



Fluorescence-guided selective arterial clamping during RAPN provides better early functional outcomes based on renal scan compared to standard clamping

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Abstract

To compare the functional and operative outcomes of robot-assisted partial nephrectomy with selective arterial clamping guided by near infrared fluorescence imaging (NIRF-RAPN) versus a cohort of patients who underwent standard RAPN without selective arterial clamping (S-RAPN). 62 consecutive patients underwent RAPN from January 2016 to May 2017: the last 20 patients underwent NIRF-RAPN. Preoperative and postoperative renal scan at 1 month were performed to evaluate the glomerular filtration rate (GFR) of the operated renal unit and total function. Functional and operative outcomes of cases were compared with a cohort of 42 patients undergoing S-RAPN. Selective clamping was performed in 15 patients (75%), whereas five (25%) cases were converted to S-RAPN, due to incomplete ischemic appearance of the tumor after selective clamping. Median tumor diameter was 40 mm in both groups. Median selective clamping was 24 min in both groups. Operative time (206' vs 190') and blood loss (200 vs 170 cc) were comparable. No major complications have been reported in the NIRF-RAPN group, whereas three acute hemorrhages with embolization were found in the S-RAPN group. The analysis of renal scan data revealed that a greater loss of GFR in the operated renal unit was observed after S-RAPN compared to NIRF-RAPN [21.5% vs. 5.5%; $p=0.046$], as well as total GFR loss [8% vs 0%; $p=0.007$]. The use of NIRF imaging was associated with improved short-term renal functional outcomes compared to RAPN without selective arterial clamping. To our knowledge, this is the first comparative study analyzing the GFR obtained from renal scan.

Keywords Near infrared fluorescence · Robotic · Partial nephrectomy · Renal ischemia · Renal scan

Introduction

According to international guidelines, partial nephrectomy (PN) should be performed in small renal masses when- ever technically feasible [1, 2]. Some studies have compared the surgical outcomes of PN, performed via different approaches: robot-assisted (RAPN), laparoscopic, and open [3]. The need to preserve the healthy renal parenchyma, with the same oncological results, has been the topic of numerous studies [4–8]. Several retrospective studies prove the benefits of nephron-sparing surgery with reduction of

comorbidities and thus improved long-term survival [9, 10]. Traditionally, the renal artery is clamped during PN to create a bloodless field for the excision of neoplasm and renal renorrhaphy, but this skill has the potential to cause renal damage via prolonged ischemia and perfusion/reperfusion injury. To preserve the healthy renal parenchyma, ischemia time should be as short as possible. While renal volume loss was also important in renal function impairment [11], the necessity to reduce the duration of clamping was confirmed by Thompson et al. [12] in patients with a solitary kidney. Hereafter, there is growing interest in developing a safe and effective method to obtain selective ischemia limited only to the tumor and right adjacent normal parenchyma, leaving blood flow to the remainder tissue uninterrupted during surgery. Several techniques of obtaining this goal have been described [13–16]. Recently, the use of a near-infrared fluorescence (NIRF) imaging system with indocyanine green (ICG) dye has been described during robot-assisted partial nephrectomy (RAPN) as an adjunctive means of identifying

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the renal vasculature and parenchymal perfusion, analyzing the variation of kidney function as expressed by estimated glomerular filtration rate (eGFR) [17–19]. In the present study, we compare the operative and functional outcomes of RAPN with selective arterial clamping guided by near infrared fluorescence imaging (NIRF-RAPN) versus a cohort of patients who underwent standard RAPN without selective arterial clamping (S-RAPN). The effects on renal function as expressed by GFR obtained with renal scan were compared.

