Oncology

Perioperative and Oncologic Outcomes Associated with Simultaneous Radical Cystectomy and Nephroureterectomy

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OBJECTIVE To compare the perioperative and oncologic outcomes associated with RCNU to a matched cohort undergoing RC alone. Simultaneous radical cystectomy and nephroureterectomy (RCNU) for synchronous upper tract and bladder urothelial carcinoma is an uncommon procedure. Sparse literature exists comparing outcomes in patients treated with radical cystectomy (RC) alone versus RCNU.

METHODS Adults treated with RCNU for urothelial carcinoma of the bladder (UCB) and upper tract urothelial carcinoma (UTUC) between 1980 and 2020 were identified. Patients were matched 2:1 to patients undergoing RC alone for UCB based on age (+/- 5 years), gender, BMI (+/- 5), Charlson Comorbidity Index, pathologic staging (stage ≤pT2 vs >pT2), and receipt of neoadjuvant chemotherapy. Outcomes included overall survival (OS), recurrence free survival (RFS), cancer specific survival (CSS), 30-day complications, length of stay (LOS), operative time, and estimated blood loss (EBL).

RESULTS A total of 39 patients undergoing RCNU were identified and matched to 74 patients undergoing RC. There were no significant differences in LOS, EBL, or 30-day complication rates. Operative time was significantly longer in the RC cohort. OS (HR 0.58, CI 0.35-0.97, P = .036) was significantly better for patients undergoing RC alone, while no significant difference was noted in RFS (HR 0.65, 0.34-1.24) and CSS (HR 0.58, CI 0.31-1.08, P = .08).

CONCLUSIONS Patients undergoing RCNU had significantly lower OS compared to a matched group of patients undergoing RC alone. Perioperative outcomes between the groups did not differ significantly. This data can inform patient counseling for treatment of this rare disease state. UROLOGY 00: 1−7, 2022. © 2022 Elsevier Inc.

Urothelial cell carcinoma (UCC) is thought to arise from a panurothelial "field defect," and this may allow for development of multifocal, synchronous or metachronous urothelial tumors of the upper tract and bladder urothelium. Upper tract urothelial carcinoma (UTUC) is less common than urothelial carcinoma of the bladder (UCB), representing only 5%-10% of all urothelial carcinoma, with a projected 83,180 cases of bladder cancer and 4010 cases of ureteral cancer projected in the United States in 2022.[1] Indications for radical cystectomy (RC) include muscle-invasive UCB (MIBC), BCG unresponsive disease, recurrent high grade non-muscle invasive bladder cancer (NMIBC), or non-muscle invasive disease with variant histology.[2,3] Nephroureterectomy is typically recommended in the setting of high-grade and invasive UTUC or endoscopically unmanageable disease.[4]

Radical cystectomy (RC) is known to be associated with significant perioperative morbidity and mortality. Overall complication rates range from 60%-70%, with high-grade (Clavien ≥III) complications reported in 10%-20% of patients.[5-7] Perioperative mortality following RC ranges from 1% to 3% at large tertiary referral centers.[8-10] Simultaneous radical cystectomy and nephroureterectomy (RCNU) is an infrequent urologic procedure performed in select patients. Indications for RCNU include UCB meeting criteria for RC in combination with a non-functioning renal unit or concurrent UTUC. However, concurrent UTUC and UCB is uncommon, presenting in only 17% of patients with UTUC.[11] Due to the rarity of this procedure, current literature is sparse and provides little guidance for clinicians regarding expected perioperative and oncologic outcomes.

Although RCNU has been examined previously, literature regarding expected perioperative and oncologic outcomes is limited to small case series. While radical

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cystectomy is seldom combined with nephroureterectomy, it is unknown whether addition of nephroureterectomy poses increased perioperative risk. Our group sought to compare perioperative and oncologic outcomes in patients undergoing RCNU for multifocal urothelial carcinoma of the bladder and upper tract to a matched cohort undergoing radical cystectomy alone (RC).

