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Original Article: Clinical Investigation

Purely off-clamp robotic partial nephrectomy: Preliminary 3-year oncological and functional outcomes

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Abbreviations & Acronyms
ASA = American Society of Anesthesiologists
CKD = chronic kidney disease
cT = clinical tumor
eGFR = estimated glomerular filtration rate
Off-C = off-clamp
Off-RPN = off-clamp robotic partial nephrectomy
On-C = on-clamp
PN = partial nephrectomy
POD = postoperative day
RCC = renal cell carcinoma
RF = renal function
RN = radical nephrectomy

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Objectives: To describe our surgical technique and to report perioperative, 3-year oncological and functional outcomes of a single-center series of purely off-clamp robotic partial nephrectomy.

Methods: A prospective renal cancer institutional database was queried, and data of consecutive patients treated with purely off-clamp robotic partial nephrectomy between 2010 and 2015 in a high-volume center were collected. Perioperative complications, and 3-year oncological and functional outcomes were assessed. Univariable and multivariable analyses were carried out to identify independent predictors of renal function deterioration.

Results: Out of 308 patients treated, 41 (13.3%) experienced perioperative complications, 2.9% of which were Clavien grade ≥3. The 3-year local recurrence-free survival and renal cell carcinoma-specific survival rates were 99.5% and 97.9%, respectively. No patient with preoperative chronic kidney disease stage ≤3B developed severe renal function deterioration (chronic kidney disease stage 4) at 1-year follow up. At multivariable analysis, preoperative estimated glomerular filtration rate ($P = 0.005$) was the only independent predictor of a new-onset chronic kidney disease stage ≥3 in patients with preoperative chronic kidney disease stages 1 or 2.

Conclusions: Off-clamp robotic partial nephrectomy is a safe surgical approach in tertiary referral centers, with adequate oncological outcomes and negligible impact on renal function.

Key words: off-clamp, oncological outcomes, partial nephrectomy, renal function, robotic.

Introduction

PN is the standard of care for cT1a renal tumors[1,2] and, if technically feasible, has been proven to be oncologically safe for T1b neoplasms.[3] With on-C PN being the standard of care, off-C PN remains a questionable option, because of the potential increased risk of intraoperative bleeding and consequently increased risk of positive surgical margins. In contrast, the main goal of nephron-sparing techniques is maximal preservation of RF. In the past decade, several attempts were made to minimize ischemia time, the only surgeon-modifiable factor affecting RF. This has led to the development of different surgical techniques.[4]

Notwithstanding, minimally ischemic or purely off-C PN are challenging surgical techniques, requiring advanced surgical skills.

The primary aim of the present study was to show the safety of purely off-RPN, and to show the oncological and functional outcomes of a single-center series enumerating 308 consecutive robot-assisted procedures.

Methods

Study population

From August 2010 to December 2015, a total of 308 patients with a renal mass underwent off-RPN. Preoperative work-up included clinical and laboratory evaluation, and cross-

sectional imaging with 1-mm cuts and three-dimensional rendering of the tumor and vascular anatomy in selected cases, such as those with hilar and completely intraparenchymal tumors.[5]

Overall, 257 patients (83.4%) underwent elective PN, and 51 patients (16.6%) underwent PN with an imperative indication (solitary kidney, multiple tumors and/or baseline eGFR <60 mL/min/1.73 m^2).

Contraindications to PN were: gross hematuria and evidence of renal collecting system infiltration at preoperative imaging.

Statistical analysis

A retrospective analysis of a prospective, institutional review board-approved, renal cancer database was carried out for all patients with a renal tumor treated with off-RPN between August 2010 and December 2015.

Preoperative and postoperative RF was assessed with serum creatinine levels and eGFR according to the Modification of Diet in Renal Disease formula.[6] Complications were classified with the Clavien–Dindo scale.[7]

Kaplan–Meier analysis was carried out to evaluate local recurrence-free survival, cancer-specific survival and overall survival rates. Oncological outcomes were assessed at 1-, 2- and 3-year follow up.

The risk of developing RF deterioration after surgery, based on CKD stage, was estimated using the Kaplan–Meier method. Functional results were computed at 1, 2 and 3 years after surgery. Univariable and multivariable Cox regression analyses were carried out to identify the independent predictors of RF deterioration. All *P*-values <0.05 were considered statistically significant. Statistical analysis was carried out using SPSS software v.24.0 (IBM Corp, Armonk, NY, USA).

Preoperative preparation, surgical approach and instrumentation

A weight-based single dose of cefazolin (2–3 g) was given intravenously before treatment, and anticoagulation treatment was discontinued and replaced with low-molecular weight heparin 7 days before surgery. Bowel preparation was not routinely carried out.

Surgical technique

Patients were placed in an extended flank position, and side docking with transperitoneal five-port access was carried out using a 30° scope. A camera port was placed on the pararectal line at the level of the umbilicus, and two robotic ports were placed along the midclavicular and anterior axillary line, respectively. Two 12-mm ports for the assistant surgeon were placed at the midline, between the camera and the robotic ports, creating a "U" shape focused on the tumor (Video S1). A three-arm configuration was used, and Hot Shears monopolar curved scissors (Intuitive Surgical, Sunnyvale, CA, USA), ProGrasp forceps (Intuitive Surgical) and a large needle driver were used to carry out the renorrhaphy. The two 12-mm assistant ports allowed the introduction of one or two suction irrigation devices and a Weck clip (Teleflex, Wayne, PA, USA) applier.