Methods

Study design and data collection

We analyzed a prospectively-maintained database collecting data on 62 patients undergoing RAPN from October 2015 to June 2017 at the Department of Urology, Santa Chiara Hospital, Trento, Italy. From December 2016, all cases were performed with a selective arterial clamping guided by NIRF; in previous cases a standard clamping of the main renal artery was performed. The patients performed a preoperative abdominal angio-TC. All cases were assessed by a dedicated radiologist and preoperative reconstructions of the arterial anatomy up to the tertiary vessels were generated. Renal function was evaluated by serum creatinine and GFR using a renal scan with Tc 99m-DTPA (diethylene-triaminopentacetic acid). This examination is performed before surgery and at 1 month from intervention.

All complications that occurred within 30 days of discharge have been recorded, defined and graduated according to the Clavien–Dindo system [20]. Comorbidities were evaluated according to the age-adjusted Charlson Comorbidity Index (CCI) [21] and preoperative risk assessment by the American Society of Anesthesiologist (ASA score) and the 2009 TNM for pathological evaluation.

The clinical, operative, perioperative, and pathological variables are shown in Table 1.

The functional results are summarized in Table 2: global GFR (total GFR). GFR of the single kidney unit (single GFR) and serum creatinine performed preoperatively and at 1 month after surgery.

Surgical details

RAPNs were performed through a transperitoneal approach by use of a 4- or 5-trocar technique: a 12-mm port for the camera (30° downward lens) through a small pararectal incision; three robotic instrument ports are placed in a line configuration; one or two assistant ports are placed laterally to the camera port. Renal hilar vessels were dissected to allow access for clamp placement. Gerota's fascia was opened and the fat was cleaned off the renal capsule to expose the

tumor. The tumor is excised using minimal electrocautery and mainly cold scissors. One central running suture in the tumor bed ensures reduction in hemorrhage by precise suturing of visible bleeding and repair of pelvicalyceal system, if necessary. A renorrhaphy employing the sliding clip technique closes the defect over a bolster. The hilar clamp is removed by the assistant at the end of the reconstruction of renal parenchyma.

Fluorescence and vascular phase

The fluorescence-capable da Vinci Si System (Intuitive, Sunnyvale, CA, USA) was used, associating the normal light and near-infrared fluorescence imaging. After switching to NIRF, the surgical field is illuminated in shades of black and grey, and the fluorescent dye is overlaid in green. Intraoperatively, the vessels are freed up to the secondary or tertiary vascular branches whenever possible. The bulldog clamp is placed on the predetermined arterial branch or branches (Fig. 1). The decision of which branches to clamp is based on the preoperative CT images, to interrupt the blood flow as distal as possible and in the meantime to have a field as clean as possible, and confirmed intraoperatively based on the fluorescence outcomes. Indocyanine green is diluted to 2.5 mg/ml and the first solution is given intravenously as a bolus of 5 mg by the anesthesiologist directly after arterial clamping. After the administration of the dye, the light can be switched to NIRF. After 30–50 s, usually following the liver fluorescence, a thorough assessment of the kidney perfusion is performed (Fig. 2). At this point, two basic circumstances can occur. If the entire mass and at least 1–2 cm of the surrounding parenchyma are fully ischemic, the excision is immediately begun. If the mass or the surrounding parenchyma are still perfused, the distal branches are declamped and a more proximal clamping is performed. Once the mass is excised and the renorrhaphy is completed, a new bolus of 2.5 mg indocyanine green is given intravenously to check that the kidney is fully perfused.

Statistical analysis

Distribution of continuous variables are reported as median and interquartile range (IQR) (25th; 75th percentiles). Categorical variables are presented as numbers and percentages. The comparison between subgroups (surgical approach) was performed using Student *t* test or Mann–Whitney *U* test for continuous variables. Qualitative data were compared by the χ^2 test or Spearman correlation. *p* values were considered significant when less than or equal to 0.05. All analyses were performed using the SPSS software (IBM Corp., Armonk, NY).

