# Critical analysis of 30 day complications following radical nephroureterectomy for upper tract urothelial carcinoma

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LIN Y-K, DELIERE A, LEHMAN K, HARPSTER LE, KAAG MG, RAMAN JD. Critical analysis of 30 day complications following radical nephroureterectomy for upper tract urothelial carcinoma. *Can J Urol* 2014; 21(4):7369-7373.

**Introduction:** Patients with upper tract urothelial carcinoma (UTUC) are often elderly and comorbid owing to associated risk factors for developing this malignancy. Perioperative complications may be significant in such a surgical population. We define the incidence and risk factors associated with perioperative complications occurring within 30 days of radical nephroureterectomy (RNU).

*Materials and methods:* Medical records of 92 consecutive patients undergoing RNU were reviewed. Complications occurring within 30 days of surgery were graded using the modified Clavien-Dindo classification. The number, severity, and type of complications were recorded. Minor complications were classified as Clavien II or less, while major complications were Grade III or greater. Univariate and multivariate analyses determined variables associated with complications.

**Results:** Fifty-seven men and 35 women with a median age of 70 years were included. Three-quarters

#### Introduction

Radical nephroureterectomy (RNU) with an ipsilateral bladder cuff remains the gold standard for managing high grade, muscle-invasive, or bulky upper tract urothelial carcinoma (UTUC).<sup>1</sup> Contemporary oncologic outcomes

Accepted for publication May 2014

Address correspondence to Dr. Jay D. Raman, Division of Urology, Penn State Milton S. Hershey Medical Center, 500 University Drive, H055, Hershey, PA 17033-0850 USA of the cohort underwent a minimally invasive RNU and 45% had a regional lymph node dissection. Final pathology noted that 53% had muscle-invasive and 70% had high grade UTUC. Overall, 35 patients (38%) experienced complications within 30 days of RNU including 11 (12%) with major complications. Ten patients (11%) had multiple complications. Hematologic, gastrointestinal, and infectious etiologies comprised over 75% of complications. On univariate analysis, patient age, ECOG performance status, surgical approach, nonorgan confined disease, and cardiac history were associated with complications. In a multivariate model including these variables, only ECOG  $\geq$  2 (OR 3.9, 95% CI 1.6-7.4, p < 0.001) was independently associated with post-RNU complications.

**Conclusion:** Almost 40% of patients in this cohort experienced a perioperative complication after RNU. One-third of complications were Clavien III or greater. Poor performance status conferred a four-fold greater risk of a perioperative complication. Such knowledge may guide patient counseling and surgical expectations for the postoperative period.

**Key Words:** transitional cell carcinoma, Clavien grading system, nephroureterectomy

following RNU demonstrate durable responses.<sup>2</sup> Many patients with UTUC are elderly and comorbid largely owing to associated risk factors for developing this malignancy. As such, perioperative complications may be significant in such a surgical population.

Complications following RNU are incompletely defined in the literature. In 2004, Rassweiler and colleagues reviewed laparoscopic and open RNU series and broadly reported that major and minor complications occurred in approximately 0 to 29% and 0 to 45% of cases, respectively.<sup>3</sup> A more recent population based study from Hanna et al compared

open and laparoscopic RNU and noted a higher rate of intraoperative complications for the open approach (4.7% versus 2.1%, p = 0.002) but no difference in postoperative complications (17% versus 15%, p = 0.24).<sup>4</sup> Collectively, these observations are difficult to contextualize given the absence of a standardized grading system, lack of patient specific data, and heterogeneity in surgical approach and experience.

Therefore, to better define complications following RNU, we critically reviewed 30 day events occurring after surgery using a standardized, validated classification system.<sup>5</sup> The goal was to define the incidence and severity of complications and to identify risk factors associated with perioperative events. We believe that such knowledge would play a critical role in appropriate preoperative patient counseling as well as surgical expectations following surgery.

### Materials and methods

Electronic medical records from 92 patients with clinically localized, non-metastatic UTUC who underwent a RNU between 2003 and 2013 were retrospectively reviewed. RNU was performed via open or minimally invasive techniques with regional lymphadenectomy at the discretion of the treating surgeon. Four surgeons performed all cases included in this analysis. In general, patients treated with open RNU was predominantly comprised of those treated in an earlier time frame (2003-2006) and those with enlarged peri-hilar lymph nodes detected on preoperative imaging. Patients who received neoadjuvant radiation or chemotherapy were excluded from analysis. All specimens were histologically confirmed to be urothelial carcinoma. Tumor classification was assigned according to the 2002 AJCC-UICC TNM classification, while grading was assessed by the 2004 WHO/ISUP consensus classification.

