Perioperative outcomes and complication predictors associated with open and minimally invasive nephroureterectomy

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Introduction: Minimally invasive nephroureterectomy (MINU) and open nephroureterectomy (ONU) have similar oncological outcomes for treatment of upper tract urothelial carcinoma (UTUC). We investigated perioperative outcomes and predictors of complications associated with MINU and ONU.
Material and methods: Using the National Surgical Quality Improvement Program (NSQIP) database, 912 patients were identified that underwent radical nephroureterectomy for UTUC between 2005 and 2013. Logistic regression and contingency table methods used preoperative covariates to predict rates of major (Clavien-Dindo grade ≥ 3) and 16 common perioperative complications. Additional comparisons between treatment groups were performed using unpaired t-tests, Wilcoxon rank-sum tests, or Fisher's Exact tests. P values were adjusted to maintain an experiment-wise $p < 0.05$.
Results: A total of 625 (69%) and 287 (31%) patients underwent MINU and ONU, respectively. ONU was associated with a higher rate of major complications (OR: 2.5, CI: 1.2-5.1, $p < 0.03$). The incidence of pulmonary embolism (bias adjusted OR: 24, CI: 1.3-441, $p < 0.003$), postoperative pneumonia (OR: 4.9, CI: 1.7-16, $p < 0.0016$), and transfusion (OR: 2.7, CI: 1.8-4.0, $p < 0.0001$) was higher for ONU compared to MINU. There were no significant differences in the incidence of other complications. MINU took longer on average (median 223 versus 213 mins, $p < 0.02$). Time to discharge was longer for ONU (median 5 versus 4 days, $p < 0.0001$). No other covariates were independent predictors of major complications regardless of surgical approach.
Conclusions: Occurrence of major complications were higher for ONU compared to MINU. These data suggest that MINU is an acceptable surgical option with lower morbidity compared to ONU for the management of UTUC.

Key Words: minimally invasive surgery, NSQIP, upper tract urothelial carcinoma, complications, nephroureterectomy

Introduction

An increasing number of radical nephroureterectomies (RNUs) are being performed using minimally invasive techniques. Studies have demonstrated equivalent

oncological outcomes between open nephroureterectomy (ONU) and minimally invasive nephroureterectomy (MINU) with a reduction in pulmonary, thromboembolic, and transfusion related complications in the MINU group.[1] However, most studies are retrospective, single center reports, and consist of relatively small sample sizes.[1]

Subjectivity in describing the severity of symptoms and lack of a consensus related to classification of postoperative surgical complications limits comparisons among surgical procedures. The Clavien-Dindo system is a validated, reproducible method of classifying surgical complications in order to compare surgical outcomes.[2] Major (Clavien-Dindo ≥ 3) complications require some form of intervention and are the most relevant in clinical practice.

We investigated perioperative outcomes and predictors of complications associated with ONU and MINU using the National Surgical Quality Improvement Program (NSQIP) database. Application of Clavien-Dindo classification to the NSQIP database affords the opportunity to report overall and major complications in a standardized manner.

Materials and methods

Database source

The NSQIP database is a risk-adjusted, 30 day postoperative outcomes-based quality initiative maintained by the American College of Surgeons, which holds information on nearly three million hospitalizations from more than 500 sites. Randomly selected patient samples from each site are collected from medical records and software-based checks are incorporated for maintaining data quality. The program, whose goal is to improve the quality of patient care by identifying factors affecting optimum care, is voluntary and designed to help hospitals reduce surgical morbidity and mortality.

