Original Article

Retrograde transurethral injection of indocyanine green better assists complete transperitoneal nephroureterectomy in a single-position

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Background: Complete transperitoneal nephroureterectomy (CTNU) in a single-position is an advanced surgical technique for the treatment of upper urinary tract urothelial carcinoma (UTUC), performed entirely through a transperitoneal approach without the need for patient repositioning. Indocyanine green (ICG) has been extensively studied in urologic surgery, with applications ranging from sentinel lymph node mapping to tumor localization. This study aimed to evaluate the performance of retrograde ureteral fluorescence imaging in CTNU.

Methods: This retrospective cohort enrolled 81 patients diagnosed with UTUC and underwent single-position CTNU. Cohorts were divided into two groups according to whether the ICG was applied. Perioperative data and oncology outcomes were recorded and analyzed.

Results: In total, 81 eligible participants were finally included, with 40 in the ICG group and 41 in the non-ICG group. The ICG group presented significantly shorter ureter identification time (8.5±3.3 *vs.* 17.3±4.2 min, P<0.001) and duration of surgery (132±40 *vs.* 162±49 min, P=0.003), as well as lower estimated blood loss (EBL) (108±94 *vs.* 183±126 mL, P=0.003) compared to the non-ICG group. The rates of intravesical and extravesical carcinoma recurrence were comparable between the two groups. At a median follow-up of 16.7 months, there were no significant differences in terms of the recurrence-free survival (RFS) and overall survival (OS) between groups.

Conclusions: ICG guided ureteral fluorescence imaging in single-position CTNU showed significant advantages in precisely and effectively locating the ureter, with improved surgical outcomes. Meanwhile, the enhanced visualization of the ureteral intramural segment and bladder cuff facilitated the complete removal of the specimen en bloc and the watertight closure of the bladder.

Keywords: Upper urinary tract urothelial carcinoma (UTUC); radical nephroureterectomy (RNU); indocyanine green (ICG); retrograde ureteral fluorescence imaging; surgical outcomes

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Introduction

Radical nephroureterectomy (RNU) is the gold-standard treatment for upper urinary tract urothelial carcinoma (UTUC) (1). Laparoscopic RNU has been increasingly considered as an alternative and showed comparable oncological outcomes over traditional open surgery (2). Recent studies have also reported that complete transperitoneal nephroureterectomy (CTNU) in a single-position provides surgeons with clearer anatomical landmarks, wider operating space, reduced surgical time and similar oncologic outcomes, while avoiding intraoperative repositioning (3,4).

Exposing the renal hilum is a critical step in CTNU. It represents a more challenging technique due to the surrounding intra-abdominal organs and adipose, compared to the retroperitoneal approach. Typically, the ureter serves as an important anatomical landmark to localize the renal hilum. However, it is difficult to distinguish the ureter from vascular structures due to their similar appearance and proximity to the posterior peritoneum, particularly in cases of obesity or with a history of abdominal surgery (5,6). Additionally, operating in a complex area can increase the risk of accidental ureter damage, likely leading to cancer spreading.

Indocyanine green (ICG) is a non-toxic and non-radioactive near-infrared fluorescence contrast agent with a specific binding affinity to blood hemoglobin (7). The ICG guided fluorescence imaging has demonstrated great value in optical molecular imaging and surgical imaging (8,9). ICG has been extensively studied in urologic surgery, with applications ranging from sentinel lymph node mapping to tumor localization (9,10). The objective of this study is to evaluate the utilization of ICG guided ureteral real-time imaging through catheterization in CTNU, and to validate its superiority with regards to perioperative and prognostic outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-247/rc).

Highlight box

Key findings

- Retrograde transurethral injection of indocyanine green (ICG) better assists complete transperitoneal nephroureterectomy (CTNU) in a single-position.

What is known and what is new?

- CTNU is an advanced surgical technique, performed entirely through a transperitoneal approach without the need for patient repositioning.
- This study introduces retrograde transurethral injection of ICG for enhanced visualization during CTNU. This novel technique reduces surgery time and blood loss, improves ureter identification, facilitates complete specimen removal and watertight bladder closure, and enhances postoperative recovery, marking a significant advancement in the surgical treatment of upper urinary tract urothelial carcinoma (UTUC).

