Predictors of the Transition from Off to On Clamp Approach during Ongoing Robotic Partial Nephrectomy: Data from the CLOCK Randomized Clinical Trial

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Abbreviations and Acronyms
CLOCK = CLamp vs Off Clamp the Kidney during robotic partial nephrectomy
eGFR = estimated glomerular filtration rate
PN = partial nephrectomy
RAPN = robot assisted PN
R.E.N.A.L. = radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, location relative to polar lines, hilar
SIB = surface-intermediate-base

Purpose: We sought to identify predictive factors of the transition from off clamp to on clamp robotic partial nephrectomy following an intraoperative decision.

Materials and Methods: In the multicenter, randomized, prospective CLOCK (CLamp vs Off Clamp the Kidney during robotic partial nephrectomy) trial 152 and 149 of the 301 patients with a localized renal mass were assigned to undergo off clamp and on clamp robotic partial nephrectomy, respectively. Surgery was done at a total of 7 referral institutions by 1 surgeon per institution. A localized renal mass was defined as having a R.E.N.A.L. (radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, location relative to polar lines, hilar) score less than 10. Surgeons had similar experience with at least 100 previous robotic partial nephrectomies. All patients underwent a preoperative and a 6-month renal scan. The current study deals with one of the secondary end points of the trial, comparing cases finalized as clampless (off robotic partial nephrectomy group) with those which were converted (shift robotic partial nephrectomy group).

Results: Of the 152 patients randomized to off clamp 61 (40%) were shifted to on clamp robotic partial nephrectomy following an intraoperative decision. The transition from off to on clamp robotic partial nephrectomy is associated with renal mass diameter and complexity. Under the specific conditions of the current trial no harm was related to this decision.

Key Words: kidney neoplasms, nephrectomy, robotic surgical procedures, surgical instruments, morbidity
PARTIAL nephrectomy is the gold standard treatment of technically resectable cT1 renal tumors.\textsuperscript{1,2} It provides oncologic outcomes comparable to those of radical nephrectomy but confers a survival advantage due to greater preservation of renal function.\textsuperscript{3,4} The robotic approach to PN is gaining popularity with respect to its open and laparoscopic counterparts, providing more favorable perioperative and functional outcomes.\textsuperscript{5–9}

Along with the baseline quality of the parenchyma and the amount of healthy tissue sacrificed by resection and sutures the major modifiable factor responsible for the functional decrease after PN is ischemic insult secondary to artery clamping.\textsuperscript{10,11} Accordingly several alternatives have been suggested, including delayed clamping, early unclamping and selective clamping at various degrees up to the extreme of no clamping with favorable functional outcomes in cases of suboptimal baseline renal function.\textsuperscript{12–14} However, this approach is generally reserved only for less complex masses because facing resection with the kidney perfused is technically more demanding and carries the risk of major bleeding.\textsuperscript{15} Thus, this approach requires accurate case selection but the indication still remains mostly subjective and attempts at rationalization are sparse.\textsuperscript{16}

A common practice is to attempt clampless resection and eventually proceed to clamping if needed. Although this approach is widespread, to our knowledge it has been unreported and the literature provides no data on the incidence of aborted off clamp procedures.

We report the analysis of a secondary end point of the CLOCK randomized clinical trial to identify predictors of transition in the clamping approach during ongoing clampless RAPN. We also assessed inherent morbidity.

**MATERIALS AND METHODS**

The CLOCK study (ClinicalTrials.gov NCT02287987) is a multicenter randomized, controlled trial performed by the AGILE Group (Italian Group for Advanced Laparo-Endoscopic Surgery), which opened recruitment in September 2014 and closed it in October 2018. The full protocol was recently published.\textsuperscript{17} The primary end point of the trial was the difference in renal function at 6 months, for which a minimal sample size of 202 cases was estimated.

Participating surgeons, who were directly involved in the trial design, conformed to a well-defined profile. They were 35 to 40 years old, educated in current Italian courses in medicine and urology, and experienced with renal laparoscopic surgery. Each had been involved in robotics since 2010 or 2011 with approximately 100 to 200 procedures per year as the first operator and at least 100 previous RAPNs (median 160).

Study approval was obtained from the Ethics Committee (registration No. NP 1814). Patients who provided informed consent were randomly assigned in a 1:1 ratio to clamp or off clamp RAPN. The assignment was determined by a web based system after the candidate was assessed as eligible. The system was used to gather all study information, which was accessible only to the trial statistician (MS).

