International Urology and Nephrology
https://doi.org/10.1007/s11255-019-02126-0

UROLOGY - REVIEW

Intraoperative ICG-fluorescence imaging for robotic-assisted urologic surgery: current status and review of literature

Ram A. Pathak[1] · **Ashok K. Hemal**[1]

Received: 25 December 2018 / Accepted: 7 March 2019
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Abstract

Purpose With the availability of near-infrared fluorescence (NIRF) imaging using indocyanine green dye (ICG) to the robotic platform, utility of this imaging technology has evolved significantly across the board for ablative and reconstructive procedures. Herein, we describe the potential indications of indocyanine green for both oncologic and non-oncologic applications in robot-assisted laparoscopic urologic surgery.

Methods A narrative mini-review was performed in November 2018 using PubMed, Scopus, EMBASE, and Web of Science databases utilizing the following search phrase: "indocyanine green fluorescence robotic surgery" resulting in 104 articles of which 30 articles had urologic-pertinent applications. All 30 articles, and the references within, were reviewed and judged for scientific integrity and merit. Articles with non-novel findings or similar conclusions to original papers were omitted.

Results ICG does not have a urologic FDA indication, though it has been used off-label for urologic surgery since 2006. Fluorescence-augmented surgery with ICG can facilitate oncologic surgery in the adrenal gland, kidney, bladder, prostate, and retroperitoneum, in addition to lymph node dissection for various malignant pathologies. ICG-NIRF can enhance non-oncologic surgery including ureterolysis, ureteroureterostomy, ureteral re-implantation, pyeloplasty, and urinary diversion in both the adult and pediatric populations.

Conclusions Although it is not necessary to utilize fluorescence-enhanced surgery in all cases, the authors find the utilization of ICG-NIRF in complex and highly technical surgeries useful.

Keywords ICG · Molecular guided · Prostatectomy · Cystectomy · Adrenalectomy · Urinary diversion · Ureter · Pyeloplasty · Kidney · Nephroureterectomy · Robot · Partial nephrectomy · Reconstruction · Laparoscopy · Robotic

Introduction

Robotic technology enables the performance of complex urologic surgeries with greater precision, miniaturization of instruments, and smaller incisions than traditional laparoscopic or open approaches. An evolution is image-guided surgery: the principle that optical enhancements can improve visualization of internal anatomical structures and facilitate surgery. Real-time intraoperative identification of malignant versus benign tissue can help surgical outcomes by simultaneously decreasing positive surgical margin and local recurrence rate while preventing over-aggressive resection of vital structures. A particular enhancement that has been utilized significantly for both oncologic and non-oncologic surgeries is indocyanine green (ICG) with near-infrared fluorescence (NIRF). In contrast to white light, NIRF, with the addition of fluorophores (ICG), permits deeper photon penetration, superb optical contrast, less scatter, and a high signal-to-background ratio [1, 2]. Optical enhancement using ICG-NIRF has been shown to facilitate surgical performance in both the oncologic and non-oncologic settings and is the crux of this review article.

ICG received initial FDA approval in 1959 (NDA 011525). Based on the most recent labeling package insert submitted in 2015, the current FDA-approved indications for ICG include determination of cardiac output, hepatic function, and liver blood flow, as well as, ophthalmic angiography [3]. ICG has been used off-label for urologic surgery since 2006 [4]. Initially described for open partial

✉ Ashok K. Hemal
ahemal@wakehealth.edu

Ram A. Pathak
rpathak@wakeheatlh.edu

[1] Department of Urology, Wake Forest Baptist Medical Center, Winston-Salem, NC 27157-1094, USA

Published online: 22 March 2019

nephrectomy in the urologic literature, intravenous injection of ICG was utilized to clearly demarcate the vasculature and fluorescence patterns of the tumor in 15 patients [4]. The technology was later developed in a laparoscopic and robotic cohort utilizing the Endoscopic SPY Imaging System [5]. The da Vinci surgical platform (Intuitive Surgical, Sunnyvale, CA) equipped with Firefly technology (Novadaq Technologies, Mississauga, ON) allows surgeon-controlled utilization of NIRF. The robotic application was first studied in patients with suspected renal cell carcinoma. Subsequently, other urologic organs have been extensively studied including prostate [6], bladder [7], and adrenal gland [8].

