Ann Surg Oncol (2019) 26:1127–1133
https://doi.org/10.1245/s10434-019-07203-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

Survival in Patients with High-Grade Colorectal Neuroendocrine Carcinomas: The Role of Surgery and Chemotherapy

Adam C. Fields, MD[1], Pamela Lu, MD[1,2], Benjamin M. Vierra, MS[1], Frances Hu, MD[1], Jennifer Irani, MD[1], Ronald Bleday, MD[1], Joel E. Goldberg, MD, MPH[1], Garrett M. Nash, MD, MPH[3], and Nelya Melnitchouk, MD, MSc[1,2]

[1]Department of Surgery, Division of Colorectal Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Center for Surgery and Public Health, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Memorial Sloan Kettering Cancer Center, New York, NY

ABSTRACT

Background. Colorectal neuroendocrine tumors are a rare malignancy, yet their incidence appears to be increasing. The optimal treatment for the high-grade subset of these tumors remains unclear. We aimed to examine the relationship between different treatment modalities and outcomes for patients with high-grade neuroendocrine carcinomas (HGNECs) of the colon and rectum.

Methods. The National Cancer Database (2004–2015) was used to identify patients diagnosed with colorectal HGNECs. The primary outcome was overall survival. A Cox Proportional hazard model was used to identify risk factors for survival.

Results. Overall, 1208 patients had HGNECs; 452 (37.4%) patients had primary tumors of the rectum, and 756 (62.5%) patients had primary tumors of the colon. A total of 564 (46.7%) patients presented with stage IV disease. The median survival was 9.0 months [95% confidence interval (CI) 8.2–9.8]. In multivariable analysis, surgical resection [hazard ratio (HR) 0.54, 95% CI 0.44–0.66; $p < 0.001$], chemotherapy (HR 0.74, 95% CI 0.69–0.79; $p < 0.001$), and rectum as the primary site of tumor (HR 0.62, 95% CI 0.51–0.76; $p < 0.001$) were associated with better overall survival, while older age (HR 1.01, 95% CI 1.00–1.01; $p = 0.02$) and the presence of metastatic disease (HR 3.34, 95% CI 2.69–4.15; $p < 0.001$) were associated with worse survival.

Conclusions. Patients with colorectal HGNECs selected for chemotherapy and surgical resection of the primary tumor demonstrated better overall survival than those managed without resection. Patients who were able to undergo systemic chemotherapy may benefit from potentially curative resection of the primary tumor.

Neuroendocrine tumors of the colon and rectum represent a rare malignancy, which has previously been poorly characterized, and exhibit a wide range of histologies with differing clinical behaviors. Although neuroendocrine tumors are rare, accounting for < 1% of colorectal tumors, the incidence may be increasing.[1,2] While prior studies have focused on the well-differentiated subset of these malignancies, little is known about the optimal treatment of high-grade neuroendocrine carcinomas (HGNECs) of the colon and rectum.[3]

In 2010, the World Health Organization presented a classification system for Neuroendocrine Neoplasms of the Digestive System, where histology was separated into three grades. Grade 3, also designated as neuroendocrine carcinomas (NECs), is defined by the presence of a mitotic count > 20 per high-power field and/or Ki-67 index > 20%, with large and small cell subtypes.[4] In prior reports, large and small cell subtypes have been shown to behave similarly, without significant differences in survival.[3,5] Colorectal HGNECs behave aggressively, with the majority of patients presenting with metastatic disease at the time of

Adam C. Fields and Pamela Lu MD were co-first authors on this work.

