Open, laparoscopic, and robotic radical nephroureterectomy for upper tract urothelial carcinoma

Comparing outcomes and the tetrafecta as a composite marker of surgery quality

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ABSTRACT

INTRODUCTION: The purpose of this study was to compare surgical outcomes and costs between robotic radical nephroureterectomy (RNU), laparoscopic radical nephroureterectomy (LNU), and open radical nephroureterectomy (ONU), and to assess the relevance of the tetrafecta as a composite outcome on survival parameters after nephroureterectomy (NU).

METHODS: Operative and oncologic followup data was retrospectively collected on patients who underwent NU from 2006–2022 at our institution. The tetrafecta was defined as a true bladder cuff, lymph node dissection, negative surgical margins, and no postoperative complications. Cox proportional hazards regression was used to assess the impact of surgical approach on survival outcomes.

RESULTS: A total of 248 patients were included in the analysis (145 RNU, 61 LNU, and 42 ONU). The complication rate differed by approach and was lowest in RNU ($p<0.01$). Cancer-specific survival (CSS) differed between ONU and RNU patients, with ONU patients 2.51 times as likely to die from their cancer. Retroperitoneal recurrence-free survival (RPFS) differed between ONU and RNU patients, with ONU patients 7.22 times more likely to experience a retroperitoneal recurrence ($p=0.0013$). Variable surgical costs were lower in LNU compared to ONU ($p=0.028$) and direct inpatient hospital costs were lowest with RNU ($p<0.01$). Eighty-one patients met criteria for the tetrafecta. RNU patients were more likely to achieve the tetrafecta compared to LNU ($p<0.01$) and ONU ($p<0.01$) patients. No differences in survival parameters existed between patients who did and did not achieve the tetrafecta.

CONCLUSIONS: Most oncologic outcomes after NU do not differ by approach on long-term followup; however, CSS and RPFS appear to differ between RNU and ONU. ONU has traditionally been considered the approach with the lowest cost; however, our analysis demonstrates both RNU and LNU require lower costs than ONU, depending on the cost parameter analyzed. Among all approaches, the tetrafecta is best achieved with RNU.

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a relatively uncommon malignancy, making up approximately two new cases per 100 000 person-years, but its incidence is rising and is associated with poor long-term outcomes.[1-3] Risk factors for worse overall survival include tumor stage, location, age, lymphovascular invasion, and hydronephrosis.[4,5] Prior work has indicated that operative approach may impact postoperative recurrence of UTUC.[4,6,7]

While select patients may be managed endoscopically or with segmental resection, nephroureterectomy (NU) remains the preferred treatment; NU may be performed using open (ONU), laparoscopic (LNU), or robotic (RNU) approaches. While studies comparing two of these three surgical approaches have been published, very few studies have compared all three surgical approaches.[8-16] Moreover, due to heterogeneity in findings, definite conclusions can be difficult to draw on the superiority of one operative approach over another. This is relevant, as RNU is quickly replacing other approaches.[9,10]

Globally, cost implications may drive surgical approach and very few investigations compare cost differences among surgical approaches to NU.[9,16] Some evidence exists that the transition to the new da Vinci™ robotic platform may reduce the cost of NU, but further investigation is required.[17] Currently, there are at least eight robotic systems

KEY MESSAGES

- Most oncologic outcomes after nephroureterectomy do not differ by approach aside from cancer-specific survival and retroperitoneal-free survival, which favors robotic over open nephroureterectomy.
- The tetrafecta is best achieved with the robotic approach to nephroureterectomy.
- Both robotic and laparoscopic nephroureterectomy are cheaper than open nephroureterectomy.

worldwide that have entry into operating rooms, so use of this technology will continue to increase. In addition, there has been a recent drive towards the use of composite outcomes in operative approaches as a measure of surgical quality.

Composite outcomes combine multiple peri- and postoperative factors to provide a single, simplified measure of procedural efficacy and may be used to predict long-term oncologic outcomes. For patients with UTUC undergoing NU, multiple studies have attempted to develop composite outcomes.[18-20] The utility of these composite outcomes, however, has not yet been validated. The primary aim of this study was to examine the peri- and postoperative and oncologic outcomes for patients undergoing various approaches to NU for UTUC. Secondary aims were to analyze cost differences between the surgical approaches and to examine the clinical utility of the tetrafecta as a composite outcome.

METHODS

Patient selection

Following institutional review board approval, data were retrospectively collected on all consecutive patients undergoing NU at our institution from 2006–2022. Patients were categorized by surgical approach (RNU, LNU, or ONU). A comprehensive preoperative assessment, including laboratory workup, imaging, and patient counseling on the three operative approaches, occurred before every NU, but the ultimate surgical choice was at the operating surgeon's discretion. ONU was performed using either a midline approach or a combination of subcostal and Gibson incisions. RNU was performed according to previously described single-docking techniques using the different da Vinci™ robotic platform as they evolved (Intuitive Surgical, Inc. Sunnyvale, CA, U.S.).[21] Patients were excluded if NU was performed for non-oncologic etiologies.

