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ORIGINAL ARTICLE – ENDOCRINE TUMORS

# Lymphovascular Invasion Is Associated with Lymph Node Involvement in Small Appendiceal Neuroendocrine Tumors

**Andrew M. Blakely, MD[1], Mustafa Raoof, MD[1], Philip H. G. Ituarte, PhD, MPH[1], Yuman Fong, MD[1], Gagandeep Singh, MD[1], and Byrne Lee, MD, FACS[1]**

Department of Surgery, City of Hope National Medical Center, Duarte, CA

## ABSTRACT

**Background.** Appendiceal neuroendocrine tumors (NETs) are incidentally found in up to 1% of appendectomy specimens. The association of lymphovascular invasion (LVI) with risk of regional lymph node involvement is unclear.

**Methods.** From the National Cancer Database, 2004–2015, this study identified patients who had tumors 2 cm or smaller with one or more lymph nodes (LNs) pathologically evaluated. The histology was defined as typical, goblet cell, or composite NETs. Patient demographics, tumor characteristics, and treatment variables were analyzed.

**Results.** The histologies for the 1767 identified patients were typical ($n = 921$, 52.1%), goblet cell ($n = 556$, 31.5%), and composite ($n = 290$, 16.4%). The tumor grades were low (70.4%), moderate (18.6%), and high (11%). The overall LN positivity was 17%. Of 1052 tumors evaluated, 215 (20.4%) had LVI. Overall survival decreased with node involvement (mean 84 vs. 124 months; $p < 0.0001$, log-rank). In the multivariate logistic regression analysis, LVI was independently associated with node involvement [odds ratio (OR) 5.0; $p < 0.0001$] after adjustment for patient age and tumor histologic subtype, size, and grade. In the subset analysis of typical NETs, tumor size of 1–2 cm (ref. < 1 cm; OR 5.5; $p < 0.001$) and presence of LVI (ref. absence of LVI; OR 4.8; $p < 0.0001$) were the only factors independently associated with LN involvement.

**Conclusions.** Node involvement is associated with worse overall survival in appendiceal NETs. The presence of LVI was strongly associated with lymph node involvement. An appendectomy specimen showing LVI should prompt strong consideration of colectomy with regional lymphadenectomy even for small, typical appendiceal NETs.

The overall annual incidence of gastrointestinal NETs in the United States is approximately 6 in 100,000 and rising.[1] Appendiceal NETs constitute about 3% of all primary sites.[2] Appendiceal NETs are identified in 0.3–0.9% of all appendectomy specimens, most commonly after resection for presumed appendicitis.[3,4] Tumors of neuroendocrine origin represent the most common incidental malignancy after appendectomy.[5]

Treatment recommendations for appendiceal NETs are provided by several expert consensus guidelines.[6–8] Histologic subtype has been recognized as an important determinant of tumor biology.[9] For typical NETs, right colectomy is accepted as standard treatment for primary tumors larger than 2 cm in diameter. For tumors smaller than 1 cm, completion colectomy is recommended for a positive resection margin or involvement at the base of the appendix. Management of tumors 1–2 cm in size is more controversial, but most guidelines suggest completion right colectomy in the setting of lymphovascular invasion (LVI), high tumor grade, or mesoappendiceal invasion.

In contrast, for goblet cell tumors, right colectomy is recommended for any tumor size, although it has been suggested that tumors smaller than 1 cm without other high-risk features may be adequately treated with appendectomy.[10] Finally, treatment of composite NETs follows

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A. M. Blakely, MD
e-mail: ablakely@coh.org

that of the adenocarcinoma component, which generally entails colectomy because they have been described as the most aggressive subtype of appendiceal NETs.[9,11]

The clinical relevance of LVI for small appendiceal NETs is as a potential marker of regional involvement and risk for subsequent mesenteric lymphadenopathy.[12] However, literature supporting LVI as a prognostic factor is limited by small patient numbers among few studies.[13–15]

We analyzed the National Cancer Database (NCDB) given its larger, more representative patient cohort for a better evaluation of LVI as a predictor of lymph node involvement in small appendiceal NETs with a diameter of 2 cm or less. We hypothesized that LVI is associated with node involvement, which would better support existing treatment recommendations and potentially inform surgical decision-making regarding colectomy with regional lymphadenectomy after appendectomy.

## METHODS

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Patients captured within the database represent 70% of those with new cancer diagnoses treated at approximately 1500 Commission on Cancer-designated centers across the United States.

Given the de-identified nature of the data, this study was exempted from City of Hope institutional review board approval. The 2015 Participant User File (PUF) was queried for all patients with a diagnosis of colon cancer because appendiceal cancer is included in the colon cancer patient file.

