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Original Research Article

Feasibility of injected indocyanine green for ureteral identification during robotic left-sided colorectal resections

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A R T I C L E I N F O

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A B S T R A C T

Background: Ureteral identification is essential to performing safe colorectal surgery. Injected immunofluorescence may aid with ureteral identification, but feasibility without ureteral catheterization is not well described.
Methods: Case series of robotic colorectal resections where indocyanine green (ICG) injection with or without ureteral catheter placement was performed. Imaging protocol, time to ureteral identification, and factors impacting visualization are reported.
Results: From 2019 to 2020, 83 patients underwent ureteral ICG injection, 20 with catheterization and 63 with injection only. Main indications were diverticulitis (52%) and cancer (36%). Median time to instill ICG was faster with injection alone than with catheter placement (4min vs 13.5min, $p < 0.001$). Median time [IQR] to right ureter (0.3 [0.01–1.2] min after robot docking) and left ureter (5.5 [3.1–8.8] min after beginning dissection) visualization was not different between injection alone and catheterization.
Conclusion: ICG injection alone is faster than with indwelling catheter placement and equally reliable at intraoperative ureteral identification.

Introduction

Identifying and preserving the abdominal and pelvic ureter are critical to performing safe colorectal resections. Visualizing ureteral peristalsis and an understanding of the anatomical landmarks defining the ureter's course are the foundation for identification. However, identifiers may be obscured in patients with high adiposity or inflammatory or malignant disease processes. Iatrogenic ureteral injuries are fortunately rare, with an incidence of 0.24–1.95%.[1–5] Injuries are particularly morbid and costly,[6] especially when missed intraoperatively. Therefore, techniques to aid with intraoperative ureteral identification are of particular interest in cases where the ureters are at high risk for injury, such as distal colorectal resections.

Ureteral catheterization with temporary stents traditionally has been used for intraoperative detection.[7] However, prophylactic or routine use of these intraoperative catheters has been controversial, and benefits may only be limited to open surgery.[8–10] The use of indocyanine green (ICG), a Food and Drug Administration approved water-soluble dye, is described for several applications of surgical imaging, including during urologic and gynecologic surgery.[11–14] With the availability of newer laparoscopic and robotic platforms with built-in near-infrared (NIRF) filters for fluorescent visualization, smaller sized studies have suggested ureteral identification with non-invasive fluorescence alone.[15,16]

The aim of this study is to assess the feasibility of injecting ureteral ICG in consecutive colorectal resections for ureteral identification. Criteria for identifying patients who are appropriate candidates for ICG injection with or without ureteral stent placement has not previously been reported. In this study, we detail our experience and technique of ICG injection at a single, tertiary care referral center. We hypothesize that intra-ureteral ICG will safely and reliably aid with bilateral ureteral identification and will be faster to perform without stent placement.

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Material & methods

This study was approved by the Benaroya Research Institute Institutional Review Board.

Data source and study population

A single-institution, retrospective chart review was performed to capture all patients undergoing joint ureteral ICG injection and robotic left-sided colorectal resections from January 2019–December 2020. All patients were 18 years or older. The cohort was divided into two groups, ICG injection alone vs ICG injection with indwelling catheter placement, as described below. Patients who underwent ureteral catheterization without ICG were excluded. In order to minimize the heterogeneity of the cohort, we limited this evaluation to left-sided resections. Specifically, we excluded right sided colon resections and rectal prolapse operations. In addition, we excluded laparoscopic resections as the laparoscopic platforms at our institution do not currently have built-in NIRF filters for fluorescent visualization. Videos of the cases are routinely captured at our institution. Intra-operative videos of robotic resections were assessed by a single viewer (CS) who collected times of key portions of the operation. In instances where video footage was interrupted or accidently deleted (n = 18 of 83 cases), other clinical data that was available was used in our analysis, and the missing component noted in our results.