First Received: 22 November 2018;
Published Online: 31 January 2019

A. C. Fields, MD
e-mail: acfields@partners.org

N. Melnitchouk, MD, MSc
e-mail: nmelnitchouk@bwh.harvard.edu

diagnosis, and low reported median survival of 5–11 months.[6] While the past few decades have shown improvement in survival from colorectal adenocarcinomas, the same survival benefits have not been seen with NECs.[2] Given the paucity of data available for colorectal NECs, treatments have generally been extrapolated from that of pulmonary NECs, with platinum-based chemotherapy as a cornerstone.[6–9] Unlike colorectal adenocarcinomas, surgery alone is rarely curative for HGNECs, and its utility in prolonging survival has been questioned in prior studies.[10,11] However, much of the available data have resulted from single-institution studies evaluating outcomes of small patient populations.[11–14]

Our aim was to evaluate the treatments and outcomes for patients with HGNECs of the colon and rectum using the National Cancer Database (NCDB), a national, prospectively collected, cancer-specific database. Our goal was to better understand the association between different treatment modalities and survival in HGNECs of the colon and rectum.

MATERIALS AND METHODS

Data

The NCDB Participant User Files from 2004 to 2015 were utilized for this study. The NCDB is jointly supported by the American College of Surgeons and American Cancer Society, and is able to capture more than 70% of new cancer diagnoses in the US. Oncologic data are recorded from Commission on Cancer sites nationwide. NCDB data collection methodology and auditing practices have been previously described.[15] Briefly, local registrars extract de-identified patient data and pass this data to the national office. This investigation was reviewed and deemed exempt by the Brigham and Women's Hospital Institutional Review Board.

Population

The NCDB was queried to identify patients who were diagnosed with colorectal neuroendocrine tumors. The International Classification of Diseases for Oncology codes for small cell neuroendocrine tumors (8041) and large cell neuroendocrine tumors (8013) were used. Patients were included if they had high-grade (poorly differentiated or undifferentiated) NECs, but were excluded if they had low-grade tumors (well or moderately differentiated) or had missing follow-up data.

Study Variables

Patient demographics, clinical characteristics, and tumor features were analyzed, and treatment data with surgery, chemotherapy, and radiation were collected. The primary outcome was overall survival. Secondary outcomes included risk factors for survival (i.e. chemotherapy, surgical resection) and predictors of survival following surgery, such as lymph node status and margin positivity.

Statistical Analysis

Descriptive statistics are presented as medians with interquartile ranges (IQRs), as well as totals with proportions. A Cox proportional hazard model was used to determine risk factors for overall survival. Factors included in the multivariate model were age, surgery, chemotherapy, radiation therapy, the presence of metastatic disease, and primary site (rectum vs. colon), which were determined a priori based on clinical knowledge. Survival was estimated using the Kaplan–Meier method. Two sided p values < 0.05 were considered significant for all tests run. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), Version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics

A total of 1208 patients were identified (Fig. 1). The demographics, tumor characteristics, and treatment are summarized in Table 1. Overall, 452 patients (37.4%) had primary tumors of the rectum, and 756 (62.5%) had primary tumors of the colon. The median age at diagnosis was 65 years (IQR 54–76), 50% of patients were female, and the majority of patients were White; 652 patients (54.0%) had small cell histology, and 556 (46.0%) patients had large cell histology. The most prevalent disease stage was stage 4. With regard to treatment modalities, 741 patients (61.3%) underwent surgery, 778 patients (64.4%) underwent chemotherapy, and 256 patients (21.2%) underwent radiation therapy.

Survival

The median survival for patients with HGNECs in this cohort was 9.0 months [95% confidence interval (CI) 8.2–9.8]; 3-year survival was 17.8% and 5-year survival was 13.3%. Median survival was 18.0 months (95% CI 13.7–22.4) in patients without metastatic disease at diagnosis, and 5.9 months (95% CI 4.7–7.0) in patients with