Patient selection from the PUF was performed as shown in Fig. 1. Appendiceal cancer patients were selected based on International Classification of Disease for Oncology, 3rd edition (ICD-O-3) topographical code C181, and

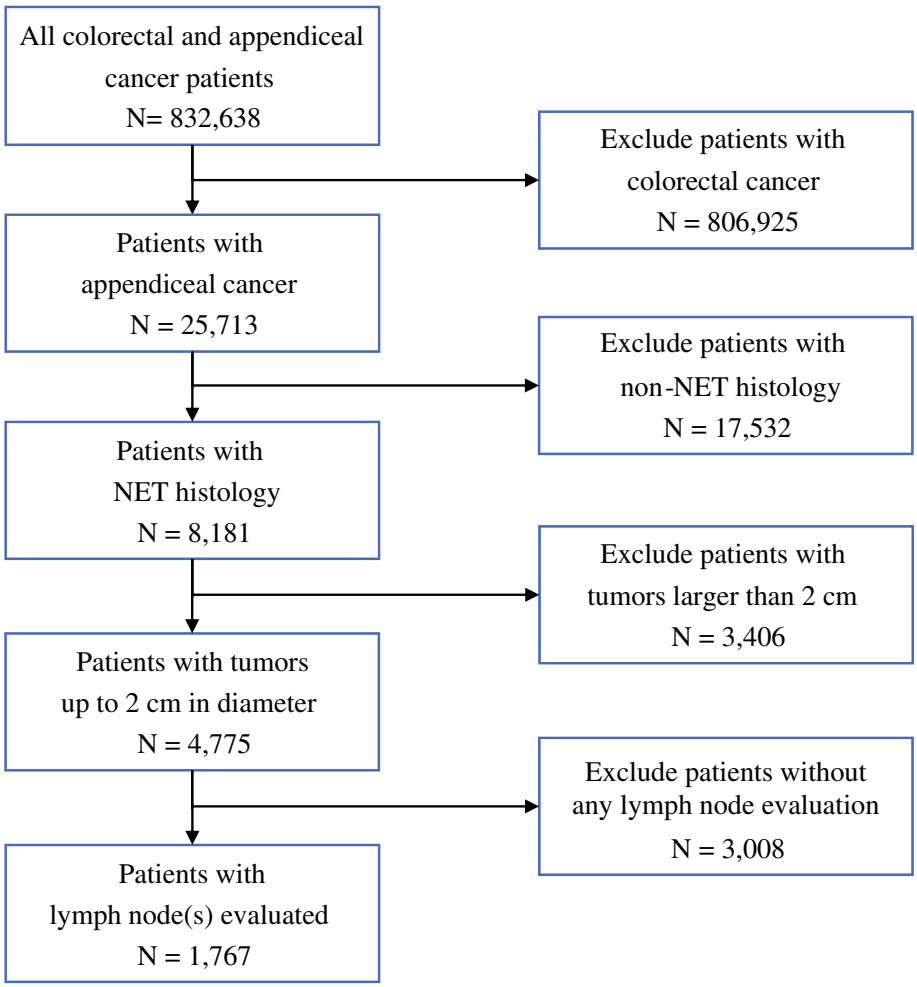


**FIG. 1** Patient-selection flow diagram

neuroendocrine tumor histology was identified using ICD-O-3 morphologic codes. Three histologic groupings were created as follows: typical, goblet cell, and composite tumors. The histology codes were 8240, 8241, 8242, and 8249 for typical NETs, 8243 for goblet cell tumors; and 8244 and 8245 for composite tumors.[16]

Patients who had tumors 2 cm in diameter or smaller and one or more lymph node evaluated were selected for the initial analysis. Surgical procedure codes 20 through 32 indicated appendectomy or segmental colectomy less extensive than right hemicolectomy, whereas codes 40 and 41 indicated right hemicolectomy, as described in other NCDB studies of appendiceal cancer patients.[17] The NCDB began specifically capturing LVI status in 2010.

Data analysis was performed with Stata/MP software, version 14.0 (StataCorp, College Station, TX, USA) and JMP Pro, version 14.1 (SAS Institute, Cary, NC, USA). Statistical significance was defined as $p$ a value lower than 0.05 or 95% confidence intervals (95% CIs) that exclude 1.0 for all outcomes.

