# Ureteroenteric Anastomotic Strictures Following Robotic Radical Cystectomy: Extracorporeal Versus Intracorporeal Approaches in the Indocyanine Green Era

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#### What's known on the subject? and What does the study add?

Benign ureteroenteric stricture formation after radical cystectomy is a common complication which is difficult to manage. This study shows the possible benefical effect of intraoperative indocyanine green utilization during robotic radical cystectomy in order to prevent benign ureteroenteric stricture formation.

#### Abstract

**Objective:** The aim of this study was to compare the early period iatrogenic benign ureteroenteric anastomotic stricture formation between robotic radical cystectomy with extracorporeal urinary diversion, robotic radical cystectomy with intracorporeal urinary diversion [without using indocyanine green (ICG)] and robotic radical cystectomy with intracorporeal urinary diversion (with using ICG).

**Materials and Methods:** A total of 30 patients (59 renal units) who underwent robotic radical cystectomy and urinary diversion intracorporeally or extracorporeally for muscle-invasive bladder cancer between 2014 and 2021 were included in this study. We retrospectively reviewed the demographic data and perioperative results. The primary endpoint of our study was the ureteroenteric stricture formation rate at the 6<sup>th</sup> week after the single-J ureteral catheter removal.

**Results:** From our study cohort; 13 of these patients (26 renal units) urinary diversions were performed using extracorporeal approach (group 1), 10 of these patients (20 renal units) urinary diversions were performed by intracorporeal approach without using ICG (group 2) and 7 of these patients (13 renal units) urinary diversions were performed by intracorporeal approach with using ICG (group 3). The overall incidence of early period ureteroenteric stricture formation (post-operative 6<sup>th</sup> week after the single J catheter removal) was 8.5% (5 renal units); 11.5% (3 renal units) after extracorporeal approach (group 1); 10% (2 renal units) after intracorporeal approach without using ICG (group 2). None of the patients with intracorporeal approach using ICG (group 3) had a demonstrable ureteroenteric stricture at post-operative 6<sup>th</sup> week after the single J catheter removal.

Conclusion: Robotic intracorporeal urinary diversion with using ICG is a promising approach in terms of preventing benign ureteroenteric strictures.

Keywords: Robotics, cystectomy, indocyanine green

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# Introduction

The optimal treatment for muscle-invasive bladder carcinoma is radical cystectomy with urinary diversion and perioperative complication rates of this surgery may extend up to 70% (1,2). The incidence of benign ureteroenteric strictures after radical cystectomy is reported between 2.6% and 13% in the literature (3-9). The management of these strictures may be difficult and can cause obstruction, hydronephrosis, urinary stones and eventually kidney malfunction (10). Although it's thought that ischemia induced scar formation at the anastomosis may play a role in the development of the ureteroenteric anastomotic stricture; the exact mechanism is not well-known (5). Even though the best surgical principles are followed, including meticulous tissue handling and periureteric adventitial tissue preservation, vascularization of ureters can be jeopardized and eventually lead to ureteroenteric stricture development. Distal ureter vascularization may be assessed subjectively but is prone to error when inspected under white light and when using an open approach. Near-infrared fluorescence (NIRF) imaging after indocyanine green (ICG) injection has been proposed as a useful method for real-time imaging during the operation. ICG (Akorn, Lake Forest, IL) is a nontoxic and FDA approved near-infrared fluorescent dye, visualized by the assistance of an infrared camera, and cannot be identified under white light (11). The application of the Firefly technology (Novadag Technologies, Mississauga, ON, Canada) integrated with the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) has provided wide adoption of ICG usage in robotic surgeries. console surgeon can intraoperatively switch on the NIRF system when required, permitting shifting between white light and near-infrared light, leading real-time identification of the fluorescence of ICG (12). Unlike inspection under white light; ICG usage may aid better evaluation of tissue vascularization, thereby improving recognition and consequently excision of non-viable distal ureteric segments provided before ureteroenteric anastomosis.

In this study, we compared the incidence of the iatrogenic ureteroenteric strictures six weeks after three procedures: Robotic radical cystectomy with extracorporeal urinary diversion; robotic radical cystectomy with intracorporeal urinary diversion without ICG; and robotic radical cystectomy with intracorporeal urinary diversion using ICG.

