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Ischemia time in partial nephrectomy: to rush really matters?

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Abstract

Aim: The growth in the incidence of small renal masses has led the implementation of laparoscopic partial nephrectomy to become the technique of choice. However, arterial clamping and secondary renal ischemia still mean a controversial issue due to the risk of renal failure. Our objective is to evaluate the existing literature and its relationship to our experience.

Methods: We performed a retrospective study of our series over six years. We analyzed different clinical, perioperative and postoperative functional outcome variables and compared the relationship between tumor complexity and the need for ischemia as well as the relation between ischemia time and renal function over a follow-up time of 6 months. For the discussion, we led a review of the literature on the subject and the paradigm shift that has taken place over the years.

Results: A total of 148 patients, most of them male (68.2%) with an average age of 62.4 [standard deviation (SD) 1.7] years, had a Charlson index of 3 [interquartile range (IQR) 1-4]. The average R.E.N.A.L. score was 6 (IQR 5-8). Intraoperative complications were observed in 8.1% of the cases, most of which involved bleeding from a major artery or vein (7.4%). Postoperative complications occurred in 23.6% of the patients, the majority being classified as Clavien 2. Arterial clamping was carried out in 52.7% of the interventions, with a median ischemia time of 8 min (IQR 0-18). The average hospital stay was three days (IQR 2-5). Previous median glomerular filtration rate (GFR) was 83 mL/min/1.73 m^2 (IQR 66.2-93.6). On the first postoperative day, the median GFR was 78.4 (SD 21.8), and at 6 months, it was 75.2 (SD 22). We found no statistically significant differences between having hypertension or diabetes mellitus and GFR after surgery, but we found differences in the correlation of a Charlson index ≥ 3 and deterioration of renal function, being the *P* values 0.01, 0.08 and 0.00 for the first postoperative day, after three and 6 months, respectively. No statistically significant differences were found in whether having a previous chronic kidney disease influenced the decision to perform arterial clamping or not, with a *P* value of 0.104. Statistically significant differences were found in the relationship between R.E.N.A.L. score and ischemia time.

Conclusion: Renal tumors with a higher R.E.N.A.L. score involve the need to accomplish a longer arterial clamping, but its relationship with the deterioration of renal function is unclear, since there are other risk factors, such as patient's comorbidities.

Keywords: Renal cell carcinoma, partial nephrectomy, renal ischemia

INTRODUCTION

Renal cell carcinoma constitutes around 3% of all cancers, with the highest incidence in Western countries. This higher rate in Europe and North America is said to have its cause in a greater prevalence of incidental small renal masses (SRMs) in conditions where abdominal and pelvic imaging is more commonly conducted[1]. A SRM is a ≤ 4 cms (T1a) solid or cystic lesion with contrast enhancement, typically incidentally diagnosticated[2]. Reports indicate that 80% of SRMs are malignant, most of them being low grade and at an early phase[3].

For little and confined renal masses, partial nephrectomy (PN) is the usual agreeing with the most universally used management guidelines[4-6]. The preference for PN over radical nephrectomy (RN) is clearly related to a decreased risk of chronic kidney disease (CKD), since association of RN with development of postoperative CKD is well described and accepted and postoperative development of estimated glomerular filtration rate (eGFR) < 45 is associated with increased risk of overall mortality[7]. Therefore, PN has emerged as the standard for most clinical T1 and T2 Renal Cell Carcinoma and may be considered an option in selected T3a tumors with indication for nephron preservation.

However, PN still conveys the possibility of renal failure resultant of the deletion of nephrons and/or as an effect of ischemic damage produced by arterial clamping. The significance of these aspects and the lasting clinical consequences of renal failure remain issues of debate[8]. Off-clamp or segmental clamping methods in PN could remove ischemia from the procedure, but their technical execution presents challenges, and no unquestionable functional benefits have been illustrated[9].

We attempt to provide a narrative review of the data concerning the association between ischemia and functional outcomes following PN, as well as a debate of new improvements and constant investigation. In addition, we analyzed the characteristics of patients undergoing PN in our center and their oncological and functional outcomes in relation to ischemia time.

