International and Multi-institutional Assessment of Factors Associated With Performance and Quality of Lymph Node Dissection During Radical Nephrectomy

E. Charles Osterberg, Shay Golan, M. Pilar Laguna Pes, Scott E. Eggener, Bogdan Petrut, Shrawan K Singh, Petros Sountoulides, Levent N. Türkeri, and J. Stuart Wolf Jr.

OBJECTIVE To determine factors associated with performance and quality of lymph node dissection during radical nephrectomy.

MATERIALS AND METHODS Using an International Data Registry, we performed multilevel logistic regression to determine the association of surgical approach (open surgery vs minimally invasive surgery), institutional experience (low, moderate, and high tertiles), and institutional preference (minimally invasive surgery, balanced, and open surgery tertiles) with the performance of lymph node dissection in subgroups by clinical stage and nodal status.

RESULTS Among 1,742 patients undergoing radical nephrectomy, 312 (18%) underwent lymph node dissection, which was associated with stage (28% for ≥cT2 vs 9.3% for cT1), and nodal status (68% for ≥cN1 vs 13% for cN0). Open surgery was significantly associated with performing lymph node dissection in all subgroups. Institutional experience and institutional preference had no association with performing lymph node dissection in the ≥cN1 group. The number of nodes removed was greater for open surgery (mean 5.9) vs minimally invasive surgery (mean 3.4); this held true even when stratified by stage and nodal status.

CONCLUSION In this large dataset, open surgical radical nephrectomy is associated with more frequent performance and higher quality of lymph node dissection, which may owe to selection bias but also could reflect technical concerns. In the patient population in whom lymph node dissection is recommended (≥cN1), this is not explained by institutional experience or preference. Lymph node dissection may be under-utilized for ≥cN1 disease and over-utilized for cN0 disease, at least according to practice guidelines. UROLOGY 129: 132−138, 2019. © 2019 Elsevier Inc.

The role of lymph node dissection (LND) for renal cell carcinoma (RCC) remains controversial. It provides pathologic staging but has a debatable therapeutic benefit.[1] The only randomized controlled trial on the topic has demonstrated no benefit of LND in low risk patients.[2] However, observational studies suggest there may be an oncologic benefit of LND among high risk patients.[3,4] Currently, guidelines from both the American Urological Association and the European Association of Urology recommend performing LND in patients with clinically enlarged or concerning regional lymphadenopathy.[5,6] The purpose of our study is to evaluate the performance and quality of LND; specifically, if any preoperative, intraoperative or postoperative factors are associated with the performance and quality of LND at the time of RN for RCC.

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From the University of Texas, Austin, TX; the Rabin Medical Center, Petach Tiva, Israel; the AMC University Hospital Amsterdam, Amsterdam, the Netherlands; the Medipol University, Istanbul, Turkey; the University of Chicago, Chicago, IL; the Oncological Institute, Cluj-Napoca, Romania; the Postgraduate Institute of Medical Education & Research, Chandigarh, India; the General Hospital of Veria, Veria, Greece; and the Acibadem University Altunizade Hospital, Istanbul, Turkey

Address correspondence to: J. Stuart Wolf, M.D. Dell Medical School of the University of Texas at Austin, Health Discovery Building, 1701 Trinity Street, Austin, TX 78712. E-mails: stuart.wolf@austin.utexas.edu; wolfjsjr@yahoo.com

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MATERIALS AND METHODS

Patient Population

The Clinical Research Office of the Endourological Society (CROES) collects and studies multi-institutional and international data that is clinically validated. Using a web-based platform, data are directly entered by participating centers. For this study, 90 sites world-wide entered data on consecutive new renal cancer patients encountered over a period of one year, starting in 2010. Enrollment closed in 2012, but annual follow-up continues.[7] A flow

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diagram of patient selection is presented in Figure 1. Patients with missing age (n = 3), missing clinical stage (n = 199), known metastatic disease (n = 255), or missing surgical details were excluded. Patients over the age 18 with documented clinical stage, surgical approach, and presence or absence of LND who underwent a RN were included in the analysis.

Response Variables

The presence or absence of LND at the time of RN was the main dependent (response) variable. Secondary response variables included the quality or lymph node count on final pathology. LND was performed at the surgeon's discretion and a standardized template was not employed throughout the study period.