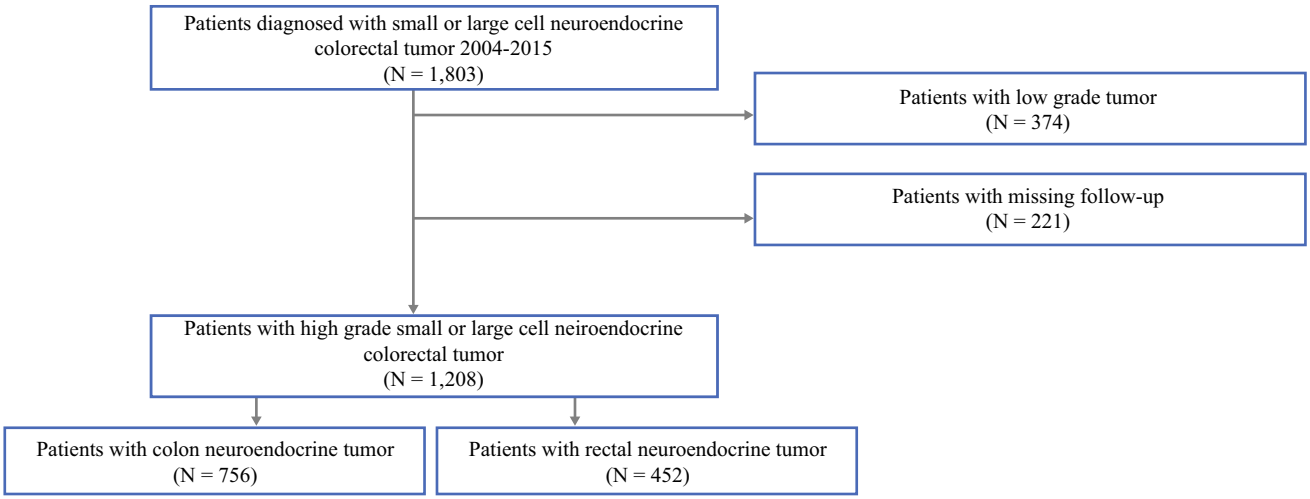

FIG. 1 Patient selection

TABLE 1 Patient characteristics

Variable	Tumor location	
	Colon (*N* = 756)	Rectum (*N* = 452)
Age, years [median (IQR)]	67 (57–76)	62 (51–74)
Female sex	380 (50.3)	224 (49.6)
Race		
White	661 (88.0)	392 (87.7)
Black	70 (9.3)	43 (9.6)
Other	20 (2.7)	12 (2.7)
Histology		
SCC	327 (43.3)	325 (71.9)
LCC	428 (56.7)	127 (28.1)
AJCC stage		
I	21 (3.5)	17 (10.9)
II	49 (8.1)	11 (7.1)
III	202 (33.3)	58 (37.2)
IV	335 (55.2)	70 (44.9)
LVI	245 (32.5)	62 (13.7)
Tumor size, cm [median (IQR)]	6.0 (4.0–8.0)	4.6 (3.0–7.0)
Surgery	593 (78.6)	148 (32.8)
Chemotherapy	430 (58.7)	348 (78.9)
Radiation	35 (4.7)	221 (41.5)

Data are expressed as *n* (%) unless otherwise specified

IQR interquartile range, *SCC* small cell carcinoma, *LCC* large cell carcinoma, *AJCC* American Joint Committee on Cancer, *LVI* lymphovascular invasion

metastatic disease ($p < 0.001$). In patients without metastatic disease, 3-year survival was 36.2% and 5-year survival was 29.8%, while in patients with metastatic disease, 3-year survival was 5.9% and 5-year survival was 4.1%.

Patients who underwent surgical resection had a median survival of 10.5 months (95% CI 9.4–11.6) compared with 6.9 months (95% CI 62–7.6) for patients who did not undergo surgery ($p < 0.001$) (Fig. 2). Patients with negative lymph nodes had a median survival of 23.9 months (95% CI 15.0–32.9) compared with 8.9 months (95% CI 7.9–10.0) for patients with positive lymph nodes ($p < 0.001$) (Fig. 3a). Furthermore, patients with negative surgical margins had a median survival of 12.3 months

