Indocyanine Green (ICG) in Urologic Surgery

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Indocyanine green (ICG) is a dye used for fluorescent-guided surgery. This review article addresses the recent surge in reported uses of ICG in various surgical fields and provides a comprehensive and up to date review of the uses of ICG in urologic surgery. UROLOGY 132: 10–17, 2019. © 2019 Elsevier Inc.

There has been a surge in the reported uses of indocyanine green (ICG) in various surgical fields. Indeed, a PubMed search of the words "indocyanine green" shows that in the 20-year span between 1998, 2008, and 2018, the number of published articles per year rose from 192 to 264 to 961, respectively. Despite this increase in reported uses of ICG, there is legitimate controversy regarding the efficacy of many of these techniques because few randomized controlled clinical trials on the subject have been performed.[1-5] Urology has adopted this technology in many procedures and the question remains which of these uses are most effective.

HISTORY OF FLUORESCENCE IN MEDICINE

The story of fluorescence in medicine begins in 1896 when Helmholtz wrote about fluorescence in the eyes of insects. By 1911, Stubel recognized that almost all human tissues can fluoresce and he catalogued the different colors emitted by various tissues when excited by filtered ultraviolet light. Over the next few decades, different uses of fluorescence phenomena were investigated, but a decisive moment came in 1943 when Herly brought a UV light and filter to the operating room to differentiate benign and malignant tissue after removing the surgical specimens. He reported that 199 of 200 diagnoses made with filtered ultraviolet were consistent with microscopic diagnoses.[6]

In 1946, Moore injected a fluorescent dye intravenously to help intraoperative differentiation of normal and neoplastic tissue based on the degree of fluorescence of each tissue.[7] He reported 9 failures to identify neoplastic tissue of 46 attempts. Since this technique was not fully reliable, fluorescence-guided surgery did not become a standard technique of the 20th century oncologic surgeries. But the potential utility of fluorescence was never abandoned, and indeed a fluorescent dye called ICG has been used for over 50 years.[8]

HOW FLUORESCENCE WORKS

Fluorescence is caused by incident light that excites the target and causes light emission of a particular wavelength. This phenomenon is harnessed by shining excitation light of a particular wavelength through a filter that only allows the wavelength of that excitation light to pass. The target becomes excited and emits fluorescent light that then passes through a second filter that only allows the wavelength of that fluorescent light to pass. Because the other wavelengths of light have been filtered out, a sensor receives only the fluorescent light.

ICG IN MEDICINE AND ITS SAFETY PROFILE

ICG is a fluorescent dye that was developed by Kodak Research Laboratories in 1955. It was Food and Drug Administration (FDA) approved in 1959 and has been used for retinal angiography, liver clearance testing, and cardiac output monitoring.[9] Among the commercially available fluorophores, ICG is particularly useful for fluorescence-guided surgery because its excitation peak (780 nm) and emission peak (820 nm) are in near-infrared (NIR). This spectrum of light is best suited for intraoperative imaging because wavelengths below 700 nm are absorbed by molecules in tissues, such as hemoglobin and myoglobin, whereas wavelengths above 900 nm are limited by water and lipid absorption wavelengths.[10] ICG thus has the perfect excitation and emission profile to be used in vivo for fluorescence-guided surgery.

ICG has a well-documented safety profile. In a survey of 3774 ICG angiograms performed on 2820 patients between 1984 and 1992, Obana et al reported 13 cases of adverse reactions (10 of which did not require treatment), 1 case of a painful vein, and 2 cases of hypotension that required treatment for shock.[11] The mechanism underlying shock is unclear, although some have proposed it is due to the iodide in ICG. However, adverse events have

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occurred in iodide-free preparations of ICG and ICG has been used safely in patients with recorded iodine allergies. Of note, the first case of anaphylactic shock after intravenous ICG use during robotic partial nephrectomy (PN) was reported in 2017.[12] Still, the clinical potential of ICG seems to outweigh its almost negligible risks.