METHODS

We retrospectively studied 148 patients who underwent laparoscopic PN (LPN) at our center between March 2015 and January 2021. We obtained the ethical approval for the study from our internal Institutional Review Board (IRB) committee, with Approval No: 23-038. Besides, the consent to participate was obtained from every patient.

Surgical technique

Despite small differences in technical details between surgeons, our surgical technique involves transperitoneal laparoscopic access with four trocars (11, 12, 5, and 5 mms). The retroperitoneum access is performed through the Told's line, moving the bowel segment to the middle line. Then, the Psoas muscle is identified as a landmark to find the ureter and the gonadal vein at the level of the lower renal pole, which are dissected in an ascending way until we locate the renal hilum [Figure 1]. Dissection of the renal artery and vein and referral with vessel loop of the artery (or arteries) is performed. Subsequently, the renal tumor is located, dissecting the Gerota fascia and removing the fat surrounding the kidney as much as necessary for tumor resection and subsequent suturing of the renal bed. We mark the circumference of the tumor [Figure 2], and arterial clamping is performed if it is thought to be necessary, either from the main renal artery or from a branch directed toward the tumor [Figure 3]. We usually perform the tumor enucleation to preserve as much renal parenchyma as possible [Figure 4]. Immediately afterward, suturing is started, first in the deep plane of the bed to ensure the water-tightness of the urinary tract (in case of opening) and closure of deep vessels, and then another upper renorrhaphy, including the renal parenchyma [Figure 5]. The clamp (Bulldog) is then removed from the artery, and hemostasis is checked. The usage of cellulose-type hemostatic material is optional [Figure 6]. Lastly, the perirenal fat is then sutured if feasible. We leave a drain in the surgical bed, and we close the skin wounds.

Patients, clinical parameters, statistical analysis

A careful selection of patients was carried out. The inclusion criteria were as follows: all patients were operated on in our center by PN or tumorectomy, either robotic or laparoscopic, of any age, due to a renal mass. Patients whose surgery was turned into open surgery were excluded from the analysis.

We studied clinical, perioperative and histopathological variables together with oncological and functional outcomes. The different preoperative variables studied were sex, age, Charlson index, body mass index (BMI), smoking, GFR before surgery and laterality. As perioperative variables, we selected: intraoperative complications, postoperative complications, need for ischemia and hospital stay. As follow-up variables, we selected: GFR 1st day after surgery and GFR after 6 months.

After surgery and during the hospitalization period, a blood test was performed to assess creatinine (ng/dL) and GFR estimation (mL/min/1.73 m^2) on the first and third day. After discharge, a close follow-up of the patient was established, with a review and renal function analysis at three and 6 months and then at one year.

We will describe the data obtained with mean and median with their respective standard deviations and interquartile ranges. We divided the patients into three groups depending on the ischemia time (1: zero ischemia; 2: ischemia < 20 min; and 3: ischemia ≥ 20 min). Using Pearson's chi-square test, we analyzed the relationship between different comorbidities such as hypertension and diabetes mellitus as well as the Charlson index with the eGFR after surgery. We performed a hypothesis test using the analysis of variance (ANOVA) test to see if there was a relation between tumor complexity (R.E.N.A.L. score) and the necessity of arterial clamping reflexed with the three named groups (1: zero ischemia; 2: ischemia < 20 min; and 3: ischemia ≥ 20 min), with subsequent multivariate analysis. Finally, we rated the relationship between ischemia time and short- and long-term renal function, respectively, the first day after surgery and after 6 months.

Evidence acquisition for discussion

We piloted complete English language literature research for original and review manuscripts using the Medline database and literature through June 2023. We searched for the following terms: partial

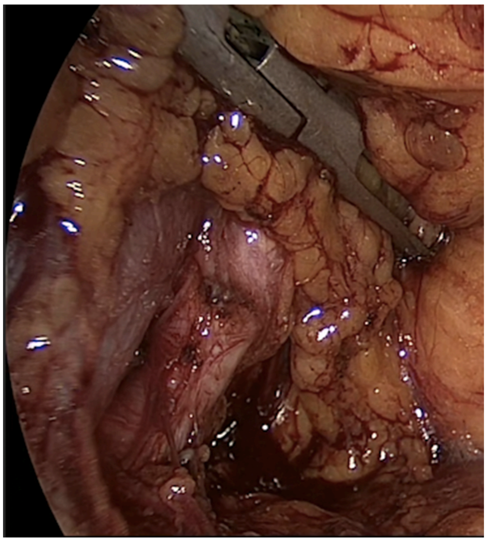

Figure 1. Renal pedicle after ascending dissection.