Categorical variables were summarized using counts and percentages, with group differences assessed by Pearson's Chi square test. Continuous variables were expressed as medians and interquartile ranges (IQRs), with group differences assessed by the Kruskal–Wallis rank test. Multivariate logistic regression was used to identify factors associated with lymph node involvement, with results expressed as odds ratios (ORs) and 95% CIs.

Overall survival was modeled using the Kaplan–Meier method with log-rank testing, stratifying by node-positive and node-negative patient groups. Receiver operating characteristic (ROC) curves were created to determine the optimal cutoff size for the best prediction of lymph node involvement, reported as area under the curve (AUC) ± standard error (SE) with sensitivity and specificity.

## RESULTS

For the analysis, 1767 patients with appendiceal NETs were identified (Fig. 1). The median patient age was 50 years (IQR 39–61). Overall, 981 patients (55.5%) were female, 89.5% were white, 7.5% were black, and 3.1% were of other or unknown race. Insurance types were private (65.7%), Medicare (18.8%), Medicaid (6.5%), and other (9%). Tumor size was 1–2 cm for 1174 (66.4%) of the patients. The histologies were typical ($n$ = 921, 52.1%), goblet cell ($n$ = 556, 31.5%), and composite ($n$ = 290, 16.4%).

Tumor grade was available for 1003 patients (56.8%) overall. Among these patients, the tumors were low grade for 706 patients (70.4%), moderate grade for 187 patients (18.6%), and high grade for 110 patients (11.0%). At least 12 lymph nodes were examined in 1178 patients (66.7%). The overall rate of lymph node involvement was 17%. In 215 (20.4%) of 1052 evaluated tumors, LVI was present.

Procedure codes were evaluable for 1683 patients, 66% of whom underwent right hemicolectomy. The remaining patients had segmental resection.

Of the overall patient cohort, 1424 patients (80.6%) had follow-up data. The median follow-up period was 46.5 months (IQR 27.4–78.5 months). Kaplan–Meier analysis of overall survival was performed, with patients grouped by lymph node involvement (Fig. 2). The median follow-up period was similar for both node-positive patients (47.8 months; IQR 27.4–78.5 months) and node-negative patients (46.1 months; IQR 24.5–73.3 months; $p$ = 0.14).

Median overall survival was not reached for either group. The mean survival was 84 months for the node-positive patients, whereas it was 124 months for the node-negative patients ($p < 0.0001$, log-rank).

### *Lymph Node Involvement*

The uni- and multivariate analyses were stratified by lymph node positivity (Table 1). In the univariate analyses, the factors associated with positive lymph nodes were younger age at diagnosis, typical NET histology, high tumor grade, tumor size of 1–2 cm, examination of 12 or more lymph nodes, LVI, and performance of right hemicolectomy. These variables then were included in a multivariate logistic regression model, which determined that nodal involvement was independently associated with high grade, tumor size of 1–2 cm, 12 or more examined lymph nodes, and LVI. Decreased likelihood of lymph node involvement was associated with goblet cell or composite histology.

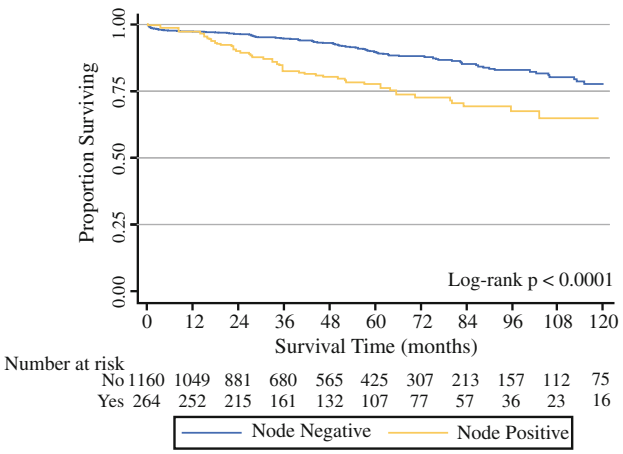


**FIG. 2** Kaplan-Meier analysis of overall survival by node involvement

**TABLE 1** Univariate analyses of patient, disease, and treatment factors stratified by lymph node status and multivariate analysis of odds of having positive lymph node(s)

