Prognostic Significance of Lymph Node Metastases in Small Intestinal Neuroendocrine Tumors

Michelle Kang Kim^a Richard R.P. Warner^a Stephen C. Ward^c Noam Harpaz^c
Sasan Roayaie^e Myron E. Schwartz^d Steven Itzkowitz^a Juan Wisnivesky^b

Divisions of ^aGastroenterology and ^bGeneral Internal Medicine, Department of Medicine, and ^cDepartment of Pathology, Mount Sinai School of Medicine, ^dMount Sinai Liver Cancer Program, Mount Sinai Hospital, and ^eLiver Cancer Program, Hofstra-North Shore Long Island Jewish School of Medicine, New York, N.Y., USA

Key Words

Small intestine · Neuroendocrine tumor · Carcinoid · Staging · Lymph node

Abstract

Background/Aims: Current staging guidelines for small intestinal neuroendocrine tumors (SI-NETs) differentiate between the presence (N1) and absence (N0) of lymph node (LN) metastases. However, the prognostic significance of the extent of LN involvement remains unknown. In this study, we used data from a population-based cancer registry to examine whether involvement of a higher number of LNs is associated with worse survival. **Methods:** We used the Surveillance, Epidemiology, and End Results (SEER) database to identify patients with histologically confirmed, surgically resected SI-NETs diagnosed between 1988 and 2010. Patients were classified into three groups by the LN ratio (number of positive LNs/number of total LNs examined, LNR): ≤ 0.2 , >0.2 – 0.5 , and >0.5 . We used the Kaplan-Meier method and Cox models to assess NET cancer-specific survival differences (up to 10 years from diagnosis) according to LNR status. **Results:** We identified 2,984 surgically resected patients with stage IIIb (N1, M0) SI-NETs with detailed LN data. More

than half of the NETs were located in the ileum. A higher LNR was significantly associated with worse NET cancer-specific survival ($p < 0.0001$). Ten-year NET-specific survival was 85, 77, and 74% for patients in the ≤ 0.2 , >0.2 – 0.5 , and >0.5 LNR groups, respectively. In stratified analyses, higher LNR groups had worse survival only in early tumor (T1, T2) disease ($p < 0.0001$). **Conclusions:** The extent of LN involvement provides independent prognostic information on patients with LN-positive SI-NETs. This information may be used to identify patients at high risk of recurrence and inform decisions about the use of adjuvant therapy.

© 2015 S. Karger AG, Basel

Introduction

The incidence of small intestinal neuroendocrine tumors (SI-NETs) has tripled over the last several decades, likely due to an increased performance of imaging and endoscopic procedures [1, 2]. The clinical course may vary from slowly progressive to highly aggressive disease with heterogeneous patient outcomes. This variability poses significant challenges in treatment and medical decision making. Therefore, accurate staging is critical in

the management of SI-NET patients; it informs treatment selection and discussions about prognosis and guides eligibility for clinical trials.

In SI-NET patients, the presence of lymph node (LN) involvement is associated with worse survival and may have important treatment implications [3]. In both the American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society (ENETS) staging classifications, SI-NETs are classified as N0 or N1 disease based on the absence or presence of LN metastases, respectively (see Appendix) [4, 5]. Ten-year cancer-specific survival is 87% for N0 disease, as compared to 77% for N1 cases [3]. However, there is considerable survival heterogeneity even among NET patients with N1 disease [6, 7]. While not considered in the NET classification, the extent of LN involvement (i.e., the number of positive regional nodes) is an established predictor of survival in other cancers [8–15]. However, it remains unknown whether this potential prognostic factor provides additional information beyond tumor (T) and node (N) status in SI-NETs.

In this study, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) cancer registry to assess the prognostic impact of the extent of LN involvement among patients with SI-NETs. We hypothesized that more extensive LN involvement will accurately discriminate patients with worse disease-specific survival.

Subjects and Methods

Study Population

We identified patients with SI-NETs (site codes: C170–173, 178, and 179; histological codes: 8240–8250, 8150–8156, and 9091) diagnosed between 1988 and 2010 from the SEER database, a national cancer registry that collects information from incident malignancies across several areas of the USA [16]. We included all patients 18 years of age or older with pathologically confirmed SI-NETs and without a history of other cancers. We excluded cases diagnosed at autopsy or on death certificates or cancers with incomplete staging information. We further limited the cohort to patients with surgically resected stage IIIb disease [any T, N1, M0: tumor of any size and depth (T1–T4), no regional LN metastasis (N0), and no distant metastasis (M0)] [5]. We also identified all resected stage I–IIIa patients, who were used as a reference population.

