International Journal of Colorectal Disease (2021) 36:745–756
https://doi.org/10.1007/s00384-020-03809-2

ORIGINAL ARTICLE

Poorer prognosis for neuroendocrine carcinoma than signet ring cell cancer of the colon and rectum (CRC-NEC): a propensity score matching analysis of patients from the Surveillance, Epidemiology, and End Results (SEER) database

Youwei Chen[1] · Jiangfeng Tu[1] · Shishi Zhou[2] · Jianfei Fu[2] · Qinghua Wang[2]

Accepted: 23 November 2020 / Published online: 7 January 2021

Abstract

Purpose Colorectal neuroendocrine carcinomas (CRC-NECs) are rare, comprising < 1% of colorectal cancers. This study aimed to assess the incidence, clinicopathologic characteristics, prognostic factors, and treatment outcomes of CRC-NEC.

Methods We analysed the Surveillance, Epidemiology, and End Results (SEER) database to identify patients from 20 to 74 years old diagnosed with CRC-NEC or common CRC (non-NEC) during 2004–2013. Log-rank testing was conducted to assess survival differences. A competing-risks regression model was used to adjust for covariate effects in the propensity score-matched (PSM) cohort, and adjusted hazard ratios (HRs) were calculated for the raw and PSM cohorts.

Results We identified 67,484 patients (344 CRC-NEC and 67,140 non-NEC). Lymph node metastasis (LNM) was more common in CRC-NEC (75.29%, $n = 259$) than in non-NEC (51.53%, $n = 34{,}600$) ($P < 0.001$); 56.40% ($n = 194$) of CRC-NECs were located on the right side, while 18.31% ($n = 63$) were located on the left side, with a statistically significant difference in distribution ($P < 0.001$) compared to that in non-NEC CRC. Multivariate analysis indicated that a left-side location was an independent adverse prognostic factor for CRC-NEC ($P = 0.043$). CRC-NEC had the poorest cancer-specific survival (median CSS, 9.0 months) among assessed cancers, even poorer than that of signet ring cell cancer (median CSS, 24.0 months). However, both radical operation ($P = 0.007$) and chemotherapy ($P = 0.008$) were beneficial for CSS.

Conclusion NEC is a rare and extremely aggressive tumour with a poor prognosis. Right-side NEC has a better prognosis than left-side NEC. Early diagnosis, radical surgery, and chemotherapy are imperative for improving survival.

Keywords Neuroendocrine carcinomas · Colon and rectum · Survival analysis · Epidemiologic study characteristics · SEER program

Background

Neuroendocrine neoplasms (NENs), originating from peptidergic neurons and neuroendocrine cells, are a heterogeneous group of rare tumours with distinct clinical behaviours [1]. According to the World Health Organization (WHO) classification of 2010, neuroendocrine carcinomas (NECs) are defined as poorly differentiated, high-grade malignant neoplasms composed of small cells or intermediate to large cells. The current grading system for NEC classification is based on the Ki-67 proliferation index or mitotic count. For the diagnosis of NEC, the patient should have a Ki-67 index or mitotic count higher than 20%. If the mitotic count and Ki-67 index are different, the higher of the two is used [2]. The incidence of NEN has been rising in recent decades [3–6]. Only approximately 5% of all gastrointestinal NENs have a Ki-67 index higher than 20% [7, 8]. This frequency might differ by organ, at approximately 7% in the pancreas [8] and up to 40% in the colon [9]. NEC of the colon and rectum (CRC-NEC) is rare, comprising less than 1% of colon and rectal cancers [10].

✉ Jianfei Fu
11218276@zju.edu.cn

✉ Qinghua Wang
wqhw1001@zju.edu.cn

[1] Department of Gastroenterology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310014, Zhejiang Province, China

[2] Department of Medical Oncology, Affiliated Jinhua Hospital, Zhejiang University School of Medicine, 351 Mingyue Road, Jinhua 321000, Zhejiang Province, China

NEC has a poor prognosis, and the survival ranges from 38 months for patients with localized disease to 5 months in the metastatic setting [11]. The median survival of metastatic NEC patients could be as short as 1 month for patients who received only best supportive care and up to 12 to 19 months for those treated with best available therapy [6, 12]. It has been reported that only 5% of NEC patients are long-term survivors [8]. The median overall survival of CRC-NEC patients is 13.2 to 14.7 months [13, 14], with 5-year overall survival (OS) rates of 8 to 16.3% [14, 15]. However, previous publications are limited to small retrospective series [10].

Due to the low incidence and the lack of large randomized clinical studies of CRC-NEC, the prognostic factors and survival of CRC-NEC remain unclear. Therefore, the objective of this study was to investigate the clinicopathologic characteristics, prognostic factors, and treatment outcomes of patients with CRC-NEC using data from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Study population

The best way to explore the prognostic factors of a rare disease, such as CRC-NEC, is to conduct a large population-based study. In this study, we identified individuals diagnosed with microscopically confirmed adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma (non-NEC) or CRC-NEC of the colon or rectum from the SEER database during the period from 2004 to 2013. The SEER dataset is supported by the US National Cancer Institution and is an authoritative source of information on cancer statistics from the population-based cancer registries, which covers 28% of the US population [16, 17]. It is publicly accessible for studies in cancer epidemiology and health policy, and SEER Stat software (SEER Stat 8.3.6) was used to access the data (reference number: 12296-Nov2018). Patients diagnosed after 2013 were excluded from the study to ensure adequate follow-up. Data regarding clinicopathological variables, such as age and year at diagnosis, marital status, race, sex, tumour grade, tumour type, tumour site, adjuvant chemotherapy, insurance status, carcinoembryonic antigen (CEA), tumour deposit, peritoneum invasion, survival time, and cause of death, were retrieved.

The specific inclusion criteria were as follows: (1) patients were diagnosed from 2004 to 2013; (2) site record ICD-O-3 was limited to the colon and rectum with pathologically confirmed diagnosis (C18.0–18.7, C 18.9, C 19.9, C 20.9); (3) histological type ICD-O-3 was limited to large cell neuroendocrine carcinoma, small cell carcinoma, neuroendocrine carcinoma, adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma (8013/3, 8041/3, 8246/3, 8140/3, 8480/3, 8490/3); (4) TNM staging was clear (staging based on 6th or 7th American Joint Committee on Cancer (AJCC) system according to the version of the day); and (5) patient age was limited to 20 to 74 years old. The exclusion criteria were as follows: (1) patients without information of age or race at diagnosis; (2) patients with multiple primary tumours; (3) patients with survival time less than 1 month; and (4) patients with low-grade (well or moderately differentiated) neuroendocrine carcinoma [18] (Fig. 1).

