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The current paradigm for ischemia in kidney surgery

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ABSTRACT

Purpose

Partial nephrectomy is the accepted standard of care for treatment of small renal mass. The primary goal while performing a partial nephrectomy is cancer control with secondary important goals of maximizing renal function preservation with minimal perioperative morbidity. Recent studies have highlighted the importance of renal parenchymal quality and quantity after surgery rather than duration of ischemia in determining the long-term renal function.

Our objectives are to review the available data regarding perioperative renal function optimization with special interest on ischemia during partial nephrectomy highlighting the controversies and establishing future lines of investigation.

Material and Methods

A comprehensive literature review was performed between 1970 and 2014 via MEDLINE, PUBMED and COCHRANE. Review was consistent with the PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analysis) criteria. We used MESH terms for search including “acute kidney injury/failure,” “carcinoma, renal cell/ carcinoma of kidney/ neoplasm of kidney,” “kidney failure, chronic/end-stage kidney disease,” “ischemia-reperfusion,” “warm ischemia/cold ischemia”. Relevant reviews were also included. Abstracts from major urological/surgical conferences were reviewed. All studies included were performed in adults, were written in English and had an abstract available for review.

Results

Our traditional knowledge of renal ischemia is derived from animal studies, kidney transplant and retrospective partial nephrectomy studies that indicate the risk of renal function impairment from every single minute of ischemia. Careful evaluation of historical studies highlight the flaws of the use of ischemia duration as a dichotomous marker (25 or 30 min) while predicting renal functional outcomes. Recent studies have demonstrated no effect of duration of ischemia on ultimate kidney function both in the short and long term. Quality and quantity of parenchyma preserved after surgery are the key predictors of ultimate renal function after PN. Traditionally PN has been performed with hilar occlusion to provide relatively bloodless surgical field allowing effective oncologic control during tumor excision with secure management of blood vessels, collecting system and renal reconstruction. Selective clamping and nonclamping techniques have been proposed to obviate the perceived harmful effects of ischemia. Albeit, they convert a complex surgery into a more challenging procedure; potentially limiting the widespread use of PN for management of renal cancers. Promising urine and blood-based biomarkers (NGAL, KIM-1) in the context of critical care settings and global stress have shown to predict acute kidney injury. Within the PN environment, the utility of those markers still needs to be further investigated. None of the studies have proven its usefulness in the setting of PN up to date.

Conclusion

The use of a single cut off value for duration of ischemia time as a dichotomous value for renal functional outcomes in the setting of partial nephrectomy is flawed based on

available evidence. Renal ischemia is a controversial topic with a shifted paradigm within the last decade. Current evidence has shown that patients with two kidneys undergoing NSS can tolerate ischemia times of more than 30 minutes without a clinically significant decline in renal function. Biomarkers predictive of renal tubular injury failed to predict acute kidney injury in the context of partial nephrectomy. Indications for partial nephrectomy could be significantly expanded, as the safety of limited renal ischemia is now better understood.

INTRODUCTION

In the United States, RCC accounted for almost 65,000 new cancer diagnoses in 2015 and contributed to approximately 13,570 cancer-related deaths[1]. The incidence of RCC has been gradually increasing over the past several years.

Stage migration has occurred over the past 2-3 decades, with more localized tumors being found in the modern era. Corresponding 5-year overall survival rates for localized disease exceed 90%. Small renal masses (SRM) are now commonly encountered, and most series demonstrate that approximately 20% of such tumors are benign, and only 20% harbor potentially aggressive histologic features[2]. Partial nephrectomy (PN) has become the gold standard for treatment of SRM. The primary goal while performing a PN is cancer control with secondary relevant goals of maximizing renal function preservation with minimal perioperative morbidity. The subject of renal ischemia has captured the attention of our specialty over the past 5 decades as it applied to performing anatrophic nephrolithotomy for complex stones to renal transplant and most recently while performing PN for renal masses. Limiting renal ischemia to less than 25-30 minutes in order to prevent renal injury and long-term renal functional decline has been accepted in our specialty for decades. However, a thorough evaluation of the historical evidence on whose basis we have been accepting the 25-30 min cut off for safe renal ischemia highlights several flaws. Indeed recent reports have pointed to the quality and quantity of the preserved renal parenchyma after PN to be more important predictors of long-term renal function.