Explanatory Variables

Several independent factors were obtained, including: age, gender, body mass index, patient comorbidities, clinical stage, clinical symptoms, tumor laterality, and tumor multifocality. The type of surgical approach (open surgery versus MIS) and the institutional location (Asia, Europe, Africa, North America,

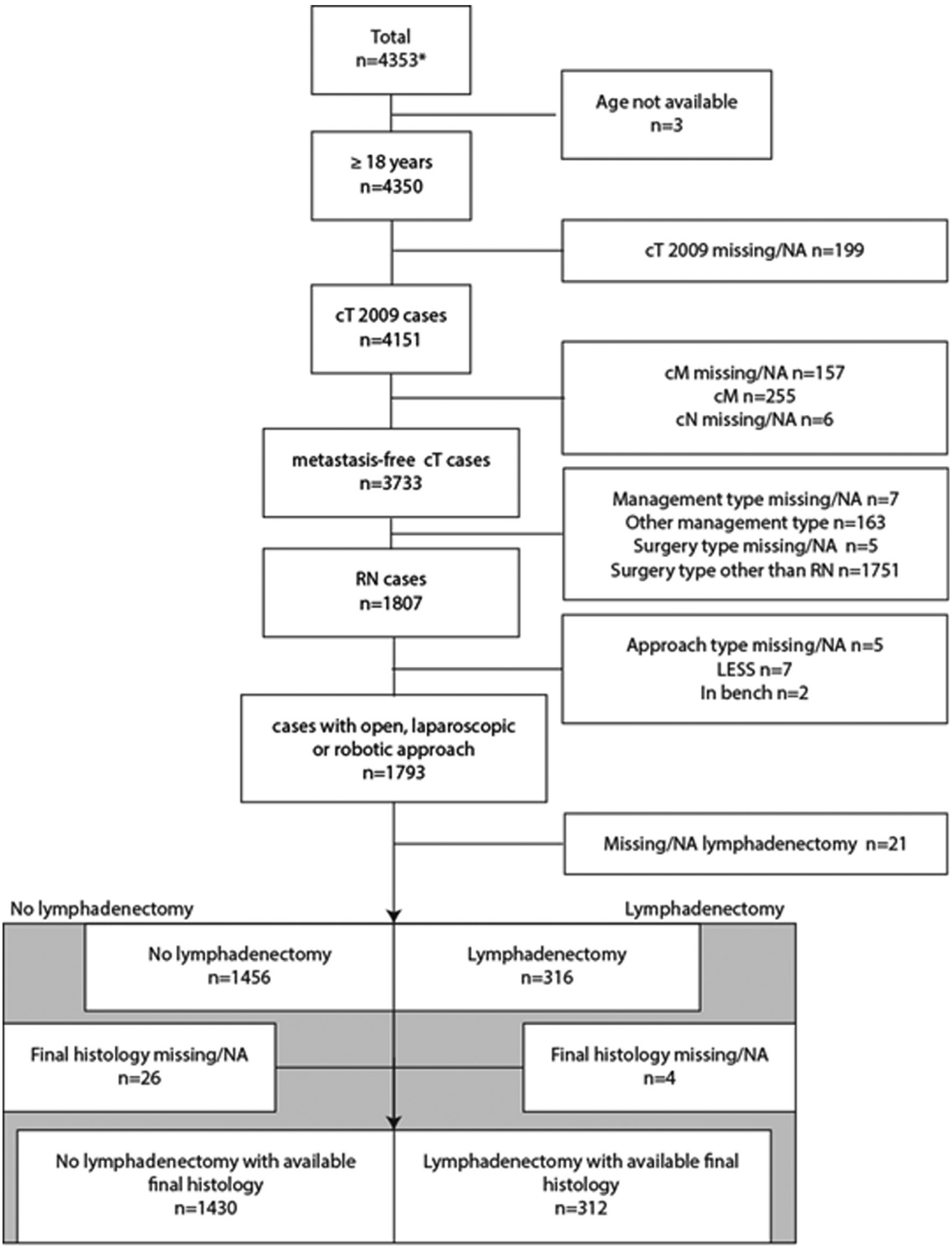

Figure 1. Flow diagram of patient inclusion/exclusion.