Table 1 Preoperative demographic and tumor characteristics, operative, perioperative and pathological results expressed as median (interquartile range) or number (%)

	S-RAPN (<i>n</i> = 42)	NIRF-RAPN (<i>n</i> = 15)	<i>p</i>
Demographic characteristics			
Age (years)	66 (58–72)	61 (54–65)	0.45
Men (no)	27 (64.3)	12 (75)	0.39
BMI (Kg/m ²)	27 (24–30)	27 (23–29)	0.94
ASA score (no)			0.74
1	3 (7)	2 (13.3)	
2	35 (83.3)	12 (80)	
3	4 (9.5)	1 (6.7)	
Charlson comorbidity index	3 (3–4)	2 (2–3)	0.41
Tumor characteristics			
Tumor size (cm)	4 (3–4.5)	4 (3–4.5)	0.92
PADUA risk group (no)			0.46
1	18 (42.9)	6 (40)	
2	17 (40.5)	5 (33.3)	
3	7 (16.7)	4 (26.7)	
Right-sided tumors (no)	21 (50)	10 (66.7)	0.37
Operative and perioperative (<i>n</i> = 20)			
Operative time (min)	206 (180–255)	190 (152–230)	0.71
Blood loss (ml)	200 (100–450)	170 (150–300)	0.14
Ischemia time (min)	24 (20–30)	24 (18–30)	0.92
Transfused patients (no)	6 (14.3)	1 (5)	0.58
Complications Clavien–Dindo (no)			0.13
1	6 (14.3)	1 (5)	
2	7 (16.7)	1 (5)	
3	3 (7.1)	0 (0)	
Conversion (no)	2 (4.8%)	0 (0)	0.39
Hospital stay (days)	5 (5–7)	5 (4–6)	0.76
Pathological (<i>n</i> = 15)			
Histotype (no)			0.078
Benign	5 (11)	5 (33.3)	
Clear cell	24 (57.1)	8 (57.1)	
Papillary	11 (26.2)	0 (0)	
Chromophobe	2 (4.8)	2 (14.3)	
Pathological stage (no)			0.72
pT1a	22 (59.5)	5 (50)	
pT1b	15 (40.5)	5 (50)	
Positive surgical margins (no)	3 (7.1)	0 (0)	0.025

Bold value is statistically significant

Table 2 Functional results (1 month) express as median (interquartile range): GFR s (single renal unit); GFR t (total)

	S-RAPN (<i>n</i> = 42)	NIRF-RAPN (<i>n</i> = 15)	<i>p</i>
GFR s (ml/min)	50.4 (40.2–60.8)	49 (44.2–56.2)	0.95
GFR s 1 month (ml/min)	37 (29–50)	47.5 (37–56)	0.22
ΔGFR s (%)	21.5 (6–36)	5.5 (0.6–15)	0.046
GFR t (ml/min)	98 (85–123)	101 (87–113)	0.95
GFR t 1 month (ml/min)	91 (78–113)	102 (88–115)	0.3
ΔGFR t (%)	8 (0–14.8)	0 (0–0.9)	0.007
Preoperative serum creatinine	1 (1–1)	1 (1–1)	0.28
Postoperative serum creatinine (1 month)	1 (0.9–1.1)	0.9 (0.6–1)	0.06

Bold values are statistically significant

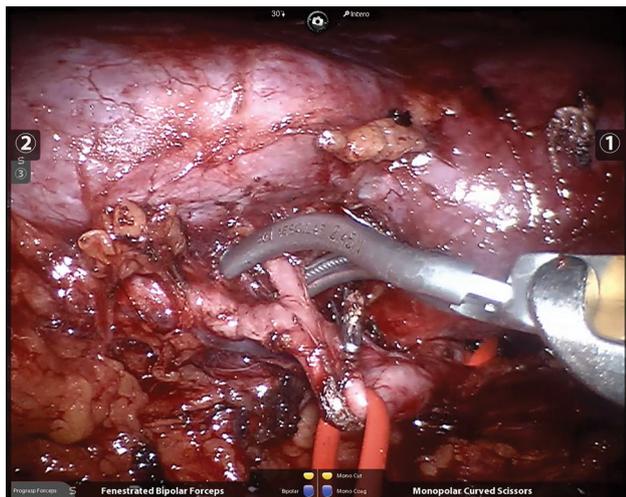


Fig. 1 The bulldog clamp is placed on the predetermined arterial branch or branches