What is the implication, and what should change now?

- Randomized controlled trial with a larger sample will play a key role in ICG guided ureteral fluorescence imaging for the treatment of UTUC. Extended follow-up in future studies would provide a more comprehensive evaluation of long-term patient outcomes.

Methods

Study population

In this retrospective analysis, electronic medical records from Beijing Friendship Hospital were examined to identify patients suffering UTUC from January 1, 2020, to June 30, 2023. The case selection methodology, as outlined in *Figure 1*, was rigorously designed to ensure data integrity. The inclusion criteria were as follows: (I) patients aged 18 years or older; (II) patients who underwent CTNU for UTUC. The exclusion criteria were: (I) patients with tumors located in the distal ureter; (II) patients with distant metastases at the time of preoperative evaluation; (III) patients treated with open surgical techniques; (IV) patients with a history of concurrent bladder tumors at or before surgery; (V) pregnant or lactating women. Based on the inclusion and exclusion criteria, this study enrolled a total of 81 patients, of whom 40 underwent retrograde ICG urethrography.

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Beijing Friendship Hospital (No. BFH20240422001). All patients provided written informed consent before participation in the study. Patients were stratified into the ICG group and the non-ICG group according to whether they received a retrograde transurethral injection of ICG. A comprehensive evaluation of patient perioperative clinical data was conducted, including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA), preoperative

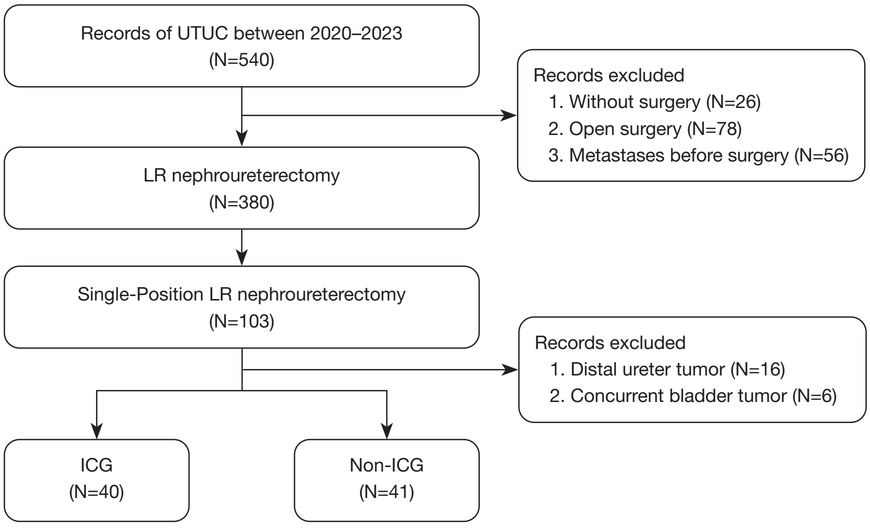

Figure 1 Patient selection flow chart. UTUC, upper urinary tract urothelial carcinoma; LR, laparoscopic radical; ICG, indocyanine green.

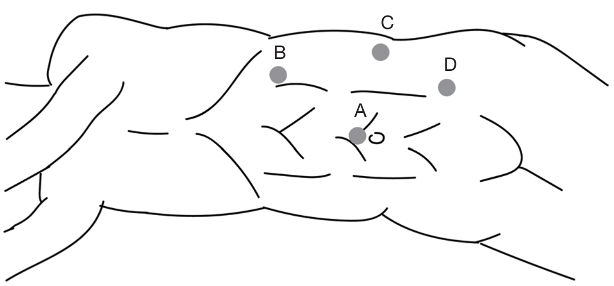

Figure 2 Trocar placement in complete transperitoneal nephroureterectomy. A port: 1–2 cm above the umbilicus. B port: pararectus, below rib cage. C port: anterior axillary line, at the level of umbilicus. D port: pararectus, at the level of iliac crest.