and South America) were collected as well. MIS included both laparoscopic and robotic modalities. The CROES database contains institutional-level but not surgeon-level data. As such, we devised institution-level surrogates for potentially confounding variables such as surgeon training, experience and technique preference. Institutional preference was defined as predominately MIS, a balanced approach, or predominantly open surgery if the proportion of open surgery was less than 36%, 36%-72%, or more than 72% respectively (approximate equivalent tertiles by size). Institutional experience was stratified based on RN surgical volume (≤ 19 or fewer/year = low, 20-40/year = moderate, ≥41/year = high) (approximate equivalent tertiles by size). Clinical and pathologic staging were collected in accordance with the 2010 American Joint Committee on Cancer classification.[8] Preoperative lymphadenopathy was determined by computed tomography or magnetic resonance imaging.

Statistical Methods

Chi-squared tests were used for categorical variables and *t* tests were used for continuous variables in the descriptive tables to compare between the presence or absence of LND. Univariate logistic analyses were used to determine the association of surgical approach, institutional experience, and institutional preference with the performance of LND, in subgroups by clinical stage and nodal status. A multilevel model was used to correct for correlates between contributing institutional data. Multivariate multilevel logistic regression was then performed to determine the association of surgical approach, adjusting for potential confounders (selected on basis of clinical relevance) such as age, gender, presence of comorbidities, diagnostic type, clinical T/N stage, tumor size, tumor multifocality, tumor laterality, institutional preference, and institutional experience. Sub-group by clinical T/N stage was also considered. Furthermore, we looked at the outcomes of lymph node yield (Poisson regression) and malignant lymph node yield (negative binomial regression). All statistical analyses were performed using Stata Statistical Software: Release 13. College Station, TX. Statistical significance was defined as $P \leq 0.05$.

RESULTS

Baseline Demographics

In total, 1,742 patients underwent RN for renal cancer, of whom 312 (18%) underwent LND and had final pathology available for review, compared to 1430 (82%) who did not undergo a LND and had final pathology available for review. Table 1a and 1b highlights baseline demographics, intraoperative, and pathologic characteristics among our cohorts. Frequency of presenting clinical stages among the total cohort were cT1 (55%), cT2 (22%), cT3 (18%), cT4 (5%), Nx-0 (91.8%), cN1 (6.2%), and cN2 (2.1%). There were a mean of 5.2 and a median of 3 lymph nodes removed. The mean and median number of malignant lymph nodes was 1 and 0, respectively. Pathologic stages among the total cohort were pT1 (50%), pT2 (13.1%), pT3 (32.6%), pT4 (3.4), pNx-0 (95.2%), pN1 (2.9%), pN2 (2%).

Univariate Analysis

Patients who underwent LND, were younger (mean [standard deviation]) (60 [13] vs 62 [13] years, $P = 0.01$), had a lower BMI

