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Collaborative Review – Kidney Cancer

Assessing the Impact of Ischaemia Time During Partial Nephrectomy

Frank Becker [a,*], *Hein Van Poppel* [b], *Oliver W. Hakenberg* [c], *Christian Stief* [d], *Inderbir Gill* [e], *Giorgio Guazzoni* [f], *Francesco Montorsi* [g], *Paul Russo* [h], *Michael Stöckle* [i]

[a] *Department of Urology, University of Saarland, Kirrbergerstrasse, Homburg/Saar, Germany*
[b] *Department of Urology, University Hospitals Leuven, Leuven, Belgium*
[c] *Department of Urology, University Hospitals Rostock, Rostock, Germany*
[d] *Department of Urology, University Hospitals München – Großhadern, Munich, Germany*
[e] *Department of Urology, University of Southern California (USC), Los Angeles, USA*
[f] *Department of Urology, Fondazione San Raffaele del Monte Tabor, Milan, Italy*
[g] *Department of Urology, University Vita Salute San Raffaele, Milan, Italy*
[h] *Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, USA*
[i] *Department of Urology, Universtiy of Saarland, Homburg/Saar, Germany*

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Abstract

Context: The impact of applying renal ischaemia during nephron-sparing surgery to avoid renal damage in the treated kidney has gained importance in different surgical techniques.

Objective: The main objective of the present study is to point out the limit of renal ischaemia times for warm and cold ischaemia approaches. Important results of research on renal ischaemia and different surgical techniques as well as results of clinical studies concerning renal function after renal ischaemia in partial nephrectomy are highlighted.

Evidence acquisition: A Medline literature research was performed, combining queries on the key-words *nephron-sparing surgery*, *partial nephrectomy*, and *ischemia*. Links to related articles and cross-reading of citations in related articles were surveyed, as were reviews, letters to editors, and information collected from urologic textbooks. The references formed the basis of this review article, with selection and deletion based on the relevance and importance of the content. In a final step, interactive peer review by the expert panel of coauthors completed the review.

Evidence synthesis: Renal ischaemia research showed an increasing renal damage proportional to ischemic time. Current clinical data support safe ischaemia times, within 20 min of warm ischaemia and up to 2 h of cold ischaemia, to minimise renal ischemic damage. To date, no ischaemia dose-response curve or algorithm is available to predict the risk of acute kidney injury and chronic kidney disease in patients undergoing intraoperative ischaemia. In general, there seems to be a higher risk for comorbidity caused by renal damage in patients suffering from kidney tumour.

Conclusions: If ischaemia is required, the tumour should be removed within 20 min of warm ischaemia, regardless of surgical approach. Efforts should be made to start immediately with cold ischaemia, if the feasibility within this span of time seems to be jeopardised. Thus, cold ischaemia times up to 2 h can be tolerated by the kidney, depending on the individual method. Nevertheless, cold ischaemia with ice slush should be kept as short as possible—at best within 35 min. In ischemic nephron-sparing surgery, one of the surgeon's main aims should be to avoid loss of renal function. Only after optimal preoperative appraisal and planning can the best postoperative outcomes for renal function be achieved.

* Corresponding author. University Clinics of Saarland, Department of Urology, Kirrbergerstrasse, D-66421 Homburg/Saar. Tel. + 49 (0)6841 1624700.
E-mail address: frank.becker@uks.eu (F. Becker).

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1. Introduction

Open partial nephrectomy (OPN) has become the standard procedure for management of small renal tumours, especially since publication of the current *European Urological Association Guidelines on Treatment of Renal Cancer* in 2007 [1]. In addition, the incidence of small renal masses fulfilling the prerequisites for nephron-sparing surgery (NSS) has been steadily rising [2,3].

For larger tumours >4 cm in diameter, however, the same guidelines recommend laparoscopic radical nephrectomy [1], despite recent studies on NSS demonstrating improved renal function and life expectancy resulting from the preservation of healthy parenchyma [4–7]. Furthermore, elective OPN for these larger tumours has shown oncologic results equivalent to radical nephrectomy (RN) in experienced centres [8–10]. Although these data support the concept of organ-sparing surgery in localised renal masses independent of tumour diameter, whenever possible and feasible, partial nephrectomy (PN) still appears to be underutilised [11,12].

Whether laparoscopic PN (LPN) can combine preservation of renal function by NSS with the minimal invasiveness of laparoscopy remains to be seen. During LPN, cooling is more complex, and mean ischaemia time seems to be longer than in OPN. In the latter, cooling is being increasingly omitted because ischaemia times within 20 min can be achieved in general. In most instances, the mean diameter of tumours treated by LPN is somewhat smaller compared with OPN (2.7 vs 3.5 cm [13] and 2.8 vs 3.3 cm [14], respectively).

Thus, the maximum tolerable ischaemia time in PN is essential in the quest for the optimal approach. This review of all organ-sparing procedures with appropriate experimental data and clinical history of renal ischaemia attempts to answer this question. Furthermore, data on a new technique, robotic PN (RPN), are analysed because RPN appears to combine a minimally invasive approach with the quality, speed, and dexterity of OPN [15,16]. Warm ischaemia (WI) and cold ischaemia (CI), renal tolerance time, medical preservation of the clamped kidney, and the pathophysiology of reperfusion injury following ischaemia are highlighted.

2. Evidence acquisition

Literature research included Medline queries on the keywords *nephron-sparing surgery, partial nephrectomy*, and *ischaemia*. Links to related articles and cross-reading of citations in related articles were surveyed, as were reviews, letters to editors, and information collected from urologic textbooks. These references formed the basis of this review article, with selection and deletion based on the relevance and importance of the content. A literature list with 79 references remained. In a final step, interactive peer review by the expert panel of coauthors completed this review [17].

3. Evidence synthesis

In general, it has to be stated that only few well-designed, scientifically performed studies in the realm of renal ischaemia during PN are available that prove an optimal approach. Every paper has to be analysed critically in terms of methodology and content that could be driven by the personal preferences of the author.

3.1. *Intention of renal preservation*

Whereas resection of small tumours without clamping the kidney vessels provides oncologically adequate surgery and minimises perioperative complications or loss of renal function, intraoperative ischaemia of the affected kidney often becomes necessary. Ischaemia diminishes intraoperative renal haemorrhage and improves access to the intrarenal collecting system by reducing renal tissue turgor. Furthermore, ischaemia allows better visualisation of the tumour extent and allows complete tumour resection, sometimes without healthy margin. It also allows easier closure of the parenchyma. Nevertheless, an understanding of renal responses to ischaemia and knowledge of the methods available for protecting the kidney if the period of vascular occlusion exceeds the limit of safe tolerance are indispensable [18].

