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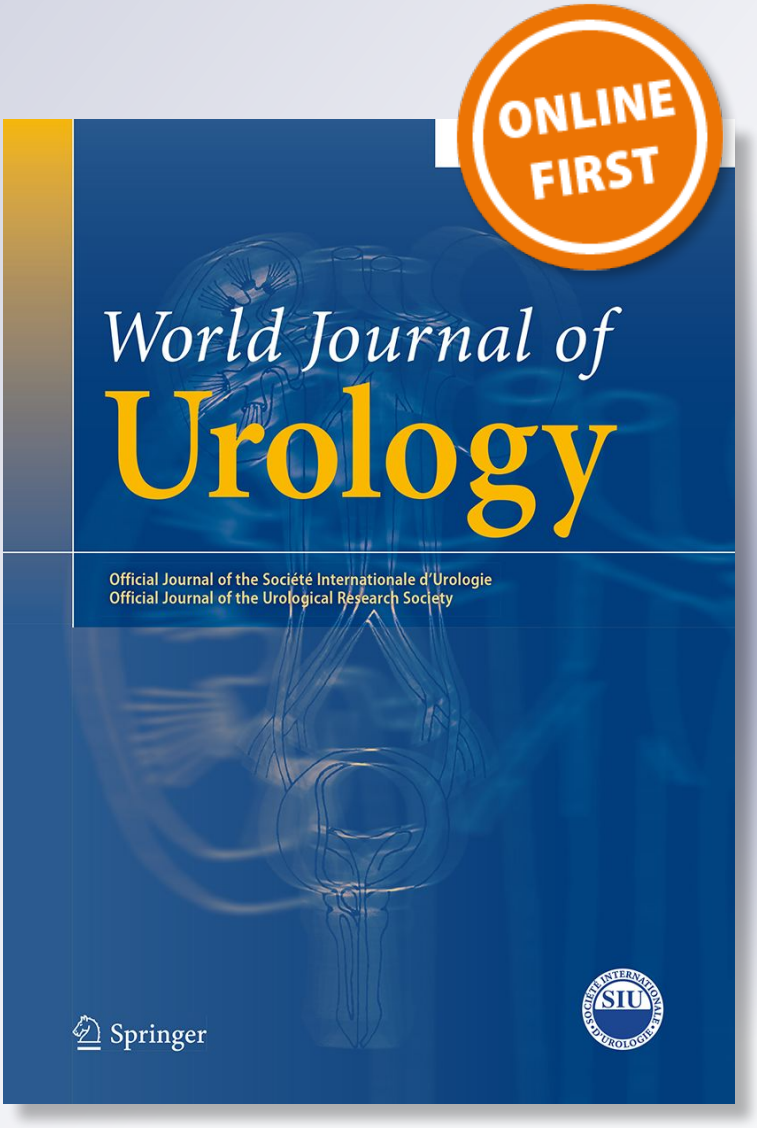

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TOPIC PAPER

Safety of on- vs off-clamp robotic partial nephrectomy: per-protocol analysis from the data of the CLOCK randomized trial

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Abstract

Purpose To compare the safety of on- vs off-clamp robotic partial nephrectomy (RAPN).

Methods 302 patients with RENAL masses ≤ 10 were randomized to undergo on-clamp (150) vs off-clamp (152) RAPN (CLOCK trial—ClinicalTrials.gov NCT02287987) at seven institutions by one experienced surgeon per institution. Intra-operative data, complications, and positive surgical margins were compared.

Results Due to a relevant rate of shift from the assigned treatment, the per-protocol analysis only was considered and the data from 129 on-clamp vs 91 off-clamp RAPNs analyzed. Tumor size (off-clamp vs on-clamp, 2.2 vs 3.0 cm, $p < 0.001$) and RENAL score (5 vs 6, $p < 0.001$) significantly differed. At univariate analysis, no differences were found regarding intra-operative estimated blood loss (off- vs on-clamp, 100 vs 100 ml, $p = 0.7$), post-operative complications rate (19% vs 26%, $p = 0.2$), post-operative anemia (Hb decrease > 2.5 g/dl 26% vs 27%, $p = 0.9$; transfusion rate 3.4% vs 6.3%, $p = 0.5$; re-intervention due to bleeding 1.1% vs 4%, $p = 0.4$), acute kidney injury (4% vs 6%, $p = 0.8$), and positive surgical margins (3.5% vs 8.2%, $p = 0.1$). At multivariate analysis accounting for tumor diameter and complexity, considering the on-clamp group as the reference category, a significant difference was noted in the off-clamp group exclusively for blood loss (OR 0.3, 95% CI 0.09–0.52, $p = 0.008$).

