Near infrared fluorescence imaging system for laparoscopic partial nephrectomy

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Introduction: *Recently, the use of indocyanine green (ICG) with near infrared fluorescence (NIRF) imaging has emerged as an alternative technique for the real-time delineation of resection margins during partial nephrectomy (PN). We aimed to assess the feasibility of using NIRF imaging with ICG during laparoscopic partial nephrectomy (LPN) to delineate the margin between normal renal parenchyma and renal cortical tumors.*

Materials and methods: *A retrospective comparison of real-time tumor margin identification and operative outcomes was conducted for 83 patients who underwent LPN with NIRF imaging (IMAGE1 system) and 74 patients who did not.*

Results: *Tumor margins were identified in 82% of cases in the NIRF group, with a rate of 79% for the clear cell renal carcinoma cases only. Volume of blood loss was higher for the NIRF than normal imaging group ($p = 0.015$), while the warm ischemia time was significantly shorter ($p < 0.01$) for the NIRF group. There was no significant difference in the pre to postoperative change in estimated glomerular filtration rate ($p = 0.38$) or rate of severe complications (Clavien grade ≥ 3; $p = 0.88$). The rate of positive surgical margins was comparable between the groups (3%; $p = 0.91$).*

Conclusions: *NIRF imaging with ICG during LPN was safe and feasible, although the surgical outcomes with NIRF alone was not significantly superior to the ones with conventional methods.*

Key Words: nephrectomy, laparoscopy, optical imaging

Introduction

Partial nephrectomy (PN) is the standard treatment for small renal masses as it sufficiently preserves the remaining renal function and improves patient prognosis,[1,2] as well as providing outcomes which are comparable to those after radical nephrectomy (RN) in terms of cancer control and survival.[3] Laparoscopy has become a more common approach for PN (LPN) in recent years due to its minimal invasiveness.[1-3] Despite its promise, one disadvantage of PN is the risk of positive surgical margins,[4] though this can be avoided by ensuring sufficient resection margin. However, excessive resection of renal parenchyma and damage to the parenchyma during renorrhaphy can both contribute to decreased postoperative renal

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function. The ideal goal, from the perspective of renal function preservation, is to resect tumors using the smallest possible margins.[5] Because it is difficult to confirm tumor localization and the margins between the tumor and normal kidney parenchyma during LPN, intraoperative ultrasound is generally used to establish resection margins. However, the resection margin that is visible on ultrasound images can sometimes differ from the actual tumor contours, which can result in positive surgical margins or excessive resection margins.

Recently, the use of indocyanine green (ICG) with near infrared fluorescence (NIRF) imaging has emerged as an alternative technique for the real-time delineation of resection margin during PN.[6-9] ICG binds with the α1 lipoprotein when injected into the bloodstream and emits fluorescence with a peak wavelength of 835 nm when excited by infrared beams near 805 nm. Visualization of this fluorescence is currently used for liver function testing, fundoscopy, circulatory function testing, and cerebral blood flow assessment during neurosurgical procedures.[10] In the field of renal cell carcinoma (RCC), it is most commonly used to detect clear cell RCC. In these cases, expression of bilitranslocase, the protein to which ICG binds, is lower in cancerous than normal tissue. Since ICG uptake is less likely in the former, the resultant difference in fluorescence between these tissues can be used, during LPN, as an auxiliary technique to localize the tumor and delineate its borders for resection. However, as conventional laparoscopy systems detect light, white light cannot be used for NIRF imaging, making it impossible to visualize the surrounding tissues.[11,12]

This problem can be overcome by using the IMAGE1 system (Karl Storz, Tuttlingen, Germany), which extracts spectroscopic images of any wavelength component from images obtained via spectral estimation using SPECTRA. This method provides net tissue structure recognition. Specifically, the system filters out the bright red portions of the visible spectrum and expands the remaining color portions, making it easier to differentiate between tissue types.[13] This allows the reconstruction of images emphasizing only blue and green, enabling ICG fluorescence (of which blue is the main component) to be more clearly detected. In addition, because narrow-band filters are not utilized, the brightness of conventional laparoscopes can be maintained. This allows visualization of surrounding tissues, which would otherwise be difficult, and facilitates manipulation using forceps.

