Differing Clinical Courses and Prognoses in Patients With Gastric Neuroendocrine Tumors Based on the 2010-WHO Classification Scheme

Beom Su Kim, MD, PhD, Young Soo Park, MD, PhD, Jeong Hwan Yook, MD, PhD, Sung Tae Oh, MD, PhD, and Byung-Sik Kim, MD, PhD

Abstract: The aim of this study is to test the prognostic accuracy of the 2010-WHO classification for post surgery survival in nonmetastatic gastric neuroendocrine tumor (NET) cases. Whether the 2010-WHO classification of NETs can predict relapse after surgical resection has not yet been established.

We selected 175 nonmetastatic gastric NET patients at Asan Medical Center, Seoul, Korea between 1996 and 2013. All tumors were classified using the WHO-2010 scheme.

Among 175 patients with gastric NETs, we diagnosed 39 cases as WHO grade 1, 13 cases as grade 2, 66 cases as grade 3 (neuroendocrine carcinomas; NECs), and 57 cases as mixed with adenocarcinoma. Patients with grade 3 had a lower relapse-free survival (RFS) and overall survival (OS) than those with WHO grade 1/2 and had a lower OS than patients with mixed type tumors. Patients with grade 1/2 had a better OS than patients with mixed type. There was no significant difference in RFS and OS between small and large cell type lesions. Among WHO grade 1/2 patients with <1 cm sized lesions, none exhibited lympho-vascular, perineural, mucosal, or submucosal invasion, and we detected no lymph node metastases or recurrences.

Our findings strongly suggest that WHO grade 3 behaves more aggressively than adenocarcinoma. Additionally, the survival of cases with large and small cell NEC was similar. Among WHO grade 1/2 patients who had <1 cm lesions, none exhibited lympho-vascular, perineural, mucosal, or submucosal invasion and all could be treated by endoscopic resection or minimally invasive surgery without node dissection.

INTRODUCTION

The incidence of gastric neuroendocrine tumors (NETs) have increased over the past few decades\(^2\) although the incidence is lower than that of other gastrointestinal organs.\(^1,3\) Several guidelines of diagnosis and treatment of gastric NETs have been published due to the heterogeneity in biology and in clinical behavior of the tumor.\(^4,5\) Rindi et al\(^6\) classified gastric NETs into 3 subtypes of carcinoids; type 1 associated with chronic atrophic gastritis, which shows good prognosis;\(^7,8\) and type 2 associated with multiple endocrine neoplasia type 1 and Zollinger–Ellison syndrome, which usually shows good prognosis but with a few exceptions showing aggressive behavior.\(^9,10\) Type 3 refers to sporadic cases associated with the greatest malignancy potential, presenting the poorest prognosis among the 3 types.\(^11\) By contrast, Kim et al\(^12\) reported that regardless of the type, carcinoids that are not yet advanced can be effectively treated with minimal endoscopic or laparoscopic surgery.

In 2000, the World Health Organization (WHO)\(^13\) proposed a classification scheme for gastroenteric NETs (WHO-2000), and this was updated in 2010 (WHO-2010).\(^14\) In WHO-2000, pure NETs were classified into 1 of 3 tumor categories: well-differentiated endocrine tumors (WDETs) that exhibited benign behavior; well-differentiated endocrine carcinomas (WDECs) that showed low-grade malignant behavior; and poorly differentiated endocrine carcinomas (PDECs) that displayed high-grade malignant behavior.

In 2006, the European Neuroendocrine Tumor Society (ENETS) proposed a new grading system for NETs\(^5,15,16\) that was based on the Ki-67 index (grade 1, ≤2%; grade 2, 3%–20%; and grade 3, >20%) and the WHO-2010 adopted the Ki-67 labeling index and/or mitotic index for NETs. Grade 3 was classified into 2 types of high grade neuroendocrine carcinomas (NECs): large cell (LC) NECs and small cell (SC) NECs. Additionally, WHO-2010 defined mixed adenoneuroendocrine carcinomas (MANECs) that contained neuroendocrine cells (exceeding at least 30% of all tumor cells) mixed with none

