Lymphovascular Invasion Predicts Clinical Outcomes in Patients With Node-Negative Upper Tract Urothelial Carcinoma

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ABSTRACT

Purpose

To assess the association of lymphovascular invasion (LVI) with cancer recurrence and survival in a large international series of patients treated with radical nephroureterectomy (RNU) for upper urinary tract urothelial carcinoma (UTUC).

Patients and Methods

Data were collected on 1,453 patients treated with RNU at 13 academic centers and combined into a relational database. Pathologic slides were rereviewed by genitourinary pathologists according to strict criteria. LVI was defined as presence of tumor cells within an endothelium-lined space.

Results

LVI was observed in 349 patients (24%). Proportion of LVI increased with advancing tumor stage, high tumor grade, presence of tumor necrosis, sessile tumor architecture, and presence of lymph node metastasis (all $P < .001$). LVI was an independent predictor of disease recurrence and survival ($P < .001$ for both). Addition of LVI to the base model (comprising pathologic stage, grade, and lymph node status) marginally improved its predictive accuracy for both disease recurrence and survival (1.1%, $P = .03$; and 1.7%, $P < .001$, respectively). In patients with negative lymph nodes and those in whom a lymphadenectomy was not performed ($n = 1,313$), addition of LVI to the base model improved the predictive accuracy of the base model for both disease recurrence and survival by 3% ($P < .001$ for both). In contrast, LVI was not associated with disease recurrence or survival in node-positive patients ($n = 140$).

Conclusion

LVI was an independent predictor of clinical outcomes in nonmetastatic patients who underwent RNU for UTUC. Assessment of LVI may help identify patients who could benefit from multimodal therapy after RNU. After confirmation, LVI should be included in staging of UTUC.

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INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) accounts for approximately 10% of all renal tumors and for approximately 5% of all urothelial carcinomas.^{1,2} Radical nephroureterectomy (RNU) with excision of a bladder cuff is the standard of care for UTUC. Accurate estimates of the clinical stage and prognosis are essential for patient counseling and informed decision making. Accurate risk estimates are also required for prospective clinical trial design to ensure homogeneous patient groups.

Several studies have evaluated risk factors for cancer recurrence and survival after RNU in small

cohorts of patients with UTUC. Patient age, pathologic stage, tumor grade, tumor location, lymph node involvement, and surgical approach have all been shown to predict disease recurrence or survival after RNU.³⁻⁹ Recently, lymphovascular invasion (LVI) has been reported to be associated with survival in small single-institution data sets.^{10,11} LVI is an essential and important step in the systemic dissemination of cancer cells.^{12,13} We hypothesized that LVI is associated with micrometastases and, therefore, could identify patients without lymph node involvement who are at increased risk of cancer recurrence and mortality despite apparently effective RNU. Therefore, we assessed the prognostic

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value of LVI in a large international series of UTUC patients treated with RNU focusing on patients without lymph node metastasis.

PATIENTS AND METHODS

Patient Selection

This was an institutional review board–approved study with all participating sites providing the necessary institutional data sharing agreements before initiation of the study. A total of 13 academic centers worldwide provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen, and the final data set was produced for the current analysis.

This study comprised 1,453 patients who underwent RNU with ipsilateral bladder cuff resection between 1987 and 2007. Median patient age was 69.7 years (range, 27 to 97 years). Regional lymphadenectomy was generally performed in patients with suspicious lymph nodes on preoperative axial imaging or with adenopathies detected during intraoperative examination. Extended lymphadenectomy was not routinely performed. Neoadjuvant and adjuvant chemotherapy regimens were administered to 42 patients (2.9%) and 169 patients (11.6%), respectively.

