

Concurrent radical cystectomy and nephroureterectomy indications and outcomes: a systematic review and comparative analysis

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Abstract

Introduction: Urothelial carcinoma can arise from the urinary bladder or from the upper urinary tract. In some instances, urinary bladder cancer (UBC) and upper tract urothelial carcinoma (UTUC) can be concurrently diagnosed, necessitating a combined radical cystectomy (RC) with radical nephroureterectomy (RNU). A systematic review was done on the combined procedure exploring outcomes and indications, in addition to a comparative analysis between the combined procedure and cystectomy alone.

Methods: For the systematic review, three databases (Embase, PubMed, and Cochrane) were queried, selecting only studies that included intraoperative and perioperative data. For the comparative analysis, using the NSQIP database, CPT codes for RC and RNU were used to identify two cohorts, one with RC and RNU and one with RC alone. A descriptive analysis was performed on all preoperative variables, and propensity score matching (PSM) was performed. Postoperative events were then compared between the two matched cohorts.

Results: For the systematic review, 28 relevant articles were included amounting to 947 patients who underwent the combined procedure. The most common indication was synchronous multifocal disease, the most common approach was open surgery, and the most common diversion technique was using an ileal conduit. Almost 28% of patients required blood transfusion and remained in the hospital for an average of 13 days. The most common postoperative complication was prolonged paralytic ileus. For the comparative analysis, 11,759 patients were included of which 97.5% underwent RC only and 2.5% underwent the combined procedure. After PSM, the cohort that had undergone the combined procedure showed an increased risk of renal injury, increased readmission rates, and increased reoperation rates. Whereas the cohort that had undergone RC only showed an increased risk of deep venous thrombosis (DVT), sepsis, or septic shock.

Conclusion: A combined RC and RNU is a treatment option for concurrent UCB and UTUC that should be cautiously utilized as it is associated with high morbidity and mortality. Patient selection, discussion of the risks and benefits of the procedure, and explanation of the available treatment options remain the most important pillars in managing patients with this complex disease.

Keywords: bladder cancer, radical cystectomy, radical nephroureterectomy, urothelial carcinoma

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Introduction

Urothelial carcinoma can arise throughout the urinary tract and can be broadly divided into upper tract urothelial carcinoma (UTUC) and urinary bladder cancer (UBC). More than 90% of urothelial carcinomas arise from the bladder, whereas UTUC constitutes only 5–10% of all urothelial carcinomas.¹ UBC accounted for around 573,000 new cases of cancer worldwide in 2020, making it the 10th most commonly diagnosed malignancy.² It also resulted in 200,000 deaths globally.³ Radical cystectomy remains the gold standard treatment for muscle-invasive bladder carcinoma (MIBC)⁴ and recurrent high-risk non-MIBC.⁵ However, radical nephroureterectomy with bladder cuff excision is the treatment of choice for high-risk non-metastatic UTUC.⁶

UBC and UTUC have histopathological similarities and share common risk factors,⁷ so the possibility of synchronous tumors should be considered. In patients with primary diagnosed UTUC, the presence of a concomitant bladder tumor is around 17% and can be as high as 33% depending on the primary tumor location.⁸ In comparison, the incidence of UTUC is 2.6% for patients with primary diagnosed superficial bladder tumors.⁹ This highlights the multifocal nature of urothelial carcinoma and that any primary urothelial tumor is an important risk factor for developing another tumor along the rest of the urinary tract.¹⁰

The management of concurrent UTUC and MIBC is challenging, but in certain instances, a combined one-step nephroureterectomy and radical cystectomy is needed^{11–13} since it allows for decreasing the morbidity of a staged procedure and avoiding the anesthetic risk of multiple surgeries. In other instances, patients with end-stage renal disease (ESRD) and urothelial carcinoma could be considered for a combined procedure involving both upper tracts known as complete urinary tract extirpation (CUTE).^{11,14} This treatment strategy precludes the need for urinary diversion in such patients and obviates the risk for metachronous recurrence in the urinary tract.

The literature regarding concurrent unilateral or bilateral nephroureterectomy and radical cystectomy is scarce and mostly involves small case series and case reports. The aim of this study is to

perform a systematic review of the literature on concurrent radical cystectomy and nephrectomy procedures, and describe the indications, clinical outcomes, and procedure safety. Moreover, using the American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) database, we sought to compare the combined procedure to radical cystectomy alone, which is classically known to be more morbid than radical nephrectomy.

Methodology

Systematic review

Nephroureterectomy is indicated concurrently with radical cystectomy in some clinical situations. Data regarding the perioperative outcomes of this combined procedure are scarce and needed in order to provide patients with optimal surgical care when taking the decision to perform a concurrent cystectomy and nephrectomy.

The systematic literature search was initially performed in December 2020 using Embase, PubMed, and Cochrane databases. The search was done using MeSH terms and keywords. ‘Cystectomy’, ‘urinary bladder’, ‘urinary bladder neoplasms’, and ‘urinary diversion’ combined with ‘nephrectomy’ were the main MeSH terms adopted. The search was complemented with the use of different combinations of keywords synonyms of the two procedures with asterisks for potential variants, including but not limited to: heminephrectomy, nephroureterectomy, bladder excision/removal, and kidney excision/removal. No limits were applied.

Two authors (N.F.A.H. and M.Z.) separately reviewed all results to select relevant studies and case series of concurrent nephroureterectomy with radical cystectomy. Few discrepancies were resolved by open discussion.

Our review included studies reporting perioperative outcomes and complications only. All non-comparative studies reporting intraoperative and perioperative data (operative time, blood loss, transfusion rate, lengths of hospital stay, complication rates) and oncologic data (cancer-free survival, cancer-specific survival, overall survival) of the combined procedure were collected.

Studies mainly describing surgical technique, staged procedures, or single case reports were not included in our review. After discussing the studies at hand and due to the very limited number of articles meeting our criteria, we decided to include data from congress abstracts.