Participants were recruited at outpatient clinics. Those eligible for study inclusion had normal coagulative function, preoperative eGFR greater than 60 ml/minute/1.73 m\textsuperscript{2}, a normal contralateral kidney and a renal mass with a R.E.N.A.L. score of 10 or less.\textsuperscript{18} We calculated eGFR by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.\textsuperscript{19} Split renal function was determined by renal scintigraphy at baseline and 6 months after surgery. Comorbidities were summarized using the Charlson-Romano index.\textsuperscript{20} Intraoperative bleeding severity was quantified on a scale of 0—no bleeding to 5—bleeding faster than could be removed by suction. Postoperative complications were classified according to the Clavien-Dindo system\textsuperscript{21} and the resection strategy was documented by the SIB score.\textsuperscript{22,23}

The protocol regulated surgical steps, requiring each arm to completely remove perinephric fat and perform suspension on a loop of the artery. In the on clamp arm tumor resection and inner renorrhaphy were mandatorily done using ischemia while in the off clamp group the artery remained unclamped during the procedure. Preoperative transarterial embolization and intraoperative controlled deep systemic hypotension were not allowed. At closure the CLOCK trial had recruited 301 cases, including 149 on clamp and 152 off clamp, preponderantly at a total of 3 centers (Florence, Chieti and Brescia) indicated as high volume.

In the current study we investigate a secondary end point, that is the transition of the clamping approach in participants allocated to the clampless arm. Of the 152 cases randomized to clampless RAPN 61 (40%) were indeed intraoperatively converted to on clamp (the shift RAPN group). The remaining 91 cases (60%) were completed without hilar clamping (the off RAPN group). We compared preoperative features to identify transition predictors, and intraoperative and postoperative data to assess inherent morbidity.

Categorical variables were summarized as the absolute and relative frequencies, and numerical variables are shown as the mean ± SD or the median and IQR as appropriate. We used the Kruskal-Wallis rank test and the Fisher exact test to compare medians and proportions, respectively, between the study groups. The association of clinical features with the shift from a clampless to a clamped procedure was investigated by binary logistic regression and measured as the OR. All tests were 2-sided with p <0.05 considered significant. All calculations were performed with Stata®, version 15.0.

**RESULTS**

Baseline patient features were similar in the off and shift RAPN groups. Conversely tumor features were
significantly unbalanced as the shift RAPN group had larger (3.5 vs 2.2 cm) and more complex masses (R.E.N.A.L. score 7 vs 6, each p < 0.001, supplementary table 1, https://www.jurology.com). Retroperitoneal vs transperitoneal surgical access was also unbalanced with a significantly greater prevalence of the transperitoneal approach in the shift RAPN group (89% vs 78%, p = 0.047). Multivariate models including unbalanced preoperative features revealed that tumor diameter (OR 1.4, p = 0.009) and the R.E.N.A.L. score (each unit OR 1.4, p = 0.006) were independently associated with the transition from off to on clamp surgery (supplementary table 2, https://www.jurology.com).

Four risk classes were identified in a multivariate model with the R.E.N.A.L. score as a discrete variable, including no risk—R.E.N.A.L. score 4 (OR 1), low risk—score 5-6 (OR 1.8, p = 0.311), intermediate risk—score 7-8 (OR 3.6, p = 0.031) and high risk—score 9 or greater (OR 6.6, p = 0.019, supplementary table 2, https://www.jurology.com, and see figure).

In conversion cases intraoperative data showed significantly longer operative time, greater blood loss, longer suture time, greater adoption of 2-layer renorrhaphy and hemostatic use. Median warm ischemia time in the shift RAPN group was 15 minutes (IQR 12–18). In cases finalized in clampless fashion there was higher insufflation pressure during resection.

The postoperative complication rate was similar in the off and shift RAPN groups (25.3% and 24.6%, respectively) and complications were generally low grade. Postoperatively transfusions were administered in 4 of 91 (4.4%) vs 1 of 61 patients (1.6%) in the off vs shift RAPN groups (p not significant). Drainage time was longer for shift RAPN (3 vs 2 days, p = 0.004) while time to discharge home was similar (see table).

As shown by the SIB score, no difference was found in the pathological pT3a stage or the positive surgical margin rate according to the resection strategy (see table).

