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Real-time indocyanine green angiography with the SPY fluorescence imaging platform decreases benign ureteroenteric strictures in urinary diversions performed during radical cystectomy

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Abstract

Background: Ischemia is thought to contribute to benign ureteroenteric stricture (UES) after radical cystectomy with urinary diversion (RCUD). Our institution adopted the use of ureteral perfusion assessment during all RCUDs using real-time indocyanine green angiography using the SPY fluorescence imaging platform (Stryker Corp., Kalamazoo, MI, USA). This guides the location of ureteral transection prior to ureteroenteric anastomosis. We sought to compare UES rates before and after adoption of SPY.

Methods: A retrospective chart review was undertaken for the first 47 consecutive cases of RCUD using SPY as well as the previous 47 consecutive cases, which were performed without SPY. Fisher's exact and Wilcoxon rank-sum tests were used to compare benign UES rates and the length of ureter excised during anastomosis. A $p < 0.05$ indicated statistical significance.

Results: Median follow up was 12.0 months for SPY cases and 24.3 months for non-SPY cases. The UES rate for SPY RCUDs was 0% (0/93 ureters) compared with 7.5% (7/93 ureters) for non-SPY RCUDs ($p = 0.01$). Amongst SPY RCUDs, 86 ureters had no hydronephrosis and 7 had mild hydronephrosis with reflux on loopogram. A total of 34.4% of ureters (32/93) had poor distal perfusion, requiring a more proximal anastomosis. The median length excised for ureters with poor distal perfusion was 3.8 cm, compared with 2.2 cm for ureters with good distal perfusion ($p < 0.0001$). No complications attributable to the use of SPY were noted.

Conclusion: Use of SPY to assess ureteral perfusion was associated with a decrease in the UES rate after RCUD. A total of 34.4% of ureters demonstrated poor distal perfusion, requiring a significantly more proximal ureteroenteric anastomosis.

Keywords: bladder cancer, indocyanine green, near-infrared fluorescence imaging, ureteral stricture, urinary diversion

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Introduction

Treatment of bladder cancer has evolved over the last several decades with the advent of new technology. Minimally invasive cystectomy is associated with less blood loss, higher nodal yields, shorter length of stay, and overall lower rates of perioperative complications compared with open surgery.[1] Despite these advances, the rate of long-term complications remains relatively unchanged at 5–25%.[2,3]

A challenging complication encountered after radical cystectomy with urinary diversion (RCUD) is the development of benign ureteroenteric stricture

(UES). Despite numerous variations in ureteroenteric anastomotic technique and diversion types, the rate of UES has not significantly changed over the last three decades, ranging from 2% to 13%.[4–7] While the exact cause of UES is not always known, ureteral blood supply is known to be tenuous and ischemia is thought to be a significant contributor to UES. These can cause significant morbidity in the form of prolonged hospital stays, hospital readmissions, the need for invasive interventions or revision surgery, and possibly loss of the renal unit.

Indocyanine green (ICG) fluorescence has emerged as a tool to assess tissue perfusion. ICG was United States Food and Drug Administration (US FDA)-approved in 1959 for medical use. It is administered intravenously and is rapidly bound to plasma proteins with minimal leakage into the interstitium. It becomes fluorescent when excited with near-infrared light, allowing for its detection within tissue with specially designed cameras.[8] With the aid of a high definition camera and software-imposed green fluorescence, intravenously administered ICG may be used to identify vessel perfusion and differentiate tissue density.[9] ICG has gained wide applicability in many fields of surgery, including for the assessment of muscle perfusion for flaps,[10] anastomotic perfusion at the time of rectal surgery,[11] and skin flap perfusion after mastectomy.[12]

The development of FireFly technology (Intuitive Surgical, Sunnyvale, CA, USA) in 2011 allowed use of ICG with the da Vinci robotic surgery platform, extending the usage of ICG in urology to include partial nephrectomy[13] as well as the assessment of ureteral perfusion at the time of ureteral reimplantation, ureteropelvic junction repair, ureterolysis, and ureteroureterostomy.[14] ICG has also been instilled directly into the renal pelvis and ureter to aid in ureteral localization during ureteroureterostomy, ureterolysis, and pyeloplasty.[15–17] Freitas and colleagues also described the use of ICG at the time of robot-assisted radical cystectomy, reporting on 10 patients who received ICG injection during intracorporeal urinary diversion allowing for assessment of ureteral perfusion *via* the FireFly system.[18]

Recently, the SPY fluorescence imaging platform was created which displays not only the presence of ICG, but also provides a color-graded quantitative assessment of the amount of ICG within tissue. The technology was initially developed by Novadaq Technologies Inc. (Mississauga, ON, Canada), which was then acquired by Stryker Corp. (Kalamazoo, MI, USA). SPY imaging displays the level of detected ICG in tissues from gray (meaning low levels of ICG) to red (meaning high levels of ICG). This provides a 'heat-map' view of the ureter that reflects vascular perfusion. Unlike the FireFly system that is limited to the intracorporeal assessment of ureteral perfusion using the da Vinci robot, the SPY platform can be used in both open surgery using a handheld camera (SPY-PHI) and minimally invasive surgery using an endoscopic camera (PINPOINT). In this study, we evaluated the safety and efficacy of ureteral vascular perfusion assessment at the time of ureteroenteric anastomosis using real-time ICG angiography with the SPY fluorescence imaging platform and the subsequent impact on UES rate.

