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Surgery in Motion

"Ride the Green Light": Indocyanine Green–marked Off-clamp Robotic Partial Nephrectomy for Totally Endophytic Renal Masses

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Abstract

Background: Complexity of robot-assisted partial nephrectomy (RAPN) mostly depends on tumor size and location. Totally endophytic renal masses represent a surgical challenge in terms of both intraoperative identification and anatomical dissection.
Objective: To detail a novel technique for marking preoperatively endophytic renal tumors with transarterial superselective intrarenal mass delivery of indocyanine green (ICG)-lipiodol mixture, in order to enhance surgical margins control during purely off-clamp (OC) RAPN with the use of near-infrared fluorescence imaging.
Design, setting, and participants: Between June and July 2017, 10 consecutive patients with totally endophytic renal masses underwent preoperative ICG tumor marking immediately followed by RAPN.
Surgical procedure: Preoperative superselective transarterial delivery of a lipiodol-ICG mixture (1:2 volume ratio) into tertiary-order arterial branches feeding the renal mass prior to transperitoneal OC-RAPN.
Measurements: Clinical data were prospectively collected in our institutional RAPN dataset. Perioperative, pathological, and functional outcomes of RAPN were assessed.
Results and limitations: Median tumor size was 3 cm (interquartile range 2.3–3.8). The median PADUA score was 10 (9–11). Angiographic procedure was successful in all patients. Median operative time was 75 min (65–85); median estimated blood loss was 250 ml (200–350). No conversion to on-clamp PN or radical nephrectomy was needed. All patients had uneventful perioperative course; median hospital stay was 3 d (2–3). At discharge, median hemoglobin (Hgb) and percent estimated glomerular filtration rate (eGFR) drop were 3.3 g/dl (2.1–3.3) and 11% (10–20%), respectively. Surgical margins were negative in all cases. One-year median ipsilateral renal volume and 1-yr eGFR percent decreases were 11.7% (6–20.9%) and 12.2% (5.3–13.7%), respectively.
Conclusions: We described a novel technique to simplify challenging RAPN based on ICG superselective transarterial tumor marking. Key benefits include quick intraoperative identification of the mass with improved visualization and real-time control of resection margins.
Patient summary: Robot-assisted partial nephrectomy (RAPN) for totally endophytic renal masses is a technically demanding surgical procedure, sometimes requiring radical nephrectomy. This novel technique significantly simplified surgical complexity in our Institution. Further studies with larger cohorts are warranted to confirm whether this technique provides relevant intraoperative and functional advantages.
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1. Introduction

For totally endophytic renal masses, partial nephrectomy (PN) generally represents a challenging procedure, with longer warm ischemia times (WITs), a higher rate of urinary system violation, and more frequent postoperative complications than those reported for standard and smaller lesions [1]. Nephrometry scores provided clinically relevant information, with all these tools being predictive of perioperative complications [2,3]. Several series have demonstrated that, in experienced hands, robot-assisted (RA) PN for complex renal tumors is feasible with short WIT, acceptable complication rates, and favorable long-term renal functional outcomes, despite an expected slightly higher risk of positive surgical margins due to the anatomical complexity of these lesions [4].

Although tumor size conventionally represents a stronger predictor of perioperative complications, it is common experience that smaller and totally endophytic lesions represent a surgical challenge, especially in terms of tumor identification and resection strategy [5]. Intraoperative use of an ultrasound probe is considered a standard option for totally endophytic tumors, in order to score the resection area on kidney surface before deepening dissection to develop a cleavage plan of the renal mass. However, once renal mass is identified, there is no room for further use of the ultrasound probe, especially for nonspheroidal-shaped tumors [6].

Near-infrared fluorescence imaging (NIFI) is conventionally used during RAPN with a standard intravenous injection of 5 ml indocyanine green (ICG). This technique has the potential to differentiate normally perfused healthy parenchyma (appearing as green) from nonperfused renal masses [7]. Indeed, NIFI was considered transiently helpful in identifying the vascular anatomy and not helpful at all for endophytic tumors [8].

Lipiodol-ethanol mixture has widely been used for achieving embolization of hepatocellular carcinoma in patients unfit for surgery; the mixture is clearly visible on noncontrast computed tomography (CT) phase and allows a proper assessment of the treated area [9]. Taking advantage of our long-term experience with preoperative superselective transarterial embolization (STE) before PN [10–12], we selected 10 consecutive patients with totally endophytic renal masses and performed purely off-clamp (OC) RAPN following superselective transarterial delivery of ICG-lipiodol mixture.

