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Maximilian Pallauf

David D'Andrea

Frederik König

Ekaterina Laukhtina

Takafumi Yanagisawa

See next page for additional authors

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Authors

Maximilian Pallauf, David D'Andrea, Frederik König, Ekaterina Laukhtina, Takafumi Yanagisawa, Morgan Rouprêt, Siamak Daneshmand, Hooman Djaladat, Alireza Ghoreifi, Francesco Soria, Kazutoshi Fujita, Stephen A. Boorjian, Aaron M. Potretzke, Andrea Mari, Mathieu Roumiguié, Alessandro Antonelli, Alberto Bianchi, Zine-Eddine Khene, John P. Sfakianos, Marcus Jamil, Joost L. Boormans, Jay D. Raman, Nico C. Grossmann, Alberto Breda, Axel Heidenreich, Francesco Del Giudice, Nirmish Singla, Shahrokh F. Shariat, and Benjamin Pradere

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Diagnostic Accuracy of Clinical Lymph Node Staging for Upper Tract Urothelial Cancer Patients: A Multicenter, Retrospective, Observational Study

Maximilian Pallauf, David D'Andrea, Frederik König, et al.

Correspondence: Benjamin Pradere (email: benjaminpradere@gmail.com).

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Study Need and Importance: Upper tract urothelial cancer (UTUC) is a rare but aggressive urological malignancy. Treatment options for the management are based on accurate staging. However, the performance of conventional cross-sectional imaging (CCI) for clinical lymph node staging (N-staging) remained poorly investigated. In this study, we present robust data on the performance of CCI for UTUC N-staging, which will aid physicians in treatment planning and patient counseling.

What We Found: In a multicenter, retrospective, observational study, we assessed 865 UTUC patients who received preoperative CCI before curative intended radical surgery and lymph node dissection. Comparing clinical and pathological N-staging results, we detected low sensitivity but high specificity of CCI. Of 224 patients with pathologically confirmed node-positive disease, CCI missed 168 (75%). On the other hand, of 115 patients with lymph nodes classified as suspicious of tumor invasion on CCI, pathological examination confirmed 56 (49%). Clinically node-positive disease increased the likelihood of reaching pathological confirmation approximately 3 times. We further stratified patients based on the lymph node size, tumor location, and the year of diagnosis. Although we detected statistically significant differences in comparing clinical and pathological N-staging results within the subgroups, these trends did not reach statistical significance for diagnostic accuracy.

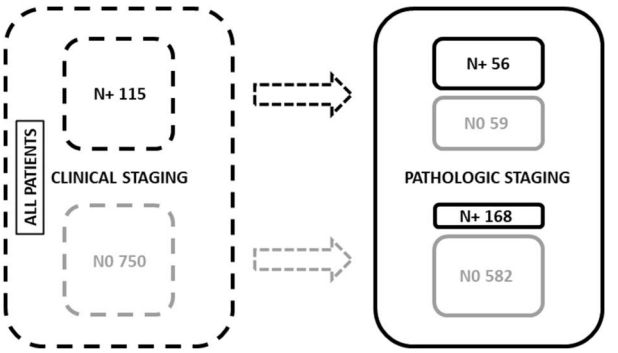

Figure. Illustration of change between the clinical and the pathological N-stage for all patients.

Limitations: The study is limited by the retrospective design and missing central radiological and pathological review. However, the study design permitted including a large patient cohort, promoting the applicability of our findings to routine clinical practice. Further, we conducted sensitivity analyses to account for these limitations, showing comparable results.

Interpretation for Patient Care: In summary, our study reveals that CCI works most effectively as a rule-in but not a rule-out test. Therefore, lymph node dissection should remain the standard during radical surgery to obtain accurate N-staging in high-risk UTUC patients. However, lymph nodes suspicious of tumor invasion on CCI could be a strong argument for early systemic treatment (see Figure).

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Diagnostic Accuracy of Clinical Lymph Node Staging for Upper Tract Urothelial Cancer Patients: A Multicenter, Retrospective, Observational Study

Maximilian Pallauf,[1,2] David D'Andrea,[1] Frederik König,[1,3] Ekaterina Laukhtina,[1] Takafumi Yanagisawa,[1,4] Morgan Rouprêt,[5] Siamak Daneshmand,[6] Hooman Djaladat,[6] Alireza Ghoreifi,[6] Francesco Soria,[7] Kazutoshi Fujita,[8] Stephen A. Boorjian,[9] Aaron M. Potretzke,[9] Andrea Mari,[10] Mathieu Roumiguié,[11] Alessandro Antonelli,[12] Alberto Bianchi,[1,12] Zine-Eddine Khene,[13] John P. Sfakianos,[14] Marcus Jamil,[15] Joost L. Boormans,[16] Jay D. Raman,[17] Nico C. Grossmann,[1,18,19] Alberto Breda,[20] Axel Heidenreich,[1,21] Francesco Del Giudice,[22] Nirmish Singla,[23] Shahrokh F. Shariat,[1,24,25,26,27,28] Benjamin Pradere,[1,29]* and Contributors