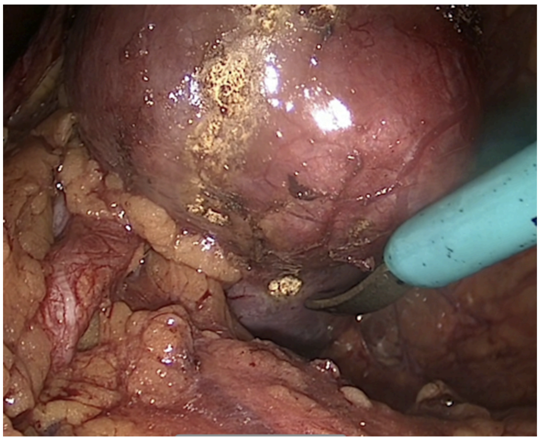

Figure 2. Renal tumor marking with laparoscopic scissors.

tumorectomy, ischemia time and CKD. The combination of terminologies found 67 related articles, being 30 the final number of papers selected for this work. Studies with the highest level of evidence and significance to the debated topics were selected with the agreement of the authors.

RESULTS

A total of 148 patients were operated on in the time described, most of whom were male (68.2%). The average age was 62.4 [standard deviation (SD) 1.7], with a Charlson index of 3 [interquartile range (IQR) 1-4] and a body mass index of 28.2 (SD 4.8). The 52% tumors were on the left kidney, and the R.E.N.A.L. score was 6 on average (IQR 5-8).

Intraoperative complications were observed in 8.1% of cases, most of which involved bleeding from a major artery or vein (7.4%), which in all cases led to conversion to open surgery. Postoperative complications occurred in 23.6% of cases, with the majority classified as Clavien 2. Concerning the need for arterial clamping, it was carried out in only 52.7% of the interventions, with a median ischemia time of 8 min (IQR

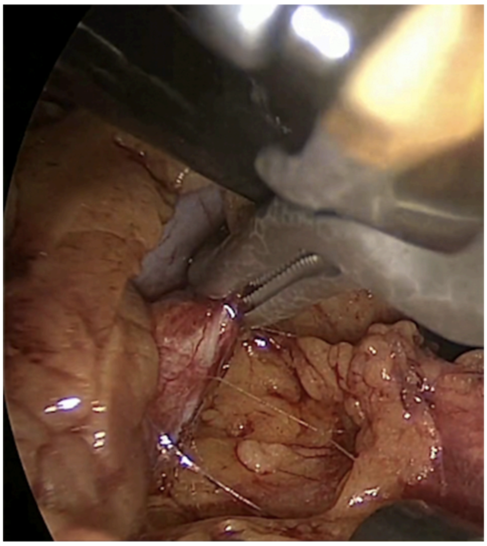

Figure 3. Arterial clamping with laparoscopic bulldog.

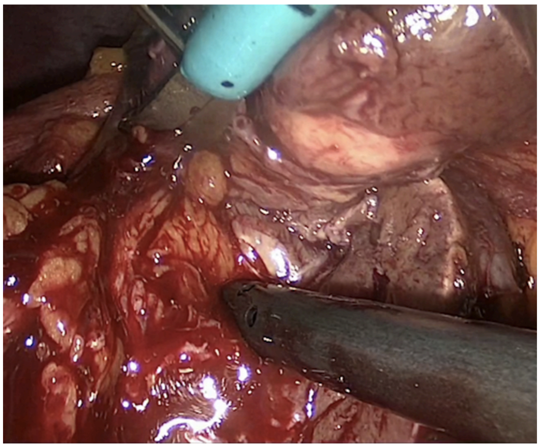

Figure 4. Tumor enucleation.

