surgeon. In general, cold ischemia has been used liberally in OPN for those cases where a longer clamping time was expected. Surface hypothermia is generally instituted immediately after vascular clamping and maintained for 10 min before commencing tumor resection [66]. Indeed, there is clear evidence of the protective role of renal cooling with respect to functional injury, with longer periods of cold ischemia harming the nephrons similarly to shorter periods of warm ischemia [5] and [67]. Yossepowitch et al [68] analyzed RF with eGFR in 592 OPNs with a median CIT of 35 min. At multivariable analysis, CIT was significantly associated with early postsurgical eGFR changes, but not with a significant eGFR decrease 12 mo after surgery [68]. According to Iida et al, a CIT <44 min significantly decreases the probability of the new onset of eGFR <45 ml/min per 1.73 m^2[69]. Several techniques to duplicate the renoprotective effects of cold ischemia in LPN and robotic PN have been reported, including cold renal arterial and ureteric perfusions and laparoscopic ice-slush placement, but they have not been routinely applied in clinical practice [51] and [70].

According to recent studies, when the principles of good clinical practice are applied (ie, when relatively short warm ischemia intervals are achieved and hypothermia is liberally used when indicated), ischemia time does not seem to be the strongest factor to influence long-term postoperative RF, overcome by the quality and quantity of renal parenchyma preserved [4], [5], [35] and [71]. However, although there are not consistent data showing a significant association of intraoperative ischemia with ESRD in patients with bilateral kidneys, WIT remains a strong predictor of ARF and of need for dialysis after PN in solitary kidneys [33] and [35].

3.3.2. Preoperative renal function

It is intuitive that ultimate RF after PN depends also on the quality of the renal parenchyma that is preserved. This can be estimated by the assessment of preoperative RF, which is determined by several factors, including age, comorbidities, body habitus, and prior history of renal diseases and/or renal surgery.

There is solid evidence that the presence of baseline CKD is a major predictor of postoperative ARF and ESRD after PN either in the single and bilateral kidney setting [5], [15], [35], [71] and [72].

Most recent studies indicate that preoperative eGFR is an independent predictor of a significant decrease in eGFR in solitary kidneys and in differential contribution of the operated organ in presence of bilateral kidneys after adjusting for other patient, tumor, and surgery-related factors [5], [35], [37] and [73]. Preoperative RF may also have a dominant role over the number of residual nephrons in determining RF because hyperfiltration of the remaining nephrons may compensate, to a certain degree, for their decreased number.

These data clearly indicate that in clinical practice, preoperative RF is an important factor to consider along with other patient and tumor characteristics in decision making, patient counseling, and surgical planning of NSS.

3.3.3. Amount of renal parenchyma preserved

In several studies of PN in either solitary and bilateral kidneys that included the amount of preserved renal parenchyma after surgery in the assessment of predictors for postoperative renal impairment, the percentage of parenchyma preserved remained a significant and independent determinant of ultimate global RF and/or function of the operated kidney [4], [5], [41], [42] and [67]. These findings are in line with the common evidence of the good functional outcomes of cadaveric kidneys that are transplanted after being kept in ice for several hours [41]. In these cases the facts that the kidney is used in its entirety and the previous RF is good overcome the damage due to the long cold ischemia injury.

It is also interesting to note that studies have shown the amount of kidney removed was also one of the strongest predictors of WIT (or vice versa) [5], indicating that longer ischemia times are closely linked with larger tumors requiring a more complex resection and reconstruction. The same holds true for other tumor characteristics that increase the challenge of NSS (eg, endophytic rate, nearness to renal sinus and collecting system, central location). In fact, studies using the available anatomic classification nephrometry systems have shown a strong correlation among higher surgical complexity of renal tumors, longer WIT, and poorer functional outcomes [67], [74], [75], [76], [77] and [78].

Overall, studies have shown that a 5% increase in the amount of kidney preserved correlates with a 17% reduction in the risk of de novo stage 4 CKD [35]. The amount of preserved parenchyma depends partially on the surgical technique but primarily on tumor size and location, which influence the amount of vascularized tissue that can be spared. Reviewing the pre- and postoperative imaging of a series of 98 PNs, Aertsen et al observed that loss of healthy renal parenchyma was highest in patients with renal sinus tumor involvement ($p = 0.003$), tumors with anterior location ($p = 0.006$), and high-grade postoperative complications ($p = 0.001$), which were significantly more frequent when the urinary collecting system was involved ($p = 0.008$) [79].

Preserved parenchymal volume before and after PN can be measured by intraoperative visual estimation by surgeons or by evaluation of CT images with different methods [4], [5], [41], [42] and [67]. No clear recommendation on the best modality can be done based on the current evidence. However, Tobert et al recently demonstrated that surgeon assessment provides a reliable estimate of parenchymal volume preservation comparable to that obtained with more complex and time-intensive, imaging-based alternatives [80].