Table 1a. Baseline demographic comparisons among cohorts

		No LND (n = 1430)	LND (n = 312)	Total (n = 1742)	*P* Value
Age, mean (sd)/ med [iqr]/ range		62.3 (12.5)/ 63.0 [54.0-72.0]/ [19.0-91.0] (n = 1430)	60.3 (13.3)/ 60.0 [53.0-70.0]/ [20.0-89.0] (n = 312)	62.0 (12.7)/ 63.0 [54.0-71.0]/ [19.0-91.0] (n = 1742)	0.01
Gender, n (%)	Male	928 (64.9)	205 (65.7)	1133 (65.0)	0.79
	Female	502 (35.1)	107 (34.3)	609 (35.0)	
	Total	(n = 1430)	(n = 312)	(n = 1742)	
BMI, mean (sd)/ med [iqr]/ range		27.3 (4.8)/ 26.7 [24.2-29.7]/ [10.5-52.3] (n = 1322)	26.4 (4.9)/ 26.0 [23.5-28.9]/ [15.4-50.5] (n = 285)	27.2 (4.9)/ 26.5 [24.1-29.6]/ [10.5-52.3] (n = 1607)	<0.01
ASA, n (%)	I	221 (17.2)	54 (19.4)	275 (17.6)	0.07
	II	709 (55.1)	140 (50.2)	849 (54.2)	
	III	338 (26.3)	75 (26.9)	413 (26.4)	
	IV	19 (1.5)	10 (3.6)	29 (1.9)	
	Total	(n = 1287)	(n = 279)	(n = 1566)	
cT stage, n (%)	cT1a	342 (23.9)	25 (8.0)	367 (21.1)	<0.01
	cT1b	525 (36.7)	64 (20.5)	589 (33.8)	
	cT2a	235 (16.4)	54 (17.3)	289 (16.6)	
	cT2b	69 (4.8)	24 (7.7)	93 (5.3)	
	cT3a	179 (12.5)	62 (19.9)	241 (13.8)	
	cT3b	33 (2.3)	38 (12.2)	71 (4.1)	
	cT3c	0 (0.0)	7 (2.2)	7 (0.4)	
	cT4	47 (3.3)	38 (12.2)	85 (4.9)	
	Total	(n = 1430)	(n = 312)	(n = 1742)	
cN stage, n (%)	Nx-0	1384 (96.8)	214 (68.6)	1598 (91.8)	<0.01
	N1	35 (2.4) *	73 (23.4)	108 (6.2)	
	N2	11 (0.8) *	25 (8.0)	36 (2.1)	
	Total	(n = 1430)	(n = 312)	(n = 1742)	

* These were presumably hilar lymph nodes found in the specimen despite not performing LND.BMI: body mass index; LND: lymph node dissection.

Table 1b. Intraoperative and pathologic comparisons among cohorts

		No LND (n = 1430)	LND (n = 312)	Total (n = 1742)	*P* Value
Approach, n (%)	Open Surgery	653 (45.7)	250 (80.1)	903 (51.8)	<0.01
	Laparoscopic	758 (53.0)	58 (18.6)	816 (46.8)	
	Robotic	19 (1.3)	4 (1.3)	23 (1.3)	
Malignant Pathology (largest or most invasive tumor), N (%)	Clear cell	973 (74.7)	204 (69.2)	1177 (73.7)	<0.01
	Papillary I	100 (7.7)	17 (5.8)	117 (7.3)	
	Papillary II	51 (3.9)	19 (6.4)	70 (4.4)	
	Chromophobe	96 (7.4)	11 (3.7)	107 (6.7)	
	Other RCC	30 (2.3)	14 (4.7)	44 (2.8)	
	Urothelial	24 (1.8)	12 (4.1)	36 (2.3)	
	Lymphoma	1 (0.1)	0 (0.0)	1 (0.1)	
	Metastasis	7 (0.5)	5 (1.7)	12 (0.8)	
	Other	21 (1.6)	13 (4.4)	34 (2.1)	
	Total	(n = 1303)	(n = 295)	(n = 1598)	
pT staging, n (%)	T1a	321 (26.2)	21 (8.4)	342 (23.2)	<0.01
	T1b	357 (29.1)	39 (15.6)	396 (26.8)	
	T2a	120 (9.8)	25 (10.0)	145 (9.8)	
	T2b	35 (2.9)	14 (5.6)	49 (3.3)	
	T3a	348 (28.4)	103 (41.2)	451 (30.6)	
	T3b	14 (1.1)	15 (6.0)	29 (2.0)	
	T3c	6 (0.5)	8 (3.2)	14 (0.9)	
	T4	25 (2.0)	25 (10.0)	50 (3.4)	
	Total	(n = 1226)	(n = 250)	(n = 1476)	
pN stage, n (%)	Nx-0	1224 (98.4)	211 (79.6)	1435 (95.2)	<0.01
	N1	13 (1.0)	30 (11.3)	43 (2.9)	
	N2	6 (0.5)	24 (9.1)	30 (2.0)	

RCC: renal cell carcinoma.

(26.4 [4.9] vs 27.3 [4.8], *P* = 0.006), and had fewer comorbidities (78 [25] vs 481 [34], *P* = 0.004) compared to those who did not undergo LND. Preoperative characteristics were similar among groups with respect to American Society of Anesthesiologist scores.