Demographic data such as gender, age, race/ethnicity, and marital status were obtained from the SEER registry. The T, N, and M status was determined based on detailed data provided by the SEER registry on primary tumor size, depth of invasion, local extension, LN involvement, and presence/absence of distant metastases. Using this information, the cancer stage was assigned according to ENETS and AJCC staging criteria [4, 5]. The SEER registry also includes data regarding the use of surgery as part of

primary cancer treatment. We categorized the type of resection as (1) local resection (surgical code 20), (2) partial or simple resection (surgical code 30), (3) total resection (surgical code 40), or (4) debulking surgery (surgical codes 50–60).

The number of positive LNs can be used as a marker for the extent of LN involvement. However, this feature is confounded by the number of LNs removed during surgery [17–20]. This is particularly problematic as no standards exist about the number of LNs that should be removed during SI-NET operations. To address this issue, the LN ratio (LNR), defined as the ratio between the number of positive nodes and the number of LNs removed during surgical resection, has been used for other gastrointestinal cancers [17, 21–23]. Based on cutoffs used in prior studies and the distribution of LNR in the study cohort, we classified patients into three LNR groups: ≤ 0.20 , >0.2 – 0.5 , and >0.5 .

Survival time was calculated as the period from the date of diagnosis until death or the last follow-up (December 31, 2010). We used SI-NET-specific survival as the main study outcome in order to evaluate differences in cancer prognosis according to LNR categories. The cause of death was determined using SEER registry data abstracted from death certificates. Individuals who were alive at the last follow-up or who died from non-NET causes were treated as censored observations. This study was exempt from IRB review.

Statistical Analysis

We used the *t* and χ^2 tests to compare the distribution of patients' characteristics such as age, sex, race/ethnicity, marital status, tumor site, T status, and the type of surgical resection according to LNR group. We then constructed Kaplan-Meier curves to estimate SI-NET-specific survival for each LNR category; the log-rank test was used to compare survival between groups. The survival curves were plotted up to 10 years after diagnosis to assess long-term outcomes of these relatively slowly progressive tumors while avoiding estimating survival curves with small numbers of cases. We repeated the analyses within anatomic site strata to assess the association of LNR with SI-NET-specific survival among jejunoileal versus duodenal cancers. We also performed stratified analyses by T status. We used Cox proportional hazards models to evaluate the association between LNR groups and SI-NET-specific survival after adjusting for age, sex, race/ethnicity, marital status, T status, and the type of surgical resection. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, N.C., USA) using two-sided *p* values.

Results

From the SEER registry, we identified 11,464 SI-NETs diagnosed between 1988 and 2010. We excluded 2,658 patients (23%) who had other primary cancers and 1,283 (11%) who had incomplete staging information (fig. 1). From those remaining, we selected 2,984 patients with stage IIIb disease who had undergone surgical resection and had detailed LN data. As a control, we also included data on 860 resected patients with N0 disease. More than half (60%) of the stage IIIb cases were located in the ileum.

The median number of LNs removed was 10 (interquartile range: 11). Approximately 30, 39, and 31% of the cohort had an LNR of ≤ 0.2 , >0.2 – 0.5 , and >0.5 , respectively. Demographic characteristics of the study patients according to LNR group, as well as of the reference population, are shown in table 1. Patients in the highest LNR group were older ($p < 0.0001$) and more often male ($p = 0.005$). The groups were similar with respect to race/ethnicity ($p = 0.57$) and marital status ($p = 0.28$). However, cancers in the jejunum ($p < 0.0001$) and with advanced T (T3 or T4) status ($p < 0.0001$) were more common in the highest LNR category. Finally, patients in the highest LNR group were more likely to have local and partial surgical resections than total resection or debulking surgery ($p < 0.0001$).

Kaplan-Meier analysis showed progressively worse disease-specific survival with higher LNRs ($p < 0.0001$; fig. 2). Ten-year survival was 85% [95% confidence interval (CI): 81–89], 77% (95% CI: 73–80), and 74% (95% CI: 69–78) for patients in the ≤ 0.2 , >0.2 – 0.5 , and >0.5 LNR groups, respectively. As a comparison, 10-year SI-NET-specific survival for N0 disease was 85% (95% CI: 81–89).