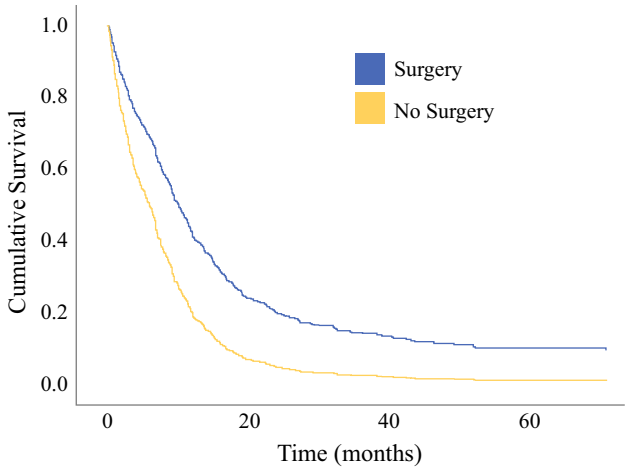

FIG. 2 Adjusted survival stratified by undergoing surgery

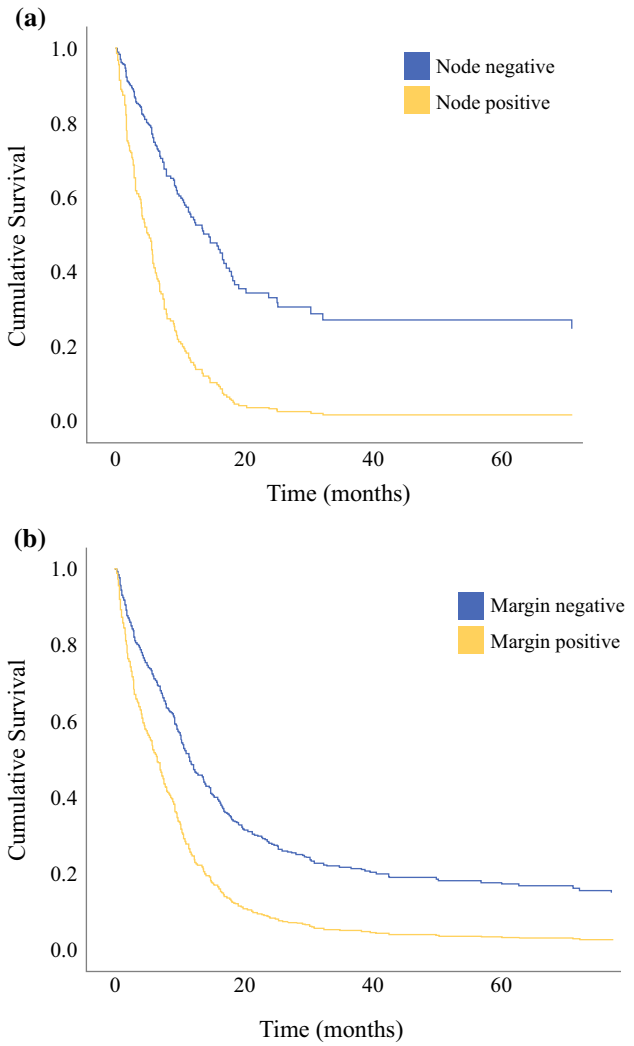

FIG. 3 Adjusted survival stratified by **a** lymph node status or **b** resection margin status

(95% CI 10.5–14.1) compared with 4.5 months (95% CI 3.0–5.9) for patients with positive surgical margins ($p < 0.001$) (Fig. 3b).

We further compared survival among patients who received no chemotherapy or surgery, only surgery, only chemotherapy, or both chemotherapy and surgery. In patients with localized disease, 5-year survival was 0% for patients not receiving chemotherapy or surgery, 15.9% for patients receiving only chemotherapy, 31.7% for patients receiving only surgery, and 37.0% for patients receiving both surgery and chemotherapy ($p < 0.001$) (Fig. 4a). In patients with metastatic disease, 5-year survival was 0% for patients not receiving chemotherapy or surgery, 1.6% for patients receiving only chemotherapy, 3.7% for patients receiving only surgery, and 6.1% for patients receiving both surgery and chemotherapy ($p < 0.001$) (Fig. 4b).