Materials and methods

Study design

After institutional review board approval was obtained, data were collected retrospectively on patients undergoing RCUD between December 2015 and March 2018. This time period included the first 47 consecutive cases (93 ureters) of RCUD using SPY as well as the previous 47 consecutive cases (93 ureters), all of which were performed without SPY. Data regarding postoperative and surveillance imaging results, the presence of hydronephrosis, perioperative characteristics including length of ureter excised (obtained from pathology report), and subsequent interventions for UES were recorded.

Intraoperative assessment of ureter

All urinary diversions were performed in an extracorporeal fashion by a single surgeon (KGC), as previously described.[19] After the extirpative portion of the RCUD was complete, the ureters were evaluated extracorporeally at the infra-umbilical midline extraction site. For non-SPY cases, the ureter was divided at a location where it appeared viable and uninjured by visual inspection and would provide the appropriate length for a tension-free anastomosis. All ureteroenteric anastomoses were performed in a Bricker fashion.

For SPY cases, perfusion assessment was performed using the PINPOINT endoscope prior to dividing the bowel for the urinary diversion. This allowed us to tailor the bowel segment length to ensure a tension-free anastomosis in situations where a large portion of ureter needed to be excised to ensure good perfusion. A total of 3 ml of ICG, followed by 10 ml of normal saline was administered intravenously. The color-segmented fluorescence mode was used to provide a 'heat-map' view of each distal ureter. For ureters with good distal perfusion, the ureter was divided at a location that would provide appropriate length for a tension-free anastomosis. For ureters with poor distal perfusion, a suture was used to mark the distal-most extent of ureteral perfusion for each ureter. The ureter was then divided proximal to this suture to ensure adequate blood supply to the anastomosis. The bowel was then divided as needed to ensure tension-free ureteroenteric anastomoses. After completing the ureteroenteric anastomoses, 3 ml of ICG was again administered and the SPY system was used to make a final perfusion assessment for each anastomosis. For ileal conduits and continent cutaneous urinary diversions, the final assessment was performed using the PINPOINT endoscope while the conduit or pouch was extracorporeal. For neobladders, the robot was re-docked and the urethral anastomosis was performed. The final assessment of each ureteroenteric anastomosis was then performed intracorporeally by inserting the PINPOINT endoscope through a port.

Follow up

Postoperatively, patients were managed *via* a standardized enhanced recovery pathway as previously described.[19] The externalized ureteral stents were removed once patients were tolerating a regular diet and prior to discharge from the hospital. Patients subsequently underwent renal ultrasound at 4–6 weeks after stent removal to assess for hydronephrosis. Subsequent computed tomography scans of the abdomen and pelvis were performed per National Comprehensive Cancer Network Clinical Practice guidelines. Ureteroenteric anastomoses were considered patent if the most recent upper tract imaging showed no significant hydronephrosis. If significant hydronephrosis was present and the patient was asymptomatic, a loopogram was obtained to assess for reflux, and if reflux was absent, a diuretic renal scan was obtained. UES was diagnosed if hydronephrosis was present, the loopogram showed no reflux, and diuretic renal scan showed $T^{1}/_{2}$ of >20 min. For symptomatic patients, a percutaneous nephrostomy tube was placed and UES was demonstrated *via* antegrade nephrostogram.

Statistical analysis

Fisher's exact tests and Wilcoxon rank-sum tests were used to compare UES rates and length of the ureter excised during ureteroenteric anastomosis. Chi-square tests were used to compare patient demographics and perioperative characteristics. A $p < 0.05$ indicated statistical significance. The reverse Kaplan–Meier method was used to calculate the median duration of follow up.

Results

Patient characteristics are displayed in Table 1. For SPY patients, the mean time required to assess ureteral perfusion before and after ureteroenteric anastomosis was 6 minutes. On initial assessment of ureteral perfusion prior to ureteroenteric anastomosis, good distal perfusion was seen in 61 out of 93 ureters (65.6%). In contrast, 32 of 93 ureters (34.4%) had poor distal perfusion. These ureters were trimmed to the point where good perfusion was seen on SPY imaging as described above. The ureteroenteric anastomosis was then performed at this location. All ureters were re-evaluated after ureteroenteric anastomosis using the SPY system, and good perfusion was seen (Figure 1). SPY cases as a whole did not require excision of more distal ureter than non-SPY cases (median 2.5 cm *versus* 2.9 cm, $p = 0.6$). However, amongst SPY cases, ureters that had good distal perfusion on initial evaluation had a median of 2.2 cm excised prior to anastomosis, compared with 3.8 cm of ureter excised in ureters that showed poor perfusion requiring a more proximal ureteroenteric anastomosis ($p < 0.0001$).

