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ARTICLE

Impact of ischemia time during partial nephrectomy on short- and long-term renal function

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ABSTRACT

Objective: Partial nephrectomy is the gold standard treatment in small renal tumours. During partial nephrectomy, the renal artery is clamped which creates transient ischemia. This can damage nephrons and may affect kidney function immediately postoperatively and on long-term.
Objective: In the present study, we investigated the effect of ischemia time during partial nephrectomy with regards to affection of renal function immediately post-operatively and 1-year post-surgery.
Materials and method: A retrospective cohort study including 124 patients who underwent partial nephrectomy at a single regional hospital in the period from 2018 to 2020 was conducted.
Results: We divided patients into subgroups based on the ischemia time: [0–8], [9–13] and [14–29] minutes. The mean value for kidney function was an eGFR (mL/min) of 73.9 before and 66.8 at a 12-month post-surgery. We found no significant correlation between ischemia time and renal function. Noticeably, none of the patients had ischemia time greater than 30 min.
Conclusion: In this cohort, the duration of ischemia time was not associated with differences in renal affection neither on short term nor long term parameters if the ischemia time was kept below 30 min.

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Introduction

Incidence of kidney cancer has increased over the last 20 years. This can be partly explained by the increased use of CT and MR imaging techniques [1]. Localized tumours are often treated surgically with nephrectomy or partial nephrectomy (PN). During PN a short clamping of the blood vessels is necessary to create a temporary state of ischemia. Vascular clamping allows the operator to work in a space with decreased blood flow, additionally decreasing the risk of excessive bleeding. However, clamping and ischemia can damage the nephrons and affect the renal function permanently [2].

The use of ischemia in PN can be done with regular clamping of the renal artery and eventually the renal vein in operations expected to stay below 25 min, this is referred to as ischemia time (IT) or warm ischemia time (WIT). If the operation is expected to surpass 45 min, it is recommended to use 'cold ischemia' where hypothermia is induced during surgery to minimize the renal ischemia and therefore limit the long term loss of renal function [3]. The PADUA-score is a score used before the surgery to determine the complexity of the operation. The score includes the following: location of the tumor, exophytic/endophytic, renal rim/renal sinus, involving urinary collections system and tumor size. The PADUA-score is considered a reliable classification for predicting WIT and complication rates [4]. A prospective study found higher rate of complications with increasing PADUA-score [5]. Other treatments include cryotherapy and radiofrequency ablation, and these have some advantages compared to PN since it can be performed without ischemia and therefore less impact on renal function [6,7].

In the present study, we investigate the correlation between IT and loss of renal function in PN. More specifically we examined if there is a specific cut-off value of IT, where the kidneys are not severely damaged.

Materials and methods

The study included all consecutive patients that underwent PN in a period from 2018 to 2020 at a single hospital. The database contained information regarding IT, total operation time, PADUA-score, gender, BMI, and age. The level of the serum-creatinine was measured on the date of surgery, one day after, and 1-year post-surgery. An estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation, which includes serum-creatinine, gender (male/female), and age [8].

To detect a trend in the effect of ischemia on renal function post-surgery, patients were stratified based on quartiles of the observed IT Continuous variables were tested for normality and presented as mean and standard deviation. Categorical variables are presented as count with percentages. Mean patient characteristics were compared across the ischemia groups with Kruskall–Wallis rank sum test for

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continuous variables and Pearson's Chi-squared test for categorical variables (see Table 1).

The pre-surgical and 1-year post-surgical eGFR were treated as repeated measurements. Moreover, it was expected that total surgical time potentially could influence post-surgical renal function. Thus, a three-way repeated measure ANOVA was performed (see Table 2). eGFR was treated as the dependent variable and ischemia, operation time, and point in time (i.e. pre-surgical and post-surgical) were the independent variables. The assumption of normality was tested and fulfilled using QQ-plots. No extreme outliers were identified. Levenes's Test for Homogeneity of Variance allowed us to accept the null hypothesis of equal variance ($p = 0.9967$). Post-hoc testing was performed with Tukey's Honestly Significant Differences with Bonferroni correction. Statistical significance was set *a priori* to a p-value < 0.05. All statistical calculations were made using R version 4.0.3 and RStudio [9,10].