The urologic oncologic and non-oncologic applications of ICG-NIRF are vast. For oncologic surgery, molecular-guided surgery can facilitate upper, combined upper and lower, and lower tract pathologies as well as lymph node dissection within the retroperitoneum and pelvis. For non-oncologic surgery, specifically reconstructive surgery, ICG-NIRF allows for deeper tissue penetration and real-time perfusion status that can aid in ureteral stricture repair, anastomotic viability, and identification of critical vasculature.

ICG pharmacodynamics

ICG, a tricarbocyanine, is a water-soluble molecule with a peak spectral absorption at 806 nm and with peak emission fluorescence at 830 nm [9]. ICG is only visualized with near-infrared fluorescence (found on the da Vinci Surgical Systems equipped with Firefly® technology). After intravenous administration, ICG becomes rapidly bound to albumin (95%) and is near-instantaneously visualized within the vasculature and target organs. ICG should not be used in patients with concomitant allergy to iodides and is considered contraindicated for these patients. Anaphylactic deaths have occurred after administration of ICG during cardiac procedures; however, no studies have found any impact of ICG on carcinogenesis, mutagenesis, and impairment of fertility [3].

ICG should be handled in with generalized sterile techniques as with an intravenously administered agent. Common drug interactions that can reduce the peak absorption of ICG include sodium bisulfate found in many heparin products [3, 9]. ICG is classified as a pregnancy category C compound and thus further research in this area is warranted prior to administering ICG in pregnant females [3].

According to the FDA, the usual dose for ICG varies with age with adults receiving 5.0 mg and children and infants receiving 2.5 mg and 1.25 mg, respectively. The total dose should be less than 2 mg/kg. For urologic applications, the authors reconstitute ICG in sterile water to formulate a 2.5 mg/ml solution, which can be injected intravenously or into the target organ as illustrated in the following sections (Table 1).

Oncologic surgery

Upper tract pathologies

Renal cancer

Regarding renal pathologies, ICG-NIRF has shown to facilitate both radical and partial nephrectomy (Table 2) secondary to the ability to identify vasculature and tumor fluorescence patterns, allow for selective and super-selective clamping, assess oncologic efficacy, and examine renorrhaphy viability [10]. Cortical renal tumors exhibit reduced expression of bilitranslocase, which binds to ICG, allowing intraoperative, real time, identification of cancerous vs. normal tissue.

In a prospective comparative study of 94 patients who underwent partial nephrectomy, ICG-NIRF was shown to decrease warm-ischemia time (15 vs. 17 min, $p = 0.01$), with no increase in positive surgical margin rate or complications despite similar preoperative tumor characteristics. Furthermore, the ICG-cohort more frequently adopted selective clamping versus total clamping [11]. The authors argue the use of ICG-NIRF facilitates nephron-sparing

Table 1 Dosage instructions for ICG with respect to pathologic organ

Pathologic organ	Dosing Instructions for 2.5 mg/ml ICG solution
Kidney	1–2 ml
Adrenal	1–4 ml
Prostate	0.4 ml
Upper tract UC	For hilar identification: 1–2 ml For retrograde (ureteral): 5 ml For bladder filling: 10 ml ICG + 100–200 ml saline
Bladder	For cystoscopic injection: 2 ml via 18-g needle For intravenous administration: 2 ml
Retroperitoneum (RPLND)	2 ml
Ureteral Reconstruction (antegrade or retrograde)	5 ml

Table 2 Applications of ICG with NIRF-augmented robotic surgery across urologic pathologies