METHODS

Between 1996 and 2014, 175 patients were diagnosed with gastric NET at the Asan Medical Center in Seoul, Korea. We selected patients who did not have distant metastasis at the time
of diagnosis and who underwent endoscopic resection or surgical resection of NETs (R0 resection). All tissues were reviewed by a pathologist and classified according to the WHO-2010 classification. Mixed type was defined as NETs mixed with adenocarcinoma. We evaluated risk factors for lymph node metastasis and prognostic factors. We evaluated the basic clinical features and survival data between WHO grades and AJCC stages. Additionally, clinical outcomes between grade 3 and mixed type, and between SC and LC type were evaluated. Relapse-free survival (RFS) was defined as the time from tumor resection to the earliest among the following outcomes: disease recurrence (local or metastatic), last follow-up without evidence of disease, or death without evidence of disease.

Numerical data were expressed as means with standard deviation using Student’s t-tests. Risk factors were analyzed using the Chi-square test (univariate analysis) or a logistic regression model (multivariate analysis). Survival data were analyzed using the Kaplan–Meier method with the log-rank test (univariate analysis) or Cox proportional hazards regression (multivariate analysis). All statistical data were analyzed using SPSS 21.0 (SPSS Inc., Chicago, IL) software. P-values < 0.05 were considered to indicate statistically significant differences.

This study received approval from Asan Medical Center’s Institutional Review Board (IRB).

RESULTS

Basic Clinicopathological Characteristics of Patients

The average follow-up period was 52.9 ± 41.5 months and the male-to-female ratio was 2.4:1. Table 1 shows the clinicopathological characteristics. Among the 175 patients with gastric NETs, we diagnosed 39 as WHO grade 1, 13 as type 2, 66 as type 3, and 57 as mixed type. Tumors were more commonly located in the lower to mid portion of the stomach. A total of 76.6% of patients underwent gastrectomy. Among 49 patients with tumor recurrences, 10 had recurrence in the remnant stomach.

WHO Subgroup Analysis: Grades 1, 2, and 3

There were distinct characteristic and clinicopathological differences among WHO grades 1, 2, and 3 (Table 2). Patients with grade 3 were older than patients with grade 1 and the tumor location of grade 3 was more predominantly in the lower portion of the stomach (P < 0.05). Notably, patients with grade 3 required more aggressive treatment and experienced both more lymph node metastases and tumor recurrence than those with grade 1 lesions (P < 0.05). However, there was no significant difference between grades 1 and 2 in age, gender, or lymph node metastasis (P > 0.05). In grade 1, 6 cases experienced tumor recurrence and all of these cases had recurrences at the remnant stomach. Additionally, 2 of 3 cases with grade 2 who experienced tumor recurrences had recurrences at the remnant stomach. By contrast, only 2 of 27 grade 3 cases with recurrences experienced recurrences at the remnant stomach, and 20 of 27 cases experienced distant recurrences. Figure 1 shows a Kaplan–Meier survival curve of RFS and overall survival (OS). Patients with grade 3 had a lower RFS and OS than the other 2 grades (P < 0.05). However, the RFS or OS of grades 1 and 2 were high and similar (P > 0.05).

Matched-Pair Analysis: Grade 1/2, Grade 3, and Mixed Type

The results of the statistical analyses are summarized in Table 3. Although patients with grade 3 required more aggressive treatment, they experienced more tumor recurrence than those with mixed type lesions (P < 0.05). Although grade 1/2 cases mostly experienced tumor recurrence at the remnant stomach, grade 3 or mixed type cases mostly experienced tumor recurrences at a distant site (P < 0.05). Patients with grade 3 had a lower OS than those with a mixed type (Figure 2). However, patients with grade 1/2 were younger and had tumor locations that were more predominantly in the upper portion of the stomach than those of patients with grade 3 or mixed type lesions (P < 0.05). Additionally, patients with grade 1/2 had better overall clinical data (except for gender) than patients with grade 3 or mixed type lesions (P < 0.05). Finally, patients with grade 1/2 had a better RFS and OS than patients with grade 3 (Figure 2), and they also had a better OS than patients with mixed type lesions.