At baseline the off and shift RAPN groups had similar global renal function (eGFR 88.2 and 86.3 ml/minute/1.73 m²) and a similar ipsilateral scintigraphy contribution (48.6% and 47.5%, respectively, supplementary table 2, https://www.jurology.com). At 6 months in the off and shift RAPN groups the decreases in eGFR (~7.6 and ~8.1 ml/minute/1.73 m²) and split renal function (~2.1% and ~2.3%) were similar, as was 12-month eGFR (~7.5 and ~8.9 ml/minute/1.73 m², respectively). However, at 6 and 12 months we observed a twofold eGFR decrease of greater than 25% in converted cases, which was not statistically significant (see table).

DISCUSSION

The goal of the CLOCK trial was to provide high level evidence comparing on and off clamp approaches to RAPN. The trial closed accrual at 48 months with 301 participants. Institutions and surgeons complied with a defined profile so that the panel of operators could be considered reasonably homogeneous. Furthermore, the trial was performed in a standardized surgical context with patient selection and surgical steps regulated by the study design and instrumentation constrained by default due to monopoly. According to our intention these boundaries should have mitigated the impact of surgeon related factors on the study end point, allowing reliable identification of the role of tumor related factors.

The conditions presented can be generalized to a relevant number of contemporary robotic institutions but it must be acknowledged that the experience or expertise of the different surgeons could have influenced whether the procedure was finalized in clampless fashion. Nonetheless, our findings would be equally useful to refine surgical planning to enable further identification of tumor features. Indeed, the unique clinical scenario of this trial indicates that the differences between the finalized and converted cases should be described granularly when clampless RAPN is or is not feasible, given that the average surgical experience is the same as that of the involved surgeons.

The first notable finding was that 40% of the masses with a R.E.N.A.L. score of 10 or less could not be effectively treated with a clampless procedure. This evidence supports the poor diffusion of this
and calls into question the claim that most cases could instead be approached by also omitting isolation of the artery. The comparison of finalized vs shifted cases demonstrated that conversion depended mainly on tumor complexity according to definite risk classes (R.E.N.A.L. score 4—no risk, 5-6—low risk, 7-8—intermediate risk and 9 or greater—high risk). Conversely patient features seemed not to be associated with the risk of shift and surgeon features were not evaluable because they were homogeneous as stated. The lack of differences between high and low volume centers corroborates this homogeneity, indicating that the case load was not influential among expert surgeons. Other groups have reported that tumor complexity influences the possibility of performing off clamp RAPN. The most updated meta-analysis showed that off clamp RAPN was performed for less complex tumors at a weighted mean difference of –0.29 and –1.30 for the R.E.N.A.L. score and the PADUA (Preoperative Aspects and Dimensions Used for Anatomical) score, respectively. The correlation between anatomical complexity and the finalization of clampless RAPN adds the R.E.N.A.L. score as a new application during surgical planning. Clearly also other systems could equally or even better fulfil this role, given the limitations of the R.E.N.A.L. score also reported by our group.

Another original finding was that in progress transition of the clamping approach did not imply additional morbidity. Accordingly a clampless approach could be safely attempted and eventually converted. However, it should be remarked that specific safety standards were observed, such as suspending the artery and dissecting all perinephric fat before resecting the tumor, so that the transition did not require additional maneuvers. Nevertheless, converted cases were probably more troublesome, as denoted by longer operative time, higher blood loss, more complex renorrhaphy, greater use of hematic agents and longer drainage time. The current study definitely indicates that the transition to clamping might also be accurately planned.

### Intraoperative and perioperative course of patients randomized to off clamp partial nephrectomy who ultimately underwent unclamped procedure (off RAPN) vs those shifted to procedure requiring artery clamping (shift RAPN)