Mobilization of the kidney and access to the tumor site

Hilum preparation was carried out only in the first 30 cases. Because hilar vessels clamping was not necessary in this initial series, this practice was abandoned and a straight access to the tumor was usually used, without any intent to identify and prepare the hilum. In polar tumors, the Gerota fascia was opened in close proximity to the tumor site, and the kidney was not completely mobilized. Nevertheless, extended mobilization of the kidney was carried out only in posterior tumors, achieving a complete domain of tumor burdens.

Tumor dissection technique

Tumor margins were circumferentially scored and incised with scissors (Fig. 1a), and blunt dissection was progressively applied to separate the tumor from the healthy parenchyma following an avascular plane, maintaining optimal bleeding control. If the tumor pseudocapsule was clearly visible, dissection was accomplished by separating it from the tumor bed without any attempt to resect normal parenchyma, facilitating pure enucleation (Fig. 1b). When dissecting the renal tumor from the healthy renal parenchyma, all encountered small arterial feeders were meticulously identified, selectively clip ligated or coagulated and transected. Alternatively, hybrid enucleation was carried out with a parenchyma incision 2–3 mm around the tumor margins. Dissection of the intermediate part and base of the tumor, however, was always carried out by developing the enucleation plane.[8] Intraoperative margins were evaluated in the specimens, but tumor bed biopsy was never carried out.

Renorrhaphy technique

For tumors with low nephrometry scores, a sutureless approach was used, and hemostasis of the surgical bed was carried out with vessel-sealing devices or with monopolar coagulation, and sometimes finalized with hemostatic agents. This approach provided successful bleeding control in >95% of patients.[9] For polar and laterally located tumors with predominantly endophytic growth patterns (intermediate to high nephrometry scores), single-layer renorrhaphy was carried out to minimize ischemic injury of healthy parenchyma. Finally, for hilar and large medially located tumors, one or more "point-specific" sutures (Fig. 1c) were selectively placed before starting sliding-clip renorrhaphy (Fig. 1e,d), to avoid the potential risk of severe ischemic injury with a deep medullary suture.[10]

Postoperative course

Pain control was achieved using intravenous non-opioid analgesics with a gradual transition to oral painkillers from the first POD. Oral intake was initiated on the first POD with clear liquids and gradually advanced to a normal diet. Patients were encouraged to ambulate soon, usually on the first POD. The drain and urethral catheter were generally removed on the first POD. Prophylaxis for deep vein thrombosis with low-molecular weight heparin was continued for 2 weeks.

