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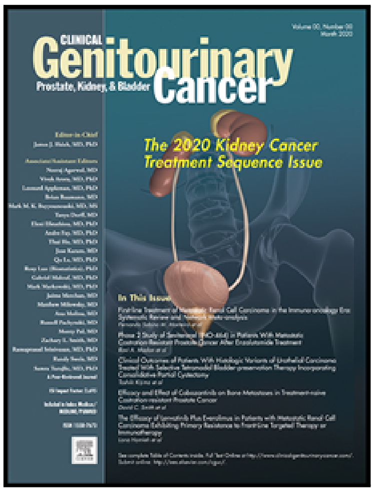

Contemporary Trends of Systemic Neoadjuvant and Adjuvant Intravesical Chemotherapy in Patients with Upper Tract Urothelial Carcinomas Undergoing Minimally Invasive or Open Radical Nephroureterectomy: Analysis of US claims on Perioperative Outcomes and Health Care Costs

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Original article

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Clinical Practice Points:

- In the US, MIS-RNU has become the option of choice in providing significant morbidity and health related advantages compared to ORNU
- According to EAU UTUC Guidelines, even if PIC is recommended and NAC is suggested, neither NAC nor PIC have been routinely incorporated into clinical practices of patients with UTUC over the past several years in the US.
- Although a growing body of evidence suggests that NAC improves survival outcomes in patients with UTUCs, our research suggests the existence of an increased perioperative risk and health cost profile for those who receive NAC.
- Further prospective randomized studies are needed to balance the risk/benefit ratio of NAC in patients with high-risk UTUC.

Abstract

Introduction: New evidence indicates that minimally invasive surgery (MIS) (laparoscopic or robotic-assisted [LNU, RANU]) reaches oncologic equivalence compared with Open Radical Nephroureterectomy (ORNU) for high-risk upper-tract urothelial carcinoma (UTUC). Recently, European Association of Urology (EAU) Guidelines suggested implementing neoadjuvant chemotherapy (NAC) to standard treatment to improve oncologic outcomes of high-risk UTUC. We aimed (**I**) To explore contemporary trends of MIS for RNU in the United

States and to compare perioperative outcomes and costs with that of ORNU. (**II**) To determine the trends of NAC and postoperative intravesical chemotherapy (PIC) administration for high-risk UTUC and to assess their contribution to perioperative outcomes and costs.

Patients and Methods: The Optum Clinformatics® Data Mart de-identified database was queried from 2003 to 2018 to retrospectively examine patients who had undergone LNU/RANU or ORNU with or without NAC and PIC. We evaluated temporal adoption trends, complications, and health care cost analyses. We obtained descriptive statistics and utilized multivariable regression modeling to assess outcomes.

Results: A total of n=492 ORNU and n=1618 LNU/RANU procedures were reviewed. The MIS approach was associated with a statistically significant lower risk of intraoperative complications (adjusted Odds Ratio [aOR], 0.48, 95%CI:0.24–0.96), risk of hospitalization costs (aOR: 0.62, 95%CI:0.49–0.78), and shorter hospital stay (aOR: 0.20, 95%CI:0.15–0.26) when compared to ORNU. Overall, adoption of NAC and PIC accounted for only n=81 and n<37 cases respectively. The implementation of NAC and higher number of cycles were associated with an increased probability of any complication rate (aOR: 2.06, 95%CI:1.26–3.36) and hospital costs (aOR: 2.12, 95%CI:1.33–3.38).

Conclusion: MIS has become the approach of choice for RNU in the US. Although recommended by guidelines, neither NAC nor post-operative bladder instillation of chemotherapy has been routinely incorporated into the clinical practice of patients with UTUC.

Keywords: UTUC; minimally invasive nephroureterectomy; neoadjuvant systemic chemotherapy; intravesical chemotherapy; perioperative outcomes; health care cost.

Abbreviations:

AUA	American Association of Urology
EAU	European Association of Urology
ORNU	Open radical nephroureterectomy
LNU	laparoscopic-assisted nephroureterectomy
UTUC	Upper-tract urothelial carcinoma
NAC	Neoadjuvant chemotherapy
MIBC	Muscle-invasive bladder carcinoma
CDM	Optum's Cliniformatics® Data Mart
RNU	Radical nephroureterectomy
MIS	Minimally invasive surgery
OS	Overall survival
AC	Adjuvant chemotherapy
PIC	Postoperative intravesical chemotherapy

Micro-abstract:

Most of the radical interventions have shifted towards more minimally invasive approaches such as laparoscopic or robotic assisted surgeries to treat UTUC. While these paradigm shifts have led to reduction of morbidity and perioperative health-care related costs over the past 15 years, our patient cohort did not receive NAC and PIC.