Stratified analyses by T status demonstrated progressively worse survival with higher LNRs in patients with early T status (T1, T2; $p < 0.0001$) but not among those with late T status (T3, $p = 0.24$; T4, $p = 0.40$; fig. 3). Among those with early disease, patients with an LNR of ≤ 0.2 had 10-year survival of 94.2% (95% CI: 90–98), as compared to 91.8% (95% CI: 87–96) for an LNR of >0.2 – 0.5 and 82.5% (95% CI: 74–91) for an LNR of >0.5 . Conversely, there was no significant association between LNR and survival in patients with T3 ($p = 0.24$) or T4 disease ($p = 0.40$). These findings persisted in stratified analyses among patients with jejunoileal or duodenal disease.

Cox analysis also showed a differential effect of LNR status on disease-specific survival, according to T status (i.e., a significant interaction between LNR and T status; table 2). In patients with early T status (T1, T2), the hazard ratio (HR) of death was 1.6 (95% CI: 0.72–3.56), 2.29 (95% CI: 1.10–4.78), and 4.52 (95% CI: 2.24–9.12) for those with LNRs of ≤ 0.2 , >0.2 – 0.5 , and >0.5 , respectively, as compared to patients with N0 disease. Conversely, in patients with T3 status, disease-specific survival in the groups with LNRs of ≤ 0.2 (HR 0.78, 95% CI: 0.18–3.28), >0.2 – 0.5 (HR 0.91, 95% CI: 0.22–3.74), or >0.5 (HR 1.00; 95% CI: 0.25–4.07) was not significantly different from that of patients with N0 disease. Similarly, disease-specific mortality among T4 patients with

Fig. 1. Flow diagram for SI-NET patients included in the study.

Fig. 2. Disease-specific survival stratified by LNR status. Disease-specific survival was progressively worse with increasing LNR ($p < 0.0001$). There was overlap of survival in patients with N0 and the lowest LNR status.

Table 1. Demographic characteristics of the study subjects (n = 2,984)

Characteristic	N0 (n = 860)	LNR			p value ^a
		≤0.20 (n = 888)	>0.2–0.5 (n = 1,168)	>0.5 (n = 928)	
Mean age (SD), years	61.2 (14.3)	59.6 (12.5)	61.7 (12.9)	62.6 (12.4)	<0.0001
Male, n (%)	434 (50.5)	454 (51.1)	583 (49.9)	527 (56.8)	0.005
Race/ethnicity, n (%)					
White	664 (77.2)	719 (81.0)	936 (80.1)	724 (78.0)	0.57
Black	114 (13.3)	98 (11.0)	129 (11.9)	124 (13.4)	
Hispanic	53 (6.2)	48 (5.4)	69 (5.9)	61 (6.6)	
Other	29 (3.4)	23 (2.6)	24 (2.0)	19 (2.1)	
Marital status, n (%)					
Single	119 (13.8)	109 (12.3)	148 (12.7)	101 (10.9)	0.28
Married	510 (59.3)	601 (67.7)	726 (62.2)	618 (66.6)	
Separated/divorced	83 (9.6)	58 (6.5)	109 (9.3)	73 (7.9)	
Widowed	107 (12.4)	93 (10.5)	143 (12.2)	102 (11.0)	
Unknown	41 (4.8)	27 (3.0)	42 (3.6)	34 (3.7)	
Cancer site, n (%)					
Duodenum	132 (15.3)	39 (4.4)	54 (4.6)	34 (3.7)	<0.0001
Jejunum	51 (5.9)	36 (4.0)	64 (5.5)	75 (8.1)	
Ileum	457 (53.1)	625 (70.4)	703 (60.2)	457 (49.3)	
Meckel's diverticulum	8 (0.9)	1 (0.1)	6 (0.5)	5 (0.5)	
Overlapping lesion	8 (0.9)	11 (1.2)	12 (1.0)	18 (1.9)	
Small intestine, NOS	204 (23.7)	176 (19.8)	329 (28.2)	339 (36.5)	
T status, n (%)					
1	191 (22.2)	84 (9.7)	38 (3.4)	11 (1.2)	<0.0001
2	256 (29.8)	221 (25.6)	223 (19.9)	132 (14.7)	
3	282 (32.8)	417 (48.2)	598 (53.3)	492 (54.9)	
4	131 (15.2)	143 (16.5)	263 (23.4)	261 (29.1)	
Surgery, n (%)					<0.0001
Local resection	52 (6.0)	21 (2.4)	33 (2.8)	43 (4.6)	
Partial/simple resection	527 (61.3)	518 (58.3)	687 (58.8)	613 (66.1)	
Total resection	142 (16.5)	189 (21.3)	238 (20.4)	164 (17.7)	
Debulking surgery	139 (16.2)	160 (18.0)	210 (18.0)	108 (11.6)	

NOS = Not otherwise specified. ^a p values reflect comparisons of the three LNR groups.

