Adjuvant Chemotherapy Versus Observation Following Resection for Patients With Nonmetastatic Poorly Differentiated Colorectal Neuroendocrine Carcinomas

Rui Mao, MD,† *Kan Li, PhD,*‡ *Jian-Qiang Cai, MD,** *Sheng Luo, PhD,*§ *Megan Turner, MD,*¶ *Dan BlazerIII, MD,*¶ *and Hong Zhao, MD**✉

Objective: The aim of this study was to determine whether adjuvant chemotherapy (AC) provides a survival benefit in patients with nonmetastatic poorly differentiated colorectal neuroendocrine carcinomas (CRNECs) following resection.

Background: There is little evidence to support the association between use of AC and improved overall survival (OS) in patients with CRNECs.

Methods: Patients with resected non-metastatic CRNECs were identified in the National Cancer Database (2004–2014). Inverse probability of treatment weighting (IPTW) method was used to reduce the selection bias. IPTW-adjusted Kaplan-Meier curves and Cox proportional hazards models were used to compare OS of patients in different treatment groups.

Results: A total of 806 patients diagnosed between 2004 and 2014 met the study entry criteria. Of these, 394 patients (48.9%) received AC. IPTW-adjusted Kaplan-Meier curves showed that median OS was significantly longer for AC versus observation [57.4 (interquartile range, IQR, 14.8–153.8) vs 38.2 (IQR, 10.4–125.4) months; $P = 0.007$]. In IPTW-adjusted Cox proportional hazards regression analysis, AC was associated with a significant OS benefit [hazard ratio (HR) = 0.73, 95% confidence interval (CI) 0.64–0.84; $P < 0.001$]. The results were consistent across subgroups stratified by pathologic T stage, pathologic N stage, and surgical margin status. Subgroup analysis according to tumor location demonstrated improved OS in the adjuvant therapy cohort among patients with left-sided neuroendocrine carcinomas (HR, 0.55; 95% CI, 0.44–0.68), but not in those with right-sided disease (HR, 0.89; 95% CI, 0.74–1.07).

Conclusions: Patients with nonmetastatic CRNECs may derive survival benefit from AC. These findings support current guidelines recommending AC in patients with poorly differentiated neuroendocrine carcinomas in the colon and rectum. Efforts in education and adherence to national guidelines for NECs are needed.

Keywords: adjuvant chemotherapy, colon and rectum, national cancer database, poorly differentiated neuroendocrine carcinomas

(*Ann Surg* 2019;xx:xxx–xxx)

Poorly differentiated neuroendocrine carcinomas (NECs), defined by morphology and a higher proliferative rate than well differentiated neuroendocrine tumors (NETs), are rare cancers.[1–2] A recent population-based study reported the annual age-adjusted incidence of NECs increased from 0.01 per 100 000 persons in 1973 to about 0.51 per 100,000 persons in 2012.[3] The gastroenteropancreatic tract is the most common site for extrapulmonary NECs, and colorectal NECs (CRNECs) account for 39% of all gastroenteropancreatic NECs.[4] The prognosis of patients with CRNECs is dismal. A recent population-based study using nationally representative data from the Surveillance, Epidemiology, and End Results (SEER) program demonstrated that patients with metastatic CRNECs had a median survival of only 2.9 to 6.2 months.[4] Patients with nonmetastatic disease had a better prognosis. The 5-year overall survival (OS) rate ranged from 50.1% to 54.5% for patients with localized disease, and 20.0% to 29.2% for those with regional disease.[4] However, the best treatment strategy for patients with nonmetastatic CRNECs remains controversial.

Many NEC patients develop recurrence rapidly after surgery, suggesting a role for adjuvant chemotherapy (AC).[5,6] The current consensus guidelines of the European Neuroendocrine Tumor Society (ENETS) state that ''most clinicians would advocate platinum-based adjuvant therapy'' after curative surgery.[7] The recommendation, based on an esophageal small cell carcinomas study in 1997, is vague. In this retrospective study, the survival was 20 months for patients receiving local therapy followed by AC versus only 5 months for those treated with local therapy only.[8] The North American Neuroendocrine Tumor Society (NANETS) guidelines and recent National Comprehensive Cancer Network (NCCN) guidelines also recommend that surgical resection and platinum-based chemotherapy are advised for resectable NECs.[9,10]

Despite these guideline recommendations, and some long-term survivors after AC treatment have been reported,[11] evidence supporting current guidelines are extremely limited. There has been only one retrospective study that has compared AC versus observation for CRNECs. The study included 132 patients with nonmetastatic CRNECs from the SEER-Medicare database and concluded that there was no significant improvement in survival for patients receiving adjuvant etoposide + platinum regimens or 5-fluorouracil-based chemotherapy compared with those without any postoperative

From the *State Key Lab of Molecular Oncology, Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; †Duke Clinical Research Institute, Duke University Medical Center, Durham, NC; ‡Merck Research Lab, Merck & Co, North Wales, PA; §Department of Biostatistics and Bioinformatics, Duke University Medical Center, Durham, NC; and ¶Department of Surgery, Duke University Medical Center, Durham, NC, USA.

✉zhaohong@cicams.ac.cn.

R.M., K.L., J-q.C. contributed equally to this work.

This work was supported by National Natural Science Foundation of China (81672461); Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) (Grant no. 2017-12M-4-002); the capital health research and development of special (2018-1-4021). S.L.s research was supported partly by the Grant R01NS091307 from National Institute of Neurological Disorders and Stroke (NINDS) and Grant R56AG062302 from National Institute on Aging (NIA).

The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

The authors report no conflicts of interest.

ISSN: 0003-4932/16/XXXX-0001

DOI: 10.1097/SLA.0000000000003562

chemotherapy.[12] Large studies that have reported improved survival associated with AC for nonmetastatic CRNECs were still lacking.

In the present study, we hypothesized that AC would be associated with a survival benefit for nonmetastatic CRNECs in a large patient cohort. Utilizing a group of matched patients from the National Cancer Database (NCDB), we compared survival in patients receiving AC after surgical resection versus those who did not.

