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Off-clamp vs on-clamp robotic partial nephrectomy: Perioperative, functional and oncological outcomes from a propensity-score matching between two high-volume centers

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ABSTRACT

Introduction: Aim of the study was to compare perioperative, functional and oncological outcomes after off-clamp vs on-clamp robotic partial nephrectomy (RPN).

Materials and methods: Patients who underwent off-clamp or on-clamp (warm ischemia) RPN were extracted from 2 institutional prospectively-maintained databases. 123 patients who underwent off-clamp RPN at one institution were excluded, so that each institution contributed with unselected patients (institution 1:on-clamp RPN vs institution 2:off-clamp). 2:1 propensity-score matching (age, sex, smoking, diabetes, hypertension, ASA score, solitary kidney, preoperative eGFR, tumor size and R.E.N.A.L.score). Perioperative outcomes were compared. A linear mixed model was fitted to eGFR as the outcome regressed on fixed effects for 1) management of clamping (on-clamp/off-clamp), 2) time (at baseline, at discharge, at 12 and 24 months postoperatively), and 3) clamp/time interaction. Survival events were compared between groups.

Results: 1983 patients were pooled. After matching, 400 on-clamp vs 200 off-clamp patients were analyzed. No significant differences were found in key perioperative outcomes. The effect of on-clamp on eGFR changed over time. At discharge, groups had similar drop in eGFR. The difference between groups was greatest at 12-months postoperatively, with on-clamp patients showing a deficit of 5 ml/min. At 24-months follow-up, this gap shrunk to 2 ml/min. There were no significant differences in overall survival ($p = 0.1$), recurrence ($\chi^2 = 0.008$, $p = 0.9$), or metastasis free survival ($\chi^2 = 0.962$ $p = 0.3$). Only one cancer-specific death occurred in off-clamp group.

Conclusion: We confirm no significant differences in the perioperative and oncological outcomes between off-clamp and on-clamp RPN. Avoided ischemia benefits renal function within 1-year follow-up after surgery. At longer follow-up, difference with on-clamp is softened.

Introduction

Beyond the aim of neoplasm removal, the goal of the PN is to maximize the preservation of renal function [1]. Several unmodifiable and modifiable factors have been described concurring in the final functional outcomes, including the patient's age and baseline renal function, the amount of preserved vascularized nephrons and the damage from prolonged ischemia time [2,3].

Specifically, from a technical point of view, the remnant vascularized nephronic mass will be the combined result of the minimization of the peri-lesional healthy parenchyma resection and suture-related damage [4]. Ischemia time is the duration of renal

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artery clamping. This step ensures a bloodless field during resection and suture and is crucial, particularly during minimally-invasive PN surgery. Trying to reduce the ischemia-related damage, some authors described no ischemia approaches [5].

The first laparoscopic PN performed avoiding the renal arterial clamping ("off-clamp" technique) was described by Guillonneau et al. [6] and aimed at completely avoiding renal ischemia, thus reducing postoperative loss of renal function. Such approach was refined and first duplicated by Gill et al. during robotic PN (RPN) [7]. A randomized study comparing off-clamp and on-clamp RPN is currently being conducted (the "CLOCK" study, clinicaltrial.gov NCT02287987). Preliminary published results of 164 randomized patients showed increased blood loss in the off-clamp cohort, but comparable positive margins rates. Data on renal functional outcomes are still awaited [8].

The most recent quantitative synthesis of studies comparing on-clamp and off-clamp RPN confirmed the higher blood losses during off-clamp RPN even though this did not translate into higher transfusion rates. Short-term and long-term renal outcomes as measured by absolute estimated Glomerular Filtration Rate (eGFR) and percent eGFR change were superior in the off-clamp group, even after a sensitivity analysis evaluating only publications with comparable RENAL scores [9]. However, there was no follow-up for renal function beyond 6 months. We tried to address this issue with the present bi-centric study, aimed to compare the perioperative, long-term functional and oncological outcomes of off-clamp vs on-clamp RPN in matched cohorts.