1.0 Introduction

Upper tract urothelial carcinomas (UTUCs) account for only 5-10% of the overall cases within the broader category of urothelial carcinomas (UCs) [**1**]. Unfortunately, approximately two-thirds of patients who present with UTUCs have invasive disease at diagnosis compared to 15-25% in those with a new bladder cancer diagnosis. According to the American and European Associations of Urology guidelines (AUA, EAU), radical nephroureterectomy (RNU) represents the standard of care for localized UTUC [**2**] with recent trends indicating an increasing predilection for minimally invasive surgical approaches (MIS) when compared with traditional open radical nephroureterectomy (ORNU). Laparoscopic (LNU) and robot-assisted nephroureterectomy (RANU) have similar oncological outcomes with the benefit of shorter postoperative recovery [**3-7**]. Also, level 1 evidence confirms that a single post-operative dose of intravesical chemotherapy (PIC), 2-10 days after surgery should be administered to reduce the risk of bladder tumor recurrence [**8-9**]. In line with evidence indicating improved survival for patients diagnosed with muscle-invasive bladder cancer (MIBC) undergoing NAC, a recent meta-analysis demonstrates that NAC increases rates of pathological downstaging, improves complete response rates, and also improves survival outcomes in UTUC treated with NAC before RNU [**10**]. In absence of randomized control trials, current EAU guidelines suggest performing NAC in cases of muscle-invasive UTUC in order to improve short- and long-term oncologic outcomes. Thus, the objective of our study was to examine the utilization of MIS for RNU in the United States between 2003 and 2018 and to compare the in-hospital outcomes and costs between ORNU vs. MIS-RNU. Also, we sought to report trends of NAC and PIC administration for UTUCs in patients treated with MIS-RNU or ORNU and to model their contribution to perioperative outcomes and health-care related costs.

2.0 Patients and Methods

2.1 Data source

We performed a retrospective cohort analysis using administrative insurance claims data from the Optum Clinformatics® Data Mart (CDM) de-identified database. Optum is a national database from adjudicated and paid insurance claims of privately insured individuals and Medicare coverage which includes 77 million enrollees in the United States. Individuals in the 2020 database represent a geographically and ethnically diverse population from a variety of age groups. The data includes patient demographic characteristics, medical claims including inpatient and outpatient services, facility claims, pharmacy claims, and socio-economic status. All costs were standardized based on Medicare Relative Value Units and other pricing methods adjusting for inflation. International Classification of Disease 9th and 10th revisions, Clinical Modification (ICD-9-CM, ICD-10-CM) codes, Current Procedural Terminology (CPT) codes were used to identify the study cohort, treatments, and co-morbidities. This method has been used in other studies [**11-13**] and given deidentified information, this study was deemed exempt from informed consent requirements by the Stanford University Medical Center Institutional Review Board.

2.2 Patients

Patients who consecutively underwent RNU between 2003 - 2018 with at least at least 6 months of enrollment both before and after the index date were identified by International Classification Diseases, 9th and 10th Revision, Clinical Modification, ICD-9/10-CM and CTP codes in order to create the cohort of interest. Affiliated codes were identified and reviewed to ensure that RNU was the primary procedure performed based on the diagnosis or concern for UTUC which included urothelial neoplasms of the renal pelvis and/or ureter. The first RNU surgery date was set as the index date. Patients age <18 years at the index date, those who underwent major surgeries within 3 months prior to, or with less than 6 months enrollment time before or after the index date were removed from the analyses. Patients receiving either MIS-RNU or ORNU were identified using specific Robot-assisted and Laparoscopic modifiers (17.49x, S2900 and 54.21 respectively) while procedures without these supplies were categorized as ORNU. For each patient, age at surgery, gender, race, level of education, patient's income, region, and year of surgery were considered. Baseline Charlson Comorbidity Index (CCI) was calculated according to Charlson and colleagues [**14**] and adapted according to Deyo and colleagues [**15**]. Patient insurance status was grouped as Medicare or Medicaid. A comprehensive list of ICD-9/10 and CPT codes and a flow chart diagram summarizing the analytical steps for the data analysis and inclusion/exclusion criteria are presented in Supplementary Tables 1a and 1b, respectively.