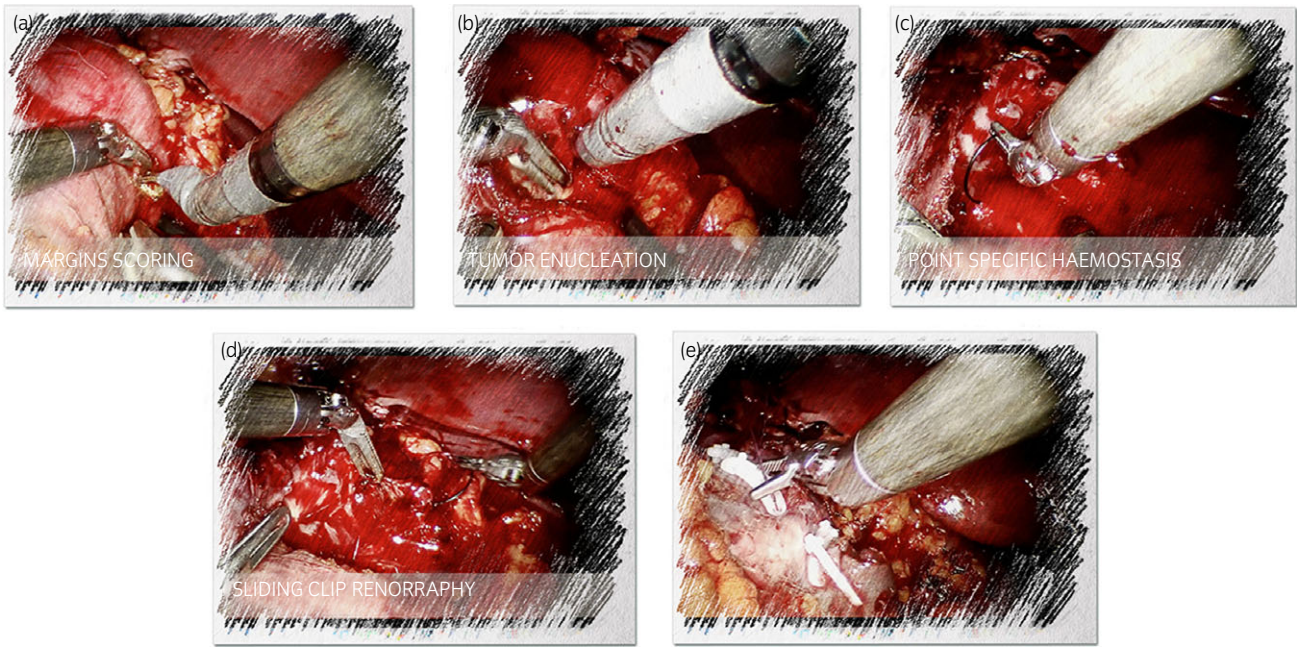


Fig. 1 (a) Tumor margin scoring. (b) Tumor enucleation. (c) Point-specific hemostasis. (d) Sliding clip renorraphy of the renal defect after tumor enucleation. (e) Suture tails tightening with Hem-o-lok clips after renal parenchyma defect complete closure.

Follow-up schedule

Abdominal ultrasonography and whole-body computed tomography scans were alternately carried out at 6-month intervals in patients with renal cell carcinoma, whereas annual abdominal ultrasonography was recommended for patients with benign lesions. The functional follow-up schedule included measurement of serum creatinine levels at discharge, at 3-month intervals for the first year, biannually for two additional years and annually thereafter.

Results

Overall, 308 patients were evaluated. Demographic and baseline clinical data are summarized in Table 1. The mean operative time was 85 min. Conversion to open surgery was not necessary in any case. Median estimated blood loss was 280 mL (interquartile range 100–350 mL).

Intraoperative and postoperative transfusion rates were 1.3% and 5.8%, respectively (overall incidence of patients receiving blood transfusion was 6.2%). Overall, 35 patients experienced perioperative complications (11.4%), whereas just four (1.3%) had severe (Clavien grade ≥3) complications. Perioperative and pathological data are reported in Table 2. The most frequent severe complications were urinary fistula requiring insertion of a double-J ureteral stent and postoperative bleeding requiring embolization. A descriptive report of all complications is provided in Table 3. At median follow up of 24 months (interquartile range 12–36 month), one patient experienced local recurrence (papillary type 2 RCC) and two patients died of disease (clear cell RCC and papillary type RCC). The 3-year local recurrence-free survival and cancer-specific survival rates restricted to RCCs were 99.5% and 97.9%, respectively (Fig. 2a,b). The 3-year overall survival rate was 94.8% (Fig. 2c).

Table 1 Demographic and baseline clinical data of all 308 patients

Characteristics	Result
Mean age, years (range)	58.9 (22–84)
Sex (male/female)	205/103
Mean body mass index, kg/m^2 (range)	26.7 (17.5–45.3)
Diabetes, *n* (%)	45 (14.6)
Cardiovascular disease, *n* (%)	35 (11.4)
ASA score, *n* (%)	
1	30 (9.7)
2	188 (61)
3	89 (29)
4	1 (0.3)
Mean size of renal tumor, cm (range)	4.23 (1–12)
Right side, *n* (%)	150 (48.7)
Hilar location, *n* (%)	91 (29.6)
Multiple tumors at presentation, *n* (%)	14 (4.5)
Bilateral tumors, *n* (%)	2 (0.6)
Solitary kidney, *n* (%)	11 (3.6)
PADUA score, mean (range)	8.3 (6–12)
Imperative indication for PN, *n* (%)	51 (16.5)
Preoperative CKD stage, *n* (%)	
CKD stage 1	92 (29.9)
CKD stage 2	172 (55.8)
CKD stage 3A	28 (9.1)
CKD stage 3B	14 (4.6)
CKD stage 4	2 (0.6)
CKD stage 5	0 (0)
Mean preoperative serum creatinine, mg/dL (range)	1.01 (0.55–2.16)
Mean preoperative eGFR, mL/min/1.73 m^2 (range)	80.10 (19.6–164.4)

At a median follow up of 24 months, mean serum creatinine levels were 1.05 mg/dL (0.5–4), with a 5% increase compared with baseline. Mean eGFR was 75.06 mL/min/1.73 m^2 (15.5–140.4), with a 6.2% decrease compared with baseline.

Only one patient (0.3%) with preoperative CKD stage 4 developed end-stage renal disease. The 1-year risk of severe RF deterioration (CKD stage ≥4) was 0% for patients with preoperative CKD stage ≤3B (Fig. 3a), whereas the 1-year risk of developing an eGFR <45 mL/min/1.73 m^2 was 0% and 4.2% for patients with preoperative CKD stages ≤2 and 3A, respectively (Fig. 3b). Furthermore, in patients with preoperative normal or mildly reduced RF (CKD stages 1–2), the risk of developing a more severe CKD condition (CKD stage ≥3) was <3% (Fig. 3c). At multivariable analysis, preoperative eGFR (P = 0.005) was the only independent predictor of new-onset CKD stage ≥3 in patients with preoperative eGFR ≥60 mL/min/1.73 m^2 (Table 4). Because of the paucity of patients with a least eGFR measurement <45 mL/min/1.73 m^2, regression analysis failed to identify independent predictors of new-onset CKD stage ≥3B (Table 5). Similarly, in patients with preoperative CKD stages 3A or 3B, any tested factor was a significant predictor of new-onset CKD stage 4 or 5 at univariable analysis (Fig. 4; Table 6).