The aim of this technique was to selectively mark the renal tumor avoiding any delivery of embolizing devices, in order to tailor the surgical strategy “riding the green light”.

Herein, we report in the enclosed video a step-by-step description of this technique, and provide perioperative and early oncological and functional outcomes.

2. Patients and methods

Baseline, perioperative, and follow-up data were recorded in our institutional review board–approved prospectively collected PN database; all eligible patients provided written informed consent to both angiographic and surgical procedures.

2.1. Inclusion and exclusion criteria

Between June and July 2017, we enrolled 10 consecutive patients with totally endophytic and solitary complex renal tumors (PADUA score ≥9 and RENAL score ≥9) who were candidates to RAPN, with a baseline estimated glomerular filtration rate (eGFR) of >60 ml/min, according to the Modification of Diet in Renal Disease Study formula. All patients underwent a preoperative CT scan contrast-enhanced imaging with a detailed assessment of renal vasculature. Patients with a solitary kidney or multiple renal masses were excluded from the study.

2.2. Preoperative angiographic ICG tumor marking

All patients received prophylactic antibiotic treatment before starting the angiographic procedure. Moderate sedation was administered. Via a right femoral approach, renal artery catheterization of the affected kidney was performed through a 7 Fr RDC Vista Brite Tip IG guiding catheter (J&J Company, Cordis Corporation, Miami Lakes, FL, USA). Subsequently, a 0.035″ GT hydrophilic Terumo Guidewire was forwarded under a continuous saline flush until the proximal third of the renal artery to obtain a selective arteriogram (Terumo Europe N.V., Leuven, Belgium). Superselective catheterization of tertiary and quaternary arterial branches supplying the tumors was performed through a Renegade HI-FLO microcatheter (Boston Scientific International S.A., Nanterre Cedex, France) on 0.014″ guidewire.

ICG mark of the renal mass was performed using an ICG-lipiodol mixture with a 2:1 ratio (1.5 ml ICG + 0.75 ml Lipiodol). This ratio had the intent to optimize the selective marking of the renal mass thanks to ICG features, while delivering a minimal amount of lipiodol just to avoid a rapid ICG washout from the renal lesion.

This compound was selectively delivered into the tertiary-order arteries feeding the tumor, in order to mark the tumor and minimize any ischemic injury to the surrounding parenchyma (Fig. 1A–C).

In case of avascular renal masses, the mixture was delivered in close proximity to the lesion in order to obtain a peripheral ICG-marked rim of healthy parenchyma. All procedures were performed by two interventional uroradiologists.

2.3. Postprocedural CT scan acquisition

Owing to intrinsic hyperintensity of lipiodol, the marked area was further measured with volume rendering noncontrast CT scan immediately following the angiographic procedure (Fig. 2A and 2B). This step was crucial to improve awareness of resection strategy, considering enucleation in case of complete intratumoral ICG delivery and “minimal margin” enucleoresection in case of less vascularized lesions, where a minimal amount of surrounding parenchyma was marked. On completion of CT scan acquisition, the patient was immediately transferred to the operating theatre.

2.4. Patient and port positioning

Surgical steps of purely OC-RAPN were recently described [13]. Patients were placed in an extended flank position, and side docking with a transperitoneal five-port access was performed using a 30° scope. 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 lines, 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. A three-arm configuration was used, and Hot Shears monopolar curved scissors (Intuitive Surgical, Sunnyvale, CA, USA), ProGrasp forceps, and a large needle driver were used to perform 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.