and postoperative white blood cells, hemoglobin, platelet, albumin and creatinine, visual analogue pain scale (VAPS), ureter identification time, during of surgery, estimated blood loss (EBL), drainage time, catheterization time, hospital stay, transfection to Intensive Care Unit (ICU) and postoperative complications. Tumor-specific data including tumor size, location, lateralization, as well as pathologic stage and grade were also documented. Pathologic stage and grade were classified using the World Health Organization (WHO) and American Joint Committee on Cancer (AJCC) grading system. The Clavien-Dindo classification system was employed to categorize postoperative complications, and follow-up data were compiled to assess long-term outcomes and the effectiveness of the surgical interventions. Patients were generally followed-up every 3 months in the first 2 years, and every 6 months from the second to the fifth years.

Surgery procedure

In the ICG group, 25 mg of ICG was prepared by diluting it in 10 mL of sterile water. All patients underwent a cystoscopy examination, after which a 5-Fr ureteral catheter was inserted into the affected ureter at a depth of 2 cm while the patient was in the lithotomy position. Subsequently, 5 mL of ICG (12.5 mg) was slowly injected through the catheter to prevent an increase in intraluminal ureteral pressure. Following the injection, patients were positioned in a 45° lateral decubitus posture, and the operating table was adjusted to the jackknife position. CTNU proceeded with patient positioning and trocar placement as delineated in *Figure 2*. Following bowel mobilization along the Toldt line, ICG enhanced visualization using a 4K fluorescence imaging system (Zhejiang Healnoc Technology Co., Ltd., Zhejiang, China) allowed for the swift and precise identification of the ureter. The time taken from the start of the laparoscopic procedure to the identification of the ureter was recorded as the ureter identification time. Subsequent dissection and upward retraction of the ureter established an avascular plane between the renal adipose capsule and psoas muscle for renal hilum access. Vascular control was achieved with a vascular gastrointestinal anastomosis (GIA) stapler (easyEndo Universal, EZISURG MEDICAL, Shanghai, China) or Hem-o-Lok clips. Subsequently, the