Table 2 Perioperative and pathological data of all 308 patients

Characteristics	Result
Mean operative time, min (range)	83 (40–180)
Mean estimated blood loss, mL (range)	280 (50–800)
Conversion rate, *n* (%)	0 (0)
To laparoscopic radical	0 (0)
To open partial	0 (0)
Intraoperative transfusion, *n* (%)	4 (1.3)
Overall transfusion, *n* (%)	19 (6.2)
Mean 24-h hemoglobin dropdown, g/dL (range)	1.9 (0.2–4.5)
Mean serum creatinine at discharge, mg/dL (range)	1.13 (0.5–4)
Mean serum creatinine increase at discharge (%)	13
Mean eGFR at discharge, mL/min/1.73 m^2 (range)	72.6 (14.9–161.6)
Mean eGFR decrease at discharge (%)	9.22
Perioperative complications, *n* (%)	35 (11.4)
Grade I	8 (2.6)
Grade II	23 (7.5)
Grade IIIa	3 (1)
Grade IIIb	0 (0)
Grade IVa	1 (0.3)
Grade IVb	0 (0)
Grade V	0 (0)
Mean duration of hospital stay, days (range)	3 (2–15)
pT stage	
pT1a	162 (52.6)
pT1b	111 (36.1)
pT2a	15 (4.9)
pT2b	7 (2.2)
pT3a	13 (4.2)
Histopathological results, *n* (%)	
Benign tumors	78 (25.3)
Oncocytoma	55 (17.8)
Angiomyolipoma	12 (3.9)
Other benign variants	11 (3.6)
Clear cell RCC	164 (53.2)
Type 1 papillary RCC	21 (6.8)
Type 2 papillary RCC	7 (2.3)
Cromophobe RCC	25 (8.2)
Mixed or other variants	13 (4.2)
Positive surgical margin, *n* (%)	4 (1.3)

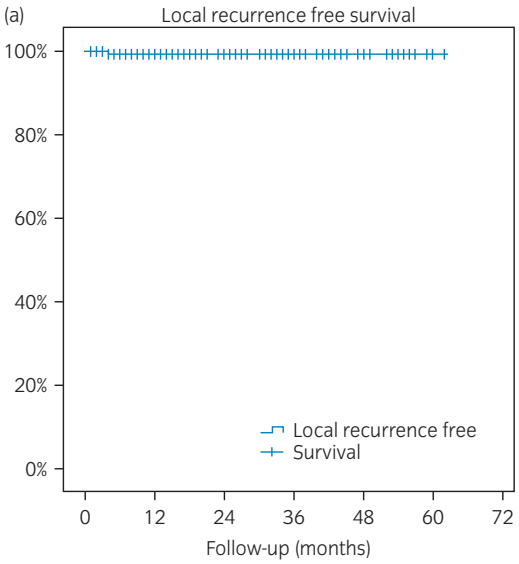
Table 3 Overall complications

Item	Result
Overall complication rate, *n* (%)	41 (13.3)
Clavien grade I, *n* (%)	8 (2.6)
Postoperative pain treated with analgesics	3 (1)
Moderate fever treated with antipyretics	1 (0.3)
Transient electrolyte disorders not requiring therapy	3 (1)
Nausea treated with anti-emetics	1 (0.3)
Clavien grade II, *n* (%)	24 (7.8)
Pleuritis	1 (0.3)
Pleural effusion	1 (0.3)
Blood transfusion	18 (5.8)
Hypoxia requiring O_2 therapy	2 (0.6)
Fever requiring antibiotics	2 (0.6)
Clavien grade IIIa, *n* (%)	7 (2.3)
Fever requiring urine drainage with JJ stent	1 (0.3)
Urinary leakage requiring nephrostomy/JJ stent placement	2 (0.6)
Renal hematoma requiring percutaneous drainage	1 (0.3)
Severe hydronephrosis requiring nephrostomy	1 (0.3)
Bleeding requiring selective arterial embolization	2 (0.6)
Clavien grade IIIb, *n* (%)	0 (0)
Clavien grade IVa, *n* (%)	2 (0.6)
Bleeding requiring selective arterial embolization and observation in ICU	1 (0.3)
Bleeding requiring salvage nephrectomy	1 (0.3)
Clavien grade IVb, *n* (%)	0 (0)
Clavien grade V, *n* (%)	0 (0)