Materials and methods

The Glickman Urological and Kidney Institute (Cleveland Clinic, Cleveland OH, USA) and the Department of Urology at Regina Elena Institute (Rome, Italy) institutional prospectively-maintained RPN databases were reviewed after local ethics committee's approval (January 2007–December 2017 and January 2010–December 2017, IRB 5065 and 1107/18, respectively). All patients who underwent RPN with off-clamp or on-clamp (warm ischemia) technique were extracted. Patients were divided into two groups by treating institution. The 123 patients who underwent off-clamp RPN at Cleveland Clinic were excluded, so that all patients from Cleveland Clinic considered for the analysis underwent on-clamp warm ischemia RPN, whilst all patients from Regina Elena Institute underwent off-clamp RPN.

The Cleveland Clinic technique of RPN with warm ischemia technique and the Regina Elena Institute technique for off-clamp RPN were previously described [10,11]. No controlled hypotensive anesthesia was performed in all off-clamp patients.

Patients' demographics and characteristics including gender, age at surgery, body mass index (BMI), smoker status (active/former smoker vs non-smoker), diabetes, hypertension, American Society of Anesthesiology (ASA) score, solitary kidney status, preoperative serum hemoglobin and creatinine (as calculated by the compensated Jaffe's assay [12]) were collected and analyzed. Glomerular Filtration Rate was estimated (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [13]. As for the tumors' characteristics, clinical size and R.E.N.A.L. nephrometry score [14] were reported.

Baseline variables were compared between the off-clamp and the on-clamp groups. The X^2 or the nonparametric Wilcoxon rank sum tests were used to compare categorical and continuous covariate differences in the overall population. Supplementary Table 1 reported the baseline comparison.

To reduce differences between the groups at baseline, patients were matched according to propensity to be treated with off-clamp RPN. This was done using the R package "MatchIt" in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). The "optimal" matching algorithm was used, which is an improved nearest-neighbor matching procedure [15].

Matching was based on unmodifiable patient's and tumor factors including age, sex, smoker status, diabetes, hypertension, ASA score, solitary kidney status, preoperative eGFR, clinical tumor size and R.E.N.A.L. nephrometry score.

The propensity score was calculated with all the aforementioned variables available. The matching was done in a ratio of 2:1 with no replacement (on-clamp: off-clamp). The balance of the baseline variables was checked for the matched cohort.

Primary endpoint

Perioperative outcomes were compared between the matched cohorts, including operative time, hemoglobin drop (preoperative vs postoperative), ischemia type and duration, postoperative complications as reported according to the Clavien classification [16] and length of hospital stay. Regarding pathological data, rate of malignant lesions, TNM stage distribution, grading and rate of positive surgical margins were reported.

Secondary endpoint

Data were analyzed using the *nlme* package version 3.1–137 of R [17]. A linear mixed model was fitted to eGFR as the outcome regressed on fixed effects for 1) management of clamping (on-clamp/off-clamp), 2) time (at baseline, at discharge, at 12 and 24 months postoperatively), and 3) interaction between clamp and time. A random intercept per subject was used with an auto-correlated AR1 correlation structure for within-subject errors. Different error variances were allowed for on-clamp and off-clamp subjects due to the observation of greater variability in eGFR among subjects who received the clamped procedure.

Tertiary endpoint

Due to the small number of observed events for the 4 outcomes of interest (recurrence-free survival, metastasis-free survival, overall and cancer-specific survival), survival analysis by Kaplan-Meier curves was considered not appropriate for the collected data (Supplementary Table 2). Instead, the proportions of observed events in the on-clamp and off-clamp groups were compared using Chi-Square independence testing. In addition, due to the exceptionally small number of observed overall deaths specifically, Fisher's exact test was used instead of Chi-square when assessing proportional differences in overall survival. Statistical analyses were performed using R v.3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). The significance level was set at $p < 0.05$.

