ORIGINAL ARTICLE

Indocyanine green use in Urology

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Summary

Purpose: Indocyanine green (ICG) is being used more and more in Urology along with advances in minimal invasive surgery, guiding excision and reconstruction, highlighting anatomic structures and functional features with oncologic guidance still being debatable. The purpose of this paper was to explore ICG use in urologic procedures.

Methods: We present our experience (37 cases) of using ICG fluorescence guidance in urologic operations performed using 3D laparoscopy and FireFly® fluorescence imaging mode of Da Vinci X robot. The operations were the following: pelvic lymphadenectomy in radical prostatectomy, totally intracorporeal orthotopic ileal neobladder reconstruction, vesicovaginal fistula repair, partial nephrectomy and pyeloplasty. Barnard's test was used to compare postoperative complications (digestive fistula, ureteral stricture) for totally intracorporeal ileal neobladders performed with (group e, 27 cases) vs. without (group 2, 28 cases) ICG quidance.

Results: ICG under near-infrared fluorescence offered a precise identification of ischemic structures- vaginal wall, distal ureteral end, ileal loop, along with vascularized tissues allowing an optimal pyeloplasty and nephron sparing surgery with partial unclamping. It also allowed the identification of a lymph node during radical prostatectomy that otherwise would not have been excised during the routinely performed pelvic lymphadenectomy. There were no complications of ICG usage and the complication rate (digestive fistula, ureteral strictures) was significantly lower (p=0.002716) for group 1 compared with group 2.

Conclusion: ICG facilitates the identification of key elements (anatomy and pathological structures) in the laparoscopic and robotic treatment of both malignant and benign urologic diseases, with possible impact on perioperative complications, along with oncologic and functional postoperative outcomes.

Key words: indocyanine green, FireFly[®] fluorescence imaging mode, laparoscopic surgery, robotic surgery, urology, reconstructive surgery

Introduction

Indocyanine green (ICG) is a water-soluble molecule normally available in powder form that can be dissolved in various solvents (sodium iodide is usually added for better solubility). It can be administered intravenously and it is eliminated with a half-life of 150-180 s, as it is cleared by the liver

and excreted entirely into the bile. ICG offers intra-operative visualization of anatomic structures along with their vascularization and lymphography under fluorescent light [1].

ministered intravenously and it is eliminated with a half-life of 150-180 s, as it is cleared by the liver urologic operations may vary: in radical prostatec-

Corresponding author: Cristina Eliza Bujoreanu, MD. Eremia Grigorescu street no.89, 400305, Cluj-Napoca, Romania. Tel: +40 770600641, Email: bujoreanucristina@yahoo.com Received: 03/08/2020; Accepted: 11/09/2020 tomy with or without lymphadenectomy, partial nephrectomy, ureteral re-implantation and reconstruction, radical cystectomy and orthotopic ileal neobladder, partial or radical adrenalectomy [2], penectomy and inguinal lymphadenectomy [3,4], kidney transplantation, sacrocolpopexy and varicocel treatment [5,6]. Nevertheless, the use of ICG during partial nephrectomies to characterize the renal vasculature and differentiate the tumor from the normal renal parenchyma was the most frequent, although ICG cannot predict malignancy [7].

Regarding the safety of ICG usage, the first anaphylactic shock reaction reported for intravenous administration of ICG happened in 2017 during a robotic partial nephrectomy. The patient was stabilized and the operation continued with no further problems [8]. Also, a study performed on Wistar rats revealed toxicity for neuronal cell cultures in concentrations higher than 75 μ M, related to the imbalance in extra and intracellular calcium homeostasis, with Gadovist reported as neuroprotective when administered 30 min before ICG [9]. The incidence of ICG complications related to ophthalmic videoangiography was reported

in the literature as mild (0.15%), moderate (0.2%) and severe (0.005%). Without any known metabolites, ICG is considered a safe, low-toxicity contrast agent and it has been shown not to pass the placenta. Anyhow, studies on fetal toxicity have not been performed yet, therefore ICG should not be used during pregnancy [10].