The modified Clavien-Dindo classification system was used to categorize perioperative complications occurring within 30 days of surgery.<sup>5</sup> Minor complications were classified as Clavien II or less, while major complications were Grade III or greater. The number, severity, type, and management of complications were recorded.

The chi-squared or Fisher-exact test evaluated the association between categorical variables, and the Mann Whitney U-test assessed for differences in continuous variables. A binomial linear regression model determined the relationship between continuous and categorical variables and perioperative complications. Only variables which were significant with a p value of < 0.05 were incorporated into the multivariate model.

All reported p values are two-sided and statistical significance was set at ≤ 0.05. Statistical analysis was performed with S-Plus Professional version 4.5 (MathSoft Inc., Seattle, WA, USA).

### Results

Clinical and pathologic characteristics for patients included in this study are shown in Table 1. Sixty-two percent of our cohort was comprised of men with a median age of all patients being 70 years and body mass index of 31. ECOG performance status ranged from 0 to 3 with an ECOG  $\geq$  2 in 14% of the group. Pulmonary, cardiac, and diabetic diseases were the leading concurrent medical diagnosis in our patients.

Three-quarters of the cohort underwent a minimally invasive RNU (laparoscopic or robotic), and 45% had a regional lymph node dissection. Management of the distal ureter was performed by extravesical (40%) or intravesical (60%) methods. Notably, over two-thirds of patients (70%) had high grade tumors, 53% had muscle invasive ( $\geq$  pT2) disease, while 7% had positive lymph nodes and 4% had positive soft tissue surgical margin. Median operative time was 330 minutes (range, 192-645) and median length of stay was 4 days (range, 2-21). Ten patients (11%) were re-admitted within 30 days of surgery.

Overall, 35 patients (38%) experienced complications within 30 days of RNU including 11 (12%) with major complications. Ten patients (11%) experienced multiple complications including 1 patient with 4 distinct events. In total, 49 complication events occurred with 35 being minor (Clavien grades I and II) and 14 being major (Clavien III-V), Table 2. Specific complications are highlighted within the Table. The patient with perioperative mortality expired on postoperative day 3 secondary to multi-organ failure presumably from fulminant sepsis. Overall, hematologic, gastrointestinal, and infectious etiologies comprised over 75% of complications.

On univariate analysis, patient age  $\geq$  70 (p = 0.03), ECOG performance status  $\geq$  2 (p=0.004), open surgical approach (p = 0.01), non-organ confined disease (p = 0.01), and cardiac history (p = 0.04) were associated with complications, Table 1. Conversely, gender, comorbidities beyond cardiac disease, operative duration, and other pathologic features (grade, lymph node, and margin status) were not associated with complications after RNU. In a multivariate model including the significant variables described above, only ECOG  $\geq$  2 (OR 3.9, 95% CI 1.6-7.4, p < 0.001) was independently associated with post-RNU complications, Table 3.

Variables	No. pts. (%)	Complication (No., %) n = 35	No complication (No., %) n = 57	p value
Gender			· • •	
Male	57 (62)	22 (63)	35 (61)	1.00
Female	35 (38)	13 (37)	22 (39)	
Age				
< 70 yrs	Median 70	9 (26)	29 (51)	0.03
≥ 70 yrs	(range, 46-87)	26 (74)	28 (49)	
Body mass index				
< 30	Median 31	14 (40)	31 (54)	0.20
≥ 30	(range, 19-46)	21 (60)	26 (46)	
ECOG status				
<2	79 (86)	25 (71)	54 (95)	0.004
≥2	13 (14)	10 (29)	3 (5)	01001
Baseline comorbidities			- (-)	
Pulmonary				
Yes	19 (21)	9 (26)	10 (18)	0.43
No	73 (79)	26 (74)	47 (82)	0.10
Cardiac				
Yes	30 (32)	16 (46)	14 (25)	0.04
No	62 (67)	19 (54)	43 (75)	
Diabetes		( ),		
Yes	19 (21)	6 (17)	13 (28)	0.60
No	73 (79)	29 (83)	44 (72)	
Surgical approach				
Lap/Robot	69 (75)	21 (30)	48 (70)	0.01
Open	23 (25)	14 (61)	9 (39)	
Tumor size				
< 2 cm	Mean 2.9	20 (57)	34 (60)	0.83
$\geq 2 \text{ cm}$	(range, 1.0-7.1)	15 (43)	23 (40)	
Tumor location		( ),		
Renal pelvis/calvx	41 (45)	13 (37)	27 (47)	0.19
Ureter	32 (35)	11 (31)	21 (37)	0.17
Both	19 (21)	9 (26)	9 (16)	
Pathologic stage				
nT2-nT4	49 (53)	25 (51)	24 (49)	0.01
pT2 pT1 pTa/pTis/pT1	43 (47)	10(23)	33 (77)	0.01
Pathologic grade		10 (20)	00(11)	
High	64 (70)	23 (66)	<i>A</i> 1 (72)	0.64
Low	28 (30)	12(34)	$\frac{11}{16}$ (28)	0.04
Low	20 (00)	12 (04)	10 (20)	
Lymphadenectomy	41 (AE)	10(E4)	(20)	0.20
ies No	41(43) 51(55)	19 (34)	22 (39)	0.20
	51 (55)	10 (40)	55 (01)	
Positive margin	4 (4)	$2(\mathbf{C})$	<b>2</b> (4)	0.64
ies	4 (4)	$\angle (0)$	$\angle (4)$	0.64
INO	00 (90)	<i>33 (94)</i>	(00) 00	