Conclusions The on-clamp and off-clamp approaches for RAPN showed a comparable safety profile.

Keywords Partial nephrectomy · Robot · Clamping · On-clamp · Off-clamp · Clampless

Introduction

The current guidelines recommend partial nephrectomy (PN) as treatment option for T1 renal masses suspicious for cancer [1, 2]. Beyond the oncological aim, the goal of PN is to maximize the preservation of renal function [2, 3].

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Several factors have been described to interplay in the functional outcomes after PN. These are represented by unmodifiable patient's factors (age, comorbidities, and baseline kidney function), and modifiable surgical factors (the renal pedicle management, the resection, and renorrhaphy technique) either determining the final amount of the preserved vascularized parenchyma and thus the ultimate renal function [4, 5].

During the last 2 decades, the ischemia time has been emphasized among the main factors of kidney function impairment after PN [6]. Nevertheless, several studies showed that ischemia time longer than 30 min could be acceptable in the setting of bilateral kidneys [7]. The aim to reduce ischemia time led some authors to push PN to the limit of no ischemia [8]. Actually, during open surgery an "off-clamp" technique is more likely to be performed given the direct hand-assisted control by the surgeon [9]. Conversely, this approach is more demanding during minimally invasive PN. First described by Guillonneau et al. [10], some authors duplicated the off-clamp approach during laparoscopic PN, showing that this is a challenging approach, requiring consistent experience. It was later reproduced with the advent of robotic surgery [11]. Robot-assisted PN (RAPN) has gained popularity in the last decade thanks to the undoubted advantages intrinsic with the robotic platform [12, 13]. As such, it has widened the indications to nephron-sparing surgery. On the other hand, it has been hypothesized that choosing an off-clamp approach might negatively impact on the perioperative outcomes. Indeed, higher blood loss could be responsible of vision worsening increasing the risk of surgical complications and positive surgical margins.

Our research group sought to raise the bar, aiming to increase the level of evidence about the topic in the setting of a randomized clinical trial (RCT), the "CLOCK" study (CLamp vs Off Clamp the Kidney during robotic partial nephrectomy; ClinicalTrials.gov NCT 02287987). The present analysis concerns with some secondary endpoints of the CLOCK trial, with the aim to compare the surgical and oncological safety of on-clamp vs off-clamp RAPN.

Materials and methods

Trial design, participants

The CLOCK Robotic study is a multi-centric RCT promoted by the AGILE group (Italian group for advanced laparo-endoscopic surgery, http://www.agilegroup.it) started in September 2014 and closed in November 2018. The study received ethics committee approval (registration number NP 1814).

The study protocol was described elsewhere [14]. Briefly, all the consecutive candidates fulfilling the inclusion criteria (preoperative glomerular filtration rate (eGFR) > 60 ml/min as estimated by the CKD-EPI equation [15]; normal contralateral kidney; renal mass complexity ≤ 10 as assessed by RENAL score [16]) were randomized to undergo on-clamp or off-clamp RAPN at 7 Institutions. At each center, only one single experienced robotic surgeon with a detailed surgical profile (35/40 years, prior experience in laparoscopic renal surgery and at least 100 RAPNs with various clamping approaches prior to the study start) was involved to ideally homogenize the surgical expertise. At baseline, a renal scan was prescribed to assess split renal function.

Sample size

The primary endpoint of the study was the baseline/postoperative eGFR variation at 3/6 months. The minimal required sample size was 102 + 102 patients, calculated on an expected difference of 20 ml/min between arms according to the best evidence available at the time of study design [17]. Considered the occurrence of shifts from the assigned arm, the enrollment period was prolonged as far as at least 200 patients underwent the desired treatment, to achieve the planned minimal sample size.

Randomization

The random sequence was computer generated with a 1:1 ratio allocation assigned by a permuted block design, stratified by center [18] and according to the complexity of the tumor based on the RENAL score. The allocation arm was notified to surgeons just before starting the procedure by a dedicated internet-based e-form, managed by an independent software house.

Interventions

The surgical strategy was strictly regulated by the study protocol: kidney defatting, renal artery isolation, and suspension were mandatory steps. In the on-clamp treatment group, tumor resection and inner renorrhaphy layer had to be done under ischemia, whereas in the off-clamp arm, the renal artery had to remain unclamped throughout the whole procedure. All the participating surgeons were able to perform both trans- and retroperitoneal accesses, adopted according to tumor's position or patient's previous surgical history. At any moment, the investigators were able to change to the alternative randomization arm, detailing the timing and the reasons of the decision.