Data collection

The electronic medical record was used to collect demographic and patient characteristics, surgical details, chemotherapy details (neoadjuvant, perioperative, and adjuvant), perioperative data, including transfusion requirement, length of stay (LOS), and postoperative complications, and histopathologic data. Not all patients had complete medical record data on chemotherapy usage. After the year 2008, intravesical mitomycin C was most frequently used perioperatively unless patients had a strict contraindication. Our institution transitioned to gemcitabine in 2020, which is typically administered prior to NU and emptied from the bladder before excision of a bladder cuff.

The modified Clavien-Dindo classification system was used to grade postoperative complications, with grade I–II being minor and III–V being major complications.

Bladder cuff excision and lymph node dissection were performed at the surgeon's discretion and patient factors at the time of presentation (i.e., septic at presentation, medical comorbidities, hostile abdomen, need to quickly complete an operation and have patient off the operating table). In general, lymph node dissection template was standardized in the manner described by Matin et al and was dependent on tumor location.[22] For proximal ureteral or renal pelvic masses, nodal dissection was carried out to the level of the ipsilateral inferior vena cava or aorta, based on side of surgery (right-precaval and retrocaval nodes, left-paraaortic nodes). For mid-ureteral masses, lymph node dissection included paraaortic nodes, along with the ipsilateral common and external iliac nodes. For distal ureteral tumors, template dissection included the ipsilateral common, external, and internal iliac nodes, along with the obturator nodes.[22] Additional nodes were taken during lymph node dissections on an as-needed basis if suspicious anatomy was encountered during an operation.

Recurrences were separated into retroperitoneal or distant metastatic recurrences. The tetrafecta was defined as having a lymphadenectomy, a true bladder cuff, negative surgical margins, and no postoperative complications.[20]

Cost data was obtained from hospital records. Total operative cost was defined as the total opera-

tive room and postoperative recovery cost based on variables such as operative time (OT), anesthesia, equipment-related, and hospital overhead costs. The total operative cost was a combination of variable and fixed costs. Variable costs included hourly staff labor, procedural materials, and equipment. Fixed costs included hospital and administrative overhead and salaried labor. Inpatient cost was defined as the cost per night of stay on a post-surgical floor bed and was $1200 USD/night.

Statistical analysis

Continuous variables were compared across the three surgical approaches using analysis of variance (ANOVA) and categorical variables were compared using Fisher's exact test. Metastasis-free survival (MFS, time-to-distant metastatic recurrence), retroperitoneal-free survival (RPFS, time-to-retroperitoneal recurrence), recurrence-specific (free) survival (RSS, time-to-any distant or locoregional site after NU), cancer-specific survival (CSS, time-to-death from UTUC-related causes), and overall survival (OS, time from surgery to death or last known date alive), were estimated at three years after NU using the Kaplan-Meier method. Log-rank tests were used to assess differences in survival between the cohorts for OS. Cox proportional hazards regression was used to assess the impact of surgical approach on survival outcomes (MFS, RSS, CSS, and OS). Logistic regression was used to analyze the relationship between surgical approach and recurrence location and examine the impact of surgical approach on achieving the tetrafecta. All statistical tests were performed using SAS, version 9.4 (Cary, NC, U.S.). Statistical significance was assumed at a $p<0.05$.

RESULTS

Patient demographics and peri- and postoperative outcomes stratified by surgical approach can be found in Table 1. A total of 248 patients underwent NU for UTUC during the study period. Of these, 145 patients underwent RNU, 61 underwent LNU, and 42 underwent ONU, with RNU increasing in adoption over time (Figure 1). Median followup was significantly longer in the ONU cohort (six years, $p<0.01$).

Age at surgery, body mass index (BMI), and race were not found to be significantly different between the surgical approaches (Table 1). OT (incision to closure) differed significantly by approach ($p<0.01$), with LNU taking the longest (261 min), followed by ONU (258 min), and RNU requiring the shortest OT (179 min) ($p<0.01$). LOS was significantly shorter for RNU com-

Table 1. Pre-treatment, surgical, and post-treatment characteristics of the study population