[1]*Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*
[2]*Department of Urology, Paracelsus Medical University Salzburg, University Hospital Salzburg, Salzburg, Austria*
[3]*Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[4]*Department of Urology, The Jikei University School of Medicine, Tokyo, Japan*
[5]*Urology Department, GRC n° 5, Predictive Onco-Uro, AP-HP, Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France*
[6]*Department of Urology, USC/Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California*
[7]*Division of Urology, Department of Surgical Sciences, San Giovanni Battista Hospital, University of Studies of Torino, Turin, Italy*
[8]*Department of Urology, Kindai University Faculty of Medicine, Osaka, Japan*
[9]*Department of Urology, Mayo Clinic, Rochester, Minnesota*
[10]*Department of Experimental and Clinical Medicine, University of Florence, Unit of Urological Oncologic Minimally-Invasive Robotic Surgery and Andrology, Careggi Hospital, Florence, Italy*
[11]*Department of Urology, CHU Institut Universitaire du Cancer de Toulouse, Toulouse, France*
[12]*Department of Urology, University of Verona, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy*
[13]*Department of Urology, University of Rennes, Rennes, France*
[14]*Department of Urology, Icahn School of Medicine at Mount Sinai, New York, New York*
[15]*Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan*
[16]*Department of Urology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands*
[17]*Department of Urology, Penn State Health, Hershey, Pennsylvania*
[18]*Department of Urology, University Hospital Zurich, Zurich, Switzerland*
[19]*Department of Urology, Luzerner Kantonsspital, Lucerne, Switzerland*
[20]*Department of Urology, Fundació Puigvert, Autonomous University of Barcelona, Barcelona, Spain*
[21]*Department of Urology, Uro-Oncology, Robot Assisted and Specialized Urologic Surgery, University Hospital Cologne, Cologne, Germany*
[22]*Department of Maternal-Infant and Urologic Sciences, "Sapienza" University of Rome, Policlinico Umberto I Hospital, Rome, Italy*
[23]*Departments of Urology and Oncology, The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland*
[24]*Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan*
[25]*Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria*
[26]*Department of Urology, Weill Cornell Medical College, New York, New York*
[27]*Department of Urology, University of Texas Southwestern, Dallas, Texas*
[28]*Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic*
[29]*Department of Urology UROSUD, La Croix du Sud Hospital, Quint-Fonsegrives, France*

Purpose: Treatment options for the management of upper tract urothelial cancer are based on accurate staging. However, the performance of conventional cross-sectional imaging for clinical lymph node staging (N-staging) remains poorly investigated. This study aims to evaluate the

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* Correspondence: Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria (telephone: +33 661 404418; email: benjaminpradere@gmail.com).

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diagnostic accuracy of conventional cross-sectional imaging for upper tract urothelial cancer N-staging.

Materials and Methods: This study was a multicenter, retrospective, observational study. We included 865 nonmetastatic (M0) upper tract urothelial cancer patients treated with curative intended surgery and lymph node dissection who had been staged with conventional cross-sectional imaging before surgery. We compared clinical (c) and pathological (p) N-staging results to evaluate the concordance of node-positive (N+) and node-negative (N0) disease and calculate cN-staging's diagnostic accuracy.

Results: Conventional cross-sectional imaging categorized 750 patients cN0 and 115 cN+. Lymph node dissection categorized 641 patients pN0 and 224 pN+. The cN-stage was pathologically downstaged in 6.8% of patients, upstaged in 19%, and found concordant in 74%. The sensitivity and specificity of cN-staging were 25% (95% CI 20; 31) and 91% (95% CI 88; 93). Positive and negative likelihood ratios were 2.7 (95% CI 2.0; 3.8) and 0.83 (95% CI 0.76; 0.89). The area under the receiver operating characteristics curve (0.58, 95% CI 0.55; 0.61) revealed low diagnostic accuracy.

Conclusions: Conventional cross-sectional imaging had low sensitivity in detecting upper tract urothelial cancer pN+ disease. However, cN+ increased the likelihood of pN+ by almost threefold. Thus, conventional cross-sectional imaging is a rule-in but not a rule-out test. Lymph node dissection should remain the standard during extirpative upper tract urothelial cancer surgery to obtain accurate N-staging. cN+ could be a strong argument for early systemic treatment.

Key Words: carcinoma, transitional cell; lymphatic metastasis; diagnostic imaging

Upper tract urothelial cancer (UTUC) is a rare disease accounting for 5%-10% of all urothelial cancers.[1] Surgical treatment is recommended in patients with nonmetastatic disease and consists of minimally invasive kidney-sparing surgery or radical surgery.[2] Perioperative systemic therapy is incorporated into the treatment algorithm for subsets of higher-risk localized UTUC cancers.[3] Accurate clinical tumor staging is essential for determining the appropriate treatment strategy regarding the tumor burden.

For UTUC, current clinical metastatic status staging is based on cross-sectional CT or magnetic resonance imaging. However, data on the performance of conventional cross-sectional imaging (CCI) for clinical lymph node staging (N-stage/-ing) remains poorly investigated.[4-6] Despite that, the accurate assessment of the N-stage is essential for elements of surgical decision-making, including the timing and need for perioperative systemic therapy and the extent of lymph node dissection (LND).[7-10]

Therefore, we compared the N-stage diagnosed with CCI (cN) with pathology reports (pN) of LND performed during radical surgery using a large retrospective multicenter study cohort. This study aimed to evaluate the diagnostic accuracy of CCI in UTUC cN-staging.

MATERIALS AND METHODS

Patient Cohort

We conducted an international, multicenter, retrospective, observational study involving 22 institutions. We included nonmetastatic (M0) UTUC patients treated with curative intended surgery between 1988 and 2019. Patients underwent LND during radical nephroureterectomy (RNU) or segmental ureterectomy. The extent and template of LND were performed at the treating surgeon's discretion.[11] All patients who received neoadjuvant treatment (systemic therapy or radiotherapy) were excluded.

All patients were preoperatively staged (local tumor stage [cT-stage]/cN-stage) with CCI. Patients received a chest, abdominal, and pelvic CT; if ineligible, they underwent magnetic resonance imaging of the abdomen and pelvis with noncontrast CT or X-ray of the chest. In each center, the imaging interpretation was performed by uroradiologists. The cN-stage was dichotomized into normal (cN0) vs suspicious for lymph node tumor invasion (cN+). The decision was based on the size, the number, and the morphology of lymph nodes in the tumor's representative landing sites.[10,12,13] We further subdivided the cN+ category based on a cutoff of >1 cm in lymph node size.[14]

In each center, uro-pathologists performed the pathological evaluation (pT-stage/pN-stage). The pT-stage, pN-stage, and tumor grade were classified according to the respective classification's valid form. This study reclassified the results following the TNM-classification eighth edition and the WHO2004/2016 grading system.[15-17]

Support: None.

Conflict of Interest: The Authors have no conflicts of interest to disclose.

Ethics Statement: This study was conducted in accordance with the Declaration of Helsinki. Each center obtained the ethics committee approval before patient data accrual.