Results

A total of 1983 patients were pooled. 1512 patients came from Cleveland Clinic, 471 from Regina Elena Institute. As aforementioned, the 123 patients "selected" for an off-clamp recorded in the Cleveland Clinic database (8%) were excluded from the analysis. The final cohorts available for the analysis included 1307 on-clamp patients from Cleveland Clinic vs 471 off-clamp patients from Regina Elena Institute. After propensity score matching, 400 on-clamp vs 200 off-clamp patients were available for the analysis. The X^2 or Wilcoxon rank sum tests were used to compare categorical and continuous covariate differences after matching and showed that matching improved the balance between the two treatment groups (Table 1, Supplementary Fig. 1).

Primary endpoint

Median warm ischemia time in on-clamp patients was 22 (IQR 17–27) minutes, with all off-clamp patients receiving 0 min of ischemia. 274 patients (68.5) had WIT ≤ 25 min. Group were comparable in hemoglobin drop (2.77 ± 1.49 vs 2.63 ± 1.42, p = 0.5) and overall postoperative complications rate (17.5 vs. 16%, p = 0.7, on-clamp vs off-clamp, respectively). Operative time was shorter for off-clamp group (150 (130–200) vs 80 (60–100), p < 0.001), whilst shorter hospitalization favored on-clamp RPN (3 (IQR 2) vs 4 (IQR 0), p < 0.001).

No differences were found in the percentages of malignant lesions (80.3 vs 83.5%, p = 0.3, on-clamp vs off-clamp), with comparable distribution of TNM stages and grading. No differences were found in the rate of positive surgical margins (3.4 vs 3%, on-clamp vs off-clamp, respectively) (Table 2).

Secondary endpoint

Ninety-seven patients (16%) had preoperative GFR < 60 ml/min (71 in the on-clamp group); 163 (27%) had GFR < 60 ml/min at discharge (114 in the on-clamp group); 162 patients (27%) had GFR < 60 ml/min at 12 months follow-up (112 in the on-clamp group).

Results in the mixed model were compared to baseline measurements on subjects who received the off-clamp procedure (this is the model intercept of 80.94 ml/min). P-values for the fixed effects were shown in Supplementary Table 3, with individual parameter estimates and 95% confidence intervals in Table 3.

The significant interaction showed that the effect on eGFR of the on-clamp procedure changed over time. At discharge, patients with both on-clamp and off-clamp procedures showed a drop in eGFR, with patients undergoing on-clamp dropping by an additional 2 ml/min. The difference between groups was greatest at 12-months postoperatively, with on-clamp patients showing a deficit of 5 ml/min. At the 24 months follow-up (based on available data from 163 to 95 patients, on-clamp vs off-clamp), this gap shrunk to 2 ml/min. Renal function was worse at discharge by 6 ml/min but recovered being not significantly different from baseline either at 12 months or at last follow-up available.

Least squares means eGFR were plotted in Fig. 1. These showed the predicted average eGFR according to time and clamping. Due to the propensity matching, eGFR levels were similar at baseline. Renal function dropped post-operatively, then at 12 months renal function improved on average for the patients who underwent an off-clamp procedure but not for those who underwent on-clamp. Renal function improved for both groups at last follow-up. The random intercepts of the mixed model had a standard deviation of 17.9 (95% CI: 16.5, 19.3), within subject errors had an autocorrelation parameter of 0.49 (95% CI: 0.41, 0.57) and on-clamp subjects had 19.6% more variability than off-clamp (95% CI: 11.7%, 28.2%).

Tertiary endpoint

Based on the statistical analysis, there were no significant differences in overall survival (p = 0.1), recurrence ($\chi^2 = 0.008$, p = 0.9), or metastasis free survival ($\chi^2 = 0.962$ p = 0.3) between on-clamp and off-clamp treatment groups (Table 4). Only one cancer-specific death occurred in the off-clamp group.