Data from all selected papers were extracted, summarized, and plotted in Excel sheets. Weighted averages were calculated for all numerical variables (age, operative time, estimated blood loss, etc.). Categorical variables were stratified, and rates/percentages were reported based on the overall number of patients included.

There was heterogeneity among the studies in reporting oncological outcomes. None of them included survival analysis except one.¹⁵ Therefore, it was not possible to summarize and draw conclusions from these variables.

Comparative analysis

Patient population. The study population consisted of patients who underwent RC with or without concurrent RN or RNU and were listed in the ACS-NSQIP between 2005 and 2017. The ACS-NSQIP is a multinational database that provides data on patients undertaking major surgical procedures. The database includes more than 150 variables, encompassing demographic factors, preoperative medical history, laboratory values, intraoperative factors, and 30-day postoperative morbidity and mortality outcomes. Data collection is performed by certified surgical clinical reviewers and is directly listed onto the ACS-NSQIP registry. Quality is assured using an intra-rater reliability (IRR) audit of participating centers. Procedures are categorized by Common Procedural Terminology (CPT) codes. Radical cystectomy cases had the following CPT codes: 51570, 51575, 51580, 51585, 51590, 51595, and 51596. Radical nephrectomy cases had the following CPT codes: 50220, 50225, 50230, 50234, 50236, 50545, 50546, 50547, 50548, and 50549. The concurrent surgery cohort was identified and combined with the RC-only cohort.

Clinical variables. The analyzed variables included patient demographics, medical history and patient health status, preoperative laboratory findings, and surgical factors. Demographic

factors were age, gender, body mass index (BMI), ethnicity, race, smoking status, and alcohol use. Medical history included diabetes, insulin use, hypertension, congestive heart failure (CHF), peripheral vascular disease (PVD), stroke or transient ischemic attack (TIA), hepatic disease including presence of esophageal varices or abdominal ascites, chronic obstructive pulmonary disease (COPD), acute renal failure, kidney dialysis, chronic steroid use, disseminated cancer, unintentional weight loss, bleeding disorders, and systemic inflammation or sepsis. Patient health status was evaluated using the American Society of Anesthesiologists (ASA) classification. Preoperative laboratory findings included serum hematocrit, platelet count, white blood cell count, creatinine, albumin, and international normalized ratio (INR). Surgical factors included surgical approach (open *versus* minimally invasive), urinary diversion type, and operation time. Outcomes studied included wound complications, infectious complications, renal injury, cardiovascular incidents, mortality, prolonged ventilation, need for reintubation, readmission, and unplanned reoperation.

Statistical analysis. A descriptive analysis was performed on all preoperative variables, associations with concurrent nephrectomy status were determined using the chi-square (χ^2) test and independent *t*-test for categorical variables and continuous variables, respectively. A total of 12 variables with significant difference were considered for propensity score matching (PSM). Matching was performed with a match tolerance on 0.001. After matching, the association of postoperative events incidence with concurrent RC/RN status was assessed using the chi-square test. All statistical analysis was conducted using the IBM SPSS Statistics v26 (IBM corp., Armonk NY, USA), and a two-sided alpha level of 0.05 was used to indicate statistical significance.

Results

Systematic review

The initial search strategies on Cochrane, Embase, and PubMed generated 6572 articles. Duplicates ($n = 927$) were removed and 5645 articles were left for screening. The screening by title and abstract excluded 5561 studies that were

irrelevant to concomitant nephroureterectomy and radical cystectomy.

A total of 84 resultant articles were sorted into 36 case reports and 48 larger studies and screened again by full text. Case reports as well as articles purely describing surgical techniques, staged procedures, or other irrelevant results were excluded.

In total, the review of literature yielded 28 relevant articles that were mostly case series and a few cohorts that described perioperative outcomes and complications of concurrent radical cystectomy and nephroureterectomy.

In total, 12 articles originated from Europe, out of which 4 were from Germany. Eight articles were from East Asia, with all except one being from Taiwan. Six articles were from the United States, and 1 article stemmed from Turkey and Chile each.

Patient demographics

Review of the 28 studies published from 2006 till 2020 included 947 patients that underwent concurrent nephroureterectomy and radical cystectomy. Mean weighted age was 66.54 years (range, 35–89 years), and 67.4% of patients were males. Of studies that reported patient comorbidity profiles using the ASA classification, 73.5% of patients were ASA class ≥ 3 (Table 1).

Surgical indication, bilateral versus unilateral nephroureterectomy

Almost all indications for radical cystectomy were muscle-invasive transitional cell carcinoma or recurrent high-risk superficial TCC of the bladder (98.4%). The indications for concurrent nephroureterectomy were more varied, with the majority (70.3%) being synchronous multifocal transitional cell carcinoma involving the upper urinary tract, some of which included patients with known ESRD and underwent bilateral concurrent nephroureterectomy known as complete urinary tract extirpation.^{14,16–19} The next most common indication was a unilateral non-functional kidney^{20–24} which accounted for 11.3% of the cases. ESRD,^{25,26} concurrent renal cell carcinoma in two cases,^{11,26} autosomal dominant polycystic kidney disease,¹¹ bilateral complex renal cysts,¹¹ and multiple oncocytomas²³ were also indications in individual instances. Overall, out of

947 patients, 426 (45%) received radical cystectomy with bilateral concurrent nephroureterectomy (Table 2).

Surgical approach and diversion type

Regarding surgical approaches, open surgery was performed in 35.7% of cases, laparoscopic surgery was adopted in 32.9%, and robotic-assisted surgery in 25.2%. In two cases, a combined approach using open radical cystectomy and laparoscopic nephroureterectomy was done.¹² In 11 cases, bilateral hand-assisted retroperineoscopic nephroureterectomy (HARN) and open extraperitoneal cystectomy were the approaches of choice.¹⁷

For patients requiring urinary diversion, an ileal conduit was the most common diversion method, accounting for nearly 82% of diversions. Other patients had ureterocutaneostomies (15.2%), and continent diversions using a neobladder were relatively rare (2.9%) (Table 2).