Outcomes

Patients' demographics, baseline characteristics, perioperative, and post-operative data were collected on electronic forms, accessible only to the project statistician. Patients' comorbidities were classified according to the Charlson–Romano index [19]. The resection technique was classified by the recently published and validated Surface-Intermediate Base (SIB) score [20, 21]. The severity of intra-operative bleeding was categorized on a scale from 0 (no bleeding) to 5 (intense bleeding exceeding the suction capacity). Post-operative complications were classified according to the Clavien–Dindo system [22]. Pathological specimen examination was done at each Institution by experienced dedicated uro-pathologists, blinded to clamping approach, according to international guidelines; no central revision of slides was done. A further renal scan was prescribed at baseline and after 3/6 months.

For the purpose of the present study—i.e., to assess the safety of on- vs off-clamp RAPN—the following endpoints were compared:

(a) Intra-operative estimated blood loss (EBL, continuous variable);
(b) Post-operative complications rate;
(c) Post-operative anemia, described by:
    (a) A decrease in hemoglobin levels ≥ 2.5 g/dl;
    (b) Transfusion rate;
    (c) Re-intervention (surgical or angiographic) due to bleeding.
(d) Post-operative acute kidney injury (AKI) rate (increase > 50% in serum creatinine [23]);
(e) Positive surgical margins (PSM).

Statistical methods

Categorical variables were summarized as absolute and relative frequencies, while numerical variables as median and interquartile range (IQR).

The Kruskal–Wallis rank test and the Fisher's exact test were used to compare medians and proportions between treatment groups, respectively. Multivariable logistic regression models were estimated to compare outcomes' distributions in off- and on-clamp approaches accounting for potential confounders. All tests were two-sided and a p value < 0.05 was considered statistically significant. All calculations were performed using Stata 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Up to October 2018, 343 patients were assessed to be enrolled in the CLOCK study; 41 patients were excluded after accounting for inclusion criteria. Actually, 302 patients were recruited: 150 were randomly assigned into the on-clamp and 152 in the off-clamp treatment group. The number of recruited patients exceeded the planned sample size because of relevant rate (61/152 patients, 40%) of change to the off-clamp arm, in relationship with tumor's diameter and complexity [24]. At a lesser extent (21/150 patients, 14%), some cases randomly assigned to the on-clamp group were shifted to the off-clamp one as well, following the surgeon's preference.

Intention-to-treat analysis

The on-clamp (150 patients) and off-clamp (152 patients) were well balanced regarding demographic and anthropometric data, serum examinations, comorbidities, and clinical size. In particular, eGFR and split renal function and renal scintigraphy were equivalent. An imbalance was noted for median RENAL score (median value off- vs on-clamp 6 vs 7, $p < 0.001$, Table 1). Given the rate of cases shifted from the assigned treatment, the intention-to-treat analysis was hindered as poorly representative of the effective treatment received by patients.

Per-protocol analysis

The per-protocol analysis included only the patients who actually completed the treatment they were allocated to, represented by 129 on-clamp vs 91 off-clamp RAPNs. A statistically significant difference, with marginal clinical relevance, was noted in clinical tumor size (off-clamp vs on-clamp group, median diameter 2.2 vs 3.0 cm, $p < 0.001$), RENAL score (median 6 vs 7, $p < 0.001$), and prevalence of cardiac disease (10% vs 24%, $p = 0.02$) (Table 1).

Several differences emerged in intra-operative data: the off clamp procedures were preferentially done by retroperitoneal approach (22% vs 8%, $p = 0.005$), within a shorter operative time (115 min vs 120 min, $p = 0.005$) and less frequently with a single-layer renorrhaphy (65% vs 84%, $p = 0.01$). In addition, the subjective perception of severe bleeding was more frequent in off-clamp group (score ≥ 3 22% vs 9%, $p = 0.01$) (Supplementary Table 1).