Table 1
Preoperative patients' demographics, clinical and disease characteristics (after-matching).

median (IQR) or no. (%)	off-clamp	on-clamp	*p-value*
No. patients	200	400	
Gender (Male)	146 (73.0)	269 (67.2)	0.2
Age (Years)	60.2 (11.6)	59.2 (12.1)	0.3
Hypertension	101 (50.5)	210 (52.5)	0.7
Diabetes	37 (18.5)	83 (20.7)	0.6
Smokers	45 (22.5)	107 (26.7)	0.3
ASA score			0.5
1-2	132 (66.0)	254 (63.5)	
3-4	68 (34.0)	146 (36.5)	
Solitary Kidney	7 (3.5)	10 (2.5)	0.7
eGFR (ml/min)	81.1 (21.4)	81.9 (24.0)	0.4
Tumor Size (cm)	4.2 (2.8)	4.0 (2.7)	0.4
R.E.N.A.L. score	7.7 (1.9)	7.5 (2.0)	0.4

Table 2
Perioperative and pathological data.

median (IQR) or no. (%)	off-clamp	on-clamp	*p-value*
No. patients	200	400	
Operative Time (min)	80 (60–100)	150 (130–200)	<0.001
Ischemia Time (min)	0	22 (17–27)	–
≤25 min		274 (68.5)	
>25 min		126 (31.5)	
Delta Hb (g/dl)	2.6 (1.4)	2.8 (1.5)	0.5
Hospital stay (days)	4 (4–4)	2 (1–3)	<0.001
Postoperative complications	32 (16.0)	70 (17.5)	0.7
Malignant histology	167 (83.5)	321 (80.3)	0.3
Positive surgical margin	5/167 (3)	11/321 (3.4)	0.8
Tumor stage (TNM)			0.3
pT1a	69 (41.3)	149 (46.4)	
pT1b	57 (34.1)	110 (34.3)	
pT2	30 (18.0)	27 (8.4)	
pT3	11 (6.6)	35 (10.9)	
Fuhrman grade[a]			0.1
1-2	76 (57.4)	139 (49.8)	
3-4	52 (42.6)	140 (50.2)	

[a] When applicable.

Table 3
Parameter estimates for the fixed effects of the eGFR model.

Variable	Estimate	95% C.I.	p-value
Intercept	80.94	(78.02, 83.85)	<0.001
Clamp	0.98	(-2.67, 4.63)	0.6
Time at Discharge	−6.22	(-7.77, −4.68)	<0.001
Time at 12 Months	−0.25	(-2.14, 1.64)	0.8
Time at Last Follow-up	0.49	(-1.55, 2.53)	0.6
Clamp * Time Interaction at Discharge	−2.92	(-4.95, −0.9)	0.005
Clamp * Time Interaction at 12 Months	−6.05	(-8.52, −3.57)	<0.001
Clamp * Time Interaction at 24 Months[a]	−2.96	(-5.64, −0.29)	0.03

[a] Based on data from 163 to 95 patients, on-clamp vs off-clamp group, respectively.

Discussion

In the present paper comparing two large datasets from institutions with consistent robotic experience, we found no significant differences when comparing on-clamp vs off-clamp RPN in most key perioperative outcomes. Namely, complications rate and hemoglobin drop were similar in the groups. While complication rate was in line with a recent quantitative synthesis of the literature on the topic [9], the similar hemoglobin drop could partially sound in contrast with the lower blood loss favoring on-clamp RPN in the literature. Nevertheless, our finding could be explained by the use of the more objective hemoglobin drop data.

Shorter operative time favored off-clamp, reasonably due to the avoided dissection of the renal pedicle in the off-clamp technique. Moreover, in the on-clamp Institution, one fellow usually accomplished the lower complexity steps of the procedure (i.e. dissection of renal pedicle, tumor exposure), thus lengthening the operative