Perioperative outcomes and complications

Total operative time was reported by most studies, with the mean being 352.8 min (range, 240.9–616.5 min). Weighted mean for estimated blood loss during the procedure was 578.6 ml (range, 207–1280 ml), and approximately 28% of patients received blood transfusions. Length of hospital stay was indicated by most series with a weighted mean of 13 days (range, 6–36 days) on average.

Regarding postoperative complications, some articles adopted a descriptive classification for listing complications while others used the Clavien-Dindo Classification (CDC).²⁷ In the former studies, the most commonly described complications were prolonged paralytic ileus,^{28,29} infectious-related adverse events,¹⁵ and postoperative mortality.^{13,28} Other mentioned complications were acute kidney failure,²⁸ ureter-intestinal anastomosis leak,²⁸ port hernia,²² and retroperitoneal hemorrhage³⁰ A total of 47 patients from the included studies had a CDC for complications. From these articles, class I, II, and III adverse events were reported as 32%, 25.5%, and 28.8%, respectively.

Comparative analysis

A total cohort of 11,759 patients was included in the NSQIP database analysis. In total, 11,465

Table 1. Summary of patients' ASA class, postoperative outcomes and complications.

Title	Operative time (min)	Blood loss (ml)	Transfusion rate	ASA Class	CDC 1	CDC 2	CDC 3	CDC 4	CDC 5
Aggressive treatment for urothelial cancer-complete urinary tract extirpation: operative feasibility in two case	360	850	1	1 was ASA 3	0	1	0	0	0
Simultaneous cystectomy and nephroureterectomy due to synchronous upper urinary tract tumors and invasive bladder cancer: open and laparoscopic approaches	348.6	816	3	-	9	3	1	2	2
Simultaneous en-bloc robot-assisted radical cystectomy and nephro-ureterectomy: technique description, outcomes, and literature summary	287	253	-	4 were ASA 2; 6 were ASA 3; 1 was ASA 4	1	1	1	0	0
Single-center experience with robot-assisted radical cystectomy with nephroureterectomy and extra- and intracorporeal urinary diversion by patients with muscle-invasive bladder cancer and upper urinary tract urothelial cell carcinoma	317.25	287	-	3 were ASA 3, 1 was ASA 2	1	0	1	0	0
Simultaneous laparoscopic nephroureterectomy and cystectomy: a preliminary report	-	-	-	-	-	-	-	-	-
Simultaneous laparoscopic nephroureterectomy and cystectomy: a preliminary report	540	755	4	7 were ASA ≥ 3	-	-	-	-	1
Laparoscopic radical cystoprostatectomy with bilateral nephroureterectomy: initial report	616.5	675	-	-	-	-	-	-	-
Complete urinary tract extirpation: a single centre series of 17 patients	-	-	-	-	-	-	-	-	-
Robot-assisted en-bloc radical cystectomy with nephroureterectomy and intracorporeal urinary diversion in ten patients with muscle-invasive bladder cancer and simultaneous upper urinary tract urothelial cell carcinoma or functionless kidney	307	207	1	3 were ASA 2, 6 were ASA 3, 1 was ASA 4	2	1	1	0	0
In bloc laparoscopic radical cystectomy and nephroureterectomy for upper and lower transitional tumors	310	600	?	-	0	0	1	0	0
A modified single mini-incision complete urinary tract exenteration for urothelial carcinoma in dialysis patients	242.5	500	-	-	-	-	-	-	-
Simultaneous laparoscopic nephroureterectomy and cystectomy: our experience	390	755	-	-	-	-	-	-	-
Urothelial tumoral disease- 'En bloc' nephroureterectomy, distoprostatectomy and urethrectomy	-	-	-	-	-	-	-	-	-
Complete urinary tract extirpation: the University of Maryland experience	356	-	4	-	-	-	-	-	-
A nationwide analysis of complete urinary tract extirpation	-	-	-	-	-	-	-	-	-
Perioperative and long term outcomes after radical cystectomy in hemodialysis patients	-	-	-	-	-	-	-	-	-
Robot-assisted en-bloc radical cystectomy with nephroureterectomy and intracorporeal urinary diversion by seven patients with muscle-invasive bladder cancer and upper urinary tract urothelial cell carcinoma. Single-center experience	296.9	238	0	2 were ASA 2, 4 were ASA 3, 1 was ASA 4	1	0	1	0	0

(Continued)

Table 1. (Continued)

Title	Operative time (min)	Blood loss (ml)	Transfusion rate	ASA Class	CDC 1	CDC 2	CDC 3	CDC 4	CDC 5
Robot-assisted cystectomy with simultaneous nephroureterectomy: Case series from a single institution	431	400	-	ASA median = 3 (range 2-4)	-	-	-	-	-
Single-session laparoscopic total urinary tract exenteration without repositioning for multifocal urothelial carcinoma in dialysis-dependent patients	397	532	2	-	0	2	0	0	0
[Synchronous tumor of the upper urinary tract with bladder cancer. Opportunity for nephroureterectomy and block-cystectomy]	-	-	-	-	1	0	1	0	0
Complete urinary tract exenteration for a dialysis patient with urothelial cancer: lower midline and extraperitoneal approach in a supine position	328	628	-	-	-	-	-	-	-
Long-term outcomes of complete urinary tract exenteration for dialysis patients with urothelial cancer	-	1280	-	ASA 3.0 ± 0.3	0	2	5	1	2
Simultaneous robot-assisted nephroureterectomy and cystectomy in patients with uremia and multifocal urothelial carcinoma	306.25	496.25	3	2 were ASA 2, 6 were ASA 3	0	0	0	0	0
Concurrent upper and lower urinary tract robotic surgery: a case series	300	416.7	-	Mean ASA 2.3 for all 6	0	2	0	0	0
Single-session laparoscopic cystectomy and nephroureterectomy	313.3	350	3	-	-	-	-	-	-
Outcomes and complications of simultaneous laparoscopic cystectomy and laparoscopic nephroureterectomy with umbilical reduced port surgery	434	773	1	All were ASA 1 or 2	-	-	-	-	-
Long-term outcome of radical cystectomy in ESRD patients with bladder urothelial carcinoma	-	-	-	-	-	-	-	-	-
Single-session laparoscopic total urinary tract exenteration without re-position for multiple urothelial carcinoma	240.9	380.5	-	-	0	0	2	0	0
Laparoscopic radical cystectomy and nephroureterectomy en bloc resection with lomboarctic and pelvic lymph node dissection	286.5	260	1	-	0	0	0	0	0

Table 2. Summary of reviewed studies, surgical approach and procedure indication.