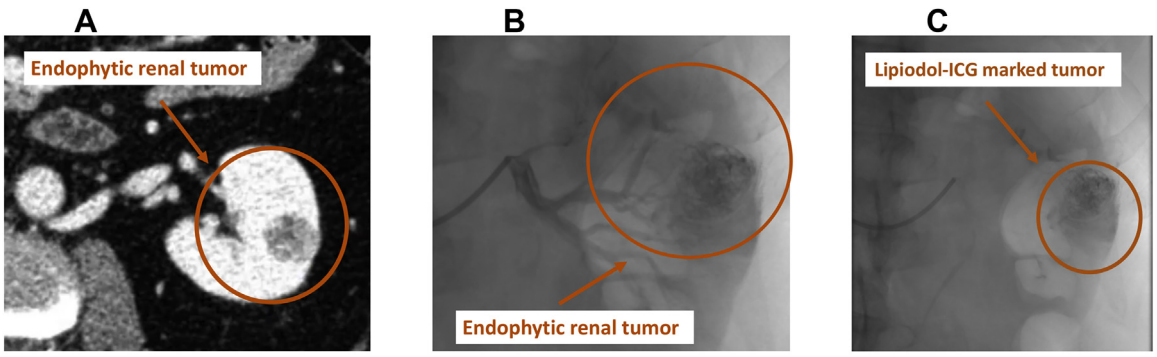

Fig. 1 – (A) Preoperative CT scan, showing a left-side 2.8 cm totally endophytic renal tumor. (B) Contrast-enhanced angiographic appearance of the mass. (C) Final appearance of lipiodol-ICG–marked tumor. CT = computed tomography; ICG = indocyanine green.

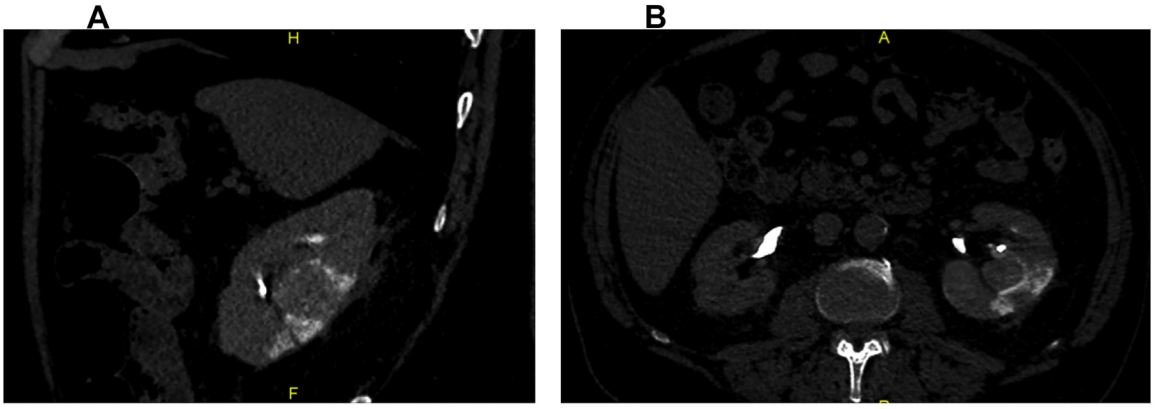

Fig. 2 – Immediate postangiographic CT scan to assess resection strategy based on estimated marked area. CT = computed tomography.

2.5. *"Ride the green light" PN*

With the use of NIFI imaging, Gerota's capsule was incised and progressively dissected until discovering the ICG-marked area (Fig. 3A and 3B). Renal parenchyma was incised without the use of intraoperative ultrasound (IUS), and surgical margins were scored with monopolar cautery under ICG fluorescence (Fig. 3C and 3D). Tumor was identified and it appeared clearly with fluorescence. A resection plane was progressively developed combining a blunt dissection with monopolar coagulation and superselective clip ligation of small feeding arterial branches. During enucleation phase, a real-time switch to conventional white light was used when selective control of arterial feeders was necessary (Fig. 3E and 3F). Two suction devices were simultaneously used in order to improve the visualization of the dissection plane. Once resection was completed, the surgical bed was inspected, and ICG-marked areas were further excised and sent for intraoperative frozen section analysis. Closure of the renal parenchyma defect was performed using a running suture with a sliding-clip technique. Eventually, a conventional 5 ml ICG bolus intravenous injection was performed to ensure maximal preservation of healthy and functioning renal parenchyma. The procedure was completed with Gerota's capsule closure and a drain was left in place.

2.6. *Postoperative course and follow-up schedule*

Deep vein thrombosis prophylaxis and early ambulation were pursued. The drain was removed when 24-h output was lower than 100 ml. Patients were usually discharged the day following flatus recovery. Follow-up visits were scheduled at 1, 3, 6, and 12 mo, including complete biochemical blood tests, physical examination, and an abdominal ultrasound. One-year CT scan with 3D volume rendering was performed, and volumetric assessment of percentage of parenchyma loss was inspected, as compared with preoperative CT scan (Supplementary Fig. 1 and 2).

