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Impact of the off-clamp endoscopic robot-assisted simple enucleation (ERASE) of clinical T1 renal tumors on the postoperative renal function: Results from a matched-pair comparison

Andrea Mari, Simone Morselli, Francesco Sessa, Riccardo Campi, Fabrizio Di Maida, Isabella Greco, Giampaolo Siena, Agostino Tuccio, Gianni Vittori, Sergio Serni, Marco Carini, Andrea Minervini*

Department of Urology, University of Florence, Careggi Hospital, Florence, Italy

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ABSTRACT

Purpose: To evaluate the surgical and functional outcomes of a matched-paired series of on-clamp vs off-clamp endoscopic robot-assisted simple enucleation (ERASE) and standardized renorrhaphy in a tertiary referral institution, to search for predictors of functional drop after surgery and to investigate the influence of off-clamp technique in patients presenting these characteristics.

Materials and methods: A matched-pair comparison of 120 on-clamp vs 120 off-clamp over 491 patients treated with ERASE was performed. Perioperative and functional outcomes were compared between groups.

Results: Patients treated with on-clamp and off-clamp technique had comparable complication and positive surgical margin rate. The off-clamp group had a significantly lower eGFR drop compared to the on-clamp group at 3rd postoperative day (POD) (1% vs 7%, $p = 0.0001$) and at 30th POD (2.5% vs 9%, $p = 0.01$) from baseline. This difference lost its statistical significance at 6th month and at last follow-up (median 40 months). At multivariable analysis the Charlson comorbidity index (OR 2.06, $p < 0.0001$), uncontrolled type 2 diabetes mellitus (OR 4.13, $p < 0.001$) were independent predictive factors of a >15% eGFR drop from baseline to last follow-up. In a subanalysis over 64 comorbid patients, those patients who underwent off-clamp ERASE had a significantly lower eGFR drop compared to the comorbid counterpart during the whole follow-up.

Conclusions: The off-clamp ERASE is a safe surgical technique with a significantly lower renal function drop compared to on-clamp ERASE in the early perioperative time. Patients with comorbidity might represent a subgroup of patients having a functional benefit after off-clamp RAPN even in the long-term period.

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Introduction

In recent years, the long-term implications of decreased renal function (RF) as a result of renal cancer surgery have been

increasingly recognized and various strategies to minimize the incidence of postoperative functional impairment have been reported [1]. Partial nephrectomy (PN) now represents the standard treatment for localized renal tumors over the complete removal of the organ [2]. In this surgical setting, volume of preserved parenchyma, ischemia time and quality of the operated kidney are the main factors that affect functional recovery [3].

Simple enucleation (SE), defined as the blunt excision of the tumor without a visible margin following the natural cleavage plane between the tumor capsule and healthy parenchyma, can maximize the amount of preserved renal parenchyma [4–7]. Pedicle clamping is performed to ensure a bloodless field and to

Abbreviations: American Society of Anesthesiologists, (ASA); Charlson comorbidity index, (CCI); Endoscopic robot-assisted simple enucleation, (ERASE); Estimated glomerular filtration rate, (eGFR); Modification of diet in renal disease, (MDRD); Partial nephrectomy, (PN); Robot-assisted partial nephrectomy, (RAPN); Simple enucleation, (SE); Warm ischemia time, (WIT).

* Corresponding author. Department of Urology, University of Florence, Careggi Hospital, San Luca Nuovo, Firenze, Florence, Italy.

E-mail address: andreamine@libero.it (A. Minervini).

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permit a perfect visualization during tumor resection. However, the use of off-clamp procedures is increasingly adopted to maximize the functional outcome after conservative surgery as prolonged ischemia time has been associated with a significantly higher RF impairment [8]. Nevertheless, a definitive functional benefit of off-clamp PN has not been proved yet [3,9,10]. Beyond a possible protective effect on postoperative RF, off-clamp PN could be associated with a higher complication and positive surgical margin (SM) rate due to a higher bleeding and a subsequent suboptimal vision [11]. Above all, plays the quality of renal parenchyma and comorbidities that are tightly related to kidney quality that represent unmodifiable factors that finally strongly affect postoperative RF setting the limits of functional recovery after PN [1,3,12,13].

The aim of this study was to evaluate the surgical and functional outcomes of a matched-paired series of on-clamp vs off-clamp endoscopic robot-assisted SE (ERASE) in a tertiary referral institution thus evaluating the role of pedicle clamping in a series of patients that had the maximum amount of vascularized renal parenchyma spared limiting confounding factors. The secondary aim was to search for predictors of functional drop after surgery and the influence of off-clamp ERASE in patients presenting these characteristics.

Materials and methods

From January 2011 to December 2014, data from 491 consecutive patients treated with ERASE were prospectively collected. All cases were performed by three surgeons highly experienced in open and laparoscopic kidney surgery. The first 25 cases performed by each surgeon, as part of the learning curve [14], and 35 zero-ischemia cases were excluded from the analysis. Overall, 344 patients, of which 120 (34.9%) undergoing off-clamp ERASE and 224 (65.1%) on-clamp ERASE, were finally enrolled.