2.3 Outcome Ascertainment

The primary outcome of the study was to ascertain trends in utilization of MIS-RNU vs. ORNU and the comparison in terms of perioperative outcomes and health care costs. The secondary outcome of interest was the trend in use of NAC and/or PIC and their contribution on perioperative complications, resource use, and direct hospital costs. ICD-9/10 and CPT codes were used to identify the surgical approach adopted as well as the systemic and/or intravesical chemotherapy drugs administered. Date of surgery was considered as the index date in order to describe temporal trends in the approach adoption and to identify type and timing for NAC or PIC schedules. Patients who received NAC before RNU were searched and subsequently included if they underwent appropriate intravenous systemic regimens within a 6-months before the index date (Supplementary table **2**). The number of NAC cycles was then manually recorded for each eligible participant and further analyzed. The use of adjuvant PIC was searched through the database up to 72 hours following the index date (Supplementary table **1b** and **2**).

Additionally, we recorded specific ICD-9/10 complications (Supplementary table **3**) that occurred both intraoperatively and/or within 90 days after the index date. We defined length of stay as the median length of hospitalization observed in the ORNU and MIS subgroups respectively. A higher cost and longer hospitalization were defined using the 75th percentile hospital costs in the entire population and the median number of days of hospitalization after index date respectively. Total hospitalization costs were estimated from the total standard cost on patient cost burdens and adjusted to 2019 U.S. dollars.

2.4 Statistical analysis

Patient demographics, clinical, and hospital characteristics for those who underwent RNU with MIS-RNU or ORNU were compared by chi-square test for categorical variables, Student's t-test for age, and Wilcoxon rank-sum test for other continuous variables. As per primary outcome, a logistic regression model was applied to explore the multivariable adjusted influence for the adoption of MIS-RNU over ORNU and the effect of administration of NAC in terms of intraoperative and/or postoperative surgical complications, higher costs, and longer hospital stay. All analyses were adjusted per CCI (< 3 vs. ≥ 3), age, gender, and obesity. Prediction probability plots were generated by logistic regressions in order to explore the relative influence of greater exposure to NAC cycles before RNU. To eliminate possible confounding effects, we performed propensity score matching to match one patient with NAC before RNU to ten patients without on age, gender, obesity, and CCI, and applied conditional logistic regression to matched cohort as a sensitivity analysis. All tests were two-sided with $p < 0.05$ considered as significant. All analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

3.0 Results

3.1 Study cohort

A cohort of 2,110 patients with a mean age of 70.4 (std 10.6) were treated with elective LRNU/RANU (n= 1,618, 76.7%) or ORNU (n= 492, 23.3%) for the management of UTUC between 2003 and 2018. Out of these, only 81 (3.8%) and less than <37 (<1.8%) patients received NAC and/or PIC, respectively. Table **1** shows baseline patient clinical, demographic, and hospital characteristics of our final cohort. Figure **1** depicts the trend in surgical approach for RNU over time (**1a**) and the relative percentages of MIS vs. ORNU by single year (**1b**). The median post-operative follow-up was 1.99 (1.00 - 4.14) and 2.07 (1.01 - 4.21) years for ORNU and MIS, respectively (Table 1). MIS's for RNU dramatically increased from 1.4% to 11.0% (p< 0.001) starting from 2007, while the level of ORNU procedures plateaued with a non-significant increase over the study period (P for trend= 0.08). Patients were equally distributed in terms of surgical approach with regard to age (p=0.88), gender (p= 0.53), ethnicity (p= 0.76), US-region (p= 0.08), as well as education and type of insurance (p=0.41 and p=0.72, respectively). Patients with cardiovascular disease and obesity had higher rates of receipt of ORNU (p= 0.04) and MIS-RNU (p=0.02), respectively. No further differences were observed between the cohorts in terms of comorbidities and overall CCI. Finally, patients in the MIS group had both lower median hospital costs (median $25,486, IQR: $16,522$ - $31,266 vs. median $27,004, IQR: $12,162 - $34,736; p=0.03) and shorter hospital stay (median 4, IQR: 3 – 6 vs. median 6, IQR: 4 – 8 days; p<0.001). There were no statistically significant differences between the number of cases of NAC or PIC between the two cohorts nor in terms of number of NAC cycles administered, which was in line with the standard of care, with a median of 3 (IQR 2 – 4).