Technique

Cystoscopy and retrograde uretero-pyelo ICG injection

ICG was prepared using 25 mg vials that were reconstituted in 10 mL of sterile water. All patients underwent rigid cystoscopy performed by urologists. The ureteral orifice was cannulated using a cone-tipped catheter (Fig. 1A) through which 5 mL of ICG (12.5 mg) followed by 5 mL of saline was flushed (Fig. 1B). The retrograde uretero-pyelo ICG injection was then repeated for the contralateral ureteral orifice. The catheter was then removed, and there was no indwelling catheter left in place for the remainder of the colorectal operation (ICG injection alone group). For patients with temporary ureteral stents placed, cannulation of the bilateral ureteral orifices was performed using a standard Seldinger technique with a Polytetrafluoroethylene (PTFE) wire with subsequent Pollack ureteral catheter advancement. Fluoroscopic guidance was at the discretion of the urologist. Then, 5 mL of ICG followed by 5 mL of saline was flushed through the stent, which was left in place for the colorectal surgery portion of the case (ICG with indwelling stent group). Foley catheter is placed at completion of cystoscopy. Our institutional practice is foley decompression of the bladder for left-sided/pelvic operations to aid with visualization. On our enhanced recovery pathway, patients have their foley catheters removed immediately after case (for cases completing early in day) or on post-operative day (POD) 1 for all others (barring clinical concern or need for prolonged catheterization, hematuria, or colovesical fistula takedown).

Robotic left-sided colorectal resections

For the purpose of this feasibility evaluation, the cohort was limited to left-sided resections to allow for meaningful objective data as the steps of medial-to-lateral dissection during sigmoid colectomy, low anterior resection (LAR), and abdominoperineal resection (APR) are generally performed in the same order by our surgeons, and the location of the ureters, both abdominal and pelvic, is particularly relevant to the steps of these operations. All patients were positioned in Modified lithotomy and then placed in Trendelenberg with slight left side up. The daVinci® Xi robotic platform was docked off the patient's left side. We typically use 4 robotic ports in diagonal orientation from right lower quadrant to left upper quadrant, and an assistant port (typically Airseal® Access Port) in the right upper quadrant. Medial-to-lateral dissection was performed in the following steps: (1) initiating dissection of the peritoneal reflection over the sacral promontory (right ureter typically identified at this point where it crosses iliac vessel bifurcation), (2) elevating the mesocolon and mesorectum off the retroperitoneum to preserve the hypogastric nerve plexus, (3) identification and preservation of the abdominal left ureter as it courses above the psoas muscle and below the gonadal vessels as dissection was carried to abdominal wall, and (4) division of the inferior mesenteric artery (IMA) vascular pedicle.

Outcomes/definitions

Relevant factors that could contribute to difficulty of case or outcomes were recorded, including patient age, gender, body mass index (BMI), relevant comorbidities, American Society of Anesthesiologists (ASA) class, indication for surgery, presence of complicated diverticulitis defined as diverticulitis associated with a systemic inflammatory response, fistula, abscess, or stricture,[17] history of prior surgery or radiation, and operation performed (colectomy, LAR, or APR). Post-operative variables included ureteral injury, length of stay (LOS), acute kidney injury (AKI) defined using

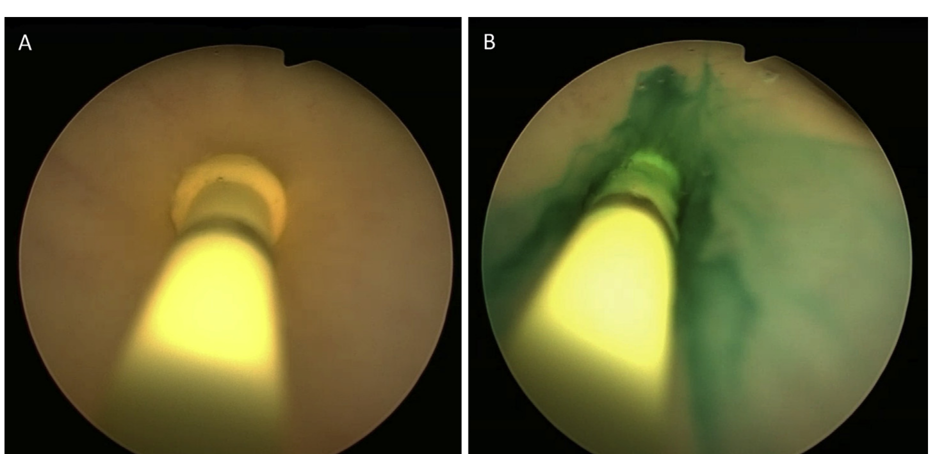

Fig. 1. Cystoscopy and cannulation of ureteral orifice with (A) cone-tipped catheter and (B) indocyanine green (ICG) injection.

the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline[18] as serum creatinine 1.5–1.9 times reference value or increase >0.3 mg/dl, urinary tract infection (UTI), and hydronephrosis.