Variable declaration

Age was grouped as less than 60 years old (< 60) and more than 60 years old (≥ 60). Race was divided into black, white, and other. Marital status was grouped as married, single, and divorced. Histology was grouped as colorectal neuroendocrine carcinoma (CRC-NEC) and common colorectal adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma (non-NEC). Differentiation grades were divided into well, moderately, and poorly differentiated and undifferentiated. Tumour location was grouped as right-side colon and left-side colon, whose cut-off was the splenic flexure, as well as rectum. Operation methods were grouped as no surgery, local excision, radical resection, and unknown. Insurance status was grouped as insured, any Medicaid, uninsured, and unknown. Chemotherapy was grouped as yes or no, regardless of the sequence. CEA, tumour deposit, and peritoneum invasion were all grouped as negative, positive, and unknown.

Statistical analyses

Survival curves were generated using the Kaplan-Meier method, followed by the log-rank test for detecting the differences in survival. The duration from the date of diagnosis until death due to cancer was calculated as the cancer-specific survival (CSS), and CSS was the primary endpoint in this study. Death due to other causes was defined as a censored observation. A competing-risks regression model was applied to conduct the multivariate analysis with backward, stepwise elimination of variables. Hazard ratios (HRs) were adjusted for age (< 60 or ≥ 60), sex, race, marital status, tumour location, T classification, N classification, staging, operation, chemotherapy, insurance status, CEA, tumour deposit, and peritoneum invasion. Variables that were believed to be associated with CSS or those with $P < 0.20$ in the univariate analysis were enrolled in multivariate analysis. The demographic and clinical characteristics of the two cohorts are summarized in Table 1.

Moreover, propensity score matching (PSM) analysis was performed to balance the differences for known potential baseline confounding variables in the populations with CRC-NEC and signet ring cell cancer (SRCC), which is considered a rare type of colorectal cancer with an extremely poor prognosis. The MatchIt R package was used to perform

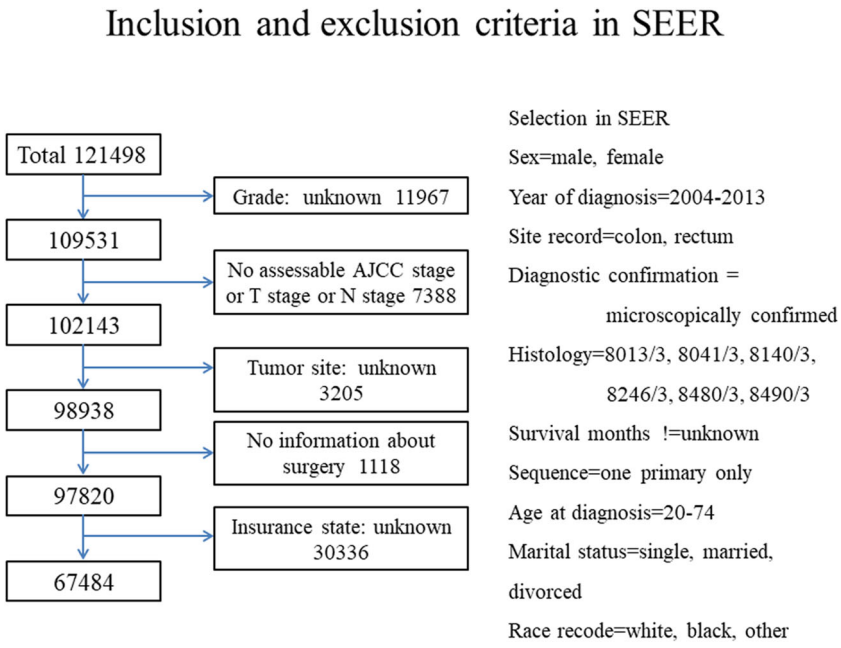

Fig. 1 The inclusion and exclusion criteria in the SEER database

bipartite-weighted propensity score matching with stratification for stage, operation method, and chemotherapy [19]. Characteristics such as grade, CEA, tumour deposit, and peritoneum invasion, which did not have a counterpart between the two groups, were excluded from the PSM procedure. Thereafter, baseline variables of the two groups were compared by a stratified logistic regression including covariates of sex, race, age, marital status, staging, grade of differentiation, T classification, N classification, tumour site, operation method, chemotherapy, and insurance status. Finally, survival curves were generated using the Kaplan-Meier method in the two PSM cohorts. The adjusted cohort was used to validate that CRC-NEC has a poorer prognosis than SRCC. All statistical analyses were conducted using R3.6.2 software (http://www.r-project.org/) or STATA/SE 15.0 software (Stata Corp LP, College Station, TX, USA), and a two-sided value of $P < 0.05$ was considered statistically significant.

Results

A total of 67,484 patients were identified from the SEER database based on the aforementioned inclusion criteria. Among all the identified patients, 344 (0.51%) were CRC-NEC patients, and 61,057 (99.49%) were non-NEC patients. The detailed clinicopathological characteristics of the two groups are presented in Table 1. The median ages of the patients in the CRC-NEC and non-NEC cohorts were 58 (range, 24 to 74 years old) and 60 (range, 20 to 74 years old), respectively. The proportion of female patients was 43.60% ($n = 150$) in the CRC-NEC group and 44.16% ($n = 29,651$) in the non-NEC group ($P = 0.835$). Advanced stage, increased depth of invasion, and greater risk of lymph node metastasis were more common in CRC-NEC patients than in non-NEC patients ($P < 0.001$). The percentage of lymph node metastasis (LNM) was 75.29% ($n = 259$) in CRC-NEC and higher than 51.53% ($n = 34,600$) in non-NEC ($P < 0.001$). In the CRC-NEC cohort, N0 was found in 24.71% ($n = 85$), while N0 accounted for 48.47% ($n = 32,540$) of patients in the non-NEC cohort. Patients with stage III/IV disease accounted for a significantly larger proportion of CRC-NEC patients than non-NEC patients (86.63% vs. 55.94%, $P < 0.001$). The majority of CRC-NECs (56.40%) were located on the right side of the colon, which was different from the distribution of non-NECs ($P < 0.001$). Chemotherapy is the main treatment for CRC-NEC (66.18%) and non-NEC (55.50%). The median CSS of CRC-NEC patients with chemotherapy was 10.0 months (interquartile range [IQR], 4.0 to 30.0 months), while the median CSS of patients without chemotherapy was 8.0 months (interquartile range [IQR], 2.0 months to not reached [NR]). There were still several significant differences in the characteristics of the 688 propensity score-matched patients despite the effort (Table 1).