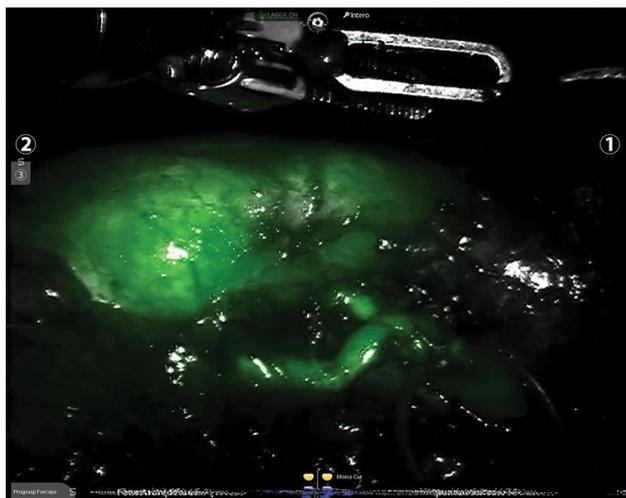


Fig. 2 After switching to NIRF, the surgical field is illuminated in shades of black and grey (right portion), and the fluorescent dye is overlaid in green (left portion)

Results

Patients' characteristics and perioperative results

62 consecutive patients underwent RAPN from October 2015 to June 2017: 42 in the S-RAPN and 20 in the NIRF-RAPN groups. Demographic and preoperative characteristics are summarized in Table 1. Patients undergoing standard clamping were 5 years older than those undergoing selective clamping but with a non-statistical significant difference ($p=0.45$). The median BMI and the Charlson

Comorbidity Index were comparable between groups. No statistically significant difference in the tumor diameter [4 (3–4.5) vs 4 (3–4.5)] nor in the PADUA Score were found, with seven (16.7%) corresponding to the higher risk group in the S-RAPN and four (26.4%) in the NIRF-RAPN ($p=0.46$).

Operative time (206' vs 190'; $p=0.71$) and blood loss (200 vs 170 cc; $p=0.14$) were comparable in the two groups. Median ischemia time was 24 min in both groups. Two patients undergoing S-RAPN were converted to an open approach with nephrectomy for bleeding.

There were 18 total complications: 16 in the standard group and 2 in the NIRF group ($p=0.13$). Only one patient (5%) in the NIRF group was transfused postoperatively compared to six patients in the standard group (14.3%) with a non-statistical significant difference ($p=0.58$). Two Clavien grade 1–2 (13.7%) occurred in the NIRF group: one fever treated with antibiotics and one transfusion; there were no Clavien grade 3 or higher complications in NIRF-RAPN. Three patients had a Clavien grade 3 complication in the S-RAPN group (postoperative embolization for bleeding). The median hospital stay (5 days, $p=0.76$) was comparable in the two groups. Pathological results showed an organ-confined disease in all patients. No positive margins were demonstrated in the NIRF-RAPN vs three in S-RAPN group (7.1%) with a statistically significant difference ($p=0.025$).

Fluorescence assessment and functional results

The final analysis of the NIRF-RAPN was performed on 15 patients while five selective clampings were converted to standard clamping due to incomplete ischemic appearance of the tumor ($n=3$) or excessive bleeding during dissection ($n=2$). The fluorescence assessment was thus informative and with an impact on the surgical pathway in 18 cases on 20 (90%), confirming ($n=15$) or not confirming ($n=3$) the feasibility of selective clamping. We have clamped a secondary artery in 11 cases and a tertiary artery in 4 cases. The analysis of renal scan data revealed a greater loss of GFR in the operated renal unit ($\Delta\text{GFRs} \%$) after S-RAPN compared to NIRF-RAPN [21.5% vs 5.5%; $p=0.046$], as well as total GFR loss ($\Delta\text{GFRt} \%$) [8% vs 0%; $p=0.007$].