Pathologic Evaluation

All surgical specimens were processed according to standard pathologic procedures, and all slides were rereviewed by genitourinary pathologists according to identical strict criteria. All pathologists were blinded to clinical outcomes. All specimens were histologically confirmed to be urothelial carcinoma. Tumors were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification. Tumor grading was assessed according to the 1998 WHO/International Society of Urologic Pathology consensus classification.¹⁴ LVI was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls. Immunohistochemistry for endothelial cells was not performed to keep with standard practice of pathologists. By agreement, the following features favored the presence of LVI: the vicinity of arterioles; the unequivocal presence of endothelial cells (at least two cells per space); the vessels invaded are occasional and isolated; spaces supposedly completely filled with cancer cells are real intravascular tumoral thrombi; the thrombus is usually floating, completely free, in the vascular lumen and shows fibrin or plasma precipitate or even RBCs around it; the tumoral thrombus is composed of tightly cohesive cells with a smooth border and a shrunk cytoplasm; and the cells in the periphery have a shell-like aspect. Any equivocal foci and foci in which tumor cells merely encroached on a vascular lumen were considered negative. No attempt was made to differentiate between vascular and lymphatic vessels because of the difficulty and lack of reproducibility when using routine light microscopic examination. The presence of concomitant carcinoma in situ and the tumor architecture were also assessed in every representative section.

To ensure validity of the pathologic data extraction, two pathologists independently reviewed specimens from 145 randomly selected patients while blinded to patient clinical parameters and the finding of the other reviewer. Inter-reader reliability measured using the intraclass correlation coefficient was greater than 0.95 for each pathologic characteristic.

Surveillance Regimen

Patients were generally observed every 3 to 4 months for the first year after RNU, every 6 months from the second through the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated. Median follow-up time for this patient cohort was 48 months (range, 0.1 to 250 months).

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not separately considered in the analysis of recurrence-free survival rate. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Death certificates were retrieved from the archived death certificates and reviewed for cause of death. Attribution of cause of death on the death certificate is in two parts. Part I lists death caused by immediate cause of death (final disease or condition resulting in death) or by underlying cause of death, and part II lists other significant conditions contributing to death but not resulting in the underlying cause given in part I. Information abstracted from each death certificate included the date of death and whether urothelial cancer was noted in part I or II. To reduce bias in attribution of cause of death, only men who had urothelial cancer listed in part I of the death certificate were considered to have died of UTUC for this study. All patients who were coded as dead of cancer had previous disease recurrence. Perioperative mortality (any death within 30 days of surgery or before discharge) was censored at time of death for urothelial cancer-specific survival (CSS) analyses.

Statistical Analysis

The impact of pathologic stage, grade, lymph node status, and LVI on recurrence-free survival and CSS was determined. For purposes of analysis, patients with negative lymph nodes and those who did not undergo lymphadenectomy were grouped together. This was based on the fact that patients with negative lymph nodes and those who did not undergo lymphadenectomy did not differ in their risks of disease recurrence and cancer-specific death (data not shown). Univariate recurrence and survival probabilities after RNU were estimated using the Kaplan-Meier method and log-rank statistic. Univariate and multivariate Cox regression models addressed time to recurrence and CSS after RNU. In all models, proportional hazards assumptions were systematically verified using the Grambsch-Therneau residual-based test. The change in predictive accuracy resulting from the addition of a variable of interest to standard predictor variables was quantified with Harrell's concordance index.^{15,16} Internal validation was performed using 200-bootstrap resamples.^{15,16} Predictive accuracy estimates were expressed as proportions and compared with the Mantel-Haenszel test. All reported *P* values are two sided, and statistical significance was set at $P \leq .05$. Nominal *P* values are given; no adjustments were made for the number of *P* values calculated. Statistical analyses were performed with S-Plus Professional software (MathSoft Inc, Seattle, WA).

RESULTS

Association of LVI With Clinical and Pathologic Characteristics

LVI was present in 349 patients (24%). Table 1 shows the association of LVI with clinical and pathologic characteristics. LVI was significantly associated with advanced tumor stage, high tumor grade, sessile architecture, presence of tumor necrosis, concomitant carcinoma in situ, and lymph node metastasis ($P < .001$ for all). Exclusion of lymph node–positive patients did not alter the statistical significance of the association of LVI with advanced tumor stage, high tumor grade, sessile architecture, and concomitant carcinoma in situ ($P < .001$ for all). Exclusion of patients who received neoadjuvant and/or adjuvant therapy did not alter the statistical significance of these associations ($P < .001$ for all).