We endeavored to clarify the state-of-the-art on the role of renal ischemia in the context of PN as well as perioperative measures to optimize renal function in the context of PN.

METHODS

We performed a systematic literature review for articles published in the last 15 years (January 1, 1970 to December 31, 2014). We searched MEDLINE, EMBASE and the Cochrane Collection. We used MESH terms for search including “acute kidney injury/failure,” “carcinoma, renal cell/ carcinoma of kidney/ neoplasm of kidney,” “kidney failure, chronic/end-stage kidney disease,” “ischemia-reperfusion,” “warm ischemia/cold ischemia”. All studies included were performed in humans older than 18 years, were written in English and had an abstract available for review.

Two authors (MCM, DP) independently established study eligibility, and disagreement was resolved by discussion. For this investigation we included original research studies and excluded commentaries, case reports and series focusing on small, short follow-up studies. See Figure 1 for study inclusion algorithm.

PERIOPERATIVE MEASURES TO OPTIMIZE RENAL FUNCTION

1. PREOPERATIVE MEASURES

CKD (Chronic Kidney Disease) is a public health care threat in the United States. By one estimate, patients with CKD constitute 14% of the US population age 20 and older, or more than 31 million people according to published data from US Renal Data System (USRDS). The cost associated to End-Stage Renal Disease (ESRD) represents more than 6% of the total Medicare budget [3]. CKD is silent in its early stages; however, it can be detected from simple clinical and laboratory measurements. Early maneuvers to slow down progression have been associated with a decreased mortality rate [4]. Patients with stage 3 CKD are 20 times more likely to die of a cardiovascular event than to reach end-stage-renal disease [5].

Approximately, between 20 and 30% of patients undergoing nephrectomy for RCC have pre-existing CKD and 20% of PN patients develop CKD grade III within the 5 years following surgery. The improved survival rates of RCC patients being >90% for stage 1 contrast with the survival rates of ESRD patients. Results from the USRDS in 2014 showed that an average 60 year old on hemodialysis has a decreased 5-year life expectancy.

Recent studies have defined 3 types of CKD that might behave differently: CKD-Medical, CKD-Surgical, CKD-medical/surgical [6]. According to the those studies, the annual decline in kidney function for patients with pre-existing CKD vs de novo CKD post-surgical would be close to 5% vs 0.7%. Moreover, the survival curves for patients with CKD-surgical approximate the survival curves of patient without CKD[7]. Further analysis of prospectively collected cohorts is required.

As progression of CKD is associated with exponential increase in cardiovascular morbidity and mortality, much of the care of patients affected by CKD is aimed to

slow down progression and addressing the medical issues that arise as a result of CKD.

Standard of care includes providing treatment to correct the specific cause or slow down deterioration of renal function, addressing cardiovascular risk factors and metabolic abnormalities related to CKD and patients' education.

In order to identify potential factors that may affect kidney function after PN and warrant further study evidence shows that four factors should be screened at preoperative visit:

1. Proteinuria (urine analysis): Proteinuria is associated with progression of CKD. The AASK (African American Study of Kidney Disease and Hypertension) included non-diabetic African-American patients with eGFR between 20 and 60 ml/min/1.73m^2. This trial results showed that higher levels of proteinuria were associated with a higher risk of decline in GFR and ESRD[8]. Other large studies have shown the association of high levels of albumin excretion and risk of cardiovascular events. A reduction of 50% of proteinuria has proven to reduce the risk of progression of CKD by up to 56%.

2. Blood Pressure: Many patients with CKD also have hypertension possibly due to higher rate of underlying essential hypertension or because CKD worsens hypertension. A meta-analysis of several trials of antihypertensive treatment on CKD patients found that the targeted systolic blood pressure to decrease progression of CKD was 110 mmHg. At systolic blood pressure of 160 mmHg a HR of 3.14 (95% CI 1.64-5.99) for progression of CKD was observed.

3. Hyperlipidemia is a common risk factor for cardiovascular disease. Statins have shown to be beneficial in primary and secondary prevention in patients with normal serum creatinine and eGFR between 50 and 59. The SHARP trial studied the use of

statins in CKD patients; a decrease in CV events was seen, however, no evidence of reduction in CKD progression was found.

4. eGFR calculated according to CKD-EPI formula in order to determine an accurate basal renal function status. Controversy in the use of several formulas for eGFR calculation seems to have settled. Clear consensus in the use of CKD-EPI from the nephrology community seems to be acceptable[9].