Upper tract pathology	
Radical nephrectomy	Vasculature Identification
	Tumor fluorescence
	Sentinel lymph node drainage
Partial nephrectomy	Vasculature identification
	Tumor fluorescence
	Selective clamping
	Super-selective clamping
	Renorrhaphy viability
Radical partial adrenalectomy	Vasculature identification
	Tumor fluorescence
	Lymph node dissection
Combined upper and lower tract pathology	
Radical nephroureterectomy	Vasculature identification
	Sentinel lymph node drainage
	Identification of bladder cuff
Non-oncologic pathology	
Reconstruction (ureterolysis, ureteroureterostomy, ureteral re-implantation, pyeloplasty, etc)	Vasculature identification (i.e., crossing vessel)
	Identification of diseased, non-viable, segments
Renal transplantation	Qualitative perfusion of renal allograft
	Quantitative perfusion of renal allograft
Sacrocolpopexy	Identification of bladder
	Identification of ureters
Lower tract pathology	
Radical prostatectomy	Identification of notable structures - Neurovascular bundle (nerve-sparing) - Seminal vesicle - Vas deferens Identification of prostate versus peri-prostatic tissue - Local extension versus possible rectal involvement
	Sentinel lymph node drainage
	Assessment of accessory obturator, pudendal, and pedicle Identification
Radical cystectomy	Identification of notable structures (if injected into prostate) - Neurovascular bundle (nerve-sparing) - Seminal vesicle - Vas deferens - Accessory obturator arteries
	Sentinel lymph node drainage
	Identification of important vasculature to facilitate: - Visualization of bowel mesentery - Facilitation of tunneling of ureter - Viability of bowel segments - Conduit - Enteroenteric anastomosis
	Partial cystectomy - Test for leakage with instillation of ICG in bladder - Assess for perfusion around repair
Retroperitoneal lymph node dissection	Identification of important vasculature
	Delineate nodal margins
	Identification of ureters

surgery, as most tumors were hypofluorescent with normal parenchyma being isofluorescent. ICG-NIRF has also been studied in centrally endophytic tumors with reliable results [12].

To further examine fluorescence patterns of renal masses and dosing strategy, robotic partial nephrectomy was performed in 79 tumors to determine the appropriate dose of ICG prior to resection [13]. Underdosing can lead to hypofluorescence of the entire renal unit while overdosing may result in inappropriate fluorescence of the renal mass. Therefore, the authors performed an initial dose and re-dose to optimize ICG dosing and found that of all renal cell carcinomas, approximately 92% demonstrated no fluorescence and there was an 86% concordance rate between histological examination and fluorescence pattern [13]. In another study involving 100 patients undergoing robotic partial nephrectomy, tumor fluorescence patterns were characterized as afluorescent, hypofluorescent, and isofluorescent [14]. All cystic lesions appeared afluorescent, with a majority (97%) of solid renal neoplasms being hypofluorescent. In fact, hypofluorescence had a positive predictive value, negative predictive value, sensitivity, and specificity of 87%, 52%, 84%, and 57% for identification of malignancy [14]. In summary, although ICG-NIRF can distinguish malignant from non-malignant tissue in most cases, fluorescence patterns cannot reliably predict malignancy in all cases.

Utilization of ICG-NIRF has shown to aid in super-selective clamping, however. In an initial series of 34 patients undergoing robotic partial nephrectomy with intraoperative identification and super-selective clamping of renal vasculature, improved eGFR rates were noted ($p = 0.03$) without any compromise to positive surgical margin rates [15].

The authors use ICG-NIRF in both complex robotic partial and radical nephrectomy cases. For difficult vasculature anatomy identified on preoperative imaging or intraoperative dissection, ICG-NIRF has allowed the authors to ensure successful clamping by injecting ICG after the placement of robotic clamps to observe for any kidney fluorescence and, hence, vascular occlusion. The authors recommend using approximately 1–2 ml of a 2.5-mg/ml-reconstituted ICG-sterile water solution injected intravenously. Moreover, for tumor identification and facilitation of tumor excision, the authors inject 1–2 ml of reconstituted ICG prior to hilar clamping. The authors, furthermore, utilize ICG-NIRF to assess perfusion of normal renal parenchyma and renorrhaphy viability post removal of the hilar clamps. In this setting, the authors believe the surgeon can assure him/herself that appropriate tensioning of renorrhaphy sutures was implemented and prolonged ischemia did not result in global impairment of the renal unit.