Table 2 summarizes the results of the univariate analysis and multivariate competing-risks regression analysis of the predictors of OS in CRC-NEC patients. In the univariate analysis, age, sex, race, marital status, tumour site, chemotherapy, insurance status, CEA, tumour deposit, and peritoneum invasion were not significantly associated with a poor prognosis in CRC-NEC. However, advanced N classification (N1: HR, 2.08, 95% CI, 1.44–3.02, $P < 0.001$; N2: HR, 2.11, 95% CI, 1.48–3.02, $P < 0.001$) and stage IV (HR, 3.91, 95% CI, 1.56–9.81, $P = 0.004$) were associated with a poor prognosis in CRC-NEC (Table 2). The results of the multivariate analysis

Table 1 Descriptive characteristics of 67,484 patients of study population within the SEER Medicare-linked database and 688 propensity score-matched patients

Characteristic	Entire cohort ($n = 67,484$)			Propensity score-matched cohort ($n = 688$)		
	CRC-NECs($n = 344$)	Non-NECs ($n = 67,140$)	*P* value	CRC-NECs ($n = 344$)	SRCC ($n = 344$)	*P* value
Age (years)			*0.036*			*0.699*
< 60	198 (57.56)	34,846 (51.90)		198 (57.56)	203 (59.01)	
≥ 60	146 (42.44)	32,294 (48.10)		146 (42.44)	141 (40.99)	
Gender			*0.835*			*0.246*
Female	150 (43.60)	29,651 (44.16)		150 (43.60)	135 (39.24)	
Male	194 (56.40)	37,489 (55.84)		194 (56.40)	209 (60.76)	
Race			*0.009*			*0.806*
White	283 (82.27)	51,383 (76.53)		283 (82.27)	286 (83.14)	
Black	42 (12.21)	8771 (13.06)		42 (12.21)	37 (10.76)	
Other	19 (5.52)	6986 (10.41)		19 (5.52)	21 (6.10)	
Marital status			*0.497*			*0.970*
Married	219 (63.66)	40,899 (60.92)		219 (63.66)	222 (64.53)	
Single	65 (18.90)	12,964 (19.30)		65 (18.90)	63 (18.32)	
Divorced	60 (17.44)	13,277 (19.78)		60 (17.44)	59 (17.15)	
Grade			*0.000*			*NA*
Well	0 (0.00)	4410 (6.57)		0 (0.00)	–	
Moderately	0 (0.00)	49,566 (73.82)		0 (0.00)	–	
Poorly	232 (67.44)	11,583 (17.25)		232 (67.44)	–	
Undifferentiated	112 (32.56)	1581 (2.35)		112 (32.56)	–	
Staging[a]			*0.000*			*0.001*
I	13 (3.78)	9921 (14.78)		13 (3.78)	20 (5.82)	
II	33 (9.59)	19,657 (29.28)		33 (9.59)	29 (8.43)	
III	90 (26.16)	23,862 (35.54)		90 (26.16)	136 (39.53)	
IV	208 (60.47)	13,700 (20.40)		208 (60.47)	159 (46.22)	
T classification[a]			*0.000*			*0.005*
T1	33 (9.59)	5216 (7.77)		33 (9.59)	25 (7.27)	
T2	44 (12.79)	8906 (13.26)		44 (12.79)	21 (6.10)	
T3	171 (49.71)	41,063 (61.16)		171 (49.71)	173 (50.29)	
T4	96 (27.91)	11,955 (17.81)		96 (27.91)	125 (36.34)	
N classification[a]			*0.000*			*0.046*
N0	85 (24.71)	32,540 (48.47)		85 (24.71)	75 (21.81)	
N1	113 (32.85)	20,340 (30.29)		113 (32.85)	91 (26.45)	
N2	146 (42.44)	14,260 (21.24)		146 (42.44)	178 (51.74)	
Tumour site			*0.000*			*0.410*
Right-side colon	194 (56.40)	25,060 (37.33)		194 (56.40)	186 (54.07)	
Left-side colon	63 (18.31)	27,443 (40.87)		63 (18.31)	77 (22.38)	
Rectum	87 (25.29)	14,637 (21.80)		87 (25.29)	81 (23.55)	
Operation methods			*0.000*			*0.010*
No surgery	92 (26.74)	4035 (6.01)		92 (26.74)	58 (16.86)	
Local excision	3 (0.87)	169 (0.25)		3 (0.87)	1 (0.29)	
Radical resection	248 (72.10)	62,460 (93.03)		248 (72.10)	283 (82.27)	
Unknown	1 (0.29)	476 (0.71)		1 (0.29)	2 (0.58)	
Chemotherapy			*0.004*			*0.521*
No	122 (35.47)	29,051 (43.27)		122 (35.47)	114 (33.14)	
Yes	222 (64.53)	38,089 (56.73)		222 (64.53)	230 (66.86)	
Insurance			*0.464*			*0.859*

Table 1 (continued)

Characteristic	Entire cohort ($n = 67,484$)			Propensity score-matched cohort ($n = 688$)		
	CRC-NECs($n = 344$)	Non-NECs ($n = 67,140$)	*P* value	CRC-NECs ($n = 344$)	SRCC ($n = 344$)	*P* value
Insured	286 (83.14)	54,505 (81.18)		286 (83.14)	281 (81.69)	
Any Medicaid	38 (11.05)	8936 (13.31)		38 (11.05)	40 (11.63)	
Uninsured	20 (5.81)	3699 (5.51)		20 (5.81)	23 (6.68)	
CEA			*0.000*			*NA*
Negative	40 (11.63)	22,656 (33.74)		40 (11.63)	–	
Positive	19 (5.52)	20,103 (29.94)		19 (5.52)	–	
Unknown	285 (82.85)	24,381 (36.32)		285 (82.85)	–	
Tumour deposit			*0.000*			*NA*
Negative	23 (6.69)	28,542 (42.51)		23 (6.69)	–	
Positive	5 (1.45)	2610 (3.89)		5 (1.45)	–	
Unknown	316 (91.86)	35,988 (53.60)		316 (91.86)	–	
Peritoneum invasion			*0.000*			*NA*
Negative	29 (8.43)	28,385 (42.28)		29 (8.43)	–	
Positive	14 (4.07)	4787 (7.13)		14 (4.07)	–	
Unknown	301 (87.50)	33,968 (50.59)	*0.036*	301 (87.50)	–	

A value of $P < 0.05$ was considered statistically significant

AJCC, American Joint Committee on Cancer; *CRC-NECs*, neuroendocrine carcinoma of the colon and rectum; *Non-NECs*, adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma; *SRCC*, signet ring cell carcinoma; *NA*, non-application

[a] Staging based on the 6th or 7th AJCC system of the colorectal carcinoma of the day when the disease was diagnosed

indicated that male sex (HR, 1.30, 95% CI, 1.01–1.68, $P = 0.042$), left-side colon location (HR, 1.44, 95% CI, 1.01–2.06, $P = 0.043$), and stage IV (HR, 4.67, 95% CI, 1.65–13.22, $P = 0.004$) had a significant negative effect on the survival of CRC-NEC patients. However, only radical surgery (HR 0.58, 95% CI 0.39–0.87, $P = 0.007$) and chemotherapy (HR 0.59, 95% CI 0.40–0.87, $P = 0.008$) had a positive significant influence on the survival of CRC-NEC, as illustrated by the multivariate analysis.