The description of the surgical technique was reported in previous papers [15,16]. For the present series, a 4S Da Vinci robot (Intuitive Surgical, Sunnyvale, CA, USA) in a three-arm configuration was always used. No healthy renal tissue was voluntarily taken during ERASE. Renorrhaphy was performed in a standardized double-layer running technique. The first suture involved the medulla that was superficially sutured (2-0 monofilament with 26 mm, 1/2 circle round bodied needle), taking care of closing any vessel and collecting system eventually opened during the extirpative phase. The second layer involved the cortical closure (2-0 polyglactin 910 suture with a 31 mm, 1/2 circle round bodied needle). In the off-clamp procedures, hilar vessels were routinely isolated before tumor resection in the majority of cases. In all on-clamp ERASEs, the clamp was always removed before the cortical layer suturing.

Comorbidity status was evaluated by Charlson comorbidity index (CCI) and the American Society of Anesthesiologists (ASA) physical status (PS) classification system and care was taken to record history of hypertensive cardiomyopathy, myocardial infarction, uncontrolled type 2 diabetes mellitus (T2DM) and uncontrolled hypertension. Surgical indication was defined as elective (localized unilateral RCC with healthy contralateral kidney), relative (localized unilateral RCC with the coexistence of comorbidities such as uncontrolled diabetes, hypertension or lithiasis that could potentially affect kidney function in the future) and imperative (bilateral tumors, multiple tumors, moderate to severe renal failure or tumors involving an anatomically or functionally solitary kidney).

The severity of complications was graded according to the modified Clavien classification [17]. The Trifecta rate was calculated as the combination of WIT < 25 min, negative SM, and no complications [18]. Patients were followed in outpatient department

every 4 months during the first two years and every six months thereafter with blood tests and ultrasound imaging. Furthermore, a yearly thorax and abdomen CT scan was performed. RF was assessed using the estimated glomerular filtration rate (eGFR) calculated with the modification of diet in renal disease (MDRD) equation. This study was approved by the local ethics committee, and informed consent was collected for all patients.

Statistical analysis

A propensity-score matching was performed to adjust for preoperative variables with multivariable logistic regression based on the covariates: tumor side, polar tumor location, clinical T, calyceal system, and sinus compression/invasion. The matching was carried out with a 1:1 ratio with respect to the surgical technique (120 off-clamp vs 120 on-clamp ERASEs) with a C statistic of 0.71 [19]. The Student t-test and the Mann-Whitney-U test were used to compare continuous to categorical variables and the Pearson's chi-square test was used to compare two categorical variables. A logistic regression was used for multivariable analysis. Statistical significance was set at $p < 0.05$. All reported p-values were two-sided. Analyses were carried out with RStudio graphical interface v.0.98 for R software environment v.3.0.2, using the packages *MatchIt*, *rms* and *stats*, and with STATA v.14.1 (StataCorp LP, College Station, TX).

Results

Preoperative characteristics of the off-clamp ($n = 120$) and on-clamp ($n = 120$) ERASE groups after propensity-score matching analysis are described in Table 1. The two groups had comparable age, clinical T stage and PADUA score. Of note, clinical T1a cases represented 90% and 89.2% of the off-clamp and the on-clamp groups, respectively; and no patient had a PADUA score ≥ 10 in both groups.

Surgical and postoperative characteristics are described in Table 2. In the on-clamp group median WIT was 15 min (IQR 12–19) and procedures with a WIT > 20 and > 25 min were 11.6% and 5.0%, respectively. No intraoperative surgical complications were registered. The off-clamp and on-clamp groups had a 3.3% and a 2.5% of overall surgical postoperative complication rate, respectively ($p = 0.91$). Positive SM and trifecta outcome were comparable between the two study groups ($p = 0.99$ and $p = 0.42$, respectively). Patients submitted to off-clamp ERASE had a significantly lower median percentage of eGFR drop compared to those submitted to on-clamp ERASE at 3rd POD (1% vs 7%, $p = 0.001$) and at 30th POD (2.5% vs 9%, $p = 0.01$) from baseline.

Functional follow-up outcomes are summarized in Table 3. Median follow-up was 39 and 41 months in off-clamp and on-clamp groups, respectively. Two (1.6%) patients in the on-clamp group and one (0.8%) patient treated with off-clamp ERASE had ipsilateral kidney recurrence distant from the primary localization and were therefore excluded from the functional follow-up analysis. No distant recurrences were reported. Patients submitted to on-clamp ERASE had a higher median percentage of eGFR drop from baseline at 6th month (7% vs 3%, $p = 0.27$) and at last follow-up (6.5% vs 3%, $p = 0.31$) compared to those submitted to off-clamp surgery, although it did not reach statistical significance. The trends of the absolute levels of Δ eGFR during follow-up from baseline in each group are shown in Fig. 1.