Does this mean that urologic surgeons should practice primary prevention? As urologist we should be aware of the general health of the patient and try to improve their overall health related outcomes. The identification of these 4 factors in the period prior to PN should prompt an early referral to specialized nephrologists. A recent publication on a large data set of patient with diabetes and CKD stage III/IV demonstrated that earlier referral to nephrology care providers decreased exponentially the risk of death in this subset of patients by more than 60% when more than 4 visits to nephrology were reported [4].

2. INTRAOPERATIVE MEASURES

Several maneuvers have been attempted to minimize the kidney injury during PN.

MEDICAL MEASURES

Simple measures to reduce ischemia damage during PN are proper preoperative hydration as well as intraoperative administration of furosemide to promote post perfusion diuresis. The use of mannitol (1ml/kg) was proven to be beneficial for optimal reperfusion in the animal setting however its role within the PN

was recently proven otherwise[10]. A recent randomized trial presented at the annual AUA meeting 2015 (unpublished) demonstrated no differences in renal function when comparing mannitol with placebo. Some authors described the use of an angiotensin-converting enzyme inhibitor, such as enalapril. It is intended to induce vasodilatation that may increase renal blood flow and prevent vasospasm caused by manipulation[11].

Dopamine, which increases diuresis after ischemic injury, was used in the early eras of PN to prevent damage. However, a recent randomized trial on patients undergoing PN with solitary kidneys demonstrated no protective effect[12]. Fenoldopam (short-acting dopamine-1 receptor agonist) has also been used in randomized trials with a 24h perfusion to prevent damage; no renoprotective effect was evidenced at comparison with the placebo arm[13]. Inosine also was thought to be protective, however, its role in PN was never proven. Clinical trials using a composition of multiple antioxidants to prevent damage are currently on going.

The use of controlled hypotensive anesthesia during PN has been claimed as a form of hilar clamping avoidance allowing a minimally bloody field. The rational behind this concept is that an oncologically correct PN could be performed without need of interruption of renal flow. The largest study on the topic was recently published as an update on a 100 PN series. With a median 50 minutes controlled hypotension, no differences in terms of eGFR preoperative and at 3 months ($p=0.969$) were observed[14]. Until date, this approach has not found general acceptability.

SURGICAL MEASURES; ROLE OF RENAL ISCHEMIA

Whether MIS or open, PN surgical technique aims to spare the maximum number of nephrons. Optimal PN has shown to imply improved renal function

outcomes, however, the only randomized trial published until date that compared radical nephrectomy vs PN outcomes failed to show improved overall survival in the PN patients population[15]. Several features of the trial have been criticized such as an early termination due to poor recruitment, very low specific-death rate (12 of the 117 deaths were cancer related) and no major differences in severe CKD at 7 years follow-up[16].

The ischemic approach started in the 1970s and 1980s with animal research protocols undertaken to develop optimal procedures to preserve kidney function when performing open caliceal surgery related to stone. Data obtained from non-heart beating donors describing renal tolerance of ischemia showed that a warm ischemia period of less than 20 minutes significantly reduced the post-transplant damage[17]. Furthermore, early studies during the 1970s on human kidneys undergoing nephrectomy described that cellular degeneration starts in the proximal tubules after 20-30 min of clamping; and above 60 minutes final cellular degeneration of the nephron results [18].

Thereafter, Ward et al[19] set 15C as the cut off in canine kidneys to remain safe at 90 minutes of cold ischemia [19]. Later on Novick et al [20] based their conclusion on canine kidney data (unpublished) and Ward's data stating that 30 min of warm ischemia would lead to irreversible renal functional changes. Our community accepted these 3 initial studies as a gospel for the next 4-5 decades showing very weak scientific evidence in the long term.

The current indications as well as the optimal temperature for cold ischemia are controversial. Published AUA and EAU guidelines suggest the use of hypothermia when a longer ischemia time (above 30 min) is expected [21] . In the open PN approach, the kidney surface cooling is the most commonly used technique to

achieve renal hypothermia. Several approaches to achieve hypothermia during laparoscopic and robotic approaches have been suggested such as entrapment of the kidney in [22]an Endocatch-II bag with the ice slush. Circulating ice cold saline after hilar clamping through a ureteral access sheath as well as direct renal artery perfusion technique have been encouraged by some authors.[23,24]

A single randomized phase III trial aimed to compare warm ischemia vs cold ischemia during PN for stage I kidney cancer (NCT00743236). The primary endpoints of this trial were creatinine clearance and eGFR at 1 year. Patient inclusion was completed in 2013 but no published data is currently available.