The main challenge presented by PN and, consequently, the main difference between PN and RN, is preservation of renal function. It has been evident for some time that in imperative indications, this aim can be reached because most patients do not require permanent dialysis. The benefit of elective NSS has been discussed controversially for a long time. In recent years, evidence has been accumulating that shows even minor loss of kidney function can reduce life expectancy and increase cardiovascular morbidity. Thus, the goal of preserving as much parenchyma as possible has gained priority [4,5].

The conclusion shared by all of the studies listed in Table 1 comparing renal function after RN and PN is that preservation of renal function is superior after elective nephron-sparing approaches than after RN, given the same conditions (healthy contralateral kidney and tumour <4 cm in diameter). Although the criterion for evaluating kidney function in several studies was solely serum creatinine rate (sCR) in a healthy contralateral kidney—a method generally considered to be imprecise—every single study showed decreased renal function following RN, despite similar oncologic results after both RN and PN, whether open or laparoscopic [5–7,19,20].

Sorbellini et al even developed a nomogram from the Memorial Sloan-Kettering Cancer Centre patient database (PN: $n = 161$, including patients with raised preoperative sCR; RN: $n = 857$) to predict the 7-yr probability of renal insufficiency in patients undergoing RN or PN [21]. In their cohort, renal insufficiency became evident in 12.3% of patients after RN and in only 3.7% of patients after PN. Unfortunately, renal insufficiency was defined as elevation of sCR >2.0 mg/dl rather than glomerular filtration rate (GFR) or creatinine clearance (CrCl). The probability of developing renal insufficiency can be calculated on the basis of the following factors: age, gender, American Society of Anaesthesiologists score, preoperative creatinine level, and percent of change in kidney volume after surgery.

Table 1 – References comparing nephron-sparing procedures with radical nephrectomy

Study	Surgical techniques	No. of patients	Renal function damage	Conclusions
Matin et al [19]	LN vs OPN	35 vs 82	25% vs 0% (sCR increase)	Better perioperative outcome after LN Better renal function 6 mo after OPN
McKiernan et al [6]	RN vs OPN	173 vs 17	9% vs 0% (creatinine failure >2.0 mg/dl)	No dialysis in either group Higher risk of CKD after RN
Huang et al [5]	RN vs OPN	204 vs 287	65% vs 20% (GFR <60 ml/min per 1.73 m^2)	RN a risk factor for developing CKD RN not standard treatment for small renal tumours Baseline kidney function in small renal tumours lower than previously thought
Clark et al [20]	RN vs OPN	37 vs 26	31.7% vs 6.1% (decrease of CrCl)	Renal function after OPN more favourable than after RN CrCl or GFR more accurate parameters for renal function than sCR
Thompson et al [7]	RN vs OPN	290 vs 358	Renal function not evaluated	Significant factors predicting survival: preoperative sCR, comorbidity index (Charlson-Romano), symptoms at presentation, diabetes, histologic subtype Favourable CSS after OPN in patients <65 yr of age explained by less renal function damage

CKD = chronic kidney disease; CrCl = creatinine clearance; CSS = cancer-specific survival; GFR = glomerular filtration rate; LN = lymph node; OPN = open partial nephrectomy; RN = radical nephrectomy; sCR = serum creatinine rate.

The nomogram could be useful for the urologist in patient counselling, clinical trial design, and creation of effective follow-up strategies for patients.

The well-designed study by Huang et al, comparing 662 patients retrospectively after RN or PN, describes long-term renal function measured by GFR [5]. It turned out that patients with small kidney tumours had less preoperative kidney function than generally expected. It is clear that renal cell carcinoma (RCC) presents in many patients who have comorbid disease affecting global renal function. Thus, RN is a significant risk factor for the development of chronic kidney disease (CKD) and should be avoided in cases of small renal cortical tumours.

Thompson et al even cite favourable cancer-specific survival after OPN compared with RN in patients <65 yr of age [7]. The authors hypothesise that because OPN causes less renal function damage and is associated with less comorbidity, it has a significant impact on survival and tumour biology. The consequences of CKD or renal function damage have been described in detail by Go et al [4]. A higher risk of death, cardiovascular events, and hospitalisation in a large community-based population was described in patients with reduced estimated GFR.

The higher risk of CKD after nephrectomy contrasts with observations on living kidney donors who showed no evidence of progressive renal function deterioration after kidney donation [22–24]. This is not surprising because kidney donors for live donor transplantation are highly selected and only undergo donor nephrectomy if they are free of any comorbidities. In contrast, renal tumour patients have a higher risk of developing CKD, and many of them have preexisting damage to global renal function before surgery.

NSS must be expected to become the standard approach for kidney tumour surgery. The intention of renal preservation is avoiding CKD, which seems to be imminent in a substantial number of patients with RCC. RN will be reduced more and more to a desperate solution for advanced disease.

3.2. *Ischaemia research and mechanisms of renal failure*

The ischemic approach to kidney surgery goes back to the 1970 s and 1980 s, when experimental research was undertaken to develop optimal procedures that preserve kidney function in open caliceal exploration for stone disease or in explanted kidneys being considered for renal transplantation.

If open stone surgery without ischaemia was not feasible, ischaemia was induced to minimise blood loss or create a bloodless surgery field for meticulous preparation and reconstruction of the kidney [18,25].

Renal transplantation surgery always attempted to achieve the shortest possible time of ischaemia to minimise renal reperfusion damage. Data derived from non-heart-beating donors describing renal tolerance of ischaemia revealed that a WI period of ≤20 min significantly reduced posttransplant kidney damage [26].

During the era of open stone surgery and the beginnings of renal transplantation, mechanisms of acute renal failure were experimentally explored [27] and are referred to up to this day [28]. The mechanism resulting from renal ischaemia primarily occurs at a vascular level, leading to vaso-obstruction and reperfusion injury that reduces renal blood flow and decreases organ activity.

On a *vascular level*, multi-inflammatory responses by interleukins lead to vasoconstriction and vascular spasms. A vicious cycle is activated by endothelial injury, causing the activation of a cytokine cascade that results in arteriolar vasoconstriction. The low renal blood flow releases angiotensin II and eicosanoids. In this state of ischemic insult, failure of oxidative phosphorylation and adenosine triphosphate (ATP) depletion cause cellular swelling by passive water diffusion into the cells, and, consequently, both the "no reflow" phenomenon and vascular *obstruction* during renal *reperfusion* occur. Free radicals resulting from ATP degradation cause further cell damage (*reperfusion injury*, a well-known phenomenon in renal transplantation) [27–32].

This led to the development of methods for prevention and treatment of acute ischemic renal failure, which included pharmacologic interaction with the renal vascular system and surgical techniques of renal ischaemia with minimum kidney manipulation [27]. Two different approaches of renal ischaemia have become established: WI and CI.