Concerning the endpoints of the study, no statistically significant difference was found between groups at univariable analysis. Indeed, intra-operative EBL (off- vs on-clamp, 100 vs 100 ml, $p = 0.7$), post-operative complications rate (Overall 19% vs 26%, $p = 0.2$; Clavien ≥ 2 8% vs 12%, $p = 0.4$), post-operative anemia (Hb decrease > 2.5 g/dl 26% vs 27%,

Table 1 Baseline features according to intention-to-treat and per-protocol analysis

Intention-to-treat analysis	On-clamp ($n=150$)	Off-clamp ($n=152$)	p value
Gender			0.8
Female	62 (41.3)	60 (39.5)	
Male	88 (58.7)	92 (60.5)	
Age, years	63.0 (54.0–70.0)	66.0 (55.0–71.0)	0.2
BMI, kg/m^2	26.3 (24.7–28.6)	26.1 (24.2–28.4)	0.3
Platelets count	220.500 (181,250–268,750)	215,500 (185,000–259,250)	0.7
Hemoglobin, g/dl	14.0 (12.9–14.9)	14.3 (13.3–15.2)	0.2
Hematocrit, %	42.4 (40.0–44.7)	42.9 (40.2–45.7)	0.3
PT, %	98.0 (94.0–100.0)	99.0 (94.0–100.0)	0.6
PTT, s	29.9 (27.9–32.2)	29.9 (27.1–32.7)	0.9
GFR, ml/min	93.1 (80.0–110.0)	92.0 (78.4–108.4)	0.7
Operated kidney % SRF	48.3 (46.0–51.0)	49.0 (47.0–52.0)	0.3
Hypertension	78 (52)	88 (57.9)	0.4
Diabetes	19 (12.7)	17 (11.2)	0.7
Vascular disease	26 (17.3)	22 (14.5)	0.5
Cardiac disease	37 (24.8)	24 (15.9)	0.06
Urinary obstruction	2 (1.4)	0 (0)	0.2
ECOG performance status			0.1
0	109 (73.2)	126 (82.9)	
1	32 (21.5)	23 (15.1)	
>2	8 (5.4)	3 (2)	
Charlson's comorbidity index			0.6
0	88 (60.3)	93 (62.8)	
1	35 (24)	38 (25.7)	
2	11 (7.5)	8 (5.4)	
>2	12 (8.3)	9 (6.1)	
Clinical tumor size, cm	3.0 (2.2–4.0)	2.6 (2.0–3.7)	0.07
RENAL score	7.0 (5.2–8.0)	6.0 (5.0–7.0)	<0.001
Per-protocol analysis	On-clamp ($n=129$)	Off-clamp ($n=91$)	p value
Gender			0.8
Female	52 (40.3)	39 (42.9)	
Male	77 (59.7)	52 (57.1)	
Age, years	62.0 (53.0–70.0)	66.0 (54.5–70.0)	0.4
BMI, kg/m^2	26.0 (24.5–28.4)	26.2 (23.9–28.8)	0.9
Platelets count	221,000 (182,000–268,000)	214,000 (186,500–254,000)	0.4
Hemoglobin, g/dl	14.0 (13.0–14.9)	14.3 (13.2–15.1)	0.3
Hematocrit, %	42.0 (40.0–44.5)	42.5 (40.1–44.9)	0.5
PT, %	97.0 (93.0–100.0)	99.0 (95.0–100.0)	0.2
PTT, s	30.0 (27.9–32.2)	29.5 (27.1–32.0)	0.4
eGFR, ml/min	86.2 (73.1–96.0)	87.9 (78.1–100.3)	0.2
GFR, ml/min	93.1 (80.0–110.0)	97.0 (83.9–111.1)	0.3
Operated kidney % SRF	48.1 (45.9–51.0)	49.0 (47.0–51.4)	0.1
Hypertension	65 (50.4)	48 (52.7)	0.8
Diabetes	14 (10.9)	11 (12.1)	0.8
Vascular disease	21 (16.3)	10 (11)	0.3
Cardiac disease	31 (24.2)	10 (11.1)	0.02
Urinary obstruction	2 (1.7)	0 (0)	0.5
ECOG performance status			0.09
0	96 (75)	80 (87.9)	

Table 1 (continued)

Per-protocol analysis	On-clamp ($n=129$)	Off-clamp ($n=91$)	p value
1	25 (19.5)	9 (9.9)	
> 2	7 (5.5)	2 (2.2)	
Charlson's comorbidity index			0.7
0	78 (62.4)	54 (62.1)	
1	27 (21.6)	22 (25.3)	
2	10 (8)	6 (6.9)	
> 2	10 (8)	5 (5.7)	
Clinical tumor size, cm	3.0 (2.2–4.0)	2.2 (2.0–3.0)	< 0.001
RENAL score	7.0 (6.0–9.0)	6.0 (4.0–7.0)	< 0.001

PT prothrombin time, *PTT* partial thromboplastin time, *SRF* split renal function, *GFR* glomerular filtration rate, *ECOG* eastern cooperative oncology group

$p=0.9$; transfusion rate 3.4% vs 6.3%, $p=0.5$; re-intervention due to bleeding 1.1% vs 4%, $p=0.4$), AKI (4% vs 6%, $p=0.8$), and PSM (3.5% vs 8.2%, $p=0.1$) were similar (Supplementary Table 1).