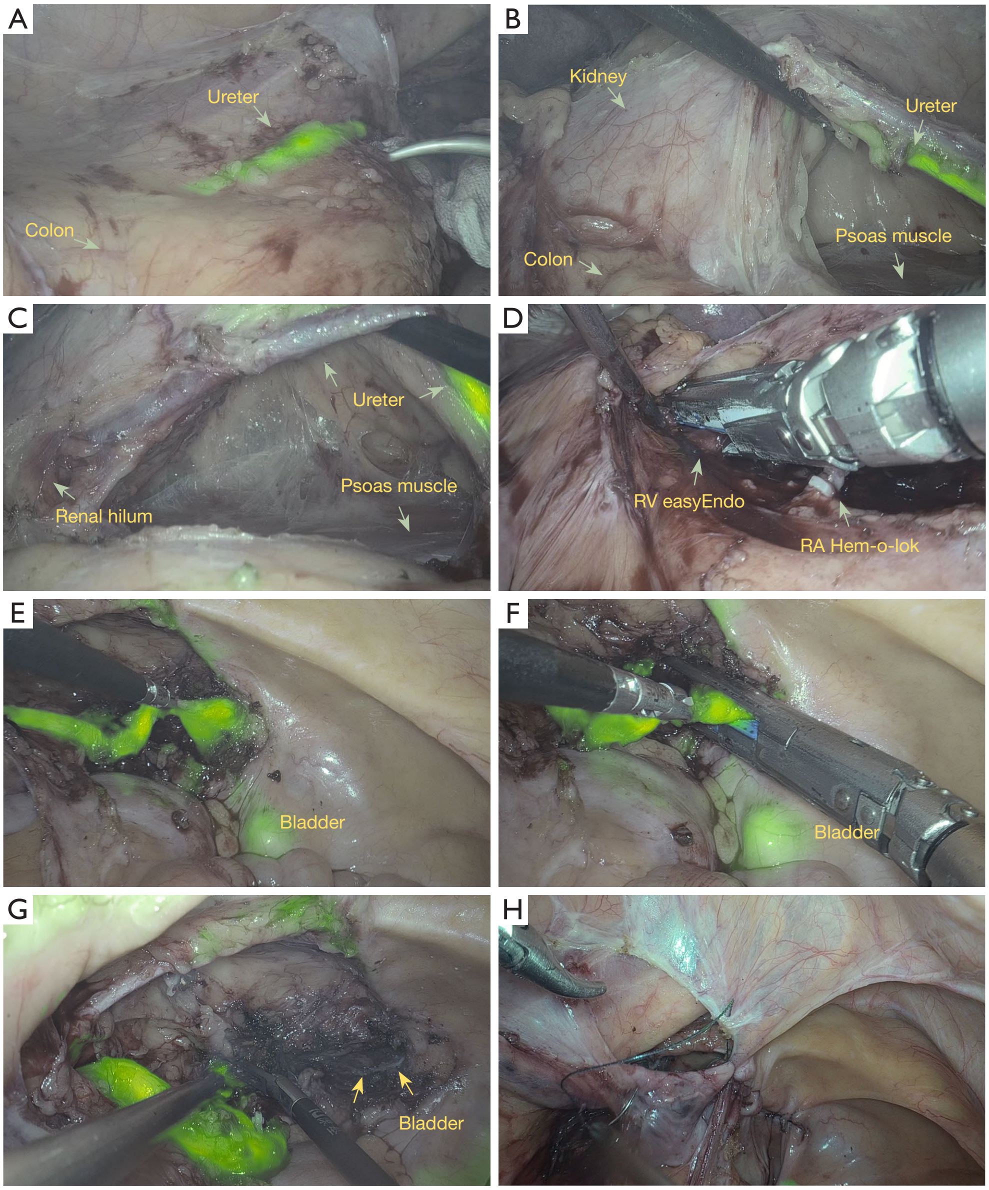

Figure 3 Representative images of complete transperitoneal nephroureterectomy. (A) Ureter identification. (B) Ureter was retracted upwards to create an avascular plane. (C) Along the ureter to locate the renal hilum. (D) Management of the renal hilum vessels. (E) The bladder cuff was totally dissected with clearly fluorescent visualization. (F) Performing BCE with tissue stapler. (G) Observed a water-tight closure of the bladder wall without any ICG leakage (indicated by yellow arrows). (H) Closing of the lateral peritoneum. RV, renal vein; RA, renal artery; BCE, bladder cuff excision; ICG, indocyanine green.

ureter below the tumor was located and secured with a Hem-o-lok clip to prevent distal tumor seeding during ureter mobilization. This approach ensured meticulous dissection of the distal ureter, especially the intramural segment and bladder cuff. Bladder cuff excision (BCE) was then performed with a tissue linear cutting stapler (easyEndo Universal, EZISURG MEDICAL). The pelvic peritoneum was closed with a 15-cm V-Loc suture. Two drainages were placed in the pelvic and perirenal space respectively (*Figure 3*).

The procedure for the non-ICG group was similar to that of the ICG group, except for the injection of ICG through the ureteral catheter.

Statistical analysis

Statistical analysis was conducted using IBM Corp.'s SPSS software (version 22.0). Analysis of variance (ANOVA) was utilized to detect significant differences among the analyzed cohorts by comparing the means across multiple groups. The Student's *t*-test was employed to evaluate intergroup differences. Overall survival (OS) and recurrence-free survival (RFS) were depicted using Kaplan-Meier survival curves.

Results

Demographic and preoperative clinical characteristics

A cohort of 81 patients was enrolled, with 40 in ICG group and 41 in non-ICG group. The median age was significantly higher in the ICG group compared to the non-ICG group (77 *vs.* 71 years, P=0.02). The BMI and ASA scores were comparable between the two groups (*Table 1*).