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Positive lymph node(s) ($n$ = 295) $n$ (%) | Negative lymph node(s) ($n$ = 1472) $n$ (%) | $p$ value | OR | 95% CI | $p$ value |
| Patient characteristics | | | | | | |
| Age at diagnosis (years) | | | | | | |
| 18–49 | 159 (54) | 674 (46) | 0.032 | Ref | – | – |
| 50–64 | 93 (31) | 532 (36) | | 0.91 | 0.66–1.25 | 0.55 |
| 65–74 | 35 (12) | 185 (13) | | 1.0 | 0.64–1.58 | 0.97 |
| ≥ 75 | 8 (3) | 81 (5) | | 0.67 | 0.30–1.49 | 0.33 |
| Sex | | | | | | |
| Female | 167 (57) | 814 (55) | 0.68 | – | – | – |
| Male | 128 (43) | 658 (45) | | | | |
| Race/ethnicity | | | | | | |
| White | 257 (87) | 1324 (90) | 0.35 | – | – | – |
| Black | 27 (9) | 105 (7) | | | | |
| Other/unknown | 11 (4) | 43 (3) | | | | |
| Insurance | | | | | | |
| Private | 208 (71) | 953 (65) | 0.26 | – | – | – |
| Medicare | 45 (15) | 288 (20) | | | | |
| Medicaid | 17 (6) | 97 (7) | | | | |
| Other | 25 (8) | 134 (9) | | | | |
| Comorbidities | | | | | | |
| None | 250 (85) | 1234 (84) | 0.56 | – | – | – |
| 1 | 37 (12) | 179 (12) | | | | |
| ≥ 2 | 8 (3) | 59 (4) | | | | |
| Clinicopathologic characteristics | | | | | | |
| Histology | | | | | | |
| Typical | 179 (60) | 742 (50) | < 0.0001 | Ref | – | – |
| Goblet cell | 58 (20) | 498 (34) | | 0.28 | 0.19–0.41 | < 0.0001 |
| Composite | 58 (20) | 232 (16) | | 0.54 | 0.35–0.82 | 0.0044 |
| Grade | | | | | | |
| Low | 113 (38) | 593 (40) | 0.014 | Ref | – | – |
| Moderate | 35 (12) | 152 (10) | | 1.2 | 0.76–2.04 | 0.39 |
| High | 30 (10) | 80 (6) | | 1.9 | 1.06–3.45 | 0.032 |
| Unknown | 117 (40) | 647 (44) | | 1.0 | 0.66–1.37 | 0.78 |
| Size (cm) | | | | | | |
| < 1 | 26 (9) | 567 (39) | < 0.0001 | Ref | – | – |
| 1–2 | 269 (91) | 905 (61) | | 6.1 | 3.93–9.33 | < 0.0001 |
| Lymphovascular invasion | | | | | | |
| Absent | 72 (24) | 765 (52) | < 0.0001 | Ref | – | – |
| Present | 80 (27) | 135 (9) | | 5.0 | 3.40–7.52 | < 0.0001 |
| Unknown | 143 (49) | 572 (39) | | 3.0 | 2.14–4.25 | < 0.0001 |
| Treatment characteristics | | | | | | |
| Resection of primary tumor | | | | | | |
| Appendectomy/ Ileocecectomy | 71 (24) | 501 (34) | 0.0033 | Ref | – | – |
| Colectomy | 210 (71) | 901 (61) | | 1.5 | 1.06–2.04 | 0.021 |
| Other/unspecified | 14 (5) | 70 (5) | | 1.8 | 0.87–3.55 | 0.12 |

**TABLE 1** continued

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Positive lymph node(s) ($n$ = 295) $n$ (%) | Negative lymph node(s) ($n$ = 1472) $n$ (%) | $p$ value | OR | 95% CI | $p$ value |
| Lymph nodes examined | | | | | | |
| < 12 | 59 (20) | 477 (32) | < 0.0001 | Ref | – | – |
| ≥ 12 | 236 (80) | 942 (64) | | 1.6 | 1.12–2.22 | 0.0095 |
| Unknown | 0 | 53 (4) | | – | – | – |

*OR* odds ratio, *CI* confidence interval

*Lymphovascular Invasion*

From 2010 to 2015, LVI status was available for 83.6% of the specimens overall (1052 of 1258 tumors), with a significantly increased rate of recorded information over time (lowest proportion, 75.3% in 2010; highest proportion, 88.4% in 2014; $p = 0.008$). Of the 1052 patients with LVI status, LVI was present in 17.6% of the typical tumors, 23% of the goblet cell tumors, and 27.4% of the composite tumors ($p = 0.016$). When the comparison was limited to 1- to 2-cm tumors ($n = 673$), the frequencies of LVI were 26.7% for the typical tumors, 24% for the goblet cell tumors, and 29.7% for the composite tumors ($p = 0.52$).