In the matched series, at univariate analysis a CCI ≥ 2 ($p < 0.001$), the ASA-PS score ≥ 3 ($p = 0.02$), the hypertensive cardiomyopathy ($p = 0.02$), the uncontrolled T2DM ($p < 0.001$) and preoperative eGFR ($p < 0.001$) were significantly associated with a >15% drop of

Table 1

Descriptive analysis of preoperative characteristics from a matched cohort of patients treated with off-clamp and on-clamp ERASE for clinical T1 renal tumors.

Preoperative Features	ERASE				p	
	Off-clamp (n = 120)		On-clamp (n = 120)			
Gender, n. %	Male	73	60.8%	72	60.0%	0.90
	Female	47	39.2%	48	40.0%	
Age (years), mean SD		62.2	12.2	61.5	11.9	0.17
BMI, median IQR		25.7	23.0–30.1	25.5	21.9–29.1	0.13
CCI score, median IQR		0.0	0.0–1.0	1.0	0.0–2.0	0.34
CCI score ≥ 2 , n. %		34	28.3%	30	25.0%	0.56
ASA PS score, median IQR		2.0	1.0–2.0	2.0	1.0–2.0	0.67
ASA PS score ≥ 3 , n. %		15	12.5%	14	11.7%	0.84
ECOG score ≥ 1 , n. %		8	6.7%	9	7.5%	0.89
Hypertensive cardiomyopathy, n. %		10	8.3%	16	13.3%	0.21
History of myocardial infarction, n. %		19	15.8%	17	14.2%	0.72
Uncontrolled DMT2, n. %		6	5.0%	10	8.3%	0.44
Surgical indication, n. %	Elective	87	72.5%	85	70.8%	0.60
	Relative	32	26.7%	32	26.7%	
	Imperative	1	0.8%	3	2.5%	
Clinical T, n. %	T1a	108	90.0%	107	89.2%	0.83
	T1b	12	10.0%	13	10.8%	
Tumor side, n. %	Right	54	45.0%	57	47.5%	0.70
	Left	66	55.0%	63	52.5%	
Clinical diameter, median IQR		2.5	1.6–3.3	2.8	2.1–3.5	0.18
Tumor location, n. %	Polar sup.	35	29.2%	44	36.7%	0.46
	Mesorenal	58	48.3%	53	44.2%	
	Polar inf.	27	22.5%	23	19.2%	
Tumor growth pattern, n. %	$\geq 50\%$ Exophytic	84	70.0%	83	69.2%	0.71
	$< 50\%$ Exophytic	34	28.3%	33	27.5%	
	Entirely endophytic	2	1.7%	4	3.3%	
Renal sinus compression/invasion, n. %		4	3.3%	3	2.5%	0.70
Calyceal system compression/invasion, n. %		6	5.0%	6	5.0%	0.99
PADUA score, median IQR		7.0	6.0–8.0	7.0	6.0–7.5	0.59
PADUA score complexity index, n. %	6–7	90	76.3%	85	73.3%	0.60
	8–9	28	23.7%	31	26.7%	
Preoperative haemoglobin, mean SD		14.2	1.4	14.3	1.4	0.88
Preoperative creatinine, median IQR		0.83	0.73–0.98	0.82	0.70–0.6	0.30
Preoperative eGFR using MDRD, median IQR		86.7	71.7–104.9	90.1	75.5–105.8	0.75
Preoperative CKD stage using eGFR, n. %	1	60	50.0%	56	46.7%	0.57
	2	47	39.2%	53	44.2%	
	3A	6	5.0%	6	5.0%	
	3B	4	3.3%	3	2.5%	
	4	3	2.5%	2	1.7%	

ASA PS, American Society of Anesthesiologists Physical Status; BMI, body mass index; CCI, Charlson comorbidity index; DMT2, Diabetes Mellitus type 2; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, modification of diet in renal disease; PADUA, Preoperative aspects and dimensions used for an anatomical classification of renal tumours; SD, standard deviation.

Table 2

Descriptive analysis of surgical and postoperative characteristics from a matched cohort of patients treated with off-clamp and on-clamp ERASE for clinical T1 renal tumors.