Table 2. Influence of LNR status on the risk of disease-specific mortality

Disease status	Number	Reference	HR	95% CI
T1T2				
LNR ≤0.2	305	T1T2, N0	1.60	0.72–3.56
LNR >0.2–0.5	261	T1T2, N0	2.29	1.10–4.78
LNR >0.5	143	T1T2, N0	4.52	2.24–9.12
T3				
LNR ≤0.2	417	T3, N0	0.78	0.18–3.28
LNR >0.2–0.5	598	T3, N0	0.91	0.22–3.74
LNR >0.5	492	T3, N0	1.00	0.25–4.07
T4				
LNR ≤0.2	143	T4, N0	0.71	0.16–3.22
LNR >0.2–0.5	263	T4, N0	0.98	0.23–4.16
LNR >0.5	261	T4, N0	0.97	0.23–4.09

Adjusted for age, sex, marital status, and primary tumor site.

Fig. 3. **a** In patients with early T status (T1, T2), disease-specific survival was progressively worse with increasing LNR ($p < 0.0001$). **b** In patients with T3 status, higher LNR was not associated with worse disease-specific survival. **c** In patients with T4 status, higher LNR was not associated with worse disease-specific survival.

LNRs of ≤ 0.2 (HR 0.71, 95% CI: 0.16–3.22), >0.2 – 0.5 (HR 0.98, 95% CI: 0.23–4.16), or >0.5 (HR 0.97, 95% CI: 0.23–4.09) was not significantly different from that of patients with N0 disease. These results persisted after adjusting for the number of LNs removed; there was no significant association between LNR and the number of LNs examined.

Discussion

Accurate staging of NETs is critical for patient management and research. While current ENETS/AJCC classifications help in the identification of groups with poor prognosis, there is still considerable heterogeneity in the outcomes of patients within specific categories. In this study, we found that the LNR, a readily available measure

of the extent of regional LN involvement, was an independent predictor of survival among patients with locoregional SI-NETs. A revised staging system which incorporates this feature may improve prognostication for patients with node-positive SI-NETs.

Our findings regarding the importance of the LNR are consistent with studies on other gastrointestinal cancers. Greenstein et al. [24] demonstrated in 838 node-positive esophageal carcinoma patients that a higher LNR was independently associated with worse outcomes. Similarly, other studies have demonstrated that LNR is an independent prognostic predictor in patients with node-positive gastric and colon cancers [17]. Our study extends these findings to SI-NET patients, demonstrating that the LNR can be used to differentiate outcomes beyond the existing TNM-based classification. A higher LNR status may reflect tumors with more aggressive biology or extensive disease.

Existing clinical, biochemical, and pathologic markers aid clinicians in their assessment of the extent of disease and response to therapy. Clinical factors such as the presence of carcinoid syndrome or carcinoid heart disease predict poor prognoses but are only present in a small subset of patients with metastatic disease, thus limiting the utility of these factors. Chromogranin A is the most frequently used tumor marker in NETs, but it is falsely elevated by the near-ubiquitous use of proton pump inhibitors [25–30]. Tumor grade (as measured by mitotic and Ki-67 indices) is incorporated into the ENETS and AJCC classifications and has been shown in multiple studies to predict prognosis, but it is not assessed routinely outside of tertiary hospitals or specialty NET centers [4, 5]. Moreover, a lack of standardization of assays and reporting further hinders its use in clinical practice. Thus, there is a need for additional prognostic factors to provide information to patients and clinicians.

While LNRs are only available for patients who undergo surgical resection, it is a simple and readily available marker. It is routinely reported as part of pathological staging and could be incorporated into revised classifications without additional cost. Importantly, routine use of the LNR can have direct clinical implications. For example, patients with a high LNR may require more aggressive monitoring and treatment. Thus, future trials should assess the potential benefit of adjuvant therapy for these high-risk individuals. Additionally, LNR information may help in selecting homogenous populations of SI-NET patients to be enrolled in clinical trials. Accurate data may also help patient-provider discussions about prognosis and facilitate informed patient decision making.