	RNU (n=145)	LNU (n=61)	ONU (n=42)	p
Gender Male, n (%) Female, n (%)	 102 (70) 43 (30)	 37 (61) 24 (39)	 18 (43) 24 (57)	0.0051
Age (years), median (IQR)	72 (63–78)	73 (66–78)	64 (60–76)	0.40
BMI (kg/m^2), median (IQR)	27.3 (24.1–30.7)	26.6 (24.2–29.8)	27.6 (22.4–33.8)	0.80
Race, n (%) White Black Hispanic Other	 134 (92) 9 (6) 1 (1) 1 (1)	 57 (93) 4 (7) 0 (0) 0 (0)	 39 (93) 1 (2) 1 (2) 1 (2)	0.56
Preoperative biopsy, n (%)	89/120 (74)	20/27 (74)	17/24 (71)	0.96
Biopsy pathology, n (%) T0/a/is T1 T2 T3 T4	 81 (91) 5 (6) 2 (2) 1 (1) 0 (0)	 10 (77) 2 (15) 1 (8) 0 (0) 0 (0)	 13 (81) 2 (12) 0 (0) 1 (6) 0 (0)	0.19
Neoadjuvant chemotherapy, n (%)	3 (2)	0/31 (0)	2/31 (6)	0.012
Neoadjuvant chemotherapy regimen, n (%) Mitomycin C Gemcitabine/cisplatin	 1 (33) 2 (67)	 –	 1 (50) 1 (50)	–
Intravesical (perioperative) chemotherapy, n (%)	104/141 (74)	49 (80)	35 (83)	0.502
Perioperative (intravesical) chemotherapy regimen, n (%) Gemcitabine Mitomycin C	 35 (33) 69 (67)	 9 (18) 40 (82)	 7 (20) 28 (80)	–
Bladder cuff, n (%)	131 (90)	47 (77)	29 (69)	<0.001
Positive surgical margin, n (%)	18 (12)	6 (10)	3 (7)	0.618
Lymph node dissection, n (%)	100 (69)	16 (26)	13 (31)	<0.001
Lymph nodes taken, median (IQR)	3 (2–6)	1.5 (0–4.5)	2 (1–8.5)	0.447
Lymph nodes positive, n (%)	14 (10)	2 (3)	2 (5)	0.083
Final pathology, n (%) Tis T1 T2 T3 T4	 55 (38) 20 (14) 21 (14) 43 (30) 6 (4)	 30 (50) 7 (12) 5 (8) 17 (28) 1 (2)	 16 (38) 9 (21) 5 (12) 7 (17) 5 (12)	0.13
Adjuvant chemotherapy, n (%)	47/141 (33)	4/37 (11)	4/29 (14)	0.005

The demographic and pre-/perioperative statistics of the study population are shown for each operative approach. P-values listed are for comparisons between all the approaches. BMI: body mass index; IQR: interquartile range; LNU: laparoscopic radical nephroureterectomy; ONU: open radical nephroureterectomy; RNU: robotic radical nephroureterectomy; SD: standard deviation.

Table 1 (cont'd). Pre-treatment, surgical, and post-treatment characteristics of the study population

	RNU (n=145)	LNU (n=61)	ONU (n=42)	p
Adjuvant chemotherapy regimen, n (%)				
Mitomycin C	1/29 (3)	1/7 (14)	1/6 (17)	
Gemcitabine	2/29 (7)	1/7 (14)	0	
Gemcitabine/cisplatin	8/29 (3)	1/7 (14)	1/6 (17)	
Carboplatin/paclitaxel	1/29 (3)	0	0	
Gemcitabine/carboplatin	9/29 (31)	3/7 (43)	4/6 (67)	
Gemcitabine/docetaxel	7/29 (24)	1/7 (14)	0	
Valrubicin	1/29 (3)	0	0	
Followup time (years), median (IQR)	2.7 (1.2–7.2)	4.2 (2.5–12.0)	6.0 (1.6–13.4)	0.0079
OT (minutes), median (IQR)	179 (130–219)	261 (179–344)	258 (180–328)	<0.0001
LOS (days), median (SD)	2 (2–3)	5 (3–7)	5 (4–7)	<0.0001
Clavien-Dindo grade, n (%)				<0.0001
0	128 (88)	44 (73)	21 (51)	
1	12 (8)	13 (22)	7 (17)	
2	3 (2)	0	3 (7)	
3	0	1 (2)	1 (2)	
4	1 (1)	2 (3)	7 (17)	
5	1 (1)	0 (0)	2 (5)	
Minor complication (CD I-II), n (%)	15 (10.3)	13 (21.3)	10 (23.8)	RNU vs. LNU (p=0.008) RNU vs. ONU (p=0.11) LNU vs. ONU (p=0.55)
Major complication (CD III-IV), n (%)	2 (1.4)	3 (4.9)	10 (23.8)	RNU vs. LNU (p=0.13) RNU vs. ONU (p<0.001) LNU vs. ONU (p=0.005)
Blood transfusion postoperatively, n (%)	4 (2.8)	10 (16.4)	4 (9.5)	<0.001
Change in creatinine, mean (SD)	0.32 (1.4)	0.17 (0.44)	-0.31 (1.8)	0.13

The demographic and pre-/perioperative statistics of the study population are shown for each operative approach. P-values listed are for comparisons between all the approaches. BMI: body mass index; IQR: interquartile range; LNU: laparoscopic radical nephroureterectomy; ONU: open radical nephroureterectomy; RNU: robotic radical nephroureterectomy; SD: standard deviation.

pared to ONU and LNU (p<0.01). Patients undergoing LNU had the highest blood transfusion rate (p<0.01).

Use of neoadjuvant chemotherapy (p=0.012) and adjuvant chemotherapy (p=0.005) perioperatively was greatest in RNU. Rates of perioperative chemotherapy (p=0.520) were similar by approach, as was the change in creatinine from preoperative baseline to most recent followup value (p=0.13).

The overall complication rate was lowest in the RNU group (p<0.01). Minor complications were significantly lower in RNU compared to LNU (p<0.01). Major complication rates were significantly lower in RNU compared to ONU (p<0.01) and LNU compared to ONU (p<0.01).