METHODS

Database and Patient Population

The NCDB is a nationwide hospital-based cancer registry that serves as a comprehensive surveillance resource for cancer care in the United States. The NCDB includes approximately 75% of new cancers in the United States and collects data from >1400 hospitals that have cancer treatment programs accredited by the American College of Surgeons Commission on Cancer (CoC). Data are coded and reported based on the Facility Oncology Registry Data Standards Manual (http://www.facs.org/cancer/coc/fordsmanual.html). This study was granted Duke University Institutional Review Board exemption as no patient, physician, or hospital identifiers were examined.

Patients with CRNECs undergoing curative-intent resection were identified from NCDB (2004–2014). Poorly differentiated neuroendocrine carcinomas were identified using the *International Classification of Diseases for Oncology, 3rd Edition* (*ICD-O-3*) morphology codes: carcinoid tumor (8240), argentaffin carcinoid tumor (8241), enterochromaffin cell tumor (8242), neuroendocrine carcinoid (8246), atypical carcinoid tumor (8249), large cell neuroendocrine carcinoma (8013), small cell carcinoma (8041), oat cell carcinoma (8042), small cell carcinoma, fusiform cell (8043), small cell carcinoma, intermediate cell (8044), and combined small cell carcinoma (8045). For patients with morphology codes 8240–8242, 8246, and 8249, only those with grade codes 3 (poorly differentiated) or 4 (undifferentiated; anaplastic) were included.[4] Sites of origin were identified using the topographical codes: C18.0, C18.2-C18.9, C19.9, and C20.9. Exclusion criteria include patients with clinical or pathological presence of distant metastases; patients with incomplete prognosis information; patients undergoing resection for palliative intent; patients who underwent treatment outside of the reporting facility; patients with unknown perioperative chemotherapy status; patients who received chemotherapy after 90 days of surgery; and those who received preoperative chemotherapy. Patients who died within 90 days following surgery were also excluded because of this period's significance as a legitimate measure of surgical quality.[13]

Patients were divided into an AC and observation (OB) group. Those who received postoperative systemic chemotherapy within 90 days after surgery were included in the AC group. Alternatively, individuals who did not receive any postoperative chemotherapy were included in the OB group.

Study Variables

The variables included in this analysis were divided into 3 categories by the types of information: patient-related demographics, tumor-related information, and treatment-related variables.

Patient-related information included race (white, black, or other), age at diagnosis, sex, insurance status (uninsured, private insurance, Medicare, or Medicaid/other government), Charlson/Deyo comorbidity score (0, 1, or 2+), year of diagnosis (2004–2009, or 2010–2014), and zip-code-based income levels (<$38,000, $38,000–$47,999, $48,000–$62,999, or >$62,999). Tumor data include tumor location (right-sided colon, or left-sided colon), tumor size, lymph node status, and pathologic T stage. Right-sided colon included transverse colon, hepatic flexure, ascending colon, and cecum. Left-sided colon included splenic flexure, descending colon, sigmoid colon, and rectum. Treatment-related factors include types of treatment facilities (community cancer program, academic program, or integrated network cancer program), diagnosis to resection time, types of surgery (local excision, partial colectomy, hemicolectomy, or total colectomy), margin status, unplanned 30-day readmissions, and postoperative treatment (AC, or observation). If AC was not administered, then the reason it was not administered to the patient was recorded.

Statistical Analysis

Under the missing at random assumption, we first performed multiple imputation by chained equations to impute missing data for race (0.7% missing), income (0.9%), types of treatment facilities (2.1%), insurance type (1.5%), lymph node status (8.8%), tumor size (6.6%), pathologic T stage (2.1%), types of surgery (1.5%), diagnosis to resection time (0.9%), surgical margin status (1.6%), and unplanned 30-day readmission (1.9%). We generated 25 complete datasets for subsequent analyses. The number of imputation was selected as the guidelines state that the number of imputations should be similar to the percentage of cases that are incomplete.[14]The missing at random assumption is plausible in our case as a wide range of variables, including all variables in the substantive analysis, were included in the imputation model.[15]

We compared the baseline characteristics between patients who underwent AC (AC group) and patients who underwent observation after surgery (OB group). The balance in covariates was assessed by using the standardized difference (SD) approach. Factors with imbalance between the 2 groups was defined as a SD >0.1. Multivariate logistic regression models were used to estimate the association of the included covariates with receipt of AC.

To account for the selection bias, the observed differences in baseline covariates between the 2 intervention groups were adjusted by using inverse probability of treatment weighting (IPTW) method. The IPTW approach is attempting to mimic a situation in which treatment is randomly allocated to individuals. Specifically, we first estimated, in each imputed dataset, the propensity score, that is, the conditional probability of receiving AC, using a multivariate logistic regression. Factors associated either with the receipt of AC or with OS were included in constructing the models, which included age, sex, race, income, Charlson/Deyo score, insurance type, facility type, year of diagnosis, time from diagnosis to resection, tumor location, tumor size, pathologic T stage, pathologic N stage, type of surgery, resection margins, and unplanned 30-day readmission. Then the estimated propensity scores from the 25 imputed datasets were combined according to the Rubin's rules,[16] and used to weight each patient with the aim of balancing the characteristics between the 2 groups.

Overall survival (OS) was calculated from the date of diagnosis to the date of last contact or death. The adjusted Kaplan–Meier curves and log-rank test based on inverse probability weights were computed to compare OS between AC group and OB group. In addition, a univariate inverse probability weighted Cox proportional hazards model was used to estimate the IPTW-adjusted hazard ratio (HR) of AC versus OB. We further performed subgroup analyses to investigate the IPTW-adjusted HR of AC versus OB according to tumor location, pathologic T stage, pathologic N stage, and surgical margin status following the previously described methodology with all baseline characteristics were rebalanced within each subgroup. If post-weighting balance cannot be achieved in certain subgroup, multivariate Cox regression models were subsequently used to