Results

In total, 124 patients were included in the study. The operations were performed as either purely laparoscopic (2), robot-assisted (109), or open PN (13). The patients had an average age of 62, and the cohort consisted primarily of male patients (66%) (Table 1). The patients all underwent PN during a period from 2018 to 2020 using warm ischemia. Average eGFR (mL/min) was 73.9 before and 66.8 at the 12-month follow-up for the unstratified population. The tumor size and T-stage was evaluated post-surgery by a pathological examination.

Patients were divided in quartiles based on IT. Age, gender, and BMI were not significantly different between the four groups. Operation time varied significantly between the four groups, with longer operation time in the groups with longer IT. Furthermore, a higher proportion of patients with a PADUA-score ≥ 8 was observed with increasing ischemia time ($p = 0.096$). Three-way repeated measures ANOVA test did not show a significant difference between IT and eGFR (Figure 1 and Table 1).

Discussion

It is well known that ischemia can affect renal function both temporarily and permanently. The question is how short IT needs to be to protect long-term renal function after PN. In the present study, we found that only few of the patients had relevant kidney affection 1-year post-operatively.

An earlier meta-analysis found that limiting IT improves renal function outcomes [11]. The analysis showed that renal function after recovery is strongly associated preoperative renal function. Warm ischemia time (WIT) is the standard in lower expected ischemia time and cold ischemia is used when the IT is expected to extend to more than 40 min. The use of cold ischemia is beneficial to warm ischemia since it raises the threshold for IT [11]. A comparative study from 2018 found cold ischemia to be superior to WIT with a significant difference in eGFR after 3 months post-surgery [3].

In a retrospective study with 668 patients, Rosen et al. found a small significant reduction in eGFR compared to the expected value in patients with longer IT, when stratifying

Table 2. A three-way ANOVA comparing eGFR with the following variables: operation time, ischemia time and time after operation.

	Degrees of freedom	*F*-value	*p*-Value
Operation time	3	1.768	0.154
Ischemia time	3	2.441	0.065
Time after operation	1	7.965	0.005

Time after operation is referring to the time of measured eGFR; pre-surgery, one-day post-surgery and 1-year post-surgery.

Table 1. Continuous variables presented as mean (SD), except estimated blood loss which is presented as mean (range) and IQR.

	Ischemia time groups				
Characteristics	0–8 min $n = 32$	9–10 min $n = 27$	11–13 min $n = 29$	13–29 min $n = 39$	*p*-Value
Age	63 (11)	62 (10)	64 (10)	62 (10)	0.9
Male	24 (75%)	17 (63%)	20 (69%)	23 (59%)	0.5
BMI	29.0 (6.5)	27.5 (3.9)	28.3 (5.4)	28.8 (6.4)	>0.9
T-stage					0.3
pT1a	26 (90%)	22 (88%)	25 (86%)	27 (87%)	
pT1b	–	2 (8%)	3 (10%)	4 (13%)	
pT2a	2 (6.9%)	–	–	–	
pT3a	1 (3.4%)	1 (4%)	1 (3.4%)	–	
Tumour size (mm)	29 (19)	27 (10)	27 (12)	33 (13)	0.1
Tumour histology					0.2
Clear cell carcinoma	19 (59.3%)	18 (66.6%)	15 (51.7%)	18 (46.2%)	
Papillary renal cell carcinoma	7 (21.9%)	5 (18.5%)	11 (38%)	8 (20.5%)	
Benign	3 (9.4%)	2 (7.4%)	–	8 (20.5%)	
Chromophobe clear cell carcinoma	–	2 (7.4%)	1 (3.4%)	4 (10.3%)	
Clear cell papillary carcinoma	3 (9.4%)	–	2 (6.9%)	1 (2.6%)	
PADUA-score					0.094
≤ 7	14 (44%)	8 (30%)	10 (34%)	6 (15%)	
≥ 8	18 (56%)	19 (70%)	19 (66%)	33 (85%)	
Preoperative eGFR	71 (22)	78 (18)	73 (18)	74 (17)	0.6
Postoperative eGFR	74 (20)	75 (19)	68 (22)	69 (18)	0.4
12 months post-operative eGFR	67 (23)	71 (19)	62 (21)	66 (20)	0.5
Operation time (minutes)	160 (39)	170 (36)	178 (42)	215 (52)	<0.001
Estimated blood loss (mL)	421 (10–3650)	196 (50–550)	406 (20–2000)	342 (50–1000)	0.2
Blood loss IQR	200	150	250	300	