Relevant oncologic outcomes can be found in Table 2. OS, RSS, and MFS at three years postoperatively were similar between the three operative groups. CSS three years after NU was significantly different between ONU and RNU (p=0.019), with ONU patients at a higher risk of cancer-specific death relative to RNU patients. No other differences in CSS were identified. RPFS three years after NU also differed between ONU and RNU patients, with the ONU approach being 7.22 times more likely to experience a retroperitoneal recurrence (p<0.01). No other differences in RPFS were identified (Figure 2).

Total operative and fixed costs did not differ by surgical approach (p>0.05). LNU was associated with significantly less cost than the ONU approach with respect to variable cost ($3803 vs. $4727, p=0.028). For inpatient cost, RNU was less costly than ONU ($2543 vs. $10 900, p<0.01) and LNU ($2543 vs. $5520, p=0.027), which was itself less costly than ONU ($5520 vs. $10 900, p<0.01) (Table 3).

In the entire cohort, 81 patients met criteria for the tetrafecta (Table 4). The likelihood of achieving the tetrafecta significantly differed based on surgical approach (p<0.01), with RNU patients most likely to achieve the tetrafecta (Table 5). OT was significantly shorter in those who did vs. those who did not achieve the tetrafecta (p=0.033). LOS was also shorter for those in whom the tetrafecta was achieved (p<0.01). Long term oncologic outcomes did not differ between those with and without the tetrafecta (Figure 3).

DISCUSSION

Herein, we compared perioperative and oncologic outcomes, as well as costs for patients undergoing RNU, LNU, and ONU for UTUC at our institution. RNU appeared to have superior outcomes with respect to OT and postoperative complications. Neoadjuvant and adjuvant chemotherapy usage was greatest with RNU relative to LNU and ONU.

Oncologic outcomes varied based on the parameter being studied. CSS was longer in RNU patients compared to ONU, and RPFS was more likely in patients who underwent ONU compared to RNU.

In studying cost, variable cost was lower in LNU compared to ONU, and direct inpatient cost was lowest with RNU compared to both LNU and ONU, likely owing to a shorter LOS with the robotic approach. Additionally, our study focused on the tetrafecta composite outcome.

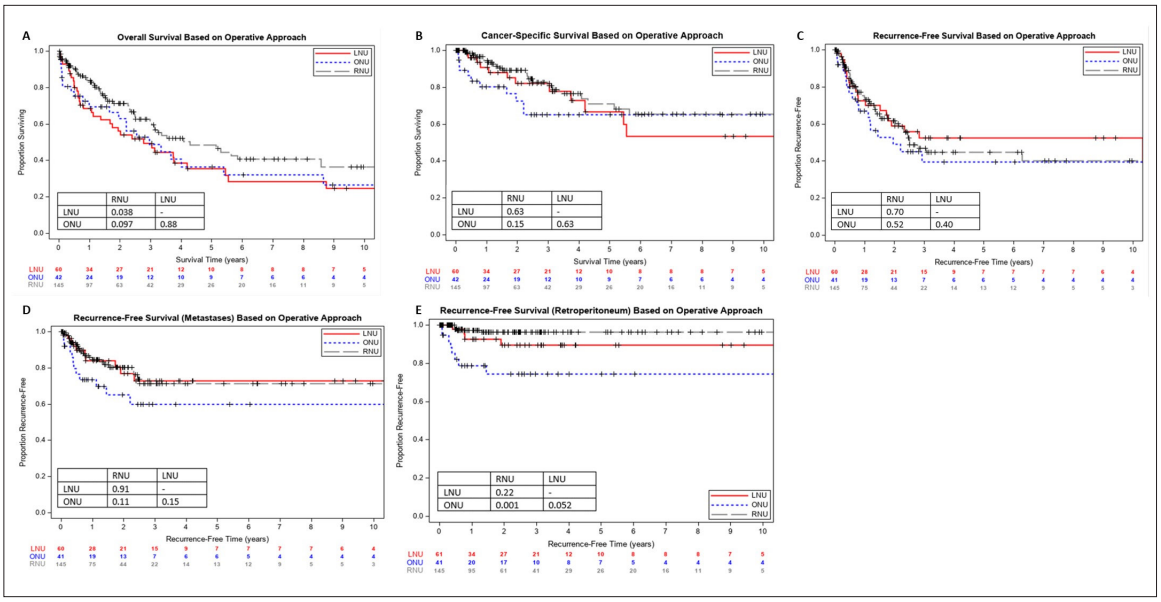

Figure 1. Nephroureterectomy (NU) by surgical approach over time. The total number of NU performed each year during the study window is included by operative approach.