PHARMACOLOGY OF ICG

The pharmacology of ICG has also been well studied. ICG is a water-soluble, anionic, and amphiphilic tricarbocyanine molecule that does not have any known metabolites. When injected intravenously, it quickly becomes protein-bound, which confines it to the intravascular compartment. The vasculature becomes fluorescent in less than a minute and tissue, such as renal parenchyma, fluoresces seconds later. ICG has a half-life of 150-180 seconds and is excreted into bile entirely by the liver using a transport protein called glutathione S-transferase; thus, a new injection of ICG can be administered during surgery after about 15 minutes.[10,13,14]

Golijanin et al elucidated the mechanism of ICG fluorescence in the kidney. They used immunohistochemistry with polyclonal antibodies to show the presence of a membrane protein called bilitranslocase in the proximal and distal convoluted tubules of normal kidney cells. Bilitranslocase transports organic anionic molecules like ICG from the blood into the cell, but is down-regulated in renal cortical tumors. This lack of bilitranslocase, the ICG carrier protein, then explains why cancerous cells are hypofluorescent under ICG near-infrared fluorescence (NIRF) compared to that seen in normal and benign tissue.[15]

The mechanism underlying intraureteral use of ICG is not as clear. Urothelial cells of the urinary tract, unlike the cells of the kidney, do not have absorption capabilities, yet ICG can be injected intraureterally to not only identify the ureter, but also to differentiate viable and nonviable ureteral tissue. One hypothesis offered by Lee et al is that ICG binds to urothelial surface proteins in viable ureteral tissue, but does not do so in nonviable ureteral tissue.[16] ICG is not yet FDA approved for intraureteral use, but as we will see below, this technique has tremendous promise.

FLUORESCENCE IMAGING TECHNOLOGIES

In 2005, the Novadaq Technologies SPY system was approved by the FDA for use in cardiac surgery and since then many more types of uses have been approved.[17,18] As of writing this paper, Novadaq, which was acquired by Stryker Corporation, markets 4 different NIRF systems on its website: SPY Elite for open surgeries, PINPOINT for endoscopic minimally invasive surgeries, SPY-PHI for visualizing blood flow and tissue perfusion with a portable handheld device, and LUNA for angiography of the extremities.[19] We have since seen the release of many NIRF systems, and as Van Den Berg et al pointed out in 2012, at least 14 different NIRF imaging systems have been used in clinical urology.[20]

The NIRF systems differ in terms of their hardware and software. For example, the Hamamatsu Phototonics' Photon detection efficiency (PDE) and Fluoptics Minatec's Fluobeam are both handheld, while the VS3 Iridium can be stationed for open and endoscopic surgery.[10] The VS3 Iridium software allows simultaneous viewing of infrared (IR) and visible light images, and it can overlay and fuse IR and visible images to highlight particular features of the anatomy.[21] The Da Vinci Si and Xi Firefly system has the Novadaq SPY imaging system incorporated into its software. From the robotic console, the surgeon can toggle back and forth between normal illumination and fluorescence modes.[22]

USES OF ICG IN OTHER SURGICAL FIELDS

Angiography and Tissue Perfusion

In colorectal surgery, ICG has been used to assess the perfusion of possible anastomoses sites before deciding where to resect the bowel. A prospective, multicenter, open label clinical trial of 139 patients undergoing left-sided colectomy and anterior resection reported an anastomotic leak rate of 1.4%, which was lower than the 3%-15% anastomotic leak rates reported in the literature.[23]

In plastic surgery, a similar idea has been applied for assessing the perfusion of skin flaps. A retrospective review of 13 deep inferior epigastric artery perforator flaps following liposuction showed that the partial flap loss and fat necrosis rates decreased from 71.4% to 0% when ICG angiography was used ($P = .02$). A different retrospective review of 40 patients showed that ICG angiography can safely be used to guide nipple sparing mastectomy and direct-to-implant breast reconstruction.[24] One wonders if these techniques can improve outcomes in transgender genital reconstruction surgeries, which have extremely high complication rates.[25] To our knowledge, no such cases have been reported.