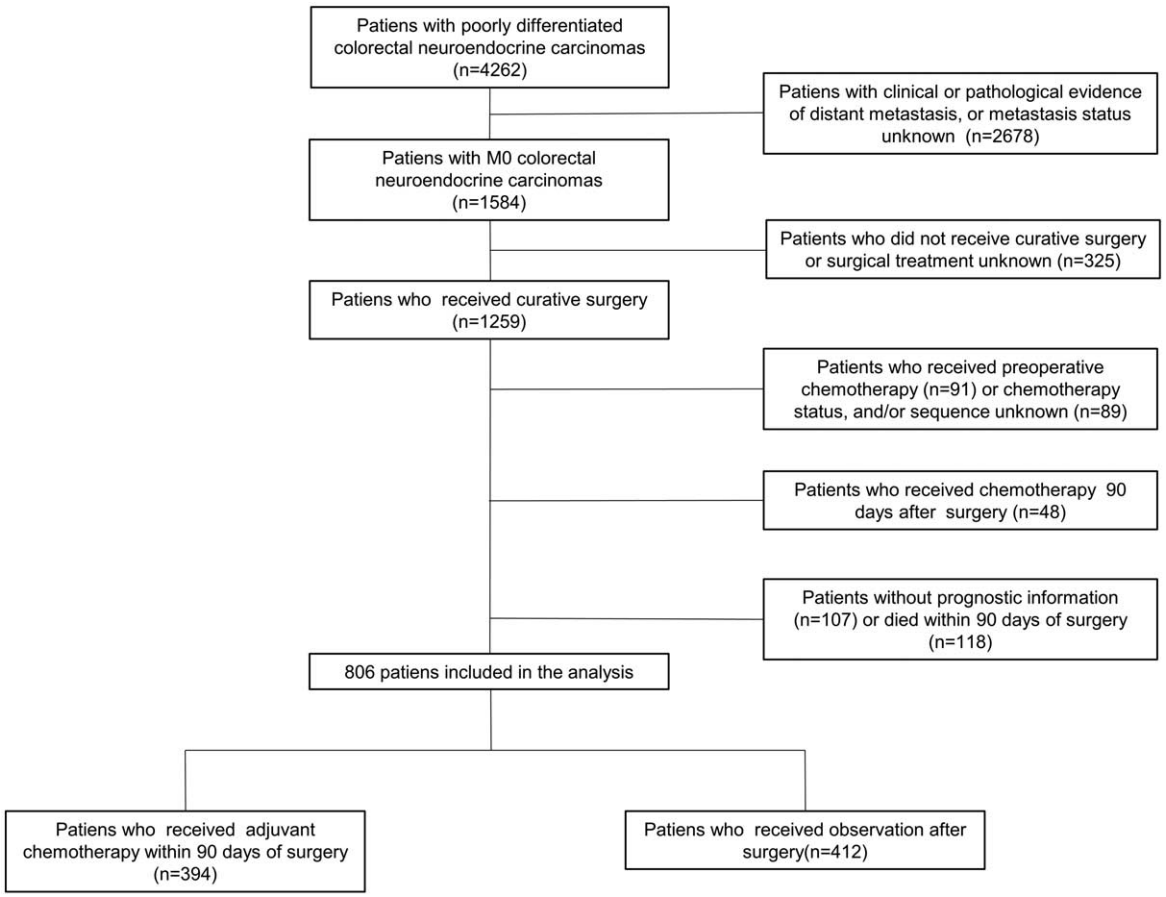

FIGURE 1. Flow diagram for the selection of the NCDB cohort included in the final analyses of this study.

perform additional covariance adjustment. We also conducted interaction test to assess the heterogeneity of treatment effect across the subgroups.

Finally, analyses based on only complete cases (639 patients) were conducted for reference. Also, we conducted additional analyses using traditional multivariate Cox models to estimate the HR of AC versus OB. Then we performed sensitivity analysis to assess the potential influence of unmeasured confounding on our primary endpoint using Ding methods without imposing any assumptions on the unmeasured confounder(s).[17] We tested the treatment effect of AC versus OB in presence of unmeasured confounders via calculating the magnitude of the joint bounding factor for different combination of the treatment-unmeasured confounders association ($OR_{AC\text{-}U}$) and the outcome-unmeasured confounders association ($HR_{OS\text{-}U}$). We also report the E-value,[18] which is the minimum strength of association that an unmeasured confounder would need to have with both the treatment and outcome to explain away a treatment–outcome association. The higher the E-value, the stronger the confounder associations must be to explain away the effect.

All statistical analyses were performed by using R, version 3.5.1 (R Core Team 2018, Vienna, Austria). All *P* values are 2-sided. A *P* value of <0.05 was considered statistically significant. The missing imputation was conducted using ''MICE package'' and the survival analyses were performed using ''survival'' package.

RESULTS

Baseline Characteristics in the Unadjusted and Adjusted Data

Overall, we identified 394 (48.9%) and 412 (51.1%) patients with nonmetastatic CRNECs, who received AC versus OB after surgery, respectively (Fig. 1). The comparisons of unadjusted and adjusted standardized differences between treatment groups are displayed in Table 1. Compared with patients in the OB group, patients who received AC were younger, more likely to have a lower Charlson/Deyo score, private insurance, and shorter time from diagnosis to resection. In addition, the AC group was characterized by a greater portion of patients with a larger-sized tumor, or locally advanced disease. After IPTW adjustment, SD for all characteristics was <0.1, indicating that the weighted population in the 2 groups was subsequently comparable.

Results of multivariable logistic regression analysis that predicted receipt of AC versus OB are listed in Table 2. Patients who were white (compared to black) or younger, had less comorbidities, larger tumors, higher T stage, lymph node metastasis, or underwent a partial/hemi colectomy (compared to local excision) were more likely to receive AC.

Reasons that AC was not administered were also analyzed based on the record of the NCDB. Of the 412 patients in the OB group, 324 (79.8%) did not receive AC because it was not part of the planned first course of therapy. AC was not administered to 43

TABLE 1. Baseline Characteristics of Patients Who Received Adjuvant Chemotherapy Versus Observation in Unweighted and Weighted Study Populations