Association of LVI With Clinical Outcomes in All Patients

Overall 2-, 5-, and 10-year recurrence-free survival estimates were 73% ($\pm 1\%$), 69% ($\pm 1\%$), and 66% ($\pm 1\%$), respectively. Overall 2-, 5-, and 10-year CSS estimates were 79% ($\pm 1\%$), 72% ($\pm$

Table 1. Association of Lymphovascular Invasion With Clinical and Pathologic Characteristics in Patients Treated With Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

Characteristic	Total		Lymphovascular Invasion				P
	No. of Patients (N = 1,453)	%	Absent (n = 1,104)		Present (n = 349)		
			No. of Patients	%	No. of Patients	%	
Sex							.324
Male	986	67.9	757	76.8	229	23.2	
Female	467	32.1	347	74.3	120	25.7	
Pathologic tumor stage							< .001
Ta	295	20.3	295	100	0	0	
Tis	28	1.9	28	100	0	0	
T1	317	21.8	268	84.5	49	15.5	
T2	269	18.5	209	77.7	60	22.3	
T3	475	32.7	282	59.4	193	40.6	
T4	69	4.7	22	31.9	47	68.1	
Grade							< .001
Low	516	35.5	463	89.7	53	10.3	
High	937	64.5	641	68.4	296	31.6	
Lymph nodes status							< .001
pNx	841	57.9	673	80	168	20	
pN0	472	32.5	390	82.6	82	17.4	
pN1-2	140	9.6	41	29.3	99	70.7	
ECOG performance status							.339
0	1,001	68.9	774	77.3	227	22.7	
1	358	24.6	262	73.2	96	26.8	
2	85	5.8	61	71.8	24	28.2	
3	9	0.6	7	77.8	2	22.2%	
Tumor necrosis							< .01
Absent	1,089	74.9	929	85.3	160	14.7	
Present	387	26.6	175	48.1	189	51.9	
Architecture							< .001
Papillary	1,066	73.4	893	83.8	173	16.2	
Sessile	387	26.6	211	54.5	176	45.5	
Tumor location							.476
Renal pelvis	958	65.9	722	75.4	236	24.6	
Ureter	495	34.1	382	77.2	113	22.8	
Concomitant carcinoma in situ							< .001
Negative	1,035	71.2	840	81.2	195	18.8	
Positive	418	28.8	264	63.2	154	36.8	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

1%), and 69% ($\pm 1\%$), respectively. LVI was significantly associated with disease recurrence and CSS (Tables 2 and 3, respectively). Five-year recurrence-free survival and CSS rates were $77\% \pm 1\%$ and $79\% \pm 1\%$, respectively, in the absence of LVI compared with $44\% \pm 3\%$ and $47\% \pm 3\%$, respectively, in the presence of LVI (Figs 1A and 1B, respectively; $P < .001$).

In multivariate analyses that adjusted for the effects of tumor stage, grade, and lymph node status, LVI was an independent predictor of both disease recurrence and CSS ($P = .008$ and $P = .002$, respectively). The predictive accuracies for prediction of disease recurrence and CSS of the base model comprising tumor stage, grade, and lymph node status were 78.2% and 78.3%, respectively. Addition of LVI marginally but statistically significantly improved the predictive accuracies of the base model for both disease recurrence and CSS to 79.3% and 80.0%, respectively (gain in predictive accuracy: 1.1% and 1.7%, respectively; $P = .03$ and $P < .001$, respectively). Analyses were rerun after stratifying by adjuvant therapy ($n = 169$; 11.6%), which resulted in consistent statistical patterns and P values. Exclusion of

patients who received neoadjuvant and/or adjuvant therapy did not alter the statistical significance of these associations.