Time to instill ICG was measured from cystoscope insertion and withdrawal extracted from surgical documentation. Total case time was measured from skin incision to closure. To standardize the time to ureteral identification, all timing was started once the robotic platform was docked and instruments inserted. The time to identify (ID) the right ureter was measured using video footage from robot docking to first right ureteral visualization with ICG, typically done by the surgeon before medial to lateral mobilization to ensure a safe point to initiate dissection. The time to ID the left ureter was measured using video footage from scoring of the peritoneal lining and to first left ureter visualization. Completion of the medial-to-lateral mobilization was designated after ligation of the IMA pedicle. The longest time a ureter could be visualized after injection was also recorded.

Statistical analysis

While the purpose of this study was primarily descriptive, some comparisons between the injection only and catheterization subgroups, as well as clinically relevant risk factors, were performed. This was not for hypothesis testing, but rather to try to quantify differences between subgroups that might inform future studies. Data were summarized using frequency distributions for categorical variables and mean $\pm$ standard deviation for normally distributed continuous variables and median with interquartile range [IQR] for variables with skewed distribution. Normally distributed continuous variables were compared using ANOVA and skewed continued variables using Wilcoxon rank-sum between the two groups. Categorical variables were compared using Pearson χ^2 statistic. A p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using Stata SE version 15 (College Park, TX).

Results

Patient demographics

Over the 2-year study period, there were 83 patients who underwent cystoscopy and retrograde uretero-pyelo ICG injection followed by robotic, left-sided colorectal resections (Table 1). Cystoscopy and ICG injection were performed across 15 urologists and colorectal resections performed across 4 surgeons. Nearly one-quarter of all patients undergoing retrograde uretero-pyelo ICG injection also had concomitant ureteral stents placement, primarily early in our experience with the first 12 cases all receiving indwelling stents (Fig. 2). 75% of ureteral stenting procedures were for diverticulitis indication.

Cystoscopy with ICG injection

Median cystoscopy and ICG injection time without stent placement was 4 [3–8] minutes (min) vs with stent placement 13.5 [10–21.5] min ($p < 0.001$). Cystoscopy times did not differ between males and females ($p = 0.24$). Over time, this procedure became quicker to perform and fewer stents were placed (Fig. 2). Prolonged cystoscopy was either due to difficulty secondary to enlarged prostate and irregular bladder trigone anatomy requiring a combination of flexible and rigid cystoscopy, corresponding to the 81-min cystoscopy, and left proximal ureteral stone requiring laser lithotripsy and stent placement, corresponding to the 55-min cystoscopy. There was one patient with urethral meatal stenosis requiring dilation and difficult access to the ureteral orifices, corresponding to the 42-min cystoscopy. There were also two cystoscopies in which an incidental bladder tumor was discovered and subsequently biopsied during the procedure, corresponding to the 30- and 37-min cystoscopies.

Intra-operative ureteral identification

Out of the 65 (78%) cases with available right ureter footage, the right ureter was able to be identified using ICG in 63 (97%) cases. Left ureter video footage was available for 66 (80%) cases, in which the left ureter was seen using ICG in 100% of cases. Median time to ID right ureter was 0.3 [0.01–1.2] min after robot docking (Fig. 3). Right ureter visualization time was slower in obese (BMI>30) patients (Table 2). Median time to ID left ureter was 5.5 [3.1–8.8] min after beginning medial-to-lateral dissection (Fig. 4). Median time to complete medial-to-lateral dissection was 14.5 [10.8–20.2] min. The ureters remained fluorescent with ICG and visible for the entire case during this series, and total case time ranged from 2.3 to 7.9 h. Median overall case time for stented cases was 4.5 [4.0–5.0] hours vs 4.2 [3.5–5.1] hours for non-stented cases.