ICG angiography is also used for cardiac angiography, but there is debate regarding its value compared to conventional angiography.[18,26,27] A recent study pointed out that NIRF technology combined with complex angiography and perfusion analysis can show physiologic response to grafting, while conventional angiography only shows coronary anatomy.[18]

Lymphography and Sentinel Lymph Node Mapping

A review article concluded that ICG lymphography may be useful to visualize lymphatic channels, aid lymphovenous bypass, stage severity of lymphedema, and assess follow-up lymphedema status. The authors also argued that ICG can improve node detection accuracy when combined with a different tracer during sentinel lymph node biopsy (SLNB) for cutaneous melanoma and suggested that ICG might be sufficient as a single tracer during SLNB for breast cancer.[8]

A retrospective study of 197 cases of sentinel lymph node mapping for uterine and cervical cancer was performed with ICG alone. The study showed that the overall detection rate of sentinel lymph nodes was 95%, with bilateral mapping in 79% of cases. If this high detection rate is validated by further studies, it may be reasonable to replace hemi-pelvic lymph node dissection (LND) with ICG-guided SLN mapping.[28]

Tumor and Anatomic Imaging

ICG has been used to aid identification of pulmonary nodules and metastases. This technique avoids the need for thoracotomy and improves the accuracy of lymph node sampling, but it is limited by depth of penetration, poor specificity, ICG leakage, and false-negative sentinel lymph nodes.[2,10]

In response to some of the limitations of ICG, a novel procedure that takes advantage of "second-window ICG" was developed. The normal half-life of ICG until it is cleared by the liver is usually a few minutes ("first-window ICG"), but if a high dosage of ICG is injected intravenously 24 hours before surgery, nanoparticles of ICG accumulate only in the tumor (second-window ICG). This phenomenon is believed to be due to the complex angiogenesis that occurs in tumors once they have outgrown their vascular nutrient supply: namely, defective endothelial cells with wide fenestrations form that allow small molecules like ICG to pass. This technique was reported successful for 14 of 18 patients who underwent meningioma resection.[4]

USES OF ICG IN UROLOGY

Partial Nephrectomy: Tumor Localization

In 2011, Tobis et al reported their initial clinical experience for 11 patients who underwent NIRF with ICG during robotic PN (RPN). The goal was to use ICG to differentiate normal and malignant tissue, and to highlight the renal vasculature. ICG was injected intravenously during surgery and the Da Vinci Si Firefly imaging system was used to detect NIRF. Ten of the 11 patients had malignancy on final pathology, and of the 10 patients with malignancy, 7 had hypofluorescent tumors and 3 had isofluorescent tumors compared to surrounding parenchyma.[29] These results were promising, but it remained unclear if ICG NIRF-guided localization of tumor could improve RPN outcomes.

In 2012, Krane et al reported the largest comparative study for ICG NIRF-guided localization of renal tumor. The study included 94 RPN patients (47 with ICG and 47 without ICG). The only statistically significant difference between the 2 groups, which were similar in demographics and tumor complexity, was 2 minutes of warm ischemia time in favor of the ICG group (from 17 minutes to 15 minutes). There was no significant difference in positive margin rates.[30] The authors concluded that saving 2 minutes of warm ischemia is not enough to justify ICG use in RPN.

A large series reported by Manny et al in 2013 supported this conclusion. The authors investigated if ICG fluorescence patterns can predict malignancy or histology patterns in RPN. They performed 100 RPN's and classified fluorescence into 3 categories: isofluorescent, hypofluorescent, and afluorescent (no visible uptake of dye). The overall rates of ICG differentiating benign and malignant tissue showed a positive predictive value of 87%, negative predictive value of 52%, sensitivity of 84%, and specificity of 57%. The authors' ICG classification system did correlate with histology, but did not have reliable prediction rates of benign vs. malignant lesions.[31]

In 2015, Bjurlin et al reviewed the literature on ICG-guided tumor localization during RPN and argued that the results were promising but inconsistent because of differences in ICG dosing.[13] However, Angell et al attempted to optimize a dosing strategy and reported a histologic prediction accuracy of only 86%. This number was admittedly not sufficient for guiding tumor margin resections, but Angell et al noted that this dosing strategy can help newer surgeons who do not have the experience to determine surgical margins without assistance.[32]

Finally, a group in Italy recently tried a novel technique for NIRF localization of renal tumors. They performed preoperative renal angiography from a right femoral approach and used superselective transarterial delivery of a novel lipiodol-ICG mixture (1:2 volume ratio). The lipidiol was intended to prevent washout of the ICG before the surgery. These authors only have experience in performing off-clamp PN and they reported that the technique improved visualization of tumor margins for the 10 patients in the study, all with negative surgical margins.[33] However, no comparative data is yet available for this technique.