METHODS

Study Population

Following institutional review board approval, a prospectively maintained single-institution radical cystectomy registry was queried for patients undergoing RCNU for UCB and UTUC between 1980 and 2021. Exclusion criteria included nephroureterectomy performed for a non-functioning renal unit, malignancy other than urothelial carcinoma, patients rendered anephric post-operatively, and patients who lacked follow-up data. Electronic medical records were available from 2001 onwards, and these records were re-reviewed to obtain information regarding diagnosis and management of this patient population.

End Points and Assessments

Patients undergoing RCNU were matched 2:1 to patients undergoing RC alone for UCB based on age (+/- 5 years), gender, BMI (+/- 5), Charlson Comorbidity Index, pathologic staging of the primary bladder tumor (≤pT2 vs >pT2), pathologic nodal stage, and receipt of neoadjuvant chemotherapy. Clinicopathologic data were collected and analyzed for all patients undergoing RCNU and RC alone. Primary endpoints included overall survival (OS), cancer specific survival (CSS), and recurrence free survival (RFS), defined as time of treatment until development of any disease recurrence, systemic or local. Secondary outcomes included 30-day overall and high-grade complication rates, length of stay (LOS), operative time, renal functional outcomes, and estimated blood loss (EBL). Complications were reported using the Clavien-Dindo grading system, and high-grade complications were defined as Clavien 3 or greater.[12] Additionally, we collected descriptive data on renal functional outcomes, urinary diversion, and utilization of pelvic and/or retroperitoneal lymph node dissection in patients undergoing RCNU. Renal functional outcomes in the RCNU cohort were determined by percent change in estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) stage progression at 3 months and 1 year. eGFR calculations were made using the CKD-EPI creatinine equation (2021). Postoperative renal functional data were not compared between the patients undergoing RCNU and those undergoing RC alone.

Statistical Analysis

Categorical variables were presented as n (%) and differences between groups were compared using $\chi 2$/Fisher's exact test. Continuous variables were summarized as mean (± standard deviation) or median (interquartile range, IQR) values, as appropriate according to data distribution, and comparison between the groups was done using *t* test or Kruskal-Wallis test. Overall survival was defined as time from cystectomy to death or last follow-up. Survival rates after diagnosis were estimated using the Kaplan-Meier method and compared using the log-rank test. Greedy method was used to match the 39 RCNU patients to 74 RC alone patients from a pool of more than 2300 based on the previously mentioned variables. SAS (version 9.4) and R (version 4.1.2) were used for all statistical analysis. All the tests were two sided and a *P*-value <.05 was considered significant.

RESULTS

In total, 74 patients underwent synchronous RCNU, of whom 28 were excluded from analysis based on nephroureterectomy having been performed for a non-functioning renal unit. Of the 46 patients with synchronous UCB and UTUC, 3 were excluded based on limited follow-up data, and 4 were anephric following surgery. The remaining 39 patients underwent RCNU for synchronous, biopsy-proven UTUC and UCB were matched to 74 patients who underwent RC alone for UCB (Table 1). Indication for cystectomy included intolerance or failure of intravesical therapy for NMIBC in 17 patients (44%), high risk NIMBC meeting criteria for upfront cystectomy in 10 patients (26%), MIBC in 6 patients (15%), high-grade NMIBC with endoscopically unmanageable disease in 3 patients (8%), and end-stage bladder with extensive history of high-grade NMIBC in 1 patient (3%). The median age was 72 (IQR 65-76) and median BMI 28 (IQR 25.4-30.1). ECOG performance status was 0-1 in 92% and 98% of RCNU and RC alone cases, respectively. Mean Charlson comorbidity index for patients undergoing RC alone was 1.4 +/- 1.6 and for RCNU it was 2.0 +/- 2.0. The remaining preoperative clinical and tumor characteristics are reported in Table 2. Combination robot-assisted radical cystectomy and hand-assist nephroureterectomy was performed in 4 patients (10%). Open RCNU with a midline incision was performed in 34 patients (87%). One patient (3%) underwent robotic cystectomy and nephroureterectomy. One patient who underwent RC received adjuvant chemotherapy and 6 patients who underwent RC were treated with adjuvant radiation. No patients undergoing RCNU received adjuvant chemotherapy or radiation.