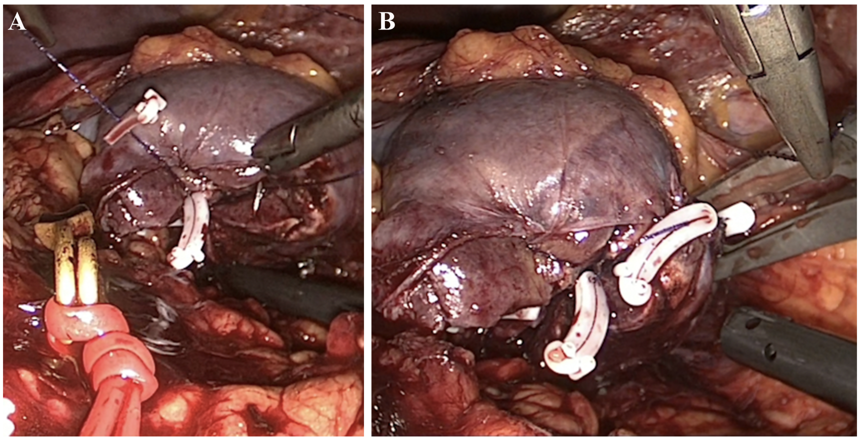

Figure 5. (A and B) Laparoscopic renorrhaphy.

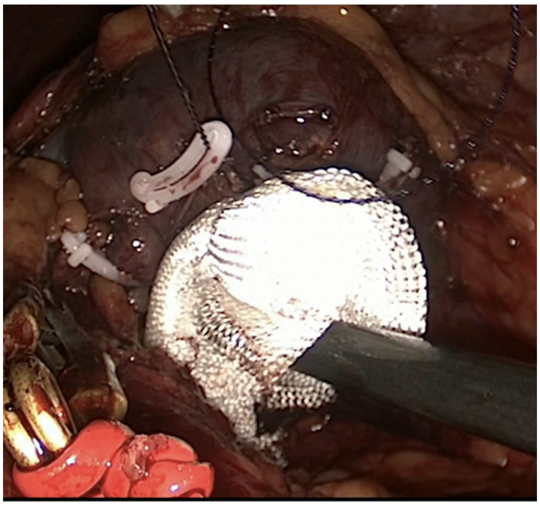

Figure 6. Cellulose-type hemostatic material.

0-18). The average hospital stay was three days (IQR 2-5). Previous median GFR was 83 mL/min/1.73 m^2 (IQR 66.2-93.6). On the first postoperative day, the median GFR was 78.4 (SD 21.8), and at 6 months, it was 75.2 (SD 22). Tables 1-3 show the most important characteristics of our patients, whether clinical, perioperative or with respect to their postoperative renal function.

After evaluating their correlation by means of chi-square, we found no statistically significant differences between having hypertension or diabetes mellitus and GFR after surgery, with *P* values of 0.022, 0.460 and 0.103 compared with one day, 3 months and 6 months after surgery, respectively, for hypertension, and *P* values of 0.106, 0.674 and 0.318 comparing with one day, 3 months and 6 months, respectively, for diabetes. However, we found statistically significant differences in the correlation of a Charlson index ≥ 3 and deterioration of renal function, with the *P* values 0.01, 0.08 and 0.00 for the postoperative day, after 3 and 6 months, respectively. These differences are shown in Figure 7. In addition, no statistically significant differences were found in whether having a previous CKD influenced the decision to perform arterial clamping, with a *P* value of 0.104.

Statistically significant differences were found in the relation, analyzed with the ANOVA test, between R.E.N.A.L. score and ischemia time. A higher renal score was related to an ischemia time between one and 19 min (*P* = 0.000) as well as a higher renal score was positively related to an ischemia time ≥ 20 min (*P* = 0.009); while there were no statistically significant differences between a higher renal score and zero ischemia time (*P* = 0.217). These differences are shown in Figure 8.