Partial Nephrectomy: Selective Arterial Clamping

Selective arterial clamping with ICG NIRF provides the surgeon with an intraoperative renal angiogram so that he or she can selectively clamp minor arteries instead of clamping the main renal artery. The goal is to improve long-term functional outcomes by reducing ischemia in normal renal parenchyma.

In 2012, Borofsky et al reported a matched pair analysis of RPN with ICG-guided selective arterial clamping (n = 27) and RPN with conventional main renal artery clamping (n = 27), all performed by the same surgeon. Short-term follow-up (mean 13.5 and 12.7 days) showed only a 1.8% loss of estimated glomerular filtration rate (eGFR) in the selective arterial clamping cohort compared to the 14.9% loss of eGFR in the conventional main renal artery clamping cohort (P= .03).[34]

Similar results were published by Harke et al in another matched pair analysis of RPN with ICG-guided selective arterial clamping (n = 21) and RPN with conventional main renal artery clamping (n = 15), all performed by the same surgeon. In this study, eGFR loss at 5-10 day

follow-up was 5.1% vs 16.1%, also in favor of selective arterial clamping.[35]

This difference in functional outcome, however, may be irrelevant in the long term. In a matched pair analysis with longer follow-up, McClintock et al showed that these trends become statistically insignificant (P= .07) at 3 months. McClintock et al suggest that perhaps eGFR is not a sensitive enough tool to detect long-term benefit of this technique.[36] On the other hand, it is likely that long-term renal function simply correlates more with renal volume preservation than ischemia time.[37]

Donor Nephrectomy and Kidney Transplantation: Vasculature Identification and Assessment of Allograft Perfusion

ICG fluorescence has been used to identify vasculature during donor nephrectomy, but the overall utility of this technique and potential difference in outcomes has yet to be demonstrated.[38] Similarly, intravascular ICG administration can show allograft perfusion during kidney transplantation and can perhaps help complex vasculature reconstruction, but the effect of this technique on long-term kidney function is as of yet unclear.[39]

Radical Prostatectomy: Identification of Neurovascular Bundle and Landmark Artery, and Sentinel Lymph Node Mapping

Kumar et al reported that 30% of neurovascular dissections were revised under ICG guidance and Mangano et al reported easier identification of the landmark artery of the neurovascular bundle with ICG.[40,41] No comparative studies of outcomes with this technique have been performed.

ICG has also been used for SLN mapping during robot-assisted radical prostatectomy (RARP), but to varying results. A systematic review of 21 studies on SLN procedures for prostate cancer found a median sensitivity of 95.2%, but the sensitivities ranged from 50% to 100%.[42] In the first prospective, randomized trial comparing fluorescence-supported extended pelvic LND (ePLND, n = 59) and regular ePLND (n = 59) during RARP, ICG-supported ePLND only produced a sensitivity of 44%.

The reasons for the discrepancies in reported sensitivities are not entirely clear, but may be due to differences in surgical approach and application site of the tracer. It is also possibly due to a phenomenon called "skip lesion," which refers to how the first lymph node in a chain can be obstructed by a high metastatic burden and cause subsequent positive lesions not to be detected. In any case, Harke et al concluded that ICG lymphography is not sensitive enough to replace ePLND for prostate cancer, but it can aid identification of lymphatic drainage and result in a higher yield of lymph nodes during RARP.[43]

Radical Cystectomy: Sentinel Lymph Node Mapping, Tumor Localization, and Mesenteric Angiography

Sentinel lymph node mapping may also be useful for bladder cancers. In 2012, Inoue et al were the first to report the safety and feasibility of SLN mapping with ICG fluorescence in bladder cancer patients. They performed radical cystectomy and PLND with ICG on 12 patients, and in 7 of those patients, a clear lymphatic pathway along the inferior vesical vessels to the internal iliac LN's was demonstrated.[44]

Polom et al performed a study comparing SLNB with the radioactive dye technetium radiocolloid and SLNB with ICG. They performed both techniques on 50 patients, using both a gamma ray detection probe and a NIRF camera during the surgery, and found that both techniques are useful for identifying lymph nodes. But they found ICG to be advantageous over radioactive dye technetium radiocolloid because it avoids radiation, is relatively cheap, and is quick and easy to use.