TABLE 1. Clinical and pathologic characteristics of 92 patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma stratified by complications after surgery

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Clavien grade	No. events (%)	Specific complication
Ι	16 (33)	GI ileus (10); atelectasis (2); fever (2); fluid overload (2)
II	19 (39)	Anemia requiring transfusion (12); UTI (4); pneumonia (3)
IIIa	4 (4)	Percutaneous drainage of infected collection (4)
IIIb	5 (10)	Wound dehiscence (2); re-operation for bleed (2); re-operation for SBO (1)
IVa	2 (4)	Transient dialysis (1); arrhythmia (1)
IVb	2 (4)	Transient dialysis + arrhythmia (1); transient dialysis + respiratory failure (1)
V	1 (2)	Death from sepsis (1)
Total	49 (100)	
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TABLE 2. Clavien grade distribution of 49 complication events occurring in 35 patients following radical nephroureterectomy

GI = gastrointestinal; UTI = urinary tract infection; SBO = small bowel obstruction

TABLE 3. Multivariable Cox regression model predicting variables associated with complications following radical nephroureterectomy

Covariate	Hazard ratio (HR)	95% CI	p value
ECOG			
0/1 versus 2/3	3.9	1.6-7.4	< 0.001
Cardiac history Yes versus no	1.8	0.9-2.2	0.09
Age < 70 yrs versus ≥ 70 yrs	1.3	0.8-1.7	0.13
Pathologic stage < pT2 versus ≥ pT2	1.15	0.7-1.1	0.71
Surgical approach Open versus laparoscopic	1.0	0.6-1.5	0.62

## Discussion

UTUC, comprising cancers of the ureter and renal pelvis, account for 5% of all urothelial malignancies and 10% of renal tumors.<sup>6</sup> RNU is the standard of care for the management of these upper tract cancers. Owing to the uncommon presentation of this malignancy, pertinent perioperative factors such as complications following surgery are poorly defined in the literature. Such considerations are paramount given that many UTUC patients are elderly and comorbid and some may require adjuvant chemotherapy following RNU for tumors with adverse pathologic features.<sup>7</sup> In such patients, perioperative complications may not only impact convalescence and recovery, but may delay or preclude the use of adjuvant therapies.

In the present study, 38% of patients undergoing RNU experienced a postoperative complication. Of the 49 total complications (observed in 35 patients), 72% were minor (Clavien grades I and II) and 28% were major (Clavien grades III-V). Hematologic, gastrointestinal, and infectious causes accounted for over 75% of observed events. Finally, one mortality case was noted in our cohort. Our data are roughly concordant with a 2004 review from Rassweiler et al who reported that minor and major complications occurred in 0 to 45% and 0 to 29% of cases, respectively, following RNU.3 Our complications events, however, are greater than that reported 15%-20% intraoperative and postoperative rate

noted by Hanna and colleagues on their review of the Nationwide Inpatient Sample (NIS) database.<sup>4</sup> A more detailed comparison is impossible given the absence of a standardized grading system to better define complications in these earlier series. Additional studies to better characterize complications following RNU are presently lacking.