Surgical and postoperative features	ERASE				p
	Off-clamp (n = 120)		On-clamp (n = 120)		
Ischemia time (min), median IQR	–	–	15	12–19	–
Ischemia time > 20 min, n. %	–	–	14	11.6%	–
Ischemia time > 25 min, n. %	–	–	6	5.0%	–
Estimated blood loss (mL), median IQR	100	50–150	90	50–150	0.84
Intraoperative time, median IQR	120	95–150	150	120–180	<0.0001
Length of staying (days), median IQR	4	3–5	4	3–5	0.21
Postoperative surgical complications, n. %	4	3.3%	3	2.5%	0.91
• Postop. Transfusions, n. % (Clavien 2)	3	2.5%	1	0.8%	0.62
• Superselective embolizations, n. % (Clavien 3)	1	0.8%	2	1.7%	0.86
Postoperative medical complications, n. %	4	3.3%	4	3.3%	0.99
• Pneumonia, n. % (Clavien 2)	2	1.7%	2	1.7%	0.99
• Postoperative arrhythmias, n. % (Clavien 2)	0	0.0%	1	0.8%	0.74
• DVT, n. % (Clavien 2)	1	0.8%	0	0.0%	0.59
• AKI, n. % (Clavien 1)	0	0.0%	1 (stage 1)	0.8%	0.69
Positive surgical margins, n. %	2	1.7%	2	1.7%	0.99
Trifecta achievement, n. %	108	90.0%	104	86.7%	0.42
Preop-3rd POD Δ eGFR, median IQR	1.1	0.0–8.5	5.5	0.0–15.6	0.001
Preop-3rd POD Δ % eGFR, median IQR	1.0%	0–10.8%	7.0%	0–16.2%	0.001
Preop-30th POD Δ eGFR, median IQR	3.2	0.0–9.2	8.9	2.5–19.7	0.01
Preop-30th POD Δ % eGFR, median IQR	2.5%	0–13.0%	9.0%	0–17.0%	0.01

See also Table 1. AKI, acute kidney injury; DVT, deep vein thrombosis; POD postoperative day.

Table 3

Descriptive analysis of follow-up characteristics from a matched cohort of patients treated with off-clamp and on-clamp ERASE for clinical T1 renal tumors and with negative oncologic follow-up.

Follow-up variables	ERASE				p
	Off-clamp (n = 119)	On-clamp (n = 118)			
Months of follow-up, median IQR	39.5	31.0–49.0	41.0	28.0–51.0	0.85
Preop-6th month Δ eGFR, median IQR	2.7	0.0–9.0	5.9	0.0–13.4	0.18
Preop-6th month Δ % eGFR, median IQR	3.0%	0–14.5%	7.0%	0–17.0%	0.27
Preop-last fwup Δ eGFR, median IQR	2.9	0.0–9.3	6.1	0.0–15.6	0.30
Preop-last fwup Δ % eGFR, median IQR	3.0%	0–14.5%	6.5%	0–20.0%	0.31
Preop-last fwup $\leq 15\%$ Δ % eGFR, n. %	99	83.2%	87	74.1%	0.08
	20	16.8%	31	25.9%	

See Table 1.

eGFR from baseline to the last follow-up, while on-clamp ERASE, gender, age, BMI, clinical T, PADUA score were not. At multivariable analysis the CCI ≥ 2 (OR 2.06, 95%CI 1.47–2.88, $p < 0.0001$) and uncontrolled T2DM (OR 4.13, 95%CI 2.98–13.45, $p < 0.001$) were independently associated with a $>15\%$ eGFR drop from baseline at last follow-up (Table 4).

A subanalysis of patients who had CCI ≥ 2 (all patients with uncontrolled T2DM were included in this group) was conducted from the matched series: 30 patients underwent off-clamp ERASE (comorbid off-clamp group) and 34 on-clamp ERASE (comorbid on-clamp group). Results are shown in Supplementary Table 1. The two groups had comparable epidemiological and nephrometric features. The off-clamp comorbid group reported a significantly lower median percentage eGFR drop compared to the on-clamp group at 3rd POD (3.5% vs 8%, $p = 0.02$), at 30th POD (4.0% vs 11.5%, $p = 0.01$), at 6th month (4% vs 13.5%, $p = 0.02$) and at last follow-up (7.5% vs 15%, $p = 0.01$) from baseline.

Table 4

Multivariable analysis for $>15\%$ -delta eGFR at last follow-up from baseline on 237 patients treated with off-clamp and on-clamp ERASE for clinical T1 renal tumors and with negative oncologic follow-up.

Preoperative and surgical factors	Multivariable analysis for preop-last fwup $>15\%$ Δ eGFR		
	OR	95% CI	p
CCI ≥ 2	2.06	1.47–2.88	<0.0001
Hypertensive cardiomyopathy	1.32	0.40–4.29	0.65
Uncontrolled Diabetes Mellitus type 2	4.13	2.98–13.45	0.001
Preoperative eGFR (continuous)	0.98	0.97–1.00	0.15
Pedicle clamping	1.40	0.66–2.96	0.38

Discussion

The lower incidence of postoperative acute kidney injury and chronic kidney disease (CKD) after off-clamp PN in the solitary kidney model has increased use of this approach for all patients, including those with solitary tumour and normal contralateral kidney. Off-clamp conservative surgery has increasingly been used to avoid the detrimental effect of ischemia on RF [3]. Although the functional benefit of the off-clamp technique has been suggested in several series both for patients with solitary kidney [20,21] and for those with normal contralateral kidney [8,11], most of the studies do not include data on resection and reconstruction technique thus potentially either underestimate or overrate the actual effect of arterial clamping.