	Unweighted Study Population, No. (%)			Weighted Study Population, %		
	Observation (N = 412; 51.1%)	Adjuvant Chemotherapy (N = 394; 48.9%)	Absolute Standardized Difference	Observation	Adjuvant Chemotherapy	Absolute Standardized Difference
Age, mean (SD), y	71.6 (13.2)	64.1 (12.3)	0.585	67.4 (14.2)	67.0 (11.6)	0.032
Male sex	166 (40.3)	193 (49.0)	0.090	45.3	44.9	0.004
Race						
White	353 (86.5)	351 (89.5)	0.030	88.1	87.4	0.006
Black	48 (11.8)	31 (7.9)	0.038	10.0	10.4	0.003
Others	7 (1.7)	10 (2.6)	0.008	1.9	2.2	0.003
Income						
<$38,000	72 (17.6)	59 (15.1)	0.025	16.8	16.4	0.003
$38,000–$47,999	87 (21.3)	91 (23.3)	0.021	22.5	22.7	0.001
$48,000–$62,999	120 (29.3)	116 (29.7)	0.001	29.7	29.2	0.004
>$62,999	130 (31.8)	124 (31.8)	0.002	31.0	31.7	0.007
Insurance type						
Medicare	271 (66.6)	182 (47.0)	0.197	55.2	56.5	0.013
Private insurance	112 (27.5)	168 (43.4)	0.161	38.0	36.6	0.014
Medicaid/other	14 (3.4)	24 (6.2)	0.027	5.0	4.6	0.003
No insurance	10 (2.5)	13 (3.4)	0.009	1.8	2.3	0.004
Facility type						
Academic	116 (28.4)	114 (30.0)	0.018	28.8	30.5	0.017
Community	246 (60.1)	220 (57.9)	0.026	58.4	56.8	0.015
Integrated Network	47 (11.5)	46 (12.1)	0.007	12.8	12.7	0.002
Charlson/Deyo Score						
0	270 (65.6)	299 (75.9)	0.104	70.6	70.9	0.002
1	106 (25.7)	78 (19.8)	0.059	23.2	23.3	0.002
≥2	36 (8.7)	17 (4.3)	0.044	6.2	5.8	0.004
Diagnosed between 2010-2014	211 (51.2)	189 (48.0)	0.032	50.1	46.9	0.032
Pathologic T3–4	275 (68.8)	328 (84.3)	0.164	75.7	76.9	0.011
Pathologic N1	194 (53.6)	308 (82.6)	0.304	66.2	69.1	0.029
Tumor size, mean (SD), centimeters	4.7 (3.1)	5.5 (3.1)	0.287	4.7 (3.1)	5.0 (3.0)	0.087
Right-sided tumor	266 (64.6)	246 (62.4)	0.021	61.9	61.6	0.003
Diagnosis to resection time, mean (SD), days	21.2 (33.0)	16.6 (22.6)	0.164	18.5 (28.9)	18.2 (24.1)	0.011
Surgical type						
Local excision	43 (10.6)	22 (5.7)	0.051	8.3	8.2	0.002
Partial colectomy	96 (23.6)	104 (26.9)	0.033	26.9	25.7	0.012
Hemicolectomy	233 (57.2)	228 (58.9)	0.018	56.7	57.2	0.005
Total colectomy	35 (8.6)	33 (8.5)	<0.001	8.1	8.9	0.008
Positive surgical margins	41 (10.1)	51 (13.1)	0.028	11.6	12.0	0.004
Unplanned 30-day readmission	22 (5.4)	21 (5.4)	<0.001	5.3	4.7	0.006

patients (10.6%) because it was contraindicated because of patient risk factors. A total of 41 patients (9.9%) refused recommended chemotherapy and 1 patient died before planned therapy. No reason was recorded for 3 patients.

AC Versus OB

Median follow-up in the weighted population was 67.4 months [interquartile range (IQR), 37.0–96.5]. IPTW-adjusted Kaplan-Meier analysis (Fig. 2) showed that median OS was significantly longer for AC versus OB [57.4 (IQR, 14.8–153.8) vs 38.2 (IQR, 10.4–125.4) months; $P = 0.007$ in IPTW-adjusted log-rank test]. The 5-year IPTW-adjusted rates of OS for AC versus OB were 49.6% and 42.8%, respectively. In IPTW-adjusted Cox proportional hazards regression analysis, AC was associated with a significant OS benefit (HR, 0.73; 95% CI, 0.64–0.84; $P < 0.001$).

Subgroup Analysis

We performed a subgroup analysis comparing the OS of patients receiving AC versus OB according to pathologic T stage, N status, tumor location and surgical margin status (Fig. 3). AC was associated with a significant OS benefit across pathologic T, N, and surgical margin subgroups, despite significant heterogeneity in the surgical margin subgroup (P-interaction <0.001). Subgroup analysis according to tumor location demonstrated improved OS in the adjuvant therapy cohort among patients with left-sided CRNECs (HR, 0.55; 95% CI, 0.44–0.60), but not in those with right-sided CRNECs (HR, 0.89, 95% CI 0.74–1.07) (P-interaction <0.001).

Sensitivity Analyses

In the complete case analysis, the median OS was significantly longer for AC versus OB (50.1 vs 31.7 months; $P = 0.004$ in IPTW-adjusted log-rank test). In IPTW-adjusted Cox proportional hazards regression analysis, AC was associated with a significant OS benefit (HR, 0.69; 95% CI, 0.59–0.80; $P < 0.001$).

Additional analyses using multivariate Cox models were conducted to estimate the HR of AC versus OB, adjusting by the 16 aforementioned factors associated with the receipt of AC. The final results were summarized via combining the estimations based on the 25 imputed datasets. It suggests that AC is associated with a significant OS benefit (HR, 0.72; 95% CI, 0.57–0.89; $P = 0.003$).

TABLE 2. Multivariable Logistic Regression Model Predicting Receipt of Adjuvant Chemotherapy Versus Observation After Surgery in the Unweighted Study Population

	OR	95% CI	*P*
Age (per year)	0.94	0.92–0.96	<0.01
Male sex	1.28	0.92–1.76	0.14
Race			
White	1		
Black	0.35	0.20–0.63	<0.01
Others	1.66	0.57–5.07	0.36
Income			
<$38,000	1		
$38,000–$47,999	1.10	0.64–1.89	0.73
$48,000–$62,999	1.08	0.64–1.82	0.77
>$62,999	1.06	0.63–1.77	0.83
Insurance type			
Medicare	1		
Private insurance	0.76	0.32–1.70	0.51
Medicaid/other	0.85	0.36–1.97	0.72
No insurance	0.58	0.16–2.09	0.40
Facility type			
Academic	1		
Community	0.93	0.65–1.32	0.72
Integrated network	0.89	0.50–1.56	0.67
Charlson/Deyo Score			
0	1		
1	0.74	0.50–1.09	0.13
≥ 2	0.48	0.24–0.92	0.03
Diagnosed between 2010 and 2014	0.95	0.69–1.32	0.77
Pathologic T3–4	1.97	1.23–3.17	0.01
Pathologic N1	4.18	2.90–6.11	<0.01
Tumor size (per cm)	1.07	1.01–1.13	0.03
Right-sided tumor	0.76	0.48–1.18	0.22
Diagnosis to resection time (per day)	0.99	0.99–1.0	0.06
Surgical type			
Local excision	1		
Partial colectomy	2.19	1.04–4.69	0.04
Hemicolectomy	2.24	1.02–5.0	0.04
Total colectomy	1.32	0.56–3.12	0.53
Positive surgical margins	0.86	0.51–1.43	0.55
Unplanned 30-day readmission	0.66	0.33–1.34	0.25

OR indicates odd ratio.