2.7. *Data collection and outcome assessment*

Collected demographic parameters were age, body mass index, gender, comorbidities, Charlson score, and American Society of Anesthesiologists score. Clinical variables were tumor size, side, location and complexity according to the PADUA and RENAL scores [14,15], preoperative Hgb, and preoperative eGFR. Main surgical outcomes, including angiographic operative time, PN operative time, conversion to on-clamp PN or radical nephrectomy, estimated blood loss (EBL), hospital stay, and complications according to Clavien-Dindo system, were reported [16]. Pathological findings, including tumor size, histology, surgical margin status, and pathological stage according to pTNM, were analyzed. CT scan volumetric estimation of residual renal volume was performed at 1-yr follow-up. One-year oncological and functional outcomes (1-yr eGFR and % eGFR variation compared with baseline) and trifecta outcomes [17,18] were reported.

3. Results

Baseline data were summarized in Table 1. Superselective transarterial delivery of ICG-lipiodol mixture was successfully performed in all patients. Median angiographic

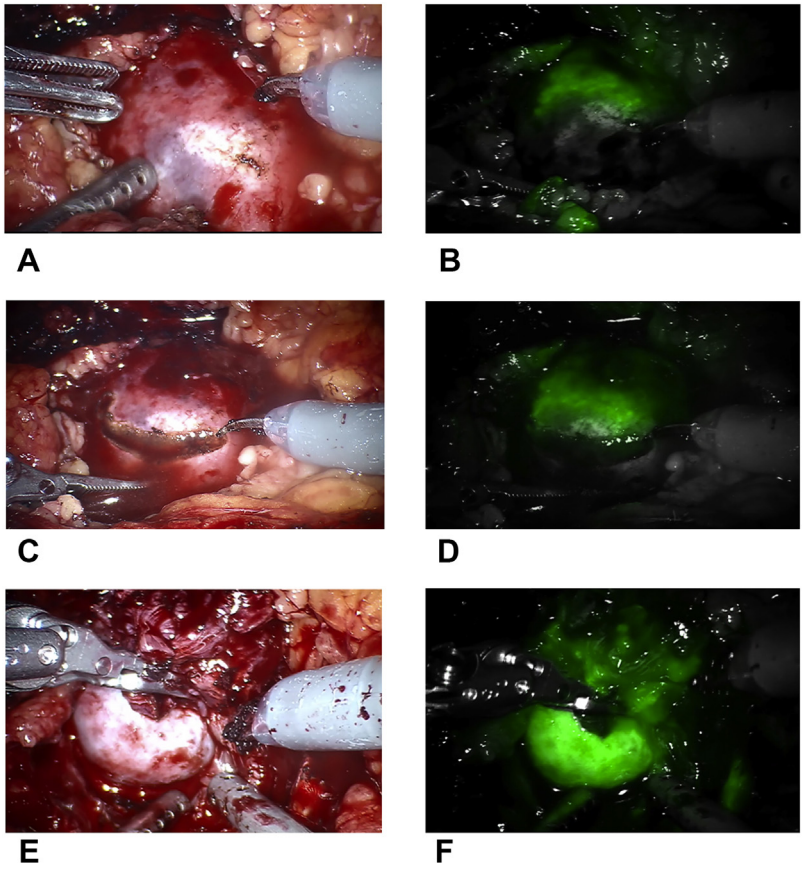

Fig. 3 – (A and B) Renal tumor intraoperative ICG near-infrared imaging identification (comparison with standard view). (C and D) intraoperative view of ICG-guided tumor margin scoring, in preparation of tumor resection (comparison with standard view). (E and F) Intraoperative view of ICG-guided enucleoresection of totally endophytic renal mass (comparison with standard view). ICG = indocyanine green.

Table 1 – Baseline and clinical data

Patients, *n*	10
Age (yr), median (IQR)	60 (52–72)
Male, *n* (%)	8 (80)
BMI (kg/m^2), median (IQR)	27.8 (22.2–31.5)
Diabetes, *n* (%)	2 (20)
Hypertension, *n* (%)	7 (70)
Charlson score, median (IQR)	5 (4–7)
ASA score, median (IQR)	2 (2–3)
Left side, *n* (%)	5 (50)
Tumor diameter (cm), median (IQR)	3 (2.3–3.8)
PADUA score, median (IQR)	10 (9–11)
RENAL score, median (IQR)	9 (9–10)
Baseline Hgb (g/dl), median (IQR)	14.9 (14.2–16)
Baseline eGFR (ml/min), median (IQR)	85 (67–104)

ASA = American Society of Anesthesiologists; BMI = body mass index; eGFR = estimated glomerular filtration rate; Hgb = hemoglobin; IQR = interquartile range.