Adrenal cancer

Robotic management of adrenal lesions has proven safe and efficacious, with emerging data on the role of ICG in this patient population [16, 17]. Initially described in 2013, three consecutive patients underwent robot-assisted partial adrenalectomy under ICG-NIRF guidance [8]. Masses were noted to be hypofluorescent, including a pheochromocytoma, lipoadenoma, and follicular lymphoid hyperplasia, and negative margins were attained. ICG-NIRF was found to be useful in assisting identification of adrenal mass and vasculature, as well as during excision in adrenal-sparing surgery (Table 2) [8].

Since then, two new articles examining the role of ICG in adrenal pathology have emerged [16, 17]. In 40 consecutive patients undergoing robotic adrenalectomy, independent, non-blinded observers demonstrated an advantage of ICG-NIRF over traditional white light for adrenal cortical tumors [17]. In another study, 10 patients underwent robotic adrenalectomy with ICG given 1, 5, 10, and 20 min prior to adrenal dissection with the goal to determine differential uptake of ICG in adrenal pathology. The authors found that adrenal uptake of ICG occurred at the 1-min mark post-injection attaining peak contrast at 5 min [16]. Conclusions of the study included that ICG-NIRF facilitated dissection in 80% of cases.

The authors utilize ICG-NIRF, especially for adrenal-sparing surgery to allow for real-time discernment of normal vs. pathologic tissue. Intravenous injection of 1–4 ml of a 2.5-mg/ml-reconstituted ICG solution during adrenal dissection can facilitate dissection and excision of adrenal mass during partial adrenalectomy.

Combined upper and lower tract pathology

Upper tract urothelial carcinoma

No publications to date have investigated the utilization of ICG-NIRF in radical nephroureterectomy for upper tract urothelial carcinoma. Aside from the benefits of vasculature identification aforementioned under *renal cancer*, the role of ICG in radical nephroureterectomy has limited uses. In literature, very few publications regarding the role of ICG-NIRF in nephroureterectomy have been reported. In one case report, a single patient with complete ureteral triplication underwent robotic partial nephroureterectomy of the upper pole atrophic moiety. Both intravenous and intraureteral ICG were used to facilitate identification of the pathologic ureter from the normal collecting system [18]. Intravesical administration of ICG has also been shown to facilitate distal ureter and bladder cuff dissection for patients undergoing radical nephroureterectomy in a video demonstration [19].

Lower tract pathology

Prostate cancer

The role of ICG-NIRF for prostate cancer is considerable and includes identification of accessory obturator arteries, as well as sentinel lymph node drainage and dissection (Table 2). A total of 50 patients underwent percutaneous injection of ICG (0.4 ml of 2.5 mg/ml ICG solution) via a spinal needle that was robotically positioned within each lobe of the prostate [6]. With respect to intraoperative structural identification, at a mean time of 10.2 min, the seminal vesicles, vas deferens, obturator nerves, and neurovascular bundles appeared afluorescent. Lymph node scintigraphy demonstrated the obturator group as the most common location of fluorescence in 52.6% of patients. 4/50 patients had node-positive disease, all of which exhibited fluorescence under NIRF. The sensitivity, specificity, positive, and negative predictive values for the detection of nodal metastasis were 100%, 75.4%, 14.6%, and 100%, respectively. In another series, 84 patients underwent transperineal prostatic injection of 25 mg ICG diluted in 5 ml of sterile water followed by extended lymph node dissection in patients undergoing RAL prostatectomy. Metastasis to lymph nodes were found in 25 patients, of which 23 were correctly identified by intraoperative ICG. Of the 82 metastatic nodes, 60% were identified by ICG, correctly staging 97% of cases [20].