Mean operative times for RC alone and RCNU were 296.4 +/- 98.9 and 335.4 +/- 55.7 minutes, respectively (*P* = .05). Median hospital LOS for patients undergoing RC alone and RCNU was 8 days (IQR 6-10). Perioperative blood transfusion was required in 60.8% and 61.5% of patients undergoing RC and RCNU, respectively. Incontinent urinary diversion was utilized in 83.8% of RC and 90% of RCNU. High grade complications (Clavien ≥3) were noted in 24.3% and 35.9% of patients undergoing RC and RCNU, respectively. The remaining perioperative outcome data is listed in Table 3. We did not find a significant difference in hospital length of stay, EBL, rates of blood transfusion, overall complication, and high-grade complications rate (all p-values >0.05). Operative time was significantly lower in the RC alone group (0 = 0.045)

Hospital length of stay in the RCNU cohort varied when considering type of diversion performed. Type of urinary diversion performed in the RCNU cohort is provided in supplemental Table 1. Diversions involving bowel incorporation (ileal conduit, orthotopic neobladder, colon conduits, and ureterosigmoidostomy) demonstrated significantly longer LOS than those not requiring bowel interposition (cutaneous ureterostomy, high ureteral ligation with nephrostomy tube placement, and procedures rendering patients anephric). Mean LOS for patients undergoing urinary diversion with bowel incorporation was 9.6 +/- 4.6 days compared to 7 +/- 2.1 days (*P* = .02).

Renal functional outcomes were assessed using percent change in eGFR and CKD upstaging, with follow-up information available on 25 and 16 patients at 3 months and 1 year,

Table 1. Matching variables for each cohort

	RC Alone (N = 74)	RCNU (N = 39)	All Patients (N = 113)	*P* Value
Age at Surgery				.8942
Median	71.5	72.0	72.0	
Q1, Q3	65.0, 77.0	65.0, 76.0	65.0, 77.0	
Gender				.7221
Female	11 (14.9%)	7 (17.9%)	18 (16.1%)	
Male	63 (85.1%)	32 (82.1%)	95 (84.8%)	
BMI				.9278
Median	28.1	28.1	28.1	
Q1, Q3	25.6, 30.0	25.3, 30.7	25.4, 30.1	
Charlson Index				.1056
Median	1	1	1	
Q1, Q3	0, 2.0	1.0, 3.0	0, 2.0	
pT Stage				.712
<pT2	54 (73.0%)	29 (74.4%)	83 (73.5%)	
pT2	12 (16.2%)	6 (15.4%)	18 (15.9%)	
>pT2	8 (10.8%)	4 (10.3%)	12 (10.6%)	
pN Stage				.7509
N0/X	71 (95.9%)	37 (94.9%)	108 (95.6%)	
N+	3 (4.1%)	2 (5.1%)	5 (4.4%)	
Neoadjuvant Chemotherapy				.8919
0 = No	67 (89.7%)	35 (89.7%)	102 (90.3%)	
1 = Yes	7 (9.5%)	4 (10.3%)	11 (9.7%)	

RC, radical cystectomy; RNCU, simultaneous radical cystectomy and nephroureterectomy; BMI, body mass index; pT stage, bladder cancer pathologic T stage at radical cystectomy; pN stage, pathologic N stage for pelvic nodal metastasis.

Table 2. Preoperative clinical characteristics

	RC Alone (N = 74)	RCNU (N = 39)	Total (N = 113)	*P* Value
Max Tumor size				.7339
Median	2.9	2.3	2.8	
IQR 1-3	1.0, 4.7	1.0, 4.1	1.0, 4.7	
Caucasian	61 (89.7%)	31 (100%)	92 (92.9%)	.0639
History of Diabetes	16 (25.0%)	10 (27.0%)	26 (25.7%)	.8224
ECOG				.2046
0	63 (85.1%)	30 (76.9%)	93 (82.3%)	
1	10 (13.5%)	6 (15.4%)	16 (14.2%)	
2	1 (1.4%)	3 (7.7%)	4 (3.5%)	
Smoking History	62 (83.8%)	31 (79.5%)	93 (82.3%)	.5694
Clinical T stage				.0022
Tis	6 (7.9%)	7 (17.5%)	13 (11.2%)	
Ta	6 (8.1%)	12 (30.8%)	18 (15.9%)	
T0	0 (0.0%)	1 (2.5%)	1 (0.9%)	
T1	17 (22.4%)	10 (25.0%)	27 (23.3%)	
T2	37 (48.7%)	8 (20.0%)	45 (38.8%)	
T3	5 (6.6%)	1 (2.5%)	6 (5.2%)	
T4	4 (5.3%)	0 (0.0%)	4 (3.4%)	
Clinically Positive Lymph Nodes	3 (5.0%)	0 (0.0%)	3 (3.2%)	.1789
Charlson Comorbidity Index				.1056
Median	1	1	1	
IQR 1-3	0.0, 2.0	1.0, 3.0	0.0, 2.0	
Neoadjuvant Chemotherapy	7 (9.5%)	4 (10.3%)	11 (9.7%)	.8919
Adjuvant Chemotherapy	1 (1.4%)	0 (0.0%)	1 (0.9%)	.4805