Predictors of Survival

In a Cox proportional hazard model, older age [hazard ratio (HR) 1.01, 95% CI 1.00–1.01; $p = 0.02$] and the

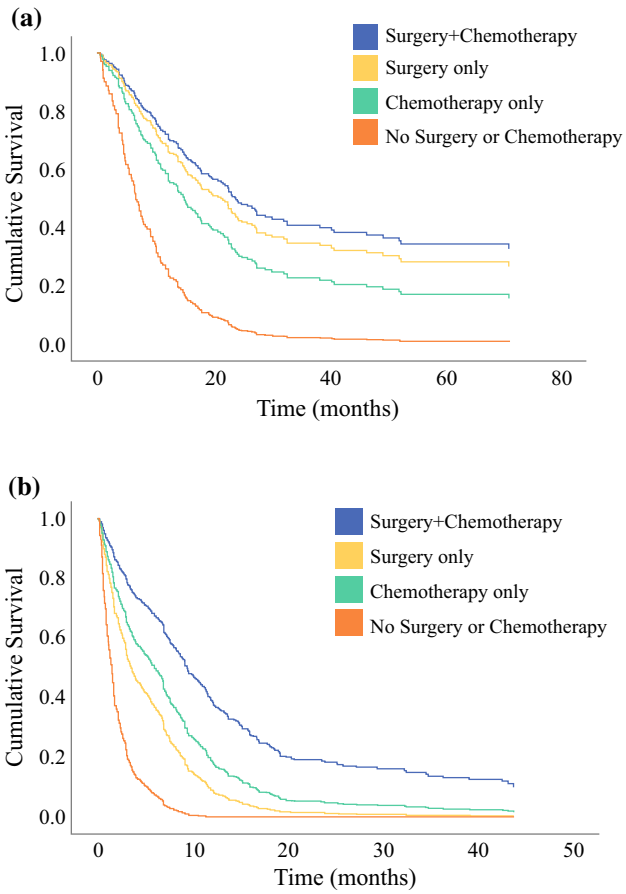

FIG. 4 Adjusted survival for patients with **a** localized disease and **b** metastatic disease, stratified by treatment with surgery and chemotherapy

presence of metastatic disease (HR 3.34, 95% CI 2.69–4.15; $p < 0.001$) were associated with worse overall survival (Table 2). Surgical resection (HR 0.54, 95% CI 0.44–0.66; $p < 0.001$), chemotherapy (HR 0.74, 95% CI 0.69–0.79; $p < 0.001$), and rectum as the primary site of tumor (HR 0.62, 95% CI 0.51–0.76; $p < 0.001$) were associated with better overall survival. Radiation therapy was not a significant predictor of overall survival (HR 1.11, 95% CI 0.88–1.40; $p = 0.39$).

In a subgroup analysis of patients with metastatic disease, surgical resection (HR 0.51, 95% CI 0.41–0.64; $p < 0.001$) and chemotherapy (HR 0.68, 95% CI 0.68–0.74; $p < 0.001$) remained associated with better overall survival.

DISCUSSION

This study of 1208 patients with HGNECs of the colon and rectum is the largest study to date that examines the association between different treatment modalities and survival. We showed that both chemotherapy and surgical intervention are associated with improved overall survival, whereas radiation therapy is not. Additionally, we demonstrated that for patients undergoing surgery, positive margins and lymph nodes are associated with decreased overall survival.

The role of surgical resection in treating HGNECs of the colon and rectum has been unclear.[16] In their review of 503 cases of small cell carcinoma of the colon, Balasubramanyam et al.[17] demonstrated that surgery was not associated with improved survival in either limited-stage disease or extensive-stage disease patients. Smith et al.[11] reviewed 126 cases of colorectal HGNECs from a single institution and also found that resection of the primary tumor had no significant association on survival for either localized or metastatic disease. In a study of 100 cases of colorectal HGNECs, Conte et al.[13] found that patients who received perioperative multimodal treatment had better survival than those who had resection alone. Recommendations have been varied with respect to surgical resection, however the North American Neuroendocrine Tumor Society (NANETS) recently released guidelines that only recommend surgical resection followed by adjuvant chemotherapy for high-grade extrapulmonary NECs staged as T1/T2N0.[18] Our results demonstrate that surgical resection is associated with better survival; however, surgical resection of the primary tumor is also associated with survival in the setting of metastatic disease, which implies this association may be due to selection bias rather than a true effect of treatment.