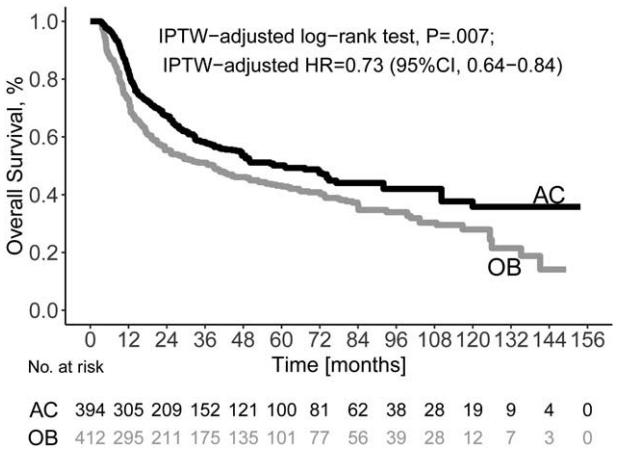

FIGURE 2. IPTW-adjusted Kaplan–Meier analysis of overall survival in patients who underwent adjuvant chemotherapy versus observation.

The magnitudes of the joint bounding factor for different combinations of the treatment-unmeasured confounders association ($OR_{AC\text{-}U}$) and the outcome-unmeasured confounders association ($HR_{OS\text{-}U}$) are depicted in Table 3. The relative risk pair ($OR_{AC\text{-}U}$, $HR_{OS\text{-}U}$) measures the strength of confounding between the treatment and the OS induced by the unmeasured confounders. The joint bounding factor shows a significant (blue area) treatment effect under various ($OR_{AC\text{-}U}$, $HR_{OS\text{-}U}$) pairs. It means that the unmeasured confounding of this strength would not suffice to explain away the treatment effect estimate. We applied the E-value method that produced $E = 2.08$ for the estimate. It suggests that the observed HR of 0.73 could be explained away by an unmeasured confounder that was associated with both the treatment and the survival outcome by a HR of 2.08-fold each, but weaker confounding could not.

DISCUSSION

Using a nationwide cancer registry, we demonstrated that AC was associated with improved OS compared with postoperative observation in patients with nonmetastatic CRNECs regardless of tumor stages. Of interest, patients with right-sided CRNECs may benefit less from AC compared to those with left-sided disease. To the best of our knowledge, the present study is the first to provide compelling evidence supporting AC for patients with resectable CRNECs. By implementing multiple imputation to missing data, the analysis gave a robust conclusion by reducing the estimation bias and improving validity in this study. In addition, in an attempt to eliminate selection bias, the population was weighted using IPTW in adjusted analyses, which has a number of potential advantages over more common matching techniques such as retaining all the samples.

The majority of data regarding chemotherapy for NECs is derived from patients with advanced disease. Although NEC is defined by both morphology and proliferative activity, several studies have reported that tumor's morphology plays a more important role in defining sensitivity to chemotherapy.[19–21] Velayoudom-Cephise et al reported 0% objective response to cisplatin-based chemotherapy in NET G3 (well differentiated NETs having a mitotic count >20 mitoses/10 HPF and/or Ki67 index >20%) patients versus 31% in large-cell NEC patients.[19] This aligns with the results of a multicenter study of 204 patients with G3 neoplasms, of whom 37 had NET G3. Similarly, in the platinum-treated population, disease control rate (33% vs 68%; $P = 0.03$) and median progression-free survival (2.4 vs 5.0 months; $P = 0.049$) were significantly lower in NET G3 compared to NEC respectively.[20] A large retrospective NORDIC study, which evaluated the effect of platinum-etoposide in patients with G3 neoplasms, also reported that patients with a Ki-67 index <55% versus >55% had a response rate of 15% and 42%, respectively.[21] The lower response rate to chemotherapy within the group of tumors with a Ki-67 <55% might be attributed to the inclusion of NET G3 in this population. In the present study, we focused on patients with morphologically poorly differentiated disease and further validate that AC should play a role in the management of patients with nonmetastatic CRNECs; administration of chemotherapy was associated with a 27% decreased risk of death.

As expected, patients with locally advanced disease are more likely to receive AC. This result may reflect that current postoperative practice could be mainly derived from evidence extrapolated from colorectal cancers (CRC),[22,23] which require AC for patients

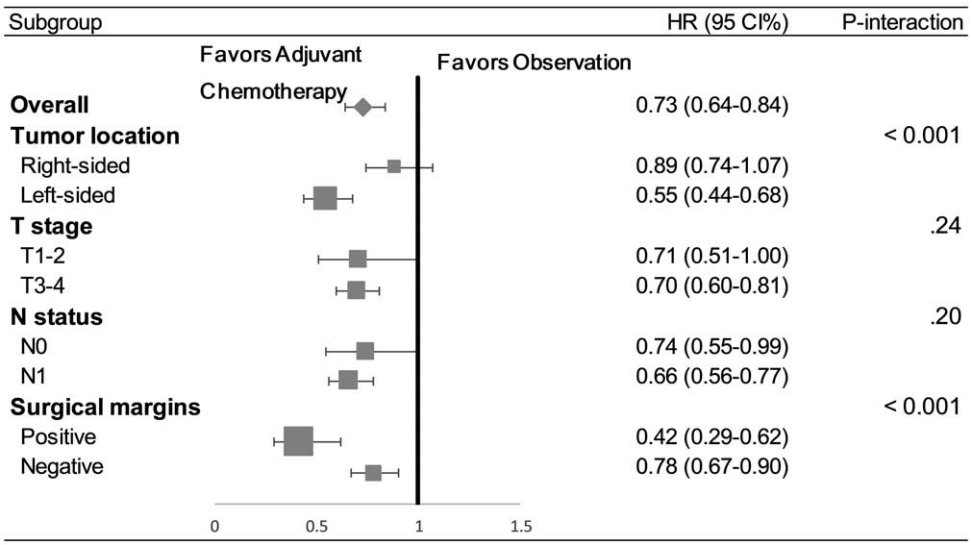

FIGURE 3. Forrest plot depicting IPTW-adjusted HRs of adjuvant chemotherapy versus observation according to baseline covariates.