To account for the baseline unbalances in tumor diameter and complexity, multivariable model analysis was performed too (Supplementary Table 2). Considering the on-clamp group as the reference category, a statistically significant difference was noted in the off-clamp group exclusively for EBL [odds ratio (OR)] 0.3, 95% confidence interval (CI) 0.08–0.52, $p=0.008$), while no significant differences emerged for the others endpoints (post-operative complications: OR 0.68, 95% CI 0.32–1.44, $p=0.3$; Hb decrease > 2.5 g/dl: OR 1.29, 95% CI 0.64–2.63, $p=0.5$; need for transfusions: OR 0.41, 95% CI 0.10–1.7, $p=0.2$; AKI: OR 1.01, 95% CI 0.27–3.76, $p=1$; PSM: OR 0.62, 95% CI 0.14–2.85, $p=0.5$).

Discussion

The CLOCK trial represents the largest randomized study attempting to assess whether an off-clamp vs an on-clamp approach to RAPN provides different outcomes. Notwithstanding the involvement of surgeons out of the RAPN learning curve and their direct involvement into the study design, the indication from randomization was disregarded in a relevant rate of cases. This mostly when the characteristic of tumors indicated on-clamp approach more suitable than the off-clamp one [24]. At a lesser extent, the surgeons shifted to off-clamp when the on-clamp approach was ethically considered as "overtreatment". This rate of shift appeared as impressive and attributable to the inclusion of masses with a wide degree of complexity and the clinical setting of a RCT. Unfortunately no comparisons with other experiences can be done, because this data so far was unreported.

These events favored a statistically significant unbalance in tumor's size and complexity that needed to be controlled by multivariable models. The herein reported comparison did not find any statistically significant difference in surgical and oncological safety between the off- vs on-clamp RAPN. Post-operative complications, anemia, AKI, and PSM were overlapping at rough comparisons and at multivariable analysis, although a favorable clinical trend, statistically insignificant, was noted for the off-clamp group. Only a statistically significantly reduced EBL was found, without clinical implications.

To the best of our knowledge, this is the largest cohort prospective randomized trial seeking for more definitive conclusion about the impact on perioperative outcomes of renal pedicle management during RAPN. These results could straight be generalized considering that the CLOCK trial was conducted within a "real life scenario" involving multiple surgeons and institutions and this should have mitigated the effects of single-surgeon-specific features. As previously reported [25], surgeon experience is a major driver of PN outcomes and the results of this study could be different in another "context". To address this issue, a detailed surgeon's profile was demanded, so that operators had a homogenous background. Furthermore, surgical context was well standardized, being patient's selection and surgical steps regulated by the study design. Definitely, the study was conducted under strict conditions concerning surgeons, patients (no CKD) and renal masses (RENAL up to 10), mainly with the intention to preserve patient's safety and favor the acceptance of a RCT regulating a surgical procedure. The results can be generalized to a considerable number of contemporary "robotic" institutions, generally provided by surgeons with similar features. At the same time, the study population is well representative of the majority of candidates to on- and off-clamp RAPN, since in presence of CKD or larger and more complex masses, most of surgeons will not opt for on- or off-clamp RAPN, respectively.

Reasonably, less experienced surgeons should expect a higher rate of transition from an attempted off- to on-clamp RAPN, and therefore during their learning curve they should limit this approach to the less complex masses. Originally, a standardized system—SIB score [20, 21]—described the dissection strategy, finding that off-clamp RAPNs were more frequently approached by enucleation, reasonably due to the intention to limit bleeding by dissecting on the plan of the tumor pseudocapsule.

Up-to-date, systematic reviews of the literature showed no impact of the technique used to manage the renal pedicle on either surgical or oncological outcomes of RAPN [26, 27]. However, the finding is debated because based on pooled analyses of mostly small sample size studies, affected by several confounders, selection bias, and heterogeneity in the surgical techniques used.