The patients with 12 or more lymph nodes evaluated were stratified by LVI status ($n = 717$) and compared by number of lymph nodes involved. Among the 176 LVI-positive patients, 66 (37.5%) had one or more positive nodes significantly more frequently than the LVI-negative patients (60 of 541, 11%; $p < 0.0001$). In addition, multiple positive nodes were found more often in LVI-positive patients (35 of 66, 53%; vs. 20 of 60, 33.3%; $p = 0.026$).

*Subset Analysis of Typical NETs*

The patients who had typical NETs with known LVI status and at least 12 examined lymph nodes ($n = 373$) were separately analyzed (Table 2). The uni- and multivariate analyses found that lymph node involvement was associated with 1- to 2-cm tumor size and LVI. In contrast to the analyses of the entire study cohort, patient age, high tumor grade, and performance of right colectomy were not associated with node involvement. Similar analyses were performed for goblet cell ($n = 232$) and composite ($n = 112$) histologies (data not shown). Among goblet cell NETs, LVI was independently associated with node involvement (OR 6.1; 95% CI 2.38–15.8; $p = 0.0002$), whereas size of 1–2 cm was not (OR 4.3; 95% CI 0.92–20.4; $p = 0.063$). In the small subset of composite NETs, node involvement was not associated with LVI (OR 2.4; 95% CI 0.74–7.73; $p = 0.15$) or 1- to 2-cm tumor size (OR 4.7; 95% CI 0.55–40.1; $p = 0.16$).

*Tumor Size*

In this study, ROC curves were constructed to determine the optimal cutoff size for predicting lymph node involvement for all histologic subtypes (Fig. 3a) and for the subset of typical NETs (Fig. 3b). Among all the histologies, the optimal cutoff size was 12 mm, with an AUC ± SE of 0.71 ± 0.014, a sensitivity of 0.79, and a specificity of 0.33 ($p < 0.0001$). For typical NETs, the optimal cutoff size was 11 mm, with an AUC ± SE of 0.77 ± 0.019, a sensitivity of 0.85, and a specificity of 0.43 ($p < 0.0001$).

## DISCUSSION

This study demonstrated that for appendiceal neuroendocrine tumors with a diameter of 2 cm or smaller, lymphovascular invasion is independently associated with lymph node involvement. This association remained even when only patients who had typical NET histology with LVI status and examination of 12 or more lymph nodes were analyzed. Consensus guidelines such as those of the North American Neuroendocrine Tumor Society (NANETS) and the European Neuroendocrine Tumor Society (ENETS) recommend completion colectomy for 1- to 2-cm tumors with LVI.[6,8] However, as noted in the United Kingdom and Ireland Neuroendocrine Tumor Society (UKINETS) guidelines commentary, before this analysis, data specifically supporting that recommendation were lacking.[7]

The finding that node involvement is independently associated with high tumor grade and tumor size of 1–2 cm (vs. < 1 cm) has been demonstrated in multiple prior studies.[14,15,18,19] Finally, ROC curves for all histologic subtypes and for the subset of typical NETs showed that tumor size cutoffs of 12 and 11 mm, respectively, have the

**TABLE 2** Subset of patients with typical histology, ≥ 12 lymph nodes examined, and known LVI status: univariate analyses of patient, disease, and treatment factors stratified by lymph node status and multivariate analysis of odds of having positive lymph node(s)

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Positive lymph node(s) ($n$ = 77) $n$ (%) | Negative lymph node(s) ($n$ = 296) $n$ (%) | $p$ value | OR | 95% CI | $p$ value |
| Age at diagnosis (years) | | | | | | |
| 18–49 | 50 (65) | 165 (56) | 0.29 | Ref | – | – |
| 50–64 | 16 (21) | 86 (29) | | 0.79 | 0.40–1.56 | 0.49 |
| ≥ 65 | 11 (14) | 45 (15) | | 1.1 | 0.49–2.52 | 0.81 |
| Grade | | | | | | |
| Low | 57 (74) | 220 (74) | 0.21 | Ref | – | – |
| Moderate | 8 (10) | 26 (9) | | 0.90 | 0.35–2.28 | 0.82 |
| High | 2 (3) | 1 (< 1) | | 1.9 | 0.16–22.4 | 0.61 |
| Unknown | 10 (13) | 49 (17) | | 0.93 | 0.41–2.10 | 0.86 |
| Size (cm) | | | | | | |
| < 1 | 7 (9) | 124 (42) | < 0.0001 | Ref | – | – |
| 1–2 | 70 (91) | 172 (58) | | 5.5 | 2.40–12.7 | < 0.0001 |
| Lymphovascular invasion | | | | | | |
| Absent | 36 (47) | 247 (84) | < 0.0001 | Ref | – | – |
| Present | 41 (53) | 49 (16) | | 4.8 | 2.52–7.94 | < 0.0001 |
| Resection of primary tumor | | | | | | |
| Appendectomy/Ileocecectomy | 21 (27) | 84 (28) | 0.36 | – | – | – |
| Colectomy | 51 (66) | 203 (69) | | | | |
| Other/unspecified | 5 (7) | 9 (3) | | | | |

*OR* odds ratio, *CI* confidence interval

highest sensitivity and specificity for predicting lymph node involvement, similar to the 10-mm cutoff used in the consensus guidelines.