with a stage II (with high risk factors) or stage III disease. However, in this study, treatment effect was consistent across different pathologic stages, emphasizing that stage is not a key determinant when considering AC for poorly differentiated CRNECs patients. In addition, the present study demonstrated that the protective effect of AC was more pronounced in patients with positive surgical margins. Therefore, positive margins should be considered as a strong indication for AC.

Interestingly, for the first time, we found that primary CRNECs' location may have a predictive value for chemotherapy. Indeed, having a left-sided primary tumor was predictive of improved survival following chemotherapy in the adjuvant setting, whereas patients with right-sided CRNECs derived less benefits from AC. It has been widely acknowledged that CRC in the right side and left side have different molecular characteristics,[24,25] leading to significant difference in survival and therapy responses.[26–29] The molecular biology of NECs is just beginning to be elucidated. Takizawa et al[30] demonstrated that CRNECs had certain similarities with CRC in the immunostaining patterns and gene mutations. The resemblance between these tumor entities may underlie the result that patients with left-sided CRNECs benefited more from AC. Better understanding of the biology of CRNECs is essential to identify individuals who may derive optimal benefit from chemotherapy.

Another important finding was that a large proportion of patients (51.1%) did not receive recommended adjuvant therapy in the study population, which in turn could compromise outcomes. The NCDB records that 79.8% of the patients did not receive AC because it was not part of the planned first course of therapy, demonstrating a significant issue about compliance to current guidelines. The NCCN published the first guidelines of neuroendocrine tumors in 2009.[31] However, the treatment practice did not evolve over time, with the ratio of OB versus AC dropping from 201:205 in 2004 to 2009 to 211:189 in 2010 to 2014. In addition, the odds of receiving AC were similar between academic and community centers (49.6% vs 47.2%), indicating that both types of cancer centers need to be better educated for management of the disease. One major reason for the poor compliance with the guidelines is probably attributed to a lack of consensus regarding the role of adjuvant therapy, as no evidence supporting the efficacy of AC existed before the present study. In addition, older patients and those with higher comorbidities were less likely to be compliant, as were patients who underwent local excision for the disease. We also identified that African-American were less likely to receive AC. The exact cause of these racial disparities is unknown. An analysis of patients with CRC from the 2003 to 2011 NCDB also suggested a decreased odd of receiving AC for black patients.[32] After all, these results indicate that barriers to access to optimal care for patients with CRNECs exist.

Present findings should be interpreted within the following limitations. First, inherent selection bias exists given the retrospective nature of this study. However, randomized studies that examine the effect of AC in patients with CRNECs are not available, and no study is recruiting for this purpose to the best of our knowledge. Although patients were well balanced on measured confounders that could have influenced treatment choice and patients' outcome by using propensity score-based analyses, unbalanced unmeasured confounders still represent a source of bias. Of note, the Ki-67 index could not be identified. However, morphologically poorly differentiated NECs are characterized by a high Ki-67 index, usually >50% to 60%.[33] In addition, our propensity score models included 30-day unplanned readmission as surrogates for postoperative complications. We also attempted to address this by conducting a sensitivity analysis to address measured confounders. The results demonstrated a moderately robust result that an unmeasured confounder should have at least a 2.08-fold stronger association with both survival/treatment, than the association between survival and treatment, to explain away the treatment effects. However, joint effect of multiple unmeasured confounders to bias results needs further investigation. Second, there is no coding for recurrence in the NCDB database. Third, some chemotherapy information is not available in the NCDB. We could not carry out an analysis on the types of chemotherapy utilized. In addition, the patients would still be classified as having had chemotherapy, even if the treatment was interrupted before completion. These could have led to an overestimation of the effect of AC. However, it remains difficult to determine which regimen is more effective for CRNECs,[6,34] and it is also unknown whether shortened or prolonged therapy may affect survival. Therefore, although the regimen or duration information could not be identified from the NCDB, it may have little effect on the conclusion. The present study establishes a good basis for further prospective studies.

TABLE 3. Magnitudes of the Joint Bounding Factor for Different Combinations of the OR_{AC-U} and the HR_{OS-U}