Reference	Institution	Sample size	Study type	Bilat. RNU	Surgical approach	Diversion type	RC indication	RNU indication
Aggressive treatment for urothelial cancer-complete urinary tract extirpation: operative feasibility in two cases	Selçuk University School of Medicine, Konya, Turkey	2	Case series	1	Open + Laparoscopic	IC	MIBC	Synchronous TCC
Simultaneous cystectomy and nephroureterectomy due to synchronous upper urinary tract tumors and invasive bladder cancer: open and laparoscopic approaches	Hospital General Universitario Ciudad Real, Servicio de Urología, Spain	15	Case series	0	10 Open, 5 Laparoscopic	-	MIBC	Synchronous TCC
Simultaneous en-bloc robot-assisted radical cystectomy and nephro-ureterectomy: technique description, outcomes, and literature summary	Department of Urology, Alfred Krupp Krankenhaus, Hellweg 100, 45276, Essen, Germany	11	Case series	0	Robotic	9 UC 2 IC	8 TCC, 1 TCC + SCC, 1 SCC, 1 Prostate CA [?]	Functionless kidney in 8 Synchronous TCC in 3
Single-center experience with robot-assisted radical cystectomy with nephroureterectomy and extra- and intracorporeal urinary diversion by patients with muscle-invasive bladder cancer and upper urinary tract urothelial cell carcinoma	Alfried Krupp Krankenhaus, Essen, Germany	4	Case series	0	Robotic	-	-	-
Simultaneous laparoscopic nephroureterectomy and cystectomy: a preliminary report	Section of Laparoscopic and Robotic Surgery, Glickman Urological Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA	8	Case series	2	Laparoscopic	ICs + neobladder	Muscle-invasive or recurrent superficial TCC of the bladder in all patients	Synchronous TCC in 6 patients (unilateral nephroureterectomy), ESRD in 2
Laparoscopic radical cystoprostatectomy with bilateral nephroureterectomy: initial report	Section of Laparoscopic and Minimally Invasive Surgery, Urological Institute, Cleveland Clinic Foundation, Cleveland, OH, USA	2	Case series	2	Laparoscopic	-	MIBC TCC	ESRD
Complete urinary tract extirpation: a single centre series of 17 patients	Department of Urology, UZLeuven, Leuven, Belgium	12	Case series	12	-	-	-	-
Robot-assisted en-bloc radical cystectomy with nephroureterectomy and intracorporeal urinary diversion in ten patients with muscle-invasive bladder cancer and simultaneous upper urinary tract urothelial cell carcinoma or functionless kidney	Department of Urology, Alfred Krupp Krankenhaus, Hellweg 100, 45276, Essen, Germany	10	Case series	0	Robotic	Intra corporeal UC in 8, extracorporeal IC in 2	MIBC TCC	Synchronous TCC in 3, other 7 had functionless kidneys
In bloc laparoscopic radical cystectomy and nephroureterectomy for upper and lower transitional tumors	Department of Urology at Clínica Indisa and University of Chile, Santiago, Chile	2	Case series	0	Laparoscopic	-	MIBC TCC	Synchronous TCC
A modified single mini-incision complete urinary tract extirpation for urothelial carcinoma in dialysis patients	Division of Urology, Department of Surgery, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung 813, Taiwan	14	Case series	14	Open	-	10 multifocal UC 3 had organ-confined bladder UC with left-sided hydronephrosis; 1 only had urinary bladder UC	9 synchronous TCC, 1 bilateral TCC

(Continued)

Table 2. (Continued)

Reference	Institution	Sample size	Study type	Bilat. RNU	Surgical approach	Diversion type	RC indication	RNU indication
Simultaneous laparoscopic nephroureterectomy and cystectomy: our experience	Unit of Urology, Jesi Hospital, Jesi, Ancona, Italy	2	Case series	0	Laparoscopic	-	-	-
Urothelial tumoral disease - 'En bloc' nephroureterectomy, cistoprostatectomy and urethrectomy	Center of Urological Surgery, Dialysis and Renal Transplantation, Fundeni Clinical Institute, Bucharest, Romania	5	Case series	0	Open	Direct or transileal ureterostomy	Multifocal kidney, bladder and urethral lesions with diffuse CIS	Multifocal kidney, bladder and urethral lesions with diffuse CIS
Complete urinary tract extirpation: the University of Maryland experience	Division of Urology, University of Maryland School of Medicine, Baltimore, Maryland	9	Case series	9	Open	Orthotopic neobladder or IC	6 had confirmed bladder urothelial carcinoma. 3 had no preoperatively confirmed malignancies, indication for surgery was a nonfunctional bladder, infection, and nephrolithiasis in two and a Bosniak 4 complex cystic mass in one	Bladder Ca patients; 3 had synchronous TCC, 1 had renal cell carcinoma (RCC) in his native right kidney, one had complex renal cysts bilaterally, and one had autosomal dominant polycystic kidney disease
A nationwide analysis of complete urinary tract extirpation	University of Iowa Carver College of Medicine, Iowa City, Iowa	317	Cohort	317	-	-	-	-
Perioperative and long term outcomes after radical cystectomy in hemodialysis patients	Medical College of Wisconsin, Department of Urology, Milwaukee, WI	400	Cohort	-	-	Conduit 285 UC 24 Neobladder < 10 None 677	Advanced stage BC	ESRD in all
Robot-assisted en-bloc radical cystectomy with nephroureterectomy and intracorporeal urinary diversion by seven patients with muscle-invasive bladder cancer and upper urinary tract urothelial cell carcinoma. Single-center experience	Department of Urology, Alfred Krupp Krankenhaus, Essen, Germany.	7	Case series	0	Robotic	Intracorporeal UC in 6 and extracorporeal IC in 1	MIBC in all 7	Synchronous TCC in 3, functionless kidney in 4
Robot-assisted cystectomy with simultaneous nephroureterectomy: case series from a single institution	Department of Urology, University of Rochester Medical Center, Rochester, NY, USA	8	Case series	0	Robotic	IC in 4, UC in 4	MIBC TCC	Synchronous TCC
Single-session laparoscopic total urinary tract exenteration without repositioning for multifocal urothelial carcinoma in dialysis-dependent patients	Department of Urology, E-Da Hospital, Kaohsiung County, Taiwan, Republic of China	12	Case series	5	Laparoscopic	-	MIBC TCC	Synchronous TCC in a patient on dialysis
[Synchronous tumor of the upper urinary tract with bladder cancer. Opportunity for nephroureterectomy and block-cystectomy]	Servicio de Urología, Hospital General Universitario, Murcia, España	8	Case series	0	-	Bricker procedure in 6, and 2 had ileal substitutions	-	-