Experimental studies on human kidneys performed by Rocca Rosetti demonstrated that cellular degeneration begins mainly in the proximal tubules after 20–30 min of clamping; after >60 min of WI, complete cellular degeneration of the nephron occurs. Based on these data, a maximum time frame of 30 min was recommended for WI. His conclusion based on CI experiments on surface cooling with medullary temperatures at about 22 °C is that CI is not tolerated for >60–70 min [25,33].

Other experiments on CI in the 1970 s attempted to define the optimal temperature for prolongation of ischaemia tolerance and prevention of renal freezing damage. This damage derives from the reduced renal blood flow and resulting increase in vascular resistance caused by hypothermia [34]. Thus, an optimal temperature not <15 °C was recommended by Ward after experiments on dog kidneys [35].

Studying rats undergoing renal ischaemia in 1981, De Maeyer et al described the optimal perioperative preparation to avoid renal injury: preischaemic hydration, intravenous application of mannitol, and infiltration of the pedicle with diluted papaverine solution [36]. More recent observations in a porcine model challenging the maximum safe duration of WI suggest that renal pedicle clamping for 75–90 min is safe for renal function. However, animal models, even if they approximate human renal physiology, must be differentiated from the clinical setting [37,38].

Advantages of reducing renal temperature after clamping the kidney were described by Ward in 1975 based on dog experiments [35]. The optimum temperature for clinical renal hypothermia seemed to be reached at 15 °C. No additional protection was found below 15 °C, but severe renal deterioration occurred at temperatures >22 °C [32]. Monitoring of renal temperature is very sophisticated, which should be considered when contemplating these data.

In conclusion, avoidance of renal perfusion or reperfusion injury by pharmacologic preconditioning as well as adherence to the experimentally confirmed renal tolerance time for WI and CI were described by McDougal [27] and Novick [18]. The approach least deleterious to renal function is PN without ischaemia. If this appears unfeasible, the choice of ischemic procedure should be made preoperatively. The maximum tolerable ischaemia time for NSS in WI should not exceed 20 min. If a cooling strategy is planned, CI should be completed within 70 min [18,27].

3.3. Clinical studies

3.3.1. Partial nephrectomy with warm ischaemia

Several clinical studies suggest that the maximum period of WI time for preservation of renal function should not exceed 20 min, whether LPN, OPN, or RPN is attempted [25,39–41] (Table 2).

Laparoscopic techniques have recently been developed that reduce intraoperative WI time and that attempt to approximate the mean ischaemia times of OPN [54–56]. Nguyen and Gill [54] describe an "early unclamping" technique, halving the previous ischaemia time from 31.1 to 13.9 min but bearing a certain risk for bleeding and ischaemia (in case of reclamping). Consequently, acceptable WI times could be maintained in centres experienced with laparoscopy. Whether robotic-assisted LPN can reach these ischemic times remains to be seen. Whether it affords similar or even more favourable ischemic times remains to be proven. Early results have reported satisfactory ischaemia times but must be documented by further large multicentric studies [15,16]. If WI does not exceed 20 min, the least damage to the kidney can be expected [39].

3.3.2. Partial nephrectomy with cold ischaemia

Efforts have been made to improve the technique of intraoperative kidney cooling. For clinical practicability, a temperature of 20–25 °C appeared to provide complete renal protection for up to 3 h of arterial occlusion [18].

Laying ice slush around the kidney was the most common technique used in OPN for surface cooling. Methods of surface cooling have also been developed for LPN and are recommended if WI is expected to exceed 20 min. After an exposure time of about 10 min by ice slush, the kidney can be clamped, and a safe CI time for a maximum of 35 min has been described [13,18,45,51].

Another technique initially developed for OPN is transarterial cooling by perfusion through the clamped renal artery with cooled Ringer's solution. This allows kidney cooling down to 5–10 °C and is reported as minimising ischemic damage by an abrupt switch of renal cells from aerobic to anaerobic processes. Theoretically, this homogeneous cooling should achieve more effective renal preservation with less ischemic and reperfusion damage than surface cooling, where a heterogeneous temperature profile of 5–19 °C is achieved [57]. These data are contrary to the experimentally defined optimum hypothermia temperature of 15 °C by Ward [35] and remain to be proven by scientifically performed studies. Cold perfusion, developed in dog experiments in the 1970 s, was proposed to replace elaborate CI approaches like autotransplantation because it allows ischaemia time up to 70 min [58].

Autotransplantation after work bench surgery is a sophisticated technique commonly used in the past for treatment of renal artery stenosis, reportedly achieving CI up to 2 h [18,59]. Today, autotransplantation has been widely abandoned, but it can still be successful as a last resort in very complex cases [60].

For laparoscopy, a number of new technical approaches to optimise and facilitate CI have been proposed because