T and N stage were different among cohorts. Increasing cT stage and cN stage were both associated with greater rate of performing LND (9.3% in cT1 vs 28.4% in ≥cT2 [*P* < 0.001] and 13.4% in cN0 versus 68.1% in ≥cN1 [*P* < 0.001]). Open surgery (as opposed to MIS) was significantly associated with performing LND across all clinical staging parameters (cT1 odds ratio [OR] 3.6, *P* < 0.001, ≥cT2 OR 4.04, *P* < 0.001, cN0 OR 4.47, *P* < 0.001 and ≥cN1 OR 2.48, *P* = 0.03). Institutional experience had variable associations in that institutions with high levels of experience (>41 RN) and moderate levels of experience (20-40 RN) both performed LND more often for ≥cT2 (OR 1.49, *P* = 0.046 and OR 1.71, *P* = 0.007 respectively), but not for ≥cN1 when compared to low levels of experience (<19 RN). Institutional preference for surgical modality also had a variable association with performance of LND in the cT1, ≥cT2 and cN0 subgroups, but in the ≥cN1 group, none had association with performing LND. Specifically, preference for open surgery was associated with LND (OR 1.89, *P* = 0.02) for cT1 tumors whereas preference for a balanced approach (36%-72% open surgery) was associated with LND for ≥ cT2 tumors (OR 1.97, *P* < 0.001) and cN0 (OR 2.02, *P* < 0.001) (Table 2a).

Open surgery was associated with greater yield of LN during LND, with mean and median yield for open surgery of 5.7 and 4, respectively, compared to a mean and median yield for MIS of 3.6 and 3 (*P* < 0.013). This finding held true even when stratified by clinical stage and nodal status (cT1 Incidence Rate Ratio [IRR] 2.36, *P* < 0.001, ≥cT2 IRR 1.22, *P* = 0.03, cN0 IRR 1.4,

Table 2a. Lymph node performance stratified by clinical stage

	cT1		≥cT2		cNO		≥cN1	
	OR	*P* value	OR	*P* value	OR	*P* value	OR	*P* value
Approach (reference = MIS)								
Open surgery	3.60	<0.01	4.04	<0.01	4.47	<0.01	2.48	0.03
Institutional experience (reference = Low)								
Moderate	1.14	0.61	1.49	0.05	1.45	0.04	0.64	0.3
High	0.69	0.19	1.71	<0.01	1.41	0.06	1.04	0.94
Institutional preference (reference = MIS)								
Balanced	1.45	0.2	1.97	<0.01	2.02	<0.01	1.19	0.7
Open surgery	1.89	0.02	1.17	0.45	1.25	0.24	1.23	0.64

Key: Low, moderate and high institutional experience = <19 procedures reported, 20-40 procedures reported and >41 procedures reported, respectively; MIS, balanced and open surgery institutional preference = <36% open surgery, 36%—72% open surgery and >72% open surgery, respectively.
OR: odds ratio.

Table 2b. Lymph node yield stratified by clinical stage

	cT1		≥cT2		cN0		≥cN1	
	IRR	*P* value	IRR	*P* Value	IRR	*P* Value	IRR	*P* Value
Approach (reference = MIS)								
Open surgery	2.36	<0.01	1.22	0.03	1.4	<0.01	2.10	<0.01
Institutional experience (reference = Low)								
Moderate	1.81	<0.01	1.22	0.01	1.48	<0.01	1.30	0.01
High	1.05	0.78	0.97	0.69	1.24	0.02	0.90	0.39
Institutional preference (reference = MIS)								
Balanced	1.47	<0.01	0.98	0.79	0.91	0.19	1.69	<0.01
Open surgery	0.98	0.91	0.69	<0.01	0.36	<0.01	1.32	0.02

Key: Low, moderate and high institutional experience = <19 procedures reported, 20-40 procedures reported and >41 procedures reported, respectively; MIS, balanced and open surgery institutional preference = <36% open surgery, 36%-72% open surgery and >72% open surgery, respectively.
IRR, incidence rate ratio.