With regard to tumor resection techniques wider resection margins probably affect the quantity of parenchyma preserved and consequently RF but do not lead to improved cancer control [1,22,23]. Indeed, in the recent years, prospective and retrospective studies from many groups have consistently demonstrated that SE achieves optimal oncologic outcomes and have confirmed that it is at least non-inferior to standard PN (enucleoresection and resection) in terms of positive margin and local recurrence rate for

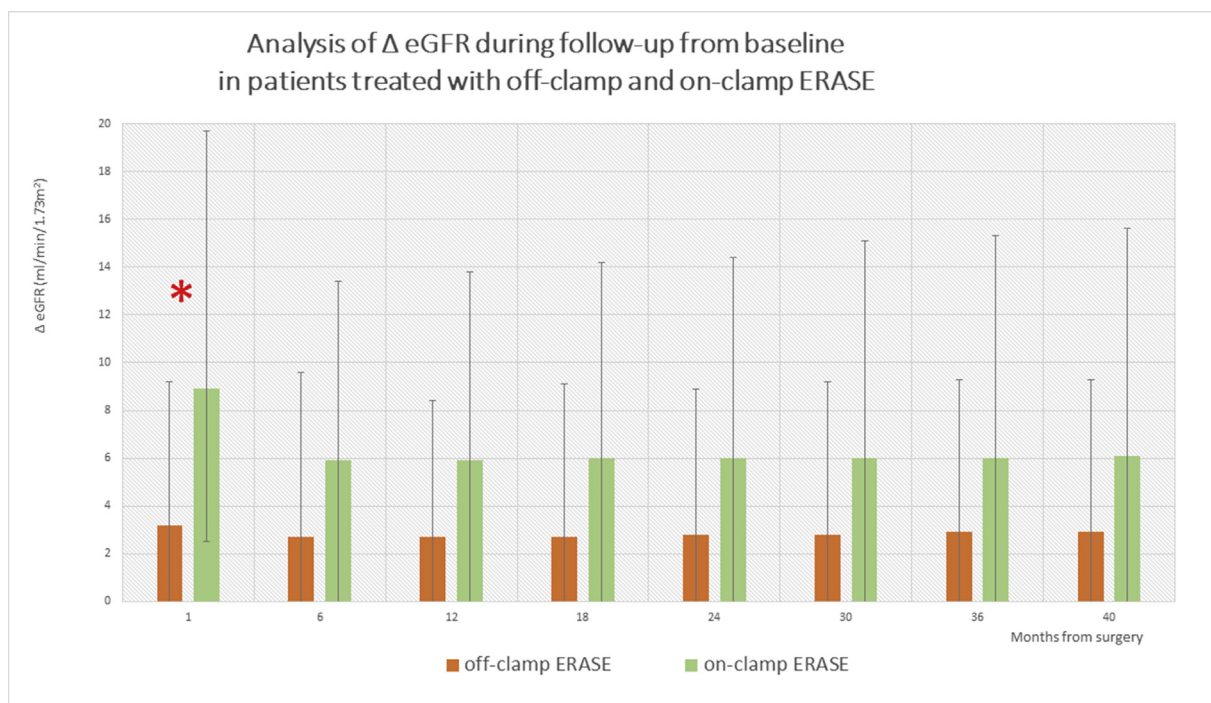


Fig. 1. Analysis of Δ eGFR during follow-up from baseline in patients treated with off-clamp and on-clamp ERASE. Colored bars represent medians, vertical lines the interquartile ranges. * represent a significant difference between the values recorded in the two groups.

malignant renal tumors [4–7,22,24]. Even the most recent EAU Guidelines do not recommend a safe margin that need to be resected along with the tumor during PN to achieve oncological efficacy [2]. Furthermore, a variable amount of healthy renal tissue is incorporated and potentially injured by renorrhaphy to achieve hemostasis. However, renal reconstruction is differently performed and not standardized. Finally, the postoperative RF have shown to be tightly related to preoperative kidney quality and comorbidities that might influence the impact of the aforementioned modifiable factors.

In the present study, the surgical and functional outcomes were analyzed from a highly selected matched-pair comparison of patients who underwent off-clamp ($n = 120$) and on-clamp ($n = 120$) ERASE with standardized renorrhaphy in a tertiary referral institution.