Table 2 – Recent studies on renal function after tumour surgery

Study	Subject matter	*n*	Mean ischaemia time	Mean tumour size	Comments
OPN					
Fergany et al [42]	OPN in solitary kidneys	400	38.1 min	4.18 cm	Renal function quantified by sCR Satisfactory long-term renal function: no increase of sCR in 21%, only minor increase in 41%; increase of sCR >50% of preoperative value in 38%; 14% permanent dialysis Significant factors for postoperative renal function: age, size of resected parenchyma, time interval after contralateral nephrectomy
Ghavamian et al [43]	OPN in solitary kidneys	76	NA	4.8 cm	Late renal insufficiency in 12.7%; acute renal failure in 12.7% Renal insufficiency declared as sCR >2.0 mg/dl 12.7% ex vivo resection
Iida et al [44]	Effect of CI (ice slush) on renal function after OPN; 3 groups (<30 min, 30–60 min, and >60 min CI)	131	NA	2.8 vs 2.9 vs 3.9 cm	Renal function compared by eGFR (pre- and >12 mo postoperatively) Cutoff time for significantly higher late-stage CKD in CI was 44 min Other risk factors for late-stage CKD: operation time, imperative indication, preoperatively elevated eGFR, age
Thompson et al [45]	Multicentric study on impact of ischaemia time in solitary kidneys	537	NA	2.0 vs 3.5 vs 4.0 cm (*n* = 85 no ischaemia; *n* = 174 WI; *n* = 278 CI)	CI performed by ice slush; sCR measurement Higher complication rate after clamping (WI and CI) Higher incidence of acute renal failure in WI >20 min or CI >35 min WI >20 min resulted in increased risk of renal insufficiency and permanent dialysis
Yossepowitch et al [46]	Description of GFR course after OPN in solitary and/or healthy contralateral kidneys	662	35 vs 31 min (two functioning kidneys vs solitary kidney)	2.5 vs 3.5 cm (two functioning kidneys vs solitary kidney)	GFR measurement: preoperative, 1 and 12 mo postoperative Length of CI time determines short-term postoperative GFR (particularly in solitary kidneys) Long-term GFR seems to be unaffected by ischaemia time
LPN					
Abukora et al [47]	Renal function comparison of 12 WI patients vs 14 CI patients after LPN	26	31.5 vs 44.5 min	2.31 vs 2.16 cm	No difference in postoperative MAG3 renal function tests up to 6 mo after both procedures No significant mean renal function loss after both procedures CI by cold arterial perfusion
Bhayani et al [48]	Renal function after LPN (without ischaemia [*n* = 42], WI <30 min [*n* = 48], and WI >30 min [*n* = 28])	118	0 vs <30 min vs >30 min (max 55 min)	2.4 vs 2.5 vs 2.8 cm	No statistically significant difference in sCR increase (+0.05 vs +0.06 vs +0.08 mg/dl) in all groups; no renal insufficiency; no permanent dialysis WI up to 55 min has no influence on long-term renal function (median: 28 mo)
Desai et al [49]	Comparison of LPN (WI <30 min [*n* = 74] or WI >30 min [*n* = 105])	179	31 min (22 vs 37 min)	2.9 cm (2.8 vs 3.1 cm)	Measured by MAG3 before and 1 mo after surgery Data suggest that clinical sequelae are minimal in WI <30 min WI >30 min, especially in advancing age and preexisting renal insufficiency, is associated with greater ischemic renal dysfunction Recovery of renal function is delayed the longer WI is required
Foyil et al [50]	Comparison of LPN (without ischaemia, WI, and CI) by long-term CrCl change	98	0 vs 27 min (WI) vs 38 min (CI)	2.4 vs 3.1 (WI) vs 2.9 cm (CI)	Measurement of CrCl (Cockcroft-Gault) Direct correlation between time of ischaemia and degree of acute renal damage Safe WI time before permanent renal damage was <45 min
Lane and Gill [51]	5-yr outcome after LPN	557	NA	2.9 cm	Mean sCR elevation from 0.9 to 1.0 mg/dl 4.1% abnormal postoperative renal function 2.0% CKD; 1.8% kidney loss
Porpiglia et al [52]	Prospective study analyzing renal function after WI >30 min	18	39.0 min (WI)	3.4 cm	Measurement of sCR, eGFR, and MAG3 within first postoperative year Recommendation: keep WI within 30 min to avoid partial renal damage
Shekarriz et al [53]	Prospective study describing postoperative renal function (MAG3)	17	22.5 min (WI)	3.0 cm	MAG3 and GFR follow-up until 3 mo postoperatively No significant negative association between clamping time and renal function change Clamping up to 44 min WI acceptable

CI = cold ischaemia; CKD = chronic kidney disease; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; LPN = laparoscopic partial nephrectomy; MAG-3 = mercaptoacetyltriglycine; OPN = open partial nephrectomy; SCR = serum creatinine rate; WI = warm ischaemia.

mean ischaemia times tend to be significantly longer than during OPN. LPN is a challenge reserved for dedicated laparoscopic surgeons to achieve haemostasis and reconstruction of the preserved kidney in an acceptable time frame [54].

In LPN, the application of cold perfusion is feasible and leads to acceptable functional results, even with a mean ischaemia time of 40 min (up to 101 min), but it remains a clinically sophisticated procedure [61,62].

Another technique of renal hypothermia can be achieved by retrograde intracavitary saline perfusion, as described by Landman et al in a porcine model as well as in case reports [63,64]. It seems to be an alternative to cold arterial perfusion or slush ice around the kidney, as described by Gill et al [57].

CI has clear benefits in protecting the kidney during long ischemic periods but should be used only if absolutely necessary, that is, if expected clamping time exceeds 20 min. Although there is no clear evidence of a postoperative benefit in ischemic periods <30 min, it is recommended, however, that WI be restricted to a maximum of 20 min [41,45]. This recommendation is based on the available clinical and experimental evidence. Only when ischaemia time is expected to exceed 30 min should CI be used a priori [30].

3.4. Other kidney-preserving methods and myths regarding the technique of partial nephrectomy

3.4.1. Artery versus pedicle clamping and effect of pneumoperitoneum

Orvieto et al [65] analysed these techniques in a solitary kidney porcine model. The result was a slight increase in sCR immediately following OPN (days 1 to 3). No increase in sCR was seen after LPN, suggesting a beneficial effect of venous compression by pneumoperitoneum. Furthermore, the different clamping techniques did not result in functional differences in this study.

No other clinical study to date has demonstrated an improvement in WI time or functional outcome after any modification of clamping technique (eg, clamping of the affected segment artery vs main artery). If only the artery and not the whole pedicle is clamped, the hypothetical effect of partial oxygenation of parenchyma caused by retrograde venous backflow must be weighed against the potentially higher risk of intraoperative venous parenchymal haemorrhage and, consequently, higher blood loss and reduced visibility.

An influence of pneumoperitoneum on functional outcome has not been evaluated systematically but appears rather unlikely under the typical low pressure of approximately 15 mm Hg [38].

3.4.2. Manual versus vascular occlusion and intermittent versus continuous clamping

Manual compression of the kidney rather than vascular clamping may sufficiently reduce blood loss during resection of small exophytic tumours, but it is only feasible during OPN or hand-assisted laparoscopy. Although a renoprotective effect has not been confirmed by controlled clinical studies, this may reduce the risk of vascular injury to the pedicle [38].

Sequential intermittent clamping with preconditioning intent has shown no benefit to renal function in animal studies but also no harm [66,67]. Concerning intermittent clamping during resection, Marberger recommends strict avoidance on the basis of older results dating back to the era of stone surgery research [25]. It disguises information about the duration of ischaemia and increases the risk of arterial damage.

3.4.3. Pharmacologic and other preservation strategies

Indispensable tools for reduction of ischaemia damage are sufficient preoperative hydration to facilitate vascular perfusion and stimulate diuresis [25] and intraoperative administration of furosemide, which promotes postperfusion diuresis and, theoretically, decreases energy requirements of cells in the thick limb of Henle loop [38].

In addition, intravenous administration of mannitol (1 ml/kg) in animal studies and clinical application has been proven to be beneficial for optimal reperfusion. It is filtered through glomeruli and inhibits tubular reabsorption of water and leucocytes by raising the osmolarity [2,57,68].

Some authors describe the use of an angiotensin-converting enzyme inhibitor, such as enalapril (1.25 mg intravenously [IV]). It is intended to induce vasodilatation that may increase renal blood flow and to prevent vasospasm caused by ischaemia or manipulation [2,58,59]. Furthermore, it can be argued that vasospasm can be avoided by careful dissection of the pedicle before clamping [25].