Categorical variables presented as *n* (%). Kruskall–Wallis rank sum test; Pearson's Chi-squared test used where appropriate.

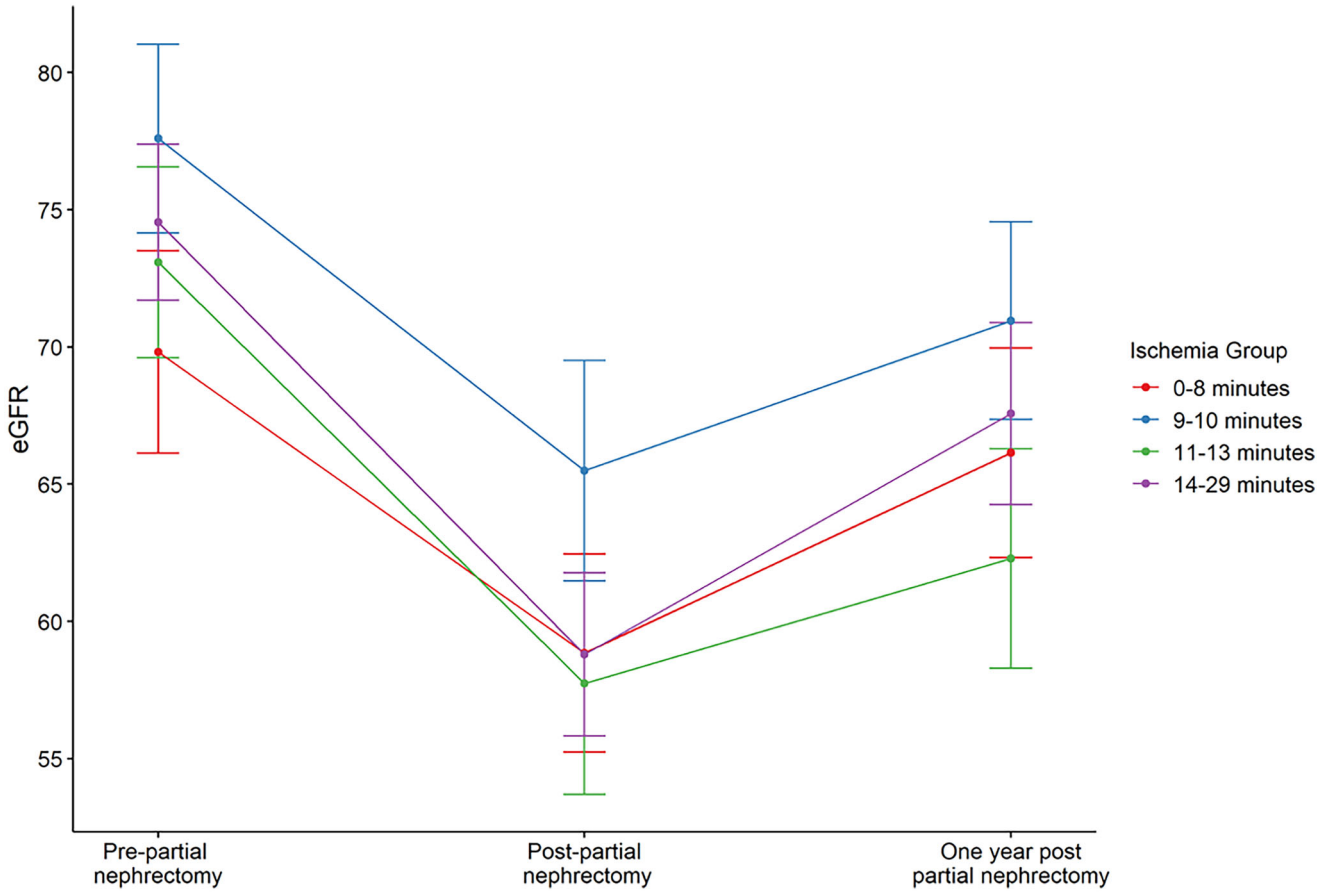

Figure 1. Ischemia subgroups as a function of eGFR pre-operative, post-operative, and 1-year post-operative. Line plot.

for gender and other factors [12]. Similar to the present study, they did not find extended WIT to be associated with a decline in renal function 1-year post surgery. However, they did find that prolonged WIT was associated with worse perioperative outcomes [12]. Another study by Wang et al. found preoperative eGFR, WIT and lesion complexity to be independent predictors of renal function preservation [13].

A newly developed technique used in PN is 'Zero ischemia'. It involves selective occlusion of the arteries supplying the tumour and was developed to avoid ischemic damage. The technique is mostly used in complex tumours and requires intraoperative imagine such as fluorescence imaging, ultrasound or augmented reality [14]. The disadvantages of this technique is the risk of bleeding and thus a bad overview during the surgery. Zargar et al. compared three ischemia groups: zero ischemia, ischemia $\leq$30 and $>$30 min [15]. They found that the zero-ischemia group to be the one with least affection of late renal function. However, they discuss that selection bias might influence the results as zero-ischemia is mostly used in small and less complex tumours, whereas IT $>$30 min is seen in larger and complex tumours. Furthermore, in support of the current cut-of value in IT below 30 min, they found no significant decrease in renal function within the group with IT $\leq$30 min. Alternatives to the PADUA-score is currently being investigated. Haung et al. found that the prediction-score, 'SPARE', was better correlated with WIT, operation time and complication rate [16]. Furthermore, they showed that SPARE had improved interobserver concordance compared to PADUA.