3.2 Outcomes

Our multivariable regression analysis demonstrated that the adoption of the MIS-RNU approach was associated with reduced risk for any type of complication (OR, 0.57, 95%CI: 0.44 - 0.72). In particular, LRNU/RANU was widely associated with an almost greater than two-fold lower risk of developing intraoperative complications (0.48, 0.24 - 0.96) and 3-month postoperative sequalae including GI tract (OR, 0.65, 95%CI: 0.43 - 0.99), hemorrhagic (OR, 0.47, 95%CI: 0.24 - 0.91), infectious (OR, 0.42, 95%CI: 0.23 - 0.76), and wound-related (OR, 0.36, 95%CI: 0.20 - 0.66) complications. Additionally, MIS-RNU was found to be significantly associated with shorter hospitalization (OR, 0.20, 95%CI: 0.15 - 0.26) and lower total hospital costs (OR, 0.62, 95%CI: 0.49 - 0.78). Table **2** provides a summary of estimates.

In our secondary outcome, we explored the multivariable adjusted effect of NAC administration for similar endpoints (Table **3**). Patients treated with NAC before RNU regardless of the surgical approach were associated with a higher risk of postoperative complications (OR, 2.06, 95%CI: 1.26 - 3.36), particularly for postoperative blood transfusions (OR, 2.64, 95%CI: 1.40 - 4.99). Similarly, the risk was increased with regard to total hospital costs in the NAC group (OR, 2.12, 95%CI: 1.33 - 3.38), but not for longer length of hospital stay (OR, 1.58, 95%CI: 0.94 - 2.64). The predicted probabilities of increasing number of NAC cycles and the significant outcomes of interest are graphically depicted in Figure **2**. Of note, a higher number of NAC cycles were associated with increased probability of higher hospital cost and longer hospital stay, while its effect was relatively less significant on the probability of developing any postoperative complications or the need for blood transfusions. Further sensitivity analysis using propensity score matching for assessing the influence of overall number of NAC cycles on perioperative outcomes by conditional logistic regression confirmed an increasing number of NAC cycles was independently associated with the increase in median hospital costs (OR, 1.19, 95%CI: 1.04 - 1.36) with no other relevant interaction with specific complications (Supplementary Table 4). Finally, not enough data was available to perform logistic regression analysis with regard of PIC other than descriptive statistics.

4.0 Discussion

Our findings corroborate that over the last 16 years in the US, there has been increasing adoption of MIS techniques to treat UTUC. We also confirm that the performance of MIS techniques was associated with improved perioperative outcomes with decreased risks of bleeding, post-operative ileus, and infectious complications.

Although there were initial concerns regarding the oncologic outcomes for MIS-RNU, the most current data suggests that the oncological outcomes of MIS-RNU and open RNU are equivalent [**16**]. In our study, an additional benefit of the MIS approach is a shorter hospital stay and lower overall costs. While similar data has been reported in several smaller retrospective cohort studies [**17-18**], our analysis has increased generalizability given our large, population-based dataset.

Our analysis also uncovered the underutilization of PIC following RNU. AUA and EAU guidelines strongly advise providing PIC in this setting to lower the rate of intravesical recurrence, based on Level 1 evidence [**3; 19**]. As the EAU guidelines have recommended PIC since 2011, the reasons as to the low rates of adherence are not clear, but they do preclude us from elaborating as to the ramifications of PIC in this cohort of patients. Our PIC cohort was chosen to allow for the greatest accuracy in capturing a representative cohort, so as not to allow for inaccuracies based on difficulty capturing those patients who undergo PIC in the outpatient setting.

Recently, an update to the 2020 UTUC EAU guidelines introduced the increasingly popular concept of platinum-based NAC before RNU in cases of higher-risk or muscle-invasive disease. So far, the data supporting this are limited and retrospective. Nevertheless, in a meta-analysis from Kim et al [**20**], the author demonstrates that NAC may also improve outcomes compared to no perioperative treatment by promoting pathological downstaging and resulting in longer OS. This seems particularly appropriate for the vast majority of UTUC candidates undergoing RNU who are commonly found to have invasive disease at diagnosis. Also, as NAC treatment is offered with maximal functional kidney status prior to RNU, there are benefits in NAC to avoid suboptimal platinum chemotherapy regimens post RNU, as these agents undergo renal clearance.

In our cohort, only 3.8% of the subjects received NAC, which reflects the lack of adherence. This very low number is discordant as to what is being recently reported from other experiences in other countries. Japanese data from Hamaya et al [**21**], reported a significantly increased use of NAC for high-risk UTUC after 2010 from a baseline of 19% (2006–2010), to 58% from 2011–2015, and to 79% from 2016–2020.