Author Contributions: Conception and design: MP, SFS, BP; data analysis and interpretation: MP, FK, EL, TY, ABi, FDG, NS, SFS, BP; data acquisition: DD, MRoup, SD, HD, AG, FS, KF, SAB, AMP, AM, MRoum, AA, ZK, JPS, MJ, JLB, JDR, NCG, ABr, AH, BP; critical revision of the manuscript for scientific and factual content: DD, FK, EL, TY, MRoup, SD, HD, AG, FS, KF, SAB, AMP, AM, MRoum, AA, ABi, ZK, JPS, MJ, JLB, JDR, NCG, ABr, AH, FDG, NS; drafting the manuscript: MP, SFS, BP; statistical analysis: MP, SFS, BP; supervision: SFS, BP.

Data Availability: Data are available on request by the corresponding author.

Variables and Outcomes

We reviewed preoperative patient and medical course characteristics and pathological findings. We compared the clinical vs the pathological N-stage. We categorized the changes into pathological upstaging (pUS), concordant staging (pCS), and downstaging (pDS). Further, we summarized the number of pN+ cases detected vs pN+ missed by CCI.

The diagnostic accuracy of cN-staging was evaluated, categorizing cases into true-positives, false-positives, true-negatives, and false-negatives. True-positives were defined as cN+ and pN+, and true negatives as cN0 and pN0.

We conducted the analyses without a stringent restriction in lymph node size for cN+ but performed separate analyses with a cutoff >1 cm. To account for the possibility of missing pN+ during surgery, we repeated the validation process using a landmark cohort and stratifying patients according to the lymph node yield. The landmark cohort excluded all pN0 patients who had tumor recurrence within a follow-up or a follow-up shorter than 6 months. Patients were categorized into low (<8 lymph nodes resected) and high (≥8 lymph nodes resected) lymph node yield as recommended by Roscigno et al.[18] We conducted separate analyses categorizing patients based on cT-stage, tumor location, and the time of diagnosis, stratified into quartiles (Q).

Statistical Analyses

We reported continuous variables as medians and interquartile ranges (IQRs) and categorical variables as frequencies and proportions. We presented time-to-event variables based on the calculated 24-month survival probability. We calculated cN-staging's sensitivity, specificity, positive and negative predictive value (PV), and positive and negative likelihood ratio (LR). The diagnostic performance of cN-staging was estimated, calculating the area under the receiver operating characteristics curve (AUC). The results are given with 95% confidence intervals (CIs).

Descriptive statistics. We compared preoperative and medical course characteristics between cN0 and cN+ patients. Continuous variables were tested for normal distribution (Shapiro-Wilk test for normality) and, if confirmed, compared by a parametric variance test (2-sample independent *t*-test). Data of continuous variables with non-normally distributed data and measured on ordinal scales were compared by nonparametric analysis of variance (Wilcoxon rank sum test). Categorical variables were compared by the exact χ^2 or Fisher's exact test. The log-rank test for Kaplan-Meier estimates was used to compare time-to-event variables.

Comparison between subgroups. We assessed the differences in cN-staging between applying no vs a cutoff of >1 cm in lymph node size for cN+. The Wilcoxon signed-rank test was used for comparing the outcomes of clinical vs pathological N-staging. DeLong's test for correlated receiver operating characteristics curves was used for AUC comparison.

We validated the outcomes of cN-staging by comparing the overall and the landmark cohort and the high and low lymph node yield cohort. The Wilcoxon rank sum test was used for comparing the outcomes of clinical vs pathological N-staging, and DeLong's test was used for comparing AUCs.

We assessed the differences in cN-staging by tumor characteristics, cT-stage (cTx-1/cT2-4), and tumor location (pelvicalyceal/ureter/both). For comparing the outcomes of clinical vs pathological N-staging, we used the Kruskal-Wallis rank sum test and the Wilcoxon rank sum test for multiple-group and pairwise comparison. DeLong's test was used for pairwise AUC comparison.

We assessed the trend of cN-staging over time by comparing the quartiles of diagnosis. Spearman's rank correlation was used for comparing the outcomes of clinical vs pathological N-staging, and DeLong's test was used for pairwise AUC comparison.

All tests were 2-sided, with the level of statistical significance set at a P value $< .05$. All statistical analyses were performed using R (Version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria, 2020).

RESULTS

Study Population

Among the 3,496 patients in our multicenter data set, 865 met the inclusion criteria. Preoperative imaging detected 115 (13%) patients with cN+ disease, of whom 68 (7.9%) had cN+ disease with a lymph node size >1 cm.

Compared to patients with cN0 disease, patients with cN+ disease were more likely to be of the Caucasian race and less likely to be of the African and Asian races: 86%, 1.4%, and 13% vs 72%, 4.2%, and 24% ($P = .03$). Bladder cancer history was more frequently present in patients with cN0 than cN+ disease: 33% vs 21% ($P = .01$). We detected no statistically significant differences between patients with cN0 and cN+ disease for all other baseline characteristics, including age, body mass index, kidney function, and smoking status.

Diagnostic ureterorenoscopy and selective upper tract urine cytology were more frequently performed in patients with cN0 than cN+ disease: 63% vs 41% ($P < .001$) and 31% vs 18% ($P = .01$). Whereas high-grade cytology was more frequently detected on selective cytology in patients with cN+ than cN0 disease (86% vs 65%, $P = .03$), no statistically significant differences were found for bladder urine cytology ($P = .4$) and tumor grade on biopsy ($P > .9$). In 14 patients (1.6%), a biopsy was taken through a percutaneous approach, which was more common among patients with cN+ than cN0 disease: 4.4% vs 1.2% ($P = .03$).

On CCI, locally advanced UTUC (≥cT2) was suspected in 383 patients (44%). Patients with cN+ disease had more advanced cT-stages ($P = .03$) and were more frequently suspected of having a multifocal disease (17% vs 8.1%, $P = .01$) than patients with cN0 disease. However, we detected no statistically significant difference in the rate of hydronephrosis ($P = .3$).