(Continued)

Table 2. (Continued)

Reference	Institution	Sample size	Study type	Bilat. RNU	Surgical approach	Diversion type	RC indication	RNU indication
Complete urinary tract exenteration for a dialysis patient with urothelial cancer: lower midline and extraperitoneal approach in a supine position	Department of Urology, Medical College and Hospital, National Cheng-Kung University, Tainan, Taiwan	10	Case series	10	HARN + open RC	-	Dialysis patients with synchronous multifocal urothelial cancer, 2 were Ta, 5 were T1, 2 were T2, and 1 was T3 TCC	Dialysis patients with synchronous multifocal urothelial cancer, 2 were Ta, 5 were T1, 2 were T2, and 1 was T3 TCC
Long-term outcomes of complete urinary tract exenteration for dialysis patients with urothelial cancer	Department of Urology, Medical College and Hospital, National Cheng-Kung University, Tainan, Taiwan	17	Case series	17	-	-	Dialysis patients with synchronous multifocal urothelial cancer	Dialysis patients with synchronous multifocal urothelial cancer
Simultaneous robot-assisted nephroureterectomy and cystectomy in patients with uremia and multifocal urothelial carcinoma	Department of Urology, Medical College and Hospital, National Cheng-Kung University, Tainan, Taiwan	8	Case series	0	Robotic	-	Metachronous or recurrent multifocal TCC in UUT and UB	Metachronous or recurrent multifocal TCC in UUT and UB
Concurrent upper and lower urinary tract robotic surgery: a case series	University of Nevada Reno School of Medicine, Reno, NV, USA	5	Case series	0	Robotic	IC: 4 intracorporeal, 1 extracorporeal	MIBC TCC	Nonfunctioning kidney in 2, multiple oncocytomas in 1, rest had TCC
Single-session laparoscopic cystectomy and nephroureterectomy	Department of Urology and Urological Oncology, Pomeranian Medical University, Szczecin, Poland	3	Case series	1	Laparoscopic	-	MIBC TCC	Afunctional kidney due to obstruction (2 cases), coexisting bilateral TCC tumors of the upper urinary tract (1 case)
Outcomes and complications of simultaneous laparoscopic cystectomy and laparoscopic nephroureterectomy with umbilical reduced port surgery	Department of Urology, Anjo Kosei Hospital, 28 Higashihirokute, Anjo-cho, Anjo, Japan	4	Case series	1	Laparoscopic	3 UC	Muscle-invasive or recurrent non-muscle invasive UC of the bladder in all patients	Renal cell carcinoma (case 1), with upper tract TCC (cases 2 and 3), and with end-stage renal disease kidney (case 4)
Long-term outcome of radical cystectomy in ESRD patients with bladder urothelial carcinoma	Department of Urology, Chang Gung Memorial Hospital – Kaohsiung Medical Center, Chang Gung University College of Medicine, No. 123, Ta-Pei Rd., Niao-Sung Hsiang, Kaohsiung Hsien, Taiwan	32	Cohort	32	Open	-	Recurrent or invasive bladder urothelial carcinoma	ESRD +/- UUT TCC
Single-session laparoscopic total urinary tract exenteration without re-position for multiple urothelial carcinoma	Department of Urology, E-Da Hospital, Kaohsiung, Taiwan	26	Cohort	13	Laparoscopic	-	-	-
Laparoscopic radical cystectomy and nephroureterectomy en bloc resection with lomboarctic and pelvic lymph node dissection	Urology Department, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania	4	Case series	0	Laparoscopic	UC	pT1G1, pT3aG3, pT2aG3, pT2G3	Concurrent TCC in 3 cases, non-functional kidney in 1 case (atrophic parenchyma, pyelonephritis)

CA, cancer; CIS, carcinoma in situ; ESRD, end-stage renal disease; HARN, hand-assisted bilateral retroperitoneoscopic nephroureterectomy; IC, ileal conduit; MIBC, muscle-invasive bladder cancer; RC, radical cystectomy; RNU, radical nephroureterectomy; SCC, squamous cell carcinoma; TCC, transitional cell carcinoma; UB, urinary bladder; UC, ureterocutaneostomy; UUT, upper urinary tract.