respectively. Preoperative renal function data was available for 30 patients, of whom 13 (43%) were noted to have advanced CKD (≥stage 3a). CKD stage progression was seen in 19 (76%) and 11 (69%) at 3 months and 1 year, respectively. No patients developed further CKD stage progression after 3 months. Mean percent change in eGFR was -34 +/- 20.4% at 3 months and -30.2 +/- 17% at 1 year. In patients with follow-up data at both time points, 9 (69%) experienced continued renal function improvement at 1 year compared to 3 months, and 5 (31%) experienced renal function decline. The mean change in eGFR in this group was +5.1 +/- 19%.

In the RCNU cohort, 8 patients (21%) did not undergo a lymph node dissection (LND). It was not completely clear why PLND was omitted in these patients upon review. Indication for

Table 3. Perioperative outcomes.

	RC Alone (N = 74)	RCNU (N = 39)	Total (N = 113)	*P* Value
Length of Hospital Stay				.6371
Median	8	8	8	
IQR 1-3	6.0-10.0	6.0-10.0	6.0-10.0	
OR time (Minutes; mean +/- SD)	296.4 (+/- 98.9)	335.4 (+/- 55.7)	305.6 (+/- 91.8)	.0452
Estimated blood loss (cc)				.5499
Median	750	825	800	
IQR 1-3	500.0-1000.0	500.0-1200.0	500.0-1175.0	
Perioperative Blood Transfusion	45 (60.8%)	24 (61.5%)	69 (61.1%)	.9399
Diversion Type				.3876
Incontinent	62 (83.8%)	35 (89.7%)	97 (85.8%)	
Continent	12 (16.2%)	4 (10.3%)	16 (14.2%)	
Clavien Complications				.6289
None	23 (31.1%)	8 (20.5%)	31 (27.4%)	
Low Grade (Clavien 1-2)	33 (44.6%)	17 (43.6%)	50 (44.2%)	
3-5 (Clavien 3-5)	18 (24.3%)	14 (35.9%)	32 (28.3%)	

cystectomy in this group was NMIBC refractory to intravesical therapy or patients presenting with high-risk NMIBC with indication for upfront radical cystectomy in 5 patients. Currently, these patients undergo PLND at our institution, and it is unclear if this reflects historical practices. The remaining indications for omitted PLND were significant underlying cardiac comorbidities with concern for prolonged time under anesthesia and significant pelvic adhesions due to history of radiation. Of the remaining patients, 23 (53%) underwent PLND alone, 1 (3%) underwent a retroperitoneal lymph node dissection (RPLND) alone, and 6 (15%) underwent a combined retroperitoneal and pelvic lymph node dissection. For patients undergoing PLND alone, the median number of lymph nodes removed was 17 (IQR 11-24.5). In patients undergoing combined RPLND and PLND, the median number of lymph nodes removed was 26 (IQR 15-36), The median number of positive nodes was 3 (IQR 0-6) and in patients with positive nodes, the median lymph node density was 19% (IQR 5.5%-52%). Five patients that did not undergo RPLND were subsequently diagnosed with retroperitoneal nodal metastasis.