Association of LVI With Clinical Outcomes in Lymph Node–Negative Patients and Patients Who Did Not Undergo Lymphadenectomy

Overall, 140 patients (9.6%) had positive lymph nodes, and 1,313 patients had either negative lymph nodes or did not undergo a lymphadenectomy. In the patients who had either negative lymph nodes or did not undergo a lymphadenectomy, LVI was an independent predictor of disease recurrence and CSS ($P = .001$ and $P < .001$, respectively; Tables 4 and 5, respectively). The predictive accuracies for prediction of disease recurrence and CSS of the base model comprising tumor stage and grade were 75.4% and 76.5%, respectively. Addition of LVI significantly improved the accuracies of the base model for prediction of both disease recurrence and CSS to 78.4% and 79.5%, respectively (gain in predictive accuracy: 3% and 3%, respectively; $P < .001$ for both). Analyses were rerun after stratifying by adjuvant

Table 2. Univariate and Multivariate Cox Regression Analyses Predicting Disease Recurrence in Patients Treated With Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma (N = 1,453)

Variable	Univariate Analysis		Multivariate Analysis	
	HR	P	HR	P
pT stage		< .001		< .001
T1 v Tis/Ta	1.72	.05	1.34	.31
T2 v Tis/Ta	4.05	< .001	2.73	< .001
T3 v Tis/Ta	9.23	< .001	5.08	< .001
T4 v Tis/Ta	36.9	< .001	14.56	< .001
Grade	4.36	< .001	2.04	< .001
Lymph node status				
Node positive v NO or Nx	4.83	< .001	1.85	< .001
Lymphovascular invasion	3.2	< .001	1.38	.008

NOTE. The predictive accuracy of the base model (pT stage, grade, and lymph node status) was 78.2%, and the predictive accuracy of the base model plus lymphovascular invasion was 79.3%. The gain in predictive accuracy related to the inclusion of lymphovascular invasion was +1.1% ($P = .03$).

Abbreviations: HR, hazard ratio; pT, pathologic tumor; Nx, lymphadenectomy not performed.

therapy, which resulted in similar predictive accuracy and P values. Exclusion of patients who received neoadjuvant and/or adjuvant therapy did not alter the statistical significance of these associations.

Association of LVI With Clinical Outcomes in Lymph Node–Positive Patients

In the 140 patients who had positive lymph nodes, LVI did not correlate with disease recurrence (hazard ratio = 1.089; $P = .711$) or with CSS (hazard ratio = 0.919; $P = .731$) in univariate analyses. Tumor stage was independently associated with disease recurrence and CSS in multivariate analyses ($P < .001$ for both). The predictive accuracies for prediction of disease recurrence and CSS of the base model comprising pathologic tumor stage and tumor grade were 64.0% and 65.2%, respectively. Addition of LVI did not improve the

Table 3. Univariate and Multivariate Cox Regression Analyses Predicting Cancer-Specific Survival in Patients Treated With Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma (N = 1,453)

Variable	Univariate Analysis		Multivariate Analysis	
	HR	P	HR	P
pT stage		< .001		< .001
T1 v Tis/Ta	1.51	.19	1.2	.56
T2 v Tis/Ta	4.07	< .001	2.83	< .001
T3 v Tis/Ta	9.14	< .001	5.33	< .001
T4 v Tis/Ta	34.37	< .001	14.21	< .001
Grade	3.99	< .001	1.82	< .001
Lymph nodes status				
Node positive v NO or Nx	4.83	< .001	1.53	.006
Lymphovascular invasion	3.41	< .001	1.51	.002

NOTE. The predictive accuracy of the base model (pT stage, grade, and lymph node status) was 78.3%, and the predictive accuracy of the base model plus lymphovascular invasion was 80.0%. The gain in predictive accuracy related to the inclusion of lymphovascular invasion was +1.7% ($P < .001$).

Abbreviations: HR, hazard ratio; pT, pathologic tumor; Nx, lymphadenectomy not performed.

Fig 1. Probability estimates of (A) recurrence-free survival and (B) cancer-specific survival in 1,453 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma stratified by lymphovascular invasion (LVI) status.

predictive accuracies of the base model for either disease recurrence or CSS (change in predictive accuracy: 0% and +0.1%, respectively).