The primary limitation of the present study is the sample size. We have numerous patients with IT close to the median and little variation in IT. Thus, it is difficult to prove a significant correlation as the data is clustered around the middle values. This would be easier to prove in larger population. Another limitation of the study is the use of eGFR as the estimate of renal function. In the present study, we used the CKD-EPI formula. However, other studies use different formulas, and thus comparisons can be difficult.

Furthermore, we have limitations in our study group since most of the operations have short IT, only four patients were above 25 min and not one patient exceeded 30 min of ischemia. This is clinically not a prominent problem in PN, since most surgeons are able to stay below the limit of 25 min.

At present, the cut-off for ischemia is 25 min at our operating center. The results from the present study suggest that this cut-off is correct. In the study by Rosen et al. no data on patients with above 30 min of ischemia time was available but short-term complications were seen in patients with ischemia time as low as 20 min [12]. However, the data in the present study suggest that ischemia below 30 min, does not benefit late renal function. The same conclusion is seen in other studies [15].

Conclusion

As seen in previous studies, the eGFR was affected immediately after surgery but was restored 1-year post-surgery. We did not find that long-term eGFR was significantly affected

by IT in the present series where all patients had ischemia time less than 30 min.

This is important information as the surgeon can focus on completely removing the tumour, having free resection margins, and secure a sufficient hemostasis. PADUA-scores $\geq$8 were correlated with longer ischemia times. However, as shown, this did not translate into long term loss of kidney function.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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