Perioperative clinical parameters

All the cases in the ICG group were successfully visualized with fluorescence imaging, enhancing the visualization of the ureter. The ICG group had a significantly reduced ureter identification time (8.5±3.3 and 17.3±4.2 min, P<0.001) and surgery duration (132±40 and 162±49 min, P=0.003) compared to the non-ICG group. The EBL was also lower in the ICG group compared to the non-ICG group (108±94 *vs.* 183±126 mL, P=0.003). Moreover, the ICG group showed expedited postoperative recovery, indicated by shorter durations of drainage (5.8±2.8 *vs.* 9.0±4.5 days, P<0.001), catheterization time (6.1±3.8 *vs.* 9.3±3.1 days, P<0.001), and hospital stay (7.6±4.1 *vs.* 11.9±4.0 days, P<0.001). There were 6 cases (15.0%) in the ICG group and 7 (17.1%) in the non-ICG group that were transferred to ICU for severe hypertension (2 cases), prevention of renal failure (3 cases) and poor recovery from anesthesia (8 cases), with no statistical difference between the two groups. There were no significant distinctions in perioperative laboratory parameters, as well as Clavien-Dindo classification. One patient (2.4%) in the non-ICG group experienced intravesical tumor recurrence, while none was reported in the ICG group. Extravesical recurrence rates were also comparable, with 7.5% in the ICG group over 17.1% in the non-ICG group (P=0.21).

Survival analysis

The median follow-up was 16.7 months, with 16.0 months for the ICG group and 17.5 months for the non-ICG group. For OS, the non-ICG group showed slightly higher survival rates compared to the ICG group, though the Log-rank test indicated that the difference was not statistically significant (P=0.17) (*Figure 4A*). For RFS, the ICG group demonstrated marginally higher survival rates, but this difference was not statistically significant either (P=0.41) (*Figure 4B*).

Discussion

RNU remains the cornerstone of treatment for localized UTUC, involving the removal of the kidney, ureter, and cuff of the bladder. CTNU is an advanced surgical technique, performed entirely through a transperitoneal approach without the need for patient repositioning. It can enhance intraoperative efficiency, decrease patient morbidity, and accelerate recovery profiles, thereby optimizing the surgical management of urological malignancies.

During CTNU, the ureter serves as an important anatomical landmark. By tracing the ureter, surgeons can effectively locate and manage the renal hilum. However, the area around the iliac vessels is dissected to trace the ureter, which potentially increases the risk of iliac vessel injury. Therefore, precise recognition and careful dissection of the ureter are critical for the success of CTNU. In this study, by a slow injection of ICG with a 5-Fr ureteral catheter, we obtained distinct ureteral fluorescent visualization in all cases, significantly aiding in the rapid and precise identification of the ureter and the renal hilum. The longest surgery in our study cohort lasted for 4 hours, with the ICG fluorescence remaining visible throughout the entirety of the procedure. This approach potentially simplifies surgery and reduces intraoperative bleeding, being crucial for patient safety and quicker recovery. The absence of ICG-related complications in our cohort highlights the safety and efficacy of this visualization method, showing clinical superiority in the implementation of upper urinary tract surgeries. None of the postoperative complications were directly related to difficulties in ureteral identification. The complications primarily included postoperative issues such as wound infections (2 cases), electrolyte imbalance (5 cases), pneumonia (6 cases), pleural effusion (1 case)

Table 1 Baseline characteristics and surgical outcomes of patients

Characteristic	Group		P value
	ICG (N=40)	Non-ICG (N=41)	
Demographics			
Age (years), median	77	71	0.02*
Sex			0.32
Male	19 (47.5)	15 (36.6)	
Female	21 (52.5)	26 (63.4)	
BMI (kg/m^2)	23.7±5.0	24.7±4.5	0.36
ASA score			0.58
2	25 (62.5)	28 (68.3)	
3	15 (37.5)	13 (31.7)	
Urologic characteristics			
Side			0.74
Left	20 (50.0)	19 (46.3)	
Right	20 (50.0)	22 (53.7)	
Location			0.41
Pelvis	26 (65.0)	23 (56.1)	
Upper ureter	14 (35.0)	18 (43.9)	
Grade			0.71
Low	36 (90.0)	38 (92.7)	
High	4 (10.0)	3 (7.3)	
Tumor size (mm)	32±18	30±16	0.50
Tumor stage (pathology)			0.83
pT1	15 (37.5)	17 (41.5)	
pT2	5 (12.5)	6 (14.6)	
pT3	18 (45.0)	14 (34.1)	
pT4	1 (2.5)	1 (2.4)	
pTis	1 (2.5)	3 (7.3)	
Laboratory parameters			
Preoperative			
WBC (10^9/L)	6.2±1.8	6.1±1.9	0.81
Hemoglobin (g/L)	120±20	123±18	0.43
Platelet (10^9/L)	215±62	213±70	0.93
Albumin (g/L)	37.8±4.4	38.5±4.0	0.43
Creatinine (μmol/L)	99±66	103±47	0.79