To prevent thrombosis of the vessels, some authors recommend the application of heparin (2000–3000 IU IV) before clamping [2,59], but no data are available to prove this benefit.

Other vasodilatatory agents, such as dopamine or diltiazem, have likewise been examined in animal studies to prohibit acute renal failure or increase renal blood flow after ischemic injury. In fact, these agents do not provide a renoprotective effect or clinical benefit [69,70]. The renoprotective effect of inosine (a purine nucleotide), described years ago, appears to have had no clinical impact because the drug is not in use for NSS [61,71].

It is a fundamental task of the anaesthesiologist to maintain intraoperative blood pressure at a normal level (systolic blood pressure: >120 mm Hg; mean blood pressure: ≥80 mm Hg) and to guarantee haemodynamic stability. This promotes kidney perfusion during the extension and maintenance phases of surgery [25,38].

3.5. Monitoring postoperative renal function

Renal scintigraphy with technetium-99m-mercaptoacetyltriglycine (MAG3) using estimated split renal function is currently the best method for exact determination of renal function loss after tissue resection and ischemic injury [72]. On the basis of changes in MAG3 reuptake and parenchymal retention, studies have demonstrated postoperative recovery of renal function within the first year after NSS [73]. MAG3 scintigraphy, however, is an extensive, expensive, and invasive investigation not considered justifiable for ethical and cost-effective reasons.

In the presence of a healthy contralateral kidney, renal function estimation by sCR is imprecise. Thus, determination of GFR by 24-h urine CrCl is recommended for improved monitoring of pre- and/or postoperative renal function. An even more simplified method is calculation of an estimated GFR (eGFR) by sCR (www.nephron.com/MDRD_GFR.cgi) [38,74].

In the hopes of establishing a more precise clinical method for monitoring acute renal injury and renal failure, studies on biomarkers that detect subclinical injury have been done. The following serum and urine biomarkers were found to be of some use in indicating acute renal injury, but they have not as yet gained clinical importance: Na^+/H^+-exchanger isoform 3, neutrophil gelatinase-associated lipocalin, kidney injury protein 1, and proatrial natriuretic peptide [31,75]. Further studies are necessary to determine the importance of these molecules.

3.6. *Comparison of different ischaemic approaches*

Table 2 contains a list of recent clinical studies describing the effect of ischaemia on renal function after PN, OPN, LPN, and RPN. OPN still seems to be the gold standard because mostly acceptable ischemic times are achievable and it allows every possible ischemic approach without additional technical complexity. Even in larger tumours, resection can often be achieved within 20 min of WI [2]. The Cleveland Clinic Foundation has not used CI for OPN since 2002 because resection was usually practicable without any ischaemia or within acceptable WI times [42].

Even if CI with ice slush is performed, a higher risk of late-stage CKD can only be expected if cutoff time exceeds 44 min, as described by Iida et al [44]. These authors define late-stage CKD as eGFR <45 ml/min per 1.73 cm^2, a cutoff at which an increase of long-term cardiovascular events can be anticipated. Other risk factors for late-stage CKD after OPN were age, operation duration, imperative indication, reduced preoperative eGFR, and decrease of eGFR 1 yr after surgery.

After comparing different OPN techniques (without ischaemia, WI, and CI) in a large multi-institutional study, Thompson et al concluded that whenever pedicle clamping is expected, WI must be completed within 20 min and CI (ice slush) within 35 min [45]. This paper, however, must be analysed critically because groups divided by different surgical approaches had different clinical features, only patients with a solitary kidney were included, and only serum creatinine levels were estimated to define renal insufficiency.

Particularly in solitary kidneys, OPN seems to be the safest surgical access with acceptable postoperative renal function. An interesting factor that influences postoperative renal function in solitary kidneys is the time since loss of the contralateral kidney. Patients with congenital solitary kidneys or with loss of the contralateral kidney ≥1 yr before surgery have more favourable postoperative renal function, explained by the development of a compensatory kidney hypertrophy that seems to develop within the first year after surgery [42].

LPN can also be performed with acceptable ischaemia times in experienced high-volume laparoscopic centres.

Table 3 – Recent studies comparing laparoscopic partial nephrectomy with robotic or open partial nephrectomy

Study	No. of patients	Techniques compared	Mean ischaemia time	Mean tumour size	Comments
Aron et al [15]	24	RPN vs LPN (matched pairs)	23 vs 22 min	2.4 vs 2.9 cm	All procedures in WI Confirms feasibility of RPN but no clear advantage or difference "Port-in-port technique" described for RPN No difference in renal function loss after both procedures (loss of eGFR: −13 ml/min in both groups)
Gill et al [13]	1799	OPN vs LPN (*n* = 771 vs *n* = 1028)	20.1 vs 30.7 min	3.5 vs 2.7 cm	Multicentric retrospective study More frequently in OPN group: higher risk group, symptomatic disease, worse performance status, larger tumours, centrally located tumours, malignant tumours, impaired renal function, or solitary kidney More frequently in LPN group: longer ischaemia time, shorter surgical time, decreased blood loss, and shorter hospital stay Outcome of renal function similar in both groups OPN remains the preferred approach (particularly in more complicated renal tumours) LPN should be performed only in experienced centres
Lane et al [41]	199	OPN vs LPN (*n* = 169 vs *n* = 30)	21 vs 29 min (WI)	3.8 vs 2.8 cm	Only solitary kidneys (imperative indication); eGFR evaluation LPN: longer mean WI time, higher proportion of WI >20 min, higher proportion of dialysis required after surgery (temporary or permanent), higher risk of postoperative complications OPN should be the preferred approach in an imperative setting

eGFR = estimated glomerular filtration rate; LPN = laparoscopic partial nephrectomy; OPN = open partial nephrectomy; RPN = robotic partial nephrectomy; WI = warm ischaemia.

Two prospective studies using MAG3 scintigraphy in only small numbers of patients surprisingly claimed preservation of renal function with WI times up to 44 min. The authors conceded that keeping WI time within 30 min avoids renal damage, but this still differs from the recommended 20-min WI for OPN [52,53].

In contrast, Foyil et al recommend CI rather than WI during LPN, particularly in patients with hypertension and diabetes. Their analysis favours treatment with CI because it resulted in no long-term renal damage in patients with these two risk factors [50].

Time will tell if shorter ischaemia times can be achieved by the minimally invasive RPN. Early results of about 65 published cases report WI times of 21–26 min. The authors confirm the feasibility of RPN and specify that this method is easier to learn even for surgeons who are inexperienced in laparoscopy [16]. Based on a direct comparison of only small numbers of RPN patients and >2000 patients with LPN, no clear advantage was demonstrated but at least comparable results and adequate ischaemia times could be expected for RPN [15].