In our series, off-clamp ERASE was not shown to be harmful or decrease Trifecta rate compared to on-clamp ERASE. Indeed, patients treated with off-clamp and on-clamp ERASE had comparable postoperative surgical ($p = 0.91$) and medical ($p = 0.99$) complication rate, positive SM ($p = 0.99$) and trifecta ($p = 0.42$) rate. Consistent with our results, Kaczmarek et al. reported no differences in terms of postoperative complication, SM, and transfusion rates in comparison to a control group of on-clamp robotic PN [11]. Of note, in the CLamp vs Off Clamp Kidney during PN (CLOCK), an Italian multicenter randomized clinical trial (ClinicalTrials.gov NCT02287987) started in September 2014 with the aim to compare RF preservation between the two techniques, the preliminary results carried out from 137 patients showed that patients who underwent off-clamp RAPN had an increased estimated blood loss (160 vs 102 mL), while the operative time, complication and SM rates were comparable between the two groups [25]. Indeed, the achievement of cancer clearance after conservative renal surgery and the safety of the intervention are paramount. Therefore, we investigated the functional outcome. Patients treated with off-clamp ERASE had a significantly lower eGFR drop from baseline at 3rd POD ($p = 0.001$) and at 30th POD ($p = 0.01$) in comparison to those treated with on-clamp ERASE. However, this difference lost its statistical significance at 6th month and at last follow-up. These results demonstrate that renal clamping determine an acute renal cellular injury thus influencing the overall RF at 3rd and at 30th POD in patients undergoing ERASE [26]. The ipsilateral RF recovery after a moderate clamping time (WIT > 25 min occurred in 5% of patients with no cases having WIT > 30 min) together with a compensatory hypertrophy of the non-affected kidney may explain the global RF improvement in patients after on-clamp ERASE at 6th month and at last follow-up [20,26].

The beneficial effect of the off-clamp approach on the early and definitive functional recovery after PN is still unclear and represents a matter of discussion within the urological literature. Concordantly, Komninos et al. reported that the off-clamp and selective artery clamp techniques during RAPN had a significantly lower eGFR drop compared to on-clamp cases at 7th POD ($p < 0.01$) [10]. However, after the sixth postoperative month, the global RF was not significantly influenced by the hilum management (as long as WIT was < 30 min). Similarly, Porpiglia et al. reported that the split RF assessed using renal scan was not significantly different in patients undergoing laparoscopic PN with off-clamp vs. modest (< 25 min) ischemia [9]. Conversely, Trehan in a meta-analysis of six observational comparative studies reported a significantly long-term lower fall in eGFR in patients who underwent off-clamp PN compared to those who underwent on-clamp PN [27]. However, the Author concluded that the longer follow-up of one of the study analyzed, compared to the others might have had a possible influence on the meta-analysis [27]. The present evidence suggests that a controlled WIT may probably not affect the functional

outcome in the majority of patients. However, this may not be true in comorbid patients.

In the present study, CCI score ≥ 2 and uncontrolled T2DM resulted to be the only factors that correlated with postoperative RF at last follow up with a 2.06 and a 4.13-fold risk to develop a > 15% delta eGFR drop from baseline. Conversely, preoperative RF and pedicle clamping were not independently associated with long-term RF impairment. Therefore, we conducted a subanalysis of patients who had a CCI score ≥ 2 from the two matched cohorts (Comorbid patients). All patients with T2DM were included in the subanalysis as having a CCI score ≥ 2 . Comorbid patients treated with off-clamp ERASE reported a significantly lower RF drop after surgery ($p = 0.02$) and at last follow-up ($p = 0.01$) in comparison to comorbid patients treated with on-clamp ERASE. This evidence may support a selective indication of off-clamp technique whenever technically feasible in patients with comorbidities (CCI score ≥ 2) to have a significantly lower RF loss.

The present study displays some limitations. Given the retrospective nature of the study and the lack of classification system in the past, no objective classification of SE could have been made in this study and future trials addressing the functional outcomes of different resection techniques should use standardized metrics to reduce this potential source of bias [28–30]. The patients involved in the matched pair analysis study had a low or mid, but not high complexity score tumors and only 10% of tumors were T1b renal tumors. For this reason, the study analyzes mainly the influence of off-clamp ERASE in this specific subgroup of tumors but it is also true that off-clamp techniques are mostly employed in tumors with this level of complexity although precise inclusion criteria for off-clamp PN have never been reported in the literature. In this regard, the CLOCK study might shed light on the real clinical benefit of the off-clamp technique and on the indications of off-clamp procedure according to the level of tumor complexity [25]. The RF impairment was analyzed based on eGFR calculated by the MDRD method, while neither novel markers of acute renal impairment nor renal scans were used.

However, it has several strengths: in fact, although the importance of non-modifiable factors on functional outcomes have been already reported for standard PN, in this study cases were selected from a large prospectively maintained database, resection technique and renorrhaphy were homogeneous throughout the study thus limiting the confounding effect of these factors on the final results. The variability of baseline RF depicts an overview of the patients who are conservatively treated for a renal tumor as in a real life scenario. Finally, no previous studies have analyzed the impact of off-clamp procedure in SE.