Comment

The primary criteria for a successful PN are negative surgical margins and the maximal preservation of kidney function. For the latter, ischemia time and tissue volume loss are of the utmost importance. Several studies with an off-clamp approach have shown significantly higher postoperative eGFR after 6 months compared to standard clamping [22, 23]. However, off-clamp PN can lead

to a reduced view of the surgical site due to the lack of a blood loss field, possibly resulting in positive margins or uncalled for resection of healthy tissue. Thompson et al. [12] demonstrated that a warm ischemia longer than 25 min and a large tumor size were independent predictors of new-onset chronic kidney disease in patients with a solitary kidney at multivariate analysis. To reduce the ischemia time, Gill et al. [13] proposed the “zero-ischemia partial nephrectomy” that is based on selective and superselective clamping, using cerebral aneurysm neurosurgical microbulldogs, of arteries of the tertiary or superior order directed to the neoplasm or to that part of kidney that hosts the tumor.

By restricting ischemia to the region of the tumor and immediately adjacent tissue, the surgeon is able to create a bloodless field ensuring adequate visibility during the resection step. Then NIRF allows the surgeon to confirm the devascularization of the tumor mass, allowing most of the healthy parenchyma to remain perfused throughout the intervention. Ficarra et al. [24] show that in the human kidneys the arterial vasculature is frequently different from that described by Graves [25, 26]. Moreover, in a significant percentage of cases, a single renal segment receives two or more branches that originate from an artery leading to another segment. From a pathophysiological point of view, the immediate consequence is that an injury or occlusion of a segmental artery cannot determine a complete segmental renal infarction. For this reason, surgeons performing RAPN have proposed the use of NIRF imaging technology to test the effectiveness of selective clamping of the segmental artery. Furthermore, recent studies have tried to demonstrate how the creation of molds using 3D printers can facilitate planning for partial nephrectomy with a realistic simulation that improves accuracy [27].

In the present study, in two patients undergoing NIRF-RAPN the selective clamping was converted to standard clamping of the main artery because of a relevant bleeding from the surgical bed. A reasonable explanation might reside in the communication between different segmental arteries that cannot be verified by NIRF which is a surface coloration.

Several studies have employed NIRF imaging to aid in selective arterial clamping during RAPN with both short- and intermediate-term follow-up demonstrating a decreased reduction of eGFR in the selective arterial clamp compared to the main artery clamp cohort [17–19]. However, in patients with a normal contralateral kidney, serum eGFR may not be a sensitive tool for assessing any benefit of this technique. The only method capable to evaluate the separate function in the single kidney is the renal scan [28]. In our study, Δ GFRs was less than 15% in the NIRF-RAPN compared to the S-RAPN ($p=0.046$); similarly, the Δ GFRt of patients undergoing standard clamping had a higher

reduction compared to those with selective clamping (8%, $p=0.007$).

These results confirm the efficacy of the technique with a higher preservation of short-term renal function using selective clamping with NIRF imaging with ICG. The absence of statistically significant differences between the preoperative variables or complications of the NIRF and the standard group shows that the two groups are homogeneous and comparable. Moreover, the use of renal scan to evaluate the GFR contributes to increase the accuracy of our results. The limits of the study are the limited number of procedures considered and the lack of a long-term functional follow-up.

Conclusions

Our initial data illustrate the validity and effectiveness of NIRF imaging during RAPN. RAPN with selective clamping combined with the use of ICG is technically feasible. NIRF imaging verifies the devascularization of the tumor and of surrounding area and ensures a nearly bloodless tumor resection without clamping of the renal hilum in most cases. In this study, we found an association between NIRF and improved short-term functional outcomes, as measured by GFR at renal scan. These preliminary results need to be confirmed in a larger study with a longer term follow-up.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee 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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