The importance of other therapeutic options in the management of small renal tumours, as ablative or observing methods, is anticipated in the future because long-term oncologic outcomes are lacking. No ischemic damage is applied to the kidney with such methods, and previous results are promising [76].

Table 3 lists the current literature directly comparing different surgical techniques and covering renal function and ischaemia. One study compares RPN with LPN but includes only 12 patients undergoing each approach, so further studies are needed to demonstrate the advantages of RPN [15].

Large series comparing OPN and LPN demonstrate higher complication rates after LPN as well as longer ischaemia times, even though mean tumour diameters were smaller. Negative aspects of OPN are higher blood loss, longer operation time, longer hospital stay, and higher analgesic requirement. Nevertheless, renal function after both procedures seems to have been equivalent in these series from highly experienced laparoscopic centres [13,77,78]. If a high risk of CKD is expected, OPN should be the preferred approach because a multivariate analysis showed a decrease of 2.2 ml/min per $1.73m^2$ for every 5 min of WI. Thus, ischaemia time should be kept as short as possible [41].

The most important aspect of all surgical techniques is to aim for limited ischaemia without compromising oncologic efficacy. Ischaemia is the strongest modifiable surgical risk [78,79].

4. Conclusions

In addition to oncologic and surgical outcome, postoperative renal function is the central issue in NSS. Profound expertise of the surgeon is indispensable to determine the optimal intraoperative technique even before approaching the tumour. If ischaemia is required, the tumour should be removed within the minimum possible duration, preferably with <20 min in WI, which is currently recommended, regardless of surgical approach. Efforts should be made to start immediately with CI if the feasibility of completing WI within this span of time seems to be jeopardised. Thus, CI times up to 2 h can be tolerated by the kidney, depending on the individual method. However, CI should also be kept as short as possible, ideally within 35 min. The CI technique used (in situ cold arterial perfusion, ice slush around the kidney, retrograde caliceal perfusion, or ex situ cold arterial perfusion with autotransplantation) depends on preoperative findings, surgical technique (open, laparoscopic, or robotic) and institutional experience. Only after optimal preoperative appraisal and planning can the best postoperative outcomes for renal function be achieved.

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References

[1] Ljungberg B, Hanbury DC, Kuczyk MA, et al. Renal cell carcinoma guideline. Eur Urol 2007;51:1502–10.
[2] Becker F, Siemer S, Humke U, Hack M, Ziegler M, Stöckle M. Elective nephron sparing surgery should become standard treatment for small unilateral renal cell carcinoma: long-term survival data of 216 patients. Eur Urol 2006;49:308–13.
[3] Uzzo RG, Novick AC. Nephron sparing surgery for renal tumours: indications techniques and outcomes. J Urol 2001;166:6–18.
[4] Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
[5] Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol 2006;7:735–40.
[6] McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology 2002;59:816–20.

[7] Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol 2008;179:468–73.
[8] Becker F, Siemer S, Hack M, Humke U, Ziegler M, Stöckle M. Excellent long-term cancer control with elective nephron-sparing surgery for selected renal cell carcinomas measuring more than 4 cm. Eur Urol 2006;49:1058–64, discussion 1063–4.
[9] Pahernik S, Roos F, Röhrig B, Wiesner C, Thüroff JW. Elective nephron sparing surgery for renal cell carcinoma larger than 4 cm. J Urol 2008;179:71–4, discussion 74.
[10] Joniau S, Vander Eeckt K, Srirangam SJ, Van Poppel H. Outcome of nephron-sparing surgery for T1b renal cell carcinoma. BJU Int 2009;103:1344–8.
[11] Hollenbeck BK, Taub DA, Miller DC, Dunn RL, Wie JT. National utilization trends of partial nephrectomy for renal cell carcinoma: a case of underutilization? Urology 2006;67:254–9.
[12] Miller DC, Hollingsworth JM, Hafez KS, Daignault S, Hollenbeck BK. Partial nephrectomy for small renal masses: an emerging quality of care concern? J Urol 2006;175:853–7, discussion 858.
[13] Gill IS, Kavoussi LR, Lane BR, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumours. J Urol 2007;178:41–6.
[14] Gill IS, Martin SF, Desai MM, et al. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumours in 200 patients. J Urol 2003;170:64–8.
[15] Aron M, Koenig P, Kaouk JH, Nguyen MM, Desai MM, Gill IS. Robotic and laparoscopic partial nephrectomy: a matched-pair comparison from a high-volume centre. BJU Int 2008;102:86–92.
[16] Kaul S, Laungani R, Sarle R, et al. Da Vinci-assisted robotic partial nephrectomy: technique and results at a mean of 15 months of follow-up. Eur Urol 2007;51:186–92, discussion 191–2.
[17] Galfano A, Novara G. Methodological bases for systematic reviews. J Androl Sci 2008;15:185–93.
[18] Novick AC. Renal hypothermia: in vivo and ex vivo. Urol Clin North Am 1983;10:637–44.
[19] Matin SF, Gill IS, Worley S, Novick AC. Outcome of laparoscopic radical and open partial nephrectomy for the sporadic 4 cm or less renal tumour with a normal contralateral kidney. J Urol 2002; 168:1356–60.
[20] Clark ATD, Breau RH, Morash C, Fergusson D, Doucette S, Cagiannos I. Preservation of renal function following partial or radical nephrectomy using 24-hour creatinine clearance. Eur Urol 2008;54:143–52.
[21] Sorbellini M, Kattan MW, Snyder ME, Hakimi AA, Sarasohn DM, Russo P. Prognostic nomogram for renal insufficiency after radical or partial nephrectomy. J Urol 2006;176:472–6, discussion 476.
[22] Chen CH, Chen YJ, Chiang CT, Chen HW, Chu SH. Risks and quality of life in living kidney donors. Transplant Proc 2004;36:1920–1.
[23] Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992;340:807–10.
[24] Shrestha A, Shrestha A, Vallance C, McKane WS, Shrestha BM, Raftery AT. Quality of life of living kidney donors: a single-center experience. Transplant Proc 2008;40:1375–7.
[25] Marberger M. Renal ischemia: not a problem in laparoscopic partial nephrectomy? BJU Int 2007;99:3–4.
[26] Nishikido M, Noguchi M, Koga S, et al. Kidney transplantation from non-heart-beating donors: analysis of organ procurement and outcome. Transplant Proc 2004;36:1888–90.
[27] McDougal WS. Renal perfusion/reperfusion injuries. J Urol 1988;140:1325–30.
[28] Secin FP. Importance and limits of ischemia in renal partial surgery: experimental and clinical research. Adv Urol 2008. p. 102461.
[29] Abuelo JG. Normotensive ischemic acute renal failure. N Engl J Med 2007;357:797–805.
[30] Derweesh IH, Novick AC. Mechanisms of renal ischaemic injury and their clinical impact. BJU Int 2005;95:948–50.
[31] Sheridan AM, Bonventre JV. Cell biology and molecular mechanisms of injury in ischemic acute renal failure. Curr Opin Nephrol Hypertens 2000;9:427–34.
[32] Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 9th ed. Philadelphia, PA: Saunders Elsevier; 2007.
[33] Rosetti SR. Impact of acute ischemia on human kidney. In: Marberger M, Dreikorn K, editors. Renal preservation.. Baltimore, MD: Williams & Wilkins; 1983. p. 21–35.
[34] Henriksen JH, Petersen HK. Renal blood flow and metabolism after cold ischaemia: reoperative measurements in patients with calculi. Clin Physiol 1984;4:41–50.
[35] Ward JP. Determination of the optimum temperature for regional renal hypothermia during temporary renal ischaemia. Br J Urol 1975;47:17–24.
[36] De Maeyer P, Oosterlinck W, De Sy W. Prevention on vasospasms during extensive renal surgery. An experimental study in rats. Eur Urol 1981;7:224–6.
[37] Laven BA, Orvieto MA, Chuang MS, et al. Renal tolerance to prolonged warm ischemia time in a laparoscopic versus open surgery porcine model. J Urol 2004;172:2471–4.
[38] Simmons MN, Schreiber MJ, Gill IS. Surgical renal ischemia: a contemporary overview. J Urol 2008;180:19–30.
[39] Thompson RH, Blute ML. At what point does warm ischemia cause permanent renal damage during partial nephrectomy? Eur Urol 2007;52:961–3.
[40] Funahashi Y, Hattori R, Yamamoto T, Kamihira O, Kato K, Gotoh M. Ischemic renal damage after nephron-sparing surgery in patients with normal contralateral kidney. Eur Urol 2009;55:209–16.
[41] Lane BR, Novick AC, Babineau D, Fergany AF, Kaouk JH, Gill IS. Comparison of laparoscopic and open partial nephrectomy for tumor in a solitary kidney. J Urol 2008;179:847–52.
[42] Fergany AF, Saad IR, Woo L, Novick AC. Open partial nephrectomy for tumour in a solitary kidney: experience with 400 cases. J Urol 2006;175:1630–3.
[43] Ghavamian R, Cheville JC, Lohse CM, Weaver AL, Zincke H, Blute ML. Renal cell carcinoma in the solitary kidney: an analysis of complications and outcome after nephron sparing surgery. J Urol 2002;168:454–9.
[44] Iida S, Kondo T, Amano T, et al. Minimal effect of cold ischemia time on progression to late-stage chronic kidney disease observed long term after partial nephrectomy. Urology 2008;72:1083–9.
[45] Thompson RH, Frank I, Lohse CM, et al. The impact of ischemia time during open nephron sparing surgery on solitary kidneys: a multi-institutional study. J Urol 2007;177:471–6.
[46] Yossepowitch O, Eggener SE, Serio A, et al. Temporary renal ischemia during nephron sparing surgery is associated with short-term but not long-term impairment in renal function. J Urol 2006;176:1339–43, discussion 1343.
[47] Abukora F, Albquami N, Nambirajan T, Ziegerhofer J, Leeb K, Janetschek G. Long-term functional outcome of renal units after laparoscopic nephron-sparing surgery under cold ischemia. J Endourol 2006;20:790–3.
[48] Bhayani SB, Rha KH, Pinto PA, et al. Laparoscopic partial nephrectomy: effect of warm ischemia on serum creatinine. J Urol 2004;172:1264–6.
[49] Desai MM, Gill IS, Ramani AP, Spaliviero M, Rybicki L, Kaouk JH. The impact of warm ischemia on renal function after laparoscopic partial nephrectomy. BJU Int 2005;95:377–83.
[50] Foyil KV, Ames CD, Ferguson GG, et al. Longterm changes in creatinine clearance after laparoscopic renal surgery. J Am Coll Surg 2007;206:511–5.