A recent propensity-score comparison matched the cases from two high-volume centers with exclusive off- or on-clamp approach [28]: 400 on-clamp vs 200 off-clamp RAPN patients were analyzed after balancing several patient's and tumor's features (including solitary kidney status, baseline eGFR, tumor size and RENAL score). The authors found no significant differences in key perioperative outcomes, confirming the literature trend once again.

Anderson et al. recently published a single-center single-surgeon prospective RCT addressing the comparison of on-clamp vs off-clamp RAPN [29]. Thirty-seven vs 34 patients were analyzed, but the observed difference in the % change of GFR between the treatment groups did not mirrored what was hypothesized at the power analysis time. A reasonable explanation might reside in the small sample size. The main point of the Anderson's RCT was finding comparable outcomes, as well as the only one shift from off-clamp to clamp detection probably sponsored by the single-surgeon setting of the study [30].

Noteworthy, our study showed no difference in the early functional outcomes, described as the change in eGFR and development of AKI. Conversely, the previous literature reported off-clamp approach to provide an advantage on immediate post-operative renal function [26–28]. Given the well-recognized negative prognostic role of AKI on late renal function [31], our finding offers another element in favor of a clamped approach with restricted ischemia time. Probably, other markers such as serum cystatin C and urinary neutrophil gelatinase-associated lipocalin would allow for an earlier detection of such damage to highlight a difference between to clamp or not [32]. The final analysis of the CLOCK trial, focused on the primary endpoint, i.e., the global and split renal function at 3/6 months, will provide further elements to this discussion.

Our data confirm that during off-clamp approach, there is a subjective perception of major bleeding, despite the EBL was definitely lower at multivariable analysis. There is consensus among the detractors of this approach that bleeding worsens the quality of resection and exposes to the risk of PSM. On the other side, the supporters claim that the direct vision of bleeders allows a more effective renorrhaphy. The results of the present trial mitigate the controversy showing equal safety between approaches and support the safety of the clampless one whenever mandatorily required, as in single kidney, baseline CKD or renal artery disease.

Despite the randomized controlled design, the present study is not devoid of limitations. The major one is that the study was not powered on the set of endpoints here investigated and, together with the lack of long-term controls, suggests caution before taking definitive conclusions, despite the consistency of results showing the equivalence between groups. Nevertheless, the results homogeneously show the equivalence between groups, improving the reliability of findings. Another major limitation is given by the unbalances of baseline tumor's dimensions and complexity that emerged as statistically significant, although with marginal clinical relevance (median difference of 0.8 cm in tumor size and 1 point in RENAL score). As a consequence, the "strengths" of randomization concerning the intention-to-treat analysis were lost, so that it was hindered as poorly representative of the received treatment. Such a consideration enters within the ongoing debate on underreported limits of RCTs, especially in surgery [33]. Other imbalances concerned trans- vs retroperitoneal approach and renorrhaphy technique, but were not included into models given that preliminary exploratory analyses—not shown—excluded a significant relationship with outcomes. However, the influence of these factors on intra- and post-operative events cannot be completely excluded, also considering the previous reports [4, 7, 34], and did not emerge reasonably due to the small size of the cohort. In addition, only expert surgeons and referral institutions joined the project and patients had baseline eGFR > 60 ml/min, a contralateral normal kidney and a renal mass RENAL ≤ 10, following the inclusion criteria. Another bias given by unmeasurable surgeon's skills, as well his/her attitude and experience towards a specific clamping approach should be considered. Finally, it could be hypothesized that the peculiar setting of a surgical RCT could have prompted some additional care to preserve patient's safety influencing the results with respect to the daily clinical practice.

Conclusions

The present study shows that the off-clamp approach to RAPN offers at least equal safety than on-clamp in terms of intra-, post-operative complications and occurrence of PSM.

Author contributions Protocol/project development: Alessandro Antonelli, Luca Cindolo, Marco Sandri, Andrea Minervini. Data collection or management: Filippo Annino, Marco Carini, Antonio Celia, Carlo, D'Orta, Bernardino De Concilio, Maria Furlan, Valentina Giommoni, Manuela Ingrosso, Andrea Mari, Gianluca Muto, Roberto Nucciotti, Angelo Porreca, Giulia Primiceri, Luigi Schips, Francesco Sessa, AlessandroVeccia. Data analysis: Marco Sandri, Alessandro Antonelli, Andrea Minervini, Riccardo Bertolo. Manuscript writing/editing: Alessandro Antonelli, Riccardo Bertolo, Marco Sandri, Alessandro Veccia, Andrea Minervini

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (NP 1814) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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