Matched-Pair Analysis of Small and Large Cell Type NEC

There were no statistically significant differences among all categories, except for lympho-vascular invasion (Table 4). Figure 3 shows Kaplan–Meier survival curve analyses. There
were no significant differences in RFS or OS between both groups ($P > 0.05$).

**Factors Influencing Patient Survival and Prognosis**

Gender, WHO grade, tumor size, depth of invasion, lympho-vascular invasion, perineural invasion, and lymph node metastasis were found to influence prognostic factors based on univariate analysis using the Kaplan–Meier method with the log-rank test. The results of Cox proportional hazards analysis (Table 5) showed that WHO grade 3, lymph node metastasis, and deep depth of invasion were independent prognostic factors ($P < 0.05$). We evaluated Cox proportional hazards analysis as 2 groups: low grade (WHO grade 1/2) and high grade (WHO grade 3/mixed type). In the low-grade group,

![Figure 1](image1.png)

**FIGURE 1.** Kaplan–Meier survival curves of RFS (A) and OS (B) among patients WHO grade 1, 2, and 3 tumors. Patients with grade 3 lesions had a lower RFS and OS than those patients with grades 1 and 2. However, the RFS and OS for grades 1 and 2 were both high and not significantly different. OS = overall survival, RFS = relapse-free survival, WHO = World Health Organization.
there was no multivariate prognostic risk factor. However, these results were similar to those shown in Table 5 for the high-grade groups (Table 6).

Factors Influencing Lymph Node Metastasis

Lymph node metastasis is the most important risk factor after minimally invasive surgery without lymph node
dissection. Lympho-vascular invasion and perineural invasion are independent risk factors that can influence lymph node metastasis in high grade NETs. Lymph node metastasis according to size distribution is summarized in Table 7. Grade 1 or 2 patients with \( \leq 1 \) cm sized lesions had no evidence of lympho-vascular, perineural, no lymph node metastasis, or tumor recurrence.

**DISCUSSION**

The lack of a uniform staging system for gastric NETs has substantially disabled clinicians to predict the risk of recurrence and prognosis of patients suffering from this tumor. Previous clinical or pathologic classifications were not utilized worldwide because of their complexity and limitation in usefulness. Nevertheless, the AJCC, ENETS, and WHO staging classifications are interchangeably used, since they allow a little better stratification and risk assessment of gastric NETs. However, their ability to predict recurrence-free survival for gastric NETs has not yet been tested. In this present study, we analyzed the RFS outcomes of 157 patients with gastric NETs. This study validates the usefulness and limitation of the WHO-2010 scheme of gastric NETs to predict RFS after resection.

![FIGURE 3. Kaplan–Meier survival curves of RFS (A) and OS (B) between small and large cell type tumors. There was no significant difference in the RFS or OS between the two. OS = overall survival, RFS = relapse-free survival.](image)

**TABLE 4.** Matched-Pair Analysis of the Clinicopathological Properties of Small and Large Cell Type NEC in the Study Series