While there is limited data on RNU complications, some comparison can be made with published rates following surgery for renal cortical tumors. Indeed, one can argue that patients undergoing RNU represent a hybrid between the conventional risks of renal tumor surgery combined with the comorbidity index of urothelial carcinoma patients. In 2004, Stephenson and colleagues reported a 17% complication rate in a cohort of 1049 patients undergoing either partial or radical nephrectomy.<sup>8</sup> Patient age, operative duration, and individual surgeon volume were factors associated with complications in the multivariate model. Recently, Aboussaly et al presented a Canadian population based review of complications after partial and radical nephrectomy.<sup>9</sup> These authors highlighted a 34% complication rate following renal tumor surgery, and specifically identified Charlson comorbidity index to be independently associated with these complications. In 2012, Hennus and colleagues used the Clavien classification system to similarly report a 34% complication rate follow partial or radical nephrectomy.<sup>10</sup> Both comorbidity index and tumor stage were independently associated with major complications.

While the biology of renal cell carcinoma differs from urothelial carcinoma, the above studies provide some reference to our observations in this study. Not surprisingly, our complication rate was somewhat higher than that reported following surgery for renal cortical neoplasms. Similarly, however, we did identify that poor performance status (measured by ECOG in our study) was independently associated with a higher risk of complications following RNU surgery. Recognition of this fact can play a key role in patient counseling and may guide realistic expectations for older and comorbid patient with upper tract neoplasms. Furthermore, such consideration may encourage the use of endoscopic therapies in certain high risk patients.

Significant perioperative complications may also impact the delivery of chemotherapy if necessary in an adjuvant setting. Hellenthal and colleagues have previously reported that only 22% of high risk (pT3N0, pT4N0 and/or lymph node positive) patients received adjuvant chemotherapy after RNU.<sup>7</sup> The rationale behind the infrequent use of chemotherapy in these high risk patients was unclear. Amongst a variety of reasons including patient and physician preference and renal function, the potential confounding impact of operative complications in these high risk patients remains a question. While our study failed to identify differences in complication rates when stratifying by pathologic stage, larger series may be better powered to investigate this difference.

We acknowledge several limitations in this study. First, the retrospective nature of the study is susceptible to biases inherent in its study design. Second, although all data was collected from detailed electronic medical record system, we understand that this may not capture all events that may have warranted treatment at an outside facility or office. This may be particularly true for minor Clavien I and II complications. Finally, owing to the infrequent presentation of UTUC, our sample size is limited and thus may not be sufficiently powered to detect significant risks factors. Nonetheless, to our best knowledge, this study presents the most critical appraisal to date of complications that occur secondary to radical surgery for UTUC. Indeed, our hope is to eventually broaden the study to a multi-institutional collaboration to improve sample size and obtain greater heterogeneity in surgical population.

#### Conclusions

Almost 40% of patients in this cohort experienced a complication within 30 days of RNU for UTUC. Additionally, approximately one-third of complications were major complications. Poor ECOG performance status ( $\geq$  2) conferred a four-fold greater risk of perioperative complications. Such knowledge may guide appropriate patient counseling as well as surgical expectations for the postoperative period.

#### References

- 1. Raman JD, Scherr DS. Management of patients with upper urinary tract transitional cell carcinoma. *Nat Clin Pract Urol* 2007;4(8):432-443.
- 2. Margulis V, Shariat SF, Matin SF et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. *Cancer* 2009;115(6):1224-1233.
- 3. Rassweiler JJ, Schulze M, Marrero R et al. Laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: is it better than open surgery? *Eur Urol* 2004;46(6):690-697.
- 4. Hanna N, Sun M, Trinh QD et al. Propensity-score-matched comparison of perioperative outcomes between open and laparoscopic nephroureterectomy: a national series. *Eur Urol* 2012;61(4):715-721.
- Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240(2):205-213.
- 6. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63(1):11-30.
- 7. Hellenthal NJ, Shariat SF, Margulis V et al. Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. *J Urol* 2009;182(3):900-906.
- 8. Stephenson AJ, Hakimi AA, Snyder ME et al. Complications of radical and partial nephrectomy in a large contemporary cohort. *J Urol* 2004;171(1):130-134.
- 9. Abouassaly R, Alibhai SM, Tomlinson GA et al. The effect of age on the morbidity of kidney surgery. J Urol 2011;186(3):811-816.
- 10. Hennus PM, Kroeze SG, Bosch JL et al. Impact of comorbidity on complications after nephrectomy: use of the Clavien Classification of Surgical Complications. *BJU Int* 2012;110(5): 682-687.