There are other reported uses of ICG during cystectomy, though they are limited to initial clinical experiences. For example, during robot-assisted orthotopic ileal neobladder formation, ICG angiography can identify vascular arcades and assess vascularity of bowel segments, which may prevent bowel and ureteral ischemic complications; as noted above, this technique has been used in colorectal surgery. In addition, ICG tumor marking might allow precise resection and tissue sampling of advanced bladder cancer and may also aid partial cystectomy by marking the margins of the tumor.[45,46]

Penile Cancer: Sentinel Lymph Node Mapping

In 2017, Bjurlin et al published a demonstrational video in *Urology* describing their novel technique for robotic inguinal lymphadenectomy using ICG NIRF for the treatment of penile cancer. They performed 10 inguinal dissections in 5 patients and reported significant reduction in morbidity compared to the open approach.[47] In 2018, Sávio et al also published a demonstrational video in *Urology*, but showed a combined partial penectomy with robotic inguinal lymphadenectomy using ICG NIRF. This surgery similarly had minimal morbidity and avoided the need for a two-stage procedure.[48] Of course, further prospective, randomized controlled studies are needed to show the efficacy of this procedure (Fig. 1; Table 1).

Ureteral Surgery: Perfusion Assessment and Structural Identification

ICG was initially administered intravenously during ureteral surgery for the purpose of assessing ureteral perfusion and viability. For example, in 2013, Bjurlin et al described 43 cases of upper urinary tract reconstruction with intravenous ICG including pyeloplasty (n = 20), ureteral reimplant (n = 13), ureterolysis (n = 7), and ureteroureterostomy (n = 2). They reported a 100% success rate (defined as radiographic and symptomatic improvement) for all of the pyeloplasty, ureteral implant, and ureteroureterostomy patients, and a 71.4% success rate for the ureterolysis patients.[36] However, one of the limitations of intravenous ICG administration is that ICG is not limited to the ureter, resulting in background fluorescence.

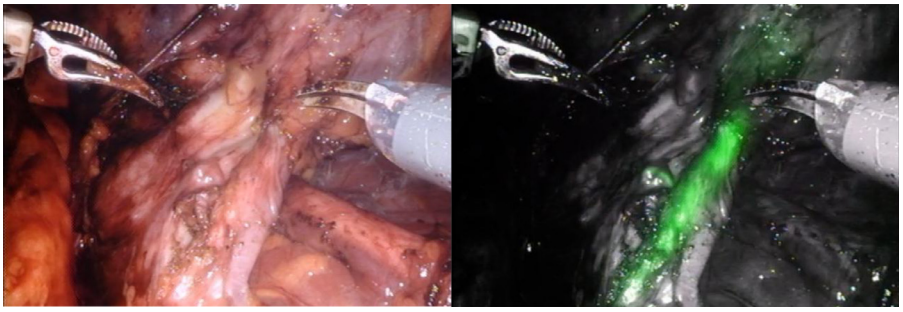

Figure 1. Photo comparisons of intraoperative visible light (left) vs intravenous ICG under NIRF (right). The renal artery is identified in green. ICG, indocyanine green; NIRF, near-infrared fluorescence. (Color version available online.)