Post-operative course

Patients who had ICG injection with indwelling stent placement had their stents removed following cessation of the colorectal operation. All patients had a Foley catheter per our institution's colorectal surgery protocol, and this was removed after a mean of 1.8 $\pm$ 1.9 days. Mean POD 1 creatinine in stented patients was 1.2 $\pm$ 0.7 mg/dl, and injection only patients was 0.8 $\pm$ 0.2 ($p < 0.001$). Fifteen percent ($n = 3$) of stented patients had an AKI post-operatively ($p = 0.002$), whereas no AKI was observed in any of the patients who underwent injection only. Patients who developed AKI resolved after intravenous hydration without sequelae. Hematuria was present in 50% of stented vs 3% injection only cases ($p < 0.001$). There were no UTIs in either group. One patient who received ICG and difficult stent placement developed right hydronephrosis post-operatively and required indwelling stent replacement. There was one ureteral injury in a stented patient in this series, which occurred after conversion to an open operation (conversion was not because of ureteral anatomy). This was identified intraoperatively and required left ureter-ureterostomy and exchange for a double J-stent. When assessing oncological surgical quality of patients diagnosed with colorectal cancer, all patients had negative margins and mean lymph nodes harvested was 17.1 $\pm$ 5.2. Complications related to the colorectal resections include 2.3% anastomotic leak rate ($n = 2$), 1.1% deep space surgical site infection ($n = 1$), and 5.8% superficial surgical site infection ($n = 5$). Mean LOS for all patients was 3.8 $\pm$ 4.7 days.

Discussion

Cystoscopy and intra-ureteral injection of ICG was significantly faster without intraoperative ureteral catheter placement. Because of the ease and reliability of injection alone, we shifted away from routine catheterization as we did in the initial part of the cohort to using only injection for the overwhelming majority of cases. Additionally, there was timely identification of both the right and left ureter using fluorescent-guidance, regardless of which approach was used. Our findings suggest that ICG injection alone was feasible and reproducible, potentially avoiding some of the known post-operative complications of ureteral catheterization.

With the increased prevalence of minimally invasive approaches in colorectal surgery,[19,20] the importance of ureteral identification is emphasized, as studies have proposed that

Table 1
Demographics of patients undergoing indocyanine green (ICG) injection.

	ICG Injection Alone (n = 63)	ICG with Indwelling Stent (n = 20)	*p*
Age, mean (SD)	61.2 (15.2)	61.3 (14.0)	*0.97*
Male	30 (48%)	10 (50%)	*0.80*
BMI, mean (SD)	28.0 (6.6)	29.9 (5.5)	*0.26*
ASA Class			*0.20*
2	40 (63%)	12 (60%)	
3	23 (37%)	7 (35%)	
4	0 (0%)	1 (5%)	
CKD	1 (2%)	2 (10%)	*0.079*
Prior Abdominal Surgery	39 (62%)	11 (55%)	*0.58*
Prior Radiation	10 (16%)	4 (20%)	*0.67*
Indication			*0.12*
Diverticulitis	28 (44%)	15 (75%)	
Complicated Diverticulitis	21 (33%)	11 (55%)	*0.90*
Cancer	26 (41%)	4 (20%)	
IBD	8 (13%)	1 (5%)	
Chronic Constipation	1 (2%)	0 (0%)	
Operation			*0.38*
Left Colectomy	1 (2%)	0 (0%)	
Sigmoidectomy	32 (51%)	14 (70%)	
LAR	21 (33%)	3 (15%)	
APR	9 (14%)	3 (15%)	

SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologists; CKD: chronic kidney disease; IBD: inflammatory bowel disease; LAR: low anterior resection; APR: abdominoperineal resection.