Methods

We present our experience (37 cases- 32 male and 5 female patients) of using ICG fluorescence guidance in 3D laparoscopic urologic operations and FireFly[®] fluorescence imaging mode in robotic urologic operations. These are the following: pelvic lymphadenectomy in radical prostatectomy (Figure 1), totally intracorporeal orthotopic ileal neobladder reconstruction (Figures 2-4), repair of vesicovaginal fistula (Figure 5), partial nephrectomy (FigureS 6,7) and pyeloplasty (Figure 8). During surgery, after exposing the tissues needed to be analyzed, ICG is injected intravenously after the powder was dissolved as follows: 25mg of ICG powder reconstituted in 20ml of distilled water. The total daily dose of ICG should be kept below 5mg/kg per body weight, as indicated by the manufacturer. The dosage used by our



Figure 1. 3D laparoscopic lymphadenectomy during radical prostatectomy. This is the case of a patient with T2 prostatic adenocarcinoma, presenting with negative lymph nodes on imaging and the following parameters: iPSA 10 ng/ml and a Gleason score of 7 (4+3). ICG was injected with transrectal ultrasound guidance into the prostate to aid lymph node mapping. After the standard bilateral pelvic lymphadenectomy was performed, a remnant lymph node is detected **(A)** and excised **(B,C)** under ICG fluorescence guidance (colored in blue). For all images: Left-3D laparoscopic image; Right-same image under ICG fluorescence.

team is presented in Table 1 for each type of surgery. When performing lymphadenectomy in prostate cancer treatment, ICG is injected under transrectal ultrasound guidance with the patient in lithotomy position before the actual operation starts, with the patient being repositioned afterwards. ICG becomes protein-bound, confined to the intravascular compartment and, in less than a min, fluorescent light allows the visualization of vascularized tissues or drainage pathways, as ICG is excited by a specific wavelength from an endoscopic light source.

In laparoscopy, the tissues that contain ICG color in blue under fluorescent light, the ischemic ones remain dark (Figures 1-3,5,6,8). In robotic surgery, when the Fire-Fly[®] fluorescence imaging mode is on, the tissues that contain ICG color in bright green and the ischemic ones remain dark (Figures 4,7).

to the intravascular compartment and, in less than a min, fluorescent light allows the visualization of vascularized tissues or drainage pathways, as ICG is excited by a specific wavelength from an endoscopic light source. Peri and postoperative data were analyzed: type of surgery, surgical approach and technique, number of cases, gender and mean age of the patients, mean duration of ICG administration and time of operation extension



Figure 2. Totally intracorporeal 3D laparoscopic ileal neobladder- vascularization of distal ureteral ends (left- 3d laparoscopic image; right-same image under ICG fluorescence). Ileal loop selection and vascularization of distal ureteral ends are verified under ICG fluorescence before performing the orthotopic ileal neobladder. Both distal ends of the ureters are visualized under fluorescence (**A**) after ICG injection and the distal end of one of the ureters turns out to be ischemic, as it is not colored with ICG due to lack of optimal vascularization. A clip is placed on the ureter to delimit the vascularized from the ischemic tissue before excision (**B**).



Figure 3. Totally intracorporeal 3D laparoscopic ileal neobladder- ileal loop selection and vascularization (left- 3D laparoscopic image, right-same image under ICG fluorescence). The selected ileal loop that will further on be molded into a new urinary pouch is analyzed under ICG fluorescence showing an ischemic ileal portion **(A)** that is marked using a clip **(B)**. The ischemic ileal segment is excised, so that the remnant ileal loop used for the neobladder has optimal vascularization.



Figure 4. Totally intracorporeal robotic ileal neobladder. Using the FireFly[®] fluorescence imaging mode on the Da Vinci X robot after administrating ICG, the vascularized tissues shine in bright green light, while the ischemic ones remain dark. The distal ischemic ureteral end is identified **(A)** and excised **(B)**. The ischemic end of the ileal loop is marked with a clip **(C)** and excised, remaining an optimally vascularized ileal loop for reconstructive surgery **(D)**.