(97.5%) underwent radical cystectomy only, and 294 (2.5%) underwent concurrent radical cystectomy and radical nephrectomy. Before matching, the cohort was significantly different in race, ethnicity, preoperative creatinine, insulin dependence, hypertensive status, history of stroke or TIA, preoperative renal failure, preoperative dialysis, presence of disseminated cancer, use of steroids for chronic conditions, ASA classification, operative time, and urinary diversion type. Table 3 shows the summary of demographic factors, laboratory results, medical history, and operative factors of the entire cohort stratified by concurrent surgery status.

The cohort was matched using the 12 significantly different preoperative and operative variables, as highlighted in Table 3. The matched cohort comprised of 510 patients, with 255 (50%) patients undergoing cystectomy only or concurrent RC and RN. After matching, the only significantly different preoperative or operative variables were smoker status ($p=0.039$) and alcohol consumption prior to operation ($p=0.001$). Table 4 provides the summary of all demographic, laboratory, medical, and operative factors of the matched cohort stratified by concurrent RC and RN status.

The matched cohort outcomes showed an increased risk of renal injury ($p=0.007$), particularly the need for dialysis postoperatively ($p=0.045$), as well as increased readmission rates ($p<0.001$) and unplanned reoperation ($p=0.001$) for patients undergoing concurrent RC and RN. On the contrary, cystectomy alone showed an increased risk of deep venous thrombosis ($p=0.015$) and sepsis or septic shock ($p=0.028$). Table 5 provides the full summary of 30-day outcomes for the matched cohort.

Discussion

Urothelial carcinoma is notorious for being a multifocal disease of the urothelial lining of the whole urinary tract whether in the bladder or the upper urinary tract. This causes urothelial carcinoma to present occasionally as synchronous lesions in the upper urothelial tracts as well as the urinary bladder. In such scenarios, the literature is scarce regarding the optimal management of patients with concurrent localized invasive urothelial carcinoma of both the bladder and the upper tracts. We sought to perform a systematic review of concurrent nephroureterectomy and

cystectomy in order to determine the associated complications as well as the oncologic outcomes. Furthermore, we utilized the ACS-NSQIP database to derive the perioperative complication rates in a large national cohort and to compare those rates to patients undergoing cystectomy alone.

Concurrent nephroureterectomy and cystectomy is a surgical procedure with non-negligible complication rates. Our review showed that significant postoperative complications affect about a third of the patients undergoing this surgical procedure. The most commonly stated complications include prolonged paralytic ileus,^{28,29} infectious-related adverse events,¹⁵ acute kidney failure,²⁸ ureter-intestinal anastomosis leak,²⁸ port hernia,²² and retroperitoneal hemorrhage.³⁰ In this study, we found that the most commonly encountered complications are surgical site infections (11%), renal failure (9%), and other infectious complications (20.6%). When compared to radical cystectomy alone, we found that renal injuries and unplanned re-operation rates are significantly higher. Kidney injury is intuitively expected due to the removal of a kidney. On the other hand, the increased rates of re-operation are a testament to the increased complexity of performing a concurrent nephroureterectomy and cystectomy when compared to radical cystectomy alone. Interestingly, urinary tract infections were significantly lower in the concurrent group, which could be explained by less uretero-intestinal anastomoses (one or none in concurrent group) when compared to the general population undergoing radical cystectomy (two uretero-intestinal anastomoses). Thus, given the morbidity of the combined procedure, the indication of a concurrent nephroureterectomy should be restricted to cases where benefit is thought to outweigh these demonstrated risks. This is especially relevant for concurrent nephroureterectomies that were performed in the setting of a nonfunctional asymptomatic kidney or other low-risk indications.

The oncologic outcomes of concurrent nephroureterectomy and cystectomy could not be compared due to the lack of proper statistical analysis given the nature of the reviewed papers in our study. Most papers were small case series that reported oncologic outcomes heterogeneously with different follow-up periods. A large-scale study focusing on oncologic outcomes with proper survival analysis is needed to answer this question. However, multifocal disease affecting

Table 3. Summary of demographic factors, preoperative laboratory results, medical history, and operative factors for the RC-only and concurrent surgery cohorts, before propensity score matching.

Factor	RC-only	Concurrent	Total	p-Value
	Count (%)	Count (%)	Count (%)	
<i>Demographics</i>				
Age				
<50	648 (6)	21 (7)	669 (6)	0.715
50 to <60	1722 (15)	41 (14)	1763 (15)	
60 to <70	3543 (31)	84 (29)	3627 (31)	
70 to <80	4346 (38)	117 (40)	4463 (38)	
>80	1206 (11)	31 (11)	1237 (11)	
Gender				
Male	9205 (80)	229 (78)	9434 (80)	0.308
Female	2260 (20)	65 (22)	2325 (20)	
Race				
White	8808 (77)	238 (81)	9046 (77)	<0.001
Black	517 (5)	14 (5)	531 (5)	
Other	180 (2)	13 (4)	193 (2)	
Ethnicity				
Hispanic	290 (3)	8 (3)	298 (3)	0.016
BMI class				
<25	3129 (28)	83 (28)	3212 (28)	0.821
25 to <30	4345 (38)	110 (38)	4455 (38)	
30 to <35	2536 (22)	65 (22)	2601 (22)	
25 to <40	886 (8)	26 (9)	912 (8)	
≥40	488 (4)	9 (3)	497 (4)	
Smoker	2665 (23)	56 (19)	2721 (23)	0.092
Alcohol use	53 (1)	1 (0)	54 (1)	1.000
<i>Preop Labs</i>				
Anemia	4133 (37)	116 (40)	4249 (37)	0.214
Abnormal SCr	1620 (15)	112 (39)	1732 (15)	<0.001
Thrombocytopenia	1134 (10)	28 (10)	1162 (10)	0.871
Hypoalbuminemia	1233 (17)	30 (15)	1263 (17)	0.548

(Continued)

Table 3. (Continued)