DISCUSSION

In this large, multicenter, international, retrospective data set of patients treated with RNU, we found that LVI was associated with established features of biologically aggressive UTUC, such as advanced stage, high tumor grade, metastases to lymph nodes, sessile tumor architecture, tumor necrosis, and concomitant carcinoma in situ. In addition, LVI was an independent predictor of both disease recurrence and CSS. When evaluated in all patients, addition of LVI to standard pathologic features improved their predictive accuracy for both disease recurrence and CSS by a small margin. This margin was larger when the analyses were restricted to patients without lymph node metastasis and patients who did not undergo a lymphadenectomy.

In agreement with previous studies,^{10,17} we found that 24% of patients treated with RNU for UTUC had LVI. In accordance with a retrospective, single-center study comprising 173 patients treated with RNU for UTUC, we found that LVI was an independent predictor of recurrence and CSS. Similarly, in bladder urothelial carcinoma, the large majority of reports have shown an association between LVI and

Table 4. Univariate and Multivariate Cox Regression Analyses Predicting Disease Recurrence in Patients With Negative Lymph Nodes or Lymphadenectomy Not Performed During Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma (n = 1,313)

Variable	Univariate Analysis		Multivariate Analysis	
	HR	P	HR	P
pT stage		< .001		< .001
T1 v Tis/Ta	1.75	.21	1.37	.28
T2 v Tis/Ta	3.68	< .001	2.66	< .001
T3 v Tis/Ta	8.8	< .001	5.47	< .001
T4 v Tis/Ta	27.91	< .001	14.35	< .001
Grade	3.71	< .001	1.99	< .001
Lymphovascular invasion	2.86	< .001	1.57	.001

NOTE. The predictive accuracy of the base model (pT stage and grade) was 75.4%, and the predictive accuracy of the base model plus lymphovascular invasion was 78.4%. The gain in predictive accuracy related to the inclusion of lymphovascular invasion was +3.0% ($P < .001$).

Abbreviations: HR, hazard ratio; pT, pathologic tumor.

tumor grade and stage, lymph node metastasis, disease progression, and CSS.^{18,19} Indeed, infiltration of the vascular and/or lymphatic structures by tumor cells is an important step in tumor dissemination; these pathways will enable the tumor cells to access to distant organs. The initial entry of neoplastic cells into the circulation occurs through the local microvascular network, including the lymphatic and blood vessels. This premise, together with the strong association of LVI with lymph node metastasis and disease recurrence/progression after apparently effective local treatment, suggests that LVI plays a role in the metastatic process.²⁰

We found that addition of LVI improved the predictive accuracy of standard prognostic models for the prediction of disease recurrence and CSS in patients with lymph node-negative disease by a statistically and clinically significant margin. In agreement with these findings, Saito et al¹¹ have reported that LVI was independently associated with disease recurrence and CSS in 135 patients with node-negative UTUC. Similar to these studies, we found a strong association between LVI and the rate of metastases to regional lymph nodes, supporting the

hypothesis that lymphatic vessel invasion precedes or occurs concurrently with lymph node metastasis. Moreover, similar to the studies in bladder cancer,^{18,19} we found that once the patient has lymph node metastases, the LVI status no longer improves our prediction of disease recurrence or CSS. In contrast, the LVI status in patients without clinically evident metastasis is an important predictor of disease recurrence and CSS because it seems to be able to identify a subgroup of patients with micrometastases or false-negative lymph node status. Although node-positive patients generally receive systemic chemotherapy, a significant number of patients with node-negative disease experience disease recurrence and mortality despite their favorable pathologic subgroup classification. Identification of patients with node-negative UTUC who are at increased risk of experiencing treatment failure with RNU remains a clinical challenge. Early recognition of these patients would allow selective administration of adjuvant chemotherapy.

We found that LVI was not associated with disease recurrence and mortality in patients with node-positive disease. This is likely a result of the strong association between LVI and nodal metastasis. Taken together, these findings suggest that LVI in the primary tissue may be associated with occult metastasis. This would imply that LVI in the primary tumor indicates that tumor cells already invaded the surrounding tissues and that they are already circulating through the systemic pathway. However, for these disseminated cells to develop into overt clinical metastases, further genetic alterations essential to the metastatic process are necessary.²¹ Nevertheless, although circulating cancer cells need to traverse additional obstacles along the multistep metastatic process to establish clinically significant metastatic disease, the simple LVI seems to be an ominous harbinger of disease progression.