## **Materials and Methods**

The data of the patients who underwent robotic radical cystectomy with extracorporeal urinary diversion and robotic radical cystectomy with intracorporeal urinary diversion were retrospectively collected. The study was approved by Acibadem Mehmet Ali Aydinlar University Medical Research Ethics Committee (ATADEK) (decision number: 2021-09/51).

In both groups, the radical cystectomy part of the operation was performed transperitoneally with six ports using Da Vinci SI or Da Vinci XI robotic systems (both from Intuitive Surgical, Sunnyvale, CA, USA). The operative approach (extracorporeal or intracorporeal urinary diversion) was at the discretion of the surgeon and was decided in consultation with the patient. All cystectomies and urinary diversions were performed by a single surgeon, Prof. Dr. Ali Riza Kural, who is very experienced in robotic surgery (≥2.500 cases) and with open surgery.

In the extracorporeal urinary diversion approach, a small midline infraumbilical incision was made at the end of the robotic cystectomy. After the removal of the cystectomy specimen, a tension-free Wallace anastomosis was performed. In conduits, the left ureter was transferred to the right side through a retromesenteric window. After the construction of the intestinal diversion, distal parts of the ureters were excised proximally to healthy tissue and only distal ureteric segments were handled at this point. Anastomosis over 6 F single J stents by 4/0 polyglactin absorbable sutures was performed after the spatulation of the ureters.

For the intracorporeal urinary diversion using ICG, the procedure was as follows. Firstly, left ureter was again transferred to the right side through a retro-mesenteric window. After this, 25 mg ICG was mixed with 10 mL-distilled water and 2 mL of this solution was injected intravenously just before the spatulation and construction of the uretero-enteric anastomosis, after isolation and construction of the neobladder or ileal loop. For the intracorporeal neobladder, the technique described by Wiklund and Poulakis (13) was used. The distal part of the ureters was assessed by the assistance of the NIRF system. After the fluorescence of small periureteric arteries within 30 secondsand ureteric wall fluorescence within 5 min due to the perfusion of ICG into the ureteric tissue. The vascularization of the neobladder or ileal conduit and bowel anastomosis were also inspected. The non-enhancing segments of the ureter (Figures 1,2) were excised and after the spatulation of the healthy vascularized distal part of the ureters, modified tension-free Wallace anastomosis was performed over 6F single J stents using Stratafix 4/0 sutures. Frozen sections of the distal ureteral segments during radical cystectomy were performed for each patient after clipping of the distal ureter. In both approaches, single J stents were left in place for 10 days.

Patient demographic records and histopathological data were reviewed. The length of the excised ureter segments was also assessed. However, excised ureteric segments suspected of malignancy on frozen section analysis were excluded from the study. Post-operative follow-up was performed by regular clinical visit with ultrasonographic examination, six weeks after the single-J catheter removal. Ureteroenteric stricture was defined as functional imaging proven obstruction that leads to hydronephrosis. Patients with suspicious strictures (clinical or radiologic) were further evaluated with mercaptuocetyltriglycine (Mag3) renal scintigraphy.

#### **Statistical Analysis**

SPSS version 21 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Continuous variables are presented as median (interquartile range – IQR) while categorical variables



Figure 1. ICG non-enhancing ureteral segment

ICG: Indocyanine green

are presented as frequency and percentage. Comparisons of the groups for continuous variables were made by Kruskal-Wallis test. Fisher's Exact test was used to analyze the categorical variables. Post hoc analyses were performed to test the significance of pairwise differences. All tests are two-sided and the significance level was set as p<0.05.