However, the clinical usefulness of NIRF imaging during LPN is not well established, with most previous studies having used the Firefly, a component of the da Vinci surgical system, rather than IMAGE1, and doing so during robot-assisted PN (RAPN) rather than LPN. The present study, therefore, aimed to assess the safety of using IMAGE1 for NIRF imaging with indocyanine green (ICG) during LPN, and to investigate whether the margins of renal cortical tumor can be identified using this technique.

Materials and methods

Ethical considerations

This study was approved by the Institutional Review Board of the Osaka City University Hospital, and informed consent was obtained from all patients for use of their data.

Patient recruitment

The study group included 157 patients who underwent LPN at Osaka City University Hospital, between July 2011 and April 2016. Of these patients, 83 had tumors removed via LPN with NIRF imaging (NIRF imaging group, starting in August 2013), with the other 74 having undergone LPN without NIRF imaging (normal imaging group). All LPN procedures were performed by a single surgeon. NIRF imaging was contraindicated in patients with severe hepatic disorder and/or a history of allergic reaction to ICG. Prior to each surgery, computed tomography or magnetic resonance imaging was conducted.

Surgical technique

General method

LPN was performed in all cases via a transabdominal approach. After reflection and retraction of the bowel, the ureter on the anterior surface of the quadratus lumborum muscle was identified and the renal pedicle was exposed by lifting the kidney. This allowed identification of the trunk of the renal artery. Only the renal artery was clamped, with no other selective arterial clamping performed. In some cases, the tumor was resected without clamping the renal artery (off-clamp), though the renal artery could be identified in all cases. To mobilize the kidney, for ease of manipulation using the forceps, a perirenal dissection was performed along Gerota's fascia, with constant awareness of the tumor location. A wide area was dissected to ensure that the tumor and surrounding normal renal parenchyma could be sufficiently identified, including resection of Gerota's fascia immediately anterior to the tumor, along with the tumor. After tumor resection, pelvicaliceal system closure was performed using

3-0 Vicryl interrupted sutures. Renorrhaphy was performed using two-layer continuous suturing, with 2-0 V-Loc used on the first layer and 0 V-Loc used on the parenchyma. Parenchyma suturing was performed in all off-clamp cases.

NIRF and normal imaging procedures

In the NIRF imaging group, the procedure involved intravenous administration of ICG, after which the tumor margins were identified based on differential fluorescence of the tumor and normal renal parenchyma. Subsequently, the location of the tumor was again confirmed using laparoscopic ultrasound. After this confirmation was made, additional ICG was administered, as needed, and hemostasis was achieved using renal artery clamps; we then proceeded with tumor resection. On the other hand, only ultrasound was used to confirm the location of the tumor before the start of the resection in the normal imaging group.

When performing the resection, the renal cortex was sharply resected, and hemostasis was performed via soft coagulation. From the vicinity of the boundary between the cortex and the medulla, blunt separation was performed along the peelable layer and enucleoresection, with minimum resection margins, was attempted.

When working on patients in the NIRF imaging group, it was possible to use a hand-operated switch to alternate between white light and NIRF imaging, as needed. Thus, we were able to establish resection margin based on the fluorescence of normal renal parenchyma.

ICG administration

ICG was administered intravenously in all cases in the NIRF group. Prior to administration, the ICG (Diagnogreen; Daiichi Pharmaceutical, Tokyo, Japan) was dissolved in distilled water to a concentration of 1.25 mg/mL. We used a maximum dose of 2 mg/kg, which was lower than the ICG dose used in previous studies for robot-assisted PN, using the da Vinci surgical system, in which the ICG dose was adjusted to 2.5 mg/mL and administered ICG solutions in doses of 1 mL.[6,9,14,15] By comparison, for the IMAGE1 system, we adjusted the ICG to 1.25 mg/mL solutions and administered the solution in doses of 1-2 mL (1.25-2.5 mg of ICG), which provided a finer control of the total dose.