Bounding factor	OR_{AC-U}													
	1.0	**1.1**	**1.2**	**1.3**	**1.4**	**1.5**	**1.8**	**2.0**	**2.2**	**2.5**	**3.0**	**3.5**	**4.0**	**5.0**
HR_{OS-U}														
1.00	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)
0.95	0.73 (0.64, 0.84)	0.73 (0.64, 0.84)	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)	0.74 (0.65, 0.85)	0.75 (0.65, 0.86)	0.75 (0.66, 0.86)	0.75 (0.66, 0.86)	0.75 (0.66, 0.87)	0.76 (0.66, 0.87)	0.76 (0.66, 0.87)	0.76 (0.67, 0.87)	0.76 (0.67, 0.88)
0.90	0.73 (0.64, 0.84)	0.74 (0.65, 0.85)	0.74 (0.65, 0.86)	0.75 (0.66, 0.86)	0.75 (0.66, 0.87)	0.76 (0.66, 0.87)	0.77 (0.67, 0.88)	0.77 (0.68, 0.89)	0.77 (0.68, 0.89)	0.78 (0.68, 0.90)	0.78 (0.69, 0.90)	0.79 (0.69, 0.91)	0.79 (0.69, 0.91)	0.79 (0.70, 0.91)
0.85	0.73 (0.64, 0.84)	0.74 (0.65, 0.85)	0.75 (0.66, 0.86)	0.76 (0.67, 0.87)	0.77 (0.67, 0.88)	0.77 (0.68, 0.89)	0.79 (0.69, 0.91)	0.79 (0.70, 0.91)	0.80 (0.70, 0.92)	0.81 (0.71, 0.93)	0.82 (0.72, 0.94)	0.82 (0.72, 0.95)	0.83 (0.72, 0.95)	0.83 (0.73, 0.96)
0.80	0.73 (0.64, 0.84)	0.75 (0.65, 0.86)	0.76 (0.67, 0.88)	0.77 (0.68, 0.89)	0.78 (0.69, 0.90)	0.79 (0.69, 0.91)	0.81 (0.71, 0.93)	0.82 (0.72, 0.95)	0.83 (0.73, 0.95)	0.84 (0.74, 0.97)	0.85 (0.75, 0.98)	0.86 (0.75, 0.99)	0.87 (0.76, 1.00)	0.88 (0.77, 1.01)
0.75	0.73 (0.64, 0.84)	0.75 (0.66, 0.87)	0.77 (0.68, 0.89)	0.79 (0.69, 0.90)	0.80 (0.70, 0.92)	0.81 (0.71, 0.93)	0.84 (0.73, 0.96)	0.85 (0.75, 0.98)	0.86 (0.76, 0.99)	0.88 (0.77, 1.01)	0.89 (0.78, 1.03)	0.90 (0.79, 1.04)	0.91 (0.80, 1.05)	0.92 (0.81, 1.06)
0.70	0.73 (0.64, 0.84)	0.76 (0.66, 0.87)	0.78 (0.69, 0.90)	0.80 (0.70, 0.92)	0.82 (0.72, 0.94)	0.83 (0.73, 0.96)	0.87 (0.76, 1.00)	0.89 (0.78, 1.02)	0.90 (0.79, 1.04)	0.92 (0.80, 1.06)	0.94 (0.82, 1.08)	0.95 (0.84, 1.10)	0.96 (0.85, 1.11)	0.98 (0.86, 1.13)
0.65	0.73 (0.64, 0.84)	0.77 (0.67, 0.88)	0.80 (0.70, 0.92)	0.82 (0.72, 0.94)	0.84 (0.74, 0.97)	0.86 (0.75, 0.99)	0.90 (0.79, 1.04)	0.93 (0.81, 1.07)	0.94 (0.83, 1.09)	0.97 (0.85, 1.11)	0.99 (0.87, 1.14)	1.01 (0.89, 1.16)	1.02 (0.90, 1.18)	1.04 (0.92, 1.20)
0.60	0.73 (0.64, 0.84)	0.77 (0.68, 0.89)	0.81 (0.71, 0.93)	0.84 (0.74, 0.97)	0.87 (0.76, 1.00)	0.89 (0.78, 1.03)	0.95 (0.83, 1.09)	0.97 (0.85, 1.12)	1.00 (0.87, 1.15)	1.02 (0.90, 1.18)	1.05 (0.92, 1.21)	1.08 (0.94, 1.24)	1.10 (0.96, 1.26)	1.12 (0.98, 1.29)
0.55	0.73 (0.64, 0.84)	0.78 (0.69, 0.90)	0.83 (0.73, 0.95)	0.87 (0.76, 1.00)	0.90 (0.79, 1.04)	0.93 (0.81, 1.07)	1.00 (0.87, 1.15)	1.03 (0.90, 1.18)	1.06 (0.93, 1.21)	1.09 (0.95, 1.25)	1.13 (0.99, 1.30)	1.16 (1.01, 1.33)	1.18 (1.03, 1.36)	1.21 (1.06, 1.39)
0.50	0.73 (0.64, 0.84)	0.80 (0.70, 0.92)	0.85 (0.75, 0.98)	0.90 (0.79, 1.03)	0.94 (0.82, 1.08)	0.97 (0.85, 1.12)	1.05 (0.92, 1.21)	1.10 (0.96, 1.26)	1.13 (0.99, 1.30)	1.17 (1.02, 1.34)	1.22 (1.07, 1.40)	1.25 (1.10, 1.44)	1.28 (1.12, 1.47)	1.31 (1.15, 1.51)
0.45	0.73 (0.64, 0.84)	0.81 (0.71, 0.93)	0.88 (0.77, 1.01)	0.94 (0.82, 1.08)	0.98 (0.86, 1.13)	1.03 (0.90, 1.18)	1.13 (0.99, 1.30)	1.18 (1.03, 1.35)	1.22 (1.07, 1.40)	1.27 (1.11, 1.46)	1.32 (1.16, 1.52)	1.37 (1.20, 1.57)	1.40 (1.23, 1.61)	1.44 (1.27, 1.66)
0.40	0.73 (0.64, 0.84)	0.83 (0.73, 0.95)	0.91 (0.80, 1.05)	0.98 (0.86, 1.13)	1.04 (0.91, 1.20)	1.10 (0.96, 1.26)	1.22 (1.07, 1.40)	1.28 (1.12, 1.47)	1.33 (1.16, 1.53)	1.39 (1.22, 1.60)	1.46 (1.28, 1.68)	1.51 (1.33, 1.74)	1.55 (1.36, 1.79)	1.61 (1.41, 1.85)
0.35	0.73 (0.64, 0.84)	0.85 (0.75, 0.98)	0.96 (0.84, 1.10)	1.04 (0.91, 1.20)	1.12 (0.98, 1.29)	1.18 (1.04, 1.36)	1.33 (1.17, 1.53)	1.41 (1.23, 1.62)	1.47 (1.29, 1.69)	1.54 (1.35, 1.78)	1.63 (1.43, 1.88)	1.70 (1.49, 1.95)	1.75 (1.53, 2.01)	1.81 (1.59, 2.09)
0.30	0.73 (0.64, 0.84)	0.88 (0.78, 1.02)	1.01 (0.89, 1.17)	1.12 (0.98, 1.29)	1.22 (1.07, 1.40)	1.30 (1.14, 1.49)	1.49 (1.30, 1.71)	1.58 (1.39, 1.82)	1.66 (1.45, 1.91)	1.75 (1.54, 2.02)	1.87 (1.64, 2.15)	1.95 (1.71, 2.24)	2.01 (1.76, 2.31)	2.09 (1.83, 2.41)
0.25	0.73 (0.64, 0.84)	0.93 (0.81, 1.07)	1.10 (0.96, 1.26)	1.24 (1.08, 1.42)	1.36 (1.19, 1.56)	1.46 (1.28, 1.68)	1.70 (1.49, 1.96)	1.83 (1.60, 2.10)	1.92 (1.69, 2.21)	2.04 (1.79, 2.35)	2.19 (1.92, 2.52)	2.29 (2.01, 2.64)	2.37 (2.08, 2.73)	2.48 (2.18, 2.86)
0.20	0.73 (0.64, 0.84)	1.00 (0.87, 1.15)	1.22 (1.07, 1.40)	1.40 (1.23, 1.62)	1.56 (1.37, 1.80)	1.70 (1.49, 1.96)	2.03 (1.78, 2.33)	2.19 (1.92, 2.52)	2.32 (2.04, 2.67)	2.48 (2.18, 2.86)	2.68 (2.35, 3.08)	2.82 (2.47, 3.24)	2.92 (2.56, 3.36)	3.07 (2.69, 3.53)