We found no statistically significant difference between ischemia time and GFR after surgery, with a *P* value of 0.144 in the case of GFR on the first postoperative day, *P* = 0.383 in the case of GFR 3 months after surgery and *P* = 0.739 6 months after surgery.

DISCUSSION

Warm ischemia time (WIT) has become a secondary factor in favor of preserved renal mass in terms of causative factors for CKD after PN.

Table 1. Clinical variables of patients operated on with a laparoscopic PN

Patients' characteristics	*N* = 148
Gender	Male: 68.2%; Female: 31.8%
Age	62.4 (SD 1.7)
Charlson's index	3 (IQR 1-4)
BMI	28.2 (SD 4.8)
Smokers	No: 69.6%; Yes: 30.4%
GFR before surgery	83 (IQR 66.2-93.6)
Laterality	Right: 52%; Left: 48%
R.E.N.A.L score	6 (IQR 5-8)

PN: Partial nephrectomy; SD: standard deviation; IQR: interquartile range; BMI: body mass index. GFR: glomerular filtration rate.

Table 2. Perioperative variables of patients intervened by PN

Perioperative variables	*N* = 148
Intraoperative complications	Yes (8.1%): - Bleeding: 7.4% - Ureteral damage: 0.7%
	No (91.2%)
Postoperative complications	Yes (23.6%): - Clavien 1: 8.1% - Clavien 2: 12.2% - Clavien 3: 2% - Clavien 4: 1.2%
	No (76.4%)
Need for ischemia	Yes (52.7%) → Time of warm ischemia: 8 (IQR 0-18)
	No (47.3%)
Previous GFR	83 (IQR 66.2-93.6)
Hospital stay	3 days (IQR 2-5)

PN: Partial nephrectomy; IQR: interquartile range; GFR: glomerular filtrate rate.

Table 3. Renal function of patients undergoing surgery throughout the follow-up period

Follow-up variables	*N* = 148
GFR 1st day after surgery	78.4 (SD 21.8)
GFR after 6 months	75.2 (SD 22)

GFR: Glomerular filtrate rate; SD: standard deviation.

Multiple reasons influence renal functional results after PN, including preoperative renal function, comorbidity, age, gender, tumor dimension, percentage of renal preserved parenchyma volume and ischemia time; and baseline GFR measured months after PN is a significant predictor of long-term survival, mostly for patients with prior CKD[10]. According to our results, we have been able to verify that a Charlson index ≥ 3 does correlate with statistically significant differences with GFR. A possible reason may be the average age of the patients included (62 years), which adds one point to the individual Charlson index.

A decade ago, studies advocated that each supplementary minute of warm ischemia through PN for tumor in a solitary kidney involved a 5% added risk of acute kidney injury (AKI), and a 6% added risk of new-onset stage 4 CKD[11]. Currently, nephron mass conservation seems to be the greatest significant factor with respect to functional recuperation after PN, with ischemia taking a back seat. However, this statement has been strongly debated over the last few years.

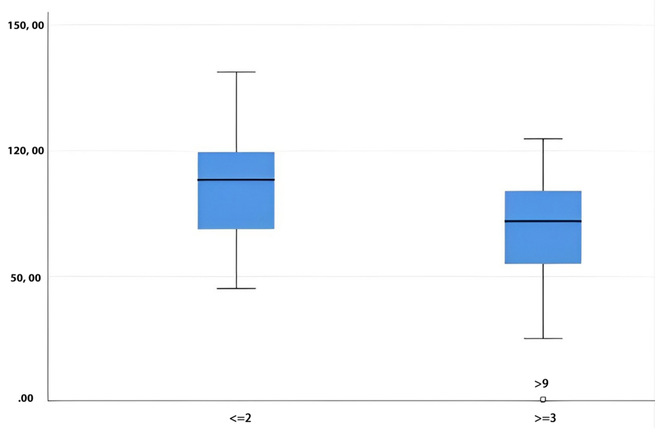

Figure 7. Correlation between Charlson index and GFR. GFR: Glomerular filtration rate.