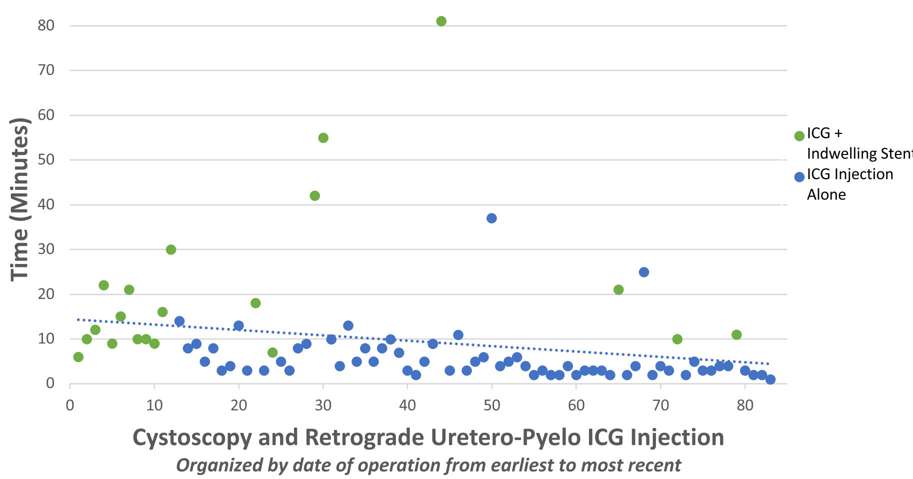

Fig. 2. Cystoscopy and retrograde uretero-pyelo indocyanine green (ICG) injection time (in minutes) with and without indwelling stent placement over 2-year study period.

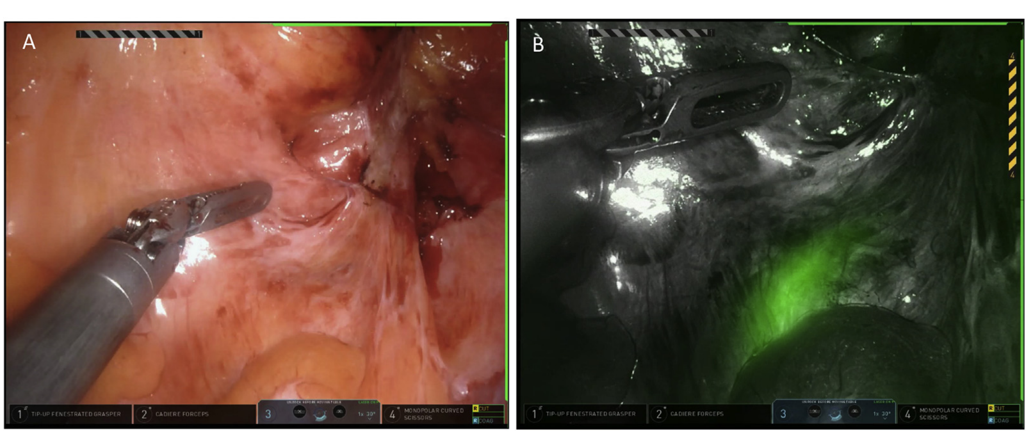

Fig. 3. Intraoperative visualization after robot docking (A) without and (B) with fluorescent indocyanine green (ICG) for right ureteral identification.

Table 2
Times (in minutes) to identify right and left ureter using indocyanine green (ICG) stratified by patient and surgery factors.

	ID Right Ureter (Minutes)	*p*	ID Left Ureter (Minutes)	*p*
Gender		*0.82*		*0.26*
Male, median [IQR]	0.3 [0.1–1.2]		6.1 [3.8–9.3]	
Female, median [IQR]	0.3 [0.1–1.2]		4.3 [2.6–7.2]	
BMI		*< 0.001*		*0.086*
< 30, median [IQR]	0.2 [0.1–0.4]		4.7 [2.9–7.4]	
> 30, median [IQR]	1.2 [0.5–2.5]		6.1 [3.4–16.4]	
Radiation		*0.017*		*0.88*
Non-Radiated, median [IQR]	0.2 [0.1–0.8]		5.6 [2.6–10.2]	
Prior Radiation, median [IQR]	0.9 [0.5–1.4]		5.2 [4.0–6.6]	
Ureteral Stents Placed		*0.11*		*0.11*
ICG Injection Alone, median [IQR]	0.2 [0.1–1.0]		5.6 [3.1–10.4]	
ICG + Stent, median [IQR]	0.6 [0.2–1.6]		4.0 [2.2–6.1]	
Type of Operation		*0.19*		*0.98*
Colectomy, median [IQR]	0.2 [0.1–0.8]		4.7 [2.8–11.3]	
LAR/APR, median [IQR]	0.5 [0.1–1.2]		5.6 [3.2–8.2]	
Diverticulitis		*0.19*		*0.18*
Non-complicated, median [IQR]	0.1 [0.1–0.4]		4.1 [2.0–6.2]	
Complicated, median [IQR]	0.2 [0.1–2.5]		5.6 [3.5–10.9]	