After ICG administration, the renal artery and renal vein were immediately imaged and the parenchyma fluorescence identified. As tumors are afluorescent at this point, the margin between the tumor and the normal renal parenchyma was clearly visible, allowing the resection margin to be marked. Normally, because sufficient fluorescence is achieved with 2.5 mg of ICG, the resection was immediately performed in off-clamp cases, after confirmation of the resection margin with laparoscopic ultrasound sonography. If the fluorescence weakened during the procedure, an additional dose was administered. In cases involving renal artery clamping, ICG was first administered before the renal artery was identified. The main trunk of the renal artery was then clamped, followed by tumor resection.

TABLE 1. **Patient and tumor characteristics**

	NIRF imaging	**Normal imaging**
Patient data		
Number of patients (n)	83	74
Age (median, years)	64 (24-87)	66 (26-83)
Sex (male/female)	61/22	55/19
Tumor location (right/left)	43/40	36/38
Past abdominal surgery	16 (19%)	14 (19%)
Tumor data		
Diameter (median, cm)	2.8 (1.0-7.3)	2.8 (1.1-6.0)
Nephrometry score (median) (low/moderate/high)	7 (4-11) 32/42/9	7 (4-11) 35/35/3
Clinical T stage (1a/1b/2a/2b)	58/23/1/1	63/10/0/0
Multiple tumors	2 (2%)	0 (0%)

NIRF = near infrared fluorescence

Statistical analysis

Statistical analyses were performed using PRISM 5.0 (GraphPad Software, Inc., La Jolla, USA). To compare surgical outcomes, pre- and postoperative parameters, complications, and pathological status between the NIRF and normal imaging groups, Student's t-test, Mann-Whitney U test and chi-squared test were used, as appropriate for the data type and distribution. Statistical significance was set at $p < 0.05$. Renal function was assessed by comparing pre-operative estimated glomerular filtration rate (eGFR) to the postoperative (day 14) eGFR.

Results

Patient and tumor characteristics

Patient background characteristics, tumor characteristics, and tumor pathology results are summarized in Tables 1 and 2. There were no significant between-group differences in terms of age, sex, and tumor location, and the average tumor size was also comparable between the two groups (2.8 cm; $p = 0.22$). The median R.E.N.A.L nephrometry score was 7 in both groups, with no between-group differences ($p = 0.17$) with regard to the proportion of cases with low scores (4-6; NIRF, 38% versus normal, 47%), moderate scores (7-9; NIRF, 51% versus normal, 47%) and high scores (10-12; NIRF, 9% versus normal, 6%). The one case in which multiple tumors were found in the same kidney occurred in the NIRF imaging group. One-stage surgery was performed in this case.

Perioperative parameters

Perioperative outcomes are shown in Table 2. The median blood loss was significantly higher in the NIRF than the normal imaging group ($p = 0.015$). However, this was likely because there was a significantly higher percentage of off-clamp cases in the NIRF than in the normal imaging group (NIRF, 37% versus normal, 17%; $p < 0.01$). When off-clamp cases are excluded, warm ischemia time (WIT) was significantly shorter in the NIRF than in the normal imaging group (NIRF, 18 versus normal, 25 min; $p < 0.01$).

Tumor fluorescence and margin identification

NIRF imaging confirmed that fluorescence was lower in tumors than in normal tissue, which enabled tumor margins and resection margins to be identified, making tumor resection with smaller margins possible. Compared to normal tissue, tumors were afluorescent. Tumor margins could be identified in 68 of the 83 cases in the NIRF group (82%), including 52 of the 66 cases of clear cell RCC in this group (79%; Table 3). However, there were three cases of completely endophytic tumors in the NIRF. If these cases are discounted, tumor margins were identified in 68 of