Almost all patients (99.7%) in this cohort received an RNU. In 37%, open surgery was performed. The open approach was more frequently chosen in patients

Table 1. *Patient Characteristics: Baseline Characteristics, Preoperative Diagnostics, Hospital Stay*

Characteristics	Overall All N = 865		Comparison cN0 vs cN+ cN0 N = 750		cN+ N = 115		*P* value
Baseline characteristics							
Age, median (IQR), y	71	(64;77)	71	(64;77)	69	(64;77)	.4[a]
Gender, No./total No. (%)							.6[b]
Male	588/865	(68)	512/750	(68)	76/115	(66)	
Female	277/865	(32)	238/750	(32)	39/115	(34)	
Race, No./total No. (%)							.03[c]
Caucasian	418/570	(73)	356/498	(72)	62/72	(86)	
African	22/570	(3.9)	21/498	(4.2)	1/72	(1.4)	
Asian	130/570	(23)	121/498	(24)	9/72	(13)	
Body mass index, median (IQR), kg/m^2	25.4	(22.9;28.7)	25.4	(23.0;28.7)	25.6	(22.7;28.6)	.8[a]
Kidney function before surgery (eGFR), mL/min/1.73 m^2, median (IQR)	58.0	(44.4;72.9)	57.6	(43.7;72.0)	58.5	(46.3;78.8)	.2[a]
Current and former smokers, No./total No. (%)	533/800	(67)	456/693	(66)	77/107	(72)	.2[b]
Bladder cancer history, No./total No. (%)	274/865	(32)	250/750	(33)	24/115	(21)	.01[b]
Preoperative diagnostics							
Bladder urine cytology present, No./total No. (%)	338/865	(39)	290/750	(39)	48/115	(42)	.5[b]
Bladder urine cytology result, No./total No. (%)							.4[a]
Negative for high grade	168/338	(50)	147/290	(51)	21/48	(44)	
Nondiagnostic	0/338	(0)	0/290	(0)	0/48	(0)	
Positive for high grade	170/338	(50)	143/290	(49)	27/48	(56)	
Selective upper tract urine cytology present, No./total No. (%)	255/865	(30)	234/750	(31)	21/115	(18)	.01[b]
Selective upper tract urine cytology result, No./total No. (%)							.03[a]
Negative for high grade	55/255	(22)	55/234	(24)	0/21	(0)	
Nondiagnostic	29/255	(11)	26/234	(11)	3/21	(14)	
Positive for high grade	171/255	(67)	153/234	(65)	18/21	(86)	
Diagnostic ureterorenoscopy performed, No./total No. (%)	517/865	(60)	470/750	(63)	47/115	(41)	< .001[b]
Endoscopic biopsy performed, No./total No. (%)	323/865	(37)	284/750	(38)	39/115	(34)	.4[b]
Percutaneous biopsy performed, No./total No. (%)	14/865	(1.6)	9/750	(1.2)	5/115	(4.4)	.03[c]
Tumor grade on biopsy, No./total No. (%)							> .9[a]
Low grade	94/299	(31)	83/263	(32)	11/36	(31)	
Nondiagnostic	22/299	(7.4)	19/263	(7.2)	3/36	(8.3)	
High grade	183/299	(61)	161/263	(61)	22/36	(61)	
T-stage stage on imaging, No./total No. (%)							.03[a]
Tx-T1	482/865	(56)	425/750	(57)	57/115	(50)	
T2	222/865	(26)	196/750	(26)	26/115	(23)	
T3	143/865	(17)	120/750	(16)	23/115	(20)	
T4	18/865	(2.1)	9/750	(1.2)	9/115	(7.8)	
N-stage on imaging (all), No./total No. (%)							
N0	750/865	(87)					
N+	115/865	(13)					
N-stage on imaging (N+ >1 cm), No./total No. (%)							
N0	797/865	(92)					
N+	68/865	(7.9)					
Tumor multifocal on imaging, No./total No. (%)	68/727	(9.4)	50/618	(8.1)	18/109	(17)	.01[b]
Hydronephrosis on imaging, No./total No. (%)	355/851	(42)	313/739	(42)	42/112	(38)	.3[b]
Hospital stay							
Side of surgery, No./total No. (%)							.051[c]
Left	359/683	(53)	300/591	(51)	59/92	(64)	
Right	320/683	(47)	287/591	(49)	33/92	(36)	
Both sides	4/683	(0.6)	4/591	(0.7)	0/92	(0)	
Surgery performed, No./total No. (%)							.3[c]
Radical nephroureterectomy	862/865	(99.7)	748/750	(99.7)	114/115	(99.1)	
Segmental ureterectomy	3/865	(0.4)	2/750	(0.3)	1/115	(0.9)	
Surgical approach, No./total No. (%)							< .001[b]
Open	254/689	(37)	212/595	(36)	42/94	(45)	
Laparoscopic	181/689	(26)	169/595	(28)	12/94	(13)	
Robotic	150/689	(22)	133/595	(22)	17/94	(18)	
Combined	104/689	(15)	81/595	(14)	23/94	(25)	
Removal of the bladder cuff, No./total No. (%)	864/865	(99.9)	749/750	(99.9)	115/115	(100)	> .9[c]
Surgery time, min	255	(190;345)	260	(190;347)	240	(187.5;303.75)	.2[a]
Blood loss during surgery, mL	200	(100;350)	200	(100;336.5)	200	(115;400)	.053[a]
Perioperative blood transfusions, No./total No. (%)	52/668	(7.8)	42/570	(7.4)	10/98	(10.2)	.3[b]
Minor perioperative complications (Clavien-Dindo 1-2), No./total No. (%)	153/689	(22)	128/589	(22)	25/100	(25)	.5[b]
Major perioperative complications (Clavien-Dindo 3-5), No./total No. (%)	62/689	(9.0)	51/589	(8.7)	11/100	(11)	.4[b]
Hospital, median (IQR), d	8	(4;13)	8	(4;13)	7	(5;11.75)	> .9[a]

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a] Wilcoxon rank sum test.
[b] Pearson's χ^2 test.
[c] Fisher's exact test.

with cN+ than cN0 disease: 45% vs 36% ($P < .001$). The median number of resected lymph nodes was 6 (IQR 2,12), and there was no statistically significant difference between patients with cN0 and cN+ disease ($P = .09$). We detected no statistically significant differences between patients with cN0 and cN+ disease for all other surgical parameters, including the rate of bladder cuff removal, the estimated perioperative blood loss, transfusion rates, complication rates, and the length of surgery and hospital stay (Table 1).