Patient selection

A total of 912 patients who underwent RNU for UTUC between 2005 and 2013 were identified using the American Medical Association's Common Procedural Terminology (CPT) codes representing the primary surgical approach (i.e., 50546 or 50548 for MINU, and 50220, 50225, 50230, 50234, or 50236 for ONU). Localization of the primary tumor site was determined using the International Statistical Classification of Diseases and Related Health Problems version 9 (ICD-9) codes: 189.1 (renal pelvis/ureteropelvic junction), 189.2 (ureter/excluding ureteric orifice). RNU for reasons unrelated to this study were excluded using ICD-9 codes (e.g., 189.0, malignant neoplasm of kidney, except pelvis; 236.91, neoplasm of uncertain behavior of kidney and ureter; 753.20, unspecified obstructive defect of renal pelvis and ureter; 753.29, other obstructive defects of renal pelvis and ureter). Thirty day postoperative complications were classified using a modified Clavien-Dindo classification scheme, Table 1.

Statistical considerations

All data were examined using numeric and graphical exploratory data analysis methods. Comparisons between treatment groups on demographic and comorbid conditions were performed using unpaired t-tests, Wilcoxon rank-sum tests, or Fisher's exact tests

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TABLE 1. **Description of Clavien-Dindo complications and related covariates in the NSQIP database**

Grade	Type	Complications
Grade 1	Any deviation from normal course, not requiring pharmacological treatment or surgical, endoscopic and radiological interventions	Superficial surgical site infection, on ventilator > 48 hours, progressive renal insufficiency, DVT requiring therapy
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications	Deep and organ space infection, pneumonia, urinary tract infections, transfusions, sepsis, and pulmonary embolism
Grade 3	Requiring surgical, endoscopic or radiological intervention	Return to operating room for any complication
Grade 4	Life-threatening complication (including CNS complications) requiring IC/ICU-management	Acute renal failure, stroke, cardiac arrest, septic shock
Grade 5	Death	Death within 30 days of surgery

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where appropriate. Contingency table and logistic regression methods were used to describe rates of risk factors and their association with occurrence of complications. Univariate (unadjusted) and multivariate logistic regression models (adjusted for age, race, ethnicity, body mass index (BMI), smoking habits, functional status, hypertension, diabetes, and COPD) were built. Odds ratios with exact 95% confidence limits are reported. In cases where odds ratios were undefined because of zero events, we used the +.5 adjustment suggested by Fleiss et al.[3] For a prior defined primary outcome (presence of a grade ≥ 3 Clavien-Dindo complication) a p value < 0.05 was considered statistically significant. To control for potential type 1 error in the 16 complications examined, a Sidak adjusted p value of .05 was considered statistically significant. Analyses were performed using SAS 9.4 (SAS institute, NC, USA).

Results

Out of 912 patients identified, 625 (69%) underwent MINU and 287 (31%) underwent ONU for UTUC. Demographics of the study population stratified by surgical approach are shown in Table 2. Patients in the MINU group were older than patients in the ONU group with a mean age of 72 years compared to 70 years (p < 0.01), respectively. Approximately 12% of the subjects had unknown race. Using the entire sample, or only the subjects with known race, no statistically significant difference in races was observed between the two surgical methods. The majority of the study population was Caucasian (81%), followed by African-American (3.1%), and other races (3.8%). The ONU group demonstrated a higher rate of pre-procedure weight loss (4%) compared to MINU (1%, p < 0.005). No other clinically or statistically significant differences in comorbidities were observed between the two groups.

The overall incidence of complications in the entire cohort was 15.9%. In the ONU group, 22% of patients had a complication compared to 13% of patients in the MINU group (OR: 1.8, CI: 1.2-2.6, p < 0.002). The unadjusted odds of 30 day perioperative complications for the two treatment groups are shown in Table 3. There was a statistically significant increased risk of pulmonary embolism (bias-adjusted OR: 24, CI: 1.3-441, p < 0.003), postoperative pneumonia (OR: 4.9, CI: 1.7-16, p < 0.0016), and transfusion (OR: 2.7, CI: 1.8-4.0, p < 0.0001) for ONU compared to MINU after adjusting for repeated measures. Although operative time was greater for MINU compared to ONU (median 223 versus 213 mins, p < 0.02), length of stay was shorter for MINU compared to ONU (median 4 versus 5 days p < 0.0001).