Factor	RC-only	Concurrent	Total	p-Value
	Count (%)	Count (%)	Count (%)	
Leukocytosis	1146 (10)	32 (11)	1178 (10)	0.584
Abnormal INR	1100 (16)	34 (18)	1134 (16)	0.464
<i>Medical history</i>				
Diabetes	2242 (20)	65 (22)	2307 (20)	0.276
Insulin use	751 (7)	28 (10)	779 (7)	0.043
Hypertension	6800 (59)	199 (68)	6999 (60)	0.004
CHF	85 (1)	0 (0)	85 (1)	0.279
PVD	19 (0)	2 (1)	21 (0)	0.096
Stroke or TIA	51 (0)	6 (2)	57 (1)	0.003
Hepatic disease	9 (0)	0 (0)	9 (0)	1.000
COPD	871 (8)	23 (8)	894 (8)	0.885
Renal failure	45 (0)	5 (2)	50 (0)	0.008
Dialysis	48 (0)	32 (11)	80 (1)	<0.001
Disseminated cancer	674 (6)	30 (10)	704 (6)	0.002
Chronic steroids	399 (4)	23 (8)	422 (4)	<0.001
Weight loss	333 (3)	7 (2)	340 (3)	0.597
Bleeding disorder	390 (3)	9 (3)	399 (3)	0.750
pRBC transfusion	203 (2)	8 (3)	211 (2)	0.225
Emergency case	44 (0)	1 (0)	45 (0)	1.000
Sepsis or SIRS	182 (2)	4 (1)	186 (2)	1.000
<i>Operative factors</i>				
ASA Class				
1	51 (0)	0 (0)	51 (0)	0.002
2	2693 (24)	44 (15)	2737 (23)	
3	7993 (70)	222 (76)	8215 (70)	
4	704 (6)	27 (9)	731 (6)	
5	3 (0)	0 (0)	3 (0)	
Operation time				
<150	242 (2)	6 (2)	248 (2)	<0.001
150 to <250	2535 (22)	35 (12)	2570 (22)	

(Continued)

Table 3. (Continued)

Factor	RC-only	Concurrent	Total	<i>p</i> -Value
	Count (%)	Count (%)	Count (%)	
250 to <350	3798 (33)	75 (26)	3873 (33)	
350 to <450	2776 (24)	81 (28)	2857 (24)	
450 to <550	1390 (12)	49 (17)	1439 (12)	
550+	724 (6)	48 (16)	772 (7)	
Urinary diversion				
Incontinent	9499 (83)	263 (89)	9762 (83)	0.003
Continent	1966 (17)	31 (11)	1997 (17)	
ASA, American Society of Anesthesiologists; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; pRBC, packed red blood cell; PVD, peripheral vascular disease; RC, radical cystectomy; SIRS, systemic inflammatory response syndrome; TIA, transient ischemic attack.				

Table 4. Summary of demographic factors, preoperative laboratory results, medical history, and operative factors for the RC-only and concurrent surgery cohorts, after propensity score matching.

Factor	RC-only	Concurrent	Total	<i>p</i> -Value
	Count (%)	Count (%)	Count (%)	
<i>Demographics</i>				
Age				
<50	18 (7)	16 (6)	34 (7)	0.920
50 to <60	39 (15)	38 (15)	77 (15)	
60 to <70	77 (30)	73 (29)	150 (29)	
70 to <80	98 (38)	99 (39)	197 (39)	
>80	23 (9)	29 (11)	52 (10)	
Gender				
Male	197 (77)	197 (77)	394 (77)	1.000
Female	58 (23)	58 (23)	116 (23)	
Race				
White	221 (87)	212 (83)	433 (85)	0.293
Black	15 (6)	12 (5)	27 (5)	
Other	3 (1)	7 (3)	10 (2)	
Ethnicity				
Hispanic	8 (3)	6 (2)	14 (3)	0.359

(Continued)

Table 4. (Continued)

Factor	RC-only	Concurrent	Total	<i>p</i> -Value
	Count (%)	Count (%)	Count (%)	
<i>BMI Class</i>				
<25	73 (29)	75 (30)	148 (29)	0.340
25 to <30	88 (35)	95 (37)	183 (36)	
30 to <35	58 (23)	52 (21)	110 (22)	
25 to <40	17 (7)	23 (9)	40 (8)	
≥40	18 (7)	9 (4)	27 (5)	
Smoker	72 (28)	52 (20)	124 (24)	0.039
Alcohol use	13 (5)	1 (0)	14 (3)	0.001
<i>Preop Labs</i>				
Anemia	106 (42)	96 (38)	202 (40)	0.424
Abnormal SCr	92 (36)	83 (33)	175 (34)	0.401
Thrombocytopenia	23 (9)	23 (9)	46 (9)	0.966
Hypoalbuminemia	28 (16)	24 (14)	52 (15)	0.625
Leukocytosis	30 (12)	29 (12)	59 (12)	0.942
Abnormal INR	24 (12)	25 (15)	49 (13)	0.426
<i>Medical history</i>				
Diabetes	48 (19)	53 (21)	101 (20)	0.579
Insulin use	13 (5)	20 (8)	33 (7)	0.208
Hypertension	172 (68)	170 (67)	342 (67)	0.851
CHF	2 (1)	0 (0)	2 (0)	0.499
PVD	1 (0)	1 (0)	2 (0)	1.000
Stroke or TIA	1 (0)	1 (0)	2 (0)	1.000
Hepatic disease	1 (0)	0 (0)	1 (0)	1.000
COPD	22 (9)	17 (7)	39 (8)	0.405
Renal failure	7 (3)	3 (1)	10 (2)	0.201
Dialysis	7 (3)	7 (3)	14 (3)	1.000
Disseminated cancer	24 (9)	26 (10)	50 (10)	0.766
Chronic steroids	15 (6)	19 (8)	34 (7)	0.478
Weight loss	6 (2)	5 (2)	11 (2)	0.761
Bleeding disorder	7 (3)	6 (2)	13 (3)	0.779
pRBC transfusion	3 (1)	8 (3)	11 (2)	0.127