In total, 224 patients (26%) had pN+ disease, which was more common in patients with cN+ than cN0 disease: 49% vs 22% ($P < .001$). The median number of tumor-positive resected lymph nodes was 2 (IQR 1,4) and was statistically different between patients with cN0 and cN+ disease: 2 (IQR 1,4) vs 2 (IQR 1,5; $P = .02$).

Locally advanced UTUC (≥pT2) was detected in 532 patients (62%) and was more common in patients with cN+ than cN0 disease: 71% vs 60% ($P = .02$). More than half of the tumors (56%) were located pelvicalyceal, 30% in the ureter, and 14% in both locations. The tumor was more often located pelvicalyceal and less often in the ureter in patients with cN+ disease compared to patients with cN0 disease: pelvicalyceal 67% vs 55% and ureter 21% vs 32% ($P = .03$). Lymphovascular invasion was more frequently detected in patients with cN+ than cN0 disease: 45% vs 28% ($P < .001$). We detected no statistically significant differences between patients with cN0 and cN+ disease for all other pathological features, including lymph-node density, tumor grading, the rates of multifocal disease, concomitant carcinoma in situ, and variant histology, and the surgical margin status.

In total, 139 patients (16%) received adjuvant chemotherapy, and the rate was higher among patients with cN+ than cN0 disease: 32% vs 14% ($P < .001$). The recurrence-free survival probability at 24 months was 71% (95% CI 68; 75) and was higher for patients with cN0 than cN+ disease: 74% (95% CI 71; 78) vs 50% (95% CI 40; 62) ($P < .001$). The overall and cancer-specific survival probabilities at 24 months were 81% (95% CI 78; 84) and 86% (95% CI 83; 89), respectively, and were higher for patients with cN0 than cN+ disease: 84% (95% CI 81; 87) vs 62% (95% CI 52; 73; $P < .001$) and 89% (95% CI 86;92) vs 67% (95% CI 58; 78; $P < .001$). Survivors were followed for a median of 20.6 months (IQR 7.3,45.8; Table 2).

Comparison of Clinical and Pathological Staging

Overall cohort. On the final specimen, the cN-stage was pDS in 6.8%, pUS in 19%, and was found pCS in 74%. When applying a cutoff of >1 cm in lymph node size for cN+, the cN-stage was pDS in 3.5%, pUS in 22%, and was found pCS in 75%. The differences were statistically significant ($P < .001$).

Validation cohorts. The landmark cohort included 719 out of 865 patients. The comparison of cN- and pN-staging revealed no statistically significant difference between the landmark and the overall cohort ($P = .06$). The low-yield lymph node group included 446, and the high-yield group included 314 patients. For 105 patients, the exact lymph node yield was unknown. The comparison of cN- and pN-staging revealed no statistically significant difference between the low- and high-yield lymph node groups ($P = .5$).

The Figure illustrates the change between the cN and the pN stage for the overall and the validation cohorts.

Subgroup analyses. We stratified patients regarding the cT stage: 482 patients with noninvasive (cTx and cTis-cT1) and 383 patients with invasive (cT2-cT4) disease. The comparison of cN- and pN-staging revealed no statistically significant difference between the noninvasive and invasive cT-groups ($P = .07$).

We stratified patients into 3 groups regarding the tumor's location: pelvicalyceal region in 478 patients, ureter in 257, and both locations in 115. The comparison of cN- and pN-staging differed between the tumor location groups ($P = .03$). Tumors present in both locations of the upper urinary tract had the cN stage more frequently pUS and less frequently pDS than tumors located pelvicalyceal: 27% vs 18% and 3.5% vs 8.8% ($P = .01$).

We stratified patients into Q1 to Q4 according to the time of tumor diagnosis: Q1 ≤2008; Q2 2009-2013; Q3 2014-2016; Q4 ≥2017. Q1 included 212 patients, Q2 199, Q3 194, and Q4 260. The comparison of cN- and pN-staging differed between Q1 to Q4 ($P = .01$). We detected a modest time-dependent decline in pUS ($P = .04$; $\rho = -0.07$).

Diagnostic Value of cN-staging

Overall cohort. Out of 224 pN+, CCI detected 56 (25%) and missed 168 (75%). When applying a cutoff of >1 cm in lymph node size for cN+, CCI detected 38 (17%) and missed 186 (83%).

The sensitivity of cN-staging was 25% (95% CI 20; 31), whereas the specificity was 91% (95% CI 88; 93). The positive PV was 49% (95% CI 41; 57), and the negative PV was 78% (95% CI 76; 79). The positive and negative LRs were 2.7 (95% CI 2.0; 3.8) and 0.83 (95% CI 0.76; 0.89). When applying a cutoff of >1 cm in lymph node size for cN+, the sensitivity of cN-staging was 17% (95% CI 12; 23), whereas the specificity was 95% (95% CI 93; 97). The positive PV was 56% (95% CI 45; 67) and the negative PV was 77% (95% CI 76; 78). The positive and negative LRs were 3.6 (95% CI 2.3; 5.7) and 0.87 (95% CI 0.82; 0.93).

The AUC for cN-staging as a diagnostic test for pN-staging was 0.58 (95% CI 0.55; 0.61) and 0.56 (95% CI 0.54; 0.59) when applying a cutoff of >1 cm in lymph node size for cN+. We detected no