TABLE 2. Demographics of 912 patients undergoing radical nephroureterectomy

Variables	MINU n (%)	ONU n (%)	p value
N	625	287	
Age (mean ± SD)	72 ± 9.8	71 ± 10	0.01
Race[†]			0.47
Caucasian	522 (93)	219 (91)	
African-American	18 (3)	10 (4)	
Others	22 (4)	13 (5)	
Hispanic	19 (3)	10 (4)	0.68
Body mass index (mean ± SD)	28 ± 5.2	28 ± 6	0.16
Smoker	148 (24)	84 (29)	0.09
Weight loss	7 (1)	12 (4)	0.005
Functional status			
Partially dependent	10 (2)	5 (2)	1
Hypertension (requiring medication)	429 (69)	206 (72)	0.35
Diabetes	120 (19)	59 (21)	0.65
COPD	50 (8)	24 (8)	0.9

[†]percentages may not add up to 100% due to missing data
MINU = minimally invasive nephroureterectomy; ONU = open nephroureterectomy; COPD = chronic obstructive pulmonary disease

TABLE 3. **Unadjusted relative odds of 30 day perioperative complications associated with ONU (n = 625) relative to MINU (n = 287) for patients undergoing radical nephroureterectomy**

Complication	MINU n (%)	ONU n (%)	OR	Exact 95% CI	Fisher's exact p value
Pulmonary embolism	0 (0)	5 (1.7)	24**	1.3-441**	0.003*
Cardiac arrest requiring CPR	2 (0.32)	5 (1.7)	5.5	0.9-58	0.03
Pneumonia	6 (0.96)	13 (4.5)	4.9	1.7-16	0.0016*
Septic shock	3 (0.48)	4 (1.4)	2.9	0.49-20	0.21
Surgical site infection	10 (1.6)	13 (4.5)	2.9	1.2-7.5	0.01
Bleeding requiring transfusion	56 (9.0)	60 (21)	2.7	1.8-4.0	0.0001*
Acute renal failure	4 (0.64)	5 (1.7)	2.7	0.59-14	0.15
Sepsis	8 (1.2)	9 (3.1)	2.5	0.84-7.5	0.07
Deep vein thrombosis	8 (1.2)	6 (2.1)	1.6	0.47-5.5	0.39
Ventilator (> 48 hours)	6 (1.0)	4 (1.4)	1.5	0.30-6.2	0.52
Unplanned intubation	9 (1.4)	6 (2.1)	1.5	0.42-4.6	0.58
Urinary tract infection	26 (4.2)	12 (4.2)	1.0	0.46-2.1	1
Progressive renal insufficiency	9 (1.4)	3 (1.0)	0.72	0.12-2.9	0.76
Wound disruption	3 (0.48)	1 (0.35)	0.72	0.01-9.1	1
Stroke with neurological deficit	5 (3.0)	1 (0.35)	0.43	0.001-3.9	0.67
Myocardial infarction	8 (1.28)	0 (0)	0.13	0.01-2.2**	0.06

*values statistically significant after adjusting for multiple comparisons using Sidak method
**values using Fleis' +.5 adjustment for zero cell frequency and asymptotic confidence limits
MINU = minimally invasive nephroureterectomy; ONU = open nephroureterectomy

A multivariate logistic regression model predicting Clavien-Dindo ≥ 3 complications with surgical approach adjusting for baseline characteristics is summarized in Table 4. The incidence of Clavien-Dindo ≥ 3 complications was 6.4%. In the ONU group, 10% of patients experienced a major complication compared to 4.8% of patients for MINU (OR: 2.1, CI: 1.2-3.7, p < 0.004). Hypertension was associated with an increased risk of complications (OR: 2.5, CI: 1.0-6.0, p < 0.04). No other covariates demonstrated statistical significance in the predictive model.