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Group		P value
	ICG (N=40)	Non-ICG (N=41)	
Postoperative			
WBC (10^9/L)	8.9±2.8	9.3±2.2	0.50
Hemoglobin (g/L)	107±18	110±15	0.48
Platelet (10^9/L)	177±49	184±52	0.54
Albumin (g/L)	37.8±4.4	38.5±4.0	0.43
Creatinine (μmol/L)	99±66	103±47	0.79
Perioperative parameters			
VAPS			
At 24 h	5.1±3.4	4.5±3.2	0.68
At discharge	4.7±2.9	4.4±3.2	0.44
Ureter identification time (min)	8.5±3.3	17.3±4.2	<0.001*
During of surgery (min)	132±40	162±49	0.003*
EBL (mL)	108±94	183±126	0.003*
Drainage time (days)	5.8±2.8	9.0±4.5	<0.001*
Catheterization time (days)	6.1±3.8	9.3±3.1	<0.001*
Hospital stay (days)	7.6±4.1	11.9±4.0	<0.001*
ICU			
Yes	6 (15.0)	7 (17.1)	0.80
No	34 (85.0)	34 (82.9)	
Clavien-Dindo classification			0.55
0	33 (82.5)	32 (78.0)	
1	2 (5.0)	0 (0.0)	
2	4 (10.0)	7 (17.1)	
3	0 (0.0)	1 (2.4)	
4	1 (2.5)	1 (2.4)	
Follow-up			
Time (months), median	16.0	17.5	0.19
Intravesical tumor recurrence	0 (0.0)	1 (2.4)	0.34
Extra-bladder recurrence	3 (7.5)	7 (17.1)	0.21

Data are presented as n (%), mean ± standard deviation or median. *, P<0.05. ICG, indocyanine green; BMI, body mass index; ASA, American Society of Anesthesiologists; WBC, white blood cell; VAPS, visual analogue pain scale; EBL, estimated blood loss; ICU, Intensive Care Unit.

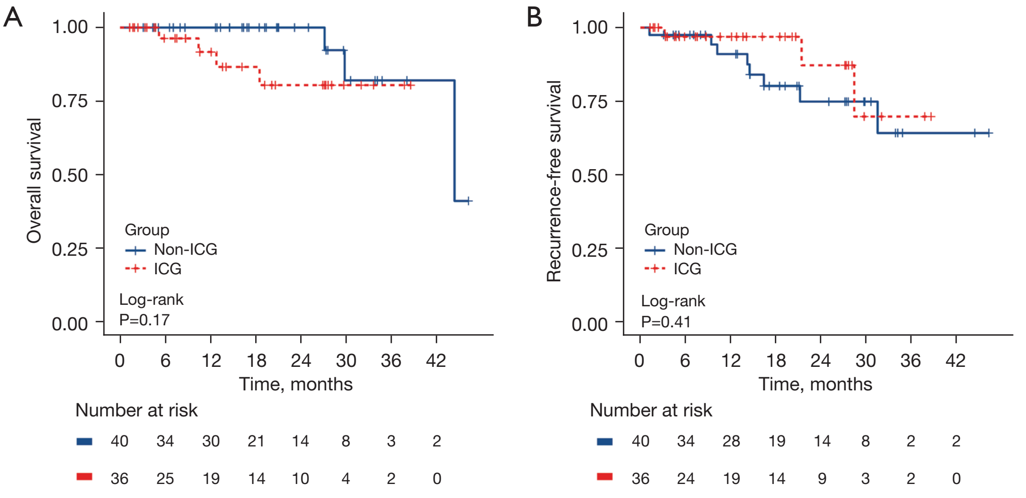

Figure 4 Kaplan-Meier curves for OS and RFS in ICG and non-ICG group. (A) OS comparison with no significant difference (P=0.17). (B) RFS comparison with no significant difference (P=0.41). Patient numbers at risk are shown below each plot. ICG, indocyanine green; OS, overall survival; RFS, recurrence-free survival.

and acute renal failure (2 cases), with similar distribution between the ICG and non-ICG groups.