Table 2. *Patient Characteristics Surgery Report and Follow-up*

Category	Characteristics	Overall All N = 865		Comparison cN0 vs cN+ cN0 N = 750		cN+ N = 115		*P* value
	Surgery report							
Pathological tumor stage, No./total No. (%)								< .001[a]
T0		8/865	(0.9)	7/750	(0.9)	1/115	(0.9)	
Ta		138/865	(16)	127/750	(17)	11/115	(9.6)	
Tis		17/865	(2.0)	16/750	(2.1)	1/115	(0.9)	
T1		170/865	(20)	150/750	(20)	20/115	(17)	
T2		137/865	(16)	124/750	(17)	13/115	(11)	
T3		334/865	(39)	283/750	(38)	51/115	(44)	
T4		61/865	(7.1)	43/750	(5.7)	18/115	(16)	
Pathological tumor stage (T0-1 vs T2-4), No./total No. (%)								.02[a]
T0-1		333/865	(39)	300/750	(40)	33/115	(29)	
T2-4		532/865	(62)	450/750	(60)	82/115	(71)	
Pathological lymph node stage, No./total No. (%)								< .001[a]
N0		641/837	(77)	582/726	(80)	59/111	(53)	
N1		86/837	(10)	71/726	(9.8)	15/111	(14)	
N2		110/837	(13)	73/726	(10)	37/111	(33)	
Pathological lymph node stage grouped (N0 vs N+), No./total No. (%)								< .001[a]
N0		641/865	(74)	582/750	(78)	59/115	(51)	
N+		224/865	(26)	168/750	(22)	56/115	(49)	
Lymph nodes resected, median (IQR), No.		6	(2;12)	6	(2;11)	7	(3;12)	.09[a]
Number of positive lymph nodes resected		2	(1;4)	2	(1;4)	2	(1;5)	.02[a]
Lymph node density (positive, all), median (IQR)		0.50	(0.22;1.00)	0.50	(0.20;1.00)	0.50	(0.25;1.00)	.8[a]
Tumor location on pathology report, No./total No. (%)								.03[b]
Pelvicalyceal		478/850	(56)	403/738	(55)	75/112	(67)	
Ureter		257/850	(30)	234/738	(32)	23/112	(21)	
Both		115/850	(14)	101/738	(14)	14/112	(13)	
Tumor multifocal on pathology report, No./total No. (%)		222/838	(27)	188/728	(26)	34/110	(31)	.3[b]
Tumor grade on pathology report, No./total No. (%)								.2[a]
Low grade		124/815	(15)	112/708	(16)	12/107	(11)	
High grade		691/815	(85)	596/708	(84)	95/107	(89)	
Lymphovascular invasion on pathology report, No./total No. (%)		250/819	(31)	201/710	(28)	49/109	(45)	< .001[b]
Concomitant carcinoma in situ on pathology report, No./total No. (%)		108/792	(14)	95/698	(14)	13/94	(14)	> .9[b]
Variant histology on pathology report, No./total No. (%)		71/865	(8.2)	61/750	(8.1)	10/115	(8.7)	.8[b]
Positive surgical margins (soft tissue and/or ureter) on pathology report, No./total No. (%)		230/761	(30)	198/668	(30)	32/93	(34)	.3[b]
Positive surgical margins—soft tissue—on pathology report, No./total No. (%)		194/822	(24)	168/716	(24)	26/106	(25)	.8[b]
Positive surgical margins—ureter—on pathology report, No./total No. (%)		52/720	(7.2)	45/631	(7.1)	7/89	(7.9)	.8[b]
	Follow-up							
Received adjuvant chemotherapy, No./total No. (%)		139/865	(16)	102/750	(14)	37/115	(32)	< .001[b]
Recurrence-free survival probability 24 mo, % (95% CI)		71	(68;75)	74	(71;78)	50	(40;62)	< .001[c]
Location of tumor recurrence (recurrence ≤24 mo), No./total No. (%)								> .9[a]
Local/nodal		50/185	(27)	38/140	(27)	12/45	(27)	
Distant		135/185	(73)	102/140	(73)	33/45	(73)	
Overall survival probability 24 mo, % (95% CI)		81	(78;84)	84	(81;87)	62	(52;73)	< .001[c]
Cancer-specific survival probability 24 mo, % (95% CI)		86	(83;89)	89	(86;92)	67	(58;78)	< .001[c]
Follow-up of survivors, median (IQR), mo		20.6	(7.3;45.8)					

Abbreviations: CI, confidence interval, IQR, interquartile range.
[a] Wilcoxon rank sum test.
[b] Pearson's χ^2 test.
[c] Log-rank test.

statistically significant difference between the AUCs ($P = .08$).

Validation cohorts and subgroup analyses. We detected no statistically significant difference in the comparison of AUCs between the landmark and the overall cohort ($P > .9$) and between the low- and high-yield lymph node group ($P = .2$). On stratification for cT stage, tumor location, or time of diagnosis, we detected no statistically significant differences between the AUCs ($P > .05$).

Tables 3 and 4 list the outcomes and the comparison between all cohorts and subgroups.

DISCUSSION

This is the first study presenting robust data assessing the diagnostic accuracy of CCI for cN-staging in UTUC. We analyzed an updated international multicenter cohort including 865 patients and validated our findings in a stepwise approach. We assessed the differences in cN-staging based on

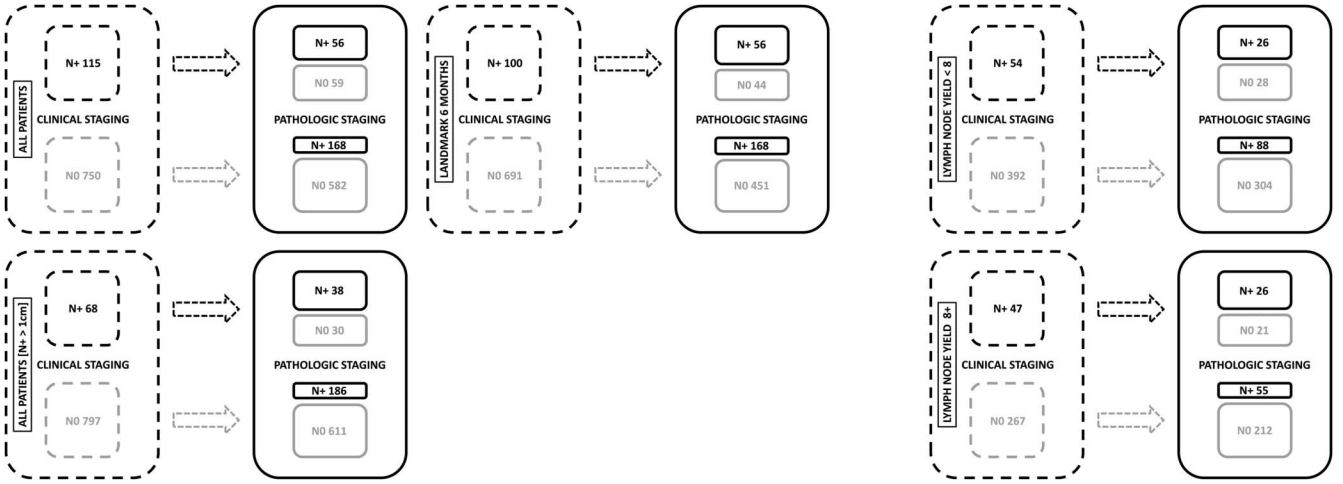

Figure. Change between the cN- and the pN-stage for the overall and the validation cohorts.