ID: identification; BMI: body mass index; IQR: interquartile range; LAR: low anterior resection; APR: abdominoperineal resection.

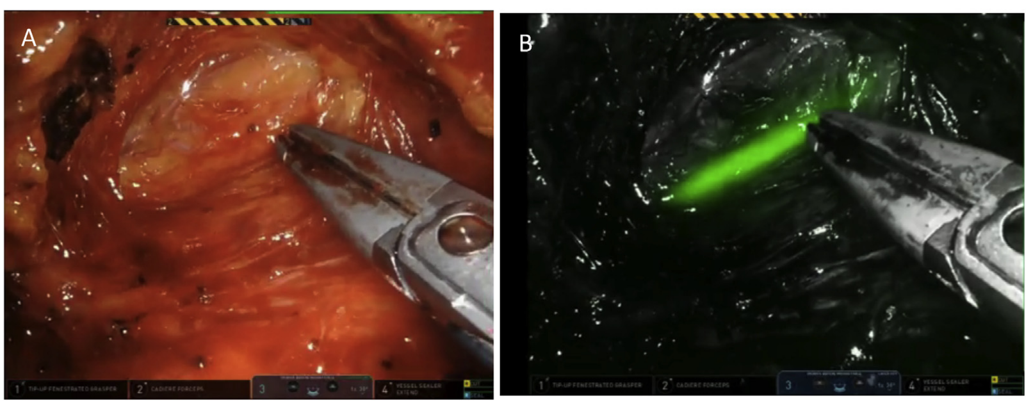

Fig. 4. Intraoperative visualization during medial-to-lateral dissection (A) without and (B) with fluorescent indocyanine green (ICG) for left ureteral identification.

minimally invasive surgery (MIS) is an increased risk factor for iatrogenic injury.[6,21] While understanding relevant surgical anatomy remains the foundation for safe surgery,[22] this anatomy can be distorted or difficult in obese patients or tissue disrupted by infection, inflammation, malignancy and radiation. Ironically, these are the pathologies that most benefit from MIS approaches,[17,23–25] making ureteral identification with MIS paramount. The diminished tactile feedback during MIS compared to open operations may make use of traditional intraoperative catheterization less effective, and as a result, techniques such as lighted stents and use of fluorescent dye have been described to aid minimally invasive ureteral localization.[26–28]

In this largest reported consecutive series of patients, intraureteral ICG reliably identified the ureter in all but two cases involving the right ureter. In one patient with complicated diverticulitis, there were severe adhesions and inflammation in the right abdomen that precluded clear visualization of the right ureter with or without ICG, and dissection to definitively identify the right ureter was discontinued as it was deemed not required to safely complete the operation. In the second patient, the right ureter did not fluoresce though the patient's tissue, but was clearly visible without the dye, and it worked appropriately on the contralateral side, which may represent a technical error during ICG instillation in that ureteral orifice or, less likely, an unrecognized obstruction (as no post-operative obstructive complication occurred). One subjective advantage of injected ICG is the ability to visualize the fluorescence through thick tissue in obese patients – something that can be further enhanced by adjusting the sensitivity of the filters on the robotic console. This potentially avoids unnecessary dissection and saves time – something that is hard to demonstrate in this type of retrospective analysis, but is suggested by the fact that the ureter was quickly identified, even in patients with BMI greater than 30 where it took 1 min longer on the right compared to patients with lower BMI. Excess visceral fat may also be present in patients with lower BMI, in which ICG can be used for image-guided ureteral identification.