### **Results**

Between April 2014 and December 2021, 30 (27 male, 3 female) robotic radical cystectomies for bladder cancer were identified and included. Baseline patient characteristics are summarized in Table 1. The median age for the extracorporeal urinary



Figure 2. ICG non-enhancing ureteral segment

ICG: Indocyanine green

Table 1. Baseline characteristics of the operative approaches							
Valuable	Robotic radical cystectomy with extracorporeal urinary diversion 13 patients 26 renal units (group 1)	Robotic radical cystectomy with intracorporeal urinary diversion (without using ICG) 10 patients 20 renal units (group 2)	Robotic radical cystectomy with intracorporeal urinary diversion (with using ICG) 7 patients 13 renal patients (group 3)	p-value			
Sex, n (%)							
Male	12 (92)	9 (90)	6 (86)	1.000*			
Female	1 (8)	1 (10)	1 (14)	1.000			
Age at RARC, years, median (Q1, Q3)	59 (58,62.5)ª	70.5 (65.73) <sup>b</sup>	69 (67-78) <sup>b</sup>	0.007**			
Smoking history, n (%)	7 (54)	6 (60)	5 (71)	0.891*			
Hypertension, n (%)	7 (54)	5 (50)	4 (57)	1.000*			
Diabetes, n (%)	3 (23)	2 (20)	2 (28)	1.000*			
Coronary artery disease, n (%)	2 (15)	1 (10)	2 (28)	0.687*			
BMI (kg/m <sup>2</sup> ), median (Q1, Q3)	28 (26.5-30.5)	28.5 (27-31)	29 (28-30)	0.881**			
Neoadjuvant chemotherapy, n (%)	5 (38)	3 (30)	2 (28.6)	0.1000*			
Pre-op hydronephrosis, n (%)	1 (8)	1 (10)	1 (14)	1.000*			
Intraoperative estimated blood loss, mL, median, (range)	400 (300-600)	425 (250-600)	425 (250-550)	0.793**			
Each subscript letter denotes a subset of operation type categories whose column proportions do not differ significantly from each other at the 0.05 level, ICG: Indocyanine green, BMI: Body mass index, *: Fisher's Exact test, **: Kruskal-Wallis test							

diversion group (group 1) was significantly lower than in both the intracorporeal urinary diversion without ICG (group 2) and the intracorporeal urinary diversion using ICG groups (group 3). No statistical differences were found in the other baseline characteristics. Five patients (38%) in the extracorporeal urinary diversion group (group 1), three (30%) in the intracorporeal urinary diversion group without ICG (group 2) and two (28.6%) in the intracorporeal urinary diversion group using ICG (group 3) received neoadjuvant chemotherapy. None of the patients in this study received pelvic radiotherapy post-operatively. Preoperative hydronephrosis was detected in one (8%) patient in the extracorporeal urinary diversion group (group 1), in one (10%) in the intracorporeal urinary diversion group without ICG (group 2) and in one patient (14%) in the intracorporeal urinary diversion group using ICG (group 3). The type of diversion and baseline histopathological characteristic of the operative approaches are shown in Table 2. When using an extracorporeal approach, the type of urinary diversion was ileal neobladder in 12 patients and ileal loop in 1 patient. When using the intracorporeal approach, the type of urinary diversion was ileal neobladder in 7 patients (6 without ICG, 1 using ICG) and ileal loop in 10 patients (4 without ICG, 6 using ICG). Intraoperative ICG was used in 7 patients (ileal neobladder in 1, ileal loop in 6) patients with 13 renal units (in

one patient concomitant robotic left nephroureterectomy was performed) in the intracorporeal urinary diversion group using ICG (group 3) for uretero-ileal anastomosis. In the intracorporeal urinary diversion group using ICG (group 3), 7 ureters on the right side required proximal resection due to poor perfusion with median length of resected ureter 23 (IQR 22.25-25.5) mm. On the left side 6 ureters (in one patient concomitant robotic left nephroureterectomy was performed) required proximal transection due to poor perfusion with a median length of the resected ureter of 28.5 (IQR 27-30) mm. The median (IQR) length of the resected distal ureter based on perfusion was 20.5 (IQR 20-22) mm for the extracorporeal urinary diversion group (group 1), 22 (20.5-25) mm for the intracorporeal urinary diversion group without ICG (group 2) and 26 (23-28.25) mm for the intracorporeal urinary diversion group using ICG (group 3). The median length of the resected distal ureter due to poor perfusion was significantly higher in the intracorporeal urinary diversion group using ICG (group 3) compared with the other two groups (p<0,.001). None of the resected ureteric segments based on perfusion revealed malignancy on final pathological examination. In the immediate post-operative 30-day period, Clavien-Dindo grade 2 complications were encountered in three patients in the extracorporeal urinary diversion group (group 1),