The CSS is illustrated in Figs. 2, 3. There was a significant difference between CRC-NEC and non-NEC patients in terms of cancer-specific survival ($P < 0.001$) (Fig. 2a). Moreover, there was a significant difference in CSS between CRC-NEC, adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma patients ($P < 0.001$) (Fig. 2b). Figure 3 shows that there was a significant difference between CRC-NEC and SRCC patients in terms of CSS ($P < 0.001$) in both the raw cohort and the PSM cohort. Kaplan-Meier survival curves illustrate how overall mortality changed with histology. CRC-NEC had the poorest CSS among the assessed tumour types (median CSS, 9.0 months), even poorer than SRCC (median CSS, 24.0 months). Interestingly, neither T classification nor N classification, which were grouped according to the TNM staging system of the colorectal carcinoma of the day when the disease was diagnosed, could well predict the CSS (Table 2, Fig. 4). Figure 5 demonstrates how the operation method and chemotherapy influence the CSS of CRC-NEC (Fig. 6).

Discussion

CRC-NECs are rare and extremely aggressive tumours, accounting for approximately 0.6% of all colorectal cancers [10], which is in agreement with our results. According to histogenesis, NEC is a neuroendocrine tumour (NET). It lacks specific clinical manifestations but shows a higher degree of malignancy and a poorer prognosis than non-NEC CRC. Poorly differentiated NEC usually leads to a poor prognosis [20]. NEC is defined both by proliferative activity and morphology, but it is reported tumour's morphology was more important to predict sensitivity to chemotherapy [21]. Due to limitations in the current grading system for neuroendocrine neoplasms, high-grade neuroendocrine carcinoma, which comprise a subgroup of differentiated neuroendocrine tumours (NET) with high proliferation rates (G3-NET), as well as undifferentiated G3-NEC (large or small cell carcinomas), is difficult to define in case of the lack of information on Ki-67 or proliferation rate in seer database. Moreover, G3-NET is a different subtype with a much lower response rate to chemotherapy compared to NEC [21]. So, we enrolled only NEC in the current study to avoid the bias brought by G3-NET. Meanwhile, the ICD-10 code C 18.1 (malignant Tumour of the Appendix) was also included into the search algorithm, raising a doubt that a better prognosis of appendix NECs may probably explain the better prognosis of right-sided NECs as a whole. However, only 816 patients were actually

Table 2 Univariate and multivariate analyses of predictors of CRC-NEC in the study population

Characteristic	*n*	1-year CSS[a]	3-year CSS[a]	5-year CSS[a]	Univariate analysis[b]			Multivariate analysis[b]		
(*n* = 344)					HR	95% CI	*P* value	HR	95% CI	*P* value
Age										
< 60	198	39.9	14.7	9.6	Reference			Reference		
≥ 60	146	34.9	19.2	10.3	0.82	0.63–1.07	*0.151*	1.02	0.78–1.35	*0.866*
Gender										
Female	150	43.3	20.0	13.3	Reference			Reference		
Male	194	33.5	13.9	7.2	1.19	0.93–1.53	*0.164*	1.33	1.02–1.72	*0.032*
Race										
White	283	39.2	17.0	9.9	Reference			Reference		
Black	42	28.6	14.3	7.1	1.29	0.86–1.94	*0.211*	1.06	0.67–1.68	*0.810*
Other	19	36.8	15.8	10.5	0.95	0.56–1.62	*0.850*	0.57	0.25–1.27	*0.170*
Marital status										
Married	219	42.0	18.7	11.0	Reference			Reference		
Single	65	27.7	7.7	4.6	1.50	1.08–2.07	*0.015*	1.38	0.96–2.00	*0.082*
Divorced	60	33.3	18.3	11.7	1.04	0.74–1.47	*0.810*	1.27	0.91–1.78	*0.156*
Tumour site										
Right-side colon	194	38.7	16.0	8.8	Reference			Reference		
Left-side colon	63	31.8	12.7	11.1	1.29	0.92–1.82	*0.144*	1.45	1.03–2.06	*0.035*
Rectum	87	40.2	20.7	11.5	0.94	0.70–1.25	*0.653*	1.13	0.78–1.65	*0.515*
Staging[c]										
I	13	53.9	38.5	23.1	Reference			Reference		
II	33	78.8	60.6	33.3	0.41	0.13–1.32	*0.135*	0.52	0.16–1.73	*0.287*
III	90	54.4	31.1	18.9	1.54	0.60–3.96	*0.367*	2.05	0.75–5.59	*0.160*
IV	208	23.1	1.9	1.0	3.91	1.56–9.81	*0.004*	6.34	2.30–17.48	*< 0.001*
T classification[c]										
T1	33	21.2	6.6	3.0	Reference			Reference		
T2	44	40.9	15.9	6.8	0.59	0.36–0.95	*0.030*	0.61	0.38–0.99	*0.044*
T3	171	45.6	21.6	13.5	0.53	0.36–0.79	*0.002*	0.62	0.40–0.95	*0.027*
T4	96	28.1	11.5	4.2	0.87	0.57–1.34	*0.533*	0.73	0.47–1.13	*0.158*
N classification[c]										
N0	85	51.8	34.1	20.0	Reference			Reference		
N1	113	32.7	12.4	8.9	2.08	1.44–3.02	*0.000*	1.18	0.86–1.62	*0.315*
N2	146	33.6	9.6	4.8	2.11	1.48–3.02	*0.000*	1.49	0.99–2.23	*0.052*
Operation										
No surgery	92	20.7	7.6	3.3	Reference			Reference		

Table 2 (continued)

Characteristic	*n*	1-year CSS[a]	3-year CSS[a]	5-year CSS[a]	Univariate analysis[b]			Multivariate analysis[b]		
(*n* = 344)					HR	95% CI	*P* value	HR	95% CI	*P* value
Radical	248	43.6	19.8	12.1	0.57	0.44–0.74	*0.000*	0.55	0.37–0.82	*0.003*
Chemotherapy										
No	122	29.5	20.5	11.5	Reference			Reference		
Yes	222	42.3	14.4	9.0	1.22	0.87–1.70	*0.252*	0.49	0.34–0.71	*< 0.001*
Insurance										
Insured	286	40.9	18.2	10.8	Reference			Reference		
Any Medicaid	38	18.4	10.5	7.9	1.16	0.74–1.84	*0.518*	1.10	0.71–1.69	*0.670*
Uninsured	20	30.0	5.0	0.0	1.36	0.90–2.06	*0.148*	1.59	0.84–3.01	*0.155*