The major strengths of our study were our large sample of SI-NETs and the availability of long-term survival data. Both of these features enabled us to detect differences in outcomes among patients with nodal disease while adjusting for established TNM-based prognostic factors. Another strength of this analysis was the use of a population-based sample, thus limiting the impact of referral bias. Finally, the detailed LN data available from the SEER registry enabled us to study nodal features that are not typically available in other cancer registries.

The major limitation of this study was the lack of available tumor grade information. Both the mitotic and Ki-67 labeling indices are recognized prognostic factors incorporated into the ENETS and AJCC classifications [4, 5]. Thus, we were not able to assess whether the LNR is an independent predictor of prognosis after controlling for tumor grade. However, most SI-NETs demonstrate a lower proliferation, suggesting that tumor grade would not be a major confounder. Moreover, the data required to calculate LNRs are free, while tumor grade assessment poses additional costs. Another limitation was that cause of death was abstracted from death certificates, thereby introducing a potential for misclassification. However, the NET-specific survival rates in the SEER registry are consistent with those reported in institution-based studies with more detailed information about causes of death [6]. Finally, the LNR may be less reliable with smaller numbers of removed LNs; we were also unable to account for LN involvement at specific locations (e.g., the mesentery) since these data are not recorded in the SEER registry.

In summary, our findings suggest that the LNR independently predicts prognosis and can further discriminate outcomes in patients with node-positive SI-NETs. More detailed LN data could be incorporated into the current staging system to allow for a better assessment of prognosis in this patient population. In addition, these data suggest that patients with high LNRs are at risk of worse outcomes and may be considered for more aggressive postoperative therapy.

Acknowledgments

This work was supported by the National Center for Advancing Translational Sciences at the National Institutes of Health (grant No. KL2TR000069 to M.K.K.) and the American Cancer Society (MRSG-14-014-01-CCE to M.K.K.).

Disclosure Statement

The authors have declared no conflicts of interest.

Appendix: AJCC and ENETS Staging and Grading Classification for SI-NETs

Primary Tumor (T)		Stage			
Tx	Primary tumor cannot be assessed	I	T1	N0	M0
T0	No evidence of primary tumor	IIa	T2	N0	M0
T1	Tumor invades lamina propria or submucosa and size ≤1 cm	IIb	T3	N0	M0
T2	Tumor invades muscularis propria or size >1 cm	IIIa	T4	M0	M0
T3	Tumor invades through muscularis propria into subserosa or into nonperitonealized tissue	IIIb	Any T	N1	M0
T4	Tumor invades visceral peritoneum (serosa) or other organs or structures	IV	Any T	Any N	M1
		Grade	Mitotic index (per 10 HPF)	Ki-67 index	
Regional lymph nodes (N)		G1	<2	<3%	
Nx	Regional lymph nodes cannot be assessed	G2	2–20	3–20%	
N0	No regional lymph node metastasis	G3	>20	>20%	
N1	Regional lymph node metastasis				
Distant metastasis (M)					
Mx					
M0	No distant metastasis	HPF = High-powered field.			
M1	Distant metastasis				

HPF = High-powered field.