Table 2. Type of diversion and baseline pathologic characteristics of the operative approaches						
	Robotic radical cystectomy with extracorporeal urinary diversion (group 1)	Robotic radical cystectomy with intracorporeal urinary diversion (without using ICG) (group 2)	Robotic radical cystectomy with intracorporeal urinary diversion (with using ICG) (group 3)			
Type of diversion, n (%)						
lleal loop	1 (8)	4 (40)	6 (86)			
lleal neobladder	12 (92)	6 (60)	1 (14)			
Pathologic stage, n (%)						
NMIBC	9 (69)	6 (60)	2 (29)			
MIBC	1 (8)	2 (20)	-			
Non-OC (≥ T3)	3 (23)	2 (20)	5 (71)			
Positive ureteral margins	-	-	-			
Nodal disease, n (%)	3 (23)	2 (20)	0			
ICG: Indocvanine green, NMIBC: Non-muscle invasive bladder cancer, MIBC: Muscle invasive bladder cancer, OC: Organ confined						

Table 3. Characteristics of the uretero-enteric strictures according to the operative approach						
	Robotic radical cystectomy with extracorporeal urinary diversion (group 1)	Robotic radical cystectomy with intracorporeal urinary diversion (without using ICG) (group 2)	Robotic radical cystectomy with intracorporeal urinary diversion (with using ICG) (group 3)			
Stricture rate, n (%)	3 (26) 3/26=11.5%	2 (20) 2/20=10%	0 (13) 0/13=0			
Laterality, n (%)						
Left	2 (66)	2 (100)				
Right	1 (33)	-				
Intervention performed, n (%)	2 (66)	-	-			
ICG: Indocyanine green						

two patients in the intracorporeal urinary diversion without ICG (group 2) group and two patients in the intracorporeal urinary diversion using ICG group (group 3). During the same period, a single Clavien-Dindo grade 3a complication (spontaneous removal of Foley catheter on post-operative day 3 in an ileal neobladder patient) occurred in the intracorporeal urinary diversion without the ICG group (group 2). This complication was managed by re-insertion of the foley catheter under local anesthesia. Finally, a Clavien-Dindo Grade 3b complication (the tip of the drain was broken during removal) occurred in one patient in the intracorporeal urinary diversion using ICG group (group 3). For this patient, the tip of the drain was removed under general anesthesia from a small incision (2 cm) at the drain removal side.

Characteristics of the uretero-enteric strictures that occurred by the group are summarized in Table 3. None of the patients in the intracorporeal urinary diversion group using ICG (group 3) had demonstrable uretero-enteric strictures in the postoperative sixth week after the single J catheter removal. Benign uretero-enteric strictures were identified in five patients, three in the extracorporeal (group 1) and two in the intracorporeal urinary diversion group without ICG (group 2) (Figure 3). Four of these strictures were observed in ileal neobladder diversion and one in the ileal loop diversion. Furthermore, four were left sided and one was right sided. Two of these ureteral strictures were managed surgically, while three were not suitable for surgical management and persisted in follow-up. Of the two patients receiving surgical management of the stricture, one (extracorporeal urinary diversion group, ileal neobladder) had left-sided ureteral stricture diagnosed by ultrasonography and confirmed with Mag3 renal scintigraphy at six weeks after the single J catheter removal. Ureteral stent replacement failed, and percutaneous nephrostomy tube placement was performed in the fifth month post-operatively and ureteral stricture excision and ureteral reimplantation over 6-F JJ stent placement the open approach was performed three weeks after this procedure. The JJ stent was removed by cystoscopy four weeks after the procedure. The other patient (extracorporeal urinary diversion group, ileal neobladder) had right-sided ureteral stricture, again diagnosed by ultrasonography and confirmed with Mag3 renal scintigraphy six weeks after J catheter removal. At the post-operative nine month, ss an antegrade nephrostogram was performed and a right distal ureteral stricture was revealed on fluoroscopy. Subsequently, three-week ureteral JJ



Figure 3. Ureteroenteric stricture distribution according to the groups

stent placement was performed. After JJ stent removal, the patient was informed about progress and agreed to definitive treatment at the post-operative 48<sup>th</sup> month. This right-sided ureteral stricture was excised via transperitoneally with a Da Vinci XI robotic system using ICG with NIRF and a ureteroileal reanastomosis over 4.8 F JJ stent was performed.