Table 2. Time-to-event outcomes after NU

	RNU (n=145)	LNU (n=61)	ONU (n=42)	p	LNU vs. RNU HR (95% CI), p	ONU vs. LNU HR (95% CI), p	ONU vs. RNU HR (95% CI), p
3-year overall survival estimate (SE), median (years)	61.2% (4.9), 4.3	50.5% (7.0), 3.04	48.7% (8.9), 3.0	0.15	1.50 (0.92, 2.457), p=0.10	1.03 (0.56, 1.88), p=0.93	1.54 (0.89, 2.68), p=0.12
3-year cancer-specific survival (SE), median (years)	80.9% (4.5)	82.5% (6.1), 5.5	65.0% (8.8)	0.041	0.96 (0.39, 2.35), p=0.93	2.61 (1.00, 6.81), p=0.050	2.51 (1.16, 5.42), p=0.019
3-year recurrence-specific survival estimate (SE), median (years)	47.0% (5.7), 2.5	53.7% (8.0), 3.9	39.6% (9.6), 3.0	0.50	0.92 (0.54, 1.54), p=0.74	1.45 (0.86, 2.77), p=0.26	1.32 (0.77, 2.28), p=0.31
3-year metastasis-free survival (SE)	73.6% (5.5)	73.7% (7.6)	61.4% (9.2)	0.18	1.05 (0.50, 2.22), p=0.90	1.83 (0.78, 4.28), p=0.16	1.92 (0.93, 3.96), p=0.076
3-year retroperitoneal-free survival (SE)	95.5% (2.3)	87.6% (5.9)	73.4% (8.4)	0.0037	2.22 (0.57, 8.68), p=0.25	3.25 (0.99, 10.6), p=0.051	7.22 (2.17, 24.0), p=0.0013

The table shows cancer survival statistics and cancer recurrence statistics. For recurrence-specific locations, the number listed is estimated recurrence-free survival at 3 years after NU. P-values listed are for comparisons between all the approaches. Competing risks proportional hazards models were used to compare recurrence-free survival among specific surgical approaches. Medians are also provided where appropriate and were not yet reached for cancer-specific, metastasis-free, or retroperitoneal-free survival. CI: confidence interval; HR: hazard ratios; LNU: laparoscopic radical nephroureterectomy; ONU: open radical nephroureterectomy; RNU: robotic radical nephroureterectomy; SE: standard error.

Due to a lack of significant oncologic differences, our results call into question the utility of the tetrafecta as a useful composite outcome for surgical quality.

Prior studies have shown OT differs based on surgical approach, but did not form a consensus on which modality was superior. Tinay et al and Lee et al compared all three approaches and found OT was greater in LNU and RNU compared to ONU.[9,11] Contradictorily, Bae et al noted that no significant difference existed in OT between RNU, LNU, and ONU.[23]

RNU provided the shortest OT in our analysis. Generally, robot-assisted surgery has been postulated to have higher OT due to docking and undocking time. Given our analysis and use of technique described by us, we believe that shorter OT time may be due to increased experience of the operative team, transition to the new da Vinci Xi robotic platform, pure robotic completion of the procedure in comparison to the laparoscopic approach (where a hybrid approach of both pure laparoscopy and hand-

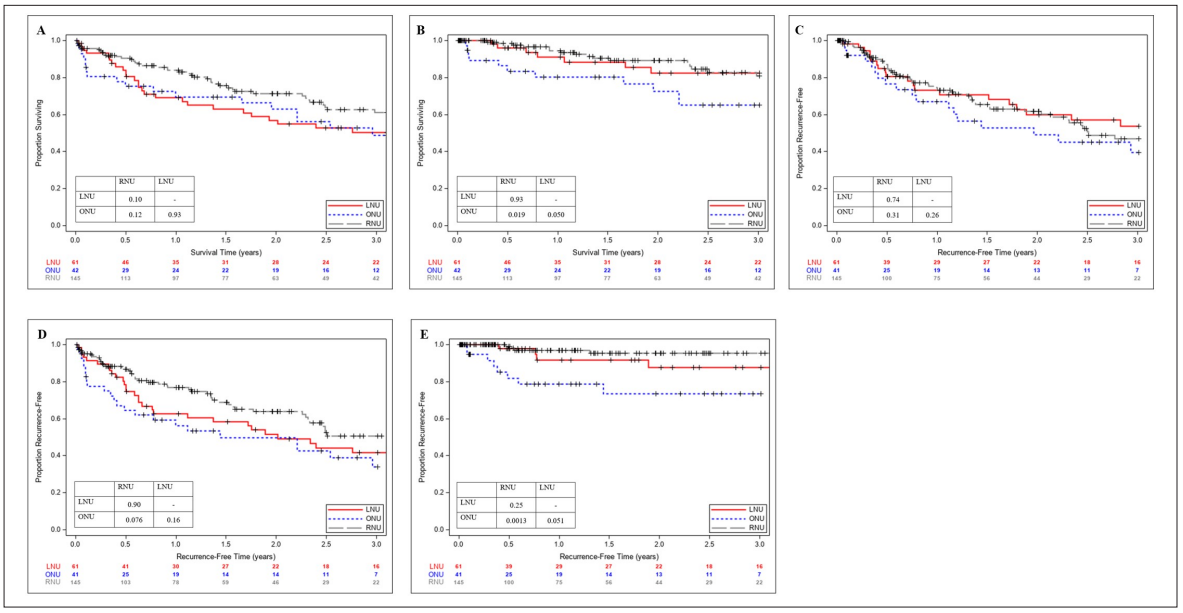

Figure 2. Oncologic outcomes by operative approach. Kaplan-Meier curves are shown comparing outcomes between robotic radical nephroureterectomy, laparoscopic radical nephroureterectomy, and open radical nephroureterectomy. The x-axis represents total survival time from the beginning of the study window. On the y-axis, cumulative survival is shown, and each number represents the cumulative percent of patients without the event of interest having occurred at a particular point in time. On the bottom portion of the plot, the number at risk at each year in the three operative groups is shown. The table on the graph compares each operative approach with associated p-values: (A) overall survival; (B) cancer-specific survival; (C) recurrence-specific survival; (D) metastasis-free survival; (E) retroperitoneal recurrence-free survival