Subsequently, 2 major US centers (Cleveland Clinic and Mayo Clinic) published their renal functional outcomes on 537 patients undergoing open PN in solitary kidneys between 1970 and 2003 [25]. Based on their results, a 20 minutes cut-off for warm ischemia and 35 minutes for cold ischemia was proposed. Moreover the same 2 groups published in 2010 similar series with PN in a solitary kidney, this time using eGFR as kidney function outcome [26]. When warm ischemia time was applied as a continuous variable in this subgroup of patients a linear decrease on kidney function with increased ischemia time was observed. The conclusions of their analysis suggested 25 minutes as the safe cut-off for warm ischemia and as a continuous variable they found that every single minute of renal ischemia led to adverse renal function. The same group analyzed the exact same cohort of patients subsequently evaluating the quality and quantity of the preserved renal parenchyma in addition to the duration of ischemia. When taking into consideration the amount of parenchyma spared after the PN and the quality of the functioning kidney before the surgery, ischemia as a continuous variable no longer predicted renal function[27]. This re-analysis provided strong evidence that parenchyma saved and quality of the

parenchyma are the two factors that matter above the others. Similar outcomes were described when 4 major institutions analyzed their long-term functional outcomes of 660 solitary kidneys with cold and warm ischemia. Once more, ischemia time did not show to be a predictor of ultimate renal function[28].

Recently, a novel prospective study evaluating impact of renal ischemia on renal structural and functional changes during partial nephrectomy was reported [29]. A total of 40 patients were enrolled in the study prospectively. The totality of patients had 2 functional kidneys and a single tumor in one kidney with an excellent overall renal baseline function. Preoperative blood and urine structural and functional biomarkers were obtained as baseline and up to 24 hours postoperative in order to allow comparison to the baseline. Renal parenchymal biopsies were obtained at baseline, sequentially during renal hilar clamping to assess renal ultra structural changes compared to the baseline, 5 minutes post clamping to assess reversibility of the change as well as post reperfusion injury. The authors reported that when correlative analyses were performed including biomarkers, electronic microscopy and immunofluorescence, minimal structural and functional changes were observed at ischemia times ranging from 15-61 min with all changes being reversible. None of the functional and structural changes had any correlation with the duration of ischemia time. Recently published data by the same group of authors on long-term renal functional outcomes showed no correlation of ischemia duration with renal function at one year follow-up[30].

Several investigators considered accounting for the specific renal functioning in the operated (quality) kidney as well as parenchyma saved (quantity). Table 1 summarizes the major series published regarding the inclusion of those parameters in order to clarify the components of the ultimate kidney equation [31].

Regarding the impact of renorraphy subtype on renal function few studies including short-term series are available. Kaouk et al. analyzed the evolution of renorraphy technique in a single institution study reporting 252 RPN.[32] In the initial experience with LPN their group performed an interrupted bolstered renorraphy, evolving to comparable results using a non-bolstered continuous horizontal mattress stitch for the capsular closure at RPN. A RCT is currently recruiting participants to evaluate the safety and feasibility of non-renorraphy (NCT02131376). The purpose of the trial is to investigate the cortical renorraphy as a novel modifiable factor affecting renal function after PN.

A single Japanese report endeavored to correlate renorraphy and renal function. It included 91 patients undergoing OPN, half of them received renorraphy and the other half excluded it. The authors failed to demonstrate a difference in kidney function amongst both groups on the short-term[35].

In summarizing the available literature over the past 5 decades it is evident that it was overly simplistic and naïve to accept ischemia duration of 25-30 min as a dichotomous and safety cut off point while performing PN to avoid ischemic renal injury.

It is in the above context that the efforts to limit or completely avoid renal ischemia should be viewed. See Table 1 for major series in the selective arterial clamping.