Table 3a. Multilevel multivariate lymph node performance

LND	OR	SE	*P* Value	95% CI
Approach (reference = MIS)				
Open surgery	5.59	1.18	<0.01	3.695-8.444
cT stage (reference = cT1)				
≥cT2	3.19	0.54	<0.01	2.284-4.442
Intercept	0.03	0.01	<0.01	0.016-0.0433

Models were corrected for confounders. Confounders that were considered: age, gender, presence of comorbidities, diagnostic type, clinical T/N stage, tumor size, tumor multifocality, tumor laterality, institutional preference, and institutional experience.
CI, confidence interval.

P < 0.001, and ≥cN1 IRR 2.1, *P* < 0.001). Moderate institutional experience was associated with higher nodal yield in cT1 (IRR 1.81, *P* < 0.001), cN0 (IRR 1.48, *P* < 0.001) and ≥cN1 (1.30, *P* = 0.009) but not patients who had ≥cT2 disease. Among highly experienced institutions, only cN0 was associated with increased node counts (IRR 1.24, *P* = 0.018). Results were variable among institutional surgical preference, with preference for open surgical approach being associated with significantly fewer lymph nodes in ≥cT2 (IRR 0.69, *P* < 0.001) and cN0 (IRR 0.36, *P* < 0.001) patients, but more lymph nodes with ≥cN1 (IRR 1.32, *P* = 0.017). Among balanced surgical modality institutions, cT1 (IRR 1.47, *P* = 0.004) and ≥cN1 (IRR 1.69, *P* < 0.001) were associated with greater lymph node yield (Table 2b).

Table 3b. Multilevel multivariate lymph node yield

Number of LNDs	IRR	SE	*P* Value	95% CI
Approach (reference = MIS)				
Open surgery	1.66	0.17	<0.01	1.360-2.023
Diagnostic type (reference = Incidental finding)				
Symptomatic tumour	1.71	0.13	<0.01	1.475-1.981
cN (reference cN0)				
≥cN1	1.39	0.10	<0.01	1.205-1.601
Intercept	1.73	0.25	<0.01	1.305-2.291

Models were corrected for confounders. Confounders that were considered: age, gender, presence of comorbidities, diagnostic type, clinical T/N stage, tumor size, tumor multifocality, tumor laterality, institutional preference, and institutional experience.

Multivariate Multilevel Regression

When multilevel logistic regression was performed, after adjusting for confounding, lymph node performance was significantly associated with open surgery (OR 5.59, 95% confidence interval [CI] 3.69-8.44, *P* < 0.001) (Table 3a) . Similarly, open surgery was significantly associated with total lymph node yield (IRR 1.66, 95% CI 1.36-2.02, *P* < 0.001) (Table 3b). This association was not significant for malignant lymph node yield. There was no effect modification present for clinical T/N stage, therefore sub-groups by clinical T/N stage were not considered.

DISCUSSION

In this large, multi-institutional, retrospective, observational study, we demonstrated in univariate analyses that both stage and clinical nodal status is associated with the performance of LND during RN. Beyond this, the decision to perform LND is associated with age, body mass index, institutional preference for surgical modality (open surgery vs MIS), and institutional experience. This is the first multi-institutional report describing how these factors impact performance and quality of LND. More importantly, in a multi-variable analysis in subgroups by clinical T/N stage, we found that open surgical RN was associated with greater performance and quality of LND across all stages. Specifically, in the ≥cN1 subgroup — which is the population in whom LND is recommended[9] — no factors except for open surgery were associated with performing LND. This held true for LND performance among moderate institutional experience and both an open surgery and balanced institutional surgical preference, which suggests that the findings cannot be completely explained by an inherent bias among surgeons who perform open surgery towards LND and/or among surgeons who perform MIS against LND. Thus, the impact of open surgery on the decision to perform LND may suggest that a technical factor, one that impacts both the decision to perform LND and the aggressiveness of LND, might be playing a role here.