Discussion

We investigated whether surgical approach (ONU versus MINU) and baseline comorbidities had a significant impact on 30 day postoperative complications. Overall complications were higher for patients who underwent ONU compared to MINU in multivariate analysis. Moreover, 30 day postoperative occurrence of pneumonia, bleeding requiring transfusions, cardiac arrest requiring CPR, and pulmonary embolism were higher for ONU compared to MINU.

In general, our findings are in agreement with what has been reported in previous studies. Hanna et al reported decreased blood transfusions and length of stay for MINU compared to ONU in an analysis of patients from the National Inpatient Sample (NIS) database.[4] Sugihara et al reported that postoperative complications, frequency of transfusions, and length of stay were more favorable for MINU compared to ONU in a large Japanese cohort of patients.[5] Furthermore, Hanske et al showed that rate of blood transfusions, length of stay, and thromboembolic events were lower for MINU compared to ONU in 896 patients from the NSQIP database.[6] In a comprehensive review of outcomes related to ONU and MINU, Rai et al reported that MINU was associated with significantly less blood loss and mean time to discharge compared to ONU.[1] A population-based analysis by Tinay et al showed that operative time was higher in the MINU group with no difference in complication rates. However, length of hospital stay was significantly lower in for MINU compared to ONU.[7]

The main limitations of our study are related to the data source. ACS NSQIP is a surgical procedure-

TABLE 4. **Multivariate predictors of major complications (Clavien-Dindo grade ≥ 3) in patients undergoing radical nephroureterectomy**

Effect	OR	95% Wald confidence interval	p value
Approach			
MINU	1.0		
ONU	2.0	1.1-3.8	0.02
Age			0.99
< 50	1.0		
50-59	0.60	0.05-7.3	0.69
60-69	0.79	0.09-6.8	0.83
70-79	0.87	0.10-7.3	0.90
80-89	0.88	0.1-7.8	0.91
Race			
Caucasian	1.0		
African-American	1.1	0.25-5.2	0.87
Hispanic	0.97	0.21-4.6	0.97
Smoking	0.68	0.30-1.5	0.35
BMI (≥ 25)	0.52	0.26-1.0	0.05
Weight loss	0.83	0.10-6.9	0.87
Functional status			
Independent			
Partially dependent	4.1	0.95-17.6	0.06
Hypertension	2.5	1.0-6.0	0.04
Diabetes	1.2	0.58-2.4	0.66
COPD	2.0	0.76-5.0	0.16

MINU = minimally invasive nephroureterectomy; ONU = open nephroureterectomy; BMI = body mass index; COPD = chronic obstructive pulmonary disease

outcome database mainly intended to identify and decrease surgery-related complications, with negligible data on cancer characteristics such as grade and clinical staging of disease. This limits our capability to categorize patients based on severity of presentation. Additionally, NSQIP participation is voluntary and it may not represent all of the health care facilities across the nation.

Our study is the first to report an increased incidence of PE with ONU compared to MINU. The rarity of this complication likely explains the lack of it being previously reported. It appears that ONU is associated with more complications compared to MINU, but the exact effect size remains unknown. This finding may be validated using other large databases. Whereas earlier studies have not used standardized metrics to determine complications, this is the first study to examine complication rates between ONU and MINU using Clavien-Dindo classification. Use

of Clavien-Dindo ontology affords the opportunity to examine complications on a scale that has not been previously reported with NSQIP. Analysis of large datasets also allows multivariate modeling, such as we have performed, to control for confounding demographic and disease features. Our work is a first step toward building models that may be used for risk stratification, patient counseling, and intervention.

Conclusion

The incidence of pulmonary embolism, pneumonia, and transfusions was higher for ONU compared to MINU. These data suggest that MINU is an acceptable surgical option for management of UTUC and is associated with lower morbidity compared to ONU. Recognition of preoperative risk factors for major complications may be beneficial during preoperative counseling and risk assessment. □

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