| Patients Characteristics | Small Cell Type (n = 14, %) | Large Cell Type (n = 52, %) | P-Value |
|--------------------------|-----------------------------|----------------------------|---------|
| Age, years               | 58.2 ± 7.5                  | 62.7 ± 9.4                 | >0.05   |
| Gender                   |                             |                            | >0.05   |
| Male                     | 11 (78.6)                   | 39 (75.0)                  |         |
| Female                   | 3 (21.4)                    | 13 (25.0)                  |         |
| Tumor site, %            |                             |                            | >0.05   |
| Upper 1/3                | 2 (14.3)                    | 9 (17.3)                   |         |
| Middle 1/3               | 3 (21.4)                    | 19 (36.5)                  |         |
| Lower 1/3                | 9 (64.3)                    | 24 (46.2)                  |         |
| Type of operation, %     |                             |                            | >0.05   |
| Endoscopic resection     | 0                           | 1 (2.0)                    |         |
| Wedge resection          | 0                           | 0                          |         |
| Gastrectomy (partial/total) | 9/5 (100.0)               | 31/20 (98.0)               | >0.05   |
| Tumor size, mm           | 54.9 ± 25.4                 | 55.8 ± 29.9                |         |
| Depth of invasion        |                             |                            | >0.05   |
| Mucosa/submucosa         | 1 (7.1)                     | 9 (17.3)                   |         |
| Muscularis propria       | 2 (14.3)                    | 11 (21.2)                  |         |
| Subserosa                | 7 (50.0)                    | 21 (40.3)                  |         |
| Serosa or more than serosa | 4 (28.6)                 | 11 (21.2)                  |         |
| Lymph node metastasis    | 8 (57.1)                    | 33 (63.5)                  | >0.05   |
| Lympho-vascular invasion | 9 (64.2)                    | 48 (92.3)                  | <0.05   |
| Adjuvant chemotherapy    | 9 (64.2)                    | 31 (59.6)                  | >0.05   |
| Recurrence               | 5 (35.7)                    | 22 (42.4)                  | >0.05   |
| Remnant stomach          | 0                           | 2 (3.8)                    | >0.05   |
| Loco-regional            | 1 (7.2)                     | 4 (7.7)                    | >0.05   |
| Distant                  | 4 (28.5)                    | 16 (30.9)                  | >0.05   |

NEC = neuroendocrine carcinoma.
They recommended the adoption of the treatment of gastrointestinal NETs according to 3 subtypes of condition. In 2004 and 2012, ENETS reported guidelines for the operated, despite increased knowledge and awareness of this condition. In 2011,27 these guidelines were both based on Rindi type and tumor size; however, they were not based on the WHO-2010 classification. Additionally, there are no guidelines for treatment according to the WHO classification. In this present study, we found that among grade 1 or 2 patients with \( \leq 1 \) cm sized lesions, there were no cases of lympho-vascular, perineural, mucosal, or submucosal invasion, or any cases of lymph node metastasis. Therefore, these patients could be treated with endoscopic resection or minimally invasive surgery without node dissection.

We found distinctive differences in tumor recurrence, typical carcinoids that are not yet advanced, could effectively be treated with minimal endoscopic or laparoscopic surgery, whereas NECs should be treated with radical gastrectomy, similar to carcinomas. The North American Neuroendocrine Tumor Society published guidelines in 201025,26 and the National Comprehensive Cancer Network did so in 2011.27 These guidelines are not sufficient to predict clinical evolution. Therefore, the recommendation of the proliferation fraction according to the ENETS scheme. This highlights that the histological classification alone is not sufficient to predict clinical evolution. Therefore, the

| TABLE 5. Multivariate Analysis of Prognostic Factors of all NETs |
|--------------------------------|-------------|----------|----------|
| Parameter                      | Hazard Ratio | 95% CI   | P-Value  |
| Age, years                     |              |          |          |
| \( \leq 60 \) (n = 79)          | 0.984        | 0.561–1.725 | >0.05    |
| >60 (n = 96)                    |              |          |          |
| Gender                         |              |          |          |
| Female (n = 51)                 | 1.65         | 0.77–3.52 | >0.05    |
| Male (n = 124)                  |              |          |          |
| Grading                        |              |          |          |
| WHO 1/2 (n = 52)                | 1.74         | 0.51–5.89 | >0.05    |
| Mixed type (n = 123)            | 3.82         | 1.14–12.83 | <0.05    |
| Grade 3 (n = 66)                |              |          |          |
| Tumor size, mm                  |              |          |          |
| \( \leq 40 \) (n = 88)          | 0.85         | 0.42–1.76 | >0.05    |
| >40 (n = 87)                    |              |          |          |
| Depth of invasion               |              |          |          |
| Non-serosa exposure (n = 153)   | 2.08         | 1.05–4.12 | <0.05    |
| Serosa exposure (n = 22)        |              |          |          |
| Lympho-vascular invasion        |              |          |          |
| No (n = 64)                     | 0.914        | 0.38–2.14 | >0.05    |
| Yes (n = 111)                   |              |          |          |
| Perineural invasion             |              |          |          |
| No (n = 125)                    | 1.42         | 0.79–2.61 | >0.05    |
| Yes (n = 50)                    |              |          |          |
| Lymph node metastasis           |              |          |          |
| No (n = 95)                     | 2.33         | 1.13–4.78 | <0.05    |
| Yes (n = 80)                    |              |          |          |

CI = confidence interval, NET = neuroendocrine tumor, WHO = World Health Organization.