A value of $P < 0.05$ was considered statistically significant

AJCC, American Joint Committee on Cancer; *CSS*, cancer-specific survival; *HR*, hazard ratio; *CRC-NECs*, neuroendocrine carcinoma of the colon and rectum; *Non-NECs*, adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma; *SRCC*, signet ring cell carcinoma

[a] Five-year overall survival rate was calculated using Kaplan-Meier methods

[b] Univariate and multivariate analyses were conducted using competing-risks regression model

[c] Staging based on the 6th or 7th AJCC system of the day when the disease was diagnosed

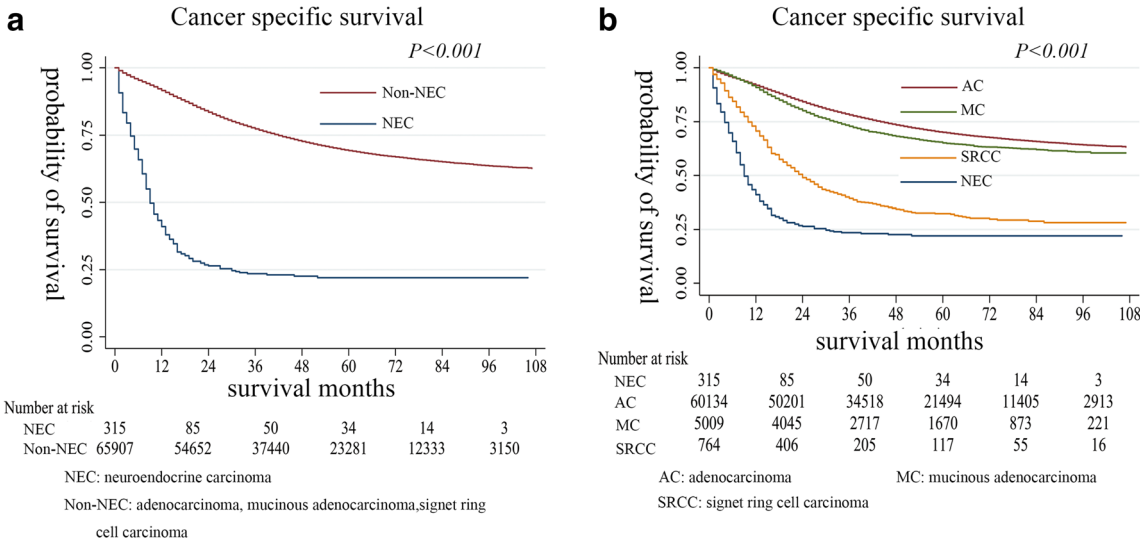

Fig. 2 Survival analysis of CRC-NEC and non-NEC patients in the entire cohort. **a** CSS between CRC-NEC and non-NEC patients. **b** The CSS between CRC-NEC, adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma patients

diagnosed as malignant tumours of the appendix from the SEER database initially, and the majority were non-NEC, with only 2 patients diagnosed as large cell neuroendocrine carcinoma and 1 patient diagnosed as small cell neuroendocrine carcinoma. After the data arrangement, no appendix NEC was finally included in the current study, left

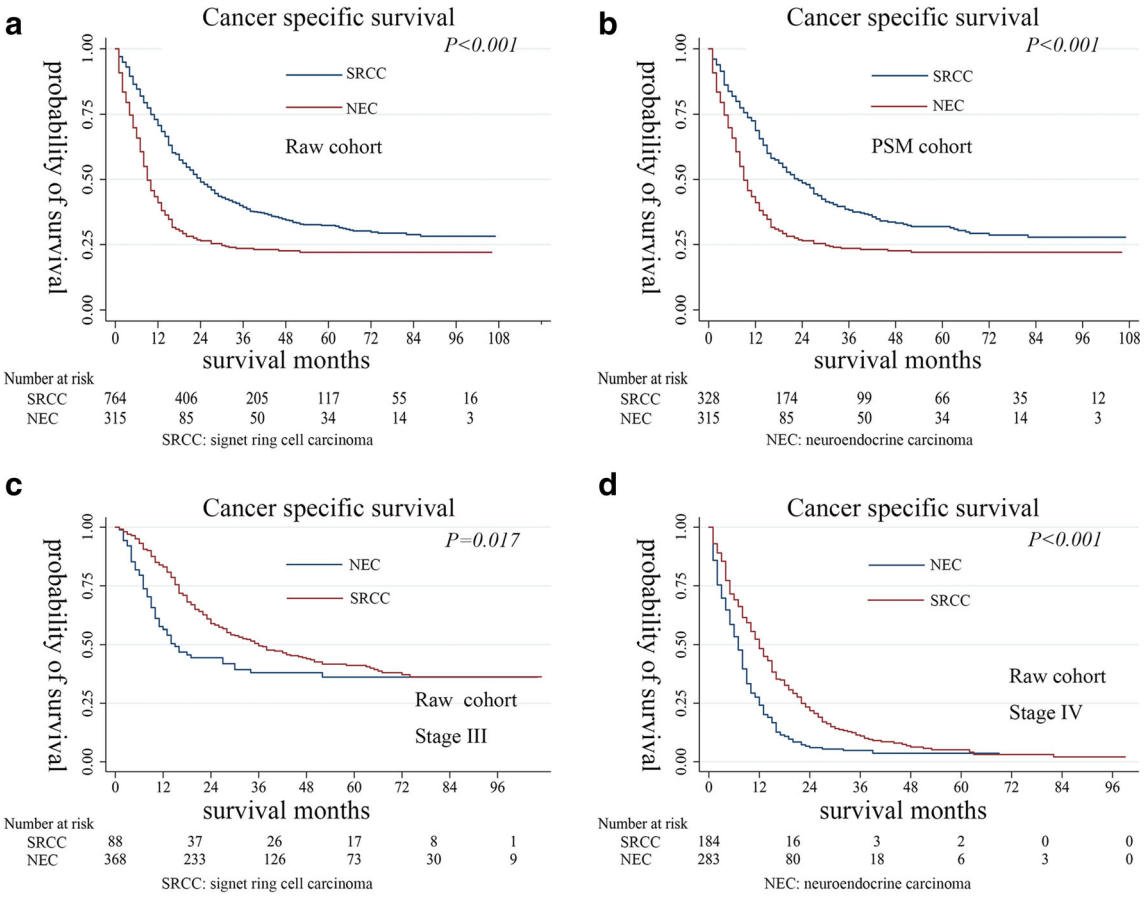

Fig. 3 Survival analysis of CRC-NEC and SRCC patients. **a** CSS between CRC-NEC and SRCC patients in the raw cohort. **b** CSS between CRC-NEC and SRCC patients in the PSM cohort. **c** CSS between CRC-NEC and SRCC patients of stage III disease in the raw cohort. **d** CSS between CRC-NEC and SRCC patients of stage IV disease in the raw cohort