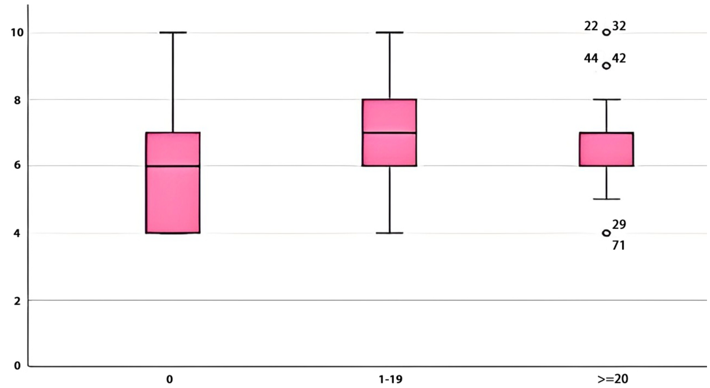

Figure 8. Simple box plot of R.E.N.A.L. score and ischemia time.

The European Association of Urology (EAU) Guidelines update in 2023[5] defend with a strong power to offer PN to patients with T1 tumors. There are three important caveats in relation to PN: time of warm ischemia, surgical margins and surgical technique. We have focused our work on the evolution of the impact of arterial clamping over the last decade.

Throughout PN, the principal artery is usually clamped to reduce blood loss and create a quite controlled field for tumor removal and subsequent reconstruction of the renal parenchyma[12]. It has been illustrated that ischemia secondary to clamped PN will probably produce damage to nephrons through numerous conjectured mechanisms, such as vasoconstriction, tubular obstruction with backflow of urine, and reperfusion injury[13-15]. With the beginning of studies that measure preserved nephronal quantity[15], irrespective of whether it is a single kidney or bilateral kidney, they conclude that the percent GFR conserved was most strongly related with the percentage of parenchymal quantity spared. Besides, several studies have measured atrophy of the conserved renal tissue for assessing the degree of possible ischemic shock on the operated kidney through clamped PN and have described no significant atrophy after clamped PN[16,17].

In our experience and following the latest recommendations published in the literature, partial nephrectomies have been performed by expert surgeons of the department, always trying to preserve as much renal mass as possible with the shortest possible arterial clamping time. The exact amount of time at which the consequences of renal ischemia become irreparable is still a controversial issue in the field. The majority are of the opinion that irreparable damage occurs after around 25 to 35 min when warm ischemia is applied[18]. New research suggests that when the length of warm ischemia is over 35 min, the kidneys only recuperate to approximately 82% of the level forecasted by the degree of nephron-mass preservation, consistent with some loss in function related to ischemia[19]. Our series shows that ischemia was necessary only in 52.7% of the patients and in those patients in whom arterial clamping was performed, the mean time was eight (IQR 0-18) min. After the analysis performed in our series, we found that there are clinically significant differences when correlating R.E.N.A.L score with ischemia time, so a higher R.E.N.A.L with the consequent complexity of the tumor has meant the need to carry out a longer ischemia time.

In the literature, we can find some examples of this paradigm change that has occurred. Thompson *et al.* evaluated solitary kidneys experiencing PN with the use of warm ischemia and concluded that longer WIT relates to renal failure, some of them even requiring renal replacement therapy[15]. Subsequently, when Thompson *et al.* reanalyzed their cohort[15], including subjective estimation of conserved parenchymal volume as a covariate, only the percent of parenchyma conserved and preoperative GFR remained essential predictors of new-onset CKD, leaving aside the WIT[11]. Thompson *et al.* conclude, in a recent publication, that in the scenery of SRM and restricted durations of warm ischemia, the outcomes observed for on-clamp and off-clamp methods were similar, and reconsider the function of ischemia as a risk factor for developing CKD[20].