Historically, the rationale for RN plus LND is based upon the premise that extirpative surgery may be curative in patients with loco-regional disease. Despite the theoretical benefits of LND for RCC, the only randomized controlled trial examining LND during RN (EORTC 30881) found no difference in overall survival.[2] The study utilized a standardized, extended LND template and had a systematic process of lymph node processing. These data called into question the utility of performing not only a template LND but also any LND whatsoever. The study, however, has been criticized for its low incidence of nodal disease (4%)[2,10] which means that it may have lacked power to detect differences in disease recurrence.[11] In higher risk patients (those with clinical nodal disease), some observational data suggest that LND may improve survival.[3] Similarly, in some patients with metastatic RCC undergoing cytoreductive RN, LND was associated with improved survival.[4] Yet, there are conflicting data in both high risk patients[12,13] and the cytoreductive settings[14] that suggest no additional benefit of LND. This discrepancy may be partially explained by selection bias and confounding in addition to low rates of LN involvement in the non-metastatic RCC setting (2-5%).[10] Conversely, distant metastases are present in roughly 60% of patients with N1 disease, which contributes to selection bias.[3]

With conflicting data on the oncologic outcomes, the decision to perform LND may be influenced by patient safety and associated risks. In the EORTC 30881 randomized trial, there was not increased morbidity when extended LND was performed.[2] This was confirmed by Gershman and associates in a propensity score-based analysis when they found no difference in high grade complications (Clavien grade $\geq$ 3) or any grade complications (Clavien grades 1-5) among balanced cohorts.[15] Furthermore, LND did not contribute to additional length of stay or estimated blood loss.

Since the aforementioned studies demonstrated questionable oncologic benefit yet proven safety of LND, we turned to alternative factors beyond stage as a potential explanation of the performance and quality of LND at the time of RN. The fact that the number of lymph nodes removed was greater for open surgery versus MIS, which held true when stratified by clinical stage and nodal status, suggests either a selection bias that is not adequately controlled for in our analysis, or a technical factor. Furthermore, open surgery was the only factor increasing both performance and quality of LND, regardless of both institutional experience and preference, for patients with ≥cN1 disease. This further reinforces the notion that surgeons performing MIS for RN should be aware of this tendency and focus on LND when it is indicated. Similar findings were reported by Capitanio et al in a multi-institutional European cohort of over 13,000 patients.[16] Their multivariate analysis showed that open surgery is an independent predictor of LND (OR 1.75, 95% Confidence Interval 1.43-2.13, $P < 0.001$) compared to MIS. In other series, the use of MIS did not impact detection of pathologic N1 disease or survival.[9,17] Of note, in other urologic cancers surgical modality and institutional experience have been found to influence LN yield. Higher lymph node yield was achieved during open surgical radical prostatectomy,[18] radical cystectomy,[19] and retroperitoneal lymph node dissection for testicular cancer[20] compared to the MIS approach.

On a broader perspective, our data confirm that guidelines are not adhered to with regards to LND in patients undergoing RN for RCC. Among patients in whom LND is recommended by both the American Urological Association and the European Association of Urology (ie patients with ≥cN1 disease undergoing RN) 32% did not undergo LND. Conversely, among patients for whom LND is not recommended (ie patients with cN0 disease), 13% of patients still underwent LND.

This study is limited by its nonrandomized, observational design across which can be associated with inherent selection, missing data, confounding variables, and recall biases. As a result, this data may not be generalizable. Neither the decision to perform LND or the extent of LND was standardized across centers. Data on the participation of resident trainees and individual surgeons are not available in the CROES database, and the database also does not include intraoperative findings such as operative time, blood loss, and hilar anatomy that might have influenced the decision about performing LND. Furthermore, the template of LND removal was not standardized. There was no standard for pathologic analysis of lymph nodes across institutions which may impact nodal counts between groups. Despite these limitations, the strength of our data is its prospective data collection of a large sample size across multi-international sites that reflects how LND during RN is being used in a "real world" setting outside of clinical trials. This information might be useful to educators and organizations producing clinical practice guidelines; if the intent is to discourage LND in association with RN for <cN1 disease and to encourage LND in association with RN for ≥cN1 disease then that is not what is being done in practice.

CONCLUSION

Open surgical RN, as opposed to MIS, is associated with more frequent performance and higher quality of LND. Importantly, in the subgroup of patients with ≥cN1 disease, this improved nodal yield was not explained by institutional experience or institutional preference. Surgeons performing minimally invasive RN should be aware of these tendencies, particularly in patients with ≥cN1 disease. Finally, in this large observational study that recorded practice among a heterogeneous group of surgeons, LND was performed less for ≥cN1 RCC and more for cN0 RCC.

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Alette Spriensma performed the statistical analysis.

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