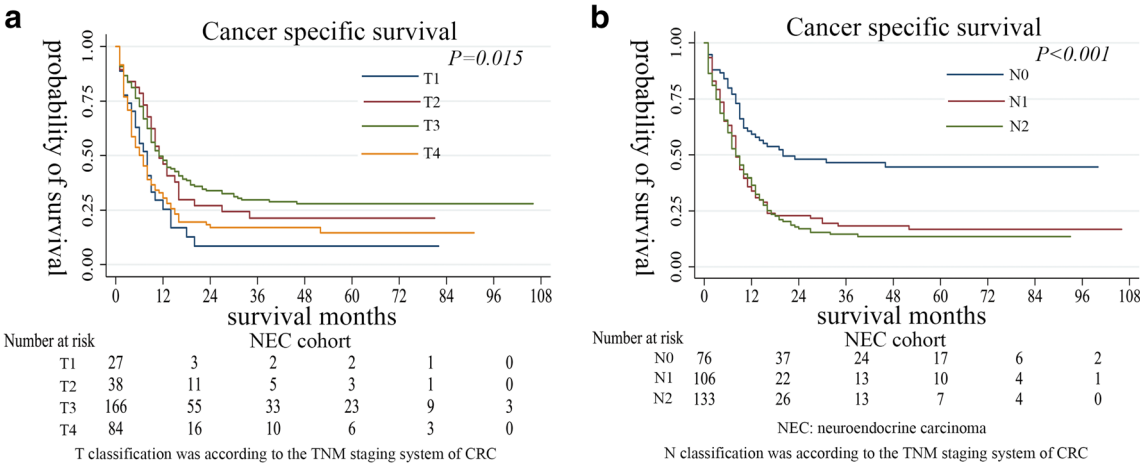

Fig. 4 Predictive value of T and N classification for prognosis of NEC. **a** Predictive value of T classification for prognosis of NEC. **b** Predictive value of N classification for prognosis of NEC

the hypothesis that the appendix may not be a frequent localization for NEC, despite of the frequent neuroendocrine tumours of all grades.

In our study, we found that the median CSS of CRC-NEC was only 9.0 (interquartile range [IQR], 4.0–30.0) months, similar to that reported by previous studies [6, 12, 18]. The

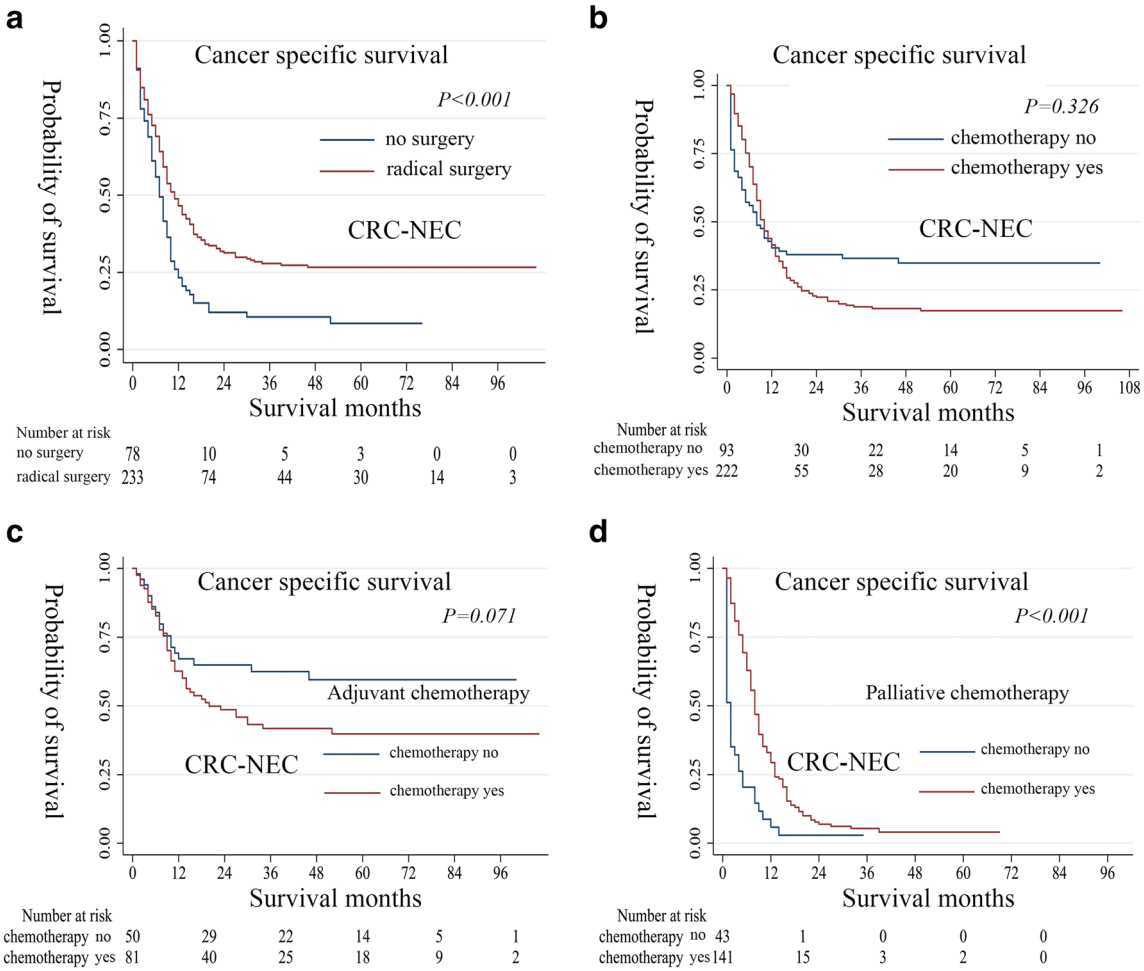

Fig. 5 CSS benefit of radical surgery and chemotherapy for CRC-NEC. **a** CSS benefit of radical surgery for CRC-NEC. **b** CSS benefit of chemotherapy for CRC-NEC