Chemotherapy has been a cornerstone of treatment for extrapulmonary HGNECs, given its histopathologic similarities to small cell lung cancer; the standard regimen for small cell lung cancer includes platinum-based agents.[3,19] Although the response of colorectal HGNECs varies with Ki-67 level, with values < 55% showing poorer responsiveness to systemic chemotherapy, NANETS guidelines recommend chemotherapy for all patients with high-grade disease.[18] Prior studies have shown that the majority of patients with colorectal HGNECs undergo chemotherapy, with proportions of patients receiving systemic treatment ranging from 49 to 90.5% in patients with localized disease, and 55–100% in patients with metastatic disease.[6,11] Our study demonstrates that 64.4% of patients undergo chemotherapy, which is consistent with prior reports. In our study, chemotherapy administration was associated with better survival for patients with both localized and metastatic disease.

It is important to note that while surgery and chemotherapy each independently appear to be associated with better survival, and that the combination of surgery and chemotherapy results in the highest overall survival, the 5-year survival for patients with localized disease undergoing both surgery and chemotherapy remains low, at 37%, which is similar to the 5-year survival for the same cohort who undergo surgery alone, at 32%. However, surgery alone is associated with an 11% 1-year survival in the metastatic setting and should be discouraged for asymptomatic patients. This prognostic information can be used when surgical and medical oncologists discuss treatment options with patients. It is essential that patients understand upfront, even when criteria are met for surgical resection (i.e. local disease) and chemotherapy (i.e. ability to tolerate chemotherapy), that survival is poor.

TABLE 2 Cox proportional hazards regression model to predict death

	Hazard ratio	95% confidence interval	*p* value
Age	1.01	1.00–1.01	0.03
Surgery	0.54	0.44–0.66	<0.001
Chemotherapy	0.73	0.68–0.79	<0.001
Radiation	1.13	0.89–1.44	0.30
Metastatic disease	3.36	2.71–4.18	<0.001
Primary site, rectum	0.63	0.51–0.77	<0.001

As 90% of extrapulmonary HGNECs are non-hormone-secreting tumors, many patients present with advanced- or late-stage disease due to the lack of early symptoms.[10] In an early series review, Hung described 80% of patients presenting with metastases.[20] Later studies continued to demonstrate the majority of patients presenting with late-stage disease, with nearly 70% of patients having metastatic disease at diagnosis.[6,17] Our data are in line with these prior reports, showing the majority of patients presenting with stage 3 or 4 disease at the time of diagnosis.

Our study has several strengths. With a total of 1208 patients, this is the largest study to date that evaluates patients with colorectal HGNECs and their treatment outcomes. With these data, we were able to show that surgical resection of primary tumors, negative surgical margins, and chemotherapy treatment are associated with survival in a large, national cohort. However, there are some limitations to consider when interpreting our results. This was a retrospective review, and the NCDB only collects data for overall survival as opposed to disease-specific survival. Moreover, we do not have detailed information on patient comorbidities or the extent of metastatic disease, both of which can influence treatment offered. Furthermore, we were unable to determine the specific regimens of systemic chemotherapy administered to patients.