Lymphovascular invasion as a pathologic feature represents invasion of malignant cells into peri-tumoral lymphatic channels and vasculature. A prospective colon cancer staging trial by Wasif et al.[20] demonstrated that LVI was associated with an increased risk of occult nodal metastasis, together with other high-risk local tumor characteristics such as high T stage and grade.

A recent Japanese multicenter retrospective study of 760 NETs, predominantly of the rectum but also including several of the colon and appendix, found that LVI was associated with a significantly higher risk of nodal metastasis.[21] The clinical importance of the status of regional lymph node involvement by gastrointestinal neuroendocrine tumors is that it provides accurate staging and guides surveillance strategies for patients after resection.[22] In addition, identification and aggressive treatment of patients at risk for regional nodal involvement may preclude the development of symptomatic mesenteric lymphadenopathy.[12]

The data on the role of LVI in predicting nodal metastases in appendiceal NETs are limited. A single-institution retrospective series of small appendiceal NETs determined that the presence of small-vessel invasion was associated with metastatic spread beyond the appendix (60% vs. 0%; $p < 0.001$).[13] The limitations of that study included small sample size (79 patients), lack of specification of the number of tumors 2 cm or smaller, and exclusion of atypical histologic subtypes.

Two recent multi-institutional analyses evaluated predictors of lymph node involvement including LVI, with approximately 400 patients in each cohort.[14,15] In the study by Rault-Petit et al.,[14] several patients with tumors larger than 2 cm were included in the analysis. In addition, whereas nearly half of the patients had LVI status documented, only 25% had one or more lymph nodes removed between the initial appendectomy and the subsequent right colectomy to evaluate the significance of LVI.

The series by Brighi et al.[15] captured LVI status in nearly 80% of patients and demonstrated an association between LVI and node involvement. The analysis, however, was predicated on the results of right colectomy,

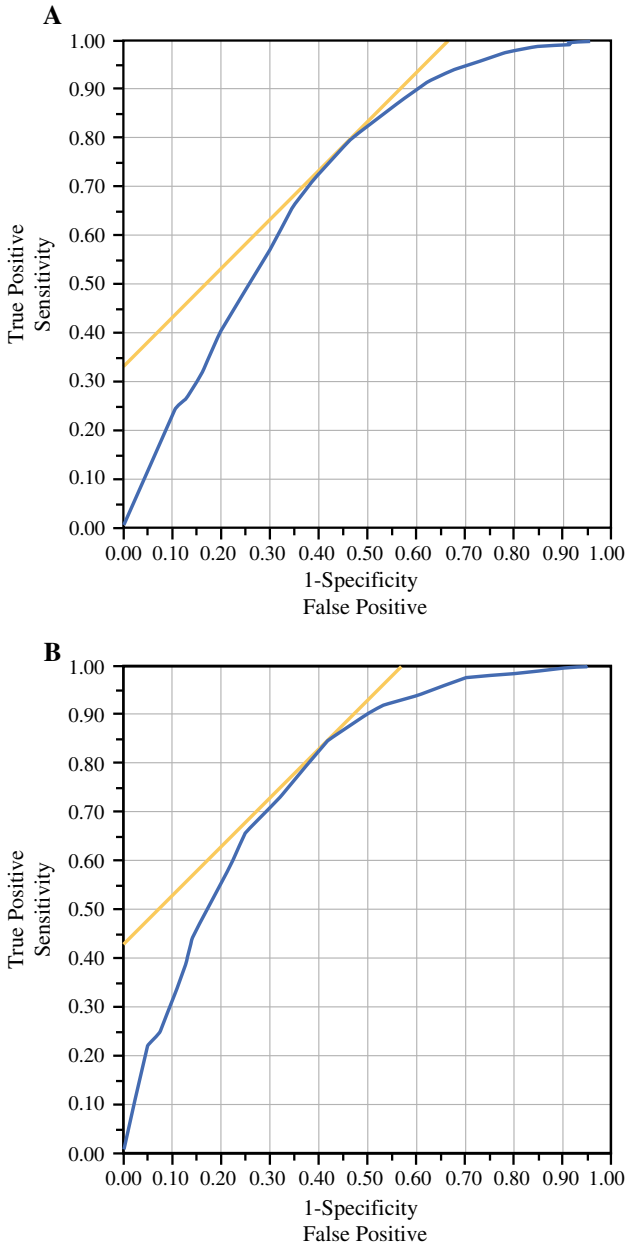


**FIG. 3** Receiver operating characteristic curves of optimal cutoff size for predicting lymph node involvement **a** among all neuroendocrine histologic subtypes and **b** among typical neuroendocrine tumors