Table 3. Cost outcomes in the study

	RNU (n=67)	LNU (n=15)	ONU (n=12)	p	LNU vs. RNU (95% CI), p	LNU vs. ONU (95% CI) p	ONU vs. RNU (95% CI), p
Total operative cost (dollars), mean (SD)	5504 (1116)	5109 (1265)	6124 (2387)	0.160	-395 (-1164, 375), p=0.31	-1015 (-2059, 28), p=0.056	621 (-224, 1465), p=0.15
Variable cost (dollars), mean (SD)	4151 (871)	3803 (1029)	4727 (1872)	0.085	-348 (-953, 257), p=0.26	-924 (-1744, -104), p=0.028	576 (-88, 1240), p=0.088
Fixed cost (dollars), mean (SD)	1353 (326)	1306 (306)	1397 (555)	0.80	-47 (-251, 157), p=0.65	-91 (-368, 185), p=0.51	44 (-179, 268), p=0.69
Inpatient cost (dollars), mean (SD)	2543 (1570)	5520 (3478)	10900 (12146)	<0.0001	2977 (347, 5607), p=0.027	-5380 (-8946, -1814), p=0.0035	8357 (5471, 11243), p<0.0001

The following table lists cost differences between the three surgical approaches. Cost is listed in USD with standard deviation (SD). P-values listed are for comparisons between all the approaches. Pairwise comparisons are also shown between specific surgical approaches. CI: confidence interval; LNU: laparoscopic radical nephroureterectomy; ONU: open radical nephroureterectomy; RNU: robotic radical nephroureterectomy; SD: standard deviation.

assist were used), and use of multiple incisions for the open approach.

Our study also found that LOS, transfusion rate, complication rate, and complication severity were different between surgical approaches, with RNU boasting the shortest LOS and LNU the greatest transfusion rate. These findings align with prior research that shows that blood loss and transfusion rates may be greater with LNU, as well as ONU relative to RNU.[8,24,25]

Complication rates were noted to be lowest for RNU, consistent with Grossman et al, who demonstrated greater overall complication rates and major complications in LNU and ONU, compared to RNU.[8] In studying major complication rates, we found both RNU and LNU to be superior to ONU, with no difference between RNU and LNU. Others, however, had contradictory results suggesting superiority of LNU or no significant differences in complication rates or severity.[9-11]

One of the many benefits of the robotic surgical approach is improved visualization and dexterity, improving ergonomics for the operating surgeon. This translate to rapid identification of various anatomical structures, allowing for an excellent radical nephrectomy, early clipping of the ureter to prevent downward seeding, lymph node dissection, bladder cuff excision, watertight closure, and an easy installation of intra or perioperative chemotherapy. Similarly, it allows for excellent control of bleeding vessels and thus lower blood loss is not completely unexpected.

Furthermore, decreased complication rate may be inherently related to decreased OT; however, surgeon comfort with surgical approach is inversely related to complication rate, and thus, this parameter may vary significantly among the many studies and institutions in the current literature.

As noted, operative approach was ultimately based on surgeon choice/preference and was not standardized; however, it is clear from Figure 1 that there was a trend toward RNU starting in 2008, with a noted decline in LNU when the da Vinci™ S robotic platform was brought to our institution, and an even sharper increase in RNU after 2014 can be seen, when the da Vinci™ Xi robotic platform was introduced.

Regarding oncologic outcomes, we found no difference in OS, RSS, and MFS among the different surgical approaches, with no difference in the rate of perioperative chemotherapy. Neoadjuvant and adjuvant chemotherapy usage was highest in the RNU group. Additionally, CSS was superior in RNU patients compared to ONU. This requires further investigation, as ONU remains a popular technique being performed in many countries that lack sufficient access to surgical robots.

We also saw increased risk of retroperitoneal recurrence with ONU compared to RNU, as RPFS was worse in ONU. A worse CSS and RPFS was also nearly statistically significant in ONU compared to LNU, and likely would have been seen in our analysis if LNU was performed more frequently at our institution over time.

In the past, laparoscopic approaches to oncologic resection have been theorized to be a risk factor for migration of tumor cells into the retroperitoneum.[26] Our results contradict this and may be directly related to visualization of involved margins at the time of NU, allowing for more complete resection with negative margins with the robotic approach and a newer, modified technique.[27] It is also possible that higher rates of neoadjuvant and adjuvant chemotherapy could be playing a role in the survival outcomes we assessed; however, the low rates of neoadjuvant and adjuvant chemotherapy overall limit the conclusions that can be drawn from them.