Median follow-up among patients alive at last follow up was 6.3 years (IQR 1.9-11.1). A total of 16 patients (41%) undergoing RCNU and 23 patients (31%) undergoing RC experienced disease recurrence. Locations of recurrence are outlined in Supplemental Table 2. At last follow-up, 61.5% (24 patients) and 58.1% (43 patients) died from any cause among the RC and RCNU groups, respectively. Median overall survival was 105 months in the RC alone arm and 38 months among those undergoing RCNU. On Kaplan-Meier analysis, overall survival (OS) was noted to be significantly greater for patients undergoing RC alone compared to RCNU (HR 0.58; 95% CI 0.35-0.97; $P = .036$) (Fig. 1A). Recurrence-free survival (RFS) approached statistical significance in the RC alone cohort (HR 0.54; 95% CI 0.28-1.02; $P = .054$) (Fig. 1B). Conversely, no statistically significant difference was noted in cancer-specific survival (HR 0.65; 95% CI 0.34-1.24; $P = .18$) (Fig. 1C).

DISCUSSION

Given the rarity of simultaneous RCNU, contemporary literature is limited to small case series primarily focused on the feasibility of minimally invasive surgical approaches.[13-15] To our knowledge, the current study represents one of the largest cohorts undergoing combined radical cystectomy and nephroureterectomy for simultaneous urothelial malignancy of the bladder and upper tract. In comparing patients undergoing RCNU and RC alone, we found no difference in hospital length of stay, EBL, rates of blood transfusion, or overall complications. As expected, operative time was significantly longer in patients undergoing RCNU. Our data provides the first evidence that RCNU carries a surgical risk profile comparable to RC alone with similar perioperative and cancer-specific survival outcomes.

While radical cystectomy remains the gold-standard for muscle invasive UCB, it is associated with significant perioperative morbidity. Historically, complication rates range from 60% to 70%, with high-grade (Clavien ≥III) complications around 10%-20% for most series.[5-7] The true incidence of complications in RCNU is unknown with substantial variability in past case series. Due to this paucity of data, clinicians reasonably extrapolate perioperative outcomes from the radical cystectomy literature. Buse *et al.* reported outcomes for 19 patients undergoing simultaneous en bloc robot-assisted radical cystectomy and nephroureterectomy.[15] The authors noted complications in 3 patients, with 1 patient experiencing a high-grade complication. Conversely, the largest prior series documenting complication rates in RCNU reported high grade complications in 30%, with perioperative morality in 2%.[16] Overall, we noted complications in 79% of patients undergoing RCNU and 70% RC alone, respectively. Additionally, there were high-grade complications (Clavien ≥3) in 36% (N = 14) and 24% (N = 18) of patients undergoing RCNU and RC, respectively. The most common high-grade complications in the RCNU cohort were urinary tract infection with sepsis (N = 4) and atrial fibrillation with rapid ventricular response (N = 3). One patient had a myocardial infarction, and one patient developed a pulmonary embolism following RCNU. There were no perioperative mortalities within 30 days; this may be attributed to the relatively young age (median