[51] Lane BR, Gill IS. 5-year outcomes of laparoscopic partial nephrectomy. J Urol 2007;177:70–4.
[52] Porpiglia F, Renard J, Billia M, et al. Is renal warm ischemia over 30 minutes during laparoscopic partial nephrectomy possible? One-year results of a prospective study. Eur Urol 2007;52:1170–8.
[53] Shekarriz B, Shah G, Upadhyay J. Impact of temporary hilar clamping during laparoscopic partial nephrectomy on postoperative renal function: a prospective study. J Urol 2004;172:54–7.
[54] Nguyen MM, Gill IS. Halving the ischemia time during laparoscopic partial nephrectomy. J Urol 2008;179:627–32.
[55] Bollens R, Rosenblatt A, Espinoza BP, et al. Laparoscopic partial nephrectomy with "on-demand" clamping reduces warm ischemia time. Eur Urol 2007;52:804–10.
[56] Baumert H, Ballaro A, Shah N, et al. Reducing warm ischaemia time during laparoscopic partial nephrectomy: a prospective comparison of two renal closure techniques. Eur Urol 2007;52:1164–9.
[57] Gill IS, Abreu SC, Desai MM, et al. Laparoscopic ice slush renal hypothermia for partial nephrectomy: the initial experience. J Urol 2003;170:52–6.
[58] Steffens J, Humke U, Ziegler M, Siemer S. Partial nephrectomy with perfusion cooling for imperative indications: a 24-year experience. BJU Int 2005;96:608–11.
[59] Humke U, Uder M. Renovascular hypertension: the diagnosis and management of renal ischemia. BJU Int 1999;84:555–69.
[60] Kemmer H, Siemer S, Stöckle M. Nephrectomy, work bench surgery, and autotransplantation: a case of a solitary left kidney with an extensive centrally located renal cell carcinoma and a tumour thrombus entering the vena cava. Eur Urol 2007;52:1518–20.
[61] Janetschek G. Laparoscopic nephron sparing surgery: ischemic renal damage. Curr Opin Urol 2006;16:45–6.
[62] Janetschek G, Abdelmaksoud A, Bagheri F, Al-Zahrani H, Leeb K, Gschwendtner M. Laparoscopic partial nephrectomy in cold ischemia: renal artery perfusion. J Urol 2004;171:68–71.
[63] Landman J, Rehman J, Sundaram CP, et al. Renal hypothermia achieved by retrograde intracavitary saline perfusion. J Endourol 2002;16:445–9.
[64] Landman J, Venkatesh R, Lee D, et al. Renal hypothermia achieved by retrograde endoscopic cold saline perfusion: technique and initial clinical application. Urology 2003;61:1023–5.
[65] Orvieto MA, Zorn KC, Mendiola F, et al. Recovery of renal function after complete renal hilar versus artery alone clamping during open and laparoscopic surgery. J Urol 2007;177:2371–4.
[66] McLoughlin GA, Heal MR, Tyrell IM. An evaluation of techniques used for the production of temporary renal ischaemia. Br J Urol 1978;50:371–5.
[67] Orvieto MA, Zorn KC, Mendiola FP, et al. Ischemia preconditioning does not confer resilience to warm ischemia in a solitary porcine kidney model. Urology 2007;69:984–7.
[68] Burke TJ, Cronin JE, Duchin KL, Peterson LN, Schrier RW. Ischemia and tubule destruction during acute failure in dogs: mannitol in protection. Am J Physiol 1980;238:F305–14.
[69] Chiu C, Sievert KD, Dahms S, Bretan Jr P. Intraoperative reperfusion blood flow predicts post warm ischemic kidney transplant survival and efficacy of preservation maneuvers. Transplant Proc 1999;31:1049–50.
[70] O'Hara Jr JF, Hsu TH, Sprung J, Cywinski JB, Rolin HA, Novick AC. The effect of dopamine on renal function in solitary partial nephrectomy surgery. J Urol 2002;167:24–8.
[71] Fitzpatrick JM, Wallace DM, Whitfield HN, Watkinson LE, Fernando AR, Wickham JE. Inosine in ischaemic renal surgery: long-term follow-up. Br J Urol 1981;53:524–7.
[72] Yasuyuki K, Yukio U, Masanori S, et al. Evaluation of renal function after laparoscopic partial nephrectomy with renal scintigraphy using 99m-technetium-mercaptoacetyltriglycerine. Int J Urol 2006;13:1371–4.
[73] Inoue Y, Kurimoto S, Kameyama S, et al. Prolonged renal parenchymal retention of 99mTc mercaptoacetyltriglycine after nephron-sparing surgery. Nucl Med Commun 2004;25:509–13.
[74] Russo P. Editorial comment on Iida S, Kondo T, Amano T, Nakazawa H, Ito F, Hashimoto Y, Tanabe K. Minimal effect of cold ischemia time on progression to late-stage chronic kidney disease observed long term after partial nephrectomy. Urology 2008; 72:1083-9.
[75] Trof RJ, Di Maggio F, Leemreis J, Groeneveld ABJ. Biomarkers of acute renal injury and renal failure. Shock 2006;26:245–53.
[76] Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma—a meta-analysis and review. J Urol 2008;179:1227–34.
[77] Porpiglia F, Volpe A, Billia M, Scarpa RM. Laparoscopic versus open partial nephrectomy: analysis of the current literature. Eur Urol 2008;53:732–43.
[78] Riggs SB, Larochelle JC, Belldegrun AS. Partial nephrectomy: a contemporary review regarding outcomes and different techniques. Cancer J 2008;14:302–7.
[79] Lane BR, Babineau DC, Poggio ED, et al. Factors predicting renal functional outcome after partial nephrectomy. J Urol 2008;180:2363–9.