TABLE 2. **Operative outcomes**

	NIRF imaging	**Normal imaging**	**p value**
Operative time (min, median (IQR))	234 (132-398)	235 (118-389)	p = 0.69
Estimated blood loss (mL, median (IQR))	100 (10-1200)	58 (5-460)	p = 0.03
Interruption of renal artery (yes/no)	52/31	61/13	p < 0.01
Warm ischemia time (min, median (IQR))	18 (1-34)	25 (4-46)	p < 0.01
Positive surgical margin	2	2	p = 0.91
Complication (Clavien classification ≤ 3)	3	4	p = 0.88
ICG doze (mg)	3.75 (2.5-10)		
ΔeGFR (mL/min./1.73 m^2, median (IQR)	9.2 ± 9.2	8.0 ± 7.7	p = 0.38
Pathologic findings			
Clear cell RCC	66	65	
Papillary RCC	11	3	
Chromophobe RCC	1	0	
Oncocytoma	2	0	
Angiomyolipoma	1	5	
Others	2	1	

NIRF = near infrared fluorescence; IQR = interquartile range; ICG = indocyanine green; ΔeGFR = change in estimated glomerular filtration rate; RCC = renal cell carcinoma

TABLE 3. **Tumor histology and fluorescence**

	Fluorescence	Hypo or afluorescent	p value
n = 83	15 (18%)	68 (82%)	
Clear cell RCC (66)	14 (21%)	52 (79%)	
Grade 1 (17)	4 (23%)	13 (77%)	p = 0.73
Grade 2 (40)	9 (23%)	31 (77%)	
Grade 3 (9)	1 (11%)	8 (89%)	
Tumor histology			
Papillary RCC (11)	0	11 (100%)	
Chromophobe RCC (1)	0	1 (100%)	
Oncocytoma (2)	0	2 (100%)	
Angiomyolipoma (1)	1 (100%)	0	
Others (2)	0	2 (100%)	

RCC = renal cell carcinoma

the 80 in the NIRF cases (85%), with clearly delineated tumor margins established in 52 of the 63 cases of clear cell RCC (83%) in this group.

The rate of identifying tumor margin according to the Fuhrman grade was as follows: G1, 77%; G2, 77%; and G3, 89%. These proportions were not significantly different from one another (p = 0.89). The 11 cases of papillary RCC all showed decreased fluorescence, but the tumor margins could still be identified.

Postoperative outcomes

There was no significant difference in the pre to postoperative change in the eGFR between groups (NIRF, 9.21 ± 9.16 versus normal, 8.03 ± 7.64 mL/min/1.73 m^2; p = 0.38). Three cases of severe complications (defined by a Clavien grade ≥ 3) were identified in the NIRF imaging group (one case each of urinary fistula, false aneurysm and small bowel injury) and four in the normal imaging group (two cases of port-site hernia, one case of ureteral injury and one case of adhesive intestinal obstruction). However, none of the adverse events were related to the use of ICG.

With regard to postoperative diagnosis, a pathological RCC was diagnosed in 146 of 157 cases. There were 2 cases (2%) with positive surgical margins in the NIRF imaging group and 2 cases (3%) in the normal imaging

TABLE 4. **Characteristics of patients with positive resection margins**

Age (years)	Imaging	Tumor size (cm)	Nephrometry score	Pathology	Fuhrman grade	Follow up (months)	Therapy
65	Normal imaging	5.4	10h	Clear cell	2	42	Nephrectomy (local recurrence)
69	Normal imaging	3.0	5a	Papillary	1	6	NED
72	NIRF imaging	5.5	10ah	Clear cell	3	12	Medication (lung metastases)
59	NIRF imaging	1.5	9h	Clear cell	3	29	NED