Also, we were able to model NAC influence in relation to perioperative outcomes which in the future should be evaluated in the patient- and tumor-related decision-making process. In particular, the administration of NAC was clearly associated with a more than 2-fold increased risk of postoperative transfusions and in developing any complication regardless of severity. In addition, the entire hospital cost in relation to the RNU procedure was significantly more expensive compared to those without NAC. Although at first glance, these findings may seem to cast a negative light on NAC for UTUC, one must realize that the likely benefits in survival and quality of life created by NAC in this setting cannot be measured by our study. To interpolate to the parallel setting of MIBC, NAC regimens are well established and NAC treatment before a planned radical cystectomy has shown to be a cost-effective measure to both extend and improve quality of life. Stevenson et al [22] demonstrated that the use of NAC for MIBC was associated with an improvement in Quality Adjusted Life Years (QALY) of approximately $6,000. Additionally, from a patient-based perspective, in our analysis, increasing the total number of NAC cycles was not associated with higher complications or probability of transfusions. From a hospital related standpoint, there was an increased likelihood of higher costs and longer hospital stay. This seems particularly timely given that recently Zennami et al [**23**] showed only 2 cycles of NAC were able to guarantee better 5-years OS and CSS thus identifying a baseline dose-density threshold able to provide the desired survival benefit. All these considerations should be properly assessed on a case-by-case basis.

Our study is not without limitations. First the dataset is administrative in nature, which relies on accurate coding of diagnoses and procedures. Additionally, procedures done prior to access to insurance and entry into the database may not have been captured. In addition, in keeping with the administrative nature of the dataset, no staging, or pathological information from RNU procedures were available, which could limit our ability to assess the indication for NAC before surgery and oncological outcomes.

5.0 Conclusion

In the US, MIS-RNU has become the option of choice in providing significant morbidity and health related advantages compared to ORNU. According to EAU UTUC Guidelines, even if PIC is recommended and NAC is suggested, neither NAC nor PIC have been routinely incorporated into clinical practices of patients with UTUC over the past several years in the US. Although a growing body of evidence suggests that NAC improves survival outcomes in patients with UTUCs, our research suggests the existence of an increased perioperative risk and health cost profile for those who receive NAC. As such, further prospective randomized studies are needed to balance the risk/benefit ratio of NAC in patients with high-risk UTUC.

6.0 Credit Author Statement:

Francesco Del Giudice: Protocol/project development, Data collection or management, Manuscript writing/editing, Data analysis.
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Shufeng Li: Data collection or management, Data analysis.

Fernandino Vilson: Manuscript writing/editing

Alessandro Sciarra: Supervision, Manuscript writing/editing

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Declaration of Competing Interest
Authors have no conflict of interest to disclose.

Relevant Disclosures
Authors have nothing to disclose.

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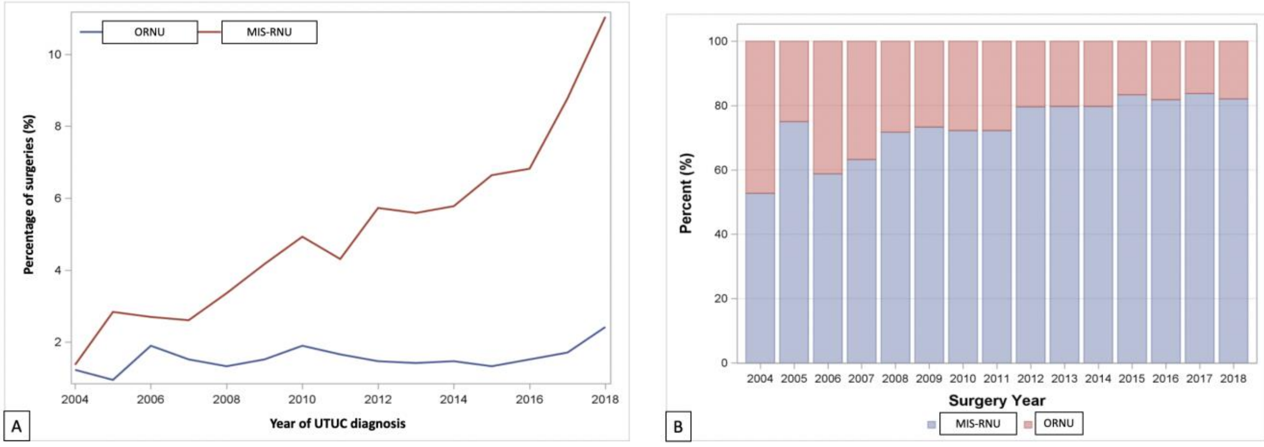