As a general rule, renal tumors should be removed with resection of a thin rim of uninvolved parenchyma or by enucleation along the plane of the tumor pseudocapsule, as a histologic tumor-free resection margin, irrespective of the width of the margin, is sufficient to achieve local control during PN [81] and [82]. The use of intraoperative ultrasound and careful planning of the tumor

dissection can optimize the amount of spared parenchyma while still achieving negative surgical margins [83]. The use of minimal or no-ischemia techniques with selective clamping of the arterial branches feeding the tumor may also decrease the potential ischemic injury on peritumoral renal parenchyma. Finally, renorrhaphy incorporates a variable amount of healthy renal tissue surrounding renal tumors and, therefore, has an impact on the amount of vital parenchyma preserved and, ultimately, on RF. Care should be taken, therefore, to reduce the amount of tissue potentially injured during parenchymal reconstruction after tumor excision. Both the efficacy of selective clamping and the check of a good perfusion of the peritumoral renal tissue after performing renorrhaphy can be facilitated by the use of near-infrared fluorescence imaging with indocyanine green, which is an interesting investigational tool in robot-assisted surgery [84]. However, further studies are needed to prove the impact of its use on postoperative RF.

3.3.4. Impact of surgical approach (open vs laparoscopic vs robotic)

In 1999, Toosy et al reported that the pneumoperitoneum induced in laparoscopy may protect the kidney from ischemic and reperfusion injury in rats [85]. Following these animal experiments, initial single-institution clinical studies of LPN reported that WIT up to 55 min did not significantly influence RF at 6 mo from surgery, suggesting that the ischemic preconditioning effect of pneumoperitoneum may, indeed, allow longer ischemic time. However, this assumption was based only on the assessment of postoperative sCr levels [61]. Subsequently, Adamy et al evaluated 987 patients with a normal contralateral kidney who were treated either by LPN or OPN, and observed that laparoscopically treated patients maintained slightly higher eGFR values than their counterparts who underwent OPN [86]. Although these data are suggestive, they were not confirmed by more recent studies that used eGFR as measure of RF, showing that surgical approach (laparoscopic vs open) did not exert an independent effect on nadir and ultimate eGFR [15] and [35].

On the other hand, due to the intrinsic technical challenges of performing tumor resection, and especially parenchymal renorrhaphy with a pure laparoscopic approach, the WIT achieved during LPN is generally longer compared to OPN (30.7 vs 20.1 min [$p < 0.001$] in the largest multi-institutional comparative study of LPN vs OPN) [46], with potential impact on postoperative functional outcomes. Longer WITs were associated with higher postoperative percent decrease in eGFR at multivariable analysis in a multicenter study on 401 LPNs with a median WIT of 29 min (interquartile range: 22–34 min) [87]. In another comparative study of LPN versus OPN for tumors <7 cm in solitary functioning kidneys, WIT was also 9 min longer ($p < 0.0001$) for LPN, with a greater proportion of patients requiring dialysis temporarily or permanently after surgery [88]. Due to the longer ischemia times, hypothermia would be desirable in challenging LPN cases, but the proposed techniques to achieve cold ischemia are not widely used.

Finally, robotic technology has the potential to reduce the technical challenges of laparoscopic surgery, thereby improving the functional outcomes of minimally invasive NSS by decreasing intraoperative renal ischemic damage [18], [19], [20] and [21]. Two systematic reviews and meta-analyses of robot-assisted PN (RAPN) versus LPN reported no significant differences in perioperative outcomes between the two techniques except for a significantly shorter WIT in the robotic group, suggesting that RAPN may better preserve nephrons [89] and [90]. Mottrie et al also showed that RAPN requires a shorter learning curve to reach WIT <20 min in the hands of surgeons with extensive robotic experience [91]. However, prospective comparative studies are needed to confirm the superiority of RAPN in preserving RF after NSS and to assess the cost-effectiveness of this surgical approach.

3.4. Research perspectives

The current evidence on renal ischemia and PN is based largely on case series and retrospective comparative studies, with all the inherent limitations. Unplanned intraoperative events that led to RN, for example, were not accounted for in the majority of PN comparative series. Additionally, there are several understudied surgical variables during PN that may contribute to RF and warrant further investigation. Several clinical questions need to be answered. What is the value of renoprotective agents (eg, mannitol and furosemide) to decrease renal ischemic damage during PN? Should hilar clamping include the artery, vein, or both? Do manual compression or selective/no ischemia techniques improve outcomes? How is cold ischemia ideally used? Further research is also needed to identify biomarkers of renal cellular injury that are associated with acute and chronic renal failure.

Although further advances in surgical techniques are warranted, the aim should be to maximize the preservation of healthy and well-vascularized renal parenchyma after surgery while achieving effective oncologic control. In this regard, prospective and randomized studies are awaited to reduce the predominant level 3–4 evidence available on which to base recommendations.

4. Conclusions

RF recovery after PN is strongly associated with the preoperative RF and the amount of preserved vascularized kidney preserved. Current evidence suggests that WIT correlates with the amount of residual functional parenchyma after PN and thus represents a significant modifiable surgical factor that impacts postoperative RF. Accordingly, prolonged warm ischemia periods (ie, >25 min) should be avoided. When longer ischemia is anticipated, cold ischemia should be used, especially in the imperative setting. Preliminary data indicate that selective or no-ischemia techniques are associated with improved RF outcomes for tumors amenable to this approach, but additional studies with higher levels of evidence are needed to confirm these findings.

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