The use of the Ki-67 index and/or mitosis in the WHO and ENETS grading systems was validated for foregut and pancreatic NENs (PanNENs) by several studies and their biological relevance and power to discriminate among prognostic groups has mostly been confirmed.19–23 However, to the best of our knowledge, no previous report of the prognostic validation of gastric NETs according to both grading systems has been published. In our present study, we found that pure poorly differentiated NECs had worse outcomes than NETs mixed with adenocarcinoma. Additionally, LC NECs had outcomes that were similar to SC NECs. Therefore, NECs would be expected to behave more aggressively than adenocarcinomas. To date, similar results have not been described by other studies.

In the past few decades, many attempts have been made to uniformly treat gut endocrine tumors. Unfortunately, because of their rarity, no structured therapeutic approach has been developed, despite increased knowledge and awareness of this condition. In 2004 and 2012, ENETS reported guidelines for the treatment of gastrointestinal NETs according to 3 subtypes of classification.5,6,24

| TABLE 6. Multivariate Analysis of the Prognostic Factors for Grade 3 NEC/Mixed Type Cases |
|--------------------------------|-------------|----------|----------|
| Parameter                      | Hazard Ratio | 95% CI   | P-Value  |
| Age, years                     |              |          |          |
| \( \leq 60 \) (n = 45)          | 0.87         | 0.48–1.57 | >0.05    |
| >60 (n = 78)                    |              |          |          |
| Gender                         |              |          |          |
| Female (n = 32)                 | 1.47         | 0.70–3.50 | >0.05    |
| Male (n = 91)                   |              |          |          |
| WHO grading                    |              |          |          |
| Mixed type (n = 57)             |              |          |          |
| Grade 3 (n = 66)                | 2.21         | 1.24–4.08 | <0.05    |
| Tumor size, cm                 |              |          |          |
| \( \leq 40 \) (n = 37)          | 0.72         | 0.42–1.82 | >0.05    |
| >40 (n = 86)                    |              |          |          |
| Depth of invasion               |              |          |          |
| Non-serosa exposure (n = 101)   | 2.03         | 1.02–4.04 | <0.05    |
| Serosa exposure (n = 22)        |              |          |          |
| Lympho-vascular invasion        |              |          |          |
| No (n = 22)                     | 0.78         | 0.37–1.94 | >0.05    |
| Yes (n = 101)                   |              |          |          |
| Perineural invasion             |              |          |          |
| No (n = 74)                     | 1.45         | 0.78–2.68 | <0.05    |
| Yes (n = 49)                    |              |          |          |
| Lymph node metastasis           |              |          |          |
| No (n = 46)                     | 2.57         | 1.18–5.64 | <0.05    |
| Yes (n = 77)                    |              |          |          |

CI = confidence interval, NEC = neuroendocrine carcinoma, WHO = World Health Organization.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.
accuracy of this paper still needs to be discussed. NETs of the stomach are very rare, so the statistical power of our analysis was limited by the relatively small number of patients. Recently, WHO-2010 defined mixed adeno-neuroendocrine carcinoma (MANEC) as a lesion that contains 30% of either component; however, we could not exactly determine the proportion of either component. Therefore, we defined NETs with any portion of adenocarcinoma as a mixed type. Finally, in our cohort, 61.5% of patients with grade 1 or 2 lesions received endoscopic resection and 98.4% of patients with grade 3 or mixed type lesions received gastrectomy. This difference between treatment methods could affect the sites of recurrence and lymph node metastasis.