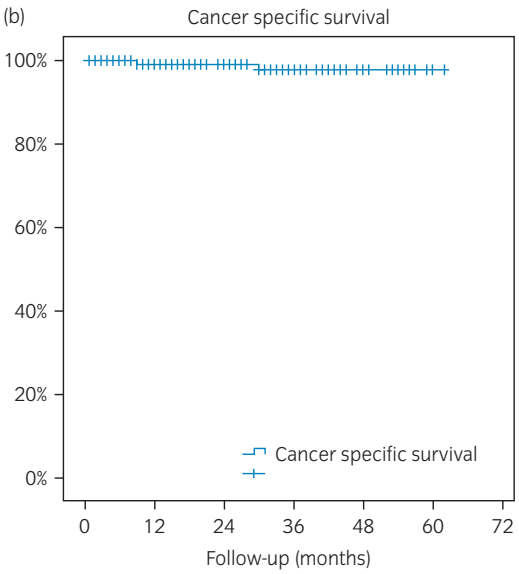
Discussion

The oncological equivalence of PN and RN for small renal tumors was shown in retrospective series,[11,12] and more recently in the European Organization for Research and Treatment of Cancer randomized phase 3 trial 30904.[13] The data from these studies have influenced current guidelines recommending PN over RN for cT1 renal tumors whenever technically feasible.[1,2] Several studies consistently reported worse RF after RN compared with PN after adjustment for diabetes, hypertension and age.[14,15] PN techniques typically involve hilar clamping, which allows precise tumor resection and closure of the renal defect in a bloodless field. Nevertheless, the temporary ischemic injury potentially undermines the intent of RF preservation.

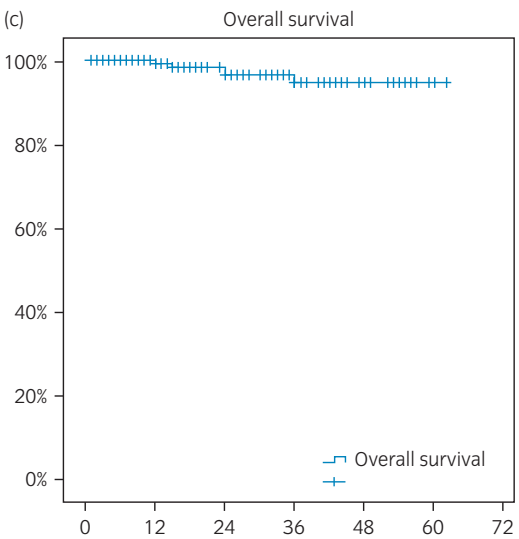
The optimal warm ischemia time is still a matter of debate, as is the effect of on-C PN on long-term RF outcomes. In a recent systematic review of the role of ischemia, the authors suggested that limited periods of warm ischemia time (<20–25 min) might have a negligible effect on RF.[16] Nevertheless, because ischemia is the only surgical modifiable parameter, the negative effect of warm ischemia time led surgeons to develop techniques to minimize renal hypoperfusion, such as preoperative superselective transarterial embolization,[17] parenchymal clamping,[18] early unclamping,[19] selective clamping[20] and zero ischemia PN.[21] These techniques were recently described as "minimally ischemic" to distinguish them from a purely off-C approach.[4] The functional benefits of these approaches are evident in selected clinical settings, such as those that require imperative PN. In patients with



Local recurrence free survival	1-yr	2-yr	3-yr
- Probabilities ± SE	99.5 ± 0.5	99.5 ± 0.5	99.5 ± 0.5
- Number at risk (events)	153 (1)	100 (1)	51 (1)

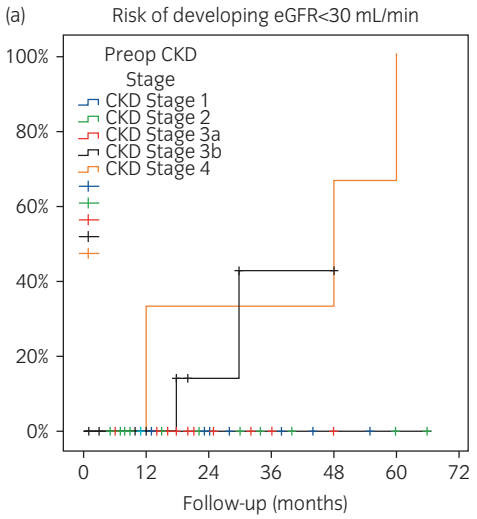


Cancer specific survival	1-yr	2-yr	3-yr
- Probabilities ± SE	99.4 ± 0.6	99.4 ± 0.6	97.9 ± 1.6
- Number at risk (events)	153 (1)	100 (1)	51 (2)

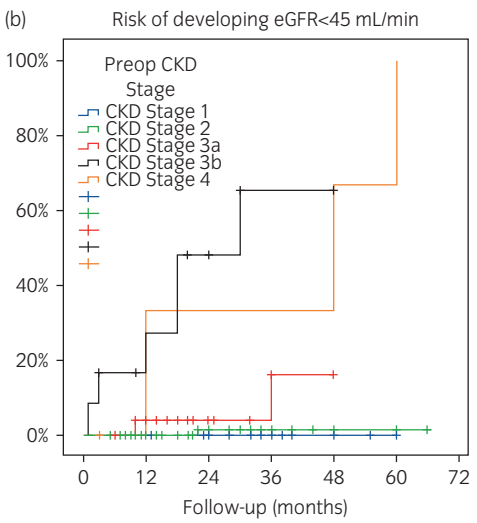


Overall survival	1-yr	2-yr	3-yr
- Probabilities ± SE	99.4 ± 0.6	96.7 ± 1.7	94.8 ± 2.4
-Number at risk (events)	155 (1)	100 (4)	52 (5)