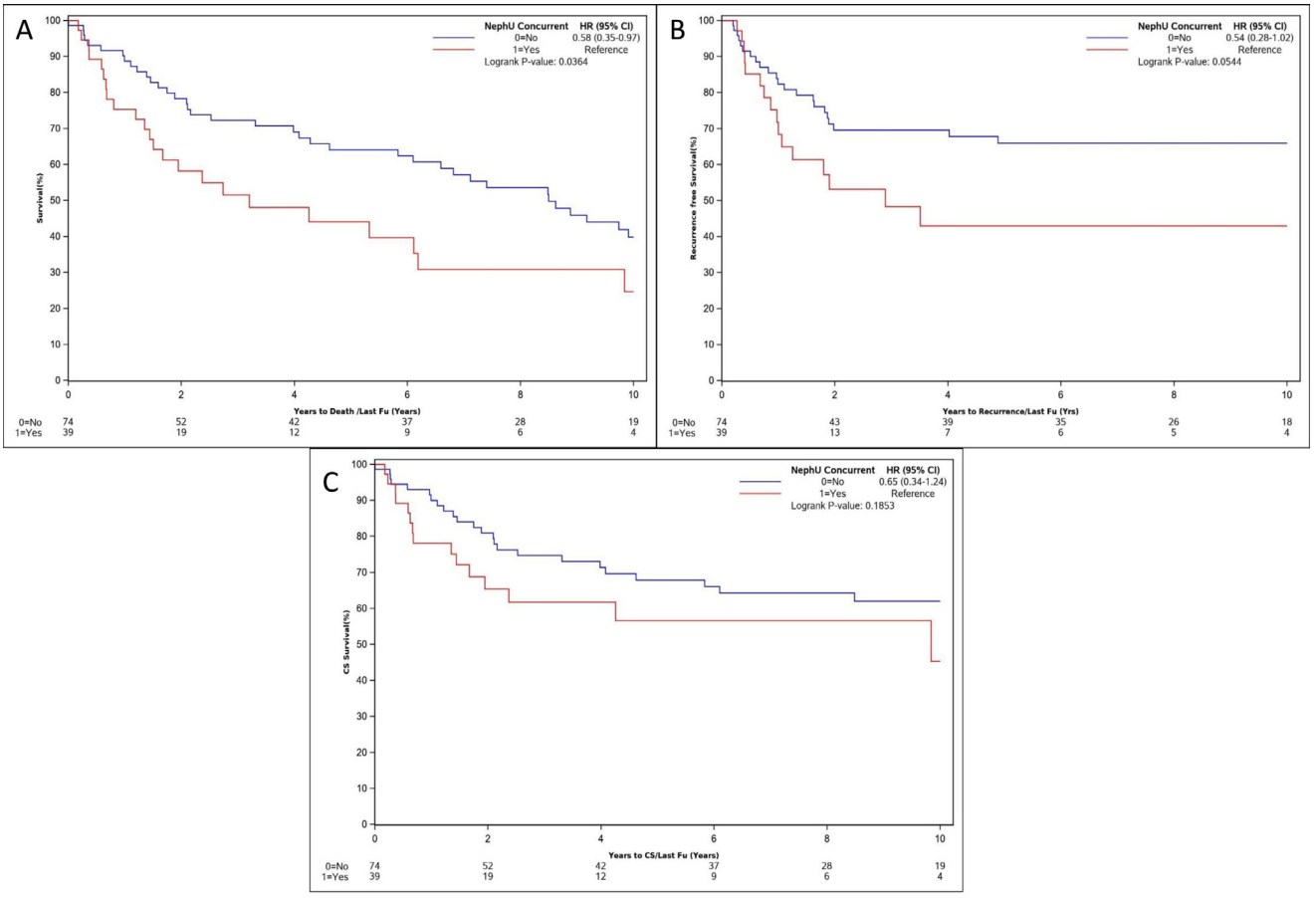

Figure 1. A-C: Kaplan-Meier analysis of overall survival (A), recurrence-free survival (B), and urothelial cancer-specific survival (C) between simultaneous radical cystectomy and nephroureterectomy and radical cystectomy alone.

72 years) and robust performance status of our cohort, as 92% of RCNU and 98% of RC patients were noted to have ECOG performance status of ≤1. High complication rates highlight the importance of proper patient selection, adherence to sound surgical principles, and the importance of diligent patient care post-operatively with an emphasis on enhanced recovery after surgery (ERAS) pathways.[17]

Notably, we found hospital length of stay varied when considering the type of urinary diversion performed. Patients undergoing urinary diversion requiring bowel anastomosis were noted to have a significantly prolonged LOS when compared to patients undergoing urinary diversion without bowel work (mean 9.6 +/- 4.6 compared to 7 +/- 2.1 days; $P = 0.03$). Cutaneous ureterostomy (CU) was the most common form of urinary diversion performed in which bowel work was not required. CU represents an attractive form of urinary diversion in RCNU patients due to shorter operative time, less blood loss, lower transfusion rates, and shorter hospital LOS.[18,19] Additionally, patients undergoing CU have been found to experience similar health-related quality of life to their counterparts undergoing ileal conduit diversion, and potentially lower intraoperative and early post-operative complication rates.[20,21] However, cutaneous ureterostomies are not without limitation, as they are prone to stomal stenosis which may require life-long stent placement and frequent exchange to prevent encrustation.[18] Although the cohorts were limited in size, our results are congruent with past studies suggesting CU is a suitable urinary diversion in patients undergoing RCNU and can potentially limit operative time and length of stay. Further study is needed to support these findings, ideally in a prospective trial setting.