The standard approach to reduce ischemic injury has been the induction of hypothermia, called cold ischemia. Renal energy spending is decreased by superficial cooling with ice which also partially improves the hostile impact of warm ischemia and reperfusion injury[21]. Since the induction of cold ischemia is still technically difficult with minimally invasive techniques, numerous surgical approaches have been proposed to reduce the duration of warm ischemia. We can reduce global renal ischemia time considerably by premature unclamping of the main renal artery, which is carried out after a first continuous suture has been made[22]. Since clamping of the principal artery implies the highest ischemic offense, this can be diminished by selective clamping of only the appropriate segmental arteries[23]. Specifically, zero-ischemia PN signifies superselective clamping of tumor-specific artery branches, which are carefully dissected and superselectively clamped with clips[24]. Off-clamp LPN or robot-assisted PN (RAPN) are technically demanding approaches. Also, some authors questioned off-clamp LPN/RAPN as potentially negatively impacting the perioperative outcomes of the surgery, increasing blood loss, worsening the vision of the operative field, and supporting the probability of complications and positive surgical margins[25].

As we can see in our series, one of the most commonly used strategies is the absence of arterial clamping (52.7%). This is probably related to the experience of the surgeons and it could generate a bias since its implementation requires a long learning curve. Another possible bias is the fact that the mean R.E.N.A.L. score was 6, so most of the tumors were easy to approach from a technical point of view. In spite of this, as we have already mentioned, there is a relationship with significant results in a longer ischemia time in those cases with a higher renal score.

Xiong *et al.* have recently reported the histologic changes in healthy renal parenchyma caused by ischemia time, consisting of measuring changes of preserved renal parenchyma from 65 patients who first underwent PN and subsequently required a RN 2.4 years later on average[26]. The authors evaluated if the ischemia duration or type of ischemia conveyed differences in advanced histologic changes with a CKD score (0-12), indicating a glomerular/tubular/interstitial/vascular status summary. Particularly, comparison of histological findings between ischemia time < 25 and ≥ 25 min and between warm ischemia and cold ischemia showed no significant difference in CKD scores between samples. However, the existence of comorbidities (hypertension, diabetes mellitus, or pre-existing CKD) was associated with significant deterioration of the histologic CKD score between the PN and RN samples, which would imply that the patient's comorbidities contribute more than the type or duration of ischemia to the objectified chronic changes in the kidney.

In the CLOCK trial[16,27], an average variance of 14 min in WIT did not significantly affect renal function at 6 months after surgery. Subsequently, in the CLOCK II trial[28], no differences were found neither in the perioperative or early functional outcomes between on-clamp and off-clamp LPN.

In order to achieve functional results, to date, the literature has focused on defining a new baseline GFR three and 6 months after surgery. Most studies have been dedicated to these time periods because they correlate with long-term overall survival, mainly for patients with prior renal failure. More recent data, however, has defined the function of ischemia in relation to the risk of AKI. AKI is frequently seen after PN in patients with a solitary kidney and, in the series by Zhang *et al.*, while AKI was observed in 45 out of 83 solitary kidneys (54%), only 38 patients (46%) were categorized as having AKI, when parenchymal mass alterations were evaluated[16]. Also, they summarize that most kidneys recuperate from AKI to 88%-99% of the level predicted by nephron-mass preservation[16]. In our study, we evaluated the GFR on the first postoperative day, at 3 and 6 months after surgery, and found no relevant differences, with no statistically significant differences in relation to the time of ischemia during surgery. This is possibly influenced by the fact that 57.5% of the patients had previous CKD.

Predicting these results is challenging. Two models have recently been published in an attempt to predict postoperative AKI and development of CKD stage 3b in patients undergoing PN or RN for kidney cancer. The authors called them RENSAFE (RENalSAFEty)[29] and conclude that male sex, American Society of Anesthesiologists (ASA) score, hypertension, R.E.N.A.L. score, preoperative eGFR < 60 and RN are predictors for AKI, while age, diabetes mellitus, preoperative eGFR < 60 and RN are predictors for CKD ≥ 3b. These are easily implementable nomograms to decide with the patient the type of nephrectomy, although the impact of AKI on post-surgical patients seems to be limited to less severe forms of CKD.

Another nomogram has recently been published[30], based on four risk categories of patients (low, intermediate favorable, intermediate unfavorable and high-risk patients), to predict the risk of CKD-upstaging at three years in patients undergoing a RAPN. The model included baseline GFR, solitary kidney status, multiple lesions, R.E.N.A.L. score, clamping technique, and postoperative AKI. It showed that, based on identified nomogram cut-offs (7% *vs.* 16% *vs.* 26%), there was a statistically significant increase in CKD-upstaging rates between low *vs.* intermediate favorable *vs.* intermediate unfavorable *vs.* high-risk patients (1.3% *vs.* 9.2% *vs.* 22% *vs.* 54.2%, respectively, $P < 0.001$).