Columns correspond to increasing imbalance in unmeasured confounders between treatment groups. Rows correspond to increasing adverse effect of unmeasured confounders on overall survival. The entries in the table for the joint bounding factor are the largest observed hazard ratio (with 95% CI) that such unmeasured confounder could explain away. As such, the present sensitivity analysis allows for testing the treatment effect of AC versus observation in presence of unmeasured confounders with varying combination of imbalance between treatment groups and impact on overall survival. The hazard ratio of AC versus observation is color coded as significant (blue), nonsignificant (orange), and reverse treatment effect (green), respectively.

CONCLUSIONS

AC should be recommended for patients with CRNECs. These findings support current European and US treatment recommendations for patients with poorly differentiated NECs. Efforts in education and adherence to national guidelines for NECs are needed. Prospective studies are still needed to establish best practice regarding choice of chemotherapeutic regimen, duration, and management of toxicities.

REFERENCES

1. Sorbye H, Strosberg J, Baudin E, et al. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer*. 2014;120:2814–2823.
2. Eads JR. Poorly differentiated neuroendocrine tumors. *Hematol Oncol Clin North Am*. 2016;30:151–162.
3. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335–1342.
4. Dasari A, Mehta K, Byers LA, et al. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. *Cancer*. 2018;124:807–815.
5. Crippa S, Partelli S, Bassi C, et al. Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. *Surgery*. 2016;159:862–871.
6. Haugvik SP, Janson ET, Osterlund P, et al. Surgical treatment as a principle for patients with high-grade pancreatic neuroendocrine carcinoma: a Nordic multicenter comparative study. *Ann Surg Oncol*. 2016;23:1721–1728.
7. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology*. 2016;103:186–194.
8. Casas F, Ferrer F, Farrus B, et al. Primary small cell carcinoma of the oesophagus: a review of the literature with emphasis on therapy and prognosis. *Cancer*. 1997;80:1366–1372.
9. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas*. 2013;42:557–577.
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. *Neuroendocrine Tumors*. 2018. Version 3.
11. Furumoto K, Kogire M, Iizuka N. Long-term survival of a patient with rectal neuroendocrine carcinoma after treatment with curative resection and adjuvant chemotherapy with capecitabine. *Cancer Chemother*. 2015;42:2485e2488.
12. Wu Z, Yu D, Zhao S, et al. The efficacy of chemotherapy and operation in patients with colorectal neuroendocrine carcinoma. *J Surg Res*. 2018;225:54–67.
13. Byrne BE, Mamidanna R, Vincent CA, et al. Population-based cohort study comparing 30- and 90-day institutional mortality rates after colorectal surgery. *Br J Surg*. 2013;100:1810–1817.
14. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2010;30:377–399.
15. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
16. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons; 2004.
17. Ding P, VanderWeele TJ. Sensitivity analysis without assumptions. *Epidemiology*. 2016;27:368–377.
18. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–274.
19. Velayoudom-Cephise FL, Duvillard P, Foucan L, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer*. 2013;20:649–657.
20. Heetfeld M, Chougnet CN, Olsen IH, et al. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2015;22:657–664.
21. 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;24:152–160.
22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. *Colon Cancer*. 2018. Version 3.
23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. *Rectal Cancer*. 2018. Version 3.
24. Loree JM, Kopetz S. Recent developments in the treatment of metastatic colorectal cancer. *Ther Adv Med Oncol*. 2017;9:551–564.
25. Baran B, Mert Ozupek N, Yerli Tetik N, et al. Difference between left-sided and right-sided colorectal cancer: a focused review of literature. *Gastroenterology Res*. 2018;11:264–273.
26. Tejpar S, Stintzing S, Ciardiello F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol*. 2016;1–8.
27. Boeckx N, Koukakis R, Beeck K, et al. Primary tumor sidedness impacts on prognosis and treatment outcome: results from three randomized studies of panitumumab plus chemotherapy versus chemotherapy or chemotherapy plus bevacizumab in 1st and 2nd line RAS/BRAF WT mCRC. *Ann Oncol*. 2017;28:1862–1868.
28. Venook A, Niedzwiecki D, Ou F, et al. Impact of primary tumor location on overall survival and progression free survival in patients with metastatic colorectal cancer: analysis of all RAS wt subgroup on CALGB/SWOG 80405 (Alliance). *J Clin Oncol*. 2016;34(suppl). abstract 3504.
29. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107. pii: dju427.
30. Takizawa N, Ohishi Y, Hirahashi M, et al. Molecular characteristics of colorectal neuroendocrine carcinoma; similarities with adenocarcinoma rather than neuroendocrine tumor. *Hum Pathol*. 2015;46:1890–1900.
31. Clark OH, Benson AB 3rd, Berlin JD, et al. NCCN Clinical Practice Guidelines in Oncology: neuroendocrine tumors. *J Natl Compr Canc Netw*. 2009;7:712–747.
32. Becerra AZ, Probst CP, Tejani MA, et al. Opportunity lost: Adjuvant chemotherapy in patients with stage III colon cancer remains underused. *Surgery*. 2015;158:692–699.
33. Crippa S, Partelli S, Belfiori G, et al. Management of neuroendocrine carcinomas of the pancreas (WHO G3): a tailored approach between proliferation and morphology. *World J Gastroenterol*. 2016;22:9944–9953.
34. 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;105:1176–1181.