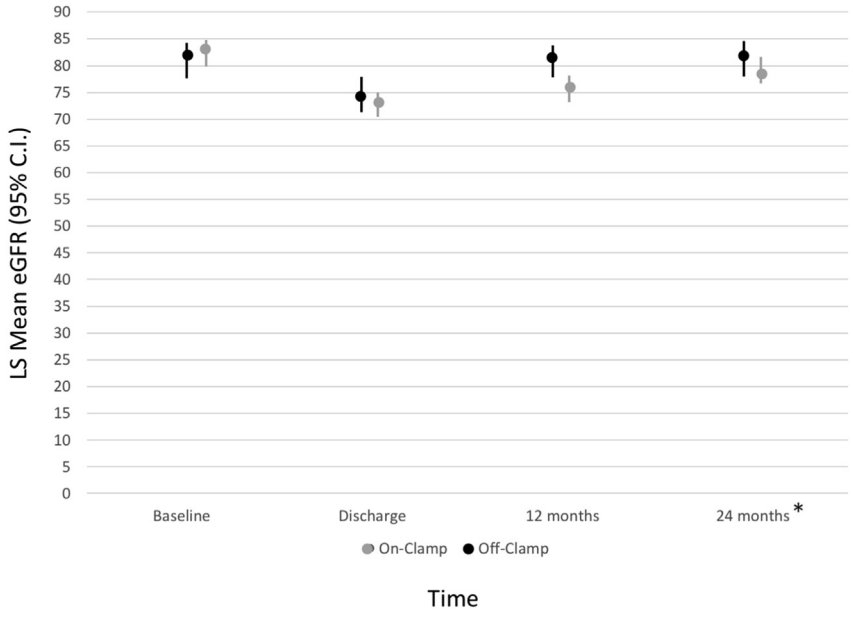

Fig. 1. Least squares means of estimated Glomerular Filtration Rate (eGFR) with 95% confidence interval at follow-up time points (baseline, discharge, 12 and 24 months post-operatively). eGFR was estimated by CKD-EPI formula. Due to the propensity matching, eGFR levels were similar at baseline. Renal function dropped post-operatively, then at 12 months renal function improved on average for the patients who underwent an off-clamp procedure but not for those who underwent on-clamp. Renal function improved for both groups at last follow-up. The random intercepts of the mixed model had a standard deviation of 17.9 (95% CI: 16.5, 19.3), within subject errors had an autocorrelation parameter of 0.49 (95% CI: 0.41, 0.57) and on-clamp subjects had 19.6% more variability than off-clamp (95% CI: 11.7%, 28.2%).
*Available data from 163 to 95 patients, on-clamp vs off-clamp, respectively.

Table 4
Oncological outcomes.

Outcome	Odds Ratio	95% C.I.	Test used	p-value
Deaths (All causes)	3.06	(0.715–14.90)	Fisher-Exact	0.1
Recurrences	1.21	(0.405–3.297)	X^2	0.9
Metastases	0.60	(0.234–1.350)	X^2	0.3

All odds ration estimations were given as odds of an event in the off-clamp treatment group over odds of an event in the on-clamp treatment group (reference). Fisher's exact test was used instead of X^2 for all cause deaths due to the low number of expected observations (<5).

time. The finding is in line with the literature reporting an average of 20 min longer operative time for on-clamp RPN [9]. Conversely, a shorter length of stay favored on-clamp RPN, likely due to the different health-care system and postoperative patient management.

Regarding renal function, patients started from comparable eGFR baseline values after matching. No differences were found at discharge, whilst off-clamp RPN had lower eGFR drop at 12 months and at 24 months postoperatively. The lack of difference in renal function at discharge could be explained by the fact that patients were discharged after a median of 2–3 days: at this time point, the observed creatinine likely precedes the expected creatinine peak occurring after acute tubular necrosis following the clamping of renal artery [18].

Regarding the trend of renal function at longer follow-up, it is interesting to note that the advantage of off-clamp observed at one year became less consistent at the last follow-up available (2 years), with on-clamp patients showing significant improvement in renal function. Our findings are in line with those reported by Cömez et al. who found no differences in renal functional outcomes at a median follow-up of 27 and 33 months for off-clamp vs on-clamp (40 vs 33 patients, respectively) [19]. Those findings contradict what reported by the other studies investigating functional outcomes, but they only had 6 months follow-ups [20–26].