operative time was 40 min (interquartile range [IQR] 30–65), and no procedure-related complications were observed. Median time interval between completion of angiographic procedure and tumor margin scoring was 100 min (70–135). NIFI was successfully used in all cases. Median operative time was 75 min (IQR 65–85), median EBL was 250 ml (200–350). No conversion to on-clamp PN or radical nephrectomy was needed. Median hospital stay was 3 d (2–3). At discharge, median Hgb drop was 3.3 g/dl (2.1–3.3). Perioperative course was uneventful in all patients (Table 2). Median percent eGFR decrease at discharge was 11% (10–20%); 1-yr median ipsilateral parenchymal volume and 1-yr eGFR percent decreases were 11.7% (6–20.9%) and 12.2% (5.3–13.7%), respectively. After adjusting for residual total renal volume, median 1-yr eGFR % modification was +2% (–9/+8.4; Table 3. Trifecta outcomes were achieved in 90% and 100% according to Hung et al. [17] and Khalifeh et al. [18] criteria, respectively (Table 4). No recurrences were observed at 1-yr follow-up (Table 2).

4. Discussion

The combined use of emerging technologies with robotic platform is progressively expanding the indications to RAPN even in the most complex scenario, with the aim of facilitating and standardizing resection of challenging renal masses for maximal preservation of renal parenchyma [19–21].

Complexity of RAPN mostly depends on tumor size and location. Although nephrometry scores provide an objective measure of tumor and consequently of procedure complexity, small and totally endophytic tumors represent a challenging procedure, especially in terms of tumor identification and resection strategy [22–24].

Table 2 – Perioperative and pathological data

Patients, *n*	10
Angiographic operative time (min), median (IQR)	40 (30–65)
Time between completion of angiographic procedure and tumor margin scoring (min), median (IQR)	100 (70–135)
Operative time (min), median (IQR)	75 (60–85)
Estimated blood loss (ml), median (IQR)	250 (200–350)
Hgb decrease at discharge (g/dl), median (IQR)	3.3 (2.1–3.3)
Conversion to on-clamp PN or RN, *n*	0
Positive surgical margins, *n* (%)	0 (0)
Length of hospital stay (d), median (IQR)	3 (2–3)
Histology, *n* (%)	
RCC	9 (90)
Oncocytoma	1 (10)
pT stage, *n* (%)	
1a	8 (80)
1b	2 (20)
1-yr recurrence rate, *n* (%)	0 (0)
30-d perioperative complications, *n* (%)	0 (0)

IQR = interquartile range; PN = partial nephrectomy; RCC = renal cell carcinoma; RN = radical nephrectomy.

Table 3 – Functional outcomes

eGFR percent decrease at discharge, median (IQR)	11 (10–20)
1-yr ipsilateral renal volume percent decrease, median (IQR)	11.7 (6–20.9)
1-yr eGFR volume-adjusted percent modification, median (IQR)[a]	+2 (−9/+8.4)
1-yr eGFR (ml/min), median (IQR)	74 (54-107)
1-yr eGFR percent decrease, median (IQR)	12.2 (5.3–13.7)

eGFR = estimated glomerular filtration rate; IQR = interquartile range.
[a] Based on residual renal volume adjustment [16].

In this context, OC-RAPN is considered a risky procedure, due to increased intraoperative bleeding, potentially mimicking tumor burdens and consequently the optimal dissection plane [25]. Furthermore, conventional use of NIFI imaging with ICG intravenous injection in this clinical setting has been considered of poor interest [8]. More recently, Hekman et al. [6] provided an overview of intraoperative imaging techniques to improve complete tumor resection in nephron-sparing surgery (NSS). IUS is a widely used technique to assist the surgeon in NSS, thanks to low costs and ease of use; it remains to be proved whether IUS has added value to support negative surgical margins. However, real-time imaging during tumor resection is not feasible, since the probe interferes with the resection, as it has to stay in close contact with the tissue.

We previously described STE before laparoscopic PN as a technique to minimize intraoperative arterial blood loss [10,11]; however, STE revealed intrinsic limitations in achieving the appropriate extent of ischemic area [26]. In this experience, we used transarterial delivery of ICG-lipiodol mixture to mark the tumor, omitting any embolization intent. This technique showed promising features and several advantages. First, it is a quick guide to identify tumor location, allowing minimal opening of Gerota's capsule and a straight access to surgical area. When selective intratumoral delivery is achieved, tumor enucleation can be performed "riding the green light," continuously switching from conventional light to near-infrared fluorescence during resection and to white light to ensure selective control of feeding arteries. On the contrary, when renal tumors are less vascularized, angiographic procedure may fail to selectively mark the tumor; in this case, the mixture is peripherally delivered, and the healthy parenchyma surrounding the tumor appears as "ICG dyed" and represents a "safety" surgical margin during resection. These data are made available for surgeons on postangiographic CT scan and can be used to tailor surgical strategy. Despite being viable and widely accepted strategies, there is no consensus about the superiority of enucleoresection versus a pure enucleation technique [27,28]. With regard to resection strategy, both techniques are not precluded; indeed, postangiographic CT scan images can be used to plan surgical resection strategy. Imaging analysis with volume rendering provides meticulous identification of both tumor contours and lipiodol-marked boundaries.