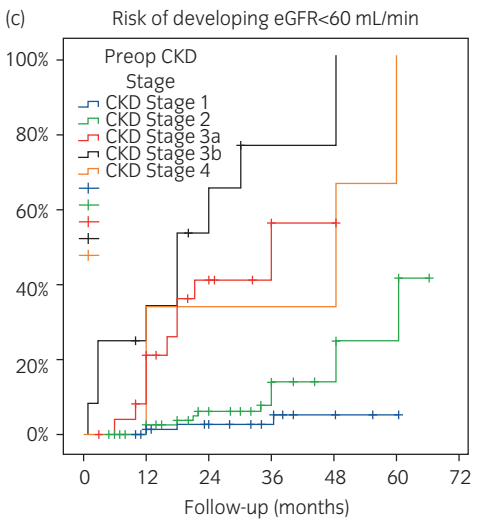
Fig. 2 Kaplan–Meier analysis showing (a) local recurrence-free survival probability, (b) cancer-specific survival probability and (c) overall survival probability.



Risk of developing eGFR<30 mL/min	1-yr	2-yr	3-yr
Preoperative CKD Stage 1 - Probabilities ± SE - Number at risk (events)	 0 69 (0)	 0 50 (0)	 0 41 (1)
Preoperative CKD Stage 2 - Probabilities ± SE - Number at risk (events)	 0 134 (0)	 0 77 (0)	 0 58 (0)
Preoperative CKD Stage 3A - Probabilities ± SE - Number at risk (events)	 0 20 (0)	 0 10 (0)	 0 7 (0)
Preoperative CKD Stage 3B - Probabilities ± SE - Number at risk (events)	 0 7 (0)	 14.3 ±13.2 3 (1)	 42.9 ± 24.9 0 (2)
Preoperative CKD Stage 4 - Probabilities ± SE - Number at risk (events)	 33.3 ± 27.2 2 (1)	 33.3 ± 27.2 1 (2)	 33.3 ± 27.2 1 (2)



Risk of developing eGFR<45 mL/min	1-yr	2-yr	3-yr
Preoperative CKD Stage 1 - Probabilities ± SE - Number at risk (events)	 0 69 (0)	 0 50 (0)	 0 41 (0)
Preoperative CKD Stage 2 - Probabilities ± SE - Number at risk (events)	 0 134 (0)	 1.2 ± 1.2 77 (1)	 1.2 ± 1.2 58 (1)
Preoperative CKD Stage 3A - Probabilities ± SE - Number at risk (events)	 4.2 ±4.1 20 (1)	 4.2 ± 4.1 10 (1)	 16.1 ± 11.8 7 (2)
Preoperative CKD Stage 3B - Probabilities ± SE - Number at risk (events)	 27.1 ±13.5 7 (3)	 47.9 ± 15.8 3 (5)	 65.3 ± 17.6 0 (6)
Preoperative CKD Stage 4 - Probabilities ± SE - Number at risk (events)	 33.3 ± 27.2 2 (1)	 33.3 ± 27.2 1 (2)	 33.3 ± 27.2 1 (2)



Risk of developing eGFR<60 mL/min	1-yr	2-yr	3-yr
Preoperative CKD Stage 1 - Probabilities ± SE - Number at risk (events)	 1.4 ± 1.4 69 (1)	 3.1 ± 2.1 50 (2)	 5.4 ± 3.1 41(3)
Preoperative CKD Stage 2 - Probabilities ± SE - Number at risk (events)	 2.9 ± 1.4 132 (4)	 6.3 ± 2.4 77 (7)	 14.1 ± 4.0 55 (12)
Preoperative CKD Stage 3A - Probabilities ± SE - Number at risk (events)	 21.1 ± 8.4 18 (5)	 58.7 ± 10.7 10 (9)	 56 ± 12.1 6 (11)
Preoperative CKD Stage 3B - Probabilities ± SE - Number at risk (events)	 34.4 ± 14 7 (4)	 64.8 ± 15.2 3 (7)	 42.9 ± 24.9 0 (2)
Preoperative CKD Stage 4 - Probabilities ± SE - Number at risk (events)	 33.3 ± 27.2 2 (1)	 33.3 ± 27.2 1 (2)	 33.3 ± 27.2 1 (2)

Fig. 3 Kaplan–Meier analysis showing the risk of developing (a) eGFR <30 mL/min for patients with preoperative CKD stage 1, 2, 3A, 3B and 4; (b) eGFR <45 mL/min for patients with preoperative CKD stage 1, 2, 3A, 3B and 4; and (c) eGFR <60 mL/min for patients with preoperative CKD stage 1, 2, 3A, 3B and 4.