In our analysis, for the first time in the literature, on-clamp and off-clamp RPN were compared in the functional outcomes on a large sample size at longer follow-up. Notably, the comparison was performed in matched-paired cohorts, after accounting for age, sex, smoker status, diabetes, hypertension, ASA score, solitary kidney status, preoperative eGFR, clinical tumor size and R.E.N.A.L. nephrometry score. Moreover, after excluding an "anecdotal" number of patients (8%) who were "selected" for an off-clamp RPN at the "on-clamp Institution", the patients were unselected.

We observed an "improvement" of renal function over time particularly in patients who underwent on-clamp RPN. We explained such an improvement in the global renal function by the higher hyperfiltration triggered rather than by a true recovery of renal function by the operated kidney [3].

Data from transplant donor literature confirms that although 50% of the functioning renal mass is removed during donor nephrectomy, compensatory hypertrophy in the remaining normal kidney will return the GFR to approximately 70% of baseline at 10–14 days [27] and approximately 75–85% of baseline at long-term follow-up [28–31].

This concept drove global renal function in on-clamp patients towards the one observed in off-clamp patients. Whether this hyperfiltration is detrimental at longer follow-up will be the goal of future studies.

Regarding the oncological outcome analysis, positive surgical margins rates were comparable between the groups, again confirming the literature [9]. To accomplish the third study endpoint, due to the small number of observed events, survival analysis was considered not appropriate. Instead, differences in the proportion of events between on-clamp and off-clamp groups were used to assess treatment efficacy. Based on this analysis there was no significant differences in recurrence-free, metastasis-free and overall survival. While a large patient pool was used to assess these outcomes, it is important to note that the low number of observed events may represent a statistical limitation. Although there are no apparent

differences in the probability of events in each group, this does not exclude the possibility of differences in hazards between the two treatment groups that can only be elucidated with larger numbers of observed events. The potential of differences in time to event between the two treatment groups could still be of important clinical relevance and may be worth further exploration in a sample with larger numbers of observed events across the treatment groups.

Several limitations in the present study must be noted. First, this is a retrospective study, thus limiting the level of evidence, with inherent selection bias. We tried to soften such bias by a rigorous propensity score matching, including covariates of interest for surgical and functional outcomes. Nevertheless, there is the potential that differences in the resection technique whose report was not standardized could have altered the analysis.

Second, the reader could argue some concerns about the evaluation of surgeons' experience. We assumed comparable experience of surgeons who contributed to the cases here analyzed, being the two institutions referral centers for RPN.

Last, regarding the evaluation of renal function, we acknowledge that a more reliable analysis with nuclear renal scan would have been preferable for a more accurate conclusion on the outcome [13]. The vast majority of patients included in the studied population had baseline GFR >60 ml/min, and the inaccuracy of formula-derived GFR estimates in populations with GFR >60 ml/min/1.73 m^2 has been reported [32]. It is possible that an over-estimation of the recovery of renal function occurred at longer follow-up. Moreover, the limited sample size of patients with GFR <60 ml/min prevented us from drawing any conclusion about the impact of the management of renal artery in such patients. We believe this is a very important point and we will try to address the issue in the setting of future studies.

Notwithstanding the limitations, we believe the present paper adding to the existing literature, with a longer-term functional evaluation after on-clamp vs off-clamp RPN, accounting for many confounders after propensity-score matching in two large cohorts of almost un-selected patients.

Conclusions

In experienced hands, we confirm that the two approaches to the management of renal pedicle do not translate into significant differences in the perioperative and oncological outcomes. The avoided ischemia in the off-clamp patient benefits renal function within one-year follow-up after surgery, whilst at longer follow-up, such difference with on-clamp patients is softened possibly by more significant hyperfiltration. Randomized trials on the topic are awaited to confirm our findings.

Conflict of interest, financial disclosures

Jihad H. Kaouk certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg. Employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patent filed, received or pending) are the following: Endocare, Inc, Intuitive.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.12.005.

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