<table>
<thead>
<tr>
<th></th>
<th>Off RAPN</th>
<th>Shift RAPN</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>No. pts</td>
<td>91</td>
<td>61</td>
<td>—</td>
</tr>
<tr>
<td>No. access (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transperitoneal</td>
<td>71 (78.0)</td>
<td>54 (88.5)</td>
<td>0.047</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>20 (22.0)</td>
<td>7 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Median mins operative time (IQR)</td>
<td>115 (85–135)</td>
<td>130 (120–165)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD intra-abdominal pressure (mm Hg)</td>
<td>13.5 ± 3.3</td>
<td>12.7 ± 1.4</td>
<td>0.042</td>
</tr>
<tr>
<td>No. Airseal® use/total No. (%)</td>
<td>67/90 (74.4)</td>
<td>45/61 (73.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Median cc estimated blood loss (IQR)</td>
<td>100 (50–150)</td>
<td>150 (80–250)</td>
<td>0.004</td>
</tr>
<tr>
<td>No. surgeon assessment of bleeding severity/total No. (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor (grade 0–2)</td>
<td>71/91 (78.0)</td>
<td>46/60 (76.7)</td>
<td></td>
</tr>
<tr>
<td>Major (grade 3–5)</td>
<td>20/91 (22.0)</td>
<td>14/60 (23.3)</td>
<td></td>
</tr>
<tr>
<td>No. hemostatic agent/total No. (%)</td>
<td>69/91 (75.8)</td>
<td>54/61 (88.5)</td>
<td>0.059</td>
</tr>
<tr>
<td>Mean ± SD suture time (mins)</td>
<td>9.3 ± 4.9</td>
<td>11.7 ± 4.9</td>
<td>0.001</td>
</tr>
<tr>
<td>No. renorrhaphy (%)</td>
<td>91/91 (100)</td>
<td>61/61 (100)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. Clavien-Dindo complication grade (%):</td>
<td></td>
<td></td>
<td>0.602</td>
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<tr>
<td>1–2</td>
<td>20 (22.0)</td>
<td>15 (24.6)</td>
<td></td>
</tr>
<tr>
<td>3 or Greater</td>
<td>3 (3.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median days drain removal (IQR)</td>
<td>2 (2–3)</td>
<td>3 (2–3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Median days length of stay (IQR)</td>
<td>4 (3–4)</td>
<td>4 (3–5)</td>
<td>0.115</td>
</tr>
<tr>
<td>No. total surface-intermediate-base score/total No. (%):</td>
<td></td>
<td></td>
<td>0.258</td>
</tr>
<tr>
<td>Enucleation (0–2 points)</td>
<td>61/88 (69.3)</td>
<td>38/59 (64.4)</td>
<td></td>
</tr>
<tr>
<td>Enucleoresection (3–4 points)</td>
<td>25/88 (28.4)</td>
<td>16/59 (27.1)</td>
<td></td>
</tr>
<tr>
<td>Resection (5 points)</td>
<td>2/88 (2.3)</td>
<td>5/59 (8.5)</td>
<td></td>
</tr>
<tr>
<td>No. pT3a/total No. (%)</td>
<td>6/88 (6.8)</td>
<td>1/57 (1.7)</td>
<td>0.246</td>
</tr>
<tr>
<td>No. pos surgical margins/total No. (%)</td>
<td>3/86 (3.5)</td>
<td>2/61 (3.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>6-Mo eGFR change:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD ml/min</td>
<td>–7.6 ± 13.6</td>
<td>–8.1 ± 15.0</td>
<td>0.749</td>
</tr>
<tr>
<td>% Greater than 25%</td>
<td>11.5</td>
<td>20.0</td>
<td>0.264</td>
</tr>
<tr>
<td>Mean ± SD % ipsilateral scintigraphic function change</td>
<td>0.575</td>
<td></td>
<td></td>
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<tr>
<td>12-Mo eGFR change:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD ml/min</td>
<td>–7.5 ± 16.0</td>
<td>–8.9 ± 16.9</td>
<td>0.696</td>
</tr>
<tr>
<td>% Greater than 25%</td>
<td>13.5</td>
<td>30.8</td>
<td>0.121</td>
</tr>
</tbody>
</table>
The off RAPN group had a less pronounced immediate reduction in eGFR (data not reported) and a lower rate of a relevant (greater than 25%) functional decrease at followup, although ultimately no significant difference emerged in functional results. Nonetheless, it should be highlighted that this equivalence in functional outcome cannot be translated to the comparison between the off and on clamp approaches for several reasons. The clamping strategy in converted cases was variable, rather resembling ultra delayed clamping. The groups differed in tumor features related to the quantity of parenchyma sacrificed. Finally, no specific sample size calculation was done on this end point. An incoming study of the primary end point of the CLOCK trial will be dedicated to this issue.