Figure 5. Endoscopic diagnosis of vesicovaginal fistula and 3D laparoscopic surgical repair. An endoscopic evaluation **(A)** of the urinary bladder confirmed the clinical suspicion of a vesicovaginal fistula in a patient that underwent hysterectomy and radiotherapy for uterine cancer. During the surgical operation **(B)**, ICG was used to analyze the vascularization of the bladder wall and of the vaginal wall. It can be observed in the image that the bladder wall is vascularized and the vaginal wall is ischemic under ICG fluorescence **(C)**. Final aspect can be observed in Figure **D**. For images **C** and **D**: Left- 3D laparoscopic image; Right-same image under ICG fluorescence.



Figure 6. 3D laparoscopic partial nephrectomy. This is the case of a renal tumor **(A,B)** located on the superior pole of the right kidney which presented 2 arterial branches **(A)**. The unclamped arterial branch under ICG fluorescence vascularized the superior pole of the right kidney, completely including the tumor lesion **(C)**, therefore, this arterial branch was clamped during the nephron sparing surgery. With selective arterial clamping, a part of the kidney underwent warm ischemia when performing the tumor excision **(D)** and the nephrorrhaphy.



Figure 7. ICG evaluation after Da Vinci X robotic partial nephrectomy was performed. The challenging tumor excision of a highly complex tumor (strictly endophytic, 7/3 cm) could have impaired the vascularization of the remnant renal parenchyma, as the tumor was in contact with vessels in the renal sinus. After the tumor excision and nephrorrhaphy were performed, the vascularization of the remnant renal tissue

due to ICG administration (min), mean Clavien-Dindo complications- 30 days postoperative, number of cases with modified operative steps due to ICG administration and further details.

Statistics

Barnard's test was used to compare postoperative complications (digestive fistula, ureteral strictures) for totally intracorporeal ileal neobladders performed minimally invasive with (group 1- 27 patients) vs. without (group 2, 28 patients) ICG guidance. A p value<0.05 was considered statistically significant.

Results

ICG under near-infrared fluorescence offered a precise identification of ischemic structures (vaginal wall, distal ureteral end, ileal loop), along with vascularized tissues allowing an optimal pyeloplasty and nephron sparing surgery with partial unclamping. During the radical prostatectomy, ICG allowed the identification of a lymph node, free of tumor tissue that otherwise would not have been excised during the routinely performed pelvic lymphadenectomy (Table 1).

There were no complications of ICG usage. The 3D laparoscopic operations required 15 min extra for the set-up of the 2D fluorescence system. This was not the case for the Firefly[®] fluorescence imaging mode activation of the Da Vinci X robot.

Three out of the 28 cases (10.71%) of totally intracorporeal ileal neobladders performed with a 3D laparoscopic approach and no use of ICG guidance, presented digestive fistula, and underwent open reintervention with resection of the fistula and a new latero-lateral anastomosis (EndoGia stapler). One case out of these 3 developed postoperative complications and the patient died 6 weeks later. Five other patients from this category presented ureteral strictures during follow-up.

No case from the 27 cases of totally intracorporeal ileal neobladders performed minimally invasive under ICG guidance developed postoperative fistulas. Details can be found in Table 2.



Figure 8. 3D laparoscopic right pyeloplasty for ureteropelvic junction obstruction. Ureteropelvic junction obstruction can be treated using various techniques. In this case, a dismembered pyeloplasty (**A**,**B**) is performed on the right kidney and both the pelvis (**C**) and the ureter (**D**) are optimally vascularized under ICG fluorescence. For images **C** and **D**: Left-3D laparoscopic image; Right-same image under ICG fluorescence (colored in blue).

The Barnard's test showed statistical difference for postoperative complications (digestive fistula and ureteral stricture) between the 2 groups (group 1- with ICG guidance vs. group 2 without ICG guidance) in performing totally intracorporeal ileal neobladder minimally invasive (p=0.002716 two-sided test, score statistic -3.004556, nuisance parameter 0.500100).