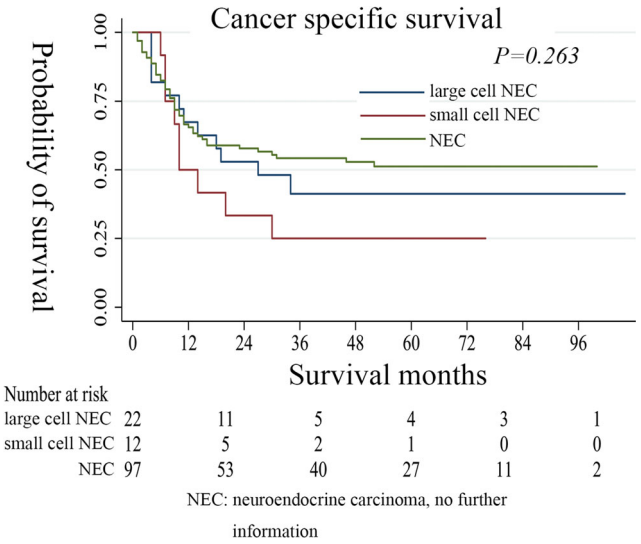

Fig. 6 Survival analysis of histological types in the NEC cohort

CSS of CRC-NEC was significantly poorer than that of adenocarcinoma and signet ring cell carcinoma based on the Kaplan-Meier survival curves ($P < 0.001$), and this was confirmed in PSM cohort. Unfortunately, after propensity score matching, which was performed by stratification for staging, operation method, and chemotherapy, there was still a statistically significant difference in characteristics as shown in Table 1, mainly in staging and operation methods. Any effort to balance the characteristics seemed to be a vain attempt, mainly due to the inherent difference between the two types of tumours. As shown in Table 1, patients with stage IV disease accounted for a significantly larger proportion of CRC-NEC patients than non-NEC patients (60.47% vs. 20.40%, $P < 0.001$), indicating CRC-NEC as a more aggressive tumour with a poor prognosis. Furthermore, CRC-NEC patients had less opportunity to accept radical operation than non-NEC patients (72.10% vs. 93.03%, $P < 0.001$). In our study, 86.63% of CRC-NEC patients were diagnosed in stage III or IV, and surgical resection was the primary treatment for CRC-NEC patients. However, for patients with metastatic CRC-NEC, a previous study reported that patients would not benefit from surgery and that surgery was not a prognostic factor for CRC-NEC [22]. Moreover, a retrospective study of 126 high-grade CRC-NEC patients reported that primary tumour resection did not improve the survival outcome [13]. In addition, a recent population-based study found that operation is not a prognostic factor in early-stage small cell CRC-NEC [15]. This result again proved that local surgery brought no benefit in terms of survival (HR, 0.89; 95% CI, 0.23–3.47; $P = 0.867$). However, radical surgery seemed to improve the prognosis, indicating that radical surgery is a necessary treatment, which was in agreement with the results of Fields et al. [18].

Efficient chemotherapy treatment for CRC-NEC has yet to be achieved [20, 23]. Our results showed that chemotherapy improved the 5-year cancer-specific survival of CRC-NEC in the univariate analysis (HR, 0.59; 95% CI, 0.40–0.87; $P = 0.008$); however, this finding was not significant in the multivariate analysis (HR, 1.22, 95% CI, 0.87–1.70; $P = 0.252$), which may be attributed to the insufficient number of samples and confounding factors. This finding agrees with results reported by a previous study that also indicated that improvement of the 5-year cancer-specific survival of CRC-NEC by chemotherapy treatment was not satisfactory [22]. The role of adjuvant chemotherapy needs further evaluation so that we will be able to better understand the overall effectiveness of chemotherapy treatment for patients with CRC-NEC, as shown in Fig. 5c that adjuvant chemotherapy brought a tendency of survival benefit without a statistic significance. Therefore, further prospective research is needed to shed light on the exact role of adjuvant chemotherapy in a large population. Recently, studies have shown that immunotherapy is a promising treatment for different types of cancers. Moreover, the relationship between NEC of the digestive system and the PD-L1 protein has been accounted for, indicating that immunotherapy may become a new treatment direction for CRC-NEC [24].

In our study, we found that the proportion of LNM and patients with stage III/IV disease was greater in CRC-NEC than in non-NEC CRC ($P < 0.001$). The LNM and stage of cancer are closely related to prognosis [4]. Therefore, it would be better to diagnose NEC earlier for an improved prognosis. Studies revealed that NEC did not benefit from advances in the prevention and treatment of colorectal adenocarcinoma over the past decade [15], which could be attributed to the fact that we did not find the tumour at early stages. Currently, the tumour, lymph node, metastases (TNM) staging system in colorectal neuroendocrine carcinoma is referred to that of colorectal adenocarcinoma; there have been a few studies assessing the value of current TNM classification. Actually, it is incredible indeed that patients with T3 CRC-NEC have the best survival demonstrated in Fig. 4, and one probable hypothesis is that patients with T3 CRC-NEC were the cohort who were more likely to accept radical surgery. The extraordinary finding was still probably or partially due to the small number of patients with T1 and T2. We stratify by T and N classification in Fig. 4 to call for the a modification of the staging system of CRC-NEC, as the current staging system may be impropriate that both the T and N classification cannot predict prognosis precisely despite of limited sample, although the conclusion may not be unshakable.

Our study showed that left-side colon NEC was an independent adverse prognostic factor for CRC-NEC ($P = 0.043$) in the multivariate analysis; however, left-side colon location in adenocarcinoma is a favourable prognostic factor accepted in routine work. There is still a lack of research about the difference in NEC in the left- and right-side colon. A previous study reported differences in the molecular biological characteristics, pathological features, clinical manifestations, and survival prognosis of left-

and right-side colon adenocarcinoma [25]. Therefore, we think that the different sensitivity to chemotherapy drugs in the left- or right-side colon could be one of the reasons why chemotherapy is an important part of treatment. Therefore, we suggest that the location of NEC could be a predictive marker for the prognosis of patients with NEC.

There are some limitations to our study. First, chemotherapy or other antitumour drugs affect the prognosis of patients. However, the SEER database lacks specific information on patient medications. Second, the SEER database lacks mitotic images and Ki-67 index-relevant information. Finally, this study is only a retrospective analysis of clinical data, and the number of NECs was small. Further study with a larger sample is desired for adequate evaluation.

Conclusions

NEC is a rare and extremely aggressive tumour with a poor prognosis. Patients with NEC on the right side of the colon have a better prognosis than those with NEC on the left side of the colon. Early diagnosis, radical surgery, and chemotherapy are imperative. Further investigations are necessary to understand the differences in behaviour based on tumour morphology and to develop novel targeted therapies to improve the outcomes of rare and aggressive NEC.