The so called “zero ischemia” was early introduced by Gill et al [36] as selective clamping that included the use of neurosurgery bulldogs to clamp uniquely the tumor feeding arteries. The misnomer of zero ischemia is difficult to imagine. According to its fundaments, every renal mass would have its own unique blood supply that would not perfuse uninvolved surrounding parenchyma overlapping the tumor negating the

premise of truly zero ischemia. Interestingly, the renal functional outcomes have not shown clinically significant difference compared to classic PN (the percent decline of GFR averages 10% as well). The superselective clamping was described a posteriori by series over the globe in tertiary centers [37,38]. It includes the use of accurate-imaging technology to identify the specific tumor feeding branches. Once more the ultimate renal functional outcomes do not seem to be extraordinary and the reproducibility of these technique seems to be one of the biggest challenges. Early-unclamping technique has also been proposed [39] with acceptable results; however it has not been widely practiced. Regarding short-term renal function, no clinically significant differences were observed between hilar clamping and early unclamping. No long-term results have been reported to date.

Smith et al [40] reported a large single-surgeon series of 164 patients with completely unclamped PN (28 solitary kidneys). Authors described an increased estimated blood loss during the procedure with an improved renal function at 1-year follow-up (21% decrease GFR vs. 4% in unclamped group for solitary kidneys) in the solitary kidney group. This improvement does not remain significant when the entire series is analyzed. Similarly, Porpiglia et al[41] recently presented their results on a 87 patients series of clampless PN. Renal scans were performed preoperatively and at 3 months after PN, thus specific kidney changes could be evaluated. In this series, no differences in short-term renal function were observed. The enthusiasm of avoiding renal ischemia in cases of unclamped PN is accompanied by increased blood loss in most studies along with potential impact on oncologic control due to lack of a bloodless field. Moreover the use of this technique in larger renal masses, polar tumors and by less experienced urologists present formidable challenges.

Several technical questions remain unanswered within this environment, is solo artery clamping any different than whole hilar clamping? Other authors have attempted manual hilar compression, the use of Kauffman clamp, intermittent clamping. Unfortunately, single descriptive series on this topics lack scientific strength to derive meaningful conclusions[42].

Scattered investigators have attempted to quantitate ischemia damage. Most of the studies that determined the concurrent guidelines in the PN field are based on clinical exploratory short series examining exclusively clinical outcomes as described above. Almost every study barring one in the field of renal ischemia in the setting of PN points to level 3-4 evidence. More studies with higher level of evidence are needed to further establish the true role of renal ischemia during PN.

3. IMMEDIATE POSTOPERATIVE MEASURES

On average, 3% of patients in the contemporary PN cohort present with a solitary kidney. Of those, around 20% develop Acute Kidney Injury (AKI) after PN due to diverse reasons besides the ischemic injury and only 3% eventually undergo dialysis in the solitary kidney population undergoing PN. When extrapolated to the overall cohort of patients undergoing PN, less than 1% of patients after PN undergo AKI significant enough to require dialysis[43]. As a consequence, the applicability of the early PN series on the contemporary PN population remains questionable. Severe AKI is associated with adverse outcomes such as prolonged ICU stay and length of stay, dialysis dependent, decreased quality of life and increased long-term mortality[44]. There is a need to find biomarkers that can predict AKI and thus prevent these adverse outcomes.

More than 35 AKI definitions have been published in the literature. The controversy of definition rises in the fact that the majority of studies have been performed on pediatric population in context of cardiac surgery, thus the applicability in adult population and in the PN surgery seems debatable. The most commonly accepted definition for AKI is the RIFFLE. It is defined as an abrupt reduction in kidney function: absolute increase in sCr ≥0.3 mg/dl; or % increase in sCr ≥ 50% (1.5 fold from baseline); or reduction in urine output (documented oliguria ≤ 0.5 ml/Kg per hour for more than six hours). The main limitation of RIFFLE is that it is based on sCr changes and urine volume. sCr levels increase in blood only after marked reduction in GFR when kidney injury has already progressed beyond some of the important structural changes in the early phase of AKI.

The ultimate clinical biomarker that would optimize treatment options in the PN immediate postoperative setting would allow, early identification of injury, stratification of severity and monitor both progression and recovery from onset of renal injury.

Multiple AKI biomarkers have been tested to various degrees in clinical setting. Table 2 describes the most commonly studied biomarkers of AKI. None of them is specific for kidney ischemic injury, thus the weakness of the results shown until date. They can be detected at different times either in urine or plasma and they are mostly originated at the kidney proximal tubule due to all kinds of stress. NGAL (Neutrophil Gelatinase-associated Lipocalin), KIM-1 (Kidney Injury Marker-1) and Cystatin C have shown to be the most promising however, other rising stars are NAG (N-acetyl-beta-D-glucosaminidase), IL-18 (Interleukine-18) or L-FABP (Liver Fatty Acid Binding Protein). Most probably a panel of these markers may end up being what triggers intervention in context of AKI.