Table 4 Univariable and multivariable Cox regression analysis to identify predictors of new onset CKD stage ≥3 in patients with preoperative CKD stages 1–2

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
	P-value	HR	Lower	Higher	*P*-value	HR	Lower	Higher
Tumor size	0.740	0.958	0.742	1.237	–	–	–	–
PADUA score	0.982	1.006	0.608	1.664	–	–	–	–
Multiple tumor	0.492	2.039	0.268	15.523	–	–	–	–
Preoperative Hb	0.123	0.810	0.619	1.059	–	–	–	–
Sex	0.506	1.364	0.547	3.398	–	–	–	–
pT >1 *vs* pT1	0.886	1.158	0.154	8.727	–	–	–	–
Diabetes	**0.013**	3.432	1.301	9.053	0.335	1.698	0.574	4.981
Hypertension	0.138	2.049	0.794	5.291	–	–	–	–
Smoking	0.054	0.127	0.017	1.018	–	–	–	–
ASA score	0.082				–	–	–	–
2 *vs* 1	0.466	2.150	0.275	16.807	–	–	–	–
3 *vs* 1	0.052	2.993	0.947	13.432	–	–	–	–
Age at surgery	**0.011**	1.051	1.011	1.093	0.315	1.023	0.979	1.068
Preoperative eGFR	**<0.001**	0.932	0.897	0.969	**0.005**	0.945	0.908	0.983
Perioperative eGFR loss ≥20%	0.255	1.655	0.695	3.941	–	–	–	–

Bold values indicate significant variables ($P < 0.05$).

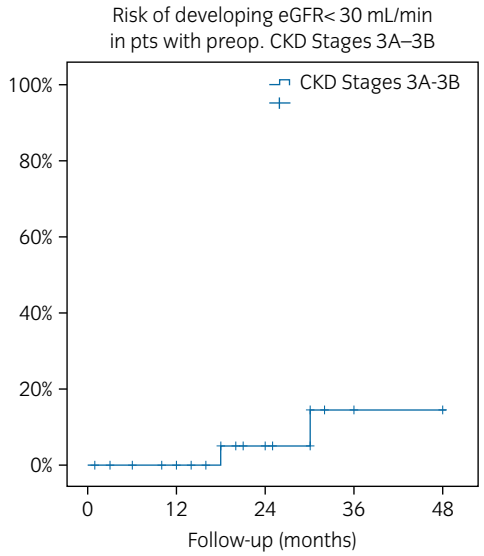
Table 5 Univariable and multivariable Cox regression analysis to identify predictors of new onset CKD stages ≥3B in patients with preoperative CKD stages 1–2–3A

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
	P-value	HR	Lower	Higher	*P*-value	HR	Lower	Higher
Tumor size	**0.004**	1.687	1.181	2.410	0.058	1.797	0.980	3.294
PADUA score	0.104	2.216	0.850	5.782	–	–	–	–
Multiple tumor	0.835	0.047	<0.001	1.272	–	–	–	–
Preoperative Hb	0.613	0.838	0.422	1.664	–	–	–	–
Sex	0.942	1.093	0.099	12.052	–	–	–	–
pT >1 *vs* pT1	0.089	8.085	0.727	89.879	–	–	–	–
Diabetes	0.668	0.040	<0.001	96 461.745	–	–	–	–
Hypertension	0.519	0.454	0.041	5.013	–	–	–	–
Smoking	0.859	1.244	0.113	13.733	–	–	–	–
ASA score	0.745				–	–	–	–
2 *vs* 1	0.673	43.801	<0.001	1.875				
3 *vs* 1	0.798	0.151	<0.001	284 343.005				
Age at surgery	0.060	1.209	0.992	1.474	–	–	–	–
Preoperative eGFR	**0.040**	0.803	0.651	0.990	0.081	0.843	0.696	1.021
Perioperative eGFR loss ≥20%	0.343	197.198	0.004	10 897 678.8	–	–	–	–

Bold values indicate significant variables ($P < 0.05$).

normal baseline RF, the adoption of these techniques remains controversial, particularly because of the need for advanced surgical skills.

Compared with on-C PN, where the tumor bed is virtually bloodless, deft suction irrigation and technical suturing for bleeding control are crucial in off-C PN to obtain proper control of resection margins and to ensure perfect bleeding control. In fact, the adoption of a purely off-C approach at "Regina Elena" National Cancer Institute, Rome, Italy, was initially reserved for renal tumors with low nephrometry scores, for which the expected risk of bleeding is relatively low. Our experience showed the feasibility of this approach for selected patients (median RENAL nephrometry and PADUA scores of 4 and 6, respectively), as well as its safety (complications were 1.9% Clavien grade 1, 6.9% Clavien grade 2 and 0% Clavien grade ≥3) and excellent functional outcomes (1-year median decrease of split RF at renal scintigraphy was 1%).[9] Larger and endophytic tumors were initially treated with preoperative superselective transarterial embolization. This technique, used in 210 consecutive cases, provides a relatively bloodless field and might have a "parachute role" at the beginning of the learning curve, when inappropriate



Risk of developing eGFR< 30 mL/min	1-yr	2-yr	3-yr	4-yr
- Probabilities ± SE	0	4.8 ± 4.6	13.4 ± 9.3	13.4 ± 9.3
- Number at risk (events)	27 (0)	13 (1)	7 (2)	4 (2)

Fig. 4 Kaplan–Meier analysis showing the risk of developing eGFR <30 mL/min for patients with preoperative CKD stage 3A and 3B.