To date, no UESs have been identified in this cohort (0/93 ureters), compared with 7.5% (7/93 ureters) in the non-SPY group ($p = 0.01$). Overall, five of seven UESs (71.4%) were left sided. The median time to diagnosis of UES in the non-SPY group was 3.7 months after RCUD (interquartile range 2.4–5.3). No ICG-related complications such as hot flashes, anaphylactic shock, hypotension, or tachycardia were seen. The median follow up was 12.0 months for the SPY group and 24.3 months for the non-SPY group.

Discussion

Despite multiple advances in RCUD technique, the problem of UES remains a challenge. The rate of strictures quoted in the literature can range from anywhere between 2% and 13%.[4–7,20] Such variability likely exists due to differing methods

Table 1. Patient characteristics.

	Non-SPY (n = 93)	SPY (n = 93)	p-value
Median age	74 (IQR 62–80)	69 (IQR 65–76)	0.3
Median body mass index (kg/m^2)	25.9 (IQR 24.6–28.8)	24.7 (IQR 23.9–30.3)	0.2
Sex			0.9
Female	18 (19.4%)	17 (18.3%)	
Male	75 (80.6%)	76 (81.7%)	
Laterality of ureteroenteric anastomosis			1.0
Left	47 (50.5%)	47 (50.5%)	
Right	46 (49.5%)	46 (49.5%)	
Diversion type			0.2
Ileal conduit	56 (60.2%)	51 (54.8%)	
Indiana pouch	5 (5.4%)	12 (12.9%)	
Studer neobladder	32 (34.4%)	30 (32.3%)	

IQR, interquartile range.

for diagnosing UES and lack of strict criteria to define what constitutes a stricture. Furthermore, postoperative follow up and management of UESs are variable with the long-term rate of ureteral stricture likely residing on the higher end quoted in the literature. Multiple techniques have been proposed to help reduce the incidence of UES. While several studies have shown that nonrefluxing anastomoses have higher stricture rates than refluxing anastomoses,[21,22] no other significant differences between techniques have been demonstrated. A recent meta-analysis examining UES after ileal conduit urinary diversion showed no differences in stricture rate between Wallace and Bricker anastomosis.[23] Similarly, no differences were seen in stricture rates between ureteroenteric anastomoses performed using running *versus* interrupted suture.[24]

Furthermore, no compelling data exist showing any difference between open cystectomy and minimally invasive cystectomy with regards to UES rate; Anderson and colleagues reported on 375 patients either undergoing open *versus* robot-assisted radical cystectomy with extracorporeal urinary diversion, finding no difference in UES rate (8.5% *versus* 12.6%, respectively).[5] Guru and colleagues found that intracorporeal urinary diversion was associated with a three-fold elevated risk of UES compared with extracorporeal diversion. However, the authors noted that intracorporeal stricture rates were significantly higher early in their series and decreased with technical changes and experience.[25] Finally, some of the largest series of robot-assisted radical cystectomy with intracorporeal diversion show stricture rates comparable with that of open radical cystectomy or robot-assisted radical cystectomy with extracorporeal diversion.[20,26]

An obstacle preventing the development of technical improvements to lower the UES rate is that the exact cause of UES is not clear. It is commonly believed that UESs are a result of ischemia and inflammation, given the tenuous blood supply to the ureter. Indeed, patients who have a postoperative urine leak or urinary tract infection, with the accompanying local inflammation, have a higher rate of UESs.[25] Furthermore, the higher rate of left ureteral strictures as opposed to right suggests that increased mobilization may be leading to anastomotic ischemia, resulting in UESs.[6]

In contrast with previous studies that use FireFly to assess for ureteral perfusion, we employ real-time ICG angiography using the SPY system. While FireFly uses the existing da Vinci camera