Cystatin C is synthesized and released to plasma by all nucleated cell at a constant rate. It is catabolized in the proximal tubular cells. Thus, under normal physiological conditions is almost undetectable in urine. It has repeatedly been proven that Cystatin C reflects GFR better than sCr. In the ICU population, plasma Cystatin C demonstrated to diagnose AKI 1.5 days in advance compared to sCr and was also able to predict need for dialysis[45]. No studies up to date have been performed in the PN population.

NGAL is a protein expressed by neutrophils and epithelial cells, such as proximal tubular cells and released in urine in response to ischemia/injury. NGAL is easily detected in the very first urine output after renal ischemia in pig models. Several authors demonstrated a correlation between urine and plasma NGAL levels proportional to the severity of the injury in the ICU/cardiac surgery settings. Urine NGAL is specific to AKI and provides valuable prognostic information in these patients [46]. A prospective study on 220 patients undergoing surgery (88 patient PN, 32 patients RN, 42 thoracic surgery) collected urine and blood samples preoperatively and postoperatively. No differences were observed in urinary NGAL between the PN and thoracic surgery group. No association was found between uNGAL and the development of AKI in the PN population[47]. These results suggest that with the improved renoprotective techniques and surgical skills, the stress injury generated during PN is not sufficient to increase release of NGAL.

KIM-1 is overexpressed in proximal tubules due to ischemic/nephrotoxic injury. It has been shown to be an early marker of AKI. Correlation between KIM-1 level and histologic severity of injury were also proven. Recent publications corroborated increased levels of KIM-1 within 2 days of cardiac-bypass only in patients with AKI. Besides in patients with diabetes and mild CKD its levels in

plasma predicted eGFR loss and risk of severe CKD at 15 years follow-up[48]. The major limitation in the PN field is that KIM-1 levels have been shown to be elevated in patients with RCC [49].

L-FABP is an excellent biomarker for early prediction of kidney diseases. A recent meta-analysis compared L-FABP with other urinary biomarkers, including KIM-1 and NGAL [50]. None of the analyzed biomarkers proved to improve current clinical practice. The potential value of L-FABP needs to be further validated in largest studies.

CONCLUSIONS

Preoperative evaluation of several parameters such as control of blood pressure, identification of proteinuria and timely consultation with a nephrologist helps optimize postoperative renal function after PN. Duration of ischemia has been historically utilized as a surrogate of renal functional outcomes after PN. A number of recent studies have found that the quality and quantity of remnant renal parenchyma after PN assumes a more important role in predicting future renal function. Current stronger level evidence supports greater tolerance of the human renal parenchyma to limited ischemia. The current practice of using a 'safe' ischemia cut-off duration time of 25-30 min is flawed. Biomarkers for early prediction of kidney failure in the context of PN seem to be encouraging but still unreliable.

FIGURES LEGENDS

Figure 1. PRISMA Algorithm for selection of studies included in the current review.

TABLE LEGENDS

Table 1. Recently Published Series on Partial Nephrectomy Functional Outcomes. Data is organized according to surgical technique used including most relevant features of each series. 1A; Series reporting Hilar Clamping. 1B; Series reporting Non-Hilar Clamping.

Table 2. Summary of Blood/Urine Markers Studied in the context of Partial Nephrectomy and Ischemia

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Table 1 A. Hilliar Clamping

Warm Ischemia

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
Lane (1169/215)	OPN (696); LPN (473)	25	N	N	16% L, 14% O	4	Updated 10 y outcomes Jurol 2013 gill, scc lane
Funahashi (32/0)	OPN (20);LPN (12)	24 O; 24 L	Y	N	14 at 3 months; 13 at 6 months;	4	to evaluate RF in operated kidney: WIT >25 min decrease in effective RPF on operated side up to 6 mo
Porpiglia (44/0)	LPN	18	Y	N	2	4	0 and 3 months renal scan
Pouliot (56/0)	LPN	30	Y	N	14	4	MAG3 @ 10 d; WIT<30 min not associated w/ RFD
Song (117/0)	LPN	28	Y	Y	29	4	Age, kidney volume loss and upper pole location as predictors of loss of RF
Thompson (362/362)	OPN (319);LPN (43)	21	N	Y	21	4	WIT,% kidney preserved, preop eGFR independent predictors AKI