lymph node size by comparing the outcomes with and without a cutoff >1 cm. Further, we accounted for the possibility of a false-negative confirmatory test by conducting a landmark analysis and stratifying patients according to the lymph node yield. On the contrary, all previous studies were published before 2000, included small cohorts of up to 86 patients, and reported a meaningful variance for sensitivity and specificity.[4-6] Therefore, this study addressed a critical gap in knowledge.

The study revealed that CCI is lacking in detecting pN+ disease. Only 25% of pN+ were detected, but 75% were missed. Despite a reasonable specificity of 91%, this has resulted in a low diagnostic accuracy (AUC 0.58). Furthermore, the negative LR (0.83) indicated that cN0 marginally reduces the likelihood of pN+ disease; conversely, the positive LR (2.7) indicated that cN+ increases the likelihood of pN+ disease almost 3 times. Thus, CCI works most effectively as a rule-in but not a rule-out test.

Notably, applying a cutoff of >1 cm in lymph node size for cN+ decreased the detection rate of pN+: only 17% of pN+ were detected, but 83% were missed. Furthermore, applying this cutoff led to a higher rate of pUS and a lower rate of pDS: 22% vs 19% and 3.5% vs 6.8% ($P < .001$). Although applying this cutoff has not led to a statistically significant decrease in diagnostic accuracy, these findings outline that the suspicion of lymph node tumor invasion should not be based on lymph node size only.

Table 3. *Overall and Validation Cohorts*

Patient cohort	Overall cohort					Landmark cohort			Lymph node yield				
Characteristic	All patients N = 865		All patients (N+ >1 cm) N = 865		*P* value	6 months N = 719		*P* value	Nodes <8 N = 446		Nodes 8+ N = 314		*P* value
Clinical vs pathological N-stage, No. (%)					< .001[a]			.06[b]					.5[b]
Downstaging	59	(6.8)	30	(3.5)		44	(6.1)		28	(6.3)	21	(6.7)	
Concordant	638	(74)	649	(75)		507	(71)		330	(74)	238	(76)	
Upstaging	168	(19)	186	(22)		168	(23)		88	(20)	55	(18)	
Prevalence, No. (%)	224	(26)	224	(26)		224	(31)		114	(26)	81	(26)	
pN+ detected vs missed, No. (%)													
Detected	56	(25)	38	(17)					26	(23)	26	(32)	
Missed	168	(75)	186	(83)					88	(77)	55	(68)	
AUC (95% CI)	0.58	(0.55;0.61)	0.56	(0.54;0.59)	.08[c]	0.58	(0.55;0.61)	> .9[d]	0.57	(0.53;0.61)	0.62	(0.56;0.67)	.2[d]
Sensitivity, % (95% CI)	25	(20;31)	17	(12;23)		25	(20;31)		23	(16;32)	32	(22;43)	
Specificity, % (95% CI)	91	(88;93)	95	(93;97)		91	(88;94)		92	(88;94)	91	(87;94)	
Predictive value, % (95% CI)													
Positive	49	(41;57)	56	(45;67)		56	(47;65)		48	(36;60)	55	(43;68)	
Negative	78	(76;79)	77	(76;78)		73	(71;74)		78	(76;79)	79	(77;82)	
Likelihood ratio (95% CI)													
Positive	2.7	(2.0;3.8)	3.6	(2.3;5.7)		2.8	(2.0;4.0)		2.7	(1.7;4.4)	3.6	(2.1;6.0)	
Negative	0.83	(0.76;0.89)	0.87	(0.82;0.93)		0.82	(0.76;0.89)		0.84	(0.76;0.94)	0.75	(0.64;0.87)	

Abbreviations: AUC, area under the receiver operating characteristics curve; CI, confidence interval.
[a] Wilcoxon signed-rank test.
[b] Wilcoxon rank sum test.
[c] DeLong's test for correlated receiver operating characteristics curves.
[d] DeLong's test.