Cystoscopy and injection of ICG alone was nearly 4 times faster than with stent placement, suggesting that the ureteral injection technique may not only have time-saving implications, but also cost-saving implications compared to traditional ureteral catheterization. For instance, at our institution a vial of ICG is relatively cheap at a charge of $90 per vial. With estimated costs of OR time as high as $60/min,[29,30] and consideration of charges for intraoperative catheters, guidewires, or fluoroscopy, it seems appealing to both save time and avoid additional charges[31] with this approach. Moreover, eliminating a ureteral catheter eliminates the risk of catheter-related complications, such as mucosal edema, reflex anuria, ureteral perforation, and ureteral obstruction.[32,33] Additionally, ICG dye is safe. No significant toxic effects have been reported in humans with a high dose of 5 mg/kg of body weight and ICG-related complications are rare, with one case report describing anaphylactic shock after intravenous administration.[11,34] In our study, we did not see adverse effects with ICG use and observed a higher incidence of hydronephrosis and AKI in stented patients compared to those without a stent, likely due to mucosal edema and reflex anuria from direct ureteral trauma.[35,36]

While our study does not address the degree to which ICG facilitates intraoperative ureteral identification, we have found that it is a reliable tool that may be used as an adjunct, especially during difficult dissections. Ureteral injuries can be discovered by leakage of ICG into the abdominal cavity and subsequent stent placement to assist with intraoperative repair. In instances when cases are converted to an open operation, handheld NIRF devices may be used to detect intra-ureteral ICG. However, in that setting, the authors' would advocate for stent placement and palpation of the ureter, utilization of anatomic landmarks, or alternative surgical maneuvers, such as higher dissection or shifting laterally, as adjuncts for safe ureteral identification. Additionally, the incidence of ureteral injury in our study was 1.2% and we are underpowered to conclude that this technique prevents iatrogenic injury. For instance, the reported rate of ureteral injury during minimally invasive colorectal resections is 1.5% in the published literature. Hypothetically, if one were to prove ICG decreased the risk of injury; to detect a change of 1.5%–1% using a 95% confidence and 80% power, over 7800 patients would be needed to adequately power the study.

Our study is limited by the small sample size, in which the technique and results may not be generalizable or reproducible in a broader population. While there were only 4 surgeons who used ICG for ureteral identification, there were 7 different urology attendings and 8 different urology residents, which can introduce variation in performing the injection procedure. There is also selection bias as some cases were selected for stent placement, while others were not. At the initiation of the study, the surgeons' and institutional norm was to place ureteral stents if there were concerns about ureteral identification. As we transitioned to ICG imaging, we initially placed stents and injected ICG through them. It became quickly clear that we were using the fluorescent visualization more than palpation of the stent itself, and that visualization was persisting through the entire operation, so we shifted to injection alone. Our surgeons still selectively apply ureteral catheterization in cases of known ureteral obstruction on pre-operative imaging or if the surgeon feels that the conversion probability is high based on the patient's disease burden. Conversion to an open operation in our series was 1.2% and because of this low conversion rate, as well as reliability of ICG injection alone, injection of ICG without stent is now the authors' preferred approach for left-sided colorectal resections. Even with injection alone, there is still the opportunity to insert a stent during the case at any time, specifically in conversion to an open operation.

Conclusion

In conclusion, compared to traditional stenting and injection, ureteral injection using ICG alone for fluorescent imaging is faster, equally safe, and reliable at bilateral ureteral identification for robotic left-sided colorectal resections. At our institution, we have transitioned to only using injected ICG without ureteral stents, unless there is a pre-operative demonstration of ureteral obstruction. As this technique is more broadly used, future studies should focus on generalizability (to laparoscopic approaches, for instance), costs and complications avoided in a prospective manner, and uptake/thresholds for surgeons who are performing left-sided resections to use ureteral identification adjuncts.

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Ethical approval

This study was approved by the ethical and scientific committee of our institution.

Informed consent

Written informed consent was exempt for this study.

Declaration of competing interest

Dr. Simianu is a consultant for C-SATs, Inc. and has received educational, travel support from Intuitive Surgical. The remaining authors report no conflicts of interest, use of off-label or unapproved drugs or products, use of previously copyrighted material.

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