A secondary study aim was to examine cost differences between the three surgical approaches, with prior consensus suggesting that ONU tends to have the least costly variant of NU. Our study found no significant cost differences between surgical approaches for NU except for lower variable costs for LNU compared

Table 4. Tetrafecta operative and oncologic outcomes

	Tetrafecta (n=81)	No tetrafecta (n=167)	p	Tetrafecta vs. no tetrafecta HR (95% CI)
Approach RNU LNU ONU	 68/145 (47%) 10/61 (17%) 3/42 (7%)	 77/145 (53%) 51/61 (83%) 39/42 (93%)	<0.0001	–
Gender Male Female	 54 (67%) 27 (33%)	 113 (68%) 54 (32%)	0.57	–
Age at surgery (years), median (IQR)	73 (64–78)	71 (63–78)	0.40	–
OT (minutes), median (IQR)	189 (154–241)	203 (143–281)	0.033	–
LOS (days), median (IQR)	2 (2–3)	3 (2–5)	<0.001	–
3-year OS (SE), median (years)	63.6% (6.3), 5.5	53.0% (4.5), 3.1	0.20	0.73 (0.45, 1.18)
3-year CSS (SE)	81.9% (5.4)	76.9% (4.3)	0.83	0.94 (0.51, 1.73)
3-year RSS (SE), median (years)	47.2% (7.5), 2.8	47.7 (5.1), 2.8	0.86	1.04 (0.67, 1.62)
3 -year metastasis-free survival (SE)	76.4% (6.2)	70.9% (4.9)	0.77	0.91 (0.48, 1.74)
3-year retroperitoneal-free survival (SE)	95.0% (2.9)	89.0% (3.0)	0.24	0.47 (0.14, 1.64)

Competing risks proportional hazards models are provided to compare those who did and did not achieve the tetrafecta for oncologic outcomes. HR and 95% CI are provided with the associated p-value. Medians are also provided where appropriate, and were not yet reached for CSS, MFS, or RSS. CI: confidence interval; CSS: cancer-specific; HR: hazard ratio; LNU: laparoscopic radical nephroureterectomy; MFS: metastasis-free; ONU: open radical nephroureterectomy; RNU: robotic radical nephroureterectomy; RSS: retroperitoneal-free survival; SE: standard error.

Table 5. Achieving the tetrafecta

Approach	Total N	Tetrafecta	Odds ratio (95% CI), p
RNU LNU ONU	145 61 42	68 (47) 10 (17) 3 (7)	RNU – LNU: 4.42 (2.08, 9.35), p=0.0001 RNU – ONU: 11.5 (3.38, 38.5), p<0.0001 LNU – ONU: 2.60 (0.67, 10.1), p=0.17

The following is a logistic regression with the tetrafecta as the outcome. The cumulative number of patients who achieved the tetrafecta are shown for each approach with percentage of the total in parentheses. Each surgical approach is compared to each other. Patients who underwent RNU were significantly more likely to achieve the tetrafecta compared to patients who underwent both LNU and ONU. CI: confidence interval; LNU: laparoscopic radical nephroureterectomy; ONU: open radical nephroureterectomy; RNU: robotic radical nephroureterectomy.

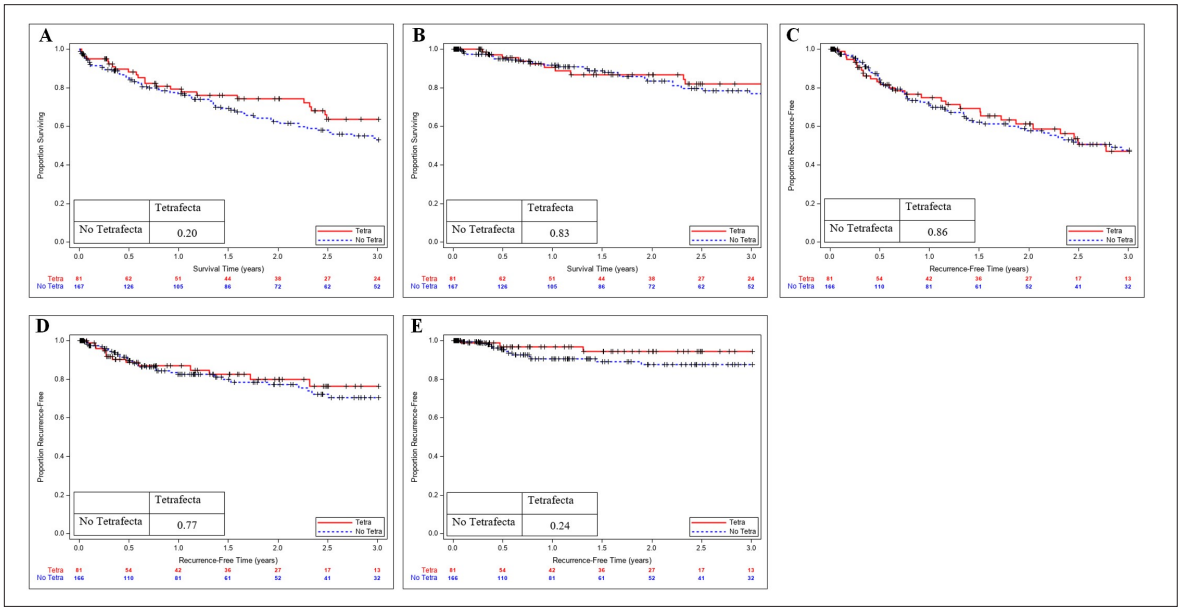

Figure 3. Oncologic outcomes by tetrafecta status. Kaplan-Meier curves are shown comparing outcomes between those who did and did not achieve the tetrafecta. The x-axis represents total survival time from the beginning of the study window. On the y-axis, cumulative survival is shown, and each number represents the cumulative percent of patients without the event of interest having occurred at a particular point in time. On the bottom portion of the plot, the number at risk at each year in those who did and did not achieve the tetrafecta is shown. The table on the graph compares each operative approach with associated p-values. (A) overall survival; (B) cancer-specific survival; (C) recurrence-specific survival; (D) metastasis-free survival; (E) retroperitoneal recurrence-free survival.

to ONU. This finding contradicts prior research that suggests ONU is most cost-effective.[28] One potential explanation for this could be cheaper disposable equipment costs in laparoscopic surgery, which has been shown to be superior to open approaches for renal surgery in the past.[29]

The minimal cost differences in our study compared to other literature should be understood in the context that RNU has been performed at our institution for over 15 years, allowing for seamless transitioning and minimal waste, in addition to reusable ports, use of clips to control vessels, and minimal use of staplers.[9] Our direct inpatient cost was also greater for ONU compared to both LNU and RNU, which can be explained by ONU having a significantly longer LOS compared to LNU and RNU.

Additionally, in evaluating achievement of the "tetrafecta" as a measure of NU quality, we elected to use the same definition as Veccia et al, who concluded that LNU was negatively associated with achieving the tetrafecta compared to RNU.[20] In our cohort, robotic surgery had the highest rate of achieving the tetrafecta, but only OT and LOS differed between those patients for whom it was achieved and those in whom it was not. While individual components of the tetrafecta are no doubt important, no differences in oncologic outcomes were noted between the two groups, calling into question its utility in marking surgical quality.[30] While use of composite outcomes in urology is gaining traction, their true value merits further investigation.

Limitations

Our study has several limitations that we acknowledge.

First, this is a retrospective study and it is therefore subject to associated limitations.

Second, the temporal distribution of ONU, LNU, and RNU being performed was not equivalent in the study, and RNU was done more recently, so oncologic differences could be due to the implementation of more contemporary oncologic care rather than operative approach. Additionally, followup time differences between ONU, LNU, and RNU patients could explain some of the oncologic outcomes we identified in our cohort. We attempted to account for this by using a relatively short time frame for our survival analysis (three years), when most patients would still be included, but recognize this may remain a potential limitation to our conclusions.

As an example, the median time to retroperitoneal recurrence in the study was not reached, but our survival curves show most events occurring before one year post-NU. Although this is true, the survival curve does not reach the 50% mark because of the large cohort of patients with longer non-event times.

Third, we have incomplete data on some patients for the use of neoadjuvant, perioperative, and adjuvant

chemotherapy in the study population. We performed an exhaustive medical record review, but some cases date back to before the use of a fully integrated electronic medical record at our institution.

Fourth, while our results question the usefulness of the tetrafecta, we provide further information on its use as a composite outcome. Further, we recognize it is likely that the surgical approaches were done at different time points on the learning curve of the operative team, affecting our results, i.e., start with open, then laparoscopic, then robotic. While we do understand the limitations of surgical outcomes displayed by single-center, high-volume robotic surgeons, our data suggest the advantages of the robotic approach in terms of oncologic control.

Furthermore, this study investigated patients over a long period during which protocols for postoperative surveillance changed, potentially accounting for a lower number of perioperative patients receiving intravesical chemotherapy. For instance, a landmark study by O'Brien et al showed that perioperative chemotherapy at the time of NU reduces the risk of bladder tumors, but was not published until 2011, and this study has patients dating all the way back to 2006.[31] Similarly, guidelines for intravesical chemotherapy evolved throughout the study window, making comparison between operative approaches complicated.

We believe our study addresses a knowledge gap by directly comparing all three commonly performed methods of NU and evaluating multiple outcomes, including surgical, oncologic, and cost.

CONCLUSIONS

In this study, we present a large series of RNU for UTUC, focusing on the effect of surgical approach on outcomes. RNU has some superior non-oncologic outcomes, including lower major complication rates, OT, and need for blood transfusion postoperatively. CSS was also superior in RNU compared to ONU patients, and retroperitoneal recurrence are less likely compared to the ONU approach. While these findings are meaningful, their worth must be weighed against the fact that most oncologic outcomes were equal across the approaches. Moreover, while some have argued ONU to be the most economical surgical approach, we showed minimal difference in cost, calling into question the notion that RNU and LNU are more expensive. In addition, we looked at the tetrafecta composite outcome for NU. Like other studies, the likelihood of achieving it varied by surgical approach; however, no relevant oncologic variables differed between patients relative to the tetrafecta, challenging how useful composite outcomes in NU are.

Ultimately, surgical approach for NU will likely continue to shift towards RNU at the centers where robotic assistance is available, but more comparative studies are needed to determine whether this shift is supported by clinical improvements in outcomes.

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