Acknowledgements The authors appreciate the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumour registries in the creation of the SEER database and the Data Management team who generously spared their time for the accomplishment and fulfilment of this project.

Authors' contributions Design of the study and drafting the manuscript: Youwei Chen. Acquisition of data, collection, and review of the literature: Jiangfeng Tu and Shishi Zhou. Critical revision of the manuscript for important content: Qinghua Wang and Jianfei Fu.

Funding The study was partially supported by a grant from the Key Program of the Jinhua Municipal Science & Technology Bureau (grant number 2018-3-001d). This study was supported by a grant from the Key Program of Scientific Research of Jinhua Central Hospital (grant number JY2016-1-02). The study was partially supported by the Medical Science & Technology Plan Project of Zhejiang Province (grant number LGF18H160029) and the General Program of Zhejiang Natural Science Foundation (grant number LY19H160020). The study was partially supported by a grant from the Key Program of the Jinhua Municipal Science & Technology Bureau (grant number 2019-3-013).

Data availability All the raw data were obtained from the publicly available SEER database with no special permission needed.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

Ethics approval and consent to participate The study was approved by the institutional review board and ethics committee of Affiliated Jinhua Hospital, Zhejiang University School of Medicine. All individual records were anonymous and de-identified prior to analysis.

Consent for publication The authors declare that they have no conflicts of interest to disclose, and all agree with the publication in International Journal of Colorectal Disease.

References

1. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A (2008) Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 9:61–72
2. Bosman FT, Carneiro F, Hruban RH (2010) WHO classification of tumours of the digestive system
3. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC (2017) Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 3:1335–1342
4. Zhang Y, Xie J, Wang J, Yang D, Jiang Z, Han G, Fu Q, Zhang Y (2016) Clinicopathological and prognostic analysis of neuroendocrine carcinoma of the colorectum. Adv Clin Exp Med 25:719–724
5. Boyar Cetinkaya R, Aagnes B, Thiis-Evensen E, Tretli S, Bergestuen DS, Hansen S (2017) Trends in incidence of neuroendocrine neoplasms in Norway: a report of 16,075 cases from 1993 through 2010. Neuroendocrinology 104:1–10
6. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofsli E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U (2013) Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol 24:152–160
7. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Díaz-Pérez JA, Martínez del Prado MP, Alonso Orduña V, Sevilla-García I, Villabona-Artero C, Beguiristain-Gómez A, Llanos-Muñoz M, Marazuela M, Alvarez-Escola C, Castellano D, Vilar E, Jiménez-Fonseca P, Teulé A, Sastre-Valera J, Benavent-Viñuelas M, Monleon A, Salazar R (2010) Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol 21:1794–1803
8. Rindi G, Falconi M, Klersy C, Albarello L, Boninsegna L, Buchler MW, Capella C, Caplin M, Couvelard A, Doglioni C, Delle Fave G, Fischer L, Fusai G, de Herder WW, Jann H, Komminoth P, de Krijger RR, la Rosa S, Luong TV, Pape U, Perren A, Ruszniewski P, Scarpa A, Schmitt A, Solcia E, Wiedenmann B (2012) TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst 104:764–777
9. Niederle MB, Hackl M, Kaserer K, Niederle B (2010) Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer 17:909–918
10. Bernick PE, Klimstra DS, Shia J, Minsky B, Saltz L, Shi W, Thaler H, Guillem J, Paty P, Cohen AM, Wong WD (2004) Neuroendocrine carcinomas of the colon and rectum. Dis Colon Rectum 47:163–169

11. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC (2014) Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer 120:2814–2823
12. Strosberg J, Nasir A, Coppola D, Wick M, Kvols L (2009) Correlation between grade and prognosis in metastatic gastroenteropancreatic neuroendocrine tumors. Hum Pathol 40: 1262–1268
13. Smith JD, Reidy DL, Goodman KA, Shia J, Nash GM (2014) A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. Ann Surg Oncol 21(9):2956–2962
14. Conte B, George B, Overman M, Estrella J, Jiang ZQ, Mehrvarz Sarshekeh A, Ferrarotto R, Hoff PM, Rashid A, Yao JC, Kopetz S, Dasari A (2016) High-grade neuroendocrine colorectal carcinomas: a retrospective study of 100 patients. Clin Colorectal Cancer 15:e1–e7
15. Shafqat H, Ali S, Salhab M, Olszewski AJ (2015) Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. Dis Colon Rectum 58:294–303
16. Fu JF, Wu LP, Jiang MJ, Tan Y, Li D, Chen F, Jiang T, du J (2016) Signet ring cell carcinoma of resectable metastatic colorectal cancer has rare surgical value. J Surg Oncol 114:1004–1008
17. Fu J, Wu L, Fu W, Tan Y, Xu T, Hong Z, Wang F, Li S (2018) How young is too young in breast cancer?—young breast cancer is not a unique biological subtype. Clin Breast Cancer 18:e25–e39
18. Fields AC, Lu P, Vierra BM, Hu F, Irani J, Bleday R, Goldberg JE, Nash GM, Melnitchouk N (2019) Survival in patients with high-grade colorectal neuroendocrine carcinomas: the role of surgery and chemotherapy. Ann Surg Oncol 26:1127–1133
19. Ackermann CJ, Guller U, Jochum W, Schmied BM, Warschkow R (2018) The prognostic value of signet ring cell histology in stage I/II colon cancer-a population-based, propensity score-matched analysis. Int J Color Dis 33:1183–1193
20. Hrabe J (2020) Neuroendocrine tumors of the appendix, colon, and rectum. Surg Oncol Clin N Am 29:267–279
21. Chiominto A, Di Sibio A, Mastropietro S et al (2019) Adjuvant chemotherapy versus observation following resection for patients with nonmetastatic poorly differentiated colorectal neuroendocrine carcinomas. BMC Cancer
22. Wu Z, Yu D, Zhao S et al (2018) The efficacy of chemotherapy and operation in patients with colorectal neuroendocrine carcinoma. J Surg Res 225:54–67
23. Pascarella MR, Mccloskey D, Jenab-Wolcott J et al (2011) Large cell neuroendocrine carcinoma of the colon: a rare and aggressive tumor. J Gastrointest Oncol 2:250–253
24. Xing J, Ying H, Li J, Gao Y, Sun Z, Li J, Bai C, Cheng Y, Wu H (2020) Immune checkpoint markers in neuroendocrine carcinoma of the digestive system. Front Oncol 28(10):132
25. Moritani K, Hasegawa H, Okabayashi K et al (2014) Difference in the recurrence rate between right- and left-sided colon cancer: a 17-year experience at a single institution. Surg Today 44(9):1685–1691