Originally in the current study we relied on a standardized and validated system to report the resection strategy, ie the SIB score.\textsuperscript{22,23} Unexpectedly the conversion rates after enucleoresection and enucleation were similar, although the enucleation strategy should provide the benefit of a bloodless dissection plan and consequently should be less prone to the need for artery clamping.\textsuperscript{27}

The possibility of improving the strategy of the clamping approach could be relevant in specific clinical scenarios. 1) Expert surgeons could identify no or low risk cases for which artery preparation could be omitted. 2) Conversion could be accurately planned with the surgical team in high risk cases. 3) Alternative approaches such as selective clamping, open PN and ablative techniques could be considered in patients at high risk and those in whom it is mandatory to avoid ischemia.

The current study has several limitations which must be acknowledged, including 1) the small cohort size, although it is comparable to that in major reported experiences on clampless RAPN; 2) the bias due to surgeon preference notwithstanding our efforts; 3) the lack of an assessment of difficult perinephric fat dissection even if such surrogates as patient age, gender and body mass index were equally distributed in finalized and converted cases; and 4) the lack of volumetric assessment to evaluate whether transition influenced the quantity of sacrificed parenchyma and renal function.\textsuperscript{28}

CONCLUSIONS

Off clamp RAPN is a challenging procedure in which feasibility depends on the anatomical complexity of the tumor. The attempt to perform an off clamp approach and subsequent intraoperative conversion to a clamped procedure seems not to be harmful when the pedicle has been preliminarily prepared. At any rate correct planning could favor surgeon comfort and in turn the achievement of the major goals of PN, which are no tumor violation, perfect hemostasis and an uneventful postoperative course.

REFERENCES


Regardless of the study findings, the 40% shift rate may be too high for a novice. Most RAPNs at nontertiary centers are done by surgeons with less experience and a lower case volume. We applaud the effort to advance science but urge caution until there is robust evidence of lasting benefit of off clamp RAPN, which in less experienced hands could lead to an adverse outcome. At the time of this writing we believe that the majority of surgeons should clamp the artery (and sometimes also the vein), perform meticulous tumor excision under excellent visualization and reconstruct the kidney securely with a reasonably short ischemia time in a manner that is comfortable for the individual surgeon. This should achieve the most important goals of no tumor violation, perfect hemostasis and functional preservation.

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As RAPN gradually takes over as the current gold standard of nephron sparing surgery, the on/off clamp debate remains alive, stimulating the discussion between adopters of one or the other approach. Regardless of the study findings, the CLOCK trial is a commendable effort (reference 17).
in article). Trying to answer a clinical question by a randomized clinical trial is the target at which we should always aim as researchers but most of the time this represents a prohibitive task.\(^2\) In this study the authors found that the more complex the tumor, the more likely the surgeon is forced to clamp after starting off clamp. They also found that starting the procedure off clamp with possible conversion to on clamp can be a safe plan, given that certain precautions are taken such as renal artery dissection and isolation for a quick conversion.

Unfortunately we are afraid that the debate will not end here. As in other procedures, the surgical strategy during robotic PN is surgeon driven. Meanwhile we should keep in mind that limiting ischemia is certainly important (especially in patients with baseline compromised renal function) but it is even more important to get a negative margin, minimize parenchymal loss and avoid complications. These are the pillars of a well performed RAPN.

### REFERENCES


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**REPLY BY AUTHORS**

We appreciate the comments on our CLOCK trial study (reference 17 in article). We agree that the choice to change the clamping approach largely depends on surgeon attitude and experience. The transition rate in our study seems notably high at 40% but to our knowledge this information was never reported before and no comparisons with previous experiences were possible.

Nevertheless, besides surgeon related factors, 2 other reasons could explain why the off clamp approach was so frequently abandoned. 1) The permissive inclusion criteria of the study (R.E.N.A.L. score 10 or less and any diameter) allowed for randomization to off clamp PN for masses generally deemed not amenable to this approach. The risk of conversion was indeed related exclusively to tumor diameter and complexity. Others have reported that the recourse to a clampless procedure is marginal for larger masses.\(^1\) 2) Robotic systems provide enhanced vision which can be a disadvantage if bleeding occurs. With the lack of haptic feedback it may force surgeons to choose clamping to restore clean vision. Hopefully the data from the CLOCK2 trial, which is identical in design but enrolls only purely laparoscopic procedures, could contribute to test this hypothesis through an indirect comparison.

Finally, it was notable that the outcomes of converted and finalized cases overlapped, reasserting that warm ischemia is only one of the factors responsible for functional damage after PN.\(^2\)

### REFERENCES