This limitation led Lee et al to try a novel, intraureteral off-label use of ICG. They reported 26 robotic-assisted ureteral reconstructions (RUR) including ureterolysis (n = 4), pyeloplasty (n = 8), ureteroureterostomy (n = 9), and ureteroneocystostomy (n = 5). There were no perioperative complications of off-label intraureteral use of ICG and at a mean overall follow-up of 12 months, all procedures were clinically and radiologically successful.[49]

Intraureteral ICG administration was helpful in many ways because, unlike with intravenous ICG use, only the urinary tract was highlighted by fluorescence. In patients with retroperitoneal fibrosis, the authors were able to easily identify the ureter and dissect the fibrosis away from the great vessels. In general, a clear path of dissection along the ureter was easily identified and in one case of an ectopic and malrotated kidney, the displaced ureter and ureteropelvic obstruction were quickly localized (see Fig. 2). Also, because viable ureteral tissue fluoresces a darker green than pathologic ureteral tissue does, stricture margins were identified in all ureteral stricture cases.[49]

The utility of intraureteral ICG is perhaps best demonstrated by its use in the most complex RUR's. In 2015, a case of robotic partial nephroureterectomy in a patient with complete ureteral triplication was reported. The patient had 3 ureters all associated with their own collecting system and their own bladder orifices. The upper-most renal moiety was chronically obstructed and the associated ureter was dilated. A partial nephroureterectomy was performed with intraureteral ICG identifying the correct ureter and associated renal pelvis. Intravenous ICG was then used to assess the perfusion of the surgical margins, indicating viability of the renal parenchyma.[50] There is little doubt that in a complex RUR such as this, ICG identification of the correct ureter and renal pelvis is extremely helpful. The assessment of viable renal parenchyma with intravenous ICG may be shown in future studies to be useful as well.

Finally, the use of ICG during robotic ureteroenteric reimplantation for the management of benign anastomotic structures has recently been described. In a retrospective review of 8 patients who underwent 10 robotic ureteroenteric reimplantations, ICG was injected antegrade and/or retrograde into the lumen of the ureter, and retrograde into the lumen of the urinary diversion. ICG facilitated identification of the strictured ureter and urinary diversion, and outlined ureteroenteric stricture margins. There were no perioperative complications of intraureteral ICG use and at median follow-up of 29 months, 8 of 10 of the ureteroenteric reimplantations were clinically and radiologically successful. The surgery is technically very difficult and innately morbid in terms of 90-day complications; but a robotic vs open approach, which is greatly facilitated by intraureteral ICG use, significantly decreases the length of stay and amount of adhesions created in case of reoperation.[51]

Table 1. Reported uses of ICG in urologic surgery

Partial Nephrectomy	**Donor Nephrectomy**	**Kidney Transplantation**
Identification of vasculature Selective arterial clamping Tumor localization	Identification of vasculature	Assessment of allograft perfusion
Radical Prostatectomy	**Radical Cystectomy**	**Penile Cancer**
Sentinel lymph node mapping Identification of neurovascular bundle and landmark artery	Sentinel lymph node mapping Tumor localization Mesenteric angiography Identification of vasculature	Sentinel lymph node mapping
Ureteral Surgery	**Adrenalectomy**	**Varicocelectomy**
Identification of ureter and renal pelvis Perfusion assessment Identification of ureteral strictures	Tumor localization Identification of vasculature	Lymphatic sparing Identification of vasculature