Editorial Comment on: Assessing the Impact of Ischaemia Time During Partial Nephrectomy

Tarik Esen
Istanbul University, Istanbul, Turkey
tarikesen@doruk.net.tr

Nephron-sparing surgery (NSS) for renal cell carcinoma (RCC) is a well-established surgical approach with excellent long-term oncologic results. Although the number of cases suitable for NSS is continuously rising, due both to increasing RCC incidence and to efforts expanding the surgical indication to almost all T1 tumors, statistics clearly show that this elegant operation is still underutilized [1]. In the era of laparoscopy and robotics, this phenomenon is rather surprising and at odds with developments in the field of radical prostatectomy.

One speculative explanation for this phenomenon could be the challenging nature and resulting steep learning curve of the operation, especially when performed laparoscopically. Although this difficult procedure has already been mastered by many, it remains the most demanding laparoscopic operation to perform. Consequently, this difficulty might influence the less experienced laparoscopic surgeon to favor laparoscopic radical nephrectomy over a relatively difficult laparoscopic NSS for a T1b or central tumor instead of offering the patient the open procedure. From the patient's perspective, this recommendation is mostly acceptable, since an open procedure occasionally harbors the risk of undergoing "undesirable" open exploration and still losing the kidney.

In this respect, the most important limiting factor for the operation is the bleeding from the tumor bed. To avoid it, laparoscopists mostly prefer to control the pedicle—in toto or just the artery—if the tumor is not too small or exophytic, and this control inevitably results in ischemia with subsequent reperfusion trauma. This outcome would usually be avoided during open surgery because simple manual compression of the parenchyma would suffice to control most of the bleeding.

Although there are no controlled studies defining the safety limits of both warm and cold ischemia, 20 min and 120 min, respectively, are well-established cut-offs derived from clinical experience with open transparenchymal stone surgery and animal studies [2]. It is clear that the laparoscopic adaptation of the parenchyma with the occasional repair of the collecting system is definitely more time consuming compared to open surgery. Yet this fact should not cause the upper limit of warm ischemia to be redefined as 40 min [3]. It is a relief to see that most groups performing laparoscopic NSS challenge this notion.

Kidney damage occurring beyond 30 min is significant and mostly irreversible, even in completely normal systems. Gill et al [4] reported 18% kidney function loss when 32 min of warm ischemia time was needed; kidney function loss was clearly was reduced to 11% by lowering the ischemic period to 14 min. Although data in the literature are missing, one can easily assume that even 30 min of warm ischemia could be very critical in patients with preexisting risk factors (eg, age, hypertension, diabetes mellitus) or already compromised renal function [5]. Unfortunately, there are no studies comparing different techniques with respect to temporary or permanent dialysis rate or creatinine clearance loss in elderly patients with diabetes and/or hypertension and/or compromised renal function.

Once again, it is not the technique itself warranting the optimal results but the experience of the individual surgeon using it. Mastering the technique should be the ultimate goal, but until then, we have to be fully aware of all possible limitations.

References

[1] Becker F, Van Poppel H, Hakenberg OW, et al. Assessing the impact of ischaemia time during partial nephrectomy. Eur Urol 2009; 56:625–35.

[2] Simmons MN, Schreiber MJ, Gill I. Surgical renal ischemia: a contemporary overview. J Urol 2008;180:19–30.

[3] Godoy G, Ramanathan V, Kanofsky JA, et al. Effect of warm ischemia time during laparoscopic partial nephrectomy on early postoperative glomerular filtration rate. J Urol 2009;181: 2438–45.

[4] Gill I, Kavoussi LR, Lane BR, et al. Comparison of 1800 laparoscopic and open partial nephrectomies for single renal tumors. J Urol 2007;178:41–6.

[5] Foyil KV, Ames CD, Ferguson GG, et al. Longterm changes in creatinine clearence after laparoscopic renal surgery. J Am Coll Surg 2008;206:511–5.

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