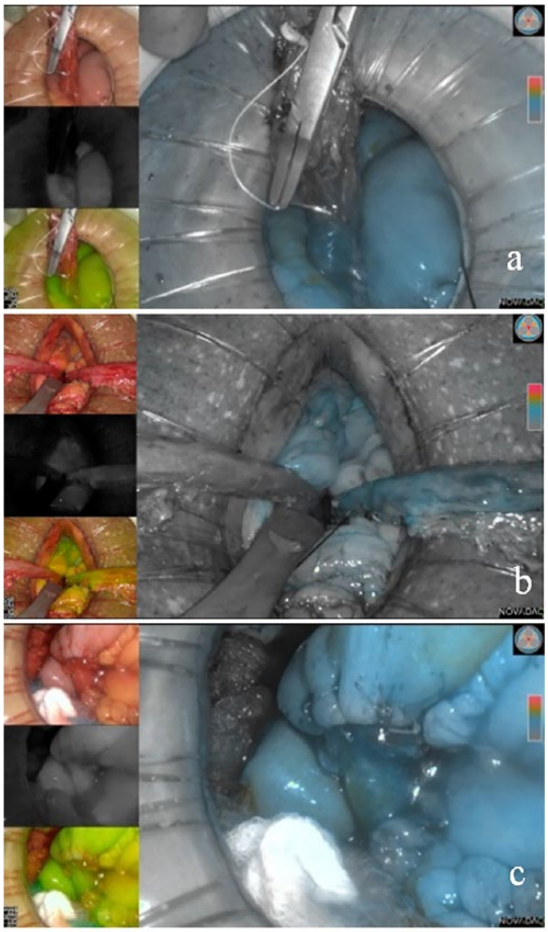

Figure 1. (a) Assessment of ureteral perfusion, with a suture marking the distal-most extent of perfusion. The image on the right is the 'heat-map' view, with blue indicating good perfusion on the heat map. On the white light view (top left), no visual cues are present to indicate poor ureteral perfusion distally. (b) The left ureter shows poor perfusion throughout, with the right ureter showing good perfusion distally. This required a significantly more proximal left ureteroenteric anastomosis. (c) The anastomosis of the left ureter from (b) is completed, with excellent perfusion noted on final assessment.

to overlay a black and white image with ICG tracer appearing green, the SPY system provides a color image with the ICG tracer appearing green. Additionally, it also provides a 'heat map' of ureteral perfusion in the color-segmented fluorescence mode, allowing improved quantitative assessment of the degree of tissue perfusion. This is especially critical in settings of questionable vascular supply, such as the ureteroenteric anastomosis. In our experience, we have noted multiple instances of ureteral perfusion that appeared adequate when assessed by FireFly, but were seen to be poorly perfused when assessed by SPY (Figure 2). In this study, the use of SPY resulted in approximately one-third of ureters being excised to a more proximal point than would have been the case under white light in order to ensure adequate blood supply at the anastomosis. Using this system, we have not seen evidence for any UES in short-term follow up.

Our study has several limitations. Our follow-up time is shorter than that reported in other series,[25] and we acknowledge that new UES may be diagnosed several years after surgery. However, in our institution's experience, benign UES after RCUD occurs early. Non-SPY patients were diagnosed with UES at a median of 3.7 months after RCUD despite having been followed for a median of 24.3 months. The relatively low number of patients in our study also limits the impact of our study. We further acknowledge that while a potentially powerful tool, SPY imaging only assesses tissue perfusion when used in the manner described in this study. Therefore, it likely does not prevent UES that occur *via* other mechanisms including local inflammation related to urine leak or urinary tract infection, or surgical factors such as excessive tension on the anastomosis. When used in the

Figure 2. Identical images obtained of bilateral distal ureters. (a) White light view with no visual cues of poor perfusion. (b) FireFly view with excellent uptake of tracer up to the distal clip. (c) PINPOINT view showing poor distal perfusion of left ureter.

manner we have described, SPY imaging does not provide any method of preventing ureteral ischemia when mobilizing the ureter in the retroperitoneum. However, it is possible that SPY imaging may prove to be useful in visualizing and preserving the ureteral blood supply during this process. This represents a potential future topic of study. Despite the aforementioned limitations, this study shows that roughly one-third of ureters had poor distal perfusion when initially assessed by SPY, requiring a more proximal ureteroenteric anastomosis than we would otherwise have performed. We found minimal increases in operating time and no morbidity associated with the use of the SPY system, suggesting that assessment of vascular perfusion of the ureter at the time of ureteroenteric anastomosis is safe and may help reduce the overall risk of UES.

Conclusion

In this study of 186 ureters in 94 patients who underwent robot-assisted RCUD, use of near-infrared fluorescence angiography using SPY was well tolerated with minimal added operating time. The use of the SPY system demonstrated poor distal perfusion in 34.4% of ureters, requiring a more proximal ureteroenteric anastomosis. Use of SPY was associated with a significantly lower UES rate.

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Conflict of interest statement

Clayton Lau, MD is a consultant for Intuitive Surgical Inc. Jonathan Warner, MD is a consultant for Olympus Corp, Coloplast, and Richard Wolf Medical Instruments Corp. The remaining co-authors declare no conflicts of interest.

Compliance with ethical standards

Institutional review board approval was obtained for this retrospective study. No informed consent was obtained or necessary given the nature of the study.

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