Table 4. *Subgroup Analyses*

Patient cohort	Clinical T-stage					Tumor location					Quartile of diagnosis									
Characteristic	cTx-1 N = 482		cT2-4 N = 383		*P* value	Pelvicalyceal N = 478		Ureter N = 257		Both N = 115	*P* value	Q1 N = 212		Q2 N = 199		Q3 N = 194		Q4 N = 260		*P* value	ρ
Clinical vs pathological N-stage, No. (%)					.07[a]						.03[b] .01[a]									.01[b] .04[c]	−0.07
Downstaging	33	(6.8)	26	(6.8)		42	(8.8)	11	(4.3)	4	(3.5)	12	(5.7)	15	(7.5)	17	(8.8)	15	(5.8)		
No difference	368	(76)	270	(71)		348	(73)	200	(78)	80	(70)	144	(68)	145	(73)	151	(78)	198	(76)		
Upstaging	81	(17)	87	(23)		88	(18)	46	(18)	31	(27)	56	(26)	39	(20)	26	(13)	47	(18)		
Prevalence, No. (%)	105	(22)	119	(31)		121	(25)	58	(23)	41	(36)	66	(31)	59	(30)	36	(19)	63	(24)		
pN+ detected vs missed, No. (%)																					
Detected	24	(23)	32	(27)		33	(27)	12	(21)	10	(24)	10	(15)	20	(34)	10	(28)	16	(25)		
Missed	81	(77)	87	(73)		88	(73)	46	(79)	31	(76)	56	(85)	39	(66)	26	(72)	47	(75)		
AUC (95% CI)	0.57	(0.53;0.61)	0.59	(0.54;0.63)	.6[d]	0.58	(0.53;0.62)	0.58	(0.52;0.63)	0.59	(0.52;0.67)	> .05[d]	0.53	(0.49;0.58)	0.62	(0.55;0.68)	0.59	(0.51;0.66)	0.59	(0.53;0.65)	> .05[d]	
Sensitivity, % (95% CI)	23	(15;32)	27	(19;36)		27	(20;36)	21	(11;33)	24	(12;40)		15	(8;26)	34	(22;47)	28	(14;45)	25	(15;38)		
Specificity, % (95% CI)	91	(88;94)	90	(86;94)		89	(86;92)	95	(90;97)	95	(87;99)		92	(86;96)	89	(83;94)	89	(83;94)	92	(88;96)		
Predictive value, % (95% CI)																					
Positive	42	(31;54)	55	(44;66)		44	(34;54)	52	(34;70)	71	(46;88)		46	(28;65)	57	(42;71)	37	(23;54)	52	(36;67)		
Negative	81	(79;83)	73	(71;75)		80	(78;82)	80	(78;82)	69	(65;73)		71	(68;73)	76	(73;80)	84	(82;87)	80	(77;82)		
Likelihood ratio (95% CI)																					
Positive	2.6	(1.6;4.2)	2.7	(1.7;4.4)		2.6	(1.7;3.8)	3.7	(1.7;8.0)	4.5	(1.5;13.5)		1.8	(0.8;4.1)	3.2	(1.7;5.7)	2.6	(1.3;5.2)	3.3	(1.8;6.4)		
Negative	0.85	(0.76;0.94)	0.81	(0.72;0.91)		0.81	(0.73;0.91)	0.84	(0.73;0.96)	0.80	(0.67;0.96)		0.92	(0.83;1.03)	0.74	(0.61;0.90)	0.81	(0.66;1.00)	0.81	(0.70;0.94)		

Abbreviations: AUC, area under the receiver operating characteristics curve; CI, confidence interval; Q, quartile.
[a] Pairwise Wilcoxon rank sum test.
[b] Kruskal-Wallis rank sum test.
[c] Spearman's rank correlation.
[d] Pairwise DeLong's test.

Stratification based on the cT stage did not influence the outcomes of cN-staging. Although the prevalence of pN+ was higher in patients with clinically invasive (31%) than noninvasive disease (22%), we detected no statistically significant differences in the comparisons of clinical vs pathological N-staging or diagnostic accuracy. Thus, noninvasive disease on cT-staging should not result in avoiding invasive lymph node staging in cN0 patients.

Moreover, the tumor's location did not influence the diagnostic accuracy of CCI. We discovered more frequent cN-stage pUS and less frequent pDS for tumors in both upper urinary tract locations than for tumors solitary located pelvicalyceal (27% vs 18% and 3.5% vs 8.8%, $P = .01$). However, we did not detect a statistically significant difference between pelvicalyceal and ureteral tumors. These findings may be explained by the aggressive features of multifocal disease rather than the tumor's location.[19,20] Therefore, the tumor's primary location should not be taken into consideration for the interpretation of cN-staging using CCI.

A recent publication assessing the diagnostic accuracy of CCI for cN-staging of bladder cancer patients confirms the independency of tumor location. The study, which analyzed 1,014 patients, revealed a sensitivity of 30% and a specificity of 84%, with only a slight concordance between cN and pN stages.[21] Overall, these findings are comparable with the results of our study, pointing out similar strengths and weaknesses for CCI in cN-staging for urothelial carcinoma regardless of the primary tumor's location.

The diagnostic accuracy of CCI for UTUC cN-staging has not improved throughout the last decades. Although we detected a decline in cN-stage pUS from Q1 to Q4 ($P = .04$; $\rho = -0.07$), the trend was modest. Furthermore, the decline of cN-stage pUS did not improve diagnostic accuracy. The lack of improvement in preoperative staging contributes to missing advancements in UTUC management and treatment outcomes.[22] Therefore, technical improvements for UTUC cN-staging are urgently needed.

Overall, we can draw 1 major conclusion regarding the management of UTUC patients. CCI for cN-staging has to be considered a rule-in but not a rule-out test. Therefore, regardless of the cN-staging, the size of the lymph nodes, the clinical T-stage, and the tumor's location, LND must remain an integral part of extirpative surgery for UTUC. This assumption is supported by the beneficial effects of LND for cN0 patients.[23] Furthermore, cN+ disease substantially increases the likelihood of pN+ disease, explaining why cN+ patients could benefit from early systemic treatment.[24] Consequently, cN+ should be considered a solid argument to propose a neoadjuvant systemic therapy. Taking the results of this study into consideration when interpreting

UTUC cN-staging results will aid in patient counseling and improve patient care.

This study has several limitations resulting from its retrospective design. First, there is the risk of selection bias and the increased possibility of missing data. Second, there was no standardization of diagnostic protocols and treatment procedures, including the extent and template of LND. Neither was there a review of radiological and pathological examinations. cN+ and pN+ diseases might have been missed or misclassified, lowering diagnostic accuracy calculations. However, the retrospective and multicentric study design permitted including a large patient cohort, promoting the applicability of our findings to routine clinical practice. Further, we conducted a landmark analysis and categorized patients based on the lymph node yield to account for the possibility of missing pN+ disease at first investigation, showing comparable results.

CONCLUSIONS

CCI had low sensitivity in UTUC cN-staging, missing 75% of pN+ disease and resulting in poor diagnostic accuracy. However, because of high specificity, cN+ increased the likelihood of pN+ by almost threefold. Thus, CCI works most effectively as a rule-in but not a rule-out test. Therefore, LND should remain the standard during RNU to obtain accurate N-staging. However, cN+ could be a strong argument for early systemic treatment.

Appendix Contributors

Riccardo Campi, Department of Experimental and Clinical Medicine, University of Florence, Unit of Urological Robotic Surgery and Renal Transplantation, Careggi Hospital, Florence, Italy: data acquisition.
Eiji Kikuchi, Department of Urology, St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan: data acquisition.
Pierre I. Karakiewicz, Department of Surgery, Université de Montréal, Montréal, Canada: scientific advisory.

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