Conclusions

Off-clamp ERASE seems to be a safe and feasible technique providing comparable perioperative outcomes and a significantly lower RF drop within one month from baseline compared to on-clamp ERASE. However, this difference lost its statistical significance at 6th month and at last follow-up. Patients with a CCI score ≥ 2 and an uncontrolled diabetes mellitus might represent a subgroup of patients having a functional benefit after off-clamp RAPN even in the long-term period.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

No study sponsor has been involved.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejso.2018.01.093>.

References

- [1] Volpe A, Blute ML, Ficarra V, Gill IS, Kutikov A, Porpiglia F, et al. Renal ischemia and function after partial nephrectomy: a collaborative review of the literature. *Eur Urol* 2015;68:61–74. <https://doi.org/10.1016/j.eururo.2015.01.025>.
- [2] Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol* 2015;67:913–24. <https://doi.org/10.1016/j.eururo.2015.01.005>.
- [3] Mir MC, Ercole C, Takagi T, Zhang Z, Velet L, Remer EM, et al. Decline in renal function after partial nephrectomy: etiology and prevention. *J Urol* 2015;193:1889–98. <https://doi.org/10.1016/j.juro.2015.01.093>.
- [4] Lapini A, Serni S, Minervini A, Masieri L, Carini M. Progression and long-term survival after simple enucleation for the elective treatment of renal cell carcinoma: experience in 107 patients. *J Urol* 2005;174:57–60. <https://doi.org/10.1097/01.ju.0000162019.45820.53>. discussion 60.
- [5] Minervini A, Ficarra V, Rocco F, Antonelli A, Bertini R, Carmignani G, et al. Simple enucleation is equivalent to traditional partial nephrectomy for renal cell carcinoma: results of a nonrandomized, retrospective, comparative study. *J Urol* 2011;185:1604–10. <https://doi.org/10.1016/j.juro.2010.12.048>.
- [6] Schiavina R, Serni S, Mari A, Antonelli A, Bertolo R, Bianchi G, et al. A prospective, multicenter evaluation of predictive factors for positive surgical margins after nephron-sparing surgery for renal cell carcinoma: the record1 Italian project. *Clin Genitourin Cancer* 2015. <https://doi.org/10.1016/j.clgc.2014.08.008>.
- [7] Minervini A, Campi R, Sessa F, Derweesh I, Kaouk JH, Mari A, et al. Positive surgical margins and local recurrence after simple enucleation and standard partial nephrectomy for malignant renal tumors: systematic review of the literature and meta-analysis of prevalence. *Minerva Urol Nefrol* 2017. <https://doi.org/10.23736/S0393-2249.17.02864-8>.
- [8] Kim EH, Tanagho YS, Sandhu GS, Bhayani SB, Figenshau RS. Off-clamp robot-assisted partial nephrectomy for complex renal tumors. *J Endourol* 2012;26:1177–82. <https://doi.org/10.1089/end.2012.0353>.
- [9] Porpiglia F, Bertolo R, Amparore D, Podio V, Angusti T, Veltri A, et al. Evaluation of functional outcomes after laparoscopic partial nephrectomy using renal scintigraphy: clamped vs clampless technique. *BJU Int* 2015;115:606–12. <https://doi.org/10.1111/bju.12834>.
- [10] Komninos C, Shin TY, Tulliao P, Han WK, Chung BH, Choi YD, et al. Renal function is the same 6 months after robot-assisted partial nephrectomy regardless of clamp technique: analysis of outcomes for off-clamp, selective arterial clamp and main artery clamp techniques, with a minimum follow-up of 1 year. *BJU Int* 2015;115:921–8. <https://doi.org/10.1111/bju.12975>.
- [11] Kaczmarek BF, Tanagho YS, Hillyer SP, Mullins JK, Diaz M, Trinh Q-D, et al. Off-clamp robot-assisted partial nephrectomy preserves renal function: a multi-institutional propensity score analysis. *Eur Urol* 2013;64:988–93. <https://doi.org/10.1016/j.eururo.2012.10.009>.
- [12] Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Renal function after partial nephrectomy: effect of warm ischemia relative to quantity and quality of preserved kidney. *Urology* 2012;79:356–60. <https://doi.org/10.1016/j.urology.2011.10.031>.
- [13] Mari A, Antonelli A, Bertolo R, Bianchi G, Borghesi M, Ficarra V, et al. Predictive factors of overall and major postoperative complications after partial nephrectomy: results from a multicenter prospective study (The RECORD 1 project). *Eur J Surg Oncol* 2017;43:823–30. <https://doi.org/10.1016/j.ejso.2016.10.016>.