BCE is a critical component of CTNU and poses a significant risk for tumor recurrence (11-14). The goal of an ideal BCE is to completely remove the specimen, minimize tumor and urine leakage, achieve R0 resection, ensure water-tight closure for early chemotherapy, with full BCE remaining the standard despite various techniques explored (15). Hattori *et al.* reported successful urine leakage prevention through stay suture and lateral patient positioning during bladder opening, with laparoscopic confirmation of the ureteral orifice and detachment of the distal ureter from the bladder cuff (16). The laparoscopic Endo-GIA tissue stapler, as initially introduced by Clayman *et al.*, reliably secures the bladder and expeditiously incises the distal end, minimizing the risk of tumor spillage (17). A meta-analysis revealed that rates of bladder recurrence after laparoscopic nephroureterectomy (LNU) using a tissue stapler ranging from 19% to 43% were comparable to the open surgery (18). In our study, we clamped the ureter in the tumor's lower segment, using Hem-o-Lok to prevent tumor seeding, applied fluorescence visualization for efficient identification of the ureterovesical junction, and deployed an Endo-GIA tissue stapler for precise bladder cuffing, thus allowing the detection of any ICG leakage and confirmation of a water-tight bladder wall.

A meta-analysis by Sharma *et al.* highlighted the risk of intravesical recurrence with preoperative ureteroscopy (URS), particularly when a biopsy is performed (19). Limited studies suggest that URS before RNU increases the risk of venous and lymphatic metastasis due to high water pressure (20). In this study, the distal ureteral tumors were excluded and the ureteral catheter was placed at a depth of approximately 2 cm, thereby ensuring the integrity of the ureteral tumor, and avoiding the potential risk of tumor dissemination. And some cases of distal ureteral tumors can be managed by resection and replantation, potentially obviating the need for ICG. Furthermore, ICG was injected at a low rate and dose to maintain low intraluminal pressure within the renal pelvis or ureter, effectively avoiding retrograde dissemination. Throughout the surgical procedure, no leakage of ICG from the ureter was observed. Follow-up data showed no significant differences in local recurrence or distant metastasis between the groups, validating the safety and efficacy of retrograde transurethral injection technique in CTNU.

There are limitations in this study. Its retrospective design limits causal inference, as retrospective analyses are susceptible to biases and confounding factors. The surgeon's expertise and patient-specific factors may have influenced the choice of surgical approach and the use of ICG. Additionally, the small cohort size may affect the generalizability of the results and the attrition also impacted the study, with four patients in the ICG group and one in the non-ICG group lost to follow-up, potentially influencing the outcomes. Moreover, the relatively brief follow-up period limits the assessment of long-term treatment efficacy and late effects. These elements necessitate a cautious interpretation of the findings and call for larger-scale prospective studies with extended follow-up for further validation.

Conclusions

To our knowledge, this is the first report of retrograde transurethral injection of ICG for ureteral visualization in CTNU. Our results indicate significant enhancements in surgical precision, attributable to the accurate localization of the ureter facilitated by ICG guided fluorescence imaging. The improved visualization of the ureteral intramural segment and bladder cuff is instrumental in the *en bloc* specimen removal. Moreover, the absence of extravesical ICG spillage signifies a watertight bladder closure, potentially influencing oncological prognosis favorably. However, validation of these findings necessitates further studies with a larger cohort and extended follow-up.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-247/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-247/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-247/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-247/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Beijing Friendship Hospital (No. BFH20240422001) and was carried out in accordance with the ethical principles outlined in the Declaration of Helsinki (as revised in 2013). All patients provided written informed consent before participation in the study. The confidentiality of patient information was maintained throughout the study, and all personal identifiers were removed from the data to protect patient privacy. The study was conducted with the highest level of integrity and adherence to ethical standards.

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