(Continued)

Table 4. (Continued)

Factor	RC-only	Concurrent	Total	p-Value
	Count (%)	Count (%)	Count (%)	
Emergency case	0 (0)	1 (0)	1 (0)	1.000
Sepsis or SIRS	6 (2)	4 (2)	10 (2)	0.523
<i>Operative factors</i>				
ASA Class				
1	1 (0)	0 (0)	1 (0)	0.926
2	44 (17)	41 (16)	85 (17)	
3	198 (78)	201 (79)	399 (78)	
4	12 (5)	13 (5)	25 (5)	
5	0 (0)	0 (0)	0 (0)	
Operation time				
<150	2 (1)	5 (2)	7 (1)	0.640
150 to <250	30 (12)	26 (10)	56 (11)	
250 to <350	67 (26)	66 (26)	133 (26)	
350 to <450	77 (30)	71 (28)	148 (29)	
450 to <550	33 (13)	44 (17)	77 (15)	
550+	46 (18)	43 (17)	89 (18)	
Urinary diversion				
Incontinent	220 (86)	228 (89)	448 (88)	0.278
Continent	35 (14)	27 (11)	62 (12)	
<small>ASA, American Society of Anesthesiologists; BMI, body mass index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; pRBC, packed red blood cell; PVD, peripheral vascular disease; RC, radical cystectomy; SIRS, systemic inflammatory response syndrome; TIA, transient ischemic attack.</small>				

multiple urinary organs might confer worse oncologic outcomes when compared to focal disease, partly due to the complexity of the curative surgery which could affect recurrence rates, but also possibly related to the inherent biologic and genetic behavior of such tumors. Moreover, systemic therapy alone or in combination with curative surgery remains another role player that may affect oncologic outcomes. This highlights the importance of patient selection and individualized treatment plans as there is no size that best fits all.

Comparing outcomes of different surgical approaches for a combined radical cystectomy and nephroureterectomy, mainly open *versus* minimally invasive, was not feasible due to the nature of the available literature and diversity of used approaches within the cases series. However, this can be foreseen to a certain limit from comparative studies of minimally invasive *versus* open radical cystectomy. Robotic-assisted surgery in RC has lower blood transfusion rate but longer operative times when compared with open surgery, with all other outcomes being comparable.^{31,32}

Table 5. Summary of 30-day postoperative outcomes in the propensity score matching cohort.

Factor	RC-only	Concurrent	Total	OR (95% CI)	p-Value
	Count (%)	Count (%)	Count (%)		
Wound class					
Clean	0 (0)	8 (3)	8 (2)		0.059
Clean/Cont.	241 (95)	231 (91)	472 (93)		
Cont.	13 (5)	15 (6)	28 (6)		
Dirty	1 (0)	1 (0)	2 (0)		
Wound disruption	4 (2)	8 (3)	12 (2)	2.03 (0.60–6.84)	0.243
Any SSI	34 (13)	27 (11)	61 (12)	0.77 (0.45–1.32)	0.339
Superficial SSI	20 (8)	14 (6)	34 (7)	0.68 (0.34–1.38)	0.287
Deep SSI	2 (1)	2 (1)	4 (1)	1.00 (0.14–7.15)	1.000
Organ space SSI	14 (6)	13 (5)	27 (5)	0.93 (0.43–2.01)	0.843
Sepsis or shock	43 (17)	26 (10)	69 (14)	0.56 (0.33–0.94)	0.028
UTI	31 (12)	20 (8)	51 (10)	0.62 (0.34–1.11)	0.104
Pneumonia	10 (4)	9 (4)	19 (4)	0.90 (0.36–2.24)	0.815
Renal injury/failure	9 (4)	24 (9)	33 (7)	2.84 (1.29–6.24)	0.007
DVT	16 (6)	5 (2)	21 (4)	0.28 (0.10–0.77)	0.015
PE	5 (2)	4 (2)	9 (2)	0.80 (0.21–3.00)	1.000
MACE	9 (4)	9 (4)	18 (4)	1.00 (0.39–2.56)	1.000
Mortality	6 (2)	6 (2)	12 (2)	1.00 (0.32–3.14)	1.000
Readmission	19 (8)	50 (20)	69 (14)	3.03 (1.73–5.31)	< 0.001
Unplanned re-op	3 (1)	17 (7)	20 (4)	6.00 (1.74–20.74)	0.001
Prolonged ventilation	11 (4)	11 (4)	22 (4)	1.00 (0.43–2.35)	1.000
Unplanned intubation	5 (2)	12 (5)	17 (3)	2.47 (0.86–7.11)	0.084

CI, confidence interval; DVT, deep venous thrombosis; MACE, major adverse cardiovascular events; OR, odds ratio; PE, pulmonary embolism; RC, radical cystectomy; SSI, surgical site infection; UTI, urinary tract infection.

Conclusion

The treatment of concurrent UBC and UTUC is a challenging task requiring a multidisciplinary approach. A combined RC and RNU is a treatment option that should be cautiously utilized as it is associated with high morbidity and mortality. Intraoperative and postoperative complications are worse when compared with RC alone. Oncologic outcomes of this combined operation need to be further investigated and notably compared with RC. This highlights the need for further research as

well as exploration of other treatment options such as a staged procedure or other nonsurgical treatments tailored to this complex disease.

Declarations

Ethics approval and consent to participate

The de-identified database (ACS-NSQIP) does not constitute human subject research; hence, no IRB approval was required. Moreover,

consent to participate was not required as no patient-identifying information is shared with data collaborators.

Consent for publication

Not applicable.

Author contributions

Marwan Zein: Writing – original draft.

Ali A. Nasrallah: Writing – original draft.

Nassib F. Abou Heidar: Conceptualization; Writing – original draft.

Jad Najdi: Writing – review & editing.

Layal Hneiny: Data curation; Methodology.

Albert El Hajj: Conceptualization; Supervision; Writing – review & editing.

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Availability of data and materials

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