Moreover, ICG-NIRF can facilitate RAL neurovascular bundle identification and preservation of the prostatic (lateral) artery has been described in a series of 50 [6] and 10 [21] patients. In the latter, the authors intravenously injected ICG and reliably found the landmark artery in 85% of cases without an increase in operative time or development of long-term complications.

Bladder cancer

Two main applications of ICG-NIRF during robot-assisted laparoscopic cystectomy exist. First, pre-cystectomy cystoscopic injection of ICG can delineate tumor location at the time of bladder dissection for either radical or partial cystectomy. Second, sentinel nodal drainage of the primary tumor may assist lymph node dissection (Table 2). The aforementioned tissue-marking properties of ICG-NIRF for prostatectomy (identification of accessory artery) can also be utilized during nerve-sparing radical cystectomy. Given the prognostic importance of lymph node dissection in bladder cancer, nodal mapping studies using ICG-NIRF should be a highlight of future studies [22].

In a preliminary efficacy and safety study, ten patients underwent cystoscopic injection of ICG and were assessed for tumor delineation and pelvic lymphangiography [7]. Sentinel lymph node drainage was identified in 90% of patients with the external iliac lymph node group being the most frequent. The time to nodal fluorescence was approximately 30 min. In this preliminary study, nodal fluorescence had 75% sensitivity and 52% specificity for the prediction of nodal metastasis [7].

With respect to partial cystectomy, intra-tumor injection of ICG was found to be safe and efficacious in localizing the bladder lesion to facilitate partial bladder resection with negative margins [23]. Moreover, utilization of ICG-NIRF can successfully circumvent the drawback or lack of tactile feedback in these cases.

We initiate robotic cystectomy with cystoscopic intra-tumor injection of 2 ml of 2.5 mg/ml of ICG via an 18-gage needle for tumor delineation and assessment of sentinel lymph node drainage. For mesenteric angiography, 2 ml of 2.5 mg/ml ICG was injected intravenously with near instantaneous fluorescence.

Retroperitoneal lymph node dissection

Retroperitoneal lymph node dissection remains a treatment strategy in patients with seminomatous and non-seminomatous (NS) germ-cell tumors (GCT) post-chemotherapy and select patients with NSGCT as primary therapy. Utilization of ICG-NIRF in this setting can facilitate vasculature identification and delineate nodal margins. In one patient, intravenous ICG was given to facilitate robot-assisted excision of retroperitoneal mass in patient post-chemotherapy for seminomatous GCT. Intraoperative molecular imaging using ICG-NIRF demonstrated a fluorescent mass within the retroperitoneum that was sharply excised [24]. Further studies in this arena are needed prior to widespread adoption of this technique.

Non-oncologic surgery

Ureteral reconstruction

Robot assistance has transformed ureteral reconstructive procedures including ureterolysis, ureteroureterostomy, ureteral re-implantation, and pyeloplasty in both the adult and pediatric populations (Table 2) [25]. The utilization of ICG in this arena centers on the ability to identify diseased segments due to a lack of vascularization. These areas appear afluorescent, hinting at a non-viable segment when ICG is injected either via a percutaneous nephrostomy tube or in retrograde manner. Combining ICG-NIRF with RAL surgery for ureteral reconstruction has shown additive benefits in the following procedures: ureteroureterostomy [26], pyeloplasty [27, 28], and ureteral re-implantation [28].

In a series of 26 robotic ureteral reconstructive cases enhanced with ICG-NIRF, the authors reported successful clinical and radiographic outcomes of four patients who underwent ureterolysis, eight patients who underwent pyeloplasty, nine patients who underwent ureteroureterostomy, and five patients who underwent ureteroneocystostomy [28]. The authors concluded that utilization of ICG-NIRF allowed the surgeon to, intraoperatively, in real time, demarcate vitalized from de-vitalized tissue in a safe, efficacious, and easily reproducible manner [28].