Table 6 Univariable Cox regression analysis to identify predictors of new onset CKD stages 4–5 in patients with preoperative CKD stages 3A–3B

			95% CI	
Univariable analysis	*P*-value	HR	Lower	Higher
Tumor size	0.155	1.328	0.898	1.965
PADUA score	0.485	0.522	0.105	2.912
Preoperative Hb	0.314	1.856	0.557	6.178
Sex	0.957	0.926	0.057	15.151
pT >1 *vs* pT1	0.271	3.743	0.296	7.908
Diabetes	0.555	2.309	0.143	7.187
Hypertension	0.906	1.183	0.073	19.103
Smoking	0.477	2.739	0.171	43.910
ASA score	0.898			
2 *vs* 1	0.989	1.122	0.873	1.234
3 *vs* 1	0.987	1.311	0.374	1.583
Age at surgery	0.506	0.962	0.858	1.078
Preoperative eGFR	0.113	0.855	0.704	1.038
Perioperative eGFR loss ≥20%	0.479	5.698	0.142	2.473

bleeding control during off-C PN could compromise visualization of the surgical field and achievement of negative surgical margins. With increased experience and availability of the robotic platform, preoperative superselective transarterial embolization has been replaced by zero ischemia PN, as described by Gill *et al.*, and subsequently by a purely off-C robotic approach.[21]

Zero ischemia PN is a complex procedure that, in expert hands, can last 3 h on average (range 1.3–6.0 h).[21] Proper skill with the intraoperative use of ultrasound/Doppler imaging and meticulous microdissection of multiple arterial branches are required. In addition, this technique is best suited for hilar and medially located renal tumors; hilar microdissection for laterally located tumors would require a large nephrotomy with consequent ischemic risks. Consequently, we progressively shifted from zero ischemia to off-RPN for all tumors, with circumscribed use of superselective microdissection for only hilar and medially located tumors, in which selective arterial feeders were peripherally identified and selectively controlled during the enucleation phase. The off-C technique is essentially based on the development of an enucleation plane, and on stepwise identification of tertiary and quaternary arterial branches feeding the tumor. Surgical tips include meticulous margin scoring, and sometimes the simultaneous use of two irrigation and suction devices to improve visualization and thus control of tumor margins. Identified feeding vessels are selectively coagulated or clip ligated and transected. Finally, clips applied in the proximity of the urinary collecting system can be removed safely during or immediately before renorrhaphy.

Another issue that is not sufficiently addressed in the literature is the potential ischemic injury incurred with extensive renorrhaphy. Renorrhaphy can be safely omitted for small and exophytic tumors, but is mandatory for larger and endophytic tumors. The use of an off-C approach could contribute to minimizing extensive renorrhaphies, thanks to optimal control of feeding arteries during dissection. Furthermore, point-specific hemostasis can be carried out before starting conventional renorrhaphy. These steps are clearly precluded with an on-C technique, in which renorrhaphy is mostly carried out with a double suture (medullary and cortical) without real-time control of bleeding sources.

A major concern about off-C approaches is the risk of unexpected intraoperative bleeding with consequently higher risks of transfusion and impaired visualization of tumor margins, potentially translating into positive surgical margins and higher risks of local recurrence. In our series, the transfusion rate was approximately 5%, and positive surgical margins occurred in approximately 1% of patients. Furthermore, the probability of 3-year local recurrence-free survival was 99.5%.

Regarding functional outcomes, the obvious benefit expected from off-RPN is the maximal preservation of RF. A retrospective comparison of zero ischemia and on-C PN by Desai *et al.* showed that zero ischemia PN was associated with a lower eGFR decrease at discharge (0% *vs* 11%; $P = 0.01$) and at last follow up (11% *vs* 17%; $P = 0.03$).[22] From a clinical standpoint, more than measuring the percentage decrease of eGFR after treatment, the real risk to be assessed is the development of severe or end-stage CKD.

In a recent analysis of 2027 patients with normal preoperative RF and a clinical T1 renal mass, Capitanio *et al.* reported end-stage renal disease rates after PN of 1.5% and 2.5% at 5 and 10 years, respectively.[23] These data are consistent with those reported by Scosyrev *et al.* (1.6% with end-stage renal disease at a median follow up of 6.7 years).[24] Functional outcomes in our series compare favorably with

those in the literature, with a 3-year risk of severe RF deterioration (CKD stage 4) of 0% not only for patients with normal baseline RF, but also for all patients with preoperative CKD stage ≤3B.

The single-center source of these outcomes is a clear limitation to acknowledge, potentially affecting feasibility, safety, oncological and functional outcomes reported. Nevertheless, a comprehensive review of the literature supported the safety and oncological effectiveness of these techniques, highlighting the need for the entire surgical team to have advanced skills. The accumulating experience with robotic surgery supports the increasing use of PN versus RN;[25] at the same time, the increasing adoption of these approaches is indirectly provided by the increasing number of reports on minimally ischemic PN techniques.[4]

Our experience supports the use of off-RPN as a feasible and safe surgical approach in tertiary referral centers, providing excellent oncological and functional outcomes. The negligible impact on postoperative RF is supported by the absence of patients developing clinically significant deterioration of RF at 1-year follow up.

Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1. Video showing step-by-step surgical technique of off-clamp robotic partial nephrectomy.