Besides inclusion in predictive tools for selection for adjuvant therapy, LVI should be considered for inclusion in the American Joint Committee on Cancer staging. In other malignancies such as hepatic²² and testicular cancer,²³ LVI has been added to the TNM staging, allowing for improved cancer staging and treatment decision making. In hepatocellular carcinoma, for example, a primary solitary tumor without vascular invasion is categorized as T1, whereas a solitary tumor with vascular invasion is categorized as T2.²² Vascular invasion has been included in category T of the TNM classification in testicular germ cell neoplasia. The presence of vascular invasion in organ-confined testicular tumor is classified as pT2 rather than pT1 disease. Patients with stage I nonseminomatous germ cell tumor and LVI are recommended to undergo adjuvant chemotherapy, whereas patients without LVI are recommended to undergo surveillance.²³ Similarly, patients with pT1-3, Nx-0 UTUC and presence of LVI could be up-staged. Our results, if confirmed in additional large, well-designed, and preferably prospective studies, suggest that LVI should be included in the staging of UTUC.

There are several limitations to our study. Our results were analyzed in a retrospective fashion. However, this is the largest reported series of patients treated with RNU for UTUC, and it is unlikely that large prospective randomized trials will be organized because of the relative rarity of this disease entity.^{24,25}

Another limitation is that patients were treated by various physicians and that the specimens were evaluated by various pathologists over a long time period. To minimize the difference in pathologic evaluation of the specimens, at the beginning of the study, we agreed on strict morphologic criteria for pathologic evaluation,

Table 5. Univariate and Multivariate Cox Regression Analyses Predicting Cancer-Specific Survival in Patients With Negative Lymph Nodes or Lymphadenectomy Not Performed During Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma (n = 1,313)

Variable	Univariate Analysis		Multivariate Analysis	
	HR	P	HR	P
pT stage		< .001		< .001
T1 v Tis/Ta	1.51	.21	1.21	.57
T2 v Tis/Ta	3.9	< .001	2.87	< .001
T3 v Tis/Ta	8.94	< .001	5.66	< .001
T4 v Tis/Ta	28.13	< .001	14.41	< .001
Grade	3.36	< .001	1.73	.002
Lymphovascular invasion	3.23	< .001	1.83	< .001

NOTE. The predictive accuracy of the base model (pT stage and grade) was 76.5%, and the predictive accuracy of the base model plus lymphovascular invasion was 79.5%. The gain in predictive accuracy related to the inclusion of lymphovascular invasion was +3.0% ($P < .001$).

Abbreviations: HR, hazard ratio; pT, pathologic tumor.

and all specimens were reread by dedicated genitourinary pathologists according to these criteria to unify the reproducibility of the diagnosis. Moreover, to ensure reproducibility and validity of the pathologic evaluation, we re-evaluated 10% of specimens at a single center and found a high degree of concordance with the original evaluation.

We decided not to use immunohistochemical staining to identify the vessels because its use is controversial and not practical for everyday clinical use.^{26,27} Moreover, we did not address the impact of the location (ie, peritumoral or outside cancer perimeter-positive invasion v intratumoral-positive invasion) on outcomes and whether lymphatic vessels and blood vessels could be considered separately. In most cases, only capillary structures are recognizable, making it difficult to distinguish lymphatics from blood vessels. Another important issue is how to distinguish actual invasion from an image of pseudo-invasion by the separation or the retraction of the surrounding stromal tissue. In our experience, vessel identification is possible with hematoxylin and eosin with sufficient reliability.

In addition, because the study period spans more than 20 years, the data may not represent current practice patterns. For example, number of lymph nodes removed, indication for surgery, and follow-up protocols have changed over time. However, the differences in practice patterns across the institutions in our study are reflective of the real world, making the conclusions of our study more generalizable.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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