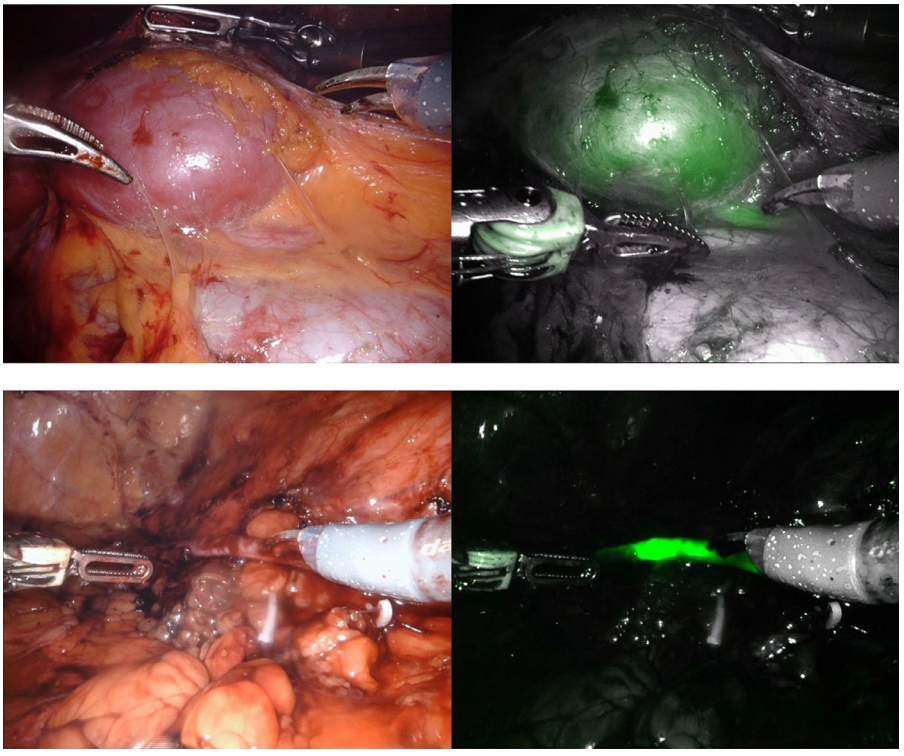

Figure 2. Photo comparisons of intraoperative visible light (left) vs intraureteral ICG under NIRF (right). The top row shows photos from a robotic heminephrectomy for a duplicated collecting system. Intraureteral ICG under NIRF identified one of the ureters and its associated renal pelvis. The bottom row shows photos from a robotic ureterolysis. Intraureteral ICG highlighted the path of the ureter under NIRF, allowing for easier ureteral dissection. ICG, indocyanine green; NIRF, near-infrared fluorescence; UPJ, ureteropelvic junction. (Color version available online.)

Adrenalectomy: Tumor and Vasculature Identification

ICG differentiation of tumor and parenchymal tissue during adrenalectomy does not seem reliable. Interestingly, however, Colvin et al reported that adrenocortical tumors tend to be hyperfluorescent and that pheochromocytomas tend to be hypoflourescent.[52] It is possible that this difference in fluorescence could yield valuable clinical information. ICG may also be helpful in identifying vasculature during adrenalectomy, but there are no randomized controlled clinical trials on the subject to date.

Pediatric Urology

Few articles on ICG use have been published in pediatric urology. To date, Herz et al are the only surgeons to report selective arterial mapping during pediatric robotic heminephrectomy. In a case series of 6 pediatric patients in the *Journal of Pediatric Urology*, Herz et al argued that selective arterial mapping with intravenous ICG is helpful for preventing innocent moiety damage that often goes unnoticed postoperatively unless there is acute ischemia or reduced renal function.[53]

Lee at el presented a case of robotic lower pole heminephrectomy with intraureteral ICG in a 13-year-old pediatric patient with a duplicated collecting system not following Weigert-Meyer law. They concluded that intraureteral ICG helped to definitively identify the ureteral anatomy intraoperatively.[54]

Interestingly, a novel technique for lymphatic sparing laparoscopic Palomo varicocelectomy in children was described. ICG was not given intravenously (which has been done for adult varicocelectomies[55,56]), but intratesticularly to visualize the lymphatic vessels under NIRF for lymphatic sparing. Eighteen month follow-up on 25 patients ranging from 12 to 16 years old revealed no varicocele recurrences and no postoperative hydroceles. Postoperative hydrocele has a 20%-30% incidence rate, so the authors claimed preliminary success with this technique.[57]

CONCLUSION

ICG has been described as "a hammer looking for a nail."[5] It remains unclear if any of the aforementioned techniques will ultimately be adopted as standard procedures. Yet, as NIRF technology and its integration with complex surgeries continue to improve, the urologic community is beginning to identify the strengths and weaknesses of different ICG techniques. That urologists are electing to repeatedly use these techniques speaks to their promise. However, we must remain focused on evidence-based medicine, especially considering the potential glamour and marketing power of fluorescent-guided robotic surgery. In the near future, we will likely see novel and more sensitive ICG

probes, such as peptide-conjugated ICG, protease-activated ICG, and ICG-loaded red blood cells, advance from the laboratory to the operating room.[58-60] Until then, the next step will be to investigate the merit of current technology with well-designed comparative studies.

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