which was performed for less than 20% of the patient population. Furthermore, the study evaluated consecutively resected appendiceal NETs without a size limit. By doing so, tumors larger than 2 cm with their inherent increased risk of LVI and nodal dissemination also were included. Each study provided ROC curve analyses to determine the optimal tumor size cutoff for predicting lymph node metastasis. These analyses were hindered by the inclusion of tumors larger than 2 cm, which likely skewed the cutoffs to 19.5 and 15.5 mm, respectively. In conjunction with the substantial detail regarding pathologic features that Rault-Petit et al.[14] and Brighi et al.[15] were able to capture, our study extended the predictive utility of LVI to appendiceal NETs 2 cm in size or smaller, further supporting the aforementioned consensus management guidelines.

The overall survival in our patient cohort was durable but significantly worse for the patients with node involvement (median not reached; mean, 84 vs. 124 months; $p < 0.0001$, log-rank). Control of disease is far more challenging when it extends beyond the organ of origin.[23] Therefore, treatment at early stages represents the best opportunity for long-term disease control and potential cure. Lymphovascular invasion has significant value for identifying patients who are candidates for more aggressive treatment of early disease, given that the majority of appendectomy specimens performed for presumed acute appendicitis will have few or no lymph nodes harvested.[3]

The question of how many regional lymph nodes should be assessed to provide adequate staging of appendiceal NETs has recently been addressed.[24] A Surveillance, Epidemiology, and End Results (SEER) database analysis using cut-point statistical modeling determined that for typical appendiceal neuroendocrine tumors 1–2 cm in diameter, evaluation of 12 or more lymph nodes was associated with improved overall survival at 5 years (100% vs. 85.7%; $p = 0.006$), which coincides with the recommended number of nodes for colon adenocarcinoma. Using this threshold, we found that patients with 12 or more examined nodes were significantly more likely to have positive regional nodes identified.

We considered that neuroendocrine tumors of the appendix exist as three entities: typical, goblet cell, and composite histologies. The three subtypes encompass a range of tumor biology, and few studies analyze all subtypes together.[9,25] In considering all the histologic subtypes in the same cohort, we were able directly to compare the locoregional aggressiveness of a range of small appendiceal NETs. Rather unexpectedly, we found that compared with typical NETs, lymph node involvement was one-fourth as likely among goblet cell tumors and half as likely among composite tumors, despite a similar frequency of LVI across histologic categories at the 1- to 2-cm tumor size. Therefore, the presence of LVI in NETs smaller than 1 cm may appropriately support the decision to perform completion right colectomy and regional node assessment across all histologic subtypes.

The limitations of databases such as the NCDB are well-described, particularly the lack of disease recurrence data. This is particularly limiting in the setting of diseases with substantial long-term survival, such as small appendiceal NETs. However, a large dataset such as that offered by the

NCDB has substantial value for aggregating adequate numbers of these unusual tumors for analysis. A limitation specific to our analysis was that the NCDB does not have a specific code for "appendectomy." However, by stratifying patients based on nodal harvest rather than length of colon removed, we believe that the more relevant end point of resection was incorporated into the analysis. Finally, because LVI has been collected only since 2010, overall survival analyses stratified by LVI were unable to detect survival differences between patient subsets at the end of the follow-up period.

In summary, lymphovascular invasion has been identified in many consensus guidelines as a harbinger of locally aggressive small appendiceal NETs that should prompt consideration of completion right colectomy. Empirical evidence to support that recommendation has been limited to date. Our analyses have shown that appendiceal NETs of any diameter with LVI should be considered for right colectomy and regional lymphadenectomy given the significant risk of regional nodal metastases, regardless of tumor grade or histologic subtype.

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**DISCLOSURES** There are no conflicts of interest.