Discussion

Sentinel lymph node mapping with ICG in pelvic malignancies, especially in endometrial and prostate cancers, show promising performance [11]. Lymph node dissection offers reliable prognosis for men diagnosed with prostatic cancer. A personalized ICG fluorescence guided lymphadenectomy with the excision of the exact lymphatic pathway could avoid the increased perioperative morbidity associated with extending the standard of limited lymphadenectomy. ICG can show sentinel prostatic drainage as it can mark target prostate tissue with limited diffusion, similar to a lymphangiography agent. In a prospective randomized trial [12] ICG showed a 44% sensitivity regarding the identification of lymph

node metastasis. Despite being low, ICG remains a great ally for lymphatic drainage understanding and tissue identification, with a higher yield of lymph nodes. However, in high risk prostate cancer, ICG could skip metastatic lymph nodes, as the tumor cells may obstruct the feeding lymphatics [13]. In our case, the lymph node identified with ICG fluorescence turned out to be free of malignancy and probably it would not have been excised without ICG guidance. A study [14] showed that the prostatic drainage pattern is complex with no distinct lymphatic pathways per prostatic anatomic region. The sentinel lymph node detection technique was not able to replace extended pelvic lymph node dissection in patients with intermediate and high risk prostate cancer. During radical prostatectomy, ICG fluorescence can also be used to identify the benchmark prostatic artery, preserving the neurovascular bundles, while assessing vascularization and hemostasis [15].

ICG was used to perform a laparoscopic heminephrectomy for left ureteral cancer in a patient with a horseshoe kidney, with intraoperative discrimination of the isthmus. When facing complicated vessel anatomy in kidney anomalies, a fluorescence-guided visualization of the vasculature

Type of surgery	Totally intracoporeal orthothopic ileal neobladder		Radical prostatectomy and pelvic lymphadenectomy	Partial nephrectomy		Vesicovaginal fistula repair	Pyeloplasty
Surgical approach and technique	3D laparoscopic- modified Studer	Da Vinci X robot assisted - pure Studer	3D laparoscopic- extraperitoneal	3D laparoscopic- transperitoneal	Da Vinci X robot - transperitoneal	3D laparoscopic	3D laparoscopic- transperitoneal
Number of cases	15	12	2	5	1	1	1
Gender (M/F)	15M	12M	2M	3M + 2F	1F	1F	1F
Mean age (y.o.)	64.2	66.85	51	35.3	36	44	38
Minutes for ICG administration	2+15* = 17	2	21 +15* = 36	2+15* = 17	2	2+15* = 17	2+15* = 17
	* minutes for 2D laparoscopy fluorescence system set-up						
Mean dosage of administered ICG (ml)	2*5	2*5	2*5	5	5	5	5
	25 mg of ICG (powder) reconstituted in 20 ml distilled water = 6.25 mg of ICG/ 5ml of solution						
Mean time of surgery extension due to ICG administration (minutes)	25.3	21.2	12	6.5	0.5	7	6
Mean Clavien-Dindo complications (30 days)	Grade II	Grade II	Grade II	Grade II	Grade II	Grade II	Grade II
Number of cases with modified operatory steps due to ICG administration	ischemic tissue excision		excision of identified lymph node mass	partial unclamping was possible	no need for due to	no need for modified operatory steps due to ICG administration	
	15/15 ureteral distal end, 4/15 ileal segment	10/12 ureteral distal end, 3/12 ileal segment	1/2	4/5			

Table 1	L. Peri and	postoperative	data for o	operatons	performed	under	ICG guidance
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Table 2. Comparison of postoperative complications (digestive fistula and ureteral stricture) with (group 1- 27 cases) vs. without ICG (group 2- 28 cases) guidance in performing minimal invasive totally intracorporeal ileal neobladder - 2x2 contingency Table for Barnard's test

Minimal invasive totally intracorporeal ileal neobladder- number of cases						
	Group 1 with ICG	Group 2 without ICG				
No postoperative complications (type ureteral strictures + digestive fistula)	27	20				
Postoperative complications ureteral strictures + digestive fistula	0	8				

can detect small aberrant but important vessels that otherwise could have been overlooked [16]. Also, in assessing kidney allograft perfusion, ICG fluorescence acted as a surrogate for the perfusion status of the transplanted organ and vascular patency. A large hypoperfusion defect detected only with ICG injection and not visible to the eye would impose intraoperative corrective actions before any irreversible damage [17].