In conclusion, we have found that cases of WHO grade 3 had poorer OS outcomes than NETs mixed with adenocarcinoma. Additionally, mixed type cases had a poorer OS than cases with WHO grade 1/2. These findings led us to speculate that NECs behave more aggressively than adenocarcinomas. We found that LC NECs had a similar RFS and OS as cases of SC NECs. Among WHO grade 1 or 2 patients with ≤1 cm sized lesions, no instances of lympho-vascular, perineural, mucosal, or submucosal invasion were noted, and no instances of lymph node metastases or recurrences were observed. Therefore, these patients could be treated with endoscopic resection or minimally invasive surgery without node dissection. We contend from this that endoscopy could be a more useful method for monitoring the recurrence of WHO grade 1 or 2 tumors, whereas CT could be a more useful method for monitoring the recurrence of grade 3 or mixed type lesions.

REFERENCES

1. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97:934–959.
2. Modlin IM, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? Am J Gastroenterol. 2004;99:23–32.
3. Godwin JD. 2nd. Carcinoid tumors. An analysis of 2,837 cases. Cancer. 1975;36:560–569.
4. Kloppel G, Couvelard A, Perren A, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology. 2009;90:162–166.
5. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology. 2004;80:394–424.
6. Rindi G, Luinetti O, Cornaggia M, et al. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. Gastroenterology. 1993;104:994–1006.
7. Borch K, Ahlen B, Ahlman H, et al. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. Ann Surg. 2005;242:64–73.
8. Burkitt MD, Pritchard DM. Review article: pathogenesis and management of gastric carcinoid tumours. Aliment Pharmacol Ther. 2006;24:1305–1320.
9. Bordi C, Falchetti A, Azzoni C, et al. Aggressive forms of gastric neuroendocrine tumors in multiple endocrine neoplasia type I. Am J Surg Pathol. 1997;21:1075–1082.
10. Norton JA, Melcher ML, Gibril F, et al. Gastric carcinoid tumors in multiple endocrine neoplasia-1 patients with Zollinger-Ellison syndrome can be symptomatic, demonstrate aggressive growth, and require surgical treatment. Surgery. 2004;136:1267–1274.
11. Rappel S, Altenhof-Hofmann A, Stoite M. Prognosis of gastric carcinoid tumours. Digestion. 1995;56:455–462.
12. Kim BS, Oh ST, Yook JH, et al. Typical carcinoids and neuroendocrine carcinomas of the stomach: differing clinical courses and prognoses. Am J Surg. 2010;200:328–333.
13. The International Agency for Research on Cancer. Pathology and Genetics of Tumours of the Digestive System. Lyon: IARC Press; 2000.
14. The International Agency for Research on Cancer. *WHO Classification of Tumours of the Digestive System*. 4th ed. Bosman TF, Carneiro F, Hruban RH, Theise ND, (Eds.). Lyon: IARC Press; 2010.

15. Rindi G, Kloppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch.* 2006;449:395–401.

16. 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.

17. Dolcetta-Capuzzo A, Villa V, Albarello L, et al. Gastroenteric neuroendocrine neoplasms classification: comparison of prognostic models. *Cancer.* 2013;119:36–44.

18. Endo S, Dousei T, Yoshikawa Y, et al. Gastric neuroendocrine tumors in our institutions according to the WHO 2010 classification. *Int Surg.* 2012;97:335–339.

19. Ekeblad S, Skogseid B, Dunder K, et al. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res.* 2008;14:7798–7803.

20. Fischer L, Kleeff J, Esposito I, et al. Clinical outcome and long-term survival in 118 consecutive patients with neuroendocrine tumours of the pancreas. *Br J Surg.* 2008;95:627–635.

21. La Rosa S, Klersy C, Uccella S, et al. Improved histologic and clinicopathologic criteria for prognostic evaluation of pancreatic endocrine tumors. *Hum Pathol.* 2009;40:30–40.

22. Pape UF, Jann H, Muller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer.* 2008;113:256–265.

23. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol.* 2010;23:824–833.

24. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology.* 2012;95:157–176.

25. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas.* 2010;39:735–752.

26. Strosberg JR, Coppola D, Klimstra DS, et al. The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. *Pancreas.* 2010;39:799–800.

27. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: Neuroendocrine tumors version 1. National Comprehensive Cancer Network; 2011; http://www.lecba-rakoviny.cz/dokumenty/NCCN_Guidelines_neuroendocrine_2011.pdf. [Accessed April 7, 2015].