Cold ischemia

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
Yossepowitch (662/70)	Open	35 B; 31 S	N	No	16% B; 30% S	4	GFR measurement preop and 12 mo; long term GFR not afected by ischemia time

Jeon (50/NS)	Open	0	N	Y	12	4	Older age and preop volume for both kidneys as predictors of low postopeGFR

Mixed Ischemia

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
Lane (C:360;W300/660)	Open/MIS	C:45;W:22	N	Y	10	4	Ischemia is not independent predictor of ultimate RF; Quality and quantity of parenchyma are top factors
Mir (C:35;W57/37)	Open/MIS	C:28;W:21	Y	Y	20	4	GFR preserved correlates with % parenchyma saved. Ischemia does not correlate with %GFR preserved
Simmons (301/17)	Open/MIS	C:40;W21	N	Y	10	4	Volume loss is primary determinant of ultimate RF
Parekh (40/0)	Open	C:48;W:32	N	N	NS	2	No impact of ischemia length on renal ultrastructure and short/long term function

Table 1B. Non-Hilliar Clamping

No Clamping

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
Porpiglia(43/0)	LPN	18	Y	N	1	4	Higher benefit :poorest baseline RF
Thompson (96/96)	Open/MIS	0	N	N	NS	3	X2 risk of AKI and CKD if warm ischemia
Smith(190/28)	Open/MIS	0	N	N	10	3	

Zero Ischemia

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
Kaczmarek (49/5)	RPN	0	N	N	10	4	Increased EBL, smaller decrease eGFR at 6 mo
Hung (78/0)	RPN	0	N	Y	8	4	No increase in urologic complications w/ similar ultimate RF as if ischemia present

Early Unclamping

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
Peyronnet (222/NS)	Open/MIS	17	N	N	9	4	reduced WIT during RPN w/o increasing morbidity

Superselective Clamping

Study (total n/solitary kidney)	Surgical Approach (n)	Ischemia time (min)	MAG3	Volumetrics	GFR decline (%)	Level of evidence	Comments
McClintock (42/NS))	RPN	0	N	N	2%D/C; 3% 3 mo	4	NIRF
Ng (22/2)	RPN	0	N	N	10	4	Segmental clamping
Shao (24/NS)	MIS	24	N	N	17	4	Segmental clamping
Desai (58/7)	MIS	0	N	N	11	4	Vascular micro dissection

RPF: Renal Plasma Flow
RF: Renal Function
D/C: At Discharge
GFR: Glomerular Filtration Rate
MIS: Minimally-Invasive Surgery
RPN: Robotic Partial Nephrectomy
LPN: Laparoscopic Partial Nephrectomy
NIRF:
CKD: Chronic Kidney Disease

	ORIGIN	OTHER LOCATIONS	DETECTION TIME (Hr)	STRENGTHS	LIMITATIONS
NGAL	Proximal tubules*	Lung, colon	0-2 (urine and plasma)	Early marker AKI; more sensitive than sCr; Levels correlated w/morbi/mortality	Elevated with inflammation
NAG	Proximal tubules*	Multiple	4 (urine)	Levels correlated w/ AKI morbi/mortality	Not specific of AKI (yes for oxidative stress)
IL-18	Mediators of inflammation	Systemic	4-12 (urine)	Levels correlated w/ AKI morbi/mortality	Non-specific to AKI
KIM-1	Proximal tubules*	None	12-18 (urine)	Levels correlate w/ severity injury	Non-specific AKI but yes to renal damage; elevated in RCC
Cystatin C	Proximal tubules*	Released by all cells into plasma at constant rate	6 (urine); 12-24 (plasma)	Serum levels: GFR; Urine levels: morbidity	Limited data; might be similar to sCr
L-FABP	Proximal tubules*	Liver	1-4 (urine)	Very early AKI marker; elevated levels after 5 min of ischemia	Specific to kidney at early time points, after from liver source

Key Definitions

Renal cell carcinoma (RCC)

Partial nephrectomy PN)

Chronic Kidney Disease (CKD)

Glomerular Filtration Rate (GFR)

Acute Kidney Injury (AKI)