Renal functional decline with resultant chronic kidney disease is an important consideration for patients undergoing RCNU. In addition to the removal of renal parenchyma associated with nephroureterectomy, radical cystectomy with urinary diversion has been noted to carry a risk of progressive renal decline, regardless of the type of diversion performed.[22,23] Furthermore, patients with urothelial carcinoma often present at an advanced age with significant competing health risks, including pre-existing CKD.[24] Similarly, we noted advanced pre-existing CKD (≥ stage III CKD) in >40% of the RCNU cohort. CKD stage progression was recognized in >70% of patients by 3 months. Renal function appeared to stabilize at this time, as no patients experienced further CKD stage progression from 3 months to 1 year. Preoperative patient counseling should include discussions of renal impairment, and early

referral to nephrology is prudent for risk factor modification to prevent future dialysis dependence.

Urothelial carcinoma is generally associated with a high rate of recurrence. We found recurrence-free survival was decreased in RCNU when compared to RC alone and approached statistical significance (HR 0.54; 95% CI 0.28-1.02) with RFS less than 3 years in the RCNU cohort. Although the underlying etiology is not completely clear, it is possible synchronous UTUC and UCB indicates more severe pan-urothelial disease posing an increased risk of subsequent recurrence and metastatic spread. Future study may investigate the role of neoadjuvant chemotherapy in patients undergoing RCNU, as this may be a group that particularly benefits from systemic therapy. Furthermore, CKD has been proposed to increase urothelial carcinoma recurrence, likely due to immunologic dysfunction.[24] A recent study by Chen *et al.* demonstrated a significant risk of contralateral upper tract recurrence following nephroureterectomy in patients with advanced CKD (eGFR <30) and tumor multifocality.[25] Additionally, 5 of 32 (16%) patients who did not undergo RPLND at the time of nephroureterectomy subsequently developed retroperitoneal nodal recurrence. Recent studies demonstrate that RPLND in patients undergoing nephroureterectomy for UTUC improves CSS, reduces risk of local recurrence, and improves survival even in clinically and pathologically node-negative disease.[26-28] Based on these findings, the current EAU guidelines recommend template-based retroperitoneal node dissection for all patients undergoing nephroureterectomy for UTUC, and this should be considered in patients meeting criteria for RCNU.[29] Overall survival was noted to be significantly longer in the RC alone cohort (HR 0.58; 95% CI 0.35-0.97; P = .04). Although it is difficult to identify the underlying cause, it may be attributed to increased risk of disease recurrence in the RCNU cohort, or other unmeasured risk factors. The RCNU cohort also developed high rates of renal dysfunction postoperatively as more than 60% of patients with available data demonstrated significant renal dysfunction (≥stage III CKD), however it is unclear if this was the underlying driver of worse overall survival. It should also be noted that the performance status and comorbidity burden of patients undergoing RCNU was worse than those undergoing RC alone, however, on final analysis this was not a statistically significant difference. The decreased performance status of the RCNU cohort may have contributed to the difference observed in overall survival between groups.

There are several notable limitations to our study. First, the retrospective design poses inherent bias and limits conclusions that can be drawn. Second, the study period spans 40 years, during which numerous advances have been made in the management of both upper tract and bladder urothelial carcinoma, as well as perioperative care, including the introduction of enhanced recovery after surgery (ERAS) pathways.[17] Given the introduction of ERAS pathways at our own institution, it is possible hospital LOS may be shortened further with continued patient accrual. Third, our cohort size is limited due to the nature of our selection criteria. Finally, this study represents a single institution experience which may have introduced selection bias that was unable to be controlled. Additional prospective, multicenter studies are warranted to confirm our results and provide increased generalizability for our findings.

CONCLUSIONS

Simultaneous UTUC and UCB can safely be managed with the combined radical cystectomy and nephroureterectomy. Patients undergoing RCNU had lower OS compared to a matched group of patients undergoing RC alone. Perioperative outcomes between the groups did not differ significantly. The similar perioperative but worse OS associated with RCNU should be considered in patient counseling for treatment of this uncommon disease state.

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SUPPLEMENTARY MATERIALS

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