## Discussion

The incidence of uretero-enteric stricture formation varies from 2.6% to 13% in the literature (3-9). The source of this difference in the published series is unclear, but it can be attributable to diagnostic criteria for uretero-enteric strictures, patient identification methods and patient population heterogeneity. Adequate vascularization of the distal ureteric segment is crucial for minimizing the uretero-enteric stricture formation. Devascularization can occur, even with minimal mobilization of the ureters, so careful handling, meticulous dissection for preserving periureteric tissue is crucial. Although the timing of uretero-enteric stricture formation after radical cystectomy is reported to vary, most are evident in the first year. Tal et al. (14) reported 75% of patients with stricture formation were diagnosed within 12 months with a median time to diagnosis of seven months. Anderson et al. (4) reported a median time of stricture diagnosis of 5.3 months; in their series of 478 patients with 60 uretero-enteric anastomotic strictures. Shah et al. (7) observed a median time to uretero-enteric stricture formation diagnosis of 10 months in their open radical cystectomy series. They identified 49 patients (2.6%) with benign uretero-enteric stricture in 1964 patients. Shen et al. (15) reported their time course of uretero-enteric stricture formation that required open revision in 33 patients after robotic radical cystectomy with extracorporeal urinary diversion. In their study cohort, they identified a total of 37 (29 unilateral, 4 bilateral) ureteroenteric strictures. Thirty-five of the 37 (94.6%) strictures were demonstrated on imaging (computerized tomography or ultrasound), performed no longer than two months after cystectomy. They recommended consideration of early imaging (by two months post-operatively) to identify uretero-enteric strictures to instigate early management to prevent renal insufficiency. To identify the uretero-enteric strictures in the early period, we also performed ultrasonographic examination six weeks after the single J catheter removal (15).

ICG fluorescence has been used in an expanding range of procedures in the robotic urological field (16). ICG is generally used during robotic partial nephrectomy operations for facilitating super-selective arterial clamping and predicting malignancy in kidney lesions (17-19). Moreover, ICG has been used for detecting sentinel lymph nodes during robotic radical prostatectomy (20). Additionally, in robotic ureteral

reconstruction procedures, intraureteric ICG instillation may facilitate the identification and localization of ureteral strictures (21). Tuderdi et al. (22) reported their transnephrostomic ICG-quided robotic ureteral reimplantation experience for benign uretero-ileal strictures after robotic cystectomy and intracorporeal neobladder in 10 patients. They identified the ureteric segment by injecting ICG in an antegrade fashion through the nephrostomy tube. In this study, only one patient developed stricture recurrence and none of the patients developed worsening of the renal function at a median of 19 months of follow-up. Ahmadi et al. (23) assessed the impact of ICG for evaluating ureteric vascularity on the rate of ureteroenteric stricture formation in 179 patients (132 non ICG and 47 ICG group) undergoing robot assisted radical cystectomy and intracorporeal urinary diversion. After a median follow-up of 12 months, they found in the ICG group that none of the patients had uretero-enteric strictures. However, in their non-ICG group, after a median 14 months of follow-up, there was a per-patient stricture rate of 10.6% and a per ureter stricture rate of 6.6% (p=0.020 and p=0.013, respectively). They concluded that; the use of ICG to assess distal ureteric vascularity during robot assisted radical cystectomy and intracorporeal diversion appears to minimize the risk of uretero-enteric strictures (23). Ericson et al. (24) compared 279 open, 382 robotic extracorporeal and 307 robotic intracorporeal radical cystectomies in terms of incidence of uretero-enteric stricture formation. They reported a benign uretero-enteric stricture incidence of 9.3% after open, 11.3% after robotic extracorporeal and 13% after robotic intracorporeal radical cystectomy. They concluded that an intracorporeal approach following radical cystectomy had increased the risk of benign uretero-enteric stricture formation, especially with less experienced surgeons. Their evidence for this was that uretero-enteric stricture formation in intracorporeal urinary diversions declined as individual surgeon's case numbers of increased in their retrospective series. Furthermore, Ahmed et al. (6) retrospectively compared 269 intracorporeal urinary diversions and 138 extracorporeal urinary diversions in their single surgeon series. They reported uretero-enteric stricture formation of 16% for intracorporeal urinary diversion and 6% for extracorporeal urinary diversion. They reported that an intracorporeal urinary diversion following robotic radical cystectomy was an independent risk factor for ureteroenteric stricture development. Robotic radical cystectomy with extracorporeal urinary diversion has also been suggested to be a risk factor for uretero-enteric strictures. Although stricture formation was not the primary endpoint and comparative statistical analyses were not implemented, the Razor randomized trial reported uretero-enteric strictures at a rate of 9% for robotic radical cystectomy with extracorporeal urinary diversion and 7% for open radical cystectomy (3). Anderson et al. (4) retrospectively compared 103 robotic radical