A great use of ICG fluorescence is for nephron sparing surgery in case of multiple renal arteries as partial clamping offers a smaller nephron area affected by the warm ischemia time frame. In the case of the patient presented in Figure 6, ICG fluorescence allowed to clamp the arterial branch that was most likely supplying the tumor positioned on the upper pole and approximate the extent/ distribution of the perfusion. One of the 3D laparoscopic nephron sparing operations performed in our department was on a horseshoe kidney presenting multiple renal arteries, with ICG fluorescence adding important data. This allowed clamping only of the renal artery vascularizing the parenchyma presenting the tumor lesion, leaving the rest of the healthy renal parenchyma without undergoing warm ischemia consequences. In Figure 7, after robotic partial nephrectomy was performed for an entirely endophytic tumor, ICG was used to verify the vascularization of the remnant parenchyma after nephrorrhaphy.

ICG can also be injected directly into the ureter, for identification of stricture areas or in the case of a partial nephroureterectomy in a patient with a complete ureteral triplication [18]. The ureter can be analyzed with ICG fluorescence, be it either for the kidney allograft or in treating an ureteropelvic junction obstruction and choosing the optimal pyeloplasty technique, dismembered or non dismembered. If a poorly perfused ureteral segment is detected, it can be trimmed off to avoid future strictures, as a study [19] on ICG fluorescence use in robot-assisted ureteral reconstructions shows. Worth mentioning, ureteral ICG administration was performed injecting it through a ureteral stent into the lumen. This was not the case of the right pyeloplasty presented in Figure 8, in which ICG was solely injected intravenously. ICG fluorescence showed optimal vascularization of the pelvis and the cranial ureter and the reconstructive surgery continued with no need for ureteral spatulation or segmental excision.

When performing a totally intracorporeal ileal neobladder, an ischemic distal ureter or ileal loop could lead to postoperative complications. A study [20] showed that the use of ICG in robotic radical cystectomy with urinary diversion minimized uretero-enteric strictures. The ICG group (47 patients, 12 months follow-up) was not associated with uretero-enteric strictures compared with the non-ICG group (132 patients, 14 months follow-up) that presented a stricture rate of 6.6%. We have used ICG guidance for all totally intracorporeal robotic-assisted ileal neobladders performed by our team and no such complications appeared during the 11-month follow-up. Regarding postoperative complications (digestive fistula, ureteral strictures), even if this is an initial set of cases, statistical difference was found between the lack vs. the usage of ICG during totally intracorporeal ileal neobladder performed minimally invasive in favor of ICG usage. A longer follow-up will provide data for statistical analysis, demonstrating the importance of ICG usage and the implication in avoiding major complications, with a larger sample of cases for optimal accurate results.

Also, a study [21] on 31 patients undergoing liver resection analyzed ICG clearance markers regarding peri and postoperative risk factors, showing a statistically significant correlation in histologically normal liver parenchyma with potential implications in preoperative planning and preventive impact on postoperative liver failure. Other authors [22] have used ICG along with Child-Pugh grading to analyze hepatic functional reserve in liver cancer patients associating cirrhosis, respectively for real time analysis of hepatic metabolism function. Therefore, ICG was an important element of clinical significance along with Child-Pugh grading to evaluate surgical complications and survival results.

In conclusion, ICG facilitates the identification of key elements (anatomy and pathological structures) in the laparoscopic and robotic treatment of both malignant and benign urologic diseases, with possible impact on oncological and functional postoperative outcomes. Although safe and with low toxicity, feasible and versatile, the use of ICG it is not yet considered a standard procedure and further investigations are necessary to discover its potential and effects in urologic operations, as literature still remains scarce on this topic.

Conflict of interests

The authors declare no conflict of interests.

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