For patients with percutaneous nephrostomy tube intact, we typically inject 5 ml of 2.5 mg/ml both antegrade and retrograde to identify the diseased segment. Otherwise, retrograde instillation is sufficient with adequate preoperative imaging studies. For pyeloplasty, an additional intravenous injection of ICG is used in cases where crossing vessels represent the pathology.

Renal transplantation

Intraoperative ICG-NIRF for renal transplantation allows the surgeon to identify in real time the vascularity of the renal allograft assess for perfusion (Table 2). In four patients undergoing renal transplantation using ICG and the Hyper-Eye Medical System (HEMS; Mizuho Ikakogyo Co., LTD, Tokyo, Japan), ICG-HEMS was safe, efficacious, and is able to prevent technical failure in anastomotic of the renal artery and vein [29]. This preliminary work may assist future applications when transitioning to robotic transplantation.

Robotic sacrocolpopexy

With pelvic organ prolapse, a significant cause of patient morbidity, RAL sacrocolpopexy remains a minimally invasive treatment strategy for the treatment of female patients. At our institution, we routinely instill ICG in the bladder and retrograde via the ureter for difficult cases requiring extensive dissection (Table 2). Retrograde instillation of 2.5 mg/ml ICG solution via 6 French ureteral catheter allowed for successful delineating of the ureter in patients undergoing RAL sacrocolpopexy [30].

Urinary diversion

Intravenous administration of ICG can help identify vasculature within the mesentery, facilitating tunneling of the left ureter through a sigmoid mesenteric window, verifying non-ischemic enteroenteric anastomosis, and ensuring viability of the conduit or diversion segment (Table 1). In terms of mesenteric angiography, intravenous administration of ICG was found to enhance surgeon confidence in minimizing ischemic enteroenteric and ureteroenteric anastomoses, as well as conduit viability [7, 31].

Future considerations

The applications of ICG in RAL surgery are vast; however, this is only the tip of the iceberg. ICG is being used in conjunction with a variety of compounds, in a hybrid phenomenon, to enhance molecular-guided surgery. Van den Berg and colleagues utilized a hybrid ICG-99Tc-nanocolloid to achieve sentinel node biopsy in ten patients with prostate cancer. The authors used a multispectral laparoscope to identify both fluorescent patterns and were able to visualize 85.3% of sentinel nodes, as well as identification of lymphatic ducts in 80% of patients [32]. ICG has also been studied in animal models when bound to PSMA to identify oncologically active tissue [33]. This may further assist in resection in cases of extracapsular extension or in RAL partial prostatectomy in select patients. ICG can also be hybridized with lipids, negating hepatic metabolism, and allowing renal metabolism; thus, intravenous injection can result in identification of the ureters without the need of cystoscopic manipulation. Lastly, ICG-NIRF may also develop into a niche in achieving personalized lymph node dissection based on preoperative risk criteria and imaging studies in prostate cancer [34].

Conclusion

The applications of ICG-NIRF are vast and include both oncologic and non-oncologic applications. In terms of oncologic applications, ICG-NIRF can be used in radical/partial nephrectomy, nephroureterectomy, radical prostatectomy, radical/partial cystectomy, and retroperitoneal lymph node dissection. In non-oncologic applications, ICG with NIRF can identify vasculature and diseased non-viable segments and is especially useful in ureterolysis, ureteroureterostomy, ureteral re-implantation, and pyeloplasty in both the adult and pediatric populations. Although ICG-NIRF is certainly not a necessity when performing robotic surgery, the authors believe it may play a role in difficult and complex cases. The future of image-guided surgery using ICG-NIRF can be promising and may provide for a more elegant and finer resection creating endless possibilities in both oncologic and non-oncologic pathologies.

Compliance with ethical standards

Conflict of interest Ram Pathak and Ashok Hemal declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants performed by any of the authors.

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