Year	ORNU	MIS-RNU	% ORNU*	% MIS-RNU*
2004	26 (5.28)	29 (1.79)	1.23	1.37
2005	20 (4.07)	60 (3.71)	0.95	2.84
2006	40 (8.13)	57 (3.52)	1.9	2.7
2007	32 (6.5)	55 (3.4)	1.52	2.61
2008	28 (5.69)	71 (4.39)	1.33	3.36
2009	32 (6.5)	88 (5.44)	1.52	4.17
2010	40 (8.13)	104 (6.43)	1.9	4.93
2011	35 (7.11)	91 (5.62)	1.66	4.31
2012	31 (6.3)	121 (7.48)	1.47	5.73
2013	30 (6.1)	118 (7.29)	1.42	5.59
2014	31 (6.3)	122 (7.54)	1.47	5.78
2015	28 (5.69)	140 (8.65)	1.33	6.64
2016	32 (6.5)	144 (8.9)	1.52	6.82
2017	36 (7.32)	185 (11.43)	1.71	8.77
2018	51 (10.37)	233 (14.4)	2.42	11.04

*The denominator is 2110, total number of surgeries of all years

Figure 1. Trend in surgical approach for RNU over time (1**a**) and the relative percentages of MIS vs. ORNU by single year (1**b**). **UTUC**: upper tract urothelial carcinoma; **ORNU**: open radical nephroureterectomy; **MIS-RNU**: minimally invasive radical nephroureterectomy.