CONCLUSIONS

Although colorectal HGNEC is a rare disease comprising $< 1\%$ of colorectal malignancies, the incidence appears to be increasing.[1,2] Given the disease's aggressive behavior, it is crucial for clinicians to recognize the pathology and understand the implications of treatment. Although the data available for this disease are sparse, there have been improvements in understanding and defining the pathology in recent years, with new grading criteria and consensus guidelines released in the past 10 years;[4,18] however, much of these data do not focus on HGNECs, but rather low-grade neuroendocrine tumors. Our study, the largest study to date examining the outcome of patients with small and large cell HGNECs, demonstrates that surgical resection and chemotherapy are associated with improved overall survival, especially when combined, although survival still remains low. In the absence of randomized controlled trials, carefully selected patients, who are also able to undergo systemic chemotherapy, may benefit from potentially curative resection of the primary tumor; however, we were unable to identify patient or tumor factors from these data, which can aid in this selection process.[21]

AUTHOR CONTRIBUTIONS All authors made substantial contributions to the design of the work, drafted the work, approved the final version submitted for publication, and agreed to be accountable for all aspects of the work.

DISCLOSURES None. No grant support or financial relationships were received for this work.

REFERENCES

1. Leoncini E, Boffetta P, Shafir M, Aleksovska K, Boccia S, Rindi G. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. *Endocrine.* 2017;58(2):368–79.
2. Shafqat H, Ali S, Salhab M, Olszewski AJ. Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. *Dis Colon Rectum* 2015;58(3):294–03.
3. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer.* 2014;120(18):2814–23.
4. Kim JY, Hong SM, Ro JY. Recent updates on grading and classification of neuroendocrine tumors. *Ann Diagn Pathol.* 2017;29:11–16.
5. Shia J, Tang LH, Weiser MR, et al. Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? *Am J Surg Pathol.* 2008;32(5):719–31.
6. Bernick PE, Klimstra DS, Shia J, et al. Neuroendocrine carcinomas of the colon and rectum. *Dis Colon Rectum.* 2004;47(2):163–69.
7. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013;24(1):152–60.
8. Brenner B, Shah MA, Gonen M, Klimstra DS, Shia J, Kelsen DP. Small-cell carcinoma of the gastrointestinal tract: a retrospective study of 64 cases. *Br J Cancer.* 2004;90(9):1720–26.
9. Walenkamp AM, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. *Cancer Treat Rev.* 2009;35(3):228–36.
10. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS Consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology.* 2016;103(2):186–94.
11. Smith JD, Reidy DL, Goodman KA, Shia J, Nash GM. A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. *Ann Surg Oncol.* 2014;21(9):2956–62.
12. Chung TP, Hunt SR. Carcinoid and neuroendocrine tumors of the colon and rectum. *Clin Colon Rectal Surg.* 2006;19(2):45–8.
13. Conte B, George B, Overman M, et al. High-grade neuroendocrine colorectal carcinomas: a retrospective study of 100 patients. *Clin Colorectal Cancer.* 2016;15(2):e1–e7.
14. Aytac E, Ozdemir Y, Ozuner G. Long term outcomes of neuroendocrine carcinomas (high-grade neuroendocrine tumors) of the colon, rectum, and anal canal. *J Visc Surg.* 2014;151(1):3–7.
15. Winchester DP, Stewart AK, Phillips JL, Ward EE. The national cancer data base: past, present, and future. *Ann Surg Oncol.* 2010;17(1):4–7.
16. Ahlman H, Nilsson O, McNicol AM, et al. Poorly-differentiated endocrine carcinomas of midgut and hindgut origin. *Neuroendocrinology.* 2008;87(1):40–46.
17. Balasubramanyam S, O'Donnell BP, Musher BL, Jhaveri PM, Ludwig MS. Evaluating treatment patterns for small cell carcinoma of the colon using the national cancer database (NCDB). *J Gastrointest Cancer.* 2018. https://doi.org/10.1007/s12029-018-0054-y.

18. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* 2013;42(4):557–77.
19. Yamaguchi T, Machida N, Morizane C, et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Cancer Sci.* 2014;105(9):1176–81.
20. Hung SS. Small cell carcinoma of the colon. A case report and literature review. *J Clin Gastroenterol.* 1989;11(3):335–39.
21. Arnold R. Endocrine tumours of the gastrointestinal tract Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. *Best Pract Res Clin Gastroenterol.* 2005;19(4):491–05.