Crocerossa *et al.* studied those variables influencing long-term renal function (one year after surgery) and assessed their relative weight[31]. They concluded with preoperative GFR, sex, ischemia technique, and percentage loss (PPL) being the best predictors of GFR PPL at one year after minimally invasive PN.

With the use of robotics in the surgical treatment of RCC, the indication for RAPN has been expanded to include the management of larger and higher complexity renal tumors[32]. A systematic review in 2023 analyzed the outcomes of RAPN for completely endophytic, large tumors (cT2-T3), solitary kidneys, recurrent tumors and hilar masses, and demonstrated favorable surgical outcomes with good preservation of renal function, without forgetting a higher likelihood of complications on those extremely challenging cases[33].

Nowadays, 2D computed tomography (CT) images can be turned into three-dimensional (3D) models, and 3D virtual reconstructions have proven to be useful tools in the surgical planning of PN[34]. Porpiglia *et al.* demonstrated, first in 2017 and then in 2019, the downgrading in complexity in nephrometric scores (RENAL and PADUA) using 3D reconstruction systems[35,36]. In 2020, they evaluated the role of 3D virtual reconstructions in the surgical guidance during RAPNs, proving that 3D guidance was associated with lower rates of ischemia, higher rate of complete enucleation and lower collecting system damaging rate, compared to intraoperative ultrasound (US) guidance[37].

We know that the short follow-up period of our patients may be a limitation of the study and that functional outcomes at one year would probably increase the impact. Therefore, future lines of research should aim to validate new nomograms with the most important risk factors of the patients in order to decide between one technique or another. This will require a longer follow-up time of our patients.

Another limitation of our study is the small sample size, with only 148 patients included. Despite the advances in knowledge about the recovery of renal function and renal ischemia and the fact that preservation of renal mass is the most important factor, we can confirm that controversies remain unresolved, and the urology community would be enriched by additional investigation with respect to the best approaches. This could include a contrast of conventional intraoperative ultrasonography with other technologies such as indocyanine green dye, and the better use of preoperative imaging including 3D reconstruction to increase surgeons' knowledge of the patient's anatomy and the relationships between the vessels and the tumor. The different surgical techniques are relevant in this regard: polar nephrectomy, enucleation, wedge resection and enucleoresection; their differences imply a greater or lesser preservation of renal mass.

Upcoming studies should also provide information to help the urology community understand when irreversible ischemic damage begins to occur with warm ischemia and which patients are at the greatest risk of irreversible ischemic damage and impaired renal function.

In conclusion, even though renal tumors with a higher RENAL score imply the need to perform a longer arterial ischemia time, its relationship with the deterioration of renal function is unclear as there are probably other factors to blame, such as the patient's previous comorbidities. Therefore, we believe more in assuring oncologic results and promoting the absence of complications during PN. Greater knowledge of the importance of the technique will be available in the future with the use of new technologies such as robotics and 3D imaging.

DECLARATIONS

Authors' contributions

Conceptualization, data curation, methodology, writing - original draft, writing - review and editing: de la Parra I

Conceptualization, methodology, supervision, writing - review and editing: Gómez Rivas J

Data curation and supervision: Serrano Á

Data curation: Vives R, Gutiérrez Hidalgo B, Hermida JF, Ibañez L

Supervision: Fernández Montarroso L, Moreno-Sierra J

Availability of data and materials
Not applicable.

Financial support and sponsorship
Not applicable.

Conflicts of interest
Gómez Rivas J is the editorial member of *Mini-invasive Surgery*, while the other authors have declared that they have no conflicts of interest.

Ethical approval and consent to participate
The study was approved by our internal Institutional Review Board (IRB) committee, with Approval No: 23-038. Besides, the consent to participate was obtained from every patient.

Consent for publication
Not applicable.

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