- [14] Pierorazio PM, Patel HD, Feng T, Yohannan J, Hyams ES, Allaf ME. Robot-assisted versus traditional laparoscopic partial nephrectomy: comparison of outcomes and evaluation of learning curve. *Urology* 2011;78:813–9. <https://doi.org/10.1016/j.urology.2011.04.065>.
- [15] Minervini A, Tuccio A, Masieri L, Veneziano D, Vittori G, Siena G, et al. Endoscopic robot-assisted simple enucleation (ERASE) for clinical T1 renal masses: description of the technique and early postoperative results. *Surg Endosc Other Interv Tech* 2015. <https://doi.org/10.1007/s00464-014-3807-0>.
- [16] Serni S, Vittori G, Masieri L, Gacci M, Lapini A, Siena G, et al. Robotic vs open simple enucleation for the treatment of T1a–T1b renal cell carcinoma: a single center matched-pair comparison. *Urology* 2014. <https://doi.org/10.1016/j.urology.2013.08.080>.
- [17] Yoon PD, Chalasani V, Woo HH. Use of Clavien-Dindo classification in reporting and grading complications after urological surgical procedures: analysis of 2010 to 2012. *J Urol* 2013;190:1271–4. <https://doi.org/10.1016/j.juro.2013.04.025>.
- [18] Khalifeh A, Autorino R, Hillyer SP, Laydner H, Eyraud R, Panumatrasamee K, et al. Comparative outcomes and assessment of triecta in 500 robotic and laparoscopic partial nephrectomy cases: a single surgeon experience. *J Urol* 2013;189:1236–42. <https://doi.org/10.1016/j.juro.2012.10.021>.
- [19] Rosenbaum PRB. The central role of the propensity score in observational studies for causal effects. *Biometrika* Apr 1983;70(1):41–55.
- [20] Lane BR, Russo P, Uzzo RG, Hernandez AV, Boorjian SA, Thompson RH, et al. Comparison of cold and warm ischemia during partial nephrectomy in 660 solitary kidneys reveals predominant role of nonmodifiable factors in determining ultimate renal function. *J Urol* 2011;185:421–7. <https://doi.org/10.1016/j.juro.2010.09.131>.
- [21] Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Every minute counts when the renal hilum is clamped during partial nephrectomy. *Eur Urol* 2010;58:340–5. <https://doi.org/10.1016/j.eururo.2010.05.047>.
- [22] Blackwell RH, Li B, Kozel Z, Zhang Z, Zhao J, Dong W, et al. Functional implications of renal tumor enucleation relative to standard partial nephrectomy. *Urology* 2017;99:162–8. <https://doi.org/10.1016/j.urology.2016.07.048>.
- [23] Simone G, Gill IS, Mottrie A, Kutikov A, Patard J-J, Alcaraz A, et al. Indications, techniques, outcomes, and limitations for minimally ischemic and off-clamp partial nephrectomy: a systematic review of the literature. *Eur Urol* 2015;68:632–40. <https://doi.org/10.1016/j.eururo.2015.04.020>.
- [24] Mukkamala A, Allam CL, Ellison JS, Hafez KS, Miller DC, Montgomery JS, et al. Tumor enucleation vs sharp excision in minimally invasive partial nephrectomy: technical benefit without impact on functional or oncologic outcomes. *Urology* 2014;83:1294–9. <https://doi.org/10.1016/j.urology.2014.02.007>.
- [25] Antonelli A, Cindolo L, Sandri M, Furlan M, Vecchia A, Palumbo C, et al. Mp49-02 perioperative morbidity of clamp vs off-clamp robotic partial nephrectomy: preliminary results from a multicentre randomized clinical trial (the clock study). *J Urol* 2017;197:e646–7. <https://doi.org/10.1016/j.juro.2017.02.1504>.
- [26] Becker F, Van Poppel H, Hakenberg OW, Stief C, Gill I, Guazzoni G, et al. Assessing the impact of ischaemia time during partial nephrectomy. *Eur Urol* 2009;56:625–34. <https://doi.org/10.1016/j.eururo.2009.07.016>.
- [27] Trehan A. Comparison of off-clamp partial nephrectomy and on-clamp partial nephrectomy: a systematic review and meta-analysis. *Urol Int* 2014;93:125–34. <https://doi.org/10.1159/000362799>.
- [28] Minervini A, Carini M, Uzzo RG, Campi R, Smaldone MC, Kutikov A. Standardized reporting of resection technique during nephron-sparing surgery: the surface-intermediate-base margin score. *Eur Urol* 2014;66:803–5. <https://doi.org/10.1016/j.eururo.2014.06.002>.
- [29] Minervini A, Campi R, Kutikov A, Montagnani I, Sessa F, Serni S, et al. Histopathological validation of the surface-intermediate-base margin score for standardized reporting of resection technique during nephron sparing surgery. *J Urol* 2015;194:916–22. <https://doi.org/10.1016/j.juro.2015.05.086>.
- [30] Antonelli A, Furlan M, Sodano M, Carobbio F, Tardanico R, Fisogni S, et al. External histopathological validation of the surface-intermediate-base margin score. *Urol Oncol* 2017;35:215–20. <https://doi.org/10.1016/j.urolonc.2016.12.011>.