NIRF = near infrared fluorescence; NED = no evidence of disease

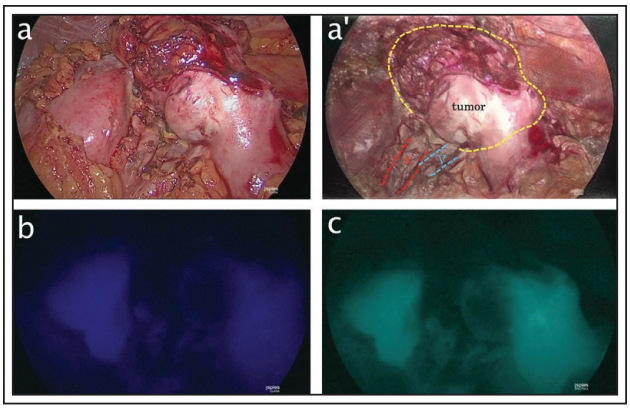

Figure 1. Comparison of **(a)** white illumination, **(a)** schema of tumor and vessels, **(b)** conventional NIRF imaging and **(c)** NIRF imaging with SPECTRA. Although it was difficult to sufficiently manipulate forceps under the light intensities used for conventional NIRF imaging, SPECTRA provided sufficient brightness to confirm surrounding tissues.

group, proportions which were not significantly different between the two groups (p = 0.91). These cases with positive margins were completely endophytic tumors and, therefore, the tumor margins could not be confirmed, even with the use of NIRF imaging. Two cases of localized positive surgical margins or distal metastasis were identified during the postoperative observation period, with additional treatment provided to these patients, Table 4.

Discussion

In our cases series, differential fluorescence provided good delineation of the tumor margins in 82% of all RCC cases. Specifically, tumor margins were identified under fluorescence in 79% of cases of clear cell RCC, and in all cases of papillary and chromophobe RCC. This difference in margin identification is likely associated to differences in tissue type between these tumors; however, accumulation of future cases is necessary because of the few cases of papillary and chromophobe RCC in our study group. Our rate of tumor margin identification was somewhat inferior to the rates that have previously been reported for successful fluorescence-based tumor identification: 65/79 (82%) and 42/47(89%) during RAPN, and 58/61 (95%) during LPN.[8,9,16] When the three completely endophytic tumors are excluded from our case series, tumor margins were identified in 85% of all RCC cases and 83% of clear cell RCC cases. This indicates that fluorescence endoscopy, using the IMAGE1 system, provides a useful auxiliary diagnostic tool for identifying tumor margins in suitable cases.

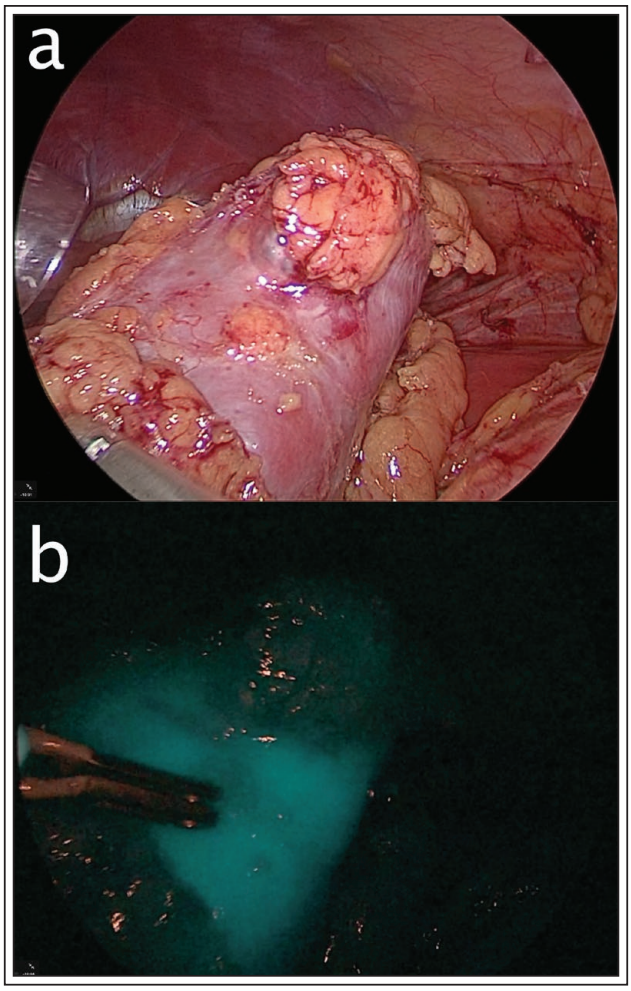

Figure 2. a) Resection under normal white illumination. **b)** Resection under NIRF imaging.