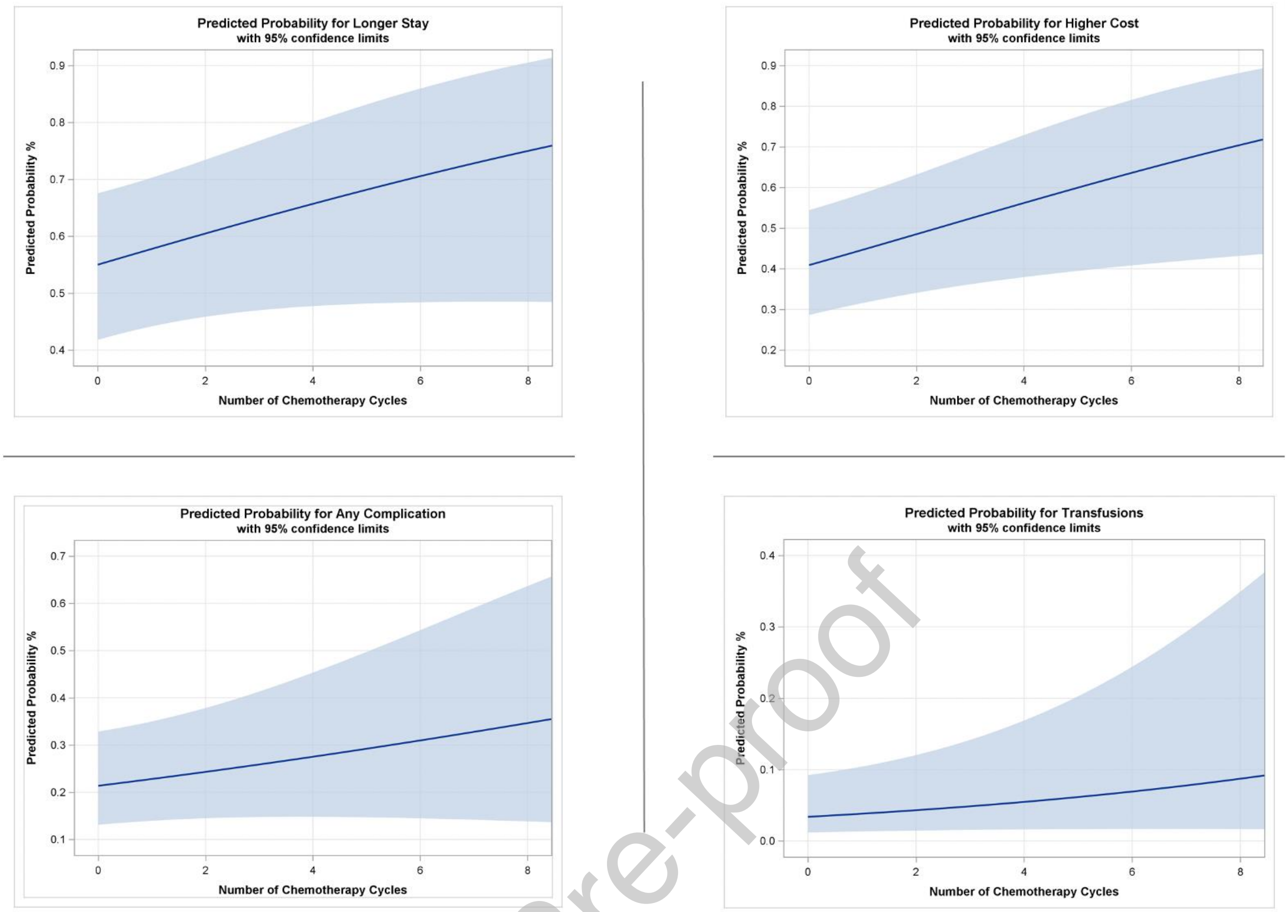

Figure 2. Prediction probability plots generated by logistic regressions exploring the relative influence of greater exposure to neoadjuvant chemotherapy (NAC) cycles and the risk for higher hospital stay (**a**), higher overall hospital cost (**b**), any complication development (**c**) and higher risk for postoperative transfusion (**d**).

Table 1. Baseline demographic, perioperative and clinical characteristics of the final cohort of study.

	ORNU n=492 (23.3%)	**MIS-RNU** n=1618 (76.7%)	**P value***
Age, mean (SD)	70.55 (9.99)	70.40 (10.82)	0.89
Pre-surgery time, year, median (IQR)	3.36 (1.58 - 5.71)	3.73 (1.84 - 6.95)	0.08
Post-surgery follow-up, year, median (IQR)	1.99 (1.00 - 4.14)	2.07 (1.10 - 4.21)	0.48
Total cost, $, median (IQR)	27,004 (12,162 - 34,736)	25,486 (16,522 - 31,266)	**0.036**
LOS, days, median (IQR)	6 (4 - 8)	4 (3 - 6)	**<0.0001**
Gender, n (%)			0.53
Female	192 (39.02)	657 (40.61)	
Male	300 (60.98)	961 (59.39)	
Insurance, n (%)			0.72
Commercial	169 (34.35)	570 (35.23)	
Medicare	323 (65.65)	1048 (64.77)	
Region, n (%)			0.09
Mid-west	135 (27.44)	415 (25.65)	
Northeast	54 (10.98)	257 (15.88)	

South	206 (41.87)	654 (40.42)	
West	97 (19.72)	290 (17.92)	
Education, n (%)			0.41
Less than 12th Grade	<11	<11	
High School Diploma	139 (28.25)	412 (25.46)	
Less than bachelor's degree	249 (50.61)	873 (53.96)	
Bachelor's degree Plus	63 (12.8)	223 (13.78)	
Unknown	30+	100+	
Race, n (%)			0.77
Asian	<11	42 (2.60)	
Black	36 (7.32)	125 (7.73)	
Hispanic	30+ (6.1+)	119 (7.35)	
Unknown	48 (9.76)	150 (9.27)	
White	368 (74.80)	1182 (73.05)	
Comorbidity, n (%)			
HTN hypertension	402 (81.70)	1312 (81.09)	0.76
Diabetes	160 (32.52)	574 (35.48)	0.23

Obesity	83 (16.87)	347 (21.45)	**0.027**
Ischemic Heart Disease	205 (41.67)	594 (36.71)	**0.047**
Cancer	473 (96.14)	1564 (96.66)	0.58
ACCI, n (%)			0.84
0	24 (4.88)	94 (5.81)	
1	28 (5.69)	96 (5.93)	
2	80 (16.26)	248 (15.33)	
≥3	360 (73.17)	1180 (72.93)	
NAC, n (%)	26 (5.28)	55 (3.40)	0.057
NAC cycles, median (IQR)	4 (3 - 4)	3 (2 - 4)	0.40

ORNU: open radical nephroureterectomy; **MIS-RNU**: minimally invasive radical nephroureterectomy; **IQR**: interquartile range; **n:** number; **LOS**: length of hospital stay; **ACCI**: age-adjusted charlson comorbidity index; **NAC**: neoadjuvant chemotherapy; **PIC**: postoperative intravesical instillation

*P values according to Wilcoxon rank-sum test or to Chi-square test when appropriate.