## REFERENCES

1. Lewis A, Li D, Williams J, Singh G. Pancreatic neuroendocrine tumors: state-of-the-art diagnosis and management. *Oncology Williston Park.* 2017;31:e1–e12.
2. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26:3063–72.
3. Alexandraki KI, Kaltsas GA, Grozinsky-Glasberg S, Chatzellis E, Grossman AB. Appendiceal neuroendocrine neoplasms: diagnosis and management. *Endocr Relat Cancer.* 2016;23:R27–41.
4. Griniatsos J, Michail O. Appendiceal neuroendocrine tumors: recent insights and clinical implications. *World J Gastrointest Oncol.* 2010;2:192–6.
5. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7970 appendectomies. *Dis Colon Rectum.* 1998;41:75–80.
6. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. *Pancreas.* 2010;39:753–66.
7. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut.* 2012;61:6–32.
8. Pape U-F, Perren A, Niederle B, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology.* 2012;95:135–56.
9. Hsu C, Rashid A, Xing Y, et al. Varying malignant potential of appendiceal neuroendocrine tumors: importance of histologic subtype. *J Surg Oncol.* 2013;107:136–43.
10. Pham TH, Wolff B, Abraham SC, Drelichman E. Surgical and chemotherapy treatment outcomes of goblet cell carcinoid: a tertiary cancer center experience. *Ann Surg Oncol.* 2006;13:370–6.
11. Brathwaite S, Yearsley MM, Bekaii-Saab T, et al. Appendiceal mixed adeno-neuroendocrine carcinoma: a population-based study of the Surveillance, Epidemiology, and End Results Registry. *Front Oncol.* 2016;6:148.
12. Farley HA, Pommier RF. Surgical treatment of small bowel neuroendocrine tumors. *Hematol Oncol Clin North Am.* 2016;30:49–61.
13. Kleiman DA, Finnerty B, Beninato T, et al. Features associated with metastases among well-differentiated neuroendocrine (carcinoid) tumors of the appendix: the significance of small-vessel invasion in addition to size. *Dis Colon Rectum.* 2015;58:1137–43.
14. Rault-Petit B, Do Cao C, Guyétant S, et al. Current management and predictive factors of lymph node metastasis of appendix neuroendocrine tumors: a national study from the French group of endocrine tumors (GTE). *Ann Surg.* 2019;270:165–71.
15. Brighi N, La Rosa S, Rossi G, et al. Morphological factors related to nodal metastases in neuroendocrine tumors of the appendix: a multicentric retrospective study. *Ann Surg.* 2018. https://doi.org/10.1097/SLA.0000000000002939.
16. Levendoglu H, Cox CA, Nadimpalli V. Composite (adenocarcinoid) tumors of the gastrointestinal tract. *Dig Dis Sci.* 1990;35:519–25.
17. Nussbaum DP, Speicher PJ, Gulack BC, et al. Management of 1- to 2-cm carcinoid tumors of the appendix: using the National Cancer Data Base to address controversies in general surgery. *J Am Coll Surg.* 2015;220:894–903.
18. Mosquera C, Fitzgerald TL, Vora H, Grzybowski M. Novel nomogram combining depth of invasion and size can accurately predict the risk for regional nodal metastases for appendiceal neuroendocrine tumors (A-NET). *J Surg Oncol.* 2017;116:651–7.
19. Mehrvarz Sarshekeh A, Advani S, Halperin DM, et al. Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. *Oncotarget.* 2017;8:99541–51.
20. Wasif N, Faries MB, Saha S, et al. Predictors of occult nodal metastasis in colon cancer: results from a prospective multicenter trial. *Surgery.* 2010;147:352–7.
21. Kojima M, Ikeda K, Saito N, et al. Neuroendocrine tumors of the large intestine: clinicopathological features and predictive factors of lymph node metastasis. *Front Oncol.* 2016;6:173.
22. Martin JA, Warner RRP, Wisnivesky JP, Kim MK. Improving survival prognostication of gastroenteropancreatic neuroendocrine neoplasms: revised staging criteria. *Eur J Cancer.* 2017;76:197–204.
23. Nash GM, Smith JD, Tang L, et al. Lymph node metastasis predicts disease recurrence in a single-center experience of 70 stages 1–3 appendix cancers: a retrospective review. *Ann Surg Oncol.* 2015;22:3613–7.
24. Raoof M, Dumitra S, O'Leary MP, Singh G, Fong Y, Lee B. Mesenteric lymphadenectomy in well-differentiated appendiceal neuroendocrine tumors. *Dis Colon Rectum.* 2017;60:674–81.
25. Shaib WL, Goodman M, Chen Z, et al. Incidence and survival of appendiceal mucinous neoplasms: a SEER analysis. *Am J Clin Oncol.* 2017;40:569–73.