The fluorescence endoscope system, which is conventionally used, provides insufficient light intensity, which makes forceps manipulation extremely difficult. The IMAGE1 system extracts a spectral image of an arbitrary wavelength component from a spectral image obtained using the spectral estimation SPECTRA process, and can reconstruct an image by assigning red, blue and green to the spectral image.[13] The IMAGE1 system also features a hand-operated switch that can be used to alternate between white and infrared light. It is, therefore, possible to reconstruct an image emphasizing only blue and green with this system, which clearly captures the blue component that is the main component of fluorescence coloring using ICG, Figure 1 and Figure 2. Because the IMAGE1 system does not use a narrow-band filter,

it is possible to maintain the same brightness as the normal endoscope and to operate forceps. However, because of the absence of narrow-band imaging and the emphasis on the blue light component, the IMAGE1 system cannot detect small differences in fluorescence to the same extent as other systems. This may explain why our results are slightly inferior to those previously reported for other systems. Additionally, detection of differential fluorescence depends on the subjective judgment of the surgeon. Future study on objective methods of converting relative fluorescence intensities into numerical values, and methods of clarifying images using contrast processing, would help improve the effectiveness of NIRF imaging.

Regarding ICG administration, most previous studies adjusted ICG to 2.5 mg/mL and used doses of 5-7.5 mg. However, since the optimum dose for the IMAGE1 system remains unclear, we prepared concentrations of 1.25 mg/mL to facilitate dose adjustment. Our median dose was 3.75 mg (range, 2.5 mg to 10 mg), which was lower than all doses previously reported. However, Angell et al were also able to sufficiently identify differences in tumor and normal tissue fluorescence at relatively low doses of ICG.[8] Thus, we believe that the concentrations and doses used in our study are acceptable.

In terms of operative outcomes, our series of positive surgical margin rate was observed in 2% of cases in the NIRF group and in 3% of cases in the normal imaging group. These results are comparable to those of previous large-scale studies, which reported positive surgical margin rates of 1.5%-6.7%.[17-19] Although the use of NIRF imaging in our study did not reduce these rates, NIRF was useful for real-time visualization of the resection margin; more cases need to be accumulated to clearly establish the maximum benefit for this technique. Of note, NIRF imaging did allow tumor resection with smaller margins, thereby reducing the amount of renal parenchyma resected and ensuring preservation of renal function. These smaller resection margin, however, did not have an impact on the postoperative change in eGFR. We believe that this finding reflects our use of an enucleoresection technique in all cases to maintain renal arterial flow near the tumor. In contrast, WIT was significantly shorter in the NIRF imaging group than in the normal imaging group (18 versus 25 min; $p < 0.01$), although the NIRF group had more complicated cases, with no interruption 31/83 (37%) versus 13/74 (18%), as it was in Krane et al's study.[9] However, it cannot be denied that this has an influence of the learning curve and updated skills of surgeon. This, combined with shorter resection times, enabled by real-time resection margin identification, likely assisted in preserving renal function to some extent. The median volume of blood loss in the NIRF imaging group was greater than that in the normal imaging group because of the higher number of cases performed without arterial clamp in the NIRF imaging group. Finally, no adverse events related to ICG administration were observed in the NIRF imaging group, indicating that there are no safety issues associated with this technique.

It is important to note that the findings of our study are limited by the retrospective design and the absence of randomization, such that the effects of selection bias cannot be excluded.

Conclusions

In this study, we confirmed the feasibility and safety of using the IMAGE1 system for NIRF imaging during LPN. Although we could not confirm that NIRF imaging alone is superior to ultrasound, its use as an auxiliary technique for tumor margin identification could lead to improvements in LPN outcomes, with smaller resection margin. □

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