In the context of totally endophytic tumors, a certain amount of healthy parenchyma is likely to be sacrificed, either to identify the tumor or to provide reasonable safety of resection margins.

With regard to functional outcomes of our initial series, we evaluated the amount of healthy parenchyma spared of the treated kidney, reporting a median value of 88.3% (IQR 79.1–94); this result compared favorably with available literature on RAPN for complex/totally endophytic renal tumors. Mir et al. [29] performed a volumetric analysis in a large cohort of 92 patients who underwent cold or warm ischemia PN for renal tumors (median RENAL score 8), and found median functioning parenchyma preservation of 83% (IQR 75–91).

Furthermore, according to Khalifeh et al. [18], trifecta outcomes (WIT <25 min, negative surgical margins, and no perioperative complications) were achieved in all cases. Conversely, if considering USC trifecta criteria (no urological complications, negative surgical margins, and <10% reduction in actual postoperative eGFR compared with predicted postoperative eGFR), nine out of 10 (90%) patients achieved the all the outcomes [17].

From a practical standpoint, NIFI also has other distinct advantages in this context. Regardless of the clinical value of

Table 4 – Trifecta outcome assessment

Hung et al. [16]	NSMs: 100%	No urological complications: 100%	APop-eGFR/PPop-eGFR ratio <10%: 90%	Trifecta: 90%
Khalifeh et al. [17]	NSMs: 100%	No perioperative complications: 100%	WIT <25 min: 100%	Trifecta: 100%

APop-eGFR = actual postoperative estimated glomerular filtration rate; NSM = negative surgical margin; PPop-eGFR = predicted postoperative estimated glomerular filtration rate; WIT = warm ischemia time.

frozen section during PN, tumor bed can be inspected with NIFI, and residual ICG-dyed areas can additionally be resected and sent for frozen section. Furthermore, after completing renorrhaphy, a conventional intravenous injection of ICG can still be used to confirm absence of ischemic injury to healthy parenchyma and therefore maximal preservation of healthy parenchyma.

However, our series is not devoid of limitations. First of all, small sample size and short follow-up preclude clinically significant conclusions. Intrinsic limitations include the need of experienced interventional radiologists and, in absence of a hybrid room, the need for a time optimization between angiographic and surgical procedure. Similarly, from a surgical standpoint, firefly technology and advanced surgical skills to perform OC-RAPN are mandatory. Eventually, this technique may not be reproducible in centers with a lack of advanced skills in both robotic surgery and interventional radiology. We also acknowledge absence of experience using a clamping technique, although a conventional on-clamp approach should theoretically not affect the ICG-lipiodol marking procedure. Furthermore, in absence of a properly designed matched pair study, no comparison can be made with the conventional IUS probe–guided on-clamp technique.

5. Conclusions

Superselective ICG tumor marking technique for totally endophytic renal masses provides the opportunity to avoid the use of IUS, allowing quick tumor identification during OC-RAPN and complete control of tumor margins during the dissection regardless of resection strategy, with negligible peri- and postoperative complications and renal function deterioration. Notably, real-time switching to NIFI and again to conventional white light is continuously performed in order to maximize benefits of enhanced vision in different surgical steps. Looking forward to standardize this technique, larger series are expected.

Author contributions: Giuseppe Simone had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Simone.
Acquisition of data: Tuderti, Anceschi, Ferriero, Costantini, Minisola, Vallati, Pizzi, Guaglianone, Misuraca.
Analysis and interpretation of data: Simone, Tuderti, Anceschi, Misuraca.
Drafting of the manuscript: Simone, Tuderti, Anceschi.
Critical revision of the manuscript for important intellectual content: Simone, Gallucci.
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Appendix A. Supplementary data

The Surgery in Motion video accompanying this article can be found in the online version at https://doi.org/10.1016/j.eururo.2018.09.015 and via www.europeanurology.com.

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