References

- Lawrence B, Gustafsson BI, Chan A, et al: The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011;40:1–18, vii.
- 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;26:3063–3072.
- Kim MK, Warner RR, Roayaie S, et al: Revised staging classification improves outcome prediction for small intestinal neuroendocrine tumors. *J Clin Oncol* 2013;31:3776–3781.
- Rindi G, Kloppel G, Couvelard A, et al: TNM staging of midgut and hindgut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007;451:757–762.
- Edge S, Byrd DR, Compton CC, et al: *AJCC Cancer Staging Manual*, ed 7. New York, Springer, 2010.
- Jann H, Roll S, Couvelard A, et al: Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer* 2011;117:3332–3341.
- Strosberg JR, Weber JM, Feldman M, et al: Prognostic validity of the American Joint Committee on Cancer staging classification for midgut neuroendocrine tumors. *J Clin Oncol* 2013;31:420–425.
- Akutsu Y, Matsubara H: The significance of lymph node status as a prognostic factor for esophageal cancer. *Surg Today* 2011;41:1190–1195.
- Chang YJ, Chen LJ, Chung KP, Lai MS: Evaluation of lymph nodes in patients with colon cancer undergoing colon resection: a population-based study. *World J Surg* 2012;36:1906–1914.
- Hirabayashi S, Kosugi S, Isobe Y, et al: Development and external validation of a nomogram for overall survival after curative resection in serosa-negative, locally advanced gastric cancer. *Ann Oncol* 2014;25:1179–1184.
- Homma Y, Hamano T, Otsuki Y, et al: The total number of lymph node metastases is a more significant risk factor for poor prognosis than positive lateral lymph node metastasis. *Surg Today* 2015;45:168–174.
- Kim SH, Yang HK, Lee JH, Lee ES: A retrospective analysis of incidence and its associated risk factors of upper urinary tract recurrence following radical cystectomy for bladder cancer with transitional cell carcinoma: the significance of local pelvic recurrence and positive lymph node. *PLoS One* 2014;9:e96467.
- Resch A, Langner C: Lymph node staging in colorectal cancer: old controversies and recent advances. *World J Gastroenterol* 2013;19:8515–8526.
- Stanisavljevic L, Sondenaa K, Storli KE, et al: The total number of lymph nodes in resected colon cancer specimens is affected by several factors but the lymph node ratio is independent of these. *APMIS* 2014;122:490–498.
- Takeno S, Yamashita SI, Yamamoto S, et al: Number of metastasis-positive lymph node stations is a simple and reliable prognostic factor following surgery in patients with esophageal cancer. *Exp Ther Med* 2012;4:1087–1091.
- Howlader N: *SEER Cancer Statistics Review, 1975–2009 (Vintage 2009 Populations)*. 2012. http://seer.cancer.gov/archive/csr/1975_2009_pops09/.
- Lee HY, Choi HJ, Park KJ, et al: Prognostic significance of metastatic lymph node ratio in node-positive colon carcinoma. *Ann Surg Oncol* 2007;14:1712–1717.
- Vinh-Hung V, Verschraegen C, Promish DI, et al: Ratios of involved nodes in early breast cancer. *Breast Cancer Res* 2004;6:R680–R688.
- Voordeckers M, Vinh-Hung V, Van de Steene J, et al: The lymph node ratio as prognostic factor in node-positive breast cancer. *Radiother Oncol* 2004;70:225–230.
- Sant M, Allemani C, Capocaccia R, et al: Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer* 2003;106:416–422.
- Nitti D, Marchet A, Olivieri M, et al: Ratio between metastatic and examined lymph nodes is an independent prognostic factor after D2 resection for gastric cancer: analysis of a large European monoinstitutional experience. *Ann Surg Oncol* 2003;10:1077–1085.
- Berger AC, Sigurdson ER, LeVoyer T, et al: Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* 2005;23:8706–8712.
- Berger AC, Watson JC, Ross EA, Hoffman JP: The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg* 2004;70:235–240, discussion 240.

- 24 Greenstein AJ, Litle VR, Swanson SJ, et al: Prognostic significance of the number of lymph node metastases in esophageal cancer. *J Am Coll Surg* 2008;206:239–246.
- 25 Nikou GC, Marinou K, Thomakos P, et al: Chromogranin A levels in diagnosis, treatment and follow-up of 42 patients with non-functioning pancreatic endocrine tumours. *Pancreatol* 2008;8:510–519.
- 26 Ter-Minassian M, Chan JA, Hooshmand SM, et al: Clinical presentation, recurrence, and survival in patients with neuroendocrine tumors: results from a prospective institutional database. *Endocr Relat Cancer* 2013;20:187–196.
- 27 Turner GB, Johnston BT, McCance DR, et al: Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours. *Gut* 2006;55:1586–1591.
- 28 Vinik AI, Silva MP, Woltering EA, et al: Biochemical testing for neuroendocrine tumors. *Pancreas* 2009;38:876–889.
- 29 Stridsberg M, Oberg K, Li Q, et al: Measurements of chromogranin A, chromogranin B (secretogranin I), chromogranin C (secretogranin II) and pancreastatin in plasma and urine from patients with carcinoid tumours and endocrine pancreatic tumours. *J Endocrinol* 1995;144:49–59.
- 30 Lawrence B, Gustafsson BI, Kidd M, et al: The clinical relevance of chromogranin A as a biomarker for gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011;40:111–134, viii.