cystectomies with extracorporeal urinary diversion and 375 open radical cystectomy cases. They reported uretero-enteric stricture in 12.6% for robotic extracorporeal urinary diversion and 8.5% for open radical cystectomy (4). More recently; Faraj et al. (25) compared uretero-enteric stricture rates between open radical cystectomy (8% stricture rate in 337 patients), robotic radical cystectomy with extracorporeal approach (9.6% stricture rate in 197 patients) and robotic radical cystectomy with intracorporeal urinary diversion (2.6% stricture rate in 39 patients). They showed that an intracorporeal urinary diversion was not associated with the uretero-enteric stricture formation. The proportion of urinary diversion type (ileal neobladder/ileal loop) in our study differed between each group. The low rate of ileal neobladder diversion (1/7) in the intracorporeal urinary diversion group using ICG (group 3) may be a factor for the low rate of uretero-enteric stricture. However, Presicce et al. (26) reported uretero-enteric stricture rates 12% for ileal loop and 15% for ileal neobladder in 210 patients with a mean followup of 30±22 months and the stricture rates between ileal loop and ileal neobladder did not differ statistically (p=0.658); it has been suggested that learning curve of the surgeon has some effects on the functional outcome in robot assisted radical cystectomy with intracorporeal urinary diversion (27). However, all procedures in our study were performed by a single surgeon who is experienced in both robotic (≥2.500 cases) and open surgery.

#### **Study Limitations**

Our study has several limitations. Firstly, it was a single center non-randomized study, and data were reviewed retrospectively with inherent selection bias. Secondly, the number of patients in our study is relatively low and larger prospective randomized studies are needed to strengthen our results. Additionally, long-term data are not available and unreported in our study. Nevertheless, this is the first study to report the possible advantages of ICG use in intracorporeal urinary diversion compared with extracorporeal urinary diversion and intracorporeal urinary diversion without ICG in the postoperative early period.

## Conclusion

Robotic cystectomy with intracorporeal diversion using ICG is a promising approach in terms of preventing benign ureteroenteric stricture formation. Further prospective studies must confirm our outcomes.

#### Ethics

**Ethics Committee Approval:** The study was approved by Acibadem Mehmet Ali Aydinlar University Medical Research Ethics Committee (ATADEK) (decision number: 2021-09/51).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

#### Authorship Contributions

Surgical and Medical Practices: M.B.T., Ö.B.A., A.R.K., Concept: M.B.T., T.D., Ö.B.A., A.R.K., Design: M.B.T., T.D., Ö.B.A., A.R.K., Data Collection or Processing: M.B.T., T.D., Ö.B.A., Analysis or Interpretation: M.B.T., T.D., İ.T., B.K.E., C.Ö., Literature Search: M.B.T., İ.T., C.Ö., Writing: M.B.T.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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