Table **2.** Multivariable adjusted logistic regression model assessing intra- and 30-days postoperative complication and perioperative outcomes according to surgical approach (i.e., ORNU serving as reference).

Outcome assessed	**ORNU**	**MIS-RNU**	**P value***	**Adjusted****
Intraoperative, n (%)	13 (2.64)	21 (1.30)	**0.0381**	0.48 (0.24 - 0.96)
Urinary, n (%)	<11	18 (1.11)	0.8446	0.93 (0.37 - 2.37)
Digestive, n (%)	34 (6.91)	73 (4.51)	**0.0337**	0.65 (0.43 - 0.99)
Respiratory, n (%)	<11	22 (1.36)	0.6622	0.85 (0.37 - 1.92)
Hemorrhagic, n (%)	15 (3.05)	24 (1.48)	**0.024**	0.47 (0.24 - 0.91)
Cardiac, n (%)	<11	20 (1.24)	0.4384	1.55 (0.53 - 4.59)
Infectious, n (%)	19 (3.86)	26 (1.61)	**0.0024**	0.42 (0.23 - 0.76)
Vascular, n (%)	<11	0	0.2332	N/A
Seromas, n (%)	<11	<11	0.1376	0.16 (0.02 - 1.78)
Wound, n (%)	20 (4.07)	25 (1.55)	**0.0007**	0.36 (0.20 - 0.66)
Others, n (%)	0	<11	1	N/A
Transfusions, n (%)	46 (9.35)	96 (5.78)	**0.0081**	0.62 (0.43 - 0.90)
Any complication, n %)	125 (25.41)	258 (15.95)	**<0.0001**	0.57 (0.44 - 0.72)

Higher cost, ≥ 75th Percentile	157 (31.91)	370 (22.87)	**<0.0001**	0.62 (0.49 - 0.78)
Longer Hospital stay, ≥ median value	418 (85.31)	868 (53.68)	**<0.0001**	0.20 (0.15 - 0.26)

ORNU: open radical nephroureterectomy; **MIS-RNU**: minimally invasive radical nephroureterectomy; **ACCI**: age-adjusted Charlson comorbidity index; **NAC**: neoadjuvant chemotherapy

*****By Chi-square test
******Adjusted by ACCI, Gender, Obesity, NAC

Table **3**. Multivariable adjusted regression assessing the impact of neoadjuvant chemotherapy (NAC) for RNU on intra-, 30-days postoperative complication and perioperative outcomes. **ORNU**: open radical nephroureterectomy; **MIS-RNU**: minimally invasive radical nephroureterectomy; **ACCI**: age-adjusted Charlson comorbidity index; **NAC**: neoadjuvant chemotherapy.

Outcome assessed	ORNU	MIS-RNU	P value*	Adjusted**
Intraoperative, n (%)	13 (2.64)	21 (1.30)	**0.0381**	0.73 (0.10 - 5.49)
Urinary, n (%)	<11	18 (1.11)	0.8446	1.01 (0.13 - 7.68)
Digestive, n (%)	34 (6.91)	73 (4.51)	**0.0337**	1.59 (0.67 - 3.81)
Respiratory, n (%)	<11	22 (1.36)	0.6622	0.81 (0.11 - 6.08)
Hemorrhagic, n (%)	15 (3.05)	24 (1.48)	**0.024**	1.10 (0.26 - 4.74)
Cardiac, n (%)	<11	20 (1.24)	0.4384	2.24 (0.51 - 9.89)
Infectious, n (%)	19 (3.86)	26 (1.61)	**0.0024**	1.07 (0.25 - 4.60)
Vascular, n (%)	<11	0	0.2332	N/A
Seromas, n (%)	<11	<11	0.1376	N/A
Wound, n (%)	20 (4.07)	25 (1.55)	**0.0007**	2.05 (0.70 - 6.02)
Others, n (%)	0	<11	1	N/A
Transfusions, n (%)	46 (9.35)	96 (5.78)	**0.0081**	2.64 (1.40 - 4.99)
Any complication, n %)	125 (25.41)	258 (15.95)	**<0.0001**	2.06 (1.26 - 3.36)

Higher cost, ≥ 75th Percentile	157 (31.91)	370 (22.87)	**<0.0001**	2.12 (1.33 - 3.38)
Longer Hospital stay, ≥ median value	418 (85.31)	868 (53.68)	**<0.0001**	1.58 (0.94 - 2.64)

***** By Chi